Studies towards the Synthesis of the Fluorescent Bases of Phenylalanine Transfer Ribonucleic Acids: Synthesis of 7-Methylwye Isolated from Extremely Thermophilic Archaebacteria

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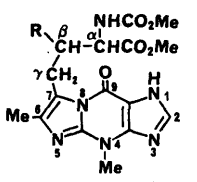
Acid- or base-catalyzed acylation of 1-benzylwye (7) provided the 7-substituted derivatives 9, 10, and 11 in poor yields. Although the reactions of lithiated 7 with electrophiles gave the 2-substituted derivatives 14, 15, 17, 20, 21, and 22, lithiation of 1-benzyl-7-bromo-2-chlorowye (23) followed by treatment with Me_2CHCH_2CHO (13) successfully introduced a side chain at the 7-position to afford 1-benzyl-2-chloro-7-(1-hydroxy-3-methylbutyl)wye (24).

Cyclization of 1-benzyl-3-methylguanine (5) with 3-bromo-2-butanone followed by catalytic hydrogenolysis afforded 7-methylwye (2b), the hypermodified base isolated from archaebacterial transfer ribonucleic acids. A more efficient route for the synthesis of 2b has been developed *via* a series of reactions: the Vilsmeier–Haack reaction of 7, reduction with $NaBH_4$, and catalytic hydrogenolysis over Pd–C.

Keywords fluorescent base; hypermodified base; 7-methylwye; 1-benzylwye; 7-substituted 1-benzylwye; lithiation; halogenation; cyclocondensation; formylation; hydrogenolysis

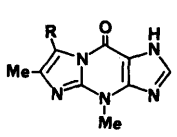
A fluorescent minor component was discovered in 1968 at the next position to the 3′-end of the anticodon of yeast phenylalanine transfer ribonucleic acid ($tRNA^{Phe}$) from which the fluorescent nucleoside was isolated.[1,2] Thiebe and Zachau have found that the fluorescent base, wybutine, is excised from the nucleoside or the $tRNA^{Phe}$ by mild acid treatment.[2] The structure of wybutine from *Saccharomyces cerevisiae* $tRNA^{Phe}$ has been elucidated as **1a** by the pioneering work of Nakanishi *et al.*[3] Thiebe *et al.* have independently drawn a similar conclusion.[4] A prototype of this unique tricyclic base, wye, has been found in *Torulopsis utilis* $tRNA^{Phe}$ and the structure has been determined to be **2a**.[5] The structure of the base, wybutoxine, isolated from $tRNAs^{Phe}$ of rat, beef, calf,[6,7] and chicken[6] liver, *Lupinus luteus*,[8] and *Geotrichum candidum*[9] has been proposed to be hydroperoxywybutine (**1c**). However, Kasai *et al.* reported that one of the fluorescent bases from rat liver $tRNAs^{Phe}$ was hydroxywybutine (**1b**) and that **1c** might be an artefact formed from **1b**.[10] An undermodified base **3** has been also found in tumorspecific $tRNAs^{Phe}$ in place of **1b**.[11] Very recently, McCloskey *et al.* isolated a new fluorescent nucleoside from unfractionated tRNAs of three extremely thermophilic archaebacteria and determined the structure of the base to be 7-methylwye (**2b**).[12] As these bases, **1**—**3**, were isolated from tRNAs in extremely minute quantities, rigorous identification of the structures, especially the absolute configurations of the side chains of **1** and **3**, has to rest on chemical synthesis. The present paper deals with model experiments directed towards the syntheses of **1** and **3** and a detailed account of the first synthesis of **2b**.[13,14]

Nakanishi *et al.* reported the synthesis of (±)-**1a** by



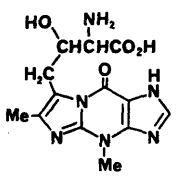
1

a: R=H
b: R=OH
c: $R=O_2H$



2

a: R=H
b: R=Me



3

cyclocondensation of 3-methylguanine (**4**) with methyl 5-bromo-2-(methoxycarbonyl)amino-6-oxoheptanoate.[15] They also reported that the reaction of 7-benzyl-3-methylguanine (**5**) with the bromoketone followed by hydrogenolysis gave a better result.[16] Since this method hardly seemed to permit a chiral synthesis, we wished to develop a new route to **1a**, which involved introduction of the side chain at the 7-position of 1-benzylwye (**7**). Compound **7** was prepared according to the reported procedure[16] as follows.

Treatment of **4**[17] with benzyl bromide in a slight modification of the reported procedure gave **5** as the monohydrate, mp 210—212 °C, in 87% yield. The original authors[16] obtained **5** as an anhydrous sample, mp 269—270 °C and the ultraviolet (UV) spectra reported are somewhat different from those of the present sample. For confirming the correctness of the structure of our sample, **5** was converted into 7-benzyl-3-methylxanthine (**6**) by alkaline hydrolysis. The structure of **6** was supported by the identity of the nuclear magnetic resonance (NMR) spectrum with the reported one,[18] the similarity to theobromine in the UV spectrum, and direct comparison with an authentic sample[19] obtained by the reaction of 1-benzyl-4-(methylamino)-1*H*-imidazole-5-carboxamide[20] with EtOCOCl. Cyclocondensation of **5** with $MeCOCH_2Br$ in the presence of NaH was reported to give **7** in 41% yield.[16,21] We obtained **7** in 83% yield using K_2CO_3 as the base. Similar reaction of **5** with MeCOCHBrMe in the presence of NaH gave 1-benzyl-7-methylwye (**8**) in only 13% yield, although Frihart *et al.* had reported that similar cyclization with 3-bromo-2-heptanone gave a satisfactory result.[16] Replacement of the base by $PhNEt_2$ or K_2CO_3 improved the yield of **8** to 22—23%. Debenzylation of **7** and 7-substituted **7** was reported to be achieved by catalytic hydrogenolysis over Pd–C in MeOH or Me_2CHOH in the presence of AcOH and aqueous HCl with special care.[16] We carried out the hydrogenolysis of **7** over Pd–C in MeOH in the presence of aqueous $HClO_4$ to give **2a** without difficulty. Similar hydrogenolysis of **8** gave **2b** in 86% yield, though the reaction took place more smoothly when the solvent was replaced by AcOH. Since this compound **2b** was synthesized[13] prior to its isolation from

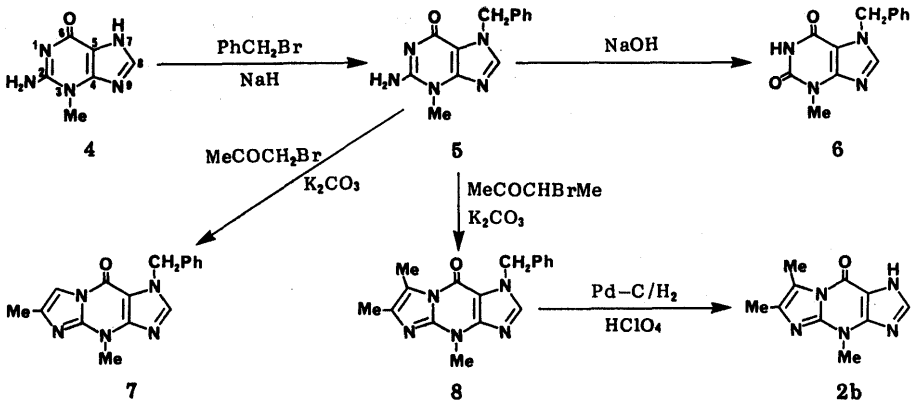
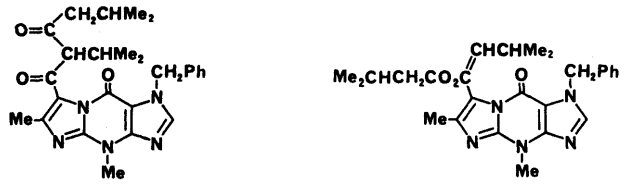


Chart 1

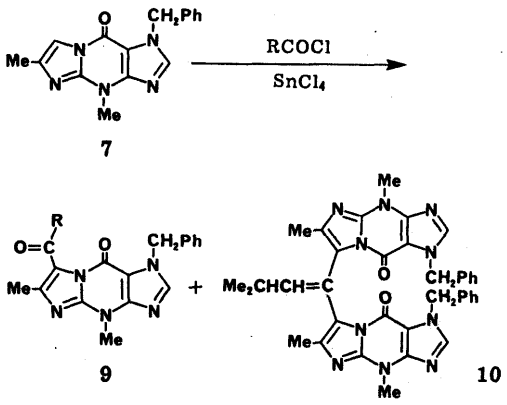
archaebacterial tRNAs, identification of the structure of the natural base was performed by comparison with the synthetic one.[12] Direct cyclocondensation of **4** with MeCOCHBrMe in the presence of $PhNEt_2$ gave **2b** in only 0.3% yield, although similar treatment of **4** with $MeCOCH_2Br$ furnished **2a** in 41% yield.[22]

If a method of C–C bond formation at the 7-position of **7** had been available, the reaction with an appropriate reagent derived from homoserine or aspartic acid would have opened a route to optically active **1**. We tried at first the Friedel–Crafts reaction of **7**. The reaction of **7** with EtCOCl in $(CH_2Cl)_2$ using $SnCl_4$ provided 1-benzyl-7-(1-oxopropyl)wye (**9a**) in 5.8% yield. The acylation was expected to occur at the electron-rich 7-position and the structure is supported by a singlet at δ 2.43 in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum due to the C(6)Me, which resonates at lower magnetic field by 0.08 ppm than a doublet of the parent compound **7**. The reaction of **7** with Me_2CHCH_2COCl (**16**) gave **9b** in 12% yield with a concomitant formation of **10**, which was supposed to be formed by the reaction of **7** and **9b** followed by dehydration. Effenberger *et al.* proposed that a combination of acyl chlorides and CF_3SO_3Ag provided a powerful means for acylation in the Friedel–Crafts reaction.[23] However, this method did not work in our case.

Since wybutosine, the parent nucleoside of **1a**, is known to be very sensitive to acid,[2] it is desirable to develop a method of introducing a carbon side chain at the 7-position of the tricyclic system under non-acidic conditions for the synthesis at the nucleoside level. The reaction of **7** with **16** in the presence of 2 eq of imidazole was attempted in vain. 4-(Dimethylamino)pyridine was found to promote the reaction of **7** and **16**. Nevertheless, the product obtained in poor yield was not the desired **9b** but **11**. We prefer the structure **11** to an alternative **12** on the basis of the IR spectrum: the carbonyl stretching band observed at 1704 cm^{-1} in $CHCl_3$ solution is assignable to the 1,3-diketone rather than the enol ester. Furthermore, its ^{1}H-NMR spectrum showed no signal due to an olefinic proton, expected for the structure **12**. Prolonged reaction did not improve the yield of **11** and the reaction with excesses of the reagent and the base gave a complex mixture of products having different numbers of acyl units. Lithiation of **7** with *n*-BuLi in tetrahydrofuran (THF) occurred at the electron-deficient 2-position, giving **14** on treatment with Me_2CHCH_2CHO (**13**) in 14% yield. When lithiated **7** was treated with **16**, the corresponding 2-acyl derivative **15** as well as **17**, the aldol condensation product of **15**, were obtained in 10% and 4.2% yields, respectively. The structure **17** was assignable on the basis of ^{1}H-NMR and mass spectra, though the stereochemistry remained to be solved.



11 12



a: R=Et
b: R=Me_2CHCH_2

Chart 2

In the expectation that lithiation of 7-bromowye (**18**) should take place at the 7-position, **18** was prepared by treatment of **7** with an equimolar amount of Br_2 in AcOH in 51% yield, together with the dibromo compound **19** in 17% yield.[24] The correctness of the site of monobromination was supported by the ^{1}H-NMR spectrum on the basis of similar reasoning to that described for **9a**. However, treatment of **18** with *n*-BuLi followed by addition of **13** again afforded **14** in 33% yield. This suggests that 1-benzyl-7-lithiowye once formed transformed into 1-benzyl-2-lithiowye in preference to the reaction with **13**. It follows that the 2-position of **7** should be protected for the lithiation at the 7-position.

For this purpose, lithiated **7** was first treated with

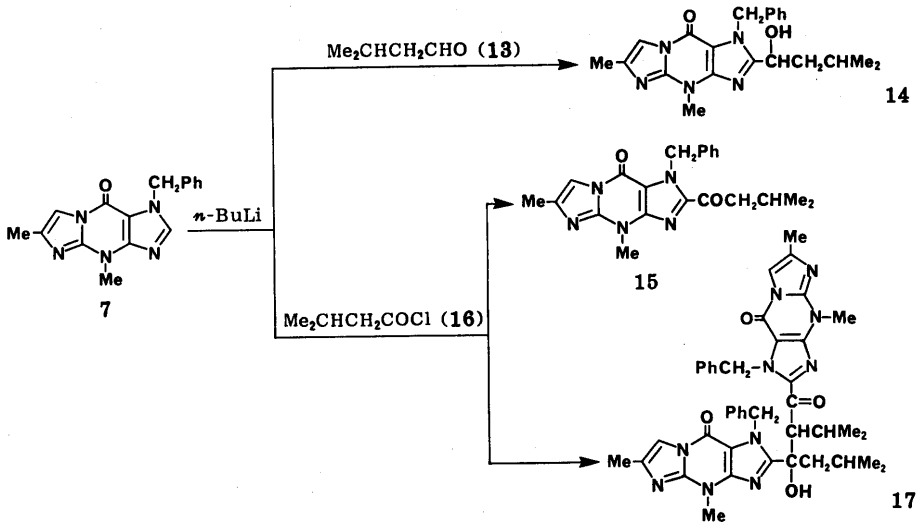


Chart 3

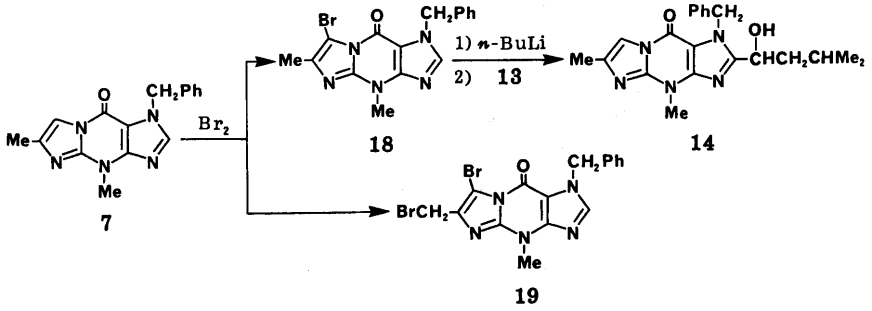
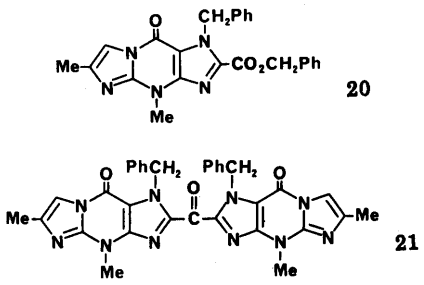


Chart 4



Me_3SiCl or *tert*-$BuMe_2SiCl$ in THF, but no silylated product was obtained in either case. Similar reaction with a slight excess of $PhCH_2OCOCl$ gave the ketone **21** in 9.5% yield as well as the desired **20** in 3.7% yield. The use of five equivalents of $PhCH_2OCOCl$ increased the yield of **20** to 10%. Chlorination at the 2-position was achieved more efficiently by the lithiation of **7** followed by treatment with *N*-chlorosuccinimide (NCS), giving 1-benzyl-2-chlorowye (**22**) in 29% yield. This compound should be a better synthetic intermediate than **20** in view of lower likelihood of side reactions and easy deprotection.

When **22** was treated with *n*-BuLi in THF at $-78\,^{\circ}C$ followed by addition of **13**, almost all of the **22** was recovered unchanged and a product obtained in 1.4% yield was supposed to be 1-benzyl-2-butylwye on the basis of the mass spectrum (MS) [*m/z*: 349 (M^+)]. The use of *tert*-BuLi instead of *n*-BuLi gave 1-benzyl-2-chloro-5-(2,2-dimethyl-1-oxopropyl)-4-[methyl[4 (or 5)-methyl-1*H*-imidazol-2-yl]amino]-1*H*-imidazole (**25**) as the monoethanolate[25] in 37% yield along with unchanged **22** (59%). We then tried the lithiation of **22** through the 7-bromo derivative **23**. Compound **22** underwent monobromination more selectively than **7** under similar conditions, and **23** was produced in 75% yield. Although lithiation of **23** with *n*-BuLi took place sluggishly, treatment of **23** with *tert*-BuLi followed by addition of **13** gave **24** in 19% yield. Compound **24** proved unstable at room temperature and the dehydrated product **26** was isolated as a mixture of (*E*)- and (*Z*)-isomers from the degradation products.

Either **24** or **26** should give 7-(3-methylbutyl)wye (**27**), a model for **1a**, on reductive treatment such as catalytic hydrogenolysis over Pd–C. Thus the above method of transformation of **7** into **24** should provide an access to wybutine [(*S*)-**1a**].[13] However, the overall yield of **24** was intolerably poor. We then tried to develop a method of constructing a C–C bond between the β and γ positions designated in the structure **1**. A formyl group at the 7-position of the tricyclic system should be useful for our purpose. We failed in an attempt to prepare 1-benzyl-7-formylwye (**28**) through 1-benzyl-7-(dimethoxymethyl)wye by cyclocondensation of **5** with $MeCOCHBrCH(OMe)_2$[26] using K_2CO_3 as the base in the presence or absence of 18-crown-6. However, the Vilsmeier–Haack reaction of **7** with a combination of $POCl_3$ and $HCONMe_2$ furnished **28**, which shows the formyl proton signal at δ 10.87 in $CDCl_3$, in 100% yield.[24] The formylation was expected to take

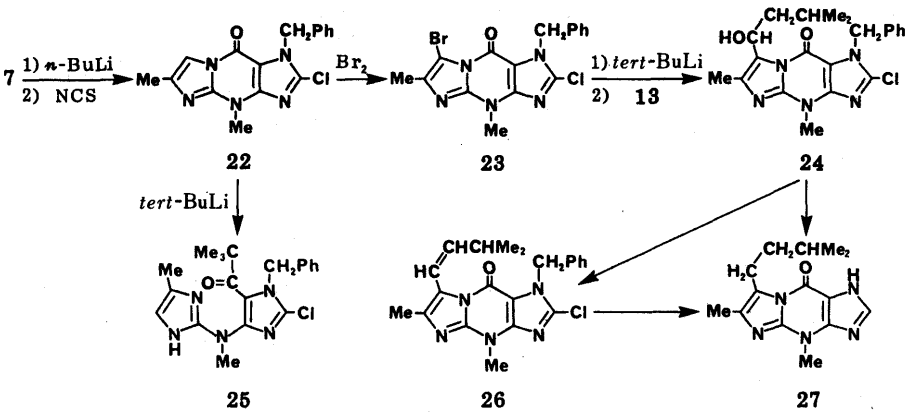


Chart 5

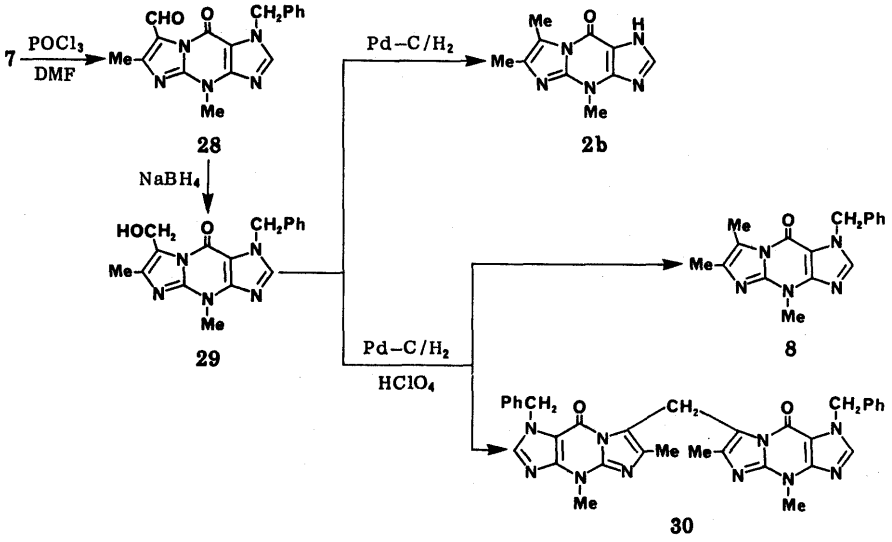


Chart 6

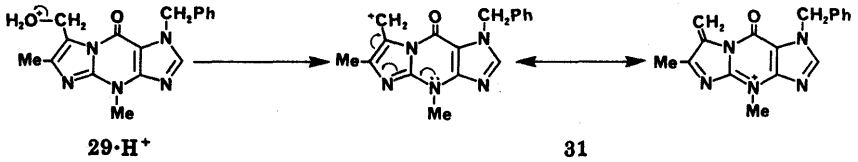


Chart 7

place at the 7-position rather than the 2-position as in the case of the Friedel–Crafts reaction or bromination described above. This is supported by the downfield shift by 0.32 ppm of the singlet due to C(6)Me, which appears as a doublet owing to a long-range interaction with the proton at the 7-position in the parent compound **7**. Such easy formylation of **7** encouraged us to try the acylation of **7** using a higher homolog of $HCONMe_2$. However, the reaction of **7** with $AcNMe_2$ and $POCl_3$ failed.

Compound **28** seemed to be a good precursor for the synthesis of the minor base **2b**, isolated from the archaebacteria.[12] Treatment of **28** with $NaBH_4$ gave the alcohol **29** in quantitative yield. When the catalytic hydrogenolysis of **29** was conducted over Pd–C in AcOH in the presence of $HClO_4$, bis(1-benzyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purin-7-yl)methane (**30**) was obtained in 13% yield as well as **8**. Probably, **30** was formed by *ipso*-substitution at the electron-rich 7-position of **29**: addition of the stabilized cation **31** to **29** followed by elimination of protonated HCHO. Prolonged hydrogenolysis of **29** over Pd–C in methanol without acid provided **2b** in 50% yield, establishing a better synthesis of **2b**. These results further support the correctness of the assigned position of the formyl group of **28**. This compound **28** has been employed as a key intermediate for the chiral syntheses of wybutine[13] and the most probable two alternatives for hydroxywybutine.[27]

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Spectra reported herein were recorded on a Hitachi 320 UV spectrophotometer, a JASCO A-202 infrared (IR) spectrophotometer, a Hitachi M-80 mass spectrometer, or a JEOL JNM-FX-100 NMR spectrometer at 25 °C with Me_4Si as an internal standard. The following abbreviations are used: br = broad, d =

doublet, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet. Flash chromatography was performed on silica gel according to the reported procedure.[28]

7-Benzyl-3-methylguanine (5) A mixture of **4**[17] (16.52 g, 0.10 mol), 50% NaH (4.80 g, 0.10 mol), and dry $HCONMe_2$ (300 ml) was stirred at room temperature for 6 h. $PhCH_2Br$ (17.10 g, 0.10 mol) was added to the mixture and the whole was then stirred at 30 °C for 2.5 h. Insoluble matter was filtered off, washed with a little $HCONMe_2$ and dried to give unchanged **4** (1.37 g, 8%). The combined filtrate and washings were concentrated *in vacuo* to leave a solid residue. This was washed successively with MeOH (60 ml), H_2O (70 ml), and MeOH (10 ml), and then dried to give $\mathbf{5}\cdot H_2O$ as a colorless solid (23.27 g), mp *ca.* 260—270 °C (dec., melted and resolidified at 205 °C). From the combined washings a solid precipitate appeared. Recrystallization of this material from MeOH gave a second crop of $\mathbf{5}\cdot H_2O$ (0.62 g). The total yield was 87%. For analysis, **5** was recrystallized from MeOH, dried over P_2O_5 at 2 mmHg and 75 °C for 3 h and then exposed to air until constant weight was reached to give $\mathbf{5}\cdot H_2O$ as colorless needles, mp 210—212 °C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 238 (sh) (9900), 269 (9700); $\lambda_{max}^{H_2O}$ (pH 1) nm (ε): 266 (9200); $\lambda_{max}^{H_2O}$ (pH 7) nm (ε): 238 (sh) (9200), 270 (9600); $\lambda_{max}^{H_2O}$ (pH 13) nm (ε): 238 (sh) (9400), 270 (9600). ^{1}H-NMR (Me_2SO-d_6) δ: 3.50 (3H, s, Me), 5.50 (2H, s, CH_2), 6.93 (2H, br, NH_2), 7.32 (5H, s, Ph), 8.05 [1H, s C(8)H]. *Anal.* Calcd for $C_{13}H_{13}N_5O\cdot H_2O$: C, 57.13; H, 5.53; N, 25.63. Found; C, 57.16; H, 5.28; N, 25.71.

7-Benzyl-3-methylxanthine (6) A mixture of $\mathbf{5}\cdot H_2O$ (185 mg, 0.677 mmol) and 10% aqueous NaOH (11 ml) was heated under reflux for 30 min. The resulting solution was cooled and then brought to pH 5 with AcOH. The precipitate that separated was collected by filtration, washed with a little H_2O, and dried. The solid was extracted with CH_2Cl_2 using a Soxhlet extractor. The combined CH_2Cl_2 extracts were concentrated *in vacuo* to leave a solid (143 mg, 83%), mp 268—275 °C. Recrystallizations from AcOH gave an analytical sample as colorless needles, mp 275—277 °C (lit.[18] mp 272—275 °C; lit.[16] mp 271 °C). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 274 (8700); $\lambda_{max}^{H_2O}$ (pH 1) nm (ε): 273 (9100); $\lambda_{max}^{H_2O}$ (pH 7) nm (ε): 273 (9300); $\lambda_{max}^{H_2O}$ (pH 13) nm (ε): 275 (9100). ^{1}H-NMR (Me_2SO-d_6) δ: 3.34 (3H, s, Me), 5.44 (2H, s, CH_2), 7.33 (5H, s, Ph), 8.22 [1H, s, C(8)H], 11.12 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.71; H, 4.56; N, 21.71. For comparison of the UV spectra, an analytically pure sample of theobromine (3,7-dimethylxanthine) was prepared by recrystallization of a commercial product[29] from AcOH. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 273 (8800); $\lambda_{max}^{H_2O}$ (pH 1) nm (ε): 273 (8900); $\lambda_{max}^{H_2O}$ (pH 7) nm (ε): 273 (9200); $\lambda_{max}^{H_2O}$ (pH 13) nm (ε): 275 (9300).

1-Benzyl-1,4-dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (7) A mixture of $\mathbf{5}\cdot H_2O$ (5.12 g, 18.7 mmol), K_2CO_3 (7.75 g, 56 mmol), and dry $HCONMe_2$ (200 ml) was stirred at room temperature for 1 h and a solution of $MeCOCH_2Br$[30] (15.37 g, 112 mmol) in $HCONMe_2$ (20 ml) was added. The resulting mixture was stirred at room temperature (26 °C) for 3.5 h and then concentrated *in vacuo* to leave a brown solid. This was partitioned between CH_2Cl_2 (200 ml) and H_2O (100 ml). The aqueous layer was washed with CH_2Cl_2 (100 ml). The combined CH_2Cl_2 solution was dried over $MgSO_4$ and removal of the solvent by evaporation gave a brown solid. This was recrystallized from MeOH (270 ml) to give **7** (3.54 g), mp 208 °C (softened below this temperature). The mother liquor was concentrated *in vacuo* and the solid residue was recrystallized from MeOH to give a second crop of **7** (0.76 g) of the same melting point. The mother liquor was again treated similarly to furnish a third crop of **7** (0.29 g) of the same melting point. The total yield was 83%. Recrystallizations from MeOH gave an analytical sample as colorless needles, mp 208—209 °C (softened below this temperature). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 233 (30500), 236 (30500), 259 (5800), 311 (6800): $\lambda_{max}^{H_2O}$ (pH 1) nm (ε): 233 (36400), 287 (9100); $\lambda_{max}^{H_2O}$ (pH 7) nm (ε): 233 (31300), 262 (5700), 312 (6600); $\lambda_{max}^{H_2O}$ (pH 13) nm (ε): 233 (30700), 262 (5700), 312 (6500). IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (d, J=0.5 Hz, CMe), 3.94 (3H, s, NMe), 5.60 (2H, s, CH_2), 7.35 [6H, s, Ph and C(7)H], 7.68 [1H, s, C(2)H]; (Me_2SO-d_6) δ: 2.22 (3H, d, J=1 Hz, CMe), 3.78 (3H, s, NMe), 5.58 (2H, s, CH_2), 7.34 [6H, s, Ph and C(7)H], 8.41 [1H, s, C(2)H]. *Anal.* Calcd for $C_{16}H_{15}N_5O$: C, 65.51; H, 5.15; N, 23.88. Found: C, 65.28; H, 5.23; N, 23.66.

1-Benzyl-1,4-dihydro-4,6,7-trimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (8) i) A mixture of $\mathbf{5}\cdot H_2O$ (137 mg, 0.50 mmol), K_2CO_3 (207 mg, 1.5 mmol), and anhydrous $HCONMe_2$ (10 ml) was stirred at room temperature for 1 h. $MeCOCHBrMe$[30] (450 mg, 3 mmol) was added to the mixture and the whole was then stirred at 30 °C for 5 h. It was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (30 ml) and H_2O (20 ml). The CH_2Cl_2 layer was dried over Na_2SO_4 and then concentrated *in vacuo* to leave a yellow oil. This was purified by preparative layer chromatography on silica gel [$CHCl_3$–MeOH (10:1, v/v)] to give **8** (36 mg, 23%), mp 192 °C. Recrystallizations from MeOH gave an analytical sample as colorless needles, mp 203 °C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 238 (29000), 260(sh) (5900), 322 (5200); $\lambda_{max}^{H_2O}$ (pH 1) nm (ε): 238 (34200), 293 (7000); $\lambda_{max}^{H_2O}$ (pH 7) nm (ε): 238 (27400), 261(sh) (5500), 323 (4900); $\lambda_{max}^{H_2O}$ (pH 13) 238 (unstable), 261(sh) (5800), 323 (4900). IR ν_{max}^{Nujol} cm^{-1}: 1695 (CO). ^{1}H-NMR (Me_2SO-d_6) δ: 2.10 [3H, s, C(6)Me], 2.54 [3H, s, C(7)Me], 3.71 (3H, s, NMe), 5.56 (2H, s, CH_2), 7.33 (5H, s, Ph), 8.34 [1H, s, C(2)H]. *Anal.* Calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.13; H, 5.59; N, 22.83.

ii) The monohydrate of **5** (273 mg, 1.0 mmol) was dried over P_2O_5 at 2 mmHg and 110 °C for 3 h to give anhydrous **5** (255 mg). This was dissolved in anhydrous $HCONMe_2$ (10 ml) and 50% NaH (48 mg, 1 mmol) was added. After the mixture had been stirred at room temperature for 2 h, $MeCOCHBrMe$[30] (170 mg, 1.1 mmol) was added. The reaction mixture was stirred at 30 °C for 18.5 h and then concentrated *in vacuo* to leave a yellow oil. This was partitioned between CH_2Cl_2 (40 ml) and H_2O (20 ml). The resulting precipitate was filtered off and dried to give unchanged $\mathbf{5}\cdot H_2O$ (58 mg, 21%). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to leave a yellow oil. This was purified on a silica gel (7 g) column [$CHCl_3$–MeOH (50:1, v/v)] to give **8** (41 mg, 13%), identical with the analytical sample described above.

iii) A mixture of $\mathbf{5}\cdot H_2O$ (137 mg, 0.50 mmol), $PhNEt_2$ (373 mg, 2.5 mmol), and anhydrous $HCONMe_2$ (10 ml) was stirred at 50 °C under N_2 for 1 h. $MeCOCHBrMe$ (150 mg, 1.0 mmol) was added and the mixture was stirred at 50 °C under N_2 for 9 h. The bromoketone (230 mg, 1.5 mmol) was added again and the mixture was stirred at 70 °C for a further 9 h. The resulting mixture was concentrated *in vacuo* and the residue was treated with CH_2Cl_2 (40 ml). The insoluble solid was filtered off and the CH_2Cl_2 solution was concentrated *in vacuo* to leave a semisolid. This was purified on a silica gel (7 g) column [$CHCl_3$–MeOH (50:1, v/v)]. The fractions containing a fluorescent substance were combined and evaporated *in vacuo* to leave a brown solid. This was further purified by preparative layer chromatography on silica gel [$CHCl_3$–MeOH (20:1, v/v)] to give **8** (34 mg, 22%).

1-Benzyl-1,4-dihydro-4,6-dimethyl-7-(1-oxopropyl)-9*H*-imidazo[1,2-*a*]purin-9-one (9a) A solution of anhydrous $SnCl_4$ (0.5 ml, 4.3 mmol) in anhydrous $(CH_2Cl)_2$ (10 ml) was added dropwise to a stirred suspension of **7** (1.17 g, 4.0 mmol) and EtCOCl (0.35 ml, 4.0 mmol) in anhydrous $(CH_2Cl)_2$ (50 ml) over a period of 40 min. The mixture was stirred at room temperature for a further 4 h. The resulting mixture was poured into saturated aqueous $NaHCO_3$ (200 ml) and extracted with CH_2Cl_2 (200 ml). The aqueous layer was extracted with CH_2Cl_2 (50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to leave a solid (1.18 g). This was recrystallized from MeOH to give **7** (812 mg). The mother liquor was concentrated *in vacuo* to leave a yellowish caramel (0.35 g). This was purified by flash chromatography [column diameter, 40 mm; AcOEt–EtOH (10:1, v/v)] to give crude **9a** (80 mg, 5.8%), mp 172—188 °C, and a second crop of **7** (82 mg, 76% total recovery). Recrystallization of crude **9a** from EtOH gave an analytical sample as colorless needles, mp 192—193 °C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 228 (21500), 255 (19200), 313 (12100). IR ν_{max}^{Nujol} cm^{-1}: 1687 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7 Hz, $\underline{Me}CH_2$), 2.43 [3H, s, C(6)Me], 2.83 (2H, q, J=7 Hz, $MeC\underline{H}_2$), 3.96 (3H, s, NMe), 5.60 (2H, s, $PhC\underline{H}_2$), 7.36 (5H, s, Ph), 7.70 [1H, s C(2)H]. MS *m/z*: 349 (M^+), 320 (M^+-Et), 293 (MH^+-EtCO). *Anal.* Calcd for $C_{19}H_{19}N_5O_2$: C, 65.31; H, 5.48; N, 20.05. Found: C, 65.41; H, 5.48; N, 20.13.

1-Benzyl-1,4-dihydro-4,6-dimethyl-7-(3-methyl-2-oxobutyl)-9*H*-imidazo-[1,2-*a*]purin-9-one (9b) Compound **7** (1.17 g, 4.0 mmol) was treated with **16** (0.50 ml, 4.08 mmol) and $SnCl_4$ (0.5 ml, 4.3 mmol) in the same way as described for **9a**. The crude product was triturated with boiling MeOH and cooled. The precipitate was filtered off and washed with a little MeOH to give **7** (702 mg). The filtrate and washings were combined and concentrated *in vacuo* to leave a slightly brown solid (0.57 g). This was purified by flash chromatography [40 mm, AcOEt–EtOH (10:1→8:1, v/v)] to give **9b** (176 mg, 12%) as a colorless solid, mp 171—172 °C and **7** (78 mg, total recovery 67%). Further elution of the column with AcOEt–EtOH (5:1, v/v) gave **10** (130 mg, 10%) as a slightly yellow glass, ^{1}H-NMR ($CDCl_3$) δ: 1.03 and 1.07 [3H each, d, J=6.5 Hz, coalesced into 1.05 (d, J=6.5 Hz) at 80 °C, $C\underline{Me}_2$],[31] 2.06 and 2.39 (3H each, s, two heterocyclic CMe's), 2.50 (1H, m, $\underline{Me}_2C\underline{H}$), 3.87 and 3.91 (3H each s, two NMe's), 5.34 (2H, s, $PhC\underline{H}_2$), 5.55 and 5.57 [1H each, unresolved AB-type d, coalesced into 5.52 (s) at 80 °C, $PhC\underline{H}_2$],[31] 5.80 (1H, d, J=10 Hz, olefinic proton), 7.23 (10H, m, two Ph's), 7.52 and 7.64 (1H each, s, two heterocyclic protons).

MS *m/z*: 652 (M^+).

Recrystallization of **9b** from EtOH gave an analytical sample as colorless needles, mp 172—173 °C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 228 (21000), 255 (19300), 312 (12200). IR ν_{max}^{Nujol} cm^{-1}: 1695 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz, CMe_2), 2.15 (1H, m, CH), 2.44 [3H, s, C(6)Me], 2.73 (2H, d, J=7 Hz, $COCH_2$), 3.95 (3H, s, NMe), 5.60 (2H, s, $PhCH_2$), 7.36 (5H, s, Ph), 7.72 [1H, s, C(2)H]. MS *m/z*: 377 (M^+), 320 ($M^+ - Me_2CHCH_2$), 293 ($MH^+ - Me_2CHCH_2CO$). *Anal.* Calcd for $C_{21}H_{23}N_5O_2$: C, 66.82; H, 6.14; N, 18.56. Found: C, 67.08; H, 6.08; N, 18.49.

(±)-1-Benzyl-1,4-dihydro-7-(2-isopropyl-5-methyl-1,3-dioxohexyl)-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (11) A mixture of **7** (293 mg, 1.0 mmol), 4-(dimethylamino)pyridine (134 mg, 1.1 mmol), **16** (121 mg, 1.0 mmol), and anhydrous $HCONMe_2$ (5 ml) was heated at 80—90 °C for 4 h and allowed to cool. The resulting precipitate was removed by filtration to give **7** (159 mg). The mother liquor was concentrated *in vacuo* and the residue was recrystallized from MeOH to give a second crop (95 mg) of **7**. The mother liquor was concentrated again *in vacuo* and the residue was chromatographed on a silica gel (5 g) column [AcOEt–EtOH (10:1, v/v)]. A third crop (13 mg, total recovery 91%) of **7** was obtained as the more polar substance. The eluate containing the less polar substance was concentrated *in vacuo* and the residue was purified by layer chromatography on silica gel [AcOEt–EtOH (10:1, v/v)] to give **11** (6 mg, 1.3% based on **7**). Recrystallization from MeOH gave colorless needles, mp 172—174 °C. IR ν_{max}^{Nujol} cm^{-1}: 1704 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (9H, d, J=7 Hz, $\underline{Me}_2CHCH_2$ and $\underline{Me}CHCH$), 0.99 (3H, d, J=7 Hz, $\underline{Me}CHCH$), 2.08 (1H, m, $Me_2C\underline{H}CH_2$), 2.43 (2H, d, J=7 Hz, $CHC\underline{H}_2$), 2.44 [3H, s overlapped with a 1H multiplet due to $Me_2C\underline{H}CH$, C(6)Me], 3.94 (3H, s, NMe), 4.11 (1H, d, J=9 Hz, CHCO), 5.58 (2H, s, $PhC\underline{H}_2$), 7.37 (5H, s, Ph), 7.74 [1H, s, C(2)H]. MS *m/z*: 461.2433 (M^+, $C_{26}H_{31}N_5O_3$ requires 461.2425), 376 ($M^+ - Me_2CHCH_2CO$), 320 ($M^+ - Me_2CHCH_2COCH$-$CHMe_2$), 293 ($M^+ - Me_2CHCH_2COCHCOCHMe_2$).

1-Benzyl-7-bromo-1,4-dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (18) A solution of Br_2 (0.96 g, 6.0 mmol) in AcOH (10 ml) was added to a solution of **7** (1.76 g, 6.0 mmol) in AcOH (80 ml) over a period of 30 min with stirring. The resulting mixture was concentrated *in vacuo* to leave a solid. This was partitioned between saturated aqueous $NaHCO_3$ (50 ml) and CH_2Cl_2 (50 ml). The aqueous layer was extracted with CH_2Cl_2 (50 ml). The combined CH_2Cl_2 extracts were dried over $MgSO_4$. Removal of the solvent by evaporation gave a yellowish solid. This was purified by flash chromatography [40 mm, AcOEt–EtOH (15:1, v/v)]. The less polar substance was obtained as a colorless solid (458 mg, 17%). This was recrystallized from AcOEt to give an analytical sample of **19** as colorless needles, mp 161—162 °C (dec.). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 241 (33200), 323 (7600). IR ν_{max}^{Nujol} cm^{-1}: 1705 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s, Me), 4.52 [2H, s, C(6)CH_2], 5.58 (2H, s, $PhC\underline{H}_2$), 7.35 (5H, s, Ph), 7.68 [1H, s, C(2)H]. *Anal.* Calcd for $C_{16}H_{13}Br_2N_5O$: C, 42.59; H, 2.90; N, 15.53. Found: C, 42.44; H, 2.76; N, 15.73.

Compound **18** was obtained as the more polar substance (1.14 g, 51%), mp 149—151 °C. Recrystallization from EtOH gave an analytical sample as colorless plates of unchanged melting point, UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 239 (31300), 260(sh), (6800), 318 (5800). IR ν_{max}^{Nujol} cm^{-1}: 1705 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s, CMe), 3.88 (3H, s, NMe), 5.59 (2H, s, CH_2), 7.35 (5H, s, Ph), 7.65 [1H, s, C(2)H]. *Anal.* Calcd for $C_{16}H_{14}BrN_5O$: C, 51.62; H, 3.79; N, 18.82. Found: C, 51.69; H, 3.67; N, 18.90.

(±)-1-Benzyl-1,4-dihydro-4,6-dimethyl-2-(1-hydroxy-3-methylbutyl)-9*H*-imidazo[1,2-*a*]purin-9-one (14) i) A solution of **7** (147 mg, 0.50 mmol) in anhydrous THF (16 ml) was cooled to −78 °C under an N_2 atmosphere and a 1.7 M *n*-BuLi solution (0.31 ml, 0.53 mmol) in hexane was added. After a 10 min delay, **13** (0.060 ml, 0.54 mmol) was added to the solution and the mixture was stirred at −78 °C for 10 min. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 4 h. The resulting mixture was concentrated *in vacuo*. The residue was partitioned between H_2O (15 ml) and CH_2Cl_2 (15 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml). The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography [20 mm, hexane–AcOEt–EtOH (4:2:1, v/v)]. The less polar fluorescent material was further purified by layer chromatography on silica gel developed with the same solvent to give **14** (27 mg, 14%). Recrystallization from EtOH gave colorless plates, mp 162—165 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, d, J=6 Hz, Me_2), 1.51 (1H, m, $Me_2C\underline{H}$), 1.78 (2H, m, $C\underline{H}_2CH$), 2.36 [3H, d, J=1 Hz, C(6)Me], 3.0 (1H, br, OH), 3.87 (3H, s, NMe), 4.82 [1H, m, C(2)CH], 5.66 and 5.80 (1H, each, d, J=16 Hz, $PhC\underline{H}_2$), 7.19—7.35 (5H, m, Ph), 7.37 [1H, q, J=1 Hz, C(7)H]. The starting material **7** (67 mg, 23%) was recovered from the more polar fraction.

ii) A solution of **18** (69 mg, 0.185 mmol) in anhydrous THF (5 ml) was cooled to −78 °C and a 1.7 M solution of *n*-BuLi (0.11 ml, 0.187 mmol) in hexane was added under N_2. After 3 min, **13** (0.025 ml, 0.22 mmol) was added and the mixture was stirred for 4 h. The reaction mixture was then allowed to warm to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 ml) and H_2O (10 ml), after being neutralized with 10% aqueous H_3PO_4. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by layer chromatography on silica gel [AcOEt–EtOH (10:1, v/v)] to give **14** (23 mg, 33%) as the less polar fluorescent material. Identity of this product with the sample obtained by method (i) was confirmed by ^{1}H-NMR spectroscopy.

1-Benzyl-1,4-dihydro-4,6-dimethyl-2-(3-methyl-1-oxobutyl)-9*H*-imidazo[1,2-*a*]purin-9-one (15) A solution of *n*-BuLi (1.7 M, 0.31 ml, 0.53 mmol) in hexane was added to a solution of **7** (147 mg, 0.50 mmol) in anhydrous THF (16 ml) at −78 °C under N_2 and the mixture was stirred for 10 min. Acyl chloride **16** (0.061 ml, 0.50 mmol) was added and the mixture was allowed to warm to room temperature after stirring for 10 min at −78 °C. The mixture was concentrated *in vacuo* and H_2O (15 ml) was added. It was then extracted with CH_2Cl_2 (4 × 15 ml) and the CH_2Cl_2 extracts were concentrated *in vacuo* after being dried over $MgSO_4$. The oily residue was purified by flash chromatography [20 mm, hexane–AcOEt–EtOH (4:2:1, v/v)] to give **15** (19 mg, 10%) as the less polar product. Recrystallization from EtOH gave slightly yellow needles, mp 143—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d, J=7 Hz, Me_2), 2.33 (1H, m, $Me_2C\underline{H}$), 2.36 [3H, d, J=1 Hz, C(6)Me)], 3.05 (2H, d, J=7 Hz, $COCH_2$), 3.97 (3H, s, NMe), 6.17 (2H, s, $PhC\underline{H}_2$), 7.21—7.33 (5H, m, Ph), 7.40 [1H, q, J=1 Hz, C(7)H]. MS *m/z*: 377.1857 (M^+, $C_{21}H_{23}N_5O_2$ requires 377.1850).

The more polar product was purified by layer chromatography on alumina [hexane–AcOEt (2:1, v/v)] to give (±)-4-(1-benzyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purin-2-yl)-3-(1-benzyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purin-2-yl)carbonyl-2,6-dimethyl-4-heptanol (**17**) (8 mg, 4.2%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (6H, br d, J=9 Hz, Me_2), 0.77 (6H, d, J=8 Hz, Me_2), 1.25—1.80 (4H, m, $Me_2C\underline{H}$ and $MeC\underline{H}C\underline{H}_2$), 2.36 (6H, d, J=1 Hz, two aromatic Me's), 2.96 (2H, br, COCH and OH), 3.97 (6H, s, two NMe's), 5.58 (4H, br, two $PhC\underline{H}_2$'s), 6.72—7.20 (10H, m, two Ph's), 7.27 and 7.28 (1H, each, q, J= 1 Hz, two aromatic protons). MS *m/z*: 755 (M^+).

The starting material **7** (37 mg, 25%) was recovered as the most polar substance.

1-Benzyl-2-benzyloxycarbonyl-1,4-dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (20) i) A solution of **7** (293 mg, 1.0 mmol) in dry THF (35 ml) was cooled to −78 °C and a 1.34 M solution of *n*-BuLi (0.75 ml, 1.0 mmol) in hexane was added under N_2. After 15 min, a solution of $PhCH_2OCOCl$ (0.19 g, 1.1 mmol) in THF (5 ml) was added and the mixture was stirred for 15 min. The mixture was then allowed to warm to room temperature and stirring was continued for a further 2.5 h. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 ml) and H_2O (60 ml) after being brought to pH 7 by addition of 10% aqueous H_3PO_4. The aqueous layer was extracted with CH_2Cl_2 (20 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography [30 mm, $CHCl_3$–MeOH (10:1, v/v)] to give a mixture of substances (146 mg) less polar than **7**. This was further fractionated by flash chromatography [20 mm, AcOEt–EtOH (10:1, v/v)]. As the most polar substance, bis(1-benzyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purin-2-yl) ketone (**21**) was obtained as a solid (29 mg, 9.5%). Recrystallization from MeOH gave orange needles, mp 278—281 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (6H, d, J=1 Hz, two CMe's), 3.94 (6H, s, two NMe's), 6.07 (4H, s, two CH_2's), 7.24 (10H, s, two Ph's) 7.41 (2H, q, J=1 Hz, two heterocyclic protons). MS *m/z*: 612 (M^+).

The fractions containing three less polar substances were combined and concentrated *in vacuo* to leave a semisolid (86 mg). This was purified by layer chromatography on silica gel [AcOEt–EtOH (20:1, v/v)] to give **20** (16 mg, 3.7%), mp 191—197 °C. Recrystallizations from EtOH gave an analytical sample as slightly yellow needles, mp 195—199 °C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 241 (24800), 285 (16300), 344 (4500). IR ν_{max}^{Nujol} cm^{-1}: 1722 (ester CO), 1692 (amide CO). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, d, J=1 Hz, CMe), 3.97 (3H, s, NMe), 5.44 (2H, s, OCH_2), 6.14 (2H, s, NCH_2), 7.25 (5H, s, $NCH_2\underline{Ph}$), 7.39 [6H, br, $OCH_2\underline{Ph}$ and C(7)H]. MS *m/z*: 427 (M^+). *Anal.* Calcd for $C_{24}H_{21}N_5O_3$: C, 67.43; H, 4.95; N, 16.39. Found: C, 67.19; H, 4.95; N, 16.40.

ii) Compound **7** (880 mg, 3.0 mmol) was treated in a manner similar to that described under method (i) except that five equivalents of $PhCH_2OCOCl$ (2.56 g, 15 mmol) was used. The crude products were separated by flash chromatography [40 mm, AcOEt–hexane (3:1, v/v)] to

give **20** (128 mg, 10%), mp 194—197 °C and the starting material **7** (134 mg, 15%).

1-Benzyl-2-chloro-1,4-dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (22) Compound **7** (293 mg, 1.0 mmol) was treated with *n*-BuLi in the same way as described for the preparation of **20** and a solution of NCS (134 mg, 1.0 mmol) in THF (5 ml) was added to the solution at −78 °C under N_2. The mixture was stirred for 15 min and then allowed to warm to room temperature, and stirring was continued for a further 100 min. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 ml) and H_2O (20 ml) after being neutralized with 10% aqueous H_3PO_4. The aqueous layer was extracted with CH_2Cl_2 (20 ml). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) (AcOEt) to give **22** (96 mg, 29%), mp 219—220 °C, and **7** (83 mg, 28%). Recrystallizations of **22** from MeOH gave an analytical sample as colorless needles, mp 219—220 °C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 235 (33300), 239(sh) (33100), 264 (8500), 267(sh) (8400), 311 (7200). IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, d, J=1 Hz, CMe), 3.91 (3H, s, NMe), 5.64 (2H, s, CH_2), 7.27—7.45 [6H, m, Ph and C(7)H]. MS *m/z*: 327 and 329 (M^+). *Anal.* Calcd for $C_{16}H_{14}ClN_5O$: C, 58.63; H, 4.31; N, 21.37. Found: C, 58.77; H, 4.26; N, 21.42.

1-Benzyl-7-bromo-2-chloro-1,4-dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (23) Br_2 (0.027 ml, 0.52 mmol) was added to a suspension of **22** (167 mg, 0.51 mmol) in AcOH (4 ml) and the mixture was stirred at room temperature for 20 min. The mixture was concentrated *in vacuo* to leave a solid residue. This was partitioned between saturated aqueous $NaHCO_3$ (10 ml) and CH_2Cl_2 (10 ml). The aqueous layer was extracted with CH_2Cl_2 (5 ml). The combined CH_2Cl_2 solutions were dried over $MgSO_4$ and concentrated *in vacuo* to leave a solid. Recrystallization from MeOH (40 ml) gave **23** (124 mg), mp 155—157 °C (dec.). A second crop (31 mg) of **23** was obtained from the mother liquor by further recrystallization from MeOH. The total yield was 75%. An analytical sample was obtained by recrystallization from MeOH as colorless needles, mp 157—159 °C (dec.). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 243 (33800), 265(sh) (8700), 320 (5800). IR ν_{max}^{Nujol} cm^{-1}: 1714 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s, CMe), 3.86 (3H, s, NMe), 5.63 (2H, s, CH_2), 7.35 (5H, m, Ph). MS *m/z*: 405, 407, and 409 (M^+). *Anal.* Calcd for $C_{16}H_{13}BrClN_5O$: 47.26; H, 3.22; N, 17.22. Found: C, 47.14; H, 3.16; N, 17.20.

(±)-1-Benzyl-2-chloro-1,4-dihydro-7-(1-hydroxy-3-methylbutyl)-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (24) *tert*-BuLi (2.3 M solution in pentane, 0.15 ml, 0.35 mmol) was added to a solution of **23** (122 mg, 0.30 mmol) in anhydrous THF (12 ml) at −78 °C. After 15 min, **13** (0.04 ml, 0.36 mmol) was added and the mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature. The mixture was 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 combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography [20 mm, $(CH_2Cl)_2$–EtOH (25 : 1, v/v and then 15 : 1, v/v)]. The starting material **23** (27 mg, 22%) was recovered as the least polar substance. From the successive eluate, crude **22** (20 mg, 20%) was obtained as a slightly yellow solid, which gave colorless needles, mp 217—218 °C, on recrystallization from MeOH. Crude **24** (38 mg) was obtained from the more polar fractions as a yellowish glass. This was purified by silica gel layer chromatography [$(CH_2Cl)_2$–EtOH (10 : 1, v/v)] to give almost pure **24** (24 mg, 19%) as a slightly yellow glass, ^{1}H-NMR ($CDCl_3$) δ: 0.88 and 0.95 (6H, d each, J=7 Hz, Me_2), 1.58 (2H, m, $CHCH_2$), 1.89 (1H, m, Me_2CH), 2.33 [3H, s, C(6)Me], 3.90 (3H, s, NMe), 4.85 (2H, m, CHOH), 5.62 and 5.72 (1H each, d, J=15 Hz, $PhCH_2$), 7.36 (5H, m, Ph).

When **24** (20 mg) was allowed to stand at room temperature for several days, at least two degradation products were found by thin-layer chromatography. From the mixture, **24** (12 mg) was recovered by flash chromatography [$(CH_2Cl)_2$–EtOH (15 : 1, v/v)]. As the less polar substance, a 5 : 1 mixture of (*E*)- and (*Z*)-**26** (2 mg) was obtained as a colorless solid, ^{1}H-NMR ($CDCl_3$) δ: 0.98 and 1.13 [a total of 6H, d each, J=7 Hz, (*Z*)- and (*E*)-Me_2], 2.22 and 2.38 [a total of 3H, s each, (*Z*)- and (*E*)-C(6)Me], 2.53 (1H, m, Me_2CH), 3.87 (3H, s, NMe), 5.5 (br) and 5.73 (dd, J=16, 7 Hz) [a total of 1H, (*Z*)- and (*E*)-MeCHCH=], 5.65 (2H, s, CH_2), 6.54 (d, J=12 Hz) and 7.16 (d, J=16 Hz) [a total of 1H, (*Z*)- and (*E*)-C(7)CH=], 7.34 (5H, s, Ph). MS *m/z*: 395.1507 and 397.1488 (M^+, $C_{21}H_{22}ClN_5O$ requires 395.1510 and 397.1482).

1-Benzyl-7-formyl-1,4-dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (28) Compound **7** (14.67 g, 50.0 mol) was added to a cold solution of $POCl_3$ (8.5 ml) in dry $HCONMe_2$ (80 ml) and the mixture was stirred at room temperature for 1.5 h. The resulting mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ (600 ml) and the precipitate was filtered off, washed successively with H_2O (400 ml) and a little EtOH, and dried over P_2O_5 *in vacuo* to give **28** (16.07 g, 100%), mp 227—228 °C (dec.). Recrystallizations from EtOH gave an analytical sample as colorless needles, mp 228—229 °C (dec.). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 226 (sh) (18600), 254 (21000), 324 (16500). IR ν_{max}^{Nujol} cm^{-1}: 1720 (formyl CO), 1700 (amide CO). ^{1}H-NMR ($CDCl_3$) δ: 2.67 (3H, s, CMe), 4.00 (3H, s, NMe), 5.64 (2H, s, CH_2), 7.37 (5H, s, Ph), 7.76 [1H, s, C(2)H], 10.87 (1H, s, CHO). MS *m/z*: 321 (M^+), 293 (M^+ − CO). *Anal.* Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.70; N, 21.80. Found: C, 63.79; H, 4.63; N, 21.89.

1-Benzyl-1,4-dihydro-7-hydroxymethyl-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (29) A mixture of **28** (321 mg, 1.0 mmol), $NaBH_4$ (57 mg, 1.5 mmol), and MeOH (50 ml) was stirred at room temperature for 30 min. The mixture was concentrated *in vacuo* to leave a solid. H_2O (10 ml) was added to the residue. The mixture was neutralized with 10% aqueous H_3PO_4 and then extracted with CH_2Cl_2 (2 × 30 ml). The CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a solid, which was dried over P_2O_5 to give **29** (322 mg, 100%), mp 169—171 °C (dec.). Recrystallizations from MeOH gave an analytical sample as colorless needles, mp 171—173 °C (dec., often showed an arbitrary melting point between 160 and 185 °C). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 241 (34200), 259(sh) (6100), 314 (6100). IR ν_{max}^{Nujol} cm^{-1}: 3280 (OH), 1704 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s, CMe), 3.92 (3H, s, NMe and 1H, t, J=7 Hz, OH), 4.82 (2H, d, J=7 Hz, CH_2OH), 5.60 (2H, s, $PhCH_2$), 7.35 (5H, s, Ph), 7.70 [1H, s, C(2)H]. *Anal.* Calcd for $C_{17}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66. Found: C, 63.18; H, 5.41; N, 21.40.

Hydrogenolysis of 29 in the Presence of Perchloric Acid A solution of **29** (647 mg, 2.0 mmol) and 70% aqueous $HClO_4$ (0.29 g, 2 mmol) in AcOH (150 ml) was hydrogenated over 10% Pd–C (0.66 g) at *ca.* 50 °C under atmospheric pressure for 5 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (25 ml) and saturated aqueous $NaHCO_3$ (25 ml). The aqueous layer was extracted with $CHCl_3$ (2 × 10 ml). The combined $CHCl_3$ extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a solid (469 mg). This was purified by flash chromatography [20 mm, AcOEt–EtOH (10 : 1, v/v)]. Compound **8** (260 mg, 42%) was obtained as the less polar product. Recrystallization from MeOH gave colorless needles, mp 203 °C, identical with the analytical sample described above. As the more polar product, **30** (79 mg, 13%) was obtained as a colorless solid. Recrystallization from $CHCl_3$–MeOH (1 : 1, v/v) gave an analytical sample as colorless needles, mp 270—273 °C (dec.). UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 241(sh) (51700), 243 (52900), 261(sh) (14900), 320 (10300). ^{1}H-NMR ($CDCl_3$) δ: 1.95 (6H, s, two CMe's), 3.89 (6H, s, two NMe's), 5.24 [2H, s, C(7)CH_2], 5.55 (4H, s, two $PhCH_2$'s), 7.31 (10H, s, two Ph's), 7.59 (2H, s, two heterocyclic protons). MS *m/z*: 598 (M^+), 306 [M^+ − (1-benzylwye − H)]. *Anal.* Calcd for $C_{33}H_{30}N_{10}O_2$: C, 66.20; H, 5.05; N, 23.40. Found: C, 65.88; H, 5.05; N, 23.36.

1,4-Dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (2a) Compound **7** (147 mg, 0.50 mmol) was dissolved in MeOH (85 ml) containing 70% aqueous $HClO_4$ (0.1 ml, 1.2 mmol) and hydrogenated over 10% Pd–C (300 mg) at *ca.* 60 °C for 10 h. The catalyst was removed by filtration and washed with hot MeOH (150 ml). The combined filtrate and washings were neutralized with saturated aqueous $NaHCO_3$ and then concentrated *in vacuo*. The residue was washed with H_2O and dried to give **2a** (70 mg, 69%), mp > 310 °C. This sample was identical with an authentic sample.[22]

1,4-Dihydro-4,6,7-trimethyl-9*H*-imidazo[1,2-*a*]purin-9-one (2b) i) A solution of **29** (1.00 g, 3.09 mmol) in EtOH (400 ml) was hydrogenated over 10% Pd–C (1.00 g) at *ca.* 50 °C under atmospheric pressure for 10 h. The catalyst (1.00 g) was added again and the reduction was continued for a further 9 h. The catalyst was filtered off and extracted with MeOH using a Soxhlet extractor. The extracts were combined with the filtrate and concentrated *in vacuo* to leave **2b**·H_2O (363 mg, 50%) as a colorless solid, mp > 300 °C. For analysis, this was recrystallized from MeOH, dried over P_2O_5 at 2 mmHg and 120 °C for 18 h, and then exposed to air until constant weight was reached to give colorless needles, mp > 300 °C. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 235 (33300), 258(sh) (5600), 312 (5200); $\lambda_{max}^{10\%\ MeOH}$ nm (ε): 236 (34300), 263 (5200), 316 (4900); $\lambda_{max}^{H_2O}$ (pH 1) nm (ε): 233 (37500), 289 (7400); $\lambda_{max}^{H_2O}$ (pH 7) nm (ε): 236 (34800), 264 (5700), 315 (4900); $\lambda_{max}^{H_2O}$ (pH 13) nm (ε): 236 (36300), 269 (6000), 306 (7000). IR ν_{max}^{Nujol} cm^{-1}: 1688 (CO). ^{1}H-NMR (Me_2SO-d_6) δ: 2.11 [3H, s, C(6)Me], 2.56 [3H, s, C(7)Me], 3.73 (3H, s, NMe), 8.12 [1H, s, C(2)H], 13.51 (1H, br, NH). *Anal.* Calcd for $C_{10}H_{11}N_5O \cdot H_2O$: C, 51.05; H, 5.57; N, 29.77. Found: C, 51.32; H, 5.34; N, 29.57.

ii) A mixture of **8** (123 mg, 0.40 mmol), 10% Pd–C (0.12 g), 70% aqueous

$HClO_4$ (0.05 ml, 0.58 mmol), and MeOH (50 ml) was shaken under H_2 at atmospheric pressure and *ca.* 60 °C for 8 h. The reduction was continued for a further 8 h with additional 10% Pd–C (0.10 g). The catalyst was filtered off and extracted with MeOH using a Soxhlet extractor. The extracts were combined with the filtrate and concentrated *in vacuo*. The residue was suspended in H_2O (15 ml) and neutralized with saturated aqueous $NaHCO_3$. The precipitate was collected by filtration, washed with H_2O (5 ml), and dried to give **2b**·H_2O (78 mg). The combined filtrate and washings were extracted with $CHCl_3$ (6 × 10 ml) and the extracts were dried over $MgSO_4$. Removal of the solvent by evaporation left a solid, which was recrystallized from MeOH to give a second crop of **2b**·H_2O (3 mg). The total yield was 86%.

iii) The hydrogenolysis described under item (ii) was completed in 8 h when the solvent was replaced by AcOH. Similar work-up gave **2b**·H_2O (81 mg, 86%).

Acknowledgment This work was supported by a Grant-in-Aid for Scientific Research (No. 59570890) from the Ministry of Education, Science and Culture, Japan.

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