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THE EFFECT OF THE C-6 SUBSTITUENT ON THE REGIOSELECTIVITY OF N-ALKYLATION OF 2-AMINOPURINES

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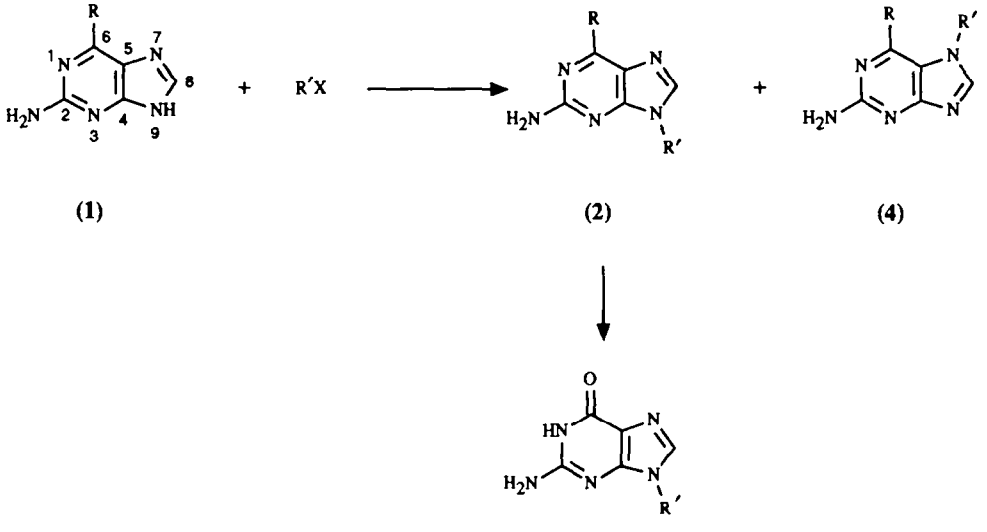
Abstract: A series of eleven 6-substituted 2-aminopurines was N-alkylated with 2-acetoxymethyl-4-iodobutyl acetate. The ratio of N-9 to N-7 alkylated products varied from 1.8:1 (6-methoxy) to 25:1 (6-isopropyl). The log of this ratio was found to correlate with a combination of resonance and lipophilicity parameters of the C-6 substituent of the purine.

Introduction

A commonly employed route to pharmaceutically important acyclic guanosine analogues involves the alkylation of a 2-amino-6-substituted purine (**1**) (often 2-amino-6-chloro-), and subsequent transformation of the resulting N-9 alkylated purine (**2**) into the corresponding guanine (**3**). A drawback to this method, however, is that the alkylation is rarely regiospecific, and although the desired N-9 isomer (**2**) is almost always the major product, the N-7 isomer (**4**) is usually present to a significant extent[1] (Scheme 1).



(**1**) (**2**) (**4**)

(**3**)

Scheme 1

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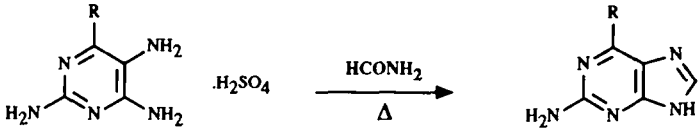
Factors known to influence the observed ratio of N-9:N-7 alkylated products include the identity of the purine and alkylating agent, the base and solvent employed, and the reaction temperature[2]. Several studies have reported ways of maximising N-9 alkylation, but few are of a systematic nature, and most refer to the design of a specific oxygenated C-6 purine substituent, subsequently transformed to hydroxyl[2a,3].

In order to assess the contribution of the C-6 purine substituent, we have determined the N-9:N-7 alkylation ratio of a series of eleven 6-substituted 2-aminopurines. The alkylating agent used in this series of experiments, 2-acetoxymethyl-4-iodobutyl acetate (**8**) was chosen because of its potential use in the preparation of the novel antiviral agent penciclovir (BRL 39123) (**3**)[4] [R′= $(CH_2)_2CH(CH_2OH)_2$] and its prodrug famciclovir (BRL 42810) (**9c**)[5], both of which are currently undergoing clinical trials for efficacy against herpesvirus infections.

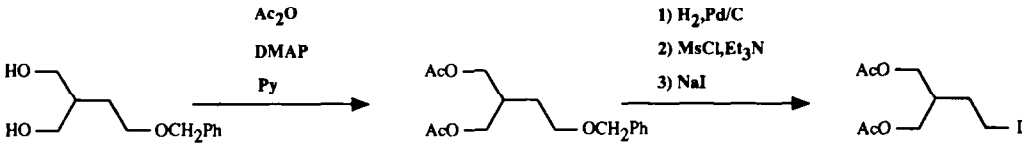
Results and Discussion

The purines used in this study were either known or available in one step from known pyrimidines (**5**)[6] (Scheme 2), and the 6-substituents were illustrative of a range of electronic and steric substituent parameters. The alkylating agent (**8**) was prepared in a straightforward manner from the diol (**6**)[7] (Scheme 3).



(5 i,k) **(1 i,k)**

Scheme 2

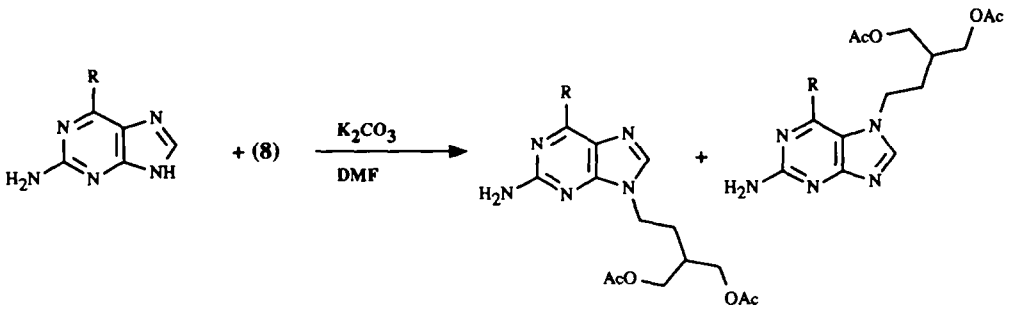


(6) **(7)** **(8)**

Scheme 3

Under the standardised conditions employed, individual purines (**1a-k**) and the iodide (**8**) (5% excess) were stirred together for 18 hours at ambient temperature in N,N-dimethylformamide (DMF) in the presence of excess potassium carbonate. T.l.c. indicated the formation of two products, but where a small amount of starting purine was still present no attempt was made to force the reaction to completion by addition of more iodide, prolonged stirring or heating. Work-up involved solvent evaporation and silica gel column chromatographic separation of the products. Fractions containing the separated isomers (**9a-k**) and (**10a-k**) were evaporated and weighed, and their purity checked by NMR and chemical analysis. The ratio was calculated from the isolated weights and in all cases was consistent with the less accurate ratio obtained by integration of the H-8 proton

signals in the ^1H NMR spectra of the crude product.



(1 a-k)

	R
a	OCH_3
b	F
c	H
d	SCH_3

(9 a-k)

	R
e	Cl
f	CH_3
g	Br
h	I

(10 a-k)

	R
i	CH_2CH_3
j	CF_3
k	$CH(CH_3)_2$

Scheme 4

The products were characterised principally by their ^1H and ^{13}C NMR spectra, which were in agreement with published data for N-9 and N-7 alkylated 2-aminopurines[1]. In particular, in the ^1H NMR spectrum the H-8 and CH_2N signals appear at higher field and the NH_2 signal at lower field for the N-9 compounds (**9a-k**) as compared with the N-7 isomers (**10a-k**). In the ^{13}C NMR spectrum the C-4, C-8 and C-1′ signals appear at higher field and the C-5 and C-6 signals at lower field for the N-9 compounds as compared to the N-7 isomers. In addition, the N-7 compounds are consistently the more polar (silica gel t.l.c.); and in the U.V. spectra the longest wavelength absorption maximum exhibits a near-constant bathochromic shift of 11.5-13.5 nm., with respect to the N-9 isomers.

The observed N-9:N-7 alkylation ratios varied from 1.8:1 for the 6-methoxy compounds (**9a,10a**) to 25:1 for the 6-isopropyl (**9k,10k**)(Table). Attempts to find a simple correlation between the observed ratios and either the steric bulk or the electronic effect of the 6-substituent on the purine ring were unsuccessful. However, multiple regression analysis of the logarithm of the ratios with a standard set of aromatic substituent parameters[8] indicated a significant dependence on the Swain and Lupton resonance parameter $\mathfrak{R}$, and the partition coefficient (lipophilicity) parameter π (Figure).

Table

	R	$\mathfrak{R}$	π	Observed N-9:N-7
a	OCH_3	-0.51	-0.02	1.8
b	F	-0.34	0.14	3.4
c	H	0.00	0.00	4.0
d	SCH_3	-0.18	0.61	3.8
e	Cl	-0.15	0.71	5.5
f	CH_3	-0.13	0.56	9.0
g	Br	-0.17	0.86	7.3
h	I	-0.19	1.12	9.0
i	CH_2CH_3	-0.10	1.02	16
j	CF_3	0.19	0.88	21
k	$CH(CH_3)_2$	-0.10	1.53	25

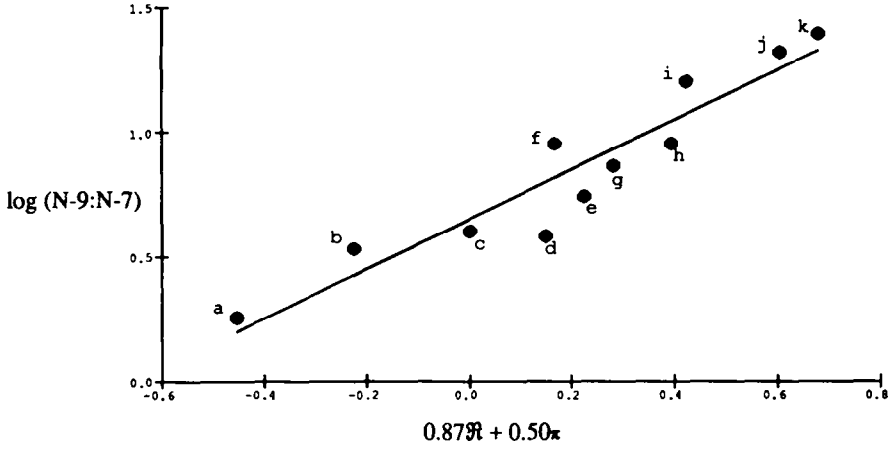


Figure. Plot of the log of the N-9:N-7 alkylation ratio against a combination of the resonance ($\mathfrak{R}$) and lipophilicity (π) parameters of the purine 6-substituents; experimentally determined ratios are shown by the circles and the line is given by the equation below.

$$\log (\text{ratio}) = 0.87\mathfrak{R} + 0.50\pi + 0.65 \quad (r = 0.94)$$

In this case, the resonance parameter $\mathfrak{R}$ is a measure of the effect of the 6-substituent on the electronic distribution in the purine anion and thus, perhaps, the innate relative nucleophilicities of the N-9 and N-7 positions. The π parameter clearly contains a steric component, and may reflect the effect of the 6-substituent on the microenvironment of the transition state for 7-alkylation. Thus small polar groups (low π) contribute to the electrostatic stabilisation of the charged transition state at the 7-position whereas large non-polar groups (high π) destabilise this transition state both sterically and by lack of electrostatic interaction.

Purines which fall outside the scope of the correlation include those which either may exist in the tautomeric 6-keto form, or may be susceptible to 6-substituent alkylation (e.g. guanine, 6-thioguanine and 2,6-diaminopurine). In addition, a lower ratio is observed than would be expected from the correlation equation above for purines with large, grossly non-spherical 6-substituents such as 6-O-benzyl and 6-S-benzyl (observed ratios of 2.0:1 and 8.5:1 respectively). Presumably this is because the bulk of the substituent can be orientated in a direction away from N-7, a factor which cannot be expressed in the π parameter.

The correlation may be used predictively, in particular it would suggest that alkylation of 2-amino-6-methylsulphinylpurine would give an alkylation ratio lower than any reported here and that similar alkylation of 2-amino-6-trimethylsilylpurine would give a much higher ratio than those described.

In conclusion, we believe that this is the first study of its type to include such a diverse set of 6-substituents, and hopefully heralds a better understanding of the factors which can lead to regioselectivity in the N-alkylation of 2-aminopurines under basic conditions.

Acknowledgements

The experimental assistance of B.M. Choudary and S. Moore is gratefully acknowledged.

Experimental

All ^{1}H NMR spectra were recorded on a JEOL GX-270 spectrometer at 270MHz in hexadeuteriodimethylsulphoxide solution. Signals are quoted as δppm downfield from internal tetramethylsilane. All ^{13}C NMR spectra were recorded on the same instrument at 67.8MHz in hexadeuteriodimethylsulphoxide solution. Signals are quoted as ppm downfield from internal tetramethylsilane. Where ^{13}C NMR assignments were ambiguous, these were resolved by recourse to proton-coupled spectra or NOE experiments. U.V. spectra were obtained on a KONTRON 810 instrument in ethanol solution. Absorbance wavelength maxima are quoted in nanometres.

2-Aminopurines (1a-k).

1c and **1e** are available commercially.

The following were prepared by literature methods:-

1a[9a], **1b**[9b], **1d**[9c], **1f**[9d], **1g**[9e], **1h**[9f], **1j**[9g].

The preparations of **1i** and **1k** are recorded below.

2-Amino-6-ethylpurine (1i).

6-Ethyl-2,4,5-triaminopyrimidine sulphate (**5i**) (prepared from a methanol solution of the free base[6] by addition of 1.5 equivalents of 30% sulphuric acid, filtration and drying of the precipitate) (20.1g, 80.1mmol) was dissolved in hot formamide (140ml), and the solution heated under reflux for 20 minutes. The reaction mixture

was cooled, and the formamide evaporated under reduced pressure. The dark green residue was dissolved in hot 3M hydrochloric acid (240ml) with decolorizing carbon treatment, filtered and the yellow filtrate neutralised to pH4 with 0.88 ammonia. After evaporation of the solvent, the residue was purified by column chromatography on silica, eluant dichloromethane - methanol 8:1. Fractions containing the desired product (Rf 0.45 dichloromethane - methanol 5.5:1) were combined and evaporated to give **1i** as a pale yellow oil which crystallized on standing (7.4g, 57%). m.p. 217-219° (water).
^{1}H NMR: 1.28 (t,3H,CH_3), 2.86 (q,2H,CH_2), 6.20 (brs,2H,NH_2), 7.97 (s,1H,H-8), 12.45 (brs,1H,NH). ^{13}C NMR: 12.52 (CH_3), 26.02 (CH_2), 123.75 (C-5), 140.07 (C-8), 154.45 (C-4), 160.36 (C-2), 162.26 (C-6).
U.V. λ_{max} 216 (ϵ 23,000), 241 (6,100), 304 (7,000).
EI-MS. m/e : 163 (M^+), 162 (M^+-H), 135 (M^+-C_2H_4).
Found; C:51.26, H:5.44, N:42.64. $C_7H_9N_5$ requires; C:51.52, H:5.56, N:42.92%.

2-Amino-6-isopropylpurine (1k).

6-Isopropyl-2,4,5-triaminopyrimidine sulphate (**5k**) (prepared from a methanol solution of the free base[6] by addition of 1.5 equivalents of 30% sulphuric acid, filtration and drying of the precipitate) (21.5g, 81.1mmol) was dissolved in hot formamide (150ml), and the solution heated under reflux for 20 minutes. The reaction mixture was cooled, and the formamide evaporated under reduced pressure. Flash column chromatography of the residue on silica, eluant dichloromethane - methanol 9:1 gave a pale solid (40g) which was dissolved in 3M hydrochloric acid (250ml), and the solution heated on a steam bath for 15 minutes. Cooling, neutralisation to pH4 with 0.88 ammonia, and evaporation afforded a residue which was purified by column chromatography on silica, eluant dichloromethane - methanol 12:1. Fractions containing the desired product (Rf 0.35 dichloromethane - methanol 9:1) were combined and evaporated to give **1k** as a pale solid (9.2g, 64%).
m.p. 199-201° (ethyl acetate).
^{1}H NMR: 1.31 (d,6H,2xCH_3), 3.41 (sp,1H,CH), 6.20 (brs,2H,NH_2), 7.98 (s,1H,H-8), 12.54 (brs,1H,NH). ^{13}C NMR: 21.09 (2xCH_3), 31.60 (CH), 123.10 (C-5), 139.98 (C-8), 154.59 (C-4), 160.44 (C-2), 165.63 (C-6).
U.V. λ_{max} 216 (ϵ 20,000), 241 (5,000), 303 (5,900).
EI-MS. m/e : 177 (M^+), 176 (M^+-H), 162 (M^+-CH_3).
Found; C:54.20, H:6.32, N:39.41. $C_8H_{11}N_5$ requires; C:54.22, H:6.26, N:39.52%.

2-Acetoxymethyl-4-benzyloxybutyl acetate (7).

To a stirred solution of 2-(2-benzyloxyethyl)propane-1,3-diol (**6**)[7] (10.0g, 47.6mmol), 4-dimethylaminopyridine (0.55g, 4.5mmol), and pyridine (12.3ml, 0.15mol) in dichloromethane (54ml) at -10°C was added dropwise acetic anhydride (13.2ml, 0.14mol) over 20 minutes. After completion of the addition, the reaction mixture was stirred for a further 1 hour at 0°C, then diluted with dichloromethane (100ml) and washed with 2M hydrochloric acid (2x50ml), saturated sodium bicarbonate solution (50ml), and brine (50ml), dried ($MgSO_4$), and evaporated to give **7** as a light yellow oil (13.2g, 94%). b.p. 160-165°/ 0.5mm.
^{1}H NMR: 1.62 (q,2H,CHC$\underline{H}_2$), 2.00 (s,6H,2xCH_3), 2.15 (m,1H,CH), 3.51 (t,2H,$CH_2C\underline{H}_2O$), 4.03 (m,4H,2xCH_2O), 4.46 (s,2H,O$C\underline{H}_2$Ph), 7.33 (m,5H,Ph). ^{13}C NMR: 20.31 (2xCH_3), 27.93 (CH$C\underline{H}_2$), 34.40 (CH), 63.73 (2xCH_2O), 67.22 ($CH_2C\underline{H}_2O$), 71.99 ($C\underline{H}_2$Ph), 127.22, 127.30, 128.09, 138.54 (Ph), 170.13 (2xCO).
Found; C:65.07, H:7.76. $C_{16}H_{22}O_5$ requires; C:65.29, H:7.53%.

2-Acetoxymethyl-4-iodobutyl acetate (8).

A solution of **7** (15.5g, 52.7mmol) in ethanol (200ml) was hydrogenated for 18 hours at ambient temperature over 10% palladium - carbon (2g). Filtration and evaporation afforded the corresponding alcohol (10.2g) as a colourless oil.

To a stirred solution of the above oil and triethylamine (10.4ml, 74.8mmol) in dichloromethane (100ml) cooled to -5°C was added a solution of methanesulphonyl chloride (4.6ml, 59.5mmol) in dichloromethane (30ml) dropwise over 30 minutes. After completion of the addition, the reaction mixture was stirred for a further 1 hour at -5°C, then washed with 2M hydrochloric acid (2x100ml), saturated sodium bicarbonate solution (100ml), and brine (100ml), dried ($MgSO_4$) and evaporated to afford the corresponding methanesulphonate (14.1g) as a pale yellow oil.

A mixture of the above oil and sodium iodide (15.0g, 0.1mol) was stirred under reflux for 2 hours in acetone (150ml), then cooled, poured into water (300ml), and extracted with diethyl ether (3x150ml). The combined ether extracts were washed with 10% sodium metabisulphite solution (250ml), and brine (250ml), dried ($MgSO_4$) and evaporated to give a pale oil. This was purified by flash column chromatography on silica, eluant hexane - diethyl ether 3:2 affording **8** as a colourless oil (13.1g, 79% from **7**).
^{1}H NMR: 1.88 (q,2H,CH_2), 2.02 (s,6H,2xCH_3), 2.10 (m,1H,CH), 3.33 (t,2H,CH_2I), 4.02 (d,4H,2xCH_2O). ^{13}C NMR: 5.01 (CH_2I), 20.48 (2xCH_3), 32.04 (CH_2), 37.87 (CH), 62.86 (2xCH_2O), 170.02 (2xCO).
EI-MS. m/e : 314 (M^+), 254 (M^+-HOAc), 211 (M^+-HOAc,Ac), 187 (M^+-I).
Found; C:34.56, H:4.99. $C_9H_{15}O_4I$ requires; C:34.42, H:4.81%.

General Procedure for the N-Alkylation of 2-Aminopurines (1a-k).

A mixture of the purine (10.0mmol), 2-acetoxymethyl-4-iodobutyl acetate (**8**) (3.30g, 10.5mmol), and anhydrous potassium carbonate (2.07g, 15.0mmol) was stirred for 18 hours at ambient temperature in dry DMF (40ml) under an atmosphere of dry nitrogen. The mixture was then filtered to remove insoluble material, which was washed well with DMF. The combined filtrates were evaporated under reduced pressure and the residue purified directly by column chromatography on silica gel (150g), eluting with various dichloromethane - methanol mixtures. Fractions containing the first-eluting N-9 isomer (**9a-k**), and the second-eluting N-7 isomer (**10a-k**) were separately combined, rigorously evaporated and weighed. The N-9:N-7 alkylated product ratio obtained from the isolated weights was checked by integration of the respective H-8 ^{1}H NMR. signals in the spectrum of the crude residue.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-methoxypurine (9a) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-methoxypurine (10a).
Column eluant dichloromethane - methanol 25:1.
9a, 48%, m.p. 114-115° (dichloromethane - diethyl ether).
^{1}H NMR: 1.83-2.05 (m,3H,$CHCH_2$), 2.00 (s,6H,2x$COCH_3$), 3.96 (s,3H,OCH_3), 4.02 (d,4H,2xCH_2O), 4.11 (t,2H,CH_2N), 6.39 (brs,2H,NH_2), 7.89 (s,1H,H-8). ^{13}C NMR: 20.57 (2xCH_3), 28.00 (CH_2), 34.45 (CH), 40.50 (CH_2N), 53.12 (OCH_3), 63.46 (2xCH_2O), 113.86 (C-5), 139.69 (C-8), 154.10 (C-4), 159.78 (C-2), 160.66 (C-6), 170.38 (2xCO).
U.V. λ_{max} 213.5 (ϵ 23,800), 250 (8,800), 282.5 (9,400).
Found; C:51.33, H:6.02, N:20.09. $C_{15}H_{21}N_5O_5$ requires; C:51.28, H:6.02, N:19.93%.

10a, 26%, m.p. 133-134° (dichloromethane - diethyl ether).
^{1}H NMR: 1.83 (q,2H,CH_2), 1.91 (m,1H,CH), 2.00 (s,6H,2x$COCH_3$), 3.97 (s,3H,OCH_3), 4.02 (d,4H,2xCH_2O), 4.24 (t,2H,CH_2N), 6.15 (brs,2H,NH_2), 8.11 (s,1H,H-8). ^{13}C NMR: 20.55 (2xCH_3), 29.53 (CH_2), 34.36 (CH), 44.36 (CH_2N), 53.33 (OCH_3), 63.58 (2xCH_2O), 105.62 (C-5), 145.29 (C-8), 156.93 (C-6), 159.70 (C-2), 163.91 (C-4), 170.38 (2xCO).
U.V. λ_{max} 213.5 (ϵ 23,100), 235sh (9,900), 295 (6,000).
Found; C:51.28, H:6.16, N:19.80. $C_{15}H_{21}N_5O_5$ requires; C:51.28, H:6.02, N:19.93%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-fluoropurine (9b) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-fluoropurine (10b).
Column eluant dichloromethane - methanol 30:1, then 20:1.
9b, 65%, m.p. 131-132° (ethyl acetate - diethyl ether).
^{1}H NMR: 1.83-2.06 (m,3H,$CHCH_2$), 1.99 (s,6H,2x$COCH_3$), 4.02 (d,4H,2xCH_2O), 4.15 (t,2H,CH_2N), 6.88 (brs,2H,NH_2), 8.13 (s,1H,H-8). ^{13}C NMR: 20.58 (2xCH_3), 27.78 (CH_2), 34.45 (CH), 40.99 (CH_2N), 63.46 (2xCH_2O), 111.50 (d,J=30Hz,C-5), 142.84 (C-8), 157.61 (d,J=12Hz,C-4), 159.24 (d,J=250Hz,C-6), 159.73 (d,J=18Hz,C-2), 170.39 (2xCO).
U.V. λ_{max} 217 (ϵ 28,200), 244 (8,200), 289.5 (7,200).
Found; C:49.47, H:5.30, N:20.58. $C_{14}H_{18}N_5O_4F$ requires; C:49.56, H:5.35, N:20.64%.
10b, 19%, m.p. 164-165° (ethyl acetate).
^{1}H NMR: 1.83-1.99 (m,3H,$CHCH_2$), 1.99 (s,6H,2x$COCH_3$), 4.02 (d,4H,2xCH_2O), 4.27 (t,2H,CH_2N), 6.60 (brs,2H,NH_2), 8.35 (s,1H,H-8). ^{13}C NMR: 20.48 (2xCH_3), 28.74(CH_2), 34.31 (CH), 44.42 (CH_2N), 63.44 (2xCH_2O), 103.29 (d,J=24Hz,C-5), 148.22 (d,J=3Hz,C-8), 155.26 (d,J=244Hz,C-6), 159.49 (d,J=15Hz,C-2), 167.59 (d,J=6Hz,C-4), 170.26 (2xCO).
U.V. λ_{max} 219 (ϵ 27,200), 303 (4,500).
Found; C:49.66, H:5.42, N:20.76. $C_{14}H_{18}N_5O_4F$ requires; C:49.56, H:5.35, N:20.64%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-aminopurine (9c) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-aminopurine (10c).
Column eluant dichloromethane - methanol 15:1.
9c,[5] 59%, m.p. 102-103° (butanol).
^{1}H NMR: 1.80-2.05 (m,3H,$CHCH_2$), 2.00 (s,6H,2x$COCH_3$), 4.03 (d,4H,2xCH_2O), 4.14 (t,2H,CH_2N), 6.45 (brs,2H,NH_2), 8.09 (s,1H,H-8), 8.57 (s,1H,H-6). ^{13}C NMR: 20.57 (2xCH_3), 27.89 (CH_2), 34.52 (CH), 40.28 (CH_2N), 63.51 (2xCH_2O), 126.98 (C-5), 142.70 (C-8), 149.05 (C-6), 153.02 (C-4), 160.51 (C-2), 170.40 (2xCO).
U.V. λ_{max} 222.5 (ϵ 27,200), 246 (5,000), 310 (7,200).
Found; C:52.19, H:6.00, N:21.75. $C_{14}H_{19}N_5O_4$ requires; C:52.33, H:5.96, N:21.79%.
10c, 15%, m.p. 168-169° (ethyl acetate).
^{1}H NMR: 1.88 (m,1H,CH), 2.00 (s,6H,2x$COCH_3$), 2.02 (q,2H,CH_2), 4.03 (d,4H,2xCH_2O), 4.30 (t,2H,CH_2N), 6.20 (brs,2H,NH_2), 8.32 (s,1H,H-8), 8.73 (s,1H,H-6). ^{13}C NMR: 20.47 (2xCH_3), 28.15 (CH_2), 34.48 (CH), 42.87 (CH_2N), 63.43 (2xCH_2O), 118.68 (C-5), 141.75 (C-6), 147.41 (C-8), 160.75 (C-2), 162.34 (C-4), 170.24 (2xCO).
U.V. λ_{max} 219 (ϵ 23,200), 255 (4,000), 323 (5,200).

Found; C:52.32, H:5.94, N:21.72. $C_{14}H_{19}N_5O_4$ requires; C:52.33, H:5.96, N:21.79%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-methylthiopurine (9d) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-methylthiopurine (10d).
Column eluant dichloromethane - methanol 30:1, then 25:1.
9d, 64%, m.p. 80-83° (ethyl acetate - diethyl ether).
^{1}H NMR: 1.80-2.00 (m,3H,$CHCH_2$), 1.99 (s,6H,2x$COCH_3$), 2.57 (s,3H,SCH_3), 4.01 (d,4H,2xCH_2O), 4.10 (t,2H,CH_2N), 6.46 (brs,2H,NH_2), 7.96 (s,1H,H-8). ^{13}C NMR: 10.76 (SCH_3), 20.58 (2xCH_3), 27.93 (CH_2), 34.43 (CH), 40.42 (CH_2N), 63.46 (2xCH_2O), 124.23 (C-5), 140.51 (C-8), 150.69 (C-4), 159.55 (C-2), 159.77 (C-6), 170.37 (2xCO).
U.V. λ_{max} 222.5 (ϵ 21,200), 245.5 (14,500), 255sh (10,800), 310.5 (11,900).
Found; C:49.28, H:5.77, N:18.84. $C_{15}H_{21}N_5O_4S$ requires; C:49.03, H:5.76, N:19.06%.
10d, 17%, m.p. 146-149° (ethyl acetate).
^{1}H NMR: 1.82-2.06 (m,3H,$CHCH_2$), 2.00 (s,6H,2x$COCH_3$), 2.62 (s,3H,SCH_3), 4.04 (d,4H,2xCH_2O), 4.34 (t,2H,CH_2N), 6.23 (brs,2H,NH_2), 8.18 (s,1H,H-8). ^{13}C NMR: 11.67 (SCH_3), 20.53 (2xCH_3), 30.47 (CH_2), 34.54 (CH), 44.63 (CH_2N), 63.51 (2xCH_2O), 116.14 (C-5), 146.90 (C-8), 152.27 (C-6), 159.66 (C-2), 160.95 (C-4), 170.27 (2xCO).
U.V. λ_{max} 217.5 (ϵ 19,000), 225sh (16,900), 241sh (11,800), 255sh (8,300), 322 (8,900).
Found; C:49.09, H:5.83, N:18.62. $C_{15}H_{21}N_5O_4S$ requires; C:49.03, H:5.76, N:19.06%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-chloropurine (9e) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-chloropurine (10e).
Column eluant dichloromethane - methanol 25:1.
9e, 75%, m.p. 134-136° (ethyl acetate - diethyl ether).
^{1}H NMR: 1.80-2.05 (m,3H,$CHCH_2$), 2.00 (s,6H,2x$COCH_3$), 4.03 (d,4H,2xCH_2O), 4.15 (t,2H,CH_2N), 6.87 (brs,2H,NH_2), 8.16 (s,1H,H-8). ^{13}C NMR: 20.47 (2xCH_3), 27.75 (CH_2), 34.45 (CH), 40.88 (CH_2N), 63.43 (2xCH_2O), 123.43 (C-5), 143.07 (C-8), 149.34 (C-6), 154.02 (C-4), 159.68 (C-2), 170.27 (2xCO).
U.V. λ_{max} 223.5 (ϵ 27,600), 248.5 (5,800), 310 (7,700).
Found; C:47.14, H:4.97, N:19.69. $C_{14}H_{18}N_5O_4Cl$ requires; C:47.26, H:5.10, N:19.68%.
10e, 15%, m.p. 159-161° (dec). (butanol).
^{1}H NMR: 1.60-2.10 (m,3H,$CHCH_2$), 2.00 (s,6H,2x$COCH_3$), 4.00 (d,4H,2xCH_2O), 4.34 (m,2H,CH_2N), 6.56 (brs,2H,NH_2), 8.33 (s,1H,H-8). ^{13}C NMR: 20.41 (2xCH_3), 29.80 (CH_2), 34.51 (CH), 44.06 (CH_2N), 63.46 (2xCH_2O), 114.65 (C-5), 141.97 (C-6), 149.28 (C-8), 159.81 (C-2), 164.24 (C-4), 170.12 (2xCO).
U.V. λ_{max} 222.5 (ϵ 23,600), 253.5sh (3,700), 323 (5,400).
Found; C:47.31, H:5.17, N:19.88. $C_{14}H_{18}N_5O_4Cl$ requires; C:47.26, H:5.10, N:19.68%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-methylpurine (9f) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-methylpurine (10f).
Column eluant dichloromethane - methanol 30:1, then 15:1.
9f, 80%, m.p. 71-73°(diethyl ether).
^{1}H NMR: 1.84-1.96 (m,3H,$CHCH_2$), 2.02 (s,6H,2x$COCH_3$), 2.50 (s,3H,CH_3-6), 4.05 (d,4H,2xCH_2O), 4.15

(t,2H,CH_2N), 6.38 (brs,2H,NH_2), 8.04 (s,1H,H-8). ^{13}C NMR: 18.83 (CH_3-6), 20.57 (2xCH_3), 27.98 (CH_2), 34.52 (CH), 40.37 (CH_2N), 63.52 (2xCH_2O), 125.86 (C-5), 141.32 (C-8), 152.42 (C-4), 158.67 (C-6), 160.13 (C-2), 170.45 (2xCO).

U.V. λ_{max} 221.5 (ϵ 25,500), 246.5 (5,300), 304 (7,600).

Found; C:51.50, H:6.59, N:20.13. $C_{15}H_{21}N_5O_4.\frac{1}{2}H_2O$ requires; C:51.64, H:6.50, N:20.07%.

10f, 9%, m.p. 175-176° (ethyl acetate).

^1H NMR: 1.81 (m,2H,CH_2), 2.00 (s,6H,2xCOCH$_3$), 2.02 (m,1H,CH), 2.60 (s,3H,CH_3-6), 4.04 (d,4H,2xCH_2O), 4.35 (t,2H,CH_2N), 6.07 (brs,2H,NH_2), 8.21 (s,1H,H-8). ^{13}C NMR: 20.60 (2xCH_3), 20.72 (CH_3-6), 29.90 (CH_2), 34.58 (CH), 44.19 (CH_2N), 63.52 (2xCH_2O), 117.18 (C-5), 147.50 (C-8), 151.44 (C-6), 160.24 (C-2), 162.52 (C-4), 170.37 (2xCO).

U.V. λ_{max} 218.5 (ϵ 22,000), 252.5 (4,000), 317 (5,500).

Found; C:53.55, H:6.36, N:20.81. $C_{15}H_{21}N_5O_4$ requires; C:53.72, H:6.31, 20.88%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-bromopurine (9g) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-bromopurine (10g).

Column eluant dichloromethane - methanol 30:1.

9g, 74%, m.p. 124-126° (ethyl acetate - diethyl ether).

^1H NMR: 1.84-2.02 (m,3H,$CHCH_2$), 2.00 (s,6H,2xCOCH$_3$), 4.03 (d,4H,2xCH_2O), 4.14 (t,2H,CH_2N), 6.90 (brs,2H,NH_2), 8.17 (s,1H,H-8). ^{13}C NMR: 20.57 (2xCH_3), 27.70 (CH_2), 34.43 (CH), 40.89 (CH_2N), 125.88 (C-5), 142.00 (C-6), 142.98 (C-8), 152.80 (C-4), 159.58 (C-2), 170.34 (2xCO).

U.V. λ_{max} 224 (ϵ 28,400), 249 (5,800), 312 (7,900).

Found; C:42.07, H:4.57, N:17.38. $C_{14}H_{18}N_5O_4Br$ requires; C:42.01, H:4.53, N:17.50%.

10g, 10%, m.p. 179-181° (dec). (ethyl acetate).

^1H NMR: 1.83-2.05 (m,3H,$CHCH_2$), 2.00 (s,6H,2xCOCH$_3$), 4.04 (d,4H,2xCH_2O), 4.39 (t,2H,CH_2N), 6.63 (brs,2H,NH_2), 8.42 (s,1H,H-8). ^{13}C NMR: 20.61 (2xCH_3), 30.04 (CH_2), 34.53 (CH), 43.82 (CH_2N), 63.57 (2xCH_2O), 116.80 (C-5), 132.91 (C-6), 149.65 (C-8), 159.77 (C-2), 163.34 (C-4), 170.34 (2xCO).

U.V. λ_{max} 223 (ϵ 24,900), 257 (3,400), 325 (5,700).

Found; C:42.07, H:4.51, N:17.54. $C_{14}H_{18}N_5O_4Br$ requires; C:42.01, H:4.53, N:17.50%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-iodopurine (9h) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-iodopurine (10h).

Column eluant dichloromethane - methanol 50:1, then 30:1.

9h, 80%, m.p. 128-132° (methanol - water).

^1H NMR: 1.83-2.03 (m,3H,$CHCH_2$), 2.00 (s,6H,2xCOCH$_3$), 4.03 (d,4H,2xCH_2O), 4.12 (t,2H,CH_2N), 6.82 (brs,2H,NH_2), 8.14 (s,1H,H-8). ^{13}C NMR: 20.58 (2xCH_3), 27.73 (CH_2), 34.42 (CH), 40.83 (CH_2N), 63.45 (2xCH_2O), 123.07 (C-6), 130.56 (C-5), 142.25 (C-8), 150.08 (C-4), 159.49 (C-2), 170.35 (2xCO).

U.V. λ_{max} 224.5 (ϵ 28,700), 243.5 (8,600), 317.5 (8,300).

Found; C:37.44, H:4.14, N:15.41. $C_{14}H_{18}N_5O_4I$ requires; C:37.59, H:4.05, N:15.65%.

10h, 9%, m.p. 190-194° (dec). (ethyl acetate -diethyl ether).

^1H NMR: 1.86 (q,2H,CH_2), 2.00 (s,6H,2xCOCH$_3$), 2.04 (m,1H,CH), 4.04 (d,4H,2xCH_2O), 4.38 (t,2H,CH_2N), 6.50 (brs,2H,NH_2), 8.39 (s,1H,H-8). ^{13}C NMR: 20.61 (2xCH_3), 30.29 (CH_2), 34.58 (CH), 43.00 (CH_2N), 63.57

(2xCH_2O), 110.60 (C-6), 120.82 (C-5), 149.62 (C-8), 159.60 (C-2), 161.20 (C-4), 170.30 (2xCO).
U.V. λ_{max} 219 (ϵ 24,600), 255 (4,900), 330 (6,000).
Found; C:37.76, H:4.16, N:15.54. $C_{14}H_{18}N_5O_4I$ requires; C:37.59, H:4.05, N;15.65%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-ethylpurine (9i) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-ethylpurine (10i).
Column eluant dichloromethane - methanol 20:1.
9i, 80%, pale oil.
^{1}H NMR: 1.27 (t,3H,$CH_2C\underline{H}_3$), 1.82-2.05 (m,3H,$CHCH_2$), 1.99 (s,6H,2x$COCH_3$), 2.86 (q,2H,$C\underline{H}_2CH_3$), 4.00 (d,4H,2xCH_2O), 4.12 (t,2H,CH_2N), 6.35 (brs,2H,NH_2), 8.01 (s,1H,H-8). ^{13}C NMR: 12.45 ($CH_2\underline{C}H_3$), 20.60 (2xCH_3), 25.75 ($\underline{C}H_2CH_3$), 27.92 (CH_2), 34.47 (CH), 40.28 (CH_2N), 63.47 (2xCH_2O), 124.98 (C-5), 141.25 (C-8), 152.52 (C-4), 160.23 (C-2), 163.10 (C-6), 170.39 (2xCO).
U.V. λ_{max} 222 (ϵ 25,600), 247 (5,500), 305 (7,800).
Found; C:54.82, H:6.77, N:19.91. $C_{16}H_{23}N_5O_4$ requires; C:55.00, H:6.64, N:20.04%.
10i, 6%, m.p. 157-159° (ethyl acetate).
^{1}H NMR: 1.28 (t,3H,$CH_2C\underline{H}_3$), 1.81 (q,2H,CH_2), 2.00 (s,6H,2x$COCH_3$), 2.03 (m,1H,CH), 2.90 (q,2H,$C\underline{H}_2CH_3$), 4.04 (d,4H,2xCH_2O), 4.34 (t,2H,CH_2N), 6.07 (brs,2H,NH_2), 8.22 (s,1H,H-8). ^{13}C NMR: 12.38 ($CH_2\underline{C}H_3$), 20.55 (2xCH_3), 26.22 ($\underline{C}H_2CH_3$), 29.66 (CH_2), 34.58 (CH), 44.42 (CH_2N), 63.49 (2xCH_2O), 116.25 (C-5), 147.68 (C-8), 155.93 (C-6), 160.35 (C-2), 162.81 (C-4), 170.31 (2xCO).
U.V. λ_{max} 217 (ϵ 22,600), 254 (3,900), 317 (5,700).
Found; C:55.10, H:6.75, N:20.08. $C_{16}H_{23}N_5O_4$ requires; C:55.00, H:6.64, N:20.04%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-trifluoromethylpurine (9j) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-trifluoromethylpurine (10j).
Column eluant dichloromethane - methanol 25:1.
9j, 92%, m.p. 94-96° (diethyl ether).
^{1}H NMR: 1.89-2.08 (m,3H,$CHCH_2$), 2.02 (s,6H,2x$COCH_3$), 4.07 (d,4H,2xCH_2O), 4.23 (t,2H,CH_2N), 7.06 (brs,2H,NH_2), 8.35 (s,1H,H-8). ^{13}C NMR: 20.48 (2xCH_3), 27.70 (CH_2), 34.53 (CH), 40.75 (CH_2N), 63.51 (2xCH_2O), 120.90 (q,J=276Hz,CF_3), 122.64 (C-5), 143.98 (q,J=36Hz,C-6), 145.42 (C-8), 156.04 (C-4), 159.95 (C-2), 170.34 (2xCO).
U.V. λ_{max} 226 (ϵ 25,200), 245 (3,700), 326 (6,500).
Found; C:46.53, H:4.75, N:18.26. $C_{15}H_{18}N_5O_4F_3$ requires; C:46.28, H:4.66, N:17.99%.
10j, 4%, m.p. 101-102° (ethyl acetate - diethyl ether).
^{1}H NMR: 1.79-2.07 (m,3H,$CHCH_2$), 2.02 (s,6H,2x$COCH_3$), 4.05 (d,4H,2xCH_2O), 4.32 (t,2H,CH_2N), 6.81 (brs,2H,NH_2), 8.62 (s,1H,H-8). ^{13}C NMR: 20.49 (2xCH_3), 28.85 (CH_2), 34.69 (CH), 45.02 (CH_2N), 63.55 (2xCH_2O), 120.59 (q,J=274Hz,CF_3), 137.91 (q,J=37Hz,C-6), 152.04 (C-8), 159.62 (C-2), 166.32 (C-4), 170.28 (2xCO).
U.V. λ_{max} 225 (ϵ 23,500), 261 (3,700), 339.5 (5,000).
Found; C:46.08, H:4.19, N:18.26. $C_{15}H_{18}N_5O_4F_3$ requires; C:46.28, H:4.66, N:17.99%.

9-(4-Acetoxy-3-acetoxymethylbutyl)-2-amino-6-isopropylpurine (9k) and
7-(4-acetoxy-3-acetoxymethylbutyl)-2-amino-6-isopropylpurine (10k).
Column eluant dichloromethane - methanol 40:1, then 20:1.
9k, 83%, pale oil.
^{1}H NMR: 1.32 (d,6H,2xCHC$\underline{H}_3$), 1.85-2.07 (m,3H,CHCH_2), 2.02 (s,6H,2xCOCH_3), 3.43 (sp,1H,C$\underline{H}$CH_3), 4.06 (d,4H,2xCH_2O), 4.15 (t,2H,CH_2N), 6.36 (brs,2H,NH_2), 8.03 (s,1H,H-8). ^{13}C NMR: 20.58 (2xCH_3), 21.04 (2xCH$\underline{C}$H$_3$), 27.96 (CH_2), 31.37 ($\underline{C}$HCH$_3$), 34.53 (CH), 40.31 (CH_2N), 63.51 (2xCH_2O), 124.26 (C-5), 141.11 (C-8), 152.68 (C-4), 160.29 (C-2), 166.63 (C-6), 170.40 (2xCO).
U.V. λ_{max} 221 (ϵ 25,300), 246 (5,500), 305 (8,200).
Found; C:55.93, H:7.00, N:19.10. $C_{17}H_{25}N_5O_4$ requires; C:56.19, H:6.93, N:19.27%.
10k, 3%, m.p. 125-127° (dichloromethane - diisopropyl ether).
^{1}H NMR: 1.29 (d,6H,2xCHC$\underline{H}_3$), 1.80 (q,2H,CH_2), 1.99 (s,6H,2xCOCH_3), 2.02 (m,1H,CH), 3.30 (sp, 1H,C$\underline{H}$CH_3), 4.04 (d,4H,2xCH_2O), 4.34 (t,2H,CH_2N), 6.03 (brs,2H,NH_2), 8.22 (s,1H,H-8). ^{13}C NMR: 20.54 (2xCH_3), 21.70 (2xCH$\underline{C}$H$_3$), 29.45 (CH_2), 30.49 ($\underline{C}$HCH$_3$), 34.55 (CH), 44.65 (CH_2N), 63.52 (2xCH_2O), 115.17 (C-5), 148.14 (C-8), 159.88 (C-6), 160.46 (C-2), 163.18 (C-4), 170.30 (2xCO).
U.V. λ_{max} 217 (ϵ 23,900), 317 (6,300).
Found; C:56.03, H:7.13, N:19.02. $C_{17}H_{25}N_5O_4$ requires; C:56.19, H:6.93, N:19.27%.

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