Purines. LXXII.[1] Oxidation of N^6-Alkyladenines with *m*-Chloroperoxybenzoic Acid Leading to N^6-Alkyladenine 1-Oxides

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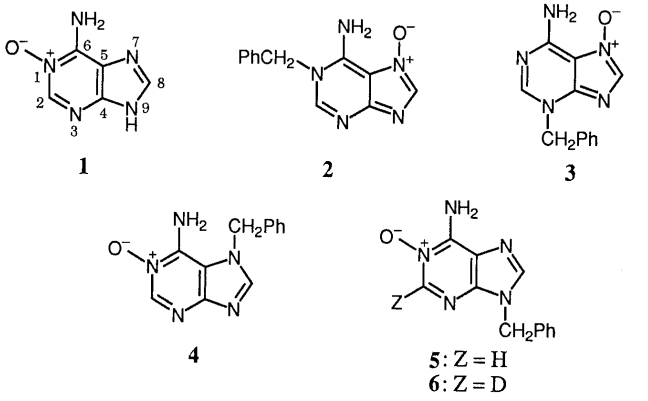
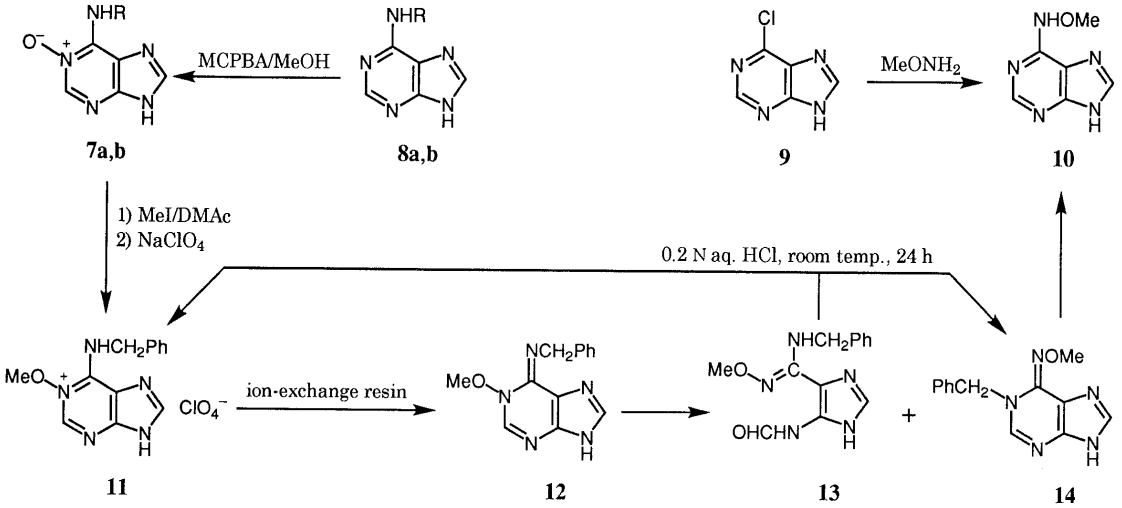
Oxidations of N^6-methyladenine (8a) and N^6-benzyladenine (8b) with *m*-chloroperoxybenzoic acid (MCPBA) in methanol have been found to afford the N(1)-oxides 7a,b in 36% and 35% yields, respectively. The structure of 7b has been established by leading it to N^6-methoxyadenine (10) through *O*-methylation, Dimroth rearrangement, and nonreductive debenzylation. On the other hand, N^6,N^6-dimethyladenine (16) afforded the N(3)-oxide 17 in 40% yield on treatment with MCPBA in methanol. On the basis of these findings, together with data accumulated for *N*-oxidations of adenine, N^x-monosubstituted adenines, and 6-substituted purines, the formation of hydrogen bonding between the 6-amino NH and the carbonyl oxygen of a peroxycarboxylic acid may account for regioselective N(1)- and N(7)-oxidations of adenine and N^x-monosubstituted adenines.

Key words N^6-alkyladenine *N*-oxidation; 1-alkoxy-N^6-alkyladenine; Dimroth rearrangement; N^6-alkyladenine 1-oxide; N^6,N^6-dimethyladenine 3-oxide; *m*-chloroperoxybenzoic acid

Adenine and 9-substituted adenines provide the N(1)-oxides (**1** and type **5**) almost exclusively in the reactions with aqueous hydrogen peroxide in acetic acid,[2] aqueous monoperoxyphthalic acid,[3] or *m*-chloroperoxybenzoic acid (MCPBA) in methanol.[4] Our recent studies have revealed that N^x-benzyladenines undergo either N(1)-oxidation or N(7)-oxidation to afford 1-benzyladenine 7-oxide (**2**),[5] 3-benzyladenine 7-oxide (**3**),[6] 7-benzyladenine 1-oxide (**4**),[7] and 9-benzyladenine-2-*d* 1-oxide (**6**),[4a] when treated with MCPBA in methanol, and that there is only a partial parallelism in regioselectivity between N^y-oxidation and N^y-alkylation.[7] This paper reports the MCPBA oxidation of N^6-benzyladenine (**8b**), the remaining positional isomer. A brief account of a part of the results reported here has been published in a preliminary form.[8]

Treatment of **8b** with MCPBA in methanol at 30 °C for 20 h furnished an *N*-oxide in 35% yield, together with 25% recovery of **8b** (Chart 1). The following chemical evidence permitted us to assign the 1-oxide structure **7b** to this *N*-oxide.[9] On methylation with methyl iodide in *N*,*N*-dimethylacetamide (DMAc) at 25 °C for 20 h, **7b** gave, after treatment of the product with aqueous sodium perchlorate, the 1-methoxy derivative as the perchlorate salt **11** in 72% yield. Conversion of **11** to the free base **12** by the use of Amberlite IRA-402 (HCO_3^-) and subsequent heating of **12** in water for 3 h produced the monocyclic amidine **13** and the Dimroth rearrangement product **14** in





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

Chart 1

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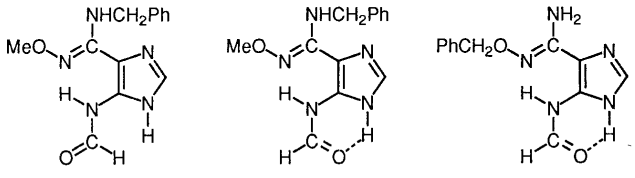


trans-**13** *cis*-**13** **15**

74% and 7% yields, respectively. Prolonged heating (18 h) afforded **13** and **14** in 16% and 56% yields, respectively. The monocycle **13** underwent recyclization in 0.2 N hydrochloric acid at room temperature in 24 h, affording both the N^6-methoxy derivative **14** and the 1-methoxy isomer (isolated as the perchlorate salt **11**) in 63% and 15% yields, respectively. All these findings were analogous to those reported previously by us for N^6,9-dimethyladenine 1-oxide[10] and for adenine 1-oxide.[11] The ^{1}H-NMR spectrum of **13** in hexadeuterated dimethyl sulfoxide showed that this compound existed as a 4:3 mixture of the *cis*- and *trans*-rotamers.[12] On the other hand, no signals assignable to *trans*-**13** could be detected in the spectrum measured in deuterated chloroform. This is probably due to stabilization of the *cis*-isomer in deuterated chloroform by intramolecular hydrogen bonding between the carbonyl oxygen and the proximate imidazole NH. The formation of such hydrogen bonding is analogous to that reported previously for the *N*-unsubstituted analogue **15**[11b] and supported by the rather low frequency of the amide I band[11b] at 1670 cm^{-1} observed in the IR spectrum of **13** in a dilute (0.005 M) solution in chloroform.

Final identification of **14** as the N^6-methoxy derivative rested on its nonreductive debenzylation leading to the formation of N^6-methoxyadenine (**10**). When debenzylated with concentrated sulfuric acid at 25 °C for 1 h in the presence of toluene,[5,6,13] **14** provided **10** in 87% yield. This sample was identical with authentic **10**[11b] synthesized from 6-chloropurine (**9**) and methoxyamine.

The UV spectra of **7b** in water at various pH's corresponded to those[2b,11a] of adenine 1-oxide (**1**) with an expected bathochromic shift of the maxima due to N^6-benzylation. This suggests the preponderance of the N(1)-oxide form over the tautomeric N(1)-OH form in water for the neutral species of **7b**, as in the case of adenine 1-oxide.[2a,14] The pK_a values of **7b** in water at 30 °C were spectrophotometrically determined to be 2.66 (basic) [for the protonated form⇌neutral form] and 8.22 (acidic) [for the neutral form⇌monoanion]. Accordingly, two absorption bands at 235 nm (ε 38700) and 274 nm (ε 11800) in the UV spectrum of **7b** in water at pH 6 are those arising from the neutral species. Because the strong UV absorption of purine *N*-oxides in the 215—240 nm region is considered to be due to >N→O or the enol anion >N–O$^-$,[15] the above strong absorption at 235 nm may be regarded as diagnostic of the N(1)-oxide structure for **7b**.

The above results reveal that the main product from the MCPBA oxidation of N^6-benzyladenine (**8b**) is the N(1)-oxide **7b**, affording another example of the preponderance of N(1)-oxidation of N^x-monosubstituted adenines. On treatment with MCPBA in methanol at

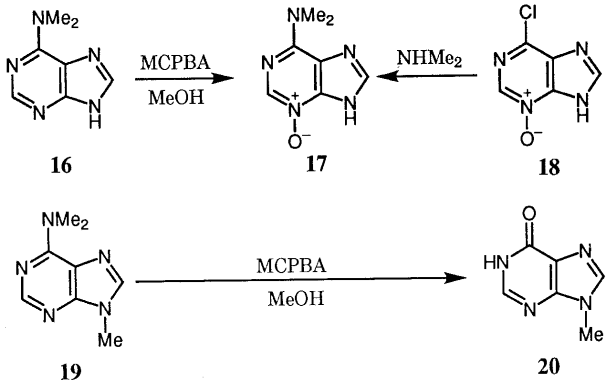
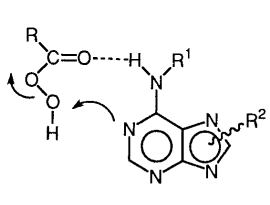


Chart 2

30 °C for 20 h, N^6-methyladenine (**8a**) also afforded the N(1)-oxide **7a**, whose structure was supported by the UV spectral similarity to **7b**, in 36% yield together with 21% recovery of **8a**. The regioselectivity is not in accord with that observed for alkylation of N^6-substituted adenines under neutral conditions[16]: benzylation of **8b** with benzyl bromide in DMAc[17] or *N*,*N*-dimethylformamide[18] takes place mainly at the 3-position. This directivity in oxidation of **8** is in general agreement with that observed in similar MCPBA oxidations of 9-substituted analogues, such as N^6,9-dimethyladenine,[10] N^6-methyladenosine,[19] and 2′,3′,5′-tri-*O*-benzoyl-N^6-methyladenosine.[19]

On the other hand, regioselective N(3)-oxidation has been reported for the following reactions of some 6-substituted purines: MCPBA[20] and monoperoxyphthalic acid oxidations[21] of 6-chloropurine (**9**), oxidation of 6-cyanopurine with hydrogen peroxide in acetic acid or with MCPBA,[22] and those of 6-methoxypurine and 6-ethoxypurine with hydrogen peroxide in acetic acid.[21] Likewise, N^6,N^6-dimethyladenine (**16**) afforded the N(3)-oxide **17** in 40% yield with 23% recovery of **16** on treatment with MCPBA under the same conditions as those employed for the oxidation of **8a** (Chart 2). The correctness of the structure **17** was established by direct comparison with authentic **17** prepared from 6-chloropurine 3-oxide (**18**) and dimethylamine. Unlike the 9-unsubstituted compound **16**, N^6,N^6,9-trimethyladenine (**19**) did not afford any *N*-oxide, but gave 9-methylhypoxanthine (**20**)[13e] in 18% yield, on treatment with MCPBA in methanol. Formation of this type of compound has already been reported[19] for the MCPBA oxidation of 2′,3′,5′-tri-*O*-benzoyl-N^6,N^6-dimethyladenosine in chloroform, in which the N^6-formyl-N^6-methyl derivative was a minor product.

The above findings suggest that at least one hydrogen on the nitrogen atom of the 6-amino group is necessary for regioselective N(1)- or N(7)-oxidation. We may thus account for regioselectivity in *N*-oxidation of unsubstituted and N^x-monosubstituted adenines with a peroxycarboxylic acid as follows. The *N*-oxidation is primarily controlled by the 6-amino group, most likely by means of hydrogen bonding with the reagent, to be oriented to either the 1- or 7-position, as illustrated in **21** and **22**; when both positions are available, as in the cases of 3-benzyladenine and 9-benzyladenine, the nitrogen atom of higher electron density undergoes oxidation. Sup-



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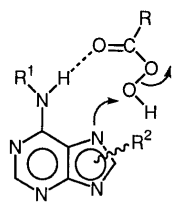

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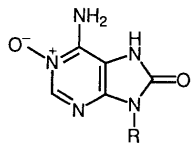

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a: R = Me
b: R = $PhCH_2$

posing that *N*-alkylation of adenines takes place at the position of higher electron density, regioselective N(7)-oxidation of 3-benzyladenine[6] and N(1)-oxidation of 9-benzyladenine[2c] are reasonable results in view of regioselective N(7)-alkylation of 3-benzyladenine and N(1)-alkylation of 9-benzyladenine.[23] Probably, the same principle is also applicable to N(1)-oxidation of adenine and N^6-alkyladenines (**8**), although we have no evidence to show that the electron densities at the 1-positions of the type-**21** and -**22** species are higher than those at the 7-positions.

However, the case is different with the reactions using trifluoroacetic acid. We have already reported that **8b** affords the N(3)-oxide and N(7)-oxide, although in poor yields,[20b] on treatment with aqueous hydrogen peroxide in trifluoroacetic acid. This outcome may be attributed to much stronger acidity of the acid than those of the usual carboxylic acids: **8b** should be almost completely protonated in trifluoroacetic acid, making the formation of species **21** or **22** unfavorable. Under these conditions, 7-benzyladenine was found to afford a complex mixture of products. 9-Benzyladenine afforded 9-benzyl-8-oxoadenine 1-oxide (**23b**), whose structure was established on the basis of UV spectral similarity to 9-methyl-8-oxoadenine 1-oxide (**23a**),[24] in 22% yield on treatment with 15% aqueous hydrogen peroxide in trifluoroacetic acid at 70 °C for 2.5 h. Compound **23b** might have been formed through N(7)-oxidation or N(3)-oxidation, followed by transformation into 9-benzyl-8-oxoadenine,[25] and subsequent N(1)-oxidation.[24]

In conclusion, the present results reveal that the main products from the MCPBA oxidation of N^6-alkyladenines (**8**) are the N(1)-oxides **7**. This regioselectivity in *N*-oxidation is not in accord with that in *N*-alkylation. Such an alteration in regioselectivity may be attributed to an anchoring effect of the 6-amino group through the formation of hydrogen bonding with a peroxycarboxylic acid. We hope that the present work will help toward interpretation and prediction of regioselectivity in *N*-oxidation of not only adenine derivatives, but also other nitrogen-containing heterocycles.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and are corrected. Spectra reported herein were recorded on a Hitachi M-80 or a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer [on solutions in 95% aqueous ethanol, 0.1 N hydrochloric acid (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous sodium hydroxide (pH 13)], a Shimadzu FTIR-8100 IR spectrophotometer, or a JEOL JNM-EX-270 NMR spectrometer. Unless otherwise stated, NMR spectra were recorded at 25 °C in hexadeuterated dimethyl sulfoxide with tetramethylsilane as an internal standard. 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.[26] The following abbreviations are used: br = broad, d = doublet, m = multiplet, s = singlet, sh = shoulder, t = triplet.

***N*^{6}-Methyladenine (8a)** A mixture of **9** (9.75 g, 63.1 mmol), methylamine hydrochloride (5.11 g, 75.7 mmol), triethylamine (20 ml), and 1-butanol (110 ml) was refluxed for 2 h, and then cooled to room temperature. The resulting precipitate was collected by filtration, washed successively with water (5 × 10 ml) and ethanol (10 ml), and recrystallized from water to afford **8a** (6.80 g, 72%), mp > 300 °C. Further recrystallization of this sample from water afforded an analytical sample of **8a** as colorless needles, mp > 300 °C [lit., mp 312—314 °C (dec.)[27]; mp 314—316 °C (dec.)[16a]]; MS *m/z*: 149 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 267 nm (ε 15700); $\lambda_{max}^{H_2O}$ (pH 1) 267 (14900); $\lambda_{max}^{H_2O}$ (pH 7) 267 (15800); $\lambda_{max}^{H_2O}$ (pH 13) 273 (15600); ^{1}H-NMR δ: 2.96 (3H, br, NHMe), 7.56 (1H, br, NHMe), 8.07 and 8.19 (1H each, s, purine protons), 12.88 [1H, br, N(9)-H]. *Anal.* Calcd for $C_6H_7N_5$: C, 48.32; H, 4.73; N, 46.95. Found: C, 48.05; H, 4.78; N, 46.92.

***N*^{6}-Methyladenine 1-Oxide (7a)** A solution of **8a** (1.49 g, 10 mmol) and MCPBA (of *ca.* 70% purity) (3.70 g, 15 mmol) in methanol (250 ml) was kept at 30 °C for 20 h and then concentrated *in vacuo*. The residue was mixed with 10% hydrochloric acid (30 ml), washed with ether (5 × 30 ml), neutralized with 10% aqueous sodium carbonate, and concentrated *in vacuo*. This residue was extracted with hot methanol (5 × 50 ml), and the methanolic extracts were concentrated *in vacuo* after addition of silica gel (10 g). The solid residue was placed on the top of a column (40 mm in diameter) for flash chromatography, and the column was eluted with chloroform–methanol (4 : 1, v/v). The starting material **8a** (308 mg, 21%), mp 293—301 °C (dec.), was recovered from earlier fractions. Crude **7a**, obtained from later fractions, was washed with methanol and dried to afford **7a** (596 mg, 36%), mp > 300 °C. Recrystallization of this sample from water afforded an analytical sample of **7a** as colorless needles, mp > 300 °C; MS *m/z*: 165 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 237 nm (ε 38900), 272 (8600); $\lambda_{max}^{H_2O}$ (pH 1) 213 (24200), 262 (13000); $\lambda_{max}^{H_2O}$ (pH 7) 234 (38100), 271 (9700); $\lambda_{max}^{H_2O}$ (pH 13) 237 (45200), 278 (9200); ^{1}H-NMR δ:[28] 3.47 (3H, d, J = 4 Hz, NHMe), 8.26 [1H, s, C(8)-H], 8.30 (1H, br, NHMe), 8.53 [1H, s, C(2)-H], 13.36 [1H, br, N(9)-H]. *Anal.* Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.57; H, 4.21; N, 42.59.

***N*^{6}-Benzyladenine 1-Oxide (7b)** A mixture of **8b** (4.51 g, 20 mmol), MCPBA (of *ca.* 70% purity) (7.40 g, 30 mmol), and methanol (480 ml) was stirred at 30 °C for 20 h, and then concentrated *in vacuo*. The residue was mixed with water (100 ml) and 10% hydrochloric acid (50 ml). The resulting precipitate was extracted with ether (2 × 50 ml). The aqueous layer was neutralized with 10% aqueous sodium hydroxide and concentrated *in vacuo*. The residue was triturated with methanol (100 ml), and an insoluble solid was removed by filtration. Silica gel (15 g) was added to the methanolic filtrate and then the mixture was concentrated *in vacuo*. The solid residue was put on the top of a column (60 mm in diameter) for flash chromatography and the column was eluted with chloroform–methanol (8 : 1, v/v). From earlier fractions, **8b** (1.14 g, 25%), mp 230—233 °C (dec.), was recovered. Compound **7b** (2.01 g) was obtained from later fractions as a colorless solid, mp 198—200 °C. Recrystallization of this sample from methanol afforded pure **7b** (1.62 g, 35%), mp 201—202 °C. Further recrystallization from methanol afforded an analytical sample of **7b** as colorless prisms, mp 201—202 °C; pK_a (in water at 30 °C and ionic strength 1.0) 2.66 ± 0.02 (basic), 8.22 ± 0.06 (acidic)[29]; MS *m/z*: 241 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 238 nm (ε 41800), 274 (11100); $\lambda_{max}^{H_2O}$ (pH 1) 211 (29100), 265 (15200); $\lambda_{max}^{H_2O}$ (pH 6) (in 0.045 M phosphate buffer at ionic strength 1.0) 235 (38700), 274 (11800); $\lambda_{max}^{H_2O}$ (pH 7) 236 (39300), 273 (12200); $\lambda_{max}^{H_2O}$ (pH 13) 239 (47300), 279 (11200); ^{1}H-NMR δ[28]: 5.24 (2H, d, J = 6 Hz, NHCH_2Ph), 7.2—7.5 (5H, m, Ph), 8.28 [1H, s, C(8)-H], 8.58 [1H, s, C(2)-H], 8.84 (1H, t, J = 6 Hz, NHCH_2Ph), 13.42

[1H, br, N(9)-H]. *Anal.* Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.86; H, 4.62; N, 29.21.

N^6,N^6-Dimethyladenine 3-Oxide (17) i) From **18** and Dimethylamine: A mixture of **18**[20b] (200 mg, 1.17 mmol) and 30% aqueous dimethylamine (10 ml) was refluxed for 3 h, and then concentrated *in vacuo*. The residue was recrystallized from water (treated with charcoal) to afford **17** (137 mg, 65%), mp 248—250 °C (dec.). Further recrystallization of this sample from water afforded an analytical sample of **17** as colorless needles, mp 249.5—250.5 °C (dec.) [lit.[20a] mp 276 °C (dec.)]; MS *m/z*: 179 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 232 nm (ε 10300), 307 (15500); $\lambda_{max}^{H_2O}$ (pH 1) 212 (11500), 225 (sh) (8500), 294 (18600); $\lambda_{max}^{H_2O}$ (pH 7) 231 (13300), 306 (17400); $\lambda_{max}^{H_2O}$ (pH 13) 234 (16000), 304 (17000); ^{1}H-NMR [D_2O; sodium 3-(trimethylsilyl)-1-propanesulfonate was used as an internal standard] δ: 3.42 (6H, s, NMe_2), 8.26 and 8.36 (1H each, s, purine protons). *Anal.* Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.68; H, 5.00; N, 38.81.

ii) By Oxidation of **16**: A solution of **16**[30] (1.63 g, 10 mmol) and MCPBA (of *ca.* 70% purity) (3.70 g, 15 mmol) in methanol (250 ml) was kept at 30 °C for 20 h. The resulting precipitate was collected by filtration, washed with methanol (5 ml), and dried to afford **17** (702 mg), mp 240—242 °C (dec.). Recrystallization of this sample from water afforded **17** (658 mg), mp 246—247 °C (dec.). The filtrate of the reaction mixture and the methanolic washings of crude **17** were combined and concentrated *in vacuo*. The residue was extracted with ether (5 × 30 ml) after addition of 10% hydrochloric acid (30 ml). The aqueous layer was neutralized with 10% aqueous sodium carbonate and then concentrated *in vacuo*. The residue was extracted with hot methanol (5 × 50 ml). The methanolic extracts were concentrated *in vacuo* after addition of silica gel (8 g). The residue was purified by flash chromatography [chloroform–methanol (4 : 1, v/v)] to afford crude **16** from earlier fractions, and crude **17** from later fractions. Crude **16** was recrystallized from ethanol to recover **16** (382 mg, 23%), mp 260—261 °C (dec.). Crude **17** was recrystallized from water to afford a second crop of **17** [63 mg; the total yield was 721 mg (40%)]. Further recrystallization of **17** from water afforded an analytical sample of **17** as colorless needles, mp 247—248 °C (dec.). *Anal.* Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.80; H, 5.02; N, 38.88. This sample was identical (by comparison of the MS, UV, IR, and ^{1}H-NMR spectra, and TLC mobility) with the one prepared by method (i).

Oxidation of N^6,N^6,9-Trimethyladenine (19) Leading to 9-Methylhypoxanthine (20) A solution of **19**[30] (886 mg, 5 mmol) and MCPBA (of *ca.* 70% purity) (6.16 g, 25 mmol) in methanol (30 ml) was kept at 30 °C for 48 h. The resulting precipitate was collected by filtration, washed with methanol (30 ml), and dried to afford **20** (137 mg, 18%), mp > 300 °C. From the filtrate and washings, the starting material **19** (230 mg, 26%), mp 109—111 °C, was recovered by means of flash chromatography [chloroform–ethanol (8 : 1, v/v)]. Recrystallization of crude **20** from water afforded an analytical sample of **20** as colorless prisms, mp > 300 °C; MS *m/z*: 150 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 251 nm (ε 10900); $\lambda_{max}^{H_2O}$ (pH 1) 250 (11100); $\lambda_{max}^{H_2O}$ (pH 7) 250 (12000); $\lambda_{max}^{H_2O}$ (pH 13) 255 (12600); ^{1}H-NMR δ: 3.73 (3H, s, Me), 8.03 (2H, s, purine protons), 12.25 (1H, br, NH). *Anal.* Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.99; H, 3.89; N, 37.32. This sample was identical (by comparison of the UV, IR, and ^{1}H-NMR spectra and TLC mobility) with authentic **20**.[13e]

N^6-Benzyl-1-methoxyadenine Perchlorate (11) A mixture of **7b** (1.60 g, 6.63 mmol) and methyl iodide (3.77 g, 26.6 mmol) in DMAc (24 ml) was stirred at 25 °C for 20 h. The resulting solution was concentrated *in vacuo*. The oily residue was dissolved in water (6 ml) and then a solution of sodium perchlorate monohydrate (1.20 g, 8.54 mmol) in water (3 ml) was added. The resulting precipitate was collected by filtration after storage in a refrigerator for 2 h, washed successively with water (1 ml) and ethanol (1 ml), and dried to afford **11** (1.69 g, 72%), mp 193—196 °C (dec.). Recrystallization of this sample from ethanol afforded an analytical sample as colorless prisms, mp 195—197 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 269 nm (ε 13700); $\lambda_{max}^{H_2O}$ (pH 1) 264 (14800); $\lambda_{max}^{H_2O}$ (pH 7) 226 (sh) (18300), 277 (14500); $\lambda_{max}^{H_2O}$ (pH 13) 273 (16300); ^{1}H-NMR δ:[31] 4.19 (3H, s, Me), 5.44 (2H, s, C<u>H</u>$_2$Ph), 7.2—7.5 (5H, m, CH_2<u>Ph</u>), 8.53 [1H, s, C(8)-H], 9.16 [1H, s, C(2)-H], 10.30 and 14.29 (1H each, br, two NH's). *Anal.* Calcd for $C_{13}H_{13}N_5O \cdot HClO_4$: C, 43.89; H, 3.97; N, 19.69. Found: 43.80; H, 3.94; N, 19.80.

Dimroth Rearrangement of N^6-Benzyl-1-methoxyadenine (12) Leading to 1-Benzyl-N^6-methoxyadenine (14) *via* *N*-Benzyl-*N'*-methoxy-5-formamidoimidazole-4-carboxamidine (13) A solution of the perchlorate **11** (190 mg, 0.534 mmol) in water (20 ml) was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (2 ml) and the column was eluted with water (30 ml). The eluates were combined and concentrated *in vacuo* to leave **12** as a colorless solid. This was heated under reflux in water (10 ml) for 3 h. The resulting solution was concentrated *in vacuo* and the residue was subjected to flash chromatography [chloroform–methanol (20 : 1, v/v)]. Compound **13** (108 mg, 74%) was obtained as a colorless oil from earlier fractions, MS *m/z*: 273 (M^+); IR $\nu_{max}^{CHCl_3}$ (at 0.005 M) cm^{-1}: 1670 (HCON); ^{1}H-NMR δ: 3.71 and 3.72 (a total of 3H, s, OMe), 4.08 (4/7 × 2H) and 4.65 (3/7 × 2H) (d each, *J* = 7 Hz, *cis*- and *trans*-NHC<u>H</u>$_2$Ph), 6.38 (4/7H) and 6.61 (3/7H) (t each, *J* = 7 Hz, *cis*- and *trans*-N<u>H</u>C<u>H</u>$_2$Ph), 7.0—7.3 [5H, m, CH_2<u>Ph</u>], 7.34 (4/7H) and 7.54 (3/7H) [s each, *cis*- and *trans*-C(2)-H], 8.23 (4/7H, d, *J* = 2 Hz, *cis*-NHC<u>H</u>O), 8.29 (3/7H, d, *J* = 12 Hz, *trans*-NHC<u>H</u>O), 9.55 (3/7H, d, *J* = 12 Hz, *trans*-N<u>H</u>CHO), 10.11 (4/7H, br, *cis*-N<u>H</u>CHO), 12.40 and 12.45 [a total of 1H, br, N(9)-H]; ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s, OMe), 4.95 (2H, d, *J* = 7 Hz, NHC<u>H</u>$_2$Ph), 5.69 (1H, t, *J* = 7 Hz, N<u>H</u>C<u>H</u>$_2$Ph), 7.2—7.4 [6H, m, CH_2<u>Ph</u> and C(2)-H], 8.33 (1H, s, NHC<u>H</u>O), 10.04 and 11.12 (1H each, br, two NH's). Compound **14** (9 mg, 7%), which was identical (by comparison of the IR spectrum and TLC mobility) with an analytical sample described below, was obtained from later fractions.

In a separate run, **12**, which was obtained from **11** (1.40 g, 3.94 mmol), was heated under reflux in water (50 ml) for 18 h. After cooling of the reaction mixture, the precipitate that resulted was collected by filtration, washed with a little ethanol, and dried to afford **14** (517 mg), mp 239—241 °C (dec.). The combined filtrate and washings were concentrated *in vacuo*, and the oily residue was purified by flash chromatography [chloroform–methanol (20 : 1, v/v)] to afford **13** (178 mg, 16%) as a colorless oil, identical (by comparison of the IR spectrum and TLC mobility) with that described above, and a second crop of **14** [47 mg; the total yield was 564 mg (56%)], mp 238—241 °C (dec.). Recrystallization of crude **14** from ethanol afforded an analytical sample of **14** as colorless prisms, mp 241—242 °C (dec.); MS *m/z*: 255 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 276 nm (ε 10900); $\lambda_{max}^{H_2O}$ (pH 1) 280 (9100); $\lambda_{max}^{H_2O}$ (pH 7) 274 (11700); $\lambda_{max}^{H_2O}$ (pH 13) 277 (13800); ^{1}H-NMR δ: 3.68 (3H, s, OMe), 4.98 (2H, s, C<u>H</u>$_2$Ph), 7.2—7.4 (5H, m, CH_2<u>Ph</u>), 7.88 [1H, d, *J* = 0.7 Hz, C(8)-H], 8.00 [1H, s, C(2)-H], 12.48 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.06; H, 5.14; N, 27.62.

Acid-Catalyzed Recyclization of 13 Leading to 12 and 14 A solution of **13** (93 mg, 0.34 mmol) in 0.2 N hydrochloric acid (6.8 ml) was kept at room temperature for 24 h, neutralized with concentrated aqueous ammonia, and then concentrated *in vacuo*. The residue was dissolved in methanol and then concentrated *in vacuo* after addition of silica gel (0.5 g). The solid residue was subjected to flash chromatography [chloroform–methanol (4 : 1, v/v)] to afford **14** (55 mg, 63%), mp 238—240 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with **14** obtained by the Dimroth rearrangement of **12**. Compound **12** was obtained from later fractions. This was suspended in water (1 ml) and then 70% aqueous perchloric acid was added to make the mixture acidic. The precipitate, which appeared from the resulting clear solution, was collected by filtration and dried to afford **11** (18 mg, 15%), mp 194—197 °C (dec.), identical (by comparison of the IR spectrum and TLC mobility) with authentic **11**.

Debenzylation of 14 Leading to N^6-Methoxyadenine (10) A mixture of **14** (307 mg, 1.20 mmol), concentrated sulfuric acid (1.8 g), and toluene (3 ml) was stirred at 25 °C for 1 h, and then poured onto ice (15 g). After mixing with additional toluene (5 ml), the aqueous layer was separated from the mixture and the organic layer was extracted with water (2 ml). The aqueous layers were combined, treated with charcoal, diluted with water to a volume of 60 ml, and passed through a column packed with Amberlite IRA-402 (HCO_3^-) (60 ml). The column was further eluted with water (120 ml). The eluates were combined and concentrated *in vacuo*. The residue was washed with water (3 ml) and dried to afford **10** (173 mg, 87%). Recrystallization of this sample from 0.005 M phosphate buffer (pH 7) afforded **10** as slightly pink minute needles, mp *ca.* 200 °C (dec.) [lit.[11b] mp *ca.* 190 °C (dec.)], identical (by comparison of the IR and ^{1}H-NMR spectra and TLC mobility) with authentic **10**.[11b]

Oxidation of 9-Benzyladenine with Trifluoroperoxyacetic Acid Leading to 9-Benzyl-8-oxoadenine 1-Oxide (23b) A solution of 9-benzyladenine (2.25 g, 10 mmol) in a mixture of trifluoroacetic acid (22.5 ml) and 15% aqueous hydrogen peroxide (11.3 ml) was heated at 70 °C for 2.5 h, concentrated to 5 ml, and neutralized with 10% aqueous sodium car-

bonate. The resulting precipitate was collected by filtration after storage of the mixture in a refrigerator overnight, washed successively with water (2 × 4 ml) and ethanol (4 ml), and dried to afford a slightly yellow solid (511 mg). The filtrate and washings were combined and concentrated to *ca.* 20 ml to afford a second crop (410 mg) of the product. The two crops of the crude product were combined and dissolved in methanol (300 ml). Silica gel (6 g) was added to the solution and the mixture was concentrated *in vacuo*. The solid residue was subjected to flash chromatography [chloroform–methanol (5 : 1, v/v)]. The crude **23b**, obtained from later fractions, was recrystallized from 50% (v/v) aqueous ethanol to afford **23b** (555 mg, 22%), mp 288—290 °C (dec.). Further recrystallization of this sample from the same solvent afforded an analytical sample of **23b** as colorless needles, mp 289—290 °C (dec.); MS *m/z*: 257 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 244 nm (ε 58700), 265 (sh) (8400); $\lambda_{max}^{H_2O}$ (pH 1) 225 (31000), 240 (sh) (10300), 277 (10500); $\lambda_{max}^{H_2O}$ (pH 7) 241 (58500), 262 (sh) (7800), 282 (sh) (5400); $\lambda_{max}^{H_2O}$ (pH 13) 243 (50200), 292 (9500); IR ν_{max}^{Nujol} cm^{-1}: 3384, 3210, 3150 (NH_2), 1711 (CO); ^{1}H-NMR δ: 4.94 (2H, s, C<u>H</u>$_2$Ph), 7.23—7.38 (7H, m, CH$_2$<u>Ph</u> and NH_2), 8.45 [1H, s, C(2)-H], 10.45 [1H, br, N(7)-H]. *Anal.* Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.93; H, 4.16; N, 27.10.

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25) It has been reported that adenine 7-oxide affords 8-oxoadenine on treatment with boiling acetic acid.[6] Migration of the oxygen function to the 8-position has also been reported for hypoxanthine 3-oxide,[21] guanine 3-oxide, 3-hydroxyxanthine, and 3-hydroxy-7,9-dimethylxanthine [Wölcke U., Pfleiderer W., Delia T. J., Brown G. B., *J. Org. Chem.*, **34**, 981—983 (1969)].
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