Note

Preparation of L-lyxose and some of its furanose derivatives*

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L-Lyxofuranose (10) differs from D-ribofuranose, an important sugar component of nucleotides, only in the absolute configuration of C-4, and it may be an interesting sugar in its biochemical aspects. For example, 2':3'-cyclic phosphates of some "anomalous" nucleosides derived from L-lyxofuranose have been found to be active substrates for several ribonucleases¹⁻³. L-Lyxose is a rare sugar, obtained only by synthetic methods; three of them use D-galactose as the starting material⁴⁻⁶ and another involves inversion of the 3-hydroxyl group of an L-arabinose derivative⁷. In this paper, we describe a new pathway to L-lyxose and its furanose derivatives that employs the most readily obtainable sugar, D-glucose, as the starting material.

1,2:5,6-Di-O-isopropylidene- α -D-gulofuranose⁸ (1) and its 3-acetate⁹ (2) can be prepared in three stages from 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose by use of recent oxidation procedures. An attempt to remove only the 5,6-O-isopropylidene group from 1 with aqueous acetic acid was unsuccessful, as the 1,2-O-isopropylidene group is also labile under such mildly acidic conditions. The free hydroxyl group on C-3 was presumed to play some role in the ready elimination of the 1,2-O-isopropylidene group from 1, because the 1,2-O-isopropylidene group of 1,2:5,6-di-O-isopropylidene- α -D-allofuranose migrates to the 2,3-positions on treatment with acid¹⁰.

The benzyl group was therefore chosen for the protection of the hydroxyl group on C-3 of 1, as the benzyl group has little tendency to migrate. Consequently, crystalline 3-O-benzyl-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose (3) was prepared from the 3-acetate 2. On treatment with aqueous acetic acid in *p*-dioxane, 3 gave the expected 3-O-benzyl-1,2-O-isopropylidene- α -D-gulofuranose (4) in 55% yield; it was accompanied by unchanged 3 and 3-O-benzyl-D-gulose. Oxidative cleavage of 4 between C-5 and C-6 with sodium periodate gave a syrupy dialdose derivative (5), which was characterized as its crystalline semicarbazone (6). Reduction of 5 with sodium borohydride afforded crystalline 3-O-benzyl-1,2-O-isopropylidene- β -L-lyxofuranose (7) in almost quantitative yield. The benzyl group of 7 was removed by hydrogenolysis in the presence of palladium-carbon, to give crystalline 1,2-O-isopropylidene- β -L-lyxofuranose (8), which, like 1, was very sensitive to acid. For

^{*}Dedicated to Dr. Nelson K. Richtmyer in honor of his 70th birthday.



removal of the isopropylidene group, 8 was treated with Dowex-50 (H^+) ion-exchange resin at room temperature, yielding syrupy L-lyxose (10) which later crystallized. The behavior of this L-lyxose in thin-layer chromatographic and gas-liquid chromatographic analyses was identical with that of authentic D-lyxose, and different from that of D-ribose (which would have been formed had epimerization occurred at C-4 of 5).

In addition to the 1,2-O-isopropylidene derivatives of L-lyxofuranose, a derivative having a free hydroxyl group on C-2 was prepared. 3-O-Benzyl-1,2-O-isopropylidene-5-O-(methoxycarbonyl)- β -L-lyxofuranose (9) was prepared from 7; compound 9 was then treated with methanolic hydrogen chloride (1%) for several hours. The main product of this methanolysis was identified as methyl 3-O-benzyl-5-O-(methoxycarbonyl)- α -L-lyxofuranose (11) on the basis of its i.r. and n.m.r.



spectra. Treatment for a longer time decreased the yield of 11, and increased the proportion of its β anomer and of an anomeric mixture of the corresponding de(methoxycarbonyl) compounds.

EXPERIMENTAL

General methods. — All melting points are uncorrected. Specific rotations were measured with a Perkin-Elmer Model 141 polarimeter and a 1-dm tube. The i.r. spectra were recorded with a Shimadzu IRS-27, Model D, i.r. spectrometer. The n.m.r. spectra were recorded at 60 MHz with a Japan Electron Optics C-60 spectrometer. T.l.c. was performed with Kieselgel G (E. Merck, Darmstadt) or with Avicel

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SF (microcrystalline cellulose, Asahikasei Co.). G.l.c. was conducted with a Shimadzu GC-4A chromatograph equipped with a glass column (1.8 $m \times 4$ mm) packed with 3% OV-17 on Shimalite W; nitrogen was used as the carrier gas.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose (3). — Benzyl chloride (200 ml) was added to a mixture of 2(27 g) and powdered potassium hydroxide (60 g). The mixture was heated for 2 h at 90° with vigorous stirring, and then evaporated in *vacuo*. The excess of benzyl chloride was completely removed from the residue by steam distillation; during this treatment, a syrupy product separated, and solidified after it had been cooled. The solid mass was extracted with ether (\sim 800 ml). The extract was thoroughly washed with water, dried (anhydrous sodium sulfate), and evaporated in vacuo, to give crude 3 (33 g), which was recrystallized from ethyl acetate-hexane; yield 27 g (74%), m.p. 129–130°, $[\alpha]_D^{25}$ +40.4° (c 1.51, chloroform).

Anal. Calc. for C₁₉H₂₆O₆: C, 65.13; H, 7.48. Found: C, 65.38; H, 7.62.

3-O-Benzyl-1,2-O-isopropylidene- α -D-gulofuranose (4). — A solution of 3 (17.2 g) in p-dioxane (400 ml) was diluted with 2:3 (v/v) water-acetic acid (400 ml), kept for 13 h at 50-55°, made neutral with sodium carbonate, and filtered. The filtrate was evaporated in vacuo, the residue was extracted with two 500-ml portions of chloroform, and the extracts were combined, washed with water, dried (anhydrous sodium sulfate), and evaporated in vacuo. The resulting syrup was chromatographed on silica gel (600 g) with 3:1 (v/v) ethyl acetate-cyclohexane as eluant, to give 4 as a syrup that crystallized; yield 8.43 g (55%), m.p. 70–74°, $[\alpha]_{D}^{21}$ +46.0° (c 1.43, chloroform); $v_{\text{max}}^{\text{KBr}}$ 3450–3200 cm⁻¹ (OH).

Anal. Calc. for C₁₆H₂₂O₆: C, 61.92; H, 7.15. Found: C, 62.33; H, 7.26.

3-O-Benzyl-1,2-O-isopropylidene- β -L-lyxo-pentodialdo-1,4-furanose (5) and its semicarbazone (6). — A solution of sodium periodate (242 mg) in water (7 ml) was added, with cooling in ice, to a solution of 4 (318 mg) in ethanol (10 ml), and the mixture was stirred for 1 h at 0°, and filtered. Water (30 ml) and chloroform (80 ml) were added to the filtrate, and the mixture was shaken. The chloroform layer was separated, washed with a little water, dried (anhydrous sodium sulfate), and evaporated in vacuo below 40°, to afford syrupy 5 (258 mg, 91%), which showed only one component (no tailing) on t.l.c. in 5:2 (v/v) ethyl acetate-cyclohexane; v_{max}^{film} 1740 cm^{-1} (>C=O).

Water was added dropwise to a solution of 5 (260 mg) in ethanol (10 ml) until the solution was faintly turbid, and the turbidity was removed with a few drops of ethanol. To the solution were added sodium acetate (750 mg) and semicarbazide hydrochloride (500 mg), and the mixture was vigorously shaken, heated in boiling water, and cooled in an ice bath, to afford crystalline 6, which was recrystallized from ethanol (240 mg, 80%); m.p. 199–200° (dec.), $[\alpha]_D^{22} - 94.6°$ (c 2.0, chloroform).

Anal. Calc. for C₁₆H₂₁N₃O₅: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.31; H, 5.94; N, 12.58.

3-O-Benzyl-1,2-O-isopropylidene- β -L-lyxofuranose (7). — Sodium borohydride (46 mg) was added in portions to a cooled solution of 5 (255 mg) in methanol (20 ml), and the mixture was stirred for 1 h at room temperature. Acetone (\sim 7 ml) was added, the mixture was evaporated to dryness *in vacuo*, and the residue was extracted with chloroform (50 ml). The extract was washed with water, dried (anhydrous sodium sulfate), and evaporated *in vacuo*, to afford a colorless syrup (247 mg, 96%) which crystallized on standing. For analysis, crude 7 was chromatographed on silica gel with 1:1 (v/v) cyclohexane-ethyl acetate; m.p. $61-62^{\circ}$, $[\alpha]_{\rm D}^{25}$ +48.6° (c 1.36, chloform), $v_{\rm max}^{\rm KBr}$ 3550 (OH), 1610, 1590, 1500 cm⁻¹ (Ph).

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Anal. Calc. for C₁₅H₂₀O₅: C, 64.27; H, 7.19. Found: C, 64.51; H, 7.10.

1,2-O-Isopropylidene- β -L-lyxofuranose (8). — A solution of 7 (2.4 g) in methanol (100 ml) was shaken with hydrogen in the presence of palladium-carbon (10%) until absorption of hydrogen ceased (~4 h), and filtered. The filtrate was diluted with aqueous sodium hydrogen carbonate (2%, 60 ml), and evaporated to dryness *in vacuo*. The residue was extracted with acetone (100 ml), and the extract was evaporated *in vacuo*, to give crystalline 8 (1.5 g, 92%), which was recrystallized from ethyl acetate; m.p. 109–111°, $[\alpha]_D^{25} - 20.5^\circ$ (c 1.55, methyl sulfoxide), v_{max}^{KBr} 3400, 3150 cm⁻¹ (OH); n.m.r. data (methyl sulfoxide- d_6 ; internal standard, sodium 2,2-dimethyl-2-silapentane-5-sulfonate): τ 4.36 (1 proton doublet, $J_{1,2}$ 3.8 Hz, H-1), 4.93 (1-proton doublet, which disappeared on addition of D₂O, $J_{OH,3}$ 5.3 Hz, OH-3), 5.42–6.51 (6 protons, complex multiplet, H-2,3,4,5,5', OH-5), 8.52 (3 protons, singlet, methyl protons of the isopropylidene group), 8.74 (3 protons, singlet, methyl protons of the isopropylidene group).

Anal. Calc. for C₈H₁₄O₅: C, 50.52; H, 7.42. Found: C, 50.38; H. 7.62.

L-Lyxose (10). — A solution of 8 (1.5 g) in water (60 ml) was stirred with Dowex 50W X8 (H⁺, 16 ml) for 2 h at room temperature, and filtered. The filtrate was evaporated *in vacuo*, to afford a colorless syrup which was mixed with ethanol (30 ml). The mixture was evaporated *in vacuo*, and the resulting syrup was kept at room temperature for two weeks, whereupon the syrupy 10 solidified gradually; yield 1.1 g (92%), m.p. 103–107°, $[\alpha]_D^{20} + 12.7^\circ$ (c 2.60, water; equil.) [lit. m.p. 105°, and $[\alpha]_D + 13.5^\circ$ (ref. 4); m.p. 104°, $[\alpha]_D + 13.9^\circ$ (ref. 5)].

The mobility of 10 (R_F 0.488) was identical with that of authentic D-lyxose (R_F 0.488), and different from that of D-ribose (R_F 0.567) when these sugars were developed twice with 12:5:4 (v/v) ethyl acetate-pyridine-water on Avicel SF (0.25 mm), with detection with aniline hydrogen phthalate. The trimethylsilyl derivative of 10 in g.l.c. (column temp. 145°, rate of carrier gas, 45 ml/min) gave two peaks (at 5.3 and 6.5 min), which correspond to the peaks given in g.l.c. by the trimethylsilyl derivatives from D-lyxose equilibrated in water, although their relative intensities were different.

3-O-Benzyl-1,2-O-isopropylidene-5-O-(methoxycarbonyl)- β -L-lyxofuranose (9). — A solution of 7 (9 g) in dry pyridine (70 ml) was cooled in an ice-salt bath (-10°). Methyl chlorocarbonate (7 g) was added dropwise, below -5° , with stirring. After the mixture had been stirred for 2 h at -10° , it was kept for 2 days at 0°, poured into water (700 ml), and extracted with dichloromethane (600 ml). The extract was successively washed with cold, aqueous sulfuric acid (2%), saturated aqueous sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated *in vacuo*, to afford syrupy 9 (10 g, 92%), which crystallized on standing. Recrystallized from cyclohexane, it had m.p. 82–84°. $[\alpha]_D^{23} - 11.5^\circ$ (c 0.981, chloroform), $v_{max}^{KBr} 1760 \text{ cm}^{-1}$ (>C=O).

Anal. Calc. for C₁₇H₂₂O₇: C, 60.35; H, 6.55. Found: C, 60.58; H, 6.42.

Methyl 3-O-benzyl-5-O-(methoxycarbonyl)- α -L-lyxofuranoside (11). — Methanolic hydrogen chloride [10% (w/w), 5 ml] was added to a solution of 9 (1.5 g) in absolute methanol (50 ml). The mixture was kept for 4 h at room temperature, made neutral with a large excess of sodium hydrogen carbonate, and filtered. The filtrate was evaporated to dryness *in vacuo*, and the residue was extracted with chloroform (100 ml). The extract was washed with water, dried (anhydrous sodium sulfate), and evaporated *in vacuo*, to give a colorless syrup (1.2 g), which showed one major spot and three minor spots on t.l.c. in 1:1 (v/v) cyclohexane-ethyl acetate. The syrup was chromatographed on silica gel with 2:1 (v/v) cyclohexane-ethyl acetate, and the major product (11) was isolated; yield 850 mg (62%), $[\alpha]_{\rm D}^{22}$ -73.0° (c 1.09, chloroform), $v_{\rm max}^{\rm film}$ 3580 (OH) and 1750 cm⁻¹ (>C=O); n.m.r. data (chloroform-d; internal standard, tetramethylsilane): τ 5.11 (1 proton, singlet, H-1), 5.31-5.45 (2 protons, broad singlet, $-CH_2$ -Ph), 5.51-5.76 (4 protons, broad singlet, H-3,4,5,5'), 5.80-6.05 (1-proton multiplet, which collapsed to an incomplete doublet on addition of D₂O, H-2), 6.24 (3 protons, singlet, $CH_3O_{\rm H}$

Anal. Calc. for C₁₅H₂₀O₇: C, 57.69; H, 6.46. Found: C, 57.50; H, 6.36.

ACKNOWLEDGMENTS

The authors express their gratitude to Dr. H. Homma and his collaborators for the elemental analyses, and to Mr. J. Uzawa for the n.m.r. spectra.

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