Purines. LXXIII.[1] Syntheses of 8-Alkoxy- and 8-Hydroxy-3-alkyladenines from 3-Alkyladenine 7-Oxides through 7-Alkoxy-3-alkyladenines

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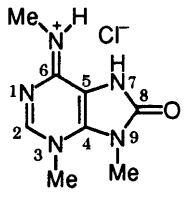
7-Alkoxy-3-alkyladenine perchlorates (9) were prepared from 3-alkyladenines (4) by *N*-oxidation followed by alkylation with alkyl halides in *N,N*-dimethylacetamide. The 7-methoxy derivatives 9d,g,j thus obtained afforded 3-methyl-8-hydroxyadenine (7a), 3-ethyl-8-hydroxyadenine (7b), and 3-benzyl-8-hydroxyadenine (7c) in 74%, 72%, and 39% yields, respectively, on treatment with boiling 0.1 N aqueous sodium hydroxide, whereas treatment of 9d, g, j with sodium methoxide in methanol at room temperature afforded 3-alkyl-8-methoxyadenines (10m, p, q) in 91%—98% yields. Similar treatment of 9d with sodium ethoxide in ethanol afforded 8-ethoxy-3-methyladenine (10n) in 89% yield. Compounds 10m, q were alternatively prepared from 9d,j in 77% and 84% yields, respectively, by treatment with 0.1 N aqueous sodium hydroxide in the presence of methanol. This method was suitable for the synthesis of the 8-benzyloxy compound 10o: it was obtained in 60% yield by treating 7-benzyloxy-3-methyladenine perchlorate (9f) with a mixture of aqueous sodium hydroxide and benzyl alcohol. Compounds 7 were alternatively prepared from 9 through 10. For example, 7c was obtained in 84% overall yield by treatment of 9j with sodium methoxide, followed by hydrolysis of the resulting 10q with boiling 1 N hydrochloric acid.

On the other hand, methylation of 3-methyladenine 7-oxide (8a) with dimethyl sulfate in 0.1 N aqueous sodium hydroxide in the absence or presence of added methanol afforded N^6,3-dimethyladenine 7-oxide (14) in 13% or 14% yield, together with 7a (4% yield) or 10m (11%).

Key words 7-alkoxy-3-alkyladenine; 3-alkyl-8-hydroxyadenine; 8-alkoxy-3-alkyladenine; 3-alkyladenine 7-oxide *O*-alkylation; nucleophilic substitution

Caissarone hydrochloride (**1**), a biologically active compound[2] isolated from the sea anemone *Bunodosoma caissarum* CORREA 1964,[3] has been synthesized by us through regioselective N(3)-methylation of N^6,9-dimethyl-8-oxoadenine as the key step.[4] Its chemical structure (**1**) is unique in that it may be regarded as a member of the 3-alkyl-8-oxoadenine family: 3-ethyl-8-hydroxyadenine (**7b**) (exists as the enol tautomer in the solid state rather than the keto tautomer)[5] is the only known example of unmodified 3-alkyl-8-oxoadenines, and neither 3, N^x- nor 3,O^8-dialkyl-8-oxoadenines have been reported, except for N^6-benzyl-3-methyl-8-oxoadenine.[6] We have already demonstrated that **1** affords the zwitterionic free base **2**, which is able to form a hetero-base pair with 2',3',5'-tri-*O*-acetylguanosine in deuterated dimethyl sulfoxide by forming intermolecular hydrogen bonding.[4b] These findings have directed our attention to the chemical properties of hitherto unknown 3,9-dimethyl-8-oxoadenine (N^6-demethylcaissarone) (**3**). A new strategy is required for the synthesis of **3**, because methylation of 9-methyl-8-oxoadenine has been reported to occur at the 1-position[7] in contrast with the regioselectivity observed for the key methylation step in the synthesis of **1**. With a view to establishing general synthetic routes to 3-alkyl-8-hydroxyadenines (**7**) and their O^8-alkyl derivatives **10** which may be applicable to the synthesis of **3**, we investigated in the present study *N*-oxidation of 3-alkyladenines (**4**) to produce the corresponding 7-oxides **8**, alkylation of **8** with alkyl halides to afford 7-alkoxy-3-alkyladenine salts (**9**), and nucleophilic substitution of **9** at the 8-position.



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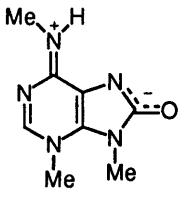

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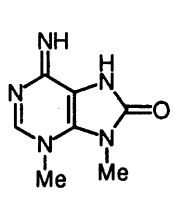

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In our previous work,[5] 3-ethyl-8-hydroxyadenine (**7b**) had been synthesized from 3-ethyladenine (**4b**) by treatment with an excess of benzyl chloroformate to give the monocycle **5b**, followed by heating with acetic acid and subsequent hydrogenolysis of the resulting N^6-(benzyloxycarbonyl)-3-ethyl-8-hydroxyadenine (**6b**). A similar approach to the 3-benzyl analogue **7c** was unsuccessful because removal of the benzyloxycarbonyl group from **6c**, effected by catalytic hydrogenation, was accompanied with unavoidable debenzylation at the 3-position.[5]

On the other hand, we have already synthesized adenine 7-oxide (**11**) from 3-benzyladenine (**4c**) through 3-benzyladenine 7-oxide (**8c**).[8] Because treatment of **11** with hot acetic acid affords 8-oxoadenine (**12**),[8] 3-benzyl-8-hydroxyadenine (**7c**) might be prepared from **8c** in a similar manner. However, heating **8c** in acetic acid under reflux for 42 h afforded a complex mixture of products. Treatment of **8c** with 1 N aqueous sodium hydroxide at room temperature for 24 h afforded a crude product, whose ^{1}H-NMR spectrum was indicative of cleavage in the pyrimidine moiety.[9] It has been reported that 3,7-dialkyladenines also undergo ring cleavage in the pyrimidine moiety on treatment with boiling 1 N aqueous sodium hydroxide.[10] Furthermore, attack of hydroxide ion on the adenine ring at the 2-position is much more facilitated by the 1-alkoxy group than by the 1-oxide or 1-alkyl group.[11] These facts led us to check the chemical

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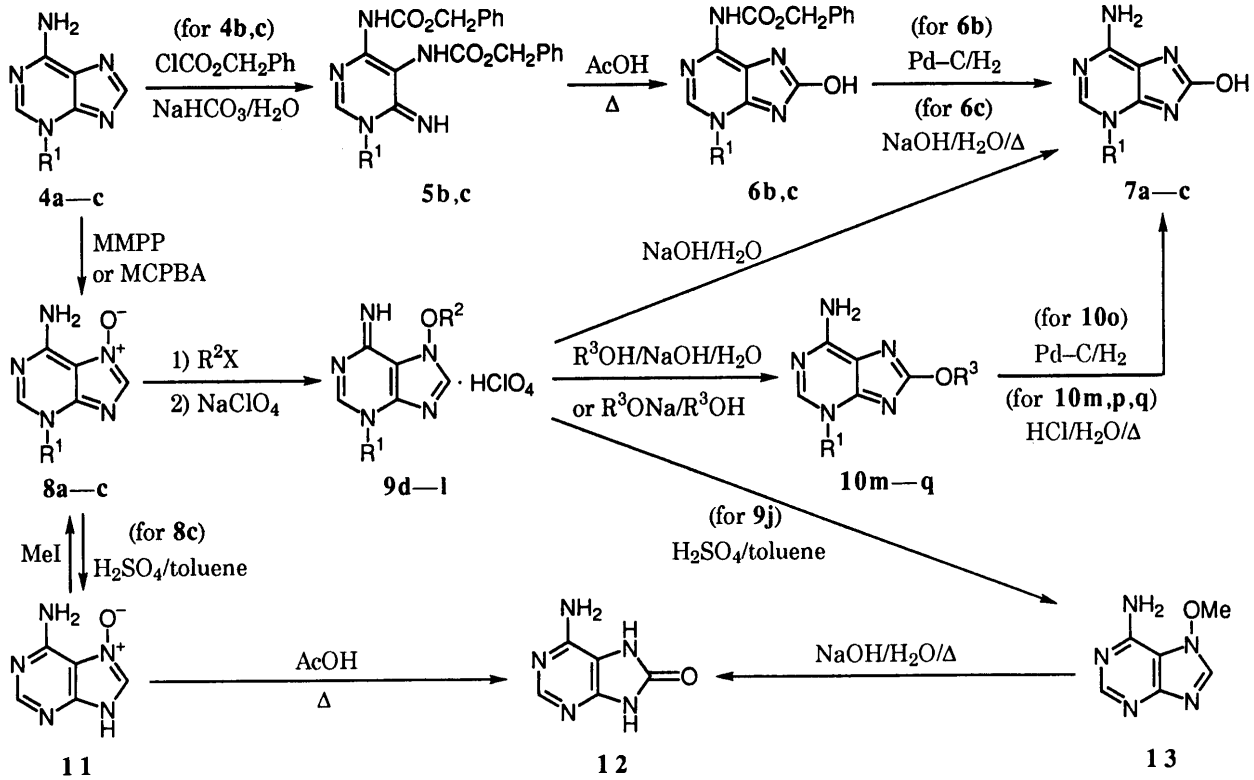

a: R^1 = Me **b**: R^1 = Et **c**: R^1 = $PhCH_2$ **d**: R^1 = R^2 = Me
e: R^1 = Me, R^2 = Et **f**: R^1 = Me, R^2 = $PhCH_2$ **g**: R^1 = Et, R^2 = Me **h**: R^1 = R^2 = Et
i: R^1 = Et, R^2 = $PhCH_2$ **j**: R^1 = $PhCH_2$, R^2 = Me **k**: R^1 = $PhCH_2$, R^2 = Et **l**: R^1 = R^2 = $PhCH_2$
m: R^1 = R^3 = Me **n**: R^1 = Me, R^3 = Et **o**: R^1 = Me, R^3 = $PhCH_2$ **p**: R^1 = Et, R^3 = Me
q: R^1 = $PhCH_2$, R^3 = Me

Chart 1

behavior of 7-methoxy-3-methyladenine perchlorate (**9d**), which had been obtained from adenine 7-oxide (**11**) by means of methylation.[8] When treated with 0.1 N aqueous sodium hydroxide at room temperature for 2 h, **9d** was attacked by hydroxide ion at the 8-position to give 8-hydroxy-3-methyladenine (**7a**) in 42% yield.[12] This hydroxide-ion attack at the 8-position stands in contrast with the cases of 3-benzyladenine 7-oxide (**8c**) and 3,7-dialkyladenines described above. The yield of **7a** was increased to 74% by heating the reaction mixture under reflux for 1.5 h. The correctness of the structure of **7a** was supported by its close UV spectral similarity to **7b**.[5] Although the 3-unsubstituted 7-methoxy compound **13** was more stable[13] than **9d**, an analogous reaction was realized with it: on treatment with boiling 0.1 N aqueous sodium hydroxide for 30 min, **13** afforded 8-oxoadenine (**12**) (isolated as the sulfate) in 81% yield.

In order to check the generality of the above synthetic utility of **9d**, we planned to prepare other 7-alkoxy-3-alkyladenine salts (**9e—l**) by alkylation of 3-alkyladenine 7-oxides (**8**). Thus, the synthesis started with *N*-oxidations of 3-methyladenine (**4a**) and 3-ethyladenine (**4b**), which were analogous to that of 3-benzyladenine (**4c**).[8] Treatment of **4a, b** with 1.5 molar eq of *m*-chloroperoxybenzoic acid (MCPBA) in methanol–acetate buffer (pH 5.5) at 30 °C for 15 h afforded the corresponding 7-oxides **8a, b** in 25% yield each. In contrast to **4c**, the 3-methyl and 3-ethyl analogues **4a, b** provided the 7-oxides **8a, b** in rather lower yields when treated with 0.75 molar eq of magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) in methanol at 30 °C for 20 h. Table 1 summarizes the results of these *N*-oxidations. Compound **8a** thus obtained was identical with an authentic sample,[8] and the correctness of the 7-oxide structure of **8b** was supported by the UV and ^{1}H-NMR spectral similarities to **8a, c**.

Table 1. *N*-Oxidation of 3-Alkyladenines (**4**) Leading to 3-Alkyladenine 7-Oxides (**8**)

Entry	Substrate	Method[a]	Product	Yield (%)	Recovery (%)
1	**4a**	A	**8a**	25	43 (**4a**)
2	**4a**	B	**8a**	15	54 (**4a**)
3	**4b**	A	**8b**	25	27 (**4b**)
4	**4b**	B	**8b**	13	48 (**4b**)
5[b]	**4c**	A	**8c**	24	29 (**4c**)
6[b]	**4c**	B	**8c**	40	51 (**4c**)

a) A: a solution of 1.5 molar eq of MCPBA in methanol was added to a solution of **4** in a mixture of methanol and 1 M acetate buffer (pH 5.5) over a period of 5 h, and the resulting mixture was kept at 30 °C for a further 15 h; B: the substrate **4** was treated with 0.75 molar eq of MMPP·$6H_2O$ in methanol at 30 °C for 20 h. *b*) Taken from ref. 8, where acetate buffer of pH 5.0 was used for method A.

Alkylation of 3-alkyladenine 7-oxides (**8a—c**) with alkyl

Table 2. Alkylation of 3-Alkyladenine 7-Oxides (**8**) with Alkyl Halides in DMAc at 30 °C for 20 h, Followed by Treatment with Aqueous Sodium Perchlorate, Leading to 7-Alkoxy-3-alkyladenine Perchlorates (**9**)

Substrate	Reagent (Molar eq)	Product	Yield (%)	Appearance[a]	mp (dec.) (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
8a·$2H_2O$	MeI (5)	**9d**	96[b]	Colorless prisms (A)	254—255	$C_7H_9N_5O\cdot HClO_4$	30.07 (30.06)	3.60 3.65	25.04 25.09)
8a·$2H_2O$	EtI (5)	**9e**	88	Colorless prisms (A)	249.5—250.5	$C_8H_{11}N_5O\cdot HClO_4$	32.72 (32.70)	4.12 4.13	23.85 23.78)
8a·$2H_2O$	$PhCH_2Br$ (3)	**9f**	89	Slightly yellow plates (A)	173—175	$C_{13}H_{13}N_5O\cdot HClO_4\cdot 1/4H_2O$[c]	43.34 (43.27)	4.06 4.06	19.44 19.44)
8b·$3H_2O$	MeI (5.4)	**9g**	86	Colorless needles (B)	250—250.5	$C_8H_{11}N_5O\cdot HClO_4$	32.72 (32.61)	4.12 4.25	23.85 23.83)
8b·$3H_2O$	EtI (5.1)	**9h**	81	Slightly yellow needles (A)	249.5—250.5	$C_9H_{13}N_5O\cdot HClO_4$	35.13 (35.06)	4.59 4.69	22.76 22.76)
8b·$3H_2O$	$PhCH_2Br$ (2.2)	**9i**	86	Yellowish prisms (C)	169—171	$C_{14}H_{15}N_5O\cdot HClO_4\cdot 1/3C_2H_5OH$[d]	45.74 (45.77)	4.71 4.75	18.18 18.12)
8c·H_2O	MeI (5)	**9j**	97	Yellowish prisms (D)	207.5—209	$C_{13}H_{13}N_5O\cdot HClO_4$	43.89 (43.83)	3.97 3.96	19.69 19.72)
8c·H_2O	EtI (5.1)	**9k**	89	Slightly yellow needles (B)	168—170	$C_{14}H_{15}N_5O\cdot HClO_4$	45.48 (45.69)	4.36 4.43	18.94 19.10)
8c·H_2O	$PhCH_2Br$ (2.2)	**9l**	91	Yellowish needles (C)	186—188	$C_{19}H_{17}N_5O\cdot HClO_4$	52.85 (52.65)	4.20 4.18	16.22 16.09)

a) The letter in parentheses refers to the recrystallization solvent with A, 50% (v/v) aqueous methanol; B, 50% (v/v) aqueous ethanol; C, 90% (v/v) aqueous ethanol; D, ethanol. *b*) Lit. yield 89%.[8] *c*) Dried over phosphorus pentoxide at 2 mmHg and 50 °C for 12 h. *d*) See Experimental.

Table 3. UV and ^{1}H-NMR Spectral Data for 7-Alkoxy-3-alkyladenine Perchlorates (**9**)

Compd.	UV spectra[a]						^{1}H-NMR Spectra in Me_2SO-d_6 Chemical shift (ppm)			
	95% EtOH		H_2O (pH 1)		H_2O (pH 7)					
	λ_{max} (nm)	$\varepsilon\times10^{-3}$	λ_{max} (nm)	$\varepsilon\times10^{-3}$	λ_{max} (nm)	$\varepsilon\times10^{-3}$	*N*-Alkyl	*O*-Alkyl	C(2)-H [C(8)-H][b]	NH
9d	281	16.6	278	15.9	278	15.9	3.94 (s)	4.24 (s)	8.77 (s) [9.11 (s)]	8.70 (br) 9.49 (br)
9e	282	16.1	279	15.5	279	15.5	3.94 (s)	1.36 (t) 4.48 (q)	8.78 (s) [9.09 (s)]	8.55 (br) 9.49 (br)
9f	282	15.0	280	14.3	280	14.1	3.89 (s)	5.44 (s) 7.35—7.50 (m)	8.71 (s) [8.63 (s)]	8.59 (br) 9.47 (br)
9g	282	16.8	279	16.3	279	16.2	1.47 (t) 4.41 (q)	4.24 (s)	8.84 (s) [9.11 (s)]	8.70 (br) 9.51 (br)
9h	282	16.4	279	15.9	279	16.1	1.47 (t) 4.41 (q)	1.37 (t) 4.48 (q)	8.84 (s) [9.08 (s)]	8.54 (br) 9.51 (br)
9i	283	14.9	280	14.3	280	14.0	1.43 (t) 4.37 (q)	5.44 (s) 7.35—7.50 (m)	8.78 (s) [8.65 (s)]	8.60 (br) 9.49 (br)
9j	283	17.5	280	16.9	280	16.8	5.59 (s) 7.30—7.54 (m)	4.23 (s)	9.05 (s) [9.08 (s)]	8.79 (br) 9.62 (br)
9k	284	17.2	281	16.7	281	16.6	5.59 (s) 7.31—7.52 (m)	1.36 (t) 4.47 (q)	9.05 (s) [9.05 (s)]	8.64 (br) 9.62 (br)
9l	284	16.0	282	15.0	282	15.1	5.55 (s) 7.30—7.47 (m)	5.43 (s) 7.30—7.47 (m)	8.98 (s) [8.63 (s)]	8.71 (br) 9.61 (br)

a) The spectra measured in 0.1 N aqueous sodium hydroxide changed rapidly. *b*) In this column, the value for the proton indicated in these brackets is shown in brackets.

halides in *N*,*N*-dimethylacetamide (DMAc) at 30 °C took place smoothly at the oxygen atoms to provide, after treatment of the products with aqueous sodium perchlorate, 7-alkoxy-3-alkyladenine perchlorates (**9d—l**) in 81%—97% yields. Table 2 summarizes the results. The 7-alkoxy-3-alkyladenine structure of **9e—l** was supported by the UV and ^{1}H-NMR spectral similarity to **9d**[8] (Table 3). Further evidence for the 7-alkoxy structure was obtained by non-reductive debenzylation[8] of 3-benzyl-7-methoxyadenine perchlorate (**9j**), which afforded 7-methoxyadenine (**13**)[8] in 72% yield. In Table 3, the purine-ring proton signals of **9** are assigned as in the case of 1-alkoxy-7-alkyladenine salts[14]; the signal of **9j** at δ 9.05 is lower in height than the very close one at δ 9.08 and is therefore assigned to the C(2)-proton. The correctness of this assignment was supported by comparison of the spectrum of **9j** with that of the C(2)-deuterated species, which was prepared from 3-benzyladenine-*2-d* 7-oxide[8] by a similar methylation.

Like the 7-methoxy compound **9d**, the 7-ethoxy and 7-benzyloxy analogues **9e, f** afforded 8-hydroxy-3-methyladenine (**7a**) on treatment with boiling 0.1 N aqueous

sodium hydroxide for 1.5 h, but in somewhat lower yields (32%—37%). 3-Ethyl-8-hydroxyadenine (**7b**)[5] and 3-benzyl-8-hydroxyadenine (**7c**) were accordingly prepared from the corresponding 7-methoxy compounds **9g, j** in 72% and 39% yields, respectively. Although the free base of **9j** could not be obtained as a pure sample owing to its tendency to undergo hydrolysis leading to **7c**, heating of the crude free base in plain water raised the yield of **7c** to 48%. The correctness of the structure of **7c** was supported by comparison of the UV and ^{1}H-NMR spectra with those of **7a, b** and was verified by direct comparison with a sample prepared by alkaline hydrolysis of **6c**.

It was suggested by means of TLC that the reaction of **9** with aqueous sodium hydroxide always gave a by-product, which was inferred to be the corresponding 8-alkoxy-3-alkyladenine (**10**).[12] A plausible mechanism for the formation of **7** and **10** is illustrated in Chart 2. The reactions with the 7-methoxy compounds **9d, j** in the presence of added methanol indeed afforded the 8-methoxy derivatives **10m, q** in 77% and 84% yields, respectively. These compounds were also obtainable in higher yields (95%—98%) by treatment of **9d, j** with sodium methoxide in methanol. The 8-ethoxy compound **10n** was similarly obtained in 89% yield from **9d** by treatment with sodium ethoxide in ethanol. The same compound was produced in 35%—44% yields when **9d, e** were treated with a mixture of 0.1 N aqueous sodium hydroxide and ethanol. However, treatment of **9d** with sodium benzylate in benzyl alcohol furnished the 8-benzyloxy compound **10o** in only 28% yield, whereas **10o** was obtained from **9d** and **9f** in 52% and 60% yields, respectively, by treatment with 0.1 N aqueous sodium hydroxide and benzyl alcohol. Thus, the above two methods complement each other for a general synthesis of 8-alkoxy-3-alkyladenines (**10**). The correctness of the structure of **10** was supported by the following experiments: the 8-benzyloxy compound **10o** was converted into **7a** in 90% yield by hydrogenolysis using hydrogen and palladium-on-carbon; the 8-methoxy compounds **10m, p, q** afforded **7a, b, c** in 73%, 77%, and 88% yields, respectively, on hydrolysis with boiling 1 N hydrochloric acid.[15] The successful hydrolysis of **10q** constitutes a more efficient two-step synthesis (84% yield) of **7c** than the direct conversion (48% yield) from **9j**. Tables 4 and 5 summarize the results of these preparations of **7** and **10**, respectively.

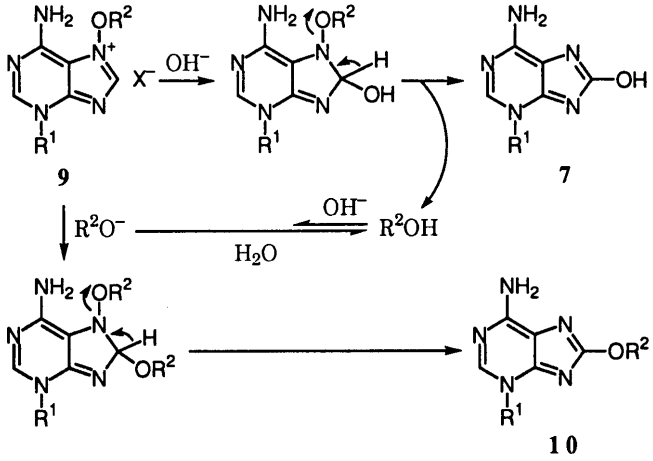

Chart 2

Having established the two-step or three-step synthesis of 3-alkyl-8-hydroxyadenines (**7**) from 3-alkyladenine 7-oxides (**8**), we next attempted the direct conversion of **8** into **7**. Treatment of 3-methyladenine 1-oxide (**8a**) with 1 molar eq of dimethyl sulfate in 0.1 N aqueous sodium hydroxide afforded the desired compound 8-hydroxy-3-methyladenine (**7a**), but in only 4% yield, together with 50% recovery of **8a** (Chart 3). The major product, obtained in 13% yield, was N^6,3-dimethyladenine 7-oxide (**14**). The correctness of the structure of **14** was confirmed by the identity of this compound with the *N*-oxide[16] obtained from the reaction of N^6,3-dimethyladenine with MCPBA. In the presence of added methanol, 8-methoxy-3-methyladenine (**10m**) was produced instead of **7a** in 11% yield, together with **14** (14% yield) and 57% recovery of **8a**.

In conclusion, we have demonstrated the synthetic utility of 3-alkyladenine 7-oxides (**8**), which undergo alkylation to afford 7-alkoxy-3-alkyladenine salts (**9**) in good yields. Compounds **9** have proved to undergo hydroxylation and alkoxylation at the 8-position, affording **7** and **10**, respectively. These compounds have potential

Table 4. Direct or Two-Step Preparation of 3-Alkyl-8-hydroxyadenines (**7**) from 7-Alkoxy-3-alkyladenine Perchlorates (**9**) or through 8-Alkoxy-3-alkyladenines (**10**)

Entry	Substrate				Product	Reaction conditions		Yield (%)
	No.	R^1	R^2	R^3		Method[a]	Time (h)	
1	**9d**	Me	Me	—	**7a**	A	2	42
2	**9d**	Me	Me	—	**7a**	B	1.5	74
3	**9e**	Me	Et	—	**7a**	B	1.5	32
4	**9f**	Me	$PhCH_2$	—	**7a**	B	1.5	37
5	**10m**	Me	—	Me	**7a**	C	2	72[b]
6	**10o**	Me	—	$PhCH_2$	**7a**	D	2	54[c]
7	**9g**	Et	Me	—	**7b**	B	1.5	72
8	**10p**	Et	—	Me	**7b**	C	3	70[d]
9	**9j**	$PhCH_2$	Me	—	**7c**	B	1.5	39
10	**9j**	$PhCH_2$	Me	—	**7c**	E	1	48
11	**10q**	$PhCH_2$	—	Me	**7c**	C	6	84[e]

a) A: kept in 0.1 N aqueous sodium hydroxide at room temperature; B: heated in 0.1 N aqueous sodium hydroxide under reflux; C: heated in 1 N hydrochloric acid under reflux; D: hydrogenated with hydrogen and 10% palladium-on-carbon in aqueous methanol at 40 °C; E: heat the corresponding free base in water under reflux. *b*) Overall yield from **9d**. *c*) Overall yield from **9f**. *d*) Overall yield from **9g**. *e*) Overall yield from **9j**.

Table 5. Conversion of 7-Alkoxy-3-alkyladenine Perchlorates (**9**) into 8-Alkoxy-3-alkyladenines (**10**)

Entry	Substrate			Product			Reaction conditions		Yield (%)
	No.	R^1	R^2	No.	R^1	R^3	Method[a]	Time (h)	
1	**9d**	Me	Me	**10m**	Me	Me	A	1	98
2	**9d**	Me	Me	**10m**	Me	Me	B	2	77
3	**9d**	Me	Me	**10n**	Me	Et	C	2	89
4	**9d**	Me	Me	**10n**	Me	Et	D	2.5	44
5	**9e**	Me	Et	**10n**	Me	Et	D	3	35
6	**9d**	Me	Me	**10o**	Me	$PhCH_2$	E	6	28
7	**9d**	Me	Me	**10o**	Me	$PhCH_2$	F	2	52
8	**9f**	Me	$PhCH_2$	**10o**	Me	$PhCH_2$	F	2	60
9	**9g**	Et	Me	**10p**	Et	Me	A	1	91
10	**9j**	$PhCH_2$	Me	**10q**	$PhCH_2$	Me	A	1	95
11	**9j**	$PhCH_2$	Me	**10q**	$PhCH_2$	Me	B	2	84

a) A: kept with 0.1 M sodium methoxide in methanol at room temperature; B: kept in 0.1 N aqueous sodium hydroxide–methanol (4:1, v/v) at room temperature; C: kept with 0.1 M sodium ethoxide in ethanol at 40 °C; D: kept in 0.1 N aqueous sodium hydroxide–ethanol (4:1, v/v) at room temperature; E: kept with 0.1 M sodium benzylate in benzyl alcohol at 40 °C; F: kept in 0.1 N aqueous sodium hydroxide–benzyl alcohol (4:1, v/v) at room temperature.

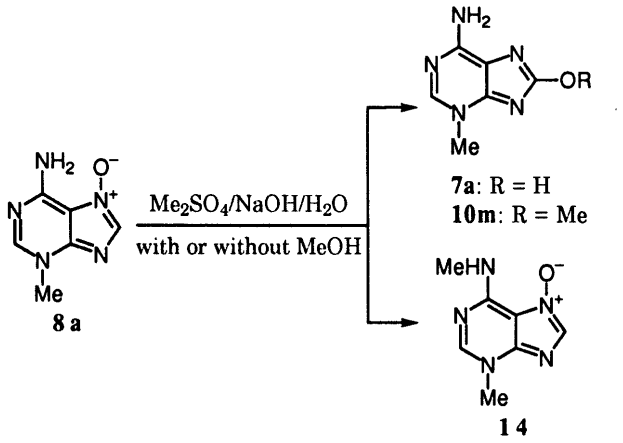

Chart 3

utility for the synthesis of novel derivatives of 8-oxoadenine (**12**). The results of initial work along this line, including the synthesis of N^6-demethylcaissarone (**3**), will shortly be reported elsewhere.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and are corrected. Spectra reported herein were recorded on either a Hitachi M-80 or a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer [for solutions in 95% aqueous ethanol, 0.1 N hydrochloric acid (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous sodium hydroxide (pH 13)], a Shimadzu FTIR-8100 IR spectrophotometer, or a JEOL JNM-EX-270 NMR spectrometer (measured at 25 °C in hexadeuterated dimethyl sulfoxide with tetramethylsilane as an internal standard). Elemental analyses and MS measurements were performed by Mr. Y. Itatani, Dr. M. Takani, and their associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[17] The following abbreviations are used: br=broad, d=doublet, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet.

3-Methyladenine 7-Oxide (8a) i) By Oxidation of **4a** with MCPBA: A solution of **4a**[18] (2.98 g, 20 mmol) in a mixture of methanol (150 ml) and 1 M acetic acid–sodium acetate buffer (pH 5.5) (140 ml) was stirred at 30 °C, and a solution of MCPBA (of 70% purity) (7.40 g, 30 mmol) in methanol (100 ml) was added dropwise over a period of 5 h. After having been stirred at 30 °C for a further 15 h, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between 10% hydrochloric acid (50 ml) and ether (50 ml). The aqueous layer was washed with ether (4 × 50 ml), neutralized with 10% aqueous sodium carbonate, and concentrated *in vacuo*. The residue was extracted with methanol (200 ml). Silica gel (8 g) was added to the methanolic extract, and the mixture was concentrated *in vacuo*. The resulting solid residue was subjected to flash chromatography [chloroform–methanol (5:1; 2:1, v/v)]. A solid obtained from earlier fractions was recrystallized from water to recover **4a** (1.27 g, 43%). Crude **8a** obtained from later fractions was recrystallized from water to afford **8a**·$2H_2O$ (1.01 g, 25%) as slightly dark prisms, mp 250—260 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **8a**·$2H_2O$.[8]

ii) By Oxidation of **4a** with MMPP: The peroxy acid MMPP·$6H_2O$ (1.86 g, 3.76 mmol) was added to a solution of **4a**[18] (745 mg, 4.99 mmol) in methanol (100 ml), and the resulting suspension was stirred at 30 °C for 20 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between 10% hydrochloric acid (20 ml) and ether (20 ml). The aqueous layer was washed with ether (4 × 20 ml), neutralized with 10% aqueous sodium carbonate, and concentrated *in vacuo*. The residue was purified by flash chromatography in a manner similar to that described above under item (i), and the crude products were separately recrystallized from water to afford **8a**·$2H_2O$ (148 mg, 15%), identical (by comparison of the IR spectrum and TLC mobility) with an authentic sample,[8] and **4a** (402 mg, 54%).

3-Ethyladenine 7-Oxide (8b) i) By Oxidation of **4b** with MCPBA: Treatment of **4b**[5] (2.45 g, 15 mmol) with MCPBA (of 70% purity) (5.55 g, 22.5 mmol) and isolation and recrystallization of the crude product were conducted in ways similar to those described above for the oxidation of **4a** [method (i)], giving **4b** (667 mg, 27%) and **8b**·$3H_2O$ (862 mg, 25%), mp 240—245 °C (dec.). Crude **8b**·$3H_2O$ was further recrystallized from water, dried over phosphorus pentoxide at 2 mmHg and room temperature for 24 h, and moisturized (by exposure to air at room temperature until a constant weight was reached) to afford an analytical sample of **8b**·$3H_2O$ as slightly yellow pillars, mp 240—245 °C (dec.); MS *m/z*: 179 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 221 nm (ε 14400), 263 (13300), 317 (3400); $\lambda_{max}^{H_2O}$ (pH 1) 278 (14700); $\lambda_{max}^{H_2O}$ (pH 7) 218 (15300), 258 (12000), 304 (4200); $\lambda_{max}^{H_2O}$ (pH 13) 261 (11100), 295 (sh) (5300); ^{1}H-NMR δ: 1.44 (3H, t, J=7 Hz, $\underline{Me}CH_2$), 4.27 (2H, q, J=7 Hz, $MeC\underline{H}_2$), 7.92 [1H, s, C(8)-H], 8.06 and 8.73 (1H each, br, NH's), 8.45 [1H, s, C(2)-H].[19] *Anal.* Calcd for $C_7H_9N_5O\cdot 3H_2O$: C, 36.05; H, 6.48; N, 30.03. Found: C, 35.86; H, 6.26; N, 29.98.

ii) By Oxidation of **4b** with MMPP: The MMPP oxidation of **4b**[5] (816 mg, 5 mmol) and purification of the product were carried out in ways similar to those described above for the oxidation of **4a** [method (ii)] to give **8b**·$3H_2O$ (150 mg, 13%) as slightly yellow pillars, mp 238—240 °C (dec.), and **4b** (389 mg, 48%). This sample of **8b**·$3H_2O$ was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

Alkylation of 3-Alkyladenine 7-Oxides (8) The procedures for benzylation of **8b** and methylation of **8c** will be described below in detail. The other alkylations were accomplished similarly.

7-Benzyloxy-3-ethyladenine Perchlorate (9i) A mixture of **8b**·$3H_2O$ (232 mg, 0.995 mmol), benzyl bromide (370 mg, 2.16 mmol), and DMAc (20 ml) was stirred at 30 °C for 20 h. The resulting slightly yellow solution was concentrated *in vacuo* by using a mechanical vacuum pump. The oily residue was washed with ether (2 × 5 ml) and dissolved in a little

water. The resulting solution was combined with a solution of sodium perchlorate monohydrate (185 mg, 1.32 mmol) in water (1 ml), and the mixture was cooled in an ice bath for 3 h. The precipitate that resulted was collected by filtration, washed successively with water (2 ml) and ethanol (2 ml), and dried to afford **9i**·1/3EtOH (328 mg, 86%), mp 150—153 °C. Recrystallization from ethanol and drying over phosphorus pentoxide at 50 °C and 2 mmHg for 24 h and then at 70 °C for 12 h furnished an analytical sample as yellowish prisms, mp 169—171 °C (dec.) (Tables 2 and 3).

3-Benzyl-7-methoxyadenine Perchlorate (9j) A mixture of **8c**·H_2O (1.67 g, 6.44 mmol) and methyl iodide (4.57 g, 32.2 mmol) in DMAc (30 ml) was stirred at 30 °C for 20 h. The resulting solution was concentrated *in vacuo* by using a mechanical vacuum pump. The residue was washed with ether (2 × 10 ml) and then dissolved in a mixture of water (10 ml) and methanol (5 ml). A solution of sodium perchlorate monohydrate (1.18 g, 8.4 mmol) in water (1 ml) was then added to the aqueous methanolic solution. The precipitate that resulted was collected by filtration, washed with water (2 × 3 ml), and dried to afford **9j** (2.23 g, 97%), mp 185—190 °C (dec.). Recrystallization of crude **9j** from ethanol afforded an analytical sample as yellowish prisms, mp 207.5—209 °C (dec.) (Tables 2 and 3).

3-Benzyl-7-methoxyadenine-*2-d* Perchlorate This compound was prepared in 80% yield from 3-benzyladenine-*2-d* 7-oxide (of 79% isotopic purity)[8] (31.6 mg, 0.13 mmol) in a manner similar to that described above for the preparation of **9j**, crystallizing in yellowish prisms, mp 204—205 °C (dec.); ^{1}H-NMR δ: 4.23 (3H, s, OMe), 5.59 (2H, s, PhC$\underline{H}_2$), 7.30—7.51 (5H, m, $\underline{Ph}CH_2$), 8.78 and 9.61 (1H each, br, NH_2), 9.05 [0.25H, s, C(2)-H], 9.08 [1H, s, C(8)-H]. The relative integral intensity of the C(2)-proton signal indicated that the isotopic purity of this sample was 75%.

Debenzylation of 9j Leading to 13 A mixture of **9j** (178 mg, 0.5 mmol), toluene (1 ml), and concentrated sulfuric acid (0.25 ml) was stirred at 35 °C for 4 h. The resulting solution was poured onto ice (1 g). The aqueous layer was separated from the organic layer, washed with toluene (2 × 5 ml), and passed through a column packed with Amberlite IRA-402 (HCO_3^-) (20 ml). The column was eluted with water (50 ml), and the eluate was concentrated *in vacuo* below 40 °C. The residue was purified by flash chromatography [ethyl acetate–ethanol (2 : 1, v/v)] to afford **13** (60 mg, 72%), mp 285—293 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **13**.[8]

8-Hydroxy-3-methyladenine (7a) i) From **9d**: Compound **9d** (250 mg, 0.894 mmol) was heated in 0.1 N aqueous sodium hydroxide (18 ml) under reflux for 1.5 h. The resulting solution was neutralized with 10% hydrochloric acid and then concentrated to a small volume. The precipitate that separated was collected by filtration, washed with water (2 × 1 ml), and dried to give **7a** (109 mg, 74%), mp > 300 °C. Recrystallization of this sample from water afforded an analytical sample of **7a** as colorless needles, mp > 300 °C; pK_a (in water at 30 °C and ionic strength 1.0)[20] 4.10 ± 0.06 (basic), 11.47 ± 0.04 (acidic); MS *m/z*: 165 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 232 nm (ε 18800), 298 (18300); $\lambda_{max}^{H_2O}$ (pH 1) 217 (22900), 287 (19400); $\lambda_{max}^{H_2O}$ (pH 7) 228 (20400), 294 (20100); $\lambda_{max}^{H_2O}$ (pH 13) 231 (sh) (9200), 306 (14900); IR ν_{max}^{Nujol} cm^{-1}: 3129 (NH_2 and OH); ^{1}H-NMR δ: 3.66 [3H, s, N(3)-Me], 6.58 (2H, br, NH_2), 8.08 [1H, s, C(2)-H], 9.31 (1H, br, OH). *Anal.* Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.40. Found: 43.38; H, 4.18; N, 42.39.

ii) By Hydrolysis of **10m**: A solution of **10m** (1.015 g, 5.66 mmol) in 1 N hydrochloric acid (100 ml) was refluxed for 2 h, neutralized with 10% aqueous sodium carbonate, and concentrated *in vacuo*. The residue was washed with water (10 ml) and then recrystallized from water to afford **7a** (685 mg, 73%), mp > 300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7a** described under method (i).

iii) By Hydrogenolysis of **10o**: A solution of **10o** (64 mg, 0.25 mmol) in a mixture of methanol (8 ml) and water (5 ml) was shaken under hydrogen in the presence of 10% palladium-on-carbon (64 mg) at atmospheric pressure and *ca.* 40 °C for 2 h. The catalyst was filtered off and washed with hot water (5 × 10 ml). The filtrate and washings were combined and concentrated *in vacuo* to give **7a** (37 mg, 90%), mp > 300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7a**.

iv) The 8-hydroxy derivative **7a** was also obtained from **9d**, **9e**, or **9f** by treatment with 0.1 N aqueous sodium hydroxide at room or refluxing temperature for 2 or 1.5 h. The results are summarized in Table 4.

3-Ethyl-8-hydroxyadenine (7b) i) From **9g**: A mixture of **9g** (260 mg, 0.885 mmol) and 0.1 N aqueous sodium hydroxide (18 ml) was refluxed for 1.5 h. The resulting solution was neutralized with 10% hydrochloric acid and then concentrated *in vacuo*. The residue was recrystallized from water (treated with charcoal) to afford **7b**·1/2H_2O (120 mg, 72%), mp > 300 °C. This was further recrystallized from water and dried over phosphorus pentoxide at 2 mmHg and 100 °C for 5 h to yield an analytical sample of **7b**·1/2H_2O as colorless prisms, mp > 300 °C; MS *m/z*: 179 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 233 nm (ε 19700), 298 (18400); $\lambda_{max}^{H_2O}$ (pH 1) 218 (24300), 287 (19500); $\lambda_{max}^{H_2O}$ (pH 7) 229 (21400), 294 (20100); $\lambda_{max}^{H_2O}$ (pH 13) 232 (sh) (9900), 306 (15300); IR ν_{max}^{Nujol} cm^{-1}: 3349, 3183, 3121 (NH_2 and OH); ^{1}H-NMR δ: 1.35 (3H, t, J = 7 Hz, $\underline{Me}CH_2$), 4.12 (2H, q, J = 7 Hz, $MeC\underline{H}_2$), 6.62 (2H, br, NH_2), 8.15 [1H, s, C(2)-H], 9.34 (1H, br, OH). *Anal.* Calcd for $C_7H_9N_5O$·1/2H_2O: C, 44.68; H, 5.36; N, 37.21. Found: 44.60; H, 5.37; N, 37.14. This sample was identical (by comparison of the IR and ^{1}H-NMR spectra, and TLC mobility) with authentic **7b**.[21]

ii) By Hydrolysis of **10p**: A solution of **10p** (96.5 mg, 0.499 mmol) in 1 N hydrochloric acid (10 ml) was refluxed for 3 h and concentrated *in vacuo*. The residue was dissolved in water (1 ml), and the solution was neutralized with concentrated aqueous ammonia. After storage of the mixture in a refrigerator overnight, the precipitate that resulted was collected by filtration, washed with water (1 ml), and dried to afford **7b**·1/2H_2O (72.3 mg, 77%), mp > 300 °C, identical (by comparison of the IR spectrum and TLC mobility) with authentic **7b** described under method (i).

3-Benzyl-8-hydroxyadenine (7c) i) From **9j** and Aqueous Sodium Hydroxide: A mixture of **9j** (300 mg, 0.843 mmol) and 0.1 N aqueous sodium hydroxide (18 ml) was heated under reflux for 1.5 h. The resulting solution was neutralized with 10% hydrochloric acid and then concentrated *in vacuo* to a volume of *ca.* 5 ml. The precipitate that separated was collected by filtration and washed with methanol (5 ml) to afford **7c** (72 mg), mp > 300 °C. The aqueous filtrate and methanolic washings were combined and concentrated *in vacuo* after addition of silica gel (2 g). The solid residue was subjected to flash chromatography [chloroform–methanol (4 : 1, v/v)] to yield a second crop of **7c** [8 mg; the total yield of **7c** was 80 mg (39%)]. Recrystallization of crude **7c** from water gave an analytical sample as slightly yellow prisms, mp > 300 °C; MS *m/z*: 241 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 237 nm (ε 21200), 300 (16400); $\lambda_{max}^{H_2O}$ (pH 1) 220 (28600), 289 (19000); $\lambda_{max}^{H_2O}$ (pH 7) 232 (22400), 295 (18200); $\lambda_{max}^{H_2O}$ (pH 13) 235 (sh) (10600), 308 (13900); IR ν_{max}^{Nujol} cm^{-1}: 3132 (NH_2 and OH); ^{1}H-NMR δ: 5.30 (2H, s, PhC$\underline{H}_2$), 6.66 (2H, br, NH_2), 7.27—7.43 (5H, m, $\underline{Ph}CH_2$), 8.32 [1H, s, C(2)-H], 9.34 (1H, br, OH). *Anal.* Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: 59.51; H, 4.42; N, 28.79.

ii) From the Free Base of **9j** and Water: A solution of **9j** (355 mg, 0.998 mmol) in water (80 ml) was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (2 ml, 2.5 eq). The column was then eluted with water (100 ml). The combined eluate was concentrated *in vacuo* to leave a yellowish oil, which was triturated with ethanol to effect crystallization. The ethanol was removed by evaporation and the residue was dried over phosphorus pentoxide to afford a yellowish solid (251 mg), mp 135—145 °C (dec.). This sample was presumed to be a 1 : 1 mixture of **7c** and the free base of **9j** on the basis of TLC analysis and the ^{1}H-NMR spectrum [δ: 4.24 (3H, s, OMe), 5.29 (2H, s, PhC$\underline{H}_2$ of **7c**), 5.47 (2H, s, PhC$\underline{H}_2$), 6.65 (2H, br, NH_2 of **7c**), 7.27—7.52 (10H, m, two $\underline{Ph}CH_2$'s), 8.20 (1H, br, NH), 8.31 [1H, s, C(2)-H of **7c**], 8.39 and 8.41 (1H each, s, purine protons), 9.36 (1H, br, OH of **7c**)].

In a separate run, **9j** (356 mg, 1 mmol) was treated with the ion-exchange resin in a manner similar to that described above. The eluate was concentrated *in vacuo* to a volume of *ca.* 50 ml and then refluxed for 1 h. The resulting solution was concentrated *in vacuo*, and the residue was dissolved in methanol. The methanolic solution was concentrated *in vacuo*, and the residue was subjected to flash chromatography [chloroform–methanol (4 : 1, v/v)]. Crude **7c** thus obtained was washed with ethanol (2 × 3 ml) and then recrystallized from water to furnish **7c** (115 mg, 48%), mp > 300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7c**.

iii) By Hydrolysis of **10q**: A solution of **10q** (1.52 g, 5.95 mmol) in 1 N hydrochloric acid (70 ml) was refluxed for 6 h, neutralized with 10% aqueous sodium hydroxide, and then cooled. The precipitate that resulted was collected by filtration, washed with water (2 × 5 ml), and dried to give **7c** (1.26 g, 88%), mp > 300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7c**.

iv) By Hydrolysis of **6c**[5] (50.1 mg, 0.133 mmol) in 1 N aqueous sodium hydroxide (2 ml) was heated under reflux for 1 h

and neutralized with 10% hydrochloric acid. The precipitate that resulted was collected by filtration, washed successively with water (1 ml) and methanol (1 ml), and dried to afford **7c** (25.3 mg, 79%), mp >300 °C, identical (by comparison of the IR spectrum and TLC mobility) with authentic **7c**.

Conversion of 13 into 12 Compound **13** (50.6 mg, 0.306 mmol) was heated in 0.1 N sodium hydroxide (8 ml) under reflux for 30 min. The reaction mixture was brought to pH 1 by addition of 6 N sulfuric acid and then concentrated to a volume of *ca.* 10 ml. The precipitate that separated was collected by filtration, washed with water (1 ml), and dried to afford **12**·1/2H_2SO_4 (49.6 mg, 81%), mp >300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **12**·1/2H_2SO_4.[5]

8-Methoxy-3-methyladenine (10m) i) From **9d** by Method A: A solution of **9d** (1.12 g, 4.01 mmol) in a 0.1 M sodium methoxide solution (80 ml) in methanol was kept at room temperature for 1 h and then concentrated *in vacuo*. The residue was dissolved in hot water (8 ml), and the solution was neutralized with 10% hydrochloric acid. The resulting mixture was concentrated again, and the residue was recrystallized from 5% aqueous ammonia to give **10m** (701 mg, 98%), mp 241—243 °C (dec.). This was further recrystallized from 5% aqueous ammonia to give an analytical sample of **10m** as colorless needles, mp 261—264 °C (dec.); MS *m/z*: 179 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 227 nm (sh) (ε 11700), 287 (13400); $\lambda_{max}^{H_2O}$ (pH 1) 210 (16800), 222 (18600), 279 (20400); $\lambda_{max}^{H_2O}$ (pH 7) 210 (19600), 225 (sh) (13200), 284 (14800); $\lambda_{max}^{H_2O}$ (pH 13) 224 (sh) (13100), 284 (14800); ^{1}H-NMR δ: 3.80 [3H, s, N(3)-Me], 3.91 (3H, s, OMe), 7.24 (2H, br, NH_2), 8.16 [1H, s, C(2)-H]. *Anal.* Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.65; H, 5.03; N, 39.03.

ii) From **9d** by Method B: A solution of **9d** (280 mg, 1 mmol) in a mixture of 0.1 N aqueous sodium hydroxide (20 ml) and methanol (5 ml) was kept at room temperature for 2 h and then neutralized with 10% hydrochloric acid. The resulting solution was concentrated *in vacuo*, and the residue was recrystallized from 5% aqueous ammonia to afford **10m** (137 mg, 77%), mp 261—264 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **10m** described above under item (i).

8-Ethoxy-3-methyladenine (10n) i) From **9d** by Method C: A solution of **9d** (1.12 g, 4.01 mmol) in a 0.1 M sodium ethoxide solution (80 ml) in ethanol was kept at 40 °C for 2 h and then treated in a manner similar to that described above for the preparation of **10m** under item (i), providing **10n**·H_2O (753 mg, 89%), mp 197—199 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **10n**·H_2O described below under item (ii).

ii) From **9d** by Method D: A mixture of **9d** (280 mg, 1 mmol), 0.1 N aqueous sodium hydroxide (20 ml), and ethanol (5 ml) was stirred at room temperature for 2.5 h. The resulting solution was neutralized with 10% hydrochloric acid and concentrated *in vacuo*. The residue was dissolved in methanol, and the solution was concentrated *in vacuo* after addition of silica gel (2 g). The residue was subjected to flash chromatography [chloroform–methanol (2 : 1, v/v)] to give crude **10n**. This was recrystallized from 5% aqueous ammonia to afford **10n**·H_2O (92 mg, 44%), mp 188—194 °C (dec.). This was further recrystallized from 5% aqueous ammonia, dried over phosphorus pentoxide at 2 mmHg and 50 °C for 10 h, and exposed to air at room temperature until a constant weight was reached, yielding an analytical sample of **10n**·H_2O as colorless needles, mp 204—205 °C; MS *m/z*: 193 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 228 nm (sh) (ε 11600), 288 (13700); $\lambda_{max}^{H_2O}$ (pH 1) 211 (17800), 222 (19800), 280 (21900); $\lambda_{max}^{H_2O}$ (pH 7) 211 (20400), 225 (sh) (13600), 285 (15800); $\lambda_{max}^{H_2O}$ (pH 13) 225 (13700), 285 (15900); ^{1}H-NMR δ: 1.31 (3H, t, J=7 Hz, MeC$\underline{H}_2$), 3.79 [3H, s, N(3)-Me], 4.33 (2H, q, J=7 Hz, MeC$\underline{H}_2$), 7.21 (2H, br, NH_2), 8.15 [1H, s, C(2)-H]. *Anal.* Calcd for $C_8H_{11}N_5O\cdot H_2O$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.29; H, 6.28; N, 33.14.

iii) From **9e** by Method D: The results are summarized in Table 5.

8-Benzyloxy-3-methyladenine (10o) i) From **9d** by Method F: A mixture of **9d** (140 mg, 0.501 mmol), 0.1 N aqueous sodium hydroxide (10 ml), and benzyl alcohol (2.5 ml) was stirred vigorously at room temperature for 2 h. After adjusting its pH to 1 with 10% hydrochloric acid, the reaction mixture was partitioned between water (10 ml) and ether (10 ml). The organic layer was separated from the aqueous layer and extracted with 10% hydrochloric acid (2×5 ml). All the aqueous layers were combined, neutralized with 10% aqueous sodium carbonate, and extracted with chloroform (4×20 ml). The chloroform extracts were combined, dried over magnesium sulfate, and concentrated to leave a yellowish oil, which was triturated with ether (3 ml) to effect crystallization. The precipitate that resulted was collected by filtration, washed with ether (0.5 ml), and dried to afford **10o** (66 mg, 52%), mp 200.5—202 °C (dec.). Recrystallization of this sample from ethanol afforded an analytical sample of **10o** as colorless prisms, mp 209—212 °C (dec.); MS *m/z*: 255 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 228 nm (sh) (ε 12600), 289 (14800); $\lambda_{max}^{H_2O}$ (pH 1) 217 (sh) (23200), 280 (22200); $\lambda_{max}^{H_2O}$ (pH 7) 225 (sh) (14400), 285 (16300); $\lambda_{max}^{H_2O}$ (pH 13) 226 (sh) (14700), 285 (16500); ^{1}H-NMR δ: 3.81 [3H, s, N(3)-Me], 5.40 (2H, s, PhC$\underline{H}_2$), 7.25—7.49 (7H, m, $\underline{Ph}CH_2$ and NH_2), 8.18 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.07; H, 5.01; N, 27.37.

ii) From **9d** by Method E: A mixture of **9d** (140 mg, 0.501 mmol) and a 0.1 M sodium benzylate solution (10 ml) in benzyl alcohol was stirred at 40 °C for 6 h. The reaction mixture was partitioned between ether (30 ml) and 10% hydrochloric acid (10 ml). The organic layer was separated from the aqueous layer and extracted with 10% hydrochloric acid (2×10 ml). The aqueous layers were combined, washed with ether (10 ml), neutralized with 10% aqueous sodium carbonate, and extracted with chloroform (3×30 ml). The chloroform extracts were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The oily residue was triturated with a mixed solvent of ether (10 ml) and hexane (10 ml). The precipitate that resulted was collected by filtration, washed with ether (2 ml), and dried to give **10o** (36 mg, 28%) as slightly yellow prisms, mp 199—200 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **10o** described above under item (i).

iii) From **9f** by Method F: Compound **9f** (356 mg, 1 mmol) was treated with a mixture of aqueous sodium hydroxide and benzyl alcohol, and the product was isolated in a manner similar to that described above under item (i), giving crude **10o** (152 mg, 60%) as slightly yellow prisms, mp 199—200 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **10o** described above under item (i).

8-Methoxy-3-ethyladenine (10p) A solution of **9g** (456 mg, 1.55 mmol) in a 0.1 M sodium methoxide solution (30 ml) in methanol was treated in a manner similar to that described above for the preparation of **10m** under item (i), affording **10p** (273 mg, 91%), mp 171—174 °C (dec.). Recrystallization of this sample from 5% aqueous ammonia yielded an analytical sample of **10p** as colorless needles, mp 204—205 °C (dec.); MS *m/z*: 193 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 229 nm (ε 12200), 287 (13400); $\lambda_{max}^{H_2O}$ (pH 1) 210 (17500), 222 (19300), 279 (20400); $\lambda_{max}^{H_2O}$ (pH 7) 211 (20200), 224 (sh) (13600), 284 (14700); $\lambda_{max}^{H_2O}$ (pH 13) 224 (sh) (13800), 284 (14900); ^{1}H-NMR δ: 1.41 (3H, t, J=7 Hz, $\underline{Me}CH_2$), 3.91 (3H, s, OMe), 4.23 (2H, q, J=7 Hz, MeC$\underline{H}_2$), 7.27 (2H, br, NH_2), 8.22 [1H, s, C(2)-H]. *Anal.* Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.56; H, 5.66; N, 36.11.

3-Benzyl-8-methoxyadenine (10q) i) From **9j** by Method A: A solution of **9j** (356 mg, 1 mmol) in a 0.1M sodium methoxide solution (20 ml) in methanol was treated in a manner similar to that described above for the preparation of **10m** under item (i), and the crude product was recrystallized from 5% aqueous ammonia–methanol (1 : 1, v/v) to afford **10q** (241 mg, 95%), mp 223—225 °C (dec.). Repeated recrystallization of this sample gave an analytical sample of **10q** as slightly yellow prisms, mp 225—226 °C (dec.); MS *m/z*: 255 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 230 nm (sh) (ε 14400), 289 (12300); $\lambda_{max}^{H_2O}$ (pH 1) 226 (21900), 281 (20200); $\lambda_{max}^{H_2O}$ (pH 7) 227 (sh) (16500), 285 (13800); $\lambda_{max}^{H_2O}$ (pH 13) 227 (sh) (16500), 285 (13700); ^{1}H-NMR δ: 3.91 (3H, s, OMe), 5.41 (2H, s, PhC$\underline{H}_2$), 7.24—7.45 (7H, m, $\underline{Ph}CH_2$ and NH_2), 8.40 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.41; H, 5.21; N, 27.41.

ii) From **9j** by Method B: A solution of **9j** (356 mg, 1 mmol) in a mixture of 0.1 N aqueous sodium hydroxide (20 ml) and methanol (5 ml) was stirred at room temperature for 2 h. The precipitate that resulted was collected by filtration, washed with water (1 ml), and dried to give **10q** (148 mg) as a slightly orange solid, mp 219—222 °C (dec.). The filtrate and washings were combined and concentrated *in vacuo*. The residue was recrystallized from 5% aqueous ammonia–methanol (1 : 1, v/v) to afford a second crop of **10q** (67 mg; the total yield was 215 mg, 84%), mp 215—218 °C (dec.). These samples were identical (by comparison of the IR spectrum and TLC mobility) with authentic **10q** described above under item (i).

Methylation of 8a with Dimethyl Sulfate in Aqueous Sodium Hydroxide i) In the Absence of Added Methanol: A mixture of **8a**·2H_2O (301 mg, 1.5 mmol), dimethyl sulfate (of *ca.* 95% purity) (200 mg, 1.5 mmol), and 0.1 N aqueous sodium hydroxide (15 ml) was stirred at

room temperature for 17 h. The resulting yellow solution was concentrated *in vacuo*. The residue was dissolved in methanol, and the solution was concentrated *in vacuo* after addition of silica gel (3 g). The remaining solid was subjected to flash chromatography [chloroform–methanol–concentrated aqueous ammonia (40 : 7 : 1, v/v)] to afford crude **14** as the fast-eluting substance. This was dissolved in hot water (0.5 ml) and then acetone (1 ml) was added to effect precipitation, affording **14**·H_2O (39 mg, 13%), mp 224.5—227 °C (dec.). Further purification of this sample by similar precipitation from a mixture of water and acetone, drying over phosphorus pentoxide at 2 mmHg and 80 °C for 15 h, and moisturizing (by exposure to air at room temperature until a constant weight was reached) furnished an analytical sample of N^6,3-dimethyladenine 7-oxide monohydrate (**14**·H_2O) as slightly yellow needles, mp 227—229 °C (dec.); MS *m/z*: 179 (M^+); UV $\lambda_{max}^{95\%EtOH}$ 225 nm (ε 14200), 273 (14600), 319 (4200); $\lambda_{max}^{H_2O}$ (pH 1) 286 (16700); $\lambda_{max}^{H_2O}$ (pH 7) 222 (14100), 271 (13700), 306 (5700); $\lambda_{max}^{H_2O}$ (pH 13) 271 (13200), 306 (5600); ^{1}H-NMR δ: 3.07 (3H, s, N^6-Me), 3.81 [3H, s, N(3)-Me], 7.87 [1H, s, C(8)-H], 8.46 [1H, s, C(2)-H], 8.65 (1H, br, NH or OH).[22] *Anal.* Calcd for $C_7H_9N_5O \cdot H_2O$: C, 42.64; H, 5.62; N, 35.51. Found: C, 42.41; H, 5.57; N, 35.43.

Later fractions of the above chromatography gave the starting material **8a**·$2H_2O$ (151 mg, 50%), mp 245—252 °C (dec.). Further elution of the column with chloroform–methanol (2 : 1, v/v) afforded crude **7a**. Recrystallization of this crude product from water afforded **7a** (11 mg, 4%), mp 292—295 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7a**.

ii) In the Presence of Added Methanol: A solution of dimethyl sulfate (of *ca.* 95% purity) (200 mg, 1.5 mmol) in methanol (*ca.* 0.5 ml) was added to a solution of **8a**·$2H_2O$ (302 mg, 1.5 mmol) in 0.1 N aqueous sodium hydroxide (15 ml), and the mixture was kept at room temperature for 2.5 h. The resulting solution was concentrated *in vacuo*. The residue was dissolved in methanol, and the solution was concentrated *in vacuo* after addition of silica gel (2 g). The solid residue was subjected to flash chromatography [chloroform–methanol (4 : 1, v/v)] to afford **10m** (30 mg, 11%), mp 261—264 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **10m**. Further elution of the column with chloroform–methanol–concentrated aqueous ammonia (20 : 7 : 1, v/v) afforded **14**·H_2O (41 mg, 14%), mp 221—222 °C (dec.), identical (by comparison of the IR spectrum and TLC mobility) with an authentic sample prepared by method (i), and the starting material **8a**·$2H_2O$ (173 mg, 57%).

References and Notes

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