

Purines. LXXVII.¹⁾ An Alternative Synthesis of *N*⁶-Demethylcaissarone from 9-Methyl-8-oxoadenine by Regioselective *N*(3)-Methylation: Utilization of the *N*(7)-Benzyl and *N*(1)-Benzyloxy Groups as Control Synthons

Taisuke ITAYA,* Tae KANAI, Mayumi SHIMADA, Toshiko NISHIKAWA, Yasutaka TAKADA, Yoshitaka HOZUMI, Shigeji MORI, Tohru SAITO, and Tozo FUJII

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan.

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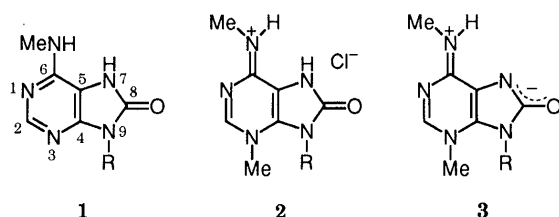
An alternative synthesis of 3,9-dimethyl-8-oxoadenine (*N*⁶-demethylcaissarone) hydrochloride (**5a**·HCl) starting from 9-methyl-8-oxoadenine (**17**) is described. The synthesis proceeded through *N*(7)-benzylation, *N*(1)-oxidation, and *O*-benzylation to afford the 1-benzyloxy derivative **25**, which afforded the ring-opened formamide derivative **26** on treatment with dilute aqueous NaOH. Methylation of the monocycle **26** with MeI in the presence of K₂CO₃, followed by acid-catalyzed cyclization and subsequent catalytic hydrogenolysis afforded **5a**·HCl. The key intermediate **25** was alternatively prepared from **17** by *N*-oxidation and subsequent *O,N*(7)-dibenylation with PhCH₂Br in the presence of K₂CO₃.

Key words 3,9-dimethyl-8-oxoadenine synthesis; 1-alkoxy-8-oxoadenine; Dimroth rearrangement; 8-oxoadenine *N*-oxidation; *N*⁶-demethylcaissarone

Caissarone hydrochloride (**2a**), a purine alkaloid isolated from the sea anemone *Bunodosoma caissarum* CORREA 1964,²⁾ has been synthesized by us through regioselective methylation of *N*⁶,9-dimethyl-8-oxoadenine (**1a**).³⁾ We have reported that **2a** affords the corresponding free base in the zwitterionic form (**3a**) on treatment with Amberlite IRA-402 (HCO₃[−]) and that **3a** is capable of forming a hetero-base pair with 2',3',5'-tri-*O*-acetylguanosine in (CD₃)₂SO through intermolecular hydrogen bonding.^{3b)} This led us to consider the corresponding nucleosides **3b**, **c** and their *N*⁶-demethyl derivatives (e.g., **5b**) as building blocks for the synthesis of functionalized nucleic acids. Unfortunately, however, similar methylation of the nucleoside analogue **1c** did not produce **3c**, but gave the 1-methyl derivative, together with a lesser amount of the *N*⁶,*N*⁶-dimethyl isomer.⁴⁾ It follows that the key to access to **3b**, **c** is how to construct a 3,9-disubstituted 8-oxoadenine unit (type **5**) as simplified in *N*⁶-demethylcaissarone (**5a**). The isomerically substituted patterns such as 9-substituted 8-oxoadenines methylated at the *N*⁶- (type **1**),^{4,5)} 1- (type **4**),^{4–6)} 7- (type **6**),^{1,6)} and *O*⁸-positions (type **7**)⁷⁾ have been synthesized from 9-substituted adenines (**8**). On the other hand, 3,9-dimethyl-8-oxoadenine (*N*⁶-demethylcaissarone) (**5a**), the prototype of the remaining *N*^x,9-disubstituted 8-oxoadenines, has recently been synthesized by us from 3-methyladenine through regioselective methylation of 3-methyl-8-hydroxyadenine.¹⁾ The nu-

cleoside analogue **5b**, however, seems to be hardly obtainable by this method.¹⁾ Thus, we tried to develop an alternative synthesis of **5a**, which might be applicable to the synthesis at the nucleoside level, in the present study. This paper reports the synthesis of **5a** from 9-methyl-8-oxoadenine (**17**) and hence from 9-methyladenine (**8**; R¹ = Me).

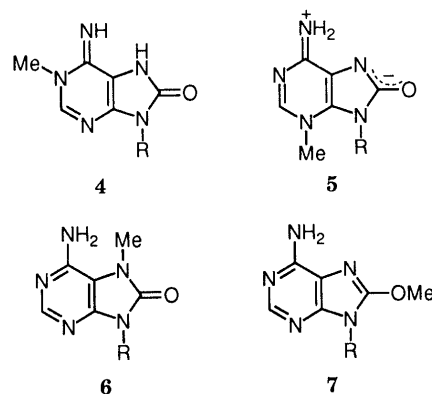
We first attempted to synthesize **5a** from the monocycle **12** (R¹ = R² = Me), the key intermediate for the synthesis of 3,9-dimethyladenine (type **13**)^{8a)} starting from 9-methyladenine (**8**; R¹ = Me). Compound **12** (R¹ = R² = Me) afforded the 2-bromo compound **15** in 58% or 52% yield on treatment with Br₂ and AcONa in AcOH or with *N*-bromoacetamide in CHCl₃ in the presence of benzoyl peroxide. An attempt to transform **15** into the 2-oxoimidazole **21a** by heating it with AcONa in AcOH resulted in the formation of a complex mixture of products. The formamide **15** was then hydrolyzed to the amine **16** (96% yield), which also gave a complex mixture of products when heated with either 1*N* aqueous NaOH, MeONa–MeOH, EtONa–EtOH, EtONa–EtOH–18-crown-6, PhCH₂ONa–Me₂SO, or AcONa–AcOH. Since **16** was found to undergo acetylation at the methylamino



a: R = Me

b: R = 2-deoxy-β-D-ribofuranosyl

c: R = β-D-ribofuranosyl



a: R = Me

b: R = β-D-ribofuranosyl

* To whom correspondence should be addressed.

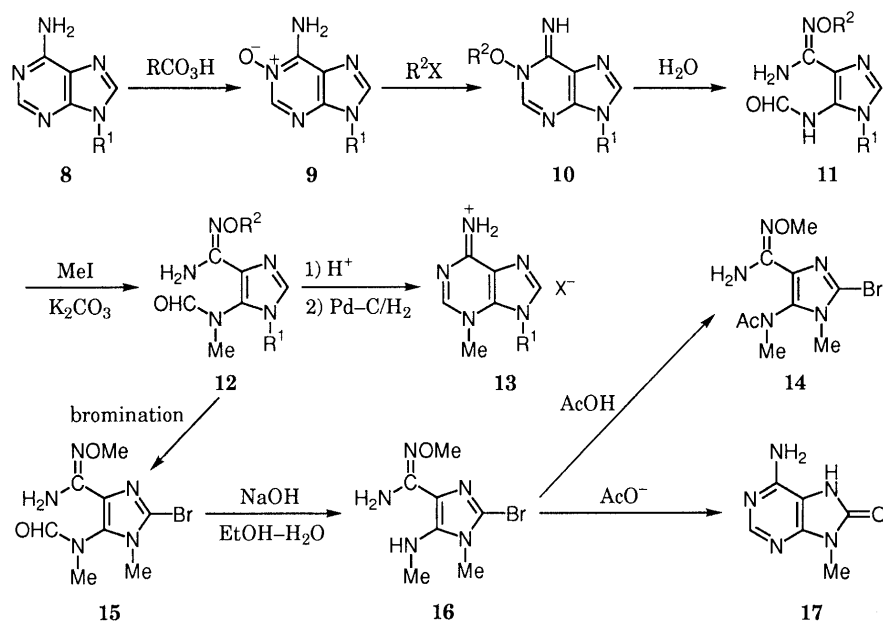


Chart 1

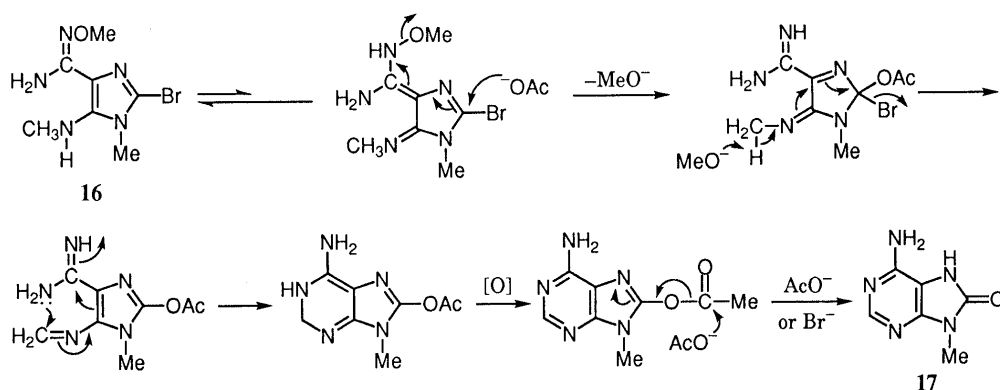


Chart 2

moiety to afford the acetamide **14** in the presence of AcOH , **16** was heated with an excess of AcOK in HCONMe_2 in the presence of 18-crown-6 at 100°C for 120 h. However, this unexpectedly furnished 9-methyl-8-oxoadenine (**17**)⁵ in 20% yield. The formamide **15** was inert under these conditions. Replacement of the solvent HCONMe_2 by Me_2SO raised the yield of **17** from **16** to 36%. Compound **17** was also obtainable in 30% yield by heating **16** with tetrabutylammonium acetate in HCONMe_2 at 100°C for 48 h. On the other hand, no trace of **17** was found when **16** was heated under reflux with an excess of MeONa in MeOH for 22 h. Although **17** was an undesirable product for this particular synthetic scheme, the mechanism of its formation deserves consideration. A plausible reaction sequence is delineated in Chart 2.

In designing a second synthetic route to the target **5a**, the synthesis was planned to follow an 8-oxo version of our previous syntheses of 3,9-dialkyladenines,^{8a} 3-methyladenosine,^{8b} and 2'-deoxy-3-methyladenosine^{8b} (**8** $\rightarrow$ **13** in Chart 1), as shown in part in Chart 3. Treatment of 9-methyl-8-oxoadenine (**17**), easily obtainable from 9-methyladenine (**8**; $\text{R}^1 = \text{Me}$) according to the literature procedure,⁵ with *m*-chloroperoxybenzoic acid (MCPBA) in MeOH at 30°C for 24 h afforded the N -oxide **18** in

98% yield. The assignment of the 8-oxo structure to **18** was based on its IR spectrum (Nujol), which displayed a carbonyl absorption band at 1694 cm^{-1} .⁵ The UV spectrum of **18** in H_2O at pH 7 exhibited a strong absorption band at 240 nm (ϵ 56400), which is indicative of the overwhelming predominance of the N -oxide tautomer over the N -OH tautomer.⁹ Although it was considered that N -oxidation occurred most likely at the 1-position on the basis of the occurrence of regiospecific N(1)-methylation of **17** on treatment with MeI in AcNMe_2 ⁵ and data accumulated for N^x -oxidation of N^x -monosubstituted adenines,⁹ final identification of **18** as the N(1)-oxide rested on the following self-consistent reaction sequence and on its conversion into the target molecule **5a** through the $O,N(7)$ -dibenzylated derivative **25** (Chart 5). Methylation of **18** with MeI in AcNMe_2 at 50°C for 3 d and subsequent treatment with Amberlite IRA-402 (HCO_3^-) afforded the 1-methoxy compound **19a** in 61% yield. The 1-methoxy structure of **19a** was supported by its UV spectral similarity to 1,9-dimethyl-8-oxoadenine (**4a**)⁵ and by its facile ring-opening in the pyrimidine moiety (*vide infra*), characteristic of 1-alkoxyadenine derivatives.^{9,10} The IR spectrum (Nujol) of **19a** lacking a carbonyl absorption band in the $1755\text{--}1680\text{ cm}^{-1}$

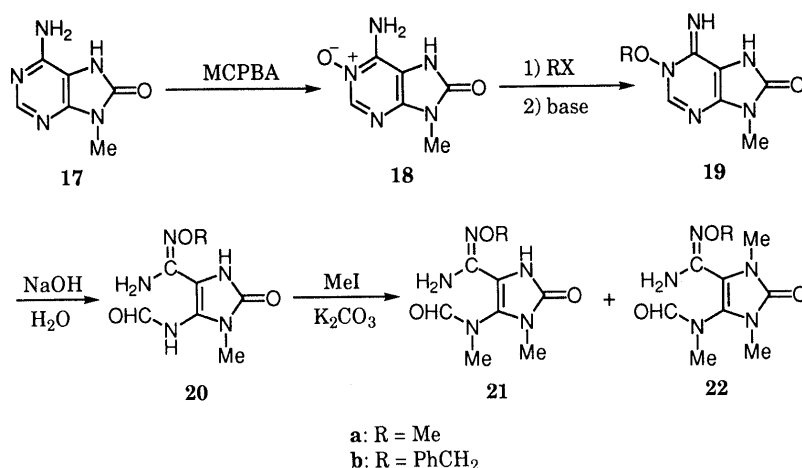


Chart 3

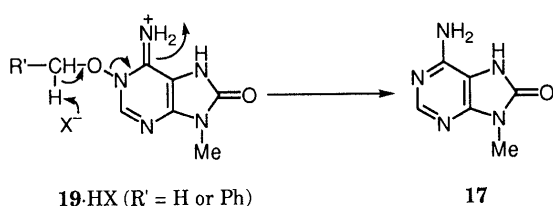


Chart 4

region^{3b)} suggests that **19a** exists as the C(8)-OH form in the solid state. The molecular absorption coefficients for **19a** measured in 95% aqueous EtOH increased with time during 2 h after dissolution, while those in H₂O were constant. Such a change in the UV spectrum is probably due to slow enol-keto tautomerization of **19a** in 95% aqueous EtOH.¹¹⁾ In the above methylation of **18** with MeI in AcNMe₂, a small amount of a by-product, which was inferred to be 1,9-dimethyl-8-oxoadenine hydriodide (**4a**·HI),⁵⁾ was found, in contrast to the previously reported smooth methylation of the 8-unsubstituted 1-oxide **9**.¹²⁾ Furthermore, treatment of **18** with PhCH₂Br in AcNMe₂ at 100 °C for 72 h afforded a complex mixture of products, from which 1-benzyl-9-methyl-8-oxoadenine^{3b)} was isolated. These N(1)-alkyl products (**4**-type products) were assumed to have been formed through the normal products **19**·HX by deoxygenation,¹³⁾ as shown in Chart 4, and subsequent N(1)-alkylation⁵⁾ of the resulting 9-methyl-8-oxoadenine (**17**). The desired 1-benzyl-oxy compound was obtained as the perchlorate **19b**·HClO₄ in 61% yield by similar benzylation of **18**, but at 50 °C for 52 h, and subsequent anion exchange.

The free base **19a** also underwent deoxygenation: treatment of **19a** with boiling H₂O gave a complex mixture of products, two of which were suggested to be **17** and the monocycle **20a** on the basis of TLC and NMR analyses. The yield of **17** was increased by prolonged heating. Compound **17** was also obtained from **19b** by similar treatment. These results suggest that the 8-oxo compounds **19** undergo ring-opening much more slowly than the 8-unsubstituted analogues **10**, so that the side reactions become relatively more important. Indeed, only a trace of **20a** was shown to be formed by means of TLC when an aqueous solution of **19a** was kept in a refrigerator for several days.¹⁴⁾ A similar relation has been reported to

hold for the Dimroth rearrangements of 1,9-dimethyl-8-oxoadenine (**4a**) and 1,9-dimethyladenine.¹⁵⁾ In dilute aqueous NaOH, however, **19a** was shown (by means of TLC) to undergo smooth ring-opening at 40 °C. Because the product **20a** exists as the anionic form under these conditions, its extraction from the strongly alkaline reaction mixture with an organic solvent was difficult. But it could be extracted with AcOEt using a continuous extractor after the pH of the reaction mixture was adjusted to 9–10. The yield of **20a**, however, was only 25% because it tended to revert to **19a** during extraction under these conditions. This difficulty was partly overcome by replacing the methoxy group in **19a** and hence in **20a** with a more lipophilic benzyloxy group. Thus, the ring-opened product **20b** obtained from the 1-benzyloxy compound **19b** could be extracted without recourse to a continuous extractor, but the yield did not exceed 26%. The next step required was regioselective methylation of **20** at the formamido group. Contrary to the previously reported successful methylation of **11** to give **12**,⁸⁾ treatment of **20a** with an equimolar amount of MeI in HCONMe₂ in the presence of a mol eq of K₂CO₃ at room temperature gave a complex mixture of products, two of which were inferred to be the desired *N*-methylformamide **21a** and the dimethylated compound **22a** on the basis of the ¹H-NMR spectrum of a partially purified sample of the mixture. Similar methylation of the benzyloxy compound **20b** gave no better results.

Having learned from the above results that protection of **19** at N(7) is necessary for efficient preparation of the ring-opened product and for successive regioselective methylation at the formamido group, we prepared 7-benzyl-9-methyl-8-oxoadenine (**23**) in 82% yield from **17** according to the procedure¹⁾ reported for the synthesis of 7,9-dimethyl-8-oxoadenine (**6a**). The correctness of the structure **23** was ensured by its UV spectral similarity to **6a**.¹⁾ Deprotection of **23** at N(7) could be accomplished by catalytic hydrogenolysis using H₂ and Pearlman's catalyst to afford **17** in 33% yield. Treatment of **23** with MCPBA in MeOH afforded the 1:1 salt of the 1-oxide **24** with *m*-chlorobenzoic acid in 90% yield. This salt liberated **24** on treatment with Amberlite IRA-402 (HCO₃⁻), and **24** afforded the 1-benzyloxy compound **25** in 83% yield by treatment with PhCH₂Br in AcNMe₂ at

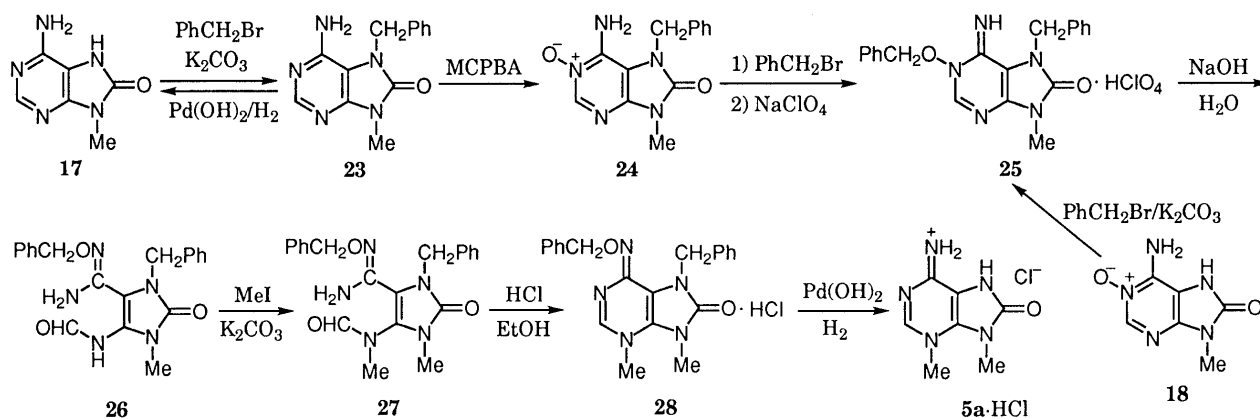
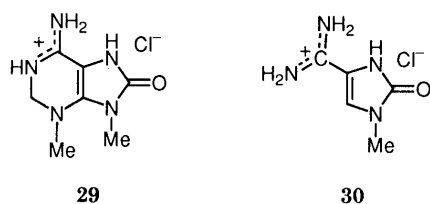


Chart 5



50°C for 4.5 h followed by anion exchange. The same compound **25** was obtainable in 26% yield from the 7-unsubstituted 1-oxide **18** by treatment with 3 mol eq of PhCH_2Br in the presence of K_2CO_3 , establishing that **18** and **24** had the *N*-oxide function at the same position. Treatment of **25** with a mixture of dilute aqueous NaOH and EtOH afforded the ring-opened product **26** in 76% yield. Regiospecific methylation of **26** was performed by treatment with MeI in HCONMe_2 at room temperature for 20 min in the presence of K_2CO_3 , giving **27** (54% yield); and **27** cyclized on treatment with HCl in EtOH to afford the 3,9-dimethyl compound **28** in 88% yield. Catalytic hydrogenolysis of **28**, the final step required for access to *N*⁶-demethylcaissarone (**5a**), was difficult owing to slow *N*(7)-debenzylation and overreduction in the pyrimidine moiety. After several unfruitful trials, we obtained **5a·HCl** in 21% yield from **28** by conducting hydrogenolysis with H_2 and Pearlman's catalyst at room temperature for 5 h. The by-products in this hydrogenolysis were presumed to be the 1,2-dihydropyrimidine **29** and the monocycle **30** on the basis of the $^1\text{H-NMR}$ spectral analysis of the crude mixture. These types of by-products have already been postulated or isolated in the case of reductive cleavage of **2a** and its *N*⁶-benzyl and *N*(3)-ethyl analogues.^{3b)} The correctness of the structure of **5a·HCl** was confirmed by direct comparison with an authentic specimen,¹⁾ finally verifying the 1-oxide structure for **18** and **24**.

In conclusion, *N*⁶-demethylcaissarone hydrochloride (**5a·HCl**) has been synthesized by means of the above 7-benzyl-8-oxo version of our general synthesis of 3,9-disubstituted adenines (**13**).⁸⁾ The present method is logically applicable to syntheses of not only 3-substituted 8-oxoadenosines (type **5b**), but also the nucleoside analogues **3b**, **c** of caissarone (**3a**).

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus, and values are corrected. MS and UV spectra were recorded on a Hitachi M-80 mass spectrometer and a Hitachi model 320 UV spectrophotometer [for solutions in 95% aqueous EtOH , 0.1 *N* aqueous HCl (pH 1), 0.005 *M* phosphate buffer (pH 7), and 0.1 *N* aqueous NaOH (pH 13)]. IR spectra were measured with a JASCO A-202 or a Shimadzu FTIR-8100 IR spectrophotometer. $^1\text{H-NMR}$ spectra were measured with a JEOL JNM-FX-100 or a JEOL JNM-EX-270 NMR spectrometer. Unless otherwise stated, they were recorded at 25°C in $(\text{CD}_3)_2\text{SO}$ with Me_4Si as an internal standard, but sodium 3-(trimethylsilyl)-1-propanesulfonate was used for a $\text{CF}_3\text{CO}_2\text{D}$ solution. Elemental analyses and MS measurements were performed by Mr. Y. Itatani, Dr. M. Takani, and their associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.¹⁶⁾ The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder.

2-Bromo-*N*'-methoxy-1-methyl-5-(*N*-methylformamido)-1*H*-imidazole-4-carboxamide (15**)** i) Bromination of **12** ($\text{R}^1 = \text{R}^2 = \text{Me}$) with Br_2 : A solution of Br_2 (2.14 g, 13.4 mmol) in AcOH (9.5 ml) was added dropwise to a mixture of **12** ($\text{R}^1 = \text{R}^2 = \text{Me}$)^{8a)} (2.007 g, 9.5 mmol), AcONa (779 mg, 9.5 mmol), and AcOH (9.5 ml) over a period of 5 min with stirring and cooling in an ice bath. The resulting frozen mixture was removed from the bath and kept at room temperature until it melted. After stirring for a further 1 h, the mixture was concentrated *in vacuo*, and H_2O (50 ml) was added to the residue. The resulting aqueous mixture was neutralized with 10% aqueous Na_2CO_3 and kept in a refrigerator for 2 d. The precipitate that resulted was collected by filtration, washed with cold H_2O (10 ml), and dried to afford **15** (1.388 g), mp 155–156°C. The filtrate and washings were combined, saturated with NaCl , and extracted with benzene (4 × 100 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The oily residue was extracted with hexane–benzene (2:1, v/v) (4 × 30 ml). The extracts were concentrated *in vacuo* to leave a solid residue, which was recrystallized twice from hexane–benzene (2:1, v/v) to afford a second crop of **15** [219 mg; the total yield was 1.607 g (58%)], mp 155–156°C. Further recrystallization of **15** afforded an analytical sample as colorless prisms, mp 155.5–156.5°C; MS m/z : 289 and 291 (M^+); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 221 nm (ϵ 14800), 250 (sh) (7400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 259 (8000); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 220 (14700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 221 (14400); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3480, 3370 (NH), 1690 (C=O); $^1\text{H-NMR}$ δ :^{17,18)} 3.00 (5/6 × 3H) and 3.27 (1/6 × 3H) (s each, MeNCHO), 3.34 (1/6 × 3H) and 3.43 (5/6 × 3H) [s each, N(1)-Me], 3.59 (5/6 × 3H) and 3.66 (1/6 × 3H) (s each, OMe), 5.72 (2H, br, NH_2), 8.02 (5/6H) and 8.25 (1/6H) (s each, CHO). *Anal.* Calcd for $\text{C}_8\text{H}_{12}\text{BrN}_5\text{O}_2$: C, 33.12; H, 4.17; N, 24.14. Found: C, 33.06; H, 4.27; N, 24.10.

ii) Bromination of **12** ($\text{R}^1 = \text{R}^2 = \text{Me}$) with *N*-Bromoacetamide: A solution of **12** ($\text{R}^1 = \text{R}^2 = \text{Me}$)^{8a)} (109 mg, 0.516 mmol), *N*-bromoacetamide (110 mg, 0.797 mmol), and benzoyl peroxide (12 mg, 0.049 mmol) in CHCl_3 (2 ml) was kept at room temperature for 90 min. The resulting brown solution was concentrated *in vacuo*, and the oily residue was washed with hexane (4 × 3 ml). The residual brown solid was extracted with hexane–benzene (2:1, v/v) (5 × 10 ml). The extracts were combined and concentrated *in vacuo*, and the residue was recrystallized from

hexane–benzene (2 : 1, v/v) to afford **15** (78 mg, 52%), mp 155–156.5 °C.

2-Bromo-*N'*-methoxy-1-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide (16) A suspension of **15** (1.74 g, 6 mmol) in a mixture of EtOH (15 ml) and 2*N* aqueous NaOH (15 ml) was stirred at room temperature for 2 h. The resulting mixture was neutralized with 10% aqueous HCl, concentrated *in vacuo* to a volume of ca. 20 ml, and kept in a refrigerator. The precipitate that deposited was collected by filtration, washed with H₂O (10 ml), and dried to afford **16** (1.50 g, 96%), mp 113–114.5 °C. Recrystallization of this sample from hexane–benzene (1 : 1, v/v) afforded an analytical sample of **16** as colorless needles, mp 113.5–114.5 °C; MS *m/z*: 261 and 263 (*M*⁺); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 228 nm (ϵ 13100), 257 (9900); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 294 (7100); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 227 (12500), 251 (sh) (9300); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 227 (12400), 251 (sh) (9200); ¹H-NMR δ : 1.91 (3H, d, *J* = 6 Hz, NHMe), 3.44 [3H, s, N(1)-Me], 3.65 (3H, s, OMe), 5.17 (1H, q, *J* = 6 Hz, NHMe), 5.62 (2H, br s, NH₂). *Anal.* Calcd for C₇H₁₂BrN₅O: C, 32.08; H, 4.61; N, 26.72. Found: C, 31.88; H, 4.71; N, 26.93.

2-Bromo-*N'*-methoxy-1-methyl-5-(*N*-methylacetamido)-1*H*-imidazole-4-carboxamide (14) A solution of **16** (262 mg, 1 mmol) in AcOH (5 ml) was kept at room temperature for 120 h and concentrated *in vacuo*. The solid residue was purified by flash chromatography [CHCl₃–EtOH (50 : 1, v/v)] to afford **14** (178 mg, 59%), mp 174.5–177 °C. Recrystallization of this sample from hexane–benzene (1 : 1, v/v) afforded an analytical sample of **14** as colorless prisms, mp 175.5–178.5 °C; MS *m/z*: 303 and 305 (*M*⁺); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 220 nm (ϵ 14800), 245 (sh) (8100); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 215 (sh) (13800), 260 (8400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 219 (14200), 250 (sh) (7400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 250 (sh) (7400); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{−1}: 3447, 3345 (NH), 1682 (C=O); ¹H-NMR δ : 1.74 (11/12 × 3H) and 2.16 (1/12 × 3H) (s each, MeCONMe), 2.97 (11/12 × 3H) and 3.22 (1/12 × 3H) (s each, MeCONMe), 3.33 (1/12 × 3H) and 3.43 (11/12 × 3H) [s each, N(1)-Me], 3.59 (11/12 × 3H) and 3.66 (1/12 × 3H) (s each, OMe), 5.62 (1/12 × 2H) and 5.72 (11/12 × 2H) (br each, NH₂). *Anal.* Calcd for C₉H₁₄BrN₅O₂: C, 35.54; H, 4.64; N, 23.03. Found: C, 35.60; H, 4.65; N, 22.99.

Reaction of 16 with AcOK Leading to 17 A mixture of **16** (262 mg, 1 mmol), AcOK (491 mg, 5 mmol), 18-crown-6 (264 mg, 1 mmol), and Me₂SO (10 ml) was stirred at 100 °C under N₂ for 120 h. The resulting suspension was concentrated *in vacuo*, and the residue was purified by flash chromatography [CHCl₃–EtOH (7 : 1, v/v)] to afford **17** (59 mg, 36%) as a yellow solid, mp >300 °C. This sample was identical (by comparison of the MS, IR, and ¹H-NMR spectra and TLC mobility) with authentic **17**.⁵⁾

9-Methyl-8-oxoadenine 1-Oxide (18) A suspension of finely pulverized **17**⁵⁾ (1.98 g, 12 mmol) in MeOH (180 ml) was stirred at 30 °C for 24 h after addition of MCPBA (of ca. 70% purity) (4.43 g, 18 mmol). The resulting mixture was cooled in a refrigerator for 1 h, and the precipitate that resulted was collected by filtration, washed with a little MeOH, and dried to afford **18** (2.13 g, 98%) as an almost colorless solid, mp >300 °C (dec.). Recrystallization of crude **18** from H₂O afforded an analytical sample of **18** as almost colorless minute needles, mp >300 °C (dec.); MS *m/z*: 181 (*M*⁺); $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 243 nm (ϵ 56000), 263 (sh) (8000); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 224 (31000), 239 (sh) (7600), 277 (10400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 240 (56400), 260 (sh) (7500), 279 (sh) (5400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 242 (49000), 291 (9500); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{−1}: 3333 (NH), 1694 (C=O); ¹H-NMR (CF₃CO₂D) δ : 3.61 [3H, s, N(9)-Me], 8.72 [1H, s, C(2)-H]. *Anal.* Calcd for C₆H₇N₅O₂: C, 39.78; H, 3.89; N, 38.66. Found: C, 39.76; H, 3.86; N, 38.70.

1-Methoxy-9-methyl-8-oxoadenine Monohydrate (19a · H₂O) A mixture of pulverized **18** (3.62 g, 20 mmol), MeI (22.7 g, 0.16 mol), and AcNMe₂ (300 ml) was stirred under N₂ at 50 °C for 3 d. A part of the starting material that remained undissolved (414 mg, 11% recovery) was filtered off, and the filtrate was concentrated *in vacuo*. The residue was washed successively with Et₂O (8 × 20 ml) and EtOH (10 ml) and dried to give crude **19a** · HI (5.32 g) as a slightly yellow solid, mp 238–240 °C (dec.). The ¹H-NMR spectrum of this sample indicated that it was contaminated (to the extent of 6 mol%) with a by-product [δ 3.33 [3H, s, N(9)-Me], 3.79 [3H, s, N(1)-Me], 8.32 (2H, br, H₂N⁺), 8.68 [1H, s, C(2)-H], 10.71 [1H, br, N(7)-H]], which was presumed to be **4a** · HI,⁵⁾ and the impurity could not be removed by recrystallization from H₂O. A solution of crude **19a** · HI (5.30 g) in H₂O (350 ml) was passed through a column packed with Amberlite IRA-402 (HCO₃[−]) (40 ml), and the column was eluted with H₂O (400 ml). The eluate was concentrated *in vacuo* to a volume of ca. 50 ml and cooled in an ice bath. The precipitate that resulted was collected by filtration, washed successively with a little H₂O and EtOH, and dried to afford **19a** · H₂O (2.57 g, 61%) as colorless

minute needles, mp 215–216 °C (dec.). This product was recrystallized from H₂O, dried over P₂O₅ at 50 °C and 2 mmHg for 10 h, and exposed to air at room temperature until a constant weight was reached, affording an analytical sample of **19a** · H₂O as colorless needles, mp 216–217.5 °C (dec.); MS *m/z*: 195 (*M*⁺); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 293 nm (unstable) (ϵ ca. 9000); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 223 (28300), 275 (10700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 222 (25000), 286 (13400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 280 (unstable); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{−1}: 1684 (C=N); ¹H-NMR δ : 3.20 [3H, s, N(9)-Me], 4.05 (3H, s, OMe), 8.48 [1H, s, C(2)-H]. *Anal.* Calcd for C₇H₉N₅O₂ · H₂O: C, 39.44; H, 5.20; N, 32.85. Found: C, 39.25; H, 5.24; N, 32.84.

A solution of **19a** · H₂O (100 mg, 0.469 mmol) in H₂O (10 ml) was heated under reflux for 5.5 h and then allowed to cool. The precipitate that deposited was collected by filtration to give **17** (29 mg, 38%), mp >300 °C, which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.⁵⁾

1-Benzyl-9-methyl-8-oxoadenine Perchlorate (19b · HClO₄) A mixture of **18** (1.45 g, 8 mmol), PhCH₂Br (5.47 g, 32 mmol), and AcNMe₂ (64 ml) was stirred at 50 °C for 52 h and then cooled with ice water. A part of the starting material **18** (162 mg, 11% recovery) that remained undissolved was removed by filtration. The filtrate was diluted with Et₂O (450 ml), and the resulting mixture was kept in a refrigerator for 2 d. The precipitate that resulted was collected by filtration, and crude **19b** · HBr (2.83 g) thus obtained was dissolved in H₂O (220 ml). The resulting solution was mixed with a concentrated aqueous solution of NaClO₄ · H₂O (2.15 g, 15.3 mmol), and the mixture was kept in a refrigerator for 3 d. The precipitate that resulted was collected by filtration, washed with H₂O (30 ml), and dried to afford **19b** · HClO₄ (1.82 g, 61%) as colorless needles, mp 209–210 °C (dec.). Purification of this sample by precipitating it several times from Me₂CO–Et₂O (2 : 5, v/v) afforded an analytical sample of **19b** · HClO₄ as colorless needles, mp 210.5–211.5 °C (dec.); $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 230 nm (ϵ 29400), 279 (9600), 285 (sh) (9500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 228 (29900), 274 (10500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 226 (29100), 286 (13400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) (unstable) 281 (14200); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{−1}: 1755 (C=O), 1688 (C=N); ¹H-NMR δ : 3.32 [3H, s, N(9)-Me], 5.40 (2H, s, PhCH₂), 7.47 (3H, m) and 7.62 (2H, m) (PhCH₂), 8.77 (2H, br, H₂N⁺), 8.93 [1H, s, C(2)-H], 10.82 [1H, br, N(7)-H]. *Anal.* Calcd for C₁₃H₁₃N₅O₂ · HClO₄: C, 42.00; H, 3.80; N, 18.84. Found: C, 41.74; H, 3.80; N, 19.01.

In a separate run, a warm solution of crude **19b** · HBr (7.76 g) in H₂O (250 ml) was brought to pH 8–9 by addition of 10% aqueous Na₂CO₃ and then allowed to cool. The precipitate that resulted was collected by filtration, washed successively with a little H₂O and EtOH, and dried to give **19b** (5.01 g), mp 183–185 °C; ¹H-NMR δ : 3.18 [3H, s, N(9)-Me], 5.28 (2H, s, PhCH₂), 7.43 (3H) and 7.56 (2H) (m each, PhCH₂), 8.16 [1H, s, C(2)-H]. Recrystallization of this sample from MeOH produced a small amount of impurity, which was presumed to be **17** by comparison of the TLC mobility. The impurity was difficult to remove by recrystallization from MeOH. A suspension of a portion (100 mg) of **19b** in H₂O (10 ml) was heated under reflux for 3 h. After cooling with ice water, the precipitate that resulted was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from H₂O to give **17** (9 mg), mp >300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **17**.⁵⁾

When the above benzylation of **18** (362 mg, 2 mmol) was conducted at 100 °C for 72 h, a complex mixture of products was obtained as an oil after removal of the solvent by vacuum distillation. This was dissolved in CH₂Cl₂ (10 ml) and extracted with H₂O (8 × 3 ml). The combined aqueous extracts were concentrated *in vacuo* to a small volume. The resulting acidic solution was neutralized by addition of 10% aqueous Na₂CO₃. The precipitate that deposited was collected by filtration and recrystallized from H₂O to give 1-benzyl-9-methyl-8-oxoadenine monohydrate^{3b)} (62 mg, 11%), mp 208–209 °C (dec.) [lit.^{3b)} mp 213–214 °C (dec.)]. This sample was identical (by comparison of the MS, IR, and ¹H-NMR spectra and TLC mobility) with an authentic specimen.^{3b)}

***N'*-Methoxy-1-methyl-2-oxo-5-formamido-1*H*-imidazole-4-carboxamide (20a)** A solution of **19a** · H₂O (310 mg, 1.45 mmol) in 0.01*N* aqueous NaOH (124 ml, 1.24 mmol) was kept at 40 °C for 2 h. The resulting solution was concentrated *in vacuo* at 35–40 °C to a volume of ca. 8 ml, during which time the pH of the solution was adjusted to 9–10 by occasional addition of 10% aqueous HCl. The solution was then extracted with AcOEt for 6 h using a continuous extractor. The AcOEt extracts were dried and concentrated *in vacuo* to a small volume, and the precipitate that resulted was collected by filtration to afford **20a** (46 mg), mp 141–142 °C (dec.); high-resolution MS *m/z*: 195.0777 (*M*⁺ –

H₂O) (C₇H₉N₅O₂ requires 195.0756); ¹H-NMR δ: 2.90 (8/13 × 3H) and 2.97 (5/13 × 3H) [s each, *cis*- and *trans*-N(1)-Me], 3.64 (5/13 × 3H) and 3.68 (8/13 × 3H) (s each, *trans*- and *cis*-OMe), 5.58 (8/13 × 2H) and 5.72 (5/13 × 3H) (brs each, *cis*- and *trans*-NH₂), 8.07 (5/13H, d, *J* = 10 Hz) and 8.25 (8/13H, s) (*trans*- and *cis*-NHCHO), 9.37 (5/13H, d, *J* = 10 Hz) and 9.71 (8/13H, s) (*trans*- and *cis*-NHCHO), 10.16 (8/13H) and 10.26 (5/13H) [brs each, *cis*- and *trans*-N(3)-H]. Extraction was continued for a further 13 h to afford a second crop of **20a** [32 mg; the total yield was 78 mg (25%)], mp 140–141 °C (dec.). Further extraction of the aqueous layer and flash chromatography [CHCl₃–EtOH (4:1, v/v)] of the extract no longer afforded pure **20a**.

N'-Benzoyloxy-1-methyl-2-oxo-5-formamido-1H-imidazole-4-carboxamide (20b) A solution of **19b**·HClO₄ (195 mg, 0.525 mmol) in 0.02 N aqueous NaOH (100 ml, 2 mmol) was kept at 40 °C for 1 h. The resulting solution was brought to pH 7 by addition of 10% aqueous HCl and then extracted with AcOEt (9 × 40 ml). The extracts were combined, dried over anhydrous MgSO₄, and concentrated *in vacuo* to leave a slightly yellow foam (153 mg). This was triturated with a little EtOH, and the precipitate that resulted was collected by filtration and dried to give **20b** (39 mg, 26%), mp 164–166 °C (dec.). Recrystallization of this sample from EtOH afforded an analytical sample of **20b** as colorless needles, mp 173–173.5 °C (dec.); MS *m/z*: 289 (M⁺); UV λ_{max}^{95% EtOH} 268 nm (ε 13100); λ_{max}^{H₂O} (pH 1) unstable; λ_{max}^{H₂O} (pH 7) 265 (11500); λ_{max}^{H₂O} (pH 13) 283 (unstable); IR ν_{Nujol}^{max} cm⁻¹: 3491, 3391 (NH), 1699, 1672 (C=O); ¹H-NMR δ: 2.91 (8/13 × 3H) and 2.97 (5/13 × 3H) [s each, *cis*- and *trans*-N(1)-Me], 4.89 (5/13 × 2H) and 4.94 (8/13 × 2H) (s each, *trans*- and *cis*-PhCH₂), 5.65 (8/13 × 2H) and 5.78 (5/13 × 2H) (s each, *cis*- and *trans*-NH₂), 7.34 (5H, m, PhCH₂), 8.07 (5/13H, d, *J* = 10 Hz) and 8.24 (8/13H, s) (*trans*- and *cis*-NHCHO), 9.40 (5/13H, d, *J* = 10 Hz) and 9.71 (8/13H, s) (*trans*- and *cis*-NHCHO), 10.20 (8/13H) and 10.28 (5/13H) [s each, *cis*- and *trans*-N(3)-H]. Anal. Calcd for C₁₃H₁₅N₅O₃: C, 53.97; H, 5.23; N, 24.21. Found: C, 53.91; H, 5.24; N, 24.02.

7-Benzyl-9-methyl-8-oxoadenine (23) A suspension of **17**⁵⁾ (6.60 g, 0.04 mol) and anhydrous K₂CO₃ (8.29 g, 0.06 mol) in HCONMe₂ (100 ml) was stirred at 90–95 °C for 1.5 h, then allowed to cool. PhCH₂Br (20.5 g, 0.12 mol) was added dropwise to the mixture with stirring at room temperature. Stirring was continued for a further 2.5 h, and the resulting mixture was concentrated *in vacuo*. The residue was neutralized with 10% aqueous HCl after addition of H₂O (100 ml). The precipitate that resulted was collected by filtration, washed successively with H₂O (100 ml) and EtOH (25 ml), and dried to give **23** (8.10 g), mp 207–214 °C. The filtrate and washings were combined and extracted with CH₂Cl₂ (3 × 50 ml). The combined extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was washed with Et₂O (6 × 15 ml) and then recrystallized from EtOH to afford a second crop of **23** [0.26 g; the total yield was 8.36 g (82%)], mp 205–215 °C. Recrystallization of crude **23** from EtOH afforded an analytical sample as colorless pillars, mp 216–217 °C; MS *m/z*: 255 (M⁺); UV λ_{max}^{95% EtOH} 273 nm (ε 11500); λ_{max}^{H₂O} (pH 1) 275 (sh) (9400), 286 (9900); λ_{max}^{H₂O} (pH 7) 273 (12100); λ_{max}^{H₂O} (pH 13) 272 (12100); IR ν_{Nujol}^{max} cm⁻¹: 3487, 3323 (NH), 1709 (C=O); ¹H-NMR δ: 3.30 [3H, s, N(9)-Me], 5.24 (2H, s, PhCH₂), 6.48 (2H, s, NH₂), 7.28 (5H, m, PhCH₂), 8.05 [1H, s, C(2)-H]. Anal. Calcd for C₁₃H₁₃N₅O: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.46; H, 5.06; N, 27.41.

Debenzylation of 23 A mixture of **23** (100 mg, 0.392 mmol), 20% Pd(OH)₂-C (100 mg), 0.1 N aqueous HCl (4 ml), and EtOH (6 ml) was shaken under H₂ at 40 °C and atmospheric pressure for 6 h. The catalyst was filtered off and washed with hot EtOH (10 × 10 ml). The filtrate and washings were combined, neutralized with saturated aqueous NaHCO₃, and concentrated *in vacuo*. The residue was dried and subjected to flash chromatography [CH₂Cl₂–MeOH (10:1 and then 5:1, v/v)] to afford **23** (30.8 mg, 31% recovery) and **17** (21.4 mg, 33%), mp 280–285 °C (dec.).

7-Benzyl-9-methyl-8-oxoadenine 1-Oxide *m*-Chlorobenzoate (1:1) (Salt) (24·*m*-ClC₆H₄CO₂H) A mixture of **23** (255 mg, 0.999 mmol) and MCPBA (of ca. 70% purity) (370 mg, 1.5 mmol) in MeOH (15 ml) was stirred at 30 °C for 19 h. The resulting solution was concentrated *in vacuo*, and the residue was washed with Et₂O (30 ml) to give crude **24·m**-ClC₆H₄CO₂H (386 mg, 90%), mp 159–161 °C. Recrystallization of this sample from H₂O afforded an analytical sample of **24·m**-ClC₆H₄CO₂H as colorless needles, mp 159.5–161 °C; UV λ_{max}^{95% EtOH} 246 nm (ε 52000), 267 (sh) (8500); λ_{max}^{H₂O} (pH 1) 228 (36600), 281 (10000); λ_{max}^{H₂O} (pH 7) 242 (55800); λ_{max}^{H₂O} (pH 13) 240 (35900), 281 (9400), 310 (3400); ¹H-NMR δ: 3.32 [3H, s, N(9)-Me], 5.30 (2H, s, PhCH₂), 7.27 (5H, m,

PhCH₂), 7.55 (3H, m, NH₂ and ClC₆H₄CO₂H), 7.70 (1H, m) and 7.90 (2H, m) (ClC₆H₄CO₂H), 8.56 [1H, s, C(2)-H], 13.34 (1H, br, CO₂H). Anal. Calcd for C₁₃H₁₃N₅O₂·C₇H₅ClO₂: C, 56.15; H, 4.24; N, 16.37. Found: C, 56.02; H, 4.04; N, 16.14.

7-Benzyl-9-methyl-8-oxoadenine 1-Oxide Monohydrate (24·H₂O) A solution of **24·m**-ClC₆H₄CO₂H (1.28 g, 2.99 mmol) in H₂O (700 ml) was passed through a column of Amberlite IRA-402 (HCO₃⁻) (7.2 ml), and the column was eluted with H₂O. The eluate (900 ml) was concentrated *in vacuo* to give crude **24·H₂O** (819 mg, 95%), mp 191–195 °C. Recrystallization of this sample was performed by dissolving it in CHCl₃ at room temperature, followed by addition of five volumes of hexane. An analytical sample of **24·H₂O** was obtained as colorless needles by drying over P₂O₅ at 2 mmHg and 50 °C for 13 h followed by exposure to air at room temperature until a constant weight was reached: mp 194–195.5 °C; MS *m/z*: 271 (M⁺); UV λ_{max}^{95% EtOH} 246 nm (ε 48800), 268 (sh) (7400); λ_{max}^{H₂O} (pH 1) 228 (27900), 241 (sh) (12200), 280 (8800); λ_{max}^{H₂O} (pH 7) 242 (54200), 262 (8200), 290 (sh) (3600); λ_{max}^{H₂O} (pH 13) 241 (34000), 281 (8800), 310 (sh) (3200); IR ν_{Nujol}^{max} cm⁻¹: 1720 (C=O); ¹H-NMR δ: 3.31 [3H, s, N(9)-Me], 5.30 (2H, s, PhCH₂), 7.27 (5H, m, PhCH₂), 7.55 (2H, s, NH₂), 8.56 [1H, s, C(2)-H]. Anal. Calcd for C₁₃H₁₃N₅O₂·H₂O: C, 53.97; H, 5.23; N, 24.21. Found: C, 53.80; H, 5.20; N, 24.02.

7-Benzyl-1-benzoyloxy-9-methyl-8-oxoadenine Perchlorate (25) i) From **24**: A mixture of **24·H₂O** (1.16 g, 4.01 mmol), PhCH₂Br (2.74 g, 16 mmol), and AcNMe₂ (32 ml) was stirred at 50 °C for 4.5 h. The resulting solution was diluted with Et₂O (200 ml) and kept in a refrigerator overnight. The precipitate that resulted was collected by filtration and dissolved in H₂O (300 ml). The aqueous solution was mixed with concentrated aqueous NaClO₄·H₂O (1.99 g, 14.3 mmol), and the mixture was kept in a refrigerator for 3 d. The precipitate that resulted was collected by filtration, washed with H₂O (30 ml), and dried to give crude **25** (1.53 g, 83%). An analytical sample of **25** was obtained as colorless needles by dissolving crude **25** in Me₂CO at room temperature and adding two volumes of Et₂O: mp 196–196.5 °C; UV λ_{max}^{95% EtOH} 233 nm (ε 24400), 277 (8600), 295 (sh) (7000); λ_{max}^{H₂O} (pH 1) 231 (25700), 279 (8900), 289 (sh) (8500); λ_{max}^{H₂O} (pH 7) 230 (22600), 274 (9300), 293 (sh) (6500); λ_{max}^{H₂O} (pH 13) (unstable) 272 (10300); IR ν_{Nujol}^{max} cm⁻¹: 3466, 3342 (NH), 1724 (C=O); ¹H-NMR δ: 3.39 [3H, s, N(9)-Me], 5.36 and 5.41 (2H each, s, two PhCH₂'s), 7.15–7.60 (10H, m, two PhCH₂'s), 8.80 (2H, brs, NH₂), 9.02 [1H, s, C(2)-H]. Anal. Calcd for C₂₀H₁₉N₅O₂·HClO₄: C, 52.01; H, 4.36; N, 15.16. Found: C, 51.97; H, 4.32; N, 15.20.

ii) From **18**: A mixture of **18** (181 mg, 1 mmol), anhydrous K₂CO₃ (207 mg, 1.5 mmol), and HCONMe₂ (20 ml) was stirred at 40 °C for 1 h, and then a solution of PhCH₂Br (518 mg, 3.03 mmol) in HCONMe₂ (3 ml) was added. The mixture was stirred at 40 °C for 24 h and then concentrated *in vacuo*, and the residue was mixed with H₂O (5 ml). This aqueous mixture was brought to pH 1 by addition of 70% aqueous HClO₄, and EtOH (3 ml) was added. The precipitate that deposited was collected by filtration and triturated with hot Me₂CO (3 ml). The insoluble solid that resulted was removed by filtration, Et₂O (20 ml) was added to the filtrate, and the ethereal mixture was cooled with ice. The precipitate that resulted was collected by filtration, washed with Et₂O, and dried to afford **25** (120 mg, 26%) as colorless needles, mp 188–190 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **25** described above under method (i).

N'-Benzoyloxy-3-benzyl-1-methyl-2-oxo-5-formamido-1H-imidazole-4-carboxamide (26) A solution of **25** (300 mg, 0.65 mmol) in a mixture of 0.02 N aqueous NaOH (97.5 ml) and EtOH (65 ml) was kept at 40 °C for 2 h. The solution was brought to pH 7 by addition of 10% aqueous HCl and then extracted with CHCl₃ (4 × 20 ml). The extracts were combined, dried over anhydrous MgSO₄, and concentrated *in vacuo* to leave a yellow foam. This was triturated with a mixture of CHCl₃ (2 ml) and hexane (20 ml), and the precipitate that resulted was collected by filtration to afford **26** (188 mg, 76%), mp 148–152.5 °C. Recrystallization of **26** was performed by dissolving it in CHCl₃ followed by addition of three volumes of hexane to afford an analytical sample of **26** as colorless needles, mp 154.5–155.5 °C; MS *m/z*: 379 (M⁺); UV λ_{max}^{95% EtOH} 263 nm (ε 10200); λ_{max}^{H₂O} (pH 1) (unstable) 277 (4700); λ_{max}^{H₂O} (pH 7) 250 (sh) (8300); λ_{max}^{H₂O} (pH 13) (unstable) 274 (9700); IR ν_{Nujol}^{max} cm⁻¹: 3458, 3296 (NH), 1709, 1693 (C=O); ¹H-NMR δ: 2.98 (7/11 × 3H) and 3.04 (4/11 × 3H) [s each, *cis*- and *trans*-N(1)-Me], 4.83 (4/11 × 4H), 4.91 and 4.92 (a total of 7/11 × 4H) (s each, two *trans*- and *cis*-PhCH₂'s), 5.84 (7/11 × 2H) and 6.09 (4/11 × 2H) (s each, *cis*- and *trans*-NH₂), 6.83–7.43 (10H, m, two PhCH₂'s), 8.08 (4/11H, d, *J* = 10.2 Hz) and 8.25 (7/11H, s) (*trans*- and *cis*-NHCHO), 9.47 (4/11H, d, *J* = 10.2 Hz) and 9.68 (7/11H, s) (*trans*- and

cis-NHCHO). Anal. Calcd for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.38; H, 5.58; N, 18.46.

***N'*-Benzyloxy-3-benzyl-1-methyl-2-oxo-5-(*N*-methylformamido)-1*H*-imidazole-4-carboxamide (27)** A mixture of **26** (290 mg, 0.764 mmol) and anhydrous K_2CO_3 (108 mg, 0.781 mmol) in $HCONMe_2$ (3 ml) was stirred at room temperature for 1 h, and then a solution of MeI (109 mg, 0.768 mmol) in $HCONMe_2$ (0.7 ml) was added. The mixture was stirred at room temperature for 20 min and then concentrated *in vacuo* to leave a yellowish foam, which was dissolved in H_2O (5 ml). The resulting solution was brought to pH 7 with 10% aqueous HCl and then extracted with $CHCl_3$ (5 × 5 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was crystallized by treating it with Et_2O (30 ml), and the crystalline material was collected by filtration, washed with Et_2O (10 ml), and dried to afford **27** (163 mg, 54%), mp 166.5–167.5 °C. Recrystallization of crude **27** from 50% (v/v) aqueous EtOH afforded an analytical sample as colorless prisms, mp 168.5–169.5 °C; MS m/z : 393 (M^+); UV $\lambda_{max}^{95\% EtOH}$ 251 nm (ϵ 8400); $\lambda_{max}^{H_2O}$ (pH 1) 255 (sh) (5400); $\lambda_{max}^{H_2O}$ (pH 7) 250 (7600); $\lambda_{max}^{H_2O}$ (pH 13) 257 (6200); IR ν_{max}^{Nujol} cm^{-1} : 3396, 3304 (NH), 1699, 1686 (C=O); 1H -NMR δ : 2.95 (1/8 × 3H), 2.96 (7/8 × 3H), 3.04 (7/8 × 3H) and 3.08 (1/8 × 3H) (s each, two Me's), 4.82 (7/8 × 2H), 4.87 (1/8 × 2H) and 4.91 (2H) (s each, two $PhCH_2$'s), 5.94 (1/8 × 2H) and 6.12 (7/8 × 2H) (brs each, NH₂), 7.01–7.36 (10H, m, two $PhCH_2$'s), 8.10 (7/8H) and 8.18 (1/8H) (s each, NCHO). Anal. Calcd for $C_{21}H_{23}N_5O_3$: C, 64.11; H, 5.89; N, 17.80. Found: C, 64.19; H, 5.95; N, 17.96.

7-Benzyl-*N*'-benzyloxy-3,9-dimethyl-8-oxoadenine Hydrochloride (28) A solution of **27** (170 mg, 0.432 mmol) in 5% ethanolic HCl (6.3 ml) was kept at room temperature for 16 h. The precipitate that resulted was collected by filtration, washed with EtOH (3 ml), and dried to afford **28** (157 mg, 88%), mp 201–202 °C (dec.). Recrystallization of this product from EtOH afforded an analytical sample of **28** as colorless prisms, mp 201–202 °C (dec.); UV $\lambda_{max}^{95\% EtOH}$ 291 nm (ϵ 17500), 340 (sh) (2400); $\lambda_{max}^{H_2O}$ (pH 1)²⁰⁾ (unstable) 232 (15900), 305 (16800); $\lambda_{max}^{H_2O}$ (pH 7)²⁰⁾ 292 (17000); $\lambda_{max}^{H_2O}$ (pH 13)²⁰⁾ (unstable) 292 (16100); IR ν_{max}^{Nujol} cm^{-1} : 1742 (C=O); 1H -NMR δ : 3.61 [3H, s, N(9)-Me], 4.02 [3H, br s, N(3)-Me], 4.95 (s) and 5.23 (brs) (2H each, two $PhCH_2$'s), 6.97–7.42 (10H, m, two $PhCH_2$'s), 8.49 [1H, br, C(2)-H]. Anal. Calcd for $C_{21}H_{21}N_5O_2 \cdot HCl$: C, 61.24; H, 5.38; N, 17.00. Found: C, 61.21; H, 5.30; N, 16.96.

3,9-Dimethyl-8-oxoadenine Hydrochloride (*N*'-Demethylcaissarone Hydrochloride) (5a · HCl) A solution of **28** (312 mg, 0.757 mmol) in MeOH (50 ml) was shaken under H_2 in the presence of 20% $Pd(OH)_2-C$ (0.31 g) at room temperature for 5 h. The catalyst was filtered off and washed with hot H_2O (100 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a colorless solid (162 mg). This was triturated with EtOH (5 ml), and the insoluble solid was collected by filtration, washed with EtOH (0.5 ml), and dried to afford **5a · HCl** (34 mg, 21%), mp 260–261 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **5a · HCl**.¹⁾

The above ethanolic filtrate and washings, obtained when crude **5a · HCl** was isolated, were combined and concentrated *in vacuo*. The residue was triturated with EtOH (1 ml), and the insoluble solid that resulted was collected by filtration and dried to give a mixture of two products, presumed to be 2,3-dihydro-3,9-dimethyl-8-oxoadenine hydrochloride (**29**) and 1-methyl-2-oxo-1*H*-imidazole-4-carboxamide hydrochloride (**30**), as a colorless solid (28 mg), mp 225–230 °C (dec.); 1H -NMR δ : 3.00 [3H, s, N(3)-Me of **29**], 3.22 [11/7 × 3H, s, N(9)-Me of **29** and N(1)-Me of **30**], 4.56 [2H, br s, C(2)-H₂ of **29**], 7.82 [4/7H, s, C(5)-H of **30**], 8.05 (4/7 × 4H, br, two NH₂'s of **30**), 8.21, 8.65 and

8.82 (1H each, br, three NH's of **29**), 10.43 [1H, brs, N(7)-H of **29**], 10.98 [4/7H, br, N(3)-H of **30**].

References and Notes

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- 14) In contrast, storage of concentrated aqueous solutions of the 8-unsubstituted analogues **10** in a refrigerator affords the monocycles **11** in good yields.^{10a)}
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- 17) For discussion of the observed complexity of the proton signals owing to *cis*–*trans* isomerism of the amido group, see ref. 9 and references cited therein.
- 18) Assigned by comparison with the 1H -NMR spectrum of **12** ($R^1 = R^2 = Me$).^{8a)}
- 19) Assigned by comparison with the 1H -NMR spectrum of *N*'-methoxy-1-methyl-5-(*N*-methylamino)-1*H*-imidazole-4-carboxamide.^{8a)}
- 20) The aqueous solution contained one-tenth volume of EtOH in order to secure complete dissolution of the sample.