Synthesis of novel unsaturated purine nucleoside

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5′-Silylated derivative of N⁶-n-propyldapenosine 1 has been converted to bixanthate 2 by reaction with CS₂ followed by alkylation. The bixanthate affords 2′, 3′-didehydro-2′, 3′-dideoxy-N⁶-n-propyldapenosine 4 on reduction with tri-n-butyltin hydride and desilylation.

Keywords: N⁶-n-propyldapenosine, bixanthate, propyldapenosine

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Dideoxynucleosides and their unsaturated derivatives have been prepared for their chemotherapeutic properties. Some of them have been proved to be potent anti-HIV agents. 2′, 3′-Unsaturated nucleosides have been synthesized directly from the corresponding ribonucleosides via their reaction with acetoxyisobutyrylcarbonsulphide and alkylation with CH₃I affords IPC. Olefinic carbohydrates and aminoglycosides from the unsaturated nucleoside viz. 2′, 3′-butyl ammonium fluoride gave a very good yield of the unsaturated nucleoside N⁶-n-propyldapenosine (Scheme 1). The nucleoside was finally characterized by elemental analysis and ¹H NMR spectroscopy.

Results and Discussion

Olefinic carbohydrates and aminoglycosides from the corresponding vic-diols via their bixanthates have been prepared by Hayashi and Barton et al. This procedure with some modifications has been used for the synthesis of the title nucleoside. The reaction of 5′-O-silyl-N⁶-n-propyldapenosine 1 with carbodisilphide and alkylation with CH₃I affords bixanthate 2 as the only reaction product. The compound 2 on treatment with tri-n-butyltin hydride afforded 3 which on removal of silyl group with tetra-n-butyl ammonium fluoride gave a very good yield of the unsaturated nucleoside viz. 2′, 3′-didehydro-2′, 3′-dideoxy- N⁶-n-propyldapenosine 4 (Scheme 1). The nucleoside was finally characterized by elemental analysis and ¹H NMR spectroscopy.

Experimental Section

Melting points are uncorrected. ¹H NMR spectra were recorded on a Bruker DR-300 spectrometer using TMS as internal standard. Microanalysis was carried on a Carlo Erba 1008 instrument. All the chemicals used were of AR grade (Sigma, BDH and E. Merck).

5′-O-tert-Butyldimethylsilyl-N⁶-n-propyldapenosine 1. To a stirred suspension of N⁶-n-propyldapenosine (0.587 g, 1.9 mmoles) and imidazole (4.5 mmoles) in DMF (10 mL) was added tert-butyldimethylsilylchloride (0.338 g, 3.96 mmoles) and the reaction mixture was stirred with the exclusion of moisture for 18 hr. The solvent was removed under reduced pressure and the residue was purified on a silica gel column using CHCl₃-MeOH (33:1) to obtain 0.667 g (83%) of 5′-O-tert-butyldimethylsilyl-N⁶-n-propyldapenosine as a colourless solid, m. p. 169-70°C.

5′-O-tert-Butyldimethylsilyl)-2′, 3′-bis-O-[[β-cyanoethyl]thio][thiocarbonyl]-N⁶-n-propyldapenosine 2. Compound 1 (0.498 g, 1.18 mmoles) was reacted with CS₂ (0.297 g, 3.96 mmoles) in the presence of 5 N aqueous NaOH (3 mL) in DMSO (5 mL) and alkylated with CH₃I (0.368 g, 2.59 mmoles). Chromatographic purification on a silica gel column using CHCl₃: MeOH (2:1) afforded 0.551 g (72%) of 5′-O-tert-butyldimethylsilyl-N⁶-n-propyldapenosine as a colourless solid, m. p. 128-29°C.

5′-O-tert-Butyldimethylsilyl)-2′, 3′-dideoxy-2′, 3′-dideoxy-N⁶-n-propyldapenosine 3. Compound 2 (0.432 g, 71 mmoles) was treated with tri-n-butyltin hydride (0.833 g, 2.86 mmoles) in the presence of azobisisobutyronitrile (0.05 g) in toluene (8 mL) at reflux. The solvent was evaporated and the residue was partitioned between acetonitrile and hexane. Evaporation of acetonitrile and purification of the residue by column chromatography using CHCl₃-MeOH (35:1) yielded 0.251 g (90%) of the product as colourless solid, m. p. 109-10°C (Found: C, 58.55; H, 8.03; N, 17.95. Calcd for C₁₉H₃₁N₅O₂Si: C, 58.57; H, 8.02; N,
17.97%); $^1$H NMR(DMSO-$d_6$): $\delta$ 0.02 (6H, s, Me$_2$Si), 0.83 (9H, s, Me$_3$Si), 3.70 (2H, d, $J=3.94$ Hz, 5'-H) 4.78-4.98 (1H, m, 4'-H), 6.22 (1H, dt, $J=1.5$, 6.14 Hz, 2'-H), 6.42 (1H, dt, $J=1.5$, 6.14 Hz, 3'-H), 6.95 (1H, m, 1'-H), 0.90 (3H, t, $J=5.0$ Hz, NHCH$_2$CH$_2$C$_3$H$_3$), 1.52 (2H, m, CH$_2$), 2.89 (2H, t, $J=5.0$Hz, CH$_2$), 8.10 (1H, s, 8-H), 8.17 (1H, s, 2-H).

2', 3'-Didehydro-2', 3'-dideoxy-N$^6$-n-propylandenosine 4. A solution of compound 3 (0.236 g, .60 mmoles) in THF was deprotected with 1M solution of tetra-n-butylammonium fluoride (1.23 mL) in THF. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on a silica gel column using CHCl$_3$-MeOH (36:1) as the eluent to obtain 0.148g (89%) final yield of the product 4.

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References


