THE CHEMISTRY OF N^x, N^y, N^z-TRIMETHYLADENINES AND MORE HIGHLY *N*-METHYLATED ADENINES

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Abstract — Various tri- and poly-*N*-substituted adenines are represented by the corresponding positional isomers of N^x, N^y, N^z-trimethyladenine and of more highly *N*-methylated adenines. The chemistry of known isomers of these tri- and poly-*N*-methylated adenines is reviewed with 120 reference citations.

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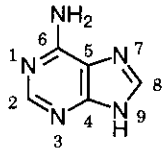
I. INTRODUCTION

Having a 4-aminopyrimidine ring and an imidazole ring in juxtaposition, the chemical structure of the important fundamental biomolecule adenine (**1**) ($C_5H_5N_5$) is characterized primarily by the high nitrogen content (51.83%): one exocyclic and four endocyclic nitrogen atoms at the N^6, 1-, 3-, 7-, and 9-positions. This permits five kinds of mono-*N*-substitution pattern, 11 kinds of di-*N*-substitution pattern, 15 kinds of tri-*N*-substitution pattern, 15 kinds of tetra-*N*-substitution pattern, 11 kinds of penta-*N*-substitution pattern, five kinds of hexa-*N*-substitution pattern, and one kind of hepta-*N*-substitution pattern for **1** in principle. Indeed, all kinds of the mono- and di-*N*-substitution patterns (with the exception that genuine 1,3-disubstituted adenines still remain unknown), most of the tri-*N*-substitution patterns, and several of the tetra-*N*-substitution patterns have been shown to occur in nature as well as by chemical



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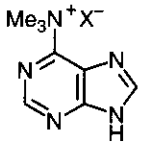

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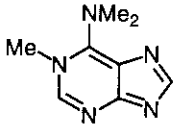

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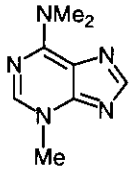

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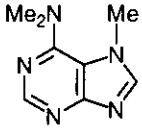

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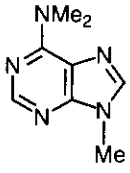

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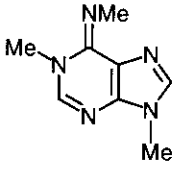

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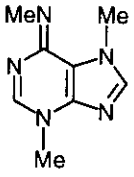

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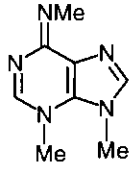

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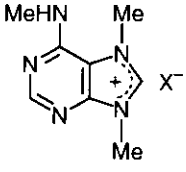

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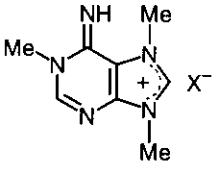

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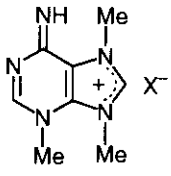

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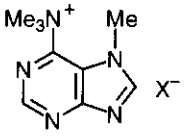

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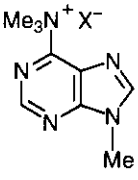

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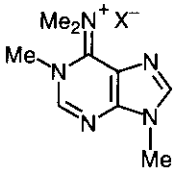

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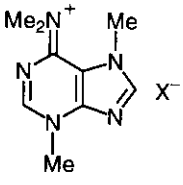

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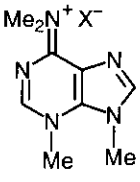

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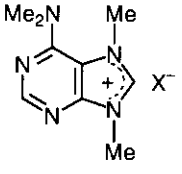

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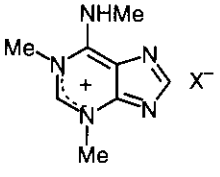

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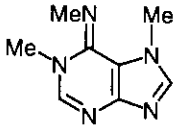

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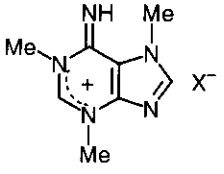

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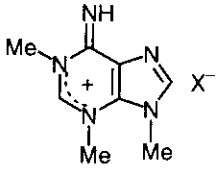

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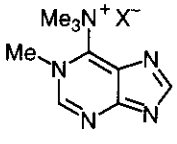

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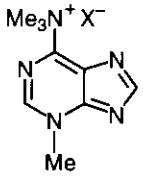

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synthesis.[1–7]

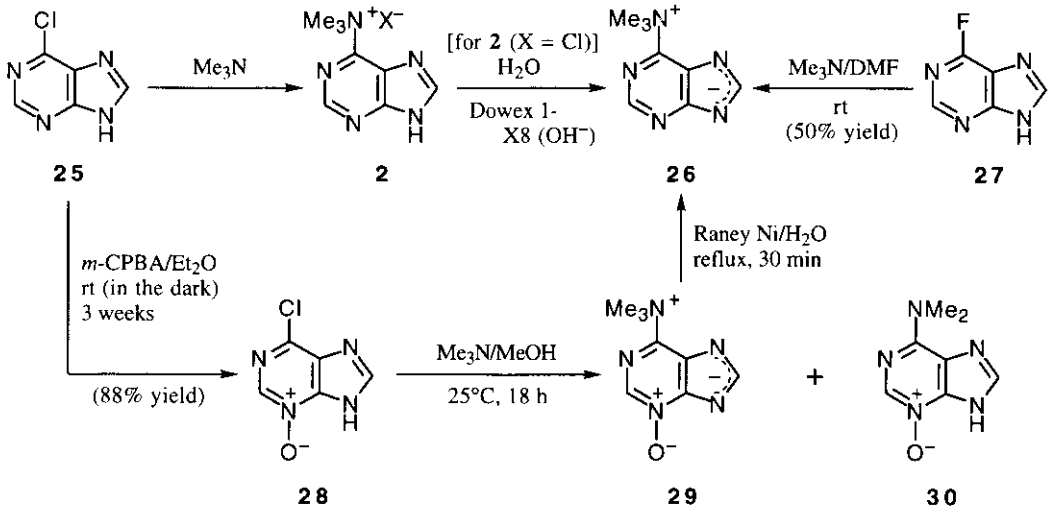
Recent review articles by us have treated the chemistry, physicochemical properties, and biological activities of the five positional isomers of N^x-methyladenine, the prototypes of mono-*N*-substituted adenines;[6] and of the 11 positional isomers of N^x,N^y-dimethyladenine, the prototypes of di-*N*-substituted adenines.[7] Although not all the possible positional isomers of N^x,N^y,N^z-trimethyladenine and of more highly *N*-methylated adenines (up to heptamethyladenine) have been known, it is the intention of the present review to treat available data for the known positional isomers in much the same sense as before[6,7] in order to supplement previous ones[1–3] by reorganizing and updating the literature through mid-1998. The positional isomers covered are N^6,N^6,N^6-trimethyladenine (**2**),[8] N^6,N^6,1-trimethyladenine (**3**), N^6,N^6,3-trimethyladenine (**4**), N^6,N^6,7-trimethyladenine (**5**), N^6,N^6,9-trimethyladenine (**6**), N^6,1,9-trimethyladenine (**7**), N^6,3,7-trimethyladenine (**8**), N^6,3,9-trimethyladenine (**9**), N^6,7,9-trimethyladenine (**10**),[8] 1,7,9-trimethyladenine (**11**)[8] (known as the N^6-methoxy derivative), 3,7,9-trimethyladenine (**12**)[8] (known as the 8-oxo derivative), N^6,N^6,N^6,7-tetramethyladenine (**13**)[8] (known as the 2-chloro derivative), N^6,N^6,N^6,9-tetramethyladenine (**14**),[8] N^6,N^6,1,9-tetramethyladenine (**15**),[8] N^6,N^6,3,7-tetramethyladenine (**16**),[8] N^6,N^6,3,9-tetramethyladenine (**17**),[8] and N^6,N^6,7,9-tetramethyladenine (**18**).[8]

To our certain knowledge, the remaining four isomers of N^x,N^y,N^z-trimethyladenine [*i. e.*, N^6,1,3-trimethyladenine (**19**),[8] N^6,1,7-trimethyladenine (**20**), 1,3,7-trimethyladenine (**21**),[8] and 1,3,9-trimethyladenine (**22**)[8]], the remaining nine isomers of tetra-*N*-methyladenine [*i. e.*, N^6,N^6,N^6,1- (**23**),[8] N^6,N^6,N^6,3- (**24**),[8] N^6,N^6,1,3-, N^6,N^6,1,7-, N^6,1,3,7-, N^6,1,3,9-, N^6,1,7,9-, N^6,3,7,9-, and 1,3,7,9-tetramethyladenines], all the 11 isomers of penta-*N*-methyladenine (*i. e.*, N^6,N^6,N^6,1,3-, N^6,N^6,N^6,1,7-, N^6,N^6,N^6,1,9-, N^6,N^6,3,7-, N^6,N^6,N^6,3,9-, N^6,N^6,N^6,7,9-, N^6,N^6,1,3,7-, N^6,N^6,1,3,9-, N^6,N^6,1,7,9-, N^6,3,7,9-, and N^6,1,3,7,9-pentamethyladenines), all the five isomers of hexa-*N*-methyladenine (*i. e.*, N^6,N^6,N^6,1,3,7-, N^6,N^6,N^6,1,3,9-, N^6,N^6,N^6,1,7,9-, N^6,N^6,N^6,3,7,9-, and N^6,N^6,1,3,7,9-hexamethyladenines), and N^6,N^6,N^6,1,3,7,9-heptamethyladenine have so far been unknown.

II. N^6,N^6,N^6-TRIMETHYLADENINE

N^6,N^6,N^6-Trimethyladenine has been synthesized in the salt form [trimethylpurin-6-ylammonium salt (**2**)] or in the zwitterionic (betaine) form [6-trimethylammoniopurinide (**26**); *N,N,N*-trimethyl-1*H*-purin-6-aminium inner salt (in *Chemical Abstracts*)]. Horwitz and Vaitkevicius[9] allowed Me_3N to bubble into a solution of 6-chloropurine (**25**) in DMF at 0°C and kept the resulting solution at room temperature overnight to obtain **2** (X = Cl) in 80% yield (Scheme 1). Reist *et al.*[10] secured **2** (X = Cl) in 83% yield from **25** by treatment with anhydrous Me_3N in a stainless steel bomb at room temperature for 2.5 h. They found that recrystallization of crude **2** (X = Cl) from MeOH gave a crys-

talline 1:1 mixture of **2** (X = Cl) and **2** (X = MeO).[10] Kiburis and Lister[11] prepared **2** (X = Cl) in 70% yield from **25** by treating the latter with Me_3N in a mixture of diglyme [bis(2-methoxyethyl) ether] and DMF at room temperature for *ca.* 2 h. Kießling *et al.*[12] obtained **2** (X = Cl) or **2** (X = Br) in over 80% yield from **25** or 6-bromopurine, respectively, by treatment with Me_3N in DMF or in $AcNMe_2$ at room temperature for several hours. Treatment of **2** (X = Cl) in H_2O with Dowex 1-X8 (OH^-) was reported to produce the zwitterion (**26**),[13] which was also obtainable in 50% yield directly from 6-fluoropurine (**27**) by reaction with Me_3N in DMF at room temperature for some hours (Scheme 1).[11] Giner-Sorolla[14] reported that treatment of 6-chloropurine 3-oxide (**28**),[15] prepared from **25** in 88% yield by *m*-CPBA oxidation (Scheme 1), with 25% methanolic Me_3N at 25°C for 18 h afforded 6-trimethylammoniopurinide 3-oxide (**29**) and N^6,N^6-dimethyladenine 3-oxide (**30**) in 61% and 12% yields, respectively, and that deoxygenation of **29** with Raney Ni in boiling H_2O for 30 min gave **26**, as identified by means of UV spectral and chromatographic analysis.

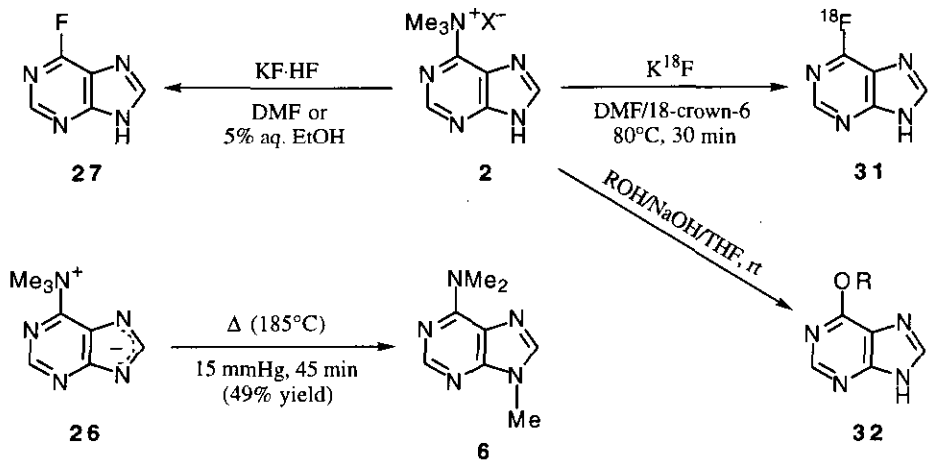


Scheme 1

The following may serve to locate papers reporting the physical properties and spectral characteristics of the salt form (**2**) and the betaine form (**26**) of N^6,N^6,N^6-trimethyladenine: the melting point for **2** (X = Cl), mp 191–193°C (decomp),[11] 191–192°C,[13a] 189–191°C (decomp),[9c] 187–189°C,[16a] 179–180°C,[9a,12] 179–180°C (decomp),[9b] or 175–180°C (decomp);[10] for a 1:1 mixture of **2** (X = Cl) and **2** (X = MeO), mp 165–232°C;[10] for **2** (X = Br), mp 181°C;[12] for **26**, mp 194°C[11] or 190–192°C;[13a,b] for **26**·picrate, mp (not particularly specified);[13a] pK_a for **2** (X = Cl), 6.85[16a] or 6.8[13a,17] or 6.46;[18] lipophilicity for **2** (X = Cl);[17] paper chromatography for **2** (X = Cl) and for a 1:1 mixture of **2** (X = Cl) and **2** (X = MeO);[10] TLC for **2** (X = Cl) and for **2** (X = Br);[12] column chromatography for **26**;[19] MS for **2** (X = Cl) and for **2** (X = Br);[12] liquid secondary-ion MS for **2** (X = Cl);[20] UV for **2** (X =

Cl) in H_2O at various pH's,[9c,10,12,16a,17] for a 1:1 mixture of **2** (X = Cl) and **2** (X = MeO) in H_2O at various pH's,[10] for **2** (X = Br),[12] and for **26** in H_2O at various pH's;[11,13a] IR for **2** (X = Cl),[11,12] for **2** (X = Br),[12] and for **26**;[11] ^{1}H NMR for **2** (X = Cl) in D_2O[11,16a] and in DMSO,[21] for a 1:1 mixture of **2** (X = Cl) and **2** (X = MeO) in D_2O,[10] and for **26** in D_2O[13a] and in TFA;[11] ^{13}C NMR for **2** (X = Cl) in DMSO-d_6.[22]

As regards the chemical behavior of **2** and **26**, Kiburis and Lister[11] reported that treatment of **2** (X = Cl) with potassium hydrogen fluoride in 5% aqueous EtOH at 60°C for 3 h or in DMF at 80°C for 2 h furnished 6-fluoropurine (**27**) in 27% or 35% yield, respectively (Scheme 2), and that **27** was convertible into adenine (**1**) (in boiling aqueous NH_3 for 1 h or in ethanolic NH_3 at room temperature for 10 d) and into hypoxanthine (in boiling H_2O for 1 h or in 0.1 N aqueous HCl at room temperature for 30 min). Irie *et al.*[23] prepared ^{18}F-labeled 6-fluoropurine (**31**) from **2** (X = Cl) in 37.7% radiochemical yield by treatment with anhydrous K^{18}F in DMF containing 18-crown-6 at 80°C for 30 min. Barlin and Young[16a] reported the reaction of **2** (X = Cl) with hot aqueous NaOH (7×10^{-2} N) for 5 min to produce hypoxanthine, as identified by means of paper chromatography, together with its kinetic results. They also reported that heating **2** (X = Cl) with 0.1 M methanolic MeONa at 50°C for 10 min gave 6-methoxypurine (**32**: R = Me) in 91% yield.[16b] Burns' group[24] synthesized eight 6-alkoxypurines [**32**: R = CH_2FCH_2, CF_3CH_2, allyl, (±)-$MeCH_2CH(Me)$, $MeCH{=}CHCH_2$, (±)-$Me(CH_2)_2CH(Me)$, Et_2CH, and $Me(CH_2)_5$] from **2** (X = Cl) by treating with appropriate alcohols and NaOH in THF at room temperature. The use of **2** (X = Cl) as a reactant for similar modification of the 6-substituent was also reported.[25]



Scheme 2

Sublimation of **26** at 185°C and 15 mmHg for 45 min was found to produce N^6,N^6,9-trimethyladenine (**6**) in 49% yield (Scheme 2).[26] Heating **26** in the presence of 2,8-dichloro-N^6,N^6-dimethyladenine was reported to give a product containing **6** and a certain

amount of 2,8-dichloro-N^6,N^6,9-trimethyladenine (**44**), suggesting that migration of a Me group in **26** proceeds inter- rather than intramolecularly.[26] Vieira and Steenken[18] have reported the results of reaction of **2** (X = Cl) with the OH radical in H_2O at pH 6–8 and 20°C. The interactions between lima bean lectin and adenine (**1**) were examined by using a series of synthetic purine analogues including **2** (with unspecified anion, X^-), and progressive methylation of the C(6)-NH_2 group was found to give decreasing binding affinity in the order NH_2 > NHMe > NMe_2 > N^+Me_3.[27]

There have been *ca.* 10 papers dealing with the biological activities of **2** (X = Cl). Merker[28] reported that it was a moderate but transient hypotensive agent in the anesthetized dog and cat. No biological activity with respect to starfish oocyte maturation was found for **2** (X = Cl) by Monsees *et al.*[17] It had some effect against Ehrlich ascites tumor, transplantable epidermoid carcinoma DC-5, and adenocarcinoma 755 in mice.[9] In humans, objective tumor regressions were also observed with this agent.[9c] It had no effect against transplantable sarcoma 180 or leukemia 1210.[9a,b] It (**2** with unspecified anion, X^-) was among a number of 6-mono- and 2,6-disubstituted purines used for prediction of activity against adenocarcinoma CA755 in mice on the basis of quantitative structure–activity relationships of purines.[29,30] Sidwell *et al.*[31] reported that **2** (X = Cl) had moderate or questionable anticytomegalovirus activity *in vitro*. The specificity of rabbit liver aldehyde oxidase (EC 1.2.3.1) toward purine and its derivatives was quantitatively studied, and **2** (with unspecified anion, X^-) was found to have low substrate efficiency.[32] Inhibition of the following enzymes by **2** (X^- = Cl^- or unspecified anion) has been reported: cyclin-dependent kinases from a variety of sources;[33] xanthine oxidase;[34] adenine phosphoribosyltransferase from Ehrlich ascites tumor cells.[35]

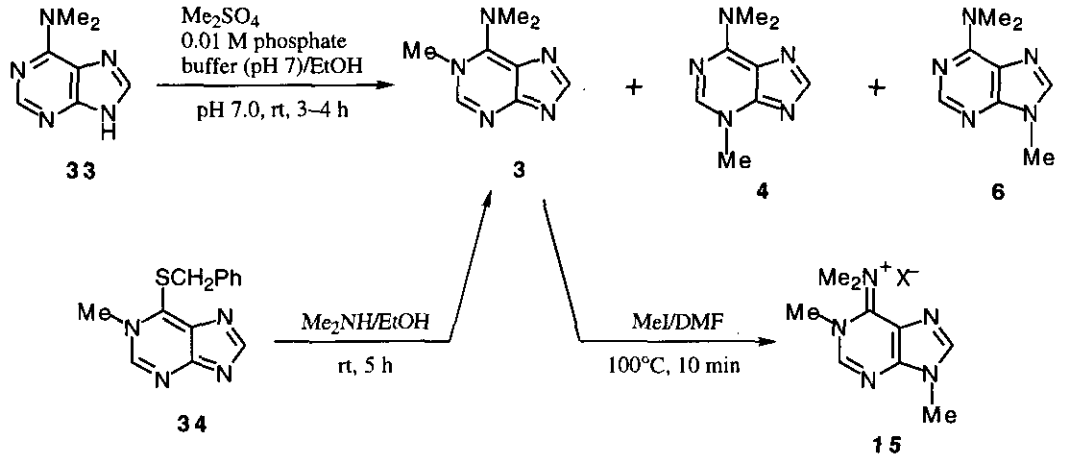
The nonbiological, technical, or engineered material uses of **26** as a chelating agent in the recovery of trace metals such as Co,[13b] of **2** (X = Cl) for preparation of jet-printing sheets,[36] and of **2** (X = Cl) as a transparentizing agent for electrophotographic migration imaging members[37] have been applied for patents.

III. N^6,N^6,1-TRIMETHYLADENINE

In 1964, Pal and Horton[38] reported that methylation of N^6,N^6-dimethyladenine (**33**) with dimethyl sulfate in a 4:1 mixture of 0.01 M phosphate buffer (pH 7.0) and EtOH at pH 7.0 and room temperature for 3–4 h gave N^6,N^6,1-trimethyladenine (**3**) (22.9% yield), N^6,N^6,3-trimethyladenine (**4**) (66%), and N^6,N^6,9-trimethyladenine (**6**) (8.3%), as shown in Scheme 3. Although they were able to obtain a crystalline picrate from **3**, the structure of **3** was inferred only by its sensitivity toward alkali. Townsend *et al.*[39] synthesized **3** unambiguously by treatment of 6-benzylthio-1-methylpurine (**34**) with ethanolic Me_2NH.

Methylation of **3** with MeI in DMF in a closed vessel at 100°C for 10 min was reported to yield N^6,N^6,1,9-tetramethyladeninium iodide (**15**: X = I).[40]

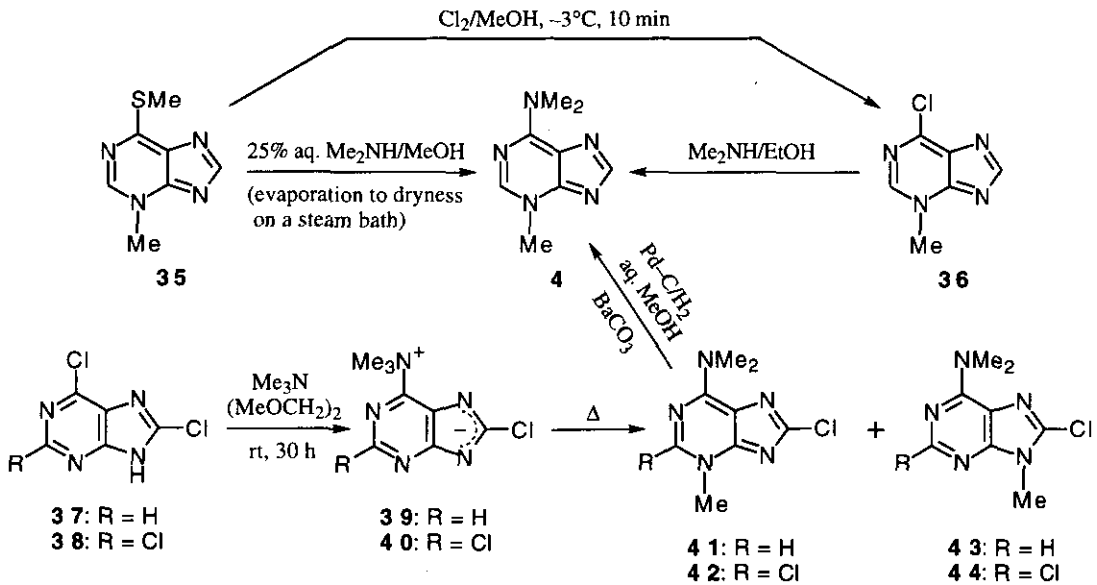
The following physical properties and spectral characteristics of N^6,N^6,1-trimethyladenine (**3**) have been reported in the literature: the melting point for the free base (**3**), mp 199–200°C;[39] for the picrate, mp 219°C;[38] paper chromatography;[39] MS;[41], UV in H_2O at various pH's;[39,42] ^1H NMR in DMSO-d_6.[39]



Scheme 3

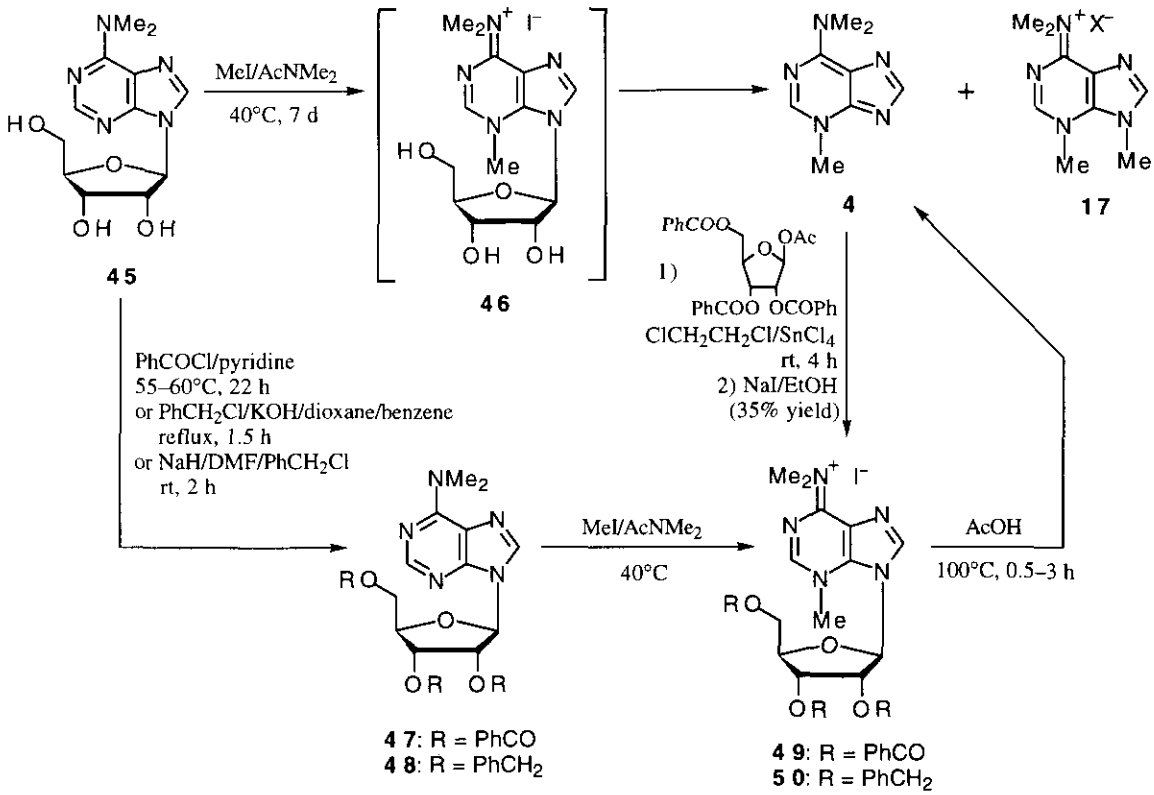
IV. N^6,N^6,3-TRIMETHYLADENINE

As described above in Section III (Scheme 3), N^6,N^6,3-trimethyladenine (**4**) was the main product from the direct methylation of N^6,N^6-dimethyladenine (**33**) with dimethyl sulfate at pH 7.0.[38] An unequivocal route to **4** was developed by Townsend *et al.*,[39] who allowed 3-methyl-6-methylthiopurine (**35**) to react with 25% aqueous Me_2NH in MeOH



Scheme 4

(Scheme 4). Bergmann *et al.*[43] prepared **4** by similar treatment of 6-chloro-3-methylpurine (**36**), which was obtainable from **35** by reaction of chlorine in cold MeOH. Separate aminations of 6,8-dichloropurine (**37**) and 2,6,8-trichloropurine (**38**) with Me_3N in 1,2-dimethoxyethane at room temperature for 30 h were reported to produce the corresponding 6-trimethylammoniopurinides (**39** and **40**) in 58% and 85% yields, respectively.[26] Sublimation of **39** at 185°C and 15 mmHg for 10 min gave the N^6,N^6,3-trimethyl isomer (**41**) (38% yield) and the N^6,N^6,9-trimethyl isomer (**43**) (38%).[26] Similar thermal isomerization (at 205°C and 15 mmHg for 45 min) of **40** afforded 2,8-dichloro-N^6,N^6,3-trimethyladenine (**42**) (12% yield) and 2,8-dichloro-N^6,N^6,9-trimethyladenine (**44**) (53%).[26] In addition, treatment of either 8-chloro-N^6,N^6-dimethyladenine or 2,8-dichloro-N^6,N^6-dimethyladenine with dimethyl sulfate in aqueous alkali was reported to give a mixture of the corresponding 3-methyl (**41** or **42**) and 9-methyl (**43** or **44**) derivatives in each case.[26] Catalytic hydrogenolysis of either **41** or **42** in aqueous MeOH containing $BaCO_3$ over 5% Pd–C catalyst yielded **4**, which was found to sublime unchanged.[26]



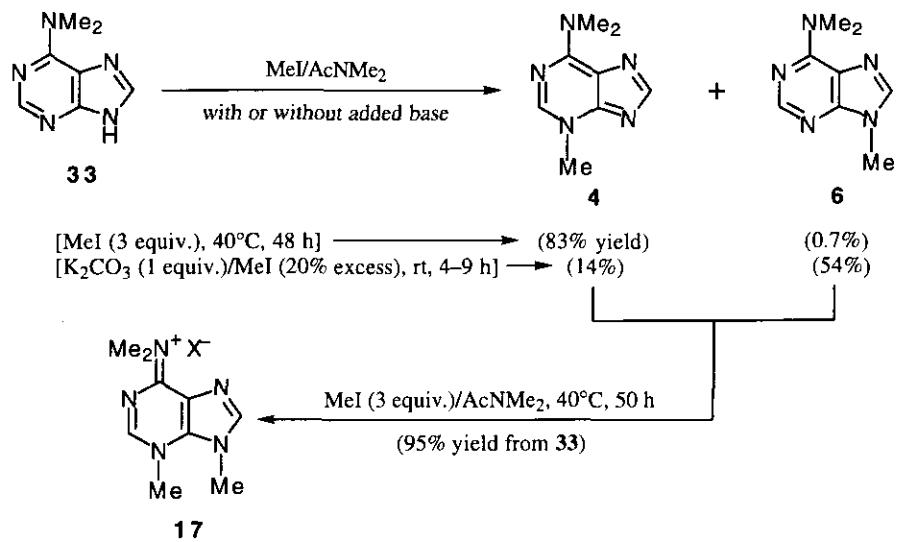
Scheme 5

In an alternative synthesis of **4** (Scheme 5), Itaya *et al.*[44] methylated N^6,N^6-dimethyladenosine (**45**) with MeI in $AcNMe_2$ at 40°C for 7 d and were able to isolate **4** (29% yield) and N^6,N^6,3,9-tetramethyladeninium iodide (**17**: X = I) (6%) from the reaction mixture.

They assumed that **4** had resulted from glycosidic bond cleavage of the primary product (**46**) by nucleophilic attack of I^- at the 1'-position; and **17** (X = I), from subsequent methylation of **4**. Thus, they converted **45** into the tri-*O*-benzoyl derivative (**47**) by treatment with benzoyl chloride and pyridine or into the tri-*O*-benzyl derivative (**48**) by treatment with benzyl chloride [KOH/dioxane/benzene (91% yield) or NaH/DMF (89% yield)] and methylated either **47** or **48** with MeI in $AcNMe_2$ at 40°C for 240 h or 144 h, respectively, to obtain the corresponding 3-methyl derivative [**49** (83% overall yield from **45**) or **50** (81% yield from **48**)].[44] Deglycosylation of **49** or **50** was then effected in AcOH at 100°C for 3 h or 30 min, giving **4** (as the picrate) in 37% or 90% yield, respectively.[44b] The free base (**4**) was obtained in 89% yield from **50** by treating the latter with boiling AcOH for 30 min.[44b] Later on, Monsees *et al.*[17] reported that methylation of **45** with MeI in $AcNMe_2$ at 65°C for 24 h afforded **4** in 9.5% yield.

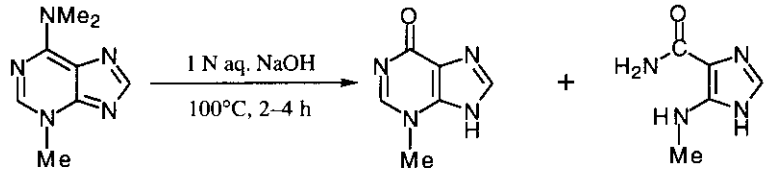
In yet another synthesis of **4**, Itaya *et al.*[45] methylated **33** with MeI in $AcNMe_2$ in the absence of added base at 40°C for 48 h to obtain a 10:1 mixture of the 3- and 9-methyl derivatives, from which **4** (83% yield) and **6** (0.7%) were isolated by chromatographic separation (Scheme 6). On the other hand, treatment of **33** with K_2CO_3 in boiling $AcNMe_2$ for 10 min and subsequent methylation with MeI (20% excess) in $AcNMe_2$ at room temperature for 4–9 h afforded a 2:7 mixture of **4** and **6**, and chromatographic purification of the mixture furnished **4** (14% yield) and **6** (54%).[45]

Muravich-Aleksandr *et al.*[40] reported that methylation of **4** with MeI in DMF in a closed vessel at 100°C for 10 min or at 20–25°C for 3–5 h gave **17** (X = I) in 96% or 77.5% yield, respectively (see Section XVII and Scheme 26), and Itaya *et al.*[46] methylated a 2:7 mixture of **4** and **6**, derived from the above methylation of **33** in the presence of K_2CO_3, with MeI in $AcNMe_2$ at 40°C for 50 h to obtain **17** (X = I) in 95% overall yield from **33** (Scheme 6).



Scheme 6

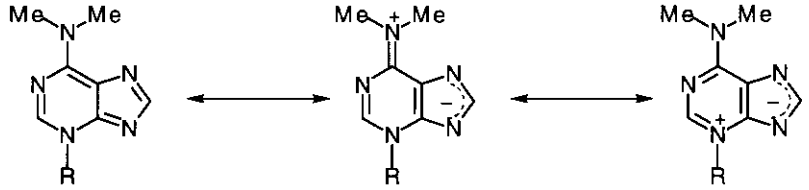
Condensation of **4** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane containing $SnCl_4$ at room temperature for 4 h, followed by treatment of the crude product with NaI in EtOH, was reported to give the 9-ribosyl derivative (**49**) in 35% yield (Scheme 5).[47] Pal and Horton[38] reported that Pauly test on **4** was negative and that treatment of **4** with 1 N aqueous NaOH at 100°C for 2–4 h produced 3-methylhypoxanthine (**51**) and 5-methylaminoimidazole-4-carboxamide (**52**) (Scheme 7), as identified by means of paper chromatography and UV spectral analysis.



4 **51** **52**

Scheme 7

The following physicochemical properties of N^6,N^6,3-trimethyladenine (**4**) have been recorded in the literature: the melting point for the free base (**4**), mp 173–174°C,[45] 172–173°C,[44b] 169–170°C,[38] or 167–168°C;[39] for **4**·picrate, mp 196–197°C (with sintering at 189°C)[44b] or 190°C;[38,43] pK_a 5.8;[17,38] lipophilicity;[17] paper chromatography;[39] MS;[17,41] UV in H_2O at various pH's,[17,38,39,45,48] in 95% aqueous EtOH,[45] or in EtOH;[49] IR (KBr);[38] ^{1}H NMR in $CDCl_3$,[45,50,51] in DMSO-d_6[17,39,52] (long-range spin–spin coupling of 0.4 Hz over four bonds between the N(3)-Me and the adjacent ring C-H protons[52]), in TFA,[40,51] or in D_2O/D_2SO_4;[52] dipole moment, 4.20 ± 0.03 D (determined in benzene at 30.0 ± 0.1°C);[49] electrocapillary curve (in 0.1 M Na_2SO_4 and in 0.1 N H_2SO_4);[53] activation parameters.[51]



53 **54** **55**

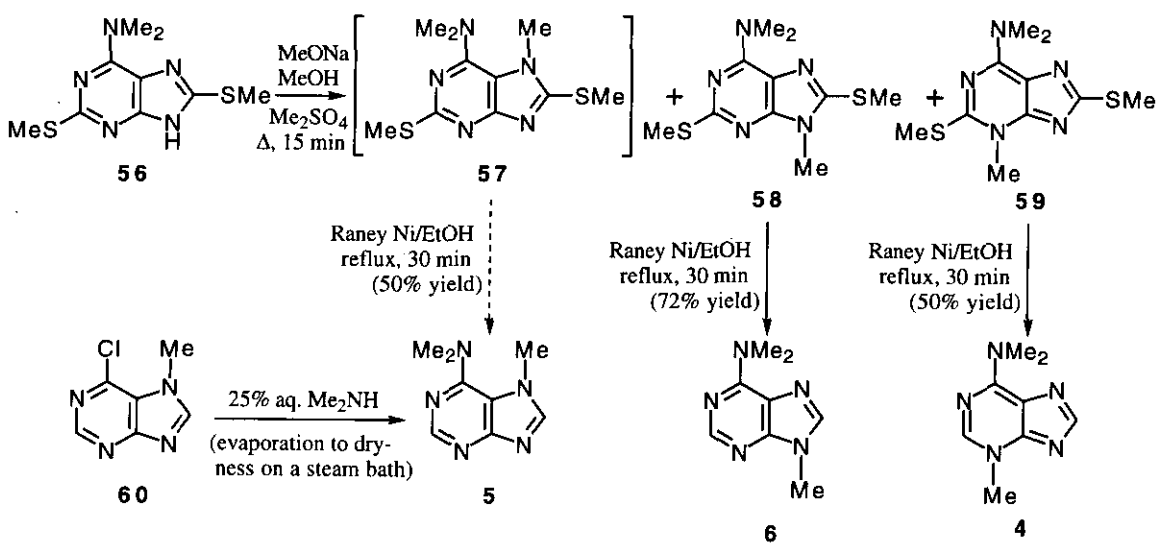
Scheme 8

The structure of 3-substituted N^6,N^6-dimethyladenine [*i. e.*, the importance of the dipolar iminium form (**54**) to the possible resonance hybrid [**53** ↔ **54** ↔ **55** (Scheme 8)], as suggested[51] by nonequivalent N^6-Me_2 signals[17,45,50,51] in the ^{1}H NMR spectrum of the free base of **4**] was substantiated by X-ray analysis of 3-(2,6-dichlorobenzyl)-N^6,N^6-dimethyladenine.[54]

As regards the biological activity of **4**, Monsees *et al.*[17] reported that this substance was able to induce oocyte maturation in the starfish *Asterias rubens*, but at very high concentrations (EC_{50} > 130 μM).

V. N^6,N^6,7-TRIMETHYLADENINE

In 1954, Baker *et al.*[55] reported that methylation of N^6,N^6-dimethyl-2,8-bis(methylthio)-adenine (**56**) with dimethyl sulfate in hot 1 N methanolic MeONa for 15 min furnished N^6,N^6,"7"-trimethyl-2,8-bis(methylthio)adenine (**57**) (27% yield) and N^6,N^6,9-trimethyl-2,8-bis(methylthio)adenine (**58**) (51%) (Scheme 9). Separate desulfurizations of the two products with Raney Ni produced two isomers described by them[55] as N^6,N^6,"7"-trimethyladenine (**5**) (50% yield) and N^6,N^6,9-trimethyladenine (**6**) (72% yield). Later on, Townsend *et al.*[39] revealed that the last of these structures had been assigned correctly and the compound was identical with a sample of **6**, mp 119–120°C, synthesized by an unambiguous route[56] (see Section VI and Scheme 10), but the structure of the first isomer, mp 168–169°C, was in reality N^6,N^6,3-trimethyladenine (**4**) since it was identical with an authentic sample prepared from 3-methyl-6-methylthiopurine (**35**) and Me_2NH (see Section IV and Scheme 4). It follows that the two products obtained by Baker and co-workers[55] from **56** by direct methylation were **59** (instead of **57**) and **58** and that the desulfurization products were **4** (instead of **5**) and **6** (Scheme 9).



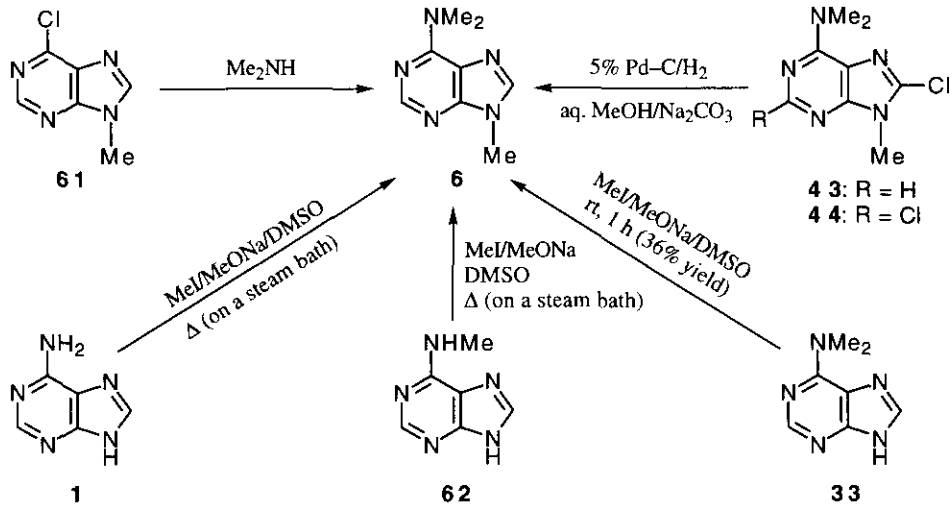
Scheme 9

The unreached isomer N^6,N^6,7-trimethyladenine (**5**) was then synthesized by treatment of a pure sample of 6-chloro-7-methylpurine (**60**)[57] with 25% aqueous Me_2NH.[39] The following physicochemical data of **5** are found in the literature: the melting point for the free base (**5**), mp 111–112°C;[39] paper chromatography;[39] MS;[41] UV in H_2O at

various pH's;[39,42] ^{1}H NMR in DMSO-d_6[39] or in D_2O.[58]

VI. N^6,N^6,9-TRIMETHYLADENINE

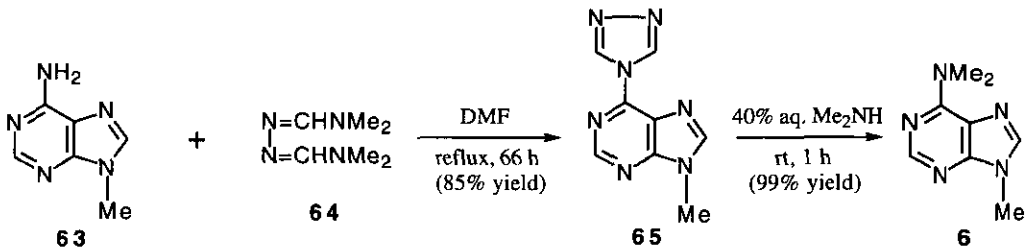
The first synthesis of N^6,N^6,9-trimethyladenine (**6**) was accomplished by Baker and coworkers[55] through a route starting with methylation of N^6,N^6-dimethyl-2,8-bis(methylthio)adenine (**56**) and proceeding *via* N^6,N^6,9-trimethyl-2,8-bis(methylthio)adenine (**58**), as described above in Section V (Scheme 9).



Scheme 10

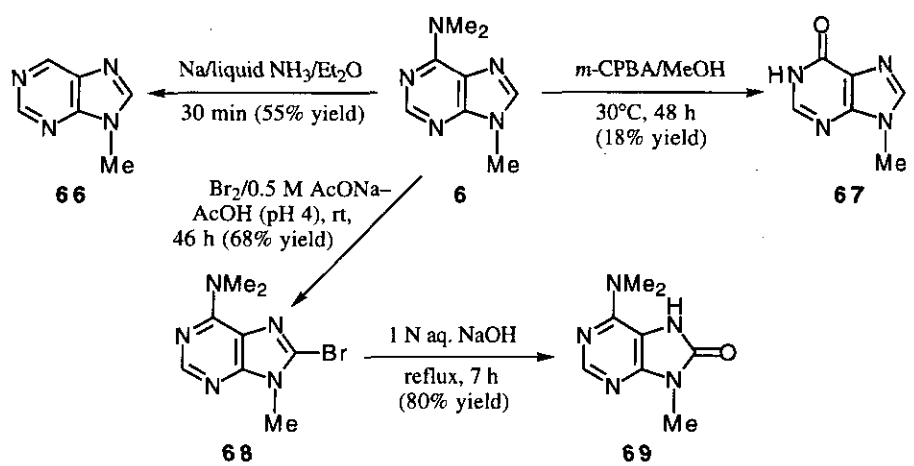
Treatment of 6-chloro-9-methylpurine (**61**) with aqueous Me_2NH in EtOH[56] or with 33% ethanolic Me_2NH at 20°C for 7 h[16a] was reported to give **6** in 78% or unspecified yield, respectively (Scheme 10). As described in Section II (Scheme 2), **6** was obtained in 49% yield by sublimation of 6-trimethylammoniopurinide (**26**) at 185°C and 15 mmHg for 45 min.[26] Kiburis and Lister[26] prepared **6** by catalytic hydrogenolysis of 8-chloro-N^6,N^6,9-trimethyladenine (**43**) or 2,8-dichloro-N^6,N^6,9-trimethyladenine (**44**) [derived from **39** or **40**, respectively (see Section IV and Scheme 4)] over 5% Pd–C catalyst in aqueous MeOH containing Na_2CO_3 (Scheme 10). See Sections III (Scheme 3) and IV (Scheme 6) for the methylation of N^6,N^6-dimethyladenine (**33**) to give **6** by the procedure of Pal and Horton[38] (dimethyl sulfate/0.01 M phosphate buffer (pH 7.0)–EtOH, pH 7.0, rt, 3–4 h; 8.3% yield) and by that of Itaya *et al.*[45] (MeI/$AcNMe_2$ in the presence or absence of K_2CO_3; 54% or 0.7% yield, respectively). Bryant and Klein[59] reported quantitative conversion of either adenine (**1**) or N^6-methyladenine (**62**) into **6** by methylation with MeI in hot DMSO containing MeONa (Scheme 10). Kelly *et al.* prepared **6** in 36% yield from N^6,N^6-dimethyladenine (**33**) by methylation with MeI under similar reaction conditions.[60]

Robins' group[61] transformed 9-methyladenine (**63**) into the 6-(1,2,4-triazol-4-yl)purine derivative (**65**) (85% yield) by treatment with 1,2-bis[(dimethylamino)methylene]hydrazine dihydrochloride (**64**·2HCl) in boiling DMF for 66 h and then converted **65** into **6** in 99% yield by treatment with 40% aqueous Me_2NH at room temperature for 1 h (Scheme 11).



Scheme 11

As regards the chemical behavior of N^6,N^6,9-trimethyladenine (**6**), Muravich-Aleksandr *et al.*[40] reported that methylation of **6** with MeI in DMF in a closed vessel at 100°C for 10 min or at 20–25°C for 3–5 h furnished N^6,N^6,3,9-tetramethyladeninium iodide (**17**: X = I) in 89% or 56.5% yield, respectively (see Section XVII and Scheme 26). See also Section IV (Scheme 6) for methylation by Itaya's group[46] of a mixture of **6** and N^6,N^6,3-trimethyladenine (**4**) to give **17** (X = I) in 95% overall yield [from N^6,N^6-dimethyladenine (**33**)].



Scheme 12

Kos and van der Plas[62] reported the reductive removal of the dimethylamino group from **6** to provide 9-methylpurine (**66**) in 53% or 55% yield, which was feasible by treatment with sodium in liquid NH_3 containing diethyl ether for 15 min or 30 min (Scheme 12). Treatment of **6** with *m*-CPBA in MeOH at 30°C for 48 h was found to produce 9-methylhypoxanthine (**67**) in 18% yield, together with 26% recovery of the

starting material (**6**).[63] Reaction of **6** with bromine in 0.5 M AcONa–AcOH buffer (pH 4) at room temperature for 46 h afforded the 8-bromo derivative (**68**) (68% yield), which was then converted into the 8-oxo derivative (**69**) in 80% yield by treatment with boiling 1 N aqueous NaOH for 7 h.[64] The reactions of **6** with the OH radical in H_2O at pH 6–8 and 20°C[18,65] and with sulfate radical anion ($SO_4^{\bullet -}$) in H_2O at pH 7–8 and 20°C[65a] have been investigated.

Interactions of **6** with the following substances have been reported: H_2O (hydration);[66] each of purine,[60b,67] 7,9-dimethylguanine, 7-methylguanosine, and 7-methylguanosine 5'-monophosphate in H_2O at 298.2 K;[67] 3,5-dichlorophenol in $CHCl_3$;[68] each of phenol, 3-bromophenol, 4-bromophenol, 3,4-dichlorophenol, 3,5-dichlorophenol, and 3,4,5-trichlorophenol in 1,2-dichloroethane or in tetrachloroethylene;[69] 4-bromophenol in CCl_4;[69] 5,6,8-trideuterio-4-nitroquinoline 1-oxide in DMSO-d_6;[70] lima bean lectin (see also Section II);[27] self-association in H_2O;[71] $[M(dien)(D_2O)]^{2+}$ (M = Pt or Pd; dien = diethylenetriamine) or *trans*-$[Pt(NH_3)_2Cl]^+$ in D_2O[71] and reactions of the resulting complex with other nucleobases such as 9-ethylguanine, 9-methyladenine (**63**), and 1-methylcytosine in D_2O.[72]

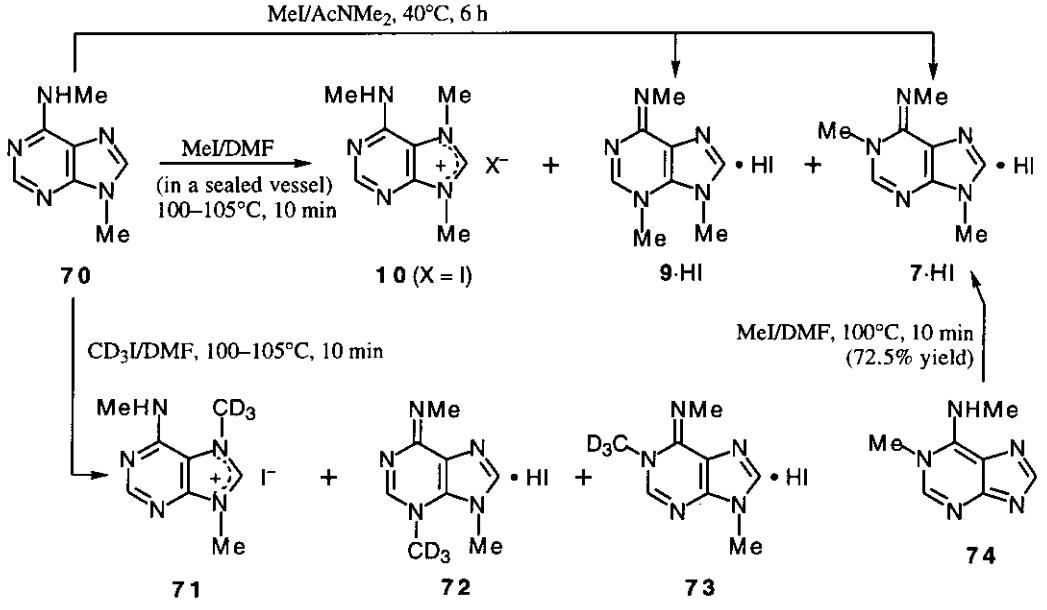
The following physicochemical properties of N^6,N^6,9-trimethyladenine (**6**) have been reported: the melting point for the free base (**6**), mp 119–120°C,[56] 118–119°C,[16a] 117–118°C,[45] 115–116°C,[60b] 115°C,[38] 114–115°C,[55] 113.5–115°C,[61b] or 113–114°C;[60a] for **6**·picrate, mp 244–245°C (decomp);[38] pK_a 4.04 (at 20°C)[18,65b] or –0.75 ± 0.20 and 4.15 ± 0.05 (at 25°C);[71] paper chromatography;[39] GC;[59] MS;[41,59,66b] UV in H_2O at various pH's,[38,39,45,55,56] in a mixture of 0.1 N HCl and 10% EtOH,[60a] in a mixture of 0.1 N NaOH and 10% EtOH,[60a] or in 95% aqueous EtOH;[45] IR;[69] far IR;[68] ^{1}H NMR in CCl_4,[45] in $CDCl_3$,[73] in DMSO-d_6,[39,60b,70,73] in D_2O,[58] or in TFA;[40] ^{13}C NMR in DMSO-d_6;[60b] ^{15}N NMR in 1,2-dichloroethane;[69] potential surface;[74] apparent molar volume[75,76] and heat capacity;[75] enthalpy of solution (in H_2O);[77,78] enthalpy of dilution (in H_2O);[76] enthalpy of hydration;[66b,74,77,78] enthalpy of sublimation.[77–79]

As regards the biological activity of N^6,N^6,9-trimethyladenine (**6**), Skinner and Shive[80] reported that it was inactive as a cytokinin in the lettuce seed germination bioassay. Kelly *et al.*[60a] found that **6** had a weak anticonvulsant activity in the maximal electroshock-induced seizure screen in Sprague–Dawley male rats. In the benzodiazepine receptor binding assay using rat brain tissue, complete loss of receptor affinity was found for **6** at 100 μM.[81] The compound (**6**) was tested for activity against apomorphine-induced aggression (fighting behavior) in rats:[82] It reduced aggressive behavior by 30% at 25 mg/kg.

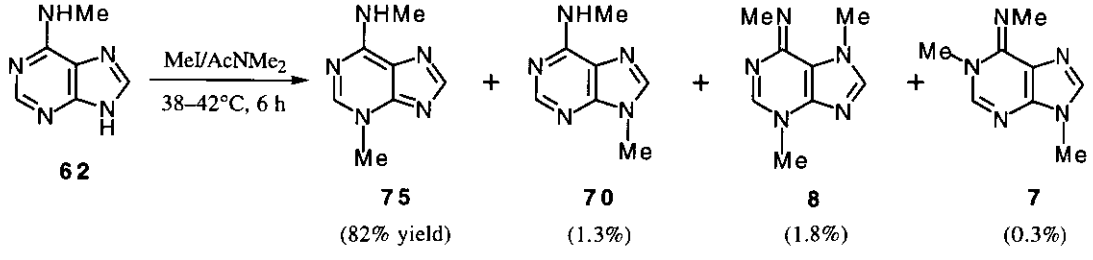
VII. N^6,1,9-TRIMETHYLADENINE

In 1973, El'tsov *et al.*[83] reported that methylation of N^6,9-dimethyladenine (**70**) with MeI in DMF in a closed vessel at 100–105°C for 10 min gave a 51:30:19 mixture (94%

yield) of N^6,1,9-trimethyladenine hydriodide (**7**·HI), N^6,3,9-trimethyladenine hydriodide (**9**·HI), and N^6,7,9-trimethyladeninium iodide (**10**: X = I), from which they were able to isolate pure samples of the three products (Scheme 13). The deuterated products (**71**–**73**) were obtained similarly by using CD_3I instead of MeI.[83] Alternatively, **7**·HI was synthesized from N^6,1-dimethyladenine (**74**) in 72.5% yield by methylation with MeI in DMF in a closed vessel at 100°C for 10 min.[83] Fujii's group[84] found that reaction of **70** with MeI in $AcNMe_2$ at 40°C for 6 h produced **7**·HI [isolated as the perchlorate salt (**7**·$HClO_4$) in 11% yield] and **9**·HI (17%). Direct methylation of N^6-methyladenine (**62**) with an excess of MeI in $AcNMe_2$ at 38–42°C for 6 h was found to provide **7** (isolated as **7**·$HClO_4$ in 0.3% yield), together with N^6,3-dimethyladenine (**75**) (82%), N^6,9-dimethyladenine (**70**) (1.3%), and N^6,3,7-trimethyladenine (**8**) (1.8%) (Scheme 14).[84] The N^6,1,9-trimethyl (**7**·HI), N^6,3,9-trimethyl (**9**·HI), and N^6,3,7-trimethyl (**8**·HI) isomers were the products (78–90% or 41% total yield) from the thermal reaction of the N^6,7,9-trimethyl isomer (**10**: X = I) at 220°C for 7–30 min or in boiling nitrobenzene for 30 min.[83]



Scheme 13



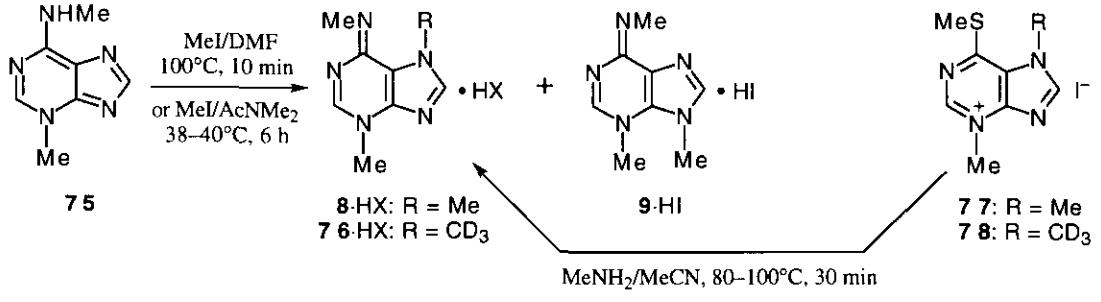
Scheme 14

Heating **7**·HI in boiling nitrobenzene for 30 min was reported to give a 18.5 : 24.0 : 57.5 mixture (30% yield) of **9**·HI, **8**·HI, and **7**·HI.[83] The polarographic reduction of **7**·HI has been investigated by Timofeeva *et al.*[85] See Section IX (Scheme 16) for the synthesis of the 8-oxo derivative (**83**) of **7**.

The following physicochemical properties of N^6,1,9-trimethyladenine (**7**) are recorded in the literature: the melting points for the free base (**7**), mp 158°C;[83] for the hydriodide (**7**·HI), mp 249–251°C;[83] for the perchlorate (**7**·$HClO_4$), mp 209–210°C[84] or 208–209°C;[83] pK_a (for **7**·HI) 10.00 ± 0.04;[83] paper chromatography for **7**·HI;[83] UV for **7**·HI in H_2O,[83] for **7**·$HClO_4$ in H_2O (at pH 1, 7, and 13) and in 95% aqueous EtOH;[84] ^{1}H NMR for **7** in $CDCl_3$;[83] electrocapillary curve for **7**·$HClO_4$ (in 0.1 M Na_2SO_4 and in 0.1 N H_2SO_4).[53]

VIII. N^6,3,7-TRIMETHYLADENINE

El'tsov *et al.*[83] reported that methylation of N^6,3-dimethyladenine (**75**) with MeI in DMF in a closed vessel at 100°C for 10 min provided N^6,3,7-trimethyladenine hydriodide (**8**·HI) (64% yield) and N^6,3,9-trimethyladenine hydriodide (**9**·HI) (16%) (Scheme 15). Alternatively, they synthesized **8**·HI in 80% yield from 3,7-dimethyl-6-methylthiopurinium iodide (**77**) by treatment in acetonitrile with a 17% solution of $MeNH_2$ in acetonitrile in a closed vessel at 80–100°C for 30 min.[83] The N(7)-CD_3 species (**76**·HI) was also prepared from 7-deuteriomethyl-3-methyl-6-methylthiopurinium iodide (**78**) in a similar manner.[83] Fujii's group[84] found that methylation of **75** with MeI in $AcNMe_2$ at 38–40°C for 6 h gave **8**·HI [isolated as the perchlorate (**8**·$HClO_4$) in 29% yield] and **9**·HI (15%), the results being in general agreement with the above results[83] obtained by the Russian research group under slightly different conditions, and that **8**·HI [isolated as the perchlorate (**8**·$HClO_4$) in 1.8% yield] was among the four products from the reaction of N^6-methyladenine (**62**) with MeI in $AcNMe_2$ at 38–42°C for 6 h (see Section VII and Scheme 14). The N^6,3,7-trimethyl compound (**8**·HI) was among the products from the methylation of 3-methyladenine or its hydriodide with MeI in DMF at 100°C or 150°C, respectively, for 4 h.[86]



75

8·HX: R = Me
76·HX: R = CD_3

9·HI

77: R = Me
78: R = CD_3

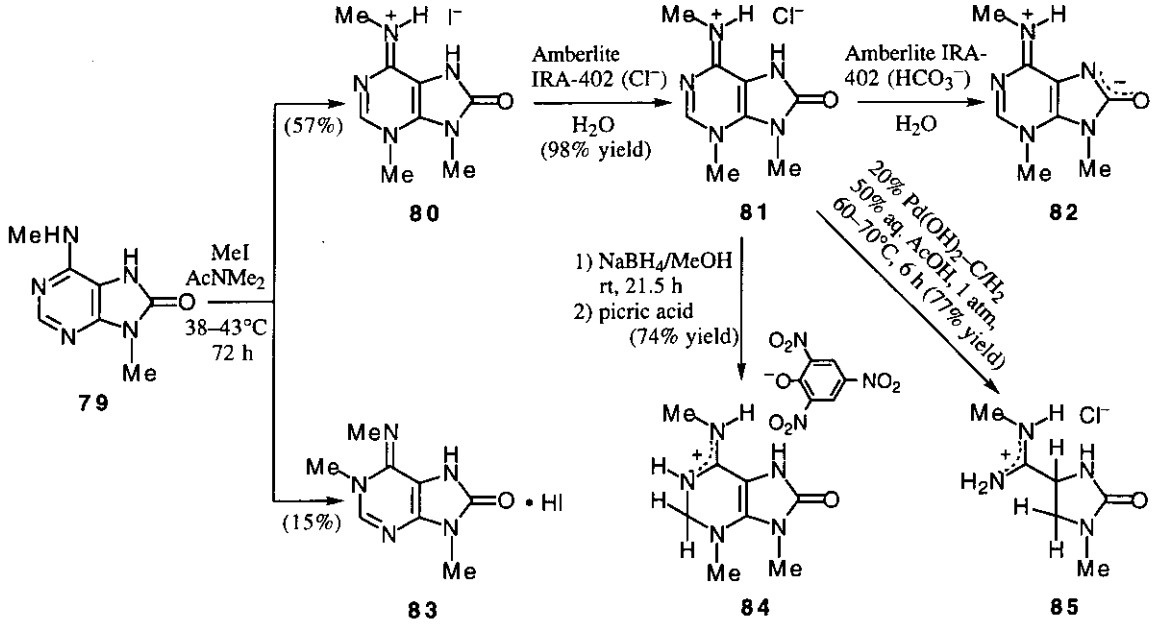
Scheme 15

When heated in boiling nitrobenzene for 30 min or 1 h, **8**·HI was recovered in 83.5% yield or furnished a 93.8 : 6.2 mixture of **8**·HI and N^6,1,9-trimethyl isomer (**7**·HI) in 52.2% yield, respectively.[83] Timofeeva *et al.*[85] have reported the results of their study on the polarographic reduction of **8**·HI.

The following physical properties and spectral characteristics of N^6,3,7-trimethyladenine salt (**8**·HX) have been reported: the melting point for the hydriodide (**8**·HI), mp 256–257°C;[83] for the perchlorate (**8**·$HClO_4$), mp 195–196°C[84] or 191–193°C;[83] pK_a (for **8**·HI) *ca.* 11.60;[83] paper chromatography for **8**·HI;[83,86] MS for **8**[41] and **76**;[41] UV for **8**·HI in H_2O;[83,86] for **8**·$HClO_4$ in H_2O at various pH's and in 95% aqueous EtOH;[84] ^{1}H NMR for **8**·HI in TFA.[83,86]

IX. N^6,3,9-TRIMETHYLADENINE

As described above in Section VII, N^6,3,9-trimethyladenine hydriodide (**9**·HI) was synthesized as one of the products from methylation of N^6,9-dimethyladenine (**70**) with MeI in DMF at 100–105°C for 10 min[83] or in $AcNMe_2$ at 40°C for 6 h[84] (Scheme 13). It was also obtainable from N^6,3-dimethyladenine (**75**) by methylation with MeI in DMF at 100°C for 10 min[83] or in $AcNMe_2$ at 38–40°C for 6 h[84] (see Section VIII and Scheme 15). See also Section VII for the formation of **9**·HI in thermal isomerization of N^6,1,9-trimethyladenine hydriodide (**7**·HI)[83] or the N^6,7,9-trimethyl isomer (**10**·HI)[83] and for the preparaton of the N(3)-CD_3 species (**72**) of **9**·HI from **70**.[83]

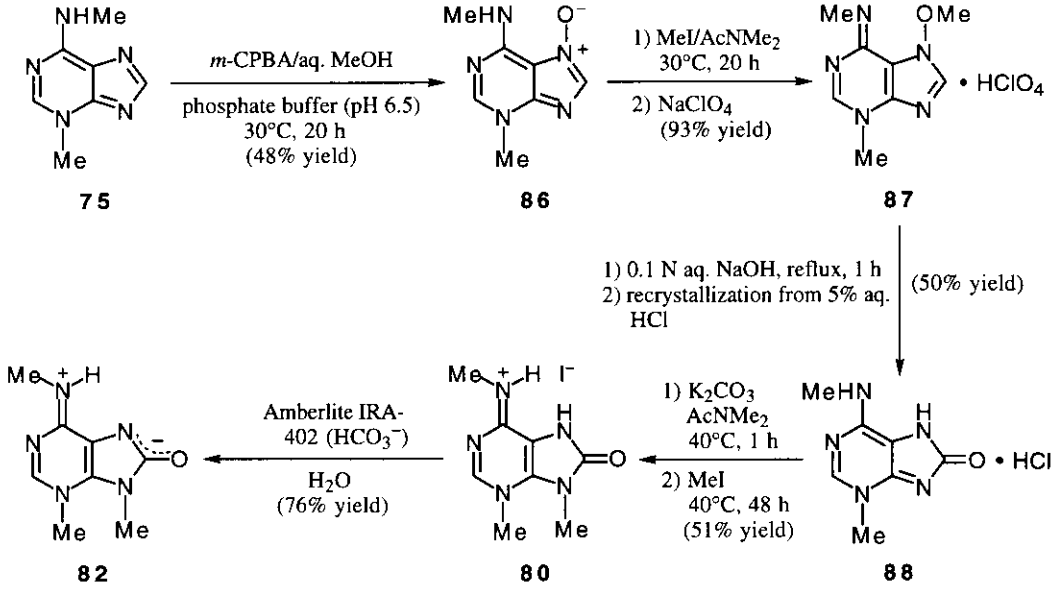


Scheme 16

Heating **9**·HI in boiling nitrobenzene for 30 min was reported to give a 53:25:22 mixture (30–40% yield) of **7**·HI, **8**·HI, and **9**·HI.[83] The polarographic reduction of **9**·HI has been investigated by Timofeeva *et al.*[85]

The following physicochemical data of N^6,3,9-trimethyladenine hydriodide (**9**·HI) are found in the literature: the melting point, mp 262–263°C (decomp)[84] or 261–262°C;[83] pK_a 11.00 ± 0.04;[83] paper chromatography;[83] UV in H2O[83] or in H_2O at various pH's and in 95% aqueous EtOH;[84] ^{1}H NMR in TFA.[83]

N^6,3,9-Trimethyladenine (**9**) occurs in nature as the 8-oxo derivative [3,6,7,9-tetrahydro-3,9-dimethyl-6-(methylimino)-8-oxopurin-7-ide (**82**) (caissarone)], a novel 8-oxopurine isolated by Zelnik *et al.*[87,88] in the form of the hydrochloride salt (**81**) from the sea anemone *Bunodosoma caissarum* Correa 1964 (Anthozoa, Actiniaria). The structure of caissarone hydrochloride (**81**) was established on the basis of spectroscopic measurements and an X-ray crystallographic analysis.[87]



Scheme 17

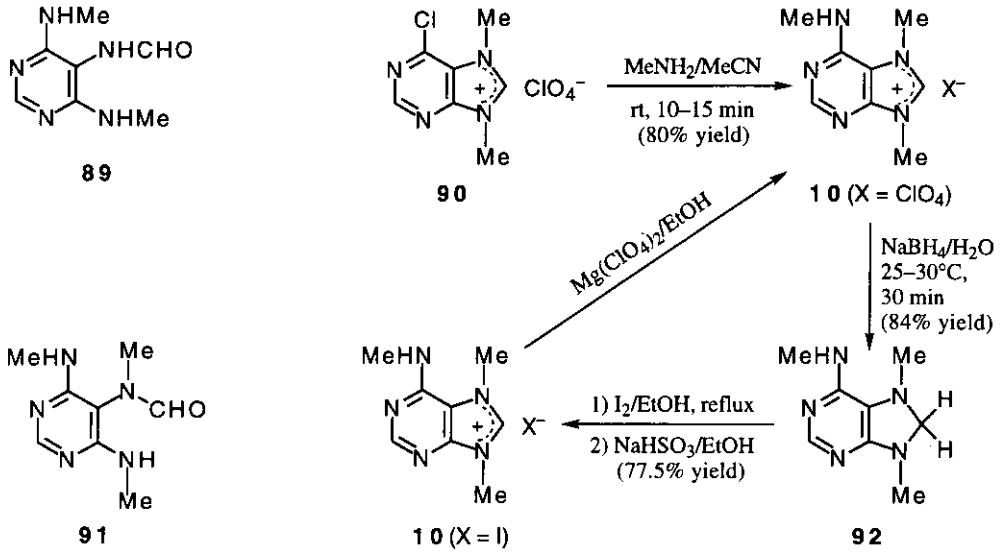
The first synthesis of **81**, achieved by Fujii's group,[64,89] started with methylation of N^6,9-dimethyl-8-oxoadenine (**79**) with MeI in $AcNMe_2$ at 38–43°C for 72 h to give the 3-methylated product [caissarone hydriodide (**80**)] (57% yield) and the 1-methylated product (**83**) (15%) (Scheme 16). Treatment of **80** with Amberlite IRA-402 (Cl^-) in H_2O provided the hydrochloride salt (**81**) (98% yield), which was identical with a natural sample[87] of caissarone hydrochloride.[64,89] Furthermore, the synthetic **81** was reduced with $NaBH_4$ in MeOH at room temperature for 21.5 h, and the resulting 1,2-dihydro derivative was isolated in the form of the picrate (**84**) (74% yield), which proved identical with that prepared from natural **81** in a similar manner.[64] In addition, catalytic hydrogena-

tion of **81** [20% $Pd(OH)_2$–C/H_2, 50% (v/v) aqueous AcOH, 1 atm, 60–70°C, 6 h] produced the monocyclic amidine salt (**85**) in 77% yield, and treatment of **81** with Amberlite IRA-402 (HCO_3^-) in H_2O furnished the free base (**82**) of caissarone.[64]

An alternative synthesis of **82** was accomplished *via* a route starting from N^6,3-dimethyladenine (**75**) and proceeding through the N(7)-oxide (**86**), the 7-methoxy compound (**87**), the 8-oxo compound (**88**), and caissarone hydriodide (**80**), as delineated in Scheme 17.[90]

X. N^6,7,9-TRIMETHYLADENINE

As described above in Section VII (Scheme 13), El'tsov *et al.*[83] obtained N^6,7,9-trimethyladeninium iodide (**10**: X = I) as one of the products from methylation of N^6,9-dimethyladenine (**70**) with MeI in DMF at 100–105°C for 10 min. Alternatively, treatment of 6-chloro-7,9-dimethylpurinium perchlorate (**90**) with a solution of $MeNH_2$ in acetonitrile for 10–15 min provided **10** (X = ClO_4) in 80% yield.[83] Conversion of **10** (X = ClO_4) into **10** (X = I) through the dihydro derivative (**92**) and direct reversion of **10** (X = I) to **10** (X = ClO_4) were also feasible, as shown in Scheme 18.[83]



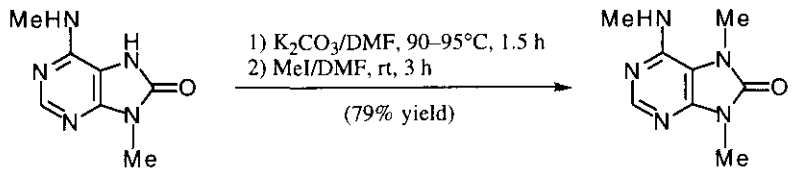
Scheme 18

In 1965, Brown and Jacobsen[91] reported that methylation of 5-formamido-4,6-bis(methylamino)pyrimidine (**89**) with MeI in MeOH at 100°C for 2 h[92] or methylation of N^6,9-dimethyladenine (**70**) with MeI at 140°C for 3 h gave a single product (mp 260–261°C), to which they assigned the structure of N^6,7,9-trimethyladeninium iodide (**10**: X = I). However, this product was not identical with a sample of **10** (X = I) obtained by the Russian workers; it had the properties and constants corresponding to N^6,3,9-trimethylade-

nine hydriodide (**9**·HI).[83]

Yamauchi *et al.*[93] isolated the ring-opened derivative (**91**) of **10** in 1% yield from the reaction mixture obtained by methylation of adenine (**1**) with trimethyl phosphate in H_2O at pH 10–11 and 60°C for 24 h. See Section VII for the thermal isomerization of **10** (X = I).[83]

The following physicochemical properties of N^6,7,9-trimethyladeninium salt (**10**) are reported in the literature: the melting point for **10** (X = I), mp 198–200°C;[83] for [**10** (X = I)]·HI, mp 245–247°C (decomp);[83] for **10** (X = ClO_4), mp 139–141°C;[83] paper chromatography for **10** (X = I);[83] UV for **10** (X = I) in H_2O,[83] for **10** (X = ClO_4) in H_2O;[83] ^1H NMR for **10** (X = I) in TFA;[83] electrocapillary curve for **10** (X = ClO_4);[53] polarography for **10** (X = ClO_4).[85,94,95]

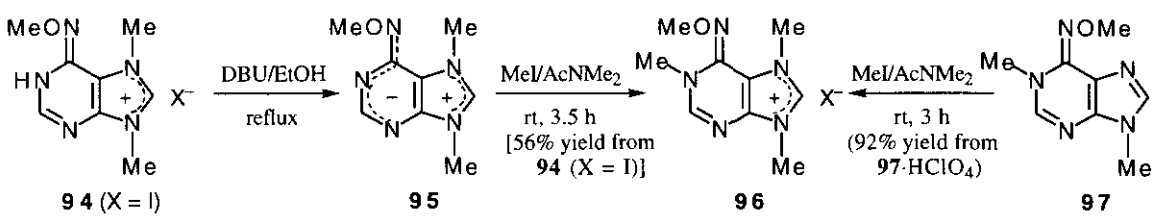


Scheme 19

The 8-oxo derivative (**93**) of **10** was synthesized from N^6,9-dimethyl-8-oxoadenine (**79**) in 79% yield by methylation with MeI in DMF containing K_2CO_3 at room temperature for 3 h (Scheme 19).[64,89] On treatment with 10% ethanolic HCl, **93** afforded the hydrochloride (**93**·HCl) in 95% yield.[64,89] See Section VII (Scheme 13) for the preparation of the N(7)-CD_3 species (**71**) of **10** (X = I) from N^6,9-dimethyladenine (**70**).

XI. 1,7,9-TRIMETHYLADENINE

1,7,9-Trimethyladenine (**11**)[8] has so far been known only as the N^6-methoxy derivative.



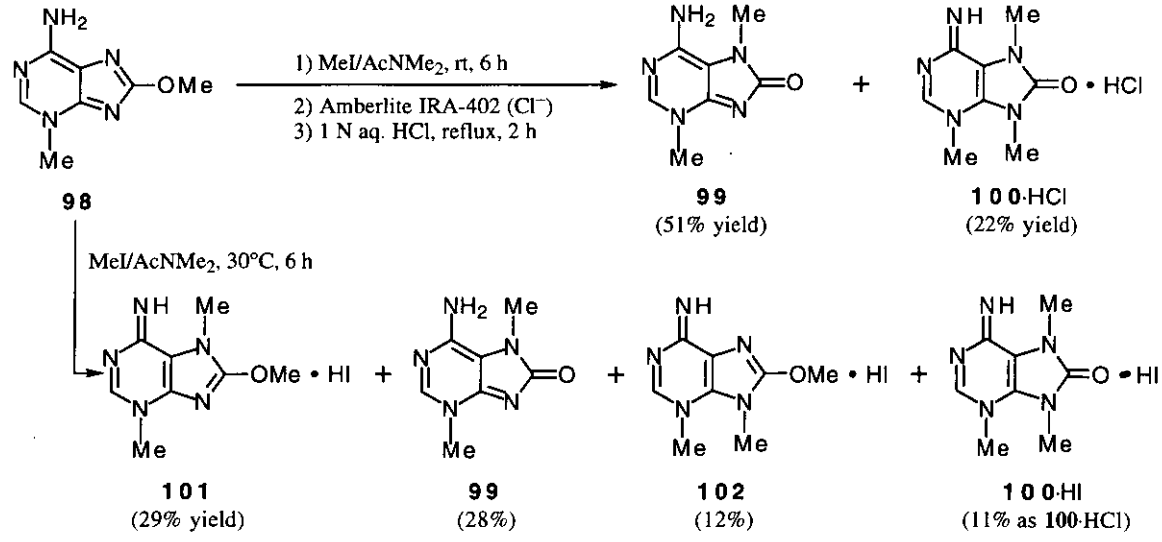
Scheme 20

Fujii's group[96] was able to prepare N^6-methoxy-7,9-dimethyladeninium iodide (**94**: X = I) in 59% yield from N^6-methoxy-9-methyladenine by methylation with MeI in $AcNMe_2$ at 30°C for 7 h or in 36% yield from N^6-methoxy-7-methyladenine by methylation with

MeI in $AcNMe_2$ at 40°C for 2 h. Treatment of **94** (X = I) with DBU in boiling EtOH gave the betaine (**95**) (Scheme 20), and methylation of **95** with MeI in $AcNMe_2$ at room temperature for 3.5 h yielded N^6-methoxy-1,7,9-trimethyladeninium iodide (**96**: X = I) [56% overall yield from **94** (X = I)], mp 230–231°C (decomp); 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; ^{1}H NMR (DMSO-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].[96] Methylation of N^6-methoxy-1,9-dimethyladenine (**97**), prepared from the corresponding perchlorate salt (**97**·$HClO_4$) by treatment with Amberlite IRA-402 (HCO_3^-) in H_2O, with MeI in $AcNMe_2$ at room temperature for 3 h also furnished **96** (X = I) in 92% overall yield (from **97**·$HClO_4$).[96] Treatment of **96** (X = I) with $NaClO_4$ in hot H_2O afforded the perchlorate [**96** (X = ClO_4)] (89% yield), 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; ^{1}H NMR (DMSO-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].[96]

XII. 3,7,9-TRIMETHYLADENINE

Up to now, 3,7,9-trimethyladenine (**12**)[8] is known only as the 8-oxo derivative (**100**).



Scheme 21

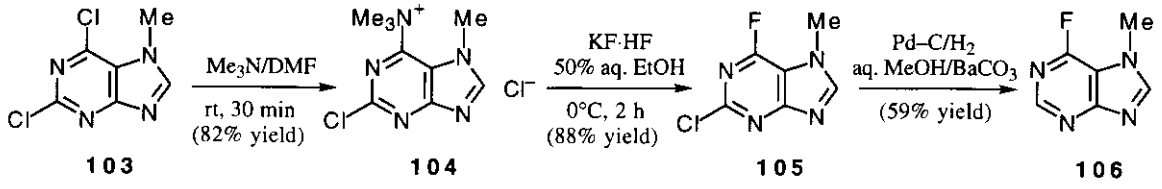
Methylation of 8-methoxy-3-methyladenine (**98**) with MeI in $AcNMe_2$ at room temperature for 6 h gave, after conversion of the products into the hydrochloride salts followed by hydrolysis in boiling 1 N aqueous HCl for 2 h, 3,7-dimethyl-8-oxoadenine (**99**) (51%

yield) and 3,7,9-trimethyl-8-oxoadenine hydrochloride (**100**·HCl) (22%) (Scheme 21).[97] In addition, methylation of **98** with MeI in $AcNMe_2$ at 30°C for 6 h, but without recourse to acid hydrolysis for product isolation, afforded 8-methoxy-3,7-dimethyladenine hydriodide (**101**) (29% yield), **99** (28%), 8-methoxy-3,9-dimethyladenine hydriodide (**102**) (12%), and **100**·HI [isolated as the hydrochloride (**100**·HCl) in 11% yield].[97] Methylation of **99** with MeI in $AcNMe_2$ at 30°C for 24 h and treatment of the product with Amberlite IRA-402 (Cl^-) in H_2O also produced **100**·HCl in 77% yield.[97]

An analytical sample of **100**·HCl·H_2O was reported to have the following physicochemical properties:[97] mp 253–254°C (decomp); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 226 nm (ε 19300), 298 (18600); $\lambda_{max}^{H_2O}$ (pH 1) 224 (20100), 294 (19300); $\lambda_{max}^{H_2O}$ (pH 7) 224 (20300), 294 (19300); $\lambda_{max}^{H_2O}$ (pH 13) unstable; IR ν_{max}^{Nujol} cm^{-1}: 3339, 3106 (NH), 1725 (C=O), 1669 (C=N); ^1H NMR (DMSO-d_6) δ: 3.57 [3H, s, N(7)-Me], 3.66 [3H, s, N(9)-Me], 4.13 [3H, s, N(3)-Me], 8.27 (2H, br, NH_2), 8.50 [1H, s, C(2)-H].

XIII. N^6,N^6,N^6,7-TETRAMETHYLADENINE

So far, N^6,N^6,N^6,7-tetramethyladenine (**13**)[8] has been known only as the 2-chloro derivative (**104**). Kiburis ad Lister[11] reported that treatment of 2,6-dichloro-7-methylpurine (**103**) with Me_3N in DMF at room temperature for 30 min produced 2-chloro-7-methylpurin-6-yltrimethylammonium chloride (**104**) [mp 178–180°C for **104**·H_2O; UV $\lambda_{max}^{H_2O}$ (pH 1) 284 nm (ε 6300); $\lambda_{max}^{H_2O}$ (pH 7) 284 (6300); ^1H NMR (D_2O) δ: 3.85 (Me_3N^+), 4.34 [N(7)-Me], 8.89 [C(8)-H]] in 82% yield (Scheme 22).



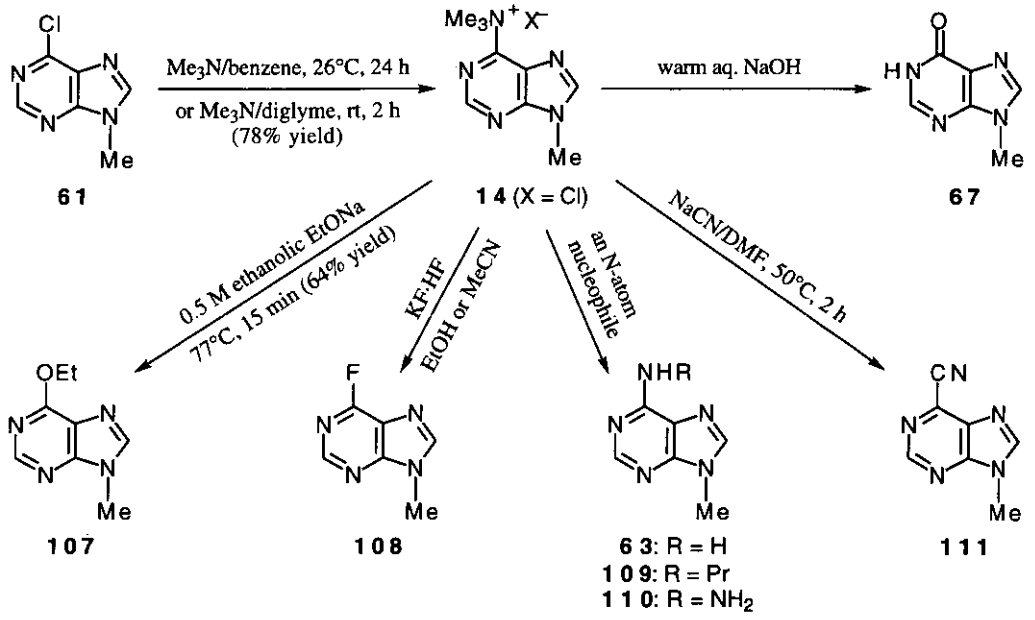
Scheme 22

On treatment with a 4% solution of potassium hydrogen fluoride in 50% aqueous EtOH at 0°C for 2 h, **104** gave 2-chloro-6-fluoro-7-methylpurine (**105**) (88% yield), which was then led to 6-fluoro-7-methylpurine (**106**) in 59% yield by hydrogenolysis using 5% Pd–C catalyst and hydrogen in MeOH containing a suspension of $BaCO_3$ in H_2O.[11]

XIV. N^6,N^6,N^6,9-TETRAMETHYLADENINE

Barlin and Young[16a] synthesized 9-methylpurin-6-yltrimethylammonium chloride (**14**: X = Cl) from 6-chloro-9-methylpurine (**61**) by treatment with Me_3N in benzene at room temperature for 24 h (Scheme 23), and Kiburis and Lister[11] employed slightly different

reaction conditions (Me_3N/diglyme, rt, 2 h) to obtain **14** (X = Cl) in 78% yield.



Scheme 23

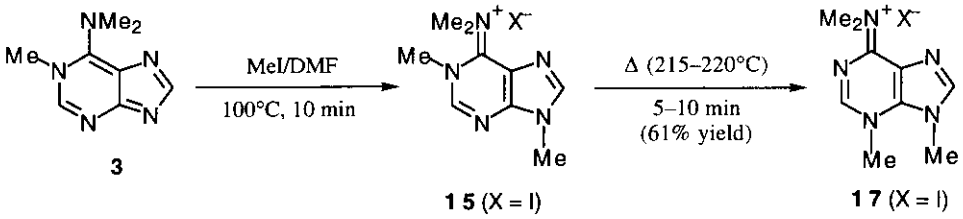
On warming in aqueous NaOH (3.5×10^{-2} M), **14** (X = Cl) gave 9-methylhypoxanthine (**67**), and a kinetic study was made of this reaction.[16a] Separate treatments of **14** (X = Cl) with 0.5 M ethanolic EtONa (77°C, 15 min), potassium hydrogen fluoride (in EtOH, 50°C, 2 h), aqueous NH_3 (*d* 0.91)–NH_4Cl (50°C, 3 h), $PrNH_2$ (in a sealed tube, 50°C, 3 h), 49% hydrazine hydrate (20°C, 15 min), and NaCN (in DMF, 50°C, 2 h) afforded 6-ethoxy-9-methylpurine (**107**) (64% yield), 6-fluoro-9-methylpurine (**108**) (in unspecified yield), 9-methyladenine (**63**) (67%), 9-methyl-N^6-propyladenine (**109**) (isolated as the picrate in 68% yield), 6-hydrazino-9-methylpurine (**110**) (33%), and 9-methylpurine-6-carbonitrile (**111**) (in unspecified yield), respectively (Scheme 23).[16b] Treatment of **14** (X = Cl) with potassium hydrogen fluoride in acetonitrile at 50–55°C for 5 h was reported to produce **108** in 37% yield.[11] The hydrated derivative of **14** (X = Cl), containing 2.5 molar equiv. of H_2O, has been found to be unstable and is slowly degraded to N^6,N^6,9-trimethyladenine (**6**) at room temperature.[11]

The following physicochemical properties of **14** (X = Cl) have been reported in the literature. For [**14** (X = Cl)·$1.5H_2O$:[16a] mp 161–162°C; UV in H_2O at pH 4.0; ^1H NMR in D_2O. For [**14** (X = Cl)]·$2.5H_2O$:[11] mp 165°C; UV in H_2O at pH 1 and 7; IR; ^1H NMR in D_2O and in DMSO-d_6.

XV. N^6,N^6,1,9-TETRAMETHYLADENINE

Muravich-Aleksandr *et al.*[40] synthesized N^6,N^6,1,9-tetramethyladeninium iodide (**15**: X

= I) [mp 178°C; paper chromatography Rf 0.40 in the BuOH–EtOH–4 N aqueous HCl (3:3:2) system; UV $\lambda_{max}^{H_2O}$ 292 nm (log ε 4.12); ^{1}H NMR (TFA) δ: 3.76 (6H, NMe_2), 4.16 [N(1)-Me], 4.23 [N(9)-Me], 8.83 and 9.58 (purine protons)] from N^6,N^6,1-trimethyladenine (**3**) by methylation with MeI in DMF in a closed vessel at 100°C for 10 min (Scheme 24). Their previous description[98] that **15** (X = I) was obtainable from N^6,N^6,7,9-tetramethyladeninium iodide (**18**: X = I)] by thermal isomerization or from N^6,N^6,9-trimethyladenine (**6**) by methylation with MeI turned out to be erroneous.



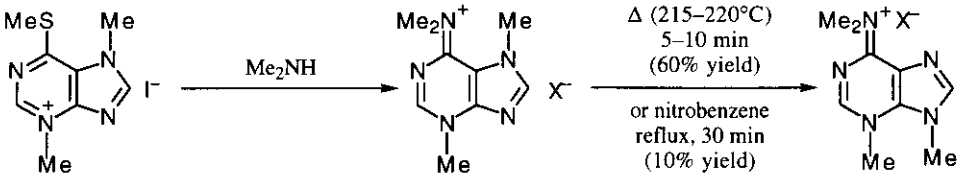
3 **15** (X = I) **17** (X = I)

Scheme 24

On heating at 215–220°C for 5–10 min, **15** (X = I) isomerized to give the N^6,N^6,3,9-tetramethyl compound [**17** (X = I)] in 61% yield.[40]

XVI. N^6,N^6,3,7-TETRAMETHYLADENINE

N^6,N^6,3,7-Tetramethyladeninium iodide (**16**: X = I) was synthesized from 3,7-dimethyl-6-methylthiopurinium iodide (**77**) and Me_2NH (Scheme 25),[40,98] as in the case of the reaction of **77** with $MeNH_2$ to give N^6,3,7-trimethyladenine hydriodide (**8**·HI) (Section VIII and Scheme 15).



77 **16** (X = I) **17** (X = I)

Scheme 25

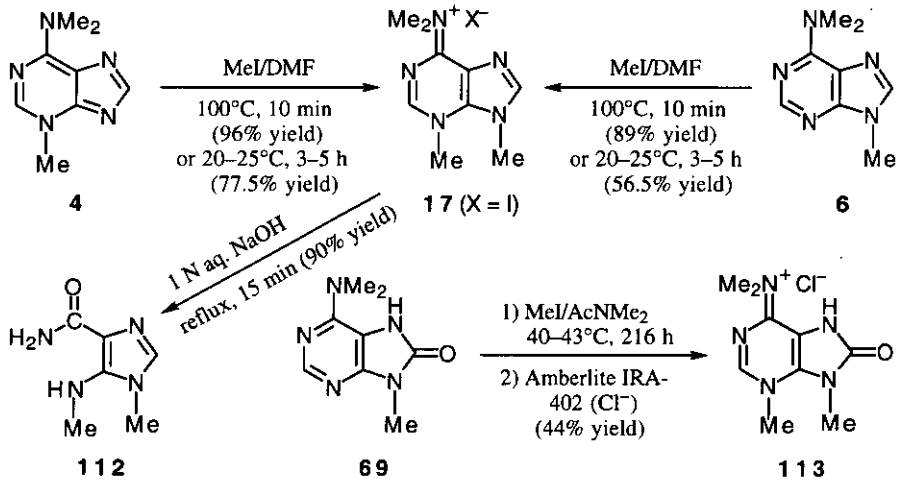
Isomerization of **16** (X = I) at 215–220°C for 5–10 min or in boiling nitrobenzene for 30 min produced the N^6,N^6,3,9-tetramethyl isomer (**17**: X = I) in 60% or 10% yield, respectively.[40]

The following physical properties and spectral characteristics of **16** have been recorded in the literature: the melting point for **16** (X = I), mp 195–197°C;[40] for **16** (X = ClO_4), mp 144–145°C;[40] paper chromatography for **16** (X = I) and for **16** (X = ClO_4);[40] UV in H_2O

for **16** (X = I) and for **16** (X = ClO_4);[40] ^{1}H NMR for **16** (X = I) in TFA;[40] electrocapillary curve for **16** (X = ClO_4);[53] polarography for **16** (X = ClO_4).[85]

XVII. N^6,N^6,3,9-TETRAMETHYLADENINE

As described above in Sections IV and VI, preparation of N^6,N^6,3,9-tetramethyladeninium iodide (**17**: X = I) from either N^6,N^6,3-trimethyladenine (**4**) or N^6,N^6,9-trimethyladenine (**6**) by methylation with MeI in DMF[40] (Scheme 26) or from a 2:7 mixture of **4** and **6** by methylation with MeI in $AcNMe_2$ (Scheme 6)[46] represents the essentially reciprocal directivity in alkylation of N^6,N^6,3-trialkyladenines[46] and N^6,N^6,9-trialkyladenines.[46,99,100] See also Section IV (Scheme 5) for the methylation of N^6,N^6-dimethyladenosine (**45**) to give rise to **17** (X = I) as a by-product. Formations of **17** (X = I) from N^6,N^6,1,9-tetramethyladeninium iodide (**15**: X = I) (Section XV and Scheme 24) and from the N^6,N^6,3,7-tetramethyl isomer (**16**: X = I) (Section XVI and Scheme 25) are described above and that from the N^6,N^6,7,9-tetramethyl isomer (**18**: X = I) will be mentioned below (Section XVIII).

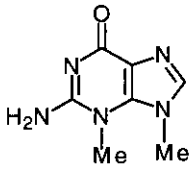


Scheme 26

The following physicochemical properties of **17** (X = I) are reported: mp 335–345°C[40] or >300°C;[46] paper chromatography;[40] UV in H_2O,[40] in H_2O at pH 1 and 7,[46] and in 95% aqueous EtOH;[46] ^{1}H NMR in DMSO-d_6[46] and in TFA;[40] electrocapillary curve for **17** (X = ClO_4);[53] polarography.[85]

As regards the chemical behavior of **17** (X = I), it demethylated to give N^6,N^6,9-trimethyladenine (**6**) in 23.4% yield when heated in boiling nitrobenzene for 30 min.[40] Itaya's group[101] reported that treatment of **17** (X = I) in boiling 1 N aqueous NaOH for 15 min furnished 1-methyl-5-(methylamino)imidazole-4-carboxamide (**112**) in 90% yield (Scheme 26) and that this hydrolysis proceeded more rapidly than that[99] of the N^6,N^6-

diethyl analogue to give the same carboxamide (**112**). This carboxamide (**112**) is useful as a starting material for the syntheses of 3,9-dimethylpurines, such as 3,9-dimethylguanine (**114**),[102] 3,9-dimethylxanthine (**115**),[102] 3,9-dimethylhypoxanthine (**116**),[103] and 3,9-dimethylisoguanine (**117**).[102c,104]



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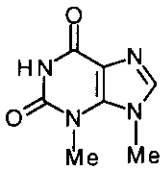

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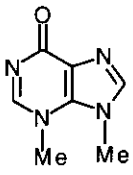

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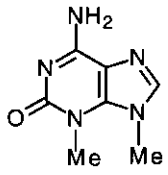

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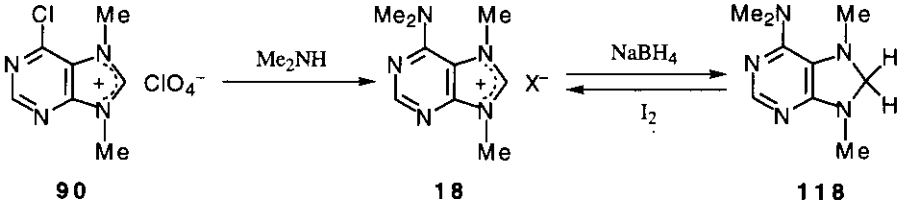
The 8-oxo derivative of **17** corresponds to N^6-methylcaissarone salt, and it was synthesized in the form of the hydrochloride (**113**) in 44% yield from N^6,N^6,9-trimethyl-8-oxoadenine (**69**) (see Section VI and Scheme 12) by methylation with MeI in $AcNMe_2$ at 40–43°C for 216 h followed by treatment of the resulting product with Amberlite IRA-402 (Cl^-) in H_2O.[64]

XVIII. N^6,N^6,7,9-TETRAMETHYLADENINE

The synthesis of N^6,N^6,7,9-tetramethyladeninium perchlorate (**18**: X = ClO_4) from 6-chloro-7,9-dimethylpurinium perchlorate (**90**) by amination with Me_2NH, reduction of **18** (X = ClO_4) with $NaBH_4$ to give the dihydro derivative (**118**), and oxidation of **118** with iodine (Scheme 27) were effected[98] as in the cases of the N^6,7,9-trimethyl series (**10** and **92**) (Section X and Scheme 18).



90 **18** **118**

Scheme 27

When heated at 215–220°C for 5–10 min or in boiling nitrobenzene for 30 min, **18** (X = I) isomerized to afford the N^6,N^6,3,9-tetramethyl compound (**17**: X = I) in 66% or 30% yield, respectively.[40]

The following physicochemical properties of **18** are recorded in the literature: the melting point for **18** (X = I), mp 168–170°C[98] or 167–170°C (melted and resolidified);[40] for **18** (X = ClO_4), mp 146–148°C;[98] paper chromatography for **18** (X = I);[40] UV for **18** (X = I) in H_2O;[40,98] ^1H NMR for **18** (X = I);[40,98] polarography for **18** (X = ClO_4).[85,94,95]

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