

Purines. XXXVII.¹⁾ Synthesis and Reduction of 3,9-Dialkyladenine Salts Deuterated at the 2-Position: Their Use in the Proton Nuclear Magnetic Resonance Study of Isotopically Unmodified Species²⁾

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The 2-deuterated species XI–XIII of 3,9-dimethyladenine salts (Ia, b) and of 3-benzyl-9-methyladenine perchlorate (Ie) have been synthesized from the alkylaminoimidazoles VII and VIII through deuterioformylation with formic-*d* acid-*d*, hydrogenolytic demethoxylation, and amidine-formamido cyclization. Comparison of the proton nuclear magnetic resonance spectra of XI–XIII with those of the isotopically unmodified species Ia, b, e permitted a distinction between C(2)- and C(8)-proton signals observed for a series of 3,9-dialkyladenine salts (Ia–I): the C(2)-proton resonates at lower field than does the C(8)-proton by 0.04–0.52 ppm. The low electron density at C(2) of I was also exemplified by the NaBH₄ reduction of 3,9-dimethyladenine perchlorate (Ib) to give the 1,2-dihydro derivative XIX. The structure of XIX was confirmed by a similar reduction of the 2-deuterated species XII, leading to XX.

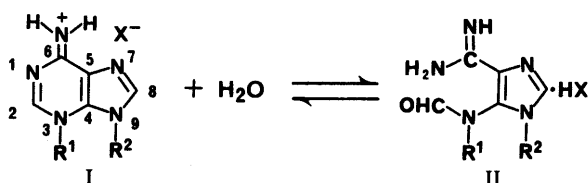
Keywords 2-deutero-3,9-dialkyladenine salt; alkylaminoimidazole; deuterioformylation; hydrogenolytic demethoxylation; amidine formamido cyclization; 3,9-dimethyladenine sodium borohydride reduction; ¹H-NMR

Previous papers^{1–3)} from our laboratory have described the syntheses of a series of 3,9-dialkyladenine salts (type I) together with the easy, reversible ring opening of the adenine moiety at the 2-position leading to equilibria with the formamidoimidazole derivatives (type II), which occurred under basic conditions. Such instability suggests that a center of low electron density in I is at C(2) rather than C(8), and this is interpretable in terms of the exocyclic iminium structure (type I), as inferred from the X-ray crystal structure⁴⁾ of 3-methyladenosine *p*-toluenesulfonate (Im)⁵⁾ as well as the results⁴⁾ of semiempirical calculation of the atomic orbital coefficients for the highest occupied molecular orbital (HOMO) of 6-imino-3,9-dimethylpurine (XVIII). If the electron density at C(2) is actually lower than that at C(8) in a 3,9-dialkyladenine salt (type I), the C(2)-proton should resonate at lower field than does the C(8)-proton in the nuclear magnetic resonance (NMR) spectrum. In order to check the validity of such differentiation, we synthesized a few 2-deuterated species and measured their ¹H-NMR spectra in the present work.

The synthesis of the 2-deuterated species XI–XIII was designed to become an isotopic version of our previous general synthesis^{3b,c)} of 3,9-dialkyladenine salts (type I). Thus, the methylaminoimidazole VII,³⁾ prepared from 1-

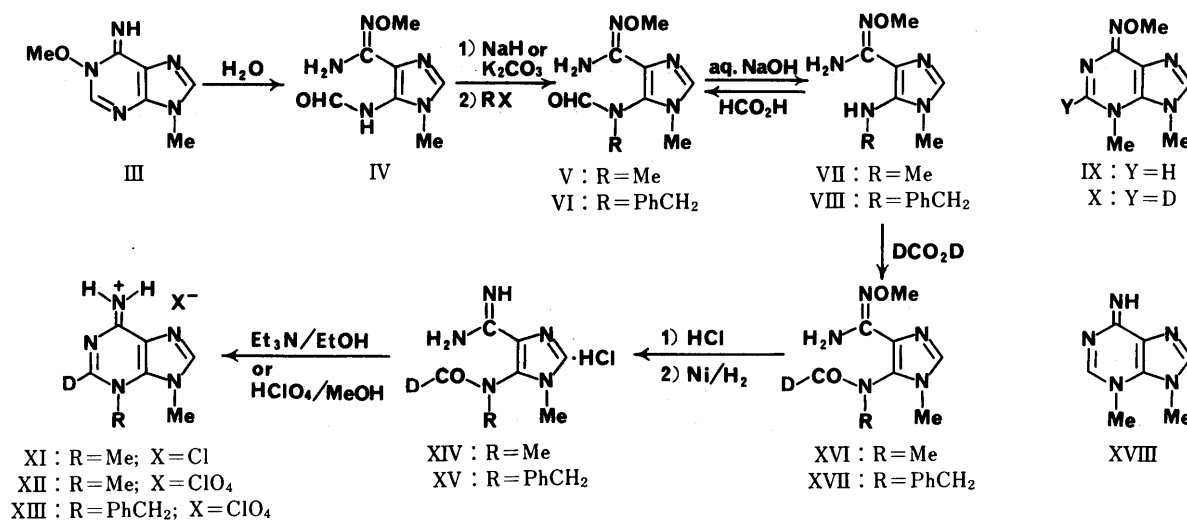
methoxy-9-methyladenine (III)⁶⁾ through the formamidoimidazole IV⁷⁾ and the *N*-methylformamido derivative V^{3b,c)} according to our previous procedure,^{3b,c)} was treated with an excess of formic-*d* acid-*d* (of over 99% isotopic purity) in MeCN at 30 °C for 24 h, giving the deuterioformamido derivative XVI in 76% yield together with a by-product presumed to be a mixture of the cyclized derivative X and the isotopically unlabeled species IX^{3a,c)} in 4% yield. The reaction conditions employed for this deuterioformylation were based on those found to be optimal in the formylation of VII with HCO₂H, which furnished V and IX in 84% and 3% yields, respectively. Hydrogenolytic demethoxylation of XVI was effected with hydrogen and Raney Ni catalyst at atmospheric pressure and 21 °C in H₂O containing 1 molar eq of HCl for 4 h, and cyclization of the resulting amidine hydrochloride XIV in boiling EtOH containing a little Et₃N for 30 min furnished the desired 2-deuterated species, 3,9-dimethyladenine-2-*d* hydrochloride (XI), in 48% yield. Alternatively, cyclization of XIV was effected in boiling MeOH in the presence of 70% aqueous HClO₄ for 7 h to produce the perchlorate salt XII in 71% yield. The correctness of the structures XVI, XI, and XII was supported by the way in which they were generated, microanalytical data, and comparison of their mass, ultraviolet (UV), and ¹H-NMR spectra with those of the known, isotopically unmodified species.³⁾ As judged from the ¹H-NMR and mass spectral data, these deuterated species had a deuterium content at the specified position equal in order of magnitude to that of the formic-*d* acid-*d* used.

A parallel sequence of conversions was then applied to the synthesis of the 3-benzyl analogue XIII, as described below. Hydrolysis of the *N*-benzylformamidoimidazole VI^{3b,c)} prepared from IV by benzylation with PhCH₂Br in HCONMe₂ in the presence of anhydrous K₂CO₃, with boiling 1 N aqueous NaOH for 1 h afforded the benzylaminoimidazole VIII in 81% yield. Treatment of VIII with an excess of formic acid in MeCN at 30 °C for 93 h gave the formamido derivative VI in 98% yield. A similar treatment of VIII with an excess of formic-*d* acid-*d* (*vide supra*) provided the deuterioformamido derivative XVII (80% yield), which was then demethoxylated by hydrogenolysis (Raney Ni/H₂, 1 atm, 21 °C, 8 h) in H₂O in the presence of



- a: R¹ = Me; R² = Me; X = Cl
- b: R¹ = Me; R² = Me; X = ClO₄
- c: R¹ = Et; R² = Me; X = ClO₄
- d: R¹ = Me₂CH; R² = Me; X = ClO₄
- e: R¹ = PhCH₂; R² = Me; X = ClO₄
- f: R¹ = *p*-(MeO)C₆H₄CH₂; R² = Me; X = ClO₄
- g: R¹ = Me; R² = Et; X = ClO₄
- h: R¹ = Et; R² = Et; X = ClO₄
- i: R¹ = PhCH₂; R² = Et; X = ClO₄
- j: R¹ = Me; R² = PhCH₂; X = ClO₄
- k: R¹ = Et; R² = PhCH₂; X = ClO₄
- l: R¹ = PhCH₂; R² = PhCH₂; X = ClO₄
- m: R¹ = Me; R² = β-D-ribofuranosyl; X = *p*-MeC₆H₄SO₃
- n: R¹ = Me; R² = 2-deoxy-β-D-ribofuranosyl; X = *p*-MeC₆H₄SO₃

Chart 1

TABLE I. ¹H-NMR Data for 3,9-Dialkyladenine Salts

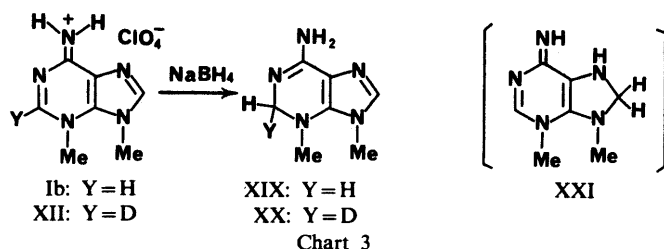
Compound				Chemical shift (δ) ^a in Me ₂ SO- <i>d</i> ₆					
No.	N(3)-R ¹	N(9)-R ²	X	N(3)-R ¹	N(9)-R ²	=NH ₂ ^{+ b}	C(2)-H	C(8)-H	Δδ ^c
Ia	Me	Me	Cl	4.21 (Me)	4.11 (Me)	9.10, 9.16	8.61	8.34	-0.27
Ib ^d	Me	Me	ClO ₄	4.19 (Me)	4.10 (Me)	9.10, 9.17	8.58	8.32	-0.26
Ic	Et	Me	ClO ₄	1.50 (CH ₂ Me) ^e 4.57 (CH ₂ Me) ^f	4.08 (Me)	9.12, 9.19	8.67	8.34	-0.33
Id ^g	Me ₂ CH	Me	ClO ₄	1.64 (CHMe ₂) ^h 5.18 (CHMe ₂) ⁱ	4.09 (Me)	9.12 ^j	8.83	8.34	-0.49
Ie	PhCH ₂	Me	ClO ₄	5.89 (CH ₂ Ph) 7.1—7.5 (CH ₂ Ph) ^k	3.75 (Me)	9.35, 9.41	8.78	8.26	-0.52
If ^g	<i>p</i> -(MeO)C ₆ H ₄ CH ₂	Me	ClO ₄	3.80 or 3.75 (OMe) 5.79 (CH ₂ Ar) 6.97, 7.19 (CH ₂ Ar) ^l	3.75 or 3.80 (Me)	9.31, 9.38	8.73	8.26	-0.47
Ig	Me	Et	ClO ₄	4.17 (Me)	1.50 (CH ₂ Me) ^e 4.52 (CH ₂ Me) ^f	9.09, 9.18	8.59	8.43	-0.16
Ih	Et	Et	ClO ₄	1.51 or 1.50 (CH ₂ Me) ^e 4.51 or 4.44 (CH ₂ Me) ^f	1.50 or 1.51 (CH ₂ Me) ^e 4.44 or 4.51 (CH ₂ Me) ^f	9.13, 9.21	8.68	8.46	-0.22
Ii	PhCH ₂	Et	ClO ₄	5.84 (CH ₂ Ph) 7.1—7.5 (CH ₂ Ph) ^k	1.11 (CH ₂ Me) ^e 4.16 (CH ₂ Me) ^f	9.34, 9.42	8.79	8.40	-0.39
Ij	Me	PhCH ₂	ClO ₄	3.94 (Me)	5.81 (CH ₂ Ph) 7.05—7.5 (CH ₂ Ph) ^k	9.19, 9.31	8.53	8.49	-0.04
Ik	Et	PhCH ₂	ClO ₄	1.22 (CH ₂ Me) ^e 4.31 (CH ₂ Me) ^f	5.75 (CH ₂ Ph) 7.0—7.5 (CH ₂ Ph) ^k	9.24, 9.34	8.64	8.49	-0.15
Il	PhCH ₂	PhCH ₂	ClO ₄	5.59 or 5.39 (CH ₂ Ph) 6.8—7.5 (CH ₂ Ph) ^k	5.39 or 5.59 (CH ₂ Ph) 6.8—7.5 (CH ₂ Ph) ^k	9.44, 9.54	8.72	8.37	-0.35
XI ^m	Me	Me	Cl	4.21 (Me)	4.11 (Me)	9.10, 9.17	—	8.34	—
XII	Me	Me	ClO ₄	4.19 (Me)	4.10 (Me)	9.10, 9.17	—	8.31	—
XIII	PhCH ₂	Me	ClO ₄	5.88 (CH ₂ Ph) 7.1—7.5 (CH ₂ Ph) ^k	3.74 (Me)	9.33, 9.40	—	8.25	—

a) Measured at 0.02–0.07 M concentration and expressed in ppm downfield from internal Me₄Si. b) Appeared as two dull one-proton singlets. c) Δδ = δ_{C(8)-H} - δ_{C(2)-H}. d) Taken from ref. 3c. e) Triplet with *J* = 7 Hz. f) Quartet with *J* = 7 Hz. g) Taken from ref. 1. h) Doublet with *J* = 6.5 Hz. i) Appeared as a broad two-proton peak. j) Septet with *J* = 6.5 Hz. k) Indistinct multiplet. l) Appeared as a pair of AB-type doublets with *J* = 8.8 Hz. m) Determined at 10⁻³ M concentration.

1 molar eq of HCl. The resulting amidine hydrochloride XV was cyclized in boiling MeOH containing 70% aqueous HClO₄ for 8 h, giving the desired perchlorate XIII in 45% yield (from XVII).

Now that the 2-deuterated species XI–XIII had become available, it was possible to compare their ¹H-NMR spectra with those of the 3,9-dialkyladenine salts (type I). Table I lists the chemical shifts for the protons of Ia–I and XI–XIII in Me₂SO-*d*₆. It may be seen that in the cases of Ia–I one of the purine proton signals falls within the range of 8.26–8.49 δ and the other, in the 8.53–8.83 δ region. Since

the C(8)-protons of the 2-deuterated species XI–XIII resonate in the former range, it is reasonable to assign the higher-field signal of each of Ia–I to the C(8)-proton, and the lower-field signal, to the C(2)-proton. This is in agreement with what we have predicted. It appears that the C(2)-protons of the 3-benzyl analogues Ie,f,i,l and the C(8)-protons of the 9-benzyl analogues Ij–l are somewhat less shielded than those of the other 3-alkyl (except for Id) and 9-alkyl analogues, respectively. This may be interpretable in terms of the effect of the electron-withdrawing (relative to a simple alkyl group) benzyl group,⁸ as we have experienced



in similar structures.^{9,10} In the cases of 3-methyladenosine *p*-toluenesulfonate (Im)⁵ and 3-methyl-2'-deoxyadenosine *p*-toluenesulfonate (In),^{5b,11} however, the purine ring protons have been reported by us to resonate at δ 8.59 and 8.74 and at δ 8.63 and 8.71, respectively, in the above C(2)-proton region, making differentiation between the C(2)- and C(8)-proton signals difficult.^{5b} Such a downfield shift of the C(8)-proton signals is also attributable to the electron-withdrawing nature of the sugar group¹² at the 9-position.^{9,10} It is also interesting that all protons of the N(9)-substituents in the 3-benzyl analogues Ie,f,i and those of the N(3)-substituents in the 9-benzyl analogues Ij,k are more shielded than those of the other 3-alkyl and 9-alkyl analogues, respectively. A similar shielding effect is seen in the 3,9-dibenzyl analogue II. These results are suggestive of a preferred conformer for the 3-benzyl or 9-benzyl analogues in which the phenyl ring of the benzyl group overhangs the N(9)- or N(3)-substituent, respectively.

With the expectation of obtaining further evidence in support of the low electron density at C(2) of 3,9-dialkyladenine salts (type I), we next investigated the NaBH₄ reduction of 3,9-dimethyladenine perchlorate (Ib) to see whether the hydride ion attack would occur at C(2) and not at C(8). Treatment of Ib with NaBH₄ in MeOH at room temperature for 30 min furnished the 1,2-dihydro derivative XIX in 77% yield. Although a partially reduced structure of this compound was apparent on the basis of its mass, UV, and ¹H-NMR spectral data, its 1,2-dihydro structure was inconclusive at this stage. In order to prove the structure of XIX and rule out the alternative 7,8-dihydro structure XXI, we then carried out the NaBH₄ reduction of the 2-deuterated species XII in a manner similar to that described above for Ib, and the desired compound XX was obtained in 73% yield. The ¹H-NMR spectra of XX and XIX in Me₂SO-*d*₆ were virtually identical except that the former displayed a one-proton singlet at δ 4.36 [C(2)-H], whereas the latter exhibited a two-proton singlet at δ 4.38 (CH₂). This unequivocally established the 1,2-dihydro structure of XIX and excluded the 7,8-dihydro structure XXI. The assignment of the 6-amino structures to XIX and XX was based on their infrared (IR) spectra in dilute solutions in CHCl₃, which showed two sharp NH₂ absorption bands at 3540 (ν_{antisym}) and 3425 cm⁻¹ (ν_{sym}).

In conclusion, the above results have established a general synthetic route to 3,9-dialkyladenine salts deuterated at the 2-position, representing a good example of the utilization of the "fission and reclosure" technology¹³ developed in our laboratory for modification of the adenine ring. As a result of the synthesis of the 2-deuterated species XI—XIII, unambiguous assignments of the C(2)- and C(8)-proton signals in the NMR spectra of isotopically unmodified 3,9-dialkyladenine salts (type I) have been made

possible: the C(2)-proton resonates at lower field than does the C(8)-proton by 0.04–0.52 ppm. The observed hydride ion attack at C(2) rather than C(8) of 3,9-dimethyladenine perchlorate (Ib) also reflects the low electron density at C(2) of 3,9-dialkyladenine salts (type I).

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 3c for details of instrumentation and measurements. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br=broad, d=doublet, m=multiplet, s=singlet, sh=shoulder.

Materials The known compounds selected for the ¹H-NMR spectroscopic study were taken from stocks which had been prepared according to published procedures: Ia—c^{3c}); Id¹); Ie^{3c}); If¹); Ig—l.^{3c}) Other compounds were synthesized as described below.

5-(Benzylamino)-N'-methoxy-1-methyl-1H-imidazole-4-carboxamide (VIII) A stirred mixture of VI^{3b,c}) (575 mg, 2 mmol) and 1N aqueous NaOH (10 ml) was heated under reflux for 1 h. After cooling, the precipitate that resulted was filtered off, washed with cold H₂O, and dried to give VIII (422 mg, 81%) as colorless scales, mp 96–97°C. Recrystallization from hexane yielded an analytical sample as colorless scales, mp 97–98°C; UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 224 nm (ϵ 14000), 252 (9050); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 250 (sh) (6150), 282 (5500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 224 (12600), 250 (sh) (8150); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 224 (12600), 250 (sh) (8150); ¹H-NMR (Me₂SO-*d*₆) δ : 3.53 [3H, s, N(1)-Me], 3.64 (3H, s, OMe), 4.21 (2H, d, *J*=7.1 Hz, CH₂Ph), 5.57 (br, NH's), 7.14–7.44 [6H, CH₂Ph and C(2)-H]. *Anal.* Calcd for C₁₃H₁₇N₅O: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.06; H, 6.75; N, 26.90.

5-(Formylmethylamino)-N'-methoxy-1-methyl-1H-imidazole-4-carboxamide (V) A solution of VII³) (220 mg, 1.2 mmol) and formic acid (>98%) (0.4 ml, 10.8 mmol) in MeCN (4 ml) was stirred at 30°C for 24 h. The reaction mixture was concentrated *in vacuo*, and the residual oil was co-evaporated with a little EtOH to leave a solid, which was dissolved in H₂O (10 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO₃⁻) (9 ml), and the column was eluted with H₂O (150 ml). The eluate was concentrated *in vacuo*, and the residue was dried and then extracted with boiling AcOEt (20 ml). The insoluble, yellowish solid that resulted was filtered off and dried to give IX (6 mg, 3%), mp 252–256°C (dec.). This sample was identical (by comparison of the IR spectrum) with authentic IX.^{3a,c})

On the other hand, concentration of the above AcOEt extracts under reduced pressure left V (214 mg, 84%) as a colorless solid, mp 154–156°C. This sample was identical (by comparison of the IR spectrum) with authentic V.^{3b,c})

5-(Formyl-*d*-methylamino)-N'-methoxy-1-methyl-1H-imidazole-4-carboxamide (XVI) A solution of VII³) (1.10 g, 6 mmol) and formic-*d* acid-*d* (of over 99% isotopic purity) (2.66 g, 55 mmol) in MeCN (24 ml) was stirred at 30°C for 24 h. The reaction mixture was concentrated *in vacuo*, and the residual oil was co-evaporated three times with EtOH (15 ml) to leave a solid, which was dissolved in H₂O (30 ml). The resulting aqueous solution was passed through a column of Amberlite IRA-402 (HCO₃⁻) (45 ml), and the column was eluted with H₂O. The eluate (680 ml) was concentrated *in vacuo*, and the residue was dried and then extracted with boiling AcOEt (100 ml). The insoluble solid [51 mg (4%); mp 248–249°C (dec.)] that resulted was collected by filtration and recrystallized from EtOH to give a by-product, presumed to be a mixture of X and the isotopically unlabeled species IX,^{3a,c}) as a slightly yellowish solid, mp 280–280.5°C (dec.); MS *m/z*: 194 (*d*₁), 193 (*d*₀); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 275 nm, 315 (sh); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 282; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 278; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) unstable; ¹H-NMR (Me₂SO-*d*₆) δ : 3.65, 3.72, and 3.88 (3H each, s, three Me's), 7.52 (dull) and 7.58 (purine ring protons).

On the other hand, the above AcOEt extracts were concentrated *in vacuo* to leave a colorless solid. Recrystallization of the solid from AcOEt afforded XVI (973 mg, 76%) as colorless prisms, mp 160–161°C; MS *m/z*: 212 (M⁺) [*d*₁ (>99%)]¹⁴); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 250 nm (sh) (ϵ 5500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 253 (7700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 250 (sh) (5700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 250 (sh) (5700); ¹H-NMR (Me₂SO-*d*₆) δ : 3.01 and 3.27 (3H, s each, DCONMe), 3.40 and 3.50 [3H, s each, N(1)-Me], 3.60 and 3.66 (3H, s each, OMe), 5.66 (2H, dull s, NH₂), 7.68 and 7.72 (1H, s each, C(2)-H).¹⁵) *Anal.* Calcd for C₈H₁₂DN₅O₂ (by H₂O/HDO gas volume analysis): C, 45.28; H, 6.17; N, 33.00. Found: C, 45.40; H, 6.48; N, 32.83.

5-(Formylbenzylamino)-N'-methoxy-1-methyl-1H-imidazole-4-carbox-

amidine (VI) A solution of VIII (156 mg, 0.6 mmol) and formic acid (>98%) (0.2 ml, 5.4 mmol) in MeCN (2 ml) was stirred at 30 °C for 93 h. The reaction mixture was concentrated *in vacuo*, and the residue was co-evaporated with a little EtOH to leave a greenish oil. Purification of the oil by means of column chromatography [silica gel (10 g), CHCl₃-EtOH (10:1, v/v)] provided VI (170 mg, 98%) as a dark greenish glass. This sample was identical (by comparison of the IR spectrum and thin-layer chromatographic mobility) with authentic VI.^{3b,c)}

5-(Formyl-*d*-benzylamino)-*N'*-methoxy-1-methyl-1*H*-imidazole-4-carboxamidine (XVII) A solution of VIII (259 mg, 1 mmol) and formic-*d* (of over 99% isotopic purity) (430 mg, 9 mmol) in MeCN (4 ml) was stirred at 30 °C for 118 h. The reaction mixture was worked up in a manner similar to that described above for VI, and the oily crude product was purified by column chromatography [silica gel (70 g), CHCl₃-EtOH (20:1, v/v)] to yield XVII (230 mg, 80%) as a pale yellowish glass, MS *m/z*: 288 (M⁺) [*d*₁ (>99%)]¹⁴⁾; UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 250 nm (sh); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 251; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 250 (sh); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 250 (sh); ¹H-NMR (Me₂SO-*d*₆) δ : 2.79 and 3.05 [3H, s each, N(1)-Me], 3.66 and 3.75 [3H, s each, OMe], 4.5—5.1 (2H, m, DCONCH₂Ph), 5.65 and 5.70 (2H, dull s each, NH₂), 7.23 (5H, m, CH₂Ph), 7.51 and 7.59 [1H, s each, C(2)-H].¹⁵⁾

5-(Formyl-*d*-methylamino)-1-methyl-1*H*-imidazole-4-carboxamidine Hydrochloride (XIV) A solution of XVI (319 mg, 1.5 mmol) in H₂O (36 ml) containing 1 N aqueous HCl (1.5 ml) was hydrogenated over Raney Ni W-2 catalyst¹⁶⁾ (0.5 ml) at atmospheric pressure and 21 °C for 4 h. The catalyst was removed by filtration and washed with H₂O (15 ml). The combined filtrate and washings were concentrated *in vacuo* to leave XIV as a pale greenish solid. This sample was directly used in the next cyclization step without purification.

5-(Formyl-*d*-benzylamino)-1-methyl-1*H*-imidazole-4-carboxamidine Hydrochloride (XV) A solution of XVII (289 mg, 1 mmol) in H₂O (26 ml) containing 1 N aqueous HCl (1 ml) was hydrogenated over Raney Ni W-2 catalyst¹⁶⁾ (0.5 ml) at atmospheric pressure and 21 °C for 8 h. The reaction mixture was worked up as described above for XIV, yielding XV (289 mg) as a faintly yellowish solid. This sample was directly used in the next cyclization step without purification.

3,9-Dimethyladenine-2-*d* Hydrochloride (XI) A solution of the total amount of crude XIV, obtained by the above hydrogenolysis of XVI (319 mg, 1.5 mmol), in EtOH (30 ml) containing Et₃N (20 mg, 0.2 mmol) was heated under reflux for 30 min. After cooling, the precipitate that deposited was collected by filtration, washed with a little EtOH, and dried to give XI [150 mg, 48% yield (from XVI)] as a colorless solid, mp 281—282 °C (dec.). The solid was recrystallized by dissolving it in MeOH and adding AcOEt to the resulting methanolic solution, affording an analytical sample of XI·1/2H₂O (dried over P₂O₅ at 4 mmHg and room temperature for 24 h) as a colorless solid, mp 285.5—287.5 °C (dec.); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 272 nm (ϵ 15500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 271 (15500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 271 (15500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) unstable; ¹H-NMR (Table I). *Anal.* Calcd for C₇H₈DN₅·HCl·1/2H₂O (by H₂O/HDO gas volume analysis): C, 40.10; H, 5.29; N, 33.40. Found: C, 40.03; H, 5.19; N, 33.41.

3,9-Dimethyladenine-2-*d* Perchlorate (XII) A solution of crude XIV (417 mg), obtained by the hydrogenolysis of XVI (424 mg, 2 mmol) according to the procedure described above, in MeOH (60 ml) containing 70% aqueous HClO₄ (580 mg, 4 mmol) was heated under reflux for 7 h. After cooling, the precipitate that resulted was filtered off, washed with a little MeOH, and dried to give XII [374 mg, 71% yield (from XVI)] as a colorless solid, mp >300 °C. Recrystallization from MeOH yielded an analytical sample as a colorless solid, mp >300 °C; UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 272 nm (ϵ 12600); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 271 (15700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 271 (15700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) unstable; ¹H-NMR (Table I). *Anal.* Calcd for C₇H₈DN₅·HClO₄ (by H₂O/HDO gas volume analysis): C, 31.77; H, 3.81; N, 26.46. Found: C, 31.83; H, 3.78; N, 26.50.

3-Benzyl-9-methyladenine-2-*d* Perchlorate (XIII) A solution of crude XV (289 mg), prepared by the above hydrogenolysis of XVII (289 mg, 1 mmol), in MeOH (30 ml) containing 70% aqueous HClO₄ (290 mg, 2 mmol) was heated under reflux for 8 h. The reaction mixture was concentrated *in vacuo* to leave a greenish solid, which was triturated with EtOH (2 ml). Filtration of the resulting ethanolic mixture left XIII [153 mg, 45% yield (from XVII)] as a colorless solid, mp 262.5 °C. Recrystallization from EtOH gave an analytical sample as a colorless solid, mp 265.5 °C; UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 273 nm (ϵ 15700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 271 (15700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 271 (15600); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) unstable; ¹H-NMR (Table I). *Anal.* Calcd for C₁₃H₁₂DN₅·HClO₄ (by H₂O/HDO gas volume analysis): C, 45.82; H, 4.14; N, 20.55. Found: C, 45.69; H, 4.12; N, 20.44.

3,9-Dihydro-3,9-dimethyl-2*H*-purin-6-amine (XIX) A suspension of Ib³⁾ (395 mg, 1.5 mmol) in MeOH (25 ml) was stirred at room temperature,

and NaBH₄ (114 mg, 3 mmol) was added portionwise over 10 min. After having been stirred at room temperature for 30 min, the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in H₂O (5 ml). The resulting aqueous solution was extracted with CHCl₃ (4 × 5 ml) after addition of saturated aqueous K₂CO₃ (5 ml). The CHCl₃ extracts were washed with saturated aqueous K₂CO₃, dried over anhydrous K₂CO₃, and concentrated *in vacuo*. The residual solid was washed with AcOEt (3 ml) and dried to give XIX (190 mg, 77%) as a faintly yellowish solid, mp 161—164 °C (dec.). Recrystallization from AcOEt produced an analytical sample as colorless minute needles, mp 168—170 °C (dec.); MS *m/z*: 165 (M⁺); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 291 nm (ϵ 5040); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 291 (5180); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 289 (5420); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 265 (sh) (4230); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (3.58 × 10⁻³ M solution) cm⁻¹: 3540 and 3425 (NH₂); ¹H-NMR (Me₂SO-*d*₆) δ : 2.66 [3H, s, N(3)-Me], 3.54 [3H, s, N(9)-Me], 4.38 (2H, s, CH₂), 7.38 [1H, s, C(8)-H], 2.0—7.0 (NH₂). *Anal.* Calcd for C₇H₁₁N₅: C, 50.89; H, 6.71; N, 42.39. Found: C, 50.95; H, 6.81; N, 42.41.

3,9-Dihydro-3,9-dimethyl-2*H*-purin-2-*d*-amine (XX) Reduction of XII (165 mg, 1 mmol) with NaBH₄ and work-up of the reaction mixture were effected in a manner similar to that described above for XIX, giving XX (122 mg, 73%) as a colorless solid, mp 160—163 °C (dec.). Recrystallization from AcOEt furnished a pure sample as colorless prisms, mp 169—170.5 °C (dec.); MS *m/z*: 166 (M⁺); UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 291 nm (ϵ 5030); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 291 (5030); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 289 (5300); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 265 (sh) (4180); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (3.37 × 10⁻³ M solution) cm⁻¹: 3540 and 3425 (NH₂); ¹H-NMR (Me₂SO-*d*₆) δ : 2.65 [3H, s, N(3)-Me], 3.54 [3H, s, N(9)-Me], 4.36 [1H, s, C(2)-H], 7.36 [1H, s, C(8)-H], 3.5—6.5 (NH₂).

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