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Purines. XXX.[1] Ring Fission of 3,7-Dialkyladenines by Alkaline Hydrolysis[2]

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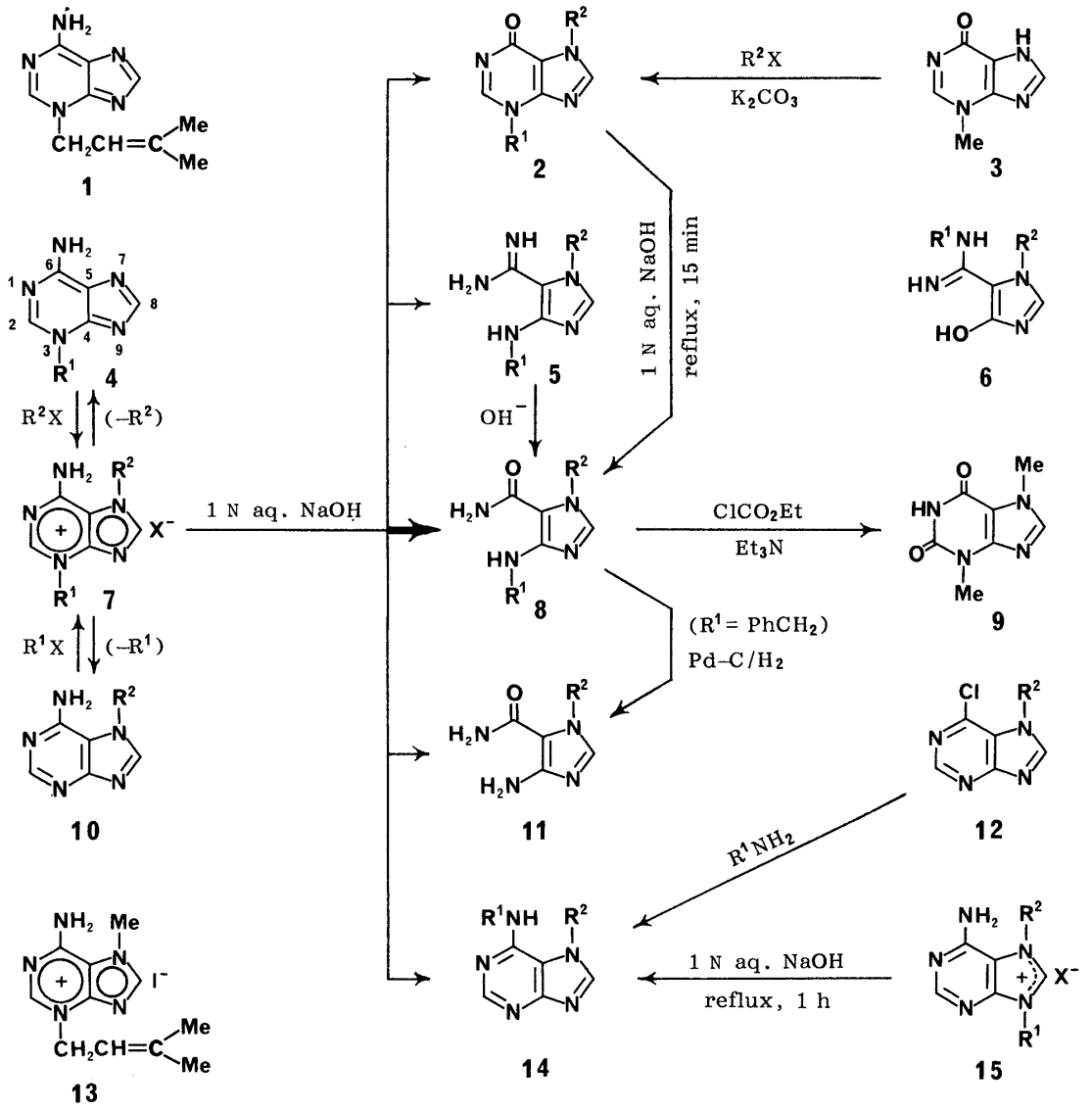
On treatment with boiling 1 N aqueous NaOH for 2 h, 3,7-dialkyladenine salts (**7**: R^1, R^2 = Me, Et, or $PhCH_2$; X = Br, I, or ClO_4) gave 1-alkyl-4-(*N*-alkylamino)-1*H*-imidazole-5-carboxamides (**8**), 1-alkyl-4-amino-1*H*-imidazole-5-carboxamides (**11**), and N^6,7-dialkyladenines (**14**) in 33—59%, 2—10%, and 2—5% yields, respectively. Under slightly milder reaction conditions, 3,7-dimethyladenine hydriodide (**7a**: X = I) afforded 1-methyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamide (**8a**) together with 3,7-dimethylhypoxanthine (**2a**) as a by-product; 7-benzyl-3-methyladenine hydrobromide (**7c**: X = Br) furnished a small amount of 1-benzyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamidine (**5c**) besides 1-benzyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamide (**8c**), 1-benzyl-4-amino-1*H*-imidazole-5-carboxamide (**11c**), and 7-benzyl-N^6-methyladenine (**14c**). These results are best interpreted in terms of pathways involving hydrolytic deamination, ring fission in the pyrimidine and imidazole moieties, cyclization, and Dimroth rearrangement. The instability of **7a** (X = I) in aqueous alkali was compared with that of the four possible N^x,9-dimethyl isomers, and the relative ease with which the adenine ring underwent hydrolytic ring fission was found to decrease in the order 3,9- (**17**) > 7,9- (**18**) > 1,9- (**19**) > 3,7- (**7a**) ≫ N^6,9-dimethyl isomer (**20**).

Keywords——3,7-dialkyladenine alkaline hydrolysis; ring fission; deamination; rearrangement; 1-alkyl-4-(*N*-alkylamino)-1*H*-imidazole-5-carboxamide; 1-alkyl-4-amino-1*H*-imidazole-5-carboxamide; N^6,7-dialkyladenine

3,7-Dialkyladenines (type **7**), easily obtainable from either 3-alkyladenines (**4**) or 7-alkyladenines (**10**) by alkylation,[3] constitute one of the 11 possible groups of positional isomers of N^x,N^y-disubstituted adenines. Triacanthine methiodide (**13**),[3a,b,4] a methylation product from the *Gleditsia triacanthos* alkaloid triacanthine (**1**),[4,5] is a representative of such 3,7-disubstitution, which also occurs in the form of intermediates in a general and convenient synthesis of 7- or 3-substituted adenines (**10** or **4**) from adenine by regioselective alkylation utilizing blocking/deblocking at the 3- or 7-position.[3a-g,6] Our continuing interest in fission and reclosure of the adenine ring[7] led us to investigate the stability of the 3,7-disubstituted ring system under alkaline hydrolytic conditions by using, as the substrates, all nine 3,7-dialkyladenines (**7a**—**i**)[3j] that carry any one of the methyl, ethyl, and benzyl groups at each of the 3- and 7-positions.

In 0.1 N aqueous NaOH (pH 13), 3,7-dimethyladenine hydriodide (**7a**: X = I) was found to be considerably stable at room temperature: its ultraviolet (UV) spectrum in this medium could be measured without any difficulty. Hydrolysis of **7a** (X = I) in 1 N aqueous NaOH at 80 °C for 30 min gave the ring-opened monocycle **8a** and the deaminated product **2a** in 39% and 1% yields, respectively, whereas that under reflux for 2 h furnished **8a** and the monodemethylated monocycle **11a** in 49% and 2% yields, respectively, but without giving any **2a**. The latter finding seemed reasonable since treatment of **2a** with boiling 1 N aqueous NaOH for 15 min afforded **8a** in 65% yield. The structure of **8a** was confirmed by its cyclization with



a: $R^1=R^2=Me$ **b**: $R^1=Me$; $R^2=Et$ **c**: $R^1=Me$; $R^2=PhCH_2$
d: $R^1=Et$; $R^2=Me$ **e**: $R^1=R^2=Et$ **f**: $R^1=Et$; $R^2=PhCH_2$
g: $R^1=PhCH_2$; $R^2=Me$ **h**: $R^1=PhCH_2$; $R^2=Et$ **i**: $R^1=R^2=PhCH_2$

Chart 1

ethyl chloroformate and Et_3N, which produced theobromine (**9**) in 47% yield; that of **2a**, by the identity with a sample prepared from 3-methylhypoxanthine (**3**) by methylation with MeI and K_2CO_3, which was patterned after the benzylation of 3-benzylhypoxanthine described by Montgomery and Thomas[8]; and that of **11a**, by the identity with a sample obtained in 91% yield from **8g** (*vide infra*) by hydrogenolytic debenzylation. Broom *et al.*[3i] suggested the formation of **2a** from **7a** (X=I) when the latter was treated with 2 N aqueous NaOH at room temperature for 4 d. In our hands, however, **7a** (X=I) was found to give **8a** as the major product together with a trace amount of **2a** under similar reaction conditions, and **8a** was isolated in 47% yield in the form of the perchlorate salt when **7a** (X=I) was treated with 1 N aqueous NaOH at 30 °C for 7 d.

Hydrolysis of **7b** (X=I) with boiling 1 N aqueous NaOH for 2 h produced **8b** and a substance presumed to be **6b** in 33% and 4% yields, respectively. A similar hydrolysis of **7e** ($X=ClO_4$) gave **8e** and **11e** in 44% and 2% yields, respectively. The structure of **11e** was

corroborated by its identity with a sample prepared in 80% yield from **8h** (*vide infra*) by catalytic hydrogenolysis. Treatment of **7c** (X = Br) with boiling 1 N aqueous NaOH for 15 min provided the monocyclic amidine **5c** (13% yield), **8c** (30%), **11c**[9] (1%), and the rearranged product **14c** (5%). Extension of the reaction time to 2 h altered the populations of the products: **8c** (43% yield), **11c**[9] (10%), and **14c** (4%). The correctness of the structure of **14c**

TABLE I. Hydrolysis of 3,7-Dialkyladenine Salts (**7**) with Boiling 1 N Aqueous NaOH for 2 h

Starting material				Product		
				Yield (%)		
No.	R^1	R^2	X	Type **8**	Type **11**	Type **14**
7a	Me	Me	I	49 (**8a**)	2 (**11a**)	—
7b	Me	Et	I	33 (**8b**)	—	—[a]
7c	Me	$PhCH_2$	Br	43 (**8c**)	10 (**11c**)	4 (**14c**)
7d	Et	Me	I	43 (**8d**)	—	—
7e	Et	Et	ClO_4	44 (**8e**)	2 (**11e**)	—
7f	Et	$PhCH_2$	Br	52 (**8f**)	4 (**11c**)	4 (**14f**)
7g	$PhCH_2$	Me	I	58 (**8g**)	—	3 (**14g**)
7h	$PhCH_2$	Et	ClO_4	59 (**8h**)	—	2 (**14h**)
7i[b]	$PhCH_2$	$PhCH_2$	Br	43 (**8i**)	—	5 (**14i**)

a) A by-product presumed to be **6b** was isolated in 4% yield. *b*) The reaction time was extended to 6.5 h because of the poor solubility of **7i**.

TABLE II. UV Spectra of 1-Alkyl-4-(*N*-alkylamino)-1*H*-imidazole-5-carboxamides (**8a—i**)

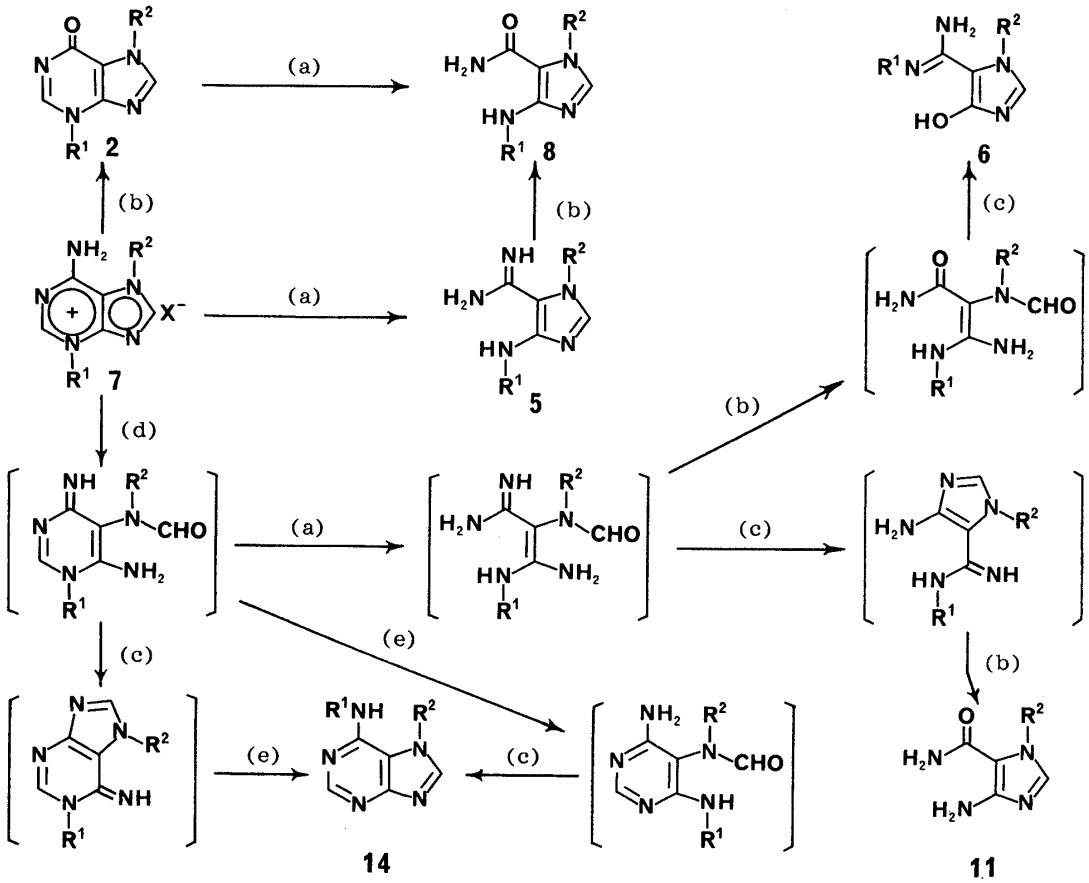
Compound	UV spectra							
	Solvent E[a]		Solvent A[b]		Solvent N[c]		Solvent B[d]	
	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
8a	293	10.1	246	6.3	289	9.3	289	9.1
			284	9.5				
8b	291	9.5	247	6.4	289	9.2	289	9.4
			284	9.5				
8c	294	9.7	250	7.0	290	8.9	290	8.8
			286	8.6				
8d	294	9.8	247	7.1	288	9.5	288	9.5
			284	9.7				
8e	292	8.8	247	6.5	289	8.7	289	8.7
			283	8.8				
8f	294	8.6	250	7.0	289	8.1	289	8.0
			285	7.8				
8g	294	11.1	249	8.5	292	10.4	292	10.5
			283	10.2				
8h	292	9.8	248	7.5	289	9.3	289	9.3
			281	8.8				
8i	294	9.7	251	8.3	290	8.7	290	8.7
			282	7.9				

a) 95% (v/v) aqueous EtOH. *b*) 0.1 N aqueous HCl (pH 1). *c*) 0.005 M phosphate buffer (pH 7). *d*) 0.1 N aqueous NaOH (pH 13).

was supported by its identity with a sample[10] synthesized from 7-benzyl-9-methyladeninium bromide (**15c**: X = Br) by rearrangement under alkaline conditions. The amidine **5c** gave **8c** in 17% yield on treatment with boiling 1 N aqueous NaOH for 1 h.

Hydrolyses of the other 3,7-dialkyladenine salts (**7**) were effected in boiling 1 N aqueous NaOH for 2 h, and the results are summarized in Table I. It may be seen that in all the hydrolyses the main product was 1-alkyl-4-(*N*-alkylamino)-1*H*-imidazole-5-carboxamide (type **8**). The rearranged product (type **14**) was isolated in low yield in many cases, and the 4-aminoimidazole-5-carboxamide derivative (type **11**) was also isolated in low yield in several cases. The structures of **14f**, **14h**, and **14i** were confirmed by comparison with samples synthesized from **15f** (X = ClO_4)[10] by rearrangement under basic conditions and from the 6-chloro derivatives **12h** and **12i** by amination with benzylamine. As shown in Table II, the UV spectra of **8b**—**i** resembled that of **8a** in four different solvents, supporting the assigned structures.

The above results indicate that the main product from alkaline hydrolysis of a 3,7-dialkyladenine salt (type **7**) is 1-alkyl-4-(*N*-alkylamino)-1*H*-imidazole-5-carboxamide (type **8**), formed by ring fission in the pyrimidine moiety with loss of C(2), and that the monodealkylated derivative **11** and the rearranged isomer **14** are by-products. Chart 2 outlines the most likely pathways to these products, suggesting the imidazole moiety of 3,7-dialkyladenine salt (type **7**) to be another, but less favored site of ring fission. The pathways include ring fission with loss of C(2), hydrolytic deamination, cyclization with dehydration, ring fission in the imidazole moiety, and Dimroth rearrangement. On the other hand, 3-alkyladenines (type **4**)



pathway (a), ring fission with loss of C(2); (b), hydrolytic deamination; (c), cyclization with dehydration; (d), ring fission; (e), a Dimroth rearrangement

Chart 2

are stable under alkaline conditions: triacanthine (**1**) (pK_a 5.4) could be recovered unchanged after treatment with hot, aqueous KOH[4]; on treatment with boiling 1 N aqueous NaOH for 50 min, 3-methyladenine (**4a**) (pK_a 5.3)[4] gave 3-methylhypoxanthine (**3**) and the monocyclic amide **16** in only 12% yield each.[11] The pK_a value for 3,7-dimethyladenine sulfate (**7a**: X=HSO_4)[3i,12] has been reported to be 11.0,[12] indicating the existence of a large population of the protonated species (**7a**) even under alkaline conditions. This may explain the easy, competitive ring fissions in the pyrimidine and imidazole moieties of **7**, which are initiated by nucleophilic attack of hydroxide ion at the 2- and 8-positions.

In order to make a comparison between the ease with which 3,7-dimethyladenine hydriodide (**7a**: X=I) undergoes ring fission under alkaline conditions and that of the four possible N^x,9-dimethyl isomers, N^6,9-dimethyladenine (**20**) was heated in 1 N aqueous NaOH under reflux. However, this isomer was found to be stable for at least 30 min. The reaction rates for ring opening of the other three isomers have already been reported from our laboratory[10,13,14] and are summarized in Chart 3. It may be seen that the relative ease with which the adenine ring undergoes hydrolytic fission decreases in the order 3,9- (**17**) > 7,9- (**18**) > 1,9- (**19**) > 3,7- (**7a**) ≫ N^6,9-dimethyl isomer (**20**).

In summary, 3,7-dialkyladenine salts (**7**) have been found to undergo hydrolytic ring fission rather easily under alkaline conditions, giving mainly 1-alkyl-4-(*N*-alkylamino)-1*H*-imidazole-5-carboxamides (**8**). Recyclization of **8** with the C(2)-precursor ethyl chlorofor-

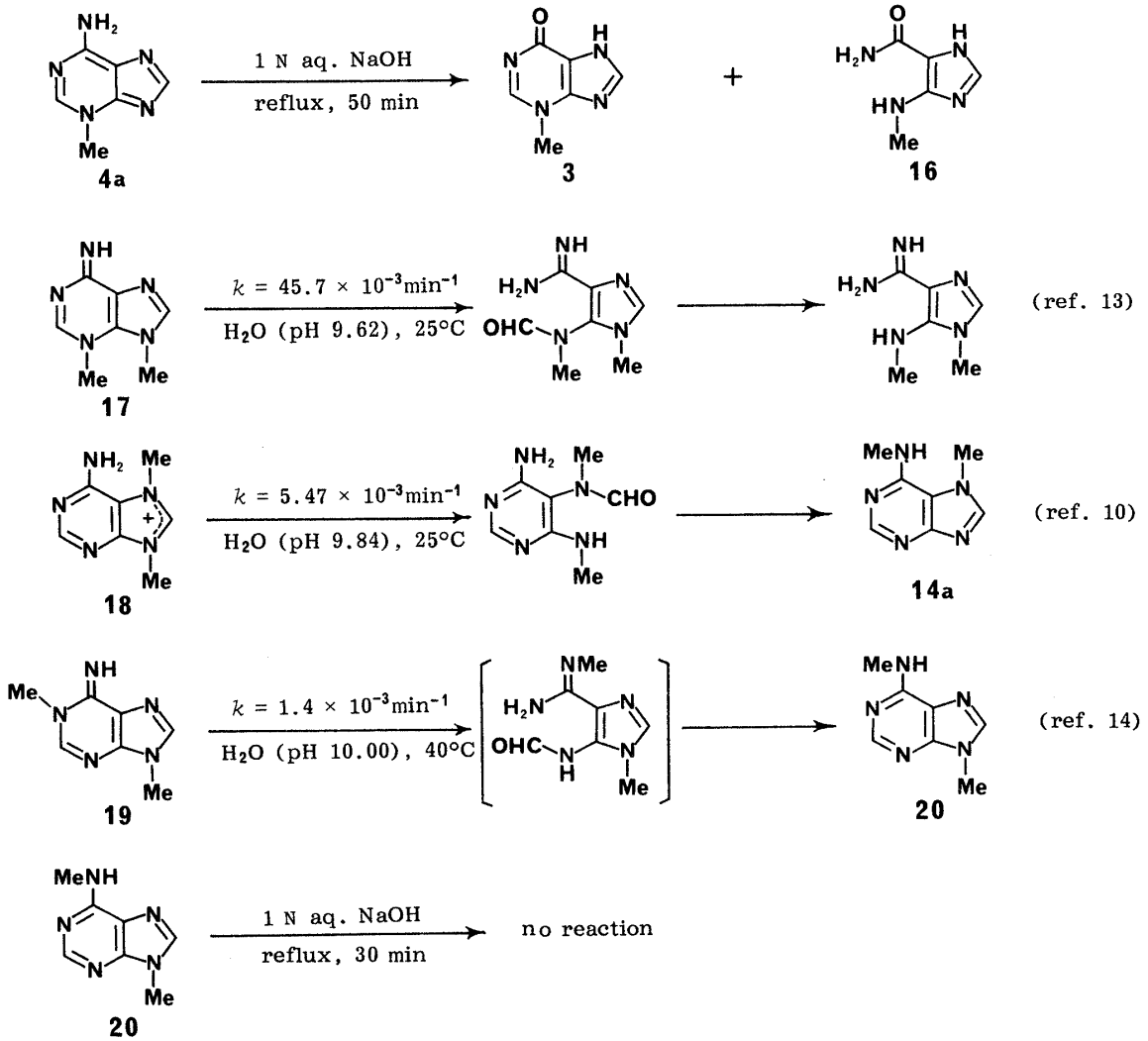


Chart 3

mate, as exemplified by the conversion of **8a** into theobromine (**9**), may provide a new, general synthetic route to 3,7-dialkylxanthines from 3- or 7-alkyladenines (**4** or **10**) and hence from adenine. A study along this line will be the subject of a forthcoming paper from our laboratory.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a Hitachi 323 or a Hitachi 320 ultraviolet (UV) spectrophotometer, a JASCO IRA-2 or a JASCO A-202 infrared (IR) spectrophotometer, a JEOL JMS-01SG or a Hitachi M-80 mass spectrometer, or a JEOL JNM-FX-100 nuclear magnetic resonance (NMR) spectrometer at 25 °C with Me_4Si as an internal standard. 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, q = quartet, s = singlet, sh = shoulder, t = triplet.

Hydrolysis of 3,7-Dimethyladenine Hydriodide (7a: X = I)——i) A stirred mixture of **7a** (X = I)[3j] (2.62 g, 9 mmol) and 1 N aqueous NaOH (45 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was neutralized with 10% aqueous HCl and concentrated *in vacuo*. The residue, after having been dried, was extracted with hot AcOEt, and the AcOEt extracts were concentrated to dryness to leave a brown solid. The solid was chromatographed on a column packed with alumina (95 g) using CH_2Cl_2–MeOH (10 : 1, v/v). Earlier fractions gave crude 1-methyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamide (**8a**) as a slightly reddish solid. The total amount of this solid was dissolved in hot EtOH (4 ml), and a solution of 70% aqueous $HClO_4$ (1.29 g) in EtOH (2 ml) was added. The precipitate that resulted was filtered off and dried to give **8a**·$HClO_4$ (1.12 g, 49%), mp 197.5—200.5 °C (dec.). Recrystallization from EtOH afforded an analytical sample as colorless needles, mp 201—203 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 238 nm (ε 3600), 292 (10200); $\lambda_{max}^{H_2O}$ (pH 1) 246 (6800), 284 (10200); $\lambda_{max}^{H_2O}$ (pH 7) 289 (9900); $\lambda_{max}^{H_2O}$ (pH 13) 289 (9800); IR ν_{max}^{Nujol} 1670 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 2.88 (3H, s, NHMe), 3.92 [3H, s, N(1)-Me], 7.29 (2H, br, $CONH_2$), 8.67 [1H, s, H(2)]. *Anal.* Calcd for $C_6H_{10}N_4O \cdot HClO_4$: C, 28.30; H, 4.35; N, 22.00. Found: C, 28.34; H, 4.33; N, 21.92.

Later fractions in the above column chromatography furnished crude 4-amino-1-methyl-1*H*-imidazole-5-carboxamide (**11a**) (23 mg, 2%) as slightly reddish needles, mp 163.5—168 °C (dec.). Recrystallization from EtOH yielded a pure sample as colorless needles, mp 187—189 °C (dec.). This sample was identical [by comparison of the IR spectrum and thin-layer chromatographic (TLC) mobility] with the one obtained from **8g** by debenzylation (*vide infra*).

In a separate experiment, crude **8a** was directly recrystallized from AcOEt to give an analytical sample of the free base **8a** as colorless, fine prisms, mp 175—176 °C (dec.) (lit.[15] mp 175—176 °C); MS *m/z*: 154 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1650 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 2.77 (3H, dull s, NHMe), 3.70 [3H, s, N(1)-Me], 5.56 (1H, br, NHMe), 6.66 (2H, br, $CONH_2$), 7.33 [1H, s, H(2)]. *Anal.* Calcd for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.81; H, 6.50; N, 36.21. Sometimes, **8a** crystallized in colorless needles, mp 180—181 °C (dec.), probably another dimorphic form.

ii) A stirred mixture of **7a** (X = I)[3j] (873 mg, 3 mmol) and 1 N aqueous NaOH (15 ml) was heated at 80 °C for 30 min. The reaction mixture was concentrated to dryness *in vacuo* in a manner similar to that described above under item (i), and the resulting residue was extracted with hot EtOH. The ethanolic extracts were concentrated to dryness, and the residual solid (860 mg) was chromatographed on an alumina column [$CHCl_3$–EtOH (20 : 1, v/v)]. Fractions containing **8a** and **2a** were combined and concentrated *in vacuo*. The resulting residue was recrystallized from AcOEt (20 ml) to give a first crop (143 mg, 31%) of **8a** as colorless needles, mp 180—181 °C (dec.). Concentration of the mother liquor, which was obtained when the first crop of **8a** was filtered off, and purification of the residue by preparative TLC [alumina, AcOEt–MeOH (5 : 1, v/v)] afforded a second crop (39 mg, 8%) of **8a** and crude 3,7-dimethylhypoxanthine (**2a**) (7 mg, 1%), mp 236—239 °C (dec.), from the higher and lower *Rf* value zones, respectively. The IR spectrum and TLC mobility of this sample of **2a** were identical with those of authentic **2a** (*vide infra*).

iii) A mixture of **7a** (X = I)[3j] (146 mg, 0.5 mmol) and 1 N aqueous NaOH (2.5 ml) was stirred at 30 °C for 7 d. The reaction mixture was passed through a column of Amberlite CG-120 (H^+) (4 ml), and the column was eluted with H_2O until the pH of the eluate became 7. Then, the column was eluted with 5% aqueous NH_3 (80 ml), and the ammoniacal eluate was concentrated to dryness *in vacuo*. The residual solid was dissolved in hot EtOH (1 ml), and a solution of 70% aqueous $HClO_4$ (144 mg) in EtOH (0.5 ml) was added. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to furnish **8a**·$HClO_4$ (60 mg, 47%), mp 198—201 °C (dec.). This sample of **8a**·$HClO_4$ was identical (by comparison of the IR spectrum) with the one described above under item (i).

Synthesis of 3,7-Dimethylhypoxanthine (2a) from 3-Methylhypoxanthine (3)——A mixture of **3**·$3/2H_2O$[16] (1.59 g, 9 mmol) and anhydrous K_2CO_3 (1.25 g, 9 mmol) in $AcNMe_2$ (250 ml) was stirred at 110—120 °C for 1 h. After

cooling, a solution of MeI (2.17 g, 15.3 mmol) in $AcNMe_2$ (20 ml) was added, and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was triturated with ether. The precipitate that resulted was separated from the ethereal layer by decantation, dried, and extracted with hot AcOEt. The AcOEt extracts were concentrated to leave a yellowish solid (1.19 g), which was chromatographed on a column packed with alumina (118 g) using AcOEt–MeOH (10 : 1, v/v) as the eluent. Earlier fractions gave a material (371 mg, 21%) presumed to be 1,*N*-dimethyl-4-(*N*-methylformamido)-1*H*-imidazole-5-carboxamide or 1-methyl-5(or 6)-(*N*-methylamino)-6(or 5)-(*N*-methylformamido)-4(1*H*)-pyrimidinone as colorless prisms, mp 137—141 °C. Recrystallization from AcOEt yielded an analytical sample, mp 144—145.5 °C; MS *m/z*: 196 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 245 nm (sh) (ε 6700); $\lambda_{max}^{H_2O}$ (pH 7) 244 (sh) (6600); $\lambda_{max}^{H_2O}$ (pH 13) unstable; IR ν_{max}^{Nujol} 1690 cm^{-1} (NCHO); NMR (Me_2SO-d_6) δ: 2.75 (3H, m, NHMe), 3.10 and 3.28 [3H, s each, N(Me)CHO],[17] 3.71 (3H, s, NMe), 7.67 and 8.17 [1H each, s, N(Me)CHO and ring proton], 7.95 (1H, br, NHMe). *Anal.* Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28.55. Found: C, 48.76; H, 6.24; N, 28.74.

Later fractions in the above chromatography provided **2a** (536 mg, 36%) as colorless prisms, mp 246—248.5 °C. Recrystallization from EtOH afforded an analytical sample, mp 248—248.5 °C (lit.[18] mp 242—245 °C); MS *m/z*: 164 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 267 nm (ε 11400); $\lambda_{max}^{H_2O}$ (pH 1) 254.5 (9900); $\lambda_{max}^{H_2O}$ (pH 7) 265 (11700); $\lambda_{max}^{H_2O}$ (pH 13) 265 (11700); NMR (Me_2SO-d_6) δ: 3.74 [3H, s, N(3)-Me], 3.97 [3H, s, N(7)-Me], 8.13 [1H, s, H(8)], 8.25 [1H, s, H(2)].[19] *Anal.* Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.09; H, 4.95; N, 34.31.

7-Benzyl-3-methylhypoxanthine (2c)——A mixture of **3**·3/2H_2O[16] (2.13 g, 12 mmol) and anhydrous K_2CO_3 (1.66 g, 12 mmol) in $AcNMe_2$ (380 ml) was stirred at 100—110 °C for 1 h. After cooling, benzyl bromide (2.47 g, 14.4 mmol) was added, and the resulting mixture was stirred at 90 °C for 1 h. After cooling, the reaction mixture was filtered in order to remove an insoluble solid. The filtrate was concentrated *in vacuo*, and the residue was triturated with ether. The precipitate that resulted was separated from the ethereal layer by decantation and extracted with hot AcOEt. Concentration of the AcOEt extracts to a small volume gave **2c** (1.89 g, 65%). Recrystallization from AcOEt furnished an analytical sample as colorless scales, mp 211—212 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 268 nm (ε 11200); $\lambda_{max}^{H_2O}$ (pH 1) 256 (10300); $\lambda_{max}^{H_2O}$ (pH 7) 267 (12100); $\lambda_{max}^{H_2O}$ (pH 13) 267 (11900); NMR (Me_2SO-d_6) δ: 3.74 [3H, s, N(3)-Me], 5.60 [2H, s, N(7)-CH_2Ph], 7.1—7.45 (5H, m, Ph), 8.27 [1H, s, H(2)], 8.38 [1H, s, H(8)]. *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.96; H, 4.80; N, 23.15.

Hydrolysis of 3,7-Dimethylhypoxanthine (2a)——A stirred mixrure of **2a** (263 mg, 1.6 mmol) and 1 N aqueous NaOH (8 ml) was heated under reflux for 15 min. After cooling, the reaction mixture was neutralized with 10% aqueous HCl and concentrated *in vacuo*. The residue, after having been dried, was extracted with hot AcOEt, and the AcOEt extracts were concentrated to a small volume. The precipitate that resulted was filtered off and dried to give **8a** (160 mg, 65%), mp 174—176 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by alkaline hydrolysis of **7a** (X = I) (*vide supra*).

Conversion of 1-Methyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamide (8a) into Theobromine (9)——A solution of ethyl chloroformate (543 mg, 5 mmol) in MeCN (3 ml) was added to a stirred mixture of **8a**·$HClO_4$ (255 mg, 1 mmol) and Et_3N (506 mg, 5 mmol) in MeCN (7 ml). The resulting mixture was stirred at room temperature for 1.5 h and then concentrated *in vacuo* to leave a colorless solid. The solid was dissolved in 1 N aqueous NaOH (10 ml), and the solution was kept at room temperature for 10 min and then neutralized with 10% aqueous HCl. The precipitate that resulted was filtered off, washed successively with H_2O and EtOH, and dried to give **9** (84 mg, 47%), mp > 300 °C; MS *m/z*: 180 (M^+). This sample was identical (by comparison of the IR spectrum and TLC behavior) with authentic theobromine (**9**).

Hydrolysis of 7-Ethyl-3-methyladenine Hydriodide (7b: X = I)——A mixture of **7b** (X = I)[3j] (3.05 g, 10 mmol) and 1 N aqueous NaOH (50 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was passed through a column of Dowex 50 W-X8 (H^+) (100 ml), and the column was eluted with H_2O until the eluate became neutral. Then, the column was eluted with 5% aqueous NH_3 (1800 ml), and the ammoniacal eluate was concentrated *in vacuo* to leave a brown oil. The oil was chromatographed on a column of silica gel (75 g) using CH_2Cl_2–EtOH (10 : 1, v/v) as the eluent. A product isolated from the earlier fractions was recrystallized from AcOEt to give a substance (59 mg, 4%) presumed to be 1-ethyl-4-hydroxy-*N*-methyl-1*H*-imidazole-5-carboxamidine (**6b**) as colorless prisms, mp 173—175 °C (dec.). Further recrystallization from AcOEt yielded an analytical sample, mp 174.5—175.5 °C (dec.); MS *m/z*: 168 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 270 nm (ε 9100); $\lambda_{max}^{H_2O}$ (pH 1) 253 (6600), 267 (sh) (6300); $\lambda_{max}^{H_2O}$ (pH 7) 267 (8800); $\lambda_{max}^{H_2O}$ (pH 13) 267 (9100); NMR ($CDCl_3$) δ: 1.47 [3H, t, *J* = 7.8 Hz, N(1)-CH_2Me], 2.88 (3H, dull d, *J* = 3.2 Hz, NHMe), 3.96 [2H, q, *J* = 7.8 Hz, N(1)-CH_2Me], 5.70 (2H, br) and 6.69 (1H, br) (OH, NH, NHMe), 7.06 [1H, s, H(2)]. *Anal.* Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.84; H, 7.37; N, 33.15.

Later fractions in the above chromatography gave a slightly brownish solid, which was recrystallized from AcOEt to yield 1-ethyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamide (**8b**) (563 mg, 33%) as slightly brownish prisms, mp 140—141.5 °C. Further recrystallization from AcOEt provided an analytical sample, mp 142—144 °C; MS *m/z*: 168 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1650 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 1.42 [3H, t, *J* = 7 Hz, N(1)-CH_2Me], 2.94 (3H, s, NHMe), 4.25 [2H, q, *J* = 7 Hz, N(1)-CH_2Me], 6.03 (2H, br, $CONH_2$), 7.29 [1H, s, H(2)]. *Anal.* Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.81; H, 7.37; N, 33.56.

Hydrolysis of 7-Benzyl-3-methyladenine Hydrobromide (7c: X = Br)——i) A mixture of **7c** (X = Br)[3j] (3.84 g,

12 mmol) and 1 N aqueous NaOH (60 ml) was heated under reflux for 15 min. The reaction mixture was cooled in an ice bath for 30 min, and the precipitate that resulted was filtered off and partitioned by extraction with a mixture of AcOEt (300 ml) and 5% aqueous NaH_2PO_4 (20 ml). The AcOEt layer was dried and concentrated to leave a first crop (707 mg) of 1-benzyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamide (**8c**). The aqueous phosphate layer was saturated with K_2CO_3 and extracted with AcOEt. The AcOEt extracts were dried (anhydrous K_2CO_3) and concentrated to leave 1-benzyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamidine (**5c**) (369 mg, 13%) as unstable, colorless prisms. Recrystallization from EtOH–hexane and drying over P_2O_5 at 4 mmHg and 50 °C for 6 h gave an analytical sample of **5c**·1/4H_2O as brownish prisms, mp 169.5—170.5 °C (dec.); MS *m/z*: 229 (M^+); NMR (Me_2SO-d_6) δ: 2.77 (3H, s, NHMe), 5.39 [2H, s, N(1)-CH_2Ph], 5.71 (1H, br, NH), 6.14 (2H, br, NH_2), 6.8—7.4 (5H, m, Ph), 7.52 [1H, s, H(2)]. *Anal.* Calcd for $C_{12}H_{15}N_5 \cdot 1/4H_2O$: C, 61.65; H, 6.68; N, 29.96. Found: C, 61.48; H, 6.40; N, 29.89.

The aqueous mother liquor, obtained after filtration of the reaction mixture, was extracted with AcOEt, and the AcOEt extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a pale yellowish solid (777 mg). The solid was chromatographed on a column of alumina (70 g) using $CHCl_3$ as the eluent, giving a second crop (490 mg) of **8c**, 7-benzyl-N^6-methyladenine (**14c**) (146 mg, 5%), and 1-benzyl-4-amino-1*H*-imidazole-5-carboxamide (**11c**) (38 mg, 1%) (eluted in that order). The first and second crops of **8c** were combined and recrystallized from AcOEt to yield colorless needles (818 mg, 30%), mp 160 °C; MS *m/z*: 230 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1635 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 2.78 (3H, br, NHMe), 5.41 [3H, br, N(1)-CH_2Ph and NHMe], 6.65 (2H, br, $CONH_2$), 7.0—7.4 (5H, m, Ph), 7.60 [1H, s, H(2)]. *Anal.* Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.54; H, 6.10; N, 24.19.

Recrystallization of the crude **14c** from benzene gave colorless prisms, mp 181—182 °C, which were identical with authentic **14c**.[10] Recrystallization of the crude **11c** from AcOEt afforded an analytical sample as colorless prisms, mp 209—210.5 °C; MS *m/z*: 216 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 274 nm (ε 8300); $\lambda_{max}^{H_2O}$ (pH 1) 250 (sh) (7100), 267 (8500); $\lambda_{max}^{H_2O}$ (pH 7) 272 (9500); $\lambda_{max}^{H_2O}$ (pH 13) 272 (9700); IR ν_{max}^{Nujol} 1650 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 5.40 [2H, s, N(1)-CH_2Ph], 6.75 (2H, s, $CONH_2$), 7.0—7.4 (5H, m, Ph), 7.58 [1H, s, H(2)]. *Anal.* Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.18; H, 5.60; N, 25.73.

ii) A mixture of **7c** (X = Br)[3j] (3.20 g, 10 mmol) and 1 N aqueous NaOH (50 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was neutralized with 10% aqueous HCl, and the precipitate that resulted was filtered off, dried, and recrystallized from AcOEt to yield a first crop of **8c**. The filtrate was extracted with AcOEt, and the AcOEt extracts were dried and concentrated. The residue was chromatographed on a column of alumina using $CHCl_3$–EtOH (30 : 1, v/v) as the eluent. The results are summarized in Table I.

Hydrolysis of 1-Benzyl-4-(*N*-methylamino)-1*H*-imidazole-5-carboxamidine (5c)——A mixture of **5c**·1/4H_2O (50 mg, 0.2 mmol) and 1 N aqueous NaOH (1 ml) was heated under reflux for 1 h. After cooling, the reaction mixture was neutralized with 10% aqueous HCl and extracted with AcOEt. The AcOEt extracts were dried and concentrated, and the residue was purified by means of preparative TLC [alumina, $CHCl_3$–EtOH (3 : 1, v/v)] to give **8c** (8 mg, 17%). This compound was identified by comparison of the IR spectrum and TLC mobility with those of an authentic sample.

Hydrolysis of 3-Ethyl-7-methyladenine Hydriodide (7d: X = I)——A mixture of **7d** (X = I)[3j] (3.05 g, 10 mmol) and 1 N aqueous NaOH (50 ml) was heated under reflux for 2 h. The reaction mixture was worked up as described above for the hydrolysis of **7b** (X = I), giving 1-methyl-4-(*N*-ethylamino)-1*H*-imidazole-5-carboxamide (**8d**) (718 mg, 43%) as brownish pillars, mp 136.5—137.5 °C (dec.). Recrystallization from AcOEt afforded an analytical sample, mp 137.5—139 °C (dec.); UV (Table II); IR ν_{max}^{Nujol} 1660 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 1.10 (3H, t, J = 7 Hz, $NHCH_2$Me), 3.22 (2H, q, J = 7 Hz, $NHCH_2$Me),[20] 3.70 [3H, s, N(1)-Me], 5.60 (1H, br, NHCH$_2$Me), 6.71 (2H, br, $CONH_2$), 7.32 [1H, s, H(2)]. *Anal.* Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.89; H, 7.42; N, 33.36.

Hydrolysis of 3,7-Diethyladenine Perchlorate (7e: X = ClO_4)——A mixture of **7e** (X = ClO_4)[3j] (2.92 g, 10 mmol) and 1 N aqueous NaOH (50 ml) was heated under reflux for 2 h. The reaction mixture was worked up as described above for the hydrolysis of **7b** (X = I), furnishing the following two products.

1-Ethyl-4-(*N*-ethylamino)-1*H*-imidazole-5-carboxamide (**8e**): This was obtained in 44% yield and recrystallized from benzene to form colorless needles, mp 125.5—126.5 °C; MS *m/z*: 182 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1635 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 1.10 (3H, t, J = 7.1 Hz, $NHCH_2$Me), 1.23 [3H, t, J = 7.2 Hz, N(1)-CH_2Me], 3.21 (2H, q, J = 7.1 Hz, $NHCH_2$Me),[20] 4.15 [2H, q, J = 7.2 Hz, N(1)-CH_2Me], 5.43 (1H, br, NHCH$_2$Me), 6.76 (2H, br, $CONH_2$), 7.41 [1H, s, H(2)]. *Anal.* Calcd for $C_8H_{14}N_4O$: C, 52.73; H, 7.74; N, 30.75. Found: C, 52.52; H, 7.66; N, 30.97.

4-Amino-1-ethyl-1*H*-imidazole-5-carboxamide (**11e**): This was obtained in 2% yield and recrystallized from AcOEt to form slightly reddish prisms, mp 129.5—132 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by debenzylation of **8h** (*vide infra*).

Hydrolysis of 7-Benzyl-3-ethyladenine Hydrobromide (7f: X = Br)——A mixture of **7f** (X = Br)[3j] (602 mg, 1.8 mmol) and 1 N aqueous NaOH (9 ml) was heated under reflux for 2 h. The reaction mixture was worked up in a manner similar to that described above for the hydrolysis of **7c** (X = Br) under item (ii), yielding **11c** and the following two products (see Table I).

1-Benzyl-4-(*N*-ethylamino)-1*H*-imidazole-5-carboxamide (**8f**): This was recrystallized from AcOEt to give an analytical sample as colorless, fine prisms, mp 163.5—164 °C; MS *m/z*: 244 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1620 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 1.11 (3H, t, J=7.2 Hz, $NHCH_2\underline{Me}$), 3.22 (2H, q, J=7.2 Hz, $NHC\underline{H}_2Me$),[20] 5.41 [3H, br, N(1)-$C\underline{H}_2Ph$ and $N\underline{H}CH_2Me$], 6.70 (2H, br, $CONH_2$), 7.0—7.4 (5H, m, Ph), 7.60 [1H, s, H(2)]. *Anal.* Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93. Found: C, 64.07; H, 6.53; N, 23.03.

7-Benzyl-N^6-ethyladenine (**14f**): This was obtained as a colorless solid, mp 127—128.5 °C, and identified by comparison of the IR spectrum and TLC mobility with those of an authentic sample[10] prepared from 7-benzyl-9-ethyladeninium perchlorate (**15f**: X=ClO_4) by rearrangement.

Hydrolysis of 3-Benzyl-7-methyladenine Hydriodide (7g: X=I)——A mixture of **7g** (X=I)[3j] (3.67 g, 10 mmol) and 1 N aqueous NaOH (50 ml) was heated under reflux for 2 h. The reaction mixture was worked up as described above for the hydrolysis of **7c** (X=Br) under item (ii), but by using $CHCl_3$–EtOH (20 : 1, v/v) as the eluent for column chromatography. The results are summarized in Table I, and the products were characterized as follows.

4-(*N*-Benzylamino)-1-methyl-1*H*-imidazole-5-carboxamide (**8g**): This was recrystallized from EtOH to form colorless prisms, mp 174 °C (lit.[15] mp 170—171 °C); MS *m/z*: 230 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1670 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 3.71 [3H, s, N(1)-Me], 4.44 (2H, unresolved m, $NHC\underline{H}_2Ph$), 6.22 (1H, dull t, J=6 Hz, $N\underline{H}CH_2Ph$), 6.74 (2H, br, $CONH_2$), 7.0—7.35 (5H, m, Ph), 7.32 [1H, s, H(2)]. *Anal.* Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.50; H, 6.30; N, 24.35.

N^6-Benzyl-7-methyladenine (**14g**): This was recrystallized from EtOH to yield colorless prisms, mp 241—241.5 °C; MS *m/z*: 239 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 278 nm (ε 17100); $\lambda_{max}^{H_2O}$ (pH 1) 282 (20400); $\lambda_{max}^{H_2O}$ (pH 7) 277 (16600); $\lambda_{max}^{H_2O}$ (pH 13) 277 (16600); NMR (Me_2SO-d_6) δ: 4.08 [3H, s, N(7)-Me], 4.73 (2H, unresolved m, $NHC\underline{H}_2Ph$), 7.1—7.5 (6H, m, $N\underline{H}CH_2\underline{Ph}$), 8.18 and 8.21 (1H each, s, purine protons). *Anal.* Calcd for $C_{13}H_{13}N_5$: C, 65.26; H, 5.48; N, 29.27. Found: C, 65.48; H, 5.35; N, 29.44.

Hydrolysis of 3-Benzyl-7-ethyladenine Perchlorate (7h: X=ClO_4)——A mixture of **7h** (X=ClO_4)[3j] (1.06 g, 3 mmol) and 1 N aqueous NaOH (15 ml) was heated under reflux for 2 h. The reaction mixture was worked up as described above for the hydrolysis of **7c** (X=Br) under item (ii), but by using $CHCl_3$–EtOH (15 : 1, v/v) as the eluent for column chromatography. The results are summarized in Table I, and the products were characterized as follows.

4-(*N*-Benzylamino)-1-ethyl-1*H*-imidazole-5-carboxamide (**8h**): This was recrystallized from EtOH to give colorless needles, mp 167—167.5 °C; MS *m/z*: 244 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1635 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 1.24 [3H, t, J=7.1 Hz, N(1)-$CH_2\underline{Me}$], 4.16 [2H, q, J=7.1 Hz, N(1)-$C\underline{H}_2Me$], 4.40 (2H, unresolved m, $NHC\underline{H}_2Ph$), 6.07 (1H, t, J=6.1 Hz, $N\underline{H}CH_2Ph$), 7.1—7.4 (5H, m, Ph), 7.41 [1H, s, H(2)]. *Anal.* Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93. Found: C, 63.99; H, 6.61; N, 23.09.

N^6-Benzyl-7-ethyladenine (**14h**): This was obtained as a colorless solid, mp 182—184 °C (dec.), and identified by comparison of the IR spectrum and TLC mobility with those of authentic **14h** prepared from 6-chloro-7-ethylpurine (**12h**) and benzylamine (*vide infra*).

Hydrolysis of 3,7-Dibenzyladenine Hydrobromide (7i: X=Br)——Alkaline hydrolysis of **7i** (X=Br)[3j] and work-up of the reaction mixture were carried out as described above for the hydrolysis of **7f** (X=Br). The results are summarized in Table I, and the products were characterized as follows.

1-Benzyl-4-(*N*-benzylamino)-1*H*-imidazole-5-carboxamide (**8i**): This was recrystallized from EtOH to form slightly yellowish scales, mp 136.5—137.5 °C; MS *m/z*: 306 (M^+); UV (Table II); IR ν_{max}^{Nujol} 1670 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 4.44 (2H, unresolved m, $NHC\underline{H}_2Ph$), 5.41 [2H, s, N(1)-$C\underline{H}_2Ph$], 6.05 (1H, t, J=6 Hz, $N\underline{H}CH_2Ph$), 6.76 (2H, br, $CONH_2$), 7.0—7.4 (10H, m, Ph's), 7.60 [1H, s, H(2)]. *Anal.* Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.70; H, 5.82; N, 18.52.

N^6,7-Dibenzyladenine (**14i**): This was obtained as a colorless solid, mp 107—130 °C, and found to be identical (by comparison of the IR spectrum and TLC mobility) with authentic **14i**·H_2O synthesized from 7-benzyl-6-chloropurine (**12i**) and benzylamine (*vide infra*).

Synthesis of 4-Amino-1-methyl-1*H*-imidazole-5-carboxamide (11a) from 8g——A solution of **8g** (460 mg, 2 mmol) in MeOH (50 ml) was hydrogenated over 10% Pd–C (690 mg) at atmospheric pressure and 40 °C for 12 h. The catalyst was filtered off and washed with MeOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a pale brownish solid (256 mg, 91%), mp 171—172.5 °C (dec.). Recrystallization from EtOH gave an analytical sample of **11a** as colorless needles, mp 187—189 °C (dec.); MS *m/z*: 140 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 274 nm (ε 8800); $\lambda_{max}^{H_2O}$ (pH 1) 246 (sh) (6400), 267 (8600); $\lambda_{max}^{H_2O}$ (pH 7) 272 (9600); $\lambda_{max}^{H_2O}$ (pH 13) 272 (9600); IR ν_{max}^{Nujol} 1687 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 3.67 [3H, s, N(1)-Me], 5.12 (2H, br, NH_2), 6.71 (2H, br, $CONH_2$), 7.26 [1H, s, H(2)]. *Anal.* Calcd for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.64; H, 5.82; N, 40.09.

The perchlorate salt of **11a** was prepared by dissolving the base in a little EtOH and adding 70% aqueous $HClO_4$. The precipitate that resulted was filtered off and recrystallized from EtOH to give an analytical sample of **11a**·$HClO_4$ as colorless needles, mp 163—164 °C. *Anal.* Calcd for $C_5H_8N_4O \cdot HClO_4$: C, 24.96; H, 3.77; N, 23.29. Found: C, 25.06; H, 3.73; N, 23.50.

Synthesis of 4-Amino-1-ethyl-1*H*-imidazole-5-carboxamide (11e) from 8h——A solution of **8h** (24.43 g, 0.1 mol) and 70% aqueous $HClO_4$ (14.35 g, 0.1 mol) in MeOH (400 ml) was hydrogenated over 10% Pd–C (12 g) at atmospheric pressure and 20 °C for 11 h. The catalyst was removed by filtration, and the filtrate was concentrated to

dryness *in vacuo*. The residual solid was recrystallized from 1-butanol to give **11e**·$HClO_4$ (20.9 g, 82%) as slightly pinkish scales, mp 122—124 °C. Further recrystallization from 1-butanol yielded an analytical sample, mp 129—130 °C. *Anal.* Calcd for $C_6H_{10}N_4O \cdot HClO_4$: C, 28.30; H, 4.35; N, 22.00. Found: C, 28.39; H, 4.40; N, 21.89.

For preparation of the free base **11e**, a solution of **11e**·$HClO_4$ (509 mg, 2 mmol) in H_2O (10 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (5 ml), and the column was eluted with H_2O (200 ml). The eluate was concentrated to dryness *in vacuo* to leave a pale brownish solid (299 mg, 97%), mp 133—134 °C. Recrystallization from AcOEt afforded an analytical sample of **11e** as colorless prisms, mp 133—134 °C; MS *m/z*: 154 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 272 nm (ε 9000); $\lambda_{max}^{H_2O}$ (pH 1) 245 (sh) (6100), 266 (8100); $\lambda_{max}^{H_2O}$ (pH 7) 271 (9200); $\lambda_{max}^{H_2O}$ (pH 13) 272 (9300); IR ν_{max}^{Nujol} 1648 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 1.23 [3H, t, *J*=7 Hz, N(1)-CH_2Me], 4.15 [2H, q, *J*=7 Hz, N(1)-CH_2Me], 5.08 (2H, br, NH_2), 6.67 (2H, br, $CONH_2$), 7.36 [1H, s, H(2)]. *Anal.* Calcd for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.71; H, 6.46; N, 36.33.

Synthesis of N^6-Benzyl-7-ethyladenine (14h) from 6-Chloro-7-ethylpurine (12h)——A solution of **12h**[21] (365 mg, 2 mmol) and benzylamine (650 mg, 6 mmol) in 1-butanol (11 ml) was stirred at 100 °C for 4 h. The reaction mixture was concentrated *in vacuo*, and the residual oil was triturated with a little H_2O. The precipitate that resulted was filtered off, washed with H_2O, and dried to give **14h** (439 mg, 87%), mp 182.5—185 °C. Recrystallization from EtOH gave an analytical sample as colorless prisms, mp 184.5—185.5 °C; MS *m/z*: 253 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 278 nm (ε 15300); $\lambda_{max}^{H_2O}$ (pH 1) 282 (19900); $\lambda_{max}^{H_2O}$ (pH 7) 276 (15900); $\lambda_{max}^{H_2O}$ (pH 13) 276.5 (15900); NMR (Me_2SO-d_6) δ: 1.38 [3H, t, *J*=7.2 Hz, N(7)-CH_2Me], 4.49 [2H, q, *J*=7.2 Hz, N(7)-CH_2Me], 4.76 (2H, unresolved m, $NHCH_2Ph$), 7.0—7.6 (6H, m, $NHCH_2Ph$), 8.23 and 8.27 (1H each, s, purine protons). *Anal.* Calcd for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.31; H, 5.98; N, 27.71.

Synthesis of N^6,7-Dibenzyladenine (14i) from 7-Benzyl-6-chloropurine (12i)——A solution of **12i**[21] (122 mg, 0.5 mmol) and benzylamine (160 mg, 1.5 mmol) in 1-butanol (4 ml) was stirred at 100 °C for 2 h. The reaction mixture was concentrated *in vacuo* to leave a yellowish solid, which was triturated with hot AcOEt. The resulting mixture was filtered while hot. On cooling, the filtrate deposited a crystalline solid (116 mg, 70%), mp 107—130 °C. Recrystallization of this solid from AcOEt and drying over P_2O_5 at 3 mmHg and room temperature for 18 h produced **14i**·H_2O as colorless prisms, mp 107—130 °C (lit.[22] mp 118—132 °C); MS *m/z*: 315 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 279 nm (ε 15600); $\lambda_{max}^{H_2O}$ (pH 1) 283 (19600); $\lambda_{max}^{H_2O}$ (pH 7) 277 (15700); $\lambda_{max}^{H_2O}$ (pH 13) 277 (15700); NMR (Me_2SO-d_6) δ: 4.67 (2H, unresolved m, $NHCH_2Ph$), 5.79 [2H, s, N(7)-CH_2Ph], 6.8—7.4 [11H, m, $NHCH_2Ph$ and N(7)-CH_2Ph], 8.24 and 8.46 (1H each, s, purine protons). *Anal.* Calcd for $C_{19}H_{17}N_5 \cdot H_2O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.26; H, 5.80; N, 21.04.

Alkaline Hydrolysis of 3-Methyladenine (4a)——A mixture of 3-methyladenine (**4a**)[23] (895 mg, 6 mmol) and 1 N aqueous NaOH (30 ml) was heated under reflux for 50 min. After cooling, the reaction mixture was neutralized with 10% aqueous HCl and concentrated *in vacuo*. The residual solid was dried and extracted with hot AcOEt. The AcOEt extracts were concentrated to leave a greenish glass. Purification of this material by column chromatography [alumina, $CHCl_3$–EtOH (3 : 1, v/v)] gave 4-(*N*-methylamino)-1*H*-imidazole-5-carboxamide (**16**) (97 mg, 12%), which was recrystallized from EtOH–ether to afford an analytical sample as slightly purplish prisms, mp 182—183 °C (dec.); MS *m/z*: 140 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 239 nm (ε 5400), 280 (13100); $\lambda_{max}^{H_2O}$ (pH 1) 245 (9400), 283 (12900); $\lambda_{max}^{H_2O}$ (pH 7) 236 (5100), 281 (14200); $\lambda_{max}^{H_2O}$ (pH 13) 230 (sh) (4200), 289 (14200); IR ν_{max}^{Nujol} 1635 cm^{-1} ($CONH_2$); NMR (Me_2SO-d_6) δ: 2.82 (3H, s, NHMe), 5.91 (1H, br, NHMe), 6.63 (2H, br, $CONH_2$), 7.22 [1H, s, H(2)]. *Anal.* Calcd for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.71; H, 5.75; N, 39.69.

On the other hand, the insoluble solid, obtained when the above extraction with AcOEt was carried out, was extracted with hot EtOH. The ethanolic extracts were concentrated, and the residue was triturated with a little H_2O. The precipitate that resulted was filtered off and dried to give 3-methylhypoxanthine sesquihydrate (**3**·3/2H_2O) (124 mg, 12%) as a gray solid, mp >300 °C, which was identified by comparison of the IR spectrum and TLC behavior with those of authentic **3**·3/2H_2O.[16]

Reaction of N^6,9-Dimethyladenine (20) with Alkali——A mixture of **20**[3i,24] (80 mg, 0.49 mmol) and 1 N aqueous NaOH (5 ml) was heated under reflux for 30 min. The reaction mixture was neutralized with 1 N aqueous HCl (5 ml) and concentrated *in vacuo*. The residue[25] was dried and extracted with five 5-ml portions of boiling benzene. The benzene extracts were combined and concentrated to dryness, recovering the starting **20** as a colorless solid (72 mg, 90%), mp 184—185 °C (lit.[24] mp 185—186 °C).

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References and Notes

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