

Purines. XXXVIII.¹⁾ A General Synthesis of 7,9-Dialkyladeninium Salts from 9-Alkyladenines by Regioselective Alkylation: Utilization of an *N*⁶-Alkoxy Group as a Control Synthon

Tozo FUJII,* Tohru SAITO, Teruyo SAKUMA, Masako MINAMI, and Isao INOUE

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan. Received August 17, 1989

A detailed account is given of the general synthetic route to 7,9-dialkyladeninium salts (16—18) from *N*⁶-alkoxy-9-alkyladenines (type 5 or 11—13), readily obtainable from 9-alkyladenines in three steps involving N(1)-oxidation, *O*-alkylation, and Dimroth rearrangement. Alkylations of *N*⁶-methoxy-9-methyladenine (5) and 9-alkyl-*N*⁶-benzyloxyadenines (11—13) with MeI, EtI, and PhCH₂Br in AcNMe₂ produced the corresponding 7-alkylated derivatives (15 and 19—21), together with small amounts of the *N*⁶-alkylated isomers (6, 8, and 9). Catalytic hydrogenolysis of the former compounds with hydrogen and Raney Ni yielded 7,9-dialkyladeninium salts (16—18).

Keywords 7,9-dialkyladenine synthesis; *N*⁶-alkoxy-9-alkyladenine; regioselective alkylation; catalytic hydrogenolysis; dealkoxylation; Dimroth rearrangement; amino-imino tautomerism; HPLC analysis; UV; ¹H-NMR

The alkoxy group at the N(1)- or *N*⁶-position of the adenine ring system (1) has been a useful and convenient "control synthon"²⁾ (or "control element"³⁾) for chemical modification of adenine derivatives including nucleosides.^{4–8)} The function of this group is based on its unique directivity in alkylation,⁹⁾ substantial removability under hydrogenolytic conditions,^{10,11)} and characteristic ability to cause facile ring opening at the C(2)-position in the case of the N(1)-alkoxy group.¹²⁾ It has been shown by us that an alkoxy group at the N(1)-position of adenine (1) itself orients alkylation to the 9-position,^{4a,c,i,m)} whereas the one in the 9-alkyladenine system directs an incoming

alkyl group to the *N*⁶-position.^{4k)} We have also revealed the effect of the *N*⁶-alkoxy group on the site of methylation of adenine,^{5d)} all five possible isomers of *N*-methyladenine,^{4g,5b,c)} and 1,9-dimethyladenine.^{5b)} Among these methylation studies, that of *N*⁶-methoxy-9-methyladenine (5)¹³⁾ may deserve particular mention, since it opened a synthetic route to hitherto unknown 7,9-dimethyladenine (type 16a),¹⁴⁾ the prototype of 7,9-disubstituted adenines. Later on, the natural occurrences of 7,9-disubstituted adenine structures in the form of agelasine (from the sea sponge *Agelas dispar*),¹⁵⁾ agelasines A—F (from the Okinawan sea sponge *A. nakamurai*),^{16,17)} and agelines A (agelasine F¹⁶⁾) and B (from a Pacific sea sponge *Agelas* sp.),¹⁸⁾ all with diterpene or modified diterpene units at the 7-position (type 2a), were reported. The existence of the 7-methyladenosine structure (3) in transfer ribonucleic acids of *Bacillus stearothermophilus*¹⁹⁾ or *B. subtilis*²⁰⁾ as a modified nucleoside component was also suggested, and 7-methyl- or 7-ethyladenosine (type 3 or 4 with unspecified X) was reported to be a by-product from methylation or ethylation of adenosine in neutral aqueous solution.²¹⁾ These reports immediately renewed our interest in the study of the chemistry of 7,9-dialkyladenines. In this paper, we present the details of our study on the extension of the above 7-methylation of *N*⁶-methoxy-9-methyladenine (5) to

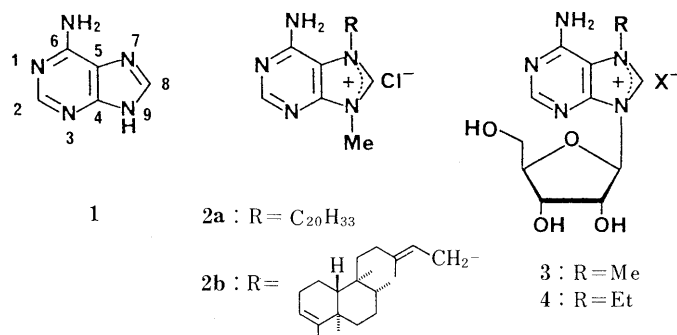


TABLE I. Alkylation of *N*⁶-Alkoxy-9-alkyladenines (5 and 11—13)

Starting material	Alkylating agent	Reaction conditions		N(7)-Alkylated product		<i>N</i> ⁶ -Alkylated product		N(7)-/ <i>N</i> ⁶ -Alkylation ^{a)}
		Temp. (°C)	Time (h)	No.	Yield (%)	No.	Yield (%)	
5	MeI	30	7	15a	59 ^{b)}	6a · HI	24 ^{b)}	2.5 (2.1) ^{c)}
5	EtI	50	28	15b	66	6b · HCl ^{d)}	23	2.9 (2.6) ^{e)}
5	PhCH ₂ Br	30	30	15c ^{d)}	54	6c · HBr	12	4.5
11	MeI	30	4	19a	58	8a	18	3.2 (3.3) ^{c)}
11	EtI	50	24	19b	77	8b · HCl ^{f)}	12	6.4 (4.9) ^{e)}
11	PhCH ₂ Br	30	24	19c ^{f)}	63	8c · HClO ₄	11	5.7
12	MeI	30	5	20a	71	9a	10	7.1
12	EtI	50	24	20b	66	— ^{g)}	—	—
12	PhCH ₂ Br	30	22	20c	65	— ^{g)}	—	—
13	EtI	50	27	21b	46	— ^{g)}	—	—
13	PhCH ₂ Br	30	23	21c	67	— ^{g)}	—	—

a) Based on the ratio of the isolated yield of the 7-alkylated product to that of the *N*⁶-alkylated product. The ratio in parentheses was obtained by HPLC analysis of the reaction mixture, as described in "Experimental." b) Taken from ref. 5b. c) Determined on the product mixture from an 8-h reaction. d) As a monohydrate. e) Determined on the product mixture from a 30-h reaction. f) Found to contain 1/3 molar eq of H₂O of crystallization. g) No attempt was made to isolate the *N*⁶-alkylated product.

alkyladenines by alkylation if the alkyl group at the 7- or 9-position could orient an incoming alkyl group to the 9- or 7-position, respectively. However, such a one-step route is not feasible since alkylation of 7- or 9-alkyladenines occurs mainly at the 3-²³⁾ or 1-position,^{4e,23d,24)} respectively. On the other hand, methylation of *N*⁶-methoxy-7-methyl-

the other hand, methylation of *N*⁶-methoxy-7-methyl-



Compound					UV spectra ^{a)}					
					95% EtOH		H ₂ O (pH 1) ^{b)}		H ₂ O (pH 7) ^{c)}	
No.	N ⁶ -OR	N(9)-R ¹	N(7)-R ²	X	$\lambda_{\max}$ (nm)	$\varepsilon \times 10^{-3}$	$\lambda_{\max}$ (nm)	$\varepsilon \times 10^{-3}$	$\lambda_{\max}$ (nm)	$\varepsilon \times 10^{-3}$
15a	MeO	Me	Me	I	291	7.9	227	20.0	226	20.1
							284	9.4	284	9.2
15b	MeO	Me	Et	I	291	7.9	226	20.0	226	20.0
							283	9.2	283	9.2
15c^{d)}	MeO	Me	PhCH ₂	Br	297	7.0	289	8.3	289	8.2
19a	PhCH ₂ O	Me	Me	I	292	8.5	226	21.6	226	21.7
							284	10.5	284	10.5
19b	PhCH ₂ O	Me	Et	I	291	7.7	226	20.7	226	21.1
							284	9.9	284	10.1
19c^{e)}	PhCH ₂ O	Me	PhCH ₂	Br	297	7.7	288	9.3	288.5	9.1
20a	PhCH ₂ O	Et	Me	I	291	9.0	226	22.6	226	22.3
							284	11.6	284	11.3
20b	PhCH ₂ O	Et	Et	I	291	8.8	226	22.5	226	22.0
							283	11.5	283	11.2
20c	PhCH ₂ O	Et	PhCH ₂	Br	297	7.7	289	9.8	289	9.7
21b	PhCH ₂ O	PhCH ₂	Et	I	295	8.8	225	24.6	225	24.6
							286	11.4	286	11.2
21c	PhCH ₂ O	PhCH ₂	PhCH ₂	Br	301	7.5	292	9.7	292	9.6
21e	PhCH ₂ O	PhCH ₂	Et	ClO ₄	293	8.8	286	10.6	286	10.3

NII-Electronic Library Service

adenine (**14**) with MeI in AcNMe₂ gives the 9-methylated product **15a** and the 3-methylated product **23** in 36% and 44% yields, respectively^{5b)} (Chart 1). A similar methylation of *N*⁶-methoxy-9-methyladenine (**5**)¹³⁾ produces the 7-methylated product **15a** and the *N*⁶-methylated product **6a**·HI in 59% and 24% yields, respectively.^{5b)} This was the reason why we tried to generalize the latter reaction for a synthesis of 7,9-dialkyladenines, although in circuitous manner. Thus, alkylation of **5**^{4b,13)} with EtI or PhCH₂Br in AcNMe₂ was carried out at 50 °C or 30 °C for 28 or 30 h, and the corresponding 7-alkylated 9-methyladenine derivative (**15b** or **15c**) as well as the *N*⁶-alkylated product (**6b** or **6c**) was obtained. In order to study the effect of the *N*⁶-benzyloxy group on regioselectivity in such alkylations, *N*⁶-benzyloxy-9-methyladenine (**11**)^{4j,13)} was also allowed to react with MeI, EtI, and PhCH₂Br under similar conditions. Table I summarizes the results of these alkylation studies. It may be seen that in all cases the reaction proceeds smoothly and the *N*⁶-alkoxy group orients the alkylation to both the 7- and the *N*⁶-position, but with a preference for the former position. The *N*⁶-benzyloxy group tends to cause the extent of the 7-alkylation to increase and that of the *N*⁶-alkylation to decrease. This change in regioselectivity may be explained in terms of a reduction in nucleophilicity of the N⁶ atom, resulting from the replacement of the *N*⁶-methoxy group by the more electron-withdrawing^{4j,o)} benzyloxy group. It is also interesting that a preference of the alkylating agent for the 7-alkylation is enhanced in the order MeI <

EtI < PhCH₂Br, regardless of the kind of *N*⁶-alkoxy group in the substrates. Characterization of all the major products as 7-alkylated derivatives was achieved by determination of their ultraviolet (UV) spectra, which turned out to be similar to those of known *N*⁶-methoxy-7,9-dimethyladeninium iodide (**15a**),^{5b)} as shown in Table II. The minor products were characterized as *N*⁶-alkyl isomers on the basis of their UV spectra, which were similar to those of known *N*⁶-methoxy-*N*⁶, 9-dimethyladenine hydriodide (**6a**·HI),^{5b)} as shown in Table III. This was also supported by hydrogenolyses (Raney Ni/H₂, EtOH, 1 atm, 50 °C, 6—8 h) of **6b** and **6c** leading to *N*⁶-ethyl-9-methyladenine (**7b**)^{4e)} (92% yield) and *N*⁶-benzyl-9-methyladenine (**7c**)²⁵⁾ (71% yield), respectively. These conversions were parallel to that^{5b)} of **6a** into **7a**.

Since the results of the above alkylation study suggested the use of the *N*⁶-benzyloxy group for an efficient 7-alkylation of 9-substituted adenines, we next carried out the reactions of *N*⁶-benzyloxy-9-ethyladenine (**12**),^{4g,i,13)} newly synthesized in 68% or 69% yield from 1-benzyloxy-9-ethyladenine hydrobromide (**22**·HBr) or perchlorate (**22**·HClO₄) by treating it with boiling 0.5 M phosphate buffer (pH 6.5) for 2 h, and of 9-benzyl-*N*⁶-benzyloxyadenine (**13**)^{4b,13)} with MeI, EtI, and PhCH₂Br in AcNMe₂ under similar conditions. Table I also includes the results of these alkylations. It may be seen that the *N*⁶-benzyloxy group is a more favorable control element for the preferential 7-alkylation than the *N*⁶-methoxy group, as expected. In the case of the methylation of **13** with MeI, the progress of the

TABLE III. UV Spectra of *N*⁶-Alkoxy-*N*⁶,9-dialkyladenines (**6** and **8**—**10**)

Compound				UV spectra							
				95% EtOH		H ₂ O (pH 1) ^{a)}		H ₂ O (pH 7) ^{b)}		H ₂ O (pH 13) ^{c)}	
No.	<i>N</i> ⁶ -OR	N(9)-R ¹	<i>N</i> ⁶ -R ²	λ _{max} (nm)	ε × 10 ⁻³	λ _{max} (nm)	ε × 10 ⁻³	λ _{max} (nm)	ε × 10 ⁻³	λ _{max} (nm)	ε × 10 ⁻³
6a ·HI	MeO	Me	Me	277	17.8	277	16.7	276	18.1	276	17.6
6b ·HCl ^{d)}	MeO	Me	Et	277	18.3	277	17.4	277	18.5	277	18.5
6c ·HBr	MeO	Me	PhCH ₂	277	19.8	280	18.7	277	19.9	277	20.1
8a	PhCH ₂ O	Me	Me	277	19.0	278	16.5	277	18.2	276.5	18.0
8b ·HCl ^{e)}	PhCH ₂ O	Me	Et	277	19.7	279	18.0	277.5	19.2	277.5	19.4
8c ·HClO ₄	PhCH ₂ O	Me	PhCH ₂	278	20.8	283	18.0	278.5	18.6	278.5	18.1
9a	PhCH ₂ O	Et	Me	277	19.9	280	16.5	278	18.2	278	18.5

a) Measured in 0.1 N aqueous HCl. b) Measured in 0.005 M phosphate buffer (pH 7). c) Measured in 0.1 N aqueous NaOH. d) As a monohydrate. e) A sample containing 1/3 molar eq of H₂O of crystallization was used.

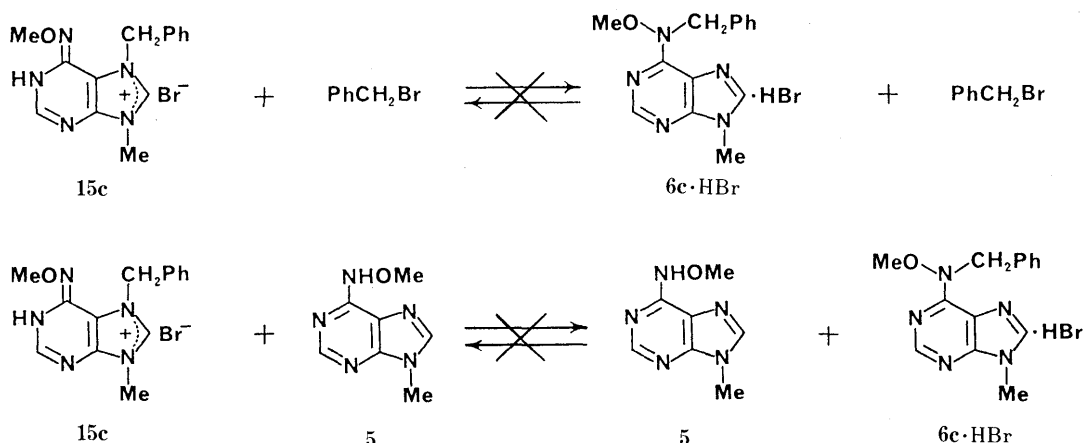


Chart 2

reaction was in effect fast. However, we were unable to isolate the products, **21a** and/or **10a**, in pure form. A problem for solution at this stage was to determine whether the formations of the 7-alkylated products (**15** and **19–21**) and the *N*⁶-alkylated products (**6**, **8**, and **9**) from *N*⁶-alkoxy-9-alkyladenines (**5** and **11–13**) by alkylation had occurred in a competitive or consecutive manner. Treatment of **15c** with an excess of PhCH₂Br in AcNMe₂ at 30 °C for 30 h showed no indication of any reaction, as monitored by thin-layer chromatographic (TLC) analysis (Chart 2). This was also the case when **6c**·HBr was treated with an excess of PhCH₂Br under similar conditions. In addition, a mixture of **15c** and **5** in AcNMe₂ or a mixture of **6c**·HBr and **5** in AcNMe₂ showed no change at 30 °C for 30 h, as monitored by TLC analysis. These observations thus supported the existence of competitive pathways for

the 7- and *N*⁶-alkylations of *N*⁶-alkoxy-9-alkyladenines (**5** and **11–13**).

Our preference for the 6-imino-1*H*-purine structures **15** and **19–21** for the expression of *N*⁶-alkoxy-7,9-dialkyladeninium salts was based on our previous conclusion drawn from the spectroscopic study of **15a**^{5b}) and on their nuclear magnetic resonance (NMR) spectra in Me₂SO-*d*₆. It may be seen from Table IV that in most cases the C(2)-H signal of the *N*⁶-alkoxy-7,9-dialkyladeninium salts (**15** and **19–21**) appeared as a dull singlet or a doublet or a set of a doublet and a singlet, which turned into a one-proton singlet on addition of D₂O. This suggests that in Me₂SO-*d*₆ solution these salts exist exclusively in the form of the N(1)-H tautomer (type **15** or **19–21**) or in two tautomeric forms, the N(1)-H tautomer and the 6-NH tautomer (type **24**), as in the case of *N*⁶-methoxy-7,9-

TABLE IV. ¹H-NMR Data for *N*⁶-Alkoxy-7,9-dialkyladeninium Salts (**15** and **19–21**) and 7,9-Dialkyladeninium Salts (**16–18**)

Compd.	Chemical shift (δ) ^a in Me ₂ SO- <i>d</i> ₆						
	<i>N</i> ⁶ -OR	N(9)-R ¹	N(7)-R ²	NH ^b	NH ₂ ^c	C(2)-H	C(8)-H
15a ^d	3.85 or 3.80 (s, Me)	3.80 or 3.85 (s, Me)	3.99 (s, Me)	12.10 (br)	—	7.83 (0.6H, d) ^e 7.84 (0.4H, s)	9.24 (s)
15b	3.88 (s, Me)	3.83 (s, Me)	1.46 (t, CH ₂ Me) ^f 4.38 (q, CH ₂ Me) ^f	12.13 (br)	—	7.87 (d) ^g 7.87 (s)	9.39 (s)
15c ^h	3.83 (s, Me)	3.83 (s, Me)	5.60 (s, CH ₂ Ph) 7.40 (m, CH ₂ Ph)	12.12 (br)	—	7.84 (s)	9.56 (s)
19a	5.11 (s, CH ₂ Ph) 7.44 (m, CH ₂ Ph)	3.83 (s, Me)	4.01 (s, Me)	12.06 (br)	—	7.87 (s)	9.30 (s)
19b	5.09 (s, CH ₂ Ph) 7.39 (m, CH ₂ Ph)	3.79 (s, Me)	1.38 (t, CH ₂ Me) ^f 4.33 (q, CH ₂ Me) ^f	12.13 (br)	—	7.85 (d) ^g	9.34 (s)
19c ⁱ	5.10 (s, CH ₂ Ph) 7.34 (m, CH ₂ Ph)	3.81 (s, Me)	5.57 (s, CH ₂ Ph) 7.34 (m, CH ₂ Ph)	12.20 (br)	—	7.86 (s)	9.53 (s)
20a	5.08 (s, CH ₂ Ph) 7.39 (m, CH ₂ Ph)	1.43 (t, CH ₂ Me) ^f 4.23 (q, CH ₂ Me) ^f	3.97 (s, Me)	12.07 (br)	—	7.80 (d) ^g 7.81 (s)	9.30 (s)
20b	5.09 (s, CH ₂ Ph) 7.40 (m, CH ₂ Ph)	1.44 (t, CH ₂ Me) ^f 4.22 (q, CH ₂ Me) ^f	1.38 (t, CH ₂ Me) ^f 4.32 (q, CH ₂ Me) ^f	12.14 (br)	—	7.84 (d) ^e 7.85 (s)	9.37 (s)
20c	5.11 (s, CH ₂ Ph) 7.36 (m, CH ₂ Ph)	1.45 (t, CH ₂ Me) ^f 4.25 (q, CH ₂ Me) ^f	5.57 (s, CH ₂ Ph) 7.36 (m, CH ₂ Ph)	12.20 (br)	—	7.87 (dull s)	9.68 (s)
21b	5.09 (s, CH ₂ Ph) 7.40 (m, CH ₂ Ph)	5.45 (s, CH ₂ Ph) 7.40 (m, CH ₂ Ph)	1.39 (t, CH ₂ Me) ^f 4.35 (q, CH ₂ Me) ^f	12.17 (br)	—	7.85 (dull s)	9.47 (s)
21c	5.10 (s, CH ₂ Ph) 7.34 (m, CH ₂ Ph)	5.47 (s, CH ₂ Ph) 7.34 (m, CH ₂ Ph)	5.58 (s, CH ₂ Ph) 7.34 (m, CH ₂ Ph)	12.23 (br)	—	7.86 (dull s)	9.67 (s)
21e	5.09 (s, CH ₂ Ph) 7.39 (m, CH ₂ Ph)	5.45 (s, CH ₂ Ph) 7.39 (m, CH ₂ Ph)	1.39 (t, CH ₂ Me) ^f 4.34 (q, CH ₂ Me) ^f	12.17 (br)	—	7.86 (dull s)	9.44 (s)
16a	—	3.89 (s, Me)	4.19 (s, Me)	—	7.93 (br)	8.44 (s)	9.57 (s)
16b	—	3.90 (s, Me)	1.49 (t, CH ₂ Me) ^f 4.61 (q, CH ₂ Me) ^f	—	7.94 (br)	8.44 (s)	9.69 (s)
16c ^h	—	3.92 (s, Me)	5.95 (s, CH ₂ Ph) 7.42 (m, CH ₂ Ph)	—	7.85 (br)	8.46 (s)	9.76 (s)
17a	—	1.49 (t, CH ₂ Me) ^f 4.34 (q, CH ₂ Me) ^f	4.17 (s, Me)	—	7.95 (br)	8.45 (s)	9.64 (s)
17b	—	1.50 (t, CH ₂ Me) ^f 4.34 (q, CH ₂ Me) ^f	1.48 (t, CH ₂ Me) ^f 4.59 (q, CH ₂ Me) ^f	—	7.96 (br)	8.47 (s)	9.70 (s)
17d	—	1.51 (t, CH ₂ Me) ^f 4.38 (q, CH ₂ Me) ^f	5.86 (s, CH ₂ Ph) 7.41 (m, CH ₂ Ph)	—	7.84 (br)	8.48 (s)	9.69 (s)
17e	—	1.50 (t, CH ₂ Me) ^f 4.34 (q, CH ₂ Me) ^f	1.48 (t, CH ₂ Me) ^f 4.59 (q, CH ₂ Me) ^f	—	7.97 (br)	8.47 (s)	9.67 (s)
17f	—	1.48 (t, CH ₂ Me) ^f 4.34 (q, CH ₂ Me) ^f	4.16 (s, Me)	—	7.95 (br)	8.45 (s)	9.60 (s)
18c	—	5.59 (s, CH ₂ Ph) 7.43 (m, CH ₂ Ph)	5.89 (s, CH ₂ Ph) 7.43 (m, CH ₂ Ph)	—	7.92 (br)	8.47 (s)	9.82 (s)
18e	—	5.55 (s, CH ₂ Ph) 7.42 (m, CH ₂ Ph)	1.49 (t, CH ₂ Me) ^f 4.59 (q, CH ₂ Me) ^f	—	8.01 (br)	8.46 (s)	9.78 (s)

a) Measured at 23–137 M concentration and expressed in ppm downfield from internal Me₄Si. The letter(s) in parentheses designate(s) the multiplicity or shape or assignment of the signal; the abbreviations are given in "Experimental." b) One-proton signal exchangeable with D₂O. c) Two-proton signal exchangeable with D₂O. d) Taken from ref. 5b. e) With *J* = 3.9 Hz. f) With *J* = 7 Hz. g) With *J* = 3.5 Hz. h) As a monohydrate. i) A sample containing 1/3 molar eq of H₂O of crystallization was used.

dimethyladeninium salts.^{5b)}

Removal of the methoxy or benzyloxy group from the 7-alkylated derivatives **15a—c**, **19a—c**, **20a—c**, **21c**, and **21e** (derived from **21b**) was then accomplished by catalytic hydrogenolysis (Raney Ni/H₂, H₂O or aqueous MeOH, 1 atm, room temperature) under conditions similar to those²⁶⁾ employed by us for the N—O bond cleavage of *N'*-alkoxy groups in imidazolecarboxamide systems. As shown in Table V, these hydrogenolyses produced the desired 7,9-dialkyladeninium salts (**16a—c**, **17a,b,d**, and **18c,e**) in acceptable yields (except for the low yields in the last two cases). Removal of the methoxy group from **15a** had previously been achieved through a two-step route consisting of the conversion of **15a** into the perchlorate **15f** (83% yield) and subsequent hydrogenolysis (Pd—C/H₂, aqueous EtOH, 1 atm, 40—50 °C, 5.5 h) leading to **16f** (92% yield).^{5b)} The correctness of the structures of the 7,9-dialkyladeninium salts thus obtained was supported by their UV spectra, which are similar to those of known **16f**,^{5b)} as shown in Table VI, and by their ¹H-NMR spectral data

TABLE V. Conversion of *N*⁶-Alkoxy-7,9-dialkyladeninium Salts (**15** and **19—21**) into 7,9-Dialkyladeninium Salts (**16—18**)

Starting material	Reaction conditions ^{a)}		Product	
	Solvent ^{b)}	Time (h)	Compound number	Yield (%)
15a	A	18	16a	80
15b	A	45	16b	81
15c^{c)}	A	52	16c^{c)}	51
19a	A	13	16a	72
19b	A	40	16b	83
19c^{d)}	A	43	16c^{c)}	60
20a	B	25	17a	65
20b	B	30	17b	70
20c	B	40	17d^{e)}	57
21c	C	40	18c	22
21e	C	34	18e	22

a) Hydrogenated over Raney Ni W-2 catalyst at atmospheric pressure and room temperature. b) The letter A stands for H₂O; B, 50% (v/v) aqueous MeOH; C, 85% (v/v) aqueous MeOH. c) As a monohydrate. d) A sample containing 1/3 molar eq of H₂O of crystallization was used. e) Isolated as the perchlorate.

(included in Table IV). It is interesting to note that Maki and co-workers utilized the *N*⁶-acyl group as a control element for a preferential 7-alkylation of 9-substituted adenines.²⁷⁾ After the 7-alkylation, they removed the *N*⁶-acyl group by treatment with hydrazine hydrate in AcOH—pyridine (1:4, v/v) at room temperature for 3 h, concluding an alternative synthesis of 7,9-dialkyladeninium iodides.^{27b,c,28)}

In conclusion, the present results have confirmed that the site of alkylation in a 9-alkyladenine is altered quite differently by the *N*⁶-methoxy group and the *N*⁶-benzyloxy group. They have also established a general synthetic route to 7,9-dialkyladeninium salts for the first time. Since the starting *N*⁶-alkoxy-9-alkyladenines (type **5** or **11—13**) are readily available from 9-alkyladenines in three steps involving N(1)-oxidation,²⁹⁾ *O*-alkylation,²⁹⁾ and Dimroth rearrangement,¹²⁾ the present synthetic route is tantamount to a route from 9-alkyladenines by regioselective alkylation utilizing an *N*⁶-alkoxy group as a control element. Interestingly, a few biologically interesting compounds have been synthesized by application of this route: 7-methyladenosine sulfate (**3**: X=1/2SO₄),¹⁴⁾ 7-methyladenosine perchlorate (**3**: X=ClO₄),^{5a)} and 7-ethyladenosine perchlorate (**4**: X=ClO₄)^{5a)} by us, and agelasine B (**2b**), a sea sponge bicyclic diterpene with the 9-methyl-7-adeninylium moiety,¹⁶⁾ by Tokoroyama's group.³⁰⁾ In a preliminary study,⁴ⁿ⁾ we have also investigated an alternative synthesis and the chemical behavior of 7,9-dialkyladeninium salts. The details will be published elsewhere shortly.

Experimental

General Comments All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 4s for details of instrumentation and measurements. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet.

***N*⁶-Benzyloxy-9-ethyladenine (**12**)** A stirred mixture of **22**·HBr²⁹⁾ (10.6 g, 30 mmol) and 0.5 M phosphate buffer (pH 6.5) (600 ml) was heated under reflux for 2 h. The reaction mixture was then cooled in an ice bath for 5 h, and the precipitate that resulted was filtered off, washed successively with H₂O and EtOH, and dried to give **12** (5.52 g, 68%) as a colorless solid, mp 183.5—188 °C. Recrystallization from EtOH afforded a pure sample as colorless needles, mp 187.5—188.5 °C [lit. mp 154—

TABLE VI. UV Spectra of 7,9-Dialkyladeninium Salts (**16—18**)

Compound				UV spectra ^{a)}					
				95% EtOH		H ₂ O (pH 1) ^{b)}		H ₂ O (pH 7) ^{c)}	
				λ _{max} (nm)	ε × 10 ⁻³	λ _{max} (nm)	ε × 10 ⁻³	λ _{max} (nm)	ε × 10 ⁻³
16a	Me	Me	I	273.5	11.6	269	12.0	270	12.0
16b	Me	Et	I	273	11.6	269	11.9	270.5	11.9
16c^{d)}	Me	PhCH ₂	Br	275	10.6	270.5	11.3	271	11.3
16f^{e)}	Me	Me	ClO ₄	273	11.5	268	11.9	269	12.1
17a	Et	Me	I	273	12.0	269	12.5	270	12.4
17b	Et	Et	I	273	11.9	269	12.5	270	12.5
17d	Et	PhCH ₂	ClO ₄	275	11.1	270	11.6	271	11.6
17e	Et	Et	ClO ₄	273	11.9	270	12.1	271	12.7
17f	Et	Me	ClO ₄	274	12.1	270	12.6	271	13.1
18c	PhCH ₂	PhCH ₂	Br	276	11.2	272	12.3	272	12.6
18e	PhCH ₂	Et	ClO ₄	274	12.5	270	13.6	271	13.5

a) Unstable in the alkaline region in H₂O. b) Measured in 0.1 N aqueous HCl. c) Measured in 0.005 M phosphate buffer (pH 7). d) As a monohydrate. e) Taken from ref. 5b.

155 °C (dec.)^{4a,31}; mp 187.5—189 °C⁴¹). This sample was identical [by comparison of the UV, infrared (IR), and ¹H-NMR spectra and TLC mobility] with authentic **12**.^{41,13}

Alternatively, a similar treatment of crude **22**·HClO₄ [mp 191.5—192 °C (dec.)], prepared from **22**·HBr (14.3 g, 41 mmol) in 96% yield by dissolving it in warm H₂O (400 ml) and adding a solution of NaClO₄ (7.53 g, 62 mmol) in H₂O (15 ml), with boiling 0.5 M phosphate buffer (pH 6.5) furnished **12** in 69% yield.

High-Performance Liquid Chromatographic (HPLC) Analysis of Products from Methylation of N⁶-Methoxy-9-methyladenine (5) Methylation of **5**^{4b} with MeI was effected in AcNMe₂ at 30 °C for 8 h in a manner similar to that^{5b} described previously. The solvent and the excess MeI were removed from the reaction mixture by distillation under reduced pressure, and the residue was subjected to HPLC analysis. The HPLC analysis was carried out on a Waters ALC/GPC 204 liquid chromatograph [Bondapak C₁₈/Porasil B, MeOH–0.02 M KH₂PO₄ (92:8, v/v), 350–400 p.s.i., 1.0 ml/min], and the peak heights of two products (**6a**·HI and **15a**), located by using a UV absorbance detector operated at 254 nm, were determined. The ratio between the two products was then estimated from calibration curves which had been obtained with pure samples of **6a**·HI^{5b} and **15a**.^{5b} The methylation reaction was run in duplicate, and the mean value of the product ratios was obtained. The result is given in Table I.

N⁶-Ethyl-N⁶-methoxy-9-methyladenine Hydrochloride (6b·HCl) and 7-Ethyl-N⁶-methoxy-9-methyladeninium Iodide (15b) A mixture of **5**^{4b} (1.79 g, 10 mmol) and EtI (6.25 g, 40 mmol) in AcNMe₂ (15 ml) was stirred at 50 °C for 28 h. After cooling, the precipitate that resulted was filtered off, washed with a little EtOH, and dried to give a first crop (1.60 g, 48%) of **15b**, mp 247—248 °C (dec.). Recrystallization from H₂O produced an analytical sample of **15b** as slightly yellowish prisms, mp 250.5—251.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₉H₁₄IN₅O: C, 32.25; H, 4.21; N, 20.90. Found: C, 32.10; H, 4.23; N, 20.87.

On the other hand, the filtrate obtained after removal of the crude **15b** was concentrated to dryness *in vacuo*. The residual solid was washed with a little ether and then dissolved in H₂O (8 ml). The resulting aqueous solution was passed through a column of Amberlite CG-400 (Cl[−]) (430 ml), and the column was eluted with H₂O. Fractions containing **15b** (X=Cl instead of I) were combined and concentrated *in vacuo* to leave a weakly hygroscopic solid. The solid was dissolved in a small amount of H₂O, and NaI (670 mg) was added to the resulting aqueous solution. The precipitate that deposited was collected by filtration, washed with a little H₂O, and dried to afford **15b** (602 mg, 18%) as a second crop. The total yield of **15b** was 2.20 g (66%).

Further elution of the ion-exchanger column with 0.5 N formic acid and concentration of the eluate under reduced pressure left **6b**·HCl·H₂O (591 mg, 23%), mp 174—175.5 °C. Recrystallization from acetone and drying over P₂O₅ at 3 mmHg and room temperature for 12 h yielded an analytical sample as colorless needles, mp 182—183.5 °C (dec.); UV (Table III); ¹H-NMR (Me₂SO-*d*₆) δ: 1.26 (3H, t, *J* = 7 Hz, CH₂Me), 3.89 [3H, s, N(9)-Me or OMe], 3.94 [3H, s, OMe or N(9)-Me], 4.36 (2H, q, *J* = 7 Hz, CH₂Me), 6.70 (3H, br, N⁺H and H₂O), 8.56 and 8.89 (1H each, s, purine protons). *Anal.* Calcd for C₉H₁₃N₅O·HCl·H₂O: C, 41.30; H, 6.16; N, 26.76. Found: C, 41.58; H, 6.16; N, 26.79.

In a separate experiment, the above ethylation was continued for 30 h, and the HPLC analysis of the reaction mixture was effected in a manner similar to that described above for the methylation of **5**. The result is given in Table I.

N⁶-Benzyl-N⁶-methoxy-9-methyladenine Hydrobromide (6c·HBr) and 7-Benzyl-N⁶-methoxy-9-methyladeninium Bromide (15c) A mixture of **5**^{4b} (1.43 g, 8 mmol) and PhCH₂Br (4.11 g, 24 mmol) in AcNMe₂ (12 ml) was stirred at 30 °C for 30 h. The precipitate that deposited was filtered off, washed successively with small amounts of AcNMe₂ and ether, and recrystallized from H₂O to give a first crop (1.41 g, 48%) of **15c**·H₂O, mp 236.5—237.5 °C (dec.). Further recrystallization from H₂O and drying over P₂O₅ at 3 mmHg and 50 °C for 15 h provided an analytical sample of **15c**·H₂O as colorless needles, mp 236.5—237.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₄H₁₆BrN₅O·H₂O: C, 45.67; H, 4.93; N, 19.02. Found: C, 45.83; H, 4.71; N, 18.96.

The filtrate, obtained when the reaction mixture was filtered to collect the crude **15c**, was diluted with ether (80 ml), and the precipitate that resulted was collected by filtration. On the other hand, the aqueous filtrate, obtained when the first crop of **15c**·H₂O was isolated, was concentrated *in vacuo*, and the residue was combined with the above second crop of precipitate. A solution of the resulting mixture in H₂O (3 ml) was then passed through a column of Amberlite CG-400 (Br[−]) (450 ml), and the

column was eluted with H₂O. Concentration of the aqueous eluate under reduced pressure left a second crop (188 mg, 6%) of **15c**·H₂O, mp 234—235 °C (dec.). The total yield of **15c**·H₂O was 1.60 g (54%).

Further elution of the above column with 0.5 N formic acid and concentration of the eluate under reduced pressure left a yellowish orange solid. The solid was recrystallized successively from EtOH and from MeOH (twice) to furnish **6c**·HBr (339 mg, 12%), mp 177.5—179.5 °C (dec.). Further recrystallization from MeOH gave an analytical sample of **6c**·HBr as colorless plates, mp 191—192 °C (dec.); UV (Table III); ¹H-NMR (Me₂SO-*d*₆) δ: 3.92 [6H, s, N(9)-Me and OMe], 5.55 (2H, s, CH₂Ph), 5.80 (br, N⁺H), 7.36 (5H, m, CH₂Ph), 8.61 and 8.99 (1H each, s, purine protons). *Anal.* Calcd for C₁₄H₁₅N₅O·HBr: C, 48.01; H, 4.61; N, 20.00. Found: C, 47.92; H, 4.64; N, 19.80.

N⁶-Benzyloxy-N⁶,9-dimethyladenine (8a) and N⁶-Benzyloxy-7,9-dimethyladeninium Iodide (19a) A mixture of **11**^{4b} (2.55 g, 10 mmol) and MeI (5.68 g, 40 mmol) in AcNMe₂ (14 ml) was stirred at 30 °C for 4 h. The precipitate that deposited was filtered off, washed with a little EtOH, and dried to give a first crop (2.14 g, 54%) of **19a**, mp 227.5—228.5 °C (dec.). Recrystallization from EtOH furnished an analytical sample of **19a** as colorless needles, mp 232.5—233.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₄H₁₆IN₅O: C, 42.33; H, 4.06; N, 17.63. Found: C, 42.31; H, 4.10; N, 17.59.

The filtrate obtained after the removal of the crude **19a** was concentrated *in vacuo*, and the residue was dissolved in H₂O. The resulting aqueous solution was passed through a column of Amberlite CG-400 (Cl[−]) (310 ml), and the column was eluted with H₂O. Concentration of the aqueous eluate under reduced pressure left a colorless solid. The solid was dissolved in a little H₂O, and NaI (120 mg) was added. The precipitate that resulted was filtered off and recrystallized from EtOH to yield a second crop (166 mg, 4%) of **19a**, mp 224—225 °C (dec.). The total yield of **19a** was 2.31 g (58%).

The ion-exchanger column was then eluted with 0.5 N formic acid, and the eluate was concentrated *in vacuo*. The residue was dissolved in warm H₂O, and the resulting aqueous solution was made alkaline by addition of 28% aqueous NH₃ and extracted with AcOEt. The AcOEt extracts were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to leave a solid. Recrystallization of the solid from hexane afforded **8a** (480 mg, 18%), mp 114.5—116 °C. Further recrystallization from hexane gave an analytical sample of **8a** as colorless pillars, mp 115—116.5 °C; UV (Table III); ¹H-NMR (Me₂SO-*d*₆) δ: 3.46 (3H, s, N⁶-Me), 3.73 [3H, s, N(9)-Me], 5.11 (2H, s, OCH₂Ph), 7.43 (5H, m, OCH₂Ph), 8.19 and 8.33 (1H each, s, purine protons). *Anal.* Calcd for C₁₄H₁₅N₅O: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.74; H, 5.65; N, 25.99.

In a separate experiment, the above methylation was continued for 8 h, and the ratio of **19a** to **8a** in the reaction mixture was determined by HPLC analysis in a manner similar to that described above for the methylation of **5**. The result is given in Table I.

N⁶-Benzyloxy-N⁶-ethyl-9-methyladenine Hydrochloride (8b·HCl) and N⁶-Benzyloxy-7-ethyl-9-methyladeninium Iodide (19b) A mixture of **11**^{4b} (2.55 g, 10 mmol) and EtI (6.25 g, 40 mmol) in AcNMe₂ (15 ml) was stirred at 50 °C for 24 h. The precipitate that resulted was filtered off, washed with a little EtOH, and recrystallized from EtOH to yield **19b** (1.36 g, 33%), mp 221.5—223 °C (dec.). Further recrystallization from EtOH gave an analytical sample of **19b** as pale yellowish needles, mp 224.5—226 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₅H₁₈IN₅O: C, 43.81; H, 4.41; N, 17.03. Found: C, 43.60; H, 4.49; N, 17.02.

The filtrate obtained after the removal of the crude **19b** was concentrated *in vacuo*. The residue was dissolved in 50% (v/v) aqueous EtOH, and the resulting solution was passed through a column of Amberlite CG-400 (Cl[−]) (310 ml). The column was then eluted with H₂O, and the combined eluates were concentrated *in vacuo* to leave, after drying over P₂O₅ at 3 mmHg and 75 °C for 3 h, a hemihydrate of **19b** (X=Cl instead of I) as a solid (1.44 g, 44%), mp 218.5—221 °C (dec.). The total yield of the 7-ethylated derivatives was 77%. Recrystallization of the chloride salt hemihydrate from EtOH produced an analytical sample as pale yellowish needles, mp 225—226.5 °C (dec.) (dried over P₂O₅ at 3 mmHg and 75 °C for 3 h); UV λ_{max}^{95% EtOH} 235 nm (ε 8800), 290 (8200); λ_{max}^{H₂O} (pH 1) 283 (10300); λ_{max}^{H₂O} (pH 7) 283 (10300); λ_{max}^{H₂O} (pH 13) unstable; ¹H-NMR (Me₂SO-*d*₆) δ: 1.37 [3H, t, *J* = 7 Hz, N(7)-CH₂Me], 3.84 [3H, s, N(9)-Me], 4.37 [2H, q, *J* = 7 Hz, N(7)-CH₂Me], 5.10 (2H, s, OCH₂Ph), 7.45 (5H, m, OCH₂Ph), 7.93 [1H, br s, C(2)-H], 9.79 [1H, s, C(8)-H], 12.35 (1H, br, NH). *Anal.* Calcd for C₁₅H₁₈ClN₅O·1/2H₂O: C, 54.79; H, 5.82; N, 21.30. Found: C, 54.78; H, 5.70; N, 21.43.

The above ion-exchanger column was then eluted with 0.5 N formic acid,

and concentration of the eluate under reduced pressure left a solid, which was recrystallized from EtOH to give **8b**·HCl·1/3H₂O (394 mg, 12%), mp 189—190 °C (dec.). Recrystallization from EtOH and drying over P₂O₅ at 3 mmHg and room temperature for 18 h afforded an analytical sample of **8b**·HCl·1/3H₂O as pale yellowish needles, 188—189 °C (dec.); UV (Table III); ¹H-NMR (Me₂SO-*d*₆) δ: 1.20 [3H, t, *J* = 7.2 Hz, N⁶-CH₂Me], 3.79 [3H, s, N(9)-Me], 4.26 [2H, q, *J* = 7.2 Hz, N⁶-CH₂Me], 5.14 (2H, s, OCH₂Ph), 5.38 (1H, br, N⁺H), 7.36 (5H, m, OCH₂Ph), 8.45 and 8.58 (1H each, s, purine protons). *Anal.* Calcd for C₁₅H₁₇N₅O·HCl·1/3H₂O: C, 55.30; H, 5.77; N, 21.50. Found: C, 55.16; H, 5.50; N, 21.78.

In a separate run, the above ethylation was continued for 30 h, and the N(7)/N⁶-alkylation ratio was determined by HPLC analysis of the reaction mixture in a manner similar to that described above for the methylation of **5**. Table I lists the results.

N⁶-Benzyl-N⁶-benzyloxy-9-methyladenine Perchlorate (8c·HClO₄) and 7-Benzyl-N⁶-benzyloxy-9-methyladeninium Bromide (19c) A mixture of **11^a** (4.08 g, 16 mmol) and PhCH₂Br (11.0 g, 64 mmol) in AcNMe₂ (24 ml) was stirred at 30 °C for 24 h. The precipitate that resulted was filtered off, washed with a little EtOH, and recrystallized from EtOH to give, after drying over P₂O₅ at 3 mmHg and 100 °C for 1.5 h, a first crop (3.40 g, 49%) of **19c**·1/3H₂O, mp 224—225 °C (dec.). Further recrystallization from EtOH and drying under similar conditions yielded an analytical sample of **19c**·1/3H₂O as colorless needles, mp 224—225 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₂₀H₂₀BrN₅O·1/3H₂O: C, 55.57; H, 4.82; N, 16.20. Found: C, 55.45; H, 4.67; N, 16.20.

The filtrate, obtained when the reaction mixture was filtered to remove the precipitate, was concentrated *in vacuo*, and the residue was dissolved in 50% (v/v) aqueous EtOH. The resulting solution was passed through a column of Amberlite CG-400 (Br[−]) (500 ml), and the column was eluted with 10% (v/v) aqueous EtOH. Concentration of the combined eluates under reduced pressure left a solid, which was recrystallized from EtOH to furnish a second crop (1.00 g, 14%) of **19c**·1/3H₂O. The total yield was 4.40 g (63%).

The above ion-exchanger column was then eluted with 0.5 N formic acid containing EtOH at 10% (v/v) concentration, and the eluate was concentrated *in vacuo*. The residue was dissolved in warm 50% (v/v) aqueous EtOH, and the resulting solution was made alkaline with 10% aqueous Na₂CO₃, concentrated to half its initial volume *in vacuo*, and extracted with AcOEt. The AcOEt extracts were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was then purified by means of column chromatography [silica gel (80 g), benzene–EtOH (6:1, v/v)] to give **8c** as a glass. The crude **8c** was dissolved in a little EtOH, and 70% aqueous HClO₄ (340 mg) was added. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give **8c**·HClO₄ (765 mg, 11%), mp 141.5—143 °C (dec.). Recrystallization from EtOH produced an analytical sample of **8c**·HClO₄ as colorless needles, mp 141.5—143 °C (dec.); UV (Table III); ¹H-NMR (Me₂SO-*d*₆) δ: 3.83 [3H, s, N(9)-Me], 5.16 (2H, s, OCH₂Ph), 5.52 (2H, s, N⁶-CH₂Ph), 7.35 (10H, m, two CH₂Ph's), 8.11 (1H, br, N⁺H), 8.44 and 8.68 (1H each, s, purine protons). *Anal.* Calcd for C₂₀H₁₉N₅O·HClO₄: C, 53.88; H, 4.52; N, 15.71. Found: C, 53.66; H, 4.44; N, 15.57.

N⁶-Benzyloxy-9-ethyl-N⁶-methyladenine (9a) and N⁶-Benzyloxy-9-ethyl-7-methyladeninium Iodide (20a) A mixture of **12^a** (3.50 g, 13 mmol) and MeI (7.38 g, 52 mmol) in AcNMe₂ (20 ml) was stirred at 30 °C for 5 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to furnish a first crop (2.85 g, 53%) of **20a**, mp 224.5—228 °C (dec.). Recrystallization from EtOH gave an analytical sample of **20a** as colorless needles, mp 225.5—227.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₅H₁₈IN₅O: C, 43.81; H, 4.41; N, 17.03. Found: C, 43.52; H, 4.36; N, 16.76.

The filtrate, obtained when the reaction mixture was filtered to remove the precipitate, was concentrated *in vacuo* to leave a pale yellowish solid, which was dissolved in warm H₂O (250 ml) containing a small amount of NaHSO₃. The resulting aqueous solution was adjusted to pH 6 by addition of saturated aqueous NaHCO₃ and extracted with benzene (3 × 50 ml). The aqueous layer, separated from the benzene layer, was concentrated *in vacuo* to a volume of ca. 30 ml and kept in a refrigerator overnight. The crystals that deposited were collected by filtration, washed successively with small amounts of H₂O and EtOH, and dried to yield a second crop (930 mg, 17%) of **20a**, mp 220—226 °C (dec.). The total yield of **20a** was 3.78 g (71%).

The above benzene extracts were combined, washed with H₂O, dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to leave a solid, mp 72—75 °C. Recrystallization of the solid from hexane afforded **9a** (380 mg, 10%), mp 75—76.5 °C. Further recrystallization from hexane gave an

analytical sample of **9a** as colorless prisms, mp 75—76.5 °C; UV (Table III); ¹H-NMR (Me₂SO-*d*₆) δ: 1.43 [3H, t, *J* = 7 Hz, N(9)-CH₂Me], 3.49 (3H, s, N⁶-Me), 4.25 [2H, q, *J* = 7 Hz, N(9)-CH₂Me], 5.16 (2H, s, OCH₂Ph), 7.28—7.72 (5H, m, OCH₂Ph), 8.37 and 8.41 (1H each, s, purine protons). *Anal.* Calcd for C₁₅H₁₇N₅O: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.53; H, 6.16; N, 24.88.

N⁶-Benzyloxy-7,9-diethyladeninium Iodide (20b) A mixture of **12^a** (3.50 g, 13 mmol) and EtI (8.11 g, 52 mmol) in AcNMe₂ (20 ml) was stirred at 50 °C for 24 h. The reaction mixture was concentrated *in vacuo*, and the residual solid was recrystallized from EtOH to give **20b** (3.65 g, 66%), mp 215—220 °C (dec.). Further recrystallization from EtOH yielded an analytical sample as colorless needles, mp 216.5—219.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₆H₂₀IN₅O: C, 45.19; H, 4.74; N, 16.47. Found: C, 45.05; H, 4.79; N, 16.44.

7-Benzyl-N⁶-benzyloxy-9-ethyladeninium Bromide (20c) A mixture of **12^a** (3.23 g, 12 mmol) and PhCH₂Br (8.21 g, 48 mmol) in AcNMe₂ (18 ml) was stirred at 30 °C for 22 h. The precipitate that resulted was filtered off, washed successively with a small amount of AcNMe₂ and ether, and dried to furnish **20c** (3.43 g, 65%), mp 201—205.5 °C (dec.). Recrystallization from EtOH gave an analytical sample as colorless prisms, mp 202—203.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₂₁H₂₂BrN₅O: C, 57.28; H, 5.04; N, 15.90. Found: C, 57.00; H, 4.97; N, 16.05.

N⁶-Benzyloxy-9-benzyl-7-ethyladeninium Iodide (21b) and Perchlorate (21e) A mixture of **13^b** (660 mg, 2 mmol) and EtI (1.25 g, 8 mmol) in AcNMe₂ (3 ml) was stirred at 50 °C for 27 h. The reaction mixture was concentrated *in vacuo* to leave a reddish brown oil. The oil was dissolved in EtOH, and the ethanolic solution was kept in a refrigerator. The crystals that deposited were collected by filtration, washed with a little EtOH, and dried to give **21b** (454 mg, 46%), mp 189.5—191 °C (dec.). Recrystallization from EtOH yielded an analytical sample as colorless prisms, mp 190—191.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₂₁H₂₂IN₅O: C, 51.76; H, 4.55; N, 14.37. Found: C, 51.68; H, 4.52; N, 14.30.

The corresponding perchlorate (**21e**) was prepared from the iodide **21b** by dissolving it in hot EtOH and adding 70% aqueous HClO₄. On cooling, the mixture deposited colorless crystals, which were filtered off and recrystallized from EtOH to provide **21e** as colorless prisms, mp 167—168.5 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₂₁H₂₂ClN₅O₃: C, 54.85; H, 4.82; N, 15.23. Found: C, 54.88; H, 4.92; N, 15.31.

7,9-Dibenzyl-N⁶-benzyloxyadeninium Bromide (21c) A mixture of **13^b** (994 mg, 3 mmol) and PhCH₂Br (2.05 g, 12 mmol) in AcNMe₂ (4.5 ml) was stirred at 30 °C for 23 h. The reaction mixture was cooled in an ice bath for 1 h, and the precipitate that resulted was filtered off, washed with ether, and dried to give **21c** (1.01 g, 67%), mp 211—214.5 °C (dec.). Recrystallization from EtOH furnished an analytical sample as colorless needles, mp 218—219 °C (dec.); UV (Table II); ¹H-NMR (Table IV). *Anal.* Calcd for C₂₆H₂₄BrN₅O: C, 62.16; H, 4.81; N, 13.94. Found: C, 62.26; H, 4.67; N, 13.69.

N⁶-Ethyl-9-methyladenine (7b) A solution of **6b**·HCl·H₂O (280 mg, 1.07 mmol) in H₂O (40 ml) was passed through a column of Amberlite IRA-402 (HCO₃[−]) (5.5 ml), and the column was eluted with H₂O. The eluate (150 ml) was concentrated to dryness *in vacuo* to leave the free base **6b** as a colorless solid, which was dissolved in EtOH (12 ml). The resulting ethanolic solution was hydrogenated over Raney Ni W-2 catalyst⁽³²⁾ (1 ml) at atmospheric pressure and 50 °C for 6 h. The catalyst was removed by filtration and washed with EtOH (45 ml). The filtrate and washings were combined and concentrated to dryness *in vacuo*, leaving **7b** (175 mg, 92%) as a colorless solid, mp 155—155.5 °C. Recrystallization from benzene gave a pure sample as colorless prisms, mp 156—157 °C (lit.^(4e) mp 156—157 °C). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7b**.^(4e)

N⁶-Benzyl-9-methyladenine (7c) A solution of **6c**·HBr (198 mg, 0.57 mmol) in H₂O (30 ml) was passed through a column of Amberlite IRA-402 (HCO₃[−]) (2.7 ml), and the column was eluted with H₂O. The eluate (110 ml) was concentrated to dryness *in vacuo*, and the residual solid was dissolved in EtOH (11 ml). The ethanolic solution was hydrogenated over Raney Ni W-2 catalyst⁽³²⁾ (0.7 ml) at atmospheric pressure and 50 °C for 8 h. Work-up of the reaction mixture was effected in a manner similar to that described above for **7b**, giving crude **7c** (96 mg, 71%), mp 108—112 °C. Recrystallization from benzene furnished a pure sample as colorless prisms, mp 124—126 °C (lit.⁽²⁵⁾ mp 125—126 °C). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **7c**.⁽²⁵⁾

Hydrogenolyses of *N*⁶-Alkoxy-7,9-dialkyladeninium Salts (15 and 19—21) Leading to 7,9-Dialkyladeninium Salts (16—18) The procedure employed for the conversion of **15a** into **16a** will be described below in detail as a typical example. The other hydrogenolyses were performed similarly, and the products were characterized as described below. Table V summarizes the reaction conditions applied and the results obtained.

7,9-Dimethyladeninium Iodide (16a) A solution of **15a**^{5b)} (800 mg, 2.49 mmol) in H₂O (100 ml) was hydrogenated over Raney Ni W-2 catalyst³²⁾ (1.5 ml) at atmospheric pressure and room temperature for 18 h. The catalyst was removed by filtration and washed with H₂O (45 ml). The filtrate and washings were combined and concentrated to dryness *in vacuo* to leave a solid. Recrystallization of the solid from 90% (v/v) aqueous EtOH gave a first crop (514 mg, 71%) of **16a**, mp 275—276 °C (dec.). The mother liquor from this recrystallization was then concentrated *in vacuo*, and the residual solid was recrystallized from 90% (v/v) aqueous EtOH to yield a second crop (68 mg, 9%) of **16a**, mp 274—275 °C (dec.). The total yield was 582 mg (80%). For analysis, the crude **16a** was further recrystallized in a similar manner, furnishing colorless needles, mp 274—275 °C (dec.) (lit.^{27c)} mp 280—281 °C); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₇H₁₀IN₅: C, 28.88; H, 3.46; N, 24.06. Found: C, 28.69; H, 3.50; N, 23.88.

7-Ethyl-9-methyladeninium Iodide (16b) This was recrystallized from 95% (v/v) aqueous EtOH to give colorless scales, mp 238—239.5 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₈H₁₂IN₅: C, 31.49; H, 3.96; N, 22.95. Found: C, 31.44; H, 3.97; N, 23.04.

7-Benzyl-9-methyladeninium Bromide (16c) This was recrystallized from H₂O and dried over P₂O₅ at 3 mmHg and room temperature for 25 h to give **16c**·H₂O as colorless prisms, mp 225—226 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₃H₁₄BrN₅·H₂O: C, 46.17; H, 4.77; N, 20.71. Found: C, 46.43; H, 4.82; N, 20.77.

9-Ethyl-7-methyladeninium Iodide (17a) This was recrystallized from 90% (v/v) aqueous EtOH to afford colorless needles, mp 264—267 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₈H₁₂IN₅: C, 31.49; H, 3.96; N, 22.95. Found: C, 31.52; H, 4.00; N, 22.65.

9-Ethyl-7-methyladeninium Perchlorate (17f) This salt was prepared from the iodide salt **17a** by dissolving it in H₂O and adding NaClO₄ (1.5 molar eq) to the resulting solution. On cooling, the mixture deposited pale yellowish crystals, which were filtered off and recrystallized from EtOH to provide **17f** as colorless prisms, mp 254.5—257.5 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₈H₁₂ClN₅O₄: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.47; H, 4.28; N, 25.18.

7,9-Diethyladeninium Iodide (17b) This was recrystallized from EtOH to furnish colorless needles, mp 254—257.5 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₉H₁₄IN₅: C, 33.87; H, 4.42; N, 21.94. Found: C, 33.83; H, 4.45; N, 21.75.

7,9-Diethyladeninium Perchlorate (17e) This salt was prepared from the iodide salt **17b** in a manner similar to that described above for **17f** and recrystallized from EtOH, giving colorless prisms, mp 260.5—263.5 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₉H₁₄ClN₅O₄: C, 37.06; H, 4.84; N, 24.01. Found: C, 36.94; H, 5.07; N, 23.78.

7-Benzyl-9-ethyladeninium Perchlorate (17d) Crude 7-benzyl-9-ethyladeninium bromide (**17c**), obtained as a glassy material from **20c** by a similar hydrogenolysis, was converted into the perchlorate **17d** in a manner similar to that described above for **17f**. The resulting crude perchlorate was recrystallized from EtOH to yield an analytical sample of **17d** as colorless needles, mp 201—202 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₄H₁₆ClN₅O₄: C, 47.53; H, 4.56; N, 19.80. Found: C, 47.56; H, 4.62; N, 19.94.

9-Benzyl-7-ethyladeninium Perchlorate (18e) The product from the hydrogenolysis of **21e** was recrystallized from EtOH to provide colorless fine prisms, mp 255—256 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₄H₁₆ClN₅O₄: C, 47.53; H, 4.56; N, 19.80. Found: C, 47.33; H, 4.60; N, 19.89.

7,9-Dibenzyladeninium Bromide (18c) This was recrystallized from EtOH to give colorless prisms, mp 193—195 °C (dec.); UV (Table VI); ¹H-NMR (Table IV). *Anal.* Calcd for C₁₉H₁₈BrN₅: C, 57.59; H, 4.58; N, 17.67. Found: C, 57.54; H, 4.58; N, 17.56.

Acknowledgment We thank the Ministry of Education, Science and Culture, Japan, for financial support of this work through a Grant-in-Aid for Special Project Research (to Professor Y. Ban).

References and Notes

- 1) Paper XXXVII in this series, T. Fujii, T. Saito, T. Nakasaka, and K. Kizu, *Chem. Pharm. Bull.*, **38**, 99 (1990).

- 2) For the term "control synthon," see E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).
- 3) For the term "control element," see S. Turner, *Chem. Brit.*, **7**, 191 (1971).
- 4) a) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971); b) T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *ibid.*, **27**, 2415 (1971); c) T. Fujii and T. Itaya, *Chem. Pharm. Bull.*, **19**, 1611 (1971); d) T. Fujii, T. Saito, and T. Itaya, *ibid.*, **19**, 1731 (1971); e) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 535 (1972); f) T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.*, **20**, 1818 (1972); g) T. Fujii, C. C. Wu, T. Itaya, S. Moro, and T. Saito, *ibid.*, **21**, 1676 (1973); h) T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *ibid.*, **22**, 2211 (1974); i) T. Fujii, S. Kawakatsu, and T. Itaya, *ibid.*, **22**, 2466 (1974); j) T. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, *ibid.*, **23**, 2643 (1975); k) T. Fujii, K. Sakamoto, S. Kawakatsu, and T. Itaya, *ibid.*, **24**, 655 (1976); l) T. Fujii, T. Itaya, T. Saito, and M. Kawanishi, *ibid.*, **26**, 1929 (1978); m) T. Fujii, I. Inoue, T. Itaya, and T. Saito, *ibid.*, **28**, 3443 (1980); n) T. Fujii, T. Saito, and I. Inoue, *Heterocycles*, **16**, 909 (1981); o) T. Fujii, T. Itaya, T. Saito, and S. Kawakatsu, *Chem. Pharm. Bull.*, **32**, 4842 (1984); p) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, and S. Nakajima, *Heterocycles*, **24**, 2449 (1986); q) T. Fujii, T. Saito, T. Itaya, K. Kizu, Y. Kumazawa, and S. Nakajima, *Chem. Pharm. Bull.*, **35**, 4482 (1987); r) T. Fujii, T. Saito, and T. Fujisawa, *Heterocycles*, **27**, 1163 (1988); s) T. Fujii, T. Itaya, T. Saito, K. Mohri, M. Kawanishi, and T. Nakasaka, *Chem. Pharm. Bull.*, **37**, 1504 (1989); t) T. Fujii, T. Saito, and T. Nakasaka, *ibid.*, **37**, 2601 (1989); u) T. Itaya, T. Saito, T. Harada, S. Katagani, and T. Fujii, *ibid.*, **37**, 3200 (1989); v) T. Fujii, T. Saito, and T. Nakasaka, *ibid.*, **37**, 3243 (1989); w) T. Saito, Y. Asahi, S. Nakajima, and T. Fujii, *Heterocycles*, **30**, 329 (1990).
- 5) a) T. Fujii and T. Saito, *Heterocycles*, **17**, 117 (1982); b) T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, *Chem. Pharm. Bull.*, **31**, 3149 (1983); c) T. Fujii, T. Saito, and T. Nakasaka, *ibid.*, **31**, 3521 (1983); d) T. Fujii, T. Saito, and T. Muramoto, *ibid.*, **31**, 4270 (1983).
- 6) a) R. B. Meyer, Jr., D. A. Shuman, R. K. Robins, J. P. Miller, and L. N. Simon, *J. Med. Chem.*, **16**, 1319 (1973); b) J. A. Montgomery and H. J. Thomas, *ibid.*, **15**, 182 (1972); c) R. B. Meyer, Jr., D. A. Shuman, and R. K. Robins, *J. Am. Chem. Soc.*, **96**, 4962 (1974); d) K. Kikugawa, H. Suehiro, R. Yanase, and A. Aoki, *Chem. Pharm. Bull.*, **25**, 1959 (1977).
- 7) a) K. Miura and T. Ueda, *Chem. Pharm. Bull.*, **23**, 2064 (1975); b) K. Miura, T. Kasai, and T. Ueda, *ibid.*, **23**, 464 (1975); c) T. Ueda, K. Miura, and T. Kasai, *ibid.*, **26**, 2122 (1978).
- 8) For a review, see T. Fujii, T. Itaya, and T. Saito, *Yuki Gosei Kagaku Kyokai Shi*, **41**, 1193 (1983).
- 9) See refs. 4a, c, i, k, m, q, and 5a—d.
- 10) See refs. 1, 4a, f, h, k—v, and 5a—c.
- 11) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, **21**, 1835 (1973).
- 12) See refs. 1, 4b, d—j, l, o—v, 5c, and 7a, b.
- 13) The existence of amino-imino equilibrium of this compound in solution has been reported by us.^{4q)}
- 14) T. Fujii, F. Tanaka, K. Mohri, T. Itaya, and T. Saito, *Tetrahedron Lett.*, **1973**, 4873.
- 15) E. Cullen and J. P. Devlin, *Can. J. Chem.*, **53**, 1690 (1975).
- 16) a) H. Nakamura, H. Wu, Y. Ohizumi, and Y. Hirata, *Tetrahedron Lett.*, **25**, 2989 (1984); b) H. Wu, H. Nakamura, J. Kobayashi, M. Kobayashi, Y. Ohizumi, and Y. Hirata, *Bull. Chem. Soc. Jpn.*, **59**, 2495 (1986).
- 17) H. Wu, H. Nakamura, J. Kobayashi, Y. Ohizumi, and Y. Hirata, *Tetrahedron Lett.*, **25**, 3719 (1984).
- 18) R. J. Capon and D. J. Faulkner, *J. Am. Chem. Soc.*, **106**, 1819 (1984).
- 19) P. F. Agris, H. Koh, and D. Söll, *Arch. Biochem. Biophys.*, **154**, 277 (1973).
- 20) B. Vold, *J. Bacteriol.*, **127**, 258 (1976).
- 21) B. Singer, L. Sun, and H. Fraenkel-Conrat, *Biochemistry*, **13**, 1913 (1974).
- 22) T. Fujii, T. Saito, T. Sakuma, M. Minami, and I. Inoue, *Heterocycles*, **16**, 215 (1981).
- 23) a) N. J. Leonard and T. Fujii, *J. Am. Chem. Soc.*, **85**, 3719 (1963); b) J. A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964); c) A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, **3**, 494 (1964); d) M. Rasmussen and N. J. Leonard, *J. Am. Chem. Soc.*, **89**, 5439 (1967); e) N. J. Leonard and

- M. Rasmussen, *J. Org. Chem.*, **33**, 2488 (1968); *f*) T. Fujii, G. C. Walker, N. J. Leonard, D. C. DeLong, and K. Gerzon, *J. Med. Chem.*, **22**, 125 (1979).
- 24) *a*) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, **1960**, 539; *b*) H. G. Windmueller and N. O. Kaplan, *J. Biol. Chem.*, **236**, 2716 (1961); *c*) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963); *d*) N. J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U.S.A.*, **51**, 73 (1964); *e*) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **30**, 3235 (1965); *f*) E. P. Lira, *J. Heterocycl. Chem.*, **5**, 863 (1968); *g*) T. Itaya, F. Tanaka, T. Fujii, and N. J. Leonard, *Chem. Pharm. Bull.*, **25**, 1449 (1977); *h*) T. Fujii and T. Saito, *ibid.*, **33**, 3635 (1985); *i*) T. Fujii, T. Saito, and N. Terahara, *ibid.*, **34**, 1094 (1986).
- 25) T. Fujii, T. Itaya, and T. Saito, *Chem. Pharm. Bull.*, **23**, 54 (1975).
- 26) See refs. 1 and 4*l*, *n*, *p*, *r*—*v*.
- 27) *a*) Y. Maki, M. Suzuki, K. Kameyama, M. Kawai, M. Suzuki, and M. Sako, *Heterocycles*, **15**, 895 (1981); *b*) Y. Maki, K. Kameyama, M. Suzuki, M. Sako, and K. Hirota, *J. Chem. Res., Synop.*, **1984**, 388; *c*) *Idem*, *J. Chem. Res. (M)*, **1984**, 3601.
- 28) *a*) Y. Maki, M. Suzuki, K. Kameyama, and M. Sako, Abstracts of Papers, 13th Congress of Heterocyclic Chemistry, Shizuoka, Japan, November 1980, pp. 217—220; *b*) *Idem*, *Heterocycles*, **16**, 185 (1981).
- 29) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, **19**, 1368 (1971).
- 30) H. Iio, K. Asao, and T. Tokoroyama, *J. Chem. Soc., Chem. Commun.*, **1985**, 774. In this work, they employed dissolving metal reduction (Zn dust/aqueous AcOH, 60°C, 18 h) instead of catalytic hydrogenolysis for removal of the *N*⁶-methoxy group from their 7-substituted *N*⁶-methoxy-9-methyladeninium intermediate possessing an allylic double bond.
- 31) The melting point rises during storage; see footnote 14 in ref. 4*l*.
- 32) R. Mozingo, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, New York, 1955, p. 181.