Purines. LXXI.[1] Preparation and Alkylation of 7-Alkyladenine 1-Oxides: A General Synthesis of 1-Alkoxy-7-alkyladenines

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7-Methyladenine (6a) and 7-ethyladenine (6b) afforded the N(1)-oxides 7a, b in 78% yield each on treatment with *m*-chloroperoxybenzoic acid at room temperature; this is analogous to the previously reported *N*-oxidation of 7-benzyladenine (6c) to give the N(1)-oxide 7c. When treated with an excess of methyl iodide, ethyl iodide, or benzyl bromide in *N,N*-dimethylacetamide at room temperature, each of the 1-oxides 7a—c underwent alkylation almost exclusively at the oxygen atom of the *N*-oxide group. The products, isolated in good yields, were the salts 8d—l·HX of the nine 1-alkoxy-7-alkyladenines, in which either the *O*-alkyl or the N(7)-alkyl group is any one of methyl, ethyl, and benzyl. The UV and ^{1}H-NMR spectral data for 8·HX and some of their free bases 8 are presented.

Key words 7-alkyladenine *N*-oxidation; 7-alkyladenine 1-oxide alkylation; 1-alkoxy-7-alkyladenine; ^{1}H-NMR; UV

We have already reported that alkylation of 9-alkyladenine 1-oxides (**1**) with alkyl halides affords 1-alkoxy-9-alkyladenine salts (**2**·HX)[2] and that the corresponding free bases **2** undergo facile ring-opening leading to the monocycles **3**. These in turn provide the Dimroth rearrangement products **4** or the deformylated products **5**, depending on the reaction conditions.[3] Compounds **3**—**5** have proved very useful as intermediates for syntheses of substituted and/or modified imidazoles and adenines.[4] On the other hand, we have recently reported that 7-benzyladenine (**6c**) affords the 1-oxide **7c** and its *m*-chlorobenzoate salt in 40% and 36% yields, respectively, on treatment with *m*-chloroperoxybenzoic acid (MCPBA) in methanol.[5] In the present work, we intended to investigate a 7-alkyl version of the chemistry of the 9-alkyladenine 1-oxides (**1**) and we report herein the first synthesis of 1-alkoxy-7-alkyladenine salts (**8**·HX).

When 7-methyladenine (**6a**)[6] was treated with an excess of MCPBA in 50% (v/v) aqueous methanol at room temperature for 24 h, 7-methyladenine 1-oxide (**7a**) was obtained in 78% yield. Similarly, 7-ethyladenine 1-oxide (**7b**) was obtained in 78% yield on treatment of 7-ethyladenine (**6b**)[6] with MCPBA in methanol at room temperature for 6 h. The 1-oxide structures were assignable to **7a, b** on the basis of the similarities to **7c**[5] in the mode of formation and in the UV spectra taken in various solvents.

Having the three 7-alkyladenine 1-oxides (**7a—c**) in hand, we next treated them separately with methyl iodide, ethyl iodide, and benzyl bromide in *N,N*-dimethylacetamide (DMAc) according to the procedure reported[2] for the alkylation of 9-alkyladenine 1-oxides (**1**). The

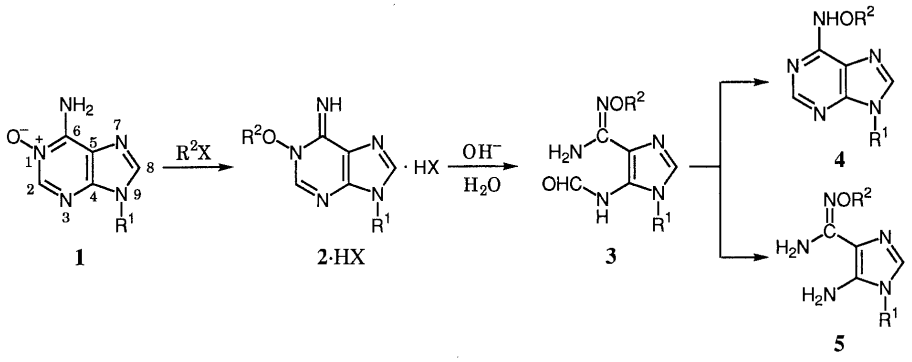
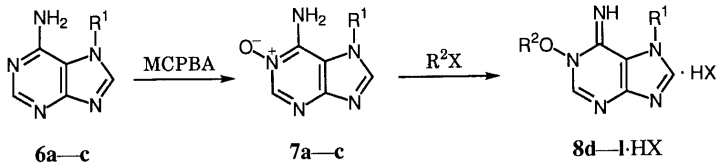


Chart 1



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

Chart 2

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Table 1. Alkylation of 7-Alkyladenine 1-Oxides (**7**)[a]

Substrate	RX	Reaction time (h)	Yield (%)	Product	Recrystn. solvent	Appearance	mp (°C)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
7a·H_2O[b]	MeI	7	80	**8d**·HI·H_2O	70% (v/v) aq. EtOH	Colorless needles	148—152 (dec.)	$C_7H_9N_5O$· HI·H_2O[c]	25.86 (25.64	3.72 3.98	21.54 21.45)
7a·H_2O	EtI	28	88	**8e**·HI	95% (v/v) aq. EtOH	Colorless needles	191—192 (dec.)	$C_8H_{11}N_5O$·HI	29.92 (29.77	3.77 3.80	21.81 21.67)
7a·H_2O	$PhCH_2Br$	1.25	90	**8f**·$HClO_4$·H_2O	50% (v/v) aq. EtOH	Colorless pillars	162—163 (dec.)	$C_{13}H_{13}N_5O$· $HClO_4$·H_2O[d]	41.78 (41.71	4.31 4.25	18.74 18.72)
7b·$2H_2O$	MeI	4.5	90	**8g**·HI	90% (v/v) aq. EtOH	Colorless prisms	155—158 (dec.)	$C_8H_{11}N_5O$·HI	29.92 (29.87	3.77 3.71	21.81 21.64)
7b·$2H_2O$	EtI	19	90	**8h**·HI	90% (v/v) aq. EtOH	Colorless needles	165—166 (dec.)	$C_9H_{13}N_5O$·HI	32.25 (32.06	4.21 4.25	20.90 20.82)
7b·$2H_2O$[e]	$PhCH_2Br$	0.75	96	**8i**·HBr	MeOH–Et_2O (1:1, v/v)	Colorless prisms	158—160 (dec.)	$C_{14}H_{15}N_5O$· HBr	48.01 (48.02	4.60 4.63	20.00 19.86)
7b·$2H_2O$	$PhCH_2Br$	0.75	88	**8i**·$HClO_4$	50% (v/v) aq. MeOH	Colorless pillars	162—163 (dec.)	$C_{14}H_{15}N_5O$· $HClO_4$	45.48 (45.27	4.36 4.29	18.94 18.84)
7c	MeI	5	73	**8j**·$HClO_4$	90% (v/v) aq. EtOH	Colorless plates	172—174 (dec.)	$C_{13}H_{13}N_5O$· $HClO_4$	43.89 (43.84	3.97 4.07	19.69 19.65)
7c	EtI	6	75	**8k**·$HClO_4$	90% (v/v) aq. EtOH	Colorless prisms	191—192 (dec.)	$C_{14}H_{15}N_5O$· $HClO_4$	45.48 (45.39	4.36 4.41	18.94 18.94)
7c	$PhCH_2Br$	4.5	90	**8l**·HBr	MeOH–Et_2O (1:2, v/v)	Colorless needles	153—156 (dec.)	$C_{19}H_{17}N_5O$· HBr	55.35 (55.23	4.40 4.33	16.99 16.98)

a) A mixture of **7** and four molar equivalents of an appropriate alkyl halide was stirred in DMAc (3 ml per mmol of **7**) at room temperature. *b*) Three ml of DMAc was used for 2.2 mmol of **7a**·H_2O. *c*) Dried over phosphorus pentoxide at 2 mmHg and room temperature for 35 h. *d*) Dried over phosphorus pentoxide at 2 mmHg and 50 °C for 10 h. *e*) For 30 mmol of **7b**·$2H_2O$, 20 ml of DMAc was used.

Table 2. UV Spectra of 1-Alkoxy-7-alkyladenine Salts (**8**·HX)

Compound	UV spectra							
	Solvent E[a]		Solvent A[b,c]		Solvent N[d]		Solvent B[c,e]	
	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
8d·HI[f]	220	36.2	223	36	223	29.7	261	11
	270	9.9	268	10	266	10.4		
8d·$HClO_4$	221	23.4	220	24	218	19.0	261	11.5
	270	9.8	268	9.5	265	10.6		
8e·HI	220	37.7	222	37.5	222	31.8	263	11.5
	270	9.6	268	9.5	266	10.3		
8f·$HClO_4$[f]	222	27.9	222	29.5	218	24.4	263	11.5
	270	9.7	268	9.5	263	10.7		
8g·HI	220	35.6	222	36	222	30.4	261	11.5
	270	9.7	268	9.5	265	10.3		
8h·HI	220	37.5	223	37.5	222	31.3	262	11.5
	270	9.5	268	9.5	265	10.0		
8h·$HClO_4$	221	23.2	221	25	219	19.3	262	11
	270	9.6	269	9	265	10.4		
8i·HBr	222	26.7	223	28.5	215 (sh)	23.8	262	11.5
	270	9.1	268	9	263	10.5		
8i·$HClO_4$	222	26.9	223	28.5	218	23.8	263	11.5
	270	9.3	268	9	264	10.3		
8j·$HClO_4$	270	8.9	219	25.5	265	10.1	263	10.5
			268	9				
8k·$HClO_4$	270	8.9	219	26.5	264	10.1	263	11
			268	9				
8l·HBr	268	8.8	220 (sh)	27.5	264	9.9	264	10
			268	8.5				

a) Measured in 95% aqueous ethanol. *b*) Measured in 0.1 N hydrochloric acid (pH 1). *c*) Not accurate because of a change of the spectrum with time. *d*) Measured in 0.005 M phosphate buffer (pH 7). *e*) Measured in 0.1 N aqueous sodium hydroxide (pH 13). *f*) As a monohydrate.

alkylation took place smoothly in a highly regioselective manner in every case to afford the corresponding monoalkylated product in the salt form (Table 1). The hydrogen halide salts **8d—l**·HX thus obtained were shown by TLC to tend to decompose to the starting materials **7a—c** during recrystallization, suggesting their 1-alkoxy structures.[7] Accordingly, some of the salts were purified after conversion into the perchlorates.

Table 3. ^{1}H-NMR Spectra of 1-Alkoxy-7-alkyladenine Salts (**8**·HX) in Me_2SO-d_6

Compound	Chemical shift (ppm)						
	Methyl protons		Methylene protons		Phenyl protons	Purine protons C(8)-H [C(2)-H][a]	NH protons
	NCH_2Me [OCH_2Me][a]	NMe [OMe][a]	NCH_2Me [OCH_2Me][a]	NCH_2Ph [OCH_2Ph][a]			
8d·HI[b]	—	4.10 (3H, s)	—	—	—	8.60 (1H, s)	9.46 (2H, br)
	[—]	[4.18 (3H, s)]	[—]	[—]		[9.10 (1H, s)]	
8d·$HClO_4$	—	4.10 (3H, s)	—	—	—	8.59 (1H, s)	9.45 (2H, br)
	[—]	[4.17 (3H, s)]	[—]	[—]		[9.09 (1H, s)]	
8e·HI	—	4.11 (3H, s)	—	—	—	8.60 (1H, s)	9.33 (2H, br)
	[1.44 (3H, t)][c]	[—]	[4.43 (2H, q)][c]	[—]		[9.06 (1H, s)]	
8f·$HClO_4$[b]	—	4.11 (3H, s)	—	—	7.40—7.53 (3H, m)	8.59 (1H, s)	9.47 (2H, br)
	[—]	[—]	[—]	[5.40 (2H, s)]	7.57—7.66 (2H, m)	[8.73 (1H, s)]	
8g·HI	1.40 (3H, t)[c]	—	4.54 (2H, q)[c]	—	—	8.69 (1H, s)	9.40 (2H, br)
	[—]	[4.19 (3H, s)]	[—]	[—]		[9.11 (1H, s)]	
8h·HI	1.40 (3H, t)[c]	—	4.55 (2H, q)[c]	—	—	8.71 (1H, s)	9.30 (2H, br)
	[1.45 (3H, t)][c]	[—]	[4.44 (2H, q)][c]	[—]		[9.08 (1H, s)]	
8h·$HClO_4$	1.40 (3H, t)[c]	—	4.54 (2H, q)[c]	—	—	8.69 (1H, s)	9.30 (2H, br)
	[1.44 (3H, t)][c]	[—]	[4.44 (2H, q)][c]	[—]		[9.07 (1H, s)]	
8i·HBr	1.35 (3H, t)[c]	—	4.55 (2H, q)[c]	—	7.38—7.52 (3H, m)	8.70 (1H, s)	9.43 (2H, br)
	[—]	[—]	[—]	[5.44 (2H, s)]	7.57—7.65 (2H, m)	[8.83 (1H, s)]	
8i·$HClO_4$	1.35 (3H, t)[c]	—	4.52 (2H, q)[c]	—	7.43—7.50 (3H, m)	8.69 (1H, s)	9.42 (2H, br)
	[—]	[—]	[—]	[5.43 (2H, s)]	7.58—7.63 (2H, m)	[8.83 (1H, s)]	
8j·$HClO_4$	—	—	—	5.83 (2H, s)	7.19—7.27 (2H, m)	8.77 (1H, s)	9.40 (2H, br)
	[—]	[4.17 (3H, s)]	[—]	[—]	7.30—7.43 (3H, m)	[9.15 (1H, s)]	
8k·$HClO_4$	—	—	—	5.84 (2H, s)	7.19—7.26 (2H, m)	8.78 (1H, s)	9.29 (2H, br)
	[1.41 (3H, t)][c]	[—]	[4.41 (2H, q)][c]	[—]	7.30—7.43 (3H, m)	[9.11 (1H, s)]	
8l·HBr	—	—	—	5.83 (2H, s)	7.11—7.59 (10H, m)	8.79 (1H, s)	9.38 (2H, br)
	[—]	[—]	[—]	[5.42 (2H, s)]		[8.93 (1H, s)]	

a) In this column, the value for the proton(s) indicated in the brackets is shown in brackets. *b*) As a monohydrate. *c*) With $J=7$ Hz.

It may be seen from Table 2 that all the salts **8d**—**l**·HX have similar UV spectra. These spectra resemble those of 1,7-dialkyladenines,[8,9] further supporting the conclusion that alkylation occurred at the oxygen atom, as in the alkylations of the 9-alkyl analogues **1**.[2] Some of the salts **8**·HX were converted into the free bases (**8d, h, i, l**) by treating them with an appropriate base. The correctness of the structures of the free bases **8** was established by comparison of their UV spectral characteristics with those of the corresponding salts **8**·HX. On catalytic hydrogenation over palladium-on-carbon, 1-benzyloxy-7-ethyladenine (**8i**) underwent debenzylation within 5 min at room temperature to afford 7-ethyladenine 1-oxide (**7b**) in 93% yield. Such easy debenzylation is analogous to that of 1-benzyloxyadenine and 9-benzyl-1-benzyloxyadenine (type **2**).[10] Finally, catalytic hydrogenolysis of 1-methoxy-7-methyladenine (**8d**) using hydrogen and Raney Ni afforded 7-methyladenine (**6a**) in 83% yield. These results led us to conclude that alkylation of 7-alkyladenine 1-oxides (**7**) affords 1-alkoxy-7-alkyladenine salts (**8**·HX) almost exclusively.

Table 3 assembles the ^{1}H-NMR spectral data for **8**·HX measured in hexadeuterated dimethyl sulfoxide. The two methyl groups in the dimethyl compound **8d**·HX were discriminated from each other by comparison of the spectrum with those of the monomethylated compounds **8e, f, g, j**·HX. The assignments for the diethyl and dibenzyl compounds **8h, l**·HX were accomplished in a similar manner. Every three- or two-proton signal that could be assigned to the α-protons of the N(7)-alkyl group appeared as an unresolved peak or a quartet, but shorter in height than that of the corresponding *O*-alkyl group. As regards the two one-proton singlets assignable to the purine protons, every one at higher field was always shorter in height than the one at lower field. These shortenings in the peak height are most likely due to unmeasurably small long-range coupling between the N(7)-methyl or N(7)-methylene protons and the C(8)-proton. Indeed, irradiation of the N(7)-methyl proton signal of **8d**·$HClO_4$ caused an increase in the peak height of the shorter purine-proton signal at δ 8.59. Further evidence was obtained in a nuclear Overhauser effect experiment with **8i**·$HClO_4$: irradiation of the N(7)-methylene proton signal brought about an 11% increase in the peak area of one of the two purine-proton signals at δ 8.69, without affecting that of the other one at δ 8.83. Thus, the shorter signal of the more shielded purine proton may be assigned to the C(8)-proton, as shown in Table 3. The purine-proton signals of 1-methoxy-9-methyladenine hydriodide (**2**·HX: $R^1=R^2=Me$, X=I) have already been assigned unambiguously.[4h] In this case also, the signals of the C(8)-proton and the N(9)-methyl protons appear as unresolved peaks but shorter in height than those of the C(2)-proton and the *O*-methyl protons, respectively, supporting the correctness of the above assignment for the ring-protons of **8**·HX. It is interesting to note that the chemical shifts of the C(8)-protons of **8**·HX are strictly controlled by the N(7)-alkyl groups regardless of the 1-alkoxy groups: the 7-methyl compounds exhibit the signals for the C(8)-protons at δ 8.59—8.60; the 7-ethyl compounds at δ

8.69—8.71; the 7-benzyl compounds at δ 8.77—8.79. Similar relationships have been observed between the 9-alkyl groups and the more shielded purine protons of 1-alkoxy-9-alkyladenine salts (type **2**·HX).[2)]

At the free base level, assignments of the signals arising from the two identical alkyl groups in the ^{1}H-NMR spectra of 1-ethoxy-7-ethyladenine (**8h**) and 7-benzyl-1-benzyloxyadenine (**8l**) were made by comparison of their chemical shifts with those of 1-benzyloxy-7-ethyladenine (**8i**). The signals of the N(7)-methylene protons of **8h, l** also appeared as a quartet and a singlet, respectively, but shorter in height than those of the corresponding *O*-methylene protons. We therefore prefer to assign the shorter signals at higher field to the C(8)-protons of the free bases (**8h, i, l**), as in the case of the corresponding salts **8**·HX described above. 1-Methoxy-7-methyladenine (**8d**) exhibited the shorter three-proton and one-proton singlets at δ 4.01 and δ 7.98. These were assigned to the N(7)-methyl protons and the C(8)-proton, respectively, on the basis of a spin-decoupling experiment.

It may be seen from Table 2 that **8** are all unstable in aqueous solution at pH 13. This is probably due to facile ring-opening, as would be anticipated by analogy with the reaction of **2**.[3)] However, it is surprising that **8** are also unstable in 0.1 N hydrochloric acid at room temperature. Under these conditions, the corresponding 9-alkyl analogues **2** are stable enough for their UV spectra to be obtainable.[2,10)] Details of these reactions of **8** will be reported elsewhere shortly.

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. UV and mass spectra were recorded on a Hitachi 320 UV spectrophotometer and a Hitachi M-80 mass spectrometer. ^{1}H-NMR spectra were measured at 25 °C in hexadeuterated dimethyl sulfoxide with a JEOL JNM-EX-270 or a JEOL JNM-GSX-500 NMR spectrometer using tetramethylsilane as an internal standard. Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

7-Methyladenine 1-Oxide (7a) A mixture of **6a**[6)] (1.79 g, 12 mmol), MCPBA (of 70% purity) (5.92 g, 24 mmol), and 50% (v/v) aqueous methanol (170 ml) was stirred at room temperature for 24 h. The resulting precipitate was filtered off, washed successively with methanol (2 × 2 ml) and ether (3 × 2 ml), and dried to afford a colorless solid (3.21 g), mp 237—239 °C (dec.), which was presumably the *m*-chlorobenzoate salt of **7a**. The filtrate and washings were combined and kept at room temperature for 15 d in order to effect decomposition of the peracid. The resulting mixture was concentrated *in vacuo*. The solid residue was partitioned between water (50 ml) and ether (100 ml). The aqueous layer was separated, washed with ether (2 × 50 ml), and concentrated *in vacuo* to leave a yellow solid. This was recrystallized from water to afford **7a**·H_2O (195 mg), mp 277—278 °C (dec.). The *m*-chlorobenzoate of **7a** described above was mixed with a saturated solution of sodium bicarbonate (919 mg, 10.9 mmol) in water. The insoluble solid was collected by filtration, washed with water (2 × 0.5 ml), dried over phosphorus pentoxide overnight, and exposed to air at room temperature until constant weight was reached to afford **7a**·H_2O [1.524 g; the total yield was 1.719 g (78%)], mp 286—287 °C (dec.). Recrystallization of this sample from water afforded an analytical sample of **7a**·H_2O after drying over phosphorus pentoxide at 2 mmHg and 50 °C for 10 h, followed by exposure to air at room temperature until constant weight was reached, as colorless needles, mp 289—290 °C (dec.); MS *m/z*: 165 (M^+), 149 ($M^+ - 16$); UV $\lambda_{max}^{95\%\ EtOH}$ 238 nm (ε 40800), 283 (7600); $\lambda_{max}^{H_2O}$ (pH 1) 220 (26400), 237 (sh) (7300), 268 (8800); $\lambda_{max}^{H_2O}$ (pH 7) 234 (42700), 277 (7700); $\lambda_{max}^{H_2O}$ (pH 13) 234 (25700), 284 (10000); ^{1}H-NMR δ: 4.01 (3H, s, NMe), 7.94 (2H, br, NH_2), 8.27 [1H, s, C(8)-H], 8.59 [1H, s, C(2)-H].[11)] *Anal.* Calcd for $C_6H_7N_5O \cdot H_2O$: C, 39.34; H, 4.95; N, 38.23. Found: C, 39.19; H, 4.91; N, 38.36.

7-Ethyladenine 1-Oxide (7b) A solution of **6b**[6)] (3.26 g, 20 mmol) and MCPBA (of 70% purity) (9.82 g, 40 mmol) in methanol (300 ml) was kept at room temperature for 3 d to give a slightly brown solution, which was negative in a test with KI-starch paper. It was concentrated *in vacuo*, and the residue was partitioned between water (250 ml) and ether (200 ml). The aqueous layer was separated, washed with ether (2 × 150 ml), and concentrated *in vacuo* to leave a yellow solid (4.17 g), mp 230—231 °C (dec.). This was recrystallized from 95% (v/v) aqueous 1-butanol to afford **7b**·$2H_2O$ (3.35 g, 78%), mp 243—244 °C (dec.). Further recrystallization of this sample from 95% (v/v) aqueous 1-butanol, drying over phosphorus pentoxide at 2 mmHg and 75 °C for 7 h, and exposure to air at room temperature until constant weight was reached, afforded an analytical sample of **7b**·$2H_2O$ as colorless needles, mp 248—249 °C (dec.); MS *m/z*: 179 (M^+), 163 ($M^+ - 16$); UV $\lambda_{max}^{95\%\ EtOH}$ 238 nm (ε 41300), 283 (7700); $\lambda_{max}^{H_2O}$ (pH 1) 221 (25700), 235 (sh) (8100), 268 (8400); $\lambda_{max}^{H_2O}$ (pH 7) 235 (42000), 277 (7500); $\lambda_{max}^{H_2O}$ (pH 13) 234 (24800), 284 (9700); ^{1}H-NMR δ: 1.34 (3H, t, J = 7 Hz, $NCH_2\underline{Me}$), 4.45 (2H, q, J = 7 Hz, $NC\underline{H}_2Me$), 7.95 (2H, br, NH_2), 8.36 [1H, s, C(8)-H], 8.62 [1H, s, C(2)-H].[11)] *Anal.* Calcd for $C_7H_9N_5O \cdot 2H_2O$: C, 39.07; H, 6.09; N, 32.54. Found: C, 39.22; H, 5.98; N, 32.73.

Alkylation of 7-Alkyladenine 1-Oxides (7) Leading to 1-Alkoxy-7-alkyladenine Salts (8·HX) The procedures employed for the preparation of **8d**·HI, **8i**·HBr, **8k**·$HClO_4$ will be described below in detail as typical examples. The other alkylations were accomplished similarly. Tables 1—3 summarize the results.

1-Methoxy-7-methyladenine Hydriodide (8d·HI) A mixture of **7a**·H_2O (403 mg, 2.2 mmol), methyl iodide (1.25 g, 8.8 mmol), and DMAc (3 ml) was stirred at room temperature for 7 h. The precipitate that deposited was collected by filtration, washed with ethanol (2 ml), and dried to afford **8d**·HI·H_2O (264 mg). The filtrate and washings were combined, and ether (30 ml) and ethanol (2 ml) were added. The resulting precipitate was collected by decantation, washed with a little ethanol, and dried to afford a second crop of **8d**·HI·H_2O [311 mg; the total yield was 575 mg (80%)], mp 148—151 °C (dec.). Recrystallization of crude **8d**·HI·H_2O from 70% (v/v) aqueous ethanol afforded an analytical sample of **8d**·HI·H_2O (see Tables 1—3).

1-Benzyloxy-7-ethyladenine Hydrobromide (8i·HBr) A mixture of **7b**·$2H_2O$ (6.46 g, 30 mmol), benzyl bromide (20.5 g, 0.12 mol), and DMAc (20 ml) was stirred at room temperature for 45 min. The precipitate that resulted was collected by filtration, washed with ethanol (5 ml), and dried to afford **8i**·HBr (9.81 g), mp 158—159 °C (dec.). The filtrate and washings were combined, and ether (200 ml) was added. The resulting precipitate was collected by filtration, washed with ethanol (5 ml), and dried to afford a second crop of **8i**·HBr [0.31 g; the total yield was 10.12 g (96%)], mp 147—149 °C (dec.). Recrystallization of crude **8i**·HBr from methanol–ether (1 : 1, v/v) afforded an analytical sample of **8i**·HBr (see Tables 1—3).

7-Benzyl-1-ethoxyadenine Perchlorate (8k·$HClO_4$) A mixture of **7c**[5)] (121 mg, 0.502 mmol), ethyl iodide (312 mg, 2 mmol), and DMAc (1.5 ml) was stirred at room temperature for 6 h to afford a yellow solution. Ether (20 ml) was added to it. The resulting precipitate was collected by filtration, washed successively with ethanol (1 ml) and ether (2 ml), and dried to afford **8k**·HI (178 mg) as a colorless solid, mp 155—157 °C (dec.). A portion (150 mg) of **8k**·HI was dissolved in warm water (2 ml), and saturated aqueous sodium perchlorate monohydrate (106 mg, 0.755 mmol) was added. The resulting precipitate was collected by filtration, washed with water (0.5 ml), and dried to afford **8k**·$HClO_4$ (117 mg, 75%), mp 191—192 °C (dec.). Recrystallization of this sample from 95% (v/v) aqueous ethanol afforded an analytical sample of **8k**·$HClO_4$ (see Tables 1—3).

1-Methoxy-7-methyladenine Perchlorate (8d·$HClO_4$) A saturated solution of sodium perchlorate monohydrate (605 mg, 4.31 mmol) in methanol was added to a warm solution of **8d**·HI·H_2O (700 mg, 2.15 mmol) in methanol (3 ml). The resulting mixture was kept at room temperature overnight. The precipitate that resulted was collected by filtration, washed with methanol (2 × 1 ml), and dried to afford **8d**·$HClO_4$ (564 mg, 94%), mp 185—187 °C (dec.). Recrystallization of this sample from 95% (v/v) aqueous ethanol afforded an analytical sample of **8d**·$HClO_4$ as colorless pillars, mp 192—193 °C (dec.); UV (Table 2); ^{1}H-NMR (Table 3). *Anal.* Calcd for $C_7H_9N_5O \cdot HClO_4$: C, 30.07; H,

3.60; N, 25.04. Found: C, 30.04; H, 3.63; N, 24.99.

1-Ethoxy-7-ethyladenine Perchlorate (8h·HClO$_4$) This compound (2.18 g, 90% yield), mp 201—202 °C (dec.), was prepared from **8h**·HI (2.64 g, 7.88 mmol) in a manner similar to that described for the preparation of **8d**·HClO$_4$. Recrystallization of crude **8h**·HClO$_4$ from methanol afforded an analytical sample of **8h**·HClO$_4$ as colorless pillars, mp 205—206 °C (dec.); UV (Table 2); ^{1}H-NMR (Table 3). *Anal.* Calcd for $C_9H_{13}N_5O \cdot HClO_4$: C, 35.13; H, 4.59; N, 22.76. Found: C, 35.07; H, 4.64; N, 22.69.

1-Methoxy-7-methyladenine (8d) A solution of **8d**·HClO$_4$ (280 mg, 1 mmol) in water (10 ml) was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (1.6 ml), and the column was eluted with water (200 ml). The eluates were combined and concentrated *in vacuo* to leave **8d** (179 mg, 100%) as a colorless solid, mp *ca.* 125 °C (dec.); ^{1}H-NMR δ: 3.95 (3H, s, OMe), 4.01 (3H, s, NMe), 7.13 (1H, br, NH), 7.98 [1H, s, C(8)-H], 8.29 [1H, s, C(2)-H]. Recrystallization of this compound was difficult.

1-Ethoxy-7-ethyladenine (8h) A solution of **8h**·HI (2.37 g, 7.07 mmol) in water (50 ml) was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (14 ml), and the column was eluted with water. The combined eluates (500 ml) were concentrated *in vacuo* and the resulting solid residue was recrystallized from hexane–benzene (1 : 1, v/v) to afford **8h** (966 mg, 66%), mp 126—127 °C. Further recrystallization of this sample from hexane–benzene (1 : 2, v/v) afforded an analytical sample of **8h** as colorless needles, mp 126—127 °C; MS *m/z*: 207 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 263 nm (ε 10700), 269 (sh) (9700); $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 221 (26000), 270 (9500); $\lambda_{max}^{H_2O}$ (pH 7) 219 (19900), 266 (10400); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 263 (11500); ^{1}H-NMR δ: 1.34 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.39 (3H, t, J=7 Hz, $NCH_2\underline{Me}$), 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.41 (2H, q, J=7 Hz, $NC\underline{H}_2Me$), 6.87 (1H, br, NH), 8.04 [1H, s, C(8)-H], 8.24 [1H, s, C(2)-H]. *Anal.* Calcd for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79. Found: C, 52.30; H, 6.43; N, 33.62.

1-Benzyloxy-7-ethyladenine (8i) A solution of **8i**·HBr (9.11 g, 26 mmol) in water (130 ml) was brought to pH 8 by addition of saturated aqueous sodium bicarbonate. The resulting precipitate was collected by filtration, washed with water (20 ml), and dried to afford **8i** (6.46 g, 92%), mp 162—164 °C. Recrystallization of crude **8i** from ethyl acetate–ethanol (2 : 1, v/v) afforded an analytical sample of **8i** as colorless prisms, mp 167—168.5 °C; MS *m/z*: 269 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 264 nm (ε 10800), 268 (sh) (9800); $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 223 (28500), 269 (9500); $\lambda_{max}^{H_2O}$ (pH 3)[12] 223 (29200), 270 (9400)[13]; ^{1}H-NMR δ: 1.39 (3H, t, J=7 Hz, $NCH_2\underline{Me}$), 4.42 (2H, q, J=7 Hz, $NC\underline{H}_2Me$), 5.15 (2H, s, $OC\underline{H}_2Ph$), 6.89 (1H, br, NH), 7.39—7.49 (3H) and 7.52—7.61 (2H) (m each, $OCH_2\underline{Ph}$), 8.05 [1H, s, C(8)-H], 8.12 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.62; H, 5.68; N, 25.76.

7-Benzyl-1-benzyloxyadenine (8l) A solution of **8l**·HBr (150 mg, 0.364 mmol) in water (40 ml) was brought to pH 7 by addition of saturated aqueous sodium bicarbonate. After storage of the mixture in a refrigerator overnight, the resulting precipitate was collected by filtration, washed with water (2 × 2 ml), and dried to afford **8l** (113 mg, 93%), mp 151.5—153 °C. Recrystallization of this sample from 50% (v/v) aqueous ethanol afforded an analytical sample of **8l** as colorless pillars, mp 158—159 °C; MS *m/z*: 331 (M^+); UV $\lambda_{max}^{95\%\ EtOH}$ 265 nm (ε 9900); $\lambda_{max}^{H_2O}$ (pH 1) (unstable) 218 (sh) (27500), 270 (8500)[13]; ^{1}H-NMR δ: 5.15 (2H, s, $OC\underline{H}_2Ph$), 5.69 (2H, s, $NC\underline{H}_2Ph$), 6.89 (1H, br, NH), 7.25—7.58 (10H, m, two Ph's), 8.14 [1H, s, C(8)-H], 8.16 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.69; H, 5.14; N, 20.95.

Hydrogenolysis of 8d over Raney Ni Leading to 6a A solution of **8d**, which was prepared from **8d**·HClO$_4$ (279 mg, 0.998 mmol) in a manner similar to that described above, in water (15 ml) was shaken under hydrogen at atmospheric pressure and *ca.* 50 °C for 4 h in the presence of Raney Ni W-2 catalyst[14] (1 ml). The catalyst was filtered off and washed with water (20 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave **6a** (124 mg, 83%) as a colorless solid, mp > 300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with an authentic sample of **6a**.[6]

Hydrogenolysis of 8i over Palladium-on-Carbon Leading to 7b A solution of **8i** (135 mg, 0.501 mmol) in ethanol (25 ml) was hydrogenated over 10% palladium-on-carbon (75 mg) at atmospheric pressure and room temperature for 5 min. The catalyst was filtered off and washed with ethanol (10 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave **7b**·2H$_2$O (100 mg, 93%) as a colorless solid, mp 241—241.5 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7b**·2H$_2$O (*vide supra*).

References and Notes

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9) It has already been reported that the UV spectra of 1-alkoxyadenine derivatives resemble those of the corresponding 1-alkyladenines.[10]
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11) The purine-proton signals were assigned by comparison with those[5] of **7c**.
12) Measured in 0.001 N hydrochloric acid.
13) The spectra in water at pH 7 and 13 were not obtained because of the poor solubility of this substance.
14) Mozingo R., "Organic Syntheses," Coll. Vol. III, ed. by Horning E. C., John Wiley and Sons, New York, 1955, pp. 181—183.