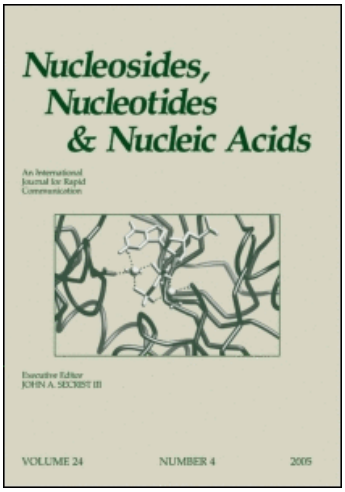

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INFLUENCE OF REMOTE STRUCTURE UPON REGIOSELECTIVITY IN THE N-ALKYLATION OF 2-AMINO-6-CHLOROPURINE : APPLICATION TO THE SYNTHESIS OF PENCICLOVIR

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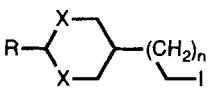
Abstract : Reaction of 2-amino-6-chloropurine with *trans*-2-alkyl-5-iodoethyl-1,3-dioxanes under basic conditions afforded N-9 and N-7 alkylated products, the product ratio obtained being dependent on the size of the 2-alkyl group. This allowed a highly regioselective key step in the synthesis of the anti-herpes agent penciclovir.

Penciclovir **6** is a potent and selective anti-herpes agent[1]. A commonly used route to N-9 substituted guanines such as **6**, many of which have important pharmaceutical properties, involves N-alkylation of 2-amino-6-chloropurine **5** and subsequent hydrolysis. A drawback to this route is that mixtures of isomers are produced[2]. Approaches designed to maximise N-9 regioselectivity include alkylation of appropriately modified guanines, but again mixtures of products are often obtained[3].

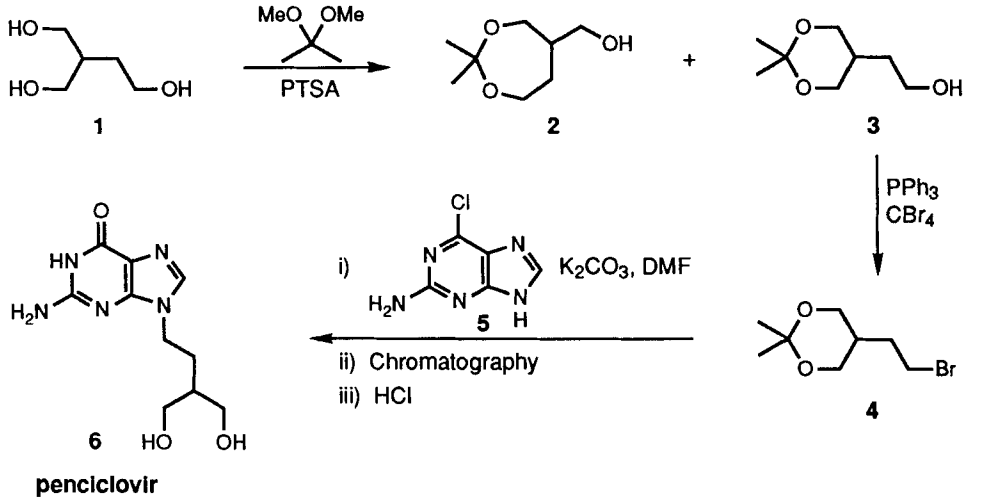
Although the nature of the alkylating agent is known to affect the product ratio obtained from 2-amino-6-chloropurine, few studies of a systematic nature have appeared[2a,4]. We report here the unexpected influence on alkylation ratio of substituent manipulation some six atoms distant from the reacting centre of a series of alkyl iodides, whose general structure is shown in Figure 1.

Penciclovir **6** has been the subject of a concise synthesis, in which the N-9 side chain is introduced with the two hydroxyls protected as an acetonide, (Scheme 1)[5]. We required a robust synthesis, suitable for the preparation of medium to large scale quantities of this molecule, and therefore examined this route. The bromide **4** on reaction with **5** gave a fair N-9:N-7 alkylated product ratio of 5.5:1, but preparation of the alcohol **3** from the readily available triol **1** was complicated by the production of approximately 10% of the 1,3-dioxepane **2**. Brewster reported similar findings when attempting

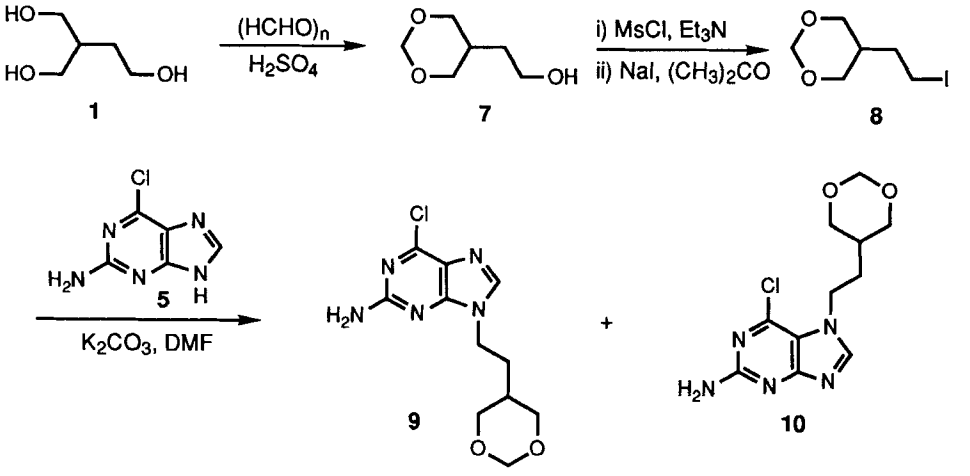


	R	n	X
a	Me	1	O
b	^{i}Pr	1	O
c	^{t}Bu	1	O
d	^{t}Bu	2	O
e	^{t}Bu	1	CH_2

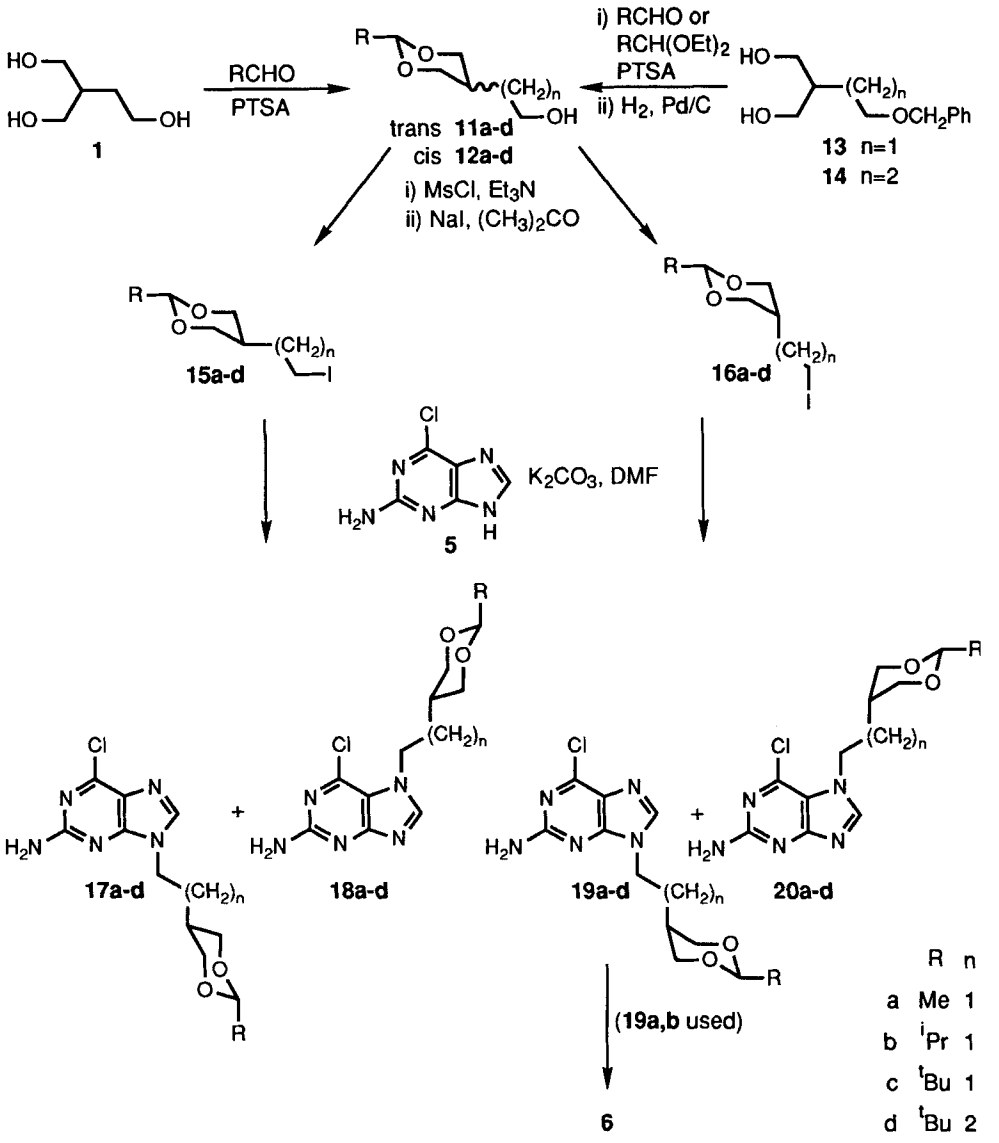
FIGURE 1



Scheme 1



Scheme 2



Scheme 3

formation of the six-membered ring acetonide from a 1-aryl derivative of **1**, and demonstrated that acetalisation rather than ketalisation affords essentially pure 1,3-dioxanes[6]. We hoped therefore to obtain an improved synthesis of **6** *via* an acetal derivative of **1**, avoiding the above problems.

Synthesis of the alkylated purines **9** and **10** *via* alkylation of **5** with the methylene acetal **8** is stereochemically straightforward, and formation of the alcohol **7** was, as

TABLE : The ratios of alkylated products obtained from reaction of **5** with iodides whose general structure is shown in Figure 1. (Determined from weight yields of chromatographically isolated products.)

				N-9:N-7 ratio	
Iodide	R	n	X	*trans* **17:18**	*cis* **19:20**
15/16a	Me	1	O	6.5	4.5
15/16b	^{i}Pr	1	O	10.5	5
15/16c	^{t}Bu	1	O	13.5	5
15/16d	^{t}Bu	2	O	6	6
15/16e	^{t}Bu	1	CH_2	4.5	4

predicted, uncomplicated by dioxepane formation, (Scheme 2). However, the N-9:N-7 product ratio from the alkylation was unacceptably low (**9**:**10**, 2.5:1) and demanded that reaction of **5** with higher acetal derivatives of **8** be examined.

The alcohols **11a-c** and **12a-c** were prepared either directly from the triol **1**[7], or by cyclisation of the monobenzyl ether **13**[8], followed by hydrogenolysis (Scheme 3). All were obtained as mixtures of *cis* and *trans* isomers, the *trans* predominating by 2 to 4:1 by either route. These isomers were separable only with difficulty, but this was of little value in any case as the subsequent iodination procedure caused equilibration.

The iodides **15a-c** and **16a-c** were prepared *via* the intermediate mesylates, readily separated by silica chromatography, and then reacted with 2-amino-6-chloropurine **5** in the presence of excess potassium carbonate under the standardised conditions used with **8**. Two alkylation products were obtained from each reaction. Purine ^{1}H and ^{13}C nmr shifts of these products were consistent with the data obtained by Kjellberg and Johansson for N-9 and N-7 alkylated 2-amino-6-chloropurines[9]. The results of the alkylations are shown in the Table. It is clear that in the *trans* series, increasing the size of R encourages N-9 alkylation at the expense of N-7, whereas in the *cis* series no such tendency is evident.

The methylene acetal **7** and derived compounds have a low energy barrier to dioxan ring inversion, although ^{1}H NMR evidence indicates that, as would be expected, the geometry having the 5-substituent equatorial is a major form in solution, (Figure 2). Eliel demonstrated that in 2,5-dialkyl-1,3-dioxanes the ring is locked in a chair form with the 2-alkyl group in an equatorial position[10]. In this conformation all H-alkyl 1,3-diaxial interactions are avoided, (this is not possible with 2,2-bisalkylated dioxanes, hence the formation of the less rigid dioxepanes from **1**). All measurable ^{1}H coupling constants for

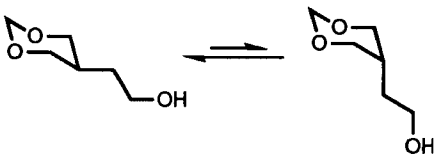


FIGURE 2

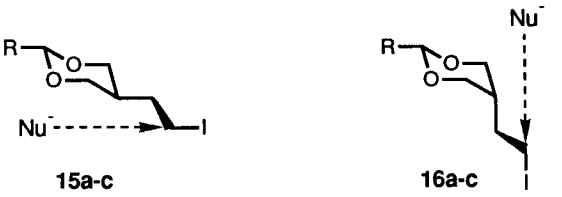
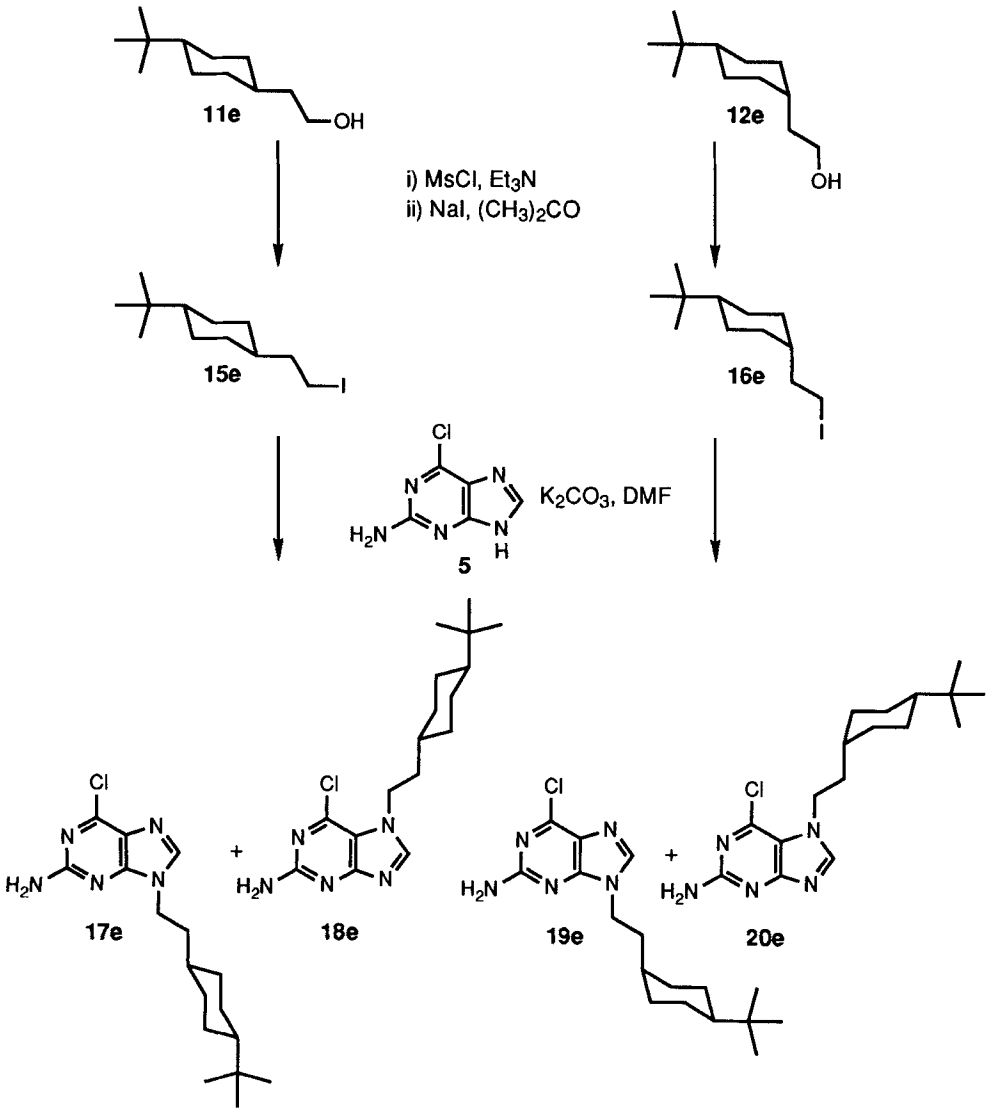


FIGURE 3

the alcohols **11a-d, 12a-d**; iodides **15a-d, 16a-d** and alkylated purines **17-20a-d** were consistent with Eliel's findings, and confirmed this geometry.

Computer modelling studies indicated that in virtually all conformations of **15a-c** and **16a-c** within 2kcal of the energy minimum the iodoethyl group adopts a staggered conformation, hence an incoming nucleophile (such as the purine anion involved here) would be most likely to approach along the axes shown in Figure 3. For the *cis* compounds **16a-c** this pathway is hindered only by the C-5 equatorial hydrogen, but for the *trans* compounds **15a-c** it is proximal to both the C-5 axial hydrogen and the C-2 alkyl group (Figure 3, the hydrogen atoms are omitted for reasons of clarity). It would appear that there is an interaction, probably predominantly steric in nature, between these dioxan ring substituents and the nucleophile, causing a subtle energy differentiation between orientations of the incoming purine anion.

To explore this further, the highly discriminating *tert*-butyl acetal was selected, and the effect of altering the C-5 alkyl iodide chain length examined. Extending the C-5 alkyl chain from iodoethyl to iodopropyl allows greatly enhanced flexibility in this part of the molecule, permitting nucleophilic attack along many vectors. It would be reasonable to predict that any effect on the N-9:N-7 alkylation ratio from the different geometry about the dioxan ring would be minimal. This is indeed the case, the experimentally observed ratios for alkylation of 2-amino-6-chloropurine **5** with the propyl iodides **15d** and **16d** (prepared from the benzyl ether **14**[11]) were near identical, contrasting strongly with the corresponding ethyl iodides **15c** and **16c**. On the other hand, reducing the C-5 alkyl chain



Scheme 4

to iodomethyl results in very rigid molecules, and alkylation reactions were very sluggish due to the severe steric congestion, preventing meaningful comparisons.

Finally, we examined the effect of replacing the two oxygen atoms with methylene units. Ring conformational rigidity is less well defined here, but again NMR evidence was consistent with the cyclohexane ring existing in a chair form, with the *tert*-butyl substituent in an equatorial position[10]. The required *tert*-butyl cyclohexyl iodides **15e**

and **16e** were separately prepared from the known alcohols **11e** and **12e**[12] (Scheme 4). In this case the *trans* iodide was only slightly more N-9 selective than the *cis*. The lower face of these molecules is considerably more congested than the respective dioxans **15c** and **16c**, and there are no lone pairs present to allow electronic interaction with the purine π-system, it therefore seems probable that these transition states have different conformations.

Regarding the purine anion, it is evident that the C-6 chlorine atom imposes a steric restraint to N-7 alkylation which is absent from the corresponding N-9 vicinity. We therefore postulate that the observed alkylation ratios reflect the degree of steric differentiation in the possible reaction pathways, and that these factors should be borne in mind when considering ways of maximising N-9 alkylation of purines.

This general route to penciclovir was exemplified by conversion of the N-9 alkylated purines **19a** and **19b** to **6** by conventional acid hydrolysis. The potential synthesis of **6** *via* the *trans tert*-butyl dioxan **15c** therefore represents a highly regioselective route to this important anti-herpesvirus agent.

EXPERIMENTAL

All ^{1}H NMR spectra were recorded on a JEOL GX-270 spectrometer at 270MHz. All ^{13}C NMR spectra were recorded on the same instrument at 67.8MHz. Signals are quoted as δppm downfield from internal tetramethylsilane. Unless otherwise stated, all NMR spectra were obtained in hexadeuteriodimethyl sulphoxide solution. The dioxan ring ^{1}H coupling constants quoted for the *trans* and *cis* 2-methyl iodides **15a** and **16a** are typical for the whole range of iodides **15a-d** and **16a-d**, and for the N-9 and N-7 alkylated purines **17a-d**, **18a-d**, and **19a-d**, **20a-d** respectively.

All mass spectra were obtained on a JEOL SX-102 instrument.

5-(2-Hydroxyethyl)-1,3-dioxane 7[13].

The diol **13**[8] (4.3g, 20.5mmol) was suspended in water (9ml), paraformaldehyde (3.5g) was added and the mixture stirred vigorously while concentrated sulphuric acid (0.8ml) was added dropwise. After completion of the addition, the mixture was heated at 90-100°C for 3.5 hours. The solution was then cooled, extracted with chloroform, washed with water and saturated sodium bicarbonate solution, and dried ($MgSO_4$). Solvent evaporation afforded an oil which was not further purified, but dissolved in ethanol (50ml) and hydrogenated over 5% Pd/C at 60psi / ambient temperature overnight. Filtration and solvent evaporation gave the alcohol **7** as a colourless oil (2.6g, 96%).

^{1}H NMR ($CDCl_3$) : 1.41 (q,2H,CH_2), 2.00 (m,2H,H-5,OH), 3.38 (dd,2H,H-4,6ax), 3.47 (t,2H,C$\underline{H_2}$OH), 3.98 (dd,2H,H-4,6eq), 4.60 (d,1H,H-2ax), 4.88 (d,1H,H-2eq).

***trans* and *cis*-5-(2-Hydroxyethyl)-2-methyl-1,3-dioxane 11a and 12a.**

A mixture of the diol **13**[8] (30.0g, 0.14mol), 1,1-diethoxyethane (60ml, 50.6g, 0.42mol) and p-toluenesulphonic acid (50mg) was stirred at ambient temp. for 72 hours. Diethyl ether (500ml) was then added, and the solution washed with 2M sodium hydroxide solution and brine, dried ($MgSO_4$), and the solvent evaporated to give a pale oil which was not further purified, but dissolved in ethanol (1000ml) and hydrogenated over 5% Pd/C at 50psi / ambient temp. overnight. Filtration and solvent evaporation gave the crude mixture of alcohols **11a** and **12a** as a pale oil, which was purified by silica column chromatography eluting with diethyl ether to give a colourless oil (12.0g, 71%).
trans ^{1}H NMR ($CDCl_3$) : 1.31 (q,2H,CH_2), 1.32 (d,3H,CH_3), 1.89 (brs,1H,OH), 2.13 (m,1H,H-5), 3.38 (m,2H,H-4,6ax), 3.65 (t,2H,C$\underline{H_2}$OH), 4.12 (dd,2H,H-4,6eq), 4.63 (q,1H,H-2). *cis* ^{1}H NMR ($CDCl_3$) : 1.31 (d,3H,CH_3), 1.64 (m,1H,H-5), 1.99 (q,2H,CH_2), 2.33 (brs, 1H,OH), 3.81 (t,2H,C$\underline{H_2}$OH), 3.95 (d,4H,H-4,6ax,eq), 4.70 (q,1H,H-2).

***trans* and *cis*-5-(2-Hydroxyethyl)-2-*iso*-propyl-1,3-dioxane 11b and 12b.**

Prepared by the same method used for the methyl compounds **11a** and **12a**, with 1,1-diethoxy-2-methylpropane instead of 1,1-diethoxyethane. The yield of **11b** and **12b** as a pale oil was 55%.
trans ^{1}H NMR ($CDCl_3$) : 0.92 (d,6H,2xCH_3), 1.29 (q,2H,CH_2), 1.77 (m,1H,CH), 2.10 (m,1H,H-5), 2.36 (brs,1H,OH), 3.34 (t,2H,H-4,6ax), 3.63 (t,2H,C$\underline{H_2}$OH), 4.11 (dd,2H,H-4,6eq), 4.17 (d,1H,H-2). *cis* ^{1}H NMR ($CDCl_3$) : 0.92 (d,6H,2xCH_3), 1.59 (m,1H,H-5), 1.77 (m,1H,CH), 1.96 (q,2H,CH_2), 2.36 (brs,1H,OH), 3.79 (t,2H,C$\underline{H_2}$OH), 3.93 (m,4H,H-4,6ax,eq), 4.28 (d,1H,H-2).

***trans* and *cis*-2-*tert*-Butyl-5-(2-hydroxyethyl)-1,3-dioxane 11c and 12c.**

A mixture of the triol **1**[7] (7.45g, 62.0mmol), trimethylacetaldehyde (7.30ml, 5.80g, 68.2mmol), and a catalytic amount of p-toluenesulphonic acid was stirred overnight at ambient temperature in tetrahydrofuran (50ml). The mixture was filtered, and the filtrate evaporated to give an oil which was purified by silica column chromatography eluting with diethyl ether to give a mixture of alcohols **11c** and **12c** as a colourless oil (10.3g, 88%).
trans ^{1}H NMR ($CDCl_3$) : 0.90 (s,9H,3xCH_3), 1.29 (q,2H,CH_2), 2.05 (brs,1H,OH), 2.08 (m,1H,H-5), 3.33 (t,2H,H-4,6ax), 3.64 (t,2H,C$\underline{H_2}$OH), 4.03 (s,1H,H-2), 4.11 (dd,2H,H-

4,6eq). *cis* ^{1}H NMR ($CDCl_3$) : 0.88 (s,9H,3xCH_3), 1.63 (m,1H,H-5), 1.95 (q,2H,CH_2), 2.15 (brs,1H,OH), 3.79 (t,2H,C$\underline{H_2}$OH), 3.95 (m,4H,H-4,6ax,eq), 4.12 (s,1H,H-2).

***trans* and *cis*-2-*tert*-Butyl-5-(3-hydroxypropyl)-1,3-dioxane 11d and 12d.**

A mixture of the diol **14**[11] (56.3g, 0.25mol), trimethylacetaldehyde (40.7ml, 32.3g, 0.37mol) and p-toluenesulphonic acid (0.5g) was stirred under reflux for 2 hours in benzene (2500ml) with a Dean and Stark apparatus attached. The cooled reaction mixture was washed with 2M sodium hydroxide (1000ml) and water (200ml), dried ($MgSO_4$) and evaporated to give a pale yellow oil. This was purified by column chromatography on silica, eluting with 10% diethyl ether in hexane to give a mixture of the *cis* and *trans* benzyl ethers as a colourless oil. This oil was dissolved in ethanol (1000ml) and hydrogenated over 5% Pd/C at 100psi / ambient temperature overnight. The reaction mixture was filtered and the filtrate evaporated to afford a mixture of the alcohols **11d** and **12d** as a colourless oil (33.7g, 63%). The components of this mixture were not separated.

^{1}H NMR ($CDCl_3$) : 0.86 (s,18H,3xCH_3 *cis,trans*), 0.9-1.8 (m,10H,CH(CH_2)$_2$ *cis,trans*), 3.24 (t,2H,H-4,6ax *trans*) 3.38 (t,2H,C$\underline{H_2}$OH *trans*), 3.43 (t,2H,C$\underline{H_2}$OH *cis*), 3.83 (d,4H, H-4,6ax,eq *cis*), 4.03 (s,2H,H-5 *cis,trans*), 4.05 (dd,2H,H-4,6eq *trans*), 4.26 (s,2H,OH).

General procedure for the preparation of iodides 8, 15a-e, 16a-e.

A solution of methanesulphonyl chloride (1.2eq.) in dichloromethane was added dropwise to a solution of the alcohol(s) (1eq.) and triethylamine (1.5eq.) in dichloromethane, the temperature being maintained below 0°C. After completion of the addition, the reaction mixture was stirred for 1 hour at -5°C, then washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and brine, dried ($MgSO_4$), and evaporated. The resulting oil was dissolved in acetone, sodium iodide (2.5eq.) added, and the mixture stirred under reflux for 2 hours. The cooled reaction mixture was poured into water, extracted with dichloromethane, washed with 10% sodium metabisulphite solution and brine, dried ($MgSO_4$) and evaporated.

The residue was purified by column chromatography on silica, eluting with toluene / hexane or diethyl ether / hexane. Where stereoisomeric products were produced, the less polar *cis* isomer eluted first.

5-(2-Iodoethyl)-1,3-dioxane 8.

Pale oil, yield 84%.

^{1}H NMR ($CDCl_3$) : 1.87 (q,2H,CH_2), 2.00 (m,1H,H-5), 3.19 (t,2H,CH_2I), 3.52 (dd, $J_{4ax,4eq}$=11.5Hz, $J_{4ax,5}$=7.5Hz, 2H,H-4,6ax), 4.01 (dd, $J_{4eq,5}$=3.8Hz, 2H,H-4,6eq), 4.71

(d,1H,H-2ax), 4.90 (d,1H,H-2eq). ^{13}C NMR ($CDCl_3$) : 2.7 (CH_2I), 32.6 (CH_2), 35.7 (C-5), 70.3 (C-4,6), 94.1 (C-2). EI-MS : 243 $(MH)^+$, 115 $(M-I)^+$.

trans and _cis_-5-(2-Iodoethyl)-2-methyl-1,3-dioxane 15a and 16a.

trans, pale oil, yield 38%.

^1H NMR ($CDCl_3$) : 1.31 (d,3H,CH_3), 1.63 (q,2H,CH_2), 2.15 (m,1H,H-5), 3.12 (t,2H,CH_2I), 3.36 (ddd, $J_{4ax,4eq}$=11.5Hz, $J_{4ax,5}$=11.3Hz, 2H,H-4,6ax), 4.09 (ddd, $J_{4eq,5}$=4.6Hz, 2H,H-4,6eq), 4.59 (q,1H,H-2). ^{13}C NMR ($CDCl_3$) : 1.5 (CH_2I), 21.0 (CH_3), 32.4 (CH_2), 35.1 (C-5), 70.9 (C-4,6), 99.2 (C-2).

CI-MS : 257 $(MH)^+$, 213 $(MH-CH_3CHO)^+$.

cis, pale oil, yield 20%.

^1H NMR ($CDCl_3$) : 1.29 (d,3H,CH_3), 1.56 (m,1H,H-5), 2.25 (q,2H,CH_2), 3.32 (t,2H,CH_2I), 3.89 (m, $J_{4ax,4eq}$=11.3Hz, $J_{4ax,5}$=2.4Hz, $J_{4eq,5}$=1.4Hz, 4H,H-4,6ax,eq), 4.69 (q,1H,H-2). ^{13}C NMR ($CDCl_3$) : 5.6 (CH_2I), 21.2 (CH_3), 32.7 (CH_2), 34.6 (C-5), 69.3 (C-4,6), 99.7 (C-2). CI-MS : 257 $(MH)^+$, 213 $(MH-CH_3CHO)^+$.

trans and _cis_-5-(2-Iodoethyl)-2-_iso_-propyl-1,3-dioxane 15b and 16b.

trans, pale oil, yield 32%.

^1H NMR ($CDCl_3$) : 0.92 (d,6H,2xCH_3), 1.63 (q,2H,CH_2), 1.79 (m,1H,CH), 2.12 (m,1H,H-5), 3.11 (t,2H,CH_2I), 3.33 (t,2H,H-4,6ax), 4.11 (dd,2H,H-4,6eq), 4.14 (d,1H,H-2). ^{13}C NMR ($CDCl_3$) : 1.6 (CH_2I), 17.0 (2xCH_3), 32.7 (CH), 32.9 (CH_2), 35.4 (C-5), 70.7 (C-4,6), 106.0 (C-2). CI-MS : 285 $(MH)^+$, 213 $(MH-(CH_3)_2CHCHO)^+$.

cis, pale oil, yield 26%.

^1H NMR ($CDCl_3$) : 0.92 (d,6H,2xCH_3), 1.54 (m,1H,H-5), 1.77 (m,1H,CH), 2.23 (q,2H,CH_2), 3.32 (t,2H,CH_2I), 3.89 (m,4H,H-4,6ax,eq), 4.26 (d,1H,H-2). ^{13}C NMR ($CDCl_3$) : 5.6 (CH_2I), 16.9 (2xCH_3), 32.8 (CH), 32.9 (CH_2), 35.0 (C-5), 69.4 (C-4,6), 106.2 (C-2). CI-MS : 285 $(MH)^+$, 213 $(MH-(CH_3)_2CHCHO)^+$.

trans and _cis_-2-_tert_-Butyl-5-(2-iodoethyl)-1,3-dioxane 15c and 16c.

trans, pale yellow solid m.p. 42-43°C, yield 60%.

^1H NMR ($CDCl_3$) : 0.90 (s,9H,3xCH_3), 1.63 (q,2H,CH_2), 2.07 (m,1H,H-5), 3.10 (t,2H,CH_2I), 3.30 (t,2H,H-4,6ax), 4.01 (s,1H,H-2), 4.12 (dd,2H,H-4,6eq). ^{13}C NMR ($CDCl_3$) : 1.6 (CH_2I), 24.7 (3xCH_3), 32.6 (CH_2), 34.7 ($\underline{C}CH_3$), 35.4 (C-5), 71.1 (C-4,6), 107.8 (C-2). CI-MS : 299 $(MH)^+$, 213 $(MH-(CH_3)_3CCHO)^+$.

cis, pale oil, yield 31%.

^1H NMR ($CDCl_3$) : 0.89 (s,9H,3xCH_3), 1.53 (m,1H,H-5), 2.23 (q,2H,CH_2), 3.34 (t,2H,CH_2I), 3.88 (m,4H,H-4,6ax,eq), 4.12 (s,1H,H-2). ^{13}C NMR ($CDCl_3$) : 5.8 (CH_2I),

24.6 (3xCH_3), 32.8 (CH_2), 35.0 ($\underline{C}CH_3$,C-5), 69.4 (C-4,6), 108.1 (C-2).
CI-MS : 299 $(MH)^+$, 213 $(MH-(CH_3)_3CCHO)^+$.

***trans* and *cis*-2-*tert*-Butyl-5-(3-iodopropyl)-1,3-dioxane 15d and 16d.**

trans, pale oil, yield 57%.
^1H NMR ($CDCl_3$) : 0.90 (s,9H,3xCH_3), 1.13 (m,2H,CHC$\underline{H}_2$), 1.78 (m,2H,C$\underline{H}_2CH_2I$), 1.94 (m,1H,H-5), 3.16 (t,2H,CH_2I), 3.30 (m,2H,H-4,6ax), 4.01 (s,1H,H-2), 4.07 (m,2H,H-4,6eq). ^{13}C NMR ($CDCl_3$) : 6.4 (CH_2I), 24.8 (3xCH_3), 29.1, 30.2 (2xCH_2), 33.5(C-5), 34.7 ($\underline{C}CH_3$), 72.0 (C-4,6), 107.8 (C-2). CI-MS : 313 $(MH)^+$.
cis, pale oil, yield 24%.
^1H NMR ($CDCl_3$) : 0.90 (s,9H,3xCH_3), 1.29 (m,1H,H-5), 1.81 (m,2H,CHC$\underline{H}_2$), 1.92 (m,2H,C$\underline{H}_2CH_2I$), 3.21(t,2H,CH_2I), 3.88 (m,4H,H-4,6ax,eq), 4.10 (s,1H,H-2). ^{13}C NMR ($CDCl_3$) : 6.6 (CH_2I), 24.6 (3xCH_3), 30.5, 31.7 (2xCH_2), 33.7 (C-5), 35.0 ($\underline{C}CH_3$), 70.1 (C-4,6), 108.1 (C-2). CI-MS : 313 $(MH)^+$.

***trans* -2-(4-tert-Butylcyclohexyl)-1-iodoethane 15e.**

Pale oil, yield 94% from **11e**[12].
^1H NMR ($CDCl_3$) : 0.84 (s,9H,3xCH_3), 0.90-1.06 (m,5H,4xHax,CH), 1.29 (m,1H,CH), 1.69-1.80 (m,4H,4xHeq), 1.72 (q,2H,CH_2), 3.22 (t,2H,CH_2I). ^{13}C NMR ($CDCl_3$) : 5.2 (CH_2I), 27.0 (2xCH_2 cyclic), 27.6 (3xCH_3), 32.4 ($\underline{C}CH_3$), 32.8 (2xCH_2 cyclic), 38.5 (CH), 41.1 (CH_2), 48.1 (CH). EI-MS : 294 M^+, 167 $(M-I)^+$, 111 $(M-I,C_4H_8)^+$.

***cis*-2-(4-tert-Butylcyclohexyl)-1-iodoethane 16e.**

Pale oil, yield 95% from **12e**[12].
^1H NMR ($CDCl_3$) : 0.83 (s,9H,3xCH_3), 0.95-1.19 (m,3H,2xHax,CH), 1.38-1.67 (m,6H, 4xHeq,2xHax), 1.80 (m,1H,CH), 1.88 (q,2H,CH_2), 3.19 (t,2H,CH_2I). ^{13}C NMR ($CDCl_3$) : 6.2 (CH_2I), 21.8 (2xCH_2 cyclic), 27.5 (3xCH_3), 29.8 (2xCH_2 cyclic), 32.5 ($\underline{C}CH_3$), 33.5 (CH), 35.0 (CH_2), 48.3 (CH). EI-MS : 294 M^+, 167 $(M-I)^+$, 111 $(M-I,C_4H_8)^+$.

General procedure for the alkylation of 2-amino-6-chloropurine 5.

A mixture of 2-amino-6-chloropurine **5** (1eq.), the iodide (1.05eq.), and potassium carbonate (1.5eq.) was stirred at ambient temperature in dry N,N-dimethylformamide for 18 hours. The reaction mixture was then filtered, the filter cake washed well with N,N-dimethylformamide, and the combined filtrates evaporated. A preliminary measure of the N-9:N-7 product ratio was had by integration of the H-8 proton signals in the ^1H NMR spectrum of the crude mixture.

The product mixture was either chromatographed directly, or taken up in dichloromethane, washed with water and brine, dried ($MgSO_4$), and evaporated prior to silica chromatography. Eluting with 2-4% methanol in dichloromethane and evaporation of the relevant fractions afforded the pure isomers, (the less polar N-9 products elute first), which were weighed. In all cases the N-9:N-7 product mass ratio was in close agreement with that determined from the ^1H NMR spectrum of the crude mixture. Reactions were normally conducted on a 10mmol scale.

2-Amino-6-chloro-9-[2-(1,3-dioxan-5-yl)ethyl]purine 9, and
2-Amino-6-chloro-7-[2-(1,3-dioxan-5-yl)ethyl]purine 10.

9, yield 53%, m.p. 165-166°C (aq. methanol).
^1H NMR : 1.70 (m,3H,H-5',CH_2), 3.44 (dd,2H,H-4',6'ax), 3.95 (dd,2H,H-4',6'eq), 4.08 (t,2H,CH_2N), 4.62 (d,1H,H-2'ax), 4.83 (d,1H,H-2'eq), 6.92 (brs,2H,NH_2), 8.18 (s,1H,H-8). ^{13}C NMR : 28.1 (CH_2), 32.1 (C-5'), 40.5 (CH_2N), 70.0 (C-4',6'), 93.1 (C-2'), 123.2 (C-5), 143.0 (C-8), 149.3 (C-6), 154.0 (C-4), 159.7 (C-2).
EI-MS 284 $(MH)^+$, 283 M^+, 224 $(M-C_2H_3O_2)^+$.
Found; C:46.82, H:4.85, N:24.92. $C_{11}H_{14}N_5O_2Cl$ requires; C:46.57, H:4.97, N:24.68%.
10, yield 20%, m.p. 190°C (dec.) (aq. methanol).
^1H NMR : 1.71 (m,3H,H-5',CH_2), 3.45 (dd,2H,H-4',6'ax), 3.97 (dd,2H,H-4',6'eq), 4.33 (t,2H,CH_2N), 4.63 (d,1H,H-2'ax), 4.85 (d,1H,H-2'eq), 6.66 (brs,2H,NH_2), 8.43 (s,1H,H-8). ^{13}C NMR : 30.1 (CH_2), 32.2 (C-5'), 43.6 (CH_2N), 70.1 (C-4',6'), 93.1 (C-2'), 114.6 (C-5), 142.1 (C-6), 149.3 (C-8), 159.7 (C-2), 164.2 (C-4).
EI-MS 284 $(MH)^+$, 283 M^+, 224 $(M-C_2H_3O_2)^+$.
Found; C:46.59, H:5.00, N:24.87. $C_{11}H_{14}N_5O_2Cl$ requires; C:46.57, H:4.97, N:24.68%.

***trans*-2-Amino-6-chloro-9-[2-(2-methyl-1,3-dioxan-5-yl)ethyl]purine 17a, and**
***trans*-2-Amino-6-chloro-7-[2-(2-methyl-1,3-dioxan-5-yl)ethyl]purine 18a.**

17a, yield 67%, m.p. 186-189°C (ethyl acetate / diethyl ether).
^1H NMR : 1.16 (d,3H,CH_3), 1.55 (q,2H,CH_2), 1.75 (m,1H,H-5'), 3.32 (ddd,2H,H-4'6'ax), 3.98 (dd,2H,H-4'6'eq), 4.05 (t,2H,CH_2N), 4.57 (q,1H,H-2'), 6.93 (brs,2H,NH_2), 8.18 (s,1H,H-8). ^{13}C NMR : 20.8 (CH_3), 27.5 (CH_2), 31.4 (C-5'), 40.4 (CH_2N), 70.3 (C-4',6'), 98.3 (C-2'), 123.3 (C-5), 143.1 (C-8), 149.4 (C-6), 154.0 (C-4), 159.8 (C-2).
EI-MS 298 $(MH)^+$, 297 M^+, 224 $(M-C_3H_5O_2)^+$.
Found; C:48.11, H:5.51, N:23.35. $C_{12}H_{16}N_5O_2Cl$ requires; C:48.41, H:5.42, N:23.52%.
18a, yield 10%, m.p. 224°C (dec.) (ethyl acetate / methanol).
^1H NMR : 1.16 (d,3H,CH_3), 1.51 (q,2H,CH_2), 1.79 (m,1H,H-5'), 3.32 (ddd,2H,H-4'6'ax), 3.97 (dd,2H,H-4'6'eq), 4.28 (t,2H,CH_2N), 4.58 (q,1H,H-2'), 6.62 (brs,2H, NH_2), 8.40

(s,1H,H-8). ^{13}C NMR : 20.8 (CH_3), 29.5 (CH_2), 31.5 (C-5'), 43.7 (CH_2N), 70.3 (C-4',6'), 98.3 (C-2'), 114.6 (C-5), 142.2 (C-6), 149.4 (C-8), 159.9 (C-2), 164.3 (C-4).
EI-MS 298 $(MH)^+$, 297 M^+, 224 $(M-C_3H_5O_2)^+$, 182 $(M-C_6H_{11}O_2)^+$.
Found; C:48.18, H:5.39, N:23.41. $C_{12}H_{16}N_5O_2Cl$ requires; C:48.41, H:5.42, N:23.52%.

***cis*-2-Amino-6-chloro-9-[2-(2-methyl-1,3-dioxan-5-yl)ethyl]purine 19a, and *cis*-2-Amino-6-chloro-7-[2-(2-methyl-1,3-dioxan-5-yl)ethyl]purine 20a.**

19a, yield 70%, m.p. 173-175°C (ethyl acetate / diethyl ether).
^1H NMR : 1.17 (d,3H,CH_3), 1.28 (m,1H,H-5'), 2.13 (q,2H,CH_2), 3.84 (t,2H,H-4'6'ax,eq), 4.17 (t,2H,CH_2N), 4.65 (q,1H,H-2'), 6.91 (brs,2H,NH_2), 8.19 (s,1H,H-8). ^{13}C NMR : 21.1 (CH_3), 29.3 (C-5'), 30.5 (CH_2), 41.2 (CH_2N), 68.8 (C-4',6'), 98.8 (C-2'), 123.3 (C-5), 143.2 (C-8), 149.3 (C-6), 154.1 (C-4), 159.8 (C-2).
EI-MS 298 $(MH)^+$, 297 M^+, 224 $(M-C_3H_5O_2)^+$.
Found; C:48.51, H:5.42, N:23.62. $C_{12}H_{16}N_5O_2Cl$ requires; C:48.41, H:5.42, N:23.52%.
20a, yield 16%, m.p. 224°C (dec.) (ethyl acetate / methanol).
^1H NMR : 1.16 (d,3H,CH_3), 1.35 (m,1H,H-5'), 2.13 (q,2H,CH_2), 3.83 (d,2H,H-4'6'ax,eq), 4.40 (t,2H,CH_2N), 4.65 (q,1H,H-2'), 6.62 (brs,2H,NH_2), 8.41 (s,1H,H-8). ^{13}C NMR : 21.1 (CH_3), 30.6 (C-5'), 31.3 (CH_2), 44.6 (CH_2N), 69.0 (C-4',6'), 98.7 (C-2'), 114.7 (C-5), 142.2 (C-6), 149.4 (C-8), 159.9 (C-2), 164.3 (C-4).
EI-MS 298 $(MH)^+$, 297 M^+, 224 $(M-C_3H_5O_2)^+$, 182 $(M-C_6H_{11}O_2)^+$.
Found; C:48.10, H:5.46, N:23.24. $C_{12}H_{16}N_5O_2Cl$ requires; C:48.41, H:5.42, N:23.52%.

***trans*-2-Amino-6-chloro-9-[2-(2-*iso*-propyl-1,3-dioxan-5-yl)ethyl]purine 17b, and *trans*-2-Amino-6-chloro-7-[2-(2-*iso*-propyl-1,3-dioxan-5-yl)ethyl]purine 18b.**

17b, yield 69%, m.p. 163-164°C (aq. methanol).
^1H NMR : 0.84 (d,6H,2xCH_3), 1.55 (q,2H,CH_2), 1.60-1.80 (m,2H,CH,H-5'), 3.30 (t,2H,H-4'6'ax), 4.02 (dd,2H,H-4'6'eq), 4.05 (t,2H,CH_2N), 4.15 (q,1H,H-2'), 6.93 (brs,2H,NH_2), 8.19 (s,1H,H-8). ^{13}C NMR : 17.0 (2xCH_3), 27.5 (CH_2), 31.7, 32.0 (CH,C-5'), 40.4 (CH_2N), 70.5 (C-4',6'), 104.7 (C-2'), 123.3 (C-5), 143.1 (C-8), 149.4 (C-6), 154.0 (C-4), 159.7 (C-2). EI-MS 326 $(MH)^+$, 325 M^+, 282 $(M-C_3H_7)^+$.
Found; C:51.42, H:6.09, N:21.34. $C_{14}H_{20}N_5O_2Cl$ requires; C:51.61, H:6.19, N:21.50%.
18b, yield 6.5%, m.p. 245°C (dec.) (aq. methanol).
^1H NMR : 0.84 (d,6H,2xCH_3), 1.51 (q,2H,CH_2), 1.67 (m,1H,CH), 1.80 (m, 1H,H-5'), 3.32 (t,2H,H-4'6'ax), 4.01 (dd,2H,H-4'6'eq), 4.17 (d,1H,H-2'), 4.28 (t,2H, CH_2N), 6.63 (brs,2H,NH_2), 8.41 (s,1H,H-8). ^{13}C NMR : 16.9 (2xCH_3), 29.4 (CH_2), 31.7, 32.0 (CH,C-5'), 43.7 (CH_2N), 70.4 (C-4',6'), 104.5 (C-2'), 114.5 (C-5), 142.1 (C-6), 149.2 (C-8), 159.9 (C-2), 164.2 (C-4). EI-MS 326 $(MH)^+$, 325 M^+, 224 $(M-C_5H_9O_2)^+$.
Found; C:51.34, H:6.12, N:21.36. $C_{14}H_{20}N_5O_2Cl$ requires; C:51.61, H:6.19, N:21.50%.

***cis*-2-Amino-6-chloro-9-[2-(2-*iso*-propyl-1,3-dioxan-5-yl)ethyl]purine 19b, and *cis*-2-Amino-6-chloro-7-[2-(2-*iso*-propyl-1,3-dioxan-5-yl)ethyl]purine 20b.**

19b, yield 74%, m.p. 143-145°C (ethyl acetate / diethyl ether).

^{1}H NMR : 0.86 (d,6H,2xCH_3), 1.29 (m,1H,H-5'), 1.69 (m,1H,CH), 2.15 (q,2H,CH_2), 3.81 (dd,2H,H-4'6'ax), 3.92 (dd,2H,H-4'6'eq), 4.20 (t,2H,CH_2N), 4.25 (q,1H,H-2'), 6.92 (brs, 2H,NH_2), 8.21 (s,1H,H-8). ^{13}C NMR : 16.7 (CH_3), 29.2 (CH_2), 30.9 (C-5'), 32.2 (CH), 41.2 (CH_2N), 69.0 (C-4',6'), 105.0 (C-2'), 123.3 (C-5), 143.1 (C-8), 149.3 (C-6), 154.1 (C-4), 159.7 (C-2). EI-MS 326 $(MH)^+$, 325 M^+, 282 $(M-C_3H_7)^+$, 224 $(M-C_5H_9O_2)^+$.

Found; C:51.70, H:6.33, N:21.32. $C_{14}H_{20}N_5O_2Cl$ requires; C:51.61, H:6.19, N:21.50%.

20b, yield 16%, m.p. 207-208°C (dec.) (ethyl acetate / methanol).

^{1}H NMR : 0.85 (d,6H,2xCH_3), 1.36 (m,1H,H-5'), 1.68 (m,1H,CH), 2.13 (q,2H,CH_2), 3.82 (dd,2H,H-4'6'ax), 3.89 (d,2H,H-4'6'eq), 4.28 (d,1H,H-2'), 4.41 (t,2H,CH_2N), 6.63 (brs,2H,NH_2), 8.41 (s,1H,H-8). ^{13}C NMR : 16.7 (2xCH_3), 31.0 (C-5'), 31.2 (CH_2), 32.2 (CH), 44.6 (CH_2N), 69.1 (C-4',6'), 104.8 (C-2'), 114.8 (C-5), 142.2 (C-6), 149.3 (C-8), 159.9 (C-2), 164.3 (C-4). EI-MS 326 $(MH)^+$, 325 M^+, 282 $(M-C_3H_7)^+$.

Found; C:51.31, H:6.27, N:21.38. $C_{14}H_{20}N_5O_2Cl$ requires; C:51.61, H:6.19, N:21.50%.

***trans*-2-Amino-6-chloro-9-[2-(2-*tert*-butyl-1,3-dioxan-5-yl)ethyl]purine 17c, and *trans*-2-Amino-6-chloro-7-[2-(2-*tert*-butyl-1,3-dioxan-5-yl)ethyl]purine 18c.**

17c, yield 77%, m.p. 176-177°C (ethyl acetate / diethyl ether).

^{1}H NMR : 0.83 (s,9H,3xCH_3), 1.54 (q,2H,CH_2), 1.73 (m,1H,H-5'), 3.29 (m,2H,H-4'6'ax), 3.90-4.10 (m,5H,H-4'6'eq,CH_2N,H-2'), 6.95 (brs,2H,NH_2), 8.19 (s,1H,H-8). ^{13}C NMR : 24.6 (3xCH_3), 27.3 (CH_2), 31.6 (C-5'), 34.4 ($\underline{C}CH_3$), 40.4 (CH_2N), 70.6 (C-4',6'), 106.5 (C-2'), 123.3 (C-5), 142.9 (C-8), 149.3 (C-6), 153.9 (C-4), 159.6 (C-2).

EI-MS 340 $(MH)^+$, 339 M^+, 282 $(M-C_4H_9)^+$.

Found; C:52.99, H:6.59, N:20.59. $C_{15}H_{22}N_5O_2Cl$ requires; C:53.02, H:6.53, N:20.61%.

18c, yield 5.6%, m.p. 263°C (dec.) (ethyl acetate / methanol).

^{1}H NMR : 0.84 (s,9H,3xCH_3), 1.51 (q,2H,CH_2), 1.78 (m,1H,H-5'), 3.31 (t,2H,H-4'6'ax), 4.03 (dd,2H,H-4'6'eq), 4.04 (s,1H,H-2'), 4.28 (t,2H,CH_2N), 6.62 (brs,2H,NH_2), 8.41 (s,1H,H-8). ^{13}C NMR : 24.7 (3xCH_3), 29.5 (CH_2), 31.8 (C-5'), 34.6 ($\underline{C}CH_3$), 43.8 (CH_2N), 70.6 (C-4',6'), 106.6 (C-2'), 114.6 (C-5), 142.2 (C-6), 149.4 (C-8), 160.0 (C-2), 164.3 (C-4). EI-MS 339 M^+, 282 $(M-C_4H_9)^+$.

Found; C:52.94, H:6.56, N:20.70. $C_{15}H_{22}N_5O_2Cl$ requires; C:53.02, H:6.53, N:20.61%.

***cis*-2-Amino-6-chloro-9-[2-(2-*tert*-butyl-1,3-dioxan-5-yl)ethyl]purine 19c, and *cis*-2-Amino-6-chloro-7-[2-(2-*tert*-butyl-1,3-dioxan-5-yl)ethyl]purine 20c.**

19c, yield 72%, m.p. 158-159°C (diethyl ether).

^{1}H NMR : 0.85 (s,9H,3xCH_3), 1.25 (m,1H,H-5'), 2.11 (q,2H,CH_2), 3.80 (dd,2H,H-

4'6'ax), 3.92 (d,2H,H-4'6'eq), 4.12 (s,1H,H-2'), 4.17 (t,2H,CH_2N), 6.88 (brs,2H,NH_2), 8.17 (s,1H,H-8). ^{13}C NMR : 24.4 (3xCH_3), 29.3 (CH_2), 30.9 (C-5'), 34.7 ($\underline{C}CH_3$), 41.2 (CH_2N), 69.2 (C-4',6'), 106.9 (C-2'), 123.4 (C-5), 143.1 (C-8), 149.5 (C-6), 154.2 (C-4), 159.8 (C-2). EI-MS 340 $(MH)^+$, 339 M^+, 282 $(M-C_4H_9)^+$.

Found; C:52.86, H:6.48, N:20.50. $C_{15}H_{22}N_5O_2Cl$ requires; C:53.02, H:6.53, N:20.61%.

20c, yield 14%, m.p. 212°C (dec.) (ethyl acetate).

^1H NMR : 0.85 (s,9H,3xCH_3), 1.34 (m,1H,H-5'), 2.11 (q,2H,CH_2), 3.82 (dd,2H,H-4'6'ax), 3.91 (dd,2H,H-4'6'eq), 4.13 (s,1H,H-2'), 4.40 (t,2H,CH_2N), 6.60 (brs,2H,NH_2), 8.39 (s,1H,H-8). ^{13}C NMR : 24.5 (3xCH_3), 31.0 (C-5'), 31.3 (CH_2), 34.8 ($\underline{C}CH_3$), 44.6 (CH_2N), 69.2 (C-4',6'), 106.8 (C-2'), 114.8 (C-5), 142.2 (C-6), 149.4 (C-8), 159.9 (C-2), 164.3 (C-4). EI-MS 340 $(MH)^+$, 339 M^+, 282 $(M-C_4H_9)^+$.

Found; C:53.10, H:6.47, N:20.39. $C_{15}H_{22}N_5O_2Cl$ requires; C:53.02, H:6.53, N:20.61%.

***trans*-2-Amino-6-chloro-9-[3-(2-*tert*-butyl-1,3-dioxan-5-yl)propyl]purine 17d, and *trans*-2-Amino-6-chloro-7-[3-(2-*tert*-butyl-1,3-dioxan-5-yl)propyl]purine 18d.**

17d, yield 50%, m.p. 187-189°C (ethyl acetate / diethyl ether).

^1H NMR : 0.84 (s,9H,3xCH_3), 0.97 (m,2H,CH_2C-5'), 1.75 (m,1H,H-5'), 1.80 (m,2H,CH_2), 3.22 (t,2H,H-4'6'ax), 4.01 (s,1H,H-2'), 4.03 (m,4H,H-4'6'eq,CH_2N), 6.90 (brs,2H,NH_2), 8.14 (s,1H,H-8). ^{13}C NMR : 24.5 ($\underline{C}H_2$C-5'), 24.7 (3xCH_3), 25.7 ($\underline{C}H_2CH_2N$), 33.3 (C-5'), 34.5 ($\underline{C}CH_3$), 43.0 (CH_2N), 71.0 (C-4',6'), 106.5 (C-2'), 123.4 (C-5), 143.1 (C-8), 149.3 (C-6), 154.0 (C-4), 159.7 (C-2).

EI-MS 354 $(MH)^+$, 353 M^+, 296 $(M-C_4H_9)^+$.

Found; C:54.25, H:6.76, N:19.90. $C_{16}H_{24}N_5O_2Cl$ requires; C:54.31, H:6.83, N:19.79%.

18d, yield 8.5%, m.p. 250-252°C (dec.) (ethyl acetate / methanol).

^1H NMR : 0.83 (s,9H,3xCH_3), 0.98 (m,2H,CH_2C-5'), 1.75 (m,1H,H-5'), 1.80 (m,2H,CH_2), 3.23 (t,2H,H-4'6'ax), 4.02 (s,1H,H-2'), 4.03 (dd,2H,H-4'6'eq), 4.25 (t,2H,CH_2N), 6.61 (brs,2H,NH_2), 8.37 (s,1H,H-8). ^{13}C NMR : 24.2 ($\underline{C}H_2$C-5'), 24.7 (3xCH_3), 27.4 ($\underline{C}H_2CH_2N$), 33.3 (C-5'), 34.5 ($\underline{C}CH_3$), 46.1 (CH_2N), 71.0 (C-4',6'), 106.5 (C-2'), 114.7 (C-5), 142.1 (C-6), 149.4 (C-8), 159.9 (C-2), 164.3 (C-4).

EI-MS 354 $(MH)^+$, 353 M^+, 296 $(M-C_4H_9)^+$.

Found; C:54.34, H:6.81, N:19.89. $C_{16}H_{24}N_5O_2Cl$ requires; C:54.31, H:6.83, N:19.79%.

***cis*-2-Amino-6-chloro-9-[3-(2-*tert*-butyl-1,3-dioxan-5-yl)propyl]purine 19d, and *cis*-2-Amino-6-chloro-7-[3-(2-*tert*-butyl-1,3-dioxan-5-yl)propyl]purine 20d.**

19d, yield 74%, m.p. 157-159°C (ethyl acetate / diethyl ether).

^1H NMR : 0.80 (s,9H,3xCH_3), 1.31 (m,1H,H-5'), 1.55 (m,2H,CH_2C-5'), 1.82 (m,2H,CH_2), 3.80 (m,4H,H-4'6'ax,eq), 4.06 (t,2H,CH_2N), 4.09 (s,1H,H-2'), 6.89

(brs,2H,NH_2), 8.16 (s,1H,H-8). ^{13}C NMR : 24.4 (3xCH_3), 25.8, 27.0 (2xCH_2), 33.1 (C-5'), 34.6 ($\underline{C}CH_3$), 43.0 (CH_2N), 69.2 (C-4',6'), 106.7 (C-2'), 123.4 (C-5), 143.2 (C-8), 149.3 (C-6), 154.1 (C-4), 159.7 (C-2). EI-MS 354 $(MH)^+$, 296 $(M-C_4H_9)^+$.
Found; C:54.31, H:6.83, N:19.79. $C_{16}H_{24}N_5O_2Cl$ requires; C:54.31, H:6.83, N:19.79%.
20d, yield 13%, m.p. 222-224°C (dec.) (ethyl acetate / methanol).
^1H NMR : 0.80 (s,9H,3xCH_3), 1.32 (m,1H,H-5'), 1.56 (m,2H,CH_2C-5'), 1.84 (m,2H,CH_2), 3.80 (m,4H,H-4'6'ax,eq), 4.09 (s,1H,H-2'), 4.30 (t,2H,CH_2N), 6.60 (brs,2H,NH_2), 8.40 (s,1H,H-8). ^{13}C NMR : 24.4 (3xCH_3), 25.5, 28.6 (2xCH_2), 33.0 (C-5'), 34.7 ($\underline{C}CH_3$), 46.3 (CH_2N), 69.2 (C-4',6'), 106.6 (C-2'), 114.8 (C-5), 142.1 (C-6), 149.4 (C-8), 159.8 (C-2), 164.3 (C-4). EI-MS 354 $(MH)^+$, 353 M^+, 296 $(M-C_4H_9)^+$.
Found; C:54.07, H:7.03, N:20.02. $C_{16}H_{24}N_5O_2Cl$ requires; C:54.31, H:6.83, N:19.79%.

***trans*-2-Amino-6-chloro-9-[2-(4-*tert*-butylcyclohexyl)ethyl]purine 17e, and *trans*-2-Amino-6-chloro-7-[2-(4-*tert*-butylcyclohexyl)ethyl]purine 18e.**
17e, yield 76%, m.p. 197-198°C (ethyl acetate / diethyl ether).
^1H NMR : 0.81 (s,9H,3xCH_3), 0.87-1.09 (m,6H,4xHax,CH_2), 1.63-1.81 (m,6H,4xHeq, 2xCH), 4.06 (t,2H,CH_2N), 6.88 (brs,2H,NH_2), 8.15 (s,1H,H-8). ^{13}C NMR : 26.6 (2xCH_2), 27.3 (3xCH_3), 32.1 ($\underline{C}CH_3$), 32.8 (2xCH_2), 34.6 (CH), 36.2 (CH_2), 41.0 (CH_2N), 47.4 (CH), 123.3 (C-5), 143.1 (C-8), 149.3 (C-6), 154.0 (C-4), 159.7 (C-2).
EI-MS 336 $(MH)^+$, 335 M^+, 300 $(M-Cl)^+$.
Found; C:60.83, H:7.77, N:20.53. $C_{17}H_{26}N_5Cl$ requires; C:60.79, H:7.80, N:20.85%.
18e, yield 18%, m.p. 273°C (dec.) (ethanol).
^1H NMR : 0.82 (s,9H,3xCH_3), 0.84-1.24 (m,6H,4xHax,CH_2), 1.65-1.82 (m,6H,4xHeq, 2xCH), 4.30 (t,2H,CH_2N), 6.59 (brs,2H,NH_2), 8.38 (s,1H,H-8). ^{13}C NMR : 26.6 (2xCH_2), 27.3 (3xCH_3), 32.0 ($\underline{C}CH_3$), 32.8 (2xCH_2), 34.7 (CH), 38.3 (CH_2), 44.3 (CH_2N), 47.4 (CH), 114.7 (C-5), 142.1 (C-6), 149.2 (C-8), 159.8 (C-2), 164.2 (C-4).
EI-MS 336 $(MH)^+$, 335 M^+, 169 (purine)$^+$.
Found; C:60.85, H:7.80, N:21.04. $C_{17}H_{26}N_5Cl$ requires; C:60.79, H:7.80, N:20.85%.

***cis*-2-Amino-6-chloro-9-[2-(4-*tert*-butylcyclohexyl)ethyl]purine 19e, and *cis*-2-Amino-6-chloro-7-[2-(4-*tert*-butylcyclohexyl)ethyl]purine 20e.**
19e, yield 76%, m.p. 159-160°C (diethyl ether).
^1H NMR : 0.81 (s,9H,3xCH_3), 0.93-1.17 (m,3H,2xHax,CH), 1.35-1.64 (m,7H,2xHax, 4xHeq,CH), 1.83 (q,2H,CH_2), 4.05 (t,2H,CH_2N), 6.88 (brs,2H,NH_2), 8.18 (s,1H,H-8). ^{13}C NMR : 21.2 (2xCH_2), 27.3 (3xCH_3), 29.2 (CH), 29.8 (2xCH_2), 30.1 (CH_2), 32.2 ($\underline{C}CH_3$), 41.8 (CH_2N), 47.8 (CH), 123.4 (C-5), 143.2 (C-8), 149.3 (C-6), 154.1 (C-4), 159.7 (C-2). EI-MS 336 $(MH)^+$, 335 M^+, 300 $(M-Cl)^+$.

Found; C:60.68, H:7.81, N:21.02. $C_{17}H_{26}N_5Cl$ requires; C:60.79, H:7.80, N:20.85%.

20e, yield 20%, m.p. 235-237°C (dec.) (ethyl acetate).

^1H NMR : 0.82 (s,9H,3xCH_3), 0.90-1.23 (m,3H,2xHax,CH), 1.38-1.64 (m,7H,2xHax, 4xHeq,CH), 1.82 (q,2H,CH_2), 4.28 (t,2H,CH_2N), 6.60 (brs,2H,NH_2), 8.40 (s,1H,H-8). ^{13}C NMR : 21.2 (2xCH_2), 27.3 (3xCH_3), 29.3 (CH), 29.9 (2xCH_2), 32.3 ($\underline{C}CH_3$), 32.4 (CH_2), 45.2 (CH_2N), 47.7 (CH), 114.7 (C-5), 142.1 (C-6), 149.5 (C-8), 159.9 (C-2), 164.3 (C-4). EI-MS 336 $(MH)^+$, 335 M^+, 169 $(purine)^+$.

Found; C:60.64, H:7.80, N:21.19. $C_{17}H_{26}N_5Cl$ requires; C:60.79, H:7.80, N:20.85%.

9-(4-Hydroxy-3-hydroxymethylbutyl)guanine 6.

cis-2-Amino-6-chloro-9-[2-(2-methyl-1,3-dioxan-5-yl)ethyl]purine **19a** (0.61g, 2.05 mmol) was dissolved in 2M hydrochloric acid (6ml), and the solution heated under reflux for 2.5 hours. The cooled reaction mixture was then neutralised with 2M sodium hydroxide solution, and the brownish precipitate filtered off and recrystallised from boiling water with charcoal treatment. The product **6** was obtained as an off-white solid in 67% yield, m.p. 279°C (dec.). Similar reaction of *cis*-2-amino-6-chloro-9-[2-(2-*iso*-propyl-1,3-dioxan-5-yl)ethyl]purine **19b** afforded **6** in a yield of 50%.

^1H NMR : 1.49 (m,1H,CH), 1.75 (q,2H,CH_2), 3.43 (m,4H,2xCH_2O), 4.05 (t,2H,CH_2N), 4.52 (t,2H,2xOH), 6.54 (brs,2H,NH_2), 7.75 (s,1H,H-8), 10.76 (brs,1H,NH). ^{13}C NMR : 28.9 (CH_2), 40.8 (CH), 41.2 (CH_2N), 61.4 (2xCH_2O), 116.6 (C-5), 137.6 (C-8), 151.3 (C-4), 153.5 (C-2), 157.1 (C-6). FAB-MS 254 $(MH)^+$, 152 $(purineH)^+$.

Found; C:47.44, H:5.95, N:27.64. $C_{10}H_{15}N_5O_3$ requires; C:47.43, H:5.97, N:27.65%.

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