Purines. LIX.[1] An Alternative Synthesis of 7-Alkyl-1-methyladenines by Regioselective Alkylation, Fission, and Reclosure of the Adenine Ring

Tozo FUJII,* Tohru SAITO, Tomoko SUZUKI, and Mayuri KUNUGI

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan.
Received June 24, 1993

7-Alkyl-1-methyladenines (12a, b) have been synthesized from 1-alkyl-4-aminoimidazole-5-carboxamides (5a, b) in two steps [hence from adenine (1) in six steps]. The synthesis started with dehydration (using $POCl_3$–$HCONMe_2$) of 5a, b, readily obtainable from 1 in four steps according to previously reported procedures, and proceeded through cyclization between the resulting 4-(dimethylaminomethyleneamino)imidazole-5-carbonitrile derivatives (8a, b) and $MeNH_2$. Similar cyclization between 1-benzyl-4-(ethoxymethyleneamino)imidazole-5-carbonitrile (11c) and $MeNH_2$ yielded 7-benzyl-1-methyladenine (12c).

Keywords 7-alkyl-1-methyladenine; carboxamide dehydration; Vilsmeier reagent; imidazolecarbonitrile; dimethylaminomethyleneamino group; cyclization

For the reason cited in our recent publication,[1] we needed to prepare 1,7-dimethyladenine (**12a**), 7-ethyl-1-methyladenine (**12b**), and 7-benzyl-1-methyladenine (**12c**). The first and second compounds (**12a, b**) have recently been synthesized by us[1] from adenosine *via* a seven-step route featuring regioselective alkylation controlled by a methoxy group at the N(1)- or N^6-position. This synthetic route represents an alternative to the general nine-step synthesis of 1,7-dialkyladenines (type **12**) from imidazole (**9**)[2,3] [through 1-alkyl-4-aminoimidazole-5-carbonitrile (**10**) and the ethoxymethyleneamino derivative **11** (Chart 1)], which was first devised by Taylor's group[4] and later extended by Leonard's[5] and Mornet's[6] groups. In the present work, yet another approach for the synthesis of the requisite **12a** and **12b** was designed on the basis of our favorite "fission and reclosure" technology[7] for modification of the adenine ring (**1**), and the Taylor–Leonard's procedure[4,5] was applied to the preparation of **12c**.

The starting point selected for the synthesis of the first target, 1,7-dimethyladenine (**12a**), was 4-amino-1-methylimidazole-5-carboxamide (**5a**), which was obtainable from adenine (**1**) in four steps *via* 3-benzyladenine (**2**),[8] 3-benzyl-7-methyladenine hydriodide (**3a**: X = I),[9] and 4-benzylamino-1-methylimidazole-5-carboxamide (**4a**)[10] according to previously reported procedures.[10] In an attempt to connect this ring-fission route to the above Taylor's route, direct conversion of **5a** into **10a** was first

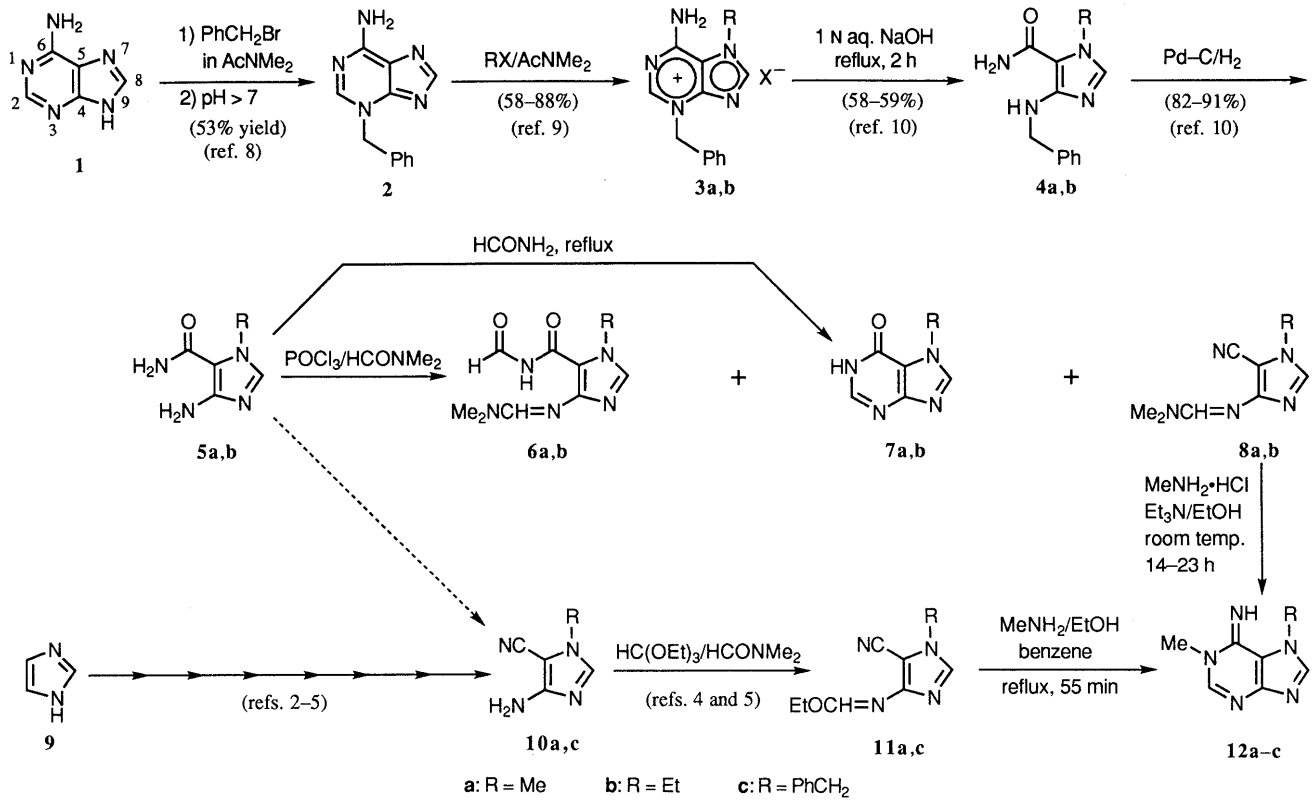

Chart 1

tried. However, dehydration experiments with **5a**·$HClO_4$ using $POCl_3$ (with or without Et_3N) under a variety of conditions were all unsuccessful.

Albert has reported that treatment of 4-amino-1-methyl-1,2,3-triazole-5-carboxamide with $POCl_3$ in $HCONMe_2$ at 25 °C gave 4-dimethylaminomethyleneamino-1-methyl-1,2,3-triazole-5-carbonitrile (60% yield), together with its *N*-formyl-5-carboxamide derivative (6%).[11] This procedure would be applicable to the dehydration of **5a** if the possible concurrent modification of the 4-amino group is permissible. On treatment with $POCl_3$ in $HCONMe_2$ below 35 °C for *ca.* 3 h, **5a**·$HClO_4$ produced 4-dimethylaminomethyleneamino-1-methylimidazole-5-carbonitrile (**8a**) in 70% yield, together with small amounts of 7-methylhypoxanthine (**7a**) and a substance inferred to be the *N*-formyl-5-carboxamide derivative **6a**. The formation of **6a** as a by-product was anticipated from the case[11] of the triazole analogue described above, and the correctness of the structure of **7a** was supported by its identity with a sample obtained from the reaction of **5a**·$HClO_4$ with boiling $HCONH_2$ for 45 min.[12]

Cyclization of **8a** was then effected with $MeNH_2$·HCl in EtOH in the presence of Et_3N at room temperature for 23 h, and the product was isolated in the form of the perchlorate salt, affording the desired compound **12a**·$HClO_4$ in 68% yield (in 12% overall yield from **1**). In this cyclization, replacement of added tertiary amine or all the amine components by $MeNH_2$ lowered the yield of **12a** to a considerable extent, and application of a higher reaction temperature appeared to cause **12a** to rearrange to isomeric N^6,7-dimethyladenine.[4]

A parallel sequence of reactions starting from the 1-ethyl homologue **5b**, obtainable from **1** through **2**,[8] **3b** (X = ClO_4),[9] and **4b**[10] according to the previously reported procedures,[10] was followed for the synthesis of the second target 7-ethyl-1-methyladenine (**12b**). Thus, **5b**·$HClO_4$ was treated with Vilsmeier reagent at room temperature for 3 h, giving **8b** in 60% yield, together with substances inferred to be **6b** (*ca.* 1%) and **7b** (*ca.* 1%). The reaction of **8b** with $MeNH_2$·HCl was carried out as described above for **8a**, and the cyclized product was isolated as the perchlorate salt, furnishing **12b**·$HClO_4$ in 51% yield (in 4.6% overall yield from **1**).

Finally, the preparation of the third target **12c** from 1-benzyl-4-(ethoxymethyleneamino)imidazole-5-carbonitrile (**11c**)[5] and $MeNH_2$ was tried according to the general procedure[4] of Taylor and Loeffler. On treatment with 40% ethanolic $MeNH_2$ in boiling benzene for 55 min, **11c** provided 7-benzyl-1-methyladenine (**12c**) in 93% yield.

In conclusion, the above reaction sequence **1**→**2**→**3**→**4**→**5**→**8**→**12** represents a new six-step synthetic route to 7-alkyl-1-methyladenine (**12**) from adenine (**1**). It features a synthetic strategy of utilizing the "fission and reclosure" technology[7] developed for modification of the adenine ring and appears to be potentially applicable as a general procedure to the synthesis of 1,7-dialkyladenines.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 10 for details of instrumentation and measurements. The solvents used for measurements of UV spectra were 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13). Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

Reaction of 4-Amino-1-methyl-1*H*-imidazole-5-carboxamide Perchlorate (5a·$HClO_4$) with Vilsmeier Reagent A solution of **5a**·$HClO_4$[10] (4.15 g, 17.2 mmol) in $HCONMe_2$ (34.5 ml) was stirred in a cooling bath, and then $POCl_3$ (7.92 g, 51.6 mmol) was added dropwise over a period of 55 min at such a rate that the inner temperature did not exceed 35 °C. After having been stirred at room temperature for 2 h, the reaction mixture was poured onto ice-water (*ca.* 17 ml). The resulting aqueous mixture was brought to pH 7 with 10% aqueous Na_2CO_3 and then extracted with $CHCl_3$ (12 × 50 ml) at that pH. The $CHCl_3$ extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a brownish yellow solid (3.10 g), which was purified by means of column chromatography [silica gel (310 g), CH_2Cl_2–EtOH (30 : 1, v/v)]. Earlier fractions gave a substance (75 mg, *ca.* 2%) inferred to be 4-dimethylaminomethyleneamino-*N*(5)-formyl-1-methyl-1*H*-imidazole-5-carboxamide (**6a**), mp 122 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3400—3200 (NH), 1721 and 1670 (CONHCO), 1625 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 3.12 and 3.14 (6H, s each, N=CH–N$\underline{Me}_2$), 3.91 [3H, s, N(1)-Me], 7.30 [s, C(2)-H], 8.47 (1H, s, N=C$\underline{H}$–NMe_2), 9.30 (1H, d, J = 10 Hz, NHC$\underline{H}$O), 11.80 (1H, dull d, J = 10 Hz, N$\underline{H}$CHO).

Middle fractions collected from the above chromatography yielded 4-dimethylaminomethyleneamino-1-methyl-1*H*-imidazole-5-carbonitrile (**8a**) (2.14 g, 70%) as a yellowish solid, mp 101—104 °C. The solid was further purified and characterized as described below.

Later fractions of the above chromatography contained 7-methylhypoxanthine (**7a**). In a separate run, however, **7a** was isolated more efficiently in the following manner. The $CHCl_3$ extracts of the reaction mixture, obtained as described above, were concentrated *in vacuo*, and the residue was extracted successively with hot benzene–hexane (1 : 1.5, v/v) and hot benzene (**8a** was obtained in 56% yield from these extracts), leaving an insoluble brown solid. Two recrystallizations of the solid from EtOH gave **7a**, mp > 300 °C, in 3.8% yield. This sample was identical (by comparison of the IR and ^{1}H-NMR spectra) with the one prepared from **5a**·$HClO_4$ and $HCONH_2$ (*vide infra*).

4-Dimethylaminomethyleneamino-1-methyl-1*H*-imidazole-5-carbonitrile (8a) The crude sample of **8a** described above was recrystallized from benzene–hexane (1 : 2, v/v) to yield an analytical sample as slightly yellowish prisms, mp 102—106 °C; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 223 nm (ε 13000), 291 (21500); $\lambda_{max}^{H_2O}$ (pH 1) 263 (16000); $\lambda_{max}^{H_2O}$ (pH 7) 222 (13800), 288 (20000); $\lambda_{max}^{H_2O}$ (pH 13) 223 (13800), 288 (20200); IR ν_{max}^{Nujol} cm^{-1}: 2205 (C≡N), 1625 (br, C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 2.95 and 3.07 (3H each, s, N=CH-N$\underline{Me}_2$), 3.63 [3H, s, N(1)-Me], 7.64 [1H, s, C(2)-H], 8.34 (1H, s, N=C$\underline{H}$-NMe_2). *Anal.* Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.18; H, 6.26; N, 39.23.

7-Methylhypoxanthine (7a) A stirred suspension of **5a**·$HClO_4$[10] (289 mg, 1.2 mmol) in $HCONH_2$ (1 ml) was heated under reflux in an atmosphere of N_2 for 45 min. The reaction mixture was concentrated *in vacuo*, and the residual oil was kept in a refrigerator for 2 d. The brown solid that resulted was collected by filtration and recrystallized from EtOH, giving brownish granules (120 mg), mp 242—245 °C. Purfication of the crystals by means of column chromatography [alumina (10 g), $CHCl_3$– MeOH (4 : 1, v/v)] afforded **7a** (37 mg, 21%), mp > 300 °C. Further purification was effected by recrystallization from EtOH to provide an analytical sample as coloress needles, mp > 300 °C [lit.[13] mp 356—357 °C (dec.)]; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 256 nm (ε 9100); $\lambda_{max}^{H_2O}$ (pH 1) 250 (10450); $\lambda_{max}^{H_2O}$ (pH 7) 255 (9760); $\lambda_{max}^{H_2O}$ (pH 13) 262 (10500); ^{1}H-NMR (Me_2SO-d_6) δ: 3.96 [3H, s, N(7)-Me], 7.94 [1H, s, C(2)-H], 8.14 [1H, s, C(8)-H], 12.0—12.4 [1H, br, N(1)-H]. *Anal.* Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.75; H, 3.95; N, 37.24.

Reaction of 4-Amino-1-ethyl-1*H*-imidazole-5-carboxamide Perchlorate (5b·$HClO_4$) with Vilsmeier Reagent *N*,*N*-Dimethylformamide (2 ml) was stirred under ice-cooling, and $POCl_3$ (460 mg, 3 mmol) was added dropwise. The mixture was stirred at room temperature for 15 min, then **5b**·$HClO_4$[10] (255 mg, 1 mmol) was added in portions under ice-cooling. The resulting mixture was again stirred at room temperature for 3 h and then poured onto ice (1.3 g). The aqueous mixture was brought to pH 7—8 by addition of anhydrous Na_2CO_3 and extracted with $CHCl_3$ (3 × 10 ml). The $CHCl_3$ extracts were combined, washed with saturated aqueous K_2CO_3 (1 ml), dried over anhydrous Na_2SO_4, and concentrated

in vacuo to leave a brownish yellow solid (190 mg), which was subjected to flash chromatography[14] [silica gel, CH_2Cl_2–EtOH (20 : 1, v/v; 10 : 1, v/v; and 5 : 1, v/v)]. Earlier fractions gave a substance (3 mg, *ca.* 1%) inferred to be 4-dimethylaminomethyleneamino-1-ethyl-*N*(5)-formyl-1*H*-imidazole-5-carboxamide (**6b**) as a colorless solid, mp 161—163 °C; IR ν_{max}^{Nujol} cm^{-1}: 3400—3200 (NH), 1720 and 1670 (CONHCO), 1625 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 1.31 [3H, t, J=7 Hz, N(1)-CH_2Me], 3.01 and 3.15 (3H each, s, H=CH–NMe_2), 4.25 [2H, q, J=7 Hz, N(1)-CH_2Me], 7.81 [1H, s, C(2)-H], 8.52 (1H, s, N=CH–NMe_2), 9.14 (1H, d, J=10 Hz, NHCHO), 12.06 (1H, dull d, J=10 Hz, NHCHO).

Middle fractions of the above chromatography afforded 4-dimethylaminomethyleneamino-1-ethyl-1*H*-imidazole-5-carbonitrile (**8b**) (115 mg, 60%) as colorless needles, mp 73—75 °C. The crystals were further purified and characterized as described below.

Later fractions collected from the above chromatography gave a substance (2 mg, *ca.* 1%) inferred to be 7-ethylhypoxanthine (**7b**)[15] as slightly yellowish needles, mp 227—243 °C; IR ν_{max}^{Nujol} cm^{-1}: 3500—3250 (NH), 1680 (br, CO); ^{1}H-NMR (Me_2SO-d_6) δ: 1.41 [3H, t, J=7 Hz, N(7)-CH_2Me], 4.34 [2H, q, J=7 Hz, N(7)-CH_2Me], 7.97 [1H, slightly dull s, C(2)-H], 8.24 [1H, s, C(8)-H], 12.29 (1H, br, NH).

4-Dimethylaminomethyleneamino-1-ethyl-1*H*-imidazole-5-carbonitrile (8b) The crude sample of **8b** described above was recrystallized from benzene–hexane (1 : 3, v/v) to furnish an analytical sample as almost colorless needles, mp 76.5—77 °C; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 223 nm (ε 13300), 291 (22000); $\lambda_{max}^{H_2O}$ (pH 1) 263 (16200); $\lambda_{max}^{H_2O}$ (pH 7) 223 (14100), 289 (21200); $\lambda_{max}^{H_2O}$ (pH 13) 223 (14200), 289 (21300); IR ν_{max}^{Nujol} cm^{-1}: 2205 (C≡N), 1625 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 1.35 [3H, t, J=7 Hz, N(1)-CH_2Me], 2.94 and 3.05 (3H each, s, N=CH–NMe_2), 3.98 [2H, q, J=7 Hz, N(1)-CH_2Me], 7.68 [1H, s, C(2)-H], 8.32 (1H, s, N=CH–NMe_2). *Anal.* Calcd for $C_9H_{13}N_5$: C, 56.53; H, 6.85; N, 36.62. Found: C, 56.46; H, 6.94; N, 36.63.

1,7-Dimethyladenine (12a) i) Cyclization of **8a** with $MeNH_2$·HCl/Et_3N: A mixture of Et_3N (880 mg, 8.7 mmol), $MeNH_2$·HCl (2.94 g, 43.5 mmol), and **8a** (1.54 g, 8.7 mmol) in abs. EtOH (80 ml) was stirred at room temperature for 23 h. The reaction mixture was concentrated *in vacuo* to leave a colorless solid. The solid was washed with benzene (3 × 20 ml) and extracted with hot MeOH (2 × 10 ml) to leave an insoluble hygroscopic solid (1.08 g) [mp 224.5—230 °C (dec.)] presumed to be **12a**·HCl. The methanolic extracts were combined and concentrated *in vacuo*, and the residue was chromatographed [alumina (220 g), CH_2Cl_2–EtOH (15 : 1, v/v; 6 : 1, v/v)] to afford the free base **12a** (210 mg) as a hygroscopic solid, mp 164—165 °C. The free base was converted into the perchlorate salt by dissolving it in warm EtOH (4.5 ml) and adding 70% aqueous $HClO_4$ (210 mg), giving a first crop (287 mg) of **12a**·$HClO_4$ as a colorless solid, mp 278—279 °C (dec.).

The crude, MeOH-insoluble **12a**·HCl described above was dissolved in H_2O (35 ml). The resulting aqueous solution was applied to a column of Amberlite IRA-402 (HCO_3^-) (11 ml), and the column was eluted with H_2O (350 ml). The eluate was concentrated *in vacuo* below 30 °C (bath temperature), and the residue was dissolved in hot EtOH (30 ml) after having been dried in a desiccator. The ethanolic solution was treated with 70% aqueous $HClO_4$ (940 mg) in the usual manner, yielding a second crop (1.26 g) of **12a**·$HClO_4$ as a colorless solid, mp 278—279 °C (dec.). The total yield of **12a**·$HClO_4$ was 1.55 g (68% from **8a**). For analysis, the crude **12a**·$HClO_4$ was recrystallized from MeOH to give a pure sample as colorless needles, mp 278—280 °C (dec.) (dried over P_2O_5 at 2 mmHg and room temperature for 35 h). *Anal.* Calcd for $C_7H_9N_5$·$HClO_4$: C, 31.89; H, 3.82; N, 26.56. Found: C, 31.80; H, 3.85; N, 26.77. The UV and ^{1}H-NMR spectral data obtained with this sample were in agreement with those[1] reported for **12a**·$HClO_4$·1/5H_2O.

ii) Cyclization of **8a** with $MeNH_2$·HCl/$MeNH_2$: A mixture of **8a** (301 mg, 1.7 mmol), $MeNH_2$·HCl (581 mg, 8.6 mmol), and 40% (w/w) ethanolic $MeNH_2$ (670 mg, 8.63 mmol) in abs. EtOH (7.2 ml) was stirred at 25 °C for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in a small amount of H_2O. The aqueous solution was applied to a column of Amberlite IRA-402 (HCO_3^-) (21 ml), and the column was eluted with H_2O (700 ml). The eluate was concentrated *in vacuo* below 30°C (bath temperature). The residue was dried and purified by column chromatography [alumina (37 g), CH_2Cl_2–EtOH (25 : 1, v/v)] to give the free base **12a** (69.6 mg, 24%) as a colorless solid, mp 128—172 °C. Five recrystallizations of the solid from benzene and drying over P_2O_5 at 2 mmHg and 50 °C for 14 h yielded an analytical sample of **12a**·3/5H_2O as colorless, hygroscopic prisms, mp 163—168 °C [lit.[4] mp 170—171 °C (for an anhydrous sample)]; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 264 nm (ε 10700), 271 (sh) (9900); $\lambda_{max}^{H_2O}$ (pH 1) 269 (9500), 282 (sh) (5300); $\lambda_{max}^{H_2O}$ (pH 7) 269 (9500), 282 (sh) (5300); $\lambda_{max}^{H_2O}$ (pH 13) 264.5 (11100); ^{1}H-NMR (Me_2SO-d_6) δ: 3.37 [3H, s, N(1)-Me], 4.00 [3H, s, N(7)-Me], 6.84 (1H, br, NH), 7.88 and 7.90 (2H, s each, purine protons). *Anal.* Calcd for $C_7H_9N_5$·3/5H_2O: C, 48.32; H, 5.91; N, 40.25. Found: C, 48.55; H, 5.91; N, 40.16.

7-Ethyl-1-methyladenine (12b) A mixture of Et_3N (1.67 g, 16.5 mmol), $MeNH_2$·HCl (5.57 g, 82.5 mmol), and **8b** (3.16 g, 16.5 mmol) in abs. EtOH (165 ml) was stirred at 25—27°C for 14 h and then cooled in an ice bath for 1 h. The colorless precipitate that resulted was filtered off, washed with a little EtOH, and dried to give crude **12b**·HCl (2.08 g), mp 255—258 °C (dec.), which was dissolved in H_2O (30 ml). The aqueous solution was applied to a column of Amberlite IRA-402 (HCO_3^-) (19.5 ml), and the column was eluted with H_2O (500 ml). Concentration of the eluate under reduced pressure below 30 °C (bath temperature) and drying of the residue over P_2O_5 at 3 mmHg and 35 °C for 24 h gave the free base **12b** (1.83 g) as a colorless solid, mp 210—227 °C. The whole of the dried solid was dissolved in hot MeOH (20 ml), and 70% aqueous $HClO_4$ (1.64 g) was added. The resulting mixture was kept in a refrigerator overnight, and the colorless minute needles that deposited were collected by filtraction, washed with a little EtOH, and dried to provide the perchlorate salt **12b**·$HClO_4$ (2.35 g, 51% from **8b**), mp 259—260 °C (dec.). This sample was identical (by comparison of the UV and IR spectra) with authentic **12b**·$HClO_4$.[1]

7-Benzyl-1-methyladenine (12c) A solution of **11c**[5] (418 mg, 1.64 mmol) in benzene (8 ml) was stirred at room temperature, and 40% (w/w) ethanolic $MeNH_2$ (2.48 g) was added. The resulting solution was heated under reflux for 55 min and then cooled to room temperature. After addition of hexane (15 ml), the reaction mixture was kept in a refrigerator overnight. The slightly pinkish needles that deposited were collected by filtration to give the base **12c** (366 mg, 93%), mp 183.5—190 °C. Recrystallization from AcOEt afforded an analytical sample of **12c** as slightly yellowish prisms, mp 190—192 °C; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 265 nm (ε 10100), 271 (sh) (9600); $\lambda_{max}^{H_2O}$ (pH 1) 272 (9300), 282 (sh) (6100); $\lambda_{max}^{H_2O}$ (pH 7) 268 (9600), 282 (sh) (6100); $\lambda_{max}^{H_2O}$ (pH 13) 265 (10800); ^{1}H-NMR (Me_2SO-d_6) δ: 3.36 [3H, s, N(1)-Me], 5.71 [2H, s, N(7)-CH_2Ph], 6.76 (1H, br, NH), 7.29 [5H, m, N(7)-CH_2Ph], 7.93 and 8.13 (1H each, s, purine protons). *Anal.* Calcd for $C_{13}H_{13}N_5$: C, 65.26; H, 5.48; N, 29.27. Found: C, 65.19; H, 5.30; N, 29.22.

References and Notes

1) Paper LVIII in this series, T. Fujii, T. Saito, K. Yamamoto, R. Ii, *Chem. Pharm. Bull.*, **41**, 2047 (1993).
2) I. E. Balaban, F. L. Pyman, *J. Chem. Soc.*, **121**, 947 (1922).
3) *a*) Y. Kikugawa, *Synthesis*, **1981**, 124; *b*) V. Caló, F. Ciminale, L. Lopez, F. Naso, P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2567.
4) E. C. Taylor, P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).
5) N. J. Leonard, K. L. Carraway, J. P. Helgeson, *J. Heterocycl. Chem.*, **2**, 291 (1965).
6) A. Er-Rhaimini, N. Mohsinaly, R. Mornet, *Tetrahedron Lett.*, **31**, 5757 (1990).
7) *a*) For a review, see T. Fujii, T. Itaya, T. Saito, *Yuki Gosei Kagaku Kyokai Shi*, **41**, 1193 (1983); *b*) T. Fujii, T. Saito, K. Tamura, *Chem. Pharm. Bull.*, **39**, 2855 (1991); *c*) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, T. Fujisawa, *ibid.*, **39**, 301 (1991), and earlier references cited therein.
8) *a*) N. J. Leonard, T. Fujii, *J. Am. Chem. Soc.*, **85**, 3719 (1963); *b*) J. A. Montgomery, H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964); *c*) T. Fujii, G. C. Walker, N. J. Leonard, D. C. DeLong, K. Gerzon, *J. Med. Chem.*, **22**, 125 (1979).
9) T. Fujii, T. Saito, I. Inoue, Y. Kumazawa, N. J. Leonard, *Chem. Pharm. Bull.*, **34**, 1821 (1986).
10) T. Fujii, T. Saito, I. Inoue, Y. Kumazawa, T. Tamura, *Chem. Pharm. Bull.*, **36**, 107 (1988).
11) A. Albert, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 461.
12) A similar cyclization of **5a**·HCl with boiling $HCONH_2$ has been reported by Prasad and Robins.[13]
13) R. N. Prasad, R. K. Robins, *J. Am. Chem. Soc.*, **79**, 6401 (1957).
14) W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
15) J. W. Hadden, L. N. Simon, A. Giner-Sorolla, Patent Specif. (Aust.) AU 554372 (1986) [*Chem. Abstr.*, **108**, 37511*s* (1988)].