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THE MECHANISM OF FORMATION OF 3-DEOXY GLUCOSULOSE FROM GLUCOSE 3-PHOSPHATE AND FROM DIFRUCTOSYL GLYCINE

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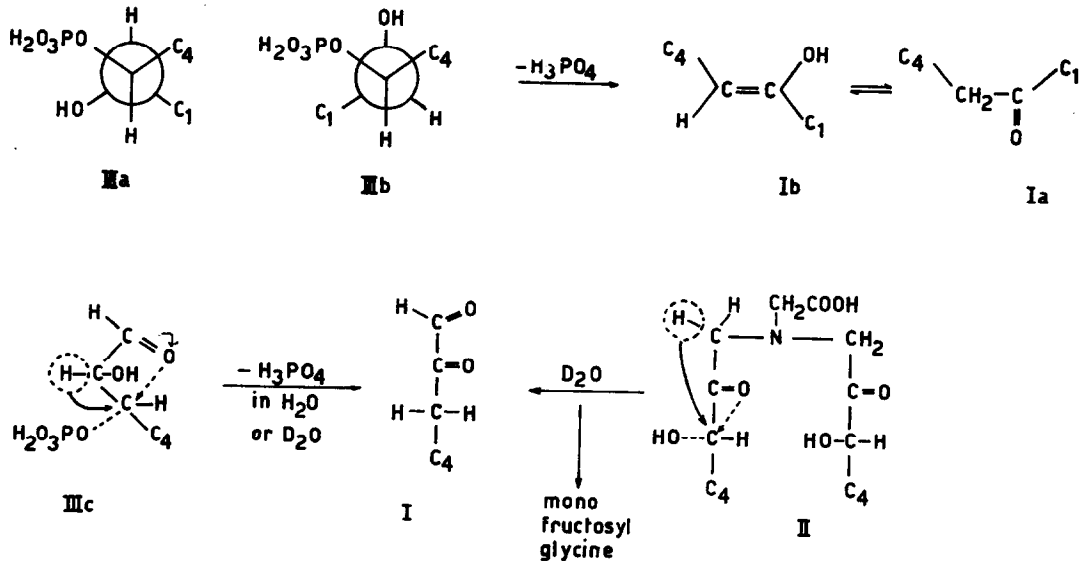
Isolation of optically pure 3-deoxy glucosulose (I) from liver extracts as the 2,4-dinitrophenyl osazone focussed our interest on the biogenetic and mechanistic aspects of its formation.

Glycosylamines, e.g.N-butyl glucosylamine[2] on Amadori rearrangement afford I in low yield but contaminated with many other products. Glucose 3-methyl ether[3] and benzyl ether[4] both gave on the action of alkali, some 3-deoxy glucosulose. The only abundant source for the osulose I found so far is the cleavage[5] of 1,1-difructosyl glycine (II) into I and monofructosyl glycine. However, difructosyl glycine is prepared from glucose and sodium glycinate under conditions[5] considered too energetic to be achieved in the tissue. 1-Fructosyl glycine, on the other hand, although present in beef liver[6] gave in our experiments only 3% of osulose I. 1-Fructosyl valine, however, was converted into I smoothly under the same conditions.

Treatment[7] of glucose 3-phosphate[8] with baryta led to glucometasaccharinic acid, probably[7] by Cannizzaro reaction of 3-deoxy glucosulose. We have now succeeded in traping I as its osazone[1,5] $[\alpha]_D^{25}$ 75° (DMSO) by heating the cyclohexylammonium salt of glucose 3-phosphate (III) in methanolic and also in aqueous solution, followed by precipitation with 2,4-dinitrophenyl hydrazine (DNPH). The assumption by Todd et al[7] is hence confirmed[9]. Furthermore, glucose 3-phosphate became an adequate starting material for the osulose.Concerning

the mechanism of rearrangement III → I an anti-elimination was assumed.[7] This is unlikely with conformer IIIa, corresponding to the furanose or pyranose form. The open chain form (IIIb), however, might lead to the deoxy osulose via enol Ib. In this case carrying out the cleavage of the cyclohexylammonium salt in D_2O should afford the osulose I, deuterated at C - 3. We have checked this possibility under a variety of conditions (40-100°, 5-20 min) but no C-D band could be detected between 1900-2200 cm^{-1} in the IR spectrum of the DNP-osazone prepared with DNPH-sulfate in D_2O. Furthermore, the signal at δ 4.42 ppm in the NMR spectrum of the same product integrates exactly for two protons as is the case with the authentic DNP-osazone, prepared in H_2O. Consequently, no incorporation of deuterium took place, which is inconsistent with the enolic intermediate Ib and hence with the concept of a β-elimination. The explanation we might offer for the failure of taking up any external proton, involves a hydride shift from C-2 to C- 3 in the open chain form IIIc of the cyclohexylammonium salt where expulsion of the phosphate anion is anchimerically assisted by the aldehyde oxygen.

An enolization mechanism was also proposed[5] for the cleavage of 1,1-difructosyl glycine. Carrying out the reaction in D_2O and then precipitating the osulose (I) with DNPH in heavy water also gave an osazone lacking any C-D band in the diagnostic IR region, and without any indication in the NMR of being deuterated in the C-3 methylene group.



Failure to incorporate deuterium provides persuasive, though negative evidence in favor of a 1,2 hydride shift in the rearrangement II→I and of a 1,3 shift in the case of III→I. This is at variance with the generally accepted theory of enolization in the Amadori rearrangement.

The pioneering views of Isbell[10] on the enolization mechanism leading from glucose to metasaccharinic acid via I is supported[11] by recent tritiation of glucose in alkaline medium.

Although the compounds II and III used in the Amadori type reactions are different from glucose and so are the conditions (pH etc.) employed, it seems still desirable to seek positive evidence in favor of the mechanism we have outlined. This work is now awaiting the preparation of labeled compounds.

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