Norimitsu Hamamichi* [1] and Tadashi Miyasaka

School of Pharmaceutical Sciences, Showa University,
Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

Received August 9, 1990

α-(Aminomethylene)-9*H*-purine-6-acetamide (**3a**) and the corresponding ethyl acetate **9** have been synthesized by catalytic hydrogenation of 6-cyanomethylenepurine derivatives **2** and **7** which were obtained by the substitution of 6-chloropurine derivatives with α-cyanoacetamide and ethyl cyanoacetate, respectively. Substitution of α-(aminomethylene)-9-(tetrahydrofuran)-9*H*-purine-6-acetamide (**3b**) with amines gave the corresponding *N*-alkyl- and *N*-arylamines **5**, which were treated with acid to give *N*-substituted α-(aminomethylene)-9*H*-purine-6-acetamides **6**. Substitution of **9** with amines gave the corresponding *N*-alkyl- and *N*-aryl substituted amines **10**.

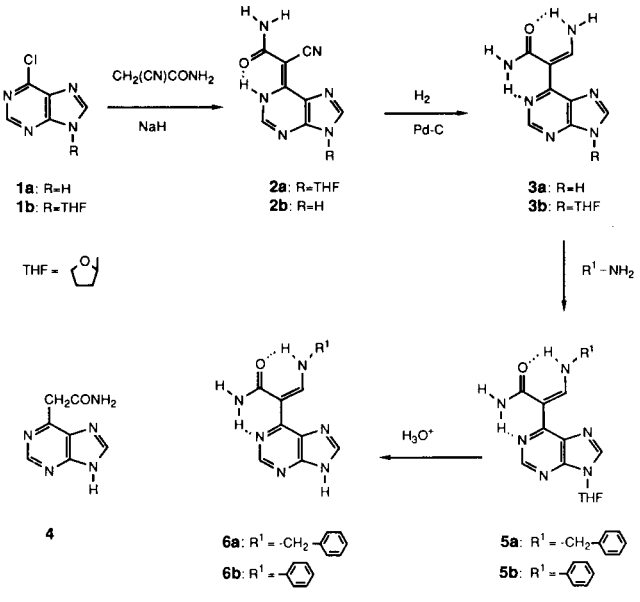
J. Heterocyclic Chem., **28**, 397 (1991).

N^6-Alkylpurine derivatives are important as biological probes for the elucidation of the mechanism of adenosine receptors [2]. Enamino-acetic acid derivatives are also versatile starting materials for the synthesis of *N*-alkyl derivatives [3] and heterocyclic compounds [4]. However, methods for the introduction of an enamine moiety into purine at position 6 have rarely been described [5]. Although 6-cyanomethylene purine derivatives can be prepared in high yield by reaction of the sodium salt of an activated cyanomethylene such as malononitrile, α-cyanoacetamide, and ethyl cyanoacetate with 6-halogenated or methylsulfonated purine derivatives [6], the conversion of the cyano group to the amino function has not been described.

In a previous publication, we described [7] the synthesis of α-(aminomethylene)-9*H*-purine-6-acetonitrile derivatives *via* purine-6-malononitriles, which exist in an enamino-nitrile tautomeric equilibrium. Also, it was found that an *N,N*-dimethylformamide (DMF)-benzene solvent system was best for the catalytic hydrogenation of purine-6-malononitrile. In the present paper, we have extended to syntheses of α-(aminomethylene)-9*H*-purine-6-acetamide **3** and the corresponding ethyl acetate **9** *via* 6-cyanomethylene derivatives **2** and **7** by means of catalytic hydrogenation in a DMF-benzene solvent system. The subsequent substitutions of **3** and **9** with amines are described.

The synthesis of (*Z*)-α-(aminomethylene)-9*H*-purine-6-acetamides **3** and their amine substituted compounds **6** are summarized in Scheme 1. Initial attempts at direct substitution of 6-chloropurine (**1a**) with α-cyanoacetamide at 90° was unsuccessful. Substitution of 6-chloro-9-(tetrahydrofuran-2-yl)-9*H*-purine (**1b**) [8] with α-cyanoacetamide using sodium hydride in DMF gave α-cyano-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetamide (**2a**) in 86% yield, which was treated with 3*N* hydrochloric acid to give α-cyanopurine-6-acetamide (**2b**) in quantative yield. Catalytic hydrogenation of **2b** over Pd-C in DMF-benzene under medium pressure (4 atmospheres) gave (*Z*)-α-(aminomethylene)-9*H*-purine-6-acetamide (**3a**) in 65% yield. The ^{1}H-nmr spectrum showed the presence of a vinyl proton at 9.66 (m) which collapsed to a singlet with deuterium oxide. The configuration of the enamino-amide moiety appears to be *Z* from the downfield chemical shift of the vinyl proton [7]. Attempts to substitute **3a** with benzylamine gave purine-6-acetamide (**4**) [9] which was obtained by addition of benzylamine at the α-position of the enamine, followed by cleavage of the carbon-carbon bond of the enamine moiety with concomitant formation of the amidine fragment [10].

Scheme 1



Catalytic hydrogenation of **2a** over Pd-C in DMF-benzene (1:1, v/v) under medium pressure (4 atmospheres) gave (*Z*)-α-(aminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetamide (**3b**) in 85% yield. In the ^{1}H-nmr spectrum the vinyl proton was found at δ 9.63 as a doublet of doublets which collapsed to a singlet with deuterium oxide. The configuration of the enamino amide moiety appears to be *Z* from the chemical shift of the vinyl proton

Table 1
^{1}H-NMR Data for **3,5** and **6** in DMSO-d_6

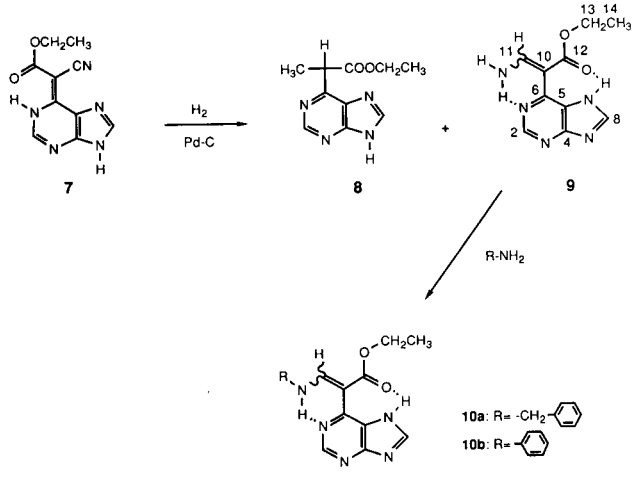
Compound	Chemical Shifts (ppm) (J in Hz) H-2 (s)	H-8 (s)	C=CH (d)	CONH (br s)	CONH (br s)	C=C-NH (m)	Others
3a	8.57	8.34	9.66	6.94	9.90-10.14 [a]		13.19 (1H, br s), 8.19 (m, NH)
3b	8.60	8.49	9.63 [b]	6.96	9.95-10.10 [a]		2.02-2.39 (4H, m), 3.83-4.29 (2H, m), 6.35 (1H, t), 8.29 (t, J = 6 Hz, NH)
5a	8.61	8.52	9.74 (J = 13)	7.10	10.10	11.04	2.08-2.42 (4H, m), 3.82-4.28 (2H, m), 4.60 (2H, d), 6.36 (1H, t), 7.36 (5H, br s)
5b	8.73	8.68	10.27 (J = 13)	7.12	10.21	12.67 [c]	2.11-3.21 (4H, m), 3.84-4.29 (2H, m), 6.40 (1H, t), 7.18-7.44 (5H, m)
6a	8.57	8.35	9.77 (J = 13)	7.17	10.18	10.98	4.60 (2H, d), 7.36 (5H, s)
6b	8.69	8.52	10.36 (J = 13)	7.13	10.30	12.67 [c]	7.06-7.53 (5H, m), 13.50 (1H, br s)

[a] m. [b] dd, J = 14 Hz, J = 8 Hz. [c] d, J = 13 Hz.

[7a]. Substitution of **3b** with benzylamine and aniline under heating gave the corresponding *N*-substituted amines **5a** in 89% yield and **5b** in 57% yield. In the ^{1}H-nmr spectrum the vinyl proton of **5a** was found at δ 9.74 (1H, d). Also the vinyl proton of **5b** was at δ 10.27 (1H, d). Treatment of **5a** and **5b** with 3*N* hydrochloric acid gave the corresponding (*Z*)-α-(*N*-benzylaminomethylene)-9*H*-purine-6-acetamide (**6a**) in 77% yield and (*Z*)-α-(*N*-phenylaminomethylene)-9*H*-purine-6-acetamide (**6b**) in 90% yield.

Catalytic hydrogenation of ethyl α-cyano-9*H*-purine-6-acetate (**7**) [6a] over Pd-C in DMF-benzene gave ethyl 2-(purin-6-yl)propionate (**8**) in 8% yield as an over reduced product and ethyl α-(aminomethylene)-9*H*-purine-6-acetate (**9**) in 63% yield. The ^{13}C-nmr spectrum of **9** in

Scheme 2



perdeuterioacetone showed the C_6 carbon at δ 160.2 ($^3J_{C\text{-}6,H\text{-}11}$ = 10.2 Hz, *E*) (Table 2) [7a]. In the ^{1}H-nmr spectrum (perdeuterioacetone) the vinyl proton was found at δ 8.53 as the major signal which collapsed to a singlet with deuterium oxide. The amino proton of the *E*-form of enamine moiety was also found at δ 11.04 [7a]. The methyl

Table 2
^{13}C-NMR Data for **9** in Perdeuterioacetone

Carbon	Chemical Shifts (ppm)	^{13}C-H Coupling Constant (Hz) C_2H	C_8H	$C_{11}H$
2	150.4	^1J = 199.5		
4	150.8	* [a]	*	
5	119.0			
6	160.2	^3J = 10.2		^3J = 10.2
8	144.1		^1J = 208.3	
10	93.7			
11	156.6			^1J = 167.3
12	168.6			
13	60.3			
14	14.7			

[a] Data not clear.

and C_2 protons showed two sets of signals which were due to geometrical isomers (*E*/*Z*). The ratio of geometrical isomers (*E*/*Z*) was found to be 99:1 by comparing the integration of C_2, vinyl and methyl protons of each isomer. Also, in deuteriodimethyl sulfoxide (DMSO-d_6) the ratio of geometrical isomers (*E*/*Z*) of **9** was 68:32 [11]. It is known that the enamino aldehyde derivative is stabilized in the *E*-form by two hydrogen bonds between the enamine moiety and the purine ring on the basis of X-ray crystallography [5]. This indicates that the *E*-form of enamino ester **9** is more favorable. On the basis of these results the geometrical isomers (*E*/*Z*) of **9** appear to exist in an enamino ester tautomeric equilibrium rather than the imino ester equilibrium [7].

Substitution of **9** with benzylamine and aniline under heating gave the corresponding ethyl α-(*N*-benzylaminomethylene)-9*H*-purine-6-acetate (**10a**) in 78% yield and α-(*N*-phenylaminomethylene)-9*H*-purine-6-acetate (**10b**) in 80% yield. The ^{1}H-nmr spectrum of **10a** in DMSO-d_6 showed two sets of vinyl protons at δ 8.03 (*Z*) and at δ 8.32 (*E*) as a doublet which collapsed to singlets with deuterium oxide, and two sets of amino protons of the enamine moiety at δ 9.33 (*Z*), and δ 11.27 (*E*) [7a]. The ratio of *E*/*Z* was

found to be 75:25. Also, the ratio (*E*/*Z*) of **10b** was 69:31.

In conclusion, the present work demonstrates that catalytic hydrogenation of α-cyanopurine-6-acetamide (**2**) and ethyl α-cyanopurine-6-acetate (**7**) to enaminopurines **3** and **9** in DMF-benzene are highly chemoselective as the enamine moieties and purine rings are uneffected. Enaminopurines **3** and **9** are also known to be versatile intermediates for the preparation of 6-*C*-substituted purine alkyl- and aryl side chains.

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}H-nmr and ^{13}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.

α-Cyano-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetamide (**2a**).

To a cold (0-5°) stirred suspension of 60% sodium hydride (1.20 g, 0.03 mole) in dry DMF (80 ml) was added dropwise a solution of α-cyanoacetamide (3.003 g, 0.035 mole) in dry DMF (15 ml) over a period of 20 minutes. The solution was stirred for 10 minutes at room temperature under argon. After this time, a solution of **1b** (2.245 g, 0.01 mole) in dry DMF (15 ml) was added to the solution and stirring was continued overnight. The solvent was evaporated *in vacuo* and the residue was adjusted to *p*H 4 with 10% acetic acid. The resulting precipitate was collected by filtration, and washed with water, then recrystallized from DMF-ethanol to give **2a** (2.319 g, 86%) as colorless needles, mp 185-188°; ir: 3490 (NH), 3380 (NH), 2370 (CN) cm^{-1}; uv (methanol): λ max (ε) 328 (32400 sh), 339 (36300) nm; ^{1}H-nmr (DMSO-d_6): δ 1.99-2.53 (4H, m), 3.90-4.20 (2H, m), 6.29 (1H, t, J = 5 Hz), 7.02 (2H, br s, NH_2), 8.39 (1H, s, C_8H), 8.43 (1H, d, J = 2 Hz, C_2H), 14.94 (1H, br s, NH); ms: m/z 272 (M$^+$), 202 (B + 1).

Anal. Calcd. for $C_{12}H_{12}N_6O_2$: C, 52.93; H, 4.44; N, 30.87. Found: C, 52.93; H, 4.43; N, 30.89.

α-Cyanopurine-6-acetamide (**2b**).

A solution of **2a** (1.360 g, 0.005 mole) in 3*N* hydrochloric acid (40 ml) was stirred for 3 hours at room temperature. The resulting precipitate was collected by filtration, and washed with water, then recrystallized from DMF-methanol to give **2b** (1.00 g, 99%) as colorless needles, mp 225-228° dec; ir: 3350 (NH), 3160 (NH), 2160 (CN) cm^{-1}; uv (methanol): λ max (ε) 331 (27500), 342 (31620) nm; ^{1}H-nmr (DMSO-d_6): δ 6.98 (2H, br s, NH_2), 8.24 (1H, s, C_8H), 8.38 (1H, d, J = 2 Hz, C_2H), 13.57 (1H, br s, NH), 14.88 (1H, br s, NH); ms: m/z 202 (M$^+$), 159; ms: m/z 246.0861 (M$^+$ Calcd: $C_{10}H_{10}N_6O_2$; 246.0881).

(*Z*)-α-(Aminomethylene)-9*H*-purine-6-acetamide (**3a**).

A solution of **2b** (0.505 g, 0.0025 mole) in DMF-benzene (1:1 v/v, 60 ml) containing saturated methanolic ammonia (13 ml) was hydrogenated over 5% Pd-C (1.5 g) at room temperature under 4.0 atmospheres pressure 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 **3a** (0.333 g, 65%) as colorless needles, mp 205-207°; ir: 3425 (NH), 3290 (NH), 3125 (NH), 1643 (CO) cm^{-1}; uv (methanol): λ max (ε) 235 (14000), 265 (11200), 330 (24500) nm; ms: m/z 204 (M$^+$), 160.

Anal. Calcd. for $C_8H_8N_6O$: C, 47.05; H, 3.95; N, 41.16. Found: C, 47.05; H, 3.84; N, 41.06.

Reaction of **3a** with Benzylamine.

A solution of **3a** (0.102 g, 0.5 mmole) and benzylamine (0.164 g, 1.5 mmoles) in DMF-ethanol (1:3 v/v, 4 ml) was refluxed with stirring for 3 days. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by preparative tlc with 20% methanol in chloroform as developing solvent to give purine-6-acetamide (**4**), which was recrystallized from methanol-hexane to give colorless needles (72 mg, 88%), mp 231-232° dec (lit [9] mp 242°); ir: 3335 (NH), 3150 (NH), 3100 (NH), 1670 (CO) cm^{-1}; uv (methanol): λ max (ε) 262 (8710), 330 (200) nm; ^{1}H-nmr (DMSO-d_6): δ 3.94 (2H, s, CH_2), 7.00 (1H, s, NH), 7.61 (1H, s, NH), 8.54 (1H, s, C_8H), 8.79 (1H, s, C_2H); ms: m/z 177 (M$^+$), 159; ms: m/z 177.0650 (M$^+$, Calcd: $C_7H_7N_5O$; 177.0629).

(*Z*)-α-(Aminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetamide (**3b**).

A solution of **2a** (1.361 g, 5.0 mmoles) in DMF-benzene (1:1 v/v, 200 ml) containing saturated methanolic ammonia (3 ml) was hydrogenated over 5% Pd-C (1.221 g) at room temperature under 4 atmospheres pressure 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 to give **3b** (1.163 g, 85%) as colorless needles, mp 192-195° dec; ir: 3360 (NH), 3280 (NH), 1637 (CO), 1545 cm^{-1}; ms: m/z 274 (M$^+$), 204 (B + 1).

Anal. Calcd. for $C_{12}H_{14}N_6O_2$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.40; H, 5.12; N, 30.75.

(*Z*)-α-(*N*-Benzylaminomethylene)-9-(tetrahydrofuran-2-yl)-9*H*-purine-6-acetamide (**5a**).

A solution of **3b** (0.548 g, 2.0 mmoles) and benzylamine (0.642 g, 6.0 mmoles) in ethanol (20 ml) was refluxed with stirred for 24 hours. After cooling, the resulting precipitate was collected by filtration, and recrystallized from methanol to give **5a** (0.647 g, 89%) as colorless needles, mp 178-179° dec; ir: 3355 (NH), 1630 (CO) cm^{-1}; uv (methanol): λ max (ε) 240 (18200), 275 (13500), 342 (32400), 350 (30900) nm; ms: m/z 294 (M$^+$), 277.

Anal. Calcd. for $C_{15}H_{14}N_6O$: C, 61.21; H, 4.79; N, 28.56. Found: C, 61.30; H, 4.74; N, 28.57.

(*Z*)-α-(*N*-Phenylaminomethylene)-9*H*-purine-"-(tetrahydrofuran-2-yl)-6-acetamide (**5b**).

A solution of **3b** (0.548 g, 2.0 mmoles) and aniline (0.558 g, 6 mmoles) in ethanol (20 ml) was refluxed with stirring for 14 days. After cooling, the resulting precipitate was recrystallized from DMF-hexane to give **5b** (0.399 g, 57%) as yellow needles, mp 204-205°; ir: 3350 (NH), 1640 (CO) cm^{-1}; uv (methanol): λ max (ε) 240 (16900), 281 (16600), 369 (35500) nm; ms: m/z 350 (M$^+$), 280 (B + 1).

Anal. Calcd. for $C_{18}H_{18}N_6O_2$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.60; H, 5.13; N, 23.85.

(*Z*)-α-(*N*-Benzylaminomethylene)-9*H*-purine-6-acetamide (**6a**).

A solution of **5a** (0.182 g, 0.5 mmole) in 1*N* hydrochloric acid (5 ml) was stirred for 5 minutes at room temperature. The solution was adjusted to *p*H 6 with saturated sodium bicarbonate, and the

resulting precipitate was collected by filtration. Recrystallization from methanol gave **6a** (0.113 g, 77%) as colorless needles, mp 215-218° dec; ir: 3330 (NH), 1640 (CO) cm^{-1}; ms: m/z 294 (M^+), 277.

Anal. Calcd. for $C_{15}H_{14}N_6O$: C, 61.21; H, 4.79; N, 28.56. Found: C, 61.30; H, 4.74; N, 28.57.

(*Z*)-α-(*N*-Phenylaminomethylene)-9*H*-purine-6-acetamide (**6b**).

A solution of **5b** (0.175 g, 0.5 mmole) in 1*N* hydrochloric acid (5 ml) was stirred for 1 hour at room temperature. The solution was adjusted to *p*H 6 with saturated sodium bicarbonate, and the precipitate was collected by filtration. Recrystallization from DMF-hexane gave **6b** (0.126 g, 90%) as yellow needles, mp 252-255° dec; ir: 3300 (NH), 1635 (CO) cm^{-1}; uv (methanol): λ max (ε) 239 (15100), 280 (15500), 368 (30900) nm; ms: m/z 280 (M^+), 240.

Anal. Calcd. for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 59.62; H, 4.26; N, 29.82.

Catalytic Hydrogenation of **7**.

A solution of **7** (0.694 g, 3 mmoles) containing saturated methanolic ammonia (5 ml) in DMF-benzene (1:1 v/v, 100 ml) was hydrogenated over 10% Pd-C (2.1 g) at room temperature under 4 atmosphere pressure. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (40 g) using 4% ethanol in chloroform as eluent and the eluate was evaporated *in vacuo* to give a solid, which was recrystallized from acetone-hexane to give ethyl 2-(purin-6-yl)propionate (**8**) (53 mg, 8%) as colorless needles, mp 88-89°; ir: 3100 (NH), 1735 (CO) cm^{-1}; uv (methanol): λ max (ε) 262 (8300) nm; ^{1}H-nmr (perdeuterioacetone): δ 1.12 (3H, t, J = 7 Hz, Me), 1.61 (3H, d, J = 7 Hz, Me), 4.11 (2H, q, J = 7 Hz), 4.55 (1H, q, J = 7 Hz, CH), 8.40 (1H, s, C_8H), 8.80 (1H, s, C_2H), 12.43 (1H, br s, NH); ms: m/z 220 (M^+), 147; ms: m/z 220.0943 (M^+, Calcd: $C_{10}H_{12}N_4O_2$: 220.0958).

Further elution with the same solvent gave ethyl α-(aminomethylene)-9*H*-purine-6-acetate (**9**) (0.444 g, 63%), which was recrystallized from acetone-hexane to give colorless prisms, mp 172-174°; ir: 3300 (NH), 1655 (CO) cm^{-1}; uv (methanol): λ max (ε) 235 (10000), 262 (12900), 330 (22400), 340 (20900, sh) nm; ^{1}H-nmr (perdeuterioacetone): δ 1.28, 1.32 (3H, 2t, J = 7 Hz, Me), 4.27 (2H, q, J = 7 Hz), 7.93 (1H, br s, NH), 8.40 (1H, s, C_8H), 8.53 (0.99H, dd, J = 13 Hz, J = 8 Hz, C=CH, *E*), 8.70 (0.01H, s, C_2H, *Z*), 8.79 (0.99H, s, C_2H, *E*), 11.04 (0.99H, br s, C=C-NH, *E*), 12.28 (1H, br s, NH); ms: m/z 234 (M^+), 167.

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.49; H, 4.75; N, 30.03. Found: C, 51.35; H, 4.69; N, 30.05.

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

A solution of **9** (0.117 g, 0.5 mmole) and benzylamine (0.160 g, 1.5 mmoles) in ethanol (5 ml) was refluxed for 6 hours. After cooling, the resulting precipitate was collected by filtration and recrystallized from acetone-hexane to give **10a** (0.126 g, 78%) as colorless needles, mp 145-146°; ir: 3280 (NH), 1680 (CO) cm^{-1}; uv (methanol): λ max (ε) 237 (8900), 269 (12300), 340 (24500), 350 (24500) nm; ^{1}H-nmr (DMSO-d_6): δ 1.22, 1.27 (3H, 2t, J = 7 Hz, Me), 4.08-4.57 (2H, m), 4.60-4.73 (2H, m), 7.35 (5H, br s, phenyl-H), 8.03 (0.25H, d, J = 14 Hz, C=CH, *Z*), 8.32 (0.75 H, d, J = 14 Hz, C=CH, *E*), 8.39 (0.75H, s, C_8H, *E*), 8.45 (0.25H, s, C_8H, *Z*), 8.71 (0.25H, s, C_2H, *Z*), 8.74 (0.75H, s, C_2H, *E*), 9.33 (0.25H, m, NH, *Z*), 11.27 (0.75H, m, NH, *E*), 12.22 (0.75H, br s, NH, *E*), 12.42 (0.25H, br s, NH, *Z*); ms: m/z 323 (M^+).

Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66. Found: C, 62.96; H, 5.44; N, 21.26.

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

The preparation of **10b** was carried out according to the method described above from **9** (0.117 g, 0.5 mmole) and aniline (0.140 g, 1.5 mmoles). The resulting precipitate was recrystallized from acetone-hexane to give **10b** (0.123 g, 80%) as yellow needles, mp 138-139°; ir: 3300 (NH), 1690 (CO) cm^{-1}; uv (methanol): λ max (ε) 232 (10500), 279 (11200), 365 (28200) nm; ^{1}H-nmr (DMSO-d_6): δ 1.17, 1.28 (3H, 2t, J = 7 Hz, Me), 4.25, 4.27 (2H, 2q, J = 7 Hz), 7.14-7.31 (1H, m, phenyl-H), 7.36-7.42 (4H, m, phenyl-H), 8.39-8.59 (1H, m, C=CH, *E*, *Z*), 8.48 (1H, s, C_8H), 8.78 (0.31H, s, C_2H, *Z*), 8.94 (0.69H, s, C_2H, *E*), 10.57 (0.31H, m, NH, *Z*), 12.50 (0.69H, m, NH, *E*); ms: m/z 309 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_5O_2$: C, 62.12; H, 4.89; N, 22.64. Found: C, 62.26; H, 4.84; N, 22.71.

REFERENCES AND NOTES

[1] Present address: Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, Va 22901, U. S. A.

[2] W. H. Moos, D. S. Szotek and R. F. Bruns, *J. Med. Chem.*, **28**, 1383 (1985).

[3] S. Trofimenko, *J. Org. Chem.*, **28**, 2755 (1963).

[4] M. H. Elnagdi, *Heterocycles*, **20**, 519 (1983), and references cited therein.

[5] D. M. Brown and A. G-Sorolla, *J. Chem. Soc.*, 128 (1971).

[6a] Z. Wakldhof, British Patent 1966, 1029696; *Chem. Abstr.*, **65**, 5472 (1966); [b] E. Hayashi and N. Shimada, *Yakugaku Zasshi*, **99**, 201 (1979).

[7a] N. Hamamichi and T. Miyasaka, *Heterocycles*, **31**, 321 (1990); [b] *Idem., J. Heterocyclic Chem.*, **27**, 835 (1990).

[8] L. R. Lewis, F. H. Schneider and R. K. Robins, *J. Org. Chem.*, **26**, 3837 (1961).

[9] J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **30**, 1528 (1965).

[10] E. N. Dozorova, N. P. Solv'eva and V. G. Granik, *Chem. Heterocyclic Compd. USSR*, **24**, 914 (1988).

[11] ^{1}H-nmr (DMSO-d_6): δ 1.14, 1.25 (3H, 2t, Me), 4.18, 4.21 (2H, 2q, CH_2), 7.92-8.24 (2.32H, m, C=CH, NH), 8.38 (0.68H, s, C_8H, *E*), 8.40 (0.32H, s, C_8H, *Z*), 8.67 (0.32H, s, C_2H, *Z*), 8.75 (0.68H, s, C_2H, *E*), 9.87 (0.68H, br s, NH, *E*), 12.33 (1H, br s, NH).