Synthesis and Characterization of D-Lyxono- γ -lactone

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Abstract : D-lyxono- γ -lactone has been prepared in two steps from galactose. The first step potassium lyxonate was obtained in 64% yield and the title compound has been isolated in next step with 75% yield. The structures of the products were characterized by IR, ^1H , ^{13}C , mass and microanalysis study.

Keywords : Lactone, Antiviral activity, Galactose, D- Lyxonate

Introduction

Oxetanocin¹, was the first example of a new family of nucleosides² containing an oxetane ring rather than a furan ring as the sugar moiety. The antiviral activity of oxetanocin and its guanine analogue **2** has stimulated considerable interest in the synthesis of oxetane-containing nucleosides^{3,4}.

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Most of these derivatives have been synthesized by Fleet's group α - and β -noroxetanocin have been made by this group⁵ but show no activity against HIV-1 *in vitro*, however a structural isomer epinoxetanocin⁶ shows considerable anti-HIV activity *in vitro*.

The azido **3** and fluoro **4** analogues of noroxetanocin have also been synthesized⁷ by Fleet's group and whilst the fluoro derivative shows no significant activity against HIV-1, the azido analogue shows significant anti-HIV activity *in vitro*.

Experimental

The ^1H NMR spectra were recorded on Hitachi-Perkin-Elmer R24B (60 MHz) or Bruker XL 500 (500 MHz) instruments (with J-values given in Hz), ^{13}C NMR spectra (with DEPT 135) either on a Bruker WP80 or XL500 instrument, and IR spectra on a Shimadzu IR-470 spectrophotometer. Mass spectra were recorded on a Kratos Concept instrument. The melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

Preparation of potassium D-lyxonate (6)

A four necked, five litre flask equipped with a heavy duty mechanical stirrer, reflux condenser and dropping funnel was charged with a solution of potassium hydroxide (168.0 g, 3 mol) in water (360 mL) and methanol (1500 mL). into the warm (30–45 °C), vigorously stirred solution was passed oxygen gas via two syringe needles and simultaneous addition of a solution of D-galactose (180.0 g, 1 mol) in water (360 mL) was made via the dropping funnel over a 4 h period. After the addition, the passage of oxygen through the solution was continued for a further two hours; methanol was added periodically throughout the reaction to replace that lost due to evaporation. Air was then bubbled through the stirred solution for 48 h. After this period the solution was diluted to twice its volume with methanol and stirred at room temperature for one day. The solid was filtered and dried under vacuum to give 130.0 g, (0.64 mol; 64%) of **6**. An analytical sample was prepared by recrystallisation (1:2 water : methanol) to give colourless cubes, m.p. 167–170 °C (dec.) [lit.⁸ 166 °C] Found : C, 29.1; H, 4.4%. Calc. for $\text{C}_5\text{H}_9\text{O}_6\text{K}$: C, 29.4; H, 4.4%] ; ^1H NMR (D_2O) : δ 3.55–3.60 (m, 2H, CH_2OH), 3.75 (dd, 1H, J 6, 3Hz, H3), 3.85 (m, 1H, H4), 4.08 (d, 1H, J 6Hz, H2) ppm; ^{13}C NMR (D_2O) : δ 64.1 (CH_2 , by Dept 135), 73.0 (CHOH), 72.4 (CHOH), 74.7 (CHOH), 180.1 (COOK), ppm; ν_{max} (Nujol) 3700–2300 bs (OH), 1600s (C=O), 1130s, 1110s, 1040s, 990s, 870s, and 830 cm^{-1} .

Preparation of D-lyxonono- γ -lactone (7)

Into a mechanically stirred suspension of potassium-D- lyxonate (173.0 g, 0.85 mol) in isopropyl alcohol (700 mL) was passed hydrogen chloride gas for twenty mins. The mixture was then cooled in ice and passage of the gas was continued for a further 20 mins. The mixture was then heated to boiling and the precipitated potassium chloride was filtered under suction and rinsed with isopropyl alcohol. The filtrate and washing were concentrated under reduced pressure to about 150 mL when the product precipitated and this was collected

by filtration (77 g). Further concentration of the mother liquor yielded a second crop of **7** giving a total yield of 94 g (0.65 mol; 76%). An analytical sample was obtained by recrystallisation (isopropyl alcohol) to give small needles, m.p. 110-111 °C (lit.⁹, 114 °C) Found : C, 40.8; H, 5.4%; (M+NH₄)⁺ = 166 (100%). Calc. for C₅H₈O₅: C, 40.5; H, 5.4 %; M 148]; ¹H NMR (D₂O) : δ 3.90 (m, 2H, H4 & H5), 4.55 (dd, 1H, H2, J_{1,2} 6Hz; J_{2,3} 3.5 Hz.), 4.60 (m, 1H, H3), 4.70 (d, 1H, J_{1,2} 6Hz, H1) ppm; ¹³C NMR (D₂O); δ 60.9 (C5, by Dept 135) 70.7 (C4), 71.7 (C3), 82.7 (C2), 179.4 (C1) ppm; ν_{max} (Nujol) 3700-3100b (OH), 1780s (C=O), 1640m, 1320m, 1200s, 1100s, 1020s, 990s, 960s, 870s, 800s and 780s cm⁻¹.

Results and Discussion

D-lyxono- γ -lactone **7** was prepared in two steps from galactose **5**.

Oxidation of an alkaline solution of D-galactose on a molar scale, by a method based on the oxidation of glucose, afforded potassium lyxonate **6** in 64% yield. The product as expected showed 5 lines in the ¹³C nmr, a series of multiplets in the ¹H NMR, broad OH and C=O stretching in the infrared, and the microanalysis results were satisfactory.

Cyclisation of **6** with hydrogen chloride gas in isopropanol⁸⁻¹² gave D-lyxono- γ -lactone **7** in 75% yield. The product again showed 5 lines in the ¹³C NMR, the mass spectrum (CI) showed a (M+NH₄)⁺ = 166 and the microanalysis results were consistent. The ¹H NMR shows H1 appearing as a doublet (J 6Hz) by coupling with the *cis* H2 which itself appears as a doublet of doublets (J 6, 3.5 Hz) by additional coupling to H3; both H4 and H5 appear as complex multiplets. The infrared shows broad OH stretching and a sharp C=O absorption at 1780 cm⁻¹ which is consistent with the molecule being a cyclic 5-membered lactone.

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References

- 1 Shimada N, Harada S, Tomisawa T, Fujii A and Takito T, *J. Antibiotics*, 1986, **39**, 1623.
- 2 Yamamoto Y, Fujioka N, Shimada N and Takahashi J, *J. Antibiotics*, 1989, **42**, 1308.
- 3 Norbeck D W and Kramer J B, *J. Amer. Chem. Soc.* 1988, **110**, 7217.
- 4 Nagai M, Kato K, Nishiyama K and Yamamura S, *Tetrahedron Lett.* 1990, **31**, 119.
- 5 Wilson F X, Fleet G W, Witty D R, Myers P, Storer R, Wallis C, Watkin D and Voget K, *Tetrahedron Asym.*, 1990, **1**, 525.
- 6 Fleet G W, Wilson F X, Storer R, Voget K, Watkin D, Witty D R and Peach J, *Tetrahedron Lett.* 1991, **32**, 1675.
- 7 Bashgal B, Chow H and Fleet G W *Tetrahedron*, 1987, **43**, 423.
- 8 Norbeck D and Kraner J, *J. Amer. Chem. Soc.*, 1988, **110**, 7217.
- 9 Humphlett W J, *Carbohydr. Res.*, 1967, **4**, 157.
- 10 Yahyazadeh A and Sharifi Z *Phosphorus, Sulfur, and Silicon*, 2006, **6**, 1339.
- 11 Al-Azmi A, Elassar A A and Booth B L, *Tetrahedron*, 2003, **59**, 2749.
- 12 Yahyazadeh A, *Russ. J. Org. Chem.*, 2003, **39**, 1718.