

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.

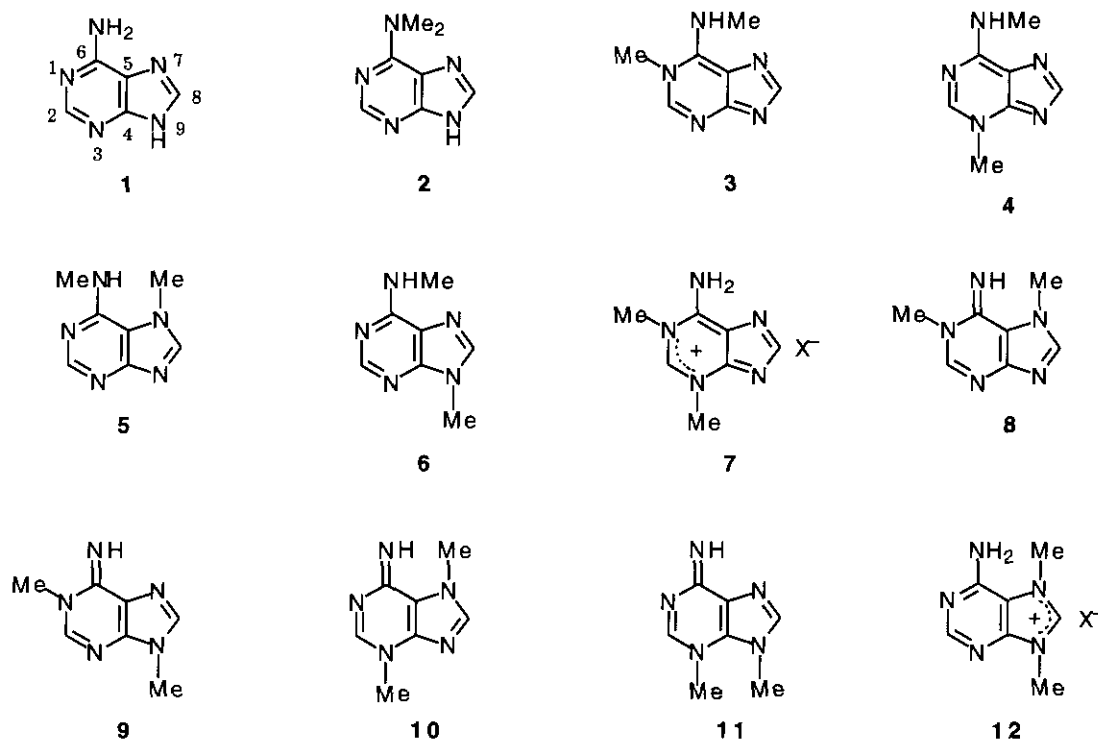
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I. INTRODUCTION

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 77) 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 ones¹⁻⁴ 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



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* Marginatus¹⁰ has been reported. As the aglycon, **2** is contained in the antibiotic puromycin [6-dimethylamino-9-[3-(*p*-methoxy-L-phenylalanyl-amino)-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's¹⁴⁻³¹ 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 callus⁴² and chlorophylls increase in cucumber cotyledons⁴³ 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 (³H-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-diastrase;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;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 cells⁸² 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

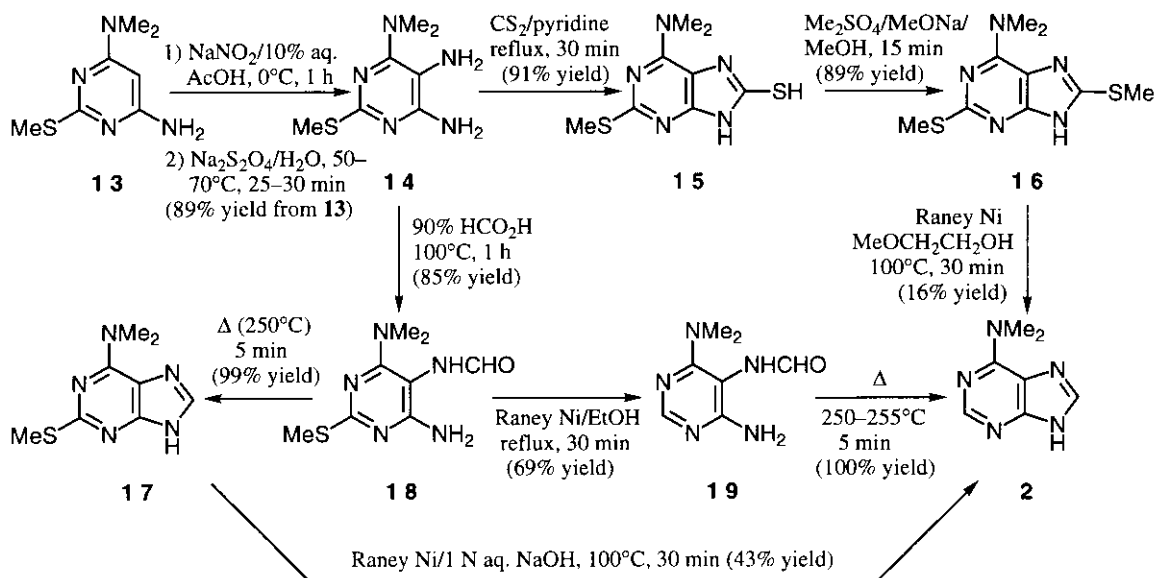
As a protein kinase inhibitor, **2** has been used in the study of the following enzymes, biological processes, and those in oocytes: gibberellin-induced elongation, reorientation of cortical microtubules, and change of isoform of tubulin in epicotyl segments of azuki bean (*Vigna angularis*) seedlings;⁹¹ *Tetrahymena* cell division in the presence or absence of okadaic acid;⁹² the programmed rearrangement of cortical skeleton in furrowing *Paramecium* and the tensegrity model of cytokinesis;⁹³ cyclic activation of histone H₁ 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 H₁-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 H₁ 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

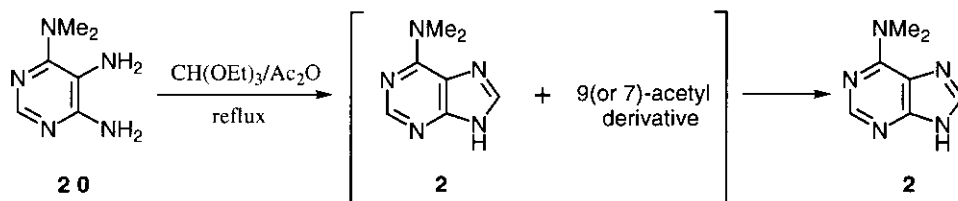
Effects of **2** on the following biological processes have also been investigated: oligogalacturonide-induced cytoplasmic acidification in tobacco cells grown in suspension cultures;¹²¹ oxygen consumption by mitochondrial preparations from soybean cells;¹²² *p*-coumaric acid disappearance and delayed 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 [³H]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 μ M) 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/Ac₂O 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.

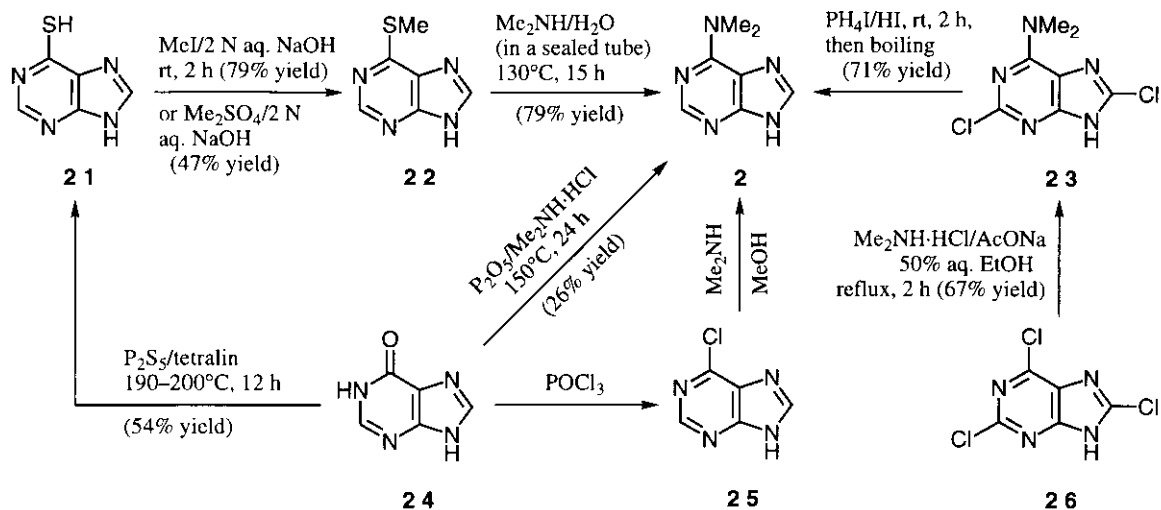
In a synthetic approach to **2** from a purine derivative, Elion *et al.*¹⁴⁵ reached **2** from hypoxanthine (**24**) *via* 6-mercaptopurine (**21**) and 6-methylthiopurine (**22**), as shown in Scheme 3. The step **22**→**2** was repeated under similar reaction conditions by Albert and



Scheme 1

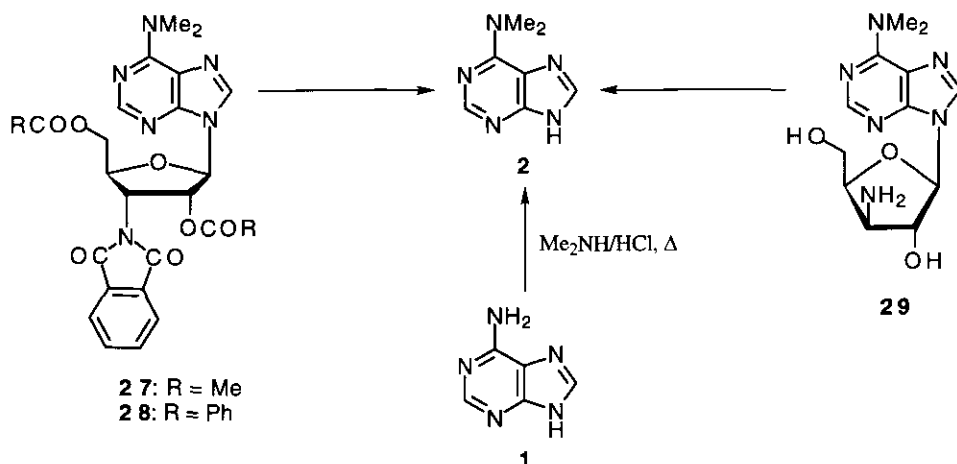


Scheme 2



Scheme 3

Brown (20% aqueous Me_2NH , 140°C , 24 h),¹⁴⁶ by Skinner *et al.*,⁵⁸ and by Okumura *et al.* ($130\text{--}135^\circ\text{C}$, 17 h, 45% yield).^{32a} Alternatively, Albert and Brown¹⁴⁶ 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 $[8\text{-}^{14}\text{C}]\text{-2}$ from $[8\text{-}^{14}\text{C}]\text{-25}$ by heating with Me_2NH in THF under an N_2 atmosphere at 50°C for 2.5 h. Girgis and Pedersen¹⁴⁹ reported a one-step 26% conversion of **24** into **2**, in which a mixture of P_2O_5 , $\text{Me}_2\text{NH}\cdot\text{HCl}$, 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 $80\text{--}83^\circ\text{C}$ 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 $20\text{--}25^\circ\text{C}$ for 17 h or 18 h was reported to provide $2\cdot 2\text{H}_2\text{SO}_4$ 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 ₂ SO ₄	210–215°C	(157)
2·picrate	247°C (158); 244–245°C (decomp) (143a); 241–242°C (decomp) (144b)	
Acid dissociation constant		
basic p <i>K</i> _a	3.87 (H ₂ O) ^{c)} (146, 160, 161, 169); 3.9 (H ₂ O) ^{d)} (165); 4.3 (H ₂ O) ^{e)} (164); 4.4 (H ₂ O) ^{d)} (163); 4.45 (H ₂ O) ^{d)} (164); 4.10 (D ₂ O) ^{c,f)} (166)	
acidic p <i>K</i> _a	9.95 (H ₂ O) ^{d)} (164); 10 (H ₂ O) ^{e)} (164); 10.0 (H ₂ O) ^{d)} (165); 10.1 (H ₂ O) ^{d)} (163); 10.5 (H ₂ O) ^{c)} (146, 160, 161, 169); 10.54 [59% (v/v) aq. EtOH] ^{c)} (162); 13.0 (DMSO) ^{c)} (167); 14.7 (MeOCH ₂ CH ₂ OH) ^{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 ₂ O at various pH's (21, 22, 145a, 147, 160, 163–165, 181, 206, 207); in methylcyclohexane, dioxane, <i>i</i> -PrOH, or H ₂ O (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 ₂ O (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- <i>d</i> ₆ (150, 170, 219, 220); in CD ₃ OD–CF ₃ CO ₂ D (50:1) (221); in H ₂ O (164); in D ₂ O (166, 222–224)	
¹³ C NMR spectrum	Solid (216); in DMSO- <i>d</i> ₆ (150, 216, 220, 225, 226)	
¹⁵ N NMR spectrum	In DMSO	(227)

(continues)

TABLE I (continued)

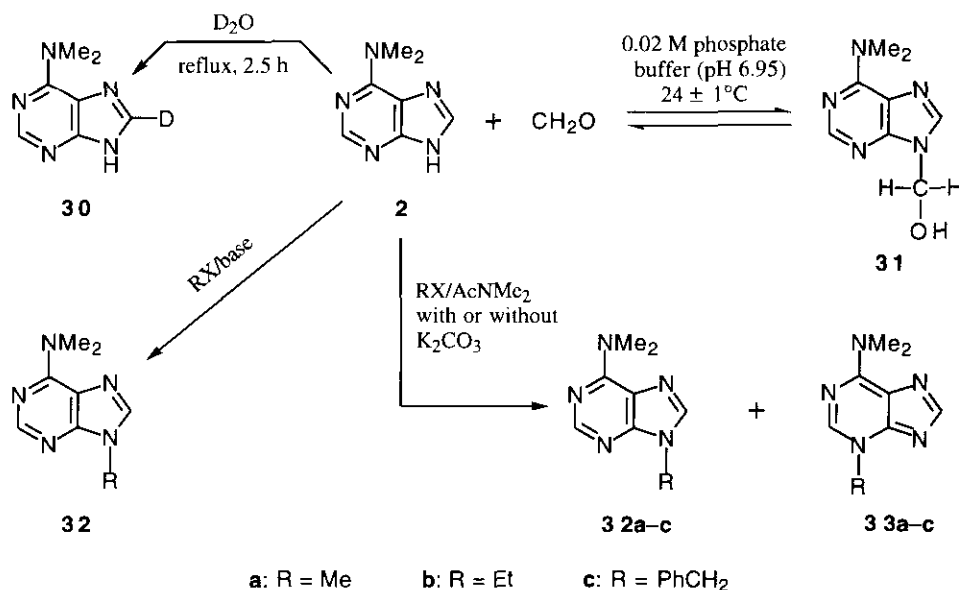
Item	Specification ^{a)}	Literature (ref. No.)
Crystal structure	2·2H ₂ O (228); 2·HCl·H ₂ O (229); 2·2HCl (229); 2·HNO ₃ (230); 2·H ₂ SO ₄ (231); (2) ₂ ·H ₂ SO ₄ ·2H ₂ O (232); 2·CCl ₃ CO ₂ H (233); (2) ₂ ·(hydroxyethenetetracarboxitrile) ₂ ·1,4-dioxane (234); 2·picrate (235)	
Polarography		(236–240)
Voltammetry		(237, 239)
Redox property		(241, 242)
Solubility	In H ₂ O (at 20°C and 100°C)	(146)
Partition coefficient	In phosphate buffer (pH 7.0)–MeOCH ₂ CH ₂ OH–BuOCH ₂ CH ₂ OH (243)	
Acidimetric differential potentiometric titration	In MeOCH ₂ CH ₂ OH (244); in MeOCH ₂ CH ₂ OH– propylene carbonate (245)	
Apparent molar volume and heat capacity	In H ₂ O at 25°C, 35°C, and 45°C (246)	
Potential surface		(247)
Enthalpy of hydration		(204, 247–249)
Enthalpy of solution	In H ₂ O	(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) ¹H 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°C²⁵⁷ and in D₂O;²²³ H₂O 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 D₂O;²⁶³ an antibody directed toward *N*⁶-(Δ^2 -isopentenyl)adenosine;²⁶⁴ Cu(I) ions in aqueous media;²⁶⁵ (ImH)[RuCl₄Im₂] (Im = imidazole) in MeOH;²⁶⁶ (4-NO₂ImH)[RuCl₄-(5-NO₂Im)₂] in CD₃OD;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)₂Rh(acac)] in MeOH, or [(CO)Rh(acac)(PPh₃)] in MeOH/CH₂-Cl₂;²⁶⁹ the Rh₂⁴⁺ formamidinate complex Rh₂(μ -form)₂(μ -O₂CCF₃)₂(H₂O)₂ (form = *N,N'*-di-*p*-tolylformamidinate anion) in H₂O;²⁷⁰ Re₂Cl₂(AcO)₄ in EtOH containing MeO-

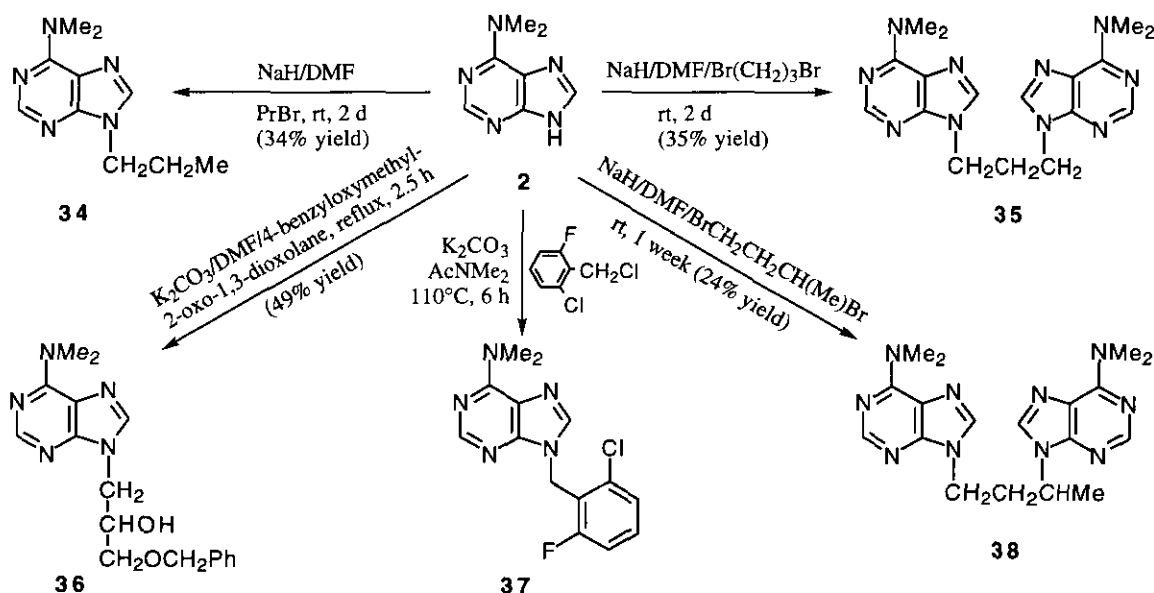
Na;²¹⁶ (Bu₄N)₂[Re₂Cl₈] in EtOH;²¹⁶ *cis*- and *trans*-[Pt(NH₃)₂Cl₂] in H₂O at 37°C;²⁷¹ HgCl₂ in EtOH/aqueous NaOH;^{206,272} MeHgOH or MeHgClO₄/MeHgOH or MeHgN-O₃/MeHgOH in boiling H₂O or MeHgNO₃ in aqueous MeCN.²²⁰



Scheme 5

As regards the chemical behavior of **2**, Albert and Brown¹⁴⁶ 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 Beauchamp²⁶⁶ prepared *N*⁶,*N*⁶-dimethyladenine-8-*d* (**30**) from **2** by heating anaerobically in refluxing D₂O for 2.5 h (Scheme 5). Kiessling *et al.*²⁷⁴ treated **2** in DMF with ³H₂ in the presence of Pd black to prepare *N*⁶,*N*⁶-dimethyl-[³H]adenine. McGhee and von Hippel²⁷⁵ 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 group²⁷⁶ 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 group²⁷⁷ reported that methylation of **2** with MeI in AcNMe₂ in the presence of K₂CO₃ 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 PhCH₂Br

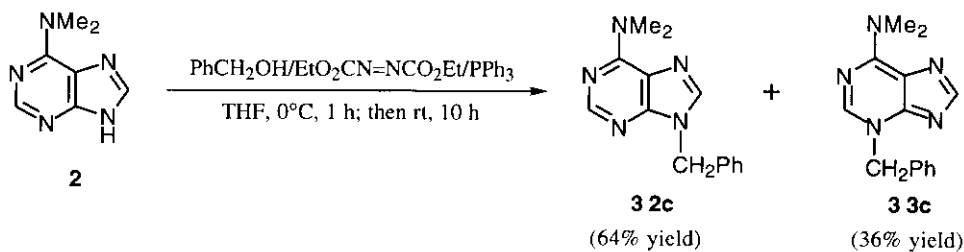
in a similar manner furnished 9-benzyl-*N*⁶,*N*⁶-dimethyladenine (**32c**) and the 3-benzyl isomer (**33c**) in 65% and 30% yields, respectively. When these alkylations were effected in the absence of K₂CO₃, the regioselectivity in alkylation suffered a complete reversal:²⁷⁷ Methylation at 40°C for 48 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 Shimizu²¹⁹ found that benzylation of **2** with PhCH₂Br in AcNMe₂ 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 Horton¹⁶³ 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%).



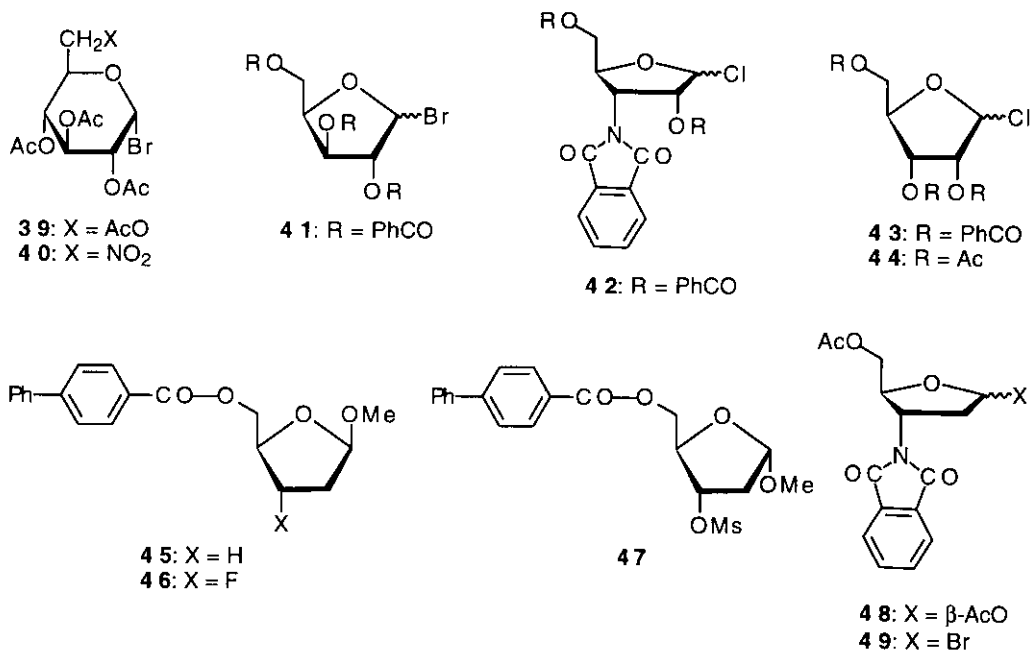
Scheme 6

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 group²⁷⁹ obtained **32a** from **2** in 36% yield by methylation (MeI/MeONa/DMSO, rt, 1 h); **32b** from **2** by ethylation (EtI/Bu₄N⁺OH⁻, CH₂Cl₂/H₂O);²⁸⁰ **32** (R = CH₂CH₂Cl) from **2** in 76% yield by alkylation (BrCH₂CH₂Cl/benzene/Bu₄N⁺Br⁻/50% aqueous NaOH, 80°C, 0.5 h).²⁸¹ Takemoto and co-workers²⁸² 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-

methylladenine (**36**) from **2** by alkylation with 4-benzyloxymethyl-2-oxo-1,3-dioxolane in the presence of K_2CO_3 . Imai and Seo²⁸⁴ 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 $110^\circ C$ 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-benzamido-piperidino)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



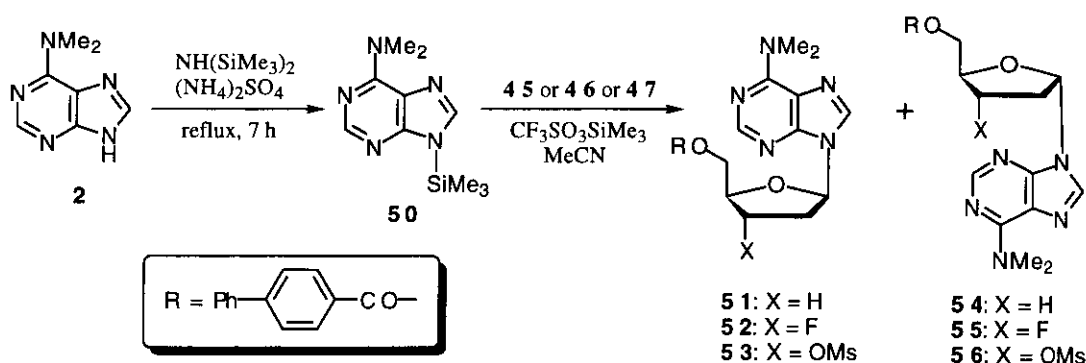
Scheme 7



Sukhodub *et al.*^{203,293} found that treatment of **2** with thio-TEPA (1,1',1''-phosphorothioylidynetrisaziridine) in H_2O at $37^\circ C$ 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 PhCH₂OH 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.

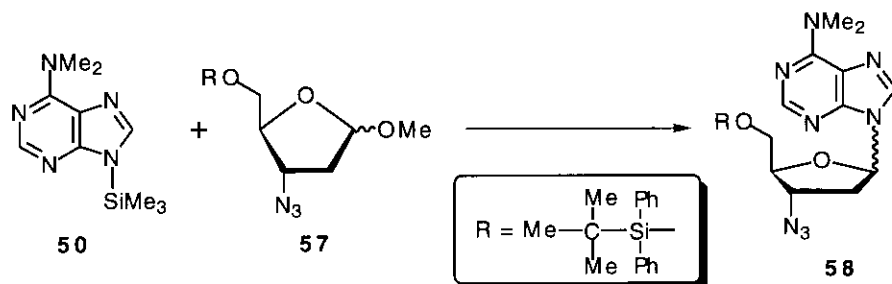
Baker *et al.*²⁷² reported condensation of the chloromercuri derivative of **2** with α -bromoacetoglucose (**39**) in boiling xylene for 1 h and deacetylation of the condensed product (26% yield) with MeONa in boiling MeOH for 45 min to give N⁶,N⁶-dimethyl-“7”- β -D-glucopyranosyladenine [reported mp 239–241°C (decomp)] in 76% yield. Baker and Schaub²⁹⁵ 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 N⁶,N⁶-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 N⁶,N⁶-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 CaSO₄ for 3 h was reported to be unsuccessful.²⁹⁷



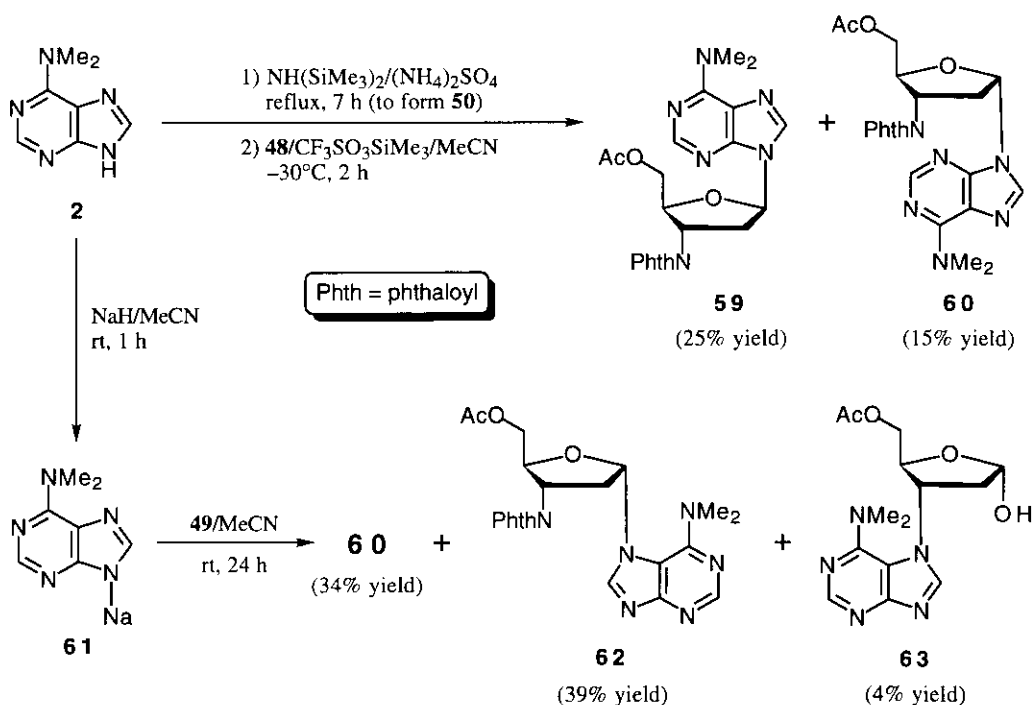
Scheme 8

Pedersen's group²⁹⁸ condensed the trimethylsilylated derivative (**50**), prepared from **2** by treating with boiling hexamethyldisilazane in the presence of (NH₄)₂SO₄, 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 ($\alpha:\beta = 4:1$) in 35% yield (Scheme 9).²⁹⁸



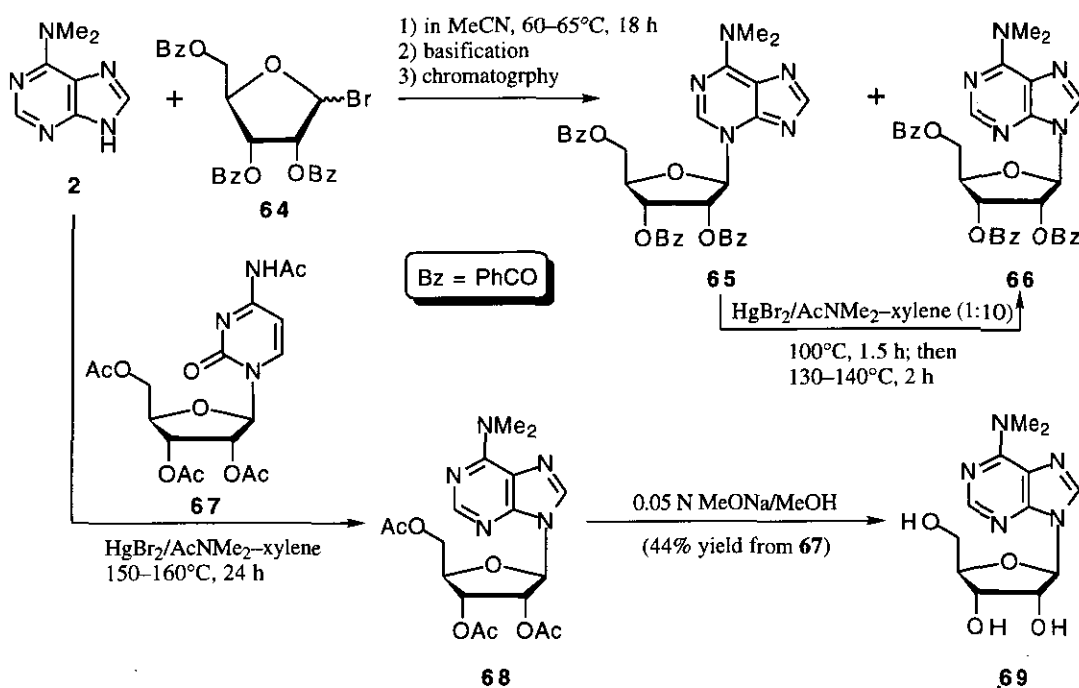
Scheme 9



Scheme 10

Pedersen's group¹⁵⁰ 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**) ($\alpha:\beta = 1:5$) in MeCN at rt for 24 h produced the 9- α -furanoside (**60**) (34%), the 7- α -

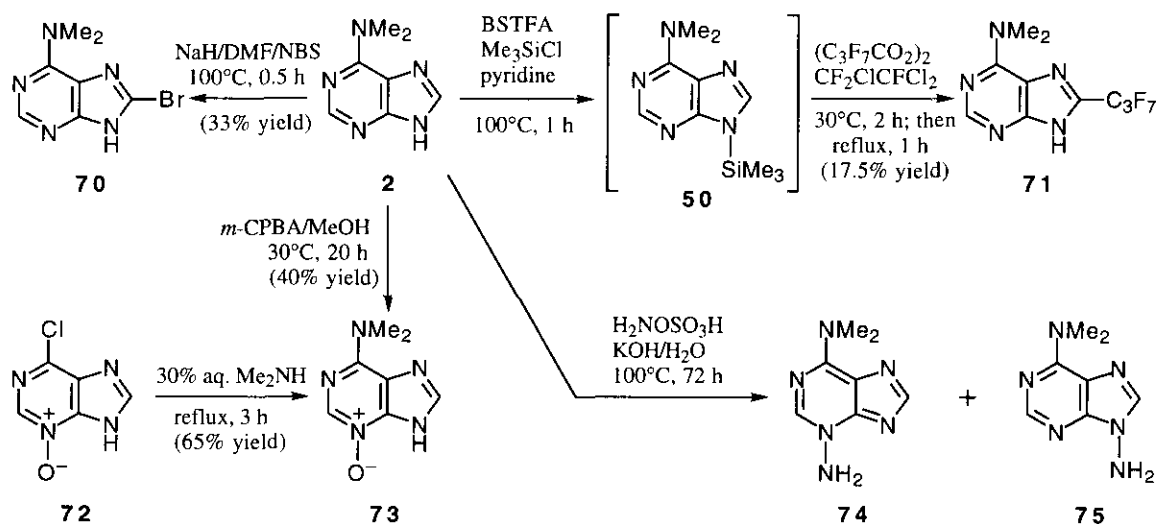
furanoside (**62**) (39%), and an unexpected product (**63**) (4%).¹⁵⁰ Miyaki and Shimizu²¹⁹ condensed **2** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**64**) in MeCN at 60–65°C for 18 h to obtain the corresponding 3-furanoside (**65**) and the 9-furanoside (**66**) in 36% and 11% yields, respectively (Scheme 11). Although **65** remained unchanged on heating at 100°C for 1.5 h in the presence of HgBr₂, N(3)→N(9) ribosyl migration took place on heating [in AcNMe₂-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-¹⁴C]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 AcONH₄ (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 deoxy-ribosyltransferase 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 Me₃SiCl and pyridine, with bis(heptafluorobutyryl) peroxide in CF₂ClCFCF₂ 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 H₂O at pH 6–8 and 20°C¹⁶⁹ and with the

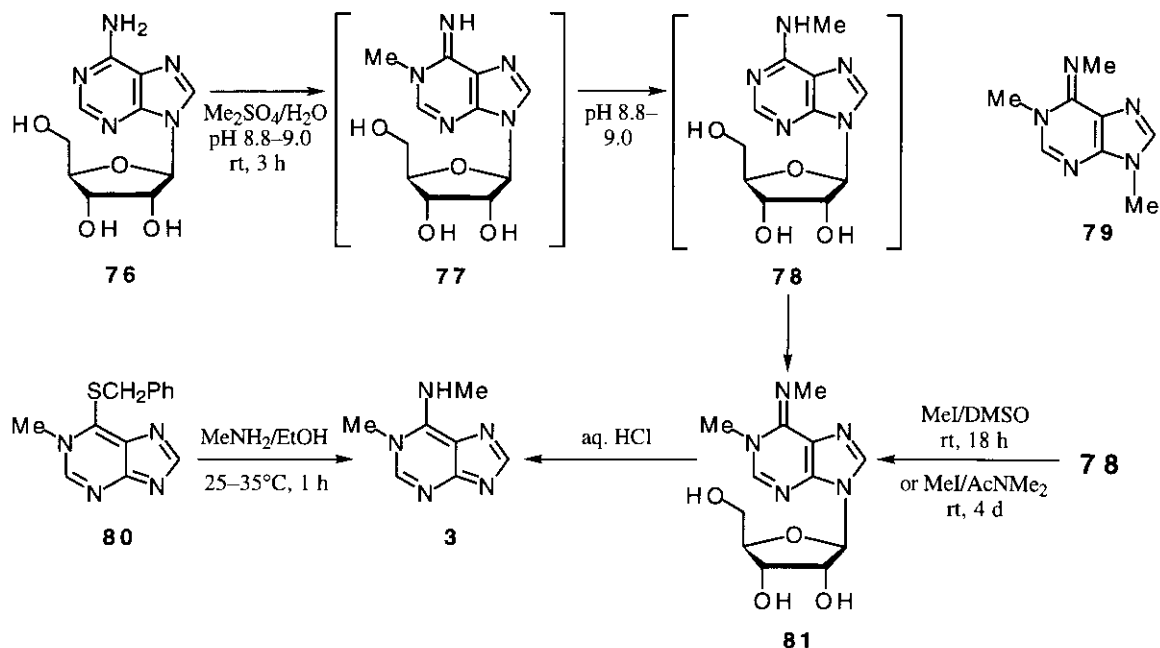
sulfate radical anion ($\text{SO}_4^{\bullet-}$) in H_2O at pH 7^{242,316} and the electron paramagnetic resonance spectrum as well as the protonation site of one-electron-reduced **2** (generated by X-Ray irradiation in a 9 M LiCl glass at 4 K)³¹⁷ have been investigated. Morimoto and Tsuda³¹⁸ reported 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 agent³¹⁹ and direct-positive color films containing **2** with wide exposure latitude³²⁰ 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 Ebert³²⁵ 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' group³²⁷ 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 Ebert³²⁵ 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 MeNH₂ 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 rearrangement³²⁸ 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 AcNMe₂ 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 $>300^{\circ}\text{C}$;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

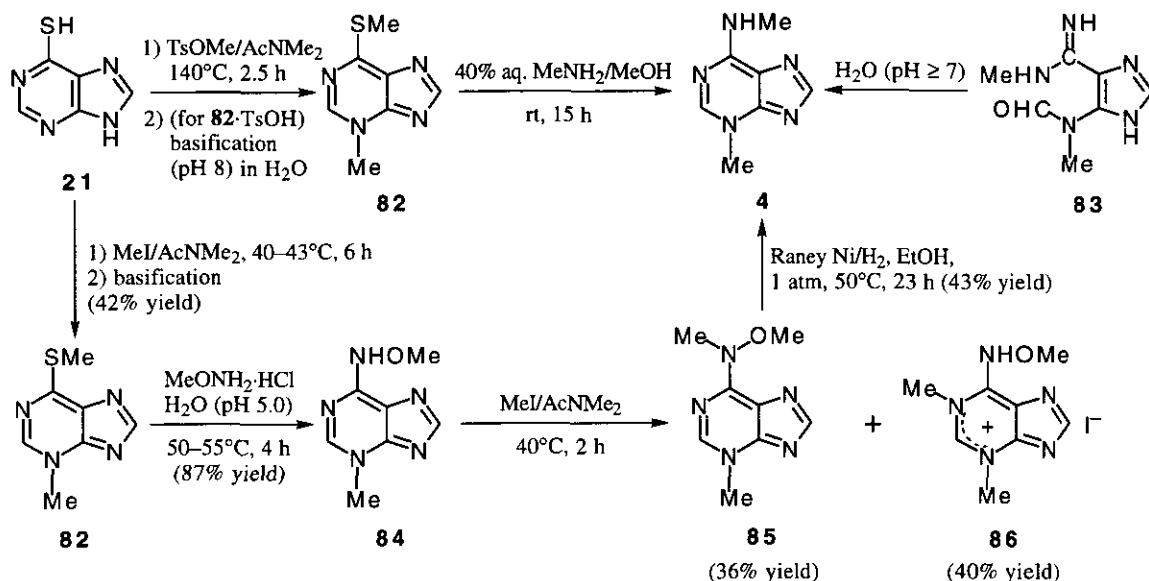


Scheme 13

*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.

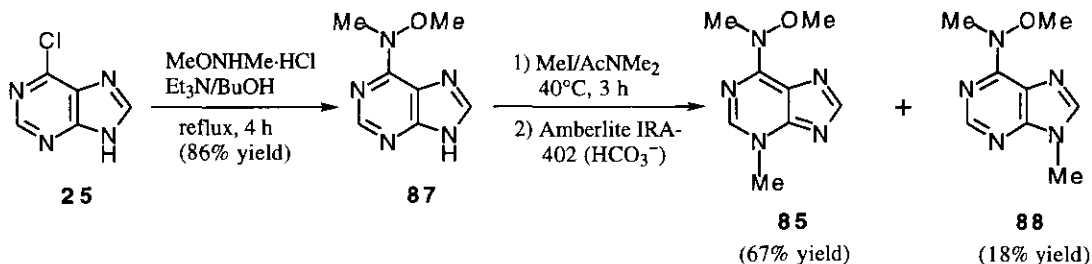
IV. *N*⁶,3-DIMETHYLADENINE

In their synthesis of *N*⁶,3-dimethyladenine (4), Jones and Robins³³⁴ 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 group³³⁵ prepared **4** from *N*'-methyl-5(4)-(N-methylformamido)imidazole-4(5)-carboxamide (**83**) [see Section VII (Scheme 28)] by cyclization in H₂O at rt under alkaline conditions. In yet another synthesis of **4**, Fujii's group³³⁶ methylated **21** with MeI in AcNMe₂ to secure **82**, which was then treated with MeONH₂ in H₂O (pH 5.0). Methylation of the resulting *N*⁶-methoxy derivative (**84**) with MeI in AcNMe₂ 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**·HClO₄). Hydrogenolysis of **85**, generated from **85**·HClO₄ by the use of Amberlite IRA-402 (HCO₃[−]), using Raney Ni catalyst and hydrogen gave **4** in 43% yield (Scheme 14).

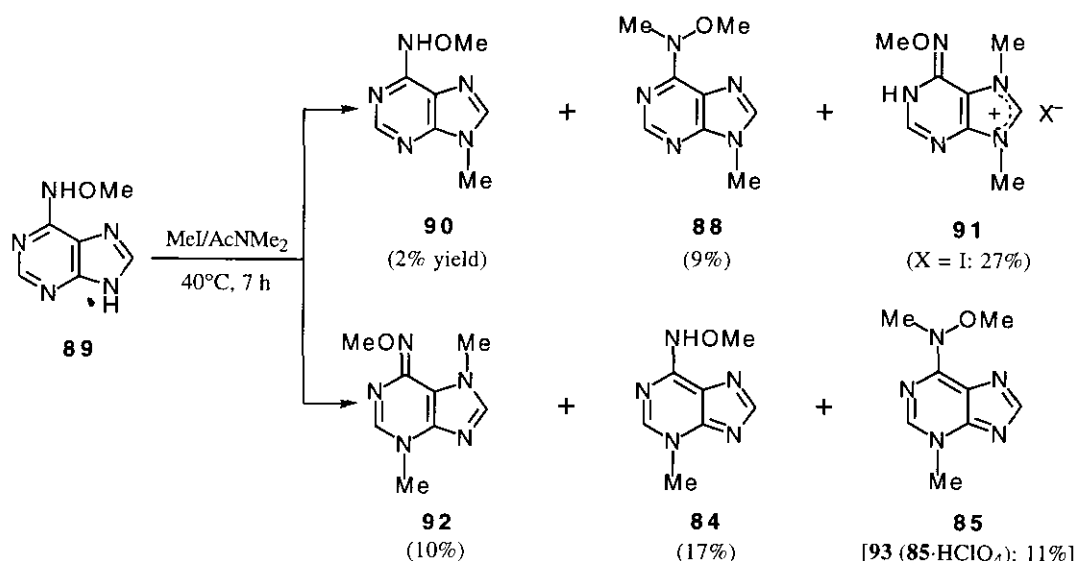


Scheme 15

Methylation of *N*⁶-methoxy-*N*⁶-methyladenine (**87**), prepared from 6-chloropurine (**25**) and *N,O*-dimethylhydroxylamine, with MeI in AcNMe₂ 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

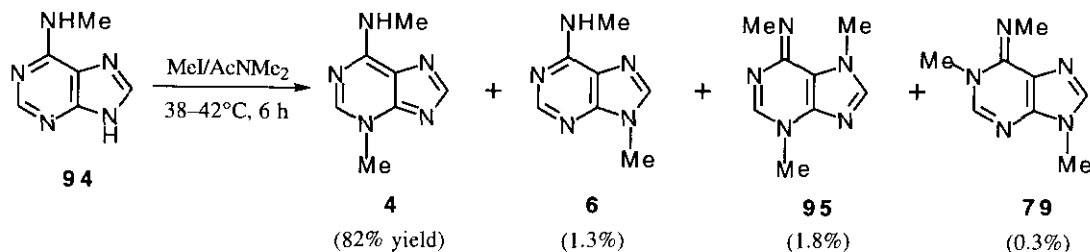
The *N*⁶-methoxy-*N*⁶,3-dimethyl derivative (**85**), isolated as the perchlorate (**93**), was also

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 AcNMe₂ 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 AcNMe₂ 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

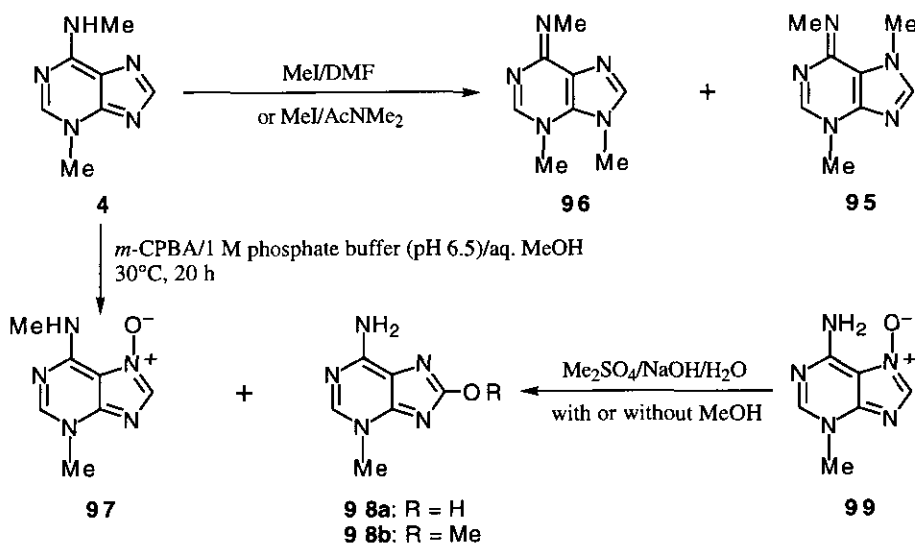


Scheme 17

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 H₂O (at various pH's)^{334,337} and in 95% aqueous EtOH;³³⁷ for **4**·HI in H₂O (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 AcNMe₂ at 38–40°C for 6 h, furnished **96**·HI (15% yield) and **95**·HClO₄ [29%, after treatment of the primary product (**95**·HI) with 70% aqueous HClO₄ 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



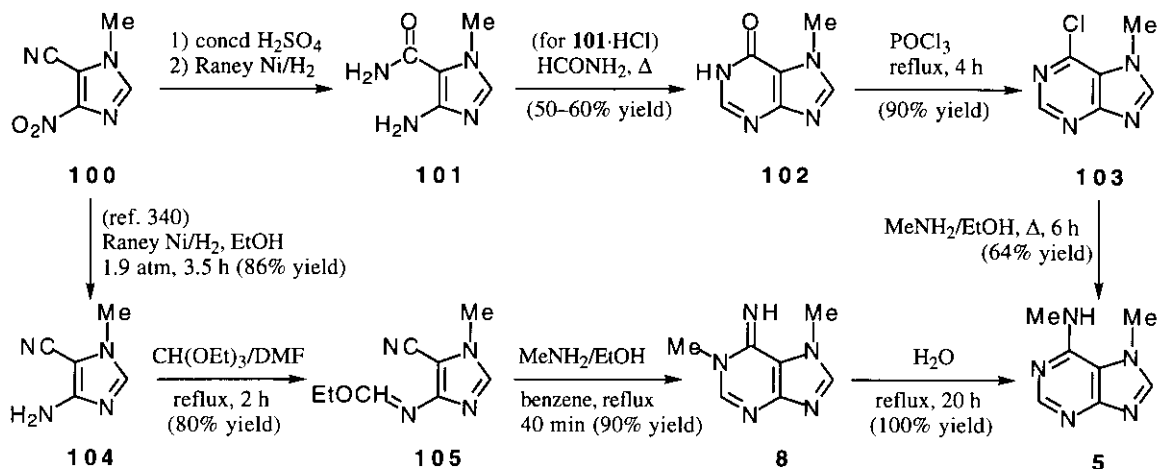
Scheme 18

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

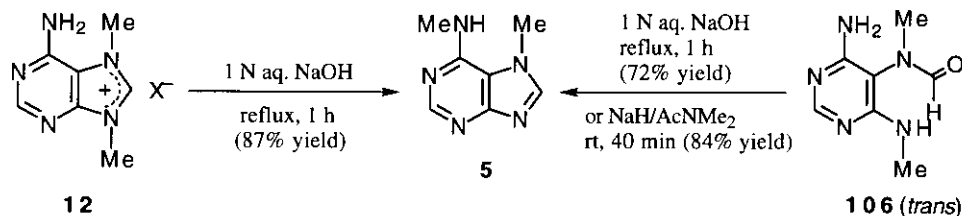
The first synthesis of *N*⁶,7-dimethyladenine (**5**), achieved by Prasad and Robins,³⁴⁰ started from 1-methyl-4-nitroimidazole-5-carbonitrile (**100**) and proceeded through 4-amino-1-methylimidazole-5-carboxamide (**101**), 7-methylhypoxanthine (**102**), and 6-chloro-7-methylpurine (**103**), as shown in Scheme 19. Alternatively, Taylor and Loeffler³⁴¹ synthesized **5** from the amino derivative (**104**)³⁴⁰ via the 4-ethoxymethylene-amino derivative (**105**), cyclization of **105** with MeNH₂ to form 1,7-dimethyladenine (**8**),

and the Dimroth rearrangement³²⁸ of **8** in boiling H₂O for 20 h. Fujii's group³⁴² found that similar treatment of **8** with boiling H₂O for 9.5 h afforded **5** (63% yield) as well as 1,7-dimethylhypoxanthine (**144**: R¹ = R² = 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 AcNMe₂ at rt for 40 min.³⁴³



Scheme 20

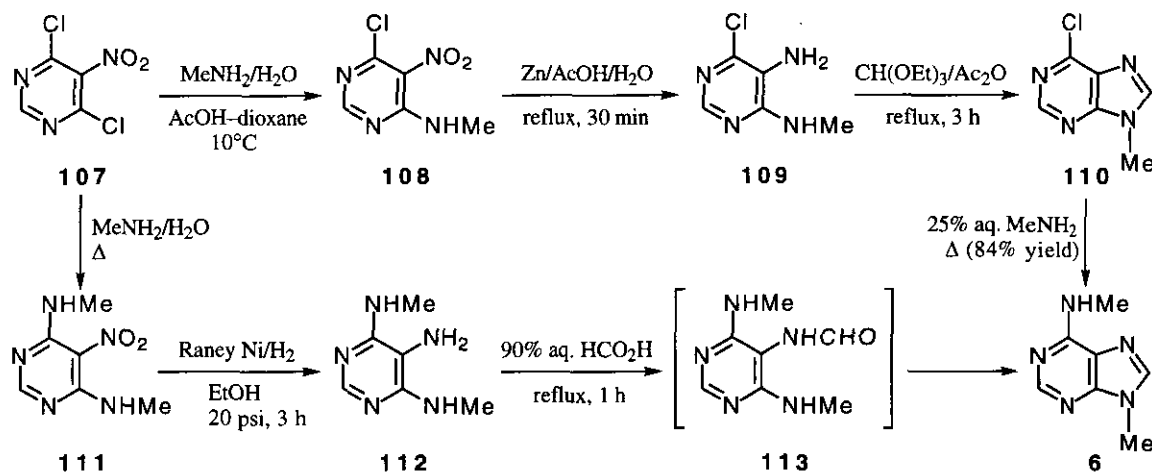
The following may serve to locate papers describing the physical properties and spectral characteristics of *N*⁶,7-dimethyladenine (**5**): the melting point for the free base (**5**), mp 300°C³⁴⁰ or 309–310°C³⁴³ or 311°C;³⁴¹ MS;¹⁹⁹ UV for the free base (**5**) in EtOH,^{340,341} in 95% aqueous EtOH,^{343b} and in H₂O (at various pH's);^{340,341,343b} for a 1:1 mixture of **5** and 1,3-dimethyluracil;³⁴⁴ ¹H NMR in CDCl₃.³⁴⁴

VI. *N*⁶,9-DIMETHYLADENINE

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

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

It was among a series of 15 *N*⁶-substituted 9-methyladenines assessed as antagonists of A₂-adenosine receptor-mediated stimulation of adenylate cyclase in membranes of human platelets and rat PC12 cells and of A₁-adenosine receptor-mediated inhibition of adenylate cyclases in membranes of rat fat cells and as inhibitors of binding of *N*⁶-[(*R*)-1-[³H]phenyl-2-propyl]adenosine to A₁-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 A₁-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

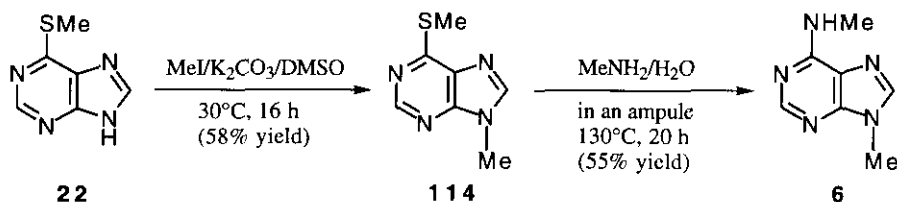


Scheme 21

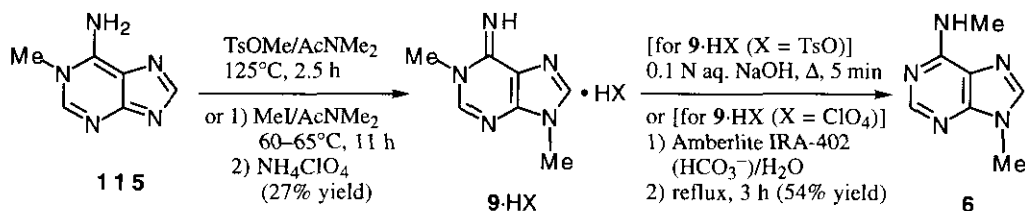
The synthesis of **6** by Robins and Lin³⁴⁹ started from 4,6-dichloro-5-nitropyrimidine (**107**) and proceeded through the 6-methylamino derivative (**108**), the 5-amino derivative (**109**), and 6-chloro-9-methylpurine (**110**) or through 4,6-bis(methylamino)-5-nitropyrimidine (**111**) and 4,6-bis(methylamino)-5-aminopyrimidine (**112**), as depicted in Scheme 21. Goldner and Carstens³⁵⁰ obtained **111** from **107** in 88% yield by amination with boiling ethanolic MeNH₂ for 45 min and cyclized **112**, prepared by reduction of **111** with Raney Ni catalyst and hydrogen in MeOH, by heating in boiling HCONH₂ for 20 min to secure **6** in 49% yield. Brown and Jacobsen³⁵¹ 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-workers³⁵² 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 MeNH₂ in EtOH at $25 \pm 1^\circ\text{C}$ to be of very low value ($<10^{-6} \text{ s}^{-1} \text{ M}^{-1}$).³⁵³

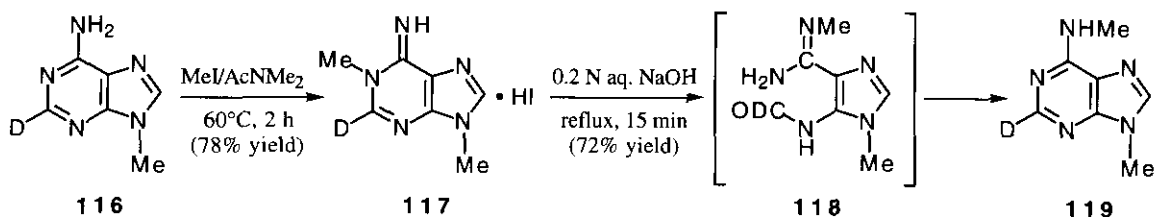


Scheme 22



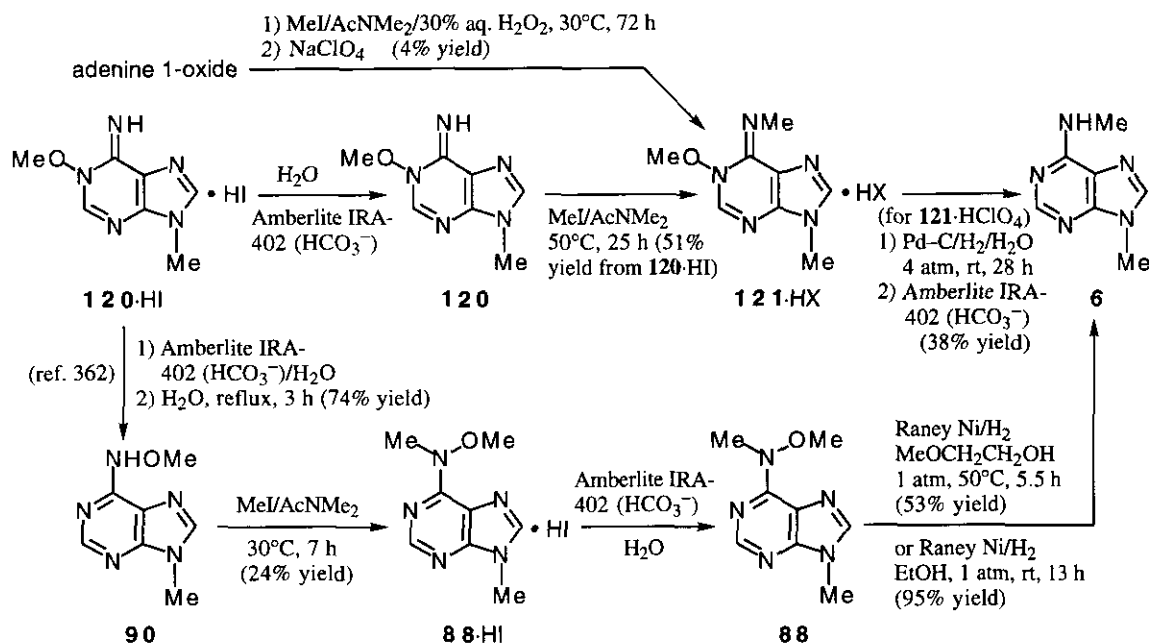
Scheme 23

Robins' group³²⁷ methylated 1-methyladenine (**115**)⁸ with methyl *p*-toluenesulfonate in AcNMe₂ at 125°C for 2.5 h to obtain 1,9-dimethyladenine *p*-toluenesulfonate [**9·HX** (X = TsO)], which underwent Dimroth rearrangement³²⁸ to afford **6** when heated in 0.1 N aqueous NaOH for 5 min (Scheme 23). Fujii's group³⁵⁴ methylated **115** with MeI in AcNMe₂ at $60\text{--}65^\circ\text{C}$ for 11 h and converted the resulting hydriodide [**9·HX** (X = I)] into the perchlorate [**9·HX** (X = ClO₄)] in 27% yield (from **115**). The perchlorate was then converted into the free base (**9**) by treating with Amberlite IRA-402 (HCO₃[−]), 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**) and the putative intermediate (**118**) 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 H₂O 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 group³⁵⁸ 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 AcNMe₂ at 38–42°C for 6 h.³³⁷



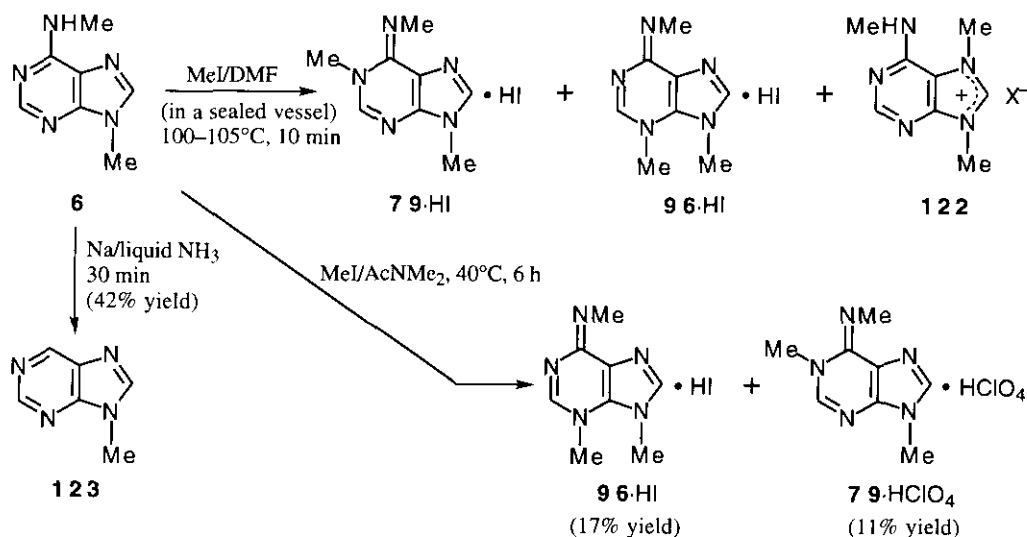
Scheme 25

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 AcNMe₂ 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 AcNMe₂ in the presence of 30% aqueous H₂O₂ also gave, after treatment of the product with NaClO₄, **121**·HClO₄ 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·HClO₄** with 10% Pd-C catalyst and hydrogen and treatment of the product with Amberlite IRA-402 (HCO₃⁻) 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 AcNMe₂ 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 (HCO₃⁻), 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 D₂O;^{223,368,374,380} H₂O vapor (hydration);²⁰⁴ butyric acid in CDCl₃ *via* hydrogen bonding;³⁶⁹ 1,3-dimethyluracil in H₂O³⁸¹ and in D₂O;³⁸²⁻³⁸⁴ 1,4- and 2,4-dimethyluracils in D₂O;³⁸⁴ poly(U) in H₂O;³⁸⁵ poly(5-bromouridylic acid) in H₂O;³⁸⁶ *p*-cresol in CDCl₃;³⁸⁷ diazepam in CDCl₃ and nitrazepam in CDCl₃;³⁸⁸ K₂PtCl₄ in 2.5 N aqueous HCl at 50°C for several hours to give Cl₃Pt(C₇H₁₀N₅)·H₂O, which reacted with aqueous NH₃ to produce *cis*-Cl₂Pt(C₇H₉N₅)(NH₃).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. N⁶,9-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 ₂ O at 20°C and ionic strength 0.01) ^{c)} (351); 4.02 ± 0.03 (H ₂ O 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 ₂ O (352); in H ₂ O at various pH's (349, 351, 354, 357); in 95% aq. EtOH (354)	
6-2-d (119)	In H ₂ O at various pH's and in 95% aq. EtOH	(356)
A 1:1 mixture of 6 and 1,3-dimethyluracil in H ₂ O		(344)
UV photoelectron spectrum		(210)
IR spectrum		(345, 367 ^{d)})
¹ H NMR spectrum		(345)
	In D ₂ O (223, 368); in CD ₃ OD (221); in MeOH (368); in DMSO- <i>d</i> ₆ (356); in CDCl ₃ (221, 352, 356, 369); in CCl ₄ (368); in liquid NH ₃ (370)	
6-2-d (119)	In DMSO- <i>d</i> ₆ and in CDCl ₃	(356)
¹³ C NMR spectrum		(345)
Crystal structure		(371, 372)
Dipole moment (in H ₂ O)	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 ₂ O	(374)
Partition coefficient	Between CHCl ₃ and H ₂ O	(375)
Partial specific volume	0.731 ml/g	(365)
Potential surface		(247)
Enthalpy of hydration		(204, 247–249)
Enthalpy of solution	In H ₂ O	(248, 249)
Enthalpy of sublimation		(248–250, 376)
Ionization potential		(210)
Electronic spectrum	Calculated by the CNDO/OPTIC-2 method	(377)
Electronic structure		(210)

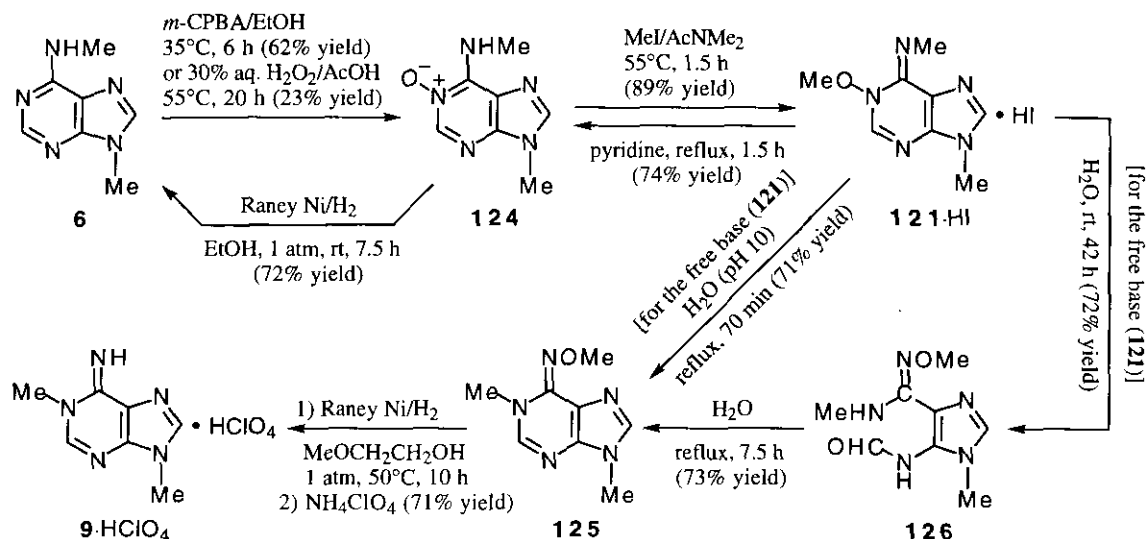
a) With or without reference number(s) in parentheses.

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)-CD₃, N(3)-CD₃, and N(7)-CD₃ species were similarly obtained by using CD₃I instead of MeI in the above reaction.³³⁰ Fujii's group³³⁷ isolated **96**·HI (17% yield) and **79**·HClO₄ (11% yield, after conversion from **79**·HI) from the reaction mixture obtained by methylation of **6** with MeI in AcN-Me₂ at 40°C for 6 h. Kos and van der Plas³⁸⁹ 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 NH₃ for 30 min.

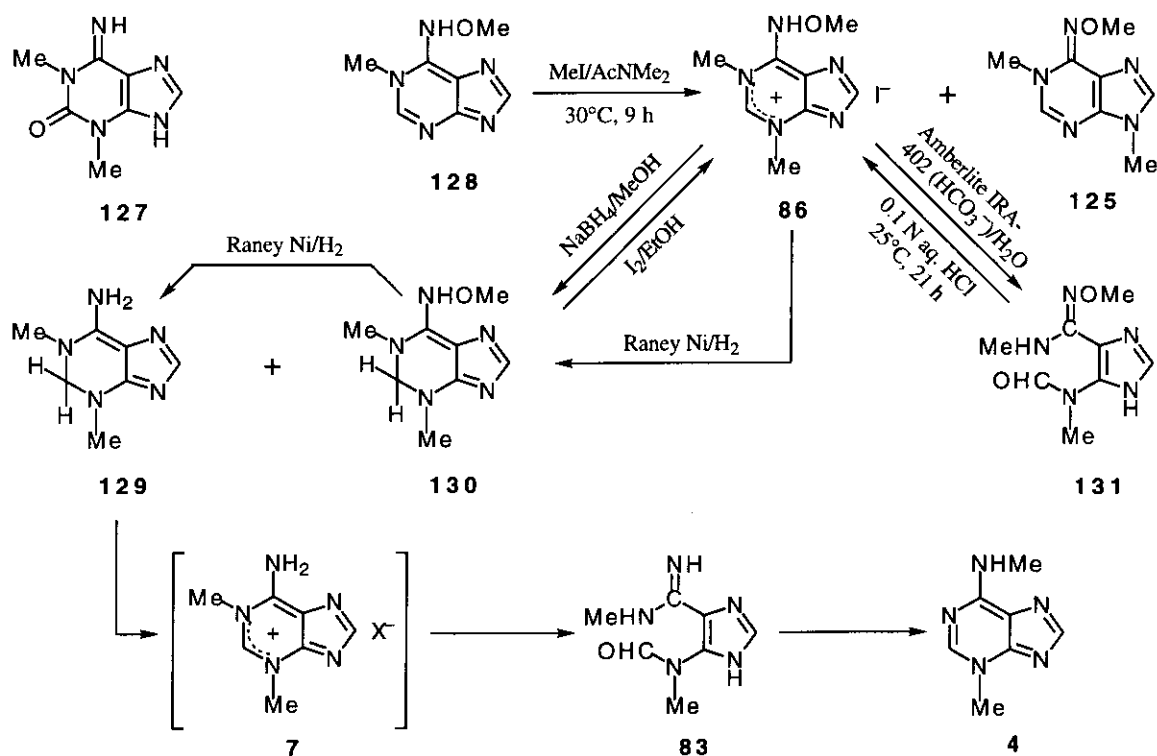


Scheme 27

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 H₂O₂ 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 AcNMe₂, 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**·HClO₄) (Scheme 25) to afford **6**. Treatment of the free base (**121**) with boiling H₂O 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 H₂O (pH 9) for 3 h.³⁵⁶ On the other hand, treatment of **121** with H₂O at rt for 42 h furnished the monocyclic compound (**126**) (72% yield), which recycled 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 group³⁶¹ 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

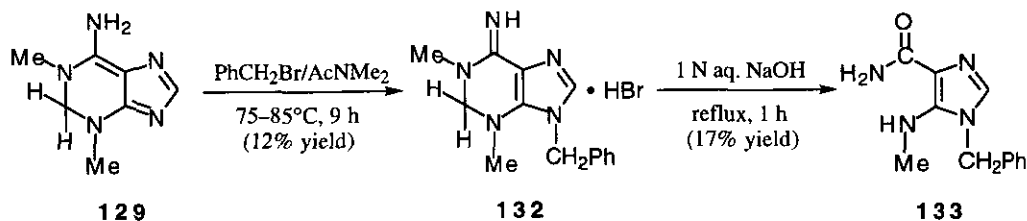
1,3-Dimethyladenine (**7**)⁷ occurs in nature as the 2-oxo derivative (1,3-dimethylisoguanine) (**127**), a new purine from the marine sponge *Amphimedon viridis*.³⁹¹ In their methylation study of adenosine (**76**) using dimethyl sulfate in DMF at 100°C for 2 h, Brookes and Lawley³⁹² isolated, after 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**: $\text{X} = \text{HSO}_4$)" 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-workers³³⁶ found that methylation of *N*⁶-methoxy-1-methyladenine (128) with MeI in AcNMe₂ 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·HClO₄ 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 NaBH₄ 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 CHCl₃ 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 H₂O 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 = ClO₄ for I) was determined instead.³³⁵ Treatment of 86 in H₂O with Amberlite IRA-402 (HCO₃[−]) at rt afforded the monocycle (131) in 92% yield. In H₂O at pH 7.72 (ionic strength 0.5) and 25°C, this ring opening proceeded at a rate of $1.36 \times 10^{-1} \text{ min}^{-1}$ (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: ClO₄[−] 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 H₂O 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

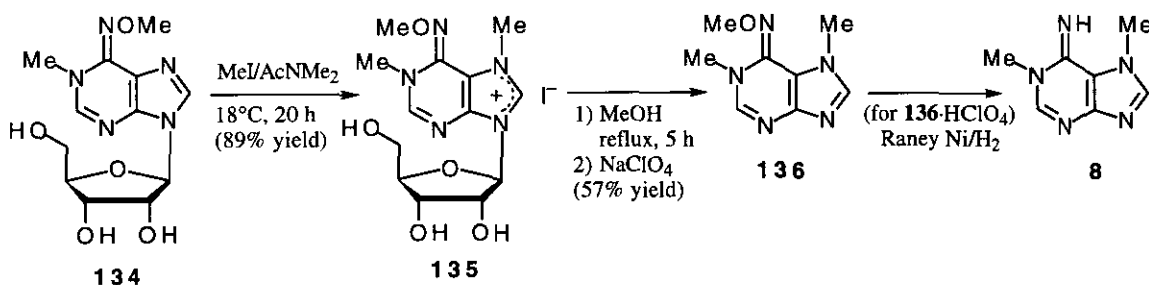


Scheme 29

VIII. 1,7-DIMETHYLADENINE

As regards the biological activity of 1,7-dimethyladenine (**8**), its inability in triggering either stimulation of $^{86}\text{Rb}^+$ 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 $^{24}\text{Na}^+$ 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

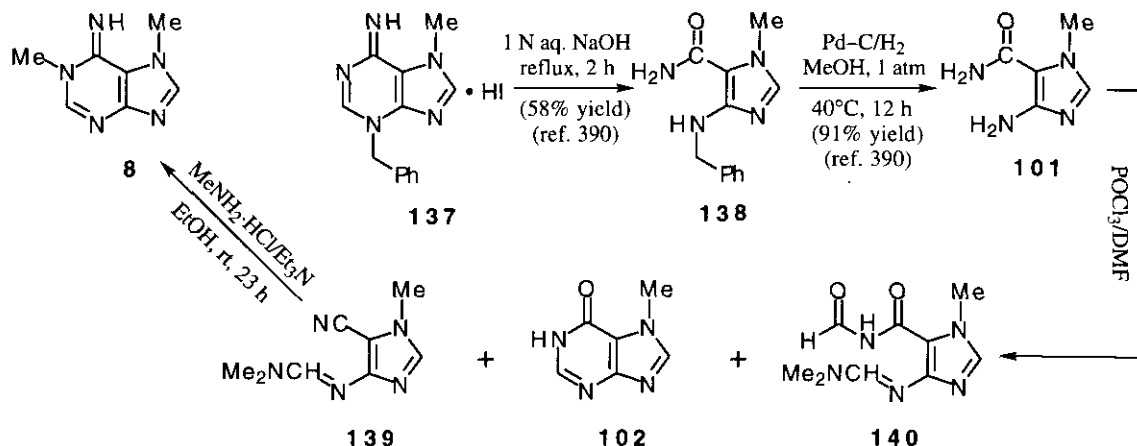
In 1960, Taylor and Loeffler³⁴¹ reported the synthesis of **8** from 4-amino-5-cyano-1-methylimidazole (**104**) through the 4-ethoxymethyleneamino derivative (**105**), as described in Section V (Scheme 19).



Scheme 30

In an alternative synthesis of **8** (Scheme 30), Fujii's group³⁹⁷ 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 ($\text{136}\cdot\text{HClO}_4$) of the aglycon in 57% yield when treated with boiling MeOH and then with NaClO_4 . The aglycon salt ($\text{136}\cdot\text{HClO}_4$) was then subjected to catalytic hydrogenolysis (Raney Ni/H_2 , H_2O , 1 atm, 20°C , 5 h), giving the desired compound ($\text{8}\cdot\text{HClO}_4$) in 47%

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

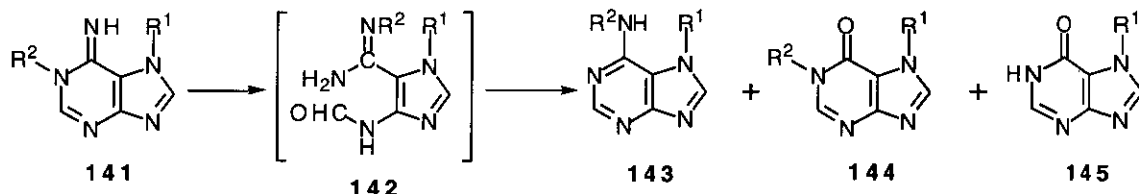


Scheme 31

In yet another synthesis of **8** (Scheme 31), Fujii's group³⁹⁸ treated 4-amino-1-methylimidazole-5-carboxamide perchlorate (**101**· HClO_4), which was obtainable³⁹⁰ from adenine (**1**) in four steps [via 3-benzyladenine, 3-benzyl-7-methyladenine hydride (**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 $\text{MeNH}_2\cdot\text{HCl}$ 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 $170\text{--}171^\circ\text{C}$;³⁴¹ for **8**· $3/5\text{H}_2\text{O}$, mp $163\text{--}168^\circ\text{C}$;³⁹⁸ for **8**· HCl (crude), mp $224\text{--}230^\circ\text{C}$ (decomp);³⁹⁸ for anhydrous **8**· HClO_4 , mp $278\text{--}280^\circ\text{C}$ (decomp);³⁹⁸ for **8**· $\text{HClO}_4\cdot 1/5\text{H}_2\text{O}$, mp $263\text{--}264^\circ\text{C}$ (decomp);³⁹⁷ $\text{p}K_a$ *ca.* 6.5³⁹⁶ or 6.50 ± 0.10 (in H_2O at $25 \pm 0.1^\circ\text{C}$);³⁹⁹ for **8**· HClO_4 , $\text{p}K_a$ 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**· $3/5\text{H}_2\text{O}$ in 95% aqueous EtOH and in H_2O (at pH 1, 7, and 13);³⁹⁸ for **8**· $\text{HClO}_4\cdot 1/5\text{H}_2\text{O}$ in 95% aqueous EtOH and in H_2O (at pH 1, 7, and 13);³⁹⁷ ^1H NMR for **8**· $3/5\text{H}_2\text{O}$ in $\text{DMSO}-d_6$,³⁹⁸ for **8**· $\text{HClO}_4\cdot 1/5\text{H}_2\text{O}$ in $\text{DMSO}-d_6$.³⁹⁷ Probably the most salient feature in the chemical behavior of 1,7-dimethyladenine (**8**) is that it undergoes Dimroth rearrangement³²⁸ 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 H₂O (Scheme 32). Thus, treatment of 1,7-dimethyladenine (**8**) (or **141**: R¹ = R² = Me) with boiling H₂O for 9.5 h gave N⁶,7-dimethyladenine (**5**) (or **143**: R¹ = R² = Me) (63% yield) as well as 1,7-dimethylhypoxanthine (**144**: R¹ = R² = Me) (3.5%).³⁴² For the concomitant deamination in the Dimroth rearrangement of **141**, Fujii's group³⁴² 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



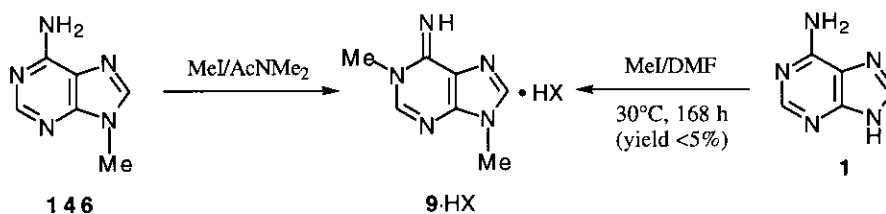
Scheme 32

IX. 1,9-DIMETHYLADENINE

There have been several papers dealing with the biological activity of 1,9-dimethyladenine (**9**). Dorée and Guerrier⁴⁰¹ 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 Dorée³⁹⁵ also reported that **9** did not show stimulation of $^{24}\text{Na}^+$ influx in fully grown prophase-blocked starfish oocytes. Yoshikuni *et al.*⁴⁰² found that **9** did not inhibit the specific binding of 1-[³H]methyladenine to cortices isolated from full-grown prophase-arrested oocytes of the starfish *Asterina pectinifera*.

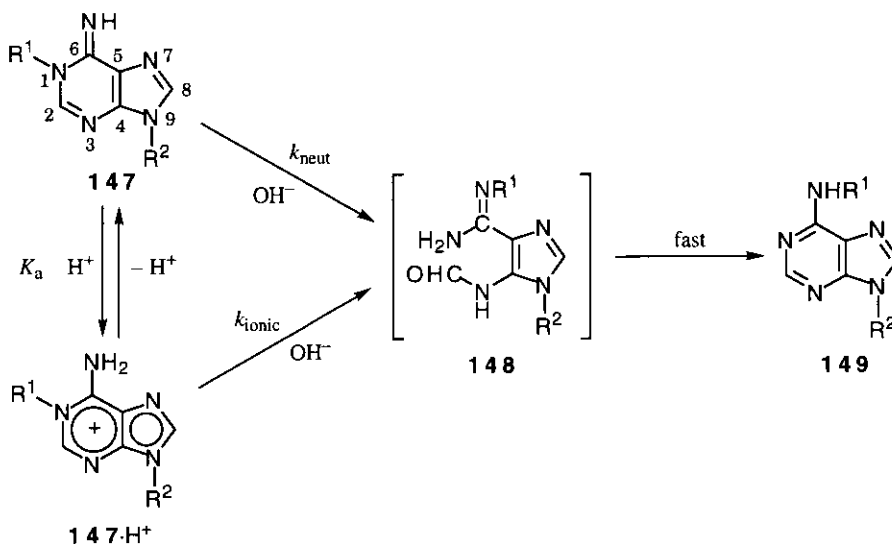
As regards the synthesis of **9**, methylation of 1-methyladenine (**115**)⁸ with methyl *p*-toluenesulfonate in AcNMe₂ to yield **9**·TsOH³²⁷ or with MeI in AcNMe₂ to yield **9**·HI (and **9**·HClO₄)³⁵⁴ is described above in Section VI (Scheme 23). The regioselectivity in

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' group³⁹⁹ conversely methylated 9-methyladenine (**146**)⁸ with MeI in AcNMe₂ 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 H₂O at pH 7–7.5³⁵⁸ or using trimethyl phosphate in H₂O at pH 9.5–10.0 and 37°C³⁵⁷ 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 Rasmussen⁴⁰⁶ 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**·HClO₄ 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

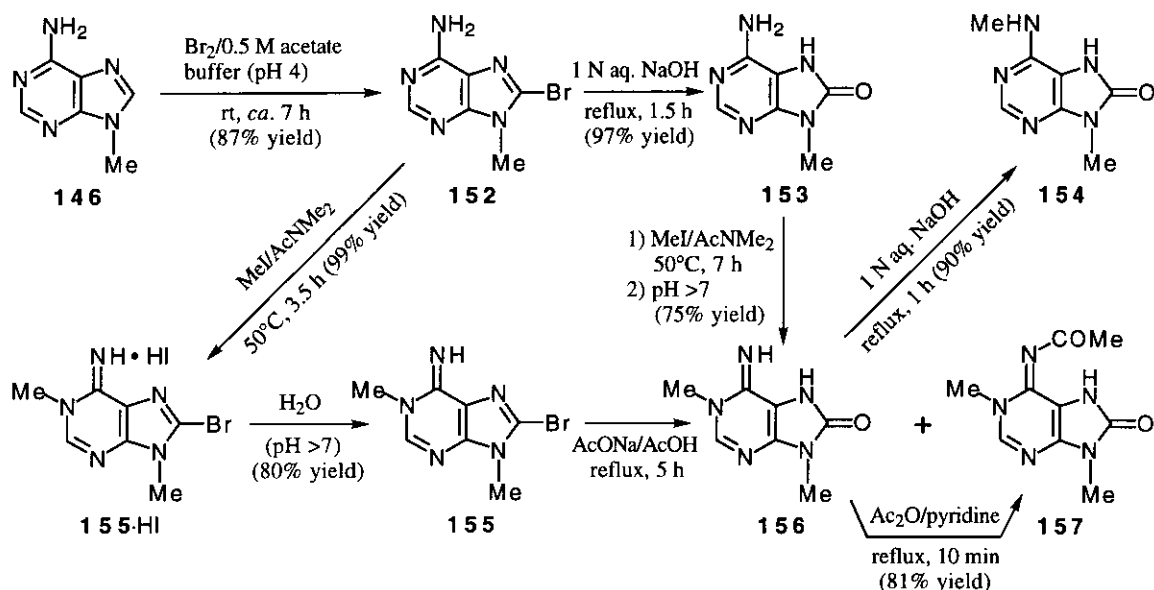
Item	Specification ^{a)}	Literature (ref. No.)
Melting point ^{b)}	Free base (9)	Not specified (399)
	9 ·HCl	Not specified (399, 408, 409)
	9 ·HI	277–278°C (decomp) (for a crude sample) (354); >310°C (410)
	9 ·HClO ₄	303–304°C (decomp) (354); not specified (399)
	9 ·TsOH	Not specified (327)
	9 -2- <i>d</i> -HI (117)	298–299°C (decomp) (356)
Acid dissociation constant		
	basic p <i>K</i> _a	9.03 ± 0.05 (H ₂ O at 25 ± 0.1°C) ^{c)} (399)
		9.08 ± 0.07 (for 9 ·HClO ₄ in H ₂ O 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 ₂ O and in dioxane	(399)
	9 ·HI	In 0.025 M phosphate buffer containing 10% EtOH (pH 7.1) (410)
	9 ·HClO ₄	In H ₂ O at various pH's and in 95% aq. EtOH (354)
	9 ·TsOH	In H ₂ O at various pH's (327)
	9 -2- <i>d</i> -HI (117)	In H ₂ O at various pH's and in 95% aq. EtOH (356)
IR spectrum	In CHCl ₃	(399)
¹ H NMR spectrum		(345)
	9 ·HClO ₄	In DMSO- <i>d</i> ₆ (356)
	9 -2- <i>d</i> -HI (117)	In DMSO- <i>d</i> ₆ (356)
¹³ C NMR spectrum		(345)
	9 ·HCl	In H ₂ O (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(NO₂)₂] in H₂O;⁴⁰⁹ **9**·HClO₄ with K₂PtCl₄ in

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

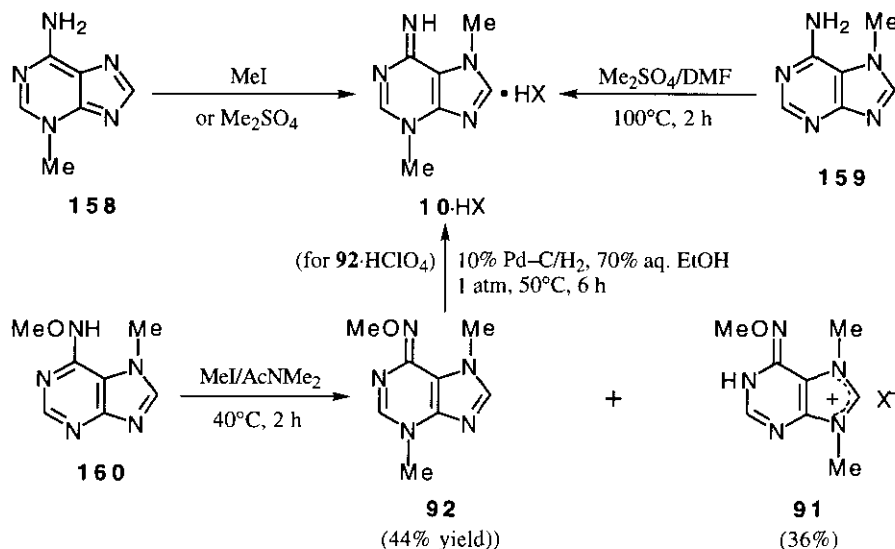
Fujii's group⁴¹⁶ was able to secure the free base (**156**) itself by two alternative syntheses starting from 8-bromo-9-methyladenine (**152**), which was obtainable from 9-methyladenine (**146**)⁸ by bromination (Scheme 36). The first route included methylation of **152** with MeI to give the 1-methylated 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' group³²⁷ 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·MeOSO₃H and that methylation of

7-methyladenine (**159**) with dimethyl sulfate in DMF at 100°C for 2 h produced 10·MeO-SO₃H, as identified by two-dimensional paper chromatography and UV spectroscopy (Scheme 37).



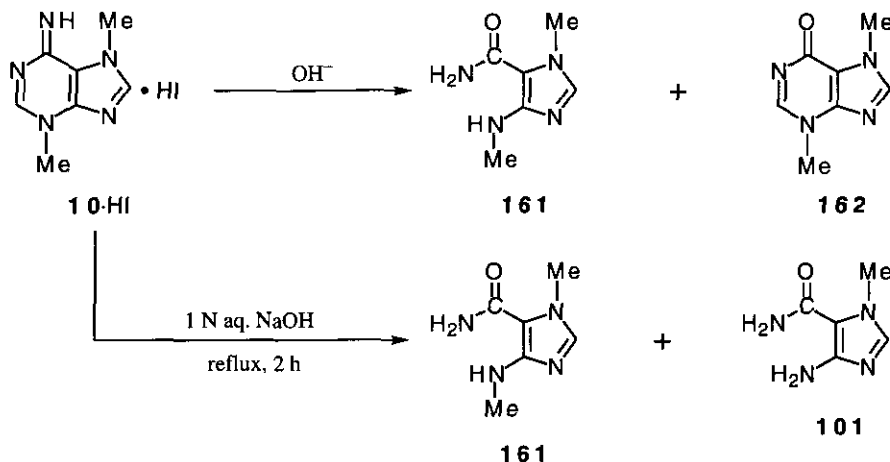
Scheme 37

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 Fujii⁴¹⁷ and by Montgomery and Thomas.⁴¹⁸ Fujii's group^{417c} methylated **158** with MeI in AcNMe₂ at 27°C for 5 h to secure **10·HI** in 67% yield. Yamauchi *et al.*³⁵⁷ methylated **158** with trimethyl phosphate in H₂O 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 Lawley³⁹² was shown to be 3,7-dimethyladenine (**10**).³²⁷

In yet another synthetic approach (Scheme 37), Fujii's group³³⁶ methylated *N*⁶-methoxy-7-methyladenine (**160**) with MeI in AcNMe₂ 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·HClO₄** using Pd–C catalyst and hydrogen afforded 3,7-dimethyladenine perchlorate (**10·HClO₄**) 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 $>300^\circ\text{C}$;^{327,417c} for **10·HClO₄**, mp $308\text{--}309^\circ\text{C}$ (decomp);³³⁶ for **10·H₂SO₄**, mp (not specified);³²⁷ for **10·MeOSO₃H**, mp (not specified);³²⁷ for **10·picrate**, mp 256°C ;³²⁷ paper chromatography for **10·HI**;³²⁷ TLC;³⁵⁷ MS;¹⁹⁹ UV in H₂O (at various pH's),³⁵⁷ for **10·HI** in H₂O (at various pH's) and

in MeOH,³²⁷ for **10**·HI in H₂O (at various pH's) and in 95% aqueous EtOH,^{417c} for **10**·HClO₄ in H₂O (at various pH's) and in 95% aqueous EtOH;³³⁶ nonfluorescent in H₂O (pH <7) at rt;⁴¹⁹ ¹H NMR for **10**·HI in DMSO-*d*₆.^{417c}



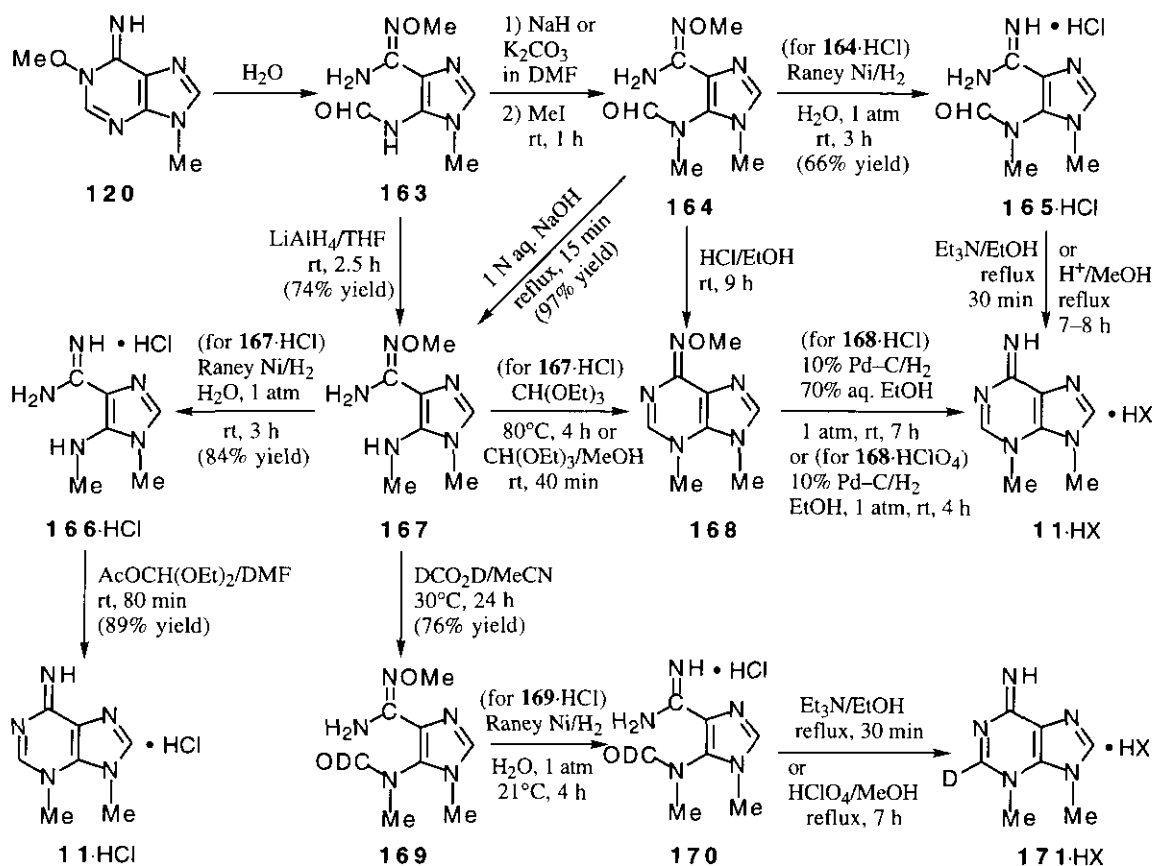
Scheme 38

As regards the chemical behavior of 3,7-dimethyladenine (**10**), Robins' group³²⁷ 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 group³⁹⁰ 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 derivatives⁴²¹ (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*-toluenesulfonate⁴²⁶ 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 DMF 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 K₂CO₃ 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/H₂, H₂O 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 HClO₄ in boiling MeOH for 7 h gave **11**·HCl or **11**·HClO₄ in 73% or 81% yield, respectively. Alternatively, **165**·HCl readily cyclized in boiling EtOH in the presence of 0.1 molar equiv. of Et₃N, furnishing **11**·HCl in 89% yield.

For the synthesis of 3,9-dimethyladenine-2-*d* (**171**), Fujii's group⁴²⁸ 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 H₂O containing one molar equiv. of HCl for 4 h, and cyclization of the resulting amidine hydrochloride (**170**) in boiling EtOH containing a little Et₃N 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 HClO₄ for 7 h, giving **171**·HClO₄ in 71% overall yield (from **169**).

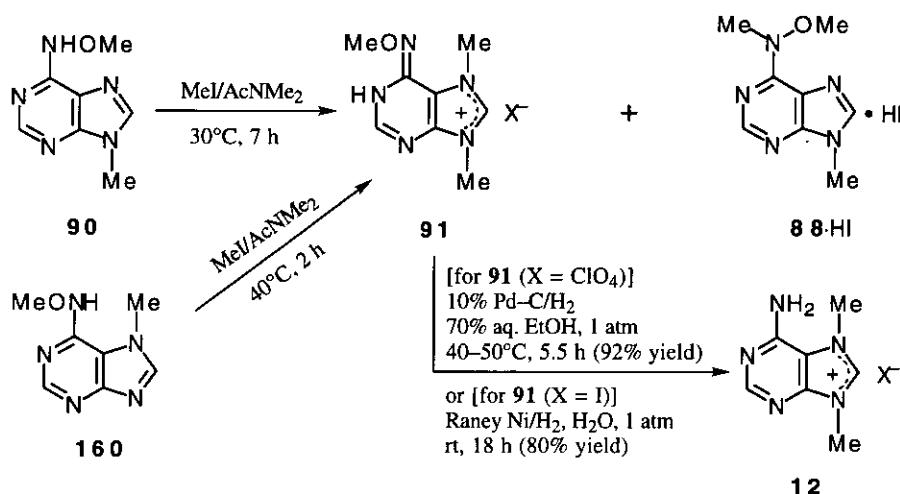
The following physical properties and spectral characteristics of 3,9-dimethyladenine (**11**) have been recorded in the literature: the melting point for **11**·HCl, mp 281–282°C (decomp);^{425b,c} for **11**·HClO₄, mp 333–334°C (decomp)^{425a} or mp >300°C;^{425b,c} for the bicarbonate salt (**11**·H₂CO₃), mp 161–162°C (decomp);^{425b,c} for **11**-2-*d*·HCl·1/2H₂O (**171**·HCl·1/2H₂O), mp 285.5–287.5°C (decomp);⁴²⁸ for **11**-2-*d*·HClO₄ (**171**·HClO₄), mp >300°C;⁴²⁸ UV for **11**·HCl,^{425b,c} for **11**·HClO₄,⁴²⁵ and for **11**·H₂CO₃^{425c} in H₂O (at various pH's) and in 95% aqueous EtOH; UV for **11**-2-*d*·HCl·1/2H₂O (**171**·HCl·1/2H₂O) and for **11**-2-*d*·HClO₄ (**171**·HClO₄) in H₂O (at various pH's) and in 95% aqueous EtOH;^{428b} ¹H NMR (DMSO-*d*₆) for **11**·HCl,^{425c,428} for **11**·HClO₄,^{425a,c,428} for **11**-2-*d*·HCl·1/2H₂O (**171**·HCl·1/2H₂O),⁴²⁸ and for **11**-2-*d*·HClO₄ (**171**·HClO₄);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 (HCO₃[−]) at rt. However, the substance isolated from the resulting solution in 97% yield was the bicarbonate salt (**11**·H₂CO₃), suggesting that the basicity of the free base is considerably high, in con-

Fujii's group⁴²⁸ reported that treatment of **11**·HClO₄ with NaBH₄ in MeOH at rt for 30 min furnished the 1,2-dihydro derivative (**172**) in 77% yield (Scheme 41); the NaBH₄ reduction of the 2-deuterated species (**171**·HClO₄) under similar conditions gave the corresponding 1,2-dihydro derivative (**173**) in 73% yield.

XII. 7,9-DIMETHYLADENINE

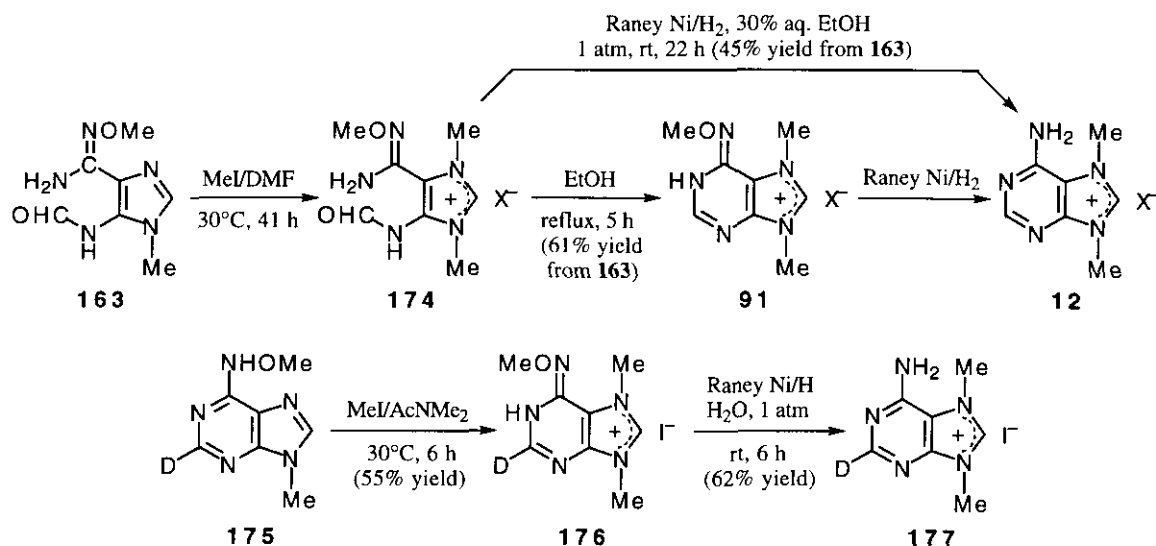
7,9-Disubstitution in the adenine series has been known to occur in nature in the form of agelasine (from the sea sponge *Agelas dispar*),⁴³⁰ agelasines A–F (from the Okinawan sea sponge *A. nakamurai*),⁴³¹ ageline A (agelasine F^{431c}) and ageline B (from a Pacific sea sponge *Agelas* sp.),⁴³² *epi*-agelasine 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 group³⁶³ reported the first synthesis of 7,9-dimethyladeninium perchlorate (**12**; X = ClO₄) (Scheme 42).



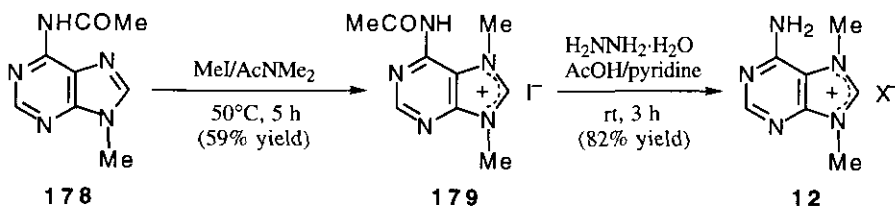
Scheme 42

The synthesis of **12** (X = ClO₄) started with methylation of *N*⁶-methoxy-9-methyladenine (**90**) with MeI in AcNMe₂ 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* = ClO₄)] (83% yield) and subsequent hydrogenolysis of **91** (*X* = ClO₄) using Pd-C catalyst and hydrogen^{336,363} or hydrogenolysis of **91** (*X* = I) in H₂O using Raney Ni catalyst and hydrogen⁴³⁷ gave **12** (*X* = ClO₄) 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



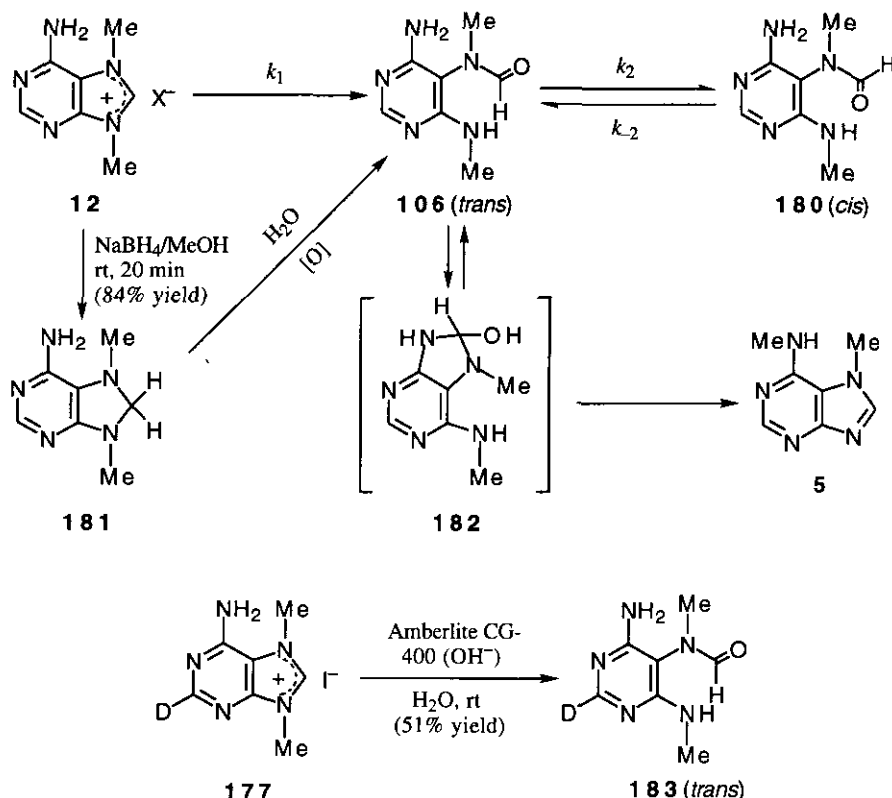
Scheme 44

In an alternative approach to 7,9-dimethyladeninium salts, Fujii's group³⁴³ 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 ClO₄) as shown above (Scheme 42), was obtained in 61% overall yield (from **163**). Alternatively, hydrogenolysis (Raney Ni/H₂) 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 group⁴⁴⁰ 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 H₂O (at various pH's) and in 95% aqueous EtOH;^{336,363} UV for **12** ($X = I$) in H₂O (at various pH's),^{437b} in 95% aqueous EtOH,^{437b} and in MeOH;^{440b} for **12-2-d** ($X = I$) (**177**) in H₂O (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}

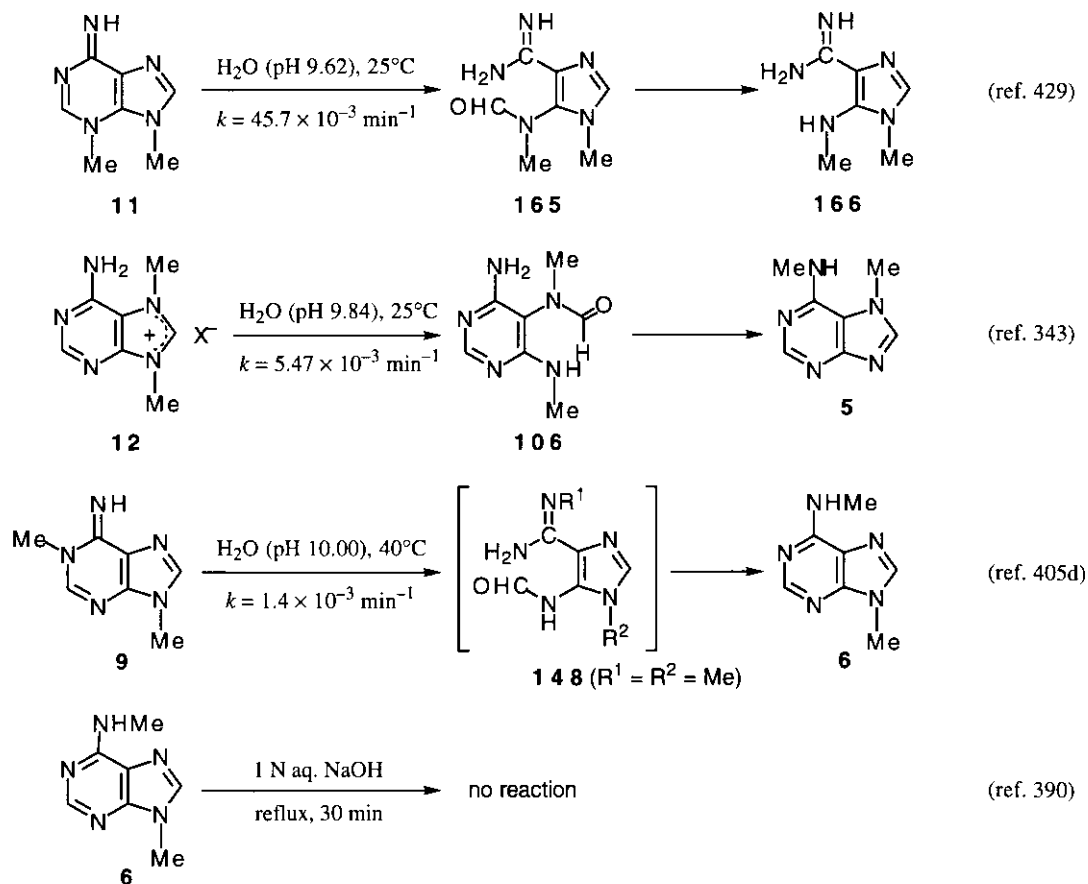


Scheme 45

As regards the chemical behavior of 7,9-dimethyladeninium salt (**12**), Fujii's group³⁴³ 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** ($\text{X} = \text{I}$) rearranged to *N*⁶,7-dimethyladenine (**5**) in 87% yield. Similar treatment of **106** or treatment of **106** with NaH in AcNMe₂ 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 H₂O, in D₂O 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 $k_1 = 5.47 \times 10^{-3} \text{ min}^{-1}$, $k_2 = 1.49 \times 10^{-3} \text{ min}^{-1}$, and $k_{-2} = 0.84 \times 10^{-3} \text{ min}^{-1}$ were obtained for **12** ($\text{X} = \text{ClO}_4$) $\rightarrow$ **106** $\rightleftharpoons$ **180** in H₂O at pH 9.84, 25°C, and ionic strength 0.50.³⁴³



Scheme 46

Fujii's group³⁴³ further reported that the NaBH₄ reduction of **12** (X = I) in MeOH at rt furnished the 7,8-dihydro derivative (**181**) in 84% yield. In H₂O at 60°C, **181** slowly decomposed to give the ring-opened derivative (**106**) in 49% yield. The results of the NaBH₄ 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.

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