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Purines. XXII.[1] Methylation of 1-, 3-, 7-, 9-, and N^6-Methyladenines Bearing a Methoxyl Group at the N^6-Position: A Synthesis of 7,9-Dimethyladenine

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In order to investigate the effect of the N^6-methoxy group on the site of methylation, N^6-methyl- (**27**), 1-methyl- (**17**), 3-methyl- (**11**), 7-methyl- (**7**), and 9-methyl-N^6-methoxyadenine (**2**) were methylated with an excess of MeI in $AcNMe_2$. The products isolated were the 3-methylated product **12**·$HClO_4$ (67% yield) and 9-methylated product **3** (18%) from **27**; 3-methylated product **15** (X=I) (44%) and 9-methylated product **18**·$HClO_4$ (38%) from **17**; **15** (X=I) (40%) and **12**·$HClO_4$ (36%) from **11**; 9-methylated product **5** (X=I) (36%) and 3-methylated product **8** (44%) from **7**; **5** (X=I) (59%) and **3**·HI (24%) from **2**. Further methylation of **18** in a similar manner was found to give N^6-methoxy-1,7,9-trimethyladeninium iodide (**33**: X=I) in 92% yield. A similar methylation of the betaine **32**, generated from **5** (X=I) by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), also produced **33** (X=I) in fair yield. The 7,9-dimethyl derivative **5** (X=I) thus obtained was converted into the perchlorate **5** ($X=ClO_4$), and hydrogenolysis of **5** ($X=ClO_4$) using Pd-C and hydrogen furnished hitherto unknown 7,9-dimethyladeninium perchlorate (**6**: $X=ClO_4$) in good yield. The substrates **11** and **27** used for the methylation study were prepared in 87 and 86% yields from 3-methyl-6-methylthiopurine (**10**) and 6-chloropurine (**26**) by amination with methoxyamine and *N,O*-dimethylhydroxylamine, respectively. For the synthesis of the substrate **17**, 1-methoxyadenosine (**25**) was methylated to give the N^6-methyl derivative **23**. Treatment of **23** with hot water and hydrolysis of the resulting isomer **21** with 98% formic acid afforded the desired compound **17**.

Keywords——regioselectivity in methylation; effect of N^6-methoxy group; N^6-methoxy-*N*-methyladenine; N^6-methoxy-N^x,N^y-dimethyladenine; N^6-methoxy-trimethyladenine; 1,3-dimethyladenine derivative; 7,9-dimethyladenine; catalytic hydrogenolysis of N–O bond; Dimroth rearrangement; hydrolysis

It is well known that an alkyl group at the 9-position of adenine (**1**) orients further alkylation to the 1-position[2] and an alkyl group at the 1-position directs an incoming alkyl group to the 9-position.[2d,3] The essentially reciprocal directivity in alkylations of 3- and 7-alkyladenines is also apparent from the formation of 3,7-dialkyladenine in each case.[2g,3a,4]

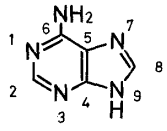

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Chart 1

The benzyl or benzhydryl group at the N^6-position has been reported to orient further alkylation to the 3-position.[4c,5] In connection with our previous studies on the synthetic utility of an easily removable alkoxyl group in alkylation,[1,6] cleavage,[7] and modification[7a,8] of the adenine ring, we investigated the effect of the N^6-methoxy group on regioselectivity in

methylation of all five possible isomers of *N*-methyladenine in the hope that the results might suggest ways to synthesize hitherto unknown positional isomers among the eleven possible N^x,N^y-dimethyladenines. A part of the results described here has been reported briefly in a preliminary form.[9]

Treatment of N^6-methoxy-9-methyladenine (**2**)[10] with an excess of MeI in $AcNMe_2$ at 30 °C for 7 h furnished the N^6-methylated product **3**·HI (24% yield) and the 7-methylated product **5** (X=I) (59% yield). The N^6-methyl structure of the minor product (**3**·HI) was assignable by hydrogenolysis of the corresponding free base using Raney nickel and hydrogen, which led to the formation of a known compound,[3b,11] N^6,9-dimethyladenine (**4**). There remains the possibility that the minor product is not **3**·HI, but one of the other possible isomers such as N^6-methoxy-1,9-dimethyladenine hydriodide (**18**·HI) and 1-methoxy-N^6,9-dimethyladenine hydriodide (**22**·HI), since they are also able to give **4** if an incidental Dimroth-type rearrangement is involved in the above conversion process. However, the observation that the ultraviolet (UV) spectra of the minor product (**3**·HI) at various pH's

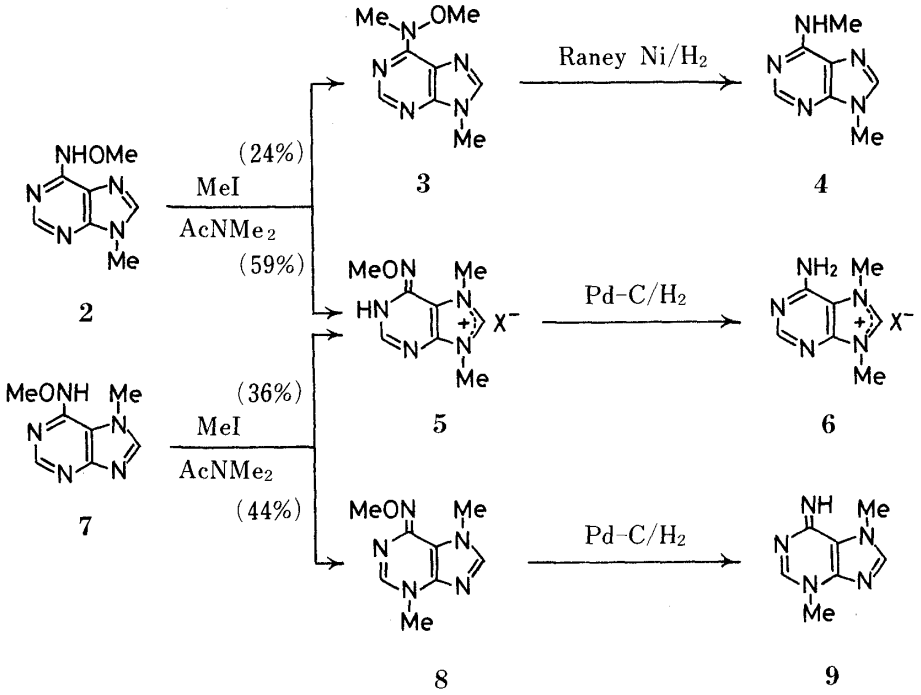


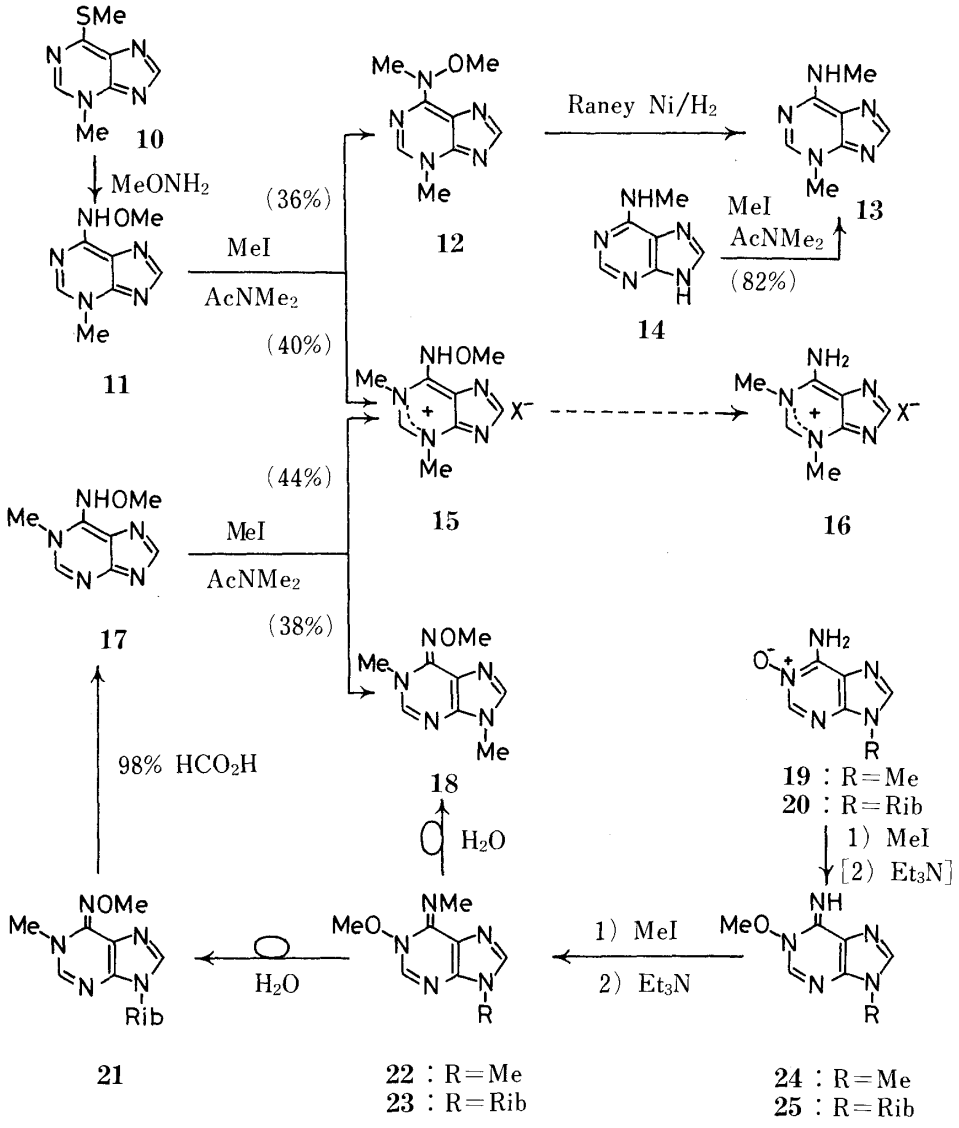
Chart 2

were quite distinct from those of **18**·HI[7a] and **22**[7a] definitely excluded this possibility. The 7,9-dimethyl structure of the major product (**5**: X=I) from the methylation of **2** was readily established by the formation of the same product in the methylation of N^6-methoxy-7-methyladenine (**7**) (*vide infra*). The observed regioselectivity is in contrast to that in the methylation of N^6,9-dimethyladenine (**4**) with MeI in $HCONMe_2$ at 100—105 °C for 10 min, which was reported to methylate the 1-, 3-, and 7-positions in a ratio of 51 : 30 : 19.[12]

On treatment with an excess of MeI in $AcNMe_2$ at 40 °C for 2 h, the 7-methyl isomer **7**[9a] produced the 9-methylated product **5** (X=I) (36% yield), identical with one of the products from the methylation of the 9-methyl isomer **2**, together with the 3-methylated product **8** (44% yield). The location of the newly introduced methyl group in **8** was established by hydrogenolysis of the corresponding perchlorate (**8**·$HClO_4$) using Pd-C and hydrogen, which afforded 3,7-dimethyladenine perchlorate (**9**·$HClO_4$), identical with a sample prepared from the known[3a] hydriodide salt **9**·HI.

The third substrate selected for methylation was N^6-methoxy-3-methyladenine (**11**), and

it was synthesized from 3-methyl-6-methylthiopurine (**10**) in 87% yield by amination with methoxyamine. The starting material **10** had previously been obtained by direct methylation



Rib=β-D-ribofuranosyl

Chart 3

of 6-mercaptopurine with methyl *p*-toluenesulfonate, but in rather low yield.[13] In the present work, we prepared it from 6-methylthiopurine in 42% yield by methylation with MeI in $AcNMe_2$. When the 3-methyl isomer **11** was treated with MeI as in the methylation of the 7-methyl isomer **7**, two methylated products were obtained. One was the N^6-methylated product **12**·$HClO_4$ (36% yield), which gave, on hydrogenolysis of the corresponding free base using Raney nickel and hydrogen, N^6,3-dimethyladenine (**13**) [identical with a sample synthesized[9b] in 82% yield from N^6-methyladenine (**14**) by methylation with MeI]. The other product was the 1-methylated product **15** (X=I) (40% yield), since it was also obtained by methylation of N^6-methoxy-1-methyladenine (**17**). In the case of methylation (MeI, $HCONMe_2$, 100 °C, 10 min) of N^6,3-dimethyladenine (**13**), El'tsov *et al.*[12] isolated the N^6,3,7-trimethyl and the N^6,3,9-trimethyl derivatives in 64% and 16% yields. This preferred site of methylation of **13** in the imidazole moiety is quite different from that of **11**, since the latter is in the pyrimidine moiety as described above.

The synthesis of the fourth substrate **17** for methylation was achieved, starting with adenosine 1-oxide (**20**), by a route essentially paralleling that (**19**→**24**→**22**→**18**)[6,7a] of our earlier synthesis of N^6-methoxy-1,9-dimethyladenine (**18**). Thus, **20** was methylated with MeI according to the previously reported procedure,[14] and the resulting crude salt (**25**·HI) was treated with Et_3N in MeOH to produce the free base of 1-methoxyadenosine (**25**) in 97% yield. Further methylation of **25** in a similar manner gave the N^6-methylated nucleoside **23** (63% yield), which was then heated in H_2O at 90 °C for 5 h, rearranging to N^6-methoxy-1-methyladenosine (**21**) (58% yield). Hydrolysis of **21** in 98% formic acid at 70 °C for 6.5 h furnished the desired substrate **17** in 75% yield. Treatment of **17** with an excess of MeI in $AcNMe_2$ at 30 °C for 9 h provided the 3-methylated product **15** (X=I) (44% yield), identical with one of the methylated products from the 3-methyl isomer **11**, as well as the 9-methylated product **18**, which was isolated as the perchlorate **18**·$HClO_4$ (38% yield). This perchlorate was identified with a sample synthesized from 1-methoxy-N^6,9-dimethyladenine hydriodide (**22**·HI)[6,7a] by a Dimroth-type rearrangement. In the methylation of N^6,1-dimethyladenine with MeI ($HCONMe_2$, 100 °C, 10 min), however, Russian workers[12] isolated only the 9-methylated product, N^6,1,9-trimethyladenine hydriodide, in 72.5% yield.

Finally, the fifth substrate **27** for methylation was synthesized from 6-chloropurine (**26**) and *N,O*-dimethylhydroxylamine in 86% yield. On treatment with an excess of MeI in $AcNMe_2$ at 40 °C for 3 h, the N^6-methyl isomer **27** gave the 3-methylated product **12**·$HClO_4$

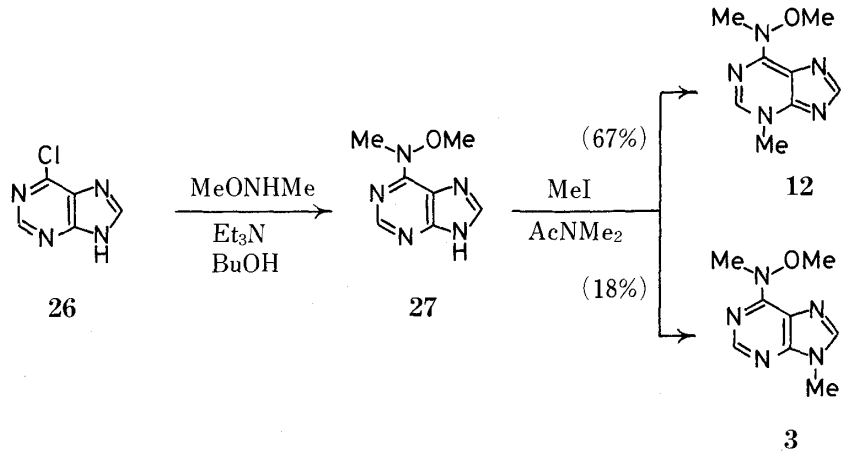


Chart 4

(67% yield) together with the 9-methylated product **3** (18% yield). The high regioselectivity at the 3-position in this case is in general agreement with what Pal and Horton[15] observed for methylation [Me_2SO_4, H_2O (pH 7), room temp., 3—4 h] of N^6,N^6-dimethyladenine, whereby the 3-, 1-, and 9-methylated products were formed in 66%, 22.9%, and 8.3% yields, respectively. Itaya *et al.*[16] also obtained N^6,N^6,3-trimethyl- and N^6,N^6,9-trimethyladenines in 83% and 0.7% yields by methylation (MeI, $AcNMe_2$, 40 °C, 48 h) of N^6,N^6-dimethyladenine.

The results of the above methylation study reveal that introduction of a methoxyl group into 3-methyladenine and 9-methyladenine at their N^6-position causes a complete change of the preferred sites of methylation reported[3a,4] for the parent bases (*vide supra*). Such a change in the directivity on methylation is moderate with the N^6-methoxy derivatives (**17** and **7**) of 1- and 7-methyladenines and is only slight with that (**27**) of N^6-methyladenine (*vide supra*). It is of interest to point out that a methoxyl group attached to all five *N*-methyladenine isomers at the N^6-position orients methylation to a considerable extent to nitrogen(s) in the same pyrimidine or imidazole moiety that the original *N*-methyl group is attached to. Also

noteworthy are the formation of the 7,9-dimethyl structure **5** from **2** or **7** by direct methylation and that of the 1,3-dimethyl structure **15** from **11** or **17**, since **5** and **15** may serve as good precursors for the syntheses of hitherto unknown 7,9-dimethyl- and 1,3-dimethyladenines, respectively.

Thus, we next focused our attention on the conversion of **5** (X=I) into the 7,9-dimethyladeninium salt (**6**). Treatment of **5** (X=I) in H_2O with Amberlite IRA-402 (ClO_4^-) produced the corresponding perchlorate **5** (X=ClO_4) in 83% yield (Chart 2). On hydrogenolysis using Pd-C and hydrogen in aqueous EtOH at 40—50 °C for 5.5 h, **5** (X=ClO_4) gave the desired compound **6** (X=ClO_4) in 92% yield. This concluded a total synthesis of 7,9-dimethyladenine for the first time. As reported briefly in a preliminary form,[8h] **6** (X=ClO_4) is unstable under basic conditions: it rearranges to N^6,7-dimethyladenine through ring opening in the imidazole moiety followed by recyclization. It is readily reduced with $NaBH_4$ to give the 7,8-dihydro derivative. The details of these chemical properties will be published elsewhere at a later date. It is interesting to note that Cullen and Devlin[17] reported, subsequent to our preliminary communication,[9a] the natural occurrence of a 7,9-disubstituted adenine structure in the form of agelasine, a major constituent of the sponge *Agelas dispar*.

Our preference for the 6-imino-1*H*-purine structure **5** for the expression of the N^6-methoxy-7,9-dimethyladeninium salt may deserve particular mention. The nuclear magnetic resonance (NMR) spectrum of **5** (X=I) in Me_2SO-d_6 showed a one-proton singlet at δ 9.24 ($C_{(8)}$-H), a set of a 0.4-proton singlet at 7.84 and a 0.6-proton doublet (J=3.9 Hz) at 7.83, and a broad one-proton peak at 12.0—12.2 (NH). On addition of D_2O, the doublet merged with the small singlet to form a one-proton singlet at δ 7.83 with the concomitant disappearance of the NH signal. The simplification of the doublet and the NH signal was also confirmed by a spin-decoupling experiment using the usual double-irradiation technique. The corresponding perchlorate **5** (X=ClO_4) also exhibited a similar NMR spectrum. In view of the intrinsic imidazolium structure of these salts in the imidazole moiety, the one-proton singlet at lower field is assignable to $C_{(8)}$-H; hence the set of the 0.6-proton doublet and the 0.4-proton singlet at higher field is assignable to $C_{(2)}$-H. It follows that in Me_2SO-d_6 solution the salt **5** (X=I or ClO_4) exists in two tautomeric forms, the 6-NH tautomer **30** and the alternative of the ring-

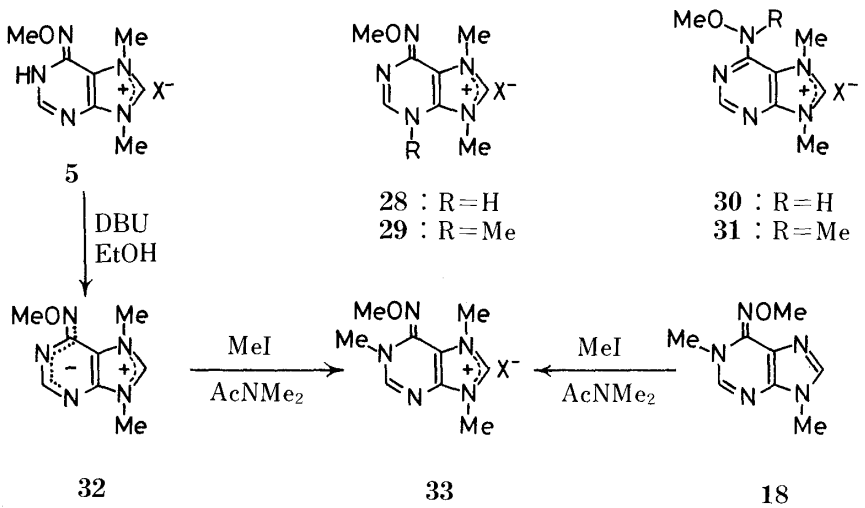


Chart 5

NH tautomer **5** or **28**, in a ratio of 1 : 1.5. The choice between the alternative structures **5** and **28** was made on the basis of the following chemical and UV spectroscopic approaches. Treatment of **5** (X=I) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in EtOH produced a betaine, presumed to be **32**, which gave, on methylation with MeI ($AcNMe_2$, room temp.,

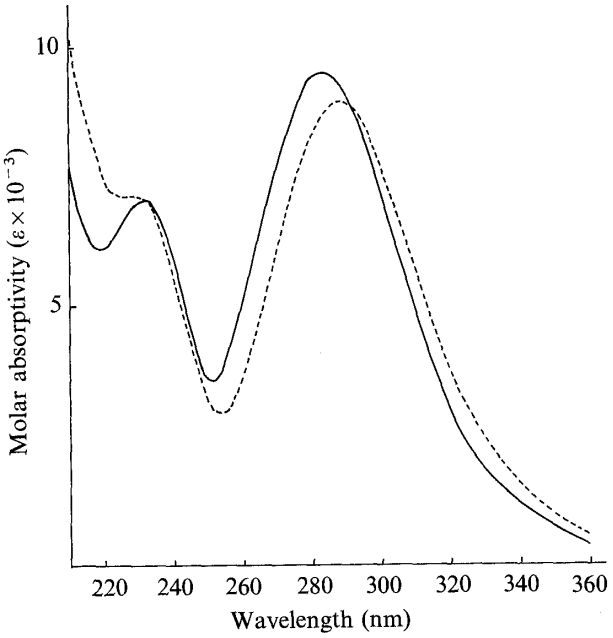


Fig. 1. UV Spectra of **5** (X = ClO_4) and **33** (X = ClO_4) in H_2O at pH 1

——, **5** (X = ClO_4); ------, **33** (X = ClO_4).

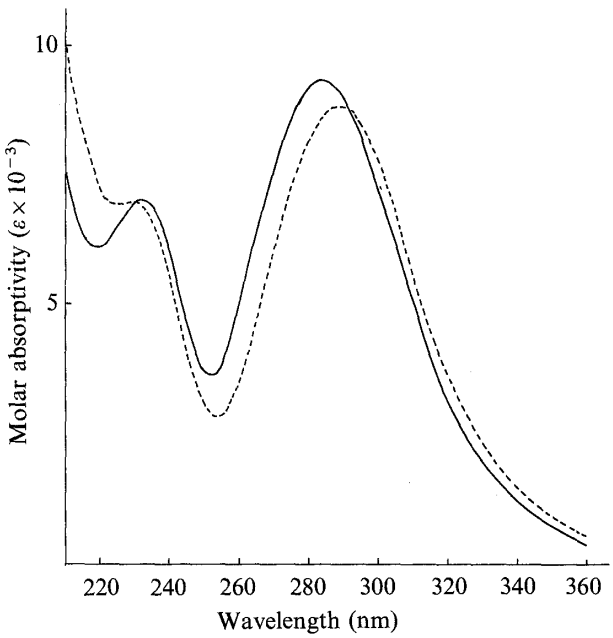


Fig. 2. UV Spectra of **5** (X = ClO_4) and **33** (X = ClO_4) in H_2O at pH 7

——, **5** (X = ClO_4); ------, **33** (X = ClO_4).

3.5 h), the 1-methylated product **33** (X = I) in 56% yield from **5** (X = I). Although the formation of the 1-methyl structure, as confirmed by its identity with a sample obtained from **18** by a similar methylation, does not necessarily suggest the possible site of deprotonation in **5** to be $N_{(1)}$, the perchlorate **33** (X = ClO_4) derived from the iodide **33** (X = I) by treatment with $NaClO_4$ in H_2O displayed UV spectra similar to those of **5** (X = ClO_4) (Figs. 1 and 2). This led us to prefer, at present, the 6-imino-1*H*-purine structure **5** to the 6-imino-3*H*-purine structure **28** for the expression of a ring-NH tautomer of N^6-methoxy-7,9-dimethyladeninium salt that is apparently predominant over the 6-NH tautomer **30** in Me_2SO-d_6 or H_2O. However, a final decision should be made when the UV spectra of the 3-methyl (**29**) and the N^6-methyl (**31**) analogues become available.

In order to synthesize 1,3-dimethyladeninium salt (**16**), considerable efforts have been devoted to the removal of the N^6-methoxy group from **15** (X = I) obtained by methylation of **11** or **17**. The results will be reported elsewhere shortly.

In conclusion, the utility of the methoxyl group in the syntheses of alkyladenines and related compounds[1,6-8] has now been extended to cover the syntheses of hitherto unknown 7,9-dimethyladeninium salt (**6**) and a 1,3-dimethyladeninium structure in the form of the N^6-methoxy derivative **15**. The importance of the present findings has also been demonstrated by our recent syntheses[8i,9a] of 7-methyl- and 7-ethyladenosines, which included alkylation of N^6-alkoxyadenosines as a key step.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 1 for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, s = singlet, sh = shoulder.

3-Methyl-6-methylthiopurine (10)——A stirred mixture of 6-methylthiopurine[18] (5.00 g, 30 mmol) and MeI (8.50 g, 60 mmol) in $AcNMe_2$ (20 ml) was kept at 40—43 °C for 6 h. The precipitate that resulted was filtered off and washed with a little EtOH to yield a first crop. The filtrate and washings were combined and concentrated *in vacuo*,

and a second crop of a solid was gathered by trituration of the resulting residue with ether (40 ml) followed by decantation. The total amount of the crude solid was dissolved in H_2O (40 ml) and the aqueous solution was made alkaline (pH 8) with conc. aqueous NH_3. The needles that resulted were collected by filtration, washed with a little cold H_2O, dried *in vacuo*, and then kept in a closed vessel saturated with H_2O until they reached constant weight, giving **10**·$2H_2O$ (2.75 g), mp 160.5—162 °C, in 42% yield. Recrystallization from H_2O produced an analytical sample of the dihydrate as colorless needles, mp 164—165 °C (dried over P_2O_5 at 3 mmHg and room temp. for 24 h and then hydrated as described above) (lit.[13] mp 163—165 °C); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 237 nm (ε 12600), 312 (19600); $\lambda_{max}^{H_2O}$ (pH 1) 235 (8400), 276 (4500), 316 (25800); $\lambda_{max}^{H_2O}$ (pH 7) 237 (11800), 312 (20400); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 2.72 (3H, s, SMe), 4.08 (3H, s, $N_{(3)}$-Me), 8.08 and 8.76 (1H each, s, purine protons). *Anal.* Calcd for $C_7H_8N_4S \cdot 2H_2O$: C, 38.87; H, 5.59; N, 25.91. Found: C, 38.93; H, 5.52; N, 25.61. This sample was identical with that prepared according to the procedure of Jones and Robins.[13]

N^6-Methoxy-3-methyladenine (11)——A mixture of **10**·$2H_2O$ (8.61 g, 39.8 mmol) and methoxyamine hydrochloride[19] (20.0 g, 240 mmol) was dissolved in H_2O (150 ml), and the pH of the solution was adjusted to 5.0 by addition of 30% aqueous KOH (*ca.* 30 ml). The resulting suspension was then stirred at 50—55 °C for 4 h, during which time the insoluble solid disappeared completely. After having been neutralized with 30% aqueous KOH, the reaction mixture was kept in a refrigerator. The precipitate that resulted was collected by filtration, washed with cold H_2O (30 ml), and dried to give **11** (6.23 g, 87%), mp 228—229.5 °C (dec.). Recrystallization from H_2O yielded an analytical sample as colorless needles, mp 229—230 °C (dec.); MS *m/e*: 179 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 295 nm (ε 14400); $\lambda_{max}^{H_2O}$ (pH 1) 223 (10300), 283 (18700); $\lambda_{max}^{H_2O}$ (pH 7) 294 (15100); $\lambda_{max}^{H_2O}$ (pH 13) 287 (11700); NMR (Me_2SO-d_6) δ: 3.51 (3H, s, $N_{(3)}$-Me), 3.74 (3H, s, OMe), 7.65 and 7.81 (1H each, s, purine protons). *Anal.* Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.08. Found: C, 46.86; H, 5.17; N, 38.94.

1-Methoxyadenosine (25)——Adenosine 1-oxide monohydrate (**20**·H_2O)[20] (12.05 g, 40 mmol) was methylated with MeI as described previously.[14] The reaction mixture was concentrated *in vacuo* to leave an oil, which was washed with three 30-ml portions of ether. The residue was dissolved in MeOH (50 ml), and the solution was kept in a refrigerator after addition of Et_3N (12 ml). The precipitate that resulted was filtered off, washed with MeOH, and dried to give **25** (11.59 g, 97%), mp 189—190 °C (dec.). Recrystallization from MeOH furnished an analytical sample as colorless prisms, mp 190—191 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 251 nm (sh) (ε 10600), 256.5 (12900), 264.5 (10700), 289 (3650); $\lambda_{max}^{H_2O}$ (pH 1) 258 (13100); $\lambda_{max}^{H_2O}$ (pH 7) 258 (12900); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 4.02 (3H, s, OMe), 6.8—7.8 (1H, br, NH), 8.23 and 8.42 (1H each, s, purine protons). *Anal.* Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.27; H, 5.10; N, 23.54.

1-Methoxy-N^6-methyladenosine (23)——A mixture of **25** (29.73 g, 0.1 mol) and MeI (99.4 g, 0.7 mol) in $AcNMe_2$ (200 ml) was stirred at room temperature for 26 h. The resulting solution was evaporated *in vacuo* to leave an oil, which was triturated with three 80-ml portions of ether. The insoluble material was dissolved in MeOH (180 ml), and Et_3N (30 ml) was added. On cooling in a refrigerator, the mixture deposited crystals, which were filtered off, washed with MeOH, and dried to give **23** (19.7 g, 63%), mp 186.5—188 °C (dec.). Recrystallization from MeOH yielded an analytical sample as colorless needles, mp 189—190 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 260.5 nm (ε 14100), 268 (sh) (11500); $\lambda_{max}^{H_2O}$ (pH 1) 262 (14500); $\lambda_{max}^{H_2O}$ (pH 7) 262 (14000); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.51 (3H, s, N^6-Me), 3.94 (3H, s, OMe), 8.18 and 8.31 (1H each, s, purine protons). *Anal.* Calcd for $C_{12}H_{17}N_5O_5$: C, 46.30; H, 5.50; N, 22.50. Found: C, 46.17; H, 5.62; N, 22.45.

N^6-Methoxy-1-methyladenosine (21)——A solution of **23** (9.34 g, 30 mmol) in H_2O (300 ml) was heated in an oil bath kept at 90 °C for 5 h. The solution was then concentrated *in vacuo*, and the residue was crystallized from MeCN–EtOH (2:1, v/v) (100 ml) to afford colorless prisms (5.61 g, 58%), mp 168.5—169.5 °C (dec.). Repeated recrystallizations from EtOH produced an analytical sample of the hemihydrate of **21** as colorless prisms, mp 171—172 °C (dec.) (dried over P_2O_5 at 3 mmHg and 65 °C for 15 h); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 270 nm (ε 14000), 321 (2000); $\lambda_{max}^{H_2O}$ (pH 1) 233 (7200), 282 (9300); $\lambda_{max}^{H_2O}$ (pH 7) 270 (14700); $\lambda_{max}^{H_2O}$ (pH 13) 270 (14500); NMR (Me_2SO-d_6) δ: 3.30 (3H, s, $N_{(1)}$-Me), 3.70 (3H, s, OMe), 7.92 and 8.04 (1H each, s, purine protons). *Anal.* Calcd for $C_{12}H_{17}N_5O_5 \cdot 1/2H_2O$: C, 44.99; H, 5.66; N, 21.87. Found: C, 44.98; H, 5.69; N, 21.65.

N^6-Methoxy-1-methyladenine (17)——A solution of **21**·$1/2H_2O$ (3.20 g, 10 mmol) in 98% formic acid (30 ml) was heated at 70 °C for 6.5 h. The resulting brown solution was concentrated *in vacuo*, and the residue was dissolved in EtOH. The ethanolic solution was then evaporated, and MeOH (10 ml) was added to the residue. The resulting methanolic solution deposited a solid on cooling in a refrigerator overnight. The solid was collected by filtration, washed with a little MeOH, and dried to give **17** (1.35 g, 75%), mp 260—262 °C . Recrystallization from EtOH produced an analytical sample as colorless prisms, mp 277.5—278.5 °C ; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 275 nm (ε 12100); $\lambda_{max}^{H_2O}$ (pH 1) 228 (6200), 278.5 (10100); $\lambda_{max}^{H_2O}$ (pH 7) 273.5 (13000); $\lambda_{max}^{H_2O}$ (pH 13) 273 (15500); NMR (Me_2SO-d_6) δ: 3.26 (3H, s, $N_{(1)}$-Me), 3.76 (3H, s, OMe), 7.79 and 7.87 (1H each, s, purine protons), 12.48 (1H, s, NH). *Anal.* Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.08. Found: C, 46.74; H, 5.11; N, 38.84.

N^6-Methoxy-N^6-methyladenine (27)——A mixture of 6-chloropurine (**26**) (1.08 g, 7.0 mmol), *N,O*-dimethylhydroxylamine hydrochloride (2.73 g, 28 mmol), Et_3N (3.54 g, 35 mmol), and 1-butanol (14 ml) was heated at reflux for 4 h. The reaction mixture was evaporated *in vacuo*, and the residue was co-evaporated twice with H_2O (3 ml) to leave a solid. Recrystallization of the solid from H_2O (3 ml) yielded **27** (1.07 g, 86%) as colorless needles, mp 200—

207 °C . Further recrystallizations from H_2O gave an analytical sample, mp 222—223 °C ; MS *m/e*: 179 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 278 nm (ε 14500); $\lambda_{max}^{H_2O}$ (pH 1) 283.5 (16900); $\lambda_{max}^{H_2O}$ (pH 7) 215 (16000), 278.5 (14500); $\lambda_{max}^{H_2O}$ (pH 13) 280 (13700); NMR (Me_2SO-d_6) δ: 3.45 (3H, s, N^6-Me or OMe), 3.85 (3H, s, OMe or N^6-Me), 8.32 and 8.37 (1H each, s, purine protons), 11.0—13.5 (1H, br, NH). *Anal.* Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.81; H, 5.01; N, 39.15.

Methylation of N^6-Methoxy-9-methyladenine (2)——A mixture of **2**[10] (3.33 g, 19 mmol) and MeI (11.0 g, 77 mmol) in $AcNMe_2$ (25 ml) was stirred at 30 °C for 7 h. The reaction mixture was then kept in a refrigerator, and the precipitate that resulted was filtered off, washed with a little EtOH, and dried to give crude N^6-methoxy-7,9-dimethyladeninium iodide (**5**: X=I) (3.50 g, 59%), mp 246—246.5 °C (dec.). Recrystallization from 90% (v/v) aqueous EtOH yielded an analytical sample of **5** (X=I) as colorless needles, mp 250—251 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 219 nm (ε 20900), 291 (8500); $\lambda_{max}^{H_2O}$ (pH 1) 226 (19000), 283 (9300); $\lambda_{max}^{H_2O}$ (pH 7) 226 (18900), 283 (9200); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ:[21] 3.80 (3H, s, $N_{(9)}$-Me or OMe), 3.85 (3H, s, OMe or $N_{(9)}$-Me), 3.99 (3H, s, $N_{(7)}$-Me), 7.83 [0.6H, d (converted into s on addition of D_2O), J=3.9 Hz] and 7.84 (0.4H, s) ($C_{(2)}$-H), 9.24 (1H, s, $C_{(8)}$-H), 12.0—12.2 (1H, br, NH, exchangeable with D_2O). *Anal.* Calcd for $C_8H_{12}IN_5O$: C, 29.92; H, 3.77; N, 21.81. Found: C, 30.04; H, 4.07; N, 21.59.

On the other hand, evaporation of the filtrate, which was obtained when the crude **5** (X=I) was separated from the reaction mixture, under reduced pressure left a solid. Two recrystallizations of the solid from EtOH gave N^6-methoxy-N^6,9-dimethyladenine hydriodide (**3**·HI) (1.41 g, 24%) as colorless needles, mp 169.5—170.5 °C (dec.), which were further recrystallized in a similar manner to produce an analytical sample, mp 170.5—171.5 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 219 nm (ε 31400), 277 (16500); $\lambda_{max}^{H_2O}$ (pH 1) 220 (22900), 276 (15700); $\lambda_{max}^{H_2O}$ (pH 7) 220 (25500), 276 (17400); $\lambda_{max}^{H_2O}$ (pH 13) 276 (16800); NMR (Me_2SO-d_6) δ: 3.83 (3H, s, N^6-Me), 3.89 (3H, s, $N_{(9)}$-Me or OMe), 3.91 (3H, s, OMe or $N_{(9)}$-Me), 8.52 and 8.89 (1H each, s, purine protons), 10.3—10.7 (1H, br, N^+H). *Anal.* Calcd for $C_8H_{12}IN_5O$: C, 29.92; H, 3.77; N, 21.81. Found: C, 29.94; H, 3.74; N, 21.99.

Hydrogenolysis of 3——i) A portion (280 mg, 0.87 mmol) of the hydriodide **3**·HI derived from **2** was dissolved in H_2O (40 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (4 ml), and the column was eluted with H_2O (60 ml). The eluate was concentrated *in vacuo* to leave a solid, which was dissolved in 2-methoxyethanol (10 ml). The resulting solution was hydrogenated over Raney Ni W-2 catalyst (0.5 ml) at atmospheric pressure and 50 °C for 5.5 h. The catalyst was removed by filtration and washed successively with hot 2-methoxyethanol and EtOH. The filtrate and washings were combined and evaporated *in vacuo*, leaving N^6,9-dimethyladenine (**4**) (75 mg, 53%), mp 182.5—185.5 °C . Recrystallization from EtOH afforded a pure sample as colorless needles, mp 185—186 °C , identical with an authentic sample[3b] of **4**.

ii) A small sample (140 mg, 0.72 mmol) of the base **3** derived from **27** was dissolved in EtOH (10 ml). The ethanolic solution was then hydrogenated over Raney Ni W-2 catalyst (*ca.* 0.3 g) at atmospheric pressure and room temperature for 13 h. The catalyst was filtered off and washed with EtOH (10 ml). The filtrate and washings were combined and evaporated *in vacuo* to dryness to leave a colorless solid (112 mg, 95%), mp 184—185 °C. Recrystallization of the solid from benzene provided **4** as colorless prisms, mp 185—186 °C, which were identical with an authentic sample.[3b]

N^6-Methoxy-7,9-dimethyladeninium Perchlorate (5: X=ClO_4)——A solution of the iodide **5** (X=I) (1.93 g, 6 mmol) in H_2O (110 ml) was passed through a column of Amberlite IRA-402 (ClO_4^-) (24 ml), and the column was eluted with H_2O (500 ml). Concentration of the eluate under reduced pressure left a solid, which was recrystallized from H_2O to furnish **5** (X=ClO_4) (1.46 g, 83%) as colorless needles, mp 257—259 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 235 nm (ε 7900), 291 (8100); $\lambda_{max}^{H_2O}$ (pH 1) 232 (7000), 283 (9500); $\lambda_{max}^{H_2O}$ (pH 7) 232 (7000), 283 (9300); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ:[21] 3.80 (3H, s, $N_{(9)}$-Me or OMe), 3.85 (3H, s, OMe or $N_{(9)}$-Me), 3.99 (3H, s, $N_{(7)}$-Me), 7.83 [0.6H, d (converted into s on addition of D_2O), J=3.4 Hz] and 7.84 (0.4H, s) ($C_{(2)}$-H), 9.23 (1H, s, $C_{(8)}$-H), 12.0—12.2 (1H, br, NH). *Anal.* Calcd for $C_8H_{12}ClN_5O_5$: C, 32.72; H, 4.12; N, 23.85. Found: C, 33.02; H, 4.34; N, 24.00.

7,9-Dimethyladeninium Perchlorate (6: X=ClO_4)——A solution of **5** (X=ClO_4) (587 mg, 2 mmol) in 70% (v/v) aqueous EtOH (360 ml) was hydrogenated over 10% Pd-C (600 mg) at atmospheric pressure and 40—50 °C for 5.5 h. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure left crude **6** (X=ClO_4) (484 mg, 92%), mp 261—264.5 °C (dec.). Recrystallizations from 50% (v/v) aqueous EtOH produced an analytical sample as colorless pillars, mp 276—277 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 273 nm (ε 11500); $\lambda_{max}^{H_2O}$ (pH 1) 268 (11900); $\lambda_{max}^{H_2O}$ (pH 7) 269 (12100); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ:[21] 3.85 (3H, s, $N_{(9)}$-Me), 4.14 (3H, s, $N_{(7)}$-Me), 7.89 (2H, s, NH_2, exchangeable with D_2O), 8.40 (1H, s, $C_{(2)}$-H), 9.50 (1H, s, $C_{(8)}$-H). *Anal.* Calcd for $C_7H_{10}ClN_5O_4$: C, 31.89; H, 3.82; N, 26.57. Found: C, 31.90; H, 3.94; N, 26.64.

Methylation of N^6-Methoxy-7-methyladenine (7)——A stirred mixture of **7**[9a] (125 mg, 0.7 mmol) and MeI (300 mg, 2.1 mmol) in $AcNMe_2$ (2 ml) was kept at 40 °C for 2 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give **5** (X=I) (80 mg, 36%), mp 248—249 °C (dec.), which was identified with a sample derived from **2** (*vide supra*). The filtrate and washings were combined and concentrated *in vacuo*, and the residue was chromatographed on alumina (10 g). Fractions eluted with $CHCl_3$–EtOH (100:1, v/v) (*ca.* 40 ml) gave N^6-methoxy-3,7-dimethyladenine (**8**) (60 mg, 44%), mp 199—202 °C . Recrystallization from benzene provided an analytical sample as slightly yellowish prisms, mp 203—204.5 °C; MS *m/e*: 193 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 291 nm

(ε 11200); $\lambda_{max}^{H_2O}$ (pH 1) 276 (14100); $\lambda_{max}^{H_2O}$ (pH 7) 290 (11900); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.46, 3.66, and 3.83 (3H each, s, two NMe's and OMe), 7.61 and 7.75 (1H each, s, purine protons). *Anal.* Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.58; H, 5.74; N, 36.44.

N^6-Methoxy-3,7-dimethyladenine Perchlorate (8·$HClO_4$)——To a solution of **8** (88 mg, 0.46 mmol) in EtOH (1 ml) was added a mixture of 70% aqueous $HClO_4$ (110 mg, 0.77 mmol) and EtOH (0.5 ml), and the resulting mixture was kept in a refrigerator. The crystals that formed were collected by filtration, washed with EtOH, and dried to give **8**·$HClO_4$ (122 mg, 91%), mp 182—184 °C (dec.). Recrystallization from EtOH furnished an analytical sample as slightly yellowish needles, mp 187—188 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 287 nm (ε 10900); $\lambda_{max}^{H_2O}$ (pH 1) 276 (14200); $\lambda_{max}^{H_2O}$ (pH 7) 290 (12000); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.76, 3.90, and 3.91 (3H each, s, three Me's), 8.19 and 8.74 (1H each, s, purine protons). *Anal.* Calcd for $C_8H_{12}ClN_5O_5$: C, 32.72; H, 4.12; N, 23.85. Found: C, 32.45; H, 4.05; N, 23.75.

Hydrogenolysis of 8·$HClO_4$——A solution of **8**·$HClO_4$ (120 mg, 0.41 mmol) in 70% (v/v) aqueous EtOH (20 ml) was hydrogenated over 10% Pd-C (180 mg) at atmospheric pressure and 50 °C for 6 h. The catalyst was removed by filtration and washed with 70% (v/v) aqueous EtOH. The filtrate and washings were combind and concentrated *in vacuo* to leave a colorless solid (97 mg). Recrystallization of the solid from 90% (v/v) aqueous EtOH (20 ml) gave 3,7-dimethyladenine perchlorate (**9**·$HClO_4$) (64 mg, 59%), mp 303—304 °C (dec.). Further recrystallization in the same way yielded an analytical sample as colorless prisms, mp 308—309 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 225 nm (ε 9500), 279 (14700); $\lambda_{max}^{H_2O}$ (pH 1) 223 (11400), 277 (16700); $\lambda_{max}^{H_2O}$ (pH 7) 223 (11400), 277 (16700); $\lambda_{max}^{H_2O}$ (pH 13) 282 (14800). *Anal.* Calcd for $C_7H_{10}ClN_5O_4$: C, 31.89; H, 3.82; N, 26.56. Found: C, 31.85; H, 3.83; N, 26.42. This sample was identical with that prepared from authentic 3,7-dimethyladenine hydriodide (**9**·HI)[3a] (*vide infra*).

3,7-Dimethyladenine Perchlorate (9·$HClO_4$)——An authentic sample of **9**·HI was prepared according to the published method.[3a] A portion (160 mg, 0.55 mmol) of the sample was dissolved in hot H_2O (2 ml) and a solution of $NaClO_4 \cdot H_2O$ (230 mg, 1.64 mmol) in H_2O (0.3 ml) was added while hot. The mixture was then kept in a refrigerator, and the crystals that deposited were filtered off, washed with a little H_2O, and dried to yield **9**·$HClO_4$ (137 mg, 94%), mp 303—304 °C (dec.). Recrystallization from 90% (v/v) aqueous EtOH gave an analytical sample as colorless prisms, mp 308—309 °C (dec.). *Anal.* Calcd for $C_7H_{10}ClN_5O_4$: C, 31.89; H, 3.82; N, 26.56. Found: C, 31.62; H, 3.73; N, 26.39.

Methylation of N^6-Methoxy-3-methyladenine (11)——A mixture of **11** (179 mg, 1 mmol) and MeI (430 mg, 3 mmol) in $AcNMe_2$ (3 ml) was stirred at 40 °C for 2 h. The precipitae that resulted was filtered off, washed with EtOH, and dried to give N^6-methoxy-1,3-dimethyladeninium iodide (**15**: X=I) (129 mg, 40%), mp 248—249 °C (dec.). Recrystallization from 90% (v/v) aqueous EtOH produced an analytical sample as slightly yellowish plates, mp 249—250 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ unstable; $\lambda_{max}^{H_2O}$ (pH 1) 223 nm (ε 20300), 274 (14600); $\lambda_{max}^{H_2O}$ (pH 7 and 13) unstable; NMR (Me_2SO-d_6) δ:[22] 3.48 (3H, s, $N_{(1)}$-Me), 3.76 (3H, s, $N_{(3)}$-Me), 3.90 (3H, s, OMe), 8.26 (1H, s, $C_{(8)}$-H), 9.28 (1H, s, $C_{(2)}$-H), 13.6 (br, NH). *Anal.* Calcd for $C_8H_{12}IN_5O$: C, 29.92; H, 3.77; N, 21.81. Found: C, 29.93; H, 3.69; N, 21.88.

On the other hand, the mother liquor, which was obtained on filtration of the reaction mixture, was concentrated *in vacuo*, and the residue was dissolved in H_2O (20 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (ClO_4^-) (2 ml), and the column was eluted with H_2O. The eluate (80 ml) was evaporated *in vacuo*, and the residue was recrystallized twice from EtOH to furnish N^6-methoxy-N^6,3-dimethyladenine perchlorate (**12**·$HClO_4$) (105 mg, 36%), mp 228—229 °C . Further recrystallization gave an analytical sample as colorless prisms, mp 229—230 °C; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 227 nm (ε 10300), 292 (19600); $\lambda_{max}^{H_2O}$ (pH 1) 226 (9600), 290 (21200); $\lambda_{max}^{H_2O}$ (pH 7) 225 (11700), 291 (18300); $\lambda_{max}^{H_2O}$ (pH 13) 225 (13100), 294 (16400); NMR (Me_2SO-d_6) δ: 3.63 (3H, s, N^6-Me), 3.92 (3H, s, $N_{(3)}$-Me), 4.00 (3H, s, OMe), 8.72 and 8.81 (1H each, s, purine protons). *Anal.* Calcd for $C_8H_{12}ClN_5O_5$: C, 32.72; H, 4.12; N, 23.85. Found: C, 32.69; H, 4.14; N, 23.53.

Hydrogenolysis of 12——A solution of **12**·$HClO_4$ (400 mg, 1.36 mmol) in H_2O (15 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (3 ml), and the column was eluted with H_2O. The eluate (50 ml) was evaporated *in vacuo* to dryness. The resulting free base **12** was then hydrogenated in EtOH (25 ml) over Raney Ni W-2 catalyst (0.5 ml) at atmospheric pressure and 50 °C for 23 h. The catalyst was removed by filtration and washed with EtOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a solid. Recrystallization of the solid from H_2O provided N^6,3-dimethyladenine (**13**) (95 mg, 43%) as colorless needles, mp > 300 °C , identical with a sample synthesized[9b] from N^6-methyladenine (**14**) by methylation with MeI.

N^6-Methoxy-1,3-dimethyladeninium Perchlorate (15: X=ClO_4)——To a hot solution of **15** (X=I) (323 mg, 1.01 mmol) in H_2O (3.5 ml) was added a solution of $NaClO_4$ (618 mg, 5.05 mmol) in H_2O (0.8 ml), and the resulting mixture was kept in a refrigerator. The slightly yellowish prisms that resulted were filtered off, washed with a little H_2O, and dried to give **15** (X=ClO_4) (278 mg, 94%), mp 289—291 °C (dec.). Recrystallization from 70% (v/v) aqueous EtOH afforded an analytical sample as almost colorless prisms, mp 289—291 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ unstable; $\lambda_{max}^{H_2O}$ (pH 1) 275 nm (ε 14700); $\lambda_{max}^{H_2O}$ (pH 7 and 13) unstable; NMR (Me_2SO-d_6) δ:[22] 3.48 (3H, s, $N_{(1)}$-Me), 3.76 (3H, s, $N_{(3)}$-Me), 3.91 (3H, s, OMe), 8.24 (1H, s, $C_{(8)}$-H), 9.24 (1H, s, $C_{(2)}$-H), 13.58 (1H, br, NH). *Anal.* Calcd for $C_8H_{12}ClN_5O_5$: C, 32.72; H, 4.12; N, 23.85. Found: C, 32.56; H, 3.89; N, 23.66.

Methylation of N^6-Methoxy-1-methyladenine (17)——A mixture of **17** (358 mg, 2 mmol) and MeI (1.13 g, 8 mmol) in $AcNMe_2$ (3 ml) was stirred at 30 °C for 9 h. The precipitate that resulted was filtered off, washed with a

little 90% (v/v) aqueous EtOH, and dried to yield N^6-methoxy-1,3-dimethyladeninium iodide (**15**: X=I) (282 mg, 44%), mp 224.5—226.5 °C (dec.). Recrystallization of this sample from 90% (v/v) aqueous EtOH gave slightly yellowish plates, mp 249—250 °C (dec.), identical with a sample derived from **11** by methylation (*vide supra*).

On the other hand, the filtrate, which was obtained when the crude **15** (X=I) was isolated, was evaporated *in vacuo*, and the residue was triturated with two 5-ml portions of ether. The insoluble solid that resulted was filtered off and dissolved in boiling EtOH (13 ml). After addtion of 70% aqueous $HClO_4$ (210 mg), the ethanolic solution was kept in a refrigerator. The crystals that deposited were collected by filtration, washed with EtOH, and dried to afford N^6-methoxy-1,9-dimethyladenine perchlorate (**18**·$HClO_4$) (222 mg, 38%), mp 209—211 °C (dec.). Recrystallization from EtOH furnished colorless needles, mp 221—223 °C (dec.), which were identical with an authentic sample described below.

N^6-Methoxy-1,9-dimethyladenine Perchlorate (18·$HClO_4$)——1-Methoxy-N^6,9-dimethyladenine hydriodide (**22**·HI)[6,7a] (2.73 g, 8.5 mmol) was converted into the base **18** according to the previously reported procedure,[7a] and the product was treated with 70% aqueous $HClO_4$ (1.46 g) in EtOH to afford **18**·$HClO_4$ (1.87 g, 75%), mp 220.5—222 °C (dec.). Recrystallization from EtOH gave an analytical sample as colorless needles, mp 228—229 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 273 nm (ε 12100); $\lambda_{max}^{H_2O}$ (pH 1) 231 (6700), 283 (9700); $\lambda_{max}^{H_2O}$ (pH 7) 271 (14500), 312 (sh) (2300); $\lambda_{max}^{H_2O}$ (pH 13) 271 (14200), 312 (sh) (2200); NMR (Me_2SO-d_6) δ: 3.35, 3.79, and 3.83 (3H each, s, two NMe's and OMe), 8.20 (1H, s, $C_{(2)}$-H), 9.19 (1H, s, $C_{(8)}$-H). *Anal.* Calcd for $C_8H_{12}ClN_5O_5$: C, 32.72; H, 4.12; N, 23.85. Found: C, 32.86; H, 4.18; N, 23.85.

Methylation of N^6-Methoxy-N^6-methyladenine (27)——A stirred mixture of **27** (717 mg, 4 mmol) and MeI (1.70 g, 12 mmol) in $AcNMe_2$ (10 ml) was kept at 40 °C for 3 h. The reaction mixture was then concentrated *in vacuo*, and the residual solid was dissolved in H_2O (3 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (10 ml), and the column was eluted with H_2O. Concentration of the eluate (200 ml) under reduced pressure left an oily residue, which was chromatographed on alumina (60 g). Earlier fractions eluted with CH_2Cl_2 gave N^6-methoxy-N^6,9-dimethyladenine (**3**) (137 mg, 18%), mp 94—95 °C . Recrystallization from hexane yielded an analytical sample as colorless prisms, mp 95—96 °C ; MS *m/e*: 193 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 276 nm (ε 17600); $\lambda_{max}^{H_2O}$ (pH 1) 275.5 (16600); $\lambda_{max}^{H_2O}$ (pH 7 and 13) 276 (17800); NMR (Me_2SO-d_6) δ: 3.50, 3.77, and 3.86 (3H each, s, two NMe's and OMe), 8.23 and 8.37 (1H each, s, purine protons). *Anal.* Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.80; H, 5.64; N, 36.24.

In the same chromatography, later fractions eluted with CH_2Cl_2–EtOH (20 : 1, v/v) yielded crude **12**, which was dissolved in EtOH (2.5 ml). The ethanolic solution was then acidified by addition of a mixture of 70% aqueous $HClO_4$ (0.44 g, 3 mmol) and EtOH (0.5 ml). The crystals that resulted were filtered off, washed with a little EtOH, and dried to give **12**·$HClO_4$ (782 mg, 67%), mp 229—230 °C . This sample was identical with that derived from **11** by methylation (*vide supra*).

Conversion of 3 into 3·HI——A portion (58 mg, 0.3 mmol) of the base **3** obtained by methylation of **27** was dissolved in EtOH (0.5 ml), and a solution of 57% aqueous HI (80 mg, 0.36 mmol) in EtOH (0.5 ml) was added. The resulting mixture was kept in a refrigerator, and the crystals that deposited were filtered off, washed with a little EtOH, and dried to yield **3**·HI (55 mg, 57%), mp 169—170 °C (dec.), as a first crop. The filtrate and washings were combined, and ether (5 ml) was added to deposit a second crop (8 mg) of a solid, mp 169—170 °C (dec.). The total yield was 66%. On recrystallization from EtOH, the crude **3**·HI afforded slightly yellowish plates, mp 170.5—171.5 °C (dec.), identical with a sample derived from **2** by methylation (*vide supra*).

N^6-Methoxy-7,9-dimethyladenine (32)——A mixture of **5** (X=I) (963 mg, 3 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (1.14 g, 7.5 mmol) was dissolved in boiling absolute EtOH (9 ml). On cooling, the reaction mixture deposited colorless needles, which were filtered off, washed with cold absolute EtOH (3 ml), and dried to give the betaine **32** (347 mg), mp 215 °C (dec.); UV $\lambda_{max}^{H_2O}$ (pH 1 and 7) 232 and 284 nm; $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.59, 3.65, and 3.97 (3H each, s, two NMe's and OMe), 7.54 (1H, s, $C_{(2)}$-H), 8.82 (3H, s, $C_{(8)}$-H).

N^6-Methoxy-1,7,9-trimethyladeninium Iodide (33: X=I)——i) From **32**: To a suspension of **32** (135 mg) in $AcNMe_2$ (2 ml) was added MeI (300 mg, 2.1 mmol), and the mixture was stirred at room temperature for 3.5 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to afford **33** (X=I) [151 mg, 39% from **5** (X=I)], mp 229—230 °C (dec.). On the other hand, addition of ether (20 ml) to the above filtrate produced a second crop (68 mg, 17%) of a slightly yellowish solid, mp 220—223 °C (dec.). The total amount (219 mg, 56%) of the solid was then recrystallized from EtOH to yield an analytical sample of **33** (X=I) as slightly yellowish prisms, mp 230—231 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 294 nm (ε 8000); $\lambda_{max}^{H_2O}$ (pH 1) 226 (20500), 289 (8800); $\lambda_{max}^{H_2O}$ (pH 7) 226 (20300), 289 (8800); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.38 (3H, s, $N_{(1)}$-Me), 3.78 (3H, s, OMe or $N_{(9)}$-Me), 3.85 (3H, s, $N_{(9)}$-Me or OMe), 3.97 (3H, s, $N_{(7)}$-Me), 8.29 (1H, s, $C_{(2)}$-H), 9.37 (1H, s, $C_{(8)}$-H). *Anal.* Calcd for $C_9H_{14}IN_5O$: C, 32.25; H, 4.21; N, 20.90. Found: C, 32.44; H, 4.25; N, 20.98.

ii) From **18**: The perchlorate **18**·$HClO_4$ (1.03 g, 3.5 mmol) was dissolved in warm H_2O (4 ml), and the aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (7.5 ml). The column was eluted with H_2O and the eluate (*ca.* 200 ml) was concentrated *in vacuo* to dryness. The residual base **18** was suspended in a mixture of MeI (2.48 g, 17.5 mmol) and $AcNMe_2$ (7 ml), and the suspension was stirred at room temperature for 3 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give **33** (X=I) (1.04 g, 88%), mp

230—231 °C (dec.). A second crop (40 mg) of **33** (X=I) was obtained by addition of ether to the above filtrate. The total yield was 1.08 g (92%). Recrystallization of the crude product from EtOH produced an analytical sample as slightly yellowish prisms, mp 230—231 °C (dec.), identical with a sample prepared by method (i).

***N*^{6}-Methoxy-1,7,9-trimethyladeninium Perchlorate (33: X=ClO_4)**——To a hot solution of **33** (X=I) (100 mg, 0.3 mmol) in H_2O (0.5 ml) was added a solution of $NaClO_4$ (55 mg, 0.45 mmol) in H_2O (0.3 ml). The resulting mixture was kept in a refrigerator, and the slightly yellowish prisms that formed were collected by filtration, washed with a little H_2O, and dried to give **33** (X=ClO_4) (82 mg, 89%), mp 207—208 °C . Recrystallization from H_2O furnished an analytical sample as colorless prisms, mp 207—208 °C ; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 233 nm (ε 7400), 294 (7900); $\lambda_{max}^{H_2O}$ (pH 1) 229 (7100), 289 (8900); $\lambda_{max}^{H_2O}$ (pH 7) 229 (7000), 289 (8800); $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ: 3.38 (3H, s, $N_{(1)}$-Me), 3.77 (3H, s, OMe or $N_{(9)}$-Me), 3.85 (3H, s, $N_{(9)}$-Me or OMe), 3.97 (3H, s, $N_{(7)}$-Me), 8.27 (1H, s, $C_{(2)}$-H), 9.34 (1H, s, $C_{(8)}$-H). *Anal.* Calcd for $C_9H_{14}ClN_5O_5$: C, 35.13; H, 4.59; N, 22.76. Found: C, 35.18; H, 4.55; N, 22.77.

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