N^x-OXYGENATED ADENINES: THEIR CHEMISTRY, PHYSICOCHEMICAL PROPERTIES, AND BIOLOGICAL ACTIVITIES

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Abstract —— 6-Hydroxyaminopurine (**2**), 6-nitrosopurine (**3**), 6-nitropurine (**4**), adenine 1-oxide (**5**), adenine 3-oxide (**6**), adenine 7-oxide (**7**), and 9-hydroxyadenine (**8**) may be accepted as members of the N^x-oxygenated adenine family. The chemistry, physicochemical properties, and biological activities of these N^x-oxygenated adenines are reviewed with 214 reference citations.

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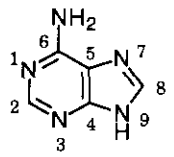
I. INTRODUCTION

Adenine (**1**) is a biologically significant fundamental heterocycle, which has a bicyclic ring system consisting of a 4-aminopyrimidine and an imidazole ring in juxtaposition.[1] Because it carries one exocyclic and four endocyclic nitrogen atoms at the N^6-, 1-, 3-, 7- and 9-positions, seven basic kinds of *N*-oxygenated derivative are possible in principle, regardless of their tautomeric form problems.

All these N^x-oxygenated adenines have been known by chemical synthesis in the form of 6-hydroxyaminopurine (**2**), 6-nitrosopurine (**3**), adenine 1-oxide (**5**), adenine 3-oxide (**6**), adenine 7-oxide (**7**), and 9-hydroxyadenine (**8**); with the exception that 6-nitropurine (**4**) still remains unknown.

Thus, the chemistry, physicochemical properties, and biological activities of N^x-oxygenated adenines have been treated in previous reviews in several forms.[1–7] The aim of the present review is to supplement the previous ones by reorganizing (in part) and updating the literature through the late part of 1998. Certainly, the chemistry and reactions of the seven N^x-oxygenated adenines (**2**–**8**) highlighted below will carve out a unique

and impressive niche in the purine chemistry.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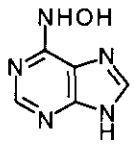
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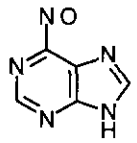
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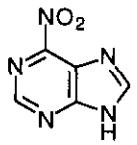
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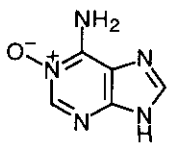
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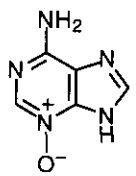
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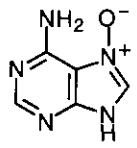
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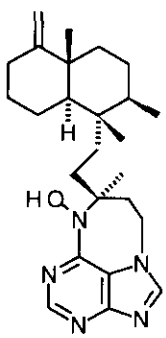
II. 6-HYDROXYAMINOPURINE

The N^6-hydroxyadenine structure has recently been shown to occur in nature in the form of asmarines A–C (**9**–**11**), novel cytotoxic metabolites isolated from the Red Sea sponge *Raspailia* sp.[8] The prototype of such N^6-hydroxyadenine structures is 6-hydroxyaminopurine (**2**), whose synthesis was first reported by Bendich *et al.* in 1957. They allowed 6-chloropurine (**12**) to react with hydroxylamine in boiling EtOH for 6 h,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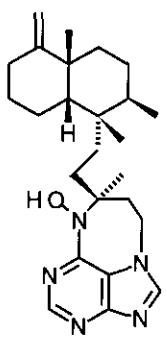
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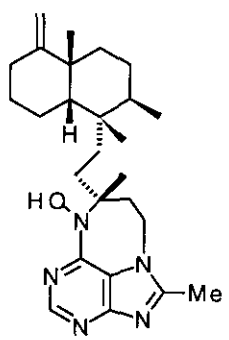
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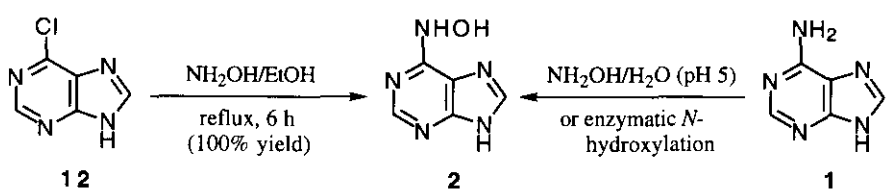
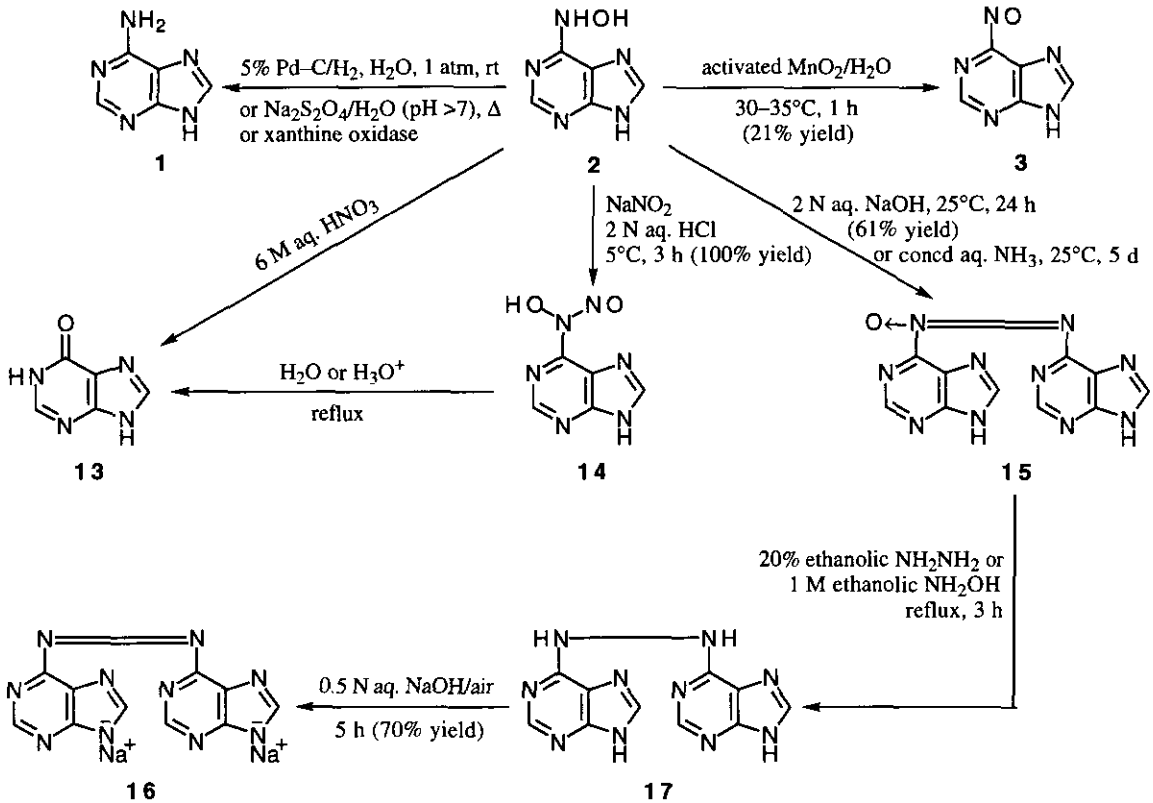


12 **2** **1**

Scheme 1

obtaining **2** in 95%–quantitative yield (Scheme 1).[9] The reaction of adenine (**1**) with hydroxylamine to form **2** was known to proceed much more slowly than that of cytosine to give N^4-hydroxycytosine.[10] The same type of replacement of the amino group at the adenine nucleoside and nucleotide levels has been investigated.[10,11] Clement and Kunze[12] reported the hepatic microsomal *N*-hydroxylation of **1** to **2**, which proceeded *in vitro* by aerobic incubations with 3-methylcholanthrene- or isosafrole-induced microsomal fractions of rat liver homogenates and NADPH.

The following physicochemical properties of 6-hydroxyaminopurine (**2**) have been reported in the literature: the melting point, mp 260°C (decomp)[9b] or mp 254°C (decomp);[9a] solubility in H_2O at 20 ± 2°C;[9] pK_a 3.80, 9.83, and >12 (in H_2O);[9] pK_a 12.7 (in DMSO);[13] TLC;[12] HPLC;[12,14] UV in H_2O at various pH's;[9,15] distribution of the spin density on atoms of the exocyclic N–OH group in the lower triplet state;[16] electronic structure.[17]

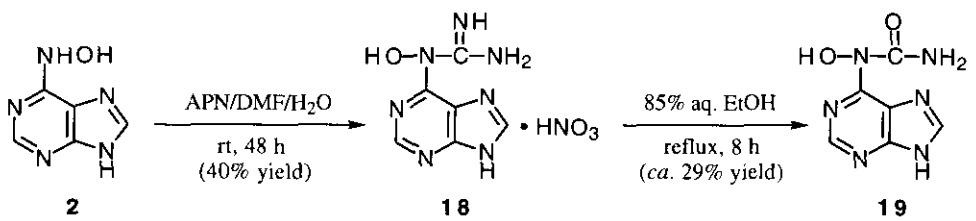


Scheme 2

Bendich *et al.* reported that 6-hydroxyaminopurine (**2**) was soluble in AcOH and insoluble in the usual organic solvents;[9b] it was not recrystallized easily from H_2O since it decomposed on boiling to give a deeply colored solution;[9b] this decomposition, probably due to oxidation, was more rapid in the presence of charcoal;[9b] **2** reduced alkaline phos-

phomolybdate reagent as well as ammoniacal silver nitrate,[9] and produced a deep blue color when mixed with a dilute solution of ferric chloride;[9b] although **2** was quite stable in 1 N aqueous HCl[9a] and was not altered by the action of concd aqueous HCl or HF even after prolonged contact at 10°C, it was rather unstable at values of pH above 9.[9] Reduction of **2** to adenine (**1**) was achieved by catalytic hydrogenolysis in H_2O at room temperature using hydrogen and 5% Pd–C catalyst[9] or by heating with an alkaline solution of sodium dithionite (Scheme 2).[9b] This reduction to **1** was also feasible by xanthine oxidase (EC 1.2.3.2) from both rat and rabbit liver cytosolic fractions or from cow milk.[14] Oxidation of **2** in H_2O containing AcONa with activated MnO_2 at 30–35°C for 1 h furnished 6-nitrosopurine (**3**) in 21% yield.[18]

On treatment with 6 M aqueous HNO_3, **2** strongly effervesced to give hypoxanthine nitrate (**13**·HNO_3).[9b] Nitrosation of **2** in 2 N aqueous HCl with aqueous $NaNO_2$ at 5°C for 3 h produced 6-(*N*-nitroso)hydroxyaminopurine (**14**), which showed an inhibitory activity against several mouse tumors and leukemias, in quantitative yield,[18] and **14** was converted into hypoxanthine (**13**) when boiled in H_2O or in aqueous acid solutions.[18] Exposure of **2** to 2 N aqueous NaOH at 25°C for 24 h afforded the disodium salt of 6,6'-azoxypurine (**15**), and treatment of the salt with AcONa and 20% aqueous AcOH gave the free base (**15**) in 61% yield (from **2**).[18] The dipotassium salt of **15** was also obtainable in 37% yield by similar treatment of **2** with 2 N aqueous KOH.[18] A suspension of **2** in concd aqueous NH_3 yielded **15** (57% yield) after standing at 25°C for 5 d.[18] The azoxy compound (**15**) was reduced to N^6,N^6-bisadenine (**17**) by refluxing with 20% ethanolic hydrazine or 1 M ethanolic hydroxylamine for 3 h, and air oxidation of **17** in 0.5 N aqueous NaOH for 5 h afforded 6,6'-azopurine disodium salt (**16**) in 70% yield.[18]



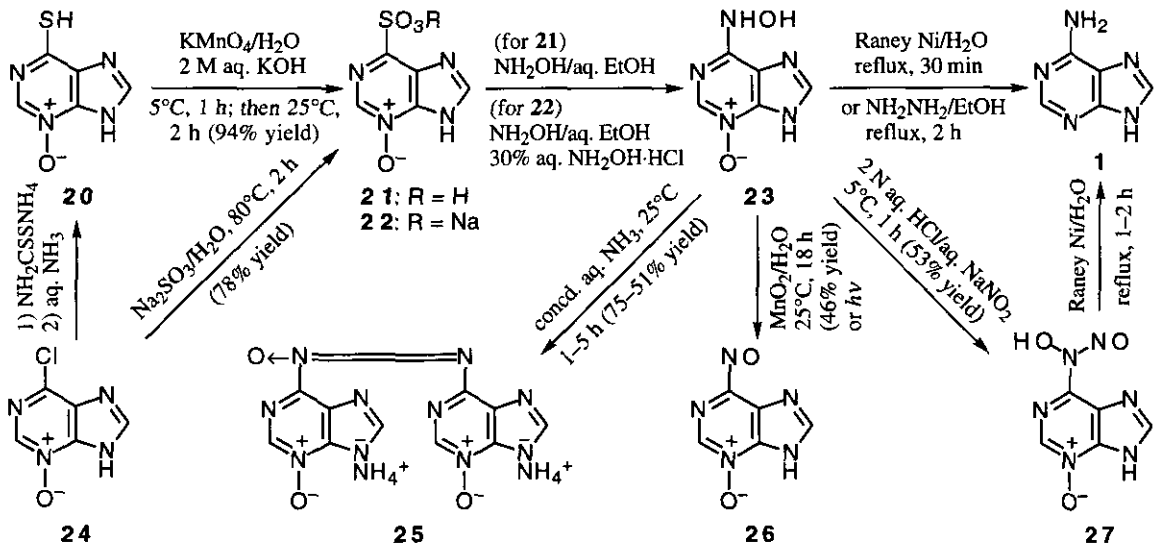
APN = 1-amidino-3,5-dimethylpyrazole nitrate

Scheme 3

As shown in Scheme 3, treatment of **2** with 1-amidino-3,5-dimethylpyrazole nitrate in aqueous DMF at room temperature for 48 h gave 6-(1-hydroxyguanidino)purine nitrate (**18**) in 40% yield.[19] Catalytic hydrogenolysis of **18** (10% Pd–C/H_2, MeOH, 1 atm, room temperature, 16 h) provided adenine nitrate (**1**·HNO_3) in 99% yield, and treatment of **18** with boiling 85% aqueous EtOH for 8 h produced 6-(1-hydroxyureido)purine (**19**) in *ca.* 29% yield.[19] Treatment of **2** or its triacetyl derivative with a variety of oxidizing agents (AcO_2H, CF_3CO_3H, and *m*-CPBA) resulted in no reaction, or the formation of hypoxan-

thine (**13**).[20]

The 3-oxide (**23**) of **2** was prepared from 6-chloropurine 3-oxide (**24**) as delineated in Scheme 4. Treatment of **24** with ammonium dithiocarbamate in EtOH at 65°C for 2 h, followed by treatment of the reaction product with aqueous NH_3, gave 6-mercaptopurine 3-oxide (**20**) in 88% yield.[21] Oxidation of **20** with aqueous $KMnO_4$ in 2 M aqueous KOH at 5°C for 1 h and then at 25°C for 2 h afforded purine-6-sulfonic acid 3-oxide (**21**) in 94% yield.[21] The sodium salt (**22**) was prepared from **24** in 78% yield by treatment with sodium sulfite in H_2O at 80°C for 2 h.[20] Stirring a mixture of **21** and ethanolic NH_2OH in H_2O at 25°C for 4–5 d[21] or stirring a mixture of **22** and 0.6 M ethanolic NH_2OH in H_2O containing a little 30% aqueous NH_2OH·HCl at 25°C for 15 d[20] furnished **23** in 72% or 59% yield, respectively. However, treatment of **24** with ethanolic NH_2OH gave 6-hydroxyaminopurine (**2**).[20] Reduction of **23** with Raney Ni in boiling H_2O for 30 min or with boiling 20% ethanolic hydrazine for 2 h gave adenine (**1**).[20] The 3-oxide (**23**) reacted in concd aqueous NH_3 at 25°C for 1 or 5 h to form 6,6'-azoxypurine 3,3'-dioxide diammonium salt (**25**) in 75%[20] or 51%[21] yield, respectively. The azoxy compound (**25**) was transformed to N^6,N^6-bisadenine (**17**) upon treatment with Raney Ni in boiling H_2O for 30 min.[20] Oxidation of **23** with activated MnO_2 in H_2O at 25°C for 18 h gave 6-nitrosopurine 3-oxide (**26**) (46% yield),[22] which was also spontaneously formed from **23** by exposure to diffused light for 30 months.[22] Nitrosation of **23** in 2 N aqueous HCl with aqueous $NaNO_2$ at 5°C for 1 h furnished 6-(*N*-nitrosohydroxyamino)purine 3-oxide (**27**) in 53% yield.[22] When treated with Raney Ni in boiling H_2O for 1–2 h, **27** gave a solution containing exclusively adenine (**1**).[22]



Scheme 4

Apparent association constants of complexes of riboflavin with 6-substituted purines including 6-hydroxyaminopurine (**2**) have been measured.[23] The interactions between

lima bean lectin and adenine (**1**) were examined using a series of synthetic purine analogues including **2**.[24] The use of **2** in an oligonucleotide primer for DNA sequencing or polymerase chain reactions has been applied for a patent.[25]

As regards the biological activities of 6-hydroxyaminopurine (**2**), it was found to be toxic to cells of mouse sarcoma 180 in tissue culture as seen in mitotic inhibition and induction of nuclear degeneration when compared with normal embryo skin fibroblasts over a concentration range of 0.001 to 0.1 mM;[9,26] it prolonged the survival time of mice with transplanted sarcoma 180 ascites cells,[27] or leukemia L1210 or P815;[28] it blocked the conversion of inosinate into adenylate and guanylate in Ehrlich ascites cells.[29] Addition of 0.2% adenine (**1**) to a partially purified diet prior to the injection of **2** into mice bearing implants of sarcoma 180 ascites cells resulted in a decrease in the inhibition produced by this agent.[30] Application of higher doses (>10–10^3 IU/kg) of L-asparaginase to leukemic mice resulted in longer survival times and many 50-day survivors, and **2** potentiated the effect of this enzyme.[31] The 3-oxide (**23**) was reported to be weakly toxic to mice, to cause very slight inhibition of leukemia L5178Y/Ca55, and to prolong slightly the survival time of mice with leukemia LE1210S.[20] Duality of the anticancer and carcinogenic effects in mice with L1210 leukemia and in rats, respectively, of **2** and its 3-oxide (**23**) has been studied.[32]

Investigated also were mutagenic activities of **2** (and **23**) in the following microorganisms, mammalian cells *in vitro*, or mammalian bodies: phage T_4 (grown in *Escherichia coli* bacteria B-Berkeley);[33] *E. coli*;[34–38] (of **23** in *E. coli*);[36] *Salmonella typhimurium*;[34, 35,39–42] *Bacillus subtilis*;[43] *Streptomyces antibioticus*;[43] *Candida maltosa*;[44] *C. tropicalis*;[45] *Chlamydomonas reinhardii*;[46] *Neurospora crassa*;[47–49] *Aspergillus nidulans*;[50–52] *Saccharomyces cerevisiae*;[34,35,38,39,43,53–70] L5178Y mouse lymphoma cells;[71,72] Chinese hamster cells;[73] Syrian hamster embryo cells;[74,75] *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-resistant HeLa cells;[76] teratogenic effects on rats[77,78] and on pregnant Wistar rats.[79] A review on the mutagenic nucleic acid base analogues including **2** has appeared.[80]

Miller *et al.*[81] reported that **2** was able to serve as a substrate for adenine nucleoside phosphorylase from extracts of epimastigotes of the Peru strain of *Trypanosoma cruzi*. The compound (**2**) was reported to inhibit the enzyme adenine phosphoribosyltransferase from Ehrlich ascites tumor cells[82] and from monkey liver,[83] and correlation between structure and activity with purine derivatives as inhibitors of this enzyme was studied.[84] Bach and Fellig[85] reported that **2** weakly stimulated the respiration of *Chlorella vulgaris*.

III. 6-NITROSOPURINE

6-Nitrosopurine (**3**) was first synthesized by Giner-Sorolla[18] from 6-hydroxyaminopurine (**2**) by oxidation with activated MnO_2 (see Section II and Scheme 2). It gave a posi-

tive Liebermann test (nitroso function) and negative ferric chloride and phosphomolybdate tests (absence of NHOH function).[18] Treatment of **3** with Raney Ni in boiling 5% aqueous NH_3 for 3 h produced adenine (**1**) and hypoxanthine (**13**).[18] When **3** was heated with a 1 M solution of NH_2OH in 95% aqueous EtOH at reflux for 1 h, the UV spectra and paper chromatography showed that the reaction product contained a mixture of adenine (**1**) and hypoxanthine (**13**).[18] Similar treatment of **3** with 20% ethanolic hydrazine gave **1** and unidentified products.[18] On treatment with aniline at 110–120°C for 2 h, **3** afforded a crude product with UV spectral and chromatographic properties identical to those of **1**.[18] Heating **3** in 1 N aqueous HCl at 80°C for 1 h gave **13**, together with unidentified products.[18] Some derivatives of **3**, such as 6,6'-azoxypurine (**15**), 6,6'-azoxypurine 3,3'-dioxide diammonium salt (**25**), and 6-nitrosopurine 3-oxide (**26**) have been synthesized as described in Section II (Schemes 2 and 4).

The following physicochemical properties of 6-nitrosopurine (**3**) have been reported in the literature: the melting point, mp 195°C (with explosion when inserted at 185°C);[18] solubility in H_2O, 155 mg/L at 25 ± 1°C;[18] UV in H_2O at pH 1, 6.8, and 13.[18]

The compound (**3**) did not exhibit inhibition of mouse leukemia L1210, sarcoma 180 (ascites), Ridgway osteogenic sarcoma, and Murphy–Sturn lymphosarcoma.[18]

IV. 6-NITROPURINE

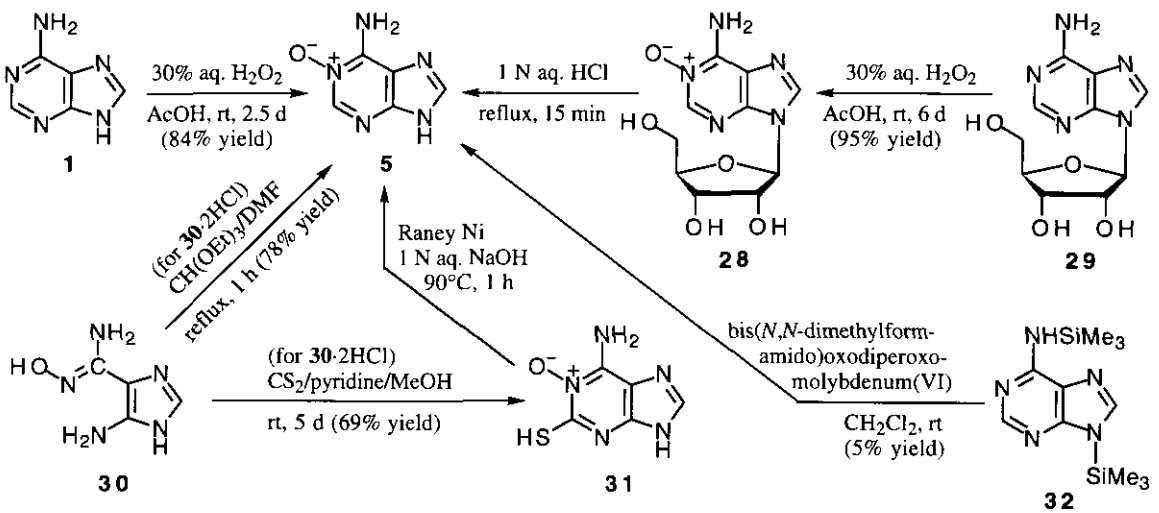
To the best of our knowledge, 6-nitropurine (**4**) is an N^6-oxygenated adenine hitherto unknown to exist. However, Boerth and Harding[86] have reported the results of semiempirical (INDO) and *ab initio* (STO-3G) molecular orbital calculations performed on the neutral, N(7)-protonated, and C(8)-deprotonated species of **4**.

V. ADENINE 1-OXIDE

Adenine 1-oxide (**5**) was first synthesized by Brown and co-workers,[87] who treated a solution of adenine (**1**) in AcOH with 30% aqueous H_2O_2 at room temperature for 2.5 d to obtain **5** in 84% yield (Scheme 5). Similar *N*-oxidation of **1** in AcOH at 65°C for 48 h and that of **1** in H_2O with 0.002% aqueous H_2O_2 at 37°C were also reported.[88] The structure of **5** was established by means of degradation reactions (*vide infra*).[89]

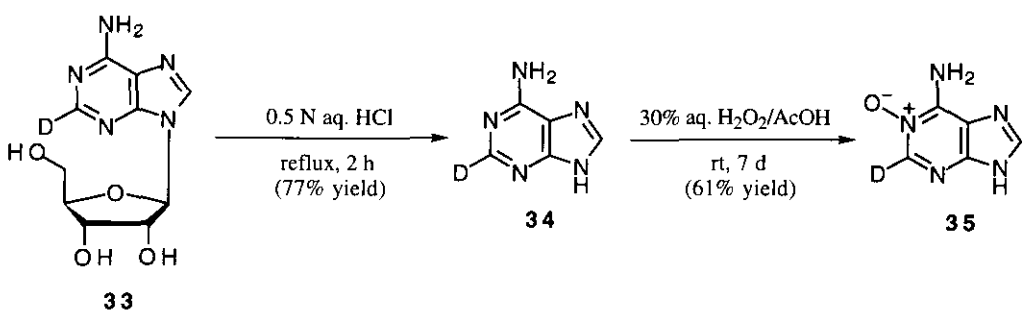
Hydrolysis of adenosine 1-oxide (**28**), obtained in 95% yield from adenosine (**29**) by oxidation with 30% aqueous H_2O_2 in AcOH at room temperature for 6 d, with boiling 1 N aqueous HCl for 15 min produced **5**, as identified by means of paper chromatographic and UV spectral analysis.[87] Treatment of 2',3'-*O*-isopropylideneadenosine with 30% aqueous H_2O_2 in AcOH at room temperature for 5 d gave 2',3'-*O*-isopropylideneadenosine 1-oxide (43.5% yield), which was also shown to yield **5** on hydrolysis with boiling 1 N aqueous HCl for 1–2 min.[87] Cresswell and Brown[90] secured **5** in 78% yield by cyclization of 5-aminoimidazole-4-carboxamidoxime dihydrochloride (**30**·2HCl) with

triethyl orthoformate in boiling DMF for 1 h. They also cyclized **30**·2HCl with CS_2 in a mixture of pyridine and MeOH at room temperature for 5 d, obtaining 2-mercaptoadenine 1-oxide (**31**) in 69% yield.[90] Desulfurization of **31** with Raney Ni in 1 N aqueous NaOH at 90°C for 1 h then gave a mixture of **5**, **1**, and the starting material (**31**).[90] Oxidation of the bis(trimethylsilyl)adeine (**32**) with bis(*N*, *N*-dimethylformamido)oxodiperoxomolybdenum(VI) in CH_2Cl_2 at room temperature was reported to give **5** (5% yield) and adenine (**1**).[91]



Scheme 5

Fujii's group[92] was able to prepare adenine-*2-d* 1-oxide (**35**) in 61% yield by peracetic acid oxidation (30% aqueous H_2O_2/AcOH, room temperature, 7 d) of adenine-*2-d* (**34**), which was obtained from adenosine-*2-d* (**33**) in 77% yield by hydrolysis with boiling 0.5 N aqueous HCl for 2 h (Scheme 6).



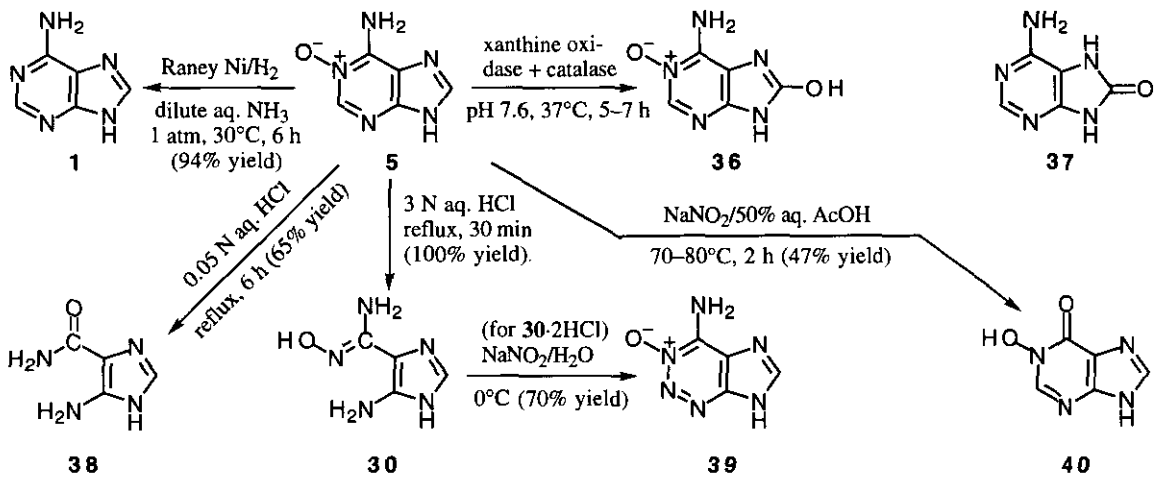
Scheme 6

Adenine 1-oxide (**5**) is known to occur as a partial structure in H_2O_2/AcOH-treated nucleotides, such as adenosine 2'-, 3'-, and 5'-monophosphates, and 5'-diphosphate;[93] in H_2O_2-treated adenosine 5'-monophosphate and deoxyadenylic acid;[93] in monoperoxyphthalic acid-treated (at pH 5) 2'-deoxyadenosine and its 5'-phosphate;[94] in H_2O_2/Ac-

OH-treated DNA or RNA;[95,96] in monoperoxyphthalic acid-treated (at pH 7) DNA;[97] in *m*-CPBA-treated (at pH 7) 2'-deoxyadenosine 5'-monophosphate or DNA.[98,99]

N-Oxygenation of adenine (**1**) to form the N(1)-oxide (**5**) by the *9000 g* supernatant or microsomal fraction of rat liver homogenates was reported by Clement and Kunze.[100] However, studies on *in vitro metabolism of* **1** using hepatic microsomes from hamster, mouse, and rat[101,102] and from guinea pig, rabbit, and dog[102] indicated that **1** was apparently not susceptible to microsomal *N*-oxidation.

The following may serve to locate papers reporting the physicochemical properties of adenine 1-oxide (**5**): the melting point for an anhydrous sample (white filamentous crystals) of **5**, decomp point 297–307°C,[87] mp 300°C (colorless leaflets),[88] or mp 300°C (slow decomp);[91] for **5**·H_2O (colorless heavy prisms), mp >300°C;[103] for the 2-deuterated species (**35**·H_2O), mp >300°C;[92] solubility in H_2O at 25°C[87] and in AcOH and other solvents;[88] lipophilicity;[104] pK_a 2.6, 9.0, and *ca.* 13 (in H_2O);[87,89,104] pK_a 2.69, 8.845, and *ca.* 15.4 (in H_2O at 20°C);[105] pK_a 2.73 and 8.83 (in D_2O at 27°C);[106] partition coefficient in a saline solvent system;[107] paper chromatography for **5**[87–89,93,95,96,108,109] or for **5**·H_2O;[103] *TLC*;[12,110] *HPLC*;[100–102] *column chromatography*;[111] paper electrophoresis;[96] MS for **5**[91,112] and for the 2-deuterated species (**35**·H_2O);[92b] UV for **5**[87,89,91,104] or **5**·H_2O[103] in H_2O at various pH's; ^1H NMR for **5** in D_2O[106] and in CD_3CO_2D,[101] for **5**·H_2O in DMSO-d_6[92] and for 2-deuterated species (**35**·H_2O) in DMSO-d_6;[92] tautomeric structure;[113] crystal structure for **5**[89] and for the complex **5**–H_2SO_4;[114] polarography;[115–117] MO calculation.[118]



Scheme 7

As regards the chemical behavior of adenine 1-oxide (**5**), Brown and co-workers[87] reported that **5** was quite stable in neutral aqueous solutions over long period, that there was no tendency for the oxide to lose oxygen and revert to adenine (**1**), and that, in aqueous solution, there was no tendency for a transfer of oxygen between **5** and **1**

molecules. When heated in AcOH for 20 min on a steam bath, **5** was partly converted into an unidentified material resembling **1** in R_f and UV spectrum.[87] With Pauly reagent, **5** gave a transient pink color.[89] Ikawa *et al.*[119] reported that adenine (**1**) itself gave very little color with Folin–Ciocalteau phenol reagent and the N(1)-oxide (**5**) did not affect the color greatly.

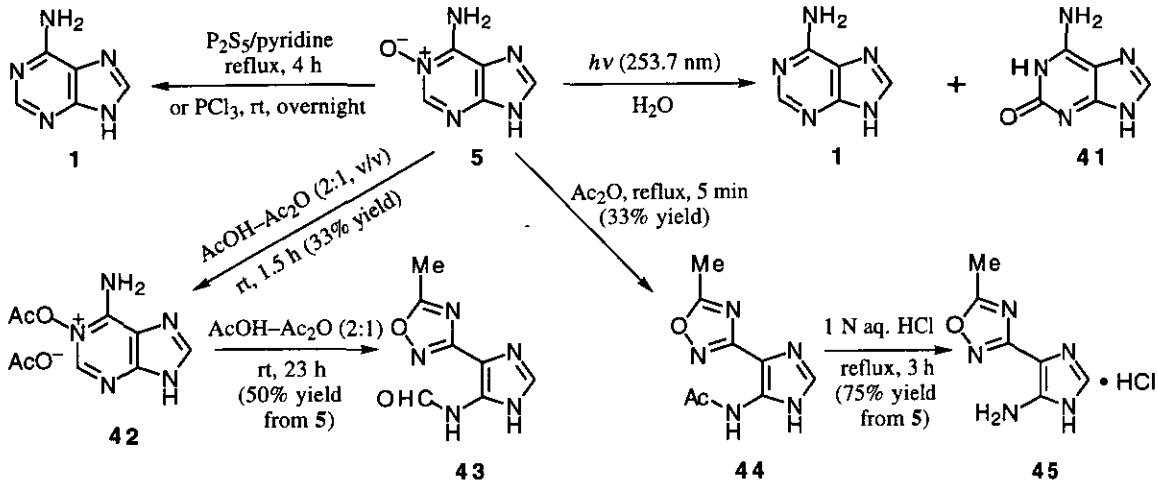
Reduction of **5** with hydrogen and Raney Ni afforded **1** (Scheme 7).[87] This reduction was also feasible by commercial milk xanthine oxidase (EC 1.2.3.2) in the presence of sodium dithionite under anaerobic conditions;[120] by an amine *N*-oxide reductase from *Escherichia coli* in the presence of sodium dithionite and benzyl viologen;[121] and by molybdenum(IV,VI) complexes.[122]

Treatment of **5** with boiling 3 N aqueous HCl for 30 min produced **30**·2HCl in quantitative yield and that with boiling 0.05 N aqueous HCl for 6 h furnished 5-aminoimidazole-4-carboxamide hydrochloride (**38**·HCl) in 65% yield.[89] Sundaralingam and Hecht[123] reported the results of an X-ray analysis of a Cu(II) complex of **30**. Sletten *et al.*[124] treated **5** in 0.5 N aqueous H_2SO_4 with aqueous $CuSO_4$ to obtain *catena*-μ-(5-aminoimidazole-4-carboxamidoxime) diaquo copper(II) sulfate trihydrate [$[Cu(C_4H_7N_5O)(H_2O)_2SO_4]\cdot 3H_2O$] and reported the crystal structure of this complex. Nerdal and Sletten[106] showed by means of ^1H NMR spectroscopy that the hydrolysis of **5** to **38** proceeded in two steps at pH <0.2 and qualitatively determined Cu(II) coordination on the basis of spin–lattice (T_1) measurements at 90 and 400 MHz. Treatment of **30**·2HCl in H_2O with $NaNO_2$ at 0°C produced 2-azaadenine 1-oxide (**39**) in 70% yield, concluding a two-step synthesis of **39** from **5**.[125]

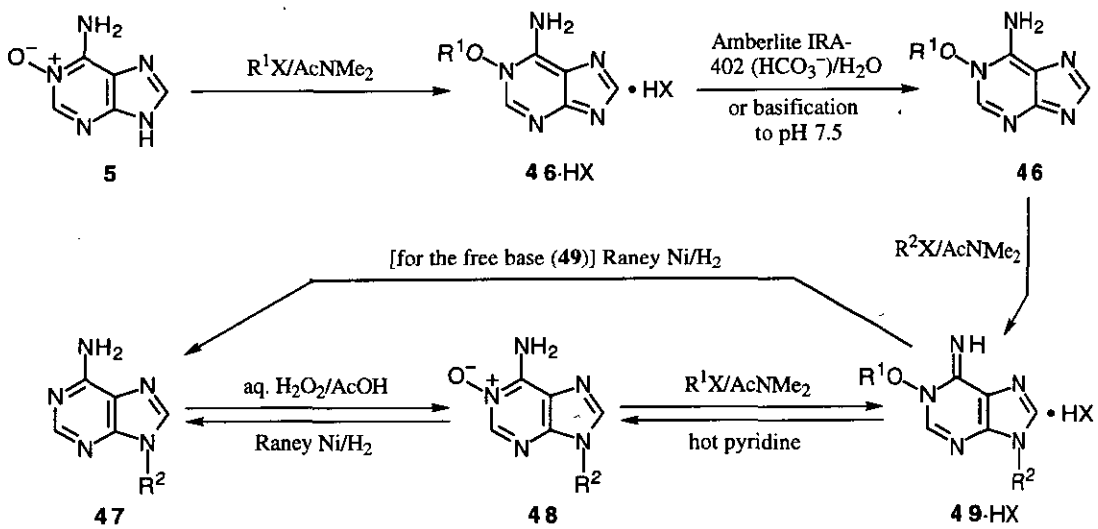
Diazotization of **5** in 50% aqueous AcOH with $NaNO_2$ gave 1-hydroxyhypoxanthine (**40**) in 47% yield.[109] Incubation of **5** in 0.15 M phosphate buffer (pH 7.6) at 37°C with commercial milk xanthine oxidase in the presence of catalase for 5–7 h was reported to form 8-hydroxyadenine 1-oxide (**36**).[126] In rats, [8-^{14}C]adenine 1-oxide was, in part, reduced to adenine (**1**) and guanine nucleotides; and a large portions were oxidized to ^{14}C-labeled **36**, some of which was reduced to 8-oxoadenine (or 8-hydroxyadenine) (**37**), and both appeared in the urine.[127]

Brown's group[128] demonstrated that adenine (**1**) can be obtained from the reaction of **5** with P_2S_5 or PCl_3 (Scheme 8). However, no reaction was observed when **5** was treated with $POCl_3$.[129] Photolysis of **5** to form **1** and isoguanine (**41**) was studied,[108,130] and kinetics of the changes induced in **5** under UV-irradiation and under γ-irradiation from a ^{60}Co source were reported.[131]

Scheme 8 also includes the reactions of **5** with AcOH–Ac_2O (2:1, v/v) at room temperature to give the *O*-acetyl derivative (**42**) and the ring-opened derivative (**43**) and those of **5** leading to **45** through **44**.[132] Stöhrer and Salemnick[133] developed a method for the preparation *in situ* of the *O*-acetyl ester (type **42**) by treatment of **5** with Ac_2O in phosphate buffer (pH 7.4) and found that the resulting *O*-acetyl ester of **5** did not oxidize iodide ion to iodine.



Scheme 8



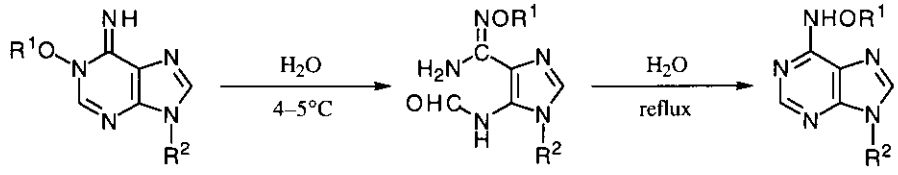
Scheme 9

Fujii's group[103,134] found that the reaction of **5** with alkyl halides or alkyl *p*-toluenesulfonates in $AcNMe_2$ resulted in *O*-alkylation, giving 1-alkoxyadenine salts (**46**·HX) in good yields (Scheme 9). These salts were readily converted into the corresponding free bases (**46**) by the use of Amberlite IRA-402 (HCO_3^-) or basification to pH 7.5.[103,134] Treatment of 1-alkoxyadenines (**46**) with alkyl halides in $AcNMe_2$ at room temperature produced 1-alkoxy-9-alkyladenine salts (**49**·HX).[103,134–136] In addition, alkylation of **5** with alkyl iodide in $AcNMe_2$ in the presence of H_2O_2 provided a convenient one-step procedure for preparation of 1-alkoxy-9-alkyladenine hydriodide [**49**·HI ($R^1 = R^2$)].[137] A clear O→N(9) alkyl migration was demonstrated by the reaction of **46** with an alkyl halide (R^2X) less reactive than that (R^1X) whose alkyl group was the same as in **46**,[138]

suggesting the use of **49**·HX as possible alkylating reagents.[139] Thus, treatment of **49**·HX with hot pyridine furnished 9-alkyladenine 1-oxide (**48**) and 1-alkylpyridinium salt,[136,139,140] and this route to **48** from **46** (hence from **1** through **5**) was successfully applied to the syntheses of adenine 1-oxides carrying an allylic side chain at the 9-position.[136] Kamiya's group[141] reported the reaction of **5** at N(9) with 2,3-*O*-isopropylidene-D-erythronolactone [in boiling DMF in the presence of K_2CO_3 (for 8 h) or Na_2CO_3 (12 h) or in $AcNMe_2$ (12 h) or DMSO (6 h) in the presence of Na_2CO_3 at 160°C], which resulted in the formation of 9-(3-carboxy-2,3-isopropylideneoxypropyl)adenine 1-oxide. Deoxygenation of the N(1)-oxides (**48**) or dealkoxylation of the free bases (**49**) of 1-alkoxy-9-alkyladenines using hydrogen and Raney Ni catalyst afforded 9-alkyladenines (**47**) in good yields.[103,134] Thus, the reaction sequence **1**→**5**→**46**→**49**·HX→**49**(or **48**)→**47** constituted a new route for the synthesis of 9-alkyladenines (**47**) starting from adenine (**1**).[103,134]

In the case of 9-substituted adenines (**47**), the N(1)-oxides (**48**) were also obtained by similar peroxycarboxylic acid oxidation.[87,92,135,142–144] Treatment of **48** with alkyl halides in $AcNMe_2$ at room temperature gave the corresponding 1-alkoxyadenine salts (**49**·HX) in good yields.[92,135,140,142,144–146] Similar treatment of the 2-deuterated species of **48** gave the corresponding 9-substituted 1-alkoxyadenine-2-*d* salts.[92]

It is noteworthy that the 1-alkoxyadenine derivatives (types **46**·HX and **49**·HX) were considerably reactive,[147] as in the case of 1-alkoxypyridinium salts.[148] The major characteristic reactions observed were (i) reductive cleavage of the N–O bond,[103,134] (ii) O→N(9) alkyl migration in the reaction of **46** with an alkyl halide,[138] (iii) alkylation of various nucleophiles,[139] (iv) nonreductive cleavage of the N–O bond,[149] and (v) hydrolytic ring fission between N(1) and C(2). Probably the most salient feature of the chemical behavior is that under item-v, which occurs very easily and whereby subsequent recyclization of the product (**50**) to form the N^6-alkoxyadenine derivatives (**51**) [Dimroth rearrangement (**49**→**50**→**51**)[150]] becomes feasible (Scheme 10).

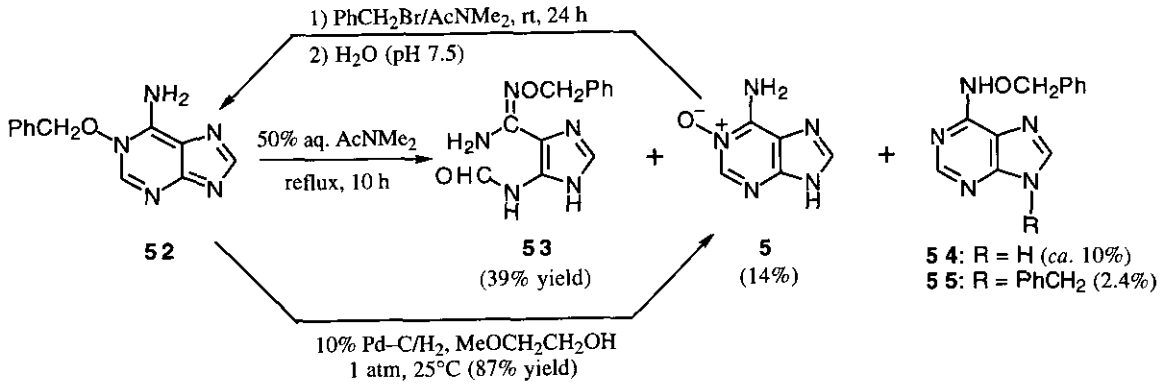


49 **50** **51**

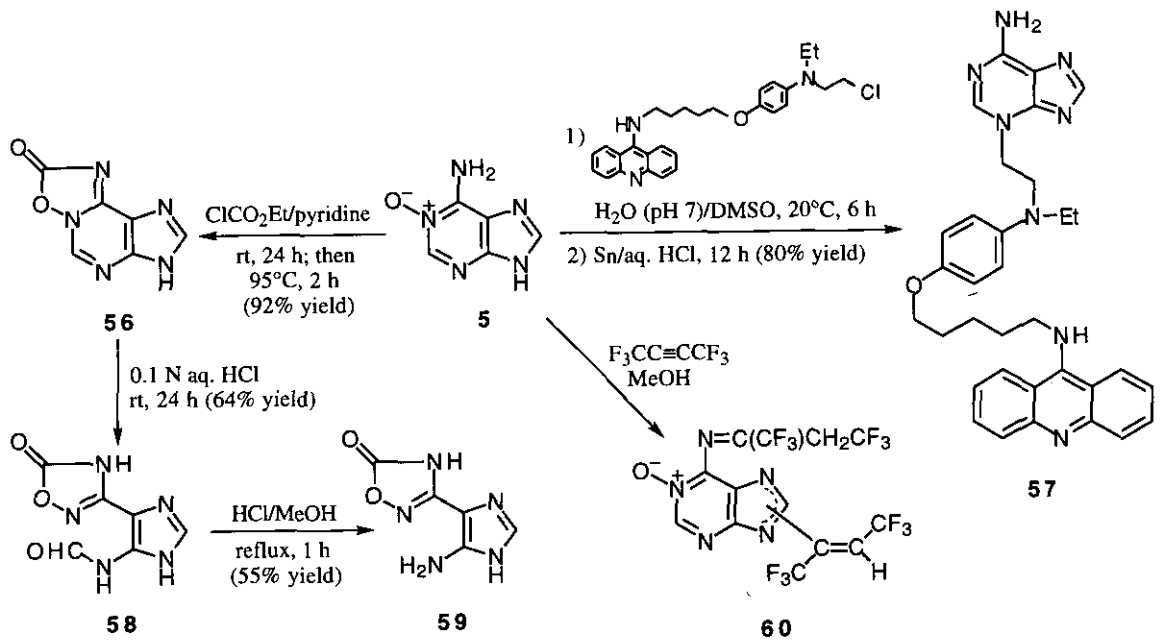
Scheme 10

Catalytic hydrogenolysis of 1-benzyloxyadenine (**52**), prepared from adenine 1-oxide (**5**) in 95% overall yield by benzylation with $PhCH_2Br$ (in $AcNMe_2$ at room temperature for 24 h) and basification (pH 7.5) of the product (**52**·HBr) in H_2O,[103,134] using hydrogen and 10% Pd–C catalyst in 2-methoxyethanol at 1 atm and 25°C for a few minutes gave **5** in 87% yield with a trace of adenine (**1**) (Scheme 11).[103] When heated in 50% aqueous

$AcNMe_2$ under reflux for 10 h, **52** produced the ring-opened derivative (**53**) (39% yield), adenine 1-oxide (**5**) (14%), N^6-benzyloxyadenine (**54**) (*ca.* 10%), and 9-benzyl-N^6-benzyloxyadenine (**55**) (2.4%).[151]



Scheme 11



Scheme 12

Devlin[152] was able to condense **5** with ethyl chloroformate in pyridine at room temperature for 24 h and then at 95°C for 2 h to obtain the tricyclic compound (**56**) in 92% yield (Scheme 12). At room temperature in 0.1 N aqueous HCl for 24 h, **56** furnished the ring-opened derivative (**58**) (64% yield), which was deformylated to the aminoimidazole (**59**) (55% yield) on treatment with boiling methanolic HCl for 1 h.[152] Davidson *et al.*[153] reported that the reaction of **5** and hexafluorobut-2-yne in MeOH produced **60**, arising from electrophilic attack at C(6)-NH_2 and at either N(7) or N(9), with an isomer arising from alkenylation at N(3) [or N(9) or N(7)]. Reaction of **5** with 9-[[5-[4-[*N*-ethyl-*N*-(2-

chloroethyl)amino]phenoxy]pentyl]amino]acridine in a mixture of H_2O (pH 7) and DMSO at 20°C for 6 h, followed by Sn/HCl reduction, was reported to form the N(3)-alkylated adenine (**57**) (80% yield), as identified by HPLC analysis.[154] It is interesting to note that this regioselectivity in alkylation of **5** appears to be in disagreement with that of **5** or 1-alkoxyadenines (**46**) described above (see also Scheme 9).

Incubation of a mixture of **5**, 1-β-D-arabinofuranosyluracil, wet cell paste of *Enterobacter aerogenes* AJ 11125 in 30 mM potassium phosphate buffer (pH 7.0) at 60°C for 15 h was reported to produce 9-β-D-arabinofuranosyladenine 1-oxide in 45% yield.[155] Fathi *et al.*[156] effected an enzymatic transglycosylation from 5'-deoxythymidine to **5** in 0.02 M phosphate buffer at 37°C for 3–5 d, obtaining 2',5'-dideoxyadenosine 1-oxide in low yield (in the region of 10%).

An example of the nonbiological, technical, or engineered material uses of **5** may be seen in a patent for an invention of thioether hydraulic fluids (or aircraft engine lubricants) containing **5**.[157]

Adenine 1-oxide complexes with the following metal ions have been investigated: divalent metal ions in the form of $MnCl_2$, $FeSO_4$, $ZnSO_4$, $Co(ClO_4)_2$, $Ni(ClO_4)_2$, and $Cu(ClO_4)_2$;[105] first row transition metal perchlorates;[158] $HgCl_2$ [crystal structure of $(C_5H_5N_5O)HgCl_2$];[159] $CuSO_4$ [allowed to react with **5** in 1 N aqueous NaOH; crystal structure of the resulting complex $Cu(C_5H_3N_5O)_2Na_2(H_2O)_8$].[160]

As regards the biological activity of adenine 1-oxide (**5**), Brown *et al.*[161] reported that **5** had little effect on tissues in culture and it partially fulfilled the adenine requirement of certain bacteria. It did not substitute for adenine (**1**) in blocking the inhibition of sarcoma 180 *in vitro* by diazooxonorleucine.[161] However, the isolation of 2,8-dihydroxyadenine from the kidneys of mice which received large amounts of **5** implies that the *N*-oxide function can be removed *in vivo*.[161] Henderson[162] reported that **5** at 10^{-3} M concentration did not inhibit purine biosynthesis *de novo* in Ehrlich ascites tumor cells *in vitro*. The N(1)-oxide (**5**), guanine 3-oxide, and 3-hydroxyxanthine had no inhibitory effect on 24 solid mouse and rat tumors, but **5** had a marked inhibitory effect on Ehrlich ascites carcinoma Line I and Taper ascites liver tumor.[163] Henderson's group[164] tested 161 purine analogues and derivatives including **5** for their ability to inhibit 10 parameters of purine metabolism in Ehrlich ascites tumor cells incubated *in vitro* with [^{14}C]hypoxanthine. They found that **5** inhibited adenine phosphoribosyltransferase from Ehrlich ascites tumor cells by 67% at 1.0 mM concentration and by 46.6% at 0.1 mM;[82] its inhibition constant was compared with those obtained for analogues of **1**.[165] In addition, **5** at 1 mM concentration did not inhibit inosinate dehydrogenase activity in intact Ehrlich ascites tumor cells *in vitro*, but inhibited nucleotide formation from [^{14}C]hypoxanthine by 18.9%.[166]

Although the oncogenicity assay response to **5** was variable, a sufficient incidence of tumors in both Sprague–Dawley and Wistar rats (at a dose level of 10 mg/week for 26 weeks) was observed, indicating that **5** is at least a moderately oncogenic purine *N*-

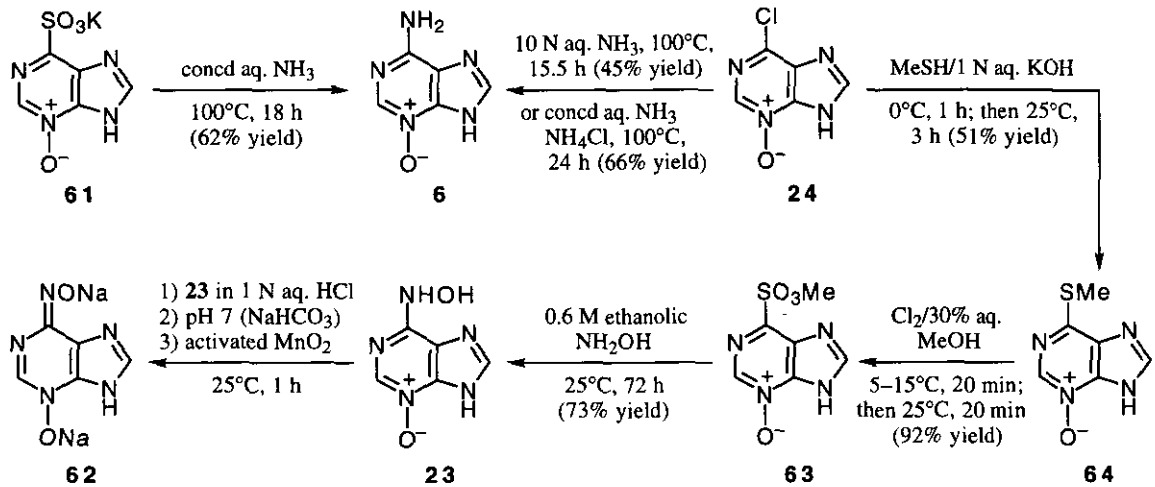
oxide.[167] The mutagenic activity of **5** in *Salmonella typhimurium*,[42] *Bacillus subtilis*,[43] *Streptomyces antibioticus*,[43] and *Saccharomyces cerevisiae*[43] has also been investigated.

Adenine- or adenosine-uptake into human blood platelets is a carrier-mediated process, and **5** has been found to act as a weak competitive inhibitor.[168,169]

When measured 24 h after oral administration of **5** (175 mg/kg), the plasma urea nitrogen and creatinine levels in mice were not increased, indicating lack of **5**-induced nephrotoxicity.[170] Uehara *et al.*[171] reported that adenine (**1**) as well as **5** accelerated the riboflavin-sensitized photoinactivation of *Escherichia coli* tRNA. No biological activity with respect to oocyte maturation in the starfish *Asterias rubens* has been reported for **5**.[104]

VI. ADENINE 3-OXIDE

Adenine 3-oxide (**6**) was first synthesized by Brown's group[172] from the potassium salt (**61**) of purine-6-sulfonic acid 3-oxide (**21**) in 62% yield by treatment with concd aqueous NH_3 at 100°C for 18 h (Scheme 13). In an alternative synthesis of **6**, Kawashima and Kumashiro[173a] allowed 6-chloropurine 3-oxide (**24**) to react with 10 N aqueous NH_3 at 100°C for 15.5 h to secure **6** in 45% yield, and Giner-Sorolla[174] effected this reaction in concd aqueous NH_3 containing NH_4Cl at 100°C for 24 h to obtain **6** in 66% yield.[173b] The latter author also reported a four-step conversion of **24** into the disodium salt (**62**) of 6-nitrosopurine 3-oxide (**26**) through **64**, **63**, and **23** (Scheme 13).[174] Another procedure for **23**→**26** and chemical behavior and biological activity of N^6-oxygenated adenine 3-oxides are described earlier in Section II (see also Scheme 4).

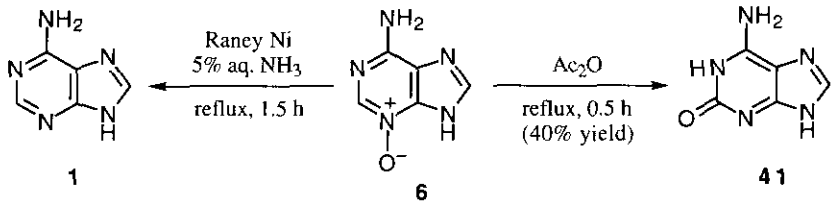


Scheme 13

The following physicochemical properties have been reported for adenine 3-oxide (**6**): the

melting point for **6**, mp >280°C;[173] for **6**·0.5H_2O, decomp point >350°C;[172] pK_a 2.85 ± 0.06 and 6.91 ± 0.07 (in H_2O at 20–22°C);[172] paper chromatography;[172,173] TLC;[12] HPLC;[100] UV in H_2O at various pH's;[172,173] tautomeric structure.[172]

As regards the chemical behavior of **6,** Brown's group[172] reported the formation of a 1:1 complex with $(NH_4)_2SO_4$. Treatment of **6** with Raney Ni in boiling 5% aqueous NH_3 for 1.5 h gave adenine (**1**) in excellent yield (Scheme 14).[172] This reduction of the *N*-oxide function was also feasible under anaerobic conditions by commercial milk xanthine oxidase (EC 1.2.3.2) in the presence of sodium dithionite.[120] Reaction of **6** with boiling Ac_2O for 0.5 h produced isoguanine (**41**) in 40% yield.[175]



Scheme 14

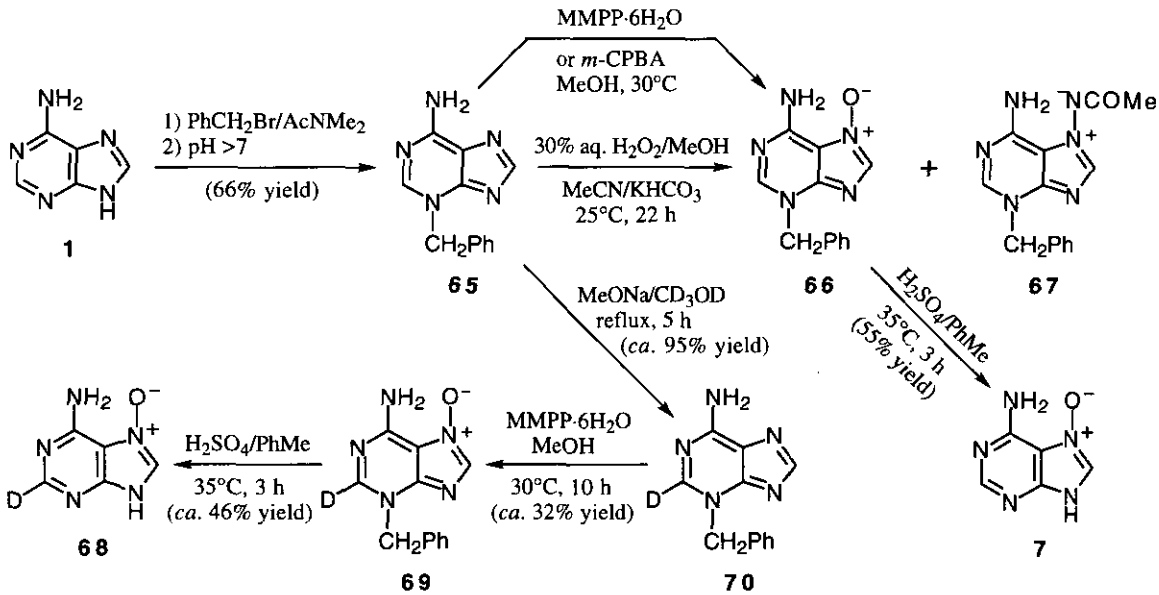
VII. ADENINE 7-OXIDE

As already described above in Section V, adenine (**1**) undergoes *N*-oxidation preferentially at 1-position to produce adenine 1-oxide (**5**) in good yield (Scheme 5) on treatment with 30% aqueous H_2O_2 in AcOH at room temperature. This regioselectivity appears to reflect the generalization[176] that on *N*-oxidation pyrimidine compounds form only mono-*N*-oxides, whereas imidazoles are resistant to *N*-oxidation.

In 1968, however, Rhaese[177] claimed that treatment of adenine (**1**) with 0.1 M H_2O_2 in 0.01 M phosphate buffer (pH 7.0) at 37°C for 5 d afforded adenine 7-oxide (**7**) (isolated as a monohydrate sensitive to UV light) in 5% yield without any detectable formation of the N(1)-oxide (**5**). He further claimed that the N(7)-oxide was among the products of X-ray irradiation of **1** in 0.05 M phosphate buffer (pH 7.0).[177] Later on, these results were allegedly reproduced by Yamamoto,[178] who further asserted that **7** bound noncovalently to urease, an SH protein, in an experiment using a sample of **7** prepared by the method of Rhaese. This unusual regioselectivity of *N*-oxidation of **1** was so striking as to appear questionable. Moreover, the chemical and spectroscopic evidence[177–179] adduced by both authors appeared insufficient to allow definitive assignment of the N(7)-oxide structure to their samples, which they thought to be the new *N*-oxide (**7**).

Thus, Fujii and co-workers[180] reexamined the H_2O_2/buffer oxidation procedure[177] of Rhaese for **1**, but completely failed to reproduce his results; they were unable to obtain any *N*-oxide from **1**. This led them to design a three-step route for the synthesis of adenine 7-oxide (**7**)[181] from adenine (**1**) (Scheme 15):[180] Treatment of 3-benzyladenine (**65**), readily obtainable from adenine (**1**) in 66% yield according to the literature

procedure,[182] with magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) in MeOH at 30°C for 20 h or with *m*-CPBA in MeOH–1 M acetate buffer (pH 5.0) (1:1, v/v) at 30°C for 15 h gave 3-benzyladenine 7-oxide (**66**) in 40% or 24% yield, respectively. The use of 30% aqueous H_2O_2 in AcOH at room temperature or *m*-CPBA in AcOH at 30°C as the oxidizing agent was found to be ineffective. Debenzylation of **66** with concd sulfuric acid at 35°C in the presence of toluene for 3 h afforded the desired compound, adenine 7-oxide (**7**), in 55% yield. Characterization of **7** as the N(7)-oxide was easily achieved by measurement of its UV spectrum, which was different from those of the three known isomeric *N*-oxides (**5**, **6**, and **8**), and by its chemical reactions including deamination and methylation (see Scheme 16). In addition, the location of the oxygen function in **66** and **7** was confirmed by X-ray crystallographic analysis.[180b]

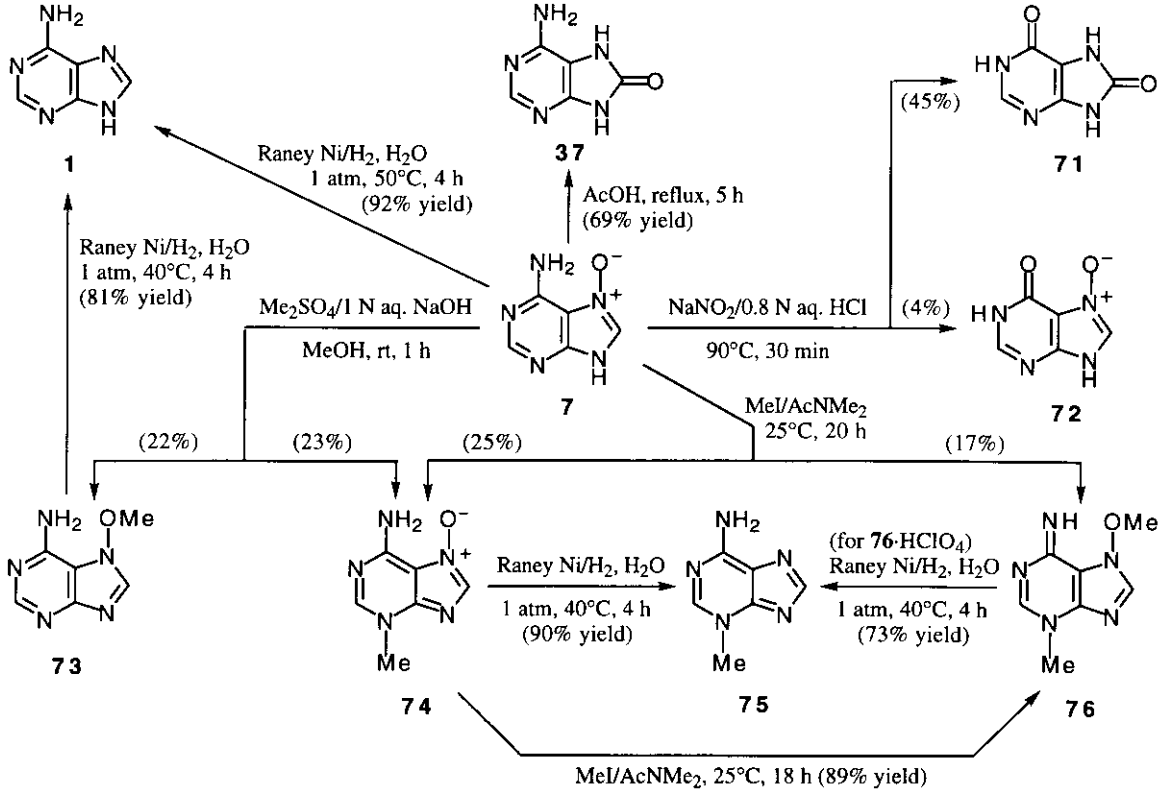


Scheme 15

Fujii's group[180b] further found that treatment of **65** with a large excess of 30% aqueous H_2O_2 in MeOH in the presence of MeCN and $KHCO_3$ at 25°C for 22 h produced the N(7)-oxide (**66**) (12% yield) and 7-acetamido-3-benzyladenine (**67**) (1%), together with 28% recovery of **65**. The crystal structure of **67** was also presented.[180b] The C(2)-deuterated species [**69** (of 79% isotopic purity) and **68** (of 78% isotopic purity)] were also prepared by following a parallel synthetic route starting from 3-benzyladenine-*2-d* (**70**) (of 85% isotopic purity), which was obtained from **65** according to the method of Maki *et al.*[183]

As in the case of 3-benzyladenine (**65**) described above, 3-methyladenine (**75**) and 3-ethyladenine (**77**) underwent peroxycarboxylic acid oxidation at N(7), giving **74** and **78** in 13–25% yields (Scheme 17).[184] Separate treatments of **66**, **74**, and **78** with alkyl halide (R^2X) in $AcNMe_2$ at 30°C furnished the corresponding 7-alkoxy derivatives (**79**)

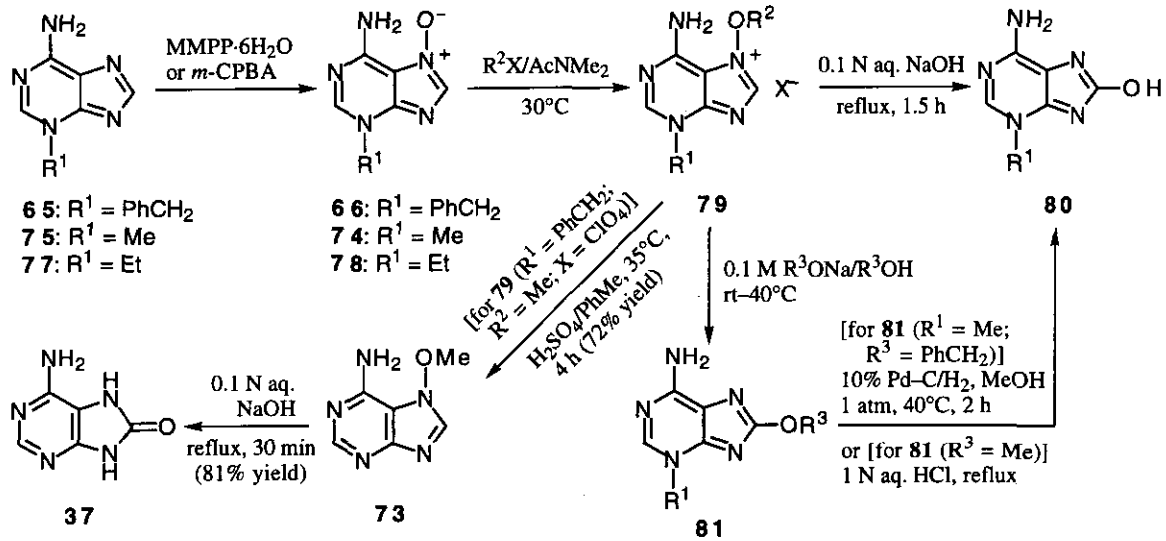
(81–97% yields), which afforded 3-alkyl-8-hydroxyadenine (**80**) in 32–74% yields on treatment with boiling 0.1 N aqueous NaOH for 1.5 h.[184] Treatment of **79** (X = ClO_4) with 0.1 N R^3ONa in R^3OH (R^3 = Me, Et, or $PhCH_2$) at room temperature–40°C gave 8-alkoxy-3-alkyladenines (**81**) in 28–98% yields, and hydrolysis of **81** (R^3 = Me) with boiling 1 N aqueous HCl or hydrogenolysis (10% Pd–C/H_2, MeOH, 1 atm, 40°C, 2 h) of **81** (R^3 = $PhCH_2$) provided **80** in 73–90% yields.[184] Debenzylation of 3-benzyl-7-methoxyadenine perchlorate (**79**: R^1 = $PhCH_2$; R^2 = Me; X = ClO_4) with concd sulfuric acid in the presence of toluene at 35°C for 4 h gave 7-methoxyadenine (**73**) (72% yield), which provided 8-oxoadenine (**37**) in 81% yield on treatment with boiling 0.1 N aqueous NaOH for 30 min.[184]



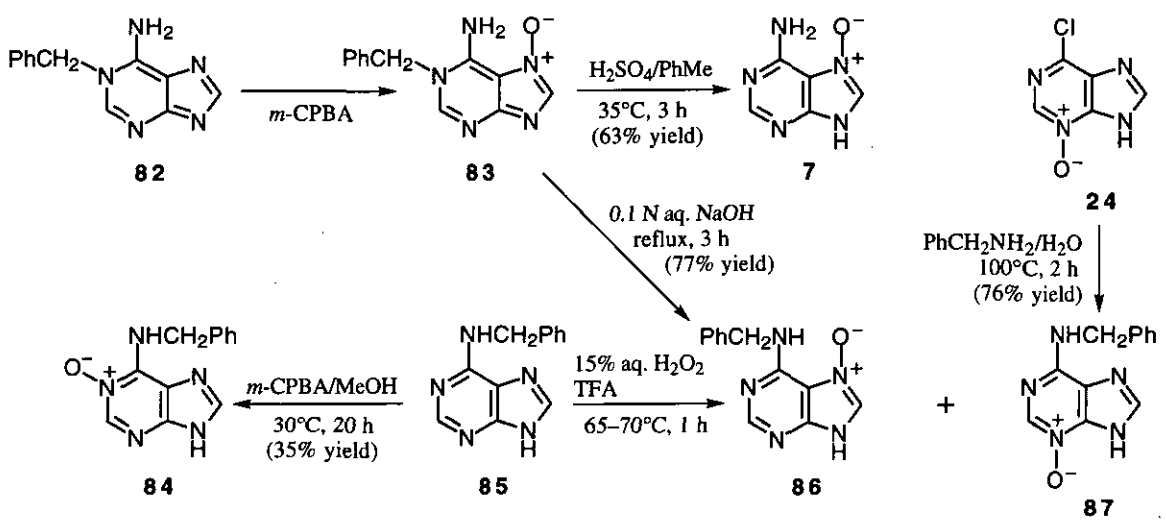
Scheme 16

In an alternative synthesis of **7** (Scheme 18), Fujii's group[185] oxidized 1-benzyladenine (**82**) with *m*-CPBA in MeOH at 30°C for 14 h or in MeOH–0.5 M phosphate buffer (pH 6.6) at 30°C for 20 h and obtained 1-benzyladenine 7-oxide (**83**) in 13% or 19% yield. The structure of **83** was unequivocally established by an X-ray crystallographic analysis. Debenzylation of **83** with concd sulfuric acid in the presence of toluene at 35°C for 3 h gave **7** in 63% yield. When heated in boiling 0.1 N aqueous NaOH for 3 h, **83** underwent Dimroth rearrangement[150] to provide N^6-benzyladenine 7-oxide (**86**) in 77% yield.[186] Oxidation of N^6-benzyladenine (**85**) with 15% aqueous H_2O_2 in TFA at 65–70°C for 1

h[187] was found to produce the N(7)-oxide (**86**) (4% yield) and the N(3)-oxide (**87**) (4%), the latter of which was identical with a sample prepared according to the literature procedure[173a] from 6-chloropurine 3-oxide (**24**) and benzylamine.[186] On the other hand, *m*-CPBA oxidation of **85** in MeOH at 30°C for 20 h was shown to give the N(1)-oxide (**84**) in 35% yield, together with 25% recovery of **85**.[188]



Scheme 17



Scheme 18

Apart from the H_2O_2 oxidation of adenine (**1**) described above, it has been reported that the primary product from the reaction of **1** with H_2O_2 under UV irradiation,[189] from that with hydroxyl radical generated by water radiolysis[190] or by photolysis of 4-mercaptopyridine 1-oxide,[190] or from electrochemical oxidation of **1** in H_2O in the pH range

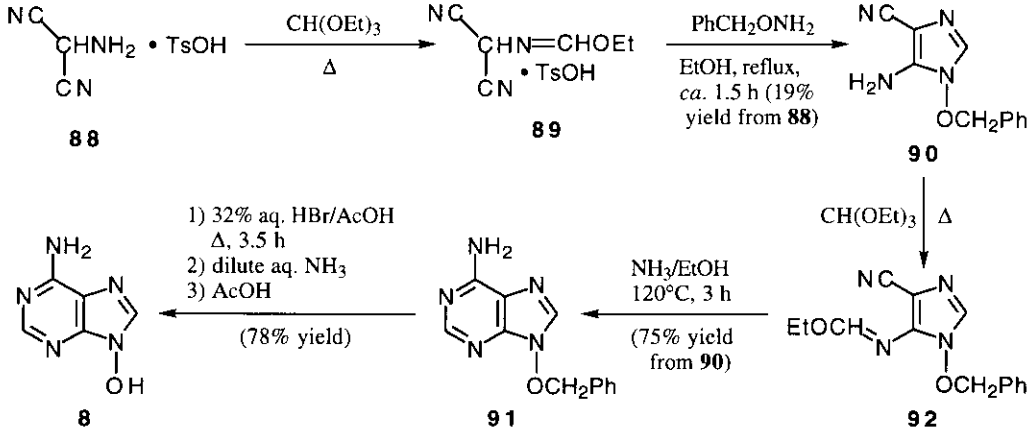
3.0–11.2[191] was 8-oxoadenine (or 8-hydroxyadenine) (**37**).

The following physicochemical properties of adenine 7-oxide (**7**) have been recorded in the literature: the melting point for **7**, mp >300°C;[180] for the 2-deuterated species (**68**), mp >300°C;[180b] for **7**·HCl, mp >300°C (decomp);[180b] pK_a 3.4 and 5.75 (in H_2O at 30°C and ionic strength 1.0);[180b] MS for **7**;[180b] UV (in H_2O at various pH's and in 95% aqueous EtOH) for **7** and for **7**·HCl;[180b] ^{1}H NMR for **7** in DMSO-d_6 and in D_2O, for the 2-deuterated species (**68**) in DMSO-d_6 and in D_2O, and for **7**·HCl in D_2O;[180b] tautomeric structure in H_2O;[180b] crystal structure for **7**·H_2O.[180b]

In a test for antileukemic activity against murine L5178Y cells, each of adenine 7-oxide (**7**) and 3-benzyladenine 7-oxide (**66**) was found to be only very weakly cytotoxic at a concentration of 50 μg/mL.[180b,192] In the tobacco callus bioassay for cytokinin activity, each of N^6-benzyladenine 1-oxide (**84**), the N(3)-oxide (**87**), and the N(7)-oxide (**86**) was active at 4 μM concentration, being less active than the parent base (**85**), an typical synthetic cytokinin, by a factor of 40.[186]

VIII. 9-HYDROXYADENINE

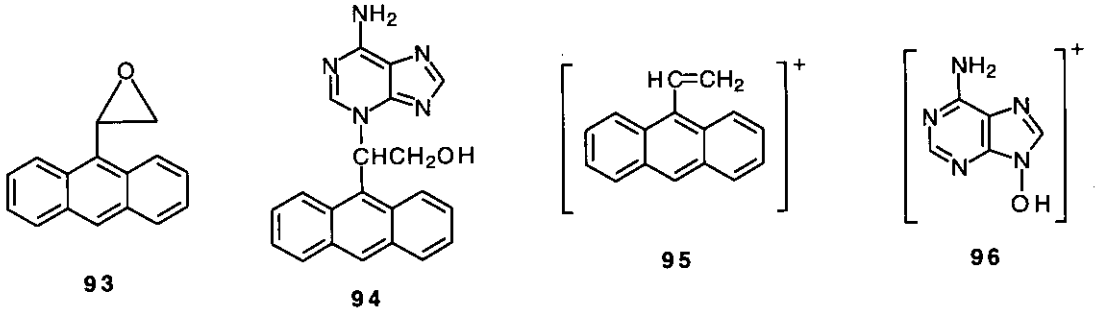
In 1977, Watson[193] reported a five-step synthesis of 9-hydroxyadenine (**8**) from aminomalononitrile *p*-toluenesulfonate (**88**) as depicted in Scheme 19. The synthesis by him started with heating a mixture of **88** and triethyl orthoformate on a steam bath to give the imino ether tosylate (**89**) and proceeded through 5-amino-1-benzyloxyimidazole-4-carbonitrile (**90**), the ethoxymethyleneaminoimidazole derivative (**92**), and 9-benzyloxyadenine (**91**).



Scheme 19

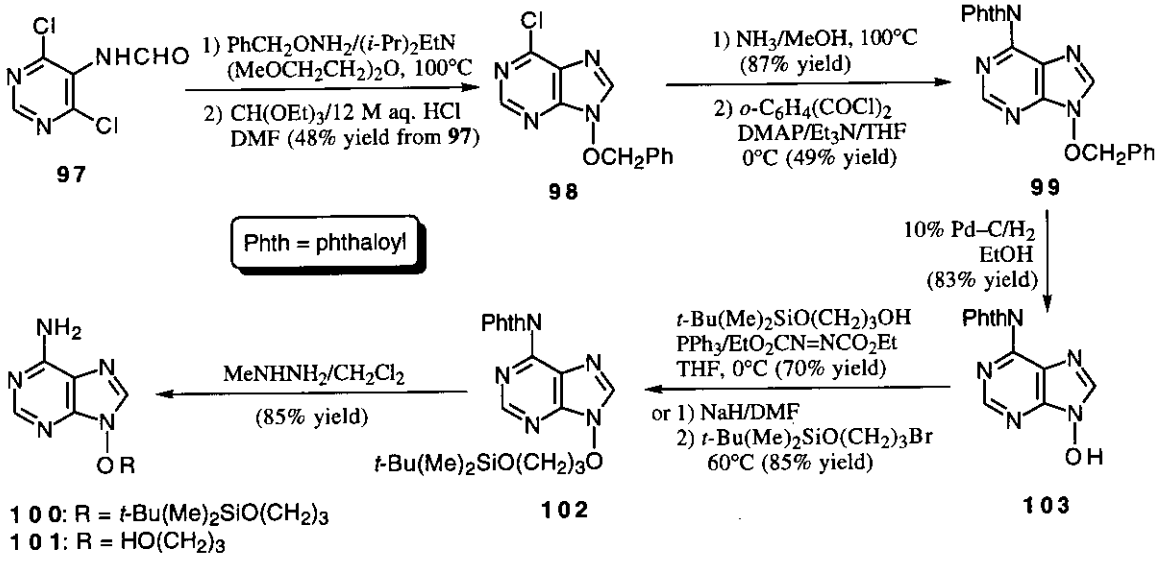
Yang and Chang[194] reported selective alkylation of calf thymus DNA at N(3) of the adenine moiety with carcinogenic 9-anthryloxirane (**93**) and that the mass spectrum of the N(3)-adduct (**94**), obtained by acid hydrolysis of the modified DNA, exhibited abundant

ions corresponding to the molecular formulas of $C_{16}H_{12}^+$ (**95**) and $C_5H_5N_5O^+$ (**96**).



93 **94** **95** **96**

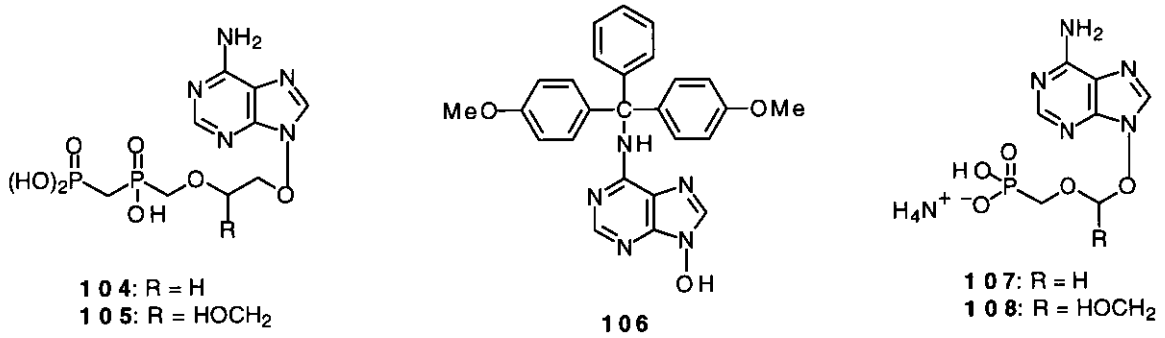
The following physicochemical properties of 9-hydroxyadenine (**8**) have been reported in the literature:[193] pK_a 3.59 ± 0.05 and 5.7 ± 0.1; UV in H_2O at pH 1, 4.6, and 10; tautomeric structure.



97 **98** **99** **103** **102**

100: R = t-Bu(Me)$_2$SiO(CH$_2$)$_3$
101: R = HO(CH$_2$)$_3$

Scheme 20



104: R = H
105: R = HOCH$_2$

106

107: R = H
108: R = HOCH$_2$

In a synthesis of the adenine acyclonucleoside (**101**), Harnden and Wyatt[195] converted the 4,6-dichloropyrimidine (**97**) into **100** through **98**, **99**, **103**, and **102**, as illustrated in Scheme 20. Deprotection of the acyclic substituent in **100** to give **101** was effected by treatment with boiling 5 N aqueous HCl in EtOH or with bromotrimethylsilane in either CH_2Cl_2 or DMF.[195]

The syntheses of the diphosphonate derivatives (**104** and **105**) from **103**,[196] that of the phosphonate derivative (**107**) from 9-hydroxyadenine (**8**),[197] and that of **108** from 9-benzyloxyadenine (**91**) through N^6-(4,4'-dimethoxytrityl)-9-hydroxyadenine (**106**)[197,198] have also been reported.

IX. APPENDIX

For ready comparison, available data concerning acid dissociation constants and UV and ^{1}H NMR spectra of the six mono-*N*-oxygenated adenines (**2**, **3**, and **5**–**8**) are tabulated below in Tables I–III.

TABLE I. pK_a Values of N^x-Oxygenated Adenines

Compound (No.)	Solvent	Method[a]	pK_a		Literature (ref. No.)
			basic	acidic	
6-Hydroxyaminopurine (**2**)	H_2O	(U, T)	3.80	9.83, >12	(9b)
	DMSO	(T)		12.7	(13)
Adenine 1-oxide (**5**)	H_2O	(U)	2.6	9.0, *ca.* 13	(87, 89)
	H_2O[b]	(T)	2.69	8.845, *ca.* 15.4	(105)
	D_2O[c]	(N)	2.73	8.83	(106)
Adenine 3-oxide (**6**)	H_2O[d]	(U, T)	2.85 ± 0.06	6.91 ± 0.07	(172)
Adenine 7-oxide (**7**)	H_2O[e]	(U)	3.4	5.75	(180b)
9-Hydroxyadenine (**8**)	H_2O	(U)	3.59 ± 0.05	5.7 ± 0.1	(193)

a) The letter(s) in parentheses refer(s) to the determination method with N, ^{1}H NMR spectroscopy; T, titrimetry; U, UV spectrophotometry.

b) At 20°C.

c) At 27°C.

d) At 20–22°C.

e) At 30°C and ionic strength 1.0.

TABLE II. UV Spectral Data of N^x-Oxygenated Adenines[a)]

Compound (No.)	Solvent	pH	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	Literature (ref. No.)
6-Hydroxyaminopurine (**2**)	H_2O	1.2	271	13.3	(15)
		1.23	271	13.3	(9b)
		6.7	268	11.8	(15)
		6.73	268	11.8	(9b)
		>9	unstable		(9b, 15)
6-Nitrosopurine (**3**)	H_2O	1	266, 332		(18)
		6.8	268, 338	4.62, 6.99	(18)
		13	249, 316		(18)
Adenine 1-oxide (**5**)	H_2O	1.0	258.5	11.5	(87, 89)
		7.0	231, 262.5	41.5, 8.1	(87, 89)
		7	263	8.1	(104)
		13.0	233, 275	46.2, 7.4	(87, 89)
5·H_2O	H_2O	1	259	12.4	(103)
		7	232, 263	42.3, 8.0	(103)
		13	234, 274	49.2, 7.2	(103)
Adenine 3-oxide (**6**)	H_2O	0	224,[b)] 277	5.8, 8.5	(172)
		5	229, 293	9.0, 7.0	(172)
		10	231, 278,[b)] 290	11.7, 5.7, 6.3	(172)
Adenine 7-oxide (**7**)	95% E[c)]		246,[b)] 271	5.4, 9.1	(180b)
	H_2O	1	274	11.5	(180b)
		4.1	243, 267	8.2, 8.9	(180b)
		7	235, 284	12.4, 6.1	(180b)
		13	235, 285	13.0, 6.2	(180b)
7·HCl	95% E[c)]		272	9.7	(180b)
	H_2O	1	274	12.1	(180b)
		7	235, 284	13.1, 6.4	(180b)
		13	235, 285	13.4, 6.4	(180b)
9-Hydroxyadenine (**8**)	H_2O	1	215, 261	17.4, 13.0	(193)
		4.6	245, 259	11.8, 12.1	(193)
		10	234, 262	20.8, 9.0	(193)

a) Taken from the literature recording λ_{max} values together with molar absorptivities for N^x-oxygenated adenines. *b*) Shoulder. *c*) 95% aqueous EtOH.

TABLE III. ^{1}H NMR Spectral Data of N^x-Oxygenated Adenines

Compound (No.)	Chemical shift (δ)[a] in DMSO-d_6				Literature (ref. No.)
	C(2)-H	C(8)-H	NH_2	NH	
6-Hydroxyaminopurine (**2**)	8.38[b]	8.34[b]			(101)
Adenine 1-oxide (**5**)[c]	8.59 8.76[b]	8.29 8.37[b]	———[d] 	———[d] 	(92) (101)
Adenine-2-*d* 1-oxide (**35**)[e]	———	8.28	———[d]	———[d]	(92)
Adenine 7-oxide (**7**)	8.17	8.35	7.01	12.0–13.0	(180b)
Adenine-2-*d* 7-oxide (**68**)	———	8.34	6.95	12.0–13.0	(180b)

a) In ppm downfield from internal Me_4Si. *b*) Measured in CD_3CO_2D. *c*) In the form of a monohydrate (**5**·H_2O). *d*) No clear signal was observed. *e*) In the form of a monohydrate (**35**·H_2O).

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REFERENCES AND NOTES

1. J. H. Lister, 'Fused Pyrimidines. Part II: Purines,' ed. by D. J. Brown, Wiley–Interscience, New York, 1971.
2. G. Shaw, 'Rodd's Chemistry of Carbon Compounds,' 2nd ed., Vol. IV, Part L, ed. by S. Coffey, Elsevier Scientific Publishing Co., Amsterdam, 1980, Chapter 57, pp. 1–115.
3. G. Shaw, 'Comprehensive Heterocyclic Chemistry,' Vol. 5, ed. by K. T. Potts, Pergamon Press, Oxford, 1984, Chapter 4.09, pp. 499–994.
4. E. Ochiai, 'Aromatic Amine Oxides,' Elsevier Publishing Co., Amsterdam, 1967.
5. A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, New York, 1971.
6. G. B. Brown, *Prog. Nucleic Acid Res. Mol. Biol.*, 1968, **8**, 209.
7. A. Albini and M. Alpegiani, *Chem. Rev.*, 1984, **84**, 43.
8. T. Yosief, A. Rudi, Z. Stein, I. Goldberg, G. M. D. Gravalos, M. Schleyer, and Y. Kashman, *Tetrahedron Lett.*, 1998, **39**, 3323.
9. (a) A. Bendich, A. Giner-Sorolla, and J. J. Fox, 'The Chemistry and Biology of Purines,' ed. by G. E. W. Wolstenholme and C. M. O'Connor, Little, Brown and Co., Boston, 1957, pp. 3–16; (b) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, 1958, **80**, 3932.

10. (a) E. I. Budowsky, E. D. Sverdlov, and G. S. Monastyrskaya, *J. Mol. Biol.*, 1969, **44**, 205; (b) E. I. Budowsky, *Prog. Nucleic Acid Res. Mol. Biol.*, 1976, **16**, 125.
11. E. I. Budowsky, E. D. Sverdlov, and G. S. Monastyrskaya, *Biochim. Biophys. Acta*, 1971, **246**, 320.
12. B. Clement and T. Kunze, *Biochem. Pharmacol.*, 1990, **39**, 925.
13. U. Mikstais, A. P. Kreshkov, N. T. Smolova, and A. Veveris, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 1977, 435 (*Chem. Abstr.*, 1978, **88**, 44543).
14. B. Clement and T. Kunze, *Biochem. Pharmacol.*, 1992, **44**, 1501.
15. A. Giner-Sorolla, S. O'Bryant, J. H. Burchenal, and A. Bendich, *Biochemistry*, 1966, **5**, 3057.
16. D. Yu. Yakovlev, N. A. Simukova, E. I. Budowsky, V. O. Chekhov, F. A. Savin, and Yu. V. Morozov, *J. Photochem.*, 1982, **20**, 253.
17. V. O. Chekhov, E. I. Budovskii, Yu. V. Morozov, and F. A. Savin, *Mol. Biol. (Moscow)*, 1979, **13**, 497 (*Chem. Abstr.*, 1979, **91**, 85576).
18. A. Giner-Sorolla, *J. Heterocycl. Chem.*, 1970, **7**, 75.
19. S. P. Dutta, R. J. Bernacki, A. Bloch, and G. B. Chheda, *Nucleosides Nucleotides*, 1990, **9**, 151.
20. A. Giner-Sorolla, *J. Med. Chem.*, 1969, **12**, 717.
21. A. Giner-Sorolla and J. T. Segarra, 'Nucleic Acid Chemistry,' Part 4, ed. by L. B. Townsend and R. S. Tipson, Wiley, New York, 1991, pp. 1–7.
22. A. Giner-Sorolla, J. Longley-Cook, M. McCravey, G. B. Brown, and J. H. Burchenal, *J. Med. Chem.*, 1973, **16**, 365.
23. J. A. Roth and D. B. McCormick, *Photochem. Photobiol.*, 1967, **6**, 657.
24. D. D. Roberts, P. Arjunan, L. B. Townsend, and I. J. Goldstein, *Phytochemistry*, 1986, **25**, 589.
25. D. M. Brown and P. V. S. K. T. Lin, **PCT Int. Appl. WO 93 05,176** (18 Mar 1993) (*Chem. Abstr.*, 1993, **118**, 249291).
26. For a summary of the toxicologic and chemotherapeutic study of **2** and its derivatives, see A. Giner-Sorolla, *Galencia Acta*, 1966, **19**, 97 (*Chem. Abstr.*, 1968, **68**, 11303).
27. A. C. Sartorelli, A. L. Bieber, P. K. Chang, and G. A. Fischer, *Biochem. Pharmacol.*, 1964, **13**, 507.
28. J. H. Burchenal, M. Dollinger, J. Butterbaugh, D. Stoll, and A. Giner-Sorolla, *Biochem. Pharmacol.*, 1967, **16**, 423.
29. P. F. Pecora and M. E. Balis, *Biochem. Pharmacol.*, 1964, **13**, 1071.
30. A. C. Sartorelli and H. F. Upchurch, *Cancer Res.*, 1963, **23**, 1077.
31. J. H. Burchenal, D. Benvenisti, and M. Dollinger, *Recent Results Cancer Res.*, 1970, **33**, 102.
32. A. Giner-Sorolla, J. H. Burchenal, and C. Lopez, *Med. Chem. Adv., Proc. Int. Symp., 7th 1980*, 1981, 55 (ed. by F. G. De las Heras and S. Vega, Pergamon, Oxford, Engl.).
33. E. B. Freese, *Mutat. Res.*, 1968, **5**, 299.
34. Y. I. Pavlov and N. N. Khromov-Borisov, *Genetika (Moscow)*, 1984, **20**, 1270 (*Chem. Abstr.*, 1984, **101**, 205304).
35. Y. I. Pavlov, V. N. Noskov, E. K. Lange, E. V. Moiseeva, M. R. Pshenichnov, and N. N. Khromov-Borisov, *Mutat. Res.*, 1991, **253**, 33.
36. V. Murray, *Mutat. Res.*, 1987, **177**, 189.
37. Y. I. Pavlov, V. V. Suslov, P. V. Shcherbakova, T. A. Kunkel, A. Ono, A. Matsuda, and R. M. Schaaper, *Mutat. Res.*, 1996, **357**, 1.
38. S. G. Kozmin, R. M. Schaaper, P. V. Shcherbakova, V. N. Kulikov, V. N. Noskov, M. L. Guetsova, V. V. Alenin, I. B. Rogozin, K. S. Makarova, and Y. I. Pavlov, *Mutat. Res.*, 1998, **402**, 41.
39. Y. I. Pavlov, E. K. Lange, and N. N. Khromov-Borisov, *Issled. Biol. Deistviya Antropogen. Faktorov, Zagryaznyayushch. Vodoemy, Irkutsk*, 1979, 11 (*Chem. Abstr.*, 1980, **93**, 198982).

40. M. McCartney, E. C. McCoy, H. S. Rosenkranz, and A. Giner-Sorolla, *Mutat. Res.*, 1985, **144**, 231.
41. T. G. Rossman, M. Molina, L. Meyer, P. Boone, C. B. Klein, Z. Wang, F. Li, W. C. Lin, and P. L. Kinney, *Mutat. Res.*, 1991, **260**, 349.
42. J. W. Gorrod, C. Ioannides, S. P. Lam, and S. Neville, *Environ. Health Perspect.*, 1993, **101**(Suppl. 3), 21.
43. N. P. Mikhailova, E. F. Sorokoletova, N. N. Khromov-Borisov, L. R. Davidenkov, and A. I. Ginak, *Genetika* (*Moscow*), 1987, **23**, 1414 (*Chem. Abstr.*, 1988, **108**, 1945).
44. E. N. Durasova, N. P. Mikhailova, E. F. Sorokoletova, and K. A. Vy'unov, *Mikrobiologiya*, 1989, **58**, 760 (*Chem. Abstr.*, 1990, **112**, 52123).
45. I. A. Popova, P. A. Pogorelyi, M. V. Gache, and N. N. Khromov-Borisov, *Genetika* (*Moscow*), 1990, **26**, 1551 (*Chem. Abstr.*, 1991, **114**, 78479).
46. G. A. Iroshnikova, E. V. Karpova, and K. V. Kvitko, *Genetika* (*Moscow*), 1986, **22**, 767 (*Chem. Abstr.*, 1986, **105**, 73741).
47. F. J. de Serres and H. E. Brockman, *Prog. Clin. Biol. Res.*, 1986, **209A**(Genet. Toxicol. Environ. Chem., Pt. A), 209.
48. H. E. Brockman, F. J. de Serres, T.-M. Ong, and C. Y. Hung, *Mutat. Res.*, 1987, **177**, 61.
49. H. E. Brockman, F. J. de Serres, C. Y. Hung, and T. Ong, *Mutat. Res.*, 1989, **218**, 1.
50. N. Babudri, D. Salvini, S. Pimpinelli, and G. Morpurgo, *Mutat. Res.*, 1994, **321**, 19.
51. N. Babudri, G. Morpurgo, A. Marini, and G. Prantera, *Antonie van Leeuwenhoek*, 1997, **71**, 249.
52. S. Pimpinelli, A. Marini, N. Babudri, and G. Morpurgo, *Curr. Genet.*, 1997, **32**, 331.
53. C. Cassier, R. Chanet, J. A. P. Henriques, and E. Moustacchi, *Genetics*, 1980, **96**, 841.
54. Y. I. Pavlov and N. N. Khromov-Borisov, *Genetika* (*Moscow*), 1981, **17**, 1406 (*Chem. Abstr.*, 1981, **95**, 182038).
55. E. L. Ivanov, S. V. Koval'tsova, and V. G. Korolev, *Genetika* (*Moscow*), 1987, **23**, 784 (*Chem. Abstr.*, 1987, **107**, 172268).
56. E. L. Ivanov, S. A. Bulat, V. G. Korolev, and S. V. Koval'tsova, *Genetika* (*Moscow*), 1987, **23**, 1383 (*Chem. Abstr.*, 1987, **107**, 172275).
57. Y. I. Pavlov, V. N. Noskov, Y. O. Chernov, and D. A. Gordenin, *Genetika* (*Moscow*), 1988, **24**, 1752 (*Chem. Abstr.*, 1989, **110**, 35145).
58. I. V. Fedorova, V. G. Korolev, and L. M. Gracheva, *Genetika* (Moscow), 1989, **25**, 937 (*Chem. Abstr.*, 1989, **111**, 109992).
59. G. F. Nesterova and A. A. Filatov, *Genetika* (*Moscow*), 1976, **12**, 111 (*Chem. Abstr.*, 1976, **85**, 2398).
60. W. G. Sorenson, J. P. Simpson, and T.-M. Ong, *Mutat. Res.*, 1981, **82**, 95.
61. K. V. C. L. Da Silva and J. A. P. Henriques, *Mutagenesis*, 1987, **2**, 187.
62. E. L. Ivanov, S. N. Sadykov, and I. K. Koroleva, *Genetika* (*Moscow*), 1990, **26**, 30 (*Chem. Abstr.*, 1990, **113**, 146489).
63. E. F. Sorokoletova, T. E. Ogorodnikova, N. P. Mikhailova, K. A. V'yunov, and V. P. Andreev, *Biotekhnologiya*, 1990, 22 (*Chem. Abstr.*, 1991, **114**, 3185).
64. I. V. Fedorova, S. V. Kovaltsova, and E. L. Ivanov, *Genetika* (*Moscow*), 1992, **28**, 54 (*Chem. Abstr.*, 1992, **117**, 208758).
65. V. Noskov, K. Negishi, A. Ono, A. Matsuda, B. Ono, and H. Hayatsu, *Mutat. Res.*, 1994, **308**, 43.
66. V. N. Noskov, K. Staak, P. V. Shcherbakova, S. G. Kozmin, K. Negishi, B.-C. Ono, H. Hayatsu, and Y. I. Pavlov, *Yeast*, 1996, **12**, 17.
67. P. V. Shcherbakova, V. N. Noskov, M. R. Pshenichnov, and Y. I. Pavlov, *Mutat. Res.*, 1996, **369**, 33.

68. P. V. Shcherbakova and Y. I. Pavlov, *Genetics*, 1996, **142**, 717.
69. S. G. Kozmin, V. D. Domkin, A. M. Zekhnov, and Yu. I. Pavlov, *Russ. J. Genet.* (*Transl. of Genetika* (*Moscow*)), 1997, **33**, 487.
70. I. V. Fedorova, L. M. Gracheva, S. V. Kovaltzova, T. A. Evstuhina, S. Y. Alekseev, and V. G. Korolev, *Genetics*, 1998, **148**, 963.
71. F. H. Sobels, J. W. I. M. Simons, A. A. Van Zeeland, and A. G. A. C. Knaap, *Comm. Eur. Communities*, [*Rep.*] *EUR* **1980**, EUR 6388, Environ. Res. Programme, 302 (*Chem. Abstr.*, 1980, **93**, 39110).
72. A. G. A. C. Knaap, P. M. Khan, and J. W. I. M. Simons, *Mutat. Res.*, 1982, **96**, 259.
73. A. G. A. C. Knaap, B. W. Glickman, and J. W. I. M. Simons, *Mutat. Res.*, 1981, **82**, 355.
74. J. C. Barrett, *Proc. Natl. Acad. Sci. U. S. A.*, 1981, **78**, 5685.
75. T. Tsutsui, H. Maizumi, and J. C. Barrett, *Mutat. Res.*, 1985, **148**, 107.
76. R. Ishida and K. R. Utsumi, *Carcinogenesis* (*London*), 1990, **11**, 1209.
77. G. Kury, S. Chaube, and M. L. Murphy, *Arch. Pathol.*, 1968, **86**, 395.
78. L. Mercier-Parot and H. Tuchmann-Duplesis, *C. R. Soc. Biol.*, 1973, **167**, 5 (*Chem. Abstr.*, 1973, **79**, 61731).
79. S. Chaube and M. L. Murphy, *Biochem. Pharmacol.*, 1969, **18**, 1147.
80. N. N. Khromov-Borisov, *Mutat. Res.*, 1997, **379**, 95.
81. R. L. Miller, C. L. K. Sabourin, and T. A. Krenitsky, *Biochem. Pharmacol.*, 1987, **36**, 553.
82. J. F. Henderson and R. E. A. Gadd, *Cancer Chemother. Rep., Suppl.*, 1968, **1**, 363.
83. T. A. Krenitsky, S. M. Neil, G. B. Elion, and G. H. Hitchings, *J. Biol. Chem.*, 1969, **244**, 4779.
84. M. Martin and R. Carbó, *Afinidad*, 1974, **31**, 757 (*Chem. Abstr.*, 1975, **82**, 108128).
85. M. K. Bach and J. Fellig, *Plant Physiol.*, 1960, **35**, 36.
86. D. W. Boerth and F. X. Harding, Jr., *J. Am. Chem. Soc.*, 1985, **107**, 2952.
87. M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 2755.
88. H. von Euler and H. Hasselquist, *Ark. Kemi*, 1958, **13**, 185.
89. M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 2759.
90. R. M. Cresswell and G. B. Brown, *J. Org. Chem.*, 1963, **28**, 2560.
91. S. A. Matlin, P. G. Sammes, and R. M. Upton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2481.
92. (a) T. Saito, H. Hayashibara, Y. Kumazawa, T. Fujisawa, and T. Fujii, *Heterocycles*, 1990, **31**, 1593; (b) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, and T. Fujisawa, *Chem. Pharm. Bull.*, 1991, **39**, 301.
93. M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 1959, **81**, 1734.
94. H. Klenow and S. Frederiksen, *Biochim. Biophys. Acta*, 1961, **52**, 384.
95. H. von Euler, H. Hasselquist, and O. Heidenberger, *Chem. Ber.*, 1959, **92**, 2266.
96. H. von Euler, H. Hasselquist, D. Nomura, and H. Erret, *Ark. Kemi*, 1960, **16**, 187.
97. F. Cramer and H. Seidel, *Z. Naturforsch.*, 1963, **18b**, 510.
98. J. F. Mouret, F. Odin, M. Polverelli, and J. Cadet, *Chem. Res. Toxicol.*, 1990, **3**, 102.
99. N. Signorini, D. Molko, and J. Cadet, *J. Chim. Phys. Phys.-Chim. Biol.*, 1997, **94**, 313.
100. B. Clement and T. Kunze, *Arch. Pharm.* (*Weinheim, Ger.*), 1993, **326**, 25.
101. S. P. Lam, F. Devinsky, and J. W. Gorrod, *Eur. J. Drug Metab. Pharmacokinet.*, 1987, **12**, 239.
102. S. P. Lam, D. J. Barlow, and J. W. Gorrod, *J. Pharm. Pharmacol.*, 1989, **41**, 373.
103. T. Fujii and T. Itaya, *Tetrahedron*, 1971, **27**, 351.
104. T. Monsees, L. Meijer, and B. Jastorff, *Eur. J. Biochem.*, 1993, **213**, 155.
105. D. D. Perrin, *J. Am. Chem. Soc.*, 1960, **82**, 5642.
106. W. Nerdal and E. Sletten, *Inorg. Chim. Acta*, 1986, **114**, 41.
107. J. P. Garel, D. Filliol, and P. Mandel, *J. Chromatogr.*, 1973, **78**, 381.

108. G. B. Brown, G. Levin, and S. Murphy, *Biochemistry,* 1964, **3**, 880.
109. J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, 1966, **31**, 966.
110. A. Guranowski and Z. Schneider, *Biochim. Biophys. Acta*, 1977, **482**, 145.
111. L. Sweetman and W. L. Nyhan, *J. Chromatogr.*, 1968, **32**, 662.
112. R. B. van Breemen, C.-R. Huang, D. Nikolic, C. P. Woodbury, Y.-Z. Zhao, and D. L. Venton, *Anal. Chem.*, 1997, **69**, 2159.
113. J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, 1971, **36**, 2639.
114. P. Prusiner and M. Sundaralingam, *Acta Crystallogr., Sect. B*, 1972, **28**, 2142.
115. G. Horn, *Monatsber. Deut. Akad. Wiss. Berlin*, 1961, **3**, 386 (*Chem. Abstr.*, 1962, **57**, 3196*g*).
116. C. R. Warner and P. J. Elving, *U. S. At. Energy Comm.* **COO-1148-95** (1965) (*Chem. Abstr.*, 1965, **63**, 15860*a*).
117. C. R. Warner and P. J. Elving, *Collect. Czech. Chem. Commun.*, 1965, **30**, 4210.
118. M. Borbil, R. Nutiu, M. Mracec, and Z. Simon, *Rev. Roum. Biochim.*, 1978, **15**, 3.
119. M. Ikawa, C. A. Dollard, and T. D. Schaper, *J. Agric. Food Chem.*, 1988, **36**, 309.
120. G. Stöhrer and G. B. Brown, *J. Biol. Chem.*, 1969, **244**, 2498.
121. M. Sagai and M. Ishimoto, *J. Biochem. (Tokyo)*, 1973, **73**, 843.
122. (a) E. W. Harlan, J. M. Berg, and R. H. Holm, *J. Am. Chem. Soc.*, 1986, **108**, 6992; (b) S. F. Gheller, B. E. Schultz, M. J. Scott, and R. H. Holm, *ibid.*, 1992, **114**, 6934; (c) B. E. Schultz, S. F. Gheller, M. C. Muetterties, M. J. Scott, and R. H. Holm, *ibid.*, 1993, **115**, 2714.
123. M. Sundaralingam and S. M. Hecht, *J. Chem. Soc. D*, 1971, 240.
124. E. Sletten, T. Marthinsen, and J. Sletten, *Inorg. Chim. Acta*, 1985, **106**, 1.
125. M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 1960, **82**, 3189.
126. G. B. Brown, M. A. Stevens, and H. W. Smith, *J. Biol. Chem.*, 1958, **233**, 1513.
127. (a) D. Dunn, M. H. Maguire, and G. B. Brown, *J. Biol. Chem.*, 1959, **234**, 620; (b) For an earlier review on the chemistry and metabolism of adenine 1-oxide (**5**), see G. B. Brown, *Proc. Intern. Congr. Biochem., 4th, Vienna, 1958,* 1960, **13**, 111 (*Chem. Abstr.*, 1960, **54**, 13306*d*).
128. R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *J. Org. Chem.*, 1965, **30**, 408.
129. H. Kawashima and I. Kumashiro, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 639.
130. F. Cramer and G. Schlingloff, *Tetrahedron Lett.*, 1964, 3201.
131. G. Levin, R. B. Setlow, and G. B. Brown, *Biochemistry*, 1964, **3**, 883.
132. M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 1960, **82**, 1148.
133. G. Stöhrer and G. Salemnick, *Cancer Res.*, 1975, **35**, 122.
134. T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.*, 1965, **13**, 1017.
135. T. Fujii, T. Saito, and Y. Kumazawa, *Chem. Pharm. Bull.*, 1990, **38**, 1392.
136. (a) T. Fujii, I. Inoue, T. Itaya, and T. Saito, *Heterocycles*, 1979, **12**, 1543; (b) *Idem*, *Chem. Pharm. Bull.*, 1980, **28**, 3443.
137. T. Fujii, S. Kawakatsu, and T. Itaya, *Chem. Pharm. Bull.*, 1974, **22**, 2466.
138. (a) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.*, 1966, **14**, 1452; (b) T. Fujii and T. Itaya, *ibid.*, 1971, **19**, 1611.
139. T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.*, 1972, **20**, 958.
140. T. Fujii, T. Itaya, T. Saito, and S. Kawakatsu, *Chem. Pharm. Bull.*, 1984, **32**, 4842.
141. A. Tensho, T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, **U.S. 3,813,394** (28 May 1974) (*Chem. Abstr.*, 1974, **81**, 49986).
142. (a) T. Fujii, C. C. Wu, T. Itaya, and S. Yamada, *Chem. Ind. (London)*, 1966, 1598; (b) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, 1971, **19**, 1368.
143. T. Fujii, T. Saito, T. Itaya, and K. Yokoyama, *Chem. Pharm. Bull.*, 1973, **21**, 209.
144. (a) T. Fujii, T. Saito, and T. Fujisawa, *Heterocycles*, 1988, **27**, 1163; (b) *Idem*, *Chem. Pharm. Bull.*, 1994, **42**, 1231.

145. T. Fujii, C. C. Wu, T. Itaya, S. Moro, and T. Saito, *Chem. Pharm. Bull.*, 1973, **21**, 1676.
146. T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, *Chem. Pharm. Bull.*, 1983, **31**, 3149.
147. For a recent review on the chemistry of 1-alkoxyadenine derivatives, see T. Fujii and T. Itaya, *Rev. Heteroat. Chem.*, 1997, **16**, 257. (In that paper, pages 274 and 275 were mistakenly interchanged owing to a printing error.)
148. See ref. 5, pp. 448–450 and pp. 550–552.
149. T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.*, 1972, **20**, 1818.
150. For a recent review on the Dimroth rearrangement in the adenine series including that of 1-alkoxyadenine derivatives, see T. Fujii and T. Itaya, *Heterocycles*, 1998, **48**, 359.
151. T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.*, 1971, **19**, 1731.
152. J. P. Devlin, *Can. J. Chem.*, 1976, **54**, 2804.
153. (a) J. L. Davidson, I. E. P. Murray, and P. N. Preston, *J. Chem. Res.* (*S*), 1981, 126; (b) *Idem*, *J. Chem. Res.* (*M*), 1981, 1601.
154. T. J. Boritzki, B. D. Palmer, J. M. Coddington, and W. A. Denny, *Chem. Res. Toxicol.*, 1994, **7**, 41.
155. T. Utagawa, H. Morisawa, S. Yamanaka, A. Yamazaki, F. Yoshinaga, and Y. Hirose, *Agric. Biol. Chem.*, 1985, **49**, 2167.
156. R. Fathi, K. J. Nawoschik, M. Zavoda, and A. F. Cook, *Nucleosides Nucleotides*, 1997, **16**, 1907.
157. J. D. Sullivan, **U.S. 3,939,084** (17 Feb 1976) (*Chem. Abstr.*, 1976, **85**, 8093).
158. C. M. Mikulski, R. De Prince, T. Ba Tran, F. J. Iaconianni, L. L. Pytlewski, A. N. Speca, and N. M. Karayannis, *Inorg. Chim. Acta*, 1981, **56**, 163.
159. M. D. Poojary and H. Manohar, *Inorg. Chim. Acta*, 1984, **93**, 153.
160. E. Sletten, T. Marthinsen, and J. Sletten, *Inorg. Chim. Acta*, 1984, **93**, 37.
161. G. B. Brown, D. A. Clarke, J. J. Biesele, L. Kaplan, and M. A. Stevens, *J. Biol. Chem.*, 1958, **233**, 1509.
162. J. F. Henderson, *Biochem. Pharmacol.*, 1963, **12**, 551.
163. (a) K. Sugiura, *Cancer Chemother. Rep., Suppl.*, 1968, **1**, 383; (b) Similar results have also been reported: K. Sugiura and G. B. Brown, *Cancer Res.*, 1967, **27**, 925.
164. C. M. Smith, G. Zombor, and J. F. Henderson, *Cancer Treat. Rep.*, 1976, **60**, 1567.
165. R. E. A. Gadd and J. F. Henderson, *Can. J. Biochem.*, 1970, **48**, 295.
166. (a) C. M. Smith, L. J. Fontenelle, H. Muzik, A. R. P. Paterson, H. Unger, L. W. Brox, and J. F. Henderson, *Biochem. Pharmacol.*, 1974, **23**, 2727; (b) J. F. Henderson and C. M. Smith, *Proc. Int. Congr. Chemother., 8th*, 1973, **3**, 152 (*Chem. Abstr.*, 1976, **84**, 53822).
167. K. Sugiura, M. N. Teller, J. C. Parham, and G. B. Brown, *Cancer Res.*, 1970, **30**, 184.
168. J. J. Sixma, H. Holmsen, and A. C. M. Trieschnigg, *Biochim. Biophys. Acta*, 1973, **298**, 460.
169. J. P. M. Lips, J. J. Sixma, and A. C. Trieschnigg, *Biochem. Pharmacol.*, 1980, **29**, 43.
170. T. Minami, H. Nakagawa, M. Nabeshima, E. Kadota, K. Namikawa, H. Kawaki, and Y. Okazaki, *Biol. Pharm. Bull.*, 1994, **17**, 1032.
171. K. Uehara, T. Hayakawa, T. Nabeshima, and M. Yamamura, *Yakugaku Zasshi*, 1973, **93**, 794 (*Chem. Abstr.*, 1974, **80**, 10700).
172. I. Scheinfeld, J. C. Parham, S. Murphy, and G. B. Brown, *J. Org. Chem.*, 1969, **34**, 2153.
173. (a) H. Kawashima and I. Kumashiro, **Japan. 70 28,783** (19 Sep 1970) (*Chem. Abstr.*, 1971, **74**, 42375); (b) For an earlier work of Y. Mizuno and E. Ohtsuka to obtain **6** by cyclization of 4,6-diamino-5-formamidopyrimidine 1-oxide, see the first page of ref. 173a and Y. Mizuno, 'Kakusan Kagaku,' Part I, Asakura Publishing Co., Tokyo, 1970, p. 73.
174. A. Giner-Sorolla, *J. Heterocycl. Chem.*, 1971, **8**, 651.

175. (a) U. Wölcke, W. Pfleiderer, T. J. Delia, and G. B. Brown, *J. Org. Chem.*, 1969, **34**, 981; (b) A recent alternative synthesis of isoguanine (**41**) from adenine 3-oxide (**6**) involves methylation of **6** with MeI in $AcNMe_2$ at 30°C for 24 h to give 3-methoxyadenine in 44% yield and subsequent treatment of the product with 0.1 N aqueous NaOH at room temperature for 1 h to afford **41** in 38% yield: T. Itaya, T. Kanai, Y. Takada, M. Kaneko, K. Yasuhara, and T. Fujii, *Chem. Pharm. Bull.*, 1999, **47**, 554.
176. See ref. 4, pp. 50–51.
177. H.-J. Rhaese, *Biochim. Biophys. Acta*, 1968, **166**, 311.
178. O. Yamamoto, *J. Radiat. Res.*, 1980, **21**, 239.
179. (a) H.-J. Rhaese and E. Freese, *Biochim. Biophys. Acta*, 1968, **155**, 476; (b) H.-J. Rhaese, E. Freese, and M. S. Melzer, *ibid.*, 1968, **155**, 491.
180. (a) T. Fujii, K. Ogawa, T. Saito, K. Kobayashi, and T. Itaya, *Heterocycles*, 1994, **38**, 477; (b) T. Fujii, K. Ogawa, T. Saito, K. Kobayashi, T. Itaya, T. Date, and K. Okamura, *Chem. Pharm. Bull.*, 1995, **43**, 53.
181. For a recent review on the N(7)-oxides of purines related to nucleic acids, see T. Fujii, T. Itaya, and K. Ogawa, *Heterocycles*, 1997, **44**, 573.
182. T. Fujii, G. C. Walker, N. J. Leonard, D. C. DeLong, and K. Gerzon, *J. Med. Chem.*, 1979, **22**, 125, and references cited therein.
183. Y. Maki, M. Suzuki, and K. Ozeki, *Tetrahedron Lett.*, 1976, 1199.
184. T. Itaya, Y. Takada, and T. Fujii, *Chem. Pharm. Bull.*, 1996, **44**, 2025.
185. T. Fujii, K. Ogawa, T. Saito, T. Itaya, T. Date, and K. Okamura, *Chem. Pharm. Bull.*, 1995, **43**, 321.
186. T. Fujii, Y. Takada, K. Ogawa, T. Itaya, and S. Matsubara, *Chem. Pharm. Bull.*, 1995, **43**, 325.
187. These reaction conditions were identical to those employed by Nasyr *et al.* [I. A. Nasyr, G. P. Mozgovaya, Yu. V. Karabanov, I. V. Boldyrev, V. P. Borisenko, and V. M. Cherkasov, *Fiziol. Akt. Veshchestva*, 1982, **14**, 91 (*Chem. Abstr.*, 1983, **99**, 48877)] to obtain an *N*-oxide [mp 222–224°C (decomp)] in 33% yield from **85**.
188. (a) T. Fujii, K. Ogawa, and T. Itaya, *Heterocycles*, 1994, **37**, 219; (b) T. Itaya, K. Ogawa, Y. Takada, and T. Fujii, *Chem. Pharm. Bull.*, 1996, **44**, 967.
189. R. M. B. Dias and A. J. S. C. Vieira, *J. Chim. Phys. Phys.–Chim. Biol.*, 1993, **90**, 899.
190. A. J. S. C. Vieira, J. P. Telo, and R. M. B. Dias, *J. Chim. Phys. Phys.–Chim. Biol.*, 1997, **94**, 318.
191. R. N. Goyal, A. Kumar, and A. Mittal, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1369.
192. T. Fujii, K. Ogawa, T. Itaya, T. Date, J. Inagaki, and F. Nohara, *Chem. Pharm. Bull.*, 1995, **43**, 408.
193. A. A. Watson, *J. Org. Chem.*, 1977, **42**, 1610.
194. N. C. Yang and C.-W. Chang, *Proc. Natl. Acad. Sci. U. S. A.*, 1985, **82**, 5250.
195. M. R. Harnden and P. G. Wyatt, *Tetrahedron Lett.*, 1990, **31**, 2185.
196. A. Parkin, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2983.
197. C. U. Kim, J. C. Martin, B. Y. Luh, and P. F. Misco, **Eur. Pat. Appl. EP 494,370** (15 Jul 1992) [**US Appl. 619,856** (29 Nov 1990)] (*Chem. Abstr.*, 1992, **117**, 212896).
198. C. U. Kim, B. Y. Luh, and J. C. Martin, *Tetrahedron Lett.*, 1992, **33**, 25.

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