Synthesis of 3-(6-Alkylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentopyranoses and Their Reduction to 3-(6-Alkylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentitols

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3-(6-Alkylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentopyranoses **3** were prepared by condensation of unprotected 2-deoxy-D-ribose (**2**) with N^6-alkyladenines **1** in a phosphorus pentoxide reagent mixture. Reduction of the pentoses **3** gave the corresponding 3-(6-alkylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentitols **4**. The structures of **3** and **4** were determined by ^{13}C nmr, ^{1}H nmr and 2D ^{1}H nmr (COSY).

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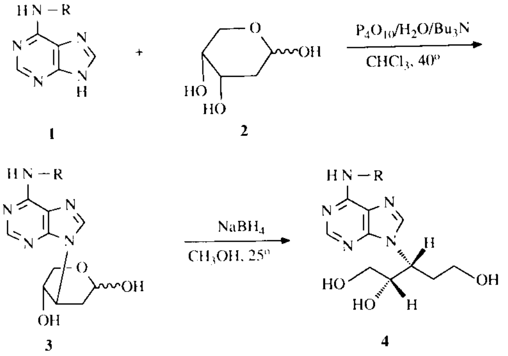
A phosphorus pentoxide reagent composed of tributylammonium phosphate and trimetaphosphate has been useful in coupling of purines to unprotected 2-deoxy-D-ribose (**2**) at C-3 [1,2]. Here we have used a similar method for the synthesis of 3-(6-alkylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentopyranoses **3**. Thus using a reagent prepared from phosphorus pentoxide, water and tributylamine in chloroform, afforded coupling of 2-deoxy-D-ribose (**2**) with the cytokinin active [3,4] compounds N^6-benzyladenine (**1a**) and N^6-(3-methyl-2-buten-1-yl)adenine (**1b**) after 7 days at 40° to give **3a** (44% yield) and **3b** (41% yield), respectively, as precipitates. Although the corresponding *erythro* isomer of **3** was not observed in the precipitate, its formation cannot be excluded in the reaction mixture, the problem being that aqueous workup resulted in fragmentation of the product **3** into the starting purine derivative [1,2]. By reduction of **3a** and **3b** with sodium borohydride in methanol we obtained the corresponding pentitols **4a** (90% yield) and **4b** (85% yield).

Scheme 1



1, 3, 4	R
a	$-CH_2-Ph$
b	$-CH_2-CH=C(CH_3)_2$

The mechanism [2] for the condensation reaction between N^6-acyladenines and 2-deoxy-D-ribose (**2**) in the phosphorus pentoxide reagent is believed to be a Michael type addition reaction to an α,β-unsaturated sugar aldehyde formed *in situ* by ring opening of 2-deoxy-D-ribose (**2**) and subsequent dehydration. The N^6-alkyladenines **1** is believed to add in a similar manner to 4,5-dihydroxy-2-pentenal which is the α,β-unsaturated aldehyde formed by ring opening of 2-deoxy-D-ribose (**2**).

The ^{13}C nmr spectra of the compounds were assigned by comparison with analogous coupling products [1,2]. The ^{1}H nmr spectra were assigned from ^{1}H-^{1}H homonuclear-shift-correlated 2D nmr spectra. Furthermore, the ^{1}H nmr spectrum of compounds **3a** and **3b** showed that H-3' in both compounds had large coupling constants to H-2' and H-4'. This proved the *threo*-configuration of **3a** and **3b** in a $^4C_1$-conformation.

It was believed that the new purine pentitols **4** could show anti-viral activity like the drugs acyclovir [5,6] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG) [7,8]. However, the compounds **3a,b** and **4a,b** did not show any significant activity at 100 μM against Herpes Simplex Virus, type 1 (HSV-1), strain McIntyre, when tested in a continuous cell line from rabbit cornea (SIRC) which was maintained in Eagle's MEM containing 1% fetal calf serum (FCS) and the test compound. The compounds were also devoid of any activity against HIV-1 (strain HTLV-IIIB) in MT-4 cells. MT-4 cells were incubated with virus, washed and added in a proportion of 1:10 to uninfected MT-4 cells which had been preincubated in test compound containing culture medium (RPM 1640 containing 10% FCS) for 2 hours. The MT-4 cells were maintained in culture medium likewise containing the test compound. Expression of HIV in culture medium was quantitated by HIV antigen detection ELISA [9].

EXPERIMENTAL

The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker C 250 FT spectrometer with TMS as internal standard, δ [ppm], J = Hz. Dimethyl sulfoxide-d$_6$ was used as the solvent. Column chromatography: Silica gel (0.040-0.063 mm, Merck). The microanalyses were carried out at NOVO-NORDISK Microanalytical Laboratory A/S, NOVO Allé, DK-2800 Bagsvaerd.

Preparation of the Phosphorus Pentoxide Reagent.

Water (21.14 g, 1.173 moles) was added dropwise with stirring to phosphorus pentoxide (100.0 g, 0.352 mole) in chloroform (400 ml). Chloroform (200 ml) was added and the inhomogeneous mixture was heated on an oil bath at 80° for 30 minutes. The suspension was allowed to cool to room temperature and tributylamine (136.0 g, 0.734 mole) was added under vigorous stirring and the reaction mixture became a clear solution. The solution was cooled to room temperature and chloroform was added to a total volume of 1000 ml.

3-(6-Benzylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentopyranose (**3a**).

N^6-Benzyladenine (**1a**) (5.6 g, 25.0 mmoles), phosphorus pentoxide reagent (115 ml) and tributylamine (13.6, g, 75 mmoles) were mixed and stirred at 80° for 1 hour. The mixture was cooled to 40° and 2-deoxy-D-ribose (**2**) (6.7 g, 50.0 mmoles) was added. The reaction mixture was stirred at 40° for 7 days. The precipitate was filtered off and recrystallized from ethanol to give the anomeric mixture of **3a** as white crystals, α:β ratio = 5:1, yield 3.72 g (44%), mp 233-234°; ^{1}H nmr: predominant anomer, δ 1.96 (dd, 1H, 2'-H$_e$, J = 12 and 4 Hz), 2.48 (td, 1H, 2'-H$_a$, J = 13 and 3 Hz), 3.58-3.77 (m, 2H, 5'-H), 4.17 (td, 1H, 4'-H, J = 10 and 6 Hz), 4.61-4.82 (m, 3H, 3'-H and CH$_2$), 5.16 (br s, 1H, 4'-OH), 5.26 (s, 1H, 1'-H), 6.41 (br s, 1H, 1'-OH), 7.17-7.37 (m, 5H, Ar-H), 8.18 (s, 1H, 8-H), 8.25 (s, 2H, NH and 2-H); ^{13}C nmr: predominant anomer, δ 35.92 (C-2'), 42.89 (CH$_2$), 54.46 (C-3'), 62.44 (C-5'), 66.98 (C-4'), 89.86 (C-1'), 126.42, 127.04 and 128.03 (Ar), 140.16 and 140.28 (C-8 and Ar), 151.73 (C-2), 154.34 (C-6); ^{13}C nmr: selected data for the β-anomer, δ 37.80 (C-2'), 57.40 (C-3'), 66.40 (C-4'), 67.20 (C-5'), 94.63 (C-1').

Anal. Calcd. for $C_{17}H_{19}N_5O_3$ (341.37): C, 59.81; H, 5.61; N, 20.52. Found: C, 59.58; H, 5.71; N, 20.21.

2,3-Dideoxy-3-(6-(3-methyl-2-buten-1-ylamino)purin-9-yl)-D-*threo*-pentopyranose (**3b**).

In a method similar to that described for **3a**, *N*^{6}-(3-methyl-2-buten-1-yl)adenine (**1b**) (0.9 g, 4.43 mmoles) was reacted with 2-deoxy-D-ribose (**2**) (1.19 g, 8.86 mmoles). The precipitate was isolated, washed with chloroform (100 ml) and recrystallized from 96% ethanol to give the anomeric mixture of **3b** as white crystals, α:β ratio = 5:2, yield 0.58 g (41%), mp 221-223°; ^{1}H nmr: predominant anomer, δ 1.70 (s, 3H, CH$_3$), 1.91 (s, 3H, CH$_3$), 1.95 (dd, 1H, 2'-H$_e$, J = 13 and 4 Hz), 2.47 (td, 1H, 2'-H$_a$, J = 13 and 3 Hz), 3.6 (dd, 1H, 5'-H$_e$, J = 11 and 6 Hz), 3.72 (t, 1H, 5'-H$_a$, J = 11 Hz), 4.10-4.20 (m, 3H, 4'-H and CH$_2$), 4.63 (ddd, 1H, 3'-H, J = 13, 11 and 4 Hz), 5.25 (s, 1H, 1'-H), 5.30 (t, 1H, CH, J = 7 Hz), 7.63 (br s, 1H, NH), 8.19 (s, 2H, 2-H and 8-H); ^{13}C nmr: predominant anomer, δ 17.69 (CH$_3$), 25.23 (CH$_3$), 35.93 (C-2'), 37.66 (CH$_2$), 54.37 (C-3'), 62.44 (C-5'), 66.37 (C-4'), 89.84 (C-1'), 119.47 (C-5), 122.25 (CH), 132.89 (=C<), 140.02 (C-8), 151.72 (C-2), 154.20 (C-6); selected data for β-anomer, δ 37.66 (C-2'), 57.31 (C-3'), 66.96 (C-4'), 67.13 (C-5'), 94.51 (C-1').

Anal. Calcd. for $C_{15}H_{21}N_5O_3$ (319.37): C, 56.41; H, 6.63; N, 21.93. Found: C, 56.36; H, 6.55; N, 21.88.

3-(6-Benzylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentitol (**4a**).

A mixture of 3-(6-benzylaminopurin-9-yl)-2,3-dideoxy-D-*threo*-pentopyranose (**3a**) (1.71 g, 5.0 mmoles) and sodium borohydride (1.89 g, 50.0 mmoles) was added in portions of 0.25 g to methanol (120 ml) during 30 minutes at room temperature. After stirring for 20 minutes, analytical tlc with methylene chloride/methanol (9:1) showed no further reaction. The clear solution was neutralized with concentrated hydrochloric acid and the white precipitate of sodium chloride was filtered off and the filtrate was evaporated *in vacuo*. The crude product was suspended in absolute ethanol and the insoluble sodium chloride was filtered off. After evaporation *in vacuo* boric acid was removed by coevaporation with methanol (3 x 100 ml) to give **4a** as a white foam, yield 1.54 g (90%); ^{1}H nmr: δ 2.19 (m, 2H, 2'-H), 3.21 (m, 2H, 5'-H), 3.36 (q, 2H, 1'-H, J = 5 Hz), 3.97 (m, 1H, 4'-H), 4.78 (br s, 2H, CH$_2$), 4.84 (q, 1H, 3'-H, J = 5 Hz), 7.22-7.43 (m, 5H, Ar-H), 8.18 (s, 1H, 8-H), 8.26 (s, 1H, 2-H), 8.51 (t, 1H, NH, J = 6 Hz); ^{13}C nmr: δ 33.84 (C-2'), 43.11 (CH$_2$), 53.36 (C-3'), 57.27 (C-1'), 62.92 (C-5'), 71.78 (C-4'), 118.45 (C-5), 126.61, 127.19 and 128.16 (Ar), 139.92 (C-8), 141.03 (Ar), 149.29 (C-4), 151.54 (C-2), 153.97 (C-6).

Anal. Calcd. for $C_{17}H_{21}N_5O_3$ x 0.75 H_2O (356.90): C, 57.21; H, 6.35; N, 19.62. Found: C, 57.33; H, 6.26; N, 19.41.

2,3-Dideoxy-3-[6-(3-methyl-2-buten-1-ylamino)purin-9-yl]-D-*threo*-pentitol (**4b**).

A solution of **3b** (0.44 g, 1.37 mmoles) in methanol (40 ml) was stirred at room temperature and sodium borohydride (0.52 g, 13.7 mmoles) was slowly added during 30 minutes. After 2 hours concentrated hydrochloric acid was added to the clear solution until *p*H = 6, the white precipitate of sodium chloride was filtered off and the filtrate was evaporated *in vacuo*. The crude product was suspended in absolute ethanol and the insoluble sodium chloride was filtered off. After evaporation *in vacuo* the boric acid was removed by coevaporation with methanol (3 x 100 ml) and the crude product was purified by silica column chromatography with methylene chloride/methanol (9:1) as eluent to give **4b** as white crystals, yield 0.37 g (85%), mp 141-143°; ^{1}H nmr: δ 1.67 (s, 3H, CH$_3$), 1.71 (s, 3H, CH$_3$), 2.01-2.27 (m, 2H, 2'-H), 3.14 (m, 2H, 5'-H), 3.29 (m, 2H, 1'-H), 3.90 (m, 1H, 4'-H), 4.13 (m, 2H, CH$_2$), 4.46 (t, 1H, 1'-OH, J = 5 Hz), 4.60 (t, 1H, 5'-OH, J = 6 Hz), 4.77 (m, 1H, 3'-H), 5.23 (d, 1H, 4'-OH, J = 6 Hz), 5.32 (t, 1H, CH, J = 7 Hz), 7.65 (br s, 1H, NH), 8.03 (s, 1H, 8-H), 8.17 (s, 1H, 2-H); ^{13}C nmr: δ 17.64 (CH$_3$), 21.87 (CH$_3$), 33.76 (C-2'), 37.90 (CH$_2$), 53.08 (C-3'), 57.19 (C-1'), 62.80 (C-5'), 71.73 (C-4'), 118.51 (C-5), 122.13 (CH), 132.92 (=C<), 140.41 (C-8), 149.22 (C-4), 151.75 (C-2), 154.15 (C-6).

Anal. Calcd. for $C_{15}H_{23}N_5O_3$ x 1.0 H_2O (339.39): C, 53.08; H, 7.42; N, 20.63. Found: C, 53.10; H, 7.28; N, 20.49.

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