FIVE N^x-METHYLADENINES: THEIR CHEMISTRY, PHYSICOCHEMICAL PROPERTIES, AND BIOLOGICAL ACTIVITIES

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Abstract —Various mono-*N*-substituted adenines are represented by the corresponding five possible isomers of N^x-methyladenine, namely, 9-methyladenine (**2**), 7-methyladenine (**3**), 3-methyladenine (**4**), 1-methyladenine (**5**), and N^6-methyladenine (**6**). The chemistry, physicochemical properties, and biological activities of these N^x-methyladenines are reviewed with 366 reference citations.

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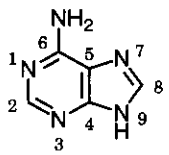
I. INTRODUCTION

Adenine (**1**), a biologically important heterocycle, bears one exocyclic and four endocyclic nitrogen atoms, so that five kinds of mono-*N*-substitution pattern are possible in principle. Indeed, all these substitution patterns (with a variety of substituents) have been shown to occur in nature as well as by chemical synthesis.[1–4] The prototypes of such five mono-*N*-substituted adenines are 9-methyladenine (**2**), 7-methyladenine (**3**), 3-methyladenine (**4**), 1-methyladenine (**5**), and N^6-methyladenine (6-methylaminopurine) (**6**). Since they could serve as the standard compounds for the corresponding substitution patterns, expert information on them should be made as readily accessible as possible. Thus, the chemistry, physicochemical properties, and biological activities of N^x-methyladenines have been treated in previous reviews in several forms.[1–4] It is the intention of the present review article to supplement the previous ones by reorganizing (in part) and updating the literature through the late part of 1997.



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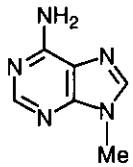

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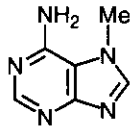

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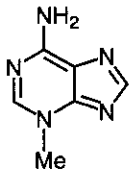

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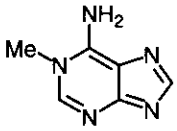

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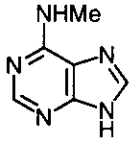

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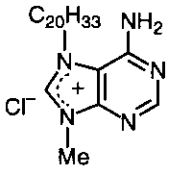

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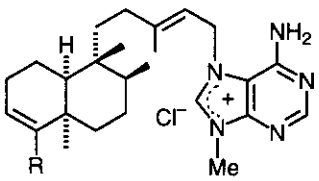

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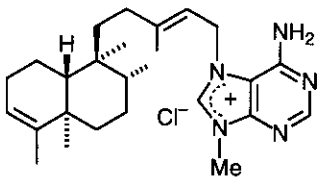

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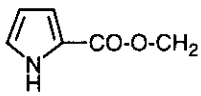
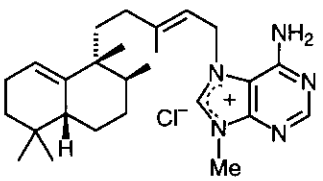
9: R =  (ageline B)



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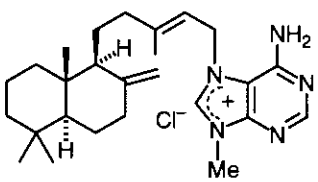

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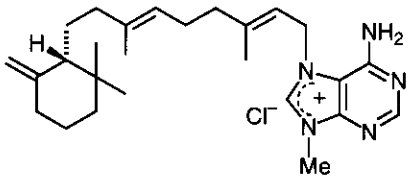

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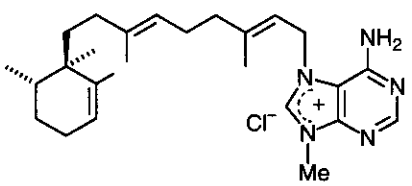
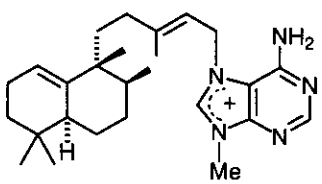


1 4 [agelasine F (ageline A)]



1 5 (*epi*-agelasine C)

II. 9-METHYLADENINE

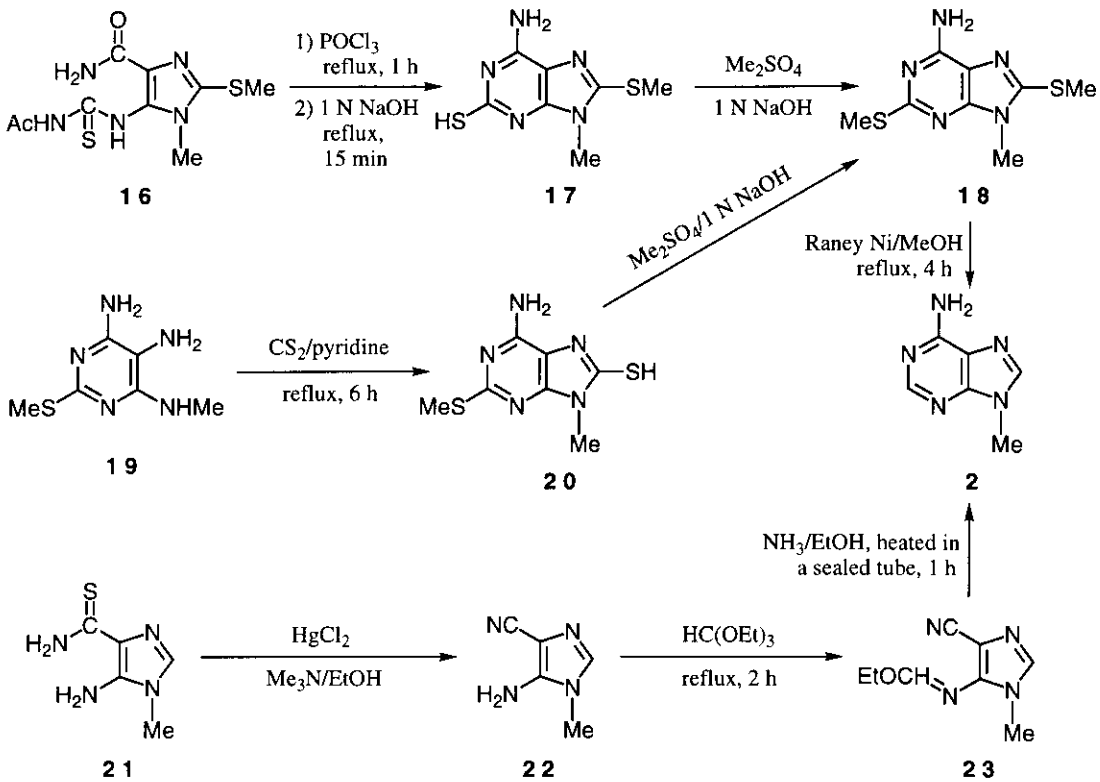
9-Methyladenine (**2**) occurs in nature as a partial structure in agelasine (**7**) (from the sea sponge *Agelas dispar*),[5] agelasines A–F (**8**, **10–14**) (from the Okinawan sea sponge *A. nakamurai*),[6] ageline A (agelasine F[6c]) (**14**) and ageline B (**9**) (from a Pacific sea sponge *Agelas* sp.),[7a] and *epi*-agelasine C (**15**) (from the marine sponge *Agelas mauritiana*),[8] all with diterpene or modified diterpene units at the 7-position.[7b] Agelasine (**7**) has been reported to give **2** on heating in xylene under reflux and to release **2**·HCl by catalytic hydrogenolysis (5% Pd–C/H_2) in EtOH.[5]

As regards the biological activities of **2**, it has been reported to be a weak inhibitor of adenosine deaminase;[9] a weak competitive inhibitor of human erythrocyte membrane phosphatidylinositol 4-kinase;[10] and a weak antagonist of the activation of A_1 adenosine receptor.[11] It is devoid of the ability to replace 1-methyladenine (**5**) in triggering meiosis in the starfish *Marthasterias glacialis* and *Asterias rubens* oocytes,[12] and it is also devoid of the ability to inhibit the **5**-dependent induction of meiosis.[12]

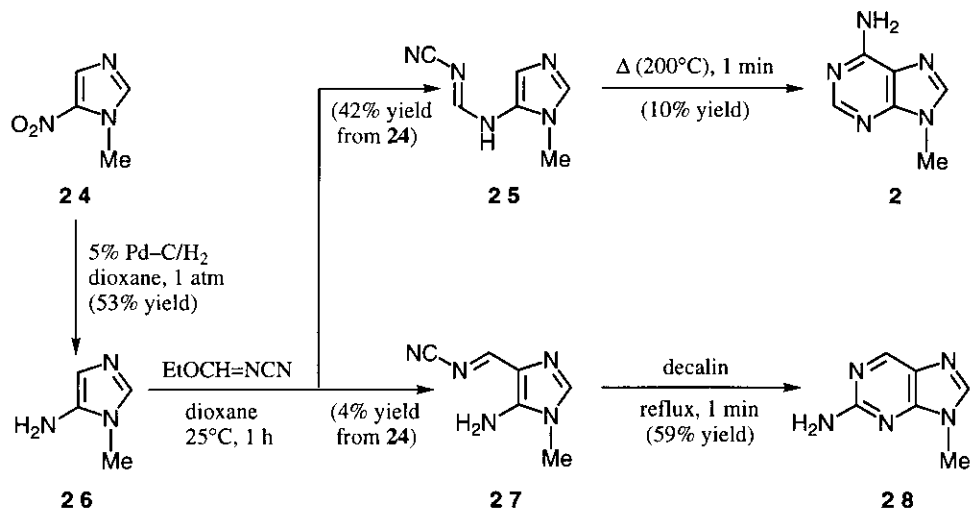
The syntheses of 9-methyladenine (**2**) so far reported can be classified into four types according to the structures of their starting materials: (i) from imidazole derivatives, (ii) from pyrimidine derivatives, (iii) from purine derivatives, and (iv) from adenine (**1**).

The syntheses of type-i include the work of Cook and Smith,[13] who treated the thioureidoimidazole (**16**) successively with $POCl_3$ and 1 N NaOH to obtain 6-amino-2-mercapto-9-methyl-8-methylthiopurine (**17**) (Scheme 1). On methylation with dimethyl sulfate and alkali, **17** produced the 2,8-bis(methylthio) derivative (**18**), which was also prepared from 5,6-diamino-4-methylamino-2-methylthiopyrimidine (**19**) through 8-mercapto-9-methyl-2-methylthioadenine (**20**). Reductive desulfurization of **18** with Raney Ni yielded 9-methyladenine (**2**). Shaw and Butler[14] synthesized **2** from 5-amino-1-methylimidazole-4-carbothioamide (**21**) through the amino nitrile (**22**) and the ethoxymethylidene derivative (**23**) (Scheme 1). The synthesis of **2** by Ramsden's group[15] started with the catalytic hydrogenation of 1-methyl-5-nitroimidazole (**24**) (Scheme 2). Treatment of the resulting amine (**26**) with *N*-cyanoformimidate in dioxane gave the *N*-condensation product (**25**) and the *C*-condensation product (**27**) in 42% and 4% yields (from **24**), respectively. On heating at 200°C for 1 min, **25** produced **2** in 10% yield. Similar treatment of **27** afforded 2-amino-9-methylpurine (**28**) in 59% yield.

The type-ii syntheses of **2** include that of Howard *et al.*,[16] which started from 4,6-diamino-2-methylthiopyrimidine (**29**) and proceeded through the D-xylosylamino derivatives (**30** and **31**) (Scheme 3). Conversion of **31** into **2** was effected by methylation with MeI in the presence of NaOEt, followed by glycosidic hydrolysis with dilute sulfuric acid and reductive desulfurization with Raney Ni. Daly and Christensen[17] synthesized **2** from 4-amino-6-chloro-5-nitropyrimidine (**32**)[18] *via* the methylamino derivative (**33**) and 4,5-diamino-6-methylaminopyrimidine (**34**) (Scheme 4).[10] The synthesis of **2** by Robins and Lin[19a] started from 4,6-dichloro-5-nitropyrimidine (**35**) and proceeded through the 6-



Scheme 1



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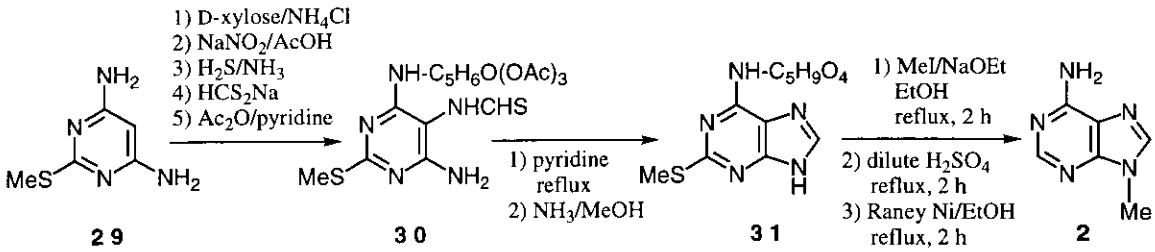
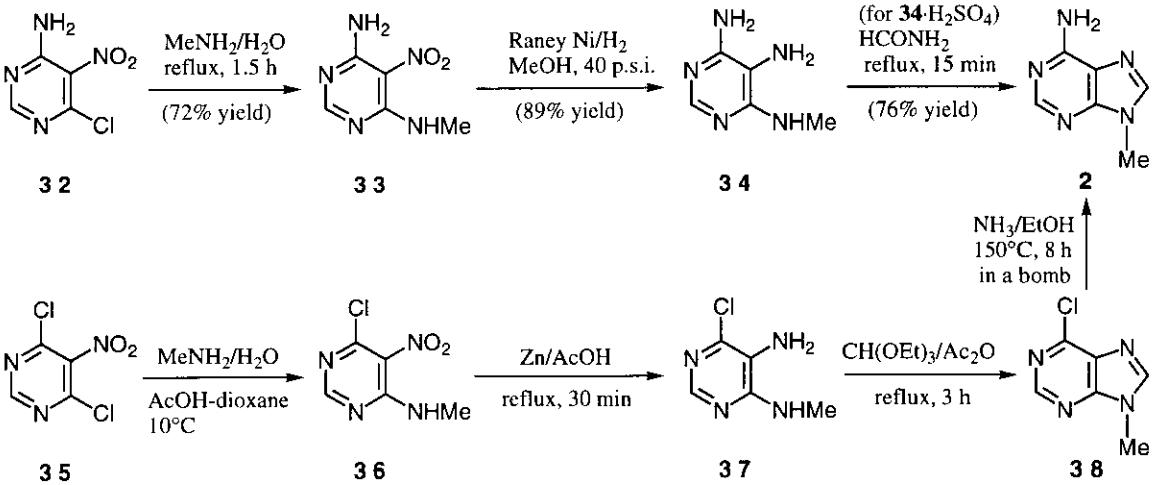


Scheme 3



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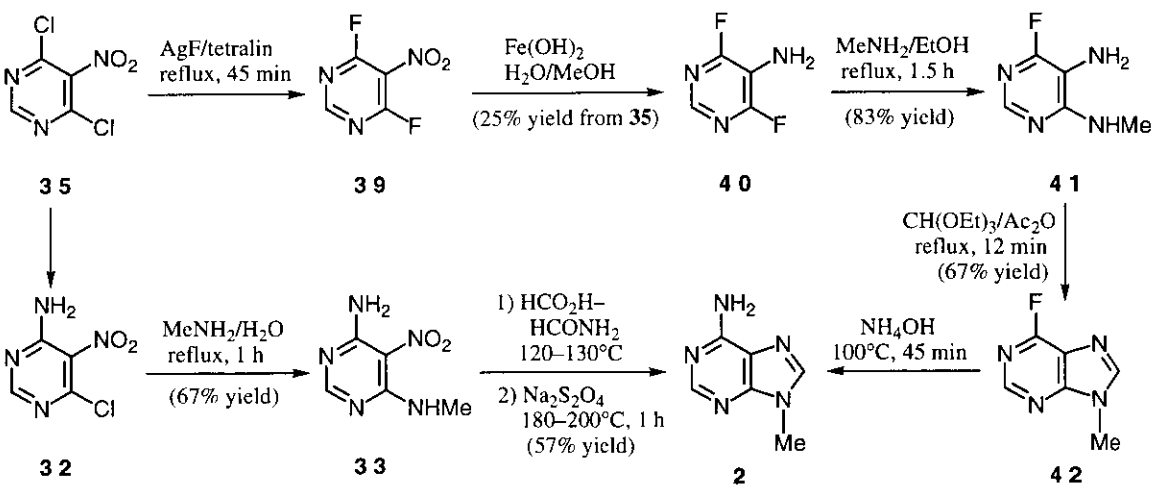

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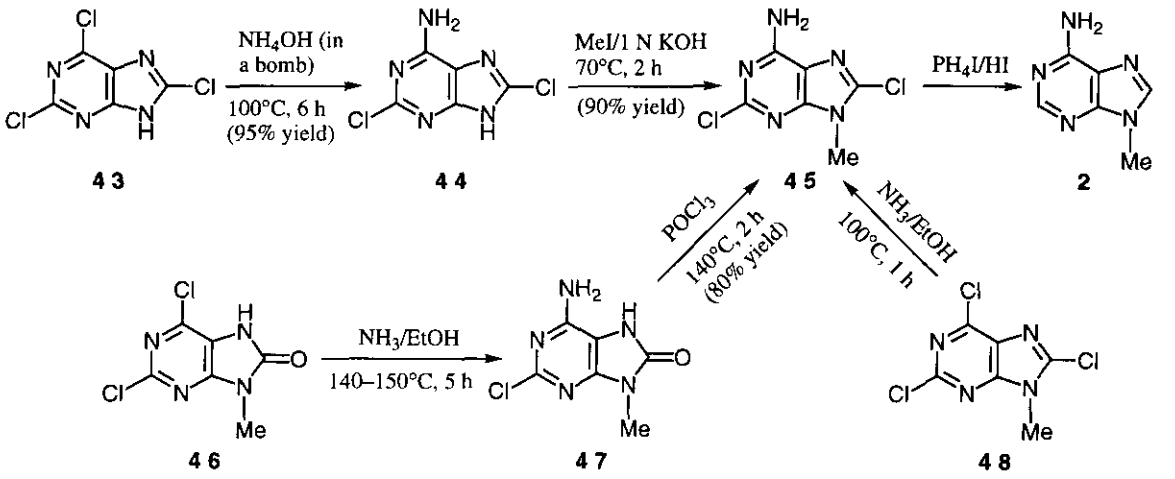

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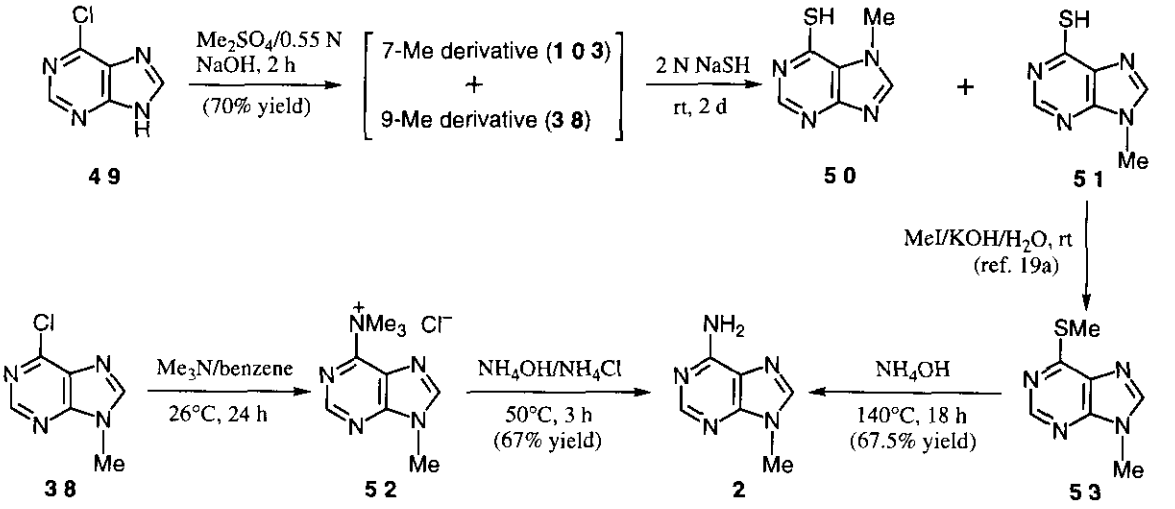

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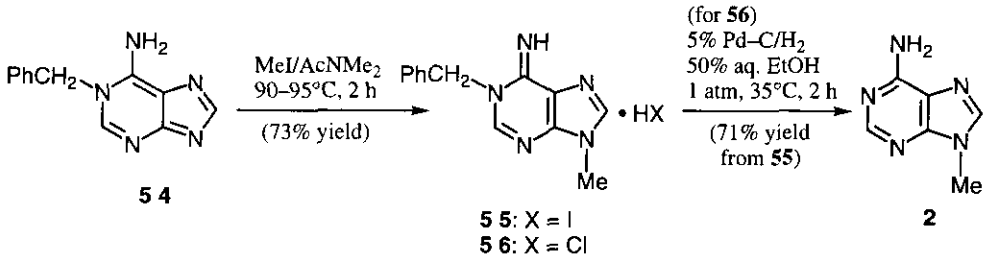


Scheme 8

methylamino derivative (**36**), the 5-amino derivative (**37**), and 6-chloro-9-methylpurine (**38**),[19b] as depicted in Scheme 4. Beaman and Robins[20] obtained **2** by amination of 6-fluoro-9-methylpurine (**42**), prepared from **35** through 4,6-difluoro-5-nitropyrimidine (**39**), the 5-amino derivative (**40**), and 5-amino-4-fluoro-6-methylaminopyrimidine (**41**) (Scheme 5). Takahashi[21] prepared **2** from **35** through **32** and **33** by modification of the procedures[17] of Daly and Christensen, as shown in Scheme 5.

TABLE I. One-Step Methylation of Adenine (**1**) to Produce 9-Methyladenine (**2**)

Reagent	Reaction conditions			Yield of **2** (%)	Literature (ref. No.)
	Solvent	Temp. (°C)	Time (h)		
MeI/NaOH	EtOH	warming	1	40	(29)
MeI/NaOH	EtOH	reflux	1	65	(44)
Me_2SO_4	H_2O (pH 7.0)[a]	40	—[b]	—[c]	(30a)
$Me_4N^+OH^-$	Nil	170–200[d]	6	77	(31)
MeI/K_2CO_3	$AcNMe_2$	35	1.5	38–42	(32)
MeI/K_2CO_3	DMF	—	—	—	(33)
$(MeO)_3P(O)$	H_2O (pH 10–11)	60	24	27	(34)
MeBr/$Bu_4N^+F^-$	THF	rt	1	95	(35)
$(MeO)_3P(O)$/$Bu_4N^+F^-$	THF	25	1	80[e]	(35a)
$(MeO)_3P(O)$/$Bu_4N^+F^-$	THF	22	16	84[f]	(36)
Me_2SO_4/$Bu_4N^+F^-$	THF	22	0.5	84[g]	(37)
Me_2SO_4/$Bu_4N^+OH^-$	THF	22	16 or 0.5	57[h]	(36, 37)
Me_2SO_4/$Bu_4N^+F^-$	THF	22	16	80[e]	(36)
$MeSO_3Me$/$Bu_4N^+F^-$	THF	22	0.5	81[i]	(36)
MeI	DMF	30	168	**2**:**4** = 0.54	(38)
MeI/NaH	DMF	30	16	**2**:**3**:**4** = 77:6:17	(39)
MeBr/$Bu_4N^+OH^-$	CH_2Cl_2/H_2O	20	24	50	(40)
MeI/$Bu_4N^+OH^-$	CH_2Cl_2/H_2O	20	12	98	(40)
$(CO_2Me)_2$/*t*-BuOK	DMF	reflux	1	43	(41)
$(MeO)_2RP(O)$[j]/NaH	DMF	100	6	30	(42)
$ROCO_2Me$[k]/NaH	DMF	60	20	18	(43)

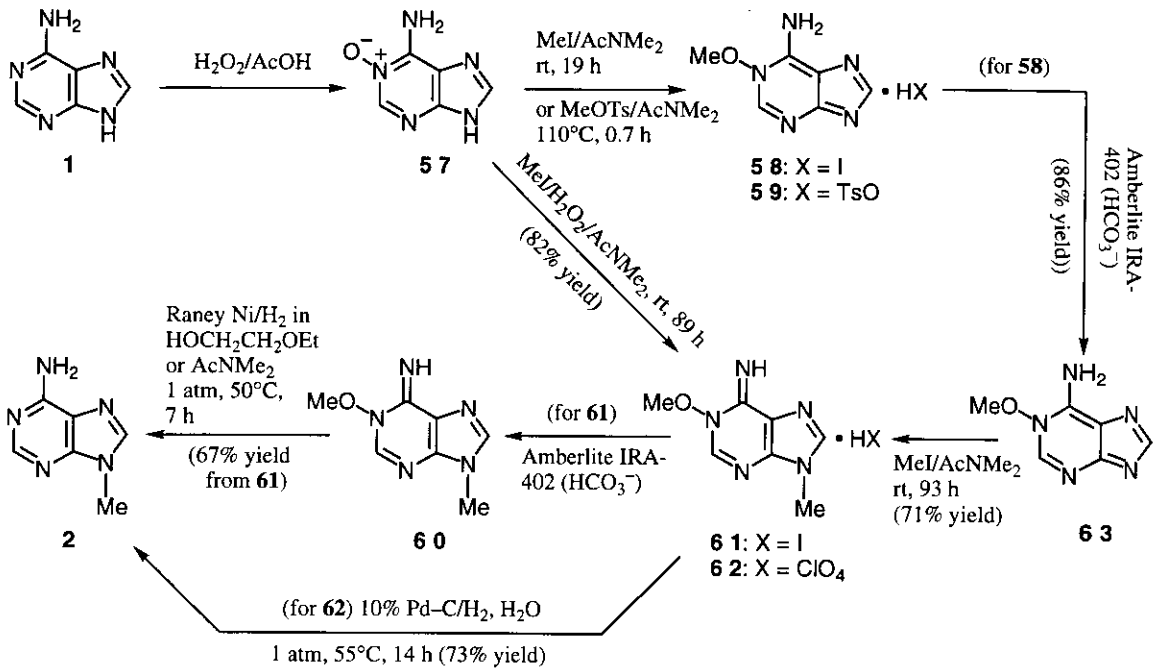
a) In 0.1 M phosphate buffer. *b*) Until the whole of the methylating agent was consumed. *c*) Not specified. The main product was 3-methyladenine (**4**). *d*) Under reduced pressure (0.05 mmHg). *e*) Accompanied by the formation of **4** (20% yield). *f*) With the by-product (**4**) (16% yield). *g*) With the by-product (**4**) (15% yield). *h*) With the by-product (**4**) (31% yield). *i*) With the by-product (**4**) (18% yield). *j*) R = $ClCH_2CH_2OCH_2$. *k*) R = $(PhCH_2OCH_2)_2(HC{\equiv}C)C$.

The remarkable example, now only of classical importance, of the type-iii syntheses is Fischer's synthesis[22] of **2** from uric acid through 2,6,8-trichloropurine (**43**), 2,8-dichloroadenine (**44**), and 2,8-dichloro-9-methyladenine (**45**) (Scheme 6). The last compound (**45**) was alternatively prepared from **46** *via* **47**[23] or from the trichloro derivative (**48**).[24]

Elion[25] methylated 6-chloropurine (**49**) with dimethyl sulfate to a mixture of 6-chloro-7-methylpurine (**103**) and 6-chloro-9-methylpurine (**38**), and the mixture was converted into an easily separable mixture of 7- and 9-methylpurine-6-thiols (**50** and **51**). The 9-methyl isomer (**51**) was *S*-methylated, and the resulting 6-methylthio derivative (**53**) was converted into **2** by amination (Scheme 7). Barlin and Young[26] converted **38**[27] into **2** through (9-methylpurin-6-yl)trimethylammonium chloride (**52**)[28a] (Scheme 7). They also converted **52** into 6-fluoro-9-methylpurine (**42**), an alternative synthetic precursor for **2**,[20] by treatment with potassium hydrogen difluoride in EtOH at 50°C for 2 h.[26] Adamiak *et al.*[28b] obtained 1-(9-methylpurin-6-yl)pyridinium chloride from 9-methylhypoxanthine (**80**) in 70% yield by treatment in pyridine with 4-chlorophenyl dichlorophosphate and 1,2,4-triazole at rt for 20 h, and the pyridinium salt was quantitatively transformed into **2** by treatment with concd aqueous NH_3 at rt for 1 h.

The syntheses of 9-methyladenine (**2**) from adenine [type-iv (*vide supra*)] so far reported may be divided into two groups, namely, one-step methylation and multistep synthesis. In the one-step methylation (**1**→**2**) of historical importance, reported by Krüger[29] in 1894, **1** was treated with MeI in warm EtOH in the presence of NaOH for 1 h to produce **2** in 40% yield. Since then, many variations[30–44] in the methylation procedure have appeared, as can be seen from Table I.

The multistep syntheses of **2** from **1** include that of Leonard and Fujii,[45] who treated 1-benzyladenine (**54**) [obtainable from adenosine (**143**),[45,46] and hence from **1**] with MeI to give 1-benzyl-9-methyladenine hydriodide (**55**) (Scheme 8). The hydriodide salt (**55**) was then debenzylated by conversion (with AgCl) into the hydrochloride (**56**) and hydrogenolysis with Pd–C/H_2, yielding **2**. Fujii's group[47] found that the reaction of adenine 1-oxide (**57**), obtainable from **1** in good yield by direct oxidation with 30% aqueous H_2O_2 in AcOH at rt,[47b,48] with MeI in $AcNMe_2$ at rt[47] or with methyl *p*-toluenesulfonate in $AcNMe_2$ at 110°C[47b] resulted in *O*-methylation, giving the 1-methoxyadenine salt (**58** or **59**) in 93% or 36% yield, respectively (Scheme 9). The hydriodide (**58**) was readily converted into the corresponding free base (**63**) by the use of Amberlite IRA-402 (HCO_3^-), and **63** afforded 1-methoxy-9-methyladenine hydriodide (**61**) when treated with MeI in $AcNMe_2$ at rt.[47] The hydriodide (**61**) was alternatively prepared from the N(1)-oxide (**57**) in a one-step manner by methylation with MeI in $AcNMe_2$ in the presence of 30% aqueous H_2O_2.[49] Catalytic hydrogenolysis of the free base (**60**), prepared from **61** by the use of Amberlite IRA-402 (HCO_3^-), produced **2** in 67% overall yield (from **61**).[47] The catalytic hydrogenolysis of the perchlorate (**62**) over Pd–C was rather slow, but gave **2** in 73% yield.[47b] Shugar's group[50] reported that UV irradiation (at 254 nm) of **60** at pH 4.20 or 10.46 resulted in the formation of **2** in 46% or 58% yield, respectively. Fujii's group prepared **2** from **61** through the imidazole derivatives (**64**[51] and **65**)[52] or through 9-methyladenine 1-oxide (**66**)[53] and the 1-(4-nitrobenzyloxy) derivatives (**67** and **68**)[54] (Scheme 10). Muravich-Aleksandr *et al.*[55] reported that conversions of 3-methyladenine hydriodide (**4**·HI) and 1-methyladenine hydriodide (**5**·HI), products from



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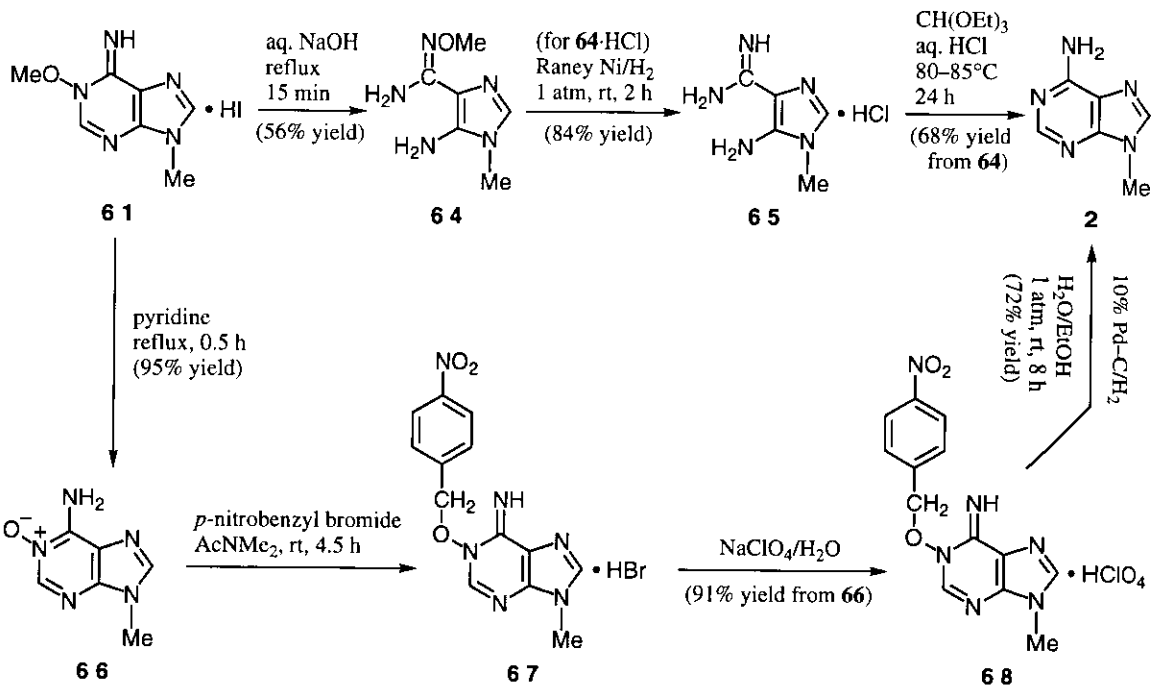
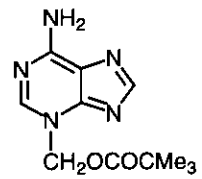


Scheme 10



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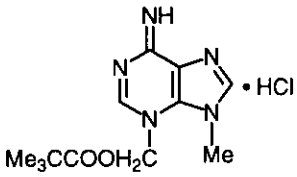

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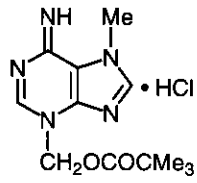

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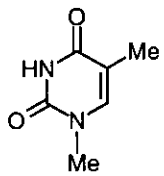

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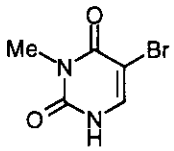

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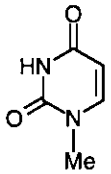

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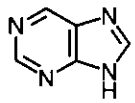

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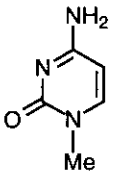

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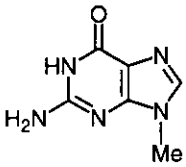

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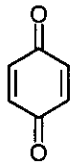

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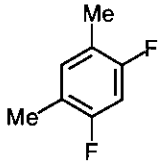

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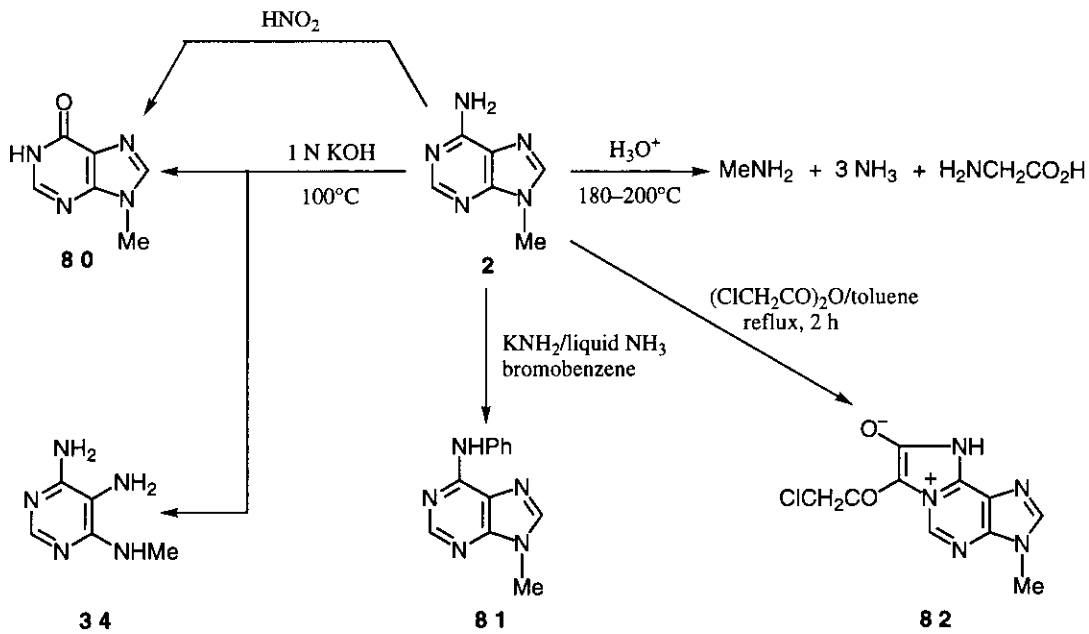


80 2 34 81 82

Scheme 11

methylation of adenine (**1**) with MeI in DMF at 20–30°C, into **2**·HI occurred at their melting points. The preparation of **2** by Kohda's group[56] started with reaction of **1** with chloromethyl pivalate in DMF at rt for 5 d to give 3-(pivaloyloxymethyl)adenine (**69**) in 8% yield. Methylation of **69** with MeI in DMF[57] at 60°C for 5 h gave a *ca.* 1:1 mixture of the 9- and 7-methylated derivatives (**70** and **71**), and subsequent hydrolysis of the mixture with 25% aqueous NH_3 at rt for 2 h afforded 9-methyladenine (**2**) and 7-methyladenine (**3**) in 15% and 18% yields, respectively.

Table II represents the fruits of an additional comprehensive survey of papers describing the physical properties and spectral characteristics of 9-methyladenine (**2**).[58–121]

There have been a certain number of papers dealing with molecular interactions between **2** and nitrogenous bases related to nucleic acids or between **2** and other organic compounds: **2**–1-methylthymine (**72**) (in H_2O);[115] a crystalline, hydrogen-bonded 1:1 complex of **2** and **72**;[82,83] **2**–3-methyl-5-bromouracil (**73**) (a crystalline complex);[88a] **2**–**72** (*in vacuo*);[117,122,123] **2**–1-methyluracil (**74**) (*in vacuo*);[117,122] **2**–**74**–**74** (*in vacuo*);[117,122] **2**–purine (**75**) (in H_2O at 298.2 K);[58] **2**–**72** (in H_2O) (the Watson–Crick hydrogen bonding present was unaffected by the presence of Cp_2VCl_2);[124] **2**–1-methylcytosine (**76**) (*in vacuo*);[123,125] **2**–**2** (in the gas phase);[126] **2**–**72** (in the gas phase);[126–128] **2**–**72** (in the solid state);[127] **2**–**74** (in $CHCl_3$);[126] **2**–**76** (in the gas phase);[126] **2**–9-methylguanine (**77**) (in the gas phase);[126] **2**–*p*-benzoquinone (**78**) (in H_2O at 293 K);[129] and **2**–2,4-difluoro-1,5-dimethylbenzene (**79**) (in the gas phase).[128]

Interactions of **2** with the following metal ions or metal complexes have also been investigated: $Ni(ClO_4)_2$ or $Cu(ClO_4)_2$ (in H_2O at 298.2 K);[60] $Cu(NO_3)_2$ (in D_2O or H_2O);[105a,130] $Cu(NO_3)_2$–ethylenediamine (in D_2O);[130] $Zn(NO_3)_2$ or $ZnCl_2$ (in D_2O or H_2O);[105a] Cp_2MoCl_2 (in H_2O);[131] a water-soluble (η^5-pentamethylcyclopentadienyl)-rhodium aqua complex (in D_2O);[132] *cis*- and *trans*-$Pt(NH_3)_2Cl_2$ (in H_2O);[133,134] *cis*-Pt(ethyleneimine)$_2Cl_2$ (in H_2O);[133] K_2PtCl_4 (in 0.1 N and 3 N aqueous HCl);[90,135,136] *cis*-$Pt(NH_3)_2Cl_2$ and [Pt(diethylenetriamine)Cl]Cl (at pH 6–7.5 and 50°C for 24 h);[71] $[(MeHg)_3O]OH$ (in EtOH);[66] MeHgOH (in H_2O;[93,137] in MeCN or DMF[101,138]). Treatment of Pt(9-methyladenine)Cl_3, prepared according to the literature procedure,[90] with 25% aqueous NH_3 provided $[(NH_3)_3Pt(9\text{-methyladenine})]Cl_2 \cdot 2H_2O$ as a crystalline solid.[136] Oxidation of the solid with 10% aqueous H_2O_2 gave *trans*-$[(OH)_2(NH_3)_3Pt(9\text{-methyladenine})]Cl_2$ (in 45% yield), which was also characterized as $[(OH)_2(NH_3)_3Pt\text{-}(C_6H_7N_5)](ClO_4)_2$ (58% yield).[136]

Hydrolysis of **2** with concd hydrochloric acid or sulfuric acid (a 1:2 mixture of concd sulfuric acid and H_2O) at 180–200°C for 12 h produced methylamine, ammonia, and glycine (Scheme 11).[22,29] Alkaline hydrolysis of **2** with 1 N aqueous KOH in a sealed tube at 100°C for 5 h furnished 9-methylhypoxanthine (**80**) (14% yield) and 4,5-diamino-6-methylaminopyrimidine (**34**) (5%) with 80% recovery of **2**.[139] Reaction of **2** with bromobenzene in liquid NH_3 containing KNH_2 at –33°C for 2 h afforded 9-methyl-N^6-phenyladenine (**81**) in 20% yield.[103] Deamination of **2** with $NaNO_2$ in dilute sulfuric acid at

TABLE II. 9-Methyladenine (**2**): Physical and Spectral Characteristics

Item	Specification[a]	Literature (ref. No.)
Melting point[b]	310°C (19a); 308–310°C (22, 23); 302–304°C[c] (15b); 301–302°C[c] (31); 301°C (58); 300–303°C (11); 300–302°C (10); 300–302°C (decomp) (25); 300°C[d] (17); 298–299°C (14); >280°C (21); >270°C (29)	
Acid dissociation constant		
basic pK_a	3.25 (50% aqueous DMF)[e] (59); 3.9 (H_2O)[f] (30a, 56); 4.45 ± 0.03[e,g] (60); 3.88 ± 0.01 (H_2O)[e,h] (61); 3.69 ± 0.02 (DMSO)[e,h] (61); 3.92 (H_2O)[f,i] (62); 3.2 (63)	
acidic pK_a	unmeasurable[e] (64); 16.7[f,j] (65); 17.0[f,h] (66)	
Paper chromatography		(25, 30b, 50, 67–69)
TLC		(34, 42, 70)
Ion-exchange chromatography		(71)
HPLC		(42, 105b,c)
MS		(15b, 44, 72, 73)
HRMS		(35b, 43)
UV spectrum	In H_2O at various pH's (17, 19a, 25, 30, 31, 33, 34, 42, 56, 59, 71, 74–77); in MeOH (76); in EtOH (78); in methylcyclohexane (75); in MeCN (75); in $(MeO)_3P(O)$ (75); in aqueous DMSO[k] (65); in a solvent mixture (11); in the vapor phase (75, 79); in an argon matrix (80)	
UV photoelectron spectrum		(81)
Polarized electronic spectrum		(82–85)
Phosphorescence spectrum		(86)
IR spectrum		(15b, 79, 80, 87–99)
Raman spectrum		(87, 93, 99)
^{1}H NMR spectrum	In DMSO-d_6 (15b, 41b, 42, 56, 58, 66, 68, 100–102, 145); in liquid NH_3 (103); in D_2O (44, 71, 104, 105a); in CD_3CO_2D (105b,c)	
^{13}C NMR spectrum	In DMSO-d_6 (41b, 42, 56, 58, 78, 100, 102); in DMSO (106); *in liquid NH_3 (103)*	
^{15}N NMR spectrum	In DMSO-d_6 (102, 107)	
Crystal structure	Free base (**2**) (3, 108); **2**·2HBr (3, 109)	
Tautomeric structure		(79, 110, 111)
Dipole moment		(3, 63, 97, 112, 121)
Transition moment		(113)
Anodic peak potential	+1.68 V (in DMF)	(114)
Solubility	In H_2O (at 20–40°C)	(115)
Distribution coefficient	Between H_2O and $CHCl_3$ (116); between H_2O and 2-butanol (116)	
Heat of solution	In DMSO or H_2O	(61, 75)
Heat of protonation	In DMSO or H_2O	(61)
Heat of vaporization		(75, 79)
Vapor pressure	At 140°C, 170°C, and 185°C	(75)
Heat of sublimation	At 170–230°C	(117)

(*continues*)

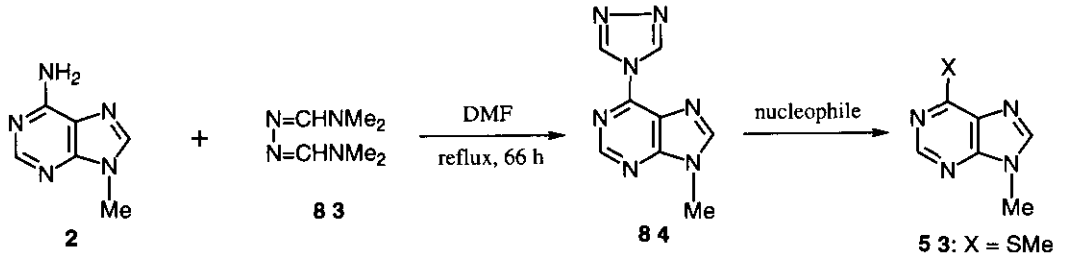
TABLE II (*continued*)

Item	Specification[a)]	Literature (ref. No.)
Gas-phase structure	By the *ab initio* LCAO-MO method	(118)
Triplet $\pi \rightarrow \pi^*$ transition energies	By the SCF MO method	(119)
HOMO and LUMO energies	Calculated by the MNDO method	(63)
π-Electron distribution	By the SCF MO method	(120)
Electronic structure	Under the INDO MO approximation	(121)

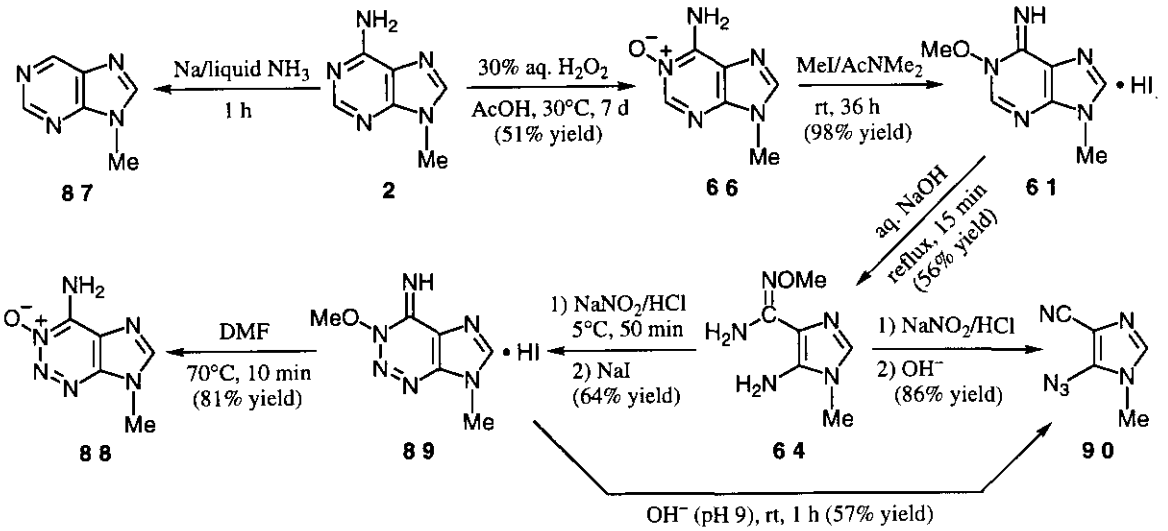
a) With or without reference number(s) in parentheses. *b*) Reported for an analytical sample. *c*) In a sealed tube. *d*) With sublimation. *e*) Titrimetric. *f*) Spectral. *g*) In 0.1 M aqueous $NaClO_4$ at 298.2 K. *h*) At 25°C. *i*) At 20°C. *j*) In aqueous DMSO containing $Me_4N^+OH^-$. *k*) Containing $Me_4N^+OH^-$.

70°C[23] or in dilute hydrochloric acid at 90°C for 0.5–1 h[25,44,140] gave **80** in 37–80% yield. Maki's group[141a] reported the conversion of **2** into the mesoionic imidazopurine derivative (**82**) (45.5% yield) on treatment with chloroacetic anhydride in boiling toluene (Scheme 11).[141b,c] Robins' group[142] transformed **2** into the 6-(1,2,4-triazol-4-yl)purine derivative (**84**) (85% yield) by treatment with 1,2-bis[(dimethylamino)-methylene]hydrazine dihydrochloride (**83**·2HCl) in boiling DMF for 66 h (Scheme 12). Separate treatments of **84** at rt in DMF with NaOMe/MeOH for 0.5 h, in DMF with NaSMe for 1.5 h, and with 40% aqueous Me_2NH for 1 h produced 6-methoxy-9-methylpurine (**85**) (in 97% yield), 9-methyl-6-methylthiopurine (**53**) (84%), and N^6,N^6,9-trimethyladenine (**86**) (99%), respectively.[142]

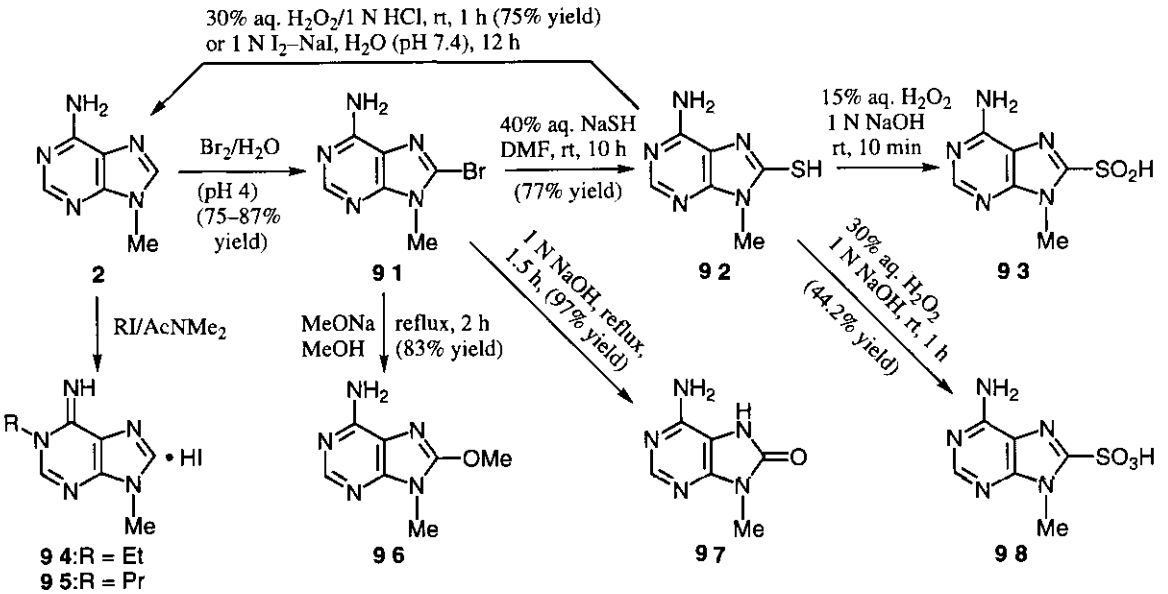
Kos and van der Plas[143] have reported the reductive deamination of **2** to provide 9-methylpurine (**87**) in 46% yield, which was effected with sodium in liquid NH_3 for 1 h (Scheme 13). Oxidation of **2** with 30% aqueous H_2O_2 in AcOH at 30°C for 7 d gave the N(1)-oxide (**66**) in 51% yield (Scheme 13).[144] Oxidation of the 2-deuterated species[145] of **2** with *m*-CPBA in MeOH at rt for 4 h afforded 9-methyladenine-2-*d* 1-oxide in 65% yield.[145b,146] Methylation of **66** with MeI in $AcNMe_2$ at rt for 36 h furnished the 1-methoxy derivative (**61**) (98% yield),[144] which was then converted into the monocycle (**64**)[51] by heating in aqueous NaOH (Schemes 10 and 13). Treatment of **64** with $NaNO_2$ in 1 N aqueous HCl at 0–3°C for 2 h and subsequent basification of the reaction mixture with aqueous Na_2CO_3 to pH 9 gave 5-azido-1-methylimidazole-4-carbonitrile (**90**) in 86% yield.[147] When the primary product from the diazotization of **64** in 1 N aqueous HCl was treated with NaI instead of aqueous Na_2CO_3, 1-methoxy-9-methyl-2-azaadenine hydriodide (**89**) was isolated in 64% yield, and treatment of **89** with aqueous Na_2CO_3 at pH 9 and rt for 1 h gave **90** in 57% yield, completing a five-step conversion of **2** into **90**.[147] On heating in DMF at 70°C for 10 min, **89** readily underwent C–O bond cleavage to give the *N*-oxide (**88**) in 81% yield, thus concluding a five-step conversion of **2** into **88**.[147]



Scheme 12



Scheme 13



Scheme 14

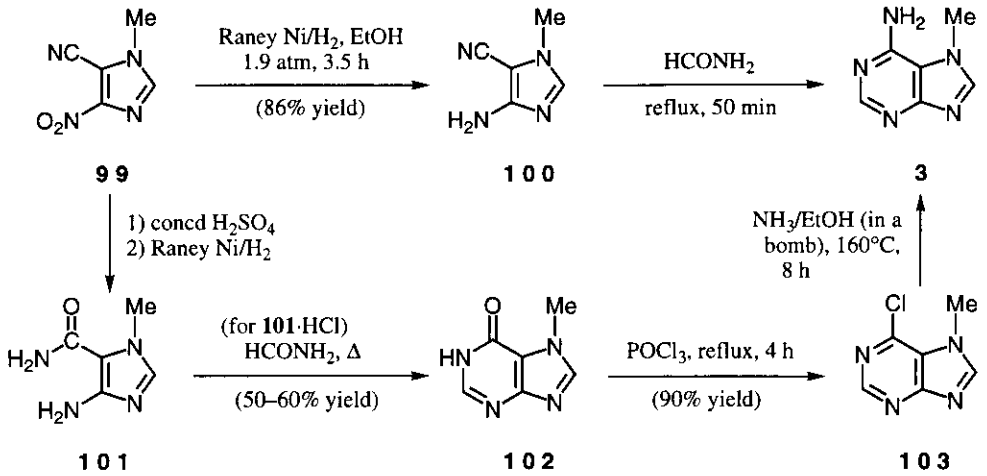
Bromination of **2** with Br_2 in 0.25 M or 0.5 M acetate buffer (pH 4) at rt for *ca.* 7 h produced the 8-bromo derivative (**91**) in 75% or 87% yield (Scheme 14).[148,149] Treatment of **91** with boiling 1 N aqueous NaOH for 1.5 h gave the 8-oxo derivative (**97**) in 97% yield.[149] Treatment of **91** with MeONa in boiling MeOH for 2 h provided the 8-methoxy derivative (**96**) in 83% yield.[150] Other reactions of **91** to give **2**,[151] the 8-sulfinic acid (**93**), and the 8-sulfonic acid (**98**) through the 8-mercapto derivative (**92**), as shown in Scheme 14, were also reported.[148b] Alkylations of **2** in $AcNMe_2$ with EtI (75–80°C, 7 h) and with PrI (90–95°C, 8 h) gave the corresponding 1-alkylated products (**94** and **95**) in 64% and 36% yields, respectively (Scheme 14).[51b] Methylation of **2** with trimethyl phosphate in H_2O at pH 9.5–10.0 and 37°C for 24 h was reported to form 1,9-dimethyladenine (type **193**) and N^6,9-dimethyladenine (**194**) in 2% and 3% yields, respectively.[34]

Kohda's group[152a] determined the pseudo-first-order rate constant ($k = 1.3 \times 10^{-1}$ h^{-1}) for deuterium labeling at C(8) of **2** in a phosphate-buffered D_2O solvent at pD 8.26 and 70°C.[152b] Arce[153] reported the transient absorption spectrum produced by 266-nm ns laser flash photolysis of an aqueous solution of **2**, and a few photochemical intermediates were proposed. Vieira and Steenken[62] studied the reaction of **2** with the OH radical in H_2O at pH 6–8 and 20°C by using pulse radiolysis with optical and conductance detection.

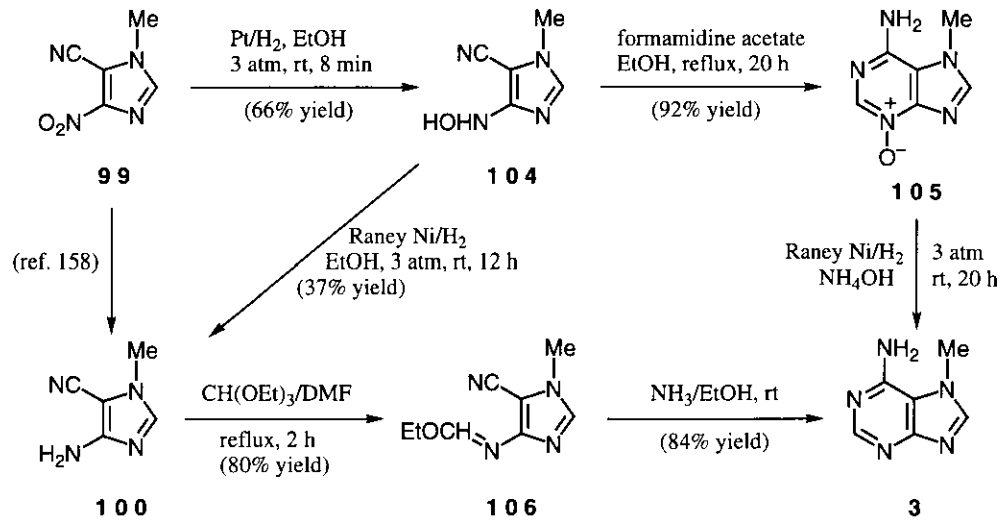
In vitro metabolism of adenine (**1**), 9-methyladenine (**2**), and 9-benzyladenine (**147**) using hepatic microsomes of hamster, mouse, and rat was investigated by Gorrod's group.[105b] The results indicated that **1** was apparently not susceptible to microsomal *N*-oxidation. *N*-Oxidation of **2** was also not detected, whereas *N*-demethylation (to give **1**) was observed with hepatic microsomes derived from hamster and rat but not from mouse. With 9-benzyladenine (**147**), both N(1)-oxide formation and N(9)-debenzylation occurred with microsomes of all species in various amounts. The metabolic *N*-oxidation study was then extended to include 9-benzhydryladenine and 9-trityladenine as the substrates and hepatic microsomes from guinea pig, rabbit, and dog.[105c] Although N(1)-oxide formation occurred with 9-benzyladenine (**147**) and 9-benzhydryladenine using lever preparations of all species examined, that of **1**, **2**, or 9-trityladenine was not observed.[105c]

III. 7-METHYLADENINE

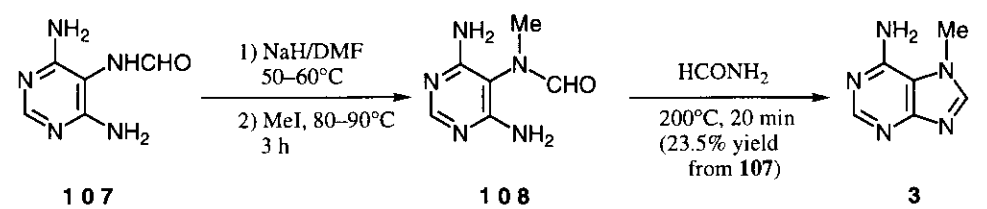
The existence of 7-methyladenine (**3**) in the form of the 7-methyladenosine structure (type **123**) in tRNA's of *Bacillus stearothermophilus*[154] and *B. subtilis*[155] has been suggested. The toxicity and anticancerogenic property of **3** against Ehrlich mouse carcinoma and against other transplantable mouse cancers have been studied.[156] Young's group[10] reported that **3** was a weak competitive inhibitor of human erythrocyte membrane phosphotidylinositol 4-kinase. Dorée *et al.*[12] reported that **3** was devoid of the



Scheme 15



Scheme 16



Scheme 17

ability to replace 1-methyladenine (**5**) in triggering meiosis in the starfish *Marthasterias glacialis* and *Asterias rubens* oocytes. No cytokinin activity was observed for **3**.[157]

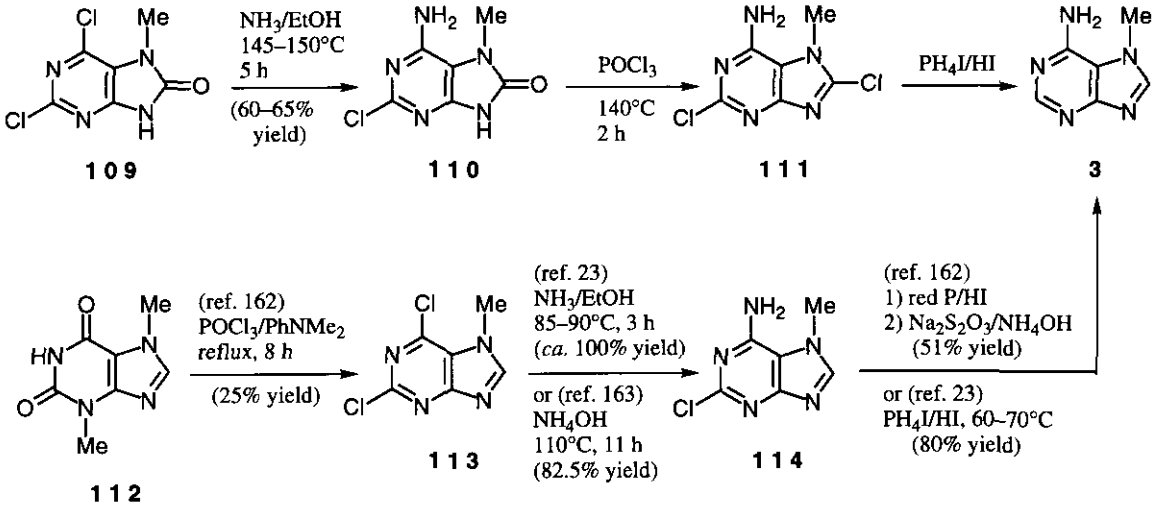
Prasad and Robins[158] synthesized 7-methyladenine (**3**) from 1-methyl-4-nitroimidazole-5-carbonitrile (**99**) *via* the 4-amino derivative (**100**) or *via* 4-amino-1-methylimidazole-5-carboxamide (**101**), 7-methylhypoxanthine (**102**), and 6-chloro-7-methylpurine (**103**), as shown in Scheme 15. Taylor and Loeffler's synthesis of **3** started from **99** and proceeded through the 4-hydroxyamino derivative (**104**) and the N(3)-oxide (**105**) (Scheme 16).[159] An alternative synthesis by them started from **99** and proceeded through **100** (or *via* **104**[159]) and the 4-ethoxymethyleneamino derivative (**106**).[160]

In the synthesis of **3** from a pyrimidine derivative by Denayer's group,[161] 4,6-diamino-5-formamidopyrimidine (**107**) was first treated with NaH in DMF and then methylated with MeI to give the 5-(*N*-methylformamido) derivative (**108**) (Scheme 17). Cyclization of **108** to **3** was then effected in $HCONH_2$ at 200°C for 20 min. Fischer's synthesis[23] of **3** started from 2,6-dichloro-7-methyl-8-oxopurine (**109**) and proceeded through the 6-amino-2-chloro derivative (**110**) and 2,8-dichloro-7-methyladenine (**111**) or from 2,6-dichloro-7-methylpurine (**113**) and through 2-chloro-7-methyladenine (**114**) (Scheme 18). Uretskaya *et al.*[162] obtained **113** from theobromine (**112**) in 25% yield by treating the latter with $POCl_3$ and $PhNMe_2$, and they converted **114**, obtainable from **113** by the known procedure,[23,163] into **3** by reduction with red P/HI in 51% yield (Scheme 18). Elion's synthesis[25] of **3** started from 7-methylpurine-6-thiol (**50**), obtainable from 6-chloropurine (**49**) by a two-step route (see Scheme 7), and proceeded *via* the 6-carboxymethylthio derivative (**115**), as delineated in Scheme 19.

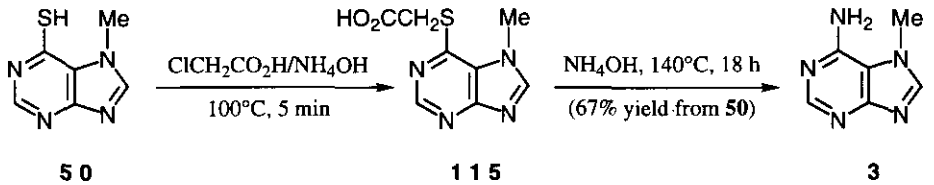
7-Methyl-2'-deoxyadenosine [type **123** (H for C(2')-OH)] and 7-methyladenosine (type **123**) have been assumed to occur, although to a slight extent, as very unstable partial structures in methylated DNA[164] (and deoxyadenylic acid[164a]) and RNA[165] [and poly(A)[166]] molecules,[167] respectively, from which **3** has been hydrolyzed and identified. Singer *et al.*[168] reported that 7-methyladenosine [type **123** with unspecified anion (X^-)] was only a by-product of methylation of adenosine (**143**) in neutral aqueous solution. Thus, these direct methylations of nucleic acids and of adenosine at the nucleotide and nucleoside levels, followed by hydrolysis, are not competent enough to serve as a method for the preparation of **3** because of their low efficiency.

Yamauchi *et al.*[34] found that **3** was a by-product (6% yield) from the methylation of adenine (**1**) with trimethyl phosphate in H_2O (pH 9–12) at 25°C for 48 h. Beasley and Rasmussen[38] also found that methylation of **1** with MeI in DMF at 30°C for 168 h produced a minor amount of **3**, and the low efficiency in producing **3** was not improved when the methylation was carried out in the presence of NaH at 30°C for 16 h.[39]

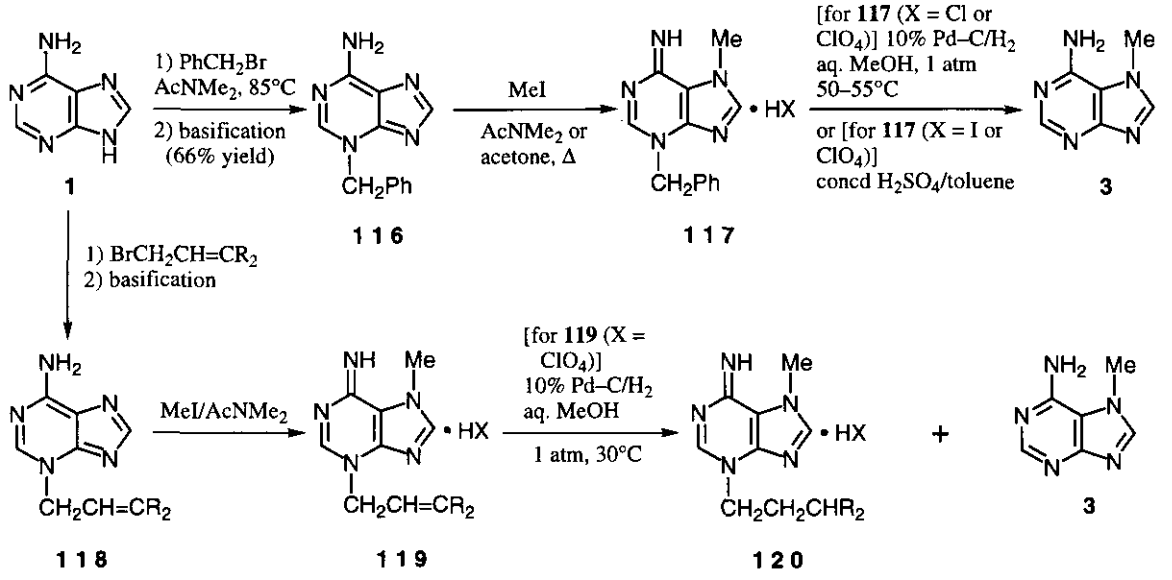
Leonard's group[169] devised a convenient synthetic route to **3** from adenine (**1**) by regioselective methylation utilizing blocking/deblocking at the 3-position, as depicted in Scheme 20. Thus, treatment of **1** with $PhCH_2Br$ in $AcNMe_2$ at 85°C furnished, after



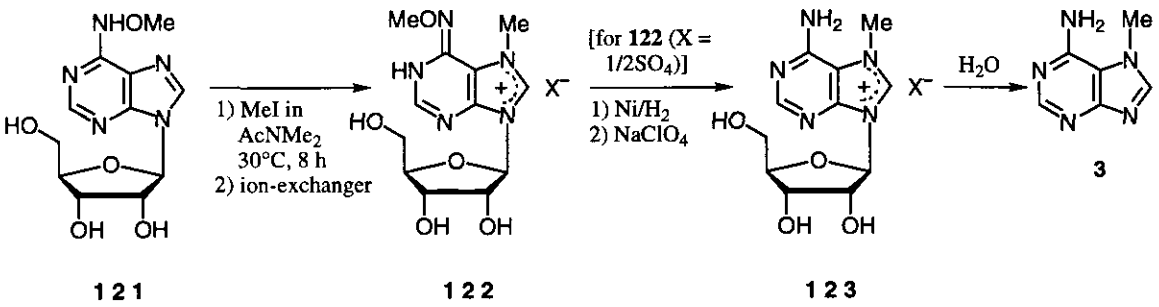
Scheme 18



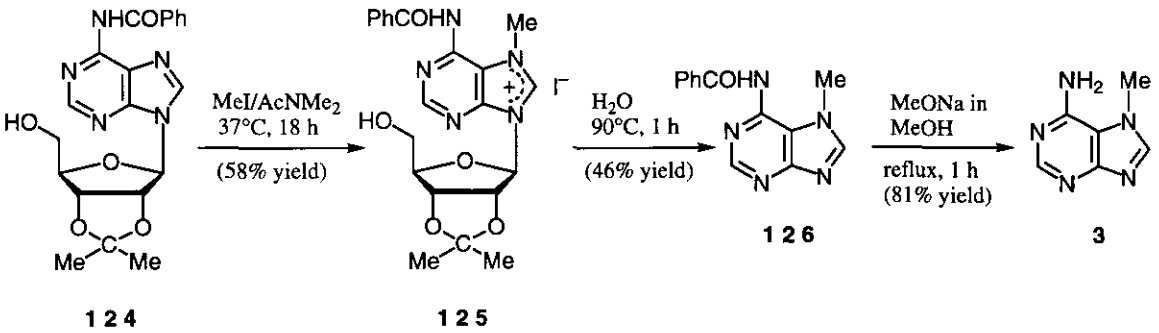
Scheme 19



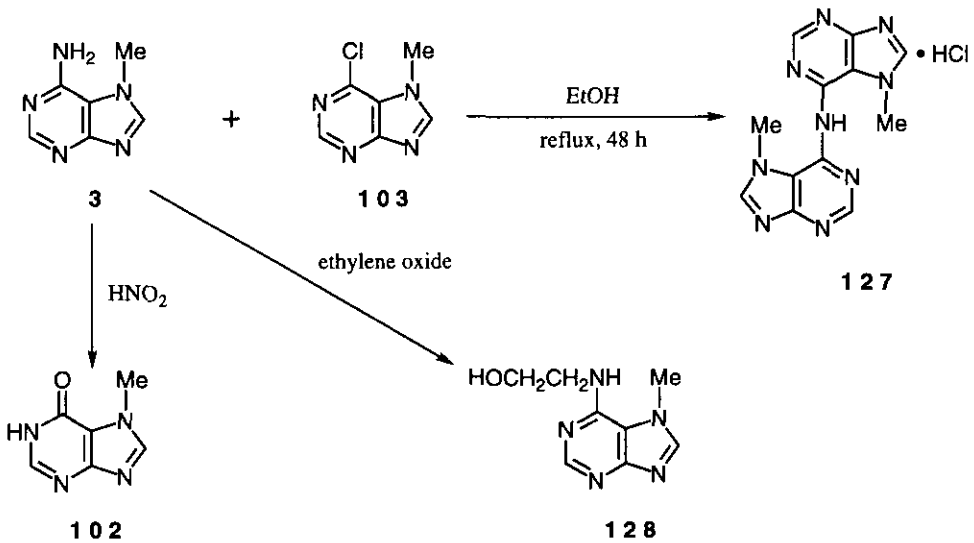
Scheme 20



Scheme 21



Scheme 22



Scheme 23

basification, 3-benzyladenine (**116**) in 66% yield. When heated with MeI in $AcNMe_2$ or acetone, **116** underwent methylation mainly at the 7-position, giving 3-benzyl-7-methyladenine hydriodide [**117** (X = I)] in 58% overall yield (from **1**). The hydriodide [**117** (X = I)] was readily converted into the hydrochloride salt [**117** (X = Cl)] or the perchlorate salt [**117** (X = ClO_4)]. Hydrogenolysis of **117** (X = Cl or ClO_4) using hydrogen and Pd–C catalyst produced **3** in good yield. Alternatively, **117** (X = I or ClO_4) was debenzylated efficiently by treatment with concd sulfuric acid in the presence of toluene at 30°C for 3 h or at 60°C for 30 min, giving **3** in 85% or 93% yield, respectively.[169c] Deblocking of an allylic group at the 3-position was much less effective than that of the benzyl group. In the cases of catalytic hydrogenolyses of 3-allyl-7-methyladenine salt [**119a** (X = I or ClO_4)] and of 3-(3-methyl-2-butenyl)-7-methyladenine perchlorate [**119b** (X = ClO_4)] [prepared from **1** *via* **118** (Scheme 20)], the major products were the hydrogenated salts (**120a** and **120b**), while the hydrogenolyzed product (**3**) was only detected by paper chromatography.[169a,b]

In another approach utilizing an alkoxy group as a control synthon for alkylation of the adenine ring,[170] Fujii *et al.*[171] methylated N^6-methoxyadenosine (**121**)[145,170,172] with MeI in $AcNMe_2$ at 30°C for 8 h, and methylated products were isolated by means of column chromatography [Amberlite CG-400 (HSO_4^- and/or SO_4^{2-}), H_2O followed by 0.5 N formic acid], obtaining the 7-methylated product [**122** (X = 1/2SO_4)] in 55% yield together with the N^6-methyl isomer as a minor product (Scheme 21). Removal of the N^6-methoxy group from **122** (X = 1/2SO_4) was then effected by catalytic hydrogenolysis over Raney Ni catalyst (H_2O, 1 atm, rt, 9 h) to produce 7-methyladenosine sulfate [**123** (X = 1/2SO_4)], which was converted into the perchlorate [**123** (X = ClO_4)] in 53% overall yield [from **122** (X = 1/2SO_4)] by treatment with $NaClO_4$ in H_2O. On heating in H_2O at 98–100°C for 40 min, **123** (X = ClO_4) afforded **3** in 84% yield. In 0.1 N aqueous HCl at 25°C, **123** (X = ClO_4) was found to undergo glycosidic hydrolysis at a rate of 2.22×10^{-3} min^{-1} (half-life 5.2 h).[171b,c] On treatment with 1 N aqueous NaOH at 60°C for 3 h, it was also hydrolyzed to give **3** in 44% yield.[171b,c] Imagawa's group[173] found that **123** (X = ClO_4) was hydrolyzed in buffer (pH 8.0–8.5) at 37°C by both *N*-methylnucleoside hydrolase (obtained from tea-leaf extracts) and adenosine nucleosidase, producing **3**. However, the enzyme activity of the latter was higher than that of the former.

In yet another synthetic approach, Maki's group[174] obtained **3** from the N^6-benzoyladenosine derivative (**124**) through the 7-methyl derivative (**125**) and N^6-benzoyl-7-methyladenine (**126**), as depicted in Scheme 22. The synthesis of **3** from 3-(pivaloyloxymethyl)adenine (**69**) *via* the 7-methylated derivative (**71**) in rather low overall yield by Kohda's group[56] is referred to in Section II. Morita *et al.*[77] heated a mixture of HCONHMe, $HCONH_2$, and $POCl_3$ in a sealed vessel at 120°C for 12 h and obtained **3** in 5% yield.

Table III may serve to locate papers describing the physical properties and spectral characteristics of 7-methyladenine (**3**), with additional references.[175–182]

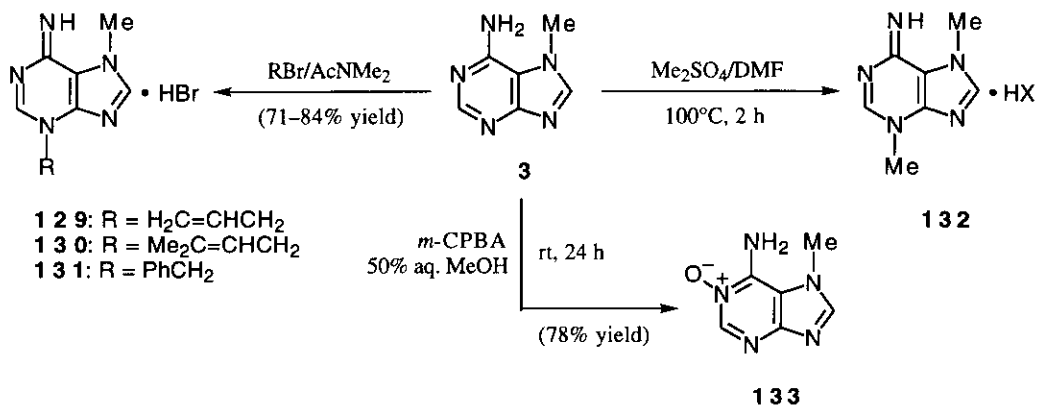
TABLE III. 7-Methyladenine (**3**): Physical and Spectral Characteristics

Item	Specification[a]	Literature (ref. No.)
Melting point[b]	>300°C (10); 351°C (23); 323°C (decomp) (25); 344–346°C (decomp) (158); 344–345°C (161a,b); 345–346°C (162); 349–350°C (decomp) (169a,c)	
3·$HClO_4$	285–287°C (decomp) (169c)	
Acid dissociation constant		
basic pK_a	3.6 (50% aqueous DMF)[c] (59, 77); 3.5 (50% aqueous DMF) (161a); 3.6 (63); 3.6 (H_2O)[d] (56); 4.2 (H_2O)[d] (30a)	
acidic pK_a	14.7[d,e] (65)	
Paper chromatography		(25, 67a,b, 68, 69, 165b, 168)
TLC		(34)
Ion-exchange chromatography		(164b)
HPLC		(164h, 173, 175)
MS		(72, 176)
UV spectrum	In H_2O at various pH's (25, 30a, 34, 56, 59, 74, 76, 77, 158, 161a,b, 164a, 168, 169c); isosbestic point (77, 161a,b); in MeOH (76); in EtOH (78, 169c); in aqueous DMSO[f] (65); in a modified HPLC-effluent (175); in a solvent mixture (177)	
UV photoelectron spectrum		(81)
Fluorescence spectrum		(175, 177, 178)
Fluorescence excitation spectrum		(177)
Phosphorescence spectrum		(177)
IR spectrum		(88b, 94, 164h, 179)
^1H NMR spectrum	In DMSO-d_6 (56, 68, 164h, 180); in liquid NH_3 (103); in D_2O (104)	
3·HCl	In DMSO-d_6 (181)	
3·$HClO_4$	In DMSO (169c)	
^{13}C NMR spectrum	In DMSO-d_6 (56, 78, 181); in DMSO (106)	
Crystal structure	**3**·2HCl	(109, 182)
Tautomeric structure		(111, 179)
Dipole moment		(63)
Anodic peak potential	+1.17 V (in DMF)	(114)
HOMO and LUMO energies	By the MNDO method	(63)

a) With or without reference number(s) in parentheses. *b*) Reported for an analytical sample. *c*) Titrimetric. *d*) Spectral. *e*) In aqueous DMSO containing tetramethylammonium hydroxide. *f*) Containing tetramethylammonium hydroxide.

As regards the chemical behavior of **3**, deamination with $NaNO_2$ in dilute sulfuric acid at 70°C gave 7-methylhypoxanthine (**102**) in quantitative yield (Scheme 23).[23] Reaction of **3** with 6-chloro-7-methylpurine (**103**) in boiling EtOH for 48 h afforded the N^6-substituted product (**127**).[158] Heating a mixture of **3**, ethylene oxide, and 25% aqueous AcOH in a sealed tube on a steam bath for 12 h produced the N^6-(2-hydroxyethyl) derivative (**128**) in 26% yield.[162]

Leonard's group[169a,b] found that heating **3** with allyl bromide, 3-methyl-2-butenyl bromide, or benzyl bromide in $AcNMe_2$ yielded (71–84%) the corresponding 3,7-disubstituted derivative (**129**, **130**, or **131**) (Scheme 24). Robins' group[183] methylated **3** with dimethyl sulfate in DMF at 100°C for 2 h to obtain the 3,7-dimethyl derivative [**132** (X = $MeOSO_3$)]. These results determine the preferred site of alkylation of **3** to be the 3-position.



Scheme 24

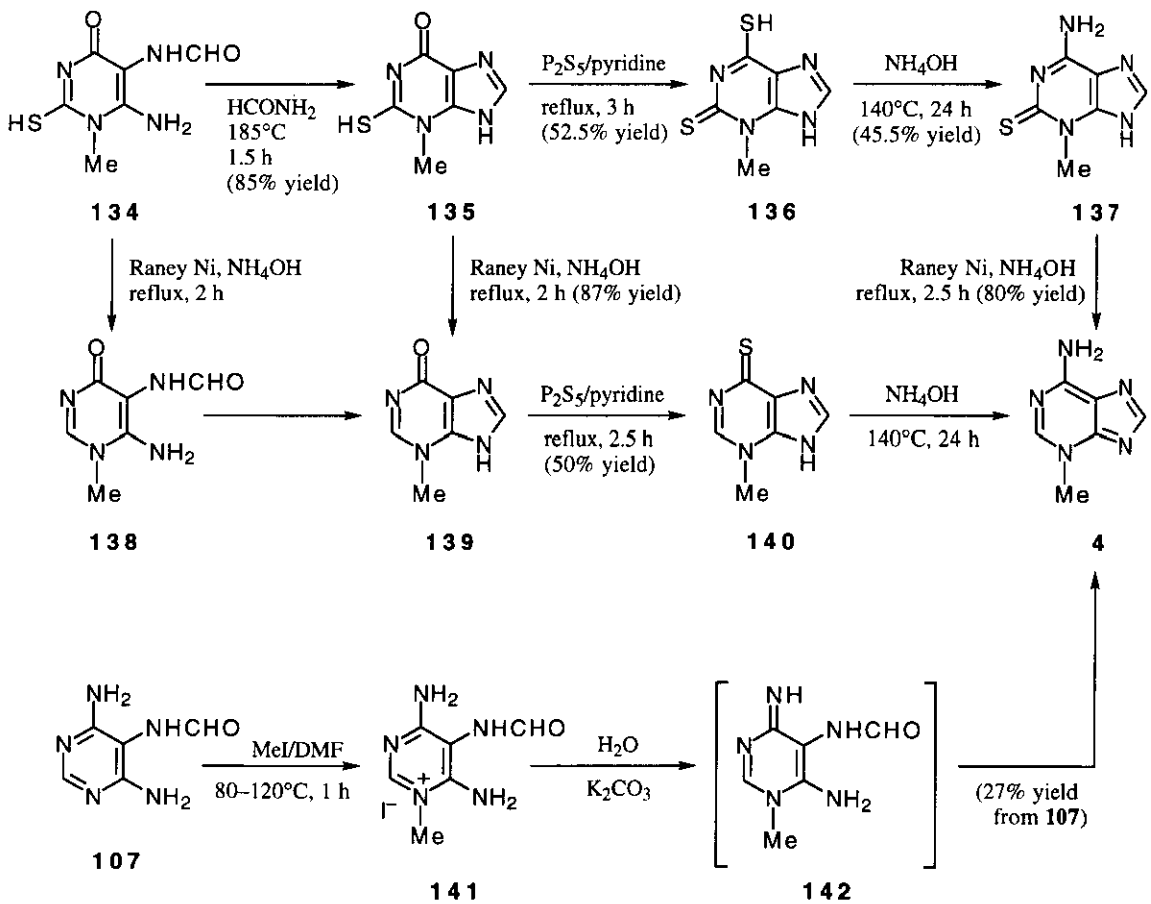
Oxidation of **3** with *m*-CPBA in 50% aqueous MeOH at rt for 24 h furnished the N(1)-oxide (**133**) (78% yield), and separate alkylations of **133** with MeI, EtI, and $PhCH_2Br$ in $AcNMe_2$ at rt for 1.25–28 h afforded the corresponding 1-alkoxy-7-methyladenine salts in 80–90% yields.[184,185]

The pseudo-first-order rate constant (k = 1.3 h^{-1}) for deuterium labeling at C(8) of **3** in a phosphate-buffered D_2O solvent at pD 8.26 and 70°C was determined.[152a] Arce[153] reported the transient absorption spectrum produced by 266-nm ns laser flash photolysis of an aqueous solution of **3** and proposed a few photochemical intermediates.

IV. 3-METHYLADENINE

2'-Deoxy-3-methyladenosine (type **162**) has been assumed to occur as a partial structure in methylated DNA molecules.[186] As far as DNA sequencing by the original Maxam–Gilbert method[187] is concerned, dimethyl sulfate methylates the 2'-deoxyguanosines in DNA at the 7-position and the 2'-deoxyadenosines at the 3-position,

rendering the glycosidic bond of the methylated families labile to hydrolysis on heating at neutral pH. Whereas the methylation of the latter is considerably slower than that of the former, release of 3-methyladenine (**4**) by hydrolysis from the 2'-deoxy-3-methyladenosines in methylated DNA is considerably faster than that of 7-methylguanine from the 2'-deoxy-7-methylguanosines. This forms a basis for distinguishing between the adenines (**1**) and guanines in DNA.[186,187] Both humans and laboratory animals were found to excrete low levels of **4** in the urine when they were not exposed to exogenous methylating agents, indicating that the majority of urinary 3-methyladenine (**4**) was dietary in origin.[188] Thus, the analysis of urinary **4** remains a good integrated measure of DNA methylation by methylating carcinogens.[188]



Scheme 25

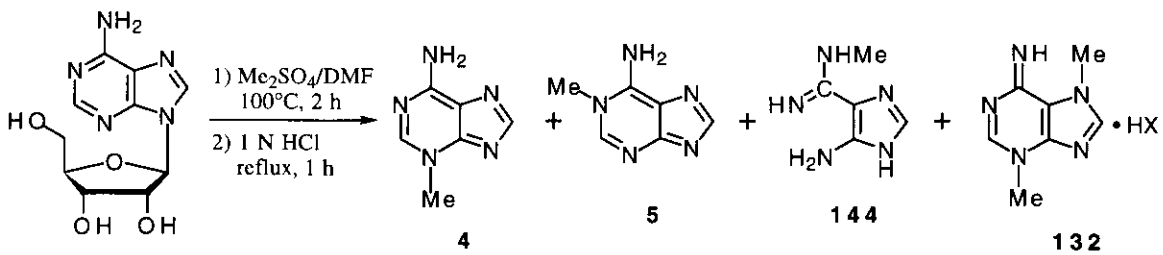
Although loss of **4** from methylated DNA *in vivo* could be explained in terms of chemical depurinylation alone, active enzymic excision has also been suggested.[189] This led to the isolations of 3-methyladenine-DNA glycosylase in partially purified form from both bacterial and mammalian sources.[164g,190,191] The enzymic release of **4** from methyl-

ated DNA has been reported to be markedly dependent on the secondary structure of the DNA.[190,191d]

Murthy and Deorukhakar[192] cultured diploid yeast (*S. cerevisiae* BZ34) auxotrophic to adenine (**1**) in synthetic medium supplemented with 3-methyladenine (**4**) and found that no growth occurred, whereas the **1**-supplemented cultures grew to stationary phase over 48-h period. No cytokinin activity was observed for **4**.[157] Monsees *et al.*[63] found that **4** was a weak inhibitor of 1-methyladenine-induced maturation of the starfish oocytes. Young *et al.*[10] reported that **4** was a weak competitive inhibitor of human erythrocyte membrane phosphatidylinositol 4-kinase.

In the synthesis of 3-methyladenine (**4**) from a pyrimidine derivative by Elion,[25] 4-amino-5-formamido-2-mercapto-3-methylpyrimidin-6-one (**134**) was heated in $HCONH_2$ to give 2-mercapto-3-methylhypoxanthine (**135**) (Scheme 25). Dethiolation with Raney Ni transformed **135** into 3-methylhypoxanthine (**139**). An alternative route to **139** was the dethiolation of **134** to give **138**, followed by cyclization to **139**. However, difficulties were encountered in obtaining **138** in a pure state because some deformylation as well as cyclization occurred under the alkaline conditions employed for the dethiolation. The thiation of **139** leading to **140** proceeded rather smoothly with P_2S_5 in pyridine. Although **140** would be converted into **4** with concd aqueous NH_3 at 140°C for 24 h, a better synthesis of **4** proved to be the thiation of **135** to give the dithio derivative (**136**), followed by conversion into **137** and subsequent desulfurization with Raney Ni.[25]

Denayer's group[161] synthesized **4** from **107** by alkylation with MeI in DMF in the absence of added base, followed by treatment of the resulting quaternary salt (**141**) with aqueous K_2CO_3 (Scheme 25). This methylation of **107** at the endocyclic nitrogen presents a sharp contrast with that at the exocyclic nitrogen,[161] carried out in the presence of NaH and utilized for the synthesis of 7-methyladenine (**3**) (see Scheme 17).

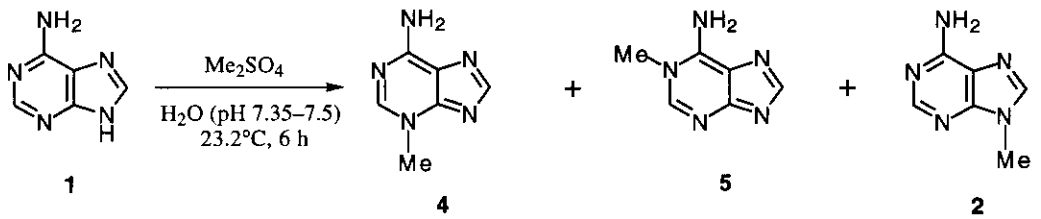


143 **4** **5** **144** **132**

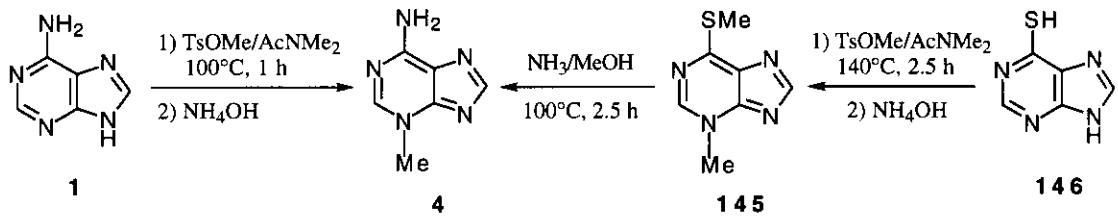
Scheme 26

3-Methyladenine (**4**) has been isolated, although only in a minute amount, from methylated DNA[164,187b,189–191,193,194] [and 2'-deoxyadenylic acid[164a,196] or 2'-deoxyadenosine (**154**)[195]] and RNA[69,165b,193,194] [and poly(A),[165] adenylic acid,[196] or adenosine (**143**)[168,196]] molecules.[167] Brookes and Lawley[196] methylated adenosine (**143**) with dimethyl sulfate in DMF and hydrolyzed the product mixture to obtain **4** (7% yield), 1-

methyladenine (**5**) (31%), the imidazole derivative (**144**) (20%), and 3,7-dimethyladenine salt (**132**) (6%) (Scheme 26).[197]



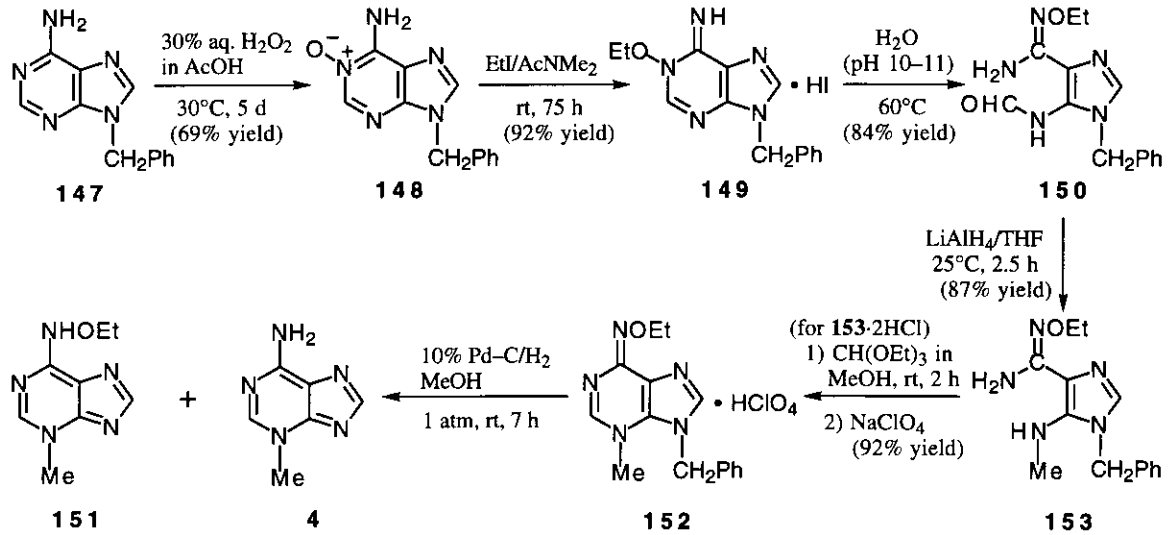
Scheme 27



Scheme 28

Pal[30a] found that treatment of adenine (**1**) with dimethyl sulfate, under conditions similar to those employed by Reiner and Zamenhof,[30b] gave **4**, **5**, and 9-methyladenine (**2**) in 44%, 14%, and 5.3% yields, respectively (Scheme 27). Jones and Robins[198] prepared **4** uncontaminated with other isomers in good yield by methylation of **1** with methyl *p*-toluenesulfonate in $AcNMe_2$ and treatment of the resulting **4**·TsOH with aqueous NH_3 (Scheme 28). Alternatively, they obtained **4** from 6-mercaptopurine (**146**) through 3-methyl-6-methylthiopurine (**145**).[198] Methylation of **1** with MeI in DMF at 20–30°C was reported to produce **4**·HI and **5**·HI.[55,199] The main products from a similar reaction at 150°C were **4**·HI and the 3,7-dimethyl derivative (**132**).[55] Yamauchi *et al.* methylated **1** in DMF with trimethyl phosphate at 140°C for 2 h[200] or with dimethyl methylphosphonate at 140°C for 9 h[200] or in H_2O (pH 10–11) with trimethyl phosphate at 60°C for 24 h[34] to obtain **4** in 45%, 61%, or 6% yield, respectively. Ogilvie *et al.* methylated **1** in THF with Me_2SO_4/Bu_4NF at 22°C for 0.5 h[37] (or for 16 h[36]) or with Me_2SO_4/Bu_4NOH at 22°C for 0.5 h[37] (or for 16 h[36]) or with $(MeO)_3PO/Bu_4NF$ in THF at 25°C for 1 h[35a] (or at 22°C for 16 h[36]), or with $MeSO_3Me/Bu_4NF$ in THF at 22°C for 0.5 h[36] to obtain 3-methyladenine (**4**) and 9-methyladenine (**2**) in 15% and 84%[37] (or 20% and 80%[36]), or in 31% and 57%,[36,37] or in 20% and 80%[35a] (or 16% and 84%[36]), or in 18% and 81% yields,[36] respectively. Beasley and Rasmussen[38] reported that methylation of **1** with MeI in DMF at 30°C for 168 h gave a mixture of methylated products (63% yield), which included **4** (56%) and **2** (30%). When the methylation was effected in the presence of NaH at 30°C for 16 h, the products included **4** (17%), **3** (6%), and **2** (77%).[39] The enzy-

mic conversion of **1** into **4** has been reported by Axelrod and Daly.[67a] They incubated a mixture of a dialyzed soluble supernatant fraction obtained from rabbit lung, *S*-adenosyl[*Me*-^{14}C]methionine, adenine (**1**), and phosphate buffer (pH 7.9) at 37°C for 90 min and found that the enzymically formed metabolite had the same R_f values as **4** in six solvent systems.

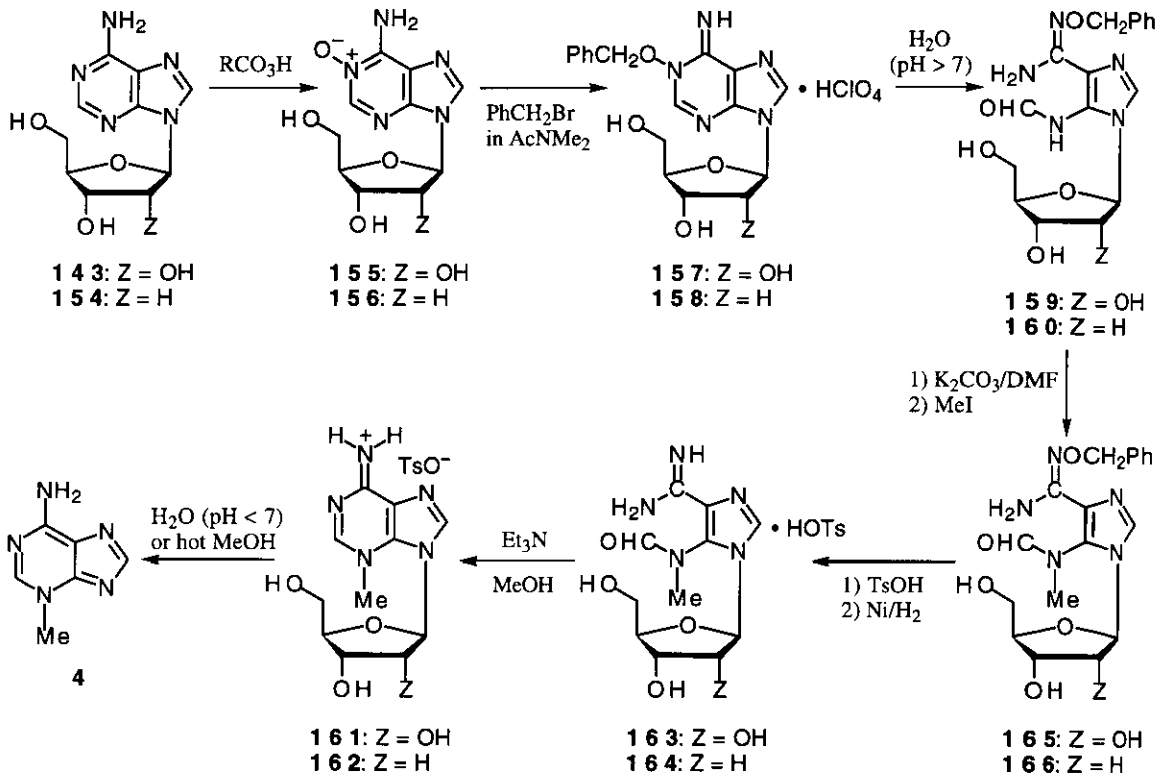


Scheme 29

A multistep synthesis of **4** from 9-benzyladenine (**147**) was reported by Fujii's group (Scheme 29):[201] Treatment of 9-benzyl-1-ethoxyadenine hydriodide (**149**), obtainable from **147** through the N(1)-oxide (**148**),[144] in H_2O at pH 10–11 and 60°C gave the formamidoimidazole derivative (**150**), which was then led to 9-benzyl-N^6-ethoxy-3-methyladenine perchlorate (**152**) *via* the methylaminoimidazole (**153**). Hydrogenolysis of **152** using 10% Pd–C catalyst and hydrogen in MeOH resulted in debenzylation to form **4** (25% yield) and N^6-ethoxy-3-methyladenine (**151**) (38%).[201]

Multistep syntheses of **4** from adenosine (**143**) *via* 3-methyladenosine *p*-toluenesulfonate (**161**) and from 2'-deoxyadenosine (**154**) *via* 2'-deoxy-3-methyladenosine *p*-toluenesulfonate (**162**) were also accomplished by Fujii's group (Scheme 30):[202] Methylation of the formamidoimidazole (**159**), prepared from **143** through the N(1)-oxide (**155**) and 1-benzyloxyadenosine perchlorate (**157**), with MeI in DMF in the presence of anhydrous K_2CO_3 at rt for 9 h gave the *N*-methylformamido derivative (**165**) in 86% yield. Next **165** was hydrogenolyzed with Raney Ni catalyst and hydrogen (1 atm, rt, 70 min) in H_2O containing 1 molar equiv. of TsOH, and crude **163** that resulted was treated with a little Et_3N in MeOH at rt for 48 h, producing **161** in 53% yield (from **165**).[202a,c] A parallel sequence of conversions starting from **154** and proceeding through **156**, **158**, **160**, **166**, and **164** afforded **162**.[202b,c] On treatment with 0.1 N aqueous HCl at 27°C for 1 h, **161** furnished **4** in 92% yield.[202a,c] Treatment of **162** with H_2O at pH 3.34 and 20°C for

45 min or with boiling MeOH for 30 min gave **4** in 60% or 99% yield, respectively.[202b,c] At pH 1 and 25°C, **161** (half-life 17 min) underwent glycosidic hydrolysis (depurinylation) some thousand times faster than did adenosine (**143**) itself.[202a,c] At pH 3.34 and 25°C, the 2-deoxyribosyl analogue (**162**) (half-life 2.7 min) was depurinylated 370 times more rapidly than the ribosyl analogue (**161**) (half-life 1010 min).[202b,c] Imagawa's group[173] reported that **161** was hydrolyzed in buffer (pH 8.0–8.5) at 37°C by *N*-methylnucleoside hydrolase obtained from tea-leaf extracts, giving **4**.



Scheme 30

For papers describing the physical properties and spectral characteristics of 3-methyladenine (**4**), the reader is referred to Table IV, which includes additional references.[203–211]

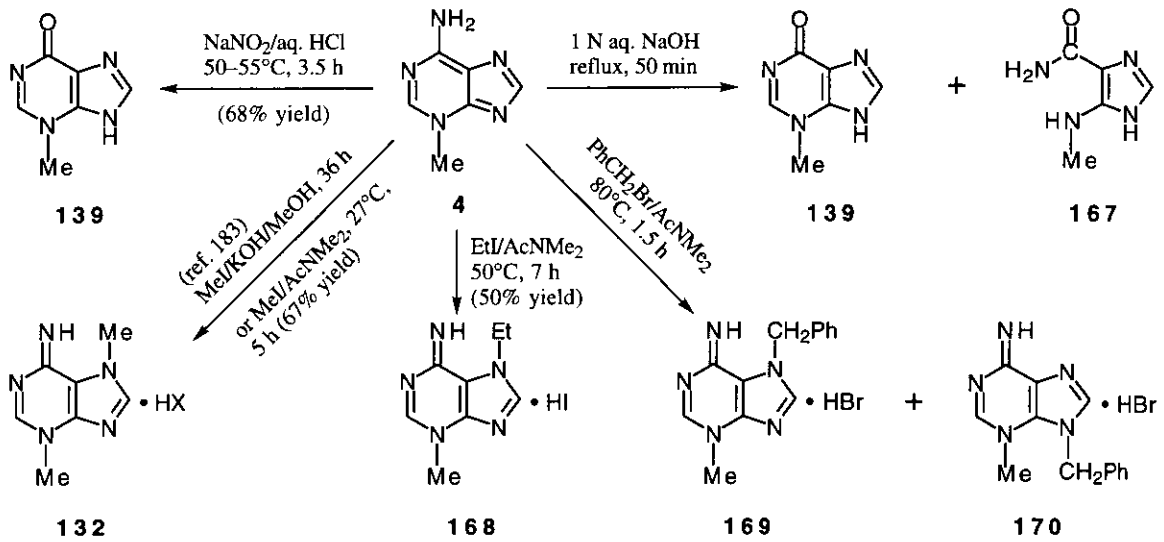
As regards molecular interactions between 3-methyladenine (**4**) and other organic or inorganic molecules, Glüsenkamp *et al.*[209] reported high specificity and affinity of the monoclonal antibody EM-6-47 for **4**. Yamagata *et al.*[212] have found by means of X-ray crystallographic analysis that **4** strongly stacks with the indole ring of tryptophan. Sakaguchi and Ishino[206] confirmed the existence of N(9)–Co(II) binding in the complex $[Co(H_2O)_2(C_6H_7N_5)_2](NO_3)_2{\cdot}3H_2O$ obtained from **4** and $Co(NO_3)_2{\cdot}6H_2O$ in H_2O. Orbell *et al.*[121] synthesized *cis*-diamminebis(3-methyladenine)platinum(II) nitrate trihydrate [*cis*-$[(NH_3)_2Pt(\mathbf{4})_2](NO_3)_2{\cdot}3H_2O$] by heating a mixture of **4** and *cis*-$(NH_3)_2Pt(NO_3)_2$ in

TABLE IV. 3-Methyladenine (**4**): Physical and Spectral Characteristics

Item	Specification[a]	Literature (ref. No.)
Melting point[b]	Sublimed above 250°C[c] (10); 291–292°C (decomp) (25); 309–311°C (59); 310–313°C (198)	
4·H_2O	302°C (161a,b)	
Sulfate	268–270°C (196); 268–270°C (decomp) (161b)	
Picrate	Sublimed above 270°C (196)	
4·TsOH·1/4H_2O	209–210°C (198)	
Acid dissociation constant		
basic pK_a	5.3 (50% aqueous DMF)[d] (59); 5.3 (50% aqueous DMF) (77, 161a,b); 6.1 (H_2O)[e] (30a, 56); 5.7 (H_2O)[e] (88b); 5.3 (63)	
Paper chromatography		(25, 67a, 68, 69, 165b, 168, 190, 193–196, 198)
TLC		(34)
Ion-exchange chromatography		(164b, 189)
HPLC		(164h, 173, 191b–d,f, 203)
GC		(188)
Paper electrophoresis		(88b)
MS		(72, 164h, 188, 204, 205)
UV spectrum	In H_2O at various pH's (25, 30a, 34, 56, 59, 63, 76, 77, 88b, 161a,b, 168, 195, 196, 198); isosbestic point (77, 161a,b); in MeOH (76); in the vapor phase (79)	
IR spectrum	(79, 88b, 164h, 206)	
^{1}H NMR spectrum	In DMSO-d_6 (56, 68, 121, 164h, 180, 181, 206, 211); in DMSO-d_6/1% CF_3CO_2D (207); in acetone-d_6 (207); in D_2O (pD 4.8) (206)	
4·HCl	In DMSO-d_6 (at 60°C) (181)	
^{13}C NMR spectrum	In DMSO-d_6 (56); in CD_3OD (207)	
Crystal structure	**4**·HCl	(208)
Tautomeric structure		(79, 88b, 111, 179, 209)
Dipole moment		(3, 63, 121)
Polarography		(210)
Cyclic voltammetry		(114, 210)
Anodic peak potential	+1.54 V (in DMF)	(114)
Heat of vaporization		(79)
HOMO and LUMO energies	By the MNDO method	(63)
Electronic structure	Under the INDO MO approximation	(121)

a) With or without reference number(s) in parentheses. *b*) Reported for an analytical sample. *c*) For a sample that contained 7.0% H_2O. *d*) Titrimetric. *e*) Spectral.

aqueous DMF at 80°C for 1 h. Sheldrick and Gross[211] synthesized several methylmercury(II) complexes of **4** by treating a mixture of **4** and methylmercury(II) hydroxide in H_2O at various pH's and rt.



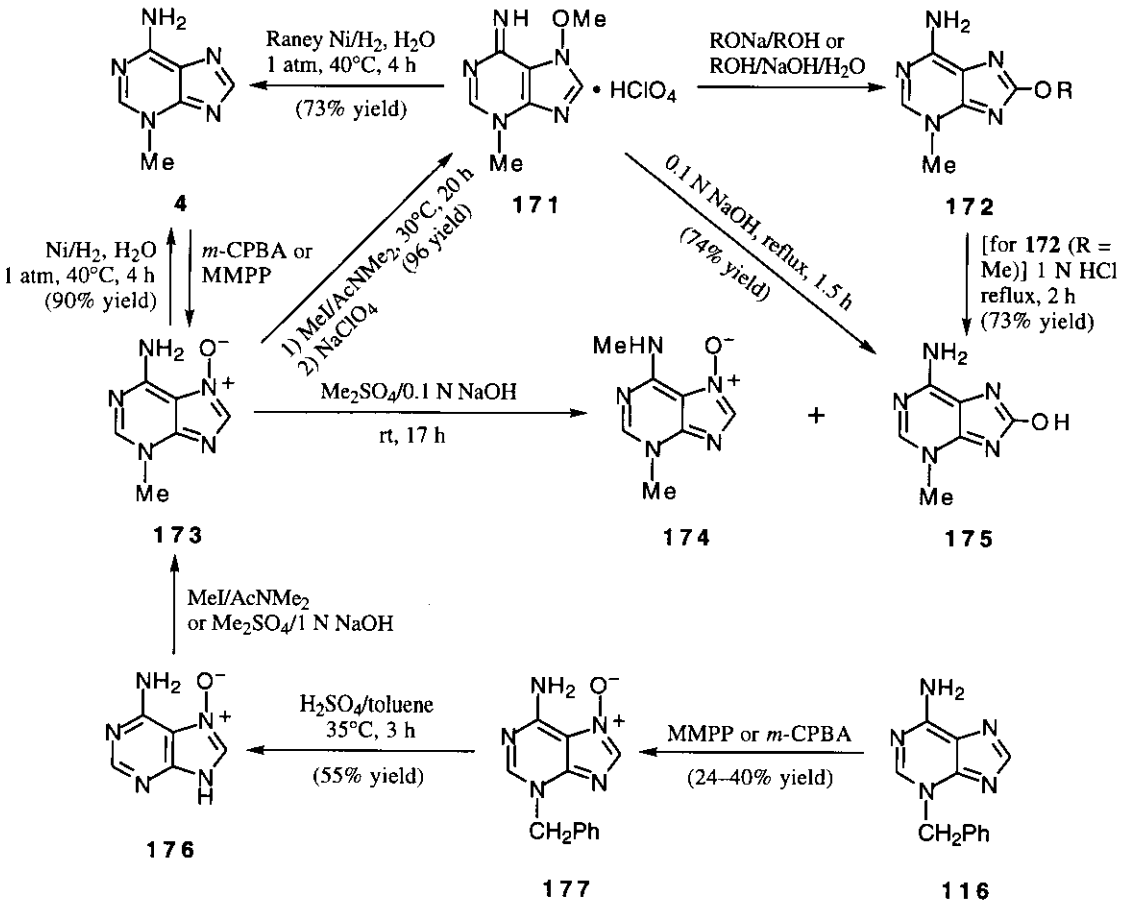
Scheme 31

Although Jones and Robins[198] reported that **4** could not be changed to 3-methylhypoxanthine (**139**) under the standard diazotization conditions, Itaya and Matsumoto[213] were able to realize this conversion under the reaction conditions as shown in Scheme 31. Pal and Horton[88b] showed by paper chromatographic analysis that **4** gave **139** and the imidazolecarboxamide (**167**) on heating with 1 N aqueous NaOH at 100°C for 2–4 h. Fujii's group[214] treated **4** with boiling 1 N aqueous NaOH for 50 min and isolated **139** (12% yield) and **167** (12%) from the reaction mixture.

Robins' group[183] methylated **4** (0.4 g) with MeI in MeOH containing KOH for 36 h and obtained the 3,7-dimethyl derivative [**132** (X = I)] (0.2 g) (Scheme 31). Fujii's group[215] obtained **132** (X = I) in 67% yield from **4** by methylation with MeI in $AcNMe_2$ at 27°C for 5 h. A similar alkylation of **4** with EtI gave the 7-ethyl-3-methyl derivative (**168**) in 50% yield.[215] Benzylation of **4** with $PhCH_2Br$ in $AcNMe_2$ at 80°C for 1.5 h afforded the 7-benzyl-3-methyl derivative (**169**) (61% yield) and the 9-benzyl-3-methyl isomer (**170**) (9%).[215] Yamauchi *et al.*[34] treated **4** with trimethyl phosphate in H_2O (pH 9.5–10.0) at 60°C for 24 h and found the formation of **132** in 14% yield with 70% recovery of **4**. The preferential 7-alkylation of **4** has now been successfully applied by Ohba *et al.* to the racemic[216] and chiral[217] syntheses of agelasimine-A and agelasimine-B, novel 7-substituted 3-methyladenine-related bicyclic diterpenoids isolated[218] from the orange sponge *Agelas mauritiana*.

Oxidation of **4** with *m*-CPBA in MeOH–acetate buffer (pH 5.5) at 30°C for 15 h was found to give the N(7)-oxide (**173**) in 25% yield with 43% recovery of **4** (Scheme 32).[219]

Alternatively, treatment of **4** in MeOH with magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) at 30°C for 2 h afforded **173** in 15% yield with 54% recovery of **4**.[219] The reactions of 3-methyladenine 7-oxide (**173**) so far investigated[219,220] are illustrated in Scheme 32.



Scheme 32

Wong and Keck[221] determined the pseudo-first-order rate constants for deuterium labeling at C(2) ($k = 2.51 \times 10^{-5}$ s^{-1}) and at C(8) ($k = 5.58 \times 10^{-7}$ s^{-1}) of **4** in D_2O at pD 6–7 and 100°C. At pD 8.26 and 70°C, however, Kohda's group[152a] observed no labeling at C(8) and determined the rate constant for deuterium labeling at C(2) to be 4.4×10^{-3} h^{-1} (1.22×10^{-6} s^{-1}).

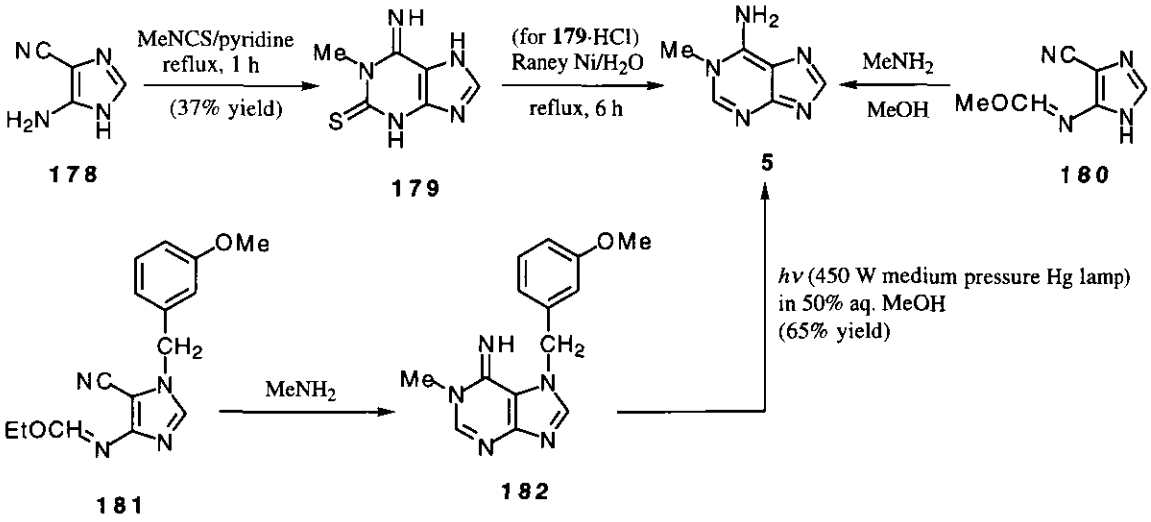
V. 1-METHYLADENINE

A purine base ($C_6H_7N_5$) isolated from a giant siliceous sponge (genus *Geodia*) has been named "spongopurine" and identified as 1-methyladenine (**5**).[222] Kanatani *et al.* iso-

lated a meiosis-inducing substance from ovaries of the starfish *Asterias amrensis* and identified it to be **5**.[223] Later on, Cimino *et al.*[224] found **5**, together with 6-imino-1,9-dimethyl-8-oxopurine, in the 1-butanol extracts of the English channel sponge *Hymeniacidon sanguinea* Grant and identified it in the form of acetylspongopurine. It has been reported that **5** was among the urinary methylated purines in both normal and tumor-bearing mice.[225] The existence of 1-methyladenine (**5**) in the form of the 1-methyladenosine structure in RNA's from a number of sources has also been reported.[226]

Dorée *et al.*[12] have investigated the specificity of the 1-methyladenine receptors, which are localized on the cell membrane of starfish oocytes in *Marthasterias glacialis* and *Asterias rubens*, using various substituted adenines. Yoshikuni *et al.*[227] prepared 1-[^{3}H]methyladenine and studied its binding to cortics isolated from full-grown prophase-arrested oocytes of the starfish *Asterina pectinifera*. Monsees *et al.*[63] reported that the EC_{50} value (the concentration for inducing 50% oocyte maturation in *Asterias rubens*) for **5** was 0.01 μM; 0.08 ± 0.01 μM (in *Asterina pectinifera*).[228]

Murthy and Deorukhakar[192] cultured diploid yeast (*S. cerevisiae* BZ34) auxotrophic to adenine (**1**) in synthetic medium supplemented with **5** and found that no growth occurred, whereas the **1**-supplemented cultures grew to stationary phase over 48-h period. In the tobacco callus bioassay for cytokinin activity, **5** was found to be inactive.[229] In the competitive inhibitory assay for human erythrocyte membrane phosphatidylinositol 4-kinase, **5** was found to be inactive.[10]



Scheme 33

In a synthetic approach to 1-methyladenine (**5**) from an imidazole derivative, Grözinger and Onan[230] treated the aminoimidazolecarbonitrile (**178**) with methyl isothiocyanate in pyridine to obtain 1-methyl-6-imino-2-thioxopurine (**179**), which was isolated in the

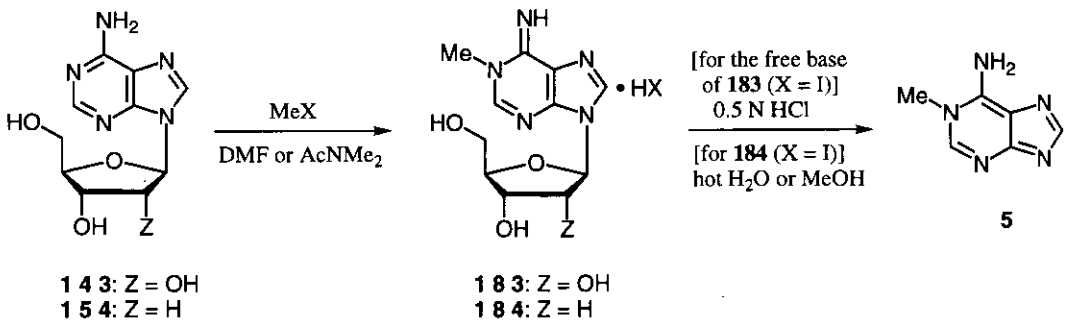
form of the hydrochloride salt (**179**·HCl) (Scheme 33). Desulfurization of **179**·HCl with Raney Ni in boiling H_2O gave **5**. Suzuki and Kumashiro[231] obtained **5** from the methoxymethyleneamino derivative (**180**) and methylamine. Mornet's group[232] cyclized 1-(3-methoxybenzyl)-4-ethoxymethyleneaminoimidazole-5-carbonitrile (**181**) with methylamine to prepare the 1,7-disubstituted adenine (**182**), which produced **5** in 65% yield when subjected to photolysis (Scheme 33).

The formation of 1-methyladenine (**5**) by methylation of DNA[164a,c,193,233] [and deoxyadenylic acid[164a,193,196,233] or deoxyadenosine (**154**)[193,195]] and RNA[69,193–195,233–235] [and poly(A),[166] adenylic acid,[196,233] or adenosine (**143**)[168,196,236]] molecules, followed by hydrolysis of the resulting products, has been known.[167]

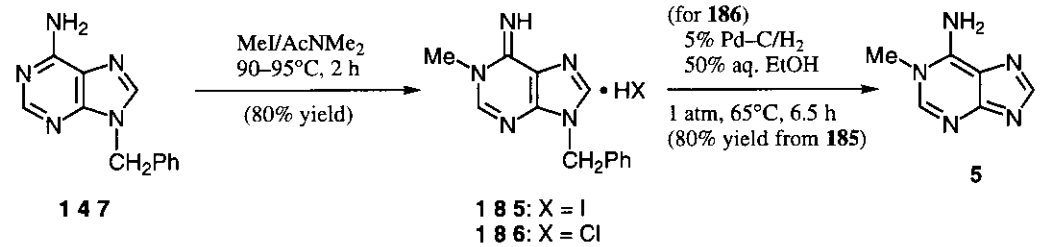
As mentioned in Section IV, methylation of adenosine (**143**) with dimethyl sulfate in DMF, followed by acid hydrolysis, gave several products, among which **5** was the main product (31% yield).[196] See also Section IV for the formation of **5** in the methylation of adenine (**1**) with dimethyl sulfate carried out by Pal[30a] and by Reiner and Zamenhof;[30b] with MeI in DMF by the Russian research group.[55,199]

Jones and Robins[237] treated adenosine (**143**) in DMF with methyl *p*-toluenesulfonate at rt for 24 h or in $AcNMe_2$ with MeI at 28°C for 18 h to isolate 1-methyladenosine·TsOH [**183** (X = TsO)] or 1-methyladenosine·HI [**183** (X = I)] in good yield (Scheme 34). The free crystalline base prepared from **183** (X = I) was then hydrolyzed in 0.5 N aqueous HCl at 100°C for 45 min to produce **5**. Similar methylations of 2'-deoxyadenosine (**154**) gave 2'-deoxy-1-methyladenosine·TsOH [**184** (X = TsO)] and **184** (X = I), respectively, in good yields, and treatment of **184** (X = I) with H_2O at 100°C for 20 min or with boiling MeOH for 30 min yielded **5**.[237] Yoshikuni *et al.*[227] prepared 1-[^{3}H]methyladenine from **143** in 70% yield by treating the latter with [^{3}H]methyl iodide in a mixture of HMPA and toluene at 28°C for 20 d and hydrolyzing the resulting 1-[^{3}H]methyladenosine with 1-methyladenosine ribohydrolase in phosphate buffer (pH 7). Toraya *et al.*[228] have recently reported the synthesis of 1-methyl-[2-^{3}H]adenine, which involves methylation of [2-^{3}H]adenosine with MeI in $AcNMe_2$ at rt for 66 h and hydrolysis of the methylated product with 0.5 N aqueous HCl at 96°C for 10 min.

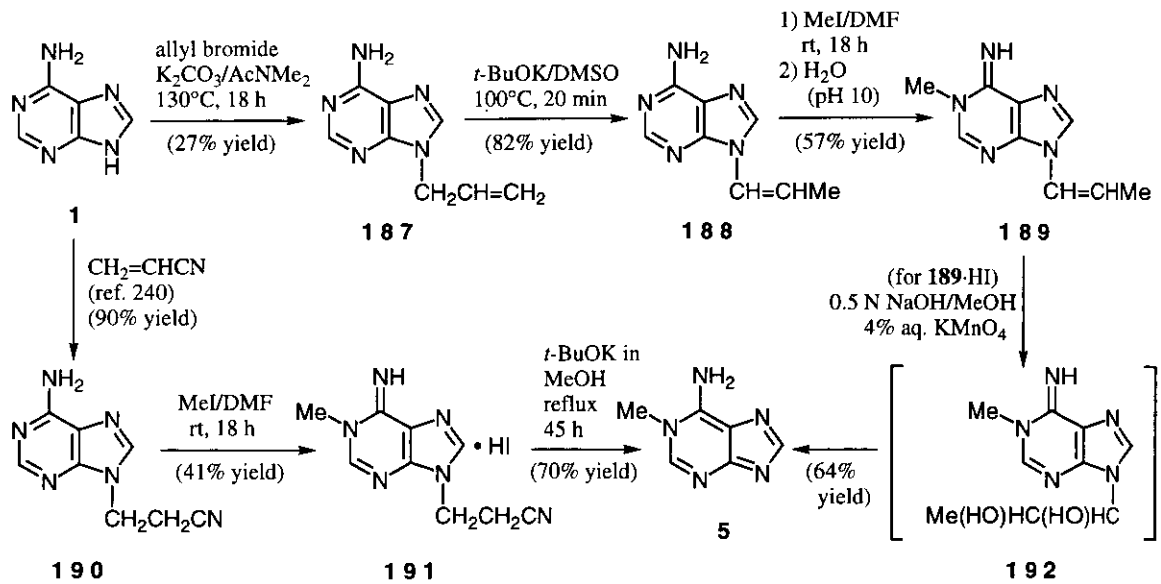
In a multistep synthesis of **5** from **1**, Leonard and Fujii[45] methylated 9-benzyladenine (**147**) (obtainable[32] from **1** in 61% yield by benzylation with $PhCH_2Cl/AcNMe_2$ in the presence of K_2CO_3) with MeI in $AcNMe_2$ to obtain 9-benzyl-1-methyladenine hydriodide (**185**) (Scheme 35). The hydriodide (**185**) was then debenzylated by conversion (with AgCl) into the hydrochloride (**186**) and catalytic hydrogenolysis using Pd–C and hydrogen, producing **5** in good overall yield. The multistep synthesis of **5** from **1** by Montgomery and Thomas[238] proceeded through 9-allyladenine (**187**), 9-(1-propenyl)adenine (**188**), 1-methyl-9-(1-propenyl)adenine (**189**), and the unstable intermediate (**192**), as shown in Scheme 36. Lira's synthesis[239] included cyanoethylation of **1** to form 9-(2-cyanoethyl)adenine (**190**),[240] methylation of **190** with MeI, and retro-Michael reaction of the resulting 9-(2-cyanoethyl)-1-methyl derivative (**191**) (Scheme 36).



Scheme 34



Scheme 35



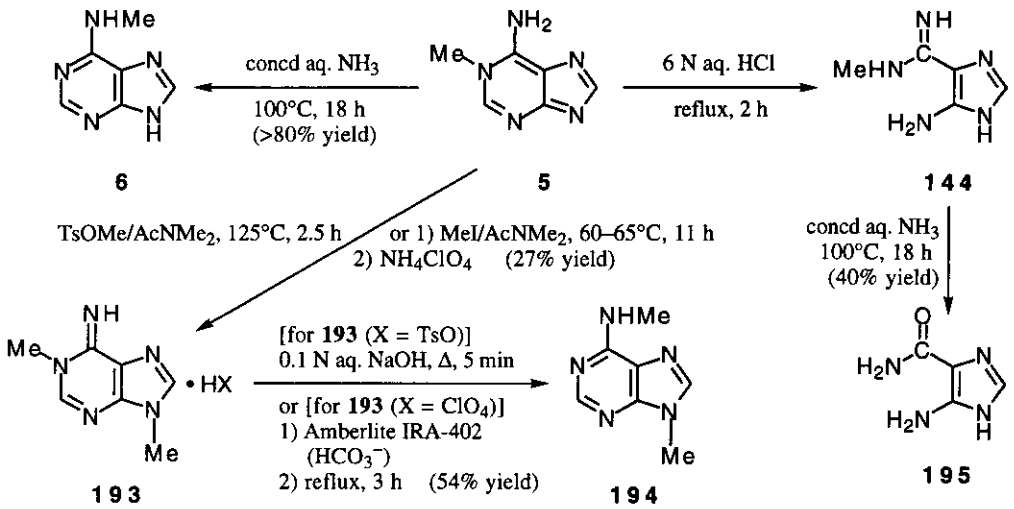
Scheme 36

TABLE V. 1-Methyladenine (**5**): Physical and Spectral Characteristics

Item	Specification[a]	Literature (ref. No.)
Melting point[b]	>300°C (10); 296–299°C (decomp) (237); 297–299°C (decomp) (45)	
Sulfate	276–278°C (196)	
Picrate	253–255°C (196); 255–257°C (222b); 257–258°C (230); 263°C (236)	
Acid dissociation constant		
basic pK_a	7.2 (H_2O)[c] (56, 196, 241); 6.95 (50% aqueous DMF)[d] (59); 7.11 ± 0.05 (H_2O) (at 25 ± 0.1°C)[c] (179); 7.35 ± 0.03 (H_2O) (at 12 ± 0.2°C)[c] (179); 7.1 (63)	
acidic pK_a	11.0 (H_2O)[c] (196, 241); 11.9 (50% aqueous DMF)[d] (59)	
Paper chromatography		(67a, 68, 69, 168, 193–196, 225a, 226a, 236, 237, 241, 273b)
TLC		(242)
HPLC		(164h, 173, 175, 203)
Electrophoresis		(222b)
Paper electrophoresis		(88b, 226a)
MS		(72, 204, 205, 243)
UV spectrum	In H_2O at various pH's (56, 59, 63, 76, 77, 88b, 168, 175, 179, 195, 196, 225a, 226a, 236, 237, 241, 244); in MeOH (76)	
Relaxation spectrum in H_2O		(179)
IR spectrum		(98, 245, 246)
Sulfate		(222b)
Hydrochloride		(245)
Raman spectrum		(245)
Hydrochloride		(245)
^{1}H NMR spectrum	In DMSO-d_6	(56, 68)
5·HNO_3	In DMSO-d_6	(181)
^{13}C NMR spectrum	In D_2O	(56)
Tautomeric structure		(110, 111, 179, 245–247)
Dipole moment		(63)
Polarography		(210)
Cyclic voltammetry		(210)
No anodic response		(248)
Heat of sublimation		(117)
HOMO and LUMO energies	By the MNDO method	(63)

a) With or without reference number(s) in parentheses. *b*) Reported for an analytical sample. *c*) Spectral. *d*) Titrimetric.

Table V locates papers recording the physical properties and spectral characteristics of 1-methyladenine (**5**), with additional references.[241–248]



Scheme 37

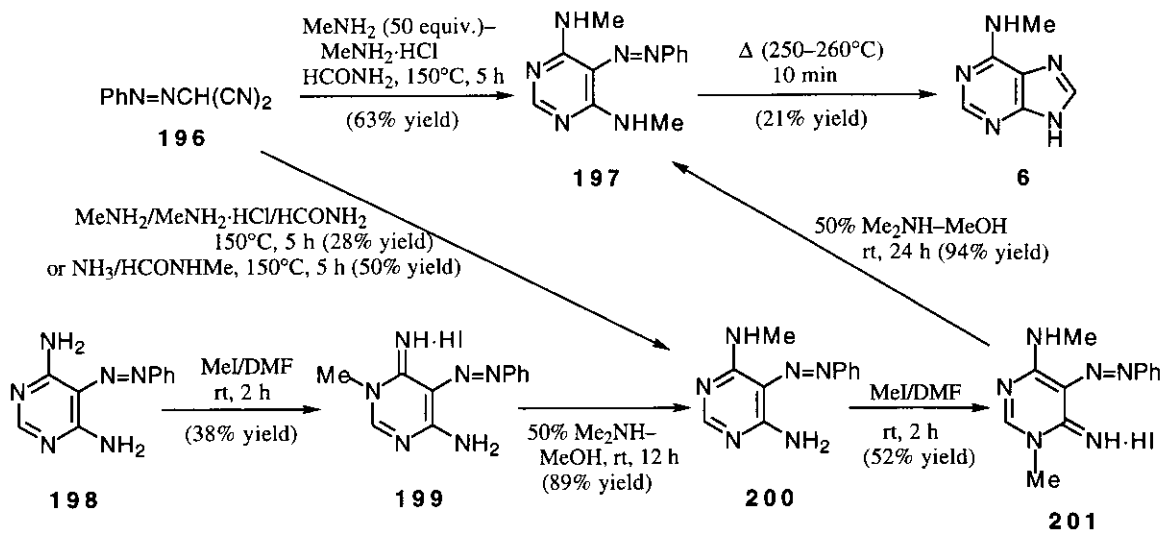
The following reactions of **5** have been reported. On treatment with concd aqueous NH_3 at 100°C for 18 h,[196] **5** underwent Dimroth rearrangement[249] to give N^6-methyladenine (**6**) in over 80% yield (Scheme 37) (see also Section VI). Action of boiling 6 N aqueous HCl on **5** resulted in the ring opening in the pyrimidine moiety, giving 5-amino-*N'*-methylimidazole-4-carboxamidine dihydrochloride (**144**·2HCl), which afforded 5-aminoimidazole-4-carboxamide (**195**) in 40% yield when heated in concd aqueous NH_3 at 100°C for 18 h.[196] Robins' group[183] methylated **5** with methyl *p*-toluenesulfonate in $AcNMe_2$ to obtain 1,9-dimethyladenine *p*-toluenesulfonate [**193** (X = TsO)], and **193** (X = TsO) was heated in 0.1 N aqueous NaOH for 5 min. The UV spectrum of the resulting solution was found to be identical to that of N^6,9-dimethyladenine (**194**). Methylation of **5** with MeI in $AcNMe_2$ and treatment of the resulting **193**·HI with NH_4ClO_4 gave the perchlorate [**193** (X = ClO_4)] in 27% overall yield.[51b] The Dimroth rearrangement[249] of **193** (X = ClO_4) was effected by treating it with Amberlite IRA-402 (HCO_3^-) and heating the resulting free base in boiling H_2O for 3 h, providing **194** in 54% yield.[51b] Cimino *et al.*[224] acetylated a mixture containing **5** with Ac_2O in boiling pyridine for 1 h and have recorded the MS and ^1H NMR spectral data for the resulting acetylspongopurine.

VI. N^6-METHYLADENINE

The last positional isomer N^6-methyladenine (**6**) was isolated, together with N^6-(3-methyl-2-butenyl)adenine (a potent cytokinin) and nicotinamide, first from *Corynebacterium fascians* growing in a medium to which adenine (**1**) had been added.[250] Subsequently,

the same three compounds were obtained when **1** was not added to the medium.[250] The compound (**6**) has also been reported to occur in blue coral (code No. NIO-156) in the form of the 2-hydroxy derivative (2-hydroxy-N^6-methyladenine) possessing cytokinin activity.[251] The existence of **6** in the form of 2'-deoxy-N^6-methyladenosine structure in DNA's[252–256] and in the form of N^6-methyladenosine structure in RNA's[226a,c,257] from a number of sources has been known.

N^6-Methyladenine (**6**) has been reported to have very weak or no cytokinin activity in certain test systems.[229,258,259] Dorée *et al.*[12] reported that **6** was devoid of the ability to replace 1-methyladenine (**5**) in triggering meiosis in the starfish *Marthasterias glacialis* and *Asterias rubens* oocytes. The toxicity and anticancerogenic property of **6** against Ehrlich mouse carcinoma and against other transplantable mouse cancers have been studied.[156] The N^6-methyl compound (**6**) was an effective inhibitor of azaserine-induced formylglycinamide ribonucleotide accumulation in both sensitive and resistant H.Ep. No. 2 cells in culture.[260] It was also reported to be an inhibitor of adenine uptake into nucleotides of guinea pig cortical slices;[261] and to be an inhibitor of nonspecific adenosine deaminase [EC 3.5.4.4, adenosine aminohydrolase, *Aspergillus oryzae*] from Takadiastase.[262] Love and Remy[263] examined various methylated purines for their effects on growth of purine-requiring mutants of *Escherichia coli*, strains W-11 and B-96, and for their effects on purine biosynthesis. They found that **6** stimulated the accumulation of purine precursor derivatives (the ribosides of 5-aminoimidazole and 5-aminoimidazole-4-carboxamide) beyond its ability to support growth. A vasodilator composition containing **6** has been applied for a patent.[264]

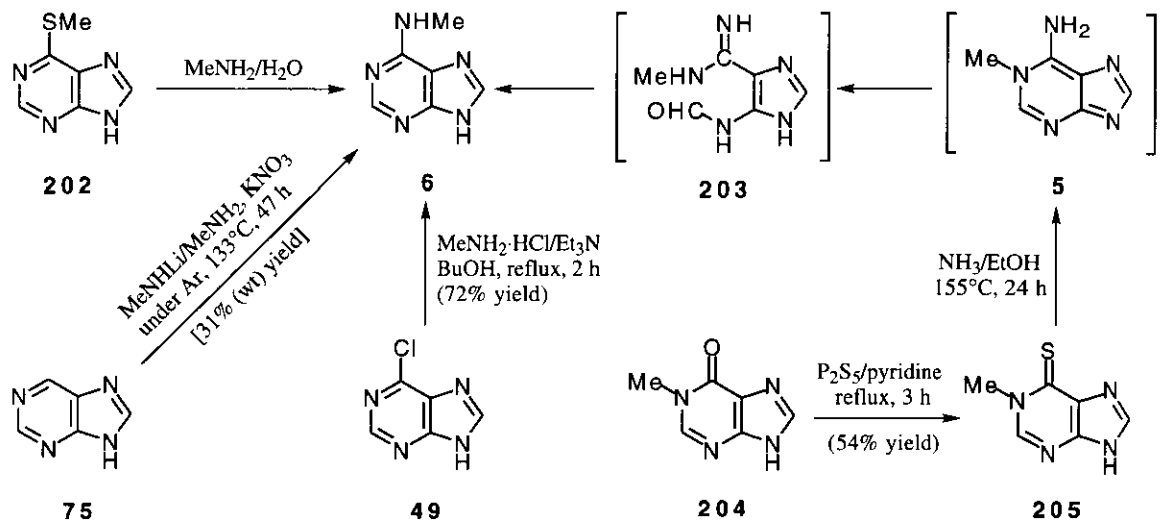


Scheme 38

In a synthetic approach to **6** from a pyrimidine derivative, Mano *et al.*[265a] prepared **6** from phenylazomalononitrile (**196**) *via* **197** or *via* **200** (which was also obtainable from

198 *via* **199**), **201**, and **197** (Scheme 38). Alternatively, **6** was obtained from **200** by reduction and subsequent cyclization with ethyl orthoformate.[265b]

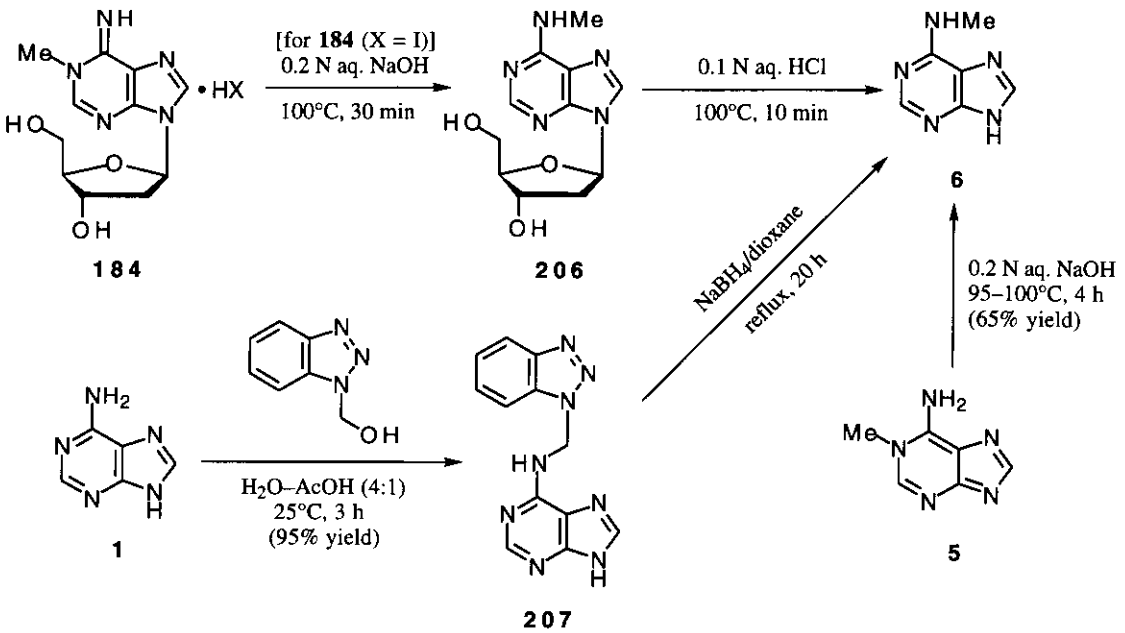
In an approach from a purine derivative, Elion *et al.*[266] heated a mixture of 6-methylmercaptopurine (**202**) and 25% aqueous $MeNH_2$ in a sealed tube at 130°C for 17 h, obtaining **6** in 72% yield (Scheme 39). Okumura *et al.*[267] and Sakata *et al.*[268] separately obtained **6** in 74% and 81% yields, respectively, from similar reactions of **202** effected at 130–140°C for 14 h and for 18 h. Reaction of purine (**75**) with MeNHLi in $MeNH_2$ under argon in the presence of KNO_3 at 133°C for 47 h has been reported to produce **6** in 31% (weight) yield.[269] In an attempt to prepare the 1-methyl isomer (**5**), Elion[25] treated 1-methylhypoxanthine (**204**) with P_2S_5 in boiling pyridine to obtain 1-methylpurine-6-thione (**205**) in 54% yield. Subsequent treatment of **205** with ethanolic NH_3 at 155°C for 24 h resulted in the formation of a small amount of **6**, which was presumed to have occurred through the Dimroth rearrangement[249] of **5** once formed (**5**→**203**→**6**) (Scheme 39). In an open vessel, reaction of $MeNH_2$·HCl with 6-chloropurine (**49**) in boiling 1-butanol containing Et_3N for 2 h produced **6** in 72% yield.[270] A similar procedure utilizing 40% aqueous $MeNH_2$ has been reported.[183]



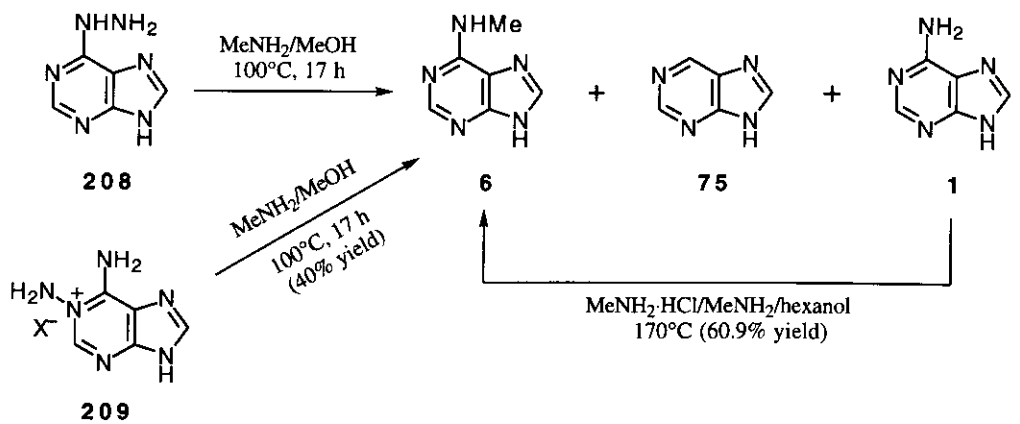
Scheme 39

The formation of N^6-methyladenine (**6**) by methylation of DNA[164a,193] [and deoxyadenylic acid[164a,193] or deoxyadenosine (**154**)[164a,193]] and RNA[69,193,271] [and poly(A),[166] adenylic acid,[196] or adenosine (**143**)[168,183,196,272]] molecules and hydrolysis of the resulting products has been known. Jones and Robins[237] subjected 2'-deoxy-1-methyladenosine hydriodide [**184** (X = I)], prepared by methylation of 2'-deoxyadenosine (**154**) (Section V and Scheme 34), to Dimroth rearrangement under alkaline conditions and hydrolyzed the resulting N^6-methyl isomer (**206**) with 0.1 N aqueous HCl to obtain **6** (Scheme 40), which was alternatively prepared[273a] in 65% yield from 1-methyladenine

(**5**) by heating with 0.2 N aqueous NaOH at 95–100°C for 4 h (see also Section V and Scheme 37). Incubation of **5** in H_2O at pH 7.2 and 100°C for 18 h resulted in 96% conversion into **6** with 4% recovery of **5**, as analyzed by means of paper chromatography.[273b] Katritzky *et al.*[274] prepared **6** from adenine (**1**) through the N^6-(benzotriazol-1-yl)methyl derivative (**207**)[274b] in 75% overall yield (Scheme 40).



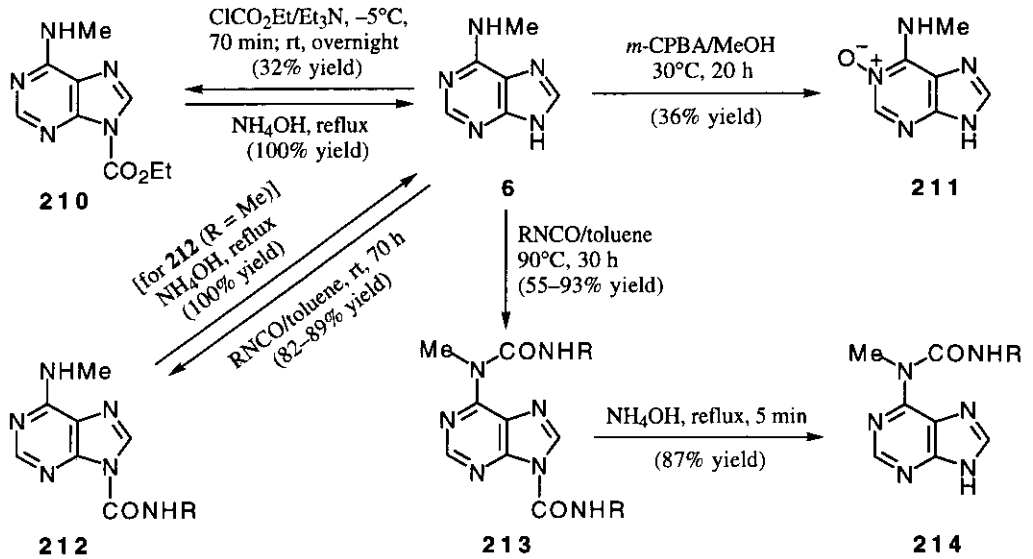
Scheme 40



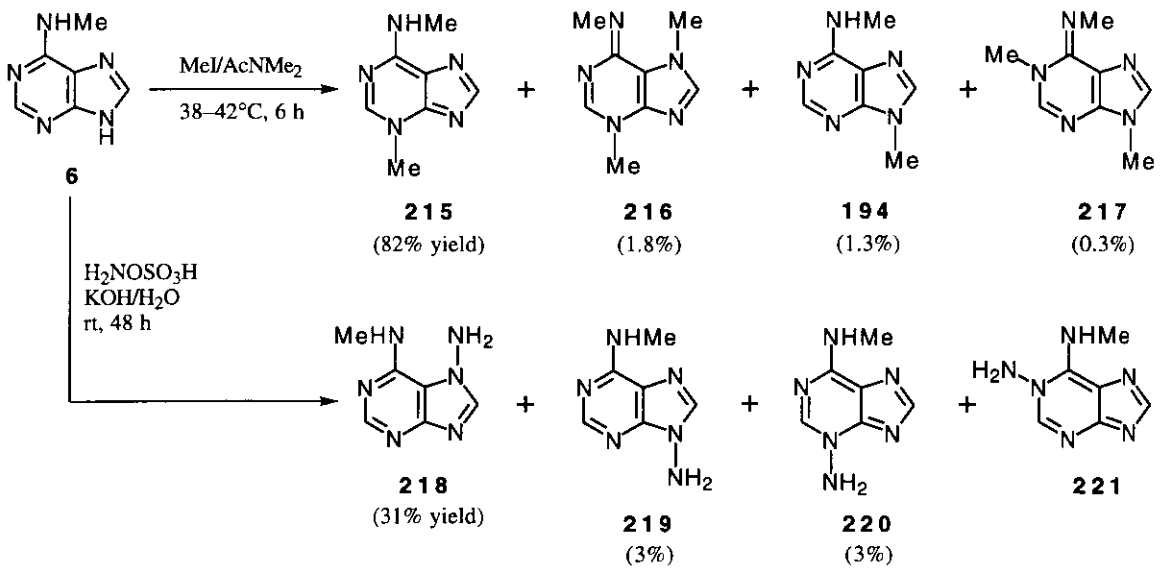
Scheme 41

Reaction of 1-aminoadeninium mesitylenesulfonate [**209** (X = 2,4,6-$Me_3C_6H_2SO_3$)] with $MeNH_2$ in MeOH at 100°C for 17 h was found to produce **6** in 40% yield (Scheme 41).[275] Similar treatment of 6-hydrazinopurine (**208**) gave **6** (25% yield), purine (**75**) (10%), and adenine (**1**) (15%).[275] Perlberger and Duc[276] claimed that **6** was obtained in 60.9% yield

by "exchange amination" of **1** with excess $MeNH_2$ and $MeNH_2$·HCl in hexanol in an autoclave at 170°C. Similar exchange amination of **1** with $MeNH_2$ in the presence of HCl has also been reported.[277]



Scheme 42



Scheme 43

References to the physical properties and spectral characteristics of N^6-methyladenine (**6**) are indicated by number in Table VI, with some additions.[278–293]

TABLE VI. N^6-Methyladenine (**6**): Physical and Spectral Characteristics

Item		Specification[a]	Literature (ref. No.)
Melting point[b]		319–320°C (183); 314–316°C (265a); 314–316°C (decomp) (273a); 312–314°C (decomp) (266); 308°C (267); 306°C (278); 304–305°C (decomp) (25); >300°C (270)	
	Hydrochloride	316–318°C (183); 289°C (25)	
	Picrate	230–260°C (250); 257°C (236)	
Acid dissociation constant			
	basic pK_a	4.18 and <1 (H_2O)[c] (278); 4.1 (H_2O[d] or D_2O[e]) (279); 4.2 (H_2O)[d] (62, 241)	
	acidic pK_a	9.99 (H_2O)[c] (278); 10 (D_2O)[e] (279); 10.0 (H_2O)[d] (62, 241, 279)	
Paper chromatography			(25, 30b, 67–69, 168, 183, 193, 195, 226a, 236, 237, 256, 273b, 278, 298)
TLC			(70, 242, 254, 280, 281)
HPLC			(56, 175)
GC			(242, 282)
MS			(72, 205, 243, 250, 265a, 270, 282–286)
	Picrate		(250)
UV spectrum		In H_2O at various pH's (25, 30b, 59, 88b, 168, 175, 183, 196, 236, 241, 242, 244, 250, 265a, 266, 270, 273a, 279, 287, 298) In MeOH (183) In 95% aqueous EtOH (270, 273a)	
	Picrate		(250)
	TMS derivative	In hexane	(242)
UV photoelectron spectrum			(81)
Polarized electronic spectrum			(84, 85)
Fluorescence spectrum			(288)
IR spectrum			(88b, 265a)
	TMS derivative		(242)
^1H NMR spectrum		In DMSO-d_6 (265a, 270); in CD_3OD–CF_3CO_2D (50:1) (289); in D_2O (279)	
	TMS derivative	In CCl_4	(242)
^{13}C NMR spectrum		In DMSO-d_6	(290)
Crystal structure		**6**·HCl (291); **6**·picrate (292)	
Dipole moment			(63)
Polarography			(210)
Voltammetry			(293)
Cyclic voltammetry			(114, 210)
Anodic peak potential		+1.58 V (in DMF)	(114)
Solubility		In H_2O (at 20°C and 100°C)	(278)

(*continues*)

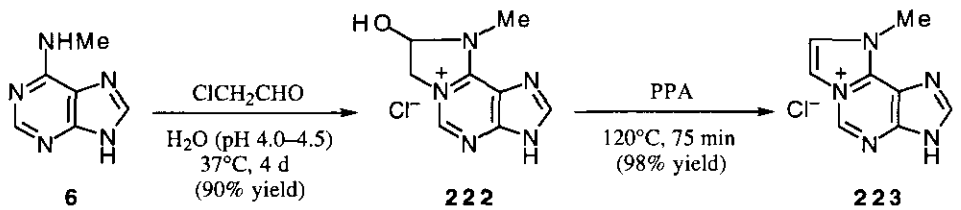
TABLE VI (*continued*)

Item	Specification[a)]	Literature (ref. No.)
Singlet and triplet $\pi\rightarrow\pi^*$ transition energies		(119)
HOMO and LUMO energies	Calculated by the MNDO method	(63)

a) With or without reference number(s) in parentheses. *b*) Reported for an analytical sample. *c*) Potentiometric. *d*) UV spectral. *e*) ^{1}H NMR spectral.

Interactions of **6** with the following substances have been reported: iodine (in H_2O);[294] *riboflavin* [*in aqueous buffer* (pH 4)];[294] *cis*-$Pt(NH_3)_2Cl_2$ and *trans*-$Pt(NH_3)_2Cl_2$ (in H_2O).[134]

Chheda's group[295a] prepared the urethane derivative (**210**) and the carbamoyl derivatives (**212**, **213**, and **214**) from **6** by the reactions illustrated in Scheme 42. Oxidation of **6** with *m*-CPBA in MeOH was found to afford the N(1)-oxide (**211**) in 36% yield, with 21% recovery of **6**.[270] Fujii's group[273a] found that treatment of **6** with 3 molar equiv. of MeI in $AcNMe_2$ at 38–42°C for 6 h gave N^6,3-dimethyladenine (**215**) (82% yield), N^6,3,7-trimethyladenine (**216**) (1.8%), N^6,9-dimethyladenine (**194**) (1.3%), and N^6,1,9-trimethyladenine (**217**) (0.3%) (Scheme 43).[295b–d] *Kohda's group*[56] *reported that amination of* **6** with hydroxylamine-*O*-sulfonic acid in alkaline medium furnished the 7-amino (**218**) (31% yield), 9-amino (**219**) (3%), 3-amino (**220**) (3%), and 1-amino (**221**) (in very low yield) derivatives (Scheme 43). The 1-amino derivative (**221**) was alternatively prepared from **6** in 11% yield by amination with 2,4-dinitrophenoxyamine in DMF at 95°C for 2 h.[56]



Scheme 44

Leonard's group[296] has shown that **6** reacts with chloroacetaldehyde in H_2O at pH 4.0–4.5 to give 7,8-dihydro-8-hydroxy-9-methylimidazo[2,1-*i*]purinium chloride (**222**) in 90% yield and that **222** is dehydrated with PPA to afford 9-methylimidazo[2,1-*i*]purinium chloride (**223**) in over 90% yield (Scheme 44).

The reaction of **6** with the OH radical in H_2O at pH 6–8 and 20°C has been investigated by Vieira and Steenken[62] by using pulse radiolysis with optical and conductance detection. The following biochemical transformations of **6** have been reported: demethylation by rat liver microsomal enzymes;[297] metabolism to the nucleoside monophosphate level

by intact Ehrlich ascites cells;[298] deoxyribosylation utilizing thymidine and the nucleoside deoxyribosyltransferase (EC 2.4.2.6) from *Lactobacillus leichmannii*.[299]

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