A new method of synthesis of aldosuloses

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As a new approach to the synthesis of aldosuloses (osones), epimeric pairs of the allylic alcohols, 1 and 2, and 4 and 5, were oxidized to the corresponding vinyl ketones, 3 and 6, respectively. Degradation of the latter by reductive ozonolysis and hydrolysis gave D-glycero-tetrosulose and D-arabino-hexosulose (α-glucosone), respectively.

There has recently been renewed biological interest in the aldosuloses, or osones, as 3-deoxy-sugar D-arabino-hexosulose is formed when mammalian liver is treated with arsenious oxide (1), and there is probably a connection between mammalian tissue α-keto-aldehyde concentrations and rates of cell division (2). In commencing a study of aldosuloses it was apparent that there are few satisfactory general methods available for their synthesis. Methods of synthesis were reviewed by Bayne and Fewster (3), who mentioned the low yields associated with the oxidation of reducing aldoses, and the deficiencies of the osazone-cleavage method. Subsequent work has included the oxidation of acetone-protected methyl glycosides at C-2, using chromium trioxide (4) or ruthenium tetroxide (5), and the conversion of diazomethyl ketone acetates into the acetates of aldosulose hydrazones (6–8), or into the acetates of aldosulose dithioacetals (9). Most of the derivatives formed in these reactions are not convertible into free aldosuloses, but the aldosulose dithioacetal acetates are exceptional, as they can be successively deacetylated and demercaptalated (9). Hence the diazomethyl ketone → thioacetal route provides a general method of aldosulose synthesis, although little information is available concerning its efficiency.

A new route to the aldosuloses has been devised in this laboratory, and is based on the following sequence of reactions (where R-CHO is an O-isopropylidene derivative of an aldehydo sugar):

\[
R-CHO \rightarrow R-CHOH-CH=CH_2 \rightarrow R-CO-CH=CH_2 \rightarrow R-CO-CHO \rightarrow \text{aldosulose}
\]

A hydroxyl-protected aldehydo sugar is vinylated to give a pair of epimeric allylic alcohols as described in previous reports (10, 11). Oxidation of the mixed epimeric alcohols with activated manganese dioxide gives a single vinyl ketone, which is successively ozonolyzed and hydrolyzed to form an aldosulose. The vinyl group, which serves as a potential aldehydo function, makes it possible to obtain the keto group by allylic oxidation, thereby eliminating the need for steps involving aldehyde group protection. Acetal or ketal protecting groups fulfil all the requirements for hydroxyl protection, as they are unaffected by Grignard reagents, manganese dioxide or ozone, but can be removed from a protected aldosulose with acetic acid (12).

The procedure has been used to synthesize D-glycero-tetrosulose (see Scheme 1), which cannot be prepared by hydrolysis of D-erythrose phenylosazone (13) and, to the author’s knowledge, has not been synthesized previously. The mixed epimeric pentenetriols 1 and 2 were oxidized in 41% yield to 4,5-isopropylidenedioxy-D-glycero-1-pent-3-ene (3). Confirmation of the structure of 3 was obtained from the infrared (i.r.) spectrum, which showed absorption bands
due to the conjugated carbonyl group and double bond. The low-field ABX system of the nuclear magnetic resonance (n.m.r.) spectrum was attributed to the vinylic protons. The values of the coupling constants were similar to those reported for vinyl ketones (14, 15; see Table 1), and proton $H_A$ resonated at low field as a result of deshielding by the carbonyl group.

Reductive ozonolysis and deketalization of 3 gave a product from which the main component was isolated chromatographically. This substance, a syrup obtained in 18% yield from 3, was shown by the following methods to be $D$-glycero-tetrosulose. On paper chromatograms it migrated faster than glucose, as a single spot which gave an instant red color with alkaline triphenyltetrazolium chloride, a reagent which is known to react faster with alduloses than with aldoses (3). Treatment of the syrup with phenylhydrazine - acetic acid in the cold, or with 2,5-dichlorophenylhydrazine in hot 1-propanol¹ (conditions which preclude conversion of aldoses into osazones) gave $D$-glycero-tetrosulose bis-phenylhydrazone (16) and bis-2,5-dichlorophenylhydrazone (17), respectively. Formation of these derivatives, previously prepared from

¹Conversion of D-erythrose into D-glycero-tetrosulose bis-2,5-dichlorophenylhydrazone requires the inclusion of acetic acid in the reaction mixture (17).
d-erythrose under more drastic conditions, can only be explained by assuming that the hydrzones had condensed with d-glycerol-tetrosulose.

Borohydride reduction of d-glycerol-tetrosulose should proceed nonstereoselectively, to give a 1:1 mixture of erythritol and d-threitol. Accordingly, a portion of the syrup was treated with sodium borohydride, followed by acetic anhydride, using the conditions described by Sjöström et al. (18). Gas–liquid partition chromatography (g.l.p.c.) of the product revealed the presence of equal weights of two compounds with retention times of erythritol tetraacetate and d-threitol tetraacetate, thus giving further evidence for the tetrosulose structure.

Application of the procedure to the mixed heptenitetol epimers, 4 and 5, gave, in 55% yield, vinyl ketone 6, whose i.r. and n.m.r. spectra had similar characteristics to those of compound 3. Degradation of 6 afforded chromatographically pure d-arabino-hexosulose (d-glucosone) in 37% yield. The identity of the latter was checked by co-chromatography with a reference sample, and by the preparation of two osazones, using the reaction conditions already described for the tetrosulose.

These examples show that allylic oxidation is an effective way of forming the 2-keto group of an aldosulose, in a synthetical route which should be of general applicability.

Experimental

Thin-layer plates, coated with silica gel, were developed with benzene–ethanol 4:1, and sprayed with the alkaline permanganate reagent (19). Paper chromatograms were developed with 1-butanol–acetic acid–water 4:1:5 (solvent system a), or phenol–water 4:1 (solvent system b), or ethyl acetate–acetic acid–formic acid–water 18:3:1:4 (solvent system c). Rates of movement are quoted relative to that of d-glucose (Rf = 1.0). Compounds were visualized with ammoniacal silver nitrate (20) or with alkaline triphenyltetrazolium chloride (21).

Nuclear magnetic resonance spectra of C-vinyl compounds were obtained at 60 MHz, using tetramethylsilane as the internal standard. For personal use only.

**TABLE I**

Nuclear magnetic resonance parameters for vinyl groups of vinyl ketones*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Observed lines (2)</th>
<th>Chemical shifts (2)†</th>
<th>Coupling constants (Hz)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA</td>
<td>HB</td>
<td>HC</td>
</tr>
<tr>
<td>3</td>
<td>2.97, 3.12</td>
<td>3.50, 3.55</td>
<td>4.15, 4.20</td>
</tr>
<tr>
<td>6</td>
<td>2.95, 3.11</td>
<td>3.45, 3.52</td>
<td>4.07, 4.12</td>
</tr>
<tr>
<td>Methyl vinyl ketone (13)‡</td>
<td>3.73</td>
<td>3.82</td>
<td>4.12</td>
</tr>
<tr>
<td>Phenyl vinyl ketone (14)‡</td>
<td>18.4</td>
<td>10.8</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Line assignments were based on the assumption that J_1 > J_2 > J_3.
†Values obtained by second-order analysis. A check of relative line intensities by computer showed that J_1+ and J_2+ have the same sign.
‡Values quoted from the literature. Only relative shifts are available for vinyl vinyl ketone. Protons H_A, H_B, and H_C resonate at successively higher magnetic fields, the chemical shift differences being ΔH_A 0.75, and ΔH_C 1.48 p.p.m.

**TABLE II**

Chromatographic data for C-vinyl compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rf*</td>
<td>0.27</td>
<td>0.27</td>
<td>0.54</td>
<td>0.33</td>
<td>0.33</td>
<td>0.55</td>
</tr>
<tr>
<td>T†</td>
<td>0.18</td>
<td>0.19</td>
<td>0.11</td>
<td>0.49</td>
<td>0.57</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Silica gel t.l.c. (for conditions see Experimental).
†Gas–liquid partition chromatography (for definitions see Experimental).
A solution of 1,2-O-isosorbide-6-threo (and L-erythra)-4-pentene-1,2,3-triol (1 and 2, 4.0 g) in tetrahydrofuran (200 ml) was stirred with manganese dioxide (40 g) for 1 h at room temperature. The mixture was filtered on a sintered funnel (M), which resulted in the volume of the combined filtrate and washings was restored to 200 ml. The resulting solution was treated with two further batches (40 g each) of manganese dioxide. Each addition was followed by stirring and filtration as before. Analysis of the final solution by g.l.p.c. showed that the proportions of 1, 2, and 3 were 2:3:95, respectively. (In separate experiments it was established that these proportions were not altered significantly by further manganese dioxide treatment.) Water, which had been adsorbed from the atmosphere during the filtrations, was removed with sodium sulfate, and the solution was concentrated at 35° and 15% per min) was bubbled through for 25 min. The solution, at 0°, was stirred under hydrogen (atmospheric pressure) in the presence of platinum oxide (50 mg). When gas absorption had ceased the solution was filtered and concentrated to dryness. The residue was heated with 85% aqueous acetic acid (20 ml) for 18 h at 50°. The resulting solution was concentrated, and residual acetic acid was removed by co-distillation with ethanol. The residue, dissolved in water, was passed quickly through Rexyn 203 (OH) resin, and concentrated to a syrup which, after drying over phosphorus pentoxide, weighed 0.39 g. Paper chromatography (solvent a) revealed a main component, R<sub>a</sub> 2.0, which gave an immediate, permanent, red color with the triphenyltetrazolium spray. Minor impurities, R<sub>a</sub> 1.4-2.0, and R<sub>a</sub> 3.0, were detectable by silver nitrate. A portion (0.25 g) of the syrup was purified by preparative paper chromatography on Whatman 3MM paper, using solvent a. The final product was a syrup (0.13 g, 18%), [α]<sub>p</sub><sup>21</sup> + 5° (c, 4.1 in water), which migrated as a single spot in both systems a (R<sub>a</sub> 2.0) and system c (R<sub>a</sub> 2.2). In system b it moved as a single spot, R<sub>b</sub> 0.51, tailing to R<sub>b</sub> 0.25.

**D-glycero-Tetrosulose Bis-phenylhydroazine**

Hydrazine derivatives were prepared from D-glycero-tetrosulose which had not been purified by chromatography. To a solution of crude D-tetrosulose (8 mg) in water (1.5 ml) was added 1 ml of phenylhydrazine reagent. After 10 min the osazone (15 mg) was precipitated by addition of water, and had m.p. 164-165°, undepressed when mixed with a sample prepared from D-erythrose; lit. m.p. 164-165° (16).

**D-glycero-Tetrosulose Bis-2,5-dichlorophenylhydroazine**

A solution of crude D-tetrosulose (34 mg) in 95% aqueous 1-propanol (10 ml) was heated on a boiling water-bath for 30 min with 2,5-dichlorophenylhydroazine (200 mg). The solvents were removed and the residue was dissolved in acetic acid (3 ml). Precipitation with water gave the title compound (76 mg), m.p. 208-213°, and m.p. 217-219° after recrystallization from benzene-ethyl acetate (1:1). The m.p. was undepressed on mixing with a sample prepared from D-erythrose; lit. m.p. 219-220° (17).
**d-arabin-Hexosulose**

Ketone 6 (1.5 g) was subjected to ozonolysis and hydrolysis, as described for compound 3, but with the omission of any chromatographic purification of the product. The final product, a syrup (0.39 g, 37%), \( [a]_D = 2^\circ \) (c, 4.4 in water), was chromatographically identical to an authentic sample of d-arabin-hexosulose. Chromatograms developed with solvent a showed spots at \( R_f \) 0.64 and \( R_f \) 0.77–1.19, with streaking at \( R_f \) 0.41–1.46, as described by Petuely (23). In solvent b the product moved as a single spot, \( R_f \) 0.25. All the above spots gave the immediate red coloration with triphenyltetrazolium chloride.

**d-arabin-Hexosulose Bis-phenylhydrazone**

The phenylhydrazone reagent (0.5 ml) was added to a solution of d-arabin-hexosulose (50 mg) in water (3 ml). The precipitated osazone (90 mg, 89%) was collected after 10 min, and, after recrystallization from aqueous pyridine, had m.p. 206–208°, \( [a]_D = 75 \rightarrow -41^\circ \) (c, 0.7 in pyridine – ethanol 2:3) (2 days); lit. \( [a]_D = 40^\circ \) (equilibrium value, in pyridine – ethanol 2:3).

**d-arabin-Hexosulose Bis-2,5-dichlorophenylhydrazone**

2,5-Dichlorophenylhydrazone (250 mg) was added to a solution of d-arabin-hexosulose (50 mg) in 95% aqueous 1-propanol. The mixture was heated for 30 min on a boiling water-bath. The product (78 mg, 56%), m.p. 241–242°, crystallized on cooling, and was washed successively with 50% aqueous acetic acid and water; lit. m.p. 242° (25).

**Acknowledgments**

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