THE PURINES

Supplement 1

This is the fifty-fourth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

ARNOLD WEISSBERGER, *Founding Editor*

THE PURINES

Supplement 1

John H. Lister

Former Senior Research Fellow
The Australian National University
Canberra, Australia

With an Essay by

M. David Fenn

Northern Territory University
Darwin, Australia



AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS, INC.

NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

This text is printed on acid-free paper.

Copyright © 1996 by John Wiley & Sons, Inc.

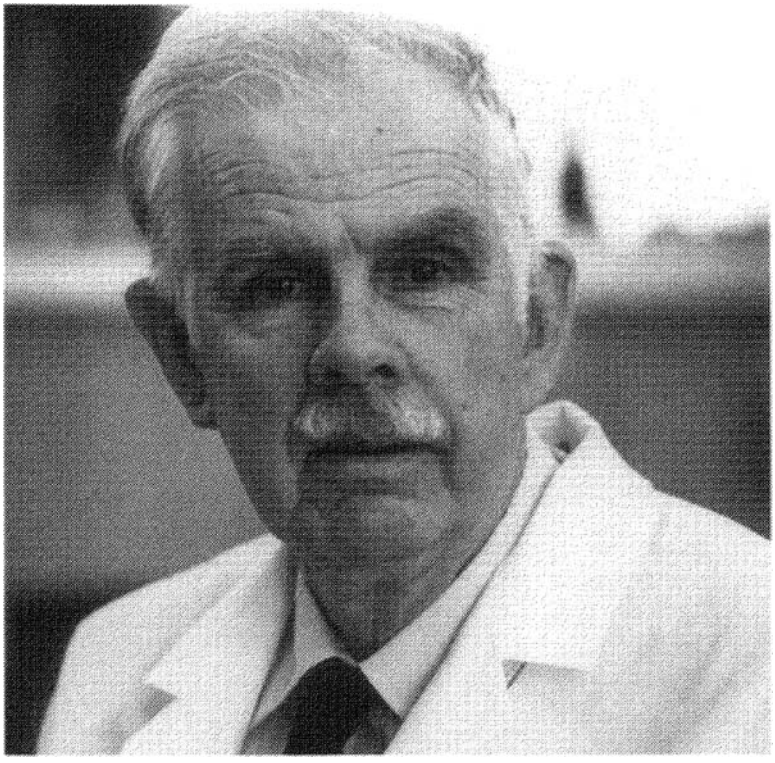
All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012.

Library of Congress Cataloging in Publication Data:

Lister, John Henry.
The purines. Supplement I / by John H. Lister ; with an essay by M. David Fenn.
p. cm.
"An Interscience publication."
Includes index.
ISBN 0-471-08094-2 (cloth: alk. paper)
1. Purines. I. Title.
QD401.F96, pt. 2. Suppl.
547'.596—dc20 95-45002

10 9 8 7 6 5 4 3 2 1



DR. D. J. BROWN

An Appreciation

Although now retired, Des Brown, former Head of Medical Chemistry in the John Curtin School of Medical Research, the Australian National University, still retains an active involvement in the chemistry of pyrimidines and related derivatives, which has been his major interest for over four decades. This commitment is reflected in his authorship of the collected works, *The Pyrimidines*, in the *Heterocyclic Compounds* series and a further work in the same series, *Pteridines*, which forms Part 3 of a composite Volume 24 devoted to *Fused Pyrimidines*. To these achievements should be added his many contributions, both practical and literary, to this important area of heterocyclic chemistry.

J. H. L.

The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship or Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance which impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes are of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction created as many problems as it solved, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry* and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

As Dr. Lister has stated so cogently in his Preface, this Supplement is indeed intended to be precisely that—an addition/expansion to his previous volume on purine chemistry, which appeared as Vol. 24, Part II in the present series in 1971. A deliberate attempt has been made to concentrate on updating those areas of purine chemistry that, in the author's judgment, merit discussion on the basis of utility, novelty, or fundamental interest. Readers should therefore note that Volume 24, Part II and the present Supplement together constitute a rigorous and fairly exhaustive treatment of purine chemistry; either volume alone would

be inadequate. Dr. Lister is to be commended for his lucid and beautifully organized presentation of an extremely active field that is of immense interest to both chemistry and biology.

Department of Chemistry
Princeton University
Princeton, New Jersey

EDWARD C. TAYLOR

Preface

At any point in time, a subject can be reviewed in the light of its past, present, and future perspectives. In this supplementary volume to the original, which appeared in 1971, the basic aim is to explore the first two of these aspects and to indicate possible future trends or developments. The major emphasis in the parent volume centered on the synthetic approaches available, but in the two decades since its publication a shift away from these has been noted. More emphasis is now being placed on investigations of the nature and reactions of the purine system. New or improved syntheses continue to appear; in many cases the introduction of novel and sometimes esoteric reagents enables these previously unattainable preparations to be made. Because of their ubiquitous distribution, naturally occurring purines continue to attract the interest of workers in diverse scientific disciplines, with significant data being disseminated over an ever-proliferating number of journals. In an attempt to survey the literature, a selective approach has been adopted in this volume, and the reader's forgiveness is sought if a point of particular interest appears to have been overlooked. One aspect of this is seen in comparison of the chapter contents with those of the parent volume; the omission of a particular section or topic indicates that significant or novel features have not been noted.

In a work of this nature, the author can only be one of the players, and the final outcome is the result of many efforts, large and small. I wish to record my deep appreciation to Wilf Armarego for so elegantly producing the majority of the formulas; these were supported by supplementary ones drawn by Maxine Tyler. I am also grateful to David Fenn for contributing a timely exposition of the present state of the NMR of purine derivatives; this work fills a gap in the current literature. The interest and encouragement expressed by my colleagues during the preparation of this volume has been most gratifying; in particular, the support of Des Brown has been greatly valued. It would be remiss of me not to acknowledge the patience and forbearance shown by Professor E. C. Taylor as editor who, like the policeman in the *Pirates of Penzance*, does not have a happy lot when dealing with tardy authors. I owe a special debt to Mandi Weymes, who carried out the onerous task of transforming the rough copy to the final printout with great cheerfulness. My thanks are also given to the University of Hull for the use of the library and to Kathy Rabl of the Australian National University for her kindness in obtaining the photograph of Dr. Brown. Lastly, a special "thank you" goes to my wife, June, and children, Catherine and David, for all their help and support, in many ways, throughout the writing process.

Kirkella, England JOHN H. LISTER

Contents

	List of Tables	xiii
I.	Introduction to the Purines (*H*1)	1
II.	Synthesis from Pyrimidines	21
III.	Purine Syntheses from Imidazoles and Other Precursors (*H*91)	61
IV.	Purine and *C*-Alkyl, *C*-Aryl, and *N*-Alkyl Derivatives (*H*117)	83
V.	Halogenopurines (*H*135)	99
VI.	Oxo-(Hydroxy-) and Alkoxypurines (*H*203)	133
VII.	Thioxo- and Selenoxopurines and Derivatives (*H*269)	179
VIII.	The Amino (and Amino-Oxo)purines (*H*309)	213
IX.	The Purine Carboxylic Acids and Related Derivatives (*H*367)	283
X.	Nitro-, Nitroso-, and Arylazopurines (*H*401)	303
XI.	Purine-*N*-Oxides (*H*409)	307
XII.	The Reduced Purines (*H*427)	325
XIII.	Enlarged Purine-Containing Structures (*New*)	337
XIV.	The Spectra of Purines (*H*507)	347
XV.	Systematic Tables of Simple Purines	385
REFERENCES		425
INDEX		455

List of Tables

TABLE 1	Trivial Names of Purines	3
TABLE 2	8-Thioxopurines Derived from Ring Closures with Carbon Disulfide	37
TABLE 3	Uric Acid Derivatives Derived from Alkyl Chlorocarbonate Cyclizations	38
TABLE 4	Examples of Approaches Used to Form 7- and 9-Alkyl Derivatives of Halogenopurines	131
TABLE 5	Alkylation of Theophylline and Other 1,3-Dialkylxanthines to 1,3,7-Trialkylxanthines	154
TABLE 6	Examples of 8-Thioxopurine Formation by the Traube Reaction with 4,5-Diaminopyrimidines	181
TABLE 7	Alkylation of Adenine Under Phase-Transfer Catalysis Conditions	257
TABLE 8	Examples of Approaches Used for *N*-Alkylation of Adenines	257
TABLE 9	Examples of 7- and 9-Alkylation of Guanines	260
TABLE 10	^{1}H Spectra of Some Simple Purines	349
TABLE 11	^{13}C Spectra of Some Simple Purines	363
TABLE 12	^{15}N Spectra of Simple Purines	369
TABLE 13	References for Nitrogen Chemical Shifts	370
TABLE 14	Alkyl and Aryl Purines	387
TABLE 15	*C*- and *N*-Alkyl and Aryl Adenines	388
TABLE 16	Other Aminopurines Including *N*-Aminopurines	390

TABLE 17 Carboxy, Alkoxycarbonyl, Carbamoyl and Related Purines 395

TABLE 18 Halogenopurines 397

TABLE 19 *C*- and *N*-Alkyl Hypoxanthines 398

TABLE 20 *C*- and *N*-Alkyl Xanthines 400

TABLE 21 Other Oxopurines and Alkoxypurines 404

TABLE 22 Thioxo and Alkylthiopurines 406

TABLE 23 Amino-Oxopurines 410

TABLE 24 Amino-Thioxopurines 413

TABLE 25 Oxo-Thiopurines 415

TABLE 26 Reduced Purines 418

TABLE 27 Miscellaneous Purines 419

TABLE 28 Isotopically Labeled Purines 422

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER I

Introduction to the Purines (*H*1)

1. Introduction (*H*1) . . . 2
2. Nomenclature and Notation (*H*5) . . . 2
3. Chemistry of the Purines (*H*9) . . . 2
   A. Electrophilic Substitution (*H*9) . . . 2
      a. At a Carbon Atom (*H*10) . . . 2
      b. At a Nitrogen Atom (*N*-Alkylation) (*H*10) . . . 4
   B. Nucleophilic Substitution (*H*11) . . . 5
      a. The ANRORC Reaction (*New*) . . . 5
   C. Group Interconversions (*H*14) . . . 6
      a. Interchange of Halogen Atoms (*H*14) . . . 6
      b. Oxo- to Aminopurines (*H*14) . . . 6
      c. Oxo- to Chloropurines (*H*15) . . . 6
      d. Oxo- to Thioxopurines (*H*15) . . . 6
      e. Thioxo- and Methylthio- to Oxopurines (*H*16) . . . 7
      f. Thioxo- and Methylthio- to Chloropurines (*H*16) . . . 7
      g. Thioxo- and Selenoxo- to Aminopurines (*H*17) . . . 7
      h. Interchange of Amino Groups (*H*17) . . . 7
      i. Amino- to Oxopurines (*H*17) . . . 8
      j. Amino- to Halogenopurines (*H*17) . . . 8
      k. Halogeno- to Alkylpurines (*New*) . . . 8
      l. Amino- to Thioxo- and Selenoxopurines (*New*) . . . 9
      m. Amino Group to Hydrogen (*New*) . . . 9
   D. Addition Reactions (*H*18) . . . 9
      a. The Michael Reaction (*H*18) . . . 9
      b. Quaternary Derivatives (*H*18) . . . 10
      c. *N*-Oxides (*H*19) . . . 10
      d. Addition to Double Bonds (*H*19) . . . 10
      e. The Chichibabin Reaction (*New*) . . . 11
   E. Substituent Modification (*H*19) . . . 11
      a. Amino Groups (*H*20) . . . 11
      b. Oxo Groups (*H*20) . . . 12
      c. Thioxo Groups (*H*21) . . . 12
      d. Methyl and Other Alkyl Groups (*H*21) . . . 12
   F. Radical Reactions (*New*) . . . 12
   G. Proton Exchange at Carbon Atoms (*New*) . . . 13
4. Physical Properties (*H*25) . . . 16
   A. Electronic Considerations (*H*25) . . . 16
      a. Protonation (*H*25) . . . 17
      b. 7H—9H Prototropy (*New*) . . . 18
      c. Tautomerism in Amino-, Oxo-, and Thioxopurines (*New*) . . . 18

B. Crystal Structure (*H*26) 19
5. Literature of the Purines 20

1. INTRODUCTION (*H*1)

In the parent work this chapter was devoted to a history and an outline summary of the preparation, reactions, and properties of purines. The same format is followed here, with topics requiring the addition of new data being highlighted, as are those that need further elaboration or correction of earlier results. Areas that have not changed significantly, for example, nucleophilic substitution, are only briefly surveyed. However, the section dealing with aspects of group interconversions is accorded more generous coverage in view of the significant developments made in reactions of this type. Many of the innovations result from chemotherapeutic studies, a large number of which are in the areas of antiviral activity and neoplasia. The search for medicinal compounds in nature has greatly enlarged the number of naturally occurring purines known; these are listed in Table 1 together with important derivatives from other sources. Proton exchanges at C-8 of purines, innovations with radical participation, and the ANRORC reaction are also covered in this chapter.

2. NOMENCLATURE AND NOTATION (*H*5)

To maintation conformity with the parent work the older nomenclature has been retained. For example, xanthine using substitutive names, is represented as 1,2,3,6-tetrahydro-2,6-dioxopurine rather than the current purine-2,6-dione. Overuse of this system in the oxopurines is however, avoided where possible by citing them as derivatives of hypoxanthine, xanthine, uric acid, and guanine. Reference made to earlier work in the parent volume uses the form adopted by D. J. Brown in *The Pyrimidines* in which the original page number, preceded by the letter *H*, is given in parentheses.

3. CHEMISTRY OF THE PURINES (*H*9)

A. Electrophilic Substitution (*H*9)

a. At a Carbon Atom (H10)

Reactions of this type are usually confined to C-8, but the nature of the substitution, which may be ionic or radical in character, is often difficult to classify. Examples available include 8-methylpurines formed from diazomethane treatment, various 8-alkenylpurines obtained from interaction with sodium alkoxides

TABLE 1. Trivial Names of Purines

Trivial Name	Source	Purine Base	Ref.
Acyclovir	Synthesis	Guanine	1662
Adenomycin	Bacterium *S. griseoflavus*	Adenine	1604
Ageline A and B	Pacific sponge *Agelas sp.*	9-Methyladenine	1888
Agrocyn 84	Bacterium *Agrobacterium radiobacter*	Adenine	1698
Ara A	Bacterium *S. Antibioticus*	Adenine	1623
(±)-Aristeromycin	Bacterium *S. citricolor n.s.p.*	Adenine	1586
Arprinocid R	Synthesis	Adenine	1524
Ascamycin	*Streptomyces* cultures	2-Chloroadenine	1602
Azathioprine	Synthesis	6-(Imidazol-5-yl) thiopurine	1374
6-BAP	Synthesis	6-Benzylaminopurine	1152
Caissarone	Sea anemone *Bunodesorma caissarum*	6-Methylamino-3, 9-dimethyl-8-oxopurine	1850
Carbovir	Synthesis	Guanine	1668
Coformycin[a]	Bacterium *S. Kaniharaensis*	Imidazodiazepine	1103
Cyclaridine	Synthesis	Adenine	1591
DHPA	Synthesis	Adenine	1688
DHPG	Synthesis	Guanine	1270
Discadine	Slime mold *Dictyostelium discoideum*	6-Alkenylamino-3-methlpurine	1611
Doridosine	Marine microfauna *Anisodoris nobilis*	1-Methylisoguanine	1682
Eritadenine	Synthesis of D- and L-Forms	Adenine	1581
Exotoxin	Bacterium *B. thuringiensis*	Adenine	1597
Gonyautoxin II and III	Shellfish *Mya arenaria*	Reduced 2, 8-Diminopurine	1630
Guancyclovir	Synthesis	Guanine	1841
Imuran (*see* Azathioprine)			
Lupinic acid	Pea plant metabolite *Lupinus augustifolius*	6-Alkenylamino purine	1608
Neplanocin A	*Actinoplanacea Ampullariella s.p.*	Adenine	1591
Oxetanocin	Bacterium *B.megaterium*	Adenine	1848
Pentostain[a]	Bacterium *S. antibioticus*	Imidazodiazepine	1626
Phidolopin	Marine microfauna *Phidolopora pacifica*	Theophylline	1691
Raphanitin	Radish leaves	6-Alkenylamino purine	986
Saxitoxin	Shellfish *Saxidomus giganteus*	Reduced 2, 8-Diaminopurine	1629
Sinefungin	Bacterium *S. griseolous*	Adenine	1594

(cont.)

TABLE 1. *(cont.)*

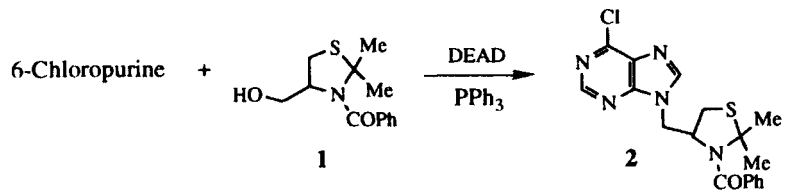
Trivial Name	Source	Purine Base	Ref.
Spongoadenosine (*see* Ara A)			
Tedania (*see* Doridosine)	Sponge *Tedania digitata*	1-Methyl-isoguanosine	1681
Verdan (*see* 6-BAP)			
Vidarabine (*see* Ara A)			
Wybutine	Yeast *Saccharomyces cerevisiae*	Imidazo [1, 2-*a*] purine	1824
Wybutosine	Yeast *Torulopsis utilis*	Imidazo [1, 2-*g*] purine	1653
Wyosine	Synthesis	Imidazo [1, 2-*a*] purine	1649
Y-Base (or Wye base)	Yeast *Torulopsis utilis*	Imidazo [1, 2-*g*] purine	1650
Zovirax (*see* Acyclovir)			

[a] Purine analogs.

of allyl and crotyl alcohols, and 8-benzylations occurring in aqueous solution with benzyl halides.

b. At a Nitrogen Atom (N-Alkylation) (H10)

A number of innovations to alkylation techniques have been introduced recently. The two most significant are: (1) phase transfer catalysis (PTC), which affords high yields with either liquid–solid or liquid–liquid phases containing tetraalkylammonium salts as catalysts and using conventional alkylating agents; and (2) the completely different Mitsunobu reaction, in which alcohols are the alkylating species and react by an intermolecular dehydration in the presence of a diethylazodicarboxylate (DEAD) and triphenylphosphine combination in THF. Ambient temperatures are usually sufficient and the reaction provides generous yields. The reaction between 6-chloropurine and the hydroxymethylthiazolidine (**1**) giving the 9-alkyl derivative (**2**) is typical of this approach. Other novel routes include trimethylphosphate with a tetrabutylammonium fluoride catalyst



1 **2**

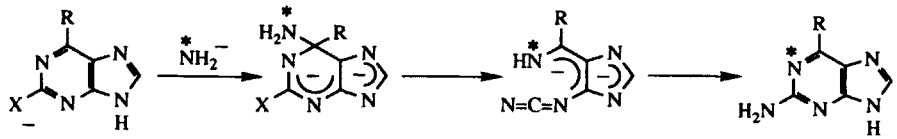
for *N*-methylation of adenine, guanine, and xanthine in a haloalkane solvent; alkylation of xanthine derivatives is also possible with trialkylphosphates in aqueous solution. More restricted in scope is the use of trimethylphosphite without solvent, which requires a higher temperature (130°C); other homologous trialkylphosphites appear to have no alkylating function. Among various other reagents showing methylating potential are tetramethylammonium hydroxide and 6-trimethylammoniopurines. Even alkylations made under the usual conditions benefit from the presence of a tetrabutylammonium salt catalyst.

B. Nucleophilic Substitution (*H*11)

A number of reaction rate studies, notably with chloro-, methylthio-, and methylsulfonylpurines have been carried out, the last of these groups showing a more enhanced activity toward replacement compared with the other two substituents. Somewhat unexpected is the order of reactivity of 8 > 6 >> 2 for the methylsulfonylpurines compared with that of 6 > 8 > 2 found in other nucleophilic substitutions. This activation of the sulfonyl moiety is seen in a successful substitution occurring when the chloropurine analog failed to react. A monograph covering mainly nucleophilic reactions of methylthiopurines is available.[1943]

a. The ANRORC Reaction (New)

This specialized form of nucleophilic attack is through the amide anion (NH_2^-) derived from potassium amide dissolved in liquid ammonia. In the S_N (ANRORC) reaction (Addition of Nucleophile, Ring Opening, Ring Closing), an apparent case of simple group substitution in fact entails fission of the pyrimidine ring and reclosure in which insertion of the amide nitrogen into the ring at N-1 occurs. Elucidation of the mechanism by means of labeled $K^{15}NH_2$ (IR, ^1H NMR) shows that the formation of 2-aminopurine from either the 2-fluoro, 2-chloro, or 2-methylthio analogs follows the pathway in Scheme 1. Initially σ adduct forms with fission of the 1,6-bond then following to give the imidazole anion as a common intermediate from any of the precursors. On subsequent recyclization to the 2-aminopurine, the product contains the label at the 1-position. The reaction has limited scope and the presence of substituents at C-6 in some cases precludes any reaction taking place. For example, 2-chloro-6-phenylpurine affords the N-1 labeled 2-aminopurine, but 2-chloro-6-methylpurine is unreacted. An interesting extension is for the conversion of a number of 6- and 8-substituted 1-amino-



Scheme 1

purines to the *N*-deaminated analogs in which the products also contain a label at the N-1 position. In these examples, labeled ammonia in methanol is the reagent. Use of this procedure to prepare ^{15}N-1 labeled purines is of practical value in view of the various types of 1-aminopurines that undergo the reaction. A review of this topic covering ring degradation of azines including purines is available.[1942] It should be noted that the Chichibabin reaction also occurs under the same conditions (see Section 3.D.e).

C. Group Interconversions (*H*14)

a. Interchange of Halogen Atoms (H14)

The indirect route from chlorine to fluoro using formation of an intermediate trimethylammonio drivative before reaction with fluoride ion has been followed on a number of occasions since first used to prepare 6-fluoropurine (*H*144). At present, the conversion of an 8-bromopurine to the 8-fluoro analog by means of potassium fluoride in acetonitrile containing an 18-crown-6-ether has not been well studied. In the absence of this catalyst no interchange occurs (see Chapter V, Section 1.G.b).

b. Oxo- to Aminopurines (H14)

Use of phosphoramides at elevated temperatures will convert an oxo group directly to an amino group (see Chapter VI, Section 6.G). Somewhat similar is an approach using phosphorus pentoxide and the hydrochlorides of primary and secondary amines. Following silylation of the oxo group, amination is possible with ammonia, amine salts, or amines with Lewis acids. Reaction of hypoxanthine derivatives with phenylphosphorodiamidic acid gives the 6-aminopurine analogs. A more recent alternative to the older procedure with phosphoryl chloride–amine mixtures is using 4-chlorophenylphosphorodichloridate.

c. Oxo- to Chloropurines (H15)

An improved chlorination of 9-substituted guanines using the standard phosphoryl chloride–dimethylaniline mixture is claimed by employing acetonitrile as solvent (see Chapter V, Section 1.B.b). In the formation of 2,6-dichloropurines from xanthines, better yields result from replacing dimethylaniline in the above mixture with triethylamine or another aliphatic tertiary amine.

d. Oxo- to Thioxopurines (H15)

No significant innovations are described, most conversions with phosphorus pentasulfide now appear to favor β-picoline as solvent in place of pyridine.

Sulfolane has been a successful medium for thiation of guanine to thioguanine. By use of a combination of pyridine with trifluoroacetic acid and subsequent treatment with sodium hydrogen sulfide, the unprotected form of guanosine can be transformed into the 6-thioxo analog (see Chapter VI, Section 6.B).

e. Thioxo- and Methylthio- to Oxopurines (H16)

Reaction rates for the hydrolysis of alkylthiopurines show that the order of nucleophilic displacement follows the sequence 6 > 8 > 2 in both acid and alkali. Hydrolyzing thioxo groups is less facile, but is aided by incorporation of an oxidizing agent such as hydrogen peroxide in an alkaline medium. Satisfactory conversions of 6-thioxo and 6-methylthiopurines to the oxopurine analogs under acid conditions have utilized either *m*-chloroperbenzoic acid (MCPBA) in chloroform or peroxyacetic acid for this purpose (see Chapter VI, Section 1.F).

f. Thioxo- and Methylthio- to Chloropurines (H16)

Chlorine in acetonitrile or hydrochloric acid converts both thioxo and methylthio groups to the halogen atom (see Chapter V, Section 1.C). Use of controlled conditions, notably a low temperature, are recommended to obviate the explosion hazard present when a buildup of methyl hypochlorite occurs using the older procedures employing methanol as solvent.

g. Thioxo- and Selenoxo- to Aminopurines (H17)

The usually rigorous conditions required for such transformations limits the usefulness for aminopurine preparations (see Chapter VII, Section 1.C.f). Application of this approach to more stable derivative amino groups is more successful, both 2- and 6-hydrazinopurines result from the thioxo analogs and similar precursors can be used to obtain analogous hydroxyaminopurines.

h. Interchange of Amino Groups (H17)

Until fairly recently alkylation of amino groups to alkylamino homologs by direct alkylation was encountered only rarely usually as a side reaction from an attempted *N*-alkylation of the nucleus (see Chapter VIII, Section 5.G.a). With the introduction of trimethylanilinium methoxide, a stepwise methylation to methylamino and then to dimethylamino is possible with 2- and 6-aminopurines. Under solid–liquid phase transfer conditions, highly active alkylating agents such as allyl bromide convert adenine to the 6-allylamino and 6-diallylaminopurines. Enhancement of the activity of the 6-amino group due to the presence of a 1-methoxy substituent allows direct alkylation in DMA to the monoalkylaminop-

urines, subsequent removal of the 1-methoxy group being made reductively. Similar 6-amino group activity resulting in ease of alkylation is found in adenine-1-oxide. The conversion of amino groups by acylation and subsequent reduction is a well-documented route, but more recent use of azamethine precursors derived from 6-aminopurines with aldehydes or dimethylformamide diacetal also gives 6-alkylaminopurines on reduction. A new reagent for transforming a 2-amino- to a 2-dimethylaminopurine is benzodithiolylium tetrafluoroborate. Reduction of the condensation product with the aminopurine with tributyltin hydride affords the dialkylaminopurine.

In the past the reverse transformation of alkylamino to amino group was confined to removal of benzyl or allyl groups by reduction or acid hydrolysis. Now stepwise oxidation with potassium permanganate or ruthenium tetroxide of dialkylaminopurines enables isolation of the mono alkylamino- and then the aminopurines (Chapter VIII, Sections 5.D.a, 5.D.b, and 5.D.c). Removal of protecting groups provides other examples, the 6-(1-oxypyrid-2-ylmethyl)aminopurine is converted to adenine on treatment with cold acetic anhydride followed by ammonia solution. Benzyl and substituted benzyl groups are eliminated by photolysis of saturated solutions of the 6-benzylaminopurines.

i. Amino- to Oxopurines (H17)

The majority of examples continue to be provided by the established routes of hydrolyses with nitrous or hydrochloric acid or alkali (see Chapter VI, Sections 1.D.a and 1.D.b). As alternatives to nitrous acid, examples using liquid nitrosyl chloride in DMF are found and other procedures employing nitrogen trioxide dissolved in aqueous alkali have proved useful.

j. Amino- to Halogenopurines (H17)

A significant advance in this reaction is application of Schiemann type reactions to 2- and 6-aminopurines. Halogen radicals are generated from CCl_4, $CHCl_3$, CH_2Br_2, and CH_2I_2 with *n*-pentyl, isopentyl or *tert*-butyl nitrites. In some cases an inorganic halide supplements the alkyl halide, as in formation of a bromopurine with dibromomethane and antimony(III) bromide. Fluoroboric acid combined with sodium nitrite is used to form 2-fluoropurine derivatives, the 6-fluoro analogs are best prepared by potassium fluoride treatment of 6-trimethylammoniopurines through nucleophilic rather than radical-type replacements (see Chapter V, Sections 1.D, 1.E, 1.F, and 1.G.c).

k. Halogeno- to Alkylpurines (New)

These transformations result from the introduction of various metal complexes (see Chapter IV, Section 2.A.b.). Formation of 6-alkylpurines is possible by reaction of 6-chloropurine with alkyltriphenylphosphonium salts and *n*-butyl-

lithium. Another approach using cross-coupled reactions of tri-*n*-butylvinylstannate and a Pd(II) catalyst with 2- and 8-iodopurines gives the analogous 2- and 8-vinylpurines. Lithium diphenylcuprate features in the conversion of 6-iodo- to 6-phenylpurine. A specific reaction of 6-iodo-9-methylpurine with phenyllithium and an Fe(III) complex catalyst gives rise to 9-methyl-6-phenylpurine. The reaction is unusual as the product from 6-chloro-9-methylpurine is formed from attack at C-8, giving 6-chloro-9-methyl-8-phenylpurine. Further examples of a transition metal complex induced reaction utilize combinations with Grignard reagents to transform 6- and 8-halogeno derivatives to their 6- and 8-alkyl or -aryl analogs.

l. Amino- to Thioxo- and Selenoxopurines (New)

A reaction presently limited to amino groups at C-6 employs hydrogen sulfide or hydrogen selenide in pyridine the latter serving both as solvent and catalyst (see Chapter VIII, Section 1.A.i). Some success is reported using liquid hydrogen sulfide in forming the 6-thioxo derivative from 1-methyladenine, although adenosine failed to react. A route to 6-mercaptopurine riboside is available using the same reagent with the 6-methoxyamino analog of adenosine. Similar reactions occur using hydrogen selenide, usually under less vigorous conditions. For example, adenosine can be converted directly to the 6-selenoxopurine riboside.

m. Amino Group to Hydrogen (New)

Older methods of eliminating an amino group involved tedious multistep reactions leading to the penultimate replacement by a group capable of removal by reductive means (see Chapter IV, Section 3.A.b and Chapter VIII, Section 5.G.d). Recent radical-type reactions have demonstrated single-stage replacements by hydrogen in 2- and 6-aminopurines following treatment with pentyl nitrite in a tetrahydrofuran (THF) solvent which also serves as a proton donor. Recently, application of liquid ammonia has been shown to deaminate 6-aminopurine to an unsubstituted C-6 derivative. The reaction has considerable scope for further investigation, one noteworthy point is that not only primary but also mono- and dialkylaminopurines react likewise. Unlike the nitrite-induced reactions, these are not radical but ionic in character, with the amino group being lost as ammonia or amide anion.

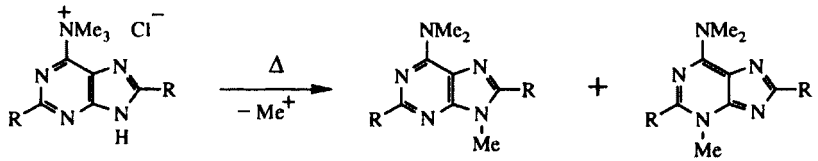
D. Addition Reactions (*H*18)

a. The Michael Reaction (H18)

The examples noted in the alkylation tables are most representative of the reaction in purines. In addition to *N*-alkylation, some use has been made of the procedure to form annelated ring derivatives.

b. Quaternary Derivatives (H18)

Trimethylammoniopurines are desirable intermediates in a number of nucleophilic displacements. Reaction rate studies show the quaternary group reactivity is many times greater than that of a chlorine atom at the same position and approaches that of the highly active methylsulfonyl group. Breakdown of the quaternary group on heating liberates a methyl cation available for *N*-methylation, as demonstrated by the conversion of 6- trimethylammoniopurines (**3**) to a mixture of 9- (**4**) and 3-methyl-6-dimethylaminopurines (**5**). Investigations show only endoalkylation is involved, with no participation from a methyl group intramolecular rearrangement.



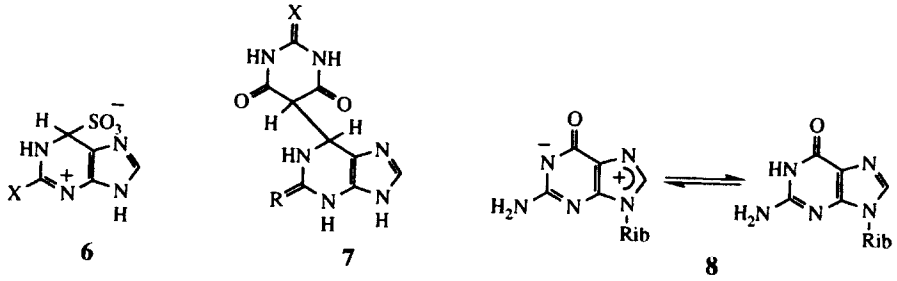
3 **4** **5**

c. N-Oxides (H19)

Previously only the 1-, 3-, and 7-oxides were described, but by employing an adaptation of the Shaw synthesis for *N*-alkylpurines from imidazoles using *N*-benzyloxyimidazoles, 9-benzyloxypurines resulted. Debenzylation to the purine-9-oxide follows from acid treatment. The established rearrangement of 3-hydroxyxanthines by means of acetic anhydride to uric acids is now found to extend to the 7- and 9-oxides also. Corresponding 8-oxopurines are obtained when 3- or 7-hydroxyguanines react similarly with anhydrides.

d. Addition to Double Bonds (H19)

Unlike many other unsaturated heterocycles, purines are notable for their inability to form stable adducts with water. Under photolytic conditions, alcohols react with purine and its riboside by addition across the 1,6-double bond, giving 6-hydroxyalkyl-1,6-dihydropurines (*H*19). Analogous derivatives are obtained from 2-aminopurine. Where a substituent is already located at C-6, the addition occurs at the 7,8-double bond instead. The inherent instability of the dihydro derivatives leads to a rapid oxidation in air to the purine. Although the reactions described above are radical, a corresponding addition occurs under ionic conditions between hydrogen sulfite ions and 6-unsubstituted purines having oxo, thioxo, or amino groups at C-2. Moderately stable derivatives such as **6** (R = H, NH_2, OH, SH) are obtained, which are further stabilized if C-8 contains an electron-withdrawing group such as trifluoromethyl. Identification of the 1,6-



6 7 8

dihydropurine structure follows from comparisons of the UV spectra with those of known adducts of corresponding 8-azapurines and from ^{1}H NMR data. Although crystalline forms have been isolated, decomposition occurs rapidly in water or on heating. Somewhat more stable adducts arise from interactions between purine or the 2-oxo or 2-thioxo derivatives with barbituric acid or 2-thiobarbituric acid. The respective products (7, R = O or S, X = O) and (7, R = O or S, X = S), however, decompose on attempted crystallization from water.

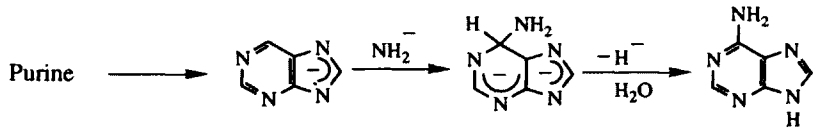
e. The Chichibabin Reaction (New)

Under the conditions used for the S_N (ANRORC) reaction (potassium amide in liquid ammonia, noted in Section 3.B.a) some 6-unsubstituted purines undergo a different transformation, giving 6-aminopurines as products. The route is notable for forming adenine from purine in quantitative yield, with the 2- and 8-methylpurines reacting likewise. Mechanistic studies (^{1}H and ^{13}C NMR) using $K^{15}NH_2$ show that removal of a proton by the reagent is followed by addition of the amide ion to form a dianion adduct (Scheme 2). This event is somewhat unusual because the reaction presupposes nucleophilic attack by an amide anion on the purine, which is also present in an anionic form. Adenine results from removal of a hydride ion and interaction with the quenching medium. No ring opening is involved and all the labeled nitrogen is confined to the 6-amino group.

E. Substituent Modification (*H*19)

a. Amino Groups (H20)

The various metatheses between primary amino groups and mono- and dialkylamino forms and vice versa are summarized in (Section 3.C.h) of this chapter. Condensation reactions with alkene derivatives give rise to tricyclic derivatives,



Scheme 2

the third ring resulting from linking the amino nitrogen with N-1. Many of these compounds exhibit a pronounced fluorescence in solution.

b. Oxo Groups (H20)

Under conditions employed for *N*-alkylation of oxopurines, *O*-alkylation is rare and is usually a minor side reaction. Riboside derivatives appear more susceptible to *O*-alkylation—with trimethylanilinium methoxide (TAMM) guanosine, but not inosine or xanthosine, is converted to the 6-methoxy analog. The same 9-riboside with bis(tri-*n*-butyltin)oxide forms the 6-*O*-(*n*-butylstannyl) purine converted on reaction with alkoxide ions to 6-alkoxy derivatives. Silylation provides another means of oxygen activation, reagents for this include trichloromethylchlorosilane, hexamethyldisilazane or the more recently introduced *O,N*-bistrimethylsilylacetamide. The *O*-silylated products given by both oxopurines and their 9-ribosides undergo ready displacement with alkoxides and other ions.

c. Thioxo Groups (H21)

The potential of trialkyl orthoesters and tetraalkoxymethanes for *S*-alkylation is well-documented (Chapter VII, Section 1.C.b)—the alkyl group arises from the alkoxy moieties of the reagents. The bromodiphenylmethyl group is a useful protecting agent for thioxo groups and is readily removed by treatment with trifluoroacetic acid (Chapter VII, Section 2.A.b). An unusual demethylating procedure for methylthio groups utilizes liquid ammonia to form the thioxopurines (Chapter VII, Section 2.B.d).

d. Methyl and Other Alkyl Groups (H21)

Azamethine derivatives obtained from reacting 6-methylpurines with the Vilsmeier reagent are readily hydrolyzed to 6-aldehydopurines (Chapter IV, Section 2.C.b). An alternative route to the same 6-formylpurines uses an improved oxidation (SeO_2) of the 6-methyl precursors (Chapter IV, Section 2.C.c). With benzaldehyde, 6-methylpurine undergoes a Knoevenegal reaction, forming 6-styrylpurine. Conversion of an 8-methyl to the 8-ethylpurine homolog occurs on metalation with *n*-butyllithium followed by methyl iodide treatment (Chapter IV, Section 2.A.e).

F. Radical Reactions (*New*)

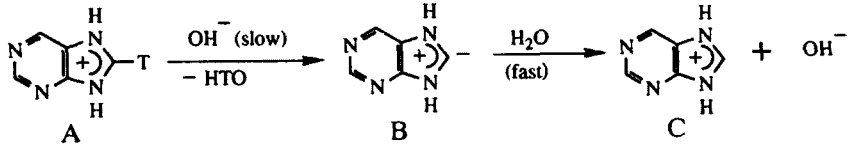
These reactions are now encountered in a wide range of synthetic procedures. The numerous examples of the replacement of amino groups by halogens or

hydrogen provide illustrations of the preparative potential of such reactions. In other transformations, 6-iodopurines are converted to the corresponding 6-ketonyl, -phenyl or -heterocyclyl purines. Alcohols in radical forms add to purines to give 6- or 8 -hydroxyalkyl derivatives; with carboxylic acids and esters, and also amino acids, the alkyl moiety of the acid or ester is incorporated at C-6 or C-8 with concomitant loss of the carboxyl and amino groups. With *tert*-butyl acetate, direct introduction of an 8-methyl group is possible, while insertion of chlorine at the same position occurs with MCPBA. The rearrangement of 3- 7-, and 9-oxides under the influence of anhydrides also appears to be a radical reaction. A synthesis of 2-halogeno- and 2-halogenoalkyl-hypoxanthines has been demonstrated through radical-promoted ring closure of 4-amino-5-carbamoylimidazoles. Radical propagation is effected by photolytic or irradiation means (UV, γ or X rays) or is chemically induced using pentyl, butyl and other nitrites, or butyl peroxide and related reagents such as MCPBA and ammonium peroxidisulfate. The sources of the halogen and haloalkyl radicals employed are tetrachloromethane, chloroform, dibromomethane, and diiodomethane with fluorine from fluoroboric acid.

G. Proton Exchange at Carbon Atoms (*New*)

Although the most usual reactions associated with carbon atoms are those with nucleophiles, the considerable number of electrophilic replacements reported illustrates the complexity of the electron distribution in the pruine ring system and its susceptibility to perturbing influences of diverse nature and character. The most widely studied are isomeric exchanges of the C-8 proton with either deuterium or tritium. Reactions with protons at C-6 and C-2 are generally negligible, although activation of the 2-proton under certain circumstances, as noted later, is possible. The significant part played by the ionic state is demonstrated by the results of studies on a number of purines made over a wide pH range. Using purines labeled at C-8 with radioactive ^{3}H, the exchange with hydrogen in aqueous solution is quantified by the resulting yield of HTO in the medium.[1056] Exemplifying this technique are examinations of the parent member[1056,1356] and 9-alkylated derivatives,[1056] adenine[1356] hypoxanthine and the 9-methyl homolog,[1319] guanine,[1319] 6-mercaptopurine,[1399] and xanthine,[1327,1799,1800] theophylline,[1326,1327] caffeine,[1326,1327] and other *N*-methylated analogs.[1327] Nucleoside derivatives of the above also investigated include adenosine,[1356,1559] inosine,[1319] guanosine,[1319] 6-mercaptopurine-9-β-D-ribofuranoside,[1399] xanthosine,[1327] zwitterionic forms or salts derived from N-1 or N-7 methylation,[1628,1634,1635] and the naturally occurring puromycin.[1399] The influence of nucleotide groups on the 8-proton has similarly been investigated[1822].

An alternative approach, using purines deuteriated at the 8-position, monitors the exchange rate by noting the increase in size of the 8-H signal in the ^{1}H NMR when water is introduced. Examples of this procedure are found with purine and 9-alkylated homologs,[1056] hypoxanthine, and the majority of the mono- and

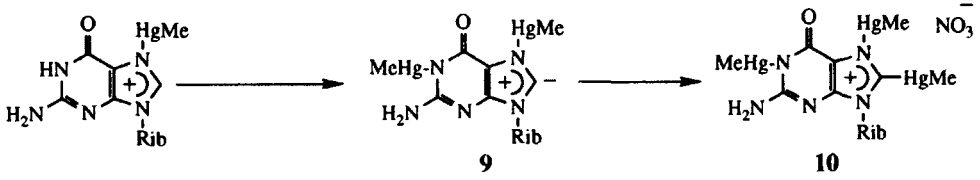


Scheme 3

di-*N*-methylated derivatives.[1280] Similar studies with the ribosides of various 6-substituted purines have been made.[1398] The proposed exchange mechanism (Scheme 3) is supported by findings from both tritium and deuterium labeling work. At low pH values an initial protonation at N-7 (A) is a prerequisite for removal of the proton at C-8 by a hydroxide ion. Formation of the ylid intermediate (B) is the rate-determining step, followed by a more rapid reprotonation (C) by the water present.[1056] Linear free-energy relationships, determined subsequently, lend support to the mechanism[1801] and molecular orbital calculations favor the presence of the ylid intermediate in the reaction.[1802] Under more alkaline conditions (pH > 9), replacement of the hydrogen at C-8 operates by a different mechanism, involving direct attack on the position catalyzed by a hydroxide ion. In this case removal of the proton can be from the neutral molecule or a mono- or dianionic form.[1334]

In the general situation it follows that any factor that intensifies the positive charge at N-7 in the imidazole ring will facilitate proton abstraction at C-8. The anomalous position of 7-alkylated oxopurines, such as theobromine and caffeine, which also lose protons under these conditions, may be due to the alternative protonation of an oxygen. In view of the N-9 protonation of the 7-methylxanthine cation observed from X-ray crystallographic work,[1803] protonation of a carbonyl group seems unlikely, by the lower exchange rates obtained seem to reflect a more distant location for the cationic center.[1801] Both purine and adenine also pose questions as, unlike most other purines, both undergo initial protonation at N-1 not N-7.[1804] Exchange rate data, however, point toward the possibility of some contribution from cations of the latter type arising during the reactions.[1357,1559]

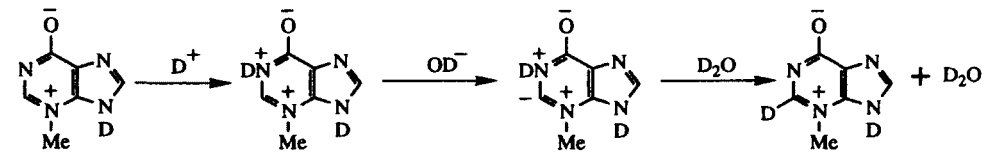
The quaternary salts or zwitterions derived from N-7 alkylation of 9-alkyl- or 9-ribosylpurines show enhanced C-8 proton exchange because of the localized charge in the imidazole ring.[1357,1628,1634] In the zwitterions, partial neutralization of the positive charge by the accompanying negative charge in the pyrimidine ring reduces the lability of the 8-proton shown by lowered exchange rates.[1634] At low pH the 1-methylated derivatives of inosine or guanosine show activities not much greater than those of inosine and guanosine, indicating an initial protonation at N-7 occurs in all cases. The significant rate increases shown by inosine and guanosine, but not by their 1-methyl analogs, on increasing the hydroxide ion concentration is attributed to some zwitterion formation by the former pair. This is effected through an N-1 to N-7 prototropic shift, as exemplified by guanosine (**8**).[1634] After initial reactions at N-7 and N-1, metal complexing reagents with inosine or guanosine give ylid intermediates, illustrated by (**9**), from guanosine and



9 **10**

Scheme 4

methyl mercury(II) nitrate. The reaction is of interest in that with incease in pH the ylid reacts at C-8 with more of the reagent, rather than the expected proton, giving the 1,7,8-trisubstituted guanosine (10)[1643] (Scheme 4). Other examples of this type of reaction have been reported.[1637,1805] Ionic states influencing the exchange reaction are classified as having the proton activating factor (paf) at low pH, the metal activating factor (maf) for complexes, and the zwitterion activating factor (zaf). These three facilitate proton removal to varying degrees, but where an anionic form is involved, the anion deactivating factor (daf) operates as a reaction inhibitor.[1357] As a generalization, the activation factor sequence follows the order paf > maf > zaf > neutral molecule.[1805] A number of 3-alkylated purines exhibit anomalous behavior in that the proton removed first is from C-2 rather than C-8. Studies with deuteriated 3-methylhypoxanthine[1280,1402] indicate a mechanism (Scheme 5) in which the purine in the canonical forms (**11**) undergoes initial protonation favoring N-1 rather than N-7, possibly because of the proximity to the negative charge on the oxygen, to give a derivative (**12**) having the C-2 position sited between two charged nitrogen atoms and therefore capable of ready deprotonation to the ylid (**13**). Subsequent reprotonation in the deuteriated medium affords the 2-^{2}H labeled 3-methylhypoxanthine (**14**). Both 3-methyladenine and the 6-mercaptopurine analog react likewise, but in these derivatives the activity of the proton at C-8 is reduced by many orders of magnitude.[1402] Loss of the 2-H signal on heating with deuterium oxide is also a feature of transition metal complexes of 3-benzyl- and 3-methyladenine.[1808] Although substituents on ring carbon atoms have little effect on the 8-H exchange rate, significant perturbations of the electrons may result from alkylation of nitrogens in either ring. Enhancement of removal of the proton at C-8 is found with 9-riboside derivatives,[1398] even more pronounced effects with the 9-methyl, 9-ethyl, and 9-benzyl derivatives are demonstrated using ^{1}H NMR.[1458] Theoretical treatment (SCF–MO calculations) supports the weakening effect exerted by the 9-substituent on the bond[1553] in adenine derivatives. Further activation at C-8 occurs



11 **12** **13** **14**

Scheme 5

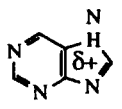
with 9-benzyladenine following acylation of the amino group, although the proton at C-2 remains unaffected. It is significant also that unlike most adenine derivatives the 6-acetamidopurines are shown (^{1}H NMR) to protonate in acid at N-1 rather than N-7 prior to the exchange occurring.[1458] It is noteworthy that the formation of unlabeled xanthine occurs through concomitant removal of the ribose moiety during detritiation of xanthosine. Aspects of the exchange reaction are discussed in two reviews[1809,1884] and a short monograph.[1810]

4. PHYSICAL PROPERTIES (*H*25)

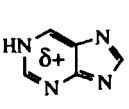
A. Electronic Considerations (*H*25)

The combination of a π-electron excessive imidazole ring with a π-electron deficient pyrimidine ring in purines was proposed by Albert to represent the ground state of the ring system resulting from a redistribution of electrons between the two rings. This view has been modified by the results of CNDO/2 calculations which showed that this effect is possible in the 7(H)- and 9(H)-protomers, and the relative charge states of the purines can be represented by (**15A**) and (**15B**), reflecting a net electron loss from the five membered ring to the other ring. By contrast, the corresponding 1(H) and 3(H) protomeric forms (**15C** and **15D**) possess quinonoid structures and have the more positive character associated with the pyrimidine moieties.[1827] Consideration must therefore be given to the effects of prototropy on the electron state of the derivative when mechanisms are being formulated.

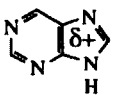
π - electron flow ⟵ π - electron flow ⟶



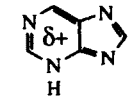
15 A



15 C



15 B



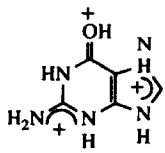
15 D

Developments in the theoretical treatments on the activity of purines were much in evidence in the years immediately following 1970.[1033,1043] Modifications and refinements of the existing SCF–MO approaches led to the CNDO/2 method to account for ground-state properties such as heats of formation, total energies, and ionizing potentials. Subsequently, the MINDO algorithm (Modified INDO),

a variation of CNDO/2, has appeared, which also gives good correlations with some ground-state properties. Application of the MINDO method is illustrated by calculating the heats of formation of the various tautomers of purine, which result in exothermic values for the 7(H)/9(H) protomers but endothermic ones for the quinonoid forms of the 1(H)/3(H) analogs.[1042] Linear free-energy equations, relating Hammett constants to pK_a values, derived for monosubstituted purines are considered, within certain limitations, to be capable of application to pK_a evaluations of polysubstituted purines. Such results could provide molecular parameters from which correlations between structure and biological activity might be made.[2015]

a. Protonation (H25)

The ongoing interest in this topic is evident in the number of publications devoted to it. Much of the work documented covers old ground but introduces new approaches or techniques to the task. With purine, the parent member, initial protonation occurs at N-1,[1036,1038,1046] but in more acidic media the N-1, N-9 dication[1038] forms, which on further acid treatment yields the N-1, N-3, N-9 trication.[1038,1039] Adenine gives possibly more than one mono cation, but both N-1, N-9 di- and N-1, N-3, N-9 trications can be identified.[1038,1039] Using magnetic susceptibility calculations (IGLO method) with localized orbitals and ^{13}C, ^{14}N, ^{15}N, magnetic resonance spectra, protonation is predicted to occur at N-1, N-3, and N-7, but N-9 is suggested as an alternative for the latter site in view of the small energy differences existing between them.[1904] A similar study of the dication by the STO-3G algorithm gives the preferred order of protonation as N-1, N-7 > N-3, N-7 > N-1, N-3,[1901], the first of these assignments is confirmed by the results of crystallographic analysis.[1552] At low temperature, guanine in acid solution may provide more than one mono cation, but in stronger acid an N-3, N-7 diprotonated ion results, giving on further treatment a trication formulated as **16** which contains a protonated oxygen moiety.[1038] In the solid state hypoxanthine, present as the 7(H) protomer, forms the mono cation through protonation at N-9.[1324] With the isomeric 8-oxopurine, N-1 appears to be the most suitable site for ion formation[1249] based upon CNDO/2 calculations. A less clear picture is presented by the protonation of the dioxopurines, xanthine can have either N-7 or N-9 as mono ion center, with N-7 being more favored[1923] but with the 6,8-dioxo isomer N-3 as the preferred protonation position.[1246]



16

b. 7(H)—9(H) Prototropy (New)

The identification of a number of purines as 7(H) or 9(H) tautomers has been clarified or confirmed by various new studies. An examination by UV photoelectron spectroscopy of purine suggests that in the gas phase the 9(H) tautomer predominates.[1034] While this is also the case with purine in solutions,[1036,1043,1553] in the solid state X-ray crystallography shows that only the 7(H) protomer is present. In the latter case hydrogen bonding at N-9 may be a deciding factor in tautomer[1322] formation since MO calculations show little difference between energy levels at the two ring nitrogens.[1043] Prototropy in adenine has been the subject of studies involving photoelectron spectroscopy,[1034] the thermodynamic procedures,[1549] ^{13}C magnetic resonance,[1036,1322] and AMI quantum calculations,[1900] with concordant results showing the predominence of the 9(H) protomer in all phases. Investigations of this kind with hypoxanthine[1324,1923,1946,1947] and 6-mercaptopurine[1396,1397] using ^{13}C and ^{1}H NMR and crystallographic analysis indicate that the 7(H) tautomers are the most stable, but with the former purine the near equality of energy levels of the nitrogens explains past conflicting results. Based upon UV and ^{1}H NMR investigations, the 8-oxopurine isomer appears to form the 1(H) protomer.[1249] The established depiction of guanine as a 7(H) tautomer is further confirmed by AMI quantum chemical calculations.[1900] Xanthine, like hypoxanthine, exhibits the 7(H) protomeric form, but in aqueous solution the MCD spectrum also reveals the presence of a considerable amount of the 9(H) protomers.[1694] Results of X-ray crystallographic examination of the xanthine anion indicate that N-9 rather than N-7 carries the imidazole hydrogen.[1329] Formulation of an N-7 protomer for 6-mercaptopurine follows from ^{13}C NMR studies[1322] and throws doubt on an earlier claim for the 9(H) analog.[1323]

c. Tautomerism in Amino-, Oxo-, and Thioxopurines (New)

Detailed reviews covering this topic by the Pullmans[1033] and by Elguero and co-workers[1945] are available. Recent work with advanced laser raman spectroscopy on aqueous solutions of adenine of varying pH shows how the ionic state of the purine is related to the resonance tautomer[1903] present; this observation presumably extends to the effect of protonation on other purines. Significant additions to existing knowledge of adenines and other aminopurines are few. As the amino has lower energy than the imino group, it is where possible the preferred form. Exemplifying this is 1-methyladenine, in which the expected 6-imino tautomer is not observed (^{1}H NMR, UV) a 6-amino derivative being found in the solid state[1796] and in polar solutions.[842] On changing to a nonpolar solvent the UV spectrum is for 6-imino-1-methylpurine, but on increasing the polarity of the medium the spectrum reverts to that of the 6-amino derivative.[1475] In contrast the isomeric 3-methyladenine gives only the appropriate 6-amino spectrum in

either polar or nonpolar media.[1475] Although guanine has amino and oxo groups capable of tautomeric modification, the most stable form in a polar dielectric solvent is shown by AMI quantum calculations to be the 2-amino-6-oxo-9(H)-purine. In practice, however, some contribution from a 2-amino-6-hydroxy tautomer appears highly probable under these conditions.[1900] The question of oxo hydroxy tautomerism is still a focus of attention. However, the present concensus, based on theoretical calculations[1360] and physical determinations, is that hydroxy tautomers are not usually found except in the case of certain 6-oxopurines, notably hypoxanthine[1924,1925] and guanine,[1900] where evidence exist that some of the hydroxy tautomers are present in solution. Tautomerism in thioxopurines largely parallels that of the oxo analogs. With 6-mercaptopurine the 6-thioxo form is predominant.[1322]

B. Crystal Structure (*H*26)

The generally held view of the essentially planar ring system has been disproved as a result of X-ray analysis of a number of purines in which the imidazole rings are flat but the pyrimidine moiety and the substituent groups exhibit out-of-plane deformations. A dihedral angle of about 0.5°–1.0° is generally found between the ring planes, increasing to 1.16° for 6-mercaptopurine, which also shows a 1.5° out-of-plane deformation of the carbon–sulfur bond.[1397] Protonation has an effect on the interplane angle, as demonstrated by the different angles shown by the monocation[1551] and dication[1552] of adenine. The change in inclination between the two ions results from bond length alterations arising from the changes in ionic states. Examination of 1,3,9-trimethylxanthine shows a buckling of the pyrimidine ring, with the carbonyl moiety forced out of plane. Diagnostic studies provide insights into the location of hydrogen atoms, notably after protonation, and establish predominant tautomeric structures. The first practical evidence that protonation of an adenine is possible at N-3 is obtained from inspection of the dihydrochloride of 7-methyladenine.[1565] Other protonation results are noted earlier (Section 4.A.a). Both 1-alkyl-[1796] and 3-akyladenines[1567] show the presence of an amino rather than an imino group in the solid state. In the second example the N-3 alkyl group increases the ring angle at the 3-position as compared with that observed at N-3 in the 9-ethyl analog.[1567] Other tautomeric features disclosed are loss of hydrogen from N-3 and N-7 in the anion of xanthine and location of the imidazole proton at N-9 rather than N-7 as in the neutral molecule.[1329] The absence of hydrogen from N-1 in 3-methylguanine, predicted by MO calculations, is confirmed by crystallography.[1531] An unusual finding with 9-ethylguanine in the crystal is the formation of duplexes comprised of an N-7 protonated unit linked by hydrogen bonding to the same nitrogen of a neutral guanine molecule.[1948] Much of the latest work is centered around metal complexation of purines and establishing the nitrogen atoms involved in ligand attachment.

5. LITERATURE OF THE PURINES

An article dealing with a specialized topic for a particular class of derivative is not noted below but referred to in the appropriate chapter. More general treatments of purine chemistry are encountered either as chapters or sections as part of larger works on heterocycles or as monographs in journals; no major work has appeared over the past two decades. Theoretical implications for practical results are discussed by Tougard,[1961] with an updated review by Bergmann and co-workers on electrophilic and nucleophilic substitutions and controlling influences.[1943] Coverage of a number of physicochemical topics has been made.[1962] A most informative and comprehensive overview is due to Shaw,[1963] and a similar contribution by the same author occurs in another publication.[1964] Other works of like nature are by Lunt[1965] and an article in Italian by Lister.[1966] Selected reaction topics are reviewed by Yoneda in two papers in Japanese.[1967,1968] A volume by Hurst contains a short synopsis of the various syntheses and reactions of purines with additional chapters covering their participation and significance in metabolic processes.[1969] More detailed information on these latter aspects can be found in the collected papers on the physiological and pharmacological effects of purines and their analogs.[1970]

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER II

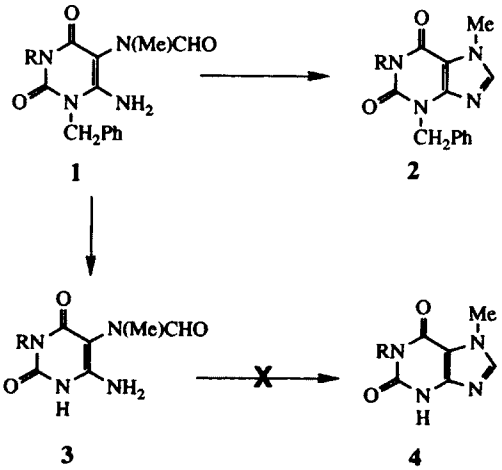
Synthesis from Pyrimidines

1. Using 4,5-Diaminopyrimidines (The Traube Synthesis) 22
   B. Cyclization with Formic Acid (*H*33) 22
   C. Cyclization with Dithioformic Acid (*H*38) 24
   D. Cyclization with Other Carboxylic Acids (*H*41) 24
   E. Cyclization with Acid Anhydrides (*H*44) 26
   F. Cyclization with Acid Chlorides (*H*47) 29
   G. Cyclization with Orthoesters and Diethoxymethyl Acetate (*H*50) 30
   H. Cyclization with Formamide (*H*53) 32
   I. Cyclization with Other Amides (*H*56) 32
   J. Cyclization with *N,N*-Dialkylamides and Phosphoryl Chloride (*H*57) 33
   K. Cyclization with Amidines (*H*58) 34
   M. Cyclization with Urea (*H*59) 34
   N. Cyclization with Thiourea (*H*60) 35
   O. Cyclization with Cyanates, Isocyanates and Derivatives (*H*61) 35
   P. Cyclization with Isothiocyanates (*H*62) 36
   R. Cyclization with Carbon Disulfide (*H*64) 37
   S. Cyclization with Phosgene (*H*67) 37
   U. Cyclization with Chlorocarbonic Ester (*H*68) 37
   V. Cyclization with Aldehydes and Ketones (*H*69) 38
   W. Cyclization with Cyanogen Derivatives (*H*71) 41
   X. Cyclization with Tetraalkoxymethanes and Thioxo Analogs 41
   Y. Cyclization with Miscellaneous Reagents (*New*) 42
2. Syntheses from 4-Amino-5-nitro- and 4-Amino-5-nitroso-pyrimidines (*H*72) and from 4-Amino-5-azopyrimidines (*New*) 44
   A. Cyclization Involving Reduction of a 5-Nitro or 5-Nitroso Group (*H*72) 44
   B. Cyclization through Cyclodehydration (*H*74) 47
   C. Cyclization Involving Reaction of a 5-Azo Group (*H*73) 48
3. Syntheses from 5-Amino-4-oxopyrimidines (*H*76) 51
4. Syntheses from 4-Amino-5-unsubstituted-pyrimidines (*H*78) 51
5. Purines Derived from Pyrimidine-Containing Heterocycles (*H*81) 54
   A. From Thiazolo [5,4-*d*]pyrimidines (*H*81) 54
   B. From Oxazolo [5,4-*d*]pyrimidines (*H*82) 54
   F. From Thiadiazolo [3,4-*d*]pyrimidines (*New*) 55
   G. From Furazano [3,4-*d*]pyrimidines (*New*) 55
   H. From Other Purines (*New*) 56
   I. From Pteridines (*New*) 56
   J. From Pyrimido [4,5-*e*]*asym*triazines (6-Azapteridines) and Pyrimido[5,4-*e*]*asym*triazines (7-Azapteridines) (*New*) 57
   K. From Imidazo [4,5-*d*][1,3]thiazines (*New*) 58
   L. From Imidazo [4,5-*d*][1,3]oxazines (*New*) 59
   M. From Pyrimido [4,5-*d*][1,4]diazepines (*New*) 59

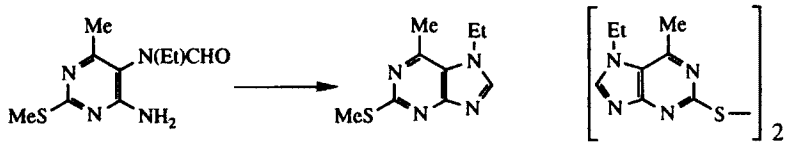
1. USING 4,5-DIAMINOPYRIMIDINES (THE TRAUBE SYNTHESIS)

B. Cyclization with Formic Acid (*H*33)

Although now largely superseded by trialkyl orthoformates for the preparation of 8-unsubstituted-purines, formic acid still has a useful place in purine syntheses. Most cyclizations are two-stage reactions, but direct closure examples are to be found. Both 3-isobutyl-1-methylxanthine[830] and the 7-benzyl homolog[831] result from heating the diaminopyrimidine precursors (100°C, 1 h) in 97% formic acid. In the more usual procedure formation of theophylline,[1005] theobromine,[1005] and 1,3-diallylxanthine require isolation of the intermediate 4-amino-5-formamidopyrimidines and further heating (reflux, 0.5 h) in 10% sodium hydroxide.[832] Fusion conditions (210°C, 0.5 h) replace the alkali treatment for ring closure to 6-ethyl-9-methyl-2-methylthio- and 9-ethyl-6-methyl-2-thioxopurine.[1188] A rare example of a 6-chloropurine formed from this approach is by heating (120°C) a 4-alkylamino-6-chloro-5-formamidopyrimidine in diethoxymethyl acetate[1209] (see Section 1.G). Both 6-amino-1-benzyl-5-*N*-methylformamidouracil (**1**, R = H) and the 3-methyl analog (**1**, R = Me) give the respective 7-methylxanthines (**2**, R = H) and (**2**, R = Me) in ethanolic ammonia under reflux[833] but the debenzylated starting materials (**3**, R = H) and (**3**, R = Me), under the same conditions are not cyclized to either **4** (R = H) or **4** (R = Me).*
Formic acid employed in one synthesis of 3-methylisoguanine required the intermediate 5-formamidopyrimidine to be formed at 100°C in a sealed vessel with conversion to 3-methylisoguanine being effected by further heating under



* The behavioral difference shown between 1- and 3-alkylxanthines is a recurring theme. The nature of the alkyl group and the particular ring nitrogen on which it is located can profoundly alter the chemistry of the derivative undergoing the reactions.



5 6 7

reduced pressure.[859] The facility with which a 5-formamido group in a pyrimidine will undergo *N*-alkylation provides a convenient route to 7-alkylpurines (see *H*35). A recent example with 4-amino-5-formamido-6-methyl-2-methylthiopyrimidine and ethyl iodide gave rise to the 5-(*N*-ethyl)formamido derivative (**5**), affording the required 7-ethylpurine (**6**) on heating in dimethylformamide with anhydrous potassium carbonate.[834] When using acid conditions to form halogenopurines (formic acid, reflux), the halogen is at risk of hydrolysis, as in the attempted closure of 4-amino-6-chloro-5-(*N*-cyclopentyl)formamidopyrimidine giving 7-cyclopentylhypoxanthine.[835] A mixture of dimethylformamide and hydrochloric acid is a useful cyclizing medium, but consideration must be given to the nature of substituent groups present. On subjecting the 5-formamidopyrimide (**5**), for example, to this treatment a significant amount of the dipurin-2-yl disulfide (**7**)[834] is also formed in addition to the expected purine (**6**). Under these conditions hydrolysis of the methylthio group to thioxo followed by oxidation to the disulfide seems most likely. No corresponding disulfide is found when an alkaline medium (dimethylformamide, potassium carbonate, reflux, 1 h) is employed to form 1-methyl-2-thioxopurine from the corresponding 4-amino-5-formamidopyrimide.[836] A mixture of phosphorus pentoxide and phosphoric acid is useful for the removal of elements of water, but when this reagent was reacted with 4,6-bis(3-*N*-methylureido)-5-formamidopyrimide (**8**) the product was not the expected 9-carbamoyl derivative (**9**) but the 9-unsubstituted purine (**10**). Loss of the carbamoyl group must occur only after ring closure and be due to the severity of the conditions (150°C, 3 h) employed. Prolonged heating in hexamethyldisilazane (130°C, 4 h) was required to prepare a series of purine-3-oxide derivatives from the corresponding formamidopyrimidine oxides;[838] these are detailed in Chapter XI, Section 1.B.



9 8 10

A regiospecific synthesis of 8-^{13}C adenine involves an elegant transformylation by means of ^{13}C-labeled *N*-formylmorpholine, prepared from ^{13}C sodium formate and morpholine and 2,4,5-triaminopyrimidine. On heating the two in dilute hydrochloric acid, a satisfactory yield (61%) of 8-^{13}C labeled adenine (**12**) results, the intermediate formamidopyrimidine (**11**) being isolatable using modified



11 12

conditions.[839] Extended Traube* reactions are reported in which the 8-hydroxy group of uric acid derivatives is replaced by hydrogen on heating with a formic acid–trimethylamine mixture. The 1-methyl and 1,3-dimethyl homologs of xanthine are also formed in this way.[939]

C. Cyclization with Dithioformic Acid (*H*38)

No noteworthy use of this reagent has been reported, although the application of derivatives of other thioacids is occasionally encountered in the literature, for example, esters of dithiocarbamic acid and trithiocarbonic acid (see Section 1.Y).

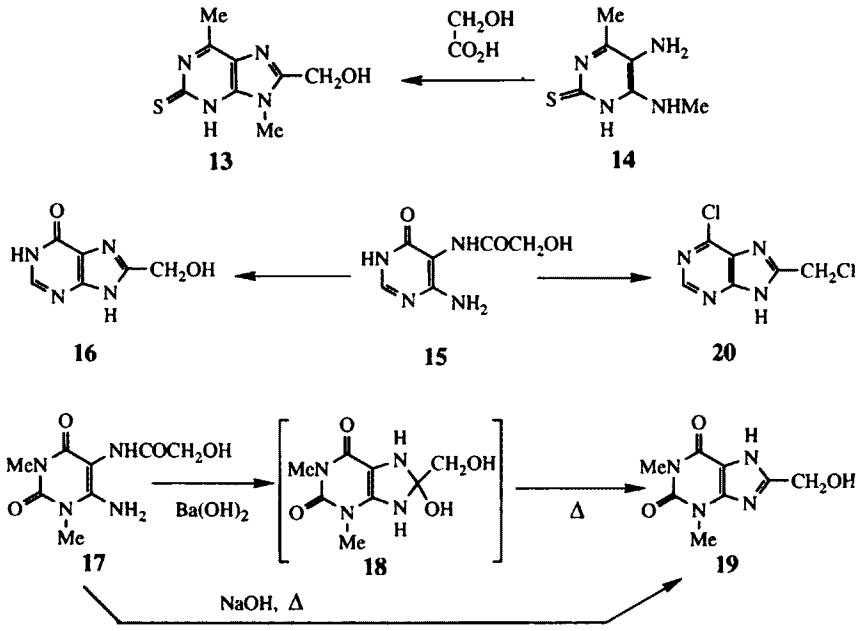
D. Cyclization with Other Carboxylic Acids (*H*41)

Homologs of formic acid have in the past been used extensively in the preparation of 8-substituted purines. Like formic acid they usually suffer the disadvantage of requiring a two-stage reaction. Orthoesters and their derivatives, by contrast, afford the 8-substituted purine directly and are therefore the more obvious reagents of choice. However, while orthoesters, are suitable for simple substituents at C-8, such as methyl, ethyl, propyl, and benzyl, the lack of suitable orthoesters with larger alkyl groups limits their application. For syntheses of more complex 8-alkylpurines, recourse to the more widely available carboxylic acids or their esters is usually taken.

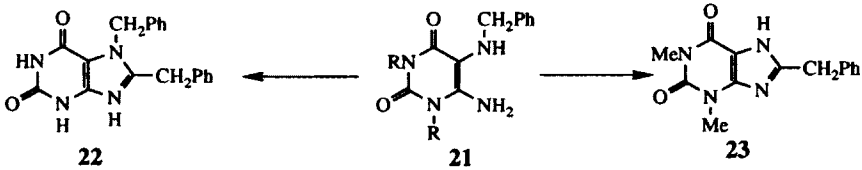
Direct conversion to 8-trifluoromethylpurine occurs on heating (110°C, 24 h) 4,5-diaminopyrimidine with trifluoroacetic acid.[840] Similar conditions (100°C, 3 h) are utilized in forming the 8-hydroxymethylpurine (**13**) from glycollic acid and the 5-amino-6-methylaminopyrimidine[841] (**14**). On fusion of the same acid with 4,5-diamino-6-oxopyrimidine only the 5-acylated pyrimidine (**15**)† results, requiring strong heating with potassium acetate (200°C) to effect closure to 8-hydroxymethylhypoxanthine (**16**).[842] It is noteworthy that from attempts to cyclize **15** to **16** in hot aqueous sodium hydroxide, only starting material is recovered. This result contrasts with the successful formation of 8-hydroxymethyl

* This term is applied to the transformation of one purine into another by heating it with a cyclizing reagent. A change of atom or group at C-8 results from opening of the imidazole ring, with reacylation of the 5-amino group of the pyrimidine followed by recyclization to the new purine.

† An earlier publication, reference 790, eroneously identified the 5-acylaminopyrimidine (**15**) as a hydrated form of the purine (**16**).



derivatives of adenines[790,842] and xanthines[830,843] using glycollic acid followed by alkali. In this synthetic route the acid can be replaced by ethyl glycollate with equal facility.[790,842] Cyclization of **17** made with barium hydroxide initially gives the unstable dihydro derivative (**18**), showing a molecular ion peak at 228, which forms the required 8-hydroxymethyltheophylline (**19**) on thermal elimination of water. A direct transformation from **17** to **19** is possible using a stronger alkali such as sodium hydroxide. Use of a mixture of phosphoryl chloride and diethylaniline to cyclodehydrate **15** gives the purine (**20**), in which chlorination of both hydroxy functions has occurred.[844] Illustrating the diversity of 8-substituted purines resulting from carboxylic acid closures are those from cyclopentyl carboxylic acid[845] (with alkali), methoxyacetic acid[846] (alkali, 100°C), and phenylacetic acid.[847] Condensation of the latter with the 5-benzylaminouracil (**21**, R = H) gives 7,8-dibenzylxanthine (**22**), but with the 1,3-dimethylated uracil (**21**, R = Me) an anomalous reaction occurs, affording 8-benzyltheophyline (**23**) through concomitant loss of the 7-benzyl group.[847] Various aldonic acids afford 8-(polyhydroxyalkyl)adenines on condensation with 4,5,6-triaminopyrimidine.[1992] Controlled conditions allow only one carboxyl group of a dicarboxylic acid to react, forming 8-carboxyalkylpurines. With an excess of the diaminopy-

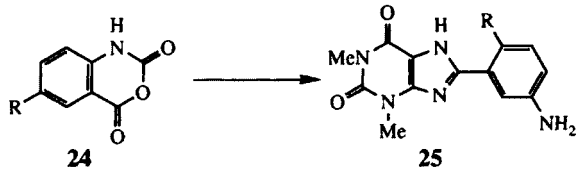


rimidine present, di(purin-8-yl)alkanes result, as exemplified by 1,3-di(adenin-8-yl)propane from glutaric acid and 4,5,6-triaminopyrimidine.[1101] Illustrating a novel route to 8-phenylpurines under mild conditions is formation of an 8-(4-sulfophenyl)purine from a diaminouracil and the potassium salt of 4-sulfobenzoic acid in the presence of an alkyl carbodiimide and final cyclization (70°C, 5 min) in sodium hydroxide.[893] A series of 8-alkyl-1,3-dipropylxanthines results from similar diimide-induced condensations and closures in dioxan with alkali or in phosphoryl chloride.[1886] The replacement of acids by their esters, sometimes with advantages for the reaction, has been noted already. Lactones also provide a route to 8-hydroxyalkylpurines, as seen, for example, in the direct formation of various 8-(3-hydroxypropyl)xanthines with butyrolactone.[830]

E. Cyclization with Acid Anydrides (*H*44)

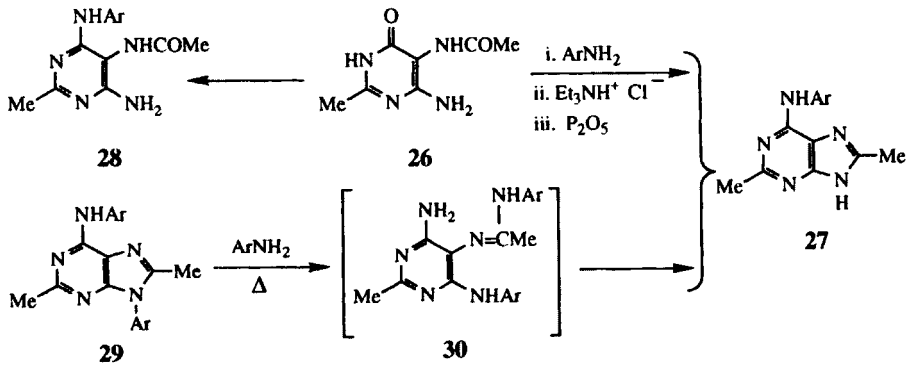
Acid anhydrides, like carboxylic acids, still have some application to the synthesis of 8-alkylpurines, although now they have largely been replaced by the more versatile anhydride–orthoester combination reagents. A disadvantage of anhydrides is their ability to acylate other substituents, notably amino but to a lesser degree oxo (hydroxy) groups also, which may pose problems when deacylation is required. By contrast any corresponding substituted-amino derivatives (i.e., azamethines) obtained from ortho ester closures readily revert to the amino forms on mild treatment. The remarks made concerning closure with acids apply equally to those with anhydrides, notably that in the majority of cases a two-stage reaction is involved. At present, most interest is centered on the second of these, namely, the best means of effecting ring closure of the 5-acylamino-4-aminopyrimidine. A diverse range of reagents is available for this, some of which extend the reaction by enabling group modifications, concomitant with cyclization, to be made.

The application of acetic anhydride to form 8-methylpurines is well documented, typified by the formation of 2-chloro-6,8,9-trimethylpurine directly from 5-amino-2-chloro-6-methyl-4-methylaminopyrimidine (reflux, 6 h)[848] and 2,3-dihydro-8-methyl-2-thioxopurine and the 6,8,9-trimethyl homolog, both requiring alkali treatment (aq NaOH, reflux, 0.5 h) of the 5-acetamidopyrimidine to complete the cyclization.[860] Failure to form either 6-ethyl-8,9-dimethyl-2-methylthio- or 9-ethyl-6,8-dimethyl-2-methylthio-purine with this anhydride is attributed to the operation of steric factors.[1188] Exemplifying the more complex reagents used are crotonic anhydride with 4,5,6-triaminopyrimidine (240 °C, 1 h), giving the 6-amino-8-crotylpurine as the acylated 6-amino derivative,[790] pentanoic anydride, and the same triaminopyrimidine product, requiring heating with toluenesulfonic acid in diphenylether (220°C, 5 h) to cyclize the 5-acylamino intermediate to 8-butyladenine.[849] More esoteric examples are provided by the isatoic anhydrides [3,1-benzoxazine-2,4(1*H*, 3*H*)-diones] (**24**, R = H or Cl) which convert 5,6-diaminouracil derivatives into 8-arylxanthines of the type **25** (R = H or Cl) in a high-boiling solvent (sulfolane, reflux, 0.5 h).[850] Metatheses of oxo to



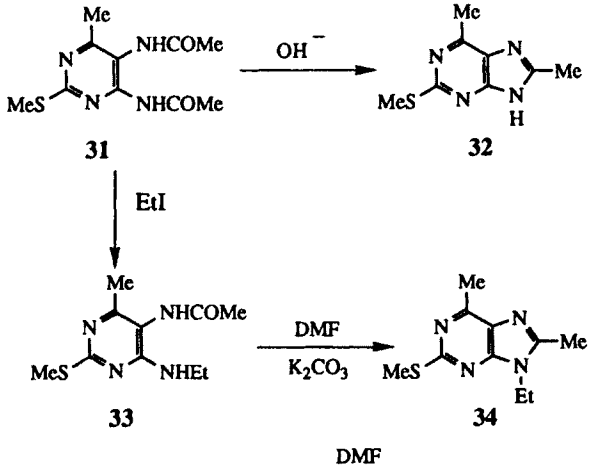
24 25

chloro, which occurs when 5-acylamino-4-amino-oxopyrimidines are heated with dimethylaniline and phosphoryl chloride, is used to prepare a series of 8-alkyl-6-chloropurines.[842] A useful recent addition to syntheses of this type involves a one-pot direct conversion of oxopyrimidines to aminopurines in good yields through ring closure in a mixture of phosphorus pentoxide and triethylamine hydrochloride containing an aromatic amine. On prolonged heating (200°C, > 2 h), with aniline as the amine, 5-acetamidopyrimidine (**26**) gives the 6-anilinopurine (**27**).[851] Subsequent work has shown that a secondary aliphatic amine can replace the aromatic amine affording the 6-dialkylamino anaolog of **27**.[852] Band on the evidence available, replacement of oxo by amino group appears to occur prior to the cyclization stage.* Studies of the aromatic amine reaction show that steric factors can influence the ring-closure mode. If the aromatic ring is unsubstituted or contains a small substituent at an *ortho* position, an analog of **27** is produced from the intermediate (**28**). If both *ortho* positions are occupied, a 6-aminopurine (**29**, Ar = *o*-substituted-phenyl) results. The course of the reaction is largely governed by substituent size. A mixture of **27** and **29** can result, which on longer heating with the amine is converted to **27** only.[853] In these cases **29** is the likely precursor of **27** and undergoes further arylamine attack and fission of the imidazole ring with subsequent recyclization of the intermediate (**30**) to **27** through the primary amino group. A further demonstration of the versatility of 5-acylaminopyrimidines in purine syntheses is the effect of alkyl halides on 4,5-bisacylaminopyrimidines. Unlike 5-acylamino-4-aminopyrimidines, which undergo *N*-alkylation of the 5-acylamino group, the bisacylamino analog alkylates at the 4-acylamino group, during which the acyl moiety[834] is lost. This reaction allows the prepara-



28 26 27 29 30

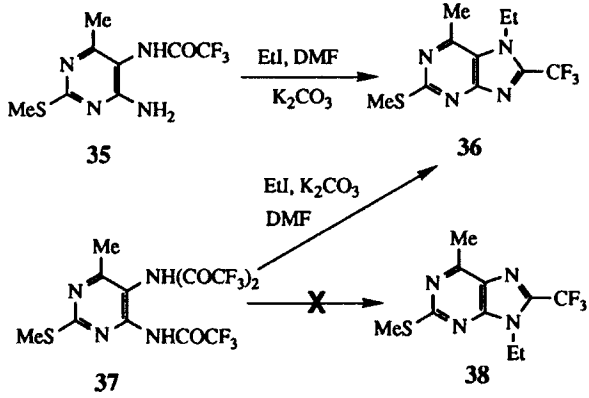
*Direct replacement of oxo (hydroxy) groups by amino groups is also found in purines (see Chapter VI, Section 6.G).



tion of either a 9-substituted or 9-unsubstituted purine from the same 4,5-diaminopyrimidine as, for example, either 6,8-dimethyl-2-methylthio- (**32**) or 9-ethyl-6,8-dimethyl-2-methylthio-purine (**34**) from 4,5-bisacetamido-6-methyl-2-methylthiopyrimidine (**31**) or the ethylated product (**33**). If the mixed anhydride, formic acetic anhydride, or a formic acid and acetic anhydride mixture is used, the analogous 4,5-bisformamidopyrimidine to **31** obtained can be likewise ethylated and ring closed to 9-ethyl-6-methyl-2-methylthiopurine.[854] Studies with trifluoroacetic anhydride as cyclizing reagent produce unexpected results. When heated with 4,5-diamino-6-methyl-2-methylthiopyrimidine (100°C, 2 h), the expected 5-trifluoroacetamido derivative (**35**) results. On attempted ethylation in cold DMF (EtI, K_2CO_3), a spontaneous ring closure to the 7-ethylpurine (**36**) occurs. Introduction of three trifluoroacetyl groups takes place when the diaminopyrimidine described above and the anhydride react in the cold. Surprisingly,* on ethyl iodide treatment the product (**37**) gives the 7-ethylpurine (**36**) rather than the expected 9-ethyl isomer (**38**). Infrared examination of the initial alkylation product revealed the presence of carbonyl and amino groups, indicating that the cyclization is extremely facile and takes place during the final workup.[854]

When uric acid is heated with acetic, propanoic, or *n*-butyric anhydride an extended Traube reaction occurs, forming the respective 8-methyl-, 8-ethyl-, or 8-*n*-propyl- xanthines.[940] This procedure with isobutyric anhydride however gives a rearranged product (see Chapter VI, Section 14).

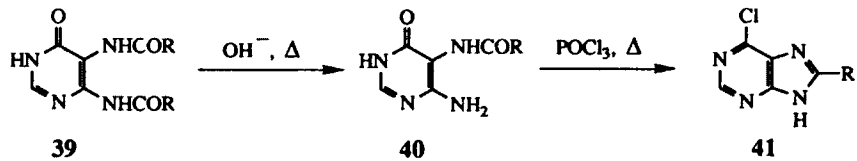
* This result was unexpected as the triacetylated analog of **37** after ethylation cyclizes to the 9-ethylpurine[834] (**34**). A rationale for this anomalous behavior can be formulated if, prior to the ethylation step, two of the trifluroacetyl groups, one from each of the amino groups, are lost. Alkylation in this case would then give **35**. On further examination the triacylated derivative (**37**) is found to have two highly labile trifluoroacetyl groups, especially when alkali is present.[854]



F. Cyclization with Acid Chlorides (*H47*)

Since use of this type of reagent was reviewed in the original volume, few new examples have appeared in the literature. No significant developments or extensions to the method have been noted. All cyclizations are of the two-stage type.

Reaction at ambient temperature of 4,5,6-triaminopyrimidine with pivaloyl chloride (Me_3CCOCl) in pyridine gives the 5-acylaminopyrimidine, which hot aqueous alkali converts to 8-*tert*-butyladenine. Similarly derived is 8-isopropyladenine from isobutyryl chloride.[842] When the same two acid chlorides and 4,5-diamino-6-oxopyrimidine were reacted, the corresponding 4,5-bisacylamino derivatives (**39**, R = CMe_3) and (**39**, R = $CHMe_2$) resulted. On treatment with hot aqueous alkali, deacylation at the 4-position occurred without cyclization taking place. Both of the products (**40**) underwent ring closure to the respective 6-chloro-8-*tert*-butyl-(**41**, R = CMe_3) and 6-chloro-8-isopropyl-purine (**41**, R = $CHMe_2$) in hot phosphoryl chloride.[842] Other examples of direct conversion of oxopyrimidines to both 2-chloro- and 6-chloro-purines, are illustrated by a similar preparation of a series of 6-chloro-8-phenylpurines[856] and of 2-chloro-8-phenylpurine, in good yield (76%), from 4-amino-5-benzamido-1,2-dihydro-2-oxopyrimidine (phosphoryl chloride, reflux, 6 h).[857] In cases where strong dehydrating conditions are needed, but use of phosphoryl chloride is precluded or not desirable, phosphorus pentoxide in phosphoric acid (85%) is a valuable alternative. After aroylation of 4,5,6-triaminopyrimidine with various substituted benzoyl chlorides (NaOH, 21°C, 1 h), the 5-benzamidopyrimidines could be cyclized in this acid mixture (165°C, 1.5 h)[858] to 8-phenyladenines.



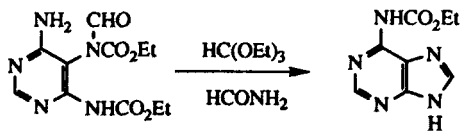
The facility with which *N*-substituted-5-benzamidopyrimidines undergo ring closure to the corresponding 7-substituted-8-phenylpurines is illustrated by the formation of 1,7-dimethyl-8-phenylhypoxanthine, under mild conditions (3% NaOH, 100°C, 10 min), from 4-amino-1,6-dihydro-1-methyl-5-(*N*-methyl)benzamido-6-oxopyrimidine.[872] Present interest in the use of xanthines as adenosine antagonists has led to this approach being utilized to form a range of 8-alkyltheophyllines.[2005]

G. Cyclization with Orthoesters and Diethoxymethyl Acetate (*H*50)

Direct cyclization of diaminopyrimidines is possible with (1) an orthoester alone, (2) an orthoester–acid mixture, (3) an orthoester–acid anydride mixture, or (4) diethoxymethyl acetate. The choice of the most suitable reagent depends largely upon the groups present in the purine being prepared.

Triethyl orthoformate in ethanol (78°C, 5 h) with 4,5-diamino-2,3-dihydro-3-hydroxy-2-oxopyrimidine gives a good yield (**ca.** 80%) of 2,3-dihydro-3-hydroxy-2-oxo purine.[861] Some workers, however, have tended to favor orthoester–acid combinations, as in forming 9-benzyl-6-chloropurine (triethyl orthoformate, ethanesulphonic acid)[862] and the 9-(2-fluorobenzyl) analog.[863] Various 9-benzyladenine derivatives[1210] and examples of erythro and threo forms of 9-(ω-hydroxyalkyl) adenines[1211,1212] have also resulted from this approach. Replacing the sulfonic acid by hydrochloric acid is effective for cyclizing a 4,5-diamino-6-substituted-aminopyrimidine to the corresponding 6-substituted-aminopurine.[864]

The same orthoester–acid mixture converts a number of 4,5-diamino-6-chloropyrimidines into 6-chloropurines in good yields (ca. 70%),[865] including ring closure of a sugar-containing 6-chlorodiaminopyrimidine, using the orthoester in hydrogen chloride saturated dioxan (20°C, 2 h), to the 6-chloropurine nucleoside.[1754] It is noteworthy that under the mild conditions used no significant hydrolyses of the halogens appear to take place. A further example of this procedure is 9-(2-hydroxyethyl)-1,3-dimethylxanthine.[938] In a medium composed of equal amounts of triethyl orthoformate and formamide, the *N*-formylated 4,5-bisethoxycarbonylaminopyrimidine (**42**) cyclizes (80°C, 20 min) to 6-ethoxycarbonylaminopurine (**43**) in reasonable yield (55%), the second ethoxycarbonyl group being lost from the N-7 nitrogen after ring closure has occurred.

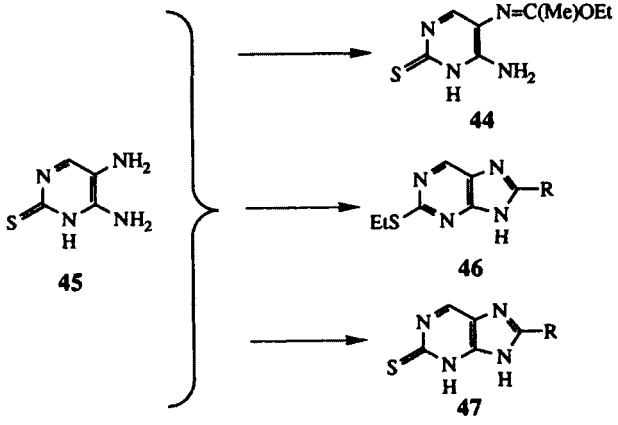


42 **43**

The introduction of trialkyl orthoester–acid anhydride mixtures for purine syntheses was initially widely welcomed because it appeared to provide a means of ring closure having many advantages with few, if any, disadvantages of the reagents then available. Later studies modified this view somewhat when it was

shown that not only is the ratio of ester to anhydride significant, but that the mixture can also function as an alkylating agent, thioxo groups in particular are easily transformed into their alkylthio analogs in this way. Purines resulting from straightforward orthoester–anhydride closures include 2,6,9-trimethyl- (reflux 4 h),[860] 2-dimethylamino-6,9-dimethyl- (reflux, 4 h),[860] and 2-methoxy-6,9-dimethyl-purine (reflux, 4 h)[860] from triethyl orthoformate together with 8-methyl homologs using triethyl orthoacetate–acetic anhydride.[860] Failure of the latter mixed reagent to cyclize the appropriate pyrimidines to 6-ethyl-8,9-dimethyl- and 9-ethyl-6,8-dimethyl-2-methylthiopurine suggests that steric factors are operating.[1188] Preparations of 8-ethyl-2-methylthio-, 8-ethyl-6-methyl-2-methylthio-, and 8-ethyl-2-ethylthio-purines are achieved likewise with triethyl orthopropionate–propionic anhydride and the corresponding 4,5-diamino-2-alkylthiopyrimidine.[866] The optimum ratio of orthoester to anhydride is found to be 2:1. A large excess of anhydride gives rise to unidentified diacylated purines. Conversely, with the orthoester predominant, a mixture containing a purine and the uncyclized intermediate is obtained. The latter case is exemplified by isolation of the 4-amino-5-α- ethoxyethylideneaminopyrimidine (**44**) from the action of triethyl orthoacetate and a small amount of anydride on 4,5-diamino-2,3-dihydro-2-thioxopyrimidine (**45**).[860]

When cyclization of 4,5-diamino-thioxopyrimidines is attempted with a suitable ester–anhydride ratio, the product is an alkylthiopurine resulting from ring closure and an accompanying alkylation of the thioxo group.[866] 2-Ethylthiopurines derived in this way from **45** include the 8-methyl (**46**, R = Me) (triethyl orthoacetate–acetic anhydride, reflux, 4 h), 8-ethyl (**46**, R = Et) (triethyl orthopropionate–propionic anhydride, 4 h), and 8-phenyl (**46**, R = Ph) (triethyl orthobenzoate–acetic anhydride, 4 h) derivatives.[866] Exceptions were noted with trialkyl orthoformate mixtures in which ring closure without any *S*-alkylation usually occurred. With trimethyl orthoformate, however, some 2-methylthiopurine is obtained with **45**. By reducing the heating period to minutes *S*-alkylation can be eliminated almost completely and the thioxopurines (**47**) obtained; an

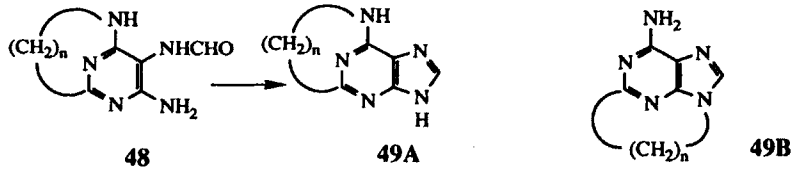


alternative approach to heat (2 h) the cyclizing mixture prior to reaction with the diaminopyrimidine. Available evidence indicates that the alkylating species are labile products initially formed by orthoester–anhydride interaction, the alkyl group arising from the alkoxy group of the ester.[866] Diethoxymethyl acetate remains the best reagent for preparing 8-unsubstituted purines, with few untoward side reactions being encountered. Recent examples noted include 2-methylthio-6-phenyl- (63%) (reflux, 3 h),[857] 2-chloro-6- phenyl- (60%) (reflux, 3 h),[867] and 6-amino-2,3-dihydro-3-methyl-2-oxo-purine (3-methylisoguanine) (35%).[859] Surprisingly, the latter is not obtained when triethyl orthoformate and acetic anhydride are used instead.[859]

H. Cyclization with Formamide (*H*53)

With the introduction of reagents requiring less rigorous conditions, the popularity of the relatively high-boiling formamide has declined quite drastically. This is apparent from even a cursory glance at the current literature in which relatively few examples are now to be found. Use of this amide to form 8-unsubstituted purines is largely confined to high-melting and poorly soluble derivatives, notably those of oxo- and thioxopurines, exemplified by the syntheses of 9-benzyl-, 9-cyclohexyl-, and 9-(2-hydroxyethyl)-hypoxanthines (180°C, 1.5 h).[869] The addition of formic acid, favored by some workers, has been used to prepare 3-benzyl-1,2,3,6-tetrahydro-6-oxo-2-thioxopurine (180°C, 2 h)[826] and 6-amino-2,3-dihydro-3-methyl-2-oxopurine (180°C, 3 h).[859] The yield of the latter purine (77%) is more than double that obtained (35%) using diethoxymethyl acetate for the closure[859] (Section 1.G).

With 4,5,6-triaminopyrimidines, the choice of cyclization modes between N-5 and either N-4 or N-6 is influenced by various factors. In the case of the cyclic derivatives (**48**), structural controls operate. For those with chain lengths up to seven carbon atoms, the C-2 to N-6 linked isomer (**49A**, $n < 8$) predominates. With over eleven carbon atoms, the alternative form (**49B**, $n > 10$) is the major product. The intermediate derivative (**48**, $n = 9$) affords almost equal amounts of the two isomers.[1728]



48 **49A** **49B**

I. Cyclization with Other Amides (*H*56)

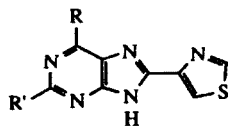
These derivatives provide a direct route to 8-substituted purines but, like formamide, have been largely replaced by more convenient reagents. However, while

this is now the case for purines with simple substituents at the 8-position, recourse to amide-type ring closures is still necessary where more complex 8-substituents are involved and no suitable alternative reagents are available.

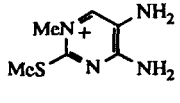
4,5,6-Triaminopyrimidine and cinnamamide fused together (230°C, 3 h) give 8-styryladenine[790] (90%). High temperatures (195°C, 1 h) were required for reacting 4-carbamoylthiazole with 4,5-diamino-2-methylthiopyrimidine in polyphosphoric acid in the formation of the 8-(4-thiazolyl)purine (**50**, R = SMe, R′ = H) (195°C, 60 min). Similarly obtained were (**50**) (R = NH_2, R′ = SH) (190°C, 60 min) and (**50**) (R = NH_2, R′ = SMe) (180°C, 30 min).[870] Hydrolysis of a thioxo group occurred on attempted closure of 4,5-diamino-1,2,3,6-tetrahydro-2,6-dithioxopyrimidine with this amide; the product was the 2-thioxohypoxanthine (**50**, R = OH, R′ = SH) and not the bisthioxo analog (**50**, R = R′ = SH).[870] Loss of a benzyl group* is observed when 4-amino-5-benzylamino-1,3-dimethyluracil and phenylacetamide are fused (250°C, 5 min), forming the 8-benzyl-[847] rather than the expected 7,8-dibenzyl-1,3-dimethylxanthine. Reaction of 4,5,6-triamino-2-oxopyrimidine with acetamide provides a useful route to 8-methylisoguanine.[2019]

J. Cyclization with *N,N*-Dialkylamides and Phosphoryl Chloride (*H*57)

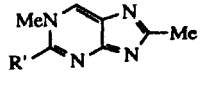
A variety of amides has been employed in the preparation of Vilsmeier reagents for use in low-temperature cyclizations of diaminopyrimidines. For 8-unsubstituted purines, dimethyl formamide and phosphoryl chloride (50°C, 0.5 h) are employed, as in the formation of 7-methyl- and 1,7-dimethyl-xanthine from the respective 6-amino-5-methylamino- and 6-amino-3-methyl-5-methylaminouracil.[838] Changing to dimethylacetamide gives 8-methylpurines exemplified by 8-methyl-2-methylthiopurine from 4,5-diamino-2-methylthiopyrimidine and the 1-methyl homolog (**52**) from the diaminopyrimidine iodide[871] (**51**) with 8,9-dimethyl-2-methylthiopurine also formed in this way, all ring closures being effected at room temperature.[871] The successful syntheses of 6-ethyl-8,9-dimethyl- and 9-ethyl-6,8-dimethyl-2-methylthiopurines using this approach are in striking contrast to the failures experienced on attempted cyclizations with acetic anhydride alone or with an orthopropionate ester[1188] (Section 1.G). Formation of a 8-ethyl derivative is exemplified in 8-ethyl-2-ethylthiopurine using *N,N*-dimethylpropionamide.[834] Intramolecular cyclization involving the 5-amino group of the pyrimidine occurs on treating the diaminopyrimidine (**53**) with dimethylfor-



50

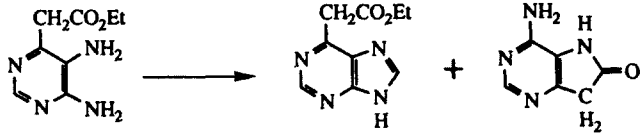


51



52

* A relevant observation is that this same group is removed on ring closure of the above diaminopyrimidine with phenylacetic acid (see Section 1.D).

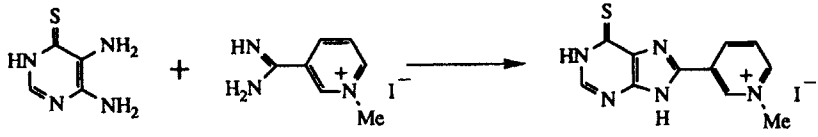


53 54 55

mamide–phosphoryl chloride, resulting in a mixture of the purine (**54**) and 4-amino-5*H*-pyrazolo[3,2-*d*]pyrimidin-6-one (**55**)* being obtained.

K. Cyclization with Amidines (*H*58)

In spite of the severe fusion conditions required, amidines continue to be favored for preparation of some 8-substituted purines, notably those having oxo- or thioxo- groups in the pyrimidine ring. Acetamidine hydrochloride and 4,5-diamino-3-benzyl-1,2,3,6-tetrahydro-6-oxo-2-thioxopyrimidine (sodium acetate; 150 °C, 5 min) yield the corresponding 8-methyl-6-oxo-2-thioxopurine.[873] while 1-benzyl-8-methylhypoxanthine[873] and 8-methyl-9-phenylpurine[942] arise similarly. Various 8-phenylpurines result from benzamidine hydrochloride fusions employing temperatures around 180°C and brief (3–10 min) reaction times. Examples such as the 2-thioxo analog of 8-phenyltheophylline from 4,5-diamino-1,2,3,6-tetrahydro-1,3-dimethyl-6-oxo-2-thioxopyrimidine and the more simple 9-methyl-8-phenylpurine from 5-amino-4-methylaminopyrimidine[875] show the versatility of the method by which other 8-phenylpurines have been formed.[872,1226] In some fusions the starting materials are 4-amino-5-formamidopyrimidines,[872,873] the formyl group undergoing facile displacement prior to closure. A novel 8-(3-pyridyl)-6-thioxopurine (**58**) is obtained from nicotinamidine methiodide (**57**) and 4,5-diamino-1,6-dihydro-6-thioxopyrimidine (**56**), but a higher temperature (200°C) to that used above and a longer heating time (0.5 h)[876] are required. This work has also afforded a wide range of analogs.[877]



56 57 58

M. Cyclization with Urea (*H*59)

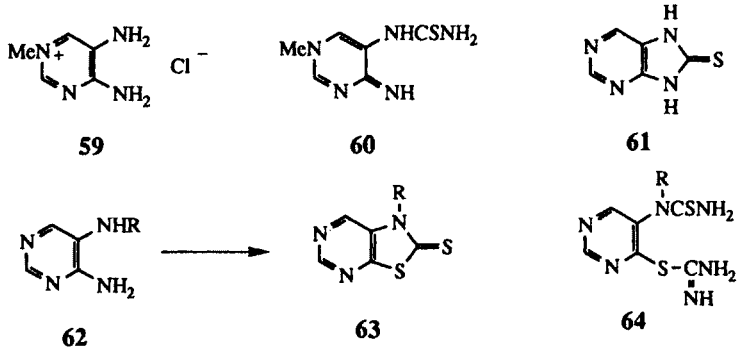
This continues to be the most favored route for 8-oxopurine formation which, in spite of the forcing conditions employed, generally affords satisfactory to good yields. Recently reported are syntheses for 2,3-dihydro-6,9-dimethyl-8-oxo-2-

* On ring closure of **53** with diethoxymethyl acetate, the only product isolated was the 9(?)-acetylated form of the ethoxycarbonylmethylpurine (**54**).[171]

thioxo-(190°C, 0.25 h)[860,878] and 2-amino-1,6,7,8-tetrahydro-9-methyl-6,8-dioxopurine[879] together with various thioxo analogs of uric acid[880] (200°C, 0.25 h) in 70–90% yields. Closure of 5-amino-6-chloro-4-methylaminopyrimidine to 6-chloro-7,8-dihydro-9-methyl-8-oxopurine (180 °C, 0.5 h) is not surprising since the 9-benzyl analog which has been similarly prepared[155] also exhibits a deactivated halogen attributed to the presence of the 8-oxo group.

N. Cyclization with Thiourea (*H*60)

Current literature still contains many examples of this well-tried and tested route to 8-thioxopurines. These range from simple derivatives such as 8-thioxopurine itself[836] to the highly substituted 3-benzyl-1,2,3,6,7,8-hexahydro-2,6-dioxo-8-thioxopurine.[881] The method in practical terms is more suited to higher melting compounds, for example, oxo-[882,883] or aminopurines;[857,881,884,885] anomalous behavior is observed with some less-substituted analogs. When 4,5-diamino-1-methylpyrimidinium chloride (**59**) and thiourea are heated for a short time (190 °C, 0.25 h), the product is the 5-thioureidopyrimidine (**60**), which requires further heating (210°C, 0.5 h) to effect ring closure to the demethylated 8-thioxopurine (**61**).* The latter conditions will also convert **59** directly to the purine (**61**).[836] Aromatization resulting from loss of the methyl group appears to be a prerequisite for cyclization in both cases. Attempted ring closures of the 5-alkylamino-4-aminopyrimidines (**62**, R = Me or Et) gave no 8-thioxopurines but the 1-alkyl-2,3-dihydro-2-thioxothiazolo[5,4-*d*]pyrimidines (**63**, R = Me or Et)[274] as sole products. It is postulated that **63** arises from attack by a second molecule of thiourea on the 5-thioureidopyrimidine initially formed, displacing the 4-amino group; the product (**64**) then cyclizes with elimination of guanidine.[274]



O. Cyclization with Cyanates, Isocyanates and Derivatives (*H*61)

Under reflux conditions methyl isocyanate and 4,5-diamino-1,2,3,6-tetrahydro-2-oxo-6-thioxopyrimidine in pyridine (3 h) give the corresponding 5-(*N*-

* Removal of an *N*-methyl group during a ring closure of this type is well documented (*H*60).

methylureido)pyridine intermediate which is converted to 1,2,3,6,7,8-hexahydro-9-methyl-2,8-dioxo-6-thioxopurine on prolonged heating (reflux; 5 h) in hydrochloric acid.[886]

P. Cyclization with Isothiocyanates (*H*62)

Methyl isothiocyanate with 4,5-diamino-1,2,3,6-tetrahydro-6-oxo-2-thioxopyrimidine forms 1,2,3,6,7,8-hexrahydro-9-methyl-6-oxo-2,8-dithioxopurine by a two-stage reaction requiring hydrochloric acid treatment (reflux, 3 h) to effect closure.[887] Both the 3-methyl (**65**) and 1-methyl (**66**) isomers of 6-amino-5-benzylthioureidouracil, obtained from the corresponding 5,6-diaminomethyluracil and benzyl isothiocyanate,[888] give the same 9-benzyl-8-thioxopurine (**67**) when cyclized in hot hydrochloric acid.[889] These results are rationalized by assuming that **65** undergoes "normal" closure to **67** on elimination of ammonia, but an alternative Fischer-type cyclization of **66** occurs through the adjacent 6-oxo (hydroxy) group. The 6-amino-1-methylpurine product then suffers a rapid hydrolysis of the amino moiety to **67** as a result of the acidic conditions present. Upon thermal ring closures of **65** and **66** in DME, benzylamine is evolved in both cases, giving 1-methyl-(**68**) and 3-methyl-2,6-dioxo-8-thioxopurine (**69**) respectively.[889]

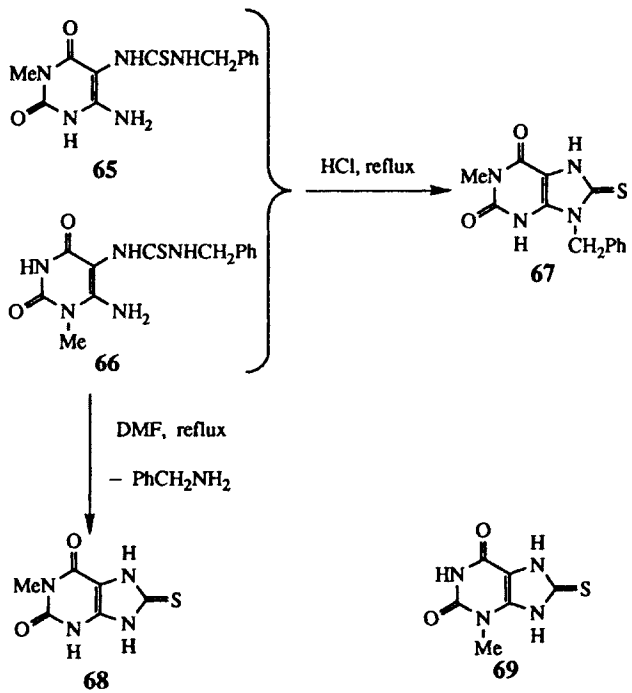


TABLE 2. 8-Thioxopurines Derived from Ring Closures with Carbon Disulfide

Purine	Reaction	Yield (%)	Ref.
2,3,7,8-Tetrahydro-6-methyl-2,8-dithioxo-	Pyridine; reflux, 6 h	78	860
2,3,7,8-tetrahydro-6,9-dimethyl-2,8-dithioxo-	Pyridine; reflux, 6 h	46	860
3,6,7,8-tetrahydro-3-methyl-6-oxo-8-thioxo-	Pyridine; reflux, 5 h		883
3-benzyl-3,6,7,8-tetrahydro-6-oxo-2-thioxo-	Pyridine, NaOH (aq); reflux, 3.5 h		883
1,6,7,8-tetrahydro-1-methyl-2-methylthio-6-oxo-8-thioxo-	Pyridine; reflux, 5 h	82	890
1,2,3,6,7,8-hexahydro-3-methyl-2-oxo-6,8-dithioxo-	Pyridine, NaOH(s); reflux, 5 h	57	890
1,2,3,6,7,8-hexahydro-3-methyl-6-oxo-2,8-dithioxo-	Pyridine, NaOH(s); reflux, 5 h	80	887
1,2,3,6,7,8-hexahydro-1-methyl-2,6-dioxo-8-thioxo-	Pyridine; reflux, 5 h		886

R. Cyclization with Carbon Disulfide (H64)

There is little choice between this approach and that using thiourea (Section 1.N) for forming 8-thioxopurines. Significant advances are lacking in the use of this reagent. A noteworthy point is that the usual reaction temperature achieved in boiling pyridine is significantly raised by the addition of *N,N*-dimethylformamide,[1236] which is utilized in synthesizing the 8-thioxo derivative of eritadenine. Preparation of oxopurines usually requires reflux conditions, with solid or aqueous sodium hydroxide added to the pyridine to aid solubility. Among the wide range of 8-thioxo derivatives[860,883,886,887,890] are a number of 3-methylated homologs derived from 4,5-diamino-3-methylpyrimidines[883,887,890] (Table 2). No examples of a Dimroth rearrangement involving relocation of the methyl group from N-3 to the 4-amino group of the pyrimidine are reported to occur prior to cyclization. Rearrangements of this type, however, are known to occur during previous carbon disulfide closures (*H*66).

S. Cyclization with Phosgene (*H*67)

In view of the practical disadvantages associated with this reagent, it is not surprising to find only an occasional literature reference to its use in the preparation of 8-oxopurines. In one such example, phosgene dissolved in toluene and 5-amino-4-isopropylaminopyrimidine are reacted (reflux; 5 h), giving 7,8-dihydro-9-isopropyl-8-oxopurine.[827]

U. Cyclization with Chlorocarbonic Ester (*H*68)

Although this route to 8-oxopurines was pioneered a century ago, the use of ethyl chlorocarbonate still persists, more specifically for the syntheses of uric acid derivatives[833,891] (Table 3).

TABLE 3. Uric Acid Derivatives Derived from Alkyl Chlorocarbonate Cyclizations

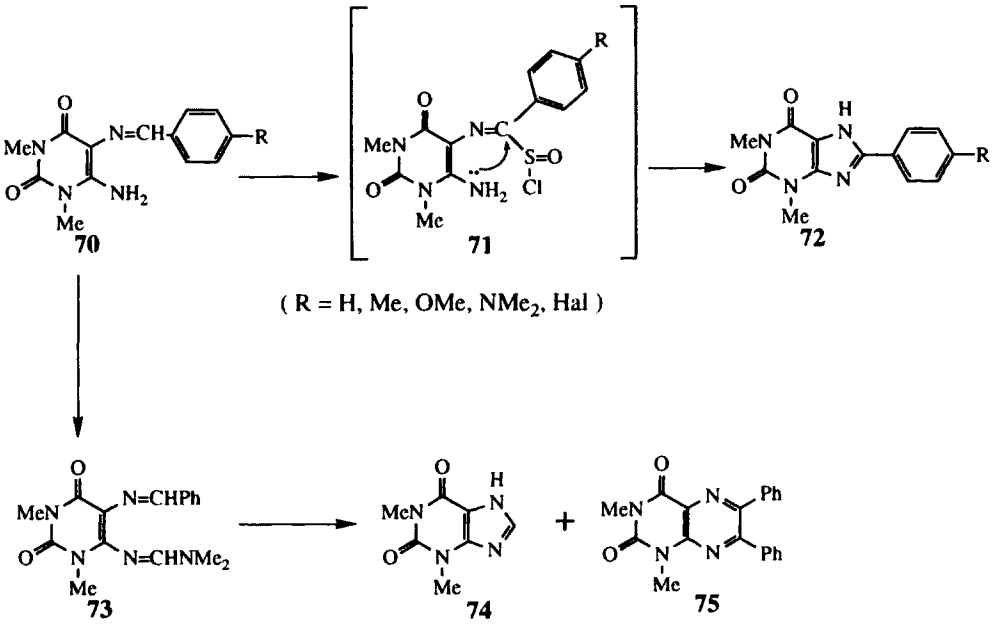
Uric Acid	Reaction	Yield (%)	Ref.
1-Methyl	5*N*-NaOH; reflux, 0.5 h	52	891
3-Methyl	5*N*-KOH; reflux, 1 h	65	891
7-Methyl	NaOEt, 240°C, 1.5 h	91	833
	NaOEt, EtOH; reflux, 4 days	81	833
1,7-Dimethyl	5*N*-NaOH; reflux, 1 h	49	891
	NaOEt, 250°C, 1 h	76	833
1,9-Dimethyl	Metal bath; 320°C, 5 min	50	891
3,7-Dimethyl	5*N*-KOH; reflux, 1 h	74	891
3,9-Dimethyl	$NaHCO_3$, H_2O; reflux, 1 h	85	891
7,9-Dimethyl	5*N*-KOH; reflux, 1 h	49	891
1,3,9-Trimethyl	Oil bath; 270°C, 0.75 h	76	891
3-Benzyl-7-methyl	DMF, NaH; 110°C, 0.25 h	86	833
3-Benzy-1,7-dimethyl	DMF, NaH; 130°C, 0.75 h	77	833

In recent work[833] alkaline cyclization of the intermediate 5-ethoxycarbonylaminopyrimidine has been effected advantageously by utilizing sodium hydride in dimethylformamide as an alternative to the aqueous sodium or potassium hydroxide usually employed.

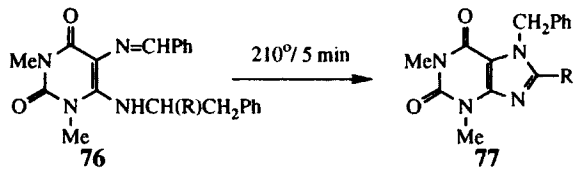
Carbobenzoxychloride finds a use in extended Traube reactions for the conversion of 3-benzyl- and 3-ethyl-adenine to the analogous 8-oxo-6-aminopurines.[941]

V. Cyclization with Aldehydes and Ketones (*H69*)

Initially, aldehydes and ketones were considered to have only a limited application for purine syntheses, but have now been shown to be versatile reagents. Their early use in the formation of 8-substituted purines has now been extended and allows modifications to be made to groups at N-7 or N-9 of the imidazole moiety. To date the majority of aldehydes used have been aromatic, usually benzaldehyde derivatives. The 5-benzylideneaminopyrimidine first formed then undergoes ring closure to an 8-phenylpurine in the presence of an oxidizing agent. The most widely used oxidant, iron(III) chloride, is applied to the preparation of 8-phenyltheophylline[892] (ethanol; 100°C) and a number of 8-substituted phenyl derivatives of xanthine[893] and 1,3-dimethyl[894] and 1,3-dipropyl[894] homologs. A successful alternative to ethanolic iron(III) chloride is iron(III) oxide in dimethylformamide (100°C, 4 h).[894] The anil obtained from 4-nitrobenzaldehyde and 5,6-diaminouracil did not react with iron chloride, but cyclized with the oxide to the purine in hot thionyl chloride.[893] The latter oxidizing agent also converts (reflux, 5 min) the anils (**70**) to the respective purines (**72**) via the proposed intermediates (**71**).[895] Diethyl azidocarboxylate (DEAD) in glyme is a recently introduced oxidant employed in forming 8-phenyl- and 8-cyclohexyl-1,3-dialkylxanthines.[1887] A more unusual oxidation is the closure with *N*-bromosuccinimide in chloroform



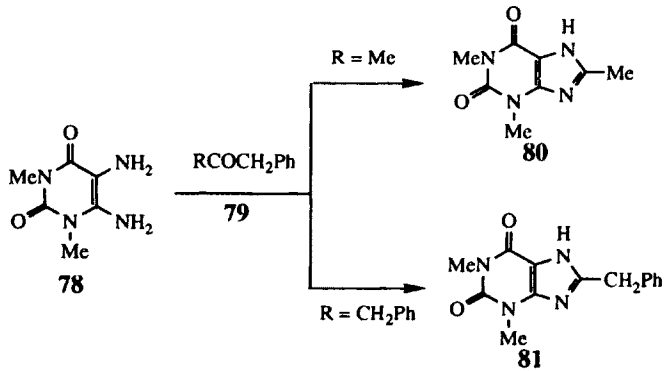
(reflux, 1.5 h) of 4-amino-5-benzylideneamino-2-chloropyrimidine to 2-chloro-8-phenylpurine.[857] While isolation of the anil before ring closure is the usual practice, examples of one-pot reactions are found, as in the formation of 2-methylthio-6,8-diphenylpurine on heating 4,5-diamino-2-methylthio-6-phenylpyrimidine with benzaldehyde (reflux, 0.25 h) in methanol containing copper(II) acetate as oxidizing agent,[896] and in the adoption of a similar procedure for preparing a series of 2,6-diamino-8-arylpurines in which 2,4,5,6-tetraaminopyrimidine, and benzaldehydes are reacted in nitrobenzene containing 4-methylbenzenesulfonyl chloride.[1006] Atmospheric oxidation alone was sufficient to covert some anils of 4,5-diamino-1,3-dipropyluracil to the purines on brief heating in aqueous sodium hydroxide[897] (10%). In boiling formamide the anil (**70**, R = H) gave only a trace of 8-phenyltheophylline; the major product (39%) was theophylline (**74**), from reductive degradation of the anil to the diaminouracil analog and then ring closure by the formamide. A minor product (25%) of the reaction is 6,7-diphenyllumazine.[898] Theophylline also results when **70** (R = H) and dimethylformamide diethylacetal are heated in ethanol (reflux; 4 h), the intermediate bisazinopyrimidine (**73**) requiring photolysis (sunlight, 10 h) of the ethanolic solution during which benzaldehyde and dimethylamine are lost and **74** is produced in 80% yield.[899] The outcome of a reaction between an anil similar to **70** and triethyl orthoformate is a mixture of purine and a 6,7-diphenyllumazine derivative (**75**); this result parallels that noted above using formamide.[900] A demonstration of the synthetic potential of anil groups adjacent to 4-alkylamino groups is the intramolecular cyclization of the 4-(2-phenylethylamino)pyrimidine (**76**, R = H) in hot nitrobenzene to 7-benzyltheophylline (**77**, R = H). By using the 4-(1-benzyl-2-phenylethylamino)pyrimidine (**76**, R = CH_2Ph), 7,8-dibenzyltheophylline (**77**,



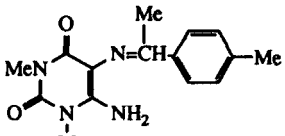
76 77

R = CH_2Ph) results. Both oxidative cyclizations involve loss of a benzyl group concomitant with ring closure since no evidence for the existence of an 8,8-dibenzylpurine is found[901] in the latter preparation. An improved reaction is reported using dimethylformamide in place of nitrobenzene.[901] Examples using nonaromatic aldehydes are fewer in number, but the action of cyclohexanecarboxaldehyde with 5,6-diamino-1,3-dipropyluracil is noteworthy. At ambient temperature in a methanol–acetic acid solution, spontaneous oxidative cyclization gives a good yield (65%) of 8-cyclohexyl-1,3-dipropylxanthine.[845] A related 8-cyclohexylxanthine preparation uses DEAD oxidation in glyme[1887] and a number of 8-alkyl homologs are obtained from cyclizations with iron(III) chloride in ethanol.[1886]

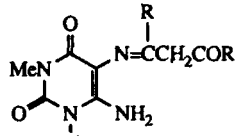
To date ketones have not made a significant contribution to synthetic procedures. When 5,6-diamino-1,3-dimethyluracil (**78**) in ethanol is heated with benzylmethyl ketone (**79**) or the bisulfite adduct, 8-methyltheophylline (**80**) results. With dibenzyl ketone the product is the 8-benzyl analog (**81**). In both ring closures a benzyl group is lost, signified by pronounced odor of toluene.[901] With the 4-methyl analog of acetophenone and **78**, the initial condensation product (**82**) on melting is converted to the 8-(4-methylphenyl)theophylline during which a *C*-methyl group is abstracted.[902] Extensions of this route using 1,3-diketones produce purines rather than the expected diazepines, as found when **78** and acetylacetone interact in ethanol containing acetic acid, giving **83** (R = Me), from which 8-methyltheophylline results on thermolysis. Similarly, dibenzoylmethane and 78 give 8-phenyltheophylline via **83** (R = Ph).[902] Acetone and acetophenone are the respective by-products, with no diazepines of the type (**84**) being detected.



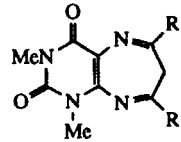
78 80 81



82



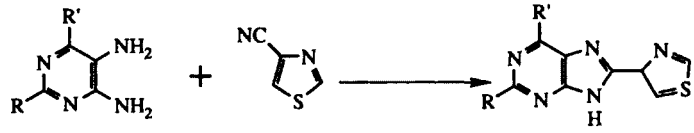
83



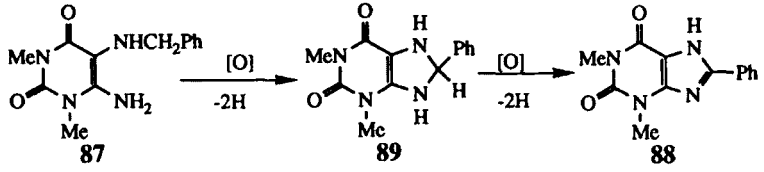
84

W. Cyclization with Cyanogen Derivatives (*H*71)

Heating a difunctional nitrile such as cyanogen bromide with a 4,5-diaminopyrimidine in methanol provides a direct route to an 8-aminopurine. Obtained in reasonable yield this way are 2,8-diamino- (47%),[903] 2,8-diamino-6-methyl- (30%),[903,904] 2,8-diamino-6-hydroxymethyl- (46%),[903,904] and 8-amino-2,3-dihydro-3,6-dimethyl-purine (? %).[904] With a monofunctional reagent of the alkyl or aryl carbonitrile type, the corresponding 8-alkyl(or aryl)purine is formed. The range of 8-(4-thiazolyl) purines (**86**) obtained[870] with 4-cyanothiazole (**85**) in polyphosphoric acid at 200°C (0.5–3.0 h) and various 4,5-diaminopyrimidines illustrates this reaction. The isolation of 8-phenyltheophylline (**88**) from the attempted preparation of 7,8-dibenzyltheophylline, by the action of benzyl carbonitrile on 6-amino-5-benzylamino-1,3-dimethyluracil (**87**), does not appear to involve direct nitrile intervention but rather an oxidative closure of **87**, brought about by the conditions used (270°C, 4 h), in which an intermediate dihydro derivative (**89**) takes part.[847]



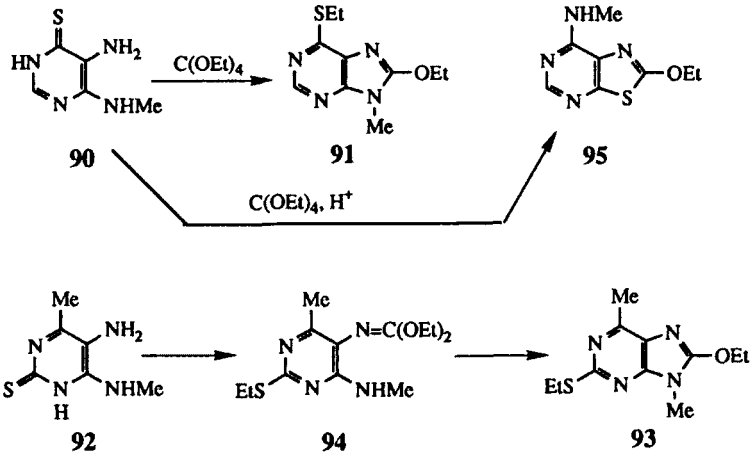
85 86



87 89 88

X. Cyclization with Tetraalkoxymethanes and Thioxo Analogs

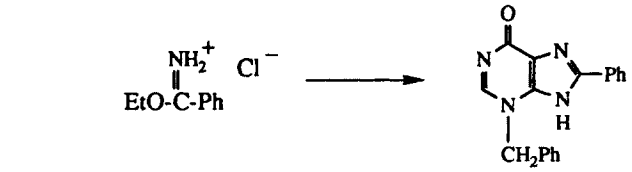
Introduction of these derivatives as cyclizing agents in the Traube syntheses[905] makes possible for the first time direct preparation of 8-alkoxypurines. With this class of reagent a one-step reaction is the norm, but where isolation of the 5-diethoxymethyleneaminopyrimidine intermediate is desirable, purine formation is carried out subsequently by thermal means. This procedure is recommended for both 2- and 6-alkylthiopurines. Direct ring closure is achieved by heating the



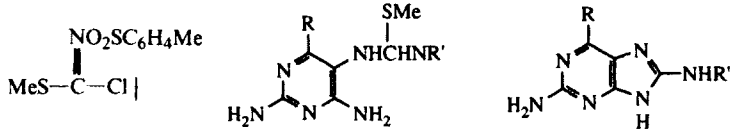
diaminopyrimidine in the tetraalkoxymethane for some hours, as exemplified by the preparation of 8-ethoxy-9-methylpurine from 5-amino-4-methylaminopyrimidine and tetraethoxymethane. By contrast, the same conditions with 4-amino-5-methylaminopyrimidine did not produce the isomeric 8-ethoxy-7-methylpurine until acetic acid (1 mol equiv.) was added. A disadvantage of this type of reagent, shared with the related trialkyl orthoesters, is the potential that it will act as an *S*-alkylating agent if thioxo groups are present. For example, tetraethoxymethane with the diamine (**90**) affords the 6-ethylthio- (**91**) rather than the 6-thioxopurine. In the same way, a 2-ethylthiopurine (**93**) is obtained from closure of a 4,5-diamino-2-thioxopyrimidine (**92**) after isolation of the uncyclized intermediate (**94**). The structure of the latter shows that *S*-alkylation precedes cyclization. Under acid conditions 4,5-diamino-6-thioxopyrimidines undergo the alternative ring closure to thiazolopyrimidines; in the presence of acetic acid (80°C, 4 h) 2-ethoxy-7-methylaminothiazolo[5,4-*d*]pyrimidine (**95**) is obtained. Tetrapropoxymethane affords the analogous cyclized products to **91** and **95**. The same workers[905] also demonstrated the suitability of tetraalkylthiomethanes for this reaction. In a simple illustration, 8-methylthiopurine results from a two-stage process with 4,5-diaminopyrimidine and tetrakismethylthiomethane; the initial product 4-amino-5-(bismethylthiomethyleneamino)pyrimidine forms the purine on heating (200°C, 1 h).[905] However, both 4,5-diaminopyrimidine and the 6-chloro homolog could not be converted to the respective 8-ethoxypurines with tetraethoxymethane, only the diethoxymethyleneaminopyrimidines result, which resist all attempts at closure.

Y. Cyclization with Miscellaneous Reagents (*New*)

This section embraces cyclizing reagents reported in the literature which cannot be accommodated comfortably into any of the orthodox categories. All are bifunctional and give rise to 8-substituted purines. Ethyl benzimidate, as

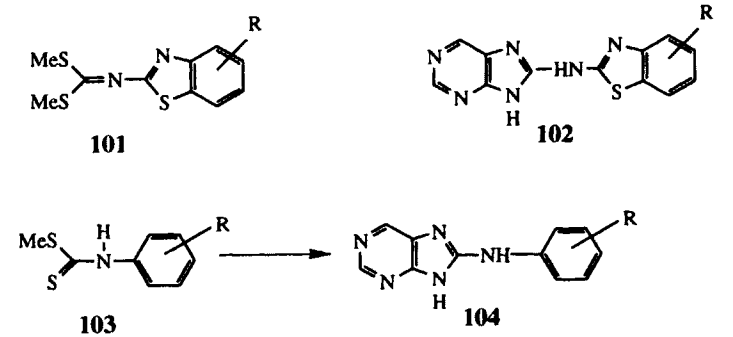


96 97



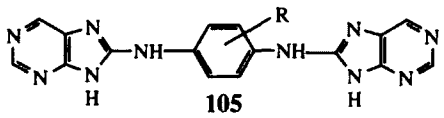
98 (R' = *p*-Toluenesulfonyl) 99 100

hydrochloride salt (**96**), in hot ethanol with 4,5-diamino-3-benzyl-3,6-dihydro-6-oxopyrimidine (reflux, 3 h) forms 3-benzyl-8-phenylhypoxanthine[872] (**97**). A somewhat more complex reagent, providing a less direct route to 8-aminopurines, is *N*-(methylthiochloromethyl)-*p*-toluenesulfonimide (**98**). Halogen interaction with the 5-amino group of the diaminopyrimidine forms the product (**99**), which on mild treatment (DMF, NEt_3, 20°C), in the presence of silver nitrate as desulfurizing agent, gives the sulfonylated purines (**100**, R = H or Me, R′ = 4-methylbenzenesulfonyl). Following reaction with anhydrous hydrogen fluoride (21°C, 40 h), the corresponding 8-aminopurines (**100**, R = H or Me, R′ = H) are obtained.[906] Two other routes reported[907] recently afford 8-aminopurines which, although at present of fairly limited application, have the potential for further development. The first uses Schiff bases such as (**101**), derived from ethyl trithiocarbonic acid [$CS(SEt)_2$], which condense with 4,5-diaminopyrimidine in diethylbenzene (reflux, 15–30 h) providing good yields (~90%) of 8-(2-benzothiazolylamino)purines (**102**). Somewhat shorter reaction times are required to convert the same diaminopyrimidine to related 8-substituted-aminopurines by means of methyldithiocarbamic acid [$CS(NH_2)SMe$] derivatives. With mercury(II) oxide as desulfurizing agent in DMF (reflux, 6 h), formation of 8-anilinopurines (**104**) results with the *N*-substituted dithiocarbamic acid[907] (**103**).



101 102

103 104



105



106

An extension using bis(dithiocarbamic esters) with the same catalyst and solvent (50°C, 48–72 h) affords 1,4-di(purin-8-ylamino)benzenes (**105**) in good (>70%) yields.[1885]

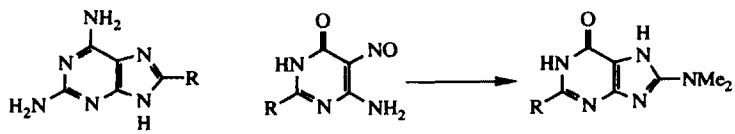
2. SYNTHESES FROM 4-AMINO-5-NITRO- AND 4-AMINO-5-NITROSO-PYRIMIDINES (*H*72), ALSO FROM 4-AMINO-5-AZOPYRIMIDINES (*New*)

Sections A and B below, as before (*H*72), relate to respective cyclizations involving either prior reduction of the 5-nitro or -nitroso group or a cyclodehydration in which one of these groups participate in the removal of elements of water.

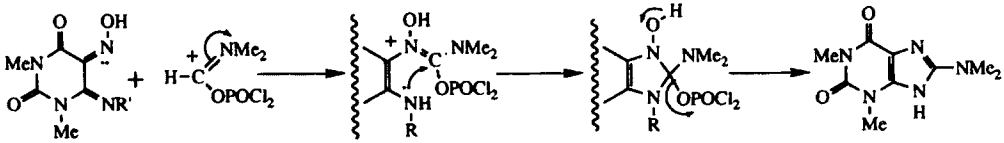
Because of the numerous examples currently available of closures using 5-azopyrimidines, these are now accorded separate treatment in Section II.C.

A. Cyclization Involving Reduction of a 5-Nitro or 5-Nitroso Group (*H*72)

When the bisulfite adducts of dibenzyl ketone and benzylmethyl ketone are heated in butanol (reflux, 6 h) with 6-amino-1,3-dimethyl-5-nitrosouracil, the respective products are 8-benzyl-1,3-dimethyl- and 1,3,8-trimethylxanthine. Reduction of the nitroso group to amino is obviously due to the bisulfite present since the ketones alone do not give cyclized products[901] (compare Section 1.V). A more straightforward reduction occurs with the diacylated nitrosopyrimidine (**106**, R = adamantyl or adamantylmethyl) with zinc dust in acetic acid (reflux; 1.5 h). Conversion of the 6-acylaminopurine initially formed to the 2,6-diaminopurine (**107**) is made in ethanol saturated with hydrogen chloride (reflux; 3 h).[908] The Vilsmeier reagent (phosphoryl chloride and dimethylformamide) reacts with various 4-amino-5-nitrosohydroxypyrimidines (130–160°C, 1 h), forming the corresponding 8-dimethylamino-hydroxypurine, as exemplified by the hypoxanthine derivative (**109**, R = SMe) from 4-amino-1,6-dihydro-2-methylthio-6-oxopyrimidine (**108**, R = SMe).[909,910] Replacing the amide above with

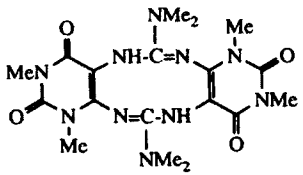


107 108 109

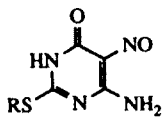


Scheme 1

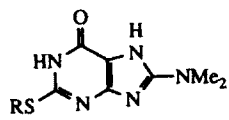
methylformamide gives 8-methylaminopurines,[909,910] while with *N*-methyl-*N*-phenylformamide 8-(*N*-methylanilino) analogs are obtained.[909,910] It should be noted that with formamide itself and phosphoryl chloride, no 8-aminopurines result. In one example only a low yield of a pyrimido[4,5-*d*]pyrimidine is isolated on reaction with 6-amino-1,3-dimethyl-5-nitrosouracil. At low temperatures (20°C, 3 h) the Vilsmeier reagent with the same dimethyluracil derivative affords the dimerized derivative (**110**) which on further heating with the reagent or on sublimation yields 8-dimethylaminotheophylline.[910] Care must be exercised if 2-methylpyrimidines are employed since past reactions have produced 2-chloromethylpurines.[910] The closure mechanism envisages an initial nucleophilic attack by the nitroso group nitrogen on the anil carbon of the reagent, followed by cyclization of the resulting nitrone adduct to the purine, with an accompanying loss of oxygen and dichlorophosphoric acid (Scheme 1).[910] Support for the intermediacy of structures related to purine-7-oxides is given by the participation of similar reactions and starting materials in the syntheses of the latter derivatives (see Chapter XI, Section 1.C). An interesting result is noted on replacing the phosphoryl chloride with 4-methylbenzenesulfonylchloride. Reaction in dimethylformamide with 6-amino-1,3-dimethyl-5-nitrosouracil results in the 8-methylamino- instead of the expected 8-dimethylaminotheophylline. This anomaly is attributed to an initial *O*-sulfonylation of the *N*-oxide group and subsequent fission of the *O*-benzenesulfonyl moiety, followed by reaction of the liberated sulfonyloxy ion with the dimethylamino group. The amino group, reacting in a methyleneamino form, suffers a methyl group abstraction and formation of the methylamino moiety.[911] The application of the diethoxyacetal derivative of dimethylformamide was studied by the same workers, who found that at ambient or lower temperatures, in an excess of the reagent as solvent, 8-substituted-aminopurines are formed, as illustrated by the 8-dimethylaminohypoxanthines (**112**, R = alkyl) from the 2-alkylthio-6-oxopyrimidines (**111**). Corresponding preparations of 6-aminopurines may result in isolation of azamethine analogs of the type (**113**), but aqueous hydrolysis readily gives the



110



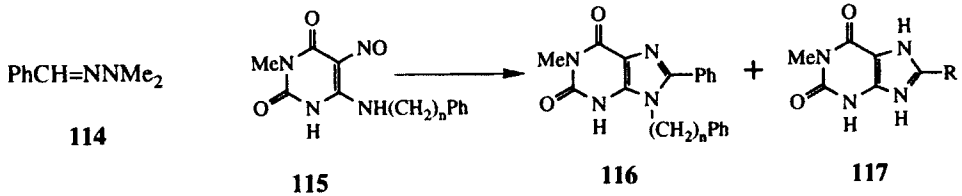
111



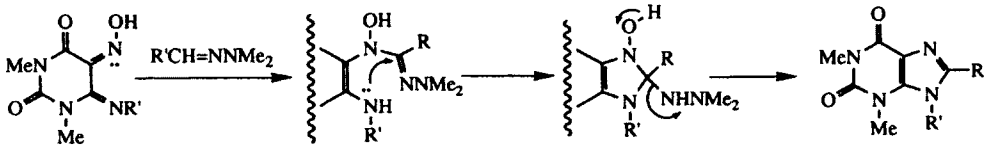
112



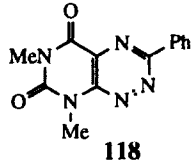
113



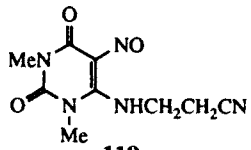
6-amino-8-dimethylaminopurine.[912] A route to 8-alkyl- and 8-aryl-purines uses 1,1-dimethylhydrazones of alkyl and aryl aldehydes with aminonitropyrimidines in dimethylformamide under prolonged reflux conditions.[913] Successful conversions to 8-phenylxanthines have been effected with the benzaldehyde hydrazone (**114**) and the 1-methyl, 3-methyl, and 1,3-dimethyl homologs of 6-amino-5-nitrosouracil. Competing side reactions are a feature of nitrosouracils possessing a 6-alkylamino group. Thus, while both the 6-benzylamino- (**115**, $n = 1$) and 6-(2-phenylethylamino)-uracil (**115**, $n = 2$) and benzaldehyde hydrazone (**114**) give the respective 9-benzyl- (**116**, $n = 1$) and 9-(2-phenylethyl)-8-phenylpurine (**116**, $n = 2$) as major products, lesser amounts (10–25%) of 1-methyl-8-phenyl- (**117**, R = Ph) and 1-methyl-8-benzyl-hypoxanthine (**117**, R = CH_2Ph), derived from the alternative cyclodehydration reaction, are also present.[913] Attempted ring closure under the same conditions of the 6-*n*-propylamino- and 6-*n*-butylamino analogs of **115** give only 8-ethyl-1-methyl- and 1-methyl-8-*n*-propyl-hypoxanthines as products of cyclodehydration, no 9-alkyl-8-phenylpurines are detected.[913] Preparation of 8-alkyl- and 8-unsubstituted purines is brought about using aliphatic aldehydes and formaldehyde, respectively. From a practical standpoint, since hydrazone formation with these derivatives is very facile, a mixture of aldehyde and 1,1-dimethylhydrazine works equally well. However, the dimethylhydrazine in the reaction cannot be replaced by hydrazine, because a 7-azalumazine will result, as exemplified by the 6-phenyl analog (**118**) from 6-amino-1,3-dimethyl-5-nitrosouracil and benzaldehyde hydrazone.[914] The mechanism envisaged for the dimethylhydrazone ring closures parallels that for the Vilsmeier reagent in which initial attack by the nucleophilic α-carbon atom of the hydrazone on the nitroso group gives a hydroxylamino intermediate and subsequent intramolecular cyclization, involving the C-4 amino group and the anil carbon atom. This is followed by splitting off of dimethylhydrazine, and deoxygenation results in the requisite purine derivatives[913] (Scheme 2).



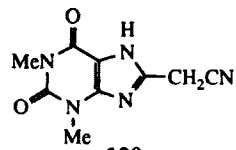
Scheme 2



118



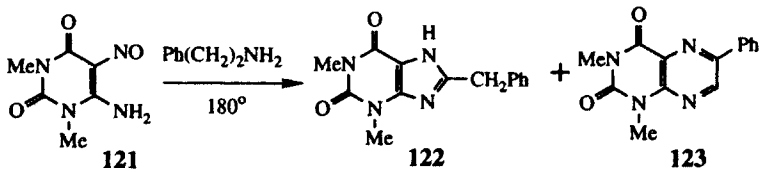
119



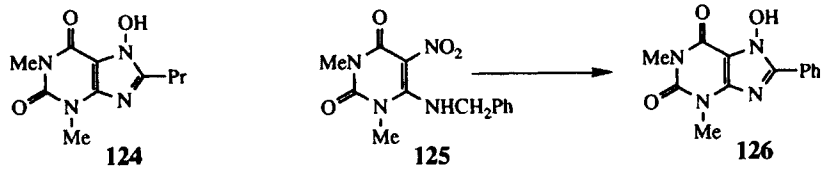
120

B. Cyclization through Cyclodehydration (*H*74)

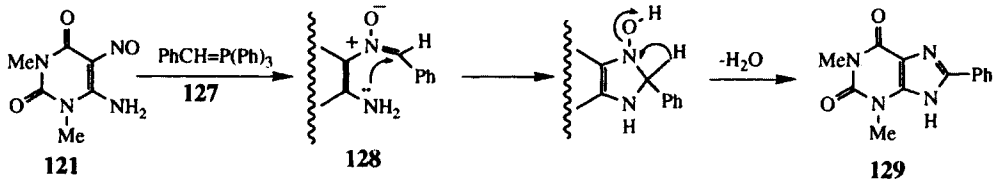
Since the initial studies were reported, extensions of the procedure have widened the range of purines that can be prepared. Both 5-nitro- and 5-nitroso-4-aminopyrimidines have been cyclized, using the Ehrlich Sachs reaction,[915] in which involvement of the oxygen of the 5-substituent with an active methylene moiety in the 4-amino group occurs. Illustrative of this is formation of 8-cyanomethyltheophylline (**120**) from the 6-(2-cyanoethylamino)-5-nitrosouracil (**119**) in a high boiling solvent of butanol or toluene.[916] Related 1,3-dialkyl- and diphenylxanthines result on briefly heating the uracil precursors in ethanol or dimethylformamide.[917] Both 8-ethyl- and 8-*n*-propyl-1-methylxanthine were obtained after cyclodehydration of the 6-*n*-propylamino- and 6-*n*-butylamino-3-methyluracils in dimethylformamide (reflux, 6 h).[913] A series of α,ω-di(purin-8-yl)alkanes from the corresponding bis(5-nitrosopyrimidin-6-ylamino)alkanes is also formed.[917] Earlier work (*H*75) showed that the reaction can be extended to include a 4-amino-5-nitrosopyrimidine and a separate alkylamine for forming the lower homologous 8-alkylpurine. More recent studies do not indicate clearly whether the reaction pathway involves an initial transamination or condensation of the methylene group. The activity of methylene groups present is a significant factor, as shown by isolation of 8-benzyltheophylline (**122**) and 6-phenyllumazine (**123**) in yields of 11% and 41%, respectively, following fusion of 6-amino-1,3-dimethyl-5-nitrosouracil (**121**) with phenylethylamine hydrochloride. When *n*-propylamine is used, the two heterocycles are obtained, but in this case 8-ethyl-1,3-dimethylxanthine forms the larger component (37%) compared with the lower yield (19%) of the 6-methyllumazine analog of **123**. Increasing methylene group activity, therefore, appears to favor pteridine rather than purine formation.[918] In subsequent investigations the amines were replaced by the corresponding thiols; with 2-phenylethanethiol both purine (**122**) and lumazine (**123**) were obtained in a 4:1 ratio, but other complex products were also present.[892] The corresponding 8-phenyl- and 8-methyltheophyllines were isolated with phenylmethanethiol and ethanethiol.[892] At present, insufficient evidence exists to



121 **122** **123**



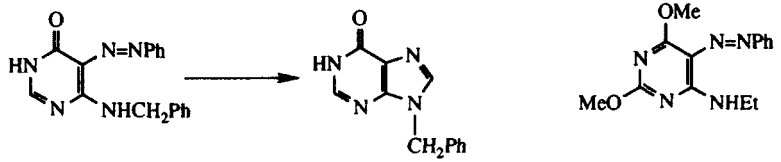
advance a rationale for this reaction, as the reducing potential of thiols and the facility with which thiol groups can replace 4-amino groups in pyrimidines must be considered. Various aldehydes have been condensed with 4-amino-5-nitrosouracil, affording 8-alkyl-7-hydroxypurines—butyraldehyde, for example, gave 7-hydroxyxanthines (**124**).[919] Corresponding 7-hydroxyxanthines are also reported from reactions with formaldehyde[920] and benzaldehyde.[921] Deoxygenation to 8-alkylpurines is carried out in boiling phosphate buffer.[920] While the 7-oxidopurines are the result of adduct formation, those derived from 4-amino-5-nitropyrimidines are the products of cyclodehydration and prototropic shifts, as exemplified by 7-hydroxy-1,3-dimethyl-8-phenylxanthine (**126**) which was obtained from the 6-benzylaminouracil (**125**) in ethanol (reflux, 20 h) containing anhydrous potassium carbonate.[922] The preparation of purine-7-oxides is dealt with in more detail later (see Chapter XI, Section 1.C). A new route to 8-arylxanthine derivatives is demonstrated using benzylidenetriphenylphosphorane (**127**), prepared from triphenylphosphine and a benzyl halide, with the aminonitrosouracil (**121**) in tetrahydrofuran (reflux, 0.5 h). In the presence of a base, a Wittig-type reaction gives rise to the nitrone derivative (**128**), which then cyclizes, losing water and forming 8-phenyltheophylline (**129**)[923] (Scheme 3). Evidence for participation of a Wittig-type reaction follows from the observation that no reaction takes place in the absence of base or triphenylphosphine.



Scheme 3

C. Cyclization Involving Reaction of a 5-Azo Group (*H*73)

The original concept of this approach was for a one-pot synthesis in which reduction of the azo group to amino was carried out in the cyclizing medium itself. In a fairly recent example, conversion of 4-benzylamino-1,6-dihydro-6-oxo-5-phenylazopyrimidine (**130**) to 9-benzylhypoxanthine (**131**) resulted from catalytic reduction (H_2, Pd-carbon) in formic acid followed by heating.[869] In a similar preparation, the 2,6-dimethoxy-5-phenylazopyrimidine (**132**) was readily reduced (zinc dust, formic acid), but on ring closure (reflux, 4 h) the product

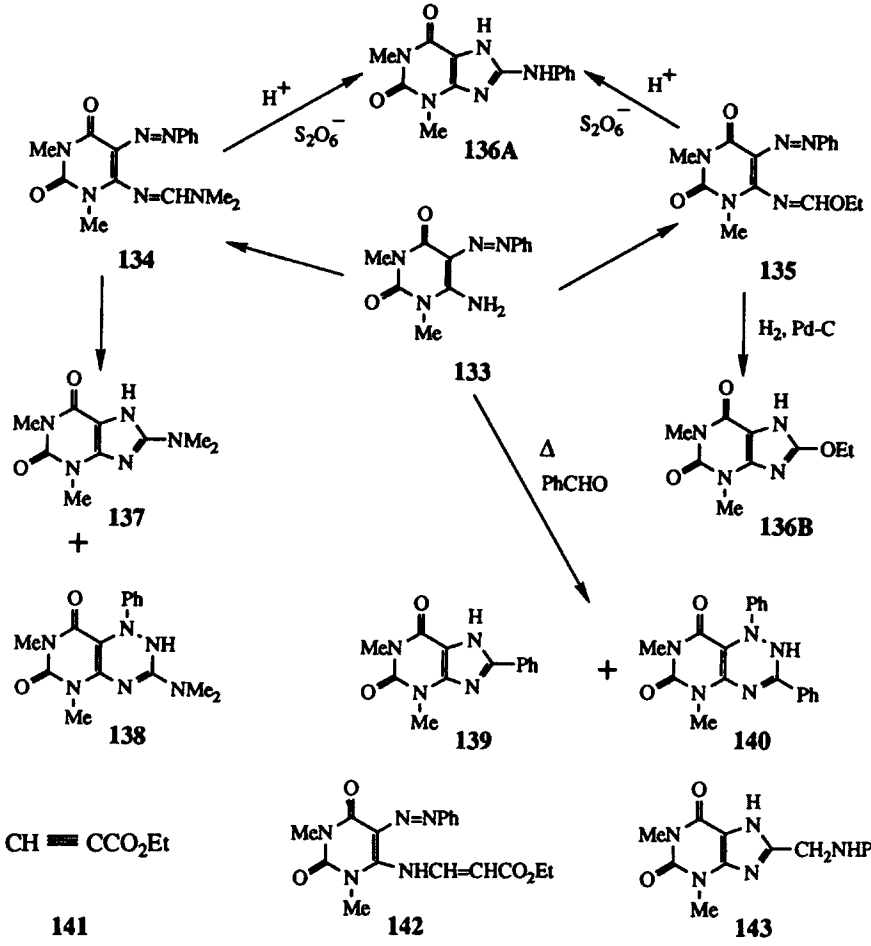


130 **131** **132**

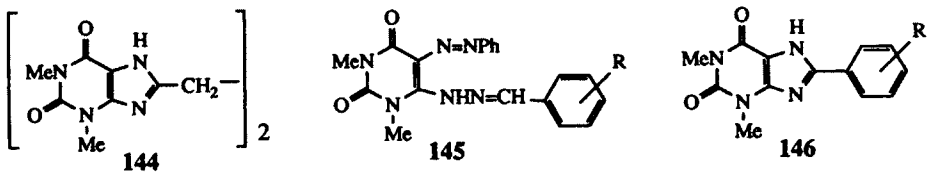
obtained, 9-ethylxanthine, resulted from an accompanying hydrolysis of the alkoxy groups.[924] Modification of the amino group at the 5-position of the pyrimidine precursor extends the scope of the reaction by enabling a selection of 8-substituted purines, notably 8-amino derivatives, to be synthesized. Reduction of the azo group in these cases is not always a prerequisite for ring closure to occur, since Michael-type adducts can offer an alternative pathway to purine formation.

The possible results of the reductive approach are shown by reaction of **133** with dimethylformamide diethylacetal, which forms the 4-dimethyl aminomethylideneaminopyrimidine (**134**). Reduction with sodium dithionite in formic acid (95°C, 5 min) gives the 8-anilinopurine (**136A**).[925] By replacing the diethylacetal with a mixture of dimethylformamide and triethyl orthoformate, the ethoxymethylideneamino analog (**135**) initially formed is cyclized to the same purine (**136A**) under identical conditions.[925,926] It is, however, pertinent to point out the importance of both reduction and ring-closure procedures in this reaction. Earlier workers using the same amide–orthoester mixture on a 4-amino-5-phenylazopyrimidine incorporated hydrogen sulphide as reducing agent. From this one-step synthesis the 8-unsubstituted purine resulted (*H*73). Further indications of the significance of the experimental environment are provided by the catalytic reduction of **135** (H_2, Pd-carbon) from which 8-ethoxytheophylline (**136B**) is obtained.[925] The mechanism suggested for the formation of the 8-anilinopurines assumes liberation of an arylamine on reduction of the azo group. The amine then displaces either the dimethylamino group in **134** or the ethoxy group in **135** prior to an intramolecular rearrangement and aromatization to the 8-aminopurine. Substituted anilino derivatives are also prepared by this route.[925,926]

Diverse reagents are used in the nonreductive approaches. Fusion of the intermediate (**134**) produces a mixture of the two main components—8-dimethylaminotheophylline (**137**) and the dihydro-6-azalumazine (**138**).[927] The isolation in small amounts of the 7-anilino homolog of **137** indicates that it is an intermediate in the reaction pathways, since on heating aniline is lost and **137** is obtained.[927] With benzaldehyde in place of the acetal an analogous reaction ensues, giving 8-phenyltheophylline (**139**) and the 5,7-diphenyldihydrolumazine (**140**). A noteworthy feature of this reaction is that 6-amino-1-methyl-5-phenylazouracil, like the 1,3-dimethylated homolog (**133**), is converted to the corresponding 8-phenylxanthine in the same way, but forms no associated dihydrolumazine. This is also the case with related non-*N*-methylated uracils.[927] The Michael reaction adduct (**142**) resulting from heating ethyl propiolate (**141**) with the uracil (**133**) is closed to 8-phenylaminomethyltheophylline (**143**) on treatment (reflux, 3 h) with a mixture (1:5) of hydrochloric and acetic acids.[928] For this

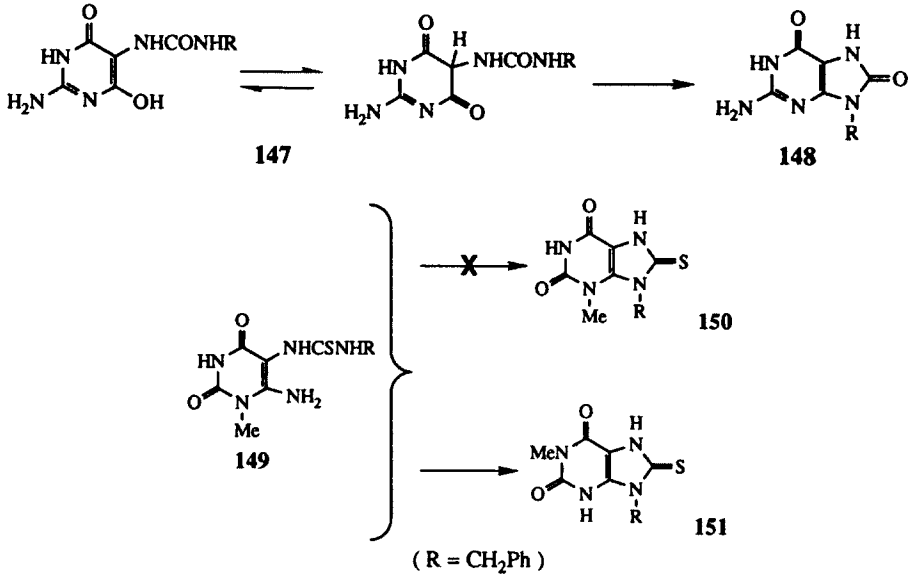


transformation, the complex mechanism proposed involves an intermediate seven-membered ring derivative.[928] On introduction of a methoxy or other electron-releasing group into the benzene ring of **142**, an alternative cyclization operates, giving 1,2-di(theophyllin-8-yl)ethane[928] (**144**). Starting from 6-hydrazino-1,3-dimethyl-5-phenylazouracil interaction with benzaldehyde yields the hydrazone (**145**), which on fusion gives a low yield (11%) of the 8-phenylpurine (**146**) to together with other products, including thiazolo[4,5-*d*]pyrimidine and pyrazolo[3,4-*d*]pyrimidine. In this type of reaction the possibility of radical mechanisms being involved has been raised.[929]



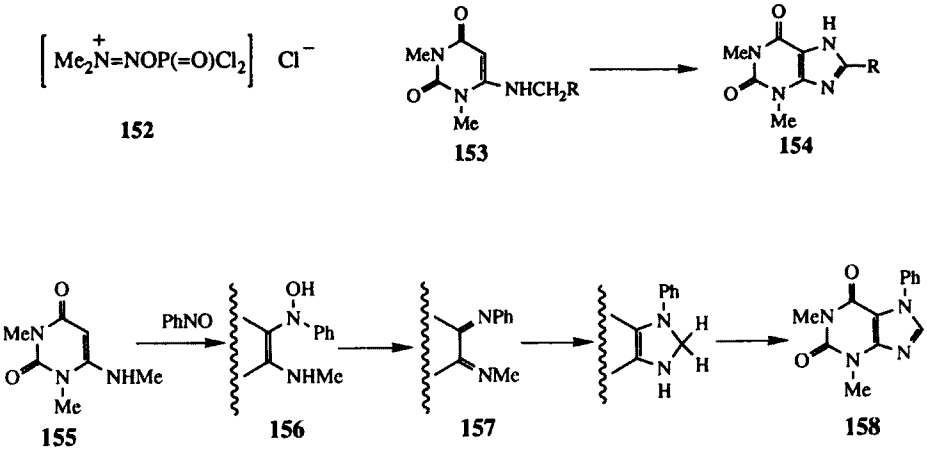
3. SYNTHESES FROM 5-AMINO-4-OXOPYRIMIDINES (*H*76)

Although this synthetic route is now only of historic interest, isolated examples occasionally surface. A series of 9-substituted derivatives of 2-amino-6,8-dioxopurine (**148**) results from cyclizing the appropriate 2-amino-1,6-dihydro-4-hydroxy-6-oxo-5-(N^1-alkylureido)pyrimidine (**147**) in hydrochloric or polyphosphoric acid.[932] An inadvertent application arises from the attempted synthesis of a 3-methyl-8-thioxoxanthine (**150**, R = CH_2Ph) from the 5-thioureidouracil (**149**). Through cyclization occurring with the oxo rather than the amino group, the 1-methyl isomer (**151**) is obtained after acid hydrolysis of the pyrimidine intermediate.[889]



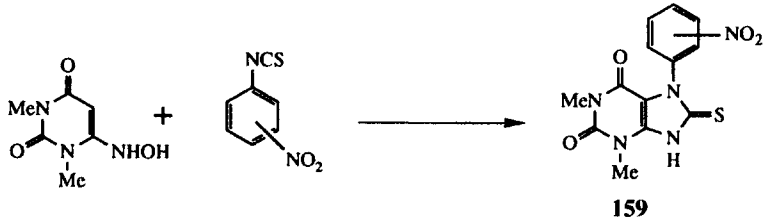
4. SYNTHESES FROM 4-AMINO-5-UNSUBSTITUTED-PYRIMIDINES (*H*78)

After nitrosation of 4-benzylamino-1,6-dihydro-6-oxopyrimidine with sodium nitrite in acidified formamide, followed by sodium dithionite reduction and thermal cyclization, 9-benzylhypoxanthine (26%)[869] results. A more elaborate procedure investigated by Yoneda, using *N*-nitrosodimethylamine as nitrosating reagent,[930] converted 6-benzylamino-1,3-dimethyluracil directly to 8-phenyltheophylline in good yield (84%). In this cyclodehydration, a chloropyrimidine scavenger is used for the liberated dimethylamine. Surprisingly, only a dimeric condensation product is obtained with the monomethylated uracil analog. Combining the nitrosoamine with phosphoryl chloride affords a Vilsmeier-type

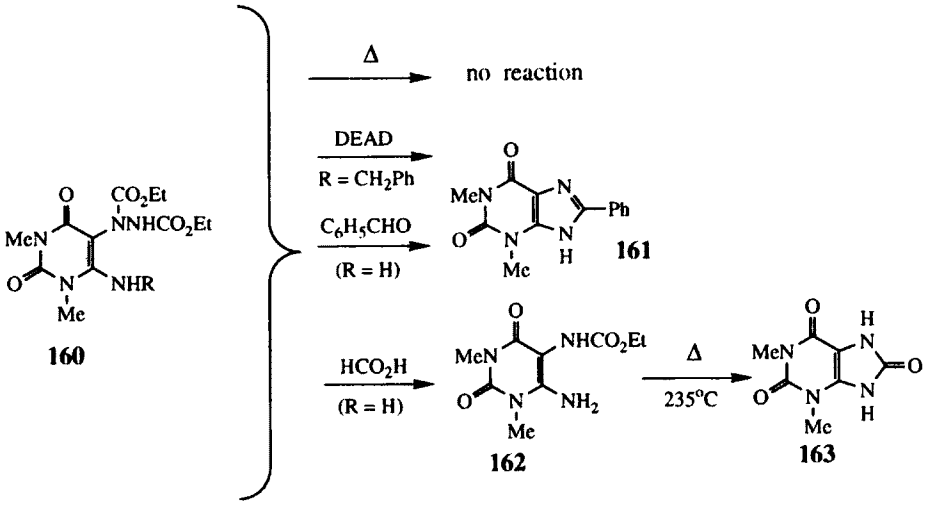


Scheme 4

reagent (**152**), which allows nitrosation and purine formation to take place under mild conditions (90°C, 5 min). This route converts the 6-benzylamino- (**153**, R = Ph), 6-*n*-propylamino- (**153**, R = Et), and 6-butylamino-1,3-dimethyluracil (**153**, R = *n*-Pr) to the respective 8-phenyl- (**154**, R = Ph), 8-ethyl- (**154**, R = Et), and 8-*n*-propyltheophyllines (**154**, R = *n*-Pr).[930] A novel route to 7-phenylpurines entails heating the pyrimidine with nitrosobenzene in acetic anhydride for a short time (reflux, 0.5 h). With 1,3-dimethyl-6-methylaminouracil (**155**), the initial adduct (**156**) presumed formed then loses the elements of water, resulting in the imine (**157**), which after ring closure is oxidized to the purine (**158**) (Scheme 4).[931] Theophylline derivatives so prepared include the 7-phenyl, 8-methyl-7-phenyl, and 7,8-diphenyl homologs,[931] together with a range of substituted-phenyl analogs. The use of nitrophenylisothiocyanates with a 6-hydroxylaminouracil in the presence of a triethylamine catalyst is also a new approach. The exothermic reaction is complete within a few minutes, giving excellent yields (~90%) of the 7-(nitrophenyl)-8-thioxopurine (**159**) noted in Scheme 5. Activation of the isothiocyanate by the nitro group seems necessary since phenylisothiocyanate itself does not undergo this reaction.[933] This site is favorably disposed toward formation of Michael-type adducts since it results from the electrophilic character of the 5-position in a uracil. Diethyl azodicarboxylate with a 6-alkylaminouracil in equimolar amounts gives a 6-alkylamino-5-(1,2-diethoxycarbonylhydrazino)

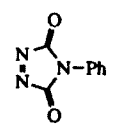


Scheme 5

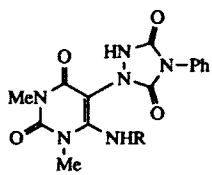


Scheme 6

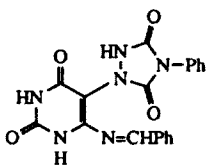
uracil (**160**).[934,935] On thermolysis the adduct (**160**, R = CH_2Ph) did not give any purine, but on heating with an excess of DEAD (180°C, 2 h), 8-phenyltheophylline results in 40% yield.[935] In formic acid (97%, reflux, 1 h) monodecarboxylation of **160** (R = H) occurred yielding the 5-ethoxycarbonylamino analog (**162**) converted on heating (235°C, < 1 h) to 1,3-dimethyluric acid (**163**).[934] The 6-aminouracil (**160**, R = H) is also cyclized to an 8-phenyltheophylline on prolonged heating (180°C, 4 h) with an aryl aldehyde (Scheme 6).[935] A related series of reactions occurs if the DEAD is replaced by 3,5-dioxo-4-phenyl-1,2,4-triazolines (**164**). The Michael adduct (**165**), formed at ambient temperature in dioxan, undergoes oxidative ring closure in heated nitrobenzene (reflux, 6 h), and two hydrogen atoms are abstracted in the process.[936,937] Using this treatment with **165** (R = CH_2Ph) yields 8-phenyltheophylline (**161**), and the same product results on heating 4-amino-5-triazolylpyrimidine (**165**, R = H) with benzaldehyde.[937] These two preparative results indicate that the pyrimidine anil (**166**) is an intermediate in the oxidative cyclization. Analogous 8-phenylhypoxanthines are similarly obtained.[936,937] Under more forcing conditions, using higher temperatures, an alternative nonoxidative cyclization occurs through nucleophilic attack by the 6-amino group on the thiazolylcarbonyl carbon, leading to a 9-alkyl-6,8-dioxopurine. With the 6-phenylethylaminopyrimidine (**167**), for example, the product is a 2-substituted-6,8-dioxo-9-phenylethylpurine (**168**).[936]



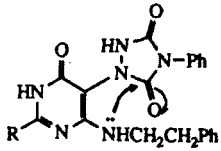
164



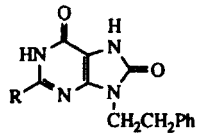
165



166



167



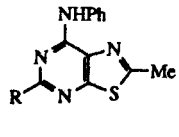
168

5. PURINES DERIVED FROM PYRIMIDINE-CONTAINING HETEROCYCLES (*H*81)

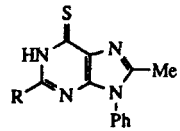
The majority of the reactions noted below have only limited practical application for the preparation of purines, but for completeness the most significant transformations are given.

A. From Thiazolo[5,4-*d*]pyrimidines (*H*81)

Conversion of the 7-anilino-2-methylthiazolo[5,4-*d*]pyrimidine (**169**, R = H) and the 5-methyl homolog (**169**, R = Me) to the isomeric purines (**170**, R = H and Me) is brought about by hydrolysis in 2*M* sodium hydroxide followed by heating (28°C, 15 min) of the ring-opened intermediate.[943] Similar conditions (20°C, 18 h) convert 5-amino-7-hydrazinothiazolo[5,4-*d*]pyrimidine to 2,9-diamino-1,6-dihydro-6-thioxopurine, a 3:1 yield of product to starting material being obtained. This reaction provides a facile route to 9-aminopurines.[1010]



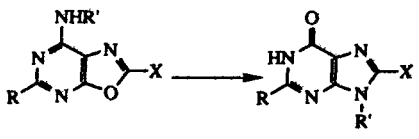
169



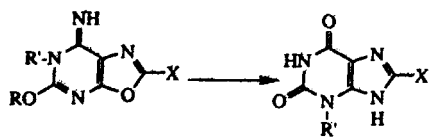
170

B. From Oxazolo[5,4-*d*]pyrimidines (*H*82)

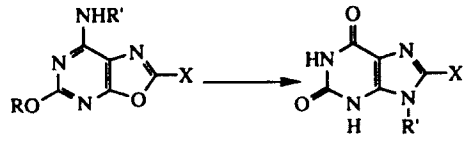
Rearrangement of 7-amino- (**171**) and related 6-alkyl-7-aminooxazolo[5,4-*d*]pyrimidines (**173**) either in aqueous alkali or hot formamide (200°C) gives 9-alkylhypoxanthines[1102] (**172**) and 3-alkylxanthines[953] (**174**), but carrying out a



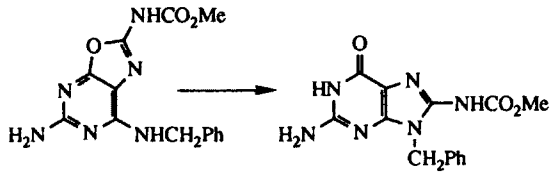
171 172



173 174

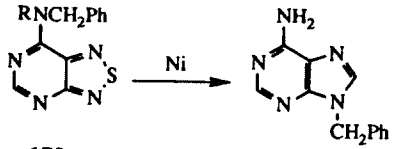


175 176



177 178

Dimroth rearrangement of the precursor (**173**) to **175** (R = OMe or OEt) opens up a modified route to 9-alkylxanthines (**176**).[953] Formation of 1-oxidohypoxanthine occurs with 7-aminooxazolo[5,4-*d*]pyrimidine-1-oxide in cold alkali on standing (2 days).[944] In addition to hypoxanthine and xanthine derivatives, this approach is also applicable to the preparation of guanines. Thermal rearrangement of the oxazolo[5,4-*d*]pyrimidine (**177**) in methanol or acetonitrile affords the 8-amino-9-benzylguanine derivative (**178**), possibly through the involvement of a transient carbodiimide intermediate.[1106]



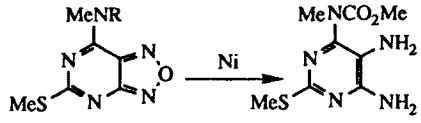
179 180

F. From Thiadiazolo[3,4-*d*]pyrimidines (*New*)

Derivatives of 7-benzylamino-[1,2,5,]-thiadiazolo[3,4-*d*]pyrimidine (**179**, R = H) with formic acetic anhydride give the formyl analogs (**179**, R = CHO) which, following reductive desulfurization with Raney nickel, undergo cyclization through the formyl moiety, yielding 9-benzyladenines (**180**).[945]

G. From Furazano[3,4-*d*]pyrimidines (*New*)

These derivatives are oxygen analogs of the thiadiazolo[3,4-*d*]pyrimidines (Section 5.F) and undergo the same kind of rearrangement to purines. For example, 7-methylamino-5-methylthiofurazano[3,4-*d*]pyrimidine (**181**, R = H) is readily acetylated to **181** (R = COMe), and on catalytic hydrogenation (Pd-carbon, $MeCO_2H$) or reduction with zinc dust in acetic acid (reflux, 2 h), gives 6-



181 **182**

amino-8,9-dimethyl-2-methylthiopurine on cyclization of the intermediate reduction product (**182**).[946] This route has practical value because syntheses of 2-, 8-, and 9-sustituted adenines are possible, as illustrated by its use in an unambiguous preparation of the antiviral agent acyclovir[947] (Chapter VIII, Section 9.A). It should be noted that the presence of a methylthio- or similar group is obligatory because 2-unsubstituted furazanopyrimidines are unstable. The removal or replacement of an unwanted alkylthio group from C-2 of the purine product is, however, usually a simple operation.

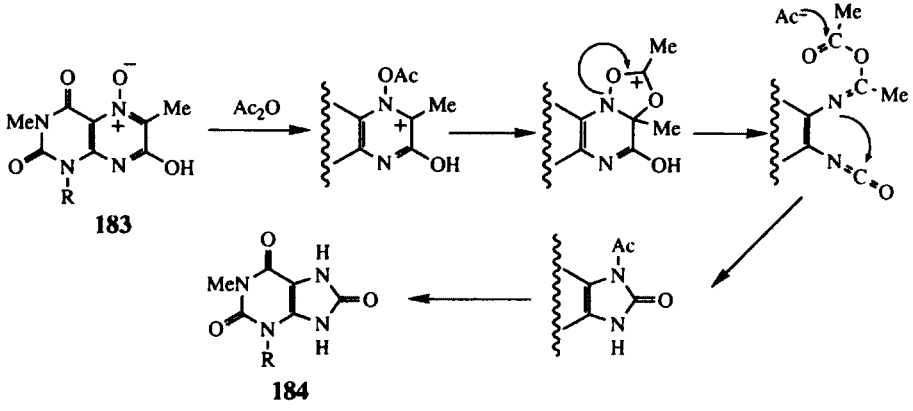
H. From Other Purines (*New*)

Numerous examples are documented of purine interconversion by means of the extended Traube synthesis in which opening of the imidazole ring occurs on heating with a cyclizing reagent and on subsequent reclosure a new purine having a different substituent at C-8 is obtained (Sections 1.B, 1.E, and 1.U).

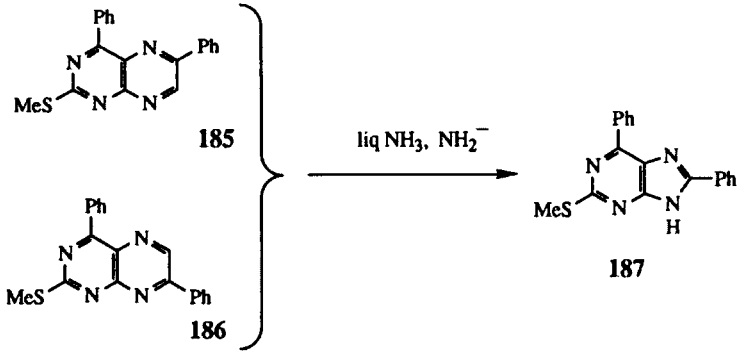
A new reaction of this type, which involves opening of the pyrimidine rather than the imidazole ring, is reported in the transformation of xanthine into hypoxanthine on treatment with *N*-benzylformamide. In this case, removal of oxygen at C-2 is preceded by formylation at N-3, subsequent fission of the pyrimidine ring, and benzylamination of the resulting imidazole. Reclosure to hypoxanthine occurs with a concomitant loss of carbon dioxide and benzylamine.[1234]

I. From Pteridines (*New*)

Contraction of the pyrazine ring in the pteridine-5-oxides (**183**, R = Me and Ph) occurs on heating with acetic anhydride (reflux, 0.25 h), from which the uric acid derivatives (**184**, R = Me and Ph)[948,949] are obtained. Viewed mechanistically, the initial reaction is acylation of the 5-oxo group, which participates in dioxazole ring formation, with subsequent fission of the C-6 to C-7 bond, followed by recyclization to the 7-acetylated uric acid analogs, from which the purines (**184**) are obtained on hydrolysis (Scheme 7). Support for the mechanistic pathway is obtained using a ^{14}C-7 labeled pteridine (**183**, R = Me) from which a uric acid derivative (**184**, R = Me) with the labeled atom at C-8 is produced.[949] More recently, an example of the same purine being formed from different pteridine isomers was reported. Both 2-methylthio-4,6-diphenyl- (**185**) and 2-methylthio-4,7-diphenyl-pteridine (**186**) in liquid ammonia containing potassium amide at low temperature (–33°C, 1 h) are transformed in low yield (20%) into 2-methylthio-6,8-diphenylpurine (**187**) with mainly starting material (>60%) being recov-



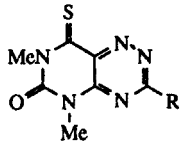
Scheme 7



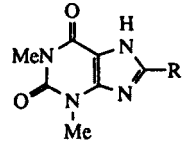
ered.[896] These ANRORC-type reactions are best explained through nucleophilic attack by the amide ion at C-6 in **185** and C-7 in **186**, followed by rearrangement to the purine, with elimination of the particular carbon under attack.[896] The author's claim of carrying out the first pteridine to purine transformation is somewhat doubtful in view of the results of the action of acetic anhydride on pteridine-*N*-oxides[949] noted above.

J. From Pyrimido[4,5-*e*]*asym*triazines (6-Azapteridines) and Pyrimido [5,4-*e*]*asym*triazines (7-Azapteridines) (*New*)

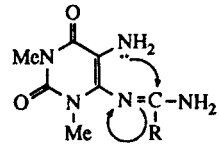
Both 6-aza- and 7-aza-pteridines will undergo contraction of the triazine ring with elimination of a nitrogen atom and formation of an imidazole ring. For example, on prolonged heating in formic acid (180°C, 18h) containing sodium dithionite, the 4-thioxo-6-azapteridine (**188**, R = pyridyl) is converted in acceptable yield (ca. 50%) to the 8-pyridylxanthine (**189**, R = pyridyl) with an accompanying replacement of the thioxo group by oxo.[950] Conversion of the 4-oxo analogue of **188** to the same purine (**189**) suggests that dethiation of **188** occurs prior to the rearrangement. A likely reaction pathway entails reductive fission of



188

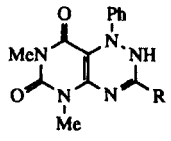


189

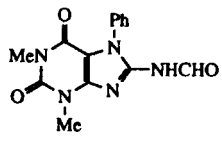


190

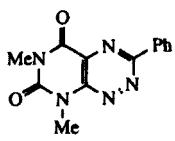
the bond between C-5 and C-6, with ring opening to a 6-amidino-5-aminouracil (**190**). The cyclic derivative, arising from the ensuing nucleophilic attack by the 5-amino group on the amidine carbon, then undergoes elimination of ammonia and transformation to the purine. The 5,6-dihydro-6-azapteridines with the same reagent mixture and conditions are likewise converted to 8-substituted purines. In this way the 5,7-diphenylazapteridine (**191**, R = Ph) affords 7,8-diphenyltheophylline, but similar treatment of the 7-dimethylamino analog (**191**, R = NMe_2) gives the 8-formamidopurine (**192**) resulting from formylation and cyclization with concomitant elimination of the dimethylamino group.[947]



191

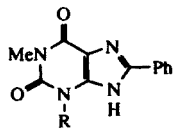


192

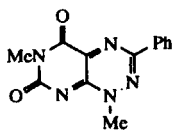


193

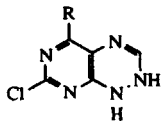
Conversion of isomeric 7-azapteridines and the 7,8-dihydro analogs to the respective purines can be made using the reagent described above, but more recent studies demonstrate that this type of interconversion is also possible under nonreductive conditions. Heating the 6-phenyl-7-azapteridine (**193**) in formamide (190°C, 6 h) produces 8-phenyltheophylline (**194**, R = Me); other examples are quoted.[951] A reaction pathway assumes formamide is the attacking nucleophile, leading to formation of a 6-amino-5-benzylideneaminouracil, which on oxidative cyclization is converted to the purine.[951] Supporting this assumption is the observation that under this treatment the 3,8-dimethyl-6-phenyl derivative (**195**) gives 1-methyl-8-phenylxanthine (**194**, R = H); the loss of the 8-methyl group shows that the two adjacent ring nitrogen atoms suffer displacement by the formamide nucleophile during ring opening. Comparable reactions of 7,8-dihydro-7-azapteridines occur in hot 90% formic acid (reflux, 10 h), both 2-chloro- (**196**, R = H) and 2-chloro-4-methyl-dihydroazapteridine (**196**, R = Me) are converted to the corresponding 9-formamido-2-oxopurines (**197**, R = H and Me)[952] with the not unexpected hydrolysis of the halogen taking place, presumably after the purine is formed.



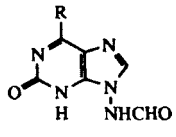
194



195



196



197

K. From Imidazo[4,5-*d*][1,3]thiazines (*New*)

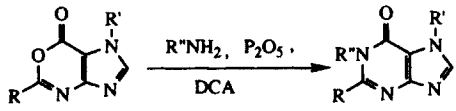
Under alkaline conditions rearrangement of 4,5-dihydro-7-imino-5-thioxoimidazo[4,5-*d*][1,3]thiazine (**198**) to 2,6-dithioxoxanthine (**199**) occurs.[954] In the same way the 5-anilino analog of **198** is converted to the corresponding 2-anilino-6-thioxopurine derivative.[955] A mechanism akin to that operating in the Dimroth rearrangement most likely participates, with opening of the thiazine ring resulting from an initial nucleophilic attack by hydroxide ion followed by rotation of the C-5 to C-6 bond before reclosure to the purine.



198 **199**

L. From Imidazo[4,5-*d*][1,3]oxazines (*New*)

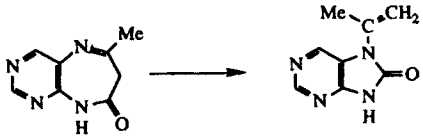
A number of hypoxanthine derivatives of the type (**201**) have resulted from short heating (240°C, 0.25 h) of 7-oxoimidazo[4,5-*d*][1,3]oxazines (**200**) with an amine hydrochloride in a mixture of *N*,*N*-dimethylcyclohexylamine (DCA) and phosphorus pentoxide[956] in which the overall effect is replacement of the ring oxygen by nitrogen. Provided suitable imidazo[4,5-*d*]oxazines are at hand (see Chapter III, Section 1.F), this reaction could serve as a useful route to 1-substituted-hypoxanthines, although the high temperature involved would preclude preparation of possible thermolabile derivatives.



200 **201**

M. From Pyrimido[4,5-*b*][1,4]diazepines (*New*)

Prolonged heating (reflux, 9 h) of 3,5-dihydro-2-methyl-4-oxopyrimido[4,5-*b*][1,4]diazepine (**202**) with sodium in 2-ethoxyethanol converts it into 7-isopropenyl-8-oxopurine (**203**). This reaction appears at this time of academic interest only, with no apparent practical application.[827]



202 **203**

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER III

Purines Syntheses from Imidazoles and Other Precursors (*H*91)

1. Using Imidazoles (*H*91) 61
   A. Syntheses from 4,5-Dicarbamoylimidazoles 62
   B. Syntheses from 4(5)-Amino-5(4)-carbamoylimidazoles (*H*93) 62
      b. Cyclization with Esters and orthoesters (*H*94) 62
      c. Cyclization with Amides (*H*95) 63
      g. Cyclization with Isothiocyanates (*H*97) 63
      h. Cyclization with Chlorocarbonic Esters (*H*98) 64
      i. Cyclization with Diethylcarbonate (*H*99) 64
      l. Cyclization with Acid Anhydrides (*New*) 64
      m. Cyclization with Cyanogen bromide and Related Derivatives (*New*) 65
      n. Cyclization with Halogenoalkanes and -alkenes (*New*) 66
   D. Syntheses from 4(5)-Amino-5(4)-amidinoimidazoles (*H*100) 67
   E. Syntheses from 4(5)-amino-5(4)-cyanoimidazoles (*H*102) 69
      a. Cyclization with Orthoesters (*H*102) 69
      b. Cyclization with Amide-like Reagents (*H*103) 70
      c. Cyclization with Isocyanates (*New*) 71
      d. Cyclization with Isothiocyanates (*New*) 72
      e. Cyclization with Carbon Disulfide (*New*) 73
   F. Syntheses from 4(5)-Amino-5(4)-alkoxycarbonylimidazoles (*H*104) 73
      a. Cyclization with Isocyanates (*H*104) 73
      b. Cyclization with Urea (*H*105) 74
      c. Cyclization with Isothiocyanates (*H*105) 74
      d. Cyclization with Amide-like Reagents (*New*) 75
      e. Cyclization with Orthoesters (*New*) 75
   G. Syntheses from 4-Amino-5-aroylimidazoles (*H*106) 76
   I. Syntheses from 4-Amino-5-(cyanoformimidoyl) imidazoles (*New*) 76
   J. Syntheses from 4(5)-Amino-5(4)-unsubstituted-imidazoles (*New*) 77
2. Using Acyclic Precursors (*H*107) 77
   A. The One-Step Synthesis (*H*107) 77
   B. Abiotic Synthesis (*H*110) 80
   C. Biological Synthesis (*H*112) 82

The introduction of new reagents and techniques, both for preparation of starting materials and for ring closing them to purines, has given imidazoles an increased value as precursors in purine syntheses. A significant feature of imidazoles having one of the ring nitrogens alkylated is that the resulting purine is

specifically 7- or 9-substituted. This property, combined with the generally mild conditions required for cyclizations to the purine, has been used advantageously to convert imidazole-*N*-ribosides to the corresponding purine nucleosides. Also notable is the application of *N*-oxido precursors for conversion to the hitherto unknown 9-hydroxypurines.

1. USING IMIDAZOLES (*H*91)

A. Syntheses from 4,5-Dicarbamoylimidazoles

Absence of recent data on this long-established route seems to indicate that replacement by the methods described in the sections following has been generally accepted and it is now largely of historical importance.

B. Syntheses from 4(5)-Amino-5(4)-carbamoylimidazoles (*H*93)

These derivatives, together with those of 4(5)-amino-5(4)-alkoxycarbonylimidazoles (Section F), continue to provide the majority of starting materials for oxopurine preparations from imidazoles. Derivatives of hypoxanthine, xanthine, guanine, and isoguanine are obtainable using a suitable cyclizing reagent. In view of the accessibility of ribosides of imidazoles, this route is widely encountered in oxopurine nucleoside syntheses. Use of this procedure is the basis for facile syntheses of the 1- and 9-*N*-oxides of hypoxanthines, xanthines, and guanines (Chapter XI, Sections 1.A and 1.D).

b. Cyclization with Esters and Orthoesters (H94)

Ethyl formate continues to be used widely to prepare 2-unsubstituted hypoxanthine derivatives. Examples derived from the appropriate 1-substituted-5-amino-4-carbamoylimidazole include the 9-benzyloxy-,[957] 9-benzyloxy-8-methyl-,[958] and a variety of 9-ribosyl-hypoxanthines,[959] all reactions being carried out under reflux conditions in the presence of a sodium alkoxide. By using 2-arylazoimidazoles, the corresponding 8-arylazohypoxanthines are obtained by this procedure.[960] Alternatively, with triethyl orthoformate cyclizations, 3-cyclohexylhypoxanthine is obtained from 4-amino-5-cyclohexylaminomidazole.[869] This approach has been extended to the preparation of a number of 3,9-dialkylhypoxanthines from 1-alkyl-5-alkylamino-4-carbamoylimidazoles using a triethyl orthoformate–acetic anhydride combination.[1996] Similar conditions give 1-aminohypoxanthine on ring closure of 4-aminoimidazole-5-carboxylic acid hydrazide.[961] In the latter case a prolonged period under reflux (26 h) with the orthoester and an acid caralyst gives the 1-ethoxymethylideneaminoimidazole

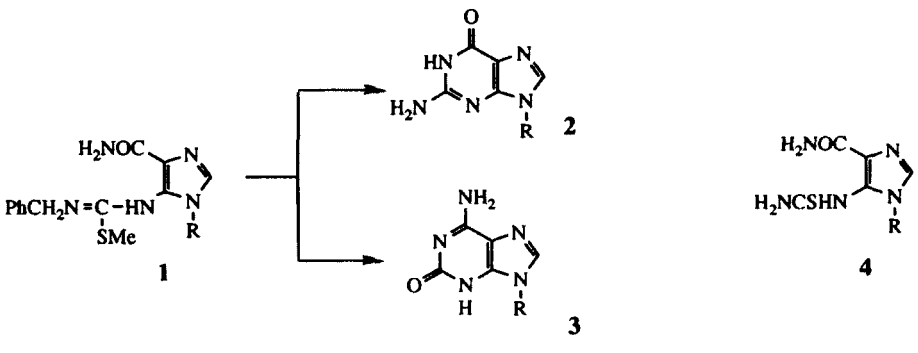
converted to 1-aminohypoxanthine on mild acid hydrolysis (20°C, 19 h)). With triethyl orthoacetate, the 2-methyl homolog results.[961] A series of 2,9-dialkyl derivatives of 1-aminohypoxanthine is reported from direct closure of the respective imidazoles (85°C, 2 h) with orthoesters in the presence of trifluoroacetic acid.[1007]

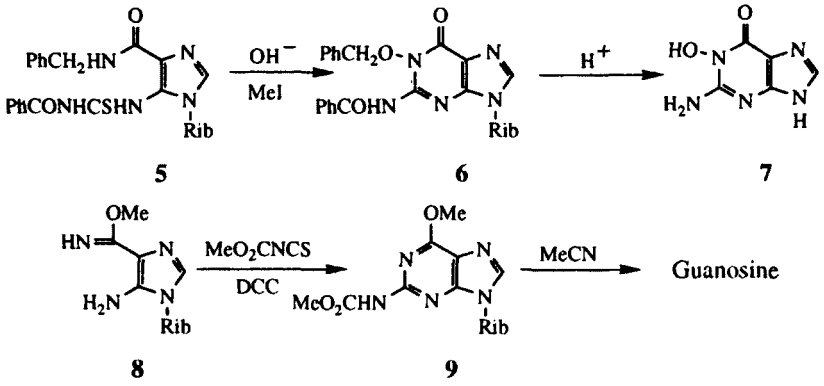
c. Cyclization with Amides (H95)

No significant application of these derivatives for imidazole cyclizations is apparent in the recent literature. One related reaction involving acetamidine acetate is used to prepare 9-substituted derivative of 2-methylpoxanthine.[962] An unusual route to 2-methoxymethylhypoxanthines is reported in which a cyclizing mixture of chloroacetamide and sodium methoxide[1021] is employed.

g. Cyclization with Isothiocyanates (H97)

Further studies of the original application of benzoylisothiocyanate to guanine synthesis (*H*98) show that treatment of the *S*-methylated intermediate (1, R = H or alkyl) with ammonia yields guanines (**2**); but when stronger bases are used, alkali-stable isoguanines (**3**) are formed.[963] This procedure has given 9-benzyloxy-,[957] 9-benzyloxy-8-methyl-,[958] 9-(3-benzyloxypropoxy)-[1209] and related 9-alkylguanines,[1209] and 3,9-dimethylguanines.[964] In a recent development, the 9-alkylguanines (2, R=Me, Et, *i*-Pr, and CH_2Ph), obtained in over 90% yields, together with guanosine (53%) and the 9-hydroxyalkoxymethyl derivatives acyclovir (85%) and guancyclovir (61%), are formed by a shorter route involving cyclization of the thioureidoimidazoles (**4**) in sodium hydroxide catalyzed by Ag(II), Cu(II), or Hg(II) ions.[1841] The synthesis of 1-hydroxyguanine (**7**) utilizes the riboside of 5-amino-4-(*N*-benzyloxycarbamoyl) imidazole first converted by benzoyl isothiocyanate to the 5-thioureido derivative (**5**). Treatment of the latter with methyl iodide in alkali gives the 2-benzamidopurine riboside (**6**) from which the aglycone (**7**) is liberated by acid hydrolysis.[968] A new route to the riboside





guanosine requires the carbamoyl group fixed in the enol configuration and closure to the purine with methoxycarbonyl isothiocyanate (MeO_2CNCS) and 1,3-dicyclohexylcarbodiimide (DCA) ar room temperature. Cyclodesulfurization of the methyl 5-aminoimidazole-4-carboximidate (**8**) gives the 6-methoxy 2-methoxycarbonylaminopurine (**9**), which is converted to guanosine by brief heating with iodotrimethylsilane in acetonitrile.[965]

h. Cyclization with Chlorocarbonic Esters (H98)

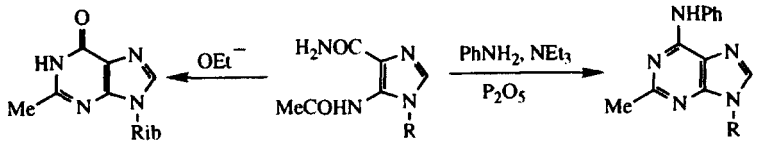
The preparation of a series of 3,9-dialkylxanthines under mild conditions is reported from 1-alkyl-5-alkylamino-4-carbamoylimidazoles. Ring closure of the intermediate 5-ethoxycarbonylaminoimidazole occurs at room temperature in dimethylformamide in the presence of sodium hydride.[969]

i. Cyclization with Diethylcarbonate (H99)

A low yield (20%) of 9-benzyloxy-8-methylxanthine is obtained when 5-amino-1-benzyloxy-4-carbamoylimidazole and diethylcarbonate [$(EtO)_2CO$] are heated (reflux, 6 h) with sodium in ethanol.[1958]

l. Cyclization with Acid Anhydrides (New)

Although anhydrides are one of the oldest group of cyclizing agents used in the Traube synthesis, they have appeared only recently on the scene in imidazole closures. This route provides a ready formation of 2-alkyl- or 2-aryl-6-oxopurines through a two-stage reaction involving acylation and subsequent ring closure, which may be either alkali or fusion induced. An example is acetylation of the 5-amino-4-carbamoylimidazole which gives the 5-acetamido analog (**10**, R=β-D ribosyl) and is converted to 2-methylinosine (**11**) in ethanolic sodium ethoxide

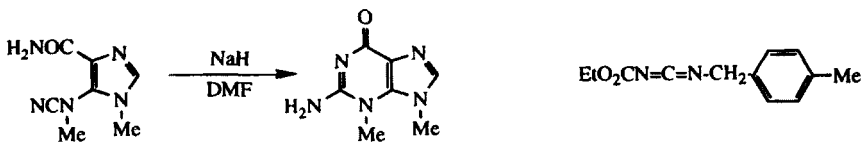


11 **10** **12**

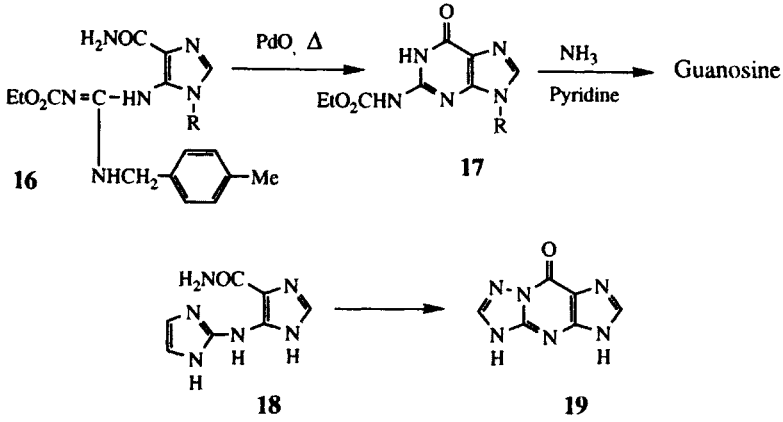
(90°C, 4 h).[966] Fusion, on the other hand, is employed to cyclize 1-benzyl-4-carbamoyl-5-trifluoroacetamidoimidazole, prepared from the aminoimidazole and trifluoroacetic anhydride, to 9-benzyl-2-trifluoromethylhypoxanthine.[967] Both 7- and 9-alkyl-2-phenylhypoxanthines result from closure of the appropriate *N*-alkyl-4(5)-benzamido-5(4)-carbamoylimidazole in ethanol containing potassium hydroxide or hydrazine.[962] Attempts to prepare 1-methylhypoxanthine derivatives using *N*-methylcarbamoylimidazoles were not successful.[962] An interesting development of the method is a direct conversion of the acetamidoimidazole (**10**, R = H) to 6-anilino-2-methylpurine (**12**, R = H) following treatment with aniline and triethylamine in conjuction with phosphorus pentoxide (180°C, 18 h).[1020] Past experience favors 2-methylhypoxanthine as an intermediate in view of the ready conversion of 6-oxo-to 6-aminopurines which occurs under these conditions (see Chapter 6, Section VI.G). With *N*-methylaniline the 6-*N*-methylanilinopurine is obtained[1020] likewise.

m. Cyclization with Cyanogen Bromide and Related Derivatives (New)

Treatment of 4-carbamoyl-1-methyl-5-methylaminoimidazole with cyanogen bromide gives the 5-cyanoamino derivative (**13**), which cyclizes to 3,9-dimethylguanine (**14**) in either ethanolic sodium ethoxide (reflux, 7 h) or dimethylformamide containing sodium hydride (room temperature). In general, the latter procedure is claimed to give the best results, with yields of 87% possible. Ring closure is very facile and takes place in boiling water (65%) or dilute sodium hydroxide at room temperature (48%). Homologs of **14** possessing ethyl and benzyl groups at N-1 and N-3 are also reported.[969] Cyclizations involving the highly electrophilic carbodiimides included here are illustrated by the formation of guanosine from 5-amino-4-carbamoylimidazole-1-riboside and 1-(ethoxycarbonyl)-3-(4-methylbenzyl)carbodiimide (**15**). The condensation product (**16**), after removal of the benzyl group (PdO, cyclohexene) is cyclized on prolonged heating (48 h) to the purine (**17**) and then guanosine is obtained on treatment with ammonia in pyridine[970] (45°C, 48 h). Of relevance to reactions involving guanidino



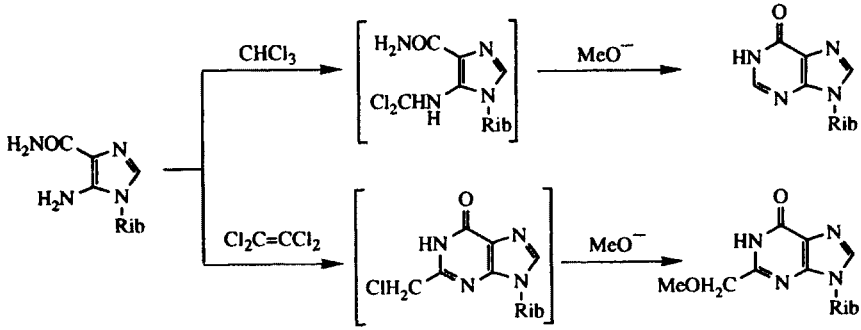
13 **14** **15**



groups is isolation of 5,9-dihydro-9-oxoimidazo[1,2-*a*]purine (**19**) when 4-carbamoyl-5-(2-imidazolyl)imidazole (**18**) is reacted wth sodium hydroxide (reflux, 1 h).[1008]

n. Cyclization with Halogenoalkanes and -alkenes (New)

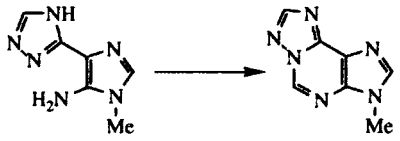
The recent synthesis of inosine from a closure with chloroform and sodium methoxide is notable because the ribosyl group is not protected. In this case, the actual cyclizing agent is the dichlorocarbene (:CCl_2), formed by methoxide ion attack on the chloroalkane, giving the 5-dichloromethylaminoimidazole intermediate from which the hypoxanthine forms spontaneously (Scheme 1).[1021] Improved yields are claimed on replacing the chloroform with either tetrachloro- or hexachloroethane in sodium hydroxide.[1021] An extension of this approach using chloroalkanes has been reported;[1030] the end product with 1,1,2-trichloroethene and sodium methoxide is 2-methoxymethylinosine, which results from methoxylation of the 2-chloromethylpurine precursor (Scheme 1). With tetrachloroethene, the 2-dichloromethyl homolog obtained undergoes partial dehalogenation to the 2-chloromethylpurine on catalytic hydrogenation.[1030]



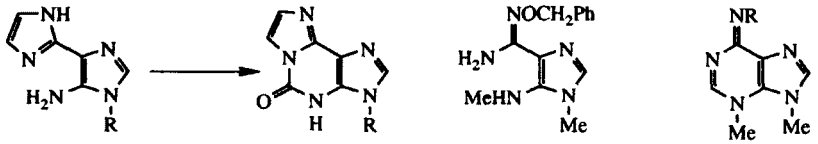
Scheme 1

D. Syntheses from 4(5)-Amino-5(4)-amidinoimidazoles (*H*100)

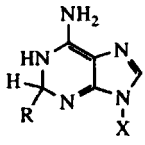
Amidinoimidazoles, which are fairly readily obtained by degradation of the pyrimidine moiety of adenines, are useful precursors for the preparation of other types of purines. Both acid and alkaline conditions can be used for cyclizations; the reagents employed include orthoesters, amides, acid anhydrides, and ketones. Triethyl orthoformate with derivatives of 4-amino-5-amidinoimidazole is a route to 9-cyclohexyl-,[971] 2-ethyl-9-methyl-,[972] and 2,9-dimethyl-adenine.[972] Among the more exotic examples is ring closure of the 1,2,4-triazolylimidazole (**20**), derived from alkaline degradation of 1-amino-9-methyladenine, to 7-methyl-*sym*-triazolo [3,2-*i*] purine[973,1009](**21**). Somewhat similar in type is the reaction of 5-amino-4-(imidazol-1-yl)imidazole nucleotide (**22**) with *N, N'*-carbonyldiimidazole, which gives the 2-oxoethenopurine (**23**, R = cyclic ribosylphosphate).[1881] Alternatively, using cyanogen bromide, carbon disulfide, and triethyl orthoacetate as ring-closing agents yields 2-amino-, 2-thioxo-, and 2-methylpurine analogs, respectively.[1881] Ring closure of *N*-benzyloxyamidines of the type (**24**) affords 6-alkoxyamino-3,9-dialkylpurines (**25**, R = OCH_2Ph) initially; these can then undergo loss of the alkoxy group, by catalytic hydrogenation or heating in pyridine, giving 3,9-dialkyladenines such as (**25**, R = H).[974,975] Other cyclizing agents reported are trifluoroacetamide, for forming 2-trifluoromethyladenines,[972] while 2-thioxo-9-cyclopentyladenine results from reacting carbon disulfide with 4-amidino-5-amino-1-cyclopentylimidazole in alkaline dimethylformamide at ambient temperature.[976] A further route to 2-thioxoadenines involves application of *N,N'*-thiocarbonyldiimidazole in dimethyl sulfoxide as a new ring-closure reagent,[972] the corresponding *N,N'*-carbonyldiimidazole, using the same approach, forms the 2-oxo analogs (isoguanines).[972] Under oxidative conditions both alkyl and aryl aldehydes condense, giving the 2-alkyl- or -aryladenines (**27**, R = *n*-Bu, isoBu, Ph; X = ribofuranosylphosphate). Oxidation of the unisolated dihydro intermediate (**26**) is effected either atmospherically, with oxygen and palladium in methanol, or by chloranil in dimethylformamide.[972] It should be noted that the aldehyde route enables adenines to be formed that have larger 2-alkyl



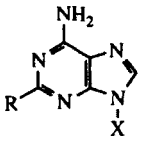
20 **21**



22 **23** **24** **25**



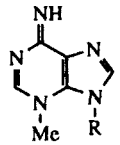
26



27

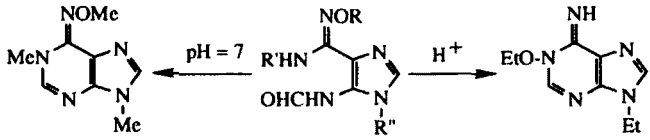


28



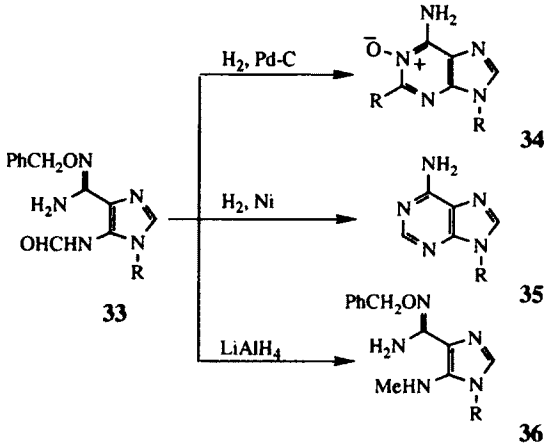
29

groups than are possible using trialkyl orthoesters as cyclizing agents, the latter usually restricted to forming 2-methyl- or 2-ethyladenines.[972] In many cases, fission of the pyrimidine ring of adenine derivatives gives amidinoimidazoles containing a formylated amino group; such compounds will undergo reclosure to purines under either acid or alkaline conditions. The formamidinoimidazoles (**28**, R = Me, Et, CH_2Ph) in ethanolic triethylamine (reflux, 0.5 h) or methanolic hydrochloric acid (reflux, 8 h) afford the respective 9-alkyl-3-methyladenines[975] (**29**). The riboside analog (**28**, R=ribosyl) is converted to 3-methyladenosine under alkaline conditions, whereas in dilute acid (20°C, 1 h) 3-methyladenine results thorugh concomitant loss of the ribose moiety.*[977] By using *N*-alkoxy modified amidino groups, alternative cyclization modes operate. With the amidoxime derivative (**30**, R = R′ = R″ = Me), conversion to 6-methoxyamino-1,9-dimethylpurine (**31**) occurs in hot water.[978] Other similar closures to 6-alkoxyaminopurines under neutral conditions are recorded.[979,980] By contrast, in acid media the amidoxime nitrogen is involved in nucleophilic attack on the carbon of the formamido group, forming a 1-alkoxyadenine. A good illustration is 1-ethoxy-9-ethyl-6-iminopurine (**32**), which results from dilute prechloric acid treatment of the imidazole (**30**, R = R′ = R″ = Et) at room temperature.[981] Related examples are available.[976,982] Under reductive influences the amidoximinoimidazoles ring close either to 1-oxidopurines or the deoxygenated analog. Catalytic hydrogenation with palladium–carbon in ethanol of the imidazole (**33**, R = cyclopentyl) affords 1-oxido-9-cyclopentyladenine (**34**, R = cyclopentyl).[976] The riboside of **33** (R = ribosyl) is likewise transformed into 1-oxidoadenosine (**34**, R = ribosyl).[983] Changing the catalyst to Raney nickel causes loss of benzyloxy group and subsequent cyclization to the 9-alkyladenine (**35**) derivative.[976] Studies indicate that with either catalyst cyclization of the imidazole derivative occurs spontaneously with hydrogenolysis of the benzyloxy group.[976,983] It is worth noting that reduction of 4(5)-formamidoimidazoles (**33**) to the 4(5)-methylamino homologs (**36**), by means of lithium aluminium hydride in tetrahydrofuran,[974,975]



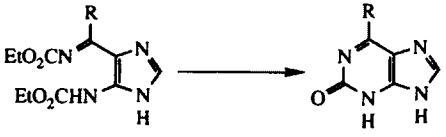
31 **30** **32**

* The presence of a methyl group at N-3 in adenosine is reported to produce a thousandfold increase in ease of hydrolytic cleavage of the glycosidic bond.



provides routes to 9-alkyl- and 3-methyl-9-alkyl-adenines by employing a common precursor.

The ring-opened products from treatment of 9-unsubstituted adenines*[984] and 6-alkylamino analogs[984, 985] with diethyl pyrocarbonate (ethoxyformic anhydride) are the 5(4)-carbethoxyamino-4(5)-*N*-carbethoxyamidinoimidazoles (**37**, R = NH_2, NHEt, NEt_2), from which the corresponding isoguanines (**38**, R = NH_2, NHEt, NEt_2) are obtained on heating (120°C, 13 h) in aqueous ammonia.



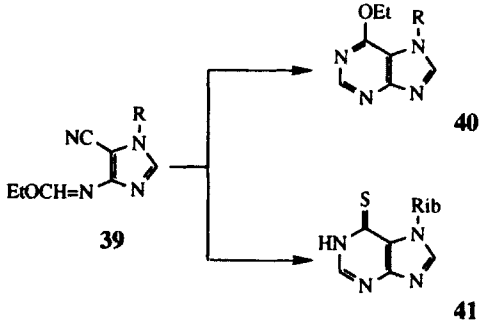
E. Syntheses from 4(5)-Amino-5(4)-cyanoimidazoles (*H*102)

Since the parent volume appeared, new reagents for cyclization have been introduced which extend the original range of purine preparations from 6-amino derivatives to include those with oxo or thioxo group at this position.

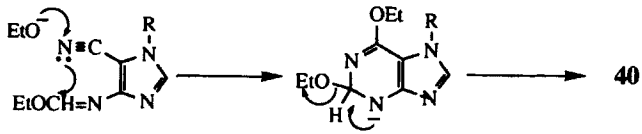
a. Cyclization with Orthoesters (H102)

Either alone or combined with acetic anhydride, triethyl orthoformate is still widely favored for the preparation of adenines lacking a C-2 substituent. Illustrating this are 9-benzyloxy-,[990] 8-methyl-9-benzyloxy-,[990] and various [973] 7-

* In the case of 9-substituted adenines, use of this reagent leads to pyrimidine derivative through opening of the imidazole ring.



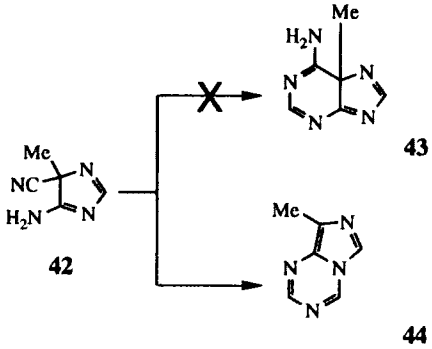
and 9-ribosyladenines.[974] The ethanolic ammonia usually used for closure of an alkoxymethylidenoaminoimidazole intermediate is replaced by liquid ammonia in forming 7-benzyl-2-*n*-butyladenine from 4-amino-1-benzyl-5-cyanoimidazole and trimethyl orthopentanoate.[849] Diethoxymethyl acetate is employed with the aminoimidazole to yield the intermediate **39**, which is converted to the 7-riboside of 6-ethoxypurine (**40**, R = ribosyl) on heating with the stoichiometric amount of sodium ethoxide. With an excess of alkoxide the product is the aglycone 6-ethoxypurine (**40**, R = H). Formation of 6-thioxopurine-7-riboside (**41**) from **39** in hot hydrogen sulfide saturated pyridine further illustrates the versatility of this type of cyclization.[989] The same 6-ethoxypurine is notable in affording the first example of an alkoxypurine derived from ring closure of an *o*-aminonitrile derivative. A mechanism advanced invokes ethoxide addition at the nitrile carbon with subsequent ring closure and aromatization of the purine[989] (Scheme 2). A novel route to adenosine-1-oxide is provided by the action of ethanolic hydroxylamine on the riboside of 4-cyano-5-ethoxymethylideneaminoimidazole.[1029] The 2-methyl- and 2-ethyl- adenosine-1-oxides are similarly derived from the appropriate 5-ethoxyalkylideneaminoimidazoles[1029] (see Chapter XI, Section 1.A).



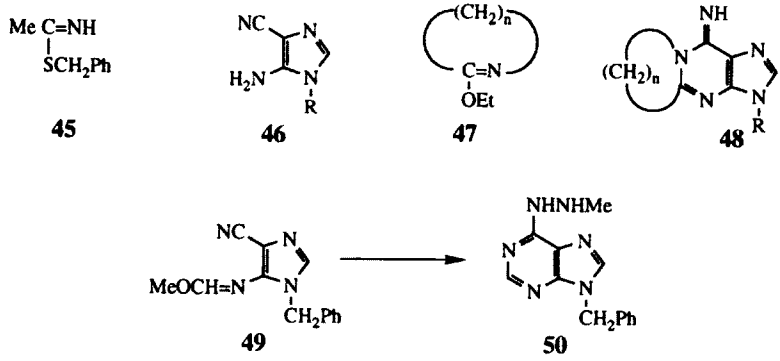
Scheme 2

b. Cyclization with Amide-like Reagents (H103)

Conventional one-step closures of 4-amino-5-cyano-1,2-dimethylimidazole with formamide and urea give the 7,8-dimethyl derivatives of adenine and isoguanine respectively.[991] An attempted preparation of the highly strained 5-methyladenine (**43**) with formamidine and the 4-methyl-4*H*-imidazole (**42**) failed, the product being 4-amino-8-methylimidazo[1, 5-*a*] triazine (**44**).[992] Both amides and thioamides, reacting as their ether derivatives, find application in syntheses. For



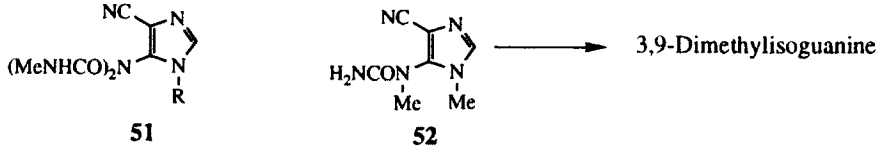
example, the *S*-benzyl ether of thioacetamide (**45**), with the imidazole (**46**, R = H) in pyridine (reflux, 6 h), produces 2-methyladenine,[993] while cyclic imidates of the type (**47**, n = 3 to 11) give a range of tricyclic adenine derivatives (**48**, R = ribosyl) from **46** (R = ribosyl).[994] Interaction of the methoxymethylideno derivative (**49**) and an excess of methylhydrazine in toluene (reflux, 16 h) with a trifluoroacetic acid catalyst affords 9-benzyl-6-(β-methylhydrazino) purine*[1879](**50**).



c. Cyclization with Isocyanates (New)

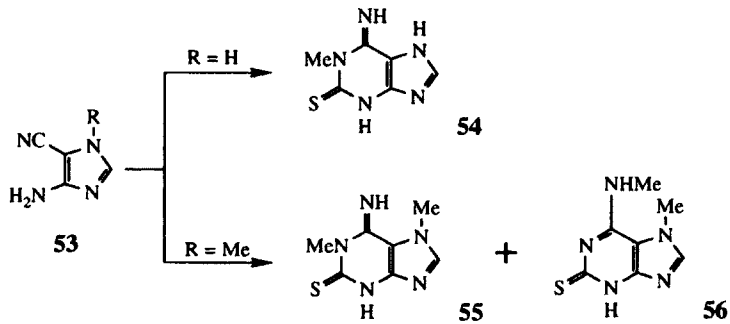
A variety of 1-alkyl and 1-arylisoguanosine nucleosides result directly from prolonged heating of the imidazole with alkyl or aryl isocyanates.[995] By carrying out the reaction in dimethylformamide, the intermediate 5-*N,N*-dicarbamoylimidazole, for example (**51**, R = ribosyl), is isolatable, requiring methanolic ammonia treatment to form 1-methylisoguanosine.[996] Comparatively milder conditions (sodium hydroxide, 20°C) convert the ureido derivative (**52**) to 3,9-dimethylisoguanine.[997]

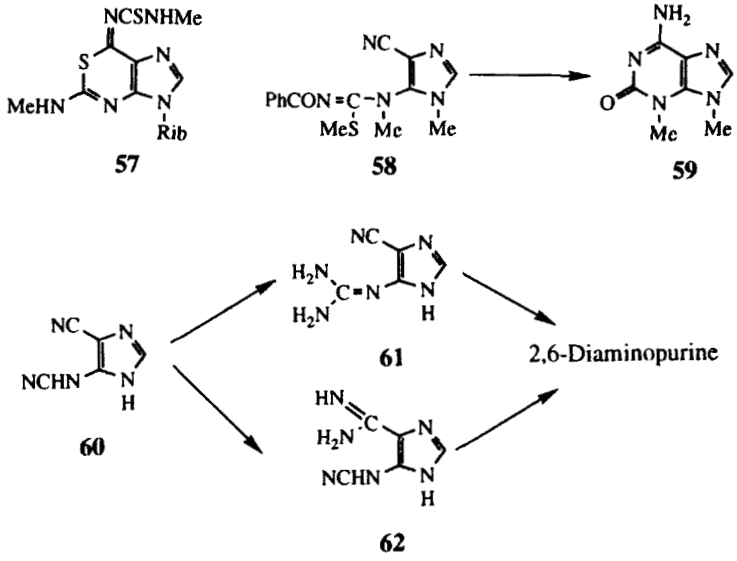
* This synthesis is notable for forming a 6-β-methylhydrazinopurine, whereas the alternative route using nucleophilic displacement of a 6-halogeno- or 6-methylsulfonylpurine with the same hydrazine would give the 6-(α-methylhydrazino) isomer (Chapter VIII, Section 7.A.a).



d. Cyclization with Isothiocyanates (New)

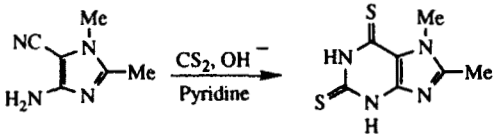
The usual products arising from these reagents are 2-thioadenines (thioisoguanines), as exemplified by formation of the 1-methyl analog (**54**) from the imidazole (**53**, R = H) and methyl isothiocyanate[998] in pyridine (reflux, 1h). Under similar conditions, the 7-methyl homolog (**53**, R = Me) gives both the expected 1,7-dimethylated purine (**55**) and also the isomeric 7-methyl-6-methylaminopurine (**56**) resulting from a Dimroth rearrangement of **55**.[998] Isothiocyanates with alkyl groups larger than methyl give only the 1-alkyl analog of **55**; steric considerations appear to inhibit any subsequent rearrangement. An unexpected product, indicated by NMR to be the imidazo[5,4-*d*] [1,3]thiazine (**57**) rather than 2-thioisoguanosine, is obtained with the imidazole (**46**, R = ribosyl) and methyl isothiocyanate.[995] Reaction of benzoyl isothiocyanate with 4-cyano-1-methylaminoimidazole, followed by *S*-methylation, gives the thioester (**58**), which undergoes hydrolysis and ring closure to 3,9-dimethylisoguanine (**59**) in boiling ammonia solution.[964] Replacement of the amino group by a cyanoamino group in the imidazole enables an amino group to be located at C-2 of the purine. This approach with 4(5)-cyano-5(4)-cyanoaminoimidazole (**60**) gives 2,6-diaminopurine on treatment with aminonia. Ethanolic ammonia (100°C, 5 h) or potassium amide in liquid ammonia are about equally effective, but different reaction pathways are followed. In ethanolic solution, adduct formation with the cyanoamino gorup yields the intermediate (**61**) whereas the liquid ammonia reaction generates an amino derivative (**62**) through involvement of ionic intermediates.[999] Inspection of **61** and **62** shows that addition of the NH_2 takes place at different cyano moieties.





e. Cyclization with Carbon Disulfide (New)

Standard reaction conditions used with carbon disulfide in pyridine, in the presence of potassium hydroxide, will convert 4-amino-5-cyano-1,2-dimethylimidazole (**63**) to the 2,6-dithioxopurine (**64**).[991] The 9-riboside of the latter is derived likewise from the imidazole riboside.[1352]

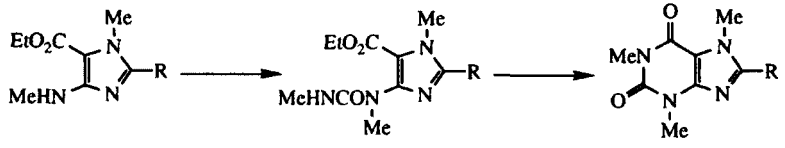


F. Synthesis from 4(5)-Amino-5(4)-alkoxycarbonylimidazoles (*H*104)

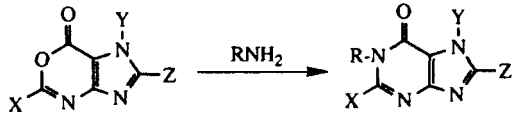
The reagements mainly employed are those already well established in practice, but these are now being supplemented by amides, amidines, and amines which extend the syntheses to include 6-oxopurines substituted at N-1.

a. Cyclization with Isocyanates (H104)

Methyl isocyanate in pyridine with the 4-methylaminoimidazole (**65**, R = Me) gives the ureido derivative (**66**, R = Me), which alkali treatment converts to



65 66 67



68 69

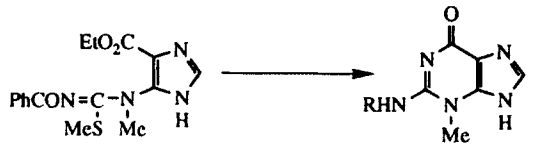
1,3,7,8-tetramethylxanthine (**67**, R = Me).[991] The methyl ester analog of **66** (R = H) is cyclized to caffeine (**67**, R = H) on heating alone.[1000] Over 20 derivatives of hypoxanthine, with various substituents at the 1-, 2-, 7-, and 8-positions, are derived from 4-acylamino- or 4-aroylamino-5-ethoxycarbonylimidazoles on reaction with an alkyl or arylamine in *N,N*-dimethylcyclohexylamine containing phosphorus pentoxide (150°C, 0.5–2.0 h).[956] The particular amine used determines the alkyl or aryl group at N-1 of the purine. By replacing the amine with ammonium chloride, hypoxanthines unsubstituted at N-1, can result, although the possibility of an alternative ring closure to an imidazo[4,5-*d*][1,3]oxazine (**68**) exists with some steric situations. Conversion of the latter to hypoxanthines (**69**) occurs readily on heating with the amine reagent. This result points toward these derivatives being likely intermediates in the cyclization reaction pathway.[956] In the preparation of 8-methylthiohypoxanthines by this procedure, some demethylation to 8-thioxo analogs is reported.[956]

b. Cyclization with Urea (H105)

This route is employed to afford 7,8-dimethylxanthine directly, in 50% yield, from fusion (190°C, 1.5 h) with 4-amino-5-ethoxycarbonyl-1,2-dimethylimidazole.[991]

c. Cyclization with Isothiocyanates (H105)

Heating with methyl isothiocyanate in pyridine converts 4-amino-5-ethoxycarbonyl-1,2-dimethylimidazole to the 4-*N*-methylthioureido analog, which requires alkali treatment to form 1-ethyl-1,2,3,6-tetrahydro-7,8-dimethyl-6-oxo-2-thioxopurine[991] in 98% yield. Methylation of the product from reaction between 4-ethoxycarbonyl-5-methylaminoimidazole and benzoyl isothiocyanate gives the *S*-methylthioureido derivative (**70**), which is transformed in weak ethanolic ammonia (2%) under extremely mild conditions (4°C, 7 days) into the 3-methylguanine (**71**, R = PhCO), from which **71** (R = H) results through debenzoylation



70 71

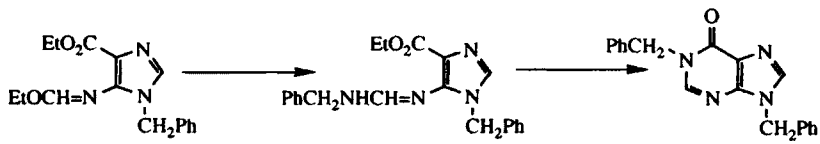
using dilute acid hydrolysis.[1001] Utilization of this procedure now enables isothiocyanate ring closures to extend to the formation of 2-aminopurines.

d. Cyclization with Amide-like Reagents (New)

Formamide closure of the 1,2-dimethylimidazole (190°C, 3 h) gives a satisfactory yield (57%) of 7,8-dimethylhypoxanthine.[991] Formation of 3-methylhypoxanthine results from prolonged heating of 4-ethoxycarbonyl-5-methylaminoimidazole with formamidine acetate in an ethanol–butanol mixture.[1001] Other alkyl- or arylhypoxanthines similarly derived are the 7-phenyl homolog from closure of 4-amino-5-ethoxycarbonyl-1-phenylimidazole with a formamide–acetic anhydride mixture[1877] as well as 2,7-diphenyl- and 2-methyl-7-phenylhypoxanthine and related derivatives from fusion of the same imidazole with thiobenzamide and thioacetamide, respectively, and a formic acid catalyst.[2033] With cyanamide in place of the thioamides, under closed-vessel conditions (70°C, 72 h) in the presence of acetic anhydride, 7-phenylguanine is the only product.[2033] An attempted synthesis of 3-methylguanine from 4-ethoxycarbonyl-5-methylaminoimidazole using cyanamide or guanidine for cyclization was unsuccessful.[1001] It should be noted, however, that formamidine acetate in acetonitrile is successfully employed to form adenosine in this way.[1002]

e. Cyclization with Orthoesters (New)

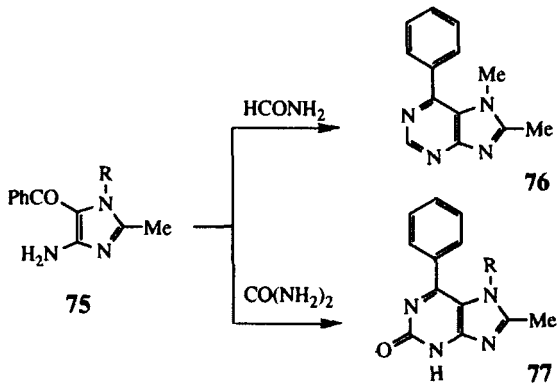
Although othoesters have had wide application to ring closures in Traube syntheses and also with 4(5)-amino-5(4)-carbamoylimidazoles, their use with other types of imidazoles is virtually nonexistent. The potential of such closures is shown, however, by the product (**72**), resulting from the reaction of 5-amino-1-benzyl-4-ethoxycarbonylimidazole with triethyl orthoformate, then being converted to **73** with benzylamine in xylene (reflux, 7 h) and finally to 1,9-dibenzylhypoxanthine (**74**) in warm ethanol.[1003] This provides a useful new approach to unambiguous syntheses of 1-substituted hypoxanthine derivatives.



72 73 74

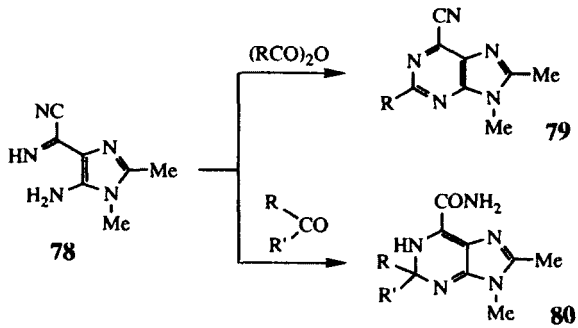
G. Syntheses from 4-Amino-5-aroylimidazoles (*H*106)

Closure of *C*- and *N*-alkyl derivatives of 4-amino-5-benzoylimidazole with-some of the usual cyclizing agents gives the appropriate 6-phenylpurines. The imidazole (**75**, R = Me) with formamide affords 7,8-dimethyl-6-phenylpurine (**76**), while fusion with urea converts it to the 2-oxopurine (**77**, R = Me). The compound **77** is similarly prepared (R = H) from the imidazole (**75**, R = H).[991] Urethane in the presence of zinc chloride (190°C, 2 h) is occasionally encountered in 2-oxo-6-phenylpurine preparations.[991]



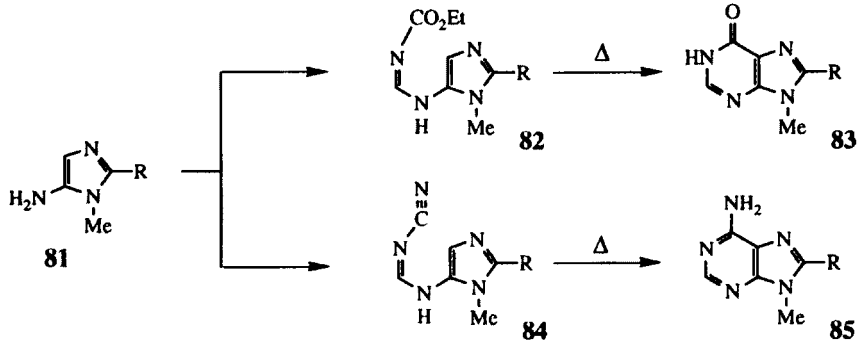
I. Syntheses from 4-Amino-5-(cyanoformimidoyl)imidazoles (*New*)

The imidazole (**78**) formed by condensing diaminomalononitrile with *N*-methylacetonitrilium trifluoromethane sulfonate reacts exothermically[1004] or on warming[1878] (70°C) with an excess of acetic anhydride, giving good yields of the 2-alkyl-6-cyanopurines (**79**, R=Me, Et, CF_3). Hydrolyses of the 6-cyano- to 6-carbamoylpurines is effected with aqueous sodium carbonate. Aldehydes and ketones with **78** cause cyclization to 1,2-dihydropurines (**80**), during which concomitant conversion of the cyano group to a carbamoyl group occurs (see Chapter XII, Section 1.A.d).



J. Syntheses from 4(5)-Amino-5(4)-unsubstituted-imidazoles (*New*)

This approach provides a novel route to adenine and hypoxanthine derivatives by use of high-temperature intramolecular cyclizations of imidazole intermediates. With ethoxymethylideneurethane (EtOCH:NCO_2Et), the 5-aminoimidazoles (**81**, R = H, Me and *i*-Pr) are first converted to the intermediates (**82**), which on fusion give generous yields (> 90%) of the 8,9-dialkylhypoxanthines (**83**, R = H, Me, and *i*-Pr). An alternative closure with ethyl *N*-cyanoformimidate (EtOCH:NCN) gives the intermediate (**84**, R = H) closing at 190°C to 9-methyladenine (**85**, R = H) in low yield.[1880]



2. USING ACYCLIC PRECURSORS (*H*107)

The main efforts in this topic have been directed either to developments and improvements to existing procedures or to examination of the mechanistic pathways involved. Only a limited amount of work of practical significance has been reported on these prebiotic-type syntheses.

A. The One-Step Synthesis (*H*107)

Purine, in appreciable yield, results from heating formamide in air for a prolonged period (optimum 28 h) at around 170°C.[1011] Although this refutes an earlier observation that pressure conditions are obligatory (*H*108), the temperature range employed is critical. A detailed mechanism proposes that the thermal breakdown products of formamide, namely water, hydrogen cyanide, ammonia, and formic acid (Eq. 1) are the building blocks which interact with formylformamidine (**86**), the latter arising from autocondensation of formamide[1012] (Eq. 2).

$$HCONH_2 \rightleftharpoons HCN + H_2O \qquad (1)$$

$$HCONH_2 + H_2O \rightleftharpoons HCO_2H + NH_3 \rightleftharpoons HCO_2^- \; NH_4^+$$

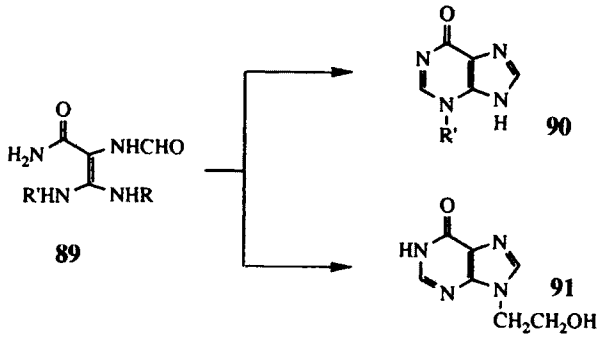
$$2\,HCONH_2 \rightleftharpoons \underset{\mathbf{86}}{H_2NCH{=}NCHO} + H_2O \qquad (2)$$

$$H_2NCH{=}NCHO + 2\,\overset{*\,*}{HCN} \longrightarrow \underset{\mathbf{87}}{\text{(pyrimidine adduct)}} \qquad (3)$$

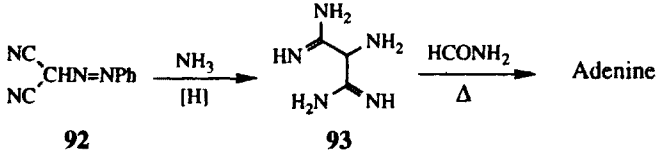
Mass spectral results combined with ^{13}C and ^{15}N NMR coupling data, obtained from products of the reaction between labeled hydrogen cyanide and formylformamidine, indicate that an initial pyrimidine adduct (**87**)[1013,1014] formed (Eq. 3) then undergoes formylation, followed by ring closure to purine in which participation of an intermediate 8-formylamino-7, 8-dihydropurine (**88**) is possible.[1012] Heating formamide with additional hydrogen cyanide gives adenine rather than purine. From NMR studies with various combinations of labeled (^{13}C and ^{15}N) and unlabeled reagents, it is concluded that two molecules of the amide and three molecules of hydrogen cyanide are involved in the synthesis of adenine, the formamide contributing the elements for both the C-2 to N-1 and C-8 to N-9 bonds of the ring system[1015] (Eq. 4). Support for this rationale comes from studies with labeled formamide which indicate that cleavage of the amide C-N bond occurs at some point and is then reformed, regenerating starting material.[1825] An improved synthesis of adenine employing milder thermal treatment has been described which uses formamide containing phosphorus oxides and nitric acid. Under these conditions a contributing factor must be conversion of part of the amide present to hydrogen cyanide.[1016]

$$3\,\overset{*\,*}{HCN} + 2\,HCONH_2 \longrightarrow \underset{\mathbf{88}}{\text{(purine)}} \qquad (4)$$

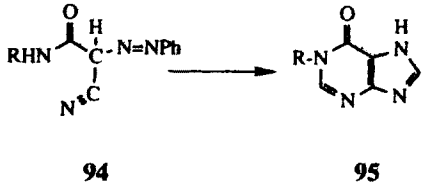
Simultaneous closure of both pyrimidine and imidazole rings using branched-chain acyclic precursors has been shown to be an attractive synthetic approach (*H*108). However, because the same reagent is involved in both ring formations, the end products are purines having the same alkyl groups at C-2 and C-8. Ambiguities are to be found—for example, the amidinoacetamido derivative (**89**, R = H, R′ = CH_2Ph), which hot triethyl orthoformate converts to 3-benzylhypoxanthine (**90**, R′ = CH_2Ph),[869] and similarly the cychohexyl analog (**90**, R′ = C_6H_{11}) derived from (**89**, R = H, R′ = C_6H_{11}).[869] However, if the starting material

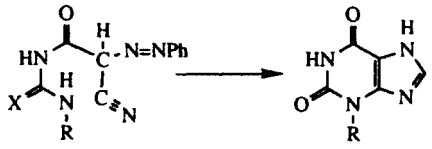


has a less bulky substituted-amino group, as in **89**[R=H, R′=$(CH_2)_2OH$], brief heating with the same orthoester in dimethylformamide affords 9-(2hydroxyethyl)hypoxanthine[869] (**91**). The 3- and 9-alkylated products, obtained in 60% yields, are found (thin layer chromatography), associated with small amounts of the alternate 9- or 3-alkyl isomer.[869] Surprisingly, neither type of ring closure can be effected with either triethyl orthoformate–acetic anhydride, diethoxymethyl acetate, or formamide.[869] These bicyclizations may have relevance to purine biosynthesis since *trans*-α,β–diformamido-β-(5′-phosphoribosylamino)acrylamide (**89**, R = ribosyl-5′-phosphate, R′ = CHO) has been identified as a substrate in the de novo pathway.[1028] A novel route covering the preparation of adenines, hypoxanthines, xanthines, and guanines employs derivatives of phenylazomalonic acid as acyclic precursors. Reactions utilize temperature, pressure (150°C, 80 kg/cm^2), and reducing conditions (catalytic hydrogenation) in formamide containing dissolved ammonia. Adenine, in 70% yield, is formed from phenylazomalononitrile (**92**) with a nickel catalyst,[1017] a slightly better yield obtains using palladium–carbon in its place.[1018] A pathway involving formylation and bicyclization of the intermediate (**93**) derived from ammonia and the nitrile is assumed (Eq. 5). The same treatment applied to the carbamoylmalononitriles (**94**) gives hypoxanthine (**95**, R = H) from (**94**, R = H)[1017,1019] and the corresponding 1-methyl- (**95**, R = Me),[1017,1019] 1-benzyl-(**95**, R = CH_2Ph),[1017] 1-*n*-propyl- (**95**, R = *n*-Pr),[1019] and 1-cyclohexyl-hypoxanthine (**95**,R = C_6H_{11})[1019] from the appro-



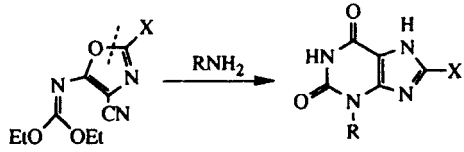
(5)



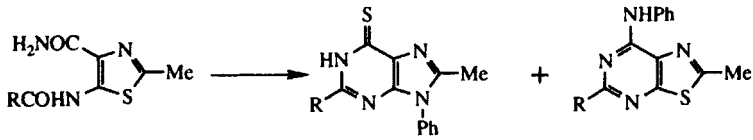


96 **97**

priate *N*-substituted amide (**94**, R = Me, CH_2Ph, *n*-Pr, and C_6H_{11}). The versatility of the approach is seen in the formation of xanthine[1018] (**97**, R = H) and the 3-methyl homolog[1018] (**97**, R = Me) with the respective 2-cyano-2-phenylazoacetylureas (**96**, R = H, X = O) and (**96**, R = Me, X = O),[1018] while guanine, in similar yield (90%), results from the guanidino analog (**96**, R = H, X = NH).[1018] An unusual reaction occurs between 4-cyano-5-diethoxymethylideneamino-1,3-oxazole (**98**) and alkylamines; the resulting 3-alkylxanthines (**99**, R = alkyl) are the products of a bicyclization step necessitating a prior opening of the oxazine ring.[953] Of more academic than practical interest is the high temperature (240°C) conversion of 4-acylamino-5-carbamoylthiazoles (**100**, R = H or Me) to 6-thioxopurines (**101**) using aniline derivatives with triethylamine and phosphorus pentoxide.[943] The ratio of purine (**101**) to 7-aminothiazolo[5,4-*d*] pyrimidine (**102**) in the product mixture is governed by the particular aniline and thiazole taking part.



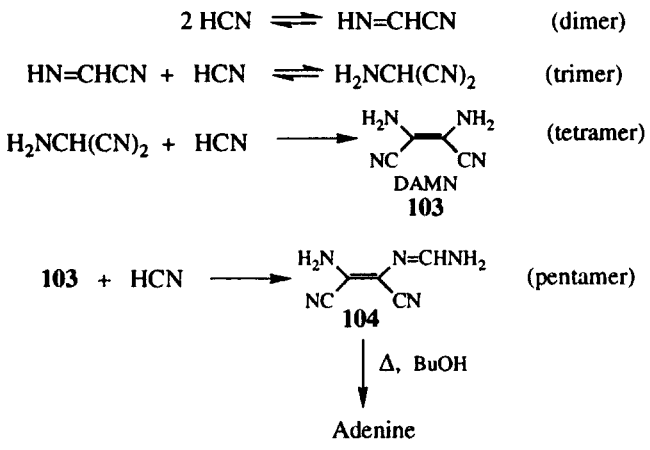
98 **99**



100 **101** **102**

B. Abiotic Syntheses (*H*110)

The part played by hydrogen cyanide in the abiotic synthesis of purines, in particular that of adenine, is at the center of any mechanistic speculation. Early theories advocating direct polymerization of hydrogen cyanide into diameric forms, which then reacted with formamidine, are now considered to be of questionable value.[1022] Current thinking envisages that the cyanide oligomer is increased in size by a stepwise addition of hydrogen cyanide units until the tetramer, diaminomaleonitrile (DAMN) (**103**), is formed[1014] (Scheme 3). Reaction of **103** with formamidine acetate gives adenine, but solvent effect is important. In aqueous media the 4-amino-5-cyanoimidazole initially formed is



Scheme 3

slowly converted to adenine,[1023] but under nonaqueous conditions the pentameric form, *N*-(aminomethylidene)diaminomaleonitrile (**104**), is identified[1024] as the significant precursor by undergoing a rapid transformation into adenine in butanol (100°C, 0.5 h).[1023,1024] An alternative pathway to adenine from DAMN has been advanced[1025] which precludes the involvement of an imidazole intermediate, in this case the precursor is 6-amino-8-carbamoylpurine.[1025] In a recent program a mixture of potassium cyanide, ammonia, and water containing semiconductor particles of titanium dioxide and cadmium(II) sulfide and a catalyst of Pd-carbon, upon irradiation with a Xe lamp (500 W, 20°C, 24 h), gave hypoxanthine as one of the products, but no adenine or guanine was identified[1882] in the mixture.

Recent studies of the "primordial soup" type involve exposure to a high-frequency electrical discharge of a 3:1:2 mixture of methane, ammonia, and water.[1026] Among the products obtained are adenine, guanine, hypoxanthine, and hydrogen cyanide. The near-quantitative conversion of DAMN (**103**) to 4-amino-5-cyanoimidazole, the precursor of adenine, on exposure to UV radiation (350 nm) in water at room temperature[1027] sheds further light on the understanding of abiotic synthesis in view of the known facile oligomerization of hydrogen cyanide[1014] to DAMN (**103**).

For an up-to-date perspective on the chemistry of prebiological natural products formation, the review by Eschenmoser and Lowenthal should be consulted.[1883]

C. Biological Syntheses (*H*112)

The detailed investigations into various facets of this subject are too complex to be reviewed in simple terms and are outside the scope of this volume. It is,

however, of interest to note that an investigation (^{13}C NMR) of the synthesis of adenine and guanine by the yeast *Saccharomyces cerevisiae* shows that the pathway followed is identical to that in the biosynthesis of the same purines by bacteria and higher life forms.[1938]

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER IV

Purine and *C*-Alkyl, *C*-Aryl, and *N*-Alkyl Derivatives (*H*117)

1. Purine (Unsubstituted) 83
A. Preparation of Purine (*H*117) 84
B. Properties of Purine (*H*118) 84
C. Reactions of Purine (*H*119) 86
2. *C*-Alkyl and -Arylpurines (*H*120) 87
A. Preparation of Alkylpurines (*H*120) 87
b. By Conversion of Halogens to Alkyl Groups (*H*122) 88
e. By Other Methods (*H*123) 90
C. Reaction of Alkylpurines (*H*124) 91
b. Methyl to Carboxypurines (*H*125) 92
c. Other Oxidations of Alkylpurines (*H*126) 92
d. Halogenation of Alkylpurines (*H*127) 93
e. Benzaldehyde with Methylpurines (*New*) 93
f. Other Reactions (*New*) 94
3. The *N*-Alkylpurines (*H*129) 94
A. Preparation of *N*-Alkylpurines (*H*129) 94
a. By Direct Alkylation (*H*129) 95
b. By Other Means (*H*130) 95
C. Reactions of *N*-Alkylpurines (*H*131) 96
4. Natural Occurrence (*H*132) 97

Studies on purine itself are now confined mainly to physicochemical aspects, most of the simple chemistry having been extensively explored in the early years. Formation and reactions of *C*- and *N*-alkyl and -aryl derivatives, however, continue to attract attention. Since the isolation of the nucleoside nebularine in 1954, no naturally occurring derivatives containing purine or a simple alkyl homolog appear to have been identified.

1. PURINE (UNSUBSTITUTED)

The relative paucity of published work on the parent member is in sharp contrast to the abundance of literature devoted to the widespread nucleic acid bases, such as adenine, hypoxanthine, and guanine, and to the various xanthines found in nature.

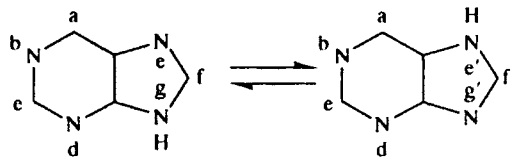
A. Preparation of Purine (*H*117)

The availability, both commercially and from existing simple syntheses, of purine has diminished the need for new preparative routes. As part of studies on abiotic synthetic pathways, a significant yield of purine (21%) resulted from prolonged heating of formamide (18°C, 18 h).[1011] The reaction is dependent upon a restricted temperature range between 160 and 200°C. More conventional is a Traube synthesis of a C-6 deuteriated derivative, from the labeled diaminopyrimidine and formic acid,[1048] and a reduction of the 3-oxide with Raney nickel in water.[1057] In another route, the same metal catalyst is employed to remove both oxygen and selenium from 3-oxido-6-selenoxopurine.[1142] A more recent approach is the deamination of 1-aminopurine by methanolic ammonia[1404] (ANRORC reaction).

B. Properties of Purine (*H*118)

The neutral molecule can exist in the 1H, 3H, 7H, or 9H protomeric forms. Energy values derived from MINDO calculated heats of formation[1042] and modified CNDO calculations[1043] show that stability follows the order 9H > 7H > 3H > 1H. The near predominance of the 7H and 9H protomers reflects their much greater stability compared with those of the 1H and 3H forms. Results of CNDO/2 calculations on the four tautomeric states indicate a π-electron-deficient imidazole ring features in both 7H and 9H protomers, but the reverse is true for the 1H and 3H analogs in which the pyrimidine rings are now the most electron depleted, and where quinonoid structures are present.[1827] Theoretical evaluations of triplet states have been made with MCNDO/2 calculations.[1677] Later studies using laser flash photolysis on radical cations and anions of both purine and the 6-methyl homolog have demonstrated the presence of these energy levels.[1831] Average values of the interbond angles of the 7H and 9H tautomers have been obtained from crystallographic data,[1031,1032] as illustrated by **1A** and **1B** for the respective 9- and 7-tautomers. The ratio of the two tautomers present,

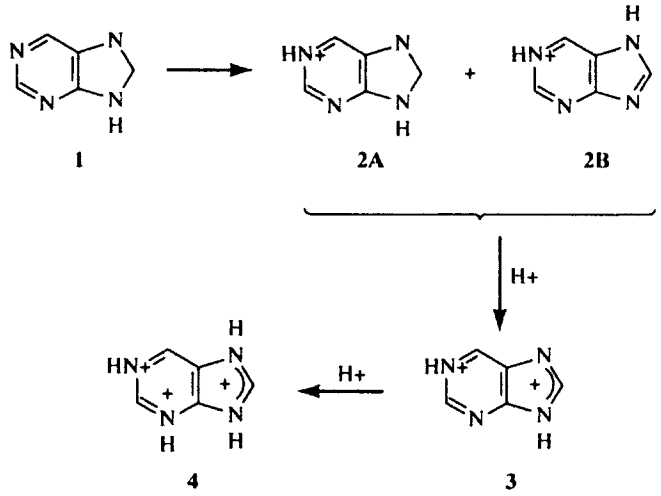
Interbond angles in purine 7/9 (H)-tautomers



1A

a. 119.2°
b. 117.9°
c. 125.5°
d. 112.6°
e. 103.9°
e'. 106.8°
f. 112.8°
g. 108.4°
g'. 104.3°

1B

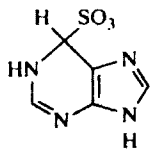


under various conditions, has been investigated using theoretical and practical procedures, including CNDO/2 calculations,[1033] UV spectra and dipole moments,[1033,1044] gas-phase UV photoelectron spectra,[1034] shifts in ^{15}N NMR as a function of pH,[1035,1826] ^{13}C NMR shifts, and ^{13}C-^{1}H NMR coupling[1037] constants. In the solid state, only the 7H isomer is present, linked together in molecular chains through hydrogen bonding between the N-7 proton of one purine and N-9 of the adjacent molecule.[1032] Equal amounts of the two tautomers coexist in aqueous solution, either as neutral molecules[1035,1037] or as cations,[1035,1037] but in aprotic media (e.g., dimethyl sulfoxide), the 9H tautomer is more favored.[1035] This also appears to be the case in the gaseous phase, where it is the more stable form in the prevailing isolated environment.[1034] Identification of the three possible sites of protonation has been made. Initial proton addition[1035,1037,1038] is almost solely at N-1 (trifluoroacetic acid), forming the cationic tautomers (**2A**) and (**2B**). Calculations show the latter to be the most stable purine ion,[1046] but in solution both tautomers are equally represented. The dication (**3**), also capable of tautomeric forms, arises from protonation of an imidazole nitrogen[1037,1038] (fluorosulfonic acid), while the trication (**4**) results from the treatment with a fluorosulfonic acid mixture containing sulfur dioxide and antimony pentafluoride, the third proton being located at N-3.[1038] Calorimetric determinations of orders of protonation using heats of solution failed, owing to solvent interaction effects. However, the same workers,[1039] using ^{13}C NMR, confirmed that proton addition follows the order N-1 → N-7/9 → N-3. The results from potentiometric and calorimetric studies with the monocation conjugate acid (**2**) show it to be a slightly stronger acid in dimethyl sulfoxide than in water, hydrogen bonding appears to be a significant factor in this result.[1040] Enthalpy determinations indicate that similar solution effects are also responsible for the self-association of purine in aqueous solution.[1041] In contrast, association of the purine anion in the same medium does not occur, but stacking is observed if a similar-sized flat molecule, like 1,3-dimethyluracil, is also present.[2031] The intercalation of purine with

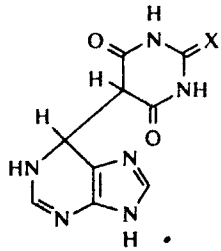
single-strand DNA in aqueous solution has been investigated with NMR, and the configuration adopted between the nucleic acid bases has been determined.[1045] A highly stable 2:1 complex forms with urea in the solid state. Stacking of the purine bases is similar to that in crystalline purine itself, but differs in that the imidazole proton is located at N-9 instead of N-7.[1355] Transfer rates of the proton at C-8, studied with 8-tritiated purine,[1356] are found to be highest following prior protonation of N-7 in the imidazole ring.[1056] An adaptation of the Perrin equation enables a pK_a value at a given temperature to be compared with that derived at the same temperature from displacement rate–pH profiles of the 8-proton.[1320] The relaxation spectrum of the homologous 6-methyl derivative in aqueous solution has also been reported.[1991]

C. Reactions of Purine (*H*119)

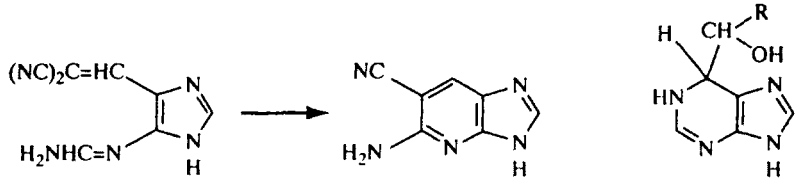
In dimethylformamide containing triethylamine, reaction with 1-chloro-ethylethylether gives the expected 9-(1-ethoxyethyl)purine.[1832] Illustrating the change in alkylation in the absence of base is the action of benzyl bromide in dimethylacetamide (80°C, 2 h), which gives 1-benzylpurine as the major product, together with minor amounts of the 3-, 7-, and 9-benzyl isomers.[826] At higher temperatures (> 140°C), thermolytic rearrangement to a mixture of 7- and 9-benzylpurine occurs[826] (see Section 3.A.a). Although formation of stable covalent hydrates has not been achieved in purines, the corresponding adducts with hydrogen sulphite ions can be isolated. The dihydropurine analog (**5**) is stable as the cationic form, but rapidly decomposes to purine in neutral aqueous solution.[1047] Compounds with active methylene groups (e.g., barbituric acid), form similar adducts with the purine 1,6-double bond, giving a product of the type (**6**, X = O or S), which possesses a high stability.[1048] Although similar adduct formation is expected with the more reactive malononitrile, in practice, spontaneous fission of the pyrimidine ring occurs, possibly to the imidazole (**7**), with subsequent recyclization to 5-amino-6-cyanoimidazo[4.5-*b*]pyridine (**8**) and a detectable loss of hydrogen cyanide.[1049] The direct introduction of an amino group at C-6, using potassium amide in liquid ammonia, also involves 1,6-double bond addition shown by adenine, formed in the Chichibabin reaction using ^{15}N-labeled amide, containing all the activity in the 6-amino group.[1050] Preparation of 1-aminop-



5



6



7 8 9

urine, isolated as the mesitylenesulfonate, involves direct *N*-amination of purine with hydroxylamine-*O*-mesitylene sulfonic acid* (N.B., this is potentially explosive!) in dichloromethane and methanol,[1051] but the 9-amino isomer is obtained if hydroxylamine-*O*-sulfonic acid is used for amination.[1314] Reactions with radicals generated by UV photolysis of alcohols have been examined further; the products are intramolecularly bonded 1,6-dihydropurines like **9** (R = H, Me, Et), in which the N-1 proton is donated by the alcohol alkyl group.[1052] Diastereomeric forms are shown by the ethanol adduct.[1053] Butyl radicals, from treating pivalic acid [$(Me)_3CCO_2H$] with ammonium peroxidisulfate and silver nitrate, convert the purine into the 6,8-di-*tert*-butyl homolog.[1050] A radical-induced expansion of the pyrimidine ring to the seven-membered ring analog is possible with the naturally occurring nucleoside nebularine under similar conditions (see Section 4). Metal complexation with mercury(II) chloride occurs through N-7 as indicated by the C-8 proton shift;[1054] corresponding copper(II) and zinc salt complexes are also formed.[1055] Binding sites vary using more bulky organometallic reagents—a 1,7-disubstituted product forms with allylpalladium(II) chloride, but with triphenylphosphoran gold(I) chloride only the N-9 derivative is obtained. The same ring nitrogen is involved in forming the titanocene derivative with $(C_5H_5)_2TiCl$ and similar metallocenes.[1354] Reduction of purine, largely using polarographic techniques, is described in (Chapter XII, Section 1.A.a). Following oxidation with either hydrogen peroxide in acetic acid or *m*-chloroperoxybenzoic acid, a mixture containing both 1- and 3-*N*-oxides is obtained (see Chapter XI, Section 1.A)[1057]

2. *C*-ALKYL AND -ARYLPURINES (*H*120)

A. Preparation of Alkylpurines (*H*120)

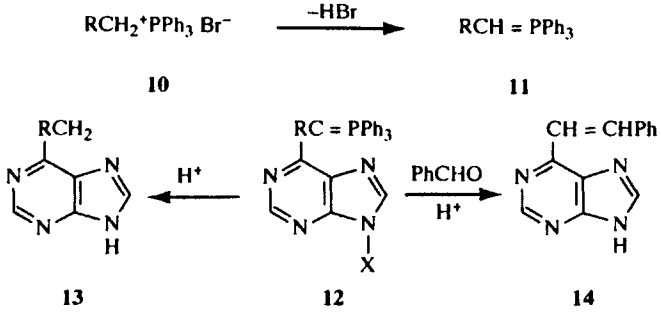
To this end, the Traube synthesis or the removal of halogen atoms or thioxo groups from alkylpurine derivatives, which were previously favored, are now used infrequently. Recent attention has centered upon direct or indirect replacements of a halogen by an alkyl group. In the former case, reagents of the Wittig or Grignard type are involved, whereas in the indirect case, compounds with active methylene groups are utilized and further modification of the product is

* This reagent had only been used previously to *N*-aminate bases in nucleosides (*H*317).

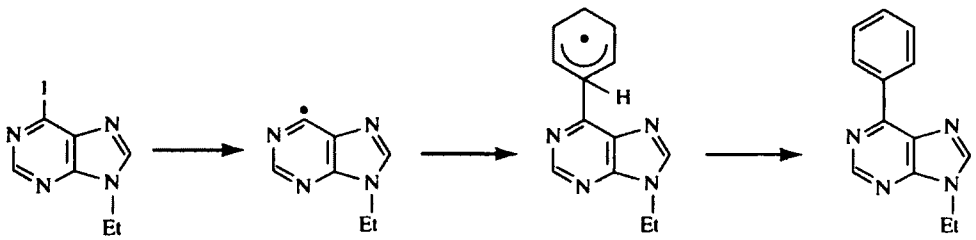
needed to obtain the alkylpurine. Many of the reactions with the halogenopurines are often equally successful if the methylsulfonyl- or methylthiopurine analogs are used in their place.

b. By Conversion of Halogens to Alkyl Groups (H122)

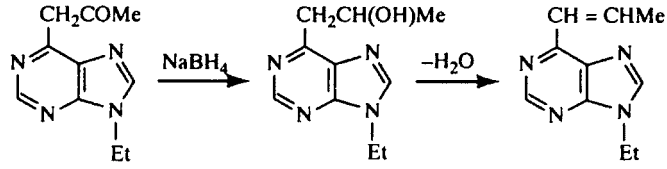
Treatment of 6-chloropurine, as the N-9 protected tetrahydropyranyl homolog, with an alkyltriphenylphosphonium salt in the presence of *n*-butyllithium, affords the appropriate 6-alkyl-9-(tetrahydropyran-2-yl)purine. Mild acid hydrolysis removes the protecting group. Purines so derived from 6-chloropurine include 6-methyl-,[1058,1059] 1,6-dimethyl-, 6-ethyl-,[1059] and 6-benzylpurine.[1059] Metatheses of this kind envisage an in situ conversion of the phosphonium salt (**10**, R = alkyl) to the ylid derivative (**11**) which, following a Wittig reaction with the halogenopurines, forms the intermediates (**12**, R = H, Me, or Ph; X = tetrahydropyran-2-yl) from which the 6-alkylpurines (**13**, R = H, Me, Ph) are obtained after aqueous alkali treatment. On reaction of **12** with benzaldehyde, the *trans*-6-phenylethenyl derivative (**14**) results, which is converted to 6-phenylethylpurine by hydrogenation.[1059] Similar examples using phosphonium salts are available.[1060] Various organometal complexes have been introduced as catalytic adjuncts in Grignard-type reactions for the introduction of alkyl groups. The mild conditions usually needed favor them especially for use in nucleoside preparations. The 2-iodo congener of nebularine, for example, is converted to the 2-vinyl analog by a palladium(II) chloride catalyzed cross-coupled reaction with tri-*n*-butylvinylstannate.[1105] These conditions also convert a 2-iodoinosine derivative to the 2-vinyl analog,[1875] while 8-vinyl- and 8-allyladenosine result from the 8-iodopurine, following reaction with the appropriate alkenyltributylin and a tetrakis (triphenylphosphine)palladium catalyst.[1936] Along similar lines is the low-temperature (−45°C) formation of 9-benzyl-6-phenylpurine from the 6-iodopurine using lithium diphenylcuprate.[1061] By contrast, a Chichibabin-type reaction, giving 8-phenyl derivatives, occurs when 7- and 9-methyl-6-chloropurine react with phenyllithium under oxidative conditions in the presence of Kochi's catalyst [tris(dibenzoylmethido)iron(III)]. Phenylation at C-8, occurring without involvement of the halogen, is attributed to the weaker electron acceptor property of the



chlorine compared with that of iodine.[1061] Grignard reagents, in association with transition metal chloride complexes, replace 6- or 8- halogens by alkyl groups. This reaction, presently confined to suitably protected nucleosides, converts 6-chloropurine riboside into the 6-ethyl, 6-phenyl, 6-cyclohexyl, and other analogs, employing a catalyst of 1,3-bis(diphenylphosphine)propanenickel dichloride [Ni(dppp)Cl_2] with the appropriate Grignard reagent.[1062] Slightly more vigorous treatment is needed in the transformation of 8-chloro or 8-bromo derivatives of adenosine, inosine, or guanosine to their 8-methyl analogs; the catalyst in this instance is bis(triphenylphosphine)palladium dichloride {Pd[$P(Ph)_3$]$_2Cl_2$}[1063] and 8-allyl and 8-phenyl groups are similarly introduced.[1063] An alternative route to 8-methyladenosine and -guanosine from the 8-bromo derivatives involves lithiation at C-8 with *n*-butyllithium and subsequent displacement of the metal atom by methyl using methyl iodide.[1064] The reaction can be extended by further metalation with the same alkyllithium and alkyl iodide to convert the 8-methyl- to an 8-ethylpurine.[1065] After lithiation with lithium diisopropylamide, the adenine base in the nucleoside cordycepin likewise forms the 8-methyl analog.[1862] The purinyl radical is involved in the formation of 9-ethyl-6-phenylpurine following UV irradiation of 9-ethyl-6-iodopurine in benzene.[1066] A suggested mechanistic sequence involves homolysis of the carbon–iodine bond with interaction of the resulting purinyl radical with benzene. Release of a hydrogen radical affords 9-ethyl-6-phenylpurine[1066] (Scheme 1). In the same way, the protected 9-ribosides of 2-iodo- and 6-chloro-2-iodopurine are converted to the respective 2-phenyl-[1095] and 2.6-diphenylpurine[1096] analogs. The early work on condensation of halogenopurines with the active methylene group of malonic ester (*H*122) has been extended. Derivatives of 6-chloropurine, including the 9-phenyl,[1067] 9-tetrahydrofuranyl,[1068] 9-tetrahydropyranyl,[1069] and others,[1068] on reacting with malononitrile, ethyl cyanoacetate, and related compounds, give purines with 6-carboxyalkyl or potential carboxyalkyl groups, which generally undergo a facile decarboxylation to alkylpurines.[171] A variation of this reaction under photolytic conditions is between the sodium enolate of ketones and 9-ethyl-6-iodopurine. Acetone,[1070] for example, gives the 6-acetonylpurine (**15**), which is readily reduced to the alcohol (**16**) with sodium borohydride and then dehydrated to the alkene (**17**) with potassium bisulfate in toluene.[1071] An anomalous case of *C*-arylation is observed when the 6-chloro derivative, from chlorination of 8-phenyltheophylline, reacts with *N*,*N*-dimethylaniline, giving a 6-(4-dimethylaminophenyl)-



Scheme 1

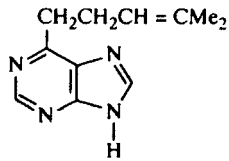


15 16 17

purine rather than the expected quaternary derivative.[1107] The same 6-aminoaryl substituent is found in the product obtained from phosphoryl chloride–dimethylaniline treatment of theobromine[1110] (see Chapter II, Section 1.J).

e. By Other Methods (H123)

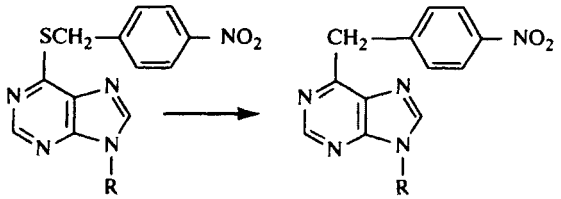
The appropriate Grignard reagent and 6-methylthiopurine react in the presence of a catalyst of either $Ni(dppp)Cl_2$ or $Ni[P(Ph)_3]_2Cl_2$ forming 6-alkylpurines[1072] This reaction, paralleling that with the same reagents and 6-chloropurines (see preceding Section 1.d), affords inter alia 6-phenyl-, 6-*n*-butyl-, 6-*n*-pentyl-, and 6-(2-phenylethyl)- purines.[1072] Phosphorous and hydrogen iodide reduces 2,8-diamino-6-hydroxymethylpurine to the 6-methyl analog.[904] Examples of acid decarboxylation leading to 6-methylpurines are noted with both 6-ethoxycarbonylmethyl[171] and 6-bisethoxycarbonylmethyl[1099] derivatives. A minor yield of 6-methylpurine results on UV irradiation of the 1-oxide derivative.[1073] Metathesis to a homologous purine is found when the dianionic form of 6-methylpurine is treated with 3-methylbut-2-enyl bromide, affording a 25% yield of 6-(4-methylpent-3-enyl)purine (**18**).[1097] Ammonia in methanol (ANRORC reaction) is used to remove *N*-amino groups from various 1-amino-*x*-alkylpurines as a route to 2-, 6-, and 9-methyl- and 8-phenylpurines.[1404] A novel route to 6-phenylpurines from adenine derivatives uses he Gomberg–Bachmann reaction, in which replacement of the amino group is effected with isopentyl nitrite in benzene and involves intermediate purinyl radicals.[967] The condensation of 6-methylsulfonylpurine with ethyl cyanoacetate and malononitrile gives the same two products as are obtained from 6-chloropurine (see previous Section 2.d). These undergo like conversions to 6-alkylpurines.[1079] Examples of similar condensations forming 6-alkylidenopurines (DMF, NaH, reflux) utilize 6-methylthiopurines in place of the 6-methylsulfonyl and 6-chloro derivatives previously reported.[1871] Direct introduction of an alkyl group at C-8, and less often at C-2 and C-6, is a feature of radical reactions. Illustrating this are *C*-methylations with methyl radicals derived from diazomethane[871] or *tert*-butyl hydroperoxide,[1074,1075,1100,1459] or diacetyl peroxide in the presence of iron(II) ions.[1076] An alternative approach uses



18

UV-irradiated *tert*-butylperacetate as radical source.[1077] Benzylation is effected by either thermal means[847] or irradiation with benzylbromide[847] or toluene with ammonium persulfate and an iron(II) sulfate catalyst.[1078] Reaction of caffeine with alanine or serine under UV light produces 8-ethylcaffeine in low yield. With 2-aminobutyric acid or threonine, both ethyl and propyl radicals are generated, giving rise to a mixture of 8-ethyl- and 8-propylcaffeine.[1099]

A transformation of purine into the 6,8-bis-*tert*-butyl homolog by means of pivalic acid and ammonium peroxidisulfate is noted in Section 1.C.[1050] Radical involvement is also seen in the conversion of caffeine and 6-benzamidopurine to the respective 8-(cyclohexyl)- and 8-(adamant-1-yl)-purines using cyclohexyl and adamant-1-yl carboxylates with visible light and an *N*-hydroxy-2-thioxopyridine sensitizer under anaerobic conditions.[1111] Examples of thermally produced radicals arise from the decomposition of 6-aryltriazenopurines obtained from adenine and benzene diazonium ions. The products are 8-aryladenines arising from attack at C-8 by phenyl radicals from the aryltriazene moiety.[858] Confirmation that the unusual reaction between theophylline and but-2-enyl bromide does give 8-(but-2-enyl)theophylline rather than the expected 7-(but-2-enyl) isomer is obtained from a recent investigation[847] of the original workers' (*H*123) claims. The observation that 9-methylpurine undergoes transformation to the 8-phenyl derivative when treated with bromobenzene is explained by an in situ conversion of the halobenzene into the more reactive benzyne under the prevailing conditions, with subsequent C-8 addition[875] occurring. Modification of an existing alkyl group is exemplified by metalation with butyllithium of an 8-methylpurine and reaction of the product with methyl iodide, producing the 8-ethylpurine analog.[1065] Formation of 6-alkyl derivatives from 6-alkylthiopurines by excision of sulfur through the Eschenmoser contraction reaction (Scheme 2) is brought about on heating in dimethylformamide with triphenylphosphine.[1350] The rearrangement of alkoxypurines to the isomeric 8-alkylated oxopurines is discussed in Chapter VI, Section 8.D.



(R = 2′, 3′, 5′-*O*-triacetyl-β-D-ribofuranosyl)

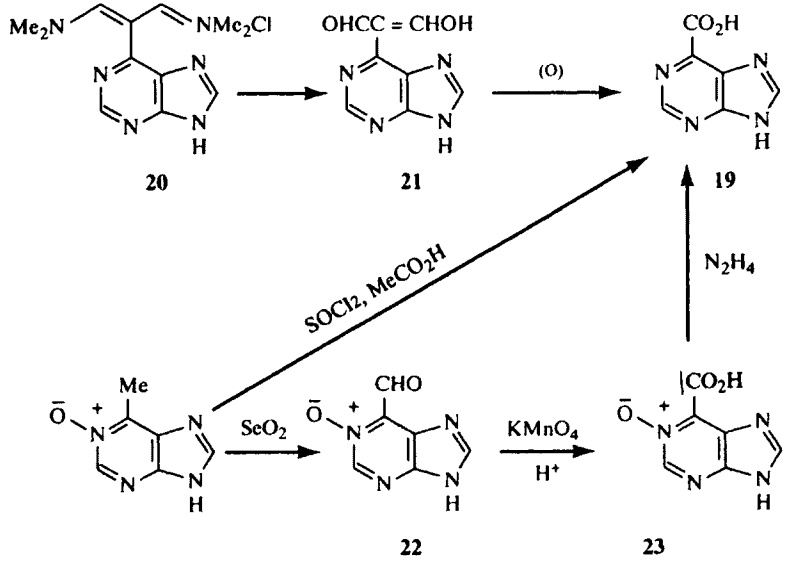
Scheme 2

C. Reactions of Alkylpurines (*H*124)

These are grouped under two main classifications. The first deals with reactions of the *C*-alkyl groups, for which a methyl group is usually cited, whereas the other covers diverse reactions of the ring system itself.

b. Methyl to Carboxypurines (H125)

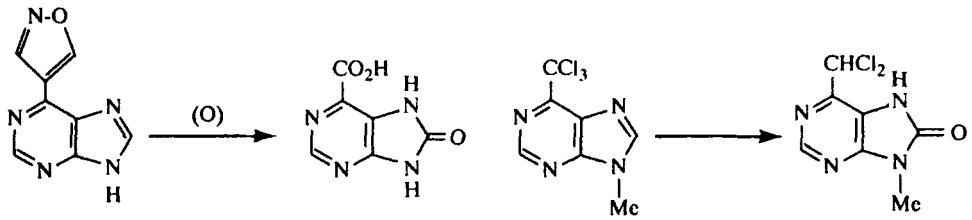
Methyl groups are best converted to a more active form prior to oxidation. Previously, the Ortoleva–King reaction was favored,[1082] using iodine in pyridine, to form methylenepyridinium iodides (*H*125). Some recent examples of such conversions with 6-methylpurines have been reported.[1057,1080] These derivatives, however, seem inferior to styrylpurines, prepared by the Knoevenegal reaction (see Section 2.C.e), toward oxidation. The 6-styrylpurine (**14**), for example, derived from the 6-methyl analog, is oxidized efficiently (59%) to the 6-carboxypurine (**19**) by means of aqueous potassium permanganate, compared with a 48% yield using the quaternary salt.[1081] The Vilsmeier reagent (phosphoryl chloride–dimethylformamide) converts 6-methylpurine to the bisazamethine salt (**20**), which readily hydrolyzes to the aldehyde (**21**). A low yield (18%) of **19** results from oxidation of **21** with alkaline permanganate.[791] The same acid (**19**) is formed when 6-methylpurine-1-oxide reacts with thionyl chloride in acetic acid.[1080] This involves initial formation of a 6-trichloromethylpurine with subsequent hydrolysis and deoxygenation of the product. Oxidation of the same purine-1-oxide with selenium dioxide gives the 6-formyl derivative (**22**), which in acidified permanganate is further oxidized to the 6-carboxy analog (**23**). Reduction to **19** is achieved in hot aqueous hydrazine.[1057]



c. Other Oxidations of Alkylpurines (H126)

The oxidation of 6-methyl- to 6-formyl-purines with selenium dioxide has been noted above (see Section 2.C.b). After treatment of the Vilsmeier reagent product

(**20**) with hydroxylamine, the resulting isoxazolyl derivative (**24**) gives the 6-carboxy-8-oxopurine (**25**) on reaction with acidified permanganate.[791] The mixture of the 1- and 3-oxides obtained from 6-methylpurine with *m*-chloroperbenzoic acid is the first example of two oxides being obtained from the same reaction.[1057] It should be noted that the same purine treated with peroxyacetic acid (*H*126) was reported to form only the 1-oxide. Supporting the latter reaction is isolation of the 1-oxido derivative from 6,9-dimethylpurine, as sole product using the same oxidizing agent.[1073] Under neutral conditions, oxidation of purin-6-ylmethylenepyridinium-1-oxide iodide to 1-hydroxyhypoxanthine occurs with potassium permanganate.[1057] The same product results using 6-styrylpurine-1-oxide as starting material.[1057] The acetic-anhydride-induced rearrangement of 3-hydroxy-8-methylxanthine to 8-hydroxymethylxanthine also occurs with 3-hydroxy-8-methylguanine.[1235] Mechanistic details of the reaction are discussed in Chapter XI, Section 3.C.



24 **25** **26** **27**

d. Halogenation of Alkylpurines (H127)

The 9-methyl homolog of 6-methylpurine behaves like the parent compound in forming the 6-trichloromethyl derivative (**26**) when warmed with sulfuryl chloride in trifluoroacetic acid. On prolonged heating in aqueous hydrochloric acid (100°C, 24 h), rearrangement to the 6-dichloromethyl-8-oxopurine (**27**) follows.[1083] The 7-methyl isomer of **26**, however, does not undergo this rearrangement,[1084] steric factors possibly intervening. A route to 6-tribromomethylpurine is by the action of bromine in acetic acid on the aldehyde derivative (**21**) from 6-methylpurine (see Section 1.C.b). Both the 1- and 3-oxide of 6-methylpurine give the 6-bromomethyl analogs when heated with *N*-bromosuccinimide in trifluoroacetic acid.[1080] These examples of monobromination contrast with the dibromination, which 6-methylpurine undergoes under the same conditions (*H*127). Attempts to halogenate 8-methyladenine were unsuccessful.[790]

e. Benzaldehyde with Methylpurines (New)

A number of examples of the Knoevenegal reaction are available. Condensation of the aldehyde with 6-methylpurine in acetone containing hydrogen chloride

results in a 95% yield of 6-styrylpurine;[1081] the 1-oxide congener of the latter is not formed by direct oxidation, but from 6-methylpurine-1-oxide using an excess of aldehyde as solvent and hydrogen chloride.[1057] Alkaline conditions convert both the 7- and 9-phenyl derivatives of 8-methylpurine to the respective 7- and 9-phenyl-8-styrylpurines, a sodium methoxide catalyst being employed.[942] Corresponding derivatives from substituted aromatic aldehydes are also given.[942] Alternative condensations carried out in acetic anhydride at 190°C were also successful, but gave lower yields.[942]

f. Other Reactions (New)

Direct *C*-amination leading to 6-aminopurines is demonstrated by the formation of adenine and the 2- and 8-methyl homologs from purine and 2- and 8-methylpurine, respectively, using potassium amide in ammonia.[1050] It should be noted that although the conditions suggest that ANRORC-type reactions are operating, the aminations are shown to occur through nucleophilic attack by an amide ion, no ring fission taking place.[1050] Isomeric *N*-aminopurines result from hydroxylamine-*O*-mesitylenesulfonic acid treatment. Representative 1-amino derivatives are formed by purine and also by the homologous 2- and 8-methylpurines, 9-methylpurine, and the 8-phenyl homolog.[1051] Failure to obtain the corresponding derivative with 6,8-di-*tert*-butylpurine is possibly a result of steric factors operating.[1051] The rearrangement of 3-hydroxy-8-methylxanthines to 8-hydroxymethylxanthines on acid anhydride treatment is dealt with in Chapter XI, Section 3.C.

3. THE *N*-ALKYLPURINES (*H*129)

The most significant advances made are concerned with preparative aspects; but overall impressions apart from these are of a largely unchanged picture for syntheses and reactions.

A. Preparation of *N*-Alkylpurines (*H*129)

In addition to direct alkylation procedures, the removal of various atoms or groups from substituted *N*-alkylated purines provides an alternative route.

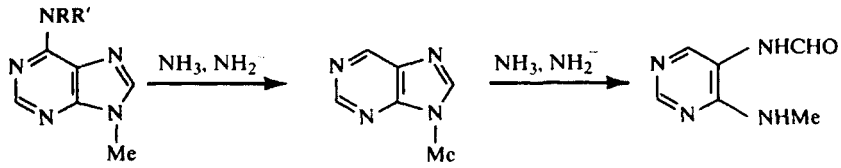
a. By Direct Alkylation (H129)

Reaction of benzyl bromide with purine in dimethylformamide at 80°C produces a mixture of 1-benzyl- (45%), 3-benzyl- (14%), 7-benzyl- (1%), and 9-benzylpurine (3%). At higher temperature (140°C) and longer time (48 h), only

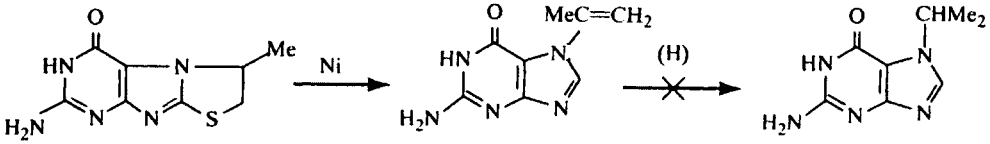
the 7-benzyl (15%) and 9-benzyl (3%) isomers are found.[826] Dimethylformamide, as the dimethyl or diethyl acetal, can function as both solvent and alkylating agent.[1086] With this approach, purine gives a mixture of the 7-methyl (45%) and 9-methyl (30%) derivatives.[1087] Ethyl 4-methylbenzene sulfonate and sodium hydride in dimethylformamide (25°C, 10 h) ethylate purines to the 9-ethyl homolog.[1094] Vinyl acetate in the presence of mercury(II) chloride (40°C, 30 days) gives both 7- and 9-vinylpurines which yield the corresponding 7- and 9-ethylhomologs on catalytic hydrogenation.[1215] A repeat alkylation of 6-methylpurine with dimethyl sulfate in methanolic potassium hydroxide (*H*129) gives some 6,7-dimethylpurine as a minor product in addition 3- and 9-methyl derivatives.[1089] Under aprotic conditions, a 6-methyl-9-substituted-purine with methyl iodide undergoes methylation at N-1.[842] From methylation of 8-phenylpurine with methyl iodide in acetonitrile, only 1-methyl-8-phenylpurine is obtained.[1088]

b. By Other Means (H130)

Recent preparations of 7-methylpurine by well-tried catalytic hydrogenation procedures are noted.[1087,1090] The same route gives the 9-methyl isomer (**29**) from the 6-chloropurine.[1090] An alternative new approach entails deamination of 9-methyladenine derivatives with potassium amide in liquid ammonia followed by quenching with ammonium sulfate. In this way **29** can be obtained from either 6-amino- (**28**, R = R′ = H), 6-methylamino- (**28**, R = H, R′ = Me), or 6-dimethylamino-9-methylpurine (**28**, R = R′ = Me).[1091] No amino group removal occurs, however, if the ammonium sulfate quenching step is omitted.[875] Although adenine itself is not converted to purine in this way, the deamination of 9-(tetrahydropyran-2-yl)adenine with subsequent hydrolytic removal of the tetrahydropyranyl group with acid provides a route to purine indirectly.[1091] Other examples involving deaminations are the formation of 9-ethyl-[1092,1094] and 9-benzylpurine[1092] from the corresponding 9-alkyladenine on reaction with pentyl nitrite while exposed to UV irradiation. Under these conditions the amino group undergoes a radical-induced removal.[1092] Dethiation with Raney nickel affords both 3- and 9-methyl derivatives of 8-phenylpurine from the appropriate 6-thioxopurines.[1088] The same procedure gives 9-ethylpurine from the 2,6-dithioxo analog.[1187] A novel variation of this reaction is the desulfurization of a thiazolo[2,3-*f*]purine using a nickel alloy to give 7-isopropenylguanine (Scheme 3), although, somewhat unexpectedly, the product resisted catalytic reduction (Pt or Pd, H_2) to the 7-isopropyl



28 **29** **30**

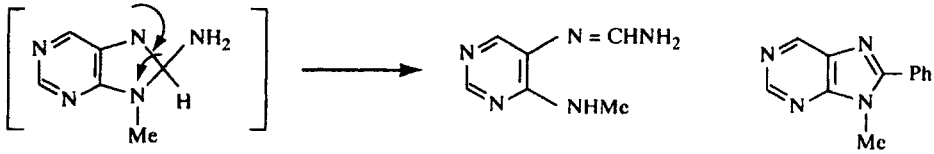


Scheme 3

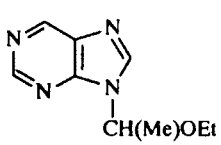
homolog.[1203] A different preparation of 9-methyl-8-phenylpurine, involving treatment of 9-methylpurine with bromobenzene in liquid ammonia, is noted[875] in Section 3.C. Acid hydrolysis removes a tetrahydropyranyl group from N-9, giving 1,6-dimethyl purine.[842] The 6,9-dimethyl isomer results from deoxygenation of the 1-oxide upon UV irradiation, but an equal amount of 6-methyl-2-oxopurine is also formed through rearrangement.[1073] Preparation of the same dimethylpurine by a Traube synthesis is reported.[1073] An illustration of formation of an *N*-alkenyl- from an *N*-alkyl-purine is the sodium-methoxide-induced abstraction of hydrogen chloride from 9-(2-chloroethyl)purine, giving 9-vinyladenine.[1201] A largely academic route to 7-isopropenyl-8-oxopurine occurs on thermal rearrangement of a pyrimido[4,5-*b*][1,4] diazepine[827] (see Chapter II, Section 8.M).

C. Reactions of *N*-Alkylpurines (*H*131)

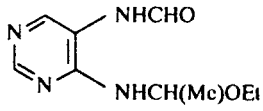
Rearrangement of 1-benzylpurine on heating in dimethylacetamide gives a mixture of the 7- and 9-benzyl isomers. Similarly, 3-benzylpurine forms these same two isomers, together with some 1-benzylpurine, the latter disappearing, due to the above rearrangement on prolonged heating.[826] The instability of 9-methylpurine toward alkali because of nonanion formation (*H*131) is reflected in its degradation to 5-formamido-4-methylaminopyrimidine (**30**) when treated with potassium amide–liquid ammonia.[875] The ring-opening reaction is highlighted by the conversion of purine to adenine under the same conditions.[1050] Fission of the imidazole ring follows after the σ amino adduct (**31**) is formed from amide anion (NH_2) addition, the resulting amidino derivative (**32**) undergoing hydrolysis to **30**.[875] If bromobenzene is present, the C-8 phenylated homolog (**33**) is obtained through the intervention of benzyne derived from the bromobenzene.[875] Similar ring fission follows aqueous sodium hydroxide treatment of 9-(1-ethoxyethyl)purine (**34**), giving initially the 5-formamido-4-substituted aminopyrimidine (**35**) with subsequent reclosure to the 7,8-dihydropurine intermediate (**36**) and concomitant oxidation, affording 8-methylpurine as a main product.[1833]



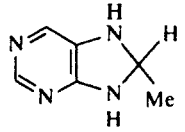
31 **32** **33**



34



35

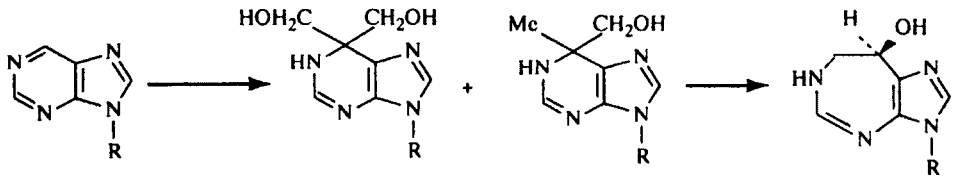


36

Acid reflux conditions with 6,9-dimethylpurine-1-oxide produce pyrimidine ring fission to 4-acetyl-5-aminoimidazole. Similar treatment of 1,6-dimethyl-9-(tetrahydropyran-2-yl)purine iodide leads to removal of the 9-substituent.[842] At low temperatures (−80°C), 9-(tetrahydropyran-2-yl) purine undergoes lithiation at C-8 with butyllithium.[1093] In acid media, 7,9-dialkylpurine salts exhibit a 4-electron reduction to the 1,2,3,6-tetrahydro analog. Only the pyrimidine ring is reduced at low pH (see Chapter XII, Section 1.A.a).

4. NATURAL OCCURRENCE (*H*132)

A new synthesis of nebularine (**37**, R = β-D-ribofuranosyl) utilizes deselenization of 6-methylselenopurine riboside with Raney nickel in methanol[1348]. This approach appears to be superior to a previous one involving nickel desulfurization of the 6-methylthiopurine analog. Early results of UV irradiation of *O*-triacetylated nebularine reported formation of a 6-hydroxymethyl adduct in methanol.[1103] More detailed investigations showed that under anaerobic conditions, a diastereomeric mixture of 1,6-dihydro-6(*R*,*S*)-hydroxymethylpurines is obtained, but if oxygen is present, the products are the reduced forms of the ribosides of 1,6-dihydro-6,6-bis(hydroxymethyl)purine (**38**, R = riboside triacetate) and (*R*,*S*)-1,6-dihydro-6-(hydroxymethyl)-6-methylpurine (**39**, R = riboside triacetate), together with the ribosides of 6-methyl- and 6-hydroxymethylpurine.[1828] The results support earlier findings by Wolfendun,[1829] but differ from those reported by another group[1830] examining this reaction. Expansion of the pyrimidine ring of nebularine to the naturally occurring seven-membered ring analog coformycin (**40**, R = β-D-ribofuranosyl) is by methanesulfonylation of the alcohol group of the anaerobic product, 1,6-dihydro-6-hydroxymethylpurine riboside, noted above, followed by treatment with potassium *tert*-butoxide.[1103] Crystallographic studies establish that the resulting derivative is coformycin.[1104] Using a palladium(II) catalyst and tri-*n*-butylvinylstannate with 2-iodonebularine, conversion to the 2-vinylpurine nucleoside occurs.[1105]



R = 2', 3', 5'-tri-*O*-acetyl-β-D-ribofuranosyl

37 38 39 40

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER V

Halogenopurines (*H*135)

1. The Preparation of 2-, 6-, and 8-Halogenopurines (*H*135) 100
   A. Chloropurines by Cyclization of Chloro-4,5-diaminopyrimidines (*H*135) 100
   B. By Chlorination of Oxopurines (*H*135) 100
      a. In Simple Purines 100
      b. In the Presence of Amino Groups (*H*138) 101
      d. In the Presence of *N*-Alkyl Groups (*H*139) 101
   C. By Replacement of Thioxo or Methylthio Groups (*H*141) 102
   D. By Other Means (*H*142) 102
   E. Preparation of 2-, 6-, and 8-Bromopurines (*H*143) 103
   F. Preparation of 2-, 6-, and 8-Iodopurines (*H*143) 104
   G. Preparation of 2-, 6-, and 8-Fluoropurines (*H*144) 104
      b. By Replacement of Chlorine or Other Halogen Atom (*H*144) 105
      c. By Replacement of Amino Groups (*H*145) 105
      d. By Other Means (*New*) 106
2. Preparation of 8-Halogenopurines by Direct Halogenation (*H*146) 106
3. Preparation of Extranuclear Halogenopurines (*H*148) 106
   A. By Direct Halogenation (*H*148) 107
   B. From Hydroxyalkylpurines (*H*149) 107
   C. From Halogenopurines (*H*150) 107
   D. By Synthesis (*H*150) 108
   E. By Other Means (*H*151) 109
5. Reactions of 2-, 6-, and 8-Halogenopurines (*H*152) 109
   B. Removal of Halogen Atoms (*H*154) 109
      a. In the Presence of Only Alkyl Groups (*H*154) 110
      b. In the Presence of Amino Groups (*H*155) 110
      c. From *N*-Alkylated Oxopurines (*H*157) 110
   C. Replacement of 2-, 6-,and 8-Halogens by Amino Groups (*H*158) 111
      a. With One Halogen Atom (*H*158) 111
      b. With Two Halogen Atoms (*H*160) 113
      c. With Three Halogen Atoms (*H*162) 115
      d. With Halogeno-aminopurines (*H*163) 115
      e. With Chloro-oxopurines (*H*165) 115
      f. With Chloro-thioxo (and -methylthio) purines (*H*167) 116
   D. Replacement of 2-, 6-, and 8-Halogens by Hydrazino, Hydroxyamino, Azido, and Related Groups (*H*169) 117
   E. Replacement of 2-, 6-, and 8-Halogens by Alkoxy Groups (*H*171) 119
   F. Replacement of 2-, 6-, and 8-Halogens by Oxo Groups (*H*175) 120
      a. With Alkali (*H*175) 120
      b. With Acid (*H*177) 120
   G. Replacement of 2-, 6-, and 8-Halogens by Alkyl (or Aryl) thio Groups (*H*179) . . . 121
   H. Replacement of 2-, 6-, and 8-Halogens by Thioxo Groups (*H*181) 121

a. With Sulfides (*H*181) 121
b. With Thiourea (*H*183) 122
I. Replacement of Halogens by Sulfo and Thiocyanato Groups (*H*185) 122
J. Replacement of Halogens by Other Groups (*H*185) 123
6. Reactions with Extranuclear Halogen Atoms (*H*186) 124
A. Replacement by Amino Groups (*H*186) 125
B. Replacement by Hydroxy and Alkoxy Groups (*H*188) 127
C. Replacement by Other Groups (*H*189) 127
7. *N*-Alkylhalogenopurines (*H*191) 127
A. Preparation of *N*-Alkylated Halogenopurines (*H*191) 128
a. By Direct Synthesis (*H*191) 128
b. By Replacement of Groups by Halogens (*H*191) 128
c. By Alkylation (*H*192) 128

1. THE PREPARATION OF 2-, 6-, AND 8-HALOGENOPURINES (*H*135)

The established procedures, namely the Traube synthesis, using halogeno-4,5-diaminopyrimidines, together with the halogenation of thioxo-, methylthio-, and oxo-purines, remain the most widely used. There is, however, an increasing application of the displacement of amino groups by halogen through radical-initiated reactions. Such procedures have the advantages associated with the milder conditions employed and are therefore much favored in halogenopurine nucleoside syntheses.

A. Chloropurines by Cyclization of Chloro-4,5-diaminopyrimidines (*H*135)

Recent illustrations are found throughout Chapter II. Note also extensions of the reaction in which oxo-4,5-diaminopyrimidines with phosphoryl chloride undergo concomitant cyclization and halogenation to chloropurines. Examples of the formation of 2-chloro-[857] and 6-chloro-purines[856] using this method are available.

In the presence of dialkylamides (Vilsmeier reagent) ring closure is effected with phosphoryl choride, but chlorination of the oxo function is absent and only oxopurines result.[909] From a practical standpoint, a recent shorter preparation of 2-amino-6-chloropurine and 9-substituted analogs, based on a new facile synthesis of the 2,5-diamino-4,6-dichloropyrimidine precursors, is worthy of attention.[1861]

B. By Chlorination of Oxopurines (*H*135)

a. In Simple Purines

Only minor improvements have been introduced to the use of phosphoryl chloride-dialkylaniline and, to a lesser extent, thionyl chloride-dialkylamide

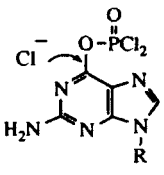
(Bosshard reagent), mixtures. Such modifications are usually adopted in the presence of other solvents.

b. In the presence of Amino Groups (H138)

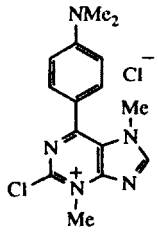
Established procedures[1108] for chlorination of 9-substituted guanines to 2-amino-6-chloropurine derivatives have been improved using a phosphoryl chloride–dimethylaniline mixture in acetonitrile and a much-reduced temperature (70°C)[1109] Investigation by ^{31}P NMR shows that the 6-chloropurine arises from chloride ion attack on the intermediate phosphorodichloridate (**1**, R = ribosyl triacetate).[1109]

d. In the Presence of N-Alkyl Groups (H139)

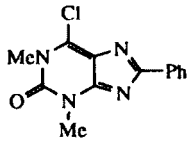
Mono-*N*-alkylated oxopurines show varied halogenation patterns. Whereas the 7- and 9-methyl derivatives undergo uncomplicated chlorinations with phosphoryl chloride–dimethylaniline or Bosshard reagent, no success is obtained with 2-, 6-, and 8-oxo-1-methylpurines. The 2-chloropurine, however, was formed in low yield from 3-methyl-2-oxopurine.[836] An unwanted feature common to many chlorinations of this type is removal of pyrimidine *N*-methyl groups, but this reaction is utilized advantageously in a number of preparations. A recognized route to 2,6-dichloro-7-methylpurine from phosphoryl chloride treatment of theobromine (*H*139), for example, is still in vogue.[1087,1110] In like manner, 8-chlorotheobromine is converted to 2,6,8-trichloro-7-methylpurine through loss of a methyl group at N-3.[1110] With phosphoryl chloride containing dimethylaniline, theobromine is partly transformed into 2,6-dichloro-7-methylpurine. Also formed is the 6-(4-dimethylaminophenyl)purine (**2**), in which the 3-methyl group remains intact. A further example showing the disparate effect of the two chlorinating agents is 8-phenyltheophylline, which with phosphoryl chloride in sulfolane (250°C) gives the highly reactive 6-chloro derivative (**3**) but if dimethylaniline is also present, the 6-(4-dimethylaminophenyl) analog (**4**) results.[1107] Halogenation using triethylamine or another aliphatic tertiary amine in place of the arylamine leads to improved yields of the dichloropurine, as exemplified in a conversion of 1,9-dimethylxanthine to 2,6-dichloro-9-methylpurine in 75% yield.[1112]



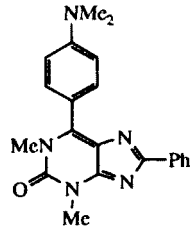
1



2



3



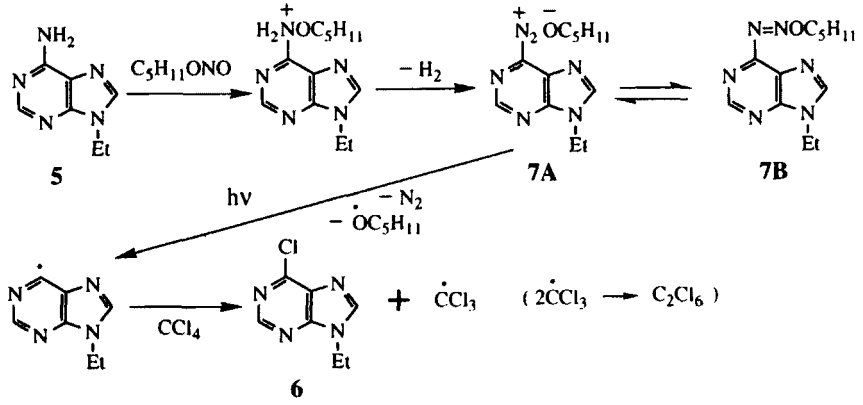
4

C. By Replacement of Thioxo or Methylthio Groups (*H*141)

Chlorination of 2-amino-6-thioxo- or 2-amino-6-methylthiopurine is the preferred route to the versatile intermediate 2-amino-6-chloropurine. The risk of explosion, due to buildup of methyl hypochlorite, associated with this preparation has now been overcome by carrying out the reaction in an acetonitrile solvent (at < 60°C) or in hydrochloric acid (at < 15°C). A less dangerous hazard, however, is present because the original procedure is carried out at ambient temperature, which allows decomposition of the hypochlorite to occur as it is formed.[1113] Similar examples using chlorine in acetonitrile include 2-amino-8-methyl-,[1130] 2-carboxymethylamino-,[1114] and 9-carboxymethyl-6-chloropurine from the 6-thioxo analogs. Partial replacement occurs in methanol of 2,6-bismethylthiopurine, giving only 6-chloro-2-methylthiopurine.[870]

D. By Other Means (*H*142)

In the parent volume the formation of chloropurines from their amino analogs is rarely encountered. However, this approach is now the route of choice for preparing many 2- and 6-chloro- and other halogeno-purines. As the reactions are a radical-initiated displacement type, the low temperature and other conditions required are well suited to purine nucleoside preparations, and these provide the majority of examples. Radical sources are varied; for example, a mixture of dichloromethane and pyridine hydrochloride or dichloroethane and antimony trichloride combined with *tert*-butyl nitrite converts the 9-(2′, 3′, 5′-tri-*O*-acetyl-ribosyl) derivatives of 2-amino-6-chloro- and 2-amino-6-fluoropurines to the 2-chloro analogs.[1115] More extensive application of this reaction utilizes tetrachloromethane containing isopentyl nitrite[1866] under reflux, also by means of pentyl nitrite and radiation (W-lamp) at ambient temperature, as illustrated in the transformation of 9-ethyladenine (**5**) into 6-chloro-9-ethylpurine[1094] (**6**). The pathway (Scheme 1) envisages an initial conversion of **5** to an equilibrium mixture of diazonium (**7A**) and azo (**7B**) derivatives which decompose on irradiation to the purinyl radical. Reaction of the latter with the haloalkane affords the product (**6**) together with the trichloromethyl radical, which undergoes self-association, producing hexachloroethane in detectable amounts.[1094] Related radical involvement occurs in the formation of 6-chloro-8-(thiazol-4-yl)purine from the analogous 6-hydrazinopurine by the established, but little exploited, route using iron(III) chloride.[870] Some 8-chloropurines have also arisen from radical reactions, as with a 9-substituted guanine using dry hydrogen chloride combined with *m*-chloroperbenzoic acid.[1100] The same reagent gives 8-chloroadenosine and -guanosine in either a dimethylformamide or hexamethylphosphoric triamide solvent.[1122] More forcing conditions (150°C) are employed in displacing a nitro group at C-8 of theophylline by chlorine, using 4-methylbenzensulfonyl chloride in dimethylformamide-pyridine. Some contamination of the 8-chlorotheo-

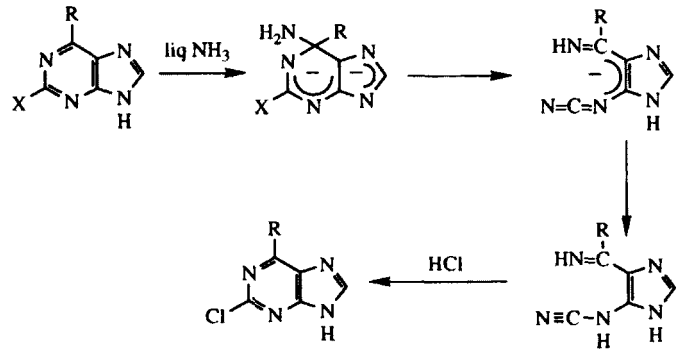


Scheme 1

phylline product (43%) by the 8-dimethylamino (24%) and the 8-pyridinium quaternary (18%) derivatives is found.[911] A novel route to 2-chloro and other 2-halogenopurines utilizes the ANRORC reaction with liquid ammonia and 2-substituted-purines as starting material. The ring-opened imidazole intermediates are ring closed to 2-chloropurines with hydrogen chloride (Scheme 2).[867] Rearrangement of either 3-acetoxyxanthine with methanesulfonyl chloride[1120] or 7-hydroxyxanthine[920] with sodium chloride to 8-chloroxanthine, and similarly 3-hydroxyguanine[1116] to the 8-chloro analog, are treated in more detail in Chapter XI, Section 3.C.

E. Preparation of 2-, 6-, and 8-Bromopurines (*H*143)

The acetylated ribosides of 2-amino-6-fluoro- and 2-amino-6-chloropurine afford the respective 2-bromo-6-fluoro[1115] and 2-bromo-6-chloro[1115,1117] analogs on treatment with antimony tribromide in either dibromomethane containing



Scheme 2

tert-butyl nitrite or tribromomethane with *n*-pentyl nitrite.[1863] Radical conditions are also applied in the conversion of 6-amino- to 6-bromo-9-ethylpurine upon irradiation (W-lamp) in tribromomethane containing *n*-pentyl nitrite.[1094] An example of a thioxo to bromo transformation occurs on treating the potassium salt of 2-thioxoinosine with bromine in hydrobromic acid (0°C, 2 h).[1229] Hydrobromic acid reacts with the ring-opened derivatives obtained from the ANRORC reaction on 2-substituted purines to give 2-bromopurines[867] (see Section 1.D). Direct bromination is still widely used for many 8-bromopurines; recent examples include some 9-alkylguanines,[1100] including 9-benzylguanine.[1118] The more unorthodox route to 8-bromoxanthine by rearrangement of 3-acetoxyxanthine in the presence of bromide ion[1116] is detailed elsewhere (Chapter XI, Section 3.C).

F. Preparation of 2-, 6-, and 8-Iodopurines (*H*143)

Radical reaction conditions, paralleling those used for chloro- and bromopurine preparations, are adopted in forming 2-iodo-[1095,1863] and 6-iodopurines[1066,1094] from the corresponding 2- and 6-amino analogs. A typical example of the long-established procedure for halogen metathesis is seen in the conversion of 9-benzyl-6-chloropurine to the 6-iodo derivative by cold strong hydroiodic acid[1119] (55%). In this context, a point of interest is the reinvestigation of the action of a hydriodic acid–phosphonium iodide mixture on 2,6-dichloro-7-methylpurine.[1120] The product, claimed by Fischer to be 2-iodo-7-methylpurine (*H*144), is found to be 2-chloro-6-iodo-7-methylpurine. Some 2-iodopurines have resulted from hydriodic acid treatment on the ANRORC reaction products from 2-substituted purines.[867] Direct iodination at C-8 using iodine chloride in methanol[1121] converted a 9-alkylated guanine into the 8-iodo derivative[1100] when use of *N*-iodosuccinimide had failed to accomplish this. The established route to 8-iodopurines by displacement of an 8-thioxo group with iodine in sodium hydrogen carbonate solution is effective in forming 8-iodoisoguanine.[885] An attempt to rearrange 3-acetoxyxanthine to 8-iodoxanthine using iodide ion failed; reduction occurred, giving xanthine, which contrasted with successful 8-halogenations achieved when chloride or bromide ion was employed (see Section 1.D and 1.E). Diazotization of 8-iodoguanine with nitrite ion in trifluoroacetic acid provides a route to 8-iodoxanthine.[1351] A derivative of 8-iodoadenosine results from interaction between 8-lithioadenosine and iodine.[1862]

G. Preparation of 2-, 6-, and 8-Fluoropurines (*H*144)

Amino- and chloropurines are still the usual precursors, the former mainly for the syntheses of 2-fluoro derivatives (although some application to the 6-fluoro analogs is known), whereas the latter are confined to use in 6-fluoropurine preparations. A variety of approaches is available for preparing 8-fluoropurines.

b. By Replacement of Chlorine or Other Halogen Atoms (H144)

A prerequisite is initial quaternization of 6-chloropurine with trimethylamine to the 6-trimethylamino derivative, either as the betaine or salt. Displacement by the fluoride ion is effected in ethanol, acetonitrile, or dimethylformamide; the best results are achieved in aprotic solvents, owing to the weak electrophilic nature and tendency to solvation of this ion. Using potassium fluoride or potassium hydrogen fluoride as ion source, products include 6-fluoro-,[1122] 6-fluoro-9-methyl-,[1122,1140] 2-amino-6-fluoro-,[1122] 2-chloro-6-fluoro-,[1122] and 2-chloro-6-fluoro-7-methylpurine[1122] from the appropriate 6-chloro analogs. Catalytic hydrogenation of the last purine affords 6-fluoro-7-methylpurine.[1122] Failure to displace the quaternary group at C-6 from either the 2-chloro- or 2,8-dichloropurine possibly reflects the more acid character of these derivatives, which hinders the prior protonation step necessary for displacement to occur. An advantage of this method is that unprotected ribosyl groups present are not affected, as seen in the formation of the 9-ribosides of 6-fluoro-[1122] and 2-amino-6-fluoropurine.[1109] The latter derivative arises (93%) on treating the 6-chloropurine riboside with a catalytic amount of trimethylamine* and an excess of potassium fluoride in dimethylformamide at room temperature.[1109] Direct interchange of halogen takes place when the acetylated riboside of 6-amino-8-bromopurine reacts with potassium fluoride in acetonitrile containing 18-crown-6-ether (1,4,7,10,13,16-hexaoxacyclooctodecane) under pressure (120°C, 48 h), giving some 6-amino-8-fluoro derivative (25%).[1123] This success sharply contrast with the failure of earlier halogen interchanges of this type employing metal fluorides.[1361]

c. By Replacement of Amino Groups (H145)

The Schiemann reaction involving sodium nitrite and fluoroboric acid treatment remains the favored method for 2-fluoropurine syntheses. Displacement of a 6-amino group by fluorine under these conditions is, however, sometimes encountered. Recent examples of 2-aminopurine conversions include 2-fluoro-,[867] 2-fluoro-9-methyl-,[999] and 6-chloro-2-fluoropurine[1124] as well as the protected (acetylated) riboside of the latter dihalogenopurine.[1115] The analogous riboside of 2,6-diaminopurine gives only a low yield (17%) of 2-fluoro-adenosine admixed with some isoguanosine (6%) formed by a competitive *C*-2-hydroxylation.[1125] This result is surprising in view of one reported using the protected 5′-deoxyriboside of the same purine in which both 6-amino-2-fluoro (19%) and 2,6-difluoro (30%) derivatives were obtained.[1126] Diazotization under nonaqueous conditions is made with 60% hydrofluoric acid in pyridine containing *tert*-butyl nitrite. By this means the 2-aminopurine ribosides converted to the corresponding 2-fluoro

*If an excess of trimethylamine is employed, 6-dimethylaminopurine riboside is produced even when ambient temperatures[1109] are used.

analogs include 6-amino-2-fluoro-[1115] (48%), 2,6-difluoro-,[1115] (63%), and 6-chloro-2-fluoropurine.[1115] Other examples are available.[1127]

d. By Other Means (New)

Replacement of a 8-nitro group occurs on heating (100°C, 16 h) the purine in liquid hydrogen fluoride under pressure. Both 8-fluoro-theophylline (55%) and -caffeine (62%) are so obtained.[1128] The rearrangement of 3-oxidopurines with fluoride ion to 8-fluoropurines is not possible, owing to the competition from water acting as a stronger nucleophile, as illustrated by the isolation of uric acid formed by preferential 8-hydroxylation following fluoride ion treatment of 3-hydroxyxanthine.[1116]

2. PREPARATION OF 8-HALOGENOPURINES BY DIRECT HALOGENATION (*H*146)

Some details relevant to this procedure are given in the sections dealing with general halogenations (Sections 1.D, 1.E and 1.F). Also pertinent to direct halogenation is the rearrangement of 3-oxidopurines in the presence of halogen ions (see Chapter XI, Section 3.C). Under reflux conditions, the expected 8-chloro derivative (*H*146) does not result when caffeine and tetrachloromethane in nitrobenzene interact; the product mixture contains both 8-chloro-3,7-bis(chloromethyl)-1-methyl- and 8-chloro-1,3,7-tris(chloromethyl)-xanthine through concomitant *N*-methyl halogenation[1130] taking place. Radical reactions are becoming increasingly important since they are employed in the formation of 8-chloro-adenine[1100,1129] and various -guanine[1129] analogs using *m*-chloroperbenzoic acid in an aprotic solvents. Although this procedure is suitable for 8-bromo derivatives,[1129] the older direct bromination methods are more facile, for example, with *N*-bromosuccinimide in DMF.[1864] Other halogenating reagents include iodine chloride in methanol, which with 9-alkyladenines gives the 8-iodopurines,[1121] while adenosine in DMF (20°C, 24 h) is converted to the 8-chloro derivative (38%) by tetra-*n*-butylammonium iodotetrachloride (n-Bu_4NICl_4).[1508] The same 8-chloropurine nucleoside obtains with *tert*-butyl hypochlorite (Me_3COCl) in DMF; analogous halogenations with the 6-methylamino- and 6-dimethylaminopurine nucleosides are also possible with the reagent.[1997]

3. PREPARATION OF EXTRANUCLEAR HALOGENOPURINES (*H*148)

Continuing interest in both *C*-halogenoalkyl and *N*-halogenoalkyl derivatives is due largely to their function as intermediates in a variety of reactions. Special attention, however, has been accorded to the trifluoromethyl group which,

although generally chemically inert, has relevance to studies of reactions in biological systems because of similarity in size to that of the methyl group.

A. By Direct Halogenation (*H*148)

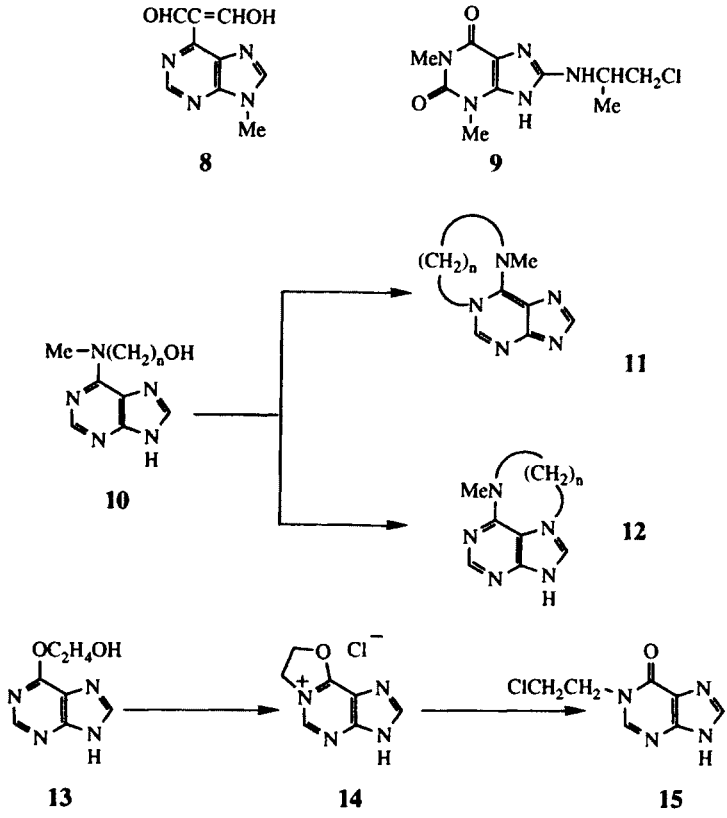
Chlorination with sulfuryl chloride in trifluoroacetic acid at 60°C converts 6,7-dimethyl-[1084] and 6,9-dimethylpurine[1083] to the corresponding 6-trichloromethyl derivatives. Use of the same reagent mixture on 6-methyl-1-oxidopurine gives 6-carboxy-1-oxidopurine through hydrolysis of the initially formed 6-trichloromethyl derivative.[1080] Although *N*-bromosuccinimide in the same acid (*H*127) converts 6-methylpurine to the dibromo- and tribromomethyl analogs, this treatment with the 1- and 3-oxides of the purine affords only the respective 6-monobromomethylpurine-*N*-oxides.[1080] An indirect conversion of a methyl group resulting in the formation of 9-methyl-6-tribromomethylpurine follows bromination of the malonaldehyde derivative (**8**), the latter arising from treatment of 6,9-dimethylpurine with Vilsmeier reagent.[791] A failure to halogenate 8-methyladenine is recorded.[790]

B. From Hydroxyalkylpurines (*H*149)

The facile halogenation of hydroxyalkyl groups is well documented, with numerous examples available from past and current work. A typical case is the thionyl chloride conversion of 2-(theophyllin-8-yl) amino-*n*-butanol to the chloro analog (**9**).[1132] Some caution is required if the hydroxyalkyl chain length exceeds three atoms since ring formation through endoalkylation involving an adjacent ring nitrogen is possible following halogenation. Exemplifying this are purines of the type (**10**, $n = 2$, 3, or 4) which cyclize to the tricyclic derivatives (**11**, $n = 2$ and 3) or (**12**, $n = 4$) either spontaneously or on standing following thionyl chloride tratment.[1141] From an attempted chlorination with this reagent under reflux conditions of the 6-(2-hydroxyethyl)aminopurine (**13**) the cyclized transient oxazolopurine (**14**) initially formed then ring opens to 1-(2-chloroethyl) hypoxanthine (**15**).[1133]

C. From Halogenopurines (H150)

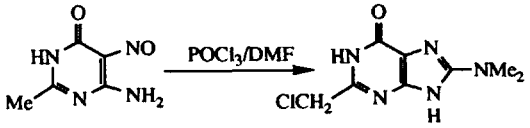
Trifluoromethyl groups displacing halogens at C-6 and C-8 is reported with purine nucleosides under mild conditions (ambient temp., 12 h) using a trifluoromethyl–copper complex. Purine bases reacted in this way include 6-chloropurine, 8-bromohypoxanthine, and 8-iodoadenine, forming the appropriate 6- or 8-trifluoromethyl derivative in reasonable (~ 40%) yield.[1134] Use of trifluoromethyl iodide and copper powder in hexamethylphosphorous triamide in place of the complex failed with 8-iodoadenosine—only the iodine at C-8 was removed.[1134] The condensation of compounds containing active methylene



groups to form purine precursors of 6-halogenoalkyl derivative has been noted (Chapter IV, Section 2.A.d).

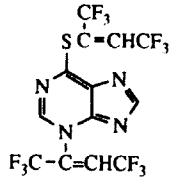
D. By Synthesis (*H*150)

The reactivity of halogenoalkyl groups renders them generally unsuitable substituents to be present during synthetic procedures. An exception is the trifluoromethyl group, which remains intact under these conditions, for which examples have been noted, see Chapter 2, Sections 1.D and 1.E. An example of inadvertent chloroalkylpurine formation occurs in the ring closure of 4-amino-2-methyl-5-nitroso-6-oxopyrimidine (**16**) with phosphoryl chloride–dimethylformamide, the product being the 2-chloromethylpurine[909,910] (**17**).



16 17

Some routes to *N*-halogenoalkylpurines from the *N*-hydroxyalkyl derivatives parallel those used for the *C*-halogenoalkylpurines. Direct *N*-alkylation with α,ω-halogenoalkanes provides an alternative approach, although the possibility of interpurine linking requires a careful controlling of the reactant ratios employed. Representative derivatives are 6-chloro-9-(2-chloroethyl)- and 6-chloro-9-(3-chloropropyl)-purines from reactions of 6-chloropurine with 1-bromo-2-chloroethane and the corresponding 1,3-dihalogenopropane in dimethylformamide containing potassium carbonate.[1138] A variation using epichlorohydrin for alkylation of adenine gives the 9-(3-hydroxyprop-2-yl) derivative.[1139] Somewhat akin to a Michael reaction is formation of the 3-alkenyl-derivative (**18**) as one of the products obtained from 6-mercaptopurine and hexafluorobut-2-yne ($CF_3C{:}CCF_3$) in which the sulfur moiety also reacts. Some of the 7- (or 9-) alkenyl isomer is also present, but the ultimate composition of the product mixture is determined by the solvent medium employed.[1375]



18

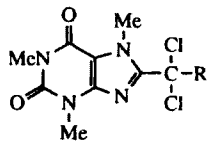
E. By Other Means (*H*151)

Bromotrichloromethane in the presence of di-*tert*-butylperoxide transforms caffeine into a mixture of 8-trichloromethyl (**19**, R = Cl) and 8-pentachloroethyl (**19**, R = CCl_3) derivatives.[1135] Available evidence indicates that formation of the latter occurs by a trichloromethyl radical addition to the former rather than from a direct pentachloroethyl radical attack on caffeine.[1135] The minor product (**20**) isolated is notable in that it is related to an oxidation transformation product of uric acid[1136,1137] (Chapter VI, Section 9.A.a).

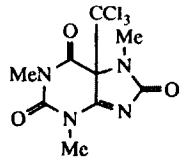
5. REACTIONS OF 2-, 6-, AND 8-HALOGENOPURINES (*H*152)

B. Removal of Halogen Atoms (*H*154)

Catalytic hydrogenation with a palladium–carbon catalyst is still the most widely favored for removal of chlorine. Dehalogenation of bromo- and iodop-



19



20

urines on the other hand has been effected with either conventional reagents or the more recently introduced organometallic derivatives.

a. In the Presence of Only Alkyl Groups (H154)

Examples of simple chlorine removal by hydrogen over palladium include 9-methylpurine from the 6-chloro derivative[1090] and the 7-methyl isomer from 2,6-dichloro-7-methylpurine.[1090] An improved synthesis of the latter is claimed if barium hydroxide is present.[1087] The inert nature of fluorine under these conditions is shown by the preparation of 6-fluoro- and 6-fluoro-7-methylpurine from the respective 2-chloropurines.[1022] Hydrogenolysis surprisingly fails to dehalogenate a 9-alkoxyalkyl-6-chloropurine, but the chlorine is removed by Seela's method[1143] with boron trichloride in dichloromethane at low temperature (−78°C, 3 h).[1127] The selectivity of hydrogenation in dehalogenation is demonstrated by the results of sodium borohydride reductions of 2,6-dichloro-7-methyl-[1145] and 6-chloro-7,9-dimethylpurine [1144] (as perchlorate salts); imidazole ring reduction occurs, leaving the halogens intact. The latter purine does, however, undergo electrochemical reduction to the 7,9-dimethylpurine salt[1144] (see Chapter XII, Section 1.A.c). An attempted ANRORC rearrangement of 2-chloro-6-methylpurine with potassium amide in liquid ammonia failed, but some 6-methylpurine (10%) was isolated from the starting material.[867] Butyllithium treatment of 6-iodo-9-tetrahydropyranylpurine at low temperature results in iodine removal and concomitant metalation to 8-lithio-9-tetrahydropyranylpurine.[1093]

b. In the Presence of Amino Groups (H155)

Hydrogenolysis still provides examples of efficient conversion of aminochloro- to aminopurines. Removal of one or two halogens is shown in the formation of 9-benzyl-6-dimethylaminopurine from the 2-chloro derivative,[1149] 9-phenyl-6-dimethylaminopurine using the 8-chloro analog,[1146] and both 6-dimethylamino-3-methyl and the 9-methyl isomer from the 2,8-dichloropurine precursors.[1147] More esoteric dehalogenations occur with potassium amide in liquid ammonia, as in the conversion of 2-chloro-9-methyl- to 9-methyladenine.[1091,1092] Prolonged treatment, however, may result in deamination.[1092] Two novel halogen displacements from C-8 are the formation of adenosine (44%) from either the 8-bromo analog, by means of a mixed reagent comprising *N,O*- bistrimethylsilylacetamide, potassium fluoride, and dicyclohexyl-18-crown-6-ether in acetonitrile[1148] (100°C, 18 h), or by the action of trifluoromethyl iodide and copper powder in hexamethylphosphoric triamide (100°C, 40 h) on 8-iodoadenosine.[1093]

c. From N-Alkylated Oxopurines (H157)

The conventional method using hydriodic acid under reflux is employed to prepare 1-methylxanthine from the 8-chloro analog.[1130]

C. Replacement of 2-, 6-, and 8-Halogens by Amino Groups (*H*158)

This still remains the most widely used route for aminopurine preparations.

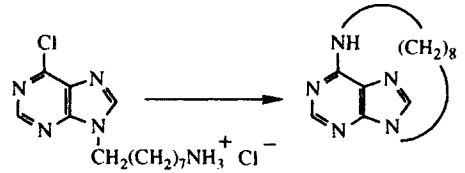
a. With One Halogen Atom (H158)

Increasing use of liquid ammonia in closed vessels is being made to replace a halogen by an amino group—a 2-chloro-9-substituted-hypoxanthine is converted (150°C, 5 h) to the guanine analog[1214] and several 9-benzyladenines are prepared (45°C, 21 h) in this way from the 6-chloropurines.[1210] Although formation of 2-aminopurine from either the 2-chloro or 2-fluoro derivative by means of potassium amide in liquid ammonia (20–70 h) appears to be a similiar type of substitution, use of a ^{15}N-labeled amide shows a more complex reaction of the ANRORC type is involved.[867] Isolation of 2-dimethylaminopurine rather than the quaternary salt (see below) follows treatment of 2-chloropurine with trimethylamine in acetone (100°C, 4.5 h). The vigorous conditions reflect the relative inactivity of the halogen at this position and preclude the presence of any quaternized product.[1150] By contrast, the 9-methyl homolog shows halogen activation through alkylation at N-9 in yielding the quaternary form in benzene (50°C, 24 h) under mild conditions, but at a higher temperature (150°C, 2 h) affords 2-dimethylamino-9-methylpurine[1150] directly. Piperidine, as both reagent and solvent, converts 2-chloro- to 2-piperidino-6,8,9-trimethylpurine[848] on prolonged (110°C, 30 h) heating. The condensation of 2-fluoro- and 2-fluoro-6-methylpurine with glycine requires several hours in aqueous potassium carbonate for conversion to the 2-carboxymethylaminopurines.[1114]

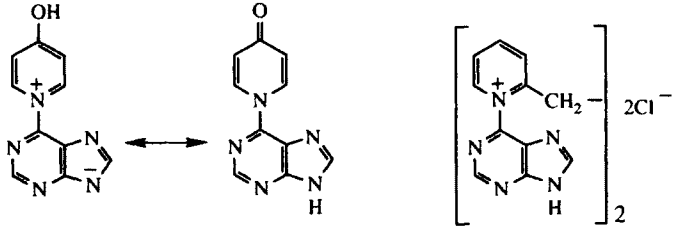
Analogs of adenine, prepared from 6-chloropurines and ammonia or amines, provide the most frequently encountered examples. The near quantitative yield of adenine obtained from 6-chloropurine with four equivalents of potassium amide in liquid ammonia (−30°C, 20 h),[1155] with formation of the same purine using ammonia in *n*-butanol (150°C, 10 h) as previously reported (*H*158), is worthy of comparison.

A much faster adenine preparation utilizes 6-fluoropurine and aqueous ammonia (100°C, 1 h), but ethanolic ammonia provides a slower (20°C, 10 days) approach.[1122] Sealed-tube conditions (100°C, 24 h) are needed to convert 6-chloro-3-oxidopurine to the adenine analog, but much milder treatment (25°C, 4 days) in 40% aqueous dimethylamine gives the 6-dimethylamino homolog.[1142] Some examples of the diversity of amines reacted with 6-chloropurine are numerous hydroxyalkylamines in ethoxyethanol or *n*-butanol[1151] (120°C, 3 h), *l*-amphetamine in ethanol (78°C, 72 h) affording the (*R*)-isomer[1153], 7-aminomethylbenz[*a*]anthracene in dimethylsulfoxide (90°C, 2 days),[1154] and the plant growth factor zeatin (see adenine monograph in Chapter VIII, Section 9.A) formed using 4-hydroxy-3-methylbut-2-enylamine in butanol (reflux, 2 h) containing triethylamine.[1204,1205] The trans form of this amine is employed to synthesize the biologically active (*E*)-6-(4-hydroxy-3-but-2-enylamino)purine.[1206,1207]

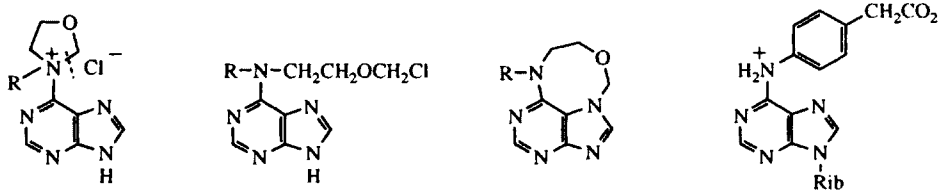
Reaction with an excess of 2-diethylaminoethylamine as solvent occurs under reflux conditions[857] and new preparations of α,ω-bis(purin-6-ylamino)alkanes employing suitable aliquots of 1,2-diaminoethane[1138] and 1,3-diaminopropane are reported.[1101] The unusual cyclic adenine derivative (**22**) results from intramolecular amination on heating (MeCN, 12 h) 6-chloro-9-(8-aminooctamethylene)purine hydrochloride[1867] (**21**). With tertiary amines in *n*-butanol, the corresponding quaternary derivative is given by trimethylamine, one equivalent in ethoxymethanol produces the betaine (Alpurine[36]) directly.[1147] The same reaction with 3-oxido-6-chloropurine gives a mixture of the 6-trimethylammonio- (61%) and 6-dimethylamino-oxidopurines (12%).[1142] Among other amines used are *N*-methylpiperidine, 2-hydroxyethyldimethylamine, and pyridine.[1156] Products with either betaine (**23**) or quinonoid (**24**) forms are possible using pyridines having a tautomeric group at the 4-position.[1156] The bispurinyl derivative (**25**) is also known.[1156] Various *N*-alkyloxazolidines with 6-chloropurines give rise to unstable quaternary chlorides (**26**, R = alkyl) undergoing spontaneous ring fission with rearrangement to **27**. Neither intermediate is isolated and the tricyclic final product (**28**) is the result of a subsequent endoalkylation.[1141] Corresponding sulfur analogs using thiazolidines are given.[1141] With *N*-methyloxazolidine the end product is 7,8-dihydro-8-methyl-6*H*-[1,3,6]oxadiazocine[3,4,5-*g*,*h*]purine (**28**, R = Me).[1141] A novel route affording quaternized derivatives from oxopurines



21 **22**



23 **24** **25**



26 **27** **28** **29**

directly utilizes chlorination of hypoxanthines with 4-chlorophenylphosphorodichloridate in pyridine, representative products being *N*-purin-6-ylpyridinium chloride[1157,1306] and the 9-methyl homolog.[1274] Selected examples of 9-substituted adenines from the 6-chloropurines and aqueous or alcoholic ammonia include the 9-vinyl- (MeOH; 60°C, 48 h),[1158] 9-benzyl-,[862] 9-(1,3-dihydroxypropyl)- (65°C, 2 h)[865] 9-(1,4-dihydroxybutyl) (65°C, 22 h),[865] 9-(hydroxyethoxymethyl)-,[1159] and erythro and threo forms of a number of 9-(hydroxyalkyl)adenines.[1211,1212] Homologous derivatives are also found.[1159,1160] Halogen reactivity may allow competing substitution reactions to participate. Ethanolic ammonia with the 9-deoxyarabinoside of 6-chloropurine (80°C, 20 h), for example, gives not only the expected adenine deoxyarabinoside (67%) but also some 6-ethoxypurine nucleoside (11%).[1161] Heating in aqueous ammonia was the preferred route to 9-(1-ethoxyethyl)adenine.[842] With sealed-vessel conditions and moderate temperatures (45°C, 21 h), liquid ammonia alone converts 6-chloro-9-(3-hydroxymethylbenzyl)- and the 9-(3-cyanobenzyl) and 9-(4-cyanobenzyl) analogs to the adenine derivatives.[1210] The use of liquid ammonia–potassium amide with 6-chloropurine itself produces adenine in 96% yield (see above), but this contrasts with the poor yield (6%) of 9-methyladenine when 6-chloro-9-methylpurine is treated likewise. The formation of an equal amount of 6-chloro-7,8-dihydro-9-methyl-8-oxopurine[875] during this reaction is noteworthy. Amination of 6-chloro-*N*-alkylpurines is reported with methylamine,[862,863,1162] dimethylamine,[862,1149,1150,1162,1163] ethylamine,[1158,1162,1163] diethylamine,[1162] *n*-propylamine,[1162] *tert*-butylamine,[1162] benzylamine,[1160] hydroxyethylamine,[862] piperidine,[785] aniline,[862] and others; most reactions take place in alcoholic solution under reflux. The riboside of 6-chloropurine with 4-aminophenylacetic acid in the presence of triethylamine gives the 6-arylaminopurine (**29**).[1197] Heating with dimethylamine in acetonitrile is needed to convert the perchlorate salt of 6-chloro-7,9-dimethylpurine to the 6-dimethylamino analog.[1164]

Quaternization of 6-chloro-9-methylpurine is facile with trimethylamine in benzene (25°C, 24 h) or other aprotic solvent;[1150] however, under aqueous conditions 6-chloro-9-vinylpurine forms no quaternary derivative, but through alkaline hydrolysis 9-vinylhypoxanthine[1158] is obtained instead.

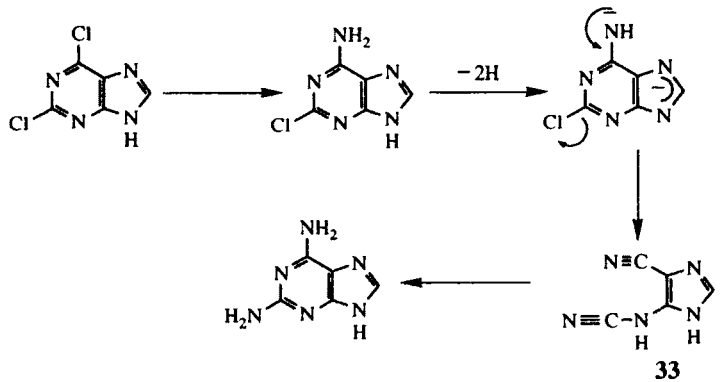
Pressure conditions are needed for dimethylamination of 8-chloropurine (100°C, 3 h), although a shorter heating period (100°C, 0.5 h) suffices for the more reactive 8-chloro-9-methyl homolog.[1150] Quaternization of 8-chloropurine occurs readily with trimethylamine in acetone (25°C, 24 h). Only 8-dimethylamino-9-methylpurine results from this treatment on 8-chloro-9-methylpurine;[1150] failure to form a quaternary chloride is attributed to steric inhibition.[1150]

b. With Two Halogen Atoms (H160)

Further demonstrations of the enhanced activity of a halogen at C-6 compared with that located at either C-2 or C-8 are given by dichloro-, dibromo-, and mixed dihalogenopurines. Only the 6-aminopurine results under nonforcing conditions

(< 100°C) from 9-benzyl-2,6-dichloropurine with dimethylamine,[1149] from various 6,8-dichloro-9-arylpurines and methylamine,[1146] and following ethanolic ammonia treatment of 2,6-dibromopurine.[1117] Amination of mixed dihalogeno derivatives is exemplified by formation of 6-amino-2-bromopurine deoxyriboside from the 2-bromo-6-chloro analog using ethanolic ammonia[1117] and 2-fluoroadenine from 6-chloro-2-fluoropurine (100°C, 3 h).[1124] In contrast to these conditions, leaving the isomeric 2-chloro-6-fluoropurine in methanolic ammonia (0°C, 76 h) yields 2-chloroadenine.[1122] Extending the heating times when using these purines leads to replacement of both halogens—examples include formation of 2,6-diaminopurine and the 9-methyl homolog from 6-chloro-2-fluoro-[1124] and 2,6-dichloro-9-methylpurine[1092] respectively. Both 2-fluoro-6-methylamino- and 2,6-bismethylaminopurine are similarly obtained from 6-chloro-2-fluoropurines.[1124]

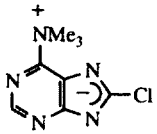
Equivalent amounts of trimethylamine and 2,6-dichloropurine give 2-chloro-6-trimethylammoniopurine chloride, but with the amine in excess the betaine form results. The isomeric 8-chloro betaine (**30**) from 6,8-dichloropurine is similarly formed.[1147] On reducing the amine used to one equivalent, only the trimethylammonium salt (**31**) of the starting material is isolated through a preferential involvement with the acidic proton at N-9 in the purine.[1147] With 6-chloro-2-fluoropurine this amination gives a mixture of 2-fluoro-6-trimethylammoniopurine betaine and 6-dimethylamino-2-fluoropurine.[1124] A detailed study of the action of potassium amide in liquid ammonia on 2,6-dichloropurine is reported using ^{15}N-labeling. Low yields of 6-amino-2-chloro-(12%) and 2,6-diaminopurine (13%) are obtained. It should be noted that the former product arises from a simple nucleophilic substitution of the halogen at C-6, whereas the latter is formed by a complex reaction pathway involving among others removal of the halogen at C-2 and subsequent ring opening to an imidazole and recyclization to 2,6-diaminopurine (Scheme 3).[999]



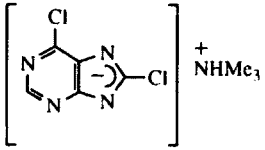
Scheme 3

c. With Three Halogen Atoms (H162)

Triethylamine in excess converts 2,6,8-trichloropurine to the 2,8-dichloropurine betaine (**32**). As with 6,8-dichloropurine, no quaternary salt forms on limiting the amine—the product is the trimethylammonium salt derived from interaction at N-9 with the acidic[1147] proton.



30



31



32

d. With Halogeno-aminopurines (H163)

Conversion of 6-amino-2-chloropurine to 2,6-diaminopurine is effected through potassium amide in liquid ammonia treatment. Although an apparent case of nucleophile substitution of halogen is involved, an investigation shows that the reaction at one stage includes ring opening to a 5-cyano-4-cyanoaminoimidazole intermediate[999] (**33**). The acetylated riboside of the aminochloropurine discussed above with trimethylamine or in acetonitrile gives the 6-amino-2-dimethylaminopurine derivative; the conditions used preclude any quaternary group formation.[1109]

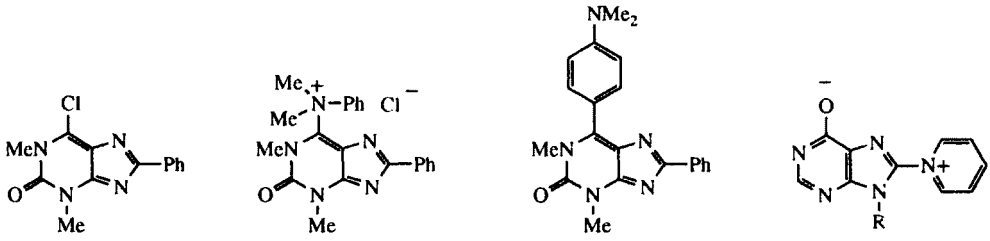
Aminations of 2-amino-6-chloropurine are usually more facile. Hot methanolic ammonia, however, does not afford 2,6-diaminopurine, but this compound is obtained (reflux, 1.5 h) using the more reactive 2-amino-6-fluoropurine.[1122] Other amines used with the chloropurine include diphenylmethylamine in *n*-butanol (reflux, 150 h)[864] and 4-nitroaniline in ethanol (reflux, 18 h).[1165] Surprisingly, at room temperature, trimethylamine with the triacylated riboside of the purine above gives no quaternary product but only the 6-dimethylamino derivative.[1109] The 3-oxide of 2-amino-6-chloropurine requires extensive heating (100°C, 12 h) in aqueous ammonia to form the corresponding 2,6-diamino derivative.[1166]

The reaction of potassium amide in liquid ammonia on 2-amino-6-chloropurine, also studied in some detail,[999] proceeds through involvement of a common intermediate imidazole (**33**) when both this purine and the isomeric 6-amino-2-chloro derivative undergo transformation into 2,6-diaminopurine.[999]

e. With Chloro-oxopurines (H165)

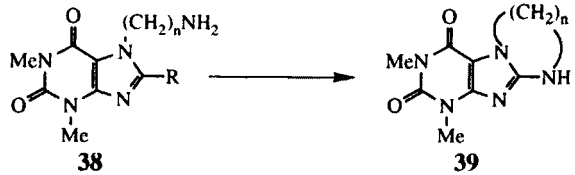
The majority of reactions covered in this section involve 8-halogeno-*N*-alkylxanthine derivatives, but examples of aminations at C-2 and C-6 halogens are also noted. Heating 2-chlorohypoxanthine in benzylamine (120°C, 2 h) affords the 2-

benzylaminopurine.[1444] Aniline and various derivatives react with 2-bromohypoxanthine in 2-methoxyethanol[1167,1168] (reflux, 2.5 h). Both alicyclic and aromatic amines react readily with the unstable 6-chloropurine (**34**)[1107] giving 6-morpholino, 6-piperidino, and 6-aniline derivatives. Dimethylaniline, however, does not give the expected quaternary salt (**35**), but rather the 6-(4-dimethylaminophenyl)purine (**36**),* which results from an electrophilic attack at C-6 by the phenyl cations[1107] generated.



34 **35** **36** **37**

Replacement of 8-halogens is exemplified by the reaction between 8-bromotheophylline and 2-aminobutanol[1132] or piperazine or its *N*-alkylated homologs.[1169] Methyl- and dimethylamine are similarly reacted with the analogous 3-isobutyl-1-methylxanthine derivative.[830] Dimethylformamide also functions as a dimethylaminating agent,[1170] as demonstrated by the metathesis of 8-chloro- to 8-dimethylamino-theophylline on heating the former in the amide.[910] A novel route to the inosine betaine (**37**, R = 2,3,5-tri-*O*-benzoylribosyl) from the corresponding 8-bromoinosine utilizes a mixed reagent of pyridine and nitrosyl chloride in a dimethylformamide solvent.[1171] Aminoalkyl side chains may condense with nuclear halogens forming tricyclic derivatives. The examples shown (**39**, *n* = 2, 3, or 4) are obtained from the appropriate 7-aminoalkyl-8-halogenotheophyllines (**38**, R=Cl or Br) on heating in aqueous sodium hydroxide or triethylamine in benzene.[1199]



38 **39**

f. With Chloro-thioxo (and -methylthio) purines (H167)

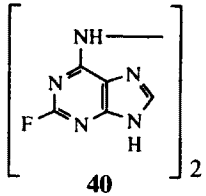
Prolonged heating is required (100°C, 24 h) to convert 2-chloro-6-thioxopurine to the 2-carboxymethylamino derivative using glycine in aqueous potassium carbonate. By contrast, both the 2-fluoro analog of the starting material and

*Formation of similar derivatives has been reported[1107,1110] following chlorination of *N*-alkyl-6-oxopurines with a phosphoryl chloride–dimethylaniline mixture.

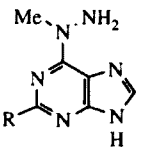
2-fluoro-6-methylthiopurine condense much faster (3 h) with the same amino acid under this treatment.[1114]

D. Replacement of 2-, 6-, and 8-Halogens by Hydrazino, Hydroxyamino, Azido, and Related Groups (*H*169)

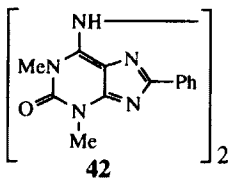
Exemplifying 2-halogen replacement is formation of 2-hydrazinoinosine from hydrazine hydrate treatment (130°C, 3 h) of the 2-bromo nucleoside.[1229] The same reagent at room temperature transforms 6-chloro-9-vinylpurine into the 6-hydrazino analog,[1163] but reflux conditions are used to convert 6-chloropurine to 6-(*N*-amino)methylaminopurine by interaction with ethanolic methylhydrazine.[1172] More reactivity is shown by the halogen in 6-chloro-3-oxidopurine in forming the product with the same reagent at room temperature.[1172] The attempted hydrazination of an 8-bromoadenine derivative involving prolonged heating (48 h) resulted in formation of the corresponding 6,8-diaminopurine.[1100] Similar aminations resulted from hydrazination attempts with 8-halogenopurines are recorded (*H*169). Successful conversions of 8-bromoisoguanosine derivatives to 8-hydrazino analogs (100°C, 2.5 h) are not[995] however unknown (*H*169). Use of sealed-vessel conditions affords 8-(*N*-aminomethylamino)adenosine with the 8-bromopurine and methanolic methylhydrazine.[1173] Cooler conditions suffice (5°C, 1 h) to obtain 6-hydrazino-2-fluoropurine from 6-chloro-2-fluoropurine and ethanolic hydrazine.[1124] A bispurinyl derivative (**40**) arises if the purine is in excess, but on hydrogenation (Raney Ni) is reduced to 2-fluoroadenine.[1124] The dihalogenopurine above in ethanolic methylhydrazine at 50°C gives the 6-(*N*-aminomethylamino)purine (**41**, R = F), but under reflux conditions both halogens are replaced, giving **41** [R = $N(NH_2)Me$].[1172] The highly reactive 6-chloro derivative, from chlorination of 8-phenyltheophylline, is reported to give the bis compound (**42**) with hydrazine.[1107]



40



41



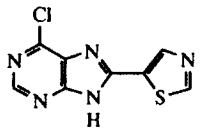
42

Largely as a result of studies of metabolic hydroxylation of amines,[1174,1175] interest in hydroxyaminopurines has grown over the last few years. This has led to the preparation of quite diverse derivatives, usually from halogenopurine precursors.

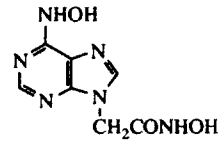
Fairly rigorous treatment (reflux, 10 h) is required with ethanolic hydroxylamine to convert 2-fluoro- to 2-hydroxyaminopurine.[1124] Some difficulty* is

*From a practical standpoint, it is worth noting that the corresponding 6-methylsulfonyl-8-thiazolylpurine reacts more readily with hydroxylamine.[870] This is a further example where the methylsulfonyl group may be superior to a halogen for this type of nucleophilic displacement.

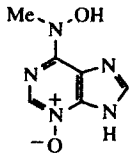
found in reaction (70°C, 5 h) with the 6-chloro-8-substituted purine (**43**); only a low yield of 6-hydroxyamino results.[870] The contrasting ease of displacement found with 6-chloropurine itself, compared with that of **43**, is attributed to an electron-withdrawing effect of the thiazolyl group in the latter case. More facile 6-chloro substitutions occur with 9-benzyl-6-chloropurine in ethanolic hydroxylamine with base (NaOH)[983] and with 9-carboxymethyl- and 2-carboxymethylamino-6-chloropurine in hydroxylamine with potassium carbonate (reflux, 1 h). In the former purine, hydroxyamination of the carboxyl group to the amide (**44**) also occurs.[870] Prolonged exposure to cold ethanolic hydroxylamine (5°C, 48 h) converts 6-chloro-2-fluoro- to mainly 2-fluoro-6-hydroxyaminopurine, although some 2,6-bishydroxyaminopurine forms even under these mild conditions.[1124] In like manner, the 2-hydroxyamino derivative is given by 2-fluoroadenine.[1124] Corresponding reactions with *N*-methylhydroxylamine are possible at slightly raised temperatures, as illustrated by isolation of 2-(*N*-methyl)hydroxyaminohypoxanthine from the 2-chloro[1227] derivative (reflux) and 2-fluoro-6-(*N*-methyl)hydroxyaminopurine from the 6-chloro analog (25°C), both in ethanolic solution. Reflux conditions with the latter give the expected 2,6-bis(*N*-methylhydroxyamino)purine.[1124] The analogous reaction with 6-chloro-3-oxidopurine gives the light-sensitive 6-(*N*-methylhydroxyamino) derivative[1142] (**45**), which is readily deoxygenated by nickel to the parent purine. An illustration of the enhanced activity of a fluorine at C-2 is given by the formation of 2-hydroxyamino-6-thioxopurine in ethanolic solution at room temperature.[1124] Related hydroxylamine derivatives reacted include the methoxyamine and the ethoxy homolog, the latter converting a 6-chloro-(reflux, 2 h) into a 6-ethoxyaminopurine (**46**, R = H).[981] An anomalous result obtains on heating the 3-oxido derivative of this halogenopurine with ethanolic methoxyamine containing a trace of alkali in which the product is the 6-ethoxy-rather that the expected 6-methoxyaminopurine because of a base-catalyzed substitution by the solvent.[1142] Methanolic methoxyamine at pH 9 with 6-chloro-2-fluoropurine (reflux, 3 h) gives the 2-fluoro-6-methoxyamino analog (**46**, R = F), which is converted by hydroxylamine to 2-hydroxyamino-6-methoxyaminopurine (**46**, R=NHOH).[1124]



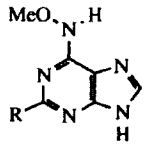
43



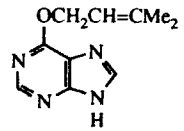
44



45



46



47

The use of halogenopurines as precursors in the formation of azidopurines is not widely practiced because the alternative route entailing nitrous acid treatment of hydrazinopurines Chapter VIII, Section 7.C.a) is more convenient. Recent examples of the halogenopurine approach are treatment of the triacylated riboside of 2-amino-6-chloropurine with sodium azide in acetonitrile cotaining a catalytic amount of trimethylamine (21°C, 12 h). The conditions employed in this reaction are unusually mild, and the possibility of a trimethylammonium group involvement in the displacement cannot be discounted.[1109] Some groups have claimed that the procedure originally employed[1185] to prepare 8-azido- from 8-bromoadenine gives rise to mixtures of product and starting material.[1186] More successful replacement of bromine in the 9-arabinosides of 8-bromoadenine and -xanthine is effected by use of lithium azide in dimethylformamide (65°C, 19 h).[1196]

E. Replacement of 2-, 6-, and 8-Halogens by Alkoxy Groups (*H*171)

Reaction conditions required with sodium alkoxides are determined largely by the location of the halogen and the presence or absence of *N*-alkyl groups, the latter often facilitating the replacement. The 2-methoxy derivatives of 7- and 9-methylpurine obtained from the respective 2-chloropurine and cold sodium methoxide (20°C, 4 days) illustrate this phenomenon, but 2-chloropurine itself requires a sealed vessel and elevated temperatures (150°C, 35 h) to effect methoxylation.[1176] Typical alkoxylations of 6-halogenopurines are 6-chloropurine with 3-methylbut-2-enol and sodium hydride in dioxan (100°C, 24 h),[1177] which form **47** and the 3-oxide of this purine with sodium ethoxide (reflux, 3 h).[1142] A comprehensive range of derivatives, from 6-ethoxy- to 6-decyloxypurines is reported to occur by anionic interaction with 6-chloropurine in tetrahydrofuran under reflux.[1868] The facile interaction of sodium methoxide with both 6-chloro-7-methyl- and 6-chloro-9-methylpurine (20°C, 0.5 h) is a further demonstration of the effect on halogen activation of *N*-alkyl groups.[1176] More vigorous conditions are needed when the sodium salts of allyl (reflux, 15 h) and propargyl alcohol (reflux, 2 h) react with 9-benzyl-6-chloropurine in an excess of the alcohols as solvent.[1221]* Similarly formed is 6-allyloxy-2-chloro- from 2,6-dichloropurine.[1208]

Reactions of 2-amino-6-chloropurine are reported with sodium 2-methoxyethoxide (reflux, 18 h) in *n*-butanol,[1179] sodium benzyloxide in butanol† (100°C).[1178] and sodium allyloxide (reflux, 24 h) in dioxan.[1178] The 3-oxide of this purine is likewise converted to the 6-methoxy analog.[1166]

*Both allyloxy and benzyloxy serve as protected forms of oxo groups, but from a practical standpoint the use of the lower-boiling allyl alcohol (b.p. 97°C), compared with benzyl alcohol (b.p. 206°C), makes the formation of allyloxy derivatives preferable where possible.

†If an excess of sodium benzyloxide combined with a trace of benzaldehyde is used in this reaction (150°C, 5 h), the product is 2-benzylamino-1,6-dihydro-6-oxopurine.[1178] The benzylation of amino groups by means of benzyl alcohol has been examined in detail.[1181]

Brief heating of 2-amino-6-chloropurine with sodium but-2-enyloxide in dioxan or the parent alcohol (100°C) gives mainly the 6-*O*-alkylated purine, but with longer reaction times rearrangement occurs.[1178] Like transformations are reported with other unsaturated alkoxypurines[1180] (see Chapter VI, Section 8.D). Nuclear *N*-alkylation takes place when 2-amino-6-chloro-8-methylpurine and sodium 3-methylbut-2-enyloxide react—both 3- and 7-alkylpurines are produced[1131] (Chapter VI, Section 8.D).

A few examples of 8-alkoxylations are available—these include 8-methoxy-9-methylpurine (20°C, 1 h) from the 8-chloropurine[1176] and near-quantitative yields when methoxylation of the acetylated riboside of 6-amino-8-fluoropurine to the 8-methoxy analog is effected in methanol containing catalytic amounts of sodium hydroxide or hydrochloric acid.[1123] Cases of inadvertent halogen displacement by ethoxy are noted elsewhere (see Sections 5.C.a and 5.D).

F. Replacement of 2-, 6-, and 8-Halogens by Oxo Groups (*H*175)

a. With Alkali (H175)

The acknowledged instability of halogenopurines having a deficiency of strong electron-releasing groups toward alkali is apparent in both 7- and 9-methyl-2-chloropurine. In sodium hydroxide, the former affords a mixture of 7-methyl-2-oxopurine and 4-amino-2-chloro-5-methylaminopyrimidine,[1182] and the latter yields the corresponding 9-methyl-2-oxopurine together with an unidentified product, both occurring in substantial yields.[836] No reaction occurs with 6-fluoropurine owing to a predominance of the anionic form,[1122] but 6-chloro-3-methylpurine behaves like the 2-chloro-*N*-methyl derivatives in forming the hydrolysis product 3-methylhypoxanthine admixed with 4-cyano-5-methylaminoimidazole[836] (80°C, 3 h). Conversion of 6-chloro-9-vinylpurine to 9-vinylhypoxanthine occurs on treatment with aqueous trimethylamine (20°C, 3 h); the mild conditions needed indicate that a hydrolytic involvement of the quaternary derivative could be responsible.[1158] A route to 3-oxidoguanine is provided by interaction of sodium hydroxide (80°C, 3 h) with 2-amino-6-chloro-3-oxidopurine.[1166] Aqueous potassium carbonate at room temperature is sufficient to transform a 9-alkoxyalkyl-6-chloro-2-iodopurine into the 2-iodohypoxanthine analog.[1214] Only the halogen at C-6 is hydrolyzed in 2,6-dichloro-7-methyl-8-thioxopurine using 2 *M*-sodium hydroxide.[1865]

b. With Acid (H177)

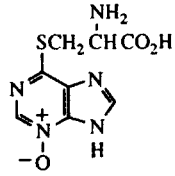
The ready hydrolysis of 6-fluoropurine in water (100°C, 1 h) to hypoxathine suggests that the process is autocatalyzed by the acid formed.[1122] The easier conditions required for conversion of the same fluoropurine (20°C, 0.5 h) to the product described above using 0.1 *M*-hydrochloric acid lend support to this theory.[1122] Various 9-substituted hypoxanthines arise from similar dilute acid

hydrolyses of the corresponding 6-chloropurine.[865,1183,1184] The formation of 2-chlorohypoxanthine from the 6-fluoro analog (20°C, 1 h) reflects the ease of displacement under these conditions.[1122]

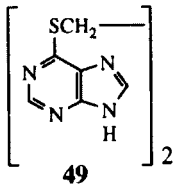
Examples derived from 2-amino-6-halogenopurines include guanine from 2-amino-6-fluoropurine (20°C, 3 h) in dilute hydrochloric acid, while under more rigorous conditions, using 2*M*-acid, 2-amino-6-chloro-3-oxidopurine is converted to 3-hydroxyxanthine, which involves a concomitant amino group hydrolysis.[1166] Sodium acetate in acetic acid (reflux 3 h) was effective in hydrolyzing an 8-bromoadenine derivative to the 8-oxo analog.[1100] Both 1,3-dimethyl- and 1,3,7-trimethyluric acid are the result of rapid hydrolyses of 8-fluoro-theophylline and -caffeine, respectively.[1123]

G. Replacement of 2-, 6-, and 8-Halogens by Alkyl (or Aryl) thio Groups (*H*179)

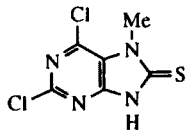
As alkylation of thioxo groups is still, where possible, the more favored route to alkyl (aryl) thiopurines, the alternative approach of alkylthiolation of halogenopurines still has only limited application. Mercaptans employed with 6-chloro-3-oxidopurine include methanethiol in methanolic alkali,[1142] cysteine (80°C, 2 h), giving **48**,[1114] and the corresponding derivative formed from glutathione.[1114] A new preparation of 1,2-bis(purin-6-ylthio)ethane (**49**) in 50% yield, using 6-chloropurine with 1,2-dimercaptoethane in butanol (120°C, 2 h) containing triethylamine,[1138] has been reported.



48



49



50



51

A novel utilization of a photolytically induced (450-W lamp, 6 h), free-radical reaction is seen in the conversion of the triacylated riboside of 2-iodopurine into the 2-methylthio analog with dimethyl disulfide in benzene.[1095] Diphenyl disulfide with 9-ethyl-6-iodopurine in dimethylformamide under UV irradiation reacts similarly, forming the 9-ethyl-6-phenylthio derivative.[1066] This type of group metathesis depends upon the susceptibility of the weak disulfide linkage to ready homolytic fission, thus liberating alkyl(aryl)thio radicals.[1220]

H. Replacement of 2-, 6-, and 8-Halogens by Thioxo Groups (*H*181)

a. With Sulfides (H181)

Prolonged heating (reflux, 20 h) of the 2-chloro derivative with sodium hydrosulfide forms 6,8,9-trimethyl-2-thioxopurine.[848] A good yield (83%) of ^{35}S labeled

6-thioxopurine (6-mercaptopurine) is claimed from an improved procedure of treating 6-chloropurine with ^{35}S-barium sulfide in pyridine containing barium hydroxide and potassium carbonate.[1160,1189] In a cooled solution (0°C) of hydrogen sulfide-saturated sodium hydroxide, 2,6-dichloropurine is selectively converted to the 2-chloro-6-thioxo analog quantitatively.[1114] An aprotic solvent is employed in the transformation of 8-fluoro- into 8-thioxoadenosine by sodium hydrosulfide in dimethylformamide.[1123] Comparable reactions with sodium hydroselenide are usually more rapid and require less vigorous conditions. The ribosides of 6-seleno-[1228] and 2-amino-6-selenopurine (selenoguanosine) [1190-1192] are readily formed in methanol (20°C, 0.25 h). Related 8-selenopurines likewise obtained from 8-bromo derivatives are exemplified by 8-selenoadenosine[1193,1194] and 8-selenohypoxanthine.[1193]

b. With Thiourea (H183)

Under reflux, ethanolic thiourea readily (1 h) produces the 2-thioxo ánalog from 2-chloro-8-phenylpurine.[857] With the same reagent and treatment, substitution of the halogen moiety occurs in 9-carboxymethyl-[1114] (3 h) and 9-vinyl-6-chloropurine[1163] (2 h). A lower temperature (60°C, 2 h) suffices for forming the 6-thioxo derivative from 6-chloro-3-oxidopurine using ammonium dithiocarbamate ($NH_2CS_2NH_4$) in place of thiourea.[1142] Selective replacement, a feature also found with use of sodium hydrosulfide (see 5.H.a), occurs with 6-chloro-2-fluoropurine since only the 6-thioxopurine results.[1124] In the case of 2,6,8-trichloro-7-methylpurine, the product with thiourea in ethanol is the 8-thioxo derivative[1865] (**50**); this contrasts with earlier use (*H*182) of aqueous sulfide solutions affording the trithioxo analog. Thiolation of 2-amino-6-chloropurines occurs under the same conditions, as in the reaction with 2-amino-6-chloro-8-cyano-9-methylpurine[879] (reflux, 2 h). From the attempted conversion of 2-amino-6-chloro-3-oxidopurine, the replacement of chlorine by thioxo was accompanied by a reductive removal of the 3-oxide group, giving thioguanine.[1166] With selenourea the analogous reactions are possible under comparable conditions. Note that the successful formation of 3-oxido-6-selenoxopurine (**51**) from the chloropurine analog (reflux, 2 h) is possible without the ensuing removal of the oxygen,[1142] as discussed in the above thiolation.Conditions for the metatheses to 8-selenoxo derivatives of 8-bromo-adenosine and -guanosine[1195] reflect those normally used in 8-thioxopurine preparations.

I. Replacement of Halogens by Sulfo and Thiocyanato Groups (*H*185)

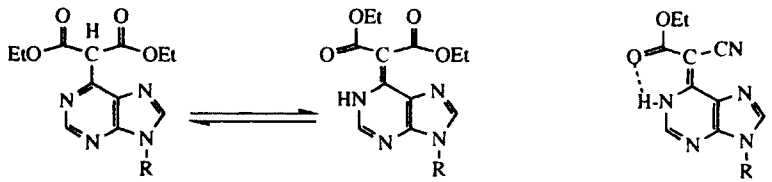
Formation of sulfopurines by interaction of halogenopurine with sodium sulfite is not often encountered. Mild heating of 2,6-dichloropurine with the aqueous reagent (70°C, 3 h) displaces both halogens, forming the disodium salt of 2,6-disulfopurine.[1124] The more usual route to this type of derivative is by

oxidation of purines with sulfur-containing groups (see Chapter VII, Section 4.A).

A preparation of a 6-thiocyanatopurine derivative is reported on treating the 6-chloro analog with potassium thiocyanate in dimethyl sulfoxide.[1222]

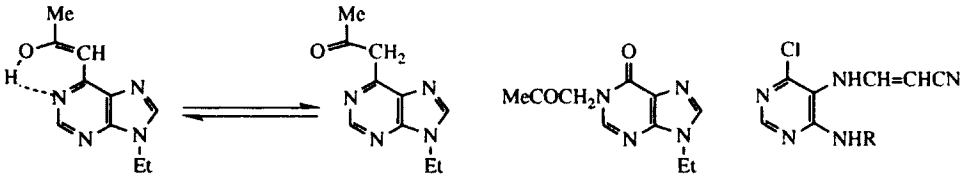
J. Replacement of Halogen Atoms by Other Groups (*H*185)

This aspect received only brief coverage in the parent volume, being restricted largely to interaction of the halogen with compounds containing active methylene groups. More recent extensions of this work, showing condensation of various 6-chloropurines with malonodinitrile,[1067,1855] ethyl cyanoacetate,[1067] phenylacetonitrile,[1067] acetophenone,[1067] acetylacetone,[1067] and cyanoacetamide[1068] have already been documented (Chapter IV, Section 2.A.d). NMR studies on the product (**52**) from chloropurine and sodium diethyl malonate indicate that in protic solvents such as water or methanol the structure **52A** predominates, but the alternative form **52B** is the major component in chloroform, dimethyl sulfoxide, or other aprotic media.[1069] The product obtained with methyl cyanoacetate consists of only a single tautomer (**53**); strong hydrogen bonding



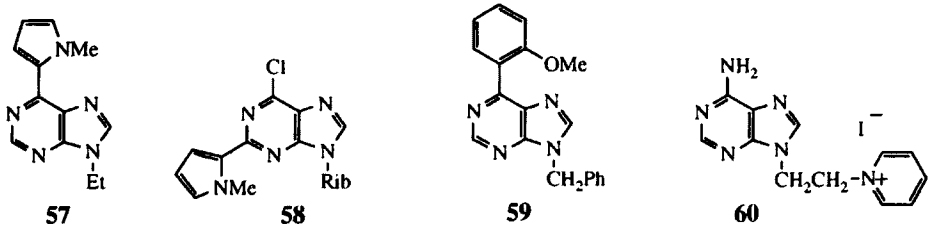
52A **52B** **53**

would account for this configuration being assumed.[1069] Examples of condensation of malonic ester with 8-chloropurines are also known.[1231-1233] Under UV irradiation, simple ketones can react in the enol form, the potassium derivative of acetone with 9-ethyl-6-iodopurine affords both enol (**54A**) and keto (**54B**)[1070,1071] tautomers. In chloroform, the hydrogen-bonded **54A** is the major tautomer (80%), but this ratio reduces to 50% in aqueous solutions.[1071] Corresponding tautomers have been identified in the products obtained from acetophenone, cyclopentanone, cyclohexanone, and related ketones.[1071] The extent of radical participation in this S_RN^1 reaction is demonstrated by the low yield (22%) obtained from a dark reaction, which is further reduced to 6% with a *p*-dinitrobenzene radical scavenger present.[1071] Under the conditions described above, more complex reactions are possible following the initial substitution; isolation of 1-acetonyl-9-ethylhypoxanthine (**55**) from the 6-iodopurine and bromoacetone is attributed to hydrolytic cleavage of an intermediate azirinium derivative.[1071] No halogen involvement occurs in the low-temperature (–40°C) reaction of a 9-alkyl-6-chloropurine with acetonitrile containing sodium hydride, but the product (**56**, R = alkyl) results from nucleophilic attcks at C-8 by nitrile with subsequent imidazole ring fission.[1069]



54A **54B** **55** **56**

Application of radical reactions to preparative procedures is of increasing significance, notably for replacement of halogen atoms by alkyl and aryl groups, as described earlier (Chapter IV, Section 2.A.d.). Insertion of π-excessive heterocycles extends the range to include *N*-methylpyrrole, 2-methlfuran, and thiophene derivatives. These react regiospecifically through the carbon adjacent to the heteroatom as exemplified by **57** from 9-ethyl-6-iodopurine and *N*-methylpyrrole.[1066] However, the same heterocycle with 6-chloro-2-iodopurine riboside initially gives the 2-substituted derivative (**58**), which is converted by prolonged irradiation to the 2,6-di(*N*-methylpyrrol-2-yl)purine[1096] riboside. Six-membered aromatics show corresponding reactions. The major product from the action of anisole on 9-benzyl-6-iodopurine is now shown to be 9-benzyl-6-(2-methoxyphenyl)purine[967] (**59**), although an earlier claim had suggested the product was a mixture of 6-(3-methoxyphenyl)- and 6-(4-methoxyphenyl)-purines.[1119]



57 **58** **59** **60**

The use of Grignard and similar reagents together with Wittig-type reactions as routes to alkylpurines from their halogen counterparts is detailed in Chapter IV, Section 2.A.d. Extensions of these procedures now allow conversion of 2-iodopurines to their 2-cyanomethyl (Chapter IX, Section 4.A) and 2-acetonyl (Chapter IX, Section 6.A) derivatives. Replacement of halogen by a cyano (carbonitrile) group is treated in Chapter IX, Section 4.A.a.

6. REACTIONS WITH EXTRANUCLEAR HALOGEN ATOMS (*H*186)

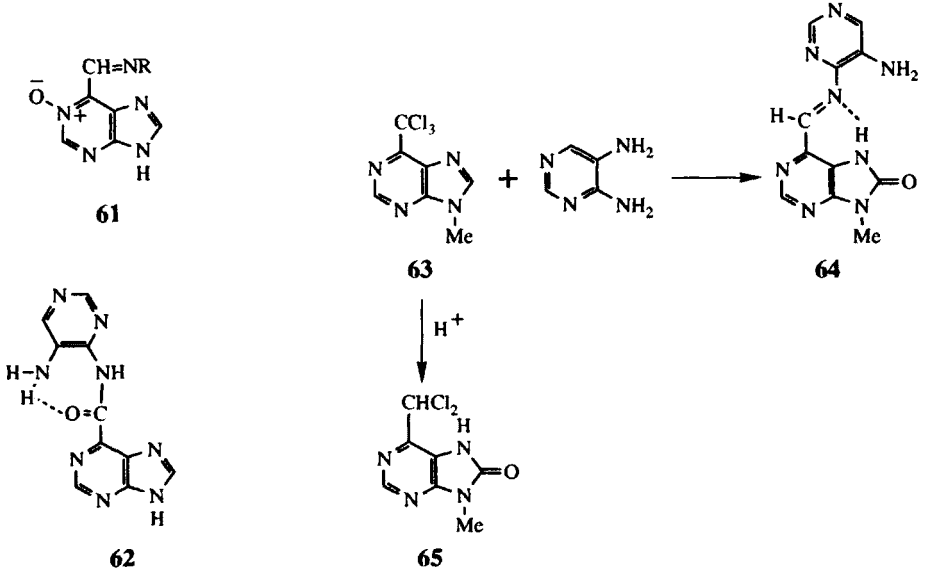
Interest in halogenomethylpurines continues because of their ready conversion to derivatives of aldehydopurines. Numerous examples of longer-chain halogenoalkylpurines undergoing nucleophilic substitution are also available. The coenzyme I model compound (**60**) derived from 9-(2-chloroethyl)adenine

and nicotinamide[1433] is one illustration. The ability of such alkyl side chains to be involved in endoalkylation of proximate ring nitrogen atoms to form tricyclic derivatives is being actively studied.

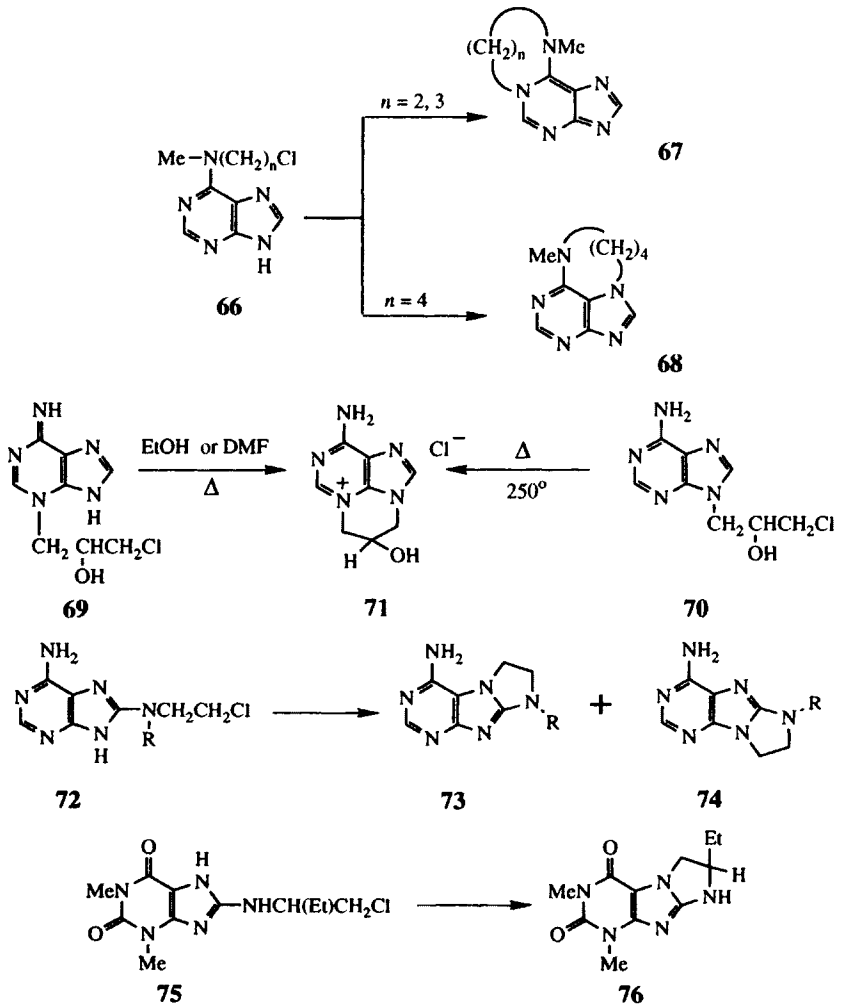
A. Replacement by Amino Groups (*H*186)

Amination of 2-chloromethyl-8-dimethylaminohypoxanthine occurs with aniline and morpholine under reflux,[909,910] whereas ambient temperature suffices to convert 8-chloromethyltheophylline to the 8-anilinomethyl analog.[928] Hydrazine and hydroxylamine react with both 1-oxido- and 3-oxido-6-bromomethylpurine and the products are temperature dependent. Below 25°C, both hydrazine (**61**, R = H) and hydroxyamino (**61**, R = OH) derivatives of the 1-oxide are obtained, but with hydrazine at this temperature the 3-oxide is reduced to the hydrazone of the parent purine. The corresponding reduction with hydroxylamine requires reflux conditions.[1080]

The highly fluorescent solutions produced when 6-trichloromethylpurine and 4,5-diaminopyrimidine interact[1199,1200] is associated with the rigid structure of the product (**62**) produced by hydrogen bonding between carbonyl oxygen and the second amino group.[1199] No comparable compound forms with 9-methyl-6-trichloromethylpurine (**63**), which undergoes rearrangement to the azamethine derivative (**64**) of an 8-oxopurine.[1083] The (*E*)-enantiomer[1083] obtained is a consequence of hydrogen bonding between the azamethine nitrogen and the imidazole proton. By condensing 6-dichloromethyl-9-methyl-8-oxopurine (**65**) with the diaminopyrimidine, the same enantiomer[1083] results.



Some long-chain halogenoalkylpurines can be converted to tricyclic compounds through endoalkylation, usually by thermal means. Examples of spontaneous cyclization, however, occur with derivatives such as **66** on leaving in dimethylformamide containing sodium hydride. With short chains (**66**, n = 2 or 3), the N-1 linked products (**67**, n = 2 or 3) are obtained, on extending the chain (**66**, n = 4), the N-7 bonded derivative (**68**) results.[1141] Heating is required to convert either 3-(**69**) or 9-(3-chloro-2-hydroxypropyl)adenine (**70**) to the cyclized product (**71**). Closure of the 3-alkyl isomer (**69**) is carried out in protic or aprotic solvents under reflux, but a higher temperature (250°C) is needed with the 9-isomer.[1139] With 8-(2-chloroethylamino)purines of the type (**72**, R= alkyl), the availability of either N(7) or N(9) leads to isomeric mixtures of **73** and **74**.[1202] Chiral and racemic forms (**76**) result from heating (110°C) 8-(1-chlorobut-2-yl-



amino)theophylline (**75**) in dimethyl sulfoxide containing 1,8-diazobicyclo[5,4,0]undec-7-ene (DBU).[1032] It is noteworthy that this dehydrohalogenation does not occur with the more usual basic reagents like pyridine, triethylamine, or potassium hydroxide.[1032] Other aspect of polycyclic purine derivatives are dealt with elsewhere (Chapter XIII).

B. Replacement by Hydroxy and Alkoxy Groups (*H*188)

Hydrolyses of halogens, usually in acid media, are well documented, with numerous examples cited in the literature. Cases of unexpected or secondary reactions are, however, not unusual. In aqueous hydrochloric acid (100°C, 24 h), 9-methyl-6-trichloromethylpurine (**63**) undergoes qualitative rearrangement to the 6-dichloromethyl-8-oxo derivative (**65**), but the 7-methyl isomer of **63** is unchanged by acid treatment.[1083] Although the parent 6-trichloromethylpurine also resists attack by dilute acid at low pH values (<1), it undergoes hydrolysis and rearrangement to 6-formyl-8-oxopurine. This event appears to reflect the enhanced electrophilic character of the carbon at the 8-position following protonation in the strong acid,[1084] but alternative mechanisms have also been proposed.[1083] An inadvertent hydrolysis occurs during an acylation of 6-chloro-8-chloromethylpurine with acetal giving as product 6-chloro-9-(1-ethoxyethyl)-8-hydroxymethylpurine.[842] Alkaline hydrolysis is less predictable since dehydrohalogenation is a possible side reaction; a representative example is isolation of 9-(2,3-epoxypropyl)adenine from the 9-(2-hydroxy-3-chloropropyl) analog on leaving in cold (20°C, 24 h) potassium hydroxide.[1201] Preparations of 9-vinyladenine and -hypoxanthine from the 9-(2-chloroethyl) derivatives using sodium methoxide in dioxan (20°C, 24 h)[1201] are examples of an established procedure (*H*190) for abstraction of a hydrogen halide.

C. Replacement by Other Groups (*H*189)

Substitution of halogen by hydrogen in the reduction of a 2-chloromethylhypoxanthine to the corresponding 8-dimethylamino-1,6-dihydro-1,2,3-trimethyl-6-oxopurine is made with triphenylphosphine in dimethylformamide.[910] Sodium sulfite in methanol converts 9-(2-chlorethyl)- and 9-(3-chloropropyladenine to the respective 9-(alkyl-ω-sulfonic acid) under reflux conditions.[1349]

7. *N*-ALKYLHALOGENOPURINES (*H*191)

The majority of examples are derivatives of 7- and 9-alkyl-6-chloropurines, which are suitable precursors for the corresponding 6-amino-(adenine or isoguanine) or 6-oxopurines (hypoxanthine or guanine).

A. Preparation of *N*-Alkylated Halogenopurines (*H*191)

a. By Direct Synthesis (H191)

No significant advances have been made and the most useful general approach is still by a Traube synthesis involving a halogeno-4,5-diaminopyrimidine with either a trialkylorthoester or diethoxymethyl acetate as cyclizing agent (Chapter II, Section 1.G). Examples of a less widely used synthesis can be found in which incorporation of phosphoryl chloride with the cyclizing reagent enables direct conversion of 2- or 6-oxo-4,5-diaminopyrimidines into chloropurines to be made (Chapter II, Sections 1.D and 1.F).

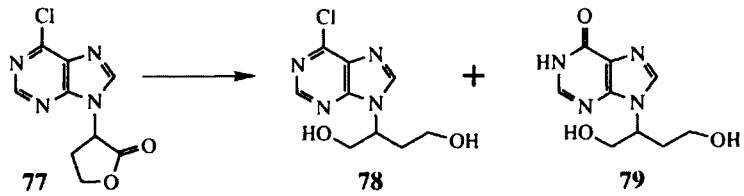
b. By Replacement of Groups by Halogen (H191)

Oxo groups are the most widely used, but oxopurines containing *N*-alkyl groups impose a risk that the latter will be removed during chlorination, especially if phosphoryl chloride alone is employed.[1100] Although addition of a dialkylaniline reduces this possibility, a further complication may be introduced in which electrophilic substitution occurs, giving purine possessing *p*-dimethylaminophenyl substituents[1107,1110] (see Section 1.B.d). Cases of failure to chlorinate simpler *N*-methyl-oxopurines are reported.[836] Routes involving thioxo or methylthio group displacement are still being actively pursued (Section 1.C), and the exploitation of radical means to convert aminopurines to the chloro, bromo, iodo, and fluoro analogs is increasingly important (Sections 1.D, 1.E, 1.F, and 1.G.e).

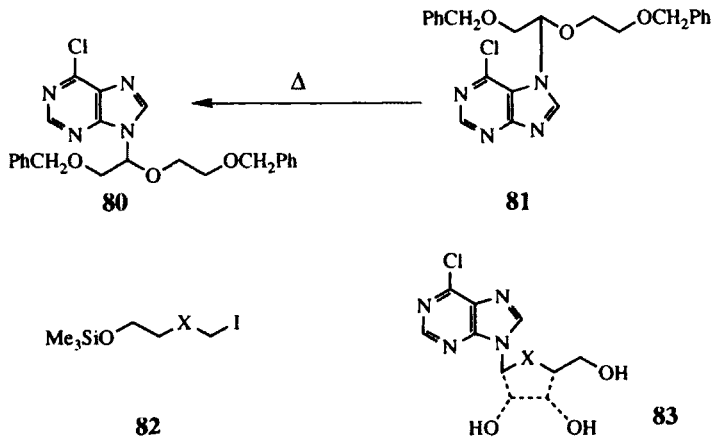
c. By Alkylation (H192)

The antiviral activity of 9-alkoxyalkylpurines has led to renewed interest in alkylation of purines, especially 6-chloropurines, in view of their potential for transformation into other purine derivatives. Both 7- and 9-alkylated purines are possible products, but the 9-alkylpurine is often the predominent or only isomer isolated. With halide derivatives as alkylating agents, dimethyl sulfoxide containing potassium carbonate is the usual medium, the reaction proceeding at room temperature or below. Change of solvent in some cases[1213,1214] to dimethylformamide with sodium hydride favors formation of only the 9-alkylated purine rather than a mixture of 7- and 9-alkyl isomers.[1184] Various separations of the isomers described include preferential solvation in polar solvents[1183] of the 9-isomer, chromatography on silica gel,[1066] or flash chromatography[1149] based upon Still's procedure.[1225]

The only product with α-bromobutyrolactone is the 9-alkyl derivative (**77**), which is reduced by sodium borohydride to 6-chloro-9-(1,4-dihydroxybut-2-

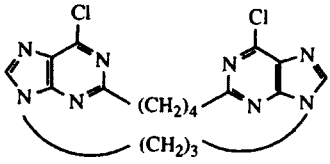


yl)purine (**78**) together with some of the hydrolyzed product (**79**).[1160] Alkylation of 6-chloropurine with 1,3-dibenzyloxy-2-chloromethyloxypropane in dimethylformamide–triethylamine in the cold gives both 7-(**81**) and 9-alkyl (**80**) isomers. Isomerization of the former to the 9-isomer occurs on heating, which would explain the isolation of only **80** when alkylation is effected at a higher temperature.[1127] Alkyl halides activated by trimethylsilylation in situ allows low-temperature alkylations to be made using alicyclic precursors. Both 1,3-dioxolane and 1,3-dioxothiolane with trimethylsilyl iodide form linear iodoethers and -thioethers of the type (**82**, X = O or S).[1159,1213] Reaction of these excellent alkylating agents occurs in aprotic solvents (dimethylformamide or cyclohexene, –63°C) containing sodium hydride. Such conditions favor 9-alkyl-chloropurine formation (e.g., **83**), but on changing the base to potassium carbonate, some 7-alkylpurine (5%) is obtained.[1213] The analogous 9-alkyl derivative results with 2-chloro-6-iodopurine.[1214] Related examples arise with 6-chloro-, 2,6-dichloro-, and 2-amino-6-chloropurines on treating the 9-trimethylsilylated derivatives with 2-acetoxyethoxymethyl bromide in benzene (reflux, 3 h) containing mercury(II) cyanide.[1230] The alkylations are highly regiospecific for the 9-isomers, with yields of 83–93% claimed.[1230] The structural similarity of the alkoxyalkyl moiety to a partial structure of the ribosyl group is the rationale advanced for such syntheses.[1213] The use of bis-6-chloropurines, linked by an alkane chain, is well established. Extensions of these studies produced bispurines interconnected by two or three chains, giving rise to purinophane derivatives (Chapter XIII, Section

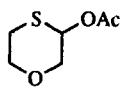


2). An example (**84**) is obtained from alkylation (DMSO, K_2CO_3) of the C-2 linked bis-6-chloropurine with 1,3-dibromopropane.[1358]

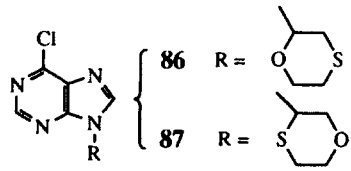
Acetoxy derivatives can function as alkylating agents in acid-catalyzed reactions. With 6-chloropurine in the presence of 4-methylbenzenesulfonic acid (90°C), reaction with 3-acetoxy-1,4-oxathiane (**85**) produces nearly equal amounts of the 9-(oxathian-2-yl) (**86**) and 9-(oxathian-3-yl) (**87**) isomers.[1216,1217] The reaction is of a Michael type—the alkylating moiety appears to be 1,4-oxathiene arising from abstraction of a hydrogen and the acetoxy group.[1216] The corresponding acetoxy-dioxan and -dithiane derivatives, in which the pair of heteroatoms (either O or S) in the rings are the same, can give only the single 9-alkylated product.[1217] Similar considerations apply to the formation of **88** (51%) from the same halogenopurine and ethyl 2-acetoxy-*N*-acetylalanine, in which the active agent is the acylimine carbanion (**89**) derived from a base-promoted abstraction of acetic acid. Some of the 7-isomer in low yield (9%) also results.[1218] The ethoxyethyl group can serve as a useful protecting group for the imidazole proton; the purine (**90**) is formed by heating the 9-unsubstituted derivative in acetaldehyde diethylacetal.[1842]

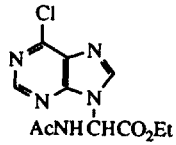


84

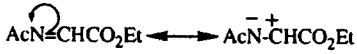


85

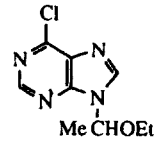




88



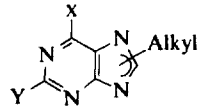
89



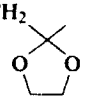
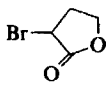
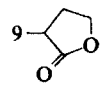
90

Alkylation of 8-halogenopurines at N-3 and N-9 is largely influenced by the size of the halogen atom. On treating 8-chloroadenine with 2,3,5-tri-*O*-benzylribofuranosylbromide in dimethylformamide (50°C, 72 h), the product mixture contains 22% of the 3-ribosylpurine and 12% of the 9-isomer. The steric effect is more evident when 8-iodoadenine is used—the respective yields are (30%) 3-riboside and only 5% 9-riboside.[1219] Selective ribosylation at N-3 is also a feature of 8-iodoisoguanine.[884] A more comprehensive survey of alkylation is given in Table 4, showing the range of conditions and the effect of these on the nature and type of products obtained.

TABLE 4. Examples of Approaches Used to Form 7- and 9-Alkyl Derivatives of 6-Halogenopurines

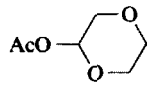
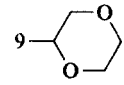
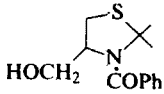
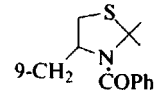


R = CH_2Ph, R′ = COMe, R″ = $SiMe_3$

Purine	Alkylating Agent	Medium, Catalyst	Alkylation Products	Ref.
X = Cl, Y = H	$BrCH_2CH_2Cl$	DMSO, K_2CO_3	9-CH_2CH_2Cl (57%)	1138
	$ClCH_2OEt$	DMSO, K_2CO_3	9-CH_2OEt	1223
	$BrCH_2CH(OEt)_2$	DMF, NaH	9-$(CH_2CH(OEt)_2$	1382
	$ClCH_2O(CH_2)OR$	DMSO, K_2CO_3	9-$CH_2O(CH_2)_2OR$	1223
	$BrCH_2O(CH_2)_2OR'$	C_6H_6, $Hg(CN)_2$	9-$CH_2O(CH_2)_2OR'$ (80%)	1230
	$ICH_2O(CH_2)_2OR''$ [a]	C_6H_{10},[d] NaH	9-$CH_2O(CH_2)_2OR''$	1159
		DMF, NaH	9-Isomer	1213,1214
		DMF, K_2CO_3	9-Isomer (trace 7-isomer)	1213
	$ICH_2S(CH_2)_2OR''$ [a]	DMF, NaH	9-$CH_2S(CH_2)_2OH$	1213
	$ClCH_2OCH(CH_2OR)_2$	DMF, NEt_3	9-$CH_2OCH(CH_2OR)_2$ [b]	1127
	$BrCH_2CH_2$ 	DMF, K_2CO_3	9-Isomer	1184
		DMF, NaH	9-Isomer (54%) 7-Isomer (13%)	1184
	$BrCH_2CH_2$ 	DMSO, K_2CO_3	9-Isomer (trace 7-isomer)	1183
	CH_2:$CHCO_2Me$	H_2SO_4, $MeCO_2H$, $Hg(CO_2Me)_2$	9-CH=CH_2 (70%)	1215
	$MeCO_2Et$	H_2SO_4 $Hg(CO_2Me)_2$	9-CH=CH_2	1201
	m-$NCC_6H_4CH_2Br$	DMF, K_2CO_3	9-$CH_2C_6H_4CN$ (54%) 7-Isomer (13%)	1210
		DMSO, K_2CO_3		1160

(*cont.*)

TABLE 4. (*Cont.*)

Purine	Alkylating Agent	Medium, Catalyst	Alkylation Products	Ref.
		$MeC_6H_4SO_3H$		1217
		DEAD,[c] Ph_3P		1941
	$R'HNCHCO_2Et$ OCOMe	DMF, NaH	9-CH(NHR')CO_2Et (51%) 7-Isomer (9%)	1218
X = I, Y = H	EtI	DMSO, K_2CO_3	9-C_2H_5 (55%) 7-C_2H_5 (11%)	1066
X = F, Y = H	MeI	DMSO, K_2CO_3	9-Me (46%) 7-Me (8%)	1122
X = Y = Cl	CH_2=$CHCO_2Me$	H_2SO_4, $MeCO_2H$, $Hg(CO_2Me)_2$	9-CH = CH_2 (80%)	1215
	$BrCH_2O(CH_2)_2OR'$	C_6H_6, $Hg(CN)_2$	9-$CH_2O(CH_2)_2OR'$ (80%)	1230
X = I, Y = Cl	$ICH_2O(CH_2)_2OR''$[a]	DMF, NaH	9-$CH_2O(CH_2)_2OR''$	1214
X = Cl Y = NH_2	CH_2OR $Br(CH_2)_2CH$ CH_2OR	DMF, K_2CO_3	9-$(CH_2)_2CH(CH_2OR)_2$	1184
	$ClCH = C(CH_2OR)_2$	DMSO, K_2CO_3	9-CH = $C(CH_2OR)_2$	1224
	$BrCH_2O(CH_2)_2OR'$	C_6H_6, $Hg(CN)_2$	9-$CH_2O(CH_2)_2OR'$ (80%)	1230

[a] Bisdimethylsilyl purine.
[b] 7-Isomer rearranges thermally to the 9-isomer.
[c] Mitsunobu dehydration.
[d] Cyclohexene.

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER VI

Oxo-(Hydroxy-) and Alkoxypurines (*H*203)

1. Preparation of 2-, 6-, and 8-Oxopurines (*H*203) 134
   A. Synthesis from Pyrimidines (*H*204) 134
   B. Syntheses from Imidazoles (*H*204) 134
   C. From Halogenopurines (*H*205) 135
   D. From Aminopurines and Related Derivatives (*H*205) 135
      1. In the Absence of Other Groups (*H*205) 135
      2. In the Presence of Other Groups (*H*205) 135
   E. From Alkoxypurines (*H*207) 136
   F. From Thioxo- and Alkylthiopurines (*H*208) 136
   G. By Reduction of Benzyloxy Groups (*H*209) 138
   H. By Conversion of Other Groups (*H*209) 138
   I. By Rearrangement of Purine-*N*-Oxides (*H*209) 138
   J. By Other Routes (*H*210) 139
   K. By Free-Radical Attack (*H*210) 139
   L. By Enzymic Oxidation (*H*210) 140
2. Preparation of *N*-Alkylated Oxopurines (*H*211) 140
   A. By the Traube Synthesis (*H*204) 140
   B. From Imidazoles (*H*211) 140
   C. By Direct Alkylation (*H*211) 141
   D. By Other Means (*H*211) 141
3. The Extranuclear Hydroxypurines (*H*212) 141
   A. Preparation (*H*212) 141
   B. Reactions of Extranuclear Groups (*New*) 144
4. Preparation of Alkoxypurines (*H*214) 145
   A. By Traube and Other Ring Closures (*H*214) 145
   B. By Displacement of Halogen or Other Substituent (*H*214) 145
   C. By *O*-Alkylation (*H*215) 146
   D. By Other Routes (*H*216) 147
5. Properties of Oxo- and Alkoxypurines (*H*216) 147
6. Reactions of Oxopurines (*H*217) 149
   B. Oxo to Thioxo Group (*H*217) 149
   C. Replacement of Oxo by Hydrogen (*H*220) 149
   D. *N*-Alkylation of Oxopurines (*H*220) 150
      a. Monooxopurines (*H*221) 150
      b. Dioxopurines (*H*223) 152
      c. Trioxopurines (*H*228) 157
   F. Acylation of Oxopurines (*H*231) 157
   G. Oxo to Amino Group (*H*232) 158
   H. Trimethylsilylation of Oxopurines (*New*) 159
7. Reactions of *N*-Alkyl-Oxopurines (*H*233) 159
   A. Replacement of *N*-Alkyl Groups by Hydrogen (*H*233) 160

B. Rearrangement of *N*-Alkyl Groups (*H*234) 160
C. Degradation of *N*-Alkylpurines (*H*234) 161
a. With Alkali (*H*234) 161
b. With Acid (*H*236) 162
8. Reactions of Alkoxypurines (*H*236) 162
A. Alkoxy- to Oxopurine (*H*236) 162
B. Hydrogenolysis of Alkoxy Groups (*H*237) 163
C. Alkoxy to Amino Group (*H*238) 163
D. Rearrangement (*H*238) 164
E. Other Reactions (*H*239) 166
9. Oxidation of Oxopurines (*H*239) 166
A. Under Acid Conditions (*H*239) 167
a. With Chlorine in Acid or Aqueous Media (*H*240) 167
b. With Chlorine in Nonaqueous Media (*H*242) 168
B. Under Alkaline or Neutral Conditions (*H*243) 168
C. By Electrochemical or Enzymatic Means (*New*) 169
11. Hypoxanthine (*H*250) 170
12. Xanthine (*H*251) 172
13. The *N*-Methylated Xanthines (*H*253) 173
A. Theophylline (*H*253) 173
B. Theobromine (*H*254) 174
C. Caffeine (*H*254) 175
14. Uric Acid (*H*256) 176
A. Preparation (*H*256) 176
B. Reactions (*H*257) 177

1. PREPARATION OF 2-, 6-, AND 8-OXOPURINES (*H*204)

A. Syntheses from Pyrimidines (*H*204)

More recent examples of the use of Traube cyclization to form a variety of oxopurines are given in Chapter II. Use of methoxy-4,5-diaminopyrimidines in such reactions can lead directly to an oxopurine as exemplified by 9-ethylxanthine from closure of 5-amino-4-ethylamino-2,6-dimethoxypyrimidine in formamide.[924] The current interest in xanthine derivatives in the medical sphere for use as adenosine antagonists has resulted in the establishment of extensive synthetic programs for these derivatives. The use of aldehydes in oxidative ring closures has given a range of 8-alkylxanthines.[1886,1887]

B. Syntheses from Imidazoles (*H*204)

The application of imidazoles as oxopurine precursors has widened as a result of new reagents and techniques developed for ring closure. These are elaborated in Chapter III.

C. From Halogenopurines (*H*205)

Illustrations of the use of acid and alkali hydrolyses are noted in Chapter V, Sections 5.F.a and 5.F.b.

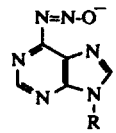
D. From Aminopurines and Related Derivatives (*H*205)

a. In the Absence of Other Groups (H205)

Among the newer approaches is alkaline hydrolysis of purin-6-yltrimethylammonium chloride (NaOH, 10°C, 5 min) to hypoxanthine or the isomeric 8-oxopurine from the appropriate quaternary salt upon more severe (closed vessel, 150°C, 5 h) treatment. In the latter case, some 8-dimethylaminopurine also forms through thermal degradation.[1150] Under acid conditions, the 6-imino group of 1-methylisoguanine is rapidly hydrolyzed, forming 1-methylxanthine.[1242] A route to 2, 8-dioxopurine is by reaction of cold nitrous acid on the 2-amino-8-oxo analog.[903]

b. In the Presence of Other Groups (H205)

Topical examples of the transformation with nitrous acid of adenine derivatives to the corresponding hypoxanthines include the 8-hydroxymethyl-,[842] 9-acetonyl,[1237] 9-carboxymethyl-,[1238] and 9-propyladenines.[1239] The formation of 8-methylselenohypoxanthine from the adenine analog is a demonstration of the inert character of the methylseleno group toward acids compared with that of the analogous methylthiopurine.[1193] Mechanistic studies show that hypoxanthine formation occurs through nitrosation of the amino group giving purin-6-yl diazotates such as (**1**, R = Pr), which is converted to the 6-oxopurine by the acid conditions.[1239] Alternative reagents to nitrous acid are found in the preparation of 8-bromohypoxanthine from 8-bromoadenine, using gaseous nitrogen trioxide in aqueous alkali[1240] (21°C, 1 h). To obviate any hydrolysis of the furanosyl moiety, a nonaqueous medium (DMF) containing nitrosyl chloride is employed to convert 9-β-D-arabinofuranosyladenine to the hypoxanthine analog.[1241] Although guanine is readily hydrolyzed by nitrous acid to xanthine, the 3-methyl homolog is unchanged by this treatment, but alkaline solution causes a rapid



1

transformation to 3-methylxanthine. Participation of mesoionic states could explain this unusual amino group reactivity.[1531] The latter xanthine, together with the 1-methyl isomer, results from dilute hydrochloric acid treatment (100°C, 3 h) of the respective 1-[1242] and 3-methylisoguanines.[859] The more rigorous acid treatment needed in these cases reflects the general deactivation of the 6-amino group owing to the presence of a methyl group at N-3.[859] An exception occurs in the successful transformation of 3-methyladenine to the hypoxanthine derivative in *N*-sodium hydroxide (85°C, 0.5 h),[836] although earlier workers had reported that the adenine derivative underwent degradation to an imidazole if an elevated temperature was employed. Shorter periods in hot sodium hydroxide (100°C, 5 min) are sufficient to convert both the 2- and 6-trimethylammonio-9-methylpurinium chloride to the respective 2- and 6-oxo-9-methylpurines.[836] Kinetic studies made of hydroxide ion displacement of a trimethylammonio group show that first-order kinetics obtain with respect to both reactants and all reactions are bimolecular.[1150] Use of nitrous acid to remove an *N*-amino group is a route to 9-benzylhypoxanthine from the 1-amino analog.[1007]

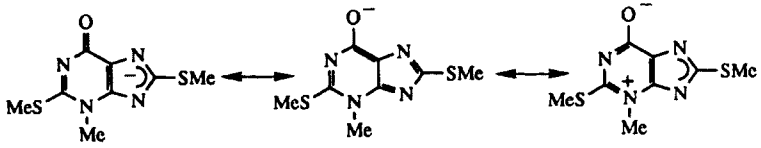
E. From Alkoxypurines (*H*207)

Revelant details are covered in Sections 8.A, 8.B, and 8.D.

F. From Thioxo- and Alkylthiopurines (*H*208)

Reaction rate studies of acid[882,890] and alkaline hydrolyses have been carried out and the order of replacement of alkylthio groups at C-2, C-6, and C-8 were determined (see Chapter VII, Section 2.B.b). Anion formation inhibits group displacement in alkali of simple 2,6-, 2,8-, and 6,8-bismethylthio- and 2,6,8-tris-methylthiopurine,[886,890] but the corresponding 1-, 3-, 9-, and possibly 7-methyl homologs, for which anionic forms are precluded, undergo facile hydrolyses to the respective *N*-methyl–oxopurines,[886] which is assisted by polarization of the methylated ring nitrogens and the inducing of charged centers for nucleophilic attack[886]. Isolation of the 6-oxopurine following alkaline methyl iodide treatment of 1-methyl-2,8-bismethylthio-6-thioxopurine is viewed as the result of initial formation of the 6-methylthio derivative, which undergoes hydrolysis as the stabilizing effect of anion formation is no longer available.[886, 890]

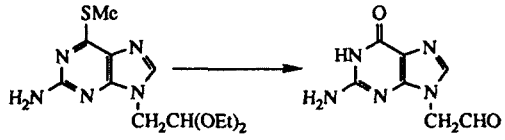
Conversion to the corresponding oxopurine in alkali occurs with 1-methyl-2-methylthio-[836] and 1-methyl-6-methylthio,[836] but similar treatment of 1-methyl-8-methylthiopurine yields 4-amino-5-formyl-2-methylthioimidazole as a result of a preferential hydroxide ion attack at C-2 of the purine. Degradation to imidazoles also occurs with 7- and 9-methyl-2-methylthiopurine.[836] The reported isolation of 4-cyano-5-methylaminoimidazole from the 3-methyl-6-methylthio isomer is at odds with earlier findings (*H*25) claiming 3-methylhypoxanthine as product. Alkylthio-oxopurines in alkali usually participate as the anion, as seen in the



2A **2B** **2C**

conversion of 1-methyl-6-methylthio-8-oxopurine to the analogous 6,8-dioxopurine.[1243] The reluctance of an 8-methylthio group to undergo hydrolytic displacement is attributed to the adoption of canonical forms, which are illustrated in the case of the 3-methyl-2,8-dimethylthio derivative of hypoxanthine by the structures (**2A**, **2B**, and **2C**) which favor nucleophilic attack at C-2.[886] Exemplifying this is the formation of 3,7-dimethyl-8-methylthioxanthine from either 3,7-dimethyl-2,6,8-trismethylthio (2*M*-NaOH, reflux, 2 h)[887] or the 6,8-dimethyl-thio-2-oxo analog (2*M*-NaOH, reflux, 0.25 h).[882] By contrast with 7,9-dimethyl-8-methylthiohypoxanthine, which has the positive center located in the imidazole moiety, only slow hydrolysis of the thio group is possible in cold alkali.[883]

Acid media are usefully employed in hydrolyzing a series of 6-methylthiopurines by boiling in 6*M*-hydrochloric acid until evolution of methanethiol ceases.[876] A weaker acid medium (0.1*M*-HCl) under reflux affords 9-vinylhypoxanthine from the 6-benzylthio analog.[1244] Typical examples of hydrolyses of methylthio-oxopurines include 1-methyl- and 1,3-dimethyl-6-methylthio-2-oxopurines with acetic acid (90°C, 0.5 h) giving 1-methylxanthine and theophylline,[1245] but only a limited yield (20%) of 3-methylxanthine is obtained even on prolonged heating (2 h) of the 3-methyl-6-methylthio analog.[1245]. A preparation of 1,7,9-trimethyluric acid follows strong acid treatment (50% HCl, reflux, 48 h) of the analogous 2-methylthio-6,8-dioxopurine.[891] Although heating in 6*M*-HCl (reflux, 6 h) to obtain 3,7-dimethyluric acid from the 8-methylthio analog[1187] and formation of 9-ethylxanthine likewise from the 2,6-dithioxopurine is typical,[1887] some thio derivatives are less susceptible; for example, 1-methyl-2-methylthio-6-oxo-8-thioxopurine on acid treatment yields only 8-thioxo-1-methylxanthine.[890] Incorporation of an oxidizing agent facilitates thioxo to oxo group conversions through formation of easily hydrolyzable sulfo groups. Alkaline hydrogen peroxide at room temperature affords 1,9- and 3,9-dimethyl- and 3,7,9-trimethyl-6,8-dixopurines from the appropriate 8-oxo-6-thioxopurines.[1246] Either acid or alkali is suitable for hydrolyzing 6-methylsulfonylpurines—characteristic examples from the 6-methylsulfonyl analogs are 9-phenylhypoxanthine[1079] and the 7-methyl, 3,7-dimethyl, and 7,9-dimethyl derivatives of 6,8-dioxopurines.[1246] Irradiation by UV under acid conditions oxidizes 6-mercaptopurine aerobically to hypoxanthine, but no reaction occurs in the absence of air.[1247] The oxidative approach also yields inosine from the ribosides of 6-mercapto- or 6-methylthiopurine using peroxyacetic acid[1398] (60°C, 3 h). Alternatively, *m*-chloroperbenzoic acid (MCPBA) in chloroform at 0°C forms the 8-oxo analog of 2,8-dimethyl-8-methylthiopurine.[878] Chlorine in aqueous acid oxidizes the 2-amino-6-methylthiopurine (**3**) to a 9-formylmethyl-



3 4

guanine[1244,1248] (**4**). The reported formation of 3-methylhypoxanthine from the 6-methylthio derivative in 8 *M*-acetic acid seems to be the result of hydrolysis of the air-oxidized intermediate 6-methylsulfonylpurine.[836] Only partial oxidation of 2,8-bismethylthiopurine occurs when treated with permanganate in acetic acid (25°C, 2 h) giving 2-methylsulfonyl-8-oxopurine.[1047]

G. By Reduction of Benzyloxy Groups (*H*209)

A recent example is formation of the 9-β-D-arabinofuranoside derivative of uric acid by hydrogenolysis (Pd–carbon) of 8-benzyloxyxanthine arabinoside.[1196] A reaction of the same type is abstraction of an allyl group from 6-allyloxy-2-chloropurine riboside, but in this case the product is inosine, which results from concomitant removal of the halogen also.[1208]

H. By Conversion of Other Groups (*H*209)

A variety of unrelated reactions mainly concerned with manipulation of other substituents in oxopurines to afford simple oxopurines are included under this heading. Displacement of groups by hydrogen are exemplified by formation of 3-methyl-2-oxo-[836] and 1-methyl-8-oxopurine[1249] from the respective 6-thioxo analogs using alkaline Raney nickel, Deoxygenation in boiling phosphate buffer of 7-oxidopurines is a route to the parent 8-phenylxanthines.[921] More drastic conditions used to selectively remove the oxygens at C-2 from uric acid and xanthine to form the corresponding xanthines and hypoxanthines involve heating with formic acid and triethylamine[939] and with benzyl formamide,[1234] respectively. Thermal decarboxylation converts 6-carboxy-8-oxo- to 8-oxopurine.[791] Conventional approaches such as group hydrolyses of sulfonyl- and sulfinylpurines are noted elsewhere (Chapter VII, Section 4.B). More esoteric approaches are seen in the transformation of 6-methyl-1-oxidopurine by the Ortoleva–King reagent or Knoevenegal reaction and oxidative hydrolyses of the products to hypoxanthine-1-oxide (Chapter IV, Sections 2.C.b, and 2.C.e).

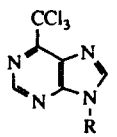
I. By Rearrangement of Purine-*N*-Oxides (*H*209)

These have been the subject of detailed investigation, as described in Chapter XI, Section 3.C. The metathesis of 1-hydroxyhypoxanthine under UV irradiation into a mixture of hypoxanthine, xanthine, and the 6,8-dioxo isomer illustrates

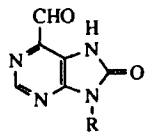
the complexity of these reactions in which pH is a determining factor for the types of purines formed.[1250] The 1-oxide of 6-methylpurine is similarly transformed into 2-oxo-6-methylpurine.[1057] However the rearrangements of 3-acyloxypurines to the 8-oxopurines[1116] used to prepare uric acid derivatives (see Chapter XI) are more familiar.

J. By Other Routes (*H*210)

The generally stable nature of oxopurines is shown by their occurrence as end products of metabolic oxidation in vivo. Various chemical oxidative approaches, sometimes involving rearrangement, are also encountered, giving diverse products, as is found in the in vivo studies. Hypoxanthine is the result of hydrolysis of purine-6-malonaldehyde with trifluoroacetic acid–hydrogen peroxide mixtures,[791] while the same purine can be obtained reductively (Raney nickel) from 6-carboxyl-1-oxidopurine.[1057] In dilute hydrochloric acid (200°C, 24 h), formation of 6-formyl-8-oxopurine (**6**, R = H) from 6-trichloromethylpurine (**5**, R = H) occurs quantitatively.[1084] The 9-methyl homolog (**5**, R = Me) rearranges to **6** (R = Me) similarly.[1083] Examples of transformations of other heterocycles include hypoxanthine from 7-oxoimidazo [4, 5-*d*] [1,3]-oxazines (Chapter II, Section 8.L) and the 3-oxide of the same purine using 7-aminooxazolo [5,4-*d*] pyrimidine-6-oxide (Chapter II, Section 8.B), while xanthines result from interconversions of dihydropyrimido [5,4-*e*]- and dihydropyrimido [4,5-*e*]-*asym*-triazines (Chapter II, Section 8.J) and uric acids from pteridines (Chapter II, Section 8.I). An isolated formation of 7-alkenyl-8-oxopurine using a pyrimido [4,5-*b*] [1,4]diazepine precursor should be noted (Chapter II, Section 8.H).



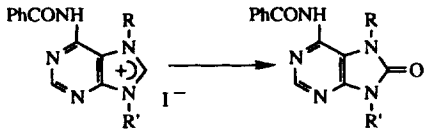
5



6

K. By Free-Radical Attack (*H*210)

The 8-oxo purines (**8**) result from direct introduction of the oxo function into the iodides of 7,9-dialkyl-6-benzamidopurines (**7**, R = Me, R′ = CH_2Ph; R = Et, R′ = Et). The products form on treatment with peroxyacetic acid (20°C, 12 h) or by UV irradiation of a methanolic solution (20°C, 8 h) through which oxygen is passing.[1426]



7 **8**

L. By Enzymic Oxidation (*H*210)

The function of xanthine oxidase in purine oxidations is well documented. Since the original work on purine conversions to uric acid derivatives, more recent studies under aerobic conditions with adenine-1-oxide,[1702] 3-hydroxy-2-oxopurine,[861] 3-hydroxyxanthine,[1699] guanine-3-oxide,[828] and related 8-^{14}C-derivatives[1700] give the analogous 8-oxopurines with retention of the *N*-oxide moiety. In sharp contrast with these results are those obtained in anaerobic environments where reduction rather than oxidation features[1701] adenine-1-oxide, for example, being converted to the parent purine under such conditions.[828] A prerequisite for this type of reaction is the presence of an electron donor with the oxidase. Such donors may be other purines present or the purine-*N*-oxide itself, provided this also possesses a readily oxidizable carbon atom.[1701]

2. PREPARATION OF *N*-ALKYLATED OXOPURINES (*H*211)

In many cases the general routes to oxopurines can apply equally well to the preparation of *N*-alkyl homologs. Representative examples are to be found in the hydrolyses of halogenopurines (Chapter V, Sections 5.F.a and 5.F.b), alkylthiopurines (Chapter VII, Section 2.B.b), and to a lesser extent with methylsulfonyl derivatives (Chapter VII, Section 7.B). Hydrolyses of amino groups of *N*-methylaminopurines offers yet another approach (Chapter VIII, Section 5.A).

A. By the Traube Synthesis (*H*204)

Applications of this procedure leading to *N*-alkylated oxopurines are noted throughout Chapter II. An excellent illustration of the versatility of the route is given by the variety of *N*-methyl uric acids obtained with different cyclizing reagents and aminouracil derivatives. Products include the 1- and 3-methyl- and the 1,7-, 1,9-, 3,7-, 3,9-, and 7,9-dimethyl- and 1,3,9,-trimethyl-uric acids among many other *N*-alkyl homologs.[891]

B. From Imidazoles (*H*211)

More recent improvements in imidazole syntheses have increased the range available and resulted in more extensive applications of these derivatives as purine precursors. Either 4-amino-5-carbamoyl- or 4-amino-5-alkoxycarbonylimidazoles are usually employed, appropriate derivatives on cyclization giving 1-, 3-, 7-, or 9-*N*-alkyloxopurines. Examples from this approach include *N*-alkylated hypoxanthines, xanthines, and guanines, including analogs of the antiviral guanine acyclovir (Chapter VIII, Section 9.B).

C. By Direct Alkylation (*H*211)

The extensive studies by Bergmann and his group on dioxopurines now include the alkylation of anions, cations, and neutral molecules of 6,8-dioxopurine derivatives (Section 6.D.b) using various conventional methylating techniques. Trialkyl esters of phosphoric acids as alkylating agents are versatile because they react with hypoxanthines and xanthines in aqueous alkali under mild conditions (20–60°C) or without solvent at higher temperatures (140–200°C) giving di- and trimethyl and -ethyl and other *N*-alkyl analogs. Similar results are reported under the latter conditions using dialkylphosphite esters. A specific route to 7-alkylhypoxanthines and -xanthines utilizes prior blocking of N-9 with a tri-*n*-butylphosphine–cobalt(III) dimethylglyoxime complexing reagent. Conventional alkyl ating agents dissolved in chloroform are used in the absence of light (4 days) at ambient temperature. Isolated examples, possibly reflecting the particular alkylating reagent in use, are found where formation of the *N*-alkylpurine is also accompanied by some of an *O*-alkylated isomer. Detailed coverage of these topics is given in Sections 6.D.a, 6.D.c.

D. By Other Means (*H*211)

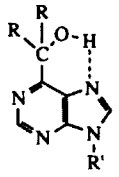
A complete summation of the diverse approaches dispersed throughout the volume is impossible, but representative example are isomerization of *O*-methyl to *N*-methylpurines, alkyl group migrations (real or apparent) between the purine ring nitrogens, the conversion of other groups in *N*-alkylpurines to oxo, and more esoteric transformations such as the desulfurization of oxopurines annelated with thiazine or thiazole rings to simple oxopurine derivatives.

3. THE EXTRANUCLEAR HYDROXYPURINES (*H*212)

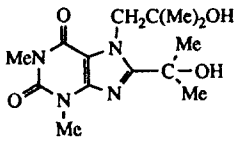
A. Preparation (*H*212)

Traube-type ring closures of 4,5-diaminopyrimidines with hydroxycarboxylic acids afford 8-hydroxyalkylpurines, whereas cyclization of 5-amino-6-hydroxyalkylaminopyrimidines with suitable reagents gives 9-hydroxyalkylpurines. Numerous examples from both closures are found throughout Chapter II.

Photoaddition of alcohols to purines under influence of UV or gamma radiation converts 6-unsubstituted-purines to the 1,6-dihydro-6-hydroxyalkyl analogs by addition across the 1,6-double bond.[1251] Nucleosides such as nebularine react in this way.[1251,1252] Isopropanol gives the diastereomers (**9**, R = Me, R′ = H) and (**9**, R = H, R′ = Me); the conformations are supported by NMR, IR and MS results.[1052] Intramolecular hydrogen bonding between the hydroxyl group and the imidazole nitrogen would be expected to contribute to formation of the preferred

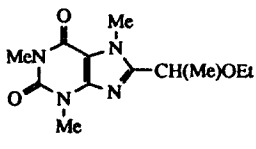


9

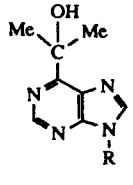


10

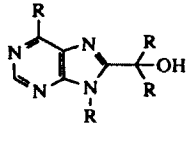
conformers.[1252] Aerial oxidation is sufficient to transform the adducts to the 6-hydroxylalkylpurines (**9**). In cases of 6-substituted purines, the photo adduct forms through either 7,8- or 8,9- double bonds, affording 8-hydroxyalkylpurines through oxidation of the dihydro form during the isolation procedure. An absence of diastereomeric forms is found in the 8-hydroxyalkylpurines examined, including those from adenine,[1252,1255] hypoxanthine,[1252] 6-ethoxypurine,[1252] guanine,[1255] and caffeine[1099,1252,1253] derived from reactions with methanol, ethannol, *n*-propanol, isopropanol, and *sec*-butanol. Various sensitizers employed with the light (>290 nm), such as aniline, acetone, carbazole, dicuminylperoxide, and di-*tert*-butylperoxide give near-quantitative yields of products.[1256] Isolation of the caffeine derivative (**10**) from interaction with isopropanol indicates that involvement of *N*-methyl groups is also a possibility.[1256] Radical inducers such as Fenton's reagent provide an alternative to irradiation, and with methanol adenine[1459] and guanine[1074] afford 8-hydroxymethyl analogs. Aliphatic and cyclic ethers with caffeine react likewise, the 8-(1-ethoxyethyl) derivative (**11**), for example,[1793] forms with diethyl ether. Analogous purines result at low temperature (–78°C) anaerobically on treating 9-tetrahydropyranylpurine in acetone with *n*-butyllithium, giving 6- and 8-(2-hydroxyprop-2-yl)purines (**12**, R = tetrahydropyranyl and **13**, R = H, R′ = Me). With an increase in temperatures, the 8-isomer is the predominant form. Likewise, from interaction of a 6-chloro-9-substituted purine with acetone and benzophenone, the respective 8-(2-hydroxyprop-2-yl)- (**13**, R=Cl, R′=Me) and 8-(2-hydroxydiphenylmethyl)-purines (**13**, R=Cl, R′=Ph) are obtained.[1093]. Purine with benzaldehyde forms 6-(α-hydroxybenzyl)purine in this manner.[1093] A series of 8-hydroxymethylxanthines and -guanines arises from rearrangements of 3-hydroxy-8-methylpurines in hot acetic anhydride followed by hydrolyses of the products. Weakly acid conditions (> 5) optimize yields and suppress formation of the 8-methylpurine[1235] (Chapter XI, Section 3.C). Direct alkylation, which provides the simplest route to *N*-hydroxyalkylpurines, is still widely practiced. The site of alkylation is usually governed by the usual procedures and conditions adopted in forming



11



12



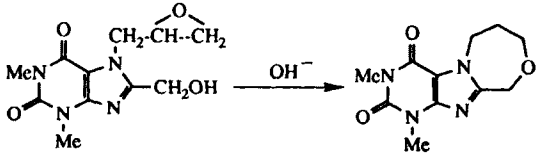
13

N-alkylpurines. Illustrative examples are the 9- and 3-(2,3-dihydroxypropyl)purines from the adenine anion (NaH, DMF) with glycidol in a 3:1 ratio.[1535] With ethylene carbonate,[1264] 9-(2-hydroxyethyl)adenine is obtained in greater yield than the 3-isomer.[1265] Use of ω-chloroalkylacetates with adenine and 6-benzylaminopurine necessitate acid hydrolyses to liberate the *N*-hydroxyalkyl derivatives.[1226] Less simple is formation of 9-(but-2-en-4-ol)adenine from an initial reaction with 1,4-dichlorobut-2-ene (NaH, DMF) which requires acid-catalyzed hydrolysis [HCl, Cu(I) Cl] of the 9-(4-chlorobut-2-enyl)purine intermediate.[1257] Hydrogenolysis (Pd–carbon) of the benzyl group yields 9-(2,4-dihydroxybutyl)adenine from the product between adenine and 1,2-anhydro-4-benzyloxybutan-1,2-diol.[1258] The 9-(2,3,5-trihydroxypentyl)analog is also formed from an alkylation with 1-benzyloxoy-5-mesyloxypentane-3,4-diol.[1259] Reactions of this type with 9-alkyladenines initially give the 1-hydroxyalkyl derivative, which under alkaline conditions can undergo a Dimroth rearrangement to the isomeric 6-hydroxyalkylaminopurine.[1472] Illustrative of N-1 alkylations are 9-ethyl-1-hydroxyethyladenine from 2-bromoethanol[1472] and 1-hydroxyethyladenosine from epoxyethane.[1473] Analogous derivatives are obtained from 9-ethylhypoxanthine[1472] and inosine,[1268] the latter being alkylated with 2-dimethylamino-1,3-dioxolane in DMF.[1268] An alternative reagent for hydroxyethylation is chloroepoxyethane in alkali, which is used to form 7-hydroxyethyl-8-alkyltheophyllines.[938] Simple epoxides in acid media react with 9-alkylguanines to give the 7-hydroxyalkyl quaternary purines, in acetic acid, epoxypropane gives both the 7-(2-hydroxypropyl) and 7-(3-hydroxyprop-2-yl) isomers in a 7:1 ratio.[1269] Other examples of epoxyalkylations of adenine and guanine are found in Tables 8 and 9, respectively. (Chapter VIII, Section 8.A.b). A more unsual application is formation of the bispurine, 2-(8-bromotheophyllin-7-yl)-3-(theobromin-1-yl) propanol, using 1-(2,3-epoxypropyl)theobromine as the alkylating agent in a reaction with 8-bromotheophylline.[1331] This route is the basis for numerous programs seeking antiviral agents and has lead to the syntheses of many 9-polyhydroxyalkyl- and 9-polyhydroxyalkoxyalkyl-purines. Compounds of this type are more adequately treated in Chapter VIII, Section 9. Guanine, usually the more soluble 2-acetamido analog, as noted above, undergoes acetylation at N-9. Reactions with 1,2-anhydro-4-benzyloxybutan-1,2-diol afford the 9-(2,4-dihydroxybutyl) derivative[1258] after debenzylation with sodium in liquid ammonia;[962] fusion of 1-acetoxymethoxy-2,3-diacetoxypropane with ethanesulfonic acid produces both 7- and 9-[(2,3-dihydroxy-1-propoxy)methyl]guanines following deacetylation with aqueous (40%) methylamine.[1260] The corresponding pair of 9- and 7-isomers in a 3:2 ratio is obtained from reaction with 1,2-benzyloxypropane and subsequent hydrogenation (Pd–carbon) for debenzylation to the 9- and 7-(1,2-dihydroxypropyl)purines.[1262] Employing trimethylsilylated guanine with 2,3-dibenzyloxy-1-propoxymethyl chloride affords the *R* and *S* enantiomers of a 9-dihydroxyalkylguanine.[1260] Condensation of acetylated guanine with the propthioxy analog in sulfolane (100°C, 6 h) with a bis(4-nitrophenyl)phosphate catalyst leads to 9-[(2,3-dihydroxy-1-propthioxy)methyl]guanine.[1261] Other examples of hydroxyalkyl groups linked to the purine through oxygen, sulfur, or

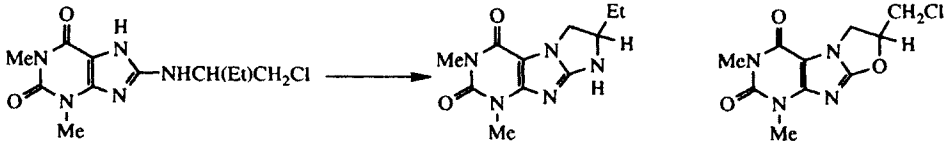
nitrogen atoms are located in Chapters VI, VII, and VIII respectively. One example of note is 8-(2-hydroxyethylthio)xanthine, which is formed when 2-hydroxyethanthiol and 3-acetoxyxanthine undergo a rearrangement in aqueous solution[1263] (Chapter XI, Section 3C).

B. Reactions of Extranuclear Groups (*New*)

A discussion of the formation of the simpler types of alcohol derivatives given by the hydroxyalkylpurines is omitted. Photolytic procedures are favored to remove 8-hydroxyalkyl moieties, UV irradiation (290 nm) is methanol containing a carbazole or DMF sensitizer converts 8-(2-hydroxyprop-2-yl)-adenine and-caffeine to the 8-unsubstituted-purines[1253]. Subsequently, hydroquinone or dimethylamine sensitizers in aqueous or methanolic solutions have been employed for dehydroxyalkylation with gamma radiation[1254]. Ease of elimination of the group increases with the number of carbons in the chain, as exemplified with caffeine derivatives that exhibit the sequence 8-hydroxymethyl < 8 -(1-hydroxyethyl) < 8-(2-hydroxyprop-2-yl)[1254]. Under the same conditions, 8-methyl- and other 8-alkyl-caffeines are not dealkylated. From treating 8-hydroxymethyltheophylline with 1-chloro-2,3-epoxypropane in dilute sodium hydroxide, the initial product (**14**) undergoes an alkali-catalyzed rearrangement to 7-hydroxyperhydro-1,4-oxazepine [3,4-*f*]theophylline[846] (**15**). Intramolecular alkylation by the chloroalkyl moiety with an adjacent ring nitrogen is a common feature following chlorination of the hydroxy group as, for example, in formation of the imidazo[1,2-*f*]purine (**17**) from 8-(1-chlorobut-2-yl)aminotheophylline[1032] (**16**). The related 7-chloromethyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7,hexahydrooxazolo[2,3-*f*]purine (**18**) from another synthesis appears to be the only other example of this class of annelated purine.[1794] Some variation in the activities of the hydroxy groups of 7-(2,3-dihydroxypropyl)caffeine is shown by reaction of only the 3-hydroxy with trityl chloride, thereby allowing the possibility of other reactions at the remaining alcohol group.[1795] Oxidation of hydroxyalkyl to formylalkyl (aldehydoalkyl) groups is noted elsewhere (Chapter IX, Section 5.B).



14 **15**



16 **17** **18**

4. PREPARATION OF ALKOXYPURINES (*H*214)

A significant advance is the use of tetraalkoxymethanes for ring closures in the Traube reaction, which enabled the first direct synthesis of 8-alkoxypurines from pyrimidines to be made. The application of *O*-alkylated phosphonates and other reagents to *O*-alkylate oxopurines directly is another notable innovation in alkoxypurine syntheses.

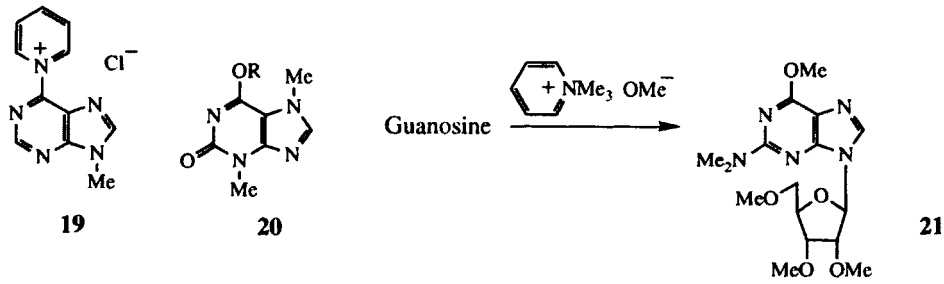
A. By the Traube and Other Ring Closures (*H*214)

A conventional preparation is 1,6-dihydro-2-methoxy-1-methyl-6-oxopurine from the 2-methoxy-4,5-diaminopyrimidine and an orthoester–anhydride mixture.[1282] Formation of 8-alkoxypurines using tetraalkoxymethanes is fully elaborated elsewhere (Chapter II, Section 1.X). Synthetic routes involving imidazole precursors are rare because existing alkoxy groups are usually destroyed by the ring-closure conditions used. One example obtained under unusually mild treatment (ambient temperature) is cyclization of the riboside of 5-aminoimidazole-4-(*O*-methyl)carboximidate with methoxy carbonylisothiocyanate followed by *N*,*N*′-1,3-dicyclohexylcarbodiimide, giving a 6-methoxypurine[965] (see Chapter III, Section 1.B.g). A more complex reaction is needed to explain the isolation of 6-ethoxypurine on heating a 4-ethoxymethylideneaminoimidazole-5-carbonitrile with sodium ethoxide (Chapter III, Section 1.E.a) and involves attack by the ethoxide ion on the cyano group[989].

B. By Displacement of Halogen or Other Substituent (*H*214)

Replacement of a chlorine or other halogen is still the route of choice, typical examples are found in Chapter V, Section 5.E. The innovations introduced are in situ chlorination of oxopurines ($POCl_3$) followed by treatment of the unisolated product with a sodium alkoxide. Representative derivatives from this approach are 6-ethoxy-3,7-dimethyl-2-methylimino- and the isomeric 2-ethoxy-3,7-dimethyl-6-methyliminopurines. To date, the reaction is limited to use with methyliminopurines and is inhibited by the presence of other amino or alkylamino groups.[1098] Condensations between 6-chloropurines and alkenyloxides are sensitive to the temperature and purine involved. Sodium allyloxide in dioxan or allyl alcohol or prolonged heating (15 h–24 h) forms the respective 6-allyloxy derivatives with 9-benzyl-6-chloro-[1221] and 2-amino-6-chloropurine[1178] and the *O*-acylated riboside of 2,6-dichloropurine.[1208] Homologous examples are 9-benzyl-6-propargyloxy-,[1221] 6-(3-methylbut-2-enyloxy)-,[1178] and 2-amino-6-cinnamyloxypurine.[1180] With temperatures above 100°C, the possibility of isomerizations of this type of alkenyloxypurine to *C*- or *N*-alkenylhypoxanthines should be noted (see Section 8.D). The susceptibility of the trimethylammonio

group to nucleophilic displacement is shown by kinetic studies to be some hundreds of time greater than for a halogen in the same purine. This applies if the group is present in either the betaine or quaternary salt form. This property allows reaction with alkoxides under very mild conditions, as in preparations of 2-ethoxy-9-methyl-[1140] (50°C, 5 min), 6-ethoxy-[1140] (55°C, 5 min), 6-ethoxy-9-methyl-[1140] (77°C, 0.25 h), and 2-amino-6-benzyloxypurine obtained at 20°C in quantitative yield.[1178,1270] The 6-pyridinium derivative (**19**) is converted to 6-methoxy-9-methylpurine in 92% yield in sodium methoxide.[1274] Esterification of the 6-oxo group in deoxyguanosines by 2,4,6-triisopropylbenzenesulfonyl chloride followed by trimethylamine (CH_2Cl_2, 0°C) gives 6-trimethylammonio derivatives converted to the 6-methoxy, 6-ethoxy, and 6-phenoxy analogs by reaction with the alcohol or phenol in alkali.[1272] Later extension of the work gives the 6-(2-trimethylsilylethoxy), 6-(2-phenylthioethoxy), and 6-(2-cyanoethoxy) derivatives.[1273] Studies with 2-, 6-, and 8-methylthiopurines show that the sulfur moiety is readily replaceable by an alkoxy[1271] group. The 2-methoxy analog of 1-methyl-2-methylthiopurine is obtained at room temperature with sodium methoxide,[1271] but reflux conditions are used to prepare 6-methoxy-3-methyl-[836] (0.5 h), 6-methoxy-9-methyl-[1271] (3 h), 8-methoxy-7-methyl-[1271] (0.25 h), and the isomeric 9-methyl-purine[1271] (1 h) from the respective 6- or 8-methylthiopurines. A series of 6-alkoxy-3,7-dimethyl-2-oxopurines (**20**, R = Me, Et, *n*-butyl, benzyl, and allyl) are obtained from the 6-methylthiopurines in the cold alcohol or DMF solution.[1871] An earlier preparation of **20** (R = Et) is by heating the 6-methylthiopurine with phosphoryl chloride followed by sodium ethoxide treatment.[1098] Substitutions involving oxidized methylthio moieties are found in the formation of 6-methoxy- and 6-phenoxy-9-phenylpurines using 6-methylsulfonyl-9-phenylpurine as precursor.[1079] Alkylseleno groups are more readily displaced than their sulfur counterparts. Use is made of the milder reaction conditions for riboside metatheses, for example, the 6-methoxylation of the ribosides of 6-benzylseleno-[1348] and 2-amino-6-methylselenopurine are typical.[1192]



19 **20** **21**

C. By *O*-Alkylation (*H*215)

In many examples encountered, especially in nucleosides, *O*-alkylation is an inadvertent side effect of *N*-alkylation. This observation supports an earlier

finding (*H*215) that oxopurine nucleosides, but not oxopurines themselves, undergo *O*-methylation with diazomethane. In aqueous alkali (pH > 10), trimethylphosphate converts deoxyguanosine mainly to the 1-methyl derivative (44%), but some 2-amino-6-methoxypurine riboside (9%) is produced.[1277] Inosine, by contrast, in an aprotic medium (DMF, K_2CO_3) with bromocyclopentane, gives the 6-cyclopentoxy derivative as the major product, together with half this amount of 1-cyclopentylinosine.[835] Quaternary methyl compounds can function as strong methylating agents; guanosine with trimethylanilinium methoxide[1275] (TAMM) in xylene (130°C) is permethylated to 2-dimethylamino-6-methoxypurine-9-(2′,3′,5′-tri-*O*-methyl)riboside[1276] (**21**). Surprisingly, neither inosine nor xanthosine undergo *O*-methylation with this reagent.[1276] A riboside-protected form of guanine reacts with bis(tri-*n*-butyltin)oxide [$(n\text{-}Bu_3Sn)_2O$] in benzene (reflux, 0.25 h), forming a 6-*O*-(*n*-butylstannyl) purine which undergoes substitution by alkoxide ions at room temperature.[1278] Direct *O*-alkylation in purines is not usual, but an exception occurs with uric acid. Following *N*-ethylation (Et_2SO_4, 65°C) in aqueous alkali, a mixed product of the expected 1,3,7,9-tetraethyluric and a 1,3,7 (or 9) -triethyl-8-ethoxyxanthine in a 2:1 ratio is formed.[1279] Similar examples of *O*-alkylation at C-8 in uric acid derivatives have been noted (*H*229). The identity of the compound isolated from methyl iodide reaction with 3-methylhypoxanthine, originally given as a 6-methoxypurine (*H*125), on reinvestigation was found to be the betaine form of 1,3-dimethylhypoxanthine.[1280]

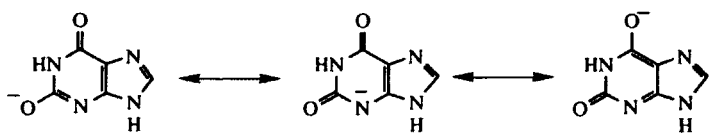
D. By Other Routes (*H*216)

All examples in this section are the result of a rearrangement of an existing purine or similar heterocycle. A solution of 3-acetoxyxanthine in methanol (20°C, 0.5 h) undergoes rearrangement to 8-methoxyxanthine. Equally good yields of analogous 8-alkoxy derivatives are obtained with other primary and secondary alcohols.[1116] No similar reaction, however, occurs with the 3-acetoxy derivative of 2-oxopurine.[861] A successful conversion of 7-hydroxyxanthine to 8-ethoxyxanthine is possible in ethanol.[920] More details of these and similar rearrangements are given in Chapter XI, Section 3.C. Isomerization of various 5-alkoxy-iminooxazolo[5,4-*d*]pyrimidines to 2-alkoxyhypoxanthines in a mixture of aqueous alkali and formamide were described earlier[953] (Chapter II, Section 8.B).

5. PROPERTIES OF OXO- AND ALKOXYPURINES (*H*216)

Extensive investigations have been and are continuing to be made into the effects of tautomerism and prototropy on the oxopurines. The methods most widely favored include X-ray crystallography, ^1H, ^{13}C, and ^{14}N NMR, IR, Raman, and UV spectroscopy, and dipole moment measurements. Different theoretical treatments have been applied to correlate calculated predictions and sites

of protonation with those established by physical methods. The long-standing question of whether both keto and enol states exist in simple oxopurines is now largely resolved. The consensus is that the keto tautomer is the major one in the solid state[1360] and in solution[1925, 1926] in the majority of cases. This also appears to be true for nucleosides, as demonstrated by Raman spectral results with inosine.[1921] An additional complication is the presence of mixtures of 7H and 9H protomers in which one form usually predominates. In hypoxanthine in DMSO, for example, ^{13}C NMR data indicate the existence of 58% of the 1H, 7H protomer and 42% of the 1H, 9H[1322] form. These results are consistent with predicted values obtained by CNDO/2 treatment.[1033] From an overview of oxopurines, it appears that the most stable forms in 2-, 6-, and 8-oxopurines, based on theoretical calculations and IR stretching frequencies are the 3H, 7H for 2-oxopurine with hypoxanthine adopting the 1H, 7H protomer, and 8-oxopurine having protons located at N-7 and N-9.[1033,1249] The correlations relate to findings in solution, but in the solid state the situation concerning the imidazole protomer is less well defined. In the solid state, crystallographic evidence supports hypoxanthine being present only as the 7H protomer,[1324] but in other states the amount of the 9H tautomer is not much less than that of the 7H isomer. Although established work shows that dipole movements of the two forms differ enough to distinguish between them, this technique is precluded by insolubility problems of the simple oxopurines in nonpolar solvents.[1033] For the dioxopurines, the xanthines are the most important, the 7H tautomer, predicted from CNDO calculations and long accepted to be the most stable form, is confirmed by ^1H NMR[1923] and dipole moment data from xanthines possessing a solubilizing group at C-8.[1922] From observations of the magnetic circular dichroism (MCD) spectrum of an aqueous solution of xanthine, a significant proportion of the 9H-protomer also appears to be present.[1694] Spectral studies with UV and ^1H NMR show that the neutral molecule of the isomeric 6,8-dioxopurine differs from that of xanthine by existing mainly as the 1H, 7H, 9H-tautomer.[1246] Current views on ion formation in monooxopurines remains largely the same as those given in the original findings of Mason.[1924] Most recent work with 8-oxopurine shows that anion formation[1249] is through hydrogen abstraction from N-9 and that the cation results from protonation[1249, 1290] at N-1. With the dioxopurines, examination of the xanthine anion in the solid state shows that both N-3 and N-7 can lose hydrogen, suggesting that canonical structures such as **22A–22C** are involved.[1329] Deductions from methylation studies with 2,8-dioxopurine are that anion formation could be through either N-7 or N-9, whereas protonation is mostly likely at N-1.[903] In the case of the isomeric 6,8-dioxopurine, anion formation is unusual in that each of the protons at N-1, N-7, and N-9 are lost with equal facility. The site of protonation is unclear, but N-3 is



22A **22B** **22C**

favored for cation formation.[1246] Further details on individual oxopurines including uric acid are given in (Sections 11 to 14) of this chapter.

6. REACTIONS OF OXOPURINES (*H*217)

B. Oxo to Thioxo Group (*H*217)

By heating the 6-oxopurines with a generous excess (> 3 mol. equiv.) of phosphorus pentasulfide in pyridine or the higher-boiling β-picoline widens the range of thioxopurines available by this established route. Metatheses of hypoxanthines to 6-thioxo analogs include the 1-*n*-butyl,[835] 7-cyclopentyl,[835] 1-methyl-8-phenyl,[872] 9-methyl-8-phenly,[872] 1,9-dimethyl-8-phenyl,[872] and 3,9-dimethyl-8-phenyl[872] derivatives. That no significant adverse reaction occurs owing to the presence of existing thioxo or methylthio groups is exemplified in thiations of 1-methyl-2-methylthio-[890](β-picoline, 6 h), 3,7-dimethyl-8-methylthio-[882] (pyridine, 0.5 h), 8-phenyl-2-thioxo-,[874] 9-methyl-8-thioxo-[882] (pyridine, 3.5 h), as well as 3-methyl-[887] and 9-methyl-2,8-dithioxo-6-oxopurines[887] (pyridine, 5 h). Further preparations using dioxopurines, which highlight the general resistance of 2- and 8-oxo groups to sulfur replacement, are formation of the corresponding 2-oxo-6-thioxo analogs from the 9-methyl-[1281](β-picoline, 4 h), 1,7-dimethyl-[1282] (pyridine, 15 h), 1,9-dimethyl[1282] (pyridine, 15 h), 3,9-dimethyl[1281] (β-picoline, 7 h), 1,3,9-trimethyl[1281] (3 h), and 1,3-dimethyl-8-phenyl[874] (β-picoline) homologs of xanthine. A 90% yield of the 6-thioxo analog of caffeine is claimed with tetraphosphorus decasulfide combined with sodium hydrogen carbonate in diglyme[1927] (110°C, 5 h). The 8-thioxo derivative of 9-methylxanthine is the precursor for the 9-methyl-2-oxo-6,8-dithioxopurine[890] (pyridine, 4 h). In view of these results, the reported conversion of 9-methylxanthine directly to the 2,6-dithioxo analog (β-picoline, 6 h) must be viewed with some reservation,[887] though with more forcing conditions a replacement of a 2-oxo group is possible (*H*219). Only the 6-thioxopurine is obtained from 1-methyl-[1249] (picoline, 2.5 h) and 9-methyl-6,8-dioxopurines[1243] (pyridine, 8 h). One preparation of 6-thioguanine from guanine made use of a sulfolane solvent.[1928] An unprotected guanosine is converted in a one-pot reaction (0°C, 24 h) by treating with pyridine containing trifluoroacetic anhydride followed by sodium hydrosulfide; the last stage involving reaction of a 6-pyridinium intermediate with the sulfide ion.[1929]

C. Replacement of Oxo by Hydrogen (*H*220)

No examples of simple replacements by hydrogen apart from those involving reduction procedures (Chapter XII) are available. The conventional routes of converting the oxo group to another which can be readily replaced, such as halogeno, thioxo, or alkylthio, are still the normal practice. A complex mecha-

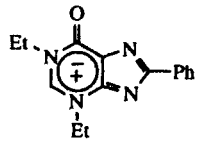
nism operates in the transformation of xanthine into hypoxanthine by rigorous heating (260°C) in *N*-benzylformamide.[1234] Loss of the 8-oxo function from treatment with formic acid and trimethylamine are cases of extended Traube reactions giving the corresponding xanthines (Chapter II, Section 1.B).

D. *N*-Alkylation of Oxopurines (*H*220)

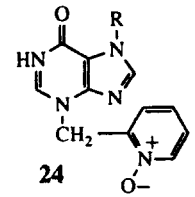
This topic, together with that of the analogous thioxopurines, has been extensively investigated by F. Bergmann and his group, who compared reactions in aprotic solvents such as DMF and acetonitrile with those in aqueous alkali. From these studies, solvent effects on alkylation sites have been determined. In the parent volume the statement that diazoalkanes were the only alkylating agents capable of both *O*- and *N*-alkylation now requires modification in view of the introduction of reagents also possessing this function (see Section 4.C). Although *O*- to *N*- alkyl rearrangements of the Hilbert–Johnson type with alkoxypurines are routes to *N*-alkyloxopurines, these and similar rearrangements are separately treated in Section 8.D. Use of ^{1}H and ^{13}C NMR[1971] and ^{15}N NMR spectra[1972] enables differentiation between derivatives alkylated at N-7 and N-9.

a. Monooxopurines (H221)

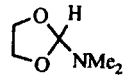
Hypoxanthine affords the 1,7-dialkyl derivative in alkaline media, but specific alkylation only at N-7 occurs in a dark reaction (20°C, 4 days) in dichloroethane or chloroform in the presence of a complex derived from tri-*n*-butylphosphine, dimethylglyoxime, and cobalt. Complexation occurring at N-9 permits formation of 7-methyl- (64%) and 7-benzyl-hypoxanthine (39%).[1283] In aprotic media (MeCN), ethyl iodide and 8-phenylhypoxanthine interact, forming the 1,3-diethylpurinium iodide which, on base ion-exchange treatment, gives the mesoionic form[1284] (**23**). Analogous 1,3-dimethyl and 1,3-dibenzyl derivatives are similarly obtained.[1284] Methylation (MeI, MeCN, 60°C, 72 h) of 3-benzyl-8-methylhypoxanthine affords the 1,8-dimethyl homolog, but under more vigorous conditions (DMF, reflux, 4 h), with 3,8-dimethylhypoxanthine, the 3-methyl group is lost and 1,7,8,9-tetramethylhypoxanthinium iodide is obtained through rearrangement of a quaternary intermediate[873] (see Section 7.B). In a similar reaction with benzyl bromide (MeCN, reflux, 20 h), the methyl at N-3 remains intact, giving 1-benzyl-3,8-dimethylhypoxanthine.[873] The effect of changing to an aqueous alkaline medium is demonstrated on reacting benzyl bromide with the



23

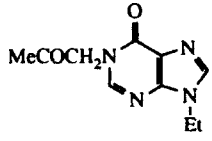


24



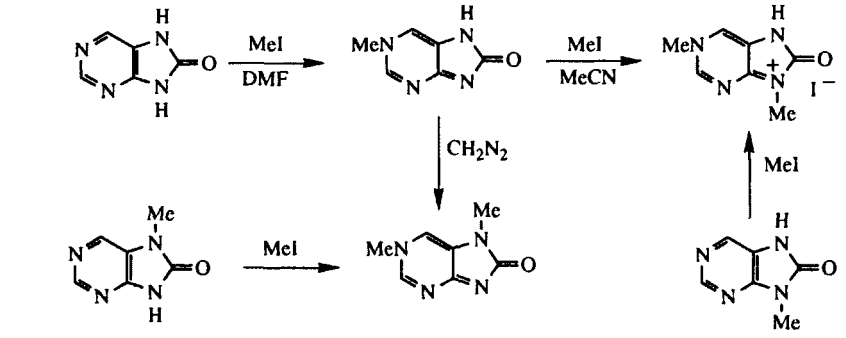
25

3-alkylhypoxanthine (**24**, R = H)—the product is the 7-benzylated purine (**24**, R= CH_2Ph). Acetic anhydride treatment removes the picolin-2-yl-*N*-oxide protecting group yielding 7-benzylhypoxanthine.[1285] Alkylation of the latter purine with ethoxycarbonylmethyl bromide (DMF, NaH) affords 7-benzyl-1-ethoxycarbonylmethylhypoxanthine.[1271] In aprotic media containing a base, 9-alkylhypoxanthines form the 1,9-dialkyl homologs. Representative examples are 9-benzyl-1-propargyl[1221] and the 1-*n*-butyl- and 1-cyclohexenylinosines—on hydrogenation, the latter gives the 1-cyclohexyl analog.[835] With 2-dimethylamino-1,3-dioxolane (**25**) as alkylating agent, inosine in DMF yields a 1-(2-hydroxyethyl) derivative.[1268] Aqueous alkali provides the basic conditions for methylation of 9-methyl-8-phenylhypoxanthine to the 1,9-dimethyl-8-phenylpurine.[872] The 1-allyl-9-benzyl derivative is by allylbromide interaction (MeOH, NaOMe) with 9-benzylhypoxanthine.[1221] Methyl iodide in an aprotic medium in the absence of base converts 1,7-,[873] 1,9-,[873] and 7,9-dimethylhypoxanthines[873,1287] to the 1,7,9,-trimethylpurinium iodide. The same trimethylated derivative is obtained using the same reagent without a solvent on 1,9-dimethylhypoxanthine complexed with mercury(II) chloride.[1309] Inosine in DMSO with benzyl bromide gives 7-benzylinosine which, through easy hydrolysis of the ribosyl moiety, provides a convenient route to 7-benzylhypoxanthine.[1286] An earlier claim[1288] to forming 1,7,9-trimethylhypoxanthine by alkylation of 1-methylhypoxanthine is now discounted.[1289] An unusual reaction is the formation of 9-benzylhypoxanthine from hypoxanthine by heating with benzylamine hydrochloride in *N*,*N*-dimethylcyclohexylamine and phosphorus pentoxide (170°C, 24 h).[1302] Using benzylamine in place of the hydrochloride salt affords only 6-benzylaminopurine.[1302] An intramolecular rearrangement would explain the isolation of 1-acetonyl-9-ethylhypoxanthine (**26**) when 9-ethyl-6-iodopurine is treated with bromoacetone enolate. The mechanism assumes that hydrolytic fission of an azirinium intermediate is involved.[1071]



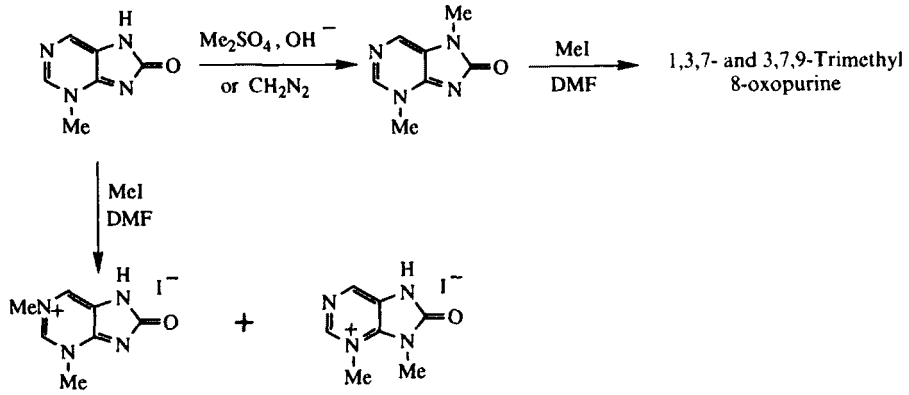
26

A good yield (ca. 90%) of the 1-methyl homolog is obtained from methyl iodide treatment in DMF (20°C, 48 h) of 7,8-dihydro-8-oxopurine. More rigorous conditions (reflux, 72 h) in acetonitrile afford the 1,9-dimethylpurine (Scheme 1), which is also formed using 9-methyl-8-oxopurine as precursor.[1290]



Scheme 1

Correspondingly, 7-methyl-8-oxopurine yields the 1,7-dimethyl analog, for which an alternative route is diazomethane treatment of the neutral molecule of the 1-methyl-8-oxopurine. Alkaline dimethylsulfate (2.5*M* NaOH) converts 3-methyl-8-oxopurine under mild conditions (20°C, 1 h) to the 3,7-dimethyl homolog (Scheme 2); diazomethane also gives the same product.[1290] A mixture of the 1,3- and 3,9-dimethyl isomers is obtained from slow methylation (20°C, 1 week) of the 3-methyl-8-oxopurine in DMF[1290] by methyl iodide.



Scheme 2

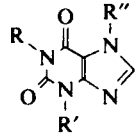
b. Dioxopurines (H223)

Selective alkylations of xanthine derivatives are now facilitated by the introduction of new reagents and procedures. Under neutral conditions as a cobalt complex (see previous Section 6.D.a), xanthine gives only the 7-methyl (86%) and 7-benzyl (77%) homologs, owing to quaternization of N-9 by the cobalt moiety.[1283] Trialkylphosphates in alkaline solution convert xanthines to a mixture of the 3,7-dialkyl and 1,3,7-trialkyl derivatives under mild (25–60°C, 48 h) condi-

tions. With trimethylphosphate, both theobromine and caffeine form, but at higher temperatures caffeine (73%) is the only product.[1291] Reagents with alkyl groups other than methyl favor formation of dialkylxanthines, which possibly indicates steric interference at N-1 by the adjacent carbonyl groups; both 3,7-diethyl- and 3,7-diallylxanthine provide representative examples.[1291] Using higher temperatures (140–200°C) without alkali, however, yields mainly 1,3,7-trialkyl derivatives.[1292] A useful innovation for improving alkylations is application of tetraalkylammonium fluoride catalysts. A restricted example is preparation of caffeine (85%) with trimethylphosphate in a chlorohydrocarbon solvent at 25°C containing tetrabutylammonium fluoride. Other trialkylphosphates are less successful, but their replacement by alkyl halides gives better results.[1293] Both dimethyl and diethylsulfate in THF give, respectively, caffeine (99%) and 1,3,7-triethylxanthine (76%) together with some (24%) of the 3,7-diethyl derivative using either tetrabutylammonium fluoride or hydroxide catalysts. Reactions are usually completed within 0.5 h, but with tetrabutylammonium bromide no reaction ensues.[1294] Phase transfer catalysis procedures with aqueous solutions of these quaternary ammonium derivatives are illustrated by the 1,3,7-trimethyl- (99%) and 1,3,7-triethylxanthines (45%) obtained in benzene or dichloromethane with methyl or ethyl bromide and tetra-*n*-butylammonium hydroxide.[1295] No significant difference in the reaction results are obtained using sodium hydroxide to replace the ammonium base in the aqueous phase. Under these conditions, no evidence for *O*-alkylation is found.[1295] A novel methylation of xanthine to caffeine (85%) occurs in DMF (100°C, 0.5 h) using trimethylselonium hydroxide.[1452] A rapid permethylation of xanthine in DMSO occurs with a methyl iodide–sodium methoxide reagent, but the absence of any *O*-methylated derivatives should be noted.[1998] Modifications or improvements to conventional alkylation practices include the use of weak alkali (pH·7.6–9.0) in forming theobromine from 3-methylxanthine.[1296] Ethylation in dimethylformamide containing potassium carbonate and a sodium iodide catalyst transforms 3-ethyl- to 1,3,7-triethylxanthine.[843] Aqueous methylation (Me_2SO_4, KOH) affords 3-benzyl-1,7-dimethylxanthine from 3-benzylxanthine.[833] In the same medium at room temperature, methylation (MeI) of 7-benzyl- to mainly* 7-benzyl-3-methylxanthine occurs with the 1,3-dimethylated homolog as secondary product.[889] More recent syntheses of caffeine from theophylline include phase transfer catalysis[1295] with trimethylphosphate[1291] and trimethylphosphite, the latter requiring more vigorous treatment (130°C) and no solvent.[1297] The phosphite esters appear to have only a limited application in alkylations and are restricted to methylations. Table 5 gives a representative selection of topical alkylations of theophylline derivatives to 1,3,7-trialkylpurines. More complex products result using alkylating agents having more than one functional group, as in the reaction of 1-chloro-2,3-epoxypropane with 8-hydroxymethyltheophylline in aqueous alkali with a Triton B catalyst producing the tricyclic derivative[889] (**27**). The steric problems sometimes encountered using reagents with more bulky alkyl groups than methyl can

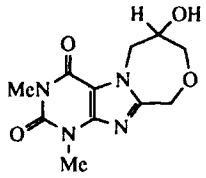
* This product was wrongly identified by Traube[181] as the isomeric 7-benzyl-1-methylxanthine.

TABLE 5. Alkylation of Theophylline and Other 1,3-Dialkylxanthines to 1,3,7-Trialkylxanthines

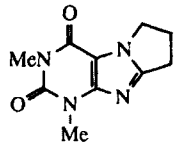


R′	R′	R″	Reagent	Conditions[a]	N7-Alkyl Group	Ref.
Me	Me	H	$(MeO)_3PO$	140–200°C	Me	1292
Me	Me	H	$(MeO)_3PO$	–60°C, OH^-	Me	1291
Me	Me	H	$(MeO)_2PO$	130°C	Me	1297
Me	Me	H	MeBr	PTC, *n*-Bu_4NOH	Me	1295
Me	Me	H	Me_2SO_4	PTC (no solv.) *n*-Bu_4NOH, OH^-, 120°C	Me	1359
Me	Me	H	$(EtO)_3PO$	140–200°C	Et	1292
Me	Me	H	$(EtO)_3PO$	60°C, OH^-	Et	1291
Me	Me	H	$(EtO)_2PO$	130°C	Et	1297
Me	Me	H	EtBr	PTC, *n*-Bu_4NOH	Et	1295
Me	Me	H	BuBr	PTC (no solv.) *n*-Bu_4NOH, OH^-, 180°C	Bu	1359
Me	Me	H	$PhCH_2Cl$	PTC, *n*-Bu_4NOH	CH_2Ph	1295
Me	Me	H	$PhCH_2Br$	PTC (no solv.) *n*-Bu_4NOH, OH, 80°C	CH_2Ph	1359
Me	Me	H	β-Propiolactone	DMF	$CH_2CH_2CO_2H$	1529
Me	Me	H	$(C_3H_6O)_3PO$	60°C, OH^-	$CH_2CH{=}CH_2$	1291
Me	Me	H	$CH_2{=}CHOAc$	$HgOAc/H^+$	$CH{=}CH_2$	1215
Me	Me	H	$Cl(CH_2)_3OH$	Na^+,DMF,100°C	$(CH_2)_3OH$	1298
Me	Me	H	$CH_2{=}CHCN$	NaOMe, Pyridine, 250°C	CH_2CH_2CN	1298
Me	Me	Me		NaOH, reflux	CH_2CH_2OH	938
Me	Me	Me	$ClCH_2CN$	K_2CO_3, DMF, 140°C	CH_2CN	938
Me	Me	Me	$CH_2{=}CHCN$	NaOMe, Pyridine, 150°C	CH_2CH_2CN	1298
Me	Me	Et		NaOH, reflux	CH_2CH_2OH	938
Me	Me	Et	$ClCH_2CN$	K_2CO_3, DMF, 140°C	CH_2CN	938
Me	Me	Et	$CH_2{=}CHCN$	NaOMe, Pyridine, 150°C	CH_2CH_2CN	1298
Me	Me	*n*-Pr		NaOH, reflux	CH_2CH_2OH	938
Me	Me	*n*-Pr	$ClCH_2CN$	K_2CO_3, DMF, 140°C	CH_2CN	938
Me	Me	*n*-Pr	$CH_2{=}CHCN$	NaOH, Pyridine, reflux	CH_2CH_2CN	1298
Me	*i*-Bu	H	MeI	K_2CO_3, DMF	Me	831
Me	*i*-Bu	H	$PHCH_2Br$	K_2CO_3, DMF	CH_2Ph	831
Me	*i*-Bu	H	$BrCH_2CH(Me)Et$	K_2CO_3, DMF	$CH_2CH(Me)Et$	831
Me	Me	CH_2OH	Me_2SO_4	NaOH	Me	843
Me	Me	CH_2OH		Triton B, H_2O, reflux		846
Et	Et	CH_2OH	Me_2SO_4	NaOH	Me	843
Me	Me	CH_2OH	$PhCH_2Br$	NaI, K_2CO_3, DMF	CH_2PH	843
Me	Me	CH_2OH	$CH_2{=}CHCH_2I$	NaI, K_2CO_3, DMF	$CH_2CH{=}CH_2$	843
Me	Me	CH_2Ph	$PhCH_2Br$	DMF, 150°C	CH_2Ph	847
Me	Me	CH_2Ph	$PhCH_2Br$	Na_2CO_3, Acetone, 20°C	CH_2Ph	901

[a] PTC = Phase transfer catalysis.



27



28

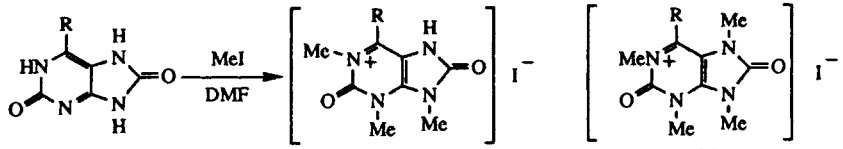
be overcome in some cases by addition of a sodium iodide catalyst (see above), as utilized in the benzylation of 8-hydroxymethyltheophylline in DMF containing potassium carbonate.[843] Similar observations apply to alkylation of the 8-cyanomethyl analog with alkyl halides other than methyl halides.[916] The absence of any steric effect by an 8-benzyl group is surprising; benzyl bromide in acetone–potassium carbonate or aqueous alkali converts 8-benzyl- to 7,8-dibenzyltheophylline at ambient temperature.[901] A demonstration of autoalkylation is the tricyclic (**28**) from heating (50°C, 18 h) 8-(3-chloropropyl)theophylline in sodium hydroxide.[1299] The attempted formation of the 7,9-dibenzyltheophylline quaternary salt from 9-benzyltheophylline and benzyl bromide in DMF gives only 7-benzyltheophylline as product. This apparent benzyl group rearrangement is discussed further in Section 7.B.

Alkylation of theobromine and related, 3,7-dialkylxanthines parallels that of theophylline in forming 1,3,7-trialkylxanthines. Phase-transfer conditions with methyl, ethyl, and benzyl bromides afford reasonable yields of the 1-methyl (56%), 1-ethyl (72%), and 1-benzyl (98%) homologs.[1295] For comparison, using trialkylphosphates on the same substrate (60°C, 48 h) yields the same or similar derivatives—1-methyl (93%), 1-ethyl (10%), and 1-allyl (16%). The low reactivity of N-1 and steric effects from the adjacent oxo groups are used to explain the poor yields of the last two.[1291] A reported failure to ethylate either theobromine or the 3,7-diethyl analog using triethylphosphate is probably due to the high temperatures used (between 140 and 200°C) and the omission of alkali.[1292]

As more information on alkylation of 2,8-dioxopurines is now available, a reappraisal of earlier results is possible. In aqueous alkali (Me_2SO_4), the parent purine behaves like the 1-methyl homolog in forming an equal mixture of the 1,3,7- and 1,7,9-trimethyl derivatives.*[903] The data suggest the alkylation sequence is 1-methyl, then a mixture of 1,7- and 1,9-dimethylpurines, and finally the respective trimethylated isomers. Under the same conditions, the 7-methyl-2,8-dioxopurine also gives the mixture of 1,3,7- and 1,7,9-trimethyl derivatives.[903]

In neutral media (DMF, MeI), alkylation of the unsubstituted purine (**29**, R = H) gives the 1,3,9-trimethylpurinium iodide[1300] (**30**, R = H); the 6-methyl analog (**30**, R = Me) is likewise formed.[903] Further alkylation of either the 1,3,7- or 1,7,9-trimethylpurines in aprotic media (MeI, DMF) yields 1,3,7,9-tetramethyl-2,8-dioxopurinium iodide (**31**).[903]

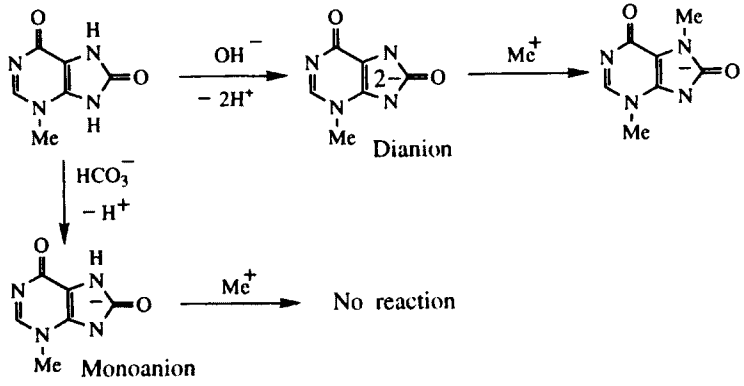
*In an early paper Johns[555] claimed 1,7,9-trimethyl-2,8-dioxopurine as the only product from methylation of either the 1,7- or 1,9-dimethyl derivatives, but the discussed above work[903] shows the correct structure of this to be the 1,3,7-trimethyldioxopurine.



29 30 31

Methylation patterns of 6,8-dioxopurines either as neutral molecules in DMF, anions in aqueous sodium hydrogencarbonate, and dianions in sodium hydroxide solution have been determined.[1246] The neutral form of the parent purine undergoes initial methylation at N-3 and subsequent conversion to the unstable, 1,3-dimethyl homolog together with some 1-methyl- and 1,9-dimethyl-6,8-dioxopurines. A notable feature is the relatively unstable nature of these derivatives. Both 1- and 3-methyl-6,8-dioxopurines afford the 1,3-dimethylated homolog, but with prolonged treatment the latter is degraded to a mixture of 1-methyl- and 1,9-dimethyl-6,8-oxopurines. The sequence of further alkylation of the 7-methyl-6,8-dioxopurine is to the 3,7-dimethyl and finally to the 1,3,7-trimethylpurine. Other routes to the latter are by methylation of either 1,7- or 3,7-dimethyl-6,8-dioxopurines. Removal of the 3-methyl group of the 1,3,7-trimethylpurine is described in Section 7.B.[1246] The isomeric 1,3,9-trimethyl-6,8-dioxopurine is obtained at room temperature from the 3,9-dimethylpurine or from the 1,3-dimethyl betaine form on heating with a 50-fold excess of MeI in DMF.[873] Prolonged heating transforms the 1,3,9- to the 1,7,9-trimethyl isomer initially, but degradation to the 1,9-dimethylpurine occurs ultimately.[873] Contrasting behavior is shown by the 9-methyl, 1,9-dimethyl, and 7,9-dimethyl derivatives, which do not undergo further reaction even at elevated temperatures.[1246]

With the monoanion of 6,8-dioxopurine, methylation at N-9 is favored initially, but the final product is the 1,7,9-trimethyldioxopurine. Intermediates in the process are the 1,9- and 7,9-dimethyl derivatives. Alkylation of the 1-, 7-, or 9-methyl dioxopurines gives the same 1,7,9-trimethyl-6,8-dioxopurine. Although the 3,9-dimethyl- is readily converted to a 3,7,9-trimethylated homolog, failure of either the 3-methyl or 3,7-dimethylpurines to react likewise may reflect steric hindrance due to the proximity of the 3-methyl group which obstructs alkylation at N-9.[1246] Reactions of the dianionic form of 6,8-dioxopurine reflect the more random charge distribution in the molecule. The formation of 1-, 3-, 7-, and 9-methyl as well as the 1,9-dimethyl and 1,7,9-trimethylpurines on alkylation illustrates this point fully. Methylation of the 1-methyl derivative gives a mixture of the 1,7- and 1,9-dimethyl derivatives, while the 3-methyl isomer is converted to the 3,7-dimethyl homolog. Reactivity of the dianion of 3-methyl-6,8-dioxopurine is in sharp contrast to the inert character of the anionic form noted above. This situation is rationalized by formulating the anion as being derived by proton loss from the sterically hindered N-9, in the case of the dianion, although both imidazole nitrogens carry negative charges, only N-7 is available for alkylation[1246] (Scheme 3). Product mixtures also arise with the 7-methyldioxopurine from which 1,7-, 3,7-, and 7,9-dimethylated purines result; 7,9- and 1,9-dimethyl- and some 1,7,9-trimethylpurine are obtained from the 9-methyl isomer.[1246]



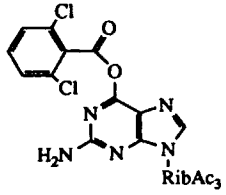
Scheme 3

c. Trioxopurines (H228)

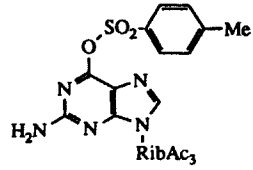
The expected 1,3,7,9-tetraethyl derivative is obtained on treating uric acid with diethyl sulfate in warm (65°C) aqueous potassium hydroxide. Also formed is 8-ethoxy-1,3,7 (or 9) -triethylxanthine as the minor component of a 2:1 mixture. Production of the *O*-ethylated isomer is aided by using low-temperature conditions.[1279] An *N*-permethylated derivative results when uric acid is treated with a methyl iodide–sodium methoxide mixture in DMSO, but the absence of *O*-methylated derivatives is notable.[1998]

F. Acylation of Oxopurines (*H*231)

Direct *O*- as opposed to *N*-acylation remains relatively uncommon. One of the few cases utilizes 2,6-dichlorobenzoyl chloride to give the *O*-acylated guanosine (**32**). Unlike benzoyl chloride this reagent forms no *N*-benzoyl derivatives.[1301] Examples of *O*-acylation of *N*-hydroxypurines are noted in Chapter XI, Section 3.B. Somewhat relevant to this section are reactions of similar character which give *O*-substituted purines of the type (**33**) using 4-bromo- and 4-methyl-benzenesulfonyl chloride.[1301]



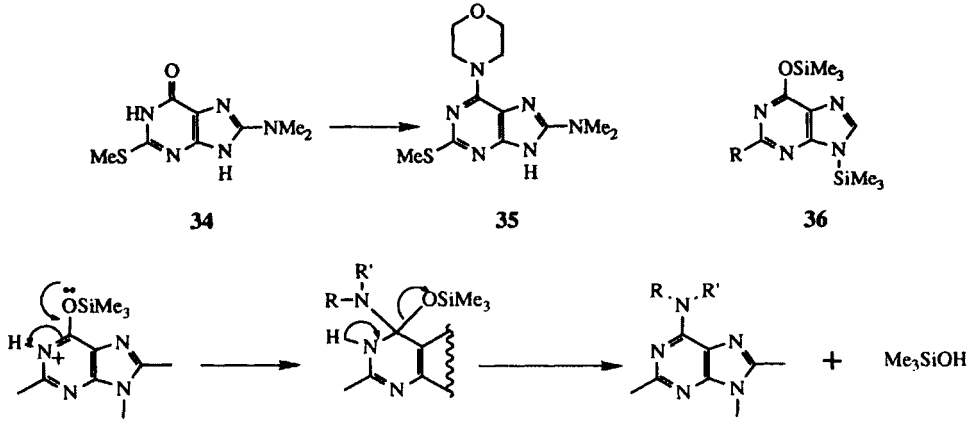
32



33

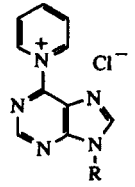
G. Oxo to Amino Group (*H*232)

The various novel routes devised range in scope from direct high-temperature interaction of amines with oxo groups to using a modified oxo group through prior reaction with phosphoryl chloride or phosphoric acid amides and extended reaction times. Heating with morpholine or piperidine (105–130°C, 3.5 h) converts 8-dimethylamino-2-methylthio-6-oxo-1,6-dihydropurine (**34**) to the 6-morpholino (**35**) and 6-piperidino derivatives.[910] The unreactive nature of the methylthio group at C-2 is noteworthy in view of the prevailing conditions. Both primary and secondary amine hydrochlorides in conjunction with phosphorus pentoxide and *N,N*-dimethylcyclohexylamine provide another direct one-step amination. Hypoxanthine undergoes a facile conversion with many amines (187°C, 14 h) to the 6-aminopurine.[1302] Benzylamine salts, giving 9-benzylhypoxanthine, are an exception, but using benzylamine itself under these same conditions affords 6-benzylaminopurine.[1302] A similar anomaly is observed between the hydrochloride of cyclohexylamine and the free base, the former converting hypoxanthine to 6-dimethylaminopurine, whereas 6-cyclohexylaminopurine is obtained with the latter.[1302] Following silylation of the oxo group of both hypoxanthine (**36**, R = H) and guanine (**36**, R = $NHSiMe_3$), amination is possible with ammonia, amine hydrochlorides, or amines combined with a Lewis acid such as mercury(II) chloride (145°C, 22 h),[1303,1304] trimethylchlorosilane, or *p*-toluensulfonic acid hydrate (140°C, 16–60 h).[1305] Acid conditions are mandatory to enable protonation to occur at N-1, thereby facilitating removal of the silyl group[1305] (Scheme 4). Corresponding 6-oxo group amination are possible with inosine, guanosine, and xanthosine.[1305] The 2-amino, 2-methylamino, and 2-dimethylamino derivatives of 3,7-dimethylhypoxanthine are converted to the 6-dimethylaminopurine analogs by dimethylamine and phosphoryl chloride treatment. As the isomeric 2-oxo-6-aminopurines are likewise transformed into the 2-dimethy-

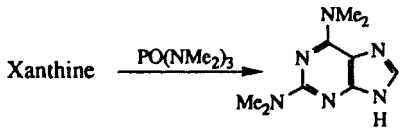


Scheme 4

laminopurines, the chlorination–amination reaction is seen to apply to both 2- and 6-oxopurines.[1098] Quaternary pyridinium derivatives of the type (**37**, R = H) result from an extension of the procedure using 4-chlorophenylphosphorodichloridate and pyridine on hypoxanthines[1306] which forms for example, the 9-benzyl homolog[1274] (**37**, R = CH_2Ph). A brief reference to the early application of phosphorus acid amides as aminating agents is given in the original work (*H*232). The versatility of this procedure is shown by subsequent reaction carried out at relatively elevated temperature (235°C). With *N,N'N''*-trisdimethylphosphoric triamide, hypoxanthine yields 6-dimethylaminopurine and the 6-benzylamino analog with *N,N'N'''*-tribenzylphosphoric triamide.[1307] Adenine and various 9-benzyl derivatives are obtained directly from hypoxanthines using phenylphosphorodiamidic acid [$P(O)(NH_2)_2OPh$], and with the appropriate amide 6-anilinopurine results.[1307] With xanthine, both oxo groups can be aminated as, for example, in the formation of 2,6-bisdimethylaminopurine[1308](**38**).



37



38

H. Trimethylsilylation of Oxopurines (*New*)

Early work on this topic was aimed at providing more volatile oxopurine derivatives for use in gas chromatography and mass spectral investigations. Current interest centers on the ability of such modified oxo groups to undergo nucleophilic displacements under nonrigorous conditions. Prolonged heating of the oxopurine with trimethylchlorosilane or hexamethyldisilazene (155°C, 16 h) affords the *O*-trimethylsilyl derivatives.[1304,1305] A mixture of the chlorosilane and *O,N*-bistrimethylsilylacetamide with triethylamine is a more recently introduced reagent.[1260] Illustrative examples of *O*-silylated derivatives are given by hypoxanthine, guanine,[1304,1305,1316] and xanthine[1316] as well as the associated inosine guanosine, and xanthosine nucleosides.[1305] Any primary or secondary amino groups present may also react, as exemplified by the tristrimethylsilylation of guanine at the oxygen, the 2-amino group, and N-9[1260] to **36**, R = $NHSiMe_3$.

7. REACTIONS OF *N*-ALKYL-OXOPURINES (*H*233)

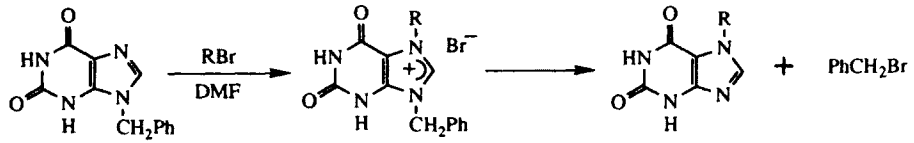
Some aspects have been reviewed recently.[1347]

A. Replacement of *N*-Alkyl Groups by Hydrogen (*H*233)

Direct displacement by hydrogen is usually confined to benzyl and like groups which are readily removed by catalytic hydrogenation or reaction with 48% hydrobromic acid. The latter treatment appears to be of more general utility, as exemplified by the debenzylation of the 3-benzyl derivatives of dimethyl-[873] (20°C, 3 days), 7-methyl-8-[883] (reflux, 0.75 h), and 1,7-dimethyl-8-methylthiohypoxanthines[883] (70°C, 3 h). By contrast, this reaction fails with 3-benzylxanthine and -uric acid derivatives.[833] Cases of thermally induced *N*-methyl group deletions show N-3 to be the most susceptible position at which this reaction takes place. Corresponding 3-methyl deficient purines result when the iodides of 1,3-dimethyl-,[873] 1,3,7-trimethyl-,[873] and 1,3,9-trimethyldioxopurines[873] are heated, the methyl being lost as methyl iodide. The possibility of this iodide causing further methylation elsewhere in the purine is discussed in Section 7.B. In a more complex example, on heating 7,9-dimethylhypoxanthinium iodide (DMF), both imidazole methyl groups are labile, giving a mixture of 9- and 7-methylhypoxanthines, the latter being a minor component.[873]

B. Rearrangement of *N*-Alkyl Groups (*H*234)

An apparent alkyl group migration occurs in the formation of 7-benzylxanthine on heating the 9-benzyl isomer with benzyl bromide or hydrobromic acid in DMF.[889,1308] Corresponding transformations occur also with the 9-benzyl-1-methyl and -1,3-dimethyl homologs.[889] The presence of halide ion is necessary for the reaction, the mechanism of which involves quaternization of the imidazole ring with a subsequent fission of the 9-benzyl group from the intermediate as benzyl bromide (Scheme 5). Further insight into the mechanism of this rearrangement is given by the isolation of two different 7-alkylpurines when another alkyl halide is mixed with the benzyl bromide before reaction with the 9-benzylpurine.[889] Examples similar in type are reported with preparations of 8-phenylcaffeine from various 9-alkyl-1-methyl-8-phenylxanthines (Scheme 6) by methylation. Precursors used include the 1,9-dimethyl-, 1-methyl-9-*n*-propyl-, and 1-methyl-9-(2-phenylethyl)-xanthines, the reaction involving group abstraction at N-9 accompanied by methylation at both the N-3 and N-7 positions. Analogous reactions take place with ethyl iodide.[913] In forming the caffeine deriv-



(R = H or CH_2Ph)

Scheme 5



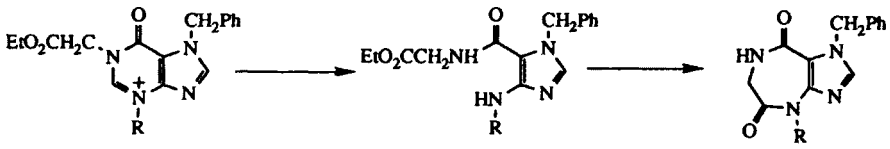
Scheme 6

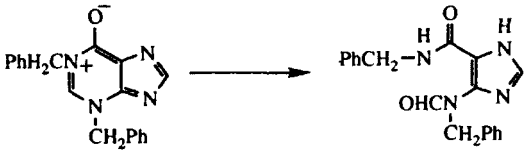
atives, it is logical to assume that methylation or ethylation at N-3 follows rather than precedes elimination of the N-9 substituent in view of the likelihood of steric interaction between groups at N-3 and N-9. The reported failure to synthesize 9-benzyl-3-methylxanthine[889] lends considerable support to this premise. Other less obvious examples are methylation of 3-methyl-8-oxopurine (DMF, 20°C, 70 h), forming an unstable mixture of 1,3- and 3,9-dimethylated purines which on standing or warming is converted to one containing the isomeric 1,9- and 1,7-dimethylpurine iodides. Such transformations arise from degradation of quaternary intermediates, entailing loss of the 3-methyl group with subsequent remethylation by regenerated methyl iodide.[1290] A similar rationale is applied to explain isolation of 1,7,8,9-tetramethylhypoxanthine on methylation (DMF, reflux) of the 3,8-dimethyl analog.[873]

C. Degradation of *N*-Alkylpurines (*H*234)

a. With Alkali (H234)

Initially, the 1-ethoxycarbonylmethyl derivatives of 3-alkyl-7-benzylhypoxanthine (**39**) undergo fission of the pyrimidine moiety forming imidazoles (**40**) which are recyclized to imidazo[4,5-*e*][1,4]diazepine-5,8-diones (**41**) in hot acetic acid.[1286] The more facile ring opening of 1,3-dibenzylhypoxanthine (**42**) to the imidazole (**43**) in hot water only is a clear indication of charge localization in the pyrimidine ring.[1310] When similarly hydrolyzed, caffeine gives the two imidazoles (**44**) and (**45**) through nucleophilic attack at the respective 1,2- and 1,6-bonds of the purine. Heating the methyl ester of **45** regenerates caffeine.[1000] Alkaline degradation of the 1,3,9-trimethyl (**46**, R = H) and 1,3,7,9-tetramethyl analogs (**46**, R = Me) of 2,8-dioxopurine, as the iodides, yields, the N^1-methylureidouracils[903,1300] (**47**, R = H and Me) with dimorphic forms reported for **47**[1300] (R = H). In these cases, open-

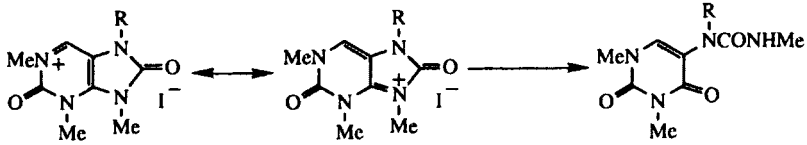




42 43



44 45



46A 46B 47

ing of the imidazole ring suggests that this is the location of the charged center of the purine salts.[1310]

b. With Acid (H236)

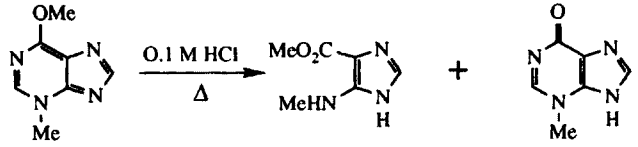
Theophylline is normally acid stable except under such destructive conditions as high temperature and strong acids (*H*236). In an aqueous solution of ethylene diamine containing a rose bengal sensitizer under UV radiation, an uncharacterized product which affords, 1,3-dimethyl-2,4(1*H*, 3*H*)pteridinedione on acid treatment is obtained.[1930]

8. REACTIONS OF ALKOXYPURINES (*H*236)

The most interesting aspects continue to be rearrangements of alkoxypurines to the isomeric *N*-alkylated oxopurines.

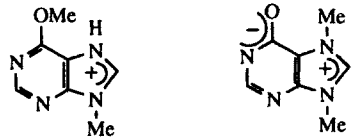
A. Alkoxy to Oxopurine (*H*236)

Hypoxanthine is only one of the products from heating 6-methoxypurine in acid (0.1 *M* HCl, reflux, 48 h); the other, in equal yield, is 4-amino-5-methoxycarbonylimidazole.[1309] An analogous result is obtained from 6-methoxy-3-methylpurine, but the imidazole derivative is now the major component (Scheme 7).



Scheme 7

Similar transformations effected by the same workers are of 6-methoxy-9-methylpurine and 6-methoxy-7,9-dimethylpurinium chloride.[1309] With the former purine in stronger acid (> 1*M*), mainly 9-methylhypoxanthine (50%) results through cation (**48**) formation suppressing competing reactions. The betaine of 7,9-dimethylhypoxanthine (**49**) forms when the 6-methoxy analog and hydrogen chloride are reacted in chloroform;[1309] other examples of this type are available.[1179] An alternative *O*-demethylation procedure utilizes trimethylsilyl iodide in hot acetonitrile to convert 6-methoxypurine riboside to inosine.[965] The formation of xanthines from 2-ethoxyhypoxanthines using malonic ester is noted in Section 8.E; see also Section 8.D for examples of the rearrangement of alkoxy- to oxopurines.



48 **49**

B. Hydrogenolysis of Alkoxy Groups (*H*237)

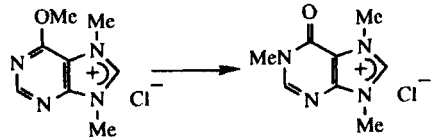
Although benzyloxy groups are readily debenzylated in this way, similar reduction conditions transform allyloxy to oxo groups with corresponding ease. Illustrating this is the hydrogenolysis (Pd–carbon) of the triacetylated riboside of 6-allyloxy-2-chloropurine to a hypoxanthine riboside in a reaction in which both the halogen atom and allyl group are removed.[1208]

C. Alkoxy to Amino Group (*H*238)

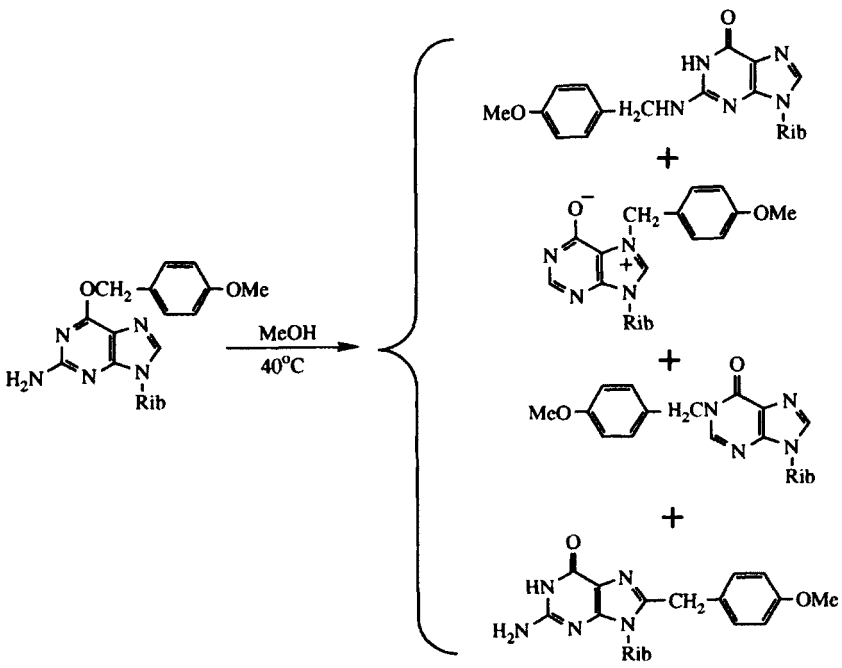
The transformation of both 2-ethoxy-6-oxo- and the isomeric 6-ethoxy-2-oxo-3,7-dimethylpurine into 3,7-dimethyl-2,6-bismethylaminopurinium chloride is achieved by treatment with a phosphoryl chloride–methylamine combination. No mechanism is advanced, but chlorination of the oxo groups with amination of the halogen and the ethoxy groups is one possibility; the alternative is hydrolysis of the alkoxy groups to oxo with chlorination of all oxo groups and then amination.[1098]

D. Rearrangement (*H*238)

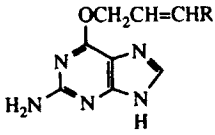
The majority of examples are thermally induced. On heating 6-methoxy-7,9-dimethylpurinium chloride (**50**) in dry methanol, a Hilbert–Johnson type rearrangement follows, giving 1,7,9-trimethylhypoxanthinium chloride[1309] (**51**). More complex in character is the isolation of four products from the 9-riboside of 2-amino-6-(4-methoxybenzyloxy)purine at 40°C in aqueous methanol. As Scheme 8 shows, these arise through 4-methoxybenzylation occurring variously at the 2-amino group, at N-1 and N-7, and also at C-8.[1311] Alkylation of guanosine by 4-methoxybenzyl chloride gives the same four products as from the thermal isomerization, suggesting that in both events ionic species participate. Neutral or alkaline conditions are best, but the reaction can also be acid catalyzed.[1311] Data amassed from various rearrangement studies with alkenyloxypurines highlight the variety of factors governing the type of reaction which takes



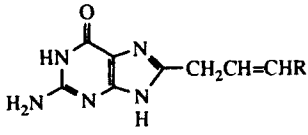
50 **51**



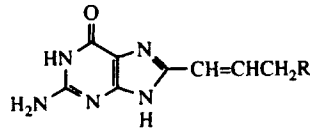
Scheme 8



52

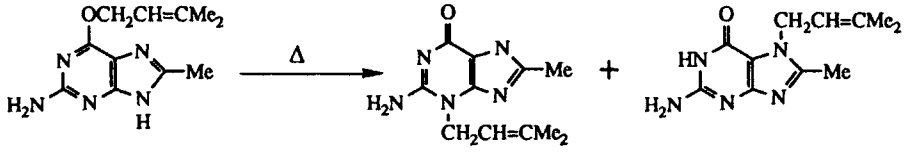


53



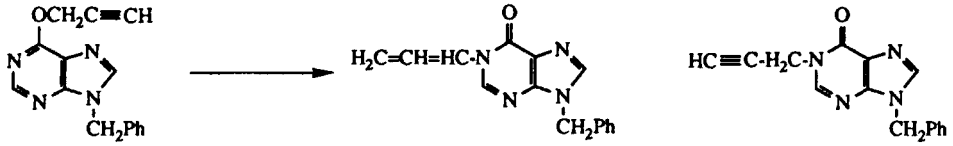
54

place.* Heating 6-allyloxy-2-aminopurine (**52**, R = H) in diglyme (150°C, 5 h) yields not only 8-allylguanine (**53**, R = H) but also the 8-(prop-1-enyl) bond inversion product[1178] (**54**, R = H). Both products are readily hydrogenated (Pd–carbon) to 8-*n*-propylguanine.[1178] The 8-crotyl analog (**53**, R = Me) results from the rearrangement (diglyme, 150°C, 5 h) of 2-amino-6-(but-2-enyloxy)purine (**52**, R = Me), but a bond-inverted secondary product is lacking. Double-bond stability during a rearrangement is also a feature of the 6-(3-methylbut-2-enyloxy) homolog.[1178] Group translocations of this type are shown by labeled compound studies to be intramolecular and involve two [3,3] sigmatropic shifts which are facilitated if amino, methyl, or similar electron-donating groups are present and the purine is reacting as the anion.[1177] The failure of 6-(3-methylbut-2-enyloxy)purine, which unlike the purines above lacks an amino group at C-2, to rearrange even on prolonged heating in dioxan (100°C, 18 h), demonstrates this point.[1177] A 1:1 mixture of 8-(3-phenylprop-2-enyl)- (**53**, R = Ph) and the inversion isomer 8-(3-phenylprop-1-enyl)-guanine (**54**, R = Ph) results on heating (150°C, 24 h) the 6-(3-phenylprop-2-enyloxy)purine (**52**, R = Ph) sodium salt in DMF or diglyme.[1180] On blocking the C-8 position, as, for example, in 8-methylguanine, the 6-alkenoxy derivative undergoes fission of the alkenyl moiety with translocations to N-3 and N-7. Exemplifying this are 3- (**56**) and 7-(4-methylbut-2-enyl)purine (**57**), which are obtained in a 2:1 mixture from the 8-methylguanine derivative (**55**) in hot dioxan.[1131] Claisen-type rearrangements are not found with 9-unsubstituted-6-alkenyloxypurines,[1177] but occur if a 9-substituent is present. Thermal isomerization (185°C, 6 h) of 6-allyloxy-9-benzylpurine gives 1-allyl-9-benzylhypoxanthine.[1221] A similar conversion (145°C, 2 h) of the 6-propargyloxy analog (**58**) to the 1-alkenylhypoxanthine (**59**) is of interest in producing an O to N rearrangement also involving a triple-bond isomerization.[1221] The expected



55 56 57

*A point of historical detail is that although rearrangements of *O*-allyl ethers of purines were first described nearly 60 years ago, no detailed study of the reaction was made until recent times, which revealed that both nitrogen and carbon atoms are involved in the isomerizations.[1178] This fact was still not appreciated as late as 1967,[2029] when it was stated that for such allyl group translocations only movement between oxygen and a ring nitrogen was considered feasible.



58 59 60

product of rearrangement, that is, 9-benzyl-1-propargylhypoxanthine (**60**), can be obtained by alkylation with propargyl bromide of 9-benzylhypoxanthine.[1221] The various bond inversions described cannot be covered by any common mechanism. With 9-allylguanine in diglyme (160°C, 24 h), transformation into 9-(pent-1-enyl)guanine demonstrates that some bond isomerizations can occur after rearrangement.[1177] An extension of this topic is found in the reaction of sodium alkenyloxides with halogenopurines, the products being *O*-alkenylpurines which have undergone bond isomerization during their formation[1131,1178] (see Chapter V, Section 5.E).

E. Other Reactions (*H*239)

Alkylations carried out in neutral media include ethereal diazomethane on 2-methoxypurine (20°C, 4 days), which gives mainly the 9-methyl homolog with a minor yield (10%) of the 7-isomer; a more complex mixture comprising approximately equal amounts of the 3-, 7-, and 9-methyl derivatives arises with 6-methoxypurine (20°C, 4 h), and with 8-methoxypurine the only significant product is the 9-methylpurine.[1176] Methyl iodide methylates 6-methoxy-9-methylpurine further (MeCN, 25°C) to 3,9-dimethyl-6-methoxypurinium iodide, which is converted to the chloride by halogen exchange using mercury(II) chloride.[1312] A correlation between sites of methylation and protonation is shown by ^{1}H NMR investigation.[1312] Neutral conditions also favor free-radical methylation, radicals being generated from *tert*-butylperacetate (32°C, 15 h) or by UV irradiation. Both 6-methoxypurine and 6-methoxy-3-methylpurine undergo *C*-methylation at the 8-position. In acid solution (D_2O, CF_3CO_2D), methylation changes to C-2 with 6-methoxy-3-methylpurine. Mainly 8-hydroxyalkylpurines are obtained from 6-ethoxypurine in alcohols when subjected to UV or gamma irradiation, but some 2,8-bis(hydroxyalkyl)purines are also formed[1252] (see Section 3.A). An unusual feature of the 2-ethoxy derivative of 3,7-dimethylhypoxanthine is that it acts as an ethylating agent as a result of *O*-dealkylation on reaction with diethyl malonate, giving theobromine and the *C*-ethylated malonic ester.[1313] Theoretical implications of the reaction based upon MO–LCAO studies have been formulated.[1232]

9. OXIDATION OF OXOPURINES (*H*239)

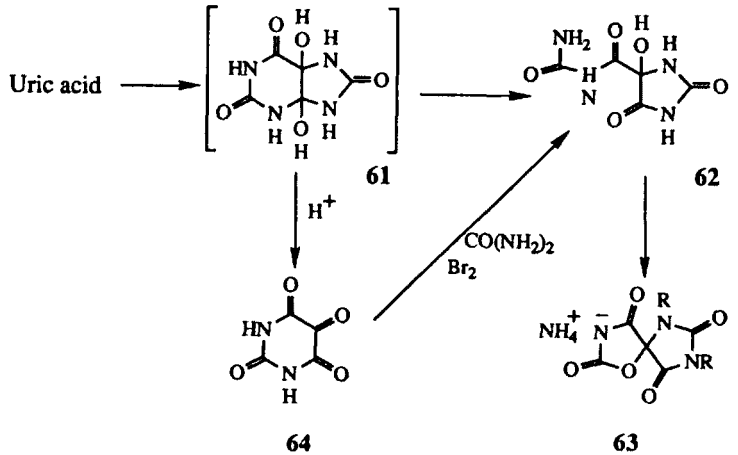
As uric acid is the end product of metabolism of many purines, the oxidative pathways involved in this process continue to be a focus of interest. Insights into

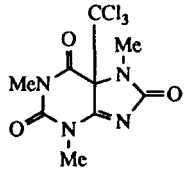
the reactions operating are provided by oxidative studies carried out by chemical, electrochemical, and enzymic means. Significant observations have shown the close similarity existing between the pathways and products from oxidations by all three methods. As a result of the more recent work with uric acids, some of the earlier results of Biltz and his group must be reexamined, particularly those in regard to structural assignments of derivatives.

A. Under Acid Conditions (*H*240)

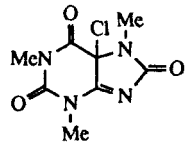
a. With Chlorine in Acid or Aqueous Media (H240)

The main results provided by Poje and his group arise from a reinvestigation of the oxidation of uric acids with chlorine in acetic acid described by Biltz. No stable glycols of the type (**61**) could be isolated, although their transient presence is detectable in the IR spectrum. The major product is alloxanic acid ureide (**62**), which possesses the physical properties described for the glycol obtained by Biltz.[1777] Structural confirmation followed from synthesis from alloxan (**64**) and urea with bromine as oxidant. These findings render suspect much of the early published work on uric acid glycols and also explain the reported failure in the past to reduce the "glycols" to the parent uric acids, the reactions actually causing degradation to hydantoin derivatives. Further structural proof of the ureides is given by X-ray examination.[1778] A facile rearrangement to the ammonium salts of caffolides (**63**) occurs with the ureides in alkaline[1779] solution. Corresponding derivatives are similarly formed from *N*-methylated uric acids. Somewhat relevant is the product (**65**) obtained by a radical reaction on caffeine by bromotrichloromethane in the presence of dibenzoylperoxide as initiator.[1135] The 5-trichloromethylisouric acid (**65**) is structurally comparable to the 5-chloro-1,3,7-trimethylisouric acid (**66**) resulting from the interaction of caffeine with chlorine in acetic acid (*H*240).





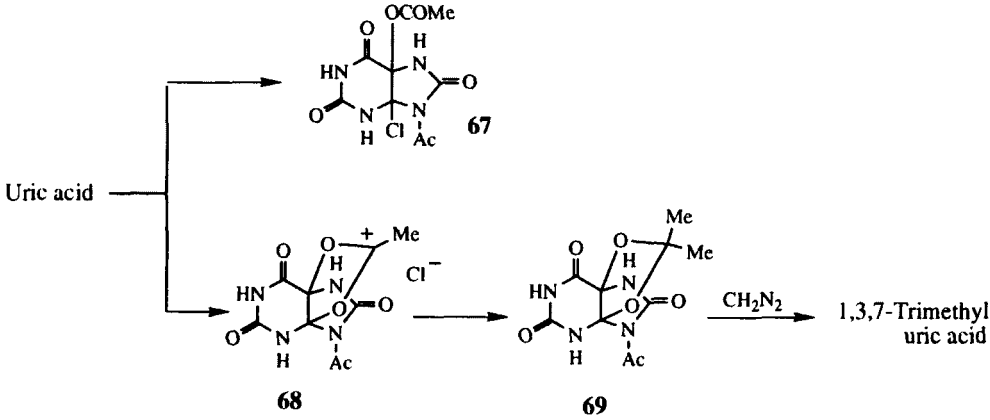
65



66

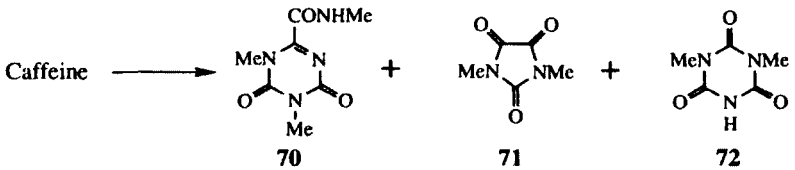
b. With Chlorine in Nonaqueous Media (H242)

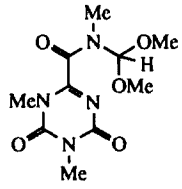
In the early literature (*H*242), the product of oxidative chlorination of uric acid in acetic anhydride was formulated as 5-acetoxy-9-acetyl-4-chloro-4,5-dihydrouric acid (**67**), but recent work supports the propellane derivative (**68**). Methanol converts this acetoxonium chloride to the cyclic orthoacetate (**69**). Adding diazomethane to the latter, followed by reductive deacylation, gives 1,3,7-trimethyluric acid, showing that the purine ring has remained intact.[1137]



B. Under Alkaline or Neutral Conditions (*H*243)

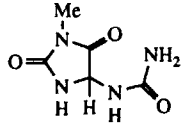
At least eight products have been identified from ozonolysis of caffeine in aqueous solution—the three major ones are 1,3-dimethyloxonic acid methylamide (**70**), 1,3-dimethyl-5-azabarbituric acid (**71**), and dimethylparabanic acid (**72**).



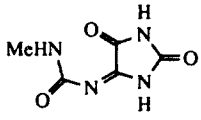


73

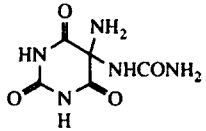
Homologous oxidation products are derived from 1-ethyl-3,7-dimethyl- and 7-ethyl-1,3-dimethylxanthine.[1337] Ozonolysis in methanol forms the adduct (**73**) through oxidative interaction with three molecules of solvent.[1337] A reexamination of earlier results of uric acid oxidations in alkaline solution by iodine shows that either an allantoin (**74**) or a dehydroallantoin (**75**) can result, depending upon whether a stoichiometric or an excessive amount of iodine is used. A comparison of the structures of the oxidation products from 1-methyluric acid suggests that the same ring is not opened in the respective bicylic precursors and that the two products arise by different routes.[1780] The oxidation product from 8-^{13}C-uric acid gives allantoin labeled at C-2, showing that no fission of the imidazole ring has occurred[1917] in this case. On changing to an alkaline potassium permanganate oxidant, 5-^{14}C-uric acid gives a transient intermediate, undergoing a 1,2-carboxyl group shift and forming allantoin-5-carboxylate as end product. A facile decarboxylation yields 2-^{14}C-allantoin.[1918] Ethanolic ammonia (0°C, 0.5 h) converts the primary oxidation product of uric acid to the ammonium salt of 5-amino-5-ureidodihydrobarbituric acid (**76**).[1781]



74



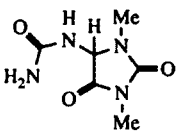
75



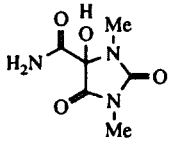
76

C. By Electrochemical or Enzymatic Means (*New*)

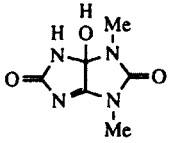
A considerable similarity appears to exist in the oxidation pathways followed using either of these approaches. Dryhurst and his group explored the graphite electrode oxidations of *N*-methylated uric acids[1136] with a more detailed study of 7,9-dimethyluric acid over a wide pH range.[1782,1783] For comparison, an enzymic oxidation with horseradish peroxidase, catalyzed by hydrogen peroxide, was made on the same purine, also at varying pH values. Following both oxidation pathways with UV revealed that the same intermediates are involved. Under alkaline conditions (pH 7–9) the ultimate product is 1,3-dimethylallantoin (**77**), but at low values (pH 3–5), 1,3-dimethyl-5-hydroxyhydantoin-5-carboxamide (**78**) is also formed.[1784] The identification of the bipentacyclic 1-hydroxy-2,4-dimethyl-



77

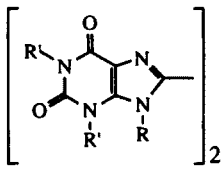


78

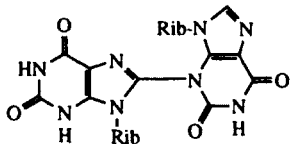


79

2,4,6,8-tetraaza-3,7-dioxo-5-enebicyclo[3.3.0]octane (**79**) as a common intermediate in both reactions is noteworthy. Derivatives of this type would explain the ready pyrimidine–imidazole interconversions frequently encountered in uric acid oxidations and also the formulation of erroneous structures by the early workers. The isolation of allantoin and alloxanic amide[1785,1786] as end products from electrooxidation of uric acid is in line with the findings above. Supporting studies on this theme[1787,1917] are reported. The availability of the hydrogen at C-8 for oxidation is ably illustrated in the formation of bistheophyllin-8-yl (**80**, R = H, R′ = Me) following similar oxidation of theophylline.[1788] Following UV irradiation of a solution containing xanthosine and 8-bromoxanthosine, the analogous riboside (**80**, R = β-D-ribofuranosyl, R′ = H) results.[1919] While the latter might also be expected to be the oxidation product of xanthosine in phosphate buffer (pH 2) at a pyrolytic graphite electrode, in practice 3-(xanthosin-8-yl)xanthosine (**81**) results from interaction between radical cation forms of xanthosine.[1920]



80



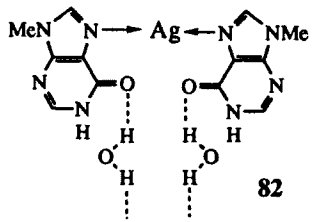
81

11. HYPOXANTHINE (*H*250)

More up-to-date preparations are a one-step synthesis in good yield (70%) involving hydrogenation (Raney nickel) of a mixture of 2-cyano-2-phenylazoacetamide, formamide, and ammonia. Alternative reduction procedures or use of ethyl 2-cyano-2-phenylazoacetate in place of the amide analog give reduced yields.[1017] Employing a high-temperature (270°C) extended Traube reaction between xanthine and *N*-benzylformamide[1234] is less productive (37%). Although aqueous acid hydrolysis of 6-methoxypurine seems an obvious approach, in practice only a minor yield (30%) of hypoxanthine results, the major product (70%) is 4-amino-5-methoxycarbonylimidazole.[1309] A trifluoroacetic acid–hydrogen peroxide mixture is reported to hydrolyze purine-6-malondialdehyde to hypoxanthine.[791] A moderate yield (40%) is obtained on UV photoreduction of 1-hydroxyhypoxanthine, but contamination of the product with xanthine (9%)

and the 6,8-dioxo isomer (trace) is found.[1250] Photolysis (UV) of 6-mercaptopurine under oxygen is a poor route[1247] (10%), but yields of 50% are claimed by a variation of these conditions.[1315]

Reactions of hypoxanthine are mainly centered around the carbonyl group. Interconversion to an amino substituent is one aspect attracting great interest. With 4-chlorophenylphosphorodichloridate in pyridine, the quaternary 6-pyridiniumpurine chloride results.[1157,1306] Several routes involving direct replacement of oxygen by amino groups are now at hand. Heating with an amine hydrochloride and *N*,*N*-dimethylcyclohexylamine and phosphorus pentoxide,[1302] or with phosphoramide derivatives, are two well-tried approaches; with the latter adenine results using phenylphosphorodiamidic acid [$P(O)OC_6H_5(NH_2)_2$].[1307] Somewhat lower temperatures can be utilized for aminations if *O*-trimethylsilylated purines are reacted with amines and a Lewis acid or with amine hydrochlorides.[1304,1305] Alkylation is detailed in Section 6.D.a. Use of a cobalt(III)–glyoxime complex allows specific N-7 alkylation[1283] by the usual alkylating agents in a chlorohydrocarbon solvent at ambient temperature. Transition metals form complexes through N-7, as illustrated by the products from dicarbonylrhodium(I) chloride[1318] and pentaammineruthenium(III) chloride.[1317] Using 7-methylhypoxanthine with the latter reagent, coordination occurs at N-9.[1317] A somewhat parallel arrangement is the dihydrated biscomplex (**82**) obtained when 9-methylhypoxanthine and silver perchlorate interact. Stabilization is achieved through hydrogen bonding between the purine dimers, involving water molecules and the 6-oxo groups.[1692] Following alkylation of both imidazole nitrogens, ^{1}H NMR line broadening of H-2 in copper(II) complexes points to N-1 as coordination site.[1693] The mold *Streptomyces antibioticus*, a source of the antiviral agent vidarabine (9-arabinofuranosyladenine), also contains minor amounts of 9-β-D-ribopyranosylhypoxanthine. The latter is an inhibitor of adenosine deaminase but shows no antiviral activity.[1208]



82

Radical attack gives rise to 8-substituted-hypoxanthines, as in the formation of 8-methyl[1077,1312] and 8-(2-hydroxyprop-2-yl)[1252] derivatives. The electrophilic nature of the C-8 position has attracted many studies of the ease of removal of the resident proton using 8-deuteriated and -tritiated hypoxanthines. These show that pH is a controlling factor—anions reacting much faster than neutral molecules[1280,1319]—but more than one mechanistic pathway operates. Calculated pK_a values of 8.5 and 11.0 for hypoxanthine at 85°C obtained[1319] from the reaction rates above for proton exchange are in close agreement with those derived from

theoretical treatment (pK_a 8.2 and 11.2).[1320] The lower values compared with those obtained practically at 25°C[1321] (pK_a 8.91 and 12.67) for hypoxanthine demonstrate the interdependence between temperature and ionization constants. New data appearing on tautomerism and protonation reflect the continuing interest in these topics. As a generalization, the 7H protomer is the more favored, although comparisons made using ^{13}C NMR show that only a small difference exists in the 7H and 9H populations (58% and 42%, respectively).[1322] In aqueous solution, similar spectral studies indicate that in this medium the 9H protomer is more likely to predominate.[1323] This viewpoint is feasible in view of the not dissimilar intrinsic stabilities of the two species.[1325] On crystallographic evidence, only the keto form of the 7H protomer is present in the solid state[1324]—this agrees with findings of ^{13}C NMR work.[1322] Further confirmation is provided at a theoretical level from core binding energy data derived from electron spectroscopy studies.[1360] In the crystal state, the hypoxanthine monocation results through N-1 protonation.[1324] Determination of ionization constants of the conjugate acid in DMSO has been carried out potentiometrically.[1040]

12. XANTHINE (*H*251)

A high yield (87%) of the purine results from a one-step synthesis involving a catalytic reduction (Ni) of a phenylazomalonic acid in a formamide and ammonia mixture.[1018] By contrast, rearrangement by UV irradiation of 1-hydroxyhypoxanthine gives only a little (9%) xanthine, increasing to 18% if the mono or dianion of the hypoxanthine is used.[1250] Improved yields of 1,3,7-trialkylated xanthines are achieved by employing recent advances in alkylating techniques. Caffeine is quantitatively achieved with methyl bromide by phase transfer catalysis using tetra-*n*-butylammonium hydroxide[1295] or, alternatively, with dimethyl sulfate and tetra-*n*-butylammonium fluoride.[1294] Lower yields of caffeine result from rigorous heating of xanthine with trimethylphosphate;[1291-1293] corresponding ethylation, however, affords a mixture of 1,3,7-triethyl- and 3,7-diethylxanthine.[1292,1294] In alkaline solution at 60°C, with triethyl and triallylphosphates, only the respective 3,7-dialkylxanthine forms in low yield.[1291] Like hypoxanthine, alkylation specifically at N-7 in the cold is possible by prior complexing with a cobalt(III)–glyoxime derivative.[1283] Replacement of both carbonyl functions by amino groups is exemplified in the 2,6-bisdimethylaminopurine from reaction (235°C, 2 h) with trisdimethylaminophosphoramide.[1307] Removal of the 2-oxo group giving hypoxanthine is brought about in hot (260°C) benzylformamide.[1234] An interpretation of results from proton transfer studies at C-8, using tritium-labeled xanthine over a range of pH values,[1326,1327] is that hydroxide ion attack is a common feature with the neutral molecule, N-7 protonated cation and monoanion species, although all mechanisms do not follow the same pathway. The dependence of the ionization constants on temperature has been demonstrated,[1327] and an equation linking decrease in values with temperature rise has been formulated.[1320] The surprisingly differing solubility figures found in the literature are a

reflection of the closeness of the first acid pK_a value to neutral pH. Small variations in the pH of the solution in this region produce significant solubility changes.[1328] In addition to the 7H tautomer, in aqueous solution the MCD spectrum shows the presence of substantial amounts of the 9H protomer.[1694] This observation parallels that given for hypoxanthine in Section 11. Various earlier investigations establishing the diketo tautomer as the major one present under most conditions are reinforced by core binding energy data obtained from electronic spectral examination of the solid state.[1360]

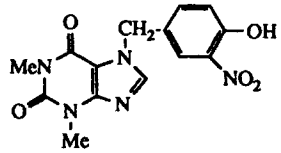
13. THE *N*-METHYLATED XANTHINES (*H*253)

These derivatives are still of interest to workers in quite diverse fields of study. Although their application in medicine, as diuretics and stimulants, has a long history, new uses continue to emerge. Current interest centers on their effect on potential coronary conditions and as antagonists for adenosine A_1 and A_2 receptor[1887] sites, and also in the treatment of gout and related diseases. The role of caffeine in a number of chemotherapeutic studies is wide ranging; it will potentiate the antibiotic action of phleomycin and may play an as yet undefined part in some mechanisms of carcinogenic or mutagenic action. The ready aqueous solubility of these derivatives in contrast to that of non-*N*-methylated xanthines makes them ideal subjects for NMR or optical spectral reaction studies. The range of *N*-methylated compounds available is especially useful in protropic configuration studies and as models for assessing keto-enol possibilities.

A. Theophylline (*H*253)

A new synthesis involves hydrolysis in acetic acid of 1,3-dimethyl-6-methylthio-2-oxopurine,[1245] while a conversion using an extended Traube reaction on 1,3-dimethyluric acid has also been reported.[939] Modified existing procedures, or new alkylations of xanthine by means of alkyl halides or trialkyl phosphates, have given theophylline[1291,1292,1295,1297] as well as the 3,7-diethyl,[1291,1292,1295,1297] -dibenzyl,[1295] and -diallyl[1215,1291] homologs. Methylations are also possible with dimethylphosphite but other alkylphosphites do not react likewise.[1297] Under pressure (50 bar), the potassium salt of theophylline undergoes a novel conversion to caffeine (140°C, 20 h) on treatment with methanol in a carbon monoxide atmosphere.[1977] A reexamination of the benzylation of theophylline in alkali (*H*123,124) shows that in addition to the expected 7-benzyl derivatives, both 8-benzyl- and 7,8-dibenzyltheophyllines are produced.[847] Experimental evidence points toward a radical mechanism operating in conjunction with a normal ionic alkylation.[847] Similar in character is the reaction with a pentaammineruthenium(II) derivative complexing through N-7 of theophylline as well as forming an isomeric C-8 linked complex.[1331] In an analogous reaction to *N*-alkylation with *o*-diphenylphosphinylhydroxylamine (DPH), conversion to

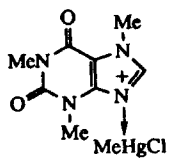
7-aminotheophylline occurs.[1330] On replacing the 8-proton by methyl, the purine reacts with Cu^{2+}, Cd^{2+}, and Zn^{2+} ions at N-7, but complexation at N-9 occurs with the Hg^{2+} ion.[1332] Using phenyl or 4-substituted-phenyl mercury(II) complexes, conclusive evidence is available (IR, ^{13}C and ^{1}H NMR, and MS) to show that the proton at N-7 is replaced.[1931] Favoring N-7 as reaction site is the similarity observed between the 8-proton signals of 7-methylxanthine and the parent xanthine compared with that of the 9-methyl derivative at a higher field. On protonation, the latter produces the larger downfield displacement, indicating that N-7 is most suitable for complexation.[1282] Studies comparable to those with hypoxanthine on proton exchange at C-8 are reported for a range of temperatures and pH values,[1326,1327] with attack by hydroxyl ions on the protonated purine shown to be the rate-determing step. Estimations of the partial molal heat capacity in water have been made.[2028] The transformation of theophylline through UV and acid treatment to a pteridine is noted in Section 7.C.b. A naturally occurring derivative is phidolopin (**83**), found in the corraline *Phidolopora pacifica* in northern Pacific water and notable for having a 4-hydroxy-3-nitrobenzyl moiety at N-7 and exhibiting both strong antifungal and antialgal properties.[1691]



83

B. Theobromine (*H*254)

An improved preparation (> 75%) is claimed by methylation (Me_2SO_4) in a weak (7%) solution of sodium hydroxide of 3-methylxanthine.[1296] Procedures followed for alkylation of theobromine to caffeine and other 1-alkyl-3,7-dimethyl homologs parallel those used with theophylline (Section 13.A), including trialkylphosphates[1291,1292] and alkyl halides in phase transfer catalysis both with[1295] and without solvent.[1359] The structure of the caffeine–mercury complex (**84**, R = phenyl or 4-substituted phenyl) from theobromine with the arylmercury(II) chloride is established by IR, ^{1}H and ^{13}C NMR, and MS studies.[1931] For 1-aminotheobromine preparation, *o*-diphenylphosphinylhydroxylamine is applied to the

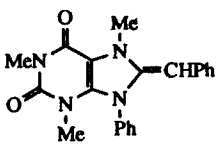


84

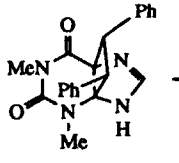
sodium salt of the purine.[1330] In the absence of an imidazole proton, reaction with a pentaammineruthenium(II) occurs at the 8-position[1331] even though the possibility of protonation at N-1 exists. Proton exchange at C-8 is found to follow the same pattern as described for xanthine, hypoxanthine, and theophylline (see previous sections) with mechanistic variations between low and high pH values[1334] and temperature changes.[1327]

C. Caffeine (*H*254)

Alkylations by novel or modified reactions of xanthine,[1291-1295] theophylline,[1291,1295,1297] theobromine,[1291,1292,1297] and other *N*-methylxanthines[843] to caffeine are extensively documented. Removal of 8-hydroxyalkyl groups photochemically from 1,3,7-trimethylxanthine derivatives is a less-conventional approach.[1253,1254] The absence of an imidazole proton precludes *N*-alkylation or similar reactions, but with pentaammineruthenium(II) C-8 becomes the reactive center in complex formation.[1331] With radical sources induced by UV or gamma radiation, 8-methyl,[1077] other 8-alkyl[1099] and 8-cycloalkyl,[1111] 8-hydroxyalkyl,[1252] and 8-heterocyclylpurines[1335] are obtained. Under similar conditions with stilbene, the major product (**85**) results from alkenylation at C-8 and phenylation at N-9, while smaller amounts of the isomeric cyclobutane adducts (**86A**) and (**86B**) are derived from addition to the purine 4,5-double bond.[1336] At least eight oxidation products are found following ozonolysis of caffeine in alkaline solution, of which 1,3-dimethyloxonic acid methylamide (see Section 9.B) is the major component. In neutral medial complete degradation results. Acidified hydrogen peroxide (6%) treatment followed by ammonia produces the purple color of the murexide reaction. Among the 10 isolated oxidation products are some identical to those from the murexide reaction with uric acids.[1932] These results are similar to those of earlier oxidations using very dilute peroxide[1933] or nitric acid.[1934] Exchange rates for proton–tritium exchanges are available which detail the effects produced by changes of temperature, pH,[1326,1327] or formation of charged forms.[1357] In acetic acid, protonation at N-9 is demonstrated by ^{1}H NMR.[1338] Stacking, with alternate molecules adopting a head-to-tail mode, occurs with the purine in aqueous solution through self-association.[1339] Benzene and similar-sized flat molecules in tetrachloromethane also form vertical stacks through intercalation in which electrostatic forces hold the aromatic ring in place over the *N*-methyl group of the imidazole ring.[1344] The molal heat capacity in

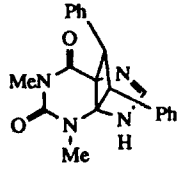


85



86A

+



86B

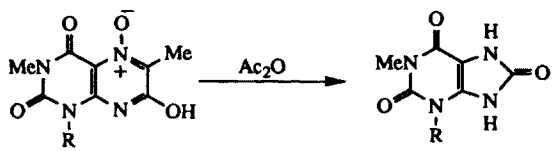
water has been determined.[2028] The nature of caffeine involvement in many biochemical processes is by no means clear. An enhancement of the lethal and mutagenic effect of UV radiation is taken to reflect some inhibition of the dark repair process in DNA being exerted.[1340] The insecticidal property shown is attributed to the ability of the purine to degrade cyclic amp;[1341] this action may also be relevant to an understanding of its function as a potentiator of the effect of the antibiotic phleomycin.[1342] Metabolism of caffeine in a number of mammalian systems gives rise to the sulfur-containing metabolite 7-methylthiomethyl-1,3-dimethylxanthine together with *S*-oxidized variants.[1343] Caffeine intercalates with anthocyanin plant pigments, resulting in considerable color augmentation. Multiple color changes passing from red to green occur on variation of pH between 3.5 and 7.0; these are attributed to π-π stacking forming stabilized pigment–purine complexes in which quinonoid base forms of the anthocyanine are involved.[2032]

14. URIC ACID (*H*256)

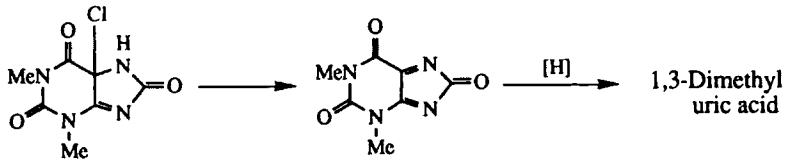
A comprehensive work by Hitchings overviews the synthesis and chemistry of uric acid up to 1978.[1959]

A. Preparation (*H*256)

Convential approaches, the major one being the Traube reaction involving ring closure of the diaminopyrimidine with ethyl chloroformate[833,891] (see Table 3, Chapter II, Section 1.U) and related carbonyl reagents,[920,934] still provide most examples of preparations of the acid and *N*-alkyl homologs. Nonstandard syntheses are trifluoroacetic or acetic anhydride induced rearrangements of 3-,[957,1116,1713] 7-,[957] and 9-hydroxyxanthines.[957] A conversion of this type of 7-hydroxyxanthine with either formaldehyde or thiolacetic acid is reported.[920] Various uric acid derivatives, including the 9-arabinofuranoside, are obtained from catalytic hydrogenation (Pd-carbon) of the 8-benzyloxypurines.[1196] Prolonged acid hydrolysis of the *N*-methylated 8-methylthioxanthine gives 3,7-dimethyluric acid[887] while the 1,7,9-trimethyl homolog arises from the 2-methylthioxanthine.[891] Other acid hydrolysis conversions are with 8-fluorotheophylline and -caffeine to 1,3-dimethyl- and 1,3,7-trimethyluric acids.[1123] Among the less orthodox routes are the thermal transformations of the 5-oxidopteridines (**87**, R = Me or Ph) in acetic anhydride to the uric acids (**88**, R = Me or Ph). Studies with 7-^{14}C-pteridines suggest that rearrangement involves participation by 7-hydroxyxanthine intermediates[948,949] (see Chapter XI, Section



87 **88**

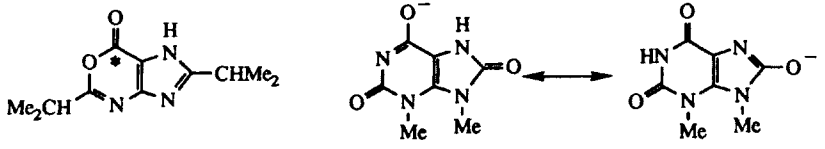


89 **90**

3.C). Pyrolytic dehydrochlorination of 5-chloro-1,3-dimethylisouric acid (**89**) in vacuo at 200°C gives an unstable dehydrouric acid (**90**) initially, which is easily reduced to 1,3-dimethyluric acid.[1915]

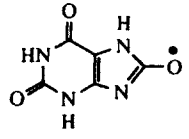
B. Reactions (*H*257)

Examples of the extended Traube reaction to replace the 8-oxo by an 8-alkyl group or hydrogen continue to appear. Formic acid gives 8-unsubstituted derivatives,[939] while corresponding 8-alkylxanthines are formed with acetic, propionic, and *n*-butyric anhydrides[940] (see Chapter II, Sections 1.B and 1.E). The anomalous product (**91**) is a lactone resulting from reaction with isobutyric acid. A complex rearrangement with cleavage of both rings and elimination of C-2, C-8, and N-1 are revealed by studies with ^{13}C-labeled uric acids.[940] Reference is made elsewhere (Section 6.D.c) to isomerization of uric acid following *N*-ethylation. The continuing investigations into the oxidation products of uric acids are detailed in Section 9. Anion formation in uric acids is found (pK_a, UV) to be in the order N-3 > N-9, but when the latter position is substituted, as in the 9-methyl homolog, N-7 is the next site for deprotonation. Initially, 3-methyluric acid suffers proton loss at N-9 and then with equal facility from either N-1 or N-7[891] In the case of the 3,9-dimethyl derivative, the monoanion is probably best portrayed as a mixture of the canonical forms (**92A**) and (**92B**).[891]



91 **92A** **92B**

The known rapid reaction of uric acid with oxidized species has led to the suggestion that it acts in vivo as a radical scavenger and antioxidant. When reacted with peroxy acids or involved in one-electron processes under neutral conditions, the urate radical (**93**) is formed.[1916]



93

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER VII

Thioxo- and Selenoxopurines and Derivatives (*H*269)

1. The 2-, 6-, and 8-Thioxopurines (*H*269) 180
A. Preparation (*H*269) 180
a. By Synthesis from Pyrimidines (*H*269) 180
b. By Syntheses from Imidazoles (*H*270) 181
c. Replacement of Halogen Atoms (*H*270) 181
d. From Oxopurines (*H*270) 182
e. From Alkylthio and Thiocyanatopurines (*H*271) 182
f. By Reduction of Disulfides (*H*272) 184
g. By Direct Introduction of Sulfur (*H*272) 184
h. By Rearrangement of Thiazolo[5,4-*d*]pyrimidines (*H*273) 185
i. By Other Means (*H*273) 185
B. Preparation of Extranuclear Thioxopurines (*H*274) 186
C. Reactions of 2-, 6-, and 8-Thioxopurines (*H*275) 186
a. Removal of Thioxo Groups (*H*275) 186
b. *S*-Alkylation (*H*278) 187
c. *N*-Alkylation (*H*280) 192
d. Thioxo- to Oxopurines (*H*281) 193
f. Thixo- to Aminopurines (*H*282) 193
h. Oxidation (*H*283) 193
i. Formylation (*H*283) 194
2. The Thioesters (*H*284) 194
A. Preparation of 2-, 6-, and 8-Alkylthiopurines (*H*284) 194
a. By Direct Synthesis (*H*285) 194
b. By *S*-Alkylation of Thioxopurines (*H*285) 195
c. From Halogenopurines (*H*285) 195
d. By Direct Introduction (*New*) 195
B. Reactions of Alkylthiopurines (*H*285) 195
a. Reductive Removal of Alkylthio Groups (*H*285) 196
b. Alkylthio- to Oxopurines (*H*286) 196
c. Alkylthio- to Aminopurines (*H*287) 197
d. Alkylthio- to Thioxopurines (*H*289) 199
e. Oxidation (*H*289) 199
g. *N*-Alkylation of Alkylthiopurines (*H*289) 199
h. Alkylthio- to Alkoxypurines (*New*) 202
i. Alkylthio- to Alkylpurines (*New*) 203
3. Dipurinyl Disulfides (*H*291) and Related Sulfides (*New*) 203
A. Preparation (*H*291) 203
B. Reactions (*H*293) 204

4. Purine Sulfenic (*New*), Sulfinic, and Sulfonic Acids (*H*293) 205
A. Preparation (*H*293 and *New*) 205
B. Reactions (*H*295) 207
5. Halogenosulfonylpurines (*H*295) 207
A. Preparation (*H*295) 207
B. Reactions (*H*296) 207
6. Sulfenamido-, Sulfinamido-, and Sulfonamido- (Sulfamoyl)purines (*H*297) 208
A. Preparation (*H*297) 208
7. Alkylsulfinyl- and Alkylsulfonylpurines (*H*298) 208
A. Preparation 208
a. Methylsulfinylpurines (*H*299) 208
b. Methylsulfonylpurines (*H*299) 209
B. Reactions (*H*300) 210
8. Thioxopurine-*S*-Oxides (*H*301) 211
9. 6-Mercaptopurine and Analogs (*H*302) 211

Although the recent chemistry of sulfur-containing purines is largely unspectacular, a continuing general interest is this class of compounds exists. Nucleophilic substitutions centered around the methylthio, and to an increasing extent the methylsulfonyl, group are frequently encountered in purine metatheses. Oxidation of thioxopurines to sulfenamide and sulfinamide derivatives is a recently introduced topic awaiting more extensive investigation.

1. THE 2-, 6-, AND 8- THIOXOPURINES (*H*269)

A. Preparation (*H*269)

The well-established routes are still in widespread use, but refinements in reagents and techniques have been introduced. In the formation of selenoxopurines the conditions required are often less rigorous than those employed for the thioxo analogs.

a. By Synthesis from Pyrimidines (H269)

The Traube reaction predominates in the preparation of 8-thioxopurines, with ring closure of the diaminopyrimidine being effected by fusion with thiourea or heating with carbon disulfide in pyridine containing solid potassium hydroxide. Fusion with selenourea does not yet appear to provide a route to 8-selenoxopurines; such derivatives are prepared by purine metatheses. Examples formed by the Traube synthesis are given in Table 6. Rearrangement of annelated pyrimidine derivatives is only of restricted application, for example, a 6-thioxopurine from a thiazolo[5,4-*d*]pyrimidine (Chapter II, Section 8.A).

TABLE 6. Examples of 8-Thioxopurine Formation by the Traube Reaction with 4,5-Diaminopyrimidines

Purine	Reagent Conditions[a]	Ref.
6-Amino-7,8-dihydro-2-phenyl-8-thioxo-	A, 185°C	881, 857
3-Benzyl-3,6,7,8-tetrahydro-6-oxo-8-thioxo-	B, NAOH, 3.5 h	883
3,6,7,8-Tetrahydro-3-methyl-6-oxo-8-thioxo-	B, NaOH, 5 h	883
1,6,7,8-Tetrahydro-9-methyl-6-oxo-8-thioxo-	A, 250°C, 1 h	883
	A, 280°C, 0.25 h	882
1,6,7,8-Tetrahydro-1-methyl-2-methylthio-6-oxo-8-thioxo-	B, NaOH, 5 h	890
1,6,7,8-Tetrahydro-2,9-dimethyl-6-oxo-8-thioxo-	A, 240°C, 10 min	878
3-Benzyl-1,2,3,6,7,8-hexahydro-2,6-dioxo-8-thioxo-	A, 200°C, 1 h	881
1,2,3,6,7,8-Hexahydro-1-methyl-2,6-dioxo-8-thioxo-	B, 5 h	886
1,2,3,6,7,8-Hexahydro-2,6-dioxo-3-phenyl-8-thioxo-	A, 210°C, 1 h	881
1,2,3,6,7,8-Hexahydro-1-methyl-2-oxo-6,8-dithioxo-	B, NaOH, 5 h	890
1,2,3,6,7,8-Hexahydro-3-methyl-6-oxo-2,8-dithioxo-	B, NaOH, 5 h	887
1,2,3,6,7,8-Hexahydro-9-methyl-6-oxo-2,8-dithioxo-	C, 3 h	887
6-Amino-2,3,7,8-tetrahydro-2-oxo-8-thioxo-	A, 180°C	884

[a]A = $CS(NH_2)_2$ fusion, B = CS_2, Pyridine, NaOH, C = MeNCS, Pyridine

b. By Synthesis from Imidazoles (H270)

No significant advances by this approach are noted—the cyclization of 4-amino-5-cyanoimidazoles with carbon disulfide giving 2,6-dithioxopurines is a variation on previous reactions of this type (Chapter III, Section 1.E). A derivative of imidazo[4,5-*d*][1,3]thiazine undergoes rearrangement to a 2,6-dithioxopurine in alkali (Chapter III, Section 8.K).

c. Replacement of Halogen Atoms (H270)

Both sulfides and thiourea and their selenium analogs remain the reagents of choice, as elaborated further in Chapter V, Sections 5.H.a and b. The aqueous alkaline conditions generally used are now superseded by aprotic media such as pyridine or dimethylformamide, as illustrated by the following reaction. A new preparation of ^{35}S-labeled 1,6-dihydro-6-thioxopurine from 6-chloropurine, in 83% yield, is reported with ^{35}S-labeled barium sulfide in pyridine containing barium hydroxide and potassium hydrogen sulfite.[1181] On treatment of 2,6-dichloropurine in cold aqueous alkaline hydrogen sulfide, a near quantitative yield of the 2-chloro-6-thioxo derivative results.[1114] Sodium hydrogen sulfide in dimethylformamide converts an acetylated nucleoside derivative of 6-amino-8-fluoropurine to the corresponding 8-thioxopurine.[1123]

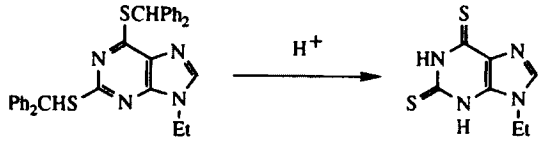
The reflux temperatures used in forming 2-amino-1,6-dihydro-6-selenopurine-9-riboside from the 6-chloro analog and methanolic sodium hydrogen selenide[1190] are unnecessary since ambient conditions are now found to be sufficient.[1191] Both 8-bromoadenosine[1193] and its 3′,5′-cyclophosphate[1194] react with hydrogen selenide in hot sodium methoxide, the corresponding 8-seleno derivative is formed from 8-bromoinosine likewise, but is isolated as the 8-methylseleno homolog following methylation.[1193] Recent examples of thioxopurines resulting from thiourea treatment include 8-phenyl-2-thioxo from the 2-chloro derivative[857] (EtOH, 80°C, 1 h), 2-fluoro-6-selenoxo from the 6-chloropurine, fluorine showing the characteristic inert character of this position in a 2,6-dihalogenopurine (EtOH, 80°, 2 h).[1124] Although the halogen in 2-amino-6-chloro-3-oxidopurine readily undergoes thiation, the product is 2-amino-1,6-dihydro-6-thioxopurine (thioguanine), owing to concomitant loss of the 3-oxido function.[1166] In contrast the related reagent, ammonium dithiocarbamate [$(H_2NCS_2)^-NH_4^+$], converts 6-chloro-3-oxidopurine under mild treatment (60°C, 2 h) to the 6-thioxo analog without reduction occurring.[1142] Use of ethanolic selenourea (reflux, 2 h) gives the 6-selenoxo derivative of the oxide above,[1142] the same reagent affording 8-selenoxoadenosine from the 8-bromo precursor.[1195] The 5′-phosphate and 3′,5′-diphosphate of 8-selenoguanosine are formed likewise.[1195]

d. From Oxopurines (H270)

This still remains essentially a specific route to 6-thioxopurines, and examples involving direct thiation of either 2- or 8-oxo groups are rarely encountered, even under forcing conditions. The topic is further elaborated in Chapter VI, Section 6.B.

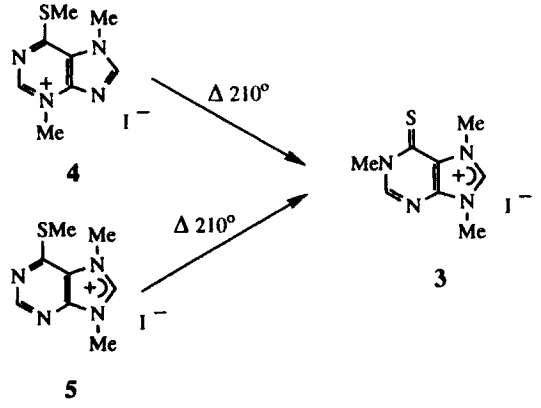
e. From Alkylthio and Thiocyanatopurines (H271)

Thiohydrolyses with hydrogen sulfide-saturated ammonia solution is now a well-established method for converting a methylthio group to a thioxo, displacement following the positional order 6 > 8 > 2. Various 6-methylthiopurines transformed in this way by hydrogen sulfide ion attack include the 3,7-dimethyl,[872] 3,9-dimethyl-8-phenyl,[872] 1-methyl-8-oxo,[1362] 1,9-dimethyl-8-oxo,[1362] 3,9-dimethyl-8-oxo,[1362] and 3,7,9-trimethyl-8-oxo[1362] derivatives. Failure to effect hydrolyses of 7,8-dihydro-6-methylthio-8-oxopurine or the 3-, 7-, and 9-methyl and the 3,7- and 7,9-dimethyl homologs is attributed largely to anion formation effects. Other factors such as resonance hybridization, zwitterionic forms, and steric constraints may, however, overrule this consideration. Hydrolysis of 3,7-dimethyl-6,8-bismethylthiopurinium iodide only involves the 6-methylthio group.[882] The versatility of displacements in thiohydrolysis reactions is ably demonstrated by formation of a 6-thioxopurine in this way from the 6-methylseleno analog.[1228] Thermal treatment in aprotic solvents alone suffices in some cases for demethylation, the 2-thioxopurine arises on heating a solution of the iodide of 3,6-dihydro-3,7-dimethyl-2-methylthio-6-oxopurine[1363] and similarly the 8-

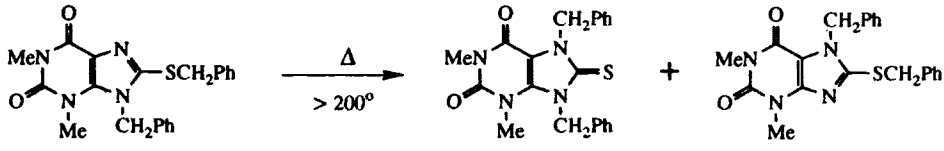


1 2

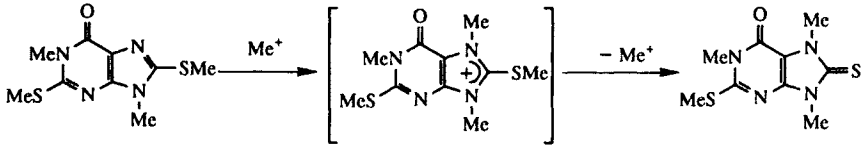
thioxo derivatives from the corresponding iodides of 9-methyl-[883] and 7,9-dimethyl-8-methylthio-6-oxopurine,[883] the latter undergoing spontaneous *S*-demethylation in dimethylformamide on standing. A notable feature of this reaction is participation of the cation form, but the neutral molecule fails to react likewise. Trifluoroacetic acid hydrolysis is used to remove both diphenylmethyl protecting groups from the 2,6-bisalkylthiopurine (**1**) forming 9-ethyl-1,2,3,6-tetrahydro-2,6-dithioxopurine (**2**)[1187] and the benzhydryl group from 6-alkylthiopurines.[1546] Inadvertent dealkylation of methylthio- and benzylthiopurines is observed under the fusion conditions employed in rearrangement attempts. Isolation of the 1,7,9-trimethyl-6-thioxopurinium iodide (**3**) results on heating (210°C) the iodides of either 3,7-dimethyl- (**4**) or 7,9-dimethyl-6-methylthiopurine (**5**).[1364] Studies with tritium-labeled *N*- and *S*-methylpurines indicate that methyl group scrambling occurs with ensuing transmethylation by the liberated methyl iodide. The greater nucleophilicity of the iodide ion is demonstrated by the failure of perchlorate salts of the purines to rearrange in the same way.[1364] Contrasting behavior is seen with the 9-benzyl-8-benzylthiotheophylline (**6**) which, as the neutral molecule, rearranges under fusion (> 200°C) to an equal mixture of the 7,9-dibenzyl-8-thioxo (**7**) and 7-benzyl-8-benzylthio (**8**)[889] isomers but as the hydrobromide salt is thermally inert.[1308] Of somewhat parallel interest



4 5 3



6 7 8



Scheme 1

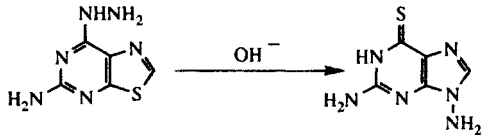
is demethylation of methylthiopurines as a result of attempted *N*-alkylations with methyl iodide. Some suitable examples are 1,7,9-trimethyl-6-thioxopurine from 1,9-dimethyl-6-methylthiopurines,[1308] and a number of 7-methylated 8-thioxopurines from the corresponding N-7 unsubstituted 8-methylthio precursors including 1-methyl-2,8-dimethylthio-6-thioxo-,[1363] 1,9-dimethyl-2,8-dimethylthio-6-oxo-,[1363] and 9-methyl-2,6,8-trimethylthiopurine.[1363] Demethylation of the sulfur group in these examples is assumed to be facilitated by formation of cationic intermediates protonated in the imidazole ring[1363] (Scheme 1). Methyl removal under different conditions occurs when 6- and 8-methylthiopurine and 9-methyl-8-methylthiopurine react with potassium amide in ammonia; this approach appears to be superior to that using hydrogen sulfide or other sulfides.[1091] In the case of 2-methylthiopurine with the same reagent, a transformation to 2-aminopurine results through an ANRORC rearrangement.[1050] A novel route to 6-selenoxopurines from the 6-methylthio analogs involves leaving the purines for a brief period in ethanolic hydrogen selenide at ambient temperature.[874] A good yield (85%) of 1,6-dihydro-9-methyl-6-thioxopurine arises from alkaline hydrolysis of the corresponding 6-thiocyanato derivative.[1365] Methylthio groups, in the oxidized methylsulphonyl form, usually undergo more facile nucleophilic displacement than the parent group. At room temperature, 6-methylsulfonylpurine is converted to the 6-thioxo analog by hydrogen sulfide in concentrated ammonia solution.[1362] The reflux conditions required with the corresponding 3-methyl-6-methylsulfonyl-8-oxo derivative may reflect the deactivation of a group at C-6 by the *N*-methyl group.[1362]

f. By Reduction of Disulfides (H272)

Treatment of 9-methylpurin-6-yl disulfide with sodium cyanide solution buffered to pH 7 produces a quantitative yield of a 1:1 mixture of 9-methyl-6-thioxo- and 9-methyl-6-thiocyanatopurine, the latter being readily converted to the former by alkaline hydrolysis.[1365] Under alkaline conditions, the *S*-oxide of dipurin-6-yl disulfide is degraded to 6-thioxopurine[1388] (see Section 3.B).

g. By Direct Introduction of Sulfur (H272)

A new fusion reaction, using a lower temperature (210°C, 2 h) than that employed previously, between sulfur and the 4-methylbenzenesulfonate salt of 7,9-dimethylhypoxanthine, affords the 8-thioxo derivative directly.[883]



Scheme 2

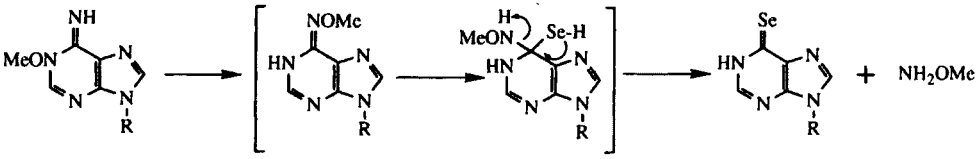
h. By Rearrangement of Thiazolo[5,4-d]pyrimidines (H273)

The major product of a mixture arising from the action of dilute alkali (*M*-NaOH, 20°C, 1 h) on 5-amino-7-hydrazinothiazolo[5,4-*d*]pyrimidine is an *N*-amino-6-thioxopurine (Scheme 2)[1010] with starting material as the minor component.

i. By Other Means (H273)

Direct displacement of amino by thioxo or selenoxo is now possible, with examples currently limited to groups located at C-6. The conditions are generally such that even derivatives with unprotected riboside groups can be reacted and, in the case of selenoxopurine preparation, this route is preferable to that involving halogen displacement (Section 1.A.c). A mixture of hydrogen sulfide or selenide in pyridine is employed, the solvent also acting as a mandatory catalyst.

With liquid hydrogen sulfide in pyridine (90°C, several days), cyclic adenosine monophosphate (cAMP) affords the 6-thioxo derivative.[1366] The higher temperature used in this instance is possible because of the stability conferred by the phosphate moiety. Activation of the amino group by ring *N*-alkylation allows conversion of 1-methyladenosine to the 6-thioxo analog with aqueous hydrogen sulfide (60°C, 46 h). Adenosine is relatively inert to this treatment, but on using the corresponding 6-methoxyamino riboside, a good yield of 6-thioinosine results[1403] (50°C, 57 h). Wider application is found for selenoxopurine preparations, the reaction with hydrogen selenide being more reliable than that with hydrogen sulfide. Examples are the 6-selenoxo derivatives from adenosine (65°C, 2–5 days),[1228,1367] AMP (65°C, 4 days), and related forms.[1228] Similar treatment of 2,6-diaminopurine-9-riboside gives the 2-amino-6-selenoxopurine analog.[1228] Surprisingly, conversion of 6-imino-1-methylpurine-9-riboside (1-methyladenosine) to the 6-selenoxo derivative is not accompanied by any Dimroth rearrangement. In contrast, the isolation of 6-selenoxopurine-9-riboside from the analogous 6-imino-1-methoxypurine can only result from an initial rearrangement of this type occurring, giving rise to an intermediate 6-methoxyaminopurine which undergoes a subsequent displacement by hydrogen selenide ion[1228] (Scheme 3).

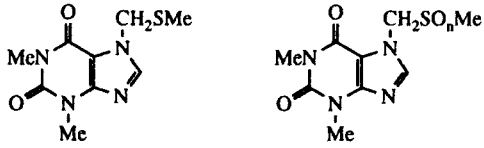


(R = cyclic riboside)

Scheme 3

B. Preparation of Extranuclear Thioxopurines (*H*274)

Condensation of the riboside of 6-methylsulfonylpurine with aminoethanthiol in cold aqueous solution affords the 6-(2-thioethylamino) analog.[1222] Preparation of the 7-methylthiomethylpurine (**9**) has been described,[1381] and the oxidized methylsulfinyl (**10**, $n = 1$) and methylsulfonyl (**10**, $n = 2$) forms occur as metabolites of caffeine in the urine of diverse mammalian species.[1343]

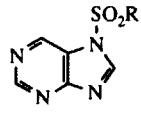


9 **10**

C. Reactions of 2-, 6-, and 8-Thioxopurine (*H*275)

a. Removal of Thioxo Groups (H275)

Conventional heat treatment with Raney nickel in alcohol or water removes the 6-thioxo group, giving 2-fluoro-,[1124] 2-amino-9-ethyl-,[1187] 9-(carboxymethyl)-,[1114] and 2-amino-purine,[1124] the latter arising by concurrent dethiation and reduction of the 2-hydroxyamino-6-thioxopurine precursor. Both thioxo groups undergo facile replacement by hydrogen in 9-ethyl-1,2,3,6-tetrahydro-2,6-thioxopurine under like conditions.[1187] Less vigorous treatment suffices for 6-selenoxopurines, as exemplified by the formation of 2-aminopurine-9-riboside (20°C, 5 min).[1190,1191] This is in sharp contrast to that required for removal of sulfur from the analogous 9-riboside. With 6-selenoxo-3-oxidopurine (H_2O, 100°C, 15 min), removal of both selenium and oxygen occurs affording purine[1142] itself. Oxopurines derived from nickel dethiation in alkaline solution include 1-methyl-8-oxo-(from 6-thioxo),[1249] 3-methyl-2-oxo[836] (from 6-thioxo), and 9-benzyl-2,6-dioxopurine[889] (from 8-thioxo). The older route using nitrous acid is utilized to eliminate the 8-thioxo group and form 9-benzyl-1-methylxanthine.[889] A two-stage oxidation



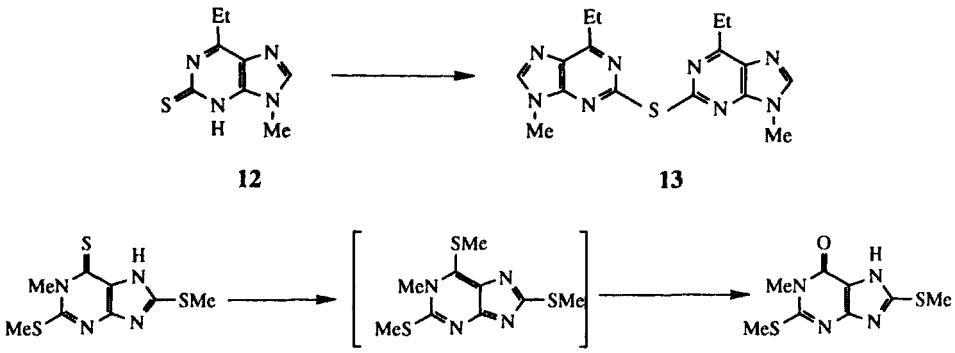
11

converts 1,6-dihydro-6-thioxopurine to 3-oxidopurine-6-sulfinic acid which, in 90% formic acid (80°C, 0.6 h), undergoes sulfinic acid group elimination giving 3-oxidopurine.[1057] An unusual loss of the sulfur group in the purine above occurs on treatment with trifluoromethyl thiosulfonates (RSO_2SCF_3, where R = Me or *p*-MeC_6H_4), the products being purinylsulfonamides of the type (**11**),[1368] with N-7 favored as sulfonylation site. A different type of sulfur extrusion is found when thioinosine is reacted with either acetonyl bromide or phenacyl bromide to give 6-acetonyl- or 6-phenacylpurine-9-β-D-ribofuranoside. In this reaction a carbon–carbon bond now joins C-6 to the ketonyl moiety.[1982]

b. S-Alkylation (H278)

Methylthiopurines continue to have widespread application as intermediates in purine metatheses because of the relative ease of displacement of the sulfur group by nucleophilic reagents. Although preparation is regarded as being a simple alkylation step, the conditions used may influence the reaction pathway toward either *S*- or *N*-alkylation or sometimes both. The situation, in general, is for low temperatures and aqueous media to favor *S*-alkylation, whereas at higher temperatures in an aprotic solvent, a predisposition toward *N*-alkylated derivatives is found. New investigations of alkylation of 6-thiotheophylline, as the sodium salt, largely support this rationale. In DMF or similar aprotic media (20°C, 24 h), the product is a separable mixture of the required 6-alkylthio-1,3-dimethyl-2-oxopurine and the isomeric 7-alkyl-6-thiotheophylline.[1988] In light of these findings, attention should be drawn to the recent trend in carrying out *S*-alkylations in aprotic media containing solid potassium carbonate rather than in aqueous alkali. Examples of this practice are given elsewhere in this section. Further points relevant to *S*- and *N*-alkylation of thioxopurines are detailed in Sections 1.C.c and 2.B.g.

Simple methylthiopurines derived from methyl iodide, or to a lesser extent dimethyl sulfate, treatment of the thioxopurine in aqueous alkali include the 1-methyl-2-methylthio,[836] 9-benzyl-6-methylthio,[862] and 2,9-dimethyl-8-methylthio[883] derivatives. Both thioxo groups are converted to given the 3- and 9-methyl-2,6-bismethylthio-[887] and corresponding 3-[887] and 9-methyl-6,8-bismethylthiopurines.[882] Methylation of three thioxo groups occurs with equal facility, giving the homologous 3- and 9-methyl-2,6,8-trismethylthiopurines.[887] Failure to achieve efficient methylation of 2-thioxo- to 2-methylthio-8- phenylpurine[857] is unexpected since the *S*-ethyl homolog has been formed by an alkylation procedure.[866]



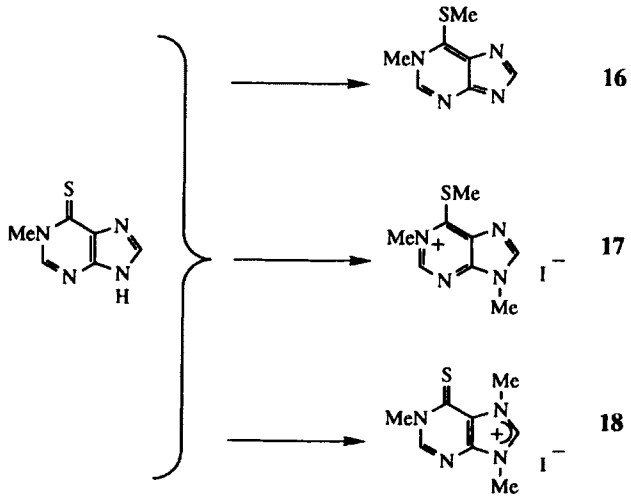
Scheme 4

Following treatment of the purine (**12**) with alkaline methyl iodide, the product is the dipurin-2-yl sulfide (**13**), arising through oxidation rather than formation of the thioether.[1188] This appears to be the first example of this type reported. Ribosides of 6-selenoxopurines have been similarly transformed into the 6-methylseleno[1228,1348] and other alkylseleno analogs. Using oxothioxopurine precursors has given rise to 7- and 9-methyl-2-methylthio-6-oxo-,[890] 3,7-dimethyl-2-methylthio-6-oxo-,[1363] 6-methylthio-8-oxo-[1243] and the 9-methyl homolog,[1243] 1,7-dimethyl-6-methylthio-2-oxo-,[1202] 2,9-dimethylthio-8-methyl-thio-6-oxo,[878] and the 3- and 9-methyl-6,8-bismethylthio-2-oxopurine.[890] The same route (Me_2SO_4) provides the 8-methylseleno derivative of inosine.[1193] Isolation of the 6-oxo- rather than the expected 6-methylthiopurine following alkaline methylation of the 6-thioxo analog reflects the susceptibility of the 6-methylthio group in the intended trismethylthio product to hydrolysis[890] (Scheme 4). Transalkylthiolation, a reaction analogous with transamination, is a means of transforming a 6-alkylthiopurine to a higher alkylthio homolog. Illustrative of this is the high yield (92%) of 6-*n*-butylthiopurine obtained from 6-methylthiopurine on heating with *n*-butylthiol. As with other examples of the reaction, acid or base catalysts are present.[1870] The action of 8-thioxanthines with benzyl bromide affords the 8-benzylthio homologs of the 1-methyl, 3-methyl, and 7- and 9-benzyl-1,3-dimethyl derivatives.[889] Selenium derivatives are well represented in alkylations of purines containing amino groups instanced by the formation of 6-methylselenoguanine,[1369] the 9-ribofuranoside[1192] of the latter, and the 6-benzylthio[1191] and 6-*p*-nitrobenzylthio[1192] derivatives. Similarly derived 8-alkylselenopurines include 8-methylselenoadenosine,[1193,1194] as well as the 8-ethylseleno[1194] and 8-benzylseleno[1194] analogs. Corresponding derivatives from 8-thioxoguanosine cyclic monophosphate are known.[1195] Use of an alkyl halide in an aprotic solvent, usually dimethylformamide, containing solid potassium carbonate is now increasingly replacing the aqueous alkaline conditions. This medium has better solvent properties and temperatures and reactions times are similar. It should be noted, however, that the possibility of *N*-alkylation occurring also exists if raised temperatures or excess alkylating agent are used.

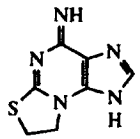


14 **15**

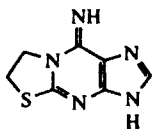
The applicability of the method is illustrated by the formation of 1-methyl-6-methylthio-[1364] (50°C), 1-methyl-6-methylthio-8-oxo- (20°C),[1243] 9-methyl-8-methylthio-6-oxo,[883] 3-benzyl-8-methylthio-6-oxo[883] (20°C), 2-amino-6-benzylthio-9-ethyl-,[1187] 2-amino-6-dibenzylmethylthio- (20°C),[1187] and 2,6-bisbenzylthio-9-ethylpurine (20°C) from the appropriate alkyl halide and thioxo- or dithioxopurine. Examples of thioxomethylthiopurines converted to bismethylthio derivatives in this way include 2,6-bismethylthio- from 6-thioxo-[887] and 2,8-bismethylthio- from 8-thioxopurines.[890] Only one thioxo group is methylated in the dithioxopurine (**14**), even at elevated temperatures, the product (**15**) reflecting the nonenolizable nature of the C-6 group.[890] The effect of thermal variation is seen in the case of 1,6-dihydro-1-methyl-6-thioxopurine—only the 6-methylthio analog (**16**) is obtained below 50°C, but as the temperature increases (90°C), *N*-methylation initially gives some 1,9-dimethylated product (**17**), and above 100°C the major component is the 1,7,9-trimethyl-6-thioxopurine (**18**) resulting from further *N*-methylation accompanied by an *S*-demethylation.[1364] Cases of *N*-alkylation due to an excess of alkylating agent are not uncommon. The effect of increasing amounts of 4-nitrobenzyl bromide on 6-mercaptopurine is an initial formation of the 6-benzylthio derivative, which is then converted to a mixture of the 3-, 7-, and 9-(4-nitrobenzyl) homologs.[1993] With an equimolar amount of methyl iodide, 6-amino-2-phenyl-8-methylthiopurine is obtained from the 8-thioxo derivative, but when in excess the 9-methyl-8-methylthio homolog is the product.[881] Similarly, 8-thioxanthines can be *S*-alkylated or *S*- and *N*-alkylated



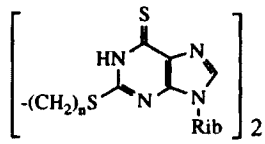
to the respective 8-methylthio- or 1,7-dimethyl-8-methylthioxanthines.[881] Corresponding bisalkylthiopurines result using limited amounts of methyl or ethyl iodide or benzyl chloride with 9-ethyl-1,2,3,6-tetrahydro-2,6-dithioxopurine, but further alkylation at N-3 occurs with increase of the reagent.[1187] The hitherto unsuspected sulfur-alkylating function of a mixture of a trialkyl orthoester and acid anhydride, normally employed in Traube-type ring closures of 4,5-diaminopyrimidines (see Chapter II, Section I.G), is shown by the formation of 2-ethylthio- (30%), 2-ethylthio-8-methyl-(78%), and 8-ethylthiopurine (70%) on heating the appropriate 2- or 8-thioxopurine with triethyl orthopropionate and either acetic or propionic anhydride.[866] Other orthoesters also serve as alkyl group donors, these arising from the alkoxy moieties of the esters. Evidence for *N*-alkylation under these conditions is absent. It should be noted that the alkylating effect is a specific function of fresh mixtures of ester and anhydride, in the optimum ratio of 2:1, and this property disappears on heating or aging.[866] Significantly the recently introduced tetraalkoxymethanes for Traube cyclizations (Chapter II, Section 1.X) are also capable of *S*-alkylation.[905] Somewhat similar is use of the reported application[1086] of dimethylformamide diacetals for converting thiophenols to the thioesters. With such reagents thioxopurines also undergo alkylation of the thioxo group but, unlike the orthoesters, the imidazole nitrogens are also involved.[1087] Dimethylformamide dimethylacetal [$Me_2COCH(OMe)_2$] converts 2,3-dihydro-2-thioxopurine to a mixture of 7-methyl- (20%) and 9-methyl-2-methylthiopurine (45%). Like mixtures of 7- and 9-methyl isomers of 8-methyl-2-methylthio-, 6-methylthio-, 8-methylthio- and 2,6-bismethylthiopurine also yield the respective thioxo- or dithioxopurine.[1087] A range of products is possible if $\alpha,\bar{\omega}$-dihalogenoalkanes are employed, illustrated by the isomeric thiazolopurines (**19** and **20**) from reaction of 1,2-dibromoethane with 2-thioxoadenine (DMA, K_2CO_3, 40°C)[1370] and with analogous derivatives from 2-thioxohypoxanthines (potassium hydroxide).[1229] Such derivatives are useful precursors of *N*-ethylpurines which they give on elimination of sulfur by Raney nickel.[1229,1370] The thiazine ring analogs arising with 1,3-dibromopropane are likewise a route to *N*-propyl derivatives.[1229] With longer-chain alkanes (> 4 carbons), *N*-alkylation is excluded and $\alpha,\bar{\omega}$-bispurin-2-ylthioalkanes of the type (**21**) are formed.[1229] A novel exocyclic ring is obtained when the product (**22**), derived from 6-mercaptopurine and epichlorohydrin ($NaHCO_3$, EtOH, 20°C), is treated with sodium methoxide (20°C, 24 h). A transformation to 1-(3-thietanyl)hypoxanthine (**23**), occurs resulting from abstraction of hydrogen chloride and attack by the oxygen of the epoxide produced on the 6-carbon followed by a subsequent fission of the carbon–sulfur bond.[1869]



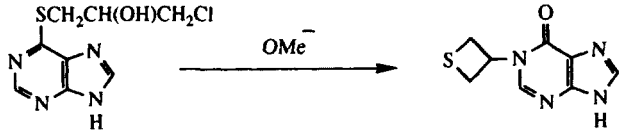
19



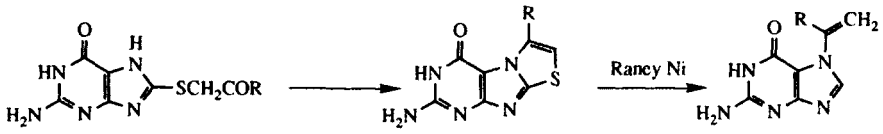
20



21

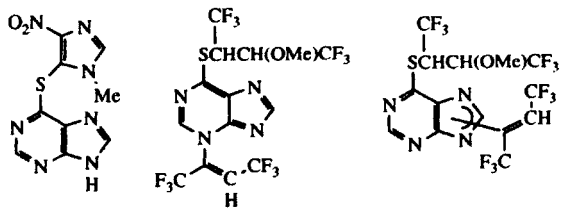


22 23

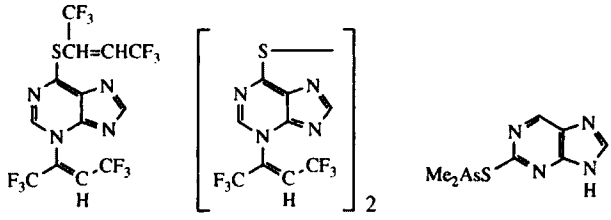


24 25 26

Various alkyl halides carrying other functional groups have been reacted with 2-, 6- and 8-thioxopurines. Examples involving chloroacetic acid, chloroacetamide, and chloroacetonitrile are treated elsewhere (Chapter IX, Section 9.B.a). Use is made of chloroacetone and related halogenoketones reacting with 8-thioxopurines to give initially 8-acylalkylthio derivatives (**24**), for example, which cyclodehydrate under acid conditions to thiazolo[2,3-f]purines (**25**).[1203] Nickel desulfurization provides the 7-alkenyl- (**26**) or 7-alkylpurine.[1203,1371-1373] Both 2- and 8-phenyl homologs of 6-(2-dimethylaminoethylthio)purine are obtained from condensing a 6-thioxo group with 2-dimethylamino-1-chloroethane, but no corresponding reaction occurs with the isomeric 8-phenyl-2-thioxopurine.[857] Other examples derived from 6-[1377] and 8-thioxopurines[1378] are to be found. Syntheses have been made of labeled forms of the immunosuppressive agent Azathioprine® (**27**) by using either 1,6-dihydro-6(^{35}S)-thioxopurine[1189] or 5-chloro-1-methyl-4-nitro-(^{14}C-4,5)imidazole[1374] in the condensations. Both products are obtained in 80% yields—the former in aqueous alkali and the other in dimethyl sulfoxide containing sodium acetate. Solvent effects, in the case of 6-thioxopurine with hexafluorobut-2-yne ($CF_3C{:}CCF_3$), appear to determine the nature of the product. In methanol, isomeric derivatives are formed in which *S*-alkenylation, through a Michael addition, is followed by addition of methanol to the double bond and subsequent *N*-alkenylation affords both the 3-alkenyl (**28**) and 7- (or 9-) alkenyl derivatives (**29**). Change of solvent to tetrahydrofuran results in formation of the proposed *S*,*N*-dialkenylated purine (**30**) together with the disulfide (**31**). NMR studies indicate that a (*Z*) configuration is adopted by the



27 28 29



30 **31** **32**

hexafluorobut-2-ene moiety in these compounds.[1375] Somewhat relevant in type, although not an alkylation, is formation of 2-(dimethylarsenylthio)purine (**32**) from interaction of 2,3-dihydro-2-thioxopurine with dimethylchloroarsine (Me_2AsCl) in cold dichloromethane.[1376] The analogous derivative from 1,6-dihydro-6-selenoxopurine is also known.[1376]

c. N-Alkylation (H280)

Examples involving both *S*- and *N*-alkylation have been noted earlier (see Section 1.C.b) as was the rearrangement of methylthiopurines to *N*-methylated thioxopurines (Section 1.A.e). Direct *N*-alkylation is best exemplified by thioxopurines having the sulfur group fixed as the thione tautomer. Some examples are the 6-thioxo analogs of 1,7-dimethyl- and 7,9-dimethylxanthine, which are converted in dilute alkali to the respective 1,3,7- and 1,7,9-trimethyl homologs (Me_2SO_4, 5°C).[1245] Similarly, benzylation has given the corresponding 7-benzyl-3-isobutyl-1-methylpurine.[831] Although 1,6-dihydro-1-methyl-2,8-methylthio-6-thioxopurine undergoes methylation at N-9, with methyl iodide in alkaline solution (20°C, 15 min), a surprising feature is the apparent hydrolysis of the 6-thioxo to a 6-oxo group under the reaction conditions used.[886] This behavior is explicable by assuming formation of a 6-methylthio intermediate, since hydrolysis of the latter is known to be extremely facile.[890]

The original conclusions reached for the Mannich-type reactions with 6-mercaptopurine, claiming that the products are 9-aminomethyl or 9-hydroxymethyl derivatives,[1379] have been challenged following further investigation.[1380] The 6-thioxopurine does form a 7-aminomethyl derivative, but with the same purine on hydroxymethylation, a mixture of 7-hydroxymethylpurine and a dihydroxymethylated product is obtained in which alkylation at the sulfur and N-3 has occurred. By contrast, the same reactions with 6-alkylthiopurines afford both 9-amino- and 9-hydroxy-methylpurines as products (Section 2.B.g). With trifluoromethylthiolsulfonates (RSO_2SCF_3, R = Me or 4-methylbenzene), an unusual alkylation transforms 6-mercaptopurine (Scheme 5) into a product resulting from alkylation at an imidazole nitrogen, possibly N-7, with concomitant elimination of the 6-thioxo group.[1368] Use of ^1H and ^{13}C NMR spectra[1971] and ^{15}N spectra[1972] to differentiate between N-7 and N-9 alkylated derivatives of 6-mercaptopurines is reported.



Scheme 5

d. Thioxo- to Oxopurines (H281)

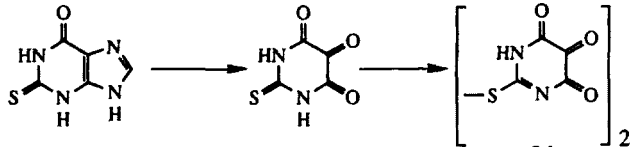
Few examples have emerged recently, and new reactions for this conversion are lacking. Direct transformation of 6-thioxo-to 6-oxopurines occurs under oxidative conditions with alkaline hydrogen peroxide.[1246] Selenoxopurines react likewise, as illustrated by the formation of theophylline and theobromine from their 6-selenoxo analogs using either the reagent above or perbenzoic acid.[874] The multistage route most frequently employed involves methylation of the thioxo group to methylthio, with subsequent oxidation to methylsulfonyl and hydrolysis with acid[878,1079] or alkali[1079,1246] to the oxopurine. Some examples of inadvertent replacement of thioxo by oxo are found following *N*-methylation in sodium hydroxide.[890] A more detailed survey of reactions of the above and of related types is given in Chapter VI, Section I.F.

f. Thioxo- to Aminopurines (H282)

Few examples are available of this little-used approach—the best involve preparation of purines with derivative amino groups. Hydrazinopurines, such as 8-hydrazino-9-methyl-, 2,6-dihydrazino-, and 2,6-dihydrazino-9-ethylpurine result, following prolonged heating of the thioxopurines (20–30 h) with hydrazine hydrate alone or in butanol.[1514] By similar means, 2-fluoro-6-(*N*-methyl)hydroxyaminopurine is obtained from interaction of the 6-thioxo analog with *N*-methylhydroxylamine.[1124] In an indirect application affording a 2-hydroxyamino derivative (69%), a 9-substituted-6-oxo-2-thioxopurine is treated with MCPBA and the oxidation product is reacted with 2*M* hydroxylamine (100°C, 0.5 h) in methoxymethanol.[1866]

h. Oxidation (H283)

The various oxidation states possible with thioxopurines include dipurinyl sulfides and disulfides (Section 3) together with the sulfenic, sulfinic, and sulfonic acids (Section 4). Most are obtained with conventional oxidizing agents. By contrast, electrochemical oxidation of an aqueous solution of 2-thioxanthine produces two significant oxidation peaks—the first corresponds to degradation to the trioxopyrimidine (**33**) and urea and the second to formation of the dipyrimidin-



33 34

2-yl disulfide (**34**). The preference for oxidation of the purine ring rather than the sulfur group reflects the ready facility of oxopurines, notably 6-oxo derivatives, to be oxidized under these conditions.[1775]

i. Formylation (H283)

Ring closure of a 6-oxo-2-thioxo-diaminopyrimidine with three equivalents of triethyl orthoformate gives in addition to the required pteridine some 2-formylthio-1,6-dihydro-6-oxopurine.[900]

2. THE THIOETHERS (*H*284)

A. Preparation of 2-, 6-, and 8-Alkylthiopurines (*H*284)

Although most derivatives continue to be made by one of the two established procedures, namely nucleophilic displacement of a halogen or alkylation of a thioxo group, some innovations to the Traube reaction now permit direct cyclizations of pyrimidines to 2-, 6-, and 8-alkylthiopurines.

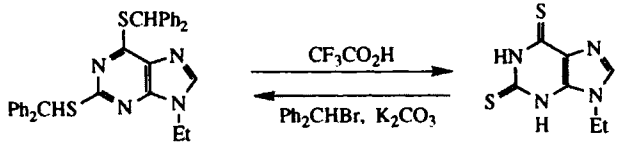
a. By Direct Synthesis (H285)

Ring closure of 2- and 6-thioxo-4,5-diaminopyrimidines with either orthoester–acid anhydride mixtures (Chapter II, Section 1.G) or tetralkoxymethanes (Chapter II, Section 1.X) may also result in concomitant *S*-alkylation. Methyl, ethyl, and propyl moieties have been introduced in this way; the alkyl group originates from the alkoxy group of the reagent. The use of tetrakismethylthiomethane for cyclization of the pyrimidine is novel and gives a one-stage formation of 8-methylthiopurines (Chapter II, Section 1.X). Likewise, of restricted application to 8-methylthio derivatives is the rearrangement of 3-acetoxypurines in the presence of aqueous methionine in which loss of the acetoxy group is accompanied by insertion of a methylthio group at C-8; both 2,3-dihydro-2-oxopurine[861] and xanthine[1116] are converted in this way (Chapter XI, Section 3.C). Methionine is also used in rearrangement of 7-hydroxyxanthine to 8-methylthioxanthine.[920] Although not strictly an example of a direct synthesis, the novel formation of 2-methylthio-6,8-diphenylpurine in low yield (20%) from either 2-

methylthio-4,6- or 2-methylthio-4,7-diphenylpteridine merits inclusion here. Both undergo an ANRORC rearrangement in liquid ammonia with potassium amide (–33°C) through nucleophilic attack by the amide ion at C-7 and C-6 of the respective pteridines.[896]

b. By S-Alkylation of Thioxopurines (H285)

Contemporary applications of the usual alkylation procedures have been discussed in Section 1.C.b. The scope of the reaction has now widened to include formation of the corresponding 6-[1191,1192,1228,1369] and 8-alkylselenopurines.[1193–1195] Examples of methyl-, ethyl-, propyl-, allyl-, benzyl-, and 4-nitrobenzylseleno derivatives are described. Protection of thioxo groups can be achieved using bromodiphenylmethane—the resulting diphenylmethylthiopurine reverts to the parent thioxo analog on heating in ethanol with trifluoroacetic acid[1187] (Scheme 6).



Scheme 6

c. From Halogenopurines (H285)

Current examples of the general type are given in Chapter V, Section 5.H. A more esoteric formation is that of 9-ethyl-6-phenylthiopurine on exposing the 6-iodopurine analog mixed with diphenyl disulfide in an aprotic solvent to UV photolysis.[1066] A similar free-radical conversion occurs of a 2-iodo- to a 2-methylthiopurine riboside.[1095]

d. By Direct Introduction (New)

The 8-lithio derivative of 3′-deoxyadenosine (cordycepin), as the *tert*-butyldimethylsilylated protected form, reacts with diphenyl diselenide, affording a moderate (50%) yield of the 8-phenylselenopurine analog.[1862]

B. Reactions of Alkylthiopurines (*H*285)

The methylthio group continues to be an invaluable asset in purine metatheses, being readily displaced by most nucleophiles either before or after oxidation to a methylsulfinyl or methylsulfonyl group. Homologous alkylthio groups

behave similarly, but show a generally reduced activity. Methylseleno groups, by contrast, undergo most displacements under less rigorous conditions. Studies with annelated cyclic thioesters have produced interesting results.

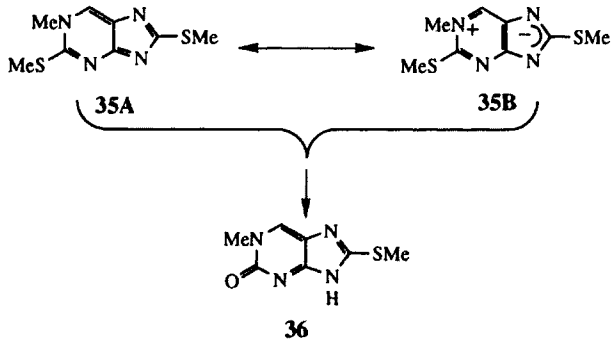
a. Reductive Removal of Alkylthio Groups (H285)

Heating with Raney nickel (EtOH, 18 h) is needed to remove a 2-methylthio group in forming a 9-benzyl-6-methylaminopurine,[1146] while similar conditions afford a 2-aminopurine nucleoside from the 6-methylseleno analog.[1192] Heating with nickel in ammonia solution provides a route to 8,9-dihydro-7-methyl-8-oxopurine from the 6-methylthio precursor.[1243]

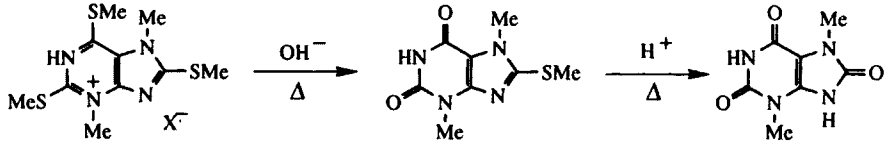
The various thiazolo[2,3-*f*]purines, resulting from the action of halogenoketones on 8-thioxopurines followed by cyclodehydration (Chapter IX, Section 9.B), provide a useful route to 7-alkenylpurines, which they give on elimination of sulfur by nickel. An example is conversion of the thiazolo[2,3-*f*]guanine (**25**, R = Ph) in this way (EtOH, NaOH, 10 h) to the 7-(1-phenylethen-1-yl) derivative (**26**, R = Ph).[1203] Analogous 7-isopentenyl forms of guanine (**26**, R = Me),[1203] hypoxanthine,[1373] and xanthine[1373] are other representatives of the procedure. Because the cyclodehydration is an alkylation reaction, these purines give only 7- rather than 9-alkenyl derivatives. Less specific is this reaction sequence with 8-thioxoadenines, which give 7- and 9-alkylated isomers through the occurrence of intermediate ring closures involving both imidazole nitrogen atoms.[1371,1372] Use of 1,2-dibromoethane rather than halogenoketones produces reduced forms of annelated purines. With 2-thioxoadenine, both the thiazolo[2,3-*b*]adenine (**20**) and the isomeric thiazolo[3,2-*a*]adenine (**19**) formed are readily converted (MeOH, 5 h) to the respective 1- and 3-ethyladenines.[1370] Likewise obtained (BuOH, 20 h) is 1-ethylhypoxanthine.[1229]

b. Alkylthio- to Oxopurines (H286)

Chapter VI, Section 1.F should be consulted for examples of this transformation being applied to form oxopurines. Kinetic aspects of the hydrolysis reaction were studied by Bergmann and the orders of displacement of methylthio groups at C-2, C-6, and C-8 from *N*-methylated derivatives were determined. Sodium hydroxide or sodium hydrogen carbonate are the usual reagents employed. With 2,6-, 2,8-, and 6,8-bismethylthio- and 2,6,8-trismethylthiopurine, repulsion due to anion formation precludes hydroxide ion attack.[886,890] In comparing the nucleophilic reactivity of halogeno- and alkylthiopurines, the corresponding di- and trichloropurines are hydrolyzed to the oxopurines under these conditions, possibly reflecting the greater leaving group character of the halogen overcoming any localized mesomeric charge effects.[890] Following *N*-methylation, the purine becomes a suitable candidate for hydrolysis since no anionic form is possible—all reactions involve neutral molecules and are pH independent. Mono-*N*-methyl



derivatives suffer attack at a methylthio group sited in the same ring as the methylated nitrogen, whereas with N_xN_y-dimethyl homologs displacement of an alkylthio group in the pyrimidine ring is favored.[886] A rationalization of the metatheses presupposes formation of a positive center through polarization of an alkylated nitrogen facilitating alkylthio group removal.[886] The hydrolysis of the 2,8-bismethylthiopurine (**35A**) to the 2-oxo-8-methylthio derivative (**36**) is explicable if a canonical form such as (**35B**) is invoked.[890] Based upon reactions with aqueous sodium hydroxide or sodium hydrogen carbonate, the order of replacement of alkylthio groups is found to be C-6 > C-2 > C-8 for the 1-methyl-,[890] C-2 > C-6 > C-8 for the 3-methyl,[882] and C-8 > C-6 > C-2 for the 9- and most likely 7-methylpurines.[882,890] The sequences for N_xN_y-dimethylpurines are less well established; those for the 3,7-dimethyl derivatives an 2 > 6 > 8. This is exemplified by the cation of 3,7-dimethyl-2,6,8-trismethylthiopurine in 2*M* sodium hydroxide (reflux, 2 h) which formed the 2,6-dioxo analog and required vigorous acid treatment (6*M* HCl, reflux 6 h) to hydrolyze the remaining alkylthio group[887] (Scheme 7).

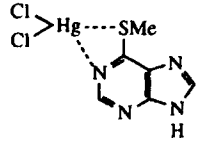


Scheme 7

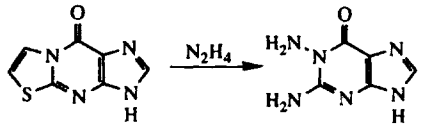
c. Alkylthio- to Aminopurines (H287)

Typical examples of this reaction continue to appear in the literature, although the number is relatively small compared with that employing replacement of a halogen or methylsulfonyl group. A failure to aminate the 2-methylthio group in a 2,6-bismethylthio-9-arylpurine is not unexpected in view of the reluctance of groups at this position to undergo nucleophilic substitution readily.[1146] A somewhat related example of interaction between 2-methylthiopurine and hydroxylamine-*O*-mesitylenesulfonic acid affords only 1-*N*-amino-2-methylthiopurine as

product (see Section 2.B.g).[1051] Successful interaction of 2-benzylthio-1,6-dihydro-6-triphenylmethyl-6-oxopurine with 2-aminoethanol, however, gives the 2-hydroxyethylamino derivative, which undergoes endocyclization with N-3 in thionyl chloride forming 5,6-dihydro-1*H*-imidazo[2,1-*b*]purine-9(8*H*)-one. Analogous 7,8-dihydroimidazo[2,1-*i*]purine-5-ones result from condensations with 3-alkyl-2,3-dihydro-6-methylthio-2-oxopurines.[1989] Conversion of the 6-alkylthio group in the bismethylthiopurine to a methylamino group at room temperature shows an unusually active 6-position.[1146] More usual conditions for replacing 6-alkylthio groups (110–190°C) with ammonia and alkylamines are applied with 6-methylthio-9-alkyl-,[1382] 2-amino-9-butylamino-6-methylthio-[1187] 2-amino-6-dibenzylmethylthio-,[1187] and related 6-benzylseleno-9-ribosylpurines.[1348] The reflux conditions employed in the last example are in contrast with the closed-vessel procedures usually required, illustrating the more reactive nature of alkylseleno groups compared with the alkylthio analogs. In nucleosides, 6-phenylthio groups are found to be useful precursors for 6-amino groups with certain 2-oxopurines.[1874] Complexing with Lewis acids, particularly mercury(II) chloride, reduces considerably the usual reaction temperatures. Aniline with 6-methylthiopurine is converted to 6-anilinopurine at 110°C in place of the 180°C previously employed. Group activation is envisaged through a complex of the type[1383] (**37**). Similar reductions of amination temperatures are possible using 9-acetyl-6-methylthiopurines; the inductive effect of the acetyl group aids methylthio group removal.[1383] Adenine in 50% yield results from methanolic ammonia treatment (100°C, 17 h) of 1-amino-6-methylthiopurine, in which alkylthio displacement and *N*-deamination occurs.[1404] The corresponding reaction occurs also with the 1-amino-2-methylthio isomer.[1404] Ethanolic ammonia solution at elevated temperature (180°C, 24 h) is required to convert 9-methyl-8-methylthiopurine to the 8-amino derivative.[875] Hot aqueous ammonia catalyzed by copper–bronze transforms a 2-amino-8-methylthio- to the 2,8-diaminopurine.[903] Two examples of nucleophilic displacement of a methylthio group by means of amide ions involve treatment in liquid ammonia (–33°C, 20 h) with potassium amide. A near quantitative yield of adenine results with 6-methylthiopurine,[1155] and preparation of 8-amino-9-methylpurine is effected similarly.[875] By using ^{15}N-labeled amide, the reactions are shown to be simple substitutions—no ring opening of the ANRORC type is involved.[1155] Cyclic alkylthio derivatives, such as the thiazolo[3,2-*a*]purine (**38**) undergo initial attack by hydrazine, forming a 2-hydrazinopurine, but subsequent reaction with the reagent at C-2 produces opening and reclosure of the pyrimidine ring, giving 1-aminoguanine (**39**) as final product.[1229] For the formation of 2,6-dihydrazinopurine from the



37



38 **39**

analogous 2,6-dimethylthio derivative, prolonged heating (12 h) with hydrazine hydrate is required.[1514]

d. Alkylthio- to Thioxopurines (H289)

A recent innovation worthy of note is the application of potassium amide–liquid ammonia mixtures to demethylation of 6- and 8-methylthiopurines. The procedure appears superior to those employing hydrogen sulfide or phosphorus pentasulfide and has the advantage of not requiring heat treatment.[1091] Demethylation generally is surveyed in Section 1.A.e.

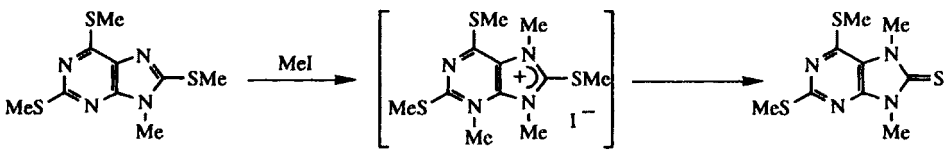
e. Oxidation (H289)

The most significant reaction of this type is the conversion of alkylthiopurines to the alkylsulfinyl- and alkylsulfonylpurines. Formation of these derivatives is detailed in Sections 7.A.a and 7.A.b.

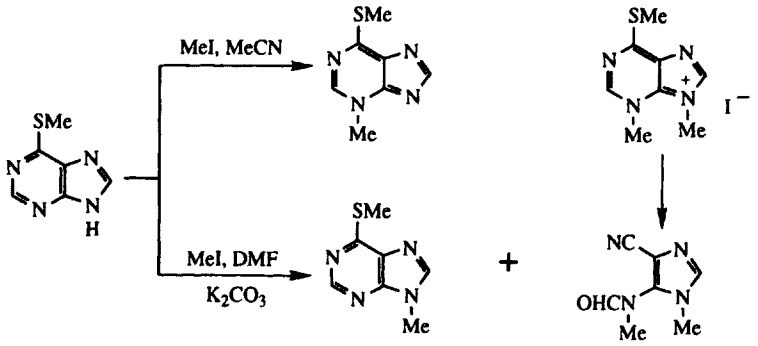
g. N-Alkylation of Alkylthiopurines (H289)

Various methylation studies have been carried out—the majority with methyl iodide in an aprotic solvent (usually dimethylformamide or acetonitrile) in the absence of a base. Generally, if a base is included, the products obtained are the same as when the reaction medium is aqueous alkali. Under the latter conditions, however, the risk of hydrolysis of methylthio groups must also be considered. The use of ethereal diazomethane as an alternative methylating agent has been explored, but in all cases the predominating alkylation occurs preferentially at an imidazole ring nitrogen.

Methyl iodide with 2-methylthiopurine (MeCN, 80°C, 1 h) gives a mixture of the 7- and 9-methyl isomers.[887] The corresponding 7,8- and 8,9-dimethyl homologs in equal amounts arise likewise from 8-methyl-2-methylthiopurine.[871] Further methylation of either the 7- or 9-methyl derivative produces the 7,9-dimethyl-2-methylpurinium iodide.[887] Under similar conditions (MeCN, 70°C), 2,6-bismethylthiopurine follows the same reaction sequence, finally forming the analogous 7,9-dimethylpurinium iodide.[887] Upon isolation, the methylation product of 9-methyl-2,6,8-trismethylthiopurine is not the expected 7,9-dimethyl iodide salt but the 7,9-dimethyl-8-thioxopurine (Scheme 8),[1363] with demethyla-

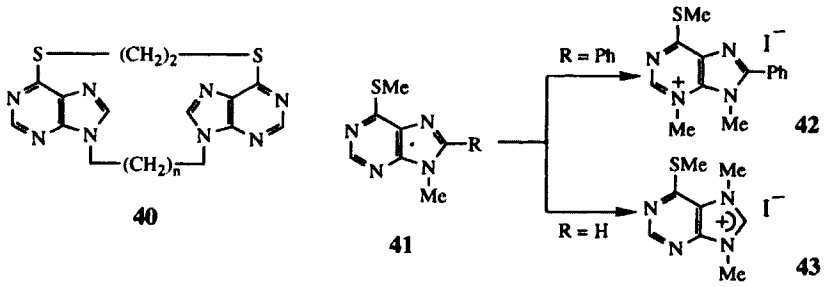


Scheme 8



Scheme 9

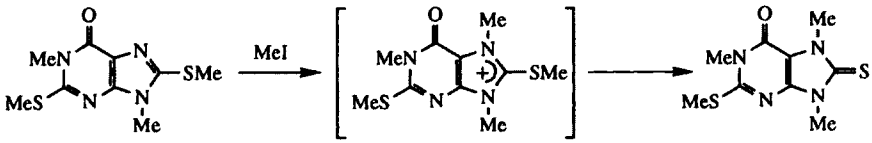
tion of the 8-methylthio group being facilitated by the charge in the imidazole ring of the intermediate. Related 8-methylthio to 8-thioxo conversions following *N*-methylation are known. On solvent change (DMF, 90°C), methylation of 7-methyl-2,6-bismethylthiopurine gives some 7,9-dimethyl derivative together with the isomeric 3,7-dimethyl-2,6-bismethylthiopurine. The latter dimethylpurine is also the alkylation product of 3-methyl-2,6-bismethylthiopurines[887] (DMF, 90°C). In the same way 6-methylthiopurine undergoes methylation at N-3 in acetonitrile (70–100°C),[785,1364] but on introduction of a base (K_2CO_3) to the medium (DMSO, 35°C), the product is 9-methyl-6-methylthiopurine together with some 4-cyano-1-methyl-5-(*N*-methylformamido)imidazole[785] (Scheme 9). Formation of this imidazole could arise from a degradation of 3,9-dimethyl-6-methylthiopurinium iodide, derived from methylation of **41** (R = H),[785] in view of the known instability of the 8-phenyl homolog (**42**). This derivative should theoretically be the more stable purine because of the effect of the aromatic substituent at C-8, but model studies show that out-of-plane alignment exits between purine and benzene rings.[872] Specific vinylation at N-9 occurs when 6-methylthio-, 6-ethylthio-, and 6-benzylthiopurine are heated (70°C, 24 h) with vinyl acetate in the presence of mercury(II) acetate.[1395] Esoteric examples of related alkali-induced (K_2CO_3) 9-alkylations are the purinophanes (**40**, *n* = 3 or 4) obtained by the action of the appropriate α,ω-dibromoalkane (DMSO, 20°C) with 1,2-bis(purin-6-ylthio)ethane[1384,1385] (Chapter XIII, Section 2). With an excess of methyl iodide, 3-methyl-6-methylthiopurine is converted to the 3,7-dimethyl iodide[887] salt.



Analogous 3-methyl and 3,7-dimethyl alkylation products are given by 6,8-bismethylthio- and 2,6,8-trismethylthiopurine.[887] Studies on the effects of an 8-phenyl group on alkylation patterns of 6-methylthiopurines show that 1-methyl-6-methylthio-8-phenylpurine, unlike the 8-unsubstituted parent compound, forms a stable 1,9-dimethyl derivative (DMF, reflux) and the 3- and 7-methyl analogs are converted to the same 3,7-dimethylated purine. Although these methylations are the same as those of the corresponding 8-unsubstituted analogs, the 9-methyl isomer (**41**, R = Ph) affords 3,9-dimethyl-6-methylthio-8-phenylpurinium iodide (**42**) rather than the expected 7,9-dimethylated derivative,[872] the analog of **43**, as in the case of the 8-unsubstituted compound. Steric factors arising from the proximity of the 6-methylthio and 8-phenyl groups direct methylation from N-7 to N-3. Both 8-methylthiopurine and the 2,8-bismethylthio homolog undergo methylation at N-1 (MeCN, 70°C) with methyl iodide.[887] New alkylation pathways, all involving ring nitrogens, are possible using diazomethane. With 2-, 6-, and 8-methylthiopurine, the predominant product in each case is the 9-methylpurine[785] together with other *N*-methylated derivatives. The minor product from 2-methylthiopurine remains unidentified, but is characterized as an *N*,8-dimethyl-2-methylthiopurine.[785] A subsequent repeat of the reaction identifies the main products as 9-methyl- and, to a lesser extent, 7-methyl-2-methylthiopurine.[871] The isolation of minor amounts of 7,8- and 8,9-dimethyl-2-methylthiopurine, however, suggests that *C*- as well as *N*-methylation occurs in the reaction. Since both isomers are formed when 8-methyl-2-methylthiopurine reacts with diazomethane, and no reaction occurs between the same reagent and 9-methyl-2-methylthiopurine, it is reasonable to assume that methylation at C-8 is the initial step.[871] With 6-methylthiopurine, a mixture of 9- and 3-methyl derivatives results.[785] Although the two corresponding isomers were reported from 8-methylthiopurine,[785] a subsequent investigation showed that all four *N*-methylpurines are present in a yield order of 9- > 3- and 1- > 7-methyl-8-methylthiopurine.[836]

Methylation patterns of methylthiooxopurines in aprotic solvents resemble those of the nonoxygen-containing compounds. The product from 2-methylthio-6-oxopurine is identical with the 7,9-dimethylpurinium iodide derived from the 7-methyl analog in the same way. With the 1-methylpurine as precursor, the corresponding 1,7,9-trimethylpurinium salt is obtained.[1363] An imidazole nitrogen is likewise involved in the conversion of the 3-methyl- to 3,7-dimethyl-2-methylthio-6-oxopurine (DMF, 20°C).[1363] The parent member of the isomeric 6-methylthio-8-oxopurines gives exclusively the 3-methylated homolog; steric hindrance of the methylthio group inhibits formation of the expected 1-methyl derivative.[1243] Other transformations in this series are the 1-methyl to 1,9-dimethyl, 3-methyl- to 3,9-dimethyl, and 7-methyl to 3,7-dimethyl analogs,[1243] with further methylation of the latter producing the 3,7,9-trimethylated form.[1243] A result at variance with the steric effect noted above is the formation of 1- and 3-methyl isomers, the former being the major component (77%) from 9-methyl-6-methylthio-8-oxopurine.[1243] With aqueous sodium carbonate and sodium hydroxide as solvents, the reacting purine species change from neutral molecules

to anions and dianions respectively. On methylation, both ions afford 7- and 9-methylated derivatives or a mixture of both.[1243] Comparisons of the reactions of 8-methylthio-6-oxopurine with those of other isomeric methylthiooxopurines noted above are restricted by the few examples available. A mixture of the 1,3-dimethyl derivative (80%) together with equal amounts of the 3- and 9-methylpurines (10%) is obtained from the parent purine in an aprotic (DMF, 20°C) medium.[883] Under anionic conditions (Na_2CO_3, 100°C) dimethyl sulfate affords both 1- and 7-methylpurines equally (50%), but with the dianion the 1,9-dimethylpurine is the main component (NaOH, 20°C) with the 7-methyl (10%) and 1-methyl (5%) analogs as minor products.[883] The dianion of 3-benzyl-8-methylthio-6-oxopurine is likewise converted to the 3-benzyl- 7-methyl homolog. In dimethylformamide, further methylation (MeI, 20°C) is possible to the 3-benzyl-1,7-dimethylpurine.[883] Alkylations of either 2,8-bismethylthio-6-oxopurine itself (MeI, DMF) or the 9-methyl homolog give 7,9-dimethyl-2,8-bismethylthio-6-oxopurinium iodide.[1363] Further methylation of the 1,9-dimethylpurine (**44**) leads to a 1,7,9-trimethyl-8-thioxo derivative (**45**) formed by an accompanying *S*-demethylation of the 8-methylthio group. The intermediate salt (**46**) is unstable and is one example among others known (see Section 1.A.e) of a spontaneous conversion of methylthio to thioxo group where there is attachment to a protonated ring. An imidazole nitrogen is also involved in the formation of the 3,7-dimethyl derivative from 3-methyl-2,8-bismethylthio-6-oxopurine with methyl iodide (MeCN, 80°C).[886] A recent investigation of the Mannich-type reactions with 6-alkylthiopurines has substantiated the original worker's findings[1379] that the products are the 9-aminomethyl and 9-hydroxymethyl derivatives. However, the later work[1380] shows that corresponding alkylations with 6-mercaptopurine give the 7- and not the 9-alkylated purines as originally[1379] claimed (Section 1.C.c). Somewhat relevant in character, although not a true case of alkylation at N-1, is the formation of 1-amino-2-methylthiopurine on reacting hydroxylamine-*O*-mesitylenesulfonic acid with 2-methylthiopurine.[1051] A point of interest is that no comparable 1-alkylated derivative of the latter purine appears to have been reported.



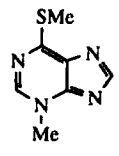
44 **46** **45**

h. Alkylthio- to Alkoxypurines (New)

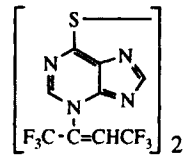
These transformations are dealt with in Chapter VI, Section 4.B. Using selected mono-*N*-methylated derivatives of 2-, 6-, and 8-methylthiopurines, kinetic studies show that displacement of methylthio by methoxy follows the order 6 > 2 > 8 for the 1-methylpurines and 6 > 8 in the case of the 3-methyl isomers.[1271]



47



48



49

Canonical forms indicate that the vastly greater activity of the alkylthio group in 1-methyl-6-methylthiopurine (**47**) over that in the 3-methyl analog (**48**) is the result of repulsion of the methoxide ion by the latter due to the negative charge associated with N-3. All the displacements are bimolecular and obey second-order kinetics.[1271]

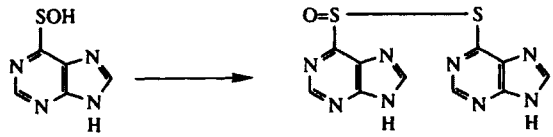
i. Alkylthio- to Alkylpurines (New)

Reaction of 6-methylthiopurine with Grignard reagents in the presence of nickel(II) chloride–phosphorus complexes gives 6-alkyl- and 6-arylpurines in good yield[1072] (see Chapter IV, Section 2.A.E). The carbanions of compounds containing reactive methylene groups give the same alkylidenepurines with 6-methylthiopurines[1871] as are formed using either 6-chloro- (Chapter IV, Section 2.A.d; Chapter V, Section 5.J) or 6-methylsulfonylpurines (Chapter IV, Section 2.A.e). Application of the Eschenmoser contraction to convert 6-alkylthio- to 6-alkylpurines[1350] is noted in Chapter IV, Section 2.A.e.

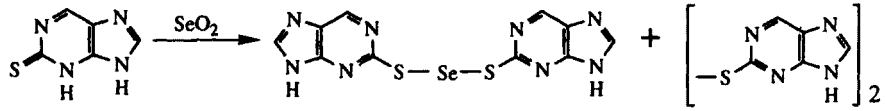
3. DIPURINYL DISULFIDES (*H*291) AND RELATED SULFIDES (*NEW*)

A. Preparation (*H*291)

The usual cold alkaline solutions of iodine oxidize 9-methyl-6-thioxopurine[1365] and 2-thioxoadenosine[1386] to the respective dipurin-6- or -2-yl disulfides. More unusual is the action of thionyl chloride in pyridine–acetonitrile in converting 8-thioxoadenosine to the dipurin-8-yl disulfide.[1387] One of the two main reaction products of 6-thioxopurine with hexafluorobut-2-yne in a tetrahydrofuran solvent is the 3-alkylated purine disulfide (**49**),[1375] but in a hydroxylic medium no oxidation to disulfide occurs.[1375] Under basic conditions, decomposition of the unstable purine-6-sulfenic acid (**50**) gives initially the thiosulfinatopurine (**51**), but

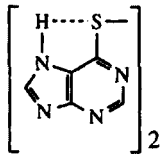


50 51



Scheme 10

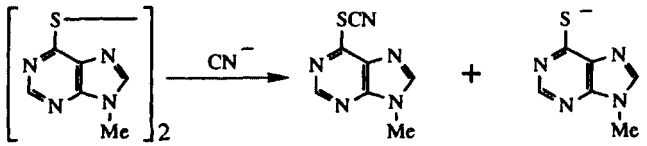
ensuing hydrolysis of this disulfide-2-oxide results in a mixture containing purine-6-sulfinic acid and 1,6-dihydro-6-thioxopurine.[1388] Of related sulfide derivatives, the isolation of a dipurinyl monosulfide following a methylation attempt with alkaline methyl iodide on a 2-thioxopurine is noted in Section 1.C.b.[1188] Polysulfide derivatives are represented by dipurinyltrisulfide analogs containing a sulfur–selenium–sulfur linkage. These, together with the corresponding dipurinyl disulfides, are formed following oxidation of 2-thioxo- or 6-thioxopurines with selenium dioxide or selenous acid[1389] (Scheme 10). The greater stability shown by the C-6 linked selenosulfides may reflect the existence of intramolecular hydrogen bonding of the type[1389] (**52**).



52

B. Reactions (*H*293)

On gentle warming in dilute hydroxide the disulfide, derived from 2-thioxoadenosine, reverts back to the parent-2-thioxopurine riboside.[1386] Equimolecular amounts of the 6-thiocyanato- and 6-thioxopurine are produced when di-9-methylpurin-6-yl disulfide and sodium cyanide react in solution buffered to pH 7[1365] (Scheme 11). The unstable character of thiosulfinate derivatives of disulfides shows in the ready stepwise transformation of **51** in basic media to purine-6-sulfinic acid and then to 1,6-dihydro-6-thioxopurine—the products with acids are a mixture of the 6-thioxopurine and hypoxanthine[1388] and both reactions are followed by UV spectroscopy.

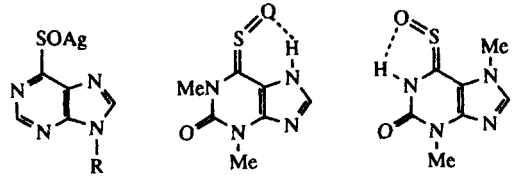


Scheme 11

4. PURINE SULFENIC (*NEW*), SULFINIC, AND SULFONIC ACIDS (*H*293)

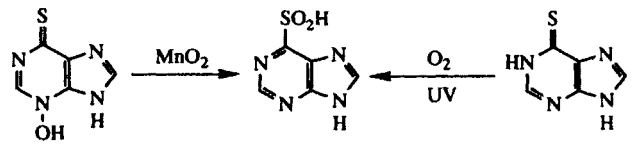
A. Preparation

Purine sulfenic acids, also encountered in the literature as purine sulfoxides or thioxopurine-*S*-oxides (*H*301), are the lowest oxidation state of the sulfoxy acids. To date, representatives are mainly limited to derivatives of 6-thioxopurines.[874] No comparable forms of oxidized 6-selenoxopurines are reported because these purines undergo ready hydrolyses to hypoxanthine analogs.[874] Preparation entails careful oxidation of the purine with an equimolar amount of *m*-chloroperbenzoic acid in a nonaqueous medium (MeOH or $CHCl_3$, 0°C). Although stability is not a feature of the free acids, isolation is possible by converting them to a silver salt,[1388] as with **53** (R = H or Me). The characteristic blue color obtained with iron(III) chloride solution denotes the presence of a sulfur monoxide derivative; further evidence is found in the UV spectra, which are dissimilar to the spectra of comparable sulfinic and sulfonic acids[1388] and indicate the presence of a sulfur monoxide moiety. Somewhat greater stability is shown by the sulfenes derived from the 6-thioxo analogs of theophylline and theobromine. The suggestion that stabilization is the result of intramolecular H-bonding of the type (**54**) and (**55**) is reasonable in view of the observed differences in the pK_a and ^1H NMR between these compounds and their 6-thioxopurine precursors.[874] Inclination of the sulfinyl groups towards N-7 and N-1, respectively, is proposed to accommodate such bonding.[874] Oxidation of an 8-thioxoadenosine in which the sulfur and N-9 are linked by a sugar moiety provides an unusual example of an 8-*S*-oxide.[1509]



53 **54** **55**

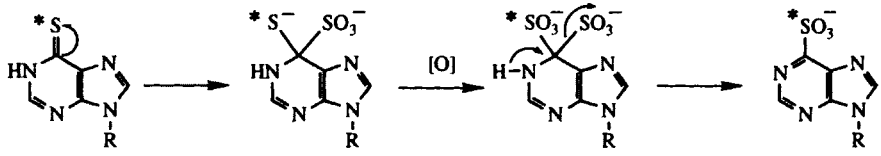
The instability of the sulfinic acid derivatives is reflected in the paucity of examples found. Even careful oxidation of thioxopurines is an uncertain preparative route since other products are more likely to result. Reaction with manganese dioxode on the 3-oxide of 1,6-dihydro-6-thioxopurine (**56**) produces purine-6-sulfinic acid, the *N*-oxide being lost in the process.[1057] The same acid (**57**) forms initially (90% yield) on aerobic UV irradiation of 6-thioxopurine (**58**), but further



56 **57** **58**

oxidation to the sulfonic acid occurs on longer exposure.[1247] Both 8-sulfino and 8-sulfoadenines are obtained from peroxide treatment of 8-thioxoadenine.[1789] A more esoteric route to the sulfinic acid (**57**), involving a base-promoted decomposition of a purinyl thiolsulfinate, is noted in Section 3.A.

Exemplifying more recent preparations of purine sulfonic acids by the established oxidation of thioxo derivatives with aqueous permanganate are with 6-thioxo-, 8-thioxo-, and 9-methyl-8-thioxopurine.[1390] Failure to convert a 2-thioxo group is not unexpected in view of similar negative results obtained from attempted oxidations aimed at 2-sulfenopurine preparations.[847] Conversion of a sulfinate to a sulfonate with oxygen under UV irradiation is noted above.[1247] Of late, more attention has been given to preparations involving nucleophilic displacement by sulfite ions; for example, 2,6-dichloropurine in aqueous sodium sulfite (70°C, 3 h) gives the 2,6-disulfopurine sodium salt.[1124] Similar displacements are possible with 6-thioxo groups in forming the 9-ribosyl derivatives of 6-sulfo- and 2-amino-6-sulfopurines,[1391] the reagents being a 3:1 mixture of *M*-sodium sulfite and *M*-sodium hydrogen sulfite in the presence of oxygen. Use of a ^{35}S-labeled purine precursor shows that the reaction mechanism involves both sulfite ion addition and thioxo oxidation to a *gem*-disulfonyl ion intermediate with restoration of aromaticity on subsequent loss of one of the sulfur groups (Scheme 12).[1391]



Scheme 12



59 **60**

Nucleophilic substitution of an 8-methylsulfonyl group occurs in aqueous potassium hydrogen sulfite the precursor (**59**) also undergoing adduct formation at the 6-position to give the sulfinic acid salt[1047] (**60**). No comparable displacement is found with a 2-methylsulfonylpurine.[1047] An unexpected hydrolysis of 6-fluorosulfonylpurine to the 6-sulfopurine with methanolic sodium methoxide is due most likely to the presence of moisture.[1390] The conversion of a series of *N*-methylated-8-oxo-6-thioxopurines to the corresponding 6,8-dioxo derivatives on treatment with hydrogen peroxide undoubtedly occurs through autohydrolysis of 6-sulfopurine intermediates.[1246]

B. Reactions (*H*295)

Hydrolyses to oxopurines have been studied by UV spectrometry with some 6-sulfopurines. Under acid conditions (2.85*M* HCl), the reaction rates obtained were three times those of the corresponding 8-sulfo derivatives.[1390] In this respect, these results reflect those from similar nucleophilic displacements carried out with 6- and 8-chloro and 6- and 8-methylthiopurines. Rates in alkali are slower, except in cases where anion formation is possible and hydrolysis is precluded.[1390] Other examples of 6-sulfenic[1388] and 6-sulfonic acid[1247] hydrolyses are available in acid solution. With basic conditions, purine-6-sulfenic acid (**50**) initially gives the thiosulfinate (**51**) and is then hydrolyzed to a mixture of the sulfinic acid (**57**) and 1,6-dihydro-6-thioxopurine.[1388] With hydroxylamine in ethanol under reflux, 2,6-disulfopurine is converted to 2,6-bishydroxyaminopurine.[1124] Removal of the acid group from 3-oxidopurine-6-sulfinic acid in hot formic acid (80°C, 0.5 h) provides a route to 3-oxidopurine.[1057] The sulfite adduct (**60**) noted earlier is also formed by the action of potassium hydrogen sulfite solution on 8-sulfopurine.[1047]

5. HALOGENOSULFONYL PURINES (*H*295)

Only isolated references are encountered, these are mainly concerned with derivatives of 6-fluorosulfonylpurine.

A. Preparation (*H*295)

Standard oxidative procedures, using chlorine with either potassium hydrogen difluoride or a hydrogen fluoride–potassium fluoride mixture, give 6-fluorosulfonylpurine[1390] and the 3-oxido[1142] derivative.

B. Reactions (*H*296)

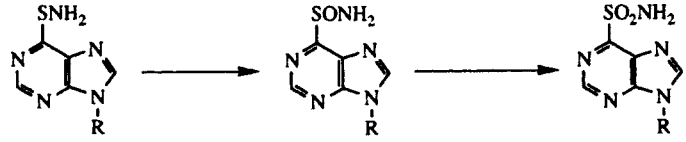
With nucleophilic reagents mild conditions lead only to displacement of halogen, whereas more vigorous treatment causes replacement of the complete halogenosulfonyl moiety. This is illustrated by the formation of purine-6-sulfonylhydrazide from the 6-fluorosulfonyl analog with cold (–10°C) methanolic hydrazine hydrate, but at a slightly higher temperature (25°C, 8 min), 6-hydrazinopurine results.[1390] The 3-oxide of 6-fluorosulfonylpurine is similarly converted to 3-oxido-6-sulfamoylpurine with liquid ammonia.[1142] An apparent hydrolysis by methanolic sodium methoxide of 6-fluorosulfonyl- to 6-sulfopurine can only be attributed to an inadvertent introduction of moisture.[1390]

6. SULFENAMIDO-, SULFINAMIDO-, AND SULFONAMIDO-(SULFAMOYL)PURINES (*H*297)

These derivatives have had only a very limited application as intermediates in purine metatheses. Under controlled oxidation conditions, the sulfenamidopurines are sequentially converted to the corresponding sulfinamido- and sulfonamidopurines.

A. Preparation (*H*297)

The 6-sulfenamides (**61**, R = H) and (**61**, R = 9-β-D-ribofuranosyl) result when thioguanine[1872] and thioguanosine[1873] are treated with chloramine solution (sodium hypochlorite–aqueous ammonia). Analogous derivatives are given by thioinosine[1873] and various related deoxynucleosides.[1872,1873] Oxidation of sulfenamides with limited (1 mol. equiv.) amounts of MCPBA in ethanol (0°C) affords sulfinamides such as (**62**), but with a fourfold excess of oxidizing agent, the corresponding sulfonamide (**63**) is obtained.[1872,1873] Under similar conditions with hydrazine hydrate and liquid ammonia, analogous derivatives to the latter are formed by 6-fluorosulfonylpurine (see Section 5.B).



61 **62** **63**

7. ALKYLSULFINYL- AND ALKYLSULFONYLPURINES (*H*298)

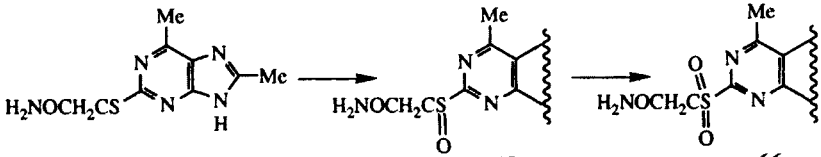
Similar tendencies toward nucleophilic displacement reactions are shown by the sulfinyl- and the more stable sulfonylpurines.

A. Preparation (*H*299)

a. Methylsulfinylpurines (H299)

Methylsulfinylpurines result from oxidation of the corresponding 2-, 6-, or 8-methylthiopurine with *m*-chloroperbenzoic acid (MCPBA) in cold (0°C) chloroform. Use of more than the stoichiometric one equivalent of oxidant per thio group leads to further oxidation and formation of methylsulfonyl derivatives. Converted in this way to the appropriate methylsulfinylpurines are 9-methyl-

2-methylthio-,[785] 6,9-dimethyl-2-methylthio,[1188] 9-methyl-6-methylthio,[785] 2, 9-dimethyl-6-methylthio,[785] 9-methyl-8-methylthio,[785] and 2,9-dimethyl-8-methylthiopurine[878], as well as the 6-oxo analog of the latter.[878] A similar transformation of the 2-carbamoylthio derivative (**64**) to the sulfoxide (**65**), and with more of the reagent to the higher oxidation state sulfone (**66**), is a further example.[841]



b. Methylsulfonylpurines (H299)

With two or more equivalents of MCPBA, 9-methyl-2-methylthio-, 9-methyl-6-methylthio-, 2,9-dimethyl-6-methylthio-, and 9-methyl-8-methylthiopurine undergo direct conversion to the corresponding 2-, 6-, or 8-methylsulfonylpurine.[785] Chlorine, one of the more usual oxidizing agents for this reaction, forms 6-methylsulfonyl-3-oxidopurine from the 6-methylthio analog in cold methanol (5°C, 20 min).[1142] Aqueous methanol is favored for the oxidation of 6-methylthio-8-(4-thiazolo)purine.[870] Both groups in 2,6-bismethylthiopurine are similarly converted, but in anhydrous methanol the product is 6-chloro-2-methylsulfonylpurine, the conditions now predisposing toward replacement of methylthio group by halogen (*H*300).[870] A series of 6-methylsulfonyl-8-oxopurines are obtained likewise, these include the parent member,* the 3-, 7-, and 9-methyl, 3,7-, 3,9-, and 7,9-dimethyl, and 3,7,9-trimethyl derivatives.[1362] The failure to oxidize the methylthio group in either the 1-methyl or 1,9-dimethyl analogs possibly points to a steric involvement of the 1-methyl with the adjacent alkylthio group.[1362] Bromine water is used in place of chlorine as a route to 6-methylsulfonylpurine from the methylthio precursor.[1392] Oxidation with cold (0°C) aqueous potassium permanganate containing acetic acid continues to be widely featured in reactions with 9-methyl-6-methylthio-,[1150] the 9-riboside analog,[1394] 8-methylthio-,[1271] and 2,8-bismethylthiopurine.[1047] Similar treatment of 3-methyl-6-methylthiopurine, however, gives 3-methylhypoxanthine as a hydrolysis product of the 6-methylsulfonylpurine initially formed.[836] Conversion of 7,8-dihydro-2-methylthio-8-oxopurine to the 2-methylsulfonyl derivative occurs likewise; the latter is also a hydrolysis product from oxidation of 2,8-bismethylthiopurine[1047] at 25°C. Formation of the novel *N*-methyl (or -aryl)

* This 7,8-dihydro-6-methylsulfonyl-8-oxopurine is derived unambiguously and differs completely from the compound of the same name isolated by earlier workers[284] following chlorine oxidation of 6,8-bismethylthiopurine in aqueous methanol. The latter product is now assumed to be the 8-methylsulfonyl-6-oxopurine isomer formed by hydrolysis of the group at the 6-position following oxidation.

sulfonylpurines following alkylation with trifluoromethylthiol sulfonates is noted elsewhere (Section 1.C.c). A preparation of a 2-phenylsulfonyl- from a 2-phenylthiopurine is reported using hydrogen peroxide and acetic acid.[1858] A mixed product of the 8-methylsulfinyl and 8-methylsulfonyl derivative results from treating a 9-benzyl- 6-dimethylamino-8-methylthiopurine with peroxyacetic acid.[2014]

B. Reactions (*H*300)

The ability of these compounds in some cases to undergo nucleophilic displacements not attainable with the corresponding chloro derivative is a useful preparative feature. Little difference in activity toward alkaline hydrolysis (*M*-NaOH) is found between methylsulfinyl and methylsulfonyl groups in a series of 9-methylpurines. The order for group displacement (8 > 6 >> 2) found in both contrasts with that already established (6 > 8 >> 2) for the analogous methylthio- and chloropurines.[785,1182] Hypoxanthine derivatives arise from both acid and alkaline treatment of 6-methylsulfonylpurines,[1079] but merely heating an aqueous solution (100°C, 4 h) converts 2,8-bismethylsulfonylpurine to the 2-methylsulfonyl-8-oxo analog.[1047] Thiohydrolysis with hydrogen sulfide in concentrated ammonia solution (20°C, 0.5 h) converts 6-methylsulfonylpurine to the 6-thioxo form more readily than the same reaction with 6-methylthiopurine.[1362] A comparative study of the reactivities of methylthio and methylsulfonyl groups in displacements in nitrogen heterocycles has been made.[1393] Alkoxylations are exemplified by 6-methoxy- and 6-phenoxy-9-phenylpurine from treatment with sodium methoxide and -phenoxide respectively.[1079] Diverse amines give rise to 6-anilino-,[1079] 6-benzylamino-,[1222] 6-(2-thioethylamino)-,[1222] and 6-(1-oxidopyrid-2-ylmethylamino)purine.[1392] The last example serves as a protected form of an amino group from which the parent aminopurine is liberated following treatment with acetic anhydride and ammonia.[1222] Reactions with piperidine (100°C, 1 h) are used in kinetic studies with 2- and 8-methylsulfonyl-9-methylpurines.[785] Examples of 6-hydrazinopurines resulting from interaction with hydrazine hydrate include the 9-phenyl,[1079] 8-(4-thiazolyl),[870] and 2-methylsulfonyl derivative from 2,6-bismethylsulfonylpurine.[870] Analogous 6-hydroxyaminopurines are obtained likewise with ethanolic hydroxylamine.[870] The need for cautious temperature observance is shown when 6-methylsulfonyl-3-oxidopurine gives the 6-hydroxyamino analog at 25°C, but at a higher temperature (80°C) hydrolysis to 3-oxidohypoxanthine occurs.[1142] The selective reaction of the methylsulfonyl group is demonstrated in the formation of the riboside of 6-azidopurine by sodium azide in methanol (25°C) when similar treatment of the 6-chloropurine riboside failed.[1222] The analogous 6-cyanopurine riboside results from condensation with sodium cyanide in dimethylformamide[1394] (20°C, 2.5 h). Compounds containing active methylene groups also react readily with 6-methylsulfonylpurines in the presence of alkali. Successful condensations are noted with acetone, acetylacetone, acetophenone, malonodinitrile, and others[1079] (see Chapter IV, Section

2.A.e). An example using ethyl acetoacetate and sodium hydride in THF is formation of 6-ethoxycarbonylmethylpurine riboside.[2034] This approach provides a suitable route for converting a 6-thio derivative to a 6-alkylpurine.

8. THIOXOPURINE-*S*-OXIDES (*H*301)

Topics previously elaborated upon under this heading are now grouped together with derivatives of sulfenic acids in Section 4.

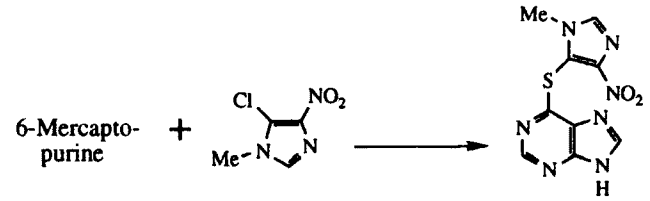
9. 6-MERCAPTOPURINE AND ANALOGS (*H*302)

No significant advances to the established methods of preparation have emerged. A number of recent syntheses are more of novel rather than practical value. An improved yield (~83%) is claimed for the ^{35}S-labeled compound from interaction of 6-chloropurine with ^{35}S-barium sulfide.[1181] Conversion of 6-methylsulfonylpurine with hydrogen sulfide at room temperature gives the unlabeled purine.[1362] Isolation of 6-mercaptopurine, following acid or alkaline hydrolyses of the thiolsulfinate of dipurin-6-yldisulfide, requires separation from other products.[1388] Ammonium dithiocarbonate reacts successfully with 3-oxido-6-chloropurine to give the oxide of 6-mercaptopurine.[1142] In contrast, thiolation of 2-amino-6-chloro-3-oxidopurine with thiourea produces thioguanine through concomitant removal of the oxide function.[1166] An innovation enabling direct replacement of an amino group by sulfur or selenium under mild conditions is seen in the formation of the cyclic nucleoside of 6-mercaptopurine from cAMP using liquid hydrogen sulfide in pyridine.[1366] The current interest in the role of selenium-containing derivatives in metabolic functions has stimulated the preparation of 6-selenoxopurine derivatives. Selenourea with 3-oxido-6-chloropurine affords the 6-selenoxo analog,[1142] and replacement of a 6-amino group effected with hydrogen selenide occurs with adenosine[1228,1367] and cAMP.[1366] The formation of 6-selenoxopurine riboside from 6-imino-1-methoxypurine following the same treatment must involve an intial Dimroth rearrangement to a 6-methoxyamino intermediate.[1228] Methanolic sodium hydrogen selenide converts 6-chloro- to 6-selenoxoguanosine and related nucleosides to the corresponding derivatives.[1190-1192] Investigations of the products from reactions of 6-mercaptopurine and other 6-thioxopurines with metal-complexing reagents show that the sulfur and N-7 are the most likely sites for bonding of the metal ion in the adducts.[1973]

The thione form of 6-mercaptopurine is shown by ^{13}C NMR to predominate (79%) as the 1H, 7H-tautomer.[1322] This is also found (^1H NMR) in aqueous solution;[2021] supporting evidence is provided by crystallographic examinations[1396,1397] and data from CNDO/2 calculations.[1033] Significant out-of-plane deformations are present, notably in the dihedral angle (1.16°C) between the five- and six-membered rings and in the inclination of the sulfur–carbon bond (1.5°) above the

plane of the pyrimidine ring.[1397] Rates of exchange for the C-8 proton with deuterium[1398,1402] and tritium[1399] have been determined for both the purine and the riboside. The mass spectrum shows two ion peaks of note apart from that of the molecular ion (15.9%). One is identified with loss of the thioxo group (3.1%) and the other is due to an $(M-1)^+$ fragment (1.2%) arising from fission of the pyrimidine ring with an associated proton loss.[1400]

In spite of the syntheses of many analogs of 6-mercaptopurine, this remains one of the most effective means for treating various leukemias. To a lesser extent, the related thioguanine serves the same purpose. Interest in the other medical application of 6-thioxopurines, as immunosuppressive agents, has developed in parallel with the increasing use of organ transplant procedures. The most widely studied 6-mercaptopurine derivative for this aspect is Azathioprine® [6-(1-methyl-4-nitroimidazol-5-yl)thiopurine] (**68**), which is formed by condensing the parent purine with the chloroimidazole (**67**) in alkaline solution. Syntheses of



67 **68**

more than 80% are recorded, including the ^{35}S-[1189] and imidazole-^{14}C[1374] labeled derivatives. Clinically it is encountered as Imuran® (Wellcome), Azamune® (Penn. Pharm.), and Verkaprine® (Berk), among others. The ready in vivo conversion of Azathioprine® to 6-mercaptopurine is advanced to explain some of the therapeutic effects. These aspects together with related information are the subjects of a number of monographs.[1401,1956,1957]

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER VIII

The Amino (and Amino-Oxo)purines (*H*309)

1. Preparation of 2-, 6-, and 8-Aminopurines (*H*309) . . . 214
   A. By the Traube Synthesis (*H*309) . . . 214
   B. By Cyclization of Imidazoles (*H*309) . . . 215
   C. From Acyclic Precursors (*H*310) . . . 215
   D. From Halogenopurines (*H*310) . . . 216
   E. From Thioxo- and Alkythiopurines (*H*310) . . . 216
   F. From Oxo- and Alkoxypurines (*H*311) . . . 217
   G. By Amination of Other Groups (*H*311) . . . 217
   H. By Reduction of Nitrogen-Containing Groups (*H*312) . . . 217
   I. By Direct Amination (*H*312) . . . 218
   J. By Other Routes (*H*313) . . . 218
   K. Secondary and Tertiary Amines Derived from Primary Aminopurines (Including the Dimroth Rearrangement) (*H*313) . . . 219
2. Preparation of *N*-Aminopurines (*H*316) . . . 219
3. Preparation of Extranuclear Aminopurines (*H*317) . . . 220
4. Properties of Aminopurines (*H*320) . . . 222
5. Reactions of Aminopurines (*H*321) . . . 224
   A. Replacement of Amino by Oxo Groups (*H*321) . . . 224
   B. Replacement of Amino Groups by Halogens (*H*322) . . . 224
   C. Formation of Azamethines (Schiff Bases) and Related Derivatives (*H*322) . . . 225
   D. Acylation of Aminopurines (*H*323) . . . 228
      a. Acetylation (*H*323) . . . 228
      b. Formylation (*H*325) . . . 229
      c. Benzoylation and Other Acylations (*H*325) . . . 230
      d. Reduction of Acylaminopurines (*H*327) . . . 231
      e. Hydrolyses of Acylaminopurines (*H*327) . . . 232
      f. Rearrangement of Acylaminopurines (*H*327) . . . 232
      h. Reactions of Acylaminopurines (*New*) . . . 233
      i. Ureido and Thioureido Derivatives (*New*) . . . 234
   E. With Formaldehyde (*H*330) . . . 235
   F. Diazo-, *N*-Nitrosoamino- (*H*331), and Triazenopurines (*H*333) . . . 235
      a. Preparation of Diazopurines (*H*331) . . . 235
      b. Reactions of Diazopurines (*H*332) . . . 236
      c. *N*-Nitrosoaminopurines (*H*332) . . . 236
      d. The Triazenopurines (*H*333) . . . 237
   G. Other Reactions of Amino Groups (*H*333) . . . 237
      a. Transformation of Amino into Other Amino Groups (*New*) . . . 238
      b. The Dimroth Rearrangement (*H*313) . . . 239
      c. Condensation Reactions (*New*) . . . 241
      d. Replacement by Hydrogen (*New*) . . . 243
      e. Replacement by Thioxo and Selenoxo Groups (*New*) . . . 243

H. Reactions of *N*-Aminopurines (*New*) . . . 244
I. Oxidation of Adenine (*New*) . . . 245
6. Reactions of Extranuclear Amino Groups (*H*334) . . . 246
7. Other Substituted Aminopurines (*H*334) . . . 247
A. Hydrazinopurines (*H*335) . . . 247
a. Preparation (*H*335) . . . 247
b. Reactions with Nitrous Acid (*H*336) . . . 248
c. Other Reactions (*H*336) . . . 248
B. Hydroxyamino- and Alkoxyaminopurines (*H*337) . . . 250
a. Preparation of Hydroxyaminopurines (*H*337) . . . 250
b. Reactions (*H*338) . . . 250
c. Alkoxyaminopurines—Preparation and Reactions (*New*) . . . 251
C. Azidopurines (*H*338) . . . 252
a. Preparation (*H*339) . . . 252
b. Reactions (*H*339) . . . 252
D. Trimethylpurinylammonium Chlorides and Related Derivatives (*H*340) . . . 253
a. Preparation (*H*340) . . . 253
b. Reactions (*H*340) . . . 254
8. The Nuclear *N*-Alkylated Aminopurines (*H*340) . . . 255
A. Preparation (*H*341) . . . 255
a. By Direct Synthesis (*H*341) . . . 256
b. By Alkylation (*H*342) . . . 256
B. Reactions (*H*348) . . . 266
9. Naturally Occurring and Other Significant Aminopurines (*H*350) . . . 269
A. Adenine (*H*350) . . . 269
a. Preparation and Properties (*H*350) . . . 269
b. Naturally Occurring and Other Notable Adenine Derivatives (*New*) . . . 272
B. Guanine (*H*354) . . . 277
C. Isoguanine (*H*357) . . . 280

The ongoing search for new therapeutic agents having specific antiviral activity has resulted in aminopurines being the most widely examined group of purine derivatives. A majority are compounds having structures based upon adenine or guanine and are derived either by synthesis or from natural sources. New compounds of the latter class continue to be isolated and identified and their potential for medical application investigated. These are discussed in monographs located at the end of the chapter.

1. PREPARATION OF 2-, 6-, AND 8-AMINOPURINES (*H*309)

Chapters II and III should be consulted for an overview of present routes employed. Some notable features, however, are highlighted in the sections following.

A. By the Traube Synthesis (*H*309)

The utility and scope of this much used preparative route have been increased by the introduction of new cyclizing reagents and techniques. Most are directed

to the synthesis of 6- and 8-aminopurines. The ^{13}C-labeling of adenine at C-8 using ^{13}C-formylmorpholine for the ring closure is worthy of mention.[839] Aliphatic amines with phosphorous pentoxide convert 5-acetamido-4-amino-6-oxopyrimidines to 6-alkylamino-8-methylpurines. This procedure entails both cyclization and replacement of a 6-oxo by an amino group.[852] The same conditions with some arylamines give initially 6-amino-9-arylpurines; these isomerize on longer heating to 6-arylaminopurines.[853] A concealed Traube-type closure is present in the transformation of an aminothiadiazolo[3,4-*d*]pyrimidine to a 9-alkyladenine following nickel desulfurization.[945]

Although direct formation of 8-aminopurines occurs on cyclization with cyanogen bromide,[904,1144] the approach is limited to primary amino groups. Both 8-mono- and disubstituted-aminopurines follow from closure of 4-amino-5-nitrosopyrimidines with hot phosphoryl chloride and a range of *N*-alkylformamides[910] or cold formamide acetals.[912] The latter reagents, in conjunction with a reducing agent, also cyclize 4-amino-5-arylazopyrimidines to 8-arylaminopurines.[925,926] The mechanism of a rearrangement of an oxazolo[5,4-*d*]pyrimidine to an 8-aminoguanine must involve some aspect of a Traube closure.[1106]

B. By Cyclization of Imidazoles (*H*309)

Increased activity in the application of imidazole precursors is largely due to the comparatively more favorable reaction conditions required compared with those needed for Traube closures. This is seen in the number of examples of the synthesis of adenosine analogs appearing in the current literature, for which extensive use of 4(5)-amino-5(4)-cyanoimidazoles is made; the substituent required at the 2-position of the purine dictates the ring-closure reagent adopted. Unsubstituted purines arise with triethyl orthoformate and ammonia treatment,[971,987,990,994] and 2-alkyl analogs from the appropriate orthoester[988] or acetimino thioether.[993] An extension of this method employs 5-aminoimidazole-4-carboxamidines as precursors.[971,972,974] The aminocyanoimidazole route is also readily adapted to formation of adenine-1-oxides,[1029] while other cyclizing modes allow the preparation of isoguanine derivatives.[964,995,997] Changing the starting material to 5-amino-4-carbamoylimidazoles enables guanines to be obtained from cyclizations with isothiocyanates,[964] cyanogen bromide,[969] or the more novel carbodiimide-phosgene-thiourea complex.[970] An alternative closure giving 6-substituted aminopurines occurs using an aliphatic or aromatic amine with phosphorus pentoxide.[1020] Further elaboration and examples are found in Chapter III, Sections 1.B, 1.D, and 1.E.

C. From Acylic Precursors (*H*310)

Although little of practical significance has emerged from various one-step syntheses of adenine, they have provided further insight into the possible

prebiotic formation of the purine from simple small molecules. Preparations include heating formamide under pressure with phosphorus pentoxide[1016] or hydrogen cyanide[1015] and *N*-(aminomethylidene)diaminomaleonitrile with formamidine acetate.[1024] Under reducing conditions, phenylazomaleononitrile combined with formamide and ammonia gives a 70% yield of adenine.[1017] Possibly the simplest synthesis (i.e., from formamide and hydrogen cyanide) has, by use of labeled derivatives, shown that adenine formation requires two molecules of formamide and three of hydrogen cyanide.[1015] More detailed treatment of this topic is given in Chapter III, Sections 2.A and 2.B.

D. From Halogenopurines (*H*310)

This continues to be one of, if not the most, widely used method for inserting amino groups (Chapter V, Sections 5.C.a to 5.C.f and 5.D). The most significant advance of late features the formation of trialkylammonium derivatives by interaction with trimethylamine[1142,1147,1150] or other tertiary bases.[1156] These have considerable preparative value because they undergo facile nucleophilic substitution of the quaternary group. The quaternization reaction is limited mainly to 6-halogenopurines, although examples from 2- and 8-halogeno analogs are known. With less reactive halogen compounds, the vigorous conditions required for quaternization induce rearrangement of any trimethylammonio derivative formed to the corresponding dimethylaminopurine.[1109,1150] A novel amination between α,ω-diaminoalkanes and di-(6-chloropurinyl)alkanes gives rise to purinophanes in which two aminopurines are linked by two[1101,1358] or more[1358] alkane chains to form rigid cage structures. The direct conversion of an 8-bromoguanine derivative to the 8-amino analog in aqueous hydrazine (95%) under reflux (48 h) is reported.[1100] More novel is use of the ANRORC rearrangement with potassium amide in liquid ammonia in forming 2-aminopurine from either the 2-chloro or 2-fluoro analogs.[867] Liquid ammonia alone in a closed vessel (45°C, 21 h) is used to replace the halogen by an amino group in several 9-benzyl-6-chloropurines.[1210]

E. From Thioxo- and Alkylthiopurines (*H*310)

Examples of direct amination of thioxo groups are rare and are generally confined to C-6 groups. Formation of 2-fluoro-6-(*N*-methyl)hydroxyaminopurine occurs in this way.[1124] By contrast, methylthio group displacement is still frequently undertaken. Activity of the alkylthio group is increased in 6-methylthiopurines by prior complexation with mercury(II) chloride.[1383] A similar enhancement is also shown using 9-acetyl-6-methylthio derivatives with subsequent hydrolytic removal of the *N*-acetyl group.[1383] More detailed treatment of these reactions is found in Chapter VII, Section 2.B.c. A noteworthy reaction is production of adenine in quantitative yield from treatment of 6-methylthiopurine with liquid ammonia containing potassium amide.[1155] Similar conditions and reagent convert-2-methylthio- to 2-aminopurine[1050] through an ANRORC

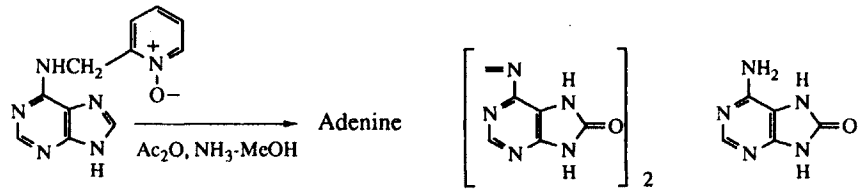
reaction. The route has also been useful for preparing 6-dialkylamino analogs of isoguanines from 6-methylthio-2-oxopurine and dialkylamines.[2019]

F. From Oxo- and Alkoxypurines (*H*311)

Following the introduction of new reagents and procedures, the scope and usefulness of the reaction has widened considerably. The initial treatment with phosphoryl chloride followed by an amine[1098,1109] has been replaced by one-step reactions with phosphoric acid amides.[1234,1307] Similar transformations occur using amines with phosphorus pentoxide in *N,N*-dimethylcyclohexylamine.[1302] Conversion of a 6-oxo to a quaternary 6-pyridinio group is effected with a pyridine and 4-chlorophenylphosphoro dichloridate mixture.[1274,1306] Replacement of oxo groups activated by *O*-silylation is possible with amine hydrochlorides or amines and a Lewis acid.[1304,1305] With some 2-methylthio-6-oxopurines, heating with an excess of piperidine or morpholine is sufficient to displace the oxygen; the reaction also highlights the inert character of the methylthio groups at C-2.[910] Examples relating to these topics are given in Chapter VI, Section 6.G.

G. By Amination of Other Groups (*H*311)

In amination reactions, the methylsulfonyl as a leaving group is an acceptable alternative to either a halogen or methylthio group. Although all three behave similarly toward nucleophiles, the positional replacement order in the latter atoms or groups is 6 > 8 >> 2, while that for the methylsulfonyl group is 8 > 6 >> 2.[785] Reactions of 2-, 6-, and 8- methylsulfonylpurines with ammonia and amines such as aniline,[1079] benzylamine,[1222] piperidine,[785] and others[1222] are described. Using 1-oxido-2-aminomethylpyridine with 6-methylsulfonylpurine, a protected form (**1**) of adenine results, the parent purine being liberated on treatment with acetic anhydide.[1392] Aqueous ammonia converts 6-sulfopurines to the adenine analogs.[1391] The displacement of quaternary ammonio groups by other amines is discussed elsewhere (Section 7.D.b).

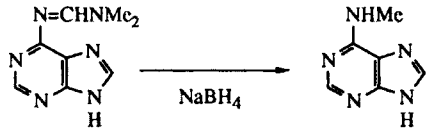


1 **2** **3**

H. By Reduction of Nitrogen-Containing Groups (*H*312)

Catalytic hydrogenation converts 6-hydroxyamino,[1124]- 6-methoxyamino[1124]- (Raney Ni) 6-ethoxyamino- (Raney Ni)[983] and 6-benzyloxyaminopurines[983]

(Pd–carbon), and others[975] to adenine derivatives. Likewise obtained is 9-methyl-6-methylaminopurine from the 6-(*N*-methoxy)methylamino deribative.[1460] Similar treatment of 2-hydroxyamino-6-thioxopurine affords 2-aminopurine through concomitant desulfurization.[1124] Examples of hydrazino groups similarly reduced to 2-,[1864] 6-,[1124] and 8-aminopurines[995] and of formation of an 8-methylamino- from an 8-(α-methylhydrazino)purine[1173] are found. Two molecules of a 6-aminopurine results on reductive fission of a 1,2-(dipurin-6-yl)hydrazide with the same reagent.[1124] The 6,6′-bisazopurine (**2**) is cleaved likewise to 8-oxoadenine (**3**) by tin and hydrochloric acid.[1427] Alkaline sodium dithionite (90°C, 4 h) readily converts 8-(4-bromophenylazo)guanine to 8-aminoguanine.[1461] Hydrazine effectively reduces a 2-hydroxyamino- to a 2-aminopurine.[1124] Examples of 6- or 8-aminopurines derived from the corresponding azido analogs utilize reductions by catalytic hydrogenation[842,1109,1405] or UV irradiation.[1222,1405] Reaction of the 6-dimethylaminomethylideneamino derivative (**4**) with sodium tetrahydroborate is a route to 6-methylaminopurine[1146] (**5**). A palladium catalyst is used in hydrogenation of 6-benzyloxyimino- to 6-aminopurines,[974] while similar treatment of 6-(*N*-nitroso)methylaminopurine eliminates the nitroso group, giving 6-methylaminopurine.[1172]



4 **5**

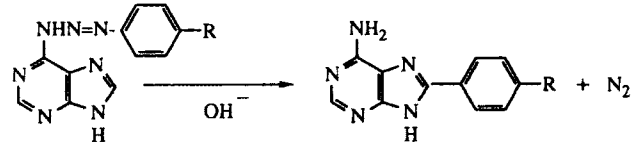
I. By Direct Amination (*H*312)

While *N*-amination is fairly frequently encountered, examples of direct *C*-amination are limited to a few cases. Conversion of purine and the 2- and 8-methyl homologs to the corresponding 6-aminopurines is accomplished by a Chichibabin type reaction with potassium amide in liquid ammonia.[1050] In this particular reaction, amide ion addition at C-6 rather than ring opening of the ANRORC type[1050] takes place. Rearrangement of 3-acetoxyxanthines and -guanines in the presence of pyridine gives rise to 8-pyridinio quaternary derivatives susceptible to facile base hydrolyses to 8-aminopurines.[1116] Similar conversions using 3-methylsulfonyloxypurines[1116] (Chapter XI, Section 3.C) are possible. A corresponding transformation of 7-hydroxyxanthine to 8-pyridinioxanthine is known.[920] Although hydroxylamine-*O*-sulfonic acid is widely used to *N*-aminate purines (Section 2) when reacted with guanosine an 8-aminopurine is obtained.[1314,1407]

J. By Other Routes (*H*313)

Conversions to aminopurines through reduction procedures (see Section 1.H) in some cases can be achieved by alternative means. Exemplifying this are hydrol-

yses in aqueous ammonia of 6-dimethylaminomethylideneamino derivatives to the 6-amino analogs[912] and formation of 6-iminopurines by the action of hot pyridine on 6-benzyloxyiminopurines.[974] Isolation of 8-aminotheophylline is claimed on thermolysis of 8-azidocaffeine; this result differs from that found with reduction reactions in that the methyl group at N-7 is also lost.[1405] More singular examples are use of strong acid conditions and a chloride ion catalyst with a 6-diazopurine[1239] and alkaline decomposition of 6-(3-phenyl-2-triazen-1-yl)purines (**6**) with an accompanying rearrangement to 8-phenyladenine derivatives[858] (**7**). Removal of the amino moiety from either 6- or 8-(1-methylhydrazino) derivatives provides routes to 6-[1172] and 8-methylaminopurines[1406] by respective oxidation with iron(III) chloride and hydrolysis with nitrous acid. A complex reaction giving 8-dimethylaminotheophylline entails heating (230°C, 6 h) 8-nitrotheophylline with dimethylformamide containing either phosphoryl chloride or *p*-toluene sulfonyl chloride.[911] A mechanism presumes formation of an 8-chloropurine intermediate and subsequent dimethylamination[911] through participation by the amide.



6 **7**

K. Secondary and Tertiary Amines Derived from Primary Aminopurines (Including the Dimroth Rearrangement) (*H*313)

In light of current knowledge, the general heading above is no longer appropriate and relevant topics are now treated under the appropriate subdivisions in Section 5 of this chapter, which deals with reactions of the amino group.

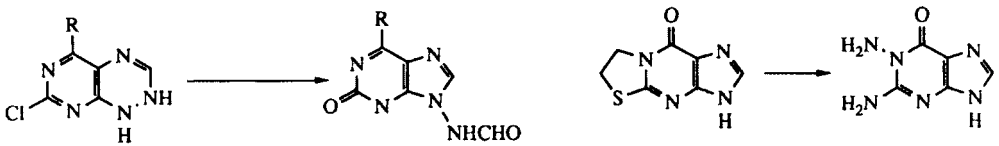
2. PREPARATION OF *N*-AMINOPURINES (*H*316)

Development of direct *N*-amination was achieved by the introduction of a number of reagents formed by combining hydroxylamine and a strong electron-withdrawing group. The early application to nucleoside work suggested a parallel between this reaction and *N*-alkylation, but subsequent results showed this premise to be invalid. In the majority of examples, the favored site is at N-1, irrespective of any substitution at other ring nitrogens. Examples of amination at N-9 are, however, claimed, using hydroxylamine-*O*-sulfonic acid with purine, adenine, and the 6-benzylamino and 6-methylthio derivatives.[1314] Adenosine with this reagent affords the 1-amino analog, but an improved yield is obtained using 2,4-dinitrophenoxyamine in dimethylformamide (37°C, 24 h).[1408] Reaction with

the more powerful hydroxylamine-*O*-mesitylenesulfonic acid* leads to the 1-amino derivatives of purine[1051] and of the 2-, 6-, and 9-methyl homologs of 8-phenylpurine.[1051] Likewise substituted are 2-aminopurine[1051,1409] and adenine[1409] together with the 7- and 9-substituted[1409] derivatives. Further exemplifying the reaction range are corresponding aminations of 2- and 8-methylthiopurines.[1051] Steric effects appear to explain failure of 6,8-bis-*tert*-butylpurine to react.[1051] The majority of products are isolated as mesitylene sulfonate salts. Theophylline and theobromine form amino analogs at N-9 and N-1, respectively, using diphenylphosphinylhydroxylamine [$Ph_2P(O)ONH_2$] at ambient temperature in aprotic media.[1330]

Examples of syntheses of 1-aminohypoxanthines by the established ring closure of 4-aminoimidazole-5-carboxylic acid hydrazides with orthoesters and an acid catalyst include the parent member,[961] and 2-methyl homolog,[961] and various 2-alkyl-9-substituted purines including† 1-amino-9-benzylhypoxanthine.[1007]

Cyclization of 5-amino-4-hydrazinopyrimidines may give either 9-aminopurines or isomeric dihydropyrimido[5,4-*e*]triazines. Conversion of the latter to the former occurs in hot formic acid with both **8** (R = H) and **8** (R = Me), with concomitant hydrolyses of the halogen giving the 9-formamidopurines (**9**, R = H and Me).[952] On treatment of 5-amino-7-hydrazinothiazolo[5,4-*d*]pyrimidine with aqueous alkali at 20°C, conversion to 9-aminothioguanine occurs. This approach is potentially useful for synthesis of other 9-aminopurines.[1010] A route to 1-aminopurines is by ring closure of 6-aminoimidazole-4-carboxylic acid hydrazides.[961] The product from interaction of hydrazine (130°C, 8 h) solution with 6,7,8,9-tetrahydro-9-oxothiazolo[3,2-*a*]purine (**10**) is 1-aminoguanine (**11**)[1229]. This is seen as formed by attack on the sulfur atom by two molecules of hydrazine with ring fission and subsequent rearrangement before final ring closure to the product.[1229]



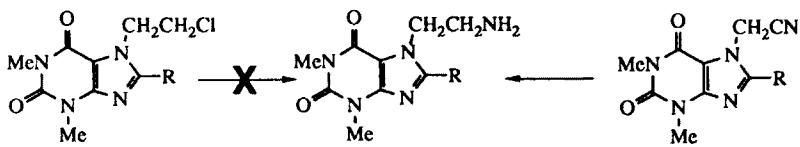
3. PREPARATION OF EXTRANUCLEAR AMINOPURINES (*H*317)

Established procedures or adaptations are used for most current examples. Earlier findings (*H*319) that adenine initially forms a 9-aminomethyl adduct in a

*Caution should be exercised in the use of this reagent. Solutions should be freshly prepared since explosions have occurred with aged samples of the reagent.[1051,1330]

†This purine appears to have been first described[1410] a decade earlier, but incorrectly designated as an imidazotriazepine.

Mannich reaction with one equivalent of amine and formaldehyde have been substantiated.[1687] Further addition occurs at the 6-amino group if an excess (>3 mol. equiv.) of amine is present. Only bis derivatives are isolated using strongly basic amines such as diethylamine and piperidine, but with morpholine, methylpiperazine, or other weaker bases, both mono and bis compounds are possible. Guanine likewise forms a disubstituted adduct involving N-9 and the 2-amino group.[1687] Reexamination of the Mannich reaction with 6-mercaptopurine indicates that N-7 (as originally proposed), rather than N-9, is the site of aminomethylation, although in this case anhydrous paraformaldehyde in ether replaced the aqueous formaldehyde previously employed.[1380] However, both studies agree that 9-aminomethylpurines are formed with 6-alkylthiopurines.[1379,1380] Exemplifying the established route of amination of halogenoalkylpurines are the 2-aminomethylhypoxanthines from 2-chloromethyl analogs[909,910] (Chapter V, Section 6.A). Failure or difficulty in aminating 8-alkyl-7-(2-chloroethyl)theophyllines (**12**, R = Et, Pr, Bu) because of the steric effect of C-8 alkyl groups is overcome by using pressure hydrogenation of the 7-cyanomethyltheophyllines (**13**) in ethanol with a nickel–cobalt catalyst.[938] The significance of the size of the alkyl group is shown by the fact that direct substitution by amine is possible with the 8-methylpurine (**12**, R = Me).[938] An interesting application is to the synthesis of the Coenzyme I model compound (**14**), involving quaternization between 9-(2-chloroethyl)adenine and nicotinamide.[1433] Routes using reduction include the catalytic hydrogenation of 1-(2-azidoethyl)hypoxanthine to the 1-(2-aminoethyl) analog.[1133] Adenine alkylated with *N*-(3-bromopropyl)phthalimide, followed by hydrazine treatment to remove the protecting group, affords the 9-(3-aminopropyl) derivative.[1101] The same procedure with theophylline is adapted to give the 7-(2-aminoethyl)- and 7-(4-aminobutyl)purines.[1198] Although direct alkylation with halogenoalkylamines is used in the case of thioxopurines, *S*-rather than *N*-alkylation predominates. Such reactions are reported with 6- and 8-thioxopurines, but not with 2-thioxopurines.[857] Potassium cyanide and ammonia used in Strecker syntheses convert various 6-substituted 9-formylmethylpurines to the 9-(2-amino-2-carboxyethyl) derivatives,[1210,1382] and corresponding 9-(3-amino-3-carboxypropyl) homologs arise from the 9-formylethylpurines.[1411] Related derivatives of this type with amino acid moieties at N-9 result from alkylation of 6-substituted purines by *C*-acetoxy-*N*-acetylalanine in cold dimethylformamide (10°C, 0.5 h) containing sodium hydride, the acetoxy functioning as a leaving group.[1218] Some 7-aminoalkyl isomer in minor amounts may also be found (see Chapter IX, Section 8.A). Radicals derived from irradiation or peroxide treatment of alkylamines generate mixtures of 8-(α-aminoalkyl)- and 8-alkylpurines

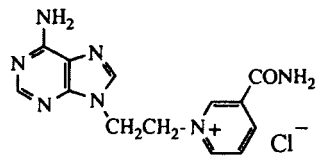


12 **13**

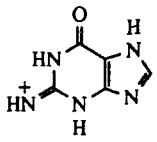
with adenine,[1412] caffeine,[1412] and others.[1415] The amount of the former product decreases as reaction time increases.[1412,1413] In contrast, total loss of the amino function and formation of only 6-alkylpurines occurs using 6-unsubstituted purines.[1414] Catalytic hydrogenation (Pd–carbon) of 6-cyanomethylenepurines affords geometrical isomers of 6-enaminopurines in which the minor (*E*) form (14%) shows hydrogen bonding between the exocyclic amino group and N-1 (^{13}C and ^{1}H NMR).[1068]

4. PROPERTIES OF AMINOPURINES (*H*320)

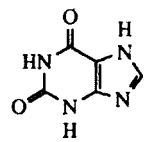
Interest in the physical properties is now largely confined to derivatives of adenine and guanine. The tautomeric form of the amino group in these compounds is confirmed by SCFMO calculations[1416] which indicate that the imino form, if present, makes only a minor contribution.[1417] To explain the resemblance of the cationic UV spectrum of 2-aminopurine to that of the unionized 2-oxopurine analog, a guanidinium structure for the former is assumed.[1424] A comparable form for the guanine cation (**15**) likewise accounts for its spectral similarity with that of neutral xanthine (**16**). Spectral correlations of this type are lost if protonation is directed to the imidazole ring. In the same way, 6-aminopurine and hypoxanthine spectra are not comparable since the former purine is lacking a guanidinium moiety.[1424]



14



15

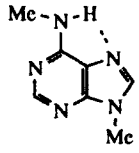


16

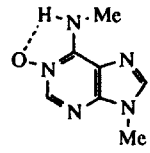
Hydrogen bonding is often of great significance, a nitrogen group or atom involved is identifiable[1418] by the downfield shift of the associated protons in high-resolution ^{1}H NMR. Owing to restricted rotation, one effect of such bonding is the adoption of preferred conformations of substituted-amino groups.[1419,1420]

Studies of this phenomenon have been carried out with 360-MHz ^{1}H NMR with 3-, 7-, and 9-alkylated derivatives of 6-alkylaminopurines among which are the 3-benzyl-6-methylamino-, 3-benzyl-6-isopropylamino-, 9-benzyl-6-methylamino-, and 9-benzyl-6-isopropylaminopurines. Factors that influence the rotational ability of a 6-amino moiety include temperature, solvent type, and the ionic state of the purine. At low temperatures, the presence of two rotamers is indicated by the nonequivalence of the proton signals of the amino substituent. On raising the temperature, the onset of rotational bahvior is indicated by coalescing of the signals to a single peak. Solvent-effect studies have demonstrated the existence of two rotamers in $CDCl_3$ (conformer ratio, 10:90), but only one form in dimethyl sulfoxide.[1894] A specific example of restricted rotation is noted with 9-methyl-6-methylaminopurine at low temperature (–20°C) in CD_3OD.[1895] In many cases,

identification of *syn* and *anti* rotamers in a mixture is not clear cut, but if conditions for hydrogen bonding are present, the spectral shift changes produced often enable the particular rotamer to be identified. With adenines having ester groups at N-7 or N-9, the shift changes in the 2H and 8H signals due to carbonyl-to-ring nitrogen bonding allow rotamer assignments to be made.[1425] The *syn* rotamer (**17**) of 9-methyl-6-methylaminopurines results from bonding between the 6-NH moiety and the N-7 position,[1419] but the *anti* form (**18**) of the 1-oxidopurine is attributed to the strong oxygen to 6-NH group bonding.[1419] Cationic forms of these *N*-alkylated adenines are usually protonated at N-7, inducing bond formation with the 6-NH group. A good example is the nonequivalence shown in the spectrum of 3-benzyladenine hydrochloride, but that of the free base shows only a broad singlet for the amino protons.[1896] On a quantitative basis, the protonation effect is demonstrated by the 10-fold increase in the *syn* conformer of 3-benzyl-6-methylaminopurine in DMSO obtained following acidification.[1894] Steric constraints imposed by the nature of the substituent of the 6-alkylamino group may also influence the predominant conformer present.[1894]

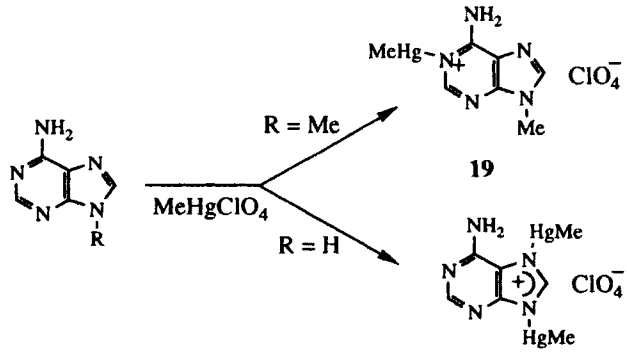


17



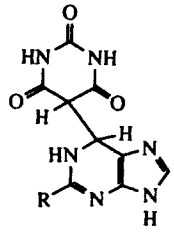
18

Interpurine bonding between pairs of 9-cyclohexyladenines in the presence of iodine produces charge-transfer complexes. Stabilization is established through electron abstraction from N-1 by iodine.[1421,1422] Metal complexation through an amino group is not usual unless the latter has an acidic proton. The adduct (**19**) forms in alkaline solution from 9-methyladenine and methylmercury perchlorate, but with adenine itself the more basic amino group is unreactive and the imidazole nitrogens are the binding sites.[1423] (**20**) Adducts of the type (**21**) form between 2-aminopurines and barbituric acid, or the 2-thioxo analog, through addition across the 1,6-double bond.[1048]



19

20



21

5. REACTIONS OF AMINOPURINES (*H*321)

The data which has accumulated on the Dimroth rearrangement is now more appropriately located here with other reactions of the amino group. Also included as a separate topic are interconversions of primary, secondary, and tertiary amines. In the parent volume the subjects of these two new sections were grouped together in Section 1.K (*H*313) under the heading of preparative procedures.

A. Replacement of Amino by Oxo Groups (*H*321)

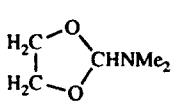
Hydrolyses with nitrous acid, hydrochloric acid, or sodium hydroxide are still the general routes applied. Newer reagents worthy of note are the use of gaseous nitrogen trioxide in aqueous acetic acid[1240] and liquid nitrosyl chloride in dimethylformamide[1241] for forming hypoxanthine derivatives. See Chapter VI, Section 1.D.a. The use of aqueous hydrogen sulfide to replace the amino group in an adenosine derivative by sulfur can be viewed as an example of thiohydrolysis[1403] (see Chapter VII, Section 1.A.i).

B. Replacement of Amino Groups by Halogens (*H*322)

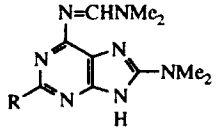
Use of halogen radicals has significantly advanced displacement reactions of this type, previous procedures having very limited applicability. Radicals, usually generated from halogenoalkanes in the presence of *m*-chloroperbenzoic acid, *tert*-butyl nitrite, or pentyl nitrite, give rise to chloro, bromo, iodo, and fluoro derivatives. Both 2- and 6- halogenopurines are obtained in this way, except in the case of fluoropurines, which are limited to the preparation of 2-fluoro- from 2-aminopurines. A survey of the reagents and reactions is given in Chapter V, Sections 1.D (chloro), 1.E (bromo), 1.F (iodo), and 1.G.c (fluoro). A route utilized specifically for fluoro derivatives and providing both the 2- and 6-halogenopurines involves displacement of quaternary amino groups by fluoride ions (Chapter V, Section 1.G.b). The inactivity of trimethylammonio groups at C-8 toward displacement precludes this approach for 8-fluoropurine formation.

C. Formation of Azamethines (Schiff Bases) and Related Derivatives (*H*322)

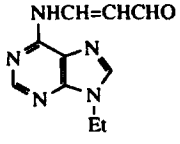
Azamethines derived from adenine and guanine derivatives continue to appear in the literature, prepared by condensation with dimethylformamide dimethyl- or diethylacetal.[1146,1428–1430,1695] The same dialkylaminomethylideneamino derivatives result if 2-dimethylamino-1,3-dioxolane (**22**) replaces dimethylformamide acetals.[1268] Corresponding ethylidene homologs of adenine form with dimethylacetamide dimethylacetal.[1428] A Traube ring closure of 2-substituted-4,6-diamino-5-nitrosopyrimidines with dimethylformamide acetal gives a mixture of the 6-amino-8-dimethylaminopurines and the azamethine analogs (**23**), the latter separating on addition of ether[912] (see Chapter II, Section 2.A). Malondialdehyde and 9-ethyladenine react at pH 4.2 (37°C), forming the prototrope (**24**) together with a 3:1 aldehyde–purine adduct (**25**) containing a methylidenecyclopropane moiety.[1431] Adenosine affords a similar adduct mixture.[1431] Formation of azamethines, without isolation, is involved converting 6-amino- to 6-alkylaminopurines[1432]—the reaction is effected by introduction of a reducing agent with the aldehyde. This conversion is discussed more fully in (Section G.a). Although stable benzylidene (anils) derivatives of aminopurines are not evident, they are possibly transient intermediates in the reaction between adenosine, *p*-nitrobenzaldehyde, and triethyl orthoformate under acid conditions (25°C, 24 h) which gives the α-ethoxy-*p*-nitrobenzylamino adduct (**26**), with guanosine giving the corresponding-2-substituted amino analog. In the absence of acid, no amino group interaction occurs.[1680] An example of an *N*-aminobenzylidene derivative (**27**) results from *N*-amination of sodium theophyllinate with *O*-diphenylphosphinylhydroxylamine in *N*-methylpyrrolidone[1330] (20°C, 6 h); acid hydrolysis released the 7-amino analog. Likewise formed from the 1-ethoxymethylideneamino derivative of hypoxanthine is the 1-amino analog.[961] Interaction of ketones with 9-amino-6-methylthiopurine leads to corresponding 9-azamethine analogs, which are readily reduced to 9-alkylamino-6-methylthiopurines.[1434]



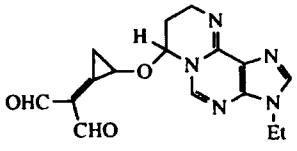
22



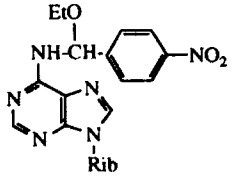
23



24

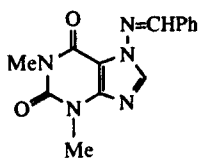


25

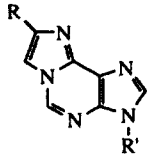


26

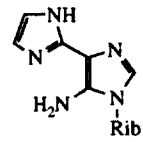
Introduction of a second functional group or atom into aldehydes and ketones widens the scope of the azamethine reaction. The products from interaction of adenines with α-halogenoaldehydes are tricyclic purines formed through condensation of the carbonyl group with the 6-amino group and concomitant intramolecular alkylation of the adjacent ring nitrogen by the alkyl halide moiety. The fluorescence exhibited by solutions of these compounds is the basis of a test for the presence of adenines in the breakdown products of nucleic acids.[1478,1479] Reaction of 9-methyladenine[1480] or adenosine[1481,1482] with bromo- or chloroacetaldehyde gives the respective 3-methyl- (**28**, R = H, R′ = Me) and 3-ribosylimidazo[2,1-*i*]purine (**28**, R = H, R′ = ribosyl). Loss of fluorescence following alkali treatment is the result of ring opening to the imidazole[1505] (**29**). The 7-ethylimidazopurine (**28**, R = Et, R′ = ribosyl) is the product from cyclization with 2-chloro-*n*-butyraldehyde.[1480] With bromomalondialdehyde only one carbonyl group reacts and the 7-formyl derivatives (**28**, R = CHO, R′ = Et or ribosyl) are obtained.[1483] These structures are not comparable with those of the adducts obtained with guanines noted below. Corresponding reactions of chloroacetaldehyde with 6-methylaminopurines initially produce dihydro adducts (**30**) which undergo facile dehydration to the aromatized forms (**31**, R = H or ribosyl).[1432,1484] The latter show only weak fluorescence in acid solution so that any fluorescence due to adenosine or other 6-aminopurines present in a mixture with them is readily detected.[1432]



27

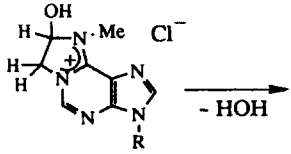


28

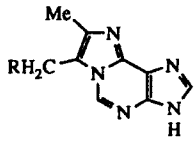


29

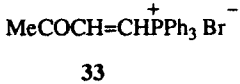
The mechanism of reagent addition, investigated by crystallographic analysis[1485] and field desorption mass spectrometry,[1484] involves carbonyl group interaction with the amino group with concomitant alkylation at N-1 by the alkyl halide moiety. Dehydration of the relatively stable carbinolamine intermediate (**30**) affords the essentially planar imidazo[2,1-*i*]purine (**31**). Other results obtained support this mechanism.[1486] A similar type is the adduct **32** (R = PPh_3) from adenine and the β-acylvinyltriphenylphosphonium bromide (**33**), which is converted in 70% yield in alkali to 7,8-dimethylimidazo[2,1,-*i*]purine[1504] (**32**,



30 **31**



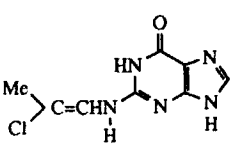
32



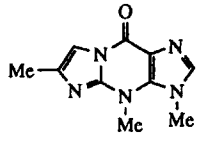
33

R = H). Related Schiff bases exhibiting fluorogenic properties are also reported from reactions with α-hydroxyaldehydes[1487] and malondialdehyde.[1488]

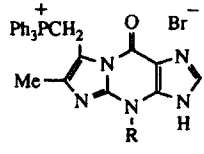
Guanines with reagents of the same type form corresponding tricyclic derivatives having an etheno bridge linking the amino group and either N-1 or N-3 on the ring. Usually, the product from guanine with 2-chloropropaldehyde is identified by ^{1}H NMR as the enamine form (**34**) of the Schiff base; no tricyclic compound appears to be present.[1489] Fluorescent derivatives having the latter structure are obtained when 3,7- and 3,9-dimethylguanine and bromoacetone react in dimethyl sulfoxide containing potassium carbonate, forming the respective 1,4,6- and 3,4,6-trimethyl-9-oxo-8,9-dihydroimidazo[1,2-*a*]purine (**35**).[964,969] Related compounds are derived from guanines and acetylvinyltriphenylphosphonium bromide (**33**). In ethanol (78°C, 7 days), a 2:1 mixture of 6-methyl-9-oxo-dihydroimidazo[1,2-*a*]purine-7-ylmethyltriphenyl phosphonium bromide (**36**, R = H) and the isomeric imidazo[2,1-*b*]purine (**37**, R = H) is obtained using guanine itself. Cyclization of 1-methylguanine gives only the expected 6,8-dimethylimidazo[2,1-*b*]purine (**37**, R = Me), while the 4,6-dimethyl analog (**36**, R = Me) is the product from 3-methylguanine.[1490] Compounds with reactive methylene groups readily displace the triphenylphosphonium moiety, as illustrated by the formation of **38** from sodio malonic ester and[1490] **36** (R = H). Reduced forms of the tricyclic system are found in adducts such as (**39**) from reaction with glyoxals. Examples from guanine and guanosine utilize glyoxal[1008,1444,1491] (**39**, R = H) and pyruvaldehyde [1444] (**39**, R = Me), but no reaction is reported with phenylglyoxal.[1444] Conformation of the linear cyclic arrangement, originally tentatively proposed,[1492] was obtained from an unambiguous synthesis.[1008] Dehydration of the dihydroxy adducts to the imidazo[1,2-*a*]purines (**40**) is effected with hydriodic acid.[1008] Homologous adducts obtained with an excess of malondialdehydes in acid solution (*M*-HCl, 40°C, 24 h) give rise to the aromatic forms (**41**, R = Me, Ph)[1488,1493] directly. Other examples of 7-substituted-10-oxo-9,10-dihydropyrimido[1,2-*a*]purines are described.[1494] The presence of a 7-substituent rather than one at the 6-position was established by synthesis of the 7-methylpyrimido[1,2-*a*]purine (**41**, R = Me).[1495] The fact that both imidazo- and pyrimidinopurines



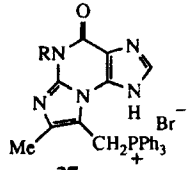
34



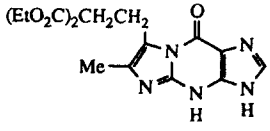
35



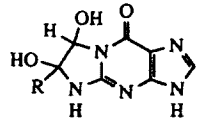
36



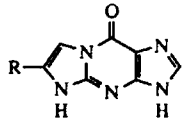
37



38



39



40

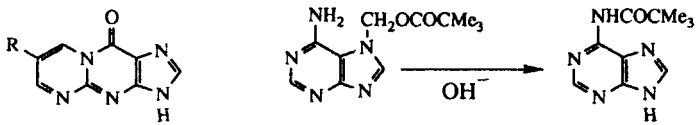
show fluorescence supports the view that this property is associated with joining of amino groups in adenine and guanine with adjacent ring nitrogens via etheno or allylideno linkages.[1493]

D. Acylation of Aminopurines (*H*323)

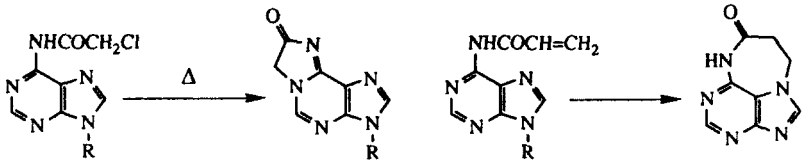
Previously, acylation reactions were used mainly for characterization of amino groups; it is now appreciated that their presence can modify significantly the reaction pathways of the parent aminopurines. This is shown in the altered alkylation sequences in adenines (Section 8.A.b.) and by further examples of rearrangements of *N*-alkyl groups in *N*-acylamino derivatives, which are not features of the parent purines (Section 5.D.f).

a. Acetylation (H323)

Acetic anhydride remains the reagent of choice for simple acetylations. Improved yields and a purer product are claimed in the presence of pyridine,[1152] as shown in a repeat acylation of both groups of 2,6-diaminopurine.[1435] A novel transformation of adenine to 6-acetamidopurine employs vinyl acetate in dimethyl sulfoxide (60°C, 24 h).[1436] Homologous acetylations with pivaloyl chloride in aprotic media (DMF or pyridine) form acylamides used as protected forms of aminopurines. Typical examples occur with 7- and 9-benzyladenines[1437] and adenosine.[1438] An alkali-induced intramolecular rearrangement of the 7-pivaloyloxymethyl derivative (**42**) is a novel route to the parent 6-pivaloylaminopurine[1437] (**43**). On prolonged heating, the expected product (**44**, R= CH_2Ph) from interaction of chloroacetic anhydride and a 9-substituted adenine in toluene (110°C, 1 h) undergoes endoalkylation at N-1 to the imidazo[2, 1-*i*]purine (**45**, R = CH_2Ph), having mesoionic characteristics in the NMR spectrum.[1439] The 9-methyl analog (**44**, R = Me) appears to react likewise, but the product awaits definite structural identification.[1440] In warm dimethyl sulfoxide (60°C, 24 h) adenine and acrylic anhydride form the tricyclic derivative (**47**), arising presumably from an intramolecular Michael addition at N-7 of the initial product (**46**).[1436] Alkylation at N-3 rather than acylation occurs if the reaction is carried out in aqueous alkali, giving 3-(2-carboxyethyl)adenine. Although 9-(2-cyanoethyl)adenine with either acryloyl chloride or anhydride would be expected to produce a 6-acylamino derivative, in practice the 1-(2-carboxyethyl)6-iminopurine (**48**) is isolated. As a first

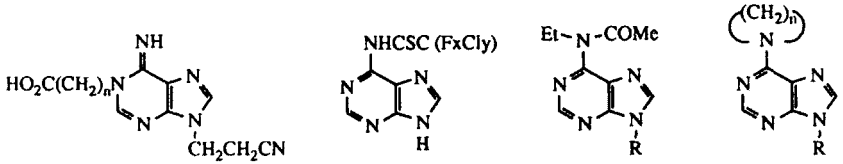


41 **42** **43**



44 **45** **46** **47**

step, formation by the initial 6-acylaminopurine of a cyclized product involving N-1 is envisaged, with ensuing hydrolytic cleavage to **48** during the workup.[1436] Examples of thioacetylation are rare, but compounds of the type (**49**) arise from treatment of adenine with trifluoro-, chlorodifluoro-, and dichlorofluoro-, but not trichloro-thioacetylchloride, in pyridine.[1441] Selective oxidation of one ethyl group of a 6-diethylaminopurine provides the *N*-ethylated acetamido analog (**50**). Temperature and reaction time are important—oxidants are either acidified potassium permanganate[1442] or ruthenium tetroxide,[1443] the latter affording the higher yields. Some cyclic alkylamino groups respond likewise—both the 6-pyrrolidino- (**51**, $n = 4$) and 6-piperidinopurines (**51**, $n = 5$) are converted to the respective lactam forms (**52**, $n = 3$)[1442,1443] and (**52**, $n = 4$).[1443] Unexpectedly, following the attempted preparation of (**52**, $n = 4$) by permanganate oxidation, a hydrolytic fission of the oxidized product occurs, forming a 6-(4-carboxy-*n*-butylamino)purine.[1442] The inductive effect of the acyl group, coupled with the electronegativity of the pyrimidine ring, are factors in stabilizing the second *N*-alkyl group in the oxidations of simple dialkylaminopurines discussed above.[1443] An improved direct acetylation of the 2-amino group in guanines is reported. A two-stage alternative route by the same workers,[1444] involving initial formation of the pyruvaldehyde adduct followed by sodium metaperiodate oxidation, gives only a low yield (10%) of the 2-acetamido purine.[1444] In hot trifluoroacetic anhydride (reflux, 6 h), guanine yields (68%) of the moisture-sensitive 2-trifluoroacetamido analog.[1444] An example of acetylation of an *N*-aminopurine is the interaction of acetic anhydride with 9-amino-6-methylthiopurine.[1434]

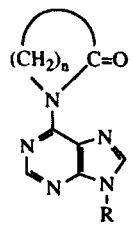


48 **49** **50** **51**

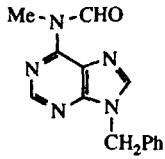
b. Formylation (H 325)

Some ring-closing reagents of the one-carbon type may give a formylated product. Exemplifying this are cyclizations of l-substituted-5-amino-4-cyanoimidazoles with formic acetic anhydride, forming 6-formamido-9-substituted purines such as the 9-cyclohexyl and 9-(2,3-dihydroxypropyl) derivatives.[971]

The same reagent directly formylates adenine,[971] the 9-(2-fluorobenzyl) analog,[1146] and 9-benzyl-6-methylaminopurine to the 6-(*N*-methyl)formamido derivatives. The latter (**53**) is formed (20°C, 16 h) in a medium of 4-dimethylaminopiperidine in dichloromethane.[862] Selective oxidations convert 6-dimethylamino-9-benzyl and acetylated-9-ribosyl derivatives to the 6-(*N*-methyl)formamido analogs using either acidified potassium permanganate[1146,1442] or ruthenium tetroxide[1443] as oxidant. The adduct (**39**, R = H) obtained from guanine and glyoxal is oxidized with sodium metaperiodate (20°C, 18 h) to the 2-formamidopurine in high yield[1444] (86%). Preparation of formylated 9-aminopurines by formic acid rearrangement of pyrimido[5,4-*e*]triazines[952] is noted in Section 2.



52



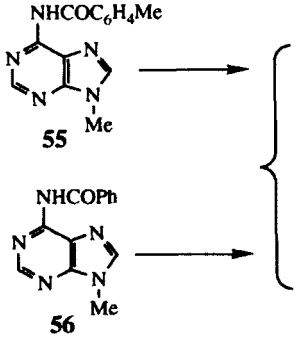
53



54

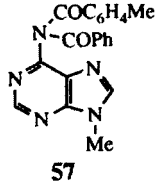
c. Benzoylation and Other Acylations (H325)

Following acid chloride treatment of 2,4,6-triamino-5-nitrosopyrimidine and reduction (Zn, $MeCO_2H$) of the nitroso group of the resulting 4,6-diacylaminopyrimidine, a spontaneous cyclodehydration ensues, forming 6-acylaminopurines of the type (**54**, R = 8-adamantyl or 8-adamantanemethyl).[908] The structure of the diaroylated derivatives of 9-substituted adenines is found to be a 6-diaroylaminopurine, rather than the 1-aroyl-6-aroylamino isomer, since the same product (**57**) is obtained either from reaction of 4-methylbenzoyl chloride with 6-benzamido-9-methylpurine (**55**) or from 9-methyl-6-(4-methylbenzoy-

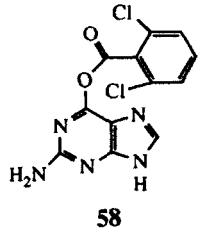


55

56



57



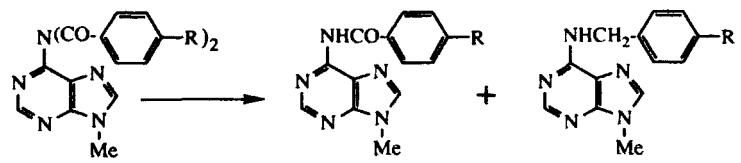
58

lamino)purine (**56**) and benzoyl chloride.[1445] Adenosine triacetate undergoes the same reactions with these reagents.[1446]

Fusion of guanine with benzoic anhydride (130°C, 16 h) improves the yield of the 2-benzamidopurine (33%). Analogous derivatives of guanosine triacetate arise from reactions with benzoyl and anisoyl chlorides,[1301] An unexpected result is formation of the *O*-aroylated derivative (**58**) when 2,6-dichlorobenzoyl chloride is used[1301]—no amino group involvement is found. The poor yield (2%) of a 6-(*N*-benzyl)benzamidopurine obtained from oxidation (RuO_4) of the 6-dibenzylamino precursor[1443] is not unexpected in view of a known case of oxidation of phenyl groups by the same reagent.[1447] Acylation-type reactions with alkyl and aryl chloroformates and carbobenzoxy chloride, forming *N*-ethoxycarbonyl derivatives, are covered in Chapter IX, Section 8.A.

d. Reduction of Acylaminopurines (H327)

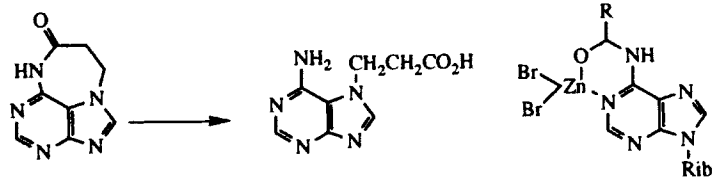
This approach provides a useful route for conversion of amino to monoalkyl- and arylaminopurines. The reducing agent is usually lithium aluminium hydride in tetrahydrofuran, but other solvents including pyridine and ether[1125] are sometimes employed. Illustrating the scope of the reaction are reductions of the 2-formamido, 2-acetamido, 2-trifluoroacetamido, and 2-benzamido analogs of guanine to the corresponding 2-methylamino, 2-ethylamino, 2-(2,2,2-trifluoroethyl)amino, and 2-benzylamino derivatives.[1444] Yields are variable—the 2-formamidopurine giving a mixture of the 2-methylamino-6-oxopurine (12%) and guanine (76%). By contrast, an 86% yield of the 2-ethylaminopurine is obtained from the 2-acetamido precursor.[1444] The foregoing reactions give rise to known 2-alkylamino derivatives, further demonstrating that the main acylation site in guanine is the 2-amino group. An example of 6-formamido group reduction is formation of 9-(2 fluorobenzyl)-6-methylaminopurine.[1146] The isolation of 6-ethylaminopurine following reaction of 9-acetyl-6-acetamidopurine involves concomitant removal of the acetyl group at N-9.[837] Following reduction of the 6-*N*,*N*-dibenzoylaminopurine (**59**, R = H) in tetrahydrofuran (20°C, 6 days), the product is a near equal mixture of the monobenzoylated derivative (**60**, R = H) and its reduced form (**61**, R= H).[1445] Under more rigorous conditions (reflux), the sole product from the homolog (**59**, R = Me) is the amino derivative (**61**, R = Me) from monodearoylation and reduction.[1445] Conversion of alkoxycarbonylamino- to aminopurines by reduction is noted elsewhere (Chapter IX, Section 9.A.a).



59 **60** **61**

e. Hydrolyses of Acylaminopurines (H327)

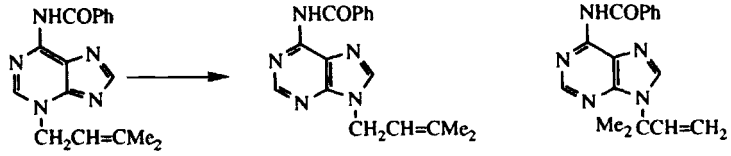
Hot aqueous ammonia is used for 2-formamidopurines,[1209] while sodium hydroxide treatment is effective with 6-formamido-[1146] and 6-benzamidopurines[1111] and for converting the cyclic derivative (**62**) to a 7-alkyladenine[1436] (**63**). Acetyl groups are removed from 2-amino groups with ammonia solution[1262] or methanolic sodium methoxide[1237] when anhydrous conditions are needed. This treatment is also appropriate for 6-acetamido-,[1237] 6-benzamido-,[1426]-and 6-pivaloylaminopurines.[1438] Nonaqueous conditions are also available using methanolic ammonia, which deacetylates[1442,1443] and debenzylates[1443,1448] 6-amino and 6-alkylamino derivatives. An unusual combination of 1,2-diaminoethane and phenol reacts (40°C, 2 h) with the 9-riboside of 6-benzamidopurine to form adenosine.[1449] The 2-benzamido derivative of guanosine reacts likewise, but more slowly.[1449] Zinc bromide in methanol is a new reagent which converts the ribosides of 6-acetamido- and 6-benzamidopurines to adenosine, deacetylation (20°C, 6 h) occurring over 100 times faster than debenzoylation.[1450] The proposed mechanism, involving attack on a bidentate chelate (**64**, R = Me or Ph) by methanol, is logical, since no reaction occurs if this alcohol is omitted[1450] and substitution of methanol by other alcohols gives slower reaction times.[1450] An example of acid treatment is the use of hydrogen chloride in ethanol to hydrolyze 2-amino-6-(8-adamantoylamino)purines to the 2,6-diamino analogs.[908]



62 **63** **64**

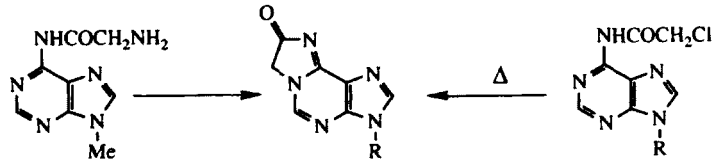
f. Rearrangement of Acylaminopurines (H327)

Continuing work on *N*-alkyl group thermal rearrangements in 6-benzamidopurines in the presence of bromide ion shows that comparable N-3 to N-9 transformations are a characteristic feature of 6-acetamido analogs also. Migrations from N-3 are found with benzyl, allyl, and 3-methylbut-2-enyl groups[811] and glycosyl moieties.[1451] The expected 9-(3-methylbut-2-enyl) derivative (**66**) results from heating (100°C, 40 h) the hydrobromide of the 3-alkenyl isomer (**65**) in dimethylformamide, but using mercury(II) bromide as ion source, a mixture containing a minor amount (3%) of **66** with the 9-(1,1-dimethylprop-2-enyl) purine (**67**) as major component (40%) is obtained. Changing to mercury(II) cyanide (140°C, 26 h) gives only the prototropic derivative (**67**) as product. Studies using ^{14}C-8 labeled purines show that while **66** results from an intermolecular reaction, the isomeric **67** is intramolecularly derived.[811] Suitable migration



65 **66** **67**

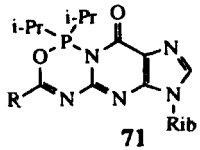
mechanisms have been formulated.[1451] Ammonia is lost on heating an aqueous solution of the 6-glycylamino-9-methylpurine (**68**) and cyclization to 3-methyl-3*H*-imidazo[2,1-*i*]purin-8-one (**69**, R = Me) follows. Structural confirmation of the product,is obtained from x-ray crystal analysis.[1462] The 3-benzyl homolog (**69**, R= CH_2Ph), formed on heating the 6-chloroacetamidopurine (**70**) in dimethylformamide, is the result of intramolecular alkylation at N-1. This reaction contrasts with that of conventional alkylation of 6-acylamino-9-substituted purines, which gives 7-alkylpurines.[1439] Intermolecular isomerization with the 2-acetamido derivative of 3-benzylguanine in dimethylacetamide (110°C, 24 h) gives a mixture of the 7- and 9-benzylguanines. Further heating of either product affords the same two isomers, of which the more thermodynamically stable[826] 9-isomer predominates.



68 **69** **70**

h. Reactions of Acylaminopurines (New)

The more general types of reaction, notably reduction to alkylamino- (Section V.D.d) and hydrolyses to aminopurines (Section 5.D.e) have been noted above. Rearrangements of *N*-alkyl groups are also treated separately (Section 5.D.f) as are the effects exerted on the sites of *N*-alkylation of aminopurines following acylation (Section 8.A.b). Both acetylated and benzoylated guanosines react with dichloro-*N*,*N*-diisopropylaminophosphine [$Cl_2PN(i\text{-}Pr)_2$] in the presence of diisopropylethylamine, forming cyclic derivatives (**71**, R = Me or Ph) in high yields (60–90%). A rapid reversion to the parent acylamino guanosine occurs on treating (20°C, 5 min) these products with trichloroacetic acid.[1457] The nature of the cyclic structure was established by various NMR (^1H, ^{31}P, ^{13}C, and ^{15}N)

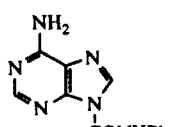


71

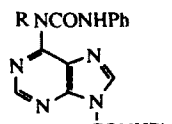
studies.[1457] Exchange of hydrogen at C-8 occurs more rapidly in 6-acetamido- and 6-benzamido-9-methylpurines than in 9-methyladenine. Significantly, the change in protonation site from N-1 in the parent adenine derivative to N-7, following acetylation or benzoylation, facilitates hydrogen removal through the positive change now residing with the imidazole ring.[1458] More profound in character is the effect of alkali on the bromide salt of the 7-phenacyl derivative of 6-benzamido-9-benzylpurine. After an initial imidazole ring fission to 4-benzamido-6-benzylamino-5-(*N*-phenacyl)formamidopyrimidine, a recyclization to 4-benzylamino-7-phenylpteridine (41%) follows.[1990]

i. Ureido and Thioureido Derivatives (New)

Although the initial reaction with isocyanates was described[1497] over three decades ago, no further studies were made until some years later. The products in a number of cases resemble those obtained from the same aminopurines with acylating agents. Addition of the reagent can occur at either the exocyclic amino group or a ring nitrogen atom. The reaction is influenced by various factors—the most significant are reagent concentration, temperature, and time. From phenylisocyanate and adenine in a 1:1 ratio in dimethyl sulfoxide (20°C), only the 9-substituted derivative (**72**) is obtained,[837] but an increase in reagent concentration (2:1) either in the cold or at 90°C produces **73** (R = H).[837] At this temperature, both adenine[1498] and adenosine[1499] in pyridine are converted to the respective 6-(3-phenylureido)purines (**74**, R = H or ribosyl). Heating with a tenfold excess of the reagent (85°C) 6-methylaminopurine forms the 6-(*N*-methyl)ureidopurine (**73**, R = Me), but at ambient temperature only condensation at N-9 occurs. Removal of a 9-carbamoyl group from these compounds is readily achieved, hydrolysis with dilute ammonia solution transforms **73** (R = Me) smoothly into[837] **75**. Although relatively less active, the alkylisocyanates, exemplified by the methyl, *n*-propyl, *tert*-butyl, and phenyl derivatives, give results which parallel those of arylisocyanates. In these products a 9-alkylureido moiety is lost in boiling water alone.[837] Use of methyl- or *n*-butylisothiocyanates extends the reactions to thio analogs, the conditions employed (2:1 reagent to adenine, 80°C) afford mainly the 9-thioureidopurine (**76**) together with a little of the isomeric 6-thioureidopurine.[837] Condensation of phenylisocyanate with a 2-amino group occurs in dimethylformamide (reflux, 10 min), forming the guanine adduct (**77**).[1498] An alternative route to 6-ureidopurines involving amination of 6-carboxyaminopurines is treated in (Chapter IX, Section 9.A.a).



72



73



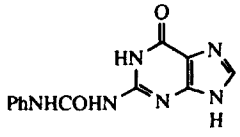
74



75



76



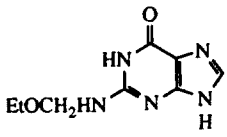
77



78

E. With Formaldehyde (*H*330)

The reaction with the 2′,3′-*O*-isopropylidene derivatives of adenosine and guanosine in aqueous solution affords unstable 6- and 2-hydroxymethylaminopurines,[1453,1454] findings which reflect earlier results with adenine. At a lower temperature (0°C) in the same medium, the triacetylated adenine-9-arabinoside forms the more stable 6-hydroxymethoxymethylaminopurine (**78**) from interaction with two molecules of the aldehyde.[1455] The relative stability shown may be a result of intramolecular hydrogen bonding between the hydroxy group and the amino group hydrogen. Under reflux conditions, the isopropylidene derivatives of adenosine and guanosine are converted to the respective 6- and 2-ethoxymethylamino adducts of the type (**79**, R = 2′, 3′-*O*-isopropylideneribosyl),[1456] showing pronounced stability in alkali. Isolation of the 6-phenylthiomethylaminopurine (**80**, R = 2-fluorobenzyl) on treatment of the 9-benzyladenine with aqueous formaldehyde and thiophenol provides a good illustration of the extension of the Mannich reaction to thiomethylation of aminopurines.[1146]



79

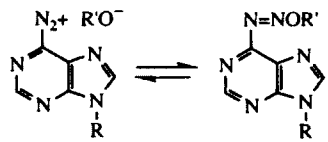


80

F. Diazo, *N*-Nitrosoamino (*H*331), and Triazenopurines (*H*333)

a. Preparation of Diazopurines (H331)

Examination of the reaction of nitrous acid or pentyl nitrite on 9-alkyladenines indicates that the *N*-nitroso derivatives initially formed (**81**, R = H or C_5H_{11}) isomerize to equilibrium mixtures of diazonium (**81A**) and azo (**81B**)[1094,1239] forms of 6-diazopurines.



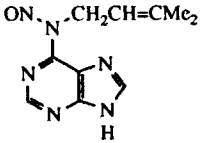
81 A 81 B

b. Reactions of Diazopurines (H332)

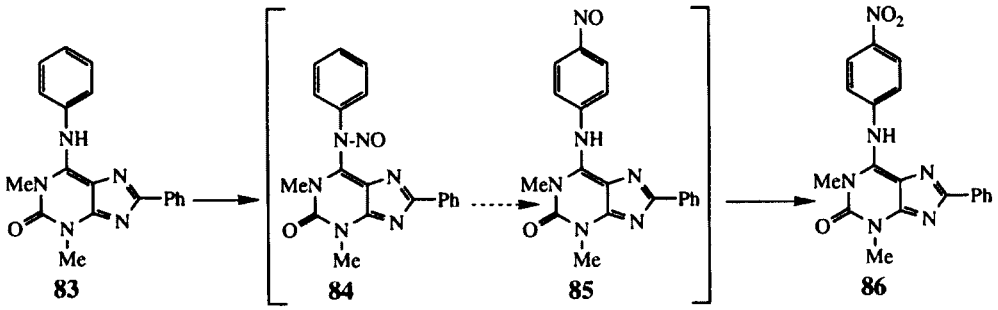
Replacement by hydrogen of a 6-diazo group prepared in situ (Gomberg–Bachmann reaction) with isopentyl[967] or *n*-pentyl[1092,1094] nitrite in tetrahydrofuran is described in Chapter IV, Section 3.A.b. Interactions with halogeh compounds forming chloro-, bromo-, iodo, and fluoropurines are elaborated in Chapter V, Sections 1.D, 1.E, 1.F, and 1.G.c, respectively. Monosubstituted benzenes, for example anisole, under similar conditions with 9-methyl- and 9-benzyl-6-diazopurine, form the expected 6-(*o*-methoxyphenyl) analogs as major products.[967] An earlier claim[1119] to have obtained only the *m*- and *p*- isomers in this reaction has been corrected.[967] Hydroxide replacement is shown by the conversion of adenine-9-arabinoside to the hypoxanthine derivative using liquid nitrosyl chloride in dimethylformamide[1241] to obtain the 6-diazotate intermediate. Under fairly alkaline conditions (pH > 11), the diazonium derivative from 9-propyladenine affords the hypoxanthine analog, but in strong acid (pH < 1) reduction to the parent adenine occurs, a chloride ion catalyst facilitating the reaction.[1239]

c. N-Nitrosoaminopurines (H332)

Examples prepared by nitrosation of alkylaminopurines with acidified sodium nitrite include 2-(*N*-nitroso)methylamino-1,6-dihydro-6-oxopurine[1227] and the 6-(*N*-nitroso) derivative (**82**) from 6-(3-methylbut-2-enylamino)purine.[1227] A new route to 2-, 6-, and 8-(*N*-nitroso)methylaminopurines is nitrous acid acting on the corresponding α-methylhydrazinopurines. A lower yield in the case of the 6-(*N*-nitroso)methyl aminopurine results is when peroxyacetic acid is used in place of nitrous acid. This approach, using hydrazino precursors, gives better yields than those obtained from direct nitrosation of 6-methylaminopurine.[1172] Likewise derived are 6-(*N*-nitroso)methylaminopurine-3-oxide and 2-(*N*-nitroso)methylamino-6-oxopurine,[1172] as noted above. Analogous *N*-nitrosohydroxyamino derivatives, formed from the hydroxyaminopurines, are described in Section 7.B.b. An explanation for the formation of the 6-(4-nitrophenylamino)purine (**86**) when nitrous acid is vigorously reacted (120°C, 2 h) with the 6-anilinopurine (**83**) proposes that the initial intermediate *N*-nitrosopurine (**84**) is generated and then undergoes a Fischer–Hepp isomerization to the 4-nitrosophenylamino derivative (**85**) with subsequent oxidation to the 4-nitrophenylaminopurine.[1463]



82



d. The Triazenopurines (H333)

Although long recognized (*H*333), these derivatives are the unstable products from interaction of the 6-amino group in adenines with a benzene diazonium salt. The instability of 6-triazenopurines is in sharp contrast to the highly stable 8-diazoniumpurines which result when guanines are treated with the same reagents (see Chapter X, Section 3). Using 4-substituted benzene diazonium hydroxides (pH 8–11) at 25°C, adenine affords the 6-(3-phenyl-2-triazen-2-yl)purines containing 4-methyl-, 4-bromo-, and 4-sulfophenyl moieties[858] as, for example, in **6** (R = Me, Br, and SO_2OH). Analogous triazenes are derived from 4-methoxymethyl- and 4-carboxyphenyldiazonium salts, but the triazenopurine from the 4-hydroxymethylphenyl salt is a mixture of the 6-[3-(4-methylphenyl)-2-triazen-1-yl]- and 6-[3-(4-formylphenyl)-2-triazen-1-yl]purines.[1994] Using adenosine in place of adenine, a 6-[3-(4-hydroxymethyl)triazenyl] derivative is obtained.[1994] The effect of hydrogen bonding between N-7 and the proton of the 6-amino group favors these derivatives adopting an (*E*)-conformation.[858] Substituted amino groups, as in 6-methylamino- and 6-acetamidopurines, show no reaction with diazonium salts. Decomposition of 6-triazenopurines in solution (pH10) on standing provides a mixture of adenine and an 8-phenyl homolog, the latter resulting from attack at C-8 of the former by a phenyl radical arising from decomposition of the liberated diazonium ion.[858] Following dithionite reduction of 6-triazenopurine, the reaction mixture contains 6-hydrazinopurine (47%), adenine (5%), and unchanged material (41%).[858]

G. Other Reactions of Amino Groups (*H*333)

The data now accumulated dictates the subdivision of this section to accommodate as separate topics the transformation of amino- into other aminopurines, the Dimroth reaction, and a miscellany of other types of amino group reactions.

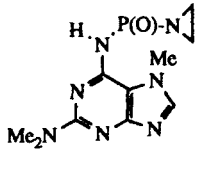
a. Transformation of Amino into other Amino Groups (New)

Conversion of amino- to alkylaminopurines by acylation followed by reduction is treated in Section 5.D.d. Until recently, direct alkylation of amino groups was rare, and examples were confined to nucleosides of aminopurines.[1467] With the introduction of trimethylanilinium methoxide,[1275] conversion of amino groups in adenines and guanines to dimethylamino is possible using dimethylaniline (18°C, 3 days) as a high-temperature solvent.[1276] The ability of the reagent to alkylate any oxo or hydroxy groups also present should be recognized. An alternative and rapid permethylation reaction of adenine or 6-methylaminopurine occurs in DMSO with a methyl iodide–sodium methoxide mixture; quantitative yields of *N*-methylated products are quoted.[1998] Oxo groups do not appear to react under these conditions. Highly reactive alkylating agents such as allyl bromide under solid–liquid phase-transfer catalysis conditions (aliquat, KOH) will react with the amino group of adenines to form 6-allylamino- and 6-diallylaminopurines. If N-9 is unsubstituted, a suitable protecting group is necessary.[1688] A more versatile two-stage procedure for mono alkylaminopurines requires treating 1-alkoxyadenines with an excess of alkyl halide in dimethylacetamide at moderate (25–80°C) temperatures. Removal of the 1-alkoxy group of the product by hydrogenation provides the 6-alkylaminopurine. Examples are 9-benzyl-6-benzylamino- and 9-ethyl-6-ethylaminopurine from their 9-alkyladenine analogs.[1466] A typical reaction consists of a mixture of a methyl iodide, in large excess, and hydrogen peroxide with adenine-1-oxide, which is converted through multiple *N*- and *O*-methylations to 1-methoxy-9-methyl-6-methylaminopurine[1717] (Chapter XI, Section 4.B). Reduction with sodium cyanoborohydride in a controlled pH range (4.0–5.0) converts the Schiff bases derived from 9-substituted adenines and the appropriate aldehydes to the 6-methylamino, -furfurylamino, and -benzylamino analogs.[1432] Related derivatives resulting from 6-aminopurine interactions with dimethylformamide diacetal are also reduced to 6-methylaminopurines.[1146] A novel route to a 9-aryl-6-methylaminopurine from the adenine analog utilizes a Mannich-type reaction with thiophenol and formaldehyde followed by sodium borohydride reduction of the resulting 6-phenylthiomethylaminopurine[1146] (**87**). A two-stage conversion of a 2-amino to a 2-dimethylamino group, presently restricted to guanosine derivatives, involves condensing the purine with benzodithiolylium tetrafluoroborate and reducing the 2-benzodithiolylaminopurine with tributyltin hydride, yielding a 2-methylaminopurine. Methylation (MeI) of the condensation product prior to reduction gives the 2-dimethylamino[1910] analog. Thermal rearrangement of 3-benzyladenines (autoclave conditions) leads to formation of some 6-benzylaminopurines together with other *N*-benzylated derivatives. Use of ^{15}N-labeled purines shows that complex multistage reactions occur which involve opening and reclosing of both rings.[1464] Salts of 3-benzyladenine, however, show no benzyl group translocation on prolonged heating (100°C, 41 h) in dimethylformamide.[1525] Outwardly similar in character is the transformation of amino- to alkylaminopurines utilizing the Dimroth rearrangement; this

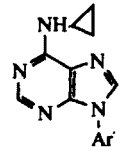
is now treated as a separate topic in Section 5.G.b. Some participation of the latter reaction during methylation of deoxyadenosine to the 1-methyladenosine analog (>55%) by trimethylphosphate (pH 7–10, 60°C) would explain the small amount (10%) of the 6-methylamino deoxriboside also present.[1277] Direct alkylation of the amino group, however, cannot be ruled out completely as deoxyguanosine with the same reagent undergoes some *O*-methylation (9%) with the expected 1-methylguanosine (44%) as major product.[1277] The 6-ethylaminopurine isolated after ethyl iodide treatment of an adenine derivative may provide a similar example.[1465] On heating the bromide salt of 6-benzoylmethylaminopurine with benzylamine in xylene, transamination to 6-benzylaminopurine occurs.[1496] An alkyl group interconversion by reduction (Adams catalyst) is used with 6-allylamino- to obtain 6-propylaminopurine.[1512] Trimethylsilylation of the 6-amino group, forming the 6,9-bistrimethylsilyl derivative, is made in dioxan or benzene with hexamethyldisilazane (reflux) or trimethylchlorosilane (20°C).[1316] The phosphoramide derivative (**88**) results from reacting phosphoryl chloride and ethylenimine with 6-amino-7-methyl-2-methylaminopurine.[1729]



87



88

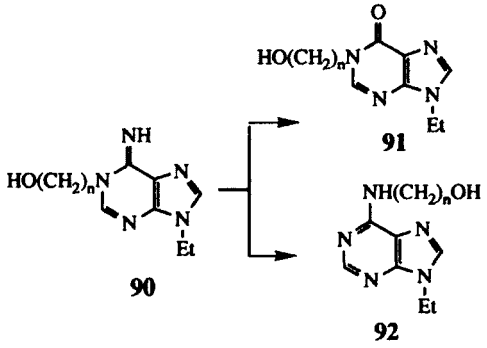


89

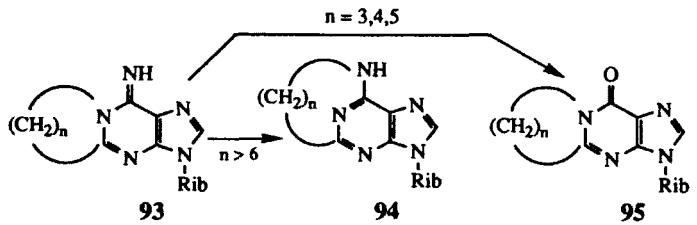
Procedures to remove alkyl groups from alkylaminopurines, and thus yield lower aminopurine homologs, are best illustrated by the stepwise oxidation of dialkylamino- to alkylamino- and aminopurines, the process being time and temperature dependent. Good examples are conversions of 6-dimethylamino-, 6-diethylamino-, and 6-dibenzylaminopurine-9-ribosides to the corresponding 6-monoalkylamino-[1146,1442,1443] and 6-aminopurines[1442] by means of potassium permanganate or ruthenium tetroxide (see Sections 5.D.a, 5.D.b, and 5.D.c). Bromine in tetrahydrofuran buffered to pH 4 removes the cyclopropyl protecting group (20°C, 20 min) from the purine (**89**), giving a 9-aryladenine.[1146] Trimethylammonio and other quaternary amino groups readily undergo the Beckmann transformation to the dialkylamino analog on heating,[1147] but are also susceptible to nucleophilic displacement by amino ions.[1140]

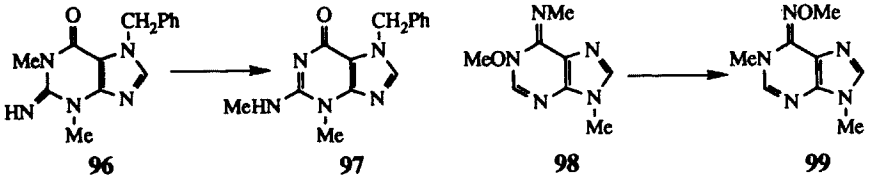
b. The Dimroth Rearrangement (H313)

The results of various studies (^{1}H and ^{15}N NMR, mass spectra) confirm the accepted mechanism for the transfer of an alkyl group from a ring nitrogen to an exocyclic amino group on an adjacent carbon atom. No alkyl group migration occurs; the reaction involves ring fission and recyclization, as demonstrated by ^{1}H NMR observations of the rearrangement of ^{15}N-labeled 1-methyladenosine[1468] to



6-methylaminopurine riboside. Initial attack by hydroxide ion at C-2 is greatly facilitated if the protonated purine takes part.[1469-1471] First-order kinetics are followed with more than a hundredfold rate increase observed for the cation over that of the neutral species,[1471] although both undergo the same rearrangement mechanism. The presence of electron-withdrawing substituents at N-9 also aids the reaction, the 9-ribosyl moiety being the most effective.[1470] The size of the alkyl group plays no significant part in the reaction, as demonstrated by relocation of the tetracyclic 1-(benz[*a*]anthracenemethyl) group to the 6-amino group in an adenosine derivative,[1154] although some cases of inhibition due to neighboring substituents on the ring have been noted.[998] Anomalous behavior is found with 1-(ω-hydroxyalkyl)-9-ethyladenines (**90**, n = 2 or 3) in phosphate buffer (pH 6–7) which are hydrolyzed to the hypoxanthine analogs (**91**, n = 2 or 3) only. Involvement of the side-chain hydroxy group, acting either as base catalyst or a nucleophilic moiety, in attack at the 6-position is proposed.[1472] Supporting this premise is the normal rearrangement undergone by derivatives with similar chain length 1-alkyl groups. Conversion to 6-(ω-hydroxyalkylamino)purines (**92**, n = 2 or 3) is nevertheless possible in solutions of higher pH value.[1472,1473] The tricyclic riboside derivatives (**93**, n = 7, 9, and 11) transform in alkali to the isomeric purines (**94**, n = 7, 9, and 11), whereas the lower homologs (**93**, n = 3 to 5) only form hypoxanthine analogs (**95**, n = 3 to 5) of the starting materials. Structural rigidity resulting from the smaller ring sizes presumably inhibits these rearrangements.[994] Similar transformations are found in a series of analogous cyclic adenine derivatives.[1728] Recent examples from the literature derived from 1-alkyladenines include the 6-methylamino derivatives of 9-methyl-[1471], 9-ethyl-,[1470] 9-benzyl-,[1146,1470] 9-(4-hydroxybutyl)-,[1470] 9-(5-hydroxypentyl)-,[1470] and 9-β-D-ribosylpurine.[1468,1469] Corresponding alkali-induced rearrangements are noted



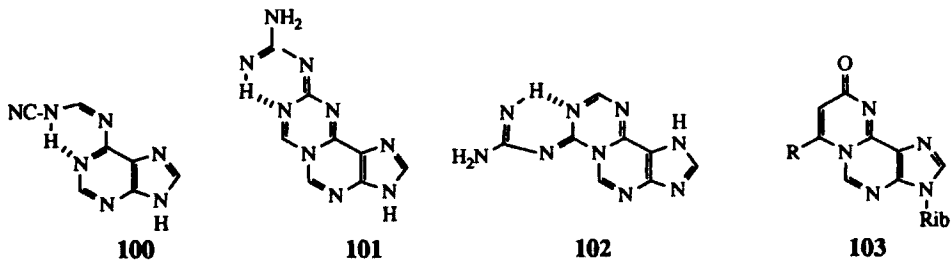


96 **97** **98** **99**

with 1-ethyl-,[1471] 1-propyl-,[1471,1472] 1-butyl-,[1472] and 1-benzyl-[1471,976] adenine derivatives together with 1-(ω-sulfoalkyl)[1474] and others.[1475] The formation of 6-propylaminopurine[1476] and 8-azido-6-benzylaminopurine[842] from the 1-alkylated isomers shows that the conversion goes equally well in the absence of a 9-substituent. Although most examples encountered relate to adenine derivatives, some 2-aminopurines behave likewise. The isolation of the 2-methylaminopurine (**97**) from methyl iodide treatment of 7-benzyl-3-methylguanine (3*M* NaOH, MeI, 100°C) appears to result from a Dimroth rearrangement of the methylation product[1477] (**96**). Variations of the reaction extend to conversions of 1-alkoxyadenines to 6-alkoxyaminopurines (Chapter XI, Section 4.B). An apparent reverse of the Dimroth occurs in transformation of the 6-methylaminopurine (**98**) into the 1-methyl isomer (**99**) in hot alkali. Under these conditions, the isomer favored is the one with the more electron-withdrawing group (methoxy > methyl) located on the exocyclic amino group.[978] Results of detailed studies of ring opening and reclosing reactions of adenines are discussed in a paper by Fujii and his co-workers.[1960]

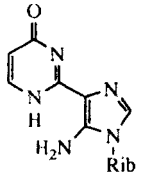
c. Condensation Reactions (New)

Elimination of an alcohol with concomitant adduct formation is a feature of interactions of adenines and guanines with unsaturated alkoxy compounds. Many of the products show characteristic fluorescence in solution and hence have potential use as purine markers. Heating adenine in hexamethylphosphoramide with methyl *N*-cyanomethanimidate* (MeOCH:NCN) produces a mixture comprising a simple condensation product (**100**) together with two highly fluorescent isomeric 1,3,5-triazino[2,1-*i*]purines, (**101**) and (**102**), formed from two molecules

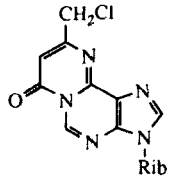


100 **101** **102** **103**

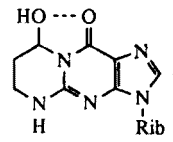
* Attention is drawn to the highly irritant and hygroscopic nature of this reagent, prepared by heating trimethyl orthoformate and cyanamide with a formic acid catalyst.[1500]



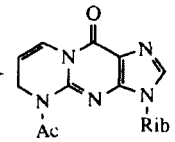
104



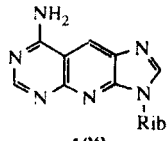
105



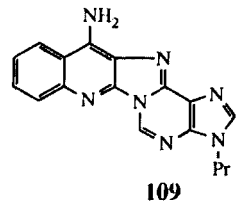
106



107

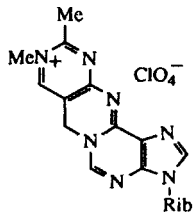


108

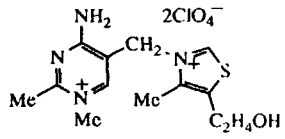


109

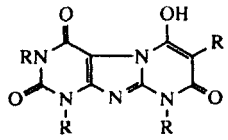
of reagent.[1500] At ambient temperature, adenosine and ethyl propiolate ($HC{:}CCO_2Et$) in ethanol at acid pH (4.5–6.0) react, giving the 9-oxopyrimido[1,2-*c*]purine (**103**, R = H).[1501] Under reflux conditions, opening of the pyrimidine ring to the imidazole (**104**) occurs.[1501] The 7-chloromethyl derivative (**103**, R = CH_2Cl) is similarly derived with ethyl 4-chlorobut-2-ynoate, but at neutral pH this condensation affords the isomeric adduct (**105**) produced by a reversed addition to the unprotected purine.[1501] Similar ring formations with guanines include a mixture of two diastereomers of the adduct (**106**) following treatment with acrolein. Conversion to the dihydropyrimidine form (**107**) is effected with acetic anhydride.[1502] The fluorescent derivative (**108**) is obtained when methyl *N*-cyanomethanimidate and guanosine are reacted,[1503] but the same riboside does not appear to form an adduct with ethyl propiolate.[1501] A Michael reaction through N-1 of 9-propyladenine, using 1-acetoxy-4-acetoxyimino-1,4-dihydroquinoline in trifluoroacetic acid (20°C, 24 h), gives the pentacyclic system[1506] (**109**). Somewhat related in the mode of condensation is the fluorescent tetracyclic salt (**110**) from adenosine and the 1-methylthiaminium ion (**111**), which involves initial alkylation by the latter of N-1 in the purine.[1507] Formation of a large number (> 60) of 6-hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*, 3*H*, 9*H*)-triones of the type (**112**, R = alkyl) results from condensing malonic esters with 8-amino-1,3-dialkylxanthines and a sodium ethoxide catalyst.[1547]



110



111

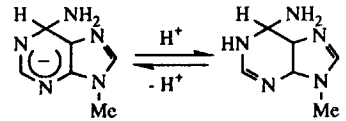


112

d. Replacement by Hydrogen (New)

The two principal routes are either by diazotization followed by displacement of the diazonium moiety with hydrogen, using a suitable proton donor, or by deamination at low temperature in liquid ammonia containing amide ions. Exemplifying the former procedure are the 9-ethyl, -benzyl, and -(2′,3′,5′-tri-*O*-acetylribosyl)purines from the corresponding adenine analogs after irradiation and treatment with *n*-pentyl nitrite, with tetrahydrofuran acting as both solvent and proton donor.[1092,1094] Successful application of the method in forming the *O*-triacetylated 6-chloropurine nucleoside from the 2-amino-6-chloropurine analog (pentyl nitrite in hot THF) shows that the route is not restricted to 6-amino derivatives.[1863]

More wider ranging in scope is the alternative deamination in liquid ammonia which permits displacement of either amino or alkylamino groups. Using this method, 9-methylpurine results from the 6-amino, 6-methylamino, or 6-dimethylamino homologs.[1091] As with the diazotization approach, 6-aminopurines appear to be the most suitable candidates, as demonstrated by isolation of 2-amino-9-methylpurine from the 2,6-diamino derivative.[999,1091] Noninvolvement of alkoxy groups is found under these conditions, as shown by the conversion of 6-amino-2-methoxy-9-methylpurine to 2-methoxy-9-methylpurine.[1091] Failure of adenine to undergo deamination suggests that the 9-substituent is a prerequisite, as is use of ammonium sulfate as quenching agent. In the absence of the latter, both 7- and 9-methyladenine retain the amino group.[875] While the diazonium replacement operates through a purinyl radical mechanism,[1092,1094] that for the amide ion–ammonia reaction involves a 1,6-double-bond reduction to the anion (**113A**) or conjugate acid (**113B**) and then loss of amide ion or ammonia on ammonium sulfate quenching.[1091] Both topics are further elaborated in Chapter IV, Section 3.A.b.



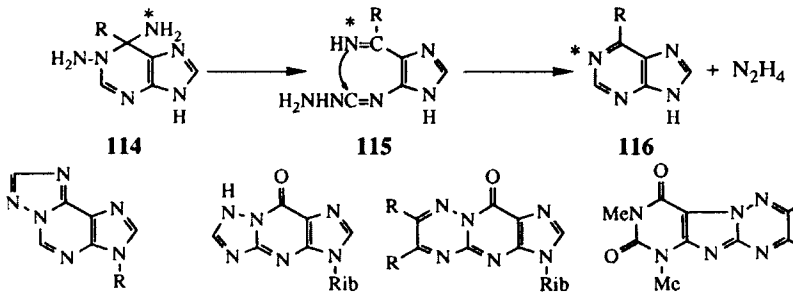
113 A **113 B**

e. Replacement by Thioxo and Selenoxo Groups (New)

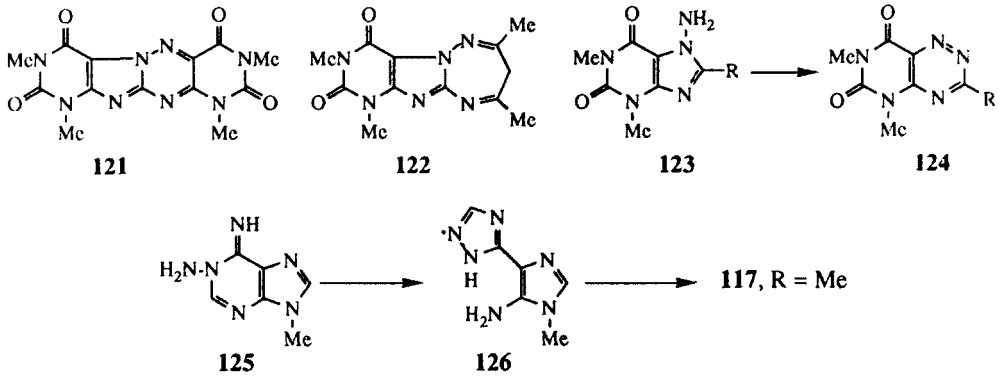
Although presently limited to 6-aminopurines, examples of direct transformation to 6-thioxo analogs are reported using either aqueous hydrogen sulfide or liquid hydrogen sulfide in pyridine. Comparable reactions with hydrogen selenide are generally more facile and productive. More detailed treatment of this topic is found in Chapter VII, Section I.A.i, which also includes examples of replacement of alkoxyamino groups by sulfur.

H. Reactions of *N*-Aminopurines (*New*)

Although both *N*- and *C*-amino groups show some characteristic reactions in common, variations encountered indicate that the analogy should not be taken too far. With nitrous acid, for example, 1-amino-9-benzylhypoxanthine is deaminated to 9-benzylhypoxanthine, and no 1-*N*-oxide is obtained.[1007] Acetylation is also possible.[1546] Removal of the *N*-amino group also occurs when the mesitylene sulfonate salt of 1-aminoadenine and methanolic ammonia are heated (100°C, 17 h) in a sealed vessel. Under these conditions, an ANRORC-type reaction operates, and in this instance some loss of a *C*-amino group occurs, resulting in a product mixture of adenine (35%) and purine[1513] (40%). A more striking illustration of this effect is conversion of the corresponding 1,2,6-triaminopurine to purine (70%) together with a little 2-aminopurine[1513] (20%). Simpler derivatives from 1-amino precursors include 2-, 6-, and 9-methylpurine as well as 8-phenylpurine and the 9-methyl homolog.[1404] Mechanistically the reaction can be viewed as proceeding by intial adduct formation with ammonia (**114**), ring opening to the imidazole (**115**), and a subsequent recyclization to the purine (**116**) accompanied by loss of hydrogen. Support for this pathway is given by isolation of an N-1 labeled purine when ^{15}N-labeled ammonia is employed.[1404] Utilization of the reaction for a general synthesis of N-1 labeled purines is indicated.[1404] The possibility that *N*-deamination may occur in part by direct displacement of the amino group is not unreasonable because removal could be facilitated through hydrazine formation on interaction with ammonia.[1404,1513] More typical amino reactions are exemplified by the azamethine derivatives formed by 1-aminohypoxanthine,[961] 7-aminotheophylline,[1330] and 9-amino-6-alkylthiopurines[1546] with benzaldehyde. Location of a *C*-amino adjacent to an *N*-amino group permits Traube and Isay condensations. Annelated purines with five-membered or larger rings formed in this way from carbonyl compounds include the *sym*-triazolo[3,2-*i*]purine[1409] (**117**, R = H) and the 9-methyl analog[973,1009] (**117**, R = Me) from appropriate 1-aminoadenines and triethylorthoformate, and the *sym*-triazolo[2,3-*a*]purine[1516] (**118**), using the Vilsmeier reagent (DMF-$POCl_3$) with 1-aminoguanine. The analogous



1,2,4-triazino[2,3-*a*]purines (**119**, R = H and Me) result from condensations with glyoxal (50°C, 1 h) and diacetyl (20°C, 10 days), respectively.[1516] Variations of this theme are closures of 7,8-diaminotheophylline with 1,2-dicarbonyl derivatives to 1,2,4-triazino[3,2-*f*]purines in polyphosphoric or boric acid. Products are illustrated by (**120**, R = R′ = H) from glyoxal, (**120**, R = R′ = Me) from diacetyl, and (**120**, R = R′ = Ph) with dibenzoyl. The unsymmetrical derivatives (**120**, R = Ph, R′ = H) and (**120**, R = Me, R′ = H) result using phenylglyoxal and pyruvic aldehyde.[1517] Of related interest is the 2,4,7,9-tetramethylpurino[7,8-*g*]-6-azapteridine (**121**), which is obtained from hydrochloric acid treatment of 7,8-diaminotheophylline, most likely formed by partial oxidation of some of the starting material to alloxan, which reacts with the remainder of the diaminotheopylline.[1518] The triazepinopurine (**122**) is derived from a closure with acetylacetone in polyphosphoric acid.[1517] An oxidation-derived imidazole ring enlargement occurs with 7-aminotheophylline (**123**, R = H) or the 8-bromo analog (**123**, R = Br) to the pyrimido[4,5-*e*]-1,2,4-triazines (**124**, R = H and Br) following treatment with lead tetraacetate.[1746,1747] A rearrangement of 1-amino-9-methyladenine (**125**) in aqueous alkali (6°C, 2 h) gives 5-amino-1-methyl-4-(1,2,4-triazol-2-yl)imidazole (**126**). Conversion of the latter to the triazolo[3,2-*i*]purine (**117**, R = Me) is effected in an orthoester–anhydride mixture under reflux.[1009]



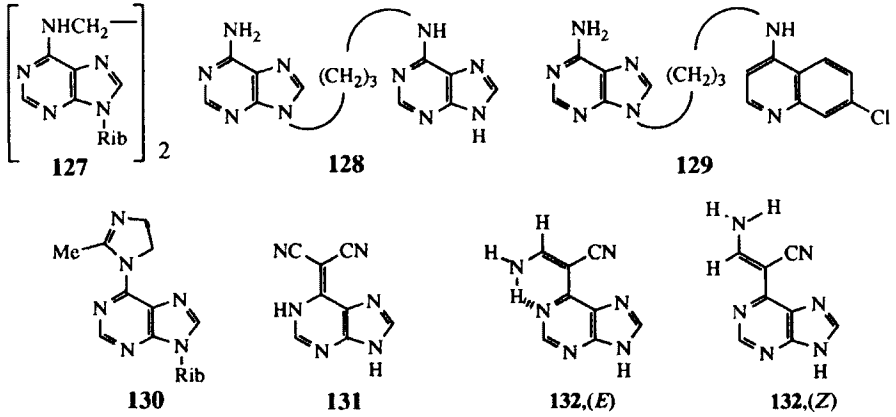
I. Oxidation of Adenine (*New*)

Over the range pH 3.0–11.2, adenine in aqueous solution with a pyrolytic graphite electrode undergoes oxidative attack at C-2, giving initially isoguanine and then 2,8-dioxoadenine on further treatment. At pH 3.0, the final products are urea, alloxan, and parabanic acid. The same three derivatives are also obtained from oxidation of either 8-oxo- or 2,8-dioxoadenine. At pH 7.0, allantoin is formed.[1905] The only identifiable product from oxidation of adenine with potassium peroxodisulfate is urea, in accord with earlier findings using acidified permanganate (*H*351) and alkaline hydrogen peroxide for oxidations.[1790] Under

gamma irradiation of adenine in aqueous solution[2022,2023] the 8-oxo analog is detected in a mixture containing degradation products that are the same or related to those found with the electrolytic oxidations. A recent comprehensive review of one-electron oxidation–reduction of purines, including adenine, should be consulted.[1906]

6. REACTIONS OF EXTRANUCLEAR AMINO GROUPS (*H*334)

The facility with which exocyclic amino groups condense with other functional groups is utilized to form linked compounds with other purines or aromatic molecules. Such derivatives, especially those containing adenine or guanine, are employed in intercalation studies on nucleic acids. Illustrations are provided by the 1,2-di(purin-6-ylamino)ethane riboside[1510] (**127**) and the unsymmetrical 6-(adenin-9-ylpropylamino)purine (**128**)[1101] from the 6-(2-aminoethylamino)- and 9-(3-aminopropyl)purines, respectively, and 6-chloropurine. Similar condensations of the 9-(3-aminopropyl) derivatives of adenine and guanine with 4,7-dichloroquinoline in dimethyl sulfoxide (110°C, 4 h) provide products of the type (**129**) used in studies of chloroquine interactions with nucleic acids.[1511] Condensations of this type also feature in the formation of more rigidly linked purine pairs detailed in the section on purinophane derivatives (Chapter XIII, Section 2). A novel route to 6-(2-methylimidazolin-1-yl)purine riboside (**130**) uses ring closure of the 6-(2-aminoethylamino)purine with trimethyl orthoacetate.[1510] The reduction product (H_2, Pd–carbon) of 6-dicyanomethylenepurine (**131**) is an equilibrium mixture (1:6) of (*E*) and (*Z*) isomers of 6-(2-amino-1-cyanoethen-1-yl)purine (**132**) with the hydrogen bonded (*E*)-form as the minor component.[1068] NMR (^1H and ^{13}C) investigations show that an enaminonitrile rather than an iminonitrile structure predominates.[1068]

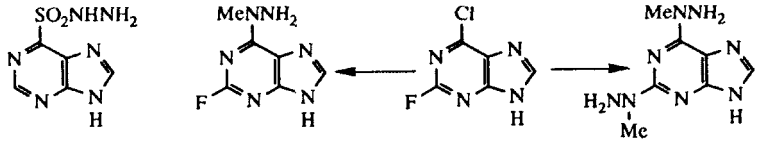


7. OTHER SUBSTITUTED AMINOPURINES (*H*334)

A. Hydrazinopurines (*H*335)

a. Preparation (H335)

Preparation of 6-hydrazino-9-vinylpurine from the 6-chloro analog (20°C, 0.5 h)[1163] exemplifies conventional practice, which utilizes halogeno- or methylthiopurine precursors. The conversion of 6-chloro-2-fluoro into the 2-fluoro-6-hydrazino derivative is a further illustration showing replacement selectivity under the conditions (5°C, 1 h) used.[1124] Several alternative functional groups are now available for displacement by hydrazine. Reactions of 2- and 6-trimethylammoniopurine salts with aqueous hydrazine (20°C, 15 min) afford 2- and 6-hydrazino-9-methylpurine respectively.[1140] A range of derivative results with sulfo-[1864] and methylsulfonylpurines; examples obtained include 6-hydrazino-8-(thiazol-4-yl)-[870] (80°C, 2 h) and 6-hydrazino-9-phenyl-[1079] (80°C, 1 h), but only 6-hydrazino-2-methylsulfonylpurine when the 2,6-bismethylsulfonyl derivative is likewise treated.[870] Interaction of 6-fluorosulfonylpurine with methanolic hydrazine under mild conditions (25°C, 8 min) gives the expected 6-hydrazino derivative, but at a lower temperature (−10°C), 6-hydrazinosulfonylpurine[1390] (**133**) is obtained. Methylhydrazine reacts in like manner. Prolonged heating of 8-thioxo- and 2,6-dithioxopurine with hydrazine hydrate, with or without a butanol solvent, gives the appropriate mono- or dihydrazinopurine.[1514] Equally successful for forming the latter is use of 2,6-bismethylthiopurine.[1514] The precursors for formations of 6-(α-methylhydrazino)purine with a methanolic reagent at 80°C include 6-chloro-, 6-methylthio-, and 6-methylsulfonylpurine.[1172] At the same temperature, 2,6-bis(α-methylhydrazino)purine (**135B**) is obtained from 6-chloro-2-fluoropurine (**134**), but cold treatment (5°C) gives only the 2-fluoro-6-(α-methylhydrazino) (**135A**) analog.[1172] Although sealed vessel conditions (100°C, 1 h) were employed with 8-bromoadenosine[1173] to prepare 8-(α-methylhydrazino)purine, later work shows that hydrazination is possible in boiling ethanol.[1406] These conditions also form 8-hydrazinoadenosine from the 8-bromo analog.[1889] A novel preparation of the 2-(α-methylhydrazino) analog of guanine is by hydrogenation (Raney Ni) of the 2-(*N*-nitroso)methylamino derivative.[1172] This reaction is unusual, as similar reductions of *N*-nitrosoaminopurines have resulted in replacement of the nitroso group by hydrogen.[1172,1227] A specific



133 **135 A** **134** **135 B**

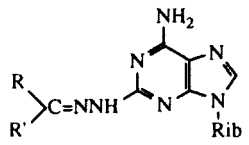
synthesis of the isomeric 6-(β-methylhydrazino)purines from 4-amino-5-cyanoimidazoles is described in Chapter III, Section 1.E.b. A mixture of 6-hydrazinopurine (47%), adenine (5%), and starting material is formed by a reductive approach involving sodium dithionite with 6-aryltriazenopurines[858] (Section 5.F.d).

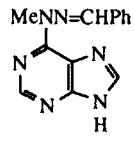
b. Reactions with Nitrous Acid (H336)

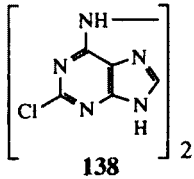
Pentyl nitrite and hydrochloric acid convert 8-hydrazinoadenosine to the 8-azido analog.[1889] In contrast, the same reagent with 8-(α-methylhydrazino) adenines eliminates the β-amino group, giving 8-methylaminoadenines.[1406] A linear azide is obtained from nitrous acid treatment of a 2-hydrazinoadenosine, but no ring closure of the product with an adjacent ring nitrogen to a tetrazole is found.[1684] Reaction of 2-, 6-, and 8-(α-methylhydrazino)purines with nitrous acid gives the respective (*N*-nitroso)methylaminopurines. These results should be compared with the effect of pentyl nitrite on methylhydrazinopurines noted above in which *N*-nitrosation is absent. In practice this approach to (*N*-nitroso) methylaminopurine formation is superior to that of direct nitrosation of the methylamino derivative.[1172]

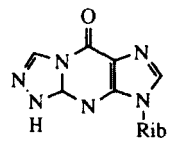
c. Other Reactions (H336)

Replacement of a 2-hydrazino group by hydrogen gives a low yield (10%) of purine following treatment with methanolic ammonia.[1513] Evidence exists suggesting that a 6-hydrazinopurine reacts likewise.[1513] A route to 6-deuteriopurine is by bubbling oxygen through an alkaline solution of 6-hydrazinopurine in deuterium oxide.[1050] Removal of an 8-hydrazino group occurs after reaction with sodium methoxide (MeOH, 20°C) or mercury(II) oxide in hot ethanol, giving adenosine.[1889] Under reductive conditions the β-amino moiety is removed, affording the analogous aminopurine. A hot aqueous solution of 2-fluoro-6-hydrazinopurine with Raney nickel gives rise to 2-fluoroadenine,[1124] while hydrogen and the same catalyst provide another route to an 8-methylaminoadenine from the 8-(α-methylhydrazino) derivative.[1173] Oxidation with iron(III) chloride transforms 6-hydrazino- to 6-chloropurines.[870] These results can be contrasted with the transformation of 6-(α-methylhydrazino)purine into 6-methylaminopurine by the same reagent.[1172] Formation of 8-bromoadenosine from the 8-hydrazino analog with bromine water provides another example of oxidative halogenation.[1889] A series of Schiff bases of the type **136** result from interaction of aldehydes and ketones with 6-amino-2-hydrazinopurine riboside. Products with acetaldehyde (R = H, R′ = Me), propaldehyde (R = H, R′ = Et), butaldehyde (R = H, R′ = Pr), and other aldehydes and also ketone derivatives such as (R = R′ = Me) and (R = R′ = Et)[1890] are reported together with the unusual hydrazone derived from 6-hydrazinopurine and 2,2,6,6-tetramethylpiperi-

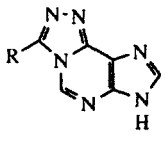

136

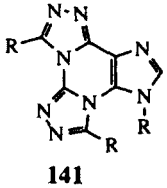

137

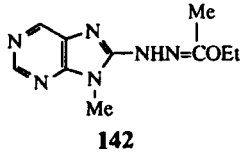

138

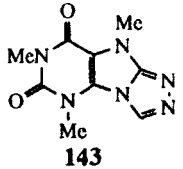

139

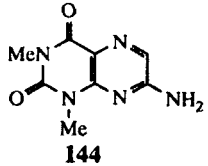
done-1-*N*-oxide.[1985] Analogous arylidenepurines are likewise prepared, such as the benzaldehyde product (**137**) from 6-(α-methylhydrazinopurine).[1172] A 1,2-di(purin-6-yl)hydrazine (**138**) obtains from condensation of 2-fluoro-6-hydrazino- with 6-chloro-2-fluoropurine.[1124] Ring closure of the 2-hydrazino analog of guanosine with triethyl orthoformate[1229] gives the *sym*-triazolo[3,2-*a*]purine (**139**). A series of tetracyclic homologs arises from treating 2,6-bishydrazinopurine with orthoesters; examples include the 3,7,9-trimethyl-bis-*sym*-triazolo[3,4-*b*: 3′4′-*i*]purine (**141**, R = Me) with trimethyl orthoacetate; the triethyl ester affords the 9-ethyl-3,7-dimethylated and triethyl orthopropionate, yields the 3,7,9-triethylated derivative.[1514] A confirmation of the tetracyclic structures is obtained from an unamgibuous synthesis of the triethyl compound (**141**, R = Et) from 9-ethyl-2,6-bishydrazinopurine.[1514] The presence of a 9-alkyl group in these products is a result of the *N*-alkylating properties of the orthoesters for which precedents exist.[866,1514,1515] Isolation of only a linear product (**142**) when 8-hydrazino-9-methylpurine and triethyl orthoacetate react may suggest steric hindrance to cyclization by the 9-methyl group since a *sym*-triazolo[4,3-*e*]purine (**143**) from 8-hydrazinocaffeine is known.[1520] Introduction of thio substituents, achieved by cyclizations with carbon disulfide, affords, for example, the tricyclic 3-thioxo derivative (**140**, R = SH) from 6-hydrazinopurine on reaction in pyridine with a triethylamine catalyst. Alkaline methyl iodide treatment gives the methylthio derivative (**140**, R = SMe).[1514] Under anaerobic thermal treatment (130°C), 8-hydrazinocaffeine undergoes a vigorous rearrangement to the 7-aminopteridine[1405] (**144**). The formation of the same pteridine on heating 8-azidocaffeine (Section 7.C.b) may indicate that a common nitrene intermediate participates in both reactions.


140


141


142

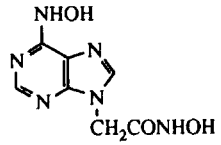

143


144

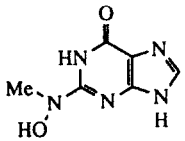
B. Hydroxyamino- and Alkoxyaminopurines (*H*337)

a. Preparation of Hydroxyaminopurines (H337)

Treatment of the halogenopurines with ethanolic hydroxylamine provides 2-hydroxyamino- and 6-amino-2-hydroxyaminopurine from the 2-fluoropurines using reflux conditions. To obviate any involvement of the sulfur, reaction with 2-fluoro-6-thioxo-1,6-dihydropurine is carried out at ambient temperature.[1124] Formation through substitution at C-6 gives 9-benzyl-6-hydroxyamino,[983] 6-hydroxyamino-8-(thiazol-4-yl)-,[870] and 2-carboxymethylamino-6-hydroxyaminopurines[1114] from the chloro analogs. The amide derivative (**145**) results when 9-carboxymethyl-6-chloropurine is reacted.[1114] At low temperature (5°C), only the 6-hydroxyaminopurine forms with 6-chloro-2-fluoropurine; reflux conditions are required to replace the second halogen.[1124] The higher activity of a methylsulfonyl group shows in the conversion of 6-methylsulfonyl-3-oxidopurine to the 6-hydroxyamino analog at 25°C, but at a higher temperature (80°C) hydrolysis predominates, giving hypoxanthine-3-oxide.[1142] Other examples of this type of methylsulfonyl group displacement are known.[870]



145



146

Interaction of the hot reagent with the disodium salt of 2,6-disulfopurine provides another route to 2,6-bishydroxyaminopurine.[1124] A poor yield of 6-hydroxyaminopurine is obtained from debenzylation of the 6-benzyloxyamino derivative by catalytic (Pd) hydrogenation.[983]

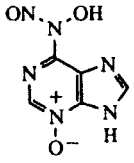
Use of *N*-methylhydroxylamine and halogenopurines gives **146** from 2-chlorohypoxanthine.[1227] Other purines reacted include the 6-chloro-2-fluoro,[1124] 2-fluoro-6-thioxo,[1124] and 6-chloro-3-oxido[1142] derivatives. The 6-(*N*-ethylhydroxyamino) and 6-(*N*-benzylhydroxyamino) derivatives of 9-ethyl-[981,1687] and 9-benzylpurines[981,1687] and the 9-methyl analogs[981] can be derived in the same way. The 2,6-bis(*N*-methylhydroxyamino)purine is formed by 6-chloro-2-fluoropurine under reflux conditions.[1124] Direct replacement of the amino by a hydroxyamino group occurs with adenine (40°C, 3 days) in weak acid solution.[725]

b. Reactions (H338)

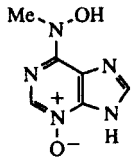
Like the parent compound, the 3-oxide of 6-hydroxyaminopurine undergoes very rapid nitrosation with nitrous acid to the 6-(*N*-nitroso)hydroxyamino derivative[1172] (**147**). A similar conversion of the 6-hydroxyaminopurine-9-ribofura-

noside occurs on prolonged exposure to ethyl nitrite at 25°C.[1172] The oxidation of (*N*-nitroso)hydroxyaminopurines to 6-nitrosopurines is noted elsewhere (Chapter X, Section 2.A).

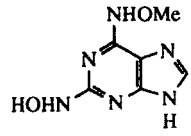
Hydrazine reduces 2-hydroxyaminoadenine to 2,6-diaminopurine,[1124] but heating with Raney nickel is used to obtain 2-chloroadenine from 2-chloro-6-hydroxyaminopurine.[1124] Only the sulfur group is affected when 1,6-dihydro-2-hydroxyamino-6-thioxopurine is treated similarly.[1124] Reduction of (*N*-methyl)hydroxyamino homologs also features nickel catalysts which afford corresponding methylaminopurines. Examples from this transformation include 2-methylaminohypoxanthine[1227] and 9-methyl-6-methylaminopurine.[1460] Use of the same catalyst to remove only the oxide moiety from 6-(*N*-methyl)hydroxyamino-3-oxidopurine (**148**) is reported.[1142]



147



148

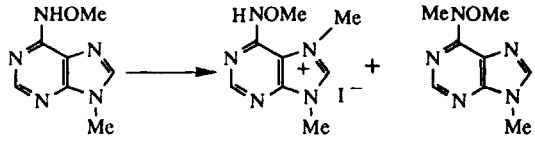


149

c. Alkoxyaminopurines (New)—Preparation and Reactions

Examples of these derivatives are limited in number, some have arisen as products of rearrangements of *N*-alkoxyadenines. Direct synthesis usually entails treatment of a halogenopurine with alkoxyamine in methanol or ethanol. Only the chlorine in 6-chloro-2-fluoropurine reacts with methoxyamine in methanol under reflux, and no disubstitution is reported.[1124] Replacement of the second halogen is possible, however, using hydroxylamine, which gives 2-hydroxyamino-6-methoxyaminopurine[1124] (**149**). Selective alkali-catalyzed alcoholysis by the ethanol solvent would account for the unexpected isolation of 6-ethoxy-3-oxidopurine from the 6-chloropurine oxide on methoxyamine treatment.[1142] Both 6-methoxyaminopurine and the 9-riboside result on treating adenine and adenosine with methoxyamine[725] under weakly acid conditions. The Dimroth rearrangement is found to be applicable to 1-alkoxyadenines, which are transformed in alkali into the 6-alkoxyimino isomers. This topic is treated more appropriately in Chapter XI, Section 4.B.

To date, reduction of an alkoxyamino to an amino group by catalytic hydrogenation is the most likely reaction to be encountered. Corresponding derivatives of adenine have been obtained from 9-benzyl-6-benzyloxyamino-[983] (Pd), 9-ethyl-6-ethoxyamino-[983] (Ni or Pd), 6-methoxyamino-7,9-dimethyl-[1460] (Pd), and 2-fluoro-6-methoxyaminopurine[1124] (Ni) in this way. Similar conditions convert 9-methyl-6-(*N*-methyl)methoxyaminopurine to 9-methyl-6-methylaminopurine.[1460] The quaternary iodide (**151**) is the major product (59%) from methylation (MeI) of 9-methyl-6-methoxyaminopurine (**150**) in dimethylacetamide



150 **151** **152**

(30°C, 7 h) together with a smaller yield (25%) of the isomeric *N*-(methyl)-methoxyaminopurine[1460] (**152**).

C. Azidopurines (*H*338)

Interest in these derivatives is now largely confined to their use in synthesis as precursors of aminopurines.

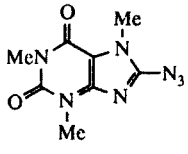
a. Preparation (H339)

Sodium azide and to a lesser degree lithium azide in aprotic or alcoholic solutions convert 6-methylsulfonyl-[1222] and 6-pyridiniopurine[1274] (DMF, 20°C) as well as 2-amino-6-chloropurine-9-β-D-riboside[1109] (MeCN, 20°C) to the 6-azido analogs. Formation of 8-azidopurines from the 8-bromo derivatives uses lithium azide. An early attempt to prepare 8-azidoadenine from the 8-bromo analog gave a mixture of 8-azidoadenine and starting material.[1185] A more successful approach to the purine involves interaction of azide ion with 8-bromoadenosine[1196] with subsequent hydrolytic cleavage of the ribosyl moiety.[1186] Other examples are available* which demonstrate the advantage of using a riboside precursor. A 2-azidopurine results from nitrous acid reacting with a 2-hydrazinopurine nucleoside.[1864] Exocylic azides, useful as side-chain intermediates, are exemplified by 1-(2-azidoethyl)hypoxanthine derived from the 1-(2-chloroethyl) analog with sodium azide in hot (100°C, 3 h) dimethylformamide.[1133]

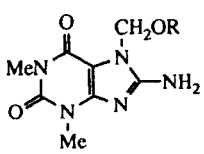
b. Reactions (H339)

Catalytic hydrogenation (Pd catalyst) is well documented with 6,8-diamino-1-methylpurine obtained from the 6-amino-8-azido analog[842] and likewise reduced is 2-amino-6-azidopurine riboside to the 2,6-diaminopurine.[1109] This approach also gives 8-aminocaffeine.[1405] Photochemical reduction is demonstrated in the conversion of 6-azidopurine riboside to adenosine following irradiation (> 280 nm).[1222] Formation of the 8-aminocaffeine derivatives (**154**, R = Et) and

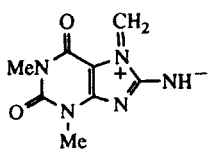
* The influence of the leaving group in the reaction must not be overlooked, as illustrated by the failure to transform 6-chloropurine riboside to the 6-azido derivative, although the latter is readily obtained from the 6-methylsulfonylpurine riboside.[1222]



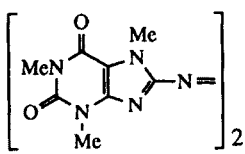
153



154

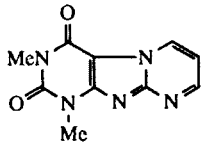


155



156

(**154**, R = $CHMe_2$) occurs on photolysis of 8-azidocaffeine (**153**) in ethanol and propanol, respectively. Such adducts arise from interaction of the solvent alchohol and a zwitterion form (**155**) derived from a nitrene intermediate.[1405] From irradiation (450-W lamp) in various alcohols of 2-azidoadenine, mainly 2,6-diaminopurine is isolated, but in methanol or ethanol, some 8-methoxy- and 8-ethoxydiaminopurine arises as a secondary product. No comparable 8-alkoxy analogs are found in isopropanol or *tert*-butanol solutions.[1911] Removal of a methyl group at N-7, probably as diazomethane, is observed on isolation of 8-aminotheophylline from reductive fusion (300°C) in air of 8-azidocaffeine.[1405] The bisderivative from azocaffeine (**156**), recovered as a minor product, was previously erroneously identified[429] as a C-8 linked biscaffeine. At a lower temperature (130°C), under anaerobic conditions, a violent rearrangement of **153** to the 7-aminopteridine (**144**) occurs.[1405] Intramolecular ring closure of 7-alkynyl-8-azidotheophyllines produces tricyclic derivatives such as **157** from the 7-propynyl derivative in DMSO. Analogous products are obtained from the 7-alkenyl analogs which contain a reduced form of the annelated pyrimidine moiety.[1892]



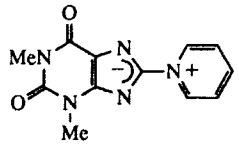
157

D. Trimethylpurinylammonium Chlorides and Related Derivatives (*H*340)

The early indications of the value of the quaternary moieties as leaving groups have now been proven to be correct. Using this approach, replacements not previously achieved with corresponding halogenopurines have been possible. Application of trimethylammonio groups as methylating agents is another novel feature of these compounds.

a. Preparation (H340)

The principal route of reacting 2-, 6-, and 8-halogenopurines with the tertiary amine is elaborated in Chapter V, Sections 5.C.a, 5.C.b, and 5.C.c. Direct con-

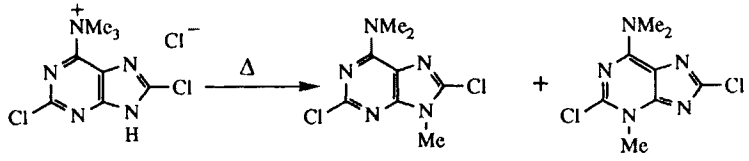


158

version of hypoxanthine derivatives to 6-pyridinio derivatives is made with 5-chlorophenylphosphorodichloridate[1157,1274,1306] in pyridine, as noted in Chapter VI, Section 6.G. Among the less-conventional approaches to 8-pyridiniumpurine formation is replacement of an 8-nitro group using a pyridine–toluenesulfonyl chloride reagent in hot (150°C, 10 h) dimethylformamide.[911] The poor yield (18%) or the product is increased to 53% if the nitropurine is replaced by the 8-chloro analog.[911] Rearrangement of 3-acetoxy derivatives of xanthine and guanine in pyridine gives the betaine forms of 8-pyridiniumxanthine (**158**) and -guanine[1116] (see Chapter XI, Section 3.C). With halogen derivatives having low nucleophilic displacement activity, the conditions required for interaction with trimethylamine produce the dimethylaminopurine, although indications of transient quaternary group formation are found.[1109] The formation of mixtures of trimethylammonio- and dimethylaminopurines encountered[1124,1142] with some halogenopurines is, therefore, not unexpected.

b. Reactions (H340)

The versatility of the trimethylammonio group in nucleophilic displacements has been the subject of kinetic reaction studies using hydroxide[1150,1519] and other ions.[1140] In the purines examined, activities of the quaternary group were up to 1600 times greater than those of a chlorine atom at this position, but some 8 times lower when compared with the methylsulfonyl derivative.[1140] Results from hydroxide ion studies indicate that displacement reactions are bimolecular, with first-order kinetics with respect to the purine and hydroxide ion.[1150] Both 2- and 6-trimethylammoniopurines, either as the betaine form or halide salt, successfully react with ammonium hydroxide,[1150] *n*-propylamine,[1140] sodium ethoxide,[1140] benzyloxide,[1270] and cyanide[1140] and with hydrazine hydrate[1140] forming the respective amino- propylamino-, ethoxy-, benzyloxy-, cyano-, and hydrazinopurines. A significant application is to the preparation of fluoropurines using potassium fluoride or hydrogenfluoride; this topic is detailed in Chapter V, Section 1.G.b. Fewer, but similar, reactions are noted with quaternary pyridinium derivatives, for example, conversion of 8-pyridino- to 8-aminoxanthine[1116] and interaction of 9-methyl-6-pyridiniopurine with both sodium azide and sodium methoxide giving the respective 6-azido- and 6-methoxypurine[1274] in 90% yields. The tendency of trimethylammonio groups to undergo the Hofmann–Martius degradation to a dimethylamino group is well established[1140,1147,1150] (*H*340). Loss of the methyl group, as a cation, provides an efficient methylating agent, as shown by transformation of 6-trimethylammo-



159 **160** **161**

niopurines into mainly 9-methyl- and, in some cases, 3-methyl-6-dimethylaminopurines. Exemplifying this is the thermal rearrangement of the quaternized 2,8-dichloropurine (**159**) to a mixture of 9- (**160**) and 3-methyl-6-dimethylamino (**161**) derivatives.[1147] By carrying out this rearrangement in the presence of a 6-dimethylaminopurine, unsubstituted at N-9, the subsequent isolation of a 9-methylated homolog of the latter demonstrates the intermolecular nature of these methylations.[1147] It is noteworthy that the formation of both 3- and 9-alkylpurines follows the same alkylation pattern as is obtained under alkaline conditions. (see Section 8.A.b). The occurrence of any further reaction with trimethylamine during hydrolysis of 2-amino-9-ethyl-6-trimethylammoniopurinium chloride to 9-ethylguanine in dichloromethane containing DBU is obviated by incorporation of 3-hydroxypropionitrile as a trapping agent[1937] for methyl ions. The preparation of other 9-substituted guanines by this route is reported.[1937]

8. THE NUCLEAR *N*-ALKYLATED AMINOPURINES (*H*340)

The significance of these compounds is mainly their relevance to ongoing studies on biological alkylation of nucleic acid bases. Derivatives of adenine and guanine continue therefore to be the main foci of interest. Anodic peak potentials from voltametric measurements with 7- and 9-alkylated adenines in dimethylformamide or acetonitrile can be used to distinguish between the 7- and 9-alkyl isomers, the former derivatives exhibiting the lower peak potentials.[1545] Magnetic resonance spectra can similarly be applied for diagnostic purposes. The C-8 signal for a 9-alkyladenine in ^{1}H NMR is upfield of that of the isomeric 7-alkyl analog and in the same way a corresponding upfield shift in the C-8 resonance is observed in the ^{13}C spectrum of the 9-substituted purine.[1971] Identification of the two isomeric *N*-alkylated purines is also possible employing ^{15}N spectra in which the greater deshielding is shown by the nitrogen of a 9- rather than a 7-alkylated derivative.[1972]

A. Preparation (*H*341)

Synthesis in most cases provides an unambiguous route to the *N*-alkylated purine, whereas the direct *N*-alkylation approach carries the risk of mixed products being obtained. Some degree of control of the site of ring nitrogen alkylation has been achieved of late through prior modification of the amino groups, usual-

ly by acylation or alkoxylation, or by choosing a particular reagent or the conditions employed. The synthetic route is not without drawbacks; apart from the nonavailability of some suitable precursors, there is the danger of rearrangements of existing *N*-alkyl groups during purine formation, a notable example being the Dimroth reaction (Section 5.G.b).

a. By Direct Synthesis (H341)

Use of the Traube synthesis makes available the range of 1-, 3-, 7-, and 9-alkyladenines and -guanines, examples of which occur throughout Chapter II. Increased use of alternative routes from imidazoles has provided adenines such as the 3-methyl-,[977] 3,9-dimethyl-,[974] 7,8-dimethyl-,[991] 3,9-diethyl-, 9-ethyl-3-methyl-[974] 9-cyclohexyl-,[971] and other derivatives.[977] Employing similar reagents for cyclizations affords 3-methyl, 3,9-dimethyl-,[969] 3,9-diethyl,-[969] 3-ethyl-9-methyl-,[969] 9-ethyl-3-methyl,[969] 9-benzyl-3-methyl-,[969] and 9-(3-hydroxypropoxy)guanine.[1209] Similarly formed are the 3,9-[964,997] and 7,8-dimethylisoguanines.[991] Further examples of syntheses of adenines and guanines are found in Chapter III.

b. By Alkylation (H342)

Present knowledge of the orientation of alkylation of adenine over the pH range can be summarized by the statement that formation of the 9-alkyl derivative, together with smaller amounts of the 3-alkyl isomer, is expected under alkaline conditions.[1523] In neutral media the same two isomers arise, but in this case the 3-alkylated derivative is now the major component.[1525] Results of studies with a variety of alkylating agents on the unionized molecule suggest that only small differences exist between the N-3 and N-9 isomer yields.[1525] Conclusions from alkylation studies in acid solution are less clear cut; in many cases the expected 3-alkyl derivative is obtained, but quite often the product is the 9-alkyl isomer, arising from an acid-induced N-3 to N-9 alkyl group rearrangement. Examples illustrating these different reaction modes are given in Tables 7 and 8 for adenine and in Table 9 for guanine.

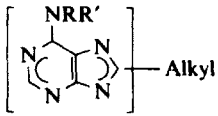
Earlier alkylation studies in alkaline media (DMF, K_2CO_3) indicated that short heating (< 110°C, 0.25–2.0 h) favors formation of 9-alkyladenines but extending the reaction time gives poly-*N*-alkylated products.[1522] Detailed investigations made subsequently with sodium adenide in dimethylformamide identify various factors participating in the reaction and influencing the site of *N*-alkylation. Among the most significant are the solvent medium, type of base, reactant concentration, and structural nature of the alkylating reagent. The overall preference for N-9 and to a lesser degree N-3 is rationalized as resulting from the existence of the most favorable S_N2 transitional states coupled with steric hindrance between the 6-amino group and the N-1 and N-7 positions.[1523] From a practical standpoint, optimization of 9-alkylpurine formation is achieved with the introduction of phase-transfer catalysis, details of which are noted below.

TABLE 7. Alkylation of Adenine Under Phase-Transfer Catalysis Conditions

Alkylating Agent	Base Catalyst	Solvent	Reaction Temperature	Alkylated Products 9-(%)	3-(%)	Ref.
Me_2SO_4	Bu_4NF	THF	20	84	15	1294
	Bu_4NOH	THF	20	57	31	1294
	Bu_4NBr, KOH	None[a]	80	47		1359
MeBr	NaOH Bu_4NOH	C_6H_6	Reflux	50		1295
	Bu_4NF	CH_2Cl_2	25	95		1293
MeI	Bu_4NOH or NaOH	CH_2Cl_2	20	90		1295
n-$C_8H_{17}Br$	KOH Aliquat 336	None[a]	80	52		1359
CH_2:$CHCH_2Br$	KOH Aliquat 336	None[a]	20	46	27	1688
$(MeO)_3PO$	Bu_4NF	CH_2Cl_2	25	80	20	1293
Et_2SO_4	Bu_4NF	THF	20	79	20	1294
$PhCH_2Cl$	Bu_4NOH or NaOH	CH_2Cl_2	80	75	Trace	1295
	Bu_4NOH	CH_2Cl_2	25	93		1293
	NaOH, H_2O	C_6H_6 or C_6H_{12}	Reflux	75	25	1521
$PhCH_2Br$	KOH, Aliquat 336	None[a]	25–80	54	10	1688
o-$FC_6H_4CH_2Cl$	Aliquat 336	Me_2CO	Reflux	85	15	1524
$C_{10}H_{15}COCH_2Br$[b]	Bu_4NBr	CH_2Cl_2 NaOH		98		1983
$PhCO_2(CH_2)_2OCH_2Cl$[c]	Bu_4NF	THF	Reflux	85		1914

[a]Solid–liquid PTC.
[b]Adamantyl-1-bromomethylketone.
[c]Bistrimethylsilyl derivative.

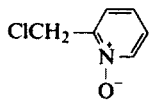
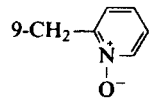
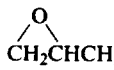
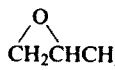
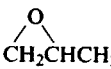
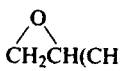
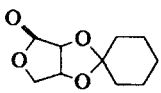
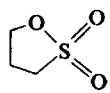
TABLE 8. Examples of Approaches Used for *N*-Alkylation of Adenines[a]

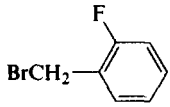
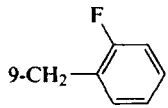
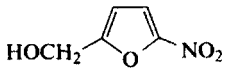
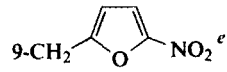
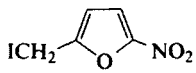
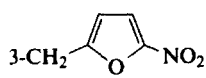
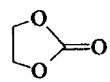
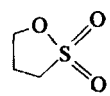
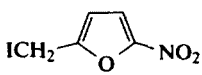
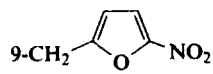


Purine	Alkylating Agent	Medium, Catalyst	Product(s)	Ref.
Alkaline Conditions				
R = R′ = H	$Cl(CH_2)_2Ph$	DMA, K_2CO_3	9-$(CH_2)_2Ph$	1522
	$ClCH_2CH$: $CHCH_2Cl$	DMF, NaH	9-CH_2CH:CH_2Cl	1540

(cont.)

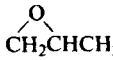
TABLE 8. *(cont.)*

Purine	Alkylating Agent	Medium, Catalyst	Product(s)	Ref.
	$BrCH_2C{:}CCH_2OR_z^b$	DMF, NaH	9-$CH_2C{:}CCH_2OR_z$	1538
	ClCH(OEt)Me	DMF, NEt_3	9-CH(Me)OEt	1984
	$BrCH_2CH(OEt)_2$	DMF, NaH	9-$CH_2CH(OEt)_2$	1201
	ICH_2CO_2H	H_2O, KOH	9-CH_2CH_2OH (22%) 3-isomer (8%)	1238
	$BrCH(CO_2Et)_2$	DMF, NaOH	9-$CH(CO_2Et)_2$	1529,1733
	$Br(CH_2)_4CO_2Et$	DMA, K_2CO_3	9-$(CH_2)_4CO_2Et$ (56%)	1470
	$ClCH_2OCOCMe_3$	Na salt, DMSO	9-$CH_2OCOCMe_3$ (81%) 3-isomer (12%)	1526
		Na salt, DMA	9-  (40%) 3-isomer (20%)	1285
		Na salt, DMF	9-$CH_2CH(OH)CH_2Me$	1578
		DMF, NaH	9-$CH_2CH(OH)CH_2OH$ (34%) 3-isomer (11%)	1535
		Na salt, DMF	9-$CH_2CH(OH)CH_2Cl$ (25%)	1139
		DMF, NaH	9-$CH_2CH(CH_2)_2OR_z$ OH	1258
		Na salt, DMF	7-$CH_2CHCHCO_2H$ OHOH	1578
		DMF, NaH	9-$CH_2CH_2CO_2H$	1529
		DMF, KOH	9-CH_2CH_2OH	1201
		DMF, NaH	9-$(CH_2)_3SO_3^-$	1474
	$CH_2{:}CHCO_2Me$	Pyridine	9-$CH_2CH_2CO_2H$ (11%)[c] 3-isomer (22%)	1733
	$ClC(NMe_2){:}NOCAr$	DMF, NEt_3	9-$C(NMe_2){:}NOCAr$ (72%)[d]	1987
	$HC{:}CCHO$	DMF, NaOMe	9-CH:CH–CHO[e]	1533

	$HC{:}CCO_2Et$	DMF, NaOMe	9-CH:CHCO$_2$Et[c]	1533
R = H, R′ = Me		Na salt, Me_2CO Aliquat 336	 3-isomer (ratio 85:15)	1146
R = R′ = Et	$BrCH_2Ph$	DMA, K_2CO_3	9-CH_2Ph (> 55%) 3-CH_2Ph (trace)	1995
R = H, R′ = Ph	Me_4NOH	160°C, 0.1 mm	9-Me (40%)	875
R = H, R′ = MeCO	$ClCH_2COMe$	DMF, K_2CO_3	9-CH_2COMe	1237
R = H, R′ = PhCO		DMF, NaH $(PhO)_3MePI$	 [e]	1448
R = H, R′ = Me_3CCO	$ClCH_2Ph$	Na salt, DMF	9-CH_2Ph (84%) 7-isomer (10%)	1437
	$Cl(CH_2)_2CMe_3$	Na salt, DMF	9-$(CH_2)_2CMe_3$ (93%) 7-isomer (7%)	1437
	$ClCH_2OCCMe_3$	Na salt, DMF	9-CH_2OCCMe_3 (85%) 7-isomer (15%)	1437
Neutral Conditions				
R = R′ = H	$BrCH_2Ph$	DMF	3-CH_2Ph 9-isomer (ratio 7.6:1)	1525
		DMF		1448
	Me_3EtPO	DMF	3-Me	1292
	$ClCH_2OCH(CH_2OR_7)_2$[b]	$Hg(CN)_2$, C_6H_6	9-$CH_2OCH(CH_2OR_7)_2$[f]	1127
		DMF	3- and 9-CH_2CH_2OH	1264
		DMF	3-$(CH_2)_3SO_3$	1474
	$MeCH(OH)CO_2Et$	DEAD, PhP_3	9-CH(Me)CO$_2$Et[c]	1859
R = H, R′ = CH_2Ph	$Me_2\overset{+}{S}(O)\bar{C}H_2$	THF	9-Me (63%)	1876
R = H R′ = MeCO	$BrCH_2Ph$	DMF	3-CH_2Ph (55%)[g] 9-isomer (29%)	811
R = H, R′ = PhCO		DMF	 3-isomer (minor prod.)[g]	1448
	$BrCH_2Ph$	DMF	3-CH_2Ph (49%) 9-isomer (19%)	811
R = R′ = Et	$BrCH_2Ph$	DMA	3-CH_2Ph (> 75%)	1995

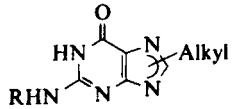
(*cont.*)

TABLE 8. *(cont.)*

Purine	Alkylating Agent	Medium, Catalyst	Product(s)	Ref.
Acid Conditions				
R = R′ = H	*i*-Pr_2SO_4	HCO_2H	3-*i*Pr 9-isomer (1:1)	1527
	$BrCH_2CH(OEt)_2$	$MeCO_2H$	9-$CH_2CH(OEt)_2$	1201
		$MeCO_2H$	3-$CH_2CH(OH)Me$	1528
		$MeCO_2H$	3-$CH_2CH(OH)CH_2Cl$ 9-isomer (5:1)	1139
	CH_2:$CHCO_2Me$	H_2SO_4, $MeCO_2H$ $Hg(CO_2Me)_2$	9-CH:CH_2 (2%)	1215
R = H, R′ = PhCO	CH_2:$CHCO_2Me$	H_2SO_4, $MeCO_2H$ $Hg(CO_2Me)$	9-CH:CH_2 (65%)	1215

[a] Examples employing phase transfer catalysis are given in Table 7.
[b] $R_z = CH_2Ph$.
[c] Michael reaction.
[d] $Ar = C_6H_4NO_2(p)$.
[e] Mitsunobu reaction.
[f] Bisdimethylsilyl derivative.
[g] Only the 9-isomer is obtained at higher temperatures.

TABLE 9. Examples of 7- and 9-Alkylation of Guanines



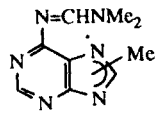
R′ = CH_2Ph, R″ = COMe, R‴ = S(:O)(Me):$NCOCF_3$

Purine	Alkylating Agent	Medium, Catalyst	Product(s)	Ref.
Alkaline Conditions				
R = MeCO	$ClCH_2CH$:$CHCH_2Cl$	DMF, NEt_3	7-CH_2CH:$CHCH_2Cl$, (8%) 9-isomer 29%	1540
	$ClCH_2COMe$	DMF, K_2CO_3	9-CH_2COMe (30%) 1-CH_2COMe (40%)	1237
R = CF_3CO	CH:CCHO	DMF,[a] NEt_3	9-CH:CHCHO (14%)	1533
Neutral Conditions				
R = H	Me_2SO_4	Bu_4NF	7-Me (23%) 9-Me (13%)	1294
6-*O*-benzyl, R = H	R‴$(CH_2)_nOH$	THF, DEAD,[b] PPh_3	9-$(CH_2)_nR'''$ (66%)	1912

R = MeCO	$BrCH_2Ph$	DMA	7-CH_2Ph (22%) 9-CH_2Ph (16%)	826
6-*O*-$SiMe_3$,[c] R = $SiMe_3$	$ClCH_2O(CH_2)_2Cl$	THF, Bu_4NF	9-$CH_2O(CH_2)_2Cl$ 50% 9-$CH_2O(CH_2)_2OH$ (50%)	1914
	$ClCH_2OCH$ $(CH_2OR')_2$	THF, Bu_4NF	9-$CH_2OCH(CH_2OR')_2$ (> 80%)	1914
Acid Conditions				
R = COMe	R″OCH_2OCH $(CH_2OR')_2$	Sulfolane, MeC_6H_4 SO_3H	9-$CH_2OCH(CH_2OR')_2$ (+some 7-isomer)	1262
	R″OCH_2OCH (OR″)CH_2OR″	$EtSO_3H$ Fusion	7-CH_2OCH(OR″) CH_2OR″ 9-CH_2CH(OR″) CH_2OR″[d]	1260
6-*O*-$SiMe_3$, R = $SiMe_3$	$ClCH_2OCH_2CH$ (OR′)CH_2OR'	Me_3SiCl, NEt_3	9-CH_2OCH_2CH(OR′) CH_2OR″	1260
R = COMe	R″OCH_2SCH $(CH_2OR')_2$	Sulfolane, $(p\text{-}O_2NC_6H_4)_2HPO_4$	9-$CH_2SCH(CH_2OR')_2$	1261

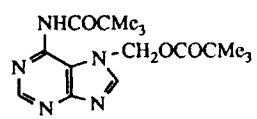
[a] Michael reaction.
[b] Mitsunobu dehydration.
[c] Tristrimethylsilyl derivative.
[d] Racemic product.
[e] (*R*)-form only.

Although innovations in alkylating procedures have appeared from time to time, the introduction of new alkylating agents is rare. Recently, more extensive application of alkyl phosphoric esters for this purpose is documented; these reagents show activity in the order phosphate > phosphonate > phosphinate.[1292] Successful use of dimethylformamide acetals is reported with some purines, but in the case of adenine the products are the 7- (4%) and 9-methyl (17%) derivatives (**162**) of the azamethine[1087] form of the purine. The latter reagents appear to be specific for alkylations in the imidazole ring. Possibly one of the most significant recent advances is the Mitsunobu reaction,[1907] which utilizes compounds with hydroxyl groups as alkylating agents. Adenine and the alkanol in THF containing triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) react by elimination of water, giving a 9-alkyladenine.[1859] Comparable in importance for alkylations is the introduction of liquid–liquid and solid–liquid phase transfer catalysis (PTC). This procedure favors maximization of the yield of the 9-isomer.



162

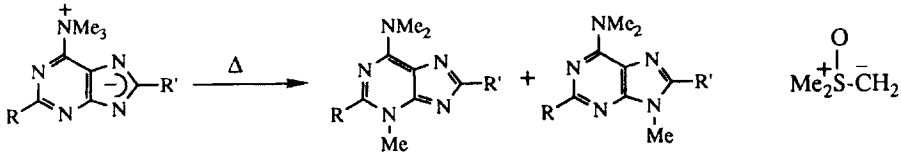
The alkali catalysts employed are usually sodium hydroxide[1295,1521] or tetra-*n*-butylammonium hydroxide;[1293-1295] both hydroxides are equally effective. Other catalysts include tetra-*n*-butylammonium fluoride,[1293,1294] benzyltriethylammonium chloride, and mixtures of high molecular weight trialkylmethylammonium chlorides, for example, Aliquat 336[1521] and Adogen 440.[1521] In these reactions the tetrabutylammonium bromide, having the largest of the halogen ions, is ineffective.[1294] Suitable organic solvents, such as dichloromethane, benzene, hexane, isoctane, and tetrahydrofuran, among others, provide the nonaqueous phase. A variation employing a solid–liquid phase reaction uses potassium hydroxide with tetra-*n*-butylammonium bromide in the absence of the organic liquid phase.[1359] The activity of the alkylating agent is significant in determining the 9- to 3-alkyl isomer ratio. With a low-activity reagent, only the 9-alkylpurine may result. Adenine and the highly reactive allyl bromide gives the 6-allylamino- and 6-diallylamino-9-allylpurines in addition to the expected 3- and 9-alkyladenine. In addition to those noted above, another infrequent example of direct amino group alkylation is provided by an adaptation of this procedure[1688] (Section 5.G.a). No evidence of any alkylation at N-7 is apparent.[1688] Similar product yields are obtained from alkylation in dry acetone containing a tetraalkylammonium salt and the alkylating agent.[1524] Representative PTC illustrations are given in Table 7. The range of alkaline alkylation studies extends to reactions of different alkylating agents with the sodium, potassium, and lithium salts of adenine in dimethyl sulfoxide. Using ^{1}H NMR monitoring, no significant variation in alkylation patterns is observed, the 9-alkylated adenine forming the major component. No disturbance of the overall picture appears on varying the concentration of the reagents. Solvent influences are important in view of the ionic character of the reactions, in dipolar aprotic media (DMF, DMSO), these effects play a minimal part, but with a protic solvent such as formamide, the yield of the 3-alkylpurine is enhanced at the expense of the 9-alkyl isomer.[1526] The alteration in the alkylation patterns of adenines containing an acylated amino group has only recently been investigated.[1437] In alkaline solution (NaH, DMF), the product is a mixture of 7- and 9-alkylpurines in which the 9-isomer either predominates or is the only product isolated.[1237,1448] Exceptions are found with 6-acylaminopurines on reaction with chloromethyl pivalate ($Me_3CCO_2CH_2Cl$), the major isomer is the 7-alkylpurine. An extreme example is the 6-pivaloylaminopurine (**163**) formed in a 40:1 ratio with the 9-alkylated isomer.[1437] In view of the apparent steric hindrance at N-7 produced by the acylamino moiety, these results are somewhat of an anomaly. One proposal claims hydrogen bonding between the NH of the acylamino group, and the carbonyl group of the alkylating agent acts as a directing influence



163

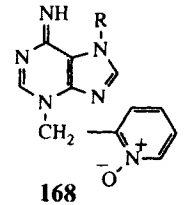
toward this particular ring nitrogen. The overriding preference in these examples for N-7 rather than N-9, however, suggests that factors as yet unappreciated may operate in such reactions.[1437] Other enahncements of alkylation following modification of the amino group are noted by comparing the respective yields of the 9-vinyl derivatives from adenine (2%) and 6-benzamidopurine (65%) on treating them with vinyl acetate[1215] and by the failure of 2,6-diaminopurine to react with an alkoxymethyl chloride (DMF, Et_3N), but to form a 9-alkoxymethylpurine (55%) on using the 2,6-bisacetamidopurine.[1127]

Further examinations of alkylation of 6-aminopurines in neutral media[1525] include a benzylation of 6-dimethylaminopurine in dimethylacetamide (110°C, 7 h), with yields of the 3-benzyl (66%) and 9-benzyl (5%) isomers of the same order as claimed for an earlier similar alkylation of this purine (*H*343). Methylation (MeI) gives analogous results with 6-alkylamino-[1532] and 6-dialkylaminopurines.[1164] Note also that 2,8-diaminopurine and the 6-methyl homolog are readily converted (MeI, DMF) to the respective 1,7,9-trimethylpurine diiodides.[903] Thermal rearrangement of 6-trimethylammoniopurines (**164**) affords a novel route to a mixture of 3- (**165**) and 9-methyl-6-dimethylaminopurines[1147] (**166**). Dimethyloxosulfonium methylide (**167**) will react with acid protons of amino or hydroxy groups. In THF and the ylid in excess (3 mol. equiv.), 6-benzylaminopurine is alkylated to the 9-methyl derivative in moderate yield (63%). Some 9-ethyladenine (10%) also results from a methylide rearrangement before alkylation occurs.[1876]



164 **165** **166** **167**

No change in alkylation patterns is found in neutral media following acylation or aroylation of the 6-amino group; both 6-acetamido- and 6-benzamidopurine with benzyl halides in dimethylformamide form mixtures of 3- and 9-benzyl derivatives[811] as reported (*H*343). At working temperatures above 100°C, an N-3 to N-9 benzyl rearrangement occurs, leaving the 9-benzyladenine as sole product[811] (see Section 5.D.f). The latter transformations are a feature of the acylated and arylated purines only and are not shown by the corresponding adenine derivatives. A further effect of the amido group is apparent on further alkylation of a 9-alkylpurine when the product is a salt of a 7,9-dialkyl derivative. Examples so formed include the iodides of 9-benzyl-7-methyl-, 9-benzyl-7-ethyl-, and 9-ethyl-7-methyl-6-benzamidopurine.[1426] Note that 6-methoxyamino-9-methylpurine with methyl iodide under similar conditions gives the corresponding 7,9-dimethylpurine iodides[1460] (Section 7.B.c). A novel route to 7-alkyladenines entails prior treatment of adenine with 1-oxypyridin-2-ylmethyl chloride and separation of the predominant (40%) 3-alkylated product (**168**, R = H) from the

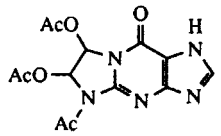


168

lesser (20%) 9-isomer. Further alkylation is possible at another position and removal of the picolyl protecting group is then effected with cold acetic acid.[1285] Prior location of removable blocking groups at N-9 of adenines is usually employed to direct alkylation to N-1. Some examples of these are 9-ribosyl groups[842,1474] and 9-ethoxyethyl[842] groups; both are readily removed in hot acetic acid. Alkaline conditions (aq. NaOH) are used to displace 9-pivaloyloxymethyl protecting groups.[1464] A more esoteric example incorporates a proton scavenger, 1,8-bisdimethylaminonaphthalene (proton sponge®), in converting adenosine to the 1-alkyl homolog[1474] (77%). Results of alkylations made under acid conditions are less frequently encountered; usually both 3- and 9-alkyl derivatives are the major products, with the former predominant.[1525] The occurrence of insignificant amounts of the 1- and 7-alkyl isomers is reported. Ethylation of adenine with ethyl methanesulfonate in formic acid (< 50°C, 4 days) affords 9- and 3-ethylated purines, the possibility of an N-3 to N-9 alkyl group rearrangement would explain the greater yield of 9-ethyladenine in this case.[1527] Similar results are recorded with isopropyl methanesulfonate.[1527] Acid-catalyzed reactions with epoxide reagents give mixtures containing either a 3-[1528] or 9-[1139,1201] hydroxyalkyladenine as the principal product. In the presence of tetrakis(triisopropylphosphite)palladium {[(*i*-PrO)$_3$P]$_4$Pd} catalyst adenine and a 3,4-epoxycyclohexene react, forming the 9-(2-hydroxy-5-cyclohexenyl)purine in 90% yield.[1986] Surprisingly, no comparable formation of *N*-aminoethylpurines takes place with ethyleneimine, even though related heterocycles react as expected with this reagent.[1530] Insolubility effects have been proposed to explain this anomalous behavior. Current alkylation approaches are given in Table 8.

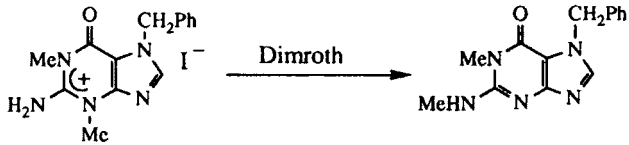
Owing to the poor solubility shown by guanine and certain derivatives in some solvents, inhibition of direct alkylation may be encountered. Low yields of 7- (23%) and 9-methylguanine (13%) occur with dimethyl sulfate and a tetrabutylammonium fluoride or -hydroxide catalyst.[1294] The reaction is specific both for the type and amount of catalyst present. The use of alkyl halides or trialkyl orthoesters in chlorinated solvents with these catalysts is unsuccessful, but under these conditions insolubility effects may be significant[1293] factors. Enhancement of solubility results from acylation of the 2-amino group. In addition to acetic anhydride, the range of other reagents used includes trifluoroacetic anhydride[1533] and palmitoyl chloride.[1477] Unlike adenine derivatives, the acylated forms show the same alkylation patterns as the parent purines. Benzylation of the 2-acetamido derivative of guanine in dimethylformamide (90°C, 7 h) gives the 7- (22%) and 9-benzyl (16%) derivatives combined with trace amounts of the 3-benzyl isomer.

The latter may be a residual initial alkylation product since N-3 to N-9 benzyl group rearrangements are established reactions.[826] Results of spectral studies by a number of groups have been applied to the question of whether N-7 or N-9 is the preferred site of alkylation.[1262,1797,1798] The use of alkanols as alkylating agents, introduced by the Mitsunobu reaction (diethyl azodicarboxylate and triphenylphosphine in THF), with the 6-benzyloxy analog of guanine give specifically 9-alkylated products in good yields (> 60%). Debenzylation to the 9-alkylguanine is by hydrogenation.[1912] The acetylated glyoxal adduct (**169**) allows an alternative regioselective alkylation of guanine to be made. In dimethylformamide containing a base, formation of the N-7 isomer is favored. With sodium hydride, the 7-



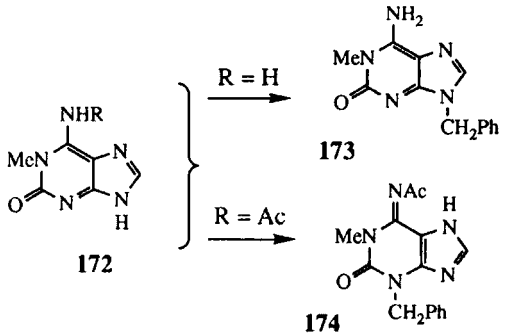
169

alkylpurine is the only product[1491] and removal of the adduct moiety is achieved using aqueous alkali. A new approach to 9-alkylated derivatives utilizes acetylation and treatment with *N,N*-diphenylcarbamoyl chloride (Ph_2NCOCl). The resulting 6-*O*-(*N,N*-diphenylcarbamoyl)purine with haloethers gives only 9-alkoxyalkylguanine derivatives.[1913] Likewise effective with related haloethers is use of tristrimethylsilylated guanine in THF with a tetrabutylammonium fluoride catalyst, which affords high yields (> 90%) of 9-substituted guanines.[1914] Acylation of 3-alkylguanines facilitates alkylation; this reaction as with the parent purine is influenced by solubility and electronic factors. While benzyl bromide in dimethylformamide (60°C, 24 h) converts 3-methylguanine to the 7-benzyl homolog, the corresponding reaction with benzyl chloride is only possible following acetylation of the amino group.[1477] Further methylation (MeI) in aqueous alkali gives initially the iodide of the 7-benzyl-1,3-dimethyl derivative (**170**), from which the final product (**171**) is the result of a Dimroth rearrangement.[1477]

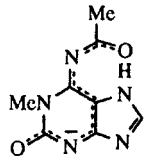


170 **171**

Isomeric aminooxopurines undergoing related reactions include methylation (MeI) at N-7 of 2-amino-7,8-dihydro-8-oxopurine in dimethylformamide[903] and benzylation ($PhCH_2Cl$) in dimethyl sulfoxide (20°C, 18 h) of the sodium salt of 1-methylisoguanine (**172**, R = H), giving 9-benzylated purine (**173**). Use of the acetylated starting material (**172**, R = MeCO) as precursor directs benzylation to N-3 (**174**) instead. The change in alkylation site from N-9 to N-3 may reflect hydrogen bonding between N-7 and the acyl group oxygen, promoting formation



172 173 174



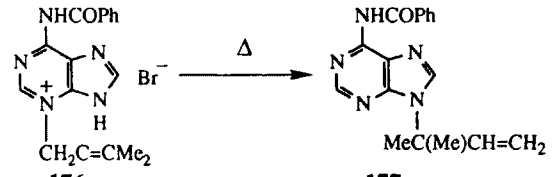
175

of a stabilized N-3 anion (**175**), which possesses a frozen 6-imino group.[1534] The formation of *N*-carboxylic acid derivatives by alkylation is described elsewhere (Chapter IX, Section 8.A). Table 9 details topical reagents and approaches for alkylation of guanine derivatives.

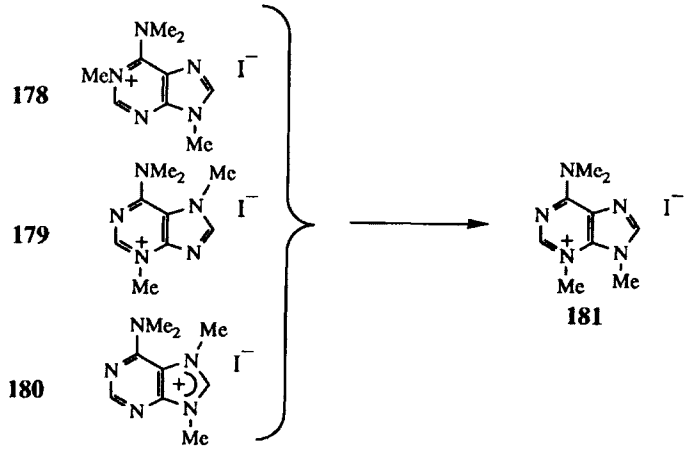
B. Reactions (*H*348)

A variety of reagents and techniques is now available for removal of ring *N*-alkyl groups which have practical value for elimination of blocking substituents. In adenines, an 1-oxy-2-picolyl group is displaced from N-3, but not N-9, by acetic anhydride.[1285] Concentrated sulfuric acid (96%) will similarly debenzylate 3-benzyladenine (60°C, 8 h), but leaves the 9-benzyl isomer unchanged.[1524] The latter reaction can be adapted to isolate 9-benzyladenine from mixed benzylation products.[1524] More scope is provided by photolytic (254 nm) procedures which remove *N*-benzyl or *N*-(*m*-substituted-benzyl) groups from the 1-, 3-, 7-, and 9-nitrogens in adenines and also from the isomeric 6-benzylaminopurines. Irradiation of saturated aqueous solutions of the 3,5-dimethoxybenzyl analogs is claimed to give quantitative yields of debenzylated adenines. Use of the 4-nitrobenzyl group to block N-3 of adenine is employed by the same workers to allow specific alkylation at N-7. Removal of the protecting group as 4-aminobenzyl alcohol is by reduction with aqueous sodium dithionite[1909] (40°C, 24 h). An illustration of the facile removal of alkyl moieties from charged species is conversion of 7,9-dimethylguanine, as the perchlorate salt, into 7-methylguanine with boiling water.[1460] Under milder conditions (70°C, 4 h), 7-methylguanosine is quantitatively demethylated to guanosine using a 50-fold excess of lithium 2-

methylpropan-2-thiolate in hexamethylphosphoramide.[1541] Thermal rearrangements are characteristic of *N*-alkyladenines and -guanines, one of which, the classic Dimroth reaction, is detailed in Section 5.G.b. With mild heating in dimethylformamide (100°C, 41 h), 3-benzyladenine, as a chloride, bromide, or toluenesulfonate salt, appears unchanged,[1525] but an intramolecular rearrangement to 6-benzylaminopurine occurs using autoclave conditions. Fission and reformation of both rings is indicated by ^{15}N labeling studies.[1464] Thermally induced alkyl migration in 6-acylaminopurines is noted in Section 5.D.f) but conversion of the 3-(3-methylbut-2-enyl)adenine (**176**) in dimethylformamide containing mercury(II) bromide (110°C, 30 h) into the prototropic 9-(1,1-dimethylprop-2-enyl) analog (**177**)[811] exemplifies both positional and group isomerization. A series of interconnected rearrangements has been identified from isolation of 3,9-dimethyl-6-dimethylaminopurinium iodide (**181**) on strong heating (220°C) of 1,9- (**178**), 3,7- (**179**), or 7,9-dimethyl-6-dimethylaminopurinium iodide (**180**).[1536] At a reduced temperature (180°C), **180** isomerizes to the 3,7-dimethyl analog (**179**).[1164] Steric rather than electronic factors are presumed responsible for corresponding reactions with analogous 6-methylaminopurines giving 7- rather, than 9-methylated end products. Transformation of the 7,9-dimethyl-6-methylaminopurinium iodide occurs thermally to a highly stable 3,7-dimethyl analog which resists further change. The same purine also results from the 1,9-dimethyl derivative.[1532] The alkali-unstable nature of 3,9-dialkyladenines is shown by the ready degradation to 5-amino-4-formamidinoimidazoles of 3,9-

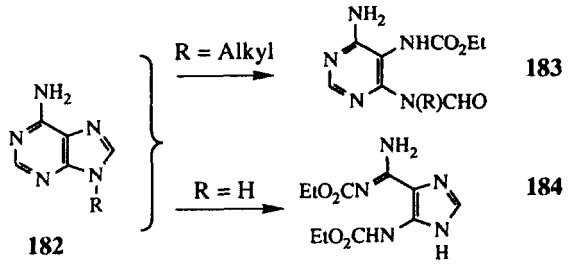


176 **177**



181

dimethyladenine[975] and the 6-diethylamino[1542] analog. With 3-methyladenosine alkaline, cleavage of the ribosyl moiety rather than ring fission occurs.[977] Under acid conditions (pH 4.5), 9-alkyladenines (**182**, R = alkyl) are usually stable, but if diethylpyrocarbonate is also present, they undergo imidazole ring fission, forming 4-alkylamino-6-amino-5-ethoxycarbonylaminopyrimidines (**183**, R = alkyl). This behavior contrasts with that of adenine (**182**, R = H) and other 6-unsubstituted aminopurines which afford imidazole derivatives (**184**) by the alternative pyrimidine ring opening.[984,985]



No translocation of the alkenyl group from N-9 is found on heating 9-(prop-2-enyl)guanine (162°C, 24 h) in diglyme, but bond isomerization to the 9-(prop-1-enyl) analog results.[1177] Alkaline hydrolysis converts 3-methylguanine to 3-methylxanthine, but the 3,9-dimethyl homolog undergoes slight degradation to a 4-carbamoyl-5-ureidoimidazole.[969] The analogous dimethylisoguanine is stable to alkali.[964,997] Hot dilute hydrochloric acid is required to hydrolyze 3-methylisoguanine to the xanthine analog.[859] Formation of a 2:1 salt–purine complex by 9-methyladenine with methyl mercury perchlorate occurs through bonding to N-1 and the 6-amino group, indicating that a highly acidic proton is associated with the latter group.[1423] Of related significance are 1:1 complexes formed between 9-alkyladenines and butyric and similar acids through hydrogen bonding involving the 6-amino group and either N-1 or N-7. In high-resolution NMR spectra, downfield shifts are shown by protons at these sites.[1418] Bonding of this type is also present in the 1:1 complexes of 9-ethyladenine with 5,5-dialkylbarbituric acids[1569,1573] and various uracil derivatives.[1570] The charge transfer complex obtained from 9-cyclopentyladenine and iodine readily dimerizes through intermolecular hydrogen bonds forming between the amino group and a ring nitrogen.[1421,1422] Cation formation in 1-alkyladenines occurs at N-9 (UV, IR, ^{13}C NMR).[1075] In the solid state, 7-methyladenine, as dihydrochloride, contains protons at N-3 and N-9 (X-ray crystallography).[1565] Further studies showing the effect of substituents at N-3 and N-7 on protonation are reported.[1566] Theoretical considerations based on positional electron densities in the molecule suggest that 9-methyladenine protonates first at N-1 and then at N-7.[1568] Although metal complexation shows some similarities with protonation, the reaction of the 9-methyl derivative in coordinating with transition metal ions initially through N-7 and then at N-1 illustrates the unreliability of parallels being drawn.[1558] Measurement of anodic peak potentials of all monomethylated adenines in dimethylformamide

is documented. In the case of the 7- and 9-methyl derivatives, the values obtained are used to distinguish between the two isomers.[1545]

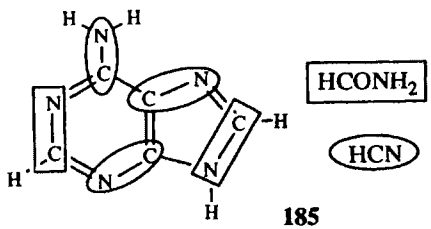
9. NATURALLY OCCURRING AND OTHER SIGNIFICANT AMINOPURINES (*H*350)

Under this general heading both natural and synthetic purines are noted with references, where appropriate, to their syntheses, properties, and importance.

A. Adenine (*H*350)

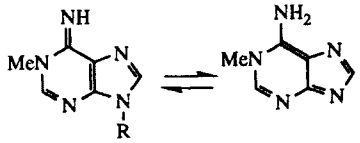
a. Preparations and Properties (H350)

Synthetic approaches include new or improved one-step[1016,1017,1024] reactions. The elucidation of the pathway followed in forming the purine by heating formamide with hydrogen cyanide has been reported.[1013,1015] Mass spectrometry and ^{13}C NMR results show that the molecule is derived from a 2:3 molecular ratio for the amide and hydrogen cyanide[1015] (**185**). A ^{13}C-8 labeled adenine results from a Traube closure of 4,5,6-triaminopyrimidine with ^{13}C-formylmorpholine.[839] Among nucleophilic displacements used are methanolic ammonia with 6-fluoropurine[1122] and the amide ion in liquid ammonia to convert either 6-chloro- or 6-methylthiopurine in quantitative yields.[1155] The same reagent transforms purine directly by means of a Chichibabin reaction involving an anionic σ-addition complex.[1050] Replacement of carbonyl by amino is achieved using hypoxanthine and phosphorodiamidic acid ester.[1307] Exploration of the physical properties is continuing both theoretically and experimentally. A comparison of data from three molecular orbital treatments (extended Hückel, CNDO/2, and CNDO/2D) shows that the last gives the best picture of the general electron dispositions.[1548] Charge-distribution patterns derived from binding energies of molecular core levels, obtained from electron spectra, also show a close resemblance to those given by CNDO/2 results.[1555] Electronic absorption spectra calculations using ab initio multireference configuration interaction (MRCI) and random-phase approximation (RPA) methods for ground-state SCMO indicate the presence of four triplet states.[1899] From similar treatment, triplet-state lifetimes have been

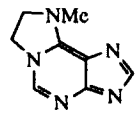


185

determined.[1677] Repeat values obtained for resonance and ionization energies and for heats of formation[1690] are consistent with those given by earlier workers. Tautomerism and protonation sites continue to be topics of interest. Relating to the former is the use of SCMO calculations to show that an amino rather than imino group predominates in all states.[1416] With *N*-alkylated homologs, some variation is possible. The claim that 1-alkyladenines exist mainly as 6-imino tautomers (**186**, R = H) in nonpolar solvents, but revert to the amino form (**187**) in more dielectric media, is supported by UV and ^{1}H NMR evidence showing a predominance of the aminopurines in solution.[842] The presence of the latter tautomers is also a feature of the solid state.[1796] By contrast, with the 3-alkyl analogs, the 6-amino group is the major component in either type of solvent and crystallographic evidence from 3-ethyladenine suggests this is also the case in the solid state.[1567] Reference compounds employed for spectral comparisons of 6-amino and 6-imino derivatives are 1,9-dimethyladenine (**186**, R = Me) and 7,8-dihydro-9-methyl-9*H*-imidazo[2,1-*i*]purine (**188**), respectively.[1475] In the gas phase, the predominant protomer of adenine appears to be the 9H form from its similarity to the spectrum of the 9-methyl rather than the 7-methyl homolog.[1034] Findings from jump relaxation studies in aqueous solution[1549] and ^{13}C spectra in dimethyl sulfoxide[1322] are in accord with those in the gaseous state and show that only a minor (15–20%) amount of the 7-protomer is present in either type of solution. Recent theoretical studies based on semiempirical AMI quantum calculations of the isolated molecule and also in a polarizable dielectric medium, using a self-consistent reactive field approach (SCRF), show the 9H tautomer to be more stable.[1900]



186 **187**

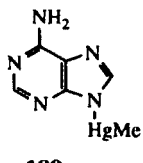


188

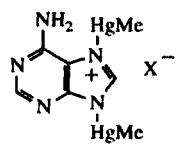
Indications from ^{15}N NMR data are that protonation of adenine in DMSO is mainly at N-1 and to a lesser degree at N-3.[849] Investigations using trifluoroacetic acid alone also show N-1 as the primary site, but with subsequent protonation at N-7 or less likely at N-9.[1038] One earlier result from analysis of the electronic spectrum using an SCFMO–CI approach appears to support N-7 as the primary site.[1572] Crystallographic examination locates the proton at N-1 in the solid state.[1551] A mixture of two or more dications is possible following diprotonation.

Near- equal amounts of the 1,7- and 1,9-diprotonated ions are shown by ^{14}N, ^{2}H quadrupole resonance results with adenine dihydrobromide.[1550] Using protonation energies derived from ab initio STO3G calculations on the localized molecular orbitals, the stability of the dications of adenine are of the order N-1, N-7 > N-3, N-7 > N-1, N-3.[1901] Formation of a 1,7-diprotonated major form is in accord with crystallographic findings for diacid[1552,1902] salt structures. The pK_a (–0.33 to –0.38) for the second protonation has been obtained in dilute H_2SO_4.[2024] Stronger acids (e.g., fluorosulfonic acid, either alone or mixed with antimony pentafluoride) afford a 1,3,7- or 1,3,9-triprotonated purine.[1038] Evidence favoring the former order is provided by laser raman spectroscopy studies which also show that the particular tautomers present are dependent upon the particular nitrogen protonated.[1903] From observation of proton shifts in ^{13}C and $^{14,15}N$ NMR spectra, the same 1,3, and 7 sites of protonation are adduced.[1904] The magnetic susceptibilities and chemical shift tensors calculated using the individual gauge for localized orbitals (IGLO) method are reported by the same worker.[1904] Following benzoylation of the amino group, protonation is shifted from N-1 to N-7.[1457] The labile nature of hydrogen at C-8 is influenced by the prevailing ionic state; the rate-determining factor is hydroxide ion attack on the N-7 protonated purine.[1559] Removal of the 8-H is facilitated if a 9-methyl group is present,[1398] as predicted by SCF–MO calculations.[1553] Lability of this hydrogen is further enhanced by acylation of the 6-amino group.[1458] On treating a solution of adenosine in deuterium oxide with deuterium and platinum(IV) oxide at ambient temperature, replacement of hydrogens at C-2 and C-8 occurs. The more labile 8-^{2}H is lost, however, simply on heating the product in water.[1554]

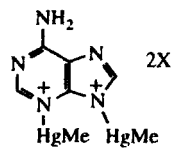
Complex formation may show some similarities with alkylation, alkaline, or neutral conditions favoring bond formation through N-9. Some examples are the products with triphenylphosphine-gold(I) chloride[1353] and methylmercury(II) perchlorate or nitrate.[1556] An increase in reagent ratio converts the latter (**189**) into the 7,9-disubstituted purine[1423] (**190**) and ultimately the 3,7,9-trisubstituted homolog[1556] (**191**). Transition-metal compounds coordinate initially through N-9 with a second bond forming at N-3 with bidentate molecules.[1558] In acid solution N-7 is favored, with an accompanying protonation at N-1. Derivatives of this type are reported with zinc[1571] and rhodium[1561] ions. In aqueous solution, enthalpy determinations suggest that adenine undergoes self-association through hydrogen bonding.[1041] With very dilute solutions containing silver ions, chains containing 1:1 purine–silver complexes are detected by linear dichroism studies.[1560] Interpretations of fragmentation patterns from earlier mass spectra results are



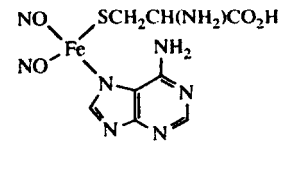
189



190



191



192

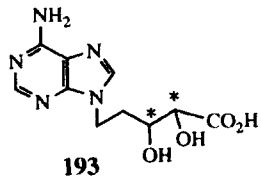
discounted following low-resolution electron ionization spectral examination of degradation products from nine differently labeled isomers.[1562] Over 90% of the initial hydrogen cyanide lost appears to arise from the N-1 to C-2 bond, and not from C-6 to the amino group moiety.[1563] Use of deuteriated adenines has led to erroneous conclusions about the molecular disintegration process.[1564] The significance of hydrogen bonding in rotational behavior of the 6-amino group in adenine and related purines is elaborated elsewhere (Section 4). Formation of fluorescent derivatives by interacting the 6-amino group with chloroacetaldehyde and other difunctional aldehydes has been noted earlier (Section 5.G.c).

Structural features of adenine[1675] and the 1-methyl homolog[1676] have been examined using magnetic circular dichroism. The possibility of metal ion participation in binding nucleic acid bases to amino acids is demonstrated in the proposed ternary complex (**192**) formed between adenine and cysteine by means of iron dicarbonyl.[1686]

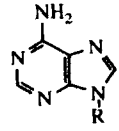
b. Naturally Occurring and Other Notable Adenine Derivatives (New)

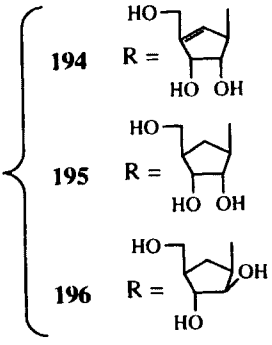
Since the original overview of naturally occurring adenine derivatives appeared in 1970 (*H*352–354), new variants have been isolated and identified and are listed in Table 1, Chapter I.

Eritadenine, first synthesized in 1970[1574,1575,1578] and designated 4-(aden-9-yl)-2(*R*),3(*R*)-dihydroxybutyric acid or 4-(aden-9-yl)-4-deoxy-D-erythronic acid (**193**) is present in *lentinus edodes* together with 2′-deoxyeritadenine and related purines.[1576] Subsequent syntheses involve either alkylation of adenine at N-9,[1575,1578–1580] an approach used for preparing pure D- and L-enantiomers[1581] and for the 3- and 7-isoeritadenine isomers,[1430] or modifications of the Traube synthesis,[1582] as in the formation of the homo and threo analogs.[1236] Numerous eritadenine derivatives have been prepared.[1465,1583,1584] Of the two natural nucleosides, neplanocin—derived from *Actinoplanacea ampullariella*[1585]—and the dihydro homolog aristeromycin—first described 13 years previously[1586] and isolated from *S. citricolor sp.*—the former is a carbocyclic analog of adenosine having a modified ribosyl moiety containing a double bond[1587] and lacking a ring oxygen (**194**)

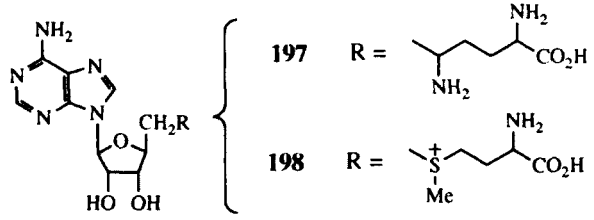


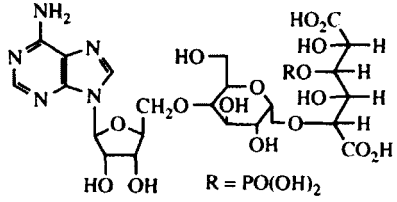
193



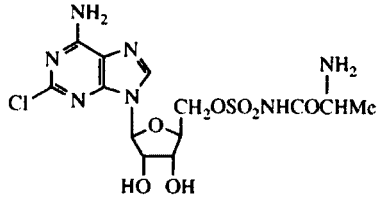


and the latter is the (–)-enantiomer of the reduced form (**195**). Antitumor and antiviral activity is shown by (–)-aristeromycin.[1588] Total syntheses of (+)-aristeromycin[1589] and the three chiral-centered (–)-neplanocin[1590,1591] and related purines[1224] have been achieved. A relationship is shown by these cyclopentane derivatives with the synthetic antiviral agent cyclaridine[1593] (**196**). An appraisal of the synthetic approaches to neplanocin A and associated nucleosides appears in a current review.[1844] A number of adenosine variants obtained from living matter differ in the nature of the substituents attached to C-5 of the ribosyl ring. Sinefungin (**197**), an antiobiotic from *Streptromyces griseolus* shows structural similarities with *S*-adenosyl methionine (**198**) and is notable for having an ornithine residue linked to the sugar through a carbon–carbon[1594] bond. The structure of the naturally occurring insecticide exotoxin (**199**), isolated inter alia by Bond from *Bacillus thuringiensis*, was identified by Sorm and co-workers[1596] as the phosphate ester of the condensation product of adenosine with 2(*R*)-2-*O*-glycosyllallonic acid. Subsequent syntheses[1597] and configurations[1598] are the work of the same school. Ascamycin differs from the nucleosides described above in having a 2-chloroadenosine base possessing an *N*-alaninylsulfamoyl substituent (**200**). Various syntheses[1599–1601] have been published and improved upon recently.[1602] The previously described (*H*353) nucleocidin (**201**) also has a sulfamoyl group at C′-5.[1603] Identification of the component parts of adenomycin, derived from

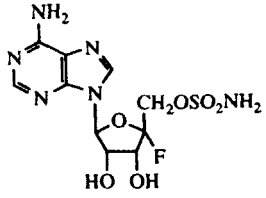




199

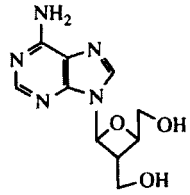


200

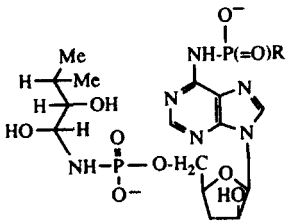


201

Streptomyces griseoflavus, using ^{1}H and ^{13}C NMR show adenosine linked through C′-5 to a complex chain of (–)-chiroinositol, L-gulosamine, and L-serine units.[1604] The recently discovered adenine glycoside oxetanocin (**202**), showing a wide spectrum activity against viral, bacterial, and tumor systems, is unusual in having the oxetanyl moiety at N-9 and is the first of this type to be found naturally. Isolated from a strain of *Bacillus megatherium*,[1846] the structure was established by crystallography[1847] and confirmed by the total synthesis.[1848] Oxetanocin is featured in a topical review on antiviral adenine nucleosides.[1844] A complex 3′-deoxyadenosine derivative, agrocin 84 (**203**), is a metabolite of *Agrobacterium radiobacter* and notable for having both 6-amino and 5′-hydroxy group phosphorylated and in forming a dibasic salt with monovalent metal cations.[1698] Agrocin 84 is effective in horticulture in controlling the formation of fruit tree galls.

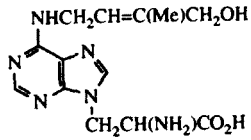


202

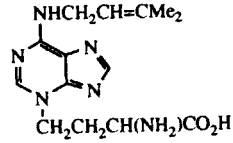


(R = 1-*O*-D-glucofuranoside)

203



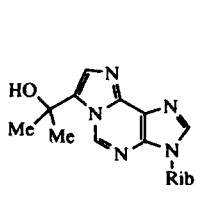
204



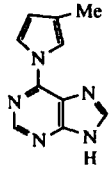
205

Many plant growth regulators, either naturally occurring or synthetic, are 6-substituted aminopurines. Following the discovery of zeatin in 1964, first attempts at synthesis produced mixtures of the biologically active trans (*E*) and the almost inactive cis (*Z*) isomer, the former showing 50 times the growth-promoting effect of the latter.[1204] Preparation of the inactive (*Z*) isomer is reported,[1204] and NMR comparisons of the two isomers show overall similar spectra but significant differences in individual chemical shifts.[1204] Other improved syntheses of both cis[1205] and trans[1205–1207,1605,2020] isomers have followed. Isomerization giving an equilibrium mixture of the corresponding 9-β-D-ribosides occurs upon UV irradiation of the trans riboside.[1606] The principal metabolites of zeatin are the 7- and 9-glucopyranosyl derivatives, the former identical with raphanatin.[986] Earlier assignments of 9-β-D-glucofuranoside structures are now shown by comparative syntheses of both glycosides to be incorrect.[986,1607] A different metabolite, lupinic acid (**204**) containing an alanine residue, is isolated from zeatin-treated rootless lupin seedlings.[1608] Discadenine[1609] (**205**), a spore-germination inhibitor derived

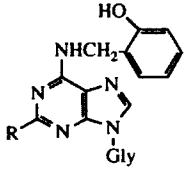
from the cellular slime mold *Dictyostelium discoideum*,[1610] and identified by synthesis[1611] as the L(+)-3-(3-amino-3-carboxypropyl) derivative of 6-(3-methylbut-2-enylamino)purine is related structurally. The latter purine riboside is present in a variety of natural sources, in *t*-RNA as a component of the anticodon loops[1612] and as a triacanthine analog with strong cytokinin activity.[1613] On prolonged aging (> 2 years), conversion occurs to a fluorescent tricyclic derivative of the type (**206**) through oxidative intramolecular cyclization.[1482] This result should be compared with the 6-(3-methylpyrrol-1-yl)purine (**207**) obtained when zeatin is oxidized with pyridine dichromate in acetic acid.[1849] The (–)-dihydrozeatin found in unripe lupin seeds also shows strong cytokinin[1614] activity. Biological aspects of the chemistry[1617] have been reviewed and use of radioactively labeled zeatin has enabled metabolic pathways to be determined.[1615] The first natural phytohormone recognized, kinetin (6-furfurylaminopurine), has long been known not to exist in the plant but to be a DNA artefact arising during thermal isolation procedures. Crystallographic studies have fully established the structure and conformation of kinetic.[1616] The synthetic cytokinin 6-benzylaminopurine (6-BAP, Verdan®) shows comparable growth-regulating activities with those of zeatin and kinetic. Trace amounts are used commercially to extend the shelf life of fresh leaf vegetables. Two related derivatives are the nucleoside of 6-*o*-hydroxybenzylaminopurine (**208**, R = H, Gly = 9-β-D-ribofuranosyl) found in leaves of *Populus robusta*,[1618] and in smaller amounts in the cuckoopint plant *Zantedeschia aethiopica*, which also contains as the major metabolite the related 2-methylthiopurine glycoside (**208**, R = SMe, Gly = 9-β-D-glucofuranosyl).[1619] Monographs and review articles covering general topics,[1620] chemistry,[1621] and structure–activity[1622] aspects of cytokinins are available. Adenine-9-β-D-arabinoside, which shows significant antitumor and antiviral properties, is encountered as ara-A or vidarabine or alternatively as spongoadenosine when isolated from *Streptomyces antibioticus*.[1623] Of relevance to ara-A is conversion to the diazepine nucleoside 2′-deoxycoformycin[1625] (**209**) found naturally in microbial sources as pentostatin.[1626] The enzymatic transformation of the purine nucleoside into deoxycoformycin by *S. antibioticus* has been followed using ^{14}C-labeled samples. Related to this ring conversion is the synthesis of coformycin from nebularine, which involves a similar ring expansion, which has been carried out under radical reaction conditions.[1103] An analog of ara A containing a 5′-methylthio group has been isolated from the nudibranch *Doris verrucosa* found in European waters.[1475] Synthesis of adenine analogs of the guanine antiviral



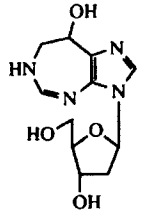
206



207

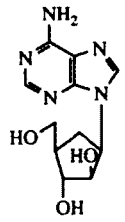


208

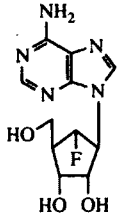


209

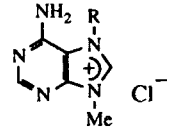
agent acyclovir (see Section 9.B) have been effected,[1127,1223,1258,1674] some derivatives such as 9-(2,3-dihydroxypropyl)adenine (DHPA) show comparable biological activity.[1688,1689] Among the nonnaturally occurring adenines is the novel carbocyclic nucleoside cyclaridine (**210**) showing antiviral effects[1591,1592] and similar testing of the related fluorocarbocyclic furanoside (**211**) is currently in progress.[1624] Aprinocid® 9-(2-chloro-6-fluorobenzyl)adenine, is employed as a coccidiostat for avian parasitic infections.[1521,1524]



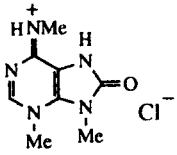
210



211



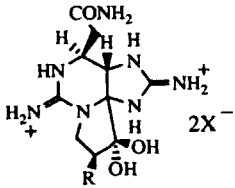
212



213

Marine environments continue to be a source of exotic aminopurines. The metabolites ageline A and ageline B from the Pacific sponge *Agelas sp.* have quaternary chloride structures (**212**, R = diterpene) formed by 9-methyladenine linked to a diterpene through N-7. In the former derivative the diterpene is striatol, and it is clerodane in the latter.[1888] Caissarone, found in the brazilian sea anemone *Bunodosoma caissarum correa*, is structurally identified by PMR, MS and crystallographic analysis as 3,6,7,8-tetrahydro-3,9-dimethyl-6-methylimino-8-oxopurine[1850] (**213**). A six-step synthesis from 9-methyladenine is reported affording a 25% overall yield.[1851]

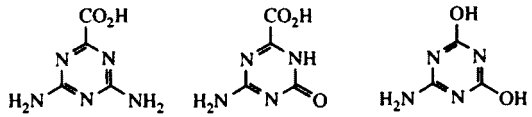
The powerful human neurotoxin saxitoxin, present in the dinoflagellate *Gonyaulax catenella* in temperate coastal waters worldwide, incorporates a reduced form of the 2,8-diaminopurine cation in the structure. First isolated in 1966,[1627] the structure (**214**, R = H) was established by crystallographic[1628] and other investigations.[1852,1853] Confirmation followed from a total stereospecific synthesis in 1975.[1629] The related derivatives gonyautoxin II (**214**, R = α-OH) and gonyautoxin (III) (**214**, R = β-OH) were extracted from the soft-shelled clam *Mya arenaria*.[1630] Other toxins of this type from similar sources have been reported subsequently.[1631,1632] A comprehensive overview covering the current knowledge of saxitoxin and its derivatives can be obtained from a recent series of papers on marine natural products chemistry.[1976]



214

B. Guanine (*H*354)

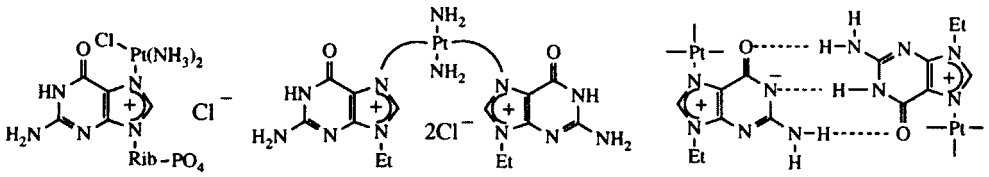
Additional data on heats of formation and ionization and resonance energy are available.[1690] Four triplet states have been identified from the electronic absorption spectrum.[1899] Tautomeric and structural aspects are of continuing interest, with the latest studies showing that the predominent tautomer may be determined by various influences present. The outcome of either semiempirical AMI quantum chemical calculations for the principal tautomer of the isolated molecule or use of a self-consistent reaction field (SCRF) approach applied to solutions in a polarizable dielectric medium is the same. These predict that the 9H tautomer has the greatest stability in the amino-oxo form with a minor contribution from the 7H analog. In solution the 9H form of the hydroxyamino tautomer is more favored and is the only one experimentally detected.[1900] An opposite viewpoint from SCFMO calculations has predicted 7H as the predominant tautomer.[1416] In the crystal the monohydrate shows that the 9H form is also present,[1633] but in the 3-methyl homolog the 7H protomer predominates.[1531] Core binding energy determinations indicate that the oxygen in guanine is in the oxo form,[1360] the same state is present in the crystal of the 3-methyl derivative.[1531] Broadening of the 8-H resonance in the PMR spectrum, originally interpreted as due to lactam–lactim tautomerism,[1417,1625] is now known to be caused by the presence of paramagnetic ion impurities.[1626,1627] The original suggestion that first protonation of guanine occurs either at N-3 or the 2-amino group is based on the similarity of the UV spectrum of the cation with that of neutral xanthine.[1424] Later PMR results support this and show further protonation at either N-7 or N-9, the dication having a p*Ka* of –1.04 to –1.06 in dilute H_2SO_4,[2024] with trication formation finally resulting through the carbonyl group being protonated.[1038] With 9-methylguanine, the monocation is formed through N-7.[1424] Rates of removal of the C-8 hydrogen either from the 8-tritiated purine or by exchange in deuterium oxide are documented for guanine,[1319] guanosine,[1319,1634,1635] and N-1 and N-7 methylated[1634–636] derivatives. The enhanced rate of removal of hydrogen from C-8 of guanosines in the presence of mercury(II) methyl ions[1637] suggests that complexing at N-1 and N-7 gives rise to charged species similar to those operating in the *N*-methylated purines above. Free-radical displacements at this position are facile, with tert-butylperoxide guanine and guanosine are converted to the 8-methyl homologs.[1074] Rotation of the 2-amino group is more restricted than for the 6-amino group of adenine, owing to a higher-energy barrier height, the effect being intensified in the more hindered 1-methylated purine.[1420] The dianion of guanine is involved in oxidation with alkaline potassium peroxodisulfate, giving a mixture of products including 2,4-diamino-*sym*-triazine-6-carboxylic acid (**215**), urea, guanidine, ammonia, and carbon dioxide. With potassium permanganate or hydrogen peroxide as oxidants, the related derivative (**216**) results. Under these conditions, 8-oxoguanine is also converted to the latter aminohydroxytriazine.[1790] The extremely rapid oxidation of guanine with potassium peroxodisulfate compared with that of adenine (over 300 times faster), is used to remove guanosine from mixtures containing other DNA bases.[1791] On ozonolysis



215 **216** **217**

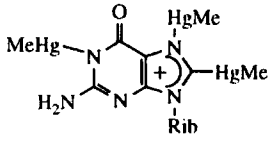
of an aqueous solution (20°C, 0.5 h), the main product is 2-amino-4,6-dihydroxy-*sym*-triazine (**217**) from an initial attack on the 4,5-double bond followed by a hydrolytic ring fission and subsequent triazine formation.[1893] A review of one-electron oxidation–reduction reactions including those of guanine is available.[1906]

The importance of guanine as a receptor centre in DNA for a variety of substrates is highlighted by the number of vastly different complexes synthesized. Formation of 1:1 purine–metal compounds occur with 1-methyl- and 1,9-dimethylguanine, for example, $[1,9\text{-}Me_2Gu(NH_3)_5Ru]Cl_3 \cdot 2H_2O$ on reaction with pentaammino ruthenium(III) chloride,[1638,1678] similar derivatives arise with dicarbonylrhodium(I) chloride,[1318] both reagents bonding with N-7 of the purine. At low pH values the clinically potent carcinostat cis platin (cisdichlorodiamino-platinum) forms a 1:1 complex with guanosine phosphate (**218**).[1639] Bis compounds linked at N-7 of the type (**219**) form between the same reagent and 9-ethylguanine[1640,1641] and also with the related 1,2-diaminoethane platinum chloride.[1642] Unusual hydrogen-bonded base pairing between the anion and neutral molecules, such as (**220**), can occur through partial proton loss at N-1 fol-

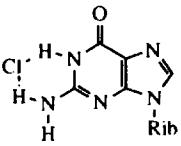


218 **219** **220**

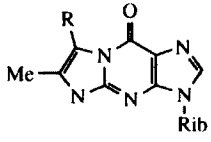
lowing cis platin complexation.[1679] In forming the hydrated 2:1 complex between 9-ethylguanine and the platinum tetrachloride ion, only extensive hydrogen bonding is proposed, both bases being protonated at N-7.[1685] At low pH, guanosine and methyl mercury(II) nitrate form the monosubstituted complex at N-7, changing to the 1,7-dimethylmercury adduct as pH is raised. Replacement of the C-8 hydrogen producing the 3:1 complex (**221**) occurs on rise in reaction temperature (50°C, 0.5 h) and exemplifies activation of the hydrogen through complexation.[1643] Location of N-7 as the site of complex formation is kinetically favored. Most divalent metals initially bind here rather than at the thermodynamically favored N-1 position.[1644] One suggestion is that the shift changes in the PMR following complex formation are due to reverse-charge chelates with the anion, notably chloride, of the type[1645] (**222**), but this view has its detractors.[1646] Unlike adenine, which forms molecular chains with silver ions in very dilute solution, guanine is shown by flow linear dichroism to give metal-linked dimers.[1647] The hydrated crystal complex of guanine and copper(II) chloride shows protonation



221



222



223

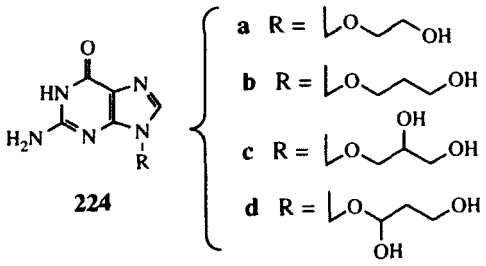
at N-7 and N-3 with copper located[1648] at N-9; a corresponding situation exists with zinc salts.[1571] Hydrogen bonding appears to be a stabilizing factor for most of these complexes. Reactions of guanine derivatives with difunctional reagents producing tricyclic derivatives through annelation between N-1 and the 2-amino group are cited in Section 5.G.c. Various approaches for facile conversions of the 6-oxo to an *O*-alkyl group include 6-*O*-stannyl,[1278] -trimethylsilyl,[1304] -trimethylsilylethyl, and 2,4,6-triisopropylbenzenesulfonyl chloride[1272] intermediates. Direct *O*-methylation is possible with trimethyl phosphate[1277] and trimethylanilinium methoxide.[1276] Under milder conditions *O*-benzoylation occurs with guanosine in pyridine by 2,6-dichlorobenzoyl chloride and *O*-sulfonylation using aromatic sulfonyl chlorides;[1301] both products are good candidates for nucleophilic replacement reactions.

In addition to the simple guanosine nucleosides are more complex naturally occurring derivatives having guanine as an integral part of the molecule. The most numerous of these are the "Y-nucleosides," tricyclic structures isolated from the *t*-RNA of brewers yeast (*Torulopsis utilis*). Wyosine (**223**, R = H), the parent member,[1649] is the 3-ribofuranoside of 4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine. Synthesis of wye base, the aglycone form, is documented,[1477,1650] as is that of the 3-methyl homolog[964,969] (3-methylwye). The structure of wybutosine [**223**, R = $CH_2CH_2CH(CO_2Me)NHCO_2Me$], derived from the same source,[1651,1652] is established by the synthesis[1655] of this and of wybutine, the racemic form of the aglycone.[1653,1654] The latter purine, which has an (*S*)-configuration, is present in *t*-RNA from *Saccharomyces cerevisiae*.[1824] Wybutoxine [**223**, R = $CH_2CH(OOH)CH(CO_2Me)NHCO_2Me$], an oxidized variant of the latter nucleoside, has been similarly investigated.[1656,1657]

Guanine bases in DNA are major receptors for polycyclic carcinogens; the site of attack on the purine is determined by the reactive center of the particular agent. Alkylating functions in the latter give rise to N-7 linked complexes, as with 7-bromomethylbenz[*a*]anthracene[1154] and the oxidized form of aflotoxin B_1.[1658] Following metabolic oxidation, the equally potent carcinogens 7,12-dimethylbenz[*a*]anthracene[1659] and benz[*a*]pyrene[1660] react with the 2-amino group. This position can also be an alternative site for 7-bromomethylbenz[*a*]anthracene attack,[1661] and it is notable that mitomycin-C, a quinone antibiotic, cross links two guanosine bases in DNA through the same amino group.[1672] The essentially covalent nature of the bonding existing between guanines and carcinogen molecules has been demonstrated.[1673]

The notable but limited success of the acyclic nucleoside 9-[(2-hydroxyethoxy)methyl]guanine[1662] (**224a**), in clinical use as acyclovir, zovirax, or ACV

as an antiherpetic agent, results from its action as an inhibitor of viral DNA polymerase.[1671] Various synthetic approaches,[947,1214,1841,1842,1914] including that for the 1-methyl homolog,[962] are documented; these usually entail ring closure of imidazole derivatives that have the requisite *N*-hydroxyalkoxymethyl side chain in situ with the hydroxy groups protected by benzylation. Following the early promising indications when used against herpes-type viruses, numerous programs were initiated for the preparation of guanine and adenine analogs. Some of the products showing antiviral acitivity include (HPG) 9-(3-hydroxypropoxy)methylguanine[1209] (**224b**) and the dihydroxy analogs (DHPG) 9-[(2,3-dihydroxy-1-propoxy)methyl]guanine[1260,1270,1663] (**224c**), of which the (*S*)-enantiomer is the biologically active form,[1260,1270] and guancyclovir, the 9-[(1,3-dihydroxy-2-propoxy)methyl] isomer[1841] (**224d**), as well as the structurally related 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine[1664] and 9-(2,4-dihydroxybutyl)guanine.[1258] Substitution of a hydroxy group by an amino in the side chain of DHPG[1665] and preparations of other derivatives[1127] including the thioxo[1261] analog are reported. Significantly good general antiviral effects are shown by the fluorinated sugar moiety in the deoxyguanosine[1666,1667] (**225**). The novel 9-cyclopentenyl derivative carbovir (**226**) also exhibits positive anti-HIV properties[1668] and a recent asymmetric synthesis of optically pure (–)-carbovir is reported.[1843] Reviews covering various aspects of the antiviral guanine derivatives include the synthesis,[1669] chemistry,[1670] and biological effects[1670] of acyclovir, an overview of carbovir preparations,[1844] and the syntheses of related carbocylic nucleosides.[1845,1935]



C. Isoguanine (*H*357)

More recent synthetic approaches to isoguanine derivatives have involved closure of imidazole precursors rather than pyrimidine-based Traube cyclizations. Typical examples are preparations of the parent purine[984,985] and the 8-methyl,[2019]

3,9-dimethyl,[964,997] and 7,8-dimethyl[991] homologs. The route is of interest in that corresponding guanine derivatives can be formed from common starting materials by suitable adaptation. More novel is a direct conversion of adenine to isoguanine by phenyl chloroformate in tetrahydrofuran at ambient temperature in which involvement of a Dimroth rearrangement is shown by the formation of 1-methylisoguanine when 6-methylaminopurine is treated[1242] in the same way. As in the case with adenines, acylation of the 6-amino group significantly influences the site of alkylation. This is shown by benzylation of 1-alkylisoguanines, which give 9-benzyl derivatives, but after conversion to the 6-acetamido analog, the alkylation products are the isomeric 3-benzyl-1-alkylisoguanines.[1534]

Lower forms of marine life, such as sponges, yield both isoguanine and adenine derivatives; the former may possibly arise from biological oxidation at C-2 of the latter. Existence of the parent nucleoside, crotonoside, and the 2-methoxy analog spongosine have long been known (*H*357). More recent discoveries of tedania, from the sponge *Tedania digitata*,[1681] doridosine in the nudibranch *Anisodoris nobilis*,[1682] and a nucleoside present in a Barbados coral *Madricis mirabilis*[1683] are notable in being the same 9-β-D-ribofuranoside of 1-methylisoguanine. Structural confirmation is obtained from the various syntheses[995,996,1840] made. The 3-(β-D-ribofuranosyl) analog of crotonoside is formed by direct ribosylation of 8-iodoisoguanine.[885]

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER IX

The Purine Carboxylic Acids and Related Derivatives (*H*367)

1. The Carboxypurines (*H*367) . . . 284
   A. Preparation (*H*367) . . . 284
      a. By Hydrolysis (*H*367) . . . 284
      b. By Oxidation (*H*370) . . . 284
2. Alkoxycarbonylpurines (Purine Esters) (*H*374) . . . 285
   A. Preparation (*H*374) . . . 285
      a. From Pyrimidine Esters (*H*374) . . . 285
      b. By Other Methods (*H*374) . . . 285
   B. Reactions (*H*375) . . . 286
3. Carbamoylpurines and Related Compounds (*H*376) . . . 287
   A. Preparation (*H*377) . . . 287
      a. From Esters and Acid Chlorides (*H*377) . . . 287
      b. By Other Means (*H*377) . . . 287
4. Purine Carbonitriles (Cyanopurines) (*H*379) . . . 288
   A. Preparation (*H*379) . . . 288
   B. Reactions of Cyanopurines (*H*380) . . . 289
      a. General Reactions (*H*381) . . . 289
      b. Reduction (*H*382) . . . 290
5. Purine Aldehydes (*C*-Formylpurines) (*H*382) . . . 290
   A. Preparation (*H*383) . . . 290
      a. By Hydrolysis (*H*383) . . . 290
      b. By Oxidation (*H*383) . . . 291
      c. By Other Means (*New*) . . . 291
   B. Reactions (*H*384) . . . 291
      b. Formation of Usual Derivatives (*H*384) . . . 291
      c. Other Reactions (*H*386) . . . 291
6. Purine Ketones and Derivatives (*H*387) . . . 292
   A. Preparation (*H*387) . . . 292
   B. Reactions (*H*388) . . . 293
      a. Reduction (*H*388) . . . 293
      b. Other Reactions (*H*388) . . . 293
7. Purine Thiocyanates (*H*389) . . . 294
   A. Preparation and Reactions (*H*389) . . . 294
8. Purine-*N*-Carboxylic Acids and Derivatives (*H*390) . . . 294
   A. Preparation and Reactions (*H*390) . . . 294
9. Purinylamino and Purinylthio Acids (*H*392) . . . 299
   A. Purinylamino Acids and Esters . . . 299
      a. Preparation and Reactions (*H*392) . . . 299

B. Purinylthio Acids and Derivatives (*H*393) 301
a. Preparation and Reactions (*H*393) 301

Interest in the simple *C*-carboxypurines is minimal, as reflected by the few new examples which have appeared in the literature. Derivatives having the acid function joined indirectly to the purine through a nitrogen or sulfur are significantly more abundant and many result from chemotherapy-oriented programs.

1. THE CARBOXYPURINES (*H*367)

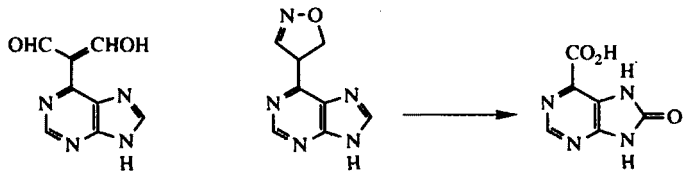
A. Preparation

a. By Hydrolysis (H367)

Representative examples of more recent data include the known 6-carboxypurine by the action of thionyl chloride on either the 1- or 3- oxide of 6-methylpurine; the reaction involves deoxygenation and hydrolysis of the intermediate 6-trichloromethylpurine.[1080] Similar in character is formation of 8-methoxycarbonylcaffeine from heating the 8-trichloromethyl analog in a methanol–chloroform mixture.[1135] Heating with 2*M* sodium hydroxide (100°C, 1 h) converts 8-cyano-9-methylguanine to the 8-carboxypurine.[879]

b. By Oxidation (H370)

Alkyl, alkenyl, and derivative groups are useful carboxy precursors. Alkaline potassium permanganate transforms 6-styrylpurine[1081] or the 6-malondialdehyde derivative (**1**)[791] to 6-carboxypurine, while 8-styryladenine with the same oxidizing agent in sulfuric acid affords the 8-carboxy analog.[790] The same product results using an 8-propenyladenine precursor.[790] Somewhat unusual in view of the mild conditions employed (60°C, 0.5 h) is formation of the 8-oxopurine-6-carboxylic acid (**3**) from 6-(isoxazol-4-yl)purine (**2**) by means of acidified potassium permanganate.[791]



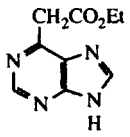
1 **2** **3**

2. ALKOXYCARBONYLPURINES (PURINE ESTERS) (*H*374)

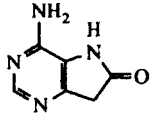
A. Preparation

a. From Pyrimidine Esters (H374)

The Traube closure of 4,5-diamino-6-ethoxycarbonylmethylpyrimidine with dimethylformamide and phosphoryl chloride is notable in forming both the expected 6-ethoxycarbonylmethylpurine (**4**) and 4-amino-5*H*-pyrazolo[3,2-*d*]pyrimidin-6-one (**5**), the latter through the alternative intramolecular cyclodehydration of the starting material.[171]



4



5

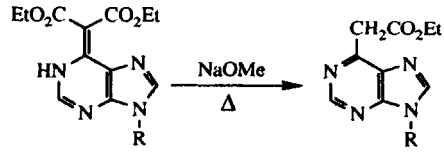


(R = Ph, $MeOCH_2$, Tetrahydrofuryl)

6

b. By Other Methods (H374)

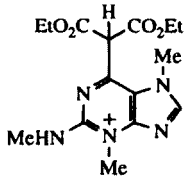
A number of carboxylic esters of the type (**6**) result when ethyl cyanoacetate reacts with 6-chloro-9-phenyl,[1067] 6-chloro-9-methoxymethyl-,[1068] 6-chloro-9-tetrahydrofuryl-,[1068] and 6-methylsulfonyl-9-phenyl-[1079] purine. Ethyl acetoacetate and sodium hydride in THF with 6-methylsulfonylpurine ribosides form the appropriate 6-ethoxycarbonylmethyl derivatives.[2034] The 6-dicarboxylic ester (**7**) from 6-chloro-9-tetrahydropyranylpurine and diethyl malonate, which suffers monodecarboxylation to the 6-carboxymethyl ester (**8**) in hot sodium methoxide,[1069] is also obtained in this manner. The product (**9**) from treatment of a 3,7-dimethylguanine with phosphoryl chloride and triethylamine followed by diethyl malonate is an extension of this approach.[1098] Corresponding malonic ester derivatives from 8-chloroxanthines are also known.[1232] The purine ylid (**10**) derived



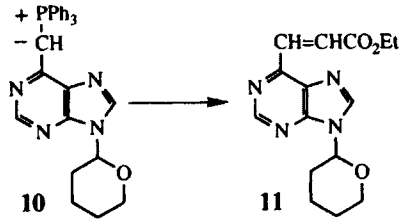
(R = Tetrahydropyranyl)

7

8



9

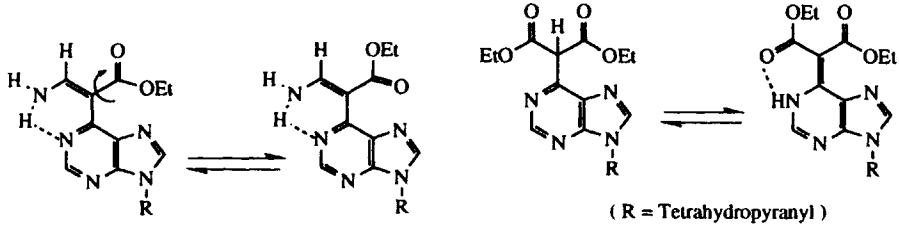


10 11

from 6-chloro-9-tetrahydropyran-1-ylpurine and methylene triphenylphosphorane at low temperature (–30°C) undergoes a Wittig reaction with ethyl glyoxalate in dimethylformamide (20°C, 16 h) forming the unsaturated acid[1060] (**11**). The same reaction converts an 8-formyladenosine derivative into the (*E*) isomer of the 8-ethoxycarbonylvinylpurine.[1862] Esterification with methanol gives esters of 8-carboxymethyl- and 8-(2-carboxyethyl)-3-isobutyl-1-methylxanthine.[830] Halogenopurines are involved in forming the 8-lithio derivatives of trimethylsilylated adenosine and guanosine from reacting the 8-bromo analogs and butyllithium. The products with ethyl chloroformate and ethyl 4-bromobutyrate give the respective 8-ethoxycarbonyl- and 8-(3-ethoxycarbonylpropyl) purines. Direct introduction of a carboxyl group is possible using carbon dioxide.[1064]

B. Reactions (*H*375)

Decarboxylations in hot dilute hydrochloric acid are used to prepare 6- and 8-methylpurines from the appropriate 6- and 8-ethoxycarbonylmethyl-[171] and -di(ethoxycarbonyl)methylpurines.[1098] Catalytic reduction (Pd, H_2) of the 6-cyanoesters (**6**, R = H or CH_2OMe) gives products (**12**, R = H or CH_2OMe) shown (^{13}C and ^1H NMR) to be mixtures of two geometrical isomers, separable by column chromatography, and having enamine configurations.[1068] Solvent effect is shown in the composition of the tautomeric mixture with 6-di(ethoxycarbonyl)methyl-9-tetrahydropyranylpurine. Hydroxylic solvents favor the saturated C-6 bond derivative (**13A**), whereas the enamine configuration (**13B**) present in aprotic media is probably stabilized by hydrogen bonding between N-1 and the carbonyl oxygen.[1069]



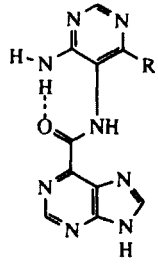
12 (Z) 12 (E) 13A 13B

3. CARBAMOYLPURINES AND RELATED COMPOUNDS (*H*376)

A. Preparation (*H*377)

a. From Esters and Acid Chlorides (H377)

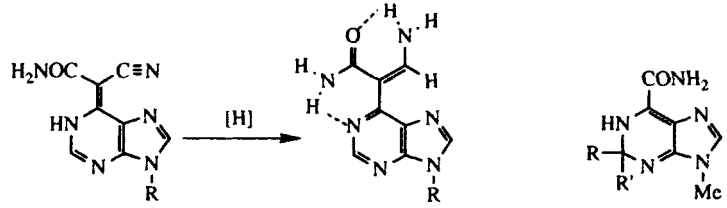
In line with earlier examples reported is formation of the highly fluorescent 6-amidopurines (**14**, R = alkyl) when 6-trichloromethylpurine and 4,5-diamino-6-alkylpyrimidines react (40°C, 24 h) at pH 4.5.[1199] A structural rigidity imposed by intramolecular hydrogen bonding between the unreacted amino group of the pyrimidine and the carbonyl oxygen would explain the fluorescent property of such compounds.[1199]



14

b. By Other Means (H377)

The 9-β-D-Riboside of 6-cyanopurine is coverted to the amide in cold water or in alkaline hydrogen peroxide.[1394] The 2-methyl and 2-amino analogs are similarly formed.[1394] The same route with aqueous sodium carbonate gives the 2-methyl, 2-ethyl, and 2-trifluoromethyl homologs of 6-carbamoyl-8,9-dimethylpurine.[1004] Nonaqueous conditions, with pyridine replacing the aqueous ammonia previously employed, are utilized in conversion of the 6-cyanopurine ribosides to the 6-thiocarbamoyl analogs with hydrogen sulfide at room temperature.[1394] The amides (**15**, R = H or CH_2OMe) from reacting 6-chloropurines with cyanoacetamide on reduction (Pd, H_2) yield only the (*Z*)-enamino carboxamide tautomers (**16**) produced by intramolecular hydrogen bonding at two sites.[1068] Condensation of acetone, methylethylketone, acetophenone, and other ketones with 5-amino-4-(cyanoformimidoyl)imidazole at ambient temperatures, giving 6-carbamoyl-1,2-dihydropurines of the type (**17**, R, and R′ = alkyl or Ph)[1004,1878] is treated in more detail in Chapter XII, Section 2.A.d. Under radical reaction conditions, induced in formamide containing ammonium persulfate and iron(II)



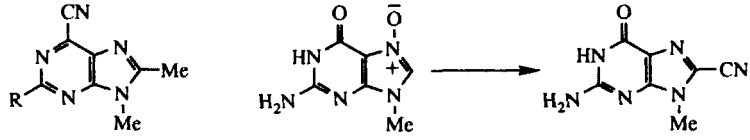
15 16 17

sulfate, both the *O*-acetylated[1394] and cyclic phosphate[1078] derivatives of guanosine undergo formamidation at C-8 in appreciable yield (63%). This novel approach has merit in its applicability to direct addition of other carbonyl moieties at C-8 (see Section 6.A).

4. PURINE CARBONITRILES (CYANOPURINES) (*H*379)

A. Preparation (*H*379)

Most examples are known compounds prepared by alternative routes; nucleophilic displacement of 6-substituted purines is the favored approach. Some typical methods are obtaining 6-cyano-9-methylpurine from the 6-trimethylammoniumpurine with sodium cyanide in dimethylformamide (50°C, 2 h)[1140] or using copper (I) cyanide in pyridine to convert the 9-β-D-ribosides of 6-iodo-, 2-amino-6-iodo-, and 6-iodo-2-methylpurine to the 6-cyano analogs.[1394]. The riboside of 6-methylsulfonylpurine is readily converted with sodium cyanide.[1394] Similarly displaced by cyanide ions are 2- and 8-methylsulfonyl groups in adenosines.[1854] Other examples of such displacements are found with 6-methylsulfonyl-[1939] and 6-(4-methylbenzenesulfonyl)purines.[1940] Cyclodehydration in hot butanol of 5-nitroso-4-(2-cyanoethylamino)-1,3-dimethyluracil is a route to 8-cyanomethyltheophylline which, on methylation, yields the caffeine homolog.[916] A range of 2-substituted 6-cyano-8,9-dimethylpurines (**18**, R = Me, Et, CF_3) results from ring closure of 5-amino-4-(cyanoformimidoyl)-1,2-dimethylmidazole with acid anhydrides at room temperature.[1004,1878]

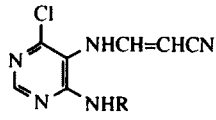


18 19 20

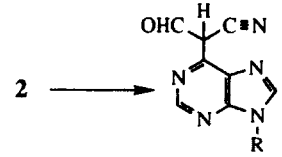
Rearrangement occurs on treating the 7-oxide of 9-methylguanine (**19**) with benzoyl chloride followed by potassium cyanide to give 8-cyano-9-methylguanine (**20**) as product. With phosphoryl chloride and thiourea, the latter affords the thioguanine analog.[879] Interaction of malonic acid derivatives with 6-substituted purines giving some cyanomethylenepurines is described in Sections 2.A.b



21



22



23

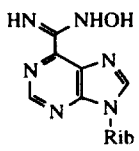
and 3.A.b. Similar condensations with phenylacetonitrile[1067,1079] and malonodinitrile[1068,1855] forming the respective products (**21**, R = Ph and R = CN) are known, but with acetonitrile itself, even when present as the anion (NaH, –40°C) in an aprotic solvent, the reaction with a 6-chloropurine fails and attack is directed to C-8, leading to the pyrimidine derivative (**22**) through concomitant imidazole ring fission.[1069] From a thermal decomposition of the 6-isoxazolylpurine (**2**) in dimethyl sulfoxide, the cyanoaldehyde (**23**) is obtained.[791] Formation of a 2-cyanomethylpurine results from a cross-coupled reaction between silylated 2-iodo-6-methoxypurine-9-riboside and tri-*n*-butyl(cyanomethyl)stannane and a palladium(II) catalyst.[1875] Another example of a side-chain nitrile is from a Wittig reaction of 8-aldehydoadenosine with cyanomethyltriphenylphosphorane in THF which affords the 8-(*E*)-cyanovinyl analog.[1862]

B. Reactions of Cyanopurines (*H*380)

The majority of examples found are basically extensions of known reactions which have been applied to riboside derivatives. Current examples of hydrolysis and thiohydrolysis to amides and thioamides are noted in Section 3.A.b and formation of 8-carboxypurines by alkaline hydrolysis has also been described (Section 1.A.a).

a. General Reactions (H381)

Reflux conditions in ethanolic hydroxylamine convert 6-cyanopurine-9-β-D-riboside to the 6-hydroxyamidino analog (**24**).[1394] In an excess of ammonia solution (20°C, 8 h), the same cyanopurine rearranges to 4-amino-8-β-D-ribofuranosylaminopyrimido [5,4-*d*]pyrimidine (**25**), the structure of which was known from earlier work[1730] and confirmed by cystallographic studies.[1731]



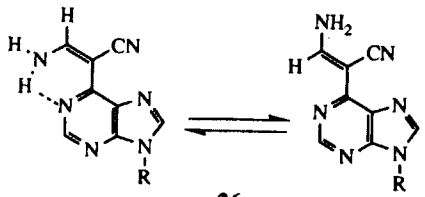
24



25

b. Reduction (H382)

Catalytic reduction of a series of 8-cyanomethyl derivatives of caffeine and 1,3,7,-trialkyl homologs with a cobalt catalyst under pressure (90°C, 120 atm) forms the corresponding 8-aminoethylxanthines.[916] The reaction fails using lithium aluminium hydride.[916] Reference to the geometrical isomerism exhibited by the reduction products from some 6-cyanomethylenopurines has been made (Sections 3.B and 4.B). Likewise, on controlled reduction of the malonodinitrile (**21**, R = CN), an equilibrium mixture of the *E* and *Z* tautomers (**26**, R = H or CH_2OMe) is obtained.[1068,1855]



26

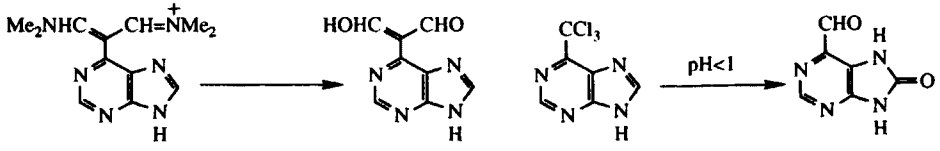
5. PURINE ALDEHYDES (*C*-FORMYLPURINES) (*H*382)

Few new examples exist and the area is still poorly represented. Most derivatives have resulted from chemical curiosity rather than from purposeful investigation.

A. Preparation (*H*383)

a. By Hydrolysis (H383)

Ethyl nitrite treatment effectively converts the hydrazone of 6-aldehydopurine-1-oxide back to the parent purine oxide.[1080] A 6-cyanomethylpurine (**23**) results from heating 6-(isoxazolylpurine) (**2**) in dimethyl sulfoxide (Section IV.A). The 6-diformylmethylpurine (**28**) is obtained from the adduct (**27**) produced by the Vilsmeier reagent reacting with 6-methylpurine.[791] Under strongly acid conditions (pH < 1), 6-trichloromethylpurine (**29**) undergoes hydrolytic rearrangement, forming a transient 6-dichloromethyl-8-oxopurine intermediate before hydrolysis to the 6-aldehydopurine (**30**) occurs.[1084]



27 **28** **29** **30**

b. By Oxidation (H383)

A new oxidation of 8-hydroxymethylcaffeine to the known 8-formylcaffeine is reported using manganese dioxide in dioxan.[916]

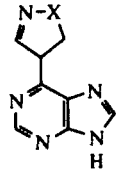
c. By Other Means (New)

Reaction of the 8-lithio derivative of 3′-dioxyadenosine with methyl formate gives the 8-formyl analog in low (36%) yield, but other products are also present.[1862]

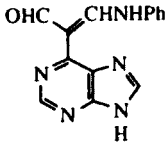
B. Reactions (*H*384)

b. Formation of the Usual Derivatives (H384)

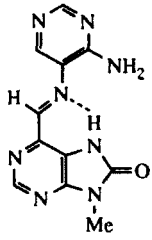
A range of substituted anilines reacted with theobromine- and caffeine-8-aldehydes affords the expected 8-azamethine derivatives.[1732] Preparation of similar derivatives of purine-6-malonodialdehyde is often more satisfactory using the adduct (**27**) instead. Condensation with hydroxylamine and hydrazines gives 6-isoxazolyl- and 6-pyrazolylpurines, including (**31**, X = O) and (**31**, X = NH) from hydrazine, (**31**, X = NPh) from phenylhydrazine, and (**31**, X = $NCSNH_2$) with thiosemicarbazide.[791] Aromatic amines react with the adduct (**27**) forming enamines of the type (**32**).[791] Somewhat similar use of an aldehyde precursor is seen in the conversion of 6-dichloromethyl-7,8-dihydro-9-methyl-8-oxopurine to the hydrogen-bonded azamethine (**33**) when reacted with 4,5-diaminopyrimidine.[1083]



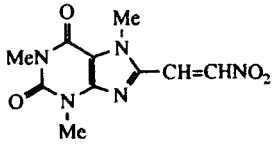
31



32



33



34

c. Other Reactions (H386)

The methylene moiety in nitromethane readily condenses with 8-formylcaffeine at low temperature (< 10°C, 0.5 h) in methanolic alkali, giving a satisfactory yield (57%) of 8-nitrovinylcaffeine (**34**).[916] A preparation of 6-tribromomethylpurine involves bromine in acetic acid on purine-6-malondialdehyde.[791] When treated with a trifluoroacetic acid–hydrogen peroxide mixture,

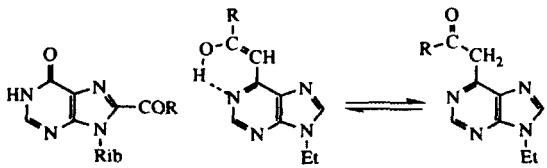
the latter aldehyde is converted to hypoxanthine.[791] A Wittig reaction with cyanomethyltriphenylphosphorane[1862] on 8-formyladenosine is noted in Section 4.A.

6. PURINE KETONES AND DERIVATIVES (*H*387)

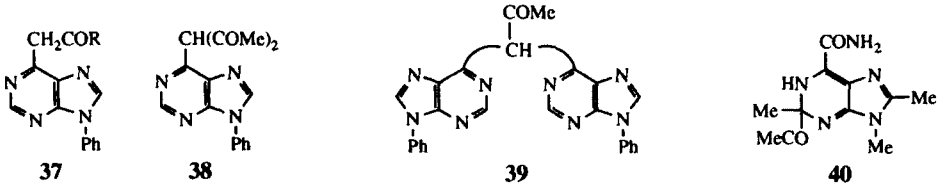
An innovation is the application of radical reactions for preparation of purines which are directly linked to a carbonyl group. More conventional approaches are used to form derivatives having the ketone moiety joined to the nucleus through a methylene group or carbon chain.

A. Preparation (*H*387)

In the presence of acidified iron(II) sulfate and an ammonium persulfate radical initiator, acetaldehyde reacts with guanosine-3′,5′-cyclic phosphate giving the 8-acetylated analog (**35**, R = Me) in practical yield (43%). Also obtained are (**35**, R = CH_2CH_2Me) from butyraldehyde (34%), (**35**, R = $CHMe_2$) with isobutyraldehyde (47%), and (**35**, R = Ph) from benzaldehyde in lower yield (14%). The danger of *C*-methylation competing with *C*-acylation precludes the use of *tert*-butyl peroxide as an alternative radical initiator to the ammonium persulfate.[1078] Inosine cyclic phosphate likewise forms 8-acetyl and 8-benzoyl derivatives, but yields are reduced (~11%) while the adenosine analog fails to acylate.[1078] Ketonyl radicals produced by irradiation of ketones interact with 9-ethyl-6-iodopurine at C-6 by halogen displacement. An 80:20 mixture of enol (**36A**) and keto forms (**36B**) is obtained in chloroform for the acetone product. Spectral indications (^{1}H NMR) are that hydrogen bonding is responsible for the predominance of the enol tautomer. A possible indication of this is that the isomer ratio falls to 50:50 in aqueous solution. Analogous reactions occur with acetophenone, cyclopentanone, and cyclohexanone, all the products showing keto-enol tautomerism. The essentially radical nature of the reaction is demonstrated by the drop in overall yield of **36** (R = Me) from 71% to 6% following addition of a radical scavenger such as *p*-nitrobenzene.[1071] These results invite a comparison with those observed when essentially the same reaction takes place in the absence of radical involvement. Condensations of either 6-chloro-9-phenyl- or 6-methylsulfonyl-9-phenylpurine with acetone, acetophenone, and acetylacetone in dimethyl sulfoxide containing potassium hydroxide (100°C, 1 h), yield the respective

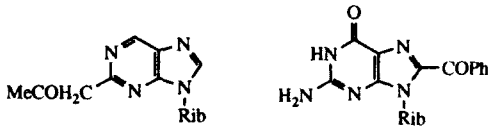


35 **36A** **36B**



37 38 39 40

ketonylpurines (**37**, R = Me),[1079] (**37**, R = Ph),[1067,1079] and (**38**),[1067,1079] but yields (between 5% and 25%) appreciably inferior to those from the radical procedures are recorded. Using an excess of the purine, the bis derivative (**39**) is obtained.[1079] Acetone and acetophenone react likewise with the furanoside of 6-mercaptopurine, giving the 6-ketonyl homologs.[1982] A rare example of a 2-acetylpurine is reported following an exothermic cyclization of 5-amino-4-(cyanoformimidoyl)-1,2-dimethylimidazole with diacetyl to the unstable 1,2-dihydropurine (**40**).[1004] From a cross-coupling reaction between a silylated derivative of 2-iodonebularine and the tin enolate of acetone in the presence of palladium (II) chloride, 2-acetonylnebularine (**41**) is obtained.[1105] This reaction provides analogous derivatives with the 9-riboside of 2-iodo-6-methoxypurine.[1875] The 8-lithio derivatives of adenosine and guanosine with benzonitrile provide a route to 8-benzoyl analogs such as **42**.[1064]



41 42

B. Reactions (*H*388)

a. Reduction (H388)

The 8-acyl derivatives of guanosine cyclic phosphate noted in the previous section, as ammonium salts in aqueous solution, are reduced with sodium borohydride to the appropriate 8-(1-hydroxyethyl)-, 8-(1-hydroxybutyl)-, 8-(1-hydroxy-2-methylpropyl)-, and 8-(α-hydroxybenzyl)guanosines.[1078] The same reagent converts 6-acetonyl-9-ethylpurine to the 6-(2-hydroxypropyl) analog.[1071]

b. Other Reactions (H388)

Phenylhydrazones, semicarbazones, phenylsemicarbazones, and thiosemicarbazones are formed by the 8-acylated guanosines.[1078] The virtual absence of any simple 2-formyl- or 2-acetylpurines may be linked to the instability shown by 2-acetyl-6-carbamoyl-1,2-dihydro-2,8,9-trimethylpurine (**40**), which loses the

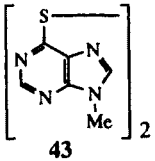
C-acetyl group on standing, leaving 1,2-dihydro-2,8,9-trimethylpurine.[1004] A like aroyl group removal is reported for the 2-benzoyl analog.[1004]

7. PURINE THIOCYANATES (*H*389)

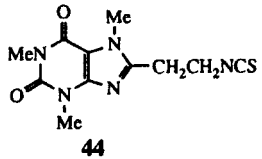
As with the aldehyde and ketone derivatives (Sections 5 and 6), examples of this class of compound are very limited.

A. Preparation and Reactions (*H*389)

Potassium thiocyanate in dimethyl sulfoxide converts 6-chloropurine-9-β-D-ribofuranoside to the 6-thiocyanoto analog.[1222] Exemplifying an alternative approach is the isolation of 9-methyl-1-6-thiocyanatopurine following cyanogen bromide treatment of the 6-thioxopurine analog in ethanol containing one equivalent of alkali.[1365] A reduced yield of the same product, together with an equal amount of 9-methyl-1,6-dihydro-6-thioxopurine, is obtained on reacting di(9-methylpurin-6-yl)disulfide (**43**) at pH 7 with sodium cyanide.[1365] Use of thiophosgene in chloroform converts 8-(2-aminoethyl)-to 8-(2-isothiocyanatoethyl)caffeine[916](**44**).



43



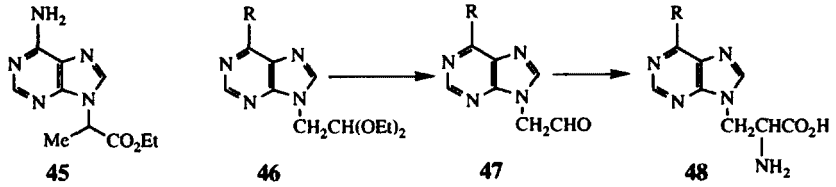
44

8. PURINE-*N*-CARBOXYLIC ACIDS AND DERIVATIVES (*H*390)

Ring closure of 5-amino-l-carboxyimidazoles with triethyl orthoformate (DMF, reflux) provides rare examples of a synthetic approach. The products obtained are the 9-(ethoxycarbonylmethyl)hypoxanthine and -adenine also the 9-(ethoxycarbonyleth-1-yl) and 9-(ethoxycarbonyleth-2-yl) homologs of the same purines.[1857] Alkylation still remains the major practical route, even though the possibility of forming more than one *N*-alkylated isomer exists. In some cases, with controlled conditions, the predominance of one of the isomers can be maximized.

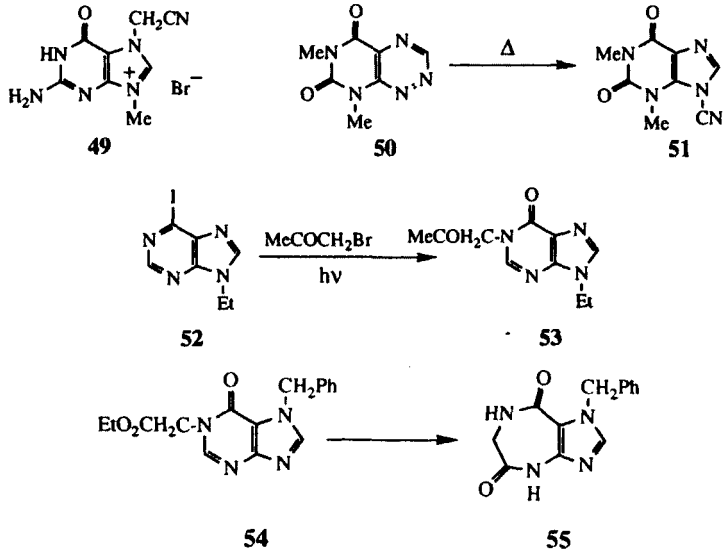
A. Preparation and Reactions (*H*390)

A mixture of the 9- (22%) and 3-carboxymethyl (8%) derivatives results from alkylation of adenine with iodoacetic acid in hot (100°C, 45 min) aqueous potas-



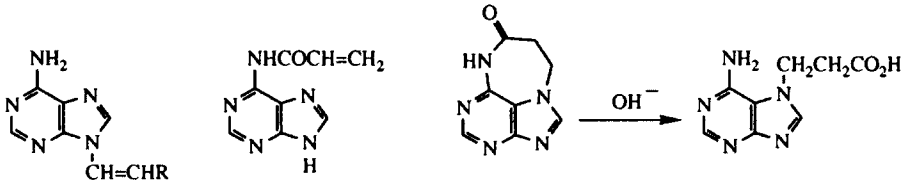
45 46 47 48

sium hydroxide.[1238] Nitrous acid converts the 9-isomer to the hypoxanthine analog, which could not be prepared by a direct alkylation route.[1238] Using ethyl 4-bromobutyrate in dimethylacetamide containing potassium carbonate, a better yield of 9-(3-ethoxycarbonylpropyl)adenine is obtained. A similar outcome is found from reaction with ethyl 5-bromovalerate, giving the 9-(4-ethoxycarbonylbutyl) homolog.[1470] The 9-bis(ethoxycarbonylmethyl)adenine arising with diethyl bromomalonate as alkylating agent (NaH, DMF) at ambient temperature is readily converted under controlled hydrolysis to either the 9-bis(carboxy)methyl- or the 9-carboxymethylpurine.[1529,1733] The Mitsunobu reaction (Chapter VIII, Section 8.A.b) converts adenine to the (*R*)-9-(ethoxycarbonyleth-2-yl) derivatives (**45**, R = Et) by interaction with (*S*)-ethyl lactate. Acid hydrolysis (5*M* HCl) provides the analogous carboxylic acid.[1859] A range of 6-substituted purines, including adenine[1201,1382] and various amino, chloro, thioxo, methylthio, benzylthio, and other[1382] derivatives, reacts with diethyl bromoacetal forming the respective 9-(2,2-diethoxyethyl)purines (**46**) and converted to the 9-formylmethyl analogs (**47**) by acid (5*M* HCl, 100°C) hydrolysis. A Strecker reaction with potassium cyanide and ammonium chloride (60°C, 5 h) on the latter purines gives the β-alanine derivatives[1201,1382,1411] (**48**). Analogous guanine and thioguanine forms arise similarly from their 9-(2,2-diethoxyethyl) precursors.[1248] Introduction of cyanomethyl groups by bromoacetonitrile in dimethylformamide (80°C, 2 h) is illustrated by formation of 7-cyanomethylguanine from guanosine in which concomitant loss of the ribose moiety occurs during the reaction.[1734] Facilitation of alkylation of guanine by prior conversion to the 6-benzyloxy analog is employed in forming 7- and 9-ethoxycarbonylmethyl, -carbamoylmethyl, and -cyanomethyl derivatives of 2-amino-6-benzyloxypurine using the appropriate bromoester, -amide, or -nitrile.[1856] The quaternary bromide (**49**) results with 9-methylguanine.[1735] Various 8-alkyl-7-cyanomethyltheophyllines, including the 8-methyl, -ethyl, -*n*-propyl, -*n*-butyl, and -benzyl derivatives, follow from alkylation of the theophylline with chloroacetonitrile.[938] Catalytic reduction (H_2, Raney Co) of the products affords appropriate 7-(2-aminoethyl)purines, which thiophosgene treatment converts to the 7-(2-thiocyanatoethyl) analogs.[938] The novel 9-cyanotheophylline (**51**) is produced when the pyrimido[5,4-*e*]-1,2,4-triazine (**50**) is heated (100°C) in xylene. Removal of the cyano group giving theophylline occurs in hot water.[1748] Under UV irradiation, 9-ethyl-6-iodopurine (**52**) with bromoacetone produces 1-acetonyl-9-ethylhypoxanthine (**53**). The expected replacement of iodine by the acetonyl moiety under these conditions is not apparent and an intermediate ring formation between C-6 and N-1, followed by hydrolytic fission, is proposed to explain the hypoxanthine isolated.[1071] The product (**54**) from



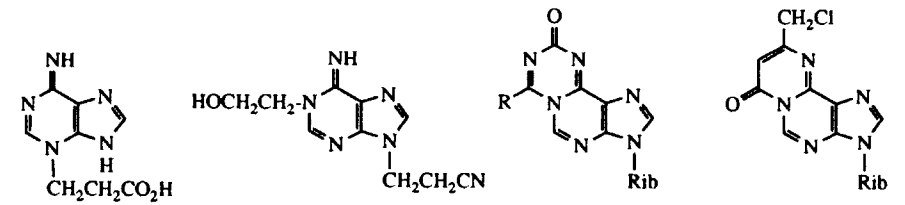
alkylation of 7-benzylhypoxanthine with ethyl bromoacetate (NaH, DMF) undergoes pyrimidine ring enlargement to the imidazo[4,5-*e*][1,4]diazepin-5, 8-dione (**55**) following reaction with methanol and then hot acetic acid. The 4-propyl and -isobutyl diazepine homologs are also reported.[1286] The particular products from interactions of adenines and alkyl chloroformates depend upon the concentrations and conditions employed. With equimolar amounts of ethyl chloroformate and the purine in basic media (pyridine, 35°C, 3 h), 9- ethoxycarbonyladenine is obtained, but with an excess of reagent (3:1) and prolonged reaction times, acylation of the 6-amino group also occurs[1736] (see Section 9.A.a). A specific route to 9-ethoxycarbonyladenine is through the thallium salt of adenine.[868,1736] The same chloroformate with 6-methylaminopurine and triethylamine base gives the 9-ethoxycarbonyl derivative, but no reaction with the methylamino group is noted.[837] An early report[868] that adenine formed a mixture of the 9- and 3-benzyloxycabonylpurines was erroneous.[1425] In ethanolic sodium ethoxide the 9-isomer predominates but under less basic conditions (aq. potassium acetate), the major products is the 7-isomer. Thermal isomerization of the latter to the 9-benzyloxycarbonyladenine occurs, however, in hot dimethyl sulfoxide.[1425]

Addition reactions with adenine provide 9-substituted purines, as exemplified by the 9-(2-carboxyethyl) derivative with β-propiolactone[1529] in dimethylformamide and the 9-(3-carboxypropyl) homolog from butyrolactone.[1578] Under reflux conditions in pyridine, a mixture of 3-(2-carboxyethyl)- (22%) and 9-(2-carboxyethyl)adenine (11%) results using methyl acrylate.[1733] Ethyl acetylene carboxylate in an alkaline medium (DMF, NaOMe, 20°C) converts adenine to the 9-carboxyvinyl analog (**56**, R = CO_2H); the corresponding aldehyde (**56**, R = CHO) results from alkenylation using prop-2-ynal.[1533] Prior conversion of guanine to the 2-trifluoroacetamide derivative as an aid to solubility, allows preparation of 9-formylvinylguanine with the same reagent (DMF, NEt_3); aqueous hydrolysis is



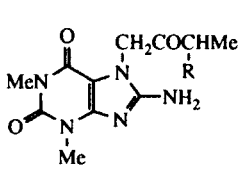
56 **57** **58** **59**

sufficient to remove the trifluoroacetyl group.[1533] A more complex reaction leading to a 7-substituted adenine occurs on treatment of adenine with acrylic anhydride (60°C, 24 h) in dimethyl sulfoxide. The diazepine product (**58**) formed from cycloaddition of the intermediate (**57**) through N-7 requires alkaline hydrolysis (60°C, 7 h) to obtain the 7-(2-carboxyethyl)adenine (**59**). Under conditions expected to favor reaction with the 6-amino group, isolation of the 3-alkylated product (**60**) following interaction of adenine and acrylic anhydride (25°C, 17 h) or acryloyl chloride (25°C, 3 h) in aquous sodium hydoroxide is unusual.[1436] Involvement of the amino group could explain formation of the 1-(2-carboxyethyl)adenine (**61**) when 9-(2-cyanoethyl)adenine is exposed to either the anhydride or acid chloride. A mechanism operating through cyclization of an intermediate 6-(2-carboxyethylamino) moiety with N-1 followed by hydrolytic fission **61** seems most likely. The reported failure of 9-(2-cyanoethyl)adenine to alkylate directly at N-1 with methyl acrylate supports this theory.[1436] Examples in which reaction with the 6-amino group is established usually involve adenine derivatives having N-9 blocked to alkylation. Adenosine shows this in forming the tricyclic adduct (**62**, R = H) on reaction with ethyl propiolate ($HC{:}CCO_2Et$) in aqueous ethanol at pH 4.5. Similarly, with the methyl or ethyl ester of 4-chlorobut-2-ynoic acid, the corresponding 7-chloromethyl-8,9-dihydro-9-oxopyrimido[1,2-*c*]purine-9-β-D-riboside (**62**, R = CH_2Cl) results in good (82%) yield. A notable feature is the reverse mode of reaction which occurs on change to pH 7 in the same solvent. The product in low yield (31%) is the isomeric 9-chloromethyl-7-oxopyrimido[1,2-*c*]purine (**63**). Structural elucidations follow from UV, IR, ^1H NMR, and X-ray crystal diffraction studies.[1501] Guanosine appears not to react under these conditions.[1501] Theophyllines give the expected 7-substituted derivatives; with propiolactone and acrylonitrile the respective 7-(2-carboxyethyl)-[1529] and 7-(2-cyanoethyl)purines are obtained.[1298] An unsual transformation of a methyl to a ketonyl group is seen when 8-azidocaffeine is irradiated

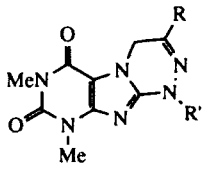


60 **61** **62** **63**

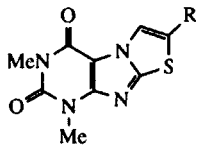
(UV) in alcohols; with ethanol and isopropanol the products in high yields (> 80% are the 7-acetonyl derivatives (**64**, R = H and Me) of 8-aminotheophylline, the reaction involving concomitant reduction of the azide group.[1405]



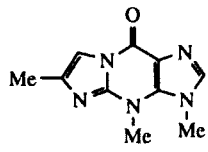
64



65

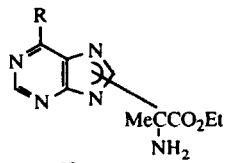


66

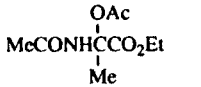


67

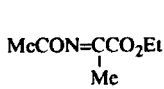
If 7-ketonyltheophyllines with a halogen, methylsulfonyl, or other reactive group at C-8, react with hydrazines tricyclic 1,4-dihydro-1,2,4-triazino[3,4-*f*] xanthines (**65**, R and R′ = H, Me, Ph) result.[1737-1739]. An 8-thiotheophylline analog with phosphoryl chloride undergoes cyclization to the thiophene derivative (**66**).[1739] A variation of this approach is found in the formation of 8,9-dihydro-3,4,6-trimethyl-9-oxoimidazo[1,2-*a*]purine (**67**) from 3,9-dimethylguanine and bromoacetone in which alkylation at N-1 is accompanied by a cyclodehydration involving the 2-amino group.[964] Not immediately apparent as being addition reactions are the 9- (**68**, R = NH_2, Cl, SH) and 7-(alanin-2-yl)purines derived from adenine and other 6-substituted purines when the anionic forms react with ethyl *N*-acetyl-2-acetoxyglycinates (**69**) in dimethylformamide (5°C, 0.5 h). Loss of the acetoxy group as acetic acid would afford reactive acylimine intermediates of the type (**70**) that are capable of Michael additions.[1218] Both isocyanates and isothiocyanates show behavior similar to that of chloroformates in their reactions with adenine; both imidazole and amino group nitrogens may be involved (see Chapter VIII , Section 5.D.i). In dimethyl sulfoxide (20°C) and restricted (< 2 mols) amounts of alkyl isocyanate, the 9-carbamoyl derivative (**71**) is obtained; isothiocyanate analogs give 9-thiocarbamoyl purines. The more reactive aryl isocyanates tend to give products resulting from reaction at both ring and amino group nitrogens, but by using equimolar ratios of reagent and purine at room temperature, 9-carbamoyl adenine is formed.[837] Demonstrating the low stability of the 9-carbamoyl groups is their facile removal in boiling water or cold sodium hydroxide or ammonia solution.[837] Corresponding additions at N-9 occur with 6-methylamino purine.[837]



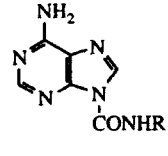
68



69



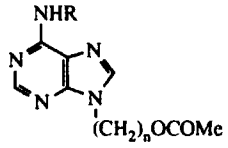
70



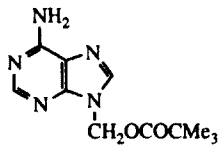
71

Use of halogenoalkyl esters for alkylation gives purines having the carboxyl moiety linked in reverse fashion to the imidazole nitrogen and separated from it

by an alkyl group linkage. These derivatives are used as synthetic intermediates because they afford the *N*-hydroxyalkylpurine analogs on hydrolysis. Representative examples are the 6-aminopurines (**72**, R = H, CH_2Ph, n = 2–4), which are converted to the 9-hydroxyalkyl derivatives by acid treatment.[1266] The 7- and 9- hydroxybutylguanines from interaction of a 2-amino-6-alkoxypurine with bromobutyl acetate are similarly obtained and subsequent hydrolysis of the products results.[1179] When halogenomethyl esters are employed, the resulting *N*-hydroxymethylpurines are unstable, undergoing ready degradation to the parent 9-unsubstituted purines. By way of illustration, the reaction product (**73**) from adenine and chloromethyl pivalate is rapidly transformed in aqueous alkali to adenine.[1437,1464]



72



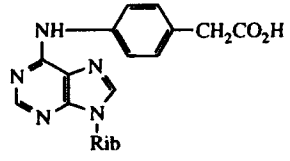
73

9. PURINYLAMINO AND PURINYLTHIO ACIDS (*H*392)

A. Purinylamino Acids and Esters

a. Preparation and Reactions (H392)

A variety of approaches is available which includes halogen or other suitable group replacement by an amino acid, direct interaction of an aminopurine with an alkyl chloroformate, syntheses from pyrimidine[864] or imidazole[970] precursors having carboxyamino group in situ and some rearrangements and other transformations. The formation of 2-carboxymethylamino-1,6-dihydro-6-thioxopurine using either the 2-chloro- or 2-fluoropurine and glycine illustrates these techniques. The parent 2- carboxymethylaminopurine together with the 6-methyl homolog are also derived from the 2-fluoropurines.[1114] Conversion of 2-ethoxycarbonylamino into a 2-amino group by potassium hydroxide is used in forming 2,6-diamino- and 2-amino-6-dimethylaminopurine.[864] Exemplifying aryl-containing moieties is the 6-(4-carboxymethylphenylamino)purine riboside (**74**) from

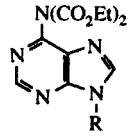


74

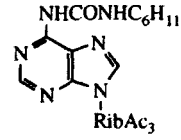
interaction of 6-chloropurine riboside and 4-aminophenylacetic acid in aqueous ethanol (80°C, 3 days) containing triethylamine under argon.[1179]



75

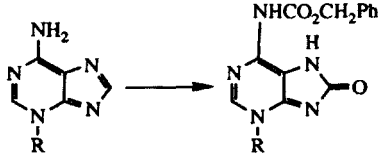


76

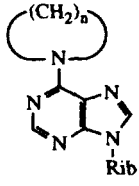


77

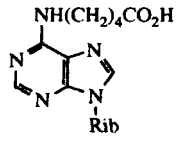
Using pressure conditions adenine is converted into 6-ethoxycarbonylamino purine by ethyl chloroformate in pyridine together with some *N,N'*,-dipurin-6-ylurea (**75**, R = H).[1736] With less vigorous treatment the 6-bis(ethoxycarbonyl)amino derivative (**76**, R = H) is obtained, but some reaction at N-9 is also possible. Both ethyl and phenyl chloroformate give the 6-substituted aminopurine with adenosine, although some disubstituted product (**76**, R = ribosyl) also results.[1740] The *O*-triacetylated derivative of adenosine forms the 6-phenoxycarbonylaminopurine in pyridine at 70°C, but when using a threefold excess of the reagent at 20°C, the 6-bis(phenoxycarbonyl)amino analog[1499] results. Removal of one phenoxycarbonyl group from the latter utilizes the stoichiometric amount of morpholine (dioxan, 20°C), but with an excess of cyclohexylamine (20°C, 1 h) this group removal is followed by amination of the product to the ureidopurine (**77**). The less-reactive 6-methoxycarbonylaminopurine only reacts with cyclohexylamine in pyridine at 100°C. Ammonia treatment gives the unsubstituted 6-ureido riboside. A 6-isocyanatopurine intermediate is presumed to be involved in these alkoxycarbonyl to ureidopurine transformations.[1499] The most satisfactory explanation for isolation of an 8-oxopurine (**79**, R = Et or Ph) following treatment of 3-ethyl- or 3-phenyladenine (**78**, R = Et and Ph) with benzylchloroformate in acetic acid assumes initial imidazole ring fission to the 4,5,6-triaminopyrimidines occurs and subsequent carbobenzoxylation of the 5-amino group and recyclization to the 8-oxopurine.[941] The oxidation product (potassium permanganate) from the riboside of 6-piperidinopurine (**80**, $n = 5$) is the 6-(4-carboxybutylamino)purine (**81**) with adenine as a minor product. Only the lactam derivative (**82**) results from oxidizing the 6-pyrrolidino analog (**80**, $n = 4$).[1442] Conversion of the methyl ester of 6-amino-4-benzylamino-2-carboxyamino oxazolo[5,4-*d*]pyrimidine (**83**, R = CH_2Ph) into 9-benzyl-8-methoxycarbonylaminoguanine (**84**) is achieved in acetonitrile under reflux. As no corresponding guanine derivative is obtained using the debenzylated precursor (**83**, R = H), this approach appears to have somewhat limited value.[1106] Isocyanates and isothio-



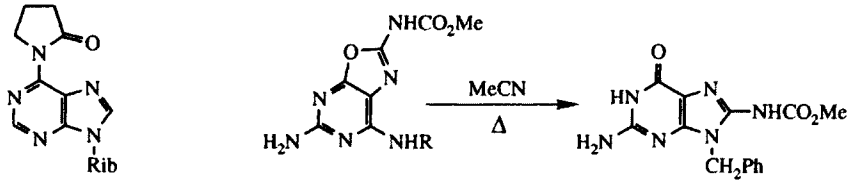
78 **79**



80

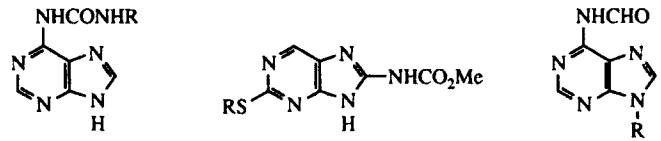


81



82 **83** **84**

cyanates will react with adenines at a ring nitrogen or at the amino group; selectivity is largely controlled by temperature and concentrations of reactions. Adenine with an alkyl isocyanate (2 mol. equiv.) at 90°C gives mainly the 6-*N'*-alkylureidopurine (**85**, R = alkyl).[837] adenosine reacts in the same manner.[1499] Corresponding derivatives arise with 6-methylaminopurine and alkyl and phenyl isocyanates, but with the latter reagents a tendency to form 9-carbamoyl-6-ureido derivatives is found.[837] By contrast, alkyl isothiocyanates under these conditions give mainly 9-thiocarbamoyladenines.[837] A novel Traube-type closure with (methoxycarbonyl)isothiocyanate and a DCC catalyst gives a range of 2-alkyl- and 2-arylthio-8-methoxycarbonylaminopurines (**86**, R = Me, Ph, *n*-Pr, *i*-Pr, and CH_2Ph) from appropriate 2-alkylthio-4,5-diaminopyrimidines.[1585] Of passing relevance is formation of formylaminopurine precursors of these acids, as illustrated by the 6-formylaminopurine[971] (**87**, R = H) and 9-substituted analogs[1860] (**87**, R = alkyl) obtained from cyclizations of 4-amino-5-formamidinoimidazoles with formic–acetic anhydride (see Chapter III, Section 1.D).



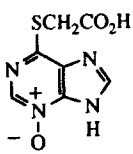
85 **86** **87**

B. Purinylthio Acids and Derivatives (*H*393)

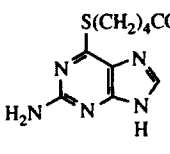
a. Preparation and Reactions (H393)

With few exceptions, the route used involves condensing a halogenoalkyl acid with a thioxopurine in an alkaline medium. The comparatively small number of applications uncovered of the alternative approach, in which a halogenopurine is condensed with a thioacid, reflects the handling problems associated with such thio derivatives and the generally reduced yields obtained.

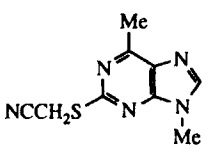
Recent illustrations include the use of chloroacetic acid in aqueous sodium hydrogen carbonate in the formation of 2-carboxymethylthio-6,8,9-trimethylpurine from the 2-thioxopurine[841,878] and the 6-carboxymethylthio derivative (**88**) from the 3-oxide of 6-mercaptopurine.[1114] Both 8-thioxo- and 8-thioxo-9-methyl-7,8-dihydropurine react likewise with this and related halogeno acids.[1741] Some



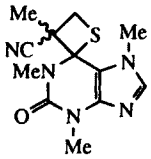
88



89

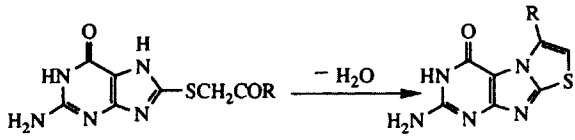


90

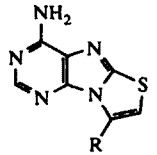


91

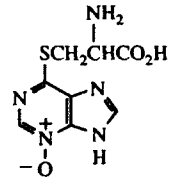
analogous amide preparations are chloroacetamide with the 2-thioxo derivatives of 6,8-dimethyl-,[848] 6,9-dimethyl-,[848,1188] and 6,8,9-trimethylpurines[848] and with 6-mercaptopurine and the 9-methyl homolog.[1741] Various *N*- and *C*-alkyl chloroacetamides have also been employed.[848,1741] Likewise, a range of 4-bromobutyl(*N*-alkyl)carboxamides gives derivatives (**89**) with 6-thioguanine (*M*-NaOH, 20°C).[1742] The 2-cyanomethylthio-6,9-dimethylpurine (**90**) is formed when the 2-thioxopurine precursor and chloroacetonitrile react in aqueous sodium hydrogen carbonate.[1741] An unusual exocyclic nitrile is the thietane adduct (**91**), occurring in two isomeric forms, produced on irradiation of the 6-thioxo derivative of caffeine with methacrylonitrile.[1743] Chloroacetone and bromoacetophenone give the expected *S*-acetonyl derivatives (**92**, R = Me and Ph) with 8-thioxoguanine in aqueous sodium hydroxide.[1203] Both products undergo cyclodehydration following methanolic hydrogen chloride and polyphosphoric acid treatment, respectively, giving the tricyclic thiazolo [2,3-*f*]purines (**93**, R = Me and Ph). Although analogous tricycles are formed by 8-thioxohypoxanthine[1373] and other 8-thioxopurines,[1371,1744] the cyclization of 8- acetonylthioadenine gives the product (**94**) as a result of involvement with the alternative imidazole nitrogen.[1372] Illustrating another less-used approach is the reaction of 6-chloropurine-3-oxide with cysteine in methanol containing sodium hydroxide (80°C, 2 h) which gives **95**. Glutathione gives the corresponding derivative with the chloropurine.[1114] A rare example of an *S*-formylated purine occurs as a secondary product (**96**) from a pteridine synthesis by ring closure of a thiouracil with triethyl orthoformate.[900]



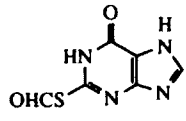
92 93



94



95



96

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER X

Nitro-, Nitroso-, and Arylazopurines (*H*401)

1. The Nitropurines (*H*401) 303
A. Preparation (*H*401) and Reactions (*H*403) 303
2. *C*-Nitrosopurines (*H*405) 303
A. Preparation, Properties, and Reactions (*H*405) 304
3. The Arylazopurines (*H*405) 304
A. Preparation and Reactions (*H*405) 304

The relatively few examples given in this chapter reflect the low level of interest in such derivatives, possibly as a result of inherent synthetic difficulties coupled with the limited scope for their application as intermediates.

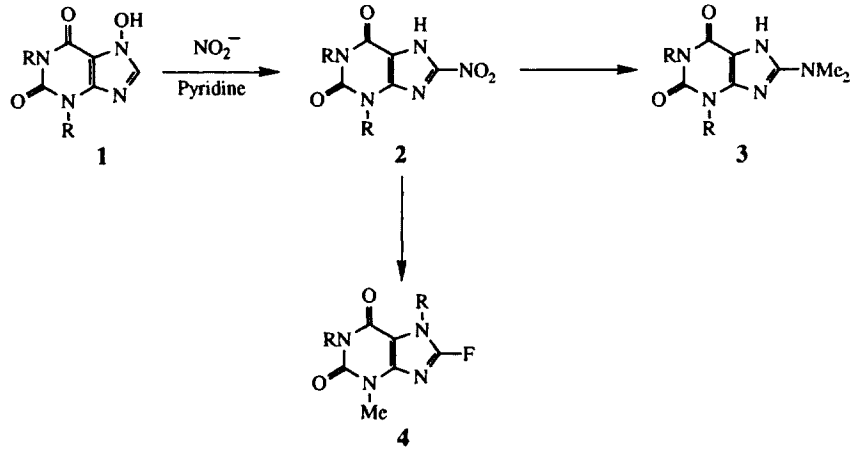
1. THE NITROPURINES (*H*401)

A. Preparation (*H*401) and Reactions (*H*403)

An indirect example is provided by rearrangement of 7-hydroxyxanthine (**1**, R=H), in boiling pyridine containing sodium nitrate, to 8-nitroxanthine[920] (**2**, R=H). Nucleophilic displacement of an 8-nitro group is demonstrated by the theophylline analog (**2**, R=Me) being converted to the 8-dimethylamino derivative (**3**, R=Me) when heated (230°C, 6 h) in dimethylformamide containing either phosphoryl or *p*-toluenesulfonyl chloride. This reaction presupposes an intermediate replacement of nitro by chlorine as the first step.[911] A relevant transformation of 8-nitrotheophylline (**2**, R=Me) and the caffeine homolog to the respective 8-fluoropurines (**4**, R=H and Me) by liquid hydrogen fluoride under pressure (100°C, 16 h) are further examples.[1128] A derivative with a carbon-linked nitropurine is the 8-(2-nitrovinyl)caffeine (**5**) resulting from interaction of 8-formylcaffeine with nitromethane (> 10°C, 0.5 h) in aqueous methanol. Catalytic hydrogenation (Raney nickel) of the product affords 8-(2-aminoethyl)caffeine.[916]

2. *C*-NITROSOPURINES (*H*405)

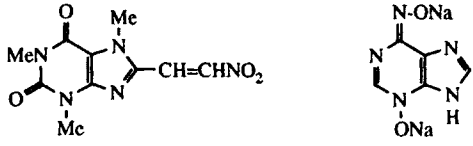
Preparations and reactions of *N*-nitrosopurines are detailed in Chapter VIII, Section 5.F.c.



1 2 3 4

A. Preparation, Properties, and Reactions (*H*405)

As an extension of the known route (*H*405) for 6-nitrosopurine, oxidation of 6-hydroxyaminopurine-3-oxide with activated manganese dioxide affords the 3-oxido congener as an unstable red crystalline derivative best stabilized as the disodium salt (**6**).[1142] In place of managanese dioxide, UV irradiation of the hydroxyamino precursor gives the same nitrosopurine.[1172]

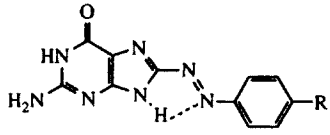


5 6

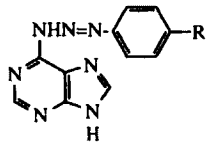
3. THE ARYLAZOPURINES (*H*405)

A. Preparation and Reactions (*H*405)

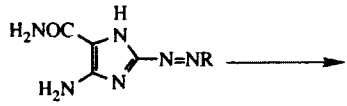
Coupling of guanine with diazotized aniline and 4-substituted anilines gives 8-diazonium purines highly stable in both acid (pH 1) and alkaline (pH 10) solutions, even at 100°C for over 24 hours. Product stability is taken to indicate the existence of intramolecular hydrogen bonding induced by an *E* conformation (7, R=H,Me,Br,SO_2OH) being adopted.[1461] Guanosine and guanylic acid give corresponding 8-azo analog.[1461] A relevant point is that as adenine derivatives give undisputed 6-triazenopurines[858,1994] (Chapter VIII, Section 5.F.d) with aryl diazonium salts such as (**8**), the product from reaction with guanines by analogy were



7

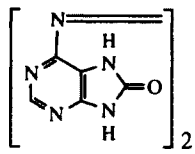


8



9 10

formulated originally (*H*333,355) as 2-triazenopurines. Sodium dithionite reduced **7** (R=Br) to 8-aminoguanine.[1461] The overall stability of the 8-arylazopurines is shown by formation of 8-phenylazohypoxanthines (**10**, R=Ph, 4-ClC_6H_4) by ring closure of the 4-amino-5-carbamoylimidazoles (**9**) in triethyl orthoformate with sodium ethoxide under reflux.[960] Adenine is transformed in a multistep reaction involving hydrogen bromide, potassium permanganate, and hydrogen peroxide into the C-6 linked azopurine derivative (**11**). Upon reduction of the product in hydrochloric acid (95°C, 2 h) with tin(II) chloride, 7,8-dihydro-8-oxoadenine results.[1427]



11

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER XI

Purine-*N*-Oxides (*H*409)

1. Preparation of Purine-*N*-Oxides (*H*409) 308
   A. Purine-1-Oxides (*H*410) 309
   B. Purine-3-Oxides (*H*411) 310
   C. Purine-7-Oxides (*H*413) 311
   D. Purine-9-Oxides (*New*) 312
2. Properties of Purine-*N*-Oxides (*H*416) 313
3. Reactions of Purine-*N*-Oxides (*H*416) 314
   A. Reduction (*H*416) 314
   B. *O*-Alkylation and *O*-Acylation (*H*418) 314
      a. *O*-Alkylation (*H*418) 314
      b. *O*-Acylation (*H*418) 315
   C. Rearrangement (*H*419) 315
      a. By Irradiation (*H*419) 316
      b. With Anhydrides (*H*419) 317
      c. By Thermal or Other Means (*H*419) 319
   D. Other Reactions (*H*422) 319
   E. Exocyclic *N*-Oxides (*New*) 320
      a. Preparation and Reactions 320
4. Purine *N*-Alkoxides (*H*423) 321
   A. Preparation (*H*423) 321
   B. Reactions (*H*423) 322
      a. Reductions (*H*423) 322
      b. Rearrangement (*H*423) 322
      c. Other Reactions (*H*424) 323
5. Biological Activity (*H*425) 324

Although many examples of the 1- and 3-oxides are now available, representatives of 7-oxides are somewhat more limited in scope, being confined to those of xanthine and guanine. When the parent volume was published, no examples of purine-9-oxides existed, but in the intervening period subsequent efforts have produced such derivatives. As a result of UV and NMR studies, the question of the tautomeric forms adopted is largely resolved. Neutral species of the oxides of hypoxanthine, xanthine, and related oxopurines are present mainly or totally as the *N*-hydroxypurine. The initial assumption that an adjacent oxo group is required for *N*-hydroxy tautomer formation is now modified to include involvement of more distant oxo groups in view of the structural identifications made for 9-hydroxyhypoxanthine and -xanthine analogs.[957,958]

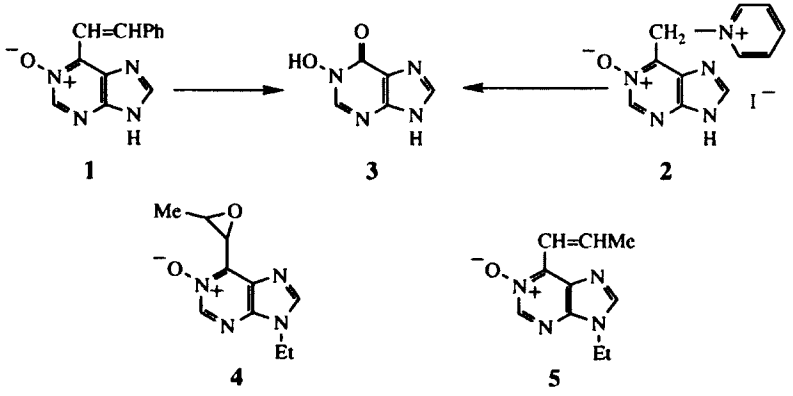
With guanine and derivatives, the situation is less clear cut, the 1-oxidopurine is a mixture of the *N*-hydroxy and *N*-oxide forms, whereas the 3-isomer shows mainly the 3-hydroxy configuration,[828] as do the 7-, 8-, and 9-methyl and the 1,7-[838]and 7,8-dimethyl[1696] derivatives. The same tautomer is also predominant for 9-hydroxyguanine,[958] but the absence of enol possibilities with either 1-methyl or 1,7-dimethylguanine shows in the formation of only the respective 3-oxide forms. Although synthesis of the 7-oxide of guanine itself is still awaited, the *N*-hydroxy tautomer would be the expected predominant species by analogy with xanthine-7-oxides.[921] An *N*-oxide form not unexpectedly features in the 7-oxide of 9-methylguanine.[920] The occurrence of 9-hydroxyguanines is noted above.[958] Both 1- and 3-oxides of adenine exist as such, although the 7-oxidopurine is lacking. A recent preparation of the 9-isomer gives a mixture consisting mainly of the 9-hydroxy together with appreciable amounts of the 9-oxide tautomer.[990] Similar *N*-oxide formation occurs in 3-oxido-2,6-diamin ›purine,[1166] but in contrast the 3-hydroxy analog exhibited by isoguanine reflects the effect of replacing the 2-amino group in the former purine by an oxo group.[1697] Ion formation is a useful aid in differentiating between *N*-oxide and *N*-hydroxy tautomeric forms. The characteristic strong absorption due to the *N*-oxide moiety, shown by the UV spectrum of the neutral molecule, is absent from the spectrum of an *N*-hydroxypurine. On converting the latter to the anion, the *N*-oxide absorption band appears as a result of proton loss from the hydroxy group. In the case of *N*-oxidopurines, anion formation involves proton removal from the imidazole ring and no significant spectral change is observed.[1697] A volume covering the chemistry of heterocyclic *N*-oxides, including those of purines, for the period up to 1971, is available.[1958]

1. PREPARATION OF PURINE-*N*-OXIDES (*H*409)

No significant advances have emerged in the synthesis of 1- and 3-oxides, direct oxidation of the purine by a peroxyacid is still the favored approach for both. The presence of a strong election-attracting group at C-6 influences the oxidation site with N-3 being preferred over N-1. With electron-releasing moieties the reverse situation applies, with N-1 being the first nitrogen oxidized.[1166] Use of the oxidant stabilizer, bis(5-*tert*-butyl-4-hydroxy-2-methylphenyl)sulfide,[1703] improves the oxidation of 6-chloropurine with *m*-chloroperbenzoic acid. Alternative routes are ring closure of a suitable imidazole in the case of 1-oxidopurines and Traube-type pyrimidine cyclizations for the 3-oxido derivatives. Formation of 7-oxidopurines and the more recently introduced 9-oxido analogs is presently restricted to Traube closures for the former and corresponding cyclization of imidazole-*N*-oxides with the latter. The range of these purines has been increased greatly by interconversion of existing oxidopurines through nucleophilic substitution reactions and rearrangements. In some cases, an initial synthesis of an *N*-benzyloxypurine is more facile, requiring a debenzylation step to liberate the *N*-oxide.

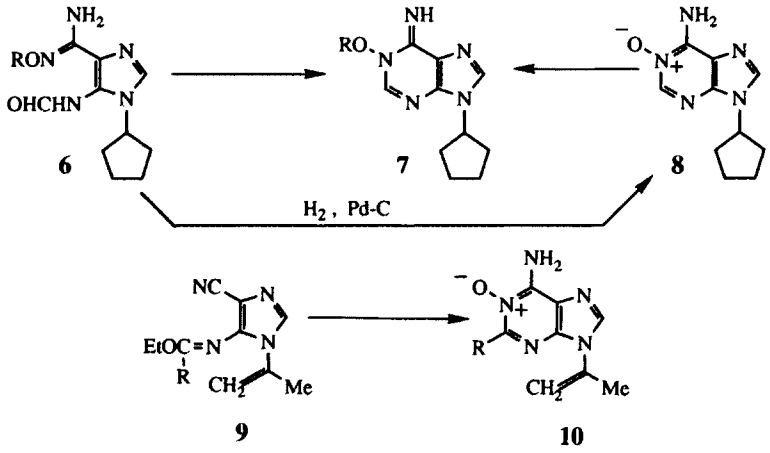
A. Purine-1-Oxides (*H*410)

Reinvestigation of the oxidation of purine confirms the product to be a mixture of the 1- and 3-oxides. The influence of the oxidizing agent is noteworthy in that with peroxyacetic acid the 1-isomer predominates but the reverse occurs with *m*-chloroperbenzoic acid.[1057] A similar mixture of oxides arises using the latter reagent with 6-methylpurine.[1057] Attempts to convert 6-methylpurine-1-oxide to purine-1-oxide by oxidative removal of the 6-methyl group failed, but under milder conditions (selenium dioxide in dimethylformamide, 25°C) 6-aldehydopurine-1-oxide is obtained which, on further oxidation with acidified potassium permanganate, gives the 1-oxide of 6-carboxypurine.[1057] Two approaches to hypoxanthine-1-oxide utilizing 6-methyl group interconversions involve either formation of 6-styrylpurine-1-oxide (**1**) with benzaldehyde and hydrogen chloride and subsequent aqueous permanganate oxidation to the hypoxanthine (**3**) or the alternative treatment with pyridine and iodine (Ortoleva–King reagent) and use of the same oxidant on the product (**2**).[1082] Further examples of direct oxidation to the 1-oxide are of 6,9-dimethylpurine (21°C, 5 days[1073]) and 8-hydroxymethyladenine[790] by peroxyacetic acid and of adenosine in low yield (< 15%) with either dibenzoyl peroxide or diacetyl peroxide.[1076] Reaction of 9-ethyl-6-propenylpurine with *m*-chloroperbenzoic acid gives mainly the *trans*-6-epoxypurine together with minor amounts of the 1-oxides of this (**4**) and the starting material (**5**).[1071] Direct preparation of the 1-oxide of adenine nucleotide is reported using potassium peroxymonosulfate (Caro's acid) in an aqueous medium (< 90°C,1 h).[1835] This reagent appears worthy of further investigation for general *N*-oxidation of purines. Monopermaleic acid has been employed in forming the 1-oxide of adenosine.[1836] Ring closure of imidazoles provides a more selective route, using 4-carboxyamidino-5-formamidoimidazoles of the type (**6**, R = CH_2Ph). Cyclization in methanolic hydrogen chloride affords the 1-benzyloxyadenines (**7**, R = CH_2Ph) requiring *O*-debenzylation to obtain the 1-oxides[976,983] (**8**). Direct conversion of **6** to **8** occurs on catalytic hydrogenation (Pd–carbon) involving a spontaneous ring closure[976,983] (20°C, 20 h). The adenosine analog is likewise formed.[983] A variation



1 3 2

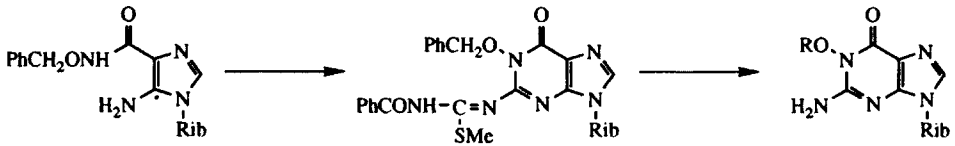
4 5



6 7 8

9 10

using the 4-cyano-5-ethoxymethylideneaminoimidazoles (**9**) in hot ethanolic hydroxylamine (80°C, 22 h) gives the adenosine derivative (**10**, R = H) as well as the 2-methyl and 2-ethyl homologs (**10**, R = Me and Et) from the appropriate ethoxyethylidene and ethoxypropylidene precursors.[1029] Alkaline degradation of 1-benzyloxyinosine to the imidazole (**11**) and subsequent treatment with benzoylisothiocyanate followed by methyl iodide affords the purine (**12**) converted either to 1-hydroxyguanine (**13**, R = H) by hydrogen bromide in acetic acid or to the 1-benzyloxy derivative (**13**, R = CH_2Ph) using dilute hydrochloric acid.[968] Conversion of **13** (R = H) to the xanthine analog occurs with nitrous acid.[968]

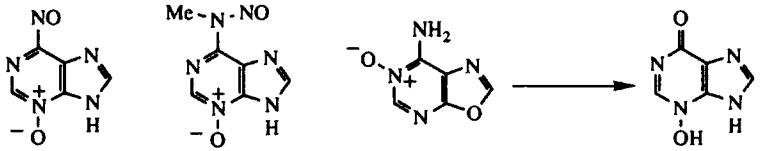


11 **12** **13**

B. Purine-3-Oxides (*H*411)

Improved yields result from direct oxidation of guanine with peroxytrifluoroacetic acid at well below (−15°C) the ambient temperatures usually employed. Likewise formed are the 3-oxides of the 1-,[838] 3-,[1704] 7-,[838] 8-,[838] and 9-methyl[838] and the 1,7-dimethyl homologs.[838] The same reagents at ambient temperature will also oxidize 7,8-dimethylguanine.[1696] Dilute hydrochloric acid hydrolysis converts these derivatives to the appropriate *N*-methylxanthine-3-oxides.[838,1704] Benzyl parabanic acid is the only product from an oxidation attempt with 9-benzylguanine. Further examples of successful oxidation procedures are with 2-amino-6-methoxy- (peroxytrifluoroacetic acid),[838]2-amino-6-chloro-(MCPBA),[1166] 6-cyano-(MCPBA or peroxyacetic acid),[1057] and 6-methylpurine (MCPBA).[1057]

An improved version of an existing procedure for 6-chloropurine oxidation is available.[1142] A specific route to purine-3-oxide involves oxidation of purine-6-sulfinic acid to the oxide with subsequent removal of the sulfur moiety by heating in formic acid (80°C, 0.5 h). An alternative approach is by thermal decarboxylation of 6-carboxypurine-3-oxide using sublimation (285°C, 10 mm Hg).[1957] The enhanced activity of the halogen in 6-chloropurine-3-oxide toward nucleophiles is utilized in forming other 6-hydroxyamino, 6-selenoxo, and 6-thioxo derivatives.[1142] Modifications to the latter purine extend the range of reactions to the 6-methylsulfonyl-, 6-fluorosulfonyl-, and 6-sulfonamidopurine-3-oxides.[1142] The unstable 6-nitrosopurine analog (**14**), from oxidation of 6-hydroxyaminopurine-3-oxide with activated manganese dioxide (**25**°C, 1 h), is stabilized by conversion to the disodium salt.[1142,1172] Treating the 6-(1-methylhydrazino)purine derivative with nitrous acid gives 6-(*N*-nitroso)methylaminopurine-3-oxide (**15**).[1172] Standard reactions afford 2-amino-6-methoxy- and 2,6-diaminopurine-3-oxides from the 6-halogeno derivatives although ethanolic thiourea, while successfully replacing the halogen by thioxo, also reduces the oxide to give only thioguanine.[1166] In this context the ready conversion of 6-chloropurine-3-oxide to the corresponding 6-selenoxo and 6-thioxo analogs should be noted.[1142]

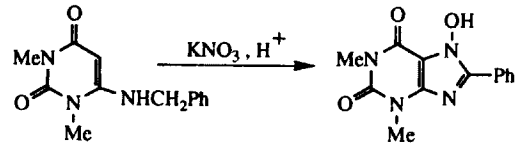


14 **15** **16** **17**

The Traube closure has had little application, largely due to a lack of suitable 4,5-diaminopyrimidine-*N*-oxides, but the synthesis of 2,3-dihydro-3-hydroxy-2-oxopurine provides a rare example of the approach.[861] A novel sodium hydroxide induced rearrangement of 7-aminooxazolo[5,4-*d*]pyrimidine-6-oxide (**16**) to hypoxanthine-3-oxide (**17**) occurs in 42% yield[944] at room temperature. Photoisomerization of 1-hydroxy- to 3-hydroxyxanthine, occurring in solution under UV irradiation, gives a restricted route, possibly confined to dioxopurines since neither of the 1-oxides of guanine or isoguanine undergo like rearrangements but suffer reduction of the oxide function only.[1705]

C. Purine-7-Oxides (*H*413)

Traube-type syntheses and derivative forms of this reaction still provide the only general routes in which the *N*-oxide function is formed on ring closure of either a 4-amino-5-nitroso- or a 4-amino-5-nitropyrimidine. Examples of the former type are various 7-hydroxyxanthines from ring closure with aldehydes of 4-amino-5-nitroso-2,6-dioxopyrimidine; these include the parent oxide (aqueous formaldehyde),[920,1834] as well as the 8-propyl-[919] (butyraldehyde) and 8-phenylxanthine (benzaldehyde) homologs.[921] Likewise formed are corresponding

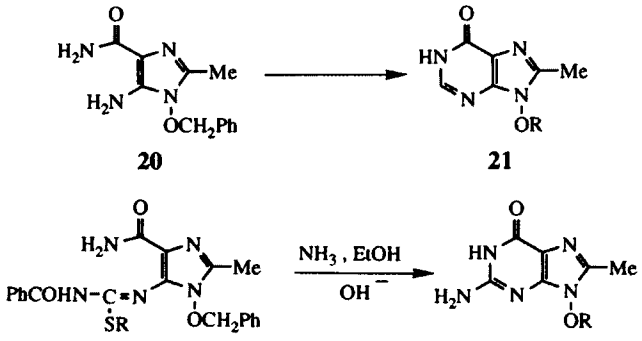


18 **19**

7-hydroxy-1-methylxanthines.[1834] In the alternative approach, an intramolecular cyclodehydration between the 5-nitro and 4-alkylamino groups of a pyrimidine is made under alkaline conditions. Derivatives obtained in this manner include the 7-oxide of 9-methylguanine[879] as well as 7-hydroxy-8-phenylxanthine[921] and the 1,3-dimethylated homolog.[922] A novel variation involves an in situ nitration of the 5-unsubstituted pyrimidine (**18**) with potassium nitrate in acetic acid (70°C, 1 h) from which a good yield (65%) of 7-hydroxy-8-phenyltheophylline (**19**) is obtained as a result of a concomitant cyclization also being involved.[1706]

D. Purine-9-Oxides (*New*)

The first examples of these derivatives immediately post dates the publication of the original volume. An adaptation of the Shaw synthesis, for forming 9-alkylpurines from *N*-alkylimidazoles, used *N*-benzyloxyimidazoles in their place, giving 9-benzyloxypurines which are readily debenzylated to the 9-oxidopurine. Exemplifying this is closure of 5-amino-1-benzyloxy-2-methylimidazole-4-carboxamide (**20**) with ethyl formate and sodium methoxide to 9-benzyloxy-8-methylhypoxanthine (**21**, R = CH_2Ph), which is transformed by hydrogen bromide in acetic acid to the 9-hydroxypurine (**21**, R = H). The xanthine analog is derived from cyclization with diethyl carbonate and sodium ethoxide (reflux, 6 h).[958] A multistage procedure is required for 8-methylguanine-9-oxide (**23**, R = H) involving initial treatment of **20** with benzoylisothiocyanate and methylation of the product (**22**, R = H) to the methylthio derivative (**22**, R = Me) followed by successive reactions with hot ethanolic ammonia and *M*-sodium hydroxide affording the 9-benzyloxyguanine (**23**, R = CH_2Ph) which is converted as above to



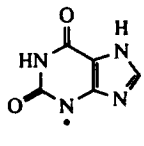
20 **21**

22 **23**

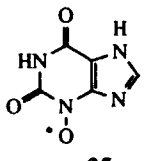
9-hydroxy-8-methylguanine. Likewise formed are 9-hydroxyhypoxanthine and -guanine, but ethyl carbonate failed to give the xanthine analog; preparation of the latter necessitated nitrous acid hydrolysis of the 9-benzyloxyguanine and subsequent debenzylation.[957] Ring closure with triethyl orthoformate followed by ethanolic ammonia of 5-amino-1-benzyloxyimidazole-4-carbonitriles gives 9-benzyloxyadenines, affording the 9-hydroxy analogs on acid treatment.[990]

2. PROPERTIES OF PURINE-*N*-OXIDES (*H*416)

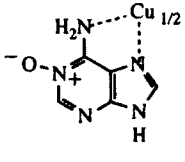
Anion formation in derivatives predominently present as the *N*-hydroxy tautomer is achieved by proton loss from the extranuclear oxygen. This is demonstrated by the similarity of the UV spectra of the anions with those of neutral molecules of similar purines having established *N*-oxide structures.[958,1057,1250] In the latter cases anions are usually formed by proton removal from the imidazole ring. Under various types of irradiation (UV, γ, or X ray), the N–O bond in the solid state can undergo homolytic fission producing radical forms.[1707] The purple product obtained with powdered 3-hydroxyxanthine irradiated at ambient temperatures is highly stable (>1 year) when dry, but undergoes immediate decomposition in both aqueous or nonaqueous solvents. Corresponding radicals are given by the 1- and 7-methylxanthine analogs.[1696] An amidogen structure of the type (**24**) based upon ESR studies was proposed,[1696] but subsequent workers, using a single crystal, claim that the nitroxyl radical (**25**) is present.[1708] In aqueous solution with hypoxanthine-3-oxide over a pH range between 0 and 7, various tautomeric species of the neutral molecule exist, each showing a different ionization pattern under irradiation.[1709] Both *N*-hydroxides of hypoxanthine and xanthine are reduced to the parent purine in solution. The complex obtained from interaction of adenine-1-oxide with Cu^{2+} ions originally accorded the purine structure[1710] (**26**) is now on crystallographic evidence shown to be the imidazole (**27**), ring opening being induced by the acid conditions used.[1711] The presence of an oxide moiety can lead to the strong hydrogen-bond formation, as exemplified in the anti rotamer formed by the 9-methyl-6-methylaminopurine-1-oxide (**28**)



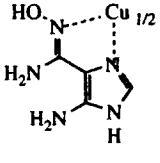
24



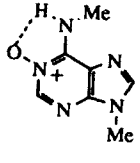
25



26



27



28

due to intramolecular bonding between oxygen and amino group. Spectral (IR, PMR) comparisons with the parent purine lacking the oxide function show that in this case the syn conformation is the preferred form. Steric interaction between *N*-7 and the methylamino group, which is weaker than hydrogen bonding, is taken to be the deciding factor.[1419]

3. REACTIONS OF PURINE-*N*-OXIDES (*H*416)

The most significant progress has been made with rearrangement studies of the oxide function involving a relocation of oxygen from nitrogen to a nearby ring carbon atom. Transformations of this type are possible with *N*-oxides, *N*-hydroxides, or *O*-acylated derivatives.

A. Reduction (*H*416)

Reactions with Raney nickel in water or alkaline solution remain the most favored for elimination of oxygen. Among the many examples available are 6-formyl-,[1057] 9-methyl-6-methylamino-,[978] and 9-benzyl-6-benzylaminopurines[1466] and the naturally occurring eritadenine[1579] from their 1-oxides. Similar reductions occur with the 3-oxides of purine,[1057] the 6-methyl homolog,[1057] and 7-hydroxyxanthine.[920] Alternative reductions are with hydrogen iodide, to convert guanine-1-oxide to the purine,[968,1250] hydrazine in deoxygenation of 6-carboxypurine-1-oxide,[1057] and other 6-substituted purine-1- and -3-oxides[1080] and hydroxylamine in similar reactions.[1080] Thermal instability is a feature of 8-substituted-7-hydroxyxanthines involving loss of the *N*-hydroxy group. Typical examples are the formation of 8-phenylxanthine and the theophylline analog on heating the 7-hydroxy derivatives in phosphate buffer,[921] dimethylformamide,[1706] or aqueous dimethyl sulfoxide.[922] Other degradation products may result from this treatment. In contrast, the corresponding 8-unsubstituted xanthines are thermostable, with no loss of the *N*-hydroxy group. Reduction occurs under UV irradiation; guanine,[1705] isoguanine,[1705] hypoxanthine,[1250] and the 1-methyl derivative[1250] are obtained from the 1-hydroxypurines by this method. Although 6-methylpurine-1-oxide and the 9-methyl homolog undergo like reductions, the reaction is complicated by other products resulting from rearrangements or ring opening.[1073] The reaction of ethanolic thiourea with 2-amino-6-chloropurine-3-oxide in giving only 2-amino-1,6-dihydro-6-thioxopurine provides an example of inadvertent reduction[1166] when similar reactions have left the oxide function intact.[1142]

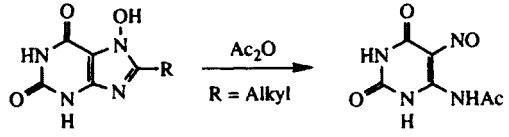
B. *O*-Alkylation and *O*-Acylation (*H*418)

a. O-Alkylation (H418)

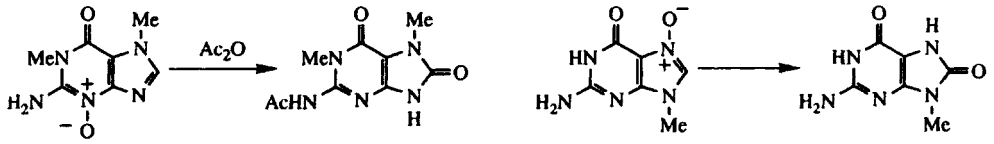
Topics relating to *O*-alkyl derivatives are discussed in Section 4A.

b. O-Acylation (H418)

Isolation of *O*-acylated purines is not possible in many cases, owing to the facility with which these compounds undergo rearrangement to oxopurines. Purines having *N*-oxide rather than *N*-hydroxy structures cannot assume stable *O*-acyl derivatives, but the occurrence of rearrangement products after reaction with an anhydride suggests involvement of some form of *O*-acylated species as reaction intermediates. Successful acylations of *N*-hydroxy derivatives with anhydride include 3-hydroxy-2,3-dihydro-2-oxopurine (20°C, 2 weeks),[861] 1-hydroxy-,[1713] and also 3-hydroxy-1-methyl-, 3-hydroxy-1-benzyl-, and 3-hydroxy-7-methylxanthine.[957,1713] With 3-hydroxyxanthine derivatives, better yields of the acetoxy ester are obtained with an acetic anhydride–acetyl chloride mixture.[1351] The acylating reagent for the 8-methylxanthine homolog comprises the anhydride and trifluoroacetic acid (20°C, 3 h).[1235] Similar treatment converts 8-unsubstituted-7-hydroxyxanthines to the 7-acetoxy derivatives,[920,957] but causes degradation of the less stable 8-alkyl- (**29**)[919] and 8-phenylxanthine[921] homologs to the acetylated 4-amino-5-nitrosopyrimidine (**30**). Unlike 3- and 7-hydroxyxanthine, the 9-hydroxy isomer gives no isolatable *O*-acylated derivative, the product being uric acid on reacting with either acetic or trifluoroacetic anhydride.[957] Oxides of guanine are likewise rearranged without isolation of the *O*-acyl intermediate, as illustrated by the formation of the 8-oxo derivative (**32**) following the action of anhydride on 1,7-dimethylguanine-3-oxide (**31**)[1712] and isomerization of 9-methylguanine-7-oxide (**33**) in acetic acid (100°C) to the 9-methyl-8-oxopurine (**34**).[879]



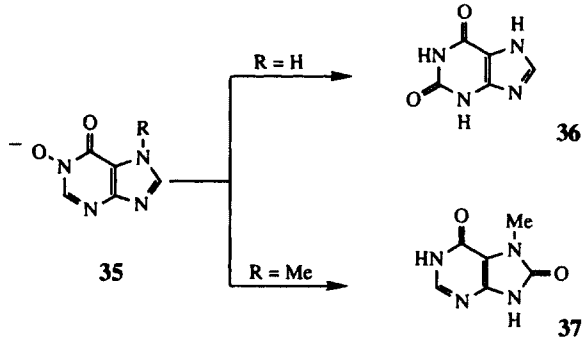
29 **30**



31 **32** **33** **34**

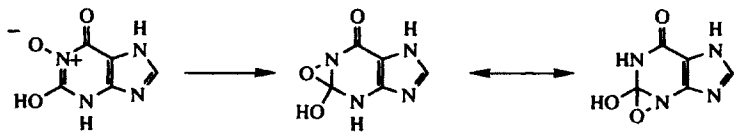
C. Rearrangement (*H*419)

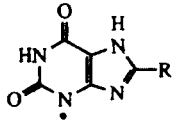
Irradiation is a prime inducer of rearrangement of *N*-oxido-, *N*-hydroxy-, and *N*-acetoxypurines. Other means include spontaneous rearrangements of *N*-acyloxy derivatives and isomerization by thermal treatment.



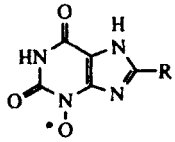
a. By Irradiation (H419)

Exposure to UV, γ, or X-irradiation, may promote reduction of the *N*-oxide to the parent purine (see Section 3.A), facilitate rearrangement to an oxopurine, or both effects may occur. Results of studies with aqueous 1-hydroxyhypoxanthine show that the course of the reaction is linked to the ionic species taking part. Both neutral molecule and the cation are reduced to hypoxanthine, but the major product from the enolate anion (**35**, R = H) is xanthine (**36**). Isolation of the 6,8-dioxopurine (**37**) as main product when the 7-methylhypoxanthine homolog (**35** R = Me) is similarly treated is noteworthy.[1250] The case of hypoxanthine 3-oxide is less clear as the neutral molecule in solution is present as a number of different tautomers, each with a characteristic response to radiation during which reduction and rearrangement may occur. These investigations show isomerization to an oxopurine is more efficient in the 3-oxides than in the 1-oxides.[1709] Unlike 1-hydroxyhypoxanthine, the neutral form and the anion of 1-hydroxyxanthine are precluded from N-1 to C-2 oxygen transitions, but instead undergo an N-1 to N-3 hydroxy group translocation.[1705] A proposed mechanism[1705] involving oxaziranе intermediates (**39A**, **39B**) derived from the nitrone form of xanthine (**38**) is similar to that advanced for conversion of 1-hydroxyhypoxanthine to xanthine.[1250] The effects of UV light on solid *N*-hydroxyxanthines has been studied using ESR.[1707] More detailed investigation with powdered 3-hydroxyxanthine shows evidence of radical formation, as indicated by the appearance of a purple solid, stable indefinitely in air but decomposing instantly in contact with water or solvents.[1696] The amidogen structure (**40**, R = H or Me) originally given[1696] has been modified by workers who favor the nitroxyl form (**41**, R = H or Me), based on results obtained using a single crystal.[1708] Examples of reactions of purines with





40

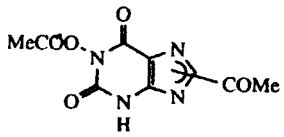


41

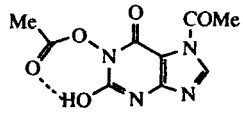
defined *N*-oxide structures are formation of corresponding 2-oxopurines from the 1-oxides of purine and 6-methylpurine in solution as neutral molecules; some reduction to the purine is found to accompany the N-1 to C-2 oxygen transition.[1057] Comparable products arise on like treatment of 6,9-dimethylpurine-1-oxide.[1073]

b. With Anhydrides (H419)

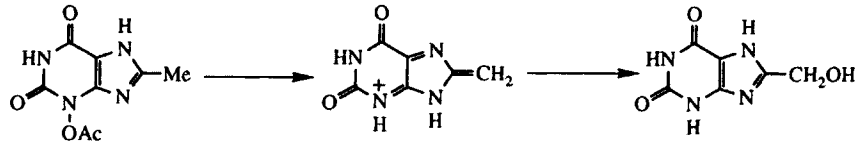
Both *N*-oxido- and *N*-hydroxypurines rearrange on treatment with acetic anhydride, but in many cases the intermediate *N*-acetoxy esters are transient species detectable only by UV and NMR spectra. With isolated acetoxypurines, rearrangement may occur spontaneously in aqueous solution or upon heating with an excess of acetic anhydride. Illustrating this are conversions of the 1-methyl,[838] 1-benzyl, 7-methyl, 9-methyl, and 7,9-dimethyl derivatives[1713] of 3-hydroxyxanthine to the corresponding *N*-alkylated uric acids in hot anhydride. Two new syntheses of uric acid have resulted similarly from 7-hydroxy-[920] and 9-hydroxyxanthine.[957] A notable exception is 1-hydroxyxanthine, which is not rearranged but gives the 1-acetoxy analog as a mixture of the 7- and 9-acetylated derivatives (**42**).[1713] Further thermal treatment only causes isomerization of the 7-acetyl group to N-9.[1713] Similarity of the UV spectrum of **42** with that of the anion of 1,7-dimethylxanthine points to the existence of intramolecular hydrogen bonding (**43**) between the acetoxy and the 2-oxo group.[1713] Both 3-[1712] and 7-oxides[879] of guanine behave like the xanthine congeners in forming the appropriate 8-oxo derivatives. Replacing the hydroxide ion in the reactions above by other nucleophiles is an effective way to introduce other groups at C-8. Initial work (*H*419), demonstrating the use of sodium chloride and methionine to form 8-chloro- and 8-methylthioxanthines, has been extended to other chloro[838,920] and methylthio[838,861,920] derivatives of xanthine and guanine[1263] as well as 8-nitropurines from treatment with sodium nitrite.[920] Innovations to the route include using ethanol to form 8-ethoxyxanthine,[920] but a variation in reaction conditions may afford uric derivatives.[861] With mercaptoethanol at neutral pH, 3-acetoxyx-



42

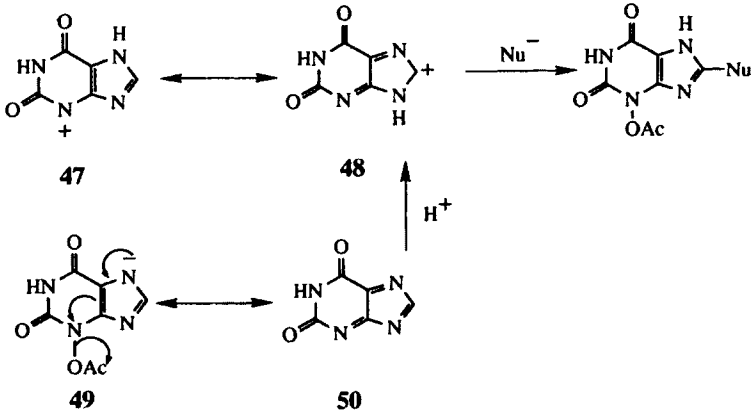


43



44 **45** **46**

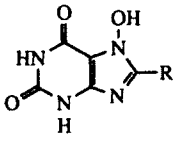
anthine is converted to 8-(2-hydroxyethylthio)xanthine.[1263] Similar transformations using 9-methylguanine-7-oxide give 8-sulfo- and 8-cyano-9-methylguanine with aqueous solutions of sodium dithionite and potassium cyanide containing benzoyl chloride respectively.[879] If the C-8 position is blocked by insertion of a methyl group in the 3-acetoxy derivatives of xanthines (**44**) and guanine, one of the rearrangement products is the 8-hydroxymethylpurine (**46**). Mechanistically this is shown by ^{1}H NMR to result from interaction of a hydroxide ion with a carbonium ion of the type (**45**) generated through fission of the ester moiety.[1235] A conspicuous failure of other types of nucleophile to react likewise may reflect a steric effect of the 8-alkyl group in the carbonium ion, inhibiting attack by the more bulky anions. The spontaneous rearrangement of 3-acetoxyxanthines to uric acids in aqueous solution is slow at low pH (< 3) values, but increases as the pH rises. Removal of the acyloxy group from the neutral molecule produces a nitrenium ion (**47**) reacting with nucleophiles in the form of the carbenium ion (**48**) at C-8. Under more alkaline conditions, the anionic form (**49**) predominates and assumes a dehydroxanthine (**50**) structure following loss of the acyloxy group and is then transformed to the carbenium ion (**48**)[1714] or to a mixture with the nitrenium ion (**47**) on protonation. The strong oxidizing action of the acetoxypurines, attributed to the nitrenium ion (**47**), shows in the liberation of halogen from inorganic bromides and iodides by the xanthine[1351] and guanine[1712] derivatives. Homolytic clearage of the *N*-OCOMe bond occurs when 3-acetoxyxanthine is exposed to UV light forming a solvent-caged amidyl radical intermediate. The latter does not, however, appear to show similarities to any of the species detected in the spontaneous rearrangements noted above.[1715]



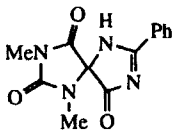
47 **48** **49** **50**

c. By Thermal or Other Means (H419)

Uric acid is the rearrangement product after heating 7-hydroxyxanthine in water.[920] Insertion of an alkyl or aryl group at C-8 induces instability, as illustrated by the 8-phenyl derivative (**51**, R = Ph) undergoing disproportionation in hot (100°C) phosphate buffer into 4-amino-5-nitrosouracil and 8-phenylxanthine.[921] Analogous reactions are found with the 8-propyl-(**51**, R = Pr) and other 8-alkylxanthines.[919] Of related significance is isolation of 8-phenyltheophylline (83%) together with some of the imidazospiroimidazole (**52**) on heating 7-hydroxy-8-phenyltheophylline in dimethyl sulfoxide.[922] The same hydroxypurine in hot dimethylformamide was previously reported (*H*422) to give 8-phenyltheophylline as the only product.



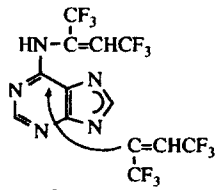
51



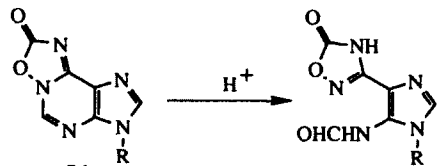
52

D. Other Reactions (*H*422)

Although adenine usually alkylates to give a mixture of 3- and 9-alkyladenines, the 1-oxide derivative forms only the 9-alkyl isomer. Use is made of this property in the synthesis of the naturally occurring nucleoside eritadenine (see Chapter VIII, Section 9.A) by directing condensation of D-erythrolactone with adenine-1-oxide to N-9. Subsequent reduction of the product to the required adenine nucleoside[1579] is with nickel. Both *N*-alkenylated isomers resulting from addition of hexafluorobut-2-yne with adenine-1-oxide in methanol have the 6-amino converted to a 6-(1-trifluoromethyl-3-trifluoroprop-2-enyl)amino group with a second reagent molecule located at N-7, N-9, or N-3 (**53**).[1375] Annelation of adenine-1-oxide or the 9-benzyl derivative with ethyl chloroformate (95°C, 2 h) affords 8-oxo-8*H*-1,2,4-oxadiazolo [2,3-*i*]purines (**54**, R = H or CH_2Ph). Under acidic conditions, ring fission of the adduct to the imidazole (**55**, R = H or CH_2Ph) occurs.[1719] The enhanced nucleophilic reactivity of the group at C-6 shown by both 1- and 3-oxidopurines is demonstrated by the ready conversion of 2-amino-



53



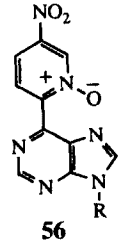
54 **55**

6-chloropurine-3-oxide to guanine-3-oxide in warm *M*-sodium hydroxide which contrasts with the inert character of 2-amino-6-chloropurine itself under these conditions.[1166] Corresponding aminations are obtained with ammonia.[1166] Similar variations between 6-chloropurine-3-oxide and the parent purine on reaction with hydrazine are reported.[1172] Under acid conditions, protonation of the oxide oxygen induces ring fission to imidazoles exemplified by the behavior of the 1-oxides of adenine[1711] and 6,9-dimethylpurine.[1073] Ring opening with alkali is found in the cases of 9-cyclopentyladenine-1-oxide and other 9-substituted purines, which are unable to form anions, producing 1-substituted-5-formamidoimidazole-4-carboxamidines.[1720] Enzymic oxidation occurs without disturbance of the *N*-oxide moiety; examples include formation of the respective 8-oxo derivatives from 2,3-dihydro-3-hydroxy-2-oxopurine[861] and guanine-3-oxide[828] on treatment with xanthine oxidase. Likewise converted is the xanthine analog to 3-hydroxyuric acid.[1699]

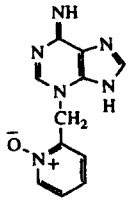
E. Exocyclic *N*-Oxides (*New*)

a. Preparation and Reactions

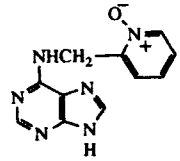
Diazotization of 9-benzyladenine with n-butyl nitrite in the presence of pyridine yields (90%) principally 2-(9-benzylpurine-6-yl)-5-nitropyridyl-*N*-oxide (**56**).[1119] From alkylation of adenine with 1-oxypyrid-2-ylmethyl chloride the products are 3-(**57**) and 9-(1-oxypyrid-2-ylmethyl)adenine with conversion of the former to 3-(1-oxypyrid-2-ylmethyl)hypoxanthine using nitrosyl chloride.[1285] The same picolyl moiety is present in the 6-substituted amino derivative (**58**) formed in low yield (20%) on reacting 6-methylsulfonylpurine with 1-oxypyrid-2-ylmethylamine.[1392] Ease of removal of the picolyl oxide group makes it a useful protecting agent for either amino or hydroxy groups and a temporary blocking group in alkylations. Preparation of 7-benzylhypoxanthine is possible by benzylation of the 3-(1-oxypyrid-2-ylmethyl)hypoxanthine with subsequent removal of the picolyl moiety with cold (20°C, 13 h) acetic anhydride followed by dilute acid.[1285] A mechanism suggested for this involves rearrangement of the *N*-oxide following *O*-acylation to the ester (**59**), which can then undergo hydrolytic fission to the 9-unsubstituted purine.[1285]



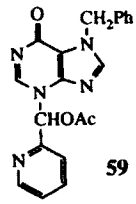
56



57



58

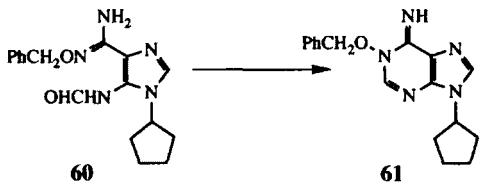


59

4. PURINE *N*-ALKOXIDES (*H*423)

A. Preparation (*H*423)

Other routes to supplement the original one of direct *O*-alkylation have emerged, but the majority of examples are still obtained by the older procedure. The usual alkylating agents convert adenine-1-oxide to the 1-methoxy,[1716,1717] 1-ethoxy,[1716,1717] and 1-benzyloxy[1716] analogs. Similarly derived is 1-methoxy-9-methylaminopurine.[978] Under oxidative conditions a tenfold excess of methyl iodide in dimethylacetamide with hydrogen peroxide (20°C, 4 days) converts adenine-1-oxide to 1-methoxy-9-methyladenine (80%). An even greater excess (>15 times) of reagent results in methylation of the 6-amino group forming 1-methoxy-9-methyl-6-methylaminopurine.[1717] Owing to their instability as bases, the methoxyadenines are usually isolated as hydroiodide salts. Alkylation of the 6-amino group in the salts is facilitated by removal of hydrogen iodide through oxidation, releasing the more reactive free base of the alkoxypurine.[1717] Related *O*-alkylations have given 1-benzyloxy-9-cyclopentylhypoxanthine[1718] as well as 1-methoxy-9-methylhypoxanthine.[1250] Acid-catalyzed ring closure of imidazole precursors such as **60** is an alternative approach to 1-benzyloxy-9-cyclopentyladenine[976] (**61**), 1-ethoxy-9-ethyladenine,[981] and other.[968] This route is referred to in Section 1.A in which 1-alkyoxypurines serve as precursors of 1-oxidopurines.



60 **61**

Few 3-alkoxypurines are available; none are described for guanine derivatives. Spectral evidence, however, indicates their presence even for purine-*N*-oxides, which are incapable of forming *N*-hydroxy tautomers.[1263] A rare example is from a Traube condensation of 3-methoxy-4,5-diaminouracil with formic acid in hexamethyldisilazane which gives 3-methoxyxanthine.[838]

Examples of 7-alkoxyxanthines are well documented (*H*418), notably theophylline derivatives derived by *O*-alkylation of the 7-oxide analogs. More recent data on these oxides are lacking.

The 9-alkoxypurines are a new series and their syntheses are allied to the 9-oxido analogs, the former being precursors of the latter. Ring closure of *N*-benzyloxyimidazoles, similar to that used for 1-alkoxypurines noted above, affords the 9-benzyloxy derivatives of guanine, hypoxanthine,[957] and the 8-methyl homologs of these two purines and of xanthine.[958] Failure to prepare 9-benzyloxyxanthine by this route is overcome by employing acid hydrolysis of 9-benzyloxyguanine.[957]

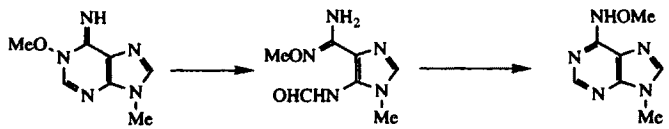
B. Reactions (*H*423)

a. Reductions (H423)

Catalytic hydrogenolysis is a selective reaction for producing conversion to the *N*-oxidopurine or for complete removal of the alkoxy group giving the parent purine. The choice of a nickel or palladium catalyst is generally of less importance than the reaction duration and the volume of the hydrogen involved. Owing to the marked instability of the alkoxypurine free bases, the iodide, bromide, or perchlorate salts are usually employed. For example, with the perchlorate of 9-benzyl-6-benzylamino-1-benzyloxypurine, one mol equivalent of hydrogen, and a palladium catalyst, the corresponding 1-oxide is obtained, but hydrogen in excess produces 9-benzyl-6-benzylaminopurine.[1466] Reduction limited only to the 1-oxide is found using 1-benzyloxyadenine hydrobromide.[1716] Complete elimination of the alkoxy group occurs with 1-methoxy- (Ni) and 1-methoxy-9-methyladenine (Pd–carbon),[1716] 1-methoxy-9-methyl-6-methylamino-(Pd–carbon),[978] and 1-ethoxy-9-ethyl-6-ethylaminopurine[1466] (Pd–carbon). Transformations of *N*-benzyloxypurines to the *N*-oxide occur in hot bromine–acetic acid mixtures favored for guanine derivatives to overcome their insolubility in other solvents. Products from this procedure include guanine-1-oxide,[968] 9-hydroxy-8-methylguanine,[958] 9-hydroxy-8-methylhypoxanthine,[958] and, in low yield, the 8-methylxanthine analog.[958] Hot pyridine converts 1-benzyloxy- to 1-oxy-9-benzyl-6-benzylaminopurine in high yield (95%) from the perchlorate salt;[1466] the same reagent removes the 4-nitrobenzyl group, giving 9-methyladenine-1-oxide.[982] Heating in ethanol alone is sufficient to *O*-debenzylate the bromide salt of 1-benzyloxy-9-cyclopentyladenine.[976] Under UV irradiation in methanol a 1-methoxy group is eliminated, as employed in the formation of 7-methylhypoxanthine.[1250]

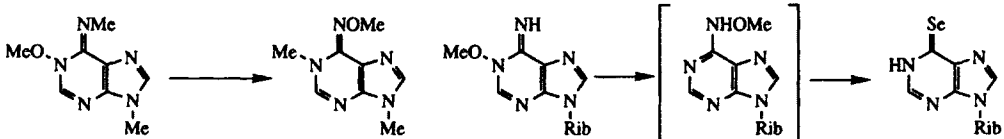
b. Rearrangement (H423)

Under alkaline conditions, 1-alkoxyadenines undergo a rearrangement paralleling the Dimroth reaction with 1-alkyladenines. (Chapter VIII, Section 5.G.b). The reactions are autocatalytic, as solutions of these purines are alkaline, and take place on warming.[981] Comparative rate studies between 1-methyl- and 1-methoxy-9-methyladenine (**62**) identify **63** as the stable ring-opened intermediate in the latter case.[1721] As in the Dimroth reaction, hydroxide ion attack at C-2 proceeds equally well with the protonated (pH < 8.5) or neutral (pH > 11.0) species; ring opening is rapid but reclosure to the 6-methoxyaminopurine (**64**) is the slow-



62 **63** **64**

er rate-determining step.[1721] Use of lower temperatures favors formation of the isolatable imidazole intermediates.[981,1721] Examples illustrating the two-stage reaction are provided by 1-methoxy-,[980,981] 1-ethoxy-,[980,981] and 1-benzyloxy-9-methyladenine[980,981]as well as 1-ethoxy-9-ethyladenine.[981] The analogous 1-alkoxyadenosine derivatives undergo the same reactions, but at a faster rate than the 9-alkyl analogs above.[1722] It should be noted that a similar rate difference is also found between 9-alkyl and 9-ribosyl derivatives in the Dimroth rearrangement with 1-alkyladenines.[980] Some rate variation is produced also by the presence of benzene ring substituents in 1-benzyloxyadenines.[982] With adenine derivatives lacking a substituent at N-9, rearrangement is more rapid and the intermediate formamidoimidazole exhibits cis-trans isomerism of the formamido group, possibly as a result of the absence of strong steric constraints by an adjacent substituent on the imidazole nitrogen.[979] These findings are in accord with those obtained from conformational studies by NMR on the related 4-amino-5-formamidopyrimidines.[888,1728] A classic representative illustration of the Dimroth character of the reaction is the isomerization of 1-methoxy-9-methyl-6-methylimino-(**65**) to 6-methoxyimino-1,9-dimethylpurine (**66**) involving the apparent interchange of groups at N-1 and N-6. The isolation of the 6-selenoxopurine riboside (**69**) on heating 1-methoxyadenosine (**67**) with hydrogen selenide in pyridine (65°C, 2 days), which is best explained by assuming an initial rearrangement to the 6-methoxyimino (**68**) intermediate, followed by nucleophilic displacement of the imino moiety by selenium,[1228] * is relevant.

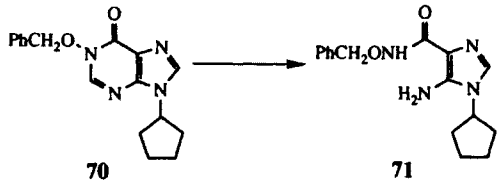


65 **66** **67** **68** **69**

c. Other Reactions (H424)

With 1-alkoxypurines lacking an amino moiety at C-6 the Dimroth rearrangement is precluded, but the same initial pyrimidine ring fission takes place as, for example, with 1-benzyloxy-9-cyclopentylhypoxanthine (**70**) forming 5-amino-1-cyclopentylimidazole-4-(*N*-benzyloxy)carboxamide (**71**).[1718] Although in aprotic solvents no Dimroth reaction is sustainable, imidazoles are obtained on heating 1-alkoxyadenine derivatives in dimethylacetamide.[979] Activation of 6-amino groups to undergo direct alkylation, a feature of 1-alkoxyadenines, has been elaborated upon elsewhere (Chapter VIII, Section 5.G.a).

* The failure to achieve a comparable selenium substitution with 1-methyladenosine, which only undergoes a Dimroth reaction to the 6-methylaminopurine, gives support to the mechanism above.[1228]



70 71

5. BIOLOGICAL ACTIVITY (*H*425)

Oncogenicity, defined as inducing neoplastic states, is the most significant biological property of certain *N*-oxides. Among the most potent oncogens are 3-hydroxyxanthine and the 1-methyl derivative, with analogous guanines showing a slightly reduced neoplastic effect. The conversion of 3-hydroxyguanine to 3-hydroxyxanthine is found to occur in vivo [1700] and in vitro with the enzyme guanase.[1724] Although the latter enzyme is reported not to convert the 1-methylguanine analog to 1-methyl-3-hydroxyxanthine,[1724] the oncogenic effect of the methylguanine-3-oxide is attributed to a slow in vivo hydrolysis to the highly active 1-methylxanthine analog.[1704] As oncogenes, the 3-hydroxyxanthines have a potential resembling that of the highly carcinogenic *N*-hydroxyacetylaminofluorene. In contrast, a lack of biological activity is found with the 7- and 9-methyl- also 7,9-dimethyl-3-hydroxyxanthine[1724] and 1-hydroxyxanthine.[1725] Derivatives with only weak activity are shown by 3-hydroxyhypoxanthine and adenine-1-oxide. Studies in vivo identify the active species of the oncogen as a transitory sulfate ester from a sulfotransferase reaction with the *N*-hydroxy moiety similar in type to that previously described for *N*-hydroxyacetylaminofluorene.[1726] The more stable 3-acetoxy esters, utilized for reaction investigations, undergo comparable transformations and permit direct comparisons to be made between biological and chemical reactivities. A point of note is that although similar oncogenicity is found with both 3-hydroxy-1-methylxanthine and 1-methylguanine-3-oxide, different pathways must operate as the latter has no *N*-hydroxy tautomer available for ester formation.[1704] Reaction at a biological receptor presupposes the ability of the purine to form an anion through loss of an imidazole proton, a viewpoint supported by the inactivity of the non-ionizable 7- and 9-methylxanthine esters noted above. Alternative mechanisms involving radical intermediates derived by homolytic fission of the *N*-acetoxy bond cannot,[1724] however, be excluded. Although mutagenicity and oncogenicity are not necessarily properties of the same derivative, the oncogenic *N*-oxides have been tested for and show significant mutagenic effects.[1727]

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER XII

The Reduced Purines (*H*427)

1. Purines Reduced in the Pyrimidine Ring (*H*427) 325
A. Preparation of 1,2-, 1,6-, and 2,3-Dihydropurines 325
a. By Electrochemical Reduction (*H*428) 325
b. By Catalytic Reduction (*H*430) 327
c. By Chemical Reduction (*H*431) 328
d. By Direct Synthesis (*H*432) 330
B. Properties and Reactions (*H*433) 331
2. Purines Reduced in the Imidazole Ring (*H*434) 331
A. Preparation of 7,8- and 8,9-Dihydropurines (*H*435) 331
a. By Electrochemical Reduction (*H*435) 332
b. By Catalytic Hydrogenation (*H*435) 332
c. By Chemical Reduction (*H*435) 333
d. By Direct Synthesis (*H*438) 334
B. Properties and Reactions (*New*) 334

This topic is subdivided, as in the original volume, into purines reduced in either the pyrimidine or the imidazole rings. Since the parent work appeared, the relatively few examples of the latter kind then described have increased considerably both in number and type.

1. PURINES REDUCED IN THE PYRIMIDINE RING (*H*427)

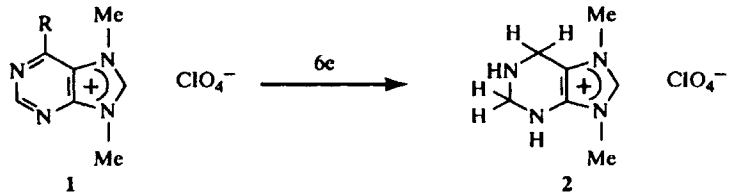
A. Preparation of 1,2- 1,6-, and 2,3-Dihydropurines

a. By Electrochemical Reduction (H428)

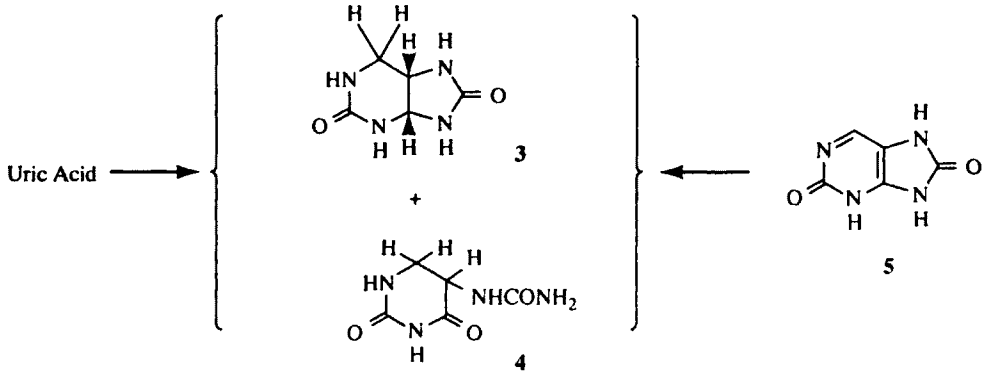
Using data obtained from various studies of micro- and macroscale reductions at mercury electrodes, the mechanistic pathway differences between reactions in aqueous and nonaqueous media have been identified. In aqueous solutions in the presence of a proton donor, usually an acid, protonation of the pyrimidine ring is a prerequisite for reduction to occur. This is demonstrated by the increasing reducibility of the purine observed with decreasing pH of the electrolyte. The inherent electron deficiency of the six-membered ring favors it for reduction, but

this may be altered by the presence of certain electron-releasing substituents and the effect of annelation with the electron-excessive imidazole ring. A combination of these factors would explain the ease or difficulty of reductions of the pyrimidine moiety in different purines.[1749,1757] Under aqueous conditions the electron-depleted pyrimidine ring is the more likely candidate for reduction. Exceptions are found with quaternary derivates having the cationic center located in the imidazole ring, making this the more reducible moiety. Under conditions favoring formation of a dication, protonation of both rings occurs and preferential reduction of the pyrimidine is observed. Exceptions to imidazole reductions, notably with *N*-methylated hypoxanthine and thiohypoxanthine analogs are considered in Section 2.A.c. The mechanism of electron additions, investigated by polarographic techniques, involves two pH-dependent steps corresponding to the sequential formation of a dihydro- and a tetrahydropurine. Each step comprises an addition of two electrons and two protons necessary for reductions of the 1,6- and 3,2-nitrogen to carbon double bonds.[1749,1750]

A combination of pulse radiolysis techniques and kinetic absorption spectra results using purine and the 9-methyl homolog point to reduction involving hydrated electrons and free radicals.[1751] A comparison of the microscale reductions of adenine, 1-methyladenine, and 6-methylaminopurine at a dropping mercury electrode with the results on a macroscale using a mercury pool electrode indicates possible pathway differences in the final formation of the same 1,2,3,6-tetrahydropurine products. Both involve an overall 6-electron reduction, but the intermediate stage at which the amino group is removed are possibly different.[1752] This may be after a 2-electron (1,6-dihydropurine)[1144,1752] or 4-electron (1,2,3,6-tetrahydropurine)[1749] reduction occurs, with UV spectral evidence favoring the former option.[1752] A similar effect with the 6-substituent is noted when either 6-chloro-(**1**, R = Cl)[1144] or 6-methylamino-7,9-dimethylpurinium perchlorate[1762] (**1**, R = NHMe) in aqueous acid (0.1 *M* HCl) undergo a 6-electron reduction giving the 1,2,3,6-tetrahydropurine (**2**) salt as product. In both examples, dication formation through the six-membered ring directs reduction to this site rather than to the quaterized imidazole ring. Supporting this rationale is the reduction of only the five membered ring when these two purines react in neutral nonaqueous media.[1144] Loss of the sulfur function occurs with 6-mercaptopurine following a 4-electron uptake at low pH (~3); hydrogen sulfide is released and 1,6-dihydropurine results. A further 2-electron wave converts the latter to 1,2,3,6-tetrahydropurine.[1753,1754] Reductions of other 6-thioxopurine derivatives give mixed products which include 7,8-dihydro derivatives or the results of ring fission (Section 2.A.a). A repeat of Tafel's reduction of uric acid at a lead cathode in



1 **2**

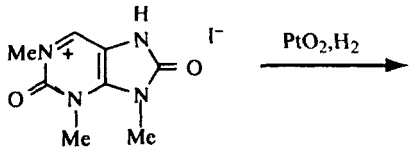


concentrated sulfuric acid and ^{1}H NMR examination of the "purone" product identifies it as the 1,4,5,6-tetrahydro form (**3**) of 2,8-dioxopurine having the 4,5-bond hydrogens in the cis conformation. A secondary product, originally termed "isopurone", is confirmed as the 5,6-dihydrouracil (**4**). Both purone and isopurone are obtained when the dioxopurine (**5**) is similarly treated,[903] suggesting that this purine is an intermediate in the reduction of uric acid. Analogous reduced purine and pyrimidine derivatives can be identified (^{1}H NMR) following the electrolysis of 2,8-diaminopurine using the same method.[903]

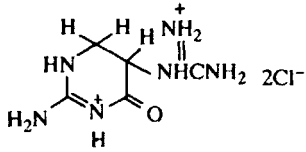
By contrast, in nonaqueous media (DMA, DMSO, or MeCN) with mercury electrodes, purine, adenine, and 6-methyl-, 6-methoxy-, 6-methylamino-, and 6-dimethylaminopurine are converted to active radical anions, through 1-electron uptakes, which undergo rapid dimerizations. Addition of potential proton donors, such as water or acids, promotes a further 4-electron gain in two 2-electron steps or, as in the case of adenine and the other 6-substituted purines, only single 4-electron reductions take place.[1749,1755] The differences in mechanistic behavior in aqueous and nonaqueous solvents can be attributed to the lower protonation activity of the latter, which is further reduced by the presence of electron-releasing groups in the purines.[1749] In nonaqueous electrolytes containing strong proton donors, the reduction patterns are basically the same as those in aqueous solutions.

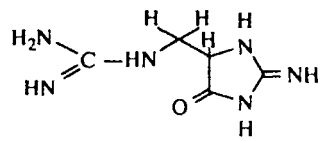
b. By Catalytic Reduction (H430)

The acid conditions usually employed predispose to protonation of the pyrimidine moiety with resulting reduction taking reaction place in this ring. Hydrogenation (PtO_2) of the 2,8-dioxopurine (**5**) in aqueous hydrochloric acid affords the unstable 1,6-dihydropurine which is isolated as the isopurone (**4**) of Tafel (Section 1.A.a). The iodide of the 1,3,9-trimethylated derivative (**6**) undergoes similar degradation on reduction to the dihydrouracil analog[903, 1300] (**7**). Analogous reductions of 2,8-diaminopurine and the 1,3,9-trimethyl homolog give similar unstable derivatives, which when isolated from the former diaminop-



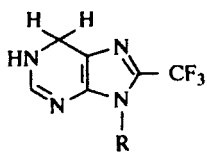
6 7



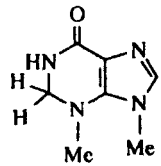


8 9

urine, were originally given the structure[903] (**8**). However, later work repeated the reduction under similar conditions, yielding evidence, in the form of a synthesis, that the product was the isomeric imidazoline (**9**).[906] Although neither the neutral molecule nor the anion of 8-trifluoromethylpurine can be reduced, the 1,6-dihydropurine (**10**, R = H) is obtained using a palladium catalyst in trifluoroacetic acid. Slightly more vigorous conditions (70°C, 4 atm) are needed to form the 9-methyl analog (**10**, R = Me). In the later reduction, however, this is the minor product; the major product results from reaction with the imidazole moiety[840] (Section 2.A.b). To appreciate the contribution of the electron-withdrawing effect of the trifluoromethyl groups in enhancing the electropositive nature of the ring system, it should be noted that the introduction of electron-releasing groups at C-6, such as amino or methylthio, is sufficient to make the purines unreducible.[840] Like hypoxanthine itself (*H429*), hydrogenation (Pd–carbon) of the 3,9-dimethyl derivative causes no reduction of the oxo group—the product is the 1,2-dihydrohypoxanthine (**11**) in good (77%) yield.[1756]



10

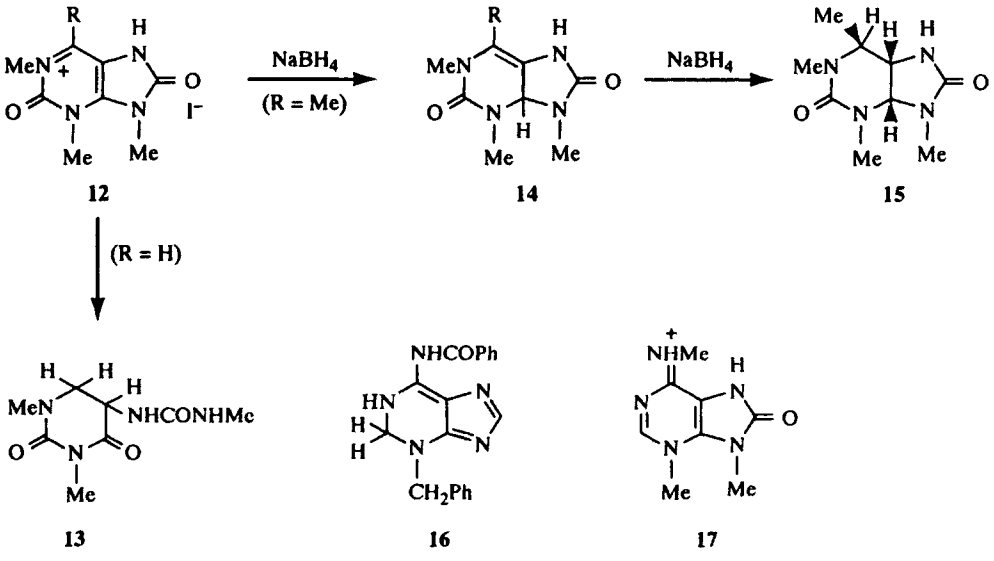


11

c. By Chemical Reduction (H431)

Unlike the acid media favored in the previous procedures, the majority of reductions by chemical means utilize neutral conditions—water or methanol at room temperature is the norm. This method is made possible through the widespread use of sodium borohydride as reducing agent in place of the older amalgams and metal–acid or metal–alkali combinations, with which a risk of ring

cleavage or degradation of the reduced purines exists. Oxo purines are reduced leaving the oxo function untouched, as in the conversion of 1,3-dimethyl-8-phenylhypoxanthine to the 2,3-dihydro analog.[1226] Although sodium borohydride reduces the cations of 1,3,9-trimethyl- (**12**, R = H) and the 6-methyl-2,8-dioxopurine (**12**, R = Me) homolog to the dihydro forms, the former is unstable, decomposing to 1,3-dimethyl-5, 6-dihydro-5-*N'*-methylureidouracil (**13**), but the latter forms the enamine (**14**), detected by ^{1}H NMR, which is capable of further reduction to the perhydropurine (**15**), which contains a reduced bridgehead double bond between C-4 and C-5.[903] Related perhydropurines of this type are similarly obtained in excellent yields from the 1,3,7-trimethyl (75%), 1,3,9-trimethyl (92%), and 1,7,9-trimethyl (99%) as well as the 1,3,7,9-tetramethyl (80%) and 1,3,6,9-tetramethyl (79%) derivatives. Likewise, purines reduced analogously are derived from 1,7,9,-trimethyl- and 1,6,7,9-tetramethyl-2,6-diaminopurines.[903] The bridgehead hydrogen atoms in both reduced 2,8-dioxo- and 2,8-diaminopurines exhibit a cis configuration.[903] In contrast with the very slow reduction to the 1,2-dihydropurine of 3-benzyladenine, that of the 6-benzamido-3-benzylpurine proceeds rapidly (0.5 h) in methanol at room temperature to the product (**16**). This further demonstrates an increased cationic effect produced in the ring by a C-6 substituent modification. Other substituent influences are highlighted by the failure to reduce the 9-benzyl derivatives of either adenine or the 6-benzamidopurine in methanol, but in acetic acid with sodium borohydride the imidazole ring is reduced (see Section 2.A.c).[1757] No difficulty is experienced in reduction to the 1,2-dihydro form of the hydrochloride of 3,9-dimethyl-6-methylimino-8-oxopurine (**17**) with sodium borohydride in aqueous solution.[1850] The same reducing agent in tetrahydrofuran converts 9-methyl-8-trifluoromethylpurine to a mixture of 1,6-dihydro- and 7,8-dihydropurines[840]

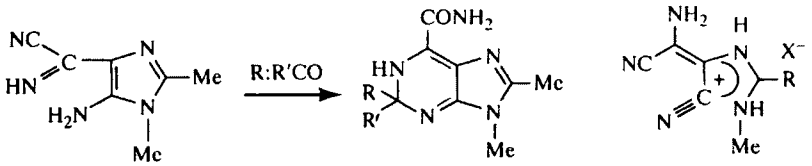


(Section 2.A.c). Raney nickel as reducing agent in hot methanol with 7,9-dimethyl-6-methylthiopurinium iodide eliminates the sulfur group, forming 1,6-dihydro-7,9-dimethylpurinium iodide.[1144] The absence of any imidazole ring reduction, in view of the positive charge associated with this area of the molecule, is noteworthy.

d. By Direct Synthesis (H432)

Synthetic routes are restricted almost solely to dihydropurine formation, these are unstable compounds readily oxidized to the parent purines. Stabilization is possible in cases where further reduction to a tetrahydro derivative can be made. The presence of certain dihydropurines in some cases is based upon ^{1}H NMR or other spectral evidence only.

Ring closure of 5-amino-4-(cyanoformimidoyl)imidazole (**18**) with acetone and a pyridine catalyst is exothermic at ambient temperature, forming the 6-carbamoyl-2,2-dimethyl-1,2-dihydropurine (**19**, R = R′ = Me) in 90% yield. Related products include the 2-ethyl-2-methyl (**19**, R = Me, R′ = Me), and 2-methyl-2-phenyl (**19**, R = Me, R′ = Ph) homologs from methylethylketone and acetophenone respectively.[1004,1837] Benzaldehyde reacts likewise to give the dihydropurine (**19**, R = H, R′ = Ph).[1004] In place of the cyanoformimidoylimidazole, the *N*-methylamidinium triflate (**20**) gives the same 1,2-dihydropurines when condensed with



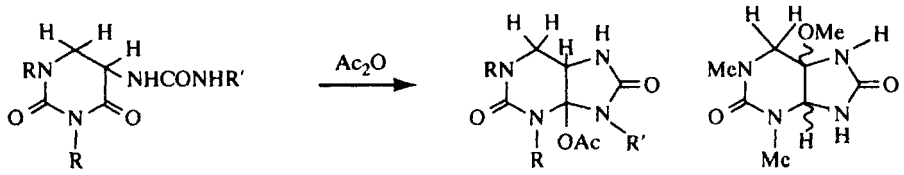
18 **19** **20**

ketones at ambient temperature.[1837] Later extensions of the imidazole synthesis have given dihydropurines unsubstituted in the imidazole moiety. Those resulting (**21**, R = Me, Et) from the aldehyde closures undergo spontaneous oxidation to the parent 2-alkylpurines on short exposure to air.[1838] Formation of a 1,2-dihydroadenosine is claimed based on ^{1}H NMR evidence, but is not isolated from reaction of benzaldehyde with the riboside of 5-aminoimidazole-4-carboxamidine. Aliphatic aldehydes appear to form corresponding dihydro derivatives.[972] An attempt to cyclize 4-carbamoyl-5-aminoimidazole riboside with chlorocar-



21 **22**

bene to 2,3-dihydroinosine was unsuccessful.[1021] Transient, but in some cases unisolatable, adducts with dihydropurine structures arise when 6-unsubstituted purines are treated with aqueous sodium hydrogen sulfite or sulfurous acid. The 1,6-dihydropurine-6-sulfonates of the type (**22**) also form with purine, the 2-amino, 2-oxo, and 2-thioxo derivatives and the 8-trifluoromethylpurine analogs of these compounds.[1047] Structural identities of the unstable products were confirmed using ^{1}H NMR and UV spectral examination. Formation of the unusual cis perhydropurines (**24**, R = Me, R′ = H) and the trimethylated form (**24**, R = R′ = Me) results from interacting the dihydrouracils (**23**, R = R′ = H) and (**23**, R = R′ = Me) with acetic anhydride (reflux, 20 min).[903,1300] Of somewhat related structural character is the 5-methoxyperhydropurine (**25**) as a minor product from heating the enamine (**14**, R = H) in methanol containing nitroacetic acid, the major product being the ring opened 5,6-dihydrouracil[903] (**23**, R = R′ = Me).



23 **24** **25**

B. Properties and Reactions (*H*433)

Some degree of stability toward oxidation in air is shown by 8-trifluoromethyl-1,6-dihydropurine and the 9-methyl homolog, even at 110°C. Only slow degradation occurs in 0.1 *M* acids and bases. Both purines have weakly basic (pK_a 3.5) character.[840] Stability is also a feature of 6-carbamoyl-2,2-dialkyl-1,2-dihydropurines which are unchanged on standing for some time in chloroform or ethanol solutions.[1004] The use of aldehydes to form 2-alkyl or -aryl-1,2-dihydropurines provides a useful route to the formation of 2-alkylpurines. Incorporation of an oxidizing agent during the initial cyclization to the dihydropurine, such as oxygen with a palladium–carbon catalyst of chloroanil in dimethylformamide or air alone, allows isolation of the parent 2-alkylpurine directly.[972] The stability of 3-benzyl-1,2-dihydroadenine is sufficient for conversion to the 6-benzamido analog to be made with benzoic anhydride in pyridine.[1757]

2. PURINES REDUCED IN THE IMIDAZOLE RING (*H*434)

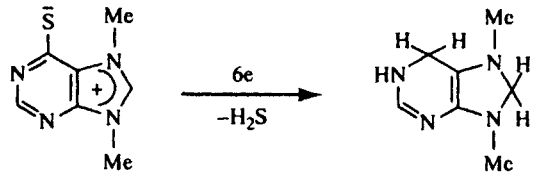
A. Preparation of 7,8- and 8,9-Dihydropurines (*H*435)

The increasing exploitation of sodium borohydride as a more versatile and efficient reducing agent has considerably extended the range of purines reduced in

the imidazole ring. Those described in the parent volume were largely derived by reduction of an 8-thioxopurine; however, use of this preparative approach is significantly lacking in the contemporary literature.

a. By Electrochemical Reduction (H435)

Employment of 7,9-dialkylated purine salts makes use of the positive charge associated with the quaternary nitrogen to direct reduction to the five-membered ring. At a dropping mercury electrode in aqueous solution containing tetraethylammonium perchlorate as enhancing electrolyte, both 7,9-dimethyl- and 1,7,9-trimethylhypoxanthine undergo 2-electron reductions, the former by two 1-electron steps and the latter by a single 2-electron process.[1758,1759] Spectral studies in the UV indicate that the products are the corresponding 7,8-dihydro derivatives. These results contrast with those of other hypoxanthine derivatives in which the pyrimidine 2,3-double bond is reduced. Following similar treatment of the 6-thioxohypoxanthine analogs, the betaine form of the purine (**26**) is obtained without formation of any dihydropurine. In more acidic buffer solution (pH~5.5), protonation effects are brought into play, and a 6-electron step with sulfur eliminated as hydrogen sulfide and the presence of the tetrahydropurine (**27**) can be demonstrated.[1758] Reduction of the 6-methylthio analog of **26** follows a similar pattern, culminating in the evolution of methanethiol. Initially, an easily oxidized 7,8-dihydropurine is formed which, in more acid solution, is further reduced to the tetrahydropurine (**27**) with an accompanying scission of the C-6 to S bond.[1758] Overall, the hypoxanthinium salts are less readily reduced than their 6-thioxo analogs.



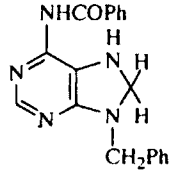
26 **27**

b. By Catalytic Hydrogenation (H435)

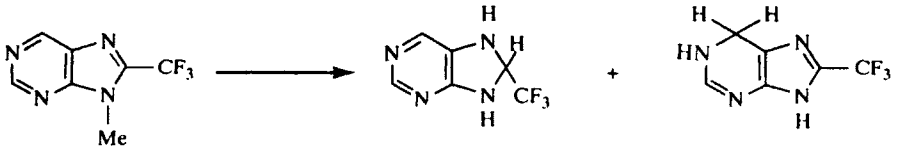
This approach has been little exploited for 7,8-dihydropurine preparation. An isolated example is the reduction (Pd–carbon) of 9-methyl-8-trifluoromethylpurine to an isomeric mixture of the 7,8-dihydro- and 1,6-dihydropurines, the former being the major component in a 2:1 ratio.[840] The isolation of only 8-trifluoromethyl-1,6-dihydropurine when the 9-unsubstituted purine analog is similarly treated,[840] without any reduction of the imidazole ring, is noteworthy.

c. By Chemical Reduction (H435)

Sodium borohydride, acting through the hydride, ion, is ideally suited for purinium salt reductions. This is well demonstrated by the variety of 7,8-dihydropurines obtained from 7,9-dialkylpurinium salts in which the cationic center resides in the imidazole ring. Comparative studies with 6-thioxopurine derivatives using potassium borohydride[1287] give results that parallel those derived by electrochemical procedures.[1758] Representative examples of 7,9-dimethyl-7,8-dihydropurines are obtained from the 7,9-dimethyl derivatives of hypoxanthine, either as iodide in methanol,[1226] perchlorate,[1287] or the betaine form[1760] in water, as well as the 6-thioxo-,[1287] 6-methylamino-[1532] (perchlorate) 6-dimethylamino-[1164] (perchlorate or iodide), 6-diethylamino-[1536] (iodide), 6-morpholino-,[1536] and 6-chloropurines.[1144] Although the reagent fails to react with 9-benzyladenine, even in acid solution, reduction to the 7,8-dihydropurine (**28**) under these conditions does occur on benzoylation of the 6-amino group.[1757] No reduction takes place in ethanolic solution. In boiling methanol, however, both 7- and 9-methyl-2,6-dichloropurine are converted to the respective 8,9- and 7,8-dihydrodichloropurines by sodium borohydride although the 7(9?)-unsubstituted-2,6-dichloropurine did not react.[1145] The combined electron drain imposed on the imidazole ring by the effects of the trifluoromethyl group and the pyrimidine ring enhances the reducibility of 9-methyl-8-trifluoromethylpurine (**29**), as illustrated by isolation of both the 7,8- (**30**) and 1,6-dihydro (**31**) derivatives; the former comprises the major product on reduction in cold (0°C) tetrahydrofuran. Achieving separation by using the adducts formed with potassium hydrogen phthalate utilizes the lower solubility of the 1,6-dihydropurine complex.[840] The critical state of the electron disposition in such compounds is shown by the failure to reduce purines having electron-releasing groups, such as amino or methylthio, at the C-6 position.[840]



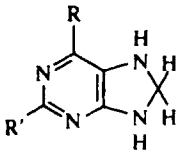
28



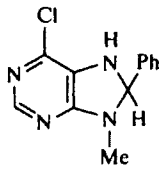
29 **30** **31**

A contrasting situation arises when electron-attracting groups are located at C-6, as shown by the facile reductions with sodium cyanoborohydride (20°C,

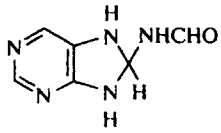
0.5 h) in dilute hydrochloric acid of 2,6-disubstituted purines incorporating 6-ethoxycarbonyl, -cyano, or -carbamoyl groups. The resulting 7,8-dihydropurines (**32**, R = CO_2Et, CN, $CONH_2$, R′ = H, EtO, MeS, NMe_2 Cl) are surprisingly stable, irrespective of the diverse character of the substituent at the 2-position.[1839] Other examples of 2,6-disubstituted purines similarly reduced with sodium borohydride to 7,8- or 8-,9-dihydropurines are 7,9-dimethylguanine and -xanthine and 1,3,7,9-tetramethylxanthine.[1760] Analogous reductions are reported for the 7-methyl-9-β-D-ribofuranosyl derivatives of guanine and xanthine.[1760]



32



33



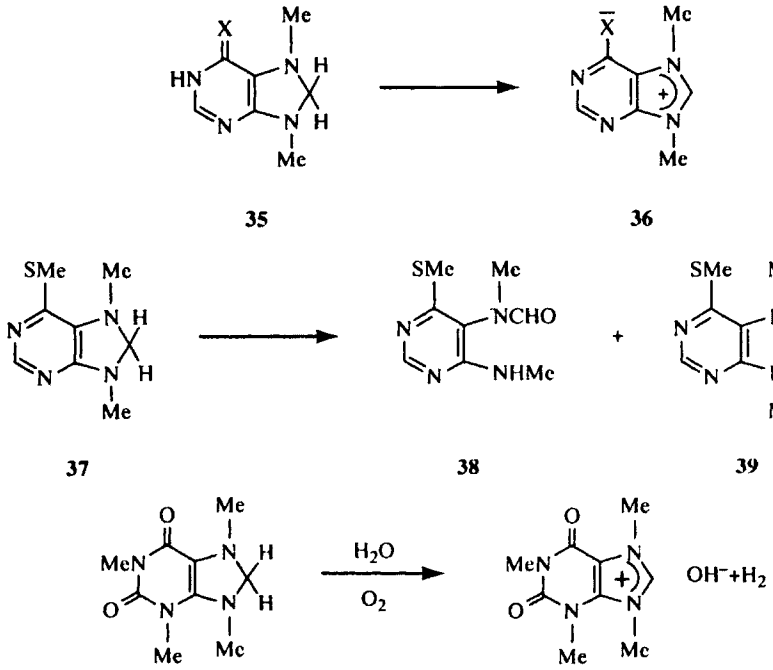
34

d. By Direct Synthesis (H435)

Current examples are few; the adduct (**33**) results from interaction between 6-chloro-9-methylpurine and phenyllithium in the presence of a transition metal complex (Kochi's catalyst). Through concomitant oxidation, some 6-chloro-9-methyl-8-phenylpurine is also formed.[1061] From the de novo synthesis of purine by thermal treatment of formamide (170°C, 10 h), some 8-formamido-7,8-dihydropurine (**34**) is found in the product mixture.[1012] Rearrangements of purines in liquid ammonia–potassium amide mixtures (−80°C) are claimed to involve dihydropurine intermediates.[875] As a result of steric effects produced by the adjacent phenyl ring on the 6-position, the action of Grignard reagents on 7-phenylpurines is directed to C-8, forming 8-substituted-8,9-dihydropurines.[1792]

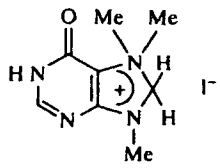
B. Properties and Reactions (*New*)

As with purines reduced in the pyrimidine ring, a tendency to facile oxidation to the parent purine is a common feature. Apart from aerial oxidation, controlled[1287] oxidations occur with oxygen and a catalyst ($AgNO_3$–I_2); iodine[1164,1536] and nitrobenzene[1061] are also useful oxidants. More stability is shown toward oxidation in air by 7,9-dimethylhypoxanthines (**35**, X = O) and the 6-thioxo analogs (**35**, X = S) which form betaines (**36**, X = O) and (**36**, X = S) of the parent purines.[1287] When charged forms of this type are precluded, for example, with oxidation product from the 6-methylthiodihydropurine (**37**), fission of the imidazole occurs, giving the 5-*N*′-methylformamidopyrimidine (**38**) and the 8-oxopurine[1287] (**39**). Other examples of this reaction are known.[1758]



Scheme 1

Investigation of the oxidizing action of water alone on dihydropurines shows that dissolved air is mainly responsible, although some interaction with water is also involved. A rise in pH from 4.5 to 8.5 due to liberated hydroxide ions is noted when a solution of 1,3,7,9-tetramethylxanthine is left standing (Scheme 1). Evolution of hydrogen is a feature of the reaction and hydride ion transfer is demonstrated by deuterium exchange. The reducing property of dihydropurines effectively converts benzylideneaniline into *N*-benzylaniline in high (90%) yield.[1760] A selective action is shown toward other carbon–nitrogen double bonds but does not extend to double bonds in ketones or other carbonyl groups. A useful pointer in cases where reduction to a 7,9-dimethyl-dihydropurine has been carried out is an appreciable shift upfield (0.5–1.0 ppm) in the ^{1}H NMR signals of the N-methyl hydrogens.[1226,1287] Longer wavelength absorptions are also observed in the UV spectra of the reduced derivatives.[1760] Methylation (MeI, EtOH) of 7,9-dimethyl-7,8-dihydropurines affords cyclic dimethylammonium iodides such as **40** from 7,9-dimethyl-7,8-dihydrohypoxanthine.[1287,1761]



40

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER XIII

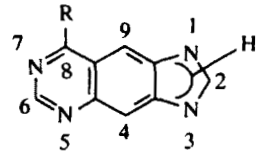
Enlarged Purine-Containing Structures (*New*)

1. The Stretched Purines (Imidazo[4,5]quinazolines) 337
A. Preparation 339
B. Properties 340
C. Reactions 341
2. The Purinophanes 342
A. Preparation 344
B. Properties and Reactions 345

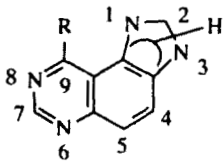
1. THE STRETCHED PURINES (IMIDAZO-[4,5]QUINAZOLINES)

The inclusion of these nonpurines in the monograph is deliberate and is justified in view of the information gained from studies of their reactions, both chemical and biochemical; this has relevance to and furthers our understanding of the chemistry of purines themselves. The concept largely resulted from the work of Nelson Leonard and his group and a comprehensive review covering all aspects of the topic is available.[1763] Such derivatives, which embody the elements of the purine structure, make it possible to study reactions of either the five- or six-membered ring which, although interconnected, are not subjected to the same mutual ring perturbations that exist in purines themselves.

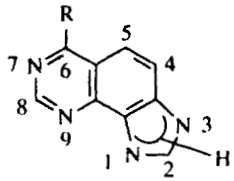
The initial stretched purines are imidazo[4,5]quinazolines and can be considered as purines, bisected along the common 4,5-bond, having a benzene or similar ring inserted to bridge the two rings. Depending upon the mode of attachment between the benzene and imidazole moiety, three tricyclic variants are possible. When all three rings have a common axis the linear (*lin*) form, imidazo[4,5-*g*]-quinazoline (**1**), arises, but where an unsymmetrical linkage is present, two angular isomers can result. The derivative (**2**), imidazo[4,5-*f*] quinazoline, having the imidazole ring inclined at 60° above the horizontal axis, is designated as the proximal (*prox*) form, while (**3**), imidazo[4,5-*h*]quinazoline, is the distal (*dist*)[1764,1765] form. Classification of the angular variants depends upon the relationship of the imidazole ring with the atom or group at C-6. Subsequent modifications to the original linear structures include reduction of the benzene ring, giving the



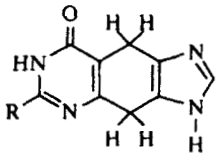
linear
1



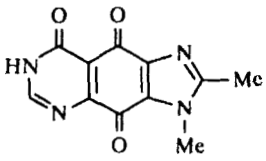
proximal
2



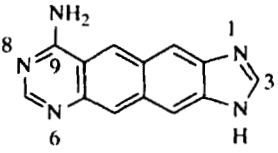
distal
3



(R=NH_2, H, OH)
4

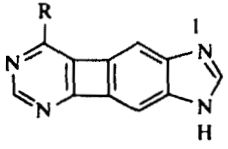


5

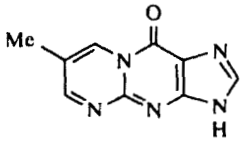


6

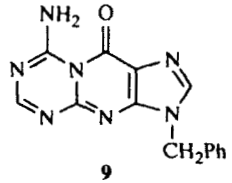
4,9-dihydro analog[1766] (**4**), and formation of the oxidized quinone bridged form[1767] (**5**). Linear expansion is achieved by replacement of the benzene by a naphthalene ring, as in naphthoadenine, 9-aminobenzimidazo[5,6-*g*]quinazoline[1768] (**6**), and by the benzocyclobutadienepurine (**7**), which is intermediate in size between the benzo- and naphthopurine derivatives.[1769] Some related linear heterocycles containing an intact purine nucleus, which are dimensionally similar in area and length, are noted in Chapter VIII, Sections 5.G.c and 5.H. These are adducts from reacting guanines with small unsaturated compounds. Exemplifying the structural similarities are pyrimido[1,2-*a*]purines[1493,1495] (**8**), and 1,3,5-triazino[1,2-*a*]purines [1118,1503] (**9**); the 1,2,4-triazino[2,3-*a*]purine ribosides (**10**) are obtained from guanosine.[1516] As a result of the biological implications, the stretched analogs of the naturally occurring purines are also represented by the corresponding riboside derivatives.



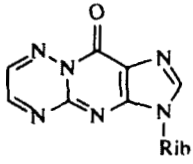
7



8



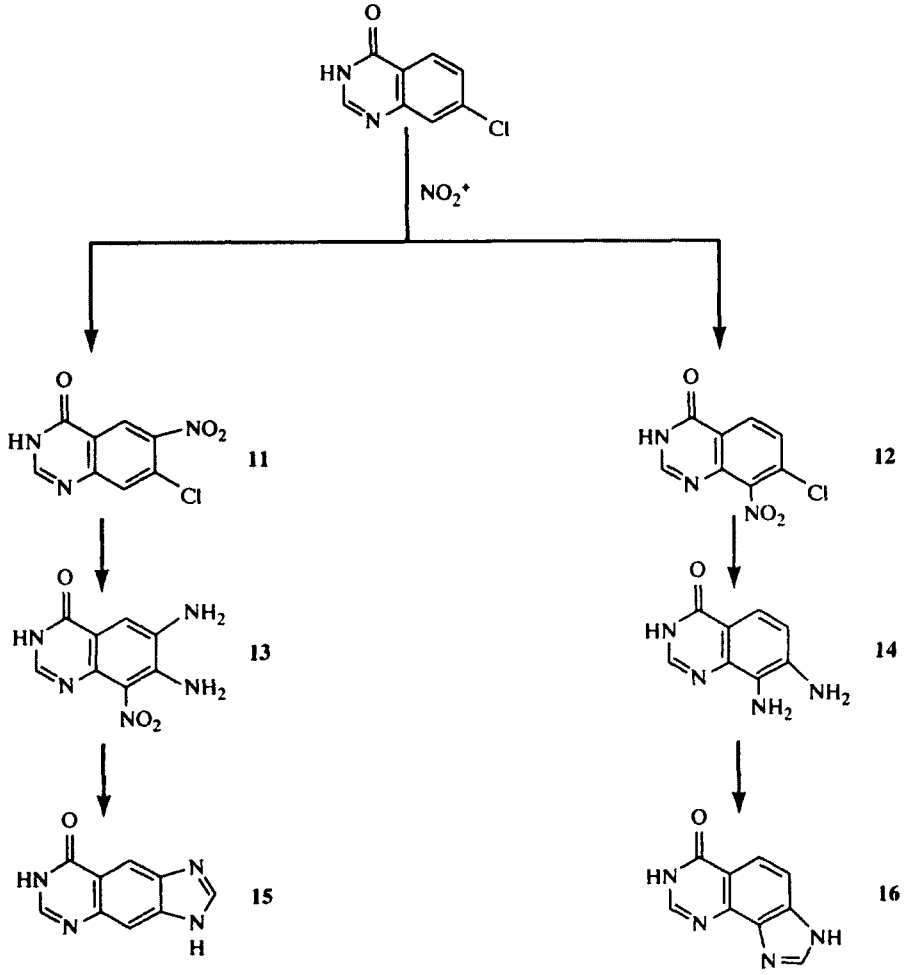
9



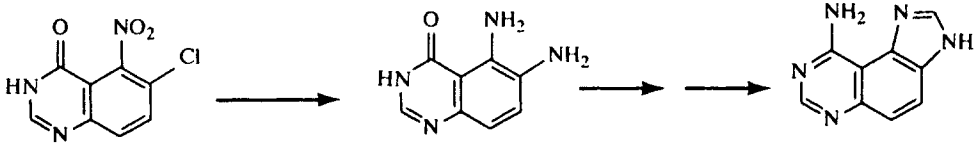
10

A. Preparation

The synthetic approaches are adaptations of the Traube closures used in purine preparations with ortho aminoquinolines in place of 4,5-diaminopyrimidines. Formation of the quinazoline illustrated in Scheme 1 is by nitration of 7-chloro-quinazolin-4-one, yielding a separable mixture of 7-chloro-6-nitro-(**11**) and 7-chloro-8-nitro-quinazolin-4-one (**12**). Amination and reduction of each isomer affords the respective 6,7- and 7,8-diaminoquinazolones (**13**) and (**14**) which, on ring closure in formic acid, form the linear benzohypoxanthine (**15**) and the angular distal form (**16**). Conversion of **15** to the 6-mercaptopurine analog occurs in pyridine with phosphorus pentasulfide and further metathesis to the adenine derivative (8-aminoimidazo[4,5-*g*]quinazoline), *lin*-benzoadenine (**1**, R = NH_2),

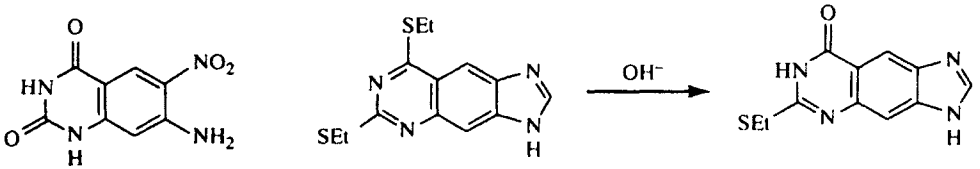


Scheme 1



17 18

is effected with ammonia in butanol at an elevated (200°C) temperature.[1764] The proximal benzoadenine variant (**18**) is similarly derived from 6-chloro-5-nitroquinazolin-4-one (**17**) following formation of the intermediate benzohypoxanthine and thioxo analogs.[1764] The corresponding *lin*-naphthohypoxanthine (benzimidazo[5,6-*g*]quinazolin-8-one) and *lin*-naphthoadenine (9-aminobenzimidazo[5,6-*g*]quinazoline) are likewise obtained. Lawesson's reagent[1770] in pyridine is used to prepare the 9-thioxo derivative (*lin*-naphthomercaptopurine) from the naphthohypoxanthine.[1768] Preparation of xanthine-type compounds utilize reduction (Pd–carbon, H_2) in formic acid of 7-amino-6-nitroquinazoline-2,4-dione (**19**) with subsequent heating to effect closure of the imidazole ring. Reaction of *lin*-benzoxanthine with phosphorus pentasulfide in pyridine gives the 6,8-dithioxo analog, which ethyl iodide converts to the 6,8-bisethylthio compound (**20**). On heating in *tert*-butanol with aqueous potassium hydroxide, transformation of the latter to the 6-ethylthiobenzohypoxanthine (**21**) occurs.[1772] A similar nucleophilic substitution approach gives *lin*-benzoguanine.[1771] Using ribofuranoside derivatives to adapt these routes allows syntheses of the linear variants of benzoinosine,[1772] benzoxanthosine,[1772] benzoguanosine,[1772] benzoadenosine,[1773] and naphthoadenosine.[1768] Some angular nucleosides have likewise been prepared.[1773]



19 20 21

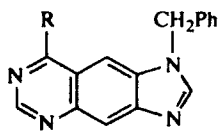
B. Properties

Introduction of the benzene ring preserves the aromaticity of the parent purine and also extends planarity to the tricyclic derivative. Differences in the structures of the linear, proximal, and distal variants are reflected in the physical properties, as exemplified in the benzoadenines by an increase in basicity which occurs in the order *prox* (pK_a 11.4) → *lin* (pK_a 11.7) → *dist* (pK_a 12.25). Initial protonation is dependent upon the substituent present. With benzoadenine the pyrimidine ring, as in adenine itself, is the site. This changes to the imidazole ring if the amino

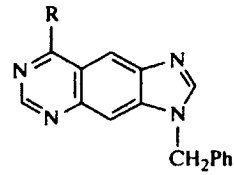
is replaced by a methylthio group, as in 8-methylthiobenzopurines.[1764] Transformation of adenine into *lin*-benzoadenine (**1**, R = NH_2) involves an increase in the lateral axis length of 2.4 Å, which extends to 4.5 Å with the naphthopurine analogs.[1768] The *lin*-benzocyclobutadienopurine (**7**), designed as a model for enzymatic studies, possesses a long axis extension of 3.9 Å, giving a molecular size intermediate between benzo- and naphthopurines.[1769] Low solubility in most solvents is a feature of benzoadenines, benzohypoxanthines, and benzoguanines. For this reason, reaction studies use the more soluble alkylthio derivatives. Although fluorescence is exhibited by solutions of naphthoadenine and naphthoadenosine, no such phenomenon is found with the benzoadenine analogs.[1768] This is unusual, since many of the structurally related pyrimido[1,2-*a*]purines[1493] and 1,3,5-triazino[1,2-*a*]purines[1118,1503] show strong fluorescences.

C. Reactions

Groups located in the pyrimidine ring of benzopurines corresponding to C-6 of purines show a comparable versatility toward nucleophilic displacements, but similar groups at the equivalent of C-2 in purines have a much-reduced tendency to replacement. On heating 6,8-bisethylthiobenzopurine (**20**) in a mixture of aqueous potassium hydroxide and *tert*-butanol, the product is the 6-ethylthiobenzohypoxanthine (**21**) in 95% yield.[1772] Amination of 6-ethylthiobenzopurines of this type require fairly rigorous conditions (140°C, 3 days) in methanolic ammonia. Heating with Raney nickel in ethanol will remove a 6-alkylthio group. Thiation of oxo groups, using phosphorus pentasulfide in pyridine or Lawesson's reagent, is illustrated by formation of the mercaptobenzopurines from *lin*-benzohypoxanthine[1764,1768] and also from the 3-benzyl and 3-cyclohexyl homologs.[1764] More prolonged heating times (>3 days) are used to replace both oxygens in benzoxanthine by sulfur.[1772] Direct conversion of a thioxo to an amino group requires a high temperature (> 200°C), as exemplified by formation of *lin*-benzoadenine from 8-thioxobenzopurines by means of ammonia in butanol.[1764,1768] Direct *N*-alkylation of *lin*-benzoadenine is precluded owing to insolubility in most solvents. Using the soluble 8-methylthiobenzopurine reaction with benzyl bromide gives a 50% mixture of the 1-benzyl (**22**, R = SMe) and 3-benzyl (**23**, R = SMe) isomers, which undergo facile amination (NH_3, *tert*-BuOH) to the respective benzoadenines (**22**, R = NH_2)[1764] and (**23**, R = NH_2). Identification of the structure of the 1-benzyl derivative is based upon ^{15}N-^{13}C



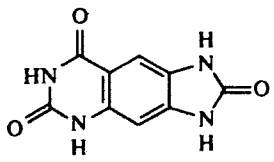
22



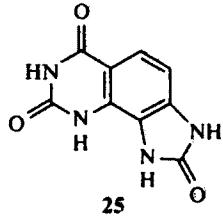
23

couplings observed using the related 7-benzyladenine as a model compound.[1774] A synthesis has established the structure of the 3-benzyl isomer.[1764] Use of the mercury salt of 6-ethylthiobenzohypoxanthine with the *O*-acetylated 1-bromo-β-D-ribofuranose in aprotic media gives the 1- and 3-β-D-ribofuranosides. As in the benzylation noted above, a 50% mixture of alkylated products results.[1772] The benzopurine ribosides undergo the same group metatheses as the bases; these transformations give rise to the linear variants of benzoguanosine, benzoinosine, benzoxanthosine,[1772] and benzoadenosine.[1949]

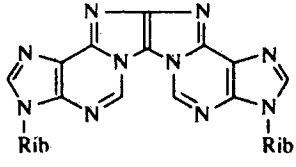
The quinonoid derivative (**5**), 2,3-dimethylimidazo[4,5-*g*]quinazolin-4,8,9-trione, results from oxidation of 2,3-dimethylbenzohypoxanthine with a mixture of dipotassium hydrogen phosphate and potassium nitrosodisulfonate (Fremy's radical) in aqueous acetone.[1767] The pathways followed in the oxidation of purines with xanthine oxidase find parallels in the enzymic reactions with benzopurines. A simple oxidation to the *lin*-benzoxanthine occurs with benzoinosine.[1772] All three variants of benzoadenine undergo conversion to the respective benzoxanthines, with the linear and proximal derivatives being further oxidized to the respective uric acid analogs (**24**) and (**25**).Comparing the rates of conversion to the trioxo derivatives with those for hypoxanthine to uric acid show that while the *lin* form oxidizes faster, the slower rate of the *prox* form may reflect a steric partial shielding of the amino group by the imidazole ring.[1773] A Birch reduction of the benzene moiety affords 4,9-dihydro derivatives of *lin*-benzohypoxanthine (**4**, R = H), *lin*-benzoguanine (**4**, R = NH_2), and *lin*-benzoxanthine (**4**, R = OH), but other benzopurines may occur as minor products.[1766] The dipurinyl riboside (**26**), composed of two adenosine molecules linked by a common ethene bridge between the 6-amino groups and the N-1 positions, is an extension of the stretched purine concept. In this derivative the distance between the two purine units is similar to that between an adenine—hypoxanthine base pair in DNA, and the structure is highly rigid. Derivatives of this type, suitably labeled, are suggested for use as markers for incorporation into the DNA helix.[1950]



24



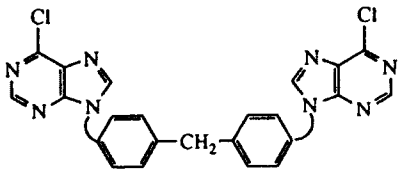
25



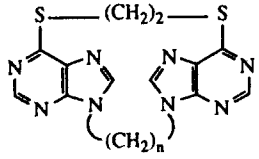
26

2. THE PURINOPHANES

Purinophanes by definition are cyclic derivatives incorporating in the ring structure one or more purine moieties. Synthesis of this type of compound, containing two purine units, was undertaken with a view to using the products as model compounds for studies of the three-dimensional base pairing present in the

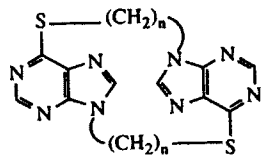


27

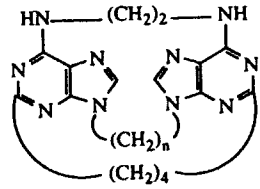


28

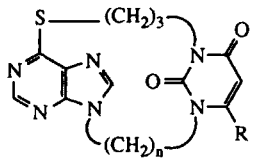
DNA helix. Modifications in the number of carbon atoms in the polymethylene chains connecting the purines enabled the interpurine distances to be varied. Early work in this area was carried out over 30 years ago (*H*55, *H*57, *H*279), producing a wide range of purine pairs usually mutually joined by single methylene chains through either N-9 or the 6-substituent. Other examples with linking sites at C-2, C-8, and N-7 are also known. Unsymmetric linking occurs between the 6-amino group of one adenine to N-9 in the other. Other workers have subsequently prepared these or similar derivatives by the same or alternative routes using these monobridged purines as starting materials for the purinophane syntheses. More recent work on the purine duplex system is illustrated by **27**, which contains a novel linkage.[1951] Investigation of the singly linked purines as possible models of base pairing in DNA has found little evidence that stacking conformations are adopted owing to the flexibility of the methylene chains.[1384] To introduce rigidity, a second bond was inserted between the purines, with the majority of products being bridged between the two 6-substituents, usually amino or thioxo,[1385] and the two N-9 positions. These derivatives exhibit a static conformation in different media and their spectra show hyperchromism in the longest wavelength band. Most interest centers on the 6-mercaptopurine derivatives[1384,1385] (**28**, n = 3 or 4), with the unsymmetrically linked (6,9)–(9′,6′) linked derivative (**29**, n = 2 or 3) showing exceptional hyperchromicity,[1952] reflecting a high order of stacking. By inserting a third linkage, an even greater degree of rigidity is imposed on the two-unit system, as shown by the bisadenines[1358] (**30**, n = 3 or 4). Subsequent extensions have included the synthesis of a number of purine–pyrimidine pairs giving products nearer in character to the base pairing in DNA.[1953] Several 6-mercaptopurine–uracil combinations of the type[1954] (**31**, n = 3 or 4) have been obtained. Purinophane monomers (i.e., compounds containing only one purine unit) are formed by interlinking two sites on the purine by the same chain, such as the 1-thia(6,9)purinophane[1954] (**32**, X = S, n = 10). Similar derivatives of this type, such as the adenine[1867] (**32**, X = NH, n = 8), together with others possessing linkages between a 6-amino group and C-2 or from C-2 to either N-7 or N-9, are documented[1728] but are not participants in purinophane programs.



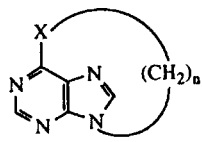
29



30



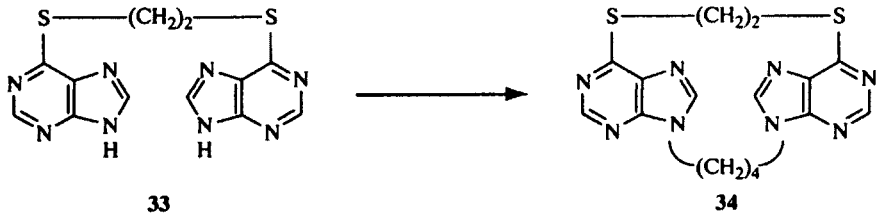
31



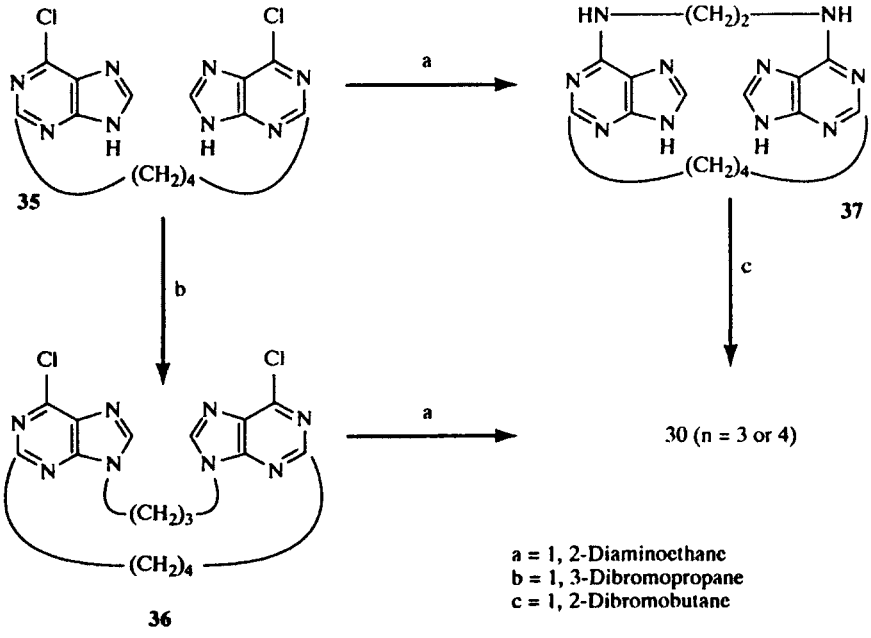
32

A. Preparation

The dipurinyl phanes are derived from the single-linked analogs illustrated by the conversion of the 6-thioxopurine derivative (**33**) to the purinophane (**34**) by means of the 1,4-dibromobutane in DMSO containing potassium carbonate.[1384]



33 34



35 37

36

30 (n = 3 or 4)

a = 1, 2-Diaminoethane
b = 1, 3-Dibromopropane
c = 1, 2-Dibromobutane

Synthesis of the triple-bridged adenine compound (**30**, $n = 3$) starts with 1,4-di(6-chloro-9-purin-2-yl)butane (**35**), which forms the intermediate (**36**) on alkylation with 1,3-dibromopropane (DMSO, K_2CO_3). The final stage involves heating the chloropurinophane with 1,2-diaminoethane in butanol.[1358] Preparation of the 9-butane linked analog (**30**, $n = 4$) is by the alternative route from **35** by reaction with 1,2-diaminoethane giving **37**, which following 1,4-dibromobutane treatment affords **30**[1358] ($n = 4$). The monopurine derivative (**32**, X = S, $n = 10$) results from endoalkylation of 6-(1-bromodecamethylenethio)purine by heating in DMSO with sodium hydride,[1954] and somewhat analogous structures are the xanthine derivatives, containing N-1 and N-3 linked by a polymethylene chain ($n = 8$, 9, and 11), formed by Traube closure of the corresponding 4,5-diaminopyrimidophane by formylation.[2057]

B. Properties and Reactions

Pronounced hypsochromic effects are shown by the longest wavelengths of the spectra. X-ray analysis of **30** ($n = 4$) shows that the two purines are face to face and head to head with an inclination of 13.9° existing between the planes of the two bases, which are 3.7 Å apart. In spite of the bonding constraints imposed, the overlapping adenine moieties have the same bond lengths and angles as in the parent adenine molecule.[1358] Similar studies of dithiapurinophane structures have been reported.[1955]

A notable feature of 6-thiapurinophanes is the enhanced susceptibility of the sulfur moiety to displacement by nucleophiles, giving 6-substituted acyclic purines.[1953,1954] An example of this reactivity is the rapid breakdown of the unsymmetrically linked thiapurine (**29**, $n = 2$) in either 0.1 *M* HCl or 0.1 *M* NaOH at ambient temperature through attack at C-6 by the hydroxide[1952] ion.

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER XIV (*H*439)

The Spectra of Purines (*H*507)

3. Magnetic Resonance Spectra (*H*507) 348
(by M. David Fenn)
A. Proton Resonance Spectroscopy 348
B. ^{13}C Resonance Spectroscopy (*H*515) 362
C. ^{15}N Resonance Spectroscopy (*New*) 362
D. Applications of NMR (*New*) 371
a. Site of Methylation (*New*) 371
b. Measurement of pK_a and Protonation Sites (*New*) 372
c. Tautomerism (*New*) 373
d. Assay of Pharmaceutical Mixtures (*New*) 374
e. References 375
4. Electron Spin Resonance Spectra (*H*516) 378
5. Mass Spectra (*H*518) 379
A. Techniques and Applications 379
a. Purine and *C*-Alkyl Derivatives (*H*520) 379
b. Adenines and 6-Alkylaminopurines (*H*520) 380
c. The Oxopurines (*H*521) 381
d. Guanine and *N*-Alkyl Derivatives (*H*521) 381
f. Thioxo- and Selenoxopurines (*H*522) 382
g. Other Purines 382
6. Magnetic Circular Dichroism (*New*) 382

The importance of UV and IR spectra has greatly diminished over the past two decades, and these techniques are now largely confined to use in theoretical studies at the submolecular level. Sections 1 and 2 covering these topics, are therefore no longer included. Current usage favors NMR and mass spectra for investigative work since both are capable of rapidly affording information on the structures and reaction mechanisms of molecules. Section 3 by M. David Fenn gives an up-to-date overview of the state of NMR which is accompanied by comprehensive tables of data on most types of purines. Section 4 is an annotation on electron-spin resonance spectra, and recent aspects of the mass spectra of various purines are given in Section 5. The final section deals with magnetic circular dichroism.

3. MAGNETIC RESONANCE SPECTRA* (*H*507)
(by M. David Fenn)

Since its inception 40 years ago, NMR spectroscopy has become one of the most valuable and widely used tools of chemistry. From a humble beginning in the laboratories of Bloch and Purcell as an instrument designed primarily to measure the magnetogyric ratio of hydrogen, NMR has given rise to nearly one hundred thousand references in the literature. All branches of chemistry have benefited from this technique, and today no chemical laboratory would be complete without at least access to a multinuclear Fourier transform spectrometer capable of performing, routinely, two-dimensional NMR.

The sheer volume of the literature necessitates that any review of NMR spectroscopy be selective. This review covers 1968–1992, and while many papers have been discarded because of incomplete or unsatisfactory reporting, the main papers on the nuclear magnetic spectroscopy of purines have been included. The problem of nomenclature has been overcome in the tables by naming all compounds as purines. Trivial names such as caffeine, xanthine, and adenine have not been used, and we have adhered to a strictly alphabetical system of listing. For example, xanthine appears as 2,6-dioxopurine and theophylline appears as 1,3-dimethyl-2,6-dioxopurine.

^{1}H, ^{13}C, and ^{15}N spectra are reviewed, but it should be noted that deuterium spectra of several 2,6-dioxo-1,3,7-trimethylpurines analogs have been obtained.[30] Surprisingly, no deuterium isotope shift was noted. Tritium spectra of 1,3-dimethyl-2,6-dioxopurine and 2,6-dioxo-1,3,7-trimethylpurine are also known.[70]

A. Proton Resonance Spectroscopy

The ^{1}H chemical shifts of some simple purines are given in Table 10. Values and assignments are as reported in the literature. In general, the ordering of the chemical shifts of the ring protons is H-8 at highest field and H-2 higher than H-6.[41] There are exceptions to this generalization, particularly if C-6 is substituted with a strong electron-withdrawing group. In this case, H-2 moves upfield relative to H-8.[11] For purines containing *N*-methyl groups, long-range coupling between the *N*-methyl and adjacent ring proton may also aid in assignment of resonances.[94] The coupling is of the order of 0.5 Hz and has been observed in other heterocyclic systems.[13] A useful observation is that for *N*-methyl groups in the imidazole ring, coupling is observed at room temperature, whereas for methyl groups in the pyrimidine ring, elevated temperatures are required. The difference in behavior between the two ring systems has been explained in terms of differing ^{14}N quadrupolar relaxation mechanisms.[94] The most obvious feature of the table is

* In this section the author has adopted some conventions and nomenclature that differ from those used elsewhere in this volume.

TABLE 10. ^{1}H SPECTRA OF SOME SIMPLE PURINES

	H-2	H-6	H-8	Other Resonances	Solvent[a]	Ref.
Purine	8.90	9.12	8.59		DMSO	1
	8.85	9.05	8.54		DMSO	3
	9.17[b]	9.38[b]	8.88[b]		DMSO	4
	9.38	9.50	9.21		D_2O	2
	9.20[b]	9.37[b]	8.85[b]		D_2O	4
	8.87[b]	8.96[b]	8.30[b]		pyr	4
	8.85[b]	9.00[b]	8.47[b]		MeOH	4
	8.95	9.15	8.60		EtOH	4
Anion	9.25	9.40	9.06		D_2O	2
——,3-allyl-6-amino	8.00		7.90	6.03(CH) 5.32,4.96(CH_2)	$CDCl_3$	21
——,7-allyl-6-Cl	8.78		8.30	6.11(CH) 5.25,5.12(CH_2)	$CDCl_3$	21
——,9-allyl-6-amino	8.22		7.82	6.00(CH) 5.23,4.76(CH_2)	$CDCl_3$	21
——,——,6-Cl	8.76		8.13	6.04(CH) 5.31,4.91(CH_2)	$CDCl_3$	21
Purine,1-amino						
Parent	9.21[c]	9.49	8.20		C/M	5
——,2-Me	[c]	9.49	8.68	3.02(2-Me)	C/M	5
——,6-Me	9.20[c]		8.54	3.08(6-Me)	C/M	5
——,9-Me	9.22[c]	9.42	8.70	4.00(9-Me)	C/M	5
——,9-Me-8-Ph	9.28[c]	9.37		7.78(Ph) 4.04(9-Me)	C/M	5
——,8-SMe	8.54	8.67		2.72(S-Me)	C/M	5
	9.00[c]	9.09		2.84(S-Me)	C/M	5
——,8-Ph	9.08[c]	9.30		7.56(Ph)	C/M	5
Purine,2-Amino						
——,3,7-diMe-6-oxo			8.04	3.58(3-Me) 3.92(7-Me)	DMSO	38
——,6-oxo			7.58		NaOD	37
Purine,6-Amino						
Parent	8.10		8.07		DMSO	23
	8.18		8.15	7.03(NH_2)	DMSO	36
	8.52		8.44		DMSO	5
	8.20		8.17		DMSO	11
	8.65		8.69		D_2O	22
	8.20		8.32		NaOD	37
——,2—deuterio			8.07		DMSO	23
——,N-oxide	8.59		8.29		DMSO	97
——,3-benzyl	8.60		7.80	5.55(CH_2) 7.39(Ph) 8.0(NH_2)	DMSO	6
	8.53		7.775	5.51(CH_2) 7.30(Ph) 7.9(NH_2)	DMSO	36
	8.88		8.75	5.87(CH_2) 7.52(Ph) 8.5(NH_2)	TFA	6
	8.56		8.00	5.56(CH_2) 7.35(Ph)	$CDCl_3$	21
——,7-benzyl	8.50		8.28	5.78(CH_2) 7.42(Ph) 6.9(NH_2)	DMSO	6
	8.53		8.18	5.88(CH_2) 7.28(Ph) 6.9(NH_2)	DMA	6
——,9-benzyl	8.32		8.30	5.41(CH_2) 7.33(Ph)	$CDCl_3$	21
	8.30		8.22	5.42(CH_2) 7.37(Ph) 7.3(NH_2)	DMSO	6
	8.14		8.24	[d]	DMSO	23

cont.

TABLE 10. *(cont.)*

	H-2	H-6	H-8	Other Resonances	Solvent[a]	Ref.
———,———,2-deuterio			8.24	[d]	DMSO	23
———,———,N-oxide	8.65		8.46	5.41(CH_2) 7.32(Ph)	DMSO	97
———,3,9-diMe-2-oxo			7.94	3.98(3-Me) 3.68(9-Me)	DMSO	38
———,3-dimethylallyl	8.30		7.75	5.47(CH) 4.90(CH_2) 1.61,1.74(Me)	DMSO	36
———,9-Et	8.15		8.15	[d]	DMSO	23
———,———,2-deuterio			8.15	[d]	DMSO	23
———,———,N-oxide	8.62		8.33	4.2(CH_2) 1.42(Me)	DMSO	97
———,3-Me	8.25		7.73	3.86(3-Me) 7.8(NH_2)	DMSO	36
	8.63		8.58	4.18(3-Me)	TFA	7
———,7-Me	8.64		8.77	4.31(7-Me)	TFA	7
———,9-Me	8.63		8.72	4.06(9-Me)	TFA	7
	8.15		8.08	*d*	DMSO	23
———,———,2-deuterio			8.08	*d*	DMSO	23
———,———,N-oxide	8.65		8.29	3.76(9-Me)	DMSO	97
Purine,5-aza						
———,2-oxo-6-thione			8.10		DMSO	1
———,6-oxo	8.36		8.36		DMSO	1
———,———,6-thione			8.10		DMSO	1
Purine,1-benzyl						
———,8-Me-6-oxo	8.72			5.45(CH_2) 7.37(Ph) 2.99(8-Me)	TFA	34
———,6-thione	8.90		8.63	5.93(CH_2) 7.32(Ph)	DMSO	6
	9.33		8.90	5.58,5.87(CH_2) 7.48(Ph)	TFA	6
Purine,3-benzyl						
———,8-Me-6-oxo	9.12			5.70(CH_2) 7.45(Ph) 2.70(8-Me)	TFA	34
———,———,2-thione				5.87(CH_2) 7.37(Ph) 2.87(8-Me)	TFA	34
———,6-SMe	8.37		8.30	5.68(CH_2) 7.37(Ph) 2.73(S-Me)	$CDCl_3$	6
	9.00		8.95	6.00(CH_2) 7.53(Ph) 3.02(S-Me)	TFA	6
———,6-thione	8.70		8.35	5.53(CH_2) 7.38(Ph)	DMSO	6
	8.82		8.72	5.82,6.25(CH_2) 7.60(Ph)	TFA	6
Purine,7-benzyl						
———,6-Cl	9.03		8.85	5.82(CH_2) 7.33(Ph)	DMSO	6
———,8-Br-1,3-diMe-2,6-dioxo				5.50(CH_2) 7.25(Ph) 3.20(1-Me) 3.37(3-Me)	DMSO	33
———,8-benzylthio-1,3-diMe-2,6-dioxo				5.26(CH_2) 7.18,7.10(Ph) 3.15(1-Me) 3.40(3-Me)	DMSO	33
———,1,3-diMe-2,6-dioxo-8-thione				5.51(CH_2) 7.45(Ph) 3.20(1-Me) 3.40(3-Me)	DMSO	33
———,2,6-dioxo			8.01	5.38(CH_2) 7.25(Ph) 10.8,11.6(NH)	DMSO	33
———,———,1,3-diMe			8.27	5.45(CH_2) 7.30(Ph) 3.19(1-Me) 3.39(3-Me)	DMSO	33
———,———,1-Me			8.11	5.45(CH_2) 7.30(Ph) 3.16(1-Me) 11.9(NH)	DMSO	33
———,———,3-Me			8.20	5.46(CH_2) 7.30(Ph) 3.35(3-Me) 11.2(NH)	DMSO	33

———,6-SMe	8.88	8.08	5.68(CH_2) 7.31(Ph) 2.72(S-Me)	$CDCl_3$	6
	9.17	8.75	5.95(CH_2) 7.52(Ph) 3.12(S-Me)	TFA	6
———,6-oxo	8.42	8.02		DMSO	6
———,6-thione	8.63	8.23	6.17(CH_2) 7.33(Ph)	DMSO	6
	8.73	8.30	6.18(CH_2) 7.35(Ph)	DMA	6
	8.82	8.58	6.23(CH_2) 7.52(Ph)	TFA	6
Purine,9-benzyl					
— —,8-benzylthio-1,3-diMe-2,6-dioxo			5.50(CH_2) 7.30,7.00(Ph) 3.23(1-Me) 3.38(3-Me) 4.40(S-CH_2)	DMSO	33
———,1,3-diMe-2,6-dioxo		7.83	5.65(CH_2) 7.30(Ph) 3.20(1-Me) 3.40(3-Me)	DMSO	33
———,— -,8-thione			5.83(CH_2) 7.40(Ph) 3.20(1-Me) 3.40(3-Me)	DMSO	33
———,2,6-dioxo		7.73	5.26(CH_2) 7.30(Ph) 10.8,12.0(NH)	DMSO	33
— -, ———,1-Me		7.75	5.30(CH_2) 7.30(Ph) 3.16(1-Me) 11.0(NH)	DMSO	33
———,———,———,8-thione			5.30(CH_2) 7.26(Ph) 3.16(1-Me) 10.5(NH)	DMSO	33
———,6-SMe	8.78	7.97	5.42(CH_2) 7.30(Ph) 2.73(S-Me)	$CDCl_3$	6
	9.03	9.22	5.77(CH_2) 7.50(Ph) 3.00(S-Me)	TFA	6
— —,6-thione	8.47	8.25	5.50(CH_2) 7.38(Ph)	DMSO	6
	9.05	8.60	5.72(CH_2) 7.53(Ph)	TFA	6
Purine,8-benzylthio					
— —2,6-dioxo-1-Me			4.43(CH_2) 7.31(Ph) 3.16(1-Me) 11.9,13.3(NH)	DMSO	33
———,———,3-Me			4.41(CH_2) 7.30(Ph) 3.33(3-Me) 10.8(NH)	DMSO	33
Purine,8-bromo-1-[3-bromo-2-oxopropyl]					
———,1,3-diMe-2,6-dioxo			3.31(1-Me) 3.55(3-Me) 5.43(CH_2) 4.06(CH_2)	DMSO	31
— —,3,7-diMe-2,6-dioxo			354(3-Me) 3.97(7-Me) 5.04(CH_2) 4.04(CH_2)	DMSO	31
Purine,7-butyl					
———,1,3-diMe-2,6-dioxo		7.54	3.42(1-Me) 3.59(3-Me) 4.92,1.86,1.35(CH_2) 0.96(CH_3)	$CDCl_3$	32
		7.57	3.40(1-Me) 3.63(3-Me) 5.13,4.30(CH_2) 1.33(Me)	$CDCl_3$	28
		7.98	3.35(1-Me) 3.53(3-Me) 4.30,1.82,1.29(CH_2) 0.90(Me)	D_2O	32
Purine,3-(carbethoxy)propyl					
———,2,6-dioxo-1-Me		7.80	3.40(1-Me) 6.21,4.15, 2.20,1.72(CH_2) 1.22(Me)	$CDCl_3$	28
Purine,3-carboxypropyl					
———,2,6-dioxo-1-Me		8.02	3.27(1-Me) 1.7,2.3,4.1(propyl)	DMSO	28

cont.

TABLE 10. *(cont.)*

	H-2	H-6	H-8	Other Resonances	Solvent[a]	Ref.
Purine,2-chloro						
——,7-Me		9.15	8.65	4.05(7-Me)	DMSO	14
——, ——,6-oxo			7.95	3.99(7-Me)	NaOD	14
Purine,6-chloro						
Parent	8.80		8.73		DMSO	11
——,7-Me	8.82		8.78	4.11(7-Me)	DMSO	14
Purine,8-chloro						
——,3-Me	8.91	8.50		4.26(3-Me)	$CDCl_3$	17
——,7-Me	8.86	9.06		3.77(7-Me)	DMSO	14
——,9-Me	9.02	9.97		3.87(9-Me)	$CDCl_3$	13
	8.96	8.89		3.84(9-Me)	D_2O	13
	9.41	9.37		4.01(9-Me)	D_2O/DCl	13
Purine,6-cyano						
Parent	9.12		8.93		DMSO	11
Purine,3-cyanoethyl						
——,2,6-dioxo-1-Me			7.81	3.34(1-Me) 4.35,2.85(CH_2)	DMSO	28
——,1-methyl-7-(pivaloyloxymethyl)			7.85	3.40(1-Me) 6.20(CH_2), 2.80,4.20,1.18($Me)_3$	$CDCl_3$	28
Purine,1,2-diamino						
Parent	[c]	8.98	8.54		DMSO	5
Purine,1,6-diamino						
Parent	8.52[c]		8.44		DMSO	5
Purine,1,7-dibenzyl						
——,6-thione	8.92		8.63	6.15,5.87(CH_2) 7.32(Ph)	DMSO	6
Purine,1,9-dibenzyl						
——,6-thione	8.90		8.43	5.90,5.43(CH_2) 7.32(Ph)	DMSO	6
Purine,3,7-dibenzyl						
——,6-thione	8.67		8.58	6.33,5.55(CH_2) 7.38(Ph)	DMSO	6
	8.13		7.78	6.18,5.42(CH_2) 7.35(Ph)	$CDCl_3$	6
	8.80		8.52	6.13,5.75(CH_2) 7.47(Ph)	TFA	6
Purine,7,9-dibenzyl						
——,1,3-diMe-2,6-dioxo-8-thione				5.85,5.68(CH_2) 7.30(Ph) 3.18(1-Me) 3.40(3-Me)	DMSO	33
——,6-thione	9.75		8.33	6.17,5.53(CH_2) 7.43(Ph)	DMSO	6
	10.20		8.25	6.67,5.63(CH_2) 7.46(Ph)	DMA	6
	10.75		8.22	6.58,5.67(CH_2) 7.36(Ph)	$CDCl_3$	6
	8.67		8.50	6.18,5.61(CH_2) 7.45(Ph)	TFA	6
Purine,2,6-dichloro						
——,7-Me			8.70	4.07(7-Me)	DMSO	14
Purine,1,3-dimethyl						
——,2,6-dioxo			7.85	3.50(1-Me) 3.67(3-Me)	$CDCl_3$	32
			7.98	3.24(1-Me) 3.44(3-Me)	DMSO	1
			8.02	3.36(1-Me) 3.55(3-Me)	D_2O	32
			7.95	3.30(1-Me) 3.48(3-Me)	D_2O	26
			7.92	3.36(1-Me) 3.56(3-Me)	MeOD	32
			7.93	3.30(1-Me) 3.53(3-Me)	D/D	25
Anion			7.27	3.27(1-Me) 3.47(3-Me)	D/D	26
Cation			7.98	3.31(1-Me) 3.51(3-Me)	D/D	26

———,———,7-Et			7.56	3.42(1-Me) 3.60(3-Me) 4.36(CH_2) 1.52(Me)	$CDCl_3$	32
			7.99	3.35(1-Me) 3.53(3-Me) 4.33(CH_2) 1.46(Me)	D_2O	32
———,———,7-propyl			7.54	3.42(1-Me) 3.60(3-Me) 4.62,1.92(CH_2) 0.95(Me)	$CDCl_3$	32
			7.98	3.35(1-Me) 3.53(3-Me) 4.27,1.83(CH_2) 0.86(Me)	D_2O	32
———,———,7-trimethylsilyl			7.50	3.28(1-Me) 3.50(3-Me) 0.50($Me)_3$	$CDCl_3$	28
———,2,6-dithione			8.25	4.27(1-Me) 4.00(3-Me)	D/D	25
———,6-SMe-2-oxo			7.98	3.72(1-Me) 3.68(3-Me) 3.31(S-Me)	D/D	10
Cation			8.29	3.80(1-Me) 3.77(3-Me) 3.35(S-Me)	D/D	10
———,2-oxo-6-thione			8.06	3.75(1-Me) 3.56(3-Me)	D/D	27
Anion			7.33	3.75(1-Me) 3.50(3-Me)	D/D	27
Cation			8.02	3.72(1-Me) 3.54(3-Me)	D/D	27
———,6-oxo-2-thione			8.15	3.76(1-Me) 3.96(3-Me)	D/D	25
———,2,6,8-trioxo				3.58(1-Me) 3.70(3-Me)	TFA	18
Purine,1,7-dimethyl						
———,2,6-dioxo			7.82	3.23(1-Me) 3.88(7-Me)	D/D	26
	[c]		7.83	3.31(1-Me) 3.94(7-Me)	D_2O	26
Anion			7.58	3.22(1-Me) 3.83(7-Me)	D/D	26
Cation			7.92	3.25(1-Me) 3.92(7-Me)	D/D	26
———,2-oxo-6-thione			7.97	3.72(1-Me) 4.05(7-Me)	D/D	27
Anion			7.87	3.70(1-Me) 4.10(7-Me)	D/D	27
Cation			7.98	3.73(1-Me) 4.15(7-Me)	D/D	27
———,6-oxo	8.28		8.12	3.64(1-Me) 4.06(7-Me)	D_2O	35
Cation	8.56		9.13	3.70(1-Me) 4.25(7-Me)	D_2O	35
———,8-Ph-6-thione	8.75			3.90(1-Me) 4.38(7-Me)[d]	DMSO	8
				4.07(1-Me) 4.57(7-Me)[d]	TFA	8
———,2,6,8-trioxo				3.54(1-Me) 3.72(7-Me)	TFA	18
Purine,1,8-dimethyl						
———,2-SMe		8.80		3.97(1-Me) 2.50(8-Me) 2.70(SMe)	DMSO	15
		8.07		3.98(1-Me) 2.77(8-Me) 2.68(SMe)	$CDCl_3$	15
		9.40		4.28(1-Me) 2.93 (8-Me) 2.98(SMe)	TFA	15
———,6-oxo	8.55			3.79(1-Me) 2.95(8-Me)	TFA	34
Purine,1,9-dimethyl						
———,2,6-dioxo	[c]		7.67	3.33(1-Me) 3.73(9-Me)	D_2O	26
			7.61	3.62(1-Me) 3.68(9-Me)	D/D	26
			7.52	3.24(1-Me) 3.61(9-Me)	D/D	26
Anion						
Cation			8.74	3.34(1-Me) 3.91(9-Me)	D/D	26
———,2-oxo-6-thione			7.65	3.62(1-Me) 3.73(9-Me)	D/D	27
Anion			7.56	3.65(1-Me) 3.51(9-Me)	D/D	27
Cation			8.64	3.70(1-Me) 3.85(9-Me)	D/D	27
———,6-oxo	8.26		7.98	3.66(1-Me) 3.80(9-Me)	D_2O	35
Cation	8.48		9.12	3.68(1-Me) 4.02(9-Me)	D_2O	35

cont.

TABLE 10. *(cont.)*

	H-2	H-6	H-8	Other Resonances	Solvent[a]	Ref.
———,8-Ph-6-thione	8.75			3.92(1-Me) 3.83(9-Me)[d]	DMSO	8
	8.75			4.08(1-Me) 4.13(9-Me)[d]	TFA	8
———,2,6,8-trioxo				3.54(1-Me) 3.56(9-Me)	TFA	18
Purine,3,7-dimethyl						
———,2,6-dioxo			7.94	3.33(3-Me) 3.84(7-Me)	DMSO	1
	[c]		7.88	3.49(3-Me) 3.95(7-Me)	D_2O	26
			7.92	3.38(3-Me) 3.88(7-Me)	D/D	26
Anion			7.60	3.33(3-Me) 3.84(7-Me)	D/D	26
Cation			7.96	3.40(3-Me) 3.91(7-Me)	D/D	26
———,6-oxo	8.39		8.23	3.97(3-Me) 4.09(7-Me)	D_2O	35
Cation	9.20		8.39	4.17(3-Me) 4.17(7-Me)	D_2O	35
— —,2-oxo-6-thione			8.04	3.41(3-Me) 4.06(7-Me)	D/D	27
Anion			7.77	3.39(3-Me) 4.04(7-Me)	D/D	27
Cation			8.04	3.43(3-Me) 4.05(7-Me)	D/D	27
———,8-Ph-6-thione	8.33			3.83(3-Me) 4.38(7-Me)	DMSO	8
	9.08			4.32(3-Me) 4.42(7-Me)	TFA	8
———,2,6,8-trioxo				3.63(3-Me) 3.70(7-Me)	TFA	18
———,6-SMe-2-oxo			7.93	3.56(3-Me) 4.06(7-Me) 2.69(SMe)	D/D	10
Cation			8.38	3.75(3-Me) 4.12(7-Me) 2.85(SMe)	D/D	10
Purine,3,8-dimethyl						
———,2-SMe		8.31		4.22(3-Me) 2.84(8-Me) 2.94(SMe)	$CDCl_3$	[f]
Purine,3,9-dimethyl						
———,2,6-dioxo			7.59	3.65(3-Me) 3.96(9-Me)	D/D	25
Anion			7.44	3.64(3-Me) 3.92(9-Me)	D/D	26
Cation			[d]	3.70(3-Me) 4.05(9-Me)	D/D	26
———,2-oxo-6-thione			7.66	3.67(3-Me) 3.94(9-Me)	D/D	25
Anion			7.39	3.63(3-Me) 3.89(9-Me)	D/D	27
Cation			8.60	3.68(3-Me) 4.16(9-Me)	D/D	27
———,8-Ph-6-thione	8.52			4.42(3-Me) 3.93(9-Me)[d]	TFA	8
———,2,6,8-trioxo				3.95(3-Me) 3.86(9-Me)	TFA	18
Purine,6,7-dimethyl						
Parent	8.50		8.23	4.13(7-Me) 2.90(6-Me)	DMSO	12
Purine,7,8-dimethyl						
———,2-SMe		8.90		3.80(7-Me) 2.59(8-Me) 2.53(S-Me)	DMSO	15
		8.61		3.77(7-Me) 2.60(8-Me) 2.60(S-Me)	$CDCl_3$	15
		9.62		4.20(7-Me) 3.11(8-Me) 2.87(S-Me)	TFA	15
Purine,7,9-dimethyl						
———,2,6,8-trioxo				3.71(7-Me) 3.59(9-Me)	TFA	18
Purine,8,9-dimethyl						
———,2-SMe		8.80		2.57(8-Me) 3.68(9-Me) 2.57(S-Me)	DMSO	15
		8.73		2.63(8-Me) 3.71(9-Me) 2.60(S-Me)	$CDCl_3$	15
		9.53		3.11(8-Me) 4.11(9-Me) 2.90(S-Me)	TFA	15

Purine,2,8-dimethylthio ———,1-Me-6-thione		4.16(1-Me) 2.76(2-SMe) 2.84(8-SMe)	$CDCl_3$	9
Purine,2,6,-dioxo	7.89		DMSO	1
	7.85		D/D	26
Anion	7.35		D/D	26
Dianion	7.23		D/D	26
Cation	7.99		D/D	26
———,1,3-diEt	8.02	4.03,4.13(CH_2) 1.21,1.31(Me)	D_2O	32
	7.95	4.07,4.16(CH_2) 1.22,1.32(Me)	MeOD	32
	7.84	4.18,4.25(CH_2) 1.31,1.39(Me)	$CDCl_3$	32
——— –,3,7-di(pivaloyloxymethyl)-1-methyl	7.82	3.40(1-Me) 1.20(Me_3)$_3$ 6.22,6.10(CH_2)	$CDCl_3$	28
———,8,-hexyl		13.2,11.45,10.66(NH) 2.40(CH_2)[d]	DMSO	24
———,———,7-OH		12.06(OH) 11.45,10.75(NH) 2.40(CH_2)[d]	DMSO	24
———,7-OH	7.97	11.45,10.75(NH)	DMSO	24
———,——– –,1-Me	7.90	12.3(OH) 11.9(NH) 3.12(1-Me)	DMSO	24
——– –,———,8-propyl		10.8,11.50(NH) 12.12(OH) 2.40(CH_2)[d]	DMSO	24
———,3-isobutyl-1-Me	8.00	3.36(1-Me) 3.88(CH_2) 2.15(CH) 0.92(Me_2)	D_2O	32
	7.85	3.34(1-Me) 3.89(CH_2) 2.23(CH) 0.93(Me_2)	MeOD	32
	7.85	3.50(1-Me) 4.01(CH_2) 2.32(CH)0.98(Me_2)	$CDCl_3$	32
———,1-Me	7.88	3.27(1-Me)	D/D	26
Anion	7.22	3.22(1-Me)	D/D	26
Dianion	7.13	3.22(1-Me)	D/D	26
Cation	8.03	3.28(1-Me)	D/D	26
———,——– –,8-thione		3.10(1-Me) 12.7(NH)	DMSO	33
———,———,7-(pivaloyloxymethyl)	7.90	3.40(1-Me) 6.22(CH_2) 1.18(Me_3)	$CDCl_3$	28
——– –,3-Me	7.92	3.45(3-Me)	D/D	25
	7.92	3.45(3-Me)	D/D	25
Anion	7.17	3.37(3-Me)	D/D	26
Dianion	7.07	3.37(3-Me)	D/D	26
Cation	7.96	3.45(3-Me)	D/D	26
———,———,8-thione		3.27(3-Me)	DMSO	33
———,7-Me	7.85	3.82(7-Me)	DMSO	1
	7.82	3.88(7-Me)	D/D	25
	7.82	3.83(7-Me)	D/D	26
Anion	7.68	3.83(7-Me)	D/D	26
Cation	7.84	3.88(7-Me)	D/D	26
———,9-Me	7.57	3.60(9-Me)	DMSO	
	7.55	3.68(9-Me)	D/D	25
Anion	7.38	3.48(9-Me)	D/D	26

cont.

TABLE 10. *(cont.)*

	H-2	H-6	H-8	Other Resonances	Solvent[a]	Ref.
Dianion			7.33	3.47(9-Me)	D/D	26
Cation			8.39	3.77(9-Me)	D/D	26
———,1,3,7-triMe(caffeine)			7.51	3.41(1-Me) 3.60(3-Me) 4.00(7-Me)	$CDCl_3$	32
			7.57	3.41(1-Me) 3.60(3-Me) 4.00(7-Me)	$CDCl_3$	29
			7.51	3.40(1-Me) 3.58(3-Me) 3.99(7-Me)	$CDCl_3$	30
			7.87	3.27(1-Me) 3.45(3-Me) 3.89(7-Me)	D_2O	25
			7.88	3.32(1-Me) 3.50(3-Me) 3.95(7-Me)	D_2O	29
			7.90	3.32(1-Me) 3.49(3-Me) 3.94(7-Me)	D_2O	29
	[c]		7.88	3.32(1-Me) 3.50(3-Me) 3.95(7-Me)	D_2O	26
			7.90	3.34(1-Me) 3.52(3-Me) 3.95(7-Me)	D_2O	32
			7.87	3.27(1-Me) 3.45(3-Me) 3.89(7-Me)	D/D	26
Cation			8.31	3.38(1-Me) 3.57(3-Me) 4.06(7-Me)	D_2O	29
Cation			7.92	3.27(1-Me) 3.47(3-Me) 3.93(7-Me)	D/D	26
———,1,3,9-triMe			7.32	3.44(1-Me) 3.78(3-Me) 3.96(9-Me)	$CDCl_3$	29
			7.64	3.34(1-Me) 3.78(3-Me) 4.00(9-Me)	D_2O	29
			7.62	3.35(1-Me) 3.76(3-Me) 3.99(9-Me)	D_2O	29
	[c]		7.62	3.35(1-Me) 3.76(3-Me) 3.99(9-Me)	D_2O	26
			7.58	3.27(1-Me) 3.70(3-Me) 3.95(9-Me)	D/D	25
Cation			8.15	3.29(1-Me) 3.73(3-Me) 4.03(9-Me)	D/D	26
Cation			8.82	3.42(1-Me) 3.85(3-Me) 4.25(9-Me)	D_2O	29
Purine,2,6-dithione						
Parent			8.10		DMSO	1
			8.19		D/D	25
———,3-Me			8.22	3.86(N-Me)	D/D	25
———,7-Me			8.13	4.08(N-Me)	D/D	25
———,1,3,7-triMe			8.23	4.25(1-Me) 3.96(3-Me) 4.15(7-Me)	D/D	25
Purine,6-iodo						
Parent	8.63		8.60		DMSO	11
Purine,2-Methoxy						
———,1-Me		8.58	8.25	4.33(O-Me) 4.00(N-Me)	$CDCl_3$	16
———,7-Me		8.71	8.06	4.09(O-Me) 3.95(N-Me) J8,Me = 0.5 H2	$CDCl_3$	13

——,9-Me		8.87	7.90	4.08(O-Me) 3.83(N-Me)	$CDCl_3$	13
Purine,6-methoxy						
Parent	8.49		8.35	No O-Me given	DMSO	3
	8.21		8.26	4.23(O-Me) 4.21(N-Me) J2–Me = 0.5 H2	$CDCl_3$	17
	8.74		8.05	4.21(O-Me) 4.10(N-Me)	DMSO	13
	8.55		8.13	4.22(O-Me) 4.11(N-Me)	D_2O	13
	8.94		8.65	4.31(O-Me) 4.24(N-Me) J2,Me = 0.5 H2	D_2O/DCl	13
	9.07		8.78	4.44(N-Me)[d]	TFA	7
——,7-Me	8.63		7.96	4.16(O-Me) 4.04(N-Me) J8, Me = 0.5 H2	$CDCl_3$	13
	8.52		8.41	4.09(O-Me) 3.98(N-Me)	DMSO	13
	8.33		8.14	4.05(O-Me) 3.91(N-Me)	D_2O	13
	8.40		8.22	3.95(N-Me)	D_2O	7
	8.99		8.76	4.25(O-Me) 4.15(N-Me)	D_2O/DCl	13
——,9-Me	8.56		7.91	4.20(O-Me) 3.89(N-Me)	$CDCl_3$	13
	8.50		7.83	4.14(O-Me) 3.81(N-Me)	$CDCl_3$	16
	8.54		8.33	4.09(O-Me) 3.81(N-Me)	DMSO	13
	8.31		8.09	4.07(O-Me) 3.76(N-Me)	D_2O	13
	8.42		8.20	3.89(N-Me)[d]	D_2O	7
	8.50		7.83	4.17(O-Me) 3.81(N-Me)	$CDCl_3$	16
	8.74		9.32	4.22(O-Me) 4.04(N-Me) J8,Me = 0.5 H2	D_2O/DCl	13
Purine,8-methoxy						
——,7-Me	9.02	8.60		4.27(O-Me) 3.60(N-Me)	$CDCl_3$	16
——,9-Me	8.80	8.76		4.26(O-Me) 3.64(N-Me)	$CDCl_3$	13
	8.75	8.80		4.23(O-Me) 3.60(N-Me)	$CDCl_3$	16
Purine,1-methyl						
Parent	9.13	9.31	8.78	4.46(1-Me)	DMSO	2
——,6-oxo	8.65		9.14	3.84(1-Me)	TFA	7
	8.29		8.17	3.66(1-Me)	D_2O	35
Anion	8.07		7.88	3.60(1-Me)	D_2O	35
Cation	8.50		9.13	3.73(1-Me)	D_2O	35
——,2-SMe		9.22	8.55	4.08(1-Me) 2.78(S-Me)	$CDCl_3$	15
		9.06	8.40	4.00(1-Me) 2.73(S-Me)	DMSO	13
——,8-Me	8.35	8.02		4.11(1-Me) 2.77(S-Me) J2,6 = 2 H2	$CDCl_3$	13
	8.68	8.49		4.19(1-Me) 2.68(S-Me)	D_2O	13
	9.12	9.12		4.37(1-Me) 2.67(S-Me)	D_2O/DCl	13
——,8-Ph-6-thione	8.73			3.90(1-Me)[d]	DMSO	8
	8.90			4.12(1-Me)[d]	TFA	8
——,6-thione	8.66		8.33	(1-Me)[d]	DMSO	3
	8.91		9.25	4.15(1-Me)	TFA	7
——,6-SMe-2-oxo			8.02	3.69(1-Me) 2.24(S-Me)	D/D	10
			7.56	3.70(1-Me) 3.19(S-Me)	D/D	10
			8.28	3.78(1-Me) 3.36(S-Me)	D/D	10
——,2-oxo-6-thioxo			7.96	3.67(1-Me)	D/D	27
Anion			7.52	3.68(1-Me)	D/D	27
Dianion			7.30	3.70(1-Me)	D/D	27
Cation			8.01	3.67(1-Me)	D/D	27
——,2,6,8-trioxo				3.58(1-Me)	TFA	18
Purine,3-Methyl						
Parent	9.23	9.31	8.65	4.61(3-Me)	DMSO	2

cont.

TABLE 10. *(cont.)*

	H-2	H-6	H-8	Other Resonances	Solvent[a]	Ref.
———,6-SMe	8.28		8.30	4.20(3-Me) 2.81(S-Me) J2,6 = 2 H2	$CDCl_3$	13
	8.64		8.23	4.17(3-Me) 2.76(S-Me)	D_2O	13
	9.05		8.77	4.31(3-Me) 2.89(S-Me)	D_2O/DCl	13
	9.11		8.86	4.42(3-Me) no S-Me given	D_2O/TFA	7
———,8-SMe	8.34	8.64		4.17(3-Me) 2.78(S-Me)	$CDCl_3$	13
	8.63	8.63		4.14(3-Me) 2.69(S-Me)	D_2O	13
	9.09	9.09		4.35(3-Me) 2.92(S-Me)	D_2O/DCl	13
———,6-oxo	9.19		8.55	4.23(3-Me)	TFA	7
	8.34		8.26	3.95(3-Me)	D_2O	35
Anion	8.00		7.83	3.90(3-Me)	D_2O	35
Dianion	9.24		8.46	4.22(3-Me)	D_2O	35
———,8-Ph-6-thione	8.44			3.95(3-Me)[d]	DMSO	8
	9.12			4.40(3-Me)[d]	TFA	8
———,2-oxo-6-thione			8.03	3.45(3-Me)	D/D	25
———,6-oxo-2-thione			8.15	3.88(3-Me)	D/D	25
———,2-oxo		8.61	8.10	3.57(3-Me)	DMSO	17
———,6-SMe-2-oxo			7.90	3.59(3-Me) 2.65(S-Me)	D/D	10
Anion			7.50	3.59(3-Me) 2.61(S-Me)	D/D	10
Cation			8.36	3.74(3-Me) 2.90(S-Me)	D/D	10
———,6-thione	9.08		8.67	1.27(3-Me)	TFA	7
———,2-oxo-6-thione			8.03	3.45(3-Me)	D/D	27
Anion			7.34	3.42(3-Me)	D/D	27
Dianion			7.17	3.40(3-Me)	D/D	27
Cation			8.04	3.47(3-Me)	D/D	27
———,2,6,8-trioxo				3.69(3-Me)	TFA	18
Purine,7-methyl						
Parent	9.03	9.15	8.71	4.28(7-Me)	D/D	2
	9.03	9.24	8.68	4.00(7-Me)	DMSO	14
———,2-SMe		8.73	8.07	3.932.68(S-Me)	$CDCl_3$	15
		9.07	8.58	3.922.55(S-Me)	DMSO	15
———,6-SMe	8.85		7.98	4.14(7-Me) 2.68(S-Me)	$CDCl_3$	13
	8.82		8.58	4.12(7-Me) 2.72(S-Me)	DMSO	14
	8.51		8.22	4.02(7-Me) 2.64(S-Me)	D_2O	13
	8.95		9.11	4.20(7-Me) 92.87(S-Me) J8,Me = 0–5 H2	D_2O/Cl	13
	9.06		9.19	4.44(7-Me) no S-Me given	TFA	7
———,8-SMe	9.01	8.66		3.75(7-Me) 2.89(S-Me)	$CDCl_3$	13
	8.90	9.02		3.78(7-Me) 2.82(S-Me)	DMSO	14
	8.76	8.81		3.71(7-Me) 2.78(S-Me)	D_2O	13
	9.17	9.17		3.91(7-Me) 2.92(S-Me)	D_2O/Cl	13
———,2-SO_2Me		9.52	9.01	4.09(7-Me) 3.46(SO_2Me)	DMSO	14
———,6-SO_2Me	9.23		9.04	4.20(7-Me) 3.76(SO_2Me)	DMSO	14
———,8-SO_2Me	9.40	9.58		4.24(7-Me) 3.70(SO_2Me)	DMSO	14
———,6-oxo	8.10		8.10	4.04(7-Me)	D_2O	35
Anion	8.10		7.93	4.01(7-Me)	D_2O	35
Cation	8.40		9.08	4.30(7-Me)	D_2O	35
	8.63		9.05	4.34(7-Me)	TFA	7
———,———,2-thione			8.02	3.93(7-Me)	D/D	25
———,2-oxo-6-thione			7.96	4.05(7-Me)	D/D	25

Purine,7-methyl						
———,6-SMe-2-oxo			8.03	4.04(7-Me) 2.70(S-Me)	D/D	10
Anion			7.93	3.96(7-Me) 2.65(S-Me)	D/D	10
Cation			8.56	4.14(7-Me) 2.81(S-Me)	D/D	10
———,6-oxo	8.22		8.00	4.00(7-Me)	DMSO	14
———,8-oxo	8.60	8.41		3.36(7-Me)	DMSO	14
———,8-Ph-6-thione	8.20			4.38((7-Me)[d]	DMSO	8
	8.60			4.38(7-Me)[d]	TFA	8
———,6-thione	8.50		9.04	4.50(7-Me)	TFA	7
	8.50		8.22	4.28(7-Me)	DMSO	14
———,8-thione	8.81	8.78		3.71(7-Me)	DMSO	14
———,2-thione		8.46	8.10	3.80(7-Me)	NaOD	10
———,2-oxo-6-thione			7.96	4.05(7-Me)	D/D	27
Anion			7.81	4.01(7-Me)	D/D	27
Dianion			7.68	4.04(7-Me)	D/D	27
Cation			7.97	4.06(7-Me)	D/D	27
———,2,6,8-trioxo				3.72(7-Me)	TFA	18
———,2-oxo		8.80	8.39	3.85(7-Me)	DMSO	14
Purine,9-methyl						
Parent	9.31	9.43	9.13	4.51(9-Me)	D_2O	2
———,2-SMe		8.91	7.88	3.81(9-Me) 2.63(S-Me)	$CDCl_3$	15
		8.98	8.41	3.752.56(S-Me)	DMSO	15
———,6-SMe	8.75		7.94	3.89(9-Me) 2.74(S-Me)	$CDCl_3$	13
	8.35		8.11	3.77(9-Me) 2.59(S-Me)	D_2O	13
	9.11		8.99	4.07(9-Me) 2.95(S-Me)	D_2O/DCl	13
	9.09		9.24	4.21(9-Me)[d]	TFA	7
———,8-SMe	8.92	8.85		3.73(9-Me) 2.83(S-Me)	$CDCl_3$	13
	8.90	8.83		3.78(9-Me) 2.88(S-Me)	$CDCl_3$	16
	8.69	8.69		3.61(9-Me) 2.73(S-Me)	D_2O	13
	9.19	9.09		3.87(9-Me) 2.87(S-Me) J2,6 = 1 H2	D_2O/DCl	13
———,2-oxo-6-thione			7.67	3.73(9-Me)	D/D	25
———,———,6-SMe			7.99	3.73(9-Me) 2.68(S-Me)	D/D	10
			7.89	3.70(9-Me) 2.67(S-Me)	D/D	10
			8.50	3.86(9-Me) 2.91(S-Me)	D/D	10
———,6-oxo	8.53		9.13	4.15(9-Me)	TFA	7
	8.17		8.04	3.84(9-Me)	D_2O	35
Anion	8.15		7.87	3.76(9-Me)	D_2O	35
Cation	8.40		9.16	4.10(9-Me)	D_2O	35
———,2-oxo-6-thione			7.67	3.73(9-Me)	D/D	27
Anion			7.53	3.48(9-Me)	D/D	27
Dianion			7.40	3.48(9-Me)	D/D	27
Cation			8.80	3.93(9-Me)	D/D	27
———,2,6,8-trioxo				3.60(9-Me)	TFA	18
Purine,8-Methyl						
———,2-SMe		8.77		2.52(8-Me) 2.52(S-Me)	DMSO	15
		9.36		3.03(8-Me) 2.83(S-Me)	TFA	15
Purine,8-methylsulphonyl						
Parent	9.67	9.37		3.50(8-Me)	DMSO	16
Purine,2-methylthio						
Parent		8.90	8.36	2.61(S-Me)	DMSO	15
Purine,6-methylthio						
Parent	8.68		8.40	[d]	DMSO	13

cont.

TABLE 10. *(cont.)*

	H-2	H-6	H-8	Other Resonances	Solvent[a]	Ref.
———,2-oxo			7.86	2.65(S-Me)	DMSO	10
Anion			7.54	2.63(S-Me)	DMSO	10
Cation			8.43	2.84(S-Me)	DMSO	10
Purine,2-oxo						
———,6-thione			8.00		DMSO	
			7.95		D/D	25
Anion			7.62		D/D	27
Dianion			7.31		D/D	27
Cation			8.02		D/D	27
———,———,1,3,7-triMe			8.06	3.96(1-Me) 3.50(3-Me) 4.08(7-Me)	D/D	25
Cation			8.05	3.71(1-Me) 3.52(3-Me) 4.10(7-Me)	D/D	27
———,———,1,3,9-triMe			7.65	3.74(1-Me) 3.74(3-Me) 3.92(9-Me)	D/D	25
Cation			8.72	3.78(1-Me) 3.78(3-Me) 4.16(9-Me)	D/D	27
Purine,6-oxo						
Parent	8.07		7.94		DMSO	1
	8.17		8.20		D_2O	7
	7.87		8.08		NaOD	37
Anion	8.10		8.01		NaOD	7
Dianion	8.00		7.80		NaOD	7
Cation	8.41		9.17		TFA	7
———,2-thione			8.05		DMSO	1
			8.04		D/D	25
———,———,1,3,7-triMe			8.11	3.74(1-Me) 3.93(3-Me) 3.99(7-Me)	D/D	25
Purine,2-thione						
Parent		8.48	8.37		DMSO	1
Purine,6-thione						
Parent	8.36		8.18		DMSO	3
	8.50		8.33		DMSO	6
	8.35		8.15		DMSO	
	9.18		8.58		TFA	6
Cation	8.49		9.27		TFA	7
Anion	8.38		8.27		NaOD	7
Dianion	8.23		8.02		NaOD	7
———,9-Me	8.54		9.18	4.18(9-Me)	NaOD	7
———,———,8-Ph	8.23			3.83(9-Me)[d]	DMSO	8
	8.62			4.22(9-Me)[d]	DMSO	8
———,8-Ph	8.27			[d]	DMSO	8
	8.70			[d]	TFA	8
Purine,1,3,7,9-tetramethyl						
———,2,6,8-trioxo				3.31 3.64 3.50 3.74	D_2O	19
				3.37 3.62 3.58 3.72	$CDCl_3$	20
				3.53 3.91 3.72 3.82	TFA	18
Purine,1,3,7-trimethyl						
———,2,6,8-trioxo				3.32 3.48 3.46	D_2O	19
				3.57 3.69 3.74	TFA	18

Purine,1,3,9-trimethyl			
———,2,6,8-trioxo	3.34 3.62 3.75	D_2O	19
	3.57 3.96 3.83	TFA	18
Purine,1,7,9-trimethyl			
———,2,6,8-trioxo	3.54 3.73 3.58	TFA	18
Purine,3,7,9-trimethyl			
———,2,6,8-trioxo	3.64 3.51 3.70	D_2O	19
	3.91 3.73 3.86	TFA	18

[a] DMSO, dimethyl sulfoxide-d_6 pyr, pyridine MeOD, methanol-d_4. EtOH, ethanol C/M, methanol-d_4 chloroform mixture. TFA, trifluoroacetic acid $CDCl_3$, chloroform-d DCl, deuterium chloride D/D, dimethyl sulfoxide: D_2O mixture 9:1 NaOD, sodium deuteroxide DMA, dimethylacetamide.
[b] Extrapolated to infinite dilution.
[c] Mesitylenesulfonate salt.
[d] No other resonances reported.
[e] Measured at 70 °C.
[f] Inferred in Ref. 15.

the wide variation in chemical shifts with change of solvent. For example, the chemical shift of purine itself varies from 8.85 to 9.38 ppm. The exact value of the chemical shift depends on the solvent used.

A considerable volume of literature exists where the self-association of purine,[71-75] association of other purines with small organic molecules,[19,20,76-88] and interaction with nucleosides[87-90] has been examined by NMR spectroscopy techniques. Although it does not deal in any great detail with the studies mentioned above, the overall conclusions arrived at are of interest.

Most studies noted significant upfield shifts with increasing concentration for protons in a wide range of purine analogs. The results have been interpreted as strong evidence for stacking of purine rings in solutions, the aggregate of molecules being stabilized by intermolecular hydrogen bonds.[75] There is evidence also that purine and its analogs will form collision complexes with aromatic compounds[19,20,84,86] or compounds containing aromatic ring systems.[80]

Mixtures of purine analogs also give rise to significant upfield shifts of purine ring protons.[75] One can, therefore, explain some of the variations in chemical shifts in Table 10 on the basis of differing concentrations. However, even when chemical shifts are extrapolated to infinite dilution, a situation where one would expect concentration effects to be minimized,[4] there is still a significant difference in chemical shifts between different solvents. One must take into account not only the nature of solvent–solute interactions, but also the effect of tautomerism on ^1H chemical shifts as the proportion of tautomers can vary greatly with choice of solvent. (This topic is dealt with in Section 3.D.c.)

The large effects of concentration and solvent render any comparison of chemical shifts in purines difficult and possibly meaningless unless adequate compensation for such effects is made. One must be careful to use pure compounds. Even

a small amount of impurity is likely to give erroneous shifts. Table 10 must therefore be seen only as a guide to ^1H chemical shifts in purine and its analogs.

B. ^{13}C Resonance Spectroscopy (*H*515)

The ^{13}C spectroscopy results of some simple purines are collected in Table 11. Values and assignments are as reported in the literature. The purine ring system has five carbons, of which two, C-4 and C-5, have no hydrogens attached. As the most effective method of relaxation is not present for these carbons, both can be expected to have relatively long relaxation times, and subsequently be of low intensity in the ^{13}C spectrum. Studies on selectively deuterated purines indicate that C-5 is always at higher field than C-4. Theoretical calculations also predict that C-5 will be more shielded than C-4.[4,44] Single-bond coupling constants may be used to distinguish between C-2 and C-6. $^1J_{C_2H_2}$ is of the same order as $^1J_{C_8H_8}$ (ca. 210 Hz), but larger than $^1J_{C_6H_6}$ (ca. 190 Hz). Assuming H-6 is present, three bond couplings will distinguish C-2 from C-8. If the ^1H spectrum has been assigned, then selective decoupling will assign the ^{13}C spectrum.[5]

In recent work, the sensitive INEPT pulse sequence has been used to assign the ^{13}C spectra of mono- and dimethyl-2,6-dioxopurines.[100]

By far the best method of assignment is two-dimensional heteronuclear cross-correlation spectroscopy. Once C-5 has been assigned, all other carbon resonances may be assigned. 8-H but not H-2 is correlated with C-5, while C-4 correlates with both H-8 and H-2. C-6 is correlated with H-2 only.[21]

^{13}C resonances, like ^1H resonances, are concentration dependent. Significant upshield shifts with increasing concentration have been reported.[4] As with ^1H spectra, the effects have been interpreted as indicating stacking of purine molecules in solution, and the remarks made in the earlier discussion on ^1H spectra are pertinent here.

Spin-lattice relaxation times have been measured for the purine molecule.[95] For protonated carbons, relaxation times are of the order of 1 s^{-1}, while the values obtained for C-4 and C-5 were of the order of 0.04 s^{-1}. The difference in relaxation times reflects the efficiency of the dipolar relaxation mechanism present for protonated carbons. With the increased sensitivity of modern spectrometers and the availability of cross-correlation spectroscopy, ^{13}C spectroscopy is probably a better method than ^1H for investigating purines.

C. ^{15}N Resonance Spectroscopy (*New*)

In spite of the vast improvement in NMR technology, obtaining ^{15}N spectra still remains one of the most elusive tasks.

Three areas of difficulty may be encountered:

1. The very long relaxation times found with purine nitrogens, particularly if the nitrogen lacks a hydrogen substituent. Under these conditions the most

TABLE 11. ^{13}C SPECTRA OF SOME SIMPLE PURINES

	C-2	C-4	C-5	C-6	C-8	Other Resonances	Solv[a]	Ref.
Purine	153.25[b]	156.04	131.84	146.75	147.22		DMSO	4
	152.16	154.79	130.41	145.59	146.16		DMSO	3
	152.15	154.70	130.45	145.55	146.10		DMSO	45
	152.10	154.77	130.46	145.02	146.09		DMSO	47
	152.16	154.79	130.41	145.59	146.14		DMSO	46
	153.00[b]	156.62	129.68	146.04	148.65		D_2O	4
	152.00	154.86	128.40	144.84	147.87		D_2O	41
	152.88[b]	155.03	132.88	145.87	146.95		pyr	4
	152.42[b]	155.38	133.58	145.42	146.92		MeOH	4
	152.37	154.90	130.88	145.47	146.44		EtOH	4
Anion	149.52	160.70	134.47	143.67	156.91		D_2O	41
Cation	148.33	158.10	128.42	139.86	152.99		D_2O	41
———,3-allyl-6-amino	143.4	149.8	120.7	155.0	152.6	51.0(CH_2) 132.1(CH) 118.8(CH_2)	DMSO	21
———,7-allyl-6-Cl	152.5	162.0	122.5	143.1	148.9	49.3(CH_2) 131.9(CH) 119.6(CH_2)	DMSO	21
———,9-allyl-6-amino	152.6	149.4	118.8	155.1	140.8	45.0(CH_2) 133.0(CH) 117.7(CH_2)	DMSO	21
———,9-allyl-6-Cl	152.0	151.7	131.5	151.0	144.9	46.3(CH_2) 130.9(CH) 119.9(CH_2)	DMSO	21
Purine,1-amino								
Parent	146.1[c]	155.3	128.9	139.1	153.0		DMSO	5
———,2-Me	156.8[c]	155.2	[d]	140.5	152.5	21.4(2-Me)	DMSO	5
———,9-Me	146.7[c]	151.7	132.1	141.4	153.8	30.4(9-Me)	DMSO	5
———,8-SMe	143.3[c]	164.8	136.3	130.6	177.1	13.5(S-Me)	DMSO	5
	145.8[c]	157.8	130.0	134.0	167.2	13.8(S-Me)	DMSO	5
———,8-Ph	146.3	157.0		137.2	161.7	[d]	DMSO	5
Purine,2-amino								
Parent	160.59	155.11	125.52	147.69	141.62		DMSO	47
———,6-Me	160.11	154.34	124.40	157.25	140.02	19.02(6-Me)	DMSO	47
———,6-SMe	159.65	151.65	123.97	159.20	138.74	10.80(S-Me)	DMSO	47
———,6-oxo	160.0	162.2	119.6	168.8	150.1		D_2O	44

cont.

TABLE 11. *(cont.)*

	C-2	C-4	C-5	C-6	C-8	Other Resonances	Solv[a]	Ref.
Purine,6-amino								
Parent	152.37	151.30	117.61	155.30	139.29		DMSO	47
	152.43	151.30	117.51	155.35	139.35		DMSO	3
	152.45	151.35	117.60	155.35	139.40		DMSO	45
	150.5	160.4	121.0	155.0	153.7		D_2O	44
———,2-Cl	152.78	152.78	116.20	155.94	140.17		DMSO	47
———,2-F	158.77	153.36	115.53	156.81	140.06		DMSO	47
———,2-Me	160.72	157.80	115.80	154.94	138.62	25.33(2-Me)	DMSO	47
———,7-Me	152.31	159.82	111.77	151.91	145.94	33.76(7-Me)	DMSO	43
———,9-Me	152.50	149.94	118.72	155.98	141.47	29.39(9-Me)	DMSO	43
———,2-SMe	163.89	152.20	115.42	154.92	138.47	13.63(S-Me)	DMSO	47
———,3-benzyl	143.4	149.7	120.3	154.9	152.5	52.0(CH_2) 136.9,128.0,128.6(Ph)	DMSO	21
———,9-benzyl	152.7	149.6	118.8	156.1	140.8	46.2(CH_2) 137.1,127.5,128.7,127.7(Ph)	DMSO	21
———,3-(but-2-enyl)	142.8	149.7	120.5	154.8	152.6	50.4(CH_2) 130.6(CH) 125.1(CH) 17.2(Me)	DMSO	21
———,9-(but-2-enyl)	152.4	149.4	118.7	155.9	140.4	44.3(CH_2) 129.1(CH) 125.9(CH) 17.2(Me)	DMSO	21
———,9-(but-3-enyl)	152.3	149.5	118.7	155.9	140.7	42.1(CH_2) 33.4(CH_2) 134.6(CH) 117.3(CH_2)	DMSO	21
Purine,6-bromo								
Parent	151.50	146.05	131.85	152.90	146.00		DMSO	45
	151.52	152.98	131.97	140.12	145.94		DMSO	47
Purine,2-chloro								
Parent	152.69	157.68	129.06	146.91	147.79		DMSO	47
———,6-OMe	151.13	156.95	116.83	159.57	143.83	54.7(O-Me)	DMSO	47
Purine,6-chloro								
Parent	151.50	154.16	129.23	147.78	146.18		DMSO	47
	151.35	147.80	129.05	154.20	146.10		DMSO	45
———,2-Et	165.01	155.11	127.70	147.59	145.99	12.61(Me)[a]	DMSO	47
Purine,6-cyano								
Parent	152.25	133.45	127.85	154.95	149.30	114.45(CN)	DMSO	45
	152.20	154.97	133.47	127.80	149.29	114.43(CN)	DMSO	47

Purine,1,2-diamino								
Parent	154.4[c]	157.5	125.4	141.6	150.0		DMSO	5
Purine,1,6-diamino								
Parent	143.2[c]	147.2	117.0	151.1	148.5		DMSO	5
Purine,2,6-diamino								
Parent	160.20	152.77	112.50	155.78	135.91		DMSO	47
Purine,2,6-dichloro								
Parent	150.98	156.23	128.51	148.10	147.44		DMSO	47
Purine,6-diethylamino								
Parent	151.91	151.08	118.46	153.07	137.86	42.19(CH_2) 13.49(Me)	DMSO	47
Purine,1,3-dimethyl								
———,2,6-dioxo	158.7	150.7	110.1	155.2	144.0	30.8(1-Me) 32.8(3-Me)	D_2O	39
	152.57	140.75	108.62	155.84	136.89	30.3(1-Me) 33.72(3-Me)	HCl	40
Cation	157.0	143.1	109.2	153.7	138.9	30.4(1-Me) 33.4(3-Me)	D_2O	39
Purine,3,7-dimethyl								
———,2,6-dioxo	151.93	142.84	109.45	155.79	138.34	32.6(3-Me) 37.4(7-Me)	HCl	40
	160.42	150.17	109.94	165.75	141.39	30.35(3-Me) 34.3(7-Me)	NaOH	40
Cation	156.0	143.5	110.0	152.3	138.9	32.8(3-Me) 37.4(7-Me)	D_2O	39
Purine,6-dimethylamino								
Parent	151.80	151.15	118.90	154.30	137.80	37.85(Me)	DMSO	45
	151.76	151.23	118.97	154.29	137.74	37.84(Me)	DMSO	47
Purine,2,6-dimethylthio								
Parent	163.75	151.83	127.86	159.78	141.99	14.02(2-SMe) 11.23(6-SMe)	DMSO	47
Purine,2,6-dioxo								
Parent	162.57	160.91	117.12	164.38	151.44		NaOH	40
	162.0	164.0	116.6	160.3	151.2		D_2O	44
Cation	156.4	140.6	108.9	152.3	137.4		D_2O	39
———,1,3,7-triMe	158.5	157.3	110.3	155.0	146.5	30.4(1-Me) 32.5(3-Me) 35.8(7-Me)	D_2O	39
	151.5	148.4	107.5	155.2	141.1	27.9(1-Me) 29.7(3-Me) 33.6(7-Me)	$CDCl_3$	30
	152.37	141.14	108.92	155.93	138.02	30.06(1-Me) 33.53(3-Me) 37.48(7-Me)	HCl	40
Cation	157.5	148.6	109.3	154.7	144.3	29.9(1-Me) 32.0(3-Me) 35.7(7-Me)	D_2O	39
Purine,2-fluoro								
Parent	158.31	158.22	128.79	147.25	147.98		DMSO	47

cont.

TABLE 11. *(cont.)*

	C-2	C-4	C-5	C-6	C-8	Other Resonances	Solv[a]	Ref.
Purine,2-iodo								
Parent	151.80	149.95	120.30	136.50	145.10		DMSO	45
	151.72	150.02	120.18	136.53	145.02		DMSO	47
Purine,6-methoxy								
Parent	151.5	155.15	118.25	159.35	142.75	53.85(O-Me)	DMSO	45
	151.28	155.16	118.12	159.29	142.51	53.66(O-Me)	DMSO	3
	151.30	155.06	118.14	159.06	142.59	53.66(O-Me)	DMSO	47
Purine,1-methyl								
Parent	144.71	142.37	134.95	136.47	166.28	43.56(1-Me)	DMSO	2
———,6-oxo	147.57	153.01	118.26	155.12	140.55	33.10(1-Me)	DMSO	3
———,6-thione	147.64	149.23	128.25	171.69	145.09	39.81(1-Me)	DMSO	3
Purine,3-methyl								
Parent	143.78	155.93	140.89	145.72	162.31	38.43(3-Me)	DMSO	2
Purine,6-methyl								
Parent	151.76	153.87	129.59	155.67	144.51	19.48(6-Me)	DMSO	47
	151.60	153.85	135.10	155.45	144.45	19.4(6-Me)	DMSO	45
Purine,7-methyl								
Parent	152.04	159.88	125.79	140.72	149.78	31.64(7-Me)	DMSO	43
	152.11	159.27	126.14	140.91	150.65	32.16(7-Me)	H_2O/Dio	2
———,6-oxo	144.37	157.02	115.48	154.63	144.37	33.31(7-Me)	DMSO	43
———,6-thione	144.74	152.68	125.87	170.40	148.33	34.66(7-Me)	DMSO	43
Purine,9-methyl								
Parent	151.89	150.93	132.89	147.42	148.77	30.56(9-Me)	H_2O	2
	151.86	151.38	133.46	147.44	147.44	29.35(9-Me)	DMSO	43
Purine,6-methylamino								
Parent	152.42	150.00	118.20	154.72	138.76	27.33(N-Me)	DMSO	47
Purine,6-methylthio								
Parent	151.54	150.10	129.39	158.50	143.21	11.273(S-Me)	DMSO	3
	151.57	150.21	129.40	158.70	143.13	11.30(S-Me)	DMSO	47
	151.6	158.6	129.35	150.2	143.15	11.35(S-Me)	DMSO	45

Purine,6-oxo								
Parent	150.2	155.5	118.0	158.9	144.8		DMSO	45
	144.63	153.19	119.20	155.39	140.20		DMSO	3
	151.7	160.8	125.0	168.0	151.3		D_2O	44
Purine,6-thione								
Parent	149.5	156.9	138.4	172.2	154.3		D_2O	44
	144.79	150.65	128.75	171.05	144.65		DMSO	3
	144.8	150.6	128.8	171.25	144.8		DMSO	45
Purine,6-trimethylamino								
Parent	150.33	151.62	137.74	156.59	147.27	54.27(N-Me)	DMSO	47

[a] DMSO, dimethyl sulfoxide-d_6. pyr, pyridine. EtOH, ethanol. $CDCl_3$, Chloroform-d. D_2O, deuterium oxide. MeOH, methanol-d_4. HCl, hydrochloric acid. NaOH, sodium hydroxide. H_2O, water. H_2O/Dio, water-dioxane mixture.

[b] Extrapolated to infinite dilution.

[c] Mesitylenesulfonate salt.

[d] No other resonances reported.

efficient relaxation mechanism is absent and relaxation times of some tens of seconds can be expected.

2. The very low inherent sensitivity of ^{15}N nuclei compared to ^{1}H (3.85×10^{-6}) which cannot be overcome by rapid pulse repetition rates. Such low sensitivity favors the use of high concentrations and high field spectrometers.

3. The negative magnetogyric ratio, which leads to a negative nuclear Overhauser enhancement, and the nuclear Overhauser effect, which must lie between 3.98 (maximum NOE) and +1 (no NOE). Thus there is a distinct possibility that the NOE may be close to zero and the signal canceled. It is not surprising, therefore, to find relatively few ^{15}N spectra of purines in the literature (Table 12).

This section does not deal in any depth with the various methods of obtaining ^{15}N spectra. However, the following comments may prove useful.

As the relaxation times of ^{15}N nuclei may be very long, use of "relaxation agents" capable of inducing considerably shortened relaxation times without causing line broadening or chemical shift displacement is often employed. The most widely used agents are the tris-acetylacetonate complexes of chromium and iron. Chromium trispivaloylmethane is also useful, but is not as efficient as the acetylacetonate complex.

Concentrations of the order of 0.05*M* are usually sufficient to reduce relaxation times to the order of 5 sec. The use of relaxation agents is likely to introduce chemical shift variations of up to 1.5 ppm, and if these agents are used, this effect must be taken into account. Moreover, since such reagents act as quenches for the nuclear Overhauser enhancement, there is some risk of canceling the ^{15}N resonance altogether.

Another approach is to suppress the nuclear Overhauser effect completely. This may be achieved to some degree by gated-decoupling techniques. Unfortunately, pulse sequences to effect this require long time delays, and complete suppression is not always achieved. The nuclear Overhauser effect may be ignored if fully coupled spectra are acquired, but this may lead to unacceptably low sensitivities and long acquisition times. This procedure, however, does aid in the assignment of resonances.

By far the most satisfactory approach is to use spin-polarization transfer techniques such as DEPT or INEPT[57] or variations of the INEPT sequence.[50,56] Such sequences are routinely available on most modern spectrometers.

One further point should be made concerning ^{15}N spectroscopy. Because of pronounced solvent effects on nitrogen chemical shifts, internal references are not recommended. External references are used exclusively in ^{15}N spectroscopy. It is generally accepted that external neat nitromethane should be used as the primary reference. However, a wide range of ^{15}N-enriched compounds have been used as references, leading to some confusion over chemical shifts. Table 13 reproduced from reference 58, is a useful conversion table. Remember to correct for magnetic anisotropy effects if accurate chemical shifts are required.[58]

The assignment of ^{15}N resonances in purines is relatively straightforward. Ring nitrogens are easily distinguished from substituent amino groups which are highly shielded and invariably occur at about 300 ppm by a substantial downfield

TABLE 12. ^{15}N SPECTRA OF SIMPLE PURINES[a]

	N-1	N-3	N-7	N-9	Other Resonances	Solvent	Ref.
Purine							
Parent	103.1	121.7	169.4	195.0		DMSO	52
	102.8	120.4	171.2	191.7		DMSO	51
	98.9	118.0	201.4	201.4		DMSO	48
	114.1	129.2	186.0	190.1		D_2O	51
	114.6	130.8	188.0	190.8		H_2O	52
	127.7	131.8	154.7	157.0		NaOH	52
	192.7	125.7	186.2	183.9		20% D_2SO_4	52
	194.2	120.2	221.9	216.8		Conc D_2SO_4	52
	182.2	123.4	194.2	205.1		TFA	52
	195.6	117.9	223.6	218.6		HSO_3F	52
Purine,2-amino-9-pentyl							
Parent	233.6	215.2	148.1	217.4		DMSO	49
Purine,6-amino							
Parent	140	145	147	205	296(NH_2)	DMSO	99
——,7-Et	144.8	138.5	222.8	137.6	303.2(NH_2)	DMSO	53
——,9-Et	147.0	156.8	142.2	216.2	301.1(NH_2)	DMSO	53
——,9-Me	140.8	150.2	136	210	[b]	DMSO	99
Purine,6-dimethylamino							
——,9-Me	148.2	160.9	138.4	233.1	[b]	DCE[c]	98
Purine,2,6-dioxo							
——,1,3,7-triMe	232	270	226	157		DCE[c]	50
Purine,7-Methyl							
Parent	114.9	122.8	253.7	149.1		D_2O	52
	112.9	121.1	233.8	147.4		D_2O	51
	102.3	109.4	237.6	137.0		DMSO	52
	189.7	119.3	227.7	149.8		20% D_2SO_4	52
	195.0	120.1	220.1	218.0		Conc D_2SO_4	52
	185.4	118.6	226.0	170.6		TFA	52
Purine,9-methyl							
Parent	113.7	137.1	149.4	248.5		D_2O	51
	117.9	138.9	151.5	230.0		D_2O	52
	103.4	130.0	140.8	239.8		DMSO	52
	193.4	133.2	150.2	221.4		20%D_2SO_4	52
	193.5	122.3	223.5	215.7		Conc D_2SO_4	52
	196.5	125.7	166.8	220.1		TFA	52
	103.9	131.1	140.2	233.1		DCE[c]	98

[a] Shifts are in ppm and negative from external nitromethane.
[b] No other resonances reported.
[c] DCE, 1,2-dichloroethane. All other solvents are as listed in the footnotes of Tables 10 and 11.

shift of over 100 ppm. Of the four ring nitrogens, those in the imidazole ring occur upfield from those in the pyrimidine ring.

For purines unsubstituted in the C-2 and C-6 position assignment may be made simply on ^{15}N-H couplings; N-1 appears as a quartet and N-3 as a doublet.[55] Similarly, assuming C-8 is unsubstituted, one may also assign N-7 and N-9 on coupling constants (N-9 always has a smaller N-H coupling constant than

TABLE 13. REFERENCES FOR NITROGEN CHEMICAL SHIFTS[a]

Reference Solvent	Concentration and Solvent	Conversion Factor
CH_3NO_2	Neat	0.0
	0.3*M* in benzene	−4.4
	0.3*M* in DMSO	+2.0
	0.3*M* in $CHCl_3$	−3.8
HNO_3	1*M* in D_2O	−4.4
	9*M* in H_2O	−14.4
	10*M* in H_2O	−18.2
	15*M* in H_2O	−31.3
NH_3	Liquid	−381.9
$NaNO_3$	1*M* in D_2O	−4.2
	2*M* in 1*M* HNO_3	−1.5
	2*M* in 2*M* HNO_3	−3.1
	7.9*M* in H_2O	−3.7
$NaNO_2$	0.3*M* in H_2O	+227.6
KNO_3	0.3 *M* in H_2O	−3.5
KNO_2	H_2O[b]	+237.1
NH_4NO_3	5*M* in 2*M* HNO_3	−4.6
	5*M* in 2*M* HCl	−5.2
	12.3*M* in H_2O	4.0
NH_4NO_3	In 1*M* HNO_3[b]	−358.6
	5*M* in 2*M* HCl	−358.0
	12.3*M* in H_2O	359.5
	15*M* in 2*M* HCl	−357.4
NH_4Cl	5.6*M* in H_2O	−352.9
	5.6*M* in 1*M* HCl	−353.3
	5*M* in 2*M* HCl	−352.5
	2.9*M* in 1*M* HCl	−351.8
	2*M* in 1*M* HCl	−355.3
$N(Me)_4Cl$	6.03*M* in H_2O	−336.7
	12*M* in H_2O	−336.7
$N(Et)_4Cl$	11*M* in H_2O	−316
	4.6*M* in H_2O	−315.8
$N(Me)_4I$	0.3*M* in H_2O	−337.3

[a] Reproduced from Ref. 58.
[b] Concentration is not given.

N-7).[48,53,54] When one or all carbons are substituted, assignment may be difficult. With either or both C-2 and C-6 substituted, the effects of the substituents must be carefully monitored. The introduction of a substituent at C-6 shields N-1 more than N-3, whereas introduction of a substituent at C-2 generally shields N-3 more than N-1.[54]

Substituent effects at C-8 are difficult to predict because of lack of data. Examination of available data for substituted pyridines and pyrroles suggests that N-9 will be more affected than N-7 by substitution at C-8.

Substitution at nitrogen shields this atom considerably. For instance, for 7-Me purine, N-7 shifts upfield by some 70 ppm, while for 9-Me purine, N-9 shifts upfield by approximately 35 ppm. This is in agreement with the prediction that N-7 is pyridine-like while N-9 is more pyrrole-like in character.

In view of the lack of ^{15}N data, assignments for highly substituted purines should be made with care.

D. Applications of NMR (*New*)

a. Site of Methylation

When purines contain exo oxygens, sulfurs, or nitrogens, the possibility of methylation at sites other than the ring nitrogens exists; NMR is a useful tool for determining the site of methylation. ^1H spectra easily distinguish methylation on sulfur from methylation at other sites. Methylthio resonances occur in a characteristic narrow range of 2.6–2.9 ppm. Distinguishing between *O*- and *N*-methylation is not simple. As a general rule, for methylation on ring nitrogens, *N*-methyl groups occur in the range 3.5–4.0 ppm, while methoxy groups resulting from methylation on exo oxygens occur in the 4.0- to 4.4-ppm range.

In purines this generalization does not hold. *N*-methyl groups in the pyrimidine ring usually occur at lower field than those in the imidazole ring.[13] However, steric hindrance between an N-7 or N-9 methyl group and a substituent at C-8,[13] or steric hindrance between methyl groups at N-3 and N-9,[67] leads to a substantial downfield shift in the methyl resonances. Thus ^1H spectra cannot be used to differentiate unequivocally between *N*- and *O*-methyl groups because of the considerable amount of overlap in the ranges of *N*- and *O*-methyl resonances.

A clear distinction between an *N*- and an *O*-methyl irrespective of steric hindrance effects can be made by ^{13}C spectroscopy. Methoxy groups occur in the range of 55 to 62 ppm, while those for ring *N*-methyl occur between 30 and 50 ppm, and the range for methylthio groups is 12–14 ppm.[59] The small amount of ^{13}C data available suggests that *N*-methyl groups in the pyrimidine ring occur at lower field than those in the imidazole ring.

Kjellberg and Johansson[60] have reported that where C-8 is unsubstituted, both H-8 and C-8 resonances are shifted upfield on substitution at N-9 relative to substitution at N-7, thus affording a method of distinguishing between 7- and 9-isomers. Similar effects have been used to distinguish between *N*-acyl derivatives.[66]

^{15}N spectroscopy has also been reported of use in assigning sites of substitutions in the purine ring.[49,54] Substitution at a nitrogen shields that nitrogen considerably. If substitution occurs at N-9, then N-3 is also shielded by 18–20 ppm, although N-1 resonances do not appear to be affected. Substitution at either C-6 or C-2 also shields N-1 more than N-3, and C-2 substitution affects N-3 more than N-1. Thus care needs to be exercised in assigning methylation at N-1 or N-3.

b. Measurement of pK_a and Protonation Sites (New)

^1H, ^{13}C, and ^{15}N NMR spectroscopy may be used to determine ionization constants and sites of protonation in purines. Protons adjacent to the site where ionization has occurred are deshielded. The deshielding results in downfield shifts which can be large on the proton scale (up to 1 ppm).[91,92] While of minor consideration in purines, it should be noted that protons adjacent to the site of ionization in heterocycles do not necessarily exhibit the largest downfield shift on ionization. Often protons beta to the site may show shifts as large as or larger than those of protons alpha to the site.[92] For virtually all purines, however, this problem will not exist. Assuming that assignment of the proton signals is correct, one should be able to determine in which ring ionization has occurred. It is not possible to distinguish from ^1H NMR individual nitrogen sites of ionization in either the pyrimidine or the imidazole ring. Thus, for 2,6-dioxopurine and its 1-, 7-, and 9-methyl and 1,7-, and 1,9-dimethyl homologs, as well as 6-thioxopurine and its 1-, 7-, and 9-methyl derivatives, a downfield shift of about 1 ppm for H-8 is observed on addition of acid, clearly indicating cation formation is in the imidazole ring.[35] For 3-methyl and 3,7-dimethyl-2,6-dioxopurine, as well as 3-methyl and 3,7-dimethyl-6-thioxopurine, a large downfield shift is observed for H-2, indicating that in these compounds cation formation occurs in the pyrimidine ring.[35]

For ^{13}C spectroscopy the situation is different. Resonances alpha to the site of ionization are shielded, while carbons beta and gamma to the site are deshielded. The upfield shift observed for alpha carbons is 5–15 ppm.[41,93] The different directions of shift for the alpha, beta, and gamma carbon enable sites of ionization to be specified with a great deal of confidence. This specificity is not reflected in ^1H NMR studies. Hence it has been shown that purine itself protonates primarily at N-1,[42] while the anion is formed by removal of a proton from N-7 and N-9 equally.[41] For 1,3,7-trimethyl-2,6-dioxopurine, cation formation is almost exclusively at N-9.[39]

^{13}C-^1H coupling constants are also useful parameters for determining the site of ionization. On ionization all carbon–proton coupling constants increase with those closest to the site of ionization showing the greatest increase. Three bond-coupling constants, on the other hand, show decreases where the carbon involved is adjacent to the site of ionization. Beta carbons show a decrease in three-bond couplings. Such differences can, as with ^{13}C chemical shifts, be used with great effect in elucidating sites of ionization. Schumacher and Gunther showed that cation formation in purine occurs at N-1, with subsequent dication formation occurring almost equally at N-7 and N-9.[68]

^{15}N spectroscopy shows promise as a method for identifying the sites of ionization.[48,55] Large upfield shifts occur on ionization of the nitrogen involved. Thus it can be shown that purine and its 7- and 9-methyl derivatives are protonated in acid almost exclusively at N-1.[55] A theoretical study of ^{15}N spectra of adenine supports this conclusion.[96]

By obtaining a series of spectra at different pH, or pD if D_2O, is the solvent, a titration curve of pH against chemical shift can be constructed and pK_a values

obtained from the inflection point on this curve. The exact position of the inflection point is best determined by using the Henderson–Hasselbach equation rather than by relying on visual estimation

$$\text{pH} = \text{p}K_a + \log \frac{\delta_{max} - \delta}{\delta - \delta_{min}}$$

Some difficulties arise when measuring pK_a by NMR spectroscopy. It is often necessary to use deuterated solvents, particularly for proton NMR, and some ambiguity exists in relation to the measurement of pD. The working rule pD = pH meter reading +0.4 is only valid below ionic strengths of 0.1, a situation which is not often encountered in NMR spectroscopy, particularly with ^{13}C and ^{15}N spectroscopy. One must also remember that when deuterated solvents are used, p$K_a(D_2O)$ rather than p$K_a(H_2O)$ is measured. The two values may differ considerably. Concentration effects must also be taken into account, and it is well known that pK_a values are concentration dependent. Ideally, measurements should be made at several concentrations and the results extrapolated to zero concentration. It is unlikely that pK_a values determined by NMR spectroscopy will be accurate, but this method allows assignment of pK_a values to various groups.

A ^1H NMR study of 2,6-dioxopurine, its methyl analogs, and 6-thioxopurine gave pK_a values within experimental error of those obtained by UV studies.[35] ^{15}N has also been used to obtain pK_a values for purine and its 7- and 9-methyl derivatives. Here the values obtained by NMR spectroscopy were somewhat lower than those reported in the literature.[55] For example, a pK_a value of 2.20 was obtained for purine, which is 0.2–0.3 lower than values reported in the literature. Similarly, results for 7- and 9-methyl purines are lower by up to 0.5 of a pK_a unit. The differences probably result because the measurements are made in a high concentration of D_2O. The technique is useful, but the pK_a values so obtained are only approximate ones.

c. Tautomerism (New)

Nuclear magnetic resonance has been used extensively to investigate tautomerism in purine and its oxo and thioxo derivatives. Chemical shift data, as well as long-range coupling constants, have proved useful in determining the proportion of the various tautomers present.

Pugmire and Grant[3] reported that a study of ^{13}C chemical shifts with corrections for the effect of the methyl group of purine and its 7- and 9-methyl derivatives indicated that only 40% of the purine molecule existed as the N-7(H) tautomer in DMSO.

Two ^{15}N chemical shift studies[52,55] concluded that in aqueous solution the populations of the two possible purine tautomers were approximately equal. One study noted that in DMSO the N-9(H) tautomer was preferred.[55] A more detailed analysis, using long-range ^{13}C-^1H coupling constants, was made by Schumacher

and Gunther.[68] In this study the authors were able to demonstrate that in aqueous solutions the N-7(H):N-9(H) ratio for purine was 48:52, while in DMSO this ratio moved in favor of the N-9(H) tautomer to 30:70. They also showed that protonation at N-1 does not affect the tautomer ratio.

There is, therefore, considerable agreement between the various studies that in aqueous solutions the tautomer populations are approximately equal, while in DMSO solution the N-9(H) tautomer is more favored.

The suggestion by Pullman[69] that the N-7(H):N-9(H) tautomer ratio is the same in DMSO and aqueous solutions is not supported by the available NMR data. The tautomeric ratio is further shifted in favor of the N-9(H) tautomer, at least in DMSO solution, by substitution at the C-6 position of amino, methoxy, or methylthio groups.[3]

Similarly, 1-methyl-, 3-methyl-, and 1,3-dimethyl-2-oxo-6-thioxopurines exist predominantly as the N-7(H) tautomers.[27]

Methylation at N-1, on the other hand, firmly favors the N-7(H) tautomer. Hence 1-methyl-6-oxopurine and 1-methyl-6-thioxopurine reveal ratios of 58:42 and 79:21, respectively, in DMSO solution.[3]

Where an oxo or thioxo substituent exists in the pyrimidine ring, the possibility of a second tautomer pair exists at N-1 and N-3. Several authors have examined oxo and thioxopurines and, while some disagreement exists, all reports are confident in predicting that with one exception the population of the possible N-3(H) tautomer is so low as to be insignificant. For 6-oxopurine the predominant pair of tautomers is N1(H):N-7(H), with the minor pair being N-1(H):N-9(H); the ratio was 58:42.[3] The same authors found a ratio of 79:11 for 6-thioxopurine. This is not in agreement with the results of Lichtenberg[35] who predicted that the N-1(H):N-9(H) tautomer pair predominated in aqueous solution. The reason for the discrepancy is not clear, but may have occurred because the Lichtenberg determination was made by UV spectroscopy and no correction was made for the effect of the methyl group.

Again, methylation at N-1 favors the N-7(H) tautomer. For 1-methyl-, 3-methyl-, and 1,3-dimethyl-2,6-dioxopurine the tautomeric proton is located predominantly, if not exclusively, on N-7.[26] The ratios calculated from ^{13}C chemical shift data were 15:85, 32:68, and 18:82, respectively.

The one exception to the above is 6-methylthio-2-oxopurine, which exists as the N-3(H):N-7(H) tautomer.[10] The rate of tautomerism of the labile proton between N-7 and N-9 has been reported to cause line broadening at C-4 and C-5.[47] For such broadening to occur, the rate of tautomeric exchange must be of the same order as the NMR time scale.

d. Assay of Pharmaceutical Mixtures (New)

Methylated purines, particularly caffeine, are common components of commercially available analgesic preparations; NMR is a useful method for analyz-

ing these mixtures. ^{1}H spectra have been used to distinguish between caffeine and other common analgesics such as phenacetin and aspirin; integration allows a calculation to be made of the relative amounts of the components in the preparation.[61,62,64]

^{13}C spectra may also be used, but in this case a paramagnetic relaxation agent, chromium tris-acetylacetone, must be added.[63] Integration gives the relative amounts of components in the mixture. Accuracy is claimed to be of the order of 5%. A more sophisticated approach has been reported using on-line, continuous flow, high-performance liquid chromatography coupled with ^{1}H NMR to analyze mixtures of caffeine, acetominophen, and aspirin. Solvent peaks were suppressed by use of a 1–1 hard-pulse sequence. As little as 1 mg of a mixture containing 50 μg of caffeine can be analyzed.[65] Although still at an experimental stage, these applications illustrate the versatility and sensitivity of modern NMR spectrometers.

e. *References*

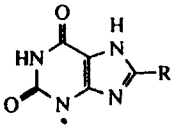
1. L. M. Twanmoh, H. B. Wood, and J. S. Driscoll, *J. Heterocycl. Chem.*, **10**, 187 (1973).
2. R. J. Pugmire, D. M. Grant, L. B. Townsend, and R. K. Robins, *J. Am. Chem. Soc.*, **95**, 2791 (1973).
3. M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.*, **97**, 4636 (1975).
4. D. M. Cheng, L. S. Kan, P. O. P. Ts'o, C. Giessner-Prettre, and B. Pullman, *J. Am. Chem. Soc.*, **102**, 525 (1980).
5. N. J. Kos, H. Jongejan, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas*, **104**, 302 (1985).
6. Z. Nieman, *Isr. J. Chem.*, **6**, 577 (1968).
7. D. Lichtenberg, F. Bergmann, and I. Ringel, *J. Magn. Reson.*, **6**, 600 (1972).
8. Z. Nieman, F. Bergmann, D. Lichtenberg, and J. Deutsch, *J. Chem. Soc.* (*C*), 1822 (1971).
9. U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Nieman, *J. Org. Chem.*, **38**, 2066 (1973).
10. D. Lichtenberg, F. Bergmann, and Z. Nieman, *J. Chem. Soc., Perkin Trans. I*, 2445 (1973).
11. J. H. Keck, R. A. Simpson, and J. L. Wong, *J. Org. Chem.*, **43**, 2587 (1978).
12. F. K. Lam and J. C. Parham, *Heterocycles*, **9**, 287 (1978).
13. G. B. Barlin and M. D. Fenn, *Aust. J. Chem.*, **36**, 633 (1983).
14. R. J. Badger and G. B. Barlin, *J. Chem. Soc., Perkin Trans. II*, 1854 (1974).
15. J. H. Lister, *Aust. J. Chem.*, **32**, 2771 (1979).
16. R. J. Badger and G. B. Barlin, *J. Chem. Soc., Perkin Trans. II*, 1176 (1976).
17. R. J. Badger and G. B. Barlin, *J. Chem. Soc., Perkin Trans. I*, 151 (1976).
18. W. Pfleiderer, *Justus Liebigs Ann. Chem*, 2038 (1974).
19. H. Jackel and H. Stamm, *Z. Naturforsch., Teil B*, **41B**, 1461 (1986).
20. A. Donesi, L. Paolillo, and P. A. Temussi, *J. Phys. Chem.*, **80**, 279 (1976).
21. N. Platzer, H. Galons, Y. Bensaid, M. Miocque, and G. Bran, *Tetrahedron*, **43**, 2101 (1987).
22. F. E. Hruska and S. S. Danyluk, *Biochem. Biophys. Acta*, **161**, 250 (1968).

23. T. Fuji, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, and S. Nakajima, *Heterocycles*, **24**, 2449 (1986).
24. G. Zvilichovsky and J. Feingers, *J. Chem. Soc., Perkin Trans. I*, 1507 (1976).
25. D. Lichtenberg, F. Bergmann, and Z. Nieman, *J. Chem. Soc. (C)*, 1939 (1971).
26. D. Lichtenberg, F. Bergmann, and Z. Nieman, *J. Chem. Soc. (C)*, 1676 (1971).
27. D. Lichtenberg, F. Bergmann, and Z. Nieman, *J. Chem. Soc., Perkin Trans. II*, 1676 (1972).
28. M. W. Hu, P. Sing, and E. F. Ullman, *J. Org. Chem.*, **45**, 1711 (1980).
29. Y. Yanuka and F. Bergmann, *Tetrahedron*, **42**, 5991 (1986).
30. J. Falconnet, J. L. Brazier, and M. Desage, *J. Labelled Compd. Radiopharm.*, **23**, 267 (1985).
31. K. H. Klein, G. Grafe, and R. Haller, *Arch. Pharm. (Weinheim)*, **302**, 16 (1969).
32. Y. Yanuka, J. Zahalka, and M. Donbrow, *J. Chem. Soc., Perkin Trans. II*, 911 (1986).
33. J. H. Lister, *Aust. J. Chem.*, **32**, 387 (1979).
34. F. Bergmann and M. Rahat, *J. Chem. Soc., Perkin Trans. I*, 239 (1976).
35. D. Lichtenberg, F. Bergmann, and Z. Nieman, *Isr. J. Chem.*, **10**, 805 (1972).
36. T. Sorrell, L. A. Epps, T. J. Kistenmacher, and L. G. Marzilli, *J. Am. Chem. Soc.*, **100**, 5756 (1978).
37. B. T. Khan, S. V. Kumari, and G. N. Goud, *J. Coord. Chem.*, **12**, 19 (1982).
38. K. Ienaga and W. Pfleiderer, *Tetrahedron Lett.*, 1447 (1978).
39. C. Nicolau and K. Hildenbrand, *Z. Naturforsch, Teil C*, **29C**, 475 (1974).
40. S-Y. Li and H-C. Chiang, *T'ai-wan K'o Hsueh*, **33**, 69 (1979).
41. R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.*, **93**, 1880 (1971).
42. R. J. Pugmire, D. M. Grant, L. B. Townsend, and R. K. Robins, *J. Am. Chem. Soc.*, **95**, 2791 (1973).
43. M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.*, **97**, 4627 (1975).
44. L. G. Purnell and D. J. Hodgson, *Org. Magn. Reson.*, **10**, 1 (1977).
45. E. Braitmeier and W. Voelter, *Tetrahedron*, **30**, 3941 (1974).
46. See Ref. 3.
47. M. C. Thorpe, W. C. Coburn, and J. A. Montgomery, *J. Magn. Reson.*, **15**, 98 (1974).
48. V. Markowski, G. P. Sullivan, and J. D. Roberts, *J. Am. Chem. Soc.*, **99**, 714 (1973).
49. G. Remaud, J. Kjellberg, N. G. Johansson, and J. Chattopadhyaya, *Tetrahedron*, **43**, 365 (1987).
50. G. Glenmarec, G. Remaud, and J. Chattopadhyaya, *Magn. Reson. Chem.*, **26**, 307 (1988).
51. N. C. Gonnella and J. D. Roberts, *J. Am. Chem. Soc.*, **104**, 3162 (1982).
52. M. Schumacher and H. Gunther, *Chem. Ber.*, **116**, 2001 (1983).
53. G. Remaud, J. Kjellberg, H. Bazin, N. G. Johansson, and J. Chattopadhyaya, *Tetrahedron*, **42**, 5073 (1986).
54. G. E. Hawkes, E. W. Randall, and W. E. Hull, *J. Chem. Soc., Perkin Trans. II*, 1268 (1977).
55. See Ref. 51.
56. S. Wimperis and G. Bodenhausen, *J. Magn. Reson.*, **69**, 264 (1986).
57. G. A. Morris and R. Freeman, *J. Am. Chem. Soc.*, **101**, 760 (1979).
58. M. D. Fenn in *Physical Methods in Heterocyclic Chemistry*, R. R. Gupja, Ed., Wiley-Interscience, New York, 1984.
59. G. B. Barlin, D. J. Brown, and M. D. Fenn, *Aust. J. Chem.*, **37**, 2391 (1984).
60. J. Kjellberg and N. G. Johansson, *Tetrahedron*, **42**, 6541 (1986).
61. K. Rehse, *Dtsch Apoth. Ztg.*, **107**, 1530 (1967).

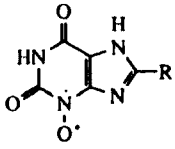
62. K. Rehse, *Arch. Pharm. (Weinheim)*, **303**, 617 (1970).
63. H.-C. Chiang and M. Imanari, *J. Taiwan Pharm. Assoc.*, **32**, 83 (1980).
64. T. J. Mason, J. P. Lorimer, and J. C. Bickerton, *Educ. Chem.*, 178 (1987).
65. D. A. Laude and C. L. Wilkins, *Anal. Chem.*, **59**, 546 (1987).
66. J. M. Ohrt, T. Srikrishan, R. Parthasarathy, S. P. Dutta, and G. B. Chheda, *J. Am. Chem. Soc.*, **100**, 5232 (1978).
67. F. Bergman, I. Tamir, A. Frank, and W. Pfleiderer, *J. Chem. Soc., Perkin Trans. II*, 35 (1979).
68. M. Schumacher and H. Gunther, *J. Am. Chem. Soc.*, **104**, 4167 (1982).
69. F. R. Prado, C. Giessner-Prettre, and B. Pullman, *Org. Magn. Reson.*, **16**, 103 (1981).
70. J. P. Bloxsidge, J. A. Elvidge, M. Gower, J. R. Jones, E. A. Evans, J. P. Kitcher, and D. C. Warrell, *J. Labelled Comp. Radiopharm.*, **18**, 1141 (1981).
71. F. R. Hruska, C. L. Bell, T. A. Victor, and S. S. Danyluk, *Biochemistry*, **7**, 3721 (1968).
72. P. Hemmes, L. Oppenheimer, R. Rhinesmith, G. Anderie, D. Saar, and F. Jordan, *J. Phys. Chem.*, **84**, 911 (1980).
73. H. Stamm and F. Timeus, *Helv. Chim. Acta*, **67**, 2161 (1984).
74. I. Hormann and B. Dreux, *Helv. Chim. Acta*, **67**, 754 (1984).
75. Y. Yanuka, J. Zahalka, and M. Donbrow, *J. Chem. Soc., Perkin Trans. II*, 911 (1986).
76. H. Stamm, *Arch. Pharm. (Weinheim)*, **302**, 174 (1969).
77. J.-L. Dimicoli and C. Helene, *J. Am. Chem. Soc.*, **95**, 1036 (1973).
78. V. L. Antopovskii, A. S. Gukovskaya, G. V. Nekrasova, B. I. Sukhorukov, and I. I. Chervin, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1040 (1973).
79. V. L. Antopovskii, A. S. Gukovskaya, G. V. Nekrasova, B. I. Sukhorukov, and I. I. Chervin, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2307 (1973).
80. A. Pastori and P. A. Temussi, *Adv. Mol. Relax. Proc.* **22**, 109 (1982).
81. Y. Nosaka, A. Akasaka, and H. Hatano, *J. Phys. Chem.*, **82**, 2829 (1978).
82. S. Andini, L. Ferrara, P. A. Temussi, F. Leij, and T. Tancredi, *J. Phys. Chem.*, **83**, 1776 (1979).
83. S. Leij, L. Ferrara, S. Sandini, and P. A. Temussi, *J. Phys. Chem.*, **83**, 2902 (1979).
84. H. Stamm and J. Stafe, *Z. Naturforsch., Teil B*, **36B**, 1618 (1981).
85. T. Ishida, M. Shibata, K. Fujii, and M. Inoue, *Biochemistry*, **22**, 3571 (1983).
86. F. Aradi and A. Foldesi, *Magn. Reson. Chem.*, **23**, 375 (1985).
87. H. Fritzsche, I. Petri, H. Schutz, K. Weller, P. Sedmera, and H. Lang, *Biophys. Chem.*, **11**, 109 (1980).
88. H. Fritzsche, H. Lang, H. Sprinz, and W. Pohle, *Biophys. Chem.*, **11**, 121 (1980).
89. L.-S. Kan, P. N. Borer, D. M. Cheng, and P. O. Ts'o, *Biopolymers*, **19**, 1647 (1980).
90. K. Weller, H. Schutz, and I. Petri, *Biophys. Chem.*, **19**, 289 (1984).
91. J. H. Bradbury and M. D. Fenn, *Aust. J. Chem.*, **22**, 357 (1969).
92. G. B. Barlin and M. D. Fenn, *Aust. J. Chem.*, **32**, 2297 (1979).
93. G. B. Barlin and M. D. Fenn, *Aust. J. Chem.*, **34**, 1341 (1981).
94. I. Tamir, *J. Magn. Reson.*, **23**, 293 (1976).
95. C. Rossi and N. Niccolai, *Chem. Phys. Lett.*, **142**, 418 (1987).
96. M. Schindler, *J. Am. Chem. Soc.*, **110**, 6623 (1988).
97. T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, and T. Fujisawa *Chem Pharm. Bull.*, **39**, 301 (1991).
98. S. Toppet, J. De Taeye, and Th. Zeegers-Huyskens, *J. Phys. Chem.*, **92**, 6819 (1988).
99. Th. Zeegers-Huyskens, *Bull. Soc. Chim. Belg.*, **97**, 23 (1988).
100. R. M. Osterman, B. A. McKittrick, and T-M Chan, *Tetrahedron Lett.*, **33**, 4867 (1992).

4. ELECTRON SPIN RESONANCE SPECTRA (*H*516)

Only limited applications of this procedure are available, requiring purines capable of radical formation. Suitable candidates are the *N*-oxide derivatives which, on exposure to ionizing radiation in the solid state, afford relatively stable radicals. The product from UV irradiation of powdered 3-hydroxyxanthine gives the same ESR spectrum as is obtained from the same purine following γ- or X-ray treatment. Virtually the same spectrum is observed when either the 1- or 7-methyl-3-hydroxyxanthines are examined in this way, but some spectral variation noted with 8-methyl-3-hydroxyxanthine is attributed to interaction between the unpaired electron and the protons of the 8-methyl group.[1696] An amidyl structure (**1**) was originally suggested as the source of the spectrum, but later workers using a crystal rather than a powder claim that the nitroxyl radical (**2**) is more likely present.[1708] Radicals similarly generated from 1- and 7-hydroxyxanthines give spectra resembling that of the 3-hydroxy isomer.[1696]



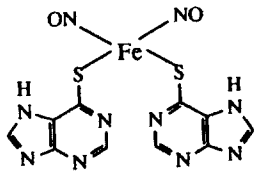
1



2

The transient purple color obtained by irradiation of solid 3-hydroxyxanthine and *N*-methylated derivatives is an indication that radical species are present. Similarly colored powders are reportedly formed from adenine, adenosine, and caffeine following exposure to gamma radiation. ESR is used to determine the dose response curves.[1981]

Spectral investigations of this type are used to study purine–metal complexes which possess unpaired electrons. Representative examples are the dinitrosyliron adducts formed by 2-, 6-, and 8-thioxopurines in which two purine anions are bonded to the dinitrosyliron through the sulfur, forming a derivative such as **3**.[1974] Radical forms of adenine derivatives produced by interaction with iron carbonyl have the resulting radicals stabilized as nitroxyl compounds by the addition of *tert*-butyl nitrite prior to the ESR examination.[1980]



3

5. MASS SPECTRA (*H*518)

The journals devoted to organic mass spectrometry should be consulted for details of specific purines. In this section, only selected points of interest or relevance are briefly noted.

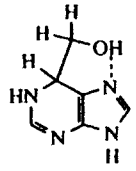
A. Techniques and Applications

Use of crown ethers which have the property of forming adducts with purines and other nitrogen heterocycles through hydrogen bonding between the ether oxygen and the ring nitrogen is a recent innovation. With both adenine and caffeine, abundance peaks corresponding to a [purine–ether–hydrogen] + complex ion are obtained.[1811] Stabilization of the imidazole ring, usually the focus of the initial degradation of the ring system, is achieved by the use of 9-trimethylsilylated derivatives. This results in the formation of a significantly different fragmentation pattern from that of the parent purine.[1813] Two techniques currently under examination with adenines are the two-step laser MS, which gives only a molecular ion peak, and the tandem MS, based on collision-induced dissociations. Both are noted in Section 5.A.b.

Diagnostic applications of ionization spectra applied to nucleoside derivatives enable the site of benzylation to be determined by differentiating between location of the group at a purine nitrogen or an oxygen of the ribosyl group.[1812] Further confirmation of the mechanistic pathway followed in the Dimroth rearrangement is obtained from MS studies.[1469] Use of a series of isotopically labeled adenines now provides the definitive degradation pattern for adenine[1562] and corrects some earlier mechanisms advanced.

a. Purine and C-Alkyl Derivatives (H520)

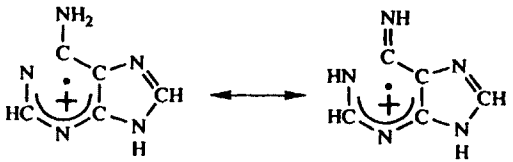
The addition products from photolysis of purine with alcohols, for example, the methanol adduct (**4**), show characteristic mass spectra resulting from an initial fission of the alcohol–purine bond, followed by a typical fragmentation of the purinyl radical ion in which sequential loss of hydrogen cyanide units occurs, as in the breakdown of purine itself.[1052]



4

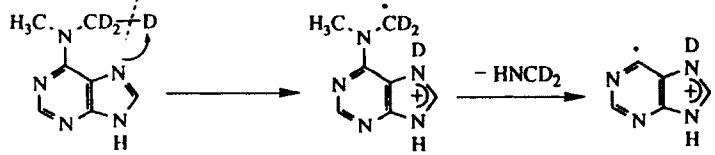
b. Adenines and 6-Alkylaminopurines (H520)

A comprehensive spectral study of adenines isotopically labeled at various atoms including ^{13}C-2, ^{14}C-8, ^{2}H-2, ^{2}H-8, and derivatives labeled with ^{15}N at the 1-, 3-, 7-, and 9-positions as well as the 6-amino group was carried out.[1562] Earlier investigators employing less extensively labeled subjects concluded that primary release of a hydrogen cyanide unit arose from C-6 and the amino group.[1563,1564] The later work shows that the main source of the hydrogen cyanide (90%) is at N-1 and C-2; the residue (8%) arises from C-2 and N-3. Fission of the pyrimidine ring between the 1- and 6-positions is most likely, leaving the amino group intact and giving intermediate ions of the type (**5**) which fragment into uncyclized rather than cyclic ions.[1562] The molecular ions from adenine and from the adenosine fragment ion (M+ = 135) give the same dissociation spectrum, indicating that identical decomposition pathways are followed. Other adenosine derivatives are assumed to behave likewise.[1562] A much simpler spectrum, consisting virtually of only the molecular ion peak (M+ = 135), is produced using two-pulse laser MS.[1897] A different technique is used to produce the spectrum of protonated adenine with tandem MS (30 eV) by means of collision-induced dissociations using ^{15}N and ^{2}H labeled material. None of the three major decomposition pathways obtained by this method have been observed in the usual electron ionization mass spectra, but a fourth minor fragmentation pattern is common to both methods, showing successive elimination of three HCN molecules. Included in the collision studies are the 1-, 2-, 3-, and 7-methyl homologs as well as the isomeric 6-methylaminopurine. Fission of the protonated pyrimidine ring at either the N-1 to C-6 or N-1 to C-2 bonds occurs initially.[1898] Spectral investigation of the Dimroth conversion of 1-methyladenosine to the 6-methylaminopurine-9-β-D-riboside provides further confirmation of the mechanistic pathway followed[1469] (Chapter VIII, Section 5.G.b), but attempts to use mass spectra to determine sites of *N*-alkylation in adenine gave only inconclusive results.[1474] With 7-methyladenine, a resonance-stabilized (M-1)+ ion is formed through interaction between the 6-amino and N-methyl group.[1400] More widely studied are corresponding derivatives of 7-methyl-6-thioxo- and 7-methyl-6-selenoxopurines, as noted in Section 5.A.f. The 7-ethyl- and 7-isopropyladenine homologs react differently on fragmentation, with the alkyl group being eliminated and an accompanying transfer of a proton to the base, forming adeninyl ions.[1527] Alkyl groups located at other ring nitrogens can undergo the same fate.[1527] The relationship between the nitrogen at the 7-position and a nearby methyl group is demonstrated in the elimination of a



5

methyleneimine fragment from 6-dimethylaminopurines. Using the unsymmetrically deuterated dimethylamino derivative (**6**), loss of equal amounts of NHC^2H_2 and N^2HCH_2 is observed following removal of a proton from the alkylamino group and protonation of N-7[1814] (**7**). During the ensuing fragmentation, the purinyl radical ion (**8**) should be involved. An example of the latter is formation of the same radical ion (**8**) in the spectrum of 6-(2-hydroxyethylamino)purine.[1473] Introduction at N-9 of a deuterated trimethylsilyl group in 6-dimethylaminopurines alters the major degradation pathway and causes one of the methyl groups to be removed, thereby stabilizing the imidazole moiety, which appears to remain intact and does not generate a hydrogen cyanide unit as might be expected.[1813] The susceptibility of other methyl groups to fission has also been studied and both *N*- and *C*-methylpurines remain largely unchanged. An exception occurs with 3-methyladenine which undergoes significant abstraction (34%) of the methyl moiety.[1813] Following monobenzylation of adenosine, a mass spectral method is reported which enables location of the benzyl group on either the purine or the riboside moiety to be ascertained.[1812]



6 **7** **8**

c. The Oxopurines (H521)

The original results for hypoxanthine, xanthine, and uric acid reported by Rice and Dudeck (*H*512) are confirmed by work which now extends to the spectra of four mono-, six di-, and four tri-*N*-methyluric acids[891] as well as 1,3,7,9-tetramethyluric acid.[891,1776] A diagnostic application of mass spectroscopy for the identification of sites of benzylation of inosine on either the base or the sugar moiety is described.[1812]

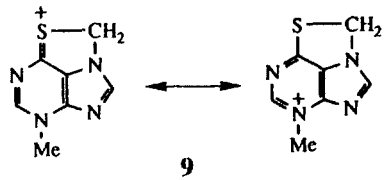
d. Guanine and N-Alkyl Derivatives (H521)

As noted with other purines, the fragmentation spectra of *N*-methylated guanine and the *O*-methyl isomer[1815] are different from those of guanines possessing higher *N*-alkyl groups. This is exemplified by the breakdown patterns for the molecular ions of 7-ethyl- and 7-isopropylguanine which show that, as with similar adenine derivatives, the *N*-alkyl fragment is split off and concomitant donation of a proton from this to the base giving the radical ion [guanine]+· occurs. Subsequent decomposition, by following the established pathway, demonstrates that the site of *N*-alkylation in guanines produces no significant effect on the over-

all fragmentation pattern.[1527] A common feature of 7-methylguanine and the isomeric *O*-methyl derivative[1815] is a relatively high abundance of the (M – 1)+ ion for which the formation of methylene bridges between the atom or group at C-6 and the N-7 position is advanced to explain these findings. Proton abstraction from the *N*- or *O*-methyl group would be a prerequisite for cyclizations of this type to take place.[1527] A method for determining the site of monobenzylation of purine nucleosides has been formulated.[1812]

f. Thioxo- and Selenoxopurines (H522)

The spectra of 6-methylthiopurines have been reported.[1816] A relatively high abundance of the (M – 1)+ ion found with the 7-methyl derivative of 6-mercaptopurine is attributed to the presence of stabilized forms containing a thiazoline ring.[872] Ion stability is enhanced by further methylation at N-3, as indicated by a doubling of the abundances. Resonance hybrids such as (**9**) would contribute toward this increase. Corresponding data are given by the 6-selenoxopurine analogs,[1400] but contrasting behavior is shown by 9-ribosyl derivatives of 6-selenoxopurines which undergo immediate expulsion of the selenoxo moiety[1817] as hydrogen selenide. Detection of the latter is used to identify a selenoxopurine. The abundance values of the nucleoside molecular ions fall between those for the corresponding oxygen and sulfur derivatives.[1817]



9

g. Other Purines

Beerbaum and his group produced spectra of mono-, di-, and trihalogenated derivatives including 6-chloro-[1818], 2,6-dichloro-,[1818] 2,6-dibromo-,[1818] and 2,6,8-trichloropurines[1819] as well as 6-amino-8-bromopurine[1820] and 2,8-dichlorohypoxanthine,[1818] 8-bromoxanthine,[1820] and 8-bromoguanine[1820] and others.[1818]

6. MAGNETIC CIRCULAR DICHROISM (*NEW*)

Interest in the application of this technique to purines, although first described over 20 years ago,[1979] has until fairly recently been largely neglected. Although of somewhat limited application, it is a useful tool for theoretical studies at the submolecular level of derivatives such as purines which possess cyclic π-electron

structures. When used in conjuction with absorption spectra in the 200- to 300-nm range, resolution of the individual bands of two overlapping ones is possible and assignment of π to π^* and n to π^* transitions can be made.[1675,1978] Investigations of molecular structures with purine and the 1-, 3-, 7-, and 9-methyl homologs show that on protonation of either 1- or 3-methylpurines the spectrum undergoes a red shift, but conversely those of the 7- and 9-methyl isomers suffer a blue shift.[1979] While an overall similarity exists between the spectral curves of all four methylated purines, a considerable variation exists in band intensity and position of each isomer compared with those of the parent purine, thereby allowing correlations between spectra and methylation sites to be formulated.[1979] Results of studies with adenine[1675] and the 1-methyl homolog,[1676] and more recently a range of oxopurines including hypoxanthine, xanthine, and their 3-methyl and 3,9-dimethyl derivatives,[1694] have been documented and in the case of the oxopurines indicate that in aqueous solution the 9(H) tautomers predominate.[1694] Sufficient divergencies exists between the MCD spectra of purines and pyrimidines to allow identification of the particular heterocycle present.[1675]

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

CHAPTER XV

Systematic Tables of Simple Purines

INTRODUCTION

Time and space preclude the inclusion of all compounds present in a survey of the literature up to the middle of 1993. A selective approach has been adopted to allow the inclusion of representative examples of most types of purine derivatives—many new ones together with some already known which may have resulted from alternative syntheses. Reference to a particular derivative does not always imply that preparative details are given, but where these are absent, other references or data contained in the paper should enable such information to be readily located.

ARRANGEMENT OF THE TABLES AND CONTENTS

In the parent volume, some 40 tables of derivatives were included. However, owing to the compound subdivisions employed, it was difficult to locate derivatives, especially those containing multifunctional groups. To overcome this problem, the number of tables has been greatly reduced: broader classifications have been used; and some prominent compounds have been assigned to individual tables (e.g., *C*- and *N*-alkylated adenines, hypoxanthines, and xanthines) with separate tables for related amino and oxopurines. To conform to the parent volume, fully substitutive nomenclature is used, except for compounds for which the accepted trivial names are adopted. The term alkyl in these compounds is employed in the wider sense and includes groups which also contain amino, halogeno, hydroxy, or other substituents. Also included with *N*-alkylated derivatives are *N*-oxides and *N*-hydroxides in the appropriate sections. Compounds excluded from the tables are as noted originally (*H*529–530), with the exception of the reduced purines, which now merit inclusion in view of increasing interest in them.

The revised table heading and classifications are as follows:

Alkyl contains both *C*- and *N*-alkyl and arylpurines, including cycloalkyl analogs.

Adenine covers only simple *C*- and *N*-alkylated derivatives.

Amino collects all aminopurines, other than adenines, as well as related hydrazino and hydroxyaminopurines. Also listed are *N*-aminopurines and acylated and aroylated derivatives of *C*- and *N*-amino forms.

Carboxy comprises a heterogeneous collection of compounds arranged alphabetically having carboxy, alkoxycarbonyl, carbamoyl, and related amide-type groups linked to the purine base through alkyl, amino, or thio units. To simplify the nomenclature, derivatives of adenine, guanine, hypoxanthine, and xanthine are listed under these trivial names.

Halogeno includes only *C*- and *N*-alkylated forms.

Hypoxanthine, Xanthine, Other Oxo are three separate tables which, in addition to the *C*- and *N*-alkylpurines, also contain *C*- and *N*-alkoxy derivatives and *N*-oxo and *N*-hydroxy analogs.

Thioxo also embraces alkylthio and seleno analogs and the corresponding oxidized forms such as sulfo- and alkylsulfonylpurines.

Amino-Oxo lists both *C*-amino- and *N*-amino- oxo derivatives as well as amino-alkoxypurines.

Amino-Thioxo contains amino-alkylthio analogs and corresponding hydroxyamino- and hydrazino-thioxopurines and various *S*-oxidized derivatives.

Oxo-Thioxo includes compounds possessing groups similar to those in the preceding two tables.

Reduced is a new heading and is made up of purines reduced in the pyrimidine or imidazole rings, or in both, including fully reduced perhydro forms. Only reduced positions are termed "hydro" and to obviate confusion with nomenclature of tautomeric purines, the reduction products of guanine, hypoxanthine, and xanthipe are classified under their trivial names.

Miscellaneous consists of purines listed alphabetically which cannot be accommodated in any of the other classifications. The majority of the purines in this general group contain two or more different functional groups.

Note: The inclusion of other data (e.g., NMR or mass spectral) with melting points, has not been adopted in view of the widespread documentation of these details in the majority of current publications. NMR results are, however, fully covered in the tables that accompany the essay by Dr. David Fenn on this topic, and relevant points of interest on mass spectra are also found in Chapter XIV.

ABBREVIATIONS

The standard abbreviations used in the original work are followed in the melting point column. The introduction of triflate salts derived from nitrilium trifluoromethane sulfonate is denoted by "trif" and "mesit" indicates a mesitylene sulfonate derivative. Use of a "greater than" (>) symbol with low or moderate temperatures reflects decomposition occurring above this point.

TABLE 14. ALKYL AND ARYL PURINES

Substituents	mp(°C)	Ref.
Unsubstituted	218	1012
9-Acetyl-6-ethyl	84–85	1059
6-Benzyl	165–166	1059
9-Benzyl	96–98	862,1092
9-Benzyl-6-phenyl	118–123	1061
9-Benzyl-6-(pyrid-2-yl)	134–137	1119
9-Benzyl-6-(pyrid-3-yl)	145–147	1119
9-Benzyl-6-(pyrid-4-yl)	138–144	1119
6,8-Bis-*tert*-butyl	194–195	1050
6-*n*-Butyl	—	1072
6-(α-Cyanobenzyl)-9-phenyl	226–228	1067,1079
1,6-Dimethyl	239–241	844
6,7-Dimethyl	228–230	1089
6,9-Dimethyl	—	1073
7,9-Dimethyl	perch. 158	1144
6,9-Dimethyl-1-oxido	125	1073
7,8-Dimethyl-6-phenyl	HCl 234–235	991
9-(1-Ethoxyethyl)	55–56	1832
6-Ethyl	240–243	1059
9-Ethyl	51–53	1092,1094
9-Ethyl-6-(1,2-dihydroxypropyl)	98–100	1071
9-Ethyl-6-(2-hydroxypropyl)	81–83	1071
9-Ethyl-6-phenyl	60–61	1066
9-Ethyl-6-prop-1-enyl	51–53	1071
6-Formyl-1-oxido	165	1057,1080
6-*n*-Hexyl	—	1072
6-(α-Hydroxybenzyl)	194	1093
6-(2-Hydroxyprop-2-yl)	177–178	1093
8-(2-Hydroxyprop-2-yl)	194–196	1093
1-Methyl	235	887
6-Methyl	234–236	1059
7-Methyl	181–183	1087,1090
9-Methyl	160–162	1087,1090
6-Methyl-3-oxido	240	1057
8-Methyl-7-phenyl	171–172	942
8-Methyl-9-phenyl	134–135	942
9-Methyl-6-phenyl	110–112	1119
9-Methyl-8-phenyl	167–168	875
6-(4-Methylbut-3-enyl)	—	1072
6-(4-Methylpent-3-enyl)	—	1072,1097
3-Oxido	288–290	1057
1-Oxido-6-styryl	212–214	1057
6-*n*-Pentyl	—	1072
6-Phenyl	—	1072
7-Phenyl-8-(2-phenylethenyl)	178–179	942
9-Phenyl-8-(2-phenylethenyl)	134–135	942
6-(2-Phenylethenyl)	133–134	1059,1072
6-Styryl	246–249	1059,1081
2,6,8,9-Tetramethyl	56–58	860

cont.

TABLE 14. *(cont.)*

Substituents	mp(°C)	Ref.
2,6,8-Trimethyl	—	860
2,6,9-Trimethyl	75–76	860
7-Vinyl	137–138	1215
9-Vinyl	113	1215

TABLE 15. *C*- AND *N*-ALKYL AND ARYL ADENINES

Substituents	mp(°C)	Ref.
Unsubstituted	—	1122, 1307, 1464
6-Acetamido-9-acetonyl	200–201	1237
9-Acetonyl	247–248	1237
3-Allyl	206–208	1688
3-(3-Aminopropyl)	2HCl	2001
3-Benzyl	276	1464, 1688
7-Benzyl	236–238	1909
9-Benzyl	230–236	983, 1293, 1295, 1359, 1464, 1522; 1688, 1716
7-Benzyl-2-*n*-butyl	185	849
1-Benzyl-9-cyclopentyl	256–257	976
9-Benzyl-3-ethyl	$HClO_4$ 256–257	975
3-Benzyl-9-ethyl	$HClO_4$ 226–227	975
3-Benzyl-9-methyl	$HClO_4$>300	975
9-Benzyl-1-methyl	iod. 260–261	1470
	perch. 229–230	1471
9-Benzyl-3-methyl	$HClO_4$ 248–249	975
9-Benzyl-1-oxido	280–281	1716
1-Benzyloxy	HBr 215	1716
9-Benzyloxy	165–166	990
1-Benzyloxy-9-benzyl	pic. 211–212	1716
1-Benzyloxy-9-cyclopentyl	HBr 177–182	976
9-Benzyloxy-8-methyl	174–175	990
3-But-2-enyl	216–220	1688
9-But-3-enyl	169–171	1688
2-*n*-Butyl	> 200	849
8-*n*-Butyl	255	849
8-*tert*-Butyl	> 300	842
1-Butyl-9-ethyl	iod. 252–253	1472
9-[(*E*)-4-Chlorobut-2-enyl]	246	1540
9-(2-Chloroethyl)	199–202	1349
9-(3-Chloropropyl)	> 300	1349
7-(2-Cyanoethyl)	> 300	1436
9-(2-Cyanoethyl)	255–258	1436
9-Cyclohexyl	197–200	971
9-Cyclopentyl	—	976
9-Cyclopentyl-1-methyl	$HClO_4$ 292–293	1470
9-Cyclopentyl-1-oxido	292	976

3,9-Dibenzyl	$HClO_4$ 206–207	975
9-(2,2-Diethoxyethyl)	—	1201
1,9-Diethyl	HI 282–283	1466
	perch. 291–292	1472
3,9-Diethyl	$HClO_4$ > 300	975
9-(1,4-Dihydroxybutyl)	—	865
9-(2,4-Dihydroxybutyl)	226–228	1258
9-(1,3-Dihydroxypropyl)	—	865
3-(2,3-Dihydroxypropyl)	> 300	1535
9-(2,3-Dihydroxypropyl)	207–209	1688, 1535
(*R*)-9-(2,3-Dihydroxypropyl)	252–254	1689
(*S*)-9-(2,3-Dihydroxypropyl)	210–211	1689
(*R,S*)-9-(2,3-Dihydroxypropyl)	200	1689
(*S*)-9-(3,4-Dihydroxybutyl)	226–227	1733
1,8-Dimethyl	> 300	844
1,9-Dimethyl	$HClO_4$ 303–304	978, 1721
2,8-Dimethyl	—	1074
2,9-Dimethyl	237–238	946
3,9-Dimethyl	$HClO_4$ 333–334	974
	HCl 281–282	975
7,8-Dimethyl	338–340	991
7,9-Dimethyl	perch. 276–277	1460
8,9-Dimethyl-2-phenyl	245–246	946
9-(1,1-Dimethylprop-2-enyl)	185	811
2,8-Diphenyl	290–291	946
9-(2,3-Epoxypropyl)	205	1201
1-Ethoxy	HI 208	1716
1-Ethoxy-9-ethyl	$HClO_4$ 272–273	1716
1-Ethoxy-9-methyl	$HClO_4$ 272	1721
9-(1-Ethoxyethyl)	154–155	1984
1-Ethyl	> 260	1370
3-Ethyl	229–232	941, 1292, 1370
9-Ethyl	195–196	983, 1094, 1292, 1522, 1716
9-Ethyl-1-(2-hydroxyethyl)	brom. 247–248	1472
9-Ethyl-7-(2-hydroxyethyl)	brom. 230–231	1472
9-Ethyl-1-(3-hydroxypropyl)	brom. 255–256	1472
1-Ethyl-9-methyl	HI 291–292	1721
3-Ethyl-9-methyl	HCl 251–252	975
8-Ethyl-1-methyl	> 300	844
9-Ethyl-1-methyl	iod. 293–294	1470
9-Ethyl-3-methyl	$HClO_4$ 294–295	974, 975
9-Ethyl-1-propyl	iod. 263–264	1472
9-Hydroxy	—	990
9-Hydroxy-8-methyl	—	990
9-(4-Hydroxy-2-oxobutyl)	211–213	1258
erythro-9-(2-Hydroxybut-3-yl)	169–173	1212
threo-9-(2-Hydroxybut-3-yl)	205–209	1212
9-(4-Hydroxybutyl)	200–201	1266, 1470
9-(4-Hydroxybutyl)-1-methyl	168–169	1470
(*E*)-9-(4-Hydroxybut-2-enyl)	200	1538, 1540
(*Z*)-9-(4-Hydroxybut-2-enyl)	230	1538
9-(4-Hydroxybut-2-ynyl)	230	1538
8-(Hydroxydiphenylmethyl)	270–271	1093

cont.

TABLE 15. *(cont.)*

Substituents	mp(°C)	Ref.
3-(2-Hydroxyethyl)	—	1264
9-(2-Hydroxyethyl)	238–239	1201, 1264, 1266
8-Hydroxymethyl	298–300	842
8-Hydroxymethyl-1-methyl	> 300	844
(*R*)-9-(1-Hydroxyprop-2-yl)	215–219	1999
(*S*)-9-(1-Hydroxyprop-2-yl)	216–219	1999
3-(2-Hydroxyprop-2-yl)	268–272	1528
8-(2-Hydroxyprop-2-yl)	244–251	1093, 1252, 1256
9-(3-Hydroxypropyl)	215–216	1266, 1733
8-Isopropyl	240–262	842, 844
1-Methoxy	HI 222	1716
1-Methoxy-9-methyl	$HClO_4$ 257–258	1716
1-Methyl	pic 257–258	998
2-Methyl	—	946, 993, 1074
3-Methyl	> 300	977, 1292
7-Methyl	—	1460
8-Methyl	—	1074
9-Methyl	302–307	1140, 1293, 1522, 1716, 1880
8-Methyl-2-phenyl	> 280	946
9-Methyl-2-phenyl	239–240	946
9-Methyl-8-phenyl	224–226	946
9-Octyl	126–127	1239, 1688
3-Oxido	350	1142
9-(3-Oxoprop-1-enyl)	258–260	1533
9-(2-Phenylethyl)	178–179	1522
1-Propyl	229	1475
9-Propyl	173–174	1239
1-Propyl-9-methyl	HI 266–268	1721
8-Styryl	350–352	790
9-[(*R*)2, (*S*) 3,5-Trihydroxypentyl]	—	2016
9-[(*S*)2, (*R*) 3,5-Trihydroxypentyl]	—	1259
9-Vinyl	196–200	1158, 1201

TABLE 16. OTHER AMINOPURINES INCLUDING *N*-AMINOPURINES

Substituents	mp(°C)	Ref.
6-Acetamido	> 260	1436
6-Acetamido-9-methoxymethyl	163–164	2007
9-Acetyl-6-methylamino	219–221	1383
9-Allyl-6-allylamino	138–142	1688
9-Allyl-6-but-3-enylamino	119	1688
9-Allyl-6-diallylamino	108–110	1688
6-Allylamino-9-(but-3-enyl)	137	1688
1-Amino	mesit. 170–172	1051
6-Amino-8-azido	tos. 197–198	1186
6-Amino-8-azido-1-benzyl	> 140	842
6-Amino-8-azido-1-methyl	> 200	842

2-Amino-6,8-bis(2-hydroxyprop-2-yl)	245–246	1252
2-Amino-6-*n*-butylamino-9-ethyl	2HCl 225	1187
6-Amino-1,6-dihydro-6-imino-9-methyl	275–276	1009
6-Amino-2-dimethylamino	295–296	946
2-Amino-6-dimethylamino-3,7-dimethyl	chlor.-	1098
6-Amino-2-dimethylamino-8,9-dimethyl	273–274	946
6-Amino-2-dimethylamino-8-methyl	271–273	946
6-Amino-2-dimethylamino-9-methyl	224–225	946
6-Amino-8-dimethylamino-2-methyl	> 300	912
6-Amino-8-dimethylamino-2-phenyl	291–293	912
2-Amino-6-diphenylmethylamino	244–246	864
2-Amino-9-ethyl	124–125	1187
6-Amino-2-hydroxyamino	270	1124
2-Amino-6-(2-hydroxyprop-2-yl)	205	1252
1-Amino-2-methyl	mesit. 182–183	1051
1-Amino-6-methyl	mesit. 202–203	1051
1-Amino-9-methyl	mesit. 202–205	1051
2-Amino-9-methyl	244–246	1880
8-Amino-9-methyl	---	875
8-Amino-6-methyl-2-methylamino	---	904
1-Amino-9-methyl-8-phenyl	mesit. 179–180	1051
6-Amino-9-methyl-8-phenyl	250–251	946
6-Amino-8-methylamino	HCl > 290	2002
1-Amino-8-phenyl	mesit. 179–180	1051
2-Amino-6-phenyl	257–259	867
2-Amino-6-(2-phenylethylamino)-	129–131	1305
2-Amino-6-trimethylammonio	chlor. 207–208	1122
6-Benzamido-9-(1,1-dimethylprop-2-enyl)	158–160	811
6-Benzamido-9-methyl	189–190	1445
9-Benzyl-6-benzylamino	172–173	1466, 1522
9-Benzyl-6-benzylamino-1-oxido	145–146	1466
9-Benzyl-6-benzylimino-1-benzyloxy-1,6-dihydro	$HClO_4$ 202–203	1466
9-Benzyl-6-benzyloxyamino	197–200, HCl 211	981
9-Benzyl-6,8-bisdimethylamino	110–111	2004
9-Benzyl-6-dimethylamino	126–128	862, 1307
9-Benzyl-6-dimethylamino-8-methyl	96–100	2004
9-Benzyl-6-dimethylamino-8-methylamino	134–136	2004
9-Benzyl-6-hydroxyamino	218–219	983
9-Benzyl-6-(2-hydroxyethylamino)	118–120	862
3-Benzyl-6-isopropylamino	108–110	1894
7-Benzyl-6-isopropylamino	160–162	1894
9-Benzyl-6-isopropylamino	86–88	1894
9-Benzyl-6-iodo	152–154	1119
3-Benzyl-6-methylamino	256–258	1894
9-Benzyl-6-methylamino	135–137	842, 1470, 1894
9-Benzyl-6-(*N*-methyl)ethylamino	56–57	862
9-Benzyl-6-(*N*-methyl)formamido	162–164	862
9-Benzyl-6-(2-methylhydrazino)	119–120	1879
9-Benzyl-6-phenylamino	187–189	862
7-Benzyl-6-pivaloylamino	153	1437
9-Benzyl-6-pivaloylamino	146	1437
6-Benzylamino	226–228	1302, 1307, 1464
6-Benzylamino-9-cyclopentyl	102–103	976

cont.

TABLE 16. *(cont.)*

Substituents	mp(°C)	Ref.
6-Benzylamino-9-ethyl	141–142	1464, 1876
6-Benzylamino-9-(2-hydroxyethyl)	—	1266
6-Benzylamino-9-(3-hydroxypropyl)	—	1266
6-Benzylamino-9-methyl	127–128 or 136–137	1876, 1445, 1471
6-(*N*-Benzyl)methylamino	223	1302
6-Benzyloxyamino	87–90	979
6-Benzyloxyamino-9-cyclopentyl	169–171	976
1-Benzyloxy-1,6-dihydro-6-imino-9-methyl	$HClO_4$ 195–196	980
6-Benzyloxyamino-9-ethyl	154–155	1722
6-Benzyloxyamino-9-methyl	232–234	980
2,6-Bisdimethylamino	248–250	1307
2,6-Bisdimethylamino-3,7-dimethyl	chlor.–	1098
2,6-Bishydroxyamino	260	1124
2,6-Bis(1-methylhydrazino)	298	1172
2,6-Bis(*N*-methylhydroxyamino)	270	1124
6-Butylamino-9-ethyl	perch. 128–129	1472
6-(*N*-Butyl)methylamino-2,8-dimethyl	125–127	852
6-Cyclohexylamino	209–210	1302
9-Cyclopentyl-6-methylamino	104–105	1470
2,6-Diacetamido	293–295	1435
1,6-Diamino-	chlor. 252	1409
	mesit. 243–244	
2,6-Diamino	—	1122, 1124
2,8-Diamino	296	903
	HCl > 300	906
2,6-Diamino-9-ethyl	225–226	1187
2,8-Diamino-6-hydroxymethyl	—	903, 904
2,6-Diamino-9-methyl	314–316	946
2,8-Diamino-6-methyl	H_2SO_4 > 270	903, 904
	HCl > 300	906
6,8-Diamino-1-methyl	> 140	844
2,6-Diamino-3-oxido	197	1166
2,6-Diamino-8-phenyl	tos. 330	1006
2,8-Diamino-1,6,7,9-tetramethyl	diiod. 306	903
2,8-Diamino-1,7,9-trimethyl	diiod. > 200	903
6-Dibenzoylamino-9-methyl	182–184	1445
6-(2,2-Diethoxyethylamino)	188–189	824
6-Diethylamino-2,8-dimethyl	154–156	852
6-Diethylamino-7,9-dimethyl	iod. 169–170	1536
6-Diethylamino-9-vinyl	81–82	1163
2,6-Dihydrazino	—	1514
6-Diisopropylamino-2,8-dimethyl	178–180	852
1,6-Dihydro-6-dimethylimino-1,7-dimethyl	iod. 248	1164
1,6-Dihydro-6-dimethylimino-1,9-dimethyl	iod. 334	1164
1,6-Dihydro-6-imino-1-methoxy-9-methyl	HI 211–213	1717
1,6-Dihydro-6-imino-7-methyl-1-phenyl	278–279	998
1,6-Dihydro-1-methoxy-9-methyl-6-methylimino	128	978
	HI 155–157	1466
	perch. 230–231	1717
1,6-Dihydro-6-methoxyimino-1,9-dimethyl	182–183	978

3,6-Dihydro-6-methoxyimino-3,9-dimethyl	266–267	974
3,7-Dimethyl-2,6-bismethylamino	chlor.–	1098
1,9-Dimethyl-6-methylamino	iod. 249–251	1532
3,7-Dimethyl-6-methylamino	iod. 256–257	1532
3,9-Dimethyl-6-methylamino	iod. 261–262	1532
7,9-Dimethyl-6-methylamino	iod. 198–200	1532
2,8-Dimethyl-6-(*N*-methyl)phenylamino	238–240	852
2,9-Dimethyl-6-(*N*-methyl)phenylamino	110–112	1020
2-Dimethylamino	219–222	1150
6-Dimethylamino	251–257	1234, 1302
8-Dimethylamino	292	1150
2-Dimethylamino-6,8-dimethyl	238–240	1188
2-Dimethylamino-6,9-dimethyl	106	860
6-Dimethylamino-1,9-dimethyl	iod. 178	1536
6-Dimethylamino-2,8-dimethyl	274–276	852
6-Dimethylamino-3,7-dimethyl	iod. 195–197	1536
6-Dimethylamino-3,9-dimethyl	iod. 335–345	1536
6-Dimethylamino-7,9-dimethyl	iod. 167–170	1536
6-Dimethylamino-3,7-dimethyl-2-methylamino	chlor.–	1098
6-Dimethylamino-9-(1-ethoxyethyl)	77–78	2003
2-Dimethylamino-6-ethyl	218–219	1188
2-Dimethylamino-6-ethyl-8,9-dimethyl	94–95	1188
2-Dimethylamino-8-ethyl-6,9-dimethyl	104–105	1188
2-Dimethylamino-9-ethyl-6,8-dimethyl	64–66	1188
2-Dimethylamino-6-ethyl-8-methyl	199–201	1188
2-Dimethylamino-6-ethyl-9-methyl	68–69	1188
2-Dimethylamino-8-ethyl-6-methyl	160–161	1188
2-Dimethylamino-9-ethyl-6-methyl	69–71	1188
6-Dimethylamino-9-[(2-hydroxyethoxy)methyl]	107–108	1100
2-Dimethylamino-9-methyl	89–90	1140, 1150
6-Dimethylamino-9-methyl	113–119	862, 1147, 1150
8-Dimethylamino-9-methyl	91	1150
6-Dimethylamino-3-oxido	276	1142
6-Dimethylamino-9-phenyl	161–163	862
6-Dimethylamino-9-phenylethyl	70–72	862
2-Dimethylamino-6,8,9-trimethyl	127	860
6-Dimethylamino-9-vinyl	146-147	1163
6-(*N*,*N*-Dimethylaminomethyleneamino)	252–255	1430
1-Ethoxy-1,6-dihydro-6-imino-9-ethyl	HI 185–186	1717
1-Ethoxy-9-ethyl-6-ethylimino	$HClO_4$ 172–173	1466
1-Ethoxy-6-imino-9-ethyl	HI 185–186	1717
6-Ethoxy-3-oxido	240	1142
6-Ethoxyamino-9-benzyl	227–228	1722
6-Ethoxyamino-9-ethyl	189–190	981
6-Ethoxyamino-9-methyl	212–214	981
6-(2-Ethoxyethylamino)	178–179	1152
6-Ethoxyimino-9-ethyl-3,6-dihydro-3-methyl	245–248	974
9-Ethyl-2,6-dihydrazino	190	1514
6-Ethyl-8,9-dimethyl-2-methylamino	128–129	1188
9-Ethyl-6-ethylamino	106–107	1466
6-(*N*-Ethyl)phenylamino-2,8-dimethyl	212–214	852
9-Ethyl-6-propylamino	100–101	1472
6-Ethyl-9-methyl-2-methylamino	144–145	1188

cont.

TABLE 16. *(cont.)*

Substituents	mp(°C)	Ref.
6-Ethyl-9-methyl-2-(*N*-methyl)formamido	140	1188
9-Ethyl-6-methylamino	142–143	1470
6-Ethylamino-9-methyl	156–157	1721
6-Formamido	250	971
6-Formamido-9-(2,3-dihydroxypropyl)	178	971
9-Formylmethyl-6-methylamino	HCl 180	1382
6-Formylmethylamino	HCl 283–285	824
6-Furylamino	265	1302, 1432
6-Furylamino-9-phenyl	128–129	1079
6-Hydrazino	240	1390
2-Hydrazino-9-methyl	184–185	1140
6-Hydrazino-9-methyl	211–212	1140
8-Hydrazino-9-methyl	281	1514
6-Hydrazino-9-phenyl	201–202	1079
6-Hydrazino-9-vinyl	165–167	1163
6-Hydrazonomethyl	—	1080
6-Hydrazonomethyl-1-oxido	250	1080
2-Hydroxyamino	260	1124
2-Hydroxyamino-6-methoxyamino	240	1124
6-Hydroxyamino-3-oxido	—	1142
9-(4-Hydroxybutyl)-6-methylamino	109–110	1470
6-(2-Hydroxyethylamino)	254–255	1151, 1152
6-(3-Hydroxypropylamino)	223–224	1151, 1152
6-[*N*-(3-Hydroxypropyl)methylamino]	178	1141
6-Hydroxyiminomethyl-3-oxido	155	1080
6-Isopropylamino-3-methyl	HCl 239–241	1894
6-Methoxyamino	190	979
6-Methoxyamino-7,9-dimethyl	iod. 250–251	1460
6-Methoxyamino-9-methyl	239, HCl 226	981
6-(*N*-Methoxy)methylamino-9-methyl	HI 170–172	1460
9-Methyl-6-methylamino	183–186	978, 1138, 1460, 1532, 1721
9-Methyl-6-methylamino-1-oxido	243–244	978
3-Methyl-6-(3-methylbut-2-enylamino)	175–176	1609
2-Methyl-6-(*N*-methyl)phenylamino	179–180	1020
9-Methyl-6-phenylamino	156–159	875
(*R*)-6-(1-Methyl-2-phenylethylamino)	190–193	1153
7-Methyl-6-pivaloylamino	190	1437
9-Methyl-6-pivaloylamino	197–198	1437
9-Methyl-2-propylamino	226	1140
9-Methyl-6-propylamino	128–130	1140, 1721
9-Methyl-2-trimethylammonio	chlor. 179–180	1150
9-Methyl-6-trimethylamonio	chlor. 161–165	1122, 1150
6-Methylamino	—	1172
6-Methylamino-3-oxido	240	1142
2-Methylamino-6-(*N*-nitroso)methylamino	265	1172
2-(1-Methylhydrazino)	236	1172
6-(1-Methylhydrazino)-3-oxido	> 240	1172
8-(1-Methylhydrazino)	266	1172
6-(*N*-Methyl)hydroxyamino-3-oxido	195	1142

6-(*N*-Nitroso)isopent-2-enylamino	> 220	1227
2-(*N*-Nitroso)methylamino	> 300	1172
6-(*N*-Nitroso)methylamino	252	1172
8-(*N*-Nitroso)methylamino	232	1172
6-(*N*-Nitroso)methylamino-3-oxido	214	1172
3-Oxido-6-trimethylammonio	bet. 202	1142
9-Phenyl-6-phenylamino	171–172	1079
6-Phenylamino-2-methyl	307–308	1020
6-(2-Phenylethylamino)	241–244	1305
6-(2-Propoxyethylamino)	176–177	1152
6-*n*-Propylamino	245–246	1512
6-Trimethylammonio	191–193	1122
	chlor. 187–189	1150
8-Trimethylammonio	chlor. 179–180	1150

TABLE 17. CARBOXY, ALKOXYCARBONYL,CARBAMOYL, AND RELATED PURINES

Substituents	mp(°C)	Ref.
Adenine/7-benzyloxycarbonyl	149–150	868
Adenine/9-benzyloxycarbonyl	163–164	868
Adenine/9(bisethoxycarbonyl)methyl	164	1733
Adenine/9-(*N*-*n*-butyl)carbamoyl	230–232	837
Adenine/9-(*N*-*n*-butyl)thiocarbamoyl	> 350	837
Adenine/9-(1-carboxyethyl)	272–278	1529
Adenine/3-(2-carboxyethyl)	273–275	1436
Adenine/7-(2-carboxyethyl)	> 300	1436
Adenine/9-(2-carboxyethyl)	265	1529, 1733
Adenine/3-carboxymethyl	314	1328
Adenine/9-carboxymethyl	275	1238, 1529
Adenine/3-(3-carboxypropyl)	285–287	2001
	HBr 250–256	
Adenine/9-ethoxycarbonyl	158–160	868, 1736
Adenine/2-ethoxycarbonylamino	> 300	864
Adenine/9-(4-ethoxycarbonylbutyl)	110–111	1470
Adenine/3-(2-ethoxycarbonylethyl)	182–183	1733
Adenine/9-(2-ethoxycarbonylethyl)	182–183	1733
Adenine/9-ethoxycarbonylmethyl	—	1857
Adenine/3-(3-ethoxycarbonylpropyl)	HBr 213–215	2001
Adenine/7-(2-methoxycarbonylethyl)	> 300	1436
Adenine/9-(2-methoxycarbonylethyl)	184–185	1436
Adenine/9-(*N*-methyl)carbamoyl	> 345	837
Adenine/9-(*N*-methyl)thiocarbamoyl	345	837
Adenine/9-(*N*-phenyl)carbamoyl	> 350	837
Adenine/9-(2-sulfoethyl)	> 350	1349
Adenine/1-(3-sulfopropyl)	NH_4–	1474
Adenine/3-(3-sulfopropyl)	NH_4–	1474
Adenine/9-(3-sulfopropyl)	—	1349, 1474
2-Amino-9-benzyl-1,6-dihydro-8-methoxycarbonylamino-6-oxo	321–322	1106
2-Amino-6-benzyloxy-7-carbamoylmethyl	227–228	1856

cont.

TABLE 17. *(cont.)*

Substituents	mp(°C)	Ref.
2-Amino-6-benzyloxy-9-carbamoylmethyl	243–244	1856
2-Amino-6-benzyloxy-7-ethoxycarbonylmethyl	175–177	1856
2-Amino-6-benzyloxy-9-ethoxycarbonylmethyl	163–164	1856
2-Amino-8-carboxy-1,6-dihydro-9-methyl-6-oxo	—	879
2-Benzyl-6-carbamoyl	252–253	1838
2-Benzylthio-8-methoxycarbonylamino	232–233	1858
6-Carbamoyl	310–315	1736, 1839
6-Carbamoyl-8,9-dimethyl-2-phenyl	277	1837
6-Carbamoyl-8,9-dimethyl-2-*n*-propyl	199–201	1837
6-Carbamoyl-8,9-dimethyl-2-trifluoromethyl	270–272	1837
6-Carbamoyl-2-methyl	250	1838
6-Carbamoyl-2-[(*E*)-prop-1-enyl]	> 250	1838
6-Carbamoyl-2,8,9-trimethyl	270–273	1837
2-(Carbamoylmeth-2-ylthio)-6,8,9-trimethyl	228–229	848
6-Carbamoylmethylthio	> 241	1741*
2-Carbamoylmethylthio-6,8-dimethyl	264–267	848
2-Carbamoylmethylthio-6,9-dimethyl	163–164	1188
2-Carbamoylmethylthio-6,9-dimethyl-7,8-dihydro-8-oxo	276–277	878
6-Carbamoylmethylthio-9-methyl	213–214	1741
2-Carbamoylmethlthio-6,8,9,-trimethyl	212–213	848
6-Carboxy	200	1080, 1081
6-Carboxy-3-oxido	285–287	1057
9-Carboxymethyl	.....	1114
9-Carboxymethyl-6-chloro	205	1114
2-Carboxymethylamino	> 200	1114
2-Carboxymethylamino-6-chloro	190	1114
2-Carboxymethylamino-1,6-dihydro-6-thioxo	> 300	1114
2-Carboxymethylamino-6-hydroxyamino	175	1114
2-Carboxymethylamino-6-methyl	> 280	1114
2-Carboxymethylamino-6-methylthio	> 300	1114
8-Carboxymethylthio	247–248	1741
2-Carboxymethylthio-6,9-dimethyl	227	2018
8-Carboxymethylthio-9-methyl	255–256	1741
6-Carboxymethylthio-3-oxido	255	1114
2-Carboxymethylthio-6,8,9-trimethyl	252–255	841
2-Chloro-6-ethoxycarbonyl	235	1839
6-Cyano	183–185	1839
2,3-Dihydro-8-methoxycarbonylamino-2-thioxo	> 300	1858
2-Dimethylamino-6-ethoxycarbonyl	213–214	1839
6-Dimethylamino-9-ethoxycarbonyl	96–97	985
6-Dimethylamino-2-ethoxycarbonylamino	> 300	864
2-(*N*,*N*-Dimethylcarbamoylmethylthio)-6,8,9-trimethyl	194	848
2-Ethoxy-6-ethoxycarbonyl	160–161	1839
6-Ethoxycarbonyl	224–225	1839
9-Ethoxycarbonyl-6-ethoxycarbonylamino	—	1736
9-Ethoxycarbonyl-6-methylamino	150–151	837
9-Ethoxycarbonyl-6-methylthio	220–222	1839
6-Ethoxycarbonylamino	310–315	868, 1736

2-Ethoxycarbonylamino-6-diphenylamino	224–226	864
6-(2-Ethoxycarbonyleth-1-yl)	88–89	1068
6-Ethoxycarbonylmethyl-9-methoxymethyl	63–64	2007
Guanine/9-benzyl-8-methoxycarbonylamino	231–232	1106
Guanine/8-methoxycarbonylamino-2-phenylthio	246–247	1858
Guanine/7-(3-sulfopropyl)	> 300	1539
Hypoxanthine/7-benzyl-1-ethoxycarbonylmethyl	148–149	1286
Hypoxanthine/9-carboxymethyl	> 300	1238
Hypoxanthine/9-ethoxycarbonylmethyl	—	1857
2-Isopropylthio-8-methoxycarbonylamino	247–252	1858
8-Methoxycarbonylamino-2-methylthio	—	1858
8-Methoxycarbonylamino-2-*n*-propylthio	253–256	1858
8-Methoxycarbonylamino-2-(prop-1-ynylthio)	228–229	1858
8-Methoxycarbonylamino-2-sulfonyl	234–236	1858
9-(*N*-Methylcarbamoyl)-6-(3-methylureido)	306–310	837
6-(*N*-Methylcarbamoylmethylthio)	233–234	1741
2-(*N*-Methylcarbamoylmethylthio)-6,8,9-trimethyl	197–198	948
9(*N*-Phenylcarbamoyl)-6-(3-phenylureido)	350–352	837
Xanthine/8-aminomethyl-7-ethoxycarbonylmethyl-1,3-dimethyl		2206
Xanthine/7-(carboxyethyl)-1,3-dimethyl	210	1529
Xanthine/7-carboxymethyl-1,3-dimethyl	—	2025
Xanthine/1,3-dimethyl-7-methylsulfinylmethyl	185–186	1343
Xanthine/8-methoxycarbonyl-1,3,7-trimethyl	—	1135

* Denotes an incorrect structural assigment was given in the literature to the compound.

TABLE 18. HALOGENOPURINES

Purine	mp(°C)	Ref.
7-Allyl-6-chloro	143–146	1688
9-Acetyl-6-chloro	128–132 (lit. 140–142)	2006
9-Allyl-6-chloro	163–167	1688
7-Benzyl-6-chloro	148–149	1119
9-Benzyl-6-chloro	93–95	1119
9-Benzyl-6-chloro-2-trifluoromethyl	98–99	967
9-Benzyl-6-phenyl-2-trifluoromethyl	121–123	967
6,8-Bis-*tert*-butyl-2-chloro	179–180	867
8-*tert*-Butyl-6-chloro	234–237	842
6-Bromo-9-ethyl	93–95	1094
6-Bromomethyl-1-oxido	161	1080
6-Bromomethyl-3-oxido	165	1080
6-Chloro-9-(2-chloroethyl)	—	1138
6-Chloro-8-chloromethyl	226	844
6-Chloro-9-(3-chloropropyl)	—	1138
6-Chloro-9-(cyclohex-3-en-1-yl)	168–169	1935
6-Chloro-7-(2,3-dihydroxypropyl)	166	1688
6-Chloro-9-(2,3-dihydroxypropyl)	102	1688
6-Chloro-8-ethyl	166	844

cont.

TABLE 18. *(cont.)*

Purine	mp(°C)	Ref.
6-Chloro-9-ethyl	78–80	1094
2-Chloro-6-fluoro	146	1122
2-Chloro-6-fluoro-7-methyl	153–154	1122
erythro-6-Chloro-9-(2-hydroxybut-3-yl)	138–142	1212
(*R*)-(+)-6-Chloro-9-(1-hydroxyprop-2-yl)	202–203	1999
(*S*)-(−)-6-Chloro-9-(1-hydroxyprop-2-yl)	199–202	1999
6-Chloro-8-(2-hydroxyprop-2-yl)	201–203	1093
2-Chloro-6-iodo-7-methylpurine	215–216	1120
6-Chloro-8-isopropyl	158–160	842, 844
6-Chloro-8-methyl	212	844
8-Chloro-3-methyl	140–145	836
6-Chloro-7-methyl-8-phenyl	197–199	1061
6-Chloro-9-methyl-8-phenyl	157–160	1061
6-Chloro-3-oxido	160	1142
2-Chloro-6-phenyl	273–274	867
2-Chloro-8-phenyl	285	857
6-Chloro-2-trifluoromethyl	202–203	2008
2-Chloro-6,8,9-trimethyl	171–172	848
6-Chloro-8-*tert*-butyl	236–237	842
6-Chloro-9-vinyl	166–167	1201
2,6-Dichloro-7-methyl	193–195	1110
2,6-Dichloro-9-methyl	154–155	1110
7-Ethyl-6-iodo	160–162	1066
9-Ethyl-6-iodo	141–145	1066, 1094
2-Fluoro	—	1124
6-Fluoro-7-methyl	135–137	1122
6-Fluoro-9-methyl	125–131	1122, 1140
2-Iodo	233–236	867
6-(2-Fluoroethoxy)	199	1868
7-Methyl-6-trichloromethyl	—	1084
9-Methyl-6-trichloromethyl	146–148	1083
2,6,8-Trichloro-7-methyl	158–160	1110
8-Trifluoromethyl	190	840
9-Methyl-8-trifluoromethyl	88	840

TABLE 19. *C*- AND *N*-ALKYL HYPOXANTHINES

Substituents	mp(°C)	Ref.
Unsubstituted	143–146	1122, 1150
9-Acetonyl	282–284	1237
1-Acetonyl-9-ethyl	102–104	1071
1-Allenyl-9-benzyl	161	1221
1-Allyl-9-benzyl	114–116	1221
1-(2-Aminoethyl)	224–226	1133
1-(2-Azidoethyl)	138–140	1133
1-Benzyl	268–269	1017
3-Benzyl	281–282	869

7-Benzyl	277–279	1283, 1285
9-Benzyl	294–298	862, 869, 1007
1-Benzyl-3,8-dimethyl	HBr 240	873
3-Benzyl-1,8-dimethyl	HI 221	873
1-Benzyl-2-methyl	263–264	956
1-Benzyl-8-methyl	—	873
1-Benzyl-2-methyl-7-phenyl	222–223	956
3-Benzyl-8-phenyl	> 290	872
9-Benzyl-1-propargyl	142	1221
9-Benzyloxy	223–223	957
1-Benzyloxy-9-cyclopentyl	198	1718
9-Benzyloxy-8-methyl	256	958
1-Butyl	220	835
9-Butyl	—	1102
1-(2-Chloroethyl)	> 300	1133
9-(2-Chloroethyl)	262	1201
1-Cyclohexenyl	255	835
1-Cyclohexyl	288	835
3-Cyclohexyl	304–306	869
9-Cyclohexyl	264–268	869
1-Cyclopentyl	233	835
7-Cyclopentyl	188	835
9-Cyclopentyl-1-hydroxy	229–230	1718
1,3-Dibenzyl	bet. 212–214	1284
1,9-Dibenzyl	210–211	1003
3,9-Dibenzyl	—	1996
1,3-Diethyl-8-phenyl	bet. 282–283	1284
9-(1,3-Dihydroxypropyl)	—	865
(*S*)-9-(2,3-Dihydroxypropyl)	244–246	1689
9-(1,4-Dihydroxybutyl)	—	865
1,8-Dimethyl	HBr > 300	873
2,3-Dimethyl	—	1312
2,8-Dimethyl	—	1074
2,9-Dimethyl	> 300	1102
3,8-Dimethyl	—	1312
3,9-Dimethyl	—	1996
7,8-Dimethyl	> 290	991
7,9-Dimethyl	iod. 257	873, 1226
	chlor. 249–250	1287
8,9-Dimethyl	> 300	1880
1,2-Dimethyl-7-phenyl	185–186	956
1,3-Dimethyl-8-phenyl	bet. 303–305	1284
	iod. > 300	1226
1,7-Dimethyl-8-phenyl	162–163	872
1,9-Dimethyl-8-phenyl	170	872
3,9-Dimethyl-8-phenyl	238–240	872
2,7-Diphenyl	339–342	2033
2,8-Diphenyl	> 360	913, 927, 937
1,7-Diphenyl-2-methyl	186–187	956
1-Ethyl	276–278	1229
9-Ethyl	264–266	1102, 1472
9-Ethyl-1-(2-hydroxyethyl)	169–170	1472
1-Ethyl-2-methyl-7-phenyl	180–181	956

cont.

TABLE 19. *(cont.)*

Substituents	mp(°C)	Ref.
9-Ethyl-3-methyl	—	1996
1-Hydroxy	340–345	1057
3-Hydroxy	—	944
9-Hydroxy	—	957
1-Hydroxy-7-methyl	> 290	1250
9-Hydroxy-8-methyl	—	958
9-[(2-Hydroxyethoxy)methyl]	217–219	1100
9-(2-Hydroxyethyl)	287–290	869
8-Hydroxymethyl	>300	842
8-(2-Hydroxyprop-2-yl)	—	1252
1-Methoxy-7-methyl	190–191	1250
2-Methoxy-1-methyl	250–257	1282
1-Methyl	> 300	1017, 1271
2-Methyl	—	1074, 1312
3-Methyl	> 300	1001
7-Methyl	—	1283
8-Methyl	—	1074
9-Methyl	—	1102, 1150
2-Methyl-1-(1-methylpropyl)-7-phenyl	177–178	956
2-Methyl-1-(2-methylpropyl)-7-phenyl	149–151	956
1-Methyl-2,7-diphenyl	229–232	956
9-Methyl-2,8-diphenyl	240	913
1-Methyl-8-phenyl	> 300	872, 1226
2-Methyl-7-phenyl	315–317	956, 2033
9-Methyl-8-phenyl	252–254	872
2-Methyl-7-phenyl-1-propyl	135–137	956
3-Oxido	—	1142
7-Phenyl	—	1877
9-Phenyl	> 300	1079, 1102
7-Phenyl-2-(pyrid-4-yl)	> 350	2033
9-Propyl	255–260	1102, 1239
1,7,8,9-Tetramethyl	HI 262	873
2-Trifluoromethyl	331–332	2008
1,3,8-Trimethyl	bet. 242	873
1,7,9-Trimethyl	iod. 206–214	1287, 1289, 1309, 1363
2,8,9-Trimethyl	> 300	1102
2,7,8-Trimethyl-1-phenyl	192–193	956
1,2,7-Triphenyl	264–265	956
9-Vinyl	288–292	1158, 1244

TABLE 20. *C*- AND *N*-ALKYL XANTHINES

Substituents	mp(°C)	Ref.
1-Acetoxy	—	1713
3-Acetoxy	—	1713
7-Acetoxy	155	920
1-Acetoxy-7-acetyl	—	1713

1-Acetoxy-9-acetyl	—	1713
3-Acetoxy-7-acetyl	—	1713
3-Acetoxy-1-benzyl	170	1713
3-Acetoxy-1-methyl	—	1713
3-Acetoxy-7-methyl	—	1713
3-Acetoxy-8-methyl	—	1235
7-(2-Acetoxyethyl)-1,3-dimethyl	105	832
3-(2-Acetoxyethyl)-1-methyl	197–198	830
1-Allyl-3,7-dimethyl	139–142	1291
7-(2-Aminoethyl)-8-benzyl-1,3-dimethyl	251–253	938
8-(2-Aminoethyl)-7-benzyl-1,3-dimethyl	HCl 227–229	916
7-(2-Aminoethyl)-1,3-dimethyl	144–145	938
7-(2-Aminoethyl)-8-ethyl-1,3-dimethyl	106–107	938
8-(2-Aminoethyl)-7-ethyl-1,3-dimethyl	207–209	843
	HCl 254–255	916
8-(2-Aminoethyl)-1,3,7-trimethyl	HCl 308–310	916
7-(2-Aminoethyl)-1,3,8-trimethyl	140–142	938
8-Aminomethyl-7-benzyl-1,3-dimethyl	—	2026
8-Aminomethyl-1,3,7-trimethyl	—	2026
7-(3-Aminopropyl)-8-benzyl-1,3-dimethyl	295–297	1298
7-(3-Aminopropyl)-1,3,8-trimethyl	245–247	1298
7-Allyl-1,3-dimethyl	101–103	1291
7-Benzyl	297–299	1283
8-Benzyl-7-(2-cyanoethyl)-1,3-dimethyl	176–177	1298
7-Benzyl-8-cyanomethyl-1,3-dimethyl	171–173	916
8-Benzyl-7-cyanomethyl-1,3-dimethyl	141–142	938
1-Benzyl-3,7-dimethyl	—	1295
3-Benzyl-1,7-dimethyl	163–164	833
7-Benzyl-1,3-dimethyl	120–121	847, 901, 1295, 1477
8-Benzyl-1,3-dimethyl	298–299	819, 847, 901, 918
9-Benzyl-1,8-dimethyl	337	913
8-Benzyl-1,3-diphenyl	290	917
1-Benzyl-3-hydroxy	—	838
7-Benzyl-3-isobutyl-1-methyl	109–111	831
1-Benzyl-8-methoxy	—	1116
3-Benzyl-7-methyl	232–234	833
3-Benzyl-9-methyl	—	969
7-Benzyl-1-methyl	272–274	889
7-Benzyl-3-methyl	272–275	889, 1477
8-Benzyl-1-methyl	> 350	913
9-Benzyl-1-methyl	268–270	889
9-Benzyl-1-methyl	325	913
9-Benzyl-1-methyl-8-phenyl	356	913
9-Benzyl-1-methyl-8-propyl	293	913
9-Benzyloxy	—	957
9-Benzyloxy-8-methyl	—	958
9-Butyl-1-methyl	257	913
8-Chloromethyl-1,3-dimethyl	237–239	843
8-Chloromethyl-7-ethyl-1,3-dimethyl	185–187	843
8-(3-Chloropropyl)	204	1299
7-(3-Chloropropyl)-1,3-dimethyl	120–121	1298

cont.

TABLE 20. *(cont.)*

Substituents	mp(°C)	Ref.
8-Crotyl-1,3-dimethyl	232–234	847
7-(2-Cyanoethyl)-1,3-dimethyl	155–157	1298
7-(2-Cyanoethyl)-1,3,8-trimethyl	201–203	1298
7-Cyanomethyl-8-ethyl-1,3-dimethyl	175–177	938
7-Cyanomethyl-1,3,8-trimethyl	236–238	938
8-Cyanomethyl-7-ethyl-1,3-dimethyl	196–197	916
8-Cyanomethyl-1,3-dimethyl	274–276	916
8-Cyanomethyl-1,3,7-trimethyl	232–234	916
8-Cyclohexyl-1,3-dipropyl	159–160	845
8-Cyclohexyl-1-methyl-3-*n*-propyl	189–191	1887
8-Cyclopentyl-1,3-diethyl	181–182	2009
8-Cyclopentyl-3-propyl	311–313	2009
8-Cyclopentyl-1,3-dipropyl	199–200	845
1,3-Diallyl	158	832
3,7-Diallyl	183–184	1291
7,9-Dibenzyl	>300	847
7,8-Dibenzyl-1,3-dimethyl	120–121	847
	132–133	901
3,7-Diethyl	179–182	1292
3,9-Diethyl	—	969
1,3-Diethyl-8-hydroxymethyl	228–230	843
1,3-Diethyl-7-methyl	129–131	843
3,7-Diethyl-1-methyl	96	1292
3,7-Diethyl-1-methyl-8-phenyl	150	913
1,3-Dimethyl (theophyline)	—	898, 899
1,7-Dimethyl	295–298	833
1,9-Dimethyl	352	913
3,7-Dimethyl (theobromine)	—	1296
3,9-Dimethyl	—	969
7,8-Dimethyl	370	991
1,3-Dimethyl-7,8-diphenyl	223	927, 931
8,8-Dimethyl-1,3-diphenyl	220	917
1,3-Dimethyl-7-methylthiomethyl	—	1343
1,3-Dimethyl-7-phenyl	195	931
1,3-Dimethyl-8-phenyl	> 350	847, 892, 897, 902, 913, 927, 929, 930, 935, 936, 937, 951, 1706
1,9-Dimethyl-8-phenyl	375	913
1,3-Dimethyl-8-phenylaminomethyl	270	928
1,3-Dimethyl-7-*n*-propyl	99–102	2012
1,3-Dimethyl-8-propyl	> 300	930, 935
1,3-Dimethyl-7-vinyl	177–178	1215
1,3-Diphenyl	327–330	917
7-(2,3-Epoxypropyl)-1,3-dimethyl	161–163	846
7-(2,3-Epoxypropyl)-8-hydroxymethyl-1,3-dimethyl	185–187	846
7-(2,3-Epoxypropyl)-8-methoxymethyl-1,3-dimethyl	229–232	846
8-Ethoxy	—	920, 1116
8-Ethoxy-1-methyl	—	1116

1-Ethyl	> 300	2010
3-Ethyl	> 300	2010
9-Ethyl	—	924
1-Ethyl-3,7-dimethyl	163–165	1295, 1337, 2011
7-Ethyl-1,3-dimethyl	148–155	1215, 1219, 1292, 1295, 1337, 2000
8-Ethyl-1,3-dimethyl	> 300	918, 930, 935
8-Ethyl-7-(2-hydroxyethyl)-1,3-dimethyl	163–164	938
3-Ethyl-8-hydroxymethyl	233–235	843
1-Ethyl-3-methyl	226–228	2010
3-Ethyl-9-methyl	—	969
8-Ethyl-1-methyl	> 300	913
9-Ethyl-3-methyl	—	969
1-Ethyl-7-methyl-3-*n*-propyl	108–110	2010
8-Ethyl-1,3,7-trimethyl	184–186	1099, 1252
8-Formyl-1,3-dimethyl	167–169	916
7-Formylmethyl-1,3-dimethyl	—	2027
3-Hydroxy	—	1166, 1699
7-Hydroxy	—	920, 1834
9-Hydroxy	—	957
3-Hydroxy-1,7-dimethyl	—	838
3-Hydroxy-1-methyl	270	838
3-Hydroxy-7-methyl	—	838
3-Hydroxy-8-methyl	—	838
3-Hydroxy-9-methyl	—	838
7-Hydroxy-1,3-dimethyl-8-phenyl	—	922
7-Hydroxy-1-hydroxymethyl	—	920
7-Hydroxy-1-methyl	—	1834
7-Hydroxy-8-methyl	> 300	921
9-Hydroxy-8-methyl	—	958
3-(2-Hydroxyethyl)-1-methyl	268	830
7-(2-Hydroxyethyl)-1,3,8-trimethyl	181–183	938
8-(1-Hydroxyethyl)-1,3,7-trimethyl	178	1252, 1256
9-(2-Hydroxyethyl)	272	1299
9-(2-Hydroxyethyl)-1,3-dimethyl	271–273	938
8-Hydroxymethyl	—	1235
8-Hydroxymethyl-3-methyl	276–278	843
8-Hydroxymethyl-1,3,7-trimethyl	231–233	843, 1256
8-(1-Hydroxypentyl)-1,3,7-trimethyl	178–179	1256
8-(3-Hydroxypropyl)	253	1299
7-(2-Hydroxypropyl)-1,3-dimethyl	132–134	2012
7-(3-Hydroxypropyl)-1,3-dimethyl	151–153	1298, 2012
8-(2-Hydroxyprop-2-yl)-1,3,7-trimethyl	199–200	1252, 1256
3-Isobutyl-1,7-dimethyl	97–100	831
3-Isobutyl-8-(hydroxymethyl)-1-methyl	216–217	830
3-Isobutyl-1-isopentyl	195–196	897
3-Isobutyl-1-isopentyl-8-phenyl	259–260	897
3-Isobutyl-1-methyl	308	830
3-Isobutyl-1-methyl-8-phenylethyl	81–83	831
3-Isobutyl-1-methyl-7-propargyl	116–118	831
8-Isopropoxy	—	1116
3-Methoxy	127	838
8-Methoxy	—	1116

cont.

TABLE 20. *(cont.)*

Substituents	mp(°C)	Ref.
8-Methoxy-1-methyl	—	1116
3-Methyl	> 300	859
7-Methyl	—	833, 1283
1-Methyl-8-phenyl	> 350	913, 935, 951
3-Methyl-8-phenyl	> 350	913, 927, 935, 936, 937
3-Methyl-8-phenyl-1-*n*-propyl	277–279	1887
1-Methyl-9-phenylethyl-8-propyl	229	913
1-Methyl-3-propenyl	210–211	830
7-Methyl-3-*n*-propyl	242–243	2010
1-Methyl-8-*n*-propyl	> 350	913
8-Nitrovinyl	216–219	916
8-(1,1,2,2,2-Pentachloroethyl)-1,3,7-trimethyl	254–255	1135
8-Phenyl	> 350	913
8-Phenyl-1,3-di-*n*-propyl	260–261	897
1,3,7,8-Tetramethyl	204–205	843
1,3,8,9-Tetramethyl	252–254	843
1,3,7-Triethyl	108–111	843, 1292
1,3,7-Triethyl-8-hydroxymethyl	144–145	843
1,3,7-Trimethyl (caffeine)		1291, 1292, 1293, 1295, 1297, 1337
1,3,8-Trimethyl	324–327	892, 902, 918
1,7,8-Trimethyl	333–334	991
1,8,9-Trimethyl	340	913
1,3,7-Trimethyl-8-phenyl	185	913
1,3,8-Trimethyl-7-phenyl	235	931
1,3,7-Trimethyl-8-*n*-propyl	111–112	1252
1,3,7-Trimethyl-8-trichloromethyl	192–193	1135
1,3,8-Triphenyl	> 350	917

TABLE 21. OTHER OXOPURINES AND ALKOXYPURINES

Purine	Mp(°C)	Ref.
6-Acetonyl-9-phenyl	175–176	1067, 1079
6-Acetonyl-9-ethyl	148–149	1071
6-Acetophenon-2-yl-9-ethyl	153–154	1071
3-Acetoxy-2,3-dihydro-2-oxo	ns.	861
8-Acetyl-1,3-dimethyl	—	116
8-Acetyl-1,3,7-trimethyl	—	116
6-Allyloxy	182	1868
6-Allyloxy-9-benzyl	650	1221
6-Benzoylmethyl-9-phenyl	223–224	1079
9-Benzyl-6-methoxy	114–116	862
9-Benzyl-2-methoxy-6-phenyl	141–143	967
9-Benzyl-6-propargyloxy	117–118	1221
9-Benzyl-1,6,7,8-tetrahydro-6,8-dioxo-2-phenyl	> 300	936
9-Benzyl-1,6,7,8-tetrahydro-2-methyl-6,8-dioxo	> 300	936

6-Benzyloxy-2,3-dihydro-3,7-dimethyl-2-oxo	—	1871
6-(But-2-enyloxy)	171	1868
(*R*)-6-(2-Butoxy)	158	1868
(*S*)-6-(2-Butoxy)	160	1868
(*R*, *S*,)-6-(2-Butoxy)	165–167	1868
6-[(Diacetyl)methyl]-9-phenyl	156–157	1079, 1067
2,3-Dihydro-3,8-dihydroxy-2-oxo	270	861
2,3-Dihydro-6,9-dimethyl-2-oxo	> 300	1073
7,8-Dihydro-1,9-dimethyl-8-oxo	HI 238–240	1290
7,8-Dihydro-2,9-dimethyl-8-oxo	295–296	878
8,9-Dihydro-1,7-dimethyl-8-oxo	HI 278–280	1290
8,9-Dihydro-3,7-dimethyl-8-oxo	335	1290
2,3-Dihydro-3-hydroxy-2-oxo	204	861
2,3-Dihydro-3-isopropyl-7,8-dimethyl-2-oxo-6-phenyl	228–229	991
2,3-Dihydro-6-methoxy-3,7-dimethyl-2-oxo	—	1871
1,8-Dihydro-1-methyl-8-oxo	> 300	1248, 1290
2,3-Dihydro-3-methyl-2-oxo	—	836
2,3-Dihydro-9-methyl-2-oxo	—	1150
8,9-Dihydro-7-methyl-8-oxo	257	1243
2,3-Dihydro-8-methyl-2-oxo-6-phenyl	> 300	991
7,8-Dihydro-8-oxo	—	1150
2,3-Dihydro-6,8,9-trimethyl-8-oxo	HI 205–208	1290
6-Ethoxy	225–226	989
6-Ethoxy-2,8-bis(2-hydroxyprop-2-yl)	200–201	1252
6-Ethoxy-2,3-dihydro-3,7-dimethyl-2-oxo	—	1098, 1871
8-Ethoxy-2,6-dimethyl-	> 224	905
6-Ethoxy-8-(2-hydroxypropyl)	201–202	1252
2-Ethoxy-9-methyl	111–112	1140
6-Ethoxy-9-methyl	115–116	1140
8-Ethoxy-7-methyl	163	905
8-Ethoxy-9-methyl	99	905
6-Formyl-7,8-dihydro-8-oxo	—	1084
3,7,8,9-Tetrahydro-1,3,7,9-tetramethyl-2,8-dioxo	iod. 217	903
6-Hexyloxy	148	1868
2-Methoxy	217–219	1176
6-Methoxy	194–195	1140
2-Methoxy-6,9-dimethyl	125–126	860
6-Methoxy-2,3-dimethyl	—	1312
6-Methoxy-3,8-dimethyl	—	1312
6-Methoxy-7,9-dimethyl	iod. 207	1309
2-Methoxy-1-methyl	> 200	1271
2-Methoxy-7-methyl	191–192	1176
2-Methoxy-9-methyl	140–141	1176
6-Methoxy-2-methyl	—	1312
6-Methoxy-3-methyl	160–162	836
6-Methoxy-7-methyl	182–184	1176
6-Methoxy-8-methyl	213–215	1312
6-Methoxy-9-methyl	150–154	1176, 1271, 1274
8-Methoxy-7-methyl	156–160	1271
8-Methoxy-9-methyl	149–150	1176, 1271
6-Methoxy-9-phenyl	164–165	1079
2-Methoxy-6,8,9-trimethyl	95–96	860

cont.

TABLE 21. *(cont.)*

Purine	Mp(°C)	Ref.
6-(3-Methylbut-2-enyloxy)	> 210	1177
6-Pentyloxy	160–161	1868
6-Phenoxy-9-phenyl	180–182	1079
1,3,7,8-Tetrahydro-1,9-dimethyl-6,8-dioxo	bet. > 300	1246
1,6,7,8-Tetrahydro-1,9-dimethyl-6,8-dioxo	> 300	1246
1,6,8,9-Tetrahydro-1,7-dimethyl-6,8-dioxo	> 300	1246
1,6,7,8-Tetrahydro-7,9-dimethyl-6,8-dioxo	> 300	1246
3,6,7,8-Tetrahydro-3,9-dimethyl-6,8-dioxo	> 300	1246
3,6,8,9-Tetrahydro-3,7-dimethyl-6,8-dioxo	> 300	1246
1,6,7,8-Tetrahydro-1-methyl-6,8-dioxo	> 300	1243, 1246
1,6,8,9-Tetrahydro-7-methyl-6,8-dioxo	> 300	1246
2.3,8,9-Tetrahydro-7-methyl-2,8-dioxo	> 300	903
3.6,7,8-Tetrahydro-3-methyl-6,8-dioxo	> 300	1246
1,2,7,8-Tetrahydro-1,7,9-trimethyl-2,8-dioxo	241–242	903
1,2,8,9-Tetrahydro-1,3,7-trimethyl-2,8-dioxo	235–238	903
1,3,7,8-Tetrahydro-1,3,9-trimethyl-6,8-dioxo	bet. 247	1246
1,3,8,9-Tetrahydro-1,3,7-trimethyl-6,8-dioxo	bet. 217	1246
3,6,7,8-Tetrahydro-3,7,9-trimethyl-6,8-dioxo	> 300	1246
1,6,7,8-Tetrahydro-2-methyl-6,8-dioxo-9-phenylethyl	> 300	936
Uric acid (1,2,3,6,7,8-Hexahydro-2,6,8-trioxopurine)	> 300	1116
Uric acid/3-benzyl-1,7-dimethyl	308–312	833
Uric acid/3-benzyl-7-methyl	> 300	833
Uric acid/1,3-dimethyl	–	934, 949, 1915
Uric acid/1,7-dimethyl	> 300	833, 891
Uric acid/1,9-dimethyl	> 300	891
Uric acid/3,7-dimethyl	> 300	883, 887
Uric acid/3,9-dimethyl	> 300	891
Uric acid/7,9-dimethyl	> 300	891, 1713
Uric acid/1-methyl	> 300	891
Uric acid/1-methyl-3-phenyl	> 300	949
Uric acid/3-methyl	> 300	891
Uric acid/7-methyl	> 300	833
Uric acid/9-methyl	> 300	1713
Uric acid/1,3,9-trimethyl	> 300	891
Uric acid/1,7,9-trimethyl	> 300	891

TABLE 22. THIOXO AND ALKYLTHIOPURINES

Purine	mp(°C)	Ref.
9-Acetyl-6-methylthio	134–136	1383
7-Benzyl-8-benzylthio-1,3-dimethyl	112–113	889
3-Benzyl-3,6-dihydro-7-methyl-8-phenyl-6-thioxo	238	872
3-Benzyl-3,6-dihydro-8-phenyl-6-thioxoy	> 260	872
9-Benzyl-6-methylthio	115–116	862
6-Benzylthio-9-vinyl	97–98	1395
2,6-Bisbenzylthio-9-ethyl	127–128	1187

cont.

2,6-Bis(diphenylmethylthio)	229–230	1187
2,6-Bis(diphenylmethylthio)-9-ethyl	84–85	1187
2,8-Bismethylsulfonyl	204	1047
6-*n*-Butylthio	148	1870
2-Cyanomethylthio-6,9-dimethyl	130–133	1741
9-Cyclopentyl-2,3-dihydro-2-thioxo	321–323	976
3,9-Diethyl-2,6-bisethylthio	id. 194	1187
7,8-Dihydro-7,9-dimethyl-2,6-bismethylthio-8-thioxo	214–216	1363
3,6-Dihydro-3,7-dimethyl-8-methylthio-6-thioxo	295	882
1,6-Dihydro-1,7-dimethyl-8-phenyl-6-thioxo	219–221	872
1,6-Dihydro-1,9-dimethyl-8-phenyl-6-thioxo	231	872
3,6-Dihydro-3,7-dimethyl-8-phenyl-6-thioxo	242	872
3,6-Dihydro-3,9-dimethyl-8-phenyl-6-thioxo	> 280	872
1,6-Dihydro-2,8-dimethyl-9-phenyl-6-thioxo	129–130	943
2,3-Dihydro-6,8-dimethyl-2-thioxo	> 300	860
1,6-Dihydro-1-methyl-2,8-bismethylthio-6-thioxo	295	890
1,6-Dihydro-1-methyl-8-phenyl-6-thioxo	> 300	872
1,6-Dihydro-7-methyl-8-phenyl-6-thioxo	> 280	872
1,6-Dihydro-8-methyl-9-phenyl-6-thioxo	185–187	943
1,6-Dihydro-9-methyl-8-phenyl-6-thioxo	> 280	872
1,2-Dihydro-1-methyl-2-thioxo	285–290	836
2,3-Dihydro-8-methyl-2-thioxo	—	860
1,6-Dihydro-6-oxo-3-(3-sulfopropyl) NH_4-		1474
2,3-Dihydro-8-phenyl-2-thioxo	303	857, 866
1,6-Dihydro-6-selenoxo	—	1280
1,6-Dihydro-6-selenoxo-3-oxido	298	1142
1,6-Dihydro-6-thioxo (see also 6-Mercaptopurine derivatives)	—	—
2,3-Dihydro-2-thioxo	> 280	866
7,8-Dihydro-8-thioxo	—	836
1,6-Dihydro-6-thioxo-3-oxido	> 230	1142
1,6-Dihydro-6-thioxo-9-vinyl	298	1163
1,6-Dihydro-1,7,9-trimethyl-6-thioxo	iod. 229–231	1364
2,3-Dihydro-6,8,9-trimethyl-2-thioxo	—	848, 860
3,7-Dimethyl-2,6-bismethylthio	iod. 168–170	887
6,9-Dimethyl-2,8-bismethylthio	151	860
3,7-Dimethyl-6,8-bismethylthio	pic. 177	882
7,9-Dimethyl-2,6-bismethylthio	iod. –	887
2,9-Dimethyl-8-methylsulfinyl	247–249	878
6,9-Dimethyl-2-methylsulfinyl	162	860
2,9-Dimethyl-8-methylsulfonyl	143	878
6,9-Dimethyl-2-methylsulfonyl	204–206	1188
1,8-Dimethyl-2-methylthio	245	871
6,8-Dimethyl-2-methylthio	213	860
7,8-Dimethyl-2-methylthio	195–198	848, 871, 1087
8,9-Dimethyl-2-methylthio	142–144	871, 1087
2,3-Dimethyl-6-methylthio	—	1312
3,8-Dimethyl-6-methylthio	—	1312
7,9-Dimethyl-6-methylthio	iod. 218–220	1364
1,9-Dimethyl-6-methylthio-8-phenyl	iod. > 225	872
3,7-Dimethyl-6-methylthio-8-phenyl	iod. > 215	872
3,9-Dimethyl-6-methylthio-8-phenyl	iod. > 225	872
3,7-dimethyl-2,6,8-trismethylthio	iod. 201–203	887

cont.

TABLE 22. *(cont.)*

Purine	mp(°C)	Ref.
6-Dimethylarsinoseleno	—	1376
2-Dimethylarsinothio	173–175	1376
9-Ethyl-2,3-dihydro-6-methyl-2-thioxo	> 230	1188
8-Ethyl-2,3-dihydro-2-thioxo	282–285	866
6-Ethyl-8,9-dimethyl-2-methylthio	122–123	1188
7-Ethyl-6,8-dimethyl-2-methylthio	110–111	834
8-Ethyl-6,9-dimethyl-2-methylthio	145–146	1188
9-Ethyl-6,8-dimethyl-2-methylthio	98–99	834, 1188
8-Ethyl-2-ethylthio	208–210	866
9-Ethyl-3-methyl-2,6-bismethylthio	iod. 235	1187
6-Ethyl-8-methyl-2-methylthio	207–209	1188
6-Ethyl-9-methyl-2-methylthio	91–92	1188
7-Ethyl-6-methyl-2-methylthio	118–119	834
8-Ethyl-6-methyl-2-methylthio	200–202	866
9-Ethyl-6-methyl-2-methylthio	67–68	1188
6-Ethyl-2-methylthio	213–214	1188
8-Ethyl-2-methylthio	208–210	866
9-Ethyl-6-phenylthio	106–108	1066
9-Ethyl-1,2,3,6-tetrahydro-2,6-dithioxo	270–271	1187
2-Ethylthio	141–143	866
8-Ethylthio	197	866
2-Ethylthio-6,9-dimethyl	93	860
2-Ethylthio-6-methyl	202–204	1188
2-Ethylthio-8-methyl	218–220	866
2-Ethylthio-9-methyl	94–96	1188
6-Ethylthio-9-methyl	103–104	1741
8-Ethylthio-9-methyl	102–103	1741
2-Ethylthio-8-phenyl	232–234	866
6-Ethylthio-9-vinyl	65–67	1395
9-Formylmethyl-1,6-dihydro-6-thioxo	> 200	1382
1,2,3,6,7,8-Hexahydro-3-methyl-2,6,8-trithioxo	> 300	887
1,2,3,6,7,8-Hexahydro-9-methyl-2,6,8-trithioxo	> 300	887
6-Hydrazinosulfonyl	> 240	1390
2-Isopropylthio-6,8,9-trimethyl	112	848
6-Mercaptopurine(1,6-Dihydro-6-thioxopurine)		
6-Mercaptopurine/1-butyl	182	835
6-Mercaptopurine/1-cyclohexyl	238	835
6-Mercaptopurine/1-cyclopentyl	215	835
6-Mercaptopurine/7-cyclopentyl	214	835
6-Mercaptopurine/7-diethylaminomethyl	178	1380
6-Mercaptopurine/3,8-dimethyl	—	1280
6-Mercaptopurine/7,9-dimethyl	chlor. 249	1287
6-Mercaptopurine/7-dimethylaminomethyl	234	1380
6-Mercaptopurine/7-dipropylaminomethyl	184	1380
6-Mercaptopurine/1-methyl		1322
6-Mercaptopurine/3-methyl	—	1280
1-Methyl-2,6-bismethylthio	pic. 206–210	887
3-Methyl-2,6-bismethylthio	177–178	887
7-Methyl-2,6-bismethylthio	175–176	1087
9-Methyl-2,6-bismethylthio	161–164	887, 1087
1-Methyl-2,8-bismethylthio	220–222	887

6-Methyl-2,8-bismethylthio	236	860
3-Methyl-6,8-bismethylthio	236–237	887
9-Methyl-6,8-bismethylthio	166	882
9-Methyl-6-methylsulfonyl	211	1150
1-Methyl-2-methylthio	143–145	836
7-Methyl-2-methylthio	179–181	1087
8-Methyl-2-methylthio	270–275	860, 871
9-Methyl-2-methylthio	130–132	1087
1-Methyl-6-methylthio	HI 217–223	1364
2-Methyl-6-methylthio	—	1312
3-Methyl-6-methylthio	165, HI 208–213	785, 1364
8-Methyl-6-methylthio	—	1312
9-Methyl-6-methylthio	173–183	1138, 1271, 1364
1-Methyl-8-methylthio	218–220, HI 210–215	836, 887
7-Methyl-8-methylthio	179–181	1087
9-Methyl-8-methylthio	146–150	1087, 1271
1-Methyl-6-methylthio-8-phenyl	> 225	872
7-Methyl-6-methylthio-8-phenyl	177	872
9-Methyl-6-methylthio-8-phenyl	231–233	872
9-Methyl-6-sulfo	—	1390
9-Methyl-6-thiocyanato	181–182	1365
3-Methyl-2,6,8-trismethylthio	168–170	887
9-Methyl-2,6,8-trismethylthio	155–156	887
8-Methylsulfonyl	> 305	1271
6-Methylsulfonyl-3-oxido	196–198	1142
6-Methylsulfonyl-9-phenyl	179–180	1079
8-Methylthio	258	836, 905
2-Methylthio-6,8-diphenyl	305	896
6-Methylthio-3-oxido	245–247	1142
6-Methylthio-9-vinyl	108–109	1395
6-Sulfino-3-oxido	Na^+	1057
6-Sulfo	—	1390
8-Sulfo	—	1390
6-Sulfonamido-3-oxido	> 300	1142
1,6,7,8-Tetrahydro-1,7-dimethyl-2-methylthio-6,8-dithioxo	280	1363
1,2,3,6-Tetrahydro-1,3-dimethyl-2-oxo-6-selenoxo	> 300	874
1,2,3,6-Tetrahydro-3,7-dimethyl-2-oxo-6-selenoxo	269–272	874
1,2,3,6-Tetrahydro-1,3-dimethyl-2-oxo-8-phenyl-2-thioxo	> 300	874
1,2,3,6-Tetrahydro-1,3-dimethyl-8-phenyl-6-sulfenyl-2-thioxo	> 300	874
1,2,3,6-Tetrahydro-1,3-dimethyl-8-phenyl-2,6-dithioxo	284–285	874
1,2,3,6-Tetrahydro-1,3-dimethyl-6-sulfenyl-2-thioxo	244–245	874
1,2,3,6-Tetrahydro-7,8-dimethyl-2,6-dithioxo	> 300	991
2,3,7,8-Tetrahydro-6,9-dimethyl-2,8-dithioxo	> 300	860
1,2,3,6-Tetrahydro-8-(2-hydroxyethylthio)-2,6-dioxo	—	1263
2,3,7,8-Tetrahydro-6-methyl-2,8-dithioxo	> 300	860
1,6,7,8-Tetrahydro-9-methyl-6,8-dithioxo	> 300	882
1,6,7,8-Tetrahydro-1-methyl-2-methylthio-6,8-dithioxo	> 300	890
6,8,9-Trimethyl-2-methylthio	103–104	860

TABLE 23. AMINO-OXOPURINES

Purine	mp(°C)	Ref.
6-Acetamido-3-benzyl-2,3-dihydro-1-methyl-2-oxo	> 250	1534
6-Acetamido-3-benzyl-2,3-dihydro-2-oxo	> 300	1534
2-Acetamido-1,6-dihydro-1,7-dimethyl-8-methoxy-6-oxo	219–220	1712
2-Acetamido-1,6-dihydro-1,7-dimethyl-6-oxo	252–254	1712
2-Acetamido-1,6-dihydro-1-(4-hydroxybut-2-enyl)-6-oxo	228–230	1540
2-Acetamido-1,6-dihydro-9-(4-hydroxybut-2-enyl)-6-oxo	252	1540
2-Acetamido-1,6-dihydro-6-oxo	> 300	1444
1-Amino-9-benzyl-1,6-dihydro-2-methyl-6-oxo	206–208	1007
6-Amino-9-benzyl-7,8-dihydro-7-methyl-8-oxo	176–177	1426
1-Amino-9-benzyl-1,6-dihydro-6-oxo	217–218	1007
2-Amino-7-benzyl-1,6-dihydro-6-oxo	> 350	826
1-Amino-9-benzyl-2-ethyl-1,6-dihydro-6-oxo	175	1007
6-Amino-9-benzyl-7-ethyl-7,8-dihydro-8-oxo	222–234	1426
2-Amino-6-benzyloxy	–	1270
2-Amino-6-benzyloxy-7-cyanomethyl	188–189	1856
2-Amino-6-benzyloxy-9-cyanomethyl	us. 191	1856
2-Amino-6-benzyloxy-7-*n*-propyl	—	1856
2-Amino-6-benzyloxy-9-*n*-propyl	—	1856
2-Amino-6-(but-2-enyloxy)	> 210	1177
1-Amino-9-*tert*-butyl-1,6-dihydro-2-methyl-6-oxo	219–220	1007
1-Amino-9-*tert*-butyl-1,6-dihydro-6-oxo	173–175	1007
1-Amino-9-cyclohexyl-1,6-dihydro-6-oxo	155	1007
2-Amino-1,6-dihydro-1,7-dimethyl-8-methoxy-6-oxo	240	1712
8-amino-2,3-dihydro-3,6-dimethyl-2-oxo	—	904
1-Amino-1,6-dihydro-2-methyl-6-oxo	265–266	961
2-Amino-8,9-dihydro-7-methyl-8-oxo	300, HI 289	903
1-Amino-1,6-dihydro-6-oxo	314	961
2-Amino-1,6-dihydro-6-oxo derivatives (see Guanine)		
6-Amino-2,3-dihydro-2-oxo derivatives, (see Isoguanine)		
6-Amino-7,8-dihydro-8-oxo	> 300	941, 1427
8-Amino-7-ethoxymethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	235–236	1405
6-Amino-3-ethyl-7,8-dihydro-8-oxo	> 300	941
6-Amino-9-ethyl-7,8-dihydro-7-methyl-8-oxo	174–175	1426
2-Amino-9-ethyl-1,6,7,8-tetrahydro-6,8-dioxo	> 300	932
2-Amino-6-methoxy-3-oxido	231–232	838
2-Amino-6-(prop-2-enyloxy)	205	1177
1-Amino-1,2,3,6-tetrahydro-3,7-dimethyl-2,6-dioxo	245–246	1330
7-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	222	1330
2-Amino-1,6,7,8-tetrahydro-1,7-dimethyl-6,8-dioxo	250–251	1712
2-Amino-1,6,7,8-tetrahydro-6,8-dioxo	> 300	932
2-Amino-1,6,7,8-tetrahydro-6,8-dioxo-9-phenyl	> 300	932
2-Amino-3,6,7,8-tetrahydro-3-hydroxy-6,8-dioxo	—	828

8-Amino-1,2,3,6-tetrahydro-7-isopropoxymethyl-1,3-dimethyl-2,6-dioxo	214–215	1405
2-Amino-1,6,7,8-tetrahydro-9-methyl-6,8-dioxo	—	879, 932
6-Benzamido-9-benzyl-7-ethyl-7,8-dihydro-8-oxo	161–162	1426
6-Benzamido-9-benzyl-7,8-dihydro-7-methyl-8-oxo	219–220	1426
2-Benzamido-1,6-dihydro-6-oxo	> 300	1444
2-Benzamido-3,6-dihydro-3-methyl-6-oxo	326	1001
6-Benzamido-9-ethyl-7,8-dihydro-7-methyl-8-oxo	200–201	1426
7-Benzyl-3,6-dihydro-3-methyl-2-methylamino-6-oxo	235	1477
9-Benzyl-6-dimethylamino-7,8-dihydro-8-oxo	256–257	2004
1-Benzyl-1,6,7,8-tetrahydro-6-imino-9-methyl-8-oxo	hy. 214–216	1851
6-Benzylamino-7,8-dihydro-9-methyl-8-oxo	207–209	1851
2-Benzylamino-1,6-dihydro-6-oxo	275–276	1444
6-Benzylimino-1,6,7,8-tetrahydro-1,9-dimethyl-8-oxo	214–215	1851
6-Benzylimino-3,6,7,8-tetrahydro-3,9-dimethyl-8-oxo	232–233	1851
2,6-Diamino-8-methoxy	302	1911
2,6-Diamino-8-ethoxy	—	1911
8-Diethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	254	909, 910
1,2-Dihydro-1,3-dimethyl-2-oxo-6-morpholino-8-phenyl	196–197	1107
1,2-Dihydro-1,3-dimethyl-2-oxo-8-phenyl-6-phenylamino	232	1107
1,2-Dihydro-1,3-dimethyl-2-oxo-8-phenyl-6-piperidino	170	1107
1,6-Dihydro-2-(*N*-hydroxy)methylamino-6-oxo	> 250	1227
1,6-Dihydro-2-methylamino-6-oxo	> 300	1444
3,7-Dimethyl-6-methylamino-2-propoxy	chlor.–	1098
1,6-Dihydro-2-(1-methylhydrazino)-6-oxo	> 300	1172
1,6-Dihydro-2-(*N*-methylhydroxylamino)-6-thioxo	240	1124
2,3-Dihydro-6-(*N*-nitroso)methylamino-2-oxo	> 300	1172
1,6-Dihydro-2-(*N*-nitroso)methylamino-6-oxo	—	1172, 1227
1,6-Dihydro-6-oxo-2-(3-phenylureido)	—	1498
7,9-Dimethyl-7,8-dihydro-6-methylamino-8-oxo	222–223	1851
8-Dimethylamino-1,6-dihydro-2-methyl-6-oxo	> 300	910
8-Dimethylamino-1,6-dihydro-2-morpholinomethyl-6-oxo	260	910
8-Dimethylamino-1,6-dihydro-6-oxo-2-phenylmethylamino	> 300	910
6-Dimethylamino-8-ethoxy-9-methyl	113	905
8-Dimethylamino-2-methylthio-6-morpholino	> 300	910
8-Dimethylamino-2-methylthio-6-piperidino	—	910
8-Dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	> 300	909, 910, 927
8-Dimethylamino-1,2,3,6-tetrahydro-2,6-dioxo	—	1116
8-Dimethylamino-1,2,3,6-tetrahydro-1,3,9-trimethyl-2,6-dioxo	295	909, 910
2-Ethoxy-3,6-dihydro-3,7-dimethyl-6-methylimino	—	1098
6-Ethoxy-2,3-dihydro-3,7-dimethyl-2-methylimino	—	1098

cont.

TABLE 23. *(cont.)*

Purine	mp(°C)	Ref.
8-Ethoxy-9-methyl-6-methylamino	151–152	905
9-Formamido-2,3-dihydro-6-methyl-2-oxo	257	952
9-Formamido-2,3-dihydro-2-oxo	309–310	952
2-Formamido-1,6-dihydro-6-oxo	> 300	1444
8-Formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7-phenyl	215	927
Guanine (2-amino-1,6-dihydro-6-oxo)	—	1122
Guanine/1-acetonyl	300	1237
Guanine/8-acetylmethylthio	> 250	1203
Guanine/1-amino	> 300	1229
Guanine/7-benzyl-1,3-dimethyl	175	1477
Guanine/7-benzyl-3-methyl	269–270	1477
Guanine/3-benzyl-9-methyl	—	969
Guanine/1-benzyloxy	HCl	968
Guanine/9-benzyloxy	—	957
Guanine/9-benzyloxy-8-methyl	—	958
Guanine/8-(but-1-enyl)	> 300	1177
Guanine/8-(but-2-enyl)	> 300	1177
Guanine/7-cyanomethyl	> 300	1734
Guanine/7-cyanomethyl-9-methyl	brom.	1735
Guanine/9-(cyclohex-3-en-1-yl)	143	1935
Guanine/3,9-diethyl	—	969
Guanine/9-(2,4-dihydroxybutyl)	250–252	1258
Guanine/3,9-dimethyl	326	964, 969
Guanine/1,7-dimethyl-3-oxido	—	838
Guanine/3-ethyl-9-methyl	—	969
Guanine/9-ethyl-3-methyl	—	969
Guanine/9-formylmethyl	—	1248
Guanine/1-hydroxy	—	968
Guanine/9-hydroxy	—	957
Guanine/3-hydroxy-7,8-dimethyl	—	1696
Guanine/9-hydroxy-8-methyl	—	958
Guanine/9-(4-hydroxy-2-oxobutyl)	> 300	1258
Guanine/7-(4-hydroxybut-2-enyl)	295	1540
Guanine/9-(4-hydroxybut-2-enyl)	274–276	1540
Guanine/7-(4-hydroxybutyl)	—	1491
Guanine/9-(4-hydroxybutyl)	—	1491
Guanine/7-(2-hydroxyethyl)-9-methyl	Ac. 160–163	1269
Guanine/8-hydroxymethyl	—	1235
Guanine/8-hydroxymethyl-9-methyl	—	879
Guanine/7-(2-hydroxypropyl)	> 300	1528
Guanine/7-[1-(2-hydroxypropyl)]-9-methyl	Ac. 238	1269
Guanine/7-[2-(1-hydroxypropyl)]-9-methyl	—	1269
Guanine/7-(isoprop-2-enyl)	> 250	1203
Guanine/3-methyl	> 300	1001, 1477
Guanine/8-methyl	—	1074
Guanine/8-methyl-1-(3-methylbut-2-enyl)	> 300	1131
Guanine/8-methyl-3-(3-methylbut-2-enyl)	> 300	1131
Guanine/8-methyl-7-(3-methylbut-2-enyl)	> 300	1131
Guanine/8-methyl-9-(3-methylbut-2-enyl)	> 300	1131

Guanine/1-methyl-3-oxido	—	838
Guanine/7-methyl-3-oxido	—	838
Guanine/8-methyl-3-oxido	—	838
Guanine/9-methyl-3-oxido	—	838
Guanine/9-methyl-7-oxido	> 300	879
Guanine/8-(3-methylbut-2-enyl)	> 300	1177
Guanine/8-(3-methylbutyl)	> 300	1177
Guanine/9-(3-oxopropyl-1-enyl)	> 300	1533
Guanine/7-phenyl	> 300	2033
Guanine/8-(prop-1-enyl)	> 300	1177
Guanine/9-(prop-1-enyl)	> 300	1177
Guanine/7-(prop-2-enyl)	>300	1177
Guanine/8-(prop-2-enyl)	> 300	1177
Guanine/9-(prop-2-enyl)	> 300	1177
Guanine/8-(propyl)	> 300	1177
Guanine/1-(3-sulfopropyl)	332	1539
6-Hydrazonomethyl-7,8-dihydro-8-oxo	> 300	1080
Isoguanine(6-amino-2,3-dihydro-2-oxo)	—	984
Isoguanine/9-acetyl-1-methyl	> 280	1534
Isoguanine/9-benzyl-1-methyl	—	1534
Isoguanine/3,7-dimethyl	—	2019
Isoguanine/3,9-dimethyl	> 300	964, 997, 2019
Isoguanine/7,8-dimethyl	317	991
Isoguanine/1-methyl	—	1242
Isoguanine/3-methyl	> 300	859, 2019
Isoguanine/8-methyl	—	2019
2-Methoxy-3,7-dimethyl-6-methylamino	chlor.–	1098
6-(*N*-Nitroso)hydroxyamino-3-oxido	140	1172
1,2,3,6-Tetrahydro-1,3-dimethyl-8-methylamino-2,6-dioxo	> 300	910, 911
1,6,7,8-Tetrahydro-1,9-dimethyl-6-methylimino-8-oxo	262–264	1851
1,3,7,8-Tetrahydro-3,9-dimethyl-6-methylimino-8-oxo	266–267	1851
1,2,3,6-Tetrahydro-1,3-dimethyl-8-(*N*-methyl)phenylamino-2,6-dioxo	260	909, 910
1,2,3,6-Tetrahydro-8-dimethylamino-1,3-dimethyl-2,6-dioxo	> 300	911
1,6,7,8-Tetrahydro-6-imino-1,9-dimethyl-8-oxo	> 300	1851
1,2,3,6-Tetrahydro-8-methylthio-2,6-dioxo-3-phenyl	300–302	881

TABLE 24. AMINO-THIOXOPURINES

Purine	mp(°C)	Ref.
9-Acetamido-6-benzylthio	200–201	1546
9-Acetamido-6-diphenylmethylthio	214–215	1546
9-Acetamido-6-methylthio	185	1546
9-Allyl-8-allylthio-6-amino-2-phenyl	144–145	881

cont.

TABLE 24. *(cont.)*

Purine	mp(°C)	Ref.
6-Amino-9-benzyl-8-benzylthio-2-phenyl	208–210	881
2-Amino-6-benzylthio-9-ethyl	HCl 110	1187
6-Amino-7,8-dihydro-2-phenyl-8-thioxo	> 300	881
6-Amino-7,8-dihydro-3-phenyl-8-thioxo	300–301	881
2-Amino-1,6-dihydro-6-thioxo(thioguanine)	—	1269, 1928
6-Amino-8-dimethylamino-2-ethylthio	323–325	912
6-Amino-8-dimethylamino-2-methylthio	310–312	912
2-Amino-6-diphenylmethylthio	227–228	1187
2-Amino-9-ethyl-1,6-dihydro-6-thioxo	301–303	1187
2-Amino-9-ethyl-6-diphenylmethylthio	206–207	1187
6-Amino-9-ethyl-8-ethylthio-2-phenyl	179–181	881
6-Amino-9-ethyl-2-methylthio	235–237	946
2-Amino-9-formylmethyl-1,6-dihydro-6-thioxo	—	1248
1-Amino-2-methylthio	mesit. 236–238	1051
1-Amino-8-methylthio	209–210	1051
6-Amino-2-methylthio	290–292	946
6-Amino-8-methylthio-2-phenyl	212–213	881
6-Amino-9-methyl-2-methylthio	263–265	946
6-Amino-9-methyl-2-methylthio-8-phenyl	266–267	946
6-Amino-9-methyl-8-methylthio-2-phenyl	212–213	881
2-Amino-6-methylseleno	218	1369
2-Amino-6-sulfenamido	> 250	1872
2-Amino-6-sulfinamido-	> 250	1872
2-Amino-6-sulfonamido-	> 250	1872
7-Benzyl-2,3-dihydro-6-methylamino-2-thioxo	269–270	998
9-Benzylideneamino-6-benzylthio	208	1546
9-Benzylideneamino-1,6-dihydro-6-thioxo	> 260	1546
9-Benzylideneamino-6-methylthio	200–201	1546
2,9-Diamino-1,6-dihydro-6-thioxo	> 260	1010
1,7-Dibenzyl-8-benzylthio-1,2,3,6-tetrahydro-2,6-dioxo-3-phenyl	134–136	881
1,6-Dihydro-2-hydroxyamino-6-thioxo	> 260	1124
2,3-Dihydro-7-methyl-6-methylamino-2-thioxo	274–275	998
1,6-Dihydro-2-(1-methylhydrazino)-6-thioxo	310	1172
1-Ethyl-1,2,3,6-tetrahydro-6-imino-7-methyl-2-thioxo	252–253	998
7-Ethylthioethyl-2,3-dihydro-6-methylamino-2-thioxo	222–224	998
6-Hydrazino-2-methylsulfonyl		870
1,2,3,6-Tetrahydro-6-imino-1,7-dimethyl-2-thioxo	276–278	998
1,2,3,6-Tetrahydro-6-imino-1-methyl-2-thioxo	HCl 272–274	998
1,2,3,6-Tetrahydro-6-imino-7-methyl-1-phenyl-2-thioxo	278–279	998
1,2,3,6-Tetrahydro-6-imino-1-phenyl-2-thioxo-	> 300	998

TABLE 25. OXO-THIOPURINES

Purine	mp(°C)	Ref.
7-Allyl-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-thioxo	—	1988
6-Allylthio-2,3-dihydro-1,3-dimethyl-2-oxo	—	1988
3-Benzyl-8-benzylthio-1,2,3,6-tetrahydro-2,6-dioxo	134–136	881
9-Benzyl-8-benzylthio-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	179–181	847
3-Benzyl-1,6-dihydro-1,7-dimethyl-8-methylthio-6-oxo	iod., us.	883
3-Benzyl-3,6-dihydro-7-methyl-8-methylthio-6-oxo	246–247	883
3-Benzyl-3,6-dihydro-2-methylthio-6-oxo	278	826
3-Benzyl-3,6-dihydro-8-methylthio-6-oxo	290	883
3-Benzyl-1,2,3,6,7,8-hexahydro-2,6-dioxo-8-thioxo	270–271	881
7-Benzyl-1,2,3,6,8,9-hyxahydro-1-methyl-2,6-dioxo-8-thioxo	—	889
9-Benzyl-1,2,3,6,7,8-hexahydro-1-methyl-2,6-dioxo-8-thioxo	—	889
7-Benzyl-1,2,3,6,7,8-hexahydro-1,3,9-trimethyl-2,6-dioxo-8-thioxo	190–191	46
7-Benzyl-1,2,3,6-tetrahydro-3-isobutyl 1-methyl-2-oxo-6-thioxo	117–119	831
3-Benzyl-1,2,3,6-tetrahydro-8-methyl-6-oxo-2-thioxo	> 300	873
3-Benzyl-1,2,3,6-tetrahydro-6-oxo-2-thioxo	> 300	826
3-Benzyl-3,6,7,8-tetrahydro-6-oxo-8-thioxo	194	883
2-Benzylthio-1,6-dihydro-6-oxo	> 300	1989
2-Benzylthio-1,6-dihydro-6-oxo-9-triphenylmethyl	267–270	1989
8-Benzylthio-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	300–302	889
8-Benzylthio-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	> 245	889
7-*n*-Butyl-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-thioxo	—	1988
6-*n*-Butylthio-2,3-dihydro-1,3-dimethyl-2-oxo	—	1988
8-Cyclopentyl-2,3-dihydro-3-methylthio-2-oxo-3-propyl	258–259	1989
1,7-Dibenzyl-8-benzylthio-1,2,3,6-tetrahydro-2,6-dioxo-3-phenyl	191–193	881
7,9-Dibenzyl-1,2,3,6,7,8-hexahydro-1,3-dimethyl-2,6-dioxo-8-thioxo	155–157	889
1,6-Dihydro-1,9-dimethyl-2,8-bismethylthio-6-oxo	210–212	886
3,6-Dihydro-3,7-dimethyl-2,8-bismethylthio-6-oxo	190	886, 1363
2,3-Dihydro-3,7-dimethyl-6,8-bismethylthio-2-oxo	225–226	882

cont.

TABLE 25. *(cont.)*

Purine	mp(°C)	Ref.
1,6-Dihydro-2,9-dimethyl-8-methylsulfinyl-6-oxo	297–298	878
3,8-Dihydro-3,7-dimethyl-6-methylsulfinyl-8-oxo	> 300	1362
3,8-Dihydro-3,9-dimethyl-6-methylsulfinyl-8-oxo	pic. 167	1362
7,8-Dihydro-7,9-dimethyl-6-methylsulfinyl-8-oxo	194–195	1362
1,6-Dihydro-1,7-dimethyl-8-methylthio-6-oxo	202–203	883
1,6-Dihydro-1,9-dimethyl-8-methylthio-6-oxo	197–198	883
1,6-Dihydro-7,9-dimethyl-8-methylthio-6-oxo	pic. 177–179	883
1,8-Dihydro-1,9-dimethyl-6-methylthio-8-oxo	> 300	1243
2,3-Dihydro-1,3-dimethyl-6-methylthio-2-oxo	–	1988
2,3-Dihydro-3,7-dimethyl-6-methylthio-2-oxo	> 300	882
3,6-Dihydro-3,7-dimethyl-2-methylthio-6-oxo	215–220	1363
3,6-Dihydro-3,7-dimethyl-8-methylthio-6-oxo	209–210	883
3,8-Dihydro-3,7-dimethyl-6-methylthio-8-oxo	284	1243
3,8-Dihydro-3,9-dimethyl-6-methylthio-8-oxo	bet. 265	1243
7,8-Dihydro-6,9-dimethyl-2-methylthio-8-oxo	279–280	860
7,8-Dihydro-7,9-dimethyl-6-methylthio-8-oxo	185	1243
3,8-Dihydro-3-methyl-6-methylsulfonyl-8-oxo	> 300	1362
1,6-Dihydro-1-methyl-2-methylthio-6-oxo	194	1363
1,6-Dihydro-9-methyl-2-methylthio-6-oxo	> 300	890
1,8-Dihydro-1-methyl-6-methylthio-8-oxo	255	1243
1,6-Dihydro-9-methyl-2,8-bismethylthio-6-oxo	> 300	890
2,3-Dihydro-9-methyl-6,8-bismethylthio-2-oxo	276–277	890
1,6-Dihydro-1-methyl-2,8-bismethylthio-6-oxo	275	890
2,3-Dihydro-3-methyl-6,8-bismethylthio-2-oxo	268–270	890
3,6-Dihydro-3-methyl-2,8-bismethylthio-6-oxo	298–299	886
2,8-Dihydro-9-methyl-2,6-bismethylthio-8-oxo	274–275	890
8,9-Dihydro-7-methyl-6-methylsulfonyl-8-oxo	295	1362
7,8-Dihydro-9-methyl-6-methylsulfonyl-8-oxo	245	1362
1,2-Dihydro-1-methyl-6-methylthio-2-oxo	us. > 220	1202
1,2-Dihydro-1-methyl-8-methylthio-2-oxo	>300	890
1,6-Dihydro-7-methyl-2-methylthio-6-oxo	>300	890
2,3-Dihydro-7-methyl-6-methylthio-2-oxo	280	1202
2,3-dihydro-9-methyl-6-methylthio-2-oxo	284-287	1202
7,8-Dihydro-7-methyl-6-methylthio-8-oxo	276	1243
7,8-Dihydro-9-methyl-6-methylthio-8-oxo	272	882,1243
1,6-Dihydro-8-methylseleno-6-oxo	280	1193
7,8-Dihydro-2-methylsulfonyl-8-oxo	>250	1047
7,8-Dihydro-6-methylsulfonyl-8-oxo	>300	1362
1,6-Dihydro-8-methylthio-6-oxo	334–335	878
2,3-Dihydro-8-methylthio-2-oxo	—	861
3,8-Dihydro-3,7,9-trimethyl-6-methylsulfonyl-8-oxo	pic.186	1362
3,8-Dihydro-3,7,9-trimethyl-6-methylthio-8-oxo	pic.177	1243
8-Ethoxy-2-ethylthio-6,9-dimethyl	79-80	905
8-Ethoxy-6-ethylthio-9-methyl	79-80	905
8-Ethoxy-9-methyl-6-methylthio	119	905
1-Ethyl-1,6-dihydro-2,7-dimethyl-6-oxo-8-methylthio	152–154	956
1-Ethyl-1,7,8,9-tetrahydro-2,7-dimethyl-6-oxo-8-thioxo	>300	956
1-Ethyl-1,2,3,6-tetrahydro-7,8-dimethyl-6-oxo-2-thioxo	300	991

2-Formylthio-1,6-dihydro-6-oxo	—	900
1,2,3,6,7,8-Hexahydro-2,6-dioxo-3-phenyl-8-thioxo	300-302	881
1,2,3,6,7,8-Hexahydro-1-methyl-2,8-dioxo-6-thioxo	>300	886
1,2,3,6,7,8-Hexahydro-3-methyl-2,8-dioxo-8-thioxo	>300	880
1,2,3,6,7,8-Hexahydro-9-methyl-2,8-dioxo-6-thioxo	>300	886
1,2,3,6,7,8-Hexahydro-3-methyl-2-oxo-6,8-dithioxo	>300	890
1,2,3,6,7,8-Hexahydro-3-methyl-6-oxo-2,8-dithioxo	>300	887
1,2,3,6,7,8-Hexahydro-3-methyl-8-oxo-2,6-dithioxo	>300	880
1,2,3,6,7,8-Hexahydro-9-methyl-2-oxo-6,8-dithioxo	>300	890
1,2,3,6,7,8-Hexahydro-9-methyl-6-oxo-2,8-dithioxo	>300	887
1,2,3,6,7,8-Hexahydro-8-oxo-2,6-dithioxo	>300	880
9-Methyl-8-propoxy-6-propylthio	55	905
1,2,3,6-Tetrahydro-1,9-dimethyl-8-methylthio-2,6-dioxo	>300	886
1,2,3,6-Tetrahydro-3,7-dimethyl-8-methylthio-2,6-dioxo	265–268	882,886,887,1363
1,6,7,8-Tetrahydro-7,9-dimethyl-2-methylthio-6-oxo-8-thioxo	>300	1363
1,2,3,6-Tetrahydro-1,3-dimethyl-2-oxo-8-phenyl-6-sulfenyl	218–219	874
1,2,3,6-Tetrahydro-1,3-dimethyl-6-oxo-8-phenyl-2-thioxo	>300	874
1,2,3,6-Tetrahydro-1,3-dimethyl-2-oxo-8-phenyl-6-thioxo	257–258	874
1,2,3,6-Tetrahydro-1,3-dimethyl-2-oxo-6-selenoxo	>300	874
1,2,3,6-Tetrahydro-3,7-dimethyl-2-oxo-6-selenoxo	269–272	874
1,2,3,6-Tetrahydro-1,3-dimethyl-2-oxo-6-sulfenyl	241–244	874
1,2,3,6-Tetrahydro-3,7-dimethyl-2-oxo-6-sulfenyl	287–290	874
1,2,3,6-Tetrahydro-1,7-dimethyl-2-oxo-6-thioxo	>300	1202
1,2,3,6-Tetrahydro-1,9-dimethyl-2-oxo-6-thioxo	>300	1202
1,6,7,8-Tetrahydro-1,9-dimethyl-8-oxo-6-thioxo	>300	1362
1,6,7,8-Tetrahydro-2,9-dimethyl-6-oxo-8-thioxo	>300	878
1,2,3,6-Tetrahydro-3,7-dimethyl-6-oxo-2-thioxo	>300	1363
3,6,8,9-Tetrahydro-3,7-dimethyl-8-oxo-6-thioxo	>300	1362
1,2,3,6-Tetrahydro-3,9-dimethyl-2-oxo-6-thioxo	293	1281
3,6,7,8-Tetrahydro-3,9-dimethyl-8-oxo-6-thioxo	>300	1362
2,3,7,8-Tetrahydro-6,9-dimethyl-8-oxo-2-thioxo	308–312	878
1,6,7,8-Tetrahydro-7,9-dimethyl-6-oxo-8-thioxo	>300	883
1,6,7,8-Tetrahydro-7,9-dimethyl-8-oxo-6-thioxo	>300	1362
1,6,7,8-Tetrahydro-1-methyl-2-methylthio-6,8-dioxo	>300	891
1,2,3,6-Tetrahydro-1-methyl-8-methylthio-2,6-dioxo	>300	886, 1116
1,2,3,6-Tetrahydro-3-methyl-8-methylthio-2,6-dioxo	>300	886
1,2,3,6-Tetrahydro-9-methyl-8-methylthio-2,6-dioxo	>300	886
1,6,7,8-Tetrahydro-1-methyl-2-methylthio-6-oxo-8-thioxo	>300	890
3,6,7,8-Tetrahydro-3-methyl-6-oxo-8-thioxo	>300	883
1,2,3,6-Tetrahydro-7-methyl-2-oxo-6-thioxo	—	1988
1,6,8,9-Tetrahydro-7-methyl-8-oxo-6-thioxo	> 300	1362
1,2,3,6-Tetrahydro-9-methyl-2-oxo-6-thioxo	> 300	1281
1,6,7,8-Tetrahydro-9-methyl-6-oxo-8-thioxo	> 300	883
1,6,7,8-Tetrahydro-9-methyl-8-oxo-6-thioxo	> 300	1243
1,7,8,9-Tetrahydro-2-methyl-6-oxo-1,7-diphenyl-8-thioxo	316–322	956

cont.

TABLE 25. *(cont.)*

Purine	mp(°C)	Ref.
1,6,7,8-Tetrahydro-2-methylthio-6,8-dioxo	> 300	886
2,3,7,8-Tetrahydro-6-methylthio-2,8-dioxo	> 300	886
1,2,3,6-Tetrahydro-8-methylthio-2,6-dioxo	—	920
1,2,3,6-Tetrahydro-8-methylthio-2,6-dioxo-3-phenyl	300–302	881
1,6,7,8-Tetrahydro-1,7,9-trimethyl-2-methylthio-6,8-dioxo	260–263	891
1,6,7,8-Tetrahydro-1,7,9-trimethyl-2-methylthio-6-oxo-8-thioxo	257	1363
1,2,3,6-Tetrahydro-1,3,7-trimethyl-8-methylthio-6-oxo-2-thioxo	218	1363
1,2,3,6-Tetrahydro-1,3,7-trimethyl-2-oxo-6-thioxo	—	1245, 1927
1,2,3,6-Tetrahydro-1,3,9-trimethyl-2-oxo-6-thioxo	> 300	1281
1,2,6,7-Tetrahydro-1,7,9-trimethyl-2-oxo-6-thioxo	bet. -	1245
3,6,7,8-Tetrahydro-3,7,9-trimethyl-8-oxo-6-thioxo	> 300	1362

TABLE 26. REDUCED PURINES

Purine	mp(°C)	Ref.
1-Acetyl-2-chloro-1,6-dihydro	213–215	2030
1-Acetyl-2-chloro-1,6-dihydro-7-methyl	192–194	2030
1-Acetyl-1,6-dihydro	188–191	2030
7-Acetyl-1,2,3,5,6,8-hexahydro-1,3-dimethyl-2-oxo	101–102 HCl 170(d)	2030
7-Acetyl-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo	196–198	2030
7(or 9)-Acetylperhydro-1,3-dimethyl-2-oxo	182–184	2030
6-Amino-3-benzyl-1,2-dihydro	HCl 164	1757
6-Amino-1,2,3,6-tetrahydro	—	1752
6-Amino-1,2,3,6-tetrahydro-1-methyl	—	1752
6-Benzamido-3-benzyl-1,2-dihydro	161	1757
6-Benzamido-9-benzyl-7,8-dihydro	184	1757
6-Carbamoyl-7,8-dihydro	315	1839
6-Carbamoyl-1,2-dihydro-2,2-dimethyl	—	1838
6-Carbamoyl-1,2-dihydro-8,9-dimethyl-2-phenyl	trif. 178	1004, 1837
6-Carbamoyl-1,2-dihydro-2-methyl	—	1838
6-Carbamoyl-1,2-dihydro-2,2,8,9-tetramethyl	trif. > 180	1004, 1837
6-Carbamoyl-1,2-dihydro-2,2,9-trimethyl-8-phenyl	trif. 195–196	1837
6-Carbamoyl-1,2-dihydro-2,8,9-trimethyl-2-phenyl	—	1004, 1837
6-Carbamoyl-2-ethyl-1,2-dihydro	—	1838

6-Carbamoyl-2-ethyl-1,2-dihydro-2,8,9-trimethyl	—	1004
6-Chloro-7,8-dihydro-7,9-dimethyl	65	1144
6-Chloro-7,8-dihydro-9-methyl-8-phenyl	147–151	1061
2-Chloro-6-ethoxycarbonyl-7,8-dihydro	235	1839
6-Cyano-7,8-dihydro	183–185	1839
1,7 (or 9)-Diacetyl-2-chloro-1,6-dihydro	182–184	2030
1,7 (or 9)-Diacetyl-1,6-dihydro	180–182	2030
7,9-Diacetylperhydro-1,3-dimethyl-2-oxo	139–141	2030
7,9-Diacetylperhydro-2-oxo	237–238	2030
cis-2,8-Diamino-1,7,9-trimethyl-*cis*-perhydro	dipic. 225	903
2,2-Dibutyl-6-carbamoyl-1,2-dihydro	—	1838
2,6-Dichloro-8,9-dihydro-7-methyl	187	1145
1,6-Dihydro	HCl 225–227	2030
1,6-Dihydro-7,9-dimethyl	iod. 213–217	1144
8,9-Dihydro-7,9-dimethyl-6-methylamino	120–124	1532
8,9-Dihydro-7,9-dimethyl-6-methylthio	180	1287
1,6-Dihydro-7-methyl-8-trifluoromethyl	135	840
8,9-Dihydro-7-methyl-8-trifluoromethyl	135, HCl 178 d	840
1,6-Dihydro-8-trifluoromethyl	194	840
6-Dimethylamino-7,8-dihydro-7,9-dimethyl	—	1164
2-Dimethylamino-6-ethoxycarbonyl-7,8-dihydro	> 190	1839
2-Ethoxy-6-ethoxycarbonyl-7,8-dihydro	199–201	1839
6-Ethoxycarbonyl-7,8-dihydro	> 250	1839
6-Ethoxycarbonyl-7,8-dihydro-2-methylthio	210–213	1839
8-Formylamino-7,8-dihydro	198–214	1012
Guanine/8,9-dihydro-7,9-dimethyl	—	1760
Hypoxanthine/1,2-dihydro-3,9-dimethyl	200–201	1756
Hypoxanthine/-8,9-dihydro-7,9-dimethyl	—	1760
Perhydro-5-methoxy-1,3,9-trimethyl-2,8-dioxo	122	903
(4*R*, 5*S*, 6*S*)-*cis*-Perhydro-1,3,6,9-tetramethyl-2,8-dioxo	178	903
cis-Perhydro-1,3,7,9-tetramethyl-2,8-dioxo	159–161	903
cis-Perhydro-1,3,7-trimethyl-2,8-dioxo	183–184	903
cis-Perhydro-1,7,9-trimethyl-2,8-dioxo	125–126	903
1,3,7,9-Tetraacetylperhydro	hy.-	2030
Xanthine/8,9-dihydro-7,9-dimethyl	—	1760
Xanthine/8,9-dihydro-1,3,7,9-tetramethyl	—	1760

TABLE 27. MISCELLANEOUS PURINES

Purine	mp(°C)	Ref.
2-Amino-8-benzoylmethylthio-1,6-dihydro-6-oxo	> 250	1203
2-Amino-9-benzyl-8-bromo-1,6-dihydro-6-oxo	> 300	1118
6-Amino-9-benzyl-2-chloro	218–219	967
6-Amino-2-bromo	—	1117
2-Amino-8-bromo-1,6-dihydro-1,7-dimethyl-6-oxo	> 250	1712
6-Amino-8-bromo-1-methyl	> 250	842, 844

cont.

TABLE 27. *(cont.)*

Purine	mp(°C)	Ref.
2-Amino-6-chloro	—	1113
2-Amino-6-chloro-8-cyano-9-methyl	—	879
2-Amino-6-chloro-9-(cyclohex-3-en-1-yl)	liq.	1935
2-Amino-8-chloro-1,6-dihydro-6-oxo	—	1116
2-Amino-6-chloro-9-(2,3-dihydroxypropyl)	HCl 189–190	2013
6-Amino-8-chloro-3-ethyl	246	941
2-Amino-6-chloro-9-(4-hydroxybutyl)	HCl 141–147	2013
2-Amino-6-chloro-8-methyl	215	1131
6-Amino-8-chloro-1-methyl	> 260	842, 844
2-Amino-6-chloro-3-oxido	157	1166
2-Amino-8-cyano-1,6-dihydro-9-methyl-6-oxo	—	879
2-Amino-8-cyano-1,6-dihydro-9-methyl-6-thioxo	—	879
6-Amino-2,3-dihydro-8-iodo-2-oxo	—	884, 885
2-Amino-1,6-dihydro-1-methyl-2-methylthio-6-oxo	—	1263
2-Amino-1,6-dihydro-9-methyl-6-oxo-8-sulfo	—	879
2-Amino-6-fluoro	300	1122
6-Amino-2-fluoro	—	1124
6-Amino-1,2,7,8-tetrahydro-2-oxo-8-thioxo	> 360	885
6-Azido-9-methyl	—	1274
9-Benzyl-8-bromo-6-dimethylamino	144–146	2004
1-Benzyl-6-chloroacetamido	150	1439
7-Benzyl-2-chloro-6-dimethylamino	130–131	1149
9-Benzyl-1,6-dihydro-6-oxo-2-trifluoromethyl	210–212	967
9-Benzyl-6-dimethylamino-2-trifluoromethyl	107–108	2008
3,7-Bischloromethyl-8-chloro-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	142–143	1130
6,8-Bisdimethylamino-2-trifluoromethyl	203–204	1864
8-Bromo-2-chloro-6-dimethylamino	283–286	1864
8-Bromo-7-(2-chloroethyl)-1,2,3,6-tetrahydro-2,6-dioxo	155	1299
8-Bromo-1,6-dihydro-6-oxo	> 300	1240
8-Bromo-6-dimethylamino	245–247	1864
8-Bromo-6-dimethylamino-9-methyl-2-trifluoromethyl	151–152	1864
8-Bromo-6-dimethylamino-2-trifluoromethyl	228–230	1864
8-Bromo-6-methylamino-2-trifluoromethyl	249–250	1864
8-Bromo-1,2,3,6-tetrahydro-9-(2-hydroxyethyl)-2,6-dioxo	212	1299
9-(4-Bromobutyl)-6-methylamino	oil	1954
6-Chloro-1,2-dihydro-1,3-dimethyl-2-oxo-8-phenyl	—	1107
6-Chloro-7,8-dihydro-9-methyl-8-oxo	278–281	875
2-Chloro-6-dimethylamino-9-methyl	140–142	1147
8-Chloro-6-dimethylamino-3-methyl	223–225	1147
8-Chloro-6-dimethylamino-9-methyl	89–92	1147
6-Chloro-8-ethoxy-9-methyl-	143	905
2-Chloro-7-methyl-6-trimethylammonio	chlor. 178–179	1122
6-Chloro-2-methylsulfonyl	—	870
8-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	> 290	911

8-Chloro-1,2,3,6-tetrahydro-2,6-dioxo	—	920
8-Chloro-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	> 290	911
8-Chloro-1,2,3,6-tetrahydro-7-methyl-2,6-dioxo	—	1116
2-Chloro-1,6,8,9-tetrahydro-7-methyl-6-oxo-8-thioxo	> 300	1865
8-Chloro-1,2,3,6-tetrahydro-1,3,7-trischloromethyl-2,6-dioxo	123–124	1130
2-Chloro-6-trimethylammonio	bet. 190–191	1147
	chlor. > 300	1122
8-Chloro-6-trimethylammonio	bet. 205–207	1147
6-Chloroacetamido-9-methyl	—	1440
2-Chloromethyl-8-dimethylamino-1,6-dihydro-6-oxo	> 300	909
6-Cyano-8,9-dimethyl-2-trifluoromethyl	115–116	1004, 1878
6-Cyano-2-ethyl-8,9-dimethyl	119–120	1004, 1878
6-Cyano-9-methyl	153–154	1140
6-Cyano-3-oxido	316–318	1057
6-Cyano-2,8,9-trimethyl	157–159	1004, 1878
2,8-Dichloro-3,6-dihydro-3,7-dimethyl-6-oxo	—	1233
2,6-Dichloro-8,9-dihydro-7-methyl-8-oxo	240–242	1865
2,6-Dichloro-8,9-dihydro-7-methyl-8-thioxo	240–242	1865
2,8-Dichloro-6-dimethylamino-3-methyl	238	1147
2,8-Dichloro-6-dimethylamino-9-methyl	208–209	1147
2,8-Dichloro-6-trimethylammonio	bet. > 200	1147
6-Dichloromethyl-7,8-dihydro-9-methyl-8-oxo	189–191	1083
6-(Dicyano)methyl-9-phenyl	> 300	1067, 1079
6-Diethylamino-2-trifluoromethyl	350–352	1864
2,3-Dihydro-7-methoxyethyl-6-methylamino-2-thioxo	234–237	998
1,6-Dihydro-6-oxo-2-trifluoroacetamido	> 300	1444
1,6-Dihydro-6-oxo-2-(2,2,2,-trifluoroethylamino)	> 300	1444
8-Dimethylamino-1,6-dihydro-2-ethylthio-6-oxo	> 300	912
8-Dimethylamino-1,6-dihydro-2-methylthio-6-oxo	> 300	912
6-Dimethylamino-2-trifluoromethyl	302–303	2008
7-Ethyl-6-methyl-2-methylthio-8-trifluoromethyl	165–166	854
9-Ethyl-6-methyl-2-methylthio-8-trifluoromethyl	98–99	854
2-Fluoro-1,6-dihydro-6-thioxo	> 300	1124
2-Fluoro-6-dimethylamino	220	1124
2-Fluoro-6-hydrazino	142	1124
2-Fluoro-6-hydroxyamino	270	1124
2-Fluoro-6-methoxyamino	> 300	1124
2-Fluoro-6-(1-methylhydrazino)	270	1172
2-Fluoro-6-(*N*-methyl)hydroxyamino	242	1124
8-Fluoro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	245–250	1123
8-Fluoro-1,2,3,6-tetrahydro-1,3,7-trimethyl-2,6-dioxo	162–163	1123
2-Fluoro-6-trimethylammonio	bet.–	1124

cont.

TABLE 27. *(cont.)*

Purine	mp(°C)	Ref.
6-Fluorosulfonyl-3-oxido	160	1142
6-Methyl-2-methylthio-8-trifluoromethyl	152–153	854
6-Methylamino-2-trifluoromethyl	180–182	1864
6-[4-(*N*-Methyl)hydroxybutylamino]	162	1141
6-Methylthio-8-trifluoromethyl	238	840
6-(3-Methylureido)	270–275	837
6-Nitroso-3-oxido	Na > 300	1142, 1172
6-(3-Phenylureido)	320	837, 1498
6-(3-*n*-Propylureido)	205–206	837
1,2,3,6-Tetrahydro-1,3-dimethyl-7-methylsulfonylmethyl-2,6-dioxo	—	1343
1,2,3,6-Tetrahydro-8-iodo-2,6-dioxo	> 300	1351
1,2,3,6-Tetrahydro-1-methyl-8-nitro-2,6-dioxo	—	1116
1,6,7,8-Tetrahydro-1-methyl-8-oxo-6-thioxo	> 300	1249
1,2,3,6-Tetrahydro-8-nitro-2,6-dioxo	—	920
6-(2,2,2-Trifluoroethoxy)	218	1868

TABLE 28. ISOTOPICALLY LABELED PURINES

Purine	Atoms Labeled	Ref.
Unsubstituted	^{2}H-2	1562
	^{2}H-6	1048, 1052
	^{2}H-8	1050, 1052, 1056, 1562
		1056
	^{2}H-8, ^{2}H-9	1056, 1356
	^{3}H-8	1826
	^{15}N-1	1826
	^{15}N-3	1826
	^{15}N-7	1826
	^{15}N-9	1826
2-Methyl-	^{2}H-2	1050, 1056
6-Methyl-	^{2}H-8	1050
	^{2}H-2, ^{2}H-8	1056
8-Methyl-	^{2}H-6	1048, 1050
9-Isopropyl-	^{2}H-6	1056
	^{2}H-8	1056
9-*tert*-Butyl-	^{2}H-8	1056
	^{3}H-8	1056
2-Acetamido-7-benzyl-1,6-dihydro-6-oxo-	^{14}C-8	826
2-Acetamido-9-benzyl-1,6-dihydro-6-oxo-	^{14}C-8	826
2-Acetamido-1,6-dihydro-6-oxo-	^{14}C-8	826
Adenine	^{2}H-2	1562
	^{2}H-8	1155, 1562
	^{3}H-2	1356
	^{3}H-8	1356, 1559, 2036

	^{13}C-2	1562
	^{14}C-8	1562, 2033
	^{15}N-1	849, 1404, 1518, 1562
	^{15}N-3	849, 1562, 1774
	^{15}N-7	1562
	^{15}N-9	849, 1464, 1562
	$^{15}NH_2$	849, 1050, 1464, 1562
Adenine/3-benzyl-	^{15}N-3	1774
	$^{15}NH_2$	1464
Adenine/7-benzyl-	^{15}N-3	1774
Adenine/9-benzyl-	^{15}N-9	1464, 1522
	$^{15}NH_2$	1464
Adenine/8-methyl-	$^{15}NH_2$	1050
Adenine/9-methyl-	^{2}H-8	1091
2-Amino-	^{15}N-1	867
2-Amino-6-phenyl-	^{15}N-1	867
2-Amino-8-phenyl-	^{15}N-1	867
2-Amino-1,6,7,8-tetrahydro-3-oxido-6,8-dioxo-	^{14}C-8	828
6-Benzamido-	^{14}C-8	811
6-Benzamido-7-benzyl-	^{14}C-8	811
6-Benzamido-9-benzyl-	^{14}C-8	811
6-Benzylamino-	^{15}N-1	1464
	^{15}N-9	1464
2-Carbamoylethylthio-6,8,9-trimethyl-	^{14}C-8	841
2-Carbamoylmethylthio-6,8,9-trimethyl-	^{14}C-8	841
2-Chloro-	^{2}H-8	867
6-Chloro-	^{2}H-8	1155
	^{15}N-9	1464
2,6-Diamino-	$^{15}NH_2$	999
1,6-Dihydro-6-selenoxo-	^{2}H-2	1280
2,9-Dimethyl-8-methylthio-	^{14}C-8	878
6,9-Dimethyl-2-methylthio-	^{14}C-8	860
6-Dimethylamino-	$C^{2}H_3$	1814
2-Fluoro-	^{15}N-1	867
Guanine	^{3}H-8	1319
Guanine/3-methylbut-2-enyl-	^{18}O	1177
Hypoxanthine/1-methyl-	^{2}H-2	1402
Hypoxanthine/3-methyl-	^{2}H-2	1280, 1402
	^{2}H-8	1402
Hypoxanthine/7-methyl-	^{2}H-8	2017
Hypoxanthine/9-methyl-	^{3}H-8	1319
Hypoxanthine/1,3-dimethyl-	^{2}H-2	1280
Hypoxanthine/3,8-dimethyl-	^{2}H-2	1280
Hypoxanthine/1,3,7-trimethyl-	1-$C^{2}H_3$	843, 1337
	3-$C^{2}H_3$	1337
	7-$C^{2}H_3$	843, 1337
6-Mercapto-(1,6-Dhydro-6-thioxo-)	^{3}H-8	1399
	^{35}S	1189
6-Mercapto-1-methyl-	^{2}H-8	1322
3-methyl-	^{2}H-8	1280
8-methyl-	^{2}H-6	1050
6-Methoxy-	^{2}H-8	2017

cont.

TABLE 28. *(cont.)*

Purine	Atoms Labeled	Ref.
2-Methylthio-	^{2}H-8	867
8-Methylthio-	^{2}H-6	1155
2,3,7,8-Tetrahydro-2,8-dioxo-1,3,9-trimethyl-	$(C^{2}H_3)_3$	903
2,3,7,9-Tetrahydro-2,8-dioxo-1,3,7-trimethyl-	$(C^{2}H_3)_3$	903
Uric acid/1,3-dimethyl-	^{14}C-8	949
Xanthine	^{3}H-8	1327
Xanthine/3-oxido-	^{14}C-8	1699
Xanthine/1,3-dimethyl-	^{3}H-8	1236, 1327
	^{14}C-8	2035
Xanthine/3,7-dimethyl-	^{3}H-8	1327
Xanthine/1,3,7-trimethyl-	^{2}H-8	1077
	^{3}H-8	1326, 1327
	1-$C^{2}H_3$	843, 1337
	3-$C^{2}H_3$	1337
	7-$C^{2}H_3$	843, 1337

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

References

The numbering of the supplement reference list continues from that of the parent volume, the concluding reference of which is 829. It has been advantageous to make occasional use of some of the older references and these have been collected and are listed separately in abbreviated form at the end of the supplement reference list. The practice of dispensing with author's initials has been maintained, except where two or more workers with the same surname are listed, in which case identifying initials are used.

830. Wells, Garst, and Kramer, *J. Med. Chem.*, **24**, 954 (1981).
831. Garst, Kramer, Wu, and Wells, *J. Med. Chem.*, **19**, 499 (1976).
832. Daly, Padgett, and Shamim, *J. Med. Chem.*, **29**, 1305 (1986).
833. Hutzenlaub and Pfleiderer, *Justus. Liebigs Ann. Chem.*, **1979**, 1847.
834. Fenn and Lister, *J. Chem. Soc. Perkin Trans. I*, **1974**, 1300.
835. Montgomery and Hewson, *J. Med. Chem.*, **15**, 1189 (1972).
836. Badger and Barlin, *J. Chem. Soc. Perkin Trans. I*, **1976**, 151.
837. Dutta, Hong, Tritsch, Cox, Parthasarthy, and Chheda, *J. Med. Chem.*, **20**, 1598 (1977).
838. Birdsall, Lee, Delia, and Parham, *J. Org. Chem.*, **36**, 2635 (1971).
839. Gmeiner and Poulter, *J. Org. Chem.*, **15**, 1322 (1988).
840. Albert, *J. Chem. Soc. Perkin. Trans. I*, **1981**, 2974.
841. D. J. Brown and Stephanson, *Aust. J. Chem.*, **29**, 1031 (1976).
842. Smith, Robins, and Tolman, *J. Chem. Soc. Perkin Trans. I*, **1973**, 1855.
843. Rybar and Antos, *Collect. Czech. Chem. Commun.*, **35**, 1417 (1970).
844. Mornet, Leonard, Theiler, and Doree, *J. Chem. Soc. Perkin Trans. I*, **1984**, 879.
845. Ukena, Padgett, Hong, and Daly, *J. Med. Chem.*, **31**, 613 (1988).
846. Rybar, Stibranyi, and Lesko, *Collect. Czech. Chem. Commun.*, **43**, 3414 (1978).
847. Bhushan and Lister, *Aust. J. Chem.*, **29**, 891 (1976).
848. Bhushan, D. J. Brown, Lister, Stephanson, and Yoneda, *Aust. J. Chem.*, **28**, 2553 (1975).
849. Gonella, Nakanishi, Holtwick, Horowitz, Kanamori, Leonard, and Roberts, *J. Am. Chem. Soc.*, **105**, 2050 (1983).
850. Yoneda and Mera, *Chem. Pharm. Bull.*, **20**, 1815 (1972).
851. El Bayouki, Nielsen, and Pedersen, *Synthesis*, **1985**, 104.
852. El Bayouki, Nielsen, and Pedersen, *Justus Liebigs Ann. Chem.*, **1985**, 1223.
853. El Bayouki, Nielsen, and Pedersen, *J. Heterocycl. Chem.*, **22**, 853 (1985).
854. Fenn and Lister, *J. Chem. Soc. Perkin Trans. I*, **1975**, 485.
855. Satchell, *Chem. Ind. (London)*, **1974**, 683.

856. Melik-Organdzhanyan, Mirzoyan, and Aroyan, *Arm. Khim. Zh.*, **28**, 53 (1975).
857. D. J. Brown and Mori, *Aust. J. Chem.*, **38**, 467 (1985).
858. Chin, Hung, and Stock, *J. Org. Chem.*, **46**, 2203 (1981).
859. Rogers and Ulbricht, *J. Chem. Soc. (C)*, **1971**, 2364.
860. D. J. Brown, Jones, Angyal, and Grigg, *J. Chem. Soc. Perkin Trans. I*, **1972**, 1819.
861. Lee, Lam, and G. B. Brown, *J. Org. Chem.*, **40**, 1547 (1975).
862. Kelley, Krochmal, Linn, McLean, and Soroko, *J. Med. Chem.*, **31**, 607 (1988).
863. Kelley and Soroko, *J. Med. Chem.*, **29**, 1133 (1986).
864. Temple, Smith, Elliot, and Montgomery, *J. Med. Chem.*, **16**, 292 (1973).
865. Lidak, Schluke, Zarinya, and Poritere, *Khim. Geterotsikl. Soedin.*, **1971**, 262.
866. Badger, D. J. Brown, and Lister, *J. Chem. Soc. Perkin Trans. I*, **1973**, 1906.
867. Kos and Van der Plas, *J. Org. Chem.*, **45**, 2942 (1980).
868. Dyer, Emmett, Nyez, and Smith, *J. Heterocycl. Chem.*, **10**, 1043 (1973).
869. Keir and Wood, *J. Chem. Soc. Perkin Trans. I*, **1976**, 1847.
870. Giner-Sorolla, Segarro, and Brooks, *J. Med. Chem.*, **21**, 344 (1978).
871. Lister, *Aust. J. Chem.*, **32**, 2771 (1979).
872. Neiman, Bergmann, Lichtenberg, and Deutsch, *J. Chem. Soc. (C)*, **1971**, 1822.
873. Bergmann and Rahat, *J. Chem. Soc. Perkin Trans. I*, **1976**, 239.
874. Bergmann, Frank, Weiler-Feilchenfeld, and Tamir, *J. Org. Chem.*, **42**, 2470 (1977).
875. Kos, Henk, Van der Plas, and Blees, *J. Org. Chem.*, **48**, 850 (1983).
876. Kleiner, *J. Chem. Soc. Perkin Trans. I*, **1973**, 739.
877. Kleiner, *J. Chem. Soc. Perkin Trans. I*, **1973**, 2019.
878. D. J. Brown and Stephanson, Aust. *J. Chem.*, **27**, 1371 (1974).
879. R. Brown, Joseph, Leigh and Swain, *J. Chem. Soc. Perkin Trans. I*, **1977**, 1003.
880. Levin, Kalmus, and Bergmann, *J. Org. Chem.*, **25**, 1752 (1960).
881. Ram, Pandey, and Vlietink, *J. Heterocycl. Chem.*, **19**, 153 (1982).
882. Bergmann, Rahat, Reichman, and Tamir, *J. Org. Chem.*, **40**, 2652 (1975).
883. Bergmann, Chen, and Rahat, *J. Chem. Soc. Perkin Trans I*, **1976**, 90.
884. Schmidt and Townsend, *J. Heterocycl. Chem.*, **10**, 687 (1977).
885, Schmidt and Townsend, *J. Chem. Soc. Perkin Trans. I*, **1975**, 1257.
886. Reichman, Bergmann, and Neiman, *J. Org. Chem.*, **38**, 3367 (1973).
887. Reichman, Bergmann, Lichtenberg, and Neiman, *J. Chem. Soc. Perkin Trans. I*, **1973**, 793.
888. Fenn and Lister, *Aust. J. Chem.*, **33**, 1611 (1980).
889. Lister, *Aust. J. Chem.*, **32**, 387 (1979).
890. Reichman, Bergmann, Lichtenberg, and Neiman, *J. Org. Chem.*, **38**, 2066 (1973).
891. Pfleiderer, *Justus Liebigs Ann. Chem.*, **1974**, 2030.
892. Youssefyeh, *J. Chem. Soc. Perkin Trans. I*, **1975**, 1857.
893. Daly, Padgett, Shamim, Butts-Lamb, and Waters, *J. Med. Chem.*, **28**, 487 (1985).
894. Jacobsen, Kirk, Padgett, and Daly, *J. Med. Chem.*, **28**, 1335 (1985).
895. Senga, Shimizu, and Nishigawa, *Chem. Pharm. Bull.*, **25**, 495 (1977).
896. Nagel and Van der Plas, *Chem. Pharm. Bull.*, **23**, 2678 (1975).
897. Daly, Padgett, and Shamim, *J. Med. Chem.*, **29**, 1520 (1986).
898. Higuchi, Nagamura, and Yoneda, *Heterocycles*, **4**, 977 (1976).
899. Yoneda, Higuchi, and Kawamura, *Heterocycles*, **4**, 1659 (1976).
900. Yoneda and Higuchi, *J. Chem. Soc. Perkin Trans. I*, **1977**, 1336.

901. Lister and Bhushan, Aust. *J. Chem.*, **31**, 381 (1978).
902. Wawzonek, *J. Org. Chem.*, **41**, 310 (1976).
903. Armarego and Reece, *J. Chem. Soc. Perkin Trans. I*, **1976**, 1414.
904. Wong, M. S. Brown, Matsumoto, Oesterlin, and Rapoport, *J. Am. Chem. Soc.*, **93**, 4633 (1971).
905. D. J. Brown and Lynn, *J. Chem. Soc. Perkin Trans. I*, **1974**, 349.
906. Wegner and Rapoport, *J. Org. Chem.*, **42**, 3065 (1977).
907. Garin, Melendez, Merchan, and Tejero, *Synthesis*, **1985**, 86.
908. Kavai, Mead, Drobniak, and Zakrzewski, *J. Med. Chem.*, **18**, 272 (1975).
909. Yoneda and Matsumura, *J. Chem. Soc., Chem. Commun.*, **1972**, 606.
910. Yoneda, Higuchi, Matsumura, and Senga, *Bull Chem. Soc. Jpn.*, **46**, 1836 (1973).
911. Yoneda and Higuchi, *Chem. Pharm. Bull.*, **22**, 1658 (1974).
912. Yoneda, Higuchi, and Hayakawa, *Synthesis*, **1975**, 264.
913. Yoneda and Nagamatsu, *J. Chem. Soc. Perkin Trans. I*, **1976**, 1547.
914. Yoneda and Nagamatsu, *Bull. Chem. Soc. Jpn.*, **48**, 2884 (1975).
915. Ehrlich and Sachs, *Ber. Dtsch. Chem. Ges.*, **32**, 234 (1899).
916. Rybar and Stybranyi, *Collect. Czech. Chem. Commun.*, **37**, 2630 (1972).
917. Fuchs, Gottlieb, and Pfleiderer, *Chem. Ber.*, **111**, 982 (1978).
918. Youssefyeh and Kalmus, *J. Chem. Soc. Chem. Commun.*, **1969**, 1426.
919. Zvilichovsky, *Tetrahedron*, **33**, 2259 (1977).
920. Zvilichovsky and G. B. Brown, *J. Org. Chem.*, **37**, 1871 (1972).
921. Zvilichovsky, Garbi, and Nemes, *J. Heterocycl. Chem.*, **19**, 205 (1982).
922. Hirota, Sugiyama, Kitadi, Senda, and Maki, *J. Chem. Soc. Perkin Trans. I*, **1984**, 583.
923. Senga, Kanazawe, and Nishigaki, *J. Chem. Soc. Chem. Commun.*, **1976**, 155.
924. Israel, Berman, and Muhammad, *Org. Prep. Procedures Int.*, **4**, 83 (1972).
925. Senga, Ichiba, Kanazawa, and Nishigaki, *J. Heterocycl. Chem.*, **15**, 641 (1978).
926. Senga, Ichiba, Kanazawa, Nishigaki, Higuchi, and Yoneda, *Synthesis*, **1977**, 264.
927. Yoneda, Higuchi, and Nagamatsu, *J. Am. Chem. Soc.*, **96**, 5607 (1974).
928. Yoneda and Koga, *J. Heterocycl. Chem.*, **19**, 813 (1982).
929. Nishigaki, Ichiba, and Senga, *J. Heterocycl. Chem.*, **19**, 769 (1982).
930. Yoneda, Senga, and Nishigaki, *Chem. Pharm. Bull.*, **21**, 260 (1973).
931. E. C. Taylor and Yoneda, *J. Org. Chem.*, **37**, 4464 (1972).
932. Perini and Tieckelmann, *J. Org. Chem.*, **35**, 812 (1970).
933. Prasad, Sandhu, and Baruah, *J. Heterocycl. Chem.*, **21**, 267 (1984).
934. E. C. Taylor and Sowinski, *J. Org. Chem.*, **39**, 907 (1974).
935. Yoneda, Matsumoto, and Higuchi, *J. Chem. Soc. Chem. Commun.*, **1975**, 146.
936. Yoneda, Kawamura, Matsumoto, and Higuchi, *J. Chem. Soc. Perkin Trans. I*, **1977**, 2285.
937. Yoneda, Matsumoto, and Higuchi, *J. Chem. Soc. Chem. Commun.*, **1974**, 551.
938. Rybar, Stibranyi, and Uher, *Collect. Czech. Chem. Commun.*, **37**, 3936 (1972).
939. Takayama, Ashizawa, Suzuki, and Sekiya, *Chem. Pharm. Bull.*, **22**, 1200 (1974).
940. Coxon, Fatiadi, Sniegoski, Hertz, and Schaffer, *J. Org. Chem.*, **42**, 3132 (1977).
941. Fujii and Satio, *Chem. Pharm. Bull.*, **21**, 1954 (1973).
942. Hayashi, Shimada, Matsuoka, and Miya, *Yakugaku Zasshi*, **99**, 207 (1979).
943. Andersen, Hamad, and Pedersen, *Justus Liebigs Ann. Chem.*, **1986**, 1255.
944. Ohtsuka and Sugimoto, *Bull. Chem. Soc. Jpn.*, **43**, 3305 (1970).

945. Hartman, Biffar, Weinstock, and Tull, *J. Org. Chem.*, **43**, 960 (1978).
946. Taylor, Beardsley, and Maki, *J. Org. Chem.*, **36**, 3211 (1971).
947. Kelley and Schaeffer, *J. Heterocycl. Chem.*, **23**, 271 (1986).
948. Hutzenlaub, Barlin, and Pfleiderer, *Angew. Chem.*, **81**, 624 (1969).
949. Hutzenlaub, Yamamoto, Barlin, and Pfleiderer, *Chem. Ber.*, **106**, 3203 (1973).
950. Yoneda, Sakuma, Ueno, and Nishigaki, *Chem. Pharm. Bull.*, **21**, 926 (1973).
951. Yoneda and Nagamatsu, *Heterocycles*, **4**, 749 (1976).
952. D. J. Brown and Sugimoto, *J. Chem. Soc.* (*C*), **1971**, 2616.
953. Ohtsuka, *Bull. Chem. Soc. Jpn.*, **46**, 506 (1973).
954. Enoki, Genda, and Fukui, Japan Patent 7.606.986 (1976); *Chem. Abstr*, **84**, 180299v (1976).
955. Omura, Marumoto, and Furukawa, *Chem. Pharm. Bull.*, **29**, 1970 (1981).
956. Nielsen and Pedersen, *Tetrahedron*, **38**, 1435 (1982).
957. Watson, *J. Org. Chem.*, **39**, 2911 (1974).
958. Watson and G. B. Brown, *J. Org. Chem.*, **37**, 1867 (1972).
959. Mackenzie, Shaw, and Robinson, *J. Chem. Soc. Perkin Trans. I*, **1977**, 1094.
960. Baig, Stevens, and Stone, *J. Chem. Soc. Perkin Trans. I*, **1982**, 1811.
961. Scheiner, Arwin, Eliacin, and Tu, *J. Heterocycl. Chem.*, **22**, 1435 (1985).
962. Parkin and Harnden, *J. Heterocycl. Chem.*, **19**, 33 (1982).
963. Yamazaki, Okutsu, and Yamada, *Nucl. Acid Res.*, **3**, 251 (1976).
964. Ienaga and Pfleiderer, *Tetrahedron Lett.*, **19**, 1447 (1978).
965. Groziak, Chern, and Townsend, *J. Org. Chem.*, **51**, 1065 (1986).
966. Panzica and Townsend, *J. Heterocycl. Chem.*, **9**, 623 (1972).
967. McKenzie and Rolfes, *J. Heterocycl. Chem.*, **24**, 859 (1987).
968. Wilson, Newsnow, and G. B. Brown, *J. Org. Chem.*, **38**, 3046 (1973).
969. Itaya and Ogawa, *Tetrahedron Lett.*, **19**, 2907 (1978).
970. Groziak, and Townsend, *J. Org. Chem.*, **51**, 1277 (1986).
971. Kadir, Shaw, and Wright, *J. Chem. Soc. Perkin Trans. I*, **1979**, 2738.
972. Meyer, Schuman, and R. K. Robins, *J. Am. Chem. Soc.*, **96**, 4962 (1974).
973. Huang, Okamoto, Maeda, and Kawazoe, *Chem. Pharm. Bull.*, **22**, 1938 (1974).
974. Fujii, Itaya, Mohri, and Saito, *J. Chem. Soc. Chem. Commun.*, **1973**, 917.
975. Fujii, Saito, and Kawanishi, *Tetrahedron Lett.*, **19**, 5007 (1978).
976. Montgomery and Thomas, *J. Med. Chem.*, **15**, 182 (1972).
977. Saito and Fujii, *J. Chem. Soc. Chem. Commun.*, **1979**, 135.
978. Fujii, Tanaka, Mohri, and Itaya, *Chem. Pharm. Bull.*, **22**, 2211 (1974).
979. Fujii, Satio, and Itaya *Chem. Pharm. Bull.*, **19**, 1731 (1971).
980. Itaya, Saito, Kawatsu, and Fujii, *Chem. Pharm. Bull.*, **23**, 2643 (1975).
981. Fujii, Itaya, Wu, and Tanaka, *Tetrahedron*, **27**, 2414 (1971).
982. Fujii, Itaya, Saito, and Kawakatsu, *Chem. Pharm. Bull.*, **32**, 484 (1984).
983. Fujii, Wu, and Itaya, *Chem. Pharm. Bull.*, **21**, 1835 (1973).
984. Leonard, MacDonald, and Reichman, *Proc. Natl. Acad. Sci. USA*, **67**, 93 (1970).
985. Leonard, MacDonald, Henderson, and Reichman, *Biochemistry*, **10**, 3335 (1971).
986. Duke, Liepa, MacLeod, Letham, and Parker, *J. Chem. Soc. Chem. Commun.*, **1975**, 964.
987. Mackenzie and Shaw, *J. Chem. Soc. Perkin Trans. I*, **1978**, 1381.
988. Hattori, Ienaga, and Pfleiderer, *Justus Liebigs Ann. Chem.*, **1978**, 1976.
989. Rousseau, Panzica, Reddick, R. K. Robins, and Townsend, *J. Org. Chem.*, **35**, 631 (1970).

990. Watson, *J. Org. Chem.*, **42**, 1610 (1977).
991. Edenhofer, *Helv. Chim. Acta*, **58**, 2192 (1975).
992. Hosmane, Bakthavachalam, and Leonard, *J. Am. Chem. Soc.*, **104**, 235 (1982).
993. Huynh-Dinh, Kolb, Gouyette, and Igolen, *J. Heterocycl. Chem.*, **12**, 111 (1975).
994. Ienaga and Pfleiderer, *Justus Liebigs Ann. Chem.*, **1979**, 1872.
995. Bartlett, Cook, Holman, McComas, Nowoswait, and Poonian, *J. Med. Chem.*, **24**, 947 (1981).
996. Cook and Bartlett, *J. Org. Chem.*, **45**, 4020 (1980).
997. Itaya and Harada, *Tetrahedron Lett.*, **23**, 2203 (1982).
998. Grozinger and Onan, *J. Heterocycl. Chem.*, **23**, 737 (1986).
999. Kos and Van der Plas, *J. Org. Chem.*, **48**, 1207 (1983).
1000. Kigasawa, Ohkubo, Shimizu, Kohagizawa, and Shoji, *Chem. Pharm. Bull.*, **22**, 2448 (1974).
1001. T. Brown, Kadir, Mackenzie, and Shaw, *J. Chem. Soc. Perkin Trans. I*, **1979**, 3107.
1002. Mackenzie, and Shaw, *J. Chem. Soc. Chem. Commun.*, **1978**, 882.
1003. Montero, Dhainaut, and Imbach, *J. Heterocycl. Chem.*, **15**, 929 (1978).
1004. Booth and Proenca, *J. Chem. Soc. Chem. Commun.*, **1981**, 788.
1005. Abramova, Kutelia, and Feklistova, *Khim-Farm. Zh.*, **9**, 32 (1975).
1006. Kuznetsov and Remizov, *Khim. Geterotsikl. Soedin.*, **1972**, 1430.
1007. Bridson, Davis, and Rener, *J. Heterocycl. Chem.*, **22**, 753 (1985).
1008. Czarnick and Leonard, *J. Org. Chem.*, **45**, 3514 (1980).
1009. Huang, Maeda, Okamoto, and Kawazoe, *Tetrahedron*, **31**, 1363 (1975).
1010. Temple, Kussner, and Montgomery, *J. Org. Chem.*, **36**, 3502 (1971).
1011. Yamada and Okamoto, *Chem. Pharm. Bull.*, **20**, 623 (1972).
1012. Yamada and Okamoto, *Yakugaku Zasshi*, **95**, 493 (1975).
1013. Yamada, Hirobe, Higashiyama, Takahashi, and Suzuki, *Tetrahedron Lett.*, **19**, 4039 (1978).
1014. Ferris, Donner, and Lotz, *J. Am. Chem. Soc.*, **94**, 6968 (1974).
1015. Yamada, Hirobe, Higashiyama, Takahashi, and Suzuki, *J. Am. Chem. Soc.*, **100**, 4617 (1978).
1016. Mikstais and Apene, *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki*, **52**, 53 (1975); *Chem. Abstr.*, **82**, 156381 (1975).
1017. Sekiya, and Suzuki, *Chem. Pharm. Bull.*, **20**, 209 (1972).
1018. Sekiya, Suzuki, and Terao, *Chem. Pharm. Bull.*, **24**, 1331 (1976).
1019. Sekiya and Suzuki, *Chem. Pharm. Bull.*, **23**, 2401 (1975).
1020. Andersen and Pedersen, *Justus Liebigs Ann. Chem.*, **1985**, 921.
1021. Okutsu and Yamazaki, *Nucl. Acid Res.*, **3**, 231 (1976).
1022. Ferris and Hagan, *Tetrahedron*, **40**, 1093 (1984).
1023. Sanchez, Ferris, and Orgel, *J. Mol. Biol.*, **30**, 223 (1967).
1024. Schuman, Shearin, and Tull, *J. Org. Chem.*, **44**, 4532 (1979).
1025. Schwartz, as detailed in reference 1022.
1026. Simionescu, Lixandru, Gorea, and Gorduza, *C. R. Acad. Sci. Ser. C.*, **280**, 685 (1975).
1027. Ferris and Kuder, *J. Am. Chem. Soc.*, **92**, 2527 (1970).
1028. Bassott and Krumdieck, *Biochemistry*, **18**, 3501 (1979).
1029. Yamazaki, Kumashiro, and Takenishi, *Chem. Pharm. Bull.*, **17**, 1128 (1969).
1030. Yamazaki and Okutsu, *J. Heterocycl. Chem.*, **15**, 353 (1978).
1031. Ringertz, *Jerusalem Symp. Quantum. Chem. Biochem.*, **4**, 61 (1971).
1032. Watson, Sweet, and Marsh, *Acta Crystallogr., Sect. B.*, **19**, 573 (1965).
1033. Pullman and Pullman, *Adv. Heterocycl. Chem.*, **13**, 77 (1971).

1034. Lin, Yu, Peng, Akiyama, Li, Lee, and Le Breton, *J. Am. Chem. Soc.*, **102**, 4267 (1980).
1035. Gonella and Roberts, *J. Am. Chem. Soc.*, **104**, 3162 (1982).
1036. Pugmire and Grant, *J. Am. Chem. Soc.*, **93**, 1880 (1971).
1037. Schumacher and Günther, *J. Am. Chem. Soc.*, **104**, 4167 (1982).
1038. Wagner and Von Philipsborn, *Helv. Chim. Acta.*, **54**, 1543 (1971).
1039. Benoit and Fréchette, *Can. J. Chem.*, **62**, 995 (1984).
1040. Benoit, Boulet, Seguin, and Fréchette, *Can. J. Chem.*, **63**, 1228 (1985).
1041. Spencer, Barton, Smith, Wolback, Powell, Kirschenbaum, Firth, Harris, and Judge, *Can. J. Chem.*, **61**, 2695 (1983).
1042. Neiman, *J. Chem. Soc. Perkin Trans. II*, **1972**, 585.
1043. Kamiya and Akahori, *Chem. Pharm. Bull.*, **21**, 1470 (1973).
1044. Pullman, Berthod, Bergmann, Neiman, Weiler-Feilchenfeld, and Bergmann, *Tetrahedron*, **26**, 1483 (1970).
1045. Chan and Kreishman, *J. Am. Chem. Soc.*, **92**, 1102 (1970).
1046. Neiman, *Isr. J. Chem.*, **10**, 819 (1972).
1047. Pendergast, *J. Chem. Soc. Perkin Trans. I*, **1975**, 2240.
1048. Pendergast, *J. Chem. Soc. Perkin Trans. I*, **1973**, 2759.
1049. Albert and Pendergast, *J. Chem. Soc. Perkin Trans. I*, **1973**, 1794.
1050. Kos, Van der Plas, and Veldhuizen, *J. Org. Chem.*, **44**, 3140 (1979).
1051. Kos, Jongejan, Van der Plas, and Veldhuizen, *Recl. Trav. Chim. Pays Bas*, **104**, 302 (1985).
1053. Linschitz and Connolly, *J. Am. Chem. Soc.*, **90**, 2979 (1968).
1054. Kan and Li, *J. Am. Chem. Soc.*, **92**, 4823 (1970).
1055. Wang and Li, *J. Am. Chem. Soc.*, **90**, 5069 (1968).
1056. Elvidge, J. R. Jones, O'Brien, Evans, and Sheppard, *J. Chem. Soc. Perkin II*, **1973**, 1889.
1057. Giner-Sorolla, Gryte, Cox, and Parham, *J. Org. Chem.*, **36**, 1228 (1971).
1058. E. C. Taylor and Martin, *J. Am. Chem. Soc.*, **94**, 2874 (1972).
1059. E. C. Taylor and Martin, *J. Am. Chem. Soc.*, **96**, 8095 (1974).
1060. Wanner, Hageman, Koomen, and Pandit, *Recl. Trav. Chim. Pays. Bas.*, **97**, 211 (1978).
1061. McKenzie and Glass, *J. Heterocycl. Chem.*, **24**, 1551 (1987).
1062. Bergstrom and Reday, *Tetrahedron Lett.*, **23**, 4191 (1982).
1063. Công-Danh, Beaucourt, and Pichet, *Tetrahedron Lett.*, **20**, 3159 (1979).
1064. Công-Danh, Beaucourt, and Pichet, *Tetrahedron Lett.*, **20**, 2385 (1979).
1065. Barton, Hedgecock, Lederer, and Motherwell, *Tetrahedron Lett.*, **20**, 279 (1979).
1066. Nair, Richardson, and Coffman, *J. Org. Chem.*, **47**, 4520 (1982).
1067. Hayashi, Shimada, and Watanabe, *Yakugaku Zasshi*, **99**, 205 (1979).
1068. Hamamichi and Miyasaki, *Tetrahedron Lett.*, **26**, 4743 (1985).
1069. Odijk and Koomen, *Tetrahedron*, **41**, 1893 (1985).
1070. Nair and Chamberlain, *J. Am. Chem. Soc.*, **107**, 2183 (1985).
1071. Nair and Chamberlain, *J. Am. Chem. Soc.*, **50**, 5069 (1985).
1072. Sugimura and Takei, *Bull. Chem. Soc. Jpn.*, **58**, 664 (1985).
1073. Lam and Parham, *J. Am. Chem. Soc.*, **97**, 2839 (1975).
1074. Maeda, Nushi, and Kawazoe, *Tetrahedron*, **30**, 2677 (1974).
1075. Kawazoe, Maeda, and Nushi, *Chem. Pharm. Bull.*, **20**, 1341 (1972).
1076. Araki, Maeda, and Kawazoe, *Tetrahedron*, **32**, 337 (1976).
1077. Zady and Wong, *J. Am. Chem. Soc.*, **99**, 5096 (1977).

1078. Christensen, Meyer, Miller, Simon, and R. K. Robins, *Biochemistry*, **14**, 1490 (1975).
1079. Hayashi and Shimada, *Yakugaku Zasshi*, **99**, 201 (1979).
1080. Giner-Sorolla, McCravey, Longley-Cook, and Burchenal, *J. Med. Chem.*, **16**, 984 (1973).
1081. Hampton, *J. Heterocycl. Chem.*, **11**, 255 (1974).
1082. Ortoleva, *Gazz. Chim. Ital.*, **30**, 509 (1900); King, *J. Am. Chem. Soc.*, **66**, 1894 (1994).
1083. Barak and Agranat, *Experientia*, **41**, 248 (1985).
1084. Barak and Agranat, *Nouv. J. Chim.*, **5**, 491 (1981).
1085. Van der Plas, *Acc. Chem. Res.*, **11**, 462 (1978).
1086. Abdulla and Brinkmeyer, *Tetrahedron*, **35**, 1675 (1979).
1087. Stanovnik, Tišler, Hribar, Barlin, and D. J. Brown, *Aust. J. Chem.*, **34**, 1729 (1981).
1088. Bergmann, Tamir, Neiman, and Lichtenberg, *Tetrahedron*, **30**, 3045 (1974).
1089. Lam and Parham, *Heterocycles*, **9**, 287 (1978).
1090. Pugmire, Grant, Townsend, and R. K. Robins, *J. Am. Chem. Soc.*, **95**, 2791 (1973).
1091. Kos and Van der Plas, *J. Org. Chem.*, **46**, 5000 (1981).
1092. Nair and Richardson, *Tetrahedron Lett.*, **20**, 1181 (1979).
1093. Leonard and Bryant, *J. Org. Chem.*, **44**, 4612 (1979).
1094. Nair and Richardson, *J. Org. Chem.*, **45**, 3969 (1980).
1095. Nair, Young, and DeSilvia, *J. Org. Chem.*, **52**, 1344 (1987).
1096. Nair and Young, *J. Org. Chem.*, **49**, 4340 (1984).
1097. Henderson, Frihart, Leonard, Schmitz, and Skoog, *Phytochemistry*, **14**, 1687 (1975).
1098. Kozlova, Nikolaeva, Ovcharova, Persiyanova, and Golovchinskaya, *Khim-Farm. Zh.*, **8**, 32 (1974).
1099. Elad and Rosenthal, *J. Chem. Soc. Chem. Commun.*, **1969**, 905.
1100. M. J. Robins, Hatfield, Balzarini, and DeClercq, *J. Med. Chem.*, **27**, 1486 (1984).
1101. Leonard and Ito, *J. Am. Chem. Soc.*, **95**, 4010 (1973).
1102. Ohtsuka, *Bull. Chem. Soc. Jpn.*, **43**, 3909 (1970).
1103. Ohno, Yagisawa, Shibehara, Kondo, and Maeda, *J. Am. Chem. Soc.*, **96**, 4326 (1974).
1104. Nakamura, Koyama, Iitaka, Ohno, Yakisawa, Kondo, Maeda, and Umezawa, *J. Am. Chem. Soc.*, **96**, 4327 (1974).
1105. Nair and Buenger, *Synthesis*, **1988**, 848.
1106. Chern, Lee, Wise, and Townsend, *J. Org. Chem.*, **53**, 5617 (1988).
1107. Senga, Nishigawa, Higuchi, and Yoneda, *Chem. Pharm. Bull.*, **20**, 1473 (1972).
1108. Townsend, in *Nucleic Acid Chemistry; Improved New Synthetic Procedures, Methods and Techniques*, Part 2, L. B. Townsend and R. S. Tipson, Eds., Wiley, New York, 1078, pp. 589–594.
1109. M. J. Robins and Uznanski, *Can. J. Chem.*, **59**, 2601 (1981).
1110. Gutorova and Golovchinskaya, *Khim-Farm. Zh.*, **7**, 27 (1973).
1111. Castagnino, Corsano, Barton, and Zard, *Tetrahedron Lett.*, **27**, 6337 (1986).
1112. Gutorova and Golovchinskaya, *USSR Patent* 311917 (1971); *Chem. Abstr.*, **75**, *151839e* (1971).
1113. Natsutavicus and Love, *J. Heterocycl. Chem.*, **11**, 77 (1974).
1114. Gomez, Greenbaum, and Giner-Sorolla, *J. Heterocycl. Chem.*, **12**, 273 (1975).
1115. M. J. Robins and Uznanski, *Can. J. Chem.*, **59**, 2608 (1981).
1116. Birdsall, Wölcke, Lee, and G. B. Brown, *Tetrahedron*, **27**, 5969 (1971).
1117. Huang, Avery, Blakley, Secrist, and Montgomery, *J. Med. Chem.*, **27**, 800 (1984).
1118. Agasimundin, Oakes, Kostuba, and Leonard, *J. Org. Chem.*, **56**, 2468 (1985).

1119. McKenzie and Epstein, *J. Org. Chem.*, **47**, 4881 (1981).
1120. McKenzie and Cassity, *J. Heterocycl. Chem.*, **20**, 1415 (1983).
1121. M. J. Robins, Barr, and Giziewicz, *Can. J. Chem.*, **60**, 554 (1982).
1122. Kiburis and Lister, *J. Chem. Soc. (C)*, **1971**, 3942.
1123. Kobayashi, Kumadaki, Ohsawa, and Murakami, *J. Chem. Soc., Chem. Commun.*, **1976**, 430.
1124. Giner-Sorolla and Burchenal, *J. Med. Chem.*, **14**, 816 (1971).
1125. Montgomery, Hewson, and Laseter, *J. Med. Chem.*, **18**, 571 (1975).
1126. Montgomery and Hewson, *J. Heterocycl. Chem.*, **9**, 445 (1972).
1127. Ogilvie, Nguyen-Ba, Gillen, Radatus, Cheriyan, Hanna, Smith, and Galloway, *Can. J. Chem.*, **62**, 241 (1984).
1128. Naik, Witkowski, and R. K. Robins, *J. Org. Chem.*, **38**, 4353 (1973).
1129. Ryu and McCoss, *J. Org. Chem.*, **46**, 2819 (1981).
1130. Ottinger, Boulvin, Reisse, and Chierdoglu, *Tetrahedron*, **21**, 3435 (1965).
1131. Holmes and Leonard, *J. Org. Chem.*, **41**, 568 (1976).
1132. Eckstein and Drabczynska, *Synthesis*, **1983**, 577.
1133. Piper, Laseter, Johnston, and Montgomery, *J. Med. Chem.*, **23**, 1136 (1980).
1134. Kobayashi, Yamamoto, Asai, and Nakano, *J. Chem. Soc. Perkin Trans. I*, **1980**, 2755.
1135. Zylber, Zylber, Chiaroni, and Riche, *Tetrahedron Lett.*, **25**, 3853 (1984).
1136. Wrona, Owens, and Dryhurst, *J. Electroanal. Chem.*, **105**, 295 (1979).
1137. Poje, Rocic, Vicokovic, and Bruvo, *J. Chem. Soc., Chem. Commun.*, **1982**, 1338.
1138. Seyama, Akahori, Sakata, Misumi, Aida, and Nagaka, *J. Am. Chem. Soc.*, **110**, 2192 (1988).
1139. Seden and Turner, *J. Heterocycl. Chem.*, **12**, 1045 (1975).
1140. Barlin and Young, *J. Chem. Soc. Perkin Trans. I*, **1972**, 1269.
1141. Griengel, Hayden, and Plessing, *J. Heterocycl. Chem.*, **21**, 333 (1984).
1142. Giner-Sorolla, *J. Heterocycl. Chem.*, **8**, 651 (1971).
1143. Seela and Menkhoff, *Justus Liebigs Ann. Chem.*, **1982**, 813.
1144. Timofeeva, Tikhonova, Muravich-Aleksandr, and El'tsov, *Zh. Obshch. Khim.*, **44**, 2013 (1974).
1145. Neiman, *Experientia*, **35**, 1418 (1979).
1146. Kelley and McClean, *J. Heterocycl. Chem.*, **23**, 1189 (1986).
1147. Kiburis and Lister, *J. Chem. Soc. (C)*, **1971**, 1587.
1148. Chung, Earl, and Townsend, *J. Org. Chem.*, **45**, 4056 (1980).
1149. Kelley, Lin, Krochmal, and Selway, *J. Med. Chem.*, **31**, 2001 (1988).
1150. Barlin and Young, *J. Chem. Soc. (B)*, **1971**, 821.
1151. Fawcett and Wright, *Phytochemistry*, **7**, 1719 (1968).
1152. Rothwell and Wright, *Proc. Roy. Soc. (B)*, **167**, 202 (1967).
1153. M. D. Taylor, Moos, Hamilton, Szotek, Patt, Badger, Bristol, Bruns, Heffner, and Mertz, *J. Med. Chem.*, **29**, 346 (1986).
1154. Dipple, Brookes, McIntosh, and Rayman, *Biochemistry*, **10**, 4323 (1971).
1155. Kos, Van der Plas, and Veldhuizen, *Recl. Trav. Chim. Pyas-Bas.*, **99**, 267 (1980).
1156. Werner and Hoffmann, *Arch. Pharm.*, **307**, 301 (1974).
1157. Adamiak, Biala, and Skalski, *Nucl. Acid Res.*, **13**, 2989 (1985).
1158. Pitha, Pitha, and Stuart, *Biochemistry*, **10**, 4595 (1971).
1159. Bryant, Keyser, and Barrio, *J. Org. Chem.*, **44**, 3733 (1979).
1160. Giller, Getsova, Govcharova, Petrulyanis, Miranova, Nazarova, and Bruk, *Khim. Geterotsikl. Soedin.*, **10**, 1680 (1974).

1161. Montgomery and Thomas, *J. Org. Chem.*, **43**, 541 (1978).
1162. Kelley, Krochmal, Lin, McClean, and Soroko, *J. Med. Chem.*, **31**, 1005 (1988).
1163. Takemo, Kawakabo, and Kondo, *Bull. Chem. Soc. Jpn.*, **44**, 1718 (1971).
1164. Muravich-Aleksandr, El'tsov, and El Sakka, *Zh. Org. Khim.*, **8**, 1110 (1972).
1165. Dutta, Tritsch, Cox, and Chheda, *J. Med. Chem.*, **18**, 780 (1975).
1166. Scheinfeld, Parham, and G. B. Brown, *J. Heterocycl. Chem.*, **19**, 1231 (1982).
1167. Wright and Dudycz, *J. Med. Chem.*, **27**, 175 (1984).
1168. Focher, Hildebrand, Freese, Giarrocchi, Noonan, Sangalli, Brown, Spadari, and Wright, *J. Med. Chem.*, **31**, 1496 (1988).
1169. Gorzyca, Zecj, Krupinska, and Czarnecki, *Farmaco. Ed. Sci.*, **29**, 802 (1974).
1170. Nishigaki, Senga, and Yoneda, *Chem. Pharm. Bull.*, **19**, 1526 (1971).
1171. Tindall, R. K. Robins, and Tolman, *J. Org. Chem.*, **37**, 3985 (1972).
1172. Giner-Sorolla, Longley-Cook, McCravey, G. B. Brown, and Burchenal, *J. Med. Chem.*, **16**, 365 (1973).
1173. Sasaki, Minamoto, Yamashita, and Fujika, *J. Org. Chem.*, **47**, 4465 (1982).
1174. Miller and Miller, *Pharmacol. Rev.*, **18**, 805 (1966).
1175. Weisburger and Weisburger, *Adv. Cancer Res.*, **5**, 331 (1958).
1176. Barlin and Fenn, *Aust. J. Chem.*, **36**, 633 (1983).
1177. Frihart and Leonard, *J. Am. Chem. Soc.*, **96**, 5894 (1974).
1178. Leonard and Frihart, *J. Am. Chem. Soc.*, **95**, 7174 (1973).
1179. Kjellberg, Liljenberg, and Johansson, *Tetrahedron Lett.*, **27**, 877 (1986).
1180. Holmes and Leonard, *J. Org. Chem.*, **43**, 516 (1978).
1181. Buehler and Pearson in *Survey of Organic Synthesis*, Wiley-Interscience, YN, 1970, p. 455.
1182. Badger and Barlin, *J. Chem. Soc. Perkin Trans. II*, **1974**, 1854.
1183. Salamone and Jordan, *Biochemistry*, **21**, 6283 (1982).
1184. Harnden, Jarvest, Bacon, and Boyd, *J. Med. Chem.*, **30**, 1636 (1987).
1185. Schmidt, Manolson, Angelides, and Poole, *FEBS Lett.*, **129**, 305 (1981).
1186. Marburg, Jorn, and Toman, *J. Heterocycl. Chem.*, **19**, 671 (1982).
1187. Israel, Muhammad, and Modest, *J. Heterocycl. Chem.*, **8**, 1019 (1971).
1188. Badger, D. J. Brown, and Lister, *J. Chem. Soc. Perkin Trans. I*, **1974**, 152.
1189. Singin and Safanova, *Khim-Farm. Zh.*, **9**, 24 (1975).
1190. Townsend and Milne, *J. Heterocycl. Chem.*, **7**, 753 (1970).
1191. Milne and Townsend, *J. Heterocycl. Chem.*, **8**, 379 (1971).
1192. Milne and Townsend, *J. Med. Chem.*, **17**, 263 (1974).
1193. Spies, *Z. Chem.*, **15**, 315 (1975).
1194. Chu, Shiue, and Chu, *J. Med. Chem.*, **17**, 406 (1974).
1195. Chu, Shiue, and Chu, *J. Med. Chem.*, **18**, 559 (1975).
1196. Lin, Cheng, Ishiguro, and Sartorelli, *J. Med. Chem.*, **28**, 1481 (1985).
1197. Jacobsen, Kirk, Padgett, and Daly, *J. Med. Chem.*, **28**, 1341 (1985).
1198. Eckstein and Drabczynska, *Synthesis*, **1970**, 581.
1199. Lachman and Cohen, *Isr. J. Chem.*, **6**, 131 (1968).
1200. Agranat and Barak, *Heterocycles*, **11**, 213 (1978).
1201. Imoto and Takemoto, *Synthesis*, **1970**, 173.
1202. Hino, Irie, and Uno, *Chem. Pharm. Bull.*, **23**, 1969 (1975).
1203. Uno, Irie, and Hino, *Chem. Pharm. Bull.*, **23**, 450 (1975).

1204. Leonard, Playtis, Skoog, and Schmitz, *J. Am. Chem. Soc.*, **93**, 3056 (1971).
1205. Mackenzie, Rugg, and Shaw, *J. Chem. Soc. Perkin Trans. I*, **1976**, 1446.
1206. Corse and Kuhnle, *Synthesis*, **1972**, 618.
1207. Mornet and Gouin, *Tetrahedron Lett.*, **19**, 167 (1977).
1208. Kern, Cook, and French, *J. Heterocycl. Chem.*, **17**, 461 (1980).
1209. Harnden, Parkin, and Wyatt, *Tetrahedron Lett.*, **29**, 701 (1988).
1210. Schaeffer, Johnson, Odin, and Hansch, *J. Med. Chem.*, **13**, 452 (1970).
1211. Woo and Baker, *J. Med. Chem.*, **25**, 603 (1982).
1212. Schaeffer and Schwender, *J. Med. Chem.*, **17**, 6 (1974).
1213. Keyser, Bryant, and Barrio, *Tetrahedron Lett.*, **20**, 3263 (1979).
1214. Barrio, Bryant, and Keyser, *J. Med. Chem.*, **23**, 572 (1980).
1215. Pitha, *J. Org. Chem.*, **40**, 3296 (1975).
1216. Vyas and Szarek, *Carbohydr. Res.*, **30**, 225 (1973).
1217. Szarek, Vyas, and Achmatowicz, *J. Heterocycl. Chem.*, **12**, 123 (1975).
1218. Nishitani, Iwasaki, Mushika, and Myoshi, *J. Org. Chem.*, **44**, 2019 (1979).
1219. Schmidt and Townsend, *J. Org. Chem.*, **37**, 2300 (1972).
1220. Grotewold and Lissi, *J. Chem. Soc. Chem. Commun.*, **1968**, 1367.
1221. Ranganathan, Rathi, Kesevan, and Singh, *Tetrahedron*, **42**, 4873 (1986).
1222. Wetzel and Eckstein, *J. Org. Chem.*, **40**, 658 (1975).
1223. Schaeffer, Gurwarra, Vince, and Bittner, *J. Med. Chem.*, **14**, 367 (1971).
1224. Haines, Tseng, and Marquez, *J. Med. Chem.*, **30**, 943 (1987).
1225. Still, Kahn, and Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
1226. Neiman, *J. Chem. Soc. (C)*, **1970**, 91.
1227. Giner-Sorolla and Taracido, *J. Heterocycl. Chem.*, **12**, 405 (1975).
1228. Shiue and Chu, *J. Heterocycl. Chem.*, **12**, 493 (1975).
1229. Marumoto, Yoshioka, and Honjo, *Chem. Pharm. Bull.*, **22**, 342 (1974).
1230. M. J. Robins and Hatfield, *Can. J. Chem.*, **60**, 547 (1982).
1231. Golovchinskaya, Korsunski, Kozlova, and Pervacheba, *Khim-Farm. Zh.*, **3**, 20 (1969).
1232. Ulyanova, Dvoryantseva, Kostyvchenko, and Sheinker, *Khim. Geterotsikl. Soedin.*, **1971**, 265.
1233. Gutorova and Golovchinskaya, *Khim-Farm. Zh.*, **7**, 432 (1972).
1234. Arutyunyan, Gounar, Gracheva, Volkova, and Zavyalova, *Izv. Akad. Nauk. S.S.S.R.*, **1969**, 2821.
1235. Sutherland and G. B. Brown, *J. Org. Chem.*, **38**, 1291 (1973).
1236. Takamura, Taga, Kanno, and Kawazu, *J. Org. Chem.*, **38**, 2891 (1973).
1237. Lee, Rice, Hall, and Armanath, *J. Med. Chem.*, **30**, 586 (1987).
1238. A. S. Jones, Lewis, and Withers *Tetrahedron*, **29**, 2293 (1973).
1239. Bunton and Wolfe, *J. Am. Chem. Soc.*, **96**, 7747 (1974).
1240. R. K. Robins, Revankar, O'Brien, Springer, Novinson, Albert, Senger, Miller, and Streeter, *J. Heterocycl. Chem.*, **22**, 601 (1985).
1241. Revankar, Huffman, Allen, Sidwell, R. K. Robins, and Tolman, *J. Med. Chem.*, **18**, 721 (1975).
1242. Pratt and Kraus, *Tetrahedron Lett.*, **22**, 2431 (1981).
1243. Bergmann, Rahat, and Lichtenberg, *J. Chem. Soc. Perkin Trans. I*, **1973**, 1225.
1244. Hofmann, Witkowski, and Schubert, *Z. Chem.*, **14**, 98 (1974).
1245. Lichtenberg, Neiman, and Bergmann, *J. Chem. Soc. Perkin Trans. I*, **1973**, 2445.
1246. Rahat, Bergmann, and Tamari, *J. Chem. Soc. Perkin Trans. I*, **1974**, 2229.

1247. Hemmens and Moore, *J. Chem. Soc. Perkin Trans. II*, **1984**, 209.
1248. Lidak, Schluke, Poritere, and Schvachkin, *Khim. Geterotsikl. Soedin.*, **1970**, 529.
1249. Lichtenberg, Bergmann, Rahat, and Neiman, *J. Chem. Soc. Perkin Trans. I*, **1972**, 2950.
1250. Lam and Parham, *J. Org. Chem.*, **38**, 2397 (1973).
1251. Evans and Wolfenden, *J. Am. Chem. Soc.*, **92**, 4751 (1970).
1252. Steinmaus, Rosenthal, and Elad, *J. Org. Chem.*, **36**, 3594 (1971).
1253. Elad, Rosenthal, Salomon, and Sperling, *J. Chem. Soc., Chem. Commun.*, **1971**, 49.
1254. Salomon and Elad, *J. Am. Chem. Soc.*, **96**, 3295 (1974).
1255. Leonov and Elad, *J. Am. Chem. Soc.*, **96**, 5635 (1974).
1256. Salomon and Elad, *J. Org. Chem.*, **38**, 3420 (1973).
1257. Una, Kokowski, and Vince, *J. Med. Chem.*, **30**, 198 (1987).
1258. Martin, Smee, and Verheyden, *J. Org. Chem.*, **50**, 755 (1985).
1259. Wang, Stam, and Salvino, *Tetrahedron Lett.*, **29**, 1107 (1988).
1260. Ashton, Canning, Reynolds, Tolman, Karkas, Liov, Davis, DeWitt, Perry, and Field, *J. Med. Chem.*, **28**, 926 (1985).
1261. McGee, Martin, Smee, Matthews, and Verheyden, *J. Med. Chem.*, **28**, 1242 (1985).
1262. Martin, Dvorak, Smee, Matthews, and Verheyden, *J. Med. Chem.*, **26**, 759 (1983).
1263. Stohrer and Salemnick, *Cancer Res.*, **35**, 122 (1975).
1264. Ustyuzhanin, Kolomeitseva, and Tikhomirova, *Zh. Obschch. Khim.*, **43**, 2093 (1973).
1265. Ueda, Kondo, Kono, Takemoto, and Imoto, *Makromol. Chem.*, **120**, 13 (1968).
1266. Mikhailov, Kobushkina, Kritsyn, Padyukova, and Florentev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1974**, 2582.
1267. Fujii, Saito, and Terahara, *Chem. Pharm. Bull.*, **34**, 1094 (1986).
1268. Holy, Bold, and Hong, *Collect. Czech. Chem. Commun.*, **36**, 2658 (1971).
1269. Roe, Paul, and Montgomery, *J. Heterocycl. Chem.*, **10**, 849 (1973).
1270. MacCoss, Chan, and Tolman, *Tetrahedron Lett.*, **26**, 1815 (1985).
1271. Badger and Barlin, *J. Chem. Soc. Perkin Trans. II*, **1976**, 1176.
1272. Gaffney and R. A. Jones, *Tetrahedron Lett.*, **23**, 2253 (1982).
1273. Gaffney and R. A. Jones, *Tetrahedron Lett.*, **23**, 2257 (1982).
1274. Adamiak, Biala, and Skalski, *Angew. Chem., Int. Ed.*, **24**, 1054 (1985).
1275. Einck, Pettit, P. Brown, and Yamauchi, *J. Carbohydr. Nucleosides, Nucleotides*, **7**, 1 (1980).
1276. Pettit, Blazer, Einck, and Yamauchi, *J. Org. Chem.*, **45**, 4073 (1980).
1277. Tanabe, Yamauchi, and Kinoshita, *Bull. Chem. Soc. Jpn.*, **52**, 3121 (1979).
1278. Tanimura, Sekine, and Hata, *Tetrahedron Lett.*, **27**, 4047 (1986).
1279. Ismail and Dakin, *J. Chromatogr.*, **110**, 182 (1975).
1280. Lichtenberg and Bergmann, *J. Chem. Soc. Perkin Trans. I*, **1973**, 789.
1281. Lichtenberg, Bergmann, and Neiman, *J. Chem. Soc. (C)*, **1971**, 1989.
1282. Lichtenberg, Bergmann, and Neiman, *J. Chem. Soc. Perkin Trans. II*, **1972**, 1676.
1283. Marzilla, Epps, Sorrell, and Kistenmacher, *J. Am. Chem. Soc.*, **97**, 3351 (1975).
1284. Coburn and Carapellotti, *Tetrahedron Lett.*, **15**, 663 (1974).
1285. Mizuno, Limn, Tsuchida, and Ikeda, *J. Org. Chem.*, **37**, 39 (1972).
1286. Bridson and Weirich, *J. Heterocycl. Chem.*, **25**, 1179 (1988).
1287. El'tsov and Muravich-Aleksandr, *Zh. Org. Khim.*, **6**, 2620 (1970).
1288. Biltz and Rakett, *Ber. Dtsch. Chem. Ges.*, **61**, 1409 (1928).
1289. Walentowski and Wanzlich, *Chem. Ber.*, **102**, 3000 (1269).

1290. Bergmann and D. J. Brown, *Aust. J. Chem.*, **32**, 859 (1979).
1291. Tanabe, Yamauchi, and Kinoshita, *Bull. Chem. Soc. Jpn.*, **49**, 3224 (1976).
1292. Yamauchi, Hayashi, and Kinoshita, *J. Org. Chem.*, **40**, 385 (1975),
1293. Ogilvie, Beaucage, and Gillen, *Tetrahedron Lett.*, **19**, 1663 (1978).
1294. Ogilvie, Beaucage, and Gillen, *Tetrahedron Lett.*, **19**, 3203 (1978).
1295. Hedayatullah, *J. Heterocycl. Chem.*, **19**, 249 (1982).
1296. Likhacheva, Zaloznaya, and Maevskaya, *Khim-Farm. Zh.*, **9**, 48 (1975).
1297. Hayashi, Yamauchi, and Kinoshita, *Bull. Chem. Soc. Jpn.*, **50**, 1510 (1977).
1298. Rybar and Stibranyi, *Collect. Czech. Chem. Commun.*, **38**, 1571 (1973).
1299. Lefebre, Rips, Martine, and Lespagnol, *J. Heterocycl. Chem.*, **22**, 105 (1985).
1300. Armarego and Reece, *Tetrahedron Lett.*, **16**, 423 (1975).
1301. Bridson, Markiewicz, and Reese, *J. Chem. Soc., Chem. Commun.*, **1977**, 791.
1302. Girgis and Pedersen, *Synthesis*, **1982**, 480.
1303. Vörbruggen, *Angew. Chem.*, **84**, 347 (1972).
1304. Vörbruggen, *Angew. Chem. Int. Ed.*, **11**, 304 (1972).
1305. Vörbruggen and Krolikiewicz, *Justus Liebigs Ann. Chem.*, **1976**, 745.
1306. Skalski, Steer, and Verrall, *J. Am. Chem. Soc.*, **110**, 2061 (1988).
1307. Arutyunyan, Gounar, and Zavyalova, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **1970**, 953.
1308. Lister, *Heterocycles*, **6**, 383 (1977).
1309. Wong and Fuchs, *J. Chem. Soc. Perkin Trans. I*, **1974**, 1284.
1310. Coburn, Carapellotti, and Glennon, *J. Heterocycl. Chem.*, **10**, 479 (1973).
1311. Moschel, Hudgins, and Dipple, *J. Am. Chem. Soc.*, **103**, 5489 (1981).
1312. Zady and Wong, *J. Org. Chem.*, **44**, 1450 (1979).
1313. Korsunski, Zozlova, Pervacheva, and Golovchinskaya, *Khim-Farm. Zh.*, **1969**, 20.
1314. Somei, Matsubara, Kanda, and Matsume, *Chem. Pharm. Bull.*, **26**, 2522 (1978).
1315. Wenska and Paszyc, *Z. Naturforsch. Teil B*, **36**, 1628 (1981).
1316. Nishimura and Iwai, *Chem. Pharm. Bull.*, **12**, 352 (1964).
1317. Kastner, Coffey, Clarke, Edmonds, and Eriks, *J. Am. Chem. Soc.*, **103**, 5747 (1981).
1318. Singh, Rosopulos, and Beck, *Chem. Ber.*, **116**, 1364 (1983).
1319. Elvidge, J. R. Jones, O'Brien, Evans, and Sheppard, *J. Chem. Soc. Perkin Trans. II*, **1974**, 174.
1320. J. R. Jones and S. E. Taylor, *J. Chem. Res. (S)*, **1980**, 154.
1321. Christensen, Rytting, and Izatt, *Biochemistry*, **9**, 4907 (1970).
1322. Chenon, Pugmire, Grant, Panzica, and Townsend, *J. Am. Chem. Soc.*, **97**, 4636 (1975).
1323. Lichtenberg, Bergmann, and Neiman, *Isr. J. Chem.*, **10**, 805 (1972).
1324. Sletten and Jensen, *Acta. Crystallogr., Sect. B*, **25**, 1608 (1969).
1325. Pullman and Pullman, *Adv. Heterocycl. Chem.*, **13**, 155 (1971).
1326. Jelinska and Sobkowski, *Tetrahedron*, **33**, 803 (1977).
1327. J. R. Jones and S. E. Taylor, *J. Chem. Soc. Perkin Trans. II*, **1979**, 1253.
1328. Lister and Caldbick, *J. Appl. Chem. Biotechnol.*, **26**, 351 (1976).
1329. Mizumo, Fujiwara, and Tomita, *Bull. Chem. Soc. Jpn.*, **42**, 3099 (1969).
1330. Klotzer, Baldinger, Karpitschka, and Knoflach, *Synthesis*, **1982**, 592.
1331. Clarke and Taube, *J. Am. Chem. Soc.*, **97**, 1397 (1975).
1332. Colacio, Lopez, and Salas, *Can. J. Chem.*, **61**, 2506 (1983).
1333. Kleine and Haller, *Monatsh. Chem.*, **100**, 1692 (1969).
1334. Jelinska, Sydlowsky, and Sobkowsky, *Tetrahedron*, **35**, 663 (1979).

1335. Leonov and Elad, *J. Org. Chem.*, **39**, 1470 (1970).
1336. Kaup and Grüter, *Angew. Chem. Int. Ed.*, **19**, 714 (1980).
1337. Kolonko, Shapiro, Barkley and Sievers, *J. Org. Chem.*, **44**, 3769 (1979).
1338. Stamm, *Justus Liebigs Ann. Chem.*, **1970**, 174.
1339. Thakkar, Tensmeyer, Hermann, and Witham, *J. Chem. Soc., Chem. Commun.*, **1970**, 524.
1340. Sideropoulos, Lumb, and Shankel, *Molec. Gen. Genetics*, **102**, 102 (1968).
1341. Nathanson, *Science*, **226**, 184 (1984).
1342. Angyal, Grigg, Badger, D. J. Brown, and Lister, *J. Gen. Microbiol.*, **85**, 163 (1974).
1343. Kamei, Matsuda, and Mormoso, *Chem. Pharm. Bull.*, **23**, 683 (1975).
1344. Hanna and Sandoval, *Biochem. Biophys. Acta*, **155**, 433 (1968).
1345. Golovchinskaya, *Russ. Chem. Rev.*, **42**, 413 (1973).
1346. Golovchinskaya, *Russ. Chem. Rev.*, **42**, 941 (1973).
1347. Golovchinskaya, *Russ. Chem. Rev.*, **43**, 2226 (1974).
1348. Milne and Townshend, *J. Chem. Soc. Perkin Trans. I*, **1973**, 313.
1349. Mundill, Fries, Woenchhaus, and Plapp, *J. Med. Chem.*, **24**, 474 (1981).
1350. Vorbrüggen and Krolikiewiecz, *Angew. Chem. Int. Ed.*, **15**, 689 (1976).
1351. Templeton and Parham, *J. Org. Chem.*, **43**, 544 (1978).
1352. Marumoto, Yoshioka, Miyashita, Shima, Imai, Kawazoe, and Honjo, *Chem. Pharm. Bull.*, **23**, 759 (1975).
1353. Rosopulos, Nagel, and Beck, *Chem. Ber.*, **118**, 931 (1985).
1354. Cozar, Marhdy, and Morneau, *Can. J. Chem.*, **64**, 751 (1986).
1355. Itai, Yamada, Okamoto, and Iitaka, *Acta Crystallogr. Sect. B*, **33**, 1816 (1977).
1356. Elvidge, J. R. Jones, and O'Brien, *J. Chem. Soc. Chem. Commun.*, **1971** (394).
1357. S. E. Taylor, *Can J. Chem.*, **58**, 86 (1980).
1358. Akahori, Hama, Sakata, and Misumi, *Tetrahedron Lett.*, **25**, 2379 (1984).
1359. Bram and Decodts, *Synthesis*, **1985**, 543.
1360. Peeling, Hruska, and McIntyre, *Can. J. Chem.*, **56**, 1555 (1978).
1361. Ikehara and Yamada, *Chem. Pharm. Bull.*, **19**, 104 (1971).
1362. Bergmann, Rahat, and Tamir, *J. Chem. Soc. Perkin Trans. I*, **1974**, 470.
1363. Reichman, Bergmann, and Lichtenberg, *J. Chem. Soc. Perkin Trans. I*, **1973**, 2647.
1364. Muravich-Aleksandr, El'tsov, and Vaskina, *Zh. Org. Khim.*, **11**, 1116 (1975).
1365. Pal and Schmidt, *J. Org. Chem.*, **39**, 1466 (1974).
1366. Meyer, Stone, and Heinzel, *J. Heterocycl. Chem.*, **15**,1511(1978).
1367. Shiue and Chu, *J. Chem. Soc. Chem.Commun.*, **1975**, 319.
1368. Weidner and Block, *J. Med. Chem.*, **15**, 564 (1972).
1369. Chu, *J. Med. Chem.*, **14**, 254 (1971).
1370. Montgomery and Thomas, *J. Heterocyclic Chem.*, **17**, 583 (1980).
1371. Uno, Irie, and Hino, *Chem. Pharm. Bull.*, **20**, 2603 (1972).
1372. Uno, Irie, and Hino, *Chem. Pharm. Bull.*, **21**, 34 (1973).
1373. Uno, Irie, and Hino, *Chem. Pharm. Bull.*, **21**, 256 (1973).
1374. Yeowell and Elion, *J. Heterocycl. Chem.*, **10**, 1017 (1973).
1375. Davidson, Murray, and Preston, *J. Chem. Res. (S)*, **1981**, 126.
1376. Sarquis and Zingaro, *J. Heterocycl. Chem.*, **10**, 909 (1973).
1377. D. J. Brown, Cowden, Lan, and Mori, *Aust. J. Chem.*, **37**, 155 (1984).
1378. D. J. Brown, Lan, and Mori, *Aust. J. Chem.*, **37**, 2093 (1984).

1379. Bryant and Harman, *J. Med. Chem.*, **10**, 104 (1967).
1380. Silver, Sloan, Waranis, and Saab, *J. Heterocycl. Chem.*, **25**, 1077 (1988).
1381. Onadera, Hirano, Kashimura, and Yajima, *Tetrahedron*, **48**, 4327 (1965).
1382. Lidak, Schluke, and Poritere, *Khim. Geterotsikl. Soedin.*, **1972**, 1561.
1383. Gracheva, Volkova, Gunar, Arutyunyan, and Zabyalov, *Izv. Akad. Nauk. SSSR. Ser. Khim.*, **1970**, 420.
1384. Hama, Sakata, and Misumi, *Tetrahedron Lett.*, **22**, 1123 (1981).
1385. Hama, Sakata, and Misumi, *Nucl. Acid Res. Spec. Publ.*, **8**, 131 (1980).
1386. Kikugawa, Suehiro, and Ichino, *J. Med. Chem.*, **16**, 1381 (1973).
1387. Sowa and Tsunoda, *Bull. Chem. Soc. Jpn.*, **48**, 3243 (1975).
1388. Benson and Jardine, *J. Med. Chem.*, **26**, 1523 (1983).
1389. Czauderna and Samochocka, *J. Chem. Soc. Perkin Trans. II*, **1983**, 765.
1390. D. J. Brown and Hoskins, *Aust. J. Chem.*, **25**, 2641 (1972).
1391. Rackwitz and Scheit, *Chem. Br.*, **107**, 2284 (1974).
1392. Mizuno, Endo, Miyoka, and Ikeda, *J. Org. Chem.*, **39**, 1250 (1974).
1393. Barlin and D. J. Brown, *J. Chem. Soc. (B)*, **1968**, 1435.
1394. Westover, Revankar, R. K. Robins, Madsen, Ogden, North, Mancuso, Rousseau, and Stephen, *J. Med. Chem.*, **24**, 941 (1981).
1395. Hoffmann, Witkowski, and Schubert, *Z. Chem.*, **14**, 15 (1974).
1396. E. Sletten, J. Sletten, and Jensen, *Acta Crystallogr. Ser. B.*, **25**, 1330 (1969).
1397. G. M. Brown, *Acta Crystallogr., Ser. B.*, **25**, 1338 (1969).
1398. Maeda, Saneyoshi, and Kawazoe, *Chem. Pharm. Bull.*, **19**, 1641 (1971).
1399. Elvidge, J. R. Jones and Salih, *J. Chem. Soc. Perkin Trans. II*, **1979**, 1590.
1400. Deutsch, Neiman, and Bergmann, *Org. Mass Spectrom.*, **3**, 1219 (1970).
1401. Elion and Hitchings, *Handbook Exp. Pharmakol.*, **38**(2), 404 (1975).
1402. Wong and Keck, *J. Chem. Soc. Chem. Commun.*, **1975**, 125.
1403. Ueda, Imazawa, Miura, Iwata, and Odajima, *Tetrahedron Lett.*, **12**, 2507 (1971).
1404. Kos, Jongejan, and Van der Plas, *Tetrahedron*, **43**, 4841(1987).
1405. Sutherland and Pickard, *J. Heterocycl. Chem.*, **11**, 457 (1974).
1406. Chattopadhyaya and Reese, *J. Chem. Soc. Chem. Commun.*, **1978**, 86.
1407. Kawazoe and Huang, *Chem. Pharm. Bull.*, **20**, 2073 (1972).
1408. Huang, Okamoto, Maeda, and Kawazoe, *Tetrahedron Lett.*, **14**, 4541 (1973).
1409. Weimar and Leonard, *J. Org. Chem.*, **39**, 3438 (1974).
1410. Panse and Kamat, *Indian. J. Chem.*, **13**, 834 (1975).
1411. Schluke, Zarinya, Lidak, and Schvachkin, *Khim. Gerotsikl. Soedin.*, **1970**, 534.
1412. Elad and Salomon, *Tetrahedron Lett.*, **12**, 4783 (1971).
1413. Stanukas, Rosenthal, and Pitts, *Tetrahedron Lett.*, **12**, 4779 (1971)
1414. Yang, Gorelic, and Kim, *Photochem. Photobiol.*, **13**, 275 (1971).
1415. Salomon and Elad, *Photochem. Photobiol.*, **19**, 21 (1974).
1416. Bodor, Dewar, and Harget, *J. Am. Chem. Soc.*, **92**, 2929 (1970).
1417. Lee and Chan, *J. Am. Chem. Soc.*, **94**, 3218 (1972).
1418. Lancelot, *J. Am. Chem. Soc.*, **99**, 7037 (1977).
1419. Dodin, Dreyfus, and Dubois, *J. Chem. Soc. Perkin Trans. II*, **1979**, 438.
1420. Rao and Rao, *J. Chem. Soc. Perkin Trans. II*, **1973**, 889.
1421. Van der Helm, Christian, and Lin, *J. Am. Chem. Soc.*, **95**, 2409 (1973).

1422. Lin, Christian, and Van der Helm, *J. Am. Chem. Soc.*, **96**, 2727 (1974).
1423. Prizant, Olivier, Rivest, and Beauchamp, *J. Am. Chem. Soc.*, **101**, 2765 (1979).
1424. Albert and Taguchi, *J. Chem. Soc. Perkin Trans. II*, **1973**, 1101.
1425. Ohrt, Srikrishnan, Parthasarathy, Dutta, and Chheda, *J. Am. Chem. Soc.*, **100**, 5232 (1978).
1426. Kameyama, Sako, Hirota, and Maki, *Synthesis*, **1983**, 849.
1427. Davis, Jadhav, and Fareed, *J. Med. Chem.*, **17**, 639 (1974).
1428. Hanessian, *J. Med. Chem.*, **16**, 290 (1973).
1429. Marsh and Tsou, *J Heterocycl. Chem.*, **13**, 885 (1970).
1430. Okumura, Oine, Yamada, Tomie, Adachi, Nagura, Kawazu, Mizoguchi and Inoue, *J. Org. Chem.*, **36**, 1573 (1971).
1431. Nair Turner, and Offerman, *J. Am. Chem. Soc.*, **106**, 3370 (1984).
1432. Sattsangi, Barrio, and Leonard, *J. Am. Chem. Soc.*, **102**, 770 (1980).
1433. Okubo and Ise, *Tetrahedron Lett.*, **14**, 321 (1973).
1434. Temple, Kussner, and Montgomery, *J. Med. Chem.*, **18**, 1225 (1976).
1435. Montgomery, Clayton, and Shortnacy, *J. Heterocycl. Chem.*, **16**, 157 (1979).
1436. Brahme and Smith, *J. Heterocycl. Chem.*, **22**, 109 (1985).
1437. Rasmussen and Chan, *Aust. J. Chem.*, **28**, 1031(1975).
1438. M. J. Robins and R. A. Jones, *J. Org. Chem.*, **39**, 113 (1974).
1439. Maki, Suzuki, Suzuki, Kameyama, and Sako, *J. Chem. Soc. Perkin Trans. I*, **1981**, 3239.
1440. Chheda and Hall, *J. Org. Chem.*, **34**, 3492 (1969).
1441. Haas and Hellwig, *Chem. Ber.*, **108**, 334 (1975).
1442. Kato, Ogawa, and Ito, *Tetrahedron Lett.*, **22**, 3205 (1981).
1443. Endo and Zemlicka, *J. Org. Chem.*, **44**, 3652 (1979).
1444. Shapiro, Cohen, Shiuey, and Maurer, *Biochemistry*, **8**, 238 (1969).
1445. Anzai and Matsui, *Bull. Chem. Soc. Jpn.*, **46**, 3228 (1973).
1446. Lyon and Reese, *J. Chem. Soc. Perkin Trans. II*, **1974**, 2645.
1447. Caputo and Fuchs, *Tetrahedron Lett.*, **8**, 4729 (1967).
1448. Fukatsu, Sawa, and Umezawa, *Bull. Chem. Soc. Jpn.*, **47**, 186 (1974).
1449. Barnett and Letsinger, *Tetrahedron Lett.*, **22**, 991 (1981).
1450. Kierzek, Ito, Bhatt, and Itakura, *Tetrahedron Lett.*, **22**, 3761 (1981).
1451. Shimizu and Miyaki, *Chem. Pharm. Bull.*, **18**, 732 (1970).
1452. Yamauchi, Nakamura, and Kinoshita, *Tetrahedron Lett.*, **20**, 1787 (1979).
1453. McGhee and Von Hippel, *Biochemistry*, **14**, 1281, 1297 (1975).
1454. McGhee and Von Hippel, *Biochemistry*, **16**, 3267, 3276 (1977).
1455. Alexander, *J. Org. Chem.*, **49**, 1453 (1984).
1456. Bridson, Jiricny, Kemal, and Reese, *J. Chem. Soc. Chem. Commun.*, **1980**, 208.
1457. Damha and Ogilivie, *J. Org. Chem.*, **51**, 3559 (1986).
1458. Maki, Suzuki, Kameyama, and Sako, *J. Chem. Soc. Chem. Commun.*, **1981**, 658.
1459. Maki, Kameyama, Sako, and Hirota, *Tetrahedron Lett.*, **24**, 799 (1983).
1460. Fujii, Taneka, Mohri, Itaya, and Saito, *Tetrahedron Lett.*, **14**, 4873 (1973).
1461. Hung and Stock, *J. Org. Chem.*, **47**, 448 (1982).
1462. Ohrt, Parthasarathy, and Chheda, *J. Am. Chem. Soc.*, **92**, 6604 (1970).
1463. Yoneda and Matsumoto, *Chem. Pharm. Bull.*, **22**, 1652 (1974).
1464. Leonard and Henderson, *J. Am. Chem. Soc.*, **97**, 4990 (1975).
1465. Okumura and 15 co-workers, *J. Med. Chem.*, **17**, 846 (1974).

1466. Fujii, Sakamoto, Kawakatsu, and Itaya, *Chem. Pharm. Bull.*, **24**, 655 (1976).
1467. Singer, Sun, and Fraenkel-Conrat, *Biochemistry*, **13**, 1913 (1974).
1468. Engel, *Biochem. Biophys. Res. Commun.*, **64**, 581 (1975).
1469. Wilson and McCloskey, *J. Org. Chem.*, **38**, 2247 (1973).
1470. Fujii and Saito, *Chem. Pharm. Bull.*, **33**, 3635 (1985).
1471. Fujii, Itayo, and Saito, *Chem. Pharm. Bull.*, **23**, 54 (1975).
1472. Fujii, Saito, and Terehara, *Chem. Pharm. Bull.*, **34**, 1094 (1986).
1473. Grenner and Schmidt, *Chem. Ber.*, **110**, 373 (1977).
1474. Carrea, Ottolina, and Riva, *Helv. Chim. Act.*, **71**, 762 (1988).
1475. Robin and Trip, *Biochemistry*, **12**, 2179 (1973).
1476. Dreyfus, Dodin, Bensaude, and Dubois, *J. Am. Chem. Soc.*, **99**, 7027 (1979).
1477. Frihart, Feinberg, and Nakanishi, *J. Org. Chem.*, **43**, 1644 (1978).
1478. Spencer, Weber, Toman, Barrio, and Leonard, *Eur. J. Biochem.*, **45**, 425 (1974).
1479. Secrist, Barrio, Leonard and Weber, *Biochemistry*, **11**, 3499 (1972).
1480. Kochetkov, Shibaev, and Kost, *Tetrahedron Lett.*, **14**, 1993 (1973).
1481. Barrio, Secrist, and Leonard, *Biochem. Biophys. Res. Commun.*, **46**, 597 (1972).
1482. Chheda, Dutta, and Mittelman, *Tetrahedron Lett.*, **15**, 433 (1974).
1483. Nair, Offerman, and Turner, *J. Org. Chem.*, **49**, 4021 (1984).
1484. Krzyzosiak, Biernat, Ciesiolka, Gornicki, and Wiewiorowski, *Pol. J. Chem.*, **53**, 243 (1979).
1485. Wang, Damman, Barrio, and Paul, *J. Am. Chem. Soc.*, **96**, 1205 (1974).
1486. Jones, Murthy, Tegg, Golling, and Moffatt, *Biochem. Biophys. Res. Commun.*, **53**, 1338 (1973).
1487. Park, Isemura, Yuki, and Takiura, *Yakugaku Zasshi*, **95**, 68 (1975).
1488. Reiss, Tappel, and Chio, *Biochem. Biophys. Res. Commun.*, **48**, 921 (1972).
1489. Goldschmidt, Duuren, and Goldstein, *Tetrahedron Lett.*, **20**, 1177 (1979).
1490. Ivanesics and Zbiral, *Monatsh. Chem.*, **106**, 417 (1975).
1491. Kjellberg and Johansson, *J. Heterocycl. Chem.*, **23**, 625 (1986).
1492. Shapiro, Cohen, Shiuey, and Maurer, *Biochemistry*, **8**, 238 (1969).
1493. Moschel and Leonard, *J. Org. Chem.*, **41**, 295 (1976).
1494. Sabbioni and Tannenbaum, *J. Org. Chem.*, **51**, 3244 (1986).
1495. Czarnik and Leonard, *J. Org. Chem.*, **46**, 815 (1981).
1496. Ranganathan, Farooqui, and Bhattacharyya, *Tetrahedron Lett.*, **26**, 2905 (1985).
1497. Huber, *Angew. Chem.*, **69**, 642 (1957).
1498. A. S. Jones and Warren, *Tetrahedron*, **26**, 791 (1970).
1499. Lyon and Reese, *J. Chem. Soc. Perkin Trans. I*, **1978**, 131.
1500. Hosmane and Leonard, *J. Org. Chem.*, **46**, 1457 (1981).
1501. Olomucki, Le Gall, and Colinart, *Tetrahedron Lett.*, **25**, 3471 (1984).
1502. Galliano and Pantarotto, *Tetrahedron Lett.*, **24**, 4491 (1983).
1503. Leonard, Hosmane, Agismundin, Kastuba, and Oakes, *J. Am. Chem. Soc.*, **106**, 6847 (1984).
1504. Zbiral and Hügl, *Tetrahedron Lett.*, **13**, 439 (1972).
1505. Yip and Tsou, *Tetrahedron Lett.*, **14**, 3087 (1973).
1506. Tohme, Courseille, Demuynck, Lhomme, and Lhomme, *Tetrahedron Lett.*, **26**, 3799 (1985).
1507. Zoltewicz and Baugh, *J. Org. Chem.*, **47**, 1353 (1982).
1508. Brentnall and Hutchinson, *Tetrahedron Lett.*, **13**, 2595 (1972).
1509. Mizuno, Kaneko, and Oikawa, *J. Org. Chem.*, **39**, 1440 (1974).
1510. Murata, Bhuta, Owens, and Zemlicka, *J. Med. Chem.*, **23**, 781 (1980).

1511. Bolte, Demuynck, and Lhomme, *J. Med. Chem.*, **20**, 106 (1977).
1512. Fuji and Nishitami, *Chem. Pharm. Bull.*, **21**, 2349 (1973).
1513. Jongejan, Kos, and Van der Plas, *Recl. Trav. Chim. Pays-Bas*, **105**, 337 (1986).
1514. D. J. Brown and Shinozuka, *Aust. J. Chem.*, **35**, 1263 (1982).
1515. Roberts and Vogt, *J. Am. Chem. Soc.*, **78**, 4778 (1956).
1516. Anderson, Rizkalla, and Broom, *J. Org. Chem.*, **39**, 937 (1974).
1517. Ueda, Adachi, Nagai, Sakakibara, and Muraka, *J. Heterocycl. Chem.*, **25**, 791 (1988).
1518. Ueda, Adachi, Sakakibara, Asano, and Nakagami, *Chem. Pharm. Bull.*, **35**, 4031 (1987).
1519. Walsh and Wolfenden, *J. Am. Chem. Soc.*, **89**, 6221 (1967).
1520. Glushkov, Golovchinskaya, and Magidson, *Zh. Obshch. Khim.*, **29**, 3742 (1959).
1521. Shinkai, Vander-Zwan, Hartner, Reamer, Tull, and Weinstock, *J. Heterocycl. Chem.*, **18**, 197 (1981).
1522. Fujii, Sakurai, and Uematsu, *Chem. Pharm. Bull.*, **20**, 1334 (1972).
1523. Rasmussen and Hope, *Aust. J. Chem.*, **35**, 525 (1982).
1524. Weinstock, Tull, Douglas, and Shinkai, *J. Org. Chem.*, **45**, 5419 (1980).
1525. Beasley and Rasmussen, *Aust. J. Chem.*, **34**, 1107 (1981).
1526. Rasmussen and Hope, *Aust. J. Chem.*, **35**, 535 (1982).
1527. Lawley, Orr, and Jarman, *Biochem. J.*, **145**, 73 (1975).
1528. Lawley and Jarman, *Biochem. J.*, **126**, 893 (1972).
1529. Kondo, Miyaki, and Takemoto, *Bull. Chem. Soc. Jpn.*, **44**, 2554 (1971).
1530. Markiw, *J. Org. Chem.*, **37**, 2165 (1972).
1531. Abola, Abraham, and Townsend, *Tetrahedron Lett.*, **17**, 3483 (1976).
1532. El'tsov, Muravich-Aleksandr, and El Sakka, *Zh. Org. Khim.*, **9**, 1280 (1973).
1533. Johnson, Pillai, Grollman, Tseng, and Takeshita, *J. Med. Chem.*, **27**, 954 (1984).
1534. Nachman, *J. Heterocycl. Chem.*, **22**, 953 (1985).
1535. Ueda, Kawabata, and Takemoto, *J. Heterocycl. Chem.*, **8**, 827 (1971).
1536. Muravich-Aleksandr, El'tsov, and El Sakka, *Zh. Org. Khim.*, **9**, 1288 (1973).
1537. La Montagne, Smith, and Wu, *J. Heterocycl. Chem.*, **20**, 295 (1983).
1538. Borcheding, Narayanan, Hasobe, McKee, Keller, and Borchardt, *J. Med. Chem.*, **31**, 1729 (1988).
1539. Goldschmidt, Frenkel, and Van Duren, *J. Heterocycl. Chem.*, **11**, 719 (1974).
1540. Hua, Korkowski, and Vince, *J. Med. Chem.*, **30**, 198 (1987).
1541. Hecht and Kozarich, *J. Chem. Soc. Chem. Commun.*, **1973**, 387.
1542. Albrecht and Heymans, *Chem. Ber.*, **66B**, 1017 (1933).
1543. McKillop, Finaud, and Hug, *Tetrahedron*, **30**, 1379 (1974).
1544. DiMenna and Piantadosi, *J. Med. Chem.*, **21**, 1073 (1978).
1545. Saito, Fukuzaki, and Fujii, *Bull. Chem. Soc. Jpn.*, **59**, 1599 (1986).
1546. Temple, Kussner, and Montgomery, *J. Med. Chem.*, **15**, 441 (1972).
1547. Blythin, Kaminski, Domalski, Spitler, Solomon, Conn, Wong, Verbiar, Bober, Chiv, Watnick, Siegel, Hilbert, and McPhail, *J. Med. Chem.*, **29**, 1099 (1986).
1548. Boyd, *J. Am. Chem. Soc.*, **94**, 64 (1972).
1549. Dreyfus, Dodin, and Bensaude, *J. Am. Chem. Soc.*, **97**, 2369 (1975).
1550. Garcia and Smith, *J. Chem. Soc. Perkin Trans. II*, **1983**, 1401.
1551. Kistenmacher and Shigematsu, *Acta Crystallog., Sect. B*, **30**, 166 (1974).
1552. Kistenmacher and Shigematsu, *Acta Crystallog., Sect. B*, **30**, 1528 (1974).

1553. Jordan and Sostman, *J. Am. Chem. Soc.*, **94**, 7898 (1972).
1554. Maeda and Kawazoe, *Tetrahedron Lett.*, **16**, 1643 (1975).
1555. Barber and Clark, *J. Chem. Soc. Chem. Commun.*, **1970**, 23.
1556. Prizant, Olivier, Rivest, and Beauchamp, *Can. J. Chem.*, **59**, 1311 (1981).
1557. Hubert and Beauchamp, *Can. J. Chem.*, **58**, 1439 (1980).
1558. Guichelaar and Reedijkm, *Recl. Trav. Chim. Pays-Bas*, **97**, 295 (1978).
1559. Elvidge, J. R. Jones, O'Brien, Evans, and Sheppard, *J. Chem. Soc. Perkin Trans. II*, **1973**, 2138.
1560. Matsuoka, Norden, and Kurucsev, *J. Chem. Soc. Chem. Commun.*, **1984**, 1573.
1561. Farrell, *J. Chem. Soc. Chem. Commun.*, **1980**, 1014.
1562. Sethi, Gupta, Jenkins, Whitehead, Townsend, and McCloskey, *J. Am. Chem. Soc.*, **104**, 3349 (1982).
1563. Shannon and Letham, *N.Z.J.Sci.*, **9**, 833 (1966).
1564. Occolowitz, *J. Chem. Soc. Chem. Commun.*, **1968**, 1226.
1565. Kistenmacher and Shigematsu, *Acta Crystallogr., Sect. B*, **31**, 211 (1975).
1566. Kistenmacher, Shigematsu, and Weinstein, *J. Mol. Struct.*, **25**, 125 (1975).
1567. Petersen and Furberg, *Acta Chem. Scand.*, **B29**, 37 (1975).
1568. Jordan, *J. Am. Chem. Soc.*, **96**, 5911 (1974).
1569. Voet and Rich, *J. Am. Chem. Soc.*, **94**, 5888 (1972).
1570. Voet and Rich, *Progr. Nucl. Acid Res. Mol. Biol.*, **10**, 183 (1970).
1571. Srinivasin and Tayler, *J. Chem. Soc. Chem. Commun.*, **1970**, 1668.
1572. Hug and Tinoco (jnr), *J. Am. Chem. Soc.*, **95**, 2803 (1973).
1573. Voet, *J. Am. Chem. Soc.*, **94**, 8213 (1972).
1574. Kamiya, Saito, Hashimoto, and Seki, *Tetrahedron Lett.*, **10**, 4729 (1969).
1575. Kawaza, Kanna, Takamura, Mizoguchi, Saito, and Okumura, *J. Chem. Soc. Chem. Commun.*, **1970**, 1047.
1576. Saito, Hashimoto, Seki, and Kamiya, *Tetrahedron Lett.*, **11**, 4863 (1970).
1577. Okumura, Oine, Yamada, Tomie, Nagura, Kawazu, Mizoguchi, and Inoue, *J. Org. Chem.*, **36**, 1573 (1971).
1578. Okumura, Oine, Yamada, Tomie, Adachi, Nagura, Kawazu, Mizoguchi, and Inove, *J. Chem. Soc. Chem. Commun.*, **1970**, 1045.
1579. Kamiya, Saito, Hashimoto, and Seki, *J. Heterocycl. Chem.*, **9**, 359 (1972).
1580. Kawazu, Kanno, Yamamura, Mizoguchi, and Saito, *J. Org. Chem.*, **38**, 2887 (1973).
1581. Holý, Vortruba, and DeClerq, *Collect. Czech. Chem. Commun.*, **47**, 1392 (1982).
1582. Kamiya, Saito, Hashimoto, and Seki, *Tetrahedron*, **28**, 899 (1972).
1583. Kanno and Kawazu, *Chem. Pharm. Bull.*, **22**, 2836 (1974).
1584. Kanno and Kawazu, *Chem. Pharm. Bull.*, **22**, 2851 (1974).
1585. Yaginuma, Muto, Tsujino, Sudate, Hayashi, and Ohani, *J. Antibiot.*, **34**, 359 (1981).
1586. Kusaka, Yamamoto, Shibatu, Muroi, Kishi, and Mizuno, *J. Antibiot.*, **21**, 255 (1968).
1587. Fukukawa, Ueda, and Harawa, *Chem. Pharm. Bull.*, **29**, 597 (1981).
1588. Madhaven and Martin, *J. Org. Chem.*, **51**, 1287 (1986).
1589. Saksena, *Tetrahedron Lett.*, **21**, 133 (1980).
1590. Deardorff, Shambayati, Myles, and Heerding, *J. Org. Chem.*, **53**, 3614 (1988).
1591. Marquez, Lim, Tseng, Markovac, Priest, Khan, and Kaskar, *J. Org. Chem.*, **53**, 5709 (1988).
1592. Vince and Daluge, *J. Med. Chem.*, **20**, 612 (1977).
1593. Marquez and Lim, *Med. Chem. Rev.*, **6**, 1 (1986).
1594. Lyga and Secrist, *J. Org. Chem.*, **48**, 1982 (1983).

1595. Bond, *J. Chem. Soc. Chem. Commun.*, **1969**, 338.
1596. Kalvoda, Prystäs, and Sörm, *Collect. Czech. Chem. Commun.*, **38**, 2529 (1973).
1597. Kalvoda, Prystäs, and Sörm, *Tetrahedron Lett.*, **14**, 4671 (1973).
1598. Prystäs, Kalvoda, and Sörm, *Collect. Czech. Chem. Commun.*, **40**, 1775 (1975).
1599. Isono, Uramoto, Osada, Ubukata, Kusakabe, Koyama, Miyata, Sethi, and McCloskey, *Nucl. Acid Res. Symp. Ser.*, **15**, 65 (1984).
1600. Ubukata, Osada, and Isono, *Nucl. Acid Res. Symp. Ser.*, **16**, 81 (1985).
1601. Ubukata and Isono, *Tetrahedron Lett.*, **27**, 3907 (1968).
1602. Castro-Pichel, Garcia-Lopez, and de las Heras, *Tetrahedron*, **43**, 383 (1987),
1603. Morton, Lancaster, Van Lear, Fulmor, and Meyer, *J. Am. Chem. Soc.*, **91**, 1535 (1969).
1604. Ogita, Otake, Miyazaki, Yonehara, McFarlane, and McNeal, *Tetrahedron Lett.*, **21**, 3203 (1980).
1605. Gregson and Shaw, *J. Chem. Soc. Perkin Trans. I.* **1985**, 187.
1606. David, Sennyey, and Sotta, *Tetrahedron Lett.*, **23**, 1817 (1982).
1607. Cowley, Jenkins, MacLeod, and Summons, *Tetrahedron Lett.*, **16**, 1015 (1975).
1608. MacLeod, Summons, Parker, and Letham, *J. Chem. Soc. Chem. Commun.*, **1975**, 809.
1609. Abe, Uchiyama, Tanaka, and Saito, *Tetrahedron Lett.*, **17**, 3807 (1976).
1610. Obata, Abe, Tanaka, Yanagisawa, and Uchiyama, *Agric. Biol. Chem.*, **37**, 1989 (1973).
1611. Seela and Hasselmann, *Chem. Ber.*, **112**, 3072 (1979).
1612. Zachau, *Angew. Chem. Int. Ed.*, **8**, 711 (1969).
1613. Rogozinska, Helgeson, and Skoog, *Physiol. Plant.*, **17**, 165 (1964).
1614. Koshimizu, Kusaki, Mitsui, and Matsubara, *Tetrahedron Lett.*, **7**, 1317 (1967).
1615. Letham and Young, *Phytochemistry*, **10**, 2077 (1971).
1616. Soriano-Garcia and Parthaswarthy, *Biochem. Biophys. Acta*, **64**, 1062 (1975).
1617. Teffer and Fosket, *Dev. Biol.*, **62**, 468 (1978).
1618. Horgan, Hewett, Purse, and Wareing, *Tetrahedron Lett.*, **14**, 2827 (1973).
1619. Chaves das Neves and Pais, *Tetrahedron Lett.*, **21**, 4387 (1980).
1620. Fleming and Howden, *Rev. Pure Appl. Chem.*, **22**, 67 (1972).
1621. Leonard, Barrio, and Secrist, *Rec. Adv. Phytochem.*, **7**, 1 (1974).
1622. Matsubara, *Phytochemistry*, **19**, 2239 (1980).
1623. Suhadolnik, *Nucleoside Antibiotics*, Wiley-Interscience, New York, 1970.
1624. Roberts, *Chem. Br.*, **27**, 518 (1991).
1625. Hanvey, Hardman, Suhadolnik, and Baker, *Biochemistry*, **23**, 904 (1984).
1626. Wood, Dion, Lange, Dahl, and Durham, *J. Heterocycl. Chem.*, **11**, 641 (1974).
1627. Schantz, Lynch, Vayvada, Matsumoto, and Rapoport, *Biochemistry*, **5**, 1191 (1966).
1628. Scheuer, *Acc. Chem. Res.*, **10**, 33 (1977).
1629. Tanino, Nakata, and Kishi, *J. Am. Chem. Soc.*, **99**, 2818 (1977).
1630. Shimizu, Buckley, Alam, Oshimi, and Fallon, *J. Am. Chem. Soc.*, **98**, 5414 (1976).
1631. Wichman, Niemczura, Schnoes, Hall, Reichardt, and Darling, *J. Am. Chem. Soc.*, **103**, 6977 (1981).
1632. Alam, Oshima, and Shimizu, *Tetrahedron Lett.*, **23**, 321 (1982).
1633. McMullan and Sundaralingam, *J. Am. Chem. Soc.*, **93**, 7050 (1971).
1634. J. R. Jones and S. E. Taylor, *J. Chem. Soc. Perkin Trans. II*, **1979**, 1587.
1635. Tomasz, Olsen, and Mercado, *Biochemistry*, **11**, 1235 (1972).
1636. Tomasz, *Biochim. Biophys. Acta*, **199**, 18 (1970).

1637. Mansy and Tobias, *J. Chem. Soc. Chem. Commun.*, **1974**, 957.
1638. Clarke and Taube, *J. Am. Chem. Soc.*, **96**, 5413 (1974).
1639. Close and Gronenborn, *J. Am. Chem. Soc.*, **103**, 1369 (1982).
1640. Schollhorn, Raudasch-Sieber, Müller, Thewalt, and Lippert, *J. Am. Chem. Soc.*, **107**, 5932 (1985).
1641. Lippert, *J. Am. Chem. Soc.*, **103**, 5691 (1981).
1642. Gellert and Bau, *J. Am. Chem. Soc.*, **97**, 7379 (1975).
1643. Buncel, Norris, Racz, and S. E. Taylor, *J. Chem. Soc. Chem. Commun.*, **1979**, 562.
1644. Marzilli, DeCastro, and Solorzano, *J. Am. Chem. Soc.*, **104**, 461 (1982).
1645. Chang and Marzilli, *J. Am. Chem. Soc.*, **96**, 3656 (1974).
1646. Yokomo, Shimokawa, and Sohma, *J. Am. Chem. Soc.*, **97**, 3827 (1975).
1647. Matsuoka, Norden, and Kurucsev, *J. Phys. Chem.*, **88**, 971 (1984).
1648. Carrabine and Sundaralingam, *J. Am. Chem. Soc.*, **92**, 369 (1970).
1649. Kasai and Goto, *Tetrahedron Lett.*, **12**, 2725 (1971).
1650. Kasai, Goto, Ikeda, Zama, Mizuno, Takamura, Matsuura, Sugimoto, and Goto, *Biochemistry*, **15**, 898 (1976).
1651. Fink, Goto, Frankel, and Weinstein, *Biochem. Biophys. Res. Commun.*, **32**, 963 (1968).
1652. Keith, Picaud, Weissenback, Ebel, Petrissant, and Dirheimer, *FEBS Lett.*, **31**, 345 (1973).
1653. Nakanishi, Furutachi, Funamizu, Grunberger, and Weinstein, *J. Am. Chem. Soc.*, **92**, 7617 (1970).
1654. Funamizu, Terahara, Feinberg, and Nakanishi, *J. Am. Chem. Soc.*, **93**, 6706 (1971).
1655. Nakatsuka, Ohgi, and Goto, *Tetrahedron Lett.*, **19**, 2579 (1978).
1656. Nakanishi, Blobstein, Funamizu, Furutachi, Van Lear, Grunberg, Lanks, and Weinstein, *Nature (London)*, **234**, 107 (1971).
1657. Feinberg, Nakanishi, Barciszewski, Rafalski, Augustyniak, and Wiewiorowski, *J. Am. Chem. Soc.*, **96**, 7797 (1974).
1658. Buchi, Fowler, and Nadzan, *J. Am. Chem. Soc.*, **104**, 544 (1982).
1659. Jeffrey, Blobstein, Weinstein, Beland, Harvey, Kasai, and Nakanishi, *Proc. Natl. Acad. Sci. USA*, **73**, 2311 (1976).
1660. Jeffrey, Jennette, Blobstein, Weinstein, Beland, Harvey, Kasai, Miura, and Nakanishi, *J. Am. Chem. Soc.*, **98**, 5714 (1976).
1661. Dipple, Brookes, Macintosh, and Rayman, *Biochemistry*, **10**, 4323 (1971).
1662. Schaeffer, Beauchamp, de Miranda, Elion, Baver, and Collins, *Nature (London)*, **272**, 583 (1978).
1663. Lin and Liu, *Tetrahedron Lett.*, **25**, 905 (1984).
1664. Harnden and Jarvest, *Tetrahedron Lett.*, **26**, 4265 (1985).
1665. Liu, Kuzmich, and Lin, *Tetrahedron Lett.*, **25**, 613 (1984).
1666. Borthwick, Butt, Biggadike, Exall, Roberts, Youds, Kirk, Booth, Cameron, Cox, Marr, and Shill, *J. Chem. Soc. Chem. Commun.*, **1988**, 656.
1667. Borthwick, Evans, Kirk, Biggadike, Exall, Youds, Roberts, Knights, and Coates, *J. Med. Chem.*, **33**, 179 (1990).
1668. S. J. C. Taylor, Sutherland, Lee, Wisdom, Thomas, Roberts, and Evans, *J. Chem. Soc. Chem. Commun.*, **1990**, 1120.
1669. Kelley, Krochmal, and Schaeffer, *J. Med. Chem.*, **24**, 1528 (1981).
1670. Chu and Cutler, *J. Heterocycl. Chem.*, **23**, 289 (1986).
1671. Scott, *Chem. Ber.*, **97**, 642 (1983).
1672. Tomasz and Lipman, *Biochemistry*, **25**, 4337 (1986).

1673. Thompson, Osborne, King, and Brookes, *Chem. Biol. Interactions*, **14**, 13 (1976).
1674. Buchanan, Millar, and Wightman, *J. Chem. Soc. Perkin Trans. I*, **1985**, 1425.
1675. Voelker, Records, Bunnenberg, and Djerassi, *J. Am. Chem. Soc.*, **90**, 6163 (1968).
1676. Linder, Weiler-Feilchenfeld, Barth, Bunnenberg, and Djerassi, *Theor. Chim. Acta*, **36**, 135 (1974).
1677. Kamiya and Akahori, *Bull. Chem. Soc. Jpn.*, **47**, 2871 (1974).
1678. G. M. Brown, Sutton, and Taube, *J. Am. Chem. Soc.*, **100**, 2767 (1978).
1679. Faggiani, Lock, and Lippert, *J. Am. Chem. Soc.*, **102**, 5418 (1980).
1680. Zemlicka and Horwitz, *J. Org. Chem.*, **36**, 2809 (1971).
1681. Quin, Gregson, Cook, and Bartlett, *Tetrahedron Lett.*, **21**, 567 (1980).
1682. Fuhrman, Fuhrman, Kim, Pavelka, and Mosher, *Science*, **207**, 193 (1980).
1683. Grozinger, Freter, Farina, and Galdczuk, *Eur. J. Med. Chem.*, **18**, 221 (1983).
1684. Yip and Tsou, *J. Org. Chem.*, **40**, 1066 (1975).
1685. Purnell and Hodgson, *J. Am. Chem. Soc.*, **98**, 4759 (1976).
1686. Basosi, Laschi, and Rossi, *J. Chem. Soc. Perkin Trans. I*, **1978**, 875.
1687. Sloan and Silver, *Tetrahedron*, **40**, 3997 (1984).
1688. Platzer, Galons, Bensaid, Miocque, and Bram, *Tetrahedron*, **43**, 2101 (1987).
1689. Holy, *Collect. Czech. Chem. Commun.*, **40**, 187 (1975).
1690. Gupta and Singh, *Indian J. Chem.*, **13**, 668 (1975).
1691. Ayer, Andersen, Cun-Heng, and Clardy, *J. Org. Chem.*, **49**, 3869 (1984).
1692. Bélanger-Gariépy and Beauchamp. *J. Am. Chem. Soc.*, **102**, 3461 (1980).
1693. Marzilli, Wilkowski, Chiang, and Kistenmacher, *J. Am. Chem. Soc.*, **101**, 7504 (1979).
1694. Vásák, Downing, Townsend, and Michl, *Tetrahedron*, **38**, 1571 (1982).
1695. Sasaki, Minamoto, and Itoh, *Tetrahedron*, **36**, 3509 (1980).
1696. Parham, Pullman, and G. B. Brown, *Tetrahedron*, **29**, 3329 (1973).
1697. Parham, Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).
1698. Lynch and Crook, *Chem. Br.*, **28**, 42 (1992).
1699. Myles and G. B. Brown, *J. Biol. Chem.*, **244**, 4072 (1969).
1700. Stöhrer and G. B. Brown, *J. Biol. Chem.*, **244**, 2494 (1969).
1701. Stöhrer and G. B. Brown, *J. Biol. Chem.*, **244**, 2498 (1969).
1702. G. B. Brown, Stevens, and Smith, *J. Biol. Chem.*, **233**, 1513 (1958).
1703. Kishi, Aratani, Tanino, Fukuyama, Goto, Inoue, Sugiura, and Kakoi, *J. Chem. Soc. Chem. Commun.*, **1972**, 64.
1704. McDonald, Stöhrer, and G. B. Brown, *Cancer Res.*, **36**, 3604 (1976).
1705. Lam, G. B. Brown, and Parham, *J. Org. Chem.*, **39**, 1391 (1974).
1706. Yoneda and Sakuma, *Chem. Pharm. Bull.*, **21**, 448 (1973).
1707. Parham, Pullman, and G. B. Brown, *Radiat. Res.*, **47**, 242 (1971).
1708. Jahan and Alexander, *Radiat. Res.*, **74**, 251 (1978).
1709. Lam and Parham, *Tetrahedron*, **38**, 2371 (1982).
1710. Weiss and Venner, *Z. Physiol. Chem.*, **350**, 230 (1969).
1711. Sundaralingam, Stout, and Hecht, *J. Chem. Soc. Chem. Commun.*, **1971**, 240.
1712. Parham, Templeton, and Teller, *J. Org. Chem.*, **43**, 2325 (1978).
1713. Birdsall, Lee, and Wölke, *Tetrahedron*, **27**, 5961 (1971).
1714. Birdsall, Parham, Wölke, and G. B. Brown, *Tetrahedron*, **28**, 3 (1972).
1715. Parham and Templeton, *Tetrahedron*, **36**, 709 (1980).

1716. Fujii and Ikaya, *Tetrahedron*, **27**, 351 (1971).
1717. Fujii, Kawakatsu, and Itaya, *Chem. Pharm. Bull.*, **22**, 2466 (1974).
1718. Montgomergy and Thomas, *J. Med. Chem.*, **15**, 1335 (1972).
1719. Devlin, *Can. J. Chem.*, **54**, 2804 (1976).
1720. Montgomery and Thomas, *J. Med. Chem.*, **15**, 182 (1972).
1721. Itaya, Tanaka, and Fujii, *Tetrahedron*, **28**, 535 (1972).
1722. Fujii, Wu, Itaya, Moro, and Saito, *Chem. Pharm. Bull.*, **21**, 1676 (1973).
1723. Fenn and Lister, *J. Chem. Soc. Perkin Trans. II*, **1976**, 29.
1724. G. B. Brown, Teller, Smullyan, Birdsall, Lee Parham, and Stöhrer, *Cancer Res.*, **33**, 1113 (1973).
1725. Sugiura, Teller, Parham, and G. B. Brown, *Cancer Res.*, **30**, 184 (1970).
1726. Stöhrer, Corbin, and G. B. Brown, *Cancer Res.*, **32**, 637 (1972).
1727. McCuen, Stöhrer, and Sirotnak, *Cancer Res.*, **34**, 378 (1974).
1728. Ienaga, Hasegawa, D. J. Brown, and Pfleiderer, *J. Chem. Soc. Perkin Trans. I*, **1988**, 593.
1729. Golovchinskaya, Nikolaeva, Korsunskii, Chernov, and Chaman, *Fr. Demande*, **2**, 226, 167 (1973); *Chem. Abstr.*, **82**, 156382e (1975).
1730. Strivastava, Revankar, R. K. Robins and Rousseau, *J. Med. Chem.*, **24**, 393 (1981).
1731. Narayan and Berman, *Carbohydr. Res.*, **44**, 169 (1975).
1732. Lugovkin, *Khim. Geterotsikl. Soedin.*, **1969**, 900.
1733. Holy, *Collect. Czech. Chem. Commun.*, **43**, 3444 (1978).
1734. Eistetter and Pfleiderer, *Chem. Ber.*, **107**, 575 (1974).
1735. Eistetter and Pfleiderer, *Chem. Ber.*, **106**, 1389 (1973).
1736. Chheda and Hong, *J. Med. Chem.*, **14**, 748 (1971).
1737. Eckstein and Zajackowska, *Farm. Ed. Sci.*, **30**, 122 (1974).
1738. Povstyanoi, Kochergin, Akimov, and Androsov, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **18**, 1316 (1975).
1739. Povstyanoi, Kochergin, Logachev, Yakubovskii, Akimov, and Androsov, *Khim. Geterotsikl. Soedin.*, **1974**, 1696.
1740. Anzai, Hunt, and Zon, *J. Org. Chem.*, **47**, 4281 (1982).
1741. D. J. Brown, Grigg, Iwai, McAndrew, Nagamatsu, and Van Heeswyck, *Aust. J. Chem.*, **32**, 2713 (1979).
1742. Cerny, Kotva, and Semonsky, *Collect. Czech. Chem. Commun.*, **37**, 2606 (1972).
1743. Fouvrey, Jouin, and Moron, *Tetrahedron Lett.*, **15**, 3005 (1974).
1744. Yurchenko, Kurmaz, and Komergin, *Khim. Geterotsikl. Soedin*, **1972**, 996.
1745. Farkas, *Collect. Czech. Chem. Commun.*, **36**, 3043 (1971).
1746. Karpitschka, Smole, and Klotzer, *Sci. Pharm.*, **49**, 453 (1981).
1747. Pozharskii, Kuzmenko, and Nanavyan, *Khim. Geterotsikl. Soedin.*, **1983**, 1564.
1748. Pfleiderer, *Hoppe-Seyler's Z. Biol. Chem.*, **369**, 527 (1988).
1749. Santhanam and Elving, *J. Am. Chem. Soc.*, **96**, 1653 (1974).
1750. Elving, Pace, and O'Reilly, *J. Am. Chem. Soc.*, **95**, 647 (1973).
1751. Moorthy and Hayon, *J. Am. Chem. Soc.*, **97**, 3345 (1975).
1752. Kwee and Lund, *Acta Chem. Scand.*, **26**, 1195 (1972).
1753. Dryhurst, *J. Electrochem. Soc.*, **116**, 1357 (1969).
1754. Dryhust, *J. Electrochem. Soc.*, **117**, 1113 (1970).
1755. Yao and Musha, *Bull. Chem. Soc. Jpn.*, **47**, 2650 (1974).
1756. Itayo and Matsumoto, *Tetrahedron Lett.*, **19**, 4047 (1978).

1757. Maki, Suzuki, and Ozeki, *Tetrahedron Lett.*, **17**, 1199 (1976).
1758. Timofeeva, Lizogub, Muravich-Aleksandr, and El'tsov, *Zh. Obshch. Khim.*, **41**, 2539 (1971).
1759. El'tsov and Muravich-Aleksandr, *Zh. Org. Khim.*, **6**, 2616 (1970).
1760. Hecht, Adams, and Kozarich, *J. Org. Chem.*, **41**, 2303 (1976).
1761. El'tsov and Muravich-Aleksandr, *Tetrahedron Lett.*, **9**, 738 (1968).
1762. Timofeeva, Tikhonova, Muravich-Aleksandr, and El'tsov, *Zh. Obshch. Khim.*, **44**, 843 (1974).
1763. Leonard and Hiremath, *Tetrahedron*, **42**, 1917 (1986).
1764. Leonard, Morrice, and Sprecker, *J. Org. Chem.*, **40**, 356 (1975).
1765. Morrice, Sprecker, and Leonard, *J. Org. Chem.*, **40**, 363 (1975).
1766. Leonard, Petrič, and Rykowski, *J. Org. Chem.*, **53**, 3873 (1988).
1767. Lee, Gilchrist, and Skibo, *J. Org. Chem.*, **51**, 4784 (1986).
1768. Stevenson and Leonard, *J. Org. Chem.*, **49**, 2158 (1984).
1769. d'Alarcao, Bakthavachalam, and Leonard, *J. Org. Chem.*, **50**, 2456 (1985).
1770. Scheibye, Pedersen, and Lawesson, *Bull. Soc. Chim. Belg.*, **87**, 229 (1978).
1771. Keyser and Leonard, *J. Org. Chem.*, **41**, 3529 (1976).
1772. Keyser and Leonard, *J. Org. Chem.*, **44**, 2989 (1979).
1773. Leonard, Sprecker, and Morrice, *J. Am. Chem. Soc.*, **98**, 3987 (1976).
1774. Weimar, Scopes, and Leonard, *J. Org. Chem.*, **41**, 3051 (1976).
1775. Malik, Goyal, and Rajeshawari, *Bull. Soc. Chim. Fr.*, **1988**, 39.
1776. Lifshitz, Bergmann, and Steinok, *Isr. J. Chem.*, **6**, 827 (1968).
1777. Poje and Rőcić, *Tetrahedron Lett.*, **20**, 4781 (1979).
1778. Poje, Paulus, and Rőcić, *J. Org. Chem.*, **45**, 65 (1980).
1779. Poje, Palković, Perina, Vicković, and Bruvo, *Tetrahedron*, **41**, 4681 (1985).
1780. Poje and Sokolić-Maravić, *Tetrahedron*, **42**, 747 (1986).
1781. Poje, Rőcić, Sikirica, Vicković, and Bruvo, *J. Med. Chem.*, **26**, 861 (1983).
1782. Chen and Dryhurst, *J. Electroanal. Chem. Interfacial Electrochem.*, **144**, 191 (1983).
1783. Chen and Dryhurst, *J. Electroanal. Chem. Interfacial Electrochem.*, **154**, 107 (1983).
1784. Chen and Dryhurst, *Bioelectrochem. Bioenerg.*, **11**, 75 (1983).
1785. Goyal, Bratjer-Toth, and Dryhurst, *J. Electroanal. Chem. Interfacial Electrochem.*, **131**, 181 (1982).
1786. Goyal, Bratjer-Toth, Dryhurst, and Nguyen, *Bioelectrochem. Bioenerg.*, **9**, 39 (1982).
1787. Chen and Dryhurst, *Bioelectrochem. Bioenerg.*, **11**, 181 (1983).
1788. Hansen and Dryhurst, *J. Electroanal. Chem. Interfacial Electrochem.*, **32**, 405 (1971).
1789. Ikehara and Ogiso, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 401 (1974).
1790. Moschel and Behrman, *J. Org. Chem.*, **39**, 1983 (1974).
1791. Moschel and Behrman, *J. Org. Chem.*, **39**, 2699 (1974).
1792. Hayashi, Shimade, and Matsuoka, *Yakugaku Zasshi*, **99**, 114 (1979).
1793. Jerumis and Martell, *Can. J. Chem.*, **48**, 1717 (1970).
1794. Haller and Werner, *Dtsch. Apoth. Ztg.*, **118**, 1421 (1978).
1795. Seita, Yamauchi, Kinoshita, and Imoto, *Bull. Chem. Soc. Jpn.*, **46**, 1563 (1973).
1796. Leonard, Duesler, and Gotankiewicz, *Acta Crystallog., Sect. B*, **37**, 296 (1981).
1797. Ogilvie, Cheriyan, and Radatus, *Can. J. Chem.*, **60**, 3005 (1982).
1798. Liu, Kumich, and Lin, *Tetrahedron Lett.*, **25**, 613 (1984).
1799. Maslova, Lesnik, and Varshavsky, *FEBS Lett.*, **49**, 181 (1974).
1800. Szydlowski and Jelinskaya, *Radiochem. Radioanal. Lett.*, **19**, 355 (1974).

1801. J. R. Jones and S. E. Taylor, *Tetrahedron Lett.*, **22**, 4525 (1981).
1802. Vaughan, Mughrabi, and Wu, *J. Org. Chem.*, **35**, 1141 (1978).
1803. Kistenmacher and Sorrell, *Acta Crystallogr. Ser. B.*, **31**, 489 (1975).
1804. Izatt, Christensen, and Rytting, *Chem. Rev.*, **71**, 439 (1971).
1805. J. R. Jones and S. E. Taylor, *J. Chem. Soc. Perkin Trans. II*, **1979**, 1773.
1806. Keck, Simpson, and Wong, *J. Org. Chem.*, **45**, 2587 (1978).
1807. Broom and Milne, *J. Heterocycl. Chem.*, **12**, 171 (1975).
1808. Sorrell, Epps, Kistenmacher, and Marzilli, *J. Am. Chem. Soc.*, **100**, 5756 (1978).
1809. Elvidge, J. R. Jones, O'Brien, Evans, and Sheppard, *Adv. Heterocycl. Chem.*, **16**, 1 (1974).
1810. Lister, *Adv. Heterocycl. Chem.*, **24**, 223 (1979).
1811. Bose, Prakash, Hu, and Edasery, *J. Org. Chem.*, **48**,1780 (1983).
1812. Cory, Yamaizumi, Smith, Knowles, Broom, and McCloskey, *J. Heterocycl. Chem.*, **16**, 585 (1979).
1813. White, Kureger, and McCloskey, *J. Org. Chem.*, **37**, 430 (1972).
1814. Von Minden, Liehr, Wilson, and McCloskey, *J. Org. Chem.*, **39**, 285 (1976).
1815. Farmer, Foster, Jarman, and Tisdale, *Biochem. J.*, **135**, 203 (1973).
1816. Deutsch, Neiman, and Bergmann, *Org. Mass. Spectrom.*, **5**, 5279 (1971).
1817. Liehe, Weise, Crain, Milne, Wise, Townsend, and McCloskey, *J. Heterocycl. Chem.*, **16**, 1263 (1979).
1818. Beerbaum, Grupe, and Cech, *Z. Chem.*, **14**, 156 (1974).
1819. Beerbaum, Grupe, and Cech, *Z. Chem.*, **13**, 309 (1973).
1820. Beerbaum, Grupe, and Cech, *Z. Chem.*, **14**, 192 (1974).
1821. J. R. Jones and S. E. Taylor, *Int. J. Chem. Kinet.*, **12**, 141 (1980).
1822. J. R. Jones and S. E. Taylor, *J. Chem. Soc. Perkin Trans. II*, **1980**, 441.
1823. Parham and Templeton, *J. Org. Chem.*, **47**, 653 (1982).
1824. Itaya and Mizutani, *Tetrahedron Lett.*, **26**, 347 (1985).
1825. Suzuki, Yamada, and Hirobe, *J. Chem. Soc. Chem Commun.*, **1978**, 485.
1826. Hawkes, Randall, and Hull, *J. Chem. Soc. Perkin Trans. II*, **1973**, 1268.
1827. Neiman, *Experienta*, **31**, 996 (1975).
1828. Buffel, McGuigan, and M. J. Robins, *J. Org. Chem.*, **50**, 2664 (1985).
1829. Wolfendun, Wentworth, and Mitchell, *Biochemistry*, **16**, 5071 (1977).
1830. Shimazaki, Nakamura, Iitaka, and Ohno, *Chem. Pharm. Bull.*, **31**, 3104 (1983).
1831. Quinones and Arce, *J. Am. Chem. Soc.*, **111**, 8218 (1989).
1832. Lönnberg, *Acta. Chem. Scand.*, **A34**, 703 (1980).
1833. Lönnberg, Lehikoinen, and Neuvonen, *Acta. Chem. Scand.*, **B36**, 707 (1982).
1834. Zvilichovsky and Feingers, *J. Chem. Soc. Perkin Trans. I*, **1976**, 1507.
1835. Kettani, Bernadou, and Meunier, *J. Org. Chem.*, **54**, 3213 (1989).
1836. Goia, Kezoi, Bârzu, Dansoreanu, and Jebeleanu, *Biochemistry*, **14**, 5593 (1975).
1837. Booth, Coster, and Proenca, *J. Chem. Soc. Perkin Trans. I*, **1987**, 1521.
1838. Alves, Booth, and Proenca, *J. Chem. Soc. Perkin Trans. I*, **1990**, 1705.
1839. Pendergast and Hall, *J. Heterocycl. Chem.*, **26**, 1863 (1989).
1840. Chern, Lin, Chen, and Townsend, *J. Org. Chem.*, **56**, 4213 (1991).
1841. Alhede, Clausen, Juhl-Christensen, McCluskey, and Preikschat, *J. Org. Chem.*, **56**, 2139 (1991).
1842. Stimac and Kobe, *Synthesis*, **1990**, 461.

1843. M. F. Jones, Myers, Robertson, Store, and Williamson, *J. Chem. Soc. Perkin Trans. I*, **1991**, 2479.

1844. Huryn and Okabe, *Chem. Rev.*, **92**, 1745 (1992).

1845. Marquez and Lim, *Med. Res. Rev.*, **6**, 1 (1986).

1846. Shimada, Hasegawa, Harada, Tomisawa, Fujii, and Takita, *J. Antibiot.*, **39**, 1623 (1986).

1847. Nakamura, Hasegawa, Shimada, Fujii, and Iitaka, *J. Antibiot.*, **39**, 1629 (1986).

1848. Nitsuma, Ichikawa, Kato, and Takita, *Tetrahedron Lett.*, **28**, 4713 (1987).

1849. Haidoune, Mornet, and Laloue, *Tetrahedron Lett.*, **31**, 1419 (1990).

1850. Zelnik, Haraguchi, Matide, Lavie, Frolow, and Weis, *J. Chem. Soc. Perkin Trans. I*, **1986**, 2051.

1851. Fujii, Saito, Mori, and Chikazawa, *Tetrahedron Lett.*, **32**, 97 (1991).

1852. Schantz, Ghazarossian, Schnoes, Strong, Springer, Pezzanite, and Clardy, *J. Am. Chem. Soc.* **97**, 1238 (1975).

1853. Bordner, Thiessen, Bates, and Rapoport, *J. Am. Chem. Soc.*, **97**, 6008 (1975).

1854. Matsuda, Nomoto, and Ueda, *Chem. Pharm. Bull.*, **27**, 183 (1979).

1855. Hamamichi and Miyasaka, *J. Heterocycl. Chem.*, **27**, 835 (1990).

1856. Moschel, McDougall, Dolan, Stine, and Pegg, *J. Med. Chem.*, **35**, 4486 (1992).

1857. Birkett, Chapleo, and Mackenzie, *Synthesis*, **1991**, 157.

1858. Ram, Evans, Wise, and Townsend, *J. Heterocycl. Chem.*, **26**, 1053 (1989).

1859. Overberger and Chang, *Tetrahedron Lett.*, **30**, 51 (1989).

1860. Fujii, Itaya, Saito, and Kawanishi, *Chem. Pharm. Bull.*, **26**, 1929 (1978).

1861. Legraverend, Boumchita, and Bisagni, *Synthesis*, **1990**, 587.

1862. Hayaki, Tanaka, Sasaki, Haraguchi, Saitoh, Takai, and Misayaka, *J. Heterocycl. Chem.*, **26**, 189 (1989).

1863. Nair and Richardson, *Synthesis*, **1982**, 670.

1864. Kelley, Linn, and Tisdale, *J. Heterocycl. Chem.*, **27**, 1505 (1990).

1865. Henry, Kiri, Larson, R. K. Robins, Alaghamandan, and Smee, *J. Med. Chem.*, **33**, 2127 (1990).

1866. Harden and Jarvest, *J. Chem. Soc. Perkin Trans. I*, **1989**, 2207.

1867. Bell and Hunter, *Tetrahedron Lett.*, **28**, 147 (1987).

1868. Burns, St Clair, Frick, Spector, Averett, English, Holmes, Krenitsky, and Koszalka, *J. Med. Chem.*, **36**, 378 (1993).

1869. Press, Hajos, and Sawyers, *Tetrahedron Lett.*, **31**, 1373 (1990).

1870. Jackman and Westphal, *Synthesis*, **1987**, 1134.

1871. Hori, Kataoka, Shimizu, Imai, Yokomoto, and Ando, *Synthesis*, **1987**, 278.

1872. Revankar, Hanna, Imamura, Lewis, Larson, Finch, Avery, and R.K. Robins, *J. Med. Chem.*, **33**, 121 (1990).

1873. Revankar, Hanna, Ramasamy, Larson, Smee, Finch, Avery, and R.K. Robins, *J. Heterocycl. Chem.*, **27**, 909 (1990).

1874. Divakar, Mottahedeh, Reese, Sanghvi, and Swift, *J. Chem. Soc. Perkin Trans. I*, **1991**, 771.

1875. Nair, Turner, Buenger, and Chamberlain, *J. Org. Chem.*, **53**, 3051 (1988).

1876. Kunieda and Witkop, *J. Org. Chem.*, **35**, 3981 (1970).

1877. Gewald and Heinhold, *Monatsh. Chem.*, **107**, 1413 (1976).

1878. Booth, Coster, and Proenca, *Synthesis*, **1988**, 389.

1879. Hosmane and Lim, *Synthesis*, **1988**, 242.

1880. Al-Shaar, Gilmour, Lythgoe, McClenaghan, and Ramsden, *J. Chem. Soc. Chem. Commun.*, **1989**, 551.
1881. Yamaji, Yuasa, and Kato, *Chem. Pharm. Bull.*, **24**, 1561 (1976).
1882. Onoe and Kawai, *J. Chem. Soc. Chem. Soc. Commun.*, **1988**, 681.
1883. Eschenmoser and Loewenthal, *Chem. Soc. Revs.*, **21**, 1 (1992).
1884. J.R. Jones and S.E. Taylor, *Chem. Soc. Revs.*, **10**, 329 (1981).
1885. Garin, Meléndez, Merchán, Merino, Orduna, Tejedor, and Tejero, *J. Heterocycl. Chem.*, **27**, 221 (1990).
1886. Shimada, Suzuki, Nonaka, and Ishii, *J. Med. Chem.*, **35**, 924 (1992).
1887. Erikson, Hiner, Feeney, Blake, Rzeszotarski, Hicks, Costello, and Abreu, *J. Med. Chem.*, **34**, 1431 (1991).
1888. Capon and Faulkner, *J. Am. Chem. Soc.*, **106**, 1819 (1984).
1889. Chattopadhyaya and Reese, *Synthesis*, **1977**, 725.
1890. Niya, Olsson, Thompson, Silvia, and Ueda, *J. Med. Chem.*, **35**, 4557 (1992).
1891. Niya, Thompson, Silvia, and Olsson, *J. Med. Chem.*, **35**, 4562 (1992).
1892. Hesek, Tegza, Rybár, and Povazanec, *Synthesis*, **1989**, 681.
1893. Matsui, Shibata, and Muramatsu, *J. Org. Chem.*, **56**, 4987 (1991).
1894. Reitz, Graden, Jordan, and Maryanoff, *J. Org. Chem.*, **55**, 5761(1990).
1895. Engel and Von Hippel, *Biochemistry*, **13**, 4143 (1974).
1896. Ishino, Sakaguchi, Morimoto, and Okitsu, *Chem. Pharm. Bull.*, **29**, 2403 (1981).
1897. Hahn, Zenobi, and Zare, *J. Am. Chem. Soc.*, **109**, 2842 (1987).
1898. Nelson and McCloskey, *J. Am. Chem. Soc.*, **114**, 3661 (1992).
1899. Petke, Maggiora, and Christoffersen, *J. Am. Chem. Soc.*, **112**, 5452 (1990).
1900. Katritzky and Karelson, *J. Am. Chem. Soc.*, **113**, 1561 (1991).
1901. Walker, Bhatia, and Hall, *J. Am. Chem. Soc.*, **109**, 7629 (1987).
1902. Langer and Huml, *Acta Crystallogr., Ser. B*, **34**, 1157 (1978).
1903. Walker, Bhatia, and Hall, *J. Am. Chem. Soc.*, **109**, 7634 (1987).
1904. Schindler, *J. Am. Chem. Soc.*, **110**, 6623 (1988).
1905. Goyal, Kumar, and Mittal, *J. Chem. Soc. Perkin II*, **1991**, 1369.
1906. Steenken, *Chem. Rev.*, **89**, 503 (1989).
1907. Mitsunobu, *Synthesis*, **1981**, 1.
1908. Er-Rhaimini, Mohsinaly, and Mornet, *Tetrahedron Lett.*, **31**, 5757 (1990).
1909. Er-Rhaimini and Mornet, *Synthesis*, **1988**, 154.
1910. Sekine and Satoh, *J. Org. Chem.*, **56**, 1224 (1991).
1911. Zing, Hixson, and Zimmermann, *Tetrahedron Lett.*, **31**, 5894 (1990).
1912. Dolle and McNair, *Tetrahedron Lett.*, **34**, 133 (1993).
1913. Zou and M. J. Robins, *Can. J. Chem.*, **65**, 1436 (1987).
1914. Hakimelahi and Khalafi-Nezhad, *Helv. Chim. Acta*, **72**, 1495 (1989).
1915. Palković and Poje, *Tetrahedron Lett.*, **31**, 6101 (1990).
1916. Simic and Jovanovic, *J. Am. Chem. Soc.*, **111**, 5778 (1989).
1917. Soklić, Modrić, and Poje, *Tetrahedron Lett.*, **32**, 7477 (1991).
1918. Poje and Sokolić-Maravić, *Tetrahedron*, **44**, 6723 (1988).
1919. Joshi and Davies, *J. Chem. Res. (S)*, **1981**, 2701.
1920. Ji, Subramanian, Van der Helm, and Dryhurst, *J. Org. Chem.*, **55**, 1291 (1990).
1921. Medeiros and Thomas, *Biochem. Biophys. Acta*, **238**, 1 (1971).

1922. Pullman, Bergmann, Weiler-Feilchenfeld, and Neiman, *Int. J. Quant. Chem.*, **35**, 103 (1969).
1923. Twanmoh, Wood, and Driscoll, *J. Heterocycl. Chem.*, **10**, 187 (1973).
1924. Mason, *J. Chem. Soc.*, 1954, 2071; D. J. Brown and Mason, *J. Chem. Soc.*, **1957**, 682.
1925. Kamiya, *Bull. Chem. Soc. Jpn.*, **46**, 2235 (1973).
1926. Kamiya, Haba, Akahori, *Chem. Pharm. Bull. Jpn.*, **21**, 1474 (1973).
1927. Lapucha, *Synthesis*, **1987**, 256.
1928. Tomson, Avots, and Kolesnikova, *Khim-Farm. Zh.*, **19**, 206 (1985).
1929. Küng and R. A. Jones, *Tetrahedron Lett.*, **32**, 3919 (1991).
1930. Ishizuro, Sawada, Hoshida, and Kawabe, *Yakugaku Zasshi*, **102**, 484 (1982).
1931. Bhatia, Kaushnik, and Sodhi, *J. Chem. Res. (S)*, **1987**, 186.
1932. Koyama and Kozuka, *J. Heterocycl. Chem.*, **27**, 667 (1990).
1933. Kozuka, Koyama, and Okitsu, *Chem. Pharm. Bull.*, **29**, 433 (1981).
1934. Kozuka, Koyama, and Okitsu, *Chem. Pharm. Bull.*, **30**, 941 (1982).
1935. Legraverend, Boumchita, and Bisagni, *J. Heterocycl. Chem.*, **27**, 1801 (1990).
1936. Moriarty, Epa, and Awasthi, *Tetrahedron Lett.*, **31**, 5877 (1990).
1937. Ashwell, Bleasdale, Golding, and O'Neill, *J. Chem. Soc. Chem. Commun.*, **1990**, 955.
1938. Kozluk and Spenser, *J. Am. Chem. Soc.*, **109**, 4699 (1987).
1939. Inoue, Nomura, and Ueda, *Nucl. Acid Symp. Ser.*, **10**, 19 (1981).
1940. Hayashi, Shimida and Miyashita, *Yakugaku Zasshi*, **96**, 1370 (1976). *Chem. Abstr.*, **86**, 121295 (1977).
1941. Iwakawa, Pinto, and Szarek, *Can. J. Chem.*, **56**, 326 (1978).
1942. Van der Plas, *Tetrahedron*, **41**, 237 (1982).
1943. Bergmann, Lichtenberg, Reichman, and Neiman, *Jerusalem Symp., Quantum Chem. Biochem.*, **6**, 397 (1974).
1944. A. Albert, *Heterocyclic Chemistry*, Athlone Press, London and New York, 1968.
1945. Elguero, Marzin, Katritzky, and Linda, *Adv. Heterocycl. Chem., Suppl. 1*, **502** (1976).
1946. Bugg, Thewalt, and Marsh, *Biochem. Biophys. Res. Commun.*, **33**, 436 (1968).
1947. J. Sletten, E. Sletten, and Jensen, *Acta Crystallogr. Ser. B*, **24**, 1692 (1968).
1948. Mandel and Marsh, *Acta Crystallogr. Sect. B*, **31**, 2862 (1975).
1949. Barrio, Liu, Keyser, Van der Lijn, and Leonard, *J. Am. Chem. Soc.*, **101**, 1564 (1979).
1950. Leonard and Devadas, *J. Am. Chem. Soc.*, **109**, 623 (1987).
1951. Párkány, Yuan, and Tsai, *J. Heterocycl. Chem.*, **28**, 465 (1991).
1952. Hama, Sakata, Misumi, Aida, and Nagata, *Tetrahedron Lett.*, **23**, 3061 (1982).
1953. Doyama, Higashii, Sakata, and Misumi, *Bull. Chem. Soc. Jpn.*, **61**, 3619 (1988).
1954. Sakata, Higuchi, Doyama, Higashii, Mitsuoka, and Misumi, *Bull. Chem. Soc. Jpn.*, **62**, 3155 (1989).
1955. Seyama, Sakata, Kasai, and Misumi, *Bull. Chem. Soc. Jpn.*, **61**, 2847 (1988).
1956. Patterson and Todd, *Handbook Exp. Pharmakol.*, **38**(2), 384 (1974).
1957. Benezra and Foss, *Anal. Profiles Drug Subst.*, **7**, 343 (1978).
1958. A. R. Katritzky and J. M. Lagowski, *Chemistry of Heterocyclic N-Oxides*, Academic, New York, 1971.
1959. G. H. Hitchings, *Handbook Exp. Pharmacology*, Springer, Berlin, 1978.
1960. Fujii, Itaya, and Saito, *Heterocycles*, **6**, 1627 (1977).
1961. P. Tougard, in E. D. Bergmann and B. Pullman, Eds., *The Purines, Theory and Experiment*, Academic, New York, 1972, p. 217.
1962. Lister, *Adv. Heterocycl. Chem.*, **24**, 215 (1979).

1963. G. Shaw, in A. R. Katritzky and C. W. Rees, Eds., *Comprehensive Heterocyclic Chemistry*, Vol. 5, Pergamon, Oxford, 1984, pp. 499–605.

1964. G. Shaw, in M. F. Ansell, Ed., Purines and Related Ring Systems, Supplement to *Rodd's Chemistry of Carbon Compounds*, Vol. IV, Part L, Elsevier, Amsterdam, 1988.

1965. E. Lunt, in D.H.R. Barton and W. D. Ollis, Eds., *Comprehensive Organic Chemistry*, Vol. 4, Pergamon, Oxford, 1979, p. 493.

1966. J. H. Lister, *Purine* in *Enciclopedia della Chimica*, Vol. IX, Uses Edizioni Scientifiche, Firenze, 1982.

1967. Yoneda, *Kagaka no Ryoiki*, **29**, 14 (1975).

1968. Yoneda, *Kagaka no Ryoiki*, **29**, 40 (1975).

1969. D. T. Hurst, *The Chemistry and Biochemistry of Pyrimidines, Purines, and Pteridines*, Wiley, Chichester, 1980.

1970. *Purines, Pharmacology and Physiological Roles*, T. W. Store, Ed., Macmillan, London, 1985.

1971. Kjellberg and Johansson, *Tetrahedron*, **42**, 6541 (1986).

1972. Remaud, Kjellberg, Bazin, Johansson, and Chattopadhyaya, *Tetrahedron*, **42**, 5080 (1986).

1973. Heitner, Lippard, and Sunshine, *J. Am. Chem. Soc.*, **94**, 8936 (1972).

1974. Basosi, Gaggelli, Tiezzi, and Valensin, *J. Chem. Soc. Perkin Trans. II*, **1975**, 423.

1975. Cimino, Crispino, De Stefano, Gavagnin, and Sodana, *Experienta*, **42**, 1301 (1986).

1976. See "Marine Natural Products Chemistry" in *Chem. Rev.*, **93**, 1671 (1993).

1977. Bott, *Chem. Ber.*, **126**, 1955 (1993).

1978. Wallace and Michl, *Tetrahedron*, **36**, 1531 (1980).

1979. Townsend, Miles, Manning, and Eyring, *J. Heterocycl. Chem.*, **10**, 419 (1973).

1980. Balsin, Gumenyuk, Solodovnikov, and Belousov, *Z. Naturforsch., Anorg. Chem. Org. Chem.*, **36B**, 400 (1981).

1981. Slifkin, Suleiman, and Phillips, *Radiat. Eff.*, **32**, 33 (1977).

1982. Yamane, Inoue, and Ueda, *Chem. Pharm. Bull.*, **28**, 157 (1980).

1983. Hedayatullah and Roger, *J. Heterocycl. Chem.*, **26**, 1093 (1989).

1984. Lönnberg, *Acta Chem. Scand.*, **A35**, 317 (1981).

1985. Marcus, Preston, and Suffolk, *Z. Naturforsch. Biosci., Teil C*, **31**, 101 (1976); *Chem. Abstr.*, **84**, 12178x (1976).

1986. Ramesh, Wolfe, Lee, Velde, and Borchardt, *J. Org. Chem.*, **57**, 5861 (1992).

1987. Ried and Woithe, *Helv. Chim. Acta*, **72**, 1860 (1989).

1988. Hayashi, Suzuki, Yasuzawa, and Ueno, *J. Heterocycl., Chem.*, **30**, 247 (1993).

1989. Shimada, Kuroda, and Suzuki, *J. Heterocycl. Chem.*, **30**, 241 (1993).

1990. Maki, Suzuki, Kameyama, Kawai, and Sako, *Heterocycles*, **15**, 895 (1981).

1991. Garland and Pakesh, *J. Phys. Chem.*, **78**, 848 (1974).

1992. El Khadem and Sindric, *Carbohydr. Res.*, **34**, 203 (1974).

1993. Wagner, *Pharmazie*, **29**, 160 (1974).

1994. Gannett, Lawson, and Toth, *Tetrahedron Lett.*, **28**, 1015 (1987).

1995. Itaya, Matsumoto, and Ogawa, *Chem. Pharm. Bull.*, **28**, 1920 (1980).

1996. Itaya and Ogawa, *Heterocycles*, **6**, 965 (1977).

1997. Ikehara, Ogiso, and Maryama, *Chem. Pharm. Bull.*, **25**, 575 (1977).

1998. Bryant and Klein, *Anal. Biochem.*, **65**, 73 (1975).

1999. Schaeffer, Johnson, Schwartz, and Schwender, *J. Med. Chem.*, **15**, 456 (1972).

2000. Sideropoulos, Lumb, and Shankel, *Molec. Gen. Genet.*, **102**, 102 (1968).

2001. Seela and Hasselmann, *Chem. Ber.*, **113**, 2043 (1980).

2002. Sasaki, Minamoto, Yamashita, Yamaguchi, and Miyaki, *J. Org. Chem.*, **46**, 5176 (1981).
2003. Lönnberg, Kappi, and Heikkinen, *Acta Chem. Scand.*, **B35**, 589 (1981).
2004. Kelley, McLean, Linn, Krochmal, Ferris, and Howard, *J. Med. Chem.*, **33**, 197 (1990).
2005. Shimada, Suzuki, Nonaka, Karasawa, Mizumoto, Ohno, Kubo, and Ishii, *J. Med. Chem.*, **34**, 466 (1991).
2006. Klemm, Johnstone, and Tran, *J. Heterocycl. Chem.*, **26**, 1519 (1989).
2007. Hamamichi and Miyasaki, *J. Heterocycl. Chem.*, **27**, 2011 (1990).
2008. Kelley, Linn, and Selway, *J. Med. Chem.*, **32**, 1757 (1989).
2009. Suzuki, Shimada, Mizumoto, Karasawa, Kubo, Nonaka, Ishii, and Kawakita, *J. Med. Chem.*, **35**, 3066 (1992).
2010. Sakai, Konno, Yamamoto, Sanae, Takagi, Hasegawa, Iwasaki, Kakiuchi, Kato, and Mizumoto, *J. Med. Chem.*, **35**, 4039 (1992).
2011. Alexander and Marienthal, *J. Pharm. Sci.*, **53**, 962 (1964).
2012. Stelmach and Connors, *J. Am. Chem. Soc.*, **92**, 863 (1970).
2013. Parkanyi and Yuan, *J. Heterocycl. Chem.*, **27**, 1409 (1990).
2014. Kelley, Linn, and Selway, *J. Med. Chem.*, **34**, 157 (1991).
2015. Neiman and Quinn, *J. Pharm. Sci.*, **70**, 425 (1981).
2016. Mikhailov, Kolobuskina, Kritzyn, and Florientov, *Tetrahedron*, **32**, 2409 (1976).
2017. Chenon, Pugmire, Grant, Panzica, and Townsend, *J. Am. Chem. Soc.*, **97**, 4627 (1975).
2018. Grigg, Edwards, and D. J. Brown, *J. Bacteriol.*, **107**, 599 (1971).
2019. Kazimierczuk and Shugar, *Acta Biochem. Pol.*, **21**, 455 (1974).
2020. Ohsugi, Ichimoto, and Ueda, *Agric. Biol. Chem.*, **38**, 1925 (1974).
2021. E. F. Evans and Sarma, *J. Am. Chem. Soc.*, **97**, 3215 (1975).
2022. Van Hemmens, *Nature (New Biol.)*, **231**, 79 (1971).
2023. Mariggi and *Teoule, C. R. Acad. Sci. Ser. C*, **279**, 1005 (1974).
2024. Budo and Tomasz, *Acta Biochem. Biophys. Acad. Sci. Hung.*, **9**, 217 (1974).
2025. Maslankiewicz, Rohloff, and Windisch, *Rocz. Chem.*, **49**, 1935 (1975).
2026. Nantka-Namirsky, Jarynowicz, and Wojciechowski, *Ata Pol. Pharm.*, **31**, 5 (1974).
2027. Lespagnol, Debaert, Blears, Devergnies, J. C. Cazin, and M. Cazin, *Ann. Pharm. Fr.*, **31**, 751 (1973).
2028. Stern and Beeninga, *J. Phys. Chem.*, **79**, 582 (1975).
2029. Thyagarajan, *Adv. Heterocycl. Chem.*, **8**, 143 (1967).
2030. Betula, *Justus Liebigs Ann. Chem.*, **729**, 73 (1969).
2031. Antonovskii, Gukovskaya, Sukhorukov, and Chervin, *Izv. Akad. Nauk SSSR Ser. Khim.*, **1974**, 2307.
2032. Haslam, *Chem. Br.*, **29**, 875 (1993).
2033. Verkoyen, Golovinsky, Müller, Kolvel, and Norpoth, *Justus Liebigs, Ann. Chem.*, **1987**, 957.
2034. Yamane, Matsuda, and Ueda, *Chem. Pharm. Bull.*, **28**, 150 (1980).
2035. Lohmann and Miech, *J. Labelled Cpd. Radiopharm.*, **11**, 515 (1975).
2036. Roehmer and Kiessling, *Isotopenpraxis*, **11**, 150 (1975).
2037. Danchev and Khristova, *Farmatsiya (Sofia)*, **25**, 1 (1975).

References from the parent volume cited in the text:

46. Blicke et al., *J. Am. Chem. Soc.*, **78**, 5857 (1956).
116. Erhart et al., *Arch. Pharm.*, **289**, 453 (1956).
171. Montgomery et al., *J. Org. Chem.*, **30**, 1528 (1965).

181. Traube et al., *Justus Liebigs Ann. Chem.*, **432**, 266 (1923).
258. Uretskaya et al., *Zh. Obshch. Khim.*, **30**, 327 (1960).
274. Bredereck et al., *Chem. Ber.*, **100**, 2280 (1967).
284. Noell et al., *J. Am. Chem. Soc.*, **81**, 5997 (1959).
429. Priewe et al., *Chem. Ber.*, **88**, 1932 (1955).
555. Johns, *J. Biol. Chem.*, **17**, 1 (1914).
725. Budowsky et al., *J. Mol. Biol.*, **44**, 205 (1969).
785. Brown et al., *J. Chem. Soc. (C)*, **1969**, 2620.
790. Giner-Sorolla et al., *J. Chem. Soc. (C)*, **1971**, 126.
791. Brown et al., *J. Chem. Soc. (C)*, **1971**, 128.
811. Shimizu et al., *Chem. Pharm. Bull.*, **18**, 570 (1970).
826. Miyaki et al., *Chem. Pharm. Bull.*, **18**, 1446 (1970).
828. Stöhrer et al., *J. Biol. Chem.*, **244**, 2498 (1969).

Chemistry of Heterocyclic Compounds, Volume 54
John H. Lister
Copyright © 1996 by John Wiley & Sons, Ltd.

Index

Abiotic synthesis, 78, 80, 215
Acyclic precursors, in synthesis, 215
Acyclovir, 63, 276, 279
  from 4-amino-5-carbamoylimidazoles, 140, 280
  analogs, 140, 280
  reviews, 280
  unambiguous synthesis, 56
Acylaminopurines, rearrangement, 232, 233
O-Acylation, 157, 315
Acylimines, as carbanion in alkylation, 130
Addition reactions, *see also* Michael and Mannich reactions
  with alcohols, 87, 141
  with ammonia, 86
  with barbituric acid, 86
  with hydrogen sulfite ions, 86
Adenine, 269–272
  alkylation sequence, 256–264
  amino group alkylation, 238
  complex formation, 271
  electron distribution, 269
  laser raman spectrum, 271
  mass spectrum, 269
  MCD spectrum, 272
  mono-, di-, and trications, 271
  permethylation, 258
  protonation, 270
  regiospecific synthesis, 23, 269
  self-association, 271
  tautomerism, 271
Adenines, synthesis, 23, 55, 72, 77, 269
Adenomycin, natural product, 273–274
Adogen 440, catalyst, 262
Aflotoxin, natural product, 279
Ageline A and B, 276
Agrocin 84, 274
Albert, Adrien, 16
Alcohols, in photo addition, 141–142
Aldehydes:
  in synthesis of 2-alkylpurines, 67, 330
  in synthesis of 8-alkylpurines, 38, 49
  in synthesis of 7-hydroxypurines, 48
Aliquat 336, catalyst, 262
Alkoxyaminopurines:
  by amino group replacement, 251
  by Dimroth reaction, 241, 322, 323
  by halogen replacement, 251
Alkyl disulfides, radical formation, 121
Alkylamino groups, rotameric forms, 222–223
Alkylation:
  at carbon, 90, 166, 171
  at nitrogen, 94, 128, 150–157, 192,199, 256–266, 335, 341
  at oxygen, 146, 238, 314, 321
  at sulfur, 187, 195
Alkylseleno groups:
  displacement by alkoxy, 146
  displacement by other nucleophiles, 195, 197
  failure with acid hydrolysis, 135
Alkylselenoguanosine, 122
Alkylselenopurines, synthesis, 184, 188, 192, 195
Alkylthio groups, order of displacement by nucleophiles, 196–197
Allantoin, by oxidation of adenine, 245
Alloxanic acid, 170
Alpurine, formation, 112
Amidogen forms of *N*-oxides, 313, 316
6-Amidopurine, fluorescence, 287
Amidyl radicals, 318, 378
7-Amino-1,3-dimethyl-2,4-dioxopteridine, 249, 253
Amino groups:
  alkylation using PTC, 238
  amino-imino tautomerism, 18
  by *C*-amination, 218
  hydrolysis, 135, 224, 236
  mechanism of hydrolysis, 135
  protecting groups, 228
  removal by radicals, 95
  replacement by halogen, 224
  restricted rotation, 222
  rotameric states, 222, 224
  transamination, 47, 239
Aminopurines, natural occurrence, 269–281
4-Amino-6(5*H*)-oxopyrazolo [3,2-*d*] pyrimidines
N-Aminopurines, 219, 244
4-Aminothiadiazolo[3,4-*d*]pyrimidine, in synthesis, 215
Ammonium dithiocarbamates, 182

Ammonium peroxidisulfate, 87
Ammonium sulfate, quenching agent, 95, 243
ANRORC reaction, 5, 218
  in adenine deamination, 95
  in *C*-aminations, 94
  in *N*-aminopurine deamination, 84
  in converting 2-amino-6-chloro- to 2,6-diaminopurine, 115
  in converting 2-chloroadenine to 2,6-diaminopurine, 115, 216
  in converting 2-halogeno- to 2-aminopurines, 111, 216
  in converting 2-methylthio- to 2-aminopurine, 216
  in coverting pteridines to purine, 56, 195
  in failure to rearrange 2-chloro-6-methylpurine, 110
  in synthesis of 2-halogenopurines, 103, 104
  intermediates in, 115
  mechanism for, 5, 244
Ara A, natural product, 273, 275
Aristeromycin, natural product, 272
O-Aroylation, 157, 230, 279
Arprinocid, natural product, 276
Aryl disulfides, as alkyl radical source, 121
Aryl triazenopurines, as radical source, 91
Ascamycin, natural product, 273
7-Azalumazine, 46
6-Azapteridines, to purines, 57
7-Azapteridines, to purines, 57
Azathioprine, 191, 212
8-Azidocaffeine:
  photolytic reduction, 252–253,
  reductive fusion of, 253

6-BAP, 275
Beckmann transformation, 239
Beerbaum, 382
Benzoadenine, 339–342
Benzodithiolylium tetrafluoroborate, in synthesis, 238
Benzoguanine, 340–342
Benzohypoxanthine, 339–342
Benzoxanthine, 340–342
3,1-Benzoxazine-2,4(1*H*, 3*H*)-diones, 26
6-Benzylaminopurine(BAP), 275
N-Benzylformamide, in xanthine to hypoxanthine, 56
Benzyltriethylammonium salts, as catalysts, 262
Betaines, *see also* Mesoionic purines
  of 1,3-dialkylhypoxanthine, 147
  of 7,9-dialkylhypoxanthine, 163
  of 8-pyridinioinosine, 116
  of 8-pyridinioguanine
  of 8-pyridinioxanthine
  of 6-trimethylammoniopurines, 112–115, 145
Biltz, 167
Bisazinopyrimidines, photolytic cyclization, 39
1,4-Bis(6-chloropurin-2-yl)butane, 345
1,8-Bisdimethylaminonaphthalene, *see* Proton sponge
1,3-Bis(diphenylphosphine)propanenickel dichloride, 89
Bis(dithiocarbamic acid)methyl ester, 44
1,2-Bis(2-fluoropurin-6-yl)hydrazine, 117
1,2-Bis(8-phenyltheophyllin-6-yl)hydrazine, 117
1,2-Bis(purin-6-ylthio)ethane, 121
3,7,9-Bis-*s*-triazolo[3, 4-*b*:3′, 4′ -*i*]purines, 249
Bond inversion, of *O*-alkenyl groups, 165–166
Bond isomerization:
  of 3-(3-methylbut-2-enyl)purines, 267
  of *O*-propargyl groups, 165–166
  of 9-(prop-2-enyl)purines, 268
  sigmatropic shifts, 165
Bosshard reagent, 101
Bromodiphenylmethane, *S*-protecting group, 12, 195
Bromotrichloromethane, 109, 167

Caffeine, 175–176
  adduct formation, 175
  C-alkylation, 175
  N-alkylation by PTC, 153, 172
  biological activity, 176
  8-fluoro, 106
  intercalation, 175
  metabolite, 176
  8-nitro, 106
  oxidation, 167
  ozonolysis, 175
  with radicals, 91
  self association, 175
  stacking effect, 175
  synthesis, 53, 75, 173, 175
Caffolides, 167
Caissarone, natural product, 276
Carbon disulfide, in synthesis, 67, 73
Carbovir, 280
Caro's Acid, 309
Chichibabin reaction, 11, 218, 269
  in *C*-6 amination, 218
  in formation of ^{15}N-6 adenine, 86
  in formation of 8-phenylpurine, 88

5-Chloro-1,3-dimethylisouric acid, 177
9-Chloromethyl-7-oxopyrimido[1,2-*c*]-purine, 297
4-Chlorophenylphosphorodichloridate, 171
4-Chloro-8-(thiazol-4-yl)purines, 102
Cisplatin, 278
Coformycin, 97, 275
Cordycepin, 87, 89, 195
Crotonoside, natural product, 281
18-Crown-6-ether, catalyst for halogen metathesis, 105
Crystallographic analysis:
of adduct formation, 226
of adenine cation, 270
of adenine dication, 271
of adenine-1-oxide-Cu complex, 313
of *N*-alkyl adenines, 270
of *N*-alkyl guanines, 177
of amidogen radical, 316
of coformycin, 97
of hypoxanthine, 17
of kinetin, 275
of 6-mercaptopurine tautomer, 17
of 3-methyl-8(8*H*)-imidazo[2,1-*i*]purine, 233
of *N*-methylxanthine ions, 14
of oxetanocin, 274
of purine protomers, 84
of purinophanes, 345
of saxitoxin, 276
of xanthine anion, 18,19
Crystal structure, 19
Cyanamide, in synthesis, 75
Cyanogen bromide, in synthesis, 65, 67
9-Cyanotheophylline, from rerrangement, 295
Cyclaridine, natural product, 276

Deamination:
from carbon 95, 243, 244
from nitrogen, 198, 244
Dehydrohalogenation, with DBU, 127
Demethylation:
at nitrogen, 35, 150, 253
at oxygen, 163
at sulfur, 74, 182–184, 189, 191, 199
Deoxycoformycin, *see* Pentostatin
4,8-Diaminopyrimido [5,4-*d*]pyrimidines, 289
1,8-Diazobicyclo [4,5,0] undec-7-ene, 127
Diazomethane, in *C*-methylation, 201
Diazotization, non aqueous, 145
Dichlorocarbene ion, in synthesis, 66
Dicuminyl peroxide, 142
N,N'-1,3-dicyclohexylcarbodiimide, 64
Dicyclohexyl-18-crown-6-ether, in C-8 debromination, 110
Diethoxymethyl acetate, in cyclization, 32, 69
Diethylazidodicarboxylate (DEAD), in oxidative cyclizations, 4, 38, 40, 53, 261, 265
Diethylcarbonate, in synthesis, 64, 312
Diethylpyrocarbonate, in synthesis, 69
4,9-Dihydro-4,6-dimethyl-9(1*H*)-oxoimidazo [1,2-*a*]purine, (Wye base), 279
7,8-Dihydro-9-methyl-9*H*-imidazo[2,1-*i*] purine, 270
7,8-Dihydro-8-methyl-6*H*-[1,3,6]-oxadiazocine [3,4,5-*gh*]purine, 112
5,9-Dihydro-9-oxoimidazo [1,2-*a*]purine, 66
8,9-Dihydro-9-oxopyrimido[1,2-*c*]purine, 297
2,3-Dihydro-2-thioxothiazolo[4,5-*d*]-pyrimidines, in synthesis, 35
1,4-Dihydro-1,2,4-triazino[3,4-*f*]xanthines, 298
8,9-Dihydro-3,4,6-trimethyl-9-oxoimidazo-[1,2-*a*]purines, 298
9-[(2,3-Dihydroxy-1-propoxy)methyl] adenine (DHPA), 280
9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine (Guancyclovir), 280
9-[(2,3-Dihydroxy-1-propoxy)methyl]guanine (DHPG), 280
Dihydrozeatin, natural product, 275
2-Dimethylamino-1,3-dioxolane, alternative to DMF, 225
Dimethylformamide, for dimethylamination, 116
Dimethylformamide diethylacetal, in synthesis, 49
6,8-Dimethylimidazo[2,1-*b*]purine, 227
7,8-Dimethylimidazo[2,1-*i*]purine, 226
Dimethyloxosulfonium methylide, methylating agent, 263
Dimroth rearrangement, 239–241, 267
of adenine to isoguanine, 281
of 1-alkoxyadenines, 251, 322
of 6-alkylamino-7-aminooxazolo[5,4-*d*]-pyrimidines, 55
of 7-benzyl-1,3-dimethylguanine, 72, 265
of 1,7-dimethylisoguanine, 72
of 1-hydroxyalkyladenines, 143, 240
of 6-imino-1-methoxypurine, 211
of 1-methyladenosine, 185, 380
reaction mechanism, 239, 322
related reaction, 59
reversed reaction, 241
spectral studies, 380
1,4-Dinitrobenzene, as radical scavenger, 123
3,5-Dioxo-4-phenyltriazoline, as alternative to DEAD, 53
N,N'-Diphenylcarbamoyl chloride, in *O*-alkylation, 265

5,7-Diphenyldihydrolumazine, 49
Diphenylphosphinylhydroxylamine, for *N*-amination, 220, 225
Dipurinyl disulfides, 203
Dipurin-2-yl sulfide, 188
Dipyrimidin-2-yl disulfides, 194
Discadine, natural product, 274–275
Doridosine, natural product, 281

Ehrlich Sachs reaction, 47
Electron spin resonance (ESR), 312, 378
Enzymic oxidation, 210
Eritadenine, 37, 319
Eschenmoser contraction, 90, 203
Ethenopurines, 67, 226, 227, 275
Ethoxymethylideneurethane, 77
Ethyl *N*-cyanoformimidate, 77
Ethyl formate, in synthesis, 62
Ethyl trithiocarbonic acid, 43

Fentons reagent, 142
Fischer cyclization, 36
  formula correction, 104
Fischer–Hepp isomerization, 236
Fluorescence:
  of 6-amidopurines, 287
  of 8,9-dihydroimidazo[1,2-*a*]purines, 227
  of 9,10-dihydropyrimido[1,2-*a*]purines, 227
  of guanine adducts, 227, 242
  of imidazo [2,1-*i*]purines, 226, 275
  and molecular planarity, 226
  of naphthoadenines, 341
  of 1,3,5-triazino[2,1-*i*]purines, 241
Furazano[3,4-*d*]pyrimidines, to adenines, 55
Fremy's radical, 342
Fujii, 241

Gamma radiation, in *C*-dehydroxyalkylation, 141
Gomberg–Bachmann reaction, 90
Gonyautoxin II and III, 276
Grignard reagents:
  with 6-chloropurines, 89
  for inserting alkyl groups, 88, 89
  with 6-methylthiopurines, 90
  with 7-phenylpurines, 334
Guancyclovir, 63, 280
Guanine, 277–280
  adduct with acrolein, 242
  amino group rotation, 277
  complex formation, 278–279
  oxidation, 277
  protonation, 277
  synthesis from imidazoles, 74, 75
  tautomerism, 277

Halogen to halogen metathesis, 104
Hexamethylphosphorous triamide, 107
Hilbert–Johnson reaction: 150, 164
  bond inversion, 165
  isomerization of triple bond, 165
  mechanism, 165
Hofmann–Martius reaction, 254
Hydrogen bonding:
  in acetoxy-oxopurines, 317
  in acylaminopurines, 262
  in adenine solutions, 270, 271
  in alcohol adducts, 141
  between amino group and ring nitrogen, 268
  between amino group and *N*-oxide, 223, 313
  between carbonyl oxygen and protonated ring nitrogen, 235, 286, 287
  in crown ethers, 379
  in disulfides, 204
  in 8-diazopurines, 304
  between molecular guanine and the anion, 278
  in 6-hydroxyalkylaminopurines, 235, 268
  in 6-ketonylpurines, 292
  between 6-oxo groups and water, 171
  in self-association of adenine, 271
  in 6-selenosulfidopurines, 204
  in stabilizing effect, 361
  in sulfines, 205
  in syn and anti rotamer formation, 222
  in triazenopurines, 237, 265, 268
Hydrogen fluoride, in liquid form, to replace 8-nitro groups by fluorine, 303
Hydrogen selenide:
  in amino to selenoxo, 323
  in methylthio to selenoxo, 184
Hydrogen sulfide, in liquid form, to replace 6-amino groups by sulfur, 185
Hydrolysis:
  of 6-amino groups, 135, 224, 236
  of 6-fluoro by autocatalysis, 120
  of 6-malonodialdohydopurine by acid, 170
  of trimethylammonio group by alkali, 135
Hydroquinone, radiation sensitizer, 144
C-Hydroxyalkylation, 142
9-[2-(Hydroxyethoxy)methyl]guanine, see Acyclovir
7-Hydroxyperhydro-1,4-oxazepin[3, 4-*f*] theophylline, 144
3-Hydroxypropionitrile, as ion trapping agent, 255

1-Hydroxy-2,4,6,8-tetraaza-3,7-dioxo-5-enebicyclo[2,3,0]octanes, as intermediates, 170
Hypoxanthine: 170
alkyl radical attack at C-8, 171
complex formation, 171
mesoionic states, 150
protomers, 147–149
specific N-7 alkylation, 171
synthesis, 56, 66, 139, 170
tautomerism, 147–149
Hypoxanthines:
from 7-aminooxazolo[5,4-*d*]pyrimidines, 54
from imidazole and dichlorocarbenes, 66
from imidazo[4,5-*d*][1,3]oxazines, 59
other imidazole closures, 75, 77

Imidazo[4,5-*d*][1,3]oxazines, 59, 74
Imidazo[1,2-*a*]purines, 227, 279, 298
Imidazo[1,2-*f*]purines, 144, 147
Imidazo[2,1-*b*]purines, 227
Imidazo[2,1-*i*]purines, 226, 228, 232, 270
Imidazo[4,5]quinazolines, *see* Stretched purines
Imidazo[5,4-*d*][1,3]thiazine, 72
Imidazo[4,5-*d*][1,3]thiazine, 58
Imuran, *see* Azothiopurine
Iodotrimethylsilane, 64
Isay condensation, 244
Isoeritadenine, *see* Eritadenine
Isoguanine, 280
from adenine, 280
from imidazoles, 67, 71, 280
in nature, 281
Isomerization, *see also* Rearrangements
7-acetyl-1-acetoxyxanthine to 9-acetyl isomer, 317
6-acylamino-3-alkylpurines to 9-alkyl isomers, 232
1-alkoxyadenines to 6-alkoxyaminopurines, 164–165
5-alkoxyiminooxazolo[5,4-*d*]purines to 2-alkylhypoxanthines, 147
alkoxypurines to *N*-alkyl-oxopurines (Hilbert–Johnson reaction), 164
6-allyloxy-2-aminopurine to 8-allylguanine, 165
6-allyloxy-9-benzylpurine to 1-allyl-9-benzylhypoxanthine, 165
5-amino-7-hydrazinothiazolo[5,4-*d*] pyrimidine to 2,9-diamino-6-thioxopurine, 185
3-benzyladenine to 6-benzylaminopurine, 267
1-benzyl-3-hydroxyxanthine to 1-benzyluric acid, 317
7-benzyloxycarbonyladenine to 9-benzyloxycarbonyl isomer, 296
1-benzylpurine to 3- and 7-benzyl isomers, 86, 96
7-chloro-1,2-dihydropyrimido[5,4-*e*]-*s*-triazine to 9-formamido-2-oxopurine, 220
1,9-dimethyl-6-dimethylaminopurine to 3,9-dimethyl-6-dimethylaminopurine, 267
3,7-dimethyl-6-dimethylaminopurine to 3,9-dimethyl-6-dimethylaminopurine, 267
7,9-dimethyl-6-dimethylaminopurine to 3,7-dimethyl-6-dimethylaminopurine, 267
7,9-dimethyl-6-dimethylaminopurine to 3,9-dimethyl-6-dimethylaminopurine, 267
1,7-dimethylguanine-3-oxide to 2-amino-1,7-dimethyl-6,8-dioxopurine, 315
3,7-dimethyl-6-methylaminopurine, 267
7,9-dimethyl-6-dimethylaminopurine to 3,7-dimethyl-6-methylaminopurine, 267
guanine-3-oxide to 2-amino-6,8-dioxopurine, 317
guanine-7-oxide to 2-amino-6,8-dioxopurine, 317
3-hydroxy-8-methylxanthine to 8-hydroxymethyluric acid, 317
1-hydroxyxanthine to 3-hydroxy isomer, 311
7-hydroxyxanthine to uric acid, 319
3-hydroxy-*N*-methylxanthines to *N*-methyluric acids, 316
9-methylguanine-7-oxide to 2-amino-9-methyl-6,8-dioxopurine, 315
7-methylhypoxanthine-1-oxide to 7-methyl-6,8-dioxopurine, 315
N-nitroso to *C*-nitroso group migration, (Fischer–Hepp reaction), 236
oxazolo[5,4-*d*]pyrimidines to 9-alkylhypoxanthines, 54
oxazolo[5,4-*d*]pyrimidines to 8-aminoguanines, 54, 215
oxazolo[5,4-*d*]pyrimidine-1-oxide to hypoxanthine-1-oxide, 55
purine-1-oxides to 2-oxopurines, 316
pyrimido[4,5-*b*][1,4]diazapines, to 7-isopropenyl-8-oxopurines, 59, 96, 139
pyrimidol[5,4-*e*]-1,2,4-triazine, to 9-cyanotheophylline, 295
thiazolo[5,4-*d*]pyrimidines to *N*-amino-6-thioxopurines, 185
thiazolo[5,4-*d*]pyrimidines to 6-mercaptopurines, 54
6-trimethyammoniopurines to

Isomerization (*Continued*)
6-dimethylamino-3 and 9-methylpurines, 255
Isopurone, 327

Johns, 155
Kinetin, natural product, 275
Knoevenegal reaction, 92, 93
Kochi's catalyst, 88, 334

Laser raman spectroscopy, 271
Lawesson's reagent, 340, 341
Leonard, Nelson, 337
Lithium azide, 119
Lithium diphenylcuprate, catalyst for *N*-alkenylation, 88
Lupinic acid, plant metabolite, 274
Liquid ammonia, *see also* ANRORC reactions
in *C*-and *N*-deamination, 243, 244
with fluorosulfonylpurines, 207
reaction with 2,6-dichloropurine, 114
Liquid hydrogen fluoride, *see* Hydrogen fluoride
Liquid hydrogen sulfide, *see* Hydrogen sulfide

Magnetic anisotropy, 368
Magnetic circular dichroism, 382
of adenines, 272
of alkylpurines, 383
Mannich reaction:
with adenine, 221
with guanine, 235
review of earlier results, 192, 202, 235
in thiomethylations, 202, 238
Mass spectra, 379
in de novo synthesis, 78
in Dimroth reaction, 379
field desorption in, 226
of purines, 379–382
of purine complexes, 226
tandem procedure, 380
two-pulse laser approach, 380
Mesoionic purines:
characteristic properties, 228
from 1,3-dialkyl-hypoxanthine 150, 161
from 3-methylguanine, 135
Metalation, with *n*-butyllithium:
to convert 8-methyl-to 8-ethylpurines, 89
C-8 lithiation of 9-substituted purines, 97
in C-8 methylation of adenosine, 89
in C-8 methylation of guanosine, 89
in 8-phenylselenocordycepin, 195
Methionine, in methylation, 194, 317
Methyldithiocarbamic acid, in synthesis, 24, 43
Methylenetriphenylphosphorane, purine ylid formation, 286
Methylhypochlorite, hazardous nature, 102
2-Methylpropan-2-thiolate, in *N*-demethylation, 266
7-Methylpyrimido[1,2-*a*]purine, 227
Methylseleno group, unreactive to acid, 135
N-(Methylthiochloromethyl)-*p*-toluene sulfonimide, 43
7-Methyl-*s*-triazolo[3,2-*i*]purine, 67
N-Methylureidouracils, 161

Michael addition:
with 3-acetoxy-1,4-oxathiane, 130
with acrylic anhydride, 228
with acylimines, 242, 298
adducts as intermediates, 49, 53
for *S*-alkenylation, 191
analogous reactions, 109
pentacyclic derivatives from, 282
Mitsonobu reaction, in *N*-alkylations, 261
with adenines, 261, 295
with guanines, 265
solvents and catalysts, 262
Murexide reaction, 175

Naphthoadenine, 338, 340, 341
Naphthohypoxanthine, 340
Nebularine, natural product, 83, 88, 97, 274, 314
conversion to coformycin, 275
methanol adduct, 97
ring expansion, 87, 97
photo addition of alcohols, 97, 141
Neplanocin A, natural product, 273
Nitrenium intermediates, 249, 253
Nitrenium ions, 318
Nitrogen trioxide, in hydrolysis, 135
Nitro group:
replacement by chloro, 102, 106
replacement by dimethylamino, 303
replacement by fluoro, 106, 303
Nitrones, of xanthine, 316
Nitrophenylisothiocyanate, 52
N-Nitrosodimethylamine, 51
Nitrosopurines:
C-nitroso derivatives, 303–305, 311
N-nitroso derivatives, 236, 311
Nitrosyl chloride, in hydrolysis, 135
8-Nitrotheophylline, to 8-dimethylaminotheophylline, 219
8-Nitroxanthine, 303, 317

Nitroxyl form:
of adenine, 378
of 3-hydroxyxanthine, 316, 368
NMR Specra, 348
Carbon-13 resonance, 362
of ionization sites, 372
of methylation sites, 371
Nitrogen-15 resonance, 362
Proton resonance, 348
in purine mixtures assays, 374
of tautomeric species, 373
Nuclear Overhauser effect:
enhancement, 368
relaxation, 368
suppression, 368

Oncogenic activity, 324
One pot reaction, *see* One step reaction
One step reactions, in purine synthesis:
in 4-amino-5-azopyrimidine cyclization, 48
in benzaldehyde cyclizations, 39
in cyanoimidazole ring closures, 70
in guanosine to thioguanosine conversion, 149
for hypoxanthine, 170
in oxopyrimidines to aminopurines, 27, 158, 217
in tetraalkoxymethane cyclization, 41
using acyclic precursors, 77, 215
for xanthine, 172
Ortoleva–King reaction, 93, 309
1,2,4-Oxadiazolo[2,3-*i*]purines, 319
Oxazolo[3,2-*a*]purine, 220
Oxazolo[5,4-*d*]pyrimidine, 300, 311
rearrangement to 8-aminoguanines, 215
Oxetanocin, natural product, 274
Oxidation:
of adenine to allantoin, 245
of aldehydes in cyclizations, 67
of alkylthio- to alkylsulfinylpurines, 208
of alkylthio- to alkylsulfonylpurines, 209
of 6-carboxypurines-1-oxide to hypoxanthine, 139
of 6-cyano to 6-amidopurine, 288
of 6-dialkylamino groups, 229, 231
by electrochemical means, 169
by enzymes, 140, 169, 320, 324
of guanine, 277
6-hydroxyamino-3-oxido- to 6-nitrosopurine, 304
of methyl- to aldehydopurines, 92
of methyl- to carboxypurines, 92
of methylhydrazino to methylaminopurines, 219
of oxopurines, 166–169
of purine, to *N*-oxides, 93, 309–311
of reduced purines, 331, 334
of selenoxo- to oxopurines, 193
of 8-styryl to 8-carboxyadenine, 284
of thioxo- to dipurinyl disulfides, 203
of thioxo- to dipyrimidyl disulfides, 193
of thioxo- to sulfinylpurines, 207
of thioxo- to sulfonylpurines, 207
of uric acids, *see* Uric acid
8-Oxo-1,2,4-oxadiazolo[2,3-*i*]purine, 319
9-Oxopyrimido[1,2-*c*]purine, 242

Ozonolysis, 169
of caffeine, 175
of guanine, 277–278

Pentostatin, natural product, 275
Perhydropurines, 331
Permethylation:
of adenine, 238
of uric acid, 157
of xanthine, 153
Phase Transfer Catalysis (PTC):
in *N*-alkylation of adenines, 261–262
in alkylation of amino groups, 238
in *N*-alkylation of xanthines, 153
catalysts for, 262
Phenylazomalonic acid, intermediate, 79
6-Phenyllumazine, 47
Phidolopin, natural product, 174
Phleomycin, natural product, 176
Phosgene-carbodiimide complex, in synthesis, 215
Photoreactions:
4,5-bisazinopyrimidine to theophylline, 39
8-azido- to 8-aminocaffeine, 253
6-azidopurine-9-riboside to adenosine, 252
8-hydroxyalkyl group, removal, 144
1-hydroxyhypoxanthine to hypoxanthine, 170
6-mercaptopurine to hypoxanthine, 170
N-oxidopurines, isomerization, 311, 316–317
Photosensitizers, in irradiation, 144
Picolin-2-yl-*N*-oxide, *N*-protecting group, 8, 151, 210, 217, 263, 266, 320
Pivaloyloxymethyl, *N*-protecting group, 264
Polyphosphoric acid, 51
Primordial soup, in prebiotic synthesis, 81
Proton exchange at C-8, 13
Proton sponge, catalyst, 264
Pteridines, as uric acid precursors, 56–57, 139
Pugmire, 373
Pullman, 374

Purine:
with alcohol radicals, 87
C-alkylation, 87, 90–91
N-alkylation, 94
conversion to adenine, 86, 218
formation by *C*-deamination, 95
formation by *N*-deamination, 84, 244
intercalation, with DNA, 85
oxidation, 309
protonation, 17
radical, 84, 89, 9, 102, 156
reduction, 325–328, 332–334
self-association, 85, 361
synthesis, 77, 95, 186
tautomeric ratio, 85
Purine adducts:
with acrolein, 242
with acylvinyltriphenylphosphonium bromide, 227
with alcohols, 87, 141
with barbituric acids, 86
with cyclobutane, 175
with dinitrosyl iron, 378
with hydrogen sulfite ions, 86
with methacrylonitrile, 301
with urea, 86
Purines:
biosynthesis, 82
mass spectra, 379–382
natural occurrence, 97, 174, 269–281
reduced, 271, 325
stretched, 337
trivial names, 3–4
ylid forms, 14, 15, 88, 285
Purinyl polysulfides, 204
Purinophanes, 129, 200
Purin-6-ylpyridinium chloride, 112, 146, 159, 171
Puromycin, natural product, 13
Purone, structure confirmation, 327
Pyrazolo[3,2-*d*]pyrimidines, 285
Pyrimidine ring enlargement, 97
to imidazo[4,5-*e*][1,4]diazapin-5,8-dione, 296
Pyrimido[4,5-*b*][1,4]diazapines, to 7-isopropenyl-8-oxopurines, 59
Pyrimido[1,2-*a*]purines, 227, 338, 341
Pyrimido[1,2-*c*]purines, 242, 277
Pyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-triones, 242
Pyrimido[4,5-*e*]-1,2,4-triazines, 245
Pyrimido[5,4-*e*]-1,2,4-triazines, 220, 230, 295

Quadrupole relaxation:
in adenine cations, 271
in *N*-methyl couplings, 348
Quaternary salts:
pyridiniopurines, 102, 112, 113, 116, 146, 149, 156, 171, 218
trimethylammoniopurines, 253–256
Quenching reagents:
for ANRORC reaction, 95, 243
for Nuclear Overhauser relaxation, 368
Radicals, 12, 106
in alkylation at C-2 and C-6, 50, 87, 90
in alkylation at C-8, 50, 90, 166, 171, 173, 221
in benzylation at C-8, 171, 173
in bromination at C-2 and C-6, 104
in chlorination at C-2 and C-6, 102
in chlorination at C-8, 102
in dark reaction, 123, 174
in *C*-deamination, 95
in *N*-deamination, 243
in iodination at C-2 and C-6, 104
in oxidation at C-8, 139
in replacing amino by chloro, 102, 224
in replacing amino by fluoro, 105, 224
in replacing amino by phenyl, 90
in ring closure of 4-amino-5-azopyrimidines, 50
Radical scavengers, 123,177
Radical sources:
from alcohols, 87
amidyl from 3-acetoxyxanthine, 318, 378
aryl from 6-aryltriazenopurine, 91
benzyl from benzyl bromide, 91
butyl from pivalic acid, 91
cyclohexyl from cyclohexyl carboxylate, 91
ethyl from alanine or serine, 91
hydroxyl from Fenton's reagent, 142
ketonyl from ketones, 89,123, 292
methyl from butyl peroxides, 90
methyl from diazomethane, 90
methylthio from dimethyl disulfide, 121
phenylthio from diphenyl disulfide, 121, 195
purinyl from diazopurines, 102
purinyl from *N*-oxides, 313
trichloromethyl from bromotrichloromethane, 102
urate from uric acid, 177
xanthinyl from xanthine, 316–317
Raphanitin, natural product, 274
Rearrangement, *see also* Dimroth rearrangement; Isomerization:
3-acetoxyxanthine to uric acid, 319
7-aminooxazolo[5,4-*d*]pyrimidine-6-oxide to hypoxanthine 3-oxide, 311
aminothiadiazolo[3,4-*d*]pyrimidine to 9-alkyladenines, 215

8-azidocaffeine to 7-amino-1,3-dimethyl-2,4-dioxopteridine, 249, 295
6-cyanopurine to 4,8-diamino[5,4-*d*]-pyrimidine, 289
6,8-dimethyl-5,7-dioxopyrimido[5,4-*e*]-1,2,4-triazine to 9-cyanotheophylline, 295
8-hydrazinocaffeine to 7-amino-1,3-dimethyl-2,4-dioxopteridine, 249, 295
imidazo[4,5-*d*]oxazines to 1-alkylhypoxanthines, 59
7-pivaloyloxymethylpurine to 6-pivaloylaminopurine, 228
6-trichloromethylpurine to 6-dichloromethyl-8-oxopurine, 93
Reduction:
acylamino- to alkylaminopurines, 231
of alkoxyaminopurines, 217–218, 251
of *N*-alkoxypurines, 322
of 6-azapteridines to purines, 57
of 5-azopyrimidines, 47–48
of azidopurines, 252
of *N*-benzyloxypurines, 322
of 6-chloropurines, 105, 110
of cyanomethylpurines, 221
of disulfides, 184
of eritadenine-*N*-oxide, 314
of furazano[3,4-*d*]pyrimidines, 55
of hydrazinopurines, 218, 248
of hydroxyaminopurines, 250
of nitrogen groups to amino, 217–218
of *N*-nitrosoaminopurines, 218, 247
of 5-nitrosopyrimidines, 44
of purine-*N*-oxides, 319
of purines, 325–328, 332–334
in removal of protecting groups, 266
of Schiff bases, 238
of triazenopurines, 237
Rose bengal, U.V. sensitizer, 162
Rotameric groups:
in alkylaminopurines, 222
in *N*-oxides, 313
Ruthenium tetroxide, in oxidation, 8, 12, 229–231, 229, 239

Saxitoxin, natural product, 276
Schiemann reaction, 105
Schiff base, 43, 225, 227, 238, 248, 249
Seela's reaction, 110
Selenium dioxide, in methyl group oxidation, 92, 309
8-Selenoadenosine, synthesis, 122
8-Selenoguanosine, synthesis, 122, 211
8-Selenohypoxanthine, synthesis, 122
Selenourea, in synthesis, 122, 182
Selenoxopurines, 181, 182, 184, 186–188, 211
Self association:
of adenine, 271
of caffeine, 175
of purine, 85, 361
of trichloromethyl radical, 102
Shaw synthesis, 312
Sigmatropic shifts, in bond isomerization, 165
Sinefungin, natural product, 273
Spongoadenosine, *see* Ara A
Spongosine, natural product, 281
Steric effects:
in *N*-alkylation, by 8-chloro, 113, 155, 201
in *C*-amination, by 8-alkyl, 21
in *N*-amination, 94
of 8-alkyl groups with anions, 155, 221, 318
in amino group rotation, 223
in Dimroth reaction, 72
in *N*-methylation, 267
in oxo to amino conversion, 27
on ring closure, 26,31
shielding of ring nitrogen by amino, 256
Still's procedure, in flash chromatography, 128
Strecker synthesis, 221, 295
Stretched purines, 337–342
Sulfur:
direct introduction at C-8, 184
excision, 187, 192, 196
Sulfur chloride-trifluoroacetic acid complex, in methyl group trifluorination, 107

Tafel, 326
Tedania, *see* Doridosine
Tetraalkoxymethanes, in synthesis, 41, 90
Tetra-*n*-butylammonium iodotetrachloride, 106
Tetrakis(triphenylphosphine)palladium, catalyst, 89
Theobromine, 153, 166, 174
by alkylation(PTC) of xanthine, 174
Theophylline, 39, 173
anomalous alkylation, 91
8-fluoro, 106, 121
8-nitro, 102, 106, 219
oxidation, 170
1,2,5-Thiadiazolo[3,4-*d*]pyrimidines, in synthesis, 55
Thiazolo[2,3-*b*]adenine, 196
Thiazolo[3,2-*a*]adenine, 196, 198
Thiazolo[2,3-*f*]purine, 191, 196, 302
desulfurization to 7-alkenylguanine, 95, 191
Thiazolo[3,2-*a*]purines, 220
Thiazolo[5,4-*d*]pyrimidines, 220

Thietan adduct, 302
Thioacetylation, 229
N,N'-Thiocabonyldiimidazole, in synthesis, 67
Thioxo group:
  alkylation, 194, 195
  direct introduction at C-8, 184
  formylation, 194
  oxidation, 208
Transalkylthiolation, 188
Transamination, 47, 239
Transmethylation, 183–184
Traube synthesis, 22–42, 84, 87, 96, 100, 128, 140, 141, 145, 176, 180, 190, 194, 214, 244, 255, 272, 280, 285, 301, 323, 339, 345
  involving cyclodehydration, 47
  in extended forms, 28, 38, 56, 150, 170, 171, 177
  in one-pot reactions, 27, 39, 48, 49
  in reaction with 1,3-diketones, 40
  in regiospecific synthesis, 269
6-Triazenopurines, 237, 304
Triazepinopurines, 245
1,2,4-Triazino[2,3-*a*]purines, 245, 338
1,2,4-Triazino[3,2-*f*]purines, 245
1,2,4-Triazino[3,2-*i*]purines, 245
1,3,5-Triazino[1,2-*a*]purines, 338, 341
1,3,5-Triazino[2,1-*i*]purines, 241
1,2,4-Triazino[3,4-*f*]xanthine, 298
s-Triazolo[2,3-*a*]purines, 244
s-Triazolo[3,2-*a*]purines, 249
s-Triazolo[3,2-*i*]purines, 244, 245
s-Triazolo[4,3-*e*]purines, 249
Tributylphosphine-cobalt(III)dimethylglyoxime, as N-blocking group, 141
Trifluoromethyl group:
  from halogen group, 107
  from methyl group, 107
Trifluoromethyl-copper complex, 150
  for 8-iodo group removal, 150
Trimethyl ammoniopurines, *see also* Betaines
  from chloropurines, 146, 163, 253
  with hydrazine, 247
  hydrolysis, 254
  with methoxides, 254
  as methylating agents, 254–255
  reaction kinetics, 254
  rearrangement, 239, 255, 263
Trimethylanilinium methoxide(TAMM):
  in *O*-methylation, 279
  in permethylation, 238
Trimethylselonium hydroxide, as methylating agent, 153
Tris(triphenylphosphine)palladium dichloride, 88

Uric acid:
  from 3-acetoxyxanthine, 318
  O-acylation, 157
  N-acylation, 176
  as antioxidant, 177
  from 7-hydroxyxanthine, 319
  permethylation, 157
  from pteridines, 56–57, 139
  as radical scavenger, 177
  reduction, 326–327
Uric acid oxidation:
  by chlorine in acids, 167
  by chlorine in nonaqueous media, 168
  by electrochemical reaction, 169
  by enzymes, 169
  reaction in neutral and alkaline media, 168
  urate radical formation, 177

Verdan®, 275
Vidarabine, *see* Ara A, 170, 171
Vilsmeier reagent, 33, 100
  adduct with 6-methylpurine, 290
  in forming azamethines, 45, 92
  in forming bisazamethinylpyrimidines, 45
  in forming 2-chloromethylpurines, 108
  in forming 8-dimethylaminopurines, 44
  in forming 6-(4-dimethylaminophenyl)-purines, 101
  in forming 6-malonoaldehydopurines, 107
  with phosphoryl chloride and *N*-nitrosodimethylamine, 51
  in forming pyrazolo[3,2-*d*]pyrimidines, 34
  in forming pyrimido[4,5-*d*]pyridines, 45
  in forming *s*-triazolo[2,3-*a*]purines, 244
C-Vinylation, with tri-*n*-butylvinylstannate, 88, 97

Wittig reaction, 48, 286, 289, 292
Wye base, 279
Wybutine, natural product, 279
Wybutosine, natural product, 279
Wybutoxine, oxidation product, 279
Wyosine, 279
Wye nucleosides, natural product, 279

Xanthine, 172
  N-alkylation, by PTC, 153
  anion, 148
  conversion to hypoxanthine, 138, 172
  MCD spectrum, 148
  permethylation, 153
  protomers, 147–148

radical, 324
synthesis, 80, 138, 172
tautomers, 148, 172–173
Xanthines, synthesis:
from dihydro[4,5-*e*]triazines, 139
from imidazole closure with diethyl carbonate, 64

Y-bases, *see* Wye base
Yoneda, 51

Zeatin, natural product, 112, 274–275
cis and trans isomers, synthesis, 274
dihydro derivatives, 275
metabolites of, 274, 275
Zovirax, see Acyclovir
Zwitter ions, 13–15,182. *See also under* Mesoionic purines