Isomerization through Cleavage and Recombination of Imidazolide Linkage in the Condensed Tricyclic System Related to Hypermodified Bases of Phenylalanine Transfer Ribonucleic Acids

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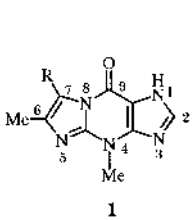
1-Benzyl-4,6-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one bearing an alkyl, a 1-alkenyl, a hydroxymethyl, a methoxymethyl, or a formyl group at the 7-position (3a—e) underwent rearrangement through fission and recyclization of the pyrimidine ring, attaining equilibrium with the corresponding positional isomer 4a—e in MeONa–MeOH at 25 °C, whereas 7-methoxycarbonyl and 7-halogeno compounds 3f—i were irreversibly converted into the rearranged products 4f—i under identical conditions. The position of equilibrium appears to be affected by the electronic factor of the substituent rather than the steric one. The pseudo-first-order rate constants measured for the reactions of 3a,b,d,f—i suggest that the reaction is accelerated by the electron-withdrawing substituent. However, the reactions of this series of compounds do not always obey the Hammett equation.

On the other hand, a linear free energy relationship ($\rho = +3.2$) was observed for the rates of rearrangement of a 6-demethyl series of compounds 9a,b,d,f,g, when σ_p^0 values were employed. The deviations from this relationship for the reactions with the 7-hydroxymethyl compound 9c and the 7-carbamoyl compound 9e are explicable in terms of the accelerative effect through intramolecular hydrogen bonding with the carbonyl oxygen at the 9-position.

Key words linear free energy relationship; tRNA hypermodified base; imidazolide methanolysis; pyrimidone fission–recyclization; hydrogen bonding catalysis; equilibrium constant

N-Acylimidazoles (imidazolides) are susceptible to nucleophilic attack.[1] The same structural unit is found in the ring system of **1**, the modified components of eukaryotic tRNAs^{Phe} and unfractionated archaebacterial tRNAs.[2] Therefore, 4,6-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (wye) (**1a**) and their analogues (*e.g.* **1b**—**f** and the nucleosides **2a**—**f**) might undergo ring fission at the N(8)–C(9) bond in the presence of a nucleophile (Nu^-) as shown in Chart 1. Indeed, we have already reported the ring fission of 1-benzyl-2-chlorowye,[2a] 3-methylwye,[3] and 1-benzyl-7-formylwye (**3e**).[2b,4] The formation of (*E*)-1-benzyl-4,7-dimethyl-6-(3-methyl-1-butenyl)-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (**4b**) in the Wittig reaction of **3e** and the formation of **4b**, its (*Z*)-isomer, and 1-benzyl-6-(methoxymethyl)-4,7-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (**4d**) in the Wittig reaction of [(1-benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-yl)methyl]triphenylphosphonium bromide (type **3**, $R = CH_2P^+Ph_3$) are explicable in terms of fission and recyclization of the pyrimidine ring.[4] Transformation of 3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-7-formylwye into its 6-formyl isomer[5] is the more obvious instance of this type of rearrangement. Similar rearrangements have also been reported for other condensed pyrimidone systems.[6] However, no systematic investigation has been reported on this type of rearrangement. This paper reports the effect of the 7-substituents on the transformations



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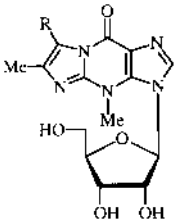
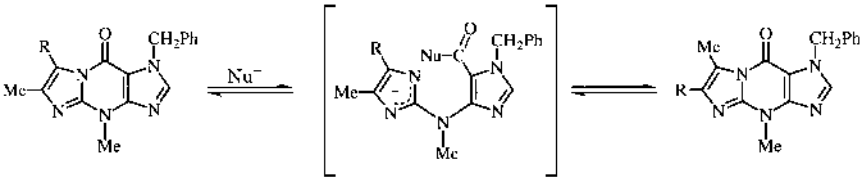


2

a: R = H
b: R = Me
c: R = $CH_2CH_2C(CO_2Me)(H)NHCO_2Me$
d: R = $CH_2CH(OH)CH(NH_2)CO_2H$

e: R = $CH_2CH(OH)CH(NHCO_2Me)CO_2Me$
f: R = $CH_2CH(O_2H)CH(NHCO_2Me)CO_2Me$



3 **4**

a: R = $CH_2CH_2CHMe_2$ **b**: R = (*E*)-CH=CHCHMe$_2$ **c**: R = CH_2OH **d**: R = CH_2OMe
e: R = CHO **f**: R = CO_2Me **g**: R = Cl **h**: R = Br **i**: R = I

Chart 1

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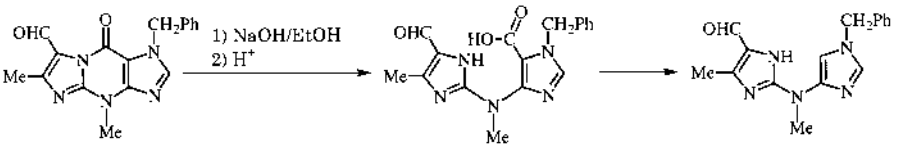


3e 5 6

Chart 2

of **3** and the 6-demethyl compounds **9** into the positional isomers **4** and **10**.

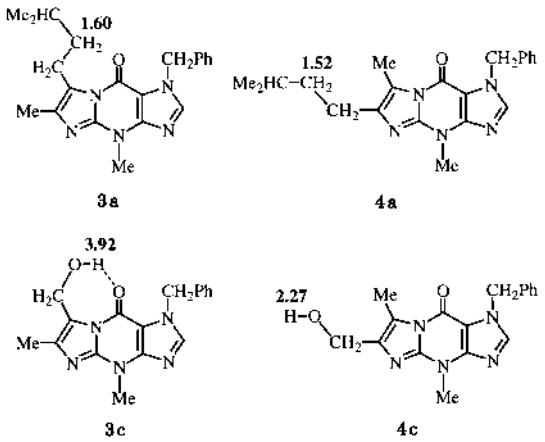
The substrates we selected were 7-substituted 1-benzylwyes **3a**—**i** because they were more easily available than the corresponding 1-unsubstituted ones (type **1**) or 3-substituted ones (type **2**). Among **3**, 1-benzyl-7-(methoxymethyl)wye (**3d**) and 1-benzyl-7-chlorowye (**3g**) had been unknown. Compound **3g** was obtained in 75% yield by treatment of 1-benzylwye (**10a**)[2a] with an equimolar amount of *N*-chlorosuccinimide in AcOH at room temperature for 3 h. Compound **3d** was conveniently prepared in 66% yield by heating the 7-hydroxymethyl compound **3c**[2a] in MeOH in the presence of Pd–C. This procedure was based on the formation of the 7-(ethoxymethyl) compound on hydrogenolysis of 4,6-dimethyl-9-oxo-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4,9-dihydro-3*H*-imidazo[1,2-*a*]purine-7-methanol, which ultimately afforded the 7-methyl compound, over Pd–C in EtOH.[5] The formation of the ethoxymethyl compound was once rationalized in terms of the stabilized carbocation generated from the 7-methanol owing to the strongly electron-donating nature of its heterocycle.[5] However, we found in the present study that **3c** underwent alcoholysis only sluggishly in boiling MeOH in the absence of Pd–C.[7]

With nine substrates **3a**—**i** in hand, we first investigated the reaction of **3e**. This compound was treated with aqueous NaOH–EtOH at 35 °C to give the carboxylic acid **5**.[4] When we attempted to isolate this compound by recrystallization from H_2O, the decarboxylated product **6** was obtained in 41% yield (Chart 2). Such easy decarboxylation observed for the 4-aminoimidazole-5-carboxylic acid **5** is comparable to that reported for 5-amino-1-β-D-ribofuranosyl-4-carboxylic acid (**7a**),[8] its 5′-phosphate,[8a,9] 2′,3′,5′-triacetate,[8c—e] 2′,3′-*O*-isopropylidene derivative,[8f] and other 1-substituted compounds **7b**—**d**[8a] (Chart 3).

7 8

a: R = β-D-ribofuranosyl b: R = cyclohexyl
c: R = carboxymethyl d: R = 2-carboxyethyl

Chart 3



3a 4a 3c 4c

To attain smooth isomerization of **3e** to **4e**, we next performed the reaction of **3e** in 0.5 M MeONa–MeOH at room temperature. A small amount of a product, which was presumed to be **4e** on the basis of its ^{1}H-NMR spectrum, was formed, but it could not be isolated. Compound **3d** also afforded a mixture of **3d** and **4d**, from which **4d** was difficult to separate. However, the rearranged products **4a**—**c** were successfully obtained from the reactions of **3a**—**c**. These reactions were shown to be reversible by treatment of **4a**—**c** thus obtained with MeONa–MeOH. The 7-methoxycarbonyl compound **3f**[10] and 7-halogeno compounds **3g**—**i**,[2a,11] on the other hand, underwent irreversible isomerization at room temperature to afford the rearranged products **4f**—**i** in 83—93% yields. The correctness of the 7-methyl structure for the products **4** was supported by the down-field shift of the heterocyclic C-Me signal owing to the anisotropic effect of the carbonyl group at the 9-position.[12] As shown in the structures below, the difference in chemical shift between the C(7)-CCH_2 protons of **3a**[4] and the C(6)-CCH_2 protons of **4a** is small. The chemical shift of the C(7)-COH proton of **3c** (δ 3.92)[2a] is much larger than that of the C(6)-COH proton of **4c** (δ 2.27), suggesting the existence of an intramolecular hydrogen bond between the OH and carbonyl oxygen of **3c** in a $CDCl_3$ solution. The IR spectrum of **3c** for a 0.001 M solution in $CHCl_3$ shows the carbonyl band at lower frequency by 12 cm^{-1} than those of **4c**, also supporting the intramolecular hydrogen bonding in **3c**.

Because neither by-products nor intermediates were detected in any reaction, the rate and equilibrium constants were conveniently determined by monitoring the UV or NMR spectral change of the reaction mixture. Table 1 summarizes the results obtained for the reactions in 0.1 M MeONa–MeOH at 25 °C. The equilibrium constant (K=1.3) for the isomerization of **3a** to **4a** suggests that a steric factor of the 7-substituent affects the thermodynamic stability to little, if any, extent, because the electronic structures of these 6,7-dialkyl compounds should resemble each other as evidenced by the close similarity of their UV spectra. We consequently suppose that the irreversible transformation of the methyl ester **3f** into **4f** is a reflection of a large difference in electronic structure, which is revealed in their quite different UV spectra.[13] Probably, the equilibrium constants for the reactions of **3b**—**e** are also controlled by a similar factor. In contrast, the conversion of the halogeno compounds **3g**—**i**

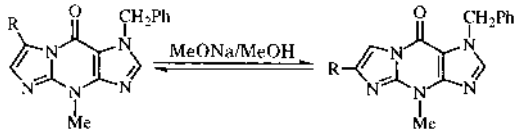
Table 1. Rate and Equilibrium Constants for the Reaction **3** ⇌ **4** in 0.1 M MeONa–MeOH at 25 °C

Substrate	R	Pseudo-first-order rate constant		Equilibrium constant
		3→**4** k_1 (min^{-1})×10^3	**4**→**3** k_{-1} (min^{-1})×10^3	K
3a	$CH_2CH_2CHMe_2$	0.18	0.14	1.3
3b	(*E*)-CH=CHCHMe$_2$	4.1	0.55	7.4
3c	CH_2OH	—	—	0.26
3d	CH_2OMe	2.0	3.7	0.54
3e	CHO	—	—	0.11
3f	CO_2Me	47	0	—
3g	Cl	88	0	—
3h	Br	79	0	—
3i	I	26	0	—

into **4g**—**i** was accompanied by very little change in the UV spectrum. Consequently, the difference in free energy between **3g**—**i** and **4g**—**i** is not likely due to the difference in perturbation of the electronic structure of the ring system, but probably due to electrostatic repulsion between the halogen atom at the 7-position and the carbonyl oxygen at the 9-position in **3g**—**i**.

Apart from the position of equilibrium, the pseudo-first-order rate constants in Table 1 suggest that the isomerization of **3** to **4** is facilitated by an electron-withdrawing substituent at the 7-position. This tendency is parallel to the fact that the rates of hydrolysis of *N*-acetylazoles increase with increasing electron-deficiency of the heterocycles.[1)] Furthermore, a linear free energy relationship has already been reported for the hydrolysis of *N*-benzoylimidazole bearing a substituent on the benzene ring.[1)] However, the reaction of **3** does not always obey the Hammett equation. For example, the methoxycarbonyl compound **3f** undergoes isomerization more slowly than do the halogeno compounds **3g**,**h**. This might be a reflection of the weakened electron-withdrawing resonance effect of the methoxycarbonyl group, which does not fully conjugate with the heterocycle owing to the steric interference by the vicinal methyl group.

In order to learn whether this type of reaction can be treated in terms of the Hammett equation, we next designed further work with a 6-demethyl series of compounds **9a**—**i** (Chart 4). Compound **9a** was produced in good yield by heating the imine **12**, which was formed on treatment of 7-benzyl-3-methylguanine (**11**)[14)] with 2-bromopropanal[15)] in Me_2NCHO at room temperature for 4 h in the presence of K_2CO_3. Alternatively, **9a** was obtained directly from **11** in 88% yield by heating with 2-bromopropanal in Me_2NCHO in the presence of K_2CO_3 at 100 °C for 4 h (Chart 5). The other substrates **9b**—**i** were prepared from 1-benzyl-6-demethylwye (**13**), which was in turn synthesized by treatment of **11** with bromoacetaldehyde in 98% yield according to the procedure for the synthesis of N^2,3-ethenoguanosine[16)] (Chart 6). Treatment of **13** with I_2 in CH_2Cl_2 in the presence of $NaHCO_3$ afforded the 7-iodo compound **9d** in 97% yield. The Vilsmeier reaction of **13** afforded the aldehyde **9g** (93% yield), from which the alcohol **9c** was obtained in 85% yield by $NaBH_4$ reduction. The 7-methoxycarbonyl compound **9f** was produced in 64% yield by treatment of **13** with $COCl_2$ in tetrahydrofuran (THF) in the presence of pyridine, followed by methanolysis. When the reaction of **13** and $COCl_2$ was



a: R = Me **b**: R = CO_2^- **c**: R = CH_2OH **d**: R = I
e: R = $CONH_2$ **f**: R = CO_2Me **g**: R = CHO
h: R = NO_2 **i**: R = $COCO_2Me$

Chart 4

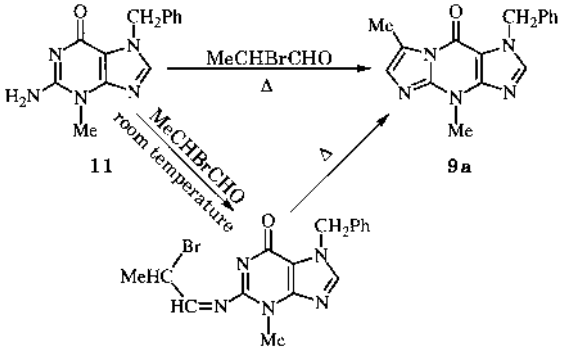


Chart 5

quenched with H_2O and then with aqueous NH_3, the 7-carboxylic acid **9b**·H^+ and the carboxamide **9e** were obtained in 26% and 16% yields, respectively. Compound **13** also reacted with $(COCl)_2$ in THF in the presence of Et_3N, producing the methyl ester **9i** in 67% yield after treatment of the reaction mixture with MeOH. Nitration of **13** with a mixture of concentrated aqueous HNO_3 and concentrated aqueous H_2SO_4 occurred at the benzene ring to provide 4-methyl-1-(4-nitrobenzyl)-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one,[17)] along with 1-(2,4-dinitrobenzyl)-4-methyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one,[18)] whereas treatment of **13** with a mixture of concentrated aqueous HNO_3 and Ac_2O at 0 °C provided the 7-nitro compound **9h** in 11% yield.

When **9b**·H^+ and **9d**—**g** were treated with 0.5 M MeONa–MeOH at room temperature for 1 h, they underwent irreversible isomerization to produce the corresponding 6-substituted compounds **10b**·H^+ and **10d**—**g** in 84—100% yields. The reaction with the 7-nitro compound **9h** under these conditions was not simple, and the 6-nitro isomer **10h** was obtained in only 37% yield. The isomerization of the 7-ketoester **9i** was accompanied by hydrolysis of the ester function owing to contaminated H_2O, providing 1-benzyl-4-methyl-α,9-dioxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-6-ethanoic acid[19)] as the ultimate product. The 6-hydroxymethyl compound **10c** was obtained by $NaBH_4$ reduction of the 6-carbaldehyde **10g** in 95% yield. The 6-substituted structures **10** are unambiguously assignable for these products on the basis of the chemical shift for each C(7)-H, which is more deshielded by 0.12—0.57 ppm than that for the C(6)-H of the corresponding 7-substituted compound **9**.[12)] As mentioned above for **3c**, the existence of an intramolecular hydrogen bond was suggested between the OH proton and the carbonyl oxygen of the 7-methanol **9c** on the basis of comparison of its chemical shift (δ 3.93) measured in $CDCl_3$

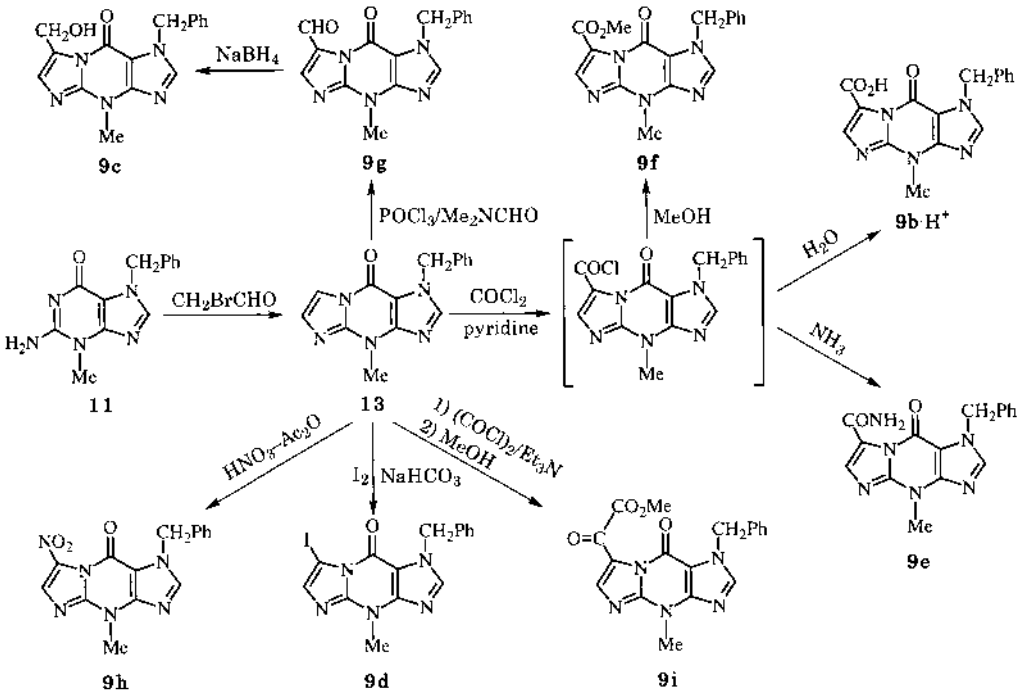
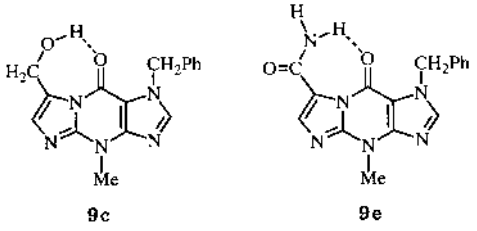


Chart 6



with that (δ 2.19) of the 6-methanol **10b**. Such hydrogen bonding was also suggested for the carboxamide **9e**: the more shielded NH protons of **9e** and **10e** show close chemical shifts (δ 5.62 and 5.47, respectively), whereas more deshielded NH proton of **9e** appears in much lower field (δ 9.78) than does that of **10e** (δ 7.03). The smaller C(9)=O frequencies obtained with dilute $CHCl_3$ solutions of **9c**,**e** than those of **10c**,**e** by 11—12 cm^{-1} are also indicative of intramolecular hydrogen bonding in **9c**,**e**.

Table 2 lists the rate constants (k_1, k_{-1}) and equilibrium constants (K) for isomerization of **9a**—**g**. As in the case of the reactions of **3c**,**e** the reactions of **9c**,**g** bearing a hydroxymethyl or formyl group are reversible. However, the equilibrium is favorable for the products **10c**,**g**, while the equilibrium is unfavorable for the products **4c**,**e**. The k_1 for the reaction of the 7-iodo compound **9d** is 2.3 times larger than that for the 7-iodo-6-methyl compound **3i**, suggesting the rate-retarding electron-donating effect of the 6-methyl group. Further enhancement of the rate was observed for the reaction of the 7-methoxycarbonyl compound **9f**, which isomerized 5.7 times faster than the 6-methyl analogue **3f**. This might be ascribed to the additional steric effect of the 6-methyl group, which weakens the inherent electron-withdrawing ability of the methoxycarbonyl group in **3f** as described above.

There are several reports including the Hammett treatment of the dissociation constant of imidazole.[20] Although Fife *et al*. reported a linear relationship between the logarithms of

Table 2. Rate and Equilibrium Constants for the Reaction **9** ⇌ **10** in 0.1 M MeONa–MeOH at 25 °C

Substrate	R	Pseudo-first-order rate constant		Equilibrium constant
		9→**10** k_1 (min^{-1})×10^3	**10**→**9** k_{-1} (min^{-1})×10^3	K
9a	Me	4.3	0	—
9b	CO_2^-	9.9	0	—
9c	CH_2OH	45	2.0	22
9d	I	61	0	—
9e	$CONH_2$	2200	0	—
9f	CO_2Me	270	0	—
9g	CHO	610	28	22

the rate constants for hydrolysis of 4-substituted *N*-(3,3-dimethylbutanoyl)imidazoles and σ_p,[21] the rate constants (k_1) for the reactions of **9** are not nicely correlated with σ_p. The σ_m gave a still poorer fit. However, a linear free energy relationship (r=0.97) was observed with ρ value of +3.2 for the rates of the reactions of **9a**,**b**,**d**,**f**,**g** as shown by the straight line and closed circles in Fig. 1, when σ_p^0[22] was used instead of σ_p. The plots for the reactions of **9c**,**e**, which are represented in Fig. 1 by open circles, lie far above the line. Smith reported the intramolecular nucleophilic catalysis by a neighboring carboxylate group for the hydrolysis of sodium salt of *N*-(2-carboxybenzoyl)imidazole (**14**).[23] Hydrolysis of *N*-acylimidazole derivatives of *N*-acetylphenylalanine and *N*-acetylvaline (**15a**,**b**) have also been shown to be catalyzed by a neighboring nucleophilic acetamido group.[24] However, the extra enhancement in the rate observed for the reactions of rigid molecules **9c**,**e** is not likely due to intramolecular nucleophilic catalysis for geometrical reasons. The absence of intramolecular nucleophilic catalysis is further supported by the k_1 value for the carboxylate **9b**, which correlates well with the substituent constant, as shown in Fig. 1. Thus, the

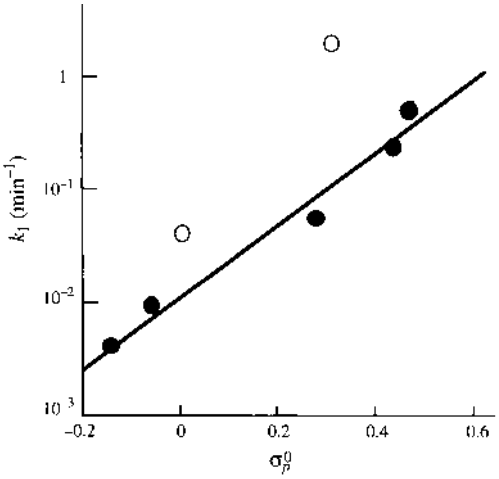
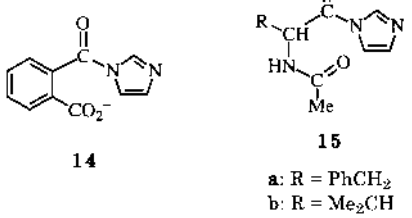


Fig. 1. Hammett Plot of Pseudo-First-Order Rate Constants (k_1) for the Isomerization of **9a**,**b**,**d**,**f**,**g** (Closed Circles) and Non-linear Plot for Those of **9c**,**e** (Open Circles)

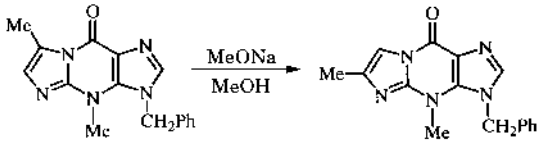


14 **15**

a: R = $PhCH_2$
b: R = Me_2CH

intramolecular hydrogen bonding, the formation of which was given for $CDCl_3$ or $CHCl_3$ solutions of **9c**,**e** as described above, may be responsible for additional enhancement in k_1 for these compounds. There is no evidence for the existence of such hydrogen bonding in MeOH, which was employed as the solvent for the reactions of **9**. However, the rate enhancement for the alkaline hydrolysis in H_2O[25] and for the methanolysis in aqueous MeOH[26] observed with hydroxy esters have been interpreted in terms of intramolecular hydrogen bond between the ester carbonyl and hydroxy groups.[27]

Finally, we measured the rate of isomerization of **16** as a more closely related model for the nucleosides **2** than the 1-benzyl analogue **9a**. Compound **16** was prepared by cyclocondensation of 9-benzyl-3-methylguanine[14] with α-bromoacetaldehyde.[15] We found that **16** underwent irreversible isomerization in 0.1 M MeONa–MeOH at 25 °C to afford **17**[14] at a rate ($k_1 = 2.4\times10^{-2}\,\mathrm{min}^{-1}$) more than five times larger than that for the reaction of **9a**.



16 **17**

Chart 7

Experimental

General Notes All melting points were determined using a Yamato MP-1 or Büchi model 530 capillary melting point apparatus and values are corrected. Spectra reported herein were recorded on a JEOL JMS-SX102A or a Hitachi M-80 mass spectrometer, a Hitachi model 320 UV spectrophotometer, a Shimadzu FTIR-8100 or a JASCO A-202 IR spectrophotometer, a JEOL JNM-GSX-500, a JEOL JNM-EX-270, or a JEOL JNM-FX-100 NMR spectrometer (measured at 25 °C with Me_4Si as an internal standard). Microanalyses were determined by Dr. M. Takani and her associates at Kanazawa University, and by Mr. M. Teranishi at Hokuriku University. Flash chromatography was performed on silica gel according to the reported procedure.[28] The following abbreviations are used: br=broad, d=doublet, dq=doublet-of-quartets, dt=doublet-of-triplets, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet.

1-Benzyl-7-(methoxymethyl)-4,6-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (3d) A solution of **3c**[2a] (199 mg, 0.615 mmol) in MeOH (90 ml) was heated under reflux over 10% Pd–C (243 mg) for 1 h. The catalyst was filtered off and washed with boiling MeOH. The filtrate and washings were combined and concentrated *in vacuo*. The residue was subjected to flash chromatography [AcOEt–MeOH (20 : 1, v/v)] to afford **3d** (138 mg, 66%), mp 132—137.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.36 [3H, s, C(6)-Me], 3.40 (3H, s, OMe), 3.91 (3H, s, NMe), 4.91 (2H, s, OCH_2), 5.63 (2H, s, $PhC\underline{H}_2$), 7.32—7.39 (5H, m, Ph), 7.60 [1H, s, C(2)-H]. Recrystallization of **3d** was difficult.

1-Benzyl-7-chloro-4,6-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (3g) A solution of *N*-chlorosuccinimide (506 mg, 3.79 mmol) in AcOH (23 ml) was added dropwise to a solution of **10a**[2a] (1.112 g, 3.79 mmol) at room temperature over a period of 80 min, and the mixture was stirred at room temperature in the dark for a further 3 h. The resulting mixture was concentrated *in vacuo*, and the residue was partitioned between $CHCl_3$ (50 ml) and 10% aqueous Na_2CO_3 (30 ml). The organic layer was washed successively with 10% aqueous Na_2CO_3 (2×30 ml) and H_2O (3×50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography [AcOEt–EtOH (20 : 1, v/v)] to afford 1-benzyl-7-chloro-6-(chloromethyl)-4-methyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (95 mg, 7%), mp 181—181.5 °C (dec.). Recrystallization of this product from EtOH afforded colorless needles, mp 186.5—187.5 °C (dec.). MS *m/z*: 361, 363, 365 (M^+); high-resolution MS *m/z*: 361.0480 ($C_{16}H_{13}Cl_2N_5O$ requires 361.0497). IR ν_{max}^{Nujol} cm^{-1}: 1713 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s, NMe), 4.63 (2H, s, $ClCH_2$), 5.58 (2H, s, $PhC\underline{H}_2$), 7.33—7.39 (5H, m, Ph), 7.69 [1H, s, C(2)-H]. Further elution of the column afforded **3g** (936 mg, 75%), mp 140—141 °C (dec.). Recrystallization of this sample from EtOH afforded an analytical sample of **3g** as colorless prisms, mp 142—142.5 °C (dec.). MS *m/z*: 327, 329 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 236 (30000), 257 (sh) (5900), 315 (5700). IR ν_{max}^{Nujol} cm^{-1}: 1692 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.28 [3H, s, C(6)-Me], 3.88 (3H, s, NMe), 5.59 (2H, s, CH_2), 7.32—7.38 (5H, m, Ph), 7.67 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{14}ClN_5O$: C, 58.63; H, 4.31; N, 21.37. Found: C, 58.31; H, 4.35; N, 21.24.

Hydrolysis of 3e A solution of **3e**[2a] (321 mg, 1 mmol) in a mixture of 1 N aqueous NaOH (10 ml) and EtOH (90 ml) was kept at room temperature for 5 h, brought to pH 5 by addition of 1 N aqueous HCl (10 ml), and concentrated *in vacuo*. The residual yellow foam was dissolved in MeOH, and insoluble solid was removed by filtration. The solution was concentrated *in vacuo* to leave crude **5**[4] as a slightly yellow solid. Recrystallization of this compound from boiling H_2O was accompanied by decarboxylation to give 2-[(1-benzyl-1*H*-imidazol-4-yl)methylamino]-1*H*-imidazole-5(4)-methyl-4(5)-carbaldehyde (**6**) (120 mg, 41%), mp 145—147 °C. Further recrystallization from H_2O gave an analytical sample of **6** as colorless needles, mp 154.5—155 °C. MS *m/z*: 295 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 237 (19400), 337 (22200); $\lambda_{max}^{H_2O}$ (pH 1) nm (ε): 225 (sh) (10600), 283 (16700); $\lambda_{max}^{H_2O}$ (pH 7) nm (ε): 230 (sh) (12400), 328 (17800); $\lambda_{max}^{H_2O}$ (pH 13) nm (ε): 338 (16700). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s, CMe), 3.45 (3H, s, NMe), 5.10 (2H, s, CH_2), 6.37, 6.38 [a total of 1H, s each, C(5′)-H], 7.16—7.45 [6H, m, Ph, C(2′)-H], 9.51 (1H, br s, CHO), 11.91 (1H, br, NH). *Anal*. Calcd for $C_{16}H_{17}N_5O$: C, 65.06; H, 5.80; N, 23.72. Found: C, 65.05; H, 5.66; N, 23.84.

Isomerization of 3a A suspension of **3a**[4] (401 mg, 1.1 mmol) was heated under reflux in 0.5 M MeONa–MeOH (66 ml) for 6 h, neutralized with 10% aqueous H_3PO_4, and partitioned between $CHCl_3$ (30 ml) and H_2O (30 ml). The aqueous layer was extracted with $CHCl_3$ (30 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residual solid was subjected to flash chromatography [AcOEt then AcOEt–EtOH (10 : 1, v/v)] to afford 1-benzyl-4,7-dimethyl-6-(3-methylbutyl)-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one monohydrate (**4a**·H_2O) (209 mg, 50%) (mp 113.5—115.5 °C) from earlier fractions and **3a** (157 mg, 39%) (mp 135.5—137.5 °C) from later fractions. Compound **4a**·H_2O was recrystallized from MeOH, dried over P_2O_5 at 2 mmHg and room temperature for 18 h, and ex-

posed to air until a constant weight was reached to afford an analytical sample of **4a**·H_2O as colorless needles, mp 118.5—120.5 °C. MS *m/z*: 363 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 238 (29200), 260 (sh) (6500), 322 (5200). IR ν_{max}^{Nujol} cm^{-1}: 1701 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, J=6 Hz, $\underline{Me}_2CH$), 1.52 (2H, dt, J=7, 7.5 Hz, $CH_2C\underline{H}_2CH$), 1.48—1.66 (1H, m, $Me_2C\underline{H}$), 2.55 [2H, t, J=8 Hz, C(6)-CH_2], 2.66 [3H, s, C(7)-Me], 3.88 (3H, s, NMe), 5.59 (2H, s, $PhC\underline{H}_2$), 7.24—7.42 (5H, m, Ph), 7.62 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{21}H_{25}N_5O$·H_2O: C, 66.12; H, 7.13; N, 18.36. Found: C, 66.24; H, 7.08; N, 18.36.

Isomerization of 3b A mixture of **3b**[4] (72 mg, 0.2 mmol) and 0.5 M MeONa–MeOH (40 ml) was stirred at room temperature for 8 h, neutralized with 10% aqueous HCl, and concentrated i*n vacuo*. The solid residue was partitioned between CH_2Cl_2 (20 ml) and H_2O (20 ml). The aqueous layer was extracted with CH_2Cl_2 (2×20 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was subjected to flash chromatography (AcOEt) to afford (*E*)-1-benzyl-4,7-dimethyl-6-(3-methyl-1-butenyl)-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one hemihydrate (**4b**·1/2H_2O) (66 mg, 89%), mp 163—164.5 °C (dec.). This sample was identical (by comparison of the IR and ^{1}H-NMR spectra and TLC mobility) with authentic **4b**·1/2H_2O.[4] Compound **3b** (5 mg, 7%) was recovered from later fractions.

Isomerization of 3c A mixture of **3c**[2a] (901 mg, 2.79 mmol) and 0.5 M MeONa–MeOH (167 ml) was heated under reflux for 11 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 ml) and H_2O (100 ml). The aqueous layer was extracted with CH_2Cl_2 (100 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography [$CHCl_3$–MeOH (20 : 1, v/v)] to afford crude **3c** (569 mg) and 1-benzyl-4,7-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-methanol (**4c**) (146 mg, 16%), mp 245—246 °C (dec.). Crude **3c** was purified by repeated flash chromatography [$CHCl_3$–EtOH (20 : 1, v/v)] and preparative TLC [silica gel, $CHCl_3$–EtOH (20 : 1, v/v)] to afford **3c** (166 mg, 18%). Crude **4c** was recrystallized from EtOH to afford an analytical sample as colorless plates, mp 260—261 °C (dec.). MS *m/z*: 323 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 237 (30400), 257 (sh) (6700), 321 (5800). IR ν_{max}^{Nujol} cm^{-1}: 3212 (OH), 1698 (CO); $\nu_{max}^{CHCl_3}$ (0.001 M) cm^{-1}: 1694 (CO).[29] ^{1}H-NMR ($CDCl_3$) δ: 2.27 (1H, br, OH), 2.73 [3H, s, C(7)-Me], 3.88 (3H, s, NMe), 4.63 (2H, br s, $HOC\underline{H}_2$), 5.58 (2H, s, $PhC\underline{H}_2$), 7.30—7.42 (5H, m, Ph), 7.64 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{17}H_{17}N_5O_2$: C, 63.15; H, 5.30; N, 21.66. Found: C, 62.93; H, 5.26; N, 21.77.

Isomerization of 3d A solution of **3d** (101 mg, 0.3 mmol) in 0.5 M MeONa–MeOH (18 ml) was stirred at room temperature for 23 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 ml) and H_2O (10 ml). The aqueous layer was extracted with CH_2Cl_2 (10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to leave a colorless solid (98 mg), which was inferred to be a *ca*. 2 : 1 mixture of **3d** and 1-benzyl-6-(methoxymethyl)-4,7-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (**4d**). Compound **4d** was difficult to separate. ^{1}H-NMR ($CDCl_3$) (for **4d**) δ: 2.75 [3H, s, C(7)-Me], 3.43 (3H, s, OMe), 3.90 (3H, s, NMe), 4.43 (2H, s, $MeOC\underline{H}_2$), 5.58 (2H, s, $PhC\underline{H}_2$), 7.35 (5H, m, Ph), 7.63 [1H, s, C(2)-H].

Isomerization of 3e A solution of **3e**[2a] (16 mg, 0.05 mmol) in 0.5 M MeONa–MeOH (3 ml) was heated under reflux for 3 h, neutralized with 10% aqueous H_3PO_4, and partitioned between $CHCl_3$ (3 ml) and H_2O (3 ml). The aqueous layer was extracted with CH_2Cl_2 (3 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to leave a colorless solid, which was inferred to be a *ca*. 8 : 1 mixture of **3e** and 1-benzyl-4,7-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-carbaldehyde (**4e**). Compound **4e** was difficult to separate. ^{1}H-NMR ($CDCl_3$) (for **4e**) δ: 3.07 [3H, s, C(7)-Me], 3.92 (3H, s, NMe), 5.57 (2H, s, CH_2), 7.70 [1H, s, C(2)-H], 10.08 (1H, s, CHO).

Isomerization of 3f A suspension of **3f**[10] (176 mg, 0.5 mmol) in 0.5 M MeONa–MeOH (60 ml) was stirred at room temperature for 1 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (20 ml) and H_2O (10 ml). The aqueous layer was extracted with $CHCl_3$ (3×20 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to leave 1-benzyl-4,7-dimethyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-carboxylic acid methyl ester (**4f**) (164 mg, 93%), mp 248—249 °C. Recrystallization of this product from MeOH afforded an analytical sample of **4f** as colorless needles, mp 248.5—249.5 °C. MS *m/z*: 351 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 237 (32900), 260 (sh) (9500), 266 (sh) (8800), 326 (8300). IR ν_{max}^{Nujol} cm^{-1}: 1713 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.11 [3H, s, C(7)-Me], 3.93, 3.95 (3H each, s, two Me's), 5.57 (2H, s, CH_2), 7.18—7.46 (5H, m, Ph), 7.68 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{18}H_{17}N_5O_3$: C, 61.53; H, 4.88; N, 19.93. Found: C, 61.55; H, 4.93; N, 20.03.

Isomerization of 3g A suspension of **3g** (233 mg, 0.71 mmol) in 0.5 M MeONa–MeOH (43 ml) was stirred at room temperature for 4 h, neutralized with 10% aqueous HCl, and concentrated *in vacuo*. The resulting solid was partitioned between CH_2Cl_2 (20 ml) and H_2O (20 ml). The aqueous layer was extracted with CH_2Cl_2 (4×10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The solid residue was subjected to flash chromatography (AcOEt) to provide 1-benzyl-6-chloro-4,7-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (**4g**) (203 mg, 87%), mp 222—222.5 °C. Recrystallization of this product from EtOH afforded an analytical sample of **4g** as colorless needles, mp 222—222.5 °C. MS *m/z*: 327, 329 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 235 (30600), 258 (sh) (6100), 314 (6000). IR ν_{max}^{Nujol} cm^{-1}: 1706 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.69 [3H, s, C(7)-Me], 3.87 (3H, s, NMe), 5.58 (2H, s, CH_2), 7.29—7.42 (5H, m, Ph), 7.65 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{14}ClN_5O$: C, 58.63; H, 4.31; N, 21.37. Found: C, 58.52; H, 4.27; N, 21.46.

Isomerization of 3h A suspension of **3h**[2a] (186 mg, 0.5 mmol) in 0.5 M MeONa–MeOH (30 ml) was stirred at room temperature for 6 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The solid residue was partitioned between CH_2Cl_2 (20 ml) and H_2O (20 ml). The aqueous layer was extracted with CH_2Cl_2 (20 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography (AcOEt) to afford 1-benzyl-6-bromo-4,7-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (**4h**) (161 mg, 87%), mp 221.5—223.5 °C (dec.). Recrystallization of this product from EtOH provided an analytical sample of **4h** as colorless needles, mp 225—226 °C (dec.). MS *m/z*: 371, 373 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 239 (33000), 260 (sh) (6500), 316 (6100). IR ν_{max}^{Nujol} cm^{-1}: 1704 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.70 [3H, s, C(7)-Me], 3.88 (3H, s, NMe), 5.58 (2H, s, CH_2), 7.30—7.41 (5H, m, Ph), 7.67 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{14}BrN_5O$: C, 51.63; H, 3.79; N, 18.81. Found: C, 51.36; H, 3.83; N, 18.72.

Isomerization of 3i A suspension of **3i**[11] (210 mg, 0.5 mmol) in 0.5 M MeONa–MeOH (30 ml) was stirred at room temperature for 6 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 ml) and H_2O (20 ml). The aqueous layer was extracted with CH_2Cl_2 (20 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was subjected to flash chromatography [AcOEt–EtOH (5 : 1, v/v)], affording 1-benzyl-6-iodo-4,7-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (**4i**) (174 mg, 83%), mp 215—216 °C (dec.). Recrystallization of **4i** from EtOH gave an analytical sample as colorless needles, mp 218—218.5 °C (dec.). MS *m/z*: 419 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 243 (34300), 261 (sh) (7800), 320 (6300). IR ν_{max}^{Nujol} cm^{-1}: 1701 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.72 [3H, s, C(7)-Me], 3.87 (3H, s, NMe), 5.58 (2H, s, CH_2), 7.29—7.42 (5H, m, Ph), 7.67 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{14}IN_5O$: C, 45.84; H, 3.37; N, 16.71. Found: C, 45.68; H, 3.45; N, 16.67.

7-Benzyl-N^2-(2-bromopropylidene)-3-methylguanine (12) A solution of 2-bromopropanal[15] (of 76% purity) (1.08 g, 6 mmol) in Me_2NCHO (2 ml) was added dropwise to a stirred mixture of **11**·H_2O[2a] (273 mg, 1 mmol), K_2CO_3 (630 mg, 4.56 mmol), and Me_2NCHO (10 ml). The resulting mixture was stirred at room temperature for 4 h and concentrated *in vacuo* using a mechanical pump. The residue was partitioned between $CHCl_3$ (10 ml) and H_2O (10 ml). The aqueous layer was extracted with $CHCl_3$ (10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to leave a viscous oil. This was triturated with AcOEt, and the resulting solid was collected by filtration to afford crude **12** (211 mg), mp 197—197.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, d, J=6.6 Hz, $\underline{Me}CH$), 2.71 [1/14×3H, d, J=1 Hz, C(7)-Me of **9a**], 3.59 (3H, s, NMe), 3.88 (1/14×3H, s, NMe of **9a**), 4.38 (1H, dq, J=6.6, 2 Hz, MeCH), 5.26 (1H, d, J=2 Hz, $MeCH\underline{H}$), 5.39, 5.50 (1H each, d, J=14.8 Hz, $C\underline{H}_2$), 5.59 (1/14×2H, s, CH_2 of **9a**), 6.77 [1/14H, q, J=1 Hz, C(6)-H of **9a**], 7.30—7.38 (m, Ph), 7.48 [1H, s, C(8)-H], 7.65 [1/14H, s, C(2)-H of **9a**]. Purification of this compound by recrystallization or chromatography on silica gel failed owing to its instability.

1-Benzyl-4-methyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (13) A mixture of bromoacetaldehyde diethyl acetal (10.89 g, 55.3 mmol), 1 N aqueous HCl (24.9 ml), and EtOH (4.2 ml) was stirred at room temperature for 4 d. The resulting solution was added to a suspension of **11**·H_2O[2a] (4.88 g, 17.9 mmol) in a mixture of 0.2 M AcONa–AcOH and EtOH (535 ml each). The mixture was brought to pH 6 by addition of 0.2 M AcONa, stirred at 37—40 °C for 24 h, and concentrated *in vacuo*. The solid residue was washed with a mixture of saturated aqueous $NaHCO_3$ (50 ml) and H_2O (200 ml), collected by filtration, and dried to afford **13** (4.91 g, 98%), mp 157—158 °C. Recrystallization of this product from MeOH afforded an analytical

sample of **13** as colorless needles, mp 163.5—164.5 °C. MS *m/z*: 279 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 231 (sh) (30500), 234 (30900), 252 (sh) (5700), 310 (7400). IR ν_{max}^{Nujol} cm^{-1}: 1694 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.97 (3H, s, Me), 5.62 (2H, s, CH_2), 7.19 [1H, d, J=1.7 Hz, C(6)-H], 7.37 (5H, m, Ph), 7.67 [1H, d, J=1.7 Hz, C(7)-H], 7.73 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.44; H, 4.62; N, 25.06.

1-Benzyl-4,7-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (9a) i) From **12**: A solution of crude **12** (97 mg) in Me_2NCHO (10 ml) was heated at 100 °C for 9 h and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (10 ml) and H_2O (10 ml). The aqueous layer was extracted with $CHCl_3$ (10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The solid residue was recrystallized from EtOH to provide **9a** (31 mg), mp 199—199.5 °C. The mother liquor was concentrated *in vacuo*, and the residue was purified by flash chromatography [$CHCl_3$–EtOH (20 : 1, v/v)] to afford a second crop of **9a** (39 mg), mp 195—197 °C.

ii) From **11**: A mixture of **11**·H_2O[2a] (2.73 g, 10 mmol), 2-bromopropanal[15] (of 76% purity) (10.81 g, 60 mmol), K_2CO_3 (6.39 g, 46 mmol), and Me_2NCHO (104 ml) was stirred at 100 °C for 4 h and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (100 ml) and H_2O (100 ml). The aqueous layer was extracted with $CHCl_3$ (100 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The solid residue was triturated with EtOH (50 ml), and insoluble solid was collected by filtration to afford **9a** (2.45 g), mp 198.5—199.5 °C. The mother liquor was concentrated *in vacuo*, and the residue was purified by flash chromatography [$CHCl_3$–EtOH (20 : 1, v/v)] to provide a second crop of **9a** (0.12 g; the total yield was 88%), mp 187.5—190 °C. Recrystallization of **9a** from EtOH afforded an analytical sample as colorless needles, mp 199—199.5 °C. MS *m/z*: 293 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 233 (29900), 255 (sh) (6100), 316 (5800). IR ν_{max}^{Nujol} cm^{-1}: 1692 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.71 [3H, d, J=1 Hz, C(7)-Me], 3.88 (3H, s, NMe), 5.59 (2H, s, CH_2), 6.78 [1H, q, J=1 Hz, C(6)-H], 7.31—7.41 (5H, m, Ph), 7.64 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.88. Found: C, 65.64; H, 5.21; N, 23.73.

3-Benzyl-4,7-dimethyl-4,9-dihydro-3*H*-imidazo[1,2-*a*]purin-9-one (16) A stirred mixture of 9-benzyl-3-methylguanine[14] (328 mg, 1.28 mmol), 2-bromopropanal[15] (of 74% purity) (1.42 g, 7.67 mmol), K_2CO_3 (874 mg, 6.32 mmol) and Me_2NCHO (20 ml) was heated at 100 °C for 3 h. The resulting mixture was neutralized with 10% aqueous H_3PO_4 and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (20 ml) and H_2O (80 ml). The aqueous layer was extracted with $CHCl_3$ (3×10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography [AcOEt–EtOH (5 : 1, v/v)] to afford **16** (230 mg, 61%) as a colorless solid, mp 211—212 °C (dec.). Recrystallization of crude **16** from AcOEt afforded an analytical sample as colorless prisms, mp 212—213 °C (dec.). MS *m/z*: 293 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 235 (28600), 298 (6800). IR ν_{max}^{Nujol} cm^{-1}: 1715, 1703 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.73 [3H, d, J=1 Hz, C(7)-Me], 3.81 (3H, s, NMe), 5.52 (2H, s, CH_2), 6.70 [1H, q, J=1 Hz, C(6)-H], 7.00—7.09 (2H), 7.35—7.44 (3H) (m each, Ph), 7.48 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.88. Found: C, 65.32; H, 5.20; N, 24.14.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylic Acid (9b·H^+) and 1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxamide (9e) A 2 M solution of $COCl_2$ in toluene (2.5 ml, 5 mmol) was diluted with dry CH_2Cl_2 (6 ml) and added dropwise to a stirred solution of **13** (279 mg, 1 mmol) and pyridine (1.6 ml) in CH_2Cl_2 (10 ml) over a period of 15 min. The mixture was stirred at room temperature for a further 4 h. The resulting suspension was diluted with CH_2Cl_2 (5 ml) and washed with H_2O (3×30 ml). The organic layer was diluted with CH_2Cl_2 (40 ml), dried ($MgSO_4$), and an 0.8% solution of NH_3 in CH_2Cl_2 (40 ml) was added. The solution was washed with H_2O (2×30 ml and 3×50 ml), dried ($MgSO_4$), and concentrated *in vacuo* to afford crude **9e** as an orange solid. The H_2O washings were combined, brought to pH 1 by addition of 10% aqueous HCl, and extracted with CH_2Cl_2 (4×20 ml). The CH_2Cl_2 extracts were combined, washed with H_2O (4×20 ml), dried ($MgSO_4$), and concentrated *in vacuo* to afford crude **9b**·H^+ (84 mg, 26%), mp 202—203 °C (dec.). Recrystallization from EtOH afforded an analytical sample of **9b**·H^+ as colorless needles, mp 206—207 °C (dec.). MS *m/z*: 323 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 251 (sh) (26700), 254 (28400), 293 (sh) (7100), 315 (9900). IR ν_{max}^{Nujol} cm^{-1}: 1711 [C(9)=O]. ^{1}H-NMR ($CDCl_3$) δ: 4.07 (3H, s, Me), 5.62 (2H, s, CH_2), 7.38 (5H, m, Ph), 7.91 [1H, s, C(2)-H], 8.22 [1H, s, C(6)-H], 14.32 (1H, br s, CO_2H). *Anal*. Calcd for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.65; H, 4.14; N, 21.49.

Crude **9e** was subjected to flash chromatography [AcOEt–EtOH (5 : 1, v/v)] to afford **9e** (51 mg, 16%), mp 263—269 °C (dec.). Precipitation of **9e** from $CHCl_3$–hexane (1 : 1, v/v) afforded an analytical sample as colorless minute needles, mp 270—271 °C (dec.). MS *m/z*: 322 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 251 (26700), 285 (7800), 311 (9900). IR ν_{max}^{Nujol} cm^{-1}: 3337, 3107 (NH_2), 1680 (CO); $\nu_{max}^{CHCl_3}$ (0.001 M) cm^{-1}: 1692 (CO). ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s, Me), 5.62 (3H, s, CH_2, NH), 7.37 (5H, s, Ph), 7.79 [1H, s, C(2)-H], 8.15 [1H, s, C(6)-H], 9.78 (1H, br, NH). *Anal*. Calcd for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.92; H, 4.42; N, 26.33.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-methanol (9c) $NaBH_4$ (57 mg, 1.5 mmol) was added to a suspension of **9g** (310 mg, 1.01 mmol) in MeOH (50 ml), and the mixture was stirred at room temperature for 30 min. Me_2CO (0.3 ml) was added to the mixture, and the whole was concentrated *in vacuo*. The residue was neutralized with 10% aqueous H_3PO_4 after addition of H_2O (9 ml) and extracted with $CHCl_3$ (2× 15 ml). The $CHCl_3$ extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give **9c**·H_2O (279 mg, 85%), mp 169—174 °C. Recrystallization from MeOH afforded an analytical sample of **9c**·H_2O as colorless needles, mp 176—177 °C. MS *m/z*: 309 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 238 (33100), 255 (sh) (6000), 314 (6400). IR ν_{max}^{Nujol} cm^{-1}: 3317 (OH), 1692 (CO); $\nu_{max}^{CHCl_3}$ (0.001 M) cm^{-1}: 1684 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.93 (1H, t, J=7.3 Hz, OH), 3.94 (3H, s, Me), 4.83 (2H, d, J=7.3 Hz, HOC$\underline{H}_2$), 5.61 (2H, s, PhC$\underline{H}_2$), 7.05 [1H, s, C(6)-H], 7.36 (5H, m, Ph), 7.73 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{15}N_5O_2\cdot H_2O$: C, 58.71; H, 5.23; N, 21.39. Found: C, 58.94; H, 5.19; N, 21.45.

1-Benzyl-7-iodo-4-methyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (9d) A solution of I_2 (1.33 g, 5.24 mmol) in CH_2Cl_2 (44 ml) was added dropwise to a stirred mixture of a solution of **13** (1.00 g, 3.58 mmol) in CH_2Cl_2 (40 ml) and a solution of $NaHCO_3$ (2.92 g, 34.8 mmol) in H_2O (40 ml) over a period of 10 min. The mixture was stirred at room temperature for 2 h and extracted with CH_2Cl_2 (8×50 ml). The CH_2Cl_2 layers were combined, washed with 5% aqueous $Na_2S_2O_3$ (2×50 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give **9d** (1.40 g, 97%), mp 174—175 °C (dec.). Recrystallization of this product from CH_2Cl_2 afforded an analytical sample of **9d** as colorless prisms, mp 176.5—177 °C (dec.). MS *m/z*: 405 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 239 (sh) (31800), 243 (34600), 256 (sh) (7400), 319 (6100). IR ν_{max}^{Nujol} cm^{-1}: 1692 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.91 (3H, s, Me), 5.61 (2H, s, CH_2), 7.19 [1H, s, C(6)-H], 7.36 (5H, m, Ph), 7.67 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{15}H_{12}IN_5O$: C, 44.46; H, 2.99; N, 17.28. Found: C, 44.37; H, 2.85; N, 17.04.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carboxylic Acid Methyl Ester (9f) A 2 M solution of $COCl_2$ in toluene (1.5 ml, 3 mmol) was added to a stirred solution of **13** (100 mg, 0.358 mmol) and pyridine (0.6 ml) in THF (4 ml) at 0 °C. The mixture was stirred at room temperature for 30 h, and MeOH (4 ml) was added. The whole was kept at room temperature for 2 d and concentrated *in vacuo*. The resulting brown solid was dissolved in CH_2Cl_2 (15 ml). The solution was washed with H_2O (5×15 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The yellowish residue was subjected to flash chromatography [$CHCl_3$–MeOH (50 : 1, v/v)] to afford a first crop of **9f** (48 mg), mp 147—159 °C. The fraction containing **9f** was further purified by flash chromatography [$CHCl_3$–MeOH (50 : 1, v/v)], followed by preparative TLC [silica gel, AcOEt–EtOH (20 : 1, v/v)] to provide a second crop of **9f** (29 mg; the total yield was 64%). Recrystallization from MeOH afforded an analytical sample of **9f** as colorless prisms, mp 166—169 °C. MS *m/z*: 337 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 247 (22500), 287 (sh) (7900), 309 (12400). IR ν_{max}^{Nujol} cm^{-1}: 1732 (CO_2Me), 1703 [C(9)=O]. ^{1}H-NMR ($CDCl_3$) δ: 3.92, 3.98 (3H each, s, two Me's), 5.64 (2H, s, CH_2), 7.37 (5H, s, Ph), 7.70 [1H, s, C(2)-H], 7.78 [1H, s, C(6)-H]. *Anal*. Calcd for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76. Found: C, 60.63; H, 4.39; N, 20.66.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-7-carbaldehyde (9g) $POCl_3$ (3.5 ml) was added dropwise to Me_2NCHO (30 ml) at 0 °C over a period of 5 min, and the solution was stirred at room temperature for 10 min. Compound **13** (2.80 g, 10.03 mmol) was added to the solution, and the mixture was stirred at room temperature for 3 h. The resulting orange solution and Me_2NCHO washings (15 ml) of the reaction vessel were poured into saturated aqueous $NaHCO_3$ (200 ml). The precipitate that resulted was collected by filtration, washed successively with H_2O (100 ml) and MeOH (20 ml), and dried to give **9g** (2.86 g, 93%) as a colorless solid, mp 197—203 °C (dec.). Recrystallization of this product from Me_2CHOH afforded an analytical sample of **9g** as colorless needles, mp 203—205.5 °C (dec.). MS *m/z*: 307 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 251 (17800), 305 (sh) (9600), 329 (16700). IR ν_{max}^{Nujol} cm^{-1}: 1705 (CO). ^{1}H-NMR ($CDCl_3$) δ: 4.04 (3H, s, Me), 5.66 (2H, s, CH_2), 7.38 (5H, s, Ph), 7.81 [1H, s, C(2)-H], 8.09 [1H, s, C(6)-H], 10.75 (1H, s, CHO). *Anal*. Calcd for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.67; H, 4.10; N, 22.69.

1-Benzyl-4-methyl-7-nitro-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one

(9h) Concentrated aqueous HNO_3 (0.5 ml) and **13** (1.00 g, 3.58 mmol) were added to Ac_2O (15 ml) in this order with stirring at 0 °C, and the solution was stirred for 9 h. Cold H_2O (50 ml) was added to the reaction mixture, and stirring was continued for a further 5 min at 0 °C. The resulting mixture was neutralized with 10% aqueous NaOH, and the precipitate that resulted was extracted with CH_2Cl_2 (3×70 ml), the CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash chromatography [$CHCl_3$–EtOH (70 : 1, v/v)] to afford **9h** (68 mg), mp 145—151 °C (dec.). Further elution of the column provided a mixture of **9h** and **13**, and **13** (259 mg, 26% recovery). The mixture of **9h** and **13** was subjected to flash chromatography [hexane–AcOEt (1 : 10, v/v)] to give a second crop of **9h** (59 mg; the total yield was 11%). Recrystallization of crude **9h** from MeOH and drying over P_2O_5 at 2 mmHg and 50 °C for 6 h afforded an analytical sample of **9h**·1/4MeOH as yellow needles, mp 158—159.5 °C. MS *m/z*: 324 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 227 (25000), 252 (12400), 309 (6200), 368 (8000). IR ν_{max}^{Nujol} cm^{-1}: 1715 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.49 (3/4H, s, 1/4MeOH), 4.01 (3H, s, NMe), 5.62 (2H, s, CH_2), 7.39 (5H, s, Ph), 7.77 [1H, s, C(2)-H], 8.06 [1H, s, C(6)-H]. *Anal*. Calcd for $C_{15}H_{12}N_6O_3$·1/4CH_3OH: C, 55.12; H, 3.94; N, 25.29. Found: C, 55.37; H, 3.97; N, 25.29. Further drying of this sample under the same conditions for another 11 h did not remove the MeOH.

1-Benzyl-4-methyl-α,9-dioxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-7-ethanoic Acid Methyl Ester (9i) A solution of $(COCl)_2$ (0.045 ml) in THF (0.5 ml) was added dropwise to a stirred solution of **13** (100 mg, 0.358 mmol) and Et_3N (0.15 ml) in THF (1.5 ml) at 0 °C, and the mixture was stirred at room temperature for 5 h. Anhydrous MeOH (3 ml) was added to the resulting suspension, and the whole was stirred at room temperature for 15 min and concentrated *in vacuo*. The residual solid was dissolved in CH_2Cl_2 (15 ml), and the solution was washed successively with H_2O (10 ml), saturated aqueous $NaHCO_3$ (3×10 ml), and H_2O (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The solid residue was recrystallized from MeOH to give **9i** (52 mg), mp 145.5—148 °C. The mother liquor of recrystallization was concentrated *in vacuo*, and the residue was subjected to flash chromatography (AcOEt) to afford a second crop of **9i** (36 mg; the total yield was 67%), mp 144.5—147 °C. Further elution of the column afforded **13** (13 mg, 13% recovery). Recrystallization of crude **9i** from MeOH afforded an analytical sample as colorless needles, mp 148—149 °C. MS *m/z*: 365 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 230 (23600), 253 (13200), 334 (10700). IR ν_{max}^{Nujol} cm^{-1}: 1753, 1699 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.85, 4.03 (3H each, s, two Me's), 5.58 (2H, s, CH_2), 7.36 (5H, m, Ph), 7.77 [1H, s, C(2)-H], 8.05 [1H, s, C(6)-H]; ^{1}H-NMR [$(CD_3)_2SO$] δ: 3.65, 3.89 (3H each, s, two Me's), 5.58 (2H, s, CH_2), 7.36 (5H, m, Ph), 8.10 [1H, s, C(6)-H], 8.61 [1H, s, C(2)-H].[30] *Anal*. Calcd for $C_{18}H_{15}N_5O_4$: C, 59.18; H, 4.14; N, 19.17. Found: C, 59.03; H, 3.91; N, 19.18.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-carboxylic Acid (10b·H$^+$) A solution of **9b**·H^+ (74 mg, 0.23 mmol) in 0.5 M MeONa–MeOH (20 ml) was stirred at room temperature for 1 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was mixed with H_2O (10 ml), and the mixture was brought to pH 3 by addition of 10% aqueous H_3PO_4. The precipitate that resulted was collected by filtration and dried to give **10b**·H^+ (73 mg, 99%), mp 293—295 °C. Recrystallization from MeOH afforded an analytical sample of **10b**·H^+ as colorless needles, mp 301—302 °C. MS *m/z*: 323 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 232 (31300), 261 (sh) (9500), 266 (9700), 321 (8300). IR ν_{max}^{Nujol} cm^{-1}: 1705 [C(9)=O]. ^{1}H-NMR [$(CD_3)_2SO$] δ: 3.82 (3H, s, Me), 5.60 (2H, s, CH_2), 7.35 (5H, m, Ph), 8.09 [1H, s, C(7)-H], 8.52 [1H, s, C(2)-H],[30] 12.72 (1H, br, CO_2H). *Anal*. Calcd for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.19; H, 4.08; N, 21.66.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-methanol (10c) $NaBH_4$ (28 mg, 0.75 mmol) was added to a suspension of **10g** (154 mg, 0.501 mmol) in MeOH (25 ml), and the mixture was stirred at room temperature for 30 min. Me_2CO (0.2 ml) was added to the mixture, and the whole was concentrated *in vacuo*. The residue was mixed with H_2O (5 ml) and neutralized with 10% aqueous H_3PO_4. The insoluble solid was collected by filtration, washed successively with H_2O and MeOH (5 ml each), and dried to provide **10c** (147 mg, 95%), mp 243—245 °C. Recrystallization from EtOH afforded an analytical sample of **10c** as colorless needles, mp 244—245 °C. MS *m/z*: 309 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 235 (31900), 258 (6400), 312 (7200). IR ν_{max}^{Nujol} cm^{-1}: 3254 (OH), 1694 (CO); $\nu_{max}^{CHCl_3}$ (0.001 M) cm^{-1}: 1696 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.19 (1H, t, J=5.5 Hz, OH), 3.96 (3H, s, Me), 4.72 (2H, d, J=5.5 Hz, HOC$\underline{H}_2$), 5.61 (2H, s, PhC$\underline{H}_2$), 7.36 (5H, s, Ph), 7.60 [1H, s, C(7)-H], 7.72 [1H, s, C(2)-H]. *Anal*. Calcd for $C_{16}H_{15}N_5O_2$: C, 62.13; H, 4.89; N, 22.64. Found: C, 62.34; H, 4.89; N, 22.69.

1-Benzyl-6-iodo-4-methyl-4,9-dihydro-3*H*-imidazo[1,2-*a*]purin-9-one (10d) A suspension of **9d** (405 mg, 1 mmol) in 0.5 M MeONa–MeOH (60 ml) was heated under reflux for 30 min. The precipitate that deposited was collected by filtration, washed successively with MeOH (5 ml) and H_2O (30 ml) to provide **10d** (339 mg, 84%), mp 208.5—209 °C. Recrystallization of this product from EtOH afforded an analytical sample of **10d** as colorless needles, mp 210—211 °C. MS *m/z*: 405 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 237 (sh) (35200), 240 (37800), 262 (8200), 312 (8000). IR ν_{max}^{Nujol} cm^{-1}: 1688 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s, Me), 5.60 (2H, s, CH_2), 7.36 (5H, m, Ph), 7.74 [1H, s, C(2)-H],[30] 7.76 [1H, s, C(7)-H]. *Anal*. Calcd for $C_{15}H_{12}IN_5O$: C, 44.46; H, 2.99; N, 17.28. Found: C, 44.48; H, 2.85; N, 17.27.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-carboxamide (10e) A solution of **9e** (40 mg, 0.12 mmol) in 0.5 M MeONa–MeOH (15 ml) was stirred at room temperature for 1 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was partitioned between H_2O (40 ml) and $CHCl_3$ (40 ml). The aqueous layer was extracted with $CHCl_3$ (40 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give **10e** (37 mg, 93%), mp 246—247 °C (dec.). Recrystallization from MeOH afforded an analytical sample of **10e** as colorless needles, mp 251—252.5 °C (dec.). MS *m/z*: 322 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 232 (31500), 262 (sh) (9500), 267 (10200), 320 (7900). IR ν_{max}^{Nujol} cm^{-1}: 1700 (CO); $\nu_{max}^{CHCl_3}$ (0.001 M) cm^{-1}: 1703 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.94 (3H, s, Me), 5.61 (2H, s, CH_2), 5.47, 7.03 (1H each, br, NH_2), 7.37 (5H, s, Ph), 7.74 [1H, s, C(2)-H], 8.27 [1H, s, C(7)-H]. *Anal*. Calcd for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.39; H, 4.33; N, 26.13.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-carboxylic Acid Methyl Ester (10f) A mixture of **9f** (118 mg, 0.35 mmol) and 0.5 M MeONa–MeOH (40 ml) was stirred at room temperature. The starting material went into solution in 3 min, and then new precipitate began to deposit. The mixture was stirred at room temperature for 1 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was partitioned between H_2O (10 ml) and CH_2Cl_2 (20 ml). The aqueous layer was extracted with CH_2Cl_2 (20 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to leave **10f** (116 mg, 98%), mp 240—243.5 °C (dec.). Recrystallization from MeOH afforded an analytical sample of **10f** as slightly yellow needles, mp 242—245 °C (dec.). MS *m/z*: 337 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 233 (33500), 262 (sh) (10600), 267 (11400), 322 (9200). IR ν_{max}^{Nujol} cm^{-1}: 1721 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.96, 4.01 (3H each, s, two Me's), 5.60 (2H, s, CH_2), 7.37 (5H, s, Ph), 7.76 [1H, s, C(2)-H], 8.30 [1H, s, C(7)-H]. *Anal*. Calcd for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76. Found: C, 60.33; H, 4.56; N, 20.68.

1-Benzyl-4-methyl-9-oxo-4,9-dihydro-1*H*-imidazo[1,2-*a*]purine-6-carbaldehyde (10g) A mixture of **9g** (2.15 g, 7 mmol) and 0.5 M MeONa–MeOH (200 ml) was stirred at 25 °C for 1 h. The starting material went into solution in 5 min to give a slightly yellow solution, from which precipitate appeared immediately. The mixture was neutralized with 10% aqueous H_3PO_4 and concentrated in *vacuo*. The residue was partitioned between H_2O (150 ml) and CH_2Cl_2 (60 ml). The aqueous layer was extracted with CH_2Cl_2 (60 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give **10g** (2.14 g, 100%), mp 204—206 °C. Recrystallization of this product from MeOH afforded an analytical sample of **10g** as colorless plates, mp 204—206 °C. MS *m/z*: 307 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 237 (29000), 266 (sh) (14600), 270 (15200), 330 (7800). IR ν_{max}^{Nujol} cm^{-1}: 1721, 1703, 1688 (CO). ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s, Me), 5.61 (2H, s, CH_2), 7.38 (5H, s, Ph), 7.79 [1H, s, C(2)-H], 8.29 [1H, s, C(7)-H], 9.97 (1H, s, CHO). *Anal*. Calcd for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.38; H, 4.15; N, 22.58.

1-Benzyl-4-methyl-6-nitro-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one (10h) A solution of **9h**·1/4MeOH (50 mg, 0.15 mmol) in 0.5 M MeONa–MeOH (17 ml) was stirred at room temperature for 1 h, neutralized with 10% aqueous H_3PO_4, and concentrated *in vacuo*. The residue was partitioned between H_2O (5 ml) and $CHCl_3$ (10 ml). The aqueous layer was extracted with $CHCl_3$ (10 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to preparative TLC (silica gel, AcOEt) to afford **10h** (18 mg, 37%). Recrystallization of crude **10h** from MeOH afforded an analytical sample of **10h** as yellow needles, mp 195—196 °C. MS *m/z*: 324 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 222 (22500), 247 (sh) (12400), 287 (10900), 350 (3400). IR ν_{max}^{Nujol} cm^{-1}: 1711 (CO). ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s, NMe), 5.60 (2H, s, CH_2), 7.38 (5H, m, Ph), 7.81 [1H, s, C(2)-H], 8.42 [1H, s, C(7)-H]. *Anal*. Calcd for $C_{15}H_{12}N_6O_3$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.50; H, 3.69; N, 25.88.

Kinetic Procedure All reactions were followed by means of ^{1}H-NMR

spectrometric or UV spectrophotometric analysis through at least 85% completion of the reaction with at least nine measurements and were found to obey pseudo-first-order kinetics.

i) The irreversible reactions were followed by UV spectrophotometry. A solution of **16** (1.5 mg) in MeOH (*ca*. 10 ml) was adjusted to a volume of 20 ml (1.0×10^{-4} M) by addition of 0.5 M MeONa–MeOH (4 ml) and MeOH, both of which had been kept at 25 °C, at 25 °C. The resulting solution was kept at 25±0.05 °C in a thermoregulated constant-temperature bath. At intervals, appropriate amounts of the resulting solution were transferred to a cuvette, which was placed in a cell compartment maintained at 25 °C, as quickly as possible. Absorbances (A_t) of the mixture at selected times were determined at 292 nm. The absorbance (A_∞) on completion of the reaction was reached in *ca*. 5 h (10 half-lives). A plot of ln ($A_\infty-A_t$) against time gave a straight line ($r=0.983$ for 10 determinations) and $k_1=2.43\times10^{-2}$ min^{-1} was estimated by linear regression analysis.[31] The rate constants (Tables 1 and 2) for the reactions of **3g** (initial concentration, 4.5×10^{-4} M; analytical wavelength, 279 nm), **3h** (1.5×10^{-4} M, 316 nm), **3i** (3.4×10^{-4} M, 284 nm), and **9a** (4.7×10^{-4} M, 277 nm) were determined similarly. The rates of the reactions of **3f** (5.0×10^{-5} M, 304 nm), **9b** (3.1×10^{-5} M, 243 nm), **9d** (4.3×10^{-5} M, 312 nm), **9e** (4.2×10^{-5} M, 254 nm), and **9f** (5.3×10^{-5} M, 285 nm) were measured by monitoring the absorbance of the reacting solution in a cuvette, which was placed in a cell compartment maintained at 25 °C.

ii) The equilibrium constants for the reversible reactions were obtained by ^{1}H-NMR spectroscopy. A solution of **3a**·H_2O (30 mg) in 0.1 M MeONa–MeOH (3.9×10^{-3} M) was prepared and kept at 25±0.05 °C in the same manner as described above under method i). At intervals, aliquots (1 ml) of the solution were withdrawn and added to 10% aqueous H_3PO_4 (0.06 ml) to quench the reaction. The resulting mixtures were partitioned between CH_2Cl_2 and H_2O (3 ml each). Colorless solids obtained by concentration of the organic layers were analyzed by ^{1}H-NMR ($CDCl_3$). For determination of **3a** and **4a**, relative areas of the C(6)-Me signal at δ 2.24 and the C(7)-Me signal at δ 2.66 were obtained. Equilibrium ($K=k_1/k_{-1}=1.34$) between **3a** and **4a**, where they exist in a ratio of 42.8: 57.2, was established in *ca*. 450 h. Treatment of the kinetic data in the usual manner[31] revealed that the reactions in both directions obey pseudo-first-order kinetics through 112 h ($r=0.998$ for 10 determinations) with $k_1+k_{-1}=3.20\times10^{-4}$ min^{-1}. The pseudo-first-order rate constants ($k_1=1.83\times10^{-4}$ min^{-1} and $k_{-1}=1.37\times10^{-4}$ min^{-1}) were estimated using the observed values for K and k_1+k_{-1}. The rate and/or equilibrium constants for the reactions of **3b**—**d** (Table 1) were obtained similarly. The equilibrium constant for the reaction of **9c** was estimated based on relative areas of C(6)- and C(7)-H signals and those of **3e** and **9g** were obtained by utilizing the signals due to the formyl groups. The value of k_1+k_{-1} for the reaction of **9c** (7.5×10^{-5} M, 265 nm) and that of **9g** (5.2×10^{-5} M, 329 nm) were measured by monitoring the absorbance of the reacting solution in a cuvette, which was placed in a cell compartment maintained at 25 °C.

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17) Slightly yellow needles, mp 228 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.99 (3H, s, Me), 5.71 (2H, s, CH_2), 7.20 [1H, d, $J=1.7$ Hz, C(6)-H], 7.50 [2H, m, C(2′)-, C(6′)-H], 7.63 [1H, d, $J=1.7$ Hz, C(7)-H], 7.83 [1H, s, C(2)-H], 8.22 [2H, m, C(3′)-, C(5′)-H].
18) A yellow solid, mp 260—269 °C (dec.). MS *m*/*z*: 369 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s, Me), 6.04 (2H, s, CH_2), 7.20 [1H, d, $J=1.7$ Hz, C(6)-H], 7.48—7.68 [2H, m, C(5′)-, C(6′)-H], 7.63 [1H, d, $J=1.7$ Hz, C(7)-H], 7.91 [1H, s, C(2)-H], 8.13—8.23 [1H, m, C(3′)-H].
19) Obtained in 64% yield, mp 266—269 °C. ^{1}H-NMR [$(CD_3)_2SO$] δ: 3.82 (3H, s, NMe), 5.60 (2H, s, CH_2), 7.26—7.42 (5H, m, Ph), 8.48 [1H, s, C(7)-H], 8.55 [1H, s, C(2)-H].[30]
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