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Received June 15, 1990

$\alpha$ -(Aminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide and the ethyl acetate, **3** and **8**, have been synthesized by catalytic hydrogenation of 6-cyanomethylene-9-methoxymethylpurine derivatives **2** and **7** which were obtained by the substitution of 6-chloro-9-(methoxymethyl)purine (**1**) with  $\alpha$ -cyanoacetamide and ethyl cyanoacetate, respectively. Substitution of **3** and **8** with amines gave the corresponding *N*-substituted  $\alpha$ -(aminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide and the ethyl acetate **4** and **10**. Reaction of **3** with piperidine gave 9-(methoxymethyl)-9H-purine-6-acetamide (**5**).

*J. Heterocyclic Chem.*, **27**, 2011 (1990).

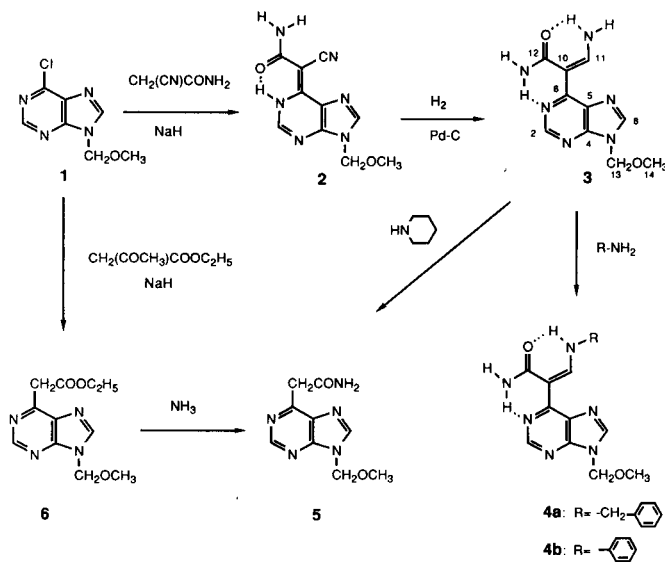
In recent years 6-*C*-substituted purine nucleosides have been found to exhibit antitumor [2] and antiviral activities [3]. Also, these compounds are important as biological probes for elucidation of the enzyme mechanism [4]. Therefore, these studies on the chemical modification of purine derivatives have been focused at position 6. It is well known that 6-cyanomethylene purine derivatives can be prepared in high yield by reaction of the sodium salt of an activated cyanomethylene with halogenated or methylsulfonated purine derivatives [5]. However, studies on conversion of the cyano group of cyanomethylene compounds into aminomethylene functions have not been described as the solubility of starting materials is limited.

In a previous publication, we described [6] the synthesis of  $\alpha$ -(aminomethylene)-9H-purine-6-acetonitrile derivatives *via* purine-6-malononitriles, which exist in an enamino nitrile tautomeric equilibrium. In the present paper, we describe a new convenient synthetic method for the preparation of  $\alpha$ -(aminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide and the ethyl acetate **3** and **8** *via* 6-cyanomethylene-9-(methoxymethyl)-9H-purine derivatives **2** and **7** by means of catalytic hydrogenation in an *N,N*-dimethylformamide (DMF)-benzene solvent system. The subsequent substitutions of **3** and **8** with amines are also described.

The syntheses of (*Z*)- $\alpha$ -(aminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide (**3**) and its amine substituted compound **4** are summarized in Scheme 1. Substitution of 6-chloro-9-(methoxymethyl)purine (**1**) [5a] with  $\alpha$ -cyanoacetamide using sodium hydride in DMF gave  $\alpha$ -cyano-9-(methoxymethyl)-9H-purine-6-acetamide (**2**) in 82% yield. Hydrogenation of **2** over 5% Pd-C in DMF-benzene (1:1 v/v) under medium pressure (4.0 atmospheres) gave the acetamide **3** in 77% yield. The <sup>1</sup>H-nmr spectrum showed the presence of a vinyl proton signal at  $\delta$  9.63 [7] as a doublet of doublets which collapsed to a singlet with deuterium oxide. Although vinyl protons normally resonate between  $\delta$  7 and 8, the large downfield shift of the vinyl proton of **3** is most probably due to an anisotropic effect of

the purine ring. In the <sup>13</sup>C-nmr spectrum the carbonyl carbon (C<sub>12</sub>) of **3** was found at  $\delta$  171.3 (<sup>3</sup>J<sub>CO,H</sub> = 8.6 Hz) [8]. Also, carbon 6 on the purine ring was found at  $\delta$  156.3 (<sup>3</sup>J<sub>C,6,H</sub> = 4.9 Hz) (Table 1). Therefore, the configuration of the enamino amide moiety appears to be *Z*-form from the chemical shift of the vinyl proton and the long-range coupling constants of <sup>13</sup>C-nmr spectrum. Interestingly, although  $\alpha$ -(aminomethylene)purine-6-acetonitrile derivatives [6] exist in an enamino nitrile tautomeric equilibrium (*E/Z*), enamino amide **3** is only found in the *Z* form.

Scheme 1



Substitution of **3** with benzylamine or aniline gave the corresponding *N*-substituted enamines **4a** and **4b** in 89% and 62% yields, respectively. In the <sup>1</sup>H-nmr spectra the vinyl protons of **4a** and **4b** were found at  $\delta$  9.75 (1H, d) and  $\delta$  10.26 (1H, d), respectively, indicating that both **4a** and **4b** are in the *Z* form. Reaction of **3** with piperidine or morpholine gave 9-(methoxymethyl)-9H-purine-6-acetamide (**5**) in 70% yield. The <sup>1</sup>H-nmr spectrum showed no enamine.

The structure was confirmed by comparison of the ir and  $^1\text{H}$ -nmr spectra of **5** with those of an authentic sample prepared by another route. Thus, reaction of **1** with ethyl acetoacetate in the presence of sodium hydride in dimethyl sulfoxide (DMSO) gave ethyl 9-(methoxymethyl)-9*H*-purine-6-acetate (**6**), *via* a retro Claisen reaction [9], which was converted to acetamide **5** with ammonia in 71% yield. The formation of acetamide **5** from **3** may occur by addition of piperidine at the  $\text{C}_{11}$  position, followed by cleavage of the carbon-carbon bond between  $\text{C}_{10}$  and  $\text{C}_{11}$  with concomitant formation of the amidine fragment [10].

Table 1  
 $^{13}\text{C}$ -NMR Data for **3** in  $\text{DMSO-d}_6$

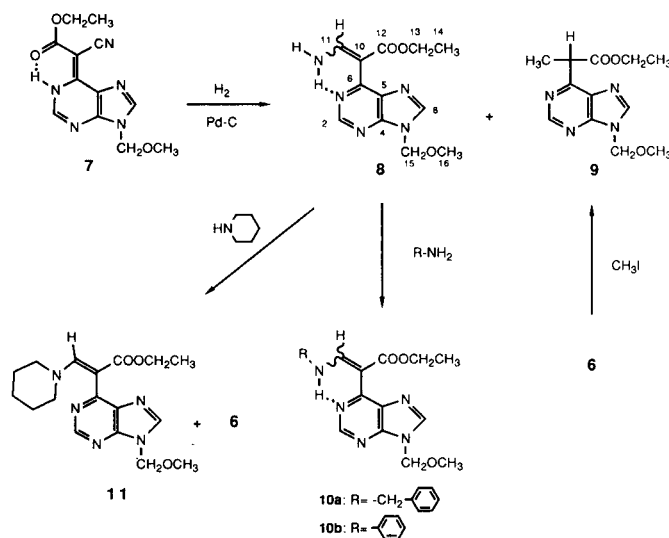
Carbon	Chemical Shifts ( $\delta$ )	$^{13}\text{C}$ -H Coupling Constant (Hz) [a]			
		$\text{C}_2\text{H}$	$\text{C}_8\text{H}$	$\text{C}_{11}\text{H}$	$\text{C}_{13}\text{H}$
2	150.6	$^1J = 202.6$			
4	149.8	* [b]	*		
5	126.2		$^3J = 11.0$		
6	156.3	$^3J = 10.9$		$^3J = 4.9$	
8	143.1		$^1J = 213.6$		$^3J = 3.7$
10	95.8			$^2J = 3.5$	
11	159.6			$^1J = 166.0$	
12	171.3			$^3J = 8.6$	
13	73.5				
14	56.4				

[a] These coupling constants were measured using deuterated ( $\text{ND}_2$  and  $\text{COND}_2$ ). [b] \* Data not clear.

Catalytic hydrogenation of ethyl  $\alpha$ -cyano-9-(methoxymethyl)-9*H*-purine-6-acetate (**7**) [5a] in DMF-benzene gave ethyl  $\alpha$ -(aminomethylene)-9-(methoxymethyl)-9*H*-purine-6-acetate (**8**) in 75% yield and ethyl 2-[9-(methoxymethyl)-9*H*-purin-6-yl]propionate (**9**) in 22% yield as an over reduced side product (Scheme 2). The geometrical isomers (*E/Z*) of **8** were quantified by  $^1\text{H}$ -nmr and  $^{13}\text{C}$ -nmr spectra. The  $^1\text{H}$ -nmr spectrum (400 MHz) showed two sets of vinyl proton signals at  $\delta$  7.90 (t) as the minor signal (*E*) and  $\delta$  8.16 (t) as the major signal (*Z*) which collapsed to singlets with deuterium oxide. In the  $^{13}\text{C}$ -nmr spectrum  $\text{C}_6$  of **7** was at  $\delta$  156.5 ( $^3J_{\text{C}_6,\text{H}_{11}} = 7.3$  Hz, *E*) as the minor signal and at  $\delta$  157.0 ( $^3J_{\text{C}_6,\text{H}_{11}} = 4.6$  Hz, *Z*) as the major signal (Table 2). Therefore, on the basis of these results the geometrical isomers of **8** seem to exist in an enamino ester tautomeric equilibrium. The ratio of geometrical isomers (*E/Z*) in deuterioacetone is 40:60 by comparison of the integration of  $\text{C}_2$ ,  $\text{C}_8$  and the vinyl protons of each isomer in the  $^1\text{H}$ -nmr spectrum. Generally the vinyl proton signal in the *Z*-form of enamino purine derivatives is found at *ca*  $\delta$  9.2-9.6. However, in the  $^1\text{H}$ -nmr spectrum of **8** the higher field vinyl signal of the *Z*-form indicates that it may be twisted out from the plane of the purine ring. It is also believed that there is an intramolecular hydrogen bond between the amino group of the enamine moiety and the ester

carbonyl group from the chemical shift of NH ( $\delta$  8.20) [11]. Also, the structure of **9** was confirmed by comparison of the ir and  $^1\text{H}$ -nmr spectra with those of an authentic sample prepared from **6** with methyl iodide.

Scheme 2

Table 2  
 $^{13}\text{C}$ -NMR Data for **8** in  $\text{DMSO-d}_6$ 

Carbon	Chemical Shifts ( $\delta$ )	$^{13}\text{C}$ -H Coupling Constant (Hz) [a]			
		$\text{C}_2\text{H}$	$\text{C}_8\text{H}$	$\text{C}_{11}\text{H}$	$\text{C}_{13}\text{H}$
2	151.4 ( <i>E</i> ) 152.1 ( <i>Z</i> )	$^1J = 201.1$ $^1J = 201.1$			
4	151.5	* [b]	*		
5	129.8 ( <i>E</i> ) 130.5 ( <i>Z</i> )				
6	156.5 ( <i>E</i> ) 157.0 ( <i>Z</i> )	$^3J = 11.7$ $^3J = 10.3$		$^3J = 7.3$ $^3J = 4.6$	
8	143.1 ( <i>E</i> ) 143.4 ( <i>Z</i> )		$^1J = 211.2$ $^1J = 211.3$		$^3J = 3.0$ $^3J = 3.0$
10	96.5 ( <i>Z</i> ) 97.1 ( <i>E</i> )			*	*
11	151.1 ( <i>E</i> ) 155.0 ( <i>Z</i> )			$^1J = 165.8$ $^1J = 167.2$	
12	168.3 ( <i>E</i> ) 168.4 ( <i>Z</i> )			$^3J = 4.4$	*
13	59.3 ( <i>Z</i> ) 59.7 ( <i>E</i> )				
14	14.6				
15	74.1				
16	56.8				

[a] These coupling constants were measured using deuterated ( $\text{ND}_2$  and  $\text{COND}_2$ ). [b] \* Data not clear.

Substitution of **8** with benzylamine or aniline gave the corresponding *N*-substituted enamines **10a** and **10b** in 90% and 50% yields respectively. In the reaction with aniline **6** was obtained in 14% yield as by-product. In the  $^1\text{H}$ -nmr spectrum the vinyl proton of **10a** showed at  $\delta$  7.85 (*E*) and  $\delta$  8.03 (*Z*). The ratio of geometrical isomers (*E/Z*) in

DMSO- $d_6$  was 46:54. Also, the ratio (*E/Z*) of **10b** in DMSO- $d_6$  was 50:50. Reaction of **8** with piperidine gave ethyl  $\alpha$ -(piperidinomethylene)-9-(methoxymethyl)-9H-purine acetate (**11**) in 30% yield together with **6** in 61% yield.

In conclusion, the present work demonstrates that catalytic hydrogenation of **2** and **7** to the corresponding  $\alpha$ -(aminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide and the ethyl acetate **3** and **8** in DMF-benzene is highly chemoselective because the enamine moiety and purine ring are unaffected. Compounds **3** and **8** are also shown to be versatile intermediates for the preparation of 6-*C*-substituted purines having alkyl or aryl substituents.

## EXPERIMENTAL

All melting points are uncorrected. The ir spectra (potassium bromide) were taken on a JASCO Model A-102 spectrophotometer. The uv spectra were measured using a Hitachi Model EPS-3T spectrophotometer. The  $^1\text{H}$ -nmr and  $^{13}\text{C}$ -nmr spectra were recorded on JEOL JNM-FX 100 and JEOL-GX 400 spectrometer using tetramethylsilane as an internal standard. The ms spectra were measured by a JEOL JMS-D300 spectrometer. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; sh, shoulder; and dd, doublet of doublets.

### $\alpha$ -Cyano-9-(methoxymethyl)-9H-purine-6-acetamide (**2**).

To a cold (0-5°) stirred suspension of 60% sodium hydride (1.40 g, 0.035 mole) in dry DMF (80 ml) was added dropwise a solution of  $\alpha$ -cyanoacetamide (3.00 g, 0.035 mole) in dry DMF (15 ml) over a period of 30 minutes, and the solution was stirred for 20 minutes at room temperature under argon. After this time, a solution of **1** (2.00 g, 0.01 mole) in dry DMF (30 ml) was added to the above solution and stirring was continued overnight. The solution was diluted with water (100 ml) and adjusted to pH 3 with 10% hydrochloric acid. The resulting precipitate was recrystallized from DMF-ethanol to give **2** (2.053 g, 82%) as colorless needles, mp 199-201° dec; ir: 3440 (NH), 3330 (NH), 3290 (NH), 2190 (CN)  $\text{cm}^{-1}$ ; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 329 (27500, sh), 339 (30200) nm;  $^1\text{H}$ -nmr (DMSO- $d_6$ ):  $\delta$  3.28 (s, 3H, OMe), 5.53 (s, 2H,  $\text{CH}_2$ ), 6.99 (br s, 2H, NH), 8.44 (s, 2H,  $\text{C}_2\text{H}$ ), 15.01 (br s, 1H, NH); ms:  $m/z$  246.0861 ( $\text{M}^+$ , Calcd:  $\text{C}_{10}\text{H}_{10}\text{N}_6\text{O}_2$ : 246.0881).

### (*Z*)- $\alpha$ -(Aminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide (**3**).

A solution of **2** (1.00 g) in DMF-benzene (1:1 v/v, 90 ml) containing saturated methanolic ammonia (5 ml) was hydrogenated over 5% Pd-C (0.70 g) at room temperature and 4.0 atmospheres of hydrogen for 24 hours. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to give a solid, which was recrystallized from methanol-hexane to give **3** (0.770 g, 77%) as colorless needles, mp 194-196° dec; ir: 3275 (NH), 3125 (NH), 1635, 1570  $\text{cm}^{-1}$ ; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 237 (16600), 264 (10700), 331 (2600) nm;  $^1\text{H}$ -nmr (DMSO- $d_6$ ):  $\delta$  3.29 (s, 3H, OMe), 5.57 (s, 2H,  $\text{CH}_2$ ), 6.99 (br s, 1H, CONH), 8.30 (br t, 1H, J = 6 Hz, C = CNH), 8.63 (s, 1H,  $\text{C}_2\text{H}$ ), 8.54 (s, 1H,  $\text{C}_8\text{H}$ ), 9.63 (dd, 1H, J = 15 Hz, J = 8 Hz, C = CH), 9.95-10.08 (m, 2H, CONH and C = C-NH); ms:  $m/z$  248 ( $\text{M}^+$ ), 204.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{N}_6\text{O}_2$ : C, 48.38; H, 4.87; N, 33.86.

Found: C, 48.39; H, 4.87; N, 33.86.

### (*Z*)- $\alpha$ -(*N*-Benzylaminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide (**4a**).

A solution of **3** (0.100 g, 0.4 mmole) and benzylamine (0.129 g, 1.2 mmoles) in ethanol (5 ml) was refluxed with stirring for 24 hours. After cooling, the resulting precipitate was filtered and recrystallized from chloroform-methanol to give **4a** (0.126 g, 89%) as colorless needles, mp 218-219° dec; ir: 3325 (NH), 1644, 1630  $\text{cm}^{-1}$ ; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 240 (29500), 272 (13200), 341 (31600), 350 (29500 sh) nm;  $^1\text{H}$ -nmr (DMSO- $d_6$ ):  $\delta$  3.29 (s, 3H, OMe), 4.62 (s, 2H,  $\text{CH}_2$ ), 7.11 (br s, 1H, CONH), 7.37 (br s, 5H, phenyl-H), 8.54 (s, 1H,  $\text{C}_8\text{H}$ ), 8.64 (s, 1H,  $\text{C}_2\text{H}$ ), 9.75 (d, 1H, J = 13 Hz, C = CH), 11.00-11.15 (m, 1H, C = C-NH); ms:  $m/z$  336 ( $\text{M}^+$ ), 320.

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{18}\text{N}_6\text{O}_2$ : C, 60.34; H, 5.36; N, 24.84. Found: C, 60.61; H, 5.41; N, 24.63.

### (*Z*)- $\alpha$ -(*N*-Phenylaminomethylene)-9-(methoxymethyl)-9H-purine-6-acetamide (**4b**).

A solution of **3** (0.100 g, 0.4 mmole) and aniline (0.112 g, 1.2 mmoles) in ethanol (5 ml) was refluxed with stirring for 20 days. After cooling, the precipitate was filtered, and recrystallized from dichloromethane-ethanol to give **4b** (81 mg, 62%) as yellow needles, mp 206-207° dec; ir: 3400 (NH), 1645, 1555  $\text{cm}^{-1}$ ; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 241 (17000), 280 (16600), 370 (34700) nm;  $^1\text{H}$ -nmr (DMSO- $d_6$ ):  $\delta$  3.32 (s, 3H, OMe), 5.62 (m, 2H,  $\text{CH}_2$ ), 7.07-7.45 (m, 5H, phenyl-H), 7.50 (br s, 1H, CONH), 8.70 (s, 1H,  $\text{C}_8\text{H}$ ), 8.76 (s, 1H,  $\text{C}_2\text{H}$ ), 10.20 (br s, 1H, CONH), 10.26 (d, 1H, J = 13 Hz, C = CH), 12.70 (d, 1H, J = 13 Hz, C = C-NH); ms:  $m/z$  324 ( $\text{M}^+$ ), 306.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{16}\text{N}_6\text{O}_2$ : C, 59.25; H, 4.97; N, 25.91. Found: C, 58.93; H, 4.91; N, 26.00.

### Reaction of **3** with Piperidine.

A solution of **3** (0.100 g, 0.4 mmole) and piperidine (0.103 g, 1.21 mmoles) in DMF-ethanol (1:3 v/v, 4 ml) was refluxed with stirring for 4 days. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by preparative tlc with 8% methanol in chloroform as developing solvent to give 9-(methoxymethyl)-9H-purine-6-acetamide (**5**) (63 mg, 70%), which was recrystallized from methanol-hexane to give colorless needles, mp 163-164°; ir: 3365 (NH), 1710 (CO), 1667  $\text{cm}^{-1}$ ; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 246 (5400), 262 (7600), 339 (510), 352 (480) nm;  $^1\text{H}$ -nmr (DMSO- $d_6$ ):  $\delta$  3.31 (s, 3H, OMe), 3.96 (s, 2H,  $\text{CH}_2$ ), 5.62 (s, 2H,  $\text{CH}_2\text{O}$ ), 7.10 (s, 1H, NH), 8.69 (s, 1H,  $\text{C}_8\text{H}$ ), 8.86 (s, 1H,  $\text{C}_2\text{H}$ ); ms:  $m/z$  221 ( $\text{M}^+$ ), 178.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{11}\text{N}_5\text{O}_2$ : C, 48.86; H, 5.01; N, 31.66. Found: C, 49.23; H, 5.03; N, 32.00.

### Ethyl 9-(Methoxymethyl)-9H-purine-6-acetate (**6**).

To a cold (0-5°) stirred suspension of 60% sodium hydride (0.225 g, 5.66 mmoles) in dry DMSO (3 ml) was added dropwise a solution of ethyl acetoacetate (0.790 g, 6.29 mmoles) in dry DMSO (1 ml) over a period of 20 minutes and the solution was stirred for 5 minutes at room temperature under argon. After this time, a solution of **1** (0.250 g, 1.25 mmoles) in dry DMSO (3 ml) was added to the above solution and stirring was continued for 2 days at 60°. After cooling, the solution was diluted with water (3 ml) and neutralized with acetic acid. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (30 g) with dichloromethane as eluent, and the sol-

vent was evaporated *in vacuo* to give a solid, which was recrystallized from hexane to give **6** (0.168 g, 53%) as colorless needles, mp 63-64°; ir: 3125 (NH), 1725 (CO), 1610 cm<sup>-1</sup>; uv (methanol): λ max (ε) 245 (5250 sh) 261 (7590), 320 (1020), 334 (830 sh) nm; <sup>1</sup>H-nmr (deuteriochloroform): δ 1.27 (t, 3H, J = 7 Hz, Me), 3.40 (s, 3H, OMe), 4.23 (q, 2H, J = 7 Hz, CH<sub>2</sub>), 4.27 (s, 2H, CH<sub>2</sub>CO), 5.63 (s, 2H, CH<sub>2</sub>O), 8.21 (s, 1H, C<sub>8</sub>H), 8.97 (s, 1H, C<sub>2</sub>H); ms: m/z 250 (M<sup>+</sup>), 220.

Anal. Calcd. for C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>: C, 52.79; H, 5.64; N, 22.39. Found: C, 53.12; H, 5.73; N, 22.75.

#### 9-(Methoxymethyl)-9H-purine-6-acetamide (**5**).

A solution of **6** (80 mg) in 15% w/w ethanolic ammonia (5 ml) was heated at 95-100° for 6 days in a sealed tube. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by preparative tlc with 5% methanol-chloroform as developing solvent to give **5** (50 mg, 71%). The compound was identical (mp, ir, and <sup>1</sup>H-nmr) with an authentic sample prepared by the substitution of **3** with piperidine.

#### Catalytic Hydrogenation of **7**.

A solution of **7** (0.500 g, 1.8 mmoles) in DMF-benzene (1:1 v/v, 50 ml) was hydrogenated over 5% Pd-C (270 mg) at room temperature and 4 atmospheres of hydrogen for 45 hours. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on neutral alumina (80 g) with dichloromethane as eluent to give a solid, which was recrystallized from hexane to give ethyl 2-[9-(methoxymethyl)-9H-purin-6-yl]propionate **9** (0.104 g, 22%) as colorless needles, mp 55-56°; ir: 3120 (NH), 2985, 1720 (CO) cm<sup>-1</sup>; uv (methanol): λ max (ε) 246 (5750), 261 (8130), 330 (40) nm; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 1.10 (t, 3H, J = 7 Hz, Me), 1.56 (d, 3H, J = 8 Hz, HC-Me), 3.30 (s, 3H, OMe), 4.06 (q, 2H, J = 7 Hz, CH<sub>2</sub>), 4.50 (q, 1H, H-C-Me exchangeable with deuterium oxide), 5.60 (s, 2H, CH<sub>2</sub>O), 8.66 (s, 1H, C<sub>8</sub>H), 8.86 (s, 1H, C<sub>2</sub>H); ms: m/z 264 (M<sup>+</sup>), 234.

Anal. Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>: C, 54.55; H, 6.10; N, 21.20. Found: C, 54.59; H, 6.05; N, 21.48.

Further elution with dichloromethane gave a solid, which was recrystallized with benzene-hexane to give ethyl α-(aminomethylene)-9-(methoxymethyl)-9H-purine-6-acetate (**8**) (0.380 g, 75%) as colorless needles, mp 120-121°; ir: 3400 (NH), 3300 (NH), 1692 (CO) cm<sup>-1</sup>; uv (methanol): λ max (ε) 235 (11000), 263 (12000), 320 (17000) nm; <sup>1</sup>H-nmr (400 Hz) (deuterioacetone): δ 1.17, 1.18 (2t, 3H, J = 7 Hz, Me), 3.36 (s, 3H, OMe), 4.17, 4.18 (2q, 2H, J = 7 Hz, CH<sub>2</sub>), 5.63, 5.65 (2s, 2H, CH<sub>2</sub>O), 6.99 (br s, 0.4 H, NH, E), 7.27 (br s, 0.6H, NH, Z), 7.90 (t, 0.4H, J = 12 Hz, C = CH, E), 8.16 (t, 0.6H, J = 12 Hz, C = CH, Z), 8.20 (br s, 1H, NH), 8.34 (s, 1H, C<sub>8</sub>H), 8.69 (s, 0.6H, C<sub>2</sub>H, Z), 8.76 (s, 0.4H, C<sub>2</sub>H, Z); ms: m/z 277 (M<sup>+</sup>), 205.

Anal. Calcd. for C<sub>12</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>·1/10H<sub>2</sub>O: C, 51.71; H, 5.42; N, 25.10. Found: C, 51.91; H, 5.10; N, 24.74.

#### Preparation of Ethyl 2-[9-(methoxymethyl)-9H-purin-6-yl]propionate (**9**).

A solution of **6** (50 mg, 0.2 mmole) and methyl iodide (45 mg, 0.3 mmole) in sodium methoxide [prepared from sodium (11 mg, 0.5 mg-atom) and absolute methanol (5 ml)] was stirred for 15 hours at room temperature. The solution was neutralized with acetic acid and evaporated *in vacuo*. The residue was dissolved in dichloromethane (20 ml), washed with water (3 x 5 ml), dried with sodium sulfate, and evaporated *in vacuo*. The residue was purified

by preparative tlc on silica gel with 4% methanol in chloroform as developing solvent to give **9** (32 mg, 60%) as a colorless syrup. The compound was identical (mp, ir, and <sup>1</sup>H-nmr) with an authentic sample described above.

#### Ethyl α-(N-Benzylaminomethylene)-9-(methoxymethyl)-9H-purine-6-acetate (**10a**).

A solution of **8** (0.100 g, 0.36 mmole) with benzylamine (0.116 g, 1.08 mmoles) in ethanol (6 ml) was refluxed with stirring for 7 hours. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (15 g) with 1% ethanol in dichloromethane as eluent. The solvent was evaporated *in vacuo* to give **10a** (0.145 g, 90%) as a colorless solid, ir: 3320 (NH), 1690 (CO), 1667 cm<sup>-1</sup>; uv (methanol): λ max (ε) 235 (10700), 270 (13000), 328 (19500) nm; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 1.13 (s, 3H, Me), 3.34 (s, 3H, OMe), 4.11, 4.12 (2q, 2H, CH<sub>2</sub>), 4.58 (s, 2H, CH<sub>2</sub>), 5.57 (s, 2H, CH<sub>2</sub>O), 7.34 (m, 5H, Ph-H), 7.85 (d, 0.46H, J = 14 Hz, C = CH, E), 8.03 (d, 0.54H, J = 14 Hz, C = CH, Z), 8.50 (s, 1H, C<sub>8</sub>H), 8.69 (s, 0.54H, C<sub>2</sub>H, Z), 8.76 (s, 0.46H, C<sub>2</sub>H, E), 9.06 (m, 0.54H, C = CNH, Z), 9.48 (m, 0.46H, C = CNH, E); ms: m/z 367.1617 (M<sup>+</sup>, Calcd. for C<sub>19</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>, 367.1647).

#### Ethyl α-(N-Phenylaminomethylene)-9-(methoxymethyl)-9H-purine-6-acetate (**10b**).

A solution of **8** (100 mg, 0.36 mmole) with aniline (105 mg, 1.08 mmoles) in ethanol (6 ml) was refluxed with stirring for 4 days. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (20 g) with 1% ethanol in dichloromethane as eluent and the solvent was evaporated *in vacuo* to give a solid, which was recrystallized from benzene-hexane to give **10b** (73 mg, 50%) as slightly yellow needles, mp 109-110°; ir: 3300 (NH), 1695 (CO), 1665 cm<sup>-1</sup>; uv (methanol): λ max (ε) 230 (12000), 284 (12600), 350 (28200) nm; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 1.19 (s, 3H, Me), 3.32 (s, 3H, OMe), 4.27 (q, 2H, CH<sub>2</sub>), 5.62 (s, 2H, CH<sub>2</sub>), 7.07-7.46 (m, 5H, phenyl-H), 8.22 (d, 0.5H, J = 13 Hz, C = CH, E), 8.55 (d, 0.5H, J = 13 Hz, C = CH, Z), 8.62 (s, 1H, C<sub>8</sub>H), 8.81 (s, 0.5H, C<sub>2</sub>H, Z), 8.95 (s, 0.5H, C<sub>2</sub>H, E), 10.32 (d, 0.5H, J = 13 Hz, C = CNH, Z), 10.61 (d, 0.5H, J = 13 Hz, C = CNH, E); ms: m/z 353.1482 (M<sup>+</sup>, Calcd. for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O<sub>3</sub>, 353.1487).

#### Reaction of **8** with Piperidine.

A solution of **8** (0.100 g, 0.36 mmole) and piperidine (0.092 g, 1.08 mmoles) in ethanol (4 ml) was refluxed for 5 days. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography on neutral alumina (25 g) with benzene-dichloromethane (1:1 v/v) as eluent to give ethyl 9-(methoxymethyl)-9H-purine-6-acetate (**6**) (55 mg, 61%). The compound was identical (mp, ir and <sup>1</sup>H-nmr) with an authentic sample.

Further elution with benzene-dichloromethane (1:1 v/v) gave ethyl α-(piperidinomethylene)-9-(methoxymethyl)-9H-purine-6-acetate (**11**) (38 mg, 30%) as a colorless solid, ir (chloroform): 3000, 1675 (CO), 1605 cm<sup>-1</sup>; uv (methanol): λ max (ε) 273 (16600), 348 (6920) nm; <sup>1</sup>H-nmr (deuterioacetone): δ 1.18 (t, 3H, Me), 1.52 (m, 6H), 3.05 (m, 4H), 3.40 (s, 3H, OMe), 4.11 (q, 2H), 5.69 (s, 2H, CH<sub>2</sub>), 7.89 (s, 1H, C = CH), 8.53 (s, 1H, C<sub>8</sub>H), 8.85 (s, 1H, C<sub>2</sub>H); ms: m/z 345 (M<sup>+</sup>), 300; ms: m/z 345.1802 (M<sup>+</sup>, Calcd. for C<sub>17</sub>H<sub>23</sub>N<sub>5</sub>O<sub>3</sub>, 345.1802).

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