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Formation of Aromatic Compounds from Carbohydrates. VIII.* Reaction of D-Erythrose in Slightly Acidic, Aqueous Solution

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The title reaction yielded 5-hydroxymethylfuran-2-carboxaldehyde (*1*), 1-[5-(hydroxymethyl)-2-furanyl]-ethanone (*2*), 1,2-benzenediol (*3*), 3-methyl-1,2-benzenediol (*4*), 3,4-dihydroxybenzaldehyde (*5*), 3,4-dihydroxybenzoic acid (*6*), (3,4-dihydroxyphenyl)-1-ethanone (*7*), formic (*8*), hydroxyacetic (*9*), 3-hydroxypropanoic acid (*10*) and hydroxyacetaldehyde (*11*). Compound *2* has not previously been identified in degradation products of carbohydrates.

Previous papers in this series have dealt with the degradation in aqueous solution of hexuronic acids,[2,3] hexoses[4,5] and pentoses[2,5] and with the low-molecular phenolic and enolic compounds that are believed to be intermediates in the formation of colour by reducing carbohydrates on heating. The degradation of D-glucose in the presence of an amine (methylamine[6] or glycine[1]) – the Maillard reaction – was also studied. Degradation of sugars (in the absence of amino compounds) at higher pH values resulted in extensive fragmentation (cleavage of carbon chains) and recombination steps. Similar products were thus obtained from D-glucose and D-xylose.[5] At pH 4.5, however, the pattern of products was more specific, and there were distinct differences between the major products from the hexuronic acid-pentose group and those from the hexoses. In the light of these results, it was of interest to study the reactions of short-chain sugars like D-erythrose and dihydroxyacetone under similar conditions. The results obtained with the latter compound – indicating that the major low-molecular products were formed without carbon cleavage – were recently reported[7] and those from the reaction of D-erythrose are presented here.

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D-Erythrose exists mainly as dimers in concentrated solution and in the syrupy state.[8–10] In dilute solution it exists essentially as a mixture of hydrated aldehydo and furanose forms.[9,10] During the present study, it was found that, on storage at room temperature, syrupy D-erythrose is slowly converted into 3-octuloses by an aldol reaction, which is readily accelerated by heating. This conversion, which is almost complete after 2.5 h at 105 °C will be discussed elsewhere.[11]

RESULTS

Chromatography of the ethyl acetate-soluble part of the brown-coloured reaction mixtures yielded compounds *1*–*7*. None of these, which were all

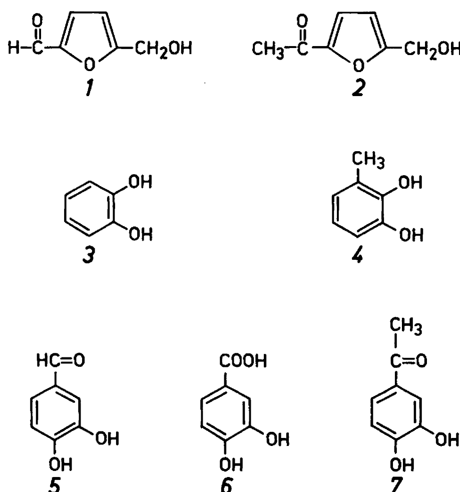

Table 1. Yields (wt. % of D-erythrose) and chromatographic properties of title reaction products *1*–*7*.

Compound	Yield/%		Rc^a	Colour	
	Exp. A	Exp. B		Spray *a*	Spray *b*
1	0.04	0.04	0.57	–	Bluish grey
2	0.15	0.16	0.69	–	Orange→green
3	<0.01	<0.01	1.00	Bluish grey	Red
4	0.03	0.12	1.28	Black	Red
5	0.01	0.01	0.47	Greenish-blue	Yellow
6	0.03	0.03	0.52	Greyish-black	Brown
7	0.01	0.01	0.47	Greenish-black	Reddish-brown

[a] Mobility in chloroform–acetic acid (9:1) in relation to compound *3*.

identical (TLC, MS, ^{1}H NMR) with authentic samples, has previously been reported from the degradation of D-erythrose. The yields and chromatographic properties are given in Table 1. Also isolated in small amounts were three mono-*O*-ethylidene compounds, originating from the acid-catalyzed rearrangement of 2,4-*O*-ethylidene-D-erythrose during the synthesis of D-erythrose. The structures of these comparatively acid-stable compounds will be discussed elsewhere.[12]

It has previously been reported that D-*gluco*-L-*glycero*-3-octulose is formed by alkaline treatment of D-erythrose.[13] In the present investigation, the reaction mixture from experiment A contained octuloses as evidenced by comparison (GLC[14] and paper chromatography) with an authentic sample of D-*gluco*-L-*glycero*-3-octulose. However, during the treatment of monomeric D-erythrose (Exps. B and C), using a freshly prepared solution which had not been concentrated to a syrup, no octuloses were detected in the reaction mixture. This showed that the syrupy D-erythrose used in experiment A from the beginning contained octuloses, which under the reaction conditions chosen, are apparently more stable towards degradation than monomeric D-erythrose. In experiment B, isomerization of D-erythrose occurred within 30 min and very little tetroses remained at the end of the reaction time. In a separate experiment (Exp. D) D-*gluco*-L-*glycero*-3-octulose was found to be more stable than erythrose when treated as in experiment B; the solution was only slightly coloured and no tetroses or higher sugars were found in significant amounts.

The reaction mixture in a separate experiment (Exp. C), using the conditions of experiment B, was investigated for low-molecular acids by GLC-MS of their benzyl ester derivatives.[15] Formic (*8*), acetic, hydroxyacetic (*9*) and 3-hydroxypropanoic acids (*10*) were identified by comparison with authentic derivatives. A sugar analysis combined with deuterium incorporation revealed the presence of hydroxyacetaldehyde (*11*) in Exp. C.

DISCUSSION

In a previous investigation on the treatment of D-erythrose under strongly acidic conditions, a C_8-pyrone was isolated.[16] In the present work, in which the sugar was treated under slightly acidic conditions, no pyrone was detected but another C_8-compound, (3,4-dihydroxyphenyl)-1-ethanone (*7*) was isolated. Four C_7-compounds, of which three were phenols (*4*–*6*) and one a furan derivative (*2*), and two C_6-compounds (*1* and *3*) were also isolated in small amounts. The formation of the furans *1* and *2* is noteworthy. The former is a typical product of the acid degradation of hexoses,[17] whereas the latter (the major product and a constituent[18] of tobacco smoke) has not, to our knowledge, previously been found among the degradation products of carbohydrates. Aldol condensation between hydroxyacetaldehyde present in the reaction mixture and D-erythrose, to yield ketohexoses, may initiate the sequence of reactions leading to the formation of compound *1*. The hydroxyacetaldehyde is probably formed by a reverse aldol condensation of erythrose and/or less probably, by hydrolytic fission of 1-deoxy-2,3-tetrodiulose. The last compound is expected to arise from D-erythrose in accordance with the known isomerization and dehydration reactions of carbohydrates in acidic solution.[17]

The low-molecular acids may originate, at least in part, from the hydrolytic carbonyl fission of 3-deoxy-

1,2-tetrosulose and 1-deoxy-2,3-tetrodiulose, two potential products of the dehydration of D-erythrose. The fact that syrupy D-erythrose readily undergoes a self-aldol condensation suggests that octuloses might be intermediates in the formation of aromatic products. However, as no octuloses were detected when monomeric D-erythrose was degraded (Exps. B and C), and since octuloses are more stable than D-erythrose towards degradation (Exps. A and D), it seems unlikely that they are important intermediates in the reaction. The catechol *3* seems to be a rather typical product of the reaction of monosaccharides and hexuronic acids [2,4,7] with dilute acid. Catechols react readily to give coloured products.

EXPERIMENTAL

Materials and methods. All solvents were mixed on a volume basis. The general procedures described earlier [7] were used with the following modifications. The TLC plates (Riedel-de Haën, silica gel and cellulose) were sprayed with (*a*) aqueous iron(III) chloride, (*b*) a solution (*v*/*v*) of *p*-anisaldehyde (5 %) and sulfuric acid (5 %) in ethanol, (*c*) ethanolic *p*-anisidinium chloride, (*d*) silver nitrate – sodium hydroxide or (*e*) resorcinol – hydrochloric acid reagents. Paper chromatography was carried out on Whatman No. 1 sheets. Column chromatography was performed with Sephadex LH-20, cellulose powder (Whatman CF 11) or silica gel (Merck 60, 230 – 400 mesh) using (A) a non-linear water – ethanol gradient, (B) butanol – ethanol – water (3:1:1), (C) light petroleum – ethyl acetate (1:1), (D) dichloromethane – acetone (4:1), (E) dichloromethane – ethanol (9:1) or (F) dichloromethane – ethanol (19:1). Sugar analysis was performed essentially according to Sawardeker *et al.*[14] GLC was conducted on a Varian Aerograph 2700 fitted with a flame ionization detector and a 1.8 m × 2 mm i.d. glass column containing 3 % SP 2340 on Supelcoport (100 – 120 mesh). Acetylated alditols were analyzed at 180 – 250 °C and benzyl esters at 80 – 250 °C, using a nitrogen flow rate of 30 ml/min and a program rate of 6 °C/min, unless otherwise stated. ^{13}C NMR spectra were recorded with a Jeol FX 90Q Fourier Transform NMR spectrometer. Solvents, reagents and reference compounds were commercial samples of good grade, unless otherwise stated. All solvents were freshly distilled before use.

D-Erythrose was synthesized by the acid hydrolysis of 2,4-*O*-ethylidene-D-erythrose,[8] obtained by periodate oxidation of 4,6-*O*-ethylidene-D-glucose as described by Schaffer [19] or by Barker and MacDonald.[20] Acid hydrolysis of the product from the latter method yielded D-glucose in addition to D-erythrose because of incomplete periodate oxidation. In experiment A, the D-erythrose consisted of a mixture of two batches, prepared by the two alternative methods. The D-glucose content in the combined starting mixture was 0.8 %. There was no indication that this had any significant effect on the pattern of products than possibly on the yield of compound *1*. In experiments B and C, D-erythrose was prepared essentially as described in Ref. 19 but the sugar was kept in a dilute solution to prevent formation of octuloses.[11] The solution contained no glucose, threose, tetrulose, or octuloses. ^{13}C NMR of the solution showed that the furanose and the aldehydrol forms of D-erythrose were preponderant, in good agreement with data previously published.[10] Small amounts of three mono-*O*-ethylidene compounds [12] were also present in the solution according to TLC analysis (solvent C, spray *b*). These were comparatively stable under the reaction conditions, since on separate treatment in acetate buffer (0.3 M, pH 4.5, 100 °C, 18 h), monitored by TLC analysis (water saturated 2-butanone, spray *b*), each compound was only partly hydrolyzed to D-erythrose.

1-[5-(Hydroxymethyl)-2-furanyl]-ethanone was synthesized from 5-hydroxymethylfuran-2-carboxaldehyde, as previously described,[21] except that the reaction time was shortened and the product was purified on a silica gel column with petroleum ether (b.p. 60 – 70 °C) – ethyl acetate (3:2) as eluent. Yield: 35 mg (15 %).

Reactions

Experiment A. D-Erythrose (75.0 g) was dissolved in 0.3 M acetate buffer of pH 4.5 (2.0 l) and refluxed for 45 h in an atmosphere of nitrogen. The reaction mixture was cooled to 20 °C and extracted with ethyl acetate, first batchwise (3 × 0.8 l), and then in a percolator for 24 h. The extracts were combined and dried with sodium sulfate. After filtration and evaporation of the solvent, the residue (9.2 g) was applied to a Sephadex LH-20 column (6 × 100 cm) and eluted with solvent A. The fractionation was monitored by TLC in dichloromethane – acetic acid (9:1).

Six main fractions, numbered in order of elution, were collected by elution with water and another two with ethanol as solvent. Fraction I (2.33 g), [three mono-ethylidene-D-erythrose derivatives (1.2 g) were isolated from this fraction [12]], II (0.79 g, *1* and *2*), III (0.64 g, no aromatic compounds detected), IV (0.60 g, *3*), V (0.20 g, *4*), VI (0.37 g, *5* and *7*), VII (0.48 g, *6*) and VIII (0.80 g, unidentified, strongly coloured products). The compounds were further purified by chromatography on silica gel columns: compounds *1* and *2*, solvent C; compound *3*,

solvent D; compounds *4*, *5*, *7*, solvent F; and compound *6*, solvent E.

After extracting the reaction mixture with ethyl acetate, an aliquot (1/10) was deionized with Dowex 50 (H^+ form). After filtration and freeze drying, the residue (2.15 g) was loaded onto a column of cellulose powder (90×2.5 cm) and eluted with solvent B. The fractionation was monitored by TLC on cellulose plates with the same solvent and also by paper chromatography with ethyl acetate – acetic acid – water (3:1:1) using spray reagents *d* and *e*. Two crude, main fractions were collected. The first (1.2 g) contained mainly undegraded and isomerized D-erythrose, but also the compounds found in fraction I above. Paper chromatography of the second fraction (0.8 g), revealed the presence of two main components, one of which corresponded to D-*gluco*-L-*glycero*-3-octulopyranose identified by comparison with an authentic sample. Sugar analysis of the components in this fraction indicated that both compounds were octuloses.

Experiment B. 2,4-*O*-Ethylidene-D-erythrose (7.3 g) was hydrolyzed in sulfuric acid (0.25 M, 150 ml) for 1.25 h at 96 °C with nitrogen bubbling through the solution. After cooling, the hydrolysate was neutralized ($BaCO_3$), filtered (Celite) and adjusted to pH 4.5 and 0.3 M with respect to acetate ion. This solution was then treated as described under experiment A. The ethyl acetate extract (0.6 g) obtained yielded compounds *1* – *7* and three mono-*O*-ethylidene derivatives of D-erythrose. Sugar analysis of aliquots withdrawn during the reaction showed that isomerization of D-erythrose occurred within 30 min and that the tetroses were degraded within 24 h. No octuloses were detected.

Experiment C. D-Erythrose was prepared and degraded as in experiment B. An aliquot (1/15) of the reaction mixture was analyzed for low-molecular acids as their benzyl esters by GLC-MS.[15] The formation of formic (*8*), hydroxyacetic (*9*) and 3-hydroxypropanoic acids (*10*) was established by comparison with authentic derivatives.

The remaining reaction mixture was extracted with diethyl ether in a percolator overnight. After evaporation of an aliquot (1/5) of the ether solution, the residue (32 mg) was reduced with sodium borodeuteride, acetylated (Ac_2O/pyridine) and subjected to GLC-MS analysis (3 % SP 2340, 80 °C). Hydroxyacetaldehyde (*11*) was identified as the corresponding 1,2-ethane-1-*d*-diol diacetate.[22]

Experiment D. D-*Gluco*-L-*glycero*-3-octulose (25 mg) was degraded and analyzed for sugars as in experiment B. No formation of D-erythrose was observed and most of the octulose remained unchanged.

Characterization and identification of compounds *1* – *11*

Compounds *1*, *3*, *4* and *6* were identical (TLC, ^{1}H NMR, MS) with commercial samples, while compounds *8* – *11* were identified by GLC/MS comparison with authentic derivatives.

Compound 2. Identical (^{1}H NMR, MS, IR) with a synthetic sample of 1-[5-hydroxymethyl)-2-furanyl]-ethanone. Amorphous. MS, *m/e* (rel. int.): 140(77, *M*), 125(93), 123(14), 111(16), 97(80), 81(10), 69(61), 52(12), 51(17), 50(11), 43(83). ^{1}H NMR ($CDCl_3$): δ 2.43 (Ac, s), 2.9 (OH, broad), 4.68 (CH_2, s), 6.43 (4-H, d, *J* 3.6 Hz), 7.13 (3-H, d, *J* 3.6 Hz).

Compounds 5 and 7 were only obtained in admixture. The identity was verified by comparison of ^{1}H NMR and TLC data with an authentic 1:1 mixture of 3,4-dihydroxybenzaldehyde and (3,4-dihydroxyphenyl)-1-ethanone.

Compound 8. The corresponding benzyl ester had MS, *m/e* (rel.int.): 136(55, *M*), 108(42), 107(32), 91 (100), 90(80), 89(23), 79(42), 77(32), 65(32), 51(31), 50(14), 41(14), 39(29).

Compound 9. The corresponding benzyl ester showed MS, *m/e* (rel.int.): 166(5, *M*), 108(6), 107(3), 91(100), 90(6), 79(5), 77(7), 65(11), 63(4), 51(6), 39(6).

Compound 10. The corresponding benzyl ester had MS, *m/e* (rel.int.): 180(4, *M*), 108(89), 107(33), 92(11), 91(100), 90(24), 89(11), 79(28), 77(15), 73(23), 65(22), 51(12), 45(12), 43(19), 39(14).

Compound 11. The MS of the corresponding 1,2-ethane[1-$^2H_1$]diolacetate agreed with that reported.[22]

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