

Preparation of 2-*C*-Hydroxymethyl-D-mannose and -D-glucose and Their Stereospecific and Irreversible Rearrangements to D-*gluco*- and D-*manno*-Heptulose under the Conditions of the Bílik Reaction

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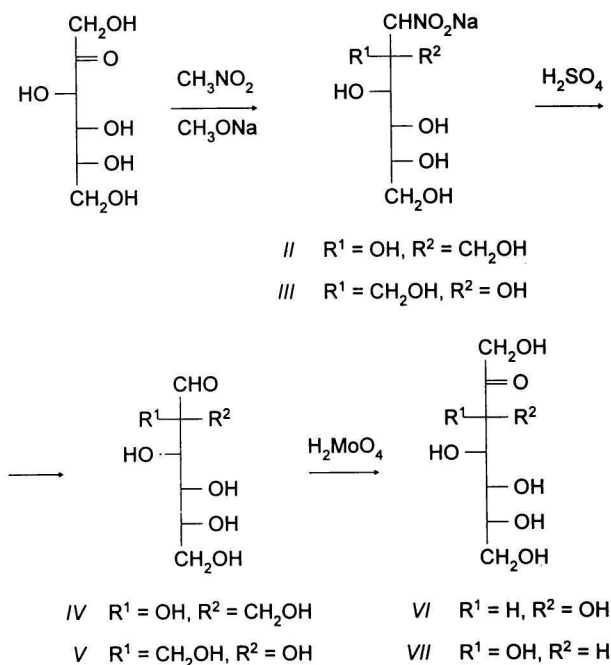
Dedicated to Professor Stephen J. Angyal in honour of his 80th birthday

Molybdcic acid-catalyzed epimerization of aldoses introduced twenty-five years ago [1] and now known as the Bílik reaction has become a universal method of preparation of formerly rare aldoses such as D-mannose [2], L-glucose [3], D-talose [4], L-ribose [5], D- and L-xylose [5], *etc.* Attempts to utilize the reaction for epimerization of ketoses were not successful; only partial, general acid-catalyzed mutual isomerization of pentuloses [6] and hexuloses [7] was observed.

According to the mechanism of the Bílik reaction [8], the carbon skeleton of a starting aldose ...⁴CHOH—³CHOH—²CHOH—¹CHO rearranges to that of epimeric aldose ...⁽⁴⁾CHOH—⁽³⁾CHOH—⁽¹⁾CHOH—⁽²⁾CHO. The rearrangement has been used also for preparation of specifically labelled aldoses [9].

We now report on a new method of synthesis of D-*manno*- and D-*gluco*-heptulose, namely a molybdcic acid-catalyzed carbon skeleton rearrangement of 2-*C*-hydroxymethyl-D-glucose and -D-mannose, respectively. The communication describes also preparation of the branched-chain aldoses by the Sowden method applied to D-fructose.

Addition of nitromethane to D-fructose (*I*, Scheme 1) in the presence of sodium methoxide followed by treatment of intermediate sodium 1-deoxy-2-*C*-hydroxymethylhexitol-1-nitronates *II* and *III* with sulfuric acid (Nef reaction) gave a mixture of 2-*C*-hydroxymethyl-D-mannose (*IV*) and -D-glucose (*V*) and the starting *I*. After removal of *I* by fermentation with baker's yeasts, 18 % of branched-chain aldoses *IV* and *V* in the ratio *ca.* 1:1 (by ¹³C NMR spectroscopy) were obtained. Separation of the mixture on a column of Dowex 50W (Ba²⁺ form) afforded chromatographically pure *IV* (sirup, [α]_D 20°C, ρ = 20 g dm⁻³, water) = + 11.0°) and *V* (sirup, [α]_D 20°C, ρ = 27



Scheme 1

g dm⁻³, water) = + 27.4°), both giving satisfactory elemental analyses.

The structures of both branched-chain aldoses *IV* and *V* were proved by NMR spectroscopy. The ¹³C chemical shifts of both anomeric carbon atoms of compound *IV* (δ = 95.2) were close to those of D-mannose (δ = 95.0 and 94.6 [10]). Similarly, the chemical shifts of both anomeric carbon atoms of *V* (δ = 99.3 and 93.0) were close to those of D-glucose (δ = 96.7 and 92.9 [10]). One-dimensional ¹³C DEPT and

^1H NOESY spectra afforded additional support of the structures of *IV* and *V*, particularly the presence of quaternary carbon atoms and the stereochemistry at them, respectively.

Treatment of branched-chain aldose *IV* in 0.5 % molybdic acid at 80°C for 3 h caused its complete transformation to D-*gluco*-heptulose (*VI*) and traces of D-*manno*-heptulose (*VII*). Heptulose *VI* was obtained after deionization of the reaction mixture with an anion exchange resin in the HCO_3^- form by crystallization in an 82 % yield.

Similar treatment of compound *V* resulted in the formation of a 4:1 mixture (by ^{13}C NMR spectroscopy) of D-*manno*-heptulose (*VII*) and D-*gluco*-heptulose (*VI*) not containing the starting material. Heptulose *VII* was obtained after column separation (Dowex 50W, Ba^{2+} form) in a 51 % yield. In a control experiment when heptulose *VII* was treated at more severe conditions (1 % molybdic acid, 95 °C, 5 h), a ca. 1:1 mixture of C-3 epimeric heptuloses *VI* and *VII* was obtained. Branched-chain aldoses *IV* and *V* were not detected in the mixture by means of ^{13}C NMR spectroscopy.

Examined physicochemical constants (m.p., $[\alpha](\text{D})$) and ^{13}C NMR spectra of heptuloses *VI* and *VII* were identical with those of the samples prepared by an independent procedure [11].

In conclusion, the observed irreversible transformation of branched-chain aldoses *IV* and *V* to respective heptuloses *VI* and *VII* catalyzed with molybdic acid is in accordance with the mechanism and thermodynamics of the Bílik reaction. The irreversibility of the

transformation is apparently a consequence of a substantially lower stability of 2-*C*-hydroxymethylaldoses in comparison with that of 2-ketoses; the branched-chain aldoses, although expected, were not formed by treatment of the 2-ketoses with molybdic acid. The transformation thus represents a new method of synthesis of ketoses. Further development of the method is in progress.

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