[Chem. Pharm. Bull. 31(12)4270—4276(1983)]

Purines. XXIV.[1] Methylation of N^6-Alkoxyadenines and N^6-Methyladenine

TOZO FUJII,* TOHRU SAITO, and TAKASHI MURAMOTO

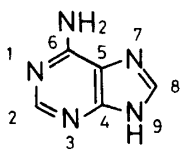
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

(Received April 14, 1983)

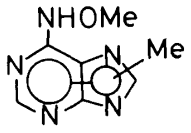
Methylation of N^6-methoxyadenine (**3**) with an excess of MeI in $AcNMe_2$ at 40 °C was found to give the 3-methylated product **8** (17% yield), 9-methylated product **4** (2%), N^6,9-dimethylated product **5** (9%), 7,9-dimethylated product **6** (27%), 3,7-dimethylated product **7** (10%), and N^6,3-dimethylated product **9** (11%). Similar treatment of N^6-benzyloxyadenine (**12**) with MeI also afforded a mixture of several products, from which the 7,9-dimethylated product **13** (X = I) was isolated in 30% yield. Similar methylation of N^6-methyladenine (**17**), prepared in 65% yield from 1-methyladenine (**16**) by a Dimroth-type rearrangement, gave the 3-methylated product **18** (82% yield), 9-methylated product **20** (1.3%), 3,7-dimethylated product **19** (1.8%), and 1,9-dimethylated product **21** (0.3%). On methylation under similar reaction conditions, **18** furnished the 9-methylated product **22** (15% yield) as well as the 7-methylated product **19** (29%), and **20** produced **22** (17%) and **21** (11%). The probable pathways to the six methylated products from **3** and those to the four methylated products from **17** are discussed.

Keywords——methylation regioselectivity; N^6-methoxyadenine; N^6-benzyloxyadenine; N^6-methyladenine; N^6,N^x,N^y-trimethyladenine; Dimroth rearrangement

Our recent methylation study[2] of the N^6-methoxy derivatives (**2**) of all the five possible *N*-methyladenine isomers has revealed 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 for the parent bases. Such a change in the directivity on methylation is moderate with the N^6-methoxy derivatives of 1- and 7-methyladenines and is only slight with that of N^6-methyladenine (**17**).[2] In the present work,[3] we investigated the methylation of the N^6-methoxy (**3**), N^6-benzyloxy (**12**), and N^6-methyl (**17**) derivatives of adenine (**1**) itself as a part of the comparative study.



1

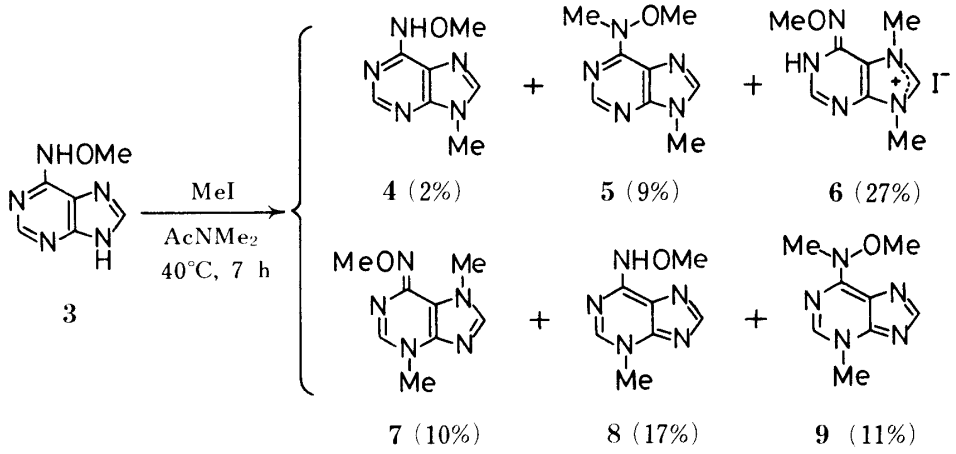


2

Chart 1

N^6-Methoxyadenine (**3**)[4] was first methylated in $AcNMe_2$ with 5 molar equivalents of MeI at 40 °C for 7 h. The precipitate that resulted was filtered off to give the 7,9-dimethylated product **6**[2] in 27% yield. Chromatographic separation of other products in the filtrate afforded five additional compounds: 3-methyl- (**8**)[2] (17% yield); 9-methyl- (**4**)[5] (2%); N^6,9-dimethyl- (**5**)[2] (9%); 3,7-dimethyl- (**7**)[2] (10%); N^6,3-dimethyl-N^6-methoxyadenine (**9**)[2] (11%). The structure of **9** was confirmed by converting it into the known perchlorate (**9**·$HClO_4$),[2] and those of the other five products, by direct comparison with authentic

samples. Remarkable was a complicated pattern of reaction products, which consisted of the two monomethylated products (**4** and **8**) and four dimethylated products (**5**, **6**, **7**, and **9**). In the light of the knowledge acquired in the course of our recent methylation study of N^6-alkoxy-N^x-methyladenines,[2] the probable pathways to the dimethylated products from **3** may be depicted as shown in Chart 2. Although we were unable to isolate the 7-methylated product **10** from the reaction mixture, the formation of **7** (and **6**) suggests its occurrence as an intermediate.[2] The second methylations of the monomethylated products **4**, **8**, and **10** should



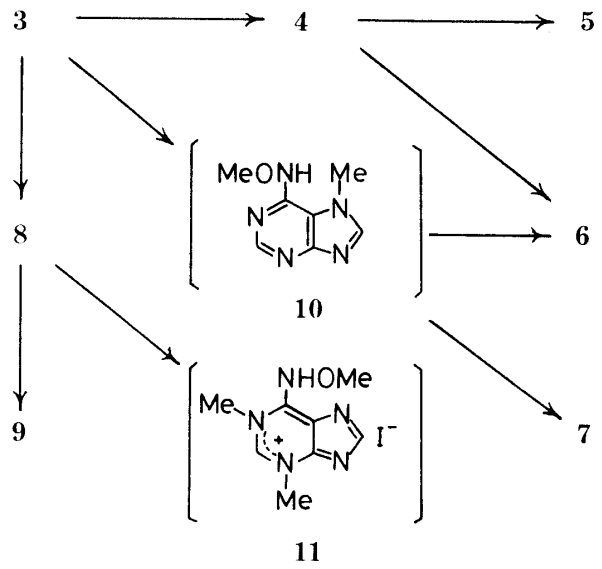


Chart 2

have taken place on their free base species, which are in equilibrium with the protonated species in $AcNMe_2$. It is known that **8** is methylated under similar reaction conditions to form **9** as well as **11**.[2] However, we failed to isolate the latter from the above reaction mixture.

N^6-Benzyloxyadenine (**12**)[4] was then treated with 5.6 molar equivalents of MeI in $AcNMe_2$ at 30—32 °C for 18 h. As in the methylation of **3** described above, the reaction mixture was found to contain several products. The major product was isolated in 30% yield and identified as N^6-benzyloxy-7,9-dimethyladeninium iodide (**13**: X=I)[6] by comparison with an authentic sample[7] prepared by methylation of N^6-benzyloxy-9-methyladenine (**15**). On treatment with $NaHCO_3$ in H_2O, the iodide **13** (X=I) furnished the free base **14** in 77% yield.

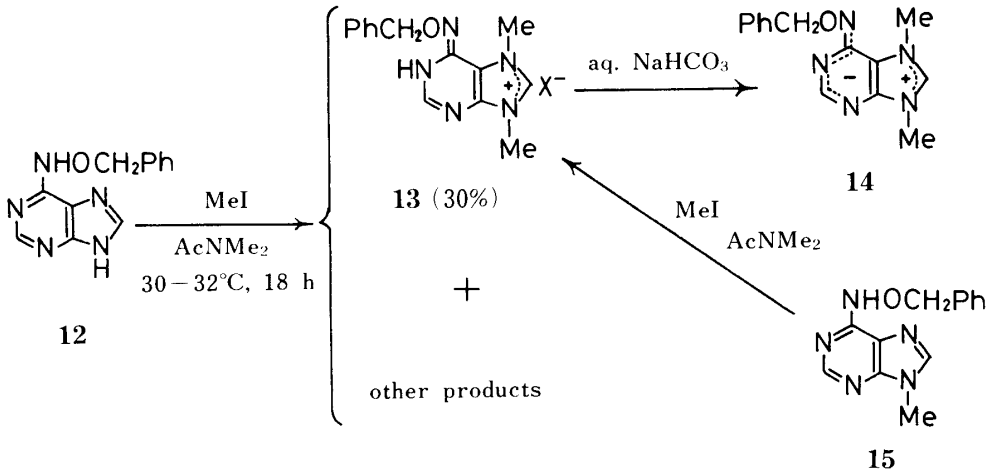
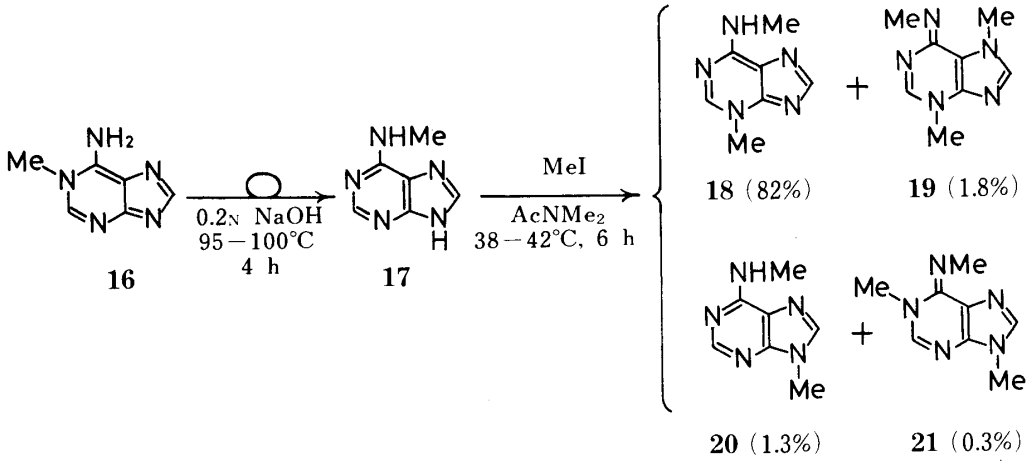


Chart 3

Finally, we carried out a similar methylation of N^6-methyladenine (**17**), which was prepared in 65% yield from 1-methyladenine (**16**)[8] according to a procedure modified from that of Brookes and Lawley.[9] Treatment of **17** with 3 molar equivalents of MeI in $AcNMe_2$ at 38—42 °C for 6 h and work-up of the reaction mixture as in the above methylation of **3** yielded



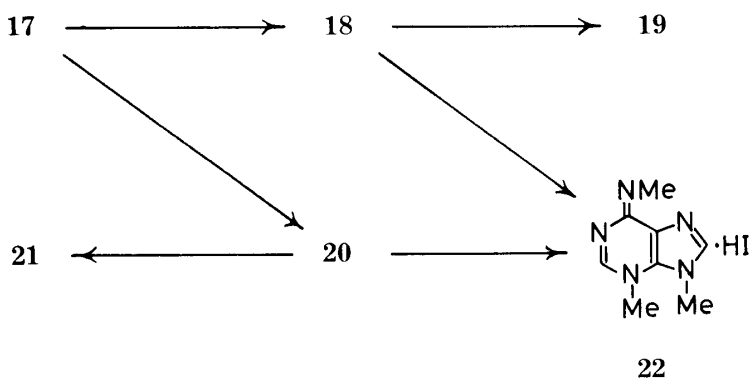


Chart 4

four products, which were isolated in appropriate forms and identified by comparison with authentic samples: N^6,3-dimethyladenine (**18**)[2,10] and its hydriodide (**18**·HI) (82% yield);

N^6,9-dimethyladenine (**20**)[11] (1.3%); N^6,3,7-trimethyladenine perchlorate (**19**·$HClO_4$)[12] (1.8%); N^6,1,9-trimethyladenine perchlorate (**21**·$HClO_4$)[12] (0.3%). When **18** was separately methylated with MeI under similar conditions, the 9-methylated product **22** (15% yield) and the 7-methylated product **19**·$HClO_4$ (29% yield) were isolated from the reaction mixture. A similar methylation of **20** gave the 3-methylated product **22** (17% yield) as well as the 1-methylated product **21**·$HClO_4$ (11% yield). The assignment of the N^6,3,9-trimethyl structure to **22** was the corollary of its formation from both **18** and **20**. These results of the methylations of **18** and **20** were in general agreement with those obtained by El'tsov *et al.*[12] under slightly different conditions ($HCONMe_2$, 100—105 °C, 10 min). Thus, the probable pathways to the four methylated products from **17** may be visualized as shown in Chart 4. Although **22** is included in these pathways, we actually failed to isolate it from the reaction mixture. In addition, the possibility that **19** and **21** might also have been formed through N^6,7- and N^6,1-dimethyladenines,[12] respectively, cannot be ruled out.

It is well known that under neutral conditions alkylation of adenine (**1**) itself occurs mainly at the 3-position.[10,13] Such regioselectivity is still operative even when the N^6-position is occupied by a benzyl,[13c,14] benzhydryl,[13c] dimethyl,[15,16] diethyl,[16] acetyl,[17] or benzoyl group,[13c,17,18] regardless of the electronic properties of the substituent. The high-yield formation (82%) of the 3-methylated product **18** from the N^6-methyl derivative **17**, observed in the present study, is also in line with this tendency. On the other hand, the N^6-methoxy derivative **3** undergoes a deep-seated methylation more easily to give the dimethylated products **5**, **6**, **7**, and **9** together with the monomethylated products **4** and **8**. According to the postulated pathways shown in Chart 2, the total yield of the products (**8** and **9**) formed through primary $N_{(3)}$-methylation is only 28% whereas that of the products (**4**—**7**) formed through primary $N_{(9)}$- or $N_{(7)}$-methylation is 48%. This alteration in regioselectivity caused by the N^6-methoxy group is particularly noteworthy since it is known[19] that replacement of the 1-methyl (or 1-alkyl) group by the methoxyl (or alkoxyl) group does not alter the high regioselectivity at the 9-position[8b,11c] in alkylation.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 19*c* for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: s = singlet, sh = shoulder.

Methylation of N^6-Methoxyadenine (3)——A mixture of **3**[4] (4.08 g, 25 mmol) and MeI (17.8 g, 125 mmol) in $AcNMe_2$ (15 ml) was stirred at 40 °C for 7 h. The precipitate that resulted was filtered off, washed with EtOH, and dried to give N^6-methoxy-7,9-dimethyladeninium iodide (**6**) (2.17 g, 27%), mp 246—247 °C (dec.). Recrystallization of this sample from 90% (v/v) aqueous EtOH yielded colorless needles, mp 248—249 °C (dec.) [lit.[2] mp 250—251 °C (dec.)], identical [by comparison of paper partition chromatographic (PPC) behavior and infrared (IR) spectrum)] with an authentic sample.[2]

On the other hand, concentration of the filtrate obtained above under reduced pressure left a reddish-brown oil. The oil was dissolved in H_2O (30 ml), the resulting aqueous solution passed through a column of Amberlite IRA-402 (HCO_3^-) (50 ml), and the column eluted further with H_2O. The eluate (500 ml) was evaporated to dryness *in vacuo*, and the residue was chromatographed on alumina (400 g). Earlier fractions eluted with $CHCl_3$–EtOH (100 : 1, v/v) afforded N^6-methoxy-N^6,9-dimethyladenine (**5**) (420 mg, 9%), mp 94.5—95.5 °C, which was recrystallized from hexane to give colorless prisms, mp 95—96 °C (lit.[2] mp 95—96 °C), identical [by mixture melting point test and comparison of thin-layer chromatographic (TLC) behavior and IR spectrum] with an authentic sample.[2] Later fractions eluted with the same solvent system yielded N^6-methoxy-3,7-dimethyladenine (**7**) (489 mg, 10%), mp 196—202 °C, which was identical (by comparison of IR spectrum and TLC behavior) with an authentic sample.[2]

Fractions eluted with $CHCl_3$–EtOH (25 : 1, v/v) gave crude N^6-methoxy-N^6,3-dimethyladenine (**9**) (575 mg) and N^6-methoxy-9-methyladenine (**4**) (105 mg, 2%), mp 239—240 °C (dec.) [lit.[5] mp 239 °C (dec.)]; PPC behavior and IR, identical with those of authentic **4**.[5] Because of its hygroscopic nature, a portion (150 mg) of the crude **9** was converted into the perchlorate (**9**·$HClO_4$) (218 mg, 11% from **3**) [mp 229—230 °C (lit.[2] mp 229—230 °C); TLC behavior and IR, identical with those of an authentic sample[2]] by dissolving it in EtOH (1 ml) and adding a mixture

of 70% aqueous $HClO_4$ (200 mg) and EtOH (1 ml).

Finally, fractions eluted with $CHCl_3$–EtOH (20 : 1, v/v) furnished N^6-methoxy-3-methyladenine (**8**) (775 mg, 17%), mp 227—228 °C (dec.) [lit.[2] mp 229—230 °C (dec.)], identical (by comparison of PPC behavior and IR spectrum) with an authentic sample.[2]

Methylation of N^6-Benzyloxyadenine (12)——A stirred mixture of **12**·EtOH[4] (7.00 g, 24.4 mmol) and MeI (19.4 g, 137 mmol) in $AcNMe_2$ (233 ml) was kept at 30—32 °C for 18 h. The reaction mixture was concentrated *in vacuo* to leave a brown solid, which was triturated with EtOH (20 ml). The resulting insoluble solid was filtered off, washed with cold EtOH, and recrystallized from EtOH (200 ml) to produce N^6-benzyloxy-7,9-dimethyladeninium iodide (**13**: X = I) (2.94 g, 30%) as colorless needles, mp 230.5—231.5 °C (dec.) [lit.[7] mp 232.5—233.5 °C (dec.)]. *Anal.* Calcd for $C_{14}H_{16}IN_5O$: C, 42.33; H, 4.06; N, 17.63. Found: C, 42.64; H, 4.09; N, 17.39. This sample was identical [by comparison of IR, ultraviolet (UV), and nuclear magnetic resonance (NMR) spectra] with an authentic sample.[7] Although the ethanolic filtrate, which was obtained when the crude **13** (X = I) was isolated, seemed to contain several other products, no attempt was made to isolate them.

N^6-Benzyloxy-7,9-dimethyladeninium Perchlorate (13: X = ClO_4)——The iodide **13** (X = I) (500 mg, 1.26 mmol) was dissolved in H_2O (100 ml) with slight warming, and a solution of $AgClO_4$ (270 mg, 1.30 mmol) in H_2O (10 ml) was added. The yellowish precipitate (AgI) that resulted was removed by filtration, and the filtrate was evaporated to dryness *in vacuo* to leave a colorless solid (455 mg, 98%). Recrystallization of the solid from EtOH produced **13** (X = ClO_4) as colorless needles, mp 220.5—221.5 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 235 nm (ε 9100), 292 (8400). *Anal.* Calcd for $C_{14}H_{16}ClN_5O_5$: C, 45.48; H, 4.36; N, 18.94. Found: C, 45.69; H, 4.47; N, 19.09.

N^6-Benzyloxy-7,9-dimethyladenine (14)——The iodide **13** (X = I) (1.20 g, 3.02 mmol) was dissolved in H_2O (40 ml) with application of heat. On addition of saturated aqueous $NaHCO_3$ (20 ml), the solution deposited fine needles immediately. After cooling, the mixture was filtered, and the needles were washed with cold H_2O (50 ml) and dried to give the free base **14** (630 mg, 77%). For analysis, it was recrystallized from EtOH to colorless needles, mp 180.5—181.5 °C (dec.); UV $\lambda_{max}^{H_2O}$ (pH 1 and 7) 228 (sh) and 284 nm; $\lambda_{max}^{H_2O}$ (pH 13) unstable; NMR (Me_2SO-d_6) δ : 3.70 and 4.01 (3H each, s, two NMe's), 4.91 (2H, s, $PhC\underline{H}_2O$), 7.42 (5H, s, Ph), 7.62 (1H, s, $C_{(2)}$–H), 8.86 (1H, s, $C_{(8)}$–H). *Anal.* Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.53; H, 5.61; N, 26.14.

The Picrate of **14**: A portion (40 mg, 0.149 mmol) of **14** was dissolved in boiling EtOH (9 ml), and a saturated solution (3 ml) of picric acid in EtOH was added. The yellow needles that resulted were filtered off, washed with EtOH, and dried to give the picrate (68 mg, 92%), mp 255.5—256.5 °C (dec.). This sample was identical (by mixture melting point test and comparison of IR spectrum) with the picrate prepared in 98% yield directly from the iodide **13** (X = I) in a similar manner.

N^6-Methyladenine (17)——A mixture of 1-methyladenine (**16**)[8] (2.00 g, 13.4 mmol) and 0.2 N aqueous NaOH (50 ml) was heated at 95—100 °C for 4 h. After cooling, the reaction mixture was neutralized (pH 7) with 10% aqueous HCl, depositing a gelatinous precipitate. The mixture was heated to dissolve the precipitate and then kept in a refrigerator. The crystals that resulted were collected by filtration and recrystallized from H_2O (60 ml) to afford **17** (1.30 g, 65%) as colorless plates, mp 314—316 °C (dec.) [lit. mp 312—314 °C (dec.);[20] mp 308 °C;[21] mp 319—320 °C[11c]]; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 266 nm (ε 15800); $\lambda_{max}^{H_2O}$ (pH 1) 266 (14900); $\lambda_{max}^{H_2O}$ (pH 7) 266 (15800); $\lambda_{max}^{H_2O}$ (pH 13) 273 (15600). *Anal.* Calcd for $C_6H_7N_5$: C, 48.32; H, 4.73; N, 46.95. Found: C, 48.30; H, 4.79; N, 46.83.

Methylation of N^6-Methyladenine (17)——A mixture of **17** (1.00 g, 6.7 mmol) and MeI (2.85 g, 20 mmol) in $AcNMe_2$ (10 ml) was stirred at 38—42 °C for 6 h. The precipitate that resulted was filtered off, washed with EtOH, and dried to give N^6,3-dimethyladenine hydriodide (**18**·HI) (1.40 g, 72%), mp 239—240 °C (dec.). Recrystallization from EtOH furnished an analytical sample as colorless plates, mp 241—242 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 290 nm (ε 13600); $\lambda_{max}^{H_2O}$ (pH 1) 224 (22100), 282 (18800); $\lambda_{max}^{H_2O}$ (pH 7) 224 (24500), 285 (14700); $\lambda_{max}^{H_2O}$ (pH 13) 223.5 (25400), 286 (14300). *Anal.* Calcd for $C_7H_{10}IN_5$: C, 28.88; H, 3.46; N, 24.06. Found: C, 28.90; H, 3.46; N, 24.08.

On the other hand, the filtrate obtained after the removal of the crude **18**·HI was concentrated to dryness *in vacuo*. The residual solid was dissolved in H_2O (30 ml), the resulting aqueous solution passed through a column of Amberlite IRA-402 (HCO_3^-) (5 ml), and the column eluted further with H_2O. The eluate (100 ml) was evaporated *in vacuo* to leave a solid. Recrystallization of the solid from H_2O (2 ml) yielded N^6,3-dimethyladenine (**18**) (80 mg, 7.3%), mp > 300 °C, as a second crop. The aqueous mother liquor of this recrystallization was then concentrated to dryness *in vacuo*, and the resulting residue was chromatographed on a column packed with alumina (40 g). Earlier fractions eluted with $CHCl_3$–EtOH (100 : 1, v/v) gave a mixture of two compounds, which were separated by preparative TLC [alumina, $CHCl_3$–EtOH (100 : 1, v/v] to yield crude N^6,9-dimethyladenine (**20**) and N^6,1,9-trimethyladenine (**21**). Recrystallization of the crude **20** from benzene furnished colorless prisms (14 mg, 1.3%), mp 182—183 °C (lit. mp 185—186 °C;[11a] mp 190—191 °C[11b]), identical with an authentic sample.[11a] Treatment of the crude **21** with 70% aqueous $HClO_4$ in a manner similar to that described above for **9**·$HClO_4$ afforded **21**·$HClO_4$ (5 mg, 0.3% from **17**) as colorless prisms, mp 209—210 °C (lit.[12] mp 208—209 °C), identical with an authentic sample.[12]

Later fractions eluted with the same solvent system in the above column chromatography yielded an additional amount (27 mg, 2.5%) of **18** as colorless needles, mp > 300 °C, which were identical with an authentic sample.[2]

Further elution of the alumina column with $CHCl_3$–EtOH (20 : 1, v/v) gave crude N^6,3,7-trimethyladenine (**19**), which produced, on treatment with 70% aqueous $HClO_4$ in the usual manner, the known perchlorate (**19**·$HClO_4$)[12]

(33 mg, 1.8% from **17**) as colorless prisms, mp 195—196 °C (lit.[12] mp 191—193 °C).

N^6,3-Dimethyladenine (18)——A portion (291 mg, 1 mmol) of the hydriodide **18**·HI, derived from the above methylation of **17**, was dissolved in hot H_2O (1 ml). The resulting solution was made alkaline (pH 9) with conc. aqueous NH_3 and then cooled. The crystals that resulted were filtered off, washed with cold H_2O (1 ml), and dried to provide the free base **18** (156 mg, 96%), mp >300 °C. Recrystallization from H_2O yielded an analytical sample as colorless needles, mp >300 °C [lit. mp >300 °C;[2] mp 314—315 °C (dec.)[10]]; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 291 nm (ε 13600); $\lambda_{max}^{H_2O}$ (pH 1) 282 (18600); $\lambda_{max}^{H_2O}$ (pH 7) 285 (14500); $\lambda_{max}^{H_2O}$ (pH 13) 286 (14100). *Anal.* Calcd for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.53; H, 5.52; N, 42.97. This sample was identical with that prepared[2] by hydrogenolysis of **9**.

Methylation of N^6,3-Dimethyladenine (18)——A mixture of **18** (326 mg, 2 mmol) and MeI (850 mg, 6 mmol) in $AcNMe_2$ (3 ml) was stirred at 38—40 °C for 6 h. The precipitate (483 mg) that resulted was filtered off, washed with EtOH (3 ml), and dissolved in boiling EtOH (90 ml), and the resulting ethanolic solution was then kept at room temperature. The crystals that deposited were filtered off, washed with EtOH, and dried to afford N^6,3,9-trimethyladenine hydriodide (**22**) (90 mg, 15%) as colorless minute prisms, mp 258—259 °C (dec.). Further recrystallization from EtOH gave a pure sample, mp 262—263 °C (dec.) (lit.[12] mp 261—262 °C); IR, identical with that of a sample obtained by methylation of **20** (*vide infra*).

On the other hand, the ethanolic filtrate obtained after the removal of **22** was concentrated to dryness *in vacuo* to leave a solid. Purification of the residue by column chromatography [alumina (30 g), $CHCl_3$–EtOH (10 : 1, v/v)] gave a colorless solid (135 mg), which yielded, after treatment with 70% aqueous $HClO_4$ (130 mg) in EtOH (3 ml), N^6, 3,7-trimethyladenine perchlorate (**19**·$HClO_4$) (159 mg, 29% from **18**) as colorless prisms, mp 193—194 °C. Recrystallization from EtOH furnished an analytical sample, mp 195—196 °C (lit.[12] mp 191—193 °C); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 286 nm (ε 18500); $\lambda_{max}^{H_2O}$ (pH 1 and 7) 284 (18500) [lit.[12] $\lambda_{max}^{H_2O}$ for **19**·HI: 284—286 nm (log ε 4.25)]; $\lambda_{max}^{H_2O}$ (pH 13) 285 (10900). *Anal.* Calcd for $C_8H_{12}ClN_5O_4$: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.53; H, 4.39; N, 25.35.

Methylation of N^6,9-Dimethyladenine (20)——A mixture of **20**[11a] (326 mg, 2 mmol) and MeI (850 mg, 6 mmol) in $AcNMe_2$ (3 ml) was stirred at 40 °C for 6 h. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give a colorless solid (241 mg). Recrystallization of the solid from EtOH (70 ml) afforded N^6,3,9-trimethyladenine hydriodide (**22**) (104 mg, 17%) as colorless minute prisms, mp 261—262 °C (dec.). Further recrystallization from EtOH gave an analytical sample, mp 262—263 °C (dec.) (lit.[12] mp 261—262 °C); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 282 nm (ε 15300); $\lambda_{max}^{H_2O}$ (pH 1) 221 (23300), 281 (15900); $\lambda_{max}^{H_2O}$ (pH 7) 221 (23100), 280 (15800) [lit.[12] $\lambda_{max}^{H_2O}$ 280—282 (log ε 4.16)]; $\lambda_{max}^{H_2O}$ (pH 13) unstable. *Anal.* Calcd for $C_8H_{12}IN_5$: C, 31.49; H, 3.96; N, 22.95. Found: C, 31.69; H, 3.91; N, 22.90.

On the other hand, the ethanolic mother liquor of the first recrystallization of the crude product was concentrated to dryness *in vacuo*. The residual solid was dissolved in 10% aqueous NH_3 (2.5 ml), and the resulting solution was extracted with five 5-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with saturated aqueous NaCl (3 ml), dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to leave a colorless solid (41 mg). Treatment of the solid with 70% aqueous $HClO_4$ (40 mg) in EtOH (0.8 ml) produced N^6,1,9-trimethyladenine perchlorate (**21**·$HClO_4$) (59 mg, 11% from **20**), mp 209—210 °C. For analysis, this product was recrystallized from EtOH to yield colorless prisms, mp 209—210 °C (lit.[12] mp 208—209 °C); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 263 nm (ε 13500); $\lambda_{max}^{H_2O}$ (pH 1 and 7) 263 (13700) [lit.[12] $\lambda_{max}^{H_2O}$ for **21**·HI: 262—264 nm (log ε 4.10)]; $\lambda_{max}^{H_2O}$ (pH 13) 263 (14900), 270 (sh) (12800), 295 (sh) (3400). *Anal.* Calcd for $C_8H_{12}ClN_5O_4$: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.54; H, 4.39; N, 25.17.

References and Notes

1) Part XXIII: T. Fujii, T. Saito, and T. Nakasaka, *Chem. Pharm. Bull.*, **31**, 3521 (1983).
2) T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, *Chem. Pharm. Bull.*, **31**, 3149 (1983).
3) Presented in part at the 2nd Symposium on Nucleic Acids Chemistry, Tokyo, Japan, October 25—26, 1974.
4) T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.*, **19**, 1731 (1971).
5) T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971).
6) By analogy with N^6-methoxy-7,9-dimethyladeninium iodide (**6**),[2] the 6-imino-1*H*-purine structure (**13**) is adopted here.
7) T. Fujii, T. Saito, T. Sakuma, M. Minami, and I. Inoue, *Heterocycles*, **16**, 215 (1981).
8) *a*) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963); *b*) N. J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U.S.A.*, **51**, 73 (1964).
9) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, **1960**, 539.
10) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 1914 (1962).
11) *a*) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 535 (1972); *b*) R. K. Robins and H. H. Lin, *J. Am. Chem. Soc.*, **79**, 490 (1957); *c*) A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, **3**, 494 (1964).
12) A. V. El'tsov, Kh. L. Muravich-Aleksandr, and I. Él'-Sakka, *Zh. Org. Khim.*, **9**, 1280 (1973) [*Chem. Abstr.*, **79**, 105193*z* (1973)].
13) *a*) B. C. Pal, *Biochemistry*, **1**, 558 (1962); *b*) N. J. Leonard and T. Fujii, *J. Am. Chem. Soc.*, **85**, 3719 (1963); *c*) J.

A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964); *d*) C. J. Abshire and L. Berlinguet, *Can. J. Chem.*, **42**, 1599 (1964); *e*) H. J. Schaeffer and R. Vince, *J. Med. Chem.*, **8**, 710 (1965); *f*) J. A. Montgomery and H. J. Thomas, *J. Am. Chem. Soc.*, **85**, 2672 (1963); *g*) M. Asai, M. Miyaki, and B. Shimizu, *Agric. Biol. Chem.*, **29**, 170 (1965); *h*) N. J. Leonard and R. A. Laursen, *Biochemistry*, **4**, 354 (1965).
14) N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, **2**, 291 (1965).
15) B. C. Pal and C. A. Horton, *J. Chem. Soc.*, **1964**, 400.
16) T. Itaya, H. Matsumoto, and K. Ogawa, *Chem. Pharm. Bull.*, **28**, 1920 (1980), and references cited therein.
17) B. Shimizu and M. Miyaki, *Chem. Pharm. Bull.*, **18**, 570 (1970).
18) See also footnote 1 in T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.*, **13**, 1017 (1965).
19) *a*) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971); *b*) T. Fujii, S. Kawakatsu, and T. Itaya, *Chem. Pharm. Bull.*, **22**, 2466 (1974); *c*) T. Fujii, I. Inoue, T. Itaya, and T. Saito, *ibid.*, **28**, 3443 (1980).
20) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).
21) F. S. Okumura, N. Enishi, H. Itoh, M. Masumura, and S. Kuraishi, *Bull. Chem. Soc. Jpn.*, **32**, 886 (1959).