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Purines. XXIII.[1] Synthesis of N^6-Alkoxy-1,3-dialkyladeninium Salts and an Attempt to Synthesize 1,3-Dimethyladenine

TOZO FUJII,* TOHRU SAITO, and TSUYOSHI NAKASAKA

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

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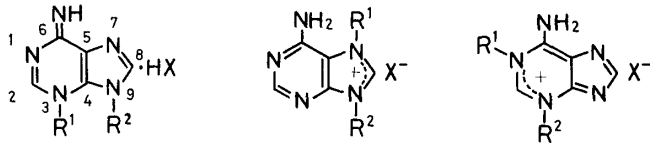
Ethylation of N^6-methoxy-3-methyladenine (**5**) with EtI in $AcNMe_2$ gave the 1-ethylated product **8** (X=I) (21% yield) and the N^6-ethylated product **11** (X=ClO_4) (33%). The N^6-benzyloxy analogue **6**, prepared from 3-methyl-6-methylthiopurine (**4**) and benzyloxyamine, was similarly methylated to produce the 1-methylated product **9** (X=Cl) (34%) as well as the N^6-methylated product **12** (X=Cl) (35%). Reduction of N^6-methoxy-1,3-dimethyladeninium iodide (**7**: X=I) with $NaBH_4$ afforded the 1,2-dihydro derivative **14** (92% yield), which reverted to **7** (X=I) on dehydrogenation with I_2 in EtOH. On hydrogenation with Raney Ni and H_2, **7** (X=I) furnished **14** (26% yield) and the N^6-demethoxy derivative **15**·HI (17%), while **14** gave **15** on similar reduction. Dehydrogenation of **15** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in $CHCl_3$ yielded a crude solid presumed to be the 1,3-dimethyladeninium salt (**18**), which readily rearranged into N^6,3-dimethyladenine (**16**) through the monocycle **17**. It has been found that hydrolysis of **7** (X=ClO_4) to give the imidazole **13** in H_2O at pH 7.72 and 25 °C proceeds *ca.* 270 times as fast as that of the 3,9-dimethyl analogue **19** to give the monocycle **20**.

Keywords——regioselectivity in alkylation; effect of N^6-alkoxy group; 1,3-dialkyladenine derivative; $NaBH_4$ reduction; catalytic hydrogenolysis; dehydrogenation; ring opening; Dimroth rearrangement

Our previous syntheses of 3,9-dialkyladenines (**1**)[2] and 7,9-dialkyladenines (**2**)[1,3] in the salt form have multiplied the number of known positional isomers among the eleven possible N^x, N^y-disubstituted adenines, and 1,3-disubstituted adenine (type **3**) is now the only isomer that remains unknown.[4-13] In related work, we also observed that methylation of N^6-



1 2 3

Chart 1

methoxy-1-methyladenine or N^6-methoxy-3-methyladenine (**5**) with MeI in $AcNMe_2$ produced N^6-methoxy-1,3-dimethyladeninium iodide (**7**: X=I) in 44% or 40% yield.[1,14] This finding is significant, since a selective removal of the N^6-methoxy group from **7** (X=I) should give a 1,3-dimethyladeninium salt (**18**), the progenitor of hitherto unknown 1,3-disubstituted adenines (type **3**). This paper describes the results of our efforts directed toward the synthesis of **18**, affording indirect but considerable evidence in support of the virtual formation of the unstable 1,3-dimethyladenine structure **18**. The syntheses of the N^6-benzyloxy derivative **9** (X=Cl) and the N^6-methoxy-1-ethyl homologue **8** (X=I) of this structure are also included.

We first tried to ethylate **5** in order to extend the scope of its alkylation. On treatment with an excess of EtI in $AcNMe_2$ at 40 °C for 30 h, **5** produced the 1-ethylated product **8**

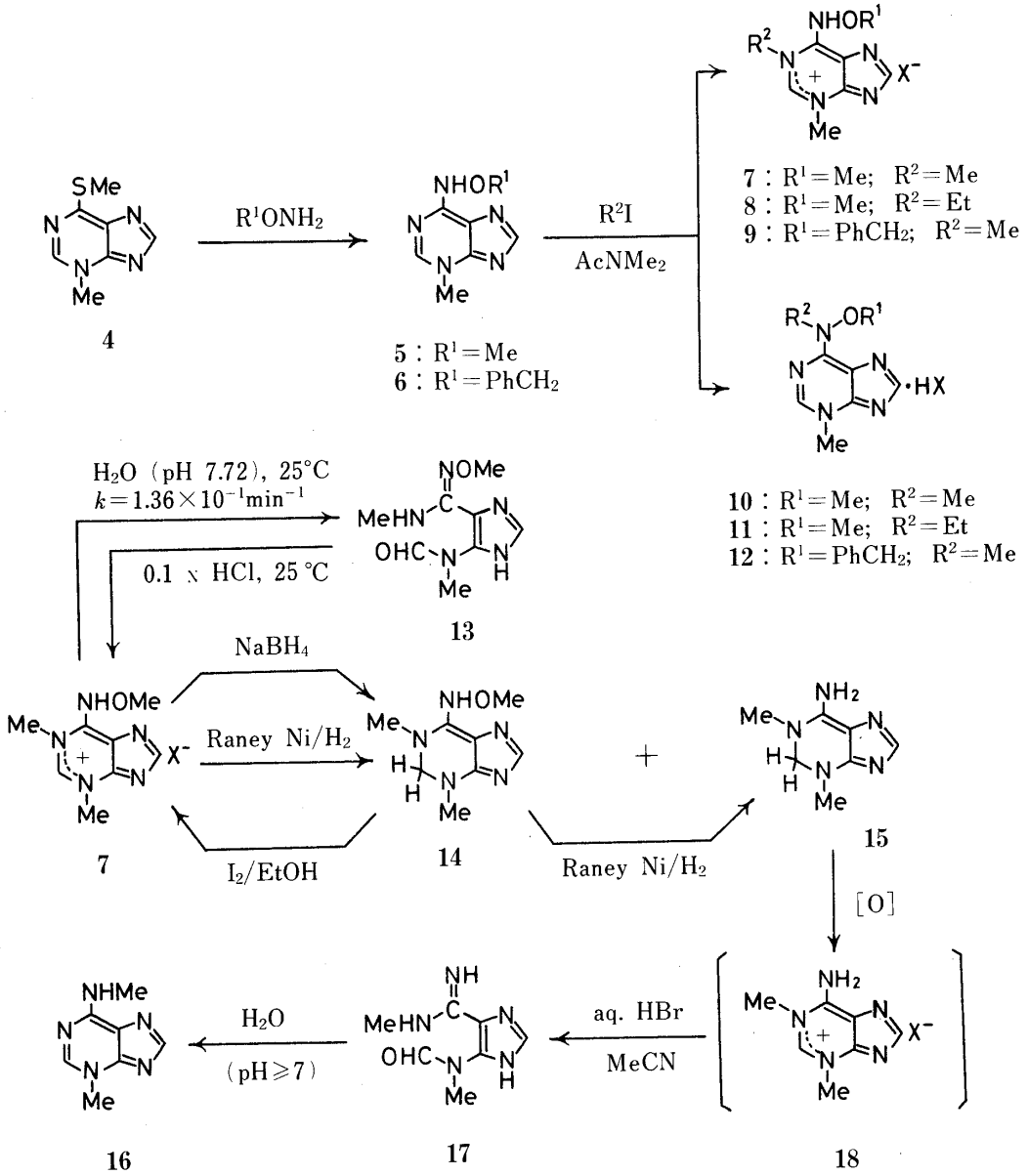


Chart 2

(X=I) (21% yield) together with the N^6-ethylated product **11** (X=I), which was isolated in the form of the perchlorate **11** ($X=ClO_4$) (33% yield). The 1-ethyl and the N^6-ethyl structures of the two products were assignable by analogy with the recently reported[1] 1-methylation (40%) and competitive N^6-methylation (36%) of **5** and on the basis of the similarity of their ultraviolet (UV) spectra with those[1] of the 1-methyl (**7**: X=I) and N^6-methyl (**10**: $X=ClO_4$) homologues.

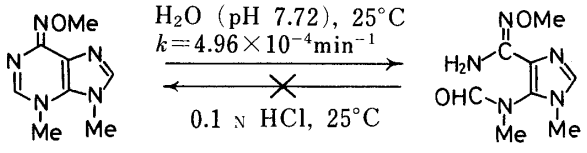
It seems probable that replacement of the N^6-methoxy group by the benzyloxy group in **5** would exert a similar directivity in an analogous alkylation. To check this, the N^6-benzyloxy analogue **6** was then synthesized from 3-methyl-6-methylthiopurine (**4**) in 57% yield by amination with benzyloxyamine. Treatment of **6** with an excess of MeI in $AcNMe_2$ at 42—44 °C for 3 h and separation of the products in the form of hydrochloride salts furnished the 1-methylated product **9** (X=Cl) (34% yield) as well as the N^6-methylated product **12** (X=Cl) (35% yield). The UV spectra of the two products resembled those[1] of the N^6-methoxy analogues **7** ($X=ClO_4$) and **10** ($X=ClO_4$), and this led to the assignments of the above

structures. Thus, the observed regioselectivity in methylation of **6** together with the previous results[1] of methylation of **5** may allow us to make the generalization that alkylation of N^6-alkoxy-3-alkyladenine occurs competitively at the 1- and the N^6-positions, but to comparable extents.

With the aim of synthesizing a genuine 1,3-dimethyladenine structure, we next tried to remove the N^6-methoxy group from **7** (X=I). On catalytic reduction using Raney nickel and hydrogen (MeOH, 3 atm, 18—20 °C, 20 h), **7** (X=I) provided two 1,2-dihydro derivatives, **14** (26% yield) and **15**·HI (17% yield), instead of the desired product **18** (X=I). The 1,2-dihydro structures of **14** and **15**·HI were supported by their nuclear magnetic resonance (NMR) spectra in Me_2SO-d_6, in which the $N_{(1)}$-methyl and the $N_{(3)}$-methyl proton signals resonated at higher field than those[1] of **7** (X=I) by 0.5—1 ppm. Oxidation of **14** with iodine in EtOH at room temperature regenerated **7** (X=I) (38% yield), which reverted to **14** in 92% yield upon reduction with $NaBH_4$ in MeOH at room temperature. In view of the lowered electron density of **7** (X=I) in the pyrimidine moiety, its reduction product **14** should have the 1,2-dihydro structure as inferred. Further reduction of **14** with Raney nickel and hydrogen (EtOH, 1 atm, 50 °C, 3 h) produced the demethoxy derivative **15** in 71% yield.

The difficulty in removing the N^6-methoxy group without partial saturation of the adeninium ring and the high-yield two-step synthesis of **15** from **7** (X=I) as described above led us to examine the dehydrogenation of **15** as an alternative route to **18**. Although trials conducted with iodine, sodium nitrite, air, or chloranil for this step all failed, treatment of **15** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in $CHCl_3$ at room temperature produced a dark brown solid presumed to be **18** (X=2,3-dichloro-5,6-dicyano-4-hydroxyphenolate). Since the solid was unstable and difficult to purify by recrystallization, conversion into the bromide salt **18** (X=Br) was attempted by treating it with conc. aqueous HBr in MeCN under ice-cooling. However, the product isolated was not the desired salt but the hydrobromide of the ring-opened derivative **17**. The hydrobromide of **17** was also found to be unstable in H_2O at room temperature at pH 7 or above: it quickly underwent recyclization to give N^6,3-dimethyladenine (**16**) in 53% yield based on the dihydro derivative **15** used. The sequence **18**→**17**→**16** thus concluded a Dimroth rearrangement.[15]

Although we have been unable to characterize the 1,3-dimethyladenine structure **18** obtained by the DDQ oxidation of **15**, the above results indicate its virtual formation and extreme instability. Since the rate of ring opening of **18** could not be measured directly, that of the N^6-methoxy derivative **7** (X=ClO_4) was determined instead. Treatment of **7** (X=I) in H_2O with Amberlite IRA-402 (HCO_3^-) afforded the monocycle **13** in 92% yield. In H_2O at pH 7.72 (ionic strength 0.5) and 25 °C, this ring opening was found to proceed at a rate of $1.36\times10^{-1}\,min^{-1}$ (half life 5.1 min). On the other hand, treatment of **13** with 0.1 N aqueous HCl at 25 °C for 21 h gave the recyclized product **7**, which was isolated as the perchlorate **7** (X=ClO_4) (53% yield). We have already found that 3,9-dimethyladenine hydrochloride (**1**: $R^1=R^2=Me$; X=Cl) undergoes similar ring opening in H_2O at 25 °C and pH 7.50 (ionic strength 0.5) at a rate of $5.07\times10^{-4}\,min^{-1}$; [2f] at pH 8.32 (ionic strength 0.5) at a rate of $2.88\times10^{-3}\,min^{-1}$ [2b] In the present work, the N^6-methoxy derivative **19**[2a,b] was also found to form the monocycle **20** (85% yield) when heated in H_2O at 60 °C for 15 h, and a rate constant



19 **20**

Chart 3

of 4.96×10^{-4} min^{-1} (half life 23 h) was determined for the reaction at pH 7.72 (ionic strength 0.5) and 25 °C. In contrast to the case of **13**, **20** did not revert to **19** in 0.1 N aqueous HCl at 25 °C. Comparison of the above rate constants reveals that introduction of a methoxyl group into 3,9-dimethyladenine (type **1**) at the N^6-position causes the ring-opening reaction to slow down slightly, and that ring opening of the N^6-methoxy-1,3-dimethyladeninium salt (**7**) in the pyrimidine moiety is *ca.* 270 times as fast as that of the 3,9-dimethyl analogue **19**. Therefore, the genuine 1,3-dimethyladenine structure (**18**) itself may be regarded as one of the most unstable dimethyladenines in H_2O under alkaline conditions.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 1 for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

N^6-Benzyloxy-3-methyladenine (6)——A stirred mixture of 3-methyl-6-methylthiopurine dihydrate (**4**·$2H_2O$)[1] (2.16 g, 10 mmol) and benzyloxyamine[16] (4.93 g, 40 mmol) in 50% (v/v) aqueous EtOH (50 ml) was heated at 50 °C, and the pH of the resulting solution was adjusted to 5.0 with 1 N aqueous HCl. After having been stirred at 50—55 °C for 8 h, the solution was again adjusted to pH 5.0 and stirring was continued at the same temperature for an additional 14 h. Concentration of the reaction mixture under reduced pressure and co-evaporation of the residue with three 50-ml portions of benzene left a semisolid, which was washed with four 50-ml portions of ether. The insoluble solid that resulted was filtered off and recrystallized twice from 30% (v/v) aqueous EtOH to give slightly yellowish prisms (1.50 g, 57%), mp 180—181 °C (sintered at *ca.* 100 °C). Further recrystallization in the same way and drying over P_2O_5 at 2 mmHg and room temperature for 24 h afforded an analytical sample of the hemihydrate of **6** as almost colorless prisms, mp 180—181 °C (sintered at *ca.* 100 °C); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 294 nm (ε 15400); $\lambda_{max}^{H_2O}$ (pH 1) 287 (19000); $\lambda_{max}^{H_2O}$ (pH 7) 295 (16400); $\lambda_{max}^{H_2O}$ (pH 13) 288 (12700); NMR (Me_2SO-d_6) δ: 3.46 (3H, s, $N_{(3)}$–Me), 4.96 (2H, s, $OC\underline{H}_2Ph$), 7.29 (5H, m, Ph), 7.57 and 7.82 (1H each, s, purine protons), 12.50 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{13}N_5O \cdot 1/2H_2O$: C, 59.08; H, 5.34; N, 26.50. Found: C, 58.92; H, 5.43; N, 26.28.

Ethylation of N^6-Methoxy-3-methyladenine (5)——A mixture of **5**[1] (538 mg, 3 mmol) and EtI (1.40 g, 9 mmol) in $AcNMe_2$ (4 ml) was stirred at 40 °C for 30 h. The precipitate that resulted was filtered off and recrystallized from EtOH to furnish 1-ethyl-N^6-methoxy-3-methyladeninium iodide (**8**: X = I) (215 mg, 21%), mp 250.5—251.5 °C (dec.). Further recrystallization from EtOH produced an analytical sample as colorless plates, mp 250.5—251.5 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 277 nm (ε 14200), 340 (1400); $\lambda_{max}^{H_2O}$ (pH 1) 223 (20900), 275 (14400); $\lambda_{max}^{H_2O}$ (pH 7 and 13) unstable (changed through an isosbestic point at 255 nm); NMR (Me_2SO-d_6) δ: 1.40 (3H, t, J = 8 Hz, $N_{(1)}$–$CH_2\underline{Me}$), 3.72 (3H, s, $N_{(3)}$–Me), 3.90 (3H, s, OMe), 4.00 (2H, q, J = 8 Hz, $N_{(1)}$–$C\underline{H}_2Me$), 8.20 (1H, s, $C_{(8)}$–H), 9.24 (1H, s, $C_{(2)}$–H), 13.48 (1H, br, NH). *Anal.* Calcd for $C_9H_{14}IN_5O$: C, 32.25; H, 4.21; N, 20.90. Found: C, 32.32; H, 4.10; N, 20.90.

On the other hand, evaporation of the filtrate, which was obtained when the crude **8** (X = I) was separated from the reaction mixture, under reduced pressure left a solid, which was dissolved in H_2O (50 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (ClO_4^-) (10 ml), and the column was eluted with H_2O. Concentration of the eluate (300 ml) under reduced pressure and recrystallization of the residue from EtOH provided N^6-ethyl-N^6-methoxy-3-methyladenine perchlorate (**11**: X = ClO_4) (305 mg, 33%), mp 194.5—195.5 °C (dec.). Repeated recrystallizations from EtOH yielded an analytical sample as slightly yellowish scales, mp 237—238 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 227 nm (ε 11400), 295 (19800); $\lambda_{max}^{H_2O}$ (pH 1) 227 (9600), 292 (21600); $\lambda_{max}^{H_2O}$ (pH 7) 226 (11700), 293 (18900); $\lambda_{max}^{H_2O}$ (pH 13) 226 (12700), 295 (17100); NMR (Me_2SO-d_6) δ: 1.26 (3H, t, J = 7 Hz, N^6–$CH_2\underline{Me}$), 3.92 (3H, s, $N_{(3)}$–Me), 4.00 (3H, s, OMe), 4.14 (2H, q, J = 7 Hz, N^6–$C\underline{H}_2Me$), 8.66 and 8.78 (1H each, s, purine protons). *Anal.* Calcd for $C_9H_{14}ClN_5O_5$: C, 35.13; H, 4.59; N, 22.76. Found: C, 35.07; H, 4.58; N, 22.80.

Methylation of N^6-Benzyloxy-3-methyladenine (6)——A mixture of **6**·$1/2H_2O$ (1.32 g, 5 mmol) and MeI (2.13 g, 15 mmol) in $AcNMe_2$ (15 ml) was stirred at 42—44 °C for 3 h. The reaction mixture was concentrated *in vacuo*, and the residual reddish brown oil was dissolved in H_2O (250 ml) after having been washed with two 15-ml portions of ether. The aqueous solution was passed through a column of Amberlite IRA-402 (Cl^-) (20 ml), and the column was eluted with H_2O (200 ml). Evaporation of the eluate under reduced pressure left a solid, which was dissolved in hot H_2O (10 ml). On cooling, the aqueous solution deposited crystals, which were collected by filtration, washed with a little H_2O, and dried to give N^6-benzyloxy-1,3-dimethyladeninium chloride (**9**: X = Cl) (553 mg, 34%) as a monohydrate, mp 227—228 °C (dec.). For analysis, it was recrystallized from H_2O and dried over P_2O_5 at 2 mmHg and room temperature for 24 h to yield slightly yellowish plates, mp 237—238 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ unstable; $\lambda_{max}^{H_2O}$ (pH 1) 274.5 nm (ε 15900); $\lambda_{max}^{H_2O}$ (pH 7 and 13) unstable (changed through an isosbestic point at 255 nm); NMR (Me_2SO-d_6) δ: 3.40 (3H, s, $N_{(1)}$–Me), 3.72 (3H, s, $N_{(3)}$–Me), 5.12 (2H, s, $OC\underline{H}_2Ph$), 7.16—7.44 (5H, m, Ph), 8.18 (1H, s, $C_{(8)}$–H), 9.55 (1H, s, $C_{(2)}$–H), 13.75 (1H, br, NH). *Anal.* Calcd for $C_{14}H_{16}ClN_5O \cdot H_2O$: C, 51.93; H, 5.60; N, 21.63.

Found: C, 52.17; H, 5.44; N, 21.59.

On the other hand, the aqueous filtrate obtained on the isolation of **9** (X = Cl) was concentrated *in vacuo* to leave a solid, which was dissolved in hot EtOH (10 ml). The resulting ethanolic solution was kept in a refrigerator, and the crystals that deposited were filtered off, washed with a little EtOH, and dried to give N^6-benzyloxy-N^6,3-dimethyladenine hydrochloride (**12**: X = Cl) (537 mg, 35%), mp 219—220.5 °C (dec.). Further recyrstallization from EtOH produced an analytical sample as colorless plates, mp 232.5—233.5 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 225 nm (ε 12500), 296.5 (17900); $\lambda_{max}^{H_2O}$ (pH 1) 225 (sh) (9950), 294 (18400); $\lambda_{max}^{H_2O}$ (pH 7) 223 (sh) (12000), 296 (17300); $\lambda_{max}^{H_2O}$ (pH 13) 296.5 (16600); NMR (Me_2SO-d_6) δ: 3.61 (3H, s, N^6–Me), 3.96 (3H, s, $N_{(3)}$–Me), 5.29 (2H, s, $OC\underline{H}_2Ph$), 7.0—7.6 (5H, m, Ph), 8.71 and 8.78 (1H each, s, purine protons), 14.11 (1H, br, N^+H). *Anal.* Calcd for $C_{14}H_{16}ClN_5O$: C, 54.99; H, 5.27; N, 22.90. Found: C, 55.04; H, 5.52; N, 22.85.

Catalytic Reduction of N^6-Methoxy-1,3-dimethyladeninium Iodide (7: X = I)——A solution of **7** (X = I)[1] (817 mg, 2.5 mmol) in MeOH (100 ml) was hydrogenated over Raney Ni W-2 catalyst (*ca.* 3.3 g) at 3 atm and 18—20 °C for 20 h. The catalyst was removed by filtration and washed with MeOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a solid. Recrystallization of the solid from EtOH gave 1,2-dihydro-1,3-dimethyladenine hydriodide (**15**·HI) (128 mg, 17%), mp 220—221.5 °C (dec.). Repeated recrystallization from EtOH yielded an analytical sample as almost colorless prisms, mp 224.5—225.5 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 323 nm (ε 7500); $\lambda_{max}^{H_2O}$ (pH 1) 317 (6500); $\lambda_{max}^{H_2O}$ (pH 7) 319 (6400); $\lambda_{max}^{H_2O}$ (pH 13) 303 (6000); NMR (Me_2SO-d_6) δ: 2.96 and 3.14 (3H each, s, two NMe's), 4.62 (2H, s, CH_2), 7.72 (1H, s, $C_{(8)}$–H), 8.48 (br, NH's). *Anal.* Calcd for $C_7H_{12}IN_5$: C, 28.68; H, 4.13; N, 23.89. Found: C, 28.71; H, 4.13; N, 24.14.

On the other hand, the mother liquor of the first recrystallization was concentrated *in vacuo*, and the resulting residue was dissolved in H_2O (50 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (8 ml), and the column was eluted with H_2O. Concentration of the eluate (300 ml) under reduced pressure left a solid, which was chromatographed on silica gel (25 g). Fractions eluted with AcOEt–EtOH (8 : 1, v/v) afforded 1,2-dihydro-N^6-methoxy-1,3-dimethyladenine (**14**) (130 mg, 26%), mp 187.5—188.5 °C (dec.). For analysis, it was recrystallized from AcOEt to form colorless prisms, mp 190—191.5 °C (dec.); MS *m/e*: 195 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 289 nm (ε 10900); $\lambda_{max}^{H_2O}$ (pH 1) 241 (10000), 327 (6800); $\lambda_{max}^{H_2O}$ (pH 7) 286 (10100); $\lambda_{max}^{H_2O}$ (pH 13) 260 (sh) (7400), 291 (11000); NMR (Me_2SO-d_6) δ: 2.68 and 2.74 (3H each, s, two NMe's), 3.70 (3H, s, OMe), 3.90 (2H, s, CH_2), 7.38 (1H, s, $C_{(8)}$–H), 11.70 (1H, br, NH). *Anal.* Calcd for $C_8H_{13}N_5O$: C, 49.22; H, 6.71; N, 35.87. Found: C, 49.24; H, 6.89; N, 35.63.

$NaBH_4$ Reduction of 7 (X = I)——A suspension of **7** (X = I)[1] (963 mg, 3 mmol) in MeOH (40 ml) was stirred at room temperature, and $NaBH_4$ (170 mg, 4.5 mmol) was added portionwise. After having been stirred for 30 min, the reaction mixture was concentrated *in vacuo*, and H_2O (20 ml) was added to the residue. The resulting aqueous mixture was adjusted to pH 8.6 by addition of 10% aqueous HCl and kept in a refrigerator, and an insoluble solid was filtered off, washed with H_2O, and dried to give **14** (346 mg) as colorless prisms, mp 190—192 °C (dec.). The aqueous filtrate and washings were combined and extracted with three 20-ml portions of $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave colorless prisms (190 mg) as a second crop. The total yield was 536 mg (92%). The sample of **14** thus obtained was identical [by comparison of infrared (IR) spectrum and thin-layer chromatographic (TLC) behavior] with that prepared by the above catalytic reduction of **7** (X = I).

N^2-Methoxy-N^1-methyl-5(4)-(*N*-methylformamido)imidazole-4(5)-carboxamidine (13)——A solution of **7** (X = I)[1] (642 mg, 2 mmol) in H_2O (30 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (10 ml), and the column was eluted with H_2O. The eluate (50 ml) was evaporated to dryness *in vacuo* to leave **13** (390 mg, 92%) as a solid, mp 111—117 °C. Recrystallization from AcOEt produced an analytical sample as colorless prisms, mp 118—119 °C; MS *m/e*: 211 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 220 nm (ε 13100); $\lambda_{max}^{H_2O}$ (pH 1) unstable (changed through an isosbestic point at 254 nm); $\lambda_{max}^{H_2O}$ (pH 7) 219 (13000); NMR (Me_2SO-d_6) δ: 2.63 and 2.49 (d each, J = 5 Hz, NH$\underline{Me}$), 3.06 (0.3H, s), and 3.10 (2.7H, s) ($\underline{Me}$NCHO), 3.55 (0.3H, s) and 3.67 (2.7H, s) (OMe), 5.9 (0.1H, br, q) and 6.17 (0.9H, q, J = 5 Hz) (N$\underline{H}$Me), 7.63 (0.1H, s) and 7.68 (0.9H, s) ($C_{(2)}$–H), 8.10 (0.1H, s) and 8.29 (0.9H, s) (MeNC$\underline{H}$O), 12.61 (1H, dull s, imidazole NH).[17] *Anal.* Calcd for $C_8H_{13}N_5O_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.43; H, 6.38; N, 33.33.

Reversion of 13 to 7 (X = ClO_4)——A solution of **13** (30 mg, 0.14 mmol) in 0.1 N aqueous HCl (6 ml) was allowed to stand in an incubator kept at 25 °C for 21 h. The reaction mixture was concentrated *in vacuo* to dryness to leave a slightly yellowish solid. The solid was dissolved in H_2O (0.3 ml), and a solution of $NaClO_4$ (30 mg, 0.25 mmol) in H_2O (0.2 ml) was added. The precipitate that resulted was filtered off, washed with a little H_2O, and dried to afford **7** (X = ClO_4) (22 mg, 53%) as a slightly yellowish solid, mp 288—289 °C (dec.) [lit.[1] mp 289—291 °C (dec.)], which was identical (by comparison of IR spectrum and TLC behavior) with an authentic sample.[1]

Oxidation of 1,2-Dihydro-N^6-methoxy-1,3-dimethyladenine (14) with Iodine——A solution of I_2 (50 mg, 0.2 mmol) in EtOH (5 ml) was added to a solution of **14** (40 mg, 0.2 mmol) in EtOH (4 ml), and the mixture was stirred at room temperature for 30 min. The precipitate that resulted was filtered off, washed with EtOH, and dried to give **7** (X = I) (25 mg, 38%), mp 249—250 °C (dec.) [lit.[1] mp 249—250 °C (dec.)], which was identified (by comparison of IR spectrum and TLC behavior) with an authentic sample.[1]

1,2-Dihydro-1,3-dimethyladenine (15)——i) From **14**: A solution of **14** (781 mg, 4 mmol) in EtOH (160 ml) was

hydrogenated over Raney Ni W-2 catalyst (*ca.* 0.9 g) at 1 atm and 50 °C for 3 h. The catalyst was removed by filtration and washed with EtOH. The filtrate and washings were combined and concentrated *in vacuo* to leave **15** (468 mg, 71%) as slightly reddish prisms, mp 251—253 °C (dec.). Recrystallization from MeOH yielded an analytical sample as colorless prisms, mp 256—257 °C (dec.); MS *m/e*: 165 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 240 nm (sh) (ε 6700), 327 (8300); $\lambda_{max}^{H_2O}$ (pH 1) 225 (9900), 317.5 (6500); $\lambda_{max}^{H_2O}$ (pH 7) 319 (6500); $\lambda_{max}^{H_2O}$ (pH 13) 235 (sh) (8200), 303 (6200); NMR (Me_2SO-d_6) δ: 2.78 and 3.05 (3H each, s, two NMe's), 4.34 (2H, s, CH_2), 7.28 (1H, s, $C_{(8)}$–H). *Anal.* Calcd for $C_7H_{11}N_5$: C, 50.90; H, 6.71; N, 42.39. Found: C, 50.90; H, 6.88; N, 42.61.

ii) From **15**·HI: A portion (150 mg, 0.51 mmol) of **15**·HI derived from **7** (X=I) by catalytic reduction was dissolved in H_2O (30 ml). The resulting aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (6.3 ml), and the column was eluted with H_2O. The eluate (90 ml) was evaporated *in vacuo* to leave **15** (83 mg, 98%), mp 238—239 °C (dec.). Recrystallization from MeOH gave a pure sample as colorless prisms, mp 252—253 °C (dec.), identical with a sample prepared by method (i).

Oxidation of 15——To a stirred suspension of **15** (248 mg, 1.5 mmol) in $CHCl_3$ (600 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (443 mg, 1.95 mmol), and the mixture was stirred at room temperature for 50 h. The insoluble material that resulted was filtered off, washed with $CHCl_3$, and dried to give a dark brown solid (475 mg) presumed to be **18** (X=2,3-dichloro-5,6-dicyano-4-hydroxyphenolate). The solid was then suspended in MeCN (50 ml), and a solution of 47% aqueous HBr (520 mg, 3 mmol) in MeCN (2 ml) was added under ice-cooling. The color of the mixture turned yellowish-orange, and the precipitate that resulted was collected by filtration, washed with MeCN, and dried to afford an almost colorless solid (301 mg) presumed to be N^1-methyl-5(4)-(*N*-methylformamido)imidazole-4(5)-carboxamidine hydrobromide (or dihydrobromide) (**17**·HBr or **17**·2HBr), mp 160—165 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 263 nm; $\lambda_{max}^{H_2O}$ (pH 1) 256; $\lambda_{max}^{H_2O}$ (pH 7) unstable (changed through three isosbestic points at 217, 234, and 261 nm); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 2.9—3.1 (3H, m, MeNH),[17] 3.14 and 3.36 (3H, s each, MeNCHO),[17] 8.00 and 8.11 (1H, s each, CHO),[17] 8.25 and 8.26 (1H, s each, imidazole proton),[17] 6.73 and 8.7—9.6 (NH's).

N^6,3-Dimethyladenine (16)——A portion (30 mg) of the crude **17**·HBr (or **17**·2HBr) derived from **15** as described above was dissolved in H_2O (0.1 ml), and the resulting solution was made alkaline by adding 28% aqueous NH_3 (0.1 ml). The colorless needles that instantly resulted were filtered off, washed with a little H_2O, and dried to give **16** (13 mg, 53% yield from **15**), mp 298—300 °C (dec.) (lit.[1] mp > 300 °C). This sample was identical (by comparison of IR spectrum and TLC behavior) with authentic **16**.[1,14]

N^2-Methoxy-1-methyl-5-(*N*-methylformamido)imidazole-4-carboxamidine (20)——A solution of **19**[2a] (193 mg, 1 mmol) in H_2O (5 ml) was heated at 60 °C for 15 h. The reaction mixture was concentrated to dryness *in vacuo* to leave **20** (180 mg, 85%) as a slightly yellowish solid, mp 159—160 °C (lit.[2b] mp 162—163 °C), which was identified (by comparison of IR spectrum and TLC behavior) with an authentic specimen.[2b]

Kinetic Procedure for Ring Opening of 7 (X=ClO_4) and 19——The reaction of **7** (X=ClO_4) to give **13** and that of **19**·$HClO_4$ to give **20** in H_2O at pH 7.72 and ionic strength 0.5 at 25 °C were followed by UV spectrophotometry. The buffer solution employed for kinetic runs was 0.1 M NaH_2PO_4–Na_2HPO_4 (pH 7.72 at 25 °C), which had been brought to ionic strength 0.5 with KCl. The substrate **7** (X=ClO_4)[1] was dissolved, at a concentration of 4.7×10^{-4} M, in the buffer solution kept at 25 ± 0.05 °C in a thermoregulated constant-temperature bath. At intervals, 2-ml samples were withdrawn and diluted with 0.2 M aqueous disodium citrate by a factor of 10 in order to quench the reaction. The optical densities of the diluted solutions at 275 nm were determined, and the concentration of the substrate was then calculated in the usual manner by utilizing the molecular absorptivity at the analytical wavelength, which had been obtained with solutions of analytically pure samples of **7** (X=ClO_4) and **13** in the appropriate mixture of buffer solution and 0.2 M aqueous disodium citrate. On the other hand, the other substrate (**19**·$HClO_4$)[2a,b] was dissolved in the buffer solution at a concentration of 5.0×10^{-4} M. Aliquots (*ca.* 3 ml) of the resulting solution were sealed in small ampules and kept at 25 ± 0.05 °C. At intervals, the contents of the ampules were taken out and diluted with H_2O, and the concentrations of the substrate and **20** were determined spectrophotometrically at 278 nm. The above two reactions were followed through at least two half-lives with seven determinations, and good pseudo-first-order kinetics was obtained in both cases. The results are summarized in the text.

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