

SYNTHESIS OF ANOMALOUSLY COUPLED NUCLEOSIDES BY ADDITION OF PURINES TO UNSATURATED SUGAR ALDEHYDES

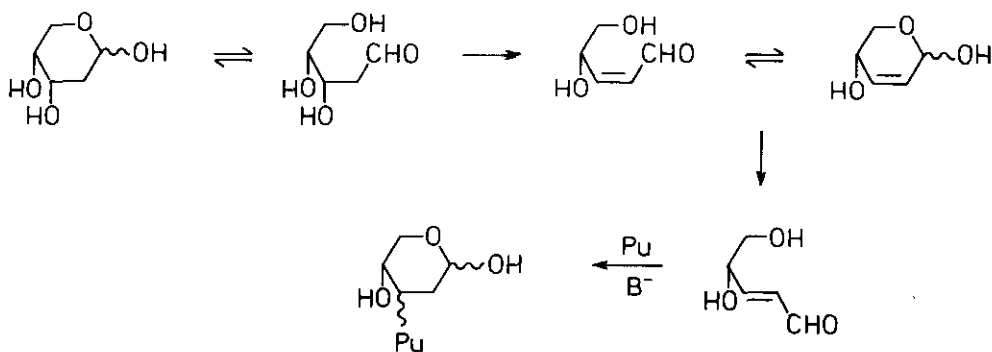
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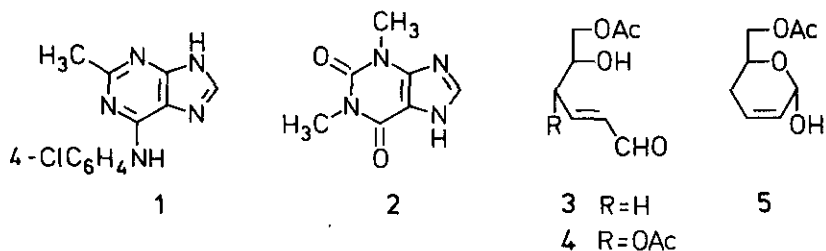
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Abstract - α,β -Unsaturated sugar aldehydes were reacted in a Michael type of reaction with purines in the presence of an organic base to give isonucleosides.

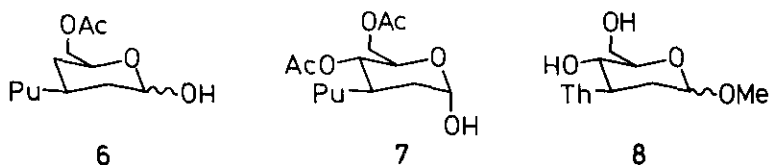
Recently, we have shown that unprotected 2-deoxy-D-ribose is anomalously coupled with nucleobases when reacted with a tributylammonium polyphosphate mixture in chloroform¹. The reaction of the 2-deoxysugar at C-3 with purines was assumed to take place via a dehydration/addition process as follows:



To prove this assumption the attention was turned to the addition of bases 1 and 2 to unsaturated sugar aldehydes 3 and 4 as well as hemiacetal 5.



Compound 3 reacted with 1 in the presence of triethylamine (TEA) in DMF at 40°C for 7 days to produce the threo adduct 6 in 20% yield. The hemiacetal 5 reacted similarly, but not in a clean reaction according to silica TLC. The aldehyde 4 easily available from tri-O-acetyl-D-glucal², was treated with 1 and TEA in DMF at 40°C for 8 days and the α -D-glucopyranose anomer 7 could be isolated in 21% yield by flash chromatography on silica with methanol/dichloromethane (1:25). In an addition reaction of theophylline (2) with the aldehyde 4 in DMF a large increase was observed in reaction rate when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of TEA. After 3 h at room temperature an adduct was isolated by adding water to the reaction mixture, neutralizing to pH 7, extraction with dichloromethane, and silica chromatography with methanol/ether (1:20). The primary adduct was deacetylated by treatment with 2% HCl in methanol at 60°C for 15 h to give a mixture of the methyl glycosides 8 in 31% overall yield from 4.



Pu = 6-(4-Chlorophenylamino)-2-methyl-9-purinyl

Th = 7-Theophyllyl

The structures and their corresponding conformations were assigned on the basis of their ¹H, ¹³C-NMR and mass spectra. 500 MHz ¹H-NMR spectra were recorded for 6 and 8³. The assignment of the shift values in the ¹H-NMR spectra was based on the use of ¹H-¹H homonuclear shift correlated 2-D NMR. With this technique it was possible to assign the axial 4a-H in the β -anomer of 6 as a quartet with J = 12 Hz. This can be explained by assuming couplings to one geminal proton and two vicinal axial protons which prove threo

configuration of **6** in the C1 conformation. This is confirmed by large couplings of the axial 3a-H to vicinal and axial orientated 2a-H and 4a-H for both α and β -anomers. In the same manner the coupling constants of 3-H in **7** and **8** prove the arabino configuration in the C1 conformation with the bulky purin-yl group at C-3 always in an equatorial position.

Characterization of **6**, **7** and **8** as follows:

6: mp 200-201°C; m/z (EI): 431 (M^+ , 11); NMR (DMSO- d_6) from the mixture of α and β -anomers (3:2).

α -anomer: $^1\text{H-NMR}$ (500 MHz) δ = 1.94-2.04 (m, 4e-H, 4a-H, 2e-H), 2.03 (s, OAc), 2.29 (t, $J_{2e,2a} = J_{2a,3} = 12\text{Hz}$, 2a-H), 2.50 (s, CH_3) 4.03-4.10 (m, 6,6'-H), 4.33 (m, $\Sigma [J] = 24\text{Hz}$, 5-H), 5.02 (tt, $J_{2a,3} = J_{3,4a} = 12\text{Hz}$, $J_{2e,3} = J_{3,4e} = 4\text{Hz}$, 3-H) 5.39 (unresolved s, 1-H), 6.01 (d, $J = 4\text{Hz}$, OH) 7.35 (d, $J = 9\text{Hz}$, ArH), 8.01 (d, $J = 9\text{Hz}$, ArH), 8.38 (s, 8'-H), 9.87 (s, NH). $^{13}\text{C-NMR}$ (63 MHz) δ = 20.62 (Ac), 25.87 (CH_3), 33.66 (C-4), 36.38 (C-2), 46.22 (C-3), 65.24 (C-6), 66.10 (C-5), 90.42 (C-1), 118.06 (C-5'), 121.7 (C-2''), 125.67 (C-4''), 128.10 (C-3''), 138.97 (C-1''), 139.57 (C-8''), 150.03 (C-4'), 151.29 (C-6'), 160.37 (C-2'), 170.21 (C=O).

β -anomer: $^1\text{H-NMR}$ (500 MHz) δ = 1.89 (q, $J_{4a,4e} = J_{3,4a} = J_{4a,5} = 12\text{Hz}$, 4a-H), 1.92-2.04 (m, 4e-H, 2a-H), 2.03 (s, OAc), 2.14 (m, $J_{2e,2a} = 12\text{Hz}$, 2e), 2.50 (s, CH_3), 3.89 (m, $\Sigma [J] = 24\text{Hz}$, 5-H), 4.03-4.10 (m, 6,6'-H), 4.79 (tt, $J_{2a,3} = J_{3,4a} = 12\text{Hz}$, $J_{2e,3} = J_{3,4e} = 4\text{Hz}$, 3H) 4.87 (ddd, $J_{1,\text{OH}} = 6\text{Hz}$, $J_{1,2e} = 2\text{Hz}$, $J_{1,2a} = 10\text{Hz}$, 1-H), 6.91 (d, $J = 6\text{Hz}$, OH), 7.35 (d, $J = 9\text{Hz}$, ArH), 8.01 (d, $J = 9\text{Hz}$, ArH), 8.35 (s, 8'-H), 9.88 (s, NH). $^{13}\text{C-NMR}$ (63 MHz) δ = 20.62 (Ac), 25.87 (CH_3), 32.87 (C-4), 38.36 (C-2), 49.51 (C-3), 65.86 (C-6), 70.01 (C-5), 94.01 (C-1), 118.06 (C-5'), 181.73 (C-2''), 125.67 (C-4''), 128.10 (C-3''), 138.97 (C-1''), 139.66 (C-8'), 150.05 (C-4'), 151.29 (C-6'), 160.37 (C-2''), 170.21 (C=O).

7: mp 200-201°C, m/z (EI): 489 (M^+ , 1.4); $^1\text{H-NMR}$ (DMSO- d_6 , 250 MHz) δ = 1.67 (s, 4-OAc), 2.03 (s, 6-OAc), 2.08 (m, 2e-H), 2.57 (s, CH_3), 2.82 (t, $J_{2a,3} = J_{2a,2e} = 13.1\text{ Hz}$, 2a-H), 4.04 (dd, $J_{5,6} = 1.6$, $J_{6,6'} = 12\text{ Hz}$, 6-H), 4.21 (dd, $J_{5,6'} = 5.1\text{ Hz}$, 6'-H), 4.30 (m, $J_{4,5} = 9.9\text{ Hz}$, 5-H), 5.05 (m, $J_{3,4} = 9.9\text{ Hz}$

$J_{2a,3} = 13.1$ Hz, $J_{2e,3} = 4.4$ Hz, 3-H), 5.25 (t, 4-H), 5.42 (m, 1-H), 6.99 (d, $J_{1,OH} = 3.7$ Hz, OH) 7.37 (d, $J_{2'',3''} = 8.9$ Hz, 3''-H), 8.05 (d 2''-H), 8.45 (s, 8'-H), 9.89 (s, NH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 63 MHz) $\delta = 19.88, 20.55$ (2Ac), 25.86 (CH_3), 35.20 (C-2), 50.71 (C-3), 62.67 (C-6), 67.36, 69.68 (C-4,C-5), 89.81 (C-1), 117.8 (C-5'), 121.67 (C-2''), 125.67 (C-4''), 128.12 (C-3''), 138.94 (C-1''), 140.38 (C-8'), 150.70 (C-4'), 151.17 (C-6'), 160.44 (C-2'), 168.80, 170.05 (2 C=O).

8: mp 269-271 $^{\circ}\text{C}$; m/z (EI): 340 (M^+ , 21); NMR (DMSO- d_6) from the mixture of α and β -anomers (2:1).

α -anomer: $^1\text{H-NMR}$ (500 MHz) $\delta = 2.04$ (dd, $J_{2a,2e} = 12$ Hz, $J_{2e,3} = 4$ Hz, 2e-H), 2.50 (hidden by DMSO, 2a-H), 3.25 (s, NCH_3), 3.31 (s, NCH_3), 3.42 (s, CH_3), 3.49 (m, 5-H), 3.54 (m, 6-H), 3.70 (m, $J_{6,6} = 11$ Hz, 6-H), 3.93 (dt, $J_{3,4} = J_{4,5} = 10$ Hz, $J_{4,OH} = 7$ Hz, 4-H), 4.60 (t, $J_{6,OH} = J_{6',OH} = 6$ Hz, 6-OH), 4.77 (m, 3-H), 4.83 (d, $J_{1,2a} = 3$ Hz, 1-H). $^{13}\text{C-NMR}$ (63 MHz) $\delta = 27.61, 29.27$ (2 CH_3), 35.66 (C-2), 53.66 (OCH_3), 57.27 (C-3), 60.79 (C-6), 67.26 (C-4), 73.84 (C-5), 96.65 (C-1), 106.12 (C-5'), 142.44 (C-8'), 148.78 (C-4'), 150.66 (C-2'), 154.04 (C-6').

β -anomer: $^1\text{H-NMR}$ (500 MHz) $\delta = 2.12$ (ddd, $J_{1,2e} = 2$ Hz, $J_{2a,2e} = 11$ Hz, $J_{2e,3} = 4$ Hz, 2e-H), 2.26 (q, $J_{1,2a} = J_{2a,3} = 10$ Hz, 2a-H), 3.25 (s, CH_3), 3.27 (m, 5-H), 3.31 (CH_3), 3.42 (s, CH_3), 3.54 (m, 6'-H), 3.74 (m, 6-H), 3.88 (dt, $J_{3,4} = J_{4,5} = 10$ Hz, $J_{4,OH} = 7$ Hz, 4-H), 4.55 (dd, 1-H), 4.59 (hidden by 6-OH, 3-H), 4.63 (t, $J_{6,OH} = J_{6',OH} = 7$ Hz, 6-OH), 5.18 (d, 4-OH). $^{13}\text{C-NMR}$ (63 MHz) $\delta = 27.61, 29.27$ (2 CH_3), 37.03 (C-2), 55.58 (CH_3), 59.47 (C-3), 60.98 (C-6), 67.25 (C-4), 78.23 (C-5), 100.32 (C-1), 106.04 (C-5'), 142.11 (C-8'), 148.78 (C-4'), 150.66 (C-2'), 154.04 (C-6').

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