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3,9-Dialkylhypoxanthines[1)]

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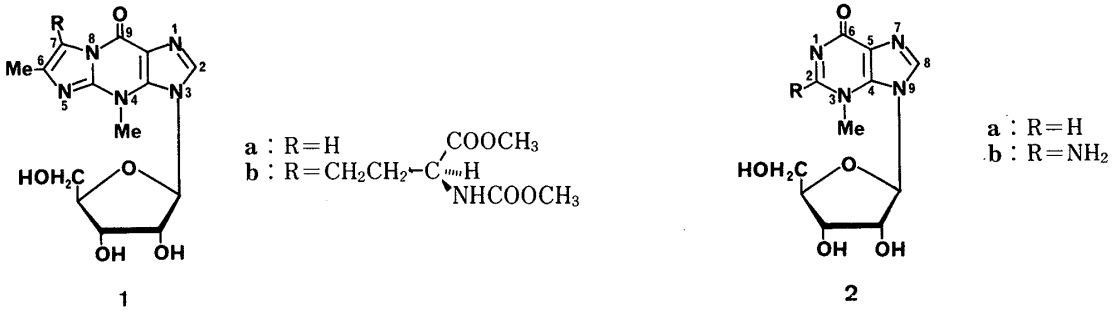
Reaction of 1-methyl-5-(methylamino)imidazole-4-carboxamide (**6a**) with a boiling mixture of ethyl orthoformate and acetic anhydride produced 3,9-dimethylhypoxanthine (**7a**) in 60% yield and 1-methyl-5-(*N*-methylformamido)imidazole-4-carboxamide (**5a**) in 39% yield. Compound **5a** was transformed into **7a** by treatment with NaH in 78% yield. Compound **7a** was alternatively prepared by cyclocondensation of **6a** with diethoxymethane followed by oxidation with I_2. The pyrimidine moiety of **7a** has been shown to be reactive: **7a** affords the 1,2-dihydro derivative **9** under reductive conditions and undergoes ring opening to **5a** in aqueous NaOH. 3-Ethyl-9-methyl- (**7b**), 3-benzyl-9-methyl- (**7c**), 9-ethyl-3-methyl- (**7d**), and 3,9-dibenzylhypoxanthine (**7e**) were also prepared from the corresponding carboxamides **6b**—**e**.

Keywords——3,9-dialkylhypoxanthine; cyclocondensation; base-promoted cyclization; 1,2-dihydrohypoxanthine; dihydropurine oxidation; purine reduction; pyrimidine ring cleavage

It is a unique feature of the putative structures **1a**, **b**[2-4)] for wyosine[2)] from *Torulopsis utilis* phenylalanine transfer ribonucleic acid (tRNA^{Phe}) and wybutosine[3)] from yeast tRNA^{Phe} that they have a 3-methylinosine (**2a**) or 3-methylguanosine (**2b**) partial structure. No natural occurrence of other 3-methyl-9-β-D-ribofuranosylpurines has been reported. In connection with the unusually labile glycosidic bonds of wyosine[2)] and wybutosine,[3b,c)] we have reported the syntheses and hydrolysis of various 3-alkyl-9-β-D-ribofuranosylpurines[4c,d,5)] and 3-β-D-ribofuranosylwye (**1a**).[4d)] In connection with the synthesis of 3-methylinosine (**2a**),[5a)] it is desirable to develop a synthetic method for hitherto unknown 3,9-dialkylhypoxanthines (**7**).



1 2

Chart 1

2′,3′-*O*-Isopropylidene-3,5′-cycloinosine,[6)] the first example of a 3,9-disubstituted hypoxanthine (type **7**), has been synthesized by intramolecular alkylation at the 3-position of 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-toluenesulfonyl)inosine. However, methylation of inosine has been reported to take place at the 1-,[7)] 7-,[7)] and O^6-position.[7b)] It has also been reported that alkylation of 9-alkylhypoxanthines occurs at the 1-position in the presence of base[8)] and at the 7-position in the absence of base.[9)] On the other hand, 3-benzylhypoxanthine has been reported to provide 3,7-[8b)] or 1,3-dibenzylhypoxanthine[10)] on benzylation with or without

K_2CO_3, respectively. Although Neiman and Bergmann claimed that 3,9-dimethylhypoxanthine (**7a**) was formed on the hydrolysis of 3,9-dimethyl-6-mercaptopurine with 50% nitric acid,[11] no evidence was given for the structure of the product. It thus appears that the most promising means of obtaining **7** is the cyclization of appropriately substituted imidazole or pyrimidine derivatives. 1-Alkyl-5-(alkylamino)imidazole-4-carboxamides (**6**)[10,12] seemed to be suitable for this purpose.

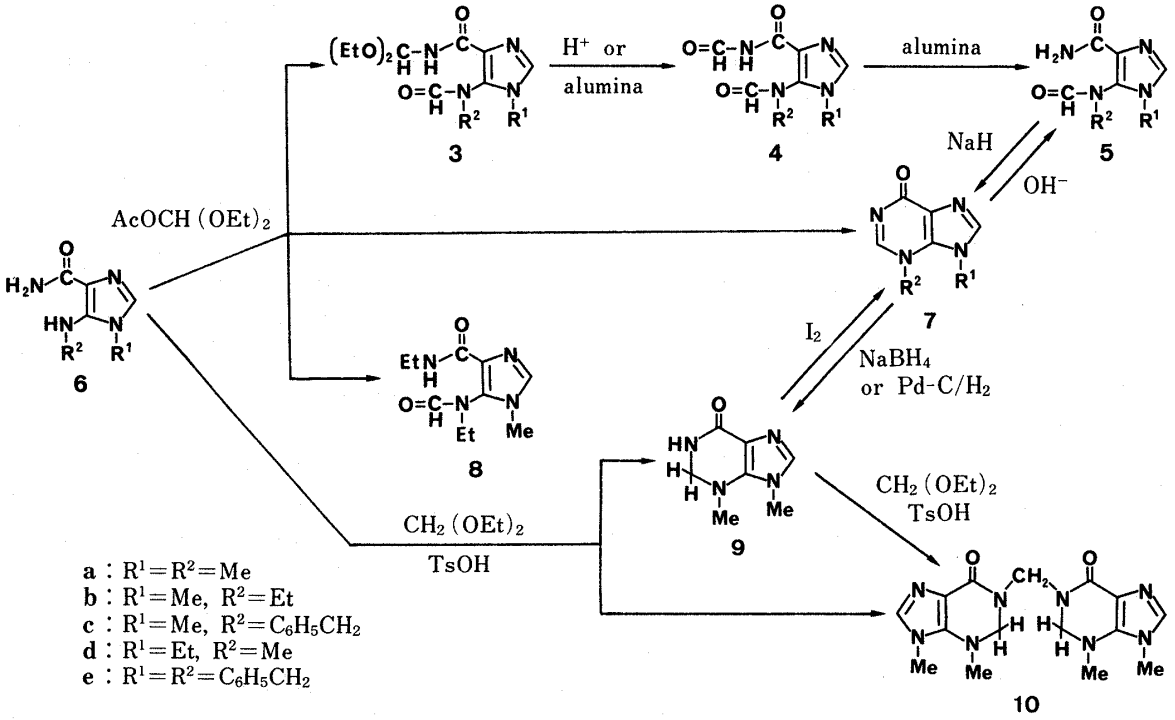


Chart 2

Although 1-benzyl-5-(benzylamino)imidazole-4-carboxamide (**6e**)[10,12b,c] was found to afford little 3,9-dibenzylhypoxanthine (**7e**) on treatment with various reagents,[10] the synthesis of **7a** was achieved in this work by heating 1-methyl-5-(methylamino)imidazole-4-carboxamide (**6a**)[12] in refluxing diethoxymethyl acetate[10,13] in 74% yield. *N*-Diethoxymethyl-1-methyl-5-(*N*-methylformamido)imidazole-4-carboxamide (**3a**), *N*-formyl-1-methyl-5-(*N*-methylformamido)imidazole-4-carboxamide (**4a**), and 1-methyl-5-(*N*-methylformamido)imidazole-4-carboxamide (**5a**) were also isolated in 5.9%, 1.7%, and 5.4% yields, respectively. We prefer the structure **3a** to an alternative, *N*-formyl-5-[(diethoxymethyl)amino]-1-methylimidazole-4-carboxamide, on the basis of the nuclear magnetic resonance (NMR) spectrum, which shows the methine proton at 5.99 ppm as a doublet due to interaction with the adjacent NH group. On treatment with acetic acid or alumina, **3a** changed into **4a**, which in turn decomposed to **5a** on further treatment with alumina. Compound **7a** was alternatively prepared by heating **6a** in a mixture of ethyl orthoformate and acetic anhydride in 60% yield, together with **5a**, which was obtained in 39% yield after treatment of the rest of the products with alumina. Compound **5a** was heated at 260 °C with the aim of obtaining an additional crop of **7a** to afford **7a** in only 20% yield. However, treatment of **5a** with NaH in Me_2NCHO gave **7a** in 78% yield. Thus, the total yield of **7a** from **6a** reached 90%. The structure of **7a** was supported by elemental analyses, the NMR spectrum, and by the ultraviolet (UV) spectral similarity to 2′,3′-*O*-isopropylidene-3,5′-cycloinosine.[6] Furthermore, it was confirmed by the chemical transformations described below. The UV-absorption characteristic reported for "3,9-dimethylhypoxanthine" by

Neiman and Bergmann[11] differs from that of the present sample of **7a**.

Compound **7a** was found to be subject to nucleophilic attack of OH^- at the 2-position to give the ring-opened product **5a** exclusively under alkaline conditions. Similar facile ring-opening of the pyrimidine moiety has been reported with 3,9-disubstituted adenines; however, these compounds equilibrate with the ring-opened derivatives.[12c,14] High reactivity of the pyrimidine ring of **7a** was also observed under reductive conditions. When **7a** was treated with $NaBH_4$, 1,2-dihydro-3,9-dimethylhypoxanthine (**9**) was produced in 72% yield. The same compound was obtained in 77% yield by catalytic hydrogenation of **7a** over Pd–C. The susceptibility of **7a** to reduction is interesting in comparison with the properties of 3,9-dialkyladenine salts.[12c,14b,15] These compounds have been reported to give the 1,2-dihydro derivatives on treatment with $NaBH_4$,[16] but may be considered to be fairly stable under the conditions of catalytic hydrogenation.[15] The 1,2-dihydro structure for **9** was unequivocally determined by direct comparison with a sample of **9**, which was obtained in 51% yield by the reaction of **6a** with an equimolar amount of diethoxymethane in the presence of *p*-toluenesulfonic acid. In this reaction, **7a** and bis(1,2-dihydro-3,9-dimethylhypoxanthin-1-yl)methane (**10**) were also obtained in 10% and 8.5% yields, respectively. Compound **10** was produced in 40% yield on treatment of **9** with diethoxymethane under similar conditions. Treatment of **9** with I_2 gave **7a** in 30% yield, providing an alternative route for the synthesis of **7a** from **6a**, though the overall yield was no more than 25%.

3-Ethyl-9-methyl- (**7b**), 3-benzyl-9-methyl- (**7c**), 9-ethyl-3-methyl- (**7d**), and 3,9-dibenzylhypoxanthine (**7e**) were synthesized in 37%—62% yield by treatment of **6b**—**e**[10,12b,c] with a mixture of triethyl orthoformate and acetic anhydride in a manner similar to that used for the synthesis of **7a**. Structural assignment of these compounds rested on elemental analyses, NMR spectroscopy, and UV spectral similarity to **7a**. In the case of the reaction of **6b**[12b,c] with diethoxymethyl acetate, careful separation of the products gave *N*-ethyl-5-(*N*-ethylformamido)-1-methylimidazole-4-carboxamide (**8**) in 4.1% yield besides *N*-diethoxymethyl-5-(*N*-ethylformamido)-1-methylimidazole-4-carboxamide (**3b**), 5-(*N*-ethylformamido)-*N*-formyl-1-methylimidazole-4-carboxamide (**4b**), 5-(*N*-ethylformamido)-1-methylimidazole-4-carboxamide (**5b**), and **7b**. The mass spectrum (MS) and the NMR spectrum of this compound were consistent with the structure **8**. Probably **8** was formed by migration of ethyl group to **6b** from the reagent prior to formylation. The formation of **8** and **3** suggests that the amido group of **6** has a considerably nucleophilic character. Similar

TABLE I. UV Absorbance Data for N^x, N^y-Dibenzylhypoxanthines in H_2O

Compound	UV spectra					
	pH 1		pH 7		pH 13	
	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
1,3-Dibenzylhypoxanthinium bromide[a]	254	10.2	245 (sh)	9.4	Unstable	
	280 (sh)	3.92	304 (sh)	0.51		
1,7-Dibenzylhypoxanthine	257	8.25[a]	257	7.57[a]	256	7.83[a]
	255	8.8[b]	256	8.4[b]	256	8.4[b]
1,9-Dibenzylhypoxanthine	252	11.3[a]	253	11.2[a]	252	11.1[a]
	253	10.6[b]	252	10.4[b]	252	10.4[b]
3,7-Dibenzylhypoxanthine[b]	256	10.1	266	11.8	267	11.7
3,9-Dibenzylhypoxanthine	256	12.1	261	13.8	Unstable	
7,9-Dibenzylhypoxanthinium bromide[a]	256	10.8	268	9.2	Unstable	

a) Taken from ref. 10. *b*) Taken from ref. 8*b*.

reactivity of the amido group of **6** has been observed in the ethoxycarbonylation of **6a**.[5b]

Among the six possible N^x,N^y-dibenzylhypoxanthines, 3,9-dibenzyl isomer (**7e**) is the last one. The isomers are readily distinguishable from each other by means of UV spectroscopy, as shown in Table I. Thus the data given in Table I are useful for identification of the positions of disubstitution on hypoxanthine.

Experimental

General Notes——All melting points are corrected. Alumina was obtained from Merck (Art. 1097). See ref. 12*b* for details of instrumentation and measurements. Microanalyses 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.

3,9-Dimethylhypoxanthine (7a)——i) A mixture of **6a**[12] (694 mg, 4.5 mmol) and diethoxymethyl acetate[10,13] (10 ml) was refluxed for 1 h and cooled. The resulting precipitate was filtered off, washed with EtOH (3 × 2 ml), and dried over P_2O_5 at 2 mmHg and 110 °C for 2 h to give **7a** (546 mg, 74% yield) as a colorless solid, mp > 300 °C.

The combined filtrate and washings were concentrated *in vacuo* to leave a brown oil (605 mg). This was subjected to alumina (30 g) column chromatography. Elution with $CHCl_3$ gave a mixture of **3a** and **4a** as a slightly yellow oil. Further elution with $CHCl_3$–EtOH (8 : 1, v/v) gave **5a** (44 mg, 5.4% yield) as a colorless solid, identical with an authentic sample described below. The mixture of **3a** and **4a** was purified on a silica gel (25 g) column with C_6H_6–EtOH (5 : 1, v/v) as an eluent to provide a mixture of **3a** and **4a** (37 mg) as a colorless oil and chromatographically pure **3a** (76 mg, 5.9% yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6H, t, J = 7 Hz, $2C\underline{H}_3CH_2$'s), 3.20 and 3.41 (a total of 3H, s, N^5-CH_3), 3.55 and 3.48 (a total of 3H, s, $N_{(1)}$-CH_3), 3.65 and 3.67 (a total of 4H, q, $2CH_2$'s), 5.99 [1H, d, J = 8 Hz, changed into s on addition of D_2O, $C\underline{H}(OEt)_2$], 7.41 and 7.38 (a total of 1H, s, $C_{(2)}$-H), 7.69 (1H, d, J = 8 Hz, NH), 8.15 and 8.27 (a total of 1H, s, CHO).[17] The mixture of **3a** and **4a** obtained by the chromatography on silica gel was dissolved in EtOH (1 ml) and AcOH (2 drops) was added to the solution. The mixture was then concentrated *in vacuo* to leave a solid residue, which was washed with a little AcOEt to give **4a** (16 mg, 1.7%) as colorless pillars, identical with an authentic sample described below.

The crude **7a** was recrystallized from MeOH and dried over P_2O_5 at 2 mmHg and 110 °C for 8 h to give an analytical sample as colorless needles, mp > 300 °C. UV $\lambda_{max}^{95\%\ EtOH}$ 258 nm (ε 10900); $\lambda_{max}^{H_2O}$ (pH 1) 255 (10400); $\lambda_{max}^{H_2O}$ (pH 7) 261 (12200); $\lambda_{max}^{H_2O}$ (pH 13) unstable. ^{1}H-NMR (D_2O) δ: 4.08 and 4.12 (3H each, s, $2CH_3$'s), 7.80 and 8.06 (1H each, s, purine protons). *Anal.* Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.05; H, 4.88; N, 34.10.

The picrate of **7a** was prepared by treatment of an aqueous solution of **7a** with a saturated solution of picric acid in H_2O. Recrystallization from MeOH gave an analytical sample as yellow needles, mp 190—191 °C (dec.). *Anal.* Calcd for $C_{13}H_{11}N_7O_8$: C, 39.70; H, 2.82; N, 24.93. Found: C, 39.69; H, 2.80; N, 25.19.

ii) A mixture of ethyl orthoformate (5 ml) and acetic anhydride (2 ml) was heated under reflux for 1 h. Compound **6a**[12] (500 mg, 3.24 mmol) was added to the mixture and the whole was refluxed for 1 h then cooled. The resulting precipitate was collected by filtration, washed successively with acetic anhydride (2 × 1 ml) and EtOH (3 × 1 ml), and dried over P_2O_5 at 2 mmHg and 110 °C for 2 h to afford **7a** (317 mg, 60% yeild) as a colorless solid, mp > 300 °C, identical with the authentic sample described above.

The combined filtrate and washings were concentrated *in vacuo* and the resulting semi-solid was adsorbed on alumina (10 g). The mixture was placed on top of a column of alumina (15 g) and the column was eluted with $CHCl_3$–EtOH (8 : 1, v/v). The eluate containing a single component was collected and concentrated to leave a solid, which was washed with EtOH (2 × 2 ml) and dried to give **5a** (230 mg, 39% yield), identical with an analytical sample described below.

iii) Compound **5a** (36 mg, 0.2 mmol) was suspended in Me_2NCHO (1 ml) and 50% NaH (10 mg, 0.21 mmol) was added. The mixture was stirred at room temperature for 30 min and then poured into cold 10% aqueous AcOH (0.5 ml). The resulting mixture was concentrated *in vacuo* to leave a solid. This was purified by chromatography on silica gel (5 g) with MeOH. The eluate containing **7a** was concentrated *in vacuo* and the resulting solid was dried over P_2O_5 at 2 mmHg and 110 °C for 4 h to give **7a** (25 mg, 78% yield), identical with the analytical sample described above.

iv) Heating of **5a** (50 mg, 0.27 mmol) at 260 °C for 30 min gave a deep brown solid. This was dissolved in hot MeOH (8 ml) and the solution was filtered. The filtrate was concentrated *in vacuo* to leave a solid, which was washed with EtOH (2 × 2 ml), and dried over P_2O_5 at 2 mmHg and 100 °C for 2 h to tive **7a** (9 mg, 20% yield) as a colorless solid, identical with the analytical sample described above.

v) A solution of I_2 (266 mg, 1.05 mmol) in MeOH (10 ml) was added to a solution of **9** (166 mg, 1 mmol) in MeOH (5 ml) and the mixture was allowed to stand at room temperature overnight. It was then concentrated *in vacuo* to leave a deep brown solid. Aqueous MeOH was added to the residue and the solution was concentrated again *in vacuo*. This operation was repeated until a colorless residue was obtained. An aqueous solution of the residue was

passed through a column of Amberlite IRA-402 (HCO_3^-) (2 ml) and the column was eluted with H_2O (50 ml). The eluate was concentrated *in vacuo* and the resulting solid was chromatographed on silica gel (5 g). Elution with MeOH gave unchanged **9** (85 mg, 51% recovery). Further elution with MeOH gave **7a** (50 mg, 30% yield), identical with the analytical sample described above, after drying over P_2O_5 at 2 mmHg and 110 °C for 4 h.

***N*-Formyl-1-methyl-5-(*N*-methylformamido)imidazole-4-carboxamide (4a)**——AcOH (3 drops) was added to a solution of **3a** (76 mg, 0.27 mmol) in MeOH (3 ml). The mixture was allowed to stand at room temperature for 10 min and then concentrated *in vacuo* to leave a solid. This was washed with a little AcOEt–MeOH (1 : 1, v/v) to give **4a** (34 mg, 61% yield), mp *ca.* 200 °C. Recrystallization from C_6H_6–AcOEt (1 : 1, v/v) gave an analytical sample as colorless pillars, mp 197—200 °C (sinters below the mp). UV $\lambda_{max}^{95\%\ EtOH}$ 263 nm (ε 10500); $\lambda_{max}^{H_2O}$ (pH 1) 218 (14500), 264 (9800); $\lambda_{max}^{H_2O}$ (pH 7) 217 (14800), 264 (10800); $\lambda_{max}^{H_2O}$ (pH 13) 239 (8200). MS *m/e*: 210 (M^+), 182 ($M^+ - CO$). ^{1}H-NMR (Me_2SO-d_6) δ: 3.11 and 3.34 (3 × 2/3H and 3 × 1/3H, s, N^5-CH_3), 3.62 and 3.52 (3 × 2/3H and 3 × 1/3H, s, $N_{(1)}$-CH_3), 7.95 (1H, s, $C_{(2)}$-H), 8.19 and 8.39 (2/3H and 1/3H, s, $CH_3NC\underline{H}O$), 9.16 (s, *cis*-NHC$\underline{H}$O) and 9.17 (d, J=9 Hz, *trans*-HNC$\underline{H}$O) (a total of 1H), 10.73 (1H, br, NH).[17] *Anal.* Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.74; H, 5.04; N, 26.67.

1-Methyl-5-(*N*-methylformamido)imidazole-4-carboxamide (5a)——i) A solution of **7a** (82 mg, 0.5 mmol) in 0.1 N NaOH (50 ml) was allowed to stand at room temperature for 10 min and then brought to pH 8 with 10% hydrochloric acid. The mixture was concentrated *in vacuo* and the resulting solid was extracted with hot MeOH (30 ml). MeOH was removed by evaporation and the residue was recrystallized from MeOH to give **5a** (70 mg, 77% yield), mp 238—242 °C. Further recrystallization from MeOH gave an analytical sample as colorless prisms, mp 244—245 °C. UV $\lambda_{max}^{95\%\ EtOH}$ 234 nm (sh) (ε 8500); $\lambda_{max}^{H_2O}$ (pH 1) no specific point; $\lambda_{max}^{H_2O}$ (pH 7) 239 (8100); $\lambda_{max}^{H_2O}$ (pH 13) 239 (8100). ^{1}H-NMR (Me_2SO-d_6) δ: 3.05 and 3.28 (3 × 3/4H and 3 × 1/4H, s, N^5-CH_3), 3.53 and 3.42 (3 × 3/4H and 3 × 1/4H, s, $N_{(1)}$-CH_3), 7.16 and 7.34 (1H each, br, NH_2), 7.72 and 7.70 (3/4H and 1/4H, s, $C_{(2)}$-H), 8.06 and 8.29 (3/4H and 1/4H, s, CHO).[17] *Anal.* Calcd for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.52; N, 30.76. Found: C, 46.00; H, 5.55; N, 30.73.

ii) A solution of **4a** (8 mg) in $CHCl_3$ (1 ml) was stirred with alumina (200 mg) at 40 °C for 1 h. The starting material disappeared completely and **5a** was found to form as a sole product. The alumina was filtered off and washed with $CHCl_3$–EtOH (10 : 1, v/v). The combined filtrate and washings were concentrated *in vacuo* to leave a solid, which was washed with EtOH to give **5a**, mp 243—245 °C, identical with the analytical sample described above.

1,2-Dihydro-3,9-dimethylhypoxanthine (9)——i) Compound **7a** (164 mg, 1 mmol) was hydrogenated over 10% Pd–C (150 mg) in AcOH (20 ml) at room temperature and atmospheric pressure for 3 h. The catalyst was filtered off and washed with AcOH (10 ml). The combined filtrate and washings were concentrated *in vacuo* to leave a partly crystallized residue. Recrystallization from MeOH (0.5 ml) gave **9** (44 mg), mp 195—198 °C (dec.). The mother liquor was chromatographed on a silica gel (10 g) column, which was eluted with MeOH to afford a second crop (83 mg, total yield 77%), mp 189—196 °C (dec.). Recrystallization from EtOH gave an analytical sample as colorless prisms, mp 200—201.5 °C (dec.). UV $\lambda_{max}^{95\%\ EtOH}$ 267 nm (ε 4800); $\lambda_{max}^{H_2O}$ (pH 1) 267 (4200); $\lambda_{max}^{H_2O}$ (pH 7) 269 (4900); $\lambda_{max}^{H_2O}$ (pH 13) 269 (4900). MS *m/e*: 166 (M^+). ^{1}H-NMR (Me_2SO-d_6) δ: 2.74 (3H, s, $N_{(3)}$-CH_3), 3.67 (3H, s, $N_{(9)}$-CH_3), 4.38 (2H, br, changed into s on addition of D_2O, CH_2), 7.18 (1H, br, NH), 7.49 (1H, s, $C_{(8)}$-H). *Anal.* Calcd for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.72. Found: C, 50.47; H, 6.11; N, 33.84.

ii) To a suspension of **7a** (246 mg, 1.5 mmol) in MeOH (15 ml) was added $NaBH_4$ (57 mg, 1.5 mmol) and the mixture was stirred at room temperature for 1 h. The resulting solution was treated with acetone (2 drops) and then neutralized with 10% hydrochloric acid. The mixture was concentrated *in vacuo* to leave a partly crystallized oily residue. This was dissolved in H_2O (5 ml) and the solution was extracted with $CHCl_3$ using a continuous extractor. The extracts were concentrated *in vacuo* to leave a partly crystallized residue. Recrystallization from EtOH gave **9** (180 mg, 72% yield) as colorless prisms, mp 201 °C (dec., sinters below the mp), identical with the analytical sample described above.

iii) Compound **6a**[12] (463 mg, 3 mmol) and diethoxymethane (312 mg, 3 mmol) were dissolved in 1 M *p*-toluenesulfonic acid solution in AcOH (45 ml) and the solution was kept at 30 °C for 168 h. The resulting yellow solution was concentrated *in vacuo* to leave a yellow oil. This was dissolved in H_2O (90 ml) and the solution was passed through a column of Amberlite IRA-402 (AcO^-) (90 ml). The column was eluted with H_2O (900 ml) until the eluate became neutral. The combined eluate was concentrated *in vacuo* to leave a partly crystallized residue. This was triturated with $CHCl_3$ (30 ml) and the precipitate was collected by filtration to afford **7a** (51 mg, 10% yield), identical with the analytical sample described above. The $CHCl_3$ solution was concentrated *in vacuo*. Repeated chromatography of the residue on alumina using $CHCl_3$–EtOH as the eluant gave **9** (253 mg, 51% yield), identical with the analytical sample described above, and **10** (46 mg, 8.5% yield) as the monohydrate, mp 277—278 °C (dec.), identical with an analytical sample described below.

Bis(1,2-dihydro-3,9-dimethylhypoxanthin-1-yl)methane (10)——A mixture of **9** (166 mg, 1 mmol), diethoxymethane (128 mg, 1.23 mmol), and 1 M solution of *p*-toluenesulfonic acid in AcOH (1.5 ml) was kept at 30 °C for 24 h. The solution was then diluted with H_2O (20 ml) and brought to pH 8 by addition of Na_2CO_3. The mixture was extracted with $CHCl_3$ (10 × 10 ml). The combined extracts were dried over $MgSO_4$ and removal of the solvent by evaporation left a colorless solid, which was recrystallized from EtOH to give **10** (72 mg, 40% yield) as colorless needles, mp 277—279 °C (dec.). Further recrystallization and drying over P_2O_5 at 2 mmHg and 50 °C

for 22 h gave an analytical sample having unchanged mp. UV $\lambda_{max}^{95\%\ EtOH}$ 271 nm (ε 10600); $\lambda_{max}^{H_2O}$ (pH 1) 226 (15600), 272 (9500); $\lambda_{max}^{H_2O}$ (pH 7) 273 (10800); $\lambda_{max}^{H_2O}$ (pH 13) 273 (10700). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (2H, s, H_2O), 2.75 (6H, s, $N_{(3)}$- and $N_{(3')}$-CH_3), 3.55 (6H, s, $N_{(9)}$- and $N_{(9')}$-CH_3), 4.86 (4H, s, $C_{(2)}$- and $C_{(2')}$-H_2), 5.12 (2H, s, $N_{(1)}$-CH_2-$N_{(1')}$), 7.28 (2H, s, $C_{(8)}$- and $C_{(8')}$-H). *Anal.* Calcd for $C_{15}H_{20}N_8O_2 \cdot H_2O$: C, 49.71; H, 6.12; N, 30.92. Found: C, 49.92; H, 6.06; N, 31.02.

3-Ethyl-9-methylhypoxanthine (7b)——i) A mixture of 5-(ethylamino)-1-methylimidazole-4-carboxamide (**6b**)[12b,c] (757 mg, 4.5 mmol) and diethoxymethyl acetate[10,13] (10 ml) was heated under reflux for 1 h and cooled. The resulting precipitate was filtered off, washed with AcOEt (3 × 2 ml), and then dried over P_2O_5 at 2 mmHg and 110 °C for 3 h to give **7b** (147 mg, 18% yield), mp 260—266 °C.

The combined filtrate and washings were concentrated *in vacuo* to leave a red oil. This was chromatographed on alumina (40 g). Elution with $CHCl_3$ (110 ml) gave a mixture of **3b**, **4b**, and **8** as a yellow oil (0.4 g). Further elution with $CHCl_3$–EtOH (8 : 1, v/v) gave **5b** (16 mg, 1.8% yield), mp 213—215 °C.

Separation of the mixture was performed on a silica gel (30 g) column. Elution with $CHCl_3$–EtOH (10 : 1, v/v) gave a mixture of **3b** and **4b** as an oil (315 mg) and **8** (41 mg, 4.1% yield) as the more polar substance, mp 120—121 °C. MS *m/e*: 224 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.14 and 1.22 (3H each, t, $2CH_3CH_2$'s), 3.35 (2H, m, $NHCH_2CH_3$), 3.52 and 3.48 (3 × 3/5H and 3 × 2/5H, s, $N_{(1)}$-CH_3), 3.5—4.2 (2H, m, N^5-CH_2CH_3), 7.05 (1H, br, NH), 7.40 and 7.38 (3/5H and 2/5H, s, $C_{(2)}$-H), 8.11 and 8.30 (3/5H and 2/5H, s, CHO).[17]

The mixture of **3b** and **4b** was further purified on a silica gel (30 g) column, developed with C_6H_6–EtOH (5 : 1, v/v). The less polar substance **3b** (256 mg, 19% yield) was obtained as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J = 7 Hz, CH_3CH_2N), 1.24 (6H, t, J = 7 Hz, $2CH_3CH_2O$'s), 3.55 and 3.51 (3 × 3/5H and 3 × 2/5H, s, $N_{(1)}$-CH_3), 3.3—4.1 (6H, m, $3CH_2$'s), 6.01 and 5.98 [3/5H and 2/5H, d, J = 8 Hz, changed into s on addition of D_2O, $CH(OEt)_2$], 7.44 and 7.42 (3/5H and 2/5H, s, $C_{(2)}$-H), 7.70 (1H, d, J = 8 Hz, NH), 8.11 and 8.30 (3/5H and 2/5H, s, CHO).[17] Compound **4b** (23 mg, 2.3% yield) was obtained as the more polar substance as a colorless solid, identical with an analytical sample described below.

Compound **7b** was recrystallized from EtOH and dried over P_2O_5 at 2 mmHg and 100 °C for 8 h to give an analytical sample as colorless needles, mp 265—268 °C. UV $\lambda_{max}^{95\%\ EtOH}$ 258 nm (ε 10500); $\lambda_{max}^{H_2O}$ (pH 1) 255 (10300); $\lambda_{max}^{H_2O}$ (pH 7), 261 (11900); $\lambda_{max}^{H_2O}$ (pH 13) unstable. ^{1}H-NMR (Me_2SO-d_6) δ: 1.41 (3H, t, J = 7 Hz, CH_3CH_2), 3.98 (3H, s, N-CH_3), 4.36 (2H, q, J = 7 Hz, CH_2), 7.85 and 8.18 (1H each, s, purine protons). *Anal.* Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.63; H, 5.84; N, 31.34.

Compound **5b** was recrystallized from Me_2CHOH to give an analytical sample as colorless pillars, mp 214—215 °C. UV $\lambda_{max}^{95\%\ EtOH}$ 234 nm (sh) (ε 8200); $\lambda_{max}^{H_2O}$ (pH 1) no specific point; $\lambda_{max}^{H_2O}$ (pH 7) 240 (8200); $\lambda_{max}^{H_2O}$ (pH 13) 240 (8200). ^{1}H-NMR (Me_2SO-d_6) δ: 0.99 and 1.04 (3 × 2/3H and 3 × 1/3H, t, J = 7 Hz, CH_3CH_2), 3.54 and 3.44 (3 × 2/3H and 3 × 1/3H, s, N–CH_3), 3.62 and 3.82 (a total of 2H, q, J = 7 Hz, CH_2), 7.10 and 7.28 (1H each, br, NH_2), 7.73 and 7.70 (a total of 1H, s, $C_{(2)}$-H), 8.01 and 8.31 (2/3H and 1/3H, s, CHO).[17] *Anal.* Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.17; N, 28.56. Found: C, 49.06; H, 6.47; N, 28.31.

ii) Compound **6b**[12b,c] (200 mg, 1.19 mmol) was treated with a preheated mixture of ethyl orthoformate (2 ml) and acetic anhydride (0.75 ml) as described under method (ii) for the preparation of **7a**. The resulting precipitate was filtered off, washed successively with AcOEt (3 ml) and AcOEt–EtOH (1 : 1, v/v) (2 ml), and dried over P_2O_5 at 2 mmHg and 100 °C for 3 h to give **7b** (102 mg, 48% yield), mp 265—266 °C, identical with the analytical sample described above. The combined filtrate and washings were concentrated *in vacuo* to leave an oil. This was treated with alumina in a manner similar to that described under method (ii) for **7a** to provide crude **5b** (116 mg). Recrystallization from EtOH gave pure **5b** (74 mg, 32% yield), identical with the analytical sample described above.

5-(*N*-Ethylformamido)-*N*-formyl-1-methylimidazole-4-carboxamide (4b)——AcOH (0.2 ml) was added to a solution of **3b** (223 mg, 0.747 mmol) in EtOH (3 ml) and the mixture was kept at 50 °C for 10 min. It was then concentrated *in vacuo* and the residue was washed with hexane–EtOH (8 : 1, v/v) (2 ml) to give **4b** (140 mg, 83% yield), mp 150—156 °C. Recrystallization from C_6H_6 gave an analytical sample as colorless minute crystals, mp 155—158 °C (sinters below the mp). UV $\lambda_{max}^{95\%\ EtOH}$ 264 nm (ε 11000); $\lambda_{max}^{H_2O}$ (pH 1) 219 (15000), 264 (10100); $\lambda_{max}^{H_2O}$ (pH 7) 219 (15200), 265 (11000); $\lambda_{max}^{H_2O}$ (pH 13) 240 (8400). MS *m/e*: 224 (M^+), 196 ($M^+ - CO$). ^{1}H-NMR (Me_2SO-d_6) δ: 1.00 and 1.06 (3 × 2/3H and 3 × 1/3H, t, J = 7 Hz, CH_3CH_2), 3.61 and 3.52 (3 × 2/3H and 3 × 1/3H, s, N–CH_3), 3.4—4.0 (2H, m, CH_2), 7.97 (1H, s, $C_{(2)}$-H), 8.15 and 8.45 (2/3H and 1/3H, s, EtNCHO), 9.17 (s, *cis*-NHCHO) and 9.18 (d, J = 9 Hz, *trans*-NHCHO) (a total of 1H), 10.70 (1H, br, NH).[17] *Anal.* Calcd for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.15; H, 5.49; N, 24.86.

3-Benzyl-9-methylhypoxanthine (7c)——5-(Benzylamino)-1-methylimidazole-4-carboxamide (**6c**)[12b,c] (1.00 g, 4.34 mmol) was heated under reflux for 40 min in a mixture of ethyl orthoformate (10 ml) and acetic anhydride (3.75 ml), which had previously been refluxed for 1 h. The mixture was allowed to cool, and the resulting precipitate was collected by filtration, washed with EtOH (3 ml), and dried to give **7c** (480 mg, 46% yield), mp 230—254 °C. Recrystallization from EtOH gave an analytical sample as colorless prisms, mp 252—254 °C (sinters below the mp). UV $\lambda_{max}^{95\%\ EtOH}$ 258 nm (ε 11700); $\lambda_{max}^{H_2O}$ (pH 1) 255 (10700); $\lambda_{max}^{H_2O}$ (pH 7) 261 (12600); $\lambda_{max}^{H_2O}$ (pH 13) unstable. ^{1}H-NMR (Me_2SO-d_6) δ: 3.69 (3H, s, CH_3), 5.69 (2H, s, CH_2), 7.15 and 7.39 (2H and 3H, m, C_6H_5), 7.78 and 8.34 (1H each, s, purine protons). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.88; H, 5.14; N, 23.47.

The combined filtrate and washings were concentrated *in vacuo* and the residue was treated with alumina in a manner similar to that described under method (ii) for **7a** to give **5c** (243 mg, 22% yield), mp 195—210 °C. Recrystallization from EtOH gave an analytical sample as colorless pillars, mp 219—220 °C. UV $\lambda_{max}^{95\%\ EtOH}$ 235 nm (sh) (ε 8900); $\lambda_{max}^{H_2O}$ (pH 1) no specific point; $\lambda_{max}^{H_2O}$ (pH 7) 241 (8400); $\lambda_{max}^{H_2O}$ (pH 13) 241 (8400). ^{1}H-NMR (Me_2SO-d_6) δ: 3.15 and 2.88 (3 × 3/5H and 3 × 2/5H, s, CH_3), 4.82 (2 × 3/5H, br, 3/5CH_2), 4.82 and 5.08 (2 × 1/5H each, AB type d, J = 14 Hz, 2/5CH_2), 7.23 (5H, s, C_6H_5), 7.57 and 7.51 (3/5H and 2/5H, s, $C_{(2)}$-H), 8.20 and 8.58 (3/5H and 2/5H, s, CHO).[17] *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.37; H, 5.44; N, 21.90.

9-Ethyl-3-methylhypoxanthine (7d)——1-Ethyl-5-(methylamino)imidazole-4-carboxamide (**6d**)[12b,c] (841 mg, 5 mmol) was treated with a preheated mixture of ethyl orthoformate (8 ml) and acetic anhydride (3 ml) in the same way as described under method (ii) for **7a**. The resulting precipitate was filtered off, washed with EtOH (2 ml), and dried over P_2O_5 at 2 mmHg and 110 °C for 2 h to afford **7d** (553 mg, 62% yield), mp 257—258.5 °C (dec.). Recrystallization from EtOH gave an analytical sample as colorless plates, mp 260—261 °C (dec.). UV $\lambda_{max}^{95\%\ EtOH}$ 256 nm (ε 11100); $\lambda_{max}^{H_2O}$ (pH 1) 254 (10500); $\lambda_{max}^{H_2O}$ (pH 7) 260 (12100); $\lambda_{max}^{H_2O}$ (pH 13) unstable. ^{1}H-NMR (Me_2SO-d_6) δ: 1.42 (3H, t, J = 7 Hz, CH_3CH_2), 3.95 (3H, s, N–CH_3), 4.37 (2H, q, J = 7 Hz, CH_2), 7.92 and 8.09 (1H each, s, purine protons). *Anal.* Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 54.17; H, 5.77; N, 31.22.

The combined filtrate and washings were concentrated *in vacuo* to leave a yellow oil (0.34 g). This was purified by preparative layer chromatography on alumina, developed with C_6H_6–EtOH (5 : 1, v/v), to give **5d** (130 mg, 13% yield), mp 190—192 °C. Recrystallization from EtOH gave an analytical sample as colorless needles, mp 195—196 °C. UV $\lambda_{max}^{95\%\ EtOH}$ 232 nm (sh) (ε 8800); $\lambda_{max}^{H_2O}$ (pH 1) no specific point; $\lambda_{max}^{H_2O}$ (pH 7) 238 (8800); $\lambda_{max}^{H_2O}$ (pH 13) 238 (8800). ^{1}H-NMR (Me_2SO-d_6) δ: 1.31 and 1.28 (3 × 3/4H and 3 × 1/4H, t, J = 7 Hz, CH_3CH_2), 3.03 and 3.25 (3 × 3/4H and 3 × 1/4H, s, N–CH_3), 3.87 and 3.76 (2 × 3/4H and 2 × 1/4H, q, J = 7 Hz, CH_2), 7.15 and 7.32 (1H each, br, NH_2), 7.80 and 7.76 (3/4H and 1/4H, s, $C_{(2)}$-H), 8.05 and 8.27 (3/4H and 1/4H, s, CHO).[17] *Anal.* Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.17; N, 28.56. Found: C, 48.97; H, 6.26; N, 28.65.

3,9-Dibenzylhypoxanthine (7e)——1-Benzyl-5-(benzylamino)imidazole-4-carboxamide (**6e**)[10,12b,c] (500 mg, 1.63 mmol) was treated with a preheated mixture of ethyl orthoformate (5 ml) and acetic anhydride (1.87 ml) as described under method (ii) for **7a**. The resulting precipitate was filtered off, washed with EtOH (2 ml), and dried to give **7e** (190 mg, 37% yield), mp 250—270 °C. Recrystallization from EtOH gave an analytical sample as colorless plates, mp 270—272 °C (sinters below the mp). UV $\lambda_{max}^{95\%\ EtOH}$ 258 nm (ε 12800); $\lambda_{max}^{H_2O}$ (Table I). ^{1}H-NMR (Me_2SO-d_6) δ: 5.26 and 5.32 (2H each, s, 2CH_2's), 6.96 and 7.32 (4H and 6H, m, 2C_6H_5's), 7.92 and 8.25 (1H each, s, purine protons). *Anal.* Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 71.95; H, 4.96; N, 17.94.

The combined filtrate and washings were concentrated *in vacuo* to leave a colorless oil. This was dissolved in $CHCl_3$ (10 ml) and the solution was allowed to stand at room temperature over alumina (5 g) for a week and filtered. The alumina was washed with $CHCl_3$–EtOH (8 : 1, v/v) (30 ml). The combined filtrate and washings were concentrated *in vacuo* and the residue was washed with a little EtOH to give **5e** (234 mg, 43% yield), mp 198—203 °C. Recrystallization from EtOH gave colorless pillars, mp 205—206 °C (lit.[10] mp 208 °C). MS *m/e*: 334 (M^+). ^{1}H-NMR (Me_2SO-d_6) δ: 4.74 (4H, br, 2CH_2's), 6.97 (2H, br, NH_2), 7.24 (10H, m, 2C_6H_5's), 7.71 (1H, s, $C_{(2)}$-H), 7.81 and 8.60 (4/5H and 1/5H, s, CHO).[17]

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References and Notes

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