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Synthesis and characterization of dihydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2(3H)-one

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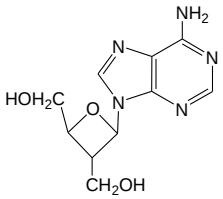
Galactose.

ABSTRACT

Dihydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2(3*H*)-one has been prepared in two steps from galactose. The first step potassium-2,3,4,5-tetrahedroxypentanoate 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, ^{1}H, ^{13}C, mass and microanalysis study.

Introduction

Oxetanocin 1, was the first example of a new family of nucleosides containing an oxetane ring rather than a furan ring as the suger moiety[1,2]. The antiviral activity of oxetanocin and its guanin analogue 2 has stimulated considerable interest in the synthesis of oxetane-containing nucleosides[3,4].



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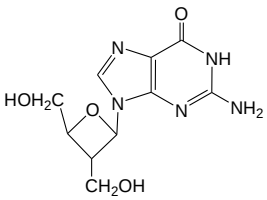

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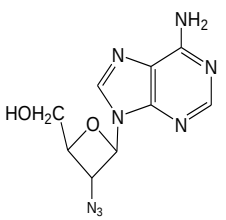
Most of these derivatives have been synthesized by Fleet's group α- and β-noroxetanocin have been made by this group but show no activity against HIV-1 in vitro, however a structural isomer epinoxoxetanocin shows considerable anti-HIV activity in vitro[5,6].

The azido **3** and fluro **4** analogues of noroxetanocin have also been synthesized 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[7].



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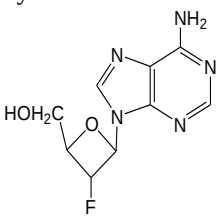

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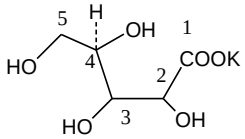
Experimental

The ^{1}H 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.



6

Preparation of Potassium-2,3,4,5-tetrahedroxypentanoate 6

A four necked, five liter 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 ^{o}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-hour 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 hours. 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,

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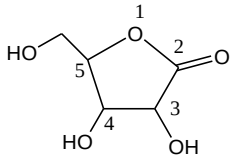
m.p. 167-170 °C (dec.) [lit.[8] 166 °C]Found : C, 29.2; H, 4.3%. Calc. for $C_5H_9O_6K$: C, 29.4; H, 4.4%] ; ^{1}H NMR (D_2O) : δ3.55-3.60 (m, 2H, CH_2OH), 3.75 (dd, 1H, J 6, 3Hz, H3), 3.84 (m,1H, H4), 4.04 (d, 1H, J 6Hz, H2) ppm; ^{13}C NMR (D_2O); δ 64.3 (CH_2, by Dept 135), 73.4 (CHOH), 72.2 (CHOH), 74.6 (CHOH), 180.2 (COOK), ppm; ν_{max} (Nujol) 3700-2300 bs (OH), 1600s (C=O), 1130s, 1110s, 1040s, 990s, 870s, and 830 cm^{-1}.



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Preparation of dihydro-3,4-dihydroxy-5-(hroxymethyl)furan-2(3*H*)-one 7

In to a mechanically stirred suspension of potassium-2,3,4,5-tetrahedroxypentanoate **6** (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 liquid yielded a second crop of **7** giving a total yield of 94 g (0.65 mol, 75%). 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%; $(M+NH_4)^+$ = 166 (100%). Calc. for $C_5H_8O_5$: C, 40.5; H, 5.4 %; M 148]; ^{1}H NMR (D_2O): δ 2.20 (s, br. 3H, OH), 3.90 (m, 2H, H5 & H6), 4.55 (dd, 1H, , J 6Hz, 3.5 Hz, H3), 4.60 (m, 1H, H_4) ppm; ^{13}C NMR (D_2O); δ60.9 (C6, by Dept 135) 70.7 (C5), 71.7 (C4), 82.7 (C3), 179.4 (C2) ppm; ν_{max} (Nujol) 3700-3100b (OH), 1780s (C=O), 1640m, 1320m, 1200s, 1100s, 1020s, 990s, 960s, 870s and 800s cm^{-1}.

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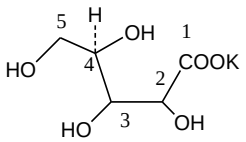

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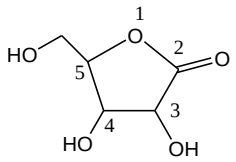

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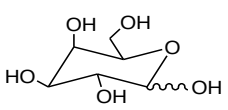
Results and Discussion

Dihydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2(3*H*)-one **7** was prepared in two steps from galactose **5**.



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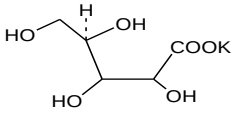

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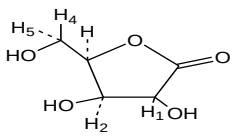

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Oxidation of an alkaline solution of D-glucose on a molar scale, by a method based on the oxidation of glucose, afforded Potassium-2,3,4,5-tetrahedroxypentanoate **6** in 64% yield. The product as expected showed 5 lines in the ^{13}C nmr, a series of multiplets in the ^{1}H NMR, broad OH and C=O stretching in the infrared, and the microanalysis results were satisfactory.

Cyclisation of **6** with hydrogen chloride gas in isopropanol[8-14] gave dihydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2(3*H*)-one **7** in 75% yield. The product again showed 5 lines in the ^{13}C NMR, the mass spectrum (CI) showed a $(M+NH_4)^+$= 166 and the microanalysis results were consistent. The ^{1}H NMR shows H3 appearing as a doublet (J 6Hz) by coupling with the cis H4 which itself appears as a doublet of doublets (J 6, 3.5 Hz) by additional coupling to H3; both H5 and H6 appear as complex multiplets. The infrared shows broad OH stretching and a sharp C=O absorption at 1770 cm^{-1} which is consistent with the molecule being a cyclic 5-membered lactone.

Acknowledgments

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