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Note

Reactions of ketoses with ethyl acetoacetate

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The reactions of L-sorbose and D-fructose with ethyl acetoacetate were reported previously[1] in relation to the possible role of enediols in the reaction of monosaccharides with β-dicarbonyl compounds, but a complete study of the possible isomeric products was not carried out. We have studied these reactions further, with the objective of obtaining furan derivatives containing polyhydroxylated β-substituents, and have found other products which throw light on the possible mechanism.

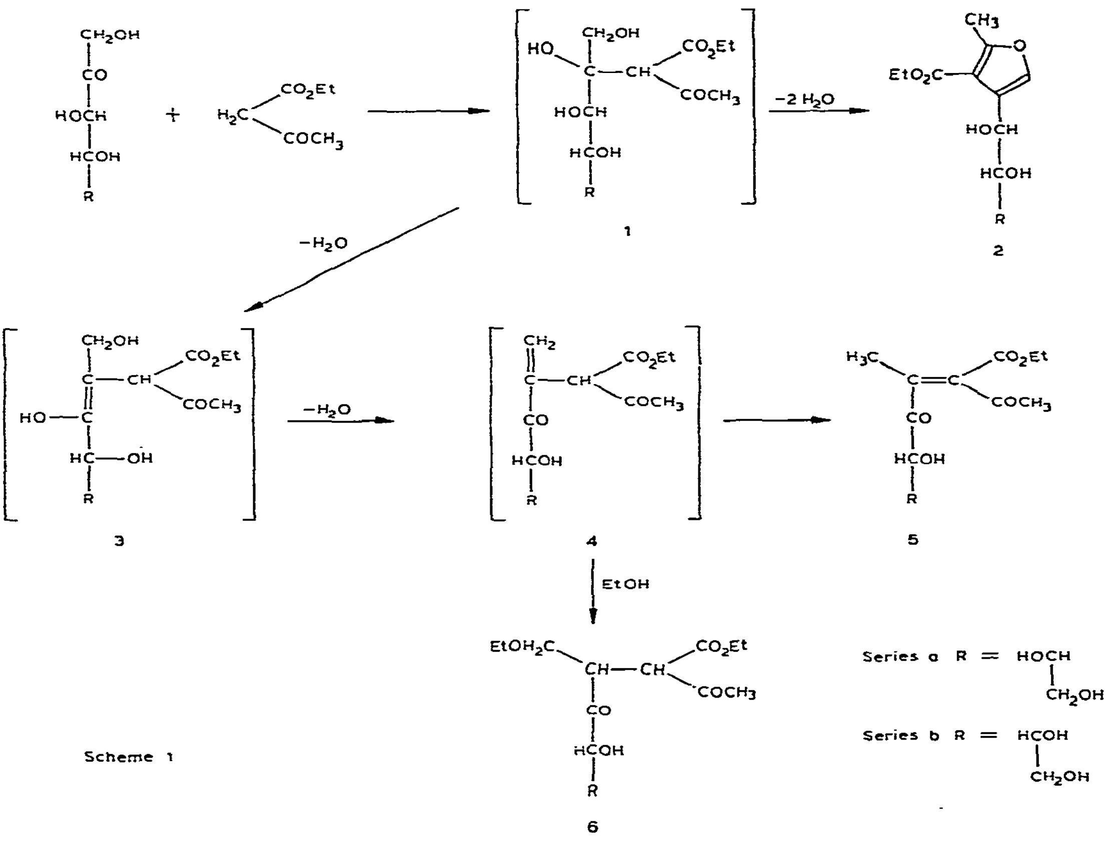
Ethyl 2-methyl-4-(L-*xylo*-tetrahydroxybutyl)-3-furoate (**2a**, 1.18%) was isolated from the reaction of L-sorbose with ethyl acetoacetate (see Experimental), together with a product (4.5%) having the acyclic structure **5a**, the formation of which requires elimination and rearrangement as shown in Scheme 1 (*cf.* refs. 2 and 3).

The mass spectrum and elemental analysis of **5a** indicated it to be an isomer of **2a**. Compound **5a** (*a*) consumed 3 mol of sodium metaperiodate, and exchange with D_2O (monitored by n.m.r. spectroscopy) confirmed the presence of three hydroxyl groups; (*b*) had i.r. absorption for ester and α,β-unsaturated ketones; and (*c*) gave an n.m.r. spectrum (see Experimental) which accorded with the assigned structure.

The proposed mechanism involves the adduct **1** of the ketose with ethyl acetoacetate, as the intermediate for both **2a** and **5a**. The formation of the β,γ-unsaturated ester **3** by dehydration of **1** is proposed, because similar dehydration reactions have been reported[4] for compounds in which an oxygen atom can contribute to the stabilisation of a double bond. The enolic and allylic character of **3** allows dehydration to form the unsaturated diketone **4**, and prototropic migration of the activated α-proton then gives the conjugated diketone **5**.

The reaction of D-fructose with ethyl acetoacetate yields two isomers (**2b** and **5b**) corresponding to **2a** and **5a**, and also the product **6b** formed by the addition of solvent ethanol to the conjugated double-bond in the proposed intermediate **4b**. The structure of **6b** was deduced from its n.m.r., i.r., and mass spectra, and its positive enol reaction and negative reaction[5] for α,β-unsaturated ketone.

The configuration at the double bond of **5a** and **5b** (two possible geometrical



Scheme 1

isomers) has not been investigated, but **5a** (crystalline product) gave sharp ^{1}H-n.m.r. signals, whereas **5b** (syrup) gave broad signals that could be due to a mixture of isomers. In both cases, only one spot was observed in t.l.c.

EXPERIMENTAL

General. — Melting points were determined with an Electrothermal melting-point apparatus and are uncorrected. I.r. spectra were recorded for KBr discs with a Unicam SP 1000 spectrometer, u.v. spectra (for methanolic solutions) with a Perkin–Elmer 124 spectrometer, ^{1}H-n.m.r. spectra with a Perkin–Elmer–Hitachi R-20B 60-MHz spectrometer, and mass spectra with a Hewlett–Packard model 5930 A spectrometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. T.l.c. was performed on Silica Gel G (Merck) with detection by iodine vapour. Column chromatography was carried out on Silica Gel 60 Merck (70–230 mesh, ASTM).

Condensation of L*-sorbose with ethyl acetoacetate.* — The reaction was carried out as previously described[1].

L-Sorbose (20 g) was well mixed with zinc chloride (12 g), ethyl acetoacetate (20 mL) in 96% ethanol (20 mL) was added, and the mixture was heated with stirring during 6 h. Water (200 mL) was added, and the solution was extracted with benzene (4 × 40 mL) and then ethyl acetate (7 × 40 mL). The latter extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product (6.7 g) was subjected to chromatography on a column (70 × 2.2 cm) of silica gel with chloroform–ethanol (12:1), to give, first, ethyl 2-*C*-acetyl-2,3-dideoxy-3-*C*-methyl-L-*threo*-hept-2-en-4-ulosonate (**5a**; 1.37 g, 4.5%), m.p. 110–113° (from ethyl acetate), $[\alpha]_D^{25}$ +119.5° (*c* 1, methanol): ν_{max} 3510, 3380, 3005, 1690, 1640, 1390, 1345, 1290, 1165, 1120, 965, 950, and 860 cm^{-1}; λ_{max}^{MeOH} 247 nm. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.30 (t, 3 H, *Me*-CH_2), 1.5 (s, 3 H, Me-C=), 2.2 (s, 3 H, Ac), 2.9–3.2 (bs, 1 H, exchangeable with D_2O, OH), 3.6–4.5 (bs, 6 H, 2 H exchangeable with D_2O), and 4.2 (q, 2 H, *CH_2*-Me). Mass spectrum: *m/z* 275 (0.5%) $(M + 1)^+$, 274 (0.07) $(M)^{+\cdot}$, 257 (1), 241 (0.5), 229 (3), 211 (2), 201 (24), 184 (2), 169 (2), 155 (100), and 138 (9).

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.54; H, 6.61. Found: C, 52.24; H, 6.60.

Compound 5a gave a negative enol reaction with ferric chloride solution, and a positive α,β-unsaturated ketone reaction (*p*-nitrophenylhydrazine with potassium hydroxide in 2-propanol)[5]. Periodate oxidation was carried out at 80° for 1 h and afforded 3 equiv. of acid.

Eluted second was ethyl 5-methyl-3-(L-*xylo*-tetrahydroxybutyl)-4-furoate (**2a**; 0.36 g, 1.18%), m.p. 78–79° (from ethyl acetate), $[\alpha]_D^{25}$ −41° (*c* 0.8, methanol); ν_{max} 1710, 1615, 1572, 1310, 1130, 1070, 1035, 985, 949, 879, and 780 cm^{-1}; λ_{max}^{MeOH} 249 nm (ε 6436). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.35 (t, 3 H, *Me*-CH_2), 2.5 (s, 3 H, Me-2), 3.2–4.7 (bs, 11 H, 5 H exchangeable with D_2O), 4.95 (d, 1 H), and 7.35 (s, 1 H, furan H-4). Mass spectrum: *m/z* 275, 274, 257, 256, 243, 241, 231, 225, 220, 213, 195, 183, and 137.

Anal. Calc. for $C_{12}H_{18}O_7 \cdot 0.5\ H_2O$: C, 50.87; H, 6.75. Found: C, 50.68; H, 6.71.

Condensation of D-*fructose with ethyl acetoacetate.* — This condensation was carried out as reported[1]. The reagent amounts and conditions were as used for L-sorbose, but for 90 h (9 h at 70°). The residue was crystallised from ethyl acetate, to yield ethyl 2-methyl-4-(D-*arabino*-tetrahydroxybutyl)-3-furoate (**2b**; 1.06 g), m.p. 154–156° (from ethyl acetate), $[\alpha]_D^{20}$ −46°(*c* 1, methanol); λ_{max}^{MeOH} 249 nm (ε 5000); ν_{max} 1725, 1610, 1570, 1430, 1300, 1130, 1105, 1040, 945, and 740 cm^{-1}. ^{1}H-N.m.r. data (Me_2SO): δ 1.30 (t, 3 H, *Me*-CH_2), 2.5 (s, 3 H, Me-2), 3.2–4.7 (bs, 10 H), 4.95–5.25 (bs, 1 H), and 7.35 (s, 1 H). Mass spectrum: *m/z* 274 (2%), 256 (0.7), 237 (7), 214 (3), 183 (50), and 137 (100).

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.54; H, 6.61. Found: C, 52.59; H, 6.63.

The mother liquor was concentrated, and the syrupy residue was eluted from a column (70 × 2.2 cm) of silica gel with chloroform–ethanol (12:1), to give **2b** (0.56 g) and a mixture (2 g) of **5b** and **6b**. This mixture was eluted from a column (60 × 1.4 cm) of silica gel with ether–hexane (10:2), to give, first, ethyl 2-*C*-acetyl-2,3-dideoxy-3-*C*-methyl-D-*erythro*-hept-2-en-4-ulosonate (**5b**) as a liquid (110 mg),

$[\alpha]_D^{25}$ +46° (*c* 1, methanol); ν_{max} 3440, 1700, 1650, 1390, 1340, 960, and 790 cm^{-1}; λ_{max}^{MeOH} 244 nm (ε 10588). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.30 (t, 3 H), 1.5 (s, 3 H), 2.25 (s, 3 H), and 3.2–4.7 (bs, 9 H, 3 H exchangeable with D_2O). Mass spectrum: *m/z* 257 (1%), 241 (2.5), 229 (2), 211 (1.5), 201 (24), 184 (2), 179 (2), 167 (7), 155 (100), 138 (13), 127 (36), 113 (21), 97 (8), 85 (33), 67 (17), and 43 (69). Compound **5b** gave a negative reaction for enol, and a positive reaction for α,β-unsaturated ketone^5.

Eluted second was the 2,3-dideoxy-3-*C*-ethoxymethylhept-4-ulosonate **6b** as a liquid (250 mg), $[\alpha]_D^{25}$ −5° (*c* 1, methanol); ν_{max} 3400, 2950, 1725, 1700, 1590, 1440, 1305, and 1110 cm^{-1}: λ_{max}^{MeOH} 248 nm (ε 5500). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.2 (t, 3 H), 1.35 (t, 3 H), 3.5 (s, 3 H), and 3.1–4.75 (bs, 15 H, 5 H exchangeable with D_2O). Mass spectrum: *m/z* 257 (0.3%), 241 (66), 224 (21), 213 (1.3), 195 (45), 179 (15), 167 (100), 151 (33), and 43 (51). Compound **6b** gave a positive reaction for enol and a negative reaction for α,β-unsaturated ketone^5.

The tetra-acetate (**7**) of **2b** had m.p. 85–86° (from ethanol), $[\alpha]_D^{25}$ +75° (*c* 1, chloroform); ν_{max} 1760, 1730, 1610, 1570, 1385, 1300, 1240, 1100, 1030, and 980 cm^{-1}; λ_{max}^{MeOH} 244 nm (ε 4190). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.45 (t, 3 H), 1.95 (s, 3 H), 2.05 (s, 3 H), 2.1 (s, 6 H), 2.55 (s, 3 H), 4.1–4.7 (bs, 4 H), 5.1–5.5 (bs, 1 H), 5.5–5.9 (dd, 1 H), 6.5 (d, 1 H), and 7.2 (s, 1 H). Mass spectrum: *m/z* 442 (0.2%), 397 (0.2), 382 (1.7), 355 (0.7), 340 (2), 322 (0.2), 297 (1.5), 280 (4.6), 83 (100), and 43 (40).

Anal. Calc. for $C_{20}H_{26}O_{11}$: C, 54.29; H, 5.88. Found: C, 54.50; H, 5.92.

The 1,2:3,4-di-*O*-isopropylidene derivative (**8**) of **2b** was a liquid, $[\alpha]_D^{25}$ −21° (*c* 1, chloroform); ν_{max} 1725, 1620, 1575, 1375, 1245, 1110, 1070, and 845 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.28, 1.23, and 1.45 (3 bs, 15 H), 2.5 (s, 3 H), 3.7–4.5 (bs, 6 H), 5.27 (d, 1 H), and 7.38 (s, 1 H). Mass spectrum: *m/z* 354, 339 (4%), 325, 309, 296 (3), 281 (1.5), 278 (2), 266 (2), 253 (4), and 43 (100).

*2-Methyl-4-(*D-arabino*-tetrahydroxybutyl)-3-furoic acid* (**9**). — Conventional saponification of **2b** gave **9**, m.p. 214–215° (from water), $[\alpha]_D^{20}$ −26° (*c* 0.5, dimethyl sulfoxide); ν_{max} 3510, 3360, 2970, 1700, 1610, 1565, 1460, 1230, 1130, 1090, 1010, and 750 cm^{-1}. ^{1}H-N.m.r. data (Me_2SO): δ 2.5 (s, 3 H), 3.2–5.4 (bs, 10 H, 5 H exchangeable with D_2O), and 7.4 (s, 1 H).

Anal. Calc. for $C_{10}H_{14}O_7$: C, 48.77; H, 5.73. Found: C, 48.75; H, 5.40.

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