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Purines. XV.[1] Conversion of N,9-Dimethyladenine into the 1,9-Dimethyl Isomer: A Reverse Operation of the Dimroth Rearrangement[2]

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Oxidation of N,9-dimethyladenine (IIIa) with *m*-chloroperbenzoic acid in ethanol or 30% aqueous hydrogen peroxide in acetic acid produced the 1-N-oxide (VIII). N-Oxide VIII underwent methylation at the oxygen atom when treated with methyl iodide in N,N-dimethylacetamide, giving 1-methoxy-N,9-dimethyladenine hydriodide (IX·HI) in 89% yield. The Dimroth rearrangement of IX to N-methoxy-1,9-dimethyladenine (XI) was readily effected by treating the free base (IX) with boiling water under mildly alkaline conditions. On the other hand, treatment of IX with water at room temperature furnished the ring-opened intermediate (X), which recyclized in boiling water to XI with the formation of a trace of the reversion product (IX). On treatment with 0.2N hydrochloric acid at room temperature, intermediate X gave both XI (62% yield) and IX (13% yield as the perchlorate). Catalytic hydrogenolysis of XI to 1,9-dimethyladenine (Ia) (71% yield as the perchlorate), effected with hydrogen and Raney nickel catalyst, completed the reaction sequence which made possible a reverse Dimroth rearrangement of IIIa to Ia.

The Dimroth rearrangement in its original scope[4] is an isomerization proceeding by ring fission and subsequent recyclization whereby a heterocyclic nitrogen and its attached substituent exchange places with an α-amino or α-imino group. Since the first observation of Rathke in 1888 on a triazine derivative,[5] the rearrangement has been found to occur in many heterocyclic systems. In the adenine series 1-alkyl derivatives (type I) commonly undergo this type of reaction, accomodating the 1-substituent on the exocyclic nitrogen (N^6)

1) Paper XIV in this series, T. Fujii and T. Nishitani, *Chem. Pharm. Bull.* (Tokyo), **21**, 2349 (1973).
2) Presented in part at the 36th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 16, 1973.
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) For leading review, see D.J. Brown, "Mechanisms of Molecular Migrations," Vol. 1, ed. by B.S. Thyagarajan, Interscience Publishers, New York, 1968, pp. 209—245.
5) B. Rathke, *Ber.*, **21**, 867 (1888).

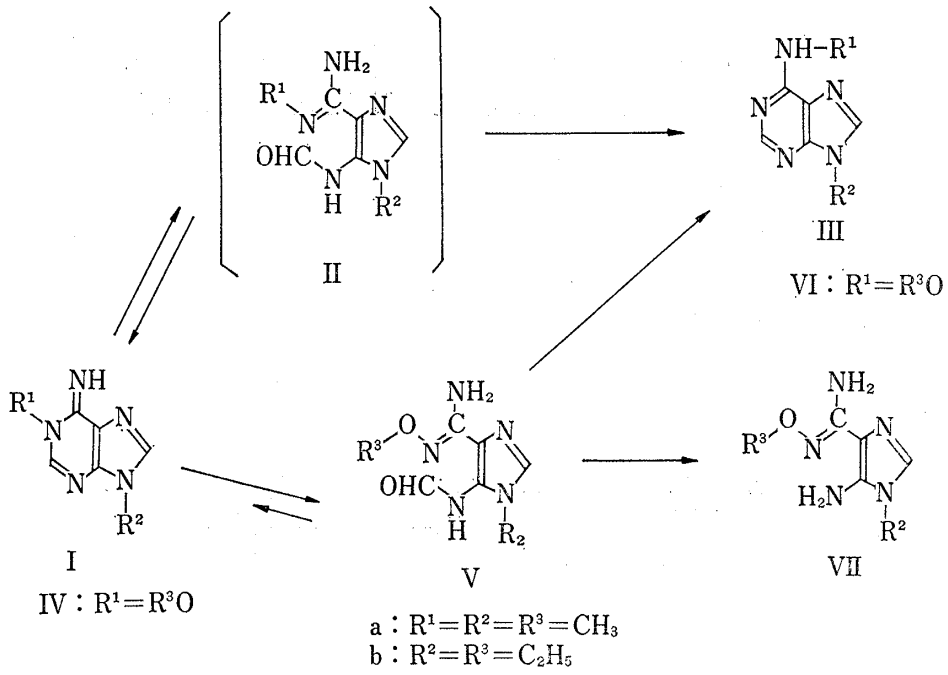

Chart 1

(type III).[6] However, no ring-opened intermediates (type II) have been detected.[6e,q]

We have found[6q,7] that 1-alkoxyadenine derivatives (type IV) also undergo rearrangement to give isomeric N^6-alkoxy derivatives (type VI),[8] but through readily isolable monocyclic intermediates (type V), and that these intermediates competitively suffer hydrolysis leading to deformylated derivatives (type VII). The rate study of the rearrangement of 1,9-dimethyladenine (Ia) and 1-methoxy-9-methyladenine (IVa) has revealed[6q] that at pH 7.60 and above Ia rearranges more rapidly than IVa, although the latter undergoes ring-opening *ca.* 30 times as fast as the former. The acceleration of the ring-opening step (IVa→Va) and the retardation of the recyclization step (Va→VIa) observed for IVa could be attributed directly to the electron-withdrawing nature of the attached methoxyl group. Upon finding these facts, it became of interest to learn whether the Dimroth rearrangement of 1-methoxy-N,9-dimethyladenine (IX) would lead to only (or at least very largely) the N-methoxy-1-methyl isomer XI rather

6) *a*) For earlier work, see Refs. 58—64 in Ref. 4; *b*) A. Coddington, *Biochim. Biophys. Acta*, **59**, 472 (1962); *c*) J.W. Jones and R.K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963); *d*) A.D. Broom, L.B. Townsend, J.W. Jones, and R.K. Robins, *Biochemistry*, **3**, 494 (1964); *e*) J.B. Macon and R. Wolfenden, *ibid.*, **7**, 3453 (1968); *f*) E.R. Garrett and P.J. Mehta, *J. Am. Chem. Soc.*, **94**, 8542 (1972); *g*) N.J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U. S.*, **51**, 73 (1964); *h*) N.J. Leonard, S. Achmatowicz, R.N. Loeppky, K.L. Carraway, W.A.H. Grimm, A. Szweykowska, H.Q. Hamzi, and F. Skoog, *ibid.*, **56**, 709 (1966); *i*) N.J. Leonard, K.L. Carraway, and J.P. Helgeson, *J. Heterocyclic Chem.*, **2**, 291 (1965); *j*) N.J. Leonard and K.L. Carraway, *ibid.*, **3**, 485 (1966); *k*) F. Skoog, H.Q. Hamzi, A.M. Szweykowska, N.J. Leonard, K.L. Carraway, T. Fujii, J.P. Helgeson, and R.N. Loeppky, *Phytochemistry*, **6**, 1169 (1967); *l*) W.A.H. Grimm and N.J. Leonard, *Biochemistry*, **6**, 3625 (1967); *m*) D.M.G. Martin and C.B. Reese, *J. Chem. Soc.* (*C*), **1968**, 1731; *n*) P. Brookes, A. Dipple, and P.D. Lawley, *ibid.*, **1968**, 2026; *o*) G.B. Chheda, R.H. Hall, and P.M. Tanna, *J. Org. Chem.*, **34**, 3498 (1969); *p*) T. Fujii, S. Sakurai, and T. Uematsu, *Chem. Pharm. Bull.* (Tokyo), **20**, 1334 (1972); *q*) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 535 (1972).

7) *a*) T. Fujii, T. Itaya, C.C. Wu, and S. Yamada, *Chem. Ind.* (London), **1966**, 1967; *b*) T. Fujii, T. Itaya, C.C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971); *c*) T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1731 (1971); *d*) T. Fujii, T. Itaya, and S. Moro, *ibid.*, **20**, 1818 (1972); *e*) T. Fujii, C.C. Wu, T. Itaya, S. Moro, and T. Saito, *ibid.*, **21**, 1676 (1973); *f*) T. Fujii, C.C. Wu, and T. Itaya, *ibid.*, **21**, 1835 (1973).

8) *a*) A. Yamazaki, I. Kumashiro, and T. Takenishi, *Chem. Pharm. Bull.* (Tokyo), **17**, 1128 (1969); *b*) T. Ueda, M. Imazawa, K. Miura, R. Iwata, and K. Odajima, *Tetrahedron Letters*, **1971**, 2507.

than a mixture of both isomers. Since the methoxyl group of XI should be removable by catalytic hydrogenolysis,[7f,9] the realization of such a complete isomerization appeared to offer a possible route to an intramolecular $N^6 \rightarrow N_{(1)}$ alkyl rearrangement.

To examine this question we first tried to introduce the methoxyl group into N,9-dimethyladenine (IIIa) at the 1-position. Treatment of IIIa with *m*-chloroperbenzoic acid in ethanol at 35° furnished 1-oxide VIII in 62% yield. The oxidation of IIIa with a combination of 30% aqueous hydrogen peroxide and acetic acid at 55° also produced VIII, but in a lower yield. Although there was a considerable similarity in ultraviolet (UV) spectrum between VIII and 9-substituted adenine 1-oxides,[10,11] that alone was not conclusive for assignment of the 1-N-oxide structure. Final identification as VIII rested on its reversion to IIIa (72% yield) by hydrogenolysis using hydrogen and Raney nickel and on its subsequent reactions themselves shown in Chart 2. Oxide VIII underwent methylation almost exclusively at the oxygen atom when treated with methyl iodide in N,N-dimethylacetamide, resulting in the formation of the 1-methoxy derivative (IX·HI) in 89% yield. The location of the third methyl group was established by demethylation with hot pyridine or ethanol leading to the starting 1-oxide (VIII) and also by catalytic hydrogenolysis of the corresponding perchlorate (IX·$HClO_4$) to afford IIIa. The chemical behavior observed was in general agreement with that[9a,11,12] of the N^6-demethyl analogues.

We next directed our attention to the Dimroth rearrangement of the methoxylated compound thus obtained. Treatment of the free base (IX), which had been freshly prepared from IX·$HClO_4$, with boiling water under mildly alkaline conditions for 70 min provided the

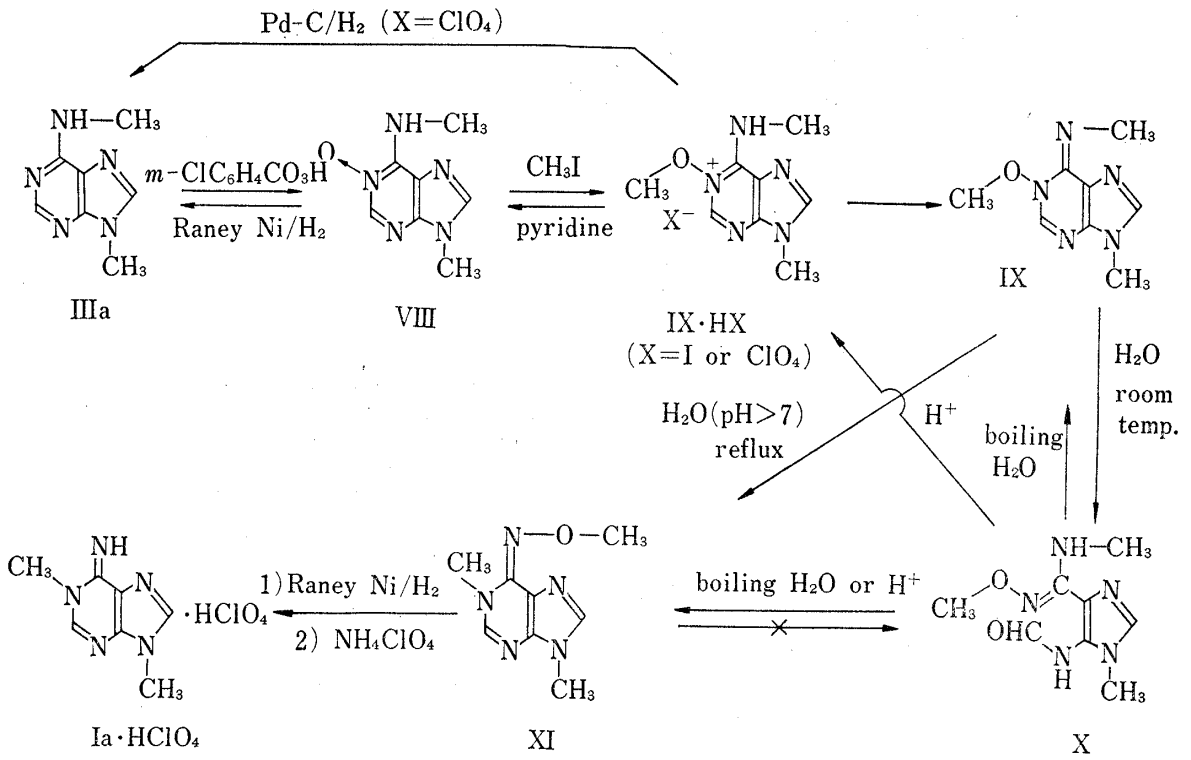

Chart 2

9) *a*) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971); *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **19**, 1611 (1971).
10) *a*) M.A. Stevens, D.I. Magrath, H.W. Smith, and G.B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958); *b*) M.A. Stevens and G.B. Brown, *ibid.*, **80**, 2759 (1958).
11) *a*) T. Fujii, C.C. Wu, T. Itaya, and S. Yamada, *Chem. Ind.* (London), **1966**, 1598; *b*) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).
12) T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.* (Tokyo), **20**, 958 (1972).

isomeric product (XI) in 71% yield. Since the catalytic hydrogenolysis of XI using Raney nickel as a catalyst gave, after converting the product into a salt form, Ia·$HClO_4$ in 71% yield, it was evident that XI had the 1-methyl structure. Accordingly, the methoxyl group of XI should be on the exocyclic nitrogen (N^6) if the process IX→XI is virtually a Dimroth rearrangement. To substantiate this point, we next tried to isolate any intermediate in the isomerization. When IX was treated with water at room temperature for 42 hr, a monocyclic compound (X) was obtained in 72% yield. The elemental composition ($C_8H_{13}O_2N_5$) of X as shown by microanalytical and mass spectral determinations indicated the gain of the elements of water to IX.

That compound X is actually an intermediate in the isomerization (IX→XI) was obvious from its chemical behavior as shown below and its spectral data (see Experimental). On treatment with boiling water for 7.5 hr, X recyclized almost exclusively to XI and reversion to IX appeared to occur only to a negligibly small extent. Under similar conditions the rearranged product (XI) gave neither the intermediate (X) nor the starting isomer (IX). These findings suggest that in the system IX⇄X⇄XI equilibrium in neutral or mildly alkaline solution favored the isomer with the more electron-withdrawing group attached to the exocyclic nitrogen. It is interesting to note that a similar importance of the electronic effect has also been observed for 1-alkyl-2-alkylimino-1,2-dihydropyrimidines.[4] Under acid conditions, by contrast, intermediate X recyclized at room temperature to both the N^6-methoxy derivative (XI) (62% yield) and the 1-methoxy derivative (IX·$HClO_4$) (13% yield). The predominant formation of the isomer with the methoxyl group attached to the N^6 atom presents a curious contrast to the case[7b] of the N-demethyl analogue, N′-ethoxy-1-ethyl-5-formamidoimidazole-4-carboxamidine (Vb), where it reverts almost exclusively to 1-ethoxy-9-ethyladenine (IVb) in 0.2N perchloric acid at room temperature.

In conclusion, it should be emphasized that the conversion of IIIa into Ia described above has demonstrated the usefulness of the methoxyl group as an easily removable directing group in the structural transformation reverse to that which occurs in the Dimroth rearrangement in the adenine series.

Experimental[13]

N,9-Dimethyladenine 1-Oxide (VIII)——i) Oxidation of IIIa with *m*-Chloroperbenzoic Acid: A solution of IIIa[6q] (4.90 g, 30 mmoles) and *m*-chloroperbenzoic acid (85% purity: 9.35 g, 46 mmoles) in ethanol was kept at 35° for 6 hr. The solution was evaporated *in vacuo* to dryness and the resulting residue was extracted with seven 100-ml portions of H_2O. The aqueous extracts were combined and evaporated *in vacuo* to dryness. The residual solid was thoroughly washed with ether, dried over conc. H_2SO_4 *in vacuo* overnight, and exposed to air until a constant weight was reached, giving VIII·$2H_2O$ (4.01 g, 62%), mp 238—241° (decomp.). Recrystallization from H_2O and drying over P_2O_5 at 2 mm Hg and 50° for 24 hr yielded colorless pillars. On exposure to air, they were turned into a dihydrate, mp 243—244° (decomp.), with gain of 1.95 molar equivalents of H_2O; UV $\lambda_{max}^{95\%\,aq.EtOH}$ 239 nm (ε 40700), 273 (7700), 302 (sh) (2600); $\lambda_{max}^{H_2O}$ (pH 1)[14] 264 (12400); $\lambda_{max}^{H_2O}$ (pH 7)[15] 236 (39200), 272 (8500), 295 (sh) (2600); $\lambda_{max}^{H_2O}$ (pH 13)[16] 236 (39400), 272 (8500), 295 (sh) (2600); NMR (DMSO-d_6) τ: 6.57 (4H, s, H_2O), 6.52 (3H, s, N^6–CH_3), 6.24 (3H, s, $N_{(9)}$–CH_3), 1.49—1.88 (1H, b, NH), 1.75 and 1.40 (1H each, s, purine protons). *Anal.* Calcd. for $C_7H_9ON_5·2H_2O$: C, 39.06; H, 6.09; N, 32.54. Found: C, 39.24; H, 6.11; N, 32.70.

ii) Oxidation of IIIa with H_2O_2 and Acetic Acid: A mixture of IIIa[6q] (4.90 g, 30 mmoles), 30% aqueous H_2O_2 (24 ml), and acetic acid (45 ml) was kept at 55° for 20 hr. To the resulting solution was added 10% palladium-on-charcoal (Pd–C) (2.0 g) and the mixture was stirred at room temperature for

13) All melting points are corrected. See Ref. 1 for details of paper chromatography, instrumentation, and measurement and for the abbreviations used. We are indebted to Mr. Y. Itatani and Misses M. Imai, S. Toyoshima, and T. Tsuji at Kanazawa University for microanalyses and NMR and mass spectral data.

14) Measured in 0.1N aqueous HCl.

15) Determined in 0.005M phosphate buffer.

16) Determined in 0.1M aqueous NaOH.

2 days. The catalyst was filtered off and washed with ethanol (50 ml). The filtrate and the washings were combined and evaporated *in vacuo* to dryness. The resulting syrup was triturated with ethanol (5 ml) and the mixture was kept in a refrigerator for 2 days. The precipitates that resulted were collected by filtration and recrystallized from H_2O to give, after drying over P_2O_5 at 2 mm Hg and 50° for 24 hr, a chromatographically pure sample (1.25 g, 23%) of VIII. On exposure to air for 2 days, it formed a dihydrate, mp 243—244° (decomp.), shown to be identical [by paper chromatography (PPC), thin-layer chromatography (TLC), mixed melting-point test, and IR spectrum] with the sample obtained by method-(i).

iii) From IX·HI: A mixture of IX·HI (321 mg, 1 mmole) and pyridine (5 ml) was heated at reflux for 1.5 hr. After cooling, the precipitates that formed were collected by filtration to give VIII·$2H_2O$ (109 mg). Evaporation of the filtrate and trituration of the resulting residue with pyridine (2 ml) gave a second crop (50 mg). Total yield, 159 mg (74%). Recrystallization from H_2O and drying in the same way as described above yielded colorless pillars, mp 243—244° (decomp.), shown to be identical (by PPC, mixed melting-point test, and IR spectrum) with a sample of VIII·$2H_2O$ prepared by method-(i).

In a separate experiment, a solution of a few mg of IX·HI in ethanol (1 ml) was refluxed for 30 min. The formation of 1-N-oxide VIII was indicated by PPC of the reaction mixture.

Hydrogenolysis of 1-Oxide VIII——A solution of VIII·$2H_2O$ (151 mg, 0.7 mmole) in ethanol (8.5 ml) was hydrogenated over Raney Ni W-2 catalyst (0.5 ml) at atmospheric pressure and room temperature for 7.5 hr, absorbing one molar equivalent of H_2. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to dryness to leave a colorless solid (82 mg, 72%) of mp 184—186°. On recrystallization from ethanol, it afforded colorless plates, mp 185—186° (lit.[6q] mp 185—186°), identical (by PPC, mixed melting-point test, and IR spectrum) with an authentic sample[6q] of IIIa.

1-Methoxy-N,9-dimethyladenine Hydriodide (IX·HI)——A stirred mixture of anhydrous VIII (1.79 g, 10 mmoles) and methyl iodide (5.67 g, 40 mmoles) in N,N-dimethylacetamide (10 ml) was kept at 55° for 1.5 hr. The precipitates that resulted were filtered off, washed successively with ethanol (2 ml) and a little ether, and dried over P_2O_5 *in vacuo* for 2 days, giving IX·HI (2.85 g, 89%), mp 150—152° (decomp.). Recrystallization from ethanol and drying over P_2O_5 at 2 mm Hg and 50° for 20 hr provided an analytical sample as colorless prisms, mp 155—157.5° (decomp.); UV $\lambda_{max}^{95\%aq.EtOH}$ 263 nm (ε 12100); $\lambda_{max}^{H_2O}$ (pH 1)[14] 263 (13300); $\lambda_{max}^{H_2O}$ (pH 7)[15] 263 (13500); $\lambda_{max}^{H_2O}$ (pH 13)[16] 255 (sh) (11600), 261 (13000), 268 (sh) (10700), 294 (sh) (2700); NMR (DMSO-d_6) τ: 6.45 (3H, d, J=4 Hz, NHC<u>H</u>$_3$), 6.15 (3H, s, $N_{(9)}$–CH_3), 5.83 (3H, s, OCH_3), 1.46 and 0.81 (1H each, s, purine protons), 0.24 (1H, dull q, N<u>H</u>CH_3). *Anal.* Calcd. for $C_8H_{12}ON_5I$: C, 29.92; H, 3.77; N, 21.81. Found: C, 29.93; H, 3.91; N, 21.95.

In a separate run, the methylation of VIII·$2H_2O$ was carried out at 30° for 23 hr and IX·HI was obtained in 76% yield.

1-Methoxy-N,9-dimethyladenine Perchlorate (IX·$HClO_4$)——To a warm solution of IX·HI (992 mg, 3.1 mmoles) in H_2O (3 ml) was added 43.4% aqueous $NaClO_4$ (1 ml), and the mixture was kept in a refrigerator for 45 min. The precipitates that resulted were filtered off, washed with H_2O (1 ml), and dried to give IX·$HClO_4$ (813 mg, 90%), mp 208—212° (decomp.). Recrystallization from H_2O and drying over P_2O_5 at 50° and 2 mm Hg for 20 hr yielded an analytical sample as colorless prisms, mp 235—238° (decomp.); UV $\lambda_{max}^{95\%aq.EtOH}$ 264 nm (ε 12200); $\lambda_{max}^{H_2O}$ (pH 1)[14] 264 (12800); $\lambda_{max}^{H_2O}$ (pH 7)[15] 264 (12800); $\lambda_{max}^{H_2O}$ (pH 13)[16] 255 (sh) (10800), 262 (12300), 269 (sh) (10200), 294 (sh) (2600); NMR (DMSO-d_6) τ: 6.39 (3H, somewhat dull, NHC<u>H</u>$_3$), 6.10 (3H, s, $N_{(9)}$–CH_3), 5.76 (3H, s, OCH_3), 1.44 and 0.79 (1H each, s, purine protons), 0.15 (1H, b, N<u>H</u>CH_3). *Anal.* Calcd. for $C_8H_{12}O_5N_5Cl$: C, 32.72; H, 4.12; N, 23.85. Found: C, 32.90; H, 4.21; N, 24.10.

Hydrogenolysis of Perchlorate IX·$HClO_4$——A solution of IX·$HClO_4$ (391 mg, 1.33 mmoles) in H_2O (45 ml) was hydrogenated over 10% Pd–C (500 mg) at 4 atmospheric pressure and room temperature for 18 hr. The hydrogenation was continued for further 10 hr with an additional amount (300 mg) of the catalyst. The catalyst was filtered off and washed with H_2O (55 ml). The filtrate and washings were combined and concentrated *in vacuo* to *ca.* 40 ml. The resulting solution was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (3 ml), and the column was eluted with H_2O (50 ml). Evaporation of the eluate under vacuum left a colorless solid (83 mg, 38%), mp 183.5—185°. Recrystallization from ethanol yielded colorless plates, mp 185—186°, identical (by PPC, mixed melting-point test, and IR spectrum) with an authentic sample[6q] of IIIa.

1-Methoxy-N,9-dimethyladenine (IX)——A solution of IX·HI (963 mg, 3 mmoles) in H_2O (90 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (3 ml). Elution with H_2O, evaporation of the eluate (130 ml) *in vacuo*, and drying of the resulting residue over P_2O_5 at 2 mm Hg and room temperature for 24 hr gave the free base (IX) as a colorless solid, mp 128—134° (decomp.), in an almost quantitative yield. However, PPC of this sample showed the presence of a small amount of X as a contaminant, which was presumed to have formed from IX in the course of the treatment. NMR (DMSO-d_6) τ: 6.52 (3H, s, NCH_3), 6.38 (3H, s, $N_{(9)}$–CH_3), 6.08 (3H, s, OCH_3), 2.15 and 1.76 (1H each, s, purine protons), and other small peaks due to impurities.

5-Formamido-N′-methoxy-N,1-dimethylimidazole-4-carboxamidine (X)——A solution of IX·HI (963 mg, 3 mmoles) in H_2O (90 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (3 ml), and the column was further eluted with H_2O (110 ml). The eluate (200 ml) was concentrated *in vacuo* to *ca.* 3 ml and allowed

to stand at room temperature for 6 hr. The mixture was then concentrated *in vacuo* to *ca.* 1.5 ml and kept at room temperature for 22 hr. The resulting mixture was finally concentrated *in vacuo* to *ca.* 1 ml, kept at room temperature for 14 hr, and evaporated *in vacuo* to dryness to leave a colorless solid. Recrystallization of the residue from ethanol produced X (456 mg, 72%) as colorless prisms, mp 190—191° (decomp.). Repeated recrystallization from ethanol and drying over P_2O_5 at 2 mm Hg and room temperature afforded an analytical sample, mp 190—191° (decomp.); UV $\lambda_{max}^{95\%aq.EtOH}$ 219 nm(ε 13400); $\lambda_{max}^{H_2O}$ (pH 1)[14] 216 (13100), 255 (sh) (5700); $\lambda_{max}^{H_2O}$ (pH 7)[15] 219 (12300); $\lambda_{max}^{H_2O}$ (pH 13)[16] 236 (12400); IR $\nu_{max}^{CHCl_3}$ (0.005M solution) cm^{-1}: 3415 (NH, CONH), 1705 (CONHAr); NMR (DMSO-d_6) τ: 7.47 (3H, d, J=5 Hz, NHC<u>H</u>$_3$), 6.63 and 6.58 (s each, $N_{(1)}$-CH_3's due to *cis-trans* isomerism[7a,b,c,e] of X), 6.46 and 6.44 (s each, OCH_3's due to *cis-trans* isomerism), 4.22 (1H, b, N<u>H</u>CH_3), 2.43 (1H, s, $C_{(2)}$-H), 1.93 (d, J=10 Hz, HCON, *trans*-X), 1.85 (s, HCON, *cis*-X), 0.62 (d, J=10 Hz, CONH, *trans*-X), 0.38 (b, CONH, *cis*-X); Mass Spectrum *m/e*: 211 (M^+). *Anal.* Calcd. for $C_8H_{13}O_2N_5$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.72; H, 6.15; N, 32.97.

N-Methoxy-1,9-dimethyladenine (XI)——i) Rearrangement of IX: A solution of IX·$HClO_4$ (410 mg, 1.4 mmoles) in H_2O (40 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (4 ml), and the column was eluted with H_2O (40 ml). The eluate was concentrated *in vacuo* to *ca.* 13 ml and heated at reflux for 30 min. The mixture was adjusted to pH 10 with aqueous NH_3 and refluxed again for 40 min. Evaporation of the resulting mixture under vacuum left a colorless solid, which was dried and washed with a little benzene to give XI (192 mg, 71%), shown to be homogeneous by TLC. Recrystallization from benzene and drying over P_2O_5 at 2 mm Hg and 40° for 24 hr provided an analytical sample as colorless prisms, mp 182—183°; UV $\lambda_{max}^{95\%aq.EtOH}$ 272 nm (ε 12000), 318 (2000); $\lambda_{max}^{H_2O}$ (pH 1)[14] 233 (5700), 284 (9100); $\lambda_{max}^{H_2O}$ (pH 7)[15] 272 (13900), 313 (sh) (2300); $\lambda_{max}^{H_2O}$ (pH 13)[16] 272 (13900), 313 (sh) (2300); NMR (DMSO-d_6) τ: 6.74 (3H, s, CH_3), 6.40 (3H, s, CH_3), 6.32 (3H, s, CH_3), 2.28 and 2.16 (1H each, s, purine protons); Mass Spectrum *m/e*: 193 (M^+). *Anal.* Calcd. for $C_8H_{11}ON_5$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.89; H, 5.72; N, 36.12.

ii) Cyclization of X in Boiling Water: A solution of X (317 mg, 1.5 mmoles) in H_2O (8 ml) was refluxed for 7.5 hr. The reaction mixture was concentrated *in vacuo* to *ca.* 2 ml and chilled in an ice bath. The precipitates that resulted were filtered off and dried over P_2O_5 at 2 mm Hg and room temperature for 60 hr to give XI (212 mg, 73%) as colorless needles, mp 182—183°. Recrystallization from benzene and drying over P_2O_5 at 2 mm Hg and 50° for 24 hr yielded an analytical sample as colorless prisms, mp 182—183°. *Anal.* Calcd. for $C_8H_{11}ON_5$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.66; H, 5.54; N, 36.14. Identity of this sample with the one obtained by method-(i) was established by PPC, mixed melting-point test, and IR spectrum.

The PPC of the reaction mixture indicated that trace amounts of IX was produced concomitantly by the reaction.

Cyclization of X to XI and IX·$HClO_4$ in Acid——Intermediate X (169 mg, 0.8 mmole) was dissolved in 0.2N aqueous HCl (8 ml) and the solution was allowed to stand at room temperature. The PPC of the reaction solution suggested that the starting material had been consumed within 5 hr. After 26 hr, the pH of the solution was adjusted to 7—8 with aqueous NH_3, and the mixture was evaporated *in vacuo* to dryness. The resulting residue was extracted with two 10-ml and four 5-ml portions of boiling benzene. The combined benzene extracts were evaporated *in vacuo* to dryness leaving a colorless solid (96 mg, 62%), mp 174—178°, shown to be homogeneous by PPC and TLC. Recrystallization from benzene furnished colorless prisms, mp 181.5—182.5°, identical (by mixed melting-point test and IR spectrum) with an authentic sample of XI.

On the other hand, the benzene-insoluble fraction, which was separated from XI by the extraction described above, was dissolved in a minute amount of H_2O, and a drop of 70% aqueous $HClO_4$ was added. The precipitates that formed were collected by filtration and dried to yield IX·$HClO_4$ (31 mg, 13%), mp 228—230° (decomp.). Recrystallization from H_2O gave colorless prisms of mp 234—235° (decomp.), undepressed in melting point on admixture with an authentic sample of the perchlorate. The IR spectra of both samples were also identical.

1,9-Dimethyladenine Perchlorate (Ia·$HClO_4$)——A solution of XI (100 mg, 0.52 mmole) in 2-methoxyethanol (10 ml) was hydrogenated over Raney Ni W-2 catalyst (1.5 ml) at atmospheric pressure and 50° for 10 hr. The catalyst was filtered off and washed successively with hot 2-methoxyethanol (20 ml) and ethanol (10 ml). The filtrate and the washings were combined and evaporated *in vacuo* to dryness. To the resulting residue was added 15% aqueous NH_4ClO_4 (1 ml), and the colorless prisms that resulted were collected by filtration, washed with H_2O (2 ml), and dried to give Ia·$HClO_4$ (96 mg, 71%), mp 303—304° (decomp.). This sample was identified with an authentic sample of the perchlorate[6q] by PPC, mixed melting-point test, and IR spectrum.

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