# 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

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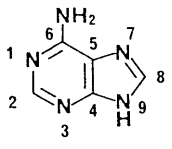
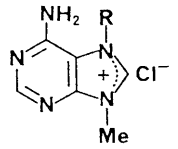
**A detailed account is given of the general synthetic route to 7,9-dialkyladeninium salts (16—18) from $N^6$-alkoxy-9-alkyladenines (type 5 or 11—13), readily obtainable from 9-alkyladenines in three steps involving N(1)-oxidation, *O*-alkylation, and Dimroth rearrangement. Alkylations of $N^6$-methoxy-9-methyladenine (5) and 9-alkyl-$N^6$-benzyloxyadenines (11—13) with MeI, EtI, and $PhCH_2Br$ in $AcNMe_2$ 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; $^1$H-NMR

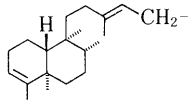
The alkoxy group at the N(1)- or $N^6$-position of the adenine ring system (**1**) has been a useful and convenient "control synthon"[2] (or "control element"[3]) for chemical modification of adenine derivatives including nucleosides.[4-8] The function of this group is based on its unique directivity 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,[4q,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 thitherto 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 F[16]) 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

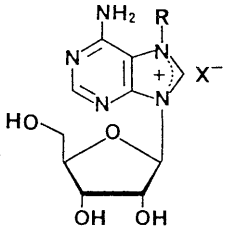


**1**



**2a** : R = $C_{20}H_{33}$

**2b** : R = 



**3** : R = Me

**4** : R = Et

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

| Starting material | Alkylating agent | Reaction conditions | | N(7)-Alkylated product | | $N^6$-Alkylated product | | N(7)-/$N^6$-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** | $PhCH_2Br$ | 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** | $PhCH_2Br$ | 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** | $PhCH_2Br$ | 30 | 22 | **20c** | 65 | —[g] | — | — |
| **13** | EtI | 50 | 27 | **21b** | 46 | —[g] | — | — |
| **13** | $PhCH_2Br$ | 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. 5*b*. *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 $H_2O$ of crystallization. *g*) No attempt was made to isolate the $N^6$-alkylated product.

other 7-alkylations of the 9-alkyl analogues, which has established a general synthetic route to 7,9-dialkyladeninium salts (**16**—**18**). A brief account of the results described here has been published in a preliminary form.[22]

In general, 7,9-dialkyladenines (types **16**—**18**) would be most directly accessible from either 7-alkyladenines or 9-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-

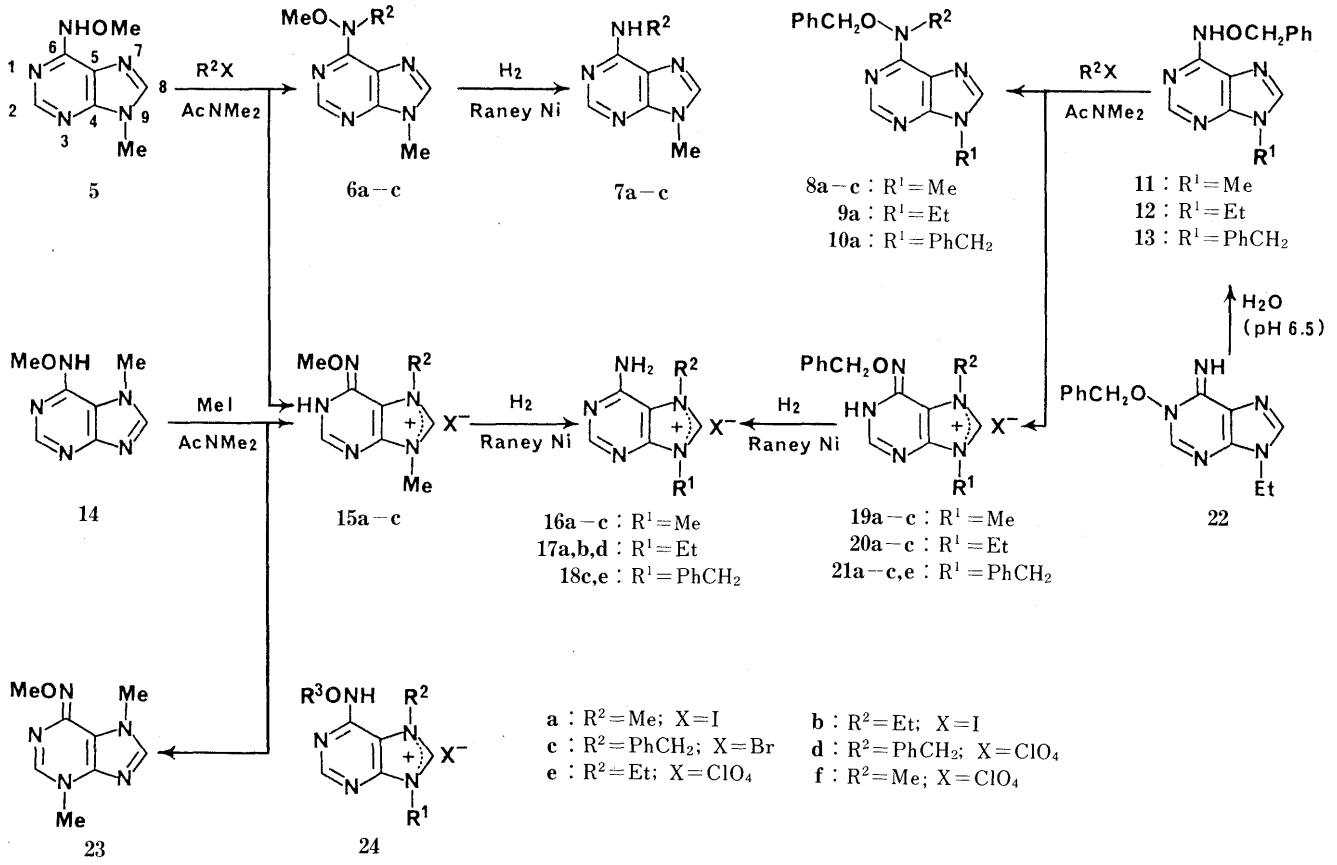



Chart 1

TABLE II. UV Spectra of $N^6$-Alkoxy-7,9-dialkyladeninium Salts (**15** and **19**—**21**)

| Compound | | | | | UV spectra[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% EtOH | | $H_2O$ (pH 1)[b] | | $H_2O$ (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** | $PhCH_2O$ | Me | Me | I | 292 | 8.5 | 226 | 21.6 | 226 | 21.7 |
| | | | | | | | 284 | 10.5 | 284 | 10.5 |
| **19b** | $PhCH_2O$ | Me | Et | I | 291 | 7.7 | 226 | 20.7 | 226 | 21.1 |
| | | | | | | | 284 | 9.9 | 284 | 10.1 |
| **19c**[e] | $PhCH_2O$ | Me | $PhCH_2$ | Br | 297 | 7.7 | 288 | 9.3 | 288.5 | 9.1 |
| **20a** | $PhCH_2O$ | Et | Me | I | 291 | 9.0 | 226 | 22.6 | 226 | 22.3 |
| | | | | | | | 284 | 11.6 | 284 | 11.3 |
| **20b** | $PhCH_2O$ | Et | Et | I | 291 | 8.8 | 226 | 22.5 | 226 | 22.0 |
| | | | | | | | 283 | 11.5 | 283 | 11.2 |
| **20c** | $PhCH_2O$ | Et | $PhCH_2$ | Br | 297 | 7.7 | 289 | 9.8 | 289 | 9.7 |
| **21b** | $PhCH_2O$ | $PhCH_2$ | Et | I | 295 | 8.8 | 225 | 24.6 | 225 | 24.6 |
| | | | | | | | 286 | 11.4 | 286 | 11.2 |
| **21c** | $PhCH_2O$ | $PhCH_2$ | $PhCH_2$ | Br | 301 | 7.5 | 292 | 9.7 | 292 | 9.6 |
| **21e** | $PhCH_2O$ | $PhCH_2$ | Et | $ClO_4$ | 293 | 8.8 | 286 | 10.6 | 286 | 10.3 |

*a*) Unstable in the alkaline region in $H_2O$. *b*) Measured in 0.1 N aqueous HCl. *c*) Measured in 0.005 M phosphate buffer (pH 7). *d*) As a monohydrate. *e*) A sample containing 1/3 molar eq of $H_2O$ of crystallization was used.

adenine (**14**) with MeI in $AcNMe_2$ 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 $PhCH_2Br$ in $AcNMe_2$ 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 $PhCH_2Br$ 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 $N^6$ 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 < $PhCH_2Br$, 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/$H_2$, 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,l,13] newly synthesized in 68% or 69% yield from 1-benzyloxy-9-ethyladenine hydrobromide (**22**·HBr) or perchlorate (**22**·$HClO_4$) 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 $PhCH_2Br$ in $AcNMe_2$ 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 | | $H_2O$ (pH 1)[a] | | $H_2O$ (pH 7)[b] | | $H_2O$ (pH 13)[c] | |
| No. | $N^6$-OR | N(9)-$R^1$ | $N^6$-$R^2$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ |
| **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** | $PhCH_2O$ | Me | Me | 277 | 19.0 | 278 | 16.5 | 277 | 18.2 | 276.5 | 18.0 |
| **8b**·HCl[e] | $PhCH_2O$ | Me | Et | 277 | 19.7 | 279 | 18.0 | 277.5 | 19.2 | 277.5 | 19.4 |
| **8c**·$HClO_4$ | $PhCH_2O$ | Me | $PhCH_2$ | 278 | 20.8 | 283 | 18.0 | 278.5 | 18.6 | 278.5 | 18.1 |
| **9a** | $PhCH_2O$ | 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 $H_2O$ of crystallization was used.

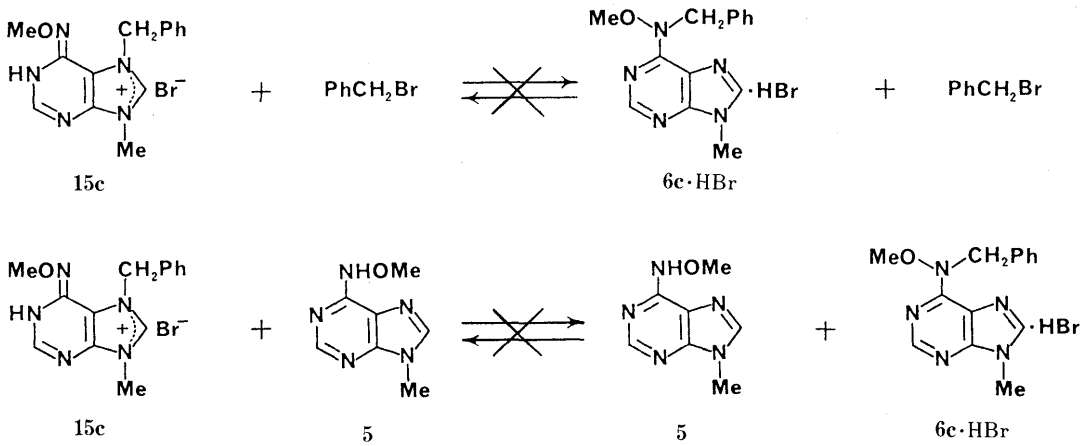



Chart 2

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 $PhCH_2Br$ in $AcNMe_2$ 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 $PhCH_2Br$ under similar conditions. In addition, a mixture of **15c** and **5** in $AcNMe_2$ or a mixture of **6c**·HBr and **5** in $AcNMe_2$ 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 $Me_2SO$-$d_6$. 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 $D_2O$. This suggests that in $Me_2SO$-$d_6$ 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. $^1$H-NMR Data for $N^6$-Alkoxy-7,9-dialkyladeninium Salts (**15** and **19**—**21**) and 7,9-Dialkyladeninium Salts (**16**—**18**)

| Compd. | Chemical shift ($\delta$)[a] in $Me_2SO$-$d_6$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | $N^6$-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 $Me_4Si$. 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 $D_2O$. *c*) Two-proton signal exchangeable with $D_2O$. *d*) Taken from ref. 5*b*. *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 $H_2O$ 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/$H_2$, $H_2O$ or aqueous MeOH, 1 atm, room temperature) under conditions similar to those[26] employed by us for the N–O bond cleavage of *N'*-alkoxy groups in imidazolecarboxamidine 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/$H_2$, 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 $^1$H-NMR spectral data (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 = 1/2$SO_4$),[14] 7-methyladenosine perchlorate (**3**: X = $ClO_4$),[5a] and 7-ethyladenosine perchlorate (**4**: X = $ClO_4$)[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.

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 $H_2O$; 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 $H_2O$ of crystallization was used. *e*) Isolated as the perchlorate.

**Experimental**

**General Comments** All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 4*s* 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**·HBr[29] (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 $H_2O$ 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 | | $H_2O$ (pH 1)[b] | | $H_2O$ (pH 7)[c] | |
| No. | $R^1$ | $R^2$ | X | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ |
| **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 $H_2O$. *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. 5*b*.

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

Alternatively, a similar treatment of crude **22**·$HClO_4$ [mp 191.5—192 °C (dec.)], prepared from **22**·HBr (14.3 g, 41 mmol) in 96% yield by dissolving it in warm $H_2O$ (400 ml) and adding a solution of $NaClO_4$ (7.53 g, 62 mmol) in $H_2O$ (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 $N^6$-Methoxy-9-methyladenine (5)** Methylation of **5**[4b] with MeI was effected in $AcNMe_2$ 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 $C_{18}$/Porasil B, MeOH–0.02 M $KH_2PO_4$ (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.

***N*$^6$-Ethyl-*N*$^6$-methoxy-9-methyladenine Hydrochloride (6b·HCl) and 7-Ethyl-*N*$^6$-methoxy-9-methyladeninium Iodide (15b)** A mixture of **5**[4b] (1.79 g, 10 mmol) and EtI (6.25 g, 40 mmol) in $AcNMe_2$ (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 $H_2O$ produced an analytical sample of **15b** as slightly yellowish prisms, mp 250.5—251.5 °C (dec.); UV (Table II); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_9H_{14}IN_5O$: 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 $H_2O$ (8 ml). The resulting aqueous solution was passed through a column of Amberlite CG-400 ($Cl^-$) (430 ml), and the column was eluted with $H_2O$. 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 $H_2O$, and NaI (670 mg) was added to the resulting aqueous solution. The precipitate that deposited was collected by filtration, washed with a little $H_2O$, 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·$H_2O$ (591 mg, 23%), mp 174—175.5 °C. Recrystallization from acetone and drying over $P_2O_5$ 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); $^1$H-NMR ($Me_2SO$-$d_6$) $\delta$: 1.26 (3H, t, $J$ = 7 Hz, $CH_2\underline{Me}$), 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, $C\underline{H}_2Me$), 6.70 (3H, br, $N^+H$ and $H_2O$), 8.56 and 8.89 (1H each, s, purine protons). *Anal.* Calcd for $C_9H_{13}N_5O$·HCl·$H_2O$: 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.

***N*$^6$-Benzyl-*N*$^6$-methoxy-9-methyladenine Hydrobromide (6c·HBr) and 7-Benzyl-*N*$^6$-methoxy-9-methyladeninium Bromide (15c)** A mixture of **5**[4b] (1.43 g, 8 mmol) and $PhCH_2Br$ (4.11 g, 24 mmol) in $AcNMe_2$ (12 ml) was stirred at 30 °C for 30 h. The precipitate that deposited was filtered off, washed successively with small amounts of $AcNMe_2$ and ether, and recrystallized from $H_2O$ to give a first crop (1.41 g, 48%) of **15c**·$H_2O$, mp 236.5—237.5 °C (dec.). Further recrystallization from $H_2O$ and drying over $P_2O_5$ at 3 mmHg and 50 °C for 15 h provided an analytical sample of **15c**·$H_2O$ as colorless needles, mp 236.5—237.5 °C (dec.); UV (Table II); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{14}H_{16}BrN_5O$·$H_2O$: 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**·$H_2O$ 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 $H_2O$ (3 ml) was then passed through a column of Amberlite CG-400 ($Br^-$) (450 ml), and the column was eluted with $H_2O$. Concentration of the aqueous eluate under reduced pressure left a second crop (188 mg, 6%) of **15c**·$H_2O$, mp 234—235 °C (dec.). The total yield of **15c**·$H_2O$ 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); $^1$H-NMR ($Me_2SO$-$d_6$) $\delta$: 3.92 [6H, s, N(9)-Me and OMe], 5.55 (2H, s, $C\underline{H}_2Ph$), 5.80 (br, $N^+H$), 7.36 (5H, m, $CH_2\underline{Ph}$), 8.61 and 8.99 (1H each, s, purine protons). *Anal.* Calcd for $C_{14}H_{15}N_5O$·HBr: C, 48.01; H, 4.61; N, 20.00. Found: C, 47.92; H, 4.64; N, 19.80.

***N*$^6$-Benzyloxy-*N*$^6$,9-dimethyladenine (8a) and *N*$^6$-Benzyloxy-7,9-dimethyladeninium Iodide (19a)** A mixture of **11**[4j] (2.55 g, 10 mmol) and MeI (5.68 g, 40 mmol) in $AcNMe_2$ (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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{14}H_{16}IN_5O$: 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 $H_2O$. The resulting aqueous solution was passed through a column of Amberlite CG-400 ($Cl^-$) (310 ml), and the column was eluted with $H_2O$. Concentration of the aqueous eluate under reduced pressure left a colorless solid. The solid was dissolved in a little $H_2O$, 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 $H_2O$, and the resulting aqueous solution was made alkaline by addition of 28% aqueous $NH_3$ and extracted with AcOEt. The AcOEt extracts were dried over anhydrous $Na_2SO_4$ 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); $^1$H-NMR ($Me_2SO$-$d_6$) $\delta$: 3.46 (3H, s, $N^6$-Me), 3.73 [3H, s, N(9)-Me], 5.11 (2H, s, $OC\underline{H}_2Ph$), 7.43 (5H, m, $OCH_2\underline{Ph}$), 8.19 and 8.33 (1H each, s, purine protons). *Anal.* Calcd for $C_{14}H_{15}N_5O$: 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.

***N*$^6$-Benzyloxy-*N*$^6$-ethyl-9-methyladenine Hydrochloride (8b·HCl) and *N*$^6$-Benzyloxy-7-ethyl-9-methyladeninium Iodide (19b)** A mixture of **11**[4j] (2.55 g, 10 mmol) and EtI (6.25 g, 40 mmol) in $AcNMe_2$ (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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{15}H_{18}IN_5O$: 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 $H_2O$, and the combined eluates were concentrated *in vacuo* to leave, after drying over $P_2O_5$ 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 $P_2O_5$ at 3 mmHg and 75 °C for 3 h); UV $\lambda_{max}^{95\%\,EtOH}$ 235 nm ($\varepsilon$ 8800), 290 (8200); $\lambda_{max}^{H_2O}$ (pH 1) 283 (10300); $\lambda_{max}^{H_2O}$ (pH 7) 283 (10300); $\lambda_{max}^{H_2O}$ (pH 13) unstable; $^1$H-NMR ($Me_2SO$-$d_6$) $\delta$: 1.37 [3H, t, $J$ = 7 Hz, N(7)-$CH_2\underline{Me}$], 3.84 [3H, s, N(9)-Me], 4.37 [2H, q, $J$ = 7 Hz, N(7)-$C\underline{H}_2Me$], 5.10 (2H, s, $OC\underline{H}_2Ph$), 7.45 (5H, m, $OCH_2\underline{Ph}$), 7.93 [1H, br s, C(2)-H], 9.79 [1H, s, C(8)-H], 12.35 (1H, br, NH). *Anal.* Calcd for $C_{15}H_{18}ClN_5O$·1/2$H_2O$: 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·1/3$H_2O$ (394 mg, 12%), mp 189—190 °C (dec.). Recrystallization from EtOH and drying over $P_2O_5$ at 3 mmHg and room temperature for 18 h afforded an analytical sample of **8b**·HCl·1/3$H_2O$ as pale yellowish needles, 188—189 °C (dec.); UV (Table III); $^1$H-NMR ($Me_2SO$-$d_6$) $\delta$: 1.20 (3H, t, $J$=7.2 Hz, $N^6$-$CH_2$Me), 3.79 [3H, s, N(9)-Me], 4.26 (2H, q, $J$=7.2 Hz, $N^6$-C$H_2$Me), 5.14 (2H, s, OC$H_2$Ph), 5.38 (1H, br, $N^+$H), 7.36 (5H, m, $OCH_2$Ph), 8.45 and 8.58 (1H each, s, purine protons). *Anal.* Calcd for $C_{15}H_{17}N_5O$·HCl·1/3$H_2O$: 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)-/$N^6$-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.

**$N^6$-Benzyl-$N^6$-benzyloxy-9-methyladenine Perchlorate (8c·$HClO_4$) and 7-Benzyl-$N^6$-benzyloxy-9-methyladeninium Bromide (19c)** A mixture of **11**[4j] (4.08 g, 16 mmol) and $PhCH_2Br$ (11.0 g, 64 mmol) in $AcNMe_2$ (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 $P_2O_5$ at 3 mmHg and 100 °C for 1.5 h, a first crop (3.40 g, 49%) of **19c**·1/3$H_2O$, mp 224—225 °C (dec.). Further recrystallization from EtOH and drying under similar conditions yielded an analytical sample of **19c**·1/3$H_2O$ as colorless needles, mp 224—225 °C (dec.); UV (Table II); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{20}H_{20}BrN_5O$·1/3$H_2O$: 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**·1/3$H_2O$. 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 $Na_2CO_3$, concentrated to half its initial volume *in vacuo*, and extracted with AcOEt. The AcOEt extracts were dried over anhydrous $Na_2SO_4$ 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 $HClO_4$ (340 mg) was added. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give **8c**·$HClO_4$ (765 mg, 11%), mp 141.5—143 °C (dec.). Recrystallization from EtOH produced an analytical sample of **8c**·$HClO_4$ as colorless needles, mp 141.5—143 °C (dec.); UV (Table III); $^1$H-NMR ($Me_2SO$-$d_6$) $\delta$: 3.83 [3H, s, N(9)-Me], 5.16 (2H, s, OC$H_2$Ph), 5.52 (2H, s, $N^6$-C$H_2$Ph), 7.35 (10H, m, two $CH_2$Ph's), 8.11 (1H, br, $N^+$H), 8.44 and 8.68 (1H each, s, purine protons). *Anal.* Calcd for $C_{20}H_{19}N_5O$·$HClO_4$: C, 53.88; H, 4.52; N, 15.71. Found: C, 53.66; H,4.44; N, 15.57.

**$N^6$-Benzyloxy-9-ethyl-$N^6$-methyladenine (9a) and $N^6$-Benzyloxy-9-ethyl-7-methyladeninium Iodide (20a)** A mixture of **12**[4g,l] (*vide supra*) (3.50 g, 13 mmol) and MeI (7.38 g, 52 mmol) in $AcNMe_2$ (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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{15}H_{18}IN_5O$: 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 $H_2O$ (250 ml) containing a small amount of $NaHSO_3$. The resulting aqueous solution was adjusted to pH 6 by addition of saturated aqueous $NaHCO_3$ 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 $H_2O$ 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 $H_2O$, dried over anhydrous $Na_2SO_4$, 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); $^1$H-NMR ($Me_2SO$-$d_6$) $\delta$: 1.43 [3H, t, $J$=7 Hz, N(9)-$CH_2$Me], 3.49 (3H, s, $N^6$-Me), 4.25 [2H, q, $J$=7 Hz, N(9)-C$H_2$Me], 5.16 (2H, s, OC$H_2$Ph), 7.28—7.72 (5H, m, $OCH_2$Ph), 8.37 and 8.41 (1H each, s, purine protons). *Anal.* Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.53; H, 6.16; N, 24.88.

**$N^6$-Benzyloxy-7,9-diethyladeninium Iodide (20b)** A mixture of **12**[4g,l] (*vide supra*) (3.50 g, 13 mmol) and EtI (8.11 g, 52 mmol) in $AcNMe_2$ (20 ml) was stirred at 50 °C for 24 h. The reation 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{16}H_{20}IN_5O$: C, 45.19; H, 4.74; N, 16.47. Found: C, 45.05; H, 4.79; N, 16.44.

**7-Benzyl-$N^6$-benzyloxy-9-ethyladeninium Bromide (20c)** A mixture of **12**[4g,l] (*vide supra*) (3.23 g, 12 mmol) and $PhCH_2Br$ (8.21 g, 48 mmol) in $AcNMe_2$ (18 ml) was stirred at 30 °C for 22 h. The precipitate that resulted was filtered off, washed successively with a small amount of $AcNMe_2$ 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{21}H_{22}BrN_5O$: C, 57.28; H, 5.04; N, 15.90. Found: C, 57.00; H, 4.97; N, 16.05.

**$N^6$-Benzyloxy-9-benzyl-7-ethyladeninium Iodide (21b) and Perchlorate (21e)** A mixture of **13**[4b] (660 mg, 2 mmol) and EtI (1.25 g, 8 mmol) in $AcNMe_2$ (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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{21}H_{22}IN_5O$: 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 $HClO_4$. 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{21}H_{22}ClN_5O_5$: C, 54.85; H, 4.82; N, 15.23. Found: C, 54.88; H, 4.92; N, 15.31.

**7,9-Dibenzyl-$N^6$-benzyloxyadeninium Bromide (21c)** A mixture of **13**[4b] (994 mg, 3 mmol) and $PhCH_2Br$ (2.05 g, 12 mmol) in $AcNMe_2$ (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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{26}H_{24}BrN_5O$: C, 62.16; H, 4.81; N, 13.94. Found: C, 62.26; H, 4.67; N, 13.69.

**$N^6$-Ethyl-9-methyladenine (7b)** A solution of **6b**·HCl·$H_2O$ (280 mg, 1.07 mmol) in $H_2O$ (40 ml) was passed through a column of Amberlite IRA-402 ($HCO_3^-$) (5.5 ml), and the column was eluted with $H_2O$. 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]

**$N^6$-Benzyl-9-methyladenine (7c)** A solution of **6c**·HBr (198 mg, 0.57 mmol) in $H_2O$ (30 ml) was passed through a column of Amberlite IRA-402 ($HCO_3^-$) (2.7 ml), and the column was eluted with $H_2O$. 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 pillars, 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 $H_2O$ (100 ml) was hydrogenated over Raney Ni W-2 catalyst[32] (1.5 ml) at atmospheric pressure and room temperature for 18 h. The catalyst was removed by filtration and washed with $H_2O$ (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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_7H_{10}IN_5$: 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_8H_{12}IN_5$: 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 $H_2O$ and dried over $P_2O_5$ at 3 mmHg and room temperature for 25 h to give **16c**·$H_2O$ as colorless prisms, mp 225—226 °C (dec.); UV (Table VI); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{13}H_{14}BrN_5 \cdot H_2O$: 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_8H_{12}IN_5$: 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 $H_2O$ and adding $NaClO_4$ (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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_8H_{12}ClN_5O_4$: 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); $^1$H-NMR (Table IV). *Anal.*Calcd for $C_9H_{14}IN_5$: 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_9H_{14}ClN_5O_4$: 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{14}H_{16}ClN_5O_4$: 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 ° (dec.); UV (Table VI); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{14}H_{16}ClN_5O_4$: 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); $^1$H-NMR (Table IV). *Anal.* Calcd for $C_{19}H_{18}BrN_5$: C, 57.59; H, 4.58; N, 17.67. Found: C, 57.54; H, 4.58; N, 17.56.

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