THE 11 POSITIONAL ISOMERS OF N^x,N^y-DIMETHYLADENINE: THEIR CHEMISTRY, PHYSICOCHEMICAL PROPERTIES, AND BIOLOGICAL ACTIVITIES

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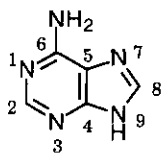
Abstract —Various N^x,N^y-disubstituted adenines are represented by the corresponding 11 possible positional isomers of N^x,N^y-dimethyladenine, namely, N^6,N^6- (**2**), N^6,1- (**3**), N^6,3- (**4**), N^6,7- (**5**), N^6,9- (**6**), 1,3- (**7**), 1,7- (**8**), 1,9- (**9**), 3,7- (**10**), 3,9- (**11**), and 7,9-dimethyladenine (**12**). The chemistry, physicochemical properties, and biological activities of these N^x,N^y-dimethyladenines are reviewed with 513 reference citations.

CONTENTS

I. INTRODUCTION

Structurally unique is adenine (**1**), an important fundamental biomolecule, in that it carries one exocyclic and four endocyclic nitrogen atoms. Accordingly, five kinds of mono-*N*-substitution pattern and 11 kinds of di-*N*-substitution pattern are possible for this heterocycle 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,[1–6] with the exception that genuine 1,3-disubstituted adenines (type **7**[7]) still remain unknown. Quite a recent review article by us has treated the chemistry, physicochemical properties, and biological activities of the five positional isomers of N^x-methyladenine, the prototypes of mono-*N*-substituted adenines.[8] The aim of the present article is to review the 11 possible positional isomers of N^x,N^y-dimethyladenine in much the same

sense in order to supplement previous ones[1–4] by reorganizing (in part) and updating the literature through the early part of 1998. The 11 positional isomers covered are N^6,N^6-dimethyladenine (**2**), N^6,1-dimethyladenine (**3**), N^6,3-dimethyladenine (**4**), N^6,7-dimethyladenine (**5**), N^6,9-dimethyladenine (**6**), 1,3-dimethyladenine (**7**),[7] 1,7-dimethyladenine (**8**), 1,9-dimethyladenine (**9**), 3,7-dimethyladenine (**10**), 3,9-dimethyladenine (**11**), and 7,9-dimethyladenine (**12**).[7]



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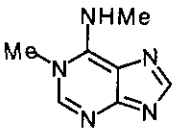

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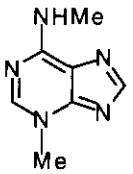

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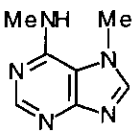

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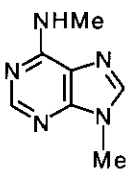

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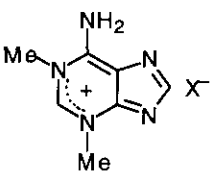

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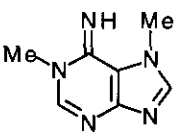

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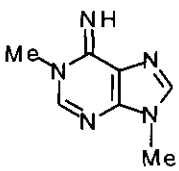

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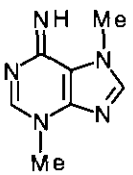

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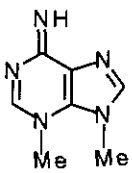

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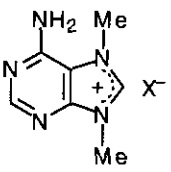

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II. N^6,N^6-DIMETHYLADENINE

N^6,N^6-Dimethyladenine (**2**) has been the most frequently investigated isomer among the 11 N^x,N^y-dimethyladenines. The occurrence of **2** in epiphytic bacteria (isolated from barley)[9] and in the headspace and essential oil of the whole plant of *Plectranthus coleoides* Marginatus[10] has been reported. As the aglycon, **2** is contained in the antibiotic puromycin [6-dimethylamino-9-[3-(*p*-methoxy-L-phenylalanylamino)-3-deoxy-β-D-ribofuranosyl]purine], a protein biosynthesis inhibitor (in both bacterial and mammalian cells) produced by *Streptomyces alboniger*;[1–3,5] and in the nucleoside antibiotics A201A, A201C, A201D, and A201E, protein biosynthesis inhibitors produced by *Streptomyces capreolus*.[5,11] The occurrence of new metabolites containing **2** in spores of *Streptomyces alboniger* has also been reported.[12] The existence of **2** in the form of 2'-deoxy-N^6,N^6-dimethyladenosine structure in DNA of some species of algae,[13] in the form of N^6,N^6-dimethyl-2'-*O*-methyladenosine structure in mRNA,[14] and in the form of

N^6,N^6-dimethyladenosine structure in RNA's[14–31] from a number of sources has been known.

N^6,N^6-Dimethyladenine (**2**) has been reported to have very weak or no cytokinin activity in certain test systems.[32–38] At 10^{-6} M concentration, **2** stimulated proliferation of *Castanea vesca* tissue *in vitro*;[39] it also had a stimulatory effect on *Betula verrucosa*.[39] It exhibited cytokinin-like effects on the cambial tissue of forest trees cultivated *in vitro*, including tissues from willow, poplar, eucalyptus, oak, beech, chestnut, elm, maple, and pine.[40] Stimulation of the growth of *Quercus* cambial tissue culture,[41] of *Fagus silvatica* cambial tissue culture,[41] and of sorghum (*Sorghum bicolor*) primary callus[42] and chlorophylls increase in cucumber cotyledons[43] by **2** were also reported. N^6,N^6-Dimethyladenine (**2**) has been tested for reversing the abscisic acid-induced inhibition of the germination of lettuce achene;[44] for inhibiting the covalent incorporation of exogenous N^6-benzyladenine into total RNA of tobacco cells, grown in shaken liquid medium;[45] for inhibition of cytokinesis [protein synthesis (^{3}H-leucine incorporation)] in *Allium sativum* root meristems;[46] for somatic embryogenesis and plant recovery from mature tissues of the olive cultivars "Canino" and "Moraiolo";[47] and for the effect on *in vitro* development of zygotic embryos of taro (*Colocasia esculenta* var. *antiquorum*).[48] A plant senescence-delaying composition containing foliar fertilizers and **2** has been applied for a patent.[49]

Investigated also are effects of **2** on the following biological processes: the multiplication of the DNA-phage λ and of the RNA-phage M12 as well as that of the host bacteria *Escherichia coli*;[50] growth of lactic acid bacteria in presence of combination with folic acid analogues;[51] growth of purine-requiring mutants of *E. coli*, strains W-11 and B-96, and purine biosynthesis;[52] inhibition of bulking for activated sludges;[53] formation of aerial mycelia and spores of *Streptomyces viridochromogenes*;[54] inhibition of germ-tube growth and appressoria formation during primary infection of barley powdery mildew;[55] adenine-induced growth inhibition of *Staphylococcus aureus*;[56] inhibition of growth of *Tetrahymena pyriformis*;[57] inhibition of regeneration of hydra whose tentacles and hypostome have been removed;[58] production of triploid eggs and larvae in the Pacific oyster *Crassostrea gigas*, the giant sea scallop *Placopecten magellanicus*, and the blue mussel *Mytilus edulis*;[59] tetraploid induction in eggs or embryos of *Mytilus edulis* during early development;[60] growth of mouse Sarcoma 180 cells;[61] activation and analysis of nondividing cell nuclei for prenatal screening, as a cytostatic factor extract supplement;[62] inhibition of apoptosis for treating neurodegenerative diseases;[63] inhibition of formylglycinamide ribonucleotide formation in human epidermoid carcinoma in cell culture;[64] induction of a persistent stellate morphology in cultured human glioma cells, without affecting the cAMP content;[65] adenosine-dependent formation of cAMP in guinea pig cerebral cortical slices;[66] inhibition of DNA synthesis in two mammalian cell lines, 3T3 and CHEF/18 fibroblasts;[67] DNA synthesis in activated mammalian oocytes;[68] the cAMP-binding sites of two high-affinity cAMP-binding proteins

from wheat germ;[69] the Ca^{2+} binding activity of an *Achlya* and *Blastocladiella* glycoprotein;[70] inhibition of hepatocytic protein degradation;[71] inhibition of autophagic sequestration and endogenous protein degradation in isolated rat hepatocytes;[72] protein synthesis and degradation in isolated rat hepatocytes;[73] and *in vitro* destruction of cyclin from clam embryos.[74]

Effects on the following enzymes have been reported: nonspecific adenosine deaminase from Taka-diastase;[75] adenine deaminase of *Pseudomonas synxantha*;[76] barley powdery mildew adenosine deaminase;[77] extracellular adenine deaminase from *Streptomyces* sp. J-350P;[78] human plasma adenosine deaminase$_2$;[79] adenosine nucleosidase (adenosine ribohydrolase, EC 3.2.2.7) from barley leaves;[80] purine-2'-deoxyribonucleosidase of *Crithidia luciliae*;[81] adenine phosphoribosyltransferase from Ehrlich ascites tumor cells[82] and from rabbit polymorphonuclear leukocyte;[83] 3'-nucleotidase (3'-ribonucleotide phosphohydrolase, EC 3.1.3.6) from wheat germ;[84] phosphodiesterase specific for cyclic nucleotides;[85] modulation of human erythrocyte acid phosphatase activity;[86] inhibition of human erythrocyte membrane phosphatidylinositol 4-kinase;[87] specificity for yeast glyceraldehyde-3-phosphate dehydrogenase at the cAMP-binding site;[88] bovine milk xanthine oxidase and rabbit liver aldehyde oxidase;[89] and oxidation of NADH by a horseradish peroxidase system.[90]

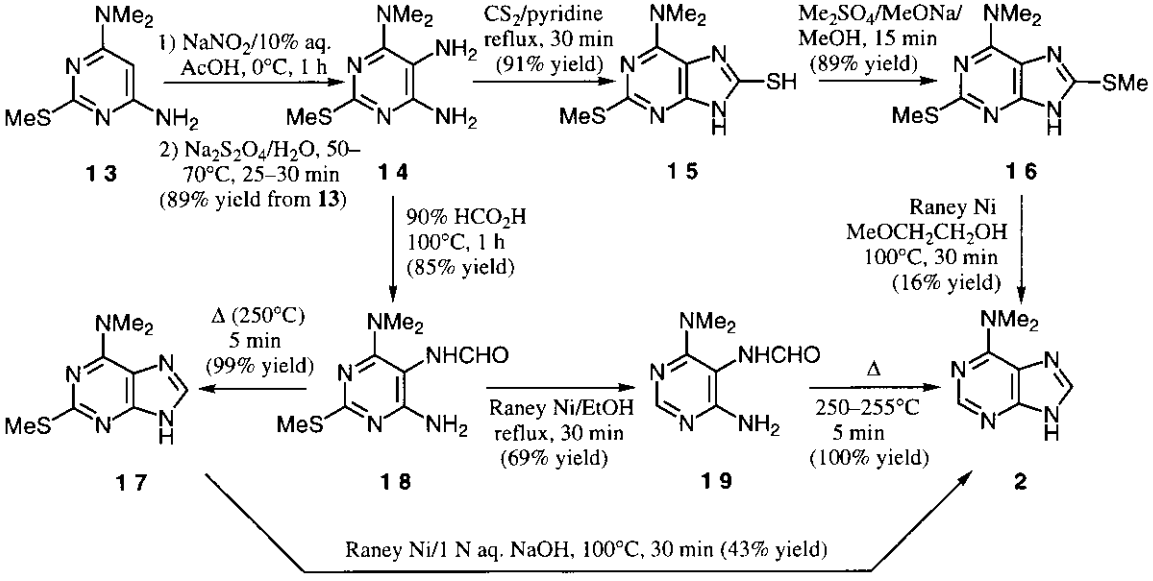
As a protein kinase inhibitor, **2** has been used in the study of the following enzymes, biological processes, and those in oocytes: gibberellin-induced elongation, reorientation of cortical microtubules, and change of isoform of tubulin in epicotyl segments of azuki bean (*Vigna angularis*) seedlings;[91] *Tetrahymena* cell division in the presence or absence of okadaic acid;[92] the programed rearrangement of cortical skeleton in furrowing *Paramecium* and the tensegrity model of cytokinesis;[93] cyclic activation of histone H_1 kinase during sea urchin egg mitotic divisions;[94] cyclin-dependent kinases from a variety of sources;[95] chromosome movement and distribution in mitosis and meiosis of grasshopper spermatocytes;[96] phosphoglycolate removal and end-joining using *Xenopus* egg extracts;[97] activation of *Xenopus laevis* eggs in the absence of intracellular Ca activity;[98] the transition to interphase in activated mouse oocytes;[99] tumor necrosis factor signal transduction in bovine aortic endothelial cells;[100] treatment of cancer in combination with taxol-type compounds;[101] cleavage in sea urchin eggs;[102] triggering meiosis in the starfish *Marthasterias glacialis* and *Asterias rubens* oocytes;[103,104] starfish oocyte maturation;[105] germinal vesicle breakdown, M-phase-promoting factor activation, and H_1-histone kinase activation in *Xenopus* oocytes, induced by either progesterone, M-phase-promoting factor transfer, or okadaic acid microinjection;[106] the transition to metaphase during the first meiotic cell division of mouse oocytes;[107] chromatin behavior at different stages of mouse oocyte maturation;[108] H_1 kinase activity and M-phase-promoting factor activation in cattle and pig oocytes;[109] *in vitro* maturation of goat oocytes;[110] activation of mammalian oocytes;[111,112] meiotic resumption and subsequent development to the blastocyst stage of bovine oocytes;[113] synchroni-

zation of cell division in eight-cell bovine embryos produced *in vitro*;[114] germinal vesicle breakdown of bovine oocytes;[115] maturation, fertilization, and development of bovine oocytes;[116] activation of unfertilized eggs of the newt *Cynops pyrrhogaster*;[117] cyclic reorientation of cortical microtubules in bean cell walls;[118] mouse embryo cleavage arrest and synchronization and subsequent development;[119] and length of cell cycles and the state of phosphorylation of putative intermediate filament proteins in sea urchin embryos.[120]

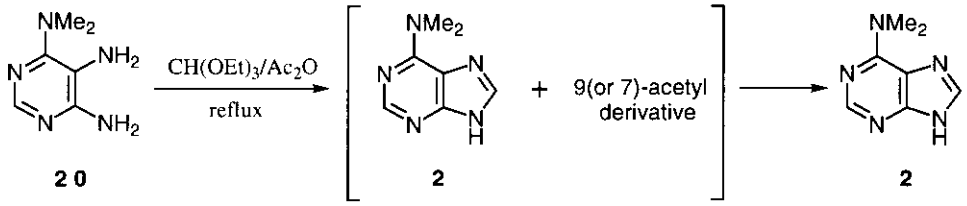
Effects of **2** on the following biological processes have also been investigated: oligogalacturonide-induced cytoplasmic acidification in tobacco cells grown in suspension cultures;[121] oxygen consumption by mitochondrial preparations from soybean cells;[122] *p*-coumaric acid disappearance and delayed inhibition of *p*-coumaric acid disappearance in a cell suspension of soybean;[123] succinate and malate oxidations in mitochondria isolated from fresh potato tuber;[124] the mutagenic effect of UV light on *Escherichia coli*, radiation resistant strain B/r;[125] energy-linked amino acid transport systems of *Achlya* (a freshwater mold);[126] production of an experimental nephrotic syndrome in rats;[127] induction of nephrotoxicity in mice;[128] GABA (4-aminobutyric acid) responses and diazepam enhancement of GABA responses, using mouse spinal cord neurons in dissociated cell culture;[129] binding, to rat brain membranes, of benzodiazepines;[130] displacement of [^{3}H]diazepam binding in rat brain;[131] regulation by GABA of the displacement of benzodiazepine antagonist binding in rat brain;[132] the benzodiazepine receptor binding in rat brain;[133] the aminophylline-resistant relaxation of isolated rabbit coronary artery;[134] induction of cell elongation in cultured fibroblasts;[135] uptake of adenosine into human blood platelets;[136] enucleation of adherent mouse peritoneal exudate cells (macrophages) in combination with centrifugation;[137] uptake of adenosine by human fibroblast lysosomes;[138] the cytokinetic, phenotypic, and molecular effects elicited in HL-60 human leukemic cells by a low dose (0.6 μM) of **2**;[139] and an assay for identifying fungicides or other anti-proliferative agents that inhibit mitosis or meiosis.[140] The use of **2** as a stabilizer for pesticides containing DDVP (phosphoric acid 2,2-dichloroethenyl dimethyl ester)[141] and a vasodilator composition containing **2**[142] have been applied for patents.

As regards the synthesis of **2**, Baker *et al.*[143a] started from 4-amino-6-dimethylamino-2-methylthiopyrimidine (**13**) and obtained **2** through **14**, **15**, and **16** or through **14**, **18**, and **19** or through **14**, **18**, and **17**,[143b] as illustrated in Scheme 1. Goldman *et al.*[144] treated 4,5-diamino-6-dimethylaminopyrimidine (**20**) with boiling $CH(OEt)_3/Ac_2O$ to obtain a mixture of **2** and its 9(or 7)-acetyl derivative (Scheme 2). Recrystallization of the mixture from EtOH afforded the acetyl derivative in 20% yield, and treatment of the ethanolic filtrate with 1 N aqueous NaOH at 100°C for 5 min afforded **2** in 66% yield.

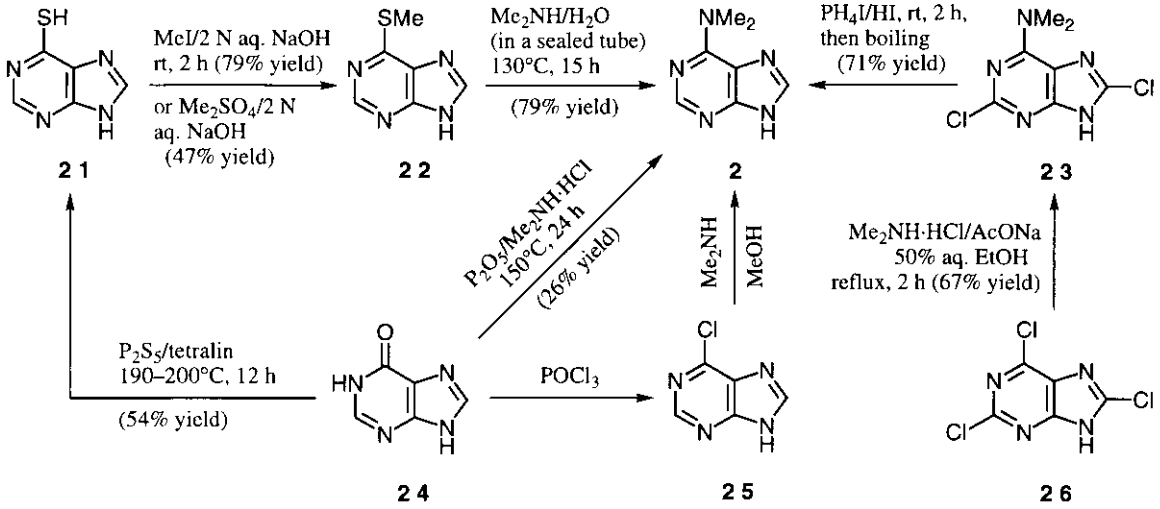
In a synthetic approach to **2** from a purine derivative, Elion *et al.*[145] reached **2** from hypoxanthine (**24**) *via* 6-mercaptopurine (**21**) and 6-methylthiopurine (**22**), as shown in Scheme 3. The step **22**→**2** was repeated under similar reaction conditions by Albert and



Scheme 1

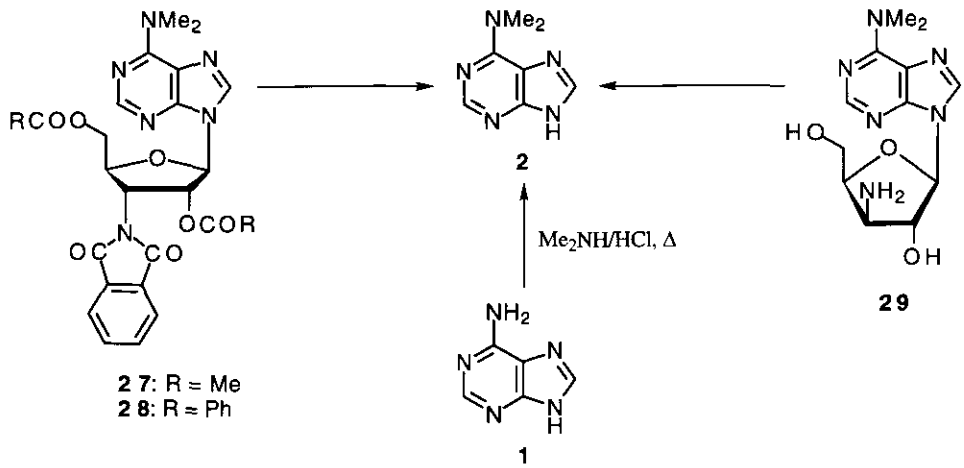


Scheme 2



Scheme 3

Brown (20% aqueous Me_2NH, 140°C, 24 h),[146] by Skinner *et al.*,[58] and by Okumura *et al.* (130–135°C, 17 h, 45% yield).[32a] Alternatively, Albert and Brown[146] heated 6-chloropurine (**25**), obtainable from **24** by chlorination with $POCl_3$, with 15% methanolic Me_2NH at 100°C for 1 h to secure **2**.[37,147] Lambe *et al.*[148] prepared [8-^{14}C]-**2** from [8-^{14}C]-**25** by heating with Me_2NH in THF under an N_2 atmosphere at 50°C for 2.5 h. Girgis and Pedersen[149] reported a one-step 26% conversion of **24** into **2**, in which a mixture of P_2O_5, Me_2NH·HCl, and **24** was heated at 150°C for 24 h. A slight modification of this procedure by Motawia *et al.*[150] improved the yield of **2** to 56%. Yet another synthesis of **2** from a purine derivative includes that of Breshears *et al.*,[147] who converted 2,6,8-trichloropurine (**26**) into **2** *via* 2,8-dichloro-6-dimethylaminopurine (**23**), as depicted in Scheme 3.



Scheme 4

The formation of N^6,N^6-dimethyladenine (**2**) by methylation of DNA[151,152] and RNA[153–155] molecules and hydrolysis of the resulting products has been known. Alcoholysis of puromycin with ethanolic HCl has been shown to give **2**, *O*-methyl-L-tyrosine, and 3-amino-3-deoxyribose,[143a,156a] and treatment of a crude sample of *O*-demethylpuromycin with ethanolic HCl at 80–83°C for 1 h gave **2** as revealed by paper chromatographic analysis.[156b] Treatment of the ribofuranosyl derivative (**27** or **28**) in a mixture of AcOH and Ac_2O with 96% sulfuric acid at 20–25°C for 17 h or 18 h was reported to provide **2**·$2H_2SO_4$ in 92% or 100% yield, respectively (Scheme 4).[157] Hydrolysis of the xylofuranosyl derivative (**29**) in boiling dilute aqueous HCl for 3 h afforded **2**, and it was isolated as the picrate in 79% yield.[158] Lambe *et al.*[148] found that only a small amount of N^6,N^6-dimethyladenine arabinoside, a potent inhibitor of varicella-zoster virus replication *in vitro*, was cleaved to **2** in rats. Preparation of **2** by exchange amination of adenine (**1**) with Me_2NH in the presence of HCl (Scheme 4) has been applied for a patent.[159]

TABLE I. N^6,N^6-Dimethyladenine (**2**): Physical and Spectral Characteristics

Item		Specification[a]	Literature (ref. No.)
Melting point[b]		265–265.5°C (87); 263–264°C (32a); 260–263°C (145b); 257–258°C (143a, 156a); 257–257.5°C (144b); 257°C (146); 256.5–257°C (144a); 251–253°C (149, 150)	
	2·HCl	251–253°C (145a, 147); 249–250°C (147)	
	2·2HCl	225–227°C (decomp)	(156a)
	2·2HBr	255–258°C (decomp)	(157)
	2·2H_2SO_4	210–215°C	(157)
	2·picrate	247°C (158); 244–245°C (decomp) (143a); 241–242°C (decomp) (144b)	
Acid dissociation constant			
	basic pK_a	3.87 (H_2O)[c] (146, 160, 161, 169); 3.9 (H_2O)[d] (165); 4.3 (H_2O)[e] (164); 4.4 (H_2O)[d] (163); 4.45 (H_2O)[d] (164); 4.10 (D_2O)[c,f] (166)	
	acidic pK_a	9.95 (H_2O)[d] (164); 10 (H_2O)[e] (164); 10.0 (H_2O)[d] (165); 10.1 (H_2O)[d] (163); 10.5 (H_2O)[c] (146, 160, 161, 169); 10.54 [59% (v/v) aq. EtOH][c] (162); 13.0 (DMSO)[c] (167); 14.7 ($MeOCH_2CH_2OH$)[c] (168)	
Paper chromatography			(16, 19, 21, 22, 25, 26, 29, 30, 146, 151, 153, 170–175)
TLC			(12, 18, 20, 24, 155, 156b, 176–179)
Column chromatography			(9, 16, 151, 180–183)
HPLC			(181, 182, 184–193)
Ion-exchange chromatography			(16, 182, 183, 188)
GC			(10, 194–197)
Electrophoresis			(30, 153, 198)
MS			(10, 197, 199–205)
UV spectrum		In H_2O at various pH's (21, 22, 145a, 147, 160, 163–165, 181, 206, 207); in methylcyclohexane, dioxane, *i*-PrOH, or H_2O (208)	
Thermal perturbation differential spectrum			(209)
UV photoelectron spectrum			(210)
Fluorescence spectrum			(208)
Fluorescence property		In acidic solution at rt (211); in ethylene glycol–H_2O (pH 7.0) at 77 K (212)	
Phosphorescence property		In EtOH at 1.4 K	(213)
IR spectrum			(10, 163)
Surface enhanced Raman scattering spectrum			(214, 215)
^{1}H NMR spectrum		In $CDCl_3$ (216); in DMSO (217, 218); in DMSO-d_6 (150, 170, 219, 220); in CD_3OD–CF_3CO_2D (50:1) (221); in H_2O (164); in D_2O (166, 222–224)	
^{13}C NMR spectrum		Solid (216); in DMSO-d_6 (150, 216, 220, 225, 226)	
^{15}N NMR spectrum		In DMSO	(227)

(*continues*)

TABLE I (*continued*)

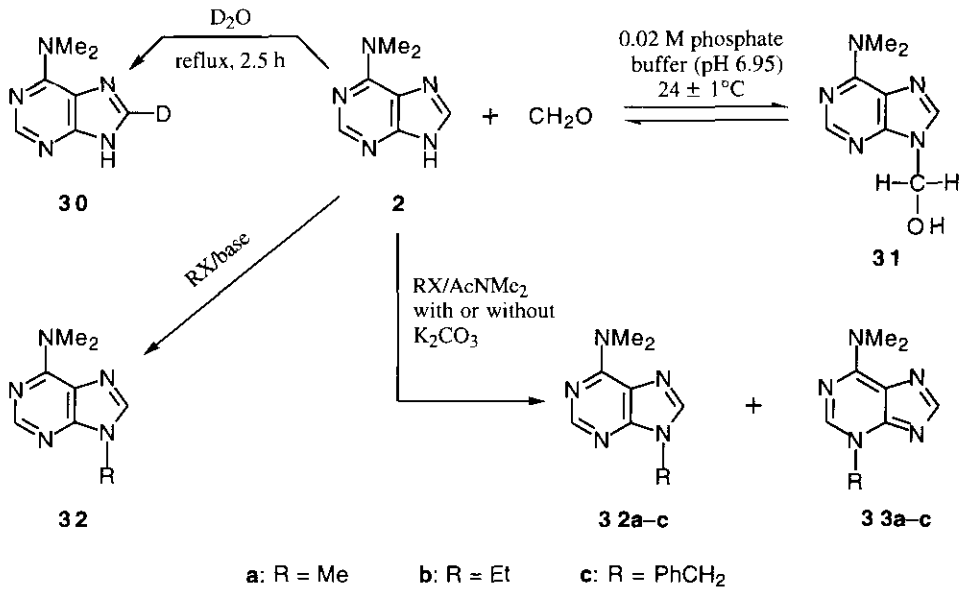
Item	Specification[a)]	Literature (ref. No.)
Crystal structure	**2**·2H_2O (228); **2**·HCl·H_2O (229); **2**·2HCl (229); **2**·HNO_3 (230); **2**·H_2SO_4 (231); (**2**)$_2$·H_2SO_4·2H_2O (232); **2**·CCl_3CO_2H (233); (**2**)$_2$·(hydroxyethenetricarbonitrile)$_2$·1,4-dioxane (234); **2**·picrate (235)	
Polarography		(236–240)
Voltammetry		(237, 239)
Redox property		(241, 242)
Solubility	In H_2O (at 20°C and 100°C)	(146)
Partition coefficient	In phosphate buffer (pH 7.0)–$MeOCH_2CH_2OH$–$BuOCH_2CH_2OH$	(243)
Acidimetric differential potentiometric titration	In $MeOCH_2CH_2OH$ (244); in $MeOCH_2CH_2OH$–propylene carbonate (245)	
Apparent molar volume and heat capacity	In H_2O at 25°C, 35°C, and 45°C	(246)
Potential surface		(247)
Enthalpy of hydration		(204, 247–249)
Enthalpy of solution	In H_2O	(248, 249)
Enthalpy of sublimation		(248–250)
Ionization potential		(210)
Singlet and triplet $\pi\rightarrow\pi^*$ transition energies		(251)
Electron density	By the LCAO MO method (219); by the INDO and STO-3G MO methods (252)	
Electronic structure		(210, 253–256)

a) With or without reference number(s) in parentheses. *b*) Reported for analytical samples, in most cases. *c*) Potentiometric. *d*) UV spectral. *e*) ^{1}H NMR spectral. *f*) For the N(1)-deuterated species.

Included in Table I are the fruits of an additional comprehensive survey of papers describing the physical properties and spectral characteristics of N^6,N^6-dimethyladenine (**2**).[160–256]

Interactions of **2** with the following substances have been reported: self-association in various aqueous media at 25°C[257] and in D_2O;[223] H_2O vapor (hydration);[204] benzanthracene;[258,259] β-cyclodextrin in phosphate buffer (pH 7) at 25°C;[260] proflavine;[261] the methyl esters of arginine, serine, and methionine in DMSO;[262] bovine serum albumin in D_2O;[263] an antibody directed toward N^6-(Δ^2-isopentenyl)adenosine;[264] Cu(I) ions in aqueous media;[265] (ImH)[$RuCl_4Im_2$] (Im = imidazole) in MeOH;[266] (4-NO_2ImH)[$RuCl_4$-(5-NO_2Im)$_2$] in CD_3OD;[267] the mixed bridged diene-rhodium(I) complex [(cod)Rh(μ-Cl)-(μ-OAc)Rh(cod)] (cod = 1,5-cyclooctadiene) in MeOH;[268] [(nbd)Rh(acac)] (nbd = norbornadiene) in MeOH, [$(CO)_2$Rh(acac)] in MeOH, or [(CO)Rh(acac)(PPh_3)] in MeOH/CH_2Cl_2;[269] the Rh_2^{4+} formamidinate complex Rh_2(μ-form)$_2$(μ-O_2CCF_3)$_2$(H_2O)$_2$ (form = *N*,*N*'-di-*p*-tolylformamidinate anion) in H_2O;[270] $Re_2Cl_2(AcO)_4$ in EtOH containing MeO-

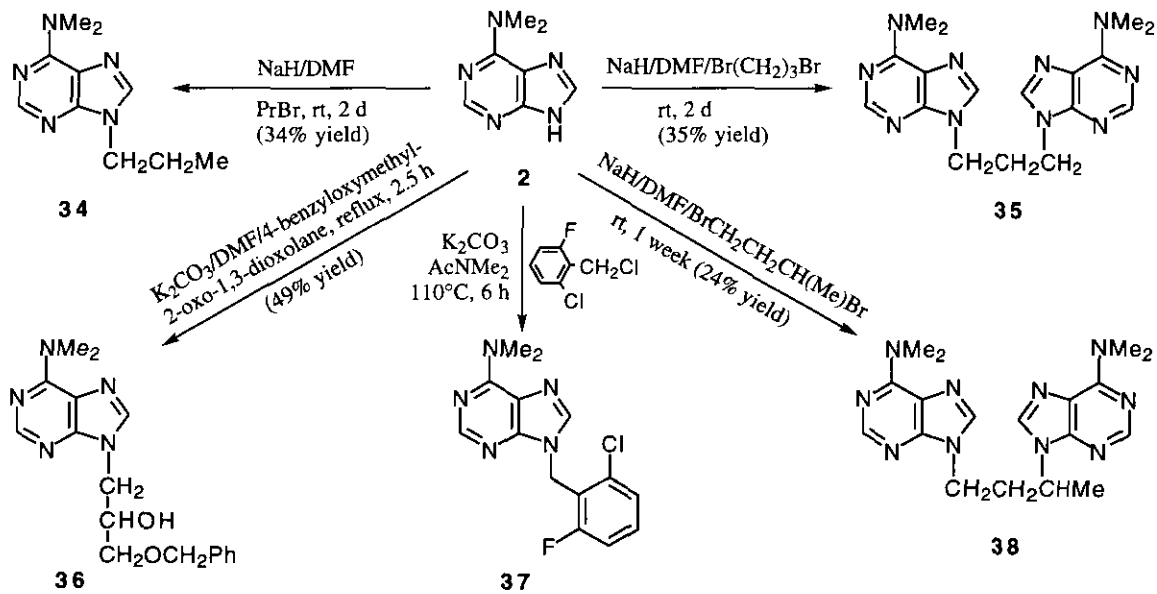
Na;[216] $(Bu_4N)_2[Re_2Cl_8]$ in EtOH;[216] *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ in H_2O at 37°C;[271] $HgCl_2$ in EtOH/aqueous NaOH;[206,272] MeHgOH or $MeHgClO_4$/MeHgOH or $MeHgNO_3$/MeHgOH in boiling H_2O or $MeHgNO_3$ in aqueous MeCN.[220]



Scheme 5

As regards the chemical behavior of **2**, Albert and Brown[146] reported its instability on heating in boiling 10 N aqueous NaOH for 1 h. The high stability of **2** in 25% aqueous TsOH at 100°C for 4 h and in a 1:1 mixture of TFA and formic acid (97–100%) at 200°C for 1.5 h was confirmed by Gordon *et al.*[273] and by Lakings *et al.*,[184] respectively. Anderson and Beauchamp[266] prepared N^6,N^6-dimethyladenine-*8-d* (**30**) from **2** by heating anaerobically in refluxing D_2O for 2.5 h (Scheme 5). Kiessling *et al.*[274] treated **2** in DMF with $^3H_2$ in the presence of Pd black to prepare N^6,N^6-dimethyl-[^{3}H]adenine. McGhee and von Hippel[275] found that the reaction of **2** with formaldehyde in 0.02 M phosphate buffer (pH 6.95) at 24 ± 1°C came to equilibrium with a product presumed to be **31**, and they determined the equilibrium constant to be 11.4 M^{-1}. Takiura's group[276] reported that the reaction of **2** or N^6-methyladenine (**94**) with glyoxal trimer hydrate in AcOH at 100°C for 6 h did not produce fluorescence, whereas adenine (**1**), 1-methyladenine (**115**), 7-methyladenine (**159**), 9-methyladenine (**146**), adenosine (**76**), AMP, ADP, ATP, and 2'-deoxyadenosine gave rise to fluorogenic reactions under similar conditions. Itaya's group[277] reported that methylation of **2** with MeI in $AcNMe_2$ in the presence of K_2CO_3 at rt for 4–9 h gave N^6,N^6,9-trimethyladenine (**32a**) and N^6,N^6,3-trimethyladenine (**33a**) in 54% and 14% yields, respectively (Scheme 5);[278] ethylation with EtI under similar reaction conditions afforded 9-ethyl-N^6,N^6-dimethyladenine (**32b**) and the 3-ethyl isomer (**33b**) in 72% and 13% yields, respectively; and benzylation with $PhCH_2Br$

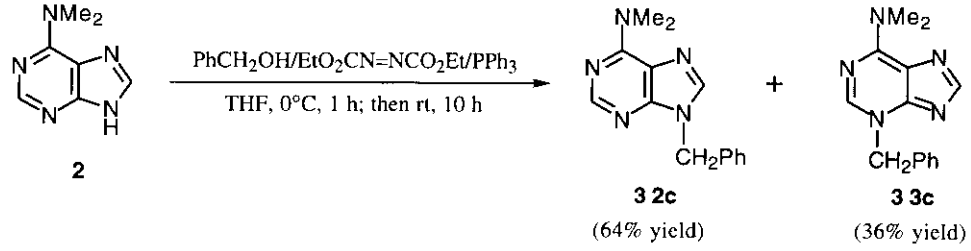
in a similar manner furnished 9-benzyl-N^6,N^6-dimethyladenine (**32c**) and the 3-benzyl isomer (**33c**) in 65% and 30% yields, respectively. When these alkylations were effected in the absence of K_2CO_3, the regioselectivity in alkylation suffered a complete reversal:[277] Methylation at 40°C for 48 h produced, after basification and chromatographic separation of the reaction products, **32a** (0.7% yield) and **33a** (83%); ethylation at 80°C for 7 h, **32b** (1.8%) and **33b** (90%); and benzylation at 40°C for 24 h, **32c** (2.8%) and **33c** (86%). Miyaki and Shimizu[219] found that benzylation of **2** with $PhCH_2Br$ in $AcNMe_2$ at 110°C for 7 h gave, after basification and chromatographic separation of the reaction products, **32c** (5%) and **33c** (66%) and that heating **33c**·HBr in DMF at 150°C for 40 h gave, after basification, **32c** in 22% yield, indicating the occurrence of N(3)→N(9) benzyl migration under these thermal conditions. Pal and Horton[163] methylated **2** with dimethyl sulfate in a mixture of 0.01 M phosphate buffer (pH 7.0) and EtOH at pH 7.0 and rt for 3–4 h and obtained, after chromatographic separation of the products, **32a** (8.3% yield), **33a** (66%), and N^6,N^6,1-trimethyladenine (22.9%).



Scheme 6

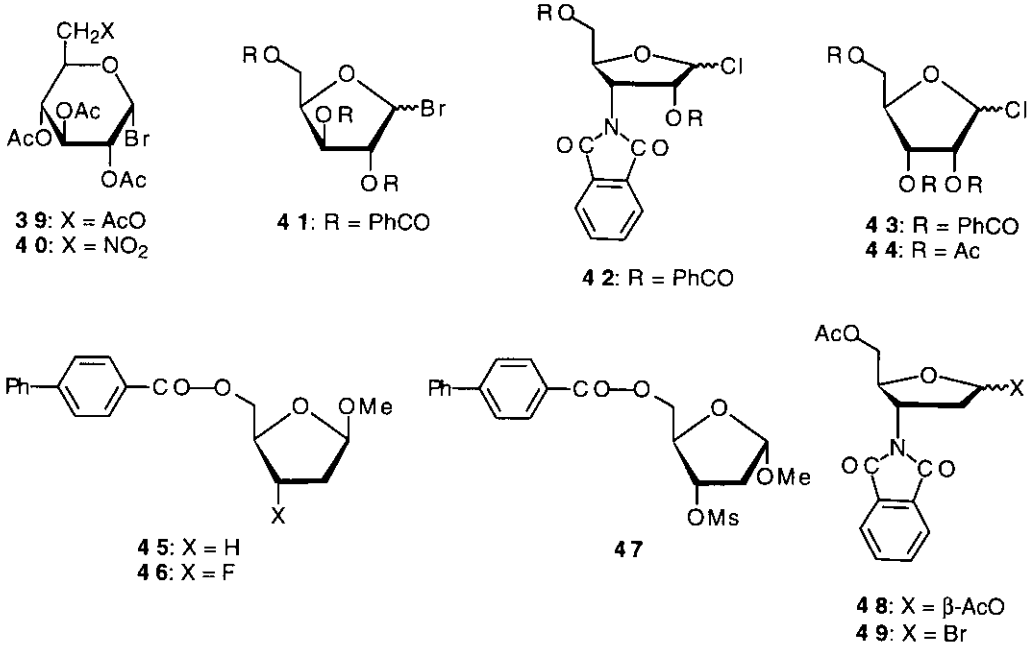
The preferential N(9)-alkylation of **2** in the presence of added base has been adopted by many research groups for the preparation of 9-substituted N^6,N^6-dimethyladenines (type **32**). Kelley's group[279] obtained **32a** from **2** in 36% yield by methylation (MeI/MeONa/DMSO, rt, 1 h); **32b** from **2** by ethylation ($EtI/Bu_4N^+OH^-$, CH_2Cl_2/H_2O);[280] **32** (R = CH_2CH_2Cl) from **2** in 76% yield by alkylation ($BrCH_2CH_2Cl$/benzene/$Bu_4N^+Br^-$/50% aqueous NaOH, 80°C, 0.5 h).[281] Takemoto and co-workers[282] synthesized **34**, **35**, and **38** from **2**, as shown in Scheme 6. They also prepared poly(N^6,N^6-dimethyl-9-vinyladenine).[282] LaMontagne *et al.*[283] synthesized 9-(3-benzyloxy-2-hydroxypropyl)-N^6,N^6-di-

methyladenine (**36**) from **2** by alkylation with 4-benzyloxymethyl-2-oxo-1,3-dioxolane in the presence of K_2CO_3. Imai and Seo[284] obtained 9-(2-chloro-6-fluorobenzyl)-N^6,N^6-dimethyladenine (**37**) by treatment of **2** with 2-chloro-6-fluorobenzyl chloride in $AcNMe_2$ in the presence of K_2CO_3 at 110°C for 6 h. Ramzaeva *et al.*[285] employed conditions of phase-transfer catalysis in the system benzene/aqueous NaOH/$Bu_4N^+Br^-$ for N(9)-alkylation of **2** with 2,6-dichlorobenzyl chloride. Many other compounds of type **32**, such as those where the N(9)-R groups are 2,6-dihalogenobenzyl;[159,286,287] 3-(4-benzamidopiperidino)propyl;[288,289] 3-[4-(aryloxymethyl)piperidino]propyl;[290] and 3-(4-aryl-1-piperazinyl)propyl,[291] have been analogously synthesized from **2** and applied for patents. N^6,N^6-Dimethyladenine (**2**) was conjugated at N(9) to Sepharose through a 12-atom spacer moiety to yield a matrix for preparation of an affinity column for purification of cytokinin oxidase.[292]



2 **3 2c** (64% yield) **3 3c** (36% yield)

Scheme 7



3 9: X = AcO
4 0: X = NO_2

4 1: R = PhCO

4 2: R = PhCO

4 3: R = PhCO
4 4: R = Ac

4 5: X = H
4 6: X = F

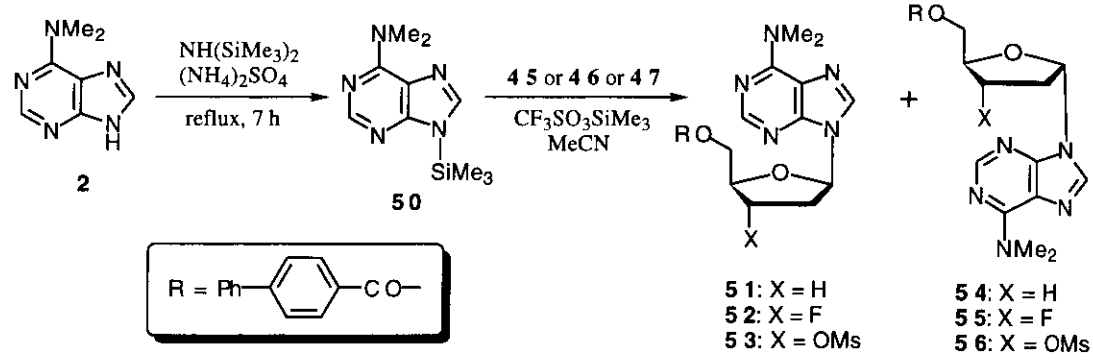
4 7

4 8: X = β-AcO
4 9: X = Br

Sukhodub *et al.*[203,293] found that treatment of **2** with thio-TEPA (1,1',1"-phosphinothioylidynetrisaziridine) in H_2O at 37°C for 3–5 d produced an N^x-(2-aminoethyl) de-

rivative, as detected by field ionization MS. Toyota *et al.*[294] reported that Mitsunobu reaction of **2** with $PhCH_2OH$ gave the N(9)-benzyl derivative (**32c**) and the N(3)-benzyl isomer (**33c**) in 64% and 36% yields, respectively (Scheme 7), but the N(7)-benzyl isomer was not detectable in the reaction mixture.

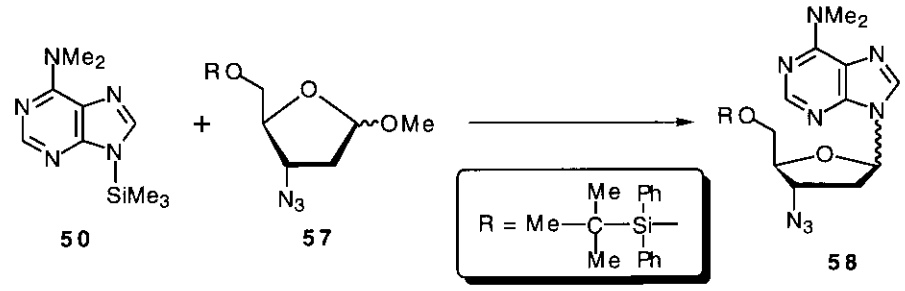
Baker *et al.*[272] reported condensation of the chloromercuri derivative of **2** with α-bromoacetoglucose (**39**) in boiling xylene for 1 h and deacetylation of the condensed product (26% yield) with MeONa in boiling MeOH for 45 min to give N^6,N^6-dimethyl-"7"-β-D-glucopyranosyladenine [reported mp 239–241°C (decomp)] in 76% yield. Baker and Schaub[295] condensed the chloromercuri derivative of **2** with 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide (**41**) and debenzoylated the condensation product in a similar manner to obtain a mixture of the "7"- and 9-xylosides (in poor yield), from which the "7"-xyloside could be isolated. In addition, Baker *et al.*[157] reported a similar condensation of the chloromercuri derivative of **2** with 2,5-di-*O*-benzoyl-3-phthalimido-3-deoxy-β-D-ribofuranosyl chloride (**42**) to produce a mixture of the corresponding "7"- and 9-nucleosides. Later on, the structures of these N^6,N^6-dimethyl-"7"-glycosyladenines were reassigned by Townsend *et al.*[170] as the corresponding 3-glycosyl derivatives, on the basis of UV and ^1H NMR spectral data. Kissman *et al.*[296] synthesized N^6,N^6-dimethyladenosine (**69**) by similar condensation of the chloromercuri derivative of **2** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (**43**) or its tri-*O*-acetyl analogue (**44**), followed by debenzoylation or deacetylation with MeONa/MeOH. The attempt to couple **2** with 2,3,4-tri-*O*-acetyl-6-deoxy-6-nitro-α-D-glucopyranosyl bromide (**40**) in boiling nitromethane in the presence of $Hg(CN)_2$ and anhydrous $CaSO_4$ for 3 h was reported to be unsuccessful.[297]



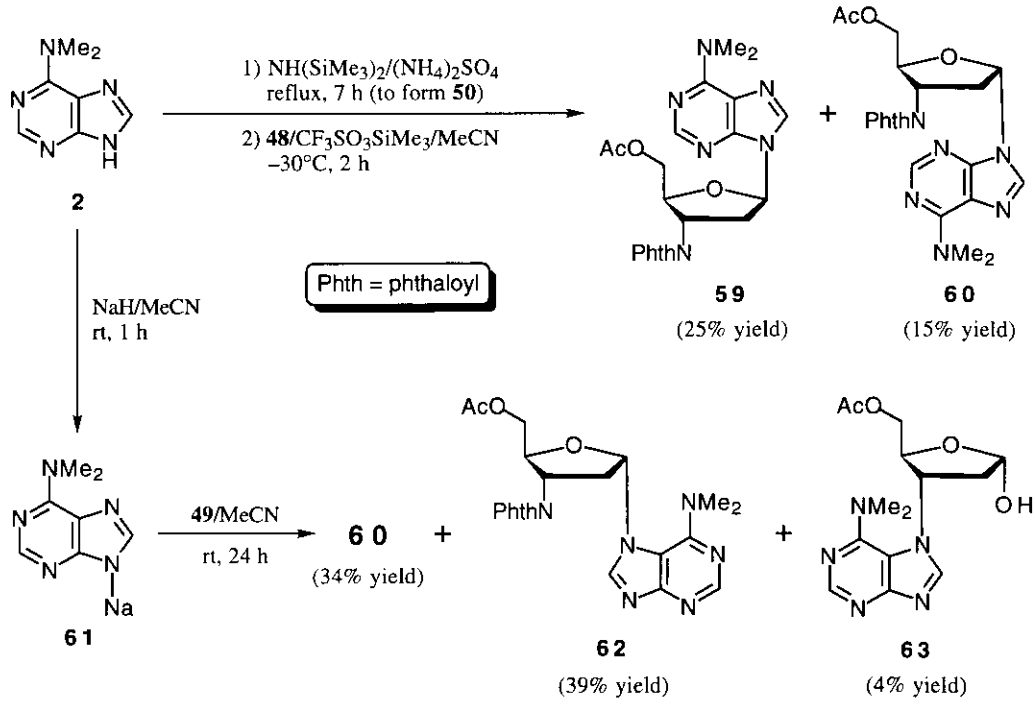
Scheme 8

Pedersen's group[298] condensed the trimethylsilylated derivative (**50**), prepared from **2** by treating with boiling hexamethyldisilazane in the presence of $(NH_4)_2SO_4$, with the sugar derivative (**45**) in MeCN in the presence of trimethylsilyl triflate at rt for 3 h to obtain the β-furanoside derivative (**51**) and its α-anomer (**54**) in 20% and 36% yields, respectively (Scheme 8). The fluorinated sugar derivative (**46**) similarly reacted with **50**

to give **52** and **55** in 13% and 18% yields, respectively.[298] Replacement of **45** or **46** by **47** in these condensations but at –30°C for 2 h resulted in the formation of **53** and **56** in 18% and 21% yields, respectively.[298] Similar condensation of **50** with the azido sugar (**57**) at –30°C to 0°C for 3 h afforded **58** as an anomeric mixture (α:β = 4:1) in 35% yield (Scheme 9).[298]



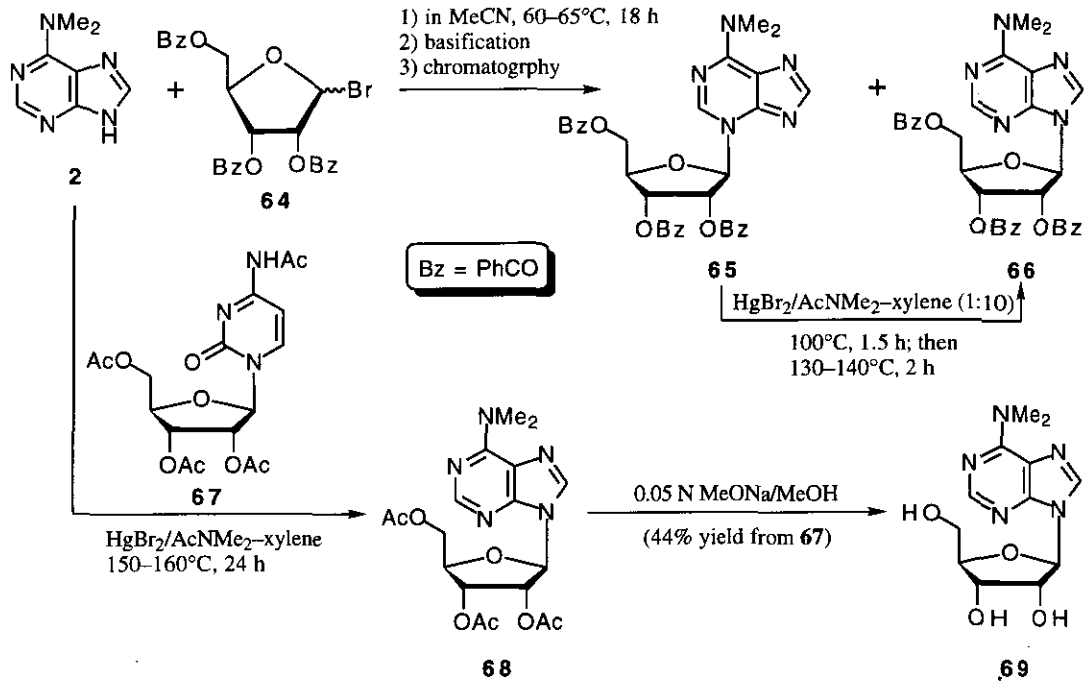
Scheme 9



Scheme 10

Pedersen's group[150] also condensed **2** with the phthalimido sugar derivative (**48**) in a similar manner to obtain the 9-β-furanoside (**59**) and the 9-α-furanoside (**60**) in 25% and 15% yields, respectively (Scheme 10). On the other hand, coupling of the Na salt (**61**), generated *in situ* from **2** by treatment with NaH in MeCN, with the glycosyl bromide (**49**) (α:β = 1:5) in MeCN at rt for 24 h produced the 9-α-furanoside (**60**) (34%), the 7-α-

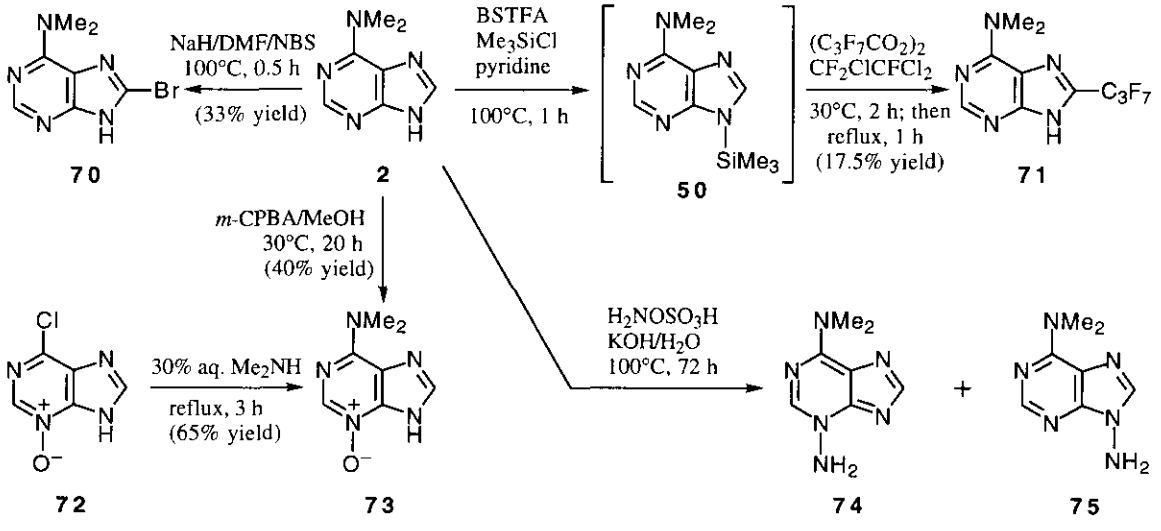
furanoside (**62**) (39%), and an unexpected product (**63**) (4%).[150] Miyaki and Shimizu[219] condensed **2** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**64**) in MeCN at 60–65°C for 18 h to obtain the corresponding 3-furanoside (**65**) and the 9-furanoside (**66**) in 36% and 11% yields, respectively (Scheme 11). Although **65** remained unchanged on heating at 100°C for 1.5 h in the presence of $HgBr_2$, N(3)→N(9) ribosyl migration took place on heating [in $AcNMe_2$–xylene (1:10, v/v)] at 100°C for 1.5 h and then at 130–140°C for 2 h, producing **66** in 36% yield.[219] One of the applications of this ribosyl migration was demonstrated by transfer of the ribosyl moiety from N^4-acetyl-2',3',5'-tri-*O*-acetylcytidine (**67**) to **2** to prepare N^6,N^6-dimethyladenosine (**69**) *via* **68**, as delineated in Scheme 11.[299]



Scheme 11

Zintchenko *et al.*[300] reported an enzymic transglycosylation from α-D-ribose 1-phosphate to **2** in phosphate buffer (pH 7.0) at 60°C using the cell paste of *Escherichia coli* BM-11. Enzymic transglycosidations from pyrimidines to **2** have also been reported: from [deoxyribosyl-^{14}C]thymidine in phosphate buffer (pH 6.0) at 40°C using *trans-N*-deoxyribosylase (EC 2.4.2.6) from *Lactobacillus helveticus*;[301] from thymidine in citrate buffer (pH 6.0) at 37°C using the nucleoside deoxyribosyltransferase (EC 2.4.2.6) from *Lactobacillus leichmannii*, giving 2'-deoxy-N^6,N^6-dimethyladenosine in 86% yield;[302] from 3'-deoxythymidine using purified thymidine phosphorylase and purine phosphorylase, giving 2',3'-dideoxy-N^6,N^6-dimethyladenosine;[303,304] from 5'-deoxythymidine in 0.02 M phosphate buffer at 37°C for 3–5 d, affording 2',5'-dideoxy-N^6,N^6-dimethyladen-

osine in low yield (in the region of 10%);[305] from 2'-deoxyuridine in 50 mM aqueous $AcONH_4$ (pH 5.7) at 37°C for 16 h in the presence of alginate gel-entrapped cells of auxotrophic thymidine-dependent strain of *Escherichia coli*, obtaining 2'-deoxy-N^6,N^6-dimethyladenosine in 70% yield;[306] from 2',3'-dideoxycytidine using a nucleoside deoxyribosyltransferase from *Lactobacillus leichmannii*[307] in 50 mM citrate buffer (pH 6.2) at 37°C for 48 h, obtaining 2',3'-dideoxy-N^6,N^6-dimethyladenosine in 78% yield;[308] from 2',3'-dideoxy-3'-fluorouridine in a phosphate buffer containing potassium azide in the presence of purine nucleoside phosphorylase and thymidine phosphorylase immobilized on DEAE cellulose;[309] and from arabinofuranosyluracil in phosphate buffer at 50°C for 5 d in the presence of uridine phosphorylase and purine nucleoside phosphorylase, giving 9-(β-D-arabinofuranosyl)-N^6,N^6-dimethyladenine.[310]



Scheme 12

Kelley *et al.*[311] reported the bromination of the anion of **2** with NBS in hot DMF to provide 8-bromo-N^6,N^6-dimethyladenine (**70**), as shown in Scheme 12, which was found to be inactive against influenza A virus. Treatment of the TMS derivative (**50**), prepared from **2** by silylation with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) in the presence of Me_3SiCl and pyridine, with bis(heptafluorobutyryl) peroxide in $CF_2ClCFCl_2$ produced the 8-(heptafluoropropyl) derivative (**71**) in low yield.[312] Oxidation of **2** with *m*-CPBA in MeOH at 30°C for 20 h afforded the N(3)-oxide (**73**) in 40% yield with 23% recovery of **2**.[313] The correctness of the structure of **73** was confirmed by direct comparison with a sample prepared from 6-chloropurine 3-oxide (**72**)[314,315] and dimethylamine (Scheme 12).[313] Amination of **2** with hydroxylamine-*O*-sulfonic acid in alkaline medium at 100°C for 72 h furnished the 3-amino derivative (**74**) in 13% yield, together with a small amount of the 9-amino derivative (**75**).[193]

The reactions of **2** with the OH radical in H_2O at pH 6–8 and 20°C[169] and with the

sulfate radical anion ($SO_4^{\bullet -}$) in H_2O at pH 7[242,316] and the electron paramagnetic resonance spectrum as well as the protonation site of one-electron-reduced **2** (generated by X-Ray irradiation in a 9 M LiCl glass at 4 K)[317] have been investigated. Morimoto and Tsuda[318] reported that the rate of alkaline hydrolysis of *p*-nitrophenyl acetate in Clark–Lubs' buffer (pH 8.2) at 25°C was enhanced in the presence of **2**. Shelf life-extended films containing **2** as a photographic antifogging agent[319] and direct-positive color films containing **2** with wide exposure latitude[320] have been applied for patents.

N^6,N^6-Dimethyladenine (**2**) was found to demethylate, as indicated by the formation of formaldehyde, by liver microsomal enzymes (obtained from rat, guinea pig, or mouse) in the presence of an NADPH-generating system.[321] However, **2** was refractory to mammalian xanthine oxidase.[322] It acted as a competitive inhibitor of the extracellular adenine deaminase from *Nocardioides* sp. J-275L.[323] Preparation of *Escherichia coli* mutants, resistant to **2**, from parental *E. coli* strains H-8311 and H-8285 by chemical mutagenesis and manufacture of L-threonine and L-isoleucine with these mutants have been applied for a patent: The production of the two amino acids was 10–20% higher than did the parental strains.[324]

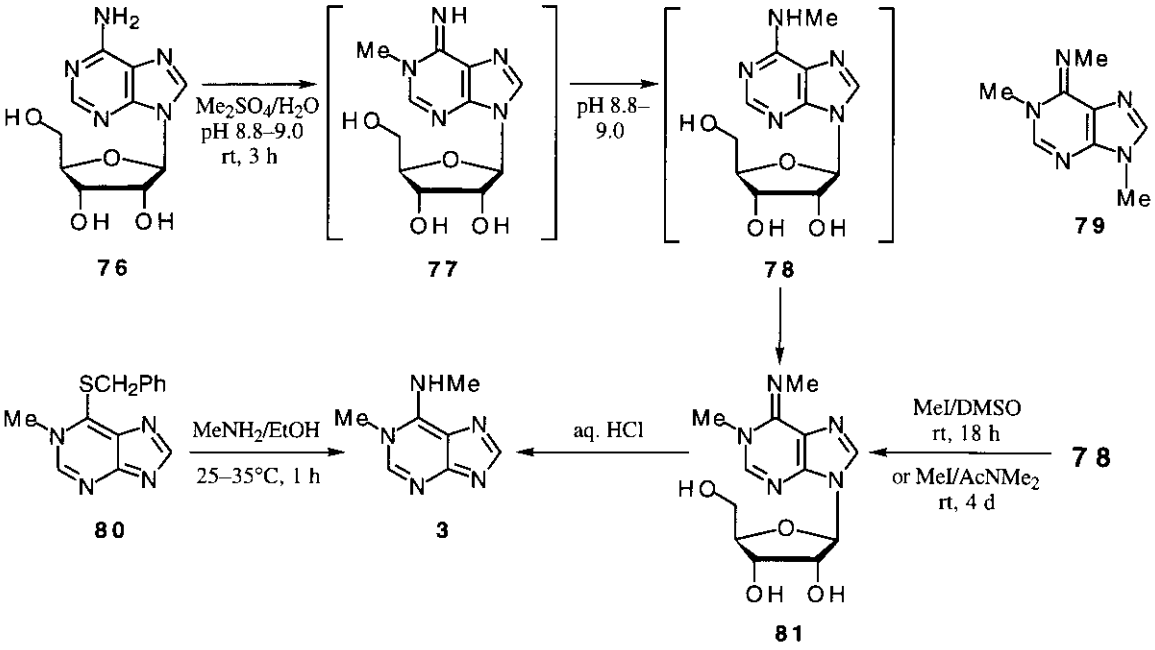
III. N^6,1-DIMETHYLADENINE

Wacker and Ebert[325] studied the methylation of adenosine (**76**) with dimethyl sulfate in H_2O at pH's 6–8, 8.8–9.0, and 13 and obtained a crystalline compound, assumed to be N^6,1-dimethyladenosine (**81**), most efficiently from the reaction carried out at pH 8.8–9.0 (Scheme 13). They claimed to have hydrolyzed this dimethylated nucleoside to N^6,1-dimethyladenine (**3**) with 2 N aqueous HCl and identified the latter base only by formation of its picrate according to the method of Bredereck *et al.*[326] Robins' group[327] methylated N^6-methyladenosine (**78**) with MeI in DMSO to obtain **81**·HI, which was converted into the free nucleoside (**81**) (identical with the one which Wacker and Ebert[325] had isolated from the direct methylation of **76**, as described above). The structure of **81**·HI was established by hydrolysis to the base (**3**), which was in turn prepared by an unambiguous synthesis from 6-benzylthio-1-methylpurine (**80**) and a saturated solution (at 25°C) of $MeNH_2$ in EtOH.[327] Robins' group explained that the above methylation of **76** by Wacker and Ebert probably proceeded through N(1)-methylation to form 1-methyladenosine (**77**), Dimroth rearrangement[328] of **77** to **78** under alkaline conditions, and N(1)-methylation of **78** to give **81**.[327] Toraya *et al.*[329] recently repeated the above **78**→**81**→**3** route with some modification: methylation of **78** with MeI in $AcNMe_2$ at rt for 4 d and hydrolysis of **81** with 0.5 N aqueous HCl at 100°C for 1 h.

Methylation of N^6,1-dimethyladenine (**3**) with MeI in DMF at 100°C (in a closed vessel) for 10 min was reported to produce N^6,1,9-trimethyladenine hydriodide (**79**·HI) in 72.5% yield.[330]

The following physical properties and spectral characteristics of N^6,1-dimethyladenine

(**3**) have been recorded in the literature: the melting point for the free base (**3**), mp >300°C;[327] for the picrate, mp 235°C[325] or mp 236°C;[327] paper chromatography;[325,327] TLC;[329] HPLC;[329] MS;[199] UV in H_2O (at various pH's)[325,327,329,331] and in a MeOH solution;[327,331] ^1H NMR in D_2O.[329]

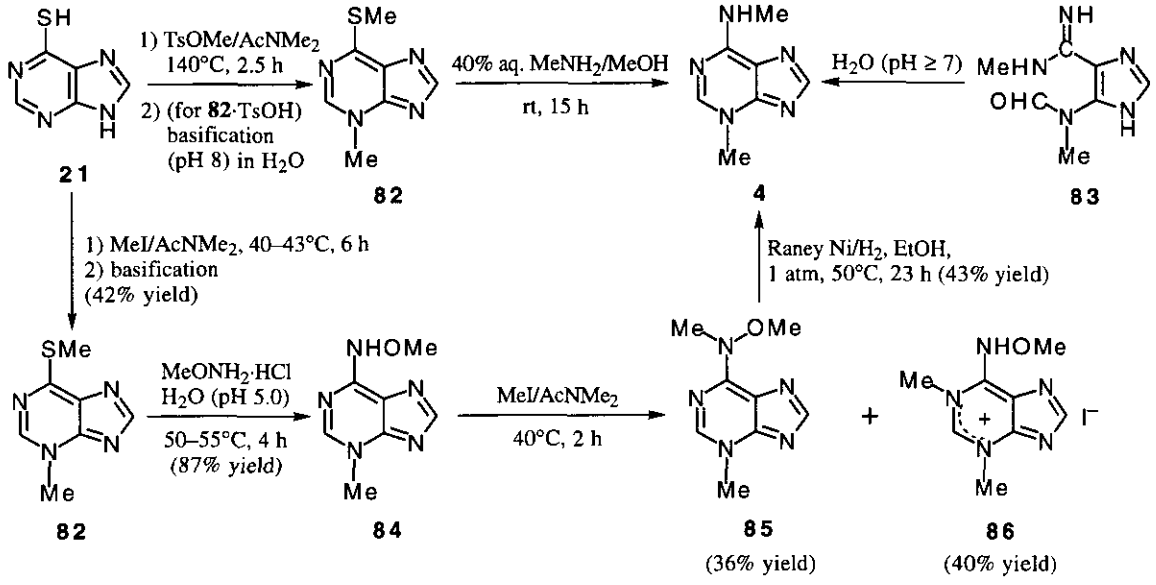


Scheme 13

N^6,1-Dimethyladenine (**3**) was among a series of synthetic purine analogues used for the study of the interactions between lima bean lectin and adenine (**1**), and the binding affinity of **3** was found to be weak.[332] Starfish oocytes are naturally arrested at the prophase stage of the first meiotic division and resume meiosis in response to the maturation-inducing hormone 1-methyladenine (**115**), which is produced and released by the ovarian follicle cells under the influence of a peptide hormone (gonad-stimulating substance) from the radial nerve.[329,333] Toraya *et al.*[329] found that the N^6-methylated derivative (**3**) still retained oocytes maturation-inducing activity, but to a much lesser extent.

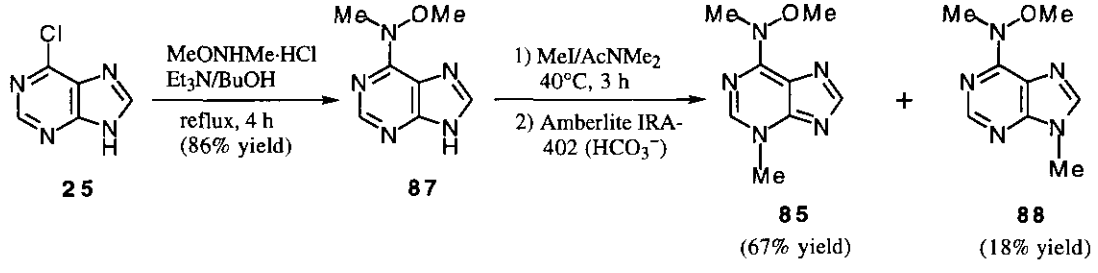
IV. N^6,3-DIMETHYLADENINE

In their synthesis of N^6,3-dimethyladenine (**4**), Jones and Robins[334] treated 6-mercaptopurine (**21**) with methyl *p*-toluenesulfonate in $AcNMe_2$ at 140°C for 2.5 h and basified a solution of the resulting tosylate salt (**82**·TsOH) to obtain the free base (**82**) in *ca.* 50% yield (Scheme 14). Treatment of **82** with aqueous $MeNH_2$ in MeOH at rt for 15 h furnished **4** in good yield.



Scheme 14

Alternatively, Fujii's group[335] prepared **4** from *N'*-methyl-5(4)-(*N*-methylformamido)imidazole-4(5)-carboxamidine (**83**) [see Section VII (Scheme 28)] by cyclization in H_2O at rt under alkaline conditions. In yet another synthesis of **4**, Fujii's group[336] methylated **21** with MeI in $AcNMe_2$ to secure **82**, which was then treated with $MeONH_2$ in H_2O (pH 5.0). Methylation of the resulting N^6-methoxy derivative (**84**) with MeI in $AcNMe_2$ afforded N^6-methoxy-1,3-dimethyladeninium iodide (**86**) (40% yield) and N^6-methoxy-N^6,3-dimethyladenine (**85**) (isolated in 36% yield in the form of **85**·$HClO_4$). Hydrogenolysis of **85**, generated from **85**·$HClO_4$ by the use of Amberlite IRA-402 (HCO_3^-), using Raney Ni catalyst and hydrogen gave **4** in 43% yield (Scheme 14).

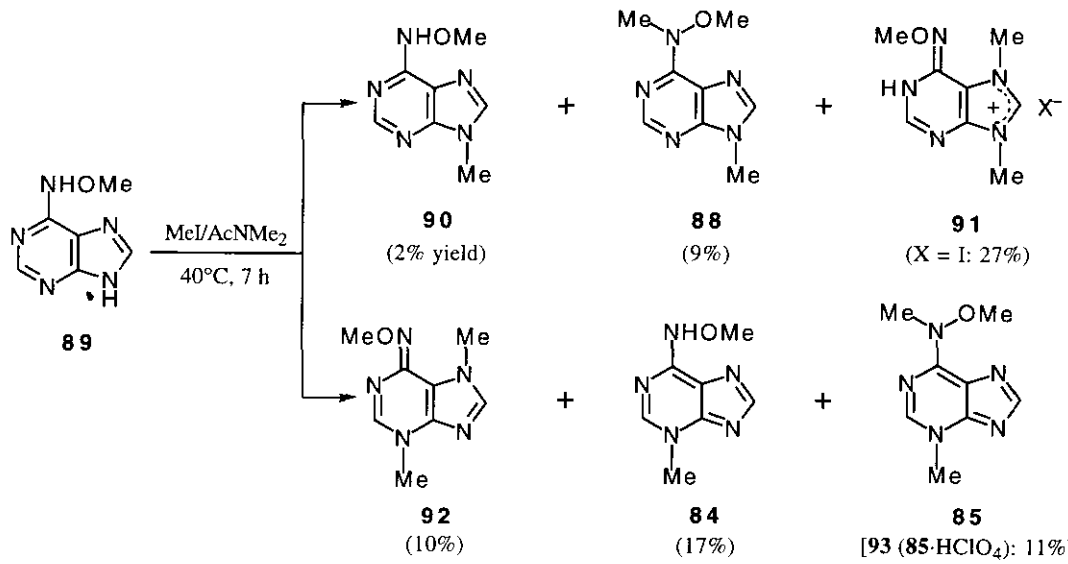


Scheme 15

Methylation of N^6-methoxy-N^6-methyladenine (**87**), prepared from 6-chloropurine (**25**) and *N*,*O*-dimethylhydroxylamine, with MeI in $AcNMe_2$ was also found to produce **85** (isolated in 67% yield as the perchlorate salt), an immediate precursor for **4**, as well as the 9-methylated product (**88**) (18%) (Scheme 15).[336]

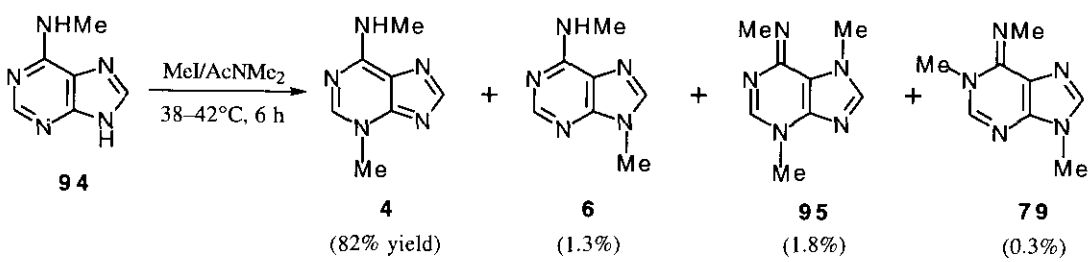
The N^6-methoxy-N^6,3-dimethyl derivative (**85**), isolated as the perchlorate (**93**), was also

among the six products (**84**, **85**, **88**, and **90–92**) obtained from the reaction of N^6-methoxyadenine (**89**) with an excess of MeI in $AcNMe_2$ at 40°C for 7 h (Scheme 16).[337]



Scheme 16

Direct methylation of N^6-methyladenine (**94**)[8] with an excess of MeI in $AcNMe_2$ at 38–42°C for 6 h was found to produce **4** in 82% yield, together with N^6,9-dimethyladenine (**6**) (1.3%), N^6,3,7-trimethyladenine (**95**) (1.8%), and N^6,1,9-trimethyladenine (**79**) (0.3%) (Scheme 17).[337]

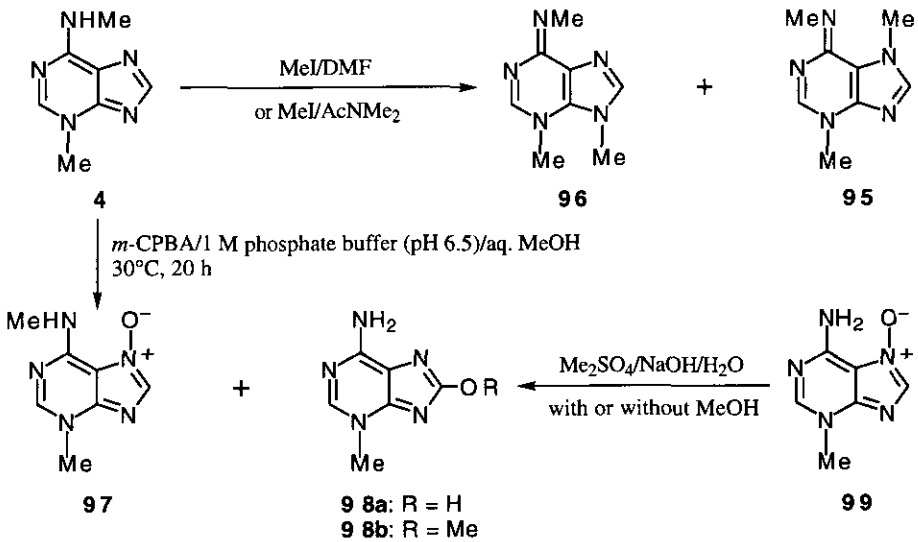


Scheme 17

The following physical properties and spectral characteristics of N^6,3-dimethyladenine (**4**) have been reported in the literature: the melting point for the free base (**4**), mp 314–315°C (decomp),[334] or mp >300°C;[336,337] for **4**·HI, mp 241–242°C (decomp);[337] TLC;[335] MS;[199] UV for the free base (**4**) in H_2O (at various pH's)[334,337] and in 95% aqueous EtOH;[337] for **4**·HI in H_2O (at various pH's) and in 95% aqueous EtOH.[337]

El'tsov *et al.*[330] reported that methylation of **4** in DMF with an excess of MeI at 100°C (in a closed vessel) for 10 min afforded N^6,3,9-trimethyladenine hydriodide (**96**·HI) (16%

yield) and N^6,3,7-trimethyladenine hydriodide (**95**·HI) (64%) (Scheme 18). Fujii *et al.*[337] found that a similar methylation of **4**, but in $AcNMe_2$ at 38–40°C for 6 h, furnished **96**·HI (15% yield) and **95**·$HClO_4$ [29%, after treatment of the primary product (**95**·HI) with 70% aqueous $HClO_4$ in EtOH], being in general agreement with the above results obtained by El'tsov *et al.*[330] Oxidation of **4** with *m*-CPBA in a mixture of 50% aqueous MeOH and 1 M phosphate buffer (pH 6.5) at 30°C for 20 h produced the N(7)-oxide (**97**) in 40% yield, together with 30% recovery of **4** (Scheme 18).[338] Treatment of 3-methyladenine 7-oxide (**99**) with one molar equiv. of dimethyl sulfate in 0.1 N aqueous NaOH at rt for 17 h gave the N^6-methyl derivative (**97**) (13% yield) and 8-hydroxy-3-methyladenine (**98a**) (4%), together with 50% recovery of **99**.[339] In the presence of added MeOH, a similar methylation of **99** at rt for 2.5 h produced **97** (14% yield) and 8-methoxy-3-methyladenine (**98b**) (11%), together with 57% recovery of **99**.[339]



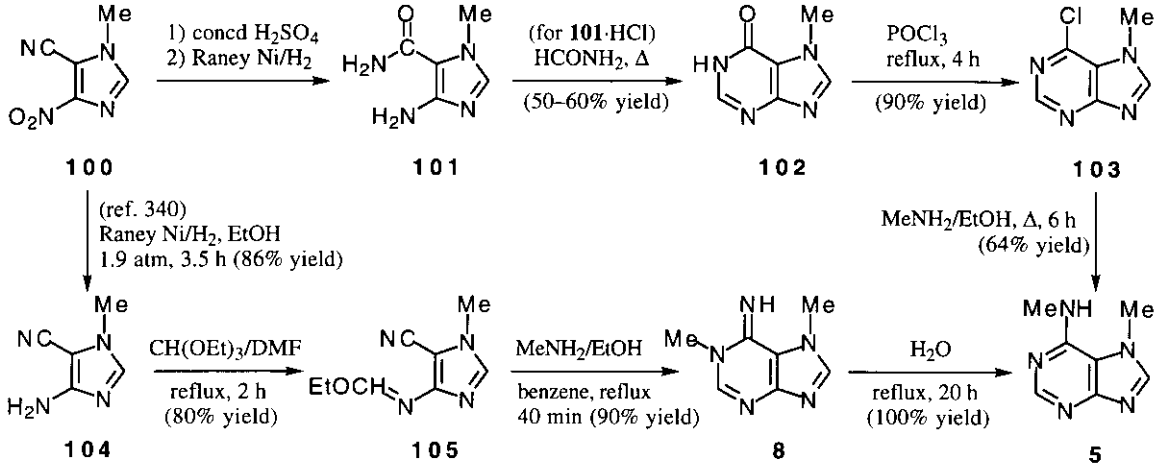
Scheme 18

Binding of **4** to lima bean lectin has been measured by a fluorimetric assay based on allosteric enhancement of 1,8-anilinonaphthalenesulfonate binding.[332]

V. N^6,7-DIMETHYLADENINE

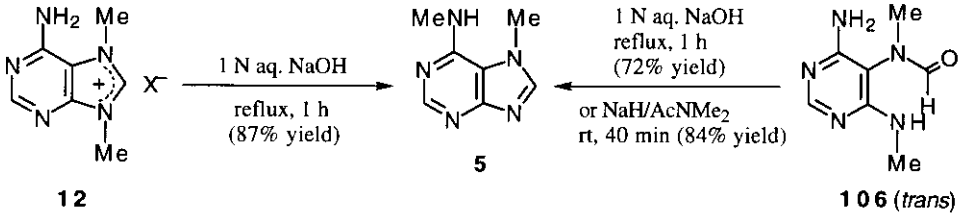
The first synthesis of N^6,7-dimethyladenine (**5**), achieved by Prasad and Robins,[340] started from 1-methyl-4-nitroimidazole-5-carbonitrile (**100**) and proceeded through 4-amino-1-methylimidazole-5-carboxamide (**101**), 7-methylhypoxanthine (**102**), and 6-chloro-7-methylpurine (**103**), as shown in Scheme 19. Alternatively, Taylor and Loeffler[341] synthesized **5** from the amino derivative (**104**)[340] *via* the 4-ethoxymethyleneamino derivative (**105**), cyclization of **105** with $MeNH_2$ to form 1,7-dimethyladenine (**8**),

and the Dimroth rearrangement[328] of **8** in boiling H_2O for 20 h. Fujii's group[342] found that similar treatment of **8** with boiling H_2O for 9.5 h afforded **5** (63% yield) as well as 1,7-dimethylhypoxanthine (**144**: $R^1 = R^2 = Me$) (3.5%).



Scheme 19

Treatment of 7,9-dimethyladeninium iodide (**12**: X = I) with boiling 1 N aqueous NaOH for 1 h resulted in rearrangement to **5** in 87% yield, and similar treatment of the *trans*-formamide (**106**) also gave **5** in 72% yield (Scheme 20) (see also Section XII).[343] Alternatively, cyclization of **106** to **5** (84%) was effected with NaH in $AcNMe_2$ at rt for 40 min.[343]



Scheme 20

The following may serve to locate papers describing the physical properties and spectral characteristics of N^6,7-dimethyladenine (**5**): the melting point for the free base (**5**), mp 300°C[340] or 309–310°C[343] or 311°C;[341] MS;[199] UV for the free base (**5**) in EtOH,[340,341] in 95% aqueous EtOH,[343b] and in H_2O (at various pH's);[340,341,343b] for a 1:1 mixture of **5** and 1,3-dimethyluracil;[344] ^1H NMR in $CDCl_3$.[344]

VI. N^6,9-DIMETHYLADENINE

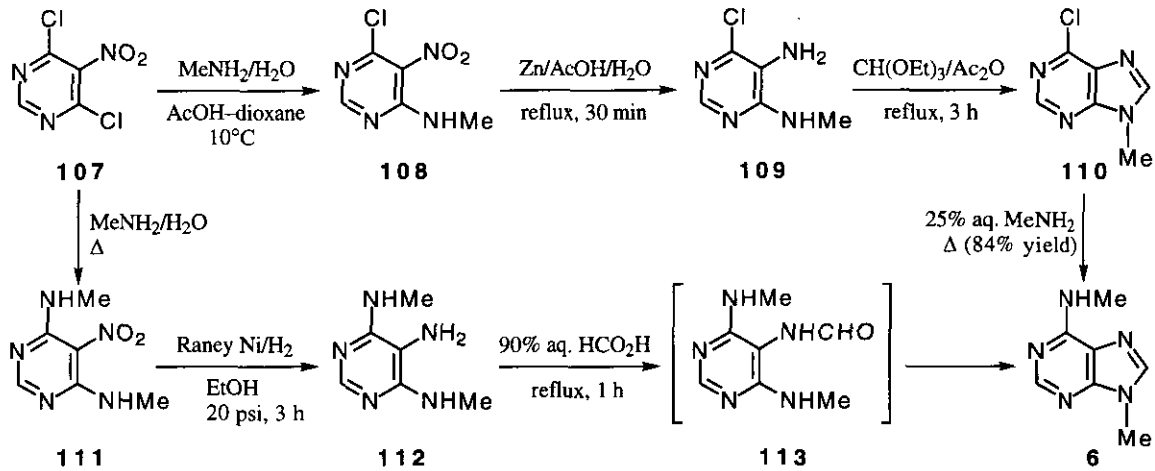
N^6,9-Dimethyladenine (**6**) was isolated, together with five organic compounds (1-hexa-

decanol, 3β-hydroxy-5α-pregnan-20-one, batyl alcohol, thymidine, and 1-methylpyridinium-2-carboxylate), from the South China Sea gorgonian *Menella spinifera* Kukenthal.[345]

It was among a series of 15 N^6-substituted 9-methyladenines assessed as antagonists of A_2-adenosine receptor-mediated stimulation of adenylate cyclase in membranes of human platelets and rat PC12 cells and of A_1-adenosine receptor-mediated inhibition of adenylate cyclases in membranes of rat fat cells and as inhibitors of binding of N^6-[(*R*)-1-[^{3}H]phenyl-2-propyl]adenosine to A_1-adenosine receptors in rat brain membranes.[346]

A method and composition including **6** have been disclosed for determining the viability of tissue with adenosine/adenosine agonist and A_1-adenosine receptor antagonist.[347]

Methods for prevention and treatment of ischemia-reperfusion and endotoxin-related injury by the use of adenosine and purino receptor antagonists including **6** have been provided.[348]

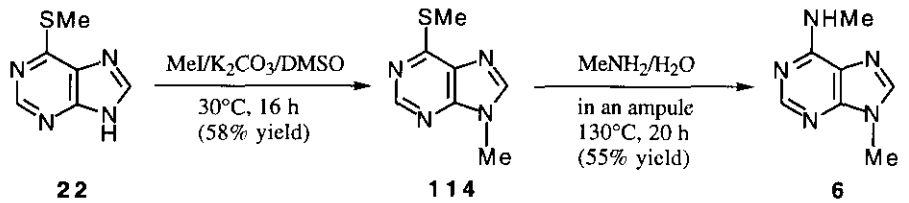


Scheme 21

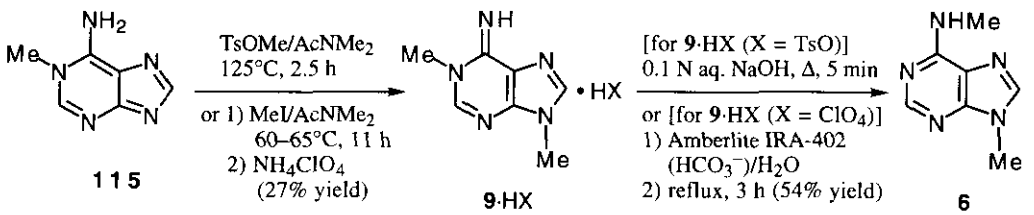
The synthesis of **6** by Robins and Lin[349] started from 4,6-dichloro-5-nitropyrimidine (**107**) and proceeded through the 6-methylamino derivative (**108**), the 5-amino derivative (**109**), and 6-chloro-9-methylpurine (**110**) or through 4,6-bis(methylamino)-5-nitropyrimidine (**111**) and 4,6-bis(methylamino)-5-aminopyrimidine (**112**), as depicted in Scheme 21. Goldner and Carstens[350] obtained **111** from **107** in 88% yield by amination with boiling ethanolic $MeNH_2$ for 45 min and cyclized **112**, prepared by reduction of **111** with Raney Ni catalyst and hydrogen in MeOH, by heating in boiling $HCONH_2$ for 20 min to secure **6** in 49% yield. Brown and Jacobsen[351] heated **112** on a steam bath with 90% formic acid for 1 h to obtain the 5-formamido derivative (**113**), which furnished **6** on heating at 250°C until effervescence ceased.

Sakata and co-workers[352] prepared **6** from 6-methylthiopurine (**22**) through 9-methyl-6-methylthiopurine (**114**), as shown in Scheme 22. They determined the rate constant for

the reaction of **114** with $MeNH_2$ in EtOH at 25 ± 1°C to be of very low value ($<10^{-6}$ s^{-1} M^{-1}).[353]

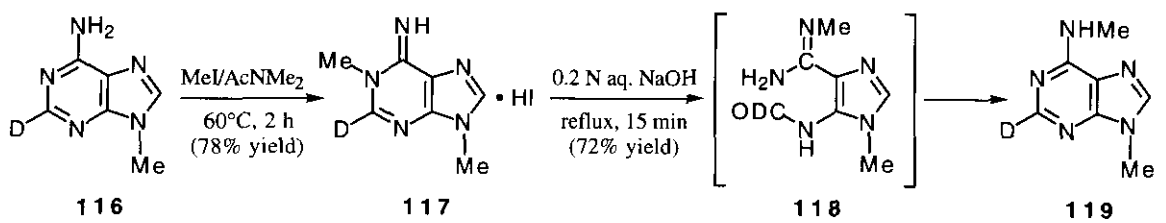


Scheme 22



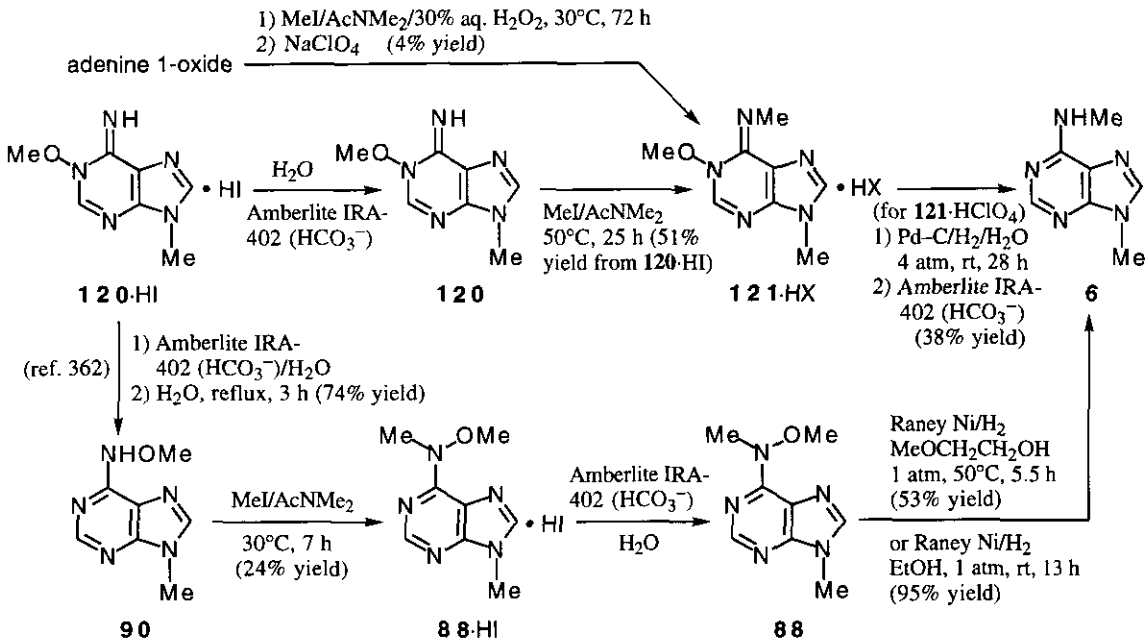
Scheme 23

Robins' group[327] methylated 1-methyladenine (**115**)[8] with methyl *p*-toluenesulfonate in $AcNMe_2$ at 125°C for 2.5 h to obtain 1,9-dimethyladenine *p*-toluenesulfonate [**9**·HX (X = TsO)], which underwent Dimroth rearrangement[328] to afford **6** when heated in 0.1 N aqueous NaOH for 5 min (Scheme 23). Fujii's group[354] methylated **115** with MeI in $AcNMe_2$ at 60–65°C for 11 h and converted the resulting hydriodide [**9**·HX (X = I)] into the perchlorate [**9**·HX (X = ClO_4)] in 27% yield (from **115**). The perchlorate was then converted into the free base (**9**) by treating with Amberlite IRA-402 (HCO_3^-), and heating of an aqueous solution of **9** under reflux for 3 h gave **6** in 54% yield. The Dimroth rearrangement of **9** to **6** under alkaline conditions was also carried out by Dodin *et al.*[355] N^6,9-Dimethyladenine-2-*d* (**119**) was prepared from 9-methyladenine-2-*d* (**116**) through 1,9-dimethyladenine-2-*d* hydriodide (**117**) by a route (Scheme 24) analogous to that employed for the preparation of the unlabeled species (**6**).[356]



Scheme 24

Methylation of adenine (**1**) with trimethyl phosphate in H_2O at pH 10–11 and 60°C for 24 h gave a mixture of six products, from which **6** (10% yield), 3-methyladenine (**158**) (6%), 9-methyladenine (**146**) (27%), and 4,6-bis(methylamino)-5-(*N*-methylformamido)pyrimidine (1%) were isolated.[357] Methylation of 9-methyladenine (**146**)[8] under similar conditions (at pH 9.5–10.0 and 37°C for 24 h) gave **6** (3%) and 1,9-dimethyladenine (**9**) (2%) with 94% recovery of the starting material.[357] Shugar's group[358] found that methylation of 9-methyladenine (**146**)[8] with dimethyl sulfate in 0.15 M phosphate buffer (pH 7.5) at pH 7–7.5 for 1.5 h gave 1,9-dimethyladenine (**9**) (*ca.* 40% yield) (see also Section IX, Scheme 33), which was quantitatively rearranged to **6** on treatment at pH 13 and 60°C for 20 min. When this methylation was effected under strongly alkaline conditions (in 2 N aqueous KOH for 1.5 h), **6** was obtained in only *ca.* 2% yield.[358]
As mentioned before (Section IV and Scheme 17), **6** (1.3% yield) was among four products from direct methylation of N^6-methyladenine (**94**) with an excess of MeI in $AcNMe_2$ at 38–42°C for 6 h.[337]



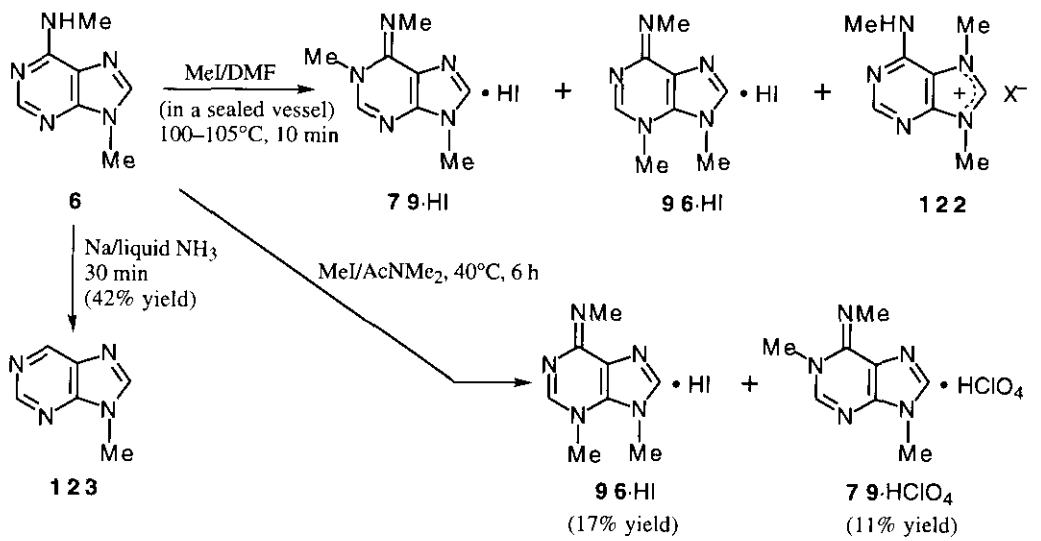
Scheme 25

In a multistep synthesis of **6** by Fujii's group,[359] 1-methoxy-9-methyladenine (**120**) obtained from its hydriodide salt (**120**·HI) was methylated with MeI in $AcNMe_2$ at 50°C for 25 h to give 1-methoxy-N^6,9-dimethyladenine hydriodide (**121**·HI) in 51% yield (Scheme 25). Direct methylation of adenine 1-oxide with MeI in $AcNMe_2$ in the presence of 30% aqueous H_2O_2 also gave, after treatment of the product with $NaClO_4$, **121**·$HClO_4$ but in only 4% yield, together with its ring-opened product, 5-formamido-*N*'-methoxy-*N*,1-dimethylimidazole-4-carboxamidine (**126**) (16%).[360] This methylation of adenine 1-oxide

to form the trimethylated product (**121**·HX) was considered to proceed *via* 1-methoxyadenine hydriodide, its free base, **120**·HI, and **120** in a one-pot manner.[360] Hydrogenolysis of **121**·$HClO_4$ with 10% Pd–C catalyst and hydrogen and treatment of the product with Amberlite IRA-402 (HCO_3^-) provided **6** in 38% yield.[361] Alternatively, methylation of N^6-methoxy-9-methyladenine (**90**) (see also Section IV, Scheme 16), prepared from **120**·HI by Dimroth rearrangement,[362] with MeI in $AcNMe_2$ at 30°C for 7 h furnished N^6-methoxy-N^6,9-dimethyladenine hydriodide (**88**·HI) in 24% yield, together with N^6-methoxy-7,9-dimethyladeninium iodide (**91**: X = I) (see also Section IV, Scheme 16) in 59% yield.[336,363] The free base (**88**) (see also Section IV, Schemes 15 and 16), obtained from **88**·HI by the use of Amberlite IRA-402 (HCO_3^-), was then hydrogenolyzed with Raney Ni catalyst and hydrogen to produce **6** in 53% or 95% yield.[336,363]

For papers describing the physical properties and spectral characteristics of N^6,9-dimethyladenine (**6**), the reader is referred to Table II, which includes additional references.[364–377]

Interactions of **6** with the following substances have been reported: self-association in aqueous solutions[365,373,378,379] and in D_2O;[223,368,374,380] H_2O vapor (hydration);[204] butyric acid in $CDCl_3$ *via* hydrogen bonding;[369] 1,3-dimethyluracil in H_2O[381] and in D_2O;[382–384] 1,4- and 2,4-dimethyluracils in D_2O;[384] poly(U) in H_2O;[385] poly(5-bromouridylic acid) in H_2O;[386] *p*-cresol in $CDCl_3$;[387] diazepam in $CDCl_3$ and nitrazepam in $CDCl_3$;[388] K_2PtCl_4 in 2.5 N aqueous HCl at 50°C for several hours to give $Cl_3Pt(C_7H_{10}N_5)\cdot H_2O$, which reacted with aqueous NH_3 to produce *cis*-$Cl_2Pt(C_7H_9N_5)(NH_3)$.[364]



Scheme 26

As regards the chemical behavior of **6**, El'tsov *et al.*[330] found that methylation of **6** with MeI in DMF at 100–105°C for 10 min gave a 51:30:19 mixture of **79**·HI, **96**·HI, and **122**

TABLE II. N^6,9-Dimethyladenine (**6**): Physical and Spectral Characteristics

Item	Specification[a]	Literature (ref. No.)
Melting point[b]	193.5–195°C (350); 193–195°C (357); 190–191°C (349); 185–186°C (351, 354); 181.5–182.5°C (352)	
6-2-*d* (**119**)	184–185°C	(356)
Acid dissociation constant		
basic pK_a	4.12 ± 0.03 (H_2O at 20°C and ionic strength 0.01)[c] (351); 4.02 ± 0.03 (H_2O at 20°C)[c] (354); 3.8 ± 0.05 (0.1 M aq. NaCl)[c] (364)	
TLC		(221, 357, 358, 365)
MS		(204, 345, 352)
6-2-*d* (**119**)		(356)
UV spectrum		(345, 366)
	In H_2O (352); in H_2O at various pH's (349, 351, 354, 357); in 95% aq. EtOH (354)	
6-2-*d* (**119**)	In H_2O at various pH's and in 95% aq. EtOH	(356)
	A 1:1 mixture of **6** and 1,3-dimethyluracil in H_2O	(344)
UV photoelectron spectrum		(210)
IR spectrum		(345, 367[d])
^1H NMR spectrum		(345)
	In D_2O (223, 368); in CD_3OD (221); in MeOH (368); in DMSO-d_6 (356); in $CDCl_3$ (221, 352, 356, 369); in CCl_4 (368); in liquid NH_3 (370)	
6-2-*d* (**119**)	In DMSO-d_6 and in $CDCl_3$	(356)
^{13}C NMR spectrum		(345)
Crystal structure		(371, 372)
Dipole moment (in H_2O)	6.6 ± 1.1 D (at 0°C), 7.9 ± 0.9 D (20°C), and 7.4 ± 0.6 D (40°C) (373)	
Neutron diffraction	In D_2O	(374)
Partition coefficient	Between $CHCl_3$ and H_2O	(375)
Partial specific volume	0.731 ml/g	(365)
Potential surface		(247)
Enthalpy of hydration		(204, 247–249)
Enthalpy of solution	In H_2O	(248, 249)
Enthalpy of sublimation		(248–250, 376)
Ionization potential		(210)
Electronic spectrum	Calculated by the CNDO/OPTIC-2 method	(377)
Electronic structure		(210)

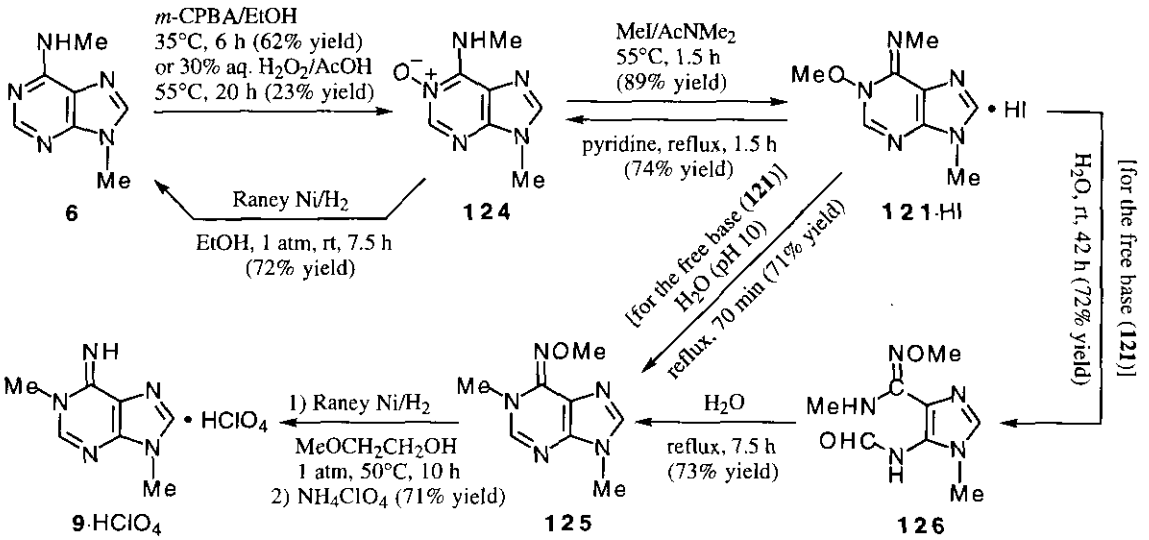
a) With or without reference number(s) in parentheses.

b) Reported for analytical samples, in most cases.

c) UV spectral.

d) In the vapor phase.

(X = I) in 94% yield (Scheme 26). The corresponding N(1)-CD_3, N(3)-CD_3, and N(7)-CD_3 species were similarly obtained by using CD_3I instead of MeI in the above reaction.[330] Fujii's group[337] isolated **96**·HI (17% yield) and **79**·$HClO_4$ (11% yield, after conversion from **79**·HI) from the reaction mixture obtained by methylation of **6** with MeI in $AcNMe_2$ at 40°C for 6 h. Kos and van der Plas[389] have reported the reductive removal of the methylamino group from **6** to provide 9-methylpurine (**123**) in 42% yield, which was effected with sodium in liquid NH_3 for 30 min.

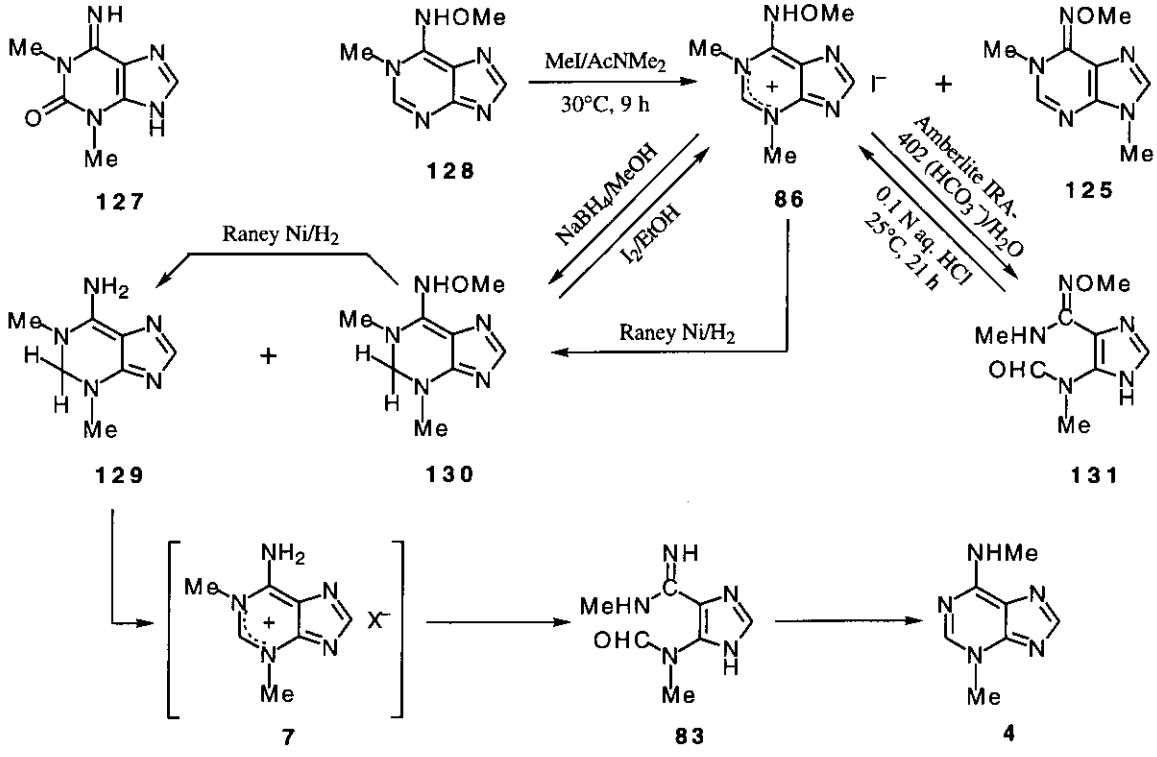


Scheme 27

A multistep conversion of **6** into 1,9-dimethyladenine (**9**), as shown in Scheme 27, has been reported by Fujii's group:[361] Oxidation of **6** with *m*-CPBA in EtOH at 35°C for 6 h gave the N(1)-oxide (**124**) in 62% yield. Alternatively, the N(1)-oxidation was accomplished with 30% aqueous H_2O_2 in AcOH at 55°C for 20 h, but in 23% yield. Later on, Dodin *et al.*[355] recorded a similar peracetic acid oxidation of **6**. Reversion of **124** to **6** (72% yield) was effected by hydrogenolysis using Raney Ni catalyst and hydrogen. The N(1)-oxide (**124**) underwent methylation almost exclusively at the N(1)-O atom when treated with MeI in $AcNMe_2$, resulting in the formation of the 1-methoxy derivative (**121**·HI) in 89% yield. The location of the third methyl group was established by demethylation with boiling pyridine (or boiling EtOH) leading to the N(1)-oxide (**124**) and also by catalytic hydrogenolysis of the corresponding perchlorate (**121**·$HClO_4$) (Scheme 25) to afford **6**. Treatment of the free base (**121**) with boiling H_2O under mildly alkaline conditions for 70 min provided the isomeric product (**125**) in 71% yield. Alternatively, this rearrangement was feasible by treating **121** with boiling H_2O (pH 9) for 3 h.[356] On the other hand, treatment of **121** with H_2O at rt for 42 h furnished the monocyclic compound (**126**) (72% yield), which recyclized almost exclusively to **125** on treat-

ment with boiling H_2O for 7.5 h. Catalytic hydrogenolysis of **125** gave, after conversion of the product into a salt form, 1,9-dimethyladenine perchlorate (**9**·$HClO_4$) in 71% yield. Thus, the above multistep conversion of **6** into **9** achieved by Fujii's group[361] has demonstrated the usefulness of the MeO group as an easily removable control synthon in the structural transformation reverse to that (**9**→**6**) which occurs in the usual Dimroth rearrangement in the adenine series.[328] Heating **6** in boiling 1 N aqueous NaOH for 30 min resulted in 90% recovery of **6**, indicating its stability under alkaline conditions.[390]

VII. 1,3-DIMETHYLADENINE



Scheme 28

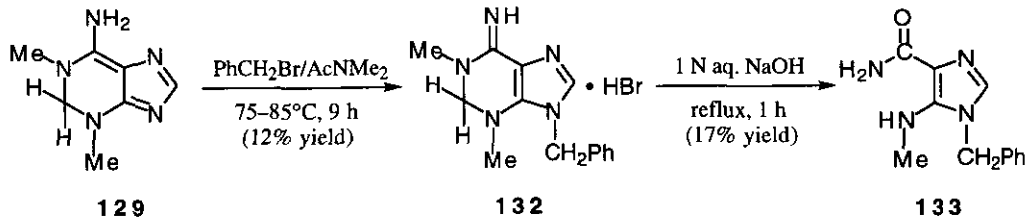
1,3-Dimethyladenine (**7**)[7] occurs in nature as the 2-oxo derivative (1,3-dimethylisoguanine) (**127**), a new purine from the marine sponge *Amphimedon viridis*.[391] In their methylation study of adenosine (**76**) using dimethyl sulfate in DMF at 100°C for 2 h, Brookes and Lawley[392] isolated, after hydrolysis of the products with boiling 1 N aqueous HCl for 1 h, a dimethyladenine in the form of the sulfate salt for which the structure "1,3-dimethyladeninium sulfate (**7**: X = HSO_4)" was proposed, although the N^6,3-methyladenine structure (**4**·H_2SO_4) was considered as a possibility by these authors. Later on, however, Broom *et al.*[327] established the structure of the above "1,3-

dimethyladenine" to be in reality 3,7-dimethyladenine (**10**).

Fujii and co-workers[336] found that methylation of N^6-methoxy-1-methyladenine (**128**) with MeI in $AcNMe_2$ at 30°C for 9 h gave N^6-methoxy-1,3-dimethyladeninium iodide (**86**) (44% yield) and N^6-methoxy-1,9-dimethyladenine (**125**) (isolated as **125**·$HClO_4$ in 38% yield) (Scheme 28). The N^6-methoxy-1,3-dimethyl compound (**86**) was alternatively obtainable from N^6-methoxy-3-methyladenine (**84**) by similar methylation (Section IV, Scheme 14).[336] With the aim of synthesizing a genuine 1,3-dimethyladenine structure, they next tried to remove the N^6-methoxy group from **86**.[335] On catalytic reduction using Raney Ni catalyst and hydrogen (MeOH, 3 atm, 18–20°C, 20 h), **86** produced two 1,2-dihydro derivatives [**130** (26% yield) and **129**·HI (17%)], instead of the desired product (**7**: X = I) (Scheme 28). Oxidation of **130** with iodine in EtOH at rt for 30 min regenerated **86** (38% yield), which reverted to **130** in 92% yield upon reduction with $NaBH_4$ in MeOH at rt for 30 min. Further reduction of **130** with Raney Ni catalyst and hydrogen (EtOH, 1 atm, 50°C, 3 h) provided the demethoxy derivative (**129**) in 71% yield. The difficulty in removing the N^6-methoxy group without partial saturation of the adeninium ring and the high-yield two-step synthesis of **129** from **86** led them to examine the dehydrogenation of **129** as an alternative route to **7**.[335] Although trials conducted with iodine, sodium nitrite, air, or chloranil for this step all failed, treatment of **129** with DDQ in $CHCl_3$ at rt for 50 h afforded a dark brown solid presumed to be **7** (X = 2,3-dichloro-5,6-dicyano-4-hydroxyphenolate). Since the solid was unstable and difficult to purify by recrystallization, conversion into the bromide salt (**7**: X = Br) was attempted by treating it with concd aqueous HBr in MeCN under ice-cooling. However, the product isolated was not the desired salt but the hydrobromide of the ring-opened derivative (**83**). The hydrobromide (**83**·HBr) was also found to be unstable in H_2O at rt at pH 7 or above: It quickly underwent recyclization to give N^6,3-dimethyladenine (**4**) in 53% yield [based on the dihydro derivative (**129**) used]. The sequence **7**→**83**→**4** thus concluded a Dimroth rearrangement.[328] Although Fujii's group has been unable to characterize the 1,3-dimethyladenine structure (**7**) obtained by the DDQ oxidation of **129**, the above results indicate its virtual formation and extreme instability. Since the rate of ring opening of **7** could not be measured directly, that of the N^6-methoxy derivative (**86**: X = ClO_4 for I) was determined instead.[335] Treatment of **86** in H_2O with Amberlite IRA-402 (HCO_3^-) at rt afforded the monocycle (**131**) in 92% yield. In H_2O at pH 7.72 (ionic strength 0.5) and 25°C, this ring opening proceeded at a rate of 1.36×10^{-1} min^{-1} (half-life 5.1 min). On the other hand, treatment of **131** with 0.1 N aqueous HCl at 25°C for 21 h gave the recyclized product (**86**) [isolated as the perchlorate (**86**: ClO_4^- for I^-) in 53% yield. The above ring opening of **86** in the pyrimidine moiety was *ca.* 270 times as fast as that of N^6-methoxy-3,9-dimethyladenine (**168**).[335] Therefore, the genuine 1,3-dimethyladenine structure (**7**) itself may be regarded as one of the most unstable dimethyladenines in H_2O under alkaline conditions.[335,390]

The dihydro derivative (**129**) was found to give the N(9)-benzylated product (**132**) when

treated with $PhCH_2Br$ in $AcNMe_2$ (Scheme 29), and alkaline hydrolysis of **132** afforded 1-benzyl-5-methylaminoimidazole-4-carboxamide (**133**).[393]



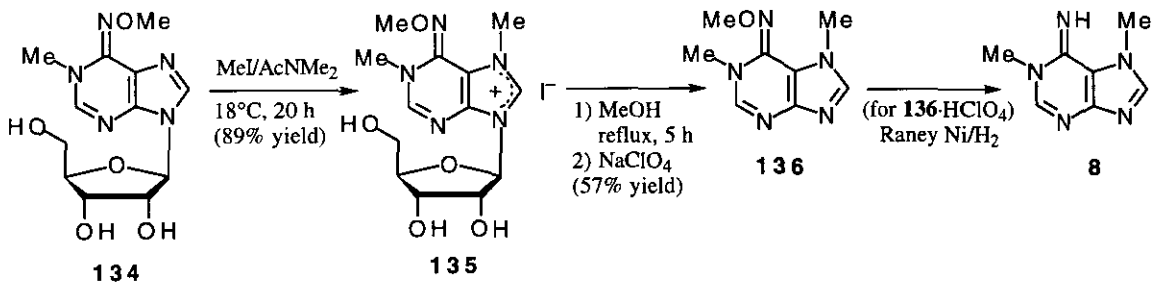
129 **132** **133**

Scheme 29

VIII. 1,7-DIMETHYLADENINE

As regards the biological activity of 1,7-dimethyladenine (**8**), its inability in triggering either stimulation of $^{86}Rb^+$ uptake alone or both this elementary event and the integrated process of germinal vesicle breakdown in *Marthasterias glacialis* oocytes have been reported.[394] Dorée disclosed that **8** did not show stimulation of $^{24}Na^+$ influx in fully grown prophase-blocked starfish oocytes.[395] The inability of **8** to replace 1-methyladenine (**115**) in releasing meiosis inhibition in starfish oocytes has also been known.[396]

In 1960, Taylor and Loeffler[341] reported the synthesis of **8** from 4-amino-5-cyano-1-methylimidazole (**104**) through the 4-ethoxymethyleneamino derivative (**105**), as described in Section V (Scheme 19).

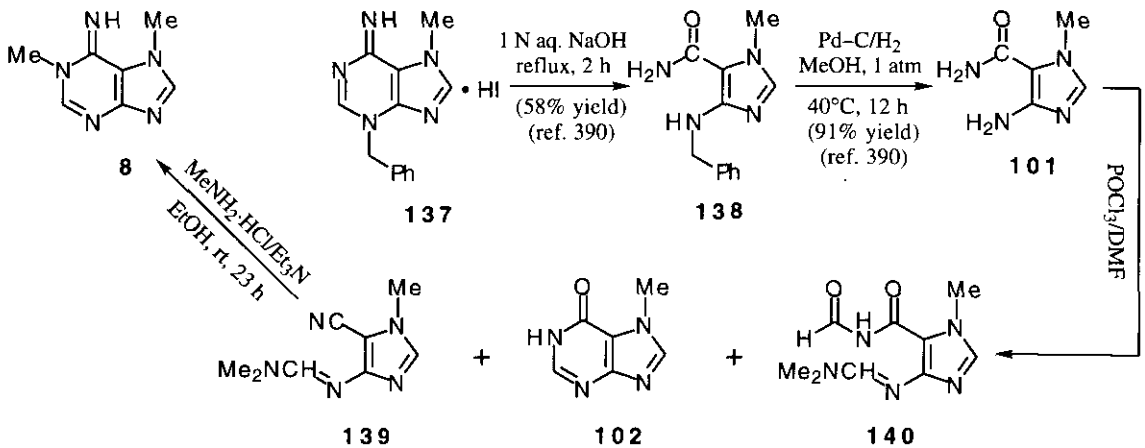


134 **135** **136** **8**

Scheme 30

In an alternative synthesis of **8** (Scheme 30), Fujii's group[397] methylated N^6-methoxy-1-methyladenosine (**134**), obtainable from adenosine (**76**) in four steps,[336] with MeI in $AcNMe_2$ to secure the N(7)-methylated product (**135**) in 89% yield. The 7-methyl derivative (**135**) was found to be susceptible to solvolysis: It afforded the perchlorate salt (**136**·$HClO_4$) of the aglycon in 57% yield when treated with boiling MeOH and then with $NaClO_4$. The aglycon salt (**136**·$HClO_4$) was then subjected to catalytic hydrogenolysis (Raney Ni/H_2, H_2O, 1 atm, 20°C, 5 h), giving the desired compound (**8**·$HClO_4$) in 47%

yield [in 7% overall yield from adenosine (**76**)].



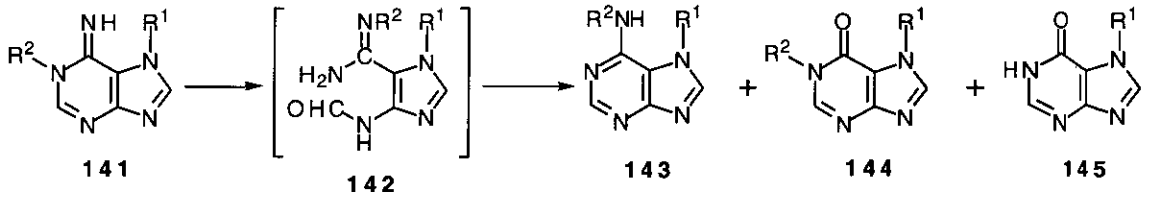
Scheme 31

In yet another synthesis of **8** (Scheme 31), Fujii's group[398] treated 4-amino-1-methylimidazole-5-carboxamide perchlorate (**101**·$HClO_4$), which was obtainable[390] from adenine (**1**) in four steps [*via* 3-benzyladenine, 3-benzyl-7-methyladenine hydriodide (**137**), and 4-benzylamino-1-methylimidazole-5-carboxamide (**138**)], with $POCl_3$ in DMF below 35°C for *ca.* 3 h to obtain 4-dimethylaminomethyleneamino-1-methylimidazole-5-carbonitrile (**139**) in 70% yield, together with small amounts of 7-methylhypoxanthine (**102**) and a substance inferred to be the *N*-formyl-5-carboxamide derivative (**140**). Cyclization of **139** was then effected with $MeNH_2$·HCl in EtOH in the presence of Et_3N at rt for 23 h, and the product was isolated in the form of the perchlorate salt, affording **8**·$HClO_4$ in 68% yield [in 12% overall yield from adenine (**1**)].

The following physical properties and spectral characteristics of 1,7-dimethyladenine (**8**) have been reported in the literature: the melting point for the free base (**8**), mp 170–171°C;[341] for **8**·3/5H_2O, mp 163–168°C;[398] for **8**·HCl (crude), mp 224–230°C (decomp);[398] for anhydrous **8**·$HClO_4$, mp 278–280°C (decomp);[398] for **8**·$HClO_4$·1/5H_2O, mp 263–264°C (decomp);[397] pK_a *ca.* 6.5[396] or 6.50 ± 0.10 (in H_2O at 25 ± 0.1°C);[399] for **8**·$HClO_4$, pK_a 7.86 ± 0.03 (in H_2O at 40°C and ionic strength 0.5);[400] MS;[199] UV for the free base (**8**) in EtOH and in 0.1 N aqueous HCl,[341] for **8**·3/5H_2O in 95% aqueous EtOH and in H_2O (at pH 1, 7, and 13);[398] for **8**·$HClO_4$·1/5H_2O in 95% aqueous EtOH and in H_2O (at pH 1, 7, and 13);[397] ^{1}H NMR for **8**·3/5H_2O in DMSO-d_6,[398] for **8**·$HClO_4$·1/5H_2O in DMSO-d_6.[397]

Probably the most salient feature in the chemical behavior of 1,7-dimethyladenine (**8**) is that it undergoes Dimroth rearrangement[328] under slightly alkaline conditions, giving N^6,7-dimethyladenine (**5**), and this affords a sound basis for one of the preparative methods for **5**, as described above in Section V (Scheme 19). In some cases, the rearrangement reactions of 1,7-dialkyladenines (**141**) leading to N^6,7-dialkyladenines (**143**)

are accompanied with hydrolytic deaminations to give 1,7-dialkylhypoxanthines (**144**)[342] and/or 7-alkylhypoxanthines (**145**),[341,342] when effected in boiling H_2O (Scheme 32). Thus, treatment of 1,7-dimethyladenine (**8**) (or **141**: $R^1 = R^2 = Me$) with boiling H_2O for 9.5 h gave N^6,7-dimethyladenine (**5**) (or **143**: $R^1 = R^2 = Me$) (63% yield) as well as 1,7-dimethylhypoxanthine (**144**: $R^1 = R^2 = Me$) (3.5%).[342] For the concomitant deamination in the Dimroth rearrangement of **141**, Fujii's group[342] has proposed possible mechanisms involving hydrolysis of the amidine moiety of the putative intermediate (**142**) [resulting from hydrolytic fission at the N(1)–C(2) bond of **141**] and/or a direct hydrolytic deamination *via* an addition–elimination at C(6). However, a recent study on the Dimroth rearrangement, hydrolytic deamination, and pyrimidine-ring breakdown of 1-alkoxy-7-alkyladenines suggests that a third mechanism, which proceeds through N(1)–C(6) bond fission, may operate in these deamination reactions.[400]



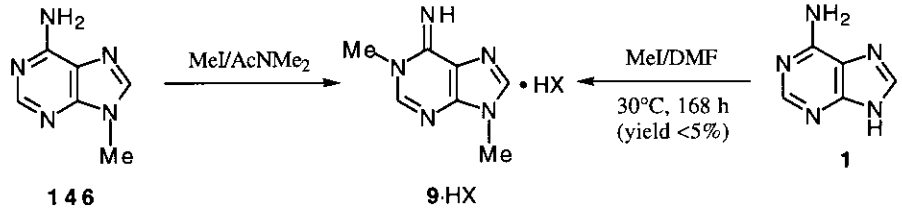
Scheme 32

IX. 1,9-DIMETHYLADENINE

There have been several papers dealing with the biological activity of 1,9-dimethyladenine (**9**). Dorée and Guerrier[401] reported that neither **9** nor 1,9-dibenzyladenine inhibited nuclear maturation of the starfish oocytes induced by 1-methyladenine (**115**). Dorée *et al.*[103] demonstrated the localization and specificity of 1-methyladenine (**115**) receptors in eggs of the starfish *Marthasterias glacialis* and *Asterias rubens* and found that **9** (2×10^{-4} M) significantly inhibited the absorption of **115** (1.5×10^{-7}, 5×10^{-8}, and 2×10^{-8} M) but did not affect the initiation of egg meiosis. 1,9-Dimethyladenine (**9**) was found to be devoid of the ability to replace **115** in triggering meiosis in the starfish oocytes and of the ability to inhibit the **115**-dependent induction of meiosis.[104] Dorée[395] also reported that **9** did not show stimulation of $^{24}Na^+$ influx in fully grown prophase-blocked starfish oocytes. Yoshikuni *et al.*[402] found that **9** did not inhibit the specific binding of 1-[^{3}H]methyladenine to cortices isolated from full-grown prophase-arrested oocytes of the starfish *Asterina pectinifera*.

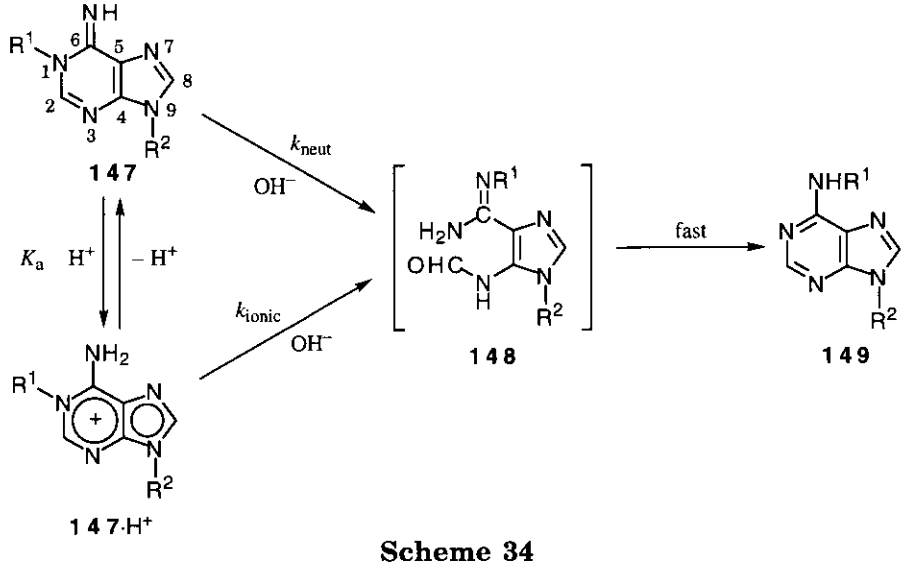
As regards the synthesis of **9**, methylation of 1-methyladenine (**115**)[8] with methyl *p*-toluenesulfonate in $AcNMe_2$ to yield **9**·TsOH[327] or with MeI in $AcNMe_2$ to yield **9**·HI (and **9**·$HClO_4$)[354] is described above in Section VI (Scheme 23). The regioselectivity in

this methylation is in general agreement with preferential N(9)-methylation of 1-benzyladenine.[403] On the basis of the fact that 9-substituted adenines are methylated most easily at N(1),[354,359,403–405] Dubois' group[399] conversely methylated 9-methyladenine (**146**)[8] with MeI in $AcNMe_2$ and isolated the product (**9**) in the form of the free base, perchlorate, and hydrochloride (Scheme 33). Analogous routes to **9** from **146** using dimethyl sulfate in H_2O at pH 7–7.5[358] or using trimethyl phosphate in H_2O at pH 9.5–10.0 and 37°C[357] and to 1,9-dimethyladenine-*2-d* hydriodide (**117**)[356] from 9-methyladenine-*2-d* (**116**) (Scheme 24) are described above in Section VI.



Scheme 33

Beasley and Rasmussen[406] found that methylation of adenine (**1**) with MeI in DMF at 30°C for 168 h (Scheme 33) gave a product mixture (63% yield), which consisted of **9** (less than 5%), 3-methyladenine (**158**) (56%), 9-methyladenine (**146**) (30%), and 7-methyladenine (**159**) (5–10%). Muravich-Aleksandr *et al.*[407] reported that methylation of **1** with MeI in DMF at 100°C gave 1-methyladenine hydriodide (**115**·HI) and **9**·HI.



Scheme 34

The multistep conversion of N^6,9-dimethyladenine (**6**) into **9**·$HClO_4$ through 1-methoxy-N^6,9-dimethyladenine hydriodide (**121**·HI) utilizing an *N*-methoxy group as a control synthon,[359,360] as described in Section VI (Scheme 27), represents an alternative syn-

thesis of 1,9-dimethyladenine (**9**).[361]

References to the physical properties and spectral characteristics of 1,9-dimethyladenine (**9**) are indicated by number in Table III, with some additions.[408–410]

TABLE III. 1,9-Dimethyladenine (**9**): Physical and Spectral Characteristics

Item		Specification[a]	Literature (ref. No.)
Melting point[b]	Free base (**9**)	Not specified	(399)
	9·HCl	Not specified	(399, 408, 409)
	9·HI	277–278°C (decomp) (for a crude sample) (354); >310°C (410)	
	9·$HClO_4$	303–304°C (decomp) (354); not specified (399)	
	9·TsOH	Not specified	(327)
	9-2-*d*·HI (**117**)	298–299°C (decomp)	(356)
Acid dissociation constant			
	basic pK_a	9.03 ± 0.05 (H_2O at 25 ± 0.1°C)[c]	(399)
		9.08 ± 0.07 (for **9**·$HClO_4$ in H_2O at 20°C)[c]	(354)
		8.94 ± 0.05 (for **9**·$HClO_4$ in 0.1 M buffers at 40°C and ionic strength 0.50)[c]	(354)
		8.96 ± 0.04 or 8.97 ± 0.03 (for **9**·$HClO_4$ in 1/9 M buffers at 40°C and ionic strength 1.0)[c]	(405d or 412b)
		9.1 ± 0.05 (in 0.1 N aq. NaCl)[c]	(364)
TLC			(358)
Paper electrophoresis		**9**·$HClO_4$	(354)
UV spectrum		In H_2O and in dioxane	(399)
	9·HI	In 0.025 M phosphate buffer containing 10% EtOH (pH 7.1)	(410)
	9·$HClO_4$	In H_2O at various pH's and in 95% aq. EtOH	(354)
	9·TsOH	In H_2O at various pH's	(327)
	9-2-*d*·HI (**117**)	In H_2O at various pH's and in 95% aq. EtOH	(356)
IR spectrum		In $CHCl_3$	(399)
^1H NMR spectrum			(345)
	9·$HClO_4$	In DMSO-d_6	(356)
	9-2-*d*·HI (**117**)	In DMSO-d_6	(356)
^{13}C NMR spectrum			(345)
	9·HCl	In H_2O	(399)
Crystal structure			
	9·HCl		(408)

a) With or without reference number(s) in parentheses. *b*) Reported for analytical samples, in most cases. *c*) UV spectral.

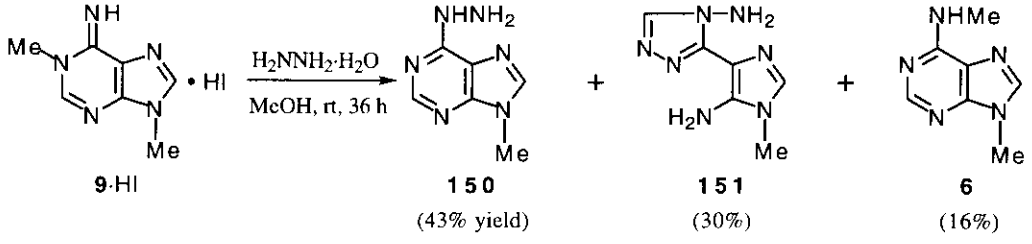
Interactions of **9** with the following substances have been reported: indole-3-acetic acid to form a 1:1 complex;[410,411] $Na[Co(acac)_2(NO_2)_2]$ in H_2O;[409] **9**·$HClO_4$ with K_2PtCl_4 in

0.1 N aqueous HCl at 22°C for 22 h to give $Cl_3Pt(C_7H_{10}N_5)\cdot H_2O$, which reacted with aqueous NH_3 to produce *cis*-$Cl_2Pt(C_7H_9N_5)(NH_3)$.[364] The latter complex was converted into *cis*-$Cl_3Pt(C_7H_{10}N_5)(NH_3)$ by treatment with 0.2 N aqueous HCl.[364]

The chemical behavior of 1,9-dimethyladenine (**9**) is characterized primarily by the ability to undergo Dimroth rearrangement[328] to give N^6,9-dimethyladenine (**6**), which affords a basis for one of the most important methods of preparing **6**, as summarized above in Section VI (Schemes 23 and 24).[327,354–356,358]

In a kinetic approach to the mechanistic problem, Fujii's group has found that the rearrangement of 9-substituted 1-alkyladenines (**147**) to the corresponding N^6-isomers (**149**), including that of **9** (or **147**: $R^1 = R^2 = Me$) to **6** (or **149**: $R^1 = R^2 = Me$), at 40°C proceeds by a mechanism involving a rate-determining initial ring opening, caused by attack of hydroxide ion on both the protonated (**147**·H^+) and the neutral species (**147**) at the 2-position, and a subsequent fast ring closure of the putative monocyclic intermediates (**148**) (Scheme 34).[328,354,405d,f,g,412] This is in general agreement with the mechanism which Macon and Wolfenden[413] proposed for the Dimroth rearrangement of 1-methyladenosine (**77**) (or **147**: R^1 = Me; R^2 = β-D-ribofuranosyl) to N^6-methyladenosine (**78**) (or **149**: R^1 = Me; R^2 = β-D-ribofuranosyl) at 25°C. The hydroxide attack on the protonated species is much faster than that on the neutral species (by a factor of 90–1100),[354,405d,f,g,412b,413] and the former is influenced by the electronic effect of a substituent at the 1-position, whereas the latter is influenced by the steric effect.[405d,g] Interestingly, the electron-withdrawing β-D-ribofuranosyl group at the 9-position accelerates the ring opening of both the protonated and the neutral species.[405d,f]

Kohda's group[414] reported that treatment of **9**·HI with hydrazine monohydrate in MeOH at rt for 36 h gave 6-hydrazino-9-methylpurine (**150**), 5-amino-1-methyl-4-(4-amino-1,2,4-triazol-3-yl)imidazole (**151**), and the Dimroth rearrangement product N^6,9-dimethyladenine (**6**), as illustrated in Scheme 35.

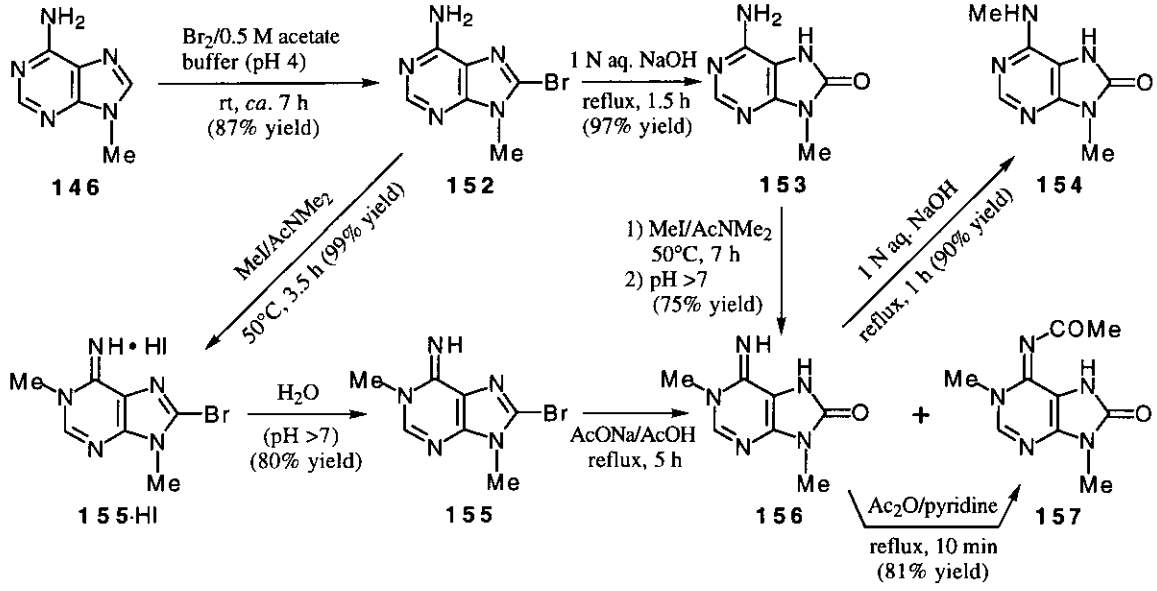


9·HI **150** (43% yield) **151** (30%) **6** (16%)

Scheme 35

It is of interest to note that 1,9-dimethyladenine (**9**) occurs in nature in the form of the 8-oxo derivative: In 1985, Cimino *et al.*[415] reported the isolation of a new purine (**156**) and known 1-methyladenine (spongopurine) (**115**), although both only as the acetyl derivative (**157** and acetylspongopurine), from the English Channel sponge *Hymeniacidon sanguinea* Grant. While the new acetyl derivative (**157**) was fully characterized by

means of spectroscopic and X-ray crystallographic analyses, the parent base (**156**) remained unknown because of the difficulty in separating **156** and **115** from each other at the free base level.[415]



Scheme 36

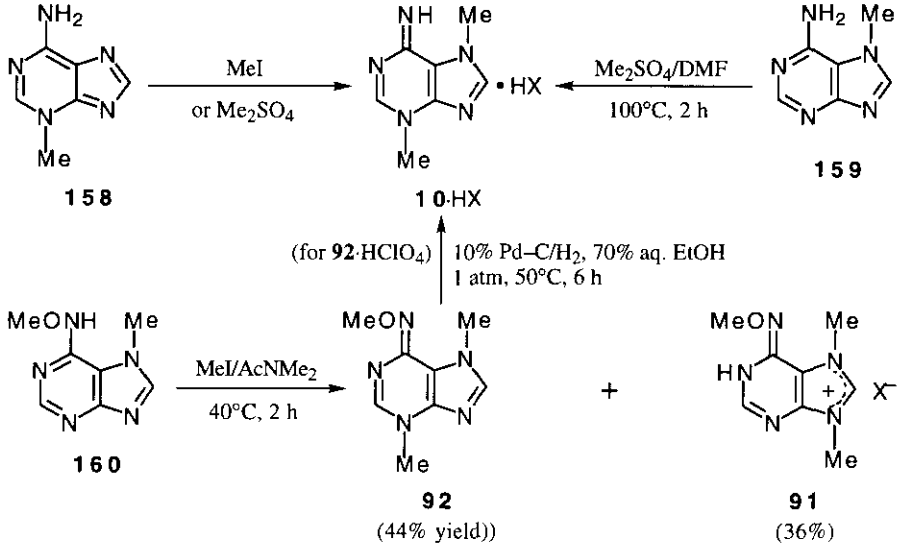
Fujii's group[416] was able to secure the free base (**156**) itself by two alternative syntheses starting from 8-bromo-9-methyladenine (**152**), which was obtainable from 9-methyladenine (**146**)[8] by bromination (Scheme 36). The first route included methylation of **152** with MeI to give the 1-methylated product (**155**·HI), conversion of **155**·HI into the free base (**155**), and treatment of **155** with AcONa in boiling AcOH to produce **156** (36% yield) and **157** (34%).

The second route included treatment of **152** with boiling 1 N aqueous NaOH and methylation of the resulting 8-oxo derivative (**153**) with MeI, affording **156** in 63% overall yield (from **146**). The rearranged isomer (**154**) and the N^6-acetyl derivative (**157**) were also synthesized from **156**. These synthetic results made it possible to characterize fully **156** itself,[416] in advance of the yet unrealized isolation of this substance from natural sources and to compare the reaction rates in the Dimroth rearrangements of **156** (to **154**) and related compounds such as **155** (to 8-bromo-N^6,9-dimethyladenine) and 1,9-dimethyladenine (**9**) [to N^6,9-dimethyladenine (**6**)].[412b]

X. 3,7-DIMETHYLADENINE

In 1964, Robins' group[327] reported that methylation of 3-methyladenine (**158**) with MeI in MeOH containing KOH at rt for 60 h or with dimethyl sulfate in DMF at 100°C for 2 h gave 3,7-dimethyladenine hydriodide (**10**·HI) or **10**·$MeOSO_3H$ and that methylation of

7-methyladenine (**159**) with dimethyl sulfate in DMF at 100°C for 2 h produced **10**·MeO-SO_3H, as identified by two-dimensional paper chromatography and UV spectroscopy (Scheme 37).



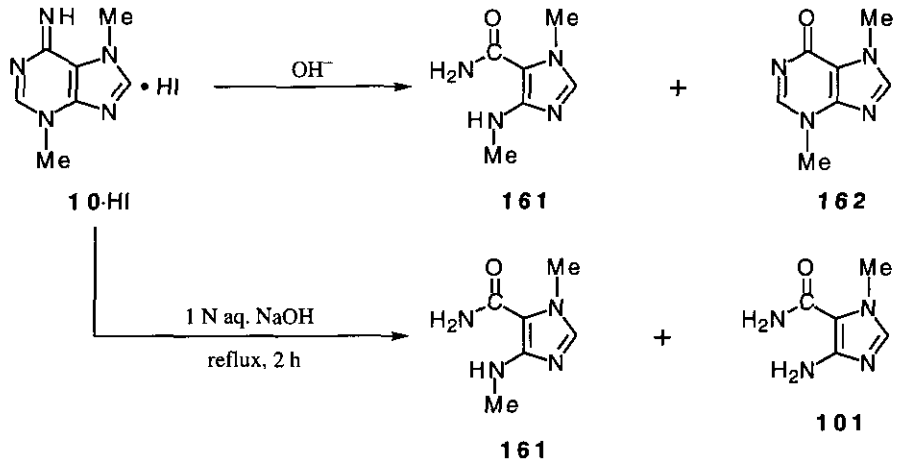
Scheme 37

The essentially reciprocal directivity in methylation of **158** and **159** was in line with that in alkylation of 3- and 7-alkyladenines reported by Leonard and Fujii[417] and by Montgomery and Thomas.[418] Fujii's group[417c] methylated **158** with MeI in $AcNMe_2$ at 27°C for 5 h to secure **10**·HI in 67% yield. Yamauchi *et al.*[357] methylated **158** with trimethyl phosphate in H_2O at pH 9.5–10.0 at 60°C for 24 h to obtain **10** in 12% yield with 70% recovery of **158**. As summarized above in Section VII, a product obtained by methylation of adenosine (**76**) and previously assigned the structure "1,3-dimethyladenine" by Brookes and Lawley[392] was shown to be 3,7-dimethyladenine (**10**).[327]

In yet another synthetic approach (Scheme 37), Fujii's group[336] methylated N^6-methoxy-7-methyladenine (**160**) with MeI in $AcNMe_2$ at 40°C for 2 h to obtain N^6-methoxy-3,7-dimethyladenine (**92**) (44% yield) and N^6-methoxy-7,9-dimethyladeninium iodide (**91**: X = I) (36%). Hydrogenolysis of **92**·$HClO_4$ using Pd–C catalyst and hydrogen afforded 3,7-dimethyladenine perchlorate (**10**·$HClO_4$) in 59% yield. Muravich-Aleksandr *et al.*[407] reported that **10**·HI and **158**·HI were the main products from the reaction of adenine (**1**) with MeI in DMF at 150°C.

The following physical properties and spectral characteristics of 3,7-dimethyladenine (**10**) are found in the literature: the melting point for **10**·HI, mp >300°C;[327,417c] for **10**·$HClO_4$, mp 308–309°C (decomp);[336] for **10**·H_2SO_4, mp (not specified);[327] for **10**·$MeOSO_3H$, mp (not specified);[327] for **10**·picrate, mp 256°C;[327] paper chromatography for **10**·HI;[327] TLC;[357] MS;[199] UV in H_2O (at various pH's),[357] for **10**·HI in H_2O (at various pH's) and

in MeOH,[327] for **10**·HI in H_2O (at various pH's) and in 95% aqueous EtOH,[417c] for **10**·$HClO_4$ in H_2O (at various pH's) and in 95% aqueous EtOH;[336] nonfluorescent in H_2O (pH <7) at rt;[419] ^1H NMR for **10**·HI in DMSO-d_6.[417c]



10·HI **161** **162** **161** **101**

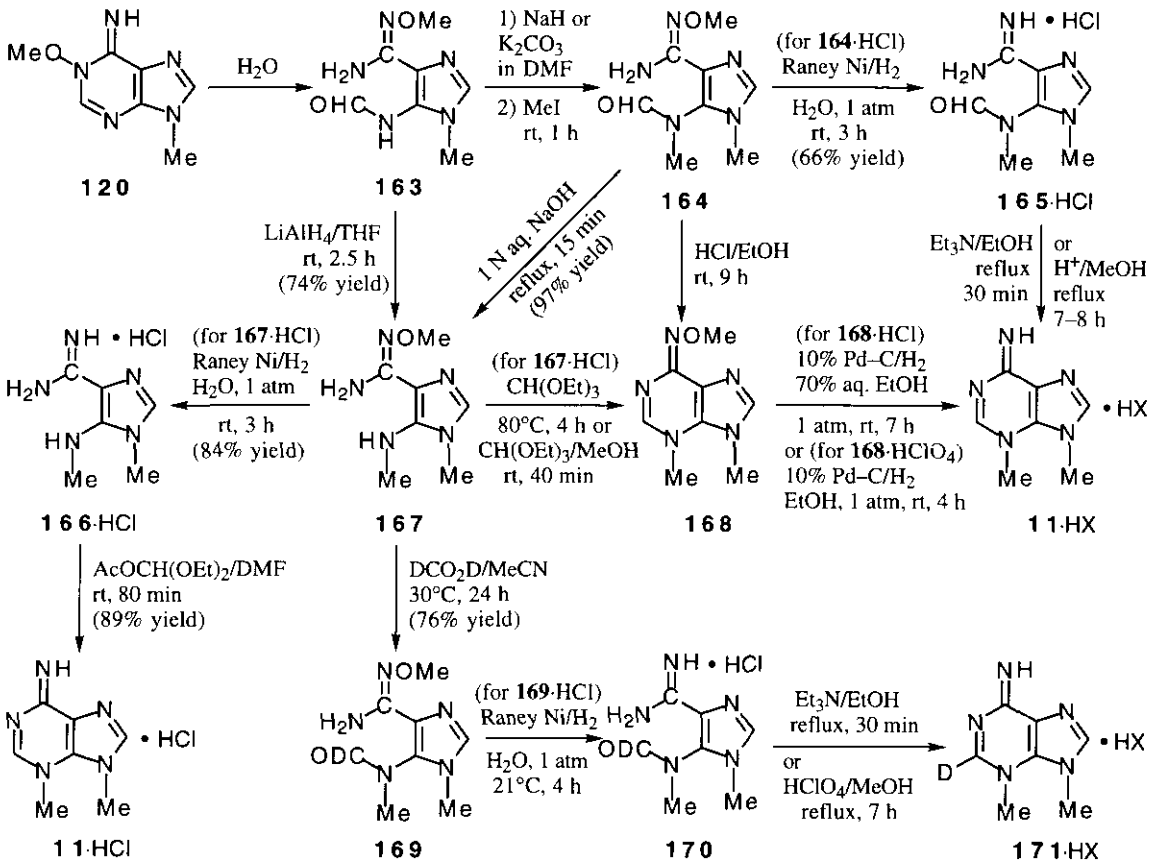
Scheme 38

As regards the chemical behavior of 3,7-dimethyladenine (**10**), Robins' group[327] observed that treatment of **10**·HI with 2 N aqueous NaOH at rt for 4 d changed the UV spectrum to λ_{max} (pH 11) 267 nm, which was similar to the spectrum of 3,7-dibenzylhypoxanthine, suggesting basic hydrolysis to occur to give the corresponding 3,7-dimethylhypoxanthine (**162**) (Scheme 38). However, Fujii's group[390] found that **10**·HI gave the ring-opened monocycle (**161**) as the major product together with a trace amount of **162** under similar reaction conditions, and **161** was isolated in 47% yield in the form of the perchlorate salt when **10**·HI was treated with 1 N aqueous NaOH at 30°C for 7 d; in 0.1 N aqueous NaOH (pH 13), **10**·HI was considerably stable at rt. Hydrolysis of **10**·HI in 1 N aqueous NaOH at 80°C for 30 min gave **161** (39% yield) and **162** (1%), whereas that under reflux for 2 h furnished **161** (49%) and the monodemethylated monocycle (**101**) (2%), but without giving any **162**.[390] Conversion of **161** into theobromine utilizing ethoxycarbonylation has enhanced the usefulness of such ring opening of **10**·HI.[390,420]

XI. 3,9-DIMETHYLADENINE

3,9-Disubstitution in the adenine series has previously been known only in cyclic derivatives[421] (*e. g.*, 3,5'-cyclo-2',3'-*O*-isopropylideneadenosine *p*-toluenesulfonate[421a]), N^6,N^6-dialkyl derivatives,[421b,422] an N^6-monomethylated derivative,[330] or an N^6-methyl-8-oxo derivative (*i. e.*, caissarone[338,423] isolated from the sea anemone *Bunodosoma caissarum* Correa 1964). It is also assumed to occur as a partial structure, in the form of 3-alkyl-2'-deoxyadenosine, in alkylated DNA molecules.[424] Although the prototype of

this disubstitution is 3,9-dimethyladenine (**11**), it remained unknown until a general synthetic route to 3,9-dialkyladenine salts,[425] eventually shown to be applicable even to the syntheses of 3-methyladenosine *p*-toluenesulfonate[426] and 2'-deoxy-3-methyladenosine *p*-toluenesulfonate,[426c,427] was established by Fujii and co-workers.



Scheme 39

In reaching 3,9-dimethyladenine (**11**) (Scheme 39), they reduced the formamidoimidazole derivative (**163**), the readily isolable ring-opened intermediate in the Dimroth rearrangement of 1-methoxy-9-methyladenine (**120**), with $LiAlH_4$ in THF at rt for 2.5 h to obtain the methylamino derivative (**167**) (74% yield), which was treated with ethanolic HCl.[425a,c] The resulting hydrochloride (**167**·HCl) was then treated with ethyl orthoformate at 80°C for 4 h or in MeOH at rt for 40 min, furnishing the cyclized product (**168**·HCl) in 87% or 94% yield, respectively. Hydrogenolysis of **168**·HCl or of **168**·$HClO_4$ using Pd–C catalyst and hydrogen in 70% aqueous EtOH or in EtOH gave **11**·HCl or **11**·$HClO_4$ in 61% or 56% yield, respectively.[425a,c] Alternatively, hydrogenation of **167** over Raney Ni catalyst in H_2O containing one molar equiv. of HCl proceeded smoothly at rt, producing the amidine hydrochloride (**166**·HCl) in 84% yield. Reaction of **166**·HCl

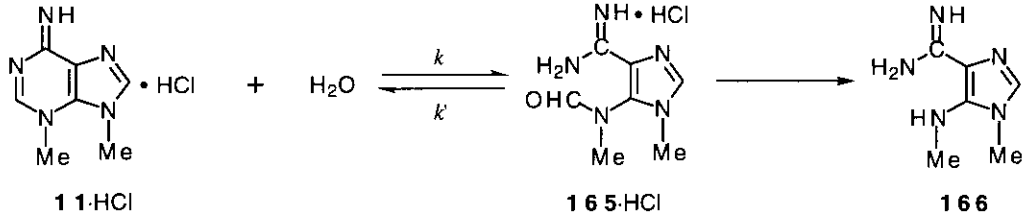
with diethoxymethyl acetate in DMF at rt for 80 min afforded **11**·HCl in 89% yield.[425c] In an alternative route to **11**,[425b,c] methylation of the Na salt of **163**, generated *in situ* from **163** and NaH in DNF at rt, with MeI in DMF at rt for 1 h produced the *N*-methylformamido derivative (**164**) in 87% yield. Similar methylation of the K salt, generated *in situ* from **163** and anhydrous K_2CO_3 in DMF at rt, also gave **164** in 84% yield. Hydrolysis of **164** with boiling 1 N aqueous NaOH for 15 min provided **167** in 97% yield. On the other hand, treatment of **164** with 5% ethanolic HCl at rt for 9 h gave the cyclized product (**168**·HCl) (47% yield), which was demethoxylated to **11**·HCl (61% yield) (*vide supra*). In an alternative permutation, **164** was converted into the demethoxy derivative (**165**·HCl) (66% yield) by catalytic hydrogenolysis (Raney Ni/H_2, H_2O containing one molar equiv. of HCl, 1 atm, rt, 3 h). Treatment of **165**·HCl with 10% methanolic HCl in boiling MeOH for 8 h or with 70% aqueous $HClO_4$ in boiling MeOH for 7 h gave **11**·HCl or **11**·$HClO_4$ in 73% or 81% yield, respectively. Alternatively, **165**·HCl readily cyclized in boiling EtOH in the presence of 0.1 molar equiv. of Et_3N, furnishing **11**·HCl in 89% yield.

For the synthesis of 3,9-dimethyladenine-*2-d* (**171**), Fujii's group[428] treated **167** with formic-*d* acid-*d* (of over 99% isotopic purity) in MeCN at 30°C for 24 h, securing the deuterioformamido derivative (**169**) in 76% yield (Scheme 39). Hydrogenolytic demethoxylation of **169** was then effected with Raney Ni catalyst and hydrogen at 1 atm and 21°C in H_2O containing one molar equiv. of HCl for 4 h, and cyclization of the resulting amidine hydrochloride (**170**) in boiling EtOH containing a little Et_3N for 30 min furnished the desired 2-deuterated species, 3,9-dimethyladenine-*2-d* hydrochloride (**171**·HCl), in 48% overall yield (from **169**). Alternatively, cyclization of **170** was effected in boiling MeOH in the presence of 70% aqueous $HClO_4$ for 7 h, giving **171**·$HClO_4$ in 71% overall yield (from **169**).

The following physical properties and spectral characteristics of 3,9-dimethyladenine (**11**) have been recorded in the literature: the melting point for **11**·HCl, mp 281–282°C (decomp);[425b,c] for **11**·$HClO_4$, mp 333–334°C (decomp)[425a] or mp >300°C;[425b,c] for the bicarbonate salt (**11**·H_2CO_3), mp 161–162°C (decomp);[425b,c] for **11**-*2-d*·HCl·1/2H_2O (**171**·HCl·1/2H_2O), mp 285.5–287.5°C (decomp);[428] for **11**-*2-d*·$HClO_4$ (**171**·$HClO_4$), mp >300°C;[428] UV for **11**·HCl,[425b,c] for **11**·$HClO_4$,[425] and for **11**·H_2CO_3[425c] in H_2O (at various pH's) and in 95% aqueous EtOH; UV for **11**-*2-d*·HCl·1/2H_2O (**171**·HCl·1/2H_2O) and for **11**-*2-d*·$HClO_4$ (**171**·$HClO_4$) in H_2O (at various pH's) and in 95% aqueous EtOH;[428b] ^1H NMR (DMSO-d_6) for **11**·HCl,[425c,428] for **11**·$HClO_4$,[425a,c,428] for **11**-*2-d*·HCl·1/2H_2O (**171**·HCl·1/2H_2O),[428] and for **11**-*2-d*·$HClO_4$ (**171**·$HClO_4$);[428] atomic orbital coefficient for the HOMO of **11** and the heat of formation estimated for **11**.[426b]

In an attempt to isolate the free base of 3,9-dimethyladenine (**11**), Fujii's group[425b,c] treated an aqueous solution of **11**·HCl with Amberlite IRA-402 (HCO_3^-) at rt. However, the substance isolated from the resulting solution in 97% yield was the bicarbonate salt (**11**·H_2CO_3), suggesting that the basicity of the free base is considerably high, in con-

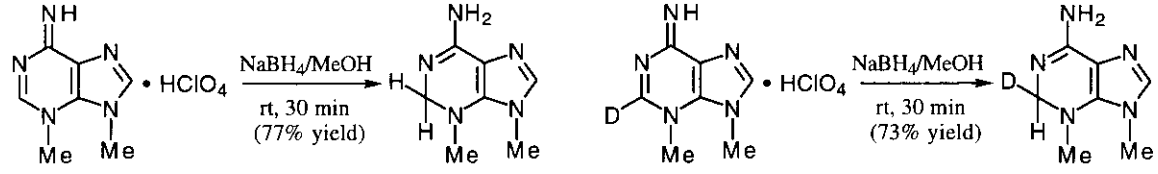
trast to the rather low basicity of the N^6-methoxy derivative (**168**) [pK_a 5.09 ± 0.03 (at 20°C) for **168**·$HClO_4$]. On the other hand, replacement of the ion-exchange resin by Amberlite CG-400 (OH^-) in the above neutralization resulted in the formation of the methylaminoimidazole (**166**), which was characterized as the hydrochloride (**166**·HCl) (61% yield). Since the same hydrochloride was obtained from **165**·HCl by a similar treatment, the observed conversion of **11**·HCl into **166** seemed to proceed through hydrolytic ring opening followed by deformylation, as delineated in Scheme 40.



11·HCl **165**·HCl **166**

Scheme 40

It was found that in aqueous $NaHCO_3$ the UV spectral changes of both **11**·HCl and **165** with time went through the same isosbestic point at 256 nm, converging on an identical spectrum. Actually, 3,9-dimethyladenine was isolated in 66% yield as the perchlorate (**11**·$HClO_4$) from a solution of **165** in 0.5 M aqueous $NaHCO_3$ which had been kept at 25°C for 6 h. All these observations indicated the existence of an equilibrium between 3,9-dimethyladenine (**11**) and the ring-opened derivative (**165**) in H_2O, and this was confirmed by following spectrophotometrically the time-courses of the ring-opening reaction of **11**·HCl and of cyclization of **165**·HCl in 0.1 M aqueous $NaHCO_3$ (pH 8.32) at 25°C: The reactions in both directions (Scheme 40) were found to obey pseudo-first-order kinetics (k = 2.88 × 10^{-3} min^{-1}; k' = 9.63 × 10^{-3} min^{-1}; $K_{eq} = k/k'$ = 0.30); the rate and equilibrium constants for the reactions in H_2O at various pH's (7.50, 8.98, 9.62. and 10.08) and ionic strength 0.5 at 25°C were also determined.[429] It is of particular interest to emphasize that among the four possible N^x,9-dimethyladenines [*i. e.*, the N^6,9- (**6**), 1,9- (**9**), 3,9- (**11**), and 7,9-dimethyl (**12**) isomers], the 3,9-dimethyl isomer (**11**) has been found to undergo hydrolytic fission of the adenine ring most rapidly under alkaline conditions (see also Section XII).[390,425c]



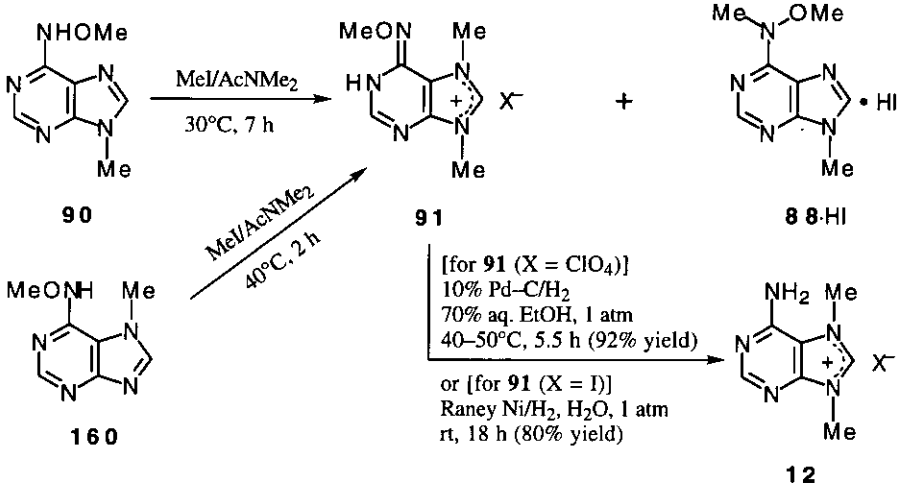
11·$HClO_4$ **172** **171**·$HClO_4$ **173**

Scheme 41

Fujii's group[428] reported that treatment of **11**·$HClO_4$ with $NaBH_4$ in MeOH at rt for 30 min furnished the 1,2-dihydro derivative (**172**) in 77% yield (Scheme 41); the $NaBH_4$ reduction of the 2-deuterated species (**171**·$HClO_4$) under similar conditions gave the corresponding 1,2-dihydro derivative (**173**) in 73% yield.

XII. 7,9-DIMETHYLADENINE

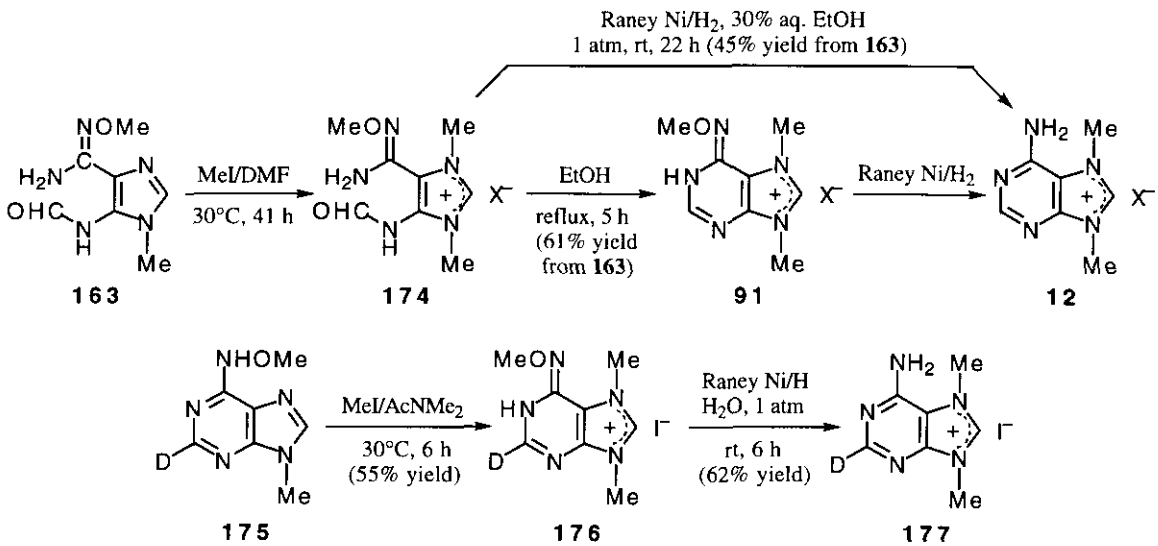
7,9-Disubstitution in the adenine series has been known to occur in nature in the form of agelasine (from the sea sponge *Agelas dispar*),[430] agelasines A–F (from the Okinawan sea sponge *A. nakamurai*),[431] ageline A (agelasine F[431c]) and ageline B (from a Pacific sea sponge *Agelas* sp.),[432] *epi*-agelasine C (from the marine sponge *Agelas mauritiana*),[433] agelasine G (from an Okinawan marine sponge *Agelas* sp.),[434] and agelasines H and I (from *Agelas* sp. collected at Yap Island),[6g] which all are 9-methyladenines with diterpene or modified diterpene units at the 7-position. The existence of the 7-methyladenosine structure in tRNA's of *Bacillus stearothermophilus*[435] and *B. subtilis*[436] as a modified nucleoside component has also been suggested, and 7-methyl- or 7-ethyladenosine has been reported to be a by-product of methylation or ethylation of adenosine (**76**) in neutral aqueous solution.[207] Although the prototype of this disubstitution is 7,9-dimethyladeninium salt (**12**), it remained unknown until 1973 when Fujii's group[363] reported the first synthesis of 7,9-dimethyladeninium perchlorate (**12**: X = ClO_4) (Scheme 42).



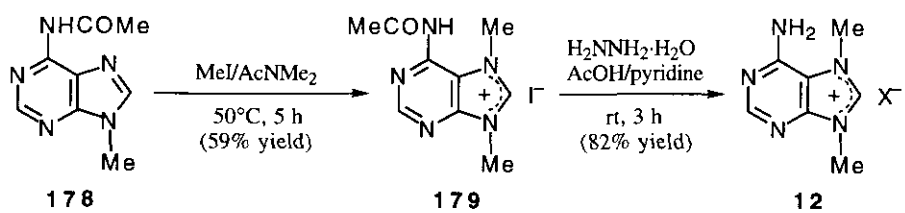
Scheme 42

The synthesis of **12** (X = ClO_4) started with methylation of N^6-methoxy-9-methyladenine (**90**) with MeI in $AcNMe_2$ at 30°C for 7 h to give the 7-methyl derivative [**91** (X = I)] (59% yield) and the N^6-methyl derivative (**88**·HI) (24%).[336,363] As described above in Section X (Scheme 37), the former product was alternatively obtainable in 36% yield

from N^6-methoxy-7-methyladenine (**160**) by similar methylation.[336] Conversion of **91** (X = I) into the corresponding perchlorate [**91** (X = ClO_4)] (83% yield) and subsequent hydrogenolysis of **91** (X = ClO_4) using Pd–C catalyst and hydrogen[336,363] or hydrogenolysis of **91** (X = I) in H_2O using Raney Ni catalyst and hydrogen[437] gave **12** (X = ClO_4) or **12** (X = I) in 92% or 80% yield, respectively. The permutation **90**→**91**→**12** has afforded a firm basis for establishing parallel ones leading to a general synthesis of 7,9-dialkyladeninium salts,[437] to syntheses of 7-methyl- and 7-ethyladenosine perchlorates,[363,438] and to an attempted synthesis of 2'-deoxy-7-methyladenosine salt.[439]



Scheme 43



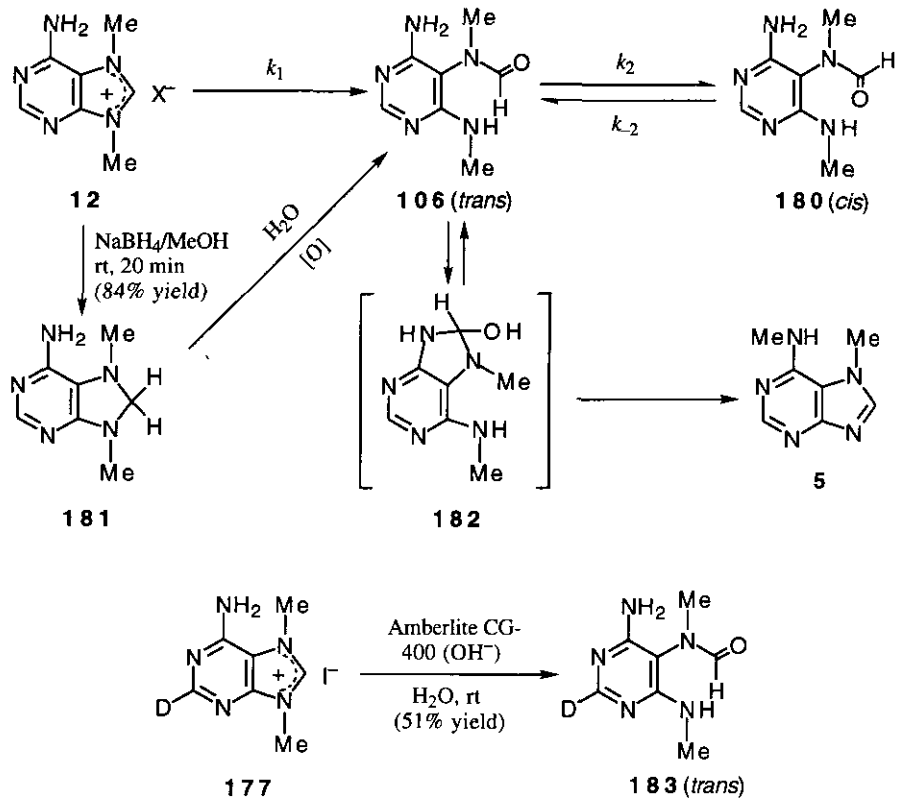
Scheme 44

In an alternative approach to 7,9-dimethyladeninium salts, Fujii's group[343] methylated the formamidoimidazole (**163**) in the absence of added base with MeI at 30°C for 41 h (Scheme 43). When a crude product presumed to be the N(3)-methylated derivative [**174** (X = I)] was treated with boiling EtOH for 5 h, N^6-methoxy-7,9-dimethyladeninium iodide [**91** (X = I)], the known penultimate intermediate for the synthesis of **12** (X = I or ClO_4) as shown above (Scheme 42), was obtained in 61% overall yield (from **163**). Alternatively, hydrogenolysis (Raney Ni/H_2) of crude **174** and spontaneous cyclization

of the resulting demethoxy derivative directly produced **12** (X = I) in 45% yield (from **163**).[343] The C(2)-deuterated species (**177**) of **12** (X = I) was also prepared from N^6-methoxy-9-methyladenine-*2-d* (**175**) through **176**, as illustrated in Scheme 43.[343b]

In yet another synthetic approach (Scheme 44), Maki's group[440] obtained **12** (X = I) from N^6-acetyl-9-methyladenine (**178**) *via* the 7-methyl derivative (**179**).

The following physical properties and spectral characteristics of 7,9-dimethyladeninium salt (**12**) have been reported: the melting point for **12** (X = ClO_4), mp 276–277°C (decomp);[336,363] for **12** (X = I), mp 267–268°C (decomp)[437a] or 274–275°C (decomp)[437b] or 280–281°C;[440b] for **12**-*2-d* (X = I) (**177**), mp 266.5–269.5°C (decomp);[343b] UV for **12** (X = ClO_4) in H_2O (at various pH's) and in 95% aqueous EtOH;[336,363] UV for **12** (X = I) in H_2O (at various pH's),[437b] in 95% aqueous EtOH,[437b] and in MeOH;[440b] for **12**-*2-d* (X = I) (**177**) in H_2O (at various pH's) and in 95% aqueous EtOH;[343b] fluorescence emission spectrum for **12** (X = ClO_4);[441] ^1H NMR (DMSO-d_6) for **12** (X = ClO_4),[336,363] for **12** (X = I),[437b,440b] and for **12**-*2-d* (X = I) (**177**).[343b]



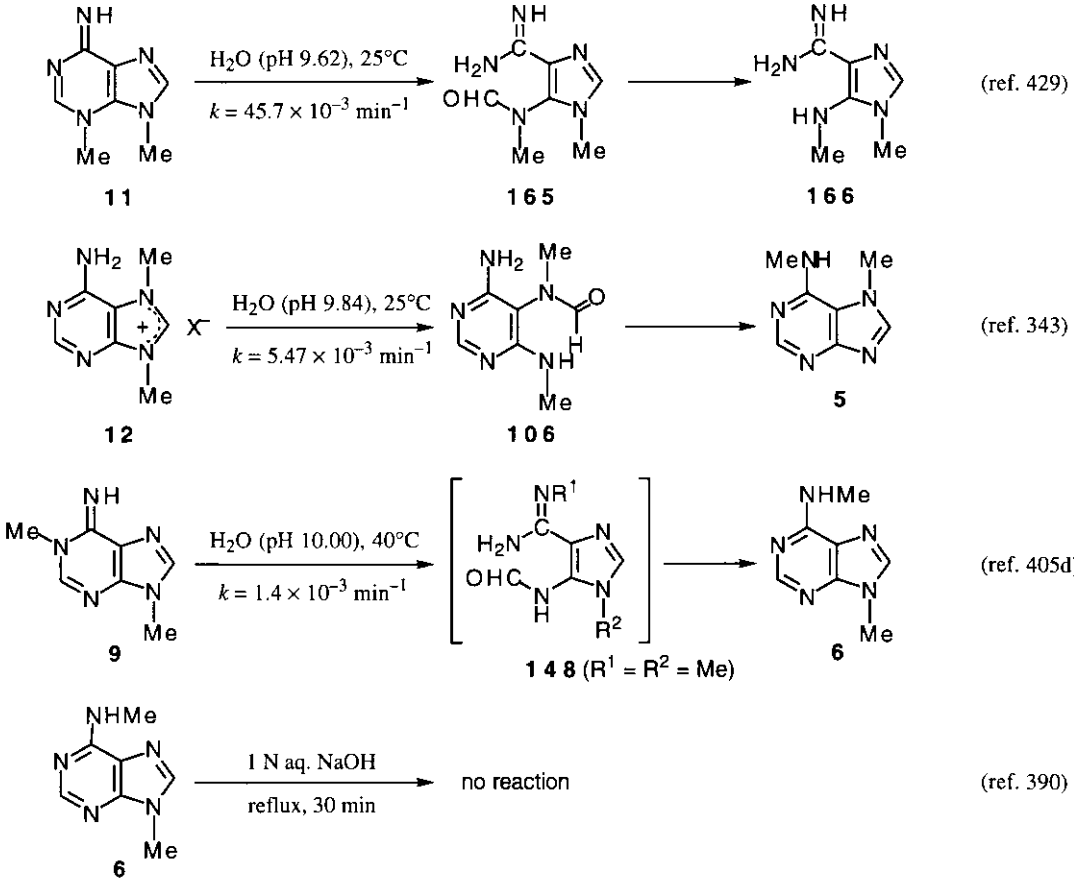
12 **106** (*trans*) **180** (*cis*) **181** **182** **5** **177** **183** (*trans*)

Scheme 45

As regards the chemical behavior of 7,9-dimethyladeninium salt (**12**), Fujii's group[343] found that **12** was unstable under mildly alkaline conditions. On treatment with 0.5 N aqueous Na_2CO_3 at rt for 30 min, **12** (X = I) produced the ring-opened derivative (**106**)

(with carbonyl oxygen *trans* to the pyrimidine ring) in 56% yield (Scheme 45). Replacement of the inorganic base by Amberlite CG-400 (OH^-) in the above treatment also afforded **106** in 83% yield. Similar treatment of the C(2)-deuterated species (**177**) gave the corresponding ring-opened derivative (**183**) in 51% yield. Under more drastic alkaline conditions, **12** underwent rearrangement:[343] On treatment with boiling 1 N aqueous NaOH for 60 min, **12** (X = I) rearranged to N^6,7-dimethyladenine (**5**) in 87% yield. Similar treatment of **106** or treatment of **106** with NaH in $AcNMe_2$ at rt for 40 min also gave **5** in 72% or 84% yield, respectively.

The ring-opened derivative (**106**) was also unstable in solution at rt, giving slowly an equilibrated mixture of **106** and its *cis* isomer (**180**) in H_2O, in D_2O at 25°C, and in DMSO-d_6 at 25°C (Scheme 45), and rate constants (k_1, k_2, and k_{-2}) for the system of reactions that produces **180** (*via* **106**) and **5** (*via* **106** and **182**) from **12** were determined: The values $k_1 = 5.47 \times 10^{-3}$ min^{-1}, $k_2 = 1.49 \times 10^{-3}$ min^{-1}, and $k_{-2} = 0.84 \times 10^{-3}$ min^{-1} were obtained for **12** (X = ClO_4)→**106**⇌**180** in H_2O at pH 9.84, 25°C, and ionic strength 0.50.[343]



Scheme 46

Fujii's group[343] further reported that the $NaBH_4$ reduction of **12** (X = I) in MeOH at rt furnished the 7,8-dihydro derivative (**181**) in 84% yield. In H_2O at 60°C, **181** slowly decomposed to give the ring-opened derivative (**106**) in 49% yield. The results of the $NaBH_4$ reduction of **12** (X = I) is in general agreement with those[330,440,442] reported for 7,9-disubstituted purines.

Now that the reaction rates for ring opening of all the four possible N^x,9-dimethyladenines under alkaline conditions have become available as summarized above, it is possible to make a comparison between them. It may be seen from Scheme 46 that the relative ease with which the adenine ring undergoes hydrolytic fission decreases in the order 3,9- (**11**) > 7,9- (**12**) > 1,9- (**9**) >> N^6,9-dimethyl isomer (**6**).[390]

Finally, as regards the biological activity of 7,9-dimethyladeninium salt (**12**), Kobayashi *et al.*[443] reported that **12** (X = Cl) had little or no inhibitory effect, even at 100 μM, on the pig brain Na^+,K^+-ATPase.

ACKNOWLEDGMENT

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