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SYNTHESIS OF MONOSACCHARIDES BY OXIDATION OF FURFURAL DERIVATIVES

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ABSTRACT

DL-Ribose, DL-arabinose, and DL-xylose have been synthesized from 2-furaldehyde. Condensation of 2-furaldehyde with pinacol followed by oxidation of the product with bromine water or lead tetra-acetate and reduction with sodium borohydride gave DL-2-(1,4-dihydroxy-*cis*-but-2-enyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**4a**). Hydroxylation of the dibenzoate of **4a** followed by debenzoylation and hydrolysis gave DL-ribose and DL-arabinose. Epoxidation of **4a** with monoperoxysuccinic acid followed by hydrolysis gave DL-xylose.

INTRODUCTION

Some attempts have been reported in the literature for the synthesis of monosaccharides from furfural derivatives utilising oxidation reactions. Addition reactions to the double bond of dihydrofuran or dihydropyran derivatives make possible the synthesis of complicated monosaccharides. The procedure of Achmatowicz *et al.*[1] was based on the methoxylation of 2-hydroxyalkylfurans *via* the bromo derivatives[2]. Hydrolysis of the resulting dimethoxydihydrofurans gave 2,3-dideoxy-DL-alk-2-enopyranosid-4-uloses, which can be converted into the various monosaccharide derivatives[3,4]. Oxidation reactions of 2-hydroxyalkylfurans with peroxy acids also gave unsaturated pyranosuloses[5]. The addition reactions of dihydrofurans obtained by the electrolytic methoxylation of furan derivatives have been applied by Šrogl *et al.*[6a,b] for the synthesis of complicated monosaccharide derivatives.

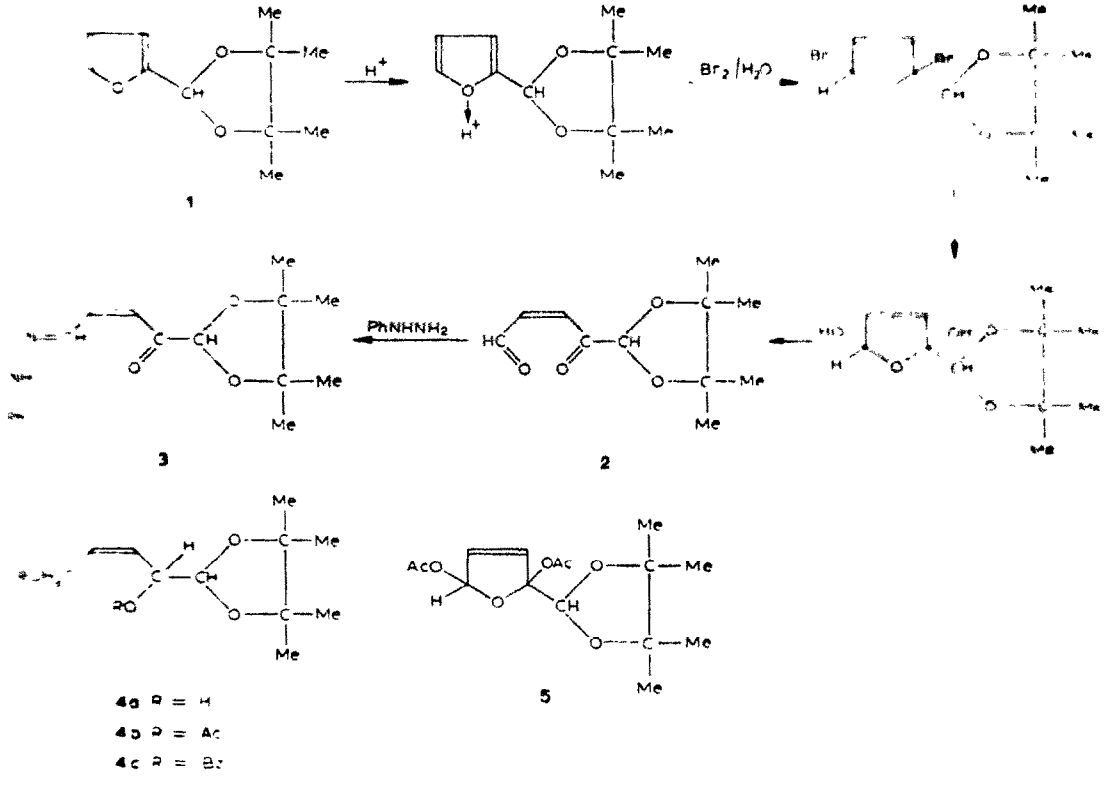
In the course of oxidation of furfural with bromine water, the bisphenylhydrazone of a dioxo compound was isolated by Hughes and Acree[7] and assumed to be a derivative of 4-oxo-4,5-dihydrofurfural. This structure was rejected by Clauson-Kaas and Fakstorp[8], who suggested that the product was the phenylhydrazone of the pent-2-en-1,5-dial-4-one (endialone). The same conclusion was reached by Szakács-Pintér and Maros[9,10]. The oxidation of furfural with chlorine[11] or the hydrolysis of 2-diacetoxymethyl-2,5-dimethoxy-2,5-dihydrofuran[12] also affords endialone which, because of its instability, is known only as its derivatives.

RESULTS AND DISCUSSION

Achmatowicz *et al.*[1] used furfuryl alcohol as a starting material, and C-1 of the resulting pentopyranosides was formed from the C-5 of the furan ring. We have used 2-furaldehyde as the starting material, with the formyl group becoming the reducing group of the aldoses. It was necessary to protect the formyl group against both acidic (oxidation) and basic conditions (borohydride reduction). Appropriate protection was accomplished by reaction with 2,3-dimethylbutane-2,3-diol to give a 4,4,5,5-tetramethyl-1,3-dioxolane derivative (**1**). The rate of hydrolysis of such derivatives is extremely slow, because protonation is hindered by the methyl groups[13]. 2-(2-Furyl)-4,4,5,5-tetramethyl-1,3-dioxolane[14] (**1**) is stable at pH 3 and 23°, but slow hydrolysis is observed at pH 2.

Oxidation of **1** with bromine water in *tert*-butyl alcohol–phosphate buffer gave the endialone **2**, which was too unstable to be isolated but could be characterised as the phenylhydrazone **3**. This derivative had λ_{max} 410 nm under neutral and acidic conditions, but at basic pH values it had a violet chromophore at λ_{max} 500 nm. This change was reversible and is characteristic of the phenylhydrazone of α,β-unsaturated oxo compounds[15].

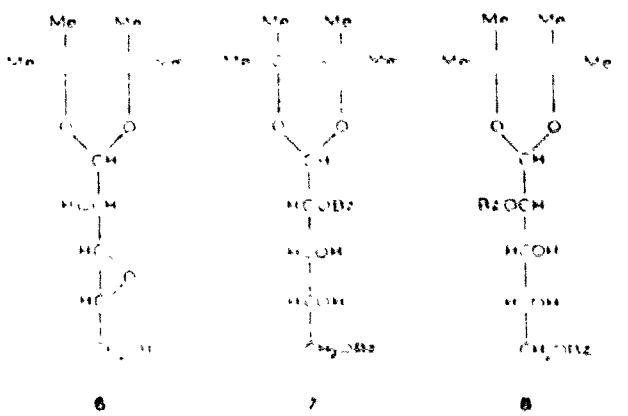
These data confirm the mechanism of the oxidation reaction of furfural with bromine water proposed by Szakács-Pintér and Maros[9,10]. The reaction sequence is shown below (**1** → **2**).



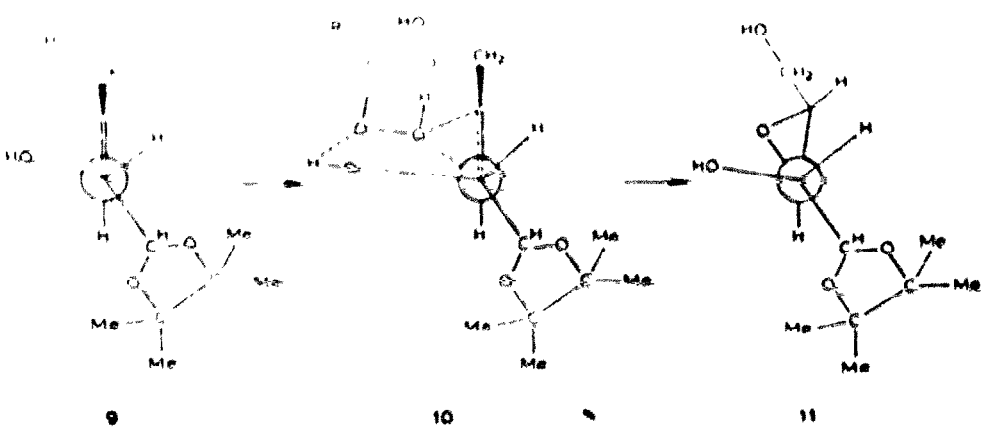
Reduction of **2** with sodium borohydride gave DL-2-(1,4-dihydroxy-*cis*-but-2-enyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**4a**), which is a cyclic acetal of DL-3,4-dideoxypent-3-enose; reduction of the double bond was not observed. Compound **4a** slowly decomposes during vacuum distillation, but can be isolated as its acetate (**4b**) or crystalline benzoate (**4c**).

Oxidation of **1** with lead tetra-acetate gave the unstable diacetoxydihydrofuran derivative[16,17] **5**, which was not isolated but was reduced with sodium borohydride to give a mixture of five compounds, from which **4a** was isolated in poor yield by chromatography.

Oxidation of **4a** with monoperoxysuccinic acid[18,19] gave the epoxide **6**. Because of the steric hindrance of the bulky dioxolane group, the most probable rotamer of **4a** is **9**. The epoxidation of α,β-unsaturated alcohols proceeds through a hydrogen-bonded intermediate[20] (*i.e.*, **10**), so that **6** has the conformation **11** and is DL-*threo*-2-(2,3-epoxy-1,4-dihydroxybutyl)-4,4,5,5-tetramethyl-1,3-dioxolane



6 **7** **8**



9 **10** **11**

Hydrolysis of **6**, which is a cyclic acetal of 3,4-anhydro-DL-arabinose, gave DL-xylose, which was converted into a phenylosazone, tetra-acetate, and toluene-*p*-sulphonylhydrazone

The hydroxylation of **4c** with hydrogen peroxide–osmium tetraoxide gave a mixture of **7** and **8**. Debenzoylation (Zemplén[24]) of the mixture followed by hydrolysis with dilute sulphuric acid gave a mixture of DL-ribose and DL-arabinose, which was fractionated by chromatography on a cation-exchange (Ba^{2+}) resin.

Additions to the double bond of **4** make possible the preparation of other pentose derivatives. We are continuing our work in this field.

EXPERIMENTAL

General. — Melting points were determined on a Kofler apparatus and are uncorrected. I.r. spectra were recorded for potassium bromide pellets with a Unicam SP-200 spectrophotometer. N.m.r. spectra were obtained with a JEOL MH-100 (100 MHz) instrument, and mass spectra with an AEI MS-902 mass spectrometer. Concentrations were performed with a rotary evaporator at 40–45°.

DL-*2-(1,4-Dihydroxy*-cis-*but-2-enyl)-4,4,5,5-tetramethyl-1,3-dioxolane* (**4a**). — (*a*) To M sodium hydroxide (240 ml), M phosphoric acid was added (~70 ml) to pH 3.8–3.9 (pH meter). A solution of **1** (10.6 g, 0.054 mol) in *tert*-butyl alcohol (50 ml) was then added. After cooling to 10–12°, a solution of bromine (2.94 ml, 0.054 mol) in *tert*-butyl alcohol (50 ml) was added dropwise, with vigorous stirring, during 30 min. The pH was kept at 3.8–4.0 by continuous addition of 2M sodium hydroxide. The solution was neutralized, and saturated with sodium chloride, and the organic layer was separated. The aqueous phase was extracted with *tert*-butyl alcohol (2 × 50 ml). The combined organic layers were diluted with water (800 ml), stirred with a solution of sodium borohydride (1.53 g, 0.0405 mol) in ethanol (100 ml) at 5° for 3 h, then acidified to pH 5, and concentrated. The syrupy residue was extracted with ether (70 ml), and the extract was dried (Na_2SO_4) and concentrated to dryness. Distillation of the residue gave **4a** (2.82 g, 25%), b.p. 161–167°/0.4 mmHg, m.p. 52–54° (from cyclohexane). N.m.r. data: δ 4.88 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1), 4.35 (q, 1 H $J_{2,3}$ 7.8 Hz, H-2), 5.55 (q, 1 H, $J_{3,4}$ 11.2 Hz, *cis* double-bond, H-3), 5.89 (octet, 1 H, $J_{4,5}$ 6 Hz, H-4), and 4.19 (d, 2 H, $J_{5,5}$ 11–12 Hz, H-5,5'). Mass spectrum: *m/e* 129 (100).

Anal. Calc. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.85; H, 9.10.

(*b*) A mixture of **1** (10.6 g, 0.054 mol), lead tetra-acetate (23.9 g, 0.054 mol), and dry, alcohol-free chloroform (200 ml) was boiled under reflux for 14 h, then cooled, filtered, washed with saturated, aqueous sodium carbonate, dried (Na_2SO_4), and concentrated. A solution of the oily residue in ethanol (150 ml) was treated with $NaBH_4$ (2.05 g, 0.054 mol) dissolved in ethanol (100 ml). After 3 h, the mixture was acidified to pH 4 with M hydrochloric acid at 0°, then stored for 10 min, neutralised with M sodium hydroxide, filtered, and concentrated. The resulting syrupy residue (6.1 g) was eluted from Silica gel G with light petroleum (b.p. 40–60°)–acetone (9:2.5) to yield **4a** (1.2 g), m.p. 50–52°, together with several unidentified products.

DL-*2-(1,4-Diacetoxy*-cis-*but-2-enyl)-4,4,5,5-tetramethyl-1,3-dioxolane* (**4b**). — Conventional treatment of **4a** (9.2 g) with acetic anhydride–pyridine gave **4b** (7.9 g, 65%), b.p. 155–162°/1 mmHg.

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.07; H, 8.29.

DL-*2-(1,4-Dibenzoyloxy-*cis-*but-2-enyl)-4,4,5,5-tetramethyl-1,3-dioxolane* (**4c**). — Conventional treatment of **4a** (1 g) with benzoyl chloride–pyridine gave **4c** (0.84 g, 74%), m.p. 91–92° (from ethanol). Mass spectrum: *m/e* 424 (0.01) M^+.

Anal. Calc. for $C_{25}H_{28}O_6$: C, 70.07; H, 6.64. Found: C, 70.50; H, 6.61.

*2-(1,4-Dioxo-*cis-*but-2-enyl)-4,4,5,5-tetramethyl-1,3-dioxolane 4'-phenylhydrazone* (**3**). — A mixture of phenylhydrazine hydrochloride (5 g) and sodium acetate (7 g) in water (200 ml) was added to **4a** (prepared from 3.5 g of **1** by bromine oxidation). The black, syrupy product which separated after 30 min was triturated with carbon tetrachloride and then recrystallised from the same solvent to give **3** (1.32 g), m.p. 143–145° (dec.), ν_{max} 1688 cm^{-1} (C=O).

Anal. Calc. for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.26. Found: C, 66.70; H, 7.28; N, 9.51.

DL-threo-*2-(2,3-Epoxy-1,4-dihydroxybutyl)-4,4,5,5-tetramethyl-1,3-dioxolane* (**6**). — Disuccinoyl peroxide (2.56 g, 0.0105 mol) was shaken with water (7 ml) at 50°, and **4a** (2.16 g, 0.01 mol) was added. The solution was kept overnight at room temperature, then filtered, diluted with water (15 ml), and neutralized with Dowex-2 X4 (HO^-) resin, and concentrated. The oily residue was dried over P_2O_5 *in vacuo* and then crystallized from ether–light petroleum to yield **6** (0.88 g, 38%), m.p. 85–86°; ν_{max} 3340 (OH) and 1270 cm^{-1} (epoxide).

Anal. Calc. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.67. Found: C, 56.72; H, 8.92.

DL-threo-*Pentose phenylosazone.* — A solution of **6** (2 g) in 0.5M sulphuric acid (40 ml) was kept at 50° for 10 min, then neutralized with Dowex-2 X4 (HO^-) resin, and concentrated. The resulting colourless syrup, which reduced Fehling's solution, was treated with a solution of phenylhydrazine (3.12 g) in water (24 ml) and acetic acid (1.92 ml) at 100° for 2 h. The product was collected from the cooled mixture, successively washed with 10% acetic acid and water, and recrystallized from ethanol to give the title product (0.58 g), m.p. and mixture m.p. 210–212°.

DL-*Xylopyranose tetra-acetate.* — Compound **6** (0.92 g) was hydrolyzed with 0.5M sulphuric acid (20 ml) at 50° to give 0.65 g of a syrupy material which, after drying over P_2O_5, was conventionally acetylated with acetic anhydride (3 ml) in pyridine (8 ml) to give the title product[21] (240 mg), m.p. 122–124°.

DL-*Xylose toluene-*p-*sulphonylhydrazone.* — A solution of the foregoing tetra-acetate (107 mg) in 0.1M methanolic sodium methoxide (4 ml) was stored for 3 h, then neutralized with AG-50 X12 (H^+) resin, and concentrated. A solution of the residue in methanol (1 ml) was treated with toluene-*p*-sulphonylhydrazine (50 mg) and then boiled under reflux for 30 min. The mixture was concentrated, and the residue was crystallized from methanol to give the title compound (82 mg), m.p. 158–159° (dec.); lit.[22] m.p. 154°.

DL-*Ribose and* DL-*arabinose.* — A solution of **4c** (3.3 g) in methanol (300 ml) was treated with 30% hydrogen peroxide (10 ml) and 1% osmium tetraoxide in *tert*-butyl alcohol (1 ml). The mixture was kept at room temperature for 4 days, and 3–4 ml portions of hydrogen peroxide (total, 14 ml) were added. The solution was

then filtered, and concentrated to 70 ml, and water (300 ml) was added. The resulting oil was separated, and dissolved in ethyl acetate (100 ml), and the solution was dried (Na_2SO_4) and concentrated. A solution of the colourless syrup (2.5 g) in 0.1M methanolic sodium methoxide (40 ml) was kept at room temperature for 3 h, then neutralized with AG-50W X12 (H^+) resin, and concentrated. The syrupy residue was hydrolysed overnight in a mixture of 2M hydrochloric acid (30 ml) and *p*-dioxane (30 ml) at room temperature, then treated with Dowex-2 X4 (HO^-) resin, and concentrated. The resulting, colourless syrup (2.1 g), which reduced Fehling's solution, contained two components (t.l.c., cellulose MN 300 G, 1-butanol–acetic acid–water, 4:1:5) which reacted with aniline hydrogen phthalate and had R_F values identical with those of ribose and arabinose. Elution of the mixture (570 mg) from a column (70 × 2 cm) of Dowex-50W X8 (Ba^{2+}) resin (50–100 mesh) with water gave DL-arabinose (28 mg) and DL-ribose (49 mg). The latter gave a toluene-*p*-sulphonylhydrazone, m.p. 161°; lit.[23] m.p. 161–162°. The former gave a tetra-acetate, m.p. 112–114°, the n.m.r. spectrum of which was identical with that described in Ref. 21.

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