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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 Species[2]

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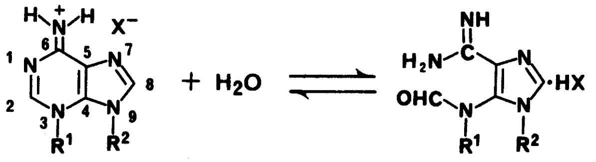
The 2-deuterated species XI—XIII of 3,9-dimethyladenine salts (Ia, b) and of 3-benzyl-9-methyladenine perchlorate (Ie) have been synthesized from the alkylaminoimidazoles VII and VIII through deuterioformylation with formic-*d* acid-*d*, hydrogenolytic demethoxylation, and amidine–formamido cyclization. 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—l): 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 $NaBH_4$ 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-deuterio-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 structure[4] of 3-methyladenosine *p*-toluenesulfonate (Im)[5] as well as the results[4] 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 IV[7] 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 HCO_2H, 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 H_2O containing 1 molar eq of HCl for 4 h, and cyclization of the resulting amidine hydrochloride XIV in boiling EtOH containing a little Et_3N 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 $HClO_4$ 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.



I II

a: $R^1 = Me$; $R^2 = Me$; $X = Cl$
b: $R^1 = Me$; $R^2 = Me$; $X = ClO_4$
c: $R^1 = Et$; $R^2 = Me$; $X = ClO_4$
d: $R^1 = Me_2CH$; $R^2 = Me$; $X = ClO_4$
e: $R^1 = PhCH_2$; $R^2 = Me$; $X = ClO_4$
f: $R^1 = p\text{-}(MeO)C_6H_4CH_2$; $R^2 = Me$; $X = ClO_4$
g: $R^1 = Me$; $R^2 = Et$; $X = ClO_4$
h: $R^1 = Et$; $R^2 = Et$; $X = ClO_4$
i: $R^1 = PhCH_2$; $R^2 = Et$; $X = ClO_4$
j: $R^1 = Me$; $R^2 = PhCH_2$; $X = ClO_4$
k: $R^1 = Et$; $R^2 = PhCH_2$; $X = ClO_4$
l: $R^1 = PhCH_2$; $R^2 = PhCH_2$; $X = ClO_4$
m: $R^1 = Me$; $R^2 = \beta$-D-ribofuranosyl; $X = p\text{-}MeC_6H_4SO_3$
n: $R^1 = Me$; $R^2 = $2-deoxy-$\beta$-D-ribofuranosyl; $X = p\text{-}MeC_6H_4SO_3$

Chart 1

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 $PhCH_2Br$ in $HCONMe_2$ in the presence of anhydrous K_2CO_3, 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/H_2, 1 atm, 21 °C, 8 h) in H_2O in the presence of

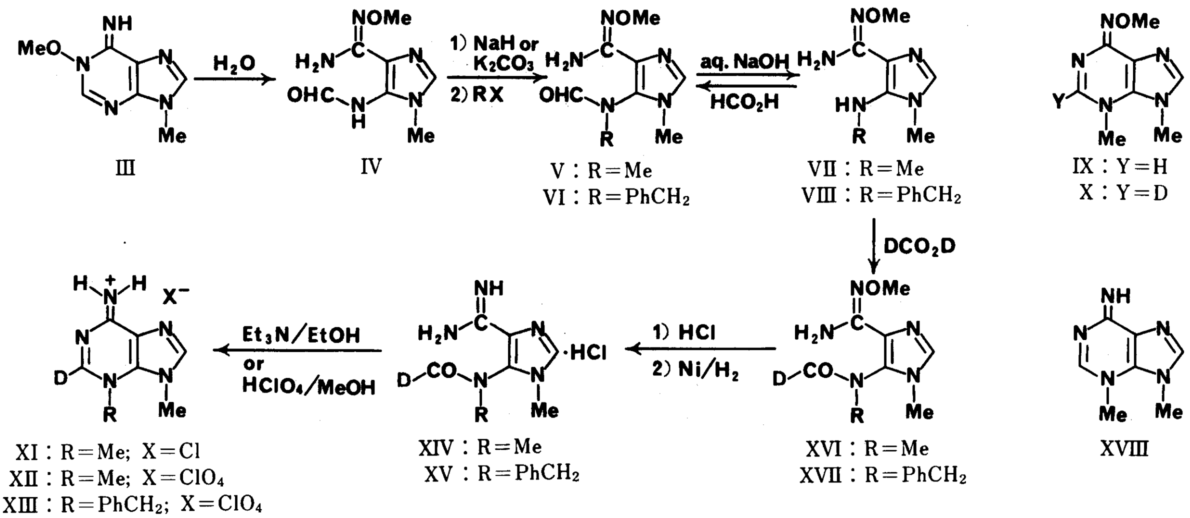


Chart 2

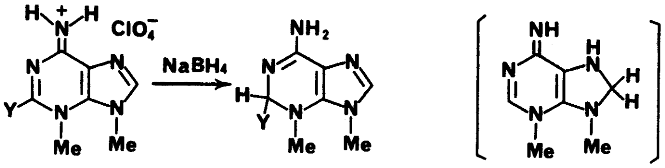
TABLE I. ^{1}H-NMR Data for 3,9-Dialkyladenine Salts

Compound				Chemical shift (δ)[a] in Me_2SO-d_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	$\Delta\delta$[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 ($CH_2\underline{Me}$)[e] 4.57 ($C\underline{H}_2Me$)[f]	4.08 (Me)	9.12, 9.19	8.67	8.34	−0.33
Id[g]	Me_2CH	Me	ClO_4	1.64 ($CH\underline{Me_2}$)[h] 5.18 ($C\underline{H}Me_2$)[j]	4.09 (Me)	9.12[i]	8.83	8.34	−0.49
Ie	$PhCH_2$	Me	ClO_4	5.89 ($C\underline{H}_2Ph$) 7.1—7.5 ($CH_2\underline{Ph}$)[k]	3.75 (Me)	9.35, 9.41	8.78	8.26	−0.52
If[g]	p-$(MeO)C_6H_4CH_2$	Me	ClO_4	3.80 or 3.75 (OMe) 5.79 ($C\underline{H}_2Ar$) 6.97, 7.19 ($CH_2\underline{Ar}$)[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 ($CH_2\underline{Me}$)[e] 4.52 ($C\underline{H}_2Me$)[f]	9.09, 9.18	8.59	8.43	−0.16
Ih	Et	Et	ClO_4	1.51 or 1.50 ($CH_2\underline{Me}$)[e] 4.51 or 4.44 ($C\underline{H}_2Me$)[f]	1.50 or 1.51 ($CH_2\underline{Me}$)[e] 4.44 or 4.51 ($C\underline{H}_2Me$)[f]	9.13, 9.21	8.68	8.46	−0.22
Ii	$PhCH_2$	Et	ClO_4	5.84 ($C\underline{H}_2Ph$) 7.1—7.5 ($CH_2\underline{Ph}$)[k]	1.11 ($CH_2\underline{Me}$)[e] 4.16 ($C\underline{H}_2Me$)[f]	9.34, 9.42	8.79	8.40	−0.39
Ij	Me	$PhCH_2$	ClO_4	3.94 (Me)	5.81 ($C\underline{H}_2Ph$) 7.05—7.5 ($CH_2\underline{Ph}$)[k]	9.19, 9.31	8.53	8.49	−0.04
Ik	Et	$PhCH_2$	ClO_4	1.22 ($CH_2\underline{Me}$)[e] 4.31 ($C\underline{H}_2Me$)[f]	5.75 ($C\underline{H}_2Ph$) 7.0—7.5 ($CH_2\underline{Ph}$)[k]	9.24, 9.34	8.64	8.49	−0.15
Il	$PhCH_2$	$PhCH_2$	ClO_4	5.59 or 5.39 ($C\underline{H}_2Ph$) 6.8—7.5 ($CH_2\underline{Ph}$)[k]	5.39 or 5.59 ($C\underline{H}_2Ph$) 6.8—7.5 ($CH_2\underline{Ph}$)[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 ($C\underline{H}_2Ph$) 7.1—7.5 ($CH_2\underline{Ph}$)[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 Me_4Si. *b*) Appeared as two dull one-proton singlets. *c*) $\Delta\delta = \delta_{C(8)\text{-}H} - \delta_{C(2)\text{-}H}$. *d*) Taken from ref. 3*c*. *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 $HClO_4$ 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 ^{1}H-NMR spectra with those of the 3,9-dialkyladenine salts (type I). Table I lists the chemical shifts for the protons of Ia—l and XI—XIII in Me_2SO-d_6. It may be seen that in the cases of Ia—l 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—l 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



Ib: Y=H
XII: Y=D

XIX: Y=H
XX: Y=D

XXI

Chart 3

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 δ8.63 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 group[12] 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 Il. 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 $NaBH_4$ 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 $NaBH_4$ 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 ^{1}H-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 $NaBH_4$ 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 ^{1}H-NMR spectra of XX and XIX in Me_2SO-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 (CH_2). 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 $CHCl_3$, which showed two sharp NH_2 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" technology[13] 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. 3*c* 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 ^{1}H-NMR spectroscopic study were taken from stocks which had been prepared according to published procedures: Ia—c[3c]; Id[1]; Ie[3c]; If[1]; Ig—l.[3c] Other compounds were synthesized as described below.

5-(Benzylamino)-*N*′-methoxy-1-methyl-1*H*-imidazole-4-carboxamidine (VIII) A stirred mixture of VI[3b,c] (575 mg, 2 mmol) and 1 N aqueous NaOH (10 ml) was heated under reflux for 1 h. After cooling, the precipitate that resulted was filtered off, washed with cold H_2O, 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); $\lambda_{\text{max}}^{H_2O}$ (pH 1) 250 (sh) (6150), 282 (5500); $\lambda_{\text{max}}^{H_2O}$ (pH 7) 224 (12600), 250 (sh) (8150); $\lambda_{\text{max}}^{H_2O}$ (pH 13) 224 (12600), 250 (sh) (8150); ^{1}H-NMR (Me_2SO-d_6) δ: 3.53 [3H, s, N(1)-Me], 3.64 (3H, s, OMe), 4.21 (2H, d, J=7.1 Hz, C$\underline{H}_2$Ph), 5.57 (br, NH's), 7.14—7.44 [6H, CH$_2\underline{\text{Ph}}$ and C(2)-H]. *Anal.* Calcd for $C_{13}H_{17}N_5O$: 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-1*H*-imidazole-4-carboxamidine (V) A solution of VII[3] (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 H_2O (10 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (9 ml), and the column was eluted with H_2O (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-1*H*-imidazole-4-carboxamidine (XVI) A solution of VII[3] (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 H_2O (30 ml). The resulting aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (45 ml), and the column was eluted with H_2O. 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); $\lambda_{\text{max}}^{H_2O}$ (pH 1) 282; $\lambda_{\text{max}}^{H_2O}$ (pH 7) 278; $\lambda_{\text{max}}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-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); $\lambda_{\text{max}}^{H_2O}$ (pH 1) 253 (7700); $\lambda_{\text{max}}^{H_2O}$ (pH 7) 250 (sh) (5700); $\lambda_{\text{max}}^{H_2O}$ (pH 13) 250 (sh) (5700); ^{1}H-NMR (Me_2SO-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, NH_2), 7.68 and 7.72 (1H, s each, C(2)-H].[15] *Anal.* Calcd for $C_8H_{12}DN_5O_2$ (by H_2O/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-1*H*-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), $CHCl_3$–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* acid-*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), $CHCl_3$–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 $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 250 nm (sh); $\lambda_{\max}^{H_2O}$ (pH 1) 251; $\lambda_{\max}^{H_2O}$ (pH 7) 250 (sh); $\lambda_{\max}^{H_2O}$ (pH 13) 250 (sh); ^{1}H-NMR (Me_2SO-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, $DCONC\underline{H}_2Ph$), 5.65 and 5.70 (2H, dull s each, NH_2), 7.23 (5H, m, $CH_2\underline{Ph}$), 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 H_2O (36 ml) containing 1 N aqueous HCl (1.5 ml) was hydrogenated over Raney Ni W-2 catalyst[16] (0.5 ml) at atmospheric pressure and 21 °C for 4 h. The catalyst was removed by filtration and washed with H_2O (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 H_2O (26 ml) containing 1 N aqueous HCl (1 ml) was hydrogenated over Raney Ni W-2 catalyst[16] (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 Et_3N (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 · 1/2H_2O (dried over P_2O_5 at 4 mmHg and room temperature for 24 h) as a colorless solid, mp 285.5—287.5 °C (dec.); UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 272 nm (ε 15500); $\lambda_{\max}^{H_2O}$ (pH 1) 271 (15500); $\lambda_{\max}^{H_2O}$ (pH 7) 271 (15500); $\lambda_{\max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Table I). *Anal.* Calcd for $C_7H_8DN_5 \cdot HCl \cdot 1/2H_2O$ (by H_2O/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 $HClO_4$ (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 $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 272 nm (ε 12600); $\lambda_{\max}^{H_2O}$ (pH 1) 271 (15700); $\lambda_{\max}^{H_2O}$ (pH 7) 271 (15700); $\lambda_{\max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Table I). *Anal.* Calcd for $C_7H_8DN_5 \cdot HClO_4$ (by H_2O/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 $HClO_4$ (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 $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 273 nm (ε 15700); $\lambda_{\max}^{H_2O}$ (pH 1) 271 (15700); $\lambda_{\max}^{H_2O}$ (pH 7) 271 (15600); $\lambda_{\max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Table I). *Anal.* Calcd for $C_{13}H_{12}DN_5 \cdot HClO_4$ (by H_2O/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 Ib[3] (395 mg, 1.5 mmol) in MeOH (25 ml) was stirred at room temperature, and $NaBH_4$ (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 H_2O (5 ml). The resulting aqueous solution was extracted with $CHCl_3$ (4 × 5 ml) after addition of saturated aqueous K_2CO_3 (5 ml). The $CHCl_3$ extracts were washed with saturated aqueous K_2CO_3, dried over anhydrous K_2CO_3, 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 $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 291 nm (ε 5040); $\lambda_{\max}^{H_2O}$ (pH 1) 291 (5180); $\lambda_{\max}^{H_2O}$ (pH 7) 289 (5420); $\lambda_{\max}^{H_2O}$ (pH 13) 265 (sh) (4230); IR $\nu_{\max}^{CHCl_3}$ (3.58×10^{-3} M solution) cm^{-1}: 3540 and 3425 (NH_2); ^{1}H-NMR (Me_2SO-d_6) δ: 2.66 [3H, s, N(3)-Me], 3.54 [3H, s, N(9)-Me], 4.38 (2H, s, CH_2), 7.38 [1H, s, C(8)-H], 2.0—7.0 (NH_2). *Anal.* Calcd for $C_7H_{11}N_5$: 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*-6-amine (XX) Reduction of XII (265 mg, 1 mmol) with $NaBH_4$ 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 $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 291 nm (ε 5030); $\lambda_{\max}^{H_2O}$ (pH 1) 291 (5030); $\lambda_{\max}^{H_2O}$ (pH 7) 289 (5300); $\lambda_{\max}^{H_2O}$ (pH 13) 265 (sh) (4180); IR $\nu_{\max}^{CHCl_3}$ (3.37×10^{-3} M solution) cm^{-1}: 3540 and 3425 (NH_2); ^{1}H-NMR (Me_2SO-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 (NH_2).

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