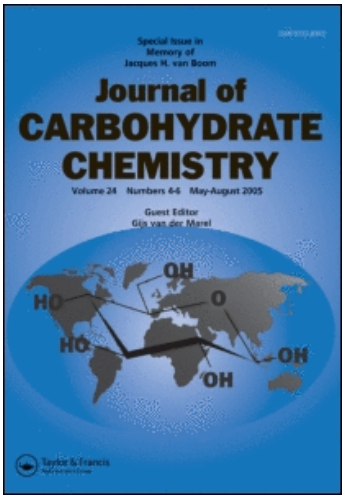

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Synthesis of Sugars From D-Ribonolactone. II. An Alternative Synthesis of D-Erythrose

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SYNTHESIS OF SUGARS FROM D-RIBONOLACTONE. II. AN ALTERNATIVE SYNTHESIS OF D-ERYTHROSE

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ABSTRACT

D-Erythrose was synthesized in four steps from D-ribono-1,4-lactone via the 3,5-O-benzylidene derivative of the latter compound. Reduction of the benzylidene D-ribonolactone, and periodate cleavage of the resulting 3,5-O-benzylidene-D-ribitol were performed in a one-flask reaction. The ensuing 2,4-O-benzylidene-D-erythrose was hydrolyzed with 10% acetic acid to obtain syrupy D-erythrose.

INTRODUCTION

In continuation of our efforts to utilize D-ribono-1,4-lactone (**1**) as starting material for the synthesis of 4-, 5-, and 6-carbon normal and deoxy sugars, we describe here the synthesis of D-erythrose (**5**). We have reported[1] the synthesis of L-erythrose from **1** via its 2,3-O-isopropylidene derivative. A number of methods are available in the literature for the preparation of **5**. These include i) Ruff degradation[2,3] of calcium D-arabinonate; ii) ozonolysis[3] of 1,4,6-tri-O-acetyl-2,3-dideoxy-D-erythro-hex-2-enopyranose, followed by hydrolysis of the acetyl groups with aqueous hydrochloric acid; iii) oxidative cleavage[3] of methyl β-D-glucofuranoside 5,6-carbonate with lead tetraacetate, and removal of the

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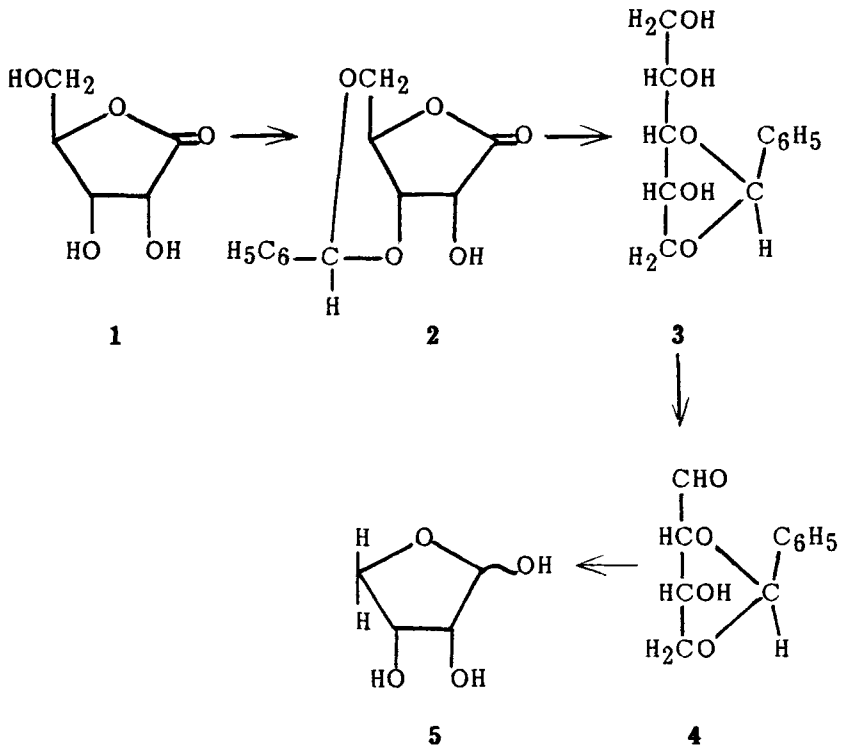
carbonate group with aqueous barium hydroxide; iv) periodate cleavage of a) 4,6-O-benzylidene-D-glucose[4] or -D-glucitol,[4] b) 1,3-O-ethylidene-D-mannitol,[5] or c) 4,6-O-ethylidene-D-glucose[6-8] or -D-glucitol,[9] followed by hydrolysis with aqueous sulfuric acid of the resultant 2,4-O-benzylidene- (**4**) or -ethylidene-D-erythrose; v) MacDonald-Fischer[10,11] degradation of D-arabinose diethyl dithioacetal;[12] vi) oxidative cleavage of D-glucose with two equivalents of lead tetraacetate, followed by hydrolysis of the 3,4-di-O-formyl-D-erythrose with aqueous hydrochloric acid;[13] and vii) borohydride reduction followed by periodate cleavage of 3,4-O-isopropylidene-D-arabinose to obtain the 2,3-O-isopropylidene-D-erythrose.[14]

Of these, the method preferred most frequently for the preparation of **5** is the one involving the periodate cleavage of 4,6-O-ethylidene-D-glucose.[6-8] In contrast, the method[4] employing the analogous 4,6-O-benzylidene-D-glucose has been largely ignored for this purpose. The reason for this is that, whereas the latter compound can be prepared[15] at best in 42% yield after considerable effort, yields of 70-87% can be achieved[8,16,17] more readily in the preparation of the former derivative. Recently, a high-yield synthesis of 3,5-O-benzylidene-D-ribono-1,4-lactone[18] (**2**) has been described,[19] which makes the preparation of D-erythrose (**5**) via the 2,4-O-benzylidene derivative **4** more attractive.

DISCUSSION

The route to **4** involved the same sequence of reactions that we and others have followed for the synthesis of 2,3-O-isopropylidene-L-[1,20,21] and -D-erythrofuranose.[14] Accordingly, **2**, prepared by the literature procedure,[19] was converted to **4** in a one-flask reaction by reduction with sodium borohydride in aqueous ethanol followed by oxidative cleavage of the intermediate 3,5-O-benzylidene-D-ribitol (**3**) with periodate; the yield of **4** was 63% overall. The intermediate **3** was isolated from a different, small-scale run and shown to be identical with **3** prepared by reduction of **2** with lithium aluminum hydride, as judged by thin-layer chromatography (TLC).[22] The 2,4-O-benzylidene-D-erythrose (**4**) was essentially homogeneous according to TLC, and its mobility was



quite different from that of both **2** and **3**. The infrared (IR) spectrum of **4** showed all the requisite peaks except for the carbonyl signal for the aldehyde group, which was very weak. However, **4** showing strong carbonyl absorption at 1715 cm^{-1}, and all the other expected peaks, was obtained from another, identical run in which the work-up procedure was slightly modified (see experimental section). Chromatographically, the products (**4**) from the two runs were identical; their IR spectra differed only in the relative intensities of some of the peaks. It (**4**) showed a mutarotation of small magnitude that is reminiscent of that reported by Schaffer[7] for 2,4-O-ethylidene-D-erythrose in water [$[\alpha]_D$ -40° —> -43.5°]. It is not clear whether equilibria between the monomeric and oligomeric forms of **4** or different anomers of the oligomeric forms, or both are responsible for its mutarotation.

Baggett et al.[23] have suggested a dimeric structure for **4**[4] on the basis that it showed neither a carbonyl absorption in the IR nor an

aldehydic proton signal in the ^1H NMR, as well as by analogy with the proposed[7] dimeric structure for 2,4-O-ethylidene-D-erythrose. However, the monomeric structure for **4**[4] was preferred by Thiem and Wessel[24] on the basis of methylation studies. Our observation of the TLC behavior of **4** suggests that it migrates as a monomer; its mobility relative to **2** and **3** was 1.5 and 2.1, respectively. For it to possess the dimeric structure, its R_2 and R_3 values would have been expected to be much smaller than observed. The fact that strong carbonyl absorption was observed by us for a preparation of **4** is highly supportive of its monomeric structure. The monomeric structure would also seem to be supported by the fact noted by Baggett et al.[23] that **4** reduces Fehling's solution whereas its ethylidene counterpart does not.

Sowden[4] removed the benzylidene group of **4** by hydrolysis with 0.1 N sulfuric acid at reflux temperature. We preferred to employ 10% acetic acid for this purpose in order to obviate the need for extra measures for removal of the sulfate ions. The hydrolysis of 2,4-O-benzylidene-D-threose under these conditions has been reported by Neish.[9] Accordingly, **4** was hydrolyzed with 10% acetic acid, and **5** was obtained as a colorless syrup in 83% yield. This product was identical with authentic D-erythrose (purchased commercially) and the L-erythrose (also prepared[1] from **1**) according to TLC. It mutarotated in water from a low to high value, reaching equilibrium after six days with an $[\alpha]_D$ of -38.4°. The direction of mutarotation observed here is in agreement with that reported[2,3,12] for **5** in the literature. Previously we have reported[1] an $[\alpha]_D$ of +36.8° (water) for the L-erythrose, which was also prepared from **1**. These two values are within the ±3° of 38° that Baxter and Perlin[20] suggested as the correct optical rotation of erythrose [(+) for the L and (-) for the D]. This suggestion[20] is corroborated by the fact that we have prepared the two enantiomers of erythrose from the same starting material (**1**) whose specific rotations fall within this range and which are opposite in sign.

Perlin and Brice[13] postulated the formation of oligomers of **5** at low temperature to explain the reported, low specific rotations for **5** and its enantiomer, and to account for the presence of more than one

component on paper chromatograms. These investigators showed[13] that keeping a solution of **5** frozen for 18 hours and then thawing lowers the specific rotation from -31° to -6°, the original value being regained after four hours at room temperature; this rotatory change was accompanied by an increase in the slower moving component at the lower temperature. Andersson, Theander, and Westerlund[25] noted the presence of signals from the anomeric protons of monomeric and oligomeric **5** in the 100-MHz ^1H NMR spectrum in deuterated acetate buffer, pH 4.5. In keeping with the postulate[13] of Perlin and Brice, these investigators determined[25] from ^1H NMR studies that heating of the solution increases the proportion of monomeric **5**. The presence of oligomers of **5** in concentrated solutions or in solutions freshly prepared from syrups was also observed by Serianni, Clark, and Barker[26] from ^{13}C NMR studies. The optical rotatory and chromatographic behavior of **5** synthesized here are consistent with these findings.[13,25,26]

Thus, the method described here should provide an excellent alternative to the existing procedures for the preparation of D-erythrose (**5**) of high purity in good yield from a readily available starting material (**1**).

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured at ambient temperature in a 1-dm cell with a Perkin-Elmer Model 241 automatic polarimeter. IR spectra were recorded with a Perkin-Elmer Model 283B infrared spectrophotometer. TLC was performed with silica gel G in 10:1 chloroform-methanol (solvent A) or 3:1:1 ethyl acetate-acetic acid-water (solvent B). Evaporations were performed under reduced pressure at 40-45 °C. Benzaldehyde was used as received from the supplier. Authentic D-erythrose was purchased from Sigma Chemical Co., St. Louis, Missouri.

3,5-O-Benzylidene-D-ribono-1,4-lactone (**2**). This was prepared in 91.5% yield essentially as described[19] by Chen and Joullie, with the modification that the crude product was washed with n-pentane prior to washing with 5% sodium hydrogen carbonate, water, and n-pentane; m.p.

230-232 °C [lit.[18,19] m.p. 233-235.5 °C and 230-231.5 °C, respectively]; $[\alpha]_D$ -173.2° (c 0.45, N,N-dimethylformamide) [lit.[18,19] $[\alpha]_D$ -174.1° and -177.0°, respectively (both in N,N-dimethylformamide)]; R_F 0.42 (solvent A). The crude product was used directly without recrystallization.

2,4-O-Benzylidene-D-erythrose (**4**). To a suspension of **2** (2.36 g, 10 mmol) in a mixture of ethanol (120 mL) and water (40 mL) was added over 2 min a solution of sodium borohydride (1.4 g, 37.8 mmol) in water (50 mL). The insoluble solid dissolved over the next 45 min to give a clear solution [the mixture gradually becomes turbid again, presumably due to the separation of the intermediate 3,5-O-benzylidene-D-ribitol (**3**)]. After 24 h, the pH was adjusted to approximately 6 with 20% aqueous acetic acid, which resulted in the dissolution of the separated material.

A solution of sodium metaperiodate (2.25 g, 10.5 mmol) in water (20 mL) was added over 5 min during which time a solid (inorganic salts) separated as fine needles. After 2 h at room temperature, the reaction mixture was evaporated, the solid gradually dissolving as the ethanol evaporated. The colorless, crystalline residue was dried by evaporation with ethanol (2 x 50 mL) and then was extracted with hot ethyl acetate (350 mL in several portions). The combined extracts were washed with water (2 x 25 mL), dried (sodium sulfate), and evaporated to obtain light yellow, syrupy **4** (1.31 g, 63%), which was essentially homogeneous according to TLC; $[\alpha]_D$ -65.3° (3 min) —> -62.6° (equilibrium, 3 h) (c 0.65, chloroform), -68.5° (c 0.27, N,N-dimethylformamide) [lit.[23] $[\alpha]_D$ -20° (N,N-dimethylformamide)]; R_F 0.64 (major), 0.02 and 0.0 (traces) (solvent A); IR (film): 3400 (OH), 1720 (vw, aldehyde carbonyl), 1105, 1075, 1030 (sh), and 1010 (C-O, C-O-C), 768 and 708 cm^{-1} (monosubstituted phenyl).

In another identical run, the inorganic solid which precipitated during the periodate reaction was filtered off and washed with 1:1 ethanol-water and finally with ethanol. The combined filtrate and washings were evaporated to dryness, and the residue was extracted with hot ethyl acetate; the filtered inorganic solid was also extracted with hot ethyl acetate. All the extracts were combined and dried (sodium sulfate), washing with water being omitted. Concentration of the extracts gave **4** as a pale yellow syrup (86% yield) which was identical with the above product on TLC. In the IR this product showed a strong aldehyde carbonyl

peak at 1715 cm^{-1}; otherwise its IR spectrum was identical to that of the above product, differing from it only in the relative intensities of some of the peaks.

D-Erythrose (5). A solution of 4 (1.23 g) in 10% aqueous acetic acid (30 mL) was heated at 100 °C for 1 h. The pale yellow solution was evaporated to dryness. The residual syrup was dissolved in water (15 mL), and the solution was washed with ether (3 x 10 mL) to remove traces of benzaldehyde. The aqueous layer was decolorized with Norit A and evaporated to obtain 5 as a colorless, thick syrup (0.59 g, 83%); $[\alpha]_D$ -15.8° (5 min) —> -36.8° (24 h) —> -38.4° (equilibrium, 6 days) (c 0.77, water) [lit.[2,3,5,7,12,13] $[\alpha]_D$ -14.5°, -18.5°, -17.0°, -41.0°, -23.1°, and -32.7°, respectively]; R_F 0.50 (major, monomer), 0.20 (minor, oligomer) (Solvent B); authentic D-erythrose and L-erythrose[1] showed similar spots.

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