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

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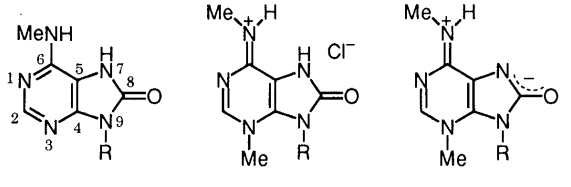
Received April 23, 1997; accepted June 23, 1997

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 K_2CO_3, 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)-dibenzylation with $PhCH_2Br$ in the presence of K_2CO_3.

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

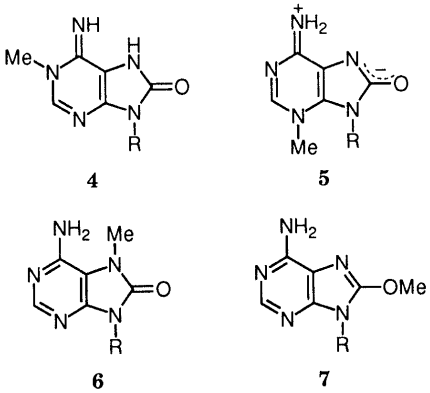
Caissarone hydrochloride (**2a**), a purine alkaloid isolated from the sea anemone *Bunodosoma caissarum* CORREA 1964,[2] has been synthesized by us through regioselective methylation of N^6,9-dimethyl-8-oxoadenine (**1a**).[3] We have reported that **2a** affords the corresponding free base in the zwitterionic form (**3a**) on treatment with Amberlite IRA-402 (HCO_3^-) and that **3a** is capable of forming a hetero-base pair with 2′,3′,5′-tri-*O*-acetylguanosine in $(CD_3)_2SO$ 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 nucleoside 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**: R^1 = Me).

We first attempted to synthesize **5a** from the monocycle **12** ($R^1 = R^2 = Me$), the key intermediate for the synthesis of 3,9-dimethyladenine (type **13**)[8a] starting from 9-methyladenine (**8**: R^1 = Me). Compound **12** ($R^1 = R^2 = Me$) afforded the 2-bromo compound **15** in 58% or 52% yield on treatment with Br_2 and AcONa in AcOH or with *N*-bromoacetamide in $CHCl_3$ 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, $PhCH_2ONa$–Me_2SO, or AcONa–AcOH. Since **16** was found to undergo acetylation at the methylamino



1 **2** **3**

a: R = Me
b: R = 2-deoxy-β-D-ribofuranosyl
c: R = β-D-ribofuranosyl



4 **5** **6** **7**

a: R = Me
b: R = β-D-ribofuranosyl

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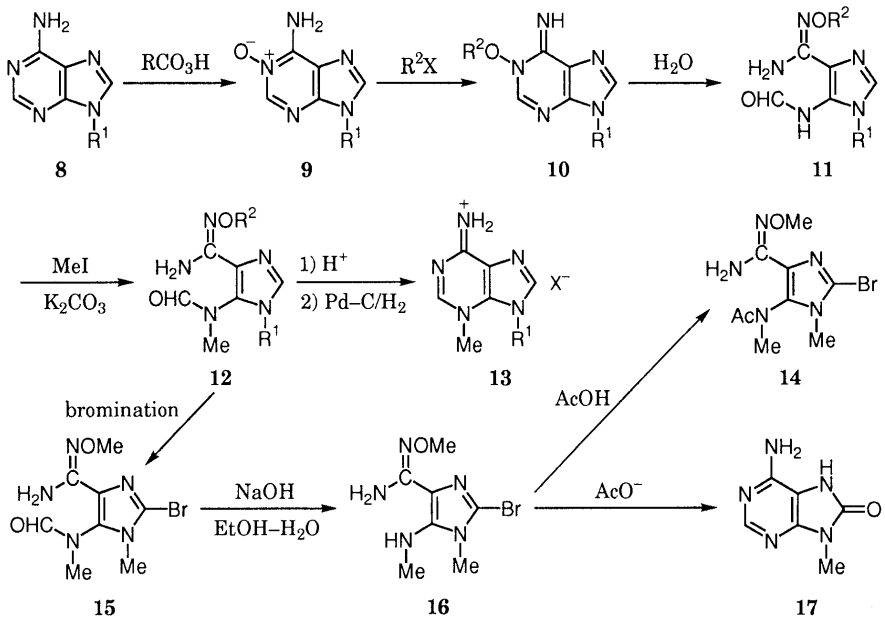


Chart 1

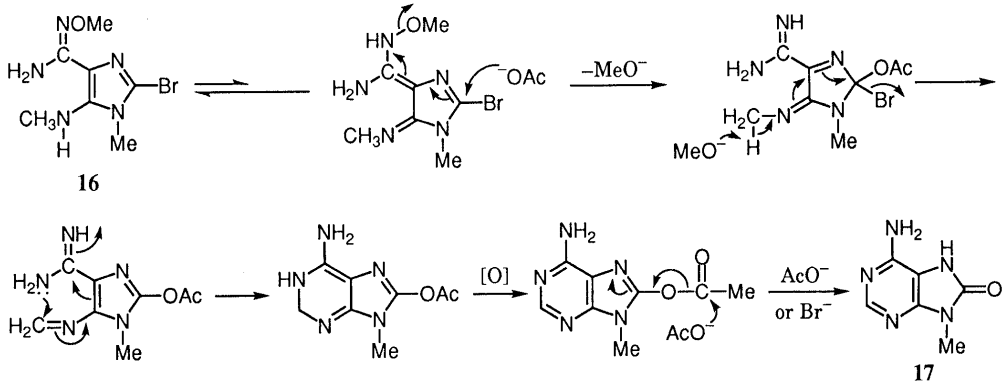
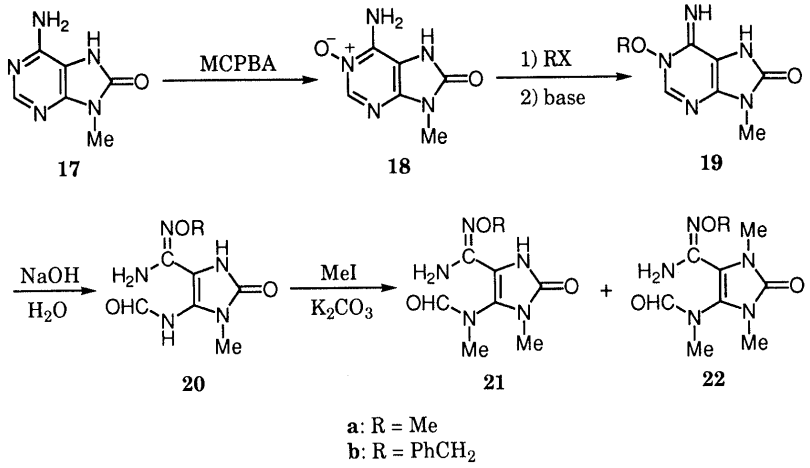


Chart 2

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**→→**13** in Chart 1), as shown in part in Chart 3. Treatment of 9-methyl-8-oxoadenine (**17**), easily obtainable from 9-methyladenine (**8**: $R^1 = Me$) 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^y-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—1680 cm^{-1}



a: R = Me
b: R = $PhCH_2$

Chart 3

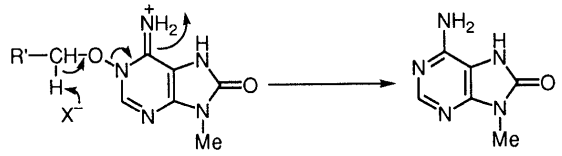


Chart 4

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 H_2O 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 $AcNMe_2$, 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 $PhCH_2Br$ in $AcNMe_2$ 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)-alkylation[5] of the resulting 9-methyl-8-oxoadenine (**17**). The desired 1-benzyloxy compound was obtained as the perchlorate **19b**·$HClO_4$ 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 H_2O 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 $HCONMe_2$ in the presence of a mol eq of K_2CO_3 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 ^{1}H-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 procedure[1] 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 H_2 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 (HCO_3^-), and **24** afforded the 1-benzyloxy compound **25** in 83% yield by treatment with $PhCH_2Br$ in $AcNMe_2$ at

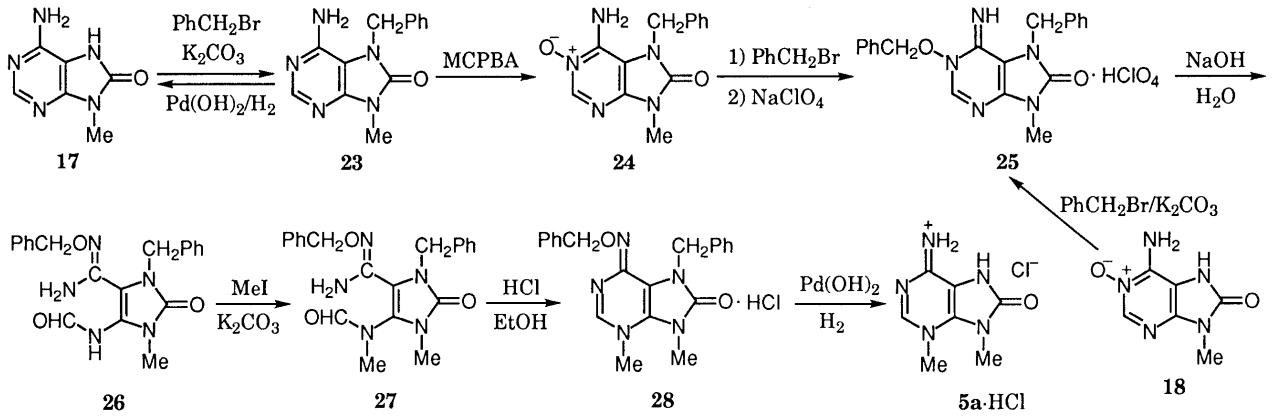
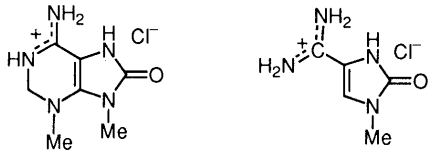


Chart 5



29 30

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-dihydropurine **29** and the monocycle **30** on the basis of the ^{1}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}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 $(CD_3)_2SO$ with Me_4Si as an internal standard, but sodium 3-(trimethylsilyl)-1-propanesulfonate was used for a CF_3CO_2D 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-carboxamidine (15) i) Bromination of **12** ($R^1 = R^2 = Me$) 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** ($R^1 = R^2 = Me$)[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 $\lambda_{max}^{95\%\,EtOH}$ 221 nm (ε 14800), 250 (sh) (7400); $\lambda_{max}^{H_2O}$ (pH 1) 259 (8000); $\lambda_{max}^{H_2O}$ (pH 7) 220 (14700); $\lambda_{max}^{H_2O}$ (pH 13) 221 (14400); IR ν_{max}^{Nujol} cm^{-1}: 3480, 3370 (NH), 1690 (C=O); ^{1}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 $C_8H_{12}BrN_5O_2$: C, 33.12; H, 4.17; N, 24.14. Found: C, 33.06; H, 4.27; N, 24.10.

ii) Bromination of **12** ($R^1 = R^2 = Me$) with *N*-Bromoacetamide: A solution of **12** ($R^1 = R^2 = Me$)[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-carboxamidine (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 H_2O (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 $\lambda_{max}^{95\%\,EtOH}$ 228 nm (ε 13100), 257 (9900); $\lambda_{max}^{H_2O}$ (pH 1) 294 (7100); $\lambda_{max}^{H_2O}$ (pH 7) 227 (12500), 251 (sh) (9300); $\lambda_{max}^{H_2O}$ (pH 13) 227 (12400), 251 (sh) (9200); ^{1}H-NMR δ:[19] 2.71 (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, NH_2). *Anal.* Calcd for $C_7H_{12}BrN_5O$: 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-carboxamidine (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 [$CHCl_3$–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 $\lambda_{max}^{95\%\,EtOH}$ 220 nm (ε 14800), 245 (sh) (8100); $\lambda_{max}^{H_2O}$ (pH 1) 215 (sh) (13800), 260 (8400); $\lambda_{max}^{H_2O}$ (pH 7) 219 (14200), 250 (sh) (7400); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (7400); IR ν_{max}^{Nujol} cm^{-1}: 3447, 3345 (NH), 1682 (C=O); ^{1}H-NMR δ:[17] 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, NH_2). *Anal.* Calcd for $C_9H_{14}BrN_5O_2$: 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 Me_2SO (10 ml) was stirred at 100 °C under N_2 for 120 h. The resulting suspension was concentrated *in vacuo*, and the residue was purified by flash chromatography [$CHCl_3$–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 ^{1}H-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 H_2O afforded an analytical sample of **18** as almost colorless minute needles, mp >300 °C (dec.); MS *m/z*: 181 (M^+); $\lambda_{max}^{95\%\,EtOH}$ 243 nm (ε 56000), 263 (sh) (8000); $\lambda_{max}^{H_2O}$ (pH 1) 224 (31000), 239 (sh) (7600), 277 (10400); $\lambda_{max}^{H_2O}$ (pH 7) 240 (56400), 260 (sh) (7500), 279 (sh) (5400); $\lambda_{max}^{H_2O}$ (pH 13) 242 (49000), 291 (9500); IR ν_{max}^{Nujol} cm^{-1}: 3333 (NH), 1694 (C=O); ^{1}H-NMR (CF_3CO_2D) δ: 3.61 [3H, s, N(9)-Me], 8.72 [1H, s, C(2)-H]. *Anal.* Calcd for $C_6H_7N_5O_2$: 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·H_2O) A mixture of pulverized **18** (3.62 g, 20 mmol), MeI (22.7 g, 0.16 mol), and $AcNMe_2$ (300 ml) was stirred under N_2 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 Et_2O (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 ^{1}H-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, H_2N^+), 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 H_2O. A solution of crude **19a**·HI (5.30 g) in H_2O (350 ml) was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (40 ml), and the column was eluted with H_2O (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 H_2O and EtOH, and dried to afford **19a**·H_2O (2.57 g, 61%) as colorless minute needles, mp 215—216 °C (dec.). This product was recrystallized from H_2O, dried over P_2O_5 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**·H_2O as colorless needles, mp 216—217.5 °C (dec.); MS *m/z*: 195 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 293 nm (unstable) (ε *ca.* 9000); $\lambda_{max}^{H_2O}$ (pH 1) 223 (28300), 275 (10700); $\lambda_{max}^{H_2O}$ (pH 7) 222 (25000), 286 (13400); $\lambda_{max}^{H_2O}$ (pH 13) 280 (unstable); IR ν_{max}^{Nujol} cm^{-1}: 1684 (C=N); ^{1}H-NMR δ: 3.20 [3H, s, N(9)-Me], 4.05 (3H, s, OMe), 8.48 [1H, s, C(2)-H]. *Anal.* Calcd for $C_7H_9N_5O_2·H_2O$: C, 39.44; H, 5.20; N, 32.85. Found: C, 39.25; H, 5.24; N, 32.84.

A solution of **19a**·H_2O (100 mg, 0.469 mmol) in H_2O (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-Benzyloxy-9-methyl-8-oxoadenine Perchlorate (19b·$HClO_4$) A mixture of **18** (1.45 g, 8 mmol), $PhCH_2Br$ (5.47 g, 32 mmol), and $AcNMe_2$ (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 Et_2O (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 H_2O (220 ml). The resulting solution was mixed with a concentrated aqueous solution of $NaClO_4·H_2O$ (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 H_2O (30 ml), and dried to afford **19b**·$HClO_4$ (1.82 g, 61%) as colorless needles, mp 209—210 °C (dec.). Purification of this sample by precipitating it several times from Me_2CO–Et_2O (2 : 5, v/v) afforded an analytical sample of **19b**·$HClO_4$ as colorless needles, mp 210.5—211.5 °C (dec.); $\lambda_{max}^{95\%\,EtOH}$ 230 nm (ε 29400), 279 (9600), 285 (sh) (9500); $\lambda_{max}^{H_2O}$ (pH 1) 228 (29900), 274 (10500); $\lambda_{max}^{H_2O}$ (pH 7) 226 (29100), 286 (13400); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 281 (14200); IR ν_{max}^{Nujol} cm^{-1}: 1755 (C=O), 1688 (C=N); ^{1}H-NMR δ: 3.32 [3H, s, N(9)-Me], 5.40 (2H, s, $PhCH_2$), 7.47 (3H, m) and 7.62 (2H, m) ($PhCH_2$), 8.77 (2H, br, H_2N^+), 8.93 [1H, s, C(2)-H], 10.82 [1H, br, N(7)-H]. *Anal.* Calcd for $C_{13}H_{13}N_5O_2·HClO_4$: 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 H_2O (250 ml) was brought to pH 8—9 by addition of 10% aqueous Na_2CO_3 and then allowed to cool. The precipitate that resulted was collected by filtration, washed successively with a little H_2O and EtOH, and dried to give **19b** (5.01 g), mp 183—185 °C; ^{1}H-NMR δ: 3.18 [3H, s, N(9)-Me], 5.28 (2H, s, $PhCH_2$), 7.43 (3H) and 7.56 (2H) (m each, $PhCH_2$), 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 H_2O (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 H_2O 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 CH_2Cl_2 (10 ml) and extracted with H_2O (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 Na_2CO_3. The precipitate that deposited was collected by filtration and recrystallized from H_2O 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 ^{1}H-NMR spectra and TLC mobility) with an authentic specimen.[3b]

***N'*-Methoxy-1-methyl-2-oxo-5-formamido-1*H*-imidazole-4-carboxamidine (20a)** A solution of **19a**·H_2O (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^+ –

H_2O) ($C_7H_9N_5O_2$ requires 195.0756); ^{1}H-NMR δ:[17] 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) (br s each, *cis*- and *trans*-NH_2), 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) [br s 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 [$CHCl_3$–EtOH (4 : 1, v/v)] of the extract no longer afforded pure **20a**.

***N'*-Benzyloxy-1-methyl-2-oxo-5-formamido-1*H*-imidazole-4-carboxamidine (20b)** A solution of **19b**·$HClO_4$ (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 $MgSO_4$, 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^+); $\lambda_{max}^{95\%\,EtOH}$ 268 nm (ε 13100); $\lambda_{max}^{H_2O}$ (pH 1) unstable; $\lambda_{max}^{H_2O}$ (pH 7) 265 (11500); $\lambda_{max}^{H_2O}$ (pH 13) 283 (unstable); IR ν_{max}^{Nujol} cm^{-1}: 3491, 3391 (NH), 1699, 1672 (C=O); ^{1}H-NMR δ:[17] 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*-PhC$\underline{H}_2$), 5.65 (8/13 × 2H) and 5.78 (5/13 × 2H) (s each, *cis*- and *trans*-NH_2), 7.34 (5H, m, $\underline{Ph}CH_2$), 8.07 (5/13H, d, J = 10 Hz) and 8.24 (8/13H, s) (*trans*- and *cis*-NHC$\underline{H}$O), 9.40 (5/13H, d, J = 10 Hz) and 9.71 (8/13H, s) (*trans*- and *cis*-N$\underline{H}$CHO), 10.20 (8/13H) and 10.28 (5/13H) [s each, *cis*- and *trans*-N(3)-H]. *Anal.* Calcd for $C_{13}H_{15}N_5O_3$: 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 K_2CO_3 (8.29 g, 0.06 mol) in $HCONMe_2$ (100 ml) was stirred at 90—95 °C for 1.5 h, then allowed to cool. $PhCH_2Br$ (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 H_2O (100 ml). The precipitate that resulted was collected by filtration, washed successively with H_2O (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 CH_2Cl_2 (3 × 50 ml). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was washed with Et_2O (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 $\lambda_{max}^{95\%\,EtOH}$ 273 nm (ε 11500); $\lambda_{max}^{H_2O}$ (pH 1) 275 (sh) (9400), 286 (9900); $\lambda_{max}^{H_2O}$ (pH 7) 273 (12100); $\lambda_{max}^{H_2O}$ (pH 13) 272 (12100); IR ν_{max}^{Nujol} cm^{-1}: 3487, 3323 (NH), 1709 (C=O); ^{1}H-NMR δ: 3.30 [3H, s, N(9)-Me], 5.24 (2H, s, PhC$\underline{H}_2$), 6.48 (2H, s, NH_2), 7.28 (5H, m, $\underline{Ph}CH_2$), 8.05 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{13}H_{13}N_5O$: 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 H_2 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 $NaHCO_3$, and concentrated *in vacuo*. The residue was dried and subjected to flash chromatography [CH_2Cl_2–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*-$ClC_6H_4CO_2H$) 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 Et_2O (30 ml) to give crude **24**·*m*-$ClC_6H_4CO_2H$ (386 mg, 90%), mp 159—161 °C. Recrystallization of this sample from H_2O afforded an analytical sample of **24**·*m*-$ClC_6H_4CO_2H$ as colorless needles, mp 159.5—161 °C; UV $\lambda_{max}^{95\%\,EtOH}$ 246 nm (ε 52000), 267 (sh) (8500); $\lambda_{max}^{H_2O}$ (pH 1) 228 (36600), 281 (10000); $\lambda_{max}^{H_2O}$ (pH 7) 242 (55800); $\lambda_{max}^{H_2O}$ (pH 13) 240 (35900), 281 (9400), 310 (3400); ^{1}H-NMR δ: 3.32 [3H, s, N(9)-Me], 5.30 (2H, s, PhC$\underline{H}_2$), 7.27 (5H, m, $\underline{Ph}CH_2$), 7.55 (3H, m, NH_2 and $ClC_6\underline{H}CO_2H$), 7.70 (1H, m) and 7.90 (2H, m) ($ClC_6\underline{H}_3CO_2H$), 8.56 [1H, s, C(2)-H], 13.34 (1H, br, CO_2H). *Anal.* Calcd for $C_{13}H_{13}N_5O_2 \cdot C_7H_5ClO_2$: 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·H_2O) A solution of **24**·*m*-$ClC_6H_4CO_2H$ (1.28 g, 2.99 mmol) in H_2O (700 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (7.2 ml), and the column was eluted with H_2O. The eluate (900 ml) was concentrated *in vacuo* to give crude **24**·H_2O (819 mg, 95%), mp 191—195 °C. Recrystallization of this sample was performed by dissolving it in $CHCl_3$ at room temperature, followed by addition of five volumes of hexane. An analytical sample of **24**·H_2O was obtained as colorless needles by drying over P_2O_5 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 $\lambda_{max}^{95\%\,EtOH}$ 246 nm (ε 48800), 268 (sh) (7400); $\lambda_{max}^{H_2O}$ (pH 1) 228 (27900), 241 (sh) (12200), 280 (8800); $\lambda_{max}^{H_2O}$ (pH 7) 242 (54200), 262 (8200), 290 (sh) (3600); $\lambda_{max}^{H_2O}$ (pH 13) 241 (34000), 281 (8800), 310 (sh) (3200); IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O); ^{1}H-NMR δ: 3.31 [3H, s, N(9)-Me], 5.30 (2H, s, PhC$\underline{H}_2$), 7.27 (5H, m, $\underline{Ph}CH_2$), 7.55 (2H, s, NH_2), 8.56 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{13}H_{13}N_5O_2 \cdot H_2O$: C, 53.97; H, 5.23; N, 24.21. Found: C, 53.80; H, 5.20; N, 24.02.

7-Benzyl-1-benzyloxy-9-methyl-8-oxoadenine Perchlorate (25) i) From **24**: A mixture of **24**·H_2O (1.16 g, 4.01 mmol), $PhCH_2Br$ (2.74 g, 16 mmol), and $AcNMe_2$ (32 ml) was stirred at 50 °C for 4.5 h. The resulting solution was diluted with Et_2O (200 ml) and kept in a refrigerator overnight. The precipitate that resulted was collected by filtration and dissolved in H_2O (300 ml). The aqueous solution was mixed with concentrated aqueous $NaClO_4 \cdot H_2O$ (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 H_2O (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 Me_2CO at room temperature and adding two volumes of Et_2O: mp 196—196.5 °C; UV $\lambda_{max}^{95\%\,EtOH}$ 233 nm (ε 24400), 277 (8600), 295 (sh) (7000); $\lambda_{max}^{H_2O}$ (pH 1) 231 (25700), 279 (8900), 289 (sh) (8500); $\lambda_{max}^{H_2O}$ (pH 7) 230 (22600), 274 (9300), 293 (sh) (6500); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 272 (10300); IR ν_{max}^{Nujol} cm^{-1}: 3466, 3342 (NH), 1724 (C=O); ^{1}H-NMR δ: 3.39 [3H, s, N(9)-Me], 5.36 and 5.41 (2H each, s, two PhC$\underline{H}_2$'s), 7.15—7.60 (10H, m, two $\underline{Ph}CH_2$'s), 8.80 (2H, br s, NH_2), 9.02 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{20}H_{19}N_5O_2 \cdot HClO_4$: 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 K_2CO_3 (207 mg, 1.5 mmol), and $HCONMe_2$ (20 ml) was stirred at 40 °C for 1 h, and then a solution of $PhCH_2Br$ (518 mg, 3.03 mmol) in $HCONMe_2$ (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 H_2O (5 ml). This aqueous mixture was brought to pH 1 by addition of 70% aqueous $HClO_4$, and EtOH (3 ml) was added. The precipitate that deposited was collected by filtration and triturated with hot Me_2CO (3 ml). The insoluble solid that resulted was removed by filtration, Et_2O (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 Et_2O, 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'*-Benzyloxy-3-benzyl-1-methyl-2-oxo-5-formamido-1*H*-imidazole-4-carboxamidine (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 $CHCl_3$ (4 × 20 ml). The extracts were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow foam. This was triturated with a mixture of $CHCl_3$ (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 $CHCl_3$ 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^+); $\lambda_{max}^{95\%\,EtOH}$ 263 nm (ε 10200); $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 277 (4700); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (8300); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 274 (9700); IR ν_{max}^{Nujol} cm^{-1}: 3458, 3296 (NH), 1709, 1693 (C=O); ^{1}H-NMR δ:[17] 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*-PhC$\underline{H}_2$'s), 5.84 (7/11 × 2H) and 6.09 (4/11 × 2H) (s each, *cis*- and *trans*-NH_2), 6.83—7.43 (10H, m, two $\underline{Ph}CH_2$'s), 8.08 (4/11H, d, J = 10.2 Hz) and 8.25 (7/11H, s) (*trans*- and *cis*-NHC$\underline{H}$O), 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-carboxamidine (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); ^{1}H-NMR δ:[17] 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 $PhC\underline{H}_2$'s), 5.94 (1/8 × 2H) and 6.12 (7/8 × 2H) (br s each, NH_2), 7.01—7.36 (10H, m, two $\underline{Ph}CH_2$'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^6-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); ^{1}H-NMR δ: 3.61 [3H, s, N(9)-Me], 4.02 [3H, br s, N(3)-Me], 4.95 (s) and 5.23 (br s) (2H each, two $PhC\underline{H}_2$'s), 6.97—7.42 (10H, m, two $\underline{Ph}CH_2$'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*^{6}-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-carboxamidine hydrochloride (**30**), as a colorless solid (28 mg), mp 225—230 °C (dec.); ^{1}H-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)-H_2 of **29**], 7.82 [4/7H, s, C(5)-H of **30**], 8.05 (4/7 × 4H, br, two NH_2's of **30**), 8.21, 8.65 and 8.82 (1H each, br, three NH's of **29**), 10.43 [1H, br s, 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 ^{1}H-NMR spectrum of **12** ($R^1 = R^2 = Me$).[8a]
19) Assigned by comparison with the ^{1}H-NMR spectrum of *N'*-methoxy-1-methyl-5-(*N*-methylamino)-1*H*-imidazole-4-carboxamidine.[8a]
20) The aqueous solution contained one-tenth volume of EtOH in order to secure complete dissolution of the sample.