Tetrahedron Vol. 43, No. 9, pp. 2101 to 2108, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

EASY ALKYLATION OF PURINE BASES BY SOLID-LIQUID PHASE TRANSFER CATALYSIS WITHOUT SOLVENT. STRUCTURAL ANALYSIS BY 2D HETERONUCLEAR ^{1}H ^{13}C CORRELATED NMR SPECTROSCOPY.

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(*Received in Belgium* 1 *December* 1986)

ABSTRACT - Solid-liquid PTC without added organic solvent promotes alkylation of purine derivatives leading in particular to an efficient synthesis of the antiviral DHPA. The location of the substituent on the ring was determined by analysis of coupling interactions through 2D δ-δ heteronuclear ^{1}H ^{13}C correlated NMR spectroscopy.

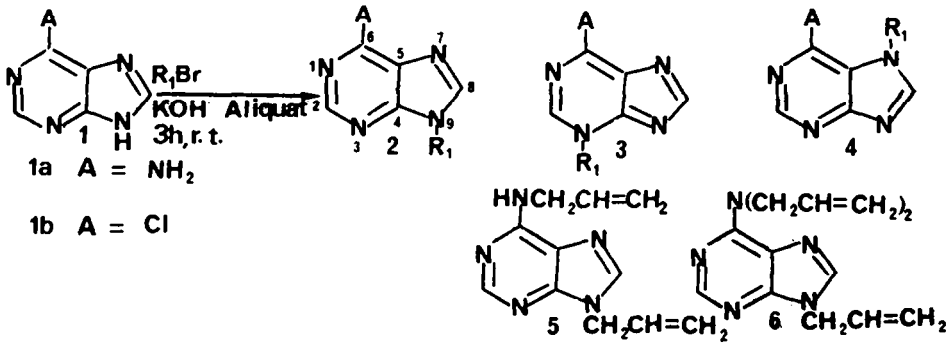
INTRODUCTION - The importance of purines with distinctive and highly interesting biological activity is continually reflected in the literature. The most important compounds such as antiviral derivatives are substituted in position 9 [1]. Purine can be alkylated under neutral or basic conditions [2]. Most of the known anionic activation methods [3] have been used for this purpose. We report here the alkylation of purine bases by solid-liquid phase transfer catalysis (PTC) without added solvent. This method has been previously used to achieve alkylations by S_N2 [4a] or Michael reactions [4b].

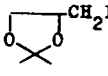
SYNTHESIS - The alkylation by solid-liquid PTC without solvent of adenine 1a led to a mixture of the 9-alkyladenine 2 and 3-alkyladenine 3. The ratio 2/3 appeared to be determined by the reactivity of the alkylating agent. With the low reactive 1-bromo octane and 1-bromo 3-butene the reaction was selective and led only to the 9-alkyladenines. It is worth noticing that 1-bromo octane was reported to be inefficient in the alkylation of adenine under liquid-liquid PTC conditions [3c]. When the highly reactive allylbromide was used, an exothermic reaction was observed. In this case, besides 9-allyladenine 2a and 3-allyladenine 3a minor amounts of 9,N^6-diallyladenine 5a and 9,N^6,N^6-triallyladenine 6 were formed. In contrast to classical anionic activation methods, 7-alkyladenines could not be detected [3a]. The reaction of adenine with 3-bromo 1,2-propanediol provides a very simple synthesis of the antiviral DHPA [5] in comparison to DHPA original synthesis [6], the absence

of DMSO which had to be eliminated by distillation facilitates the isolation of DHPA.

In order to compare our method with other PTC conditions, we tried the following alkylation procedures for the condensation of adenine on bromo-propanediol.

- Liquid-liquid PTC : DHPA could not be detected in the reaction mixture by tlc.
- Solid-liquid PTC with added organic solvent : minor amounts of DHPA (yield> 5 %) were formed, but glycidol was the main product of the reaction (yield 40 %).



	R_1Br	Products (Yield %)			
1a	$H_2C=CH-CH_2Br$	2a (46)	3a (27)	5a (2)	6 (5)
1a	$H_3C-CH=CH-CH_2Br$	2b (48)	3b (21)		
1a	$H_2C=CH-CH_2-CH_2Br$	2c (71)			
1a	$H_3C-(CH_2)_7Br$	2d (59)			
1a	$C_6H_5CH_2Br$	2e (54)	3e (10)		
1a	$HOCH_2-CHOH-CH_2Br$	2f (56)			
1a		2g (11)			
1b	$H_2C=CH-CH_2Br$	2h (58)	4h (23)		
1b	$HOCH_2-CHOH-CH_2Br$	2i (53)	4i (18)		

The biological interest [7] of 9,N^6-disubstituted adenines and the formation of small quantities of polyalkylated products when allylbromide was reacted with adenine, led us to study the application of solid-liquid PTC regarding the alkylation of the amino group of 9-alkyladenine. The base catalyzed alkylation of N^6 amino group is known to involve a DIMROTH rearrangement and usually requires vigorous conditions [2], so that the main route to N^6-alkyladenines is the reaction of 6-chloropurine with a primary or a secondary amine. We found that the N^6-alkylation of 9-alkyladenines 2 could equally be obtained by our process under moderate heating.

2			R_2Br	5	Yield %
2a : R_1	$H_2C=CHCH_2-$		$H_2C=CHCH_2Br$	5a	(72)
2b : R_1	$H_2C=CHCH_2-$		$H_2C=CH(CH_2)_2Br$	5b	(54)
2c : R_1	$H_2C=CH(CH_2)_2-$		$H_2C=CHCH_2Br$	5c	(78)

SPECTROSCOPIC STUDY - If various methods have been used for the structural characterisation of N-alkylated adenines (UV spectroscopy [8], ^{1}H NMR [3a,3b], ^{15}N NMR [9], XRay diffraction [10]) the most powerful one seems to be ^{13}C NMR spectroscopy. Comparison of ^{13}C chemical shifts from various isomers [11a] or from similar compounds [11b] were first used. More recently it was shown that the detection of long range coupling interactions involving proton(s) at the carbon of the N substituent should greatly facilitate the determination of the site of alkylation of nucleobases and purine derivatives [12]. In this work we show that the complete assignment of both the ^{1}H and ^{13}C NMR spectra of adenine and purine derivatives, as well as the univocal determination of their site of alkylation may be obtained through 2D δ-δ heteronuclear ^{1}H ^{13}C correlated NMR spectroscopy, without any need to compare several isomers and irrespective of solvents and substituents effects. The sole basic hypothesis needed is the widely accepted high field position of the C-5 signal.

The 2D NMR sequence (XH CORR) is described in the experimental part. Through proper adjustment of the fixed delays, the correlation between the ^{13}C and the ^{1}H signals can involve directly bonded carbons and protons only, or involve mainly carbons and protons remote three bonds away. Furthermore the correlation can be optimized for medium size coupling constants (circa 11 Hz) or for low size coupling constants (circa 4 Hz). The two ring protons 8-H and 2-H are first distinguished, 8-H being significantly correlated with C-5 while 2-H is not. C-6, correlated to 2-H only, is distinguished form C-4, correlated with both 2-H and 8-H. C-2 and C-8 are assigned by correlation with their respective bonded protons. The discrimination between N-7 substituted derivatives on one hand, N-3 or N-9 substituted derivatives on the other hand, relies on the observation of a correlation between the proton(s) of the N substituent and C-5 and C-4 respectively. The discrimination between substitution at the pyrimidine ring and at the imidazole ring relies on the observation of the correlation between the proton(s) of the N substituent and C-2 and C-8 respectively. Regarding an N-1 substituted derivative, correlations would be observed between the proton(s) of the substituent and the carbons C-6 and C-2.

The correlation diagrams obtained for N-3 allyladenine, N-9 allyladenine and N-7 allyl 6-chloropurine are shown in figures 1, 2 and 3.

The NMR data of all the derivatives under study are summarized in the table. A distinction between N-3 and N-9 adenine derivatives can be made from chemical shift differences since the low field shift of the ^{13}C signal of the first carbon of the substituent in the former derivatives is quite characteristic. The signals of C-2 and C-8 are almost interchanged in the two isomers.

The mono or dialkylation of the amino group in 5a or 6 induces no significant changes in the values of the chemical shifts. C-6 is long range coupled with the protons of the N-6 substituent(s) while the multiplicity of the C-5 signal is reduced according to the elimination of one or two amino protons. It is worth noticing that some of the ^{13}C signals (particularly those of the α and β carbons of the N-6 substituent(s)) are broadened due to

Figure 1

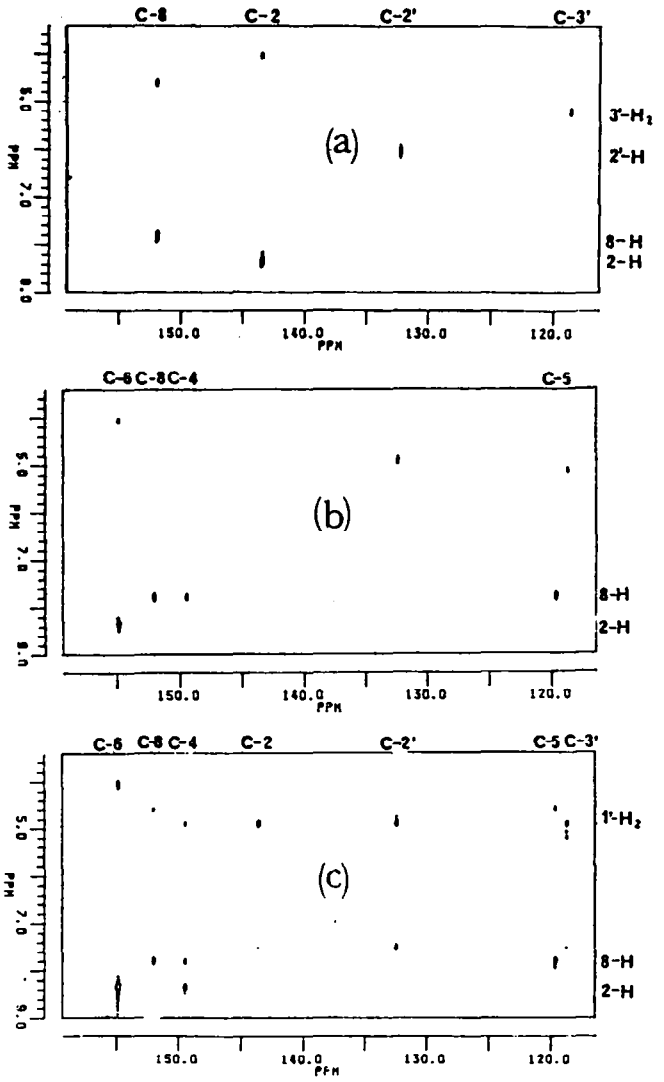


Figure 2

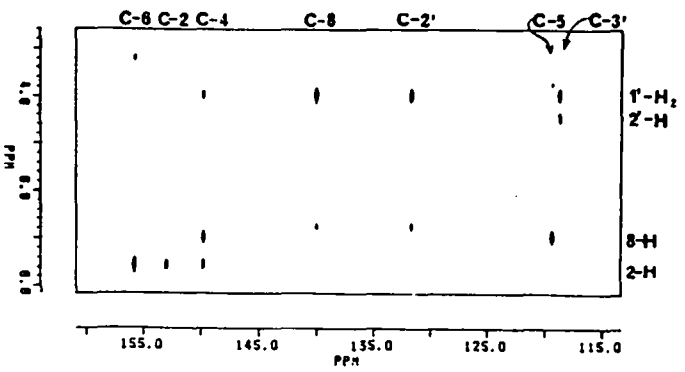


Figure 3

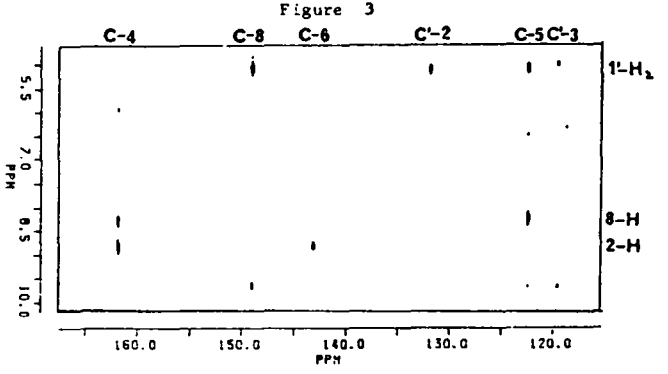


Figure 1 : Heteronuclear shift correlated 2D NMR : 3-allyladenine

a) correlations involving ^{1}J coupling

b) correlations involving ^{3}J coupling circa 11 Hz

c) correlations involving ^{3}J coupling circa 4 Hz

In the last two cases, residual signals may arise through larger J values.

Figure 2 : Heteronuclear shift correlated 2D NMR : 9-allyladenine. Correlations involving ^{3}J coupling circa 4 Hz.

Figure 3 : Heteronuclear shift correlated 2D NMR : 7-allyl 6-chloropurine. Correlations involving ^{3}J coupling circa 4 Hz.

the restricted rotation around the C-6 N-6 bond. As expected the broadening is increased at high observation frequencies (62.8 or 125 MHz). This phenomenon is not observed for the carbons of the less bulky methyl groups in N-6,N-6 dimethyl adenine but is was detected for the methyl protons of this compound in acidic medium [13].

As previously outlined [12a,14], the ^{3}J ^{13}C ^{1}H coupling through a pyridine type nitrogen are greater than the ^{3}J coupling through a substituted ring nitrogen.

The method described above for the structural identification of various alkylated adenine and chloropurine alkylated derivatives is likely to be powerful for the study of other nitrogen substituted heterocyclic compounds. In particular difficulties which may arise in the characterization of weak long range couplings in low intensity and/or broad multiplets [12a] can be overcome.

Table : ^{13}C NMR data and assignments for alkylated adenines and alkylated chloro-6 purines. Chemical shifts (δ ppm).

	C-2	C-4	C-5	C-6	C-8	C-1'[(a)]	C-2'	C-3'	C-4'	C-5'	C-6'	C-7'	C-8'
2a	152.6	149.4	118.8	156.1	140.8	45.0	133.0	117.7					
3a	143.4	149.8	120.7	155.0	152.6	51.0	132.1	118.8					
5a[(b)]	152.3	149.0	118.7	154.3	140.3	44.7	133.2	117.3					
6[(b)]	151.9	150.5	118.8	153.5	139.9	45.0	133.2	117.5					
2b	152.4	149.4	118.7	155.9	140.4	44.3	129.1	125.9	17.2				
3b	142.8	149.7	120.5	154.8	152.6	50.4	130.6	125.1	17.2				
2c	152.3	149.5	118.7	155.9	140.7	42.1	33.4	134.6	117.3				
2d	152.2	149.4	118.7	155.8	140.7	42.7	25.9	(29.2	28.4	28.2)	31.0	21.9	13.7
2e	152.7	149.6	118.8	156.1	140.8	46.2	137.1	127.5	128.7	127.7			
3e	143.4	149.7	120.3	154.9	152.5	52.0	136.9	128.0	128.6	128.0			
2f	152.0	149.6	118.5	155.7	141.4	46.2	69.6	63.3					
2g	152.2	149.6	118.3	155.8	141.1	45.1	73.4	65.9	108.7	24.9	26.3		
2h	152.0	151.7	131.5	151.0	144.9	46.3	130.9	119.9					
4h	152.5	162.0	122.5	143.1	148.9	49.3	131.9	119.6					
2i	151.2	152.2	130.7	148.8	148.2	47.3	69.3	63.5					
4i	151.3	161.6	122.2	142.1	151.8	50.0	70.4	63.4					

(a) C-1' C-8' labelling of the carbons of the N-3 or N-9 substituent.

(b) Carbons of the N-6 substituent : 5a : 52.2 135.7 114.8 ; 6 : 49.2 134.0 116.7.

Coupling constants (Hz) for 9-allyladenine 2a and 3-allyladenine 3a.

	^{1}J C-2,2-H	^{3}J C-2,αCH_2	^{3}J C-4,2-H	^{3}J C-4,8-H	^{3}J C-4,αCH_2	^{3}J C-5,8-H	^{3}J C-5,NH_2	^{3}J C-6,2-H	^{1}J C-8,8-H	^{3}J C-8,αCH_2
2a	198.7	-	11.6	4.9	3.5	11.0	4.2	11.5	211.5	3.9
3a	206.9	4.9	6.6	10.5	3.3	10.5	3.9	11.6	198.0	-

EXPERIMENTAL

Melting points were measured by using a Kofler type melting point apparatus and are uncorrected.

Spectral Data. ^1H NMR spectra were obtained on a Varian EM 390 NMR spectrometer. ^{13}C NMR spectra were recorded at 20.13 and 62.80 MHz using Bruker SY 80 and WM 250 spectrometers. ^{13}C chemical shifts and coupling constants were measured for samples dissolved in DMSO-d_6 except for compounds 2h, 4h which were studied in $CDCl_3$ (circa 0.5 M). The digital resolution was 0.3 Hz. The ^{13}C ^1H correlated 2D experiments were recorded using a Bruker WM 250 spectrometer. The applied pulse sequence (XH CORR) [15] was

^1H D1-90-D0- -D0-D3-90 BB

^{13}C D1 -180- 90-D4-FID

The data size of the time domain was 64 (f1) x 1K (f2). The time domain matrix was expanded by zero filling to 256 points in f1. Sine bell and Gaussian windows were used respectively in f2 and f1 dimensions. Resolution achieved in the frequency domain was 5 ± 1 Hz. According to the values of the coupling constants used in the correlation, the values of D3 and D4 were set to 0.0025 (J circa 200 Hz), 0.043 (J circa 10.5 Hz) D3 was set to 0.125 and D4 to 0.062 (J circa 4 Hz).

General procedure of the alkylation of adenine, 9-alkyladenines and 6-chloropurine. The heterocycle (10 mmol), finely ground potassium hydroxide (0.65 g, 11.5 mmol) and aliquat 336 [16] (0.12 g, 0.3 mmol) were vigorously shaken with a mechaninal stirrer for 10 min at room temperature. After addition of the alkylating agent (10 mmol) shaking was restarted at the appropriate temperature. The reaction was eventually cooled to room temperature and extracted with methylene chloride (3 x 20 ml) or methylene chloride - ethanol 9:1 (3 x 20 ml) for compound 2f. The products were purified by recrystallization or by chromatography on silica gel columns using the following eluents : A : CH_2Cl_2/acetone 8:2 ; B : toluene/ethanol 7:3 ; C : CH_2Cl_2/ethanol 7:3 ; D : benzene/methanol 9:1 ; E : CH_2Cl_2/methanol 9:1. Yields of chromatographically isolated products are gathered in schemes. It is specified in experimental part whenever isolation could also be realized by crystallization. Microanalysis are indicated for all new products.

Alkylation of adenine by allylbromide : the products were separated by chromatography (eluent A).

9-Allyladenine (2a). mp 163°C (benzene-methanol 9:1) (lit [17] mp 162-163°C) ; ^1H NMR ($CDCl_3$) 4.76 (d, 2H), 5.03-5.43 (m, 2H), 6.00 (m, 1H), 6.85 (s, broad, 2H), 7.82 (s, 1H), 8.22 (s, 1H).

3-Allyladenine (3a). mp 206-208°C (methanol) (lit [17] mp 207-211°C) ; ^1H NMR ($CDCl_3$) 4.96 (d, 2H), 5.13-5.50 (m, 2H), 6.03 (m, 1H), 7.20 (s, broad, 2H), 7.90 (s, 1H), 8.00 (s, 1H).

9-Allyl-6-N-allylaminopurine (5a). mp 138-142°C (ethyl acetate) ; ^1H NMR ($CDCl_3$) 4.30 (d, 2H), 4.76 (d, 2H), 5.00-5.33 (m, 4H), 5.66-6.16 (m, 2H), 7.60 (s, 1H), 8.30 (s, 1H). Anal. Calcd for $C_{11}H_{13}N_5$: C, 61.39 ; H, 6.04 ; N, 32.56. Found : C, 61.22 ; H, 6.09 ; N, 32.87.

9-Allyl-6-N-diallylaminopurine (6). mp 108-111°C (ethyl acetate) ; ^1H NMR ($CDCl_3$) 4.53 (d, 4H), 4.79 (d, 2H), 5.00-5.33 (m, 6H), 5.67-6.16 (m, 3H), 7.66 (s, 1H), 8.30 (s, 1H). Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.88 ; H, 6.66 ; N, 27.45. Found : C, 65.65 ; H, 6.73 ; N, 27.68.

Alkylation of adenine by 1-bromo-2 butene : 2b and 3b were separated by chromatography (eluent B).

9-1-(But-2-enyl) adenine (2b). mp 255-260°C (isopropyl alcohol) ; ^{1}H NMR ($CDCl_3$) 1.76 (d, 3H), 4.75 (d, 2H), 5.64 (m, 2H), 7.65 (s, broad, 2H), 7.76 (s, 1H), 8.26 (s, 1H). Anal. Calcd for $C_9H_{11}N_5$: C, 57.14 ; H, 5.82 ; N, 37.03. Found : C, 57.03 ; H, 5.89 ; N, 37.18.

3-1-(But-2-enyl) adenine (3b). mp 216-220°C (methanol) ; ^{1}H NMR ($CDCl_3$) 1.75 (d, 3H), 4.9 (d, 2H), 5.82 (m, 2H), 7.54 (s, 2H), 7.90 (s, 1H), 8.10 (s, 1H). Anal. Calcd for $C_9H_{11}N_5$: C, 57.14 ; H, 5.82 ; N, 37.03. Found : C, 56.85 ; H, 6.08 ; N, 37.31.

9-1-(But-3-enyl) adenine (2c). Was purified by chromatography (eluent B), 2c was also obtained by crystallization of the crude reaction mixture in ethyl acetate (yield 58 %) mp 169-171°C (ethyl acetate) ; ^{1}H NMR ($CDCl_3$) 2.65 (m, 2H), 4.28 (t, 2H), 4.96 (m, 1H), 5.22 (m, 1H), 7.78 (s, 1H), 8.36 (s, 1H). Anal. Calcd for $C_9H_{11}N_5$: C, 57.14 ; H, 5.82 ; N, 37.03. Found : C, 56.78 ; H, 5.95 ; N, 37.09

9-1-(Octyl) adenine (2d). Chromatography with eluent B. mp 127-128.5°C (ethyl acetate) (lit [18] mp 131°C) ; ^{1}H NMR ($CDCl_3$) 0.90 (t, 3H), 1.04-1.50 (m, 10H), 1.80-2.06 (m, 2H), 4.13 (t, 2H), 6.10 (s, broad, 2H), 7.64 (s, 1H), 8.24 (s, 1H). Anal. Calcd for $C_{13}H_{21}N_5$: C, 63.16 ; H, 8.50 ; N, 28.34. Found : C, 63.06 ; H, 8.59 ; N, 28.58.

Alkylation of adenine with benzylbromide. The benzyladenine 2e and 3e were separated by column chromatography (eluent D), 2e was also obtained by crystallization of the crude reaction mixture in ethyl acetate (yield 48 %).

9-Benzyladenine (2e). mp 232-233°C (ethanol) (lit [3b] mp 234°C) ; ^{1}H NMR ($CDCl_3$) 5.41 (s, 2H), 7.23 (s, broad, 2H), 7.33 (s, 5H), 8.20 (s, 1H), 8.32 (s, 1H).

3-Benzyladenine (3e). mp 276°C (ethanol) (lit [3b] mp 276-278°C) ; ^{1}H NMR ($CDCl_3$) 5.56 (s, 2H), 7.20-7.50 (m, 5H), 7.84 (s, 1H), 8.00 (s, broad, 2H), 8.56 (s, 1H).

9-1-(2,3-Dihydroxy propyl) adenine (DHPA) (2f). Chromatography with eluent E, 2f was also obtained by crystallization of the crude reaction mixture in isopropylalcohol (yield 52 %). mp 210°C (lit [16] 207-208°C) ; ^{1}H NMR (DMSO-d_6) 3.40 (m, 2H), 3.76-3.50 (m, 1H), 4.10-4.50 (m, 2H), 4.93 (t, 1H), 5.16 (d, 1H), 7.16 (s, broad, 2H), 8.03 (s, 1H), 8.06 (s, 1H).

Reaction of bromopropanediol with adenine under solid-liquid PTC with added organic solvent condition : The method described in the general procedure was modified by adding methylene chloride (20 ml) before the alkylating agent.

Reaction of bromopropanediol with adenine under liquid-liquid PTC conditions : the process described in ref [3c] was used.

9-1-(Dihydroxypropyl-2',3'-O-isopropyliden) adenine (2g). Chromatography with eluent C. mp 215°C (lit [6] 210-211°C) ; ^{1}H NMR (DMSO-d_6) 1.36 (s, 3H), 1.38 (s, 3H), 4.03 (m, 2H), 4.37 (m, 1H), 4.50 (m, 2H), 7.25 (s, broad, 2H), 8.17 (s, 1H), 8.28 (s, 1H).

Alkylation of 6-chloropurine by allylbromide : The products were separated by chromatography (eluent C).

9-Allyl-6-chloropurine (2h). mp 163-167°C ; ^{1}H NMR ($CDCl_3$) 4.91 (m, 2H), 5.23-5.40 (m, 2H) 6.04 (m, 1H), 8.13 (s, 1H), 8.76 (s, 1H). Anal. Calcd for $C_8H_7N_4Cl$: C, 49.35 ; H, 3.59 ; N, 28.79. Found : C, 49.23 ; H, 3.80 ; N, 28.93.

7-Allyl-6-chloropurine (4h). mp 143-146°C ; ^{1}H NMR ($CDCl_3$) 5.12 (m, 2H), 5.12-5.38 (m, 2H) 6.11 (m, 1H), 8.30 (s, 1H), 8.78 (s, 1H). Anal. Calcd for $C_8H_7N_4Cl$: C, 49.35 ; H, 3.59 ; N, 28.79. Found : C, 49.18 ; H, 3.96 ; N, 29.06.

Alkylation of 6-chloropurine by bromopropanediol : The products were separated by chromatography (eluent E).

6-Chloro-9-1-(2,3-dihydroxypropyl) purine (2i). mp 102°C (methanol). This compound has been already prepared [19] but only the hydrochloride was described. ^{1}H NMR (DMSO-d_6) 3.37 (m, 2H), 3.45-4.00 (m, 1H), 4.07-4.60 (m, 2H), 4.87 (t, 1H), 5.16 (d, 1H), 8.63 (s, 1H), 8.75 (s, 1H). Anal. Calcd for $C_8H_9ClN_4O_2$: C, 42.01 ; H, 3.94 ; N, 24.51. Found : C, 42.08 ; H, 4.15 ; N, 24.63.

6-Chloro-7-1-(2,3-dihydroxypropyl) purine (4i). mp 166°C (methanol) ; ^{1}H NMR (DMSO-d_6) 3.50 (m, 2H), 3.66-4.03 (m, 1H), 4.06-4.77 (m, 2H), 4.88 (t, 1H), 5.16 (d, 1H), 8.66 (s, 1H), 8.13 (s, 1H). Anal. Calcd for $C_8H_9ClN_4O_2$: C, 42.01 ; H, 3.94 ; N, 24.51. Found : C, 41.83 ; H, 4.07 ; N, 24.63.

6-Allylamino-9-1-buten-3-yl purine (5b). Chromatography with eluent B. mp 137°C ; ^{1}H NMR ($CDCl_3$) 2.63 (q, 2H), 4.28 (t, 2H), 4.58 (d, 2H), 5.05-5.40 (m, 4H), 5.60-6.33 (m, 3H), 7.72 (s, 1H), 8.40 (s, 1H). Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.88 ; H, 6.55 ; N, 30.56. Found : C, 62.75 ; H, 6.77 ; N, 30.68.

6-Buten-3-yl amino-9-allyl purine (5c). Chromatography with eluent B. mp 119°C ; ^{1}H NMR ($CDCl_3$) 2.45 (q, 2H), 3.78 (t, 2H), 4.78 (d, 2H), 4.85-5.25 (m, 4H), 5.63-6.28 (m, 3H), 7.70 (s, 1H), 8.36 (s, 1H). Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.88 ; H, 6.55 ; N, 30.56. Found : C, 62.59 ; H, 6.88 ; N, 30.78.

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