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Note

Ketoses and their derivatives. Part II[1]. The synthesis of methyl glycosides of 2-pentuloses by the Fischer method, but with catalysis by acetic acid*

ĽUDOVÍT STANKOVIČ, KAZIMÍR LINEK**, AND MICHAL FEDOROŇKO
Institute of Chemistry, Slovak Academy of Sciences, 809 33 Bratislava, Dúbravská cesta (Czechoslovakia)

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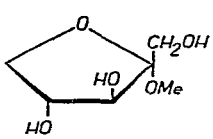
Continuing our work[1–3] on the synthesis of ketoses and their derivatives, we now describe the synthesis of four new methyl glycosides of 2-pentuloses. The synthesis was carried out by the Fischer method, which is particularly suited to the preparation of glycosides from the lower aliphatic alcohols. Usually, a disadvantage of this method is the formation of a mixture of the anomers of the pyranoside and the furanoside forms; however, the glycosidation of 2-pentuloses leads to a mixture which contains only the anomers of the furanoside.

Tipson and Brady[4] prepared a mixture of the anomers of methyl D-*erythro*-pentulofuranoside from D-*erythro*-pentulose by the catalytic action of 1% hydrogen chloride in methanol, and they used this mixture, without separation, for the synthesis of the anomers of methyl 1,3,4-tri-*O*-acetyl-D-*erythro*-pentulofuranoside and methyl 1,3,4-tri-*O*-benzoyl-D-*erythro*-pentulofuranoside. Some derivatives of glycofuranosides are biologically important sugars exhibiting an antagonistic activity towards acetylcholine, histamine, and bradykinin[5]. The furanosides have been the subject of a review by Green[6].

Hydrogen chloride has been the catalyst principally employed in the Fischer method. A cation-exchange resin in the acid form can be also used as the acid catalyst, and isolation of the product is thereby facilitated[7,8]. In the present work, we have prepared a mixture of methyl-α-D-*threo*-pentulofuranoside (**1**) and methyl β-D-*threo*-pentulofuranoside (**2**), in 81% yield, by refluxing a solution of D-*threo*-pentulose in absolute methanol containing, as the catalyst, acetic acid (4M). When L-*erythro*-pentulose was used as the starting material under the same conditions, a mixture of



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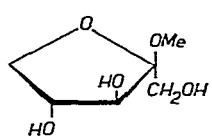

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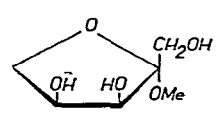

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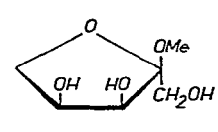

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*Dedicated to Dr. Horace S. Isbell, in honor of his 75th birthday.
**To whom communications should be addressed.

methyl β-L-*erythro*-pentulofuranoside (**3**) and methyl α-L-*erythro*-pentulofuranoside (**4**) was obtained in a yield of 64%. The advantage of this method is that acetic acid can be readily removed from the reaction mixture by evaporation under diminished pressure.

The anomeric configuration was determined from Hudson's rule; the rule has been shown to hold for all simple alkyl glycosides that have been critically checked[9].

The separation of the anomers was accomplished by cellulose-column chromatography by using, as the solvent system, 2-butanone saturated with water; this partially separates anomers **1** and **2**, and completely separates anomers **3** and **4**. The ratio of anomers **4** and **3** was found to be 1:1.9. When hydrogen chloride was used as the catalyst, the ratio of anomers **4** and **3** was found to be 1:2.2. (For the aldofuranosides, the preponderant anomer is the *trans*-1,2 glycoside; the interaction between its aglycon group and the 2-hydroxyl group is much less than for the *cis*-1,2 anomer.)

In the literature, there are only a few references concerning the anomers of ketofuranosides. The anomers of methyl D-fructofuranoside were obtained[10] in the ratio of ~1:1, and Green[6] suggested that there is, apparently, little difference between the interaction of either the aglycon methyl group or the 2-(hydroxymethyl) group with the 3-hydroxyl group. This problem needs more study, because, in the case of the methyl L-*erythro*-pentulofuranosides (**3** and **4**), the preponderant anomer is the *trans*-2,3-glycoside (**3**).

Hydrolysis of the glycosides **1**–**4** was performed by means of aqueous acetic acid (4M), and the course of the hydrolysis was monitored by paper chromatography. The hydrolysis of compounds **1** and **4** was also performed preparatively, and the respective products of the hydrolysis (D-*threo*- and L-*erythro*-pentulose) were identified by conversion into crystalline, substituted phenylhydrazones.

EXPERIMENTAL

General. — Melting points were determined on a Kofler micro hotstage. Solutions were evaporated under diminished pressure at 30–40°. Optical rotations were measured on a Bendix-Ericsson automatic polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 457 instrument. N.m.r. spectra were measured on an 80-MHz, Tesla BS-487 B spectrometer, for solutions in chloroform-*d* containing tetramethylsilane as the internal standard. Mass spectra were recorded with a Mch 1306 apparatus.

D-*threo*-Pentulose was prepared by biochemical oxidation[11] of D-arabinitol with *Acetobacter pasteurianus* B.S. 1775, and L-*erythro*-pentulose, by biochemical oxidation of ribitol with *Acetobacter suboxydans* B.S. 2356 (Czechoslovak Collection of Micro-organisms).

Descending paper-chromatography was performed on Whatman No. 1 paper with (*a*) 2-butanone saturated with water [the fraction of pentuloses (R_p 1) was used as the reference for estimation of the particular spots; single pentuloses exhibited the same mobility in this solvent system]; (*b*) 7:2 (v/v) chloroform–acetic acid containing water (1.5 ml/100 ml of the solvent system). Detection was effected with aniline

hydrogen phthalate (compounds **1**–**4**) or with potassium periodate–benzidine (compounds **3** and **4**). Preparative chromatography was performed on columns (90 × 4.5 cm) of Whatman cellulose.

Methyl glycosidation of D-threo-*pentulose.* — A solution of D-*threo*-pentulose (4 g) and acetic acid (4M) in absolute methanol (100 ml) was boiled under reflux for 8 h with the exclusion of external moisture. Acetic acid was removed by evaporation under diminished pressure, and the syrupy residue was re-evaporated with absolute methanol.

According to paper chromatography (solvent *a*), the syrupy residue consisted of compound **1** (R_p 2.3), compound **2** (R_p 1.9), and unreacted D-*threo*-pentulose. This mixture was separated by cellulose-column chromatography (solvent *a*) to give compound **1** (0.415 g, 9.5%), a mixture of anomers **1** and **2** (2.49 g, 56.9%), compound **2** (0.63 g, 14.4%), and D-*threo*-pentulose (0.31 g, 7.8%).

Methyl glycosidation of L-erythro-*pentulose.* — A solution of L-*erythro*-pentulose (3.31 g) and acetic acid (4M) in absolute methanol (83 ml) was refluxed for 8 h, and processed as just described. Paper chromatography (solvent *a*) showed that the reaction mixture contained compound **3** (R_p 3.7), compound **4** (R_p 2.2), and unreacted L-*erythro*-pentulose. The mixture was separated by cellulose-column chromatography (solvent *a*) to give compound **3** (1.504 g, 41.6%), compound **4** (0.805 g 22.2%), and unreacted L-*erythro*-pentulose (0.98 g, 29.6%).

Characterization of glycosides. — Methyl α-D-*threo*-pentulofuranoside (**1**) was obtained as a syrup; $[\alpha]_D^{20}$ +73.4° (*c* 1.0, water); ν_{max}^{film} 3400 (OH); 2950 and 2890 (CH), 2835 (CH_3), 1460 (CH_2 bending), 1440 (CH_3 bending), and 865 cm^{-1} (furan ring[12]); n.m.r. data: τ 6.19 (1-proton doublet, H-1), 6.38 (1-proton doublet, H-1′), 6.73 (3-proton singlet, OCH_3), and 5.5–6.1 (4-proton multiplet, H-3, H-4, H-5, H-5′; $J_{1,1'}$ 12 Hz).

Anal. Calc. for $C_6H_{12}O_5$: C, 43.90; H, 7.37; OCH_3, 18.91. Found: C, 43.83; H, 7.25; OCH_3, 18.96.

Methyl β-D-*threo*-pentulofuranoside (**2**) was a syrup; $[\alpha]_D^{20}$ −86.3° (*c* 1.0, water); ν_{max}^{film} 3400 (OH), 2940 and 2890 (CH), 2830 (CH_3), 1460 (CH_2 bending), 1440 (CH_3 bending), and 870 cm^{-1} (furan ring); n.m.r. data: τ 6.32 (2-proton singlet H-1, H-1′), 5.92 (1-proton doublet, H-3), 5.62 (1-proton octet, H-4), 5.84 (1-proton quartet, H-5), 6.32 (1-proton quartet, H-5′), and 6.70 (3-proton singlet, OCH_3).

Anal. Found: C. 43.88; H, 7.33; OCH_3, 18.78.

Methyl β-L-*erythro*-pentulofuranoside (**3**) was a syrup; $[\alpha]_D^{25}$ +109.2° (*c* 1.0, water); ν_{max}^{film} 3400 (OH), 2955 and 2900 (CH), 2835 (CH_3), 1465 (CH_2 bending), 1440 (CH_3 bending), and 875 cm^{-1} (furan ring); n.m.r. data: τ 6.26 (2-proton singlet, H-1, H-1′), 5.96 (1-proton doublet, H-3), 5.60 (1-proton octet, H-4), 6.25 (1-proton quartet, H-5), 5.92 (1-proton quartet, H-5′), and 6.75 (3-proton singlet, OCH_3).

Anal. Found: C, 43.96; H, 7.39; OCH_3, 18.90.

Methyl α-L-*erythro*-pentulofuranoside (**4**) was obtained as a syrup that crystallized spontaneously after being kept over phosphorus pentaoxide in a vacuum desiccator under diminished pressure; m.p. 62–65°; the product was recrystallized

from dry 2-butanone (P_2O_5, K_2CO_3) by dissolving it at 30° and keeping the solution at −5°, to yield crystals that had m.p. 68–69° and $[\alpha]_D^{25}$ −42.2° (*c* 1.0, water); ν_{max}^{KBr} 3400 (OH), 2950 and 2890 (CH), 2835 (CH_3), 1462 (CH_2 bending), 1440 (CH_3 beding), and 865 cm^{-1} (furan ring); n.m.r. data: τ 6.33 (2-proton singlet, H-1, H-1'), 6.70 (3-proton singlet, OCH_3), and 5.6–6.2 (4-proton multiplet, H-3, H-4, H-5, H-5').

Anal. Found: C, 43.85; H, 7.31; OCH_3, 18.97.

Mass spectrometric studies. — The mass spectrum of compound **4** was characterized by an intense peak of *m/e* 133 ($M^+ - 31$) ions. The presence of this peak is evidence for the molecular weight (164) and for the five-membered ring of the glycoside.

Hydrolysis of glycosides. — Hydrolysis of glycosides **1–4** (1% solution) was achieved by use of aqueous acetic acid (4M). The course of the hydrolysis (the formation of 2-pentuloses) was monitored by paper chromatography (solvent *a*). The hydrolysis of compounds **1** and **2** was complete in 2 h at 60°; compounds **3** and **4** were hydrolyzed in 30 min at 40°.

Preparative hydrolysis of **1** (0.268 g) yielded D-*threo*-pentulose (0.233 g, 95.1%). D-*threo*-Pentulose was identified by paper chromatography (solvent *b*), by the sign of the Cotton effect[13], and by conversion into the crystalline (2,4-dinitrophenyl)-hydrazone[2], m.p. 175–176°.

By preparative hydrolysis of **4** (0.27 g), L-*erythro*-pentulose was obtained (0.228 g, 92.3%); this was characterized by paper chromatography (solvent *b*), by the sign of the Cotton effect[13], and by conversion into the crystalline (*o*-nitrophenyl)-hydrazone[14], m.p. 167–168°.

Methyl glycosidation of 2-pentuloses, catalyzed by hydrogen chloride. — A solution of D-*threo*-pentulose (50 mg) in 1% hydrogen chloride in absolute methanol (5 ml) was kept for 30 min at room temperature; the hydrogen chloride was neutralized by Dowex 1 resin (regenerated with M sodium hydrogen carbonate), and the resin was filtered off and washed. Paper chromatography (solvent *a*) showed that the reaction mixture contained two compounds having the same R_p values (R_p 2.3 and 1.9) as those of glycosides **1** and **2**, and a trace of unreacted D-*threo*-pentulose.

A solution of L-*erythro*-pentulose (1.16 g) in 1% hydrogen chloride in absolute methanol (116 ml) was kept for 30 min at room temperature, and the hydrogen chloride was removed as just described. The filtrate was evaporated to dryness, giving a syrup; paper chromatography (solvent *a*) showed that the syrup contained compound **3** (R_p 3.7), compound **4** (R_p 2.2), and unreacted L-*erythro*-pentulose. The mixture was separated by cellulose-column chromatography (solvent *a*), to give compound **3** (0.395 g, 31.1%), compound **4** (0.18 g, 14.2%), and unreacted L-*erythro*-pentulose (0.15 g, 12.9%).

Methyl β-L-*erythro*-pentulofuranoside (**3**) was obtained as a syrup, $[\alpha]_D^{25}$ +108.3° (*c* 1.0, water).

Anal. Found: C, 43.83; H, 7.34; OCH_3, 18.85.

Methyl α-L-*erythro*-pentulofuranoside (**4**) had m.p. 68–69°, $[\alpha]_D^{25}$ −41.5° (*c* 1.0, water).

The i.r. spectra of glycosides **3** and **4** prepared from L-*erythro*-pentulose by

catalytic action of hydrogen chloride were identical with those of compounds **3** and **4** prepared by catalytic action of acetic acid.

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