THE PYRIMIDINES

This is the fifty-second volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

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THE PYRIMIDINES

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Dedicated to
Four of the Great Pyrimidine Chemists of Our Day

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(Novosibirsk: † 1987)

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(Oslo)

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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 of 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 that 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, and 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 were intended to be 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.

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Preface

The first edition of this work (Volume 16 of the Chemistry of Heterocyclic Compounds) comprised three volumes, of which *The Pyrimidines* covered the literature from 1818 to 1957, *The Pyrimidines*: *Supplement I* covered the decade to 1967, and *The Pyrimidines*: *Supplement II* continued the reviewing process to 1983. Shortly afterward, the first two volumes were declared out of print so that a full digest of pyrimidine literature was no longer available to newly established libraries in academic or industrial laboratories. Accordingly, it was decided to prepare a second edition of *The Pyrimidines* based on still-useful information from all volumes of the first edition plus original material that had appeared subsequently. For pragmatic reasons, the second edition had to fit within a single volume, so the task of selection and compression has been considerable. For example, much relevant historical and anecdotal material has been omitted or drastically shortened; the criteria for inclusion of "simple pyrimidines" in the Appendix Table has been tightened to exclude higher homologs and other marginal categories of not-so-simple pyrimidines; only the better-described examples of each synthesis or reaction have been chosen for outlining; and background analyses of ionization and spectral data (except for nmr) have been deleted, simply because such techniques are now seldom used in the pyrimidine field. In addition, nomenclature has been modernized completely, as outlined in Section 1.2, and the use of trivial names (e.g., uracil) has been minimized throughout. Many recent patents have been ignored in the belief that useful factual material therein has appeared subsequently in the regular literature.

On the basis of references cited in this book, the geographic and ethnic origins of papers on pyrimidine chemistry may surprise some:

United States of America	24.7%
Germany, Switzerland, and Austria	18.6%
British Commonwealth (past & present)	16.7%
Japan	14.0%
Former USSR Republics	8.3%
France, Italy, Spain, and South America	5.7%
Eastern European Countries	5.7%
Netherlands and Belgium	2.1%
Scandinavian Countries	1.3%
Israel, Arabic Countries, China, etc.	2.9%

I am greatly indebted to Dr W. B. Cowden, Dr R. F. Evans (kindly encouraged and assisted by his wife, Carmel), and Dr. M. D. Fenn for writing sections on pyrimidine *N*-oxides, hydropyrimidines, and pyrimidine nmr spec-

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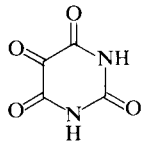
CHAPTER 1

Introduction to Pyrimidine Chemistry

After a brief historical introduction and some guidelines on nomenclature, this chapter outlines the reasons why pyrimidine chemistry is unique. In this context, it presents a summary of those reactions that occur at the pyrimidine nucleus and of those that occur at substituents directly attached to the nucleus. Although the myriad primary synthetic methods for pyrimidines are of enormous interest and practical importance, no summary is attempted in this chapter because the reactions involved are essentially aliphatic chemistry; nor are reactions at substituents remote from the nucleus here summarized, simply because such chemistry is virtually independent of the pyrimidine ring. For reduced pyrimidines, see Chapter 11.

1.1. HISTORY AND REVIEWS

In 1818, Brugnatelli isolated the first pyrimidine derivative from oxidative degradation of uric acid with nitric acid.[5549] His product, now known to be alloxan (**1**), was investigated further by Wöhler and Liebig 20 years later.[1656] In 1848, a second pyrimidine synthesis was pioneered by Frankland and Kolbe, who heated propionitrile with metallic potassium to give a pure product,[2534] shown 40 years later to be 2,6-diethyl-5-methyl-4-pyrimidinamine (**2**).[2544] A third type of synthesis was introduced in 1878 by Grimaux, who condensed malonic acid with urea to afford barbituric acid (**3**),[6128, cf. 3550] the first example of a Principal Synthesis. This general procedure has sometimes been named inappropriately after Pinner, who began his classical work in this area only in 1884,[6144] but who did have the distinction of naming the pyrimidine system and of recognizing its true nature as an hexagonal analog of benzene and pyridine.[5236] A laudable attempt by Widmann[6145] in 1888 to rename the system more logically as "miazin(e)" was never popular, and the new name was laid to rest finally in 1905 by von Meyer in these words:[2116] "Die von O. Widmann statt Pyrimidin vorgeschlagene Bezeichnung *Miazin* hat, so viele Vorzüge sie bietet, keinen Eingang gefunden." Unsubstituted pyrimidine (**4**) was prepared first in 1899 by Gabriel and Colman.[1517] Other important contributions to this classical period of pyrimidine research (mainly German and stimulated by the isolation of uracil, cytosine, and thymine from natural sources) were made



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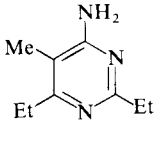

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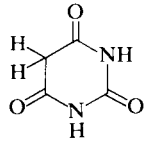

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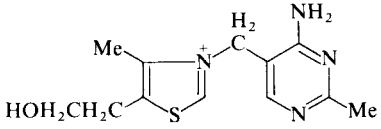
especially by Behrend,[6146] Gabriel,[6147] Fischer,[6148] Traube,[6149] and von Meyer.[6150]

About 1905, the centre of gravity of pyrimidine research shifted from Germany to Yale in the United States where Wheeler had established an active pyrimidine/purine school, eventually headed by his student, Johnson.[6151] Despite an occasional error in his voluminous papers, this "kindly, simple-mannered man" exerted a profound influence on the course of pyrimidine research during this 30 year American period.

Around 1935, a new and truly international period of pyrimidine investigations began. This was stimulated initially by Japanese work on thiamine (**5**) and subsequent syntheses in several countries (see Section 9.4.2). Momentum was maintained by the advent of useful drugs or agrochemicals: antibacterial sulfanilamidopyrimidines (e.g., sulfadiazine), antimicrobial or antimalarial pyrimidinediamines (e.g., pyrimethamine and trimethoprim), anticancer agents (e.g., fluorouracil, uracil mustard, bleomycin), specialized sedative barbiturates (e.g., thiopental), thyroid-stabilizing thiouracils (e.g., propylthiouracil), and many others (see Sections 7.1.5 and 9.4). Interest in pyrimidine chemistry was enhanced further in the postwar decades by unprecedented activity in the nucleic acid field and especially by a massive resurgence of interest in fused pyrimidines, for which a great variety of pyrimidine intermediates were required: for example, most of the syntheses of pteridines (**6**) within groups headed by Albert,[6165] Pfleiderer, Taylor, Viscontini, and others involved a considerable proportion of investigative work on appropriate pyrimidine intermediates (**7**).[5823]



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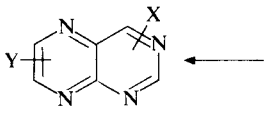

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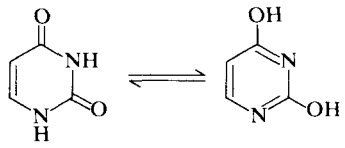
The last 10 years must be considered as a period of reduced activity in pyrimidine research. Nevertheless, several hundred original papers continue to appear each year, and many of these contain fascinating work, especially on quite esoteric primary syntheses and on all manners of useful metal-assisted reactions.

Many *general reviews* of pyrimidine chemistry have appeared. The first of these, Johnson (1918),[6152] summarized the nineteenth-century history in some

detail. The main subsequent reviews, each aiming to reflect the state of pyrimidine chemistry at the time of writing, appeared frequently but at irregular intervals: Jacobson (1920),[6153] Johnson and Hahn (1933),[6154] Johnson (1938),[6155] Lythgoe (1949),[6156] Kenner (1950),[6157] Brown (1953),[6158] Wiley (1953),[6159] Bendich (1955),[6160] Kenner and Todd (1957),[6161] Ramage and Landquist (1959),[6162] Brown (1980),[4003] Hurst (1980),[4004] Brown (1981),[4002] Brown (1984),[6081] Brown et al. (1962, 1970, 1985),[6163] and Walker (1989).[6164] Reviews of some specific aspects of pyrimidine chemistry are noted in appropriate sections of this book.

1.2. NOMENCLATURE

The vagaries of organic chemical nomenclature, especially in the area of heterocyclic chemistry, are well known. Although simple pyrimidines have always been formulated as **4** with the IUPAC numbering shown, uracil (**8**) and its derivatives have been numbered frequently with their oxy substituents at the 2- and 6-positions to conform with the exceptional numbering system of purine (**9**), still unaccountably recommended by IUPAC;[6166] cytosine (**10**, R = H) and its derivatives have suffered also from a similar ambiguity, but mainly in the older literature. The most serious confusion results from *N*-substitution in association with such trivial names. For example, methylation of cytosine (**10**, R = H) gives the product (**10**, R = Me), then known as 1- or 3-methylcytosine according to whether the amino group is considered to occupy the 4- or 6-position: in 1955, the *Journal of the Chemical Society* used one system on page 214, but the other on page 855! For this reason, trivial names are avoided in most of this book, for example, by naming the methylated cytosine (**10**, R = Me) as 4-amino-1-methyl-2(1*H*)-pyrimidinone.



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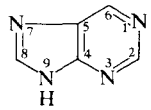

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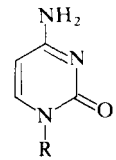

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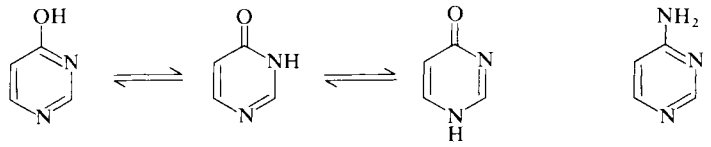
The naming of nitrogenous heterocycles bearing α- and/or γ-tautomeric groups is always confusing: for example, what is the tautomeric compound (**11**) to be called? Fortunately, it is an experimental fact that most such compounds exist predominantly with the mobile hydrogen attached to the α-nitrogen atom, so that they are named accordingly (at least in this book): thus compound **11** is known as 4(3*H*)-pyrimidinone. In contrast, compounds such as **12** invariably retain their mobile hydrogen on the exocyclic nitrogen, so that the amine (**12**) is named as 4-pyrimidinamine rather than 4(3*H*)-pyrimidinimine or the like.



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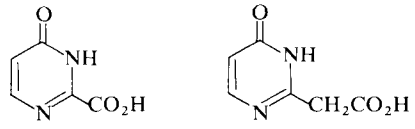
All other nomenclature in the book also follows the general IUPAC rules[6166] with one important exception. In order to keep "pyrimidine" as the principal part of each name, those groups that would normally qualify as suffixes, but which are not attached *directly* to the nucleus, are rendered as prefixes: thus the acid (**13**) is called 4-oxo-3,4-dihydro-2-pyrimidinecarboxylic acid but the related acid (**14**) is called 2-carboxymethyl-4(3*H*)-pyrimidinone rather than α-(4-oxo-3,4-dihydropyrimidin-2-yl)acetic acid; all substituted-amino groups are rendered also as prefixes.



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Although little used in this book, the more common trivial names for pyrimidines have been collected in Table 1.1 to facilitate an understanding of many original papers in which they occur.

1.3. FACTORS IN THE UNIQUITY OF PYRIMIDINE CHEMISTRY

The unique reactions and properties of pyrimidine and its derivatives are derived from their electronic structures, which in turn result from five simple structural factors. It is surprising how often such factors can be used to explain, or even predict, the most diverse experimental observations.

1.3.1. The Activated 2- and 4/6-Positions

The starred 2-, 4-, and 6-positions of pyrimidine (**15**) are naturally deficient in π-electrons by virtue of the powerful electron localization at the ring-nitrogen atoms. In this, such positions resemble qualitatively the corresponding positions of pyridine (**16**) and nitrobenzene (**17**) or 1,3-dinitrobenzene (**18**), in both of which π-electrons are localized similarly by the nitro group(s). Because the nitrogen atoms of pyrimidine (**15**) are *meta* to one another, their separate effects reinforce each other (as in 1,3-dinitrobenzene) and the resultant effect is far

TABLE 1.1. TRIVIAL NAMES OF PYRIMIDINES

Trivial Name	Systematic Name
Acetonin	2,2,4,4,6-Pentamethyl-2,3,4,5-tetrahydropyrimidine
Albomycin	An antibiotic: see Section 7.1.4.10
Alloxan	5-Oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Alloxantin	5,5′-Dihydroxy-5,5′-bipyrimidine-2,2′,4,4′,6,6′(1*H*,1′*H*,3*H*,3′*H*,5*H*,5′*H*)-hexone
Amicitin	An antibiotic: see Section 7.1.4.10
Aminobarbituric acid	2-Amino-4,6(1*H*,5*H*)-pyrimidinedione
Aneurin	See Thiamine
Bacimethrin	An antibiotic: 5-hydroxymethyl-2-methoxy-4-pyrimidinamine
Bamicitin	An antibiotic: see Section 7.1.4.10
Barbital[a]	5,5-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Barbituric acid	2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione
Blasticidin S	An antibiotic: see Section 7.1.4.10
Bleomycin	An antibiotic: see Section 9.4.5
Bromacil	5-Bromo-3-*s*-butyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione
Convicine	6-Amino-5-β-D-glucopyranosyloxy-2,4(1*H*,3*H*)-pyrimidinedione
Cyanmethine	See Kyanmethin
Cytarabine	4-Amino-1-β-D-arabinofuranosyl-2(1*H*)-pyrimidinone
Cytidine	4-Amino-1-β-D-ribofuranosyl-2(1*H*)-pyrimidinone
Cytosine	4-Amino-2(1*H*)-pyrimidinone
Dialuric acid	5-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Diaveridine	5-(3′,4′-Dimethoxybenzyl)-2,4-pyrimidinediamine
m-Diazane	1,2,3,4,5,6-Hexahydropyrimidine
m-Diazine	Pyrimidine
Dilituric acid	5-Nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Dithiouracil	2,4(1*H*,3*H*)-Pyrimidinedithione
Divicine	2,5-Diamino-5-hydroxy-4(3*H*)-pyrimidinone
Gougerotin	An antibiotic: see Section 7.1.4.10
Hydrouracil	5,6-Dihydro-2,4(1*H*,3*H*)-pyrimidinedione
Isobarbituric acid	5-Hydroxy-2,4(1*H*,3*H*)-pyrimidinedione
Isocytosine	2-Amino-4(3*H*)-pyrimidinone
Isodialuric acid	6-Hydroxy-2,4,5(1*H*,3*H*,6*H*)-pyrimidinetrione?
Isouracil	5-Hydroxy-2(1*H*)-pyrimidinone
Isouramil	6-Amino-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione
Isovioluric acid	5-Hydroxy-6-nitroso-2,4(1*H*,3*H*)-pyrimidinedione
Ketobarbituric acid	5-Oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Kyanmethin[b]	2,6-Dimethyl-4-pyrimidinamine
Lathyrine	4-(β-Amino-β-carboxyethyl)-2-pyrimidinamine
Malonurea	5,5-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Malonylurea	2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione
Methylcytosine	4-Amino-5-methyl-2(1*H*)-pyrimidinone
Miazine	Pyrimidine
Murexide	Bis(2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl)amine, ammonium salt
Orotic acid	2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid
Phleomycin	An antibiotic: see Section 9.4.5
Piperimidine	1,2,3,4,5,6-Hexahydropyrimidine
Plicacetin	An antibiotic: see Section 7.1.4.10
Primidone	5-Ethyl-5-phenyl-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione

TABLE 1.1. (*Contd.*)

Trivial Name	Systematic Name
Pseudouracil	4,6(1*H*,5*H*)-Pyrimidinedione
Pseudouric acid	5-Ureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Purpuric acid	Bis(2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl)amine
Pyramine	See Toxopyrimidine
Pyrimethamine	5-*p*-Chlorophenyl-6-ethyl-2,4-pyrimidinediamine
Sparsomycin	An antibiotic: see Section 7.1.4.10
Sulfadiazine[c]	2-Sulfanilamidopyrimidine
Spongothymidine	1-β-D-Arabinofuranosyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione?[6167]
Tartronylurea	5-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Thiamin(e)	5-(5′-β-Hydroxyethyl-4′-methylthiazolio)methyl-2-methyl-4-pyrimidinamine chloride hydrochloride
Thiobarbituric acid	2-Thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione
Thiouramil	5-Amino-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione
(2-)Thiouracil	2-Thioxo-1,2-dihydro-4(3*H*)-pyrimidinone
4-Thiouracil	4-Thioxo-3,4-dihydro-2(1*H*)-pyrimidinone
Thymidine	1-(β-2′-Deoxy-D-ribofuranosyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione
Thymine	5-Methyl-2,4(1*H*,3*H*)-pyrimidinedione
Thyminyl alcohol	5-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione
Tingitanin	See Lathyrine
Toxopyrimidine	5-Hydroxymethyl-2-methyl-4-pyrimidinamine
Trimethoprim	5-(3′,4′,5′-Trimethoxybenzyl)-2,4-pyrimidinediamine
Uracil	2,4(1*H*,3*H*)-Pyrimidinedione
Uracil mustard	5-Di(β-chloroethyl)amino-2,4(1*H*,3*H*)-pyrimidinedione
Uramil	5-Amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Uridine	1-β-D-Ribofuranosyl-2,4(1*H*,3*H*)-pyrimidinedione
Vicine	2,6-Diamino-5-β-D-glucopyranosyloxy-4(3*H*)-pyrimidinone
Violuric acid	5-Nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione
Vitamin B_1	See Thiamine
Willardiine	1-(β-Amino-β-carboxyethyl)-2,4(1*H*,3*H*)-pyrimidinedione

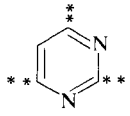
[a] For trivial names of other currently used barbiturate sedatives, see Section 7.1.5.1.

[b] The *Kyanalkine* are 2,6-dialkyl-5-(demethylenealkyl)-4-pyrimidinamines: for example, Kyanisobutin is 2,6-diisobutyl-5-isopropyl-4-pyrimidinamine.

[c] For trivial names other currently used sulfanilamidopyrimidine antibacterials, see Section 9.4.4.

greater in pyrimidine than in its isomers, pyrazine (**19**) and pyridazine (**20**), in both of which each marked position is activated by only one ring nitrogen.

The electron deficiency at the marked positions of pyrimidine (**15**) is reflected clearly in the enhanced reactivity of substituents there. For example, an halogen



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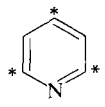

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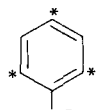

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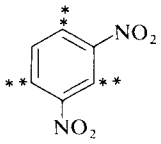

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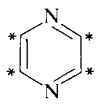

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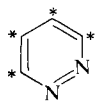

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substituent is easily displaced by nucleophilic reagents: ammonia or amines give a pyrimidinamine, water (H^+ or HO^- catalyzed) gives a pyrimidinone, sodium hydrogen sulfide gives a pyrimidinethione, sodium alkoxide gives an alkoxypyrimidine, and sodium alkylsulfide gives an alkylthiopyrimidine; likewise, carboxy group at such positions tend to lose carbon dioxide relatively easily and methyl groups undergo styrylation or oxidation relatively easily.

1.3.2. The Semiaromatic 5-Position

The unmarked 5-position in pyrimidine (**15**) is not nearly as electron-deficient as the marked positions, although it is slightly activated by the general inductive effect of the nitrogen atoms. Hence it resembles the unmarked 3- and 5-positions of pyridine (**16**) and may be described as a semiaromatic position. Consequently, a 5-halogenopyrimidine does not react easily with ammonia or amines; a 5-carboxypyrimidine is relatively stable to heat; a 5-alkoxypyrimidine is highly stable toward hydrolysis and so on; and a 5-methylpyrimidine is quite unreactive. On the other hand, electrophilic reagents attack relatively easily at a vacant 5-position, especially if assisted by one or more electron-donating groups elsewhere in the molecule: nitration, nitrosation, halogenation, and diazo-coupling take place quite readily at this position.

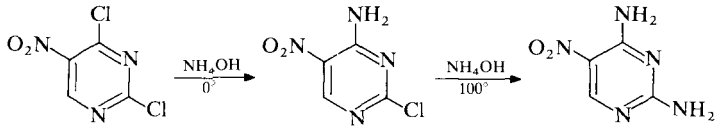
1.3.3. The Effect of Electron-Donating Groups

As just hinted, the progressive introduction of electron-donating groups into any position(s) gradually restores the π-electron depletion caused by the ring nitrogen in pyrimidine, so that the overall picture approaches more nearly to an aromatic ring. Thus a free 5-position can be nitrated, nitrosated, halogenated, or diazo-coupled with ease; in contrast, leaving groups at the 2- or 4/6-position become deactivated, so that halogeno substituents, for example, are not displaced easily by amines or hydroxyl ion.

1.3.4. The Effect of Electron-Withdrawing Groups

Powerful electron-withdrawing groups are generally located at the 5-position. Thus a 5-nitro group accentuates the electron deficiency at the 2-, 4-, and

6-positions, and a chloro substituent at any such position becomes extremely reactive to nucleophilic displacement: for example, 2,4-dichloro-5-nitropyrimidine (**21**) reacts rapidly with aqueous ammonia at 0° to afford 2-chloro-5-nitro-4-pyrimidinamine (**22**); the new electron-donating 4-amino group opposes the electron-withdrawing effect of the nitro group, so that replacement of the second chloro substituent becomes quite sluggish and the formation of 5-nitro-2,4-pyrimidinediamine (**23**) occurs relatively slowly even at 100° (°C; all temperature values are in Celsius unless noted otherwise).



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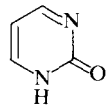
1.3.5. The Effect of Tautomeric Groups

Any 2- or 4/6-hydroxy-, mercapto-, or aminopyrimidine is tautomeric with the corresponding 2- or 4/6-oxo-, thioxo-, or iminopyrimidine in which the mobile proton usually occupies the N1- or N3-position; when necessary, such tautomerism can also involve C5 as a proton receptor. Experimental evidence as to the predominant structure in each such category is discussed later but, in general, the oxo, thioxo, and amino forms dominate. For example, 2-hydroxypyrimidine is mainly 2(1*H*)-pyrimidinone (**24**), 2,4-dimercaptopyrimidine is mainly 2,4(1*H*,3*H*)-pyrimidinedithione, and 2,4,6-trihydroxypyrimidine is mainly 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, but 4-pyrimidinamine (**12**) exists mainly as such. This type of tautomerism has implications for reactivity: for example, 2(1*H*)-pyrimidinone can undergo *O*- or *N*-methylation according to reagent and/or conditions. However, any nuclear instability resulting from a lack of formal aromaticity in compounds such as 2,4(1*H*,3*H*)-pyrimidinedione (**8**) is compensated by an inherent cyclic-amidic stability.



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1.4. THE PRIMARY SYNTHESIS OF PYRIMIDINES

The pyrimidine ring bearing various substituents may be formed directly by cyclization of one or more aliphatic fragments or by degradation, ring

expansion, ring contraction, rearrangement, or other such modification of another heterocycle. The condensation of two aliphatic fragments (with any preattached substituents), one to supply N1 + C2 + N3 and the other to supply C4 + C5 + C6 of the resulting ring, is the most used procedure and is known accordingly as the "Principal Synthesis" (see Sections 3.1–3.10); the large variety of other syntheses, using 1–5 aliphatic fragments for each, are covered in Sections 2.1–2.5; and the use of other heterocycles as synthones for pyrimidines is discussed in Section 2.6.

1.5. REACTIONS AT THE PYRIMIDINE RING

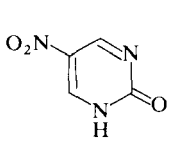
The ring atoms of pyrimidines undergo several types of reaction that are summarized briefly in this section. To maintain simplicity and avoid repetition, direct references to the original literature are generally omitted, but cross-references to subsequent detailed discussion are included, usually at the head of each section or subsection.

1.5.1. Electrophilic Attack

Electrophilic reagents usually attack the pyrimidine ring at its 5-position, the point least depleted of electrons. The process is assisted naturally by the presence of one or more electron-donating groups.

1.5.1.1. Nitration (Section 5.1.1.2)

The presence of one electron-donating group is essential for 5-nitration of a pyrimidine, but at least two such groups are needed for nitration under reasonably mild conditions. For example, the formation of 5-nitro-2(1*H*)-pyrimidinone (**25**) requires prolonged treatment with potassium nitrate in concentrated sulfuric acid at 95°, whereas 6-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione requires nitric acid–sulfuric acid at $<10°$ for a relatively short time. With appropriate precautions, nitration is possible in the presence of oxidation- or hydrolysis-labile substituents, as exemplified in the formation of 2-methylthio-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione (**26**) (HNO_3, 0°) or 6-chloro-5-nitro-2,4-pyrimidinediamine (HNO_3 in excess H_2SO_4 at 35°). 5-Phenylpyrimi-



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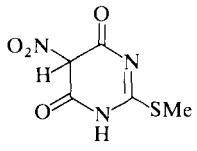

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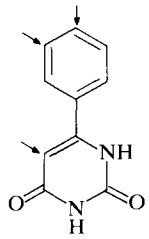
dines necessarily undergo nitration on the phenyl ring, but even phenylpyrimidines with a vacant 5-position may give 5- and/or ω-nitro derivatives: for example, according to the conditions used, 6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**27**) gives 5-nitro-6-phenyl-, 6-*p*-nitrophenyl-, 5-nitro-6-*m*-nitrophenyl-, or 5-nitro-6-*p*-nitrophenyl-2,4(1*H*,3*H*)-pyrimidinedione in reasonable yield.



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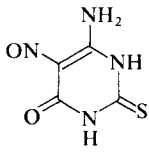
1.5.1.2. Nitrosation (Sections 5.2.1.2, 4.2.2.3)

Unlike nitric acid, nitrous acid cannot be used under vigorous conditions, so that pyrimidine substrates for nitrosation need at least two or preferably three electron-donating groups to assist the process. For example, 5-nitroso-4,6-pyrimidinediamine and 6-amino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**28**) may be made by treatment of their respective substrates in warm aqueous acid with sodium nitrite. When the 5-position is occupied, it is sometimes possible to induce 4/6-nitrosation under similar conditions, as in the formation of 5-hydroxy-6-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**29**). The ω-nitrosation of an appropriately activated methylpyrimidine may occur, thereby affording the (tautomeric) oxime of the corresponding pyrimidinecarbaldehyde: for example, 4-methyl-2(1*H*)-pyrimidinone so gives 2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde oxime (**30**) and 2-methyl-4,6(1*H*,5*H*)-pyrimidinedione gives 5-nitroso-4,6-dioxo-1,4,5,6-tetrahydro-2-pyrimidinecarbaldehyde oxime. Nitrosation is possible also in organic solvents by using a nitrite ester.



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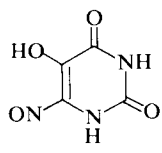

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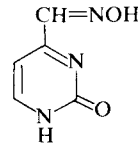

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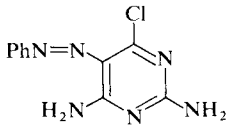
1.5.1.3. Diazo Coupling (Section 5.3.1.2)

Pyrimidine substrates with one or more electron-donating groups may be coupled under gentle conditions with diazotized amines to afford 5-arylazopyr-

imidines, such as 6-chloro-5-phenylazo-2,4-pyrimidinediamine (**31**); substrates with an occupied 5-position and at least two other electron-donating groups can undergo 4/6-coupling to afford, for example, 5-hydroxy-6-*p*-sulfophenylazo-2,4(1*H*,3*H*)-pyrimidinedione; and 4/6-methylpyrimidines may undergo extranuclear coupling to give the (tautomeric) arylhydrazone of the corresponding pyrimidinecarbaldehyde, for example, 2-amino-4-pyrimidinecarbaldehyde *p*-nitrophenylhydrazone (**32**). The process of coupling is quite important, because (with subsequent reduction) it provides a way to introduce a primary amino group under such gentle conditions that most labile passenger groups remain unaffected.



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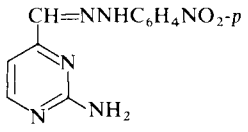

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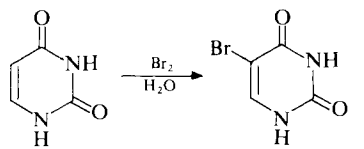
1.5.1.4. Halogenation (Sections 4.1.3, 4.2.3.5, 6.5.1)

Even unsubstituted pyrimidine will undergo 5-bromination, albeit under extreme conditions and possibly by an abnormal mechanism; the halogenation of 2- or 4-methylpyrimidine is less satisfactory because the methyl group is more susceptible than the 5-position: using *N*-halogenosuccinimides, the mono-, di-, and trihalogenomethylpyrimidines are the main products with only a little 5-halogeno-2-(or 4)-methylpyrimidine isolable. However, 5-halogenation of pyrimidines bearing one or more strongly electron-donating groups occurs very easily with elemental halogen in a solvent such as aqueous acetic acid, with an *N*-halogenosuccinimide in an appropriate solvent, or sometimes even with sulfuryl or thionyl chloride. Although 5-fluoropyrimidines are usually made indirectly, 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione may be prepared by direct fluorination with flourine, perfluoromethanol, or a graphite intercalate ($C_{19}XeF_6$) as reagent. The first product from bromination of 2,4(1*H*,3*H*)-pyrimidinedione (**33**) by aqueous bromine is indeed the 5-bromo derivative (**34**), which subsequently adds hypobromous acid to give 5,5-dibromo-6-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**35**). Although this is fairly stable, it reverts to the monobromo derivative (**34**) on prolonged boiling in dilute acid.



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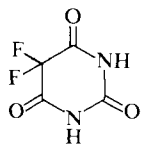

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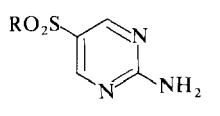
Related substrates also afford 5,5-dihalogenopyrimidines, but products such as 5,5-difluoro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**36**) clearly arise by a different route.

1.5.1.5. Sulfonation (Section 8.7.1)

The direct 5-sulfonation of pyrimidines with at least one electron-donating group is possible by using fuming sulfuric acid. However, it is much better to use chlorosulfonic acid to make a 5-chlorosulfonyl derivative that may then be converted easily into the sulfonic acid. Vigorous conditions are required: for example, 2-pyrimidinamine with an excess of chlorosulfonic acid under reflux for 8 h gives 2-amino-5-pyrimidinesulfonyl chloride (**37**, R = Cl) and thence, on treatment in ice, 2-amino-5-pyrimidinesulfonic acid (**37**, R = OH); an occupied 5-position may induce extranuclear sulfonation, as in the formation of 5-bromo-6-*p*-(chlorosulfonyl)benzyl-2,4(1*H*,3*H*)-pyrimidinedione (**38**).



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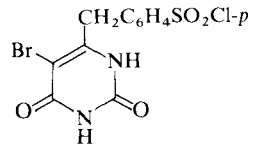

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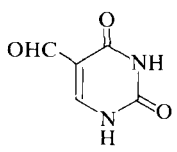
1.5.1.6. *C*-Formylation (Section 10.6.1)

The direct 5-formylation of pyrimidine substrates bearing two or more electron-donating groups may be done by the Reimer–Tiemann or the Vilsmeier reaction. Thus treatment of 2,4(1*H*,3*H*)-pyrimidinedione with chloroform/sodium hydroxide gives 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde (**39**); and treatment of 2-amino-4,6-(1*H*,5*H*)-pyrimidinedione with phosphoryl chloride/dimethyl formamide gives 2-amino-4,6-dichloro-5-pyrimidinecarbaldehyde (**40**). Other ways to achieve such *C*-formylations are illustrated in the conversion of appropriate 5-unsubstituted substrates into 2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde (boiling triethyl orthoformate); 6-methyl-2-piperidino-5-(*β*, *β*, *β*-trichloro-α-hydroxyethyl)-4(3*H*)-pyrimidinone (**41**) (chloral in refluxing pyridine) and thence (by loss of chloroform in alkali)



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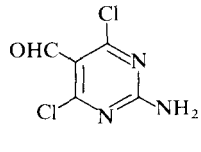

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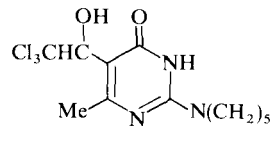

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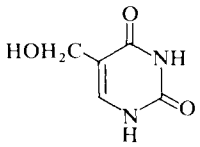
4-methyl-6-oxo-2-piperidino-1,6-dihydro-5-pyrimidinecarbaldehyde; and 4-chloro-2,6-dimethoxy-5-pyrimidine-carbaldehyde (lithiation followed by treatment with ethyl formate). Extranuclear- or *N*-formylation can occur, especially if the 5-position is insufficiently electron-rich.

1.5.1.7. Hydroxy- or Aminomethylation (Sections 7.3.1.5, 7.3.1.6, 9.1.1.4)

Pyrimidines with electron-donating substitutents will usually undergo *C*-hydroxymethylation by alkaline formaldehyde to give, for example, 5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (**42**) or even 5-hydroxy-6-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione. When other aldehydes are used, it is necessary to prelithiate the substrate before treatment with the aldehyde to give, for example, 5-α-hydroxyethyl-2,4-dimethoxypyrimidine. Hydroxyalkylation may occur also at an alkyl substituent.



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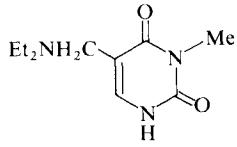

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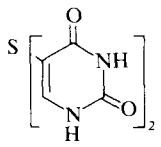
Similar substrates are amenable to 5-aminomethylation by the Mannich reaction (CH_2O plus a primary or secondary amine) to give, for example, 5-diethylaminomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**43**); such a reaction may occur at other positions in appropriate circumstances.

1.5.1.8. Formation of Dipyrimidin-5-yl Sulfides (Section 8.6.2)

2,4(1*H*,3*H*)-Pyrimidinedione, 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, and some of their simple derivatives react with sulfur mono- or dichloride in boiling formic acid to give, for example, bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)sulfide (**44**). The mechanism is obscure.



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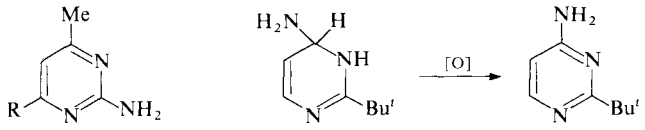
1.5.2. Nucleophilic Attack

Although the 2- and 4/6-positions of pyrimidines are predisposed to direct nucleophilic attack, only a few simple examples of such reactions are recorded.

1.5.2.1. Amination (Section 9.1.1.2)

Direct amination of the pyrimidine ring is rare, but 4-methylpyrimidine does react with sodium amide in decalin at 150° to give 4-methyl-2-pyrimidinamine (**45**, R = H), 6-methyl-2,4-pyrimidinediamine (**45**, R = NH_2), and other products. Indirect amination, involving nucleophilic addition of an amine and subsequent oxidation, is better known: for example, 2-*t*-butylpyrimidine with sodium amide in liquid ammonia at − 33°, followed by permanganate oxidation, gives 2-*t*-butyl-4-pyrimidinamine (**47**) via the adduct (**46**).



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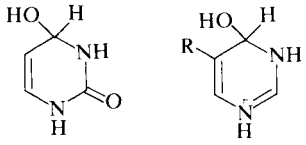
1.5.2.2. Hydroxylation (Sections 5.1.2.2, 7.1.2, 8.8.2)

Although nucleophilic 3,4-hydration can be detected in aqueous solutions of 2(1*H*)-pyrimidinone (**48**), only in pyrimidines bearing a strongly electron-withdrawing group does such hydration reach completion: thus the cations of 5-nitro-, 5-methylsulfonyl-, and 5-methylsulfinylpyrimidine exist in aqueous solution entirely as the adducts (**49**, R = NO_2, SO_2Me, or SOMe).



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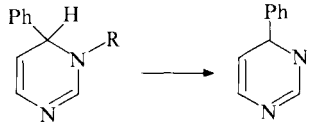
1.5.2.3. *C*-Alkylation or Arylation (Sections 4.1.3, 4.2.1.5)

Simple pyrimidines can often undergo indirect *C*-alkylation/arylation by the nucleophilic 3,4-addition of a Grignard or alkyllithium reagent followed by hydrolytic removal of the metal and subsequent oxidation of the alkyldihydro

derivative. For example, pyrimidine and phenylmagnesium bromide so gave the adduct (**50**, R = MgBr), then 4-phenyl-3,4-dihydropyrimidine (**50**, R = H), and finally 4-phenylpyrimidine (**51**).



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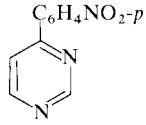
1.5.3. Free Radical Attack (Sections 4.1.2, 7.3.1.5)

Free radical attack on the pyrimidine nucleus has not been developed to any extent. However, pyrimidine slowly undergoes a Gomberg type of reaction with *p*-nitrobenzenediazonium chloride in acetate buffer to afford a separable mixture of 2- and 4-*p*-nitrophenylpyrimidine (**52**); and a variety of substrates undergo 2- or 4/6-hydroxymethylation by hydroxymethyl radicals (from ammonium peroxydisulfate/methanol) to give, for instance, 4-hydroxymethyl-2,6-dimethylpyrimidine (54%).



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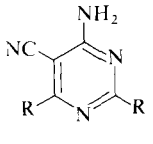
1.5.4. Photochemical Reactions (Section 7.1.3.8)

Mundane examples of photochemical attack on the pyrimidine nucleus are scattered through the literature: for example, the uv (ultraviolet) irradiation of 4-amino-5-pyrimidinecarbonitrile (**53**, R = H) in methanolic hydrogen chloride gives its 2,6-dimethyl derivative (**53**, R = Me) in good yield. In contrast, the photochemistry of 2,4(1*H*,3*H*)-pyrimidinedione (uracil), its 5-methyl derivative (thymine), and other natural bases has an extensive literature because many of the adverse effects produced in tissues by uv irradiation seem to involve dimer formation by adjacent thymine residues of DNA. Photohydration of uracil and photooxidations of thymine may be distinguished but the most important type of reaction, photodimerization, is best induced by irradiation of a frozen aqueous solution of thymine, in which the substrate molecules appear to be disposed conveniently for cyclobutane–dimer formation. The main product is the *cis–syn* entity (**54**), a U-shaped molecule in which the planes of the six-membered rings are parallel and at 90° to the cyclobutane ring; similar dimers in



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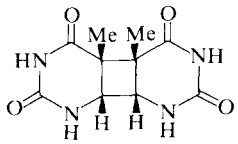

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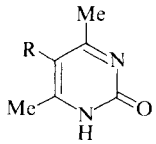
a variety of shapes are formed by irradiating frozen solutions or thin solid films of uracil, 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione, 4-amino-2(1*H*)-pyrimidinone (cytosine), and related substrates. Such dimers usually revert to monomers on irradiation in (liquid) water or other solvents.

1.5.5. Oxidative Reactions (Sections 7.1.6.1, 7.2.1.2, 7.6.1.1)

The Elbs persulfate reaction is applicable to 5-unsubstituted pyrimidines bearing electron-donating groups. Thus 4,6-dimethyl-2(1*H*)-pyrimidinone (**55**, R = H) reacts with cold alkaline persulfate to give the sulfate ester (**55**, R = OSO_3H), which undergoes hydrolysis in warm hydrochloric acid to afford 5-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**55**, R = OH); an analogous reaction via 5-acyloxypyrimidines (using dibenzoyl peroxide) is known.



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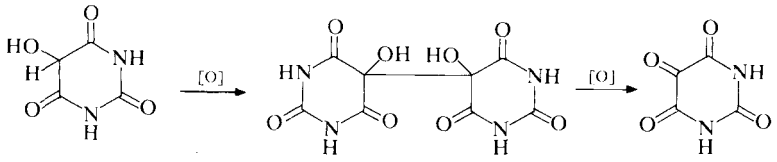
Elevation of oxidation state is possible with some pyrimidines: 5-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (dialuric acid) (**56**) may be oxidized to 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (alloxan) (**58**), probably via alloxantin (**57**).



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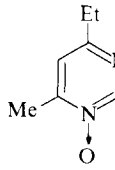
Many simple pyrimidines undergo *N*-oxide formation on treatment with an appropriate oxidant such as peroxyacetic acid. There is often an orientation problem with products from unsymmetrical substrates: for example, 4,6-dimethylpyrimidine can give only one product, viz., 4,6-dimethylpyrimidine 1-oxide, but 4-ethyl-2,6-dimethylpyrimidine can and does give both its 1- (**59**) and 3-oxide (**60**).



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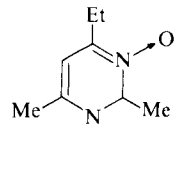

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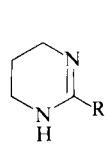
1.5.6. Nuclear Reduction (Sections 11.1.8, 11.2.4, 11.3)

Nuclear reduction of many pyrimidines occurs on hydrogenation over platinum or palladium, especially in acidic media. This treatment tends to reduce those double bonds free of any attached substituent at either end, but reduction usually stops at the tetrahydro stage by leaving the 1,2/2,3-double bond intact. Thus pyrimidine gives 1,4,5,6-tetrahydropyrimidine (**61**, R = H), 2-pyrimidinamine gave its 1,4,5,6-tetrahydro derivative (**61**, R = NH_2), and 2,4(1*H*,3*H*)-pyrimidineidione gives its 5,6-dihydro derivative (**62**); the last product is also obtained by boiling with an excess of Raney-nickel catalyst in aqueous suspension, but such treatment does not affect 4-pyrimidinamine or 4(3*H*)-pyrimidinone. Vigorous hydrogenation of 2-pyrimidinamine (cation) may give its 1,2,3,4,5,6-hexahydro derivative. Hydrogenation in neutral or alkaline media may be used to modify substituents without fear of effecting nuclear reduction. Classical chemical reducing agents, including borohydride, seldom affect the nucleus but lithium aluminum hydride may give di- or even tetrahydro derivatives.



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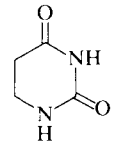

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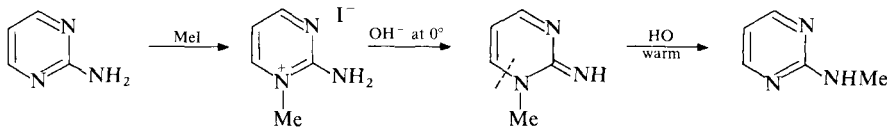
1.5.7. Quaternization at Ring Nitrogen (Sections 9.3.1.1, 9.3.2)

Pyrimidine and its simple derivatives react with alkyl halides to give 1-methylpyrimidinium halides or appropriate analogs, although the ease of such quaternizations varies according to the substituents and the reagent used. Substrates with tautomeric substituents behave abnormally. Thus 2-pyrimidinamine (**63**) gives a methiodide (**64**) that, in cold alkali, gives 1-methyl-2(1*H*)-pyrimidinimine (**65**), the anhydro base of the quaternary hydroxide corresponding to the iodide (**64**). Such imines are unstable in warm alkali: the above (**65**) undergoes Dimroth rearrangement to 2-methylaminopyrimidine (**66**); others

such as 1-methyl-4(1*H*)-pyrimidinimine (**67**, X = NH), which cannot rearrange, usually undergo facile hydrolysis to the corresponding pyrimidinone, for example, 1-methyl-4(1*H*)-pyrimidinone (**67**, X = O). Although tautomeric pyrimidinones resist direct quaternization, their nontautomeric analogs, such as 1-methyl-2(1*H*)-pyrimidinone, react easily with methyl iodide to afford, for example, the quaternary salt (**68**).



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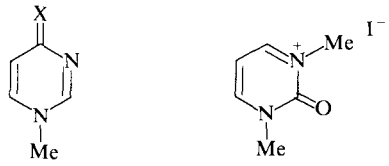


67 **68**

1.6. REACTIONS AT SUBSTITUENTS ON THE PYRIMIDINE RING

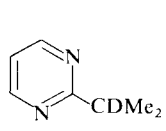
At least 90% of all known pyrimidines have been made by replacement or modification of substituents on a relatively few pyrimidine substrates, available by primary syntheses or by direct attack on the pyrimidine ring.

1.6.1. Reactions at Alkyl Groups (Section 4.2.3)

Methyl groups at the 2- or 4/6-position of pyrimidine are activated by depletion of electrons and accordingly resemble in reactivity the methyl group of 2,4-dinitrotoluene; a 5-methyl group resembles that of unsubstituted toluene. Most, but not all, of the reactions of alkyl groups are electrophilic in nature.

Deuteration. Activated methyl groups undergo acid/base-catalyzed deuterium exchange, but 5- or *N*-methyl groups do not. Deuteration of other alkyl groups appears to be confined to any proton(s) adjacent to the pyrimidine ring, to give, for example, 2-α-deutero-α methylethylpyrimidine (**69**).

Alkylidenation. Activated methyl groups are styrylated readily by treatment with benzaldehyde in the presence of a catalyst such as zinc chloride, piperidine, hydrochloric acid, or acetic anhydride to give, for example, 4,6-distyrylpyrimidine (**70**). Aliphatic aldehydes may be used successfully, albeit with difficulties.



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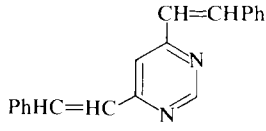

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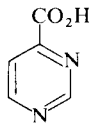
Oxidation. Methyl or styryl groups at an activated position are conveniently oxidized by permanganate or an excess of selenium dioxide to afford, for example, 4-pyrimidinecarboxylic acid (**71**) or 5-methyl-2-pyrimidinecarboxylic acid, respectively. Use of limited selenium dioxide gives the corresponding carbaldehyde, for example, 2-phenyl-4-pyrimidinecarbaldehyde (**72**). Other partial oxidations are exemplified in the conversion of 6-benzyl- into 6-α-hydroxybenzyl- or 6-benzoyl-2,4(1*H*,3*H*)-pyrimidinedione (**73**), according to the proportion of oxidant (SeO_2) employed.



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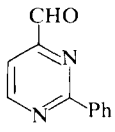

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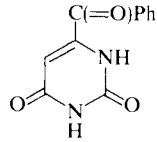

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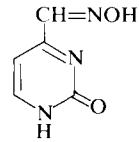

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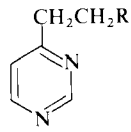
Nitrosation. Activated methyl groups may undergo α-nitrosation by nitrous acid under acidic conditions, followed by prototropy to give the corresponding aldoxime, for example, 2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde oxime (**74**). The same products may be formed from the same substrates by Claisen reaction with nitrite esters in the presence of a strong base. Homologous alkylpyrimidines react by either route to afford ketoximes.

Diazo coupling. As with nitrosation, active methyl groups undergo α-coupling with diazonium salts to give products such as 4-*p*-chlorophenylazomethyl-6-methyl-2(1*H*)-pyrimidinone, which probably exists as 6-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde *p*-chlorophenylhydrazone.

Reduction. Alkenyl and aralkenyl groups are reduced easily to their saturated equivalents, usually by catalytic hydrogenation: for example, 4-vinyl- or 4-styryl- so gave 4-ethyl- (**75**, R = H) or 4-phenethylpyrimidine (**75**, R = Ph), respectively.



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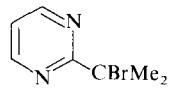
Alkylation. Methyl groups at the 2- or 4/6-position may be increased in size by alkylation with an alkyl iodide in the presence of sodium hydride or by preliminary lithiation with butyllithium followed by treatment with an alkyl halide. By such means, 4,6-dimethyl- gives 6-ethyl-4-methyl-1-phenyl-2(1*H*)-pyrimidinone and 2,4,6-trimethyl- gives 2,4-dimethyl-6-tridecylpyrimidine ($Li/C_{12}H_{25}Br$). Hydroxyalkylation occurs on treatment of 4-methylpyrimidine with paraformaldehyde to give 4-β-hydroxyethylpyrimidine (**75**, R = OH); aminoalkylation occurs on treatment of the same substrate with formaldehyde and dimethyl amine in acid (Mannich conditions) to give 4-β-dimethylaminoethylpyrimidine (**75**, R = NMe_2).

Halogenation. Progressive halogenation of a methyl group will occur, even at the 5-position. However, 2-isopropyl- gives only 2-(α-bromo-α-methylethyl)-pyrimidine (**76**) by using *N*-bromosuccinimide in limited amount. Iodination of 4-methylpyrimidine (I_2/pyridine) gives pyrimidin-4-ylpyridinium iodide as the only isolable product.



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1.6.2. Reactions at Aryl Groups (Section 5.1.1.2)

The only explored reaction of phenyl or heteroaryl groups attached to the pyrimidine ring is nitration, which usually gives a mixture of 5- and ω-nitro isomers, as mentioned in Section 1.5.1.1.

1.6.3. Reactions at Halogeno Substituents (Section 6.7)

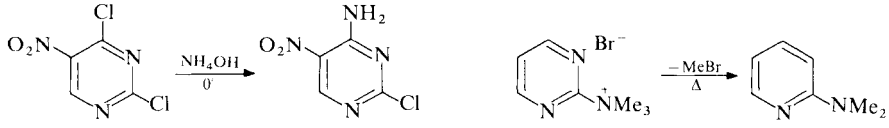
Halogenopyrimidines are the most useful intermediates in the series because they undergo all manners of nucleophilic displacements and other reactions.

Removal. An halogeno substituent at any position may be replaced easily with hydrogen, usually by catalytic hydrogenolysis over palladium in the presence of base. Zinc dust in boiling water may be used for the selective removal of a 4- in the presence of a 2- or 5-halogeno substituent; hydriodic acid often removes a 2-chloro substituent but induces hydrolysis of a 4-chloro substituent.

Aminolysis. Quantitative studies of the aminolysis of simple halogenopyrimidines reveal the following generalizations. (1) The positional order of reactivity for corresponding chloropyrimidines is $4 > 2 \gg 5$; (2) the rate for aminolysis of a given chloropyrimidine is unaffected by the chain length of a primary *n*-alkylamine but one or two α-branches thereon reduce the rate to $\sim 5\%$ or 0.1%,

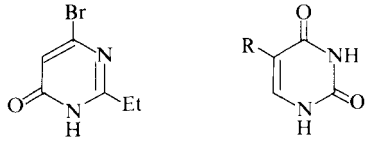
respectively; (3) an *N*,*N*-di-*n*-alkylamine reacts only about 5% as rapidly as the corresponding *N*-mono-*n*-alkylamine; (4) additional substituents on the substrate affect the rate according to their electronic nature, as exemplified by the relative rates 2-chloro-4,6-dimethyl- (1.0), 2-chloro- (10), 5-bromo-2-chloro- (200), 2-chloro-5-nitropyrimidine (3,000,000); and (5) rates for the aminolytic displacement of different halogens from the same position are in the order Br > I > Cl, but the maximal difference is only 3-fold.

Selective aminolysis of a di- or trihalogenopyrimidine can be very useful: for example, 2,4-dichloro-5-nitropyrimidine (**77**) with ice-cold aqueous ammonia gives virtually pure 2-chloro-5-nitro-4-pyrimidinamine (**78**), an extremely versatile intermediate. Active halogenopyrimidines undergo aminolysis by trimethylamine to afford the corresponding trimethylammoniopyrimidine halide (e.g., **79**); conditions must be gentle in order to avoid loss of methyl halide to give the dimethylaminopyrimidine (**80**). 5-Halogenopyrimidines undergo regular or *cine* aminolyses under relatively vigorous conditions.



77 **78** **79** **80**

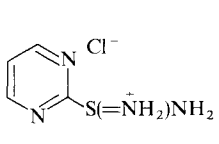
Hydrolysis and alcoholysis. Direct hydrolysis of 2- or 4/6-halogenopyrimidines to pyrimidinones may be done in warm acid or alkali; selective hydrolysis of di- or trihalogenopyrimidines is possible, especially under alkaline conditions where the initial product, such as 6-bromo-2-ethyl-4(3*H*)-pyrimidinone (**81**), forms an anion that tends to stabilize the remaining halogeno substituent(s). Most 5-halogenopyrimidines appear to need very vigorous conditions for hydrolysis, but 5-bromo-2,4(1*H*,3*H*)-pyrimidinedione (**82**, R = Br) and related substrates give their 5-hydroxy analogs (e.g., **82**, R = OH) by boiling in aqueous sodium hydrogen carbonate.



81 **82**

Alcoholysis of activated halogeno substituents invariably proceeds well in alcoholic sodium alkoxide under moderate conditions; selective alcoholysis of a di- or trihalogenopyrimidine is often possible by choosing conditions carefully. Phenolysis may be done by refluxing the chloropyrimidine with the phenol and potassium carbonate in toluene. Alcoholysis of 5-halogenopyrimidines is rarely used: reported examples require prolonged refluxing or even >100° in a sealed vessel.

Thiolysis and alkanethiolysis. Thiolysis of an activated halogenopyrimidine can be done directly by heating in aqueous or alcoholic sodium hydrogen sulfide or indirectly via the thiouronio intermediate. The first route is straightforward and can be used selectively; the indirect process is exemplified in the conversion of 2-chloropyrimidine into 2-thiouroniopyrimidine chloride (**83**) (alcoholic thiourea under reflux) followed by spontaneous or alkali-induced hydrolysis to 2(1*H*)-pyrimidinethione. Thiolysis of 5-halogenopyrimidines is seldom satisfactory, mainly because the resulting 5-pyrimidinethiols undergo aerial oxidation easily to afford the corresponding disulfides; however, the indirect route has been used successfully, for example, to make 6-amino-5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**84**) under appropriately modified conditions.



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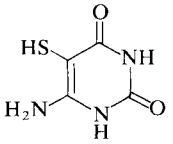

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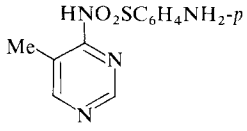
Although the preferred route to alkylthiopyrimidines is by *S*-alkylation of thiones, alkylthio- and arylthiopyrimidines may be made by treating 2-, 4/6-, or 5-halogenopyrimidines with aqueous or alcoholic alkanethiolate or arenethiolate ions, which are excellent nucleophiles; naturally, the 5-isomers need rather more vigorous conditions and selectivity can be achieved easily with polyhalogeno substrates.

Other replacements. Treatment of 2- or 4/6-halogenopyrimidines with aqueous potassium sulfite gives potassium *pyrimidinesulfonates*, which are difficult to purify from traces of inorganic salts: such sulfonates are better made by permanganate oxidation of pyrimidinethiones. Although the *sulfanilamidopyrimidines* are usually made by primary synthesis, they can be made also from the appropriate chloropyrimidines by warming with sodiosulfanilamide in dimethyl sulfoxide or molten acetamide to afford, for example, 5-methyl-4-sulfanilamidopyrimidine (**85**). Halogenopyrimidines with sodium benzenesulfinate can give simple *sulfones* such as 2-phenylsulfonylpyrimidine (**86**), but the reaction is not used much. More important is the replacement of 2-, 4/6-, or 5-halogeno substituents by thiocyanate ion to afford *thiocyanatopyrimidines*, for example, 2-ethylthio-4-methyl-6-thiocyanatopyrimidine (**87**): the reaction should neither be prolonged unduly nor done at too high a temperature if thermal isomerization to 2-ethylthio-4-isothiocyanato-6-methylpyrimidine (**88**) is to be avoided. It is



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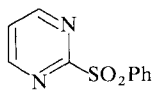

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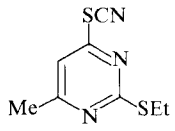

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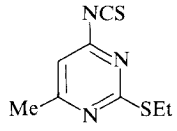

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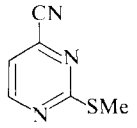

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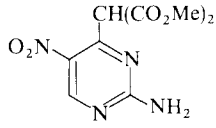

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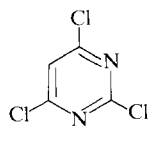
seldom satisfactory to convert activated halogenopyrimidines into *pyrimidinecarbonitriles*, but 4-iodo-2-methylthiopyrimidine with cuprous cyanide in refluxing pyridine does give 2-methylthio-4-pyrimidinecarbonitrile (**89**); strangely enough, 5-halogenopyrimidines are much more amenable to replacement by cyanide. Treatment of well-activated halogenopyrimidines with carbanionic reagents furnishes other *C–C linked substituted pyrimidines*, such as 4-di(methoxycarbonyl)methyl-5-nitro-2-pyrimidinamine (**90**); 5-halogenopyrimidines usually require lithiation prior to the formation of C–C linked derivatives, such as 5-pyrimidinecarboxylic acid. A variety of halogenopyrimidines may be converted into *bipyrimidines* under Ullmann or Busch conditions or by several related procedures.

1.6.4. Reactions at Tautomeric Oxo Substituents (Sections 6.1–6.4, 7.1.3)

Tautomeric 2- or 4/6-pyrimidinones are made easily by primary syntheses, so that they are natural candidates for metathetical conversion into a great diversity of other pyrimidines.

Halogenation. The most important reaction of pyrimidinones is their conversion into the corresponding chloropyrimidines from which a great variety of other pyrimidines may be made (see Section 1.6.3). Such chlorinations are done usually by simply boiling with neat phosphoryl chloride, to which phosphorus pentachloride or *N*,*N*-diethylaniline may be added if necessary to improve the rate or yield: products like 2-chloro-, 4,6-dichloro-, or 2,4,6-trichloropyrimidine (**91**) are so made in $>80\%$ yield. Other reagents include neat phosphorus pentachloride at $\sim 150°$ (yields often poor), thionyl chloride (seldom successful, but it does give ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate in good yield), or a Vilsmeier reagent (e.g., phosgene–dimethylformamide: chloromethylenedimethylammonium chloride formed in situ) (often successful but may induce formylation of the product). Bromopyrimidines are made less satisfactorily with phosphoryl bromide (with or without phosphorus tribromide as a



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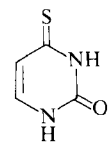

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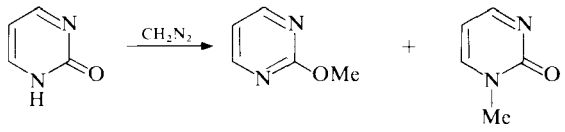
diluent/solvent) or phosphorus pentabromide; iodo- and fluoropyrimidines may be made indirectly from pyrimidinones by transhalogenation of the derived chloro- or bromopyrimidines with cold hydriodic acid or fluoride ion in a hot base, respectively.

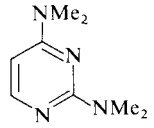
Thiation. Pyrimidinones may be converted directly into the corresponding pyrimidinethiones by warming with (purified) phosphorus pentasulfide in pyridine or xylene; an alternative indirect route is via the chloropyrimidines. The direct procedure may be used selectively for example, to convert 2,4(1*H*,3*H*)-pyrimidinedione into 4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**92**), because 4-oxo are more reactive than 2-oxo substituents toward thiation. Lawesson's reagent, 2,4-bis-*p*-methoxyphenyl-1,3-dithia-2,4-diphosphetane-2,4-disulfide, may be used for difficult thiations.

Acylation and alkylation. Acylation of a tautomeric pyrimidinone may give an *O*- or *N*-acylated product or a mixture of both. In contrast, alkylation usually gives an *N*-alkylpyrimidinone with perhaps a trace of alkoxypyrimidine; diazomethane tends to afford more *O*-alkylated product than do most other reagents: for example, 2(1*H*)-pyrimidinone (**93**) so gives 2-methoxypyrimidine (**94**) (17%) and 1-methyl-2(1*H*)-pyrimidinone (**95**) (52%).



93 **94** **95**

Aminolysis. Although most conversions of pyrimidinones into pyrimidinamines are done indirectly via chloropyrimidines or pyrimidinethiones, a direct route is available providing that the substrate and product are both sufficiently stable to withstand the vigorous conditions. For example, 2,4(1*H*,3*H*)-pyrimidinedione and phosphoric trisdimethylamide [O= =P(NMe_2)$_3$] at 235° for 1 h gives 2,4-bisdimethylaminopyrimidine (**96**) (75%). Passenger groups often fare poorly under such conditions.



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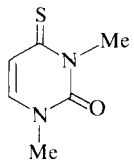
Removal. Removal of an oxo group is usually done indirectly via the corresponding chloropyrimidine or pyrimidinethione. Direct removal is successful sometimes: for example, dry distillation of 2-ethyl-6-methyl-4(3*H*)-pyrimidinone with zinc dust gives 2-ethyl-4-methylpyrimidine in low yield.

1.6.5. Reactions at Nontautomeric Oxo Substituents (Section 7.5.2)

Fixed pyrimidinones undergo few reactions. However, they are amenable to *thiation*, albeit more slowly than their tautomeric analogs. Thus 1,3-dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**97**) is formed in good yield from the corresponding dione by heating with phosphorus pentasulfide in pyridine for 90 min; Lawesson's reagent is reported to give 1-benzyl-4,6-diphenyl-2(1*H*)-pyrimidinethione from the pyrimidinone. Although *N-dealkylation* is possible, it is seldom useful. For example, 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**98**, R = H) may be obtained from its 3-cyclohexyl derivative (**98**, R = C_6H_{11}) by warming in concentrated sulfuric acid. Irradiation of regular fixed pyrimidinones may induce *Dewar isomerization*: for instance, 2,3,6-trimethyl-4(3*H*)-pyrimidinone (**99**) develops a 2,5-bond on irradiation in cold methanolic ammonia to give its Dewar isomer, 1,3,6-trimethyl-2,6-diazabicyclo[2,2,0]hex-2-en-5-one (**100**).



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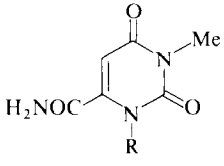

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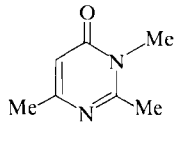

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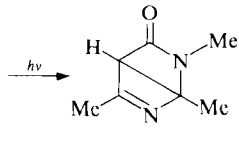

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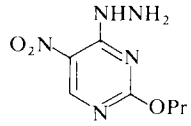
1.6.6. Reactions at Alkoxy Groups (Sections 7.1.1.4, 7.2.11, 7.4.2)

Some reactions of alkoxypyrimidines result from the ability of alkoxy substituents to act as leaving groups in nucleophilic displacements.

Aminolysis. Although 2-chloropyrimidine undergoes aminolysis approximately 40,000 times faster than does 2-methoxypyrimidine, it is quite practical to use 2- or 4/6-alkoxypyrimidines as substrates for preparative aminolyses. For example, 4-methoxypyrimidine with neat butylamine at 150° in a sealed tube affords 4-butylaminopyrimidine in good yield. Selective aminolyses of di- or trialkoxy substrates are possible, as in the conversion of 5-nitro-2,4-dipropoxy- into 4-hydrazino-5-nitro-2-propoxypyrimidine (**101**) by ethanolic hydrazine at 25°.



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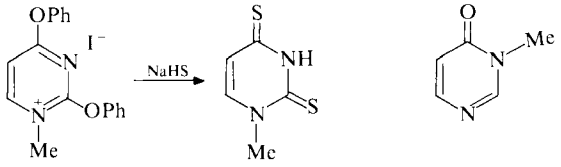
Hydrolysis. Activated alkoxypyrimidines undergo acidic or alkaline hydrolysis to the corresponding pyrimidinones; alkaline hydrolysis appears to be more selective, as in the formation of 2-ethoxy-5-methyl-4(3*H*)-pyrimidinone from the 2,4-diethoxy substrate in aqueous ethanolic alkali. Hydrolysis of 5-alkoxypyrimidines requires more vigorous conditions: thus 5-methoxy-2-phenylpyrimidine gives 2-phenyl-5-pyrimidinol by prolonged refluxing in glycol containing alkali. The same overall conversions may be achieved in any position without formal hydrolysis: for example, 2-isopropyl-4-methoxypyrimidine gives 2-isopropyl-4(3*H*)-pyrimidinone + methyl bromide on splitting (HBr/PhH, 50°); and hydrogenolysis of 4-benzyloxy-6-fluoro-2-pyrimidinamine (H_2/Pd) gives 2-amino-6-fluoro-4(3*H*)-pyrimidinone without affecting the fluoro substituent.

Other displacements. Other displacements are encountered sometimes: for example, 1-methyl-2,4-diphenoxypyrimidinium iodide (**102**) with sodium hydrogen sulfide furnishes 1-methyl-2,4(1*H*,3*H*)-pyrimidinedithione (**103**) by *thiolysis*; 2-methoxy-5-nitro- gives 2-ethoxy-5-nitropyrimidine (NEt_3, EtOH, reflux) or 5-nitro-2-propoxypyrimidine (Ag_2O, PrOH, reflux) each by *transalkoxylation.*

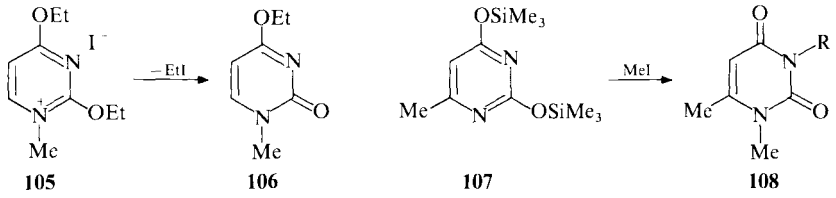


102 **103** **104**

Thermal rearrangement. The lower alkoxypyrimidines undergo a first-order thermal isomerization to *N*-alkylpyrimidinones, in which the alkyl group is attached predominantly to a ring nitrogen adjacent to the oxo substituent: for example, 4-methoxypyrimidine gives 3-methyl-4(3*H*)-pyrimidinone (**104**) (195°, sealed tube: 45%). The reaction is catalyzed by organic bases or Lewis acids and is accelerated markedly in the presence of an electron-withdrawing group: 4-methoxy-5-nitropyrimidine rearranges about 30,000 times more rapidly than 4-methoxypyrimidine.

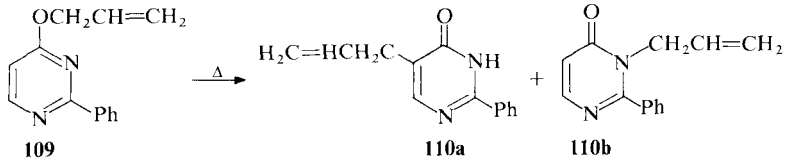
The Hilbert–Johnson reaction. This reaction involves treatment of an alkoxypyrimidine with an alkyl halide under quite gentle conditions to afford an *N*-alkylpyrimidinone in which the *N*-alkyl group is derived from the alkyl halide: the reaction proceeds via a quaternary intermediate. For example, 2,4-diethoxypyrimidine with methyl iodide in acetonitrile at 25° for 5 h gives the 1-methiodide (**105**), which gradually loses ethyl iodide to give 4-ethoxy-1-methyl-2(1*H*)-pyrimidinone (**106**). The reaction is used extensively, especially in nucleoside syntheses.[1841]

The Silyl–Hilbert–Johnson reaction. A useful variation of the foregoing Hilbert–Johnson reaction involves the use of a trialkylsiloxypyrimidine, which



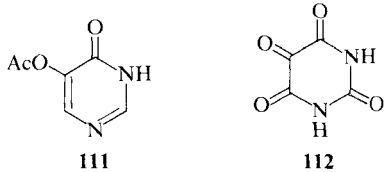
is made more easily from a pyrimidinone than is an alkoxypyrimidine. For example, 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione easily gives 4-methyl-2,6-bistrimethylsiloxypyrimidine (**107**) and thence, in refluxing methyl iodide, a separable mixture of 1,6-dimethyl- (**108**, R = H) and 1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**108**, R = Me). Tributylstannyloxypyrimidines may be used rather similarly.

Ortho-Claisen rearrangement. 4-Alkenyloxypyrimidines often undergo *ortho*-Claisen rearrangement into 5-alkenylpyrimidinones with or without inversion of the alkenyl group; the usual thermal rearrangement to 3-alkyl-4(3*H*)-pyrimidinones may occur at the same time to give a second product. Thus, for example, 4-allyloxy-2-phenylpyrimidine (**109**) in refluxing *N*,*N* -diethyl-*m*-toluidine gives a mixture of 5-allyl- (**110a**) and 3-allyl-2-phenyl-4(3*H*)-pyrimidinone (**110b**).



1.6.7. Reactions at 5-Hydroxy Groups (Section 7.2.2)

5-Pyrimidinols undergo the reactions expected of phenols, including the development of red to violet colors on treatment with ferric ion. Appropriate substrates give, for example, 5-acetoxy-4(3*H*)-pyrimidinone (**111**) (*acylation* with acetic anhydride), 4-anilino-5-methoxy-6-methylpyrimidine (*alkylation* with diazomethane), 2,4,5,6-tetrachloropyrimidine (*chlorination* with phosphorus pentachloride in phosphoryl chloride), 5-phenylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione (a specialized *aminolysis* with phenylhydrazine), 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**112**) (an indirect *oxidation*, made possible



by the peculiar tautomeric circumstances in the substrate), and 5-ethoxycarbonylmethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione [a *Wittig* hydroxylreplacement, using (ethoxycarbonylmethylene)triphenylphosphorane ($Ph_3P{=}CHCO_2Et$)].

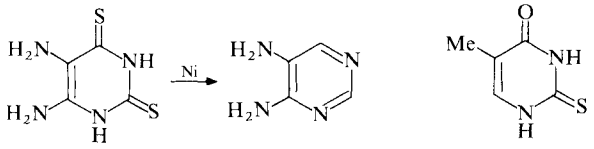
1.6.8. Reactions at *N*-Oxides (Section 7.6.3)

The *removal* of an *N*-oxide from a pyrimidine may be done by treatment with phosphorus trichloride: for example, 4-phenyl-6-styrylpyrimidine is so made from its 1-oxide. When no reducable passenger group is present, an alternative method is catalytic hydrogenation, as illustrated by such reduction of 4-ethoxy-6-*β*-piperidinoethylpyrimidine 1-oxide over Raney-nickel. Pyrimidine *N*-oxides can undergo *Reissert-like* reactions with acylating agents: for example, 4-ethoxy-6-methylpyrimidine 1-oxide with benzoyl chloride in aqueous potassium cyanide affords 4-ethoxy-6-methyl-2-pyrimidinecarbonitrile.

1.6.9. Reactions at Tautomeric Thioxo Substituents (Sections 7.1.1.5, 8.1.3)

The tautomeric pyrimidinethiones are much more reactive than are their oxygen analogs, and hence of much wider use as intermediates.

Desulfurization. The removal of sulfur from pyrimidinethiones in favor of hydrogen may be done reductively, usually by stirring with Raney-nickel catalyst (3–5 parts) in boiling water, aqueous ammonia, or ethanol. The procedure is exemplified in the conversion of 4-isopropyl-6-methyl-2(1*H*)-pyrimidinethione into 4-isopropyl-6-methylpyrimidine or of 5,6-diamino-2,4(1*H*,3*H*)-pyrimidinedithione (**113**) into 4,5-pyrimidinediamine (**114**). Other reducing agents, for example, nickel boride, are less satisfactory.

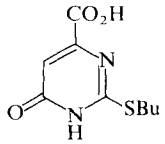


113 **114** **115**

Especially on a large scale, it may be convenient to attempt an (indirect) oxidative desulfurization: the action of hydrogen peroxide on a pyrimidinethione may remove sulfur in favor of hydrogen (desulfurization) or oxygen (oxidative hydrolysis). An example, in which only desulfurization occurs, is the conversion of 5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**115**) into 5-methyl-4(3*H*)-pyrimidinone.

S-Alkylation. A tautomeric pyrimidinethione invariably undergoes rapid *S*-alkylation: any possible *N*-, *O*-, or *C*-alkylation of the same substrate is much

slower and hence ineffective. Most thiones can be *S*-methylated in good yield simply by dissolution in dilute alkali and shaking at 20° with methyl iodide for a few minutes; higher alkyl derivatives usually need heating to complete the reactions. Hundreds of alkylthiopyrimidines, such as 2-methylthiopyrimidine or 2-butylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (**116**), are best prepared in this manner.



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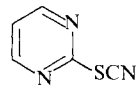

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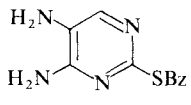
S-Cyanation. This useful process is closely akin to *S*-alkylation. It is illustrated by the conversion of 2(1*H*)-pyrimidinethione into 2-thiocyanatopyrimidine (**117**) by treatment in dilute alkali with cyanogen bromide at 10° for a few minutes.

S-Acylation. Pyrimidinethiones undergo *S*-acylation under gentle conditions, but at higher temperatures they appear to afford *N*-acyl-pyrimidinethiones (by rearrangement?). For example, 4,6-diamino-2(1*H*)-pyrimidinethione with benzoyl chloride–triethylamine at 20° gives 2-benzoylthio-4,6-pyrimidinediamine (**118**); at 80°, only 4,6-diamino-1-benzoyl-2(1*H*)-pyrimidinethione (**119**); and at 120°, only 4-amino-6-benzamido-2(1*H*)-pyrimidinethione (**120**).



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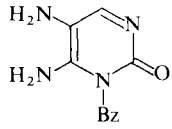

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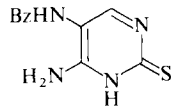

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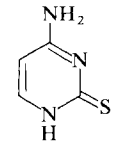

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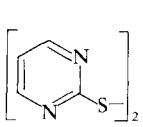
Aminolysis. Tautomeric 4-thioxo substituents undergo aminolytic displacement more easily than do 2-thioxo substituents. Accordingly, selective aminolysis of 2,4(1*H*,3*H*)-pyrimidinedithione and related substrates is achieved easily to give, for example, 4-amino-2(1*H*)-pyrimidinethione (**121**) (NH_4OH, 100°, 16 h: 91%). However, 5-nitro-2,4(1*H*,3*H*)-pyrimidinedithione gives only 2,4-bismethylamino-5-nitropyrimidine on similar treatment with aqueous methylamine.

Hydrolysis. Regular hydrolysis of pyrimidinethiones to pyrimidinones is seldom easy, although 2-ethylthio-4(3*H*)-pyrimidinethione does give 2,4(1*H*,3*H*)-pyrimidinedione on prolonged refluxing in hydrochloric acid. It is better to convert the thione into an alkylthio or alkylsulfonyl analog, which is then easier to hydrolyze (see Sections 1.6.11, 1.6.14). Alternatively, the thione may be submitted to oxidative hydrolysis with alkaline peroxide, which induces

an initial oxidation to the corresponding sulfonic or sulfinic acid, followed by regular hydrolysis thereof (see Section 1.6.13).

Oxidation. Although stable in air, tautomeric pyrimidinethiones may be oxidized to disulfides (iodine in the presence of a base), to pyrimidinesulfinic acids (cold aqueous hydrogen peroxide in an appropriately limited proportion), to pyrimidinesulfonic acids (permanganate), or to pyrimidinesulfonyl halides (chlorine or chlorine plus potassium hydrogen difluoride, to give chlorides or fluorides, respectively). Such procedures give, for example, dipyrimidin-2-yl disulfide (**122**), 6-amino-4-pyrimidinesulfinic acid (**123**), 2-pyrimidinesulfonic acid (**124**), or 4,6-dimethyl-2-pyrimidinesulfonyl chloride (**125**, X = Cl) or fluoride (**125**, X = F). Apart from the disulfides, such products are quite good intermediates for further reactions.



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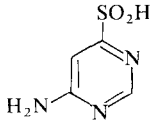

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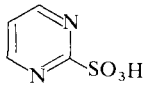

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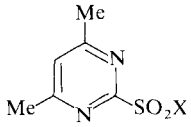

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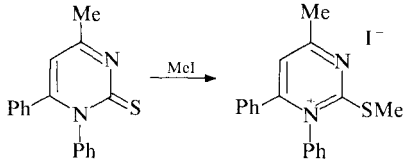
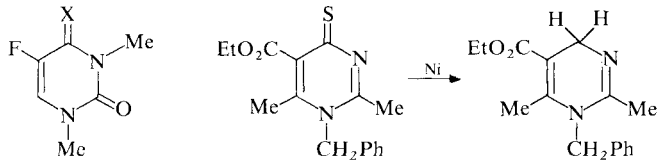
1.6.10. Reactions at Nontautomeric Thioxo Substituents (Section 8.5.2)

Although fixed pyrimidinethiones do not undergo many reactions, it is possible to *S-alkylate* such substrates: for example, 4-methyl-1,6-diphenyl-2(1*H*)-pyrimidinethione (**126**) with methyl iodide at 120° in a sealed tube gives 4-methyl-2-methylthio-1,6-diphenylpyrimidinium iodide (**127**); *aminolysis* may be used to produce corresponding imines, as in the conversion of 5-fluoro-1,3-dimethyl-4-thioxo- (**128**, X = S) into 5-fluoro-4-imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone (**128**, X = NH) by heating in ethanolic ammonia at



126 **127**



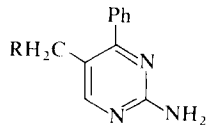
128 **129** **130**

115°; and Raney-nickel *desulfurization* is possible but necessarily involves a net reduction, as in the conversion of ethyl 1-benzyl-2,6-dimethyl-4-thioxo-1,4-dihydro-5-pyrimidinecarboxylate (**129**) into ethyl 1-benzyl-2,6-dimethyl-1,4-dihydro-5-pyrimidinecarboxylate (**130**).

1.6.11. Reactions at Alkylthio Groups (Section 8.4.2)

Like their oxygen analogs, alkylthiopyrimidines undergo nucleophilic displacement reactions, albeit reasonably slowly; they also undergo reductive and oxidative reactions.

Desulfurization. The total removal of alkylthio groups in favor of hydrogen is done usually by stirring with Raney-nickel catalyst (3–5 parts) in refluxing ethanol or water: 4,6-pyrimidinediamine is so made from its 2-methylthio derivative; 4-benzylaminopyrimidine, from its 2-carboxymethylthio derivative; and 5-methyl- (**131**, R = H), from 5-ethylthiomethyl-4-phenyl-2-pyrimidinamine (**131**, R = SEt).



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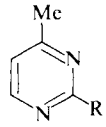
Aminolysis. Rate studies on the aminolysis of simple alkylthiopyrimidines indicate that 4-alkylthiopyrimidines react with amines more rapidly than do their 2-alkylthio isomers; that each ethylthiopyrimidine reacts more slowly than does its methylthio homolog; and that the usual substituent effects are operative. For example, to convert 4-methyl-2-methylthio- (**132**, R = SMe) into 2-butylamino-4-methylpyrimidine (**132**, R = NHBu) requires neat butylamine at 180° for 65 h (42% yield), whereas 2-methylthio-5-nitro- (**133**, R = SMe) into 2-butylamino-5-nitropyrimidine (**133**, R = NHBu) requires neat butylamine at only 20° for 1 min (95% yield)! Such aminolyses are used extensively as preparative procedures.



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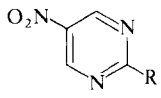
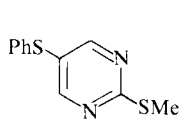


133

Hydrolysis. The hydrolysis of 2- or 4/6-alkylthiopyrimidines is done usually under acidic conditions: for example, 5-phenylthio-2(1*H*)-pyrimidinone is obtained in 95% yield by prolonged warming of 2-methylthio-5-phenylthiopyrimidine (**134**) in aqueous methanolic hydrochloric acid at 60°. (Note the



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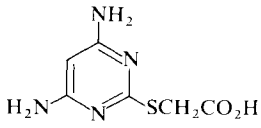

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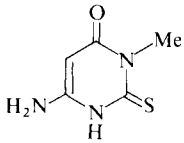
stability of the 5-thioether grouping.) A frequently used procedure for converting a pyrimidinethione into the corresponding pyrimidinone involves an (unisolated) thioether: for illustration, 4,6-diamino-2-pyrimidinethione is boiled with aqueous chloroacetic acid to give initially 2-carboxymethylthio-4,6-pyrimidinediamine (**135**) and thence 4,6-diamino-2-pyrimidinone by acidic hydrolysis.

Thiolysis. Alkylthiopyrimidines can undergo thiolysis to their usual precursors, pyrimidinethiones: although seldom used, the reaction is illustrated by the conversion of 6-amino-3-methyl-2-methylthio- into 6-amino-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**136**) by heating with aqueous sodium hydrogen sulfide. Such transformations can be done also by thiation with phosphorus pentasulfide (mechanism unresolved) or by splitting the thioether with dry hydrogen chloride, aluminum chloride, hydriodic acid, or similar.



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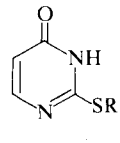

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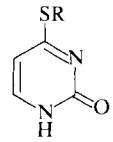
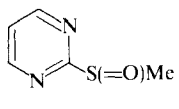


138

Transalkanethiolysis. An alkylthio group can be displaced by any alkanethiolate anion. For example, 2-methylthio- (**137**, R = Me) gives 2-phenylthio-4(3*H*)-pyrimidinone (**137**, R = Ph) by heating with thiophenol and triethylamine for several hours. A closely related reaction is that of 1-methyl-4-methylthio-2(1*H*)-pyrimidinone (**138**, R = Me) with potassium thiocyanate in refluxing acetonitrile to give 1-methyl-4-thiocyanato-2(1*H*)-pyrimidinone (**138**, R = CN).

Oxidation. All alkylthiopyrimidines undergo facile oxidation to the corresponding alkylsulfinyl- or alkylsulfonylpyrimidines, according to the proportion of oxidant, and preferably in anhydrous media to preclude hydrolysis of the resulting sulfoxides or sulfones. For example, 2-methylthio- gives 2-methylsulfinylpyrimidine (**139**) ($NaIO_4$, H_2O, 20°), 5-phenylthio- gives 5-phenylsulfin-



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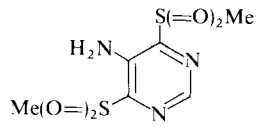

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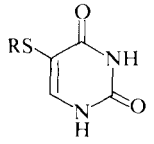
ylpyrimidine (m-$ClC_6H_4CO_3H$, $CHCl_3$), and 4,6-bismethylthio- gives 4,6-bismethylsulfonyl-5-pyrimidinamine (**140**) (m-$ClC_6H_4CO_3H$, $CHCl_3$). Alkylsulfinyl and alkylsulfonyl substituents are useful as leaving groups.

1.6.12. Reactions at 5-Mercapto Groups (Section 8.2.2)

5-Pyrimidinethiols undergo *S-alkylation*, *S-acylation*, or *oxidation* just as easily as do tautomeric pyrimidinethiones: thus, for example, 5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**141**, R = H) gives 5-carbamoylmethylthio- (**141**, R = CH_2CONH_2) (IH_2CCONH_2/alkali) or 5-acetylthio-2,4(1*H*,3*H*)-pyrimidinedione (**141**, R = Ac) (Ac_2O/pyridine) and bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)disulfide (**142**) (I_2/alkali).



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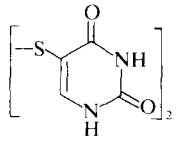

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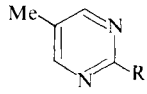
1.6.13. Reactions at Sulfo and Related Groups (Sections 8.7.2–8.7.4)

At the 2- or 4/6-position, sulfo and related groups can undergo either modification or complete replacement; in the 5-position, such groups can undergo only modification.

Typical *displacements* are exemplified in the conversion of 2,6-dimethyl-4-pyrimidinesulfonic acid into 2,6-dimethyl-4(3*H*)-pyrimidinone (HCl, 25°), 5-methyl-2-pyrimidinesulfonyl fluoride (**143**, R = SO_2F) into 2-azido-5-methylpyrimidine (**143**, R = N_3) (NaN_3, 25°), sodium 2,6-dimethyl-4-pyrimidinesulfonate into 2,6-dimethyl-4-pyrimidinecarbonitrile (KCN, dry distillation) or 4-hydrazino-2,6-dimethylpyrimidine (NH_2NH_2), and 4,6-diamino-2-pyrimidinesulfinic acid into 4,6-pyrimidinediamine (10*M* H_2SO_4).



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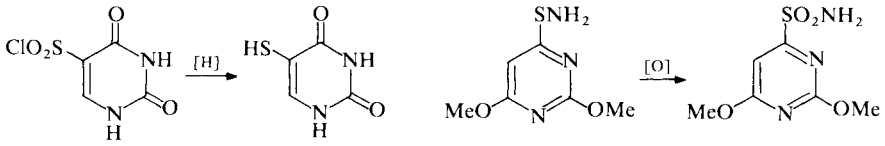
Typical *modifications* are seen in the conversion of 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride (**144**) into 5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**145**) (Zn/dilute H_2SO_4), 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonyl chloride into methyl 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonate (MeOH, 20°),



144 145 146 147

4,6-dimethyl-2-pyrimidinesulfonyl fluoride into 4,6-dimethyl-2-pyrimidinesulfonamide (liquid NH_3), and 2,6-dimethoxy-4-pyrimidinesulfenamide (**146**) into 2,6-dimethoxy-4-pyrimidinesulfonamide (**147**) ($KMnO_4$).

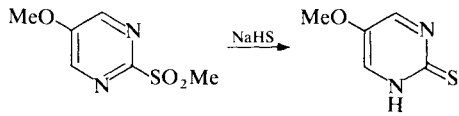
1.6.14. Reactions at Alkylsulfonyl and Alkylsulfinyl Groups (Section 8.8.2)

Because alkylsulfonyl and alkylsulfinyl substituents in the 2- or 4/6-position are such good leaving groups, most of the reported reactions of such sulfones and sulfoxides are nucleophilic replacements.

Hydrolysis. Alkaline hydrolysis is usually preferable, as in the conversion of 2-methylsulfonyl- or 4-methylsulfinylpyrimidine into 2(1*H*)- or 4(3*H*)-pyrimidinone, respectively, using dilute alkali at 25°. However, acidic conditions are not precluded.

Alcoholysis. Alcoholic alkoxide is used invariably for such alcoholyses: for example, 2-methylsulfonyl- gives 2-ethoxypyrimidine in refluxing ethanolic ethoxide; and 4-methylsulfinyl- gives 4-propoxypyrimidine in propanolic propoxide at 90°.

Thiolysis and alkanethiolysis. Such displacements are rarely useful. However, 5-methoxy-2-methylsulfonylpyrimidine (**148**) with aqueous sodium hydrogen sulfide is a used route to 5-methoxy-2(1*H*)-pyrimidinethione (**149**); and 2-ethylsulfonyl-5-fluoropyrimidine with potassium benzyl sulfide provides a way to make 2-benzylthio-5-fluoropyrimidine.



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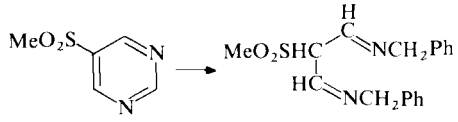
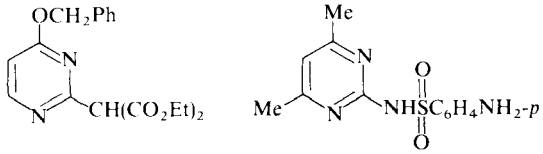
Aminolysis. Kinetic measurements indicate that simple 2- or 4/6-pyrimidinesulfones and sulfoxides undergo aminolysis substantially more rapidly than the corresponding chloropyrimidines. However, alkylsulfonylpyrimidines are seldom as easily available as are the chloropyrimidines for use as substrates. 2-Cyclohexylamino- and 2-pentylaminopyrimidine are easily made from 2-methylsulfonyl- and 2-methylsulfinylpyrimidine, respectively, by treatment

with the appropriate amine. Attempts at benzylaminolysis of 5-methylsulfonylpyrimidine (**150**) result in ring fission and the eventual formation of 1,3-bisbenzylimino-2-methylsulfonylpropane (**151**).



150 **151**

Other displacements. Other products, which may be obtained from pyrimidine sulfones or sulfoxides by displacement reactions, are exemplified by 4-benzyloxy-2-di(ethoxycarbonyl)methylpyrimidine (**152**) [$H_2C(CO_2Et)_2$, Na] 2-pyrimidinecarbonitrile (KCN, Me_2NCHO), 2-azidopyrimidine (NaN_3, Me_2NCHO), and 4,6-dimethyl-2-sulfanilamidopyrimidine (**153**) (p-$H_2NC_6H_4$-SO_2NHNa, 120°).



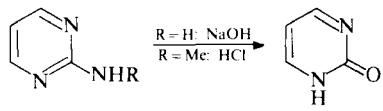
152 **153**

Reduction and oxidation. Both sulfones and sulfoxides may be reduced to thioethers: for example, 2-methylsulfonyl- and 2-methylsulfinylpyrimidine both give 2-methylthiopyrimidine on treatment with hydriodic acid. In contrast, sulfoxides may be oxidized to sulfones, which resist further oxidation: for example, 2-ethylsulfinyl- gives 2-ethylsulfonyl-5-iodopyrimidine (m-$ClC_6H_5CO_3H$, $CHCl_3$).

1.6.15. Reactions at Amino Groups (Section 9.1.6)

Position has relatively little effect on the course of reactions that affect amino groups attached directly to the pyrimidine ring.

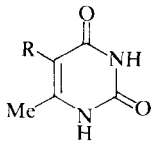
Hydrolysis. Acidic or alkaline conditions may be used for the hydrolysis of pyrimidinamines: for example, 2-methylaminopyrimidine (**154**, R = Me) or 2-pyrimidinamine (**154**, R = H) gives 2(1*H*)-pyrimidinone (**155**) (HCl at 160° or



154 **155**

NaOH at 110°, respectively); and 5-ethylamino-4-pyrimidinamine gives 5-hydroxy-4(3*H*)-pyrimidinone (HCl at 100°). An alternative (indirect) procedure, involving treatment with nitrous acid, is applicable only to primary amines: for example, 4,6-dimethyl-2-pyrimidinamine gives 4,6-dimethyl-2(1*H*)-pyrimidinone (HNO_2, AcOH) and 5-pyrimidinamine gives 5-pyrimidinol.

Replacement by halogeno groups. Diazotization of primary pyrimidinamines, followed by treatment with halogenide ion, is used to make halogenopyrimidines. For instance, diazotization of 2-pyrimidinamine in hydrochloric acid containing lithium chloride gives 2-chloropyrimidine; and diazotized 5-amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**156**, R = NH_2) with cuprous bromide gives 5-bromo-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**156**, R = Br).



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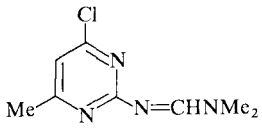
Acylation. Acylation will occur on any primary or secondary amino group attached to pyrimidine but 5-amino groups are acylated more rapidly, so that selectivity is possible. Thus 4,5-pyrimidinediamine gives 5-formamido-4-pyrimidinamine (HCO_2H, reflux), 4-pyrimidinamine gives 4-acetamidopyrimidine (Ac_2O, reflux), and 2-pyrimidinamine gives 2-benzenesulfonamidopyrimidine ($PhSO_2Cl$, pyridine).

Alkylation. The 2- or 4/6-pyrimidinamines alkylate initially on ring nitrogen (see Section 1.5.7), but 5-pyrimidinamines behave normally to give, for example, 5-β-fluoroethylamino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**156**, R = $NHCH_2CH_2F$) ($BrCH_2CH_2F$, NEt_3).

Alkylidenation. Many primary pyrimidinamines react with aldehydes, ketones, or their acetals to give alkylideneaminopyrimidines (Schiff bases); hydrazino pyrimidines behave likewise to give alkylidenehydrazinopyrimidines. Thus 4-chloro-6-methyl-2-pyrimidinamine with dimethylformamide dimethyl acetal [$Me_2NCH(OMe)_2$] gives 4-chloro-2-dimethylaminomethyleneamino-6-methylpyrimidine (**157**), 5-pyrimidinamine with *p*-nitrobenzaldehyde gives 5-*p*-nitrobenzylideneaminopyrimidine (**158**), and 2-hydrazinopyrimidine with benzaldehyde gives 2-benzylidenehydrazinopyrimidine. Such products may be reduced (if



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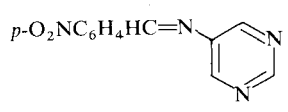

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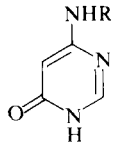
necessary as a one-pot "reductive alkylation") to give the corresponding alkylaminopyrimidines.

Removal. Because they are akin to substituted hydrazines, *N*-aminopyrimidines lose their amino group on treatment with nitrous acid: for example, 1-amino-2,4(1*H*,3*H*)-pyrimidinedione gives 2,4(1*H*,3*H*)-pyrimidinedione (HNO_2, AcOH). Regular hydrazinopyrimidines may have their hydrazino group removed oxidatively, or it may be split to produce an amino group by reductive means: for example, 2-methyl-5-nitropyrimidine is derived from its 4-hydrazino derivative with silver oxide in methanol; and 6-amino- (**159**, R = H) may be made from 6-hydrazino-4(3*H*)-pyrimidinone (**159**, R = NH_2) by treatment with an excess of Raney-nickel catalyst.



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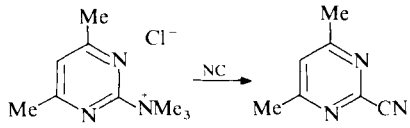
Other reactions. Of the many other minor reactions undergone by pyrimidinamines (see Section 9.1.6.8), perhaps the most interesting is the condensation of 5-pyrimidinamine with nitrosobenzene to afford 5-phenylazopyrimidine.

Displacements of the trimethylammonio group. The quaternary substituent in compounds such as 4,6-dimethyl-2-trimethylammoniopyrimidine iodide (**160**) is uniquely useful as a leaving group for displacement by anionic reagents, always provided that conditions are kept mild enough to preclude thermal monodealkylation of the substrate to the corresponding dimethylaminopyrimidine. For example, the above material (**160**) affords 4,6-dimethyl-2(1*H*)-pyrimidinone (HO^-), 2-methoxy-4,6-dimethylpyrimidine (MeO^-), or 4,6-dimethyl-2-pyrimidinecarbonitrile (**161**) (NC^-); and other trimethylammonio substrates give 4-fluoro-2,6-dimethoxypyrimidine (F^-), 4-azido-2,6-dimethoxypyrimidine (N_3^-), or 2,4-dimethyl-6-sulfanilamidopyrimidine (p-$H_2NC_6H_4SO_2NH^-$).

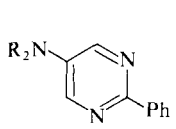


160 **161**

1.6.16. Reactions at Nitro, Nitroso, and Arylazo Groups (Sections 5.1.2, 5.2.3, 5.3.2)

Nitro-, nitroso-, and arylazopyrimidines are all used extensively to afford the corresponding pyrimidinamines by *reduction.* Catalytic hydrogenation or a

variety of other reductants may be employed: the choice is sometimes dependent on passenger groups present. For example, 5-nitro-2-phenylpyrimidine (**162**, R = O) gives 2-phenyl-5-pyrimidinamine (**162**, R = H) (H_2/Pd or NH_2NH_2/Pd), 5-nitro-2,4-pyrimidinediamine gives 2,4,5-pyrimidinetriamine ($Na_2S_2O_4/HO^-$), 6-methylamino-2-methylthio-5-nitroso- gives 5-amino-6-methylamino-2-methylthio-4(3*H*)-pyrimidinone (NaHS), and 6-amino-5-phenylazo- gives 5,6-diamino- (Zn or Fe in dilute H_2SO_4) or 6-amino-5-formamido-2,4(1*H*,3*H*)-pyrimidinedione (Zn/HCO_2H).



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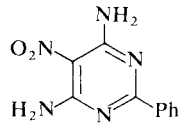

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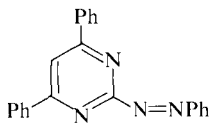
Nitrosopyrimidines can undergo *oxidation* to the corresponding nitropyrimidine, as in the conversion of 5-nitroso- (**163**, $n = 1$) into 5-nitro-2-phenyl-4,6-pyrimidinediamine (**163**, $n = 2$) by hydrogen peroxide in trifluoroacetic acid, or 2-nitroso- into 2-nitropyrimidine by ozone.

A 2- or 4/6-nitro or nitroso substituent can act as a leaving group for *aminolysis* or *alcoholysis*: for example, 2-nitro-4,6-diphenyl- gives 4,6-diphenyl-2-piperidinopyrimidine (piperidine, 20°).

A 2- or 4/6-nitrosopyrimidine can condense with primary amines to afford *arylazopyrimidines*, such as 4,6-diphenyl-2-phenylazopyrimidine (**164**) ($PhNH_2$).

All these types of substrate can undergo direct conversion into a variety of *other heterocycles* by the most diverse mechanisms. A simple example is the condensation of phenylacetaldehyde (**165**) with 6-amino-3-methyl-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone (**166**) to give 3-methyl-2-methylthio-6-phenyl-4(3*H*)-pteridinone (**167**) (a Timmis synthesis).



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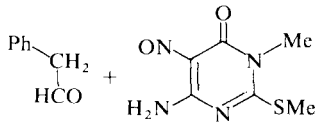
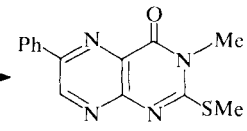


165 **166**



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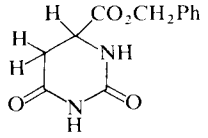
1.6.17. Reactions at Carboxy Groups (Section 10.1.2)

Decarboxylation. Decarboxylation is used extensively in the pyrimidine series, mainly as the final step in removing unwanted alkyl or related substituents: a carboxy group at the 2- or 4/6-position appears to be more easily removable than one at the 5-position. Some typical temperatures are indicated in the decarboxylation of 4,6-pyrimidinedicarboxylic acid (240°, Ph_2O), 5-bromo-2-pyrimidinecarboxylic acid (250°), and 2-amino-5-pyrimidinecarboxylic acid (300°).

Esterification. Direct esterification of pyrimidinecarboxylic acids may be done in all the usual ways, as indicated in the formation of methyl 2-pyrimidinecarboxylate (Ag salt, MeI), methyl 4-pyrimidinecarboxylate (MeOH, H_2SO_4; MeOH, HCl; or CH_2N_2), and benzyl 2,6-dioxo-1,2,3,4,5,6-hexahydro-4-pyrimidinecarboxylate (**168**) ($PhCH_2Br$, NEt_3). Indirect esterification (via acid chlorides) is also used frequently.



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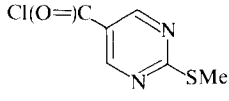

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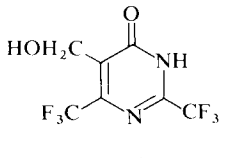
Conversion into acid chlorides. Only a few pyrimidinecarbonyl chlorides have been purified, but many more crude products have been used as intermediates for esters or amides. Appropriate carboxylic acids afford, for example, 2-methylthio-5-pyrimidinecarbonyl chloride (**169**) (purified; neat $SOCl_2$), and 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl chloride (purified; $SOCl_2$ + Me_2NCHO in PhH). Phosphorus chlorides may be used, especially if tautomeric oxo substituents are to be converted into chloro substituents at the same time.

Reduction. Conversion of a pyrimidinecarboxylic acid into the corresponding hydroxymethylpyrimidine is done usually via an ester, but several examples of direct reduction with borohydride are known. For example, 5-hydroxymethyl-2,6-bistrifluoromethyl-4(3*H*)-pyrimidinone (**170**) may be so made in good yield.



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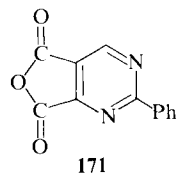

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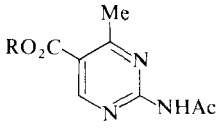
Other reactions. Several reactions of minor importance are illustrated in these examples: 2-phenyl-4,5-pyrimidinedicarboxylic acid gives its intramolecular *anhydride* (**171**) ($SOCl_2$); 2,6-diethoxy-4-pyrimidinecarboxylic acid is converted by ethyllithium into the corresponding *ketone*, 4-acetyl-2,6-diethoxypyrimidine; and 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid with sulfur tetrafluoride at 100° (sealed) undergoes *fluorination* to 5-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione.

1.6.18. Reactions at Alkoxycarbonyl Groups (Section 10.2.2)

Hydrolysis. Carboxylic esters give the corresponding acids on hydrolysis in acidic or (preferably) alkaline media: conditions are typified in the hydrolyses

of ethyl 5-pyrimidinecarboxylate (2*M* NaOH, 50°), ethyl 5,6-diamino-4-pyrimidinecarboxylate (0.5*M* Na_2CO_3, reflux), and methyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (*M* HCl, reflux).

Hydrogenolysis. Benzyl esters may be converted into acids by reduction, thereby avoiding hydrolytic conditions in the presence of any hydrolysis-prone passenger group. For example, benzyl 2-acetamido-4-methyl-5-pyrimidinecarboxylate (**172**, R = CH_2Ph) so gives 2-acetamido-4-methyl-5-pyrimidinecarboxylic acid (**172**, R = H) (H_2/Pd).



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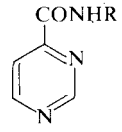

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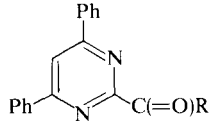
Aminolysis. Carboxylic esters usually give the corresponding carboxamides with neat, alcoholic, or aqueous ammonia or amines. Conditions are indicated in the conversion of appropriate methyl or ethyl esters into 4-pyrimidinecarboxamide (**173**, R = H) (NH_3, MeOH, 20°), 5-pyrimidinecarboxamide [NH_3, MeOH, 20°; NH_4OH, 30°; or liquid NH_3, 60° (sealed)], 4,5-pyrimidinedicarboxamide (NH_4OH, 25°), 4-pyrimidinecarboxanilide (**173**, R = Ph) ($PhNH_2$ + $PhNH_3Cl$, reflux), and 5-pyrimidinecarbohydrazide (NH_2NH_2, EtOH, reflux).

Removal. Total removal of an ester group is done by hydrolysis and a subsequent decarboxylation.

Claisen reactions. Pyrimidine esters undergo classical Claisen reactions to afford ketones. For example, methyl 4,6-diphenyl-2-pyrimidinecarboxylate (**174**, R = OMe) is so converted into 2-cyanoacetyl-4,6-diphenylpyrimidine (**174**, R = CH_2CN) (MeCN, NaH, Me_2NCHO).



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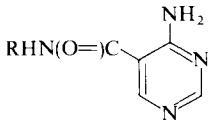
1.6.19. Reactions at Carbamoyl Groups (Section 10.3.2)

Dehydration to nitriles. The dehydration of (*N*-unsubstituted) pyrimidinecarboxamides is done normally with a phosphorus halide, as in the formation of 2- or 4-pyrimidinecarbonitrile ($POCl_3$, reflux) or 4,5-pyrimidinedicarbonitrile ($POCl_3$, xylene, reflux); however, 5-pyrimidinecarboxamide is dehydrated in much better yield by dry distillation from phosphorus pentoxide.

Hydrolysis. Pyrimidinecarboxamides are converted into carboxylic acids under acidic or alkaline conditions, as indicated in the hydrolysis of 4-amino-5-pyrimidinecarboxamide (**175**, R = H) (2*M* NaOH, 100°), 4-amino-5-pyrimidinecarboxanilide (**175**, R = Ph) (likewise), or 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (conc. HBr, reflux).



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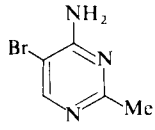

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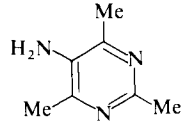

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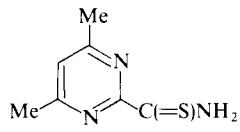
Hofmann or Curtius reactions. Regular pyrimidinecarboxamides may be degraded to pyrimidinamines under classical Hofmann conditions (NaOCl, HO^-) to give, for example, 5-bromo-2-methyl-4-pyrimidinamine (**176**) or 5-pyrimidinamine. Pyrimidinecarbohydrazides are so degraded under Curtius conditions (HNO_2, H^+) to give, for example, 5-pyrimidinamine or its 2,4,6-trimethyl derivative (**177**).

1.6.20. Reactions at Cyano Groups (Section 10.5.2)

Pyrimidinecarbonitriles undergo a variety of useful reactions involving complete displacement or modification of their cyano groups.

Hydrolysis. The uncontrolled hydrolysis of pyrimidinecarbonitriles in acid or (more usually) alkali gives the corresponding *carboxylic acids*: for example, 2-pyrimidinecarbonitrile affords 2-pyrimidinecarboxylic acid (2*M* NaOH, reflux) and 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile affords the corresponding acid (50% H_2SO_4, reflux). In contrast, controlled hydrolysis of pyrimidinecarbonitriles gives the corresponding *carboxamides*: such control is achieved by using highly concentrated acid (e.g., >95% H_2SO_4) to limit the concentration of H^+, by using alkali containing hydrogen peroxide to obtain Radziszewski conditions, or simply by using mildly basic aqueous media. Appropriate nitriles so give, for example, 2-chloro-4-pyrimidinecarboxamide (98% H_2SO_4, 20°), 5-chloro-2-pyrimidinecarboxamide (KOH, H_2O_2, 50°; without H_2O_2, only the carboxylic acid is formed), and 4,6-dimethyl-2-pyrimidinecarboxamide (dilute NH_4OH, 95°). Analogous controlled thiolyses are also possible, to give, for example, 4,6-dimethyl-2-pyrimidinecarbothioamide (**178**) (H_2S, NEt_3, Et_2O, 25°).



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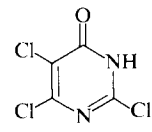

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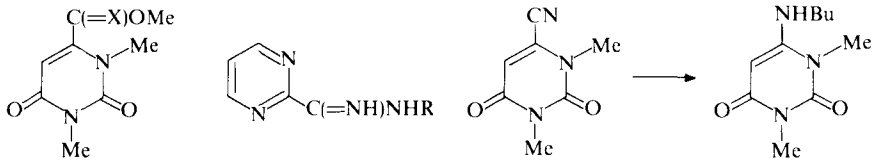
The cyano group on appropriate pyrimidinecarbonitriles may undergo an apparent nucleophilic displacement by HO^- in strong alkali to afford the corresponding *pyrimidinones*. For example, 2,5,6-trichloro-4-pyrimidinecarbonitrile gives 2,5,6-trichloro-4(3*H*)-pyrimidinone (**179**) (80%) in alkali at 0°.

Alcoholysis. The alcoholysis of pyrimidinecarbonitriles can lead also to three types of product: (1) treatment with alcoholic hydrogen chloride or alcoholic sodium alkoxide gives a *carboxamidic ester*, such as ethyl 5-pyrimidinecarboximidate (HCl, EtOH, 0°) or methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboximidate (**180**, X = NH) (NaOMe, MeOH, reflux); (2) the same treatment followed by a brief acidic hydrolysis affords a regular *carboxylic ester*, for example, methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (**180**, X = O); and (3) treatment of certain nitriles with alcoholic alkoxide causes a direct nucleophilic displacement of the cyano group to form an *alkoxy analog* such as 4-methoxy-2,6-dimethylpyrimidine (NaOMe, MeOH, reflux).

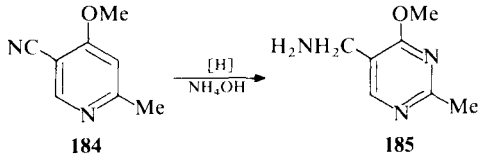
Aminolysis. Aminolysis of a pyrimidinecarbonitrile can provide two products, one by modification and the other by displacement of the cyano group. Treatment with neat ammonium benzenesulfonate at >200° or with aniline plus aluminum chloride gives an *amidine*, such as 2-pyrimidinecarboxamidine (**181**, R = H) or its *N*-phenyl derivative (**181**, R = Ph), respectively. The conversion of carbonitriles into carboxamidines can be done also by the classical route via a carboximidic ester with ethanolic ammonia. On the other hand, treatment of a 2- or 4/6-pyrimidinecarbonitrile with a primary or secondary amine can give the corresponding *aminopyrimidine*: for example, 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**182**) gives 6-butylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**183**) (neat $BuNH_2$, reflux).



180 **181** **182** **183**

Reduction and reductive hydrolysis. The complete direct reduction of 5-pyrimidinecarbonitriles to the corresponding aminomethylpyrimidines is done usually by catalytic hydrogenation in ethanolic ammonia, but other reducing agents may be used. For example, 4-methoxy-2-methyl-5-pyrimidinecarbonitrile (**184**) affords 5-aminomethyl-4-methoxy-2-methylpyrimidine (**185**) (H_2, Raney-nickel), and 4-amino-2-ethylthio-5-pyrimidinecarbonitrile affords 5-aminomethyl-2-ethylthio-4-pyrimidinamine ($LiAlH_4$).

When the foregoing hydrogenations are done in dilute acid and the amount of hydrogen is controlled, it is sometimes possible to stop reduction at the iminomethyl stage and then allow spontaneous hydrolysis to the aldehyde: for



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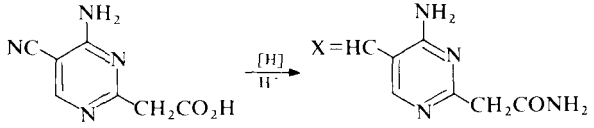


186 187

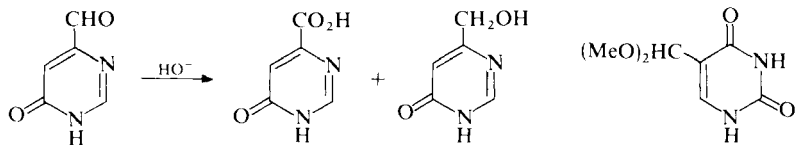
example, 4-amino-2-carbamoylmethyl-5-pyrimidinecarbonitrile (**186**) so gives 4-amino-2-carbamoylmethyl-5-pyrimidinecarbaldehyde (**187**, X = O), via the unisolated imine (**187**, X = NH) (H_2, Pd, dilute HCl).

Conversion into ketones. A pyrimidinecarbonitrile reacts with a Grignard reagent to afford a ketone, usually in poor yield: for example, 4-pyrimidinecarbonitrile in this way furnishes 4-acetylpyrimidine (MeMgBr).

1.6.21. Reactions at *C*-Formyl Groups (Section 10.6.2)

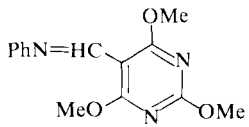
Oxidation and reduction. Pyrimidinecarbaldehydes undergo facile *oxidation* to carboxylic acids, as indicated in the formation of 5-pyrimidinecarboxylic acid ($KMnO_4$, HO^-) or 1,3,4-trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid ($K_2S_2O_8$/Ag). Aldehydes also undergo *reduction* to hydroxymethylpyrimidines, as indicated in the formation of 5-hydroxymethyl-2-methyl-4-pyrimidinamine (H_2/Pt, Pd, or Ni; or NaHg), 5-hydroxymethylpyrimidine ($LiAlH_4$), or 4-hydroxymethyl-2-methyl-6-phenylpyrimidine ($NaBH_4$). In addition, aldehydes undergo the Cannizzaro *disproportionation*: for example, 6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde (**188**) in alkali gives 6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (**189**) and 6-hydroxymethyl-4(3*H*)-pyrimidinone (**190**).

Derivatization. Pyrimidinecarbaldehydes easily form the so-called functional derivatives, commonly used to identify or characterize aldehydes. Thus an *acetal* results from warming the aldehyde with an alcohol and/or orthoester, in the presence of an anhydrous acid, as exemplified by the formation of 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde dimethyl acetal (**191**) (MeOH,



188 189 190 191

$MeC_6H_4SO_3H$-*p*) or 5-pyrimidinecarbaldehyde diethyl acetal [$HC(OEt)_3$, $MeC_6H_4SO_3H$-*p*]. A *Schiff base* (sometimes known as an *anil*) is made by treatment of the aldehyde with a primary amine to give, for example, 2,4,6-trimethoxy-5-phenyliminomethylpyrimidine (**192**) ($PhNH_2$, EtOH) or 5-*p*-chlorophenyl-6-*β*-dimethylaminoethyliminomethyl-2-thioxo-1, 2-dihydro-4 (3*H*)-pyrimidinone ($Me_2NCH_2CH_2NH_2$, EtOH). A *hydrazone* is made similarly from an aldehyde and a monosubstituted hydrazine to give, for example, 2-phenyl-5-pyrimidinecarbaldehyde phenylhydrazone (**193**). A *semicarbazone* (or thiosemicarbazone) is prepared from the aldehyde with an appropriate reagent hydrochloride in aqueous sodium acetate to give, for example, 5-pyrimidinecarbaldehyde semicarbazone (**194**, X = O) ($H_2NCONHNH_2$) or thiosemicarbazone (**194**, X = S) ($H_2NCONHNH_2$). An *oxime* is made usually from the aldehyde with freed hydroxylamine in aqueous or alcoholic solution to give, for instance, 2-pyrimidinecarbaldehyde oxime (H_2 NOH, H_2O, 60°).



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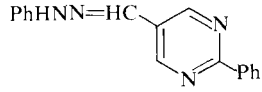

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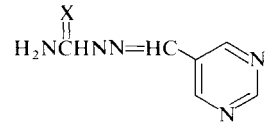
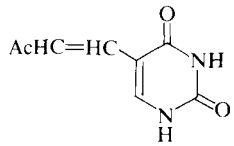


194

Other reactions

1. Just as a carboxylic acid can undergo decarboxylation, so may a pyrimidinecarbaldehyde sometimes suffer *decarbonylation*, or loss of carbon monoxide. For example, 4-amino-6-dimethylamino-5-pyrimidinecarbaldehyde in refluxing hydrochloric acid gives 6-dimethylamino-4-pyrimidinamine in good yield.
2. A pyrimidinecarbaldehyde can usually undergo *condensation with an activated methylene* reagent, as illustrated in the reaction of 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde with acetone in acetic acid containing piperidine to give 5-acetonylidenemethyl-2,4(1*H*,3*H*)-pyrimidinedione (**195**).



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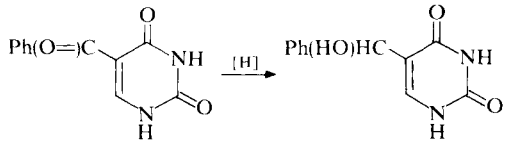
3. The formyl group of a pyrimidinecarbaldehyde can undergo *difluorination*: 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde with sulfur tetrafluoride at 100° (sealed) slowly gives 5-difluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione.

1.6.22. Reactions at Other *C*-Acyl Groups (Section 10.7.2)

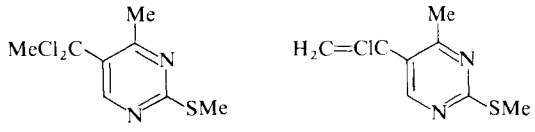
Oxidation and reduction. The *oxidation* of a pyrimidine ketone to a pyrimidinecarboxylic acid is seen in the conversion of 5-acetyl-4-methyl-2-phenylpyrimidine into 4-methyl-2-phenyl-5-pyrimidinecarboxylic acid ($KMnO_4$). The *reduction* of a pyrimidine ketone to an hydroxyalkylpyrimidine is exemplified in the conversion of 5-acetyl- into 5-α-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaBH_4$) or 6-benzoyl- (**196**) into 6-α-hydroxybenzyl-2,4(1*H*,3*H*)-pyrimidinedione (**197**) ($NaBH_4$).



196 **197**

Derivatization. Pyrimidine ketones give the usual types of functional derivative used traditionally to characterize ketones. Such products are exemplified in 5-benzoyl-2,4(1*H*,3*H*)-pyrimidinedione oxime ($HONH_2$.HCl, pyridine), ethyl 4-acetyl-2-methyl-5-pyrimidinecarboxylate phenylhydrazone ($PhNHNH_2$), and 5-acetyl-1-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione semicarbazone ($H_2NCONHNH_2$.HCl, KOAc).

Chlorination. A *C*-acetylpyrimidine may react with phosphoryl chloride or phosphorus pentachloride to give the corresponding α,α-dichloroethylpyrimidine, which can be stimulated to lose one or even two molecules of HCl. For example, 5-acetyl- gives 5-α,α-dichloroethyl- (**198**) ($POCl_3$, PCl_5), which gives 5-α-chlorovinyl- (**199**) ($AlBr_3$, distillation) and thence 5-ethynyl-4-methyl-2-methylthiopyrimidine ($KOBu^t$).



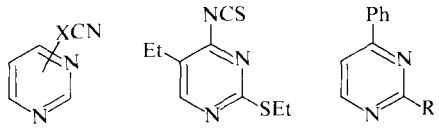
198 **199**

1.6.23. Reactions at Cyanato and Thiocyanato Groups (Section 10.8.4)

Cyanatopyrimidines (**200**, X = O) are still unknown, but thiocyanatopyrimidines (**200**, X = S) are represented reasonably well and are quite reactive.

Thermal isomerization. Thiocyanato- are converted into isothiocyanatopyrimidines by heating in an inert solvent at 100–200°. In this way can be made, for example, ethyl 2-ethylthio-4-isothiocyanato-5-pyrimidinecarboxylate (PhH,

190°, sealed) or 5-ethyl-2-ethylthio-4-isothiocyanatopyrimidine (**201**) (PhMe, reflux).

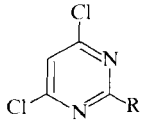


200 **201** **202**

Displacement reactions. A suitably activated thiocyanato substituent can act as a leaving group. For example, 4-phenyl-2-thiocyanatopyrimidine (**202**, R = SCN) undergoes *aminolysis* to 4-phenyl-2-pyrimidinamine (**202**, R = NH_2) (KNH_2, liquid NH_3), 1-methyl-4-thiocyanato-2(1*H*)-pyrimidinone undergoes *hydrolysis* to 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (0.1*M* HCl or NaOH, 25°), 5-nitro-4-thiocyanato-2-pyrimidinamine undergoes *alcoholysis* to 4-ethoxy-5-nitro-2-pyrimidinamine (EtONa, EtOH, 0°), and 2-chloro-5-nitro-4-thiocyanatopyrimidine undergoes (indirect) *thiolysis* to 5-nitro-2,4(1*H*,3*H*)-pyrimidinedithione (H_2NCSNH_2; then HO^-).

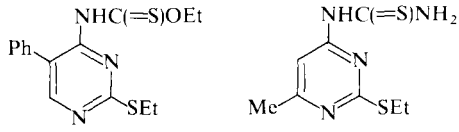
1.6.24. Reactions at Isocyanato and Isothiocyanato Groups (Sections 10.8.2, 10.8.5)

Hydrolysis. Hydrolysis of an isocyanatopyrimidine gives a carboxyaminopyrimidine that normally loses CO_2 spontaneously to afford a pyrimidinamine. Thus 4,6-dichloro-2-isocyanatopyrimidine (**203**, R = NCO) gives 4,6-dichloro-2-pyrimidinamine (**203**, R = NH_2) (H_2O–AcMe, 2°).



203

Alcoholysis. In much the same way as hydrolysis, alcoholysis of an isocyanatopyrimidine gives an alkoxycarbonylaminopyrimidine, which is much more stable than its carboxyamino analog. For example, 4,6-dichloro-2-isocyanato- (**203**, R = NCO) gives 4,6-dichloro-2-methoxycarbonylaminopyrimidine (**203**, R = $NHCO_2Me$) (MeOH, PhH, 20°); likewise, 2-ethylthio-4-isothiocyanato-5-phenyl- gives 4-ethoxy(thiocarbonyl)amino-2-ethylthio-5-phenylpyrimidine (**204**) (EtOH, reflux).

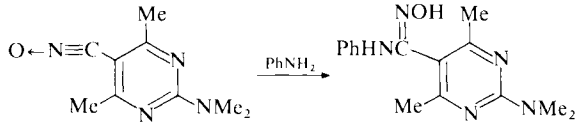


204 **205**

Aminolysis. Aminolysis of an isocyanatopyrimidine affords a ureidopyrimidine. For example, 4,6-dichloro-2-isocyanato- (**203**, R = NCO) gives 4,6-dichloro-2-*N'*-phenylureidopyrimidine (**203**, R = NHCONHPh) ($PhNH_2$, PhH, 20°); similarly, 2-ethylthio-4-isothiocyanato-6-methyl- gives 2-ethylthio-4-methyl-6-thioureidopyrimidine (**205**) (NH_4OH, Et_2O, 20°).

1.6.25. Reactions at Nitrile Oxide Groups (Section 10.8.6)

Few pyrimidinecarbonitrile oxides are known, and little information on their reactivity is reported. However, it is clear that addition of an amine is possible: 2-dimethylamino-4,6-dimethyl-5-pyrimidinecarbonitrile oxide (**206**) with aniline at 110° gives 2-dimethylamino-4,6-dimethyl-5-pyrimidinecarboxanilide oxime (**207**).



206 **207**

Chemistry of Heterocyclic Compounds, Volume 52
D. J. Brown
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CHAPTER 2

Primary Syntheses

Primary synthetic routes to pyrimidines are so numerous and so diverse that it is literally impossible to devise a system of classification that is wholly satisfactory from all points of view. Accordingly, the pragmatic approach adopted here is based primarily on the ways in which the six ring atoms of pyrimidine are supplied by the synthone or synthones used in the various methods; only for syntheses of pyrimidines from other heterocyclic systems is this approach abandoned in favor of a simplistic descriptive classification. Please be guided by the Contents table!

2.1. FROM A SINGLE SIX-ATOM SYNTHONE

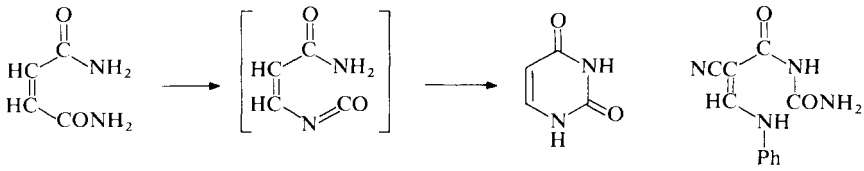
This category of syntheses is subclassified according to the bond (in the final pyrimidine) which remained unformed in the acyclic six-atom synthone. The formation of one pyrimidine from another, by ring fission and subsequent reclosure in a different sense, is also included here.

2.1.1. By Completion of the N1—C2 Bond

Such *cyclization of diamides* is represented in the treatment of maleamide (**1**) with sodium hypochlorite to give the unisolated Hofmann isocyanate (**2**) and thence 2,4(1*H*,3*H*)-pyrimidinedione (**3**) (55%);[4327] likewise, succinamide gave 5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (up to 60%),[4328,4329] while 2-phenyl- or 2,3-dimethylsuccinamide gave 6-phenyl- or 5,6-dimethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione, respectively,[4330] and other such reactions have been reported.[4331]

The *cyclization of appropriate amino carbonyl synthones* (or their equivalents) is illustrated in the following conversions.

3-Anilino-*N*-carbamoyl-2-cyanoacrylamide (**4**), easily made from *N*-(cyanoacetyl)urea with trimethyl orthoformate and aniline, into 2,4-dioxo-1-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (42%) by thermal loss of ammonia.[4332]



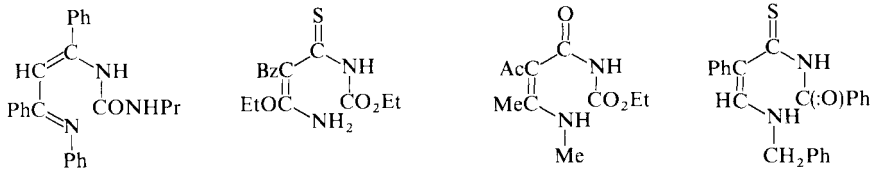
1 2 3 4

1,3-Diphenyl-3-phenylimino-1-(*N'*-propylureido)prop-1-ene (**5**) into 1,4,6-triphenyl-2(1*H*)-pyrimidinone (83%) in methanolic hydrochloric acid;[114] a different cyclization occurred in alkali: see Section 2.1.2.

3-Amino-2-benzoyl-3-ethoxy-*N*-ethoxycarbonyl(thioacrylamide) (**6**) into 5-benzoyl-4-ethoxy-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone in aqueous triethylamine.[2605]

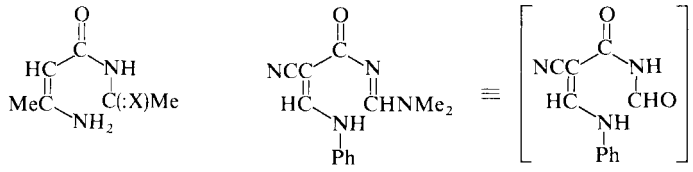
2-Acetyl-*N*-ethoxycarbonyl-3-methylaminocrotonamide (**7**) into 5-acetyl-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (88%) in aqueous trimethylamine.[796]

N-Benzoyl-3-benzylamino-2-phenyl(thioacrylamide) (**8**) into 1-benzyl-2,5-diphenyl-4(1*H*)-pyrimidinethione (95%) in aqueous ethanolic alkali.[4333]



5 6 7 8

3-(3'-Aminocrotonamido)crotonamide (**9**, X = $CHCONH_2$), the equivalent of (**9**, X = O), into 2,6-dimethyl-4(3*H*)-pyrimidinone (88%) by loss of acetamide in alkaline solution.[4334, cf. 4335]



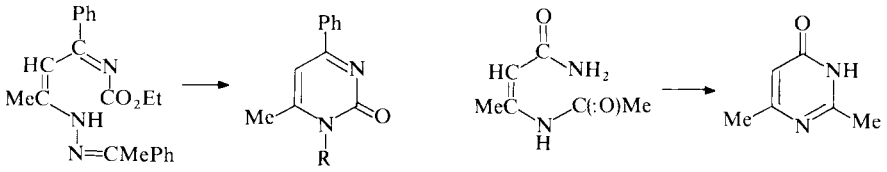
9 10 11

3-Anilino-2-cyano-*N*-(dimethylaminomethylene)acrylamide (**10**), the equivalent of (**11**), into 4-oxo-1-phenyl-1,4-dihydro-5-pyrimidinecarbonitrile (61%) by loss of dimethylamine in refluxing dimethylformamide;[147] in glacial acetic acid, a different product resulted.[147,3856]

Ethyl 3-carbamoylimino-3-diethylaminopropionate into 6-diethylamino-2,4(1*H*,3*H*)-pyrimidinedione (44%) by thermal loss of ethanol.[4353]

Also others.[6895]

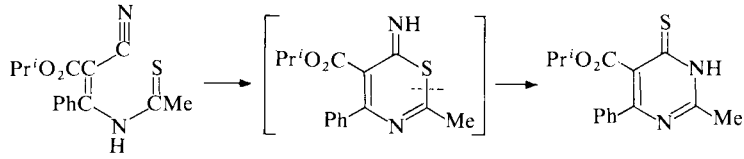
A useful reaction of the same type is exemplified in that of ethyl 3-(α-methylbenzylidenehydrazino)-1-phenylbut-2-enylideneaminoformate (**12**) with aluminum chloride in dimethylformamide to give 4-methyl-3-(α-methylbenzylidene)amino-6-phenyl-2(3*H*)-pyrimidinone (**13**, R = N:CMePh) (83%) and thence, by acidic hydrolysis, 1-amino-6-methyl-4-phenyl-2(1*H*)-pyrimidinone (**13**, R = NH_2) (78%).[34] A closely related type of cyclization was that of 3-acetamidocrotonamide (**14**), in which the acyl group attached to the amino function supplied C2 in the product, 2,6-dimethyl-4(3*H*)-pyrimidinone (**15**), formed in ~98% yield under alkaline conditions;[4336] analogously, 3-carbamoyl-2-(*N*-ethoxycarbonyl-*N*-methylamino)propionic acid in ethanolic ethoxide gave 3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (51%).[414]



12 **13** **14** **15**

Completion of the N1–C2 bond may also be achieved by *cyclization of suitable acylamino, carbamoyl, cyanoamino, or isocyanato nitriles.* Such ring closures are illustrated in the following transformations.

Isopropyl 2-cyano-3-phenyl-3-(thioacetamido)acrylate (**16**) into isopropyl 2-methyl-4-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylate (**18**) (60%), probably by rearrangement of the intermediate imino-1,3-thiazine (**17**) in the isopropanolic sulfuric acid used as the reaction medium.[197]

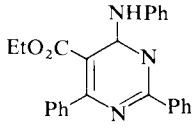


16 **17** **18**

3-Benzamido-2-cyano-3-phenylacrylonitrile into 4-oxo-2,6-diphenyl-3,4-dihydro-5-pyrimidinecarbonitrile (>95%) in ethanolic acid, probably via a 1,6-oxazine.[4338]

Ethyl 2-cyano-3-phenyl-3-(thiobenzamido)acrylate into ethyl 4-anilino-2,6-diphenyl-5-pyrimidinecarboxylate (**19**) (52%), possibly via aminolytic fission of a thiazine intermediate in the methoxyethanolic aniline acetate used as the reaction medium.[554]

Methyl 2,*N*-dicyanoacetimidate (**20**, X = OMe, Y = H) into 4-chloro-6-methoxy-2-pyrimidinamine (**21**, X = OMe, Y = H) plus 2-chloro-6-



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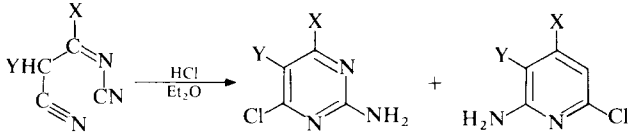


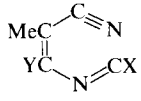
20 **21** **22**

methoxy-4-pyrimidinamine (**22**, X = OMe, Y = H), using ethereal hydrogen chloride; the addition of a Lewis acid, e.g., boron trifluoride etherate, caused exclusive formation of the second product (**22**, X = OMe, Y = H) in 93% yield.[965,966]

Ethyl 2,2,*N*-tricyanoacetimidiate (**20**, X = OEt, Y = CN) into a similar mixture (?) by using ethereal hydrogen chloride, but from which only one product, formulated as 2-amino-4-chloro-6-ethoxy-5-pyrimidinecarbonitrile (**21**, X = OEt, Y = CN) (37%), could be isolated.[997]

2,*N*-Dicyanoacetamidine (**20**, X = NH_2, Y = H) or the homologous 2,*N*-dicyanobutyramidine (**20**, X = NH_2, Y = Et) exclusively into 2-chloro-4,6-pyrimidinediamine (**22**, X = NH_2, Y = H) (51%) or its 5-ethyl derivative (**22**, X = NH_2, Y = Et) (77%), respectively, using ethereal hydrogen chloride; ethereal hydrogen bromide gave the respective 2-bromo analogs (77%, 95%).[972,1884]

3-Isocyanato-2-methylpent-2-enenitrile (**23**, X = O, Y = Et) into 6-ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (70%) (using hydrogen chloride in dioxane), presumably via the 4-chloro analog.[3068]

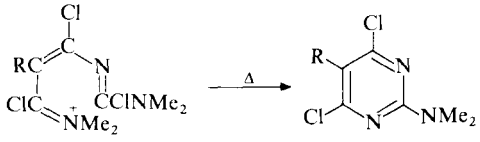


23

3-Chloro-3-(dichloromethyleneamino)-2-methylacrylonitrile (**23**, X = Cl_2, Y = Cl), equivalent to the isocyanate (**23**, X = O, Y = Cl), into 2,4,6-trichloro-5-methylpyrimidine (61%) by using ferric chloride as a catalyst.[3655]

Also other such transformations.[972,973,1004,3655,4337,4352]

The direct thermal *cyclization of 2,4,6-trichloro-1,3,7-triazaheptatrienium*



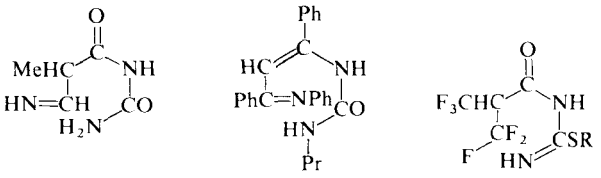
24 25

chlorides is typified by those of the 1,1,7,7-tetramethyl (**24**, R = H) and 1,1,7,7-tetramethyl-5-phenyl (**24**, R = Ph) derivatives, which gave 4,6-dichloro-2-dimethylaminopyrimidine (**25**, R = H) (33%) and its 5-phenyl derivative (**25**, R = Ph) (90%), respectively, persumably accompanied by 2 equivalents (eq) of methyl chloride in each case.[2470] Many analogs were made similarly.[3953]

2.1.2. By Completion of the N3—C4 Bond

Several types of acyclic intermediate have been used for this category of pyrimidine synthesis.

Thus *cyclization between an amino and a carbonyl (or equivalent) group* in the synthone is illustrated by the reduction of *N*-(2-cyanopropionyl)urea to the aminoaldehyde equivalent, *N*-(2-iminomethylpropionyl)urea (**26**), which underwent spontaneous cyclization with loss of ammonia to give 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (59%);[3469] by the conversion of 1,3-diphenyl-3-phenylimino-1-(*N'*-propylureido)prop-1-ene (**27**) into 4,6-diphenyl-1-propyl-2(1*H*)-pyrimidinone (75%) under alkaline conditions (cf. the alternative cyclization under acidic conditions, as reported in Section 2.1.1);[114] and by the ring closure of *S*-methyl-[3',3',3'-trifluoro-2'-(trifluoromethyl)propionyl]isothiourea (**28**) to 6-fluoro-2-methylthio-5-trifluoromethyl-4(3*H*)-pyrimidinone (83%) in the presence of triethylamine.[524] Other examples have been noted.[6073,6143]



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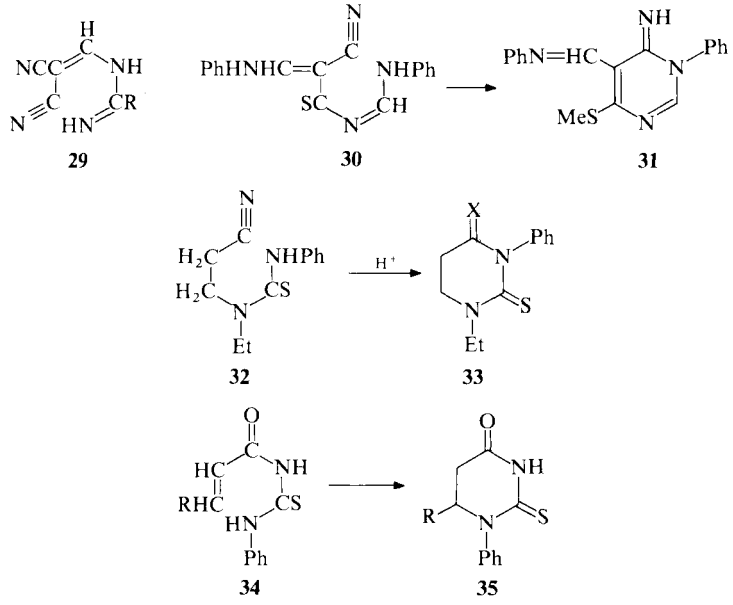
The related *cyclization between an amino and a cyano group* in the acyclic intermediate is exemplified in the treatment of 2-cyano-3-cyanoaminoacrylonitrile with concentrated hydrochloric or hydrobromic acid to give the intermediate (**29**, R = Cl or Br), which underwent spontaneous cyclization to 4-amino-2-chloro-5-pyrimidinecarbonitrile (71%) or its 2-bromo analog (63%), respectively;[478] in related closures;[4351] in the formation of 2-chloro-4,6-pyrimidinediamine (**22**, X = NH_2, Y = H) and analogs, as described in Section

2.1.1; in the ring closure of *N'*-[3'-anilino-2-cyano(thioacryloyl)]-*N*-phenylformamidine (**30**), which occurred during *S*-methylation to afford 6-methylthio-3-phenyl-5-phenyliminomethyl-4(3*H*)-pyrimidinimine (**31**) (98%);[387] and in the treatment of 3-[*N*-ethyl-*N'*-phenyl(thioureido)]propionitrile (**32**) with dilute acid to give 1-ethyl-3-phenyl-2-thioxo-1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone (**33**, X = O) (75%), clearly via the imine (**33**, X = NH).[199] Such a cyclization also gave 6-amino-3-methyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione and analogs.[3992]

It is also possible to achieve *cyclization by addition of an amino group to an ethylenic bond* to give a dihydropyrimidine. Thus *N*-cinnamoyl-*N'*-phenyl(thiourea) (**34**, R = Ph) in ethanolic ethoxide or dimethylformamide–

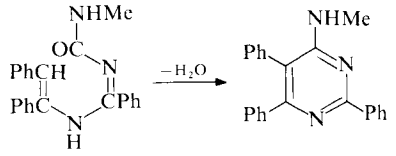


sodium hydride gave 1,6-diphenyl-2-thioxo-1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone (**35**, R = Ph) in 75–92% yield;[309,454,3767,3834] likewise, *N*-crotonoyl-*N'*-phenyl(thiourea) (**34**, R = Me) gave 6-methyl-1-phenyl-2-thioxo-1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone (**35**, R = Me) (62%),[3834] and other analogs have been made similarly.[309,454,3767,3834]

2.1.3. By Completion of the C4—C5 Bond

Although rare, this type of cyclization has been done by the elimination of water from appropriately placed carbonyl and methylene groups in the synthones. Thus treatment of *N*-(α-benzylidenebenzyl)-*N'*-(methylcarbamoyl)-benzamidine (**36**) with *p*-toluenesulfonyl chloride in pyridine gave 4-methylamino-2,5,6-triphenylpyrimidine (**37**) (65%);[4339] analogs were made similarly.[4339] A related but less simple process involved the treatment of 2,2,2-

trichloro-*N*,*N*′-bis(2′-phenylacetyl)acetamidine with an ethanolic alkali to give 6-benzyl-2-dichloromethyl-5-phenyl-4(3*H*)-pyrimidinone (62%) by elimination of both water and hydrogen chloride from the synthone;[4340] the above and related products[4340] are clearly potential 2-pyrimidinecarbaldehydes.

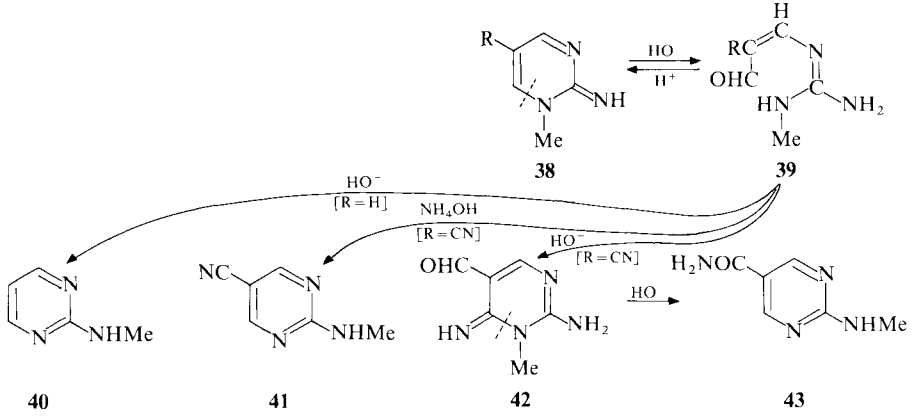


36 **37**

2.1.4. By Rearrangement of One Pyrimidine into Another

When rearrangement of a pyrimidine involves ring fission to an acyclic intermediate and subsequent recyclization to a different pyrimidine, the process may be considered fairly as a primary synthesis.

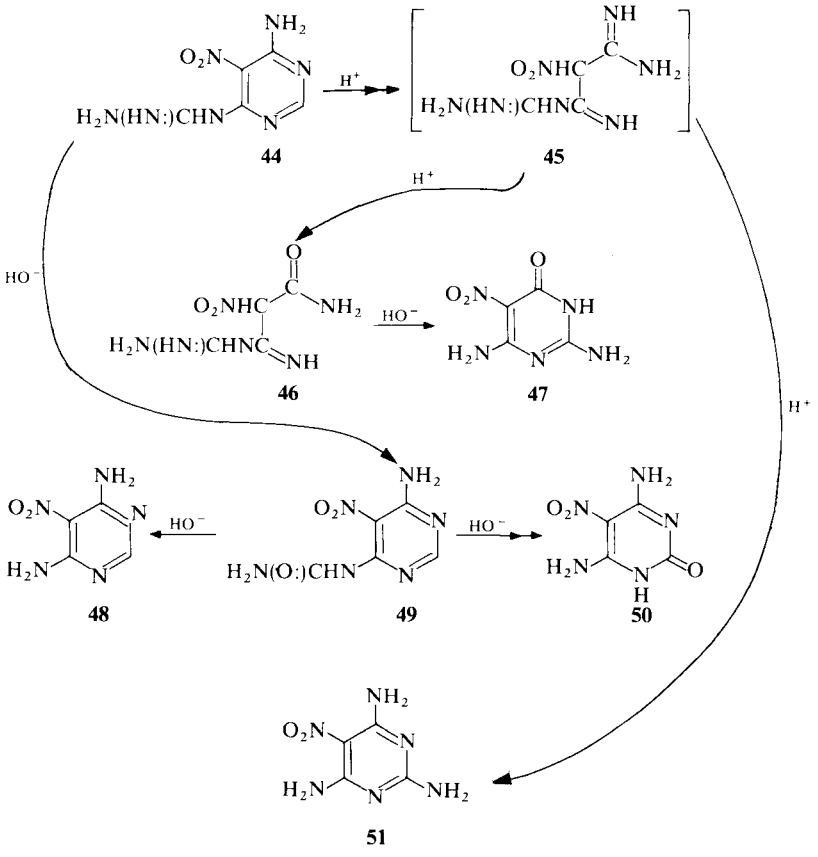
This is illustrated in the *Dimroth rearrangement* of 1-methyl-2(1*H*)-pyrimidinimine (**38**, R = H):[3378,3379,4583] in alkali the imine underwent ring fission to 3-(*N*′-methylguanidino)acrylaldehyde (**39**, R = H), which could be isolated as its oxime or recyclized, either in acid to the original substrate (**38**, R = H) or in alkali to 2-methylaminopyrimidine (**40**) (71% overall).[3379,3791] Similarly, from 2-imino-1-methyl-1,2-dihydro-5-pyrimidinecarbonitrile (**38**, R = CN) in pH 10 buffer, the acyclic 2-formyl-3-(*N*′-methylguanidine)-acrylonitrile (**39** R = CN) (50%) precipitated: treatment of this with acid gave the original imine (**38**, R = CN), treatment with aqueous ammonia gave 2-methylamino-5-pyrimidinecarbonitrile (**41**) (83%), or treatment with alkali gave 2-amino-4-imino-3-methyl-3,4-dihydro-5-pyrimidinecarbaldehyde (**42**) (75%), which underwent a further slow Dimroth rearrangement to 2-methylamino-5-pyrimidinecarboxamide (**43**).[1346] Such Dimroth rearrangements can be quite useful as syntheses: see Section 9.3.2 for a detailed review.



40 **41** **42** **43**

Of little preparative value but of considerable interest is the *Carbon rearrangement.*[1579] In acid, 6-guanidino-5-nitro-4-pyrimidinamine (**44**) underwent fission and loss of a formyl group (representing C2): the resulting (unisolated) acyclic guanidine (**45**) partly recyclized spontaneously to 5-nitro-2,4,6-pyrimidinetriamine (**51**) and partly hydrolyzed to 3-guanidino-3-imino-2-nitropropionamide (**46**), which was isolated as its hydrochloride and could be recyclized subsequently under gentle alkaline conditions to afford 2,6-diamino-5-nitro-4(3*H*)-pyrimidinone (**47**). In hot alkali, the original substrate (**44**) gave an additional product, 5-nitro-6-ureido-4-pyrimidinamine (**49**), which partly hydrolyzed further to 5-nitro-4,6-pyrimidinediamine (**48**) and partly rearranged, presumably via the ureido analog of (**45**), to give 4,6-diamino-5-nitro-2(1*H*)-pyrimidinone (**50**).[1579]

1,3-Dialkyl-2,4(1*H*,3*H*)-pyrimidinediones with an electron-withdrawing substituent at the 5-position undergo complete *replacement of N1 + plus its attached group* by treatment with a primary amine: the mechanism seems to involve 5,6-addition by the new amine, fission of the 1,6-bond, recyclization, and subsequent loss of an amine derived from the original N1 + its substitu-



ent.[282,3995] For example, 1,3-dimethyl-5-nitro- gave 1-butyl-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione ($BuNH_2$, EtOH, reflux, 20 h: 71%), 3-methyl-5-nitro-1-*p*-nitrophenyl- gave 3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (NH_3, EtOH, 20°, 4 h: 93%), and 1-methyl-2,6-dioxo-3-phenyl- gave 1-methyl-2,6-dioxo-3-propyl-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide ($PrNH_2$, 120°, 48 h, sealed: 77%; note the necessary reversal of 1/3-substituents in this example due to nomenclature rules!).[3995] See also a relevant review.[18]

More *complicated transformations* are also known. For example, 2,4-dioxo-1-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile with thiourea in refluxing ethanolic ethoxide gave ethyl 4-amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate (87%); and 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile with *N*,*N*-dimethylguanidine in refluxing ethanol gave 4-amino-2-dimethylamino-*N*-methyl-5-pyrimidinecarboxamide (24%).[6454]

2.2. FROM TWO SYNTHONES

This category of syntheses is subclassified initially according to how many of the six pyrimidine ring atoms are contained in each of the two synthones.

2.2.1. By Using a One- and a Five-Atom Synthone

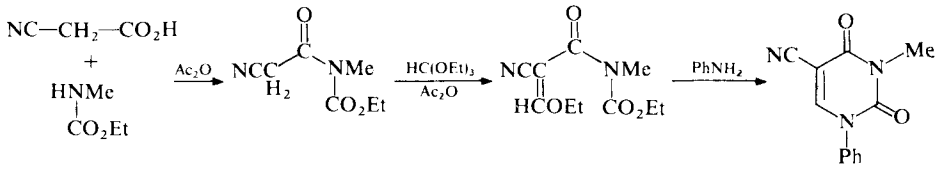
This subcategory of syntheses is further divided according to the ring atom provided by the one-atom synthone.

2.2.1.1. Where the One-Atom Synthone Provides N1

Since N1 has been provided by ammonia or a primary amine in every reported case, the typical cyclizations that follow have been grouped according to the broad type of five-atom synthone employed. Several such groups have been referred to collectively as the "Shaw synthesis," but the term has become imprecise.

From alkoxymethylene urethanes. A typical procedure was the condensation of 2-cyanoacetic acid with ethyl *N*-methylcarbamate in acetic anhydride to give ethyl *N*-(cyanoacetyl)-*N*-methylcarbamate (**52**), which reacted with triethyl orthoformate in acetic anhydride to give ethyl *N*-(2-cyano-3-ethoxyacryloyl)-*N*-methylcarbamate (**53**): warming this key intermediate with ethanolic aniline gave 1-methyl-2,6-dioxo-3-phenyl-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**54**) (83%).[1166] The following syntheses were done rather similarly.

Ethyl *N*-(2-cyano-3-ethoxyacryloyl)carbamate (**55**, R = CN) with 2-aminoethanol gave 1-β-hydroxyethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (~70%).[1318]



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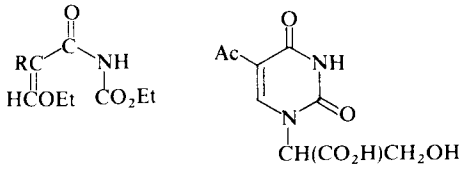
Ethyl *N*-(2-acetyl-3-ethoxyacryloyl)carbamate (**55**, R = Ac) with ammonia or methylamine gave 5-acetyl-2,4(1*H*,3*H*)-pyrimidinedione (~70%) or its 1-methyl derivative (~75%), respectively.[784]

The same intermediate (**55**, R = Ac) with L-serine or other natural amino acids gave 5-acetyl-1-α-carboxy-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (**56**) or analogous products, with retention of configuration:[784] being immune to hydrolysis by strong acids, these pyrimidines were particularly useful for the study of *N*-terminal residues in proteins.



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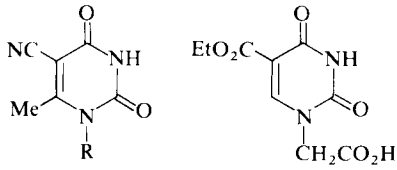
Ethyl *N*-(2-cyano-3-ethoxycrotonoyl)carbamate with hydrazine or hydroxylamine gave 1-amino-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**57**, R = NH_2) (84%) or its 1-hydroxy analog (**57**, R = OH), respectively.[1199]

Ethyl *N*-(3-ethoxy-2-ethoxycarbonylacryloyl)carbamate (**55**, R = CO_2Et) with glycine gave ethyl 1-carboxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**58**) (70%).[2986]

Also many others.[784,1166,1199,1883,2009,2778,2986,3392,4341]



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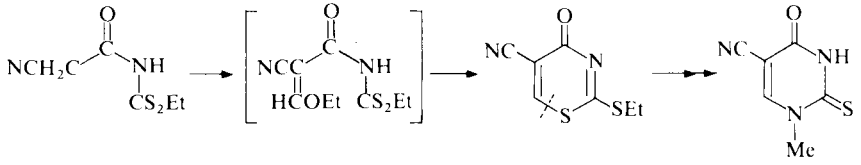
From alkoxymethylene dithiourethanes. When a dithiourethane was used, the foregoing type of synthesis took a different course. For example, treatment of *N*-(2-cyanoacetyl)dithiocarbamate (**59**) with triethyl orthoformate in acetic anhydride undoubtedly gave the ethoxymethylene derivative (**60**), which promptly cyclized to 2-ethylthio-4-oxo-4*H*-1,3-thiazine-5-carbonitrile (**61**) (~40%): sub-



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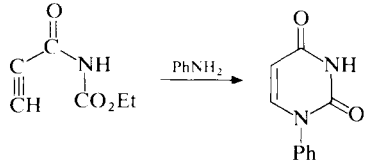
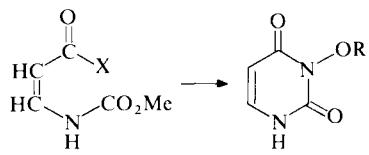
sequent treatment with methylamine induced ring opening to ethyl *N*-(2-cyano-3-methylaminoacryloyl)dithiocarbamate, which underwent reclosure in alkali to afford the originally desired 1-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**62**) (~30%).[3423]

From propynoyl urethanes. A convenient route to 5-unsubstituted pyrimidines is illustrated in the reaction of propynoyl anhydride with ethyl carbamate to give, inter alia, ethyl *N*-propynoylcarbamate (**63**), which reacted vigorously with aniline to give (after dissolution in alkali) 1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**64**) (~75%); the same product (**64**) was made also from ethyl *N*-(3-ethoxyacryloyl)carbamate (**55**, R = H).[3392]



63 64

From chloroformyl or alkoxycarbonyl urethanes. A somewhat different approach is exemplified in the conversion of 3-(methoxycarbonylamino)acrylic acid (**65**, X = OH) into its acid chloride, methyl *N*-(2-chloroformylvinyl)-carbamate (**65**, X = Cl), which reacted with *O*-benzylhydroxylamine to give methyl *N*-[2-(*N*-benzyloxycarbamoyl)vinyl]carbamate (**65**, X = $NHOCH_2Ph$): under alkaline conditions, this underwent cyclization to 3-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**66**, R = CH_2Ph) (~70%), and subsequent acidic hydrolysis gave the *N*-oxide, 3-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (**66**, R = H) (80%).[748] Rather similarly, methyl 3-(α-cyanoamino-α-methoxymethylamino)propionate (**67**, X = NCN), the equivalent of a urethane (**67**, X = O), reacted with benzylamine to give 3-benzyl-2-cyanoamino-5,6-dihydro-4(3*H*)-pyrimidinone (**68**) (61%), which on bromination–dehydrobromination and incidental hydrolysis gave 3-benzyl-2,4(1*H*,3*H*)-pyrimidinedione (**69**) (72%).[523]



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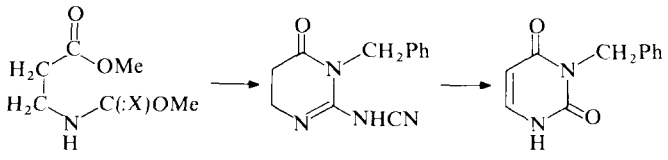

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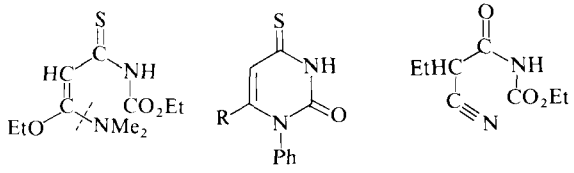
From dimethylaminomethylene urethanes. These synthones behave rather like their alkoxymethylene counterparts, but they appear to be more reactive. Thus treatment of ethyl *N*-[3-dimethylamino-3-ethoxy(thioacryloyl)]carbamate (**70**) with aniline gave 4-ethoxy- (**71**, R = OEt) (30%) rather than 4-dimethylamino-3-phenyl-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone (**71**, R = NMe_2);[2605] likewise, ethyl *N*-[(2-methyl-3-piperidino(thioacryloyl)]carbamate in ethanolic ammonia gave 5-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (86%).[3034] In a subtly different way, hydrogenation of ethyl *N*-(2-cyanobutyryl)carbamate (**72**) in the presence of aniline hydrochloride afforded (after alkaline treatment) 5-ethyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (48%).[4342]



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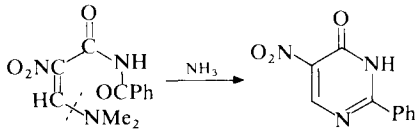
From 2-acylaminovinyl phenyl ketones. When 2-acetamidovinyl phenyl ketone was heated with ammonia at 200°, 2-methyl-4-phenylpyrimidine (11%) resulted; better yields were obtained generally when ammonia was replaced by formamide (39% yield), formamidine acetate (64%), acetamide (23%), or acetamidine hydrochloride (12%).[4396] Several homologs were made similarly,[4396] but the mechanism remains unclear, and the reaction has not been developed further.

From α,N-diacetyl-α-phenylacetamide. Treatment of the foregoing synthone with *p*-aminophenol in refluxing acetic acid for 1 h gave 1-*p*-hydrophenyl-2,6-dimethyl-5-phenyl-4(1*H*)-pyrimidinone (96%).[6140]

From a dimethylaminomethylene amide. Treatment of *N*-(3-dimethylamino-2-nitroacryloyl)benzamide (**73**) with ammonia in dimethylformamide gave 5-nitro-2-phenyl-4(3*H*)-pyrimidinone (**74**) (> 42%).[3556]

From bisdimethylaminomethylene synthones. The condensation of malononitrile with two molecules of chloromethyldimethylammonium chloride gave the azamethinium salt (**75**, R = Cl, Y = CN), which underwent aminolysis to its analog (**75**, R = NMe_2, Y = CN) and then cyclization in dilute ammonia to give 4-dimethylamino-5-pyrimidinecarbonitrile (**76**, Y = CN) (60%); 4-anilino- and



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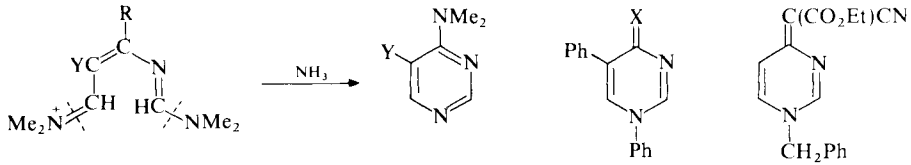

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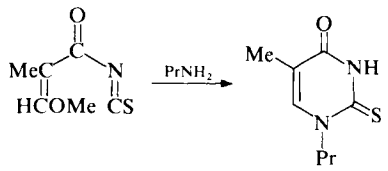
4-*N*-methylanilino-5-pyrimidinecarbonitrile were made similarly, each in ~90% yield.[2655] This type of reaction was developed subsequently to afford products such as 1,5-diphenyl-4-phenylimino-1,4-dihydropyrimidine (**77**, X = NPh) (70%),[387,4343] 4-dimethylaminopyrimidine (**76**, Y = H) (56%) from the intermediate (**75**, R = NMe_2, Y = H),[1744] 1,5-diphenyl-4(1*H*)-pyrimidinethione (**77**, X = S) (98%),[387] and products perhaps best formulated as 4-cyano(ethoxycarbonyl)methylpyrimidine and 1-benzyl-4-cyano(ethoxycarbonyl)methylene-1,4-dihydropyrimidine (**78**).[3912]

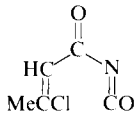
From alkoxymethylene isocyanates or isothiocyanates. Such useful syntheses are typified by the reaction of 3-methoxy-2-methylacryloyl isothiocyanate (**79**) with propylamine to give, after cyclization in alkali, 5-methyl-1-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**80**) (~60%).[1318] Some interesting variations are evident in the following examples.



79 80

3-Chlorocrotonoyl isocyanate (**81**) with aniline gave 6-methyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (~10%); note chloro in place of alkoxy as a leaving group.[2778]

3-Ethoxyacryloyl isocyanate or isothiocyanate with methylamine gave 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**82**, X = O) (~30%)[2773] or 1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**82**, X = S) (~25%),[2027] respectively.



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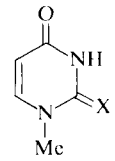
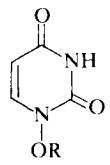


82

3-Ethoxyacryloyl isocyanate with the ethyl ester of β-alanine or with benzylamine gave 1-β-carboxyethyl- (>90%)[2014] or 1-benzyl-2,4(1*H*,3*H*)-pyrimidinedione (>80%),[1511] respectively.

3-Ethoxyacryloyl isocyanate with *O*-benzylhydroxylamine gave, after thermal cyclization, 1-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**83**, R = OCH_2Ph) (low yield) and thence 1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (unambiguously).[748]

3-Methoxy-2-methylacryloyl isocyanate with butylamine gave the intermediate, *N*-butyl-*N'*-(3-methoxy-2-methylacryloyl)urea (**84**, R = Bu), the potassium salt of which underwent thermal cyclization to 1-butyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (62%).[4344]



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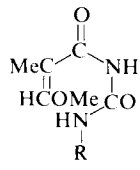
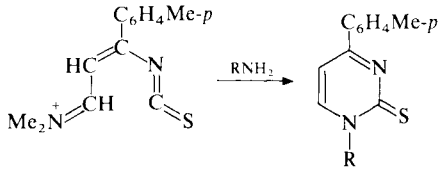


84

3-Methoxy-2-methylacryloyl isocyanate with aniline gave *N*-(3-methoxy-2-methylacryloyl)-*N'*-phenylurea (**84**, R = Ph) which, in contrast to the last example, best underwent cyclization by fusion with *p*-toluenesulfonic acid at 150° to give 5-methyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (89%).[4345]

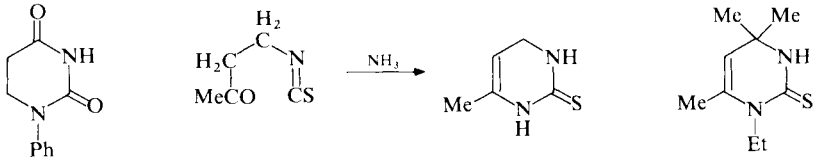
Also other examples.[3199,4345]

From dimethylaminomethylene isothiocyanates. Treatment of the perchlorate of *N*-(3-isothiocyanato-3-*p*-tolylprop-2-enylidene)-*N*,*N*-dimethylammonium (**85**) with *m*-anisidine produced 1-*m*-methoxyphenyl-4-*p*-tolyl-2(1*H*)-pyrimidinethione (**86**, R = C_6H_4OMe-*m*) (73%) with loss of dimethylamine;[4346] the same substrate (**85**) with phenacylamine hydrobromide in acetonitrile containing triethylamine or with ethanolic glycine ethyl ester gave 1-benzoylmethyl- (**86**, R = CH_2Bz) (81%) or 1-ethoxycarbonylmethyl-4-*p*-tolyl-2(1*H*)-pyrimidinethione (**86**, R = CH_2CO_2Et) (49%), respectively;[3892] and with phenylhydrazine, it gave 1-anilino-4-*p*-tolyl-2(1*H*)-pyrimidinethione (**86**, R = NHPh) (78%).[6008] Other examples are known.[6026]



85 86

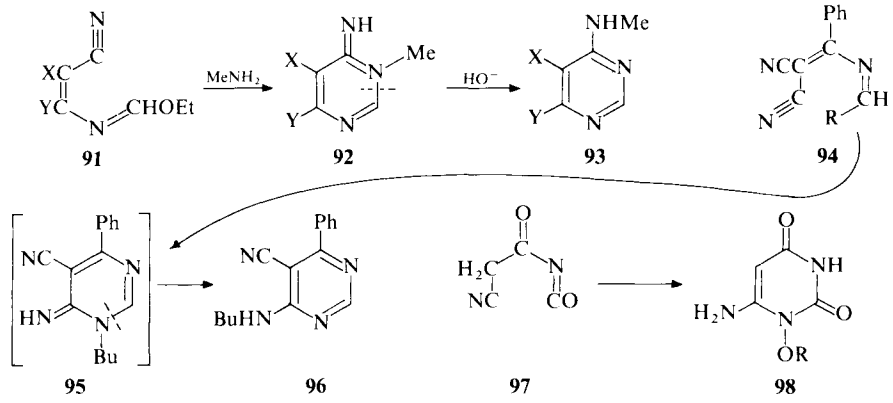
From acyl isocyanates or isothiocyanates. The use of such synthones with amines to produce hydropyrimidines is covered more logically in Section 11.1.3. For example, 3-bromopropionyl isocyanate with aniline gave, after cyclization, 1-phenyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**87**) (25%);[4113] in a different way, 4-isothiocyanato-2-butanone (**88**) with ethanolic ammonia gave a product formulated as 4-methyl-3,6-dihydro-2(1*H*)-pyrimidinethione (**89**) (40%) on nmr (nuclear magnetic resonance) evidence:[80] cf. 1-ethyl-4,4,6-trimethyl-2,3-dihydro-2(1*H*)-pyrimidinethione (**90**)[4347] and a more complicated example.[134]



87 88 89 90

From ethoxymethylene nitriles. 3-Aminoacrylonitrile reacted with triethyl orthoformate and acetic anhydride to give 3-(ethoxymethyleneamino)-acrylonitrile (**91**, X = Y = H), which underwent aminolysis and cyclization in ethanolic methylamine to afford 3-methyl-4(3*H*)-pyrimidinimine (**92**, X = Y = H), isolated as its hydriodide (70%);[2570] 5- and/or 6-alkylated derivatives were made similarly. For example, 3-(ethoxymethyleneamino)-2-methyl-crotononitrile (**91**, X = Y = Me) gave 3,5,6-trimethyl-4(3*H*)-pyrimidinimine (**92**, X = Y = Me) (70%);[2570] and analogous but more complicated products were also so made.[1571,2570] All such imines (as free bases in alkali) underwent facile Dimroth rearrangement into the corresponding methylaminopyrimidines: for example, the foregoing imines (**92**, X = Y = H or Me) gave 4-methylaminopyrimidine (**93**, X = Y = H) (93%) or 4,5-dimethyl-6-methylaminopyrimidine (**93**, X = Y = Me) (96%), respectively.[2570]

From dimethylaminomethylene nitriles. When 3-amino-2-cyano-3-phenylacrylonitrile was allowed to react with *N*,*N*-dimethylformamide dimethyl acetal, 2-cyano-3-(dimethylaminomethyleneamino)-3-phenylacrylonitrile (**94**, R = NMe_2) (91%) resulted. On heating this with a primary amine (e.g., butylamine), transamination occurred to the (unisolated) intermediate (**94**, R = NHBu), which subsequently underwent cyclization to the (unisolated) imine (**95**) and immediate Dimroth rearrangement to 4-butylamino-6-phenyl-5-pyrimidinecarbonitrile (**96**) (48%);[4348] appropriate amines likewise gave the

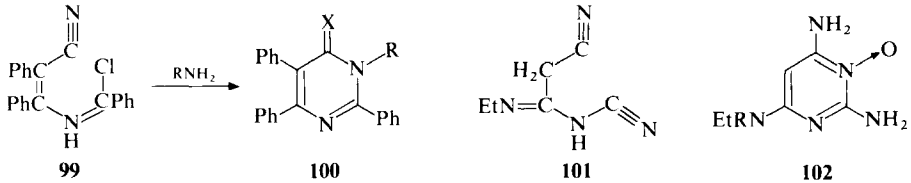


4-amino, 4-propylamino, 4-decylamino, 4-benzylamino, 4-anilino, and other such analogs, each in good yield.[4348]

From an iscyanato nitrile. Treatment of 2-cyanoacetyl chloride with silver isocyanate gave 2-cyanoacetyl isocyanate (**97**), which reacted with *O*-benzylhydroxylamine to afford 6-amino-1-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**98**, R = CH_2Ph) (85%) and thence by hydrolysis, 6-amino-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (**98**, R = H) (82%).[1338] The same product (**98**, R = H) was also obtained in low yield by thermal elimination of ammonia from *N*-(3-amino-3-hydroxyiminopropionyl)urea in boiling dimethylformamide.[1278] A procedure involving the reaction of a 2,2-dialkyl-2-cyanoacetyl isothiocyanate with an amine to give a 1,5,5-trialkyl-6-imino-2-thioxo-1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone has been mentioned without details.[4392]

From an α-chlorobenzylideneamino nitrile. 3-α-Chlorobenzylideneamino-2,3-diphenylacrylonitrile (**99**) reacted with propylamine to furnish 2,5,6-triphenyl-3-propyl-4(3*H*)-pyrimidinimine (**100**, R = Pr, X = NH), proven in structure by hydrolysis to the corresponding pyrimidinone (**100**, R = Pr, X = O);[4349] other primary amines reacted similarly to give analogs such as 2,3,5,6-tetraphenyl-4(3*H*)-pyrimidinimine (**100**, R = Ph, X = NH),[4349] but hydroxylamine apparently gave, not the expected product (**100**, R = OH, X = NH), but the isomeric 4-hydroxyamino-2,5,6-triphenylpyrimidine, possibly formed by Dimroth rearrangement therefrom.

From cyanoamino nitriles. 2,*N*-Dicyano-*N'*-ethylacetamidine (**101**) with ethanolic hydroxylamine hydrochloride gave 6-ethylamino-2,4-pyrimidinediamine

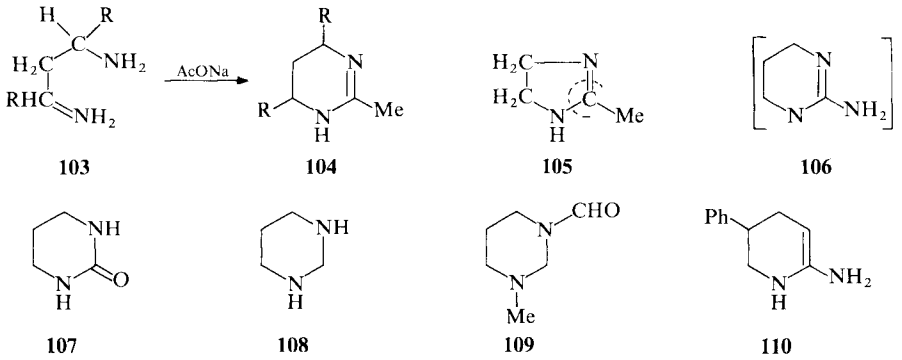


3-oxide (**102**, R = H) (49%);[2979] the 6-diethylamino analog (**102**, R = Et) (62%) was made rather similarly.[4351]

2.2.1.2. Where the One-Atom Synthone Provides C2

Although C2 can be provided by a variety of fragments such as formaldehyde, formic acid, and benzoyl chloride; this condensation is subdivided primarily according to the type of five-atom fragment employed.

From β-diamines. No aromatic pyrimidines have been made directly from 1,3-diamines, but hydropyrimidines have been so made. Such reactions are exemplified briefly in that of anhydrous 1,3-propanediamine (**103**, R = H) or 2,4-pentanediamine (**103**, R = Me) with fused sodium acetate to give 2-methyl- (**104**, R = H) (50%)[4354] or 2,4,6-trimethyl-1,4,5,6-tetrahydropyrimidine (**104**, R = Me) (62%),[4355] respectively; of 1,3-propanediamine (**103**, R = H) with 2-methyl-4,5-dihydroimidazole (**105**) to give 2-methyl-1,4,5,6-tetrahydropyrimidine (**104**, R = H) (98%);[3920] of the same substrate (**103**, R = H) with ethyl carbamate in the vapor phase over platinum catalysts to give 2-pyrimidinamine (16%) via dehydrogenation of the unisolated 1,4,5,6-tetrahydro-2-pyrimidinamine (**106**);[3891] of the same substrate (**103**, R = H) with propionic acid to give, rather analogously, 2-ethylpyrimidine;[6848] of the same substrate (**103**, R = H) with aqueous urea to give 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**107**) (90%);[3914] of 2-phenyl-1,3-propanediamine with cyanogen bromide at 20° or with *N*,*S*-dimethylisothiourea at > 200° to give 5-phenyl-1,4,5,6-tetrahydro-2-pyrimidinamine (**110**) (46%);[45] of the same substrate (**103**, R = H) with formaldehyde to give 1,2,3,4,5,6-hexahydropyrimidine (**108**) or its 1-formyl-3-methyl derivative (**109**), according to conditions;[501,4356] and in other such condensations.[73,155,265,526,3843,3890,6028] These procedures are discussed further in the context of hydropyrimidines (see Sections 11.2.1, 11.3).

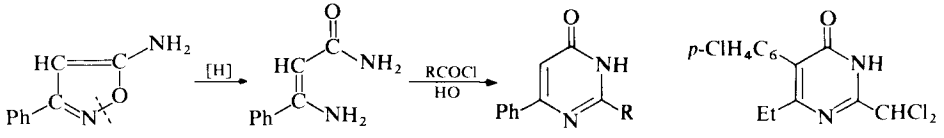


103 **104** **105** **106**

107 **108** **109** **110**

From β-amino amides. The cyclization of appropriate (unsaturated) amino amides by addition of C2 is exemplified by the reduction of 3-phenyl-5-isoxazolamine (**111**) to β-aminocinnamamide (**112**), which underwent acylation

to the corresponding β-acetamido or β-benzamido derivative and a subsequent gentle cyclization to 2-methyl-6-phenyl- (**113**, R = Me) or 2,6-diphenyl-4(3*H*)-pyrimidinone (**113**, R = Ph), respectively;[4357] analogs were made similarly,[2815] and the mild conditions permitted the survival of otherwise labile substituents: for example, 3-amino-2-*p*-chlorophenylpent-2-enamide with 2,2-dichloroacetyl chloride gave 5-*p*-chlorophenyl-2-dichloromethyl-6-ethyl-4(3*H*)-pyrimidinone (**114**).[4161] The scope of this reaction to produce 4(3*H*)-pyrimidinones is further illustrated by the following examples.



111 **112** **113** **114**

3-Amino-2-nitroacrylamide with dimethylformamide diethyl acetal gave 5-nitro-4(3*H*)-pyrimidinone (20%).[3556]

3-Aminocrotonamide with mono-, di-, or trichloroacetic anhydride followed by thermal cyclization in tetralin gave 2-chloromethyl-6-methyl- (78%), 2-dichloromethyl-6-methyl- (54%), or 6-methyl-2-trichloromethyl-4(3*H*)-pyrimidinone (10%), respectively.[2235]

3-Aminocrotonamide or its *N*-methyl derivative with ketene in acetonic triethylamine, followed by distillation, gave 5-acetyl-2,6-dimethyl- (**115**, R = H) (57%) or 5-acetyl-2,3,6-trimethyl-4(3*H*)-pyrimidinone (**115**, R = Me) (52%), respectively.[785]

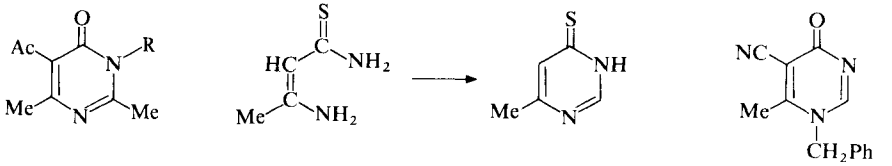
3-Aminocrotonamide with ethyl lactate or ethyl benzoate, followed by cyclization, gave 2-α-hydroxyethyl-6-methyl- (10%) or 6-methyl-2-phenyl-4(3*H*)-pyrimidinone (30%), respectively.[2820]

3-Aminocrotonamide with ethyl 2-thiophenecarboxylate or succinic anhydride, followed by cyclization, gave 6-methyl-2-thien-2′-yl- (31%)[4358] or 2-β-carboxyethyl-6-methyl-4(3*H*)-pyrimidinone (66%),[2013] respectively.

3-Amino(thiocrotonamide) (**116**) with dimethylformamide dimethyl acetal under reflux gave 6-methyl-4(3*H*)-pyrimidinethione (**117**) (68%).[167]

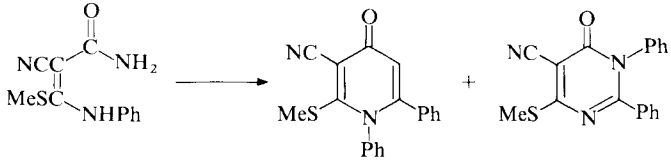
3-Benzylamino-2-cyanocrotonamide with triethyl orthoformate in acetic anhydride under reflux gave 1-benzyl-6-methyl-4-oxo-1,4-dihydro-5-pyrimidinecarbonitrile (**118**) (~60%).[146]

Also other such reactions.[151,357,366,679,2013,2575,2820,2822,2986,3292,3505,3867,3956,4358–4360]



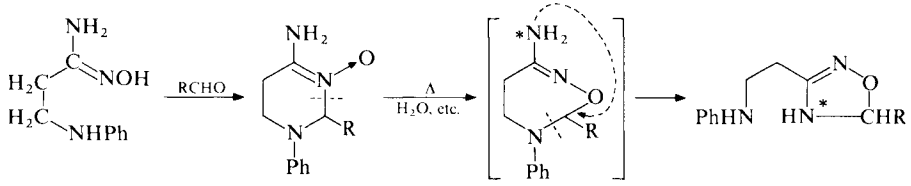
115 **116** **117** **118**

Whereas 3-anilino-2-cyano-3-(methylthio)acrylamide (**119**) reacted with benzoyl chloride in pyridine to give only the expected 4-methylthio-6-oxo-2,3-diphenyl-3,6-dihydro-5-pyrimidinecarbonitrile (**120**),[175] the same substrate (**119**) with benzoic acid and crude trimethylsilyl polyphosphate at 120° gave a separable mixture of the same product (**120**) and the isomeric 4-methylthio-6-oxo-1,2-diphenyl-1,6-dihydro-5-pyrimidinecarbonitrile (**121**), in which the latter predominated.[175,296] Other examples of this phenomenon have been described,[507] and the complicated mechanism of rearrangement has been studied.[296,507]



119 **120** **121**

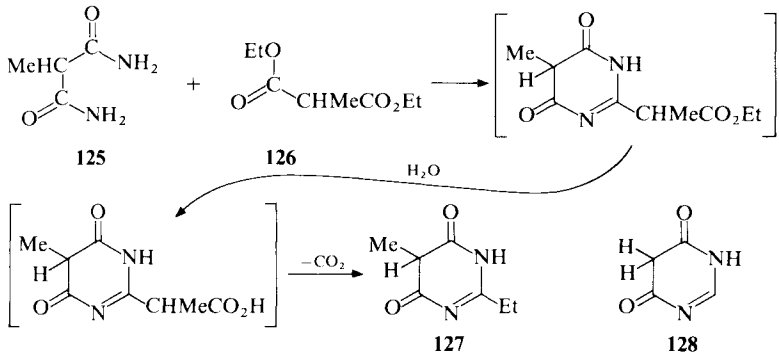
A related condensation of the amino amide oxime, 3-anilinopropionamide oxime (**122**), with acetaldehyde, butyraldehyde, or benzaldehyde furnished 2-methyl-1-phenyl- (**123**, R = Me), 1-phenyl-2-propyl- (**123**, R = Pr), or 1,2-diphenyl-1,2,5,6-tetrahydro-4-pyrimidinamine 3-oxide (**123**, R = Ph), respectively;[123,4361] these products in solution at >70° isomerized to give the corresponding oxadiazolines (**124**), for example, 3-β-anilinoethyl-5-methyl-4,5-dihydro-1,2,4-oxadiazole (**124**, R = Me).[123]



122 **123** **124**

From malondiamides with esters. In 1911 it was shown that α-alkylmalondiamides reacted with diethyl malonate or its α-alkyl derivatives to give 2,5-dialkyl-4,6(1*H*,5*H*)-pyrimidinediones:[3066] for example, α-methylmalondiamide (**125**) with diethyl α-methylmalonate (**126**) in ethanolic sodium ethoxide gave 2-ethyl-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione (**127**) by the route indicated.[3066] Some 40 years later, this reaction was simplified by condensing malondiamide with ethyl formate under similar conditions to give 4,6(1*H*,5*H*)-pyrimidinedione (**128**) (~40%).[2506, cf. 1037] The versatility of this procedure, now known as the *Remfry–Hull synthesis*, is illustrated in the following examples.

α-Ethyl- or α-phenylmalondiamide with ethyl formate gave 5-ethyl-[2506] or 5-phenyl-4,6(1*H*,5*H*)-pyrimidinedione[921,2506] (25–45%).



α-(Tetrahydropyran-2′-yloxy)malondiamide with ethyl formate gave 5-tetrahydropyran-2′-yloxy- (64%) and thence in dilute acetic acid, 5-hydroxy-4,6(1*H*,5*H*)-pyrimidinedione (56%).[1324]

α-Methylaminomalondiamide with ethyl formate gave 5-methylamino-4,6(1*H*,5*H*)-pyrimidinedione (~70%).[1981]

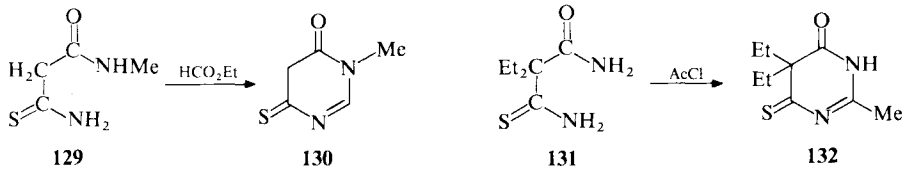
α-Butylmalondiamide with ethyl formate gave 5-butyl-4,6(1*H*,5*H*)-pyrimidinedione (39%).[4362]

Malondiamide with ethyl valerate gave the expected 2-butyl-4,6(1*H*,5*H*)-pyrimidinedione (~15%) with a separable by-product (see following subsection).[1981]

Malondiamide with diethyl oxalate gave (after saponification during workup) 4,6-dioxo-1,4,5,6-tetrahydro-2-pyrimidinecarboxylic acid (~35%).[1405]

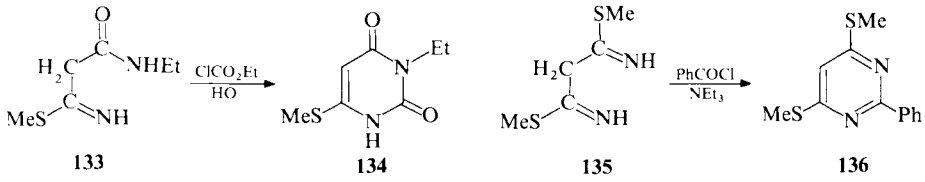
N-Methyl-2-thiocarbamoylacetamide (**129**) with ethyl formate gave 3-methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone (**130**) (39%).[909]

2-Ethyl-2-thiocarbamoylbutyramide (**131**) with acetyl chloride in acetic acid gave 5,5-diethyl-2-methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone (**132**).[2186]



N-Ethyl-3-imino-3-(methylthio)propionamide (**133**) with ethyl chloroformate gave 3-ethyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione (**134**) (33%), via an acyclic intermediate.[909]

1,3-Diimino-1,3-bismethylthiopropane (**135**) with benzoyl chloride in acetonic triethylamine gave 4,6-bismethylthio-2-phenylpyrimidine (**136**) (89%).[1786]



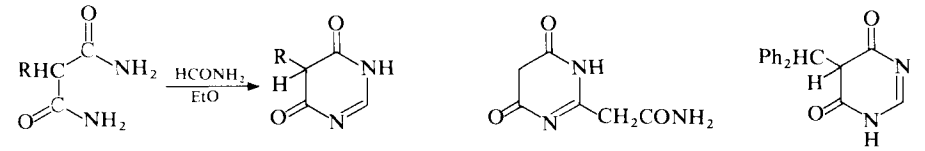
133 134 135 136

α-Ethyl-α-phenylmalondiamide with diethyl carbonate in ethanolic ethoxide gave 5-ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (~40%).[104]

Also other such examples.[909,921,1786,2186,3100,4362]

From malondiamides with amides. The ester or acyl halide used in the Remfry–Hull synthesis can often be replaced to advantage by the corresponding amide. Thus malondiamide (**137**, R = H) or its α-methylamino derivative (**137**, R = NHMe) with formamide in ethanolic sodium ethoxide gave, respectively, 4,6(1*H*,5*H*)-pyrimidinedione (**138**, R = H) in better yield (~65%)[1981] or its 5-methylamino derivative (**138**, R = NHMe) in comparable yield,[1981,3100] as compared with the use of ethyl formate; up to 88% yield of the product (**138**, R = H) was obtained with modification of conditions.[2339,2501,3100,3547,3548] Malondiamide with propionamide likewise gave 2-ethyl-4,6(1*H*,5*H*)-pyrimidinedione, albeit in poor yield on account of a substantial but separable by-product: the same byproduct was formed whenever a higher ester or amide was used in the reaction and its nature was dependent only on the malondiamide employed. In fact, treatment of malondiamide alone in ethanolic ethoxide gave a single product identical with the foregoing by-product and clearly resulting from self-condensation of the malondiamide to give 2-carbamoylmethyl-4,6(1*H*,5*H*)-pyrimidinedione (**139**),[1981] which had been synthesized unambiguously in another connexion.[1991]

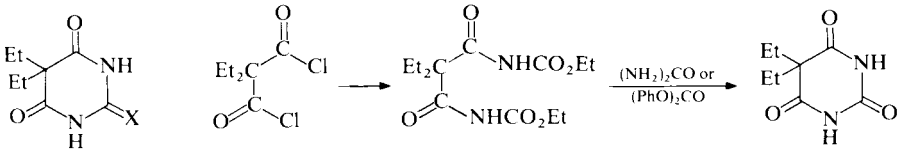
The use of appropriately α-substituted malondiamides with formamide, usually in alcoholic alkoxide, gave 5-methyl- (66%),[1832,3100] 5-ethyl-,[3100] 5-phenyl-,[3100] 5-methoxy-,[916,2206] 5-ethoxy-,[916] 5-piperidino-,[3100] and 5-diphenylmethyl-4,6(1*H*,5*H*)-pyrimidinedione (**140**) (potassium *t*-butoxide in dimethyl sulfoxide: 47% yield);[4363] also other such derivatives.[4364–4366]



137 138 139 140

From malondiamides with carbonic acid derivatives. This type of reaction leads only to derivatives of barbituric acid; the use of ethyl chloroformate and diethyl carbonate has already been mentioned under the Remfry–Hull synthesis. Although carbon dioxide itself has not been so used, carbon disulfide or carbon oxysulfide with α,α-diethylmalondiamide in ethanolic ethoxide did give

5,5-diethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**141**, X = S) or 5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**141**, X = O), respectively.[4367] Likewise, phosgene (at 150°), diphenyl carbonate, or diethyl carbonate with α,α-diethylmalondiamide gave the last-mentioned product (**141**, X = O);[4369–4372] 5-*m*-chlorophenyl-5-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione was made similarly using diethyl carbonate;[4368] α-nitromalondiamide, with phosgene in toluene at 120° (sealed), gave 5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (50%);[3413] and a variety of 5-alkyl- and 5,5-dialkyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones have been made using liquid ammonia containing sodium hydroxide as a medium.[3111]

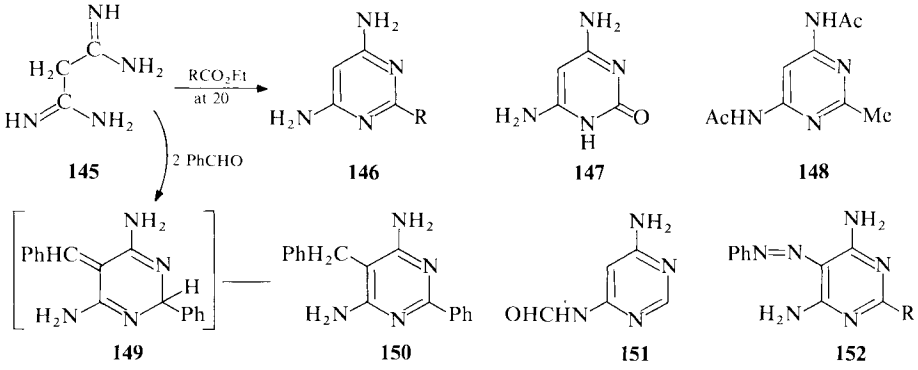


141 **142** **143** **144**

Two related procedures are best classified in this subsection. Malondiamide and its α-phenyl, α,α-diethyl, and α,α-diphenyl derivatives all reacted with oxalyl chloride in refluxing benzene to afford 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione and its 5-phenyl, 5,5-diethyl, and 5,5-diphenyl derivatives, respectively;[4372–4374] the addition of acetic anhydride facilitated such reactions, which then proceded at room temperature.[4375] *N*,*N*′-Diethoxycarbonyl-α,α-diethylmalondiamide (**143**), made from α,α-diethylmalonyl chloride (**142**) with ethyl carbamate, reacted with urea or diphenyl carbonate to give 5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**144**).[4376–4380]

From malondiamidines. Malondiamidine is less easy to prepare but far more active than malondiamide. Thus the amidine (**145**) reacted exothermically with ethyl formate or ethyl acetate to give 4,6-pyrimidinediamine (**146**, R = H) or its 2-methyl derivative (**146**, R = Me), respectively, each in good yield;[2507] it also reacted with warm ethyl benzoate to give a poor yield of the 2-phenyl derivative (**146**, R = Ph)[2377] but failed to react likewise with ethyl butyrate, diethyl malonate, ethyl pyruvate, and several other esters.[2377] The same substrate (**145**) with diethyl carbonate or ethyl chloroformate gave 4,6-diamino-2(1*H*)-pyrimidinone (**147**) in 44% or 33% yield, respectively;[2377] with diethyl oxalate it gave 4,6-diamino-2-pyrimidinecarboxylic acid (**146**, R = CO_2H) (> 80%);[2377] with acetic anhydride, it gave 4,6-diacetamido-2-methylpyrimidine (**148**) (84%);[2377] with benzaldehyde (2 mol), it gave 5-benzylidene-2-phenyl-2,5-dihydro-4,6-pyrimidinediamine (**149**), which underwent rearrangement into 5-benzyl-2-phenyl-4,6-pyrimidinediamine (**150**) (> 45%);[4381] and with hot formamide, it gave 6-formamido-4-pyrimidinamine (**151**) (28%).[3185]

Some α- or *N*-substituted malondiamidines have been used successfully in this reaction. Thus, for example, α-phenylazomalondiamidine with hot formamide gave 5-phenylazo-4,6-pyrimidinediamine (**152**, R = H) (71%);[3185] the same substrate with diethyl oxalate gave 4,6-diamino-5-phenylazo-2-pyrimidinecar-

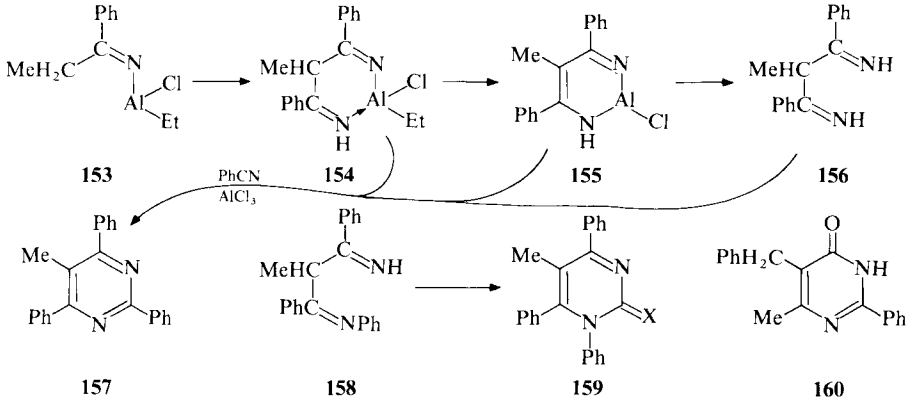


boxylic acid (**152**, R = CO_2H) (~20%);[1405] *N,N''*-diallylmalondiamidine with ethyl formate gave 4,6-bisallylaminopyrimidine (20%);[866] and *N,N''*-dimethylmalondiamidine with benzaldehyde (2 mol) gave 5-benzyl-4,6-bismethylamino-2-phenylpyrimidine (23%).[4381]

As might be expected, the half-amide–half-amidine of malonic acid (2-amidinoacetamide) with ethyl formate in ethanolic ethoxide gave 6-amino-4(3*H*)-pyrimidinone (isolated in ~25% yield as its 5-nitro derivative);[1679] 2-amidino-2-phenylazoacetamide with formamide at 150° gave 6-amino-5-phenylazo-4(3*H*)-pyrimidinone (63%);[3185] 2-amidinoacetamide with diethyl oxalate gave 4-amino-6-oxo-1,6-dihydro-2-pyrimidinecarboxylic acid (~25%);[1405] and 2-(*N*-benzylamidino)acetamide with formamide in ethanolic ethoxide gave 6-benzylamino-4(3*H*)-pyrimidinone (89%).[4382]

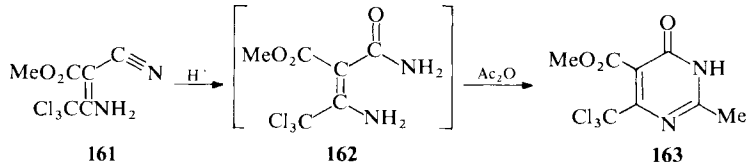
From β-diimines. Treatment of ethyl(α-ethylbenzylideneamino)aluminum chloride (**153**) with benzonitrile gave the aluminum complex (**154**), which lost ethane at 160° to give the cyclic aluminum compound (**155**) and thence on alkaline hydrolysis, 2-methyl-1,3-diphenyl-1,3-propanediimine (**156**). On heating this compound with benzonitrile at 130° in the presence of aluminum chloride, a good yield of 5-methyl-2,4,6-triphenylpyrimidine (**157**) resulted; comparable yields were also obtained by heating either of the aluminum-containing compounds **154** and **155** with benzonitrile.[4383] Variations also produced, for example, 5-ethyl-2-phenyl-4-propyl- and 5-ethyl-4-phenyl-2-propylpyrimidine.[4383] Such diimines have been used with carbonic acid derivatives to afford 2-pyrimidinones and 2-pyrimidinethiones: for example, 2-methyl-1,3-diphenyl-3-phenylimino-1-propanimine (**158**) with ethyl chloroformate in pyridine at 20° gave 5-methyl-1,4,6-triphenyl-2(1*H*)-pyrimidinone (**159**, X = O) (92%), while with carbon disulfide at 70° it gave the corresponding thione (**159**, X = S) (87%).[2008]

From miscellaneous intermediates. The use of other five-atom synthones is illustrated in the following examples. 3-Aminocrotonamide with benzaldehyde gave 2-benzylidene-3-iminobutyramide, which then reacted with a second molecule of benzaldehyde to furnish 5-benzyl-6-methyl-2-phenyl-4(3*H*)-pyrimidinone (**160**) (94%), the oxidation-state imbalance having been rectified



153 154 155 156 157 158 159 160

by the benzylidene double bond.[4384] Treatment of methyl 3-amino-2-cyano-3-trichloromethylacrylate (**161**) with acetic anhydride–acetic acid in the presence of a Lewis acid has been reported to give methyl 2-methyl-4-oxo-6-trichloromethyl-3,4-dihydro-5-pyrimidinecarboxylate (**163**) (75%), presumably via an intermediate amide (**162**).[4385] The reaction of 3-(hydroxyamino)propionaldehyde oxime (**164**) with formaldehyde gave initially 1,2,5,6-tetrahydro-1-pyrimidinol 3-oxide (**165**), which then underwent oxidation by manganese dioxide to afford pyrimidine 1,3-dioxide (**166**) in 6% yield; such reactions proved more effective when substituents were present, as in the formation of 5-methyl-4-phenylpyrimidine 1,3-dioxide (**167**) (56%).[3626,3627,4386]



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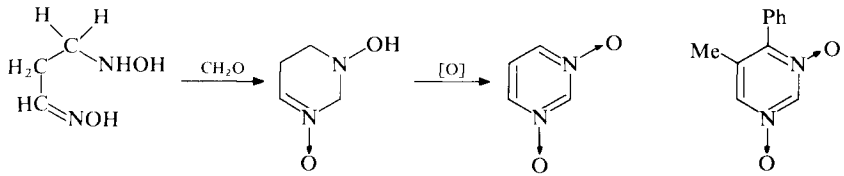

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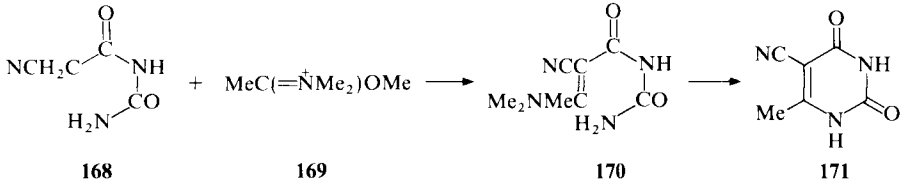
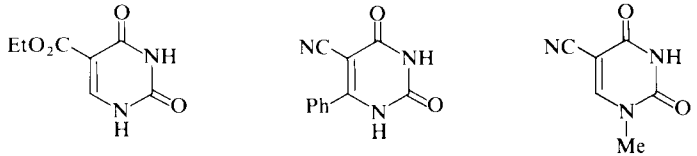
2.2.1.3. Where the One-Atom Synthone Provides C4

The insertion of C4 between the ends of a five-atom intermediate is an unusual route to a pyrimidine. However, such a process has been used in the

conversion of *N*-(cyanoacetyl)urea (**168**) by the *N*-(α-methoxyethylidene)-*N*,*N*-dimethylammonium salt (**169**) into *N*-(2-cyano-3-dimethylaminocrotonoyl)-urea (**170**) with subsequent ring closure in aqueous alkali to give 4-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**171**) (92%);[2867] appropriate variations gave such analogs as ethyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidine-carboxylate (**172**) (45%),[2867] 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydro-5-pyrimid-inecarbonitrile (**173**) (32%),[2867] and 1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**174**) (27% overall yield).[794]



168 **169** **170** **171**



172 **173** **174**

2.2.1.4. Where the One-Atom Synthone Provides C5

Completion of a pyrimidine ring by insertion of C5 does not appear to be represented at present in the literature.

2.2.2. By Using a Two- and a Four-Atom Synthone

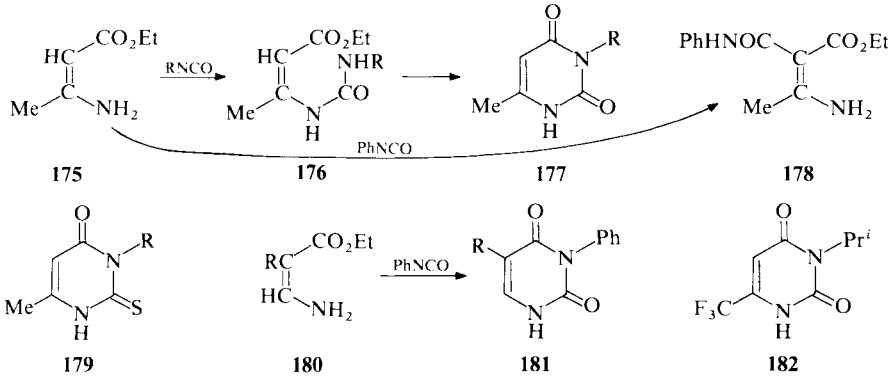
This subcategory of syntheses is further divided according to the ring atoms provided by the two-atom synthone.

2.2.2.1. Where the Two-Atom Synthone Provides N1 + C2

Most of the four-atom partners used in these procedures are β-amino esters, β-amino nitriles, β-amino amides, or similar entities, all of which are usually unsaturated: this synthesis is conveniently divided further according to the type of two-atom synthone used with such intermediates.

Using isocyanates or isothiocyanates. Ethyl 3-aminocrotonate (**175**) with methyl isocyanate gave ethyl 3-(*N'*-methylureido)crotonate (**176**, R = Me),

which cyclized easily to 3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**177**, R = Me).[3700] Phenyl isocyanate reacted similarly to give 6-methyl-3-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**177**, R = Ph), accompanied in this case by a separable by-product, ethyl 3-amino-2-(*N*-phenylcarbamoyl)crotonate (**178**), formed by attack of the isocyanate on C2 of the intermediate (**175**).[3700] The same substrate (**175**) with methyl isothiocyanate gave 3,6-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**179**, R = Me) in poor yield with the by-product, 3-amino-2-[*N*-methyl(thiocarbamoyl)]crotonate;[2841] likewise, phenyl isothiocyanate gave 6-methyl-3-phenyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**179**, R = Ph) (poor yield) and 3-amino-2-[*N*-phenyl(thiocarbamoyl)]crotonate.[3150,3700,4387] The scope of the synthesis, including the use of saturated four-atom intermediates to give (initially) dihydropyrimidines, is indicated further in the following examples.



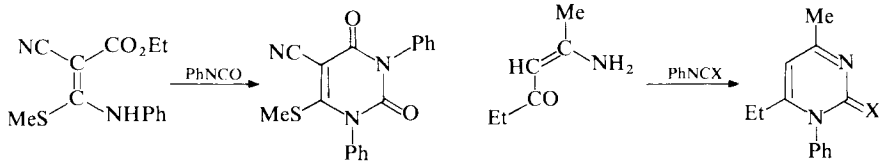
Ethyl 3-aminocrotonate (**175**) with cyclohexyl isocyanate gave, after alkaline cyclization, 3-cyclohexyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (40%).[3425]

Diethyl α-aminomethylenemalonate (**180**, R = CO_2Et) or ethyl 2-acetyl-3-aminoacrylate (**180**, R = Ac) with phenyl isocyanate gave 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (**181**, R = CO_2H) (~25%) or 5-acetyl-3-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**181**, R = Ac) (> 50%).[817]

Ethyl 3-amino-4,4,4-trifluorocrotonate with isopropyl isocyanate gave 3-isopropyl-6-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione (**182**) (> 70%).[4389, cf. 4390]

Ethyl 3-anilino-2-cyano-3-(methylthio)acrylate (**183**) with phenyl isocyanate in toluene containing triethylamine gave 4-methylthio-2,6-dioxo-1,3-diphenyl-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**184**) (80%).[3749]

Ethyl 3,3-diaminoacrylate with methyl isocyanate or methyl isothiocyanate in acetonitrile gave (after cyclization in hot alcohol) 6-amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (66%) or 6-amino-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (19%), respectively.[532]

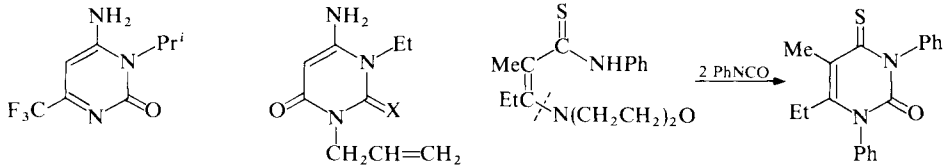


183 184 185 186

5-Aminohex-4-en-3-one (**185**) with phenyl isocyanate or phenyl isothiocyanate in dimethylformamide containing sodium hydride gave 4-ethyl-6-methyl-1-phenyl-2(1*H*)-pyrimidinone (**186**, X = O) (20%) or the corresponding thione (**186**, X = S) (58%), respectively.[82]

3-Amino-4,4,4-trifluorocrotononitrile with isopropyl isocyanate gave 4-amino-3-isopropyl-6-trifluoromethyl-2-(3*H*)-pyrimidinone (**187**) (14%).[4389]

N-Allyl-2-cyanoacetamide with ethyl isocyanate or isothiocyanate in boiling toluene gave *N*-allyl-*N*-cyanoacetyl-*N'*-ethylurea (or the corresponding thiourea), which then underwent cyclization in alkali to afford 3-allyl-6-amino-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione (**188**, X = O) (51%)[1062] or 3-allyl-6-amino-1-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**188**, X = S),[856] respectively.



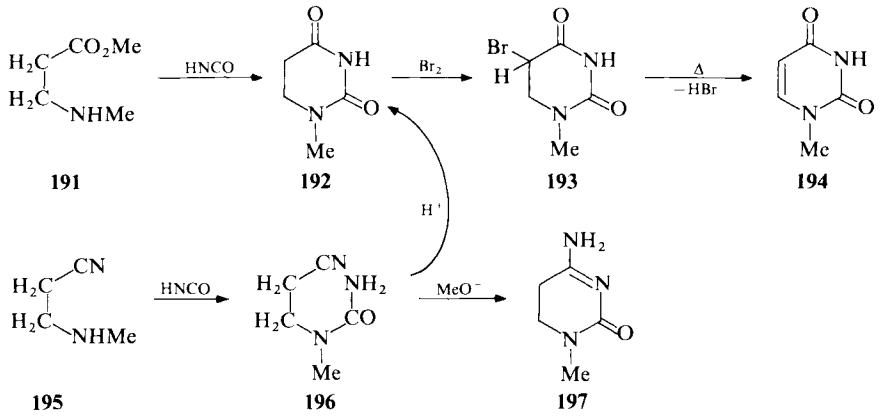
187 188 189 190

2-Methyl-3-morpholinopent-2-enethioanilide (**189**) reacted with phenyl isocyanate (2 mol): one removed morpholine as the corresponding urea; the other completed the ring to give 4-ethyl-5-methyl-1,3-diphenyl-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone (**190**) (80%).[4393]

β,*β*-Diacetyl-*α*-methylthiovinylamine with phenyl isocyanate in toluene gave 5-acetyl-4-methyl-6-methylthio-3-phenyl-2(3*H*)-pyrimidinone (80%).[6192]

Methyl 3-methylaminopropionate (**191**) with hot aqueous cyanic acid gave 1-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**192**) (~35%),[1432] which easily underwent bromination to its 5-bromo derivative (**193**) and then thermal dehydrobromination to 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**194**).[1432,3454]

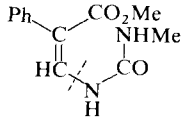
3-Methylaminopropionitrile (**195**) with cyanic acid gave the intermediate (**196**) and thence 4-amino-1-methyl-5,6-dihydro-2(1*H*)-pyrimidinone (**197**) (84%) in methanolic sodium methoxide,[3405,4391] or 1-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**192**) (55%) in acid.[3454] Homologs were made similarly.[1006,3454,4394]



2-Methyl-3-(naphthalen-1′-ylamino)propionic acid with potassium thiocyanate in acid gave 5-methyl-1-naphthalen-1′-yl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (63%).[3759]

Also other such examples.[82,529,532,912,1006,1893,2774,3405,3749,3819,4388,4389]

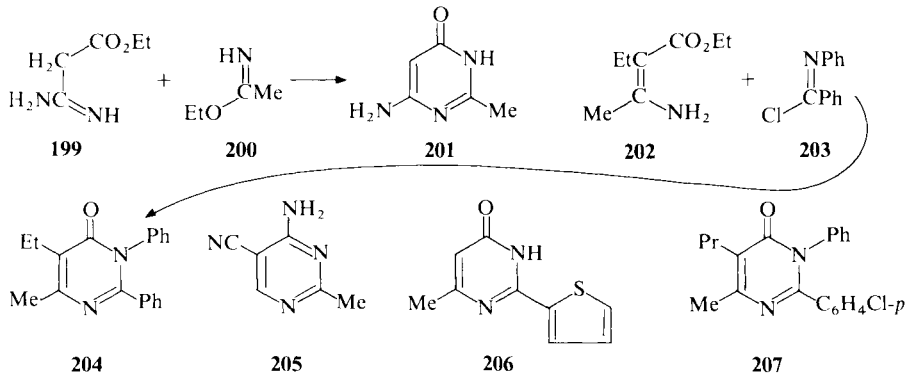
Methyl 2-formyl-2-phenylacetate reacted with *N*-methylurea in toluene to give methyl 3-*N*′-methylureido-2-phenylacrylate (**198**), which underwent thermal cyclization to 3-methyl-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (82%).[4395] Although the intermediate (**198**) was similar in type to those of the isocyanate syntheses just described, the manner of its formation requires such an overall process to be classified as a two-stage Principal Synthesis from a β-aldehydo ester and a urea (Section 3.4.3).



198

Using carboximidic esters or carboximidoyl chlorides. This type of synthesis can give quite good yields. For example, ethyl 2-amidinoacetate (**199**) with ethyl acetimidate (**200**) in methanol at 20° gave 6-amino-2-methyl-4(3*H*)-pyrimidinone (**201**) (86%),[650] while ethyl 3-amino-2-ethylcrotonate (**202**) with *N*-phenylbenzimidoyl chloride (**203**) in boiling chloroform gave 5-ethyl-6-methyl-2,3-diphenyl-4(3*H*)-pyrimidinone (**204**) (79% yield when a 2-fold excess of the amino ester was used to mop up the hydrogen chloride formed).[4397] The scope of such reactions is further illustrated in the following examples.

α-Aminomethylenemalononitrile with ethyl acetimidate gave 4-amino-2-methyl-5-pyrimidinecarbonitrile (**205**).[2971,4398]



3-Aminomethylene-2,4-pentanedione with ethyl benzimidate gave 5-acetyl-4-methyl-2-phenylpyrimidine.[2971,4398]

3-Amino-2-(ethoxymethyl)acrylonitrile (prepared in situ) with methyl acetimidate gave 5-ethoxymethyl-2-methyl-4-pyrimidinamine.[2919]

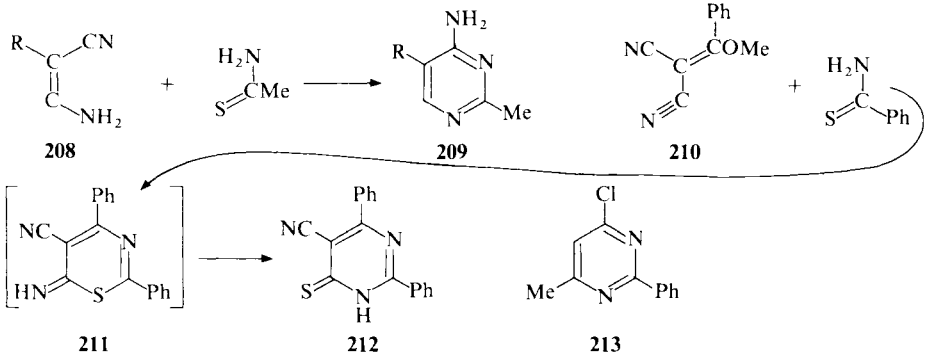
Ethyl 3-aminocrotonate with ethyl benzimidate gave 6-methyl-2-phenyl-4(3*H*)-pyrimidinone (48%).[2373]

Ethyl 3-aminocrotonate with ethyl 2-thiophenecarboximidate gave 6-methyl-2-thien-2′-yl-4(3*H*)-pyrimidinone (**206**) (44%).[2373]

Methyl 3-amino-2-propylcrotonate with *p*-chloro-*N*-phenylbenzimidoyl chloride without solvent at 155° gave 2-*p*-chlorophenyl-6-methyl-3-phenyl-5-propyl-4(3*H*)-pyrimidinone (**207**) (21%).[4397]

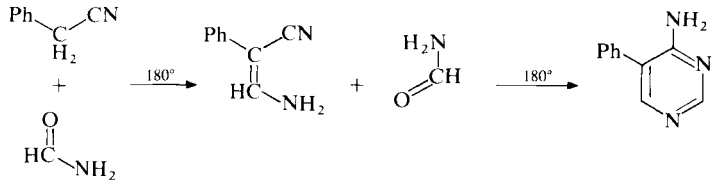
Also other close analogs.[2373,2919,2971,4397–4400]

Using thioamides. Analogous to the reactions in the last subsection are those of α-aminomethylenemalononitrile (**208**, R = CN) or ethyl 3-amino-2-cyanoacrylate (**208**, R = CO_2Et) with thiobenzamide to afford 4-amino-2-methyl-5-pyrimidinecarbonitrile (**209**, R = CN) or ethyl 4-amino-2-methyl-5-pyrimidinecarboxylate (**209**, R = CO_2Et).[856,1117,4401] Different types



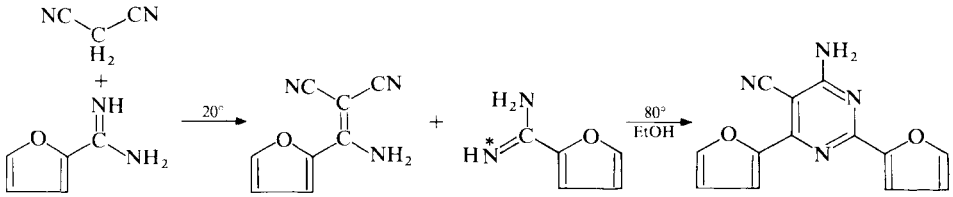
of condensation are represented by the reaction of α-(α-methoxybenzylidene)malononitrile (**210**) with thiobenzamide in propanolic sodium propoxide to give 2,4-diphenyl-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile (**212**) (70%), probably via the 1,3-thiazine (**211**);[48] also by the mechanistically obscure reaction of 3-aminocrotononitrile with *N*,*N*-dimethylbenzamide in phosphoryl chloride to give an intermediate nitrile that, on successive treatment with sodium hydrogen sulfide and iodine in benzene, gave 4-chloro-6-methyl-2-phenylpyrimidine (**213**) (27%).[4402]

Using amides or amidines. The reactions between compounds containing an activated methylene group and two molecules of formamide, formamidine, and similar are covered in Section 2.3.1. However, such reactions often proceed through an isolable intermediate, the cyclization of which by the second molecule of amide belongs logically to the present subsection. For example, when 2-phenylacetonitrile and formamide were heated under ammonia at 180° for 7 h with continuous removal of volatiles, there remained 5-phenyl-4-pyrimidinamine (**215**) (54%) and some 3-amino-2-phenylacrylonitrile (**214**): the latter (which could be made more easily from 2-formyl-2-phenylacetonitrile with ammonia) gave the pyrimidine (**215**) (52%) on similar treatment for only 1 h.[4403] These data suggested that the amino nitrile (**214**) was indeed the intermediate in the original synthesis.



214 **215**

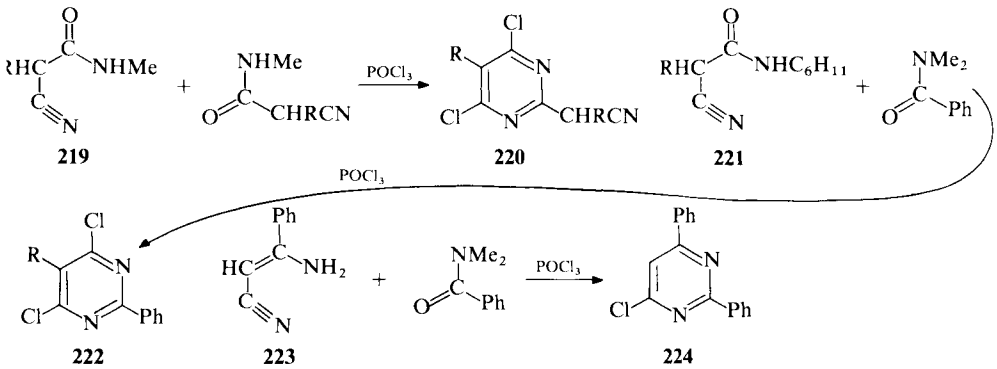
Likewise, malononitrile with 2-furancarboxamidine at room temperature gave α-[amino(furan-2′-yl)methylene]malononitrile (**216**) (30%), which reacted with a second molecule of 2-furancarboxamidine (**217**) in hot ethanol to give 4-amino-2,6-difuran-2′-yl-5-pyrimidinecarbonitrile (**218**).[1117] Since the corresponding carboximidic ester could replace the amidine successfully in such procedures, it seems highly likely that the second stage of the foregoing synthesis proceeded with the elimination of N* (as ammonia) from the new molecule of



216 **217** **218**

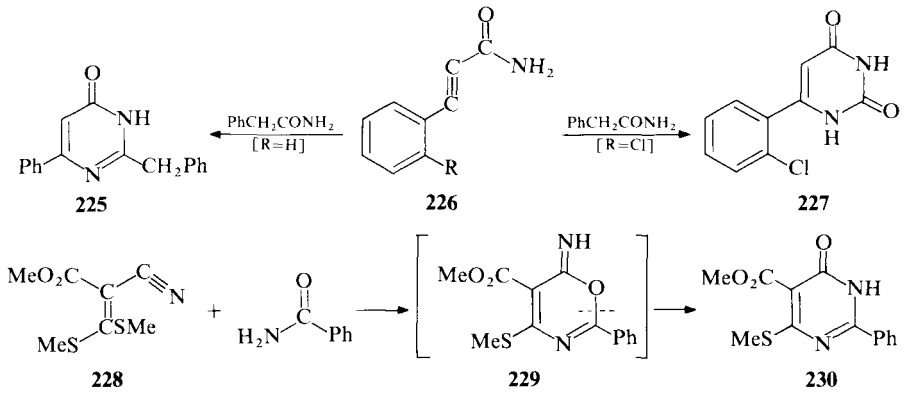
furancarboxamidine (**217**) rather than from the NH_2 of the intermediate (**216**):[1117] thus the second stage was not a Principal Synthesis because the amidine component did not supply both ring-nitrogen atoms of the resulting pyrimidine (**218**).

An entirely different sequence is that now known as the *Harris–Huppatz synthesis*. When 2-cyano-*N*-methylpropionamide (**219**, R = Me) was heated in phosphoryl chloride, self-condensation occurred to give 4,6-dichloro-2-α-cyanoethyl-5-methylpyrimidine (**220**, R = Me) with loss of the *N*-methyl groups; similar treatment of 2-cyano-*N*-methylbutyramide (**219**, R = Et) or its *N*-ethyl homolog gave a single product, 4,6-dichloro-2-α-cyanopropyl-5-ethylpyrimidine (**220**, R = Et).[2469] Two different amide molecules have also been used: 2-cyano-*N*-cyclohexylvaleramide (**221**, R = Pr) or 2-cyano-*N*-cyclohexyl-2-phenylacetamide (**221**, R = Ph) with *N*,*N*-dimethylbenzamide in phosphoryl chloride gave 4,6-dichloro-2-phenyl-5-propylpyrimidine (**222**, R = Pr) (60%)[2490] or 4,6-dichloro-2,5-diphenylpyrimidine (**222**, R = Ph) (80%),[4127] respectively. Several analogous examples have been reported,[2490,4127] and the procedure has been extended by condensation of 3-aminocinnamonitrile (**223**) with *N*,*N*-dimethylbenzamide under similar conditions to afford 4-chloro-2,6-diphenylpyrimidine (**224**) (85%).[4127]

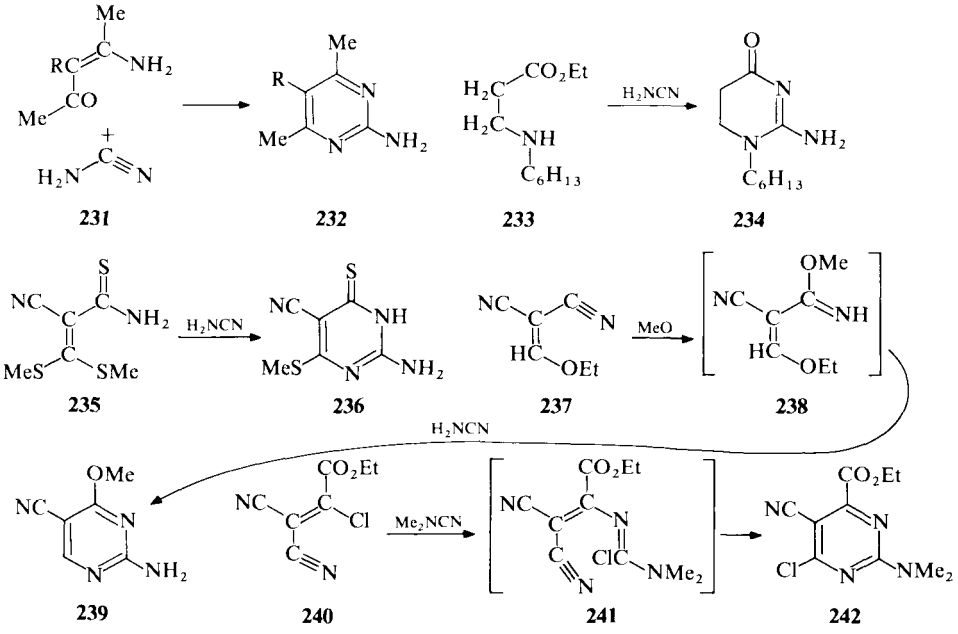


219 **220** **221** **222** **223** **224**

Other types of this synthesis are illustrated by the condensation of 3-phenylpropiolamide (**226**, R = H) with 2-phenylacetamide in benzene containing sodium to give 2-benzyl-6-phenyl-4(3*H*)-pyrimidinone (**225**) as the major product;[255] of 3-*o*-chlorophenylpropiolamide (**226**, R = Cl) with the same reagent under similar conditions to give, in contrast, 6-*o*-chlorophenyl-2,4(1*H*,3*H*)-pyrimidinedione (**227**) (~50%) (see the original paper for a possible mechanistic explanation);[255] of methyl 2-cyano-3,3-bis(methylthio)acrylate (**228**) with benzamide (in benzene–*N*,*N*-dimethylacetamide containing sodium hydride, with subsequent cyclization and rearrangement in boiling methanol) to give methyl 4-methylthio-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinecarboxylate (**230**) (68%) via the 1,3-oxazine (**229**);[3882] and of analogous intermediates with such amides.[3882]

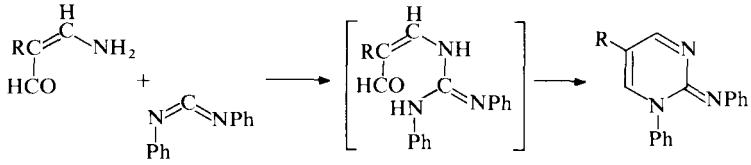


Using cyanamides. The use of cyanamide and its derivatives to complete the pyrimidine ring is illustrated by the condensation of 4-aminopent-3-en-2-one (**231**, R = H) with cyanamide in hot aqueous solution to give 4,6-dimethyl-2-pyrimidinamine (**232**, R = H) (93%);[3723] appropriate variations led to several analogs, for example, 5-benzyl-4,6-dimethyl-2-pyrimidinamine (**232**, R = CH_2Ph) (98%).[3723] Likewise, the saturated intermediate, ethyl 3-(hexylamino)propionate (**233**), with ethanolic cyanamide, gave 2-amino-1-hexyl-5,6-dihydro-4(1*H*)-pyrimidinone (**234**) (~35%).[349] Less simple examples include the condensation of 2-cyano-3,3-bis(methylthio)thioacrylamide (**235**) with cyanamide in ethanolic ethoxide to give 2-amino-4-methylthio-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile (**236**) (37%);[3752] of α-ethoxymethylene



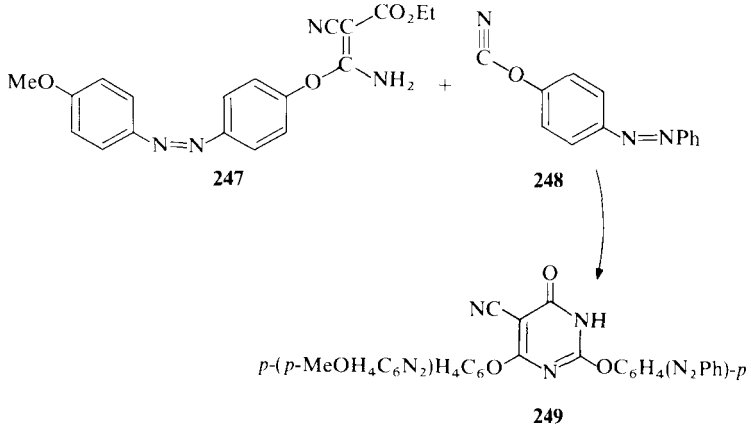
malononitrile (**237**) with cyanamide in methanolic methoxide to give 2-amino-4-methoxy-5-pyrimidinecarbonitrile (**239**) (22%), probably via the carboximidic ester (**238**);[1009] of ethyl 2-chloro-3,3-dicyanoacrylate with neat *N*,*N*-dimethylcyanamide at 90° to give ethyl 6-chloro-5-cyano-2-dimethylamino-4-pyrimidinecarboxylate (**242**) (65%), a reaction said to proceed via the unisolated intermediate (**241**);[3763] and of other such combinations.[1009,3763,4405]

Using diphenylcarbodiimide. 3-Amino-2-methylacrylaldehyde (**243**, R = Me) with neat diphenylcarbodiimide (**244**) at 120° gave 5-methyl-1-phenyl-2-phenylimino-1,2-dihydropyrimidine (**246**, R = Me) (47%) via the acyclic intermediate (**245**, R = Me);[4406] the appropriate homologous substrate (**243**, R = Et, Pr, or Pr^i) likewise gave the 5-ethyl (**246**, R = Et) (50%), 5-propyl (**246**, R = Pr) (33%), or 5-isopropyl homolog (**246**, R = Pr^i) (34%) of the original product.[4406]



243 **244** **245** **246**

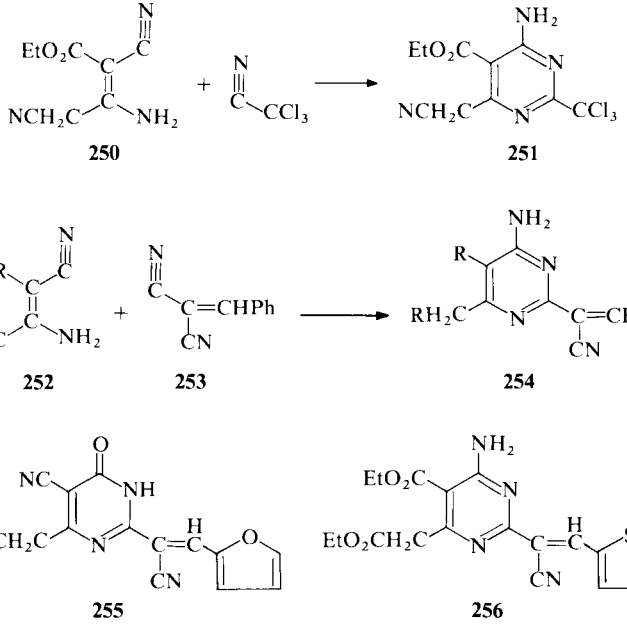
Using an aryl cyanate. This unusual synthesis is illustrated by the treatment of ethyl 2-cyanoacetate with 4-(*p*-methoxyphenyl)azophenoxy cyanate in ethereal triethylamine to give ethyl 3-amino-2-cyano-3-[*p*-(*p*′-methoxyphenylazo)phenoxy]acrylate (**247**) (80%), which was then allowed to react with *p*-phenylazophenyl cyanate (**248**) in refluxing acetonic triethylamine to afford 4-[*p*-(*p*′-methoxyphenylazo)phenoxy]-6-oxo-2-(*p*-phenylazophenoxy)-1,6-dihydro-5-pyrimidinecarbonitrile (**249**) (31%);[4407] the mechanism is unproven.



247 **248** **249**

Using a nitrile. Nitriles have been used to provide N1 + C2 in preparing pyrimidines. Thus ethyl 3-amino-2,4-dicyanocrotonate (**250**) was first treated

with sodium in toluene–ether and then with 2,2,2-trichloroacetonitrile to give ethyl 4-amino-6-cyanomethyl-2-trichloromethyl-5-pyrimidinecarboxylate (**251**) (60%);[52, cf. 541] diethyl 3-amino-2-cyanopent-2-enedioate (**252**, R = CO_2Et) with α-benzylidenemalononitrile (**253**) in refluxing ethanolic triethylamine gave ethyl 4-amino-2-(α-cyanostyryl)-6-ethoxycarbonylmethyl-5-pyrimidinecarboxylate (**254**, R = CO_2Et) (80%), confirmed in structure by nmr and ms (mass spectroscopic) data;[543] similar treatment of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**252**, R = CN) gave 4-amino-6-cyanomethyl-2-(α-cyanostyryl)-5-pyrimidinecarbonitrile (**254**, R = CN) (60%);[543] and other such reactions afforded, for example, 2-[1′-cyano-2′-(furan-2″-yl)vinyl]-4-ethoxycarbonylmethyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile (**255**) (80%) or ethyl 4-amino-2-[1-cyano-2′-(thien-2″-yl)vinyl]-6-ethoxycarbonylmethyl-5-pyrimidinecarboxylate (**256**) (78%).[3841] Although the mechanism is unclear, treatment of 3-diethylaminopropynenitrile with dry hydrogen bromide induced self-condensation and bromination to afford 4-bromo-6-diethylamino-2-(*N*,*N*-diethylcarbamoylmethyl)pyrimidine (~40%) as a major product.[4422] An unrelated self-condensation is that of 2-*p*-chlorophenyl-2-formimidoylacetonitrile to give 5-*p*-chlorophenyl-4-pyrimidinamine.[4430]

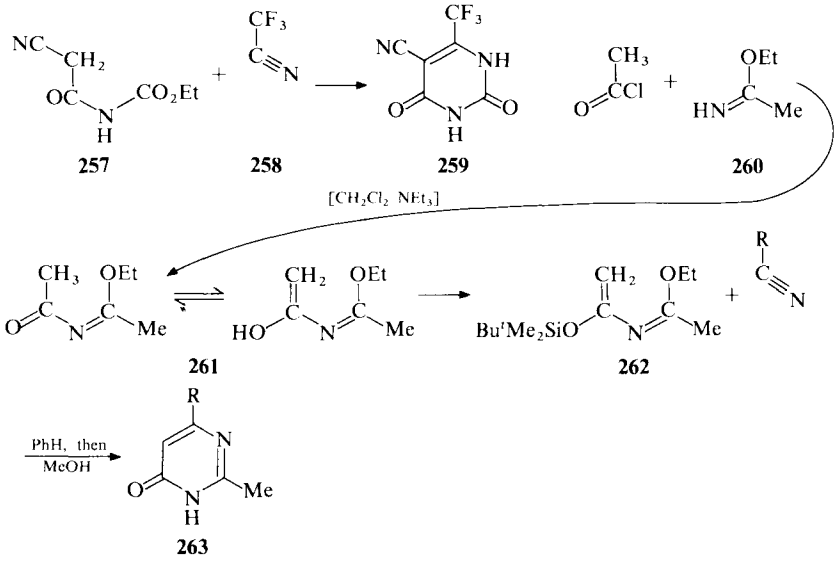


250 **251** **252** **253** **254** **255** **256**

2.2.2.2. Where the Two-Atom Synthone Provides N3 + C4

Examples in this rare category have appeared only in the last few years. Thus treatment of ethyl *N*-(2-cyanoacetyl)carbamate (**257**) in ethylene glycol

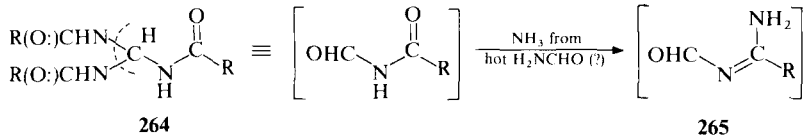
dimethyl ether, first with sodium hydride and then with trifluoroacetonitrile (**258**), gave 2,4-dioxo-6-trifluoromethyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**259**) (75%).[208] An entirely different synthesis in this category is the last stage of the following sequence. Ethyl acetimidate (**260**) was converted into its *N*-acetyl derivative (**261**), which underwent *O*-silylation by *t*-butyldimethylsilyl triflate to the intermediate (**262**): this, on treatment with tosyl cyanide or trichloroacetonitrile followed by desilylation in methanol, gave 2-methyl-6-tosyl-4(3*H*)-pyrimidinone (**263**, R = Ts) (76%) or its 6-trichloromethyl analog (**263**, R = CCl_3) (73%), respectively.[3880] Several analogs were made similarly.[3880]



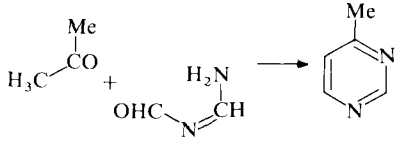
2.2.2.3. Where the Two-Atom Synthone Provides C4 + C5

This category of syntheses is subdivided according to the type of four-atom substrate used.

From N-formyl, N-cyano, or N-methylene amidines. Although *N-formylamidines* have not been used as such, trisacylaminomethanes in formamide at 150–200° have been used extensively as their equivalents: trisformamidomethane (**264**, R = H) in the presence of formamide at a high temperature (to supply ammonia?) may be regarded for practical purposes as *N*-formylformamidine (**265**, R = H), trisacetamidomethane (**264**, R = Me) as *N*-formylacetamidine (**265**, R = Me), and so on. Thus acetone (**266**), trisformamidomethane (**264**, R = H), a little *p*-toluenesulfonic acid, and formamide in a shaking autoclave at 160° [the whole process equivalent to condensation with *N*-formylformamidine



264 **265**



266 **267** **268**

(**267**)] gave 4-methylpyrimidine (**268**) (39%).[2750] The scope of such condensations (under broadly similar conditions, e.g., stirred at 170°) is indicated in a review[4410] and in the following examples.

Paraldehyde gave unsubstituted pyrimidine (8%).[2750]

Propanal gave 5-methylpyrimidine (39%).[2750]

4-Methyl-2-pentanone gave 4-isobutylpyrimidine (35%).[2750]

Acetophenone gave 4-phenylpyrimidine (72%).[2750]

2-Acetylnaphthalene gave 4-naphthalen-2′-ylpyrimidine (39%).[4408]

2-Butanone gave 4,5-dimethylpyrimidine (47%).[2750]

Propiophenone gave 5-methyl-4-phenylpyrimidine (53%).[2750]

3-Acetyl-6-methylpyridine gave 4-(6′-methylpyridin-3′-yl)pyrimidine (43%).[2750]

Dimethyl malonate gave methyl 4-oxo-3,4-dihydro-5-pyrimidinecarboxylate (48%).[1625,1969]

2-Phenylacetonitrile gave 5-phenyl-2-pyrimidinamine (61%).[4409]

2-Naphthalen-1′-ylacetonitrile gave 5-naphthalen-1′-yl-2-pyrimidinamine (28%).[3437]

2-*p*-Tolylacetonitrile gave 5-*p*-tolyl-4-pyrimidinamine (35–39%).[4411,4412]

p-Diacetylbenzene gave *p*-di(pyrimidin-4-yl)benzene (21%).[4408]

Acetophenone [using trisacetamido- (**264**, R = Me), trispropionamido- (**264**, R = Et), or trisbutyramidomethane (**264**, R = Pr)] gave 2-methyl-4-phenyl- (30%), 2-ethyl-4-phenyl- (58%), or 4-phenyl-2-propylpyrimidine (54%), respectively.[4396]

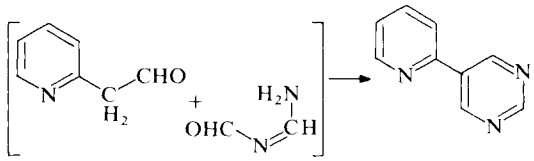
2-Cyanoacetamide gave 4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile (7%).[1625]

Malondiamide gave 4-oxo-3,4-dihydro-5-pyrimidinecarboxamide (39%).[1625]

Also other variations.[3437,4411,4412]

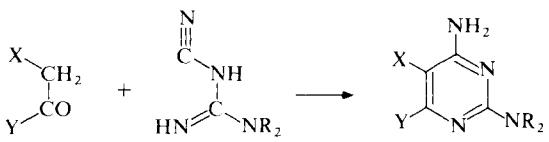
It is interesting that even heterocycles bearing only an activated methyl group will react with trisformamidomethane–formamide as if they were the

corresponding formylmethyl-heterocycles. For example, such treatment of 2-methylpyridine gave 5-pyridin-2′-ylpyrimidlne (**270**) (10%), possibly by an initial *C*-formylation to 2-formylmethylpyridine (**269**) followed by reaction of the putative formylformamidine (**267**) in the usual way; 2-methylpyrazine gave 5-pyrazin-2′-ylpyrimidine (6%); and other such reactions were reported.[4413,4414] The easily made intermediate, *N*-dimethyliminiomethyl-*N*′-*p*-tolyl-*m*-toluamidine perchlorate [$Me_2\overset{+}{N}$=CHN=C(C_6H_4Me-*m*)NHC_6H_4-*p* ClO_4^-], is clearly an *N*-formylamidine in disguise: with malononitrile in acetic acid containing triethylamine it gave 4-imino-2-*m*-tolyl-3-*p*-tolyl-3,4-dihydro-5-pyrimidinecarbonitrile (52%).[3939] Likewise, *N*-dimethylaminomethylene-*N*′-phenylbenzamidine with phenylketene gave 2,3,5-triphenyl-4(3*H*)-pyrimidinone (86%).[284,6945]



269 **270**

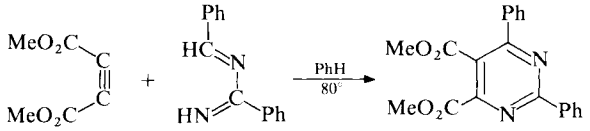
The only *N*-cyanoamidines used extensively for such syntheses have been *dicyandiamide* (*N*-cyanoguanidine) and its *N*-alkyl derivatives. The reaction was reported first in a patent,[4415] which described the use of dicyandiamide (**272**) with cyclohexanone [**271**, X + Y = $(CH_2)_4$] at 150° to give 5,6-tetramethylene-2,4-pyrimidinediamine (5,6,7,8-tetrahydro-2,4-quinazolinediamine) [**273**, R = H, X + Y = $(CH_2)_4$]. This procedure was extended initially to the use of other cyclic ketones to produce homologs such as 5,6-hexamethylene-2,4-pyrimidinediamine [**273**, R = H, X + Y = $(CH_2)_6$][4416,4417] and to the use of *N*-methyl- or *N*,*N*-dimethyldicyandiamide (**272**, R = Me) to afford products such as 2-dimethylamino-5,6-tetramethylene-2,4-pyrimidinediamine [**273**, R = Me, X + Y = $(CH_2)_4$].[4416] Only later was it applied to the formation of simple pyrimidines: phenylacetone (**271**, X = Ph, Y = Me) with dicyandiamide (**272**, R = H) at > 160° gave 6-methyl-5-phenyl-2,4-pyrimidinediamine (**273**, R = H, X = Ph, Y = Me) (27%); appropriate variations gave 6-ethyl-5-phenyl- (**273**, R = H, X = Ph, Y = Et) (20%), 5-benzyl-6-methyl- (**273**, R = H, X = CH_2Ph, Y = Me) (25%), or 6-phenyl-2,4-pyrimidinediamine (**273**, R = X = H, Y = Ph) (32%) as well as other such diamines.[3063] However, the condensation of *N*-cyanoacetamidine with neat acetylacetone containing nickel acetate at 140°



271 **272** **273**

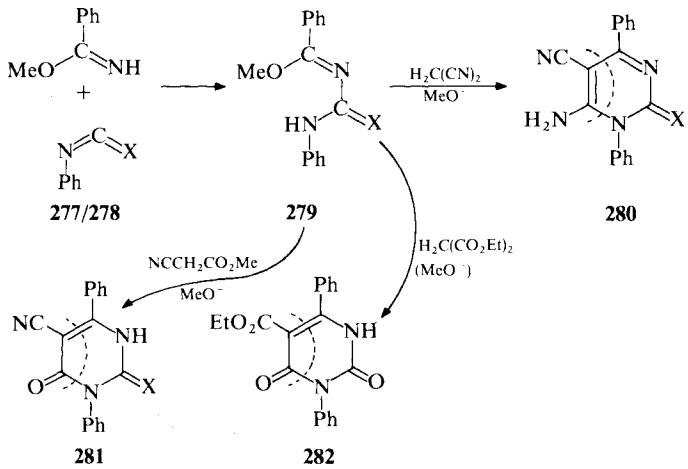
did give 5-acetyl-2,6-dimethyl-4-pyrimidinamine (60%);[6029] and a few analogs were made similarly.[6029] Broadly related condensations have been reported briefly.[6030]

The *N*-methyleneamidine, *N-benzylidenebenzamidine* (**275**), reacted with dimethyl acetylenedicarboxylate (**274**) in refluxing benzene to give dimethyl 2,6-diphenyl-4,5-pyrimidinedicarboxylate (**276**);[4418] the reaction does not appear to have been developed subsequently.



274 **275** **276**

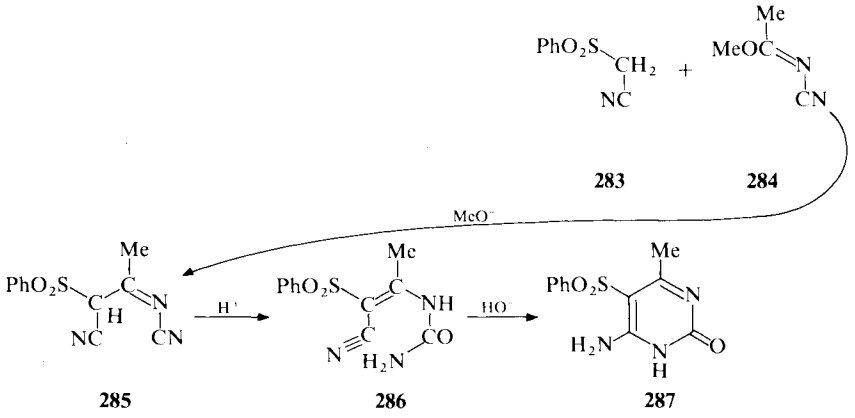
From N-carbamoyl or N-cyano carboximidates. The reaction of methyl benzimidate (**277**) with phenyl isocyanate (**278**, X = O) or phenyl isothiocyanate (**278**, X = S) gave the convenient *N-carbamoyl carboximidates*, methyl *N*-(*N*-phenylcarbamoyl)benzimidate (**279**, X = O) or methyl *N*-[*N*-phenyl(thiocarbamoyl)]benzimidate (**279**, X = S).[3873,4419] Each intermediate was treated with malononitrile or ethyl 2-cyanoacetate in methanolic methoxide to give appropriately 4-amino-2-oxo-3,6-diphenyl-2,3-dihydro- (**280**, X = O) (79%), 4-amino-3,6-diphenyl-2-thioxo-2,3-dihydro- (**280**, X = S) (71%), 2,4-dioxo-3,6-diphenyl-1,2,3,4-tetrahydro- (**281**, X = O) (56%), and 4-oxo-3,6-diphenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**281**, X = S) (40%);[3873] likewise, the intermediate (**279**, X = O) with diethyl malonate gave ethyl 2,4-dioxo-3,6-diphenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**282**) (60%);[3873] and suitable variations furnished analogs, such as 4-amino-3-ethyl-2-oxo-6-phenyl-2,3-dihydro-5-pyrimidine carbonitrile (60%).[3873] Related condensations have been reported briefly.[3997]



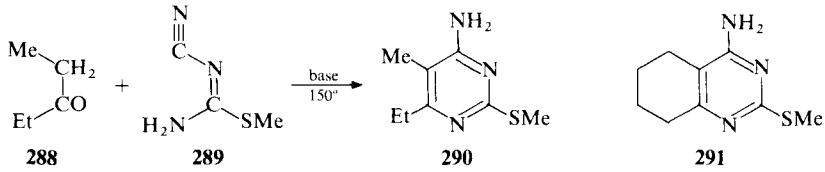
277/278 **279** **280**

281 **282**

The (indirect) use of an *N-cyano carboximidate* is exemplified in the reaction of 2-(phenylsulfonyl)acetonitrile (**283**) with methyl *N*-cyanoacetimidate (**284**) to give 3-cyanoimino-2-(phenylsulfonyl)butyrononitrile (**285**) (53%), which on gentle acidic hydrolysis gave 2-phenylsulfonyl-3-ureidocrotononitrile (**286**) and thence in alkali, 4-amino-6-methyl-5-phenylsulfonyl-2(1*H*)-pyrimidinone (**287**) (50%);[41] three analogs were made similarly.[41]

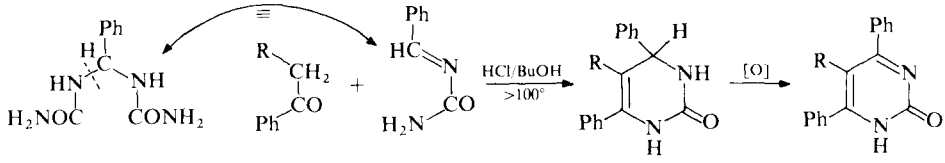


From N-cyano or N-methylene ureas or thioureas. The first of these four-atom substrates is represented by *N*-cyano-*S*-methylisothiourea (**289**), which condensed with diethyl ketone (**288**) in excess and in the presence of pyrrolidine (or unidentified "DBU") at ~150° to give 6-ethyl-5-methyl-2-methylthio-4-pyrimidinamine (**290**) (21%);[2693] several analogs were made similarly in even poorer yield, but cyclic ketones proved exceptional: for example, cyclohexanone gave 2-methylthio-5,6-tetramethylene-4-pyrimidinamine (2-methylthio-5,6,7,8-tetrahydro-4-quinazolinamine) (**291**) in 67% yield.[2693]



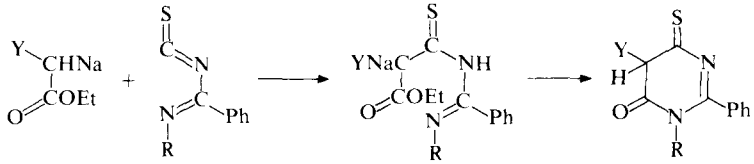
Benzylidenebisurea (α,α-diureidotoluene) (**292**) behaved as if it were *N*-benzylideneurea (**294**) when allowed to react with α-substituted acetophenones (**293**). Thus, with α-chloroacetophenone (**293**, R = Cl) in butanolic hydrogen chloride at >100°, it gave 5-chloro-4,6-diphenyl-3,4-dihydro-2(1*H*)-pyrimidinone (**295**, R = Cl) (34%), which underwent a facile dehydrogenation by tetrachlorobenzoquinone (chloranil) to afford 5-chloro-4,6-diphenyl-2(1*H*)-pyrimidinone (**296**, R = Cl) (90%);[4420] the 5-methoxy (42%), 5-phenoxy (80%), 5-acetamido (50%), and other such dihydro products (**295**) were made similarly

and then dehydrogenated in good yield to the corresponding aromatic pyrimidines (**296**).[4420] 4-Amino-2-oxo-1,2-dihydro-5-pyrimidinecarboxamide was made by a simple variation.[6035] Rather similarly, *N*-dimethylaminomethylene-*N'*-methoxycarbonyl-*S*-methylisothiourea reacted with phenylketene in benzene at 0° to give 2-methylthio-5-phenyl-4(3*H*)-pyrimidinone (96%) or with dimethyl acetylenedicarboxylate under reflux for 24 h to give dimethyl 2-methylthio-4,5-pyrimidinedicarboxylate (72%).[6072]



292 **293** **294** **295** **296**

From an iminomethyl isothiocyanate. This type of synthesis is exemplified in the condensation of α-(ethylimino)benzyl isothiocyanate (**298**, R = Et) with diethyl sodiomalonate (**297**, Y = CO_2Et) in anhydrous benzene to give diethyl sodio-α-[*N*-α-ethyliminobenzyl)(thiocarbamoyl)]malonate (**299**, R = Et, Y = CO_2Et), which underwent cyclization on acidification to afford ethyl 1-ethyl-6-oxo-2-phenyl-4-thioxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxylate (**300**, R = Et, Y = CO_2Et) (39%);[4421] analogs, such as 4-oxo-2,3-diphenyl-6-thioxo-3,4,5,6-tetrahydro-5-pyrimidinecarbonitrile (**300**, R = Ph, Y = CN) (64%) or ethyl 4-methyl-2,3-diphenyl-6-thioxo-3,6-dihydro-5-pyrimidinecarboxylate (65%), were made by appropriate variations of the synthones.[4421]



297 **298** **299** **300**

2.2.3. By Using Two Three-Atom Synthones

Because of the symmetry inherent in the pyrimidine ring, there are only two possible combinations of three-atom fragments.

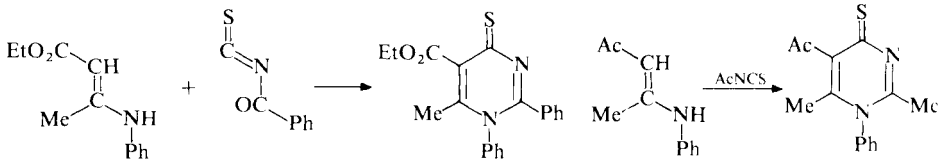
2.2.3.1. Where the Synthones Provide N1 + C2 + N3 and C4 + C5 + C6

On account of the great number and variety of pyrimidines provided by this category of primary synthesis, it has become known as the "Principal Synthesis," and Chapter 3 is devoted entirely to its discussion.

2.2.3.2. Where the Synthones Provide C2 + N3 + C4 and C5 + C6 + N1

This category of synthesis is quite small, although it contains a considerable variety of processes. Subclassification follows quite pragmatic lines.

From eneamines with C + N + C fragments. Condensations of eneamines with *acyl isothiocyanates* are quite well represented. Thus ethyl 3-anilinocrotonate (**301**) with benzoyl isothiocyanate (**302**) in ether gave ethyl 4-methyl-2,3-diphenyl-6-thioxo-3,6-dihydro-5-pyrimidinecarboxylate (**303**) (60–72%).[821,3150] The scope of the reaction, which apparently fails with acyl isocyanates, is illustrated in the following examples.



301 **302** **303** **304** **305**

Ethyl 3-methylaminocrotonate with acetyl isothiocyanate gave ethyl 1,2,6-trimethyl-4-thioxo-1,4-dihydro-5-pyrimidinecarboxylate (65–75%).[821,3150]

4-Anilinopent-3-en-2-one (**304**) with acetyl isothiocyanate gave 5-acetyl-2,6-dimethyl-1-phenyl-4(1*H*)-pyrimidinethione (**305**) (91%).[821]

3-Aminocrotononitrile with acetyl isothiocyanate gave 2,4-dimethyl-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile (28%).[4423]

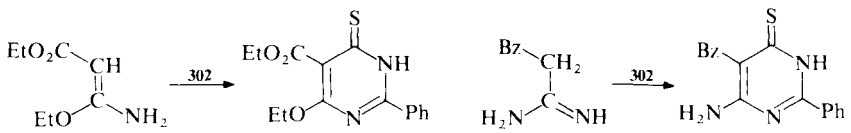
Ethyl 3-amino-3-ethoxyacrylate (**306**) with benzoyl isothiocyanate (**302**) gave (after a final cyclization in aqueous ammonia) ethyl 4-ethoxy-2-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylate (**307**) (>90%).[2953]

2-Benzoylacetamidine (**308**) with benzoyl isothiocyanate (**302**) likewise gave 6-amino-5-benzoyl-2-phenyl-4(3*H*)-pyrimidinethione (**309**) (>90%).[2953]

4-Aminopent-3-en-2-one with propionyl isothiocyanate gave 5-acetyl-2-ethyl-6-methyl-4(3*H*)-pyrimidinethione (62%).[797]

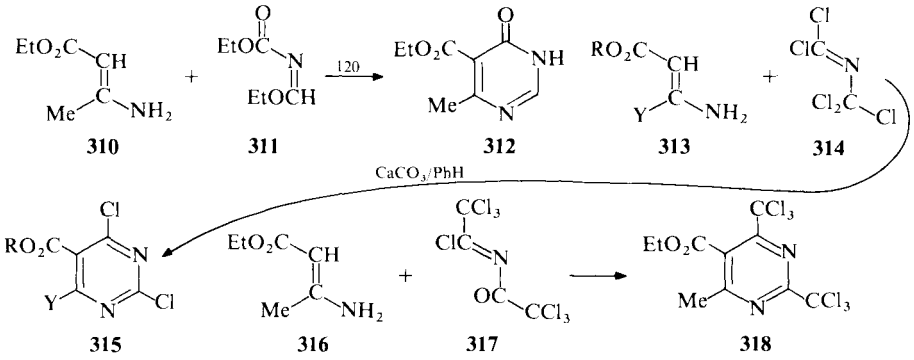
4-Methylaminobut-3-en-2-one with phenoxycarbonyl isothiocyanate gave (after cyclization) 5-acetyl-1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (72%).[821]

Also other such reactions.[797,821,822,3150,3960,3990,4424,6022]



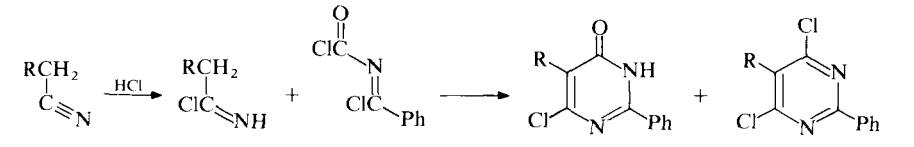
306 **307** **308** **309**

The condensation of eneamines with *N-acylcarbamic acid derivatives* is sparsely represented but should be capable of considerable development. Ethyl 3-aminocrotonate (**310**) with ethyl ethoxymethylene carbamate (**311**) at 120° gave ethyl 4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylate (**312**) (40%).[3057] In a rather similar way, ethyl 3-aminocrotonate (**313**, R = Et, Y = Me) with dichloromethylene(trichloromethyl)amine (**314**) in benzene containing calcium carbonate gave ethyl 2,4-dichloro-6-methyl-5-pyrimidinecarboxylate (**315**, R = Et, Y = Me) (71%);[2958] appropriate variations in groups R and Y of the substrate (**313**) afforded products such as cyclohexyl 2,4-dichloro-6-methyl-5-pyrimidinecarboxylate (**315**, R = C_6H_{11}, Y = Me) (80%) and ethyl 2,4-dichloro-6-phenyl-5-pyrimidinecarboxylate (**315**, R = Et, Y = Ph) (65%).[2958] In addition, ethyl 3-aminocrotonate (**316**) reacted with 2,2,2-trichloro-*N*-(tetrachloroethylidene)acetamide (**317**) in ether containing pyridine and anhydrous sodium sulfate to give ethyl 4-methyl-2,6-bistrichloromethyl-5-pyrimidinecarboxylate (**318**) (35%).[2958]



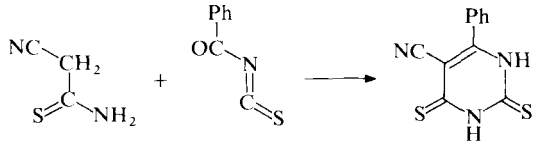
310 **311** **312** **313** **314** **315** **316** **317** **318**

From alkanimidoyl chlorides with N-(α-chlorobenzylidene)carbamoyl chloride. When a mixture of acetonitrile (**319**, R = H) and *N*-(α-chlorobenzylidene)carbamoyl chloride (**321**) in chlorobenzene was treated with dry hydrogen chloride, condensation occurred between the initially formed acetimidoyl chloride (**320**, R = H) and the fragment (**321**) to afford a separable mixture of 6-chloro-2-phenyl-4(3*H*)-pyrimidinone (**322**, R = H) and 4,6-dichloro-2-phenylpyrimidine (**323**, R = H), both in low yield;[4425] replacement of acetonitrile by its higher homologs (**319**, R = Me, Et, Pr, or Bu) gave the homologous products (**322** + **323**: R = Me, Et, Pr, or Bu).[4425]



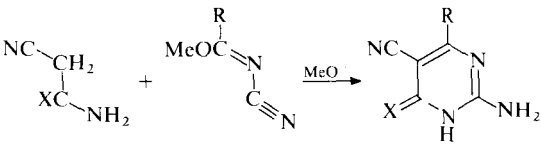
319 **320** **321** **322** **323**

From acetamides or thioacetamides with C + N + C fragments. One example of the condensation between a thioacetamide and an *aroyl isothiocyanate* has been reported briefly: 2-cyano(thioacetamide) (**324**) with benzoyl isothiocyanate (**325**) in boiling dioxane gave 4-phenyl-2,6-dithioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**326**) (85%).[3848]



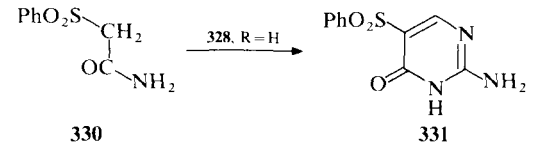
324 **325** **326**

In contrast, condensations of acetamides or thioacetamides with *N-cyano- or N-acylcarboximidates* have been better developed. Thus 2-cyanoacetamide (**327**, X = O) or 2-cyano(thioacetamide) (**327**; X = S) with methyl *N*-cyanoacetimidate (**328**, R = Me) in methanolic sodium methoxide gave 2-amino-4-methyl-6-oxo- (**329**, R = Me, X = O) (66%) or 2-amino-4-methyl-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile (**329**, R = Me, X = S) (44%), respectively;[1223] likewise, the amides (**327**, X = O or S) with methyl *N*-cyanobenzimidate (**328**, R = Ph) gave 2-amino-4-oxo-6-phenyl-3,4-dihydro- (**329** R = Ph, X = O) (77%) or 2-amino-4-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile (**329**, R = Ph, X = S) (41%) respectively.[1223] The scope of this synthesis is illustrated further in the following examples.



327 **328** **329**

2-(Phenylsulfonyl)acetamide (**330**) with methyl *N*-cyanoformimidate (**328**, R = H) gave 2-amino-5-phenylsulfonyl-4(3*H*)-pyrimidinone (**331**) (78%).[41]



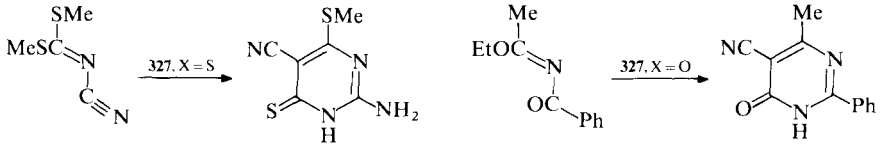
330 **331**

2-Cyano(thioacetamide) (**327**, X = S) with methyl *N*-cyano-*C*-methylthio-(thioformimidate) (**332**) gave 2-amino-4-methylthio-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile (**333**) (68–86% yield).[3747,3752,3879]

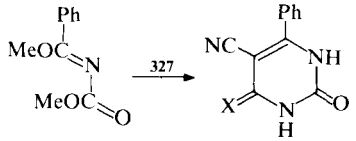
2-Cyanoacetamide (**327**, X = O) with ethyl *N*-benzoylacetimidate (**334**) gave 4-methyl-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinecarbonitrile (**335**) (52%).[31]

2-Cyanoacetamide (**327**, X = O) or 2-cyano(thioacetamide) (**327**, X = S) with methyl *N*-(methoxycarbonyl)benzimidate (**336**) gave 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydro- (**337**, X = O) (98%) or 2-oxo-4-phenyl-6-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**337**, X = S) (35%), respectively.[31]

Also other such reactions.[31,41,1223]

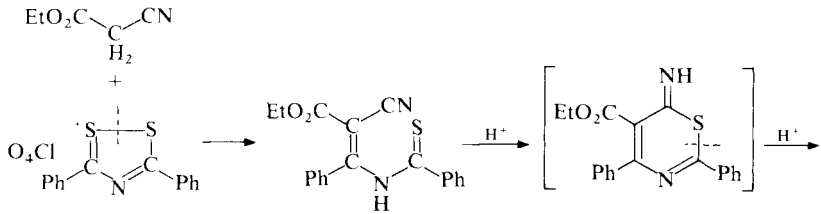


332 **333** **334** **335**

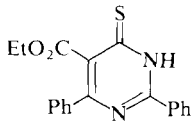


336 **337**

Routes via unisolated 1,3-thiazines or oxazines. When ethyl 2-cyanoacetate (**338**) was allowed to react with 3,5-diphenyl-1,2,4-dithiazolium perchlorate (**339**) in dimethyl sulfoxide containing anhydrous sodium acetate, ethyl 2-cyano-3-phenyl-3-thiobenzamidocinnamate (**340**) (64%) resulted: treatment of this intermediate in boiling acetic acid gave ethyl 2,4-diphenyl-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylate (**342**) (48%), presumably via the thiazine (**341**).[553] In a completely different way, treatment of 4-(3′,5′-dimethylbenzamido)methylpyridine *N*-oxide (**343**) and malononitrile (**344**) in boiling dimethylformamide

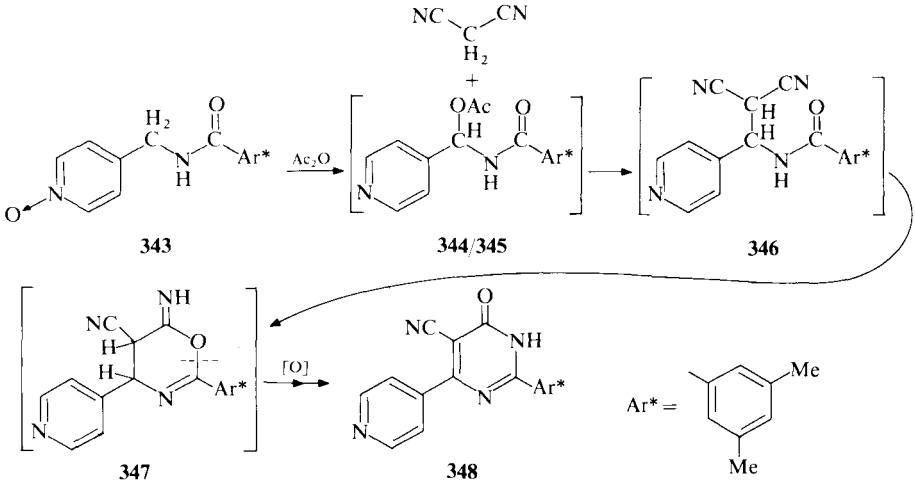


338/339 **340** **341**

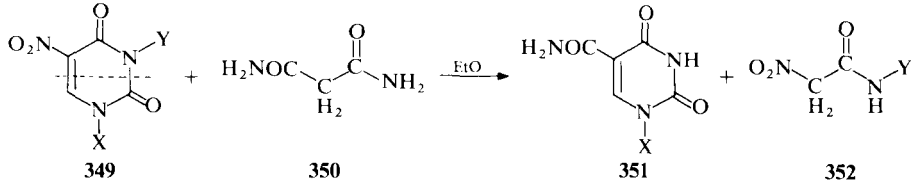


342

containing acetic anhydride gave 2-(3′,5′-dimethylphenyl)-4-oxo-6-pyridin-4′-yl-3,4-dihydro-5-pyrimidinecarbonitrile (**348**) (17%), presumably via the intermediates (**345**–**347**).[97]



From existing pyrimidines by replacement of the C5 + C6 + N1 portion. Treatment of 1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**349**, X = Y = Me) with malondiamide (**350**) in ethanolic ethoxide gave, 1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (**351**, X = Me) (84%) plus *N*-methyl-2-nitroacetamide (**352**, Y = Me).[72,3390] Similar treatment of 3-cyclohexyl-1-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**349**, X = Me, Y = C_6H_{11}) gave the same product (**351**, X = Me) (89%), but the isomeric substrate, 1-cyclohexyl-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**349**, X = C_6H_{11}, Y = Me), gave 1-cyclohexyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (**351**, X = C_6H_{11}) (86%); the reaction was also applied to two 5-nitrouridine derivatives.[72,3390]



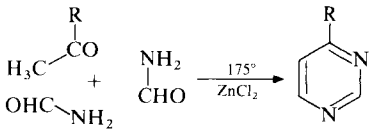
2.3. FROM THREE SYNTHONES

Of the many possible combinations within this category, only five appear to have been used to date: one type involves the condensation of three two-atom synthones, while the remaining four types involve the condensation of a one-, a two- and a three-atom synthone in each case.

2.3.1. Where the Synthones Provide C2+N3, C4+C5 and C6+N1

In all reported condensations of this type, the two C + N fragments were provided by the same type of synthone and usually by exactly the same synthone; in the Frankland–Kolbe synthesis, all three fragments were provided by the same type of synthone, specifically, an alkanenitrile. This category is subdivided according to the type of C + N synthone(s) employed.

Using formamide for both C + N fragments. The original examples of this reaction involved heating acetophenone or acetone with an excess of formamide at 170–180° in the presence of zinc chloride to afford 4-phenylpyrimidine (**353**, R = Ph) (low yield) or 4-methylpyrimidine (**353**, R = Me) (2%).[4426] More satisfactory was the reaction of 2-phenylacetonitrile with formamide at 180° under ammonia to give 5-phenyl-4-pyrimidinamine (**354**) (54%);[4403] and analogous procedures gave 5-*o*-methoxyphenyl- (7%),[4404] 5-*p*-methoxyphenyl- (23%),[4404] 5-*p*-chlorophenyl- (51%),[4404, cf. 4430] and 5-*p*-nitrophenyl-4-pyrimidinamine (~5%)[4404] as well as 5,6-trimethylene-4-pyrimidinamine (~25%),[4388] 5-(thien-2′ or 3′-yl)-4-pyrimidinamine (42% or 50%),[4427] 5-*p*-nitrophenyl-4(3*H*)-pyrimidinone (44%) (from ethyl 2-*p*-nitrophenylacetate with formamide),[4428] and 5-(pyridin-2′ or 4′-yl)pyrimidine (6% or 4%) (from 2- or 4-methylpyridine, presumably by an initial *C*-formylation followed by further reaction with two molecules of formamide).[4429]



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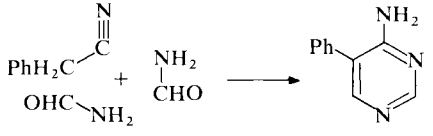
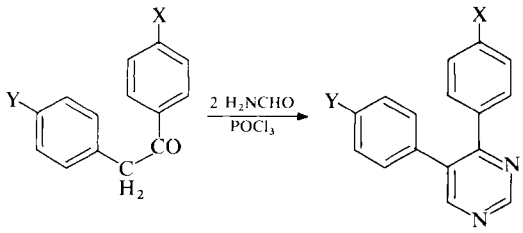
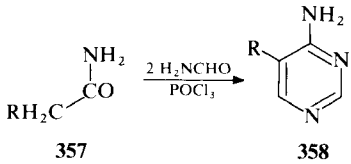


354

There are two ways to improve such reactions. The first is to use a mixture of trisformamidomethane and formamide, as discussed in Section 2.2.2.3. The second is to introduce phosphoryl chloride into the mixture. In this way, desoxybenzoin (**355**, X = Y = H) gave 4,5-diphenylpyrimidine (**356**, X = Y = H) (33%);[4431] α-(*p*-methoxybenzoyl)-*p*-nitrotoluene (**355**, X = OMe, Y = NO_2) gave 4-*p*-methoxyphenyl-5-*p*-nitrophenylpyrimidine (**356**, X = OMe, Y = NO_2) (30%);[4432] phenylacetone gave 4-methyl-5-phenylpyrimidine



355 **356**

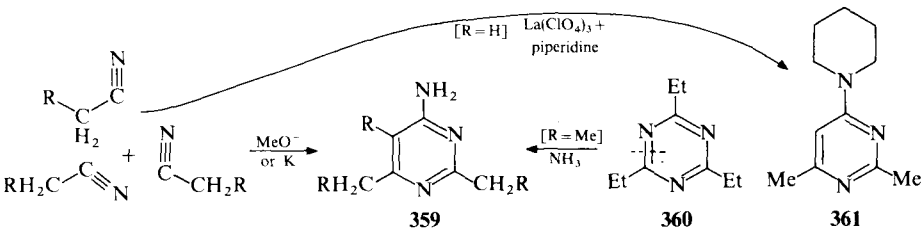


357 **358**

(13%;[4433] cf. 36%[2751] when trisformamidomethane was added also); acetamide (**357**, R = H) or butyramide (**357**, R = Pr) (with formamide and phosphoryl chloride) gave 4-pyrimidinamine (**358**, R = H) (32%) or 5-propyl-4-pyrimidinamine (**358**, R = Pr) (28%), respectively;[2652,3089] and *N,N*-dimethylacetamide gave 4-dimethylaminopyrimidine (~15%).[2652] Other examples have been reported.[6235]

Using a nitrile for both C + N fragments. The best known subcategory in this area is the *Frankland–Kolbe synthesis*, in which not only both C + N fragments but also the C + C fragment are provided by alkanenitriles. Thus alkanenitriles with a free methylene group adjacent to the cyano group undergo trimerization in the presence of an alkali metal to give 2,5,6-trialkyl-4-pyrimidinamines, the *Kyanalkine* or cyanoalkines (**359**), in which the 5-substituent has one less methylene group than have the 2- and 4-alkyl groups.

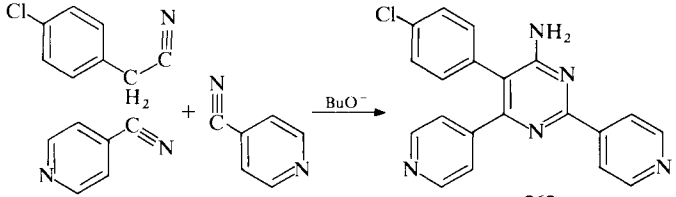
[The history of this synthesis is fascinating. In 1848, Frankland and Kolbe reported from Bunsen's laboratory in Marburg, the synthesis of *Kyanäthin* from propiononitrile with metallic potassium:[2534] this was the first primary synthesis of a pyrimidine, although its structure remained obscure for the next 40 years. The topic was kept alive by two isolated contributions from Bayer[1853,4434] on *kyanmethin* until, in 1880, a long series of papers on the reaction began to appear, mainly from von Meyer and his colleagues in Leipzig. They first improved the experimental conditions, extended the reaction to other homologs, converted them into the corresponding pyrimidinones with nitrous acid, degraded the products by bromine oxidation to give aliphatic acids, and generally explored relevant topics.[634,1718,1840,1852,1854,1902,2061,2535,2731,2814,3011, 3012,4436–4441] At last, in 1889, the structure of *Kyanäthin* was proved to be 2,4-diethyl-5-methyl-4-pyrimidinamine (**359**, R = Me) by an unambiguous synthesis of its deamination product, 2,6-diethyl-5-methyl-4(3*H*)-pyrimidinone.[2544] Soon after, von Meyer[1719] summarized the topic to that date. Only a few papers appeared subsequently,[2545,3002,4443–4446] and the work was concluded in 1905 with an excellent review[2116] that is far more interesting and detailed than the more easily available abstracts might suggest.]



Although the scope of this reaction is clearly restricted, trimerization of acetonitrile at 150° in the presence of sodium or potassium methoxide (as distinct from the originally used alkali metal) is still the preferred route to 2,6-dimethyl-4-pyrimidinamine (**359**, R = H) (54–90%);[420,648,727,2730] similar

trimerization of butryonitrile at 180° was found to be a practical route to 5-ethyl-2,6-dipropyl-4-pyrimidinamine (**359**, R = Et) (~50%).[683] Less satisfactory procedures involved trimerization of acetonitrile in ammonia under high pressure to give 2,6-dimethyl-4-pyrimidinamine (**359**, R = H) (67%);[648] trimerization of propiononitrile without a catalyst under high pressure to 2,4,6-triethyl-1,3,5-triazine (**360**) (54%) and subsequent rearrangement in methanolic ammonia to give 2,6-diethyl-5-methyl-4-pyrimidinamine (**359**, R = Me) (32%);[648] trimerization of glycolonitrile (2-hydroxyacetonitrile) at pH 8 without heating to give a product described as 4-amino-2,6-bishydroxymethyl-5-pyrimidinol (**359**, R = OH) but of puzzling instability;[609] trimerization of acetonitrile in hex-3-yne containing iron pentacarbonyl at 250° to give 2,6-dimethyl-4-pyrimidinamine (**359**, R = H) (33%);[4447] trimerization of 2-phenylacetonitrile in the presence of methyl aluminum dichloride to give, after hydrolysis, 2,6-dibenzyl-5-phenyl-4-pyrimidinamine (**359**, R = Ph) (16%);[4448] and trimerization of acetonitrile under reflux in the presence of piperidine and lanthanum perchlorate to give 2,4-dimethyl-6-piperidinopyrimidine (**361**) by a suggested mechanism not involving transamination.[4449] A product from the trimerization of malononitrile under alkaline conditions,[5969] initially thought to be 4-amino-2,6-biscyanomethyl-5-pyrimidinecarbonitrile,[945] was later shown to be an isomeric pyridine.[947]

Although the use of two different nitriles in this synthesis might be expected to lead to awkward mixtures, this is not necessarily the case as long as the nitrile providing both C + N fragments does not have a free methylene group adjacent to its cyano group. Thus the so-called *mischtrimerisierung* (mixed trimerization) of 2-*p*-chlorophenylacetonitrile (1 mol) with 4-pyridinecarbonitrile (2 mol) in butanolic sodium butoxide at 115° gave 5-*p*-chlorophenyl-2,6-dipyridin-4′-yl-4-pyrimidinamine (**362**) (97%);[4450] a variety of analogs were made similarly,[4450] while sodiophenylacetonitrile with an excess of trifluoroacetonitrile eventually gave 5-phenyl-2,6-bistrifluoromethyl-4-pyrimidinamine (46%).[273] A rather analogous result was achieved by forming the crystalline complex (**363**) from benzonitrile (2 mol) and sulfur trioxide and then allowing it to react with



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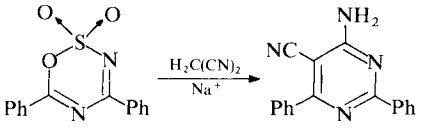
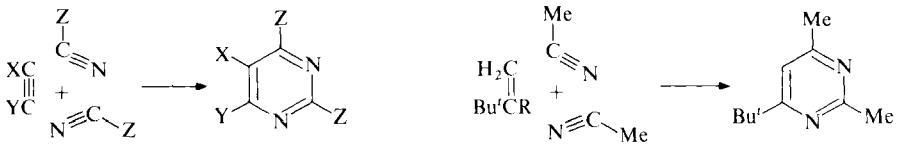


363 **364**

sodiomalononitrile in 1-methylpyrrolidin-2-one at room temperature to afford 4-amino-2,6-diphenyl-5-pyrimidinecarbonitrile (**364**) (44%)[4451] (see also Section 2.6.2).

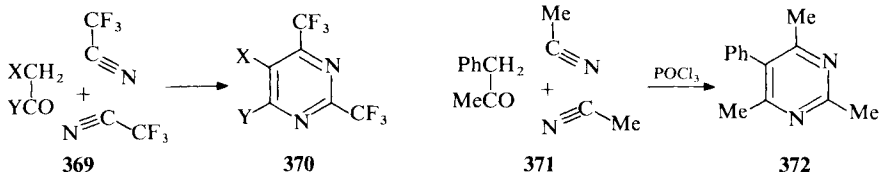
Analogous reactions, in which the C + C fragment is provided by a reagent other than a third nitrile molecule, are well represented. Thus the use of an *alkyne as the C + C fragment* is exemplified by the reaction of acetylene with acetonitrile (2 mol) at 20 atm in the presence of potassium to give 2,4-dimethylpyrimidine (**366**, X = Y = H, Z = Me) in low yield;[2574] of *N*,*N*-diethylprop-1-ynylamine (**365**, X = Me, Y = NEt_2) with 2,2,2-trifluoroacetonitrile to give 4-diethylamino-5-methyl-2,6-bistrifluoromethylpyrimidine (**366**, X = Me, Y = NEt_2, Z = CF_3) (65–75%);[19,4453] of phenylacetylene with benzonitrile in the presence of trifluoromethanesulfonic acid at 0–20° to give 2,4,6-triphenylpyrimidine (**366**, X = H, Y = Z = Ph) (98%);[6024, cf. 3938] and of cyclopropylacetylene with acetonitrile in pentane containing acetyl tetrafluoroborate to give 4-cyclopropyl-2,6-dimethylpyrimidine (**366**, X = H, Y = C_3H_5, Z = Me) (41%).[195]



365 **366** **367** **368**

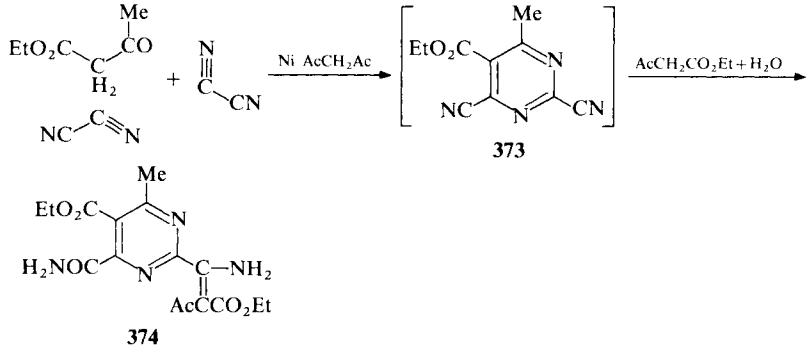
The use of a *vinyl chloride or triflate as the C + C fragment* is illustrated by the initial conversion of *t*-butyl methyl ketone by phosphorus pentachloride into 2-chloro-3,3-dimethylbut-1-ene (**367**, R = Cl) or by trifluoromethanesulfonic anhydride into 1-*t*-butylvinyl triflate [**367**, R = $O(O_2S)CF_3$]. The first of these intermediates was allowed to react with acetonitrile containing trifluoromethanesulfonic acid to give 4-*t*-butyl-2,6-dimethylpyrimidine (**368**) (58%),[3938] while the second intermediate reacted similarly with pure acetonitrile to give the same product (**368**) (68%).[518,3896] Several other such products were so made.[518,3896,3938]

The use of an *α-methylene ketone or ester as the C + C fragment* is typified by the reaction of 2-benzoylacetonitrile (**369**, X = CN, Y = Ph) (as its sodio derivative) with trifluoro- or trichloroacetonitrile to give 4-phenyl-2,6-bistrifluoromethyl-5-pyrimidinecarbonitrile (**370**, X = CN, Y = Ph) (62%)[273] or its bistrichloromethyl analog,[540,4466] respectively; of acetone (**369**, X = H, Y = Me) (disguised as its azine) with trifluoroacetonitrile to give, after 3 weeks, 4-methyl-2,6-bistrifluoromethylpyrimidine (**370**, X = H, Y = Me) (9%);[19] of diethyl malonate (**369**, X = CO_2Et, Y = OEt) as its potassio derivative with trifluoroacetonitrile in tetrahydrofuran to give ethyl 4-oxo-2,6-bistrifluoromethyl-3,4-dihydro-5-pyrimidinecarboxylate, the tautomer of **370** (X = CO_2Et, Y = OH), in 88% yield;[3921] of ethyl 2-phenylacetate with 4-pyridinecarbonitrile (in the presence of alkoxide) to give 5-phenyl-2,6-dipyridin-4′-yl-4(3*H*)-pyrimidinone (80%);[4450] and of ethyl 2-nitroacetate with the sulfur



369 370 371 372

trioxide complex (**363**) of benzonitrile to give 5-nitro-2,6-diphenyl-4(3*H*)-pyrimidinone (60%).[4451] In a different way, treatment of phenylacetone (**371**) with an excess of acetonitrile in boiling phosphoryl chloride gave a separable mixture of 2,4,6-trimethyl-5-phenylpyrimidine (**372**) (34%) and an isoquinoline (10%);[187] substituted-phenyl analogs were made similarly.[187] Likewise, ethyl methyl ketone with acetonitrile in $POCl_3$ or $(F_3CSO_2)_2O$ gave 2,4,5,6-tetramethylpyrimidine (50–70%) and the intermediates and by-products associated with such reactions have been studied.[382,6419] A virtual extension of this reaction is the facile condensation of ethyl acetoacetate with an equimolecular quantity of cyanogen in the presence of a little acetylacetone–nickel complex to give ethyl 2-(2′-acetyl-1′-amino-2′-ethoxycarbonylvinyl)-4-carbamoyl-6-methyl-5-pyrimidinecarboxylate (**374**) (41%), possibly via the intermediate pyrimidine (**373**);[4452] several analogous products were formed rather similarly.[4452,4454]



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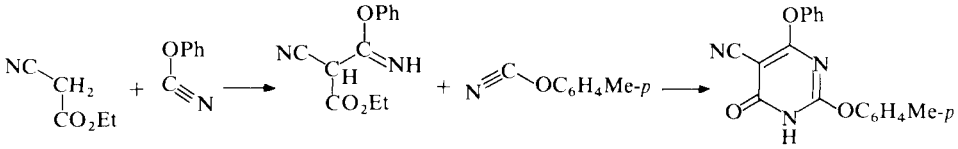
374

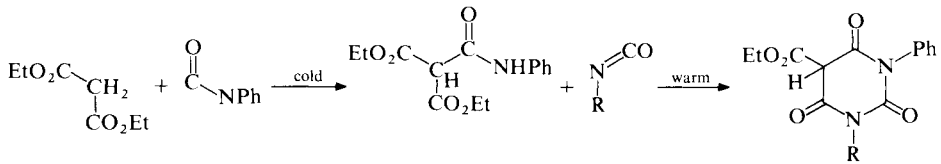
Using aryl cyanates for both C + N fragments. This category of synthesis follows quite closely the use of nitriles just described: the resulting pyrimidines will bear aryloxy rather than alkyl or aryl groups; moreover, because the intermediates are isolable easily, two different cyanates may be used to introduce variation between the 2- and the 4(6)-substituent in each product. For example, ethyl 2-cyanoacetate (**375**) reacted with phenyl cyanate (**376**) (1 mol) to give the acyclic product (**377**) which, in the presence of triethylamine, reacted with *p*-tolyl cyanate (**378**) (1 mol) to give 4-oxo-6-phenoxy-2-*p*-tolyloxy-3,4-dihydro-5-pyrimidinecarbonitrile (**379**) (68%);[4435] use of *p*-chlorophenyl cyanate (2 mol) gave 2,4-di-*p*-chlorophenoxy-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile (57%),[4435] and other variations have been reported.[4435,4442] It is naturally possible to use other C + C fragments: for



375 376 377 378 379

example, malononitrile with appropriate cyanates gave 4-amino-6-*p*-chlorophenoxy-2-phenoxy-5-pyrimidinecarbonitrile (78%),[4435] and analogous reactions have been carried out.[4435,4455]

Using isocyanates or isothiocyanates for both C + N fragments. Although there are many reported examples within this category, its full potential has not been explored. The process is best exemplified in the condensation of diethyl malonate (**380**) under reflux with phenyl isocyanate (2 mol) in the presence of triethylamine to give ethyl 2,4,6-trioxo-1,3-diphenyl-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxylate (**382**, R = Ph), initially as the triethylammonium salt (72%) from which it was easily liberated.[2909] Alternatively, diethyl malonate with phenyl isocyanate (1 mol) and triethylamine at 0° gave diethyl α-(*N*-phenylcarbamoyl)malonate (**381**), which on treatment with a different isocyanate and triethylamine under reflux gave, for example, ethyl 1-methyl-2,4,6-trioxo-3-phenyl-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxylate (**382**, R = Me) (86% on the intermediate product).[2909] The reaction is further illustrated in the following examples.



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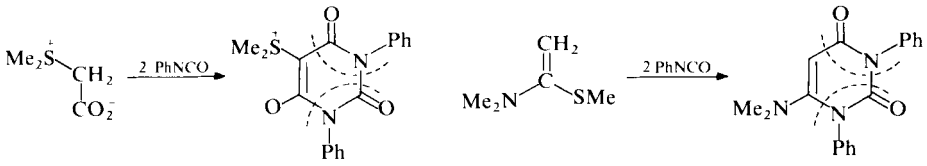
Ethyl 2-cyanoacetate with phenyl isocyanate (2 mol) and pyridine in refluxing benzene gave 2,4,6-trioxo-1,3-diphenyl-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbonitrile (17%).[4459]

Propionaldehyde with methyl isothiocyanate (2 mol) in benzene containing sodium pentyl oxide gave 1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedithione (32%).[3659]

2-(Dimethylsulfonio)acetate (thetine) (**383**) with phenyl isocyanate (2 mol) in boiling toluene gave 5-dimethylsulfonio-2,6-dioxo-1,3-diphenyl-1,2,3,6-tetrahydro-4-pyrimidinolate (**384**) (65%).[4457]

N,*N*-Dimethyl-*N*-(1-methylthiovinyl)amine (**385**) with phenyl isocyanate (2 mol) in refluxing toluene gave 6-dimethylamino-1,3-diphenyl-2,4(1*H*,3*H*)-pyrimidinedione (**386**) (92%).[399]



383 384 385 386

Triethyl(phenylethynyl)lead ($Et_3PbC{\equiv}CPh$) reacted exothermically with phenyl isocyanate to give (after hydrolysis) 1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione in unstated yield.[4456]

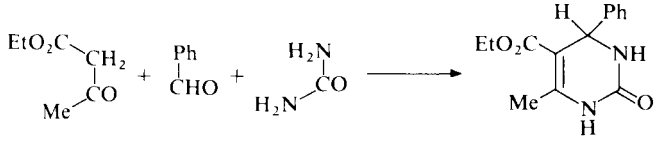
N,*N*-Dimethylacetamide with phenyl isocyanate at 80° for several days gave, inter alia, a product formulated as 5-anilino(dimethylamino)methylene-1,3-diphenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (18%).[1458]

Also other examples.[399,3659]

Using amidines for both C + N fragments. The exceptional behavior of simple amidines with unsubstituted malononitrile or ethyl 2-cyanoacetate is discussed in Sections 3.10.1 and 3.9.1, respectively: for example, malononitrile reacted with ethanolic formamidine (2 mol) to give not the expected 4,6-pyrimidinediamine, but 4-amino-5-pyrimidinecarbonitrile (45%).[1619]

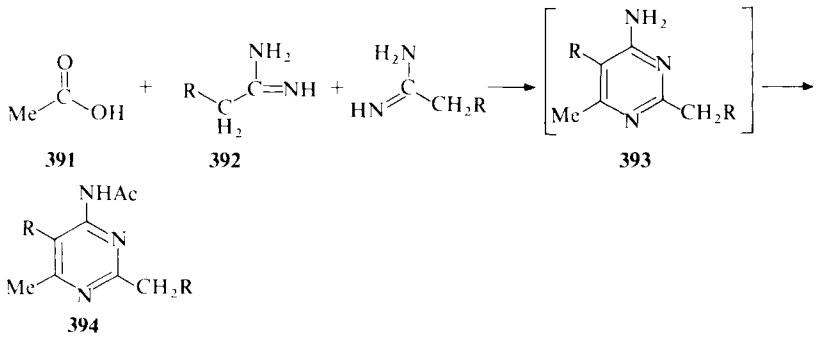
2.3.2. Where the Synthones Provide N1+C2+N3, C4+C5, and C6

The most important synthesis within this category is the *Biginelli reaction*, briefly exemplified in the original condensation of ethyl acetoacetate (**387**), benzaldehyde (**388**), and urea (**389**) in boiling ethanol to give ethyl 4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (**390**):[4460] almost a century later, novel extensions are still appearing.[98,127,144,393,498,3942,3958,4461,6230,6890] For details, see Section 11.1.6.



387 388 389 390

A potentially useful but quite undeveloped reaction is that of acetic anhydride, formulated as acetic acid (**391**) for simplicity, with acetamidine (**392**, R = H) (2 mol) to give 2,6-dimethyl-4-pyrimidinamine (**393**, R = H), isolated as 4-acetamido-2,6-dimethylpyrimidine (**394**, R = H);[2998] the fact that acetic anhydride with propionamidine (**392**, R = Me) afforded 4-acetamido-2-ethyl-5,6-dimethylpyrimidine (**394**, R = Me) indicated that C2, C4, and C5 had been provided by the amidine while C6 had come from the acetic anhydride.[2998]



391 392 393

394

The mysterious formation of 5-benzyl-2-phenyl-4(3*H*)-pyrimidinone (30%) from propynamide, *N*-methylurea, and benzaldehyde has not been explained satisfactorily.[393]

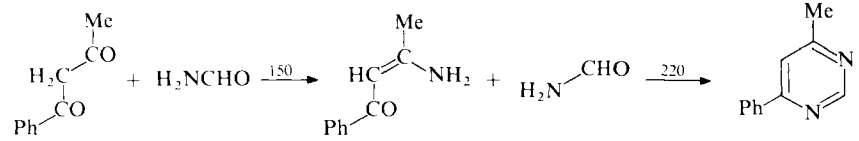
2.3.3. Where the Synthones Provide N1, C2+N3, and C4+C5+C6

All presently known syntheses within this category employ either a β-dicarbonyl compound or a β-carbonyl nitrile as the C + C + C fragment.

2.3.3.1. Using a β-Dicarbonyl or Equivalent Compound as the C + C + C Fragment

In this subcategory, the N and C + N fragments come from two molecules of formamide, a nitrile, a thiocyanate, or cyanamide, thereby providing a practical basis for further subclassification.

With formamide. Treatment of a β-dicarbonyl or equivalent compound with an excess of formamide at $\sim$ 200° is a good route to *C*-alkyl- or *C*-arylpyrimidines, with or without functional groups: it has become known as the *Bredereck synthesis.* For example, benzoylacetone (**395**) with formamide at 220° gave 4-methyl-6-phenylpyrimidine (**397**) (60%);[2752] the course of the reaction was indicated by using a lower temperature (150°) to permit isolation of the intermediate 2-amino-1-benzoylprop-1-ene (**396**), which in refluxing formamide gave the pyrimidine (**397**).[4463] The scope of the synthesis is indicated by the preparations of the following pyrimidines, using the indicated dicarbonyl or equivalent compounds with formamide at a high temperature.



395 396 397

Pyrimidine from 1,3,3-triethoxy-1-methoxypropane (yield: 65–72%),[836,2752] 1,3,3-triethoxyprop-1-ene (20%),[2752] 3,3-diethoxyprop-1-yne (40%),[3363] 3-aminoacrylaldehyde (60%),[3093] or 3-diethylaminoacrylaldehyde (64%).[836]

4-Methylpyrimidine from 4,4-dimethoxy-2-butanone (70%),[2752] 4-dimethylaminobut-3-en-2-one (40%),[2752] 4-ethoxybut-3-en-2-one (40%),[2752] 4-methoxybut-3-en-2-one (54%),[3092] or 4-chlorobut-3-en-2-one (40%).[2752]

5-Methylpyrimidine from 3-amino-2-methylacrylaldehyde (88%)[3093] or 3-diethylamino-2-methylacrylaldehyde (85%).[2749]

4,6-Dimethylpyrimidine from 2,4-pentanedione (35%),[2752] 4-imino-2-pentanone (25%),[2752] or 4-methylimino-2-pentanone (25%).[2752]

4,5-Dimethylpyrimidine from 3-chloro-2-methylcrotonaldehyde (64%).[2749]

4-Phenylpyrimidine from 2-benzoylacetaldehyde (38%),[2752] 2-benzoylvinyl acetate (45%),[2752] 1-benzoyl-2-dimethylaminoethylene (65%),[2752] or 1-benzoyl-2-chloroethylene (38%).[2752]

4-Methyl-6-phenylpyrimidine from benzoylacetone (60%),[2752] 1-benzoyl-2-propanimine (36%),[2752] 2-acetylimino-1-benzoylpropane (25%),[2752] 4-methoxy-4-phenylbut-3-en-2-one (20%),[2752] 1-benzoyl-2-ethoxyprop-1-ene (40%),[2752] or 4-chloro-4-phenylbut-3-en-2-one (60%).[2752]

4,6-Diphenylpyrimidine from dibenzoylmethane (32%),[2752] 1-benzoyl-2-phenylacetylene (35%),[3363] or 1-benzoyl-2-methoxy-2-phenylethylene (30%).[2752]

4,5-Tretramethylenepyrimidine from 2-oxocyclohexanecarbaldehyde (2-formyl- or 2-hydroxymethylenecyclohexanone) (22–30%),[2752,4463] or 2-chlorocyclohexene-1-carbaldehyde (50%).[4464]

Ethyl 5-pyrimidinecarboxylate (45%) from ethyl 2,2-diformylacetate diacetal.[1969]

5-β-Acetoxyethyl-4-methylpyrimidine (26%) from 2-β-acetoxyethyl-3-chlorocrotonaldehyde.[4465]

5-Bromo- (64%), 5-chloro- (61%), or 5-fluoropyrimidine (52%) from α-bromomalondialdehyde diacetal,[1969] α-chloromalondialdehyde diacetal,[1970] or 3-dimethylamino-2-fluoroacrylaldehyde.[3161]

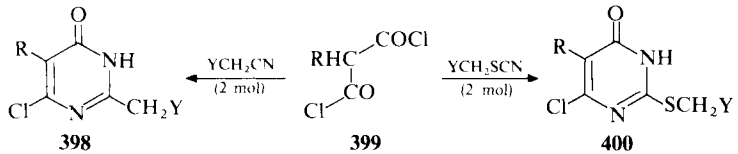
4(3*H*)-Pyrimidinone (59%) from ethyl 3-ethoxyacrylate (using triethyl orthoformate in liquid ammonia).[2821]

Also other examples.[836,1211,2749,2752,2821,3092,3093,3363,4011,4462–4464]

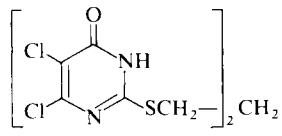
With nitriles. Malonyl chloride (**399**, R = H) with acetonitrile (2 mol) at room temperature gave 6-chloro-2-methyl-4(3*H*)-pyrimidinone (**398**, R = Y = H),[4467] which had been reported earlier as a pyridine derivative.[4468] Unfortunately, analogous reactions did sometimes give a mixture of pyrimidines and pyridines or even pyridines alone, so that the synthesis was of limited utility and its mechanism remains obscure.[1802] Some examples of its successful use were the synthesis of 6-chloro-2-chloromethyl-4(3*H*)-pyrimidinone (**398**, R = H, Y = Cl)

along with 2,3-dichloro-6-hydroxy-4(1*H*)-pyridinone from malonyl chloride (**399**, R = H) with 2-chloroacetonitrile;[1802] 6-chloro-2-fluoromethyl-4(3*H*)-pyrimidinone (**398**, R = H, Y = F) with no pyridine by-product;[1802] 5,6-dichloro-2-fluoromethyl-4(3*H*)-pyrimidinone (**398**, R = Cl, Y = F) from α-chloromalonyl chloride (**399**, R = Cl) with 2-fluoroacetonitrile;[1802] 6-chloro-2,5-dimethyl-4(3*H*)-pyrimidinone (**398**, R = Me, Y = H) (19%) from α-methylmalonyl chloride (**399**, R = Me) with acetonitrile;[759] and many other such derivatives, usually in poor yield.[759,1802]

With thiocyanates. Just as they react with nitriles (see preceding paragraph), malonyl chlorides react with simple thiocyanates to afford 2-alkylthiopyrimidines. Thus α-chloromalonyl chloride (**399**, R = Cl) with propyl thiocyanate (2 mol) at room temperature slowly gave 5,6-dichloro-2-propylthio-4(3*H*)-pyrimidinone (**400**, R = Cl, Y = Et) (38%);[927] similar reactions gave 6-chloro-2-ethylthio-5-phenyl-4(3*H*)-pyrimidinone (**400**, R = Ph, Y = Me) (36%), 5-benzyl-2-benzylthio-6-chloro-4(3*H*)-pyrimidinone (**400**, R = CH_2Ph, Y = Ph) (30%), and other such derivatives;[927] and α-chloromalonyl chloride with trimethylene bisthiocyanate gave 1,3-bis(4′,5′-dichloro-6′-oxo-1′,6′-dihydropyrimidin-2′-ylthio)propane (**401**) (10%).[927]



398 **399** **400**



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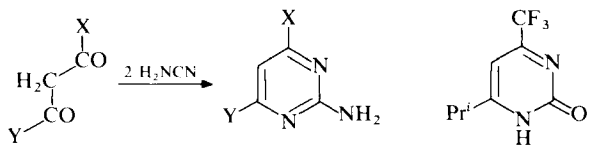
With cyanamide. In a rather similar way, β-diketones react with cyanamide (2 mol) at room temperature to give 4,6-dialkyl-2-pyrimidinamines. Thus 2,4-pentanedione (**402**, X = Y = Me) with cyanamide in aqueous potassium carbonate gave 4,6-dimethyl-2-pyrimidinamine (**403**, X = Y = Me) (43%); benzoylacetone (**402**, X = Me, Y = Ph) with ethanolic cyanamide gave 4-methyl-6-phenyl-2-pyrimidinamine (**403**, X = Me, Y = Ph) (13%); but 1,1,1-trifluoro-5-methyl-2,4-hexanedione (**402**, X = CF_3, Y = Pr^i) with methanolic



402 **403** **404**

cyanamide gave not the expected 4-isopropyl-6-trifluoromethyl-2-pyrimidinamine (**403**, X = CF_3, Y = Pr^i), but 4-isopropyl-6-trifluoromethyl-2(1*H*)-pyrimidinone (**404**) (25%).[79] The mechanism of the synthesis is obscure.[79]

2.3.3.2. Using a β-Carbonyl Nitrile as the C + C + C Fragment

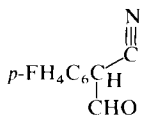
This type of synthesis has been used only with formamide (2 mol) to supply the other fragments: its present scope is indicated by the following examples.

5-*p*-Fluorophenyl-4-pyrimidinamine (62%) from 2-*p*-fluorophenyl-2-formylacetonitrile (**405**) with formamide plus ammonia at 185°.[4411]

5-*m*-Methoxyphenyl-4-pyrimidinamine (30%) from 2-formyl-2-*m*-methoxyphenylacetonitrile with formamide plus phosphoryl chloride at 150°.[4469]

5-Naphthalen-l′-yl-4-pyrimidinamine (14%) from 2-formyl-2-naphthalen-l′-ylacetonitrile with formamide–phosphoryl chloride.[4471]

6-Ethyl-5-*m*-methoxyphenyl-4-pyrimidinamine from 2-*m*-methoxyphenyl-2-propionylacetonitrile (**406**) similarly.[4469]



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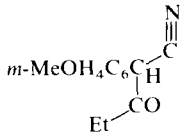

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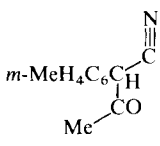
6-Methyl-5-(5′,6′,7′,8′-tetrahydronaphthalen-2′-yl)-4-pyrimidinamine from 2-acetyl-2-(5′,6′,7′,8′-tetrahydronaphthalen-2′-yl)acetonitrile similarly.[4470]

6-Methyl-5-*m*-tolyl-4-pyrimidinamine (14%) from 2-acetyl-2-*m*-tolylacetonitrile (**407**) similarly at 120°.[4473]

5-(3′,4′-Methylenedioxyphenyl)-6-phenyl-4-pyrimidinamine (50%) from 2-benzoyl-2-(3′,4′-methylenedioxyphenyl)acetonitrile similarly.[4472]

6-Phenyl-4-pyrimidinamine (**410**) (55%) from 3-imino-3-phenylpropiononitrile (**408**), equivalent to the keto nitrile (**409**), in refluxing formamide.[2752]



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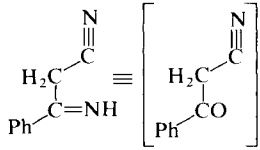
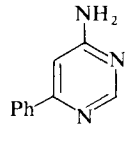


408 **409**



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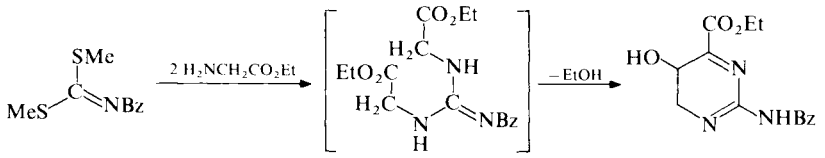
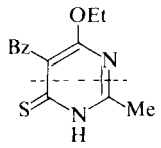
2.3.4. Where the Synthones Provide C2, N3+C4, and C5+C6+N1

This category is represented poorly. The most useful procedure is illustrated by the condensation of *N*-(bismethylthiomethylene)benzamide (**411**) with gly-

cine ethyl ester hydrochloride (2 mol) in ethanolic sodium acetate to give ethyl 2-benzamido-5-hydroxy-5,6-dihydro-4-pyrimidinecarboxylate (**413**) (85%), probably by loss of ethanol from the intermediate (**412**);[262] analogs, such as ethyl 5-hydroxy-2-*p*-nitrobenzamido- (74%) and ethyl 6-hydroxy-2-nicotinamido-5,6-dihydro-4-pyrimidinecarboxylate (81%) were made similarly.[262] 5-Benzoyl-6-ethoxy-2-methyl-4(3*H*)-pyrimidinethione (**414**) (55%) was made from acetyl isothiocyanate and ethyl 3-oxo-3-phenylpropionimidate in refluxing acetone.[6001] The syntheses of 4-methylthio-6-oxo-2-phenyl-1,6-dihydro-[3993] and 2-amino-4-ethoxy-6-methylthio-5-pyrimidinecarbonitrile[6139] fall in this category.



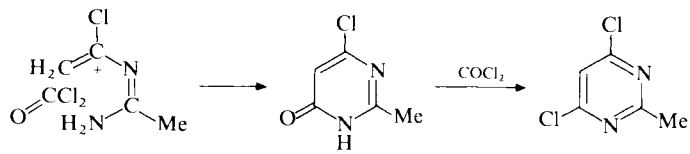
411 **412** **413**



414

2.3.5. Where the Synthones Provide N1+C2, N3+C4+C5, and C6

This type of synthesis has been reported only in one series of papers from Osaka: since these include a comprehensive review,[4474] the present treatment can be brief and somewhat simplistic. The self-condensation of nitriles under acidic conditions, with or without other reagents such as phosgene, sometimes leads to pyrimidines. Thus warming acetonitrile with dry hydroyen chloride gave intially the isolable *N*-(α-chlorovinyl)acetamidine (**415**) as its hydrochloride,[4475] which underwent treatment with phosgene to give (probably) 6-chloro-2-methyl-4(3*H*)-pyrimidinone (**416**) and thence (with more phosgene) 4,6-dichloro-2-methylpyrimidine (**417**) (> 70%);[2465] by beginning with propiononitrile, 4,6-dichloro-2-ethyl-5-methylpyrimidine (62%) resulted and other



415 **416** **417**

homologs were made similarly.[2465] The reaction could be done without isolating the intermediate (**415**); and by adjusting the proportions of acetonitrile, hydrogen chloride, and phosgene correctly, the pyrimidine (**416**) was isolated in > 55% yield.[2146,2050] Several homologs, such as 6-chloro-2-heptyl-5-hexyl-4(3*H*)-pyrimidinone (48%), were made similarly,[2050] but 2-arylacetonitriles gave mainly isoquinolines,[4476] while α-branched aliphatic nitriles gave only traces of the expected pyrimidines.[4477]

The reaction of simple amides with hydrogen chloride and phosgene also led to pyrimidines among other products. Thus acetamide, like acetonitrile, gave 4,6-dichloro-2-methylpyrimidine (**417**) (83%), but with increasing chain length, the yields of pyrimidines decreased in favor of aliphatic products: for example, lauramide (dodecanamide) gave only 22% of 4,6-dichloro-5-decyl-2-undecylpyrimidine and 78% of lauronitrile.[2285]

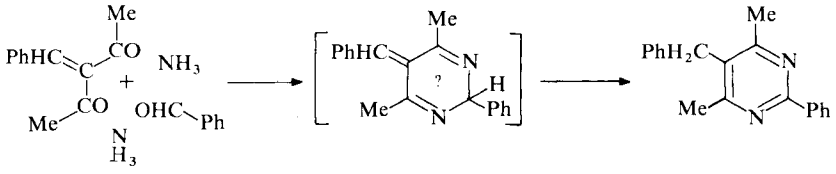
2.4. FROM FOUR SYNTHONES

Of the many possibilities within this category, only one has been used: it involves the combination of three one-atom fragments with one three-atom fragment. Another defies rationalization.[338]

2.4.1. Where the Synthones Provide N1, C2, N3, and C4+C5+C6

All the following syntheses lead directly to (unisolated) dihydropyrimidines. These may carry an unsaturated substituent to ensure automatic aromatization of the ring by rearrangement of the double bonds, or they may carry a substituent capable of producing ring oxidation by elimination with an hydrogen atom.

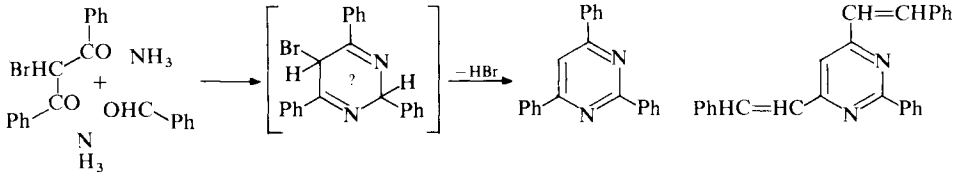
In the first type, a *5-benzylidene group ensures aromatization.* Thus 3-benzylidene-2,4-pentanedione (**418**), benzaldehyde, and ammonia (2 mol; as ammonium acetate) in glacial acetic acid at 60° gave 5-benzyl-4,6-dimethyl-2-phenylpyrimidine (**420**) via **419**.[4478] Analogous procedures gave 4,6-dimethyl-5-*m*-nitrobenzyl-2-*m*-nitrophenyl- (55%), 5-benzyl-4,6-dimethyl-2-*m* (or *p*)-nitrophenyl- (55% or 94%, respectively), 4,6-dimethyl-5-*m*-nitrobenzyl-2-phenyl- (19%), 2-*p*-chlorophenyl-4,6-dimethyl-5-pyridin-2′-ylmethyl- (53%), and 5-benzyl-4-ethyl-6-methyl-2-pyridin-3′-ylpyrimidine (53%).[4478] In fact, it is



418 **419** **420**

unnecessary to preform the benzylidenepentanedione (**418**) or other such substrate. For example, treatment of (unsubstituted) 2,4-pentanedione with *p*-chlorobenzaldehyde (2 mol) in ethanolic ammonium acetate gave 5-*p*-chlorobenzyl-2-*p*-chlorophenyl-4,6-dimethylpyrimidine (30–50%);[196] 4,6-dimethyl-2-*p*-tolyl-5-*p*-tolylmethylpyrimidine was made similarly.[196]

In the second type, *oxidation is provided by spontaneous elimination* a hydrogen halide or other such molecule from the intermediate dihydropyrimidine. Thus dibenzoylbromomethane (**421**), benzaldehyde, and ammonium acetate in acetic acid gave 2,4,6-triphenylpyrimidine (**423**) (40%) by loss of hydrogen bromide from the intermediate (**422**);[4478] when 3-chloro-2,4-pentanedione was used, the product reacted further with the remaining excess of benzaldehyde to afford 2-phenyl-4,6-distyrylpyrimidine (**424**) (58%), but by avoiding an excess of the aldehyde component, 4,6-dimethyl-2-*p*-nitrophenylpyrimidine could be isolated in 56% yield.[4478] The reaction is illustrated further by the following examples in which appropriate aldehydes were usually employed to provide C2.



421 **422** **423** **424**

By elimination of a hydrogen halide

4-Methyl-2-*p*-nitrophenyl-6-phenylpyrimidine (90%) from 1-benzoyl-3-chloroacetone.[4478]

4-Ethyl-2-*m*-nitrophenyl-6-*m*-nitrostyrylpyrimidine (83%) from 3-chloro-2,4-hexanedione.[4478]

4-*p*-Bromophenyl-2,6-diphenylpyrimidine (62%) from α-bromo-α-(*p*-bromobenzoyl)acetophenone.[4478]

By elimination of acetic acid

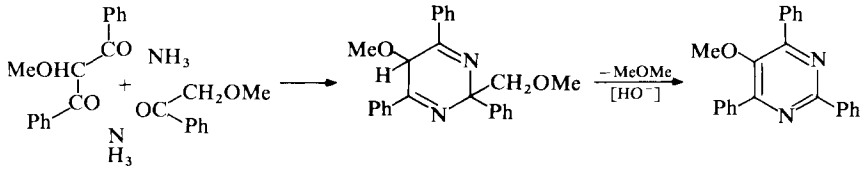
2,4,6-Triphenylpyrimidine (10%) from dibenzoylmethyl acetate.[4478]

By elimination of methanol

2,4,6-Triphenylpyrimidine (61%) from α-methoxydibenzoylmethane.[4479]

By elimination of dimethyl ether

5-Methoxy-2,4,6-triphenylpyrimidine (**428**) (70%) from α-methoxydibenzoylmethane (**425**), α-methoxyacetophenone (**426**) (in place of an aldehyde), and ammonium acetate: the isolated intermediate, 5-methoxy-2-methoxymethyl-2,4,6-triphenyl-2,5-dihydropyrimidine (**427**) lost dimethyl ether on mild alkaline treatment.[4479]



425 426 427 428

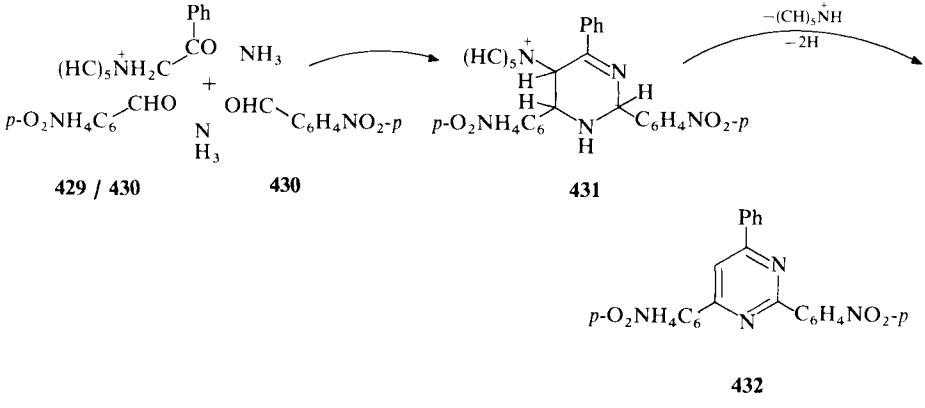
Alternatively, *extraneous oxidation* may be provided: for example air was passed through a mixture of dibenzoylmethane, benzaldehyde, and ammonium acetate in dimethyl sulfoxide containing a little acetic acid for 12 h at ~90° to produce 2,4,6-triphenylpyrimidine in 47% yield;[6298] see also Section 11.1.7.

2.5. FROM FIVE SYNTHONES

Only one known type of synthesis falls within this category: it involves the combination of four one-atom fragments with one two-atom fragment.

2.5.1. Where the Synthones Provide N1, C2, N3, C4, and C5+C6

The sole synthesis within this category involves the initial formation of a tetrahydropyrimidine for which automatic dehydrogenation is provided, partly by elimination and partly by an excess of one of the reagents, namely, an aromatic aldehyde. Thus *N*-phenacylpyridinium bromide (**429**) with an excess of *p*-nitrobenzaldehyde (**430**), and ammonium acetate in glacial acetic acid gave 2,4-di-*p*-nitrophenyl-6-phenylpyrimidine (**432**) (76%), probably through elimination of the pyridinio group (as pyridine acetate) from the intermediate (**431**), followed by further dehydrogenation by the remaining aldehyde present;[4478] *N*-phenacylisoquinolinium bromide, *N*-phenacylquinolinium bromide, or even



429 / 430 430 431 432

S,S-dimethyl-*S*-phenacylsulfonium bromide proved effective in place of the pyridinium bromide (**429**).[4478]

2.6. FROM OTHER HETEROCYCLIC COMPOUNDS

A great many pyrimidines have been prepared from other heterocyclic systems, usually by ring fission and/or rearrangement in the case of heteromonocyclic compounds or by partial degradation in the case of heterobicyclic or heteropolycyclic systems. Sometimes in the latter case, the larger molecule had itself been made from another pyrimidine or even from the selfsame pyrimidine to which it reverted on partial degradation: such useless procedures are usually ignored. This category of syntheses is subdivided according to the type of heterocyclic substrate.

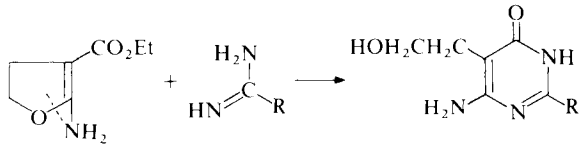
2.6.1. Pyrimidines from Four- or Five-Membered Heteromonocyclic Systems

One four-membered and several five-membered heteromonocyclic systems have been used as substrates for pyrimidine syntheses.

Azetes as substrates. This rare type of synthesis is illustrated by the conversion of 2,3,4-tri-*t*-butylazete into 4,5,6-tri-*t*-butyl-2-trifluoromethylpyrimidine via an unisolated Dewar intermediate (F_3CCN, $CHCl_3$, 20°; 91%); several highly hindered analogs were made similarly.[6141]

Furans as substrates. Three distinct procedures for the conversion of furans into pyrimidines are exemplified as follows.

1. Treatment of ethyl 2-amino-4,5-dihydro-3-furancarboxylate (**433**) with ethanolic acetamidine, benzamidine, or guanidine under reflux gave 6-amino-5-β-hydroxyethyl-2-methyl-4(3*H*)-pyrimidinone (**434**, R = Me) (30%), its 2-phenyl analog (**434**, R = Ph) (50%), or 2,6-diamino-5-β-hydroxyethyl-4(3*H*)-pyrimidinone (**434**, R = NH_2) (38%), respectively.[1314]
2. 2,5-Dimethyl-2-phenylazo-3(2*H*)-furanone (**435**) in methanolic ammonia underwent an aminolytic fission and rearrangement to give *N*-acetyl-3-amino-*N'*-phenylbut-2-enohydrazide (**436**):[8, cf. 4487] recyclization of this



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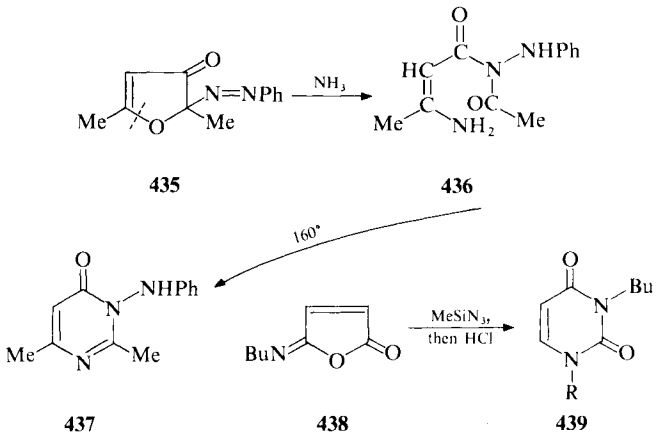


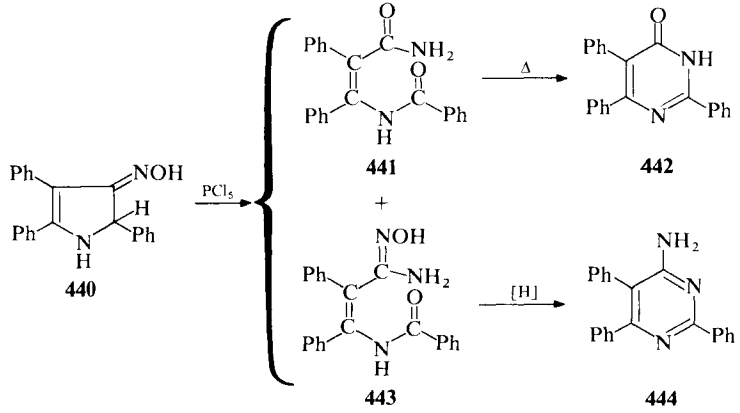
435 436 437 438 439

occurred at 160–170° to afford 3-anilino-2,6-dimethyl-4(3*H*)-pyrimidinone (**437**) (85%);[8] the 3-*p*-chloroanilino, 3-*p*-toluidino, and 3-*o*-methoxyanilino analogs were made similarly in comparable yields.[8]

3. The reaction of 5-butylimino-2(5*H*)-furanone (*N*-butylisomaleimide) (**438**) with dimethylsilyl azide in mesitylene at 110° gave 3-butyl-1-trimethylsilyl-2,4(1*H*,3*H*)-pyrimidinedione (**439**, R = $SiMe_3$) (64%) by a complicated but rational mechanism: subsequent desilylation with ethereal hydrogen chloride gave 3-butyl-2,4(1*H*,3*H*)-pyrimidinedione (**439**, R = H) (80%).[4483]

Pyrroles as substrates. Little use has been found for three unrelated procedures by which pyrroles have furnished pyrimidines.

1. Treatment of 3-hydroxyamino-2,4,5-triphenylpyrrole, formulated as the oxime (**440**), with phosphorus pentachloride in ether gave a separable mixture of two intermediates, 3-benzamido-2,3-diphenylacrylamide (**441**),



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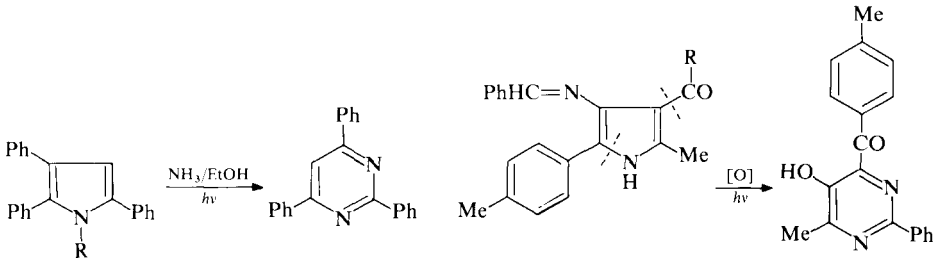
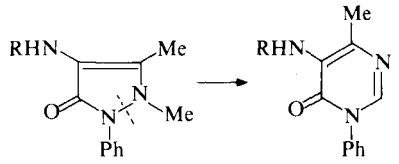
and its oxime (**443**); heating the first gave 2,5,6-triphenyl-4(3*H*)-pyrimidinone (**442**), while a zinc/acetic acid reduction of the oxime gave 2,5,6-triphenyl-4-pyrimidinamine (**444**).[4480] If the 4-position of the pyrrole was unoccupied; the 5-position of the resulting pyrimidine was also unoccupied;[4481,4482] when chloroform was used as the solvent, no intermediate could be isolated.[4481] The proposed mechanism was unconvincing.[4482]

2. Prolonged irradiation of 2,3,5-triphenyl-, 1-methyl-2,3,5-triphenyl-, 1,2,3,5-tetraphenyl-, or 2,3,5-triphenyl-1-*p*-tolylpyrrole (**445**, R = H, Me, Ph, or C_6H_4Me-*p*, respectively) in ethanolic ammonia open to the air gave 2,4,6-triphenylpyrimidine (**446**) as the main product in each case.[4484, cf. 4486]
3. Oxygenation during irradiation of an ethanolic solution of 3-acetyl- (**447**, R = Me) or 3-benzoyl-4-benzylideneamino-2-methyl-5-*p*-tolylpyrrole (**447**, R = Ph) containing methylene blue as a sensitizer, gave 4-methyl-2-phenyl-6-*p*-toluoyl-5-pyrimidinol (**448**) (~20%);[136] similar procedures gave several analogs, one of which was confirmed in structure by an X-ray analysis.[136]



445 **446** **447** **448**

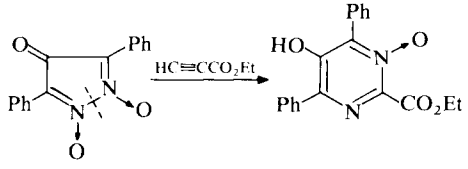
Pyrazoles as substrates. There are several ways to induce ring expansion of pyrazoles to pyrimidines. Thus, in attempting to methylate 4-anilino-1,5-dimethyl-2-phenyl-3(2*H*)-pyrazolone (**449**, R = Ph) with methyl iodide/sodium hydride in xylene, no alkylation occurred, but the product was 5-anilino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (**450**, R = Ph) (42%), in which the *N*-methyl group from the pyrazole (**449**, R = Ph) had supplied C2 of the resulting pyrimidine (**450**, R = Ph); 4-amino-1,5-dimethyl-2-phenyl-3(2*H*)-pyrazolone (**449**, R = H) with sodium hydride or a similar strong base in xylene likewise gave 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (**450**, R = H)



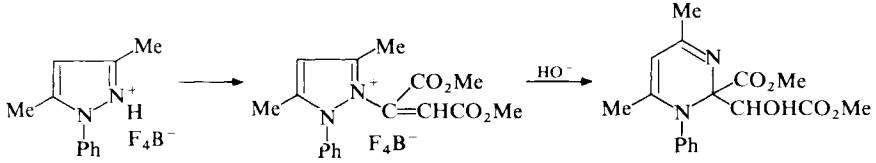
449 **450**

(40%).[2416,2417] *N*-Acylpyrazoles behaved rather similarly in the presence of hexacarbonylmolybdenum, $Mo(CO)_5$: for example, 1-acetyl- or 1-benzoyl-3,5-diphenylpyrazole with the complex in refluxing *o*-xylene gave 2-methyl-4,6-diphenyl- (30%) or 2,4,6-triphenylpyrimidine (30%), respectively.[3937]

On heating 3,5-diphenyl-4*H*-pyrazol-4-one 1,2-dioxide (**451**) with ethyl propynoate in benzene for 24 h, the major product was ethyl 5-hydroxy-4,6-diphenyl-2-pyrimidinecarboxylate 1-oxide (**452**) (20%);[4488] the mechanism remains obscure and the reaction has not been developed. In a broadly analogous way, 3,5-dimethyl-1-phenylpyrazolium tetrafluoroborate (**453**) added to the triple bond of dimethyl acetylenedicarboxylate to afford 1-[1′,2′-di(methoxycarbonyl)vinyl]-3,5-dimethyl-2-phenylpyrazolium tetrafluoroborate (**454**), which in aqueous potassium carbonate underwent ring expansion to methyl 2-hydroxy(methoxycarbonyl)methyl-4,6-dimethyl-1-phenyl-1,2-dihydro-2-pyrimidinecarboxylate (**455**) (47%): several analogs were made by essentially the same route.[352]

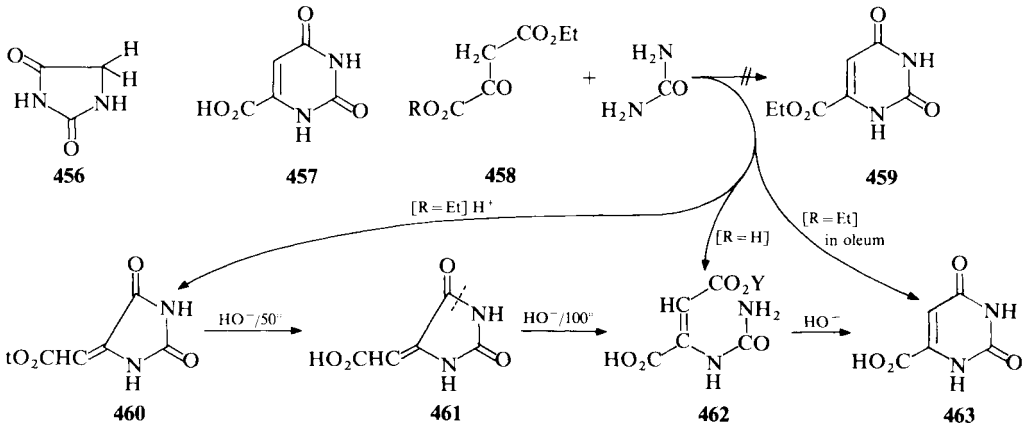


451 **452**



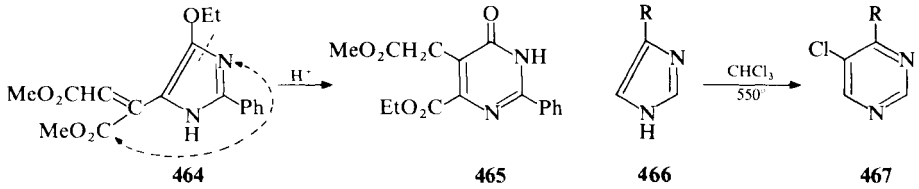
453 **454** **455**

Imidazoles as substrates. Derivatives of hydantoin [2,4-imidazolidinedione or 5*H*-imidazole-2,4(1*H*,3*H*)-dione] (**456**) often arise from reactions designed to produce orotic acid (2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid) (**457**) or related compounds directly: however, such hydantoins nearly always undergo rearrangement in alkali to afford the required pyrimidines. For example, the condensation of ethyl 2-ethoxalylacetate (**458**, R = Et) with urea under mildly acidic conditions gave not ethyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (**459**) as anticipated,[2876,2955,3391] but 5-ethoxycarbonylmethylhydantoin (**460**).[2875] On gentle alkaline treatment at 50° this underwent saponification to 5-carboxymethylenehydantoin (**461**), which, under more vigorous alkaline conditions, rearranged via the acyclic intermediate (**462**, Y = H) into 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (orotic acid) (**463**).[2875] It is interesting that the similar condensation of ethyl 2-oxalylacetate (**458**, R = H) with urea proceeded directly to the intermediate 3-ethoxycarbonyl-2-ureidoacrylate (**462**, Y = Et) and thence in alkali to orotic



acid (**463**);[1605] also that the condensation of ethyl ethoxalylacetate (**458**, R = Et) with urea in oleum gave orotic acid (**463**) directly, whereas the same condensation in concentrated sulfuric acid proceeded via hydantoin intermediates that required rearrangement in alkali.[2887] Other pyrimidines that have been made by such condensations via hydantoin or related imidazole intermediates include, for example, 5-methyl,[3051,3393] 5-butyl-,[3010] 5-ethyl-1-methyl-,[2677] and 1-aminomethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid;[1200] also 2,6-dioxo-1-phenyl-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid[2678] and 2-amino-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid [via 2-amino-5-(1′-carboxyethylidene)-5*H*-imidazol-4(3*H*)-one[3393] or the corresponding ester[1448]].

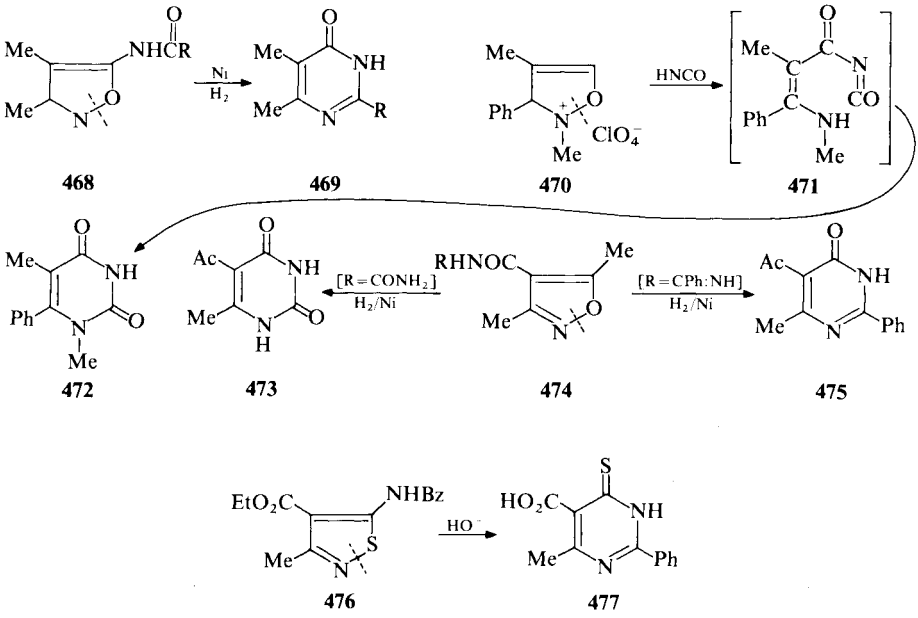
Naturally it is possible to custom-make hydantoins or other imidazoles for the purpose of rearrangement into pyrimidines. Examples of the last stage in such procedures include 5-carboxymethylenehydantoin (**461**) into orotic acid (**463**) (~90%),[3392,3577] 5-ethoxycarbonylmethylene-3-phenyl-2-thioxo-1,2-dihydro-5*H*-imidazol-4(3*H*)-one into 6-oxo-1-phenyl-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (~80%),[2778] 4-[1′,2′-di(methoxycarbonyl)-vinyl]-5-ethoxy-2-phenylimidazole (**464**) into ethyl 5-methoxycar-bonylmethyl-6-oxo-2-phenyl-1,6-dihydro-4-pyrimidinecarboxylate (**465**) (~50%) under acidic conditions,[3849] and others.[3577,3849,4490]



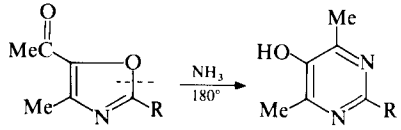
An interesting reaction of no preparative value was that of imidazole (**466**, R = H) with chloroform at 550° to give mainly 5-chloropyrimidine (**467**, R = H) (35%);[2104] 4-methylimidazole (**466**, R = Me) likewise gave mainly 5-

chloro-4-methylpyrimidine (**467**, R = Me) (20% yield) and the isomeric 4-chloro-6-methylpyrimidine (15%), while di- and trimethylimidazoles gave similar results.[2104]

Isoxazoles and isothiazoles as substrates. The use of isoxazoles as convenient starting materials for the preparation of aliphatic substrates for other types of pyrimidine synthesis has already been mentioned, for example, in Section 2.2.1.2. More direct use of isoxazoles as substrates is illustrated by the hydrogenation of 5-formamido- (**468**, R = H) or 5-valeramido-3,4-dimethylisoxazole (**468**, R = Bu) over Raney-nickel to give 5,6-dimethyl-4(3*H*)-pyrimidinone (**469**, R = H) (~70%) or its 2-butyl derivative (**469**, R = Bu) (~65%), respectively;[2109] by the treatment of 2,4-dimethyl-3-phenylisoxazolium perchlorate (**470**) with aqueous methanolic potassium cyanate to give 1,5-dimethyl-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**472**) (~20%), possibly via the intermediate (**471**);[4489] and by the hydrogenation of *N*-carbamoyl- (**474**, R = $CONH_2$) or *N*-(α-iminobenzyl)-3,5-dimethyl-4-isoxazolecarboxamide (**474**, R = CPh:NH) to give 5-acetyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**473**) (~95%) or 5-acetyl-6-methyl-2-phenyl-4(3*H*)-pyrimidinone (**475**) (~95%), respectively.[448] The similar use of an isothiazole is exemplified in the alkaline treatment of ethyl 5-benzamido-3-methyl-4-isothiazolecarboxylate (**476**) to afford 4-methyl-2-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylic acid (**477**) (80%).[4491]

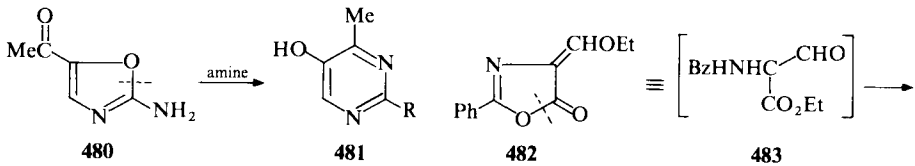


Oxazoles as substrates. Oxazoles have not been used widely as substrates for making pyrimidines. However, one type of this transformation is illustrated by the action of aqueous ammonia at 180° on 5-acetyl-4-methyl- (**478**, R = H),



478 479

5-acetyl-2,4-dimethyl (**478**, R = Me), or 5-acetyl-4-methyl-2-phenyloxazole (**478**, R = Ph) to give 4,6-dimethyl- (**479**, R = H) (88%), 2,4,6-trimethyl- (**479**, R = Me) (92%), or 4,6-dimethyl-2-phenyl-5-pyrimidinol (**479**, R = Ph) (91%), respectively;[2809] by the action of refluxing aqueous ammonia, ethylamine, or dimethylamine on 5-acetyl-2-oxazolamine (**480**) to give 2-amino- (**481**, R = NH_2) (15%), 2-ethylamino- (**481**, R = NHEt) (17%), or 2-dimethylamino-4-methyl-5-pyrimidinol (**481**, R = NMe_2) (44%), respectively, in each case accompanied by an appropriate separable imidazole in rather higher yield;[7] by the action of methanolic ammonia at 170° on 5-(2′-methoxyacetyl)-4-methyloxazole to give 4-methoxymethyl-6-methyl-5-pyrimidinol (36%);[458] and by the action of aqueous butanolic dimethylamine at 25° on 5-benzoyl-2-isoxazolamine to give 2-dimethylamino-4-phenyl-5-pyrimidinol (67%).[550] The quite different use of an oxazole as a substrate is exemplified in the condensation of 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (**482**), the equivalent of a *β*-aldehydo ester (**483**) after ring fission, with *S*-benzylisothiourea in ethanol containing triethylamine, to give 5-benzamido-2-benzylthio-4(3*H*)-pyrimidinone (**484**) (74%)[451] (cf. Section 3.4.4.)



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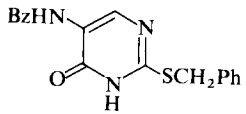
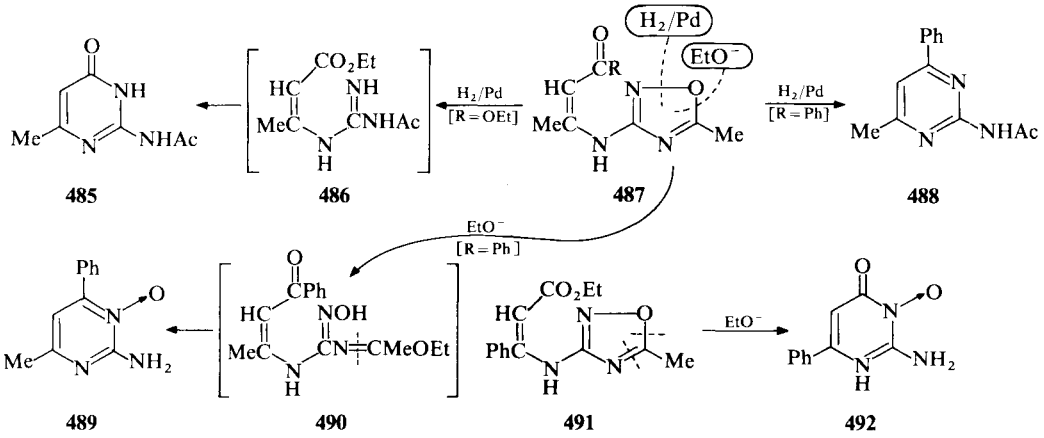


484

1,2,4-Oxadiazoles as substrates. Reductive or hydrolytic fission of 1,2,4-oxadiazoles bearing a suitable side chain at the 3-position has been used to produce pyrimidines: unfortunately, the oxadiazoles were not simple to make. Thus hydrogenation of 3-(2′-ethoxycarbonyl-1′-methylvinyl)amino-5-methyl-1,2,4-oxadiazole (**487**, R = OEt) over palladium–charcoal gave 2-acetamido-6-methyl-4(3*H*)-pyrimidinone (**485**) (~55%), probably via the intermediate (**486**);[647] 3-(2′-benzoyl-1′-methylvinyl)amino-5-methyl-1,2,4-oxadiazole (**487**, R = Ph) likewise gave 2-acetamido-4-methyl-6-phenylpyrimidine (**488**) (~55%);[647] and other analogs were made similarly.[647] In contrast, treatment of the above ketonic substrate (**487**, R = Ph) with ethanolic sodium ethoxide at 80°

gave 4-methyl-6-phenyl-2-pyrimidinamine 1-oxide (**489**) (70%), possibly via the intermediate (**490**);[291] and 3-(2′-ethoxycarbonyl-1′-phenylvinyl)amino-5-methyl-1,2,4-oxadiazole (**491**) likewise gave 2-amino-6-phenyl-4(1*H*)-pyrimidinone 3-oxide (**492**) (27%) accompanied by a separable imidazole.[291]



1,2,4-Selenadiazoles as substrates. Treatment of 3,5-diphenyl-1,2,4-selenadiazole with neat dimethyl acetylenedicarboxylate at 150° for 12 h gave dimethyl 2,6-diphenyl-4,5-pyrimidinedicarboxylate (54%, plus a byproduct).[67] Analogs were made similarly, but 1,2,4-thiadiazoles proved unsatisfactory as substrates.[67]

1,4,2-Dithiazolium salts as substrates. The reaction of such salts with malononitrile has been reported to afford pyrimidines, usually along with other products. For example, 5-dimethylamino-3-phenyl-1,4,2-dithiazolium perchlorate with malononitrile and triethylamine at 20° gave 4-amino-2-(α-cyano-β-dimethylamino-β-mercaptovinyl)-6-phenyl-5-pyrimidinecarbonitrile (49%) as the sole isolable product, unfortunately by a yet obscure mechanism.[3979]

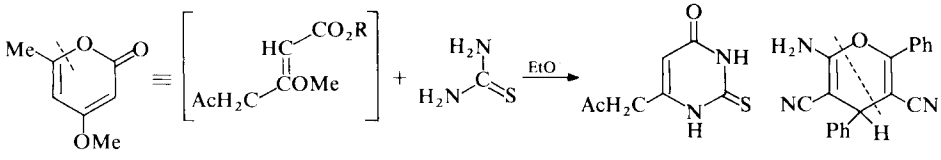
1,2,3,4-Thiatriazoles as substrates. The condensation of pentane-2,4-dione (2 mol) with 1,2,3,4-thiatriazol-5-amine appears to have given 2-diacetylmethylthio-4,6-dimethylpyrimidine.[423]

2.6.2. Pyrimidines from Six-Membered Heteromonocyclic Systems

At least nine six-membered heteromonocyclic systems with oxygen, sulfur, and/or nitrogen as heteroatom(s) have been used as substrates for pyrimidine syntheses.

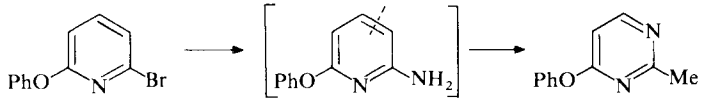
Pyrans as substrates. Pyrans have been used as equivalents for some three-carbon fragments in the Principal Synthesis. For example, 4-methoxy-6-methyl-2*H*-pyran-2-one (**493**) reacted as a β-keto ester equivalent (**494**) with thiourea in

ethanolic ethoxide to afford 6-acetonyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**495**) (79%);[746] 2,6-dimethyl-4*H*-pyran-4-one with guanidine or urea gave 4-acetonyl-6-methyl-2-pyrimidinamine (67%)[743] or 4-acetonyl-6-methyl-2(1*H*)-pyrimidinone (10%),[734] respectively; and 2-amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile (**496**) with methanolic guanidine gave 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile (33%).[346] 2,4,6-Triphenylpyrylium perchlorate underwent a more complicated reaction with guanidine to give 4,6-diphenyl-2-(2′,4′,6′-triphenylpyridinio)pyrimidine perchlorate (94%).[4492]



493 **494** **495** **496**

Pyridines as substrates. Although of no preparative value, several transformations of pyridines into pyrimidines have been reported. Thus treatment of 2,6-dichloro- or 2,6-dibromopyridine with sodium amide in liquid ammonia gave 2-methyl-4-pyrimidinamine (up to 24% yield);[689,6228] 2,3-, 2,4-, or 2,5-dibromopyridine gave the same pyrimidine but in minute yield among other products.[4493] Several 5-substituted 2-bromopyridines were examined under similar conditions: of these, 2-bromo-6-phenoxypyridine (**497**) showed up to 50% conversion into 2-methyl-4-phenoxypyrimidine (**499**) (with smaller amounts of other products),[4130] presumably by an initial aminolysis to the pyridine (**498**) followed by a Dimroth-like rearrangement involving scission of the 3,4-bond and recyclization, so that C3 of the pyridine (**497**) appeared as the methyl group on the pyrimidine (**499**).



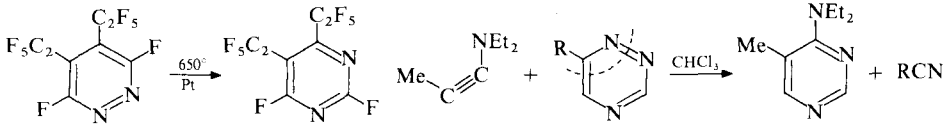
497 **498** **499**

Pyridazines and pyrazines as substrates. The formation of pyrimidines from other diazines is of little practical importance. However, pyrolysis of 3,6-difluoro-4,5-bis(pentafluoroethyl)pyridazine (**500**) over platinum at 650° gave, among other products, 2,4-difluoro-5,6-bis(pentafluoroethyl)pyrimidine;[4494,4495] 3,6-difluoro-4,5-bis(heptafluoroisopropyl)pyridazine behaved similarly under comparable conditions to give 2,4-difluoro-5,6-bis(heptafluoroisopropyl)pyrimidine,[4495] earlier described incorrectly[4496] as an isomer; 3,4,5,6-tetrafluoropyridazine over silica at 800° gave 2,4,5,6-tetrafluoropyrimidine (46%) and other products;[4496] and the same transformation was later reported under milder conditions.[3658] The action of phosphorus pentachloride

on 4-nitrosopyridazines to give pyrimidines has been reported without experimental detail.[4497]

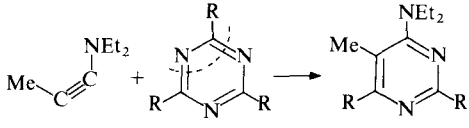
An irreversible transformation of pyrazine into pyrimidine occurred on irradiation at 253 nm in isooctane: the yield and quantum yield were minute.[4498]

1,2,4- and 1,3,5-Triazines as substrates. 1,2,4-Triazine (**503**, R = H) reacted with *N,N*-diethylprop-1-ynylamine (**502**) to give 4-diethylamino-5-methylpyrimidine (**504**) (40%) by replacement of the N1 + C6 portion of the ring; 6-phenyl-1,2,4-triazine gave the same product (**504**) (70%) along with benzonitrile (**505**, R = Ph) (77%); and several analogous pyrimidines were so made.[4093]



500 **501** **502** **503** **504** **505**

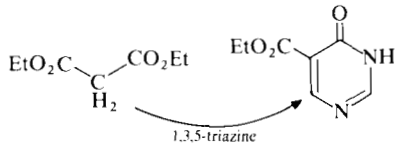
In much the same way, triethyl 1,3,5-triazine-2,4,6-tricarboxylate (**507**, R = CO_2Et) or 2,4,6-trismethylthio-1,3,5-triazine (**507**, R = SMe) reacted with *N,N*-diethylprop-1-ynylamine (**506**) to give diethyl 6-diethylamino-5-methyl-2,4-pyrimidinedicarboxylate (**508**, R = CO_2Et) (83%) or 4-diethylamino-5-methyl-2,6-bismethylthiopyrimidine (**508**, R = SMe) (86%), respectively; in the latter case, the intermediate tricyclic Diels–Alder adduct was isolable.[3840] 2,4,6-Triphenyl-1,2-dihydro-1,3,5-triazine reacted similarly with hexafluorobut-2-yne in benzene at 90° to afford 2,4-diphenyl-5,6-bistrifluoromethylpyrimidine (15%): the other fragment, benzylideneamine (PhCH:NH), was isolated after treatment with water as benzaldehyde semicarbazone.[4499]



506 **507** **508**

1,3,5-Triazine reacts in a fairly predictable way with compounds having an activated methylene group to give 4,5-disubstituted pyrimidines, in which N1, C2, N3, and C4 are supplied by the triazine: the precise mechanism is by no means proven. The scope of this synthesis is best illustrated by the following examples in which 1,3,5-triazine and the indicated synthone were usually warmed in ethanol or acetonitrile with added ethoxide where indicated (EtO^-).

Diethyl malonate (**509**) (EtO^-) gave ethyl 4-oxo-3,4-dihydro-5-pyrimidinecarboxylate (**510**) (42%);[713] neat reactants at 160°: 89%.[1620]



509 **510**

Malondiamide (EtO^-) gave 4-oxo-3,4-dihydro-5-pyrimidinecarboxamide (69%).[713]

Ethyl phenyl- or ethyl *p*-nitrophenylacetate (in pyridine containing piperidine) gave 5-phenyl- (26%) or 5-*p*-nitrophenyl-4(3*H*)-pyrimidinone (30%), respectively.[4428]

Ethyl 2-benzoylacetate (EtO^-) gave ethyl 4-phenyl-5-pyrimidinecarboxylate (no solvent at 140°: 30%).[1620]

2-Cyanoacetamide (EtO^-) gave 4-amino-5-pyrimidinecarboxamide (55%).[713]

2-Cyano(thioacetamide) (EtO^-) gave 4-thioxo-3,4-dihydro-5-pyrimidinecarbonitrile (90%) (cf. preceding entry).[713]

2-Benzoylacetonitrile (EtO^-) gave 4-phenyl-5-pyrimidinecarbonitrile (31%).[713]

Malononitrile (EtO^-) gave 4-amino-5-pyrimidinecarbonitrile (80%)[713, cf. 1620]

Ethyl 2-amidinoacetate hydrochloride gave ethyl 4-amino-5-pyrimidinecarboxylate (85%).[1633]

Ethyl 2-(*C*-ethoxyformimidoyl)acetate, $EtO(HN{:})CCH_2CO_2Et$, or its hydrochloride gave ethyl 4-amino- (56%) or ethyl 4-ethoxy-5-pyrimidinecarboxylate (51%), respectively.[1633]

Ethyl 2-benzoylacetimidate hydrochloride gave 5-benzoyl-4-ethoxypyrimidine (~95%).[1633]

2-Amidinoacetamide (base or hydrochloride) gave 4-amino-5-pyrimidinecarboxamide (53% or 72%, respectively).[1633]

2-Phenylacetamidine gave 5-phenyl-4-pyrimidinamine (75%).[1633]

Ethyl 2-cyanoacetimidate gave 4-amino-5-pyrimidinecarbonitrile (67%).[1633]

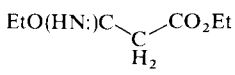
Ethyl 2-carbamoylacetimidate gave 4-ethoxy-5-pyrimidinecarboxamide (51%).[1633]

Methyl 2-cyano(thioacetimidate) hydrochloride gave 4-methylthio-5-pyrimidinecarbonitrile (64%).[1633]

2-(*N*-Methylanilino)acetonitrile (EtO^-) gave 5-*N*-methylanilino-4-pyrimidinamine (18%).[4501]

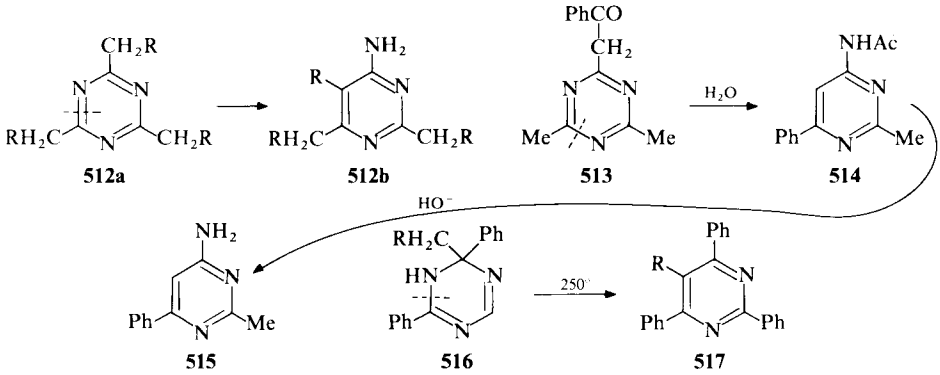
2-Thien-2′-ylacetonitrile (EtO^-) gave 5-thien-2′-yl-4-pyrimidinamine (53%);[4502] see also an analog.[485]

Some such reactions were unsuccessful in producing the expected pyrimidines.[713,1633,4500]



511

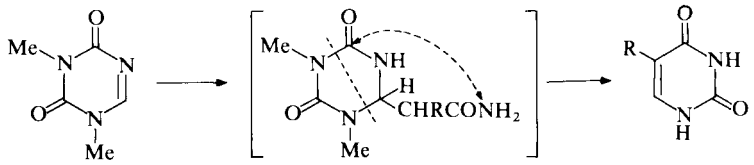
The isomerization of 1,3,5-triazines to pyrimidines can occur. Thus 2,4,6-trimethyl- (**511**, R = H) or 2,4,6-triethyl-1,3,5-triazine (**512a**, R = Me) rearranged in methanolic ammonia at 150°/8500 atm to afford 2,6-dimethyl-4-pyrimidinamine (**512b**, R = H) or 2,6-diethyl-5-methyl-4-pyrimidinamine (**512b**, R = Me) (32%), respectively.[648] More useful were the isomerizations of 1,3,5-triazinylmethyl ketones to 4-acetamidopyrimidine derivatives.[665,4503] Thus 2,4-dimethyl-6-phenacyl-1,3,5-triazine (**513**) in boiling water gave 4-acetamido-2-methyl-6-phenylpyrimidine (**514**) (~95%) and thence, on alkaline hydrolysis, 2-methyl-6-phenyl-4-pyrimidinamine (**515**) (~95%); 2-butyrylmethyl-4,6-dimethyl-1,3,5-triazine gave 2-methyl-6-propyl-4-pyrimidinamine; 2-β-acetylethyl-4,6-diethyl-1,3,5-triazine gave 2-ethyl-5,6-dimethyl-4-pyrimidinamine; and other examples were reported.[665,6850]



512a **512b** **513** **514** **515** **516** **517**

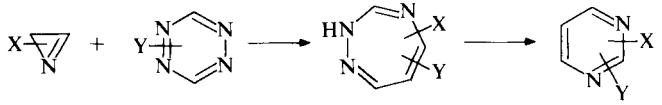
Thermolysis of 2-methyl-2,4,6-triphenyl-1,2-dihydro-1,3,5-triazine (**516** R = H) at 250° gave 2,4,6-triphenylpyrimidine (**517**, R = H) (96%) with loss of ammonia providing the required oxidation; the homolog, 2-ethyl-2,4,6-triphenyl-1,2-dihydro-1,3,5-triazine (**516**, R = Me), likewise gave 5-methyl-2,4,6-triphenylpyrimidine (**517**, R = Me) (85%); but higher homologs gave significantly lower yields of appropriate pyrimidines.[4504–4506]

Treatment of 1,3-dimethyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**518**) with malondiamide or 2-cyanoacetamide in ethanolic ethoxide or with 2-fluoroacetamide in ether containing lithium diisopropylamide gave an initial unisolated adduct (**519**, R = $CONH_2$, CN, or F) that underwent loss of *N*,*N*′-dimethylurea and recyclization to afford 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (**520**, R = $CONH_2$) (42%),[2868] the corresponding 5-carbonitrile (**520**, R = CN) (38%),[2868] or 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (**520**, R = F) (88%),[3172,3173] respectively. Analogous ring transformations have been inferred in complicated sequences under high pressure.[727,4507]



518 519 520

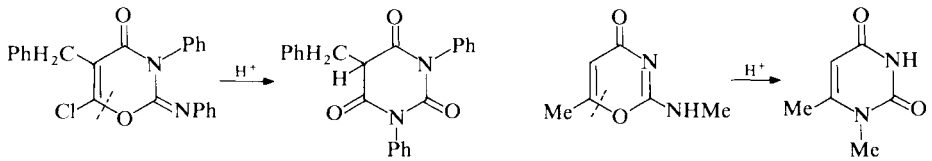
1,2,4,5-Tetrazines as substrates. It has been reported briefly thal condensation of 1-azirines (**521**) with 1,2,4,5-tetrazines (**522**) in refluxing toluene gave initially 1,2,4-triazepines (**523**) and subsequently pyrimidines (**524**).[4508]



521 522 523 524

1,3-Oxazines as substrates. 1,3-Oxazines with a suitable group next to the ring oxygen have been used extensively as substrates in pyrimidine syntheses, either by rearrangement or by aminolysis as appropriate; oxazines without such substituents have been used occasionally to make dihydropyrimidines.

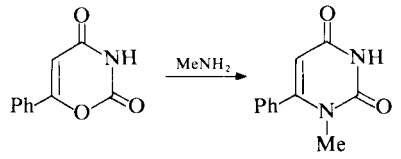
The route to pyrimidines by *rearrangement* of a suitable 1,3-oxazine is exemplified in the reaction of diphenylcarbodiimide with α-benzylmalonyl chloride to give 5-benzyl-6-chloro-3-phenyl-2-phenylimino-2,3-dihydro-4*H*-1,3-oxazin-4-one (**525**) (67%), which underwent facile rearrangement (and hydrolysis of the chloro substituent) in ethanolic sulfuric acid to give 5-benzyl-1,3-diphenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**526**) (~95%);[4509,4510] in the conversion of 3-benzyl-6-methyl-2-phenylimino-2,3-dihydro-4*H*-1,3-oxazin-4-one into 3-benzyl-6-methyl-1-phenyl-2,4 (1*H*,3*H*)-pyrimidinedione by warming in benzene containing *p*-toluenesulfonic acid;[4511] in the transformation of 6-methyl-2-methylamino-4*H*-1,3-oxazin-4-one (**527**) into 1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**528**) (76%) by boiling in glacial acetic acid;[3065] in the conversion of 6-chloro-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione into 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (45%) by aqueous methylamine, probably via aminolysis of the chloro substituent followed by rearrangement;[2805] and in the more complicated sequence when 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one was treated with thiopropionamide in dimethylformamide containing sodium hydride to give 5-acetyl-6-ethyl-2-phenyl-4(3*H*)-pyrimidinone (52%).[4512]



525 526 527 528

The more widely applicable route by *aminolysis of ring oxygen* is illustrated in the following examples.

6-Phenyl-2*H*-oxazine-2,4(3*H*)-dione (**529**) in refluxing aqueous methylamine gave 1-methyl-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**530**) (72%).[385]



529 **530**

3,6-Dimethyl-2*H*-oxazine-2,4(3*H*)-dione with ethanolamine at 95° gave 1-β-hydroxyethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (~70%).[3895,3902]

3-Ethyl-6-methyl-2*H*-oxazine-2,4(3*H*)-dione with aqueous ammonia at 20° gave 3-ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (65%).[4513]

2,4,5-Triphenyl-6*H*-1,3-oxazin-6-one with aqueous ammonia or aqueous ethanolic ethylamine at 20° gave 2,5,6-triphenyl-4(3*H*)-pyrimidinone (79%).[4135] or 3-ethyl-2,5,6-triphenyl-4(3*H*)-pyrimidinone,[4349,4520] respectively.

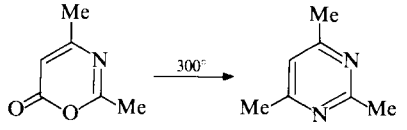
6-Methyl-6-pyridin-2′-yl-4*H*-1,3-oxazin-4-one with aqueous ethanolic ammonia at 90° gave 6-methyl-2-pyridin-2′-yl-4(3*H*)-pyrimidinone (67%).[4359]

2-Guanidino-6-methyl-4*H*-1,3-oxazin-4-one with ammonia gave 2-guanidino-6-methyl-4(3*H*)-pyrimidinone (55%).[3065]

2-Amino-6-phenyl-4*H*-1,3-oxazin-4-one with methanolic methylamine gave 2-methylamino-6-phenyl-4(3*H*)-pyrimidinone (~70%), presumably via Dimroth rearrangement of 2-amino-1-methyl-6-phenyl-4(3*H*)-pyrimidinone.[385]

Also other such reactions.[489,4514–4519,6034,6579]

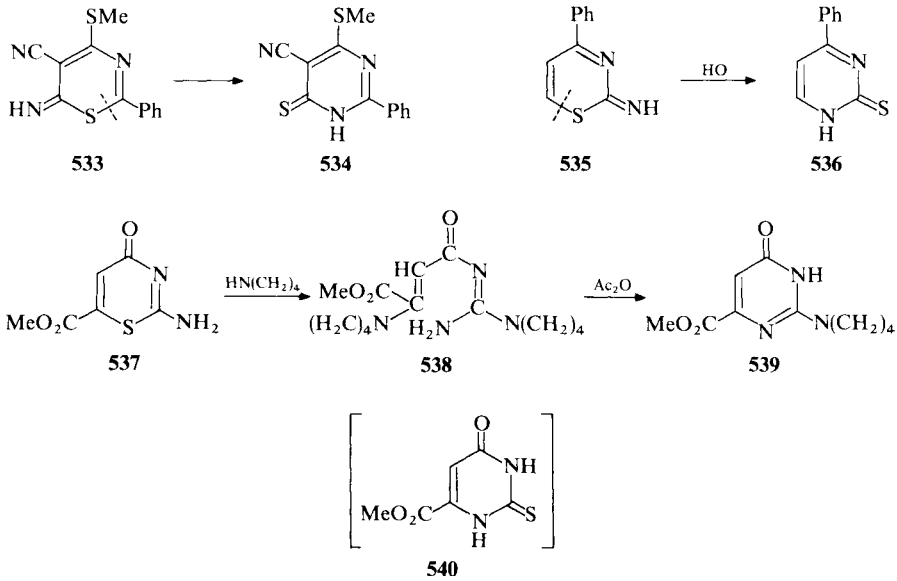
The conversion of 2,4-dimethyl-6*H*-1,3-oxazin-6-one (**531**) into 2,4,6-trimethylpyrimidine (**532**) (5%) and 2,4,6-trimethylpyridine (16%) by heating at 300° for 3 h, is more interesting than useful; 2-isopropyl- (10%) and 2-isobutyl-4,6-dimethylpyrimidine (5%) were made similarly.[2571]



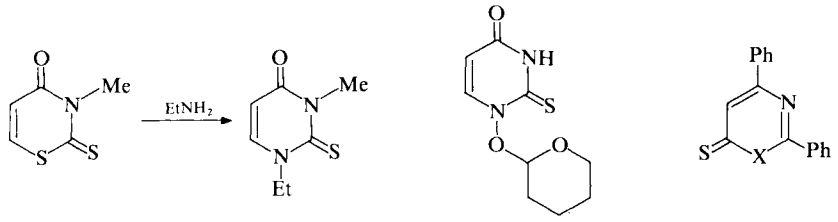
531 **532**

1,3-Thiazines as substrates. To be really useful as substrates for the synthesis of pyrimidines, 1,3-thiazines must have at least one suitable tautomeric substituent; otherwise, a dihydropyrimidine may result.[4521] 1,3-Thiazines may afford pyrimidines by a simple Dimroth-like rearrangement, by aminolytic displacement of the ring-sulfur atom, or by a combination of both.

The *rearrangement* route is typified by the conversion of 6-imino-4-methylthio-2-phenyl-6*H*-1,3-thiazine-5-carbonitrile (**533**) into 4-methylthio-2-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile (**534**) (78%) by warming in ethanolic morpholine;[3838] of 4-phenyl-2*H*-1,3-thiazin-2-imine (**535**) into 4-phenyl-2(1*H*)-pyrimidinethione (**536**) (65%) by treatment with aqueous ethanolic potassium carbonate;[4522] of 6-phenyl-2-phenylimino-5,6-dihydro-2*H*-1,3-thiazin-4(3*H*)-one into 1,6-diphenyl-2-thioxo-1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone (92%) by dissolution in dimethylformamide containing lithium hydride;[3767] of methyl 2-amino-4-oxo-4*H*-1,3-thiazine-6-carboxylate (**537**) into methyl 6-oxo-2-pyrrolidino-1,6-dihydro-4-pyrimidinecarboxylate (**539**), not by rearrangement and subsequent aminolysis of the pyrimidinethione (**540**) as might be expected in the presence of the neat pyrrolidine used, but via methyl 2-pyrrolidino-3-(*N'*,*N'*-tetramethyleneguanidinocarbonyl)acrylate (**538**) (isolated in 83% yield), which required digestion with hot acetic anhydride to afford the product (**539**) (81%);[3404] and in other such reactions.[2835,3834]

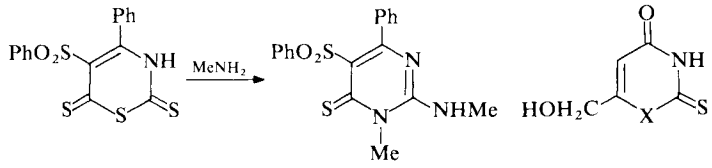


The alternative route by *aminolysis of ring sulfur* is illustrated by the conversion of 3-methyl-2-thioxo-2*H*-1,3-thiazin-4(3*H*)-one (**541**) into 1-ethyl-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**542**) (70%) by treatment with ethylamine;[2035] of 2-thioxo-2*H*-1,3-thiazin-4(3*H*)-one into 1-tetrahydropyran-2'-yloxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**543**) (21%), by treatment



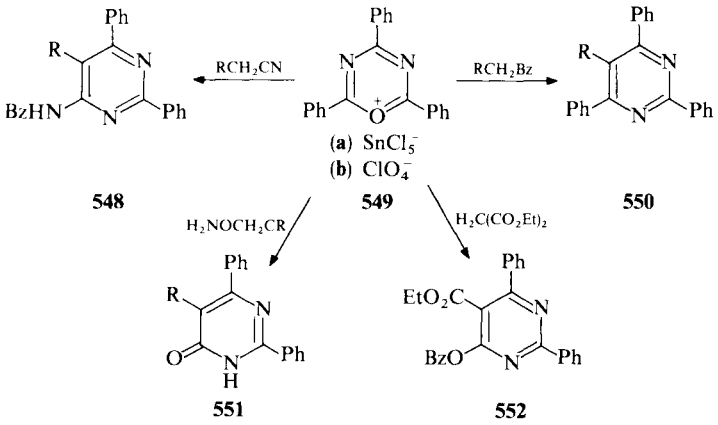
541 542 543 544

with tetrahydropyran-2-yloxyamine in dimethylformamide containing triethylamine, followed by acidic hydrolysis to 1-hydroxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (82%);[3274] of 2,4-diphenyl-6*H*-1,3-thiazine-6-thione (**544**, X = S) into 3-butyl-2,6-diphenyl-4(3*H*)-pyrimidinethione (**544**, X = NBu) (81%) by heating with methanolic butylamine;[3746] of 4-phenyl-5-phenylsulfonyl-2*H*-1,3-thiazine-2,6(3*H*)-dithione (**545**) into the 3-methyl-2-methylamino-6-phenyl-5-phenylsulfonyl-4(3*H*)-pyrimidinethione (**546**) (33%) by aqueous ethanolic methylamine at 20°;[63] of 6-hydroxymethyl-2-thioxo-2*H*-1,3-thiazin-4(3*H*)-one (**547**, X = S) into 1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**547**, X = NMe) (39%) by the action of hot aqueous methylamine;[2888] and other such reactions.[2839,3423,6415]



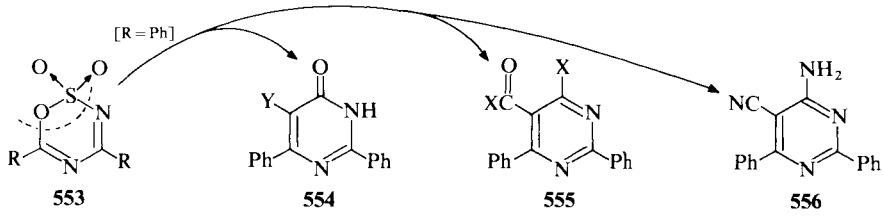
545 546 547

A 1,3,5-oxadiazine as substrate. The combination of benzonitrile (2 mol), benzoyl chloride (1 mol), and stannic chloride (1 mol) readily gave 2,4,6-triphenyl-1,3,5-oxadiazin-1-ium chloride as its stannic chloride complex (**549a**) from which the perchlorate (**549b**) was easily made.[4516] The complex (**549a**) with malononitrile, methyl 2-cyanoacetate, or 2-benzoylacetonitrile in dioxane containing triethylamine gave 4-benzamido-2,6-diphenyl-5-pyrimidinecarbonitrile (**548**, R = CN) (95%), methyl 4-benzamido-2,6-diphenyl-5-pyrimidinecarboxylate (**548**, R = CO_2Me) (86%), or 4-benzamido-5-benzoyl-2,6-diphenylpyrimidine (**548**, R = Bz) (66%), respectively.[4523] Likewise, the perchlorate (**549b**) with ethyl benzoylacetate or dibenzoylmethane gave ethyl 2,4,6-triphenyl-5-pyrimidinecarboxylate (**550**, R = CO_2Et) (76%) or 5-benzoyl-2,4,6-triphenylpyrimidine (**550**, R = Bz) (69%), respectively.[4524] The perchlorate (**549b**) with 2-benzoylacetonitrile gave a separable mixture of 2,4,6-triphenyl-5-pyrimidinecarbonitrile (**550**, R = CN) (28%) and 4-benzamido-5-benzoyl-2,6-diphenylpyrimidine (**548**, R = Bz);[4524] 2-cyanoacetamide gave 4-oxo-2,6-diphenyl-3,4-dihydro-5-pyrimidinecarbonitrile (**551**, R = CN) (45%);[4524] 2-benzoylacetamide gave 5-benzoyl-2,6-diphenyl-4(3*H*)-pyrimidinone (**551**,

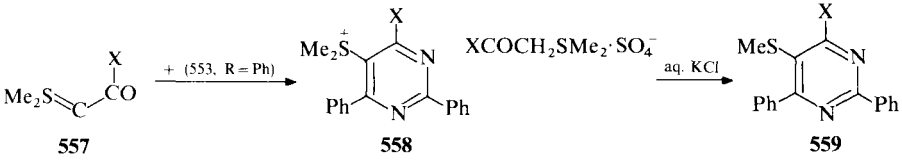


R = Bz) (88%);[4524] and diethyl malonate gave ethyl 4-benzoyloxy-2,6-diphenyl-5-pyrimidinecarboxylate (**552**) (12%).[4524] Although the mechanism must involve at least ring fission, addition of the methylene compound, and recyclization, details of the individual processes have not been determined.

1,2,3,5-Oxathiadiazines as substrates. 4,6-Diphenyl-1,2,3,5-oxathiadiazine 2,2-dioxide (**553**, R = Ph) and its 4,6-di-*p*-tolyl homolog (**553**, R = C_6H_4Me-*p*) are easily made from sulfur trioxide with benzonitrile or *p*-toluonitrile, respectively.[4527] These products reacted with several methylene compounds to afford pyrimidines. Thus the substrate (**553**, R = Ph) and diethyl sodiomalonate in dioxane gave ethyl 4-oxo-2,6-diphenyl-3,4-dihydro-5-pyrimidinecarboxylate (**554**, Y = CO_2Et) (82%); with ethyl sodioacetoacetate in an excess of the ester it gave 5-acetyl-2,6-diphenyl-4(3*H*)-pyrimidinone (**554**, Y = Ac) (65%); and with other appropriate methylene compounds in 1-methylpyrrolidin-2-one containing sodium methoxide it gave 4-oxo-2,6-diphenyl-3,4-dihydro-5-pyrimidinecarbonitrile (**554**, Y = CN) (63%), 5-nitro-2,6-diphenyl-4(3*H*)-pyrimidinone (**554**, Y = NO_2) (60%), 5-acetyl-4-methyl-2,6-diphenylpyrimidine (**555**, X = Me) (51%), 5-benzoyl-2,4,6-triphenylpyrimidine (**555**, X = Ph) (51%), or 4-amino-2,6-diphenyl-5-pyrimidinecarbonitrile (**556**) (44%).[4451] Likewise, the substrate (**553**, R = C_6H_4Me-*p*) gave 4-oxo-2,6-di-*p*-tolyl-3,4-dihydro-5-pyrimidinecarbonitrile (65%), 5-acetyl-4-methyl-2,6-di-*p*-tolylpyrimidine (46%), and 4-amino-2,6-di-*p*-tolyl-5-pyrimidinecarbonitrile (53%).[4451]



In a rather similar way, the substrate (**553**, R = Ph) reacted with the carbonyl-stabilized sulfur ylide (**557**, X = Ph) to afford the product (**558**, X = Ph) (77%), which on treatment in hot potassium chloride solution gave 5-methylthio-2,4,6-triphenylpyrimidine (**559**, X = Ph) (32%); 4-*p*-bromophenyl-5-methylthio-2,6-diphenylpyrimidine (**559**, X = C_6H_4Br-*p*) (57% overall) and several analogs were made likewise.[4526]

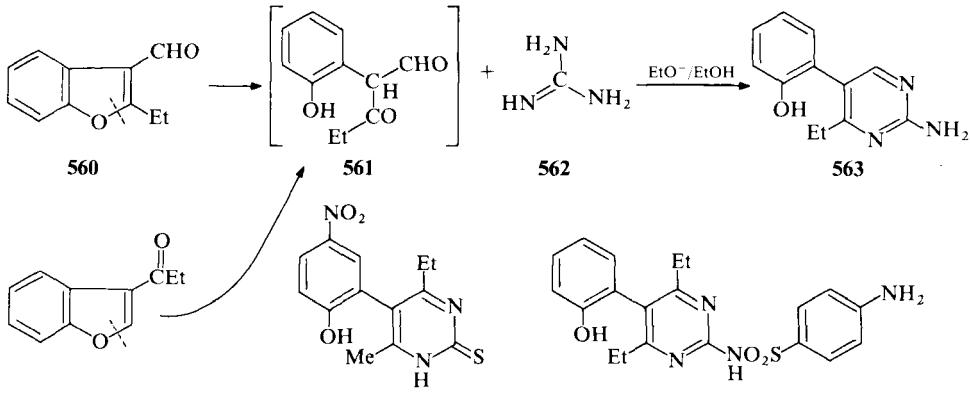


557 **558** **559**

2.6.3. Pyrimidines from Heterobicyclic Systems with a Five- and a Six-Membered Ring

There are more than 30 such systems from which pyrimidines have been obtained by appropriate degradation: only the important routes from these will be discussed in any detail.

Benzofurans as substrates. Benzofurans which bear a cyano, acyl, carboxy, alkoxycarbonyl, or carbamoyl substituent in the 3-position condense with amidines, guanidine, thiourea or urea in ethanolic ethoxide to afford a variety of 5-*o*-hydroxyphenylpyrimidines:[6224] in essence, the process amounts to a Principal synthesis in which the three-carbon fragment (with attached groups) is supplied by ring fission of the furan ring. For example, 2-ethyl-3-benzofurancarbaldehyde (**560**) or 3-propionylbenzofuran (**564**) reacted as the same *β*-aldehydo ketone (**561**) with guanidine (**562**) to give 4-ethyl-5-*o*-hydroxyphenyl-2-pyrimidinamine (**563**) (65% or 50%, respectively).[4528] Appropriate variations likewise gave the following products.



560 **561** **562** **563**

564 **565** **566**

4,6-Diethyl-5-*o*-hydroxyphenyl-2-pyrimidinamine (68%).[4528,4529]

4-Ethyl-5-*o*-hydroxyphenyl-2-methylpyrimidine (47%).[4525]

6-Ethyl-5-*o*-hydroxyphenyl-2,4-pyrimidinediamine (59%).[4528,4529]

2-Amino-6-ethyl-5-*o*-hydroxyphenyl-4(3*H*)-pyrimidinone (53%).[4528,4529]

5-*o*-Hydroxyphenyl-4-methyl-6-phenyl-2(1*H*)-pyrimidinethione (59%).[4528]

4,6-Diethyl-5-*o*-hydroxyphenyl-2(1*H*)-pyrimidinone (9%).[4528]

2-Cyanoamino-4,6-diethyl-5-*o*-hydroxyphenylpyrimidine (56%).[4530]

4-Ethyl-5-(2′-hydroxy-5′-nitrophenyl)-6-methyl-2(1*H*)-pyrimidinethione (**565**) (80%).[4531]

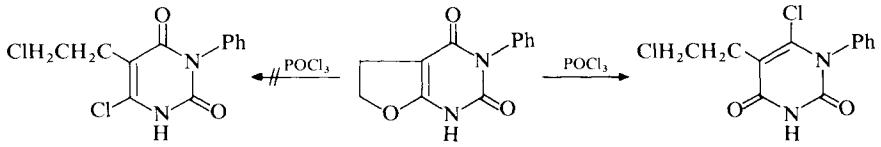
5-(3′-Bromo-6′-hydroxyphenyl)-4-ethyl-2-methyl-6-phenylpyrimidine (70%).[4532]

4,6-Diethyl-5-*o*-hydroxyphenyl-2-sulfanilamidopyrimidine (**566**) (75%).[4533]

4-Ethyl-5-(2′-hydroxy-5′-methoxyphenyl)-6-methyl-2(1*H*)-pyrimidinone (34%).[4534]

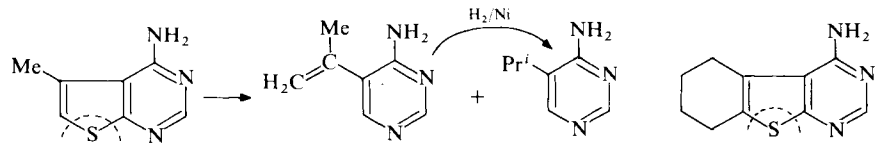
And many others reported in the same references.

Furo[2,3-d]pyrimidines as substrates. Treatment of 3-phenyl-5,6-dihydrofuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**568**) with phosphoryl chloride gave 6-chloro-5-β-chloroethyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**569**) (65%),[4536] rather than the 3-phenyl isomer (**567**) as first reported;[4537] the mechanism has been rationalized satisfactorily.[4536] Several analogs, such as 6-chloro-1-*p*-chlorophenyl-5-β-chloropropyl-2,4(1*H*,3*H*)-pyrimidinedione (55%), were made similarly.[4535,4536]



567 **568** **569**

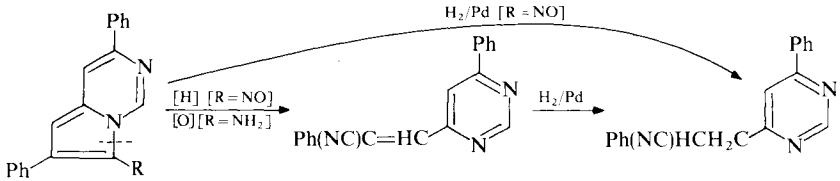
Thieno[2,3-d]pyrimidines as substrates. Desulfurization of such thienopyrimidines with Raney-nickel affords pyrimidines. Thus 5-methylthieno[2,3-*d*]-pyrimidinamine (**570**) with an excess of Raney-nickel in refluxing ethanol gave a mixture of 5-isopropenyl- (**571**) and 5-isopropyl-4-pyrimidinamine (**572**), which on hydrogenation gave the pure product (**572**) (> 51%);[3311,3312] 5,6-tetramethylenethieno[2,3-*d*]pyrimidin-4-amine (**573**) gave a separable mixture



570 **571** **572** **573**

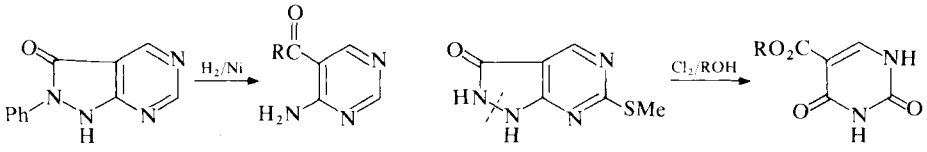
of 5-cyclohex-1′-enyl- and 5-cyclohexyl-4-pyrimidinamine;[3312] 2-phenylthieno-[2,3-*d*]pyrimidin-4(3*H*)-one gave 2-cyclohexyl-5-ethyl-4(3*H*)-pyrimidine (note reduction of the phenyl group);[4125] and 2-piperidinomethyl-5,6-tetramethylenethieno[2,3-*d*]pyrimidin-4(3*H*)-one gave 5-cyclohexyl-2-piperidinomethyl-4(3*H*)-pyrimidinone (57%).[4537]

Pyrrolo[1,2-c]pyrimidines as substrates. A few of these pyrrolopyrimidines have been degraded to pyrimidines. Thus 7-nitroso-3,6-diphenylpyrrolo[1,2-*c*]pyrimidine (**574**, R = NO) underwent reductive cleavage by cyclohexene/palladium under reflux to give 4-β-cyanostyryl-6-phenylpyrimidine (**575**) (68%); paradoxically, 7-amino-3,6-diphenylpyrrolo[1,2-*c*]pyrimidine (**574**, R = NH_2) was oxidized by lead tetracetate or dehydrogenated by palladium–charcoal (without hydrogen) to give the same product (**575**) (71% or 64%, respectively).[4538,4539] Catalytic hydrogenation of the styryl compound (**575**) or the nitroso compound (**574**, R = NO) gave 4-β-cyanophenethyl-6-phenylpyrimidine (**576**) (86% or < 5%, respectively).[4539] Several other examples have been reported.[4539,4540]



574 **575** **576**

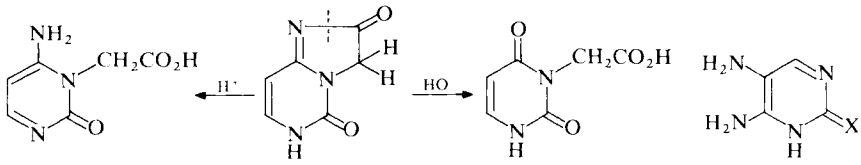
Pyrazolo[3,4-d]pyrimidines as substrates. There are several useful syntheses of pyrimidine-5-carboxylic acid derivatives from pyrazoles via pyrazolopyrimidines. For example, the easily made 2-phenyl-1-*H*-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one (**577**) was converted by hydrogenation at 150° over Raney-nickel into 4-amino-*N*-phenyl-5-pyrimidinecarboxanilide (**578**, R = NHPh) (25%) and thence by alkaline hydrolysis into 4-amino-5-pyrimidinecarboxylic acid (**578**, R = OH) (62%);[1634] 6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one (**579**) was oxidized by chlorine in water, ethanol, or butanol to give, respectively, 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (**580**, R = H) (55%), the ethyl ester (**580**, R = Et) (65%), or the butyl ester (**580**, R = Bu) (62%);[3007] and 1-phenyl- or 4-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine in aqueous dimethyl sulfoxide containing sodium hydroxide gave 4-anilino-5-pyrimidinecarbonitrile (61%) or its 6-methyl derivative (59%), respectively.[40,539]



577 **578** **579** **580**

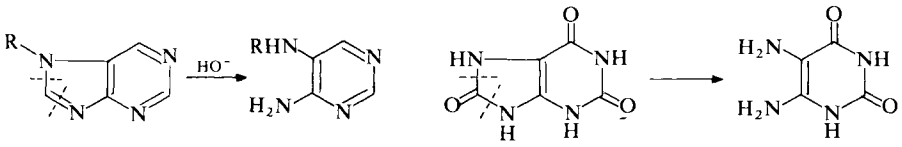
Imidazo[1,2-a]pyrimidines as substrates. Although of little practical importance, the conversion of imidazo[1,2-*a*]pyrimidin-5(1*H*)-one or the isomeric imidazo[1,2-*a*]pyrimidin-7(8*H*)-one into 2-amino-4(3*H*)-pyrimidinone can be achieved in >80% yield by oxidation with lead tetraacetate followed by mild alkaline hydrolysis.[6740]

Imidazo[1,2-c]pyrimidines as substrates. The only reported simple examples in this category appear to be the degradations of imidazo[1,2-*c*]pyrimidine-2,5(3*H*,6*H*)-dione (**582**) [itself made from 4-α-chloroacetamido-2(1*H*)-pyrimidinone] in dilute hydrochloric acid to give 4-amino-3-carboxymethyl-2(3*H*)-pyrimidinone (**581**) (~45%) or in dilute alkali to give 3-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (**583**) (~45%).[995]



581 **582** **583** **584**

Imidazo[4,5-d]pyrimidines (purines) as substrates. Although the majority of purines are made from pyrimidines, some of the reported degradations of purines to pyrimidines are, in fact, useful.[5858] For example, the hydrolyses of 2(3*H*)-purinone, 2(3*H*)-purinethione, 2-methylthiopurine, or 9-methylpurine into 4,5-diamino-2(1*H*)-pyrimidinone (**584**, X = O) (25%), 4,5-diamino-2(1*H*)-pyrimidinethione (**584**, X = S), 2-methylthio-4,5-pyrimidinediamine, or 4-methylamino-5-pyrimidinamine (>95%), respectively, were preparatively useless because the pyrimidines produced were the very ones used to make the purine substrates.[681] In contrast, 7-methylpurine (**585**, R = Me) was made easily from 2-methylaminoacetonitrile with formamidine acetate in formamide, and its subsequent alkaline hydrolysis afforded 5-methylamino-4-pyrimidinamine (**586**, R = Me) (49% overall); likewise, 5-anilino- (**586**, R = Ph) (68%), 5-ethylamino- (**586**, R = Et) (49%), and 5-β-hydroxyethylamino-4-pyrimidinamine (**586**, R = CH_2CH_2OH) (27%) were made via appropriate 7-substituted purines.[2977] Another useful procedure was the degradation of uric acid (**587**) (readily available from natural sources) to 5,6-diamino-2,4(1*H*,3*H*)-pyrimidinedione (**588**), a valuable intermediate for subsequent conversion into purines and pteridines:[598, cf. 588,599,643] an initial digestion of uric acid (**587**) in pyridine–acetic anhydride apparently gave 7-acetyluric acid and thence 8-acetoxy-7-acetyl-8-methyl-7,8-dihydro-2,6(1*H*,3*H*)-purinedione, known as the triacetate because it was first thought to be the isomeric triacetyl derivative of the final product (**588**); alkaline hydrolysis of the purified triacetate gave mainly 5-acetamido-4-amino-2,4(1*H*,3*H*)-pyrimidinedione, known as the monoacetate, and subsequent treatment of this crude product with methanolic hydrochloric acid gave the final product (**588**), as hydrochloride. The foregoing modified procedure proved more satisfactory[4541] than those originally published.



585 586 587 588

The use of purines as substrates for pyrimidine syntheses is further illustrated in the following transformations.

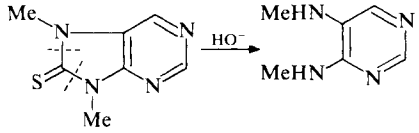
Regular purines

Uric acid (**587**) into 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (alloxan) by oxidation with nitric acid.[1656] potassium chlorate,[1138,4542] or chlorine;[4543] or into 5-amino-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (64%) by treatment with ammonium hydrogen sulfide.[1137,1163]

8-Trifluoromethyl-2(3*H*)-purinone into 4-amino-5-α,α,α-trifluoroacetamido-2(1*H*)-pyrimidinone by mild acidic hydrolysis.[1291]

6,9-Dimethyl-2-methylthiopurine into 4-methyl-6-methylamino-2-methylthio-5-pyrimidinamine (94%) in aqueous alkali.[601]

7,9-Dimethyl-8(7*H*)-purinethione (**589**) into 4,5-bismethylaminopyrimidine (**590**) (68%) in aqueous ethanolic alkali.[1774]



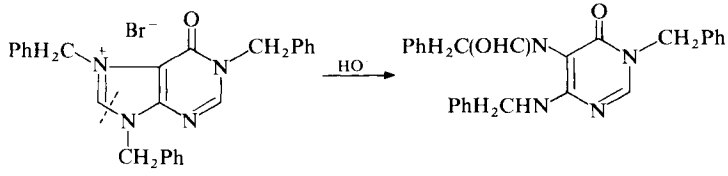
589 590

2-Amino-9-β-D-ribofuranosyl-6(1*H*)-purinone (guanosine) into 2-amino-5-ethoxycarbonylamino-6-β-D-ribofuranosylamino-4(3*H*)-pyrimidinone (40%) by treatment in warm aqueous buffer with diethyl carbonate.[2894]

Also other cases.[1593,3544,4544–4546]

Quaternized purines

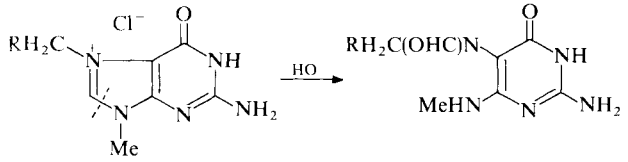
1,7,9-Tribenzyl-6-oxo-1,6-dihydropurinium bromide (**591**) into 3-benzyl-6-benzylamino-5-*N*-benzylformamido-4(3*H*)-pyrimidinone (**592**) (62%) in methanolic alkali at 20°.[4537]



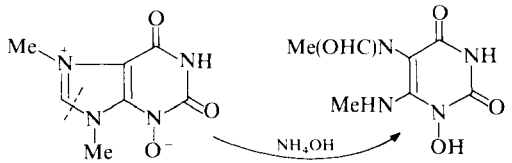
591 592

9-Benzyl-7-methyl-2,6-dioxo-1,2,3,6-tetrahydropurinium *p*-toluenesulfonate into 6-benzylamino-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione (~65%) in alkali; reductive debenzylation and acidic deformylation thence gave 6-amino-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione.[1378]

2-Amino-7-ethoxycarbonylmethyl- (**593**, R = CO_2Et) or 2-amino-7-cyanomethyl-9-methyl-6-oxo-1,6-dihydropurinium chloride (**593**, R = CN) into 2-amino-5-*N*-(carboxymethyl)formamido- (**594**, R = CO_2H) (28%) or 2-amino-5-*N*-(cyanomethyl)formamido-6-methylamino-4(3*H*)-pyrimidinone (**594**, R = CN) (39%), respectively, in mildly alkaline solution.[4549]



593 **594**



595 **596**

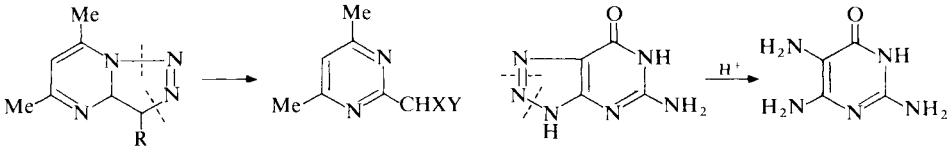
7,9-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurinium-3-olate (**595**) into 1-hydroxy-6-methylamino-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione (**596**) (51%), in aqueous ammonia.[3257]

1,3,9-Trimethyl-2,8-dioxo-2,3,7,8-tetrahydropurinium iodide into 1,3-dimethyl-5-*N'*-methylureido-2,4(1*H*,3*H*)-pyrimidinedione, in aqueous alakli.[4550]

Also other such reactions.[551,1729,2406,2608]

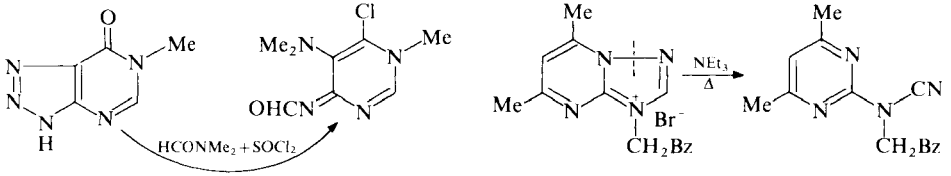
v-Triazolo[1,5-a]pyrimidines as substrates. Bromination of the readily made 5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (**597**, R = H) gave 2-dibromomethyl-4,6-dimethylpyrimidine (**598**, X = Y = Br) (90%) and thence the acetal (**598**, X = Y = OEt) of 4,6-dimethyl-2-pyrimidinecarbaldehyde;[4551] 5,7-dimethyl-3-phenyl-*v*-triazolo[1,5-*a*]-pyrimidine (**597**, R = Ph) in glacial acetic acid or acetyl chloride gave 2-α-acetoxybenzyl- (**598**, X = OAc, Y = Ph) (90%) or 2-α-chlorobenzyl-4,6-dimethylpyrimidine (**598**, X = Cl, Y = Ph) (~90%), respectively;[4044,4552] and 7-oxo-3-phenyl-4,7-dihydro-*v*-triazolo[1,5-*a*]pyrimidine-6-carboxylic acid in glacial acetic acid gave 2-α-acetoxybenzyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid (~90%).[4044]

v-Triazolo[4,5-d]pyrimidines (8-azapurines) as substrates. There are only a few examples of 8-azapurines giving pyrimidines as degradation products:



597 **598** **599** **600**

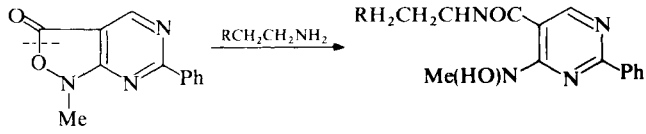
5-amino-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (**599**) in acid gave 2,5,6-triamino-4(3*H*)-pyrimidinone (**600**) (among other products) by an unknown mechanism;[4553] 6-methyl-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (**601**) with thionyl chloride–dimethyl formamide gave a product (41%) formulated on reasonable evidence as 4-chloro-6-formylimino-5-dimethylamino-3-methyl-3,6-dihydropyrimidine (**602**);[2074] and photolysis of 3-phenyl-*v*-triazolo[4,5-*d*]pyrimidine, its 7-chloro derivative, or 3-phenyl-*v*-triazolo[4,5-*d*]pyrimidine-7-carbonitrile in benzene gave 4-anilino-5-phenylpyrimidine, its 6-chloro derivative, or 6-anilino-5-phenyl-4-pyrimidinecarbonitrile, respectively, each as a minor product.[4554]



601 **602** **603** **604**

s-Triazolo[1,5-a]pyrimidines as substrates. Treatment of 5,7-dimethyl-3-phenacyl-*s*-triazolo[1,5-*a*]pyrimidin-3-ium bromide (**603**) in hot acetonitrile containing triethylamine gave 2-(*N*-cyano-*N*-phenacylamino)-4,6-dimethylpyrimidine (**604**) (35%);[200] a rather complicated example has been reported also.[4555]

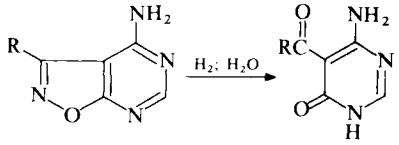
Isoxazolo[3,4-d]pyrimidines as substrates. Although 1-methyl-6-phenylisoxazolo[3,4-*d*]pyrimidin-3(1*H*)-one (**605**) was best made (88%) from ethyl 4-chloro-2-phenyl-5-pyrimidinecarboxylate with *N*-methylhydroxylamine, it proved to be a good substrate for making certain pyrimidinecarboxamides:[4556] thus treatment of (**605**) with neat β-methoxyethylamine or β-dimethylaminoethylamine gave 4-(*N*-hydroxy-*N*-methylamino)-*N*-β-methoxyethyl)- (**606**, R = OMe) (50%) or *N*-(β-dimethylaminoethyl)-4-(*N*-hydroxy-*N*-methylamino)-2-phenyl-5-pyrimidinecarboxamide (**606**, R = NMe_2) (67%), respectively; other



605 **606**

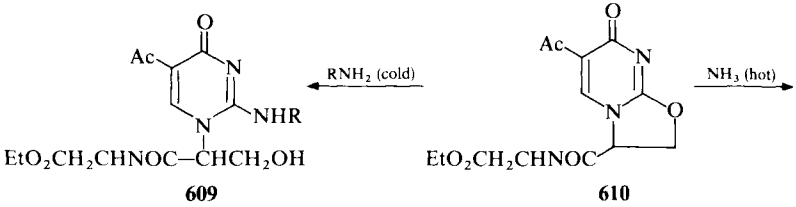
examples were reported,[4556] but much of the method's potential remains unexplored. Quite differently, 3,5,7-trimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione gave 5-acetyl-6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (H_2, Pd, MeOH, 20°: 61%).[776]

Isoxazolo[5,4-d]pyrimidines as substrates. 3-Methyl- (**607**, R = Me) and 3-phenylisoxazolo[5,4-*d*]pyrimidin-4-amine (**607**, R = Ph), which were made easily from appropriate 5-amino-4-isoxazolecarbonitriles, underwent hydrogenolytic cleavage and subsequent hydrolysis to furnish 5-acetyl-6-amino- (**608**, R = Me) (91%) and 6-amino-5-benzoyl-4(3*H*)-pyrimidinone (**608**, R = Ph) (72%), respectively;[777] no other examples appear to have been reported.

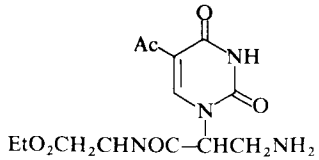


607 **608**

Oxazolo[3,2-a]pyrimidines as substrates. Several 2,3-dihydrooxazolo[3,2-*a*]pyrimidines have been used as convenient substrates for certain isocytosine, uracil, and thiouracil derivatives. Thus 6-acetyl-*N*-ethoxycarbonylmethyl-7-oxo-2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidine-3-carboxamide (**610**) in cold dilute ethanolic ammonia gave 5-acetyl-2-amino-1-[α-(ethoxycarbonylmethylcarbamoyl)-β-hydroxyethyl]-4(1*H*)-pyrimidinone, (**609**, R = H) (~50%), whereas in hot concentrated ethanolic ammonia the product was 5-acetyl-1-[β-amino-α-(ethoxycarbonylmethylcarbamoyl)ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (**611**) (~80%);[4557] the same substrate (**610**) in cold methanolic benzylamine gave 5-acetyl-2-benzylamino-1-[α-(ethoxycarbonylmethylcarbamoyl)-β-hydroxyethyl]-4(1*H*)-pyrimidinone (**609**, R = CH_2Ph) (~50%);[4557] and 6-acetyl-2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (**613**) in methanolic triethylamine or in methanolic triethylamine saturated with hydrogen sulfide gave

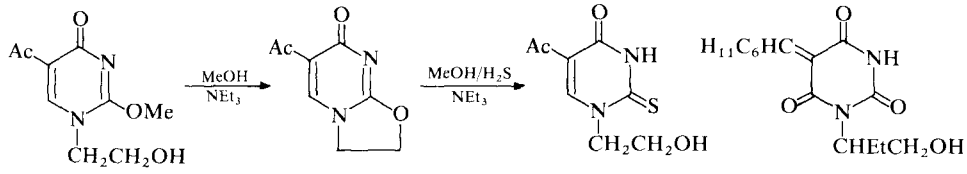


609 **610**



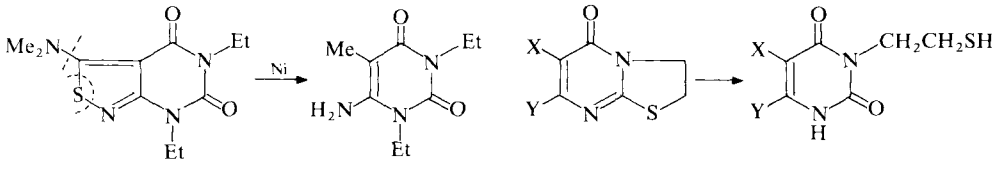
611

5-acetyl-1-β-hydroxyethyl-2-methoxy-4(1*H*)-pyrimidinone (**612**) (~85%) or 5-acetyl-1-β-hydroxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**614**) (~75%).[165] In contrast, treatment of 3-ethyl-7-oxo-2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidine-6-carbonitrile with cyclohexylamine followed by a mild hydrolysis gave 5-cyclohexylaminomethylene-1-α-(hydroxymethyl)propyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**615**) (~40%) by an interesting mechanism.[165]



612 **613** **614** **615**

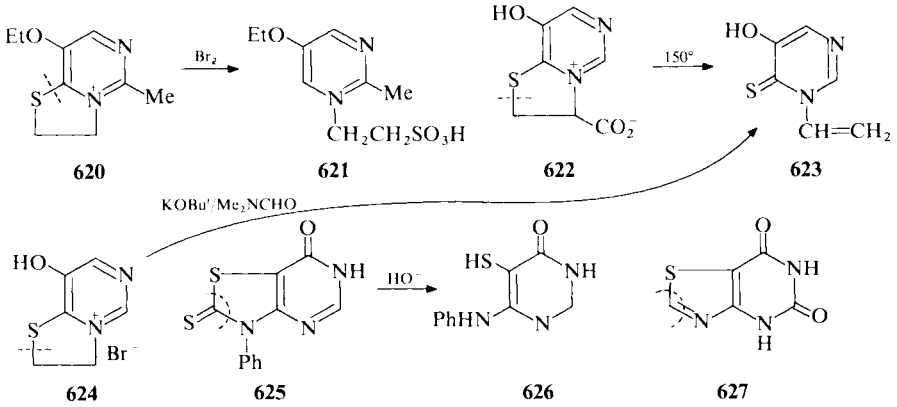
Isothiazolo[3,4-d]pyrimidines as substrates. The use of such substrates has been confined to desulfurizations. Thus treatment of 3-dimethylamino-5,7-diethylisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**616**) with Raney-nickel in refluxing butanol gave 6-amino-1,3-diethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**617**) (86%);[1058] likewise, 7-benzyl-3-ethylaminoisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione gave 6-amino-1-benzyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (49%).[1055]



616 **617** **618** **619**

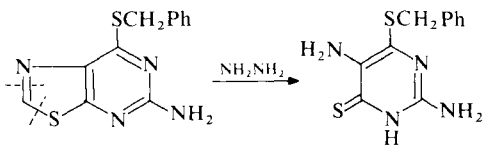
Thiazolo[3,2-a]pyrimidines as substrates. The use of 2,3-dihydro derivatives of such substrates to make 3-β-mercaptoethyl-2,4(1*H*,3*H*)-pyrimidinediones is exemplified in the hydrolysis of 6-phenyl- (**618**, X = Ph, Y = H) or 7-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**618**, X = H, Y = Ph) to afford 3-β-mercaptoethyl-5-phenyl- (**619**, X = Ph, Y = H) (54%) or 3-β-mercaptoethyl-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**619**, X = H, Y = Ph) (78%), respectively;[4548] of 6-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one to afford 1-β-mercaptoethyl-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (70%);[4548] of 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**618**, X = Y = H) to afford 3-β-mercaptoethyl-2,4(1*H*,3*H*)-pyrimidinedione (**619**, X = Y = H) (54%);[3316] and of ethyl 5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**618** X = CO_2Et, Y = H) to afford 1-β-mercaptoethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid (**619**, X = CO_2H, Y = H) (48%).[3316]

Thiazolo[3,2-c]pyrimidines as substrates. As in the preceding category, only 2,3-dihydro substrates have been used to make pyrimidines. For example, 8-ethoxy-5-methyl-2,3-dihydrothiazolo[3,2-*c*]pyrimidin-4-ium bromide (**620**) underwent oxidative ring fission in hot ethanolic bromine to give 5-ethoxy-2-methyl-3-β-sulfoethyl-4(3*H*)-pyrimidinone (**621**) (40%);[1821] 8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidin-4-ium-3-carboxylate (**622**) underwent decarboxylative fission at 150° to give 5-hydroxy-3-vinyl-4(3*H*)-pyrimidinethione (**623**) (65%);[60] 8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidin-4-ium bromide (**624**) with potassium *t*-butoxide in anhydrous dimethylformamide at 20° gave the same product (**623**) (60%);[60] and analogs were made similarly.[60]

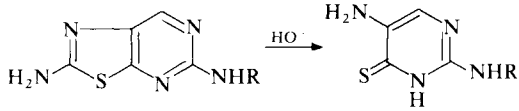


Thiazolo[4,5-d]pyrimidines as substrates. Since these substrates are easily made from thiazoles, they offer potential for degradation to 5-pyrimidinethiols. Thus 3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (**625**) in hot alkali. (with exclusion of air) gave 6-anilino-5-mercapto-4(3*H*)-pyrimidinone (**626**) (85%);[4558] likewise, thiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**627**) in hot alkali for 1 min gave 6-amino-5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (86%).[837]

Thiazolo[5,4-d]pyrimidines as substrates. Although often made from pyrimidines,[1195,3176] these substrates do offer a little-used route to 4-pyrimidinethiones. For example, treatment of 7-benzylthiothiazolo[5,4-*d*]pyrimidin-5-amine (**628**) with hydrazine in hot dioxane rather surprisingly gave 2,5-diamino-6-benzylthio-4(3*H*)-pyrimidinethione (**629**) (27%);[1301] more logically, thiazolo-[5,4-*d*]pyrimidine-2,5-diamine (**630**, R = H) or 5-ethylaminothiazolo[5,4-*d*]-

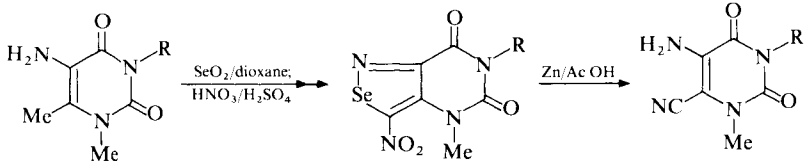


pyrimidin-2-amine (**630**, R = Et) in hot alkali gave 2,5-diamino- (**631**, R = H) (95%) or 5-amino-2-ethylamino-4(3*H*)-pyrimidinethione (**631**, R = Et) (98%), respectively.[1195]



630 **631**

Isoselenazolo[4,3-d]pyrimidines as substrates. Treatment of 5-amino-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**632**, R = Me) with selenium dioxide and a subsequent nitration of the product gave 4,6-dimethyl-3-nitroisoselenazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**633**, R = Me) in low yield;[3731] reduction of this material with zinc in acetic acid afforded 5-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**634**, R = Me) (31%), an overall sequence resulting in the replacement of the 6-methyl group in the original pyrimidine (**632**, R = Me) by a cyano group.[3731] 5-Amino-1-ethyl- (**634**, R = Et) (86%) and 5-amino-1-isopropyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**634**, R = Pr^i) (56%) were made similarly,[3731] but the reaction was not developed further.



632 **633** **634**

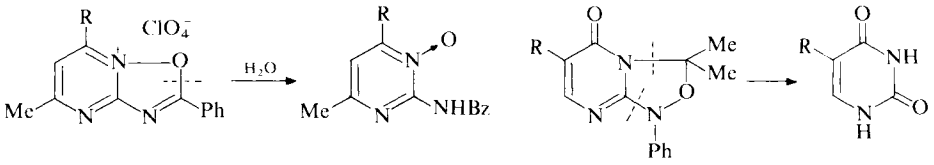
1,3,2-Diazaphospholo[4,5-d]pyrimidines as substrates. Such a substrate, 2,2,7-trichloro-3-phenyl-2,2-dihydro-1,3,2-diazaphospholo[4,5-*d*]pyrimidine, was made easily from 4-anilino-6-chloro-5-pyrimidinamine (PCl_5, PhCl, 120°, 2 h: 81%); on treatment with piperidine in benzene at 70°, this gave the 7-chloro-3-phenyl-2,2-dipiperidino analog (90%), which underwent hydrolytic ring fission in refluxing aqueous ethanol to give 4-anilino-6-chloro-5-(dipiperidinophosphinyl)aminopyrimidine (84%).[6245]

[1,2,3]Oxadiazolo[5,4-d]pyrimidines as substrates. The easily made 5-amino[1,2,3]oxadiazolo[5,4-*d*]pyrimidine-7-carbaldehyde *p*-nitrophenylhydrazone was converted into 2-amino-5-iodo-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde *p*-nitrophenylhydrazone (87%) by boiling with aqueous hydriodic acid for 90 min;[4937] another example is given in Section 6.5.2.

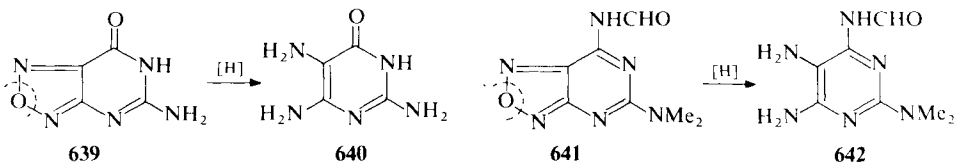
[1,2,4]Oxadiazolo[2,3-a]pyrimidines as substrates. 5,7-Dimethyl-2-phenyl- (**635**, R = Me) or 5-methyl-2,7-diphenyl[1,2,4]oxadiazolo[2,3-*a*]pyrimidin-8-ium perchlorate (**635**, R = Ph), easily made from an appropriate 1,2,4-oxadiazol-3-amine, underwent slow hydrolytic fission in aqueous acetonitrile to afford

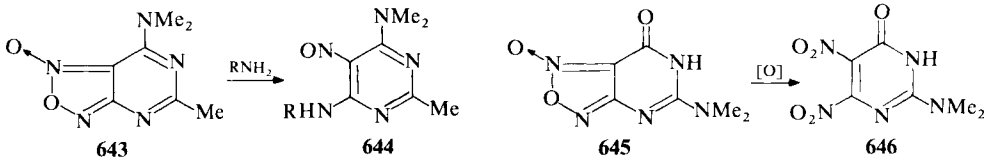
2-benzamido-4,6-dimethyl- (**636**, R = Me) (70%)[291] or 2-benzamido-4-methyl-6-phenylpyrimidine 1-oxide (**636**, R = Ph) (85%),[313] respectively.

[1,2,4]Oxadiazolo[4,3-a]pyrimidines as substrates. Ethyl 3,3-dimethyl-5-oxo-1-phenyl-1,5-dihydro-3*H*-[1, 2, 4]oxadiazolo[4,3-*a*]pyrimidine-6-carboxylate (**637**, R = CO_2Et), which was easily made in poor yield from an appropriate 1,2,4-oxadiazoline, underwent hydrolytic degradation in hot dilute acid to give (in several stages?) 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (**638**, R = CO_2H);[4559] the closely related 3,4-dimethyl-5-oxo-1-phenyl-1,5-dihydro-3*H*-[1,2,4]oxadiazolo[4,3-*a*]pyrimidine-6-carbonitrile (**637**, R = CN) was probably involved as an unisolated intermediate in a preparation of 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**638**, R = CN).[4559]



[1,2,5]Oxadiazolo[3,4-d]pyrimidines as substrates. Certain such oxadiazolopyrimidines have been useful for the preparation of pyrimidines as purine or pteridine intermediates. Thus 5-amino[1,2,5]oxadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (**639**) was hydrogenated to give 2,5,6-triamino-4(3*H*)-pyrimidinone (**640**) (61%);[403] 5-dimethylamino-7-formamido[1,2,5]oxadiazolo[3,4-*d*]-pyrimidine (**641**) similarly gave 2-dimethylamino-6-formamido-4,5-pyrimidinediamine (**642**) (80%);[2620] 5-phenyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidin-7-amine underwent zinc in acetic acid reduction to give 5-acetamido-2-phenyl-4,6-pyrimidinediamine (53%);[2620] and 7-(β,β-diethoxyethyl)amino-5-phenyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine was converted by hydrogenation at room temperature into 6-(β,β-diethoxyethyl)amino-2-phenyl-4,5-pyrimidinediamine (62%).[4560] The same system has proven invaluable in making certain nitroso- or nitropyrimidines not otherwise available easily. For example, 7-dimethylamino-5-methyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxide (**643**) reacted with ammonia or aniline to give 6-dimethylamino-2-methyl-5-nitroso-4-pyrimidine (**644**, R = H) (44%) or 4-anilino-6-dimethylamino-2-methyl-5-nitrosopyrimidine (**644**, R = Ph) (80%), respectively;[1733] also, 5-dimethylamino[1,2,5]oxadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one 1-oxide (**645**) underwent oxidation by manganese dioxide in dimethylformamide to afford a

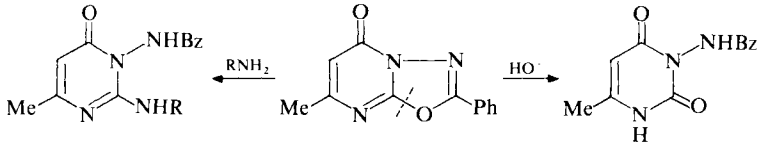




643 644 645 646

product formulated as 2-dimethylamino-5,6-dinitro-4(3*H*)-pyrimidinone (**646**) (>54%).[2615] 7-Methoxy[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 3-oxide with methoxide ion gave 2,4-dimethoxy-6-nitro-5-pyrimidinamine (32% of proven structure) by an unusual mechanism.[6196]

[*1,3,4*]*Oxadiazolo*[*3,2-a*]*pyrimidines as substrates.* 7-Methyl-2-phenyl-5*H*-[1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one (**648**) was heated briefly with neat butylamine or aniline to give 3-benzamido-2-butylamino- (**647**, R = Bu) (60%) or 2-anilino-3-benzamido-6-methyl-4(3*H*)-pyrimidinone (**647**, R = Ph) (71%), respectively;[4561] the same substrate (**648**) heated briefly with aqueous alkali gave 3-benzamido-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**649**) (72%);[1169] ethyl-2-methyl-5-oxo-5*H*-[1,3,4]oxadiazolo[3,2-*a*]pyrimidine-6-carboxylate (**650**) in alkali likewise gave ethyl 1-acetamido-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (95%);[1169] and analogous examples have been reported.[1169,4561] Deacylation of the foregoing products constitutes a good route to some *N*-aminopyrimidines.



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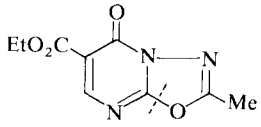

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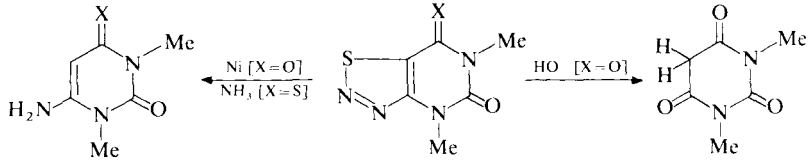
[*1,2,3*]*Thiadiazolo*[*4,5-d*]*pyrimidines as substrates.* The use of such substrates is illustrated by the conversion of 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**652**, X = O) into 6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**651**, X = O) (60%) by desulfurization with Raney-nickel or into 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**653**) (20%) by alkaline hydrolysis;[1134] also of 4,6-dimethyl-7-thioxo-6,7-dihydro[1,2,3]-thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (**652**, X = S) into 4-amino-1,3-dimethyl-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone (**651**, X = S) (94%) by heating in ethanolic ammonia.[1134] The scope of this reaction seems quite limited.



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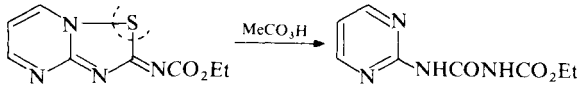
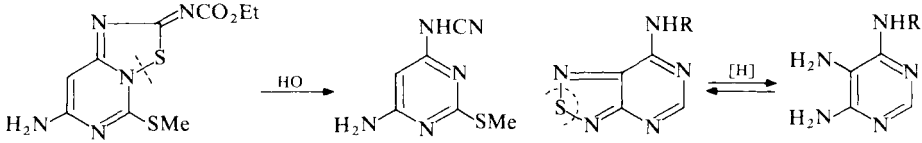
A [1,2,4]Thiadiazolo[2,3-a]pyrimidine as substrate. Only one example in this category appears to be known. 2-Ethoxycarbonylimino-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine (**654**) underwent peroxyacetic acid oxidation to give 2-(*N'*-ethoxycarbonylureido)pyrimidine (**655**) (63%).[497]



654 655

A [1,2,4]Thiadiazolo[2,3-c]pyrimidine as substrate. This category is also confined to a single example: 2-ethoxycarbonylimino-5-methylthio-2*H*-[1,2,4]-thiadiazolo[2,3-*c*]pyrimidin-7-amine (**656**) underwent alkaline hydrolysis to 6-cyanoamino-2-methylthio-6-pyrimidinamine (**657**) (26%).[497]



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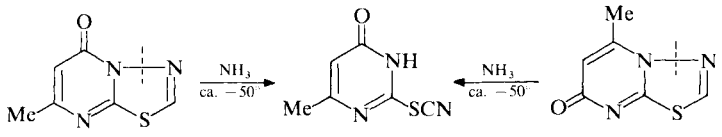
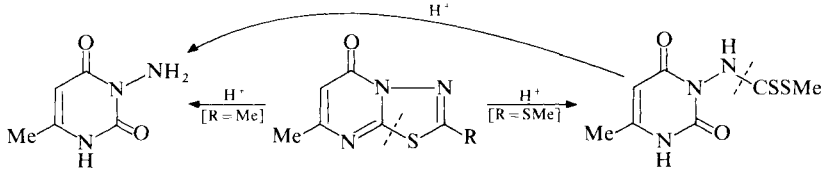
[1,2,5]Thiadiazolol[3,4-d]pyrimidines as substrates. Reductive cleavage of 7-butylamino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (**658**, R = Bu) gave 6-butylamino-4,5-pyrimidinediamine (**659**, R = Bu) (70%), from which the bicyclic compound (**658**, R = Bu) was most easily made in the first place.[4562] However, the same bicyclic compound (**658**, R = Bu) could also be made by transamination of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7-amine (**658**, R = H), which was easily prepared from commercial 4,5,6-pyrimidinetriamine (**659**, R = H). 7-Anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (**658**, R = Ph) underwent reductive cleavage by lithium aluminum hydride to 6-anilino-4,5-pyrimidinediamine (**659**, R = Ph) (70%);[2448] and [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7-amine (**658**, R = H) in pyridine with hydrogen sulfide gave 5,6-diamino-4(3*H*)-pyrimidinethione in poor yield.[2448]

[1,3,4]Thiadiazolo[3,2-a]pyrimidines as substrates. 7-Methyl-5*H*-[1,3,4]-thiadiazolo[3,2-*a*]pyrimidin-5-one (**660**) or 5-methyl-7*H*-[1,3,4]thiadiazolo-[3,2-*a*]pyrimidin-7-one (**662**) with very cold methanolic ammonia



660 661 662

gave 6-methyl-2-thiocyanato-4(3*H*)-pyrimidinone (**661**) (86% or 70%, respectively).[4565] Although the first of these reactions was reported to occur also in aqueous alkali at 20°,[3516] it appeared later that the use of such alkali on either substrate gave, in fact, 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (70–72%);[4565] the substrate (**660**) with methanolic hydrochloric acid also gave the same product exclusively.[1488] The presence of a 2-substituent in the substrate altered the reaction: for example, 2,7-dimethyl- (**664**, R = Me) or 7-methyl-2-methylthio-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (**664**, R = SMe) in hot dilute acid gave mainly 3-amino-6-methyl- (**663**) or 6-methyl-3-methylthio(thiocarbonyl)amino-2,4(1*H*,3*H*)-pyrimidinedione (**665**) (61%), respectively; the product (**665**) was eventually converted into its 3-amino analog (**663**).[1488]



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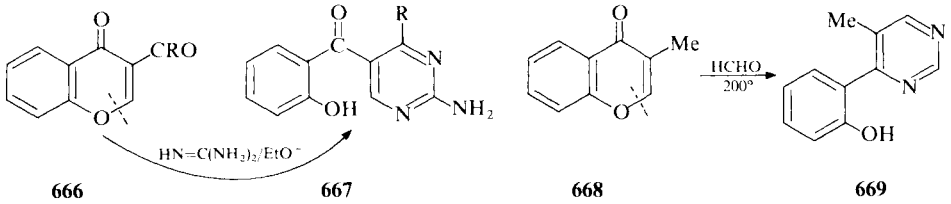
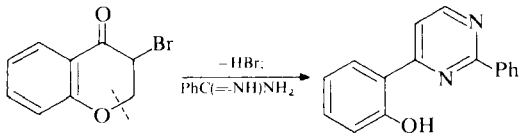
2.6.4. Pyrimidines from Heterobicyclic Systems with Two Six-Membered Rings

At present there are 13 such systems from which pyrimidines have been obtained by partial degradation: the less important of these routes are dismissed briefly.

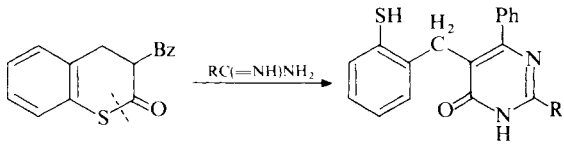
Benzo[b]pyrans (chromenes) as substrates. Some chromenes have been used (as were benzofurans; see Section 2.6.3) to supply in essence the three-carbon fragment for a Principal Synthesis by initial fission of the pyran ring. Thus 4-oxo-4*H*-chromene-3-carbaldehyde (**666**, R = H) or 3-acetyl-4*H*-chromen-4-one (**666**, R = Me) reacted with guanidine in ethanolic ethoxide to give 5-*o*-hydroxybenzoyl-2-pyrimidinamine (**667**, R = H) (46%) or 5-*o*-hydroxybenzoyl-4-methyl-2-pyrimidinamine (**667**, R = Me) (80%), respectively;[4566] the latter product had been formulated previously as the isomeric 5-acetyl-4-*o*-hydroxyphenyl-2-pyrimidinamine.[4564] The foregoing carbaldehyde (**666**, R = H) with thiourea likewise gave 5-*o*-hydroxybenzoyl-2(1*H*)-pyrimidinethione (32%).[4567] Without a 3-acyl substituent in the substrate, the possibility of an

isomeric product is removed: for example, 3-methyl-4*H*-chromen-4-one (**668**) with formamide at 200° (in place of formamidine; see Section 2.3.3.1) gave 4-*o*-hydroxyphenyl-5-methylpyrimidine (**669**) (60%).[4568] The reduced substrate, 3-bromo-4-chromanone (**670**) with benzamidine, first underwent oxidation by dehydrobromination followed by ring fission and condensation to afford 4-*o*-hydroxyphenyl-2-phenylpyrimidine (**671**).[4569] Many other examples have been reported[2936,3964,4533,4570–4573,6132] but a fundamental disadvantage of the method is the presence of an *o*-hydroxyphenyl substituent in each product.

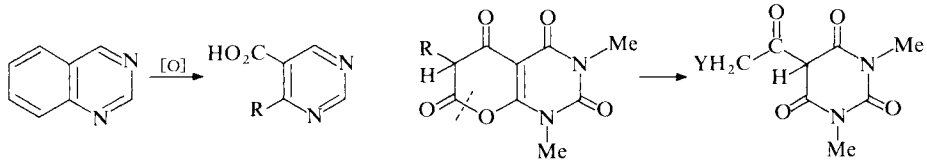




Benzo[b]thiins (*benzo[b]thiopyrans or thiochromenes*) *as substrates.* Much like the foregoing chromenes, the less accessible thiochromenes may be used as substrates in pyrimidine syntheses; each product necessarily carries an *o*-mercaptophenyl substituent. For example, 3-benzoyl(thiochromen-2-one) (**672**) with guanidine in ethanolic ethoxide or with acetamidine in ethanol gave 2-amino-5-*o*-mercaptobenzyl- (**673**, R = NH_2) (75%) or 5-*o*-mercaptobenzyl-2-methyl-6-phenyl-4(3*H*)-pyrimidinone (**673**, R = Me) (70%), respectively.[4574]



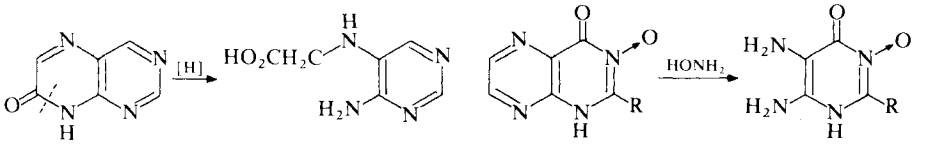
Benzopyrimidines (*quinazolines*) *as substrates.* Because the benzene ring is usually the more stable half of a quinazoline, it is rare to obtain a pyrimidine by partial degradation.[6191] However, oxidation of quinazoline (**674**) with permanganate gave 4,5-pyrimidinedicarboxylic acid (**675**, R = CO_2H) (~60%), from which the more labile 4-carboxy group was removed on distillation *in vacuo* to afford 5-pyrimidinecarboxylic acid (**675**, R = H) (~60%).[3606]



674 675 676 677

Pyrano[2,3-d]pyrimidines as substrates. Treatment of 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with malonic acid or α-methylmalonic acid in acetic anhydride gave 1,3-dimethyl- (**676**, R = H) (33%) or 1,3,6-trimethyl-5*H*-pyrano[2,3-*d*]pyrimidine-2,4,5,7(1*H*,3*H*,6*H*)-tetrone (**676**, R = Me) (43%), respectively;[4576] 1,3-diphenyl-2-thioxo-1,2-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine-4,5,7(3*H*,6*H*)-trione was made rather similarly.[4575] Such bicyclic lactones were readily degraded to pyrimidines, not otherwise easily available. For example, the substrate (**676**, R = H) in boiling ethanol or warm alkali gave 5-α-ethoxycarbonylacetyl- (**677**, Y = CO_2Et) (96%) or 5-acetyl-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**677**, Y = H (90%), respectively;[4576] and the diphenyl substrate in hot aqueous pyridine gave 5-acetyl-1,3-diphenyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (60%).[4575]

Pyrazino[2,3-d]pyrimidines (pteridines) as substrates. The degradation of pteridines may give pyrazines or pyrimidines: pteridines with 2- or 4-substituents tend to afford pyrazines, while those with 6- or 7-substituents usually afford pyrimidines, often the very ones from which they were made originally.[4577] However, a degradative process can be useful if the pteridine had not been made from a pyrimidine or if it had been modified (e.g., methylated) after its formation. Such useful routes are exemplified in the conversion of 7(8*H*)-pteridinone (**678**) into 5-(carboxymethyl)amino-4-pyrimidinamine (**679**) (95%) by dithionite reduction;[3793] 7,8-dihydro-6(5*H*)-pteridinone into 4-(carboxymethyl)amino-5-pyrimidinamine (75%) by alkaline hydrolysis;[4578] 5,8-dimethyl-6,7(5*H*,8*H*)-pteridinedione into 4,5-bismethylaminopyrimidine by alkaline hydrolysis (cf. an analogous preparation from a purine in Section 2.6.3);[1773] and 4(1*H*)-pteridinone 3-oxide (**680**, R = H) or its 2-methyl derivative (**680**, R = Me) into 5,6-diamino-4(1*H*)-pyrimidinone 3-oxide (**681**, R = H) or its 2-methyl derivative (**681**, R = Me) (~70%), respectively, by warming in aqueous hydroxylamine.[2422] Preparatively useless degradations are illustrated in the conversion of 4(3*H*)-pteridinone or its 6-methyl derivative into 5,6-diamino-4-(3*H*)-pyrimidinone (20–40%) (hydrazine hydrate);[4579] 2-methyl- or 2,6-



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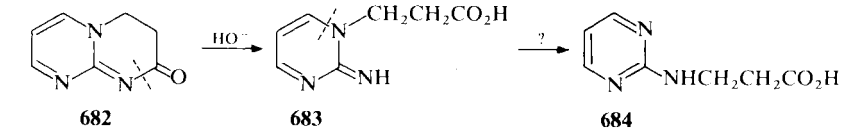
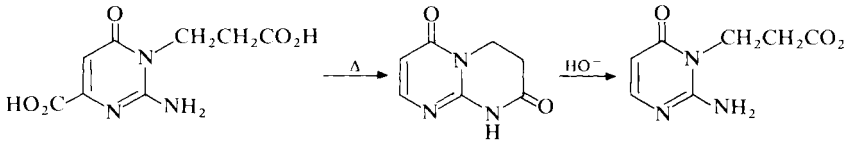
dimethyl-4(3*H*)-pteridinone into 5,6-diamino-2-methyl-4(3*H*)-pyrimidinone (~60%) (hydrazine hydrate);[4579] and in rather similar conversions mediated by hydroxylamine.[2422]

Pyrimido[1,2-a]pyrimidines as substrates. 3,4-Dihydro-2*H*-pyrimido[1,2-*a*]pyrimidine (**682**), easily made from 2-pyrimidinamine, has been reported to undergo hydrolytic fission in aqueous potassium carbonate to give 1-β-carboxyethyl-2(1*H*)-pyrimidinimine (**683**) (~45%), formulated as an isomeric betaine:[2015] the likelihood of Dimroth rearrangement to 2-(β-carboxyethyl)-aminopyrimidine (**684**) was not mentioned. During an attempted thermal 4-decarboxylation of 2-amino-1-β-carboxyethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (**685**), cyclization occurred to give 3,4-dihydro-2*H*-pyrimido[1,2-*a*]pyrimidine-2,6(1*H*)-dione (**686**): however, subsequent alkaline treatment induced ring fission to the required product, 2-amino-3-β-carboxyethyl-4(3*H*)-pyrimidinone (**687**).[982, cf. 3919]

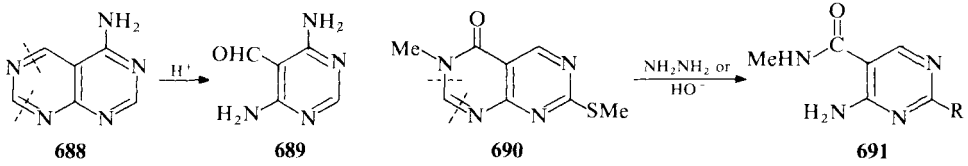


682 **683** **684**



685 **686** **687**

Pyrimido[4,5-d]pyrimidines as substrates. These pyrimidopyrimidines and their dihydro derivatives are proven convenient substrates for the preparation of a few pyrimidines.[6190] Pyrimido[4,5-*d*]pyrimidin-4-amine (**688**), easily made from 4-amino-5-pyrimidinecarbonitrile, underwent hydrolytic fission in hot dilute hydrochloric acid to give 4,6-diamino-5-pyrimidinecarbaldehyde (**689**) (72%);[443] 3-methyl-7-methylthiopyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**690**) in aqueous alkali or ethanolic hydrazine hydrate gave 4-amino-*N*-methyl-2-methylthio- (**691**, R = SMe) (66%) or 4-amino-2-hydrazino-*N*-methyl-5-pyrimidinecarboxamide (**691**, R = $NHNH_2$) (9%);[447] 1,3-dimethylpyrimido-[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**692**) with hydrazine hydrate or aqueous hydroxylamine gave 6-amino-5-hydrazonomethyl- (**693**, R = NH_2) (~90%) or 6-amino-5-hydroxyiminomethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**693**, R = OH) (~70%), respectively;[1097] 2,7-dimethyl- (**694**, R = Me) or 2,7-dipropyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine (**694**, R = Pr) in aqueous ethanolic alkali gave 5-acetamidomethyl-2-methyl- (**695**, R = Me) (63%)[3865] or 5-butyramidomethyl-2-propyl-4-pyrimidinamine (**695**, R = Pr) (47%),[1451] respectively, each of which underwent deacylation easily in ethanolic hydrogen chloride;[1451] and other examples have been reported.[4580] The mechanism of



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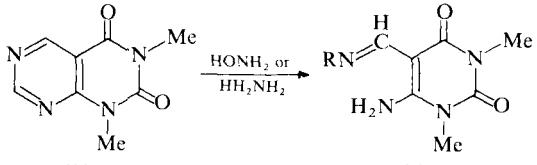

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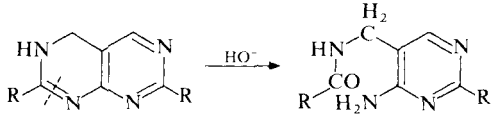
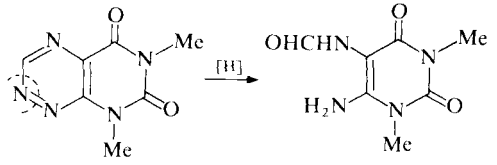


694 695

degradation of pyrimido[4,5-*d*]pyrimidine-2,4-diamine to 2,4,6-triamino-5-pyrimidinecarbaldehyde in acid has been studied by nmr measurements.[5]

Pyrimido[5,4-e]-as- and pyrimido[5,4-d]-v-triazines as substrates. These quite minor routes to pyrimidines are briefly exemplified in the conversion of 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (fervenulin) (**696**) into 6-amino-5-formamido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**697**) (38%) by hydrogenation over Raney-nickel;[1277] of the corresponding 4-oxide (**698**) into 5-acetamido-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**699**) (50%) by boiling in acetic acid–acetic anhydride;[656,6190] and of 6,8-dipiperidino[5,4-*d*]-*v*-triazine 3-oxide into 2,6-dipiperidino-4-pyrimidinecarbaldehyde oxime (Pd/H_2).[6733]



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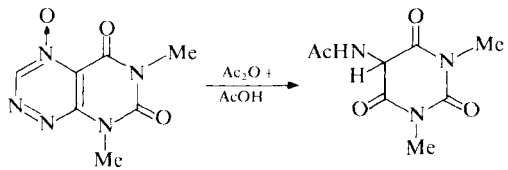

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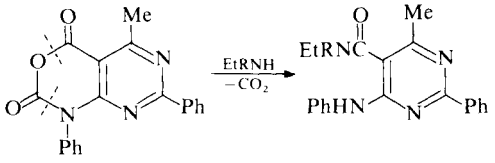
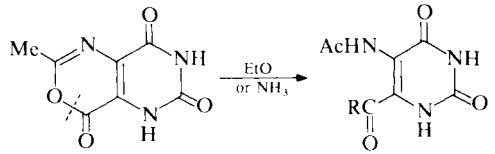
Pyrimido[4,5-d][1,3]oxazines as substrates. Treatment of 5-methyl-1,7-diphenyl-4*H*-pyrimido[4,5-*d*][1,3]oxazine-2,4(1*H*)-dione (**700**) with ethanolic ethylamine at 20° or neat diethylamine under reflux gave 4-anilino-*N*-ethyl- (**701**, R = H) (79%) or 4-anilino-*N*,*N*-diethyl-6-methyl-2-phenyl-5-pyrimidinecarboxamide (**701**, R = Et) (62%), respectively;[166] several substituted-anilino and other analogs were made similarly.[166]



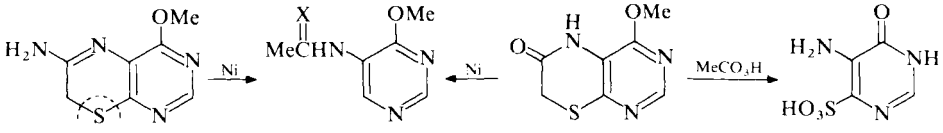
700 **701**

A pyrimido[5,4-d][1,3]oxazine as substrate. Attempts to acetylate 5-amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid afforded 2-methyl-4*H*-pyrimido[5,4-*d*][1,3]oxazine-4,6,8(5*H*,7*H*)-trione (**702**) (91%): this was converted by ethanolic ethoxide or aqueous ammonia into ethyl 5-acetamido-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (**703**, R = OEt) (60%) or 5-acetamido-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**703**, R = NH_2) (83%), respectively;[661] several analogs were so made.[661,6240]



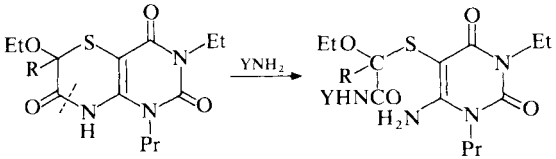
702 **703**

Pyrimido[4,5-b][1,4]thiazines as substrates. These substrates have been used to give several pyrimidines. Thus 4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazin-6-amine (**704**) underwent desulfurization by Raney-nickel to give 5-acetimidoylamino-4-methoxypyrimidine (**705**, X = NH) (70%),[674] 4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazin-6-(5*H*)-one (**706**) likewise gave 5-acetamido-4-methoxypyrimidine (**705**, X = O) (83%),[674] the same substrate (**706**) underwent peroxyacetic acid oxidation (and hydrolysis) to give 5-amino-6-oxo-1,6-dihydro-4-pyrimidinesulfonic acid (**707**) (32%),[1365] and other such reactions have been recorded.[674,1365]



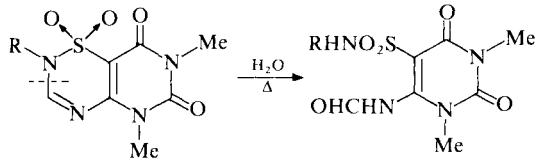
704 **705** **706** **707**

Pyrimido[5,4-b][1,4]thiazines as substrates. 6-Ethoxy- (**708**, R = H) and 6,6-diethoxy-3-ethyl-1-propyl-6*H*-pyrimido[5,4-*b*][1,4]thiazine-2,4,7(1*H*,3*H*,8*H*)-trione (**708**, R = OEt) were easily made. Treatment of each with aqueous ammonia gave 6-amino-5-(α-carbamoyl-α-ethoxymethyl)thio- (**709**, R = Y = H) (77%) or 6-amino-5-(α-carbamoyl-α,α-diethoxymethyl)thio-3-ethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione (**709**, R = OEt, Y = H) (~55%), respectively.[4581] Likewise, treatment of the substrate (**708**, R = H) with aqueous methylamine gave 6-amino-5-[α-ethoxy-α-(*N*-methylcarbamoyl)methyl]thio-3-ethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione (**709**, R = H, Y = Me) (98%).[4581] Desulfurization of all three pyrimidines gave 6-amino-3-ethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione (~80%).[4581]



708 **709**

Pyrimido[4,5-e][1,2,4]thiadiazines as substrates. Although of little practical use, hydrolytic cleavage of 2,5,7-trimethyl- (**710**, R = Me) or 2-ethyl-5,7-dimethylpyrimido[4,5-*e*][1,2,4]thiadiazine-6,8(5*H*,7*H*)-dione 1,1-dioxide (**710**, R = Et) in hot water gave 4-formamido-1,3,*N*-trimethyl- (**711**, R = Me) (88%) or *N*-ethyl-4-formamido-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonamide (**711**, R = Et) (96%), respectively.[1101]

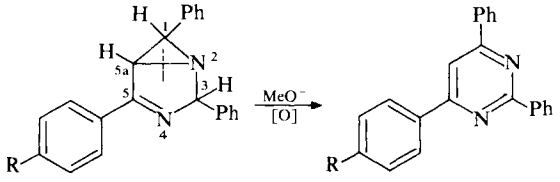


710 **711**

2.6.5. Pyrimidines from Other Heterobicyclic Systems

The following examples are of more interest than utility. 1,3,5-Triphenyl- (**712**, R = H) or 5-*p*-nitrophenyl-1,3-diphenyl-1,5a-dihydro-3*H*-azirino[1,2-*c*]imidazole (**712**, R = NO_2), which were made easily, underwent rearrangement and oxidation in methanolic sodium methoxide to afford 2,4,6-triphenyl- (**713**, R = H) (30%) or 4-*p*-nitrophenyl-2,6-diphenylpyrimidine (**713**, R = NO_2) (69%), respectively.[4582]

1-Benzoylazeto[3,2-*d*]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**714**) underwent aminolytic ring fission on refluxing with diethanolamine in ether–ethanol



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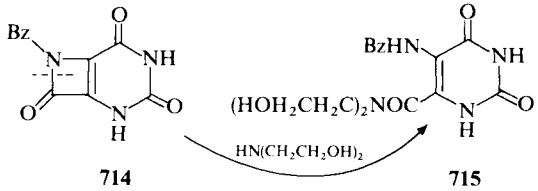
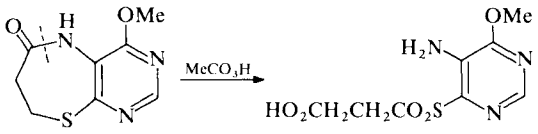


714 715

to give 5-benzamido-*N*,*N*-di(β-hydroxyethyl)-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**715**) (86%);[404] no other examples appear to have been reported.

4-Methoxy-7,8-dihydropyrimido[4,5-*b*][1,4]thiazepin-6(5*H*)-one (**716**) underwent oxidation by peroxyacetic acid to furnish 4-(β-carboxyethyl)sulfonyl-6-methoxy-5-pyrimidinamine (**717**) (36%).[1365]

The spiroheterobicyclic intermediate, 4-oxo-5-trifluromethyl-1,3-dioxin-2-spirocyclohexane, reacted with *N*,*N*′-dimethylurea in refluxing toluene to afford 1,3-dimethyl-5-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione (84%).[6169]



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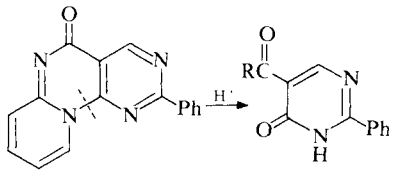
2.6.6. Pyrimidines from a Heterotricyclic and Bridged Heterobicyclic Systems

The following examples illustrate a few of the limited possibilities within this category. 2-Phenyl-5*H*-pyrido[1,2-*a*]pyrimido[5,4-*e*]pyrimidin-5-one (**718**) in refluxing dilute acid gave a separable mixture of 4-oxo-2-phenyl-*N*-(pyridin-2′-yl)-3,4-dihydro-5-pyrimidinecarboxamide (**719**, R = NHC_5H_4N-2′) (58%) and 4-oxo-2-phenyl-3,4-dihydro-5-pyrimidinecarboxylic acid (**719**, R = OH) (9%).[180]

Cyclization of the 3-amino-*N*-methyltrinorborn-5-ene-2-carboxamide (**720**, R = Me) by refluxing in triethyl orthoformate or triethyl orthoacetate gave the uncharacterized 5,8-methanoquinazoline (**721**, R = Me, X = H or Me) and thence slowly the thermolytic product, 3-methyl- (**722**, R = Me, X = H) (62%)



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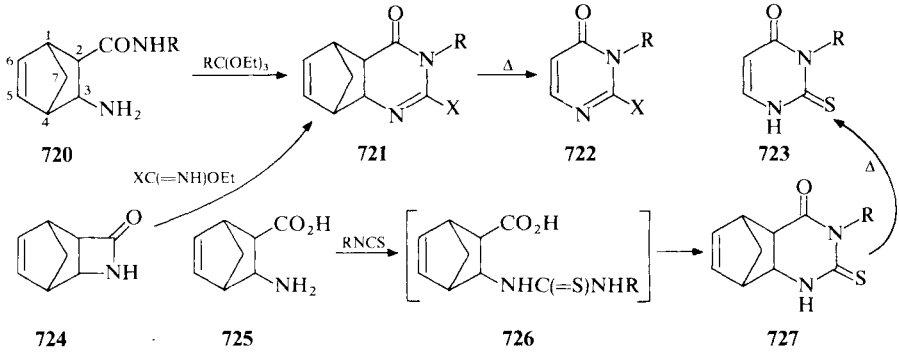

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or 2,3-di-methyl-4(3*H*)-pyrimidinone (**722**, R = X = Me) (46%), respectively;[297,3726] treatment of the trinorborn-5,6-eno[2,3]azetidinone (**724**) with ethyl acetimidate or ethyl propionimidate in refluxing ethanol gave 2-methyl- (**721**, R = H, X = Me) (91%) or 2-ethyl-4a,5,8,8a-tetrahydro-5,8-methanoquinazolin-4(3*H*)-one (**721**, R = H, X = Et) and thence, by heating in chlorobenzene containing a trace of acid, 2-methyl- (**722**, R = H, X = Me) (82%) or 2-ethyl-4(3*H*)-pyrimidinone (**722**, R = H, X = Et) (78%), respectively;[421,487] and 3-aminotrinorborn-5,6-ene-2-carboxylic acid (**725**) reacted with methyl or ethyl isothiocyanate to give successively the uncharacterized thiourea (**726**, R = Me or Et), 3-methyl- (**727**, R = Me) (60%) or 3-ethyl-2-thioxo-1,2,4a,5,8,8a-hexahydro-5,8-methanoquinazolin-4(3*H*)-one (**727**, R = Et) (65%), and thence on dry thermolysis, 3-methyl- (**723**, R = Me) (54%) or 3-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**723**, R = Et) (83%), respectively.[424,425] The original papers should be consulted for the stereochemistry of the trinorbornene substrates and methanoquinazoline intermediates.

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D. J. Brown
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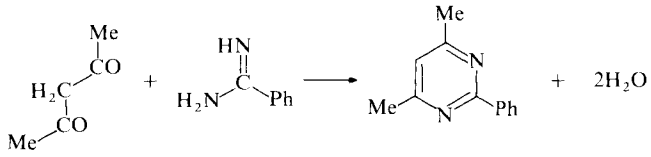
CHAPTER 3

The Principal Synthesis

Because of the vast number of pyrimidines made by that primary synthesis that involves the reaction of one molecule to supply the three-atom fragment (N1 + C2 + N3) with another to supply the three-carbon fragment (C4 + C5 + C6), the method is known as the *Principal Synthesis.* Such a procedure is exemplified in the condensation of acetylacetone (**1**) with benzamidine (**2**) to give 4,6-dimethyl-2-phenylpyrimidine (**3**).[2740,4000] These reactions are usually done under alkaline conditions, for example, in ethanolic sodium ethoxide, but other solvents and even neutral or acidic conditions have often been used to advantage in particular cases.



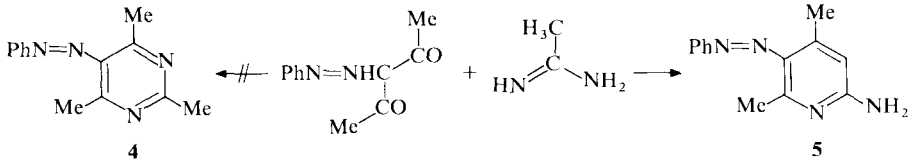
1 **2** **3**

The proven versatility of the Principal Synthesis lies in the fact that one or both functional groups of the three-carbon fragment (**1**) may be replaced by other kinds of carbonyl-containing groups (such as aldehyde or ester) or by a nitrile group: these lead respectively to nonsubstitution, to an oxo substituent, or to an amino substituent in the 4- and/or 6-position of the resulting pyrimidine. Further, by prior substitution of the methylene group of **1**, a 5-substituted pyrimidine is obtained. Likewise, the amidine (**2**) may be replaced by formamidine, guanidine, urea, or thiourea to yield a 2-unsubstituted, 2-amino-, 2-oxo-, or 2-thioxopyrimidine; moreover, when such reagents already carry an *N*-, *O*-, or *S*-alkyl group, the resulting pyrimidine bears an *N*-alkyl, 2-alkoxy, or 2-alkylthio substituent as appropriate.

In practice, not every combination cyclizes as expected, but by a careful choice of intermediates, a wide range of mono- to hexa-substituted pyrimidines or reduced pyrimidines can be produced. In the following pages a systematic survey of the Principal Synthesis is presented. Examples are given for the condensation of each of the major classes of three-carbon fragments, their equivalents, and even some analogs of lower oxidation state (which usually produce dihydropyrimidines; see also Section 11.1.1) with amidines, guanidine,

urea, thiourea, and (where data are available) with their *N*-, *S*-, or *O*-alkylated, arylated, or otherwise-substituted derivatives.

When both partners in a Principal Synthesis are unsymmetrical, the resulting pyrimidine is of ambiguous structure. Although much factual information has accumulated over the years on the correct structure of such products, a recent tendency for some authors to formulate them simply by analogy is to be deplored. Moreover, even apparently unambiguous products occasionally prove to be isomers. For example, the so-called 2,4,6-trimethyl-5-phenylazopyrimidine (**4**) from 3-phenylazo-2,4-pentanedione and acetamidine,[3697] turned out to be the isomeric 4,6-dimethyl-5-phenylazo-2-pyridinamine (**5**).[3696]



Several brief reviews of the Principal Synthesis (and other primary syntheses) of pyrimidines[4001-4004a] and dihydropyrimidines[188] have appeared of recent years.

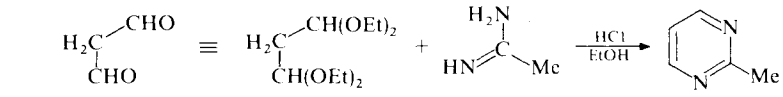
3.1. USE OF β-DIALDEHYDES

Of their nature, β-dialdehydes lead to pyrimidines unsubstituted at the 4- and 6-positions but that may carry groups at the 1-, 2-, 3-, and/or 5-positions according to the presubstitution of each substrate fragment.

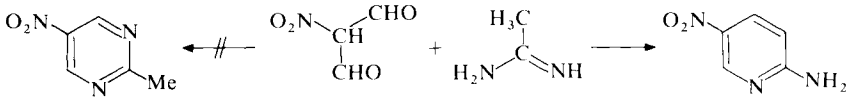
3.1.1. With Amidines

Because it is a chemical curiosity, *malonaldehyde* (**6**) is not of practical use in the Principal Synthesis. However, its diacetal, 1,1,3,3-tetraethoxypropane (**7**) has been condensed with acetamidine (**8**) in ethanolic hydrogen chloride to give 2-methylpyrimidine (**9**), albeit in only 2% yield;[3439] more satisfactory was the reaction of 4-pyridinecarboxamidine hydrochloride with 1,1,3,3-tetramethoxypropane (at 130° with only a trace of water) to give 2-pyridin-4′-ylpyrimidine (31%),[4005] or of 4-pyridinecarboxamide oxime with the same acetal to give 2-pyridin-4′-ylpyrimidine 1-oxide (in refluxing toluene–dimethylformamide with BF_3 etherate for 30 min: 79%).[6940] Although α-nitromalonalehyde (**11**) reacted abnormally with aliphatic amidines,[3410,6212] such as (**12**) to give 5-nitro-2-pyridinamine (**13**) instead of the reported[4006] 2-methyl-5-nitropyrimidine (**10**), the same substrate (**11**) did condense normally with a variety of arenecarboxamidines to afford 5-nitro-2-phenylpyrimidine (79%),[703,4006] 5-nitro-2-pyridin-3′-

ylpyrimidine (~100%),[1856] and related products.[1856,3228,4006,4007] Both α-fluoro- and α-chloromalonaldehyde have been condensed with appropriate amidines to give, for example, 5-fluoropyrimidine (formamidine: no details),[3160] 5-chloro-2-furan-2′-ylpyrimidine (39%),[4007] or 5-chloro-2-*m*-nitrophenylpyrimidine (aqueous methanol, 20°: 40%).[2212] Other such reactions have been used.[1474,3996,6021,6122]

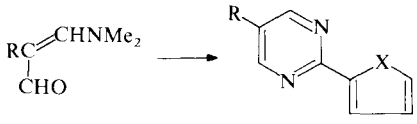


6 **7** **8** **9**



10 **11** **12** **13**

Several β-dialdehyde equivalents, which are more easily available than the parent aldehydes or their acetals, have been used quite extensively with amidines. Among the *3-aminoacroleins*, 3-dimethylamino-2-fluoroacrolein (**14**, R = F) with 2-furancarboxamidine in methanolic solution gave 5-fluoro-2-furan-2′-ylpyrimidine (**15**, R = F, X = O) (37%),[4007] 3-dimethylaminoacrolein (**14**, R = H) with 2-thiophenecarboxamidine likewise gave 2-thien-2′-ylpyrimidine (**15**, R = H, X = S) (74%),[4008] 3-piperidino-2-vinylacrolein (**16**) with isovaleramidine in methanolic acetonitrile at 25° gave 2-isobutyl-5-vinylpyrimidine (**17**) (77%),[261] 3-dimethylamino-2-phenylacrolein (**14**, R = Ph) with 3-hydroxypropionamidine in ethanol at 80° gave 2-β-hydroxyethyl-5-phenylpyrimidine (52%),[3766] and so on.[840,3954,4009] The analogous *3-alkoxyacroleins* have been represented in the reaction of 3-ethoxy-2-methylacrolein (**18**) with acetamidine to give 2,5-dimethylpyrimidine (60%),[2748] in the similar formation of several homologous 5-alkyl-2-methylpyrimidines,[2748] in the condensation of 2-*p*-bromophenyl-3-ethoxyacrolein with *p*-hexylbenzamidine to give 5-*p*-bromophenyl-2-*p*-hexylphenylpyrimidine,[4010] and in several other such reactions.[3847,4563] 6-Oxo-6*H*-pyran-3-carbaldehyde reacted in a similar way to an alkoxyacrolein with methanolic benzamidine to afford 5-β-carboxyvinyl-2-phenylpyrimidine (42%).[3888] The use of so-called *bisdimethylaminotrimethinium salts* has been reported in the reaction of the parent synthone (**19**, R = H) with benzamidine in refluxing alcoholic alkoxide to give 2-phenylpyrimidine (78%);[2318] of the homologous synthone (**19**, R = Me) with formamidine to give 5-methylpyrimidine (**20**) (88%);[2318] of the dimethylaminomethyleneamino derivative (**19**, R = N:CHNMe$_2$) with formamidine or acetamidine to give 5-dimethylaminomethyleneaminopyrimidine (**21**, R = H) (76%)[3603] or its 2-methyl derivative (**21**, R = Me),[3428] respectively; and in other such condensations.[2318,3900,4011,6170,6194]



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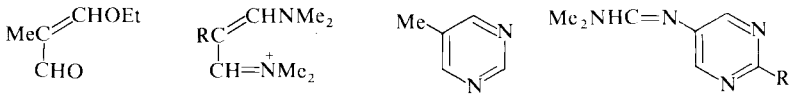

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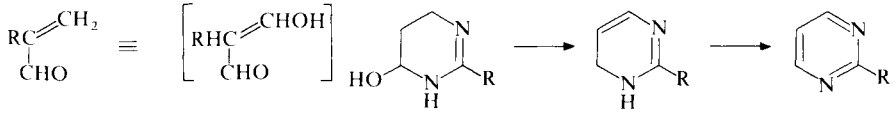
Condensations of amidines with *acrolein* (**22**, R = H), an intermediate akin to malondialdehyde but at a lower oxidation state, have been achieved satisfactorily only in recent years.[188] Thus an early attempt to cyclocondense benzamidine with acrolein (**22**, R = H), which may be considered as 3-hydroxypropionaldehyde (**23**, R = H), failed completely,[4012] probably on account of polymerization under the conditions employed. However, a successful reaction between 2-methylacrolein (**22**, R = Me) and a cyclic amidine rekindled hope in 1969,[4013] and eventually hydroquinone-stabilized acrolein (**22**, R = H) was condensed successfully with benzamidine under gentle conditions to give 2-phenyl-3,4,5,6-tetrahydro-4-pyrimidinol (**24**, R = Ph) in 96% yield;[102] this was dehydrated by boiling in acetonitrile to give a 2-phenyl-1,6 (or 1,4)-dihydropyrimidine (**25**, R = Ph) (~100%), which underwent facile permanganate or silver oxide oxidation to 2-phenylpyrimidine (**26**, R = Ph) (96%).[102] Formamidine and acetamidine behaved rather similarly with acrolein to give 3,4,5,6-tetrahydro-4-pyrimidinol (**24**, R = H), its 2-methyl derivative (**24**, R = Me), 1,6 (or 1,4)-dihydropyrimidine (**25**, R = H), and its 2-methyl derivative (**24**, R = Me), all in reasonable yield.[267,344]



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3.1.2. With Guanidines

The following *equivalents of malonaldehyde* (**6**) have been condensed with guanidine to give 2-pyrimidinamine (**26**, R = NH_2).

1,1,3,3-Tetraethoxypropane (**7**) or other such diacetal (ethanolic sodium ethoxide: 21%;[3593] ethanolic hydrogen chloride: 90%;[3593] aqueous mineral acid in acetic acid: 50–70%;[3593] guanidine nitrate or carbonate plus ammonium acetate without solvent: 30–90%[4014]).

1,3,3-Triethoxypropene (**27**, R = X = OEt) (ethanolic hydrogen chloride: 53%).[3584]

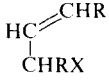
1,1-Dichloro-3,3-dimethoxypropane (**28**, R = X = OMe) (ethanolic hydrogen chloride or sulfuric acid: good yields).[4015]

1-Acetoxy-1-bromo-3,3-dichloropropane (**28**, R = OAc, X = Br) (likewise).[4015]

3-Bromo-1,3-dichloropropene (**27**, R = Cl, X = Br) (concentrated sulfuric acid at 50°: 58%).[4016]

3-Phenoxyacrolein (**29**).[3431]

Propynal (**30**) (ethanolic hydrogen chloride: 80%).[4017]



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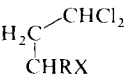

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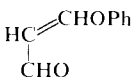

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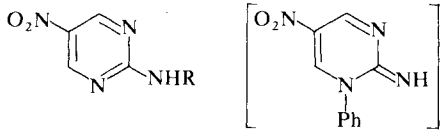
Among *α-substituted malonaldehydes or equivalents*, α-nitromalonaldehyde (**11**) as its sodio derivative has been cyclocondensed satisfactorily with guanidine carbonate in aqueous piperidine at 20° to give 5-nitro-2-pyrimidinamine (**31**, R = H) in almost quantitative yield;[703–705] the same substrate (**11**) with *N*-phenylguanidine in aqueous benzyltrimethylammonium hydroxide gave only 2-anilino-5-nitropyrimidine (**31**, R = Ph),[4018] but whether directly or at least partially by Dimroth rearrangement of the isomeric product (**32**), remains unknown. *N*,*N*-Dimethylguanidine and the dialdehyde (**11**) in aqueous piperidine gave (unambiguously) 2-dimethylamino-5-nitropyrimidine (35%), but the product was better made indirectly (85%) by *N*-methylation of 5-nitro-2-pyrimidinamine (**31**, R = H).[2644] The last mentioned compound (**31**, R = H) has also been made from the bisdimethylaminotrimethinium salt (**19**, R = NO_2) and methanolic guanidine: 82% yield.[2318] Other 5-substituted-2-pyrimidinamines were obtained by broadly similar methods. They include, for example, 5-chloro- [from α-chloromalonaldehyde: 74%;[704] from intermediate (**19**, R = Cl): 78%[2318]], 5-fluoro- (from α-fluoromalonaldehyde;[3160] from 3-dimethylamino-2-fluoroacrolein: 57%[3161]), 5-phenyl- [from 3-dimethylamino-2-phenylacrolein: 27%;[3766] from intermediate (**19**, R = Ph): 91%;[2318] from 3-hydroxy-2-phenylacrolein[4022]], and 5-vinyl-2-pyrimidinamine (**33**, R = H) (from 3-piperidino-2-vinylacrolein: 78%).[261] The use of appropriately substituted guanidines likewise gave 2-dimethylamino-5-vinylpyrimidine (**33**, R = Me) (68%),[261] 2-(*N*-carboxymethyl-*N*-methylamino)-5-ethylpyrimidine (**34**) (30%),[2748] and 2-(δ-amino-δ-carboxybutyl)amino-5-methylpyrimidine (34%).[2743] There are



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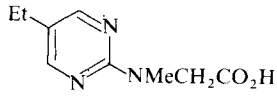

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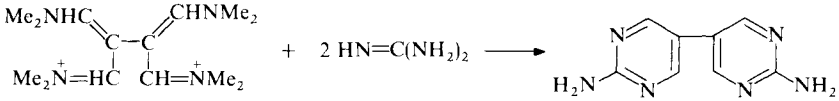

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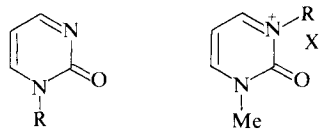
many other examples in both the foregoing categories of condensation.[132,840,1086,2743,2748,2929,2946,3603,3996,6021,6122,6170] A particularly interesting case is the reaction of the bimolecular bisdimethylaminotrimethinium salt (**35**) with guanidine in ethanolic ethoxide to give 5,5′-bipyrimidine-2,2′-diamine (**36**) (33–80%).[4019,4020]

There is at least one example of guanidine condensing with a *reduced analog of a β-dialdehyde.* Stabilized acrolein and free guanidine in methanolic acetone at − 20° gave a low yield of 2-amino-3,4,5,6-tetrahydro-4-pyrimidinol (**24**, R = NH_2);[334] no subsequent dehydration step has been reported.

3.1.3. With Ureas

The *diacetal of malonaldehyde* condensed with urea in ethanol containing hydrochloric acid to give 2(1*H*)-pyrimidinone (**37**, R = H) (73%).[125,764] The use of an appropriate *N*-alkyl-, *N*-aryl-, or *N*-alkoxyurea in the above condensation gave the following 1-alkyl-, 1-aryl-, or 1-alkoxy-2(1*H*)-pyrimidinones (**37**), in which R = Me (26–72%),[2947,3492] Et (28%),[2947] Pr (24%),[2947] Pr^i (46%),[2947] Bu (36%),[2947] Bu^i (42%),[1879] Bu^s (26%),[2947] Bu^t (18%),[2947] Ph (20%),[1879] *p*-C_6H_4Me (45%),[1879] OMe (49%),[3366] OCH_2Ph (85%),[3366] or OCH_2CO_2Et



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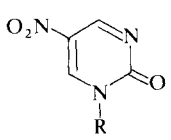
(57%).[3366] The similar use of *N,N'*-dimethylurea gave 1,3-dimethyl-2-oxo-2,3-dihydro-1-pyrimidinium chloride (or other anion according to the acid used) (**38**, R = Me, X = Cl, etc.);[1952,2810] analogs, such as 1-ethyl-3-methyl-2-oxo-2,3-dihydro-1-pyrimidinium iodide; (**38**, R = Et, X = I), were made similarly with an appropriate dialkylurea.[2810]

The following reported examples illustrate condensations between *α-substituted-malonaldehydes (or equivalents)* and ureas.

5-Nitro-2(1*H*)-pyrimidinone (**39**, R = H) from sodiomalonaldehyde and urea in dilute alkali: poor yield.[703]

5-Phenyl-2(1*H*)-pyrimidinone from 3-hydroxy-2-phenylacrolein (**40**, R = OH) and urea at 120°;[4021] or from 3-amino-2-phenylacrolein (**40**, R = NH_2) and urea in ethanolic hydrochloric acid: ~40% yield.[4023]

5-Methyl-2(1*H*)-pyrimidinone from 3-ethoxy-2-methylacrolein (**41**) or α-methylmalonaldehyde diacetal with urea in ethanolic hydrochloric acid: 69% or 74%.[1879,2748]



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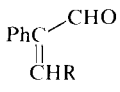

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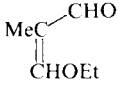

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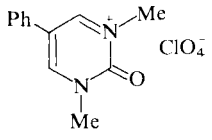

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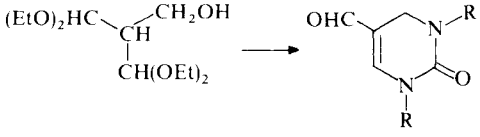
1-Methyl-5-phenyl-2(1*H*)-pyrimidinone from 3-amino-2-phenylacrolein and *N*-methylurea in ethanolic hydrochloric acid: ~ 45%;[4023] or from α-phenylmalonaldehyde or 3-dimethylamino-2-phenylacrolein with *N*-methylurea in toluene cotaining *p*-toluenesulfonic acid: 84% or 32%, respectively.[4024]

5-Fluoro-2(1*H*)-pyrimidinone from α-fluoromalonaldehyde with urea in ethanolic hydrochloric acid: 23%.[3161]

1,3-dimethyl-2-oxo-5-phenyl-2,3-dihydro-1-pyrimidinium perchlorate (**42**) from α-phenylmalonaldehyde with *N,N'*-dimethylurea in methanolic perchloric acid: 60%.[1803]

Also analogous cases.[1803,1879,2748,2810,3832,4023,4024]

In its condensations with urea or *N,N'*-dimethylurea in ethanolic hydrochloric acid, α-(hydroxymethyl)malonaldehyde diacetal (**43**) preferred to react,

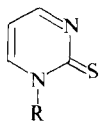


43 **44**

not as a dialdehyde, but as an aldehydo alcohol (i.e., at a *lower oxidation state*) to give 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde (**44**, R = H) (or its 1,3-dimethyl derivative (**44**, R = Me), respectively, in place of the expected 5-hydroxymethylpyrimidines.[3402]

3.1.4. With Thioureas

2(1*H*)-Pyrimidinethione (**45**) has been made by the reaction of thiourea with *malonaldehyde diacetal* (**7**) (ethanolic hydrochloric acid: 66%),[764] with 3-(*N*-methylanilino)acrolein (**46**) (at 140° without solvent: 69%),[3496] or with the bisdimethylaminotrimethinium salt (**19**, R = H) (in methanolic sodium methoxide: 60%).[1086] The unsymmetrical diacetal, 1,1,3-triethyl-3-methylpropane, has been used with thiourea or *N*-methylthiourea in ethanolic hydrochloric acid to give the parent thione (**45**, R = H) or 1-methyl-2(1*H*)-pyrimidinethione (**45**, R = Me) (55%), respectively.[3480]



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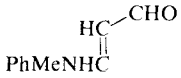

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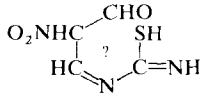

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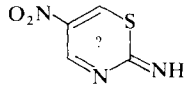

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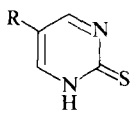
Turning to α-*substituted-malonaldehydes or their equivalents*, the condensation of sodio-α-nitromalonaldehyde with thiourea has been reported to give the acyclic intermediate (**47**) and subsequently 5-nitro-2*H*-1,3-thiazin-2-imine (**48**) but no pyrimidine.[4025] This work could not be confirmed later, and the condensation in aqueous piperidine was shown to give 5-nitro-2-piperidinopyrimidine (15%);[2321] however, 5-nitro-2(1*H*)-pyrimidinethione has been made indirectly.[1951] α-Nitromalonaldehyde reacted quite normally with *S*-methylisothiourea in aqueous *N*-ethylpiperidine to afford 2-methylthio-5-nitropyrimidine in 26–35% yield.[2321,3228] The scope of condensations in this category is further illustrated in the following examples.

5-Ethyl-2(1*H*)-pyrimidinethione (**49**, R = Et) from thiourea with (1) 3-chloro-2-ethylacrolein in hot ethanolic ethoxide: 38%;[3019] (2) 3-chloro-2-ethylacrolein in hot ethanolic hydrogen chloride: 60%;[3019] (3) 3-dimethylamino-2-ethylacrolein in hot ethanolic hydrogen chloride: 29%;[3019] (4) 3-ethoxy-2-ethylacrolein in hot ethanolic ethoxide: 70%;[2748]



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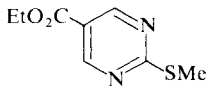
or (5) the bisdimethylaminotrimethinium salt (**19**, R = Et) in hot methanolic methoxide: 57%.[1086]

5-Phenyl-2(1*H*)-pyrimidinethione (**49**, R = Ph) from thiourea with (1) 3-amino-2-phenylacrolein in hot ethanolic hydrochloric acid: 30%;[3072] (2) 3-chloro-2-phenylacrolein in hot ethanolic hydrogen chloride: 48%;[3019] or (3) the bisdimethylaminotrimethinium salt (**19**, R = Ph) in hot methanolic methoxide: 84%.[2318]

5-Chloro-2(1*H*)-pyrimidinethione (**49**, R = Cl) from thiourea with the bisdimethylaminotrimethinium salt (**19**, R = Cl) in methanolic methoxide: 35–72%.[1086,2318]

5-Piperidino-2(1*H*)-pyrimidinethione from thiourea with 3-dimethylamino-2-piperidinoacrolein in hot methanolic methoxide: 71%.[4026]

Ethyl 2-methylthio-5-pyrimidinecarboxylate (**50**) from *S*-methylisothiourea with ethyl 3-dimethylamino-2-formylacrylate in ethanolic ethoxide: 48%.[381]



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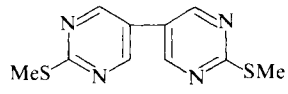

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5-*p*-Butoxyphenyl-2-methylthiopyrimidine from *S*-methylisothiourea with the bisdimethylaminotrimethinium salt (**19**, R = *p*-BuOC$_6$H$_4$) in hot pyridine: 82%.[4027]

2-Methylthio-5-pyrimidinecarbaldehyde from *S*-methylisothiourea with triformylmethane in hot ethanolic ethoxide: 33%.[6021,6122]

1,3-Dimethyl-2-thioxo-2,3-dihydro-1-pyrimidinium (salt) from *N*,*N*′-dimethylthiourea with malonaldehyde diacetal in ethanolic acid: 50% (as hydrogen sulfate).[1803]

2,2′-Bismethylthio-5,5′-bipyrimidine (**51**) from *S*-methylisothiourea with the bimolecular bisdimethylaminotrimethinium salt (**35**) in ethanolic ethoxide: 23%.[4019, cf. 4020]

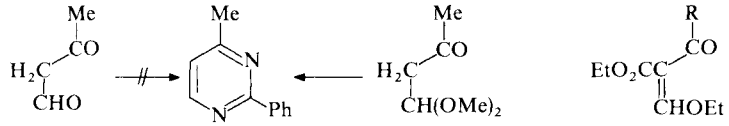
Also analogs.[1086,1803,2696,2748,3019,3072,3161,3603,4019,4020,4027,4028,6170]

3.2. USE OF β-ALDEHYDO KETONES

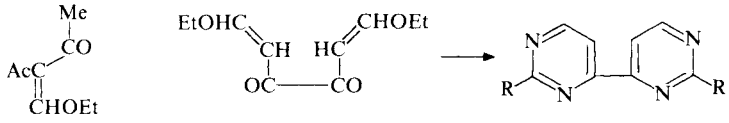
The use of a β-aldehydo ketone in the Principal Synthesis leads to a 4- or 6-substituted pyrimidine: a symmetrical N—C—N partner gives a single product, but an unsymmetrical partner gives one or both of the possible products. In practice, free aldehydo ketones are not readily available, but the judicious use of equivalents has permitted a reasonably wide scope for this category of the synthesis.

3.2.1. With Amidines

Although benzamidine failed to react with *formylacetone* (**52**),[4000] it did so with the dimethyl acetal (**54**) in boiling ethanolic ethoxide to give 4-methyl-2-phenylpyrimidine (**53**) in 53% yield;[4029] the same acetal (**54**) with 2-pyridinecarboxamidine likewise gave 4-methyl-2-pyridin-2′-ylpyrimidine (60%).[4030] The use of an *ethoxymethylene ketone* in place of an aldehydo ketone is often convenient. Thus diethyl ethoxymethyleneoxalacetate (**55**, R = CO_2Et) reacted as an aldehydo ketone (rather than as a keto ester) with appropriate amidines (as free bases in ethanol) to give diethyl 4,5-pyrimidinedicarboxylate (37%),[2530,2548] its 2-methyl derivative (45%),[1421] and analogous derivatives;[2530] ethyl ethoxymethyleneacetoacetate (**55**, R = Me) with benzamidine gave ethyl 4-methyl-2-phenyl-5-pyrimidinecarboxylate;[4031] 3-ethoxymethylene-2,4-pentanedione (ethoxymethyleneacetylacetone) (**56**) reacted as an aldehydo ketone (rather than as a diketone) with benzamidine to give 5-acetyl-4-methyl-2-phenylpyrimidine (66%);[3031] and 1,6-diethoxyhexa-1,5-diene-3,4-dione (**57**) with two molecules of formamidine or acetamidine gave 4,4′-bipyrimidine (**58**, R = H) (28%) or its 2,2′-dimethyl derivative (**58**, R = Me) (32%).[4032]



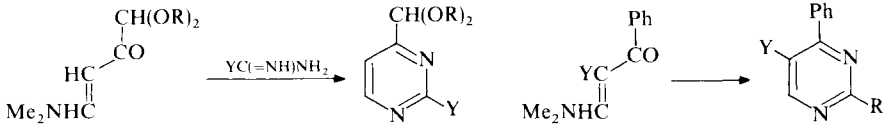
52 **53** **54** **55**



56 **57** **58**

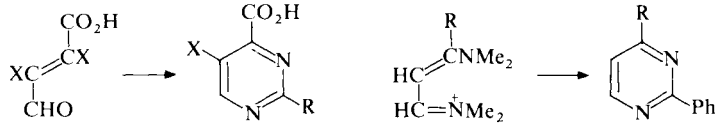
Rather similarly, the *aminomethylene ketone*, 4-dimethylamino-1,1-diethoxybut-3-en-2-one (**59**, R = Et), reacted with formamidine acetate at 115° without solvent to give 4-diethoxymethylpyrimidine (4-pyrimidinecarbaldehyde acetal) (**60**, R = Et, Y = H) in 74% yield;[2756] acetamidine and benzamidine (as free bases in ethanol) likewise afforded the 2-methyl (**60**, R = Et, Y = Me) and 2-phenyl (**60**, R = Et, Y = Ph) derivatives, respectively, in comparable yield.[2756] The homologous dimethoxy synthone (**59**, R = Me) behaved similarly with formamidine acetate to give 4-dimethoxymethylpyrimidine (**60**, R = Me, Y = H) (75%).[2584] 1-Benzoyl-1,2-bisdimethylaminoethylene (**61**, Y = NMe_2) with formamidine acetate at 160° or with benzamidine base at 110° gave 5-dimethylamino-4-phenylpyrimidine (**62**, R = H, Y = NMe_2) (39%) or 5-dimethylamino-2,4-diphenylpyrimidine (**62**, R = Ph, Y = NMe_2) (56%), respectively;[2649] 1-benzoyl-2-dimethylamino-1-methylsulfonylethylene (**61**,

Y = SO_2Me) with aqueous methanolic benzamidine gave 5-methylsulfonyl-2,4-diphenylpyrimidine (**62**, R = Ph, Y = SO_2Me) (49%);[319] and 1-benzoyl-2-dimethylamino-1-(3′-methlylisoxazol-5′-yl)ethylene (**61**, Y = heterocyclic group) with ethanolic benzamidine gave 5-(3′-methylisoxazol-5′-yl)-2,4-diphenylpyrimidine (**62**, Y = heterocyclic group) (58%).[390] More complicated equivalents have been used.[363,368]



59 **60** **61** **62**

Both *bromomucic* (**63**, X = Br) *and chloromucic acid* (**63**, X = Cl) have been employed as aldehydo ketone equivalents. Thus bromomucic acid with free benzamidine in chloroform gave 5-bromo-2-phenyl-4-pyrimidinecarboxylic acid (**64**, R = Ph, X = Br), initially as its benzamidinium salt in poor yield; chloromucic acid gave the analog (**64**, R = Ph, X = Cl).[4033] An improved procedure in aqueous solution gave the former product (**64**, R = Ph, X = Br) in 22% yield,[1856] but condensation of bromomucic acid (**63**, X = Br) with acetamidine in ethanol gave 5-bromo-2-methyl-4-pyrimidinecarboxylic acid (**64**, R = Me, X = Br) in up to 60% yield;[1479] the chloro analog (**64**, R = Me, X = Cl) was made similarly.[1479] Mucobromic acid with alcoholic pivalamidine or 2-hydroxyacetamidine gave 5-bromo-2-*t*-butyl-4-pyrimidinecarboxylic acid (**64**, R = Bu^t, X = Br)[1032] or its 2-hydroxymethyl analog (**64**, R = CH_2OH, X = Br) (35%),[1889] respectively.



63 **64** **65** **66**

The *bisdimethylaminotrimethinium salts* have been used also as aldehydo ketones. Thus the intermediates (**65**, R = Me or Ph) cyclocondensed with methanolic benzamidine to furnish 4-methyl-2-phenyl- (**66**, R = Me) (75%) or 2,4-diphenylpyrimidine (**66**, R = Ph) (66%), respectively.[2318] Bizarre condensations have proved successful also.[152–154]

3.2.2. With Guanidines

The use of *formylacetone and its equivalents* is illustrated in the formation of 4-methyl-2-pyrimidinamine (**70**, R = Me) from guanidine and the following three-carbon fragments.

Sodium salt of formylacetone (**52**): 37–51%, yield.[1217,1930,4029]

Formylacetone dimethyl acetal (**54**): 36–96% according to the conditions used.[3432,4029]

Methoxymethyleneacetone (**67**): 80%.[4029]

Methoxymethylenepropyne (**68**, R = OMe): 25–50%.[3087,4029,4034]

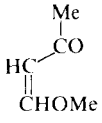
Ethoxymethylenepropyne (**68**, R = OEt): 48%.[4034]

Ethylthiomethylenepropyne (**68**, R = SEt): 15%.[3087]

Diethylaminomethylenepropyne (**68**, R = NEt_2): 35%.[3087]

Butadiyne (diacetylene): 27%.[2366]

Dimethylaminomethyleneacetone (**69**).[3436]



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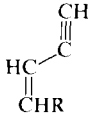

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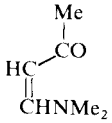

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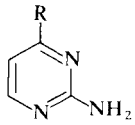

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In a similar way, the use of *benzoylacetaldehyde and equivalents* is illustrated in the formation of 4-phenyl-2-pyrimidinamine (**70**, R = Ph) from guanidine with the following synthones.

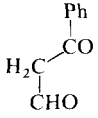
Benzoylacetaldehyde (**71**): 42%.[1217,1930,2212]

Benzoylacetylene (**72**): ~30%.[4035]

1-Benzoyl-2-dimethylaminoethylene (**73**, R = H): 84%.[3436]

The bisdimethylaminotrimethinium salt (**65**, R = Ph): 97%.[2318]

2,6-Diphenylpyrylium perchlorate: 45% (mechanism?).[149]



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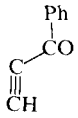

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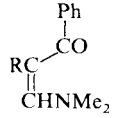

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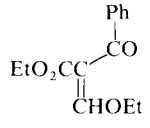
Condensations involving more *complicated aldehydo ketone equivalents and/or substituted guanidines* are illustrated in the following syntheses.

4-Diethoxymethyl-2-pyrimidinamine (**60**, R = Et, Y = NH_2) (32%) from 4-dimethylamino-1,1-diethoxybut-3-en-2-one (**59**, R = Et) with guanidine.[2756]

Ethyl 2-amino-4-phenyl-5-pyrimidinecarboxylate (**75**, R = Ph) (59%) from ethyl 2-benzoyl-3-ethoxyacrylate (**74**) with guanidine;[668] also analogous reactions.[3996]



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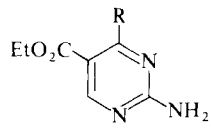

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5-Acetyl-4-methyl-2-pyrimidinamine (94%) from 3-ethoxymethylene-2,4-pentanedione (**56**) with guanidine.[3031]

5-Methyl-4-phenyl-2-pyrimidinamine (73%) from 2-benzoyl-1-dimethylaminopropene (**73**, R = Me) with guanidine.[4037]

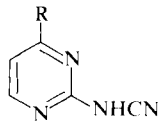
Diethyl 2-amino-4,5-pyrimidinedicarboxylate (**75**, R = CO_2Et) (57%) from diethyl ethoxymethyleneoxalacetate (**55**, R = CO_2Et) with guanidine.[1635]

2-Cyanoamino-4-methylpyrimidine (**76**, R = Me) from *N*-cyanoguanidine (dicyandiamide) with formylacetone dimethyl acetal (**54**) (75% yield) or butadiyne (**77**) (30% yield).[2366]

2-Cyanoamino-4-propylpyrimidine (**76**, R = Pr) (21%) from *N*-cyanoguanidine with 1,3-hexadiyne (**77**, R = Et).[2366]

2-Butylamino-4-methylpyrimidine (**78**, R = Bu) from *N*-butylguanidine with methoxymethylenepropyne (**68**, R = OMe).[4034]

2-Hydrazino-4-methylpyrimidine (**78**, R = NH_2) (25%) from benzylideneaminoguanidine with formylacetone, followed by acid hydrolysis of the crude 2-benzylidenehydrazino analog (**78**, R = N:CHPh).[3217]



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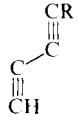

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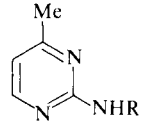

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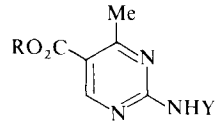
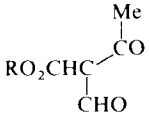


79

Ethyl 2-benzamido-4-methyl-5-pyrimidinecarboxylate (**79**, R = Et, Y = Bz) from *N*-benzoylguanidine with ethyl formylacetoacetate (**80**, R = Et).[691]

Benzyl 2-amino-4-methyl-5-pyrimidinecarboxylate (**79**, R = CH_2Ph, Y = H) (~30%) from guanidine with benzyl formylacetoacetate (**80**, R = CH_2Ph). [691]

2-Dimethylamino-5-methylsulfonyl-4-phenylpyrimidine (**81**) (51%) from *N*,*N*-dimethylguanidine with 1-benzoyl-2-dimethylamino-1-methylsulfonylethylene (**73**, R = SO_2Me).[319]



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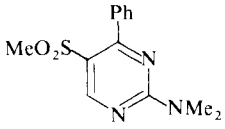
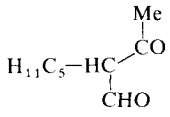


81

Ethyl 4-methyl-2-morpholino-5-pyrimidinecarboxylate (74%) from 4-morpholinecarboxamidine with ethyl ethoxymethyleneacetoacetate (**55**, R = Me).[4038]

Because of disagreement as to which side of an unsymmetrical alkyl methyl ketone undergoes formylation, the condensation product from formylated hexyl methyl ketone (**82** or **83**) with guanidine was first described[4036] as 4-methyl-5-pentyl-2-pyrimidinamine but later[1217] as the isomer, 4-hexyl-2-pyrimidinamine: the balance of evidence at the time appeared to favor the latter structure, but an unequivocal answer, based on the nmr of the product, has not been given yet. By analogy, the structures reported as 4-propyl-2-pyrimidinamine[1217,1930] and 4,5-dimethyl-2-pyrimidinamine[1930,2097,4036] require confirmation or correction. The use of reduced synthones in similar reactions has been investigated.[441]



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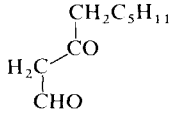

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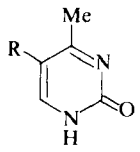
3.2.3. With Ureas

The *simple condensations* in this category are typified by that of formylacetone bis(dimethyl acetal), that is, 1,1,3,3-tetramethoxybutane, with urea in ethanolic hydrochloric acid to give 4-methyl-2(1*H*)-pyrimidinone (**84**, R = H) in 86% yield.[3482] However, the product described as 4,5-dimethyl-2(1*H*)-pyrimidinone (**84**, R = Me), which was made from urea with an acetal derived from the formylation product of ethyl methyl ketone,[2097,2823] still requires structural confirmation by nmr for reasons outlined in the preceding paragraph. In contrast, condensation of methoxymethyleneacetophenone (**85**) with urea proceeded in ethanolic ethoxide to give 4-phenyl-2(1*H*)-pyrimidinone in 40% yield,[4039] condensation of α-formyl-α-phenylacetophenone (**86**) with urea occurred simply in *N*,*N*-dimethylacetamide at 150° to give 4,5-diphenyl-2(1*H*)-pyrimidinone (37%),[4024] while condensation of 4,4-dimethoxy-1-*p*-methoxyphenyl-2-butanone (**87**) with urea required ethanolic hydrochloric acid as medium to afford 4-*p*-methoxybenzyl-2(1*H*)-pyrimidinone (65%).[439]



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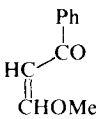

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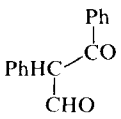

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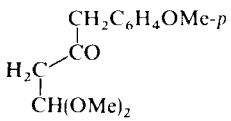
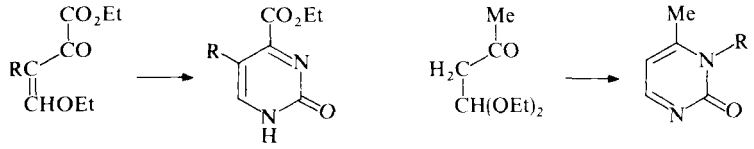


87

Some analogous but *less simple condensations* have been employed to prepare the following pyrimidines.

Diethyl 2-oxo-1,2-dihydro-4,5-pyrimidinecarboxylate (**89**, R = CO_2Et) (70%) from urea with diethyl ethoxymethyleneoxalacetate (**88**, R = CO_2Et) in two stages.[1635]

Ethyl 5-acetyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate (**89**, R = Ac) (43%) from urea with ethyl 3-acetyl-3-ethoxymethylenepyruvate (**88**, R = Ac).[1635]



88 **89** **90** **91**

1,6-Dimethyl-2(1*H*)-pyrimidinone (**91**, R = Me) (68%) as the single product from formylacetone acetal (**90**) with *N*-methylurea,[1465] followed by structural confirmation from an unambiguous synthesis[1879] and an nmr study[2742] of the product.

1-Ethyl-6-methyl-2(1*H*)-pyrimidinone (**91**, R = Et), likewise using *N*-ethylurea.[1465]

4-Diethoxymethyl-2(1*H*)-pyrimidinone (15%) from urea with 4-dimethylamino-1,1-diethoxybut-3-en-2-one (**59**, R = Et).[2756]

5-Benzoyl-4-methyl-2(1*H*)-pyrimidinone (30%) from 1-acetyl-1-benzoyl-2-dimethylaminoethylene (**61**, Y = Ac) with urea in tetrahydrofuran containing sodium hydride; the orientation was confirmed by an unambiguous synthesis.[439]

1,3,4-Trimethyl-2-oxo-2,3-dihydro-1-pyrimidinium salt (99%) from formylacetone dimethyl acetal (**54**) with *N*,*N*′-dimethylurea.[2810]

3.2.4. With Thioureas

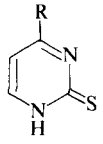
The following *formylacetone equivalents* have been used with thiourea in ethanolic hydrochloric acid to afford 4-methyl-2(1*H*)-pyrimidinethione (**92**, R = Me).

1,1,3,3-Tetramethoxybutane (**93**) (95%).[3482]

Formylacetone acetal (91%).[3432]

Formylacetone dimethyl acetal (**54**) (95%).[405]

Methoxymethylenepropyne (**68**, R = OMe) (> 90%).[764]



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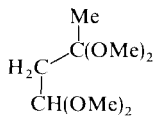

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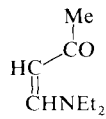


94

Ethoxymethylenepropyne (**68**, R = OEt) (94%).[3106]

Ethylthiomethylenepropyne (**68**, R = SEt) (32%).[3106]

Diethylaminomethylenepropyne (**68**, R = NEt_2) (exceptionally in ethanolic sodium ethoxide: 40% yield).[3106]

Diethylaminomethyleneacetone (**94**) (also in alkaline medium: 68%).[193]

Bisdimethylaminotrimethinium salt (**65**, R = Me) (also in alkaline medium: 63%).[1086]

Replacement of thiourea by an appropriate *S*-alkylisothiourea in the reaction with diethylaminomethyleneacetone (**94**) under alkaline conditions gave 2-ethylthio- (76%) or 2-allylthio-4-methylpyrimidine (85%);[193] the alternative use of methoxymethylenepropyne (**68**, R = Me) gave the same products in only ~30% yield.[193]

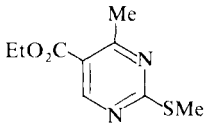
The use of *other β-aldehydo ketone equivalents* with thioureas is illustrated in the following syntheses.

5-Bromo-2-methylthio-4-pyrimidinecarboxylic acid (**64**, R = SMe, X = Br) from mucobromic acid (**63**, R = Br) with *S*-methylisothiourea in aqueous solution: 37–64%.[1935,2291]

5-Chloro-2-methylthio-4-pyrimidinecarboxylic acid (**64**, R = SMe, X = Cl) from mucochloric acid similarly: 66%.[2291]

4-Dimethylamino-2(1*H*)-pyrimidinethione (**92**, R = NMe_2) from the trisdimethylaminotrimethinium salt (**65**, R = NMe_2) with thiourea: 57%.[1086]

Ethyl-4-methyl-2-methylthio-5-pyrimidinecarboxylate (**95**) from ethyl methoxymethyleneacetoacetate with *S*-methylisothiourea in aqueous base: 54%.[2694]



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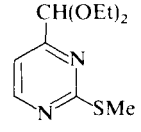

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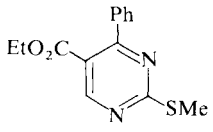

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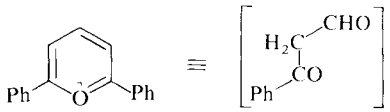
4-Diethoxymethyl-2-methylthiopyrimidine (**96**) from 4-dimethylamino-1,1-diethoxybut-3-en-2-one (**59**, R = Et) with *S*-methylisothiourea in aqueous alkali: 63%.[2756]

Ethyl 2-methylthio-4-phenyl-5-pyrimidinecarboxylate (**97**) from ethyl 2-benzoyl-3-dimethylaminoacrylate (**61**, Y = CO_2Et) with *S*-methylisothiourea in ethanol: 77%.[4040]

2,2′-Bismethylthio-4,4′-bipyrimidine (**58**, R = SMe) from 1,4-bisethoxymethylene-2,3-butanedione (**57**) with 2 mol of *S*-methylisothiourea in ethanol: 26%.[4032]

2-Benzylthio-4-phenylpyrimidine (**62**, R = SCH_2Ph, Y = H) from the 2,6-diphenylpyrylium salt (**98**), pragmatically equivalent to benzoylacetaldehyde (**99**), with *S*-benzylisothiourea in ethanol: 76%.[149]

Also other such reactions.[3917,6123]



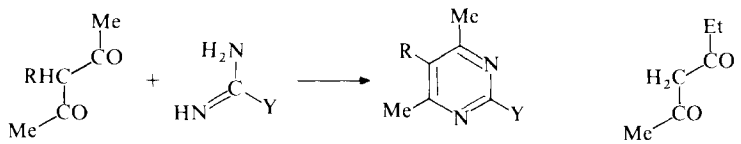
98 **99**

3.3. USE OF β-DIKETONES

Because most of the β-diketones used for the Principal Synthesis have been symmetrical, structural ambiguity in the resulting pyrimidines has been rare.

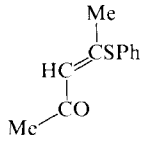
3.3.1. With Amidines

Condensations between amidines and *simple β-diketones or their equivalents* are well represented. Thus acetylacetone (**100**, R = H) reacted with acetamidine (**101**, Y = Me) in aqueous potassium carbonate at room temperature during 2 weeks to give 2,4,6-trimethylpyrimidine (**102**, R = H, Y = Me) as the principal product in 33% yield.[1611,2467,3000] In a similar way, benzamidine (**101**, R = Ph) gave 4,6-dimethyl-2-phenylpyrimidine (**102**, R = H, Y = Ph):[4000] an optimal 64% yield was obtained at pH 9–10, that is, at the highest alkalinity consistent with stability of benzamidine.[2740] Likewise, acetamidine with propionylacetone (2,4-hexanedione: **103**) or 3-methyl-2,4-pentanedione (**100**, R = Me) afforded 4-ethyl-2,6-dimethylpyrimidine or 2,4,5,6-tetramethylpyrimidine (**102**, R = Y = Me), respectively.[3000] The interesting diketone equivalent, 4-phenylthiopent-



100 **101** **102** **103**

3-en-2-one (**104**), with acetamidine (**101**, Y = Me) in ethanolic alkali gave 2,4,6-trimethylpyrimidine (**102**, R = H, Y = Me) in 76% yield (cf. 33% from acetylacetone);[238] the same intermediate (**104**) or related synthones with acetamidine or benzamidine likewise gave 4,6-dimethyl-2-phenylpyrimidine (**102**, R = H, Y = Ph) (57%), 2,4-dimethyl-6-phenylpyrimidine (62%), 4-methyl-2,6-diphenylpyrimidine (56%), and 2-methyl-4,6-diphenylpyrimidine (14%).[238] Such syntheses are further illustrated as follows.

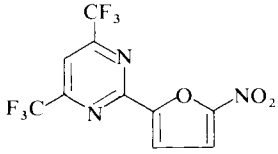


104

2-5′-Nitrofuran-2′-yl-4,6-bistrifluoromethylpyrimidine (**105**) (9%) from 5-nitro-2-furancarboxamidine with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione.[4041]

4-Diethoxymethyl-2,6-dimethylpyrimidine (47%) from acetamidine with 1,1-diethoxy-2,4-pentanedione.[2756]

2-Hydroxymethyl-4,6-dimethylpyrimidine (**102**, R = H, Y = CH_2OH) (6%) from 2-hydroxyacetamidine with acetylacetone, very slowly in aqueous potassium carbonate.[1933]



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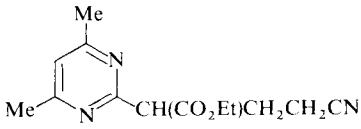
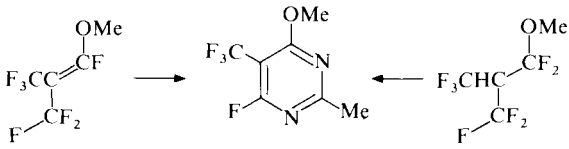


106

2-γ-Cyano-α-ethoxycarbonylpropyl-4,6-dimethylpyrimidine (**106**) (46%) from ethyl 2-amidino-4-cyanobutyrate with acetylacetone in ethanolic piperidine.[650]

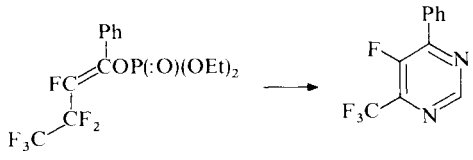
4,6-Dimethyl-2-(3′,4′,5′-trimethoxyphenyl)pyrimidine (30%) from 3,4,5-trimethoxybenzamidine with acetylacetone.[4042]

Some unusual equivalent reagents have been used in this category of the synthesis. *Polyfluoro intermediates* include 1,3,3,3-tetrafluoro-1-methoxy-2-trifluoromethylpropene (**107**) and 1,1,1,3,3-pentafluoro-3-methoxy-2-trifluoromethylpropane (**109**), both of which condensed with acetamidine in a stirred two-phase system of dichloromethane–aqueous alkali (in the presence of a little benzyltrimethylammonium chloride) to give 4-fluoro-6-methoxy-2-methyl-5-trifluoromethylpyrimidine (**108**) (40–60%, according to conditions); analogous

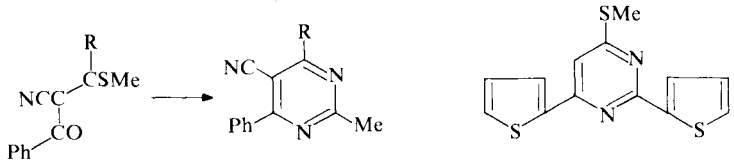


107 **108** **109**

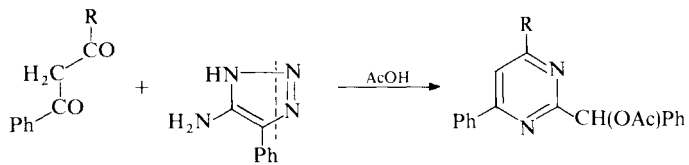
compounds were made similarly.[176] The use of some related fluorinated phosphates is exemplified in the reaction of diethyl 2,3,3,4,4,4-hexafluoro-1-phenylbut-1-en-1-yl phosphate (**110**) with formamidine in tetrahydrofuran containing a base to give 5-fluoro-4-phenyl-6-trifluoromethylpyrimidine (**111**) (66%); several analogs were made likewise.[3823] The use of *acylketene thioacetal intermediates* is exemplified in the condensation of 2-benzoyl-3,3-bismethylthioacrylonitrile (**112**, R = SMe) with acetamidine (in dimethylformamide containing triethylamine) to give 2-methyl-4-methylthio-6-phenyl-5-pyrimidinecarbonitrile (**113**, R = SMe) (91%);[4043] likewise, the modified acetal, 3-anilino-2-benzoyl-3-methylthioacrylonitrile (**112**, R = NHPh), gave 4-anilino-2-methyl-6-phenyl-5-pyrimidinecarbonitrile (**113**, R = NHPh) (52%) and several analogs were made similarly.[4043] Less simple products are typified by 4-methylthio-2,4-dithien-2′-ylpyrimidine (**114**) (32%), made from 2-(3′,3′-bismethylthioacryloyl)thiophene with 2-thiophenecarboxamidine in benzene–dimethylformamide containing sodium hydride.[49] 5-Phenyl-1,2,3-triazol-4-amine (**116**) reacted as a *pro-amidine* in its condensation with benzoylacetone (**115**, R = Me) or dibenzoylmethane (**115**, R = Ph) in boiling glacial



110 **111**



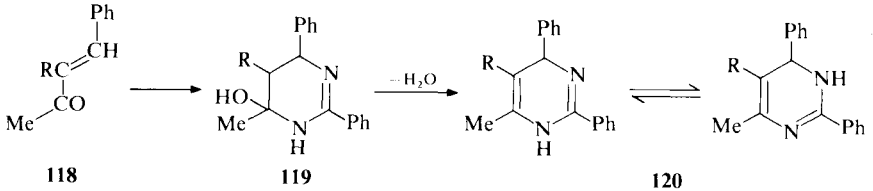
112 **113** **114**



115 **116** **117**

acetic acid to give 2-α-acetoxybenzyl-4-methyl-6-phenylpyrimidine (**117**, R = Me) (~70%) or 2-α-acetoxybenzyl-4,6-diphenylpyrimidine (**117**, R = Ph) (~75%), respectively.[4044]

The use of *reduced intermediates* akin to β-diketones in the preparation of hydropyrimidines is exemplified by the condensation of benzylideneacetone (**118**, R = H) with benzamidine in anhydrous acetone to give 4-methyl-2,6-diphenyl-3,4,5,6-tetrahydro-4-pyrimidinol (**119**, R = H) (82%), which underwent dehydration in an aprotic solvent (e.g., acetonitrile) to give 4-methyl-2,6-diphenyl-3,6 (or 1,6)-dihydropyrimidine (**120**, R = H) (98%).[267] Other such examples have been reported.[188,205,267,4322] With benzamidine in acetone, 3-benzylidene-2,4-pentanedione (**118**, R = Ac) behaved as a partially reduced β-diketone (instead of a regular β-diketone) to afford initially 5-acetyl-4-methyl-2,6-diphenyl-3,4,5,6-tetrahydro-4-pyrimidinol (**119**, R = Ac) and thence either 5-acetyl-4-methyl-2,6-diphenyl-3,6 (or 1,6)-dihydropyrimidine (**120**, R = Ac) (by loss of water in boiling benzene) or the deacetyl analog (**120**, R = H) (by loss of ethyl acetate and water in boiling ethanol).[290] The dihydro products are not always isolable: for example, α-cyanochalcone with benzamidine gave 2,4,6-triphenyl-5-pyrimidinecarbonitrile (82%) as the only product.[84] Other such examples have been reported.[4128,4324–4326,6142]



118 **119** **120**

3.3.2. With Guanidines

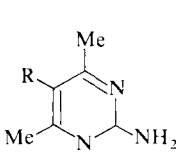
The exothermic condensation of the *simplest β-diketone*, acetylacetone, with guanidine or guanidine carbonate in an aqueous medium afforded 4,6-dimethyl-2-pyrimidinamine (**121**, R = H) in ~85% yield;[2738,2739, cf. 2736] maintained at room temperature, the reaction is significantly faster in light than in the dark.[2737] The same condensation is less satisfactory in aqueous ethanol (72% yield) because of the formation of 2-acetyl-3,5-dimethylphenol from two molecules of the diketone.[2743]

Some *other β-diketones* with guanidine gave the following products.

4,6-Dimethyl-5-phenyl-2-pyrimidinamine (**121**, R = Ph) (18%) from fusion of 3-phenyl-2,4-pentanedione with guanidine carbonate at 150°.[2114]

4,5,6-Trimethyl-2-pyrimidinamine (**121**, R = Me) (20%) from 3-methyl-2,4-pentanedione (ethanolic ethoxide).[3698]

4-Methyl-6-thien-2′-yl-2-pyrimidinamine (**122**) (43–79%) from 2-acetoacetylthiophene (150°).[4045,4046,4049]



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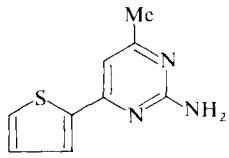

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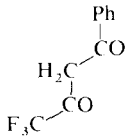

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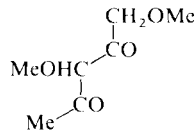


124

4,6-Dimethyl-5-phenylazo-2-pyrimidinamine (**121**, R = N:NPh) (59–70%) from 3-phenylazo-2,4-pentanedione (alcoholic alkali).[614,4050]

4-Phenyl-6-trifluoromethyl-2-pyrimidinamine (~70%) from 1-benzoyl-3,3,3-trifluoroacetone (**123**) (150°).[4048]

5-Methoxy-4-methoxymethyl-6-methyl-2-pyrimidinamine (28%) from 1,3-dimethoxy-2,4-pentanedione (**124**) (60°).[432]

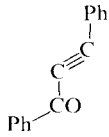
Also other products.[442,645,4047,4051,4052]

The condensations of *β-diketone equivalents with guanidine* are exemplified in the formation of the following 2-pyrimidinamines.

4,6-Diphenyl-2-pyrimidinamine (76% or 23%) from 1-benzoyl-2-phenylacetylene (**125**) (aqueous ethanol)[4053,4054] or from β-benzoyl-α-ethylthiostyrene (**126**) (ethanolic alkali),[238] respectively.

4,6-Dimethyl-2-pyrimidinamine (**121**, R = H) (57%) from the bisdimethyl-*aminotrimethinium* salt (**127**) (methanolic methoxide).[2318]

4-Methylthio-6-phenyl-2-pyrimidinamine (**129**, R = SMe) (50%) or its 4-methoxy analog (**129**, R = OMe) (70%), from 1-benzoyl-2,2-bismethylthioethylene (**128**) (sodium hydride–dimethylformamide or methanolic sodium methoxide, respectively).[4055, cf. 486,2395,4056]



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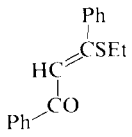

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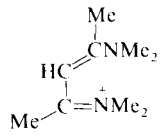

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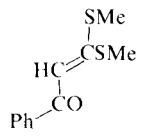

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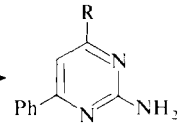

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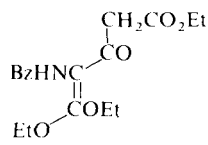
5-Benzamido-4-ethoxy-6-ethoxycarbonylmethyl-2-pyrimidinamine (**131**, R = H) (45%) from ethyl 4-benzamido-5,5-diethoxy-3-oxopent-4-enoate (**130**).[91]



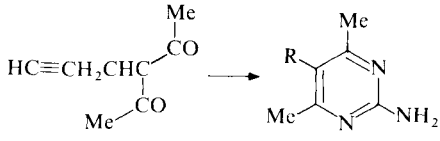
130

131

5-Fluoro-4-phenyl-6-trifluoromethyl-2-pyrimidinamine (93%) from diethyl 2,3,3,4,4,4-hexafluoro-1-phenylbut-1-enyl phosphate (**110**).[3823]

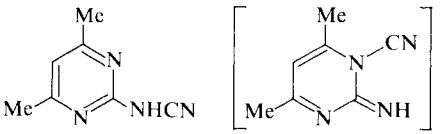
Also other pyrimidinamines.[141,433,452,3966,3973]

The condensation of 3-prop-2′-ynyl-2,4-pentanedione (**132**) with neat guanidine carbonate under reflux gave a separable mixture of the expected product (4,6-dimethyl-5-prop-2′-ynyl-2-pyrimidinamine) (**133**, R = $CH_2C{:}CH$) (15%), the 5-prop-1′-ynyl isomer (**133**, R = C:CMe) (29%), and the 5-allenyl isomer (**133**, R = $CH{:}C{:}CH_2$) (~5%), undoubtedly due to prototropic change under the conditions prevailing.[843]



132 **133**

Cyclocondensations of *N-substituted guanidines with β-diketones or their equivalents* appear to give only 2-(substituted-amino)pyrimidines, even when the formation of isomeric 1-substituted-2(1*H*)-pyrimidinimines would be possible: in any case, such imines would likely undergo Dimroth rearrangement to the isomeric (secondary) amines under the basic conditions being used. Thus the product from *N*-cyanoguanidine with acetylacetone was initially formulated[2736] as 1-cyano-4,6-dimethyl-2(1*H*)-pyrimidinimine (**135**) but was later shown[2362] to be 2-cyanoamino-4,6-dimethylpyrimidine (**134**), although some doubts appeared to persist;[2363] numerous other 4,6-dialkyl-2-cyanoaminopyrimidines have been made similarly.[161,204,216,241,388] The following syntheses further illustrate such condensations.



134 **135**

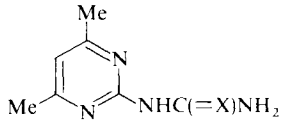
4,6-Dimethyl-2-sulfanilamidopyrimidine (~70%) from *p*-aminobenzenesulfonylguanidine with acetylacetone (160°).[4057]

4,6-Dimethyl-2-methylaminopyrimidine from *N*-methylguanidine with acetylacetone; identified by acidic hydrolysis to 4,6-dimethyl-2(1*H*)-pyrimidinone (thus avoiding any Dimroth rearrangement).[861]

2-Ethylamino-4-methyl-6-trifluoromethylpyrimidine (52%) from *N*-ethylguanidine with 1,1,1-trifluoro-2,4-pentanedione (aqueous ethanolic potassium carbonate).[4060]

2-Dimethylamino-4,6-diphenylpyrimidine (30%) from *N*,*N*-dimethylguanidine with dibenzoylmethane (ethanol).[4061]

4,6-Dimethyl-2-ureidopyrimidine (**136**, X = O) (15%) from *N*-carbamoylguanidine with acetylacetone (ethanol);[2554] also 4,6-dialkyl homologs,[2554, cf. 2573] the thioureido analog (**136**, X = S) (77%),[3862] and phenylureido analogs.[4066]



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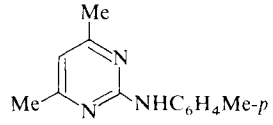


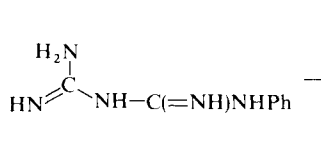
137

4,6-Dimethyl-2-*p*-toluidinopyrimidine (**137**) (80%) from *N*-*p*-tolylguanidine with acetylacetone in ethanolic sodium carbonate;[70] also many analogous 2-*p*-toluidinopyrimidines.[38,70,85,174,271]

5-Benzamido-2-dimethylamino-4-ethoxy-6-ethoxycarbonylmethylpyrimidine (**131**, R = Me) (43%) from *N*,*N*-dimethylguanidine with ethyl 4-benzamido-5,5-diethoxy-3-oxopent-4-enoate (**130**).[91]

Also many analogous condensations.[108,392,2167,2743,2964,2999,3206 (cf. 4059), 3915,4058,4062–4064]

The condensation of 1-phenylbiguanide (**138**) with acetylacetone in ethanol gave 4,6-dimethyl-2-*N'*-phenylguanidinopyrimidine (**139**) (54%);[4067] related compounds were made similarly.[4066,4067] As might be expected, biguanidine (**140**) with 1,1,1-trifluoro-2,4-pentanedione gave a separable mixture of 2-guanidinoamino-4-methyl-6-trifluoromethylpyrimidine (**141**) and *N*,*N'*-bis(4-methyl-6-trifluoromethylpyrimidin-2-yl)hydrazine (**142**);[4068] in some analogous cases, the former type of product underwent intramolecular cyclization to a triazolopyrimidine, such as 7-ethyl (or phenyl)-5-trifluoromethyl-*s*-triazolo[1,5-*a*]pyrimidin-2-amine (**143**, R = Et or Ph).[4068–4070] 1,3-Diguanidinopropane with acetylacetone in pyridine containing piperidine gave 1,3-bis(4',6'-dimethylpyrimidin-2'-ylamino)propane (75%); analogs were made similarly.[93]



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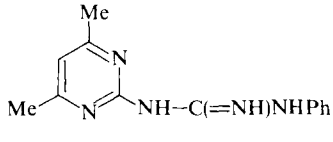

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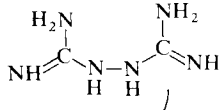

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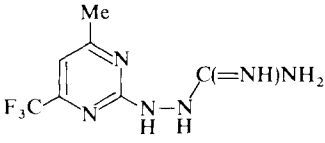

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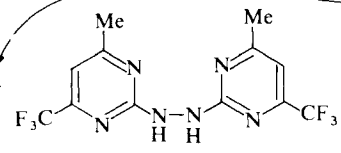

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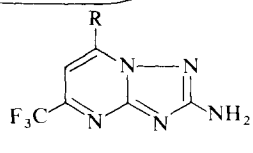
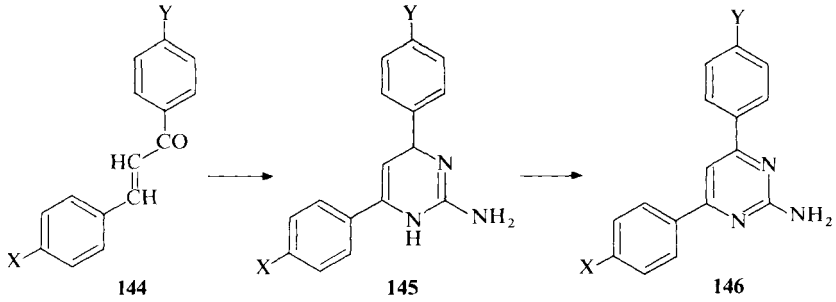


143

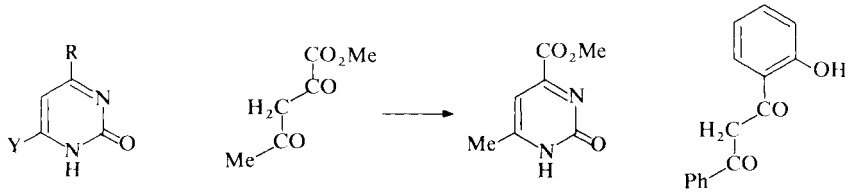
Condensations of guanidines with *partially reduced synthones* (in the form of α,β-unsaturated ketones) have been explored quite extensively: depending on the substitution pattern, dihydropyrimidines or their spontaneously aromatized derivatives may be isolated. For example, chalcone (**144**, X = Y = H) with guanidine gave 4,6-diphenyl-1,4-dihydro-2-pyrimidinamine (**145**, X = Y = H), which was reasonably stable as its hydrochloride, but which underwent rapid aerial oxidation as the free base in ethanol to afford 4,6-diphenyl-2-pyrimidinamine (**146**, X = Y = H).[2735] Both 4- (**144**, X = OMe, Y = H) and 4′-methoxychalcone (**144**, X = H, Y = OMe) with guanidine in benzene gave only one isolable product, 4-*p*-methoxyphenyl-6-phenyl-2-pyrimidinamine (**146**, X = OMe, Y = H).[30] In contrast, 4- (**144**, X = Cl, Y = H) and 4′-chlorochalcone (**144**, X = H, Y = Cl) under similar conditions gave 4-*p*-chlorophenyl-6-phenyl-1,4-dihydro-2-pyrimidinamine (**145**, X = Cl, Y = H) and 4-*p*-chlorophenyl-6-phenyl-3,6-dihydro-2-pyrimidinamine (**145**, X = H, Y = Cl), respectively, which were isolated as hydrochlorides with different melting points: oxidation of either dihydro compound gave 4-*p*-chlorophenyl-6-phenyl-2-pyrimidinamine (**146**, X = Cl, Y = H).[30] Many reports of such condensations have appeared.[75,103,307,348,470,3776,3866,3922,3972,4054,4071–4074]



3.3.3. With Ureas

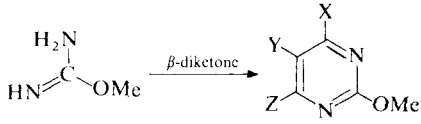
The cyclocondensations of *urea* with β-diketones has been well covered. Thus the combination of urea with acetylacetone to give 4,6-dimethyl-2(1*H*)-pyrimidinone (**147**, R = Y = Me) was first carried out nearly a century ago;[2738,4075,4076] the best media proved to be ethanolic hydrochloric acid or ethanolic sulfuric acid, both of which gave 70–80% yield of the appropriate salt.[1936,2238,2825,4077] Two stable tautomeric forms of **147** (R = Y = Me) were postulated at one time,[2825] but this view could not be maintained.[2824,4078] Although benzoylacetone was condensed with urea initially under alkaline conditions to give 4-methyl-6-phenyl-2(1*H*)-pyrimidinone (**147**, R = Me, Y = Ph),[4075] the reaction went better in ethanolic hydrochloric acid to give a 63% yield.[2267] Similar reactions with appropriate β-diketones gave 4,5,6-trimethyl- (50%),[2358,3660] 4-methyl-6-thien-2′-yl- (51%),[4049] 5-allyl-4,6-

dimethyl- (64%),[843] 4,6-dimethyl-5-propyl- (46%),[843] 4,6-dimethyl-5-prop-2′-ynyl- (65%),[843] 4-ethyl-6-phenyl- (70%),[122] and 4-phenyl-6-propyl-2(1*H*)-pyrimidinone (64%);[122] also methyl 6-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate (**149**) from methyl acetylpyruvate (**148**) with urea in methanolic hydrochloric acid (84% as urea complex),[2266] 4-*o*-hydroxyphenyl-6-phenyl-2(1*H*)-pyrimidinone (**147**, R = C_6H_4OH-*o*, Y = Ph) from *o*-hydroxydibenzoylmethane (**150**) with urea in boiling ethylene glycol (60% yield);[3852] and 4,6-diphenyl-2(1*H*)-pyrimidinone (**147**, R = Y = Ph) (76%) from 1-benzoyl-2-phenylacetylene (**125**) with urea in ethanolic ethoxide.[217] Other such reactions have been reported.[6131]



147 **148** **149** **150**

Both *O*- and *N*-substituted ureas react with β-diketones. Thus *O-methylisourea* (**151**) with appropriate diketones in aqueous potassium carbonate gave 2-methoxy-4,6-dimethyl- (**152**, X = Z = Me, Y = H) (70%),[2532] 2-methoxy-4,5,6-trimethyl- (**152**, X = Y = Z = Me) (32%),[2995] 2-methoxy-4-methyl-6-trifluoromethyl- (**152**, X = Me, Y = H, Z = CF_3) (64%),[4079] and 2-methoxy-4-phenyl-6-trifluoromethylpyrimidine (**152**, X = Ph, Y = H, Z = CF_3) (36%),[4080] as well as related compounds.[2532,2995,4079,4080]



151 **152**

Condensations between *N-substituted ureas and symmetrical β-diketones* are represented in the following examples.

1,4,6-Trimethyl-2(1*H*)-pyrimidinone (**153**, R = Me) (84%) from *N*-methylurea with acetylacetone in ethanolic sulfuric acid.[2825]

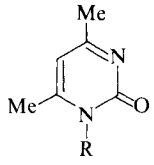
1-Methoxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**153**, R = OMe) (75%) from *N*-methoxyurea with acetylacetone in ethanolic hydrogen chloride; also analogs.[2828]

1-Benzoyl-4,6-dimethyl-2(1*H*)-pyrimidinone (**153**, R = Bz) (68%) from *N*-benzoylurea with neat acetylacetone; also analogs.[4081]

1-Benzyl-4,6-diphenyl-2(1*H*)-pyrimidinone (68%) from *N*-benzylurea with dibenzoylmethane in glacial acetic acid containing *p*-toluenesulfonic acid.[4061]

1,4,5,6-Tetramethyl-2(1*H*)-pyrimidinone (27%) from *N*-methylurea with 3-methyl-2,4-pentanedione in ethanolic hydrochloric acid.[3660]

1,3,4,6-Tetramethyl-2-oxo-2,3-dihydro-1-pyrimidinium chloride (**154**) (85%) from *N*,*N*'-dimethylurea with acetylacetone in hydrochloric acid;[2810] also other salts and homologs.[1803,2810]



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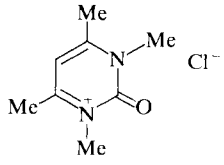
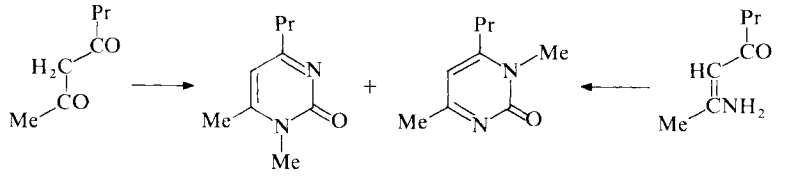
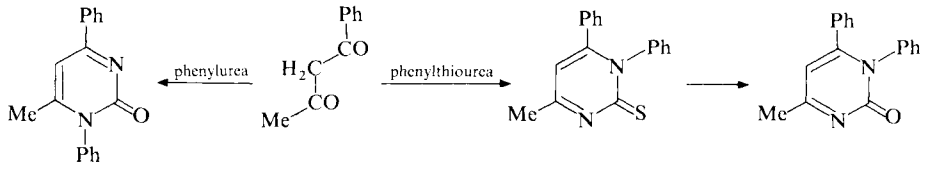


154

The reaction of an *N-substituted urea with an unsymmetrical β-diketone or equivalent* usually gives two isomeric products. For example, 2,4-heptanedione (**155**) with *N*-methylurea in ethanol furnished 1,6-dimethyl-4-propyl-2(1*H*)-pyrimidinone (**156**) and 1,4-dimethyl-6-propyl-2(1*H*)-pyrimidinone (**157**) in almost 1 : 1 ratio; in contrast, the equivalent intermediate, 2-aminohept-2-en-4-one (**158**), with *N*-methylurea in benzene containing hydrogen chloride gave the same products in 2 : 1 ratio.[4083] No useful predictive conclusions were possible from these and related data.[4083] An interesting situation arose in the reaction of benzoylacetone (**160**) with *N*-phenylurea in ethanolic hydrochloric acid, which gave mainly 4-methyl-3,6-diphenyl-2(3*H*)-pyrimidinone (**159**), whereas a similar reaction with *N*-methylthiourea gave only a product with the opposite orientation, 4-methyl-1,6-diphenyl-2(1*H*)-pyrimidinethione (**161**); the latter product was easily converted into 4-methyl-1,6-dihydro-2(1*H*)-pyrimidinone (**162**), there-



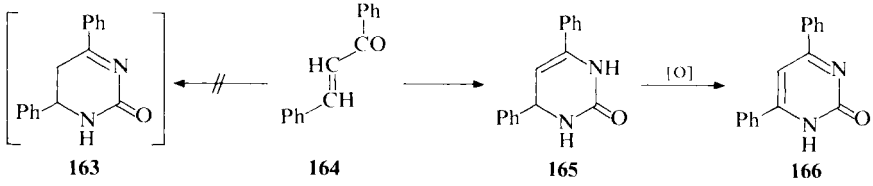
155 **156** **157** **158**



159 **160** **161** **162**

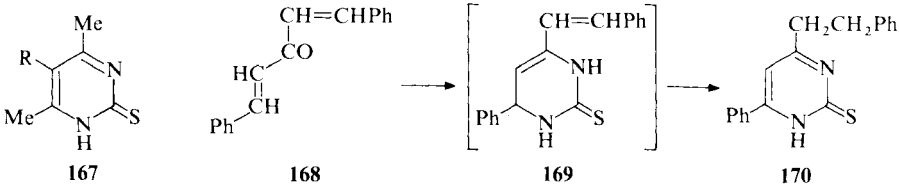
by affording a good route to the pyrimidinone not available directly.[4082] Complicated examples have been reported.[6007]

The cyclocondensation of the *reduced synthone*, β-benzoylstyrene (**164**), with urea in ethanolic ethoxide gave a dihydropyrimidine, initially formulated[4084] as 4,6-diphenyl-5,6-dihydro-2(1*H*)-pyrimidinone (**163**) but later as 4,6-diphenyl-3,4-dihydro-2(1*H*)-pyrimidinone (**165**) on nmr evidence;[217] the dihydro compound and related products all underwent oxidation by elemental selenium at 180° to 4,6-diphenyl-2(1*H*)-pyrimidinone (**166**) and appropriate analogs.[217] Other cases have been reported.[530,3945]



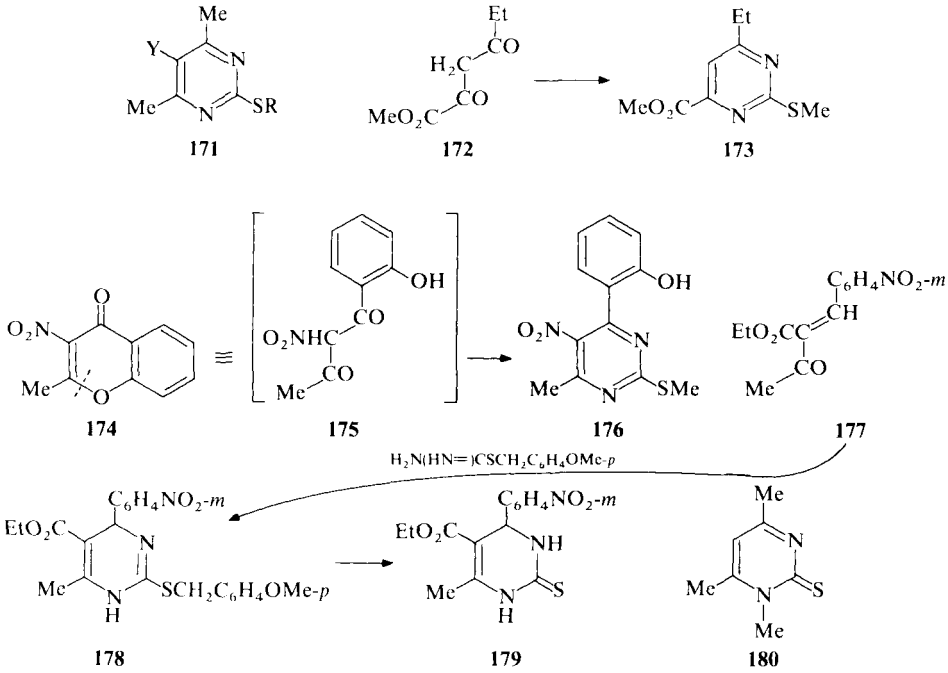
3.3.4. With Thioureas

The reaction of *thiourea* with β-diketones is usually normal. Thus thiourea with acetylacetone in ethanolic sulfuric acid or ethanolic hydrochloric acid gave 4,6-dimethyl-2(1*H*)-pyrimidinethione (**167**, R = H) as sulfate or hydrochloride, respectively, in ~90% yield: the free thione was isolated therefrom in ~60% yield.[133,764,2697,4076] Likewise, 3-methyl-2,4-pentanedione gave 4,5,6-trimethyl-2(1*H*)-pyrimidinethione (**167**, R = Me) (54%),[3302] benzoylacetone (**160**) gave 4-methyl-6-phenyl-2(1*H*)-pyrimidinethione (80%),[2656, cf. 1228] and 3-cyano-2,4-pentanedione (2-acetyl-3-oxobutyronitrile) gave 4,6-dimethyl-2-thioxo-1,2-dihydro-5-pyrimidinecarbonitrile (**167**, R = CN) (9%).[442] 4-Acetoacetylpyridine and thiourea without solvent at 160° gave 4-methyl-6-pyridin-4′-yl-2(1*H*)-pyrimidinethione, apparently in reasonable yield.[4047] An unusual variation involved condensation of 1,5-diphenylpentadien-3-one (**168**) with thiourea in methanolic methoxide to give not the styryldihydropyrimidinethione (**169**), but 4-phenethyl-6-phenyl-2(1*H*)-pyrimidinethione (**170**), perhaps because of the inbuilt dehydrogenation potential of the synthone.[4088] In a rather analogous way, 1 eq of chalcone (benzylideneacetophenone) (**144**, X = Y = H) reacted with thiourea to give mainly a 4,6-diphenyldihydro-2(1*H*)-pyrimidinethione, but when 2 eq of chalcone were used, the second molecule supplied dehydrogenation



capacity to afford 4,6-diphenyl-2(1*H*)-pyrimidinethione and α-benzylacetophenone as the only products.[4087, cf. 471,531]

The use of *S-alkylisothioureas* with β-diketones is widespread. For reasons of stability, neutral or alkaline media are generally employed, but yields are seldom good. Thus acetylacetone with *S*-methylisothiourea in aqueous potassium carbonate gave 4,6-dimethyl-2-methylthiopyrimidine (**171**, R = Me, Y = H) (62%);[2532, cf. 1046] 3-ethyl-2,4-pentanedione likewise gave 5-ethyl-4,6-dimethyl-2-methylthiopyrimidine (**171**, R = Me, Y = Et) (16%);[2995] 1-benzoyl-3,3,3-trifluoroacetone gave 2-methylthio-4-phenyl-6-trifluoromethylpyrimidine (39%);[4080] acetylacetone with *S*-benzylisothiourea in ethanolic pyridine containing potassium carbonate gave only a 3% yield of 2-benzylthio-4,6-dimethylpyrimidine (**171**, R = CH_2Ph, Y = H),[2895] which was later made (75%) by simply heating thiourea, benzyl chloride, and acetylacetone in dimethylformamide;[4085] methyl 3-propionylpyruvate (methyl 2,4-dioxohexanoate) (**172**) gave methyl 6-ethyl-2-methylthio-4-pyrimidinecarboxylate (**173**) (43%);[2266] and many other examples have been reported in the preceding references and elsewhere.[2756,4079,4086] When *S*-methylisothiourea was warmed in aqueous alcoholic triethylamine with 2-methyl-3-nitro-4-chromenone (**174**), the latter reacted as the notional diketone (**175**) to give 4-*o*-hydroxyphenyl-6-methyl-2-methylthio-5-nitropyrimidine (**176**) in 83% yield.[565] The reduced synthone, ethyl 2-acetyl-3-*m*-nitrophenylacrylate (**177**), reacted with *S*-*p*-methoxybenzylisothiourea in dimethylformamide containing sodium acetate to give a dihydropyrimidine (**178**), which underwent removal of the *S*-methoxybenzyl group by



ethanethiol in trifluoroacetic acid to give ethyl 4-methyl-6-*m*-nitrophenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**179**) in 81% overall yield.[531]

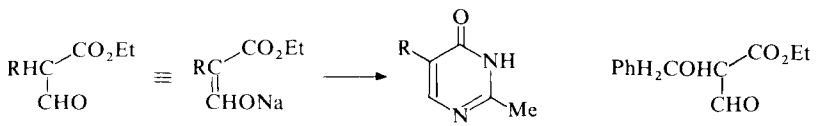
The use of *N-substituted-thioureas* in this context has been minimal. However, acetylacetone with *N*-methylthiourea in ethanolic hydrochloric acid gave 1,4,6-trimethyl-2(1*H*)-pyrimidinethione (**180**) as hydrochloride;[2697] benzoylacetone (**160**) with *N*-phenylthiourea likewise gave only 4-methyl-1,6-diphenyl-2(1*H*)-pyrimidinethione (**161**) (82%);[4082] and appropriately *p*-substituted benzoylacetones with *N*-phenylthiourea gave 4-*p*-chlorophenyl-6-methyl-3-phenyl-2(3*H*)- (50%), 4-*p*-methoxyphenyl-6-methyl-3-phenyl-2(3*H*)- (48%), and 4-methyl-1-phenyl-6-*p*-tolyl-2(1*H*)-pyrimidinethione (64%), in each case devoid of isomeric impurity.[4082] 4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinethione and analogs have been so made.[3986]

3.4. USE OF β-ALDEHYDO ESTERS

In this group of syntheses occur the preferred routes to such important pyrimidines as uracil, thymine, isocytosine, and thiouracil. For reasons of availability and stability, most β-aldehydo esters are customarily supplied as equivalent synthones.

3.4.1. With Amidines

For these condensations, the *crude sodio derivatives of α-formylated esters* are commonly used. Thus ethyl formylacetate (**181**, R = H) as its sodio derivative (**182**, R = H) underwent condensation with aqueous acetamidine to give 2-methyl-4(3*H*)-pyrimidinone (**183**, R = H) in ~30% yield.[112,689,2259] Likewise, ethyl 2-formylpropionate (**181**/**182**, R = Me) with acetamidine in ethanol gave 2,5-dimethyl-4(3*H*)-pyrimidinone (**183**, R = Me) (30%);[2108,3207] ethyl formylacetate (**181**/**182**, R = H) with propionamidine gave 2-ethyl-4(3*H*)-pyrimidinone (36%);[2149,2551] and ethyl 2-benzyloxy-2-formylacetate (**184**) with acetamidine or 2-hydroxyacetamidine gave 5-benzyloxy-2-methyl- (56%)[4089, cf. 581,1340] or 5-benzyloxy-2-hydroxymethyl-4(3*H*)-pyrimidinone (55%),[4089] respectively. Similar condensations using sodio α-formylated esters gave the following *substituted-4(3H)-pyrimidinones.*

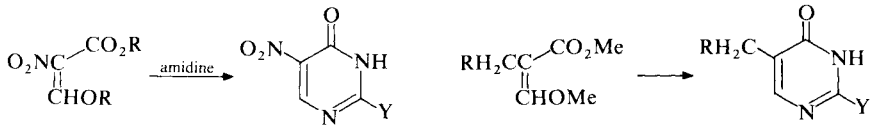


181 **182** **183** **184**

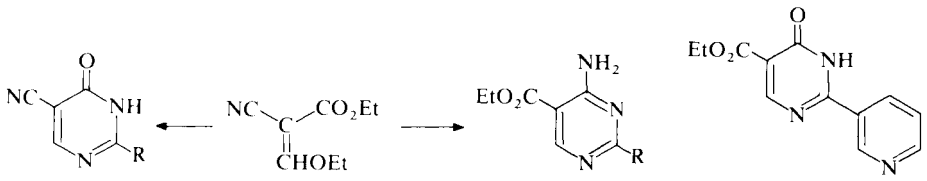
2-Methyl (or phenyl)-5-tetrahydropyran-2′-yloxy- (40–50%).[42,1324]
5-Ethoxymethyl-2-fluoromethyl- (8%).[2910]

5-Fluoro- (25%).[1262]
5-Fluoro-2-methyl- (**183**, R = F) (23%).[1262]
2-Hydroxymethyl- (83%).[2057]
2-Trifluoromethyl- (56%).[4090]
5-Allyl-2-methyl- (**183**, R = $CH_2CH{:}CH_2$) (22%).[872]
2-Phenyl- (39%).[2149,4091]
5-Methoxy-2-phenyl- (69%).[4092]
2-Benzyl- (54%).[2084]
5-Methyl-2-phenyl- (89%).[4093]
5-Formamido- (40%).[243]
5-Benzamidomethyl-2-methyl- (**183**, R = CH_2NHBz) (62%).[1414]
Also analogs.[22,689,1005,1209,2084,3129,4042,4094]

The employment of *2-alkoxymethylene esters* in place of *β*-aldehydo esters has proved convenient, mainly because such synthones can be made and purified easily. Thus, ethyl 3-ethoxy-2-nitroacrylate (ethyl 2-ethoxymethylene-2-nitroacetate) (**185**, R = Et) reacted with formamidine to give 5-nitro-4(3*H*)-pyrimidinone (**186**, Y = H),[1654] while methyl 3-methoxy-2-nitroacrylate (**185**, R = Me) with free acetamidine or benzamidine in cold ethanol gave 2-methyl-5-nitro- (**186**, Y = Me) (32%) or 5-nitro-2-phenyl-4(3*H*)-pyrimidinone (**186**, Y = Ph) (59%), respectively.[239] Likewise, methyl 3-methoxy-2-methoxymethylacrylate (**187**, R = OMe) with acetamidine or benzamidine gave 5-methoxymethyl-2-methyl- (**188**, R = OMe, Y = Me) or 5-methoxymethyl-2-phenyl-4(3*H*)-pyrimidinone (**188**, R = OMe, Y = Ph), respectively;[4095] and dimethyl 2-methoxymethyleneglutarate (**187**, R = CH_2CO_2Me) or dimethyl 2-formylglutarate with acetamidine gave 5-*β*-methoxycarbonylethyl-2-methyl-4(3*H*)-pyrimidinone (**188**, R = CH_2CO_2Me) (45%).[1209,4096] The intermediate, ethyl 2-cyano-3-ethoxyacrylate (**190**) can clearly react as a *β*-aldehydo ester, as a *β*-aldehydo nitrile, or (less likely) as a *β*-ester nitrile: in the event, it reacted with acetamidine to give 2-methyl-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile (**189**, R = Me) (89% yield) and ethyl 4-amino-2-methyl-5-pyrimidinecarboxylate (**191**, R = Me) (8% yield); in contrast, benzamidine gave mainly ethyl 4-amino-2-phenyl-5-pyrimidinecarboxylate (**191**, R = Ph) (42% yield) and only a trace of 4-oxo-2-phenyl-3,4-dihydro-5-pyrimidinecarbonitrile (**189**, R = Ph).[1600] Likewise, dimethyl α-ethoxymethylenemalonate could react as an aldehydo ester or as a diester: in fact, with acetamidine or 3-pyridinecarboxamidine it gave a single product in each case, namely, ethyl 2-methyl-4-oxo-3,4-dihydro-5-



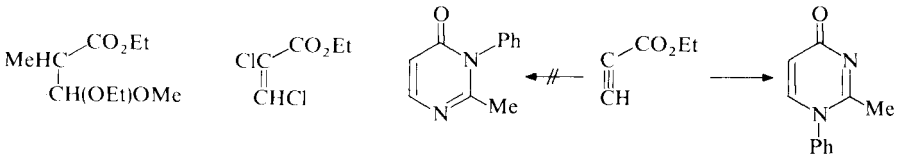
185 **186** **187** **188**



189 190 191 192

pyrimidinecarboxylate (86%)[1472,3056] or ethyl 4-oxo-2-pyridin-3′-yl-3,4-dihydro-5-pyrimidinecarboxylate (**192**) (73%),[2989] respectively.

The use of some *other equivalents* of β-aldehydo esters is exemplified in the condensation of the acetal, ethyl 3-ethoxy-3-methoxy-2-methylpropionate (**193**), with acetamidine to give 2,5-dimethyl-4(3*H*)-pyrimidinone (**188**, R = H, Y = Me) in 30% yield (cf. 28% from ethyl 3-methoxy-2-methylacrylate);[1420] of ethyl 2,3-dichloroacrylate (**194**) with benzamidine to give 5-chloro-2-phenyl-4(3*H*)-pyrimidinone (~70%);[2283] of ethyl propynoate (**196**) with *N*-phenylacetamidine to give not 2-methyl-3-phenyl-4(3*H*)-pyrimidinone (**195**) as initially reported,[3867,4097] but the isomeric 2-methyl-1-phenyl-4(1*H*)-pyrimidinone (**197**) (64%);[3726] and of methyl 6-oxo-6*H*-pyran-3-carboxylate with methanolic formamidine to give 5-β-carboxyvinyl-4(3*H*)-pyrimidinone (38%).[3888]



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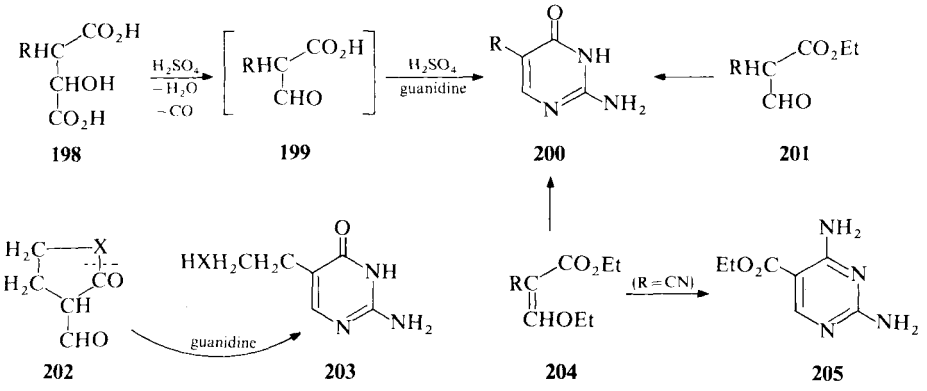
3.4.2. With Guanidines

Although (isolated) *2-formylacetic acid* (glyoxylic acid) (**199**, R = H) has been condensed with guanidine in fuming sulfuric acid to give 2-amino-4(3*H*)-pyrimidinone (isocytosine) (**200**, R = H) in 77% yield,[1348] it is better to use an older procedure (based on the Davidson–Baudisch synthesis; see Section 3.4.3). This involved the decarbonylation and dehydration of malic acid (**198**, R = H) to 2-formylacetic acid (**199**, R = H) and its subsequent condensation with guanidine, all in one pot of 20% fuming sulfuric acid: the overall yield of isocytosine (**200**, R = H) was up to 69%.[1662,4098] In much the same way, β-methylmalic acid (2-hydroxy-3-methylsuccinic acid) (**198**, R = Me) afforded 2-amino-5-methyl-4(3*H*)-pyrimidinone (**200**, R = Me) (76%).[1522]

The following products were made from *2-formylated esters* with guanidine in more conventional media.

2-Amino-5-benzyloxy-4(3*H*)-pyrimidinone (**200**, R = OCH_2Ph) (65%) from ethyl 2-benzyloxy-2-formylacetate (**201**, R = OCH_2Ph) with ethanolic guanidine.[1324, cf. 581,1340]



2-Amino-5-ethoxy-4(3*H*)-pyrimidinone (**200**, R = OEt) (45%) from ethyl 2-ethoxy-2-formylacetate (**201**, R = OEt) with guanidine carbonate at 175°.[1149]

2-Amino-5-fluoro-4(3*H*)-pyrimidinone (**200**, R = F) (27%) from ethyl 2-fluoro-2-formylacetate (**201**, R = F) with methanolic guanidine.[1264]

5-Allyl-2-amino-4(3*H*)-pyrimidinone (**200**, R = $CH_2CH{:}CH_2$) (52%) from ethyl 2-allyl-2-formylacetate (**201**, R = $CH_2CH{:}CH_2$) with ethanolic guanidine.[872]

2-Amino-5-phenylazo-4(3*H*)-pyrimidinone (**200**, R = N:NPh) (42%) from ethyl 2-formyl-2-phenylazoacetate (**201**, R = N:NPh) with guanidine in ethanolic ethoxide.[4100]

2-Amino-5-ethyl-4(3*H*)-pyrimidinone (**200**, R = Et) from methyl 2-formylbutyrate with ethanolic guanidine.[1152]

2-Amino-5-methylthio-4(3*H*)-pyrimidinone (**200**, R = SMe) (53%) from ethyl 2-formyl-2-(methylthio)acetate (**201**, R = SMe) with methanolic guanidine followed by thermal cyclization at 130°.[1567]

Also other such products.[1007,1230,1367,4099,4101,4102]

The use of *aldehydo ester equivalents with guanidine* is illustrated in the conversion of α-formyl-γ-butyrolactone, (**202**, X = O) into 2-amino-5-β-hydroxyethyl-4(3*H*)-pyrimidinone (**203**, X = O) (76%) by guanidine in methanolic alkali;[1005,1321] of the corresponding thiolactone (**202**, X = S) into 2-amino-5-β-mercaptoethyl-4(3*H*)-pyrimidinone (**203**, X = S) (62%);[1359] of ethyl 3-ethoxy-2-phenylacrylate (**204**, R = Ph) into 2-amino-5-phenyl-4(3*H*)-pyrimidinone (**200**, R = Ph) (47%);[2103] of ethyl 2-*p*-chlorophenylsulfonyl-3-ethoxyacrylate (**204**, R = $SO_2C_6H_4Cl$-*p*) into 2-amino-5-*p*-chlorophenylsulfonyl-4(3*H*)-pyrimidinone (~65%);[4104] of methyl 3-ethoxy-2-nitroacrylate, akin to (**204**, R = NO_2), into 2-amino-5-nitro-4(3*H*)-pyrimidinone (**200**, R = NO_2);[239] and of ethyl 2-cyano-3-ethoxyacrylate (**204**, R = CN) into a mixture of 2-amino-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile (**200**, R = CN)

and ethyl 2,4-diamino-5-pyrimidinecarboxylate (**205**) in which the latter predominated greatly.[1600,1601]

The condensations of *aldehydo esters or equivalents with substituted guanidines* are illustrated in the following syntheses.

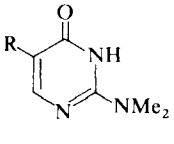
2-Dimethylamino-4(3*H*)-pyrimidinone (**206**, R = H) (83%) from malic acid (**198**) with *N*,*N*-dimethylguanidine in fuming sulfuric acid.[2083]

2-Dimethylamino-5-phenylazo-4(3*H*)-pyrimidinone (**206**, R = N:NPh) (23%) from ethyl 2-formyl-2-phenylazoacetate with *N*,*N*-dimethylguanidine in ethanolic ethoxide.[4100]

5-Carboxymethyl-2-cyanoamino-4(3*H*)-pyrimidinone (**207**) (~60%) from diethyl 2-formylsuccinate with dicyandiamide in ethanolic ethoxide.[2018]

2-Morpholino-4(3*H*)-pyrimidinone (**208**) (67%) from malic acid (**198**, R = H) with 4-morpholinecarboxamidine in fuming sulfuric acid.[2648]

Also other such syntheses.[1150,3976,4038,4101,4106,6223]



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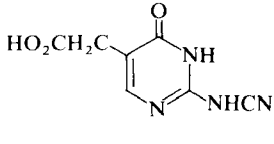

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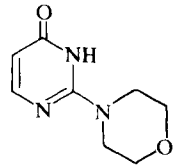

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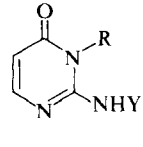

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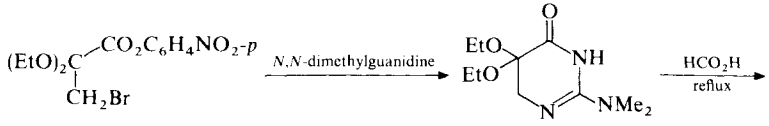
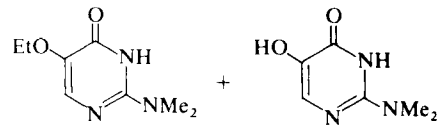
Condensation of ethyl 2-formylacetate with *N*-aminoguanidine gave a single product (17%) formulated as 2,3-diamino-4(3*H*)-pyrimidinone (**209**, R = NH_2, Y = H), rather than the isomeric 2-hydrazino-4(3*H*)-pyrimidinone (**209**, R = H, Y = NH_2), on evidence that is not totally convincing;[1573] moreover, the melting points of the product and the authentic hydrazinopyrimidinone are quite close. Another interesting reaction was that of the *reduced synthone* *p*-nitrophenyl 3-bromo-2,2-diethoxypropionate (**210**) with ethanolic *N*,*N*-dimethylguanidine to give 2-dimethylamino-5,5-diethoxy-5,6-dihydro-4(3*H*)-pyrimidinone (**211**), which underwent loss of ethanol and some solvolysis in



210 **211**

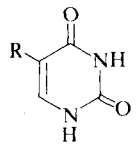


212 **213**

boiling formic acid to give a separable mixture of 2-dimethylamino-5-ethoxy- (**212**) and 2-dimethylamino-5-hydroxy-4(3*H*)-pyrimidinone (**213**).[3818] The use of reduced synthones is further illustrated in the reaction of ethyl acrylate with ethanolic guanidine to afford 2-amino-5,6-dihydro-4(3*H*)-pyrimidinone (65%);[211] of methyl acrylate with isopropanolic *N*,*N*-dimethylguanidine to give 2-dimethylamino-5,6-dihydro-4(3*H*)-pyrimidinone (>98%);[87] and of methyl acrylate with *N*-methyl- or *N*-benzylguanidine to give 2-amino-1-methyl- (>50%) or 2-amino-1-benzyl-5,6-dihydro-4(1*H*)-pyrimidinone (~80%), respectively, both of confirmed structure.[87,349]

3.4.3. With Ureas

Early attempts to prepare 2,4(1*H*,3*H*)-pyrimidinedione (uracil) (**214**, R = H) from ethyl 2-formylacetate (**181**/**182**) with urea in aqueous, alkaline, or acidic media failed.[2041,3053,3148] However, a one-pot reaction in which malic acid (**198**, R = H) was degraded to 2-formylacetic acid (**199**, R = H) and the latter was immediately condensed with urea (all in fuming sulfuric acid) did afford up to 55% of uracil (**214**, R = H);[2041] substitution of diethyl malate for malic acid decreased the yield to 31%.[1978] This general procedure became known as the *Davidson–Baudisch synthesis*, which has been extended: for example, 2-hydroxy-3-methylsuccinic acid (**198**, R = Me) so gave 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (thymine) (**214**, R = Me) (50%),[1522] and malic acid (**198**, R = H) with *N*-butylurea likewise gave 3-butyl-2,4(1*H*,3*H*)-pyrimidinedione.[1231]



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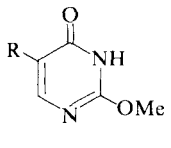

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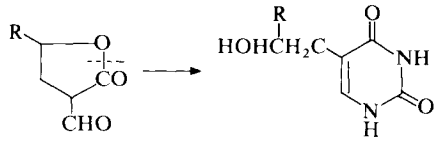
However, there are a few cases in which *free β-aldehydo esters* have been condensed successfully with ureas. Thus ethyl 2-benzyloxy-2-formylacetate with urea in ethanolic ethoxide gave 5-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**214**, R = OCH_2Ph) (70%);[1340] ethyl 2-fluoro-2-formylacetate with *O*-methylisourea likewise gave 5-fluoro-2-methoxy-4(3*H*)-pyrimidinone (**215**, R = F);[430,2158] and ethyl 2-formyl-2-*o*-hydroxyphenylazoacetate with urea in the same medium gave 5-*o*-hydroxyphenylazo-2,4(1*H*,3*H*)-pyrimidinedione (**214**, R = $N{:}NC_6H_4OH$-*o*) (16%).[4105] In fuming sulfuric acid, ethyl 2-formylpropionate or ethyl 2-formylbutyrate with urea gave 5-methyl- (**214**, R = Me) (50%) or 5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione (**214**, R = Et) (40%), respectively;[2887] ethyl 3-(3′,4′,5′-trimethoxyphenyl)propionate with urea in ethanolic hydrogen chloride gave 5-(3′,4′,5′-trimethoxybenzyl)-2,4(1*H*,3*H*)-pyrimidinedione (46%);[169] and ethyl 2-formylacetate with *N*-(*β*-amino-*β*-carboxyethyl)urea in aqueous

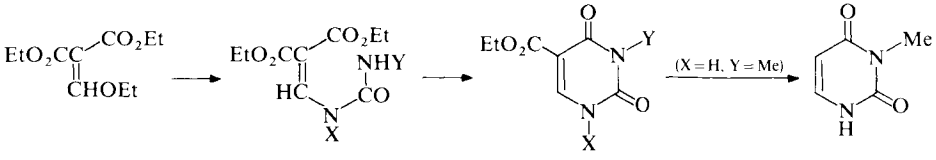
solution gave 1-β-amino-β-carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (~10%).[4107]

Condensations of *β-aldehydo ester equivalents* with ureas have been widely employed. Thus the use of *formylated lactones* is illustrated in the reaction of urea with α-formyl-γ-butyrolactone (**216**, R = H) or α-formyl-γ-valerolactone (**216**, R = Me), initially under acidic conditions to give an isolable intermediate followed by cyclization in ethanolic ethoxide, to afford 5-β-hydroxyethyl- (**217**, R = H) (54%)[2039, cf. 1321] or 5-β-hydroxypropyl-2,4(1*H*,3*H*)-pyrimidinedione (**215**, R = Me) (~30%),[3273] respectively, and in related reactions.[4108,4111]



216 **217**

Like the preceding route, *alkoxymethylene esters* often condense with ureas to give isolable acyclic intermediates that may require a separate treatment to induce ring closure. Thus, although it had been early reported[2527] that diethyl α-ethoxymethylenemalonate (**218**) did not react with urea, it was later shown that reaction did occur in ethanolic sodium ethoxide to give diethyl α-ureidomethylenemalonate (**219**, X = Y = H), which underwent a slower cyclization in the same medium to afford ethyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**220**, X = Y = H) as the sole product in ~15% yield;[904] a streamlined procedure eventually improved this yield to ~50%.[1980] When the same substrate (**218**) was treated similarly with *N*-methylurea, a similar (but uncharacterized) intermediate (**219**, X = H, Y = Me) was formed: this time, it underwent satisfactory cyclization on simply heating at 120° to afford only ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**220**, X = H, Y = Me) in 41% overall yield;[904] the position of the methyl group was checked[904] by saponification and decarboxylation to 3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**221**), which was then considered an authenticated structure and, in any case, was afterward shown to be so in another connection.[1432] The synthone (**218**) with *N*,*N*′-dimethylurea required no condensing agent: at 120° they gave ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**220**, X = Y = Me) (62%).[904] It is possible to prepare and cyclocondense the alkoxymethylene ester in one pot. Thus ethyl 2-nitroacetate, ethyl orthoformate, and urea



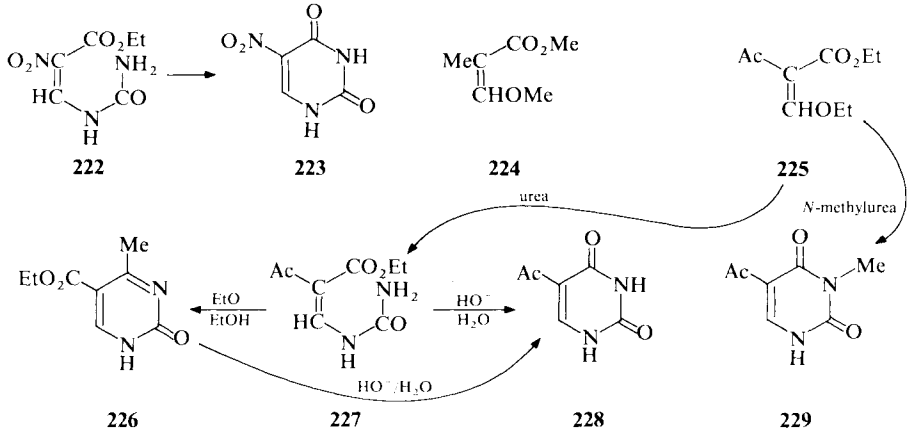
218 **219** **220** **221**

gave ethyl 2-nitro-3-ureidoacrylate (**222**), which in ethanolic potassium ethoxide afforded 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**223**) (30% overall);[2704] its 3-benzyl, 3-methyl, 3-phenyl, and 1,3-dimethyl derivatives were made similarly by using appropriate *N*-alkylated ureas,[2704] and some aspects of the mechanism have been studied.[2704,4109] The use of alkoxymethylene esters is illustrated further in the following preparations.

1-Benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (55%) from ethyl 3-ethoxyacrylate with *N*-benzyloxyurea in ethanolic ethoxide.[748]

1-Benzyloxy-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (~10%) from ethyl 3-methoxy-2-fluoroacrylate with *N*-benzyloxyurea in ethanolic ethoxide.[1265]

3-Isopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione from methyl 3-methoxy-2-methylacrylate (**224**) with *N*-isopropylurea in aqueous acid followed by cyclization of the intermediate in methanolic methoxide.[2787]



222 **223** **224** **225**

226 **227** **228** **229**

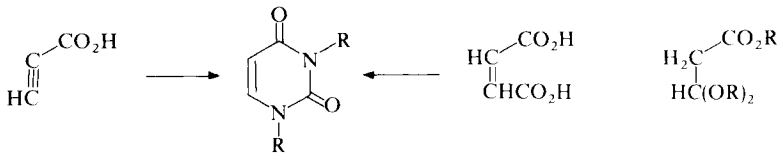
5-Acetyl-2,4(1*H*,3*H*)-pyrimidinedione (**228**) from ethyl 2-acetyl-3-ethoxyacrylate (**225**) with urea to give ethyl 2-acetyl-3-ureidoacrylate (**227**) followed by cyclization (90%) in aqueous alkali; cyclization in ethanolic ethoxide gave the alternative product, ethyl 4-methyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate (**226**) (25%), which was converted into **228** by treatment with aqueous alkali.[829]

Methyl 2-methoxy-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate (~25%) from diethyl α-ethoxymethylenemalonate with *O*-methylisourea in methanolic methoxide.[2203]

5-Acetyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**229**) as the single isolable product from heating 2-acetyl-3-ethoxyacrylate (**225**) with *N*-methylurea followed by cyclization of the intermediate in aqueous alkali.[817]

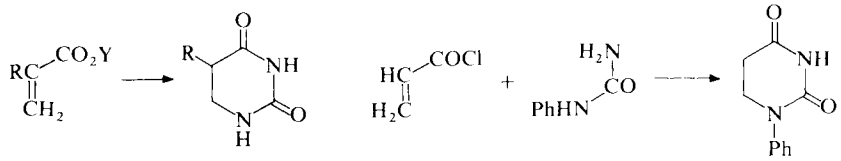
Also analogous preparations.[1338,4111]

A few *other aldehydo ester equivalents* have been used with ureas. For example, propynoic acid (**230**) with urea or *N,N'*-dimethylurea in benzene containing a little sulfuric or phosphoric acid gave 2,4(1*H*,3*H*)-pyrimidinedione (**231**, R = H) (61%) or its 1,3-dimethyl derivative (**231**, R = Me) (71%), respectively;[2771,3453] maleic acid (**232**) with urea in polyphosphoric acid gave 2,4(1*H*,3*H*)-pyrimidinedione (**231**, R = H) in 20% yield;[3623] ethyl 3,3-diethoxypropionate (**233**, R = Et) with sodio *N*-benzylurea in ethanol gave 1-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (71%);[748] and methyl 3,3-dimethoxypropionate (**233**, R = Me) with the appropriate *N*-substituted ureas in dioxane containing sodium hydride gave 1-ethyl- (61%), 1-isopropyl- (65%), 1-butyl- (66%), 1-*t*-butyl- (80%), and 1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (64%), each without any isomeric by-product.[258]



230 **231** **232** **233**

The use of *reduced synthones* akin to β-aldehydo esters is briefly illustrated by the fusion of urea with acrylic acid (**234**, R = Y = H) or 2-methylacrylic acid (**234**, R = Me, Y = H) to give 5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (hydrouracil) (**235**, R = H) (~15%) or its 5-methyl derivative (hydrothymine) (**235**, R = Me) (~25%);[3459] the corresponding esters (**234**, R = H or Me, Y = Et) behaved similarly;[4112] and *N*-phenylurea with acryloyl chloride (**236**) gave 1-phenyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**237**) (45%).[4113] Although it might be expected to react as an aldehydo ester, ethyl 2-ethoxymethyl-3-methoxyacrylate behaved as a reduced synthone with urea in acidic ethanol to afford ethyl 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (72%).[1632] 2-Dimethylaminomethylacrylic acid with urea gave 5-dimethylaminomethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**235**, R = CH NMe) (40%), said to be oxidized to a methylene–tautomer of 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione.[3468]

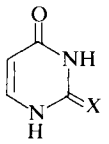


234 **235** **236** **237**

3.4.4. With Thioureas

Unlike urea, thiourea and its *S*-alkyl derivatives underwent cyclization with *ethyl 2-formylacetate* (**181**/**182**) under gentle alkaline conditions to give 2-thioxo-

1,2-dihydro-4(3*H*)-pyrimidinone (thiouracil) (**238**, X = S),[3148] 2-methylthio-4(3*H*)-pyrimidinone (**239**, R = SMe),[3053] and 2-ethylthio-4(3*H*)-pyrimidinone (**239**, R = SEt).[3053] Likewise, ethyl 2-formylpropionate gave 5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (thiothymine) (**240**, R = Me),[2698, cf. 1689] 5-methyl-2-methylthio-4(3*H*)-pyrimidinone,[3053] and 2-ethylthio-5-methyl-4-(3*H*)-pyrimidinone.[2698] The analogous use of selenourea gave 2-selenoxo-1,2-dihydro-4(3*H*)-pyrimidinone (**238**, X = Se) (53%) and its 5-methyl derivative (in low yield).[3507] The use of *other formylated esters* is illustrated by the following preparations.



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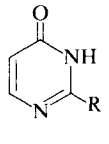

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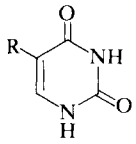

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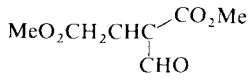

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5-Benzyloxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**240**, R = OCH_2Ph) (92%) from ethyl 2-benzyloxy-2-formylacetate with thiourea in ethanolic ethoxide.[1340]

5-Chloro-2-methylthio-4(3*H*)-pyrimidinone (38%) from ethyl 2-chloro-2-formylacetate with *S*-methylisothiourea in water at pH 11.[2243]

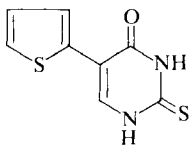
5-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**240**, R = Et) (~25%) from ethyl 2-formylbutyrate with thiourea in etherial sodium hydride.[4114, cf. 2720]

5-Ethoxycarbonylmethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (66%) from dimethyl 2-formylsuccinate (**241**) in ethanolic ethoxide; note the transesterification, which was avoidable in methanolic methoxide.[2007]

5-Fluoro-2-methylthio-4(3*H*)-pyrimidinone (low yield plus two substantial and separable byproducts) from ethyl 2-fluoro-2-formylacetate with *S*-methylisothiourea in methanolic methoxide.[326, cf. 2158]

5-Thien-2′-yl-2-thioxo-1,2-dihydro-4-(3*H*)-pyrimidinone (**242**) (11%) from ethyl 2-formyl-2-thien-2′-ylacetate with thiourea in ethanolic ethoxide.[277]

5-(6′-Methylpyridin-3′-yl)methyl- (**243**) or 5-(2′-methoxypyridin-4′-yl)-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**244**) from ethyl 2-



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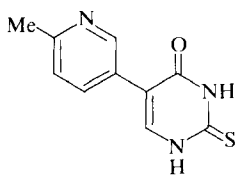

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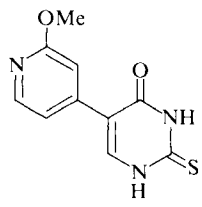

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formyl-3-(6′-methylpyridin-3′-yl)propionate or methyl 2-formyl-3-(2′-methoxypyridin-4′-yl)propionate, respectively.[322,544, cf. 3837]

Also other preparations.[702,872,910,1220,1262,1343,1573,2157,3084,3169,3302, 4101,4116–4119]

The inherent danger in using crude formylated esters for such condensations was illustrated when methyl 2-methoxyacetate was formylated with ethyl formate and the raw product was allowed to react with thiourea:[1343] the resulting (unpurified) 5-methoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**240**, R = OMe) contained about 7% of 5-methoxy-6-methoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone arising from the methyl 2,4-dimethoxy-3-oxobutyrate that was formed by self-condensation of methyl 2-methoxyacetate during preparation of the formylated intermediate.[3268]

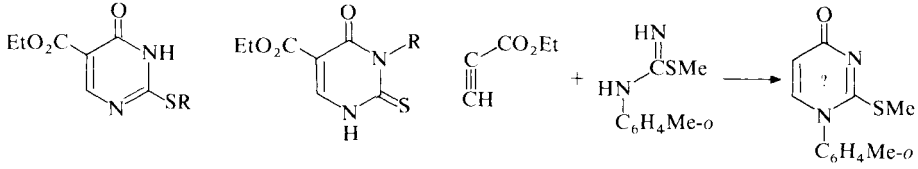
Condensations involving *aldehydo ester equivalents* with thioureas have been used frequently as indicated in the following examples.

5-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**240**, R = Me) (50%) from ethyl 3,3-diethoxy-2-methylpropionate with thiourea in ethanolic ethoxide.[3458]

Ethyl 2-butylthio-4-oxo-3,4-dihydro-5-pyrimidnecarboxylate (**245**, R = Bu) (85%) from diethyl α-ethoxymethylenemalonate (**218**) with *S*-butylisothiourea;[3761] the 2-benzylthio and 2-methylthio analogs (**245**, R = CH_2Ph or Me) (40%, 70%) were made similarly.[1631,2527,2992]

Ethyl 4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**246**, R = H) from diethyl α-ethoxymethylenemalonate with thiourea;[1631] also its 3-methyl derivative (**246**, R = Me) (79%), likewise from *N*-methylthiourea in ethanolic ethoxide.[809]

5-Nitro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**240**, R = NO_2) from ethyl 3-ethoxy-2-nitroacrylate with thiourea in aqueous alkali plus dioxane (71% yield)[1689] or in ethanolic ethoxide (6% yield).[2704]



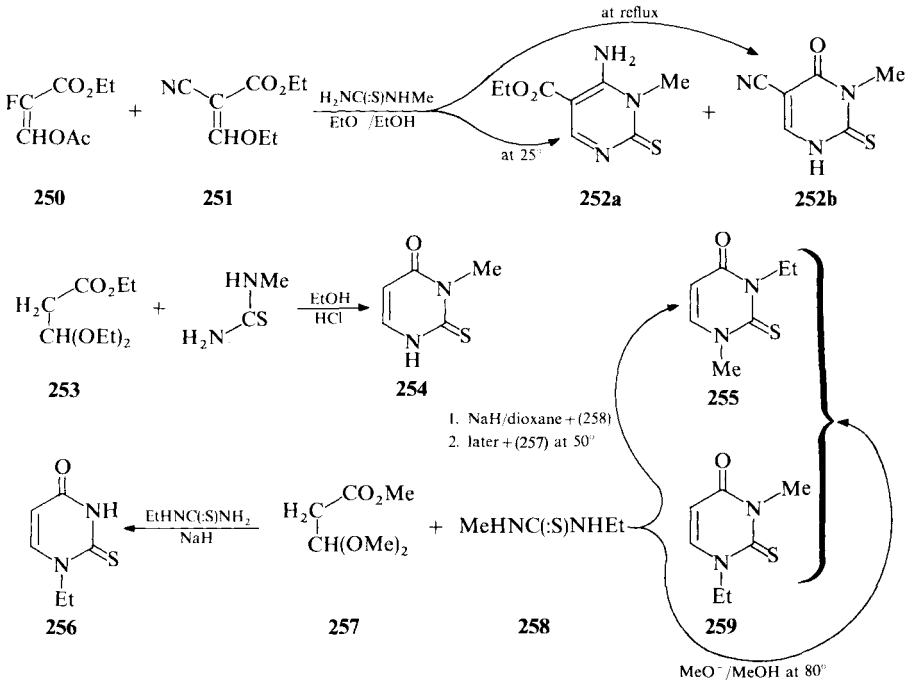
245 **246** **247** **248** **249**

2-Methylthio-1/3-*o*-tolyl-4(1/3*H*)-pyrimidinone (**249**) (70%) from ethyl propynoate (**247**) with *S*-methyl-*N*-*o*-tolylisothiourea (**248**) in ethanol.[4097, cf. 3726]

2-Benzylthio-5-fluoro-4(3*H*)-pyrimidinone (30%) from ethyl 3-acetoxy-2-fluoroacrylate (**250**) with *S*-benzylisothiourea in methanolic methoxide.[3170]

Also other examples.[451,3332,4115]

When ethyl 2-cyano-3-ethoxyacrylate (**251**) was condensed with *N*-methylthiourea in ethanolic ethoxide at 25°, the main product was ethyl 4-amino-3-methyl-2-thioxo-2,3-dihydro-5-pyrimidinecarboxylate (**252a**) (48% yield), but when the reaction was done at reflux, the main product was 1-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**252b**) (62% yield):[1508] the direction of the ambiguous reaction was therefore dependent upon temperature. Other factors also control orientation of such reactions. For example, ethyl 3,3-diethoxypropionate (**253**) with *N*-methylthiourea in ethanolic hydrochloric acid gave only 3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**254**) (21%),[3538] whereas the analogous acetal, methyl 3,3-dimethoxypropionate (**257**), with *N*-ethylthiourea under alkaline conditions gave only 1-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**256**) in 82% yield.[258] More surprisingly, treatment of the acetal (**257**) with the preformed sodium salt of *N*-ethyl-*N'*-methylthiourea (**258**) in dioxane at 50° gave only 3-ethyl-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**255**) (70% yield), whereas the same reactants (**257** + **258**) in methanolic methoxide at reflux gave a separable mixture of the same product (**255**) and its isomer, 1-ethyl-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**259**), in about equal amounts.[258]

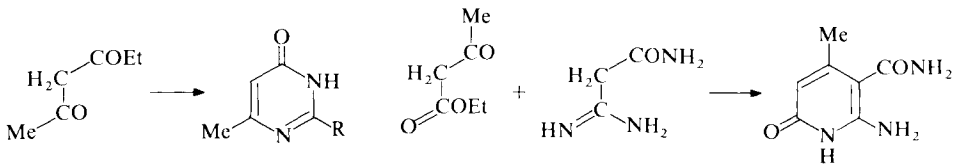


3.5. USE OF β-KETO ESTERS

Due to their availability and stability, free β-keto esters have been used more extensively than their equivalent synthones in the Principal Synthesis.

3.5.1. With Amidines

Although it reacted with formamidine to give an anomalous acyclic product,[1117] *ethyl acetoacetate* (**260**) condensed with a variety of other amidines in aqueous alkali (HO^-) or alcoholic alkoxide (MeO^-, etc.) to afford 2,6-dimethyl- (**261**, R = Me) (EtO^-: 75%),[3306, cf. 2543] 2-benzyl-6-methyl- (**261**, R = CH_2Ph) (HO^-),[2543] 6-methyl-2-propyl- (**261**, R = Pr) (MeO^-),[880] 2-butyl-6-methyl- (**261**, R = Bu) (MeO^-: 86%),[880] 6-methyl-2-phthalimidomethyl- (MeO^-: 67%),[1416] 6-methyl-2-trifluoromethyl- (**261**, R = CF_3) (EtO^-: 61%),[4090] 6-methyl-2-trichloromethyl- (**261**, R = CCl_3) (no solvent: 53%),[2117] 2-fluoromethyl-6-methyl- (**261**, R = CH_2F) (HO^-, then MeO^-: 15%),[2910] 2-(β,β-dichloro-α,α-difluoroethyl)-6-methyl- (HO^-; 52%),[4120] 6-methyl-2-pyridin-2′ (and 4′)-yl- (MeO^-: 64%, ~70%),[4121,4122] 6-methyl-2-phenethyl- (**261**, R = CH_2CH_2Ph) (HO^-: ~15%),[4123] 2-β-ethoxyethyl-6-methyl- (**261**, R = CH_2CH_2OEt) (EtO^-: 67%; HO^-: 33%),[2293,3331] 2-β-methoxyethyl-6-methyl- (**261**, R = CH_2CH_2OMe) (HO^-: 39%),[3331] and 2-cyclohexyl-6-methyl-4(3*H*)-pyrimidinone (**261**, R = C_6H_{11}) (EtO^-: 90%).[57] The condensation of 2-ami-dinoacetamide (**262**) with ethyl acetoacetate in ethanolic ethoxide at 25° gave the expected 2-carbamoylmethyl-6-methyl-4(3*H*)-pyrimidinone (**261**, R = CH_2CONH_2) in good yield, along with a separable by-product, 2-amino-4-methyl-6-oxo-1,6-dihydro-3-pyridinecarboxamide (**263**), formed by an alternative cyclization; at 80°, the ratio of products was reversed,[1997,2001, cf. 1749]

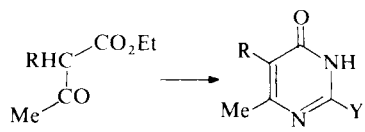


260 **261** **262** **263**

The reactions of *other β-keto esters* with amidines are illustrated in the formation of the following products.

5,6-Dimethyl-4(3*H*)-pyrimidinone (**265**, R = Me, Y = H) (24%) from ethyl 2-methyl-3-oxobutyrate (**264**, R = Me) with ethanolic formamidine.[2359]

2-Propyl-6-trifluoromethyl-4(3*H*)-pyrimidinone (**266**) (75%) from ethyl 4,4,4-trifluoro-3-oxobutyrate with methanolic butyramidine.[880]



264 **265**

5-Acetamido-2,6-dimethyl-4(3*H*)-pyrimidinone (**265**, R = NHAc, Y = Me) (60%) from ethyl 2-acetamido-3-oxobutyrate (**264**, R = NHAc) with ethanolic acetamidine.[595]

6-Methyl-2-phenyl-5-prop-2′-ynyl-4(3*H*)-pyrimidinone (**265**, R = $CH_2C{\vdots}CH$, Y = Ph) (93%) from ethyl 2-acetylpent-4-ynoate (**264**, R = $CH_2C{\vdots}CH$) with ethanolic benzamidine.[2721]

5-*p*-Chlorophenylazo-6-methyl-4(3*H*)-pyrimidinone (80%) from ethyl 2-*p*-chlorophenylazo-2-oxobutyrate with methanolic formamidine.[1552]

2-Isopropyl-6-phenyl-4(3*H*)-pyrimidinone (61%) from ethyl 2-benzoylacetate with ethanolic isobutyramidine.[1908]

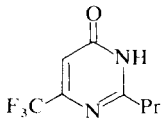
2,6-Diphenyl-4(3*H*)-pyrimidinone from ethyl 2-benzoylacetate with benzamidine in aqueous ethanolic alkali (26% yield)[4129] or in ethanolic ethoxide (70% yield).[2656]

2-Methyl-6-pyridin-2′-yl-4(3*H*)-pyrimidinone (40%) from ethyl 2-(2′-picolinoyl)acetate with acetamidine in aqueous alkali.[4130]

5-Benzyl-6-methyl-2-pent-4′-ynyl-4(3*H*)-pyrimidinone [**265**, R = CH_2Ph, Y = $(CH_2)_3C{\vdots}CH$] (57%) from ethyl 2-benzyl-3-oxobutyrate (**264**, R = CH_2Ph) with ethanolic hex-5-ynamidine.[86]

Ethyl 2-diethoxymethyl-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate (**267**) (76%) from diethyl 2-methyl-3-oxosuccinate (ethyl 2-ethoxalylpropionate) with 2,2-diethoxyacetamidine in ethanolic triethylamine.[171]

Also other such products.[121,122,396,1988,2019,2543,3908,3987,4124–4128,4131,4161]



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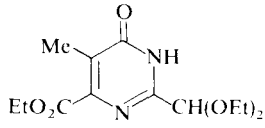
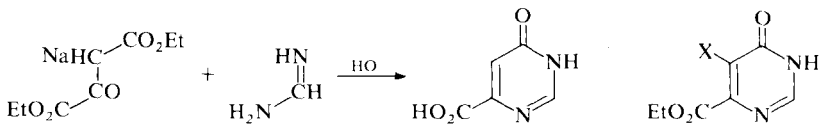


267

Any labile group, initially attached to one of the reactants, will be transferred as such to the final pyrimidine only if the reaction conditions are favorable. For example, the condensation of diethyl 2-oxo-3-sodiosuccinate (**268**) with formamidine in aqueous alkali (even at room temperature) gave 6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (**269**) (63%);[1030] likewise, diethyl 2-oxo-3-methylsuccinate with acetamidine in hot ethanolic potassium hydroxide gave



268 **269** **270**

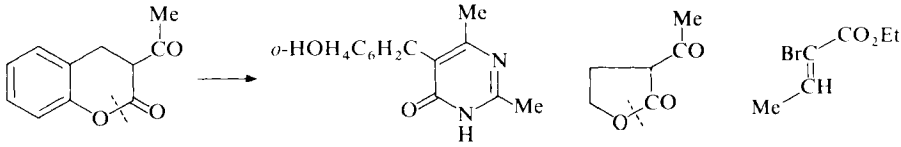
2,5-dimethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (65%).[2038] In contrast, diethyl 2-fluoro-3-oxosuccinate with formamidine in hot ethanolic sodium ethoxide gave ethyl 5-fluoro-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate (**270**) (43%),[1262] and other esters were made similarly.[1262]

Condensations of *β-keto ester equivalents* with amidines are occasionally convenient, as exemplified in the following preparations.

5-*o*-Hydroxybenzyl-2,6-dimethyl-4(3*H*)-pyrimidinone (**272**) (88%) from 3-acetyl-2-chromanone (**271**) with ethanolic acetamidine.[4132]

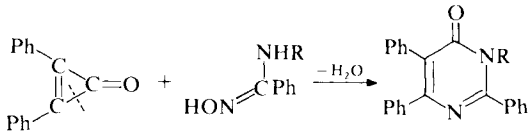
2-*p*-Chlorophenyl-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone (55%) from α-acetyl-γ-butyrolactone (**273**) with *p*-chlorobenzamidine in methanolic sodium methoxide.[4133]

6-Methyl-2-phenyl-4(3*H*)-pyrimidinone (23%) from ethyl 2-bromocrotonate (**274**) with benzamidine in cold anhydrous benzene containing triethylamine[4134] (cf. 81% from ethyl acetoacetate in ethanolic ethoxide).[2656]



271 **272** **273** **274**

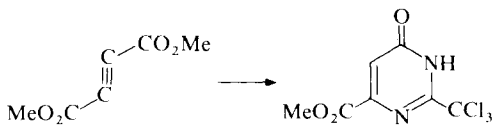
2,5,6-Triphenyl-4(3*H*)-pyrimidinone (**277**, R = H) (60%) from diphenylcyclopropenone (**275**) with benzamide oxime (**276**, R = H) in boiling toluene;[4135] *N*-phenylbenzamide oxime (**276**, R = Ph) gave 2,3,5,6-tetraphenyl-4(3*H*)-pyrimidinone (**277**, R = Ph).[109]



275 **276** **277**

4-Chloromethyl-6-fluoro-5-phenylpyrimidine (23%) from chloromethyl α-(trifluoromethyl)benzyl ketone with formamidine in refluxing toluene.[6136]

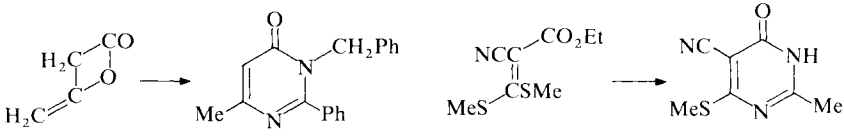
Methyl 6-oxo-2-trichloromethyl-1,6-dihydro-4-pyrimidinecarboxylate (**279**) (14%) from dimethyl acetylenedicarboxylate (**278**) with 2,2,2-trichloroacetamidine in boiling benzene.[3403]



278 **279**

3-Benzyl-6-methyl-2-phenyl-4(3*H*)-pyrimidinone (**281**) (54%) from acetonic diketene (**280**) with *N*-benzylbenzamidine followed by cyclization in boiling water;[4138] ethyl acetoacetate gave the same product (**281**) (20%).[4138,4139]

2-Methyl-4-methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile (**283**) (~50%) from ethyl 2-cyano-3,3-bis(methylthio)acrylate (**280**) with acetamidine in dimethylformamide containing sodium hydride.[88,572]



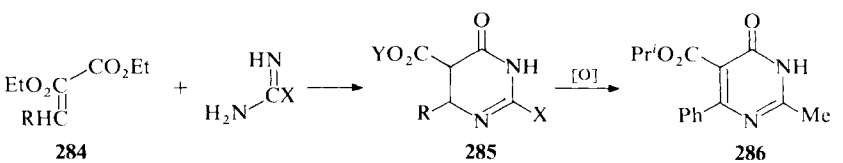
280 **281** **282** **283**

Methyl 4-methylthio-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinecarboxylate (76%) from methyl 2-methoxycarbonyl-3,3-bis(methylthio)acrylate with benzamidine in dimethyl sulfoxide containing potassium carbonate.[3882]

Also analogous cases.[55,131,740,3882,3907,4136,4137,4140,6210]

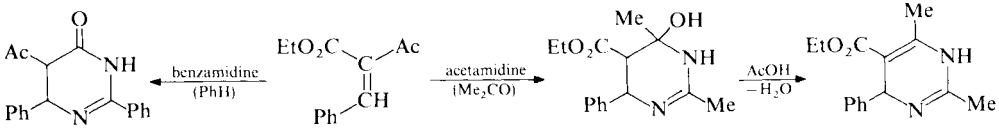
The condensation of 3-substituted propynoic esters with *N*-arylamidines has been reported to afford 2,6-disubstituted 3-aryl-4(3*H*)-pyrimidinones,[3867,3868,4097] but later evidence has suggested that these products were 2,6-disubstituted 1-aryl-4(1*H*)-pyrimidinones.[3726] Rather similarly, dimethyl penta-2,3-dienedioate reacted with methanolic benzamidine to furnish 6-methoxycarbonylmethyl-2-phenyl-4(3*H*)-pyrimidinone (42%).[3389]

Alkylidene or benzylidene derivatives of diethyl malonate or ethyl acetoacetate behave preferentially as *reduced synthones* in their reactions with amidines. Thus diethyl α-ethylidenemalonate (**284**, R = Me) reacted with acetamidine to give not 5-ethylidene-4,6(1*H*,5*H*)-pyrimidinedione, but ethyl 2,4-dimethyl-6-oxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxylate (**285**, R = X = Me, Y = Et).[1466] Likewise, diethyl α-benzylidenemalonate (**284**, R = Ph) with acetamidine in ethanolic ethoxide gave ethyl 2-methyl-4-oxo-6-phenyl-3,4,5,6-tetrahydro-5-pyrimidinecarboxylate (**285**, R = Ph, X = Me, Y = Et) (87%),[94] while the same reactants in isopropanolic isopropoxide gave the isopropyl ester (**285**, R = Ph, X = Me, Y = Pr^i) (60%), which underwent oxidation with dichlorodicyanobenzoquinone to afford isopropyl 2-methyl-4-oxo-6-phenyl-3,4-dihydro-5-pyrimidinecarboxylate (**286**) (60%).[197] Somewhat similarly, ethyl α-benzylideneacetoacetate (**288**) condensed with benzamidine (in boiling benzene



284 **285** **286**

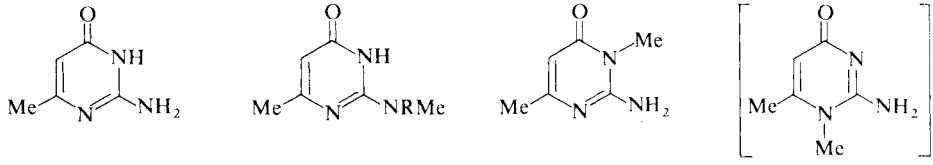
for removal of water) to give 5-acetyl-2,6-diphenyl-5,6-dihydro-4(3*H*)-pyrimidinone (**287**) (85%);[500] in contrast, the same synthone (**288**) with acetamidine in dry acetone gave initially ethyl 4-hydroxy-2,4-dimethyl-6-phenyl-3,4,5,6-tetrahydro-5-pyrimidinecarboxylate (**289**) (79%), which lost water in glacial acetic acid at 80° to give a product formulated as ethyl 2,4-dimethyl-6-phenyl-3,6-dihydro-5-pyrimidinecarboxylate (**290**) (78%).[500] Ethyl 2-cyano-3-phenylacrylate with benzamidine (+ air) gave 4-oxo-2,6-diphenyl-3,4-dihydro-5-pyrimidinecarbonitrile (57%).[48]



287 **288** **289** **290**

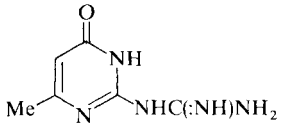
3.5.2. With Guanidines

Most β-keto esters react quite easily with guanidines. Thus 2-amino-6-methyl-4(3*H*)-pyrimidinone (**291**) resulted from the condensation of *ethyl acetoacetate* with neat guanidine carbonate at $>100°$ ($\leq 70\%$ yield),[1523,4141] with ethanolic guanidine carbonate,[959,1524] or with free guanidine in methanol (80–86% yield).[1670,4142] With methanolic *N*,*N*-dimethylguanidine, ethyl acetoacetate gave (unambiguously) 2-dimethylamino-6-methyl-4(3*H*)-pyrimidinone (**292**, R = Me) (77%).[2078] In contrast, with *N*-methylguanidine carbonate three products were possible: of these only 6-methyl-2-methylamino- (**292**, R = H) and 2-amino-3,6-dimethyl-4(3*H*)-pyrimidinone (**293**) could be isolated,[861] while the third (**294**) was not even detected by methods then available. *N*-Allylguanidine carbonate gave two analogous products, formulated as 2-allylamino-6-methyl- and 3-allyl-2-amino-6-methyl-4(3*H*)-pyrimidinone;[861] *N*-δ-hydroxybutylguanidine gave 2-δ-hydroxybutylamino-6-methyl-4(3*H*)-pyrimidinone as the major product with a separable minor product, formulated as 2-amino-1-δ-hydroxybutyl-6-methyl-4(3*H*)-pyrimidinone;[4143] biguanide (*N*-amidinoguanidine) in aqueous alcoholic alkali gave only 2-guanidino-6-methyl-4(3*H*)-pyrimidinone (**295**) ($\sim 80\%$);[4144] dicyandiamide (*N*-cyanoguanidine) gave 2-cyanoamino-6-methyl-4(3*H*)-pyrimidinone;[1050,1150] 2-guanidino-4,5-dimethylthiazole gave 2-(4′,5′-dimethylthiazol-2′-yl)amino-6-methyl-4(3*H*)-



291 **292** **293** **294**

pyrimidinone (**296**);[3862] *N*-aminoguanidine gave only 2,3-diamino-6-methyl-4(3*H*)-pyrimidinone (**297**) (40%),[32] while in contrast *N*-nitroguanidine gave only 6-methyl-2-nitroamino-4(3*H*)-pyrimidinone (53%);[1429] and other such examples have been reported.[2743,4057,4066,4145,4148,4149,6847]



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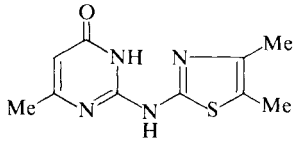

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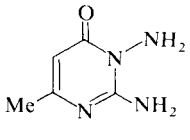

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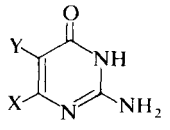
The condensations of *other β-keto esters* with guanidines are illustrated in the following syntheses.

2-Amino-6-ethyl-4(3*H*)-pyrimidinone (**298**, X = Et, Y = H) (~50%) from ethyl propionylacetate with ethanolic guanidine carbonate.[4099]

2-Amino-5-benzyl-6-methyl-4(3*H*)-pyrimidinone (**298**, X = Me, Y = CH_2Ph) (65%) from ethyl 2-acetyl-3-phenylpropionate with ethanolic guanidine.[2359]



298

2-Amino-5-*β*-ethoxyethyl-6-methyl-4(3*H*)-pyrimidinone (**298**, X = Me, Y = CH_2CH_2OEt) (45%) from ethyl 2-acetyl-4-ethoxybutyrate with neat guanidine carbonate at 175°.[1149]

2-Amino-5-phenylazo-6-trifluoromethyl-4(3*H*)-pyrimidinone (**298**, X = CF_3, Y = N:NPh) (80%) from ethyl 4,4,4-trifluoro-3-oxo-2-phenylazobutyrate with guanidine in butanolic sodium butoxide.[4146]

2-Amino-5-ethoxy-6-ethoxymethyl-4(3*H*)-pyrimidinone (**298**, X = CH_2OEt, Y = OEt) (48%) from ethyl 2,4-diethoxy-3-oxobutyrate with *t*-butanolic guanidine carbonate.[1182]

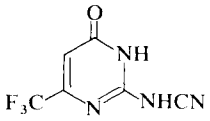
2-Dimethylamino-6-phenyl-4(3*H*)-pyrimidinone (77%) from ethyl 2-benzoylacetate with *N*,*N*-dimethylguanidine in ethanolic ethoxide.[301]

2-Dimethylamino-6-methyl-5-naphthalen-1′-ylazo-4(3*H*)-pyrimidinone (76%) from ethyl 2-naphthalen-1′-yl-3-oxobutyrate with *N*,*N*-dimethylguanidine in ethanolic ethoxide.[4100]

2-Amino-5-*γ*,*γ*-diethoxypropyl-6-methyl (or phenyl)-4(3*H*)-pyrimidinone [**298**, X = Me or Ph, Y = $CH_2CH_2CH_2(OEt)_2$] (poor yield) from ethyl 2-acetyl (or benzoyl)-5,5-diethoxyvalerate with methanolic guanidine.[667,668]

2-Amino-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (**298**, X = CO_2H, Y = H) (34%) from diethyl 2-oxo-3-sodiosuccinate (**268**) with ethanolic guanidine followed by saponification of the resulting ester.[982]

2-Cyanoamino-6-trifluoromethyl-4(3*H*)-pyrimidinone (**299**) (69%) from ethyl 4,4,4-trifluoro-3-oxobutyrate with dicyandiamide in ethanolic ethoxide.[4153]



299

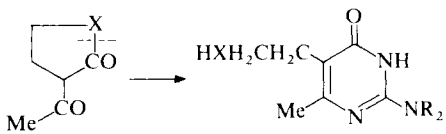
2-Amino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile (**298**, X = Me, Y = CN) (68%) from *t*-butyl 2-cyano-3-oxobutyrate with guanidine in methanolic methoxide (no other product was detected).[1447]

2-Amino-6-ethoxycarbonylmethyl-4(3*H*)-pyrimidinone (**298**, X = CH_2-CO_2Et, Y = H) or the corresponding 6-carboxymethyl compound (**298**, X = CH_2CO_2H, Y = H) (44%) from diethyl 3-oxoglutarate with hot ethanolic guanidine carbonate (1 mol or 2 mol, respectively).[949,950,988]

Also other syntheses.[226,376,595,596,635,863,981,1230, 1356, 1361, 1367, 1448, 1871, 2248,2859, 3878, 4041, 4099, 4146, 4147,4150–4152,4154–4157]

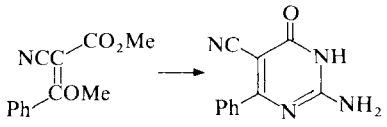
It is interesting that ethyl 2-benzoylacetate with ethanolic *N*-methylguanidine gave a separable mixture of 2-amino-3-methyl- and 2-methylamino-6-phenyl-4(3*H*)-pyrimidinone, in which the first predominated greatly.[301]

Lactones are the best *β-keto ester equivalents* for use with guanidines. Thus, α-acetyl-γ-butyrolactone (**300**, X = O) with ethanolic guanidine or *N*,*N*-dimethylguanidine gave 2-amino- (**301**, R = H, X = O) (39%)[1313] or 2-dimethylamino-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone (**301**, R = Me, Y = O) (17%),[1319] respectively;[cf. 6216] the same lactone (**300**, X = O) with neat *N*-(benzylideneamino)guanidine gave 2-benzylidenehydrazino-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone (~50%) and thence (by treatment with ethanolic hydrazine hydrate) the 2-hydrazino analog;[1303] α-acetyl-γ-thiobutyrolactone (**300**, X = S) with ethanolic guanidine gave 2-amino-5-β-mercaptoethyl-6-methyl-4(3*H*)-pyrimidinone (**301**, R = H, X = S) (62%);[1359] 3-acetyl-2-chromanone (**271**) with ethanolic guanidine gave 2-amino-5-*o*-hydroxybenzyl-6-methyl-4(3*H*)-pyrimidinone (76%);[4132] and α-butyryl-γ-butyr-

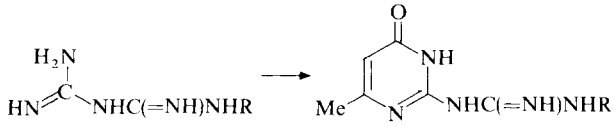


300 **301**

olactone with ethanolic guanidine gave 2-amino-5-β-hydroxyethyl-6-propyl-4(3*H*)-pyrimidinone (46%).[1206] Other types of keto ester equivalent are represented in the reaction of methyl 3-cyano-3-methoxy-3-phenylacrylate (**302**) with guanidine to give only 2-amino-4-oxo-6-phenyl-3,4-dihydro-5-pyrimidinecarbonitrile (**303**) (54%);[1009] in the reaction of dimethyl penta-2,3-dienedioate with methanolic guanidine to give 2-amino-6-methoxycarbonylmethyl-4(3*H*)-pyrimidinone (38%);[3889] and in the conversion of diketene (**280**) by aqueous biguanide (**304**, R = H) or acetonic 1-phenylbiguanide (**304**, R = Ph) into 2-guanidino-6-methyl- (**305**, R = H) (30%;[3065] better yield from ethyl acetoacetate[4144]) or 6-methyl-2-*N'*-phenylguanidino-4(3*H*)-pyrimidinone (**305**, R = Ph) (43%;[4158,4159] comparable[4158,4159] or better[4066] yield from ethyl acetoacetate), respectively. The use of unsaturated esters as *reduced synthones* akin to β-keto esters is represented by the reaction of ethyl crotonate or methyl cinnamate with alcoholic guanidine to give 2-amino-6-methyl-5,6-dihydro-4(3*H*)-pyrimidinone (61%)[211,3464] or 2-amino-6-phenyl-5,6-dihydro-4(3*H*)-pyrimidinone (41%),[211,4160] respectively.



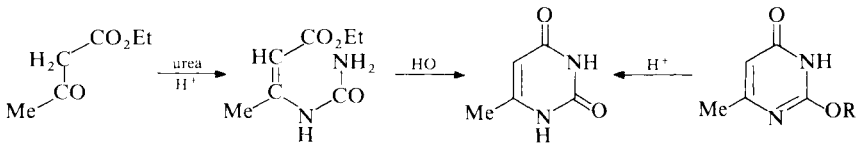
302 **303**



304 **305**

3.5.3. With Ureas

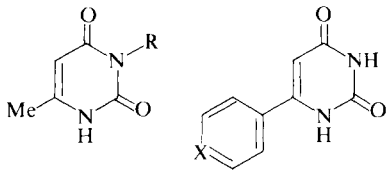
The condensation of *ethyl acetoacetate* (**306**) with urea takes place more obviously in two stages than do most Principal Syntheses. The best method,[3438] based essentially on earlier reported procedures,[771,1943,3267] involved condensation to ethyl 3-ureidocrotonate (**307**) in ethanolic hydrochloric acid, followed by cyclization in hot alkali to afford 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**308**) in 71–77% yield. Ethyl acetoacetate reacted more easily with *O*-methylisourea: a neat mixture at 50° gave 2-methoxy-6-methyl-4(3*H*)-pyrimidinone (**309**, R = Me) (90%),[2249,2935] while an aqueous mixture gave the same product (95%);[130] 2-ethoxy- (**309**, R = Et),[2935] 2-allyloxy- (**309**, R = $CH_2CH{:}CH_2$) (90%),[918] and other 2-alkoxy-6-methyl-4(3*H*)-pyrimidinones (**309**),[918] have been made similarly. The hydrolysis of such 2-alkoxypyrimidines (**309**) afforded a useful route to 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**308**).[130]



306 307 308 309

The condensation of *N*-methyl- or *N*-cyclohexylurea with ethyl acetoacetate occurred in two stages (as already discussed for urea) to give 3,6-dimethyl- (**310**, R = Me) or 3-cyclohexyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**310**, R = C_6H_{11}), respectively, each in moderate yield;[3425] *N*-hydroxyurea likewise gave 3-hydroxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**310**, R = OH),[2783] rather than the 1-hydroxy isomer previously reported.[3472] *N*-Phenylurea gave an abnormal product.[3425]

The use of *other β-keto esters* with ureas is illustrated in the preparation of the following products.



310 311

6-Adamant-1′-yl-2,4(1*H*,3*H*)-pyrimidinedione (22%) from ethyl 2-(adamant-1′-ylcarbonyl)acetate with urea in ethanolic ethoxide.[4163]

6-Pyridin-4′-yl-2,4(1*H*,3*H*)-pyrimidinedione (**311**, X = N) (38%) from ethyl 2-isonicotinoylacetate with urea at 120°.[4164]

6-Phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**311**, R = CH) (19%) from ethyl 2-benzoylacetate with urea at 135°.[301]

6-Carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (~50%) from 3-oxoglutaric acid (formed in situ from citric acid) with urea in fuming sulfuric acid.[2032]

2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinephosphonic acid (~20%) from diethyl(ethoxycarbonylacetyl)phosphonate with urea in acetic acid containing hydrogen chloride.[4162]

6-Ethyl-2-methoxy-4(3*H*)-pyrimidinone (70%) from ethyl 2-propionylacetate with *O*-methylisourea in aqueous ethanol.[130]

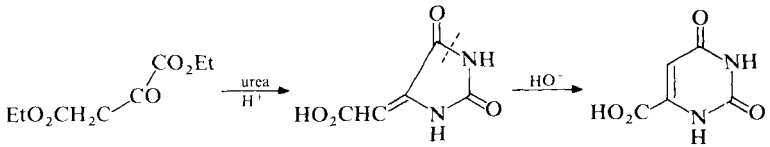
1 (or 3)-Methyl-6-pyridin-3′-yl-2,4(1*H*,3*H*)-pyrimidinedione (44%) from ethyl 2-nicotinoylacetate with *N*-methylurea at 110°; orientation was based only on ms data.[4164]

5-Ethyl-2-methoxy-6-methyl-4(3*H*)-pyrimidinone from ethyl 2-acetylbutyrate with *O*-methylisourea at 25°.[2935]

6-Ethyl-3-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (95%) from ethyl 2-propionylacetate with *N*-phenylurea in dimethylformamide + sulfuric acid + acetic anhydride, followed by alkaline cyclization.[4172]

Also other such products.[130,3944,4146]

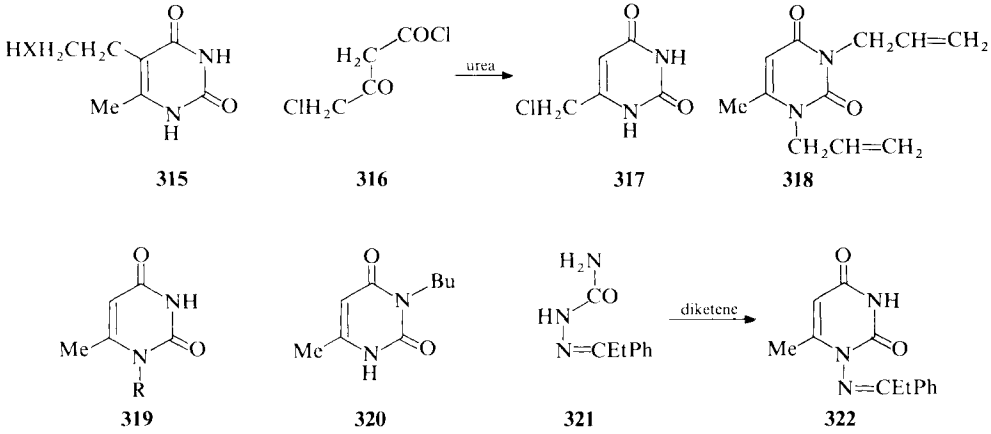
Although diethyl 2-oxosuccinate (diethyl oxalacetate) (**312**) reacted with urea to give eventually 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (orotic acid) (**314**),[2876,2955,3391] it did so via an isolable hydantoin (**313**), which required slow isomerization to the product (**314**) under alkaline conditions;[2875] *N*-methylurea likewise gave 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid.[2848] The intermediate (**313**) has been mistaken for a pyrimidine at times, as have related compounds that were undoubtedly the isomeric hydantoins.[3392] This topic has been discussed in Section 2.6. However, when monoethyl 2-oxosuccinate reacted with urea in methanol, the intermediate was not an hydantoin but simply acyclic: in alkali, it rapidly gave orotic acid (**314**) (61%);[1605] similarly, *N*-β-hydroxyethylurea gave 1-β-hydroxyethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid.[1881] The condensation of diethyl 2-oxosuccinate with urea in fuming sulfuric acid gave 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (25%) by an unexamined mechanism.[2887]



312 **313** **314**

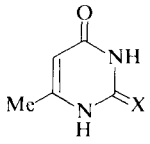
Condensations of *β-keto ester equivalents* with ureas are not very numerous. α-Acetyl-γ-butyrolactone (**300**, X = O) reacted with urea in ethanolic hydrogen chloride followed by cyclization in alkali, to give 5-β-hydroxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**315**, X = O) (45%);[3126] the corresponding thiolactone (**300**, X = S) with urea in ethanolic ethoxide gave the 5-β-mercaptoethyl analog (**315**, X = S) (15%);[1359] and α-acetyl-δ-thiovalerolactone likewise gave 5-γ-mercaptopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (17%).[1359] 4-Chloro-3-oxobutyryl chloride (**316**) with urea in acetic anhydride containing pyridine at 25° gave 6-chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione (**317**), which underwent oxidation in alkaline hydrogen peroxide to give orotic acid (**314**) in good overall yield.[2275] The reaction of diketene (**280**) with urea in boiling toluene gave 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**308**), via an acyclic intermediate, in ~25% yield.[2816,4165] However, this reaction was improved subsequently by increasing the boiling point of the solvent and/or by the addition of catalysts: *p*-toluenesulfonic acid in toluene (40% yield),[1947] mercuric sulfate in glacial acetic acid, briefly warmed (61%),[4167] pyridine in chlorobenzene (65%),[4166] pyridine in toluene at 65° (72%);[1947] mercuric sulfate in glacial acetic acid at 90°

(85%),[3473,3474] and refluxing glacial acetic acid for 6 h (91%).[1947] Diketene also condensed with *N*,*N*′-dialkylureas to give, for example, 1,3-diallyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**318**),[4165] with *N*-butylurea to give a separable mixture of 1-butyl- (**319**, R = Bu) and 3-butyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**320**) in which the former predominated,[1947, cf. 1841] with *N*-phenylurea to give only (?) 6-methyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**319**, R = Ph) (~55%),[1863] and with propiophenone semicarbazone (**321**) in refluxing acetic acid to give 6-methyl-1-(1′-phenylpropylidene)amino-2,4(1*H*,3*H*)-pyrimidinedione (**322**) (78%).[1124]



3.5.4. With Thioureas

Thioureas condense much more readily with β-keto esters than do the corresponding ureas. Thus *ethyl acetoacetate* reacted with thiourea to give 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**323**, X = S) on mere admixture (low yield),[4168] on admixture with added anhydrous potassium hydroxide (55% yield) or potassium carbonate (80%),[2765] in ethanolic hydrochloric acid,[3135] in ethanolic sodium ethoxide (almost quantitative ?),[2700] in methanolic sodium methoxide (69–99%),[227,3498,3499,3539] in aqueous alkali (75%),[1170] or in aqueous potassium carbonate (95%);[1170] the last-mentioned procedure appears to be the least troublesome. Likewise, ethyl acetoacetate with *S*-methylisothiourea in alkali,[3053] or better in aqueous sodium carbonate,[3409] gave 6-methyl-2-methylthio-4-(3*H*)-pyrimidinone (**324**, R = Me) (90%); with *S*-ethylisothiourea it similarly gave 2-ethylthio-6-methyl-4(3*H*)-pyrimidinone (**324**, R = Et) (83%);[3409] with 1,2-ethylene-bis-*S*-thiourea it gave 1,2-bis(4′-methyl-6′-oxo-1′,6′-dihydropyrimidin-2′-ylthio)ethane (**325**) (34%);[3409] with thiosemicarbazide in ethanolic ethoxide it gave 3-amino-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**326**, R = NH_2) (25%);[1573] with *N*-phenylthiourea



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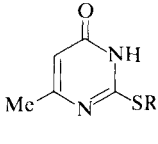

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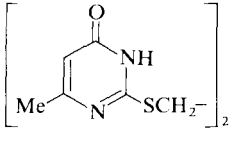

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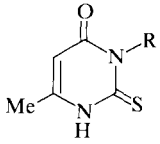

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it gave 6-methyl-3-phenyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**326**, R = Ph) (32%);[4169] and with selenourea in aqueous potassium carbonate it gave 6-methyl-2-selenoxo-1,2-dihydro-4(3*H*)-pyrimidinone (**323**, X = Se) (75%).[3508]

The similar reactions of *other β-keto esters* with thioureas are exemplified in the following preparations.

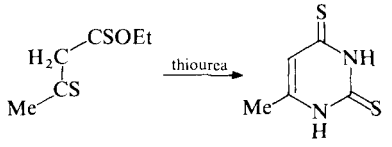
6-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (78%) from ethyl 2-propionylacetate with thiourea in ethanolic sodium ethoxide.[1684,2148]

5,6-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (93%) from ethyl 2-methyl-3-oxobutyrate (**264**, R = Me) with thiourea similarly.[1155,1684,2157,2359,2794]

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione (**328**) from *O*-ethyl 3-thioxo(thiobutyrate) (**327**) with thiourea in ethanolic ethoxide;[3479] also analogous condensations.[6200]

6-α,α-Diethoxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**329**) (43%) from ethyl 4,4-diethoxy-3-oxovalerate with thiourea in ethanolic ethoxide: warm acid thence gave the 6-acetyl analog (97%).[833]

6-Dimethoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**330**, R = H, Y = Me) (85%) or its 3-methyl derivative (**330**, R = Y = Me) (65%) from methyl 4,4-dimethoxy-3-oxobutyrate with thiourea or *N*-methylthiourea, respectively;[2578] 4-diethoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**330**, R = H, Y = Et) (80%)[1592,2854,3416] and its 3-methyl derivative (**330**, R = Me, Y = Et)[3416] were made rather similarly.



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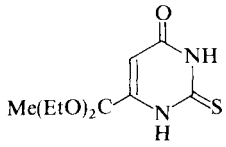

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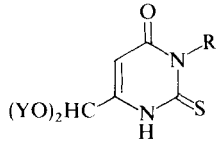

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2-Methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (63%) from diethyl 2-oxo-3-sodiosuccinate (**268**) with *S*-methylisothiourea in aqueous alkali at 25°.[1030,2889]

2-Methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide (70–80%) as for the preceding preparation but in aqueous ammonia at 5°.[1560]

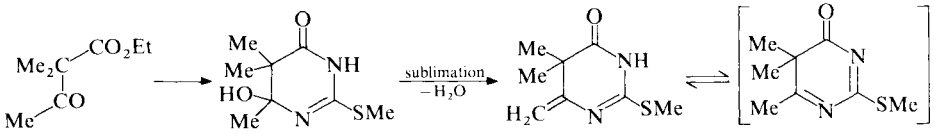
6-Dichloromethyl-2-methylthio-4(3*H*)-pyrimidinone (30%) from ethyl 4,4-dichloro-3-oxobutyrate with *S*-methylisothiourea in methanolic meth-

oxide at 25°;[3159] the 6-chloromethyl analog (40%) was made rather similarly.[2244, cf. 2243]

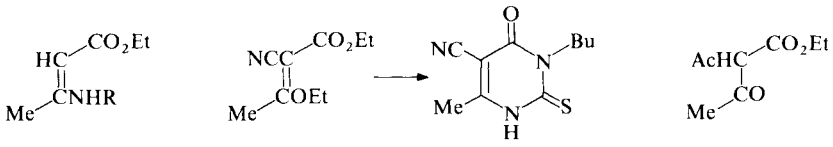
2-Ethylthio-6-*o*-nitrobenzyl-4(3*H*)-pyrimidinone (82%) from ethyl 4-*o*-nitrophenyl-3-oxobutyrate with *S*-ethylisothiourea in aqueous carbon tetrachloride (emulsion) at 25°.[4176]

Also other such preparations.[162, 182, 595, 730, 911, 1038, 1167, 1220, 1224, 1300, 1362, 1870, 1871, 2066, 2151, 2167, 2178, 2192, 2550, 2859, 2898, 3015, 3268, 3303, 3521, 3878, 4116, 4163, 4170, 4171, 4173–4175, 6068]

As might be anticipated, ethyl 2,2-dimethyl-3-oxobutyrate (**331**) reacted abnormally with *S*-methylisothiourea to give 6-hydroxy-5,5,6-trimethyl-2-methylthio-5,6-dihydro-4(3*H*)-pyrimidinone (**332**), which was stabilized by its inability to split out water from the 5,6-positions in the usual way: however, on sublimation it did lose water to give a product formulated on nmr and ms evidence as 5,5-dimethyl-6-methylene-2-methylthio-5,6-dihydro-4(3*H*)-pyrimidinone (**333**) rather than the tautomer (**334**).[4177] Ethyl 2-benzoylacetate reacted with *S*-methylisothiourea in aqueous alkali to give a separable mixture that contained very little of the expected 2-methylthio-6-phenyl-4(3*H*)-pyrimidinone but much 2-amino-6-phenyl-1,3-oxazin-4-one.[385]



A few *keto ester equivalents* have been used as partners with thioureas. Thus ethyl 3-aminocrotonate (**335**, R = H) or its 3-methylamino homolog (**335**, R = Me) with thiourea in ethanolic ethoxide gave 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**323**, X = S);[1516] ethyl 2-cyano-3-ethoxycrotonate (**336**) with *N*-butylthiourea gave only 1-butyl-4-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**337**) (46%);[809] α-acetyl-γ-butyrolactone (**300**, X = O) or the corresponding thiolactone (**300**, X = S) with thiourea in alcoholic alkoxide gave 5-β-hydroxyethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (32%)[1206] or the 5-β-mercaptoethyl analog (50%),[1359] respectively (other acylated lactones have also been so employed[3255]); diketene (**280**) with thiosemicarbazide (as its isopropylidene derivative) in glacial acetic acid gave 3-amino-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**326**, R = NH_2) (73%);[1482] diketene (**280**) with *N*-phenylthiourea likewise gave a separable mixture of 6-methyl-1 (and 3)-phenyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone in which the latter (**326**, R = Ph) predominated;[4178] and diketene (**280**) with *N*,*N*′-diphenylthiourea gave 6-methyl-1,3-diphenyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (19%) accompanied by a separable by-product.[62] Other such reactions with *N*,*S*-disubstituted isothioureas have been studied.[4179] Unaccountably, ethyl 2-acetyl-3-oxobutyrate (**338**) with thiourea in ethanolic



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ethoxide gave 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**323**, X = S) (75%) rather than either of the expected products.[1787]

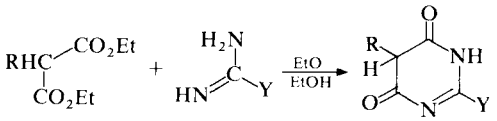
Partially *reduced equivalents* of keto esters have been made in situ and condensed with thiourea to give dihydropyrimidines, which underwent spontaneous dehydrogenation to give regular pyrimidines: for example, ethyl cyanoacetate and propionaldehyde (i.e., ethyl α-cyano-α-propylideneacetate) with thiourea in ethanolic potassium acetate under reflux for 5 h gave 4-ethyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (15–27%), initially as its potassium salt.[6173,6174]

3.6. USE OF β-DIESTERS (MALONIC ESTERS)

Almost every barbiturate has been made by a Principal Synthesis within this category, whether directly or indirectly via an amino, mercapto, or other precursor. Because of their essential symmetry, malonic esters usually give pyrimidines of unambiguous structure, even when unsymmetrical N—C—N partners are used.

3.6.1. With Amidines

The parent β-diester, *diethyl malonate* (**339**, R = H), has been condensed with formamidine (**340**, Y = H) in an excess of ethanolic sodium ethoxide at room temperature to give 4,6(1*H*,5*H*)-pyrimidinedione (**341**, R = Y = H) (80%);[1117] in a similar way, sometimes with heating, appropriate amidines (**340**) gave 2-methyl- (**341**, R = H, Y = Me) (43–87%),[1159,2784,4180] 2-ethyl- (**341**, R = H, Y = Et) (45–88%),[1118,1243] 2-propyl- (**341**, R = H, Y = Pr) (71–88%),[1456,1612] 2-isopropyl- (**341**, R = H, Y = Pr^i) (25–61%),[1875,1908] 2-butyl- (**341**, R = H, Y = Bu) (60%),[1612] 2-*t*-butyl- (**341**, R = H, Y = Bu^t) (62%),[2184] 2-fluoromethyl- (**341**, R = H, Y = CH_2F) (21%),[2910] 2-trifluoromethyl- (**341**, R = H, Y = CF_3)



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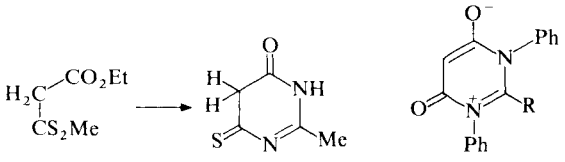
(62%),[4090] 2-hydroxymethyl- (**341**, R = H, Y = CH_2OH) (89%),[2468] 2-trichloromethyl- (**341**, R = H, Y = CCl_3) (55%),[2167] 2-cyclohexyl- (80%),[57] 2-benzyl- (**341**, R = H, Y = CH_2Ph),[4181] 2-phenyl- (**341**, R = H, Y = Ph) (81%),[4180,4183] 2-furan-2′-yl- (42%),[1117] 2-pyridin-2′-yl- (62%),[4030] and 2-pyridin-3′-yl-4,6(1*H*,5*H*)-pyrimidinedione,[4182] as well as other such products.[396,1991,2653,4198] When ethyl 2-(methylthio)thiocarbonylacetate (**342**) was allowed to react with acetamidine in dioxane, 2-methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone (**343**) (70%) resulted; in ethanolic ethoxide, some displacement of sulfur by ethoxide ion occurred to give an appreciable but separable by-product, 6-ethoxy-2-methyl-4(3*H*)-pyrimidinone.[1189] Condensation of *N*,*N*′-diphenylacetamidine or *N*,*N*′-diphenylbenzamidine with bis(2,4,6-trichlorophenyl)malonate at 140–170° in vacuo gave 2-methyl-6-oxo-1,3-diphenyl-3,6-dihydro-1-pyrimidinium-4-olate (**344**, R = Me) (79%) or its 6-oxo-1,2,3-triphenyl analog (**344**, R = Ph) (65%), respectively.[207, cf. 50]



342 **343** **344**

The analogous condensations of α-*monosubstituted malonic esters* with amidines are exemplified in the formation (usually in hot ethanolic sodium ethoxide) of the following pyrimidines.

2,5-Dipropyl-4,6(1*H*,5*H*)-pyrimidinedione (**341**, R = Y = Pr) (72%) from diethyl α-propylmalonate (**339**, R = Pr) with butyramidine (**340**, Y = Pr).[1456]

5-Butyl-4,6(1*H*,5*H*)-pyrimidinedione (**341**, R = Bu, Y = H) (98%) from diethyl α-butylmalonate (**339**, R = Bu) with formamidine (**340**, Y = H).[2186]

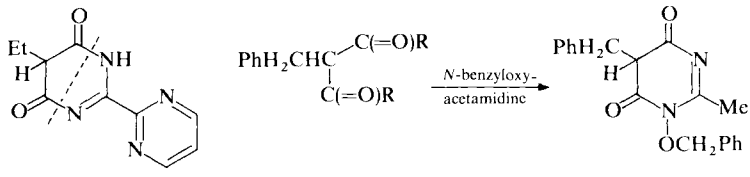
5-Chloro-2-phenyl-4,6(1*H*,5*H*)-pyrimidinedione (**341**, R = Cl, Y = Ph) (59%) from diethyl α-chloromalonate (**339**, R = Cl) with benzamidine (**340**, Y = Ph).[1875]

5-Fluoro-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione (**341**, R = F, Y = Me) from diethyl α-fluoromalonate (**339**, R = F) with acetamidine (**340**, Y = Me).[272]

5-Benzyl-2-phenyl-4,6(1*H*,5*H*)-pyrimidinedione (**341**, R = CH_2Ph, Y = Ph) (43%) from bis(2,4-dichlorophenyl) α-benzylmalonate with benzamidine (**340**, Y = Ph) as hydrochloride (no solvent: 220°).[4185]

5-Ethyl-2,2′-bipyrimidine-4,6(1*H*,5*H*)-dione (**345**) (40%) from diethyl α-ethylmalonate (**339**, R = Et) with 2-pyrimidinecarboxamidine.[3693]

5-Benzyl-1-benzyloxy-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione (**347**) from *N*-benzyloxyacetamidine with α-benzylmalonyl chloride (**346**, R = Cl) in hot



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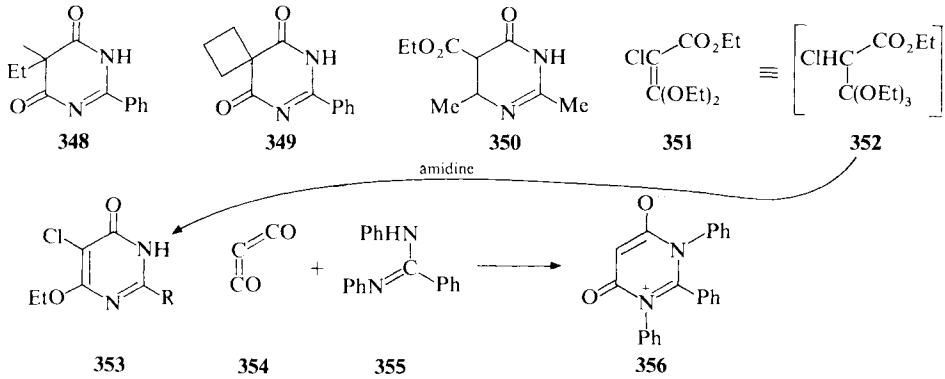
xylene (31% yield) or with neat bis(2,4,6-trichlorophenyl) α-benzylmalonate (**346**, R = $OC_6H_2Cl_3$) at 190° (69% yield).[4191]

Also other similar products.[731,732,888,1159,1337,1832,1875,1958,3105,3987, 4126,4127,4180, 4184,4186–4190,4192,4193]

It is interesting that α-benzylmalonyl chloride (**346**, R = Cl) reacted with free benzamide oxime (*N*-hydroxybenzamidine) in boiling xylene to give simply 5-benzyl-2-phenyl-4,6(1*H*,5*H*)-pyrimidinedione (**341**, R = CH_2Ph, Y = Ph), whereas the same reactants in boiling chlorobenzene containing triethylamine gave the corresponding *N*-oxide (34%).[4194]

Cyclocondensation of *α,α-disubstituted malonic esters* with amidines is only lightly represented, probably due to a lack of any use for the products. However, diethyl α,α-diethylmalonate with benzamidine in warm ethanolic ethoxide gave 5,5-diethyl-2-phenyl-4,6(1*H*,5*H*)-pyrimidinedione (**348**) (44%),[4180] while broadly similar condensations of appropriate partners gave 2-phenyl-5,5-trimethylene-4,6(1*H*,5*H*)-pyrimidinedione (**349**) (61%)[4195] and 5,5-diethyl-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione (~60%) (120° in a sealed tube).[2186] Diethyl α-ethylidenemalonate reacted, not as a β-diester, but as a reduced β-keto ester with acetamidine to give ethyl 2,4-dimethyl-6-oxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxylate (**350**).[1466]



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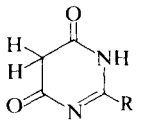
The use of *β-diester equivalents* with amidines is quite rare. At first sight, ethyl 2-chloro-3,3-diethoxyacrylate (**351**) might be mistaken for the equivalent of an aldehydo ester. However, because of its unsaturation, it is, in fact, the equivalent

of a β-orthoester ester (**352**), and as such it reacted with free acetamidine or benzamidine to afford 5-chloro-6-ethoxy-2-methyl-4(3*H*)-pyrimidinone (**353**, R = Me) (39%) or the 2-phenyl analog (**353**, R = Ph) (16%), respectively.[1002] Carbon suboxide (dioxopropadiene) (**354**) with *N*-benzyloxyacetamidine in ether (initially at −20°, later at 25°) gave 5-benzyl-1-benzyloxy-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione (**347**) (52%);[4196] likewise, the same substrate (**354**) with *N*,*N*′-diphenylbenzamidine (**355**) gave 6-oxo-1,2,3-triphenyl-3,6-dihydro-1-pyrimidinium-4-olate (**356**).[4197]

3.6.2. With Guanidines

The condensation of *diethyl or dimethyl malonate* with guanidine to give 2-amino-4,6(1*H*,5*H*)-pyrimidinedione (**357**, R = NH_2) has been done under a variety of conditions:[1149,1525,1578,1636] the best procedure involved the dimethyl ester in refluxing methanolic sodium methoxide to give a 98% yield.[1011] Similarly, *N*,*N*-dimethylguanidine gave 2-dimethylamino-4,6(1*H*,5*H*)-pyrimidinedione (**357**, R = NMe_2) (~70%),[2044] *N*-methylguanidine gave a separable mixture of 2-methylamino- (**357**, R = NHMe) and 2-amino-1-methyl-4,6(1*H*,5*H*)-pyrimidinedione (**358**) in 15 : 1 ratio,[861,1484] biguanide with 1 mol of ethanolic ester gave 2-guanidino-4,6(1*H*,5*H*)-pyrimidinedione [**357**, R = NHC(:NH)NH_2][3201] or with 2 mol of ester in methanolic methoxide gave bis(4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yl)amine (**359**) (~70%),[4144] *N*-isopropylguanidine gave only 2-isopropylamino-4,6(1*H*,5*H*)-pyrimidinedione (**357**, R = Pr^i) (70%),[2463] 4-methyl-1-piperazinecarboxamidine gave 2-(4′-methylpiperazin-1′-yl)-4,6(1*H*,5*H*)-pyrimidinedione (**360**, R = Me) (14%),[302] 4-phenyl-1-piperazinecarboxamidine gave 2-(4′-phenylpiperazin-1′-yl)-4,6(1*H*,5*H*)-pyrimidinedione (**360**, R = Ph) (48%),[394] and 5-tetrazolamine (equivalent to azidoguanidine) with neat ester at 180° gave 2-azido-4,6(1*H*,5*H*)-pyrimidinedione (**357**, R = N_3) (12%).[1717] Ethyl 2-(methylthio)thiocarbonylacetate (**342**) with guanidine in ethanol or ethanolic ethoxide gave 2-amino-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone (44–48%) plus a separable by-product, 2-amino-6-ethoxy-4(3*H*)-pyrimidinone (19%).[1189,1666] Other examples have been reported.[1050,4106,4199]



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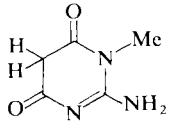

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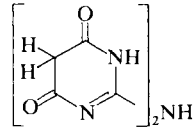

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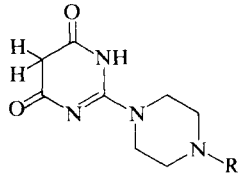

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The cyclizations of *α-substituted malonic esters* with guanidines are exemplified in the following syntheses.

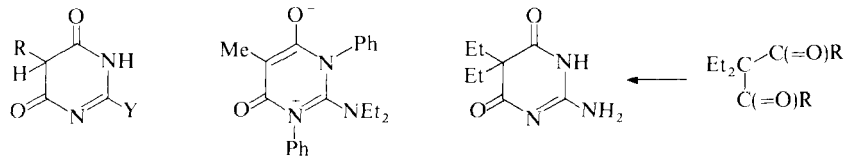
2-Amino-5-ethyl-4,6(1*H*,5*H*)-pyrimidinedione (**361**, R = Et, Y = NH_2) (80%) from diethyl α-ethylmalonate with refluxing ethanolic guanidine carbonate;[1149] free guanidine in ethanol gave a 55% yield.[1230]

2-Amino-5-nitroso-4,6(1*H*,5*H*)-pyrimidinedione (**361**, R = NO, Y = NH_2) (46% after reduction to the 5-amino analog) from diethyl α-nitrosomalonate with guanidine in ethanolic ethoxide.[2421]

2-Amino-5-methoxy-4,6(1*H*,5*H*)-pyrimidinedione (**361**, R = OMe, Y = NH_2) (70%)[1007] or its 5-phenoxy analog (**361**, R = OPh, Y = NH_2) (73%)[3885] from diethyl α-methoxy- or α-phenoxymalonate, respectively, with guanidine in ethanolic ethoxide.

5-Allyl-2-amino-4,6(1*H*,5*H*)-pyrimidinedione (**361**, R = $CH_2CH{:}CH_2$, Y = NH_2) (64%) from diethyl α-allylmalonate with guanidine in ethanolic ethoxide;[203] its 2,5-diamino analog rather similarly.[6025]

5-Benzyl-2-benzylamino-4,6(1*H*,5*H*)-pyrimidinedione (**361**, R = CH_2Ph, Y = $NHCH_2Ph$) (51%) from diethyl α-benzylmalonate with *N*-benzylguanidine in methanolic methoxide.[4203]



361 **362** **363** **364**

2-Methylamino-5-methylthio-4,6(1*H*,5*H*)-pyrimidinedione (**361**, R = SMe, Y = NHMe) (~90%; structure confirmed) from diethyl α-(methylthio)-malonate with *N*-methylguanidine in methanolic methoxide.[2471]

2-Diethylamino-5-methyl-6-oxo-1,3-diphenyl-3,6-dihydro-1-pyrimidinium-4-olate (**362**) (50%) from bis(2,4,6-trichlorophenyl) α-methylmalonate with *N*,*N*-diethyl-*N*′,*N*″-diphenylguanidine without solvent at 150°.[285]

2-Amino-5,5-diethyl-4,6(1*H*,5*H*)-pyrimidinedione (**363**) from guanidine with (1) diethyl α,α-diethylmalonate (**365**, R = OEt) in ethanolic ethoxide,[3109] (2) α,α-diethylmalonyl chloride (**364**, R = Cl) at room temperature,[3109,4205] or (3) α,α-diethylmalonic acid (**364**, R = OH) in fuming sulfuric acid.[4206]

Also other such syntheses.[256,1324,1337,1697,2531,4195,4200–4202,4204,4207,4208,4210,4211,6765]

3.6.3. With Ureas

Barbituric acid, 2,4,6(1*H*,3*H*,5*H*)-*pyrimidinetrione* (**365**, X = Y = H) was first made more than a century ago by the condensation of malonic acid with urea in the presence of phosphoryl chloride;[834,3550] acetic anhydride was used subsequently as the condensing agent.[789,1642,3413] However, the best synthesis

proved to be from diethyl malonate with urea in ethanolic sodium ethoxide, a method that was gradually developed[192,3383,3618,3642,3664,4209,4212] to definitive procedures using equimolecular proportions of the reactants and sodium alkoxide in refluxing ethanol or methanol for 5–7 h to afford barbituric acid in ~80% yield.[1376,3641] In contrast, 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**365**, X = Y = Me) (68%) was best made from malonic acid with *N*,*N*′-dimethylurea in acetic anhydride–acetic acid,[789,3739] using modified procedures to avoid a troublesome by-product;[644,2801] malonyl chloride in phosphoryl chloride[2800] and diethyl malonate in ethanolic ethoxide[2708,3706,3753] proved less satisfactory. The following preparations further illustrate the use of *α-unsubstituted malonates* with other ureas.

1-Methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**365**, X = Me, Y = H) (70%) from malonic acid with *N*-methylurea in acetic anhydride–acetic acid;[789] diethyl malonate and methylurea in alcoholic alkoxide gave lower yields.[2533,3753]

1,3-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**365**, X = Y = Et) (67%) from malonyl chloride with *N*,*N*′-diethylurea in ether;[1842] malonic acid and diethylurea in acetic anhydride gave only 15% yield.[2533]

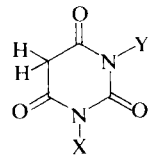
1-Methoxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**365**, X = OMe, Y = H) (81%) from diethyl malonate with *N*-methoxyurea in ethanolic ethoxide.[1338]

1-Amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**365**, X = NH_2, Y = H) (75%) from diethyl malonate and semicarbazide (as acetone semicarbazone) in ethanolic ethoxide.[1518]

2-Methoxy-4,6(1*H*,5*H*)-pyrimidinedione (**366**, R = Me) (64–84%) from diethyl or dimethyl malonate with *O*-methylisourea in methanolic methoxide.[2484,2485]

2-Cyclohexyloxy-4,6(1*H*,5*H*)-pyrimidinedione (70%) from dimethyl malonate with *O*-cyclohexylisourea.[918]

1,3-Dicyclohexyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**365**, X = Y = C_6H_{11}) (65%) from malonic acid with *N*,*N*′-dicyclohexylcarbodiimide (**367**) in



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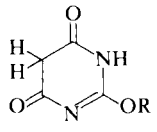

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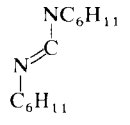

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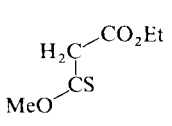

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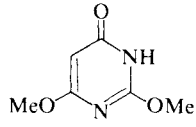

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tetrahydrofuran, whereas malonyl chloride with *N,N'*-dicyclohexylurea gave only 5.5% yield.[4216]

2,6-Dimethoxy-4(3*H*)-pyrimidinone (**369**) (~60%) from ethyl 2-[methoxy(thiocarbonyl)]acetate (**368**) with *O*-methylisourea in methanolic methoxide.[972]

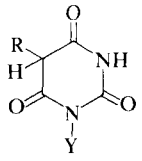
Also other examples.[54,165,285,408,467,1983,2079,3963,4213,4214,6309]

In similar ways, *α-monosubstituted malonic esters or equivalents* gave, for example, the following pyrimidines.

5-Ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**370**, R = Et, Y = H) (~80%) from diethyl α-ethylmalonate with urea in ethanolic ethoxide[3760] or in dimethylformamide containing sodium methoxide;[4114] also using sodiourea in acetone (80% yield).[4218]

5-β-Hydroxyethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**370**, R= CH_2CH_2OH, Y = H) (34%) from α-ethoxycarbonyl-γ-butyrolactone (**371**) with urea in ethanolic ethoxide.[1319]

5-Butyl-6-chloro-1,3-diphenyl-2,4(1*H*,3*H*)-pyrimidinedione (**372**) (79%) from α-butylmalonic acid with *N,N'*-diphenylurea in phosphoryl chloride, clearly *via* 5-butyl-1,3-diphenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione.[855]



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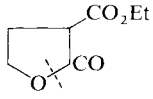

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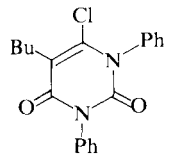

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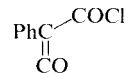

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5-Fluoro-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**370**, R = F, Y = Me) (73%) from diethyl α-fluoromalonate with *N*-methylurea in ethanolic ethoxide.[138]

1-Cyclohexyl-3-methyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (60%) from 2-chlorocarbonyl-2-phenylketene (**373**) with *N*-cyclohexyl-*N'*-methylurea in refluxing chloroform.[69]

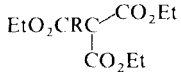
1,3-Dibenzyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (72%) from α-phenylmalonic acid with *N,N'*-dibenzylurea in chloroform–acetic acid–acetic anhydride–trifluoroacetic acid.[3754]

1-Methyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**370**, R= NO_2, Y = Me) from diethyl α-nitromalonate with *N*-methylurea in ethanolic ethoxide.[3413]

1-Amino-5-methyl (ethyl, propyl, or butyl)-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (27–51%) from the diethyl α-alkylmalonate with semicarbazide (as acetone semicarbazone) in ethanolic ethoxide.[1238,1518]

Also similar products.[559,1002,2526,2533,2721,3036,3109,3488,3952,4200,4217,4219,4220,4229,6211]

The condensation of triethyl methanetricarboxylate (**374**, R = H) or its α-methyl derivative, triethyl 1,1,1-ethanetricarboxylate (**374**, R = Me), with urea in ethanolic ethoxide gave 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**370**, R = Y = H) (71%) or its 5-methyl derivative (**370**, R = Me, Y = H) (81%), respectively, by loss of the expected 5-ethoxycarbonyl group during the reaction or workup; *N*-phenyl- or *N*,*N*′-dimethylurea behaved similarly.[3488]



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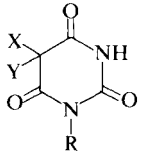
The cyclocondensation of α,α-*disubstituted malonic esters* with ureas takes place rather less readily but it is especially important as the usual route to many of the biologically active barbiturates. Thus appropriate diethyl α,α-disubstituted-malonates with ureas in ethanolic ethoxide (often at 105–110° in a sealed vessel) gave, for example, 5,5-diethyl- (**375**, R = H, X = Y = Et) (70%),[3109,3642] 5,5-diethyl-1-methyl- (**375**, R = Me, X = Y = Et),[3109] 5,5-trimethylene- (**375**, R = H, X + Y = $CH_2CH_2CH_2$) (71%),[4195] 5-acetamido-5-propyl- (**375**, R = H, X = NHAc, Y = Pr) (long reflux: 67%),[725] 5-ethyl-5-hydroxy- (**375**, R = H, X = Et, Y = OH) (reflux: 6%),[4221] 5-butyl-5-β-vinyloxyethyl- (**375**, R = H, X = Bu, Y = $CH_2CH_2OCH{:}CH_2$) (reflux: 80%),[4222] 5,5-dimethoxy- (**375**, R = H, X = Y = OMe) (refluxing methanolic methoxide: 48%),[4223] 5-ethyl-5-*p*-fluorophenyl- (55%),[4225] 5,5-diethyl-1-isopropyl- (**375**, R = Pr^i, X = Y = Et) (50%),[106] and 1-ethyl-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**375**, R = Et, X = Y = Me) (55%);[2807] analogs similarly.[46,4618]

Other methods have been used also. Thus α,α-dimethylmalonic acid with urea in phosphoryl chloride gave 5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**375**, R = H, X = Y = Me);[4224] diethyl α-ethyl-α-isopentylmalonate with urea in liquid ammonia containing potassium hydroxide gave 5-ethyl-5-isopentyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (~55%);[3643] α-ethyl-α-phenylmalonyl chloride (**376**, X = Et, Y = Ph) with *N*,*N*′-dibenzyloxyurea in refluxing toluene gave 1,3-dibenzyloxy-5-ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**377**)



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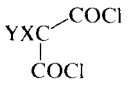

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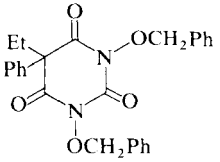

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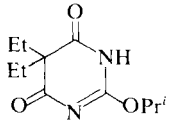

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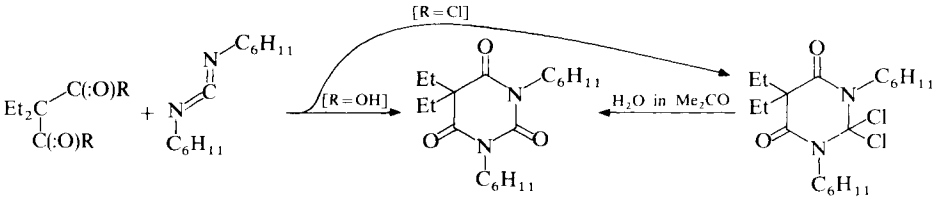
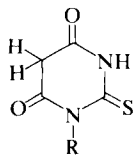
(25%);[4226] and α,α-diethylmalonyl chloride (**376**, X = Y = Et) with *O*-isopropylisourea in cold benzene–aqueous sodium carbonate gave 5,5-diethyl-2-isopropoxy-4,6(1*H*,5*H*)-pyrimidinedione (**378**) (45%).[106] In addition, α,α-diethylmalonic acid (**379**, R = OH) with *N*,*N*′-dicyclohexylcarbodiimide (**380**) (2 mol) in tetrahydrofuran gave 1,3-dicyclohexyl-5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**381**) (50%),[4216] while an essentially similar condensation gave its 5,5-dimethyl-1,3-di-*p*-tolyl analog (38%).[4227] Even more useful was the reaction of α,α-diethylmalonyl chloride (**379**, R = Cl) with the same carbodiimide (**380**) in toluene at 25° to afford 2,2-dichloro-1,3-dicyclohexyl-5,5-diethyl-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**382**) (62%) and thence, by stirring in slightly aqueous acetone, 1,3-dicyclohexyl-5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**381**) (98%);[542] analogs were made similarly.[542,4228]



379 **380** **381** **382**

3.6.4. With Thioureas

Reports on the formation of 2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (thiobarbituric acid) (**383**, R = H) from *diethyl malonate* with thiourea are rather unsatisfactory; the original vague procedure[1525,3664] was later said to give an 84% yield without any helpful additional detail.[958] However, a more normal method in ethanolic sodium ethoxide was reported to give only 45%, even when heated at 105° in a sealed vessel.[3665] The less troublesome condensation of triethyl methanetricarboxylate (**339**, R = CO_2Et) with thiourea in cold ethanolic ethoxide afforded the same product (**383**, R = H) (78%) because of a spontaneous loss of the uninvolved ethoxycarbonyl group during the reaction.[1787] Diethyl malonate reacted quite normally with *N*-methylthiourea in ethanolic ethoxide to give 1-methyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**383**, R = Me) (82%);[1575] malonic acid with *N*,*N*′-diphenylthiourea in neat acetyl chloride or chloroform–phosphoryl chloride gave 1,3-diphenyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**384**) (~40%);[3563,3883,4230] diethyl malonate with thiosemicarbazide (as its isopropylidene derivative) in ethanolic ethoxide gave 1-amino-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**383**, R = NH_2) (39%);[1518] bis(2,4,6-trichlorophenyl)malonate with *S*-ethyl-*N*,*N*′-dimethylisothiourea in refluxing etherial ethyl acetate gave 2-ethylthio-1,3-dimethyl-6-oxo-3,6-dihydro-1-pyrimidinium-4-olate (**385**, R = H) (64%);[285] malonic acid with 1,4-diphenyl(thiosemicarbazide) in acetyl chloride at 40° gave 1-anilino-3-phenyl-2-thioxo-2,3-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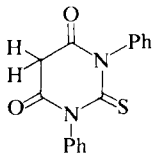
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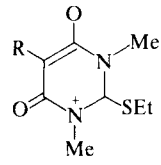
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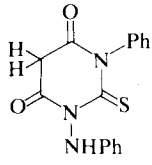
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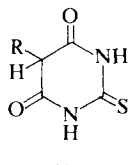
dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**386**) (55%);[457] and other examples have been recorded.[179,3962]

The condensation of α-*monosubstituted malonic esters* with thioureas appears to proceed easily (usually in refluxing alcoholic sodium alkoxide during several hours) to give, for example, 5-methyl- (**387**, R = Me) (~50%),[1046] 5-isopropyl- (**387**, R = Pr^i),[930] 5-nitroso- (**387**, R = NO),[1686] 5-amino- (**387**, R = NH_2),[3988] 5-acetamido- (**387**, R = NHAc),[6075] and 5-phenyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**387**, R = Ph) (73%),[1816] as well as some analogs.[921,4116] 5-Benzyloxy-2-ethylthio-4,6(1*H*,5*H*)-pyrimidinedione (51%) was made similarly from diethyl α-benzyloxymalonate with *S*-ethylisothiourea,[1337] while 2-ethylthio-1,3,5-trimethyl-6-oxo-3,6-dihydro-1-pyrimidinium-4-olate (**385**, R = Me) (75%) was obtained from bis(2,4,6-trichlorophenyl) α-methylmalonate with *S*-ethyl-*N*,*N*′-dimethylisothiourea in ether at 25°.[285]

Analogous cyclocondensations of α,α-*disubstituted malonic esters* with thioureas have usually been done by refluxing the reactants in ethanolic sodium ethoxide for several hours to give, for example, 5,5-dimethyl- (**388**, X = Y = Me),[3149] 5,5-diethyl- (**388**, X = Y = Et),[3109,4231] 5,5-diallyl- (**388**, X = Y = $CH_2CH{:}CH_2$),[4232,4233] 5-ethyl-5-α-methylbutyl- (**388**, X = Et, Y = CHMePr),[4233] 5-acetamido-5-allyl- (**388**, X = NHAc, Y = $CH_2CH{:}CH_2$) (66%),[725] and 1-allyl-5,5-diethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione.[4234] However, diethyl α,α-diethylmalonate with *N*-methylthiourea under similar conditions gave only a minute amount of the expected product, 5,5-diethyl-1-methyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**389**),[4235, cf. 4234] although this could be made in good yield from α,α-diethylmalonyl chloride with *N*-methylthiourea or from hydrolysis of the corresponding 4-amino analog;[4235] it may be significant that a 3-fold increase in the proportion of *N*-methylthiourea in the foregoing condensation in alcoholic alkoxide produced 5,5-diethyl-1-methyl-2-*N*′-methyl(thioureido)-4,6(1*H*,5*H*)-pyrimidinedione (**390**) in 84% yield and that the latter could be made also (in comparable yield) by thioxo displacement from **389** using *N*-methylthiourea in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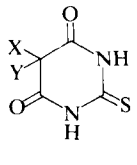
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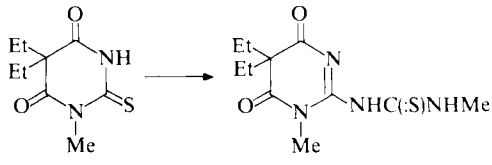
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methanolic methoxide.[4236] α-Ethyl-α-phenylmalonyl chloride with *N*-methylthiourea in refluxing toluene gave 5-ethyl-1-methyl-5-phenyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione.[350]

3.7. USE OF β-ALDEHYDO NITRILES

These intermediates lead to 4-amino-6-unsubstituted pyrimidines, which may be substituted at the 1-, 2-, 3-, and/or 5-positions according to the particular partners used. Since few free β-aldehydo nitriles are readily available and some react in an anomalous manner anyway, most Principal Syntheses in this category are performed with equivalent three-carbon reagents.

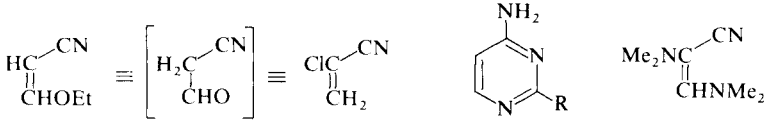
3.7.1. With Amidines

The scope of condensations between *β-aldehydo nitrile equivalents* and amidines is illustrated in the following syntheses.

2-Methyl-4-pyrimidinamine (**393**, R = Me) (50%) from 3-ethoxyacrylonitrile (**391**) with acetamidine (no solvent) at 100–160°.[3427]

2-Phenyl-4-pyrimidinamine (**393**, R = Ph) from benzamidine with 3-ethoxyacrylonitrile (**391**) (no solvent, at 100–160°: 77%)[3427] or with 2-chloroacrylonitrile (**392**) (methanolic methoxide at 20°: 39–50%).[3427,3722]

5-Dimethylamino-4-pyrimidinamine (28%) from 2,3-bisdimethylaminoacrylonitrile (**394**) with formamidine acetate at 120° without solvent.[2649]

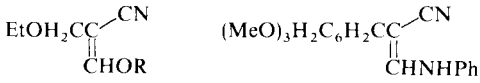


391 **392** **393** **394**

5-Ethoxymethyl-2-methyl-4-pyrimidinamine (55%) from 2-ethoxymethyl-3-methoxy- (**395**, R = Me)[924,2813] or 3-acetoxy-2-ethoxymethylacrylonitrile (**395**, R = Ac)[2914] with ethanolic acetamidine.

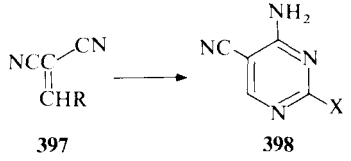
2-Phenyl-5-(3′,4′,5′-trimethoxybenzyl)-4-pyrimidineamine (77%) from 3-anilino-2-(3′,4′,5′-trimethoxybenzyl)acrylonitrile (**396**) with ethanolic benzamidine.[3346]

Also other condensations.[549,1065,1451,1463,2725,3451,4104,4237–4240]

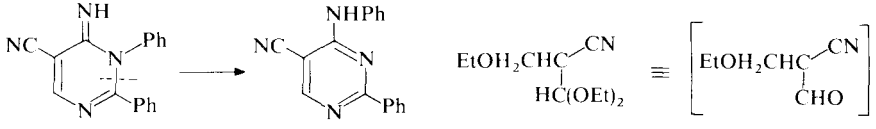


395 **396**

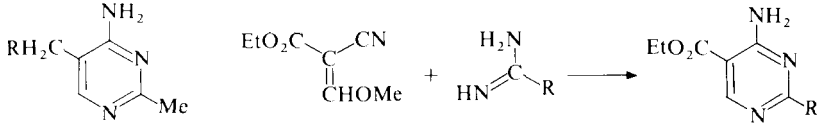
α-Ethoxymethylenemalononitrile (**397**, R = OEt) behaved as an aldehydo nitrile (rather than as a β-dinitrile) with free amidines in alcohol to give, for example, 4-amino-2-methyl- (**398**, X = Me),[1250,1466,1467] 4-amino-2-ethyl- (**398**, X = Et) (80%),[1118] 4-amino-2-pentafluoroethyl- (**398**, X = C_2F_5) (69%),[4241] 4-amino-2-cyclopropylmethyl- [**398**, X = $CH_2CH(CH_2)_2$] (75%),[4242] and 4-amino-2-phenyl-5-pyrimidinecarbonitrile (**398**, X = Ph) (35%);[1118] likewise, α-aminomethylenemalononitrile (**397**, R = NH_2) or its α-dimethylaminomethylene analog (**397**, R = NMe_2) with formamidine gave 4-amino-5-pyrimidinecarbonitrile (**398**, X = H) in 42% or ~60% yield,[1251] respectively. α-Ethoxymethylenemalononitrile (**397**, R = OEt) with *N*-phenylbenzamidine in ethanol at −10° gave 4-imino-2,3-diphenyl-3,4-dihydro-5-pyrimidinecarbonitrile (**399**) (49%), but when this product was melted or the original condensation was done at room temperature, Dimroth rearrangement ensued to afford the isomer, 4-anilino-2-phenyl-5-pyrimidinecarbonitrile (**400**) (66%), thereby incidentally proving the position of the *N*-phenyl group in **399**.[4243] Although both 2-ethoxymethyl-3-methoxyacrylonitrile (**395**, R = Me) and the acetal, 3,3-diethoxy-2-ethoxymethylpropionitrile (**401**), are clearly equivalents of 3-ethoxy-2-formylpropionitrile (**402**), the first (**395**, R = Me) reacted normally with acetamidine to give only 5-ethoxymethyl-2-methyl-4-pyrimidinamine (**403**, R = OEt) (see preceding list) whereas the second (**401**) gave a separable mixture of (**403**, R = OEt) (2.5% yield) and 5-acetamidomethyl-2-methyl-4-pyrimidinamine (**403**, R = NHAc) (63% yield).[678] The mechanism by which the latter product was formed (via a pyrimidopyrimidine intermediate) has been investigated extensively.[678,1929,2915–2918,2923,3865,4244] The condensation of ethyl 2-cyano-3-methoxyacrylate (**404**) with acetamidine or benzamidine to give ethyl 4-amino-2-methyl- (**405**, R = Me) (as a minor product) or ethyl 4-amino-2-



397 **398**



399 **400** **401** **402**

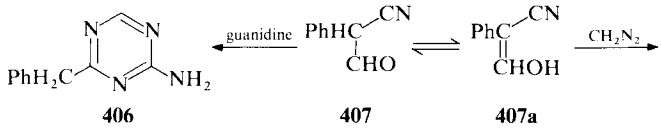


403 **404** **405**

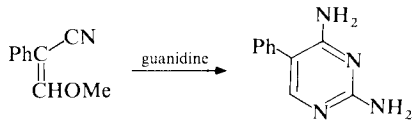
phenyl-5-pyrimidinecarboxylate (**405**, R = Ph) (as a major product),[1600] respectively, has been described in Section 3.4.1.

3.7.2. With Guanidines

The direct condensation of 2-formyl-2-phenylacetonitrile (**407**) with guanidine gave 4-benzyl-1,3,5-triazin-2-amine (**406**) instead of the expected 5-phenyl-2,4-pyrimidinediamine (**409**); this anomalous behavior was said to be due to the large proportion of highly acidic enol (**407a**) present in the reaction mixture.[4245] However, after methylation of the enol (**407a**) with diazomethane, the resulting 3-methoxy-2-phenylacrylonitrile (**408**) reacted quite normally with ethanolic guanidine to give the pyrimidine (**409**);[4238] 3-butoxy-2-phenylacrylonitrile gave **409** similarly in 78% yield.[4247] Such use of *β-aldehydo nitrile equivalents* with guanidines is further exemplified in the following syntheses.



406 **407** **407a**



408 **409**

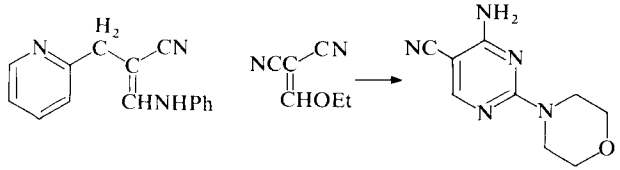
2,4-Pyrimidinediamine from guanidine with 3-ethoxyacrylonitrile (in ethanol: 57% yield),[4101] *trans*-3-chloroacrylonitrile (in acetonitrile: ~20%),[4246] or 3-anilinoacrylonitrile (in methanolic methoxide).[292]

5-Ethoxy-2,4-pyrimidinediamine (65%) from neat guanidine with 2,3-diethoxyacrylonitrile at 120° under nitrogen.[1186]

5-Pyridin-2′-ylmethyl-2,4-pyrimidinediamine (66%) from guanidine with 3-anilino-2-pyridin-2′-ylmethylacrylonitrile (**410**) in ethanol.[4248]

5-Dimethylamino-2,4-pyrimidinediamine (30%) from neat guanidine with 2,3-bisdimethylaminoacrylonitrile at 80° under nitrogen.[2649]

2,4-Diamino-5-pyrimidinecarbonitrile (81%) from guanidine with α-ethoxymethylenemalononitrile (**411**).[419]

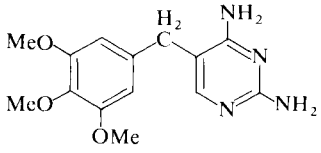


410 **411** **412**

4-Amino-2-morpholino-5-pyrimidinecarbonitrile (**412**) (88%) from 4-morpholinecarboxamidine with α-ethoxymethylenemalononitrile (**411**) in ethanol.[4038]

Also other such reactions.[11,26,416,2601,3752,4249,4250,6027]

In addition, this type of condensation has been used to prepare *trimethoprim*, 5-(3′,4′,5′-trimethoxybenzyl)-2,4-pyrimidinediamine (**413**), an antibacterial widely used in combination with sulfonamides, as well as its analogs. For example, acrylonitrile was converted into 3-methoxypropionitrile (**414**), which underwent a base-catalyzed reaction with 3,4-dimethoxybenzaldehyde to give 2-(3′,4′-dimethoxybenzylidene)-3-methoxypropionitrile (**415**), tautomeric with 2-(3′,4′-dimethoxybenzyl)-3-methoxyacrylonitrile (**416**), which was then condensed with methanolic guanidine to afford 5-(3′,4′-dimethoxybenzyl)-2,4-pyrimidinediamine (**417**) (44%).[4251] Various general routes to such products were summarized[4252] in 1976, but the following examples will indicate briefly the types of intermediate involved: trimethoprim (**413**) (~65%) from 3,3-diethoxy-2-formyl-2-(3′,4′,5′-trimethoxybenzyl)propionitrile (**418**, R = CHO) or ethyl 2-cyano-3,3-diethoxy-2-(3′,4′,5′-trimethoxybenzyl)propionate (**418**, R = CO_2Et), probably via the intermediate (**419**) formed in situ;[4253] 5-(3′,4′,5′-trimethoxyphenoxy)-2,4-pyrimidinediamine (~20%) from 3-methoxy-2-(3′,4′,5′-trimethoxyphenoxy)acrylonitrile;[2511] 5-(4′-benzyloxy-3′,5′-diisopropylbenzyl)-2,4-pyrimidinediamine (89%) from 3-anilino-2-(4′-benzyloxy-3′,5′-diisopropylbenzyl)acrylonitrile (**420**);[557] and many analogous syntheses.[555,556,2331,3926,4254–4258,6896]



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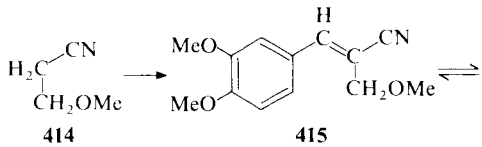
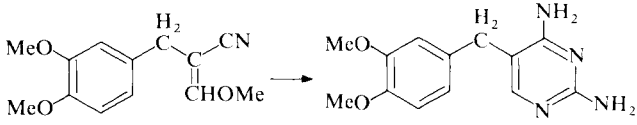
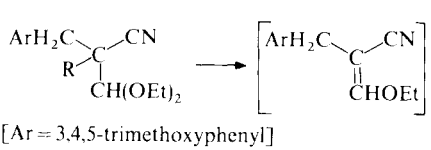


414 **415**

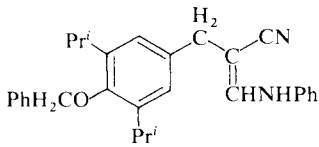


416 **417**



[Ar = 3,4,5-trimethoxyphenyl]

418 **419**



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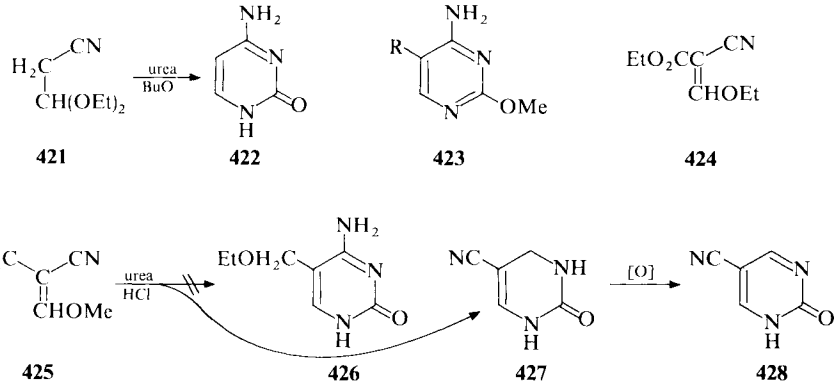
3.7.3. With Ureas

The unexpectedly rare reports of simple condensations between *β-aldehydo nitrile equivalents* and ureas are represented in the formation of 4-amino-2(1*H*)-pyrimidinone, cytosine (**422**) (32%), from 3,3-diethoxypropionitrile (**421**) with urea in refluxing butanolic sodium butoxide;[1677,4259] 4-amino-1-benzyloxy-2(1*H*)-pyrimidinone from *N*-benzyloxyurea with 3,3-diethoxy- (**421**) or 2,3-dibromopropionitrile in ethanolic ethoxide (47% or 11% yield), respectively;[1681] 4-amino-5-phenyl-2(1*H*)-pyrimidinone (48%) from 3-methoxy-2-phenylacrylonitrile (**408**) with urea in ethanolic sodium ethoxide;[4260] 4-amino-2-methoxy-5-pyrimidinecarbonitrile (**423**, R = CN) (~50%) from α-ethoxymethylenemalononitrile (**397**, R = OEt) with ethanolic *O*-methylisourea;[847] methyl 4-amino-2-methoxy-5-pyrimidinecarboxylate (**423**, R = CO_2Me) (17%), the ethyl ester (**423**, R = CO_2Et) (14%), and 2-methoxy-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile (50%) from ethyl 2-cyano-3-ethoxyacrylate (**424**) with *O*-methylisourea in methanolic methoxide;[2203] and 4-amino-3-ethyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile (84%) from α-ethoxymethylenemalononitrile (**397**, R = OEt) with *N*-ethylurea in methanolic methoxide.[864] It is interesting that 2-ethoxymethyl-3-methoxyacrylonitrile (**425**) with urea in an acidic medium gave not the expected product (**426**), but 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**427**) (47%) and thence by bromine oxidation, 2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile (**428**) (80%).[1617, cf. 913]



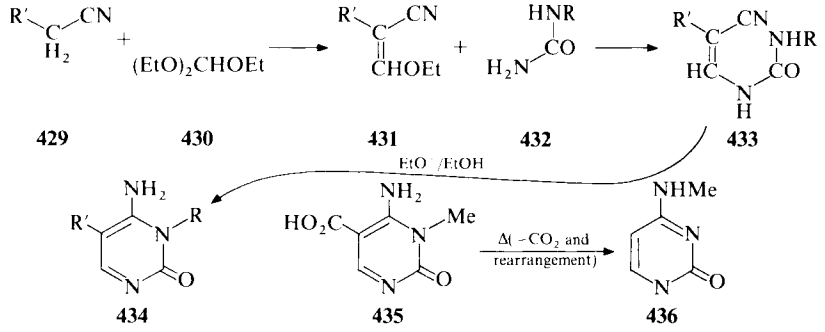
421 **422** **423** **424**

425 **426** **427** **428**

An unusual and ingenious version of the foregoing condensations is known as the *Whitehead synthesis*: as pioneered[864,2976] and subsequently extended,[794,1221,1383,1602,1603] this synthesis leads to cytosine (**422**) bearing a 3-alkyl or aryl and a 5-cyano, carboxy, ethoxycarbonyl, carbamoyl, or nitro group (**434**: R = alkyl or aryl; R′ = C, CO_2H, CO_2Et, $COHN_2$, CONH-alkyl, CON-dialkyl, or NO_2), many of which products are otherwise unavailable. The crux is the formation of a β-ureidoacrylonitrile derivative (**433**) directly from a 3-fold mixture of nitrile (**429**), orthoformic ester (**430**), and *N*-alkyl(or aryl) urea (**432**),

probably but not necessarily, via the 3-ethoxyacrylonitrile derivative (**431**);[864,2976,4109,4261] the ureido compound (**433**) is then cyclized to the substituted cytosine (**434**), usually in ethanolic ethoxide. The substituted ethoxyacrylonitrile (**431**) may be preformed and isolated if desired; alternatively, not even the ureido compound (**433**) need be isolated. Table 3.1 contains some typical examples of the synthesis.

Although the 3-alkyl-4-amino-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acids (**434**, R = CO_2H) apparently offered a facile route to 3-alkylcytosines (**434**, R′ = H) by thermal decarboxylation,[864] at least in the case of 4-amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acid (**435**), such treatment induced an unexpected Dimroth rearrangement (before or after decarboxylation?) to afford 4-methylamino-2(1*H*)-pyrimidinone (**436**).[809,1383] Although the reaction of 2-nitroacetonitrile (**429**, R′ = NO_2), triethyl orthoformate (**430**), and *N*-methylurea (**432**, R = Me) proceeded normally to 3-(*N*′-methylureido)-2-nitroacrylonitrile (**433**, R = Me, R′ = NO_2) and thence to 4-amino-3-methyl-5-nitro-2(3*H*)-pyrimidinone (**434**, R = Me, R′ = NO_2) (33%), when other *N*-alkylureas were used the ring-closure step led in each case to a mixture of 3-alkyl-4-amino-5-nitro-2(3*H*)- and 4-alkylamino-5-nitro-2(1*H*)-pyrimidinone (by rearrangement).[1221]



3.7.4. With Thioureas

Despite a relative paucity of reports, it is evident that *β-aldehydo nitrile equivalents* and thioureas react quite easily to produce pyrimidines, as illustrated in the following examples.

4-Amino-5-phenyl-2 (1*H*)-pyrimidinethione (**438**) from thiourea with 3-methoxy- (**437**, R = OMe) (63% yield)[4260] or 3-ethoxy-2-phenylacrylonitrile (**437**, R = OEt) (79% yield)[4115,4260] in ethanolic ethoxide or from thiourea, 3-anilino-2-phenylacrylonitrile (**437**, R = NHPh), and sodium ethoxide at 135° in a vacuum (68% yield).[4262]

4-Amino-5-*p*-methoxybenzyl-2(1*H*)-pyrimidinethione (~70%) from thiourea

TABLE 3.1. TYPICAL PRODUCTS OF THE WHITEHEAD SYNTHESIS[a]

Pyrimidine	Method[b]	Yield (%)[c]	Ref.
Ethyl 4-amino-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	A	96	2976
Ethyl 4-amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	B	32	864
	A	86	1383
Ethyl 4-amino-3-ethyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	B	47	864
	A	63	864
Ethyl 4-amino-3-β-hydroxyethyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	B	90	864
Ethyl 4-amino-3-benzyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	A	91	864
Ethyl 4-amino-3-hexyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	A	90	864
Ethyl 4-amino-3-cyclohexyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	A	92	794
4-Amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acid	A	62	864,1383
4-Amino-3-butyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acid	A	68	864
4-Amino-2-oxo-3-propyl-2,3-dihydro-5-pyrimidinecarboxamide	A	56	864
4-Amino-3-ethyl-2-oxo-*N*-phenyl-2,3-dihydro-5-pyrimidinecarboxamide	A	45	864

4-Amino-3-methyl-2-oxo-*N*,*N*-(3′-oxopentamethylene)-2,3-dihydro-5-pyrimidinecarboxamide	A	64	864
4-Amino-3-methyl-5-nitro-2(3*H*)-pyrimidinone	A	33	1221
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile	A	86	1602,1603
4-Amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	A	56	864
4-Amino-3-ethyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	B	84	864
4-Amino-3-β-methoxyethyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	A	96	864
4-Amino-3-*p*-chlorophenyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	C	54	864
4-Amino-2-oxo-3-phenyl-2,3-dihydro-5-pyrimidinecarbonitrile	D	61	864
4-Amino-3-benzyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	A	75	864

[a] More than 50 examples have been reported.

[b] Briefly, the methods are as follows.

A. Ethyl 2-cyanoacetate, 2-cyanoacetic acid, 2-cyanoacetamide, *N*-alkyl-2-cyanoacetamide, or malononitrile *plus* triethyl orthoformate *plus* urea or *N*-alkylurea; the ureido intermediate (**433**) was isolated.

B. Ethyl 2-cyano-3-ethoxyacrylate or α-ethoxymethylenemalononitrile *plus* urea or *N*-alkylurea in ethanolic ethoxide gave the product directly.

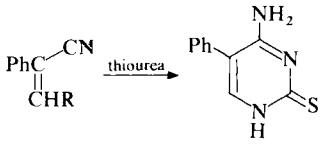
C. Malononitrile *plus* triethyl orthoformate *plus* *N*-arylurea *plus* acetic anhydride gave the product directly.

D. Malononitrile *plus* 1,3-bis(*N*-phenylcarbamoyl)formamidine gave the product directly; see also related work.[2704,4109]

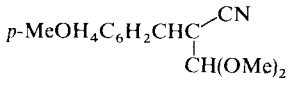
[c] The yield was calculated on the ureido intermediate (**433**) when isolated; otherwise on the primary three-carbon fragment.

with 3,3-dimethoxy-2-(*p*-methoxybenzyl)propionitrile (**439**) in alcoholic alkoxide.[560]

4-Amino-2-thioxo-1,2-dihydro-5-pyrimidinecarbonitrile (**440**) from thiourea with α-ethoxymethylenemalononitrile (**397**, R = OEt) in cold ethanolic ethoxide (~40% yield)[1250] or in aqueous acetonic alkali (12% yield).[1252, cf. 938]



437 **438**



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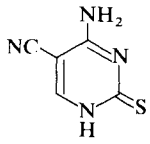
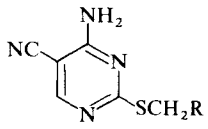


440

4-Amino-2-ethylthio-5-pyrimidinecarbonitrile (**441**, R = Me) (90%) or its 2-benzylthio analog (**441**, R = Ph) (72%) from α-ethoxymethylenemalononitrile (**397**, R = OEt) with cold ethanolic *S*-ethylisothiourea[1250] or cold aqueous acetonic *S*-benzylisothiourea,[4263] respectively.

4-Amino-3-butyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile (**442**) (95%) from α-ethoxymethylenemalononitrile (**397**, R = OEt) with *N*-butylthiourea in cold ethanolic ethoxide.[809]

4-Amino-1-methyl-2(1*H*)-pyrimidinethione (**443**) (90%) from 3-ethoxyacrylonitrile (**431**, R′ = H) with *N*-methylthiourea in ethanolic ethoxide; the unexpected orientation was checked by desulfurization to 1-methyl-4(1*H*)-pyrimidinimine (**444**).[1508]



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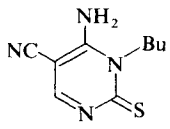

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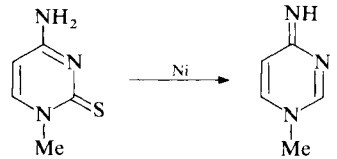
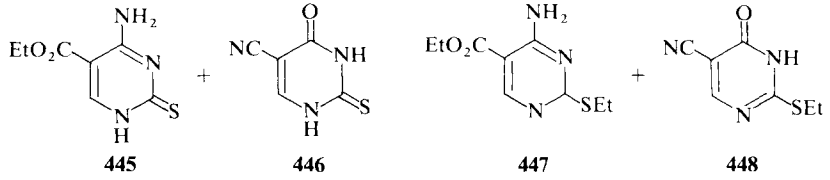


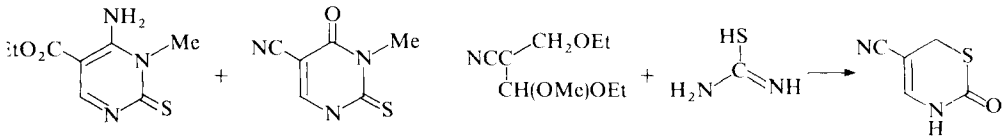
443 **444**

Even more interesting are the *less simple cases* that follow. Ethyl 2-cyano-3-ethoxyacrylate (**424**) reacts as a β-aldehydo nitrile or a β-aldehydo ester according to the thiourea presented and the conditions used. Thus the substrate (**424**) with thiourea in *hot* ethanolic ethoxide gave a separable mixture of ethyl 4-amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate (**445**) (54–80% yield) and 4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**446**) (4–14% yield),[1331,1563,1684,2983, cf. 1685] whereas in *cold* ethanolic ethoxide, the ester (**445**) (91%) appeared to be the only product;[1651] the same substrate (**424**) with *S*-methylisothiourea in cold methanol gave ethyl 4-amino-2-ethylthio-5-pyrimidinecarboxylate (**447**) (14% yield) and (after cyclization of the residue in alkali) 2-ethylthio-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile (**448**) in good yield;[1249,2863] and again, the same substrate (**424**) with *N*-methylthiourea in

cold ethanolic ethoxide gave ethyl 4-amino-3-methyl-2-thioxo-2,3-dihydro-5-pyrimidinecarboxylate (**449**) (48% yield) and 1-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**450**) (not isolated but amounting to 25% of the crude product on nmr evidence),[1508, cf. 809] whereas in *hot* ethanolic ethoxide the reaction gave the nitrile (**450**) (62% yield) and the ester (**449**) (~10% of the crude product by nmr).[1508] The potential aldehydo nitriles, 2-ethoxymethyl-3-methoxyacrylonitrile (**425**) and 3-ethoxy-2-ethoxymethyl-3-methoxypropionitrile (**451**), reacted with thiourea under acidic conditions to afford (after spontaneous hydrolytic deamination) 2-oxo-2,3-dihydro-6*H*-1,3-thiazine-5-carbonitrile (**452**) rather than a pyrimidine.[1617]



445 **446** **447** **448**



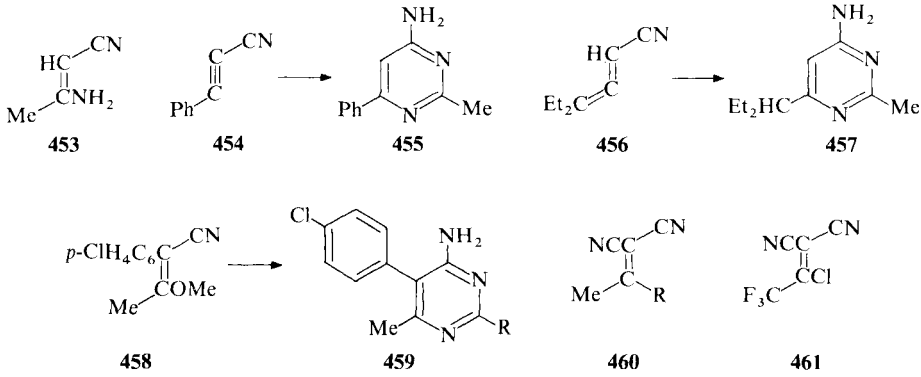
449 **450** **451** **452**

3.8. USE OF β-KETO NITRILES

Nearly all the Principal Syntheses based on β-keto nitriles have been done with equivalents thereof, partly because of relative availabilities and partly because some free ketones give abnormal condensation products.

3.8.1. With Amidines

Although the simple 3-oxobutyronitrile equivalent, 3-aminocrotononitrile (**453**) failed to react with acetamidine,[1516] the 2-benzoylacetonitrile equivalent, 3-phenylpropynenitrile (**454**), did react with ethanolic acetamidine to give 2-methyl-6-phenyl-4-pyrimidinamine (**455**) (53%);[29] likewise, 4-ethylhexa-2,3-dienenitrile (**456**) with ethanolic acetamidine gave 6-α-ethylpropyl-2-methyl-4-pyrimidinamine (**457**) (82%), albeit by a less simple mechanism.[29] The enol ether, 2-*p*-chlorophenyl-3-methoxycrotononitrile (**458**), with acetamidine or benzamidine in ethanol gave 5-*p*-chlorophenyl-2,6-dimethyl- (**459**, R = Me) or 5-*p*-chlorophenyl-6-methyl-2-phenyl-4-pyrimidinamine (**459**, R = Ph), respectively;[4238] 2-cyano-3-ethoxycrotononitrile (**460**, R = OEt) with formamidine

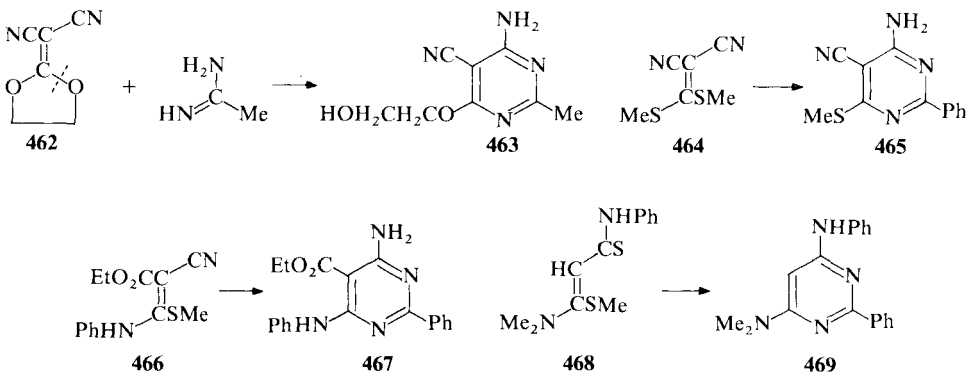


453 454 455 456 457

458 459 460 461

gave 4-amino-6-methyl-5-pyrimidinecarbonitrile (63%);[847] 2-cyano-3-methylthiocrotononitrile (**460**, R = SMe) with ethanolic benzamidine gave 4-amino-6-methyl-2-phenyl-5-pyrimidinecarbonitrile (60%);[2409] and 2-cyano-4-methyl-3-(methylthio)pent-2-enenitrile with propionamidine gave 4-amino-2-ethyl-6-isopropyl-5-pyrimidinecarbonitrile.[1208] Rather similarly, 3-chloro-2-cyano-4,4,4-trifluorocrotononitrile (**461**) with etherial 2,2,2-trifluoroacetamidine gave 4-amino-2,6-bistrifluoromethyl-5-pyrimidinecarbonitrile (62%).[4263] Less simple condensations have been reported.[4264,4265]

Several *closely related condensations* led to analogous 4-aminopyrimidines bearing an alkoxy, alkylthio, or anilino group at the 6-position; also to pyrimidines with substituted amino groups at both the 4- and 6-positions. Thus the dicyanoketene acetal, α-(ethylenedioxymethylene)malononitrile (**462**) with aqueous acetamidine afforded 4-amino-6-β-hydroxyethoxy-2-methyl-5-pyrimidinecarbonitrile (**463**) (53%);[948] the thioacetal, α-(bismethylthiomethylene)malononitrile (**464**), with aqueous benzamidine gave 4-amino-6-methylthio-2-phenyl-5-pyrimidinecarbonitrile (**465**) (30%);[1123, cf. 948] ethyl 3-anilino-2-cyano-3-methylthioacrylate (**466**) with cold benzamidine gave an acyclic intermediate, which in hot benzene containing *p*-toluenesulfonic acid afforded ethyl 4-amino-6-anilino-2-phenyl-5-pyrimidinecarboxylate



462 463 464 465

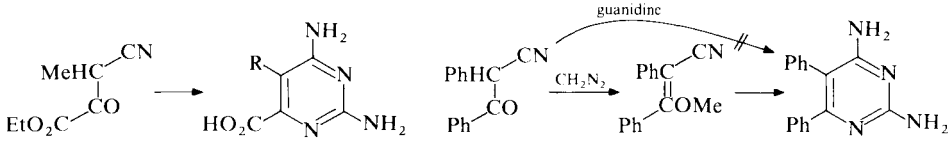
466 467 468 469

(**467**) (53%);[55] and 3-dimethylamino-3-methylthio-*N*-phenyl(thioacrylamide) (**468**) with benzamidine in ethanolic ethoxide gave 4-anilino-6-dimethylamino-2-phenylpyrimidine (**469**) in moderate yield.[157]

The use of a *reduced synthone* is exemplified in the condensation of α-(*p*-chlorobenzylidene)malononitrile with *N*-*m*-tolylbenzamidine to give (after aerial oxidation and Dimroth rearrangement) 4-*p*-chlorophenyl-2-phenyl-6-*m*-toluidino-5-pyrimidinecarbonitrile (43%);[4266-4268] also in the condensation of benzamidine with α-(*p*-chlorobenzylidene)malononitrile or 3-*p*-chlorophenyl-2-cyano(thioacrylamide) in pyridine containing anhydrous sodium acetate to give (after aerial oxidation) 4-amino-6-*p*-chlorophenyl-2-phenyl-5-pyrimidinecarbonitrile (~80%).[3735]

3.8.2. With Guanidines

The β-keto nitrile, ethyl 3-cyano-2-oxobutyrate (**470**), and appropriate homologs reacted normally with guanidine under alkaline conditions to afford 2,6-diamino-5-methyl-4-pyrimidinecarboxylic acid (**471**, R = Me) (via the unisolated ester) and its 5-alkyl homologs (**471**, R = Et, Pr, Bu, etc.), each in ~30% yield;[1183] likewise, 2-benzoyl-2-phenylazoacetonitrile with neat guanidine carbonate at 175° gave 6-phenyl-5-phenylazo-2,4-pyrimidinediamine (52%).[4279] However, most free β-keto nitriles cannot be so used: for example, 2-benzoyl-2-phenylacetonitrile (**472**) with guanidine produced, not 5,6-diphenyl-2,4-pyrimidinediamine (**474**) as first reported,[4269] but 4-benzyl-6-phenyl-1,3,5-triazin-2-amine;[4245] only after the conversion of the ketone (**472**) into its enol ether, 3-methoxy-2,3-diphenylacrylonitrile (**473**), did guanidine yield the required pyrimidine (**474**).[4238]



470 **471** **472** **473** **474**

Wide use has been made of other appropriate *enol ethers of β-keto nitriles* with guanidine (usually in ethanol) to give, for example, the following products.

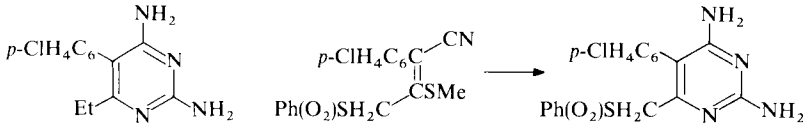
5-*p*-Chlorophenyl-6-ethyl-2,4-pyrimidinediamine (**475**) (90%) or its *m*-chlorophenyl isomer (40%) from 2-*p*-chlorophenyl-3-isobutoxypent-2-enonitrile,[4270,4272] or 2-*m*-chlorophenyl-3-methoxypent-2-enonitrile,[462] respectively.

6-Ethyl-5-thien-2′-yl-2,4-pyrimidinediamine from 3-methoxy-2-thien-2′-ylpent-2-enonitrile.[4271]

6-Benzyl-5-phenyl-2,4-pyrimidinediamine (73%) from 3-methoxy-2,4-diphenylcrotononitrile.[4375]

5-*p*-Chlorophenylthio-6-methyl-2,4-pyrimidinediamine (25%) from 2-*p*-chlorophenylthio-3-methoxycrotononitrile.[4276]

5-*p*-Chlorophenyl-6-phenylsulfonylmethyl-2,4-pyrimidinediamine (**477**) (92%) from 2-*p*-chlorophenyl-3-methylthio-4-phenylsulfonylcrotononitrile (**476**).[115]

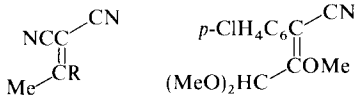


475 **476** **477**

2,4-Diamino-6-methyl-5-pyrimidinecarbonitrile (80%, 51%) from 2-cyano-3-methylthio- (**478**, R = SMe)[2409] or 2-cyano-3-ethoxycrotononitrile (**478**, R = OEt),[1123] respectively.

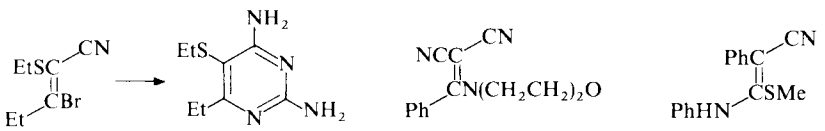
5-*p*-Chlorophenyl-6-dimethoxymethyl-2,4-pyrimidinediamine (55%) from 2-*p*-chlorophenyl-3,4,4-trimethoxycrotononitrile (**479**).[1871]

Also analogous products.[68,1448,1870,2331,4247,4249,4273,4274,4277,4278,4280–4282]

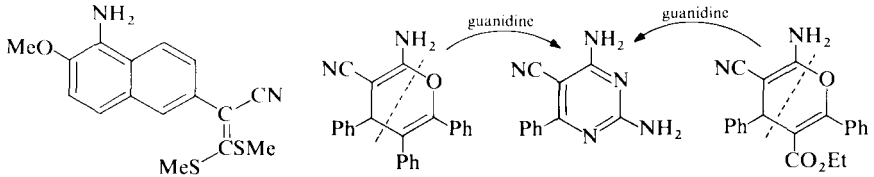


478 **479**

Limited use has been made of *other β-keto nitrile equivalents* for condensations with guanidine, usually in alcohol. Thus 3-phenylpropynenitrile (**454**) gave 6-phenyl-2,4-pyrimidinediamine (54%);[29] 4-ethylhexa-2,3-dienenitrile (**456**) gave 6-α-ethylpropyl-2,4-pyrimidinediamine (46%);[29] 3-bromo-3-ethylthiopent-2-enenitrile (**480**) gave 6-ethyl 5-ethylthio-2,4-pyrimidinediamine (**481**) (85%);[3021] 2-cyano-3-morpholino-3-phenylacrylonitrile (**482**) (with guanidine carbonate at 200°) gave 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile (83%);[528, cf. 5968] 3-anilino-3-methylthio-2-phenylacrylonitrile (**483**) gave 6-anilino-5-phenyl-2,4-pyrimidinediamine (48–65%);[452,3957] and 2-(5′-amino-6′-methoxynaphthalen-2′-yl)-3,3-bismethylthioacrylonitrile (**484**) gave 5-(5′-amino-6′-methoxynaphthalen-2′-yl)-6-methylthio-2,4-pyrimidinediamine (20%).[536] A quaint reaction is that of guanidine with 2-amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile (**485**) or with ethyl 6-amino-5-cyano-2,4-di-



480 **481** **482** **483**

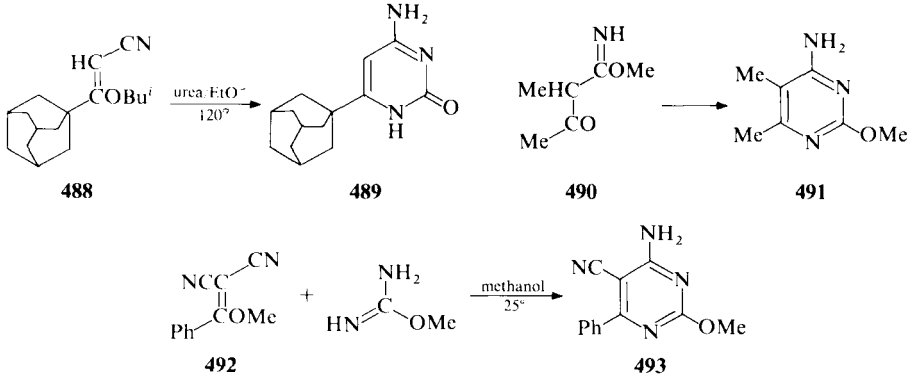


484 **485** **486** **487**

phenyl-4*H*-pyran-3-carboxylate (**487**) to give 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile in 33% or 53% yield, respectively.[346]

3.8.3. With Ureas

Condensations of β-keto nitriles or their equivalents with urea or its derivatives have been little used, perhaps because such reactions are reputed to be sluggish.[1183] Thus 3-aminocrotononitrile (**453**) failed to condense with urea,[1516] while 3-adamant-1′-yl-3-isobutoxyacrylonitrile (**488**) with urea in ethanolic ethoxide gave 4-adamant-1′-yl-6-amino-2(1*H*)-pyrimidinone (**489**) (33%) only on heating at 120° in a sealed vessel for 16 h.[4163] However, methyl 2-methyl-3-oxobutyrimidate (**490**) with methanolic *O*-methylisourea at 20° gave 2-methoxy-5,6-dimethyl-4-pyrimidinamine (**491**) (80%),[2504] 2-cyano-3-methoxy-3-phenylacrylonitrile (**492**) with methanolic *O*-methylisourea at room temperature gave 4-amino-2-methoxy-6-phenyl-5-pyrimidinecarbonitrile (**493**) (92%),[1009] and other such products were made similarly.[1009]



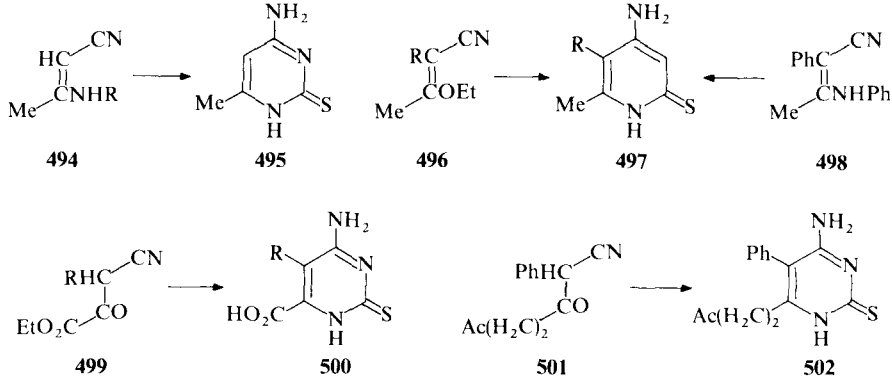
488 **489** **490** **491**

492 **493**

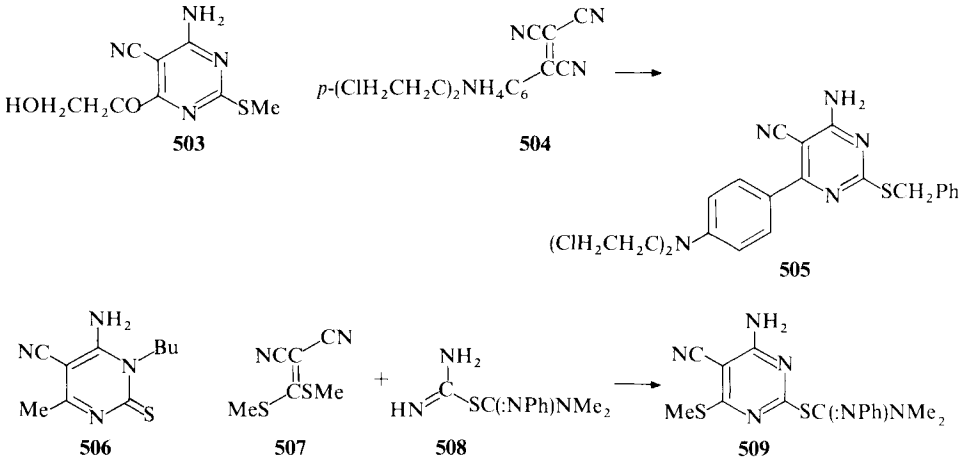
3.8.4. With Thioureas

Thioureas appear to be more amenable than ureas toward condensation with β-keto nitriles or their equivalents. For example, *unsubstituted thiourea* reacted with 3-amino- (**494**, R = H), 3-anilino- (**494**, R = Ph), or 3-(naphthalen-2′-yl)-aminocrotononitrile (**494**, R = α-$C_{10}H_7$) in refluxing ethanolic ethoxide to give

the same product, 4-amino-6-methyl-2(1*H*)-pyrimidinethione (**495**) (43–60%), with loss of ammonia, aniline, or 2-naphthalenamine, respectively;[1516] thiourea with 2-cyano-3-ethoxycrotononitrile (**496**, R = CN) in hot ethanolic ethoxide gave 4-amino-6-methyl-2-thioxo-1,2-dihydro-5-pyrimidinecarbonitrile (**497**, R = CN) (~80%);[847] thiourea with 3-ethoxy- (**496**, R = Ph) or 3-anilino-2-phenylcrotononitrile (**498**) likewise gave 4-amino-6-methyl-5-phenyl-2(1*H*)-pyrimidinethione (**497**, R = Ph) (54% or 75%, respectively);[4262] thiourea with ethyl 3-cyano-3-methylpyruvate (**499**, R = Me) in ethanolic alkali at 25° gave 6-amino-5-methyl-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid (**500**, R = Me) (37%) [analogous substrates (**499**, R = alkyl) likewise gave the appropriate 5-alkylpyrimidines (**500**, R = alkyl) (< 35%)];[1183] thiourea with 3-methoxy-2,3-diphenylacrylonitrile in hot ethanolic ethoxide gave 4-amino-5,6-diphenyl-2(1*H*)-pyrimidinethione (> 50%);[3287] and thiourea with 3,6-dioxo-2-phenylheptanenitrile (**501**) in ethanolic ethoxide gave 4-amino-6-γ-oxobutyl-5-phenyl-2(1*H*)-pyrimidinethione (**502**) (28%).[575] The reduced synthone, 2-cyano-3-phenylacrylamide, with thiourea in isopropanolic isopropoxide at 25° gave 4-amino-6-phenyl-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide (40%), apparently an air-stable product.[198]



The similar use of *substituted thioureas* is clearly possible, although the available examples are not simple. Thus α-(ethylenedioxymethylene)malononitrile (**462**) with aqueous *S*-methylisothiourea gave 4-amino-6-β-hydroxyethoxy-2-methylthio-5-pyrimidinecarbonitrile (**503**) (58%);[948] 2-cyano-3-[*p*-di(β-chloroethyl)aminophenyl]maleonitrile (**504**) with alcoholic *S*-benzylisothiourea at 25° gave 4-amino-2-benzylthio-6-[*p*-di(β-chloroethyl)aminophenyl]-5-pyrimidinecarbonitrile (**505**) (30%);[4264] 2-cyano-3-ethoxycrotononitrile (**496**, R = CN) with *N*-butylthiourea in cold methanolic methoxide gave 4-amino-3-butyl-6-methyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile (**506**) (54%);[809] and 2-cyano-3,3-bis(methylthio)acrylonitrile (**507**) with *S*-(*N*,*N*-dimethyl-*N*′-phenylamidino)isothiourea (**508**) in warm ethanol gave 4-amino-2-(*N*,*N*-dimethyl-*N*′-phenylamidino)thio-6-methylthio-5-pyrimidinecarbonitrile (**509**) (78%).[4283] A reduced synthone has been used satisfactorily.[6011]

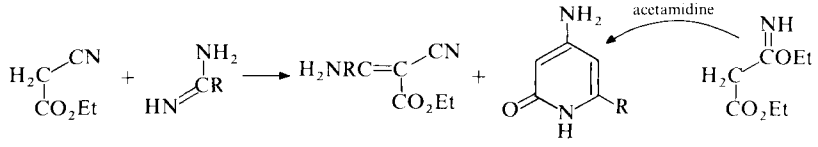


3.9. USE OF β-ESTER NITRILES

The formation of 6-amino-4(3*H*)-pyrimidinones from β-ester nitriles by the Principal Synthesis is usually reliable, especially in the presence of an excess of alcoholic sodium alkoxide.

3.9.1. With Amidines

The condensation of *ethyl 2-cyanoacetate* (**510**) with ethanolic formamidine (**511**, R = H) gave only ethyl 3-amino-2-cyanoacrylate (**512**, R = H) (80%); in the presence of alkoxide, other products were formed but not the pyrimidine (**513**, R = H).[1117] Ethyl 2-cyanoacetate (**510**) with ethanolic acetamidine (**511**, R = Me) likewise gave only ethyl 3-amino-2-cyanocrotonate (**512**, R = Me)[987,1117] but in the presence of 1 mol of sodium ethoxide, up to 37% of 6-amino-2-methyl-4(3*H*)-pyrimidinone (**513**, R = Me) plus some of the acyclic product (**512**, R = Me) were formed,[627,1553,2359] while in an excess of ethanolic ethoxide only the pyrimidine (**513**, R = Me) (81%) was formed;[1554] preconversion of ethyl 2-cyanoacetate (**510**) into ethyl 2-(*C*-ethoxyformimidoyl)acetate (**514**) followed by condensation with ethanolic acetamidine gave only the pyrimidine (**513**, R = Me).[987] Ethyl 2-cyanoacetate (**510**) with benzamidine behaved somewhat differently: in ethanol, equal yields of ethyl 3-amino-2-cyano-3-phenylacrylate (**512**, R = Ph) and 6-amino-2-phenyl-4(3*H*)-pyrimidinone (**513**, R = Ph) were formed,[1117] while in ethanolic sodium ethoxide, the latter (**513**, R = Ph) was isolated in up to 70% yield.[1117,4284–4286] Despite the preceding data, ethyl 2-cyanoacetate (**510**) with 2-dimethylamino-4-pyrimidinecarboxamidine in ethanolic ethoxide gave both 6-amino-2′-dimethylamino-2,4′-bipyrimidin-4(3*H*)-one (**515**, R = H) (42%) and



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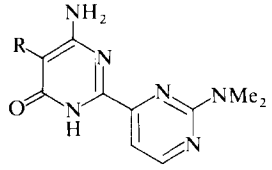

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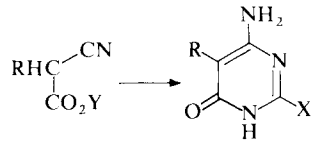

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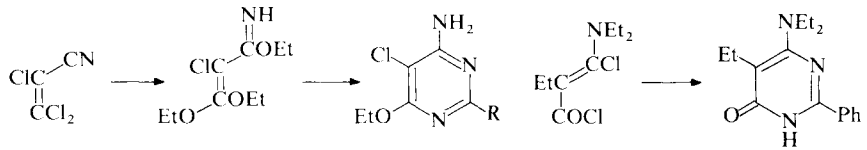
4-(α-amino-β-cyano-β-ethoxycarbonylvinyl)-2-dimethylaminopyrimidine (**512**, R = 2-dimethylaminopyrimidin-4-yl) (43%).[2656] However, ethyl 2-cyanoacetate (**510**) with 2,2,2-trifluoro- (**511**, R = CF_3) or 2-hydroxyacetamidine (**511**, R = CH_2OH) in alcoholic alkoxide gave only 4-amino-2-trifluoromethyl- (**513**, R = CF_3) (74%)[4090] or 6-amino-2-hydroxymethyl-4(3*H*)-pyrimidinone (**513**, R = CH_2OH) (69%),[1335] respectively; *p*-alkoxyphenylacetamidines behaved similarly.[6232]

When *ethyl 2-cyanoacetate is further 2-substituted*, condensation occurs with amidines to give 5-substituted pyrimidines without the formation of any aliphatic byproducts akin to **512**, even in the absence of an excess of alkoxide ion. Thus ethyl 2-cyanobutyrate (**516**, R = Y = Et) with ethanolic propionamide gave 6-amino-2,5-diethyl-4(3*H*)-pyrimidinone (**517**, R = X = Et) (91%);[1065] methyl 2-cyano-2-methoxyacetate (**516**, R = OMe, Y = Me) with formamidine in methanolic methoxide gave 6-amino-5-methoxy-4(3*H*)-pyrimidinone (**517**, R = OMe, X = H) (~70%);[1370] ethyl 2-cyano-2-nitrosoacetate (**516**, R = NO, Y = Et) in ethanolic ethoxide with acetamidine, 2,2,2-trifluoroacetamidine, or *o*-methoxybenzamidine gave 6-amino-2-methyl-5-nitroso- (**517**, R = NO, X = Me) (79%),[2421] 6-amino-5-nitroso-2-trifluoromethyl- (**517**, R = NO, X = CF_3) (32%),[4131] or 6-amino-2-*o*-methoxyphenyl-5-nitroso-4(3*H*)-pyrimidinone (**517**, R = NO, X = C_6H_4OMe-*o*) (84%),[4288] respectively; diethyl 2-cyanosuccinate (**516**, R = CH_2CO_2Et, Y = Et) with ethanolic acetamidine or benzamidine gave 6-amino-5-ethoxycarbonylmethyl-2-methyl-4(3*H*)-pyrimidinone (**517**, R = CH_2CO_2Et, X = Me) (~30%)[987,4287] or its 2-phenyl analog (**517**, R = CH_2CO_2Et, X = Ph),[4287] respectively; and ethyl 2-cyano-2-nitrosoacetate (**516**, R = NO, Y = Et) with 2-dimethylamino-4-pyrimidinecarboxamidine in ethanolic ethoxide gave 6-amino-2′-dimethylamino-5-nitroso-2,4′-bipyrimidin-4(3*H*)-one (**515**, R = NO) (77%).[2656]

A few cyclocondensations of *marginal equivalents of β-keto nitriles* with amidines have proved useful. For example, 2,3,3-trichloroacrylonitrile (**518**) with ethanolic acetamidine at room temperature gave 5-chloro-6-ethoxy-2-methyl-4-pyrimidinamine (**520**, R = Me) (40%); the reaction probably occurred via ethyl

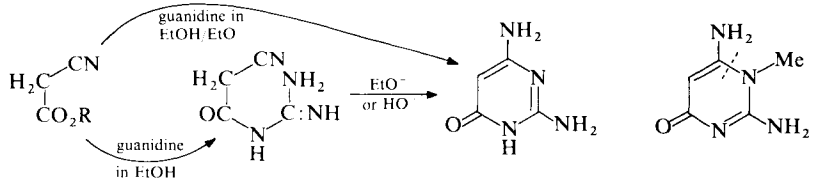
2-chloro-3,3-diethoxyacrylonitrile (**519**) since its preformation followed by treatment with acetamidine resulted in an 83% overall yield of the product (**520**, R = Me).[1002] Benzamidine with the imidic ester (**519**) likewise gave 5-chloro-6-ethoxy-2-phenyl-4-pyrimidinamine (**520**, R = Ph) (94%).[1002] 3-Chloro-3-diethylamino-2-ethylacryloyl chloride (**521**) behaved rather like a β-ester nitrile during its condensation with benzamidine in chloroform–triethylamine to give 6-diethylamino-5-ethyl-2-phenyl-4(3*H*)-pyrimidinone (**522**) (51%).[4289]



518 **519** **520** **521** **522**

3.9.2. With Guanidines

The condensation of *ethyl 2-cyanoacetate* (**523**, R = Et) or the corresponding methyl ester (**523**, R = Me) with hot ethanolic guanidine gave *N*-(cyanoacetyl)guanidine (**524**) in good yield;[1293] in the presence of 1 eq of sodium ethoxide, cyclization ensued to give 2,6-diamino-4(3*H*)-pyrimidinone (**525**) in > 80% yield based on the initial ester (**523**).[1001,2401,2436,2450,2452,2453,3680,4290] Despite earlier and confusing reports,[1083,2408,3669,4291] it now seems likely that condensation of ethyl 2-cyanoacetate (**523**, R = Et) with methylguanidine in ethanolic ethoxide gave 2,6-diamino-1-methyl-4(1*H*)-pyrimidinone (**526**) (35%) as the only primary product, which underwent slow Dimroth rearrangement under the existing conditions to afford some 6-amino-2-methylamino-4(3*H*)-pyrimidinone (6%); two other isolated products, 2,6-diamino-4(3*H*)-pyrimidinone (**525**) (35%) and 6-amino-1-methyl-2-methylamino-4(1*H*)-pyrimidinone (4%), probably arose from impurities in the methylguanidine used.[517] The reported condensations of ethyl 2-cyanoacetate with *N*-phenyl- or *N*-cyanoguanidine to give 6-amino-2-anilino-[4208] or 6-amino-2-cyanoamino-4(3*H*)-pyrimidinone,[1050] respectively, require confirmation especially in view of the disparity in reported melting point for the foregoing anilinopyrimidine and authentic material made later.[4292] No such



523 **524** **525** **526**

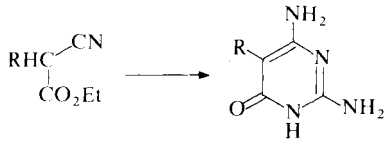
ambiguity was possible in the condensation of ethyl 2-cyanoacetate with *N,N*-dimethylguanidine to give 6-amino-2-dimethylamino-4(3*H*)-pyrimidinone (81%).[1083]

Similar cyclization reactions (usually in ethanolic ethoxide) between guanidine and *ethyl 2-substituted-2-cyanoacetates* are illustrated in the following examples.

2,6-Diamino-5-methyl-4(3*H*)-pyrimidinone (**528**, R = Me) (56%) from ethyl 2-cyanopropionate (**527**, R = Me).[1520]

2,6-Diamino-5-nitroso-4(3*H*)-pyrimidinone (**528**, R = NO) (> 70%) from ethyl 2-cyano-2-nitrosoacetate (**527**, R = NO).[1048,2421,2427]

2,6-Diamino-5-bromo-4(3*H*)-pyrimidinone (**528**, R = Br) (~ 10%) from ethyl 2-bromo-2-cyanoacetate (**527**, R = Br) with hot ethanolic guanidine; survival of the bromine substituent is remarkable but the product is better made by bromination of (**528**, R = H).[2384]



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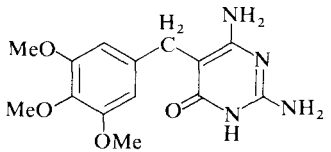

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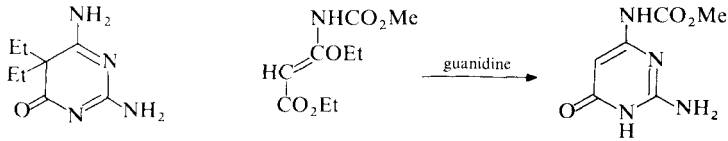
2,6-Diamino-5-β,β-diethoxyethyl-4(3*H*)-pyrimidinone [**528**, R = $CH_2CH(OEt)_2$] (60–70%) from ethyl 2-cyano-4,4-diethoxybutyrate [**527**, R = $CH_2CH(OEt)_2$].[3859,4293]

2,6-Diamino-5-(3′,4′,5′-trimethoxybenzyl)-4(3*H*)-pyrimidinone (**529**) (79% or 89%) from ethyl or methyl 2-cyano-3-(3′,4′,5′-trimethoxyphenyl)propionate;[292,558,4294] subsequent 4-chlorination and dechlorination gave trimethoprim (**413**).[4294]

2,6-Diamino-5,5-diethyl-4(5*H*)-pyrimidinone (**530**) from ethyl 2-cyano-2-ethylbutyrate.[4295]

Also other cases.[628,2453]



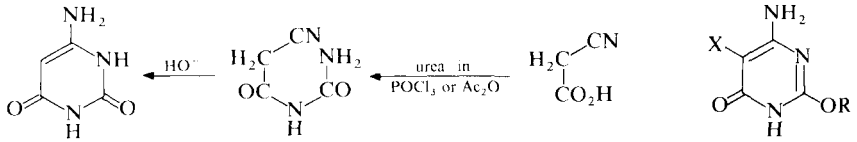
530 **531** **532**

The reactions of *β-ester nitrile equivalents* with guanidine are represented meagerly. Thus guanidine with 2,3,3-trichloroacrylonitrile (**518**) in ethanolic ethoxide or with the derived ethyl 2-chloro-3,3-diethoxyacrylimidate (**519**) in dimethylformamide gave 5-chloro-6-ethoxy-2,4-pyrimidinediamine (**520**, R

$= NH_2$) in 62% or 99% yield, respectively;[1002] rather similarly, ethyl 3-ethoxy-3-(methoxycarbonylamino)acrylate (**531**) with ethanolic guanidine gave 2-amino-6-methoxycarbonylamino-4(3*H*)-pyrimidinone (**532**) (85%).[4296] 2-Substituted-2-cyanoacetic acids have been used satisfactorily.[6551]

3.9.3. With Ureas

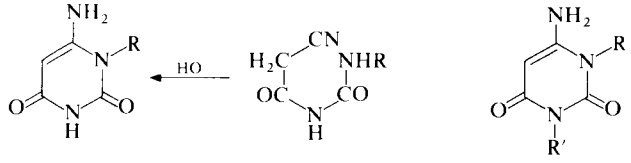
The cyclocondensation of *ethyl 2-cyanoacetate* (**510**) with urea in hot ethanolic ethoxide gave 6-amino-2,4(1*H*,3*H*)-pyrimidinedione (**533**) (67%);[1111,1499,1643,4297] sodium or sodium amide has been employed as a condensing agent,[1500] and *N*-acetylurea has been substituted for urea.[1501] 2-Cyanoacetic acid (**535**) has been used in place of its ester for such condensations: in phosphoryl chloride, the final product (**533**) was obtained in good yield, provided that the scale was kept small,[1293,2800] while in acetic anhydride, yields of up to 90% have been reported.[1111,4298–4300] However, in both media the initial product, *N*-(cyanoacetyl)urea (**534**), required subsequent cyclization in strong alkali.



533 **534** **535** **536**

The use of an *O*- or *N*-monosubstituted-urea in such condensations is possible. Thus methyl or ethyl 2-cyanoacetate (**510**) with *O*-methyl- or *O*-ethylisourea in ethanolic sodium ethoxide gave 6-amino-2-methoxy-4(3*H*)-pyrimidinone (**536**, R = Me, X = H) (~70%)[1190,1287,1288,1440] or its 2-ethoxy homolog (**536**, R = Et, X = H),[1190] respectively; the same esters (e.g., **510**) with *N*-benzyl- or *N*-phenethylurea in methanolic methoxide gave 6-amino-1-benzyl- (**537**, R = CH_2Ph) (65%)[1396] or 6-amino-1-phenethyl-2,4(1*H*,3*H*)-pyrimidinedione (**537**, R = CH_2Ph),[4302] respectively; methyl or ethyl 2-cyanoacetate with *N*-methoxy- or *N*-benzyloxyurea in alcoholic alkoxide gave 6-amino-1-methoxy- (**537**, R = OMe) (43%)[1280] or 6-amino-1-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**537**, R = OCH_2Ph) (64%),[1338] respectively; ethyl 2-cyanoacetate with *N*-dimethylaminourea in ethanolic ethoxide gave 6-amino-1-dimethylamino-2,4(1*H*,3*H*)-pyrimidinedione (**537**, R = NMe_2) (> 60%), of likely but unproven orientation;[585] 2-cyanoacetic acid (**535**) with *N*-methylurea in pyridine–phosphoryl chloride gave an initial product (**538**, R = Me), which underwent alkaline cyclization to 6-amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**537**, R = Me) in good overall yield[1106,2803, cf. 1499] and of incidentally proven[1106,4321] orientation; the same acid (**535**) with *N*-isobutylurea in acetic anhydride gave 6-amino-1-isobutyl-2,4(1*H*,3*H*)-pyrimidinedione (**537**,

R = Bu^i) via the acyclic intermediate (**538**, R = Bu^i), which was proved in orientation by nmr examination, a method proposed as generally applicable to the products of these condensations;[4303] and other examples have been reported.[1060,1062,1222,4302,4304,4305] *N*-Acetyl-*N'*-alkylureas have been used in place of *N*-alkylureas.[1048,1501,1502]



537 **538** **539**

The condensation of an *N,N'*-dialkylurea with ethyl 2-cyanoacetate is not always straightforward, but the product has an ambiguous structure only if the two alkyl groups are different. Despite one positive report (as a footnote),[627] it does appear that attempts to condense ethyl 2-cyanoacetate with *N,N'*-dimethylurea in ethanolic ethoxide have been totally unsuccessful,[586,1499] However, the condensation of 2-cyanoacetic acid with *N,N'*-dimethylurea in the presence of sodium amide (?)[1500] or in pyridine–phosphoryl chloride did give 6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**539**, R = R' = Me),[1106] albeit in poor yield;[586] acetic anhydride, with or without the addition of glacial acetic acid, provided a much better condensation medium, although a final alkaline treatment was needed to ensure cyclization to the product (**539**, R = R' = Me) in ~80% yield.[1052(?),1062,1107,1111,2392] A similar procedure using appropriate *N,N'*-dialkylureas gave 6-amino-1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione (**539**, R = R' = Et), its 1,3-dipropyl homolog (**539**, R = R' = Pr), and other such products in 70–90% yield,[586,1060,1062] although *N,N'*-diisopropylurea and related synthones with even one α-branched-alkyl grouping failed to react.[586,1062] When an unsymmetrical *N,N'*-dialkylurea is condensed with cyanoacetic acid, two isomeric products result: on the available evidence,[1062] the predominant product has the larger alkyl group at *N*-1, that is, next to the amino group. For example, *N*-ethyl-*N'*-propylurea with cyanoacetic acid in acetic anhydride followed by alkaline cyclization gave 6-amino-3-ethyl-1-propyl- (**539**, R = Pr, R' = Et) (~80%; isolated yield: 60%) and 6-amino-1-ethyl-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione (~20%; isolated yield: 5%), each identified by an unambiguous synthesis; likewise, *N*-allyl-*N'*-ethylurea gave 1-allyl-6-amino-3-ethyl- (**539**, R = $CH_2CH{:}CH_2$, R' = Et) and 3-allyl-6-amino-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione (**539**, R = Et, R' = $CH_2CH{:}CH_2$) in approximately 4 : 1 ratio.[1062]

Condensations between ureas and *2-substituted-2-cyanoacetic acids or esters* proceed quite normally, as illustrated in the following reactions.

6-Amino-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**540**, R = Me, X = Y = H) from urea with ethyl 2-cyanopropionate in ethanolic ethoxide[1263] or with

540

2-cyanopropionic acid in acetic anhydride (followed by alkaline cyclization) (58%).[3463]

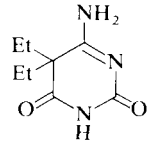
6-Amino-1-dimethylamino-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**540**, R = Me, X = NMe_2, Y = H) (~50%) from *N*-dimethylaminourea with ethyl 2-cyanopropionate in ethanolic ethoxide.[1071]

6-Amino-5-α-cyclohexylethyl-2,4(1*H*,3*H*)-pyrimidinedione (**540**, R = CH_2-MeC_6H_{11}, X = Y = H) (33%) from urea with 2-cyano-3-cyclohexylbutyric acid in acetic anhydride followed by cyclization in ethanolic ethoxide.[4175]

6-Amino-2-methoxy-5-methyl-4(3*H*)-pyrimidinone (**536**, R = X = Me) (~50%) from *O*-methylisourea with methyl 2-cyanopropionate in methanolic methoxide.[653]

6-Amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**540**, R = NO, X = Y = Me) from *N*,*N*′-dimethylurea with ethyl 2-cyano-2-nitrosoacetate in a benzene suspension of sodium ethoxide.[1048]

6-Amino-5,5-diethyl-2,4(3*H*,5*H*)-pyrimidinedione (**541**) from urea with ethyl 2-cyano-2-ethylbutyrate in ethanolic ethoxide or with 2-cyano-2-ethylbutyric acid in acetic anhydride or in phosphoryl chloride.[1499,4306–4308]



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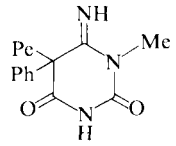

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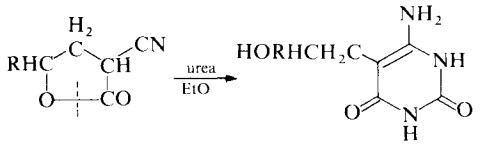
6-Imino-1-methyl-5-pentyl-5-phenyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**542**) (24%) from *N*-methylurea with ethyl 2-cyano-2-phenylheptanoate in methanolic methoxide.[570]

Also other such reactions.[991,1048,1324,2421,3859]

The condensation of *β-ester nitrile equivalents* with ureas has not been used much. However, urea with α-cyano-γ-butyrolactone (**543**, R = H) or α-cyano-γ-valerolactone (**543**, R = Me) in ethanolic ethoxide gave 6-amino-5-β-hydroxyethyl- (**544**, R = H) (33%) or 6-amino-5-β-hydroxypropyl-2,4(1*H*,3*H*)-pyrimidinedione (**544**, R = Me) (13%), respectively;[1321] urea with α-cyano-δ-



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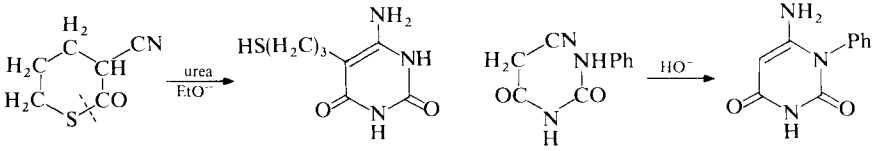

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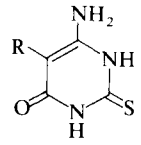
valerothiolactone (**545**) likewise gave 6-amino-5-γ-mercaptopropyl-2,4(1*H*,3*H*)-pyrimidinedione (**546**) (37%);[1359] and *N*-phenylurea with 2-cyanoacetyl chloride in chloroform containing pyridine gave *N*-(2-cyanoacetyl)-*N'*-phenylurea (**547**) and thence (in alkali) 6-amino-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**548**) (~70% overall; cf. 52% from ethyl 2-cyanoacetate).[4309]

3.9.4. With Thioureas

Thiourea and its derivatives usually react as expected with β-ester nitrile. Thus *ethyl 2-cyanoacetate* (**523**, R = Et) with thiourea in ethanolic ethoxide gave 6-amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**549**, R = H) (75–95%);[873,1298,1570,1595,1692] *N*-methylthiourea under similar conditions gave 6-amino-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**550**, X = Me, Y = H) (91%), of proven orientation;[873,1284,1575] and other appropriate *N*-alkylthioureas gave 1-allyl-6-amino- (**550**, X = $CH_2CH{:}CH_2$, Y = H),[873] 6-amino-1-γ-diethylaminopropyl- (**550**, X = $CH_2CH_2CH_2NEt_2$, Y = H) (74%),[4310] and 6-amino-1-dimethylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**550**, X = NMe_2, Y = H) (> 60%, of confirmed[4312, cf. 4311] orientation).[585] In contrast, *S*-alkylisothioureas did not react normally with ethyl 2-cyanoacetate,[1685] although it was shown later that *S*-methylisothiourea with the ester in ethanolic ethoxide did give ~1% yield of 6-amino-2-methylthio-4(3*H*)-pyrimidinone.[4313, cf. 873] *N,N'*-Dialkylthioureas react better with 2-cyanoacetic acid in acetic anhydride and/or glacial acetic acid, than with the corresponding ester in ethanolic ethoxide; for example, the acid (**523**, R = H) with *N,N'*-dimethyl- or *N,N'*-diethylthiourea in acetic anhydride gave (after alkaline cyclization) 6-amino-1,3-dimethyl- (**550**, X = Y = Me) (~70%)[1115] or 6-amino-1,3-diethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**550**, X = Y = Et),[1067] respectively. However, the same acid (**523**, R = H) with any unsymmetrical *N,N'*-dialkylurea (under similar conditions) naturally gave a mixed product, in which the isomer with the larger alkyl group at the 1-position appeared to predominate



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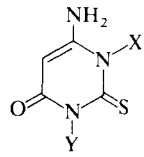

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markedly:[856,1067] from these mixtures have been isolated such major constituents as 6-amino-1-isopropyl-3-methyl- (**550**, X = Pr^i, Y = Me)[1067] or 6-amino-1-β-methylallyl-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**550**, X = $CH_2CMe{:}\ CH_2$, Y = Me).[885] *N*,*N*′-Diarylthioureas reacted satisfactorily with ethyl cyanaoacetate under acidic conditions.[6205]

Condensation of *2-substituted-2-cyanoacetic esters* with thioureas are illustrated in the following syntheses.

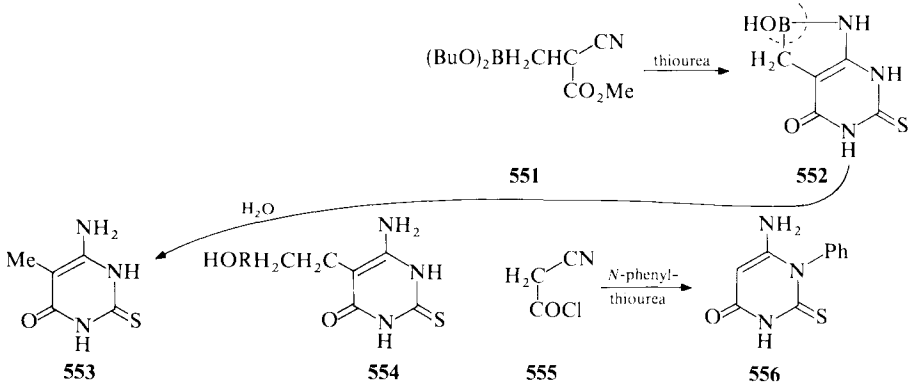
6-Amino-5-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**549**, R = Et) from ethyl 2-cyanobutyrate with thiourea in ethanolic ethoxide.[1220]

6-Amino-5-decyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**549**, R= $C_{10}H_{21}$) (~80%) from ethyl 2-cyanododecanoate similarly.[4315]

6-Amino-5-phenyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**549**, R = Ph) (7%) from ethyl 2-cyano-2-phenylacetate similarly.[972]

6-Amino-5-phenylazo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**549**, R = N:NPh) (~75%) from ethyl 2-cyano-2-phenylazoacetate similarly.[4316]

6-Amino-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**553**) from ethyl 2-cyanopropionate with thiourea in ethanolic ethoxide[1576] or from methyl 3-(dibutoxyboryl)-2-cyanopropionate (**551**) with thiourea in *t*-butanolic potassium *t*-butoxide via a bicyclic intermediate (**552**).[4317]



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A few reactions between *β-ester nitrile equivalents* and thioureas have been reported. Thiourea with α-cyano-γ-butyrolactone (**553**, R = H) in ethanolic ethoxide gave 6-amino-5-β-hydroxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**554**, R = H) (65%);[1321] α-cyano-γ-valerolactone (**543**, R = Me) likewise gave the

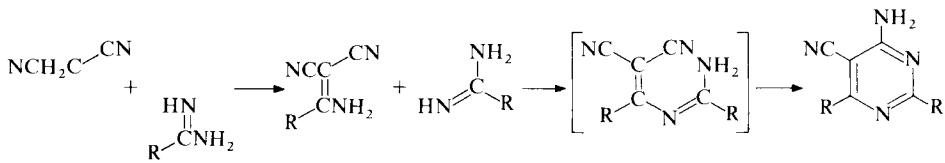
5-β-hydroxypropyl analog (**554**, R = Me) (53%);[1321] α-cyano-δ-valerothiolactone (**545**) similarly gave 6-amino-5-γ-mercaptopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (28%);[1359] and 2-cyanoacetyl chloride (**555**) with thiourea in chloroform–pyridine gave an intermediate akin to (**547**) that in alkali cyclized to 6-amino-1-phenyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**556**) (73%, cf. 68% from ethyl 2-cyanoacetate).[4309]

3.10. USE OF β-DINITRILES (MALONONITRILES)

Although β-dinitriles react fairly normally with guanidines or thioureas, they exhibit abnormalities with amidines and do not react at all with ureas.

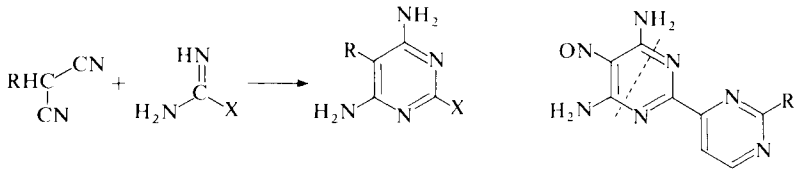
3.10.1. With Amidines

Unsubstituted *malononitrile* (**557**) with ethanolic formamidine (**558**, R = H) at 25° gave not 4,6-pyrimidinediamine, but 4-amino-5-pyrimidinecarbonitrile (**561**, R = H) (45%),[1619] almost certainly via α-aminomethylenemalononitrile (**559**, R = H) which appeared to react subsequently as a β-aldehydo nitrile with more formamidine.[1117] Benzamidine (**558**, R = Ph), 2,2,2-trifluoroacetamidine (**558**, R = CF_3), or 2-furancarboxamidine likewise gave 4-amino-2,6-diphenyl- (**561**, R = Ph) (45%)[1117] 4-amino-2,6-bistrifluoromethyl- (**561**, R = CF_3) (17%),[4131] or 4-amino-2,6-difuran-2′-yl-5-pyrimidinecarbonitrile,[1117] respectively. Under similar conditions, acetamidine (**558**, R = Me) gave an isolable acyclic product (**560**, R = Me) isomeric with 4-amino-2,6-dimethyl-5-pyrimidinecarbonitrile (**561**, R = Me),[1119] for which it was mistaken initially[1117] and to which it was converted by prolonged treatment in an excess of acetamidine.[1119]



557 **558** **559** **560** **561**

In contrast, most α-*substituted malononitriles* react normally with amidines to afford 5-substituted-4,6-pyrimidinediamines. Thus α-phenylazomalononitrile (**562**, R = N:NPh) with a appropriate alcoholic amidine gave 5-phenylazo-4,6-pyrimidinediamine (**563**, R = N:NPh, X = H) (75%)[1619] and its 2-methyl (**563**, R = N:NPh, X = Me) (~50%)[1493] or 2-trifluoromethyl derivative (**563**, R = N:NPh, X = CF_3) (68%);[4131] 5-*p*-chlorophenylazo-4,6-pyrimidinediamine (**563**, R = N:NC_6H_4Cl-*p*, X = H) was made similarly in poor yield;[1493] α-nitrosomalononitrile (**562**, R = NO) as its silver salt reacted with acetamidine hydrochloride to give the acetamidinium–nitrosomalononitrile salt, which



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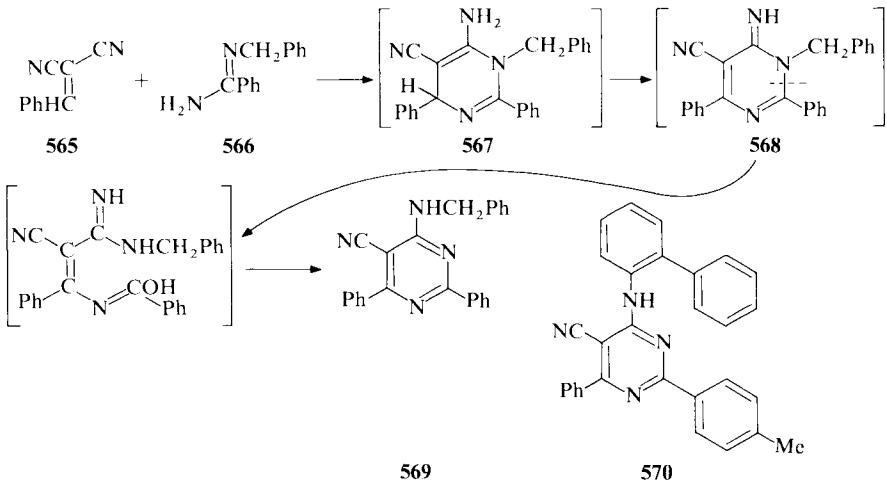
underwent cyclization on heating in 5-ethyl-2-methylpyridine (simply a high-boiling pyridine base) to afford 2-methyl-5-nitroso-4,6-pyrimidinediamine (**563**, R = NO, X = Me) (92%);[2431] the analogs (**563**, R = NO, X = Et, Pr, CH_2Ph, CF_3, or Ph) were made similarly,[2431,3557,3558] as were 2′-dimethylamino- (**564**, R = NMe_2) (84%) and 2′-methoxy-5-nitroso-2,4′-bipyrimidine-4,6-diamine (**564**, R = OMe) (78%) (from α-nitrosomalononitrile with 2-dimethylamino- or 2-methoxy-4-pyrimidinecarboxamidine, respectively);[57] and the salt from methanetricarbonitrile (**562**, R = CN) and benzamidine cyclized in hot dimethylformamide to give 4,6-diamino-2-phenyl-5-pyrimidinecarbonitrile (**563**, R = CN, X = Ph) (24%).[1123] However, α-benzylidenemalononitrile (**565**) reacted as a reduced aldehydo nitrile with *N*-benzylbenzamidine (**566**) to give initially the dihydropyrimidine (**567**) (unisolated), which underwent aerial oxidation to the pyrimidinimine (**568**) (also unisolated) and then Dimroth rearrangement to 4-benzylamino-2,6-diphenyl-5-pyrimidinecarbonitrile (**569**) (65%);[4314] this remarkable sequence proved reasonable general in producing, for example, 4-(biphenyl-2′-yl)amino-6-phenyl-2-*p*-tolyl-5-pyrimidinecarbonitrile (**570**)[4318] and related products.[4319,4320]



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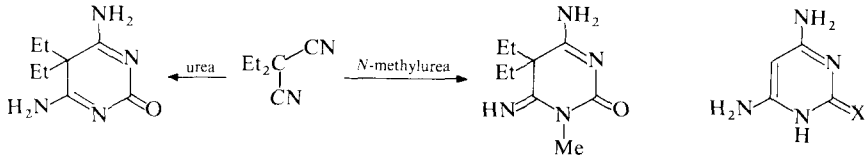
3.10.2. With Guanidines

Most reported attempts to condense unsubstituted or monosubstituted malononitrile with guanidines have been successful. Thus malononitrile (**562**, R = H)

and ethanolic guanidine, with[3634] or without[3107,3188] added sodium ethoxide, gave 2,4,6-pyrimidinetriamine (**563**, R = H, X = NH_2), conveniently isolable as its sparingly soluble sulfate in good yield; appropriately α-substituted-malononitriles with ethanolic guanidine likewise gave, for example, 5-ethyl- (**563**, R = Et, X = NH_2) (92%),[3107,3108] 5-butyl- (**563**, R = Bu, X = NH_2) (90%),[3108] 5-benzyl- (**563**, R = CH_2Ph, X = NH_2) (85%),[3108] 5-(3′,4′,5′-trimethoxybenzyl)- (77%),[1356] and 5-γ-(*p*-nitrophenoxy)propyl-2,4,6-pyrimidinetriamine (51%);[4321] but α-phenylmalononitrile with alcoholic guanidine gave only an unidentified anomalous product.[3108] α,α-Diethylmalononitrile has been reported[3107] to react with guanidine to give 5,5-diethyl-6-imino-5,6-dihydro-2,4-pyrimidinediamine and/or its tautomer. *N*,*N*-Dimethylguanidine reacted normally with malononitrile in refluxing ethanol to give 2-dimethylamino-4,6-pyrimidinediamine (**563**, R = H, X = NMe_2) (40%);[1083] the same dimethylguanidine as hydrochloride reacted with the silver salt of α-nitrosomalononitrile (**562**, R = NO) to give the dimethylguanidinium–nitrosomalononitrile salt, which in boiling α-picoline gave 2-dimethylamino-5-nitroso-4,6-pyrimidinediamine (**563**, R = NO, X = NMe_2) (29%).[2645]

3.10.3. With Ureas

Although α,α-diethylmalononitrile (**571**) has been reported[2434,4323] to condense with urea or *N*-methylurea to give 4,6-diamino-5,5-diethyl-2(5*H*)-pyrimidinone (**572**) or 4-amino-5,5-diethyl-6-imino-1-methyl-5,6-dihydro-2(1*H*)-pyrimidinone (**573**), respectively, neither malononitrile nor its α-monoalkyl derivatives have been condensed successfully with urea, *N*-alkylureas, or *O*-alkylisoureas: the preceding statement has been confirmed by typical experiments that gave no isolable pyrimidines.[4313] Usually any such required products have been made without difficulty by indirect routes: for example, 4,6-diamino-2(1*H*)-pyrimidinone (**574**, X = O) (77%) was obtained easily by a one-pot *S*-alkylation and hydrolysis of the corresponding pyrimidinethione (**574**, X = S), which had been made from malononitrile and thiourea (see Section 3.10.4) in excellent yield.[2402]

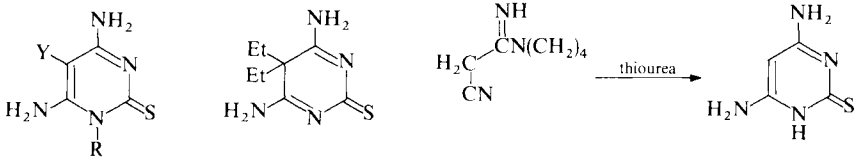


571 **572** **573** **574**

3.10.4. With Thioureas

Unlike ureas, thioureas appear to react remarkably normally with malononitrile and its derivatives, although there are not many reported examples. Thus

malononitrile with thiourea, thiosemicarbazide, or *N*-methylthiourea in refluxing ethanolic sodium ethoxide gave 4,6-diamino- (**574**, X = S) (in yield of ≤ 98%),[1298,2397,2402,3615] 1,4,6-triamino- (**575**, R = NH_2, Y = H) (34%),[1355] or 4,6-diamino-1-methyl-2(1*H*)-pyrimidinethione (**575**, R = Me, Y = H) (23%),[1575] respectively; in the last case, it proved advantageous to interrupt the reaction, isolate the acyclic intermediate, and heat the dry solid at 160–180° for 5 min to give the product (**575**, R = Me, Y = H) (35% overall).[1575] Likewise, α-ethylmalononitrile with thiourea gave 4,6-diamino-5-ethyl-2(1*H*)-pyrimidinethione (**575**, R = H, Y = Et);[2397] α-dimethylaminomalononitrile with thiourea gave 4,6-diamino-5-dimethylamino-2(1*H*)-pyrimidinethione (**575**, R = H, Y = NMe_2) (51%);[2389] and α,α-diethylmalononitrile with thiourea gave 4,6-diamino-5,5-diethyl-2(5*H*)-pyrimidinethione (**576**).[2397] Condensation of the β-dinitrile equivalent, 3-imino-3-pyrrolidinopropionitrile (**577**), with thiourea in ethanolic ethoxide, gave only 4,6-diamino-2(1*H*)-pyrimidinethione (**578**)



575 **576** **577** **578**

(~40%) by elimination of pyrrolidine rather than ammonia from the amidinonitrile (**577**).[852,2445] α-Octylmalononitrile with thiourea gave 4,6-diamino-5-octyl-2(1*H*)-pyrimidinethione (**575**, R = H, Y = C_8H_{17}) and thence the corresponding pyrimidinone ($ClCH_2CO_2H$, H_2O, reflux, 90 min: 71% overall).[6942]

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CHAPTER 4

Pyrimidine, Alkylpyrimidines, and Arylpyrimidines

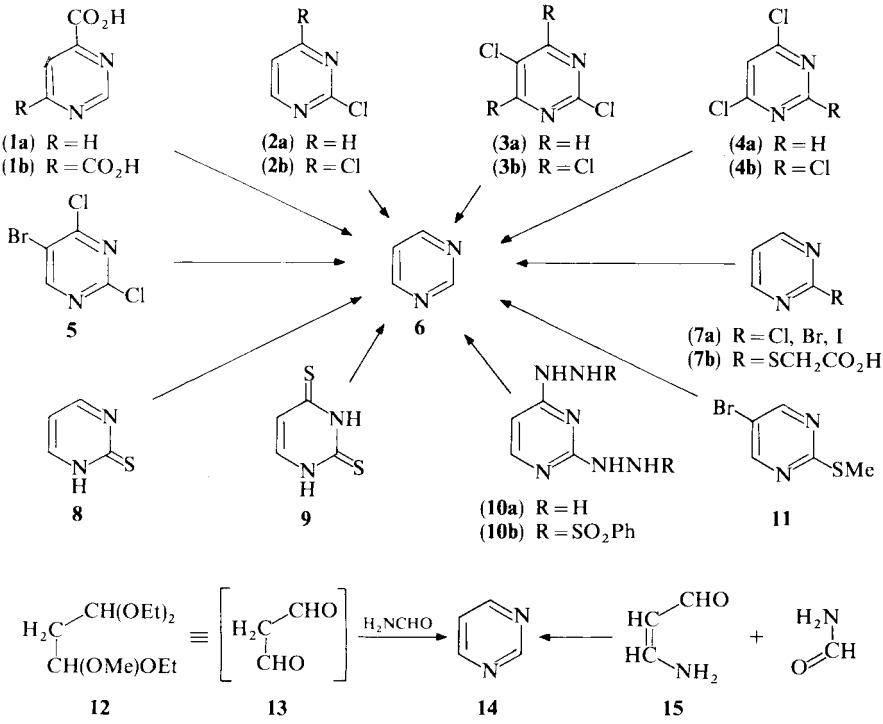
This chapter covers the preparations, properties, and reactions of pyrimidine and its simple *C*-alkyl, *N*-alkyl, or *C*-aryl derivatives. In addition, it includes methods for introducing *C*-alkyl or *C*-aryl groups into pyrimidines already bearing other substituents (functional or otherwise) and reactions specific to the alkyl or aryl group(s) in such products. For the obvious pragmatic reason, the term "alkylpyrimidine" in this chapter is deemed to include alkyl-, alkenyl-, alkynyl-, aryl-, and aralkylpyrimidines.

4.1. PYRIMIDINE

Although pyrimidine was characterized first in 1899,[1517] it remained an exceedingly rare substance for the next half-century, after which it became readily available by several synthetic routes for more thorough investigation.

4.1.1. Preparation of Pyrimidine

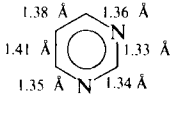
Pyrimidine (**6**) has been made indirectly by *decarboxylation* of 4-pyrimidinecarboxylic acid (**1a**) (poor yield)[1517] or 4,6-pyrimidinedicarboxylic acid (**1b**) (60%);[764,1874] by *hydrogenolysis* (under a variety of conditions but usually in the presence of a base) of 2-chloro- (**2a**) ($\leq 80\%$ as $HgCl_2$ complex),[2566] 2,4-dichloro- (**2b**) (78–91%),[711,2513,3598] 2,5-dichloro- (**3a**) (42%),[2212] 4,6-dichloro- (**4a**) (77%),[2513] 2,4,6-trichloro- (**4b**) (87%),[711,2513] 2,4,5,6-tetrachloro- (**3b**) (86%),[2513] and 5-bromo-2,4-dichloropyrimidine (**5**);[3598] by *zinc–water dechlorination* of 2,4,6-trichloro- (**4a**) (25% as $HgCl_2$ complex)[3596,4585] or 2,4,5,6-tetrachloropyrimidine (**3b**);[3597] by *hydriodic acid reduction* of 2-chloro-, 2-bromo-, or 2-iodopyrimidine (**7a**) ($\sim 40\%$);[2258] by *desulfurization* of 2(1*H*)-pyrimidinethione (**8**) with Raney-nickel (25% as $HgCl_2$ complex)[764,2566] or with hydrogen peroxide (39% as picrate),[764] of 2-carboxymethylthiopyrimidine (**7b**) with Raney-nickel (14% as picrate),[764] of 2,4(1*H*,3*H*)-pyrimidinedithione (**9**) with Raney-nickel (low yield),[1297,2566] or of 5-bromo-2-methylthiopyrimidine (**11**) with Raney-nickel (including a concomitant reductive debromination: 38%



as $HgCl_2$ complex);[1935] by *oxidative decomposition* of 2,4-dihydrazino (**10a**) ($CuSO_4$: low yield) or of 2,4-bis[*N'*-(benzenesulfonyl)hydrazino]pyrimidine (**10b**) (aqueous alkali: 66% as $HgCl_2$ complex);[2566] and by *debenzylation* of 1-benzylpyrimidinium bromide (itself made from pyrimidine) in liquid ammonia.[4584] Pyrimidine (**14**) has been made in quantity by *primary synthesis* from 1,1,3-triethoxy-3-methoxypropane (**12**) or other such equivalent of malondialdehyde (**13**) with formamide (usually containing ammonium formate) at 190° by a batch or continuous process ($\leq$ 72%);[836,2752,3363] from 3-aminoacrylaldehyde (**15**) with formamide in the presence of piperidinium acetate at 140° (60% yield);[3093] and (ineffectively) from *N*-substituted pyrazoles with trichloromethyl radicals at 550°.[3950]

4.1.2. Physical Properties of Pyrimidine

Pyrimidine is a water-soluble, colorless, hygroscopic solid of m.p. 22.5° and b.p. 124° (758 mm).[3598] It has n_D^{20} 1.4960 (as a supercooled liquid)[2752] and a dipole moment of 2.10,[4585] 2.13,[4586] 2.19,[4587] or 2.40 D.[4588] The crystal structure of pyrimidine has been determined: its orthorhombic $P\,n\,a\,2_1$ crystals had a unit cell of four molecules with the corrected bond lengths shown in formula **16**;[4589] the derived approximate bond angles (shown in **17**) broadly



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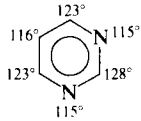

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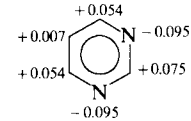

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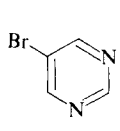
confirmed those calculated less directly.[4590–4592] Calculated values for the resonance energy of pyrimidine have varied from 8 to 40 kcal mol^{-1} relative to benzene (41 kcal mol^{-1}).[4588,4593, cf. 3946] Among many electron-distribution calculations for pyrimidine,[4588,4595–4598, etc.] that summarized in formula **18** is perhaps the most satisfactory:[4594] the employed VESCF method calculated the effective nuclear charges in the field wherein the π-electrons moved, while the occupation number of the $2p$-π atomic orbital on each conjugated atom was taken to be the π-electron density for that atom in the molecule, rather than that for the neutral isolated atom. Pyrimidine is a weak base with pK_a values 1.30–1.31 and -(6.30–7.10).[1968,3777,3812,3813,3951] It has been further characterized as its hydrochloride,[1965] picrate,[1517,2752] reineckate,[2566] and other salts;[836] as *N*-methylpyrimidinium iodide,[3598,4639] *N*-benzylpyrimidinium bromide,[4584] and other quaternary salts;[836] and as its water-insoluble mercuric chloride complex,[2212,2566] from which the base could be recovered with some difficulty by distillation with sodium sulfide.[2212] The isolation of pyrimidine from an aqueous solution was best done by continuous chloroform extraction[2752] or via the mercuric chloride complex.[2212] Pyrimidine forms an unisolable complex with iodine[6168] but a well-characterized diborane complex (m.p. 222°).[6764]

Because it is an archetypal diazine, pyrimidine has been submitted to all types of spectral investigation. The *uv spectrum* of pyrimidine in cyclohexane consisted of two peaks, λ_{max} 243 and 298 nm, with very little fine structure: the first peak was virtually unaffected by change of solvent or even by protonation, but the second was substantially altered by such changes;[3791,4599,4609] absorption by pyrimidine vapor in the 150–200-nm region,[4600] absorption by the unstable anion,[4601] and other aspects of the uv spectra have been studied.[4602–4605] The *ir* (*infrared*) *and Raman spectra* of pyrimidine have been recorded from solutions,[4606] from the crystalline solid,[4607] and from metallic complexes;[4608] other aspects have been investigated.[4610] The ^1H *nmr spectra* of pyrimidine in the usual deuterated solvents[3290,4611] or as a neat liquid[2258,4612] exhibited no unexpected features; the ionization constants of pyrimidine have been measured by the changes in spectrum during mono- and diprotonation.[3951] The ^{13}C *nmr spectra* for neutral pyrimidine[4613–4615] and for its cation[4616,4617] have been reported. As an example, the chemical shifts,[4618] short-range J values,[4619] and long-range J values[4620] for pyrimidine in perdeuteroacetone are collected in the following summary: 122.3 (ppm from TMS), $J_{C5,H2}$ 1.9 Hz, $J_{C5,H4}$ 9.5, $J_{C5,H5}$ 169, C5; 157.7, $J_{C4,H2}$ 9.1, $J_{C4,H4}$ 183, $J_{C4,H5}$ 1.9, $J_{C4,H6}$ 5.3, C4 + C6; 159.7, $J_{C2,H2}$ 203, $J_{C2,H4}$ 10.3, $J_{C2,H5}$ 0.0, C2. Despite an inherently low sensitivity ($\sim 10^{-3}$ that of ^{1}H), reasonable ^{14}N *nmr data* (δ_N: -82 to -92 ppm from

$MeNO_2$, according to solvent) have been obtained for pyrimidine by using a wide tube, long accumulation times, and a ^1H–^{14}N double resonance technique.[4621–4623] The equally difficult acquisition of *^{15}N nmr data* (especially from natural abundance samples) was also overcome for pyrimidine, which showed a single peak at − 85 ppm (from $MeNO_2$) for the neutral molecule, at − 135 for the monocation, and at − 183 for the dication;[3346,3947,4624] a variety of coupling constants have been measured.[3949] The *mass spectrum* of pyrimidine showed a molecular ion at *m/e* 80 and a dominant fragmentation mode involving loss of HCN twice to give ionized acetylene, *m/e* 26, as basepeak:[4625,4626] it remains to be shown whether C2 or C4 was lost first.

4.1.3. Reactions of Pyrimidine

Although pyrimidine resisted *nitration*,[2212] it underwent vapor-phase *bromination* in a packed tube at 220–230° to afford 5-bromopyrimidine (**19**) in ~60% yield;[1965,1971] the use of pyrimidine hydrochloride as a substrate with neat bromine at 160°,[836] or with bromine in nitrobenzene at 130°,[1965] gave 5-bromopyrimidine in 66% or 88% yield, respectively; and pyrolysis of preformed pyrimidine hydrochloride perbromide gave the same product (**19**) (70%).[1965, cf. 4627] Pyrimidine failed to *diazo-couple* with *p*-nitrobenzenediazonium salts but a slow *Gomberg reaction* did take place in sodium acetate buffer to afford a separable mixture of 2- (10% yield) and 4-*p*-nitrophenylpyrimidine (**20**) (14%).[2212] Pyrimidine underwent *attack by bases*, but usually only at elevated temperatures: long boiling in alkali gave >60% of the ring nitrogen as elemental gas and a noncrystalline solid akin to polyacrolein;[4629] aqueous hydrazine hydrate at 130° for 5 h gave pyrazole (**21**, R = H) (~75%);[2754,4630] methylhydrazine at 100° gave 1-methylpyrazole (**21**, R = Me) (~55%);[2754] aqueous methylamine at 190° gave 3-ethyl-6-methylpyridine (**22**) (**25**%) by a mechanism proved to involve an initial fragmentation to hydrogen cyanide (2 mol) and *N*-methylacetaldimine, followed by self-condensation of four molecules of the latter to give the product (**22**);[4631] and liquid ammonia containing sodium amide gave an (unisolated) adduct, which on addition of potassium permanganate gave 4-pyrimidinamine (**23**) (72%).[3948] The *reduction* of pyrimidine by hydrogenation over palladium in the presence of hydrochloric acid (1 mol) gave 1,4,5,6-tetrahydropyrimidine (98% yield as its hydrochloride).[2513] The *oxidation* of pyrimidine in warm glacial acetic acid containing peroxyacetic acid (made in situ) gave pyrimidine 1-oxide (**24**) in up to 21% yield according to the conditions;[764,836,3439] the same oxidation at 20° gave a separable mixture of



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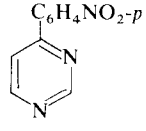

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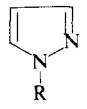

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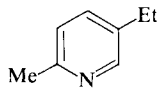

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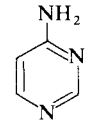

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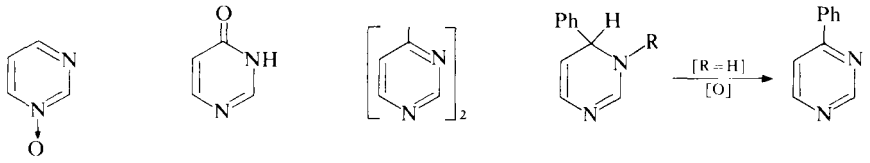

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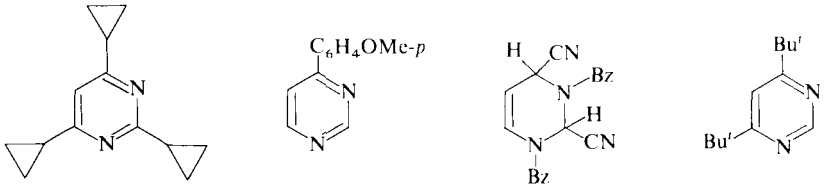
the oxide (**24**) (~3%) and 4(3*H*)-pyrimidinone (**25**) (~5%),[3632] while in the presence of sulfuric acid, only the pyrimidinone (**25**) (9%) was obtained.[170] Pyrimidine underwent a slow dehydrogenation over palladium–charcoal at 120° for 17 h to give only 4,4′-bipyrimidine (**26**) (4%); addition of pyridine 1-oxide improved the yield to 22% (140°/2 h), but other products were formed also.[4636] Most *Grignard and alkyl- or aryllithium* reagents add initially to the 3,4-bond of pyrimidine and subsequent hydrolysis and oxidation (usually by permanganate) furnishes 4-alkyl- or 4-arylpyrimidines: for example, phenylmagnesium bromide gave successively the adduct (**27**, R = MgBr), 4-phenyl-3,4-dihydropyrimidine (**27**, R = H), and 4-phenylpyrimidine (**28**) (32%);[836] likewise phenyllithium gave the adduct (**27**, R = Li), the dihydropyrimidine (**27**, R = H), and the phenylpyrimidine (**28**) (64%);[836] and similar procedures gave 4-*p*-tolyl- (51%), 4-furan-2′-yl- (53%), 4-thiazol-2′-yl- (30%), and other 4-arylpyrimidines.[836] In contrast, pyrimidine reacted with cyclopropyllithium to give (after hydrolysis and oxidation) a separable mixture of 2- (small yield) and 4-cyclopropylpyrimidine (45%): further treatment of the latter with cyclopropyllithium gave an (unseparated) mixture (47%) of 2,4- and 4,6-dicyclopropylpyrimidine, which on yet another such treatment afforded only 2,4,6-tricyclopropylpyrimidine (**29**) (51%).[4632] Other *addition reactions* have been reported. For example, pyrimidine with anisole in neat trifluoroacetic acid under reflux for 2 h gave 4-*p*-methoxyphenyl-3,4-dihydropyrimidine (63%, as hydrochloride), which underwent alkaline ferricyanide oxidation to afford 4-*p*-methoxyphenylpyrimidine (**30**) (80%);[4635] and pyrimidine with trimethylsilyl cyanide, benzoyl chloride, and a small amount of aluminum chloride in methylene chloride gave the Reissert product, 1,3-dibenzoyl-1,2,3,4-tetrahydro-2,4-pyrimidinedicarbonitrile (**31**) (59%).[4634] When a solution of pyrimidine and pivalic acid in dilute sulfuric acid containing silver nitrate was heated at 70° with ammonium persulfate, a semidirect *C-alkylation* occurred to furnish 4,6-di-*t*-butylpyrimidine (**32**) (61%).[4633]



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4.2. *C*-ALKYL- AND *C*-ARYLPYRIMIDINES

In the early days of pyrimidine chemistry, *C*-alkyl and *C*-aryl groups were dismissed as virtually nonfunctional and of little importance. It is now evident that such groups are highly functional, in that they undergo an appreciable number of reactions; they have important electronic and steric effects on the functionality and reactivity of other substituents attached to the same pyrimidine nucleus; and they profoundly modify the biological properties of bioactive pyrimidines.

4.2.1. Preparation of *C*-Alkylpyrimidines

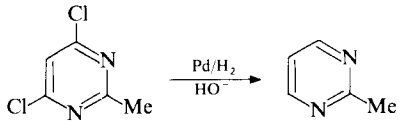
A high proportion of known simple alkyl- or arylpyrimidines (i.e., those without additional functional groups) have been made by primary syntheses, with or without subsequent modification(s). Most of the others were made by direct or indirect alkylation of existing pyrimidines.[4654]

4.2.1.1. Alkylpyrimidines by Primary Syntheses

Many simple alkylpyrimidines have been made by the Principal Synthesis, using a β-dialdehyde, β-aldehydo ketone, or β-diketone with an amidine (Sections 3.1.1, 3.2.1, 3.3.1): for example, acetylacetone with benzamidine gave 4,6-dimethyl-2-phenylpyrimidine (64%);[2740,4000] by the Bredereck synthesis (Section 2.3.3.1), as exemplified in the condensation of benzoylacetone with formamide (2 mol) at 220° to give 4-methyl-6-phenylpyrimidine (60%);[2752] and by several other syntheses described in Chapter 2.

4.2.1.2. Alkylpyrimidines by Dehalogenation

Alkylpyrimidinones are easily made and converted in alkyl halogenopyrimidines that undergo dehalogenation to alkylpyrimidines, usually by hydrogenation in the presence of a base or by treatment with zinc dust, hydriodic acid, or other reducing agent. For example, hydrogenation of 4,6-dichloro-2-methylpyrimidine (**33**) over palladium in ether–aqueous alkali at 3 atm gave 2-methylpyrimidine (**34**) (~90%).[2513,2745] Such dehalogenations are further



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illustrated by the following examples in which the yield of final product is given after each substrate.

2-Methyl- from 4-chloro-2-methylpyrimidine (H_2, Pd/C, NH_3: 84%;[1225] H_2, $Pd/BaCO_3$, NH_3: 47%;[2264] Zn, H_2O: 38%[2259]).

4-Methyl- from 2,4-dichloro-6-methyl- (H_2, Pd/C, NaOH: 80–93%;[1933,2513] H_2, Pd/C, MgO: 30–75%;[1735,2078,2264] H_2, Pd/C, NH_3: 38%;[1225] Zn, H_2O: 35%;[1517,2249,2264] H_2, $Pd/CaCO_3$[3442]), 4-chloro-6-methyl- (H_2, $Pd/BaCO_3$, NH_3: 65%[2264]), 2-chloro-4-methyl- (HI: 40%[2258]), or 5-bromo-2,4-dichloro-6-methylpyrimidine (H_2, Pd/C, MgO: 43%[1833]).

5-Methyl- from 2,4-dichloro-5-methyl- (H_2, Pd/C, NaOH: 87%[2513]), 2-chloro-5-methyl- (HI: 50%[2258]), 4-chloro-5-methyl- (H_2, $Pd/BaCO_3$, NH_3: 70%[2264]), or 2,4,6-trichloro-5-methylpyrimidine (H_2, Pd/C, MgO: 55%[1735]).

4-Pentyl- from 2,4-dichloro-6-pentylpyrimidine (H_2, $CaCO_3$[2178]).

5-Benzyl- from 5-benzyl-2,4,6-trichloropyrimidine (H_2, Ni, Na_2CO_3: 50%[4184]).

2-Phenyl- from 4-chloro-2-phenyl- (H_2, $Pd/BaCO_3$, NH_3: 84%;[2264] H_2, $Pd/BaSO_4$, NaOH[2212]), 5-chloro-2-phenyl- (H_2, $Pd/BaSO_4$, NaOH: 90%[2212]), or 5-bromo-4-chloro-2-phenylpyrimidine (Zn, H_2O: identity of product doubtful[1820]).

4-Phenyl- from 2-chloro-4-phenyl- (H_2, $Pd/BaSO_4$, NaOH[2212]), 4-chloro-6-phenyl- (H_2, $Pd/BaCO_3$, NH_3[2264]), or 2,4-dichloro-6-phenylpyrimidine (H_2, $Pd/CaCO_3$[3442]).

5-Phenyl- from 4-chloro-5-phenylpyrimidine (H_2, $Pd/BaSO_4$, NaOH[2212]).

2,4-Dimethyl- from 4-chloro-2,6-dimethylpyrimidine (Zn, H_2O: 65%[2105]).

2,5-Dimethyl- from 4,6-dichloro-2,5-dimethylpyrimidine (H_2, Pd/C, MgO[2745]).

4,6-Dimethyl- from 2-chloro-4,6-dimethyl- (HI: 78%[2258]) or 2-iodo-4,6-dimethylpyrimidine (HI: 88%[2258]).

2-Butyl-4-methyl- from 2-butyl-4-chloro-6-methylpyrimidine (H_2, $Pd/CaCO_3$[2178]).

2-Benzyl-4-methyl- from 2-benzyl-4-chloro-6-methylpyrimidine (Zn, H_2O: ~60%[3589]).

4-Benzyl-6-methyl- from 4-benzyl-2-chloro-6-methylpyrimidine (Zn, H_2O[3589]).

4-Methyl-2-phenyl- from 4-chloro-6-methyl-2-phenylpyrimidine (Zn, H_2O[2105]).

4-Methyl-6-phenyl- from 2-chloro-4-methyl-6-phenylpyrimidine (HI, red P[1228]).

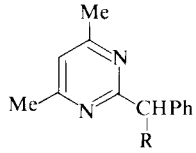
5-Methyl-2-phenyl- from 4,6-dichloro-5-methyl-2-phenylpyrimidine (H_2, Pd/C, Na_2CO_3: 48%[4184]).

5-Methyl-4-phenyl- from 4-chloro-5-methyl-6-phenylpyrimidine (H_2, Ni, Na_2CO_3: 50%[4184]).

4,6-Diphenyl- from 2-chloro-4,6-diphenylpyrimidine (HI: 41%[2258]).

The foregoing and other data suggest that (1) any 2-, 4/6-, or 5-halogenopyrimidine will undergo complete catalytic hydrogenolysis but without reduction of the pyrimidine ring, provided a base is present; (2) zinc dust in hot water will reductively dehalogenate a 4/6- but usually not a 2-halogenopyrimidine; and (3) cold hydriodic acid will convert any 2-, 4-, or 6-chloropyrimidine into its iodo analog, whereas hot hydriodic acid will cause reductive dehalogenation of a 2-halogenopyrimidine but hydrolysis of a 4/6-halogenopyrimidine.[2258]

A less conventional use of dehalogenation to prepare alkylpyrimidines is illustrated by the conversion of 2-α-chlorobenzyl- (**35**, R = Cl) into 2-benzyl-4,6-dimethylpyrimidine (**35**, R = H) (80%) by hydrogenolysis over palladium;[4044] of 6-benzyl-2-dichloromethyl- (**36**, R = Cl) into 6-benzyl-2-methyl-5-phenyl-4(3*H*)-pyrimidinone (**36**, R = H) (68%) by treatment in aqueous ammonia or acetic acid with zinc dust;[4340] of 5-chloromethyl-6-methyl- into 5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (94%) by hydrogenolysis over palladium;[698] of 2-iodomethyl-6-methyl- into 2,6-dimethyl-4-pyrimidinamine by reductive deiodination with hydriodic acid;[3748] and of 1-iodomethyl- to 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (64%) by sodium borohydride reduction in ethanol [*note*: the same substrate in boiling water gave 2,4(1*H*,3*H*)-pyrimidinedione in 87% yield].[6951]



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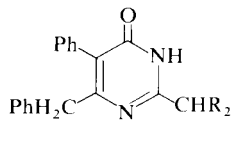

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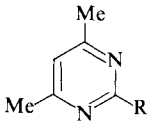
4.2.1.3. Alkylpyrimidines by Removal of Other Groups

Simple alkylpyrimidines have been made by removal of several groups other than halogen. Thus 4,6-dimethyl-2-pyrimidinecarboxylic acid (**37**, R = CO_2H), 4-methyl-2,6-diphenyl-5-pyrimidinecarboxylic acid, and 2,4,6-triphenyl-5-pyrimidinecarboxylic acid underwent *decarboxylation* on dry distillation to afford 4,6-dimethyl- (**37**, R = H),[1517] 4-methyl-2,6-diphenyl- (~80%),[4637] and 2,4,6-triphenylpyrimidine (~75%),[4637] respectively. In a different way, 4-*t*-butyl-2-methoxycarbonylmethylpyrimidine (**38**, R = CO_2Me) underwent hydrolysis to 4-*t*-butyl-2-carboxymethylpyrimidine (**38**, R = CO_2H), which, on warming at 90° for a few minutes, gave 4-*t*-butyl-2-methylpyrimidine (**38**, R = H) (98%);[1749] likewise, 5-β-carboxyvinyl-2,4(1*H*,3*H*)-pyrimidinedione lost carbon dioxide in quinoline at 200° to give 5-vinyl-2,4(1*H*,3*H*)-pyrimidinedione in small

yield.[2039] Rather analogous was the loss of acetone from 2-(3′-hydroxy-3′-methylbut-1′-ynyl)pyrimidine over potassium hydroxide at 110° to give 2-ethynylpyrimidine (40%).[3152]

The *desulfurization* of alkylpyrimidinethiones or the corresponding thioethers has been used to make simple alkylpyrimidines. Thus stirring appropriate *C*-alkylated 2(1*H*)-pyrimidinethiones with Raney-nickel, usually in hot aqueous or alcoholic base, gave 4-methyl- (20%),[764] 5-phenyl-,[4638] 4,6-dimethyl- (in acidified ethanol: 55%),[764,2566] 4-isopropyl-5-methyl- (64%),[3302] 4-methyl-6-phenyl-,[4638] and 4,5,6-trimethylpyrimidine (25%).[3302] Likewise, 4,6-dimethyl-2-methylthiopyrimidine (**37**, R = SMe) with Raney-nickel in boiling aqueous ethanol gave 4,6-dimethylpyrimidine (**37**, R = H) (77% as the $HgCl_2$ complex).[764] Analogous *deoxygenation* is much more difficult but has been used to convert 2-ethyl-6-methyl-4(3*H*)-pyrimidinone (**39**) into 2-ethyl-4-methylpyrimidine (low yield) by dry distillation with zinc dust.[2543]



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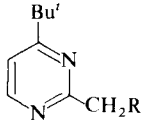

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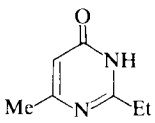

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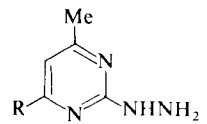

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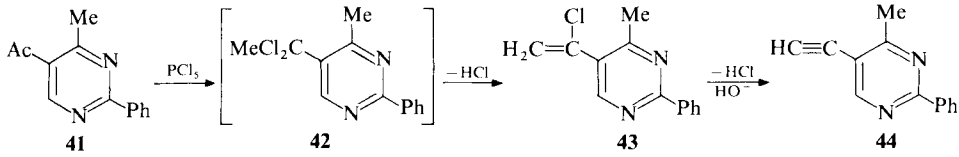
Oxidative *hydrazino group removal* in boiling aqueous cupric sulfate has been used to convert 2-hydrazino-4-methyl- (**40**, R = H) or 2-hydrazino-4,6-dimethylpyrimidine (**40**, R = Me) into 4-methyl- (~55%)[3216] or 4,6-dimethylpyrimidine (**37**, R = H) (62%, as $HgCl_2$ complex),[2566] respectively; boiling aqueous silver acetate was used to make 5-phenylpyrimidine (~65%) from its 4-hydrazino derivative.[4640] In a rather similar way, 4-β-(benzenesulfonyl)-hydrazino-2-methylpyrimidine underwent degradation to 2-methylpyrimidine (~60%) on vigorous alkaline treatment.[3441]

Although of little practical value, *debenzylation* of 1-benzyl-4,6-dimethylpyrimidinium bromide occurred in liquid ammonia to afford 4,6-dimethylpyrimidine.[4584]

4.2.1.4. Alkylpyrimidines by Eliminative Reactions

The elimination of hydrogen chloride, water, or the like from appropriate (substituted-alkyl)pyrimidines affords one route to alkenyl- or alkynylpyrimidines and thence to alkylpyrimidines if required. For example, 5-acetyl-4-methyl-2-phenylpyrimidine (**41**) with phosphorus pentachloride in hot benzene probably gave the α,α-dichloroethyl intermediate (**42**), which spontaneously lost hydrogen chloride to give 5-α-chlorovinyl-4-methyl-2-phenylpyrimidine (**43**) (> 90%) and thence, on treatment with alkali, 5-ethynyl-4-methyl-2-phenylpyrimidine (**44**) (~65%).[790] In a different way, 4-β-hydroxyethylpyrimidine gave 4-vinylpyrimidine (23%) by loss of water on addition to molten



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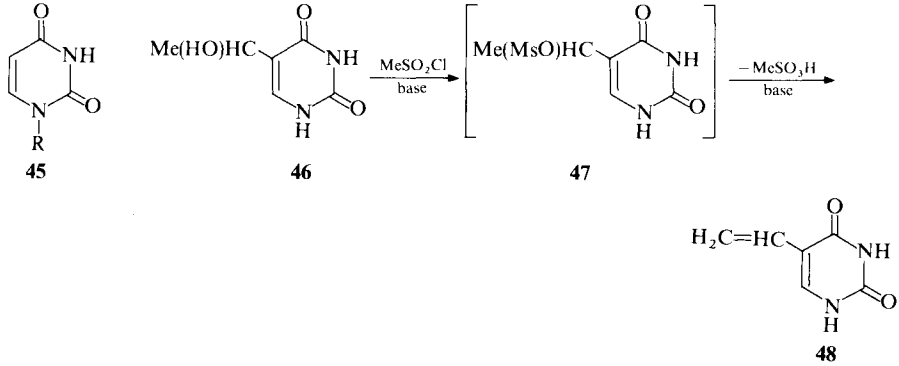
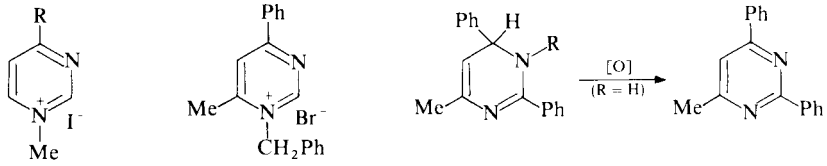
potassium hydroxide.[2078] Such processes have been used mainly to produce alkenyl- or alkynylpyrimidines that also bear functional groups. For example, 1-β-chloroethyl- (**45**, R = CH_2CH_2Cl) gave 1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione (**45**, R = CH:CH_2) (60%) in hot dimethyl sulfoxide containing potassium *t*-butoxide;[1722, cf. 1323] 5-(α-bromo-α-methylethyl)-2,4,6-trifluoro- gave 2,4,6-trifluoro-5-isopropenylpyrimidine (> 95%) on distillation with ferric chloride;[3952] 5-methyl- (47%)[1323] and 5-fluoro-1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione (40%)[741] were made like their analog (**45**, R = CH:CH_2) above; 5-α-hydroxyethyl- (**46**) gave 5-vinyl-2,4(1*H*,3*H*)-pyrimidinedione (**48**) (89%) on treatment with methanesulfonyl chloride and *N*-methylmorpholine, almost certainly by loss of methanesulfonic acid from a mesyloxy intermediate (**47**);[252, 3719] and other such cases have been reported.[450, 786, 832, 1259, 2361, 3741]



45 46 47 48

4.2.1.5. Alkylpyrimidines by Direct or Indirect Alkylation

The *N*- and *C*-alkylations of pyrimidine itself have been covered in Sections 4.1.2 and 4.1.3, respectively. The *N-alkylation* (*quaternization*) of simple *C*-alkylpyrimidines has usually been done with an appropriate alkyl iodide at room temperature for several days (or under reflux for several hours) to give, for example, 1,4-dimethyl- (**49**, R = Me),[3445] 1,4,6-trimethyl- (80%),[2754] 1-methyl-4-phenyl- (**49**, R = Ph) (67%),[4640] 1-methyl-5-phenyl- (~40%),[4640] 1,2-dimethyl- (~90%),[3441] and 1,2,4,6-tetramethylpyrimidinium iodide (~75%).[3441] Similarly, 4-methyl-6-phenylpyrimidine with benzyl bromide at 100° gave 1-benzyl-6-methyl-4-phenylpyrimidinium bromide (**50**) (98%),[4641] and many other such substrates bearing functional groups have been so *N*-alkylated.[1513, 2520, 3493]



49 **50** **51** **52**

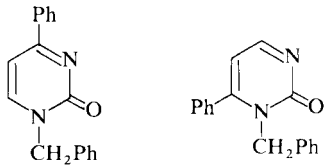
The use of *alkylmetallo reagents* for *C*-alkylation of pyrimidines lacking functional groups is rare and usually of little preparative value. However, 4-methyl-2-phenylpyrimidine and phenyllithium gave an adduct (**51**, R = Li) that on hydrolysis gave 4-methyl-2,6-diphenyl-1,6-dihydropyrimidine (**51**, R = H) (~40%) and thence, on permanganate oxidation, 4-methyl-2,6-diphenylpyrimidine (**52**) (~80%).[4642] Similar treatment of 5-methylpyrimidine gave 5-methyl-4-phenylpyrimidine (37%);[2749] and 5-thien-2′-yl- or 5-thien-3′-ylpyrimidine with butyllithium gave (after hydrolysis and ferricyanide oxidation) 4-butyl-5-thien-2′-yl- or 4-butyl-5-thien-3′-ylpyrimidine, respectively.[4427]

Such reagents have been used more often to alkylate pyrimidine substrates already bearing functional groups, as illustrated briefly in the following examples.

2-Pyrimidinamine gave its 4-phenyl derivative (PhLi, aerial oxidation: 20%).[4643]

2-Dimethylaminopyrimidine gave its 4-butyl (17%) or 4,6-dibutyl derivative (13%) [BuLi (1 or 3 mol, respectively), aerial oxidation].[2083]

1-Benzyl-2(1*H*)-pyrimidinone gave regioselectively its 4-phenyl derivative (**53**) [$PhTi(OPr^i)_3$, dichlorodicyanobenzoquinone (DDQ): 73%; or Li-$CuPh_2$, DDQ: 57%] or the isomeric 6-phenyl derivative (**54**) (PhMgI, DDQ: 68%; or BuLi, DDQ: 61%);[219,222] also many analogs.[219,222]

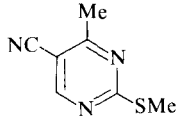


53 **54**

4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinone gave predominantly 4,4,6-trimethyl-3-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone (MeMgI: no oxidation possible) or predominantly 4,4,6-trimethyl-1-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone (MeLi: no oxidation possible);[4645] larger alkyl groups upset this regioselectivity.[4645]

1-Benzyl-5-chloro-2(1*H*)-pyrimidinone gave a separable mixture of 1-benzyl-5-chloro-4-phenylethynyl- and 1-benzyl-5-chloro-6-phenylethynyl-2(1*H*)-pyrimidinone [PhC≡CMgI, MnO_2: 18% and 39%; PhC≡C$Ti(OPr^i)_3$, MnO_2: 38% and < 1%];[221] also some analogs.[221,3828]

2-Methylthio-5-pyrimidinecarbonitrile gave its 4-methyl derivative (**55**) (MeMgI, DDQ: 45%);[43] also analogs.[43]



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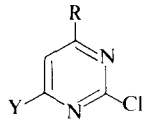

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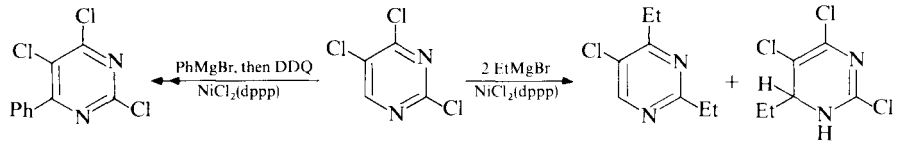
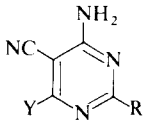
In the special case of a substrate bearing an activated halogeno substituent, an alkylmetallo reagent could add, either to an unsubstituted C,N bond (as in the foregoing examples) or to the *C*-halogenated C,N bond, with subsequent loss of hydrogen chloride (see Section 4.2.1.6). In fact, the first course is usually preferred and only when no unsubstituted C,N bond remains, does displacement of halogen occur. Thus 2-chloropyrimidine (**56**, R = Y = H) with methyllithium, followed by DDQ oxidation, gave 2-chloro-4-methylpyrimidine (**56**, R = Me, Y = H) (84%);[3734] 2-chloropyrimidine with allylmagnesium bromide gave (after hydrolysis and DDQ oxidation) 4-allyl-2-chloropyrimidine (**56**, R = $CH_2CH{:}CH_2$, Y = H) (58%) and thence, on repetition of the procedures, 4,6-diallyl-2-chloropyrimidine (**56**, R = Y = $CH_2CH{:}CH_2$) (>90%);[3943] 2,4,5-trichloropyrimidine (**58**) with phenylmagnesium bromide, even catalyzed by dichloro[1,3-bis(diphenylphosphino)propane]nickel [$NiCl_2$(dppp)], gave (after oxidation) only 2,4,5-trichloro-6-phenylpyrimidine (**57**) (37%);[3821] and other such examples have been reported.[3734, 3821, 3943, 4360, 6033] However, treatment of the foregoing substrate (**58**) with ethylmagnesium bromide (2 mol) plus catalyst led to displacement at the expense of addition, thereby giving a 70% yield of 5-chloro-2,4-diethylpyrimidine (**59**) and only a 9% yield of 2,4,5-trichloro-6-ethyl-1,6-dihydropyrimidine (**60**);[3822] other alkylmagnesium halides reacted similarly.[3822]



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

Several *other methods* of *C*-alkylation have been reported but most appear to require the presence of electron-donating functional groups on the substrates. Some of these are of minor importance[354, 3922] or rather esoteric;[3989, 5603] others are illustrated briefly in the following paragraphs.

Irradiation of 4-amino-5-pyrimidinecarbonitrile (**61**, R = Y = H) or its 2-methyl derivative (**61**, R = Me, Y = H) in 2% methanolic hydrogen chloride for several hours gave 4-amino-2,6-dimethyl-5-pyrimidinecarbonitrile (**61**, R = Y = Me) (60% or 86%, respectively); 5-aminomethyl-4-pyrimidinamine or its 2-



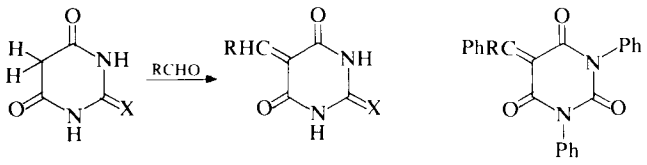
61

methyl derivative likewise afforded 5-aminomethyl-2,6-dimethyl-4-pyrimidinamine (52% or 33%, respectively).[1122,4644] Less useful photoalkylations have been described.[1850,3842,4650]

Treatment of 2-ethoxypyrimidine, pivalic acid, and silver nitrate in dilute sulfuric acid with ammonium persulfate gave 4,6-di-*t*-butyl-2-ethoxypyrimidine (68%).[4633]

Pyridine 1-oxide reacted with 4(3*H*)-pyrimidinone at 140° in the presence of Pt—Pd—C to give a separable mixture of 2-(pyridin-2′-yl)-4(3*H*)-pyrimidinone, 2,2′-bipyrimidine-4,4′(3*H*,3′*H*)-dione, and 2,4′-bipyrimidine-4,6′(1′*H*,3*H*)-dione; analogs resulted similarly.[3975]

Barbituric acid and related substrates (in which C5 is a methylene entity) undergo condensation with aldehydes and sometimes even alkylation at the 5-position.[189] For example, 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**62**, X = O) with neat benzaldehyde at 100° gave 5-benzylidene- (**63**, R = Ph, X = O) (> 98%) and thence, by reduction with zinc dust in acetic acid, 5-benzyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione;[4646] the same substrate (**62**, X = O) with hexamethylenetetramine has been reported to give the rather unstable ammonium salt of 5-methylene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**63**, R = H, X = O);[3394] 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with benzaldehyde in ethanol gave its 5-benzylidene derivative (97%);[2687,3733] 1,3-diphenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with benzaldehyde or α,α-dichloro(diphenylmethane) gave the 5-benzylidene (**64**, R = H) (98%) or the 5-diphenylmethylene derivative (**64**, R = Ph) (~50%), respectively;[4213] 2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**62**, X = S) or its 2-selenoxo analog (**62**, X = Se) with benzaldehyde in glacial acetic acid containing acetic anhydride gave the 5-benzylidene derivatives (**63**, R = Ph, X = S) (>80%) [4647] or (**63**, R = Ph, X = Se),[172] respectively; 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with dimethylformamide and phosphoryl chloride gave its 5-dimethylaminomethylene derivative (88%);[83] and many substituted-benzylidene derivatives or the like were made similarly,[172,459,3042,4646–4649] or have been implicated as unisolated intermediates.[65,3724]



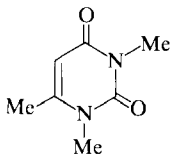
62 **63** **64**

It is possible sometimes to *C*-alkylate via a *C*-lithio derivative: for example, 5-methoxypyrimidine gave its 4-lithio derivative (BuLi, tetramethylpiperidine, THF, $-78°$) and thence 5-methoxy-4-methylpyrimidine (MeI, THF, 20°, 15 h: 47% overall); 2,4- (83%) and 4,6-dimethoxy-5-methylpyrimidine (76%) were made similarly.[6117]

Pyrimidines bearing at least two electron-donating groups have been *C*-alkylated in several ways, as illustrated in the following examples.

1,3,6-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**65**) with paraformaldehyde in dilute hydrochloric acid gave bis(1,3,4-trimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl)methane (**66**) (98%);[260] several analogs were made similarly.[260,3902]

1,3-Dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione (**67**, R = H) with 2-tosyl-1,2,3,12b-tetrahydroimidazo[1,5-*f*]phenanthridine gave several products from which the 5-methyl derivative (**67**, R = Me) (10%) was isolated.[469]



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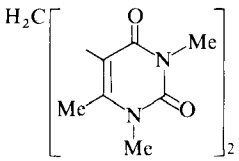

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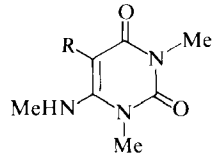

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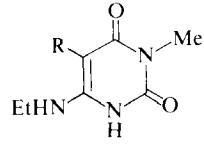


68

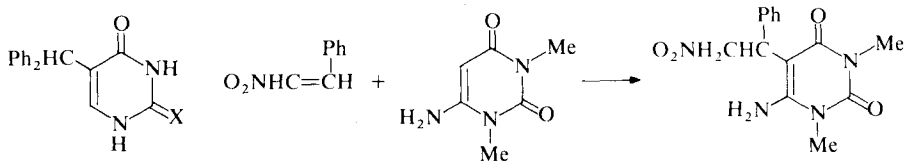
2,4(1*H*,3*H*)-Pyrimidinedione with methyl cations (generated in situ) gave small amounts of all possible monomethylated products, including the 5- and 6-methyl derivatives.[504]

6-Ethylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**68**, R = H) with *o*-fluoronitrobenzene and potassium carbonate at 160° gave the 5-*o*-nitrophenyl derivative (**68**, R = $C_6H_4NO_2$-*o*) (59%).[310] Analogous alkylations have been reported.[3815]

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione with trimethylammonium formate at 130–140° gave 5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, isolated as a salt in 80% yield; the 1,5-dimethyl (80%) and 1,3,5-trimethyl homolog (72%) were made similarly.[2808]

2,4(1*H*,3*H*)-Pyrimidinedione with diphenylmethanol and boron trifluoride etherate (or stannic chloride) in refluxing acetic acid gave the 5-diphenylmethyl derivative (**69**, X = O) (96%);[4363] 5-diphenylmethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**69**, X = S) (99%) and other analogs were made likewise,[4363] but *N*-alkylation occurred with unsuitable substrates.[4363,4651]

6-Amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**71**) added to the double bond of β-nitrostyrene (**70**) in refluxing methanol to give 6-amino-1,3-dimethyl-5-(β-nitro-α-phenylethyl)-2,4(1*H*,3*H*)-pyrimidinedione (**72**) (70%);[92] other such reactions have been described.[77,92]

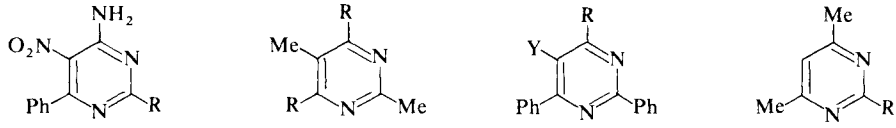


69 **70** **71** **72**

4.2.1.6. Alkylpyrimidines from Halogenopyrimidines

There are three main ways to replace a halogeno by an alkyl substituent. The first involves the use of a *carbanionic reagent*. For example, 2-chloro-5-nitro-6-phenyl-4-pyrimidinamine (**73**, R = Cl) with diethyl malonate and concentrated alkali in tetrahydrofuran gave 2-di(ethoxycarbonyl) methyl-5-nitro-6-phenyl-4-pyrimidinamine [**73**, R = $CH(CO_2Et)_2$] (~70%), which underwent hydrolysis and decarboxylation in refluxing hydrochloric acid to afford 2-methyl-5-nitro-6-phenyl-4-pyrimidinamine (**73**, R = Me) (>80%).[4652] Other examples have been reported.[145,186]

The second method involves an *alkylmetallo reagent*. Classical procedures gave low yields: 4,6-dichloro-2,5-dimethylpyrimidine (**74**, R = Cl) with ethylmagnesium bromide gave a little 4,6-diethyl-2,5-dimethylpyrimidine (**74**, R = Et) as its picrate;[3101] 4-chloro-5-ethyl-2,6-diphenylpyrimidine (**75**, R = Cl, Y = Et) with phenylmagnesium bromide gave 5-ethyl-2,4,6-triphenylpyrimidine (**75**, R = Ph, Y = Et) (? yield);[4506] 4-chloro-2,6-diphenyl-5-propylpyrimidine (**75**, R = Cl, Y = Pr) with phenyllithium gave 2,4,6-triphenyl-5-propylpyrimidine (**75**, R = Ph, Y = Pr) (? yield);[4506] and 5-bromo-2,4-dimethoxypyrimidine with butyllithium followed by methyl iodide gave crude 2,4-dimethoxy-5-methylpyrimidine and thence, on acidic hydrolysis, 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (29% overall).[3101] In 1978,[2293] the use of a nickel–phosphine complex, for example, dichloro[1,3-bis(diphenylphosphino)propane]nickel [$NiCl_2$(dppp)], was introduced to the pyrimidine series in order to catalyze such Grignard reactions: improved yields resulted, as indicated in the following examples.



73 **74** **75** **76**

2-Chloro-4,6-dimethylpyrimidine (**76**, R = Cl) with an appropriate alkylmagnesium bromide and $NiCl_2$ (dppp) gave 2-ethyl- (**76**, R = Et) (74%), 2-butyl- (**76**, R = Bu) (67%), or 2-benzyl-4,6-dimethylpyrimidine (**76**, R = CH_2Ph) (46%) and other homologs.[2293]

4-Chloro-2,6-dimethylpyrimidine likewise gave 4-ethyl- (61%) or 4-benzyl-2,6-dimethylpyrimidine (53%) and 2,4-dimethyl-6-phenylpyrimidine (81%).[2293]

2,4,6-Trichloro- or 2,4-dichloro-6-phenylpyrimidine with an excess of phenylmagnesium bromide (and catalyst) gave 2,4,6-triphenylpyrimidine (**75**, R = Ph, Y = H) in ~75%[2293] or 95%[3821] yield, respectively.

4,6-Dichloro-5-fluoropyrimidine with ethylmagnesium bromide (and catalyst) gave 2,4-diethyl-5-fluoropyrimidine (53%).[3822] 2-Methyl-4,6-diphenethylpyrimidine (67%) was made rather similarly.[64]

2,4-Dichloropyrimidine with thien-2-ylmagnesium bromide (and catalyst) gave 2,4-dithien-2′-ylpyrimidine (crude: 85%; pure: 30%).[240]

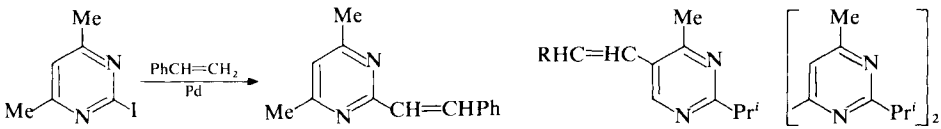
The third method involves the *palladium-catalyzed replacement* of a nuclear halogeno (preferably iodo) or an equivalent substituent by an alkenyl or alkynyl substituent, using an appropriate alkene or alkyne in the presence of triethylamine at >100°: triphenylphosphine and/or cuprous iodide are frequently added but neither may be strictly necessary.[2375] An important recent development of this reaction involves (1) the conversion of an halogenopyrimidine into its tributylstannyl analog followed by the palladium-catalyzed reaction with 1-halogenoalk-1-ene (or similar alkyne?) or (2) the palladium-catalyzed reaction of an halogenopyrimidine with a preformed 1-tributylstannylated alk-1-ene, alk-1-yne, alkane, or arene. The following examples illustrate the scope of the classical reaction and of its tin-assisted versions.

Using alk-1-enes

2-Iodo-4,6- (**77**), 4-iodo-2,6-, or 5-iodo-2,4-dimethylpyrimidine with styrene (no Ph_3P) gave 4,6-dimethyl-2- (**78**) (53%), 2,4-dimethyl-6- (50%), or 2,4-dimethyl-5-styrylpyrimidine (45%);[2374] the last-mentioned product was obtained in 75% yield from 5-bromo-2,4-dimethylpyrimidine (with Ph_3P).[2376]

5-Iodo-2-isopropyl-4-methylpyrimidine with styrene, ethyl acrylate, or acrylonitrile gave *trans*-2-isopropyl-4-methyl-5-styrylpyrimidine (**79**, R = Ph) (59%), *trans*-5-β-ethoxycarbonylvinyl-2-isopropyl-4-methylpyrimidine (**79**, R = CO_2Et) (69%), or *trans*-5-β-cyanovinyl-2-isopropyl-4-methylpyrimidine (**79**, R = CN) (81%), respectively.[2376]

4-Iodo-2-isopropyl-4-methylpyrimidine with (or without) ethyl acrylate gave only 2,2′-diisopropyl-6,6′-dimethyl-4,4′-bipyrimidine (**80**) (60–90%);[2376] in



77 **78** **79** **80**

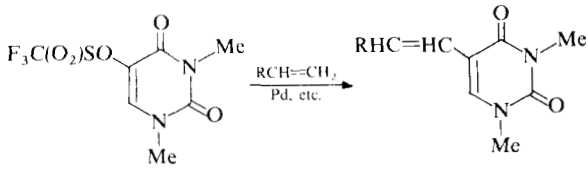
contrast, 4-iodo-2-methyl-6-phenylpyrimidine with styrene gave only 2-methyl-4-phenyl-6-styrylpyrimidine (22%),[4657] while 4,5-diiodo-2-isopropyl-6-methylpyrimidine with styrene gave only 5-iodo-2-isopropyl-4-methyl-6-styrylpyrimidine (46%).[1890]

4-Chloro-5-iodo-2,6-dimethylpyrimidine with styrene or ethyl acrylate gave only 4-chloro-2,6-dimethyl-5-styrylpyrimidine (32%)[4656] or 4-chloro-5-β-ethoxycarbonylvinyl-2,6-dimethylpyrimidine,[2177] respectively (cf. preceding entry).

5-Chloro-4-iodo-2-methylthiopyrimidine with styrene gave *trans*-5-chloro-2-methylthio-4-styrylpyrimidine (78%).[3826]

5-Iodo- or 5-bromo-2,4-dimethoxy-6-methylpyrimidine with ethyl acrylate gave 5-β-ethoxycarbonylvinyl-2,4-dimethoxy-6-methylpyrimidine in 91% or 10% yield, respectively.[257]

1,3-Dimethyl-5-trifluoromethanesulfonyloxy-2,4(1*H*,3*H*)-pyrimidinedione (**81**) with methyl vinyl ketone, methyl acrylate, or acrylonitrile gave 5-β-acetylvinyl- (**82**, R = Ac) (96%), 5-β-methoxycarbonylvinyl- (**82**, R = CO_2Me) (76%), or 5-β-cyanovinyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**82**, R = CN) (93%), respectively.[440] Also analogs.[6077]

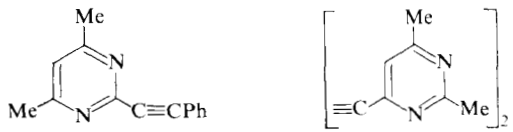


81 **82**

Using alk-1-ynes

2-Chloro-, 2-bromo-, or 2-iodo-4,6-dimethylpyrimidine with phenylacetylene gave 4,6-dimethyl-2-phenylethynylpyrimidine (**83**) in 5%, 37%, or 95% yield, respectively.[1857, cf. 4655]

4-Iodo-2,6-dimethylpyrimidine with propyne, phenylacetylene, or acetylene gave 2,4-dimethyl-6-prop-1′-ynylpyrimidine (80%), 2,4-dimethyl-6-phenylethynylpyrimidine (84%), or bis(2,6-dimethylpyrimidin-4-yl)-acetylene (**84**) (37%).[1857,2724]



83 **84**

5-Bromo-2,4-dimethylpyrimidine with phenylacetylene gave 2,4-dimethyl-5-phenylethynylpyrimidine (42%).[1857] Analogs.[6067]

2,4-Diiodo-6-methylpyrimidine with hex-1-yne gave 2,4-dihex-1′-ynyl-6-methylpyrimidine (31%).[1857,2724]

Ethyl 5-bromo-2-methyl-4-pyrimidinecarboxylate with phenylacetylene gave ethyl 2-methyl-5-phenylethynyl-4-pyrimidinecarboxylate (60%).[2177]

4-Chloro-5-iodo-2,6-dimethylpyrimidine with phenylacetylene gave 4-chloro-2,6-dimethyl-5-phenylethynylpyrimidine (66%).[4656]

5-Chloro-4-iodo-2-methylthiopyrimidine with prop-2-ynol gave 5-chloro-4-hydroxyprop-1′-ynyl-2-methylthiopyrimidine (**85**) (70%).[220]

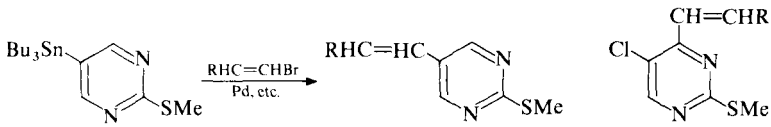
85

4,6-Diiodo-2-methylpyrimidine with 5-(trimethylsilyl)pent-4-ynylzinc iodide gave 2-methyl-4,6-bis[5′-(trimethylsilyl)pent-4′-ynyl]pyrimidine (48%) and thence in alkali, 2-methyl-4,6-bis(pent-4′-ynyl)pyrimidine (98%).[3816]

4-Chloro-5-iodopyrimidine with (trimethylsilyl)acetylene gave 4-chloro-5-trimethylsilylethynylpyrimidine (70%).[499]

Tin-assisted versions

5-Bromo-2-methylthiopyrimidine with butyllithium followed by tributyltin chloride gave 2-methylthio-5-tributylstannylpyrimidine (**86**) (70%), which reacted with bromoethylene, 1-bromopropene, or β-bromostyrene [and bis(triphenylphosphine)palladium dichloride, $(Ph_3P)_2PdCl_2$, in refluxing tetrahydrofuran or 1,2-dichloroethane under nitrogen] to afford 2-methylthio-5-vinylpyrimidine (**87**, R = H) [28%, with 2,2′-bismethylthio-5,5′-bipyrimidine (56%)], 2-methylthio-5-prop-1′-enylpyrimidine (**87**, R = Me) (89%), or 2-methylthio-5-styrylpyrimidine (**87**, R = Ph) [71%, with the foregoing bipyrimidine (24%)], respectively;[3829] 5-aryl analogs, likewise.[3970]



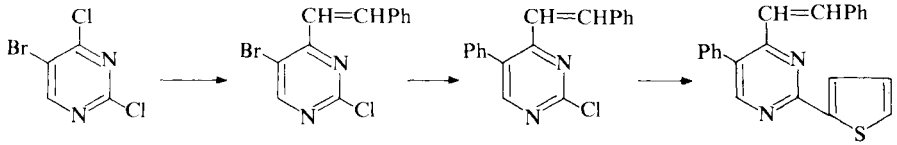
86 **87** **88**

5-Chloro-4-iodo-2-methylthiopyrimidine with β-(tributylstannyl)styrene and $(Ph_3P)_2PdCl_2$ in tetrahydrofuran under nitrogen gave 5-chloro-2-methylthio-4-styrylpyrimidine (**88**, R = Ph) (90%, cf. 78% by classical procedure);[3826] the 4-vinyl (**88**, R = H) (71%) and 4-prop-1′-enyl analog (**88**, R = Me) (90%) were made similarly.[3826]

5-Chloro-4 -iodo-2-methylthiopyrimidine with tributylphenyltin and (Ph_3P)-$PdCl_2$ in refluxing tetrahydrofuran for 24 h gave 5-chloro-2-methylthio-4-phenylpyrimidine (62%);[3826] the 4-thien-2′-yl (90%), 4-methyl (78%), 4-benzyl (60%), and other analogs were made similarly.[3826,3999]

5-Bromo-2-methoxypyrimidine with neat tributylstannylethylene and $(Ph_3P)_2PdCl_2$ (under reflux for 2 h) gave 2-methoxy-5-vinylpyrimidine (53%); 1-benzyl-5-iodo-2(1*H*)-pyrimidinone gave its 5-vinyl analog (60%) similarly.[3829]

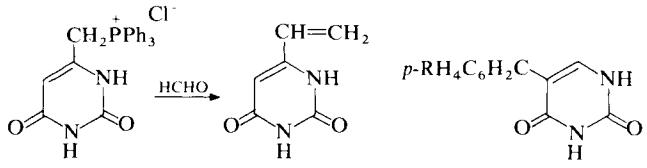
The regioselectivity of these reactions is evident in the following sequence: 5-bromo-2,4-dichloropyrimidine (**89**) (with *β*-tributylstannylstyrene) → 5-bromo-2-chloro-4-styrylpyrimidine (**90**) (73%) (with tributylphenyltin) → 2-chloro-5-phenyl-4-styrylpyrimidine (**91**) (70%) (with 2-tributylstannylthiophene) → 5-phenyl-4-styryl-2-thien-2′-ylpyrimidine (**92**) (82%), in each case done in dimethylformamide containing $(Ph_3P)_2PdCl_2$;[3831] also other examples.[3831]



89 **90** **91** **92**

Minor procedures for the replacement of halogen by alkyl substituents in pyrimidines are illustrated by the following examples.

1. The photolysis of 5-bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione in toluene gave a separable mixture of six arylated products, 1,3-dimethyl-5-(*o* + *m* + *p*)-tolyl- and 1,3-dimethyl-6-(*o* + *m* + *p*)-tolyl-2,4(1*H*,3*H*)-pyrimidinedione.[324, cf. 6172] In contrast, 6-chloro-1,3-dimethyl- gave 1,3-dimethyl-6-phenyl- (*hv*, neat PhH: 33%) or 1,3-dimethyl-5,6-hexamethylene-2,4(1*H*,3*H*)-pyrimidinedione (*hv*, PhH, F_3CCO_2H: 62%).[6137]
2. The reaction of 4-chloro-5-ethoxymethyl-2-methylpyrimidine with benzene in the presence of aluminum bromide afforded 5-benzyl-2-methyl-4-phenylpyrimidine in ~40% yield.[4653]
3. 6-Chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione with triphenylphosphine gave 6-phosphoniomethyl-2,4(1*H*,3*H*)-pyrimidinedione chloride (**93**) (84%), which reacted with paraformaldehyde to furnish 6-vinyl-2,4(1*H*,3*H*)-pyrimidinedione (**94**) (83%).[1869]
4. 5-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione with benzene or toluene in anhydrous hydrofluoric acid at 0° gave 5-benzyl- (**95**, R = H) (52%) or 5-*p*-methylbenzyl-2,4(1*H*,3*H*)-pyrimidinedione (**95**, R = Me) (59%),[4658] possibly via a fluoromethyl intermediate?



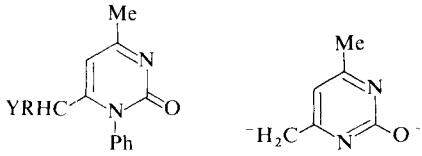
93 **94** **95**

5. 2-Chloropyrimidine with phenylboranic acid [$PhB(OH)_2$] in the presence of a palladium catalyst gave 2-phenylpyrimidine (65%).[6135]

4.2.1.7. Alkylpyrimidines by Interconversion of Alkyl Groups

Both saturated and unsaturated *C*-alkyl groups may be changed into other alkyl groups in several ways, thereby affording potentially useful routes to the new alkylpyrimidines.

Methyl groups at the 2- or 4/6-position of pyrimidine are activated and hence capable of being increased in size by *direct alkylation.* Thus 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinone (**96**, R = Y = H) with sodium hydride and methyl or ethyl iodide at 0° gave (regioselectively) 6-ethyl-4-methyl-1-phenyl- (**96**, R = Me, Y = H) (34%) or 4-methyl-1-phenyl-6-propyl-2(1*H*)-pyrimidinone (**96**, R = Et, Y = H) (35%), respectively;[61] the similar use of benzyl bromide gave a separable mixture of 4-methyl-6-phenethyl- (**96**, R = CH_2Ph, Y = H) (43%) and 6-α-benzylphenethyl-4-methyl-1-phenyl-2(1*H*)-pyrimidinone (**96**, R = Y = CH_2Ph) (11%);[61] and 1,3,6-trimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione with benzyl bromide or chloride (with added potassium iodide) gave the 6-phenethyl analog (>90%).[2996] Likewise, 4,6-dimethyl-5-phenyl-2(1*H*)-pyrimidinone, converted into its dianion (**97**) by butyllithium (2 mol), reacted with benzyl chloride to afford 4-methyl-6-phenethyl-5-phenyl-2(1*H*)-pyrimidinone (76%);[4659,4660] 2,4,6-trimethylpyrimidine with phenyllithium followed by methyl iodide or dodecyl bromide gave 4-ethyl-2,6-dimethyl- (~20%)[3000] or 2,4-dimethyl-6-tridecylpyrimidine (~30%),[4642] respectively; but an early opinion,[3589] that 4-methylpyrimidine with butyl bromide–sodium amide (or amalgam?) gave 4-pentylpyrimidine, was later withdrawn[2178] as incorrect.



96 **97**

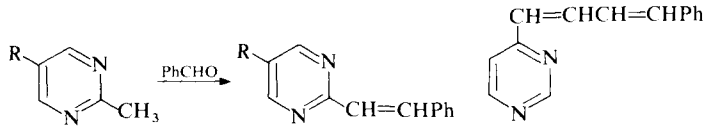
Activated methyl groups undergo *alkylidenation* (mainly *styrylation*) on treatment with an appropriate aldehyde. The following examples illustrate this

process, using benzaldehyde at ~150° with zinc chloride as catalyst unless otherwise indicated.

4-Methyl- gave 4-styrylpyrimidine (~60%);[1663] or in acetic anhydride.[3201]

2-Methyl- (**98**, R = H) or 2,5-dimethylpyrimidine (**98**, R = Me) gave 2-styrylpyrimidine (**99**, R = H) or its 5-methyl derivative (**99**, R = Me), respectively.[2745]

4-Methylpyrimidine with cinnamaldehyde at 120° gave 4-(4′-phenylbuta-1′,3′-dienyl)pyrimidine (**100**) (8%).[4662]



98 **99** **100**

2,4-Dimethylpyrimidine at 100° or 150° gave 2-methyl-4-styryl- (82%)[64] or 2,4-distyrylpyrimidine,[1663] respectively.

4,6-Dimethylpyrimidine with zinc chloride or in acetic anhydride gave 4,6-distyrylpyrimidine (70%).[2755]

4,6-Dimethyl-2-phenyl- gave 2-phenyl-4,6-distyrylpyrimidine (~35%).[2755,4663]

2,4,6-Trimethylpyrimidine with an excess of benzaldehyde gave 2,4,6-tristyrylpyrimidine (~40%)[2467,3640] but with less aldehyde a mixture of mono- and distyrylated products was formed.[1611,2757,3640]

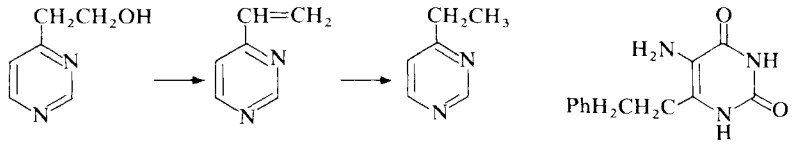
5-Bromo-2-methyl- gave 5-bromo-2-styrylpyrimidine (44%).[1935]

2-Methyl- at 190° gave 2-styryl-4(3*H*)-pyrimidinone (95%).[3481]

4,6-Dimethylpyrimidine 1-oxide (aqueous ethanolic alkali and no catalyst) gave crude 4,6-distyrylpyrimidine 1-oxide, deoxygenated in phosphoryl chloride to 4,6-distyrylpyrimidine (53% overall).[4657]

Also other cases.[64,684,1405,2733,3808,4657,4671]

When 4-methylpyrimidine was treated with paraformaldehyde in a sealed tube at 165°, the expected reaction stalled at the intermediate, 4-β-hydroxyethylpyrimidine (**101**) (87%),[2078,3246,4678] which underwent dehydration only in molten potassium hydroxide to give 4-vinylpyrimidine (**102**) (23%).[2078] For the use of substituted aldehydes, see Section 4.2.3.2.



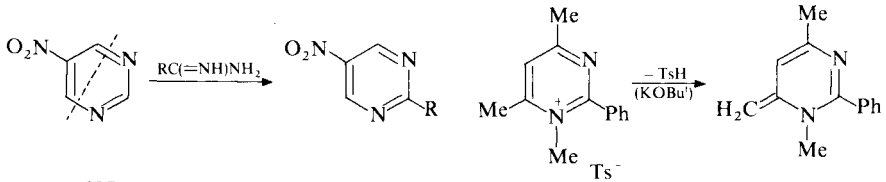
101 **102** **103** **104**

Since alkenyl- and alkynylpyrimidines may be prepared quite easily in several ways (see foregoing subsections), the *reduction of unsaturated alkyl groups* offers a fruitful route to alkylpyrimidines. For example, hydrogenation of 4-vinylpyrimidine (**102**) over palladium gave 4-ethylpyrimidine (**103**) (66%);[2078] 4-styryl- likewise gave 4-phenethylpyrimidine;[3589] and other products so made include 2,4-dimethyl-6-phenethylpyrimidine (63%),[1611] 5-amino-6-phenethyl-2,4(1*H*,3*H*)-pyrimidinedione (**104**) (64%; from the 5-nitro-6-styryl analog),[1962] 2-phenethyl-4,5-pyrimidinediamine (~60%; from the 6-chloro-2-styryl analog using $Pd/SrCO_3 + NH_2NH_2$),[684] 2-amino-5,6-bis(δ-phenylbutyl)-4(3*H*)-pyrimidinone [68%; from the 6-(4′-phenylbuta-1′,3′-dienyl) analog],[4151] 5-hydroxy-1,3-dimethyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione (98%; from the 6-allyl analog),[854] 5-benzyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (91%; from the 5-benzylidene analog using triethylammonium formate),[2808] 2,4-dimethyl-6- or 4,6-dimethyl-2-phenethylpyrimidine (from the respective phenylethynyl substrate),[1857] and others.[1182,1869,1890,3732,3733,4280,4665–4667] 5-Benzylidenepyrimidines have been used as mild oxidizing agents for aliphatic or aromatic thiols.[468]

4.2.1.8. Alkylpyrimidines by Other Procedures

Other procedures for making alkylpyrimidines are illustrated briefly in the following paragraphs.

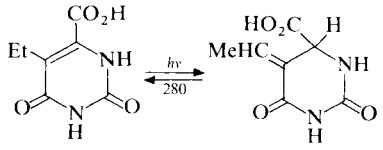
1. Treatment of 5-nitropyrimidine (**105**) with benzamidine or pivalamidine gave 5-nitro-2-phenyl- (**106**, R = Ph) (84%) or 2-*t*-butyl-5-nitropyrimidine (**106**, R = Bu^t) (87%), respectively, by a mechanism involving *ring fission and replacement* of the N1 + C2 + N3 part of the substrate (**105**);[2942] acetamidine or propionamidine (each with a mildly activated α-methylene grouping) gave 2-methyl- (**106**, R = Me) (46%) or 2-ethyl-5-nitropyrimidine (**106**, R = Et) (30%), respectively, each accompanied by an appropriate pyridine by-product;[2942] and 2-phenylacetamidine (with a strongly activated methylene) gave only the pyridine.[2942]



105 **106** **107** **108**

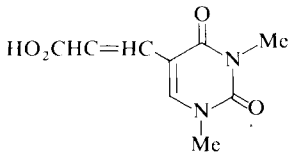
2. A virtually *irreversible prototropy* occurred when the quaternary salt, 1,4,6-trimethyl-2-phenylpyrimidinium tosylate (**107**), lost toluenesulfonic acid on treatment with potassium *t*-butoxide in an aprotic solvent to give 1,4-dimethyl-6-methylene-2-phenyl-1,6-dihydropyrimidine (**108**) (61%), a stable distillable

liquid with an appropriate nmr spectrum.[4668] In a different way, 5-ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (**109**) underwent prototropy on irradiation to give 5-ethylidene-2,6-dioxo-1,2,3,4,5,6-hexahydro-4-pyrimidinecarboxylic acid (**110**), characterized as it calcium salt by X-ray crystal analysis and other physical data;[214,215] the reaction proved thermally reversible at 280°.[215]



109 **110**

3. The reaction of *pyrimidinecarbaldehydes with methylene reagents* is unsuccessful except when the latter are strongly activated by appropriate attached groups. Thus simple styrylpyrimidines are not so available but some suitably substituted-alkenylpyrimidines can be made by this route. For example, 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde with malonic acid in refluxing pyridine gave (after spontaneous monodecarboxylation) 5-β-carboxyvinyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**111**) (78%);[95] 4-methyl-6-oxo-2-piperidino-1,6-dihydro-5-pyrimidinecarbaldehyde with *p*-nitrophenylacetic acid in piperidine at 150° gave (after spontaneous decarboxylation) 6-methyl-5-*p*-nitrostyryl-2-piperidino-4(3*H*)-pyrimidinone (**112**) (~75%);[682] and other examples have been reported.[95,682]



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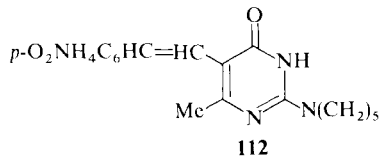
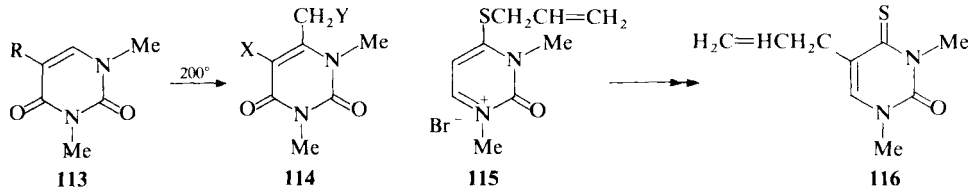


112

4. Several *thermal rearrangements* from *N*-, *O*-, or *S*-alkyl- into *C*-alkylpyrimidines have proved useful. For example, 5-allylamino- (**113**, R = $NHCH_2CH{:}CH_2$) or 5-benzyloxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**113**, R = OCH_2Ph) underwent thermal rearrangement in boiling tetralin to give 6-allyl-5-amino- (**114**, X = NH_2, Y = $CH{:}CH_2$) (24%) or 6-benzyl-5-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**114**, X = OH, Y = Ph) (31%);[854] and 4-allylthio-1,3-dimethyl-2-oxo-2,3-dihydropyrimidin-1-ium bromide (**115**) in acetonic methanol containing sodium carbonate rearranged into a methanol adduct, which lost methanol in boiling chloroform to give 5-allyl-1,3-dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**116**) (75% overall).[896] A variety of photochemical or thermal rearrangements from *S*-benzyl- to



5-benzylpyrimidines have been described briefly: for example, irradiation of 4-benzylthio-3-methyl-2(3*H*)-pyrimidinone in *t*-butanol gave, among other products, 5-benzyl-1-methyl-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone (45%).[4664] See also the last part of Section 7.4.2.2.

4.2.2. Physical Properties of *C*-Alkylpyrimidines

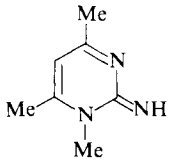
The simple alkylpyrimidines are liquids or low-melting solids similar to pyrimidine (Section 4.1.2) in properties and forming similar salts or complexes. The lower homologs are highly soluble in all manner of solvents but, as they are more lipophilic than the parent, they are more readily removed from aqueous solution by continuous extraction with chloroform or ether. As might be expected, their boiling and melting point rise with molecular weight, for example, from 2-methylpyrimidine (b.p. 138°/760 mm; m.p. − 5°) to 4,6-diphenylpyrimidine (b.p. 190°/0.01 mm; m.p. 103°). The methylpyrimidines are slightly stronger bases than pyrimidine: for example, 4-methyl- and 2,4,6-trimethylpyrimidine have pK_a 2.0 and 3.7, respectively.

4.2.3. Reactions of *C*-Alkylpyrimidines

The simple alkylpyrimidines undergo reactions analogous to those of pyrimidine (Section 4.1.3) as well as reactions directly involving their alkyl groups. When they occupy the 2- and/or the 4/6-positions, methyl (or methylene) groups are activated in the sense of that in 2,4-dinitrotoluene, but in the 5-position a methyl group almost resembles that in toluene itself.

4.2.3.1. Deuteration of Alkyl Groups

Deuterium exchange of the activated 2- or 4/6-methyl protons has been observed, but not of the (unactivated) *N*- or 5-methyl protons. Rates or $t_{1/2}$ values for such exchange under acidic or basic conditions have been reported for 4,6-dimethyl-, 4-methyl-2-methylamino-, and 4,6-dimethyl-2-methylaminopyrimidine;[2742] for 4-methyl-, 4,6-dimethyl-, 1,4-dimethyl-, 4,5,6-trimethyl-, 1,4,6-trimethyl-, and 1,4,5,6-tetramethyl-2(1*H*)-pyrimidinone;[2742,3660] for 1,4-dimethyl- and 1,4,6-trimethyl-2(1*H*)-pyrimidinimine;[2742] and for related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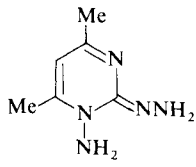
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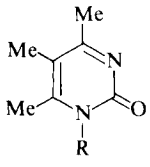

119

pyrimidines.[762,1142,3060,4670] Several of these exchange reactions were studied at 33° over a range of pH values: 1,4,6-trimethyl-2(1*H*)-pyrimidinimine (**117**)[2742] and 4,6-dimethyl-2-hydrazono-1,2-dihydro-1-pyrimidinamine (**118**),[1142] each showed marked acid–base catalysis from a minimal rate at *c* pH 4; in contrast, 4,5,6-trimethyl- (**119**, R = H) and 1,4,5,6-tetramethyl-2(1*H*)-pyrimidinone (**119**, R = Me) exhibited maximal rates at pH 4.5 and pH 5.0, respectively, apparently linked to the appropriate basic pK_a value for each compound.[3660] For comparison, rates for deuterium exchange of the (nuclear) C2 proton in analogous pyrimidinones and pyrimidinethiones were relatively slow (even at 90°) and virtually unaffected by pH changes or the addition of an *N*-methyl group.[4669] Deuteration of other alkyl groups appears to be confined to those protons adjacent to the pyrimidine ring.[4670]

4.2.3.2. Alkylidenation of Methyl Groups

The conversion of methyl- into styryl- or other (unsubstituted) alkylidenemethylpyrimidines has been noted in Section 4.2.1.7. Naturally, appropriately substituted aldehydes may be used similarly to afford alkylidenemethylpyrimidines bearing one or more extranuclear functional groups. The following styrylpyrimidines (condensing agent and yield are noted where available) were so made from appropriate methylpyrimidines and benzaldehyde derivatives.

6-*p*-Dimethylaminostyryl-2,4(1*H*,3*H*)-pyrimidinedione (in refluxing aniline: 30%).[4672]

4-*p*-Dimethylaminostyrylpyrimidine ($ZnCl_2$: ~60%).[4673]

4-*p*-Dimethylaminostyryl-6-methyl- or 4,6-bis(*p*-dimethylaminostyryl)-2(1*H*)-pyrimidinone (piperidine or HCl) according to the proportion of aldehyde used.[4673,4674]

2-Acetamido-4-*p*-dimethylaminostyryl-6-methylpyrimidine (Ac_2O: low yield).[4673]

6-*p*-Aminostyryl-5-nitro-2,4-pyrimidinediamine (HCl: 60%).[4676]

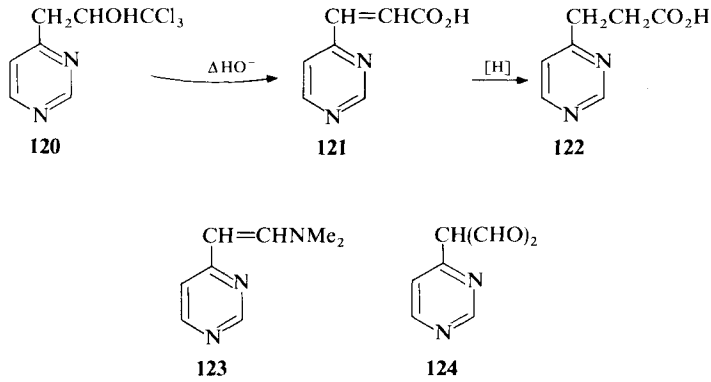
6-*p*-Methoxystyryl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (piperidine: 82%).[4677]

4-*p*-Nitrostyryl-2-pyrimidinamine (AcOH–H_2SO_4: ~85%).[4675]

4-*m*-Chlorostyrylpyrimidine (Ac_2O: 44%).[3451]

4-*m*-Chlorostyryl-2-pyrimidinamine (HCO_2H: 50%).[3451]
Also others.[246,1911,2694,3481,3980,6233]

Like formaldehyde (Section 4.2.1.7), chloral condensed with 2- or 4-methylpyrimidine in pyridine to give 2- (43%) or 4-(γ,γ,γ-trichloro-β-hydroxypropyl)-pyrimidine (**120**) (73%) without spontaneous dehydration to the corresponding alkenylpyrimidines:[1225] only in hot ethanolic alkali, did these products afford 2- (92%) or 4-β-carboxyvinylpyrimidine (**121**) (45%), which subsequently underwent hydrogenation to 2- (84%) or 4-β-carboxyethylpyrimidine (**122**) (75%), respectively.[1225] In contrast, 4-methylpyrimidine with dimethylformamide diethyl acetal, $Me_2NCH(OEt)_2$, or the phosgene–dimethylformamide complex gave immediately the unsaturated product, 4-β-dimethylaminovinylpyrimidine (**123**) (70% or 80%, respectively);[3599,4679] the same substrate with the foregoing complex (2 mol), followed by hydrolysis, gave 4-(diformylmethyl)pyrimidine (**124**) (47%).[2611,3599,4679] See also Section 4.2.3.8.



4.2.3.3. Oxidation of Alkylpyrimidines

Oxidation of appropriate *C*-alkylpyrimidines can give the corresponding carboxylic acids, carbaldehydes, alcohols, ketones, epoxides, or their derivatives. The formation of a carboxylic acid followed by decarboxylation (see Section 10.1.2) is the classical way to remove an unwanted alkyl group.

To pyrimidinecarboxylic acids. All 2- or 4/6-methyl groups are easily oxidized to the corresponding carboxy groups by permanganate or occasionally by selenium dioxide; 5- and *N*-methyl groups resist such oxidation; unsubstituted-phenyl groups (but not a fused benzene ring) appear to be immune; but hydroxyphenyl and some other substituted-phenyl groups are quite easily so oxidized. It is sometimes possible to oxidize part of a large alkenyl or a substituted-aryl group to afford a carboxyalkyl- or carboxyarylpyrimidine. The

following examples (with alkaline permanganate unless otherwise indicated) illustrate the foregoing possibilities.

4-Methylpyrimidine to 4-pyrimidinecarboxylic acid (45%;[1517] SeO_2 in pyridine: 80%[3447]).

4,6-Dimethylpyrimidine to 6-methyl-4-pyrimidinecarboxylic acid[1874] or 4,6-pyrimidinedicarboxylic acid (72%),[764,1874] according to the proportion of oxidant.

2,4-Dimethylpyrimidine to 2-methyl-4-pyrimidinecarboxylic acid (SeO_2 in pyridine: isolated as methyl 2-methyl-4-pyrimidinecarboxylate in 65% yield).[2692]

4,5-Dimethylpyrimidine to 5-methyl-4-pyrimidinecarboxylic acid only, despite an excess of oxidant.[1135]

4-Methyl-2-phenylpyrimidine to 2-phenyl-4-pyrimidinecarboxylic acid (42%).[1856]

4,6-Dimethyl-2-phenylpyrimidine to 6-methyl-2-phenyl-4-pyrimidinecarboxylic acid or 2-phenyl-4,6-pyrimidinedicarboxylic acid, according to the proportion of oxidant.[2467]

2-*p*-Hydroxyphenyl-4,6-dimethylpyrimidine to 4,6-dimethyl-2-pyrimidinecarboxylic acid (limited oxidant: ~30%).[1517]

Quinazoline (125) to 4,5-pyrimidinedicarboxylic acid (126) (~60%).[3606]

5-Bromo-2-styrylpyrimidine to 5-bromo-2-pyrimidinecarboxylic acid (in aqueous pyridine: 71%).[1935]

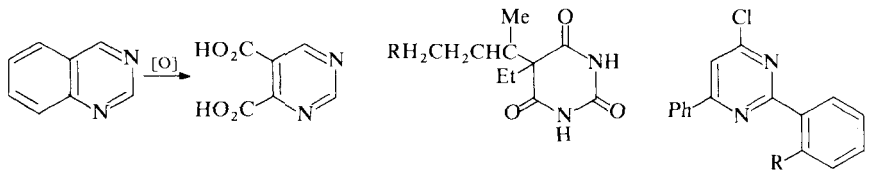
5-Chloro-2-methyl-4-pyrimidinecarboxylic acid to 5-chloro-2,4-pyrimidinedicarboxylic acid (fuming HNO_3).[1479]

2-Styryl- or 5-methyl-2-styrylpyrimidine to 2-pyrimidinecarboxylic acid or 5-methyl-2-pyrimidinecarboxylic acid, respectively (in aqueous pyridine).[2745]

2-Methyl-5-phenyl- or 5-phenyl-2-styrylpyrimidine to 5-phenyl-2-pyrimidinecarboxylic acid [SeO_2 in pyridine (61%) or $KMnO_4$ (68%), respectively].[379]

5-Butyl-2-methylpyrimidine to 5-butyl-2-pyrimidinecarboxylic acid (SeO_2 in pyridine: 27%).[3097]

5-Ethyl-5-(1′-methylpent-4′-enyl)- (**127**, R = CH:CH_2) to 5-(3′-carboxy-1′-methylpropyl)-5-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**127**, R = CO_2H) (RuO_4: 81%).[4680]



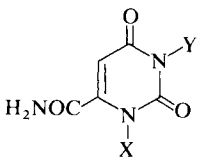
125 **126** **127** **128**

4-Chloro-6-phenyl-2-*o*-tolylpyrimidine (**128**, R = Me) to 2-*o*-carboxyphenyl-4-chloro-6-phenylpyrimidine (**128**, R = CO_2H) ($K_2Cr_2O_7$ in AcOH–H_2SO_4: 45%) with 2-*o*-carboxyphenyl-6-phenyl-4(3*H*)-pyrimidinone (22%) as a by-product.[4127]

6-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione to 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (fuming HNO_3 at 100°: ~80%).[2994]

3-Ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione to 1-ethyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (fuming HNO_3 + H_2SO_4: 43%).[4681]

The direct conversion of a methyl into an amide-type group is exemplified in the oxidation of 6-methyl-, 1,6-dimethyl-, or 1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione with potassium ferricyanide in ammonia to afford 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**129**, X = Y = H),[2872] the 3-methyl derivative (**129**, X = Me, Y = H) (~45%),[2673] or the 1,3-dimethyl derivative (**129**, X = Y = Me) (~40%),[2673] respectively; also of 4-methylpyrimidine with sulfur in a neat primary aromatic amine under reflux to give *N*-phenyl-4-pyrimidinecarbothioamide (**130**) (59%), the *N*-*p*-tolyl (46%), and other analogs.[4682]



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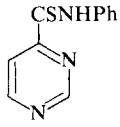

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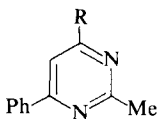

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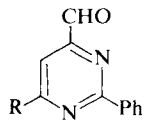
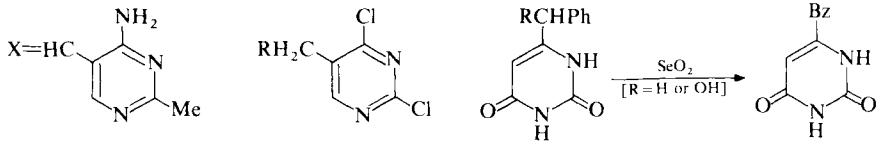


132

To pyrimidinecarbaldehydes. Any activated 2-(?) or 4/6-methyl group on a pyrimidine ring may be oxidized by a single molar equivalent of *selenium dioxide* to afford a formyl group. Thus 2,4-dimethyl-6-phenylpyrimidine (**131**, R = Me) gave 2-methyl-6-phenyl-4-pyrimidinecarbaldehyde (**131**, R = CHO) (90%);[4683] 4,6-dimethyl-2-phenylpyrimidine (with 1 or 2 mol of oxidant) gave 6-methyl-2-phenyl-4-pyrimidinecarbaldehyde (**132**, R = Me) (43%) or 2-phenyl-4,6-pyrimidinedicarbaldehyde (**132**, R = CHO) (45%), respectively;[4683] and similar procedures gave 2-phenyl- (**132**, R = H) (79%),[4684] 2,6-dioxo-1,2,3,6-tetrahydro- (32–58%),[2858,2860,2861] 5-methyl-2,6-dioxo-1,2,3,6-tetrahydro- (94%),[2858] and 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde (~25%, via its acetal).[2669]

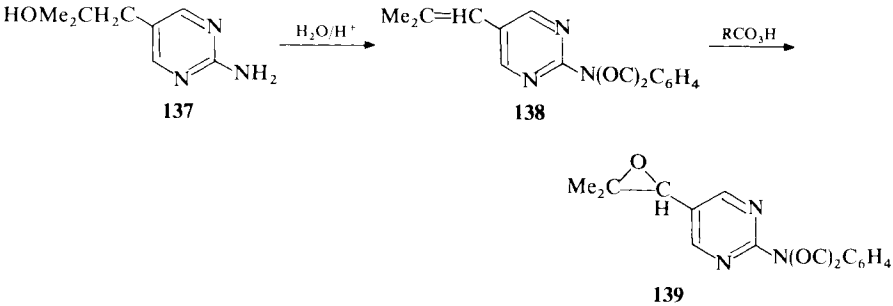
The *ozonolysis* of *C*-alkenylpyrimidines can also give pyrimidinecarbaldehydes. Thus 2,4,6-tristyrylpyrimidine gave 2,4,6-pyrimidinetricarbaldehyde (isolated as its *p*-nitrophenylhydrazone);[3640] 5-*β*-ethoxyvinyl-2-methyl-4-pyrimidinamine (**133**, X = CHOEt) gave 4-amino-2-methyl-5-pyrimidinecarbaldehyde (**133**, X = O);[1463] 5-allyl-4,6-dichloropyrimidine (**134**,

R = CH:CH_2) gave 2,4-dichloro-5-formylmethylpyrimidine (**134**, R = CHO) (59%);[888] and two styrylated pyrimidines of uncertain structure likewise gave aldehydes.[1611,2757]



133 **134** **135** **136**

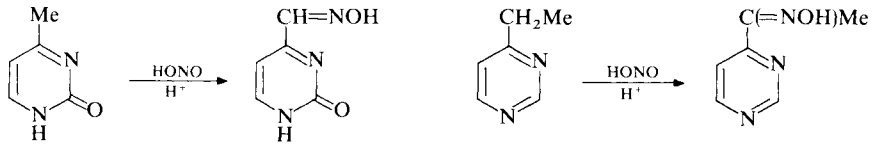
To pyrimidine alcohols, ketones, or epoxides. Such partial oxidations of alkylpyrimidines are exemplified by the conversion of 6-benzyl- (**135**, R = H) into 6-α-hydroxybenzyl-2,4(1*H*,3*H*)-pyrimidinedione (**135**, R = OH) (SeO_2, 1 mol: 38%) or into 6-benzoyl-2,4(1*H*,3*H*)-pyrimidinedione (**136**) (SeO_2, 2 mol: 31%);[4685] of 2-methyl-4-propyl- into 2-methyl-4-propionylpyrimidine (SeO_2: 20%);[122] of 4-*p*-methoxybenzyl- into 4-*p*-methoxybenzoyl-2(1*H*)-pyrimidinone (SeO_2 in AcOH: 35%);[439] of 5-(3′,4′,5′-trimethoxybenzyl)- into 5-(3′,4′,5′-trimethoxybenzoyl)-2,4-pyrimidinediamine (MnO_2 in AcOH: 56%);[4686,5617] of 5-(2′-methylprop-1′-enyl)-2-phthalimidopyrimidine (**138**) into 5-(1′,2′-epoxy-2′-methylpropyl)-2-phthalimidopyrimidine (**139**) (*m*-$ClC_6H_4CO_3H$ in CH_2Cl_2 at 0°: 51%) or (by hydration rather than oxidation) into the alcohol, 5-(2′-hydroxy-2′-methylpropyl)-2-pyrimidinamine (**137**) (hot aqueous H_2SO_4: 20%);[4687] and of 2-isopropenyl-4-phenylpyrimidine into 2-(1′,2′-epoxy-1′-methylethyl)-4-phenylpyrimidine (*m*-$ClC_6H_4CO_3H$ in hot $CHCl_3$: 85%).[1908] Treatment of 5-methyl-, 1,5-dimethyl-, 3,5-dimethyl-, or 1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione with hot aqueous sodium persulfate (1 mol) gave 5-hydroxymethyl-, 5-hydroxymethyl-1-methyl- (30%), 5-hydroxymethyl-3-methyl-, or 5-hydroxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (38%), respectively; the same oxidant (2 mol) gave 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde (41%), its 1-methyl derivative (62%), its 3-methyl derivative (58%), or its 1,3-dimethyl derivative (80%), respectively.[323] The oxidation of 5-benzylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with chromium trioxide gave the nuclear ketone, 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (alloxan), in >50% yield.[192] See also Section 10.7.1.



137 **138** **139**

To pyrimidine aldoximes or ketoximes. Activated methylpyrimidines undergo α-nitrosation under acidic conditions, followed by immediate prototropy to the corresponding aldoximes; the same products may be formed from the same substrates by Claisen reaction with a nitrite ester in the presence of a strong base. Homologous alkylpyrimidines may also react by either route to afford ketoximes.

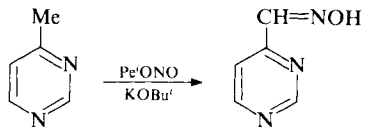
Procedures under *acidic conditions* are typified by treatment of the hydrochloride of 4-methyl-2(1*H*)-pyrimidinone (**140**) in aqueous acetic acid at 15° with sodium nitrite to give 2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde oxime (**141**) (79%).[1628,1630] Made likewise were 6-methyl-2-oxo-1,2-dihydro- (45–66%),[1628,2267] 2-oxo-6-phenyl-1,2-dihydro- (73%),[2267] 1-methyl-2-oxo-1,2-dihydro- (56%),[3400] and 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime (at 70°: ~ 75%),[1165] as well as analogs.[2257] Using a slightly different procedure, 4,6-dimethylpyrimidine hydrochloride with an alkyl nitrite (1 or 2 mol) in anhydrous ethanol (with or without some additional hydrogen chloride) gave 6-methyl-4-pyrimidinecarbaldehyde oxime (78%)[1745] or 4,6-pyrimidinedicarbaldehyde dioxime (40%),[836] respectively; 4-methylpyrimidine gave 4-pyrimidinecarbaldehyde oxime (85%);[826] and 2,6-dimethyl-4-pyrimidinecarbaldehyde oxime (51%) was made similarly.[1745] 4-Ethylpyrimidine (**142**) likewise gave the ketoxime, 4-acetylpyrimidine oxime (**143**) (78%);[826] 4-ethyl-2-methylpyrimidine gave 4-acetyl-2-methylpyrimidine oxime (67%) and thence, by treatment with ethanolic pyruvic acid containing hydrogen chloride, free 4-acetyl-2-methylpyrimidine (30%);[122] and 2-phenyl-4-propylpyrimidine gave 2-phenyl-4-propionylpyrimidine oxime (92%).[122]



140 **141** **142** **143**

The alternative (Claisen) procedure in the *presence of a strong base* is illustrated in the following examples.

4-Methylpyrimidine (**144**) with isopentyl nitrite and potassium *t*-butoxide, sodium hydride, or sodium amide gave 4-pyrimidinecarbaldehyde oxime (**145**) (40%,[3599] 10%,[3601] or 15%,[3601] respectively).



144 **145**

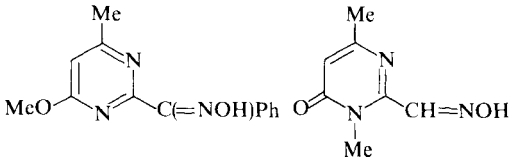
1,3,6-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione with isopentyl nitrite in ether containing potassium methoxide gave 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime (70%).[1735]

4-Methoxy-2,6-dimethylpyrimidine with sodium amide in liquid ammonia followed by ethyl nitrite gave 6-methoxy-2-methyl-4-pyrimidinecarbaldehyde oxime (63%).[3048]

4,6-Dimethylpyrimidine gave 6-methyl-4-pyrimidinecarbaldehyde oxime ($NaNH_2$, NH_3, Pe^iONO: 84%);[2525] also analogs.[3762]

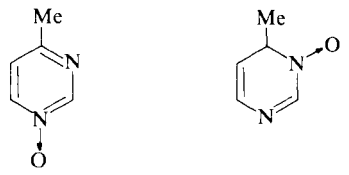
2-Benzyl-4-methoxy-6-methylpyrimidine gave 2-benzoyl-4-methoxy-6-methylpyrimidine oxime (**146**) (likewise: 74%; note reaction at the more activated benzyl group in substrate).[2525]

2,3,6-Trimethyl-4(3*H*)-pyrimidinone gave 1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinecarbaldehyde oxime (**147**) (likewise: 74%), rather than the expected isomeric 4-carbaldehyde oxime.[2522]



146 **147**

To alkylpyrimidine N-oxides. Simple alkylpyrimidines (without additional functional groups) undergo *N*-oxide formation rather more effectively than does pyrimidine itself. Thus treatment of appropriate methylpyrimidines in glacial acetic acid with hydrogen peroxide gave 2-methyl- (31%),[3439] 5-methyl- (36%),[3439] 4,6-dimethyl- (57–75%),[764,836] or 2,4,6-trimethylpyrimidine 1-oxide (30%).[3439] Similar treatment of unsymmetrical substrates can, of course, lead to two possible mono-*N*-oxides in each case: for example, although 4-methylpyrimidine was thought initially to give a single *N*-oxide of unknown configuration,[836,2762,3439,3633,4688–4690] the product was shown eventually to be a separable mixture of 4-methylpyrimidine 1- (**148**) and 3-oxide (**149**) in a ratio of 2 : 7;[3443] 2,4-dimethylpyrimidine gave, not a single *N*-oxide,[2762] but (with *m*-$ClC_6H_4CO_3H$) a separable mixture of its 1- (35%) and 3-oxide (32%);[121,4691] and other such substrates behaved similarly. 2-Phenylpyrimidine gave its 1-oxide (6%) among other products;[4691] 4-phenylpyrimidine gave its 1-oxide (24%) but no detectable 3-oxide.[4691] See also Section 7.6.1.1.



148 **149**

4.2.3.4. Reduction of Alkenyl- and Alkynylpyrimidines

Such reductions have been covered fully in Section 4.2.1.7.

4.2.3.5. Halogenation of Alkylpyrimidines

Simple alkylpyrimidines undergo α-halogenation more easily than 5-halogenation, although both may occur if conditions are sufficiently vigorous; in contrast, alkylpyrimidines bearing additional electron-donating groups undergo 5-halogenation more easily than α-halogenation. In either case it is not easy to limit α-halogenation to the monostage. The following reactions typify various processes for the *halogenation of methyl* groups.

Simple methylpyrimidines

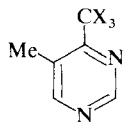
2-Methylpyrimidine gave 5-bromo-2-tribromomethylpyrimidine (Br_2 in AcOH–AcONa at 90°: 46%);[729,1974] a separable mixture of 2-bromomethyl- (19%), 2-dibromomethyl- (41%), and some 2-tribromomethylpyrimidine [*N*-bromosuccinimide (NBS) + Bz_2O_2 in boiling CCl_4];[1933] or a separable mixture of 2-chloromethyl- (10%), 2-dichloromethyl- (25%), 2-trichloromethyl-, and 5-chloro-2-methylpyrimidine [*N*-chlorosuccinimide (NCS) as above].[1933]

4-Methylpyrimidine gave 4-tribromomethyl- (77%) or 4-trichloromethylpyrimidine (79%) (Br_2 or Cl_2 in Ac_2O–AcONa–AcOH at 80°);[3605] 4-trichloromethylpyrimidine ($POCl_3$–PCl_5 at 125°: 51%);[2654] a separable mixture of 4-bromomethyl- (15%), 4-dibromomethyl- (30%), and some 4-tribromomethylpyrimidine (NBS in CCl_4 at 60°);[1933] or a separable mixture of 4-chloromethyl- (10%), 4-dichloromethyl- (30%), 4-trichloromethyl-, and 5-chloro-4-methylpyrimidine (NCS as above).[1933]

2,4-Dimethylpyrimidine gave 2-methyl-4-trichloromethylpyrimidine (refluxing $POCl_3$–PCl_5: 53%).[2654]

4,6-Dimethylpyrimidine gave 4,6-bistribromomethylpyrimidine (Br_2 in Ac_2O–AcONa–AcOH at 80°: 39%).[764]

4,5-Dimethylpyrimidine gave 5-methyl-4-trichloromethyl- (**150**, X = Cl) (59%) or 5-methyl-4-tribromomethylpyrimidine (**150**, X = Br) (85%) (Cl_2 or Br_2 likewise).[3605]



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4-Methyl-2-phenylpyrimidine gave 2-phenyl-4-trichloromethylpyrimidine (refluxing $POCl_3$–PCl_5).[4695]

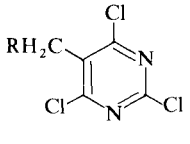
4-Methyl-6-phenylpyrimidine gave 4-bromomethyl-6-phenylpyrimidine (Br_2 in AcOH at 100°: 60%).[4641]

2-Methyl-5-phenylpyrimidine gave 5-phenyl-2-tribromomethylpyrimidine (Br_2 in boiling AcOH–AcONa: ~ 65%).[379]

Methylpyrimidines with functional groups

2-Chloro-5-methylpyrimidine hydrochloride gave 2-chloro-5-trichloromethylpyrimidine (NCS in CCl_4 with light: 40%; or SO_2Cl_2 with light: 65%).[117]

2,4,6-Trichloro-5-methylpyrimidine (**151**, R = H) gave 5-bromomethyl-2,4,6-trichloropyrimidine (**151**, R = Br) (NBS + Bz_2O_2 in boiling CCl_4: 78%; or Br_2 in boiling CCl_4 in light: 85%).[1801]



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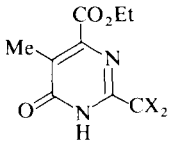

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Ethyl 2,4-dichloro-6-methyl-5-pyrimidinecarboxylate gave ethyl 2,4-dichloro-6-chloromethyl- (30%) and ethyl 2,4-dichloro-6-dichloromethyl-5-pyrimidinecarboxylate (30%) (SO_2Cl_2 at 100° or Cl_2 into neat ester at 90°) or only the latter product (Cl_2 at 135°: 84%);[2958] also two other products from further chlorination at 200° in light.[2958]

Ethyl 2,5-dimethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate (**152**, X = H) gave ethyl 5-methyl-6-oxo-2-tribromomethyl-1,6-dihydro-4-pyrimidinecarboxylate (**152**, X = Br) (Br_2 in AcOH–AcONa under reflux: 92%).[2038]

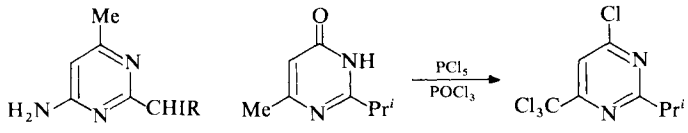
Methyl 5-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate gave its 5-bromomethyl analog (Br_2 in hot PhH in light: 69%).[2627]

5-Acetyl-4-methyl-2-phenylpyrimidine gave its 4-bromomethyl analog (Br_2 in $CHCl_3$ with light: 92%).[4693]

3-Isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave its 6-trichloromethyl analog (SO_2Cl_2 in Ac_2O–AcOH at 50° for 1 h: 63%) or 5-chloro-6-dichloromethyl-3-isopropyl-2,4(1*H*,3*H*)-pyrimidinedione (by rearrangement on continued heating for 5 h).[4390]

2,6-Dimethyl-4-pyrimidinamine gave 2-iodomethyl- (**153**, R = H) (67%) or 2-diiodomethyl-6-methyl-4-pyrimidinamine (**153**, R = I) (52%) (I_2 and H_2O_2 in CCl_4 + aqueous H_2SO_4, according to the proportions).[3748]

2-Isopropyl-6-methyl-4(3*H*)-pyrimidinone (**154**) gave 4-chloro-2-isopropyl-6-trichloromethylpyrimidine (**155**) ($POCl_3$–PCl_5 at 120°: 84%).[2496]

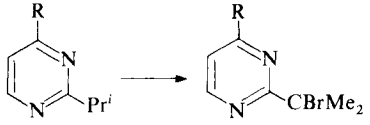


153 **154** **155**

5-Bromo-3-s-butyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave only its 6-chloromethyl analog ($POCl_3$–PCl_5: ~ 15%).[4390]

Also other examples.[1796,1903,1939,2496,3974,4694,6133]

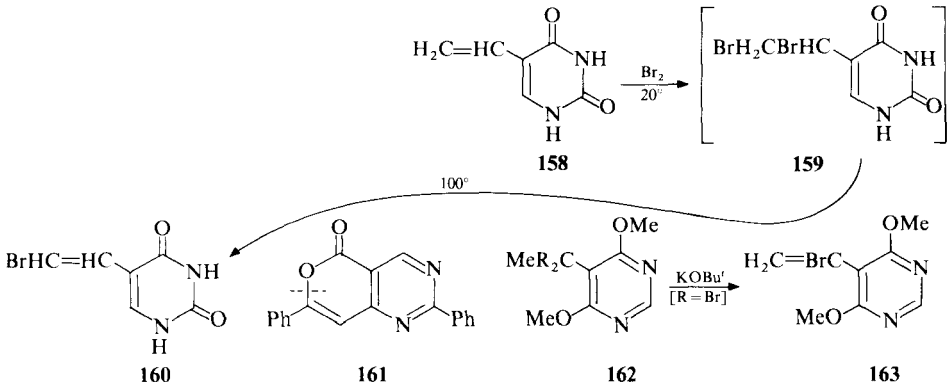
Although *halogenation of higher alkyl* groups takes place less readily than that of methyl groups, the process has proved useful. For example, 4- or 5-ethylpyrimidine with *N*-bromosuccinimide and benzoyl peroxide in boiling carbon tetrachloride (under intense irradiation for the latter substrate) gave 4- (90%) or 5-α-bromoethylpyrimidine (~ 85%), respectively;[1226] 2-isopropylpyrimidine (**156**, R = H) or its 4-phenyl derivative (**156**, R = Ph), similarly (but without light) gave 2-(α-bromo-α-methylethyl)pyrimidine (**157**, R = H) (60%) or its 4-phenyl derivative (**157**, R = Ph) (> 95%), respectively;[1908] 4-chloro- (**156**, R = Cl) or 4-fluoro-2-isopropylpyrimidine (**156**, R = F) likewise gave 2-(α-bromo-α-methylethyl)-4-chloro- (**157**, R = Cl) (~ 50%) or 2-(α-bromo-α-methylethyl)-4-fluoropyrimidine (**157**, R = F) (77%);[1907] 4,6-dichloro-5-ethyl- or 5-ethyl-4,6-dimethoxypyrimidine similarly (and apparently without light) gave 5-α-bromoethyl-4,6-dichloropyrimidine (85%) or its 4,6-dimethoxy analog (crude: 85%), respectively;[3105] 5-isobutyl-2-phthalimidopyrimidine similarly (with light) gave 5-(α-bromo-β-methylpropyl)-2-phthalimidopyrimidine (53%);[4687] and 2,4,6-trifluoro-5-isopropylpyrimidine likewise (with light) gave 5-(α-bromo-α-methylethyl)-2,4,6-trifluoropyrimidine.[3952] Other examples have been reported.[3895]



156 **157**

The *halogenation of alkenyl groups* probably always begins with addition, sometimes followed by spontaneous or base-induced loss of hydrogen halide to reform the double bond. For example, 2-methoxy-4,5-diphenyl-6-styrylpyrimidine with bromine in chloroform gave simply 4-α,β-dibromophenethyl-2-methoxy-5,6-diphenylpyrimidine;[4696] 5-vinyl-2,4(1*H*,3*H*)-pyrimidinedione (**158**) with bromine in dimethylformamide at 20° gave the addition product (**159**) (detected but not isolated), which lost hydrogen bromide on heating the solution at 100° to give 5-β-bromovinyl-2,4(1*H*,3*H*)-pyrimidinedione (**160**) (85%);[831] and 5-allyl- gave 5-β,γ-dibromopropyl-4-β-

hydroxyethylamino-2,6-dimethylpyrimidine (67%) on treatment with bromine in chloroform.[889] Bromination of 2-phenyl-4-styryl-5-pyrimidinecarboxylic acid in hot acetic acid probably gave a 4-α,β-dibromophenethyl intermediate that underwent spontaneous cyclization to afford 2,7-diphenyl-5*H*-pyrano[4,3-*d*]-pyrimidin-5-one (**161**) (67%).[4697, cf. 107] For comparison, 5-ethyl-4,6-dimethoxypyrimidine (**162**, R = H) underwent dibromination (NBS + Bz_2O_2 in CCl_4 with light) to give the α,α-dibromo derivative (**162**, R = Br), which lost hydrogen bromide in hot butanolic potassium *t*-butoxide to afford 5-α-bromovinyl-4,6-dimethoxypyrimidine (**163**) (56%).[3105] Other cases have been reported.[3981]



4.2.3.6. Claisen Reactions of Alkylpyrimidines

The Claisen reactions of alkylpyrimidines with nitrite esters to afford nitrosoalkylpyrimidines, tautomeric with pyrimidine aldoximes or ketoximes, have been discussed already in Section 4.2.3.3. Regular Claisen reactions of methylpyrimidines with carboxylate esters (or acyl halides) have also been used: activated 2- or 4/6-methyl groups but not 5- or *N*-methyl groups undergo the reaction; when the substrate bears two or three active methyl groups, only one (usually at the 4/6-position) reacts; and electron-donating groups slow the reaction while electron-withdrawing groups accelerate it. The scope and conditions of such reactions are illustrated in the preparation (from appropriate methylpyrimidines) of the following products (usually in ether: ester and base given in parentheses).

2-Ethoxalylmethylpyrimidine (**164**) (diethyl oxalate, KOEt: 38%).[1735]

4-Ethoxalylmethylpyrimidine (diethyl oxalate, KOEt: 60%).[1735]

4-Ethoxalylmethyl-2,6-dimethylpyrimidine (**165**, R = CO_2Et) (diethyl oxalate, KOEt: 43%;[1735] $NaNH_2$: 12%[1611]).

2,4-Dimethyl-6-phenacylpyrimidine (**165**, R = Ph) (ethyl benzoate, $NaNH_2$ in PhH: ~ 50%).[1611]

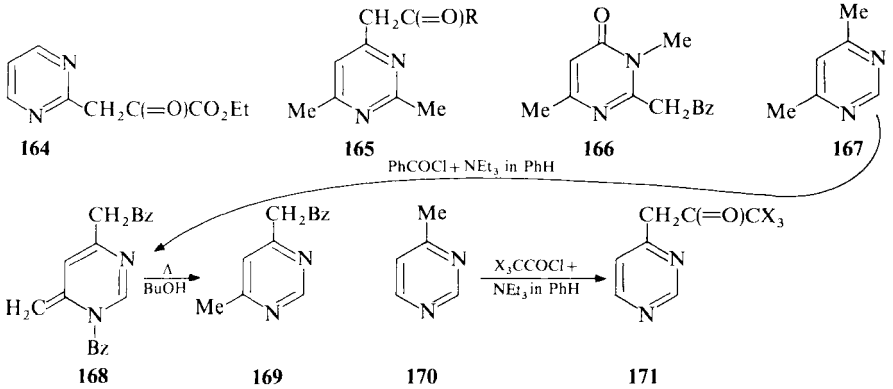
4-Acetonyl-2,6-dimethylpyrimidine (**165**, R = Me) (ethyl acetate, $NaNH_2$ in Et_2O–PhH: 31%).[1611]

4-Ethoxalylmethyl-2,6-diethoxy-5-nitropyrimidine (diethyl oxalate, NaOEt: 91%).[4699]

4,6-Dibenzyloxy-2-ethoxalylmethylpyrimidine (diethyl oxalate, KOEt in Et_2O–pyridine: 38%).[595]

3,6-Dimethyl-2-phenacyl-4(3*H*)-pyrimidinone (**166**) (ethyl benzoate, NaOEt in PhH: 46%; note unusual regioselectivity: orientation checked).[2522]

Also other examples.[686,1735,4698,4703,6197]



An interesting use of acyl chlorides in place of esters is exemplified in the treatment of 4,6-dimethylpyrimidine (**167**) with benzoyl chloride in benzene containing triethylamine to give 1-benzoyl-6-methylene-4-phenacyl-1,6-dihydropyrimidine (**168**) (78%), which debenzoylated in boiling butanol to afford 4-methyl-6-phenacylpyrimidine (**169**) (84%);[4700] the *p*-methoxyphenacyl (16%),[4700] *p*-chlorophenacyl (67%),[4700] and other analogs[4641,4702,5987] were obtained by using similar procedures; 4-methylpyrimidine (**170**) reacted with trichloro- or trifluoroacetyl chloride in benzene containing triethylamine to afford 4-γ,γ,γ-trichloroacetonyl- (**171**, X = Cl) (63%) or 4-γ,γ,γ-trifluoroacetonylpyrimidine (**171**, X = F) (16%), respectively;[4701] and both 2-trihalogenoacetonyl isomers were made similarly but in lower yields.[4701] The 5-acylation of 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione and related substrates might be considered akin to a Claisen reaction (see Section 10.7.1).

4.2.3.7. Mannich Reactions of Methylpyrimidines

Simple methylpyrimidines undergo one (or more) Mannich reactions at their activated methyl group(s), but, in the presence of electron-donating groups, the reaction may take place (instead or as well) at any unoccupied nuclear carbon atom. The scope of such reactions is indicated by the following examples in

which the substrate was usually warmed with formaldehyde (as formalin or paraformaldehyde) and an appropriate secondary amine in acidified aqueous or alcoholic solution.

4-Methylpyrimidine gave 4-β-dimethylaminoethylpyrimidine (**172**, R = H) (70%).[2078]

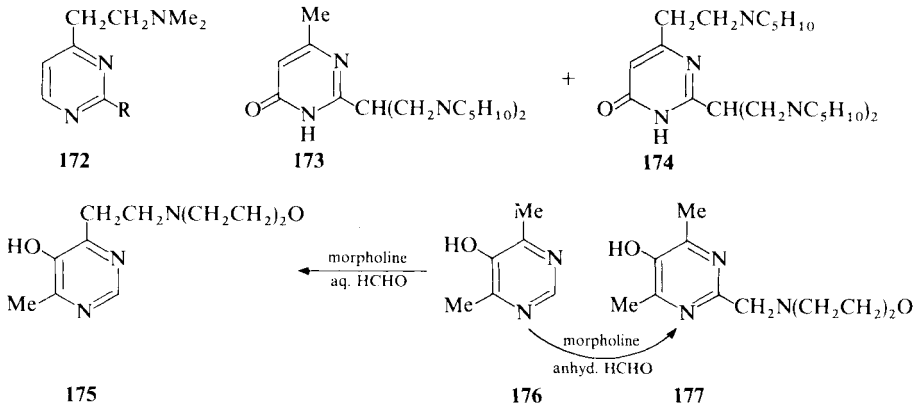
2-Dimethylamino-4-methylpyrimidine gave 2-dimethylamino-4-β-dimethylaminoethylpyrimidine (**172**, R = NMe_2) (72%).[2078]

2,6-Dimethyl-4(3*H*)-pyrimidinone gave a separable mixture of 2-di(piperidinomethyl)methyl-6-methyl- (**173**) (41%) and 2-di(piperidinomethyl)methyl-6-β-piperidinoethyl-4(3*H*)-pyrimidinone (**174**) (10%), with the likely structures based on degradative experiments.[3306]

4-Ethoxy-6-methylpyrimidine 1-oxide gave 4-di(piperidinomethyl)methyl-6-ethoxylpyrimidine 3-oxide (45%).[4657]

4,4,6-Trimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione gave 4-bis(dimethylaminomethyl)methyl-6,6-dimethyl-3,6-dihydro-2(1*H*)-pyrimidinethione (~ 40%).[4705]

4,6-Dimethyl-5-pyrimidinol (**176**) gave 4-methyl-6-β-morpholinoethyl- (**175**) (aqueous medium: 21%) or 4,6-dimethyl-2-morpholinomethyl-5-pyrimidinol (**177**) (anhydrous medium: 40%).[4704]

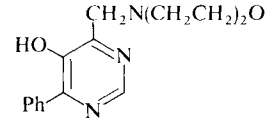


4-Phenyl-5-pyrimidinol gave 4-morpholinomethyl-6-phenyl-5-pyrimidinol (**178**) (in boiling PhCl: 66%).[23]

5-Hydroxy-2-methyl-4(3*H*)-pyrimidinone gave its 6-piperidinomethyl derivative (65%).[2628,4707]

6-Methyl-2-methylthio-4(3*H*)-pyrimidinone gave only its 5-piperidinomethyl derivative (**179**) (> 90%).[3498]

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione gave only its 5-*N*-(β-chloroethyl) aminomethyl (**180**, R = H) (20%)[4708] or 5-*N*,*N*-bis(β-chloroethyl)aminomethyl derivative (**180**, R = CH_2CH_2Cl) (58%),[4709] according to the primary or secondary amine used.



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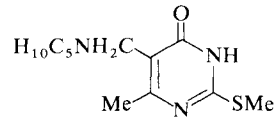

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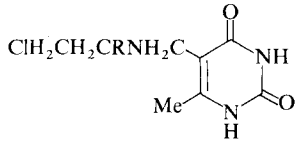

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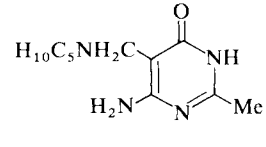


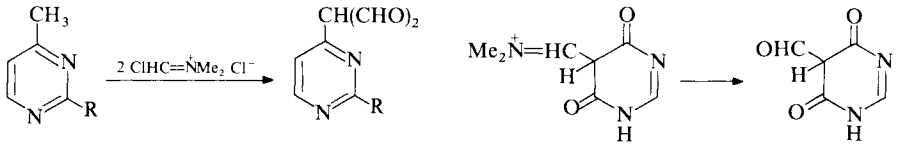
181

6-Amino-2-methyl-4(3*H*)-pyrimidinone gave its 5-piperidinomethyl derivative (**181**) (~ 60%).[1158]

Also other examples.[490,693,4706,4977,6418] See also Section 9.1.4.4.

4.2.3.8. Vilsmeier Reactions of Methylpyrimidines

The conversion of 4-methyl- into 4-diformylmethylpyrimidine by a Vilsmeier reagent has been mentioned at the end of Section 4.2.3.2. In a similar way, 4-methyl-2-phenylpyrimidine (**182**, R = Ph) with dimethylformamide–phosphoryl chloride, or chloromethylenedimethylammonium chloride (2 mol), followed by hydrolysis of the uncharacterized product, gave 4-diformylmethyl-2-phenylpyrimidine (**183**, R = Ph) (62%);[2611] and 4-methyl-2-methylthiopyrimidine (**182**, R = SMe) with dimethylformamide–phosgene (equivalent to the same reagent in situ) likewise gave 4-diformylmethyl-2-methylthiopyrimidine (**183**, R = SMe) (35%).[4121] When the substrate bears no appropriately activated methyl group but does have a free 5-position, a Vilsmeier reagent may insert a single 5-formyl group: for example, 4,6(1*H*,5*H*)-pyrimidinedione with dimethylformamide–phosphoryl chloride in chloroform at 60° gave 5-dimethylimmoniomethyl-4,6(1*H*,5*H*)-pyrimidinedione (**184**) (~ 90%), which underwent hydrolysis to 4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarbaldehyde (**185**);[2681] other examples are given in Section 10.6.1.

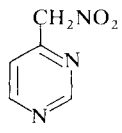


182 183 184 185

4.2.3.9. Other Reactions of Alkyl Groups

The remaining reactions of alkyl or aryl groups attached to pyrimidine are of limited importance but are exemplified briefly here.

Nitration. Simple alkylpyrimidines do not undergo regular nitration on the alkyl group or at the 5-position. However, 4-methylpyrimidine underwent de facto nitration by a Claisen reaction (involving treatment in liquid ammonia–sodium amide with propyl nitrate) to afford 4-nitromethylpyrimidine (**186**) (71%).[3542] In contrast, even simple phenylpyrimidines do undergo nitration in the phenyl group. It was reported initially that nitration of 4-phenylpyrimidine gave only its *m*-nitro derivative (**187**, X = Z = H, Y = NO_2),[2212] but subsequent work revealed that the *o*- (**187**, X = Y = H, Z = NO_2) and the *p*-isomer (**187**, X = NO_2, Y = Z = H) were formed also and that the ratio of the three isomers depended on the nitrating agent and the conditions employed.[4710,4711] Moreover, any addition of functional groups to the pyrimidine ring profoundly affected the orientation of products derived from nitration (see Section 5.1.1.2). A mononitro derivative,[4663] obtained by nitration of 4,6-dimethyl-2-phenylpyrimidine, was later shown to be the *m*-nitro isomer by unambiguous synthesis.[2212]



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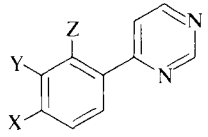

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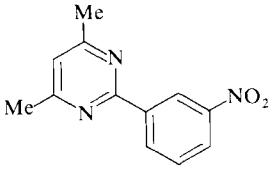
Nitrosation. The α-nitrosation of alkylpyrimidines to afford pyrimidine aldoximes or ketoximes, using either regular (acidic) or Claisen (basic) procedures, has been covered towards the end of Section 4.2.3.3.

Diazo coupling. Although diazotized amines prefer to couple with pyrimidines at the 5- or occasionally the 4-position, such coupling can, in some cases, occur at an activated methyl substituent. For example, 4-methyl- or 4,6-dimethyl-2(1*H*)-pyrimidinone with *p*-chlorobenzenediazonium chloride in an aqueous medium gave 2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde *p*-chlorophenylhydrazone (**188**, R = H) (> 98%) or its 6-methyl derivative (**189**, R= Me) (> 98%).[4712] See also Section 5.3.1.2.



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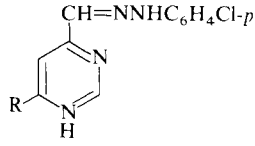

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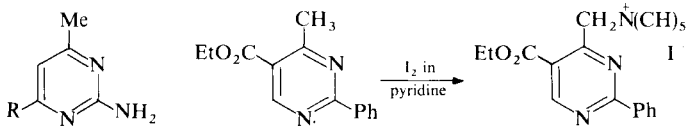
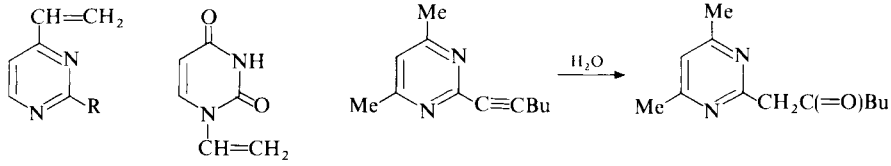
Amination. Regular Chichibabin amination of alkylpyrimidines appears to insert amino groups at unoccupied 2- and/or 4/6-positions but never at the 5- or α-positions. For example, treatment of 4-methylpyrimidine with sodium amide

in hot decalin gave a mixture of 4-methyl-2-pyrimidinamine (**190**, R = H) and 6-methyl-2,4-pyrimidinediamine (**190**, R = NH_2);[3449] 4-phenylpyrimidine in liquid ammonia containing sodium amide and some potassium nitrate gave a separable mixture of 4-phenyl-2-pyrimidinamine (60%) and 6-phenyl-4-pyrimidinamine (15%);[4713,4714] 5-phenylpyrimidine likewise gave 5-phenyl-2- and 5-phenyl-4-pyrimidinamine, each in > 45% yield allowing for a considerable recovery of substrate;[534] and 4-*t*-butylpyrimidine likewise gave 4-*t*-butyl-2- (25%) and 6-*t*-butyl-4-pyrimidinamine (30%).[4714] One apparent α-amination probably involved iodination followed by aminolysis: ethyl 4-methyl-2-phenyl-5-pyrimidinecarboxylate (**191**) in boiling pyridine containing iodine gave ethyl 2-phenyl-4-pyridiniomethyl-5-pyrimidinecarboxylate iodide (**192**) (86%).[4715] The attack of 4-phenyl-1,2,4-triazoline-3,5-dione on the 6-methyl group of 5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione to afford 6-(3′,5′-dioxo-4′-phenyl-1′,2′,4′-triazolidin-1′-yl)methyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (18%) is, perhaps, a more legitimate α-amination at least on paper.



190 **191** **192**

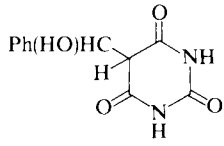
Polymerization. The polymerization (in the presence of 2,2′-azobisisobutyronitrile) and the copolymerization (with styrene) of 4-vinylpyrimidine (**193**, R = H) or its 2-dimethylamino derivative (**193**, R = NMe_2) have been studied.[2078,2666] The radical-induced formation of a poly[1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione] from its monomer (**194**) and the binding of adenosine derivatives by the polymer have been reported.[2903] The area has been reviewed in context.[4716]



193 **194** **195** **196**

Hydration. The addition of water across an alkenyl or alkynyl group affords an alcohol or ketone, respectively. Such hydration (in acidic solution) of 5-(2′-methylprop-1′-enyl)-2-phthalimidopyrimidine (**138**) to 5-(2′-hydroxy-2′-methylpropyl)-2-pyrimidinamine (**137**)[4687] has been mentioned (Section 4.2.3.3); in addition, 2-hex-1′-ynyl-4,6-dimethylpyrimidine (**195**), in refluxing aqueous acetone containing sulfuric acid and mercuric sulfate, gave 4,6-dimethyl-2-valerylmethylpyrimidine (**196**) (67%);[4655] and, in a rather analogous way, 5-

benzylidene- rapidly gave 5-α-hydroxybenzyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**197**) (80%) in cold alkali.[4649] Other additions have been reported.[362,6198]



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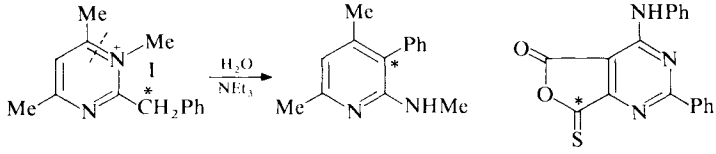

198 **199** **200**

Cyclization. Alkyl groups attached to a pyrimidine ring may become involved in the formation of new rings. For example, 2-benzyl-1,4,6-trimethylpyrimidinium iodide (**198**) in hot aqueous ethanolic triethylamine gave 2,4-dimethyl-6-methylamino-5-phenylpyridine (**199**);[4717] 2-methyl-5-nitropyrimidine in alkali for 3 h gave 5-nitro-2-pyridinamine (7%);[4717] 4-anilino-6-methyl-2-phenyl-5-pyrimidinecarboxylic acid with thionyl chloride in boiling benzene gave 4-anilino-2-phenyl-7-thioxo-5,7-dihydrofuro[3,4-*d*]pyrimidin-5-one (**200**) (73%), in which the starred carbon atom was that from the original methyl group;[264] and other such reactions have been reported.[465,4126,4718,4719]

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CHAPTER 5

Nitro-, Nitroso-, and Arylazopyrimidines

Nitro, nitroso, and arylazo groups are more easily introduced into the 5- than into the 2- or 4/6-position or an extranuclear position of pyrimidines: primary synthesis, electrophilic substitution (in the presence of sufficient electron-donating groups), or indirect synthesis may be used. Once in place, such groups may be reduced to amino groups, they may prove useful in activating other groups already present in the molecule, or they may undergo a rather limited range of other reactions.

5.1. NITROPYRIMIDINES

The powerful electron withdrawal of a nitro group is illustrated in its activation of a chloro substituent: for example, monoaminolysis of 2,4-dichloropyrimidine required ammonia at 100° for 2 h,[2311] whereas 2,4-dichloro-5-nitropyrimidine underwent a similar reaction at 0° in a few minutes;[1675] likewise, the reactivity of 2-chloro-, 2-methoxy-, or 2-methylthiopyrimidine towards aminolysis was increased 1–3 millionfold by an added 5-nitro substituent.[4721]

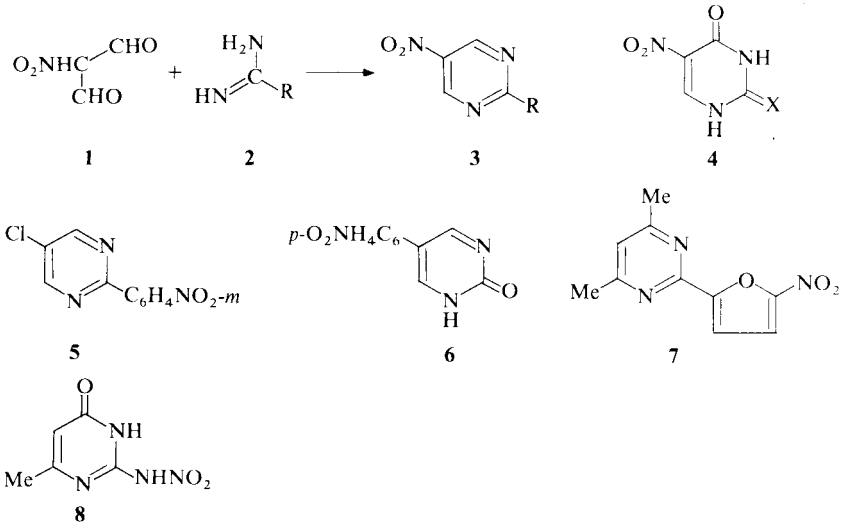
5.1.1. Preparation of Nitropyrimidines

Most nitropyrimidines have been made by nitration but sometimes it has proved convenient or necessary to make nitropyrimidines by primary or indirect syntheses, especially in the presence of labile substituents or when the nitro group was required in other than the 5-position.

5.1.1.1. By Primary Syntheses

Many examples of the primary synthesis of nitropyrimidines have been given in Chapters 2 and 3. Such processes are exemplified briefly in the condensation of α-nitromalondialdehyde (**1**) with benzamidine (**2**, R = Ph), *S*-methylisothiourea (**2**, R = SMe), guanidine (**2**, R = NH_2), or urea to afford 5-nitro-2-phenylpyrimidine (**3**, R = Ph) (79%),[4006] 2-methylthio-5-nitropyrimidine (**3**, R

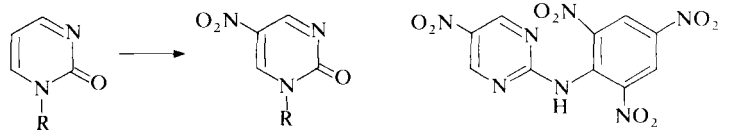
= SMe) (26%),[2321] 5-nitro-2-pyrimidinamine (**3**, R = NH_2),[703,704] or 5-nitro-2(1*H*)-pyrimidinone,[703] respectively; of ethyl 2-nitroacetate, triethyl orthoformate, and urea to give 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**4**, X = O) (35%);[2704] of ethyl 3-ethoxy-2-nitroacrylate with thiourea to give 5-nitro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**4**, X = S) (71%);[1689] of diethyl α-nitromalonate with urea to give 5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (>80%);[3413] and of methyl 3-ethoxy-2-nitroacrylate with benzamidine to give 5-nitro-2-phenyl-4(3*H*)-pyrimidinone (as a salt: 59%).[239] Many extranuclear nitropyrimidines have been made also by primary syntheses. For example, α-chloromalondialdehyde with *m*-nitrobenzamidine gave 5-chloro-2-*m*-nitrophenylpyrimidine (**5**) (40%);[2212] 2-*p*-nitrophenylacetamide with bisformamidomethane in formamide gave 5-*p*-nitrophenyl-2(1*H*)-pyrimidinone (**6**) (55%);[4409] and acetylacetone with 5-nitro-2-furamidine gave 4,6-dimethyl-2-(5′-nitrofuran-2′-yl)pyrimidine (**7**) (29%).[4041] Ethyl acetoacetate with *N*-nitroguanidine gave 6-methyl-2-nitroamino-4(3*H*)-pyrimidinone (**8**), apparently authenticated in structure.[1429]



5.1.1.2. By Nitration

The presence of at least two electron-donating groups is necessary for facile 5-nitration of a pyrimidine substrate. However, one such group is enough to permit nitration providing conditions are sufficiently vigorous and both substrate and product are sufficiently stable to survive such treatment. Thus a solution of 2(1*H*)- (**9**, R = H) or 4(3*H*)-pyrimidinone in concentrated sulfuric acid was treated with solid sodium nitrate and then heated at 95° for 20 h to give 5-nitro-2(1*H*)- (**10**, R = H) (49%) or 5-nitro-4(3*H*)-pyrimidinone (38%), respectively;[3555, cf. 582] 1-methyl-2(1*H*)-pyrimidinone (**9**, R = Me) likewise gave

its 5-nitro derivative (**10**, R = Me).[4722] Similar nitration of 2-pyrimidinamine gave only the product (**10**, R = H)[4722] but nitration of 2-picrylaminopyrimidine in refluxing fuming nitric acid for 8 h gave 5-nitro-2-picrylaminopyrimidine (**11**) (89%).[4728] The kinetics for nitration of the substrates (**9**, R = H or Me) at 115° suggested that the reactive species were the free bases, despite the overwhelming acidity pertaining.[4723]



9 **10** **11**

Regular substrates with two or more electron-donating groups required less vigorous conditions for nitration, as exemplified in the formation of the following products using fuming nitric acid (1 mol) in sulfuric acid at 30–50° unless otherwise indicated.

With two electron-donating groups

2-Amino-5-nitro-4(3*H*)-pyrimidinone.[1342]

4-Amino-5-nitro-2(1*H*)-pyrimidinone.[1585]

4-Butylamino-5-nitro-2(1*H*)-pyrimidinone (~70%).[1221]

6-Methylamino-5-nitro-4(3*H*)-pyrimidinone (>90%).[1383]

5-Nitro-4,6-pyrimidinediamine (92%).[1650]

5-Nitro-2,4-pyrimidinediamine (22%).[2294,2308]

6-Methyl-5-nitro-2,4-pyrimidinediamine.[1932]

2-Amino-6-methyl-5-nitro-4(3*H*)-pyrimidinone ($KNO_3 + H_2SO_4$ at 100°: 67%).[949]

5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione (boiling fuming HNO_3: > 80%;[1125,2295] O_2NBF_4 in sulfolane at 20°: 83%[2705]).

6-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (5–10°: 88%;[1932,2413] vigorous conditions gave 2,6-dioxo-5-nitro-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid by oxidation[1171,1172,1943]).

6-Isopropyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (10°: 75%).[617]

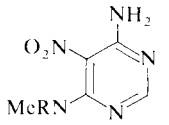
1- or 3-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (25°: > 90%).[1432, cf. 3904]

1,3-Dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (O_2NBF_4 in sulfolane at 20°: 95%).[2705]

1,3,6-Trimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (5°: 93%).[1693,2582,4724]

6-Dimethylamino- (**12**, R = Me) or 6-methylamino-5-nitro-4-pyrimidinamine (**12**, R = H) (70°: ~35% or ~70%, respectively).[2625]

5-Nitro-4,6(1*H*,5*H*)-pyrimidinedione (fuming HNO_3–AcOH at 20–40°: 71–95%).[2503,4726, cf. 1089,2246,3375,3547,3548]



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2-Butyl- or 2-*t*-butyl-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione (fuming HNO_3–AcOH at 40°: ~60%[1612,1981] or 94%,[2184] respectively).

4-Amino-5-nitro-2(1*H*)-pyrimidinone 3-oxide ($KNO_3 + H_2SO_4$ at 30°: 86%).[1587]

Also other examples.[47,72,1373,1863,2014,4725]

With three electron-donating groups

5-Nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (fuming HNO_3 at < 40°: 90%).[3550–3552]

5-Nitro-2,4,6-pyrimidinetriamine (81%).[1579, cf. 2332]

2-Amino-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione.[1578]

6-Amino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (conc. HNO_3–H_2SO_4 at 50°: 74%).[1581]

2,6-Diamino-5-nitro-4(3*H*)-pyrimidinone (78%).[1579]

4,6-Diamino-5-nitro-2(1*H*)-pyrimidinone (79%).[1579]

6-Methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (0°: ~80%).[2407]

6-Amino-2-dimethylamino-5-nitro-4(3*H*)-pyrimidinone (< 5°: 77%).[1076]

5-Nitro-2,4,6-trispicrylaminopyrimidine (fuming HNO_3 at 75°: >95%).[4728]

Also other examples.[4144]

There have been many reports of successful *5-nitrations in the presence of labile substituents* (other than thioxo) with no adverse effects thereon. For example, appropriate substrates gave the following products, usually by dissolution in concentrated sulfuric acid at a low temperature followed by treatment with fuming nitric acid and warming (if necessary) to the indicated temperature.

With alkoxy groups

2,4-Diethoxy-5-nitropyrimidine (60°: 30%).[2024]

2,4-Diethoxy- or 2,4-dimethoxy-6-methyl-5-nitropyrimidine (80°: 60%[2024] or 95%,[2582] respectively).

2,6-Dimethoxy-5-nitro-4-pyrimidinamine (10°: 65%).[2591]

4-Acetamido-2-dimethylamino-6-methoxy-5-nitropyrimidine (5°: ~80%).[638]

2-Methoxy-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione (HNO_3 only at 5°: ~75%).[2484]

With alkylthio groups

6-Amino-2-methylthio-5-nitro-4(3*H*)-pyrimidinone (HNO_3 alone at 20°: ~25%).[1091]

2-Methylthio-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione (HNO_3 alone at 0°: ~90%).[1764]

6-Dimethylamino-2-methylthio-5-nitro-4-pyrimidinamine ($KNO_3 + H_2SO_4$ at 10°: 42%).[3532]

6-Amino-3-methyl-2-methylthio-5-nitro-4(3*H*)-pyrimidinone (5°: 51%).[1076]

With halogeno substituents

6-Chloro-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (20°: 36%;[2309] ~5°: 70%).[624,1233]

6-Chloro-3-methyl- or 6-chloro-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (10°: 50–77%[619,2170,3753] or ~95%,[1000,1364,3753,4725] respectively).

2-Amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone (0–40°: 70–91%;[223,620,630,999,1021,1022] or substrate nitrate salt in H_2SO_4 at 20°: 69%[608,1025]).

2-Amino-6-chloro-3-methyl-5-nitro-4(3*H*)-pyrimidinone (0°: ~85%).[999]

6-Chloro-2-dimethylamino-5-nitro-4(3*H*)-pyrimidinone (0°: ~60%).[2080]

4-Chloro-6-methoxy-5-nitro-2-pyrimidinamine (70°: ~30%).[1364]

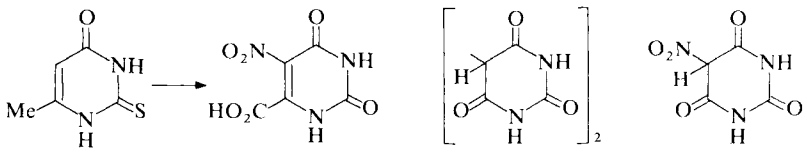
4-Chloro-2,6-dimethoxy-5-nitropyrimidine (80°: 70%).[2068]

6-Chloro-5-nitro-2,4-pyrimidinediamine (excess H_2SO_4 at 35°: 62%).[2294,2308]

5-Nitro-6-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione (100°: 59%).[4729]

5-Nitro-2-trifluoromethyl-4,6(1*H*,5*H*)-pyrimidinedione (conc. HNO_3 at 20°).[4090]

However, some 5-nitrations have been accompanied by changes to existing substituents. For example, 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone, 2-ethylthio-4(3*H*)-pyrimidinone, or 4-chloro-2-ethylthiopyrimidine with nitric acid under vigorous conditions gave 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione;[1637] 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**13**) with fuming nitric acid–sulfuric acid at 60° gave 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (**14**) (55%);[1170] and 5,5′-bipyrimidine-2,2′,4,4′,6,6′(1*H*,1′*H*,3*H*,3′*H*,5*H*,5′*H*)-hexone (hydurilic acid) (**15**),[1657] 5-mercapto-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione,[3320] 5-thioureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione,[4730,4731] or 2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxamide[3713] with nitric acid gave 5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**16**).



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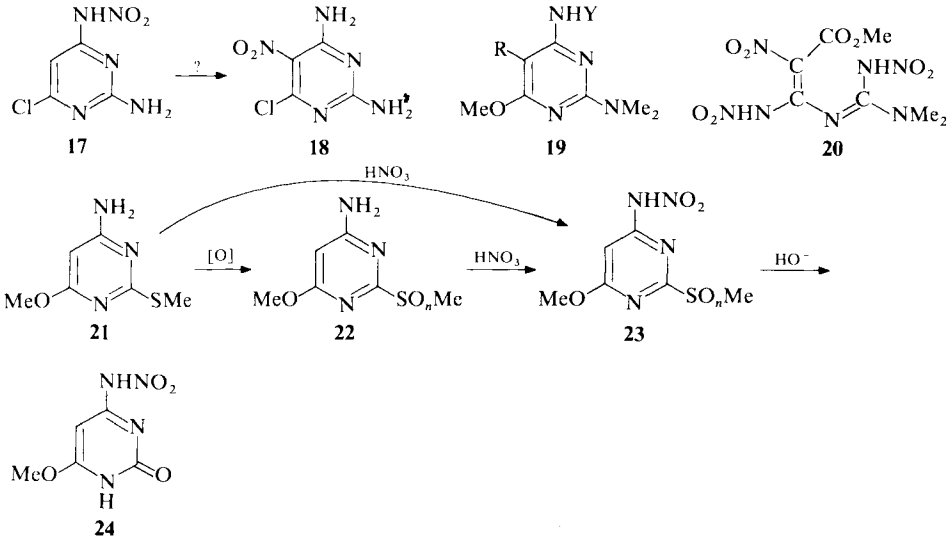
Some pyrimidinamines can undergo *N*-nitration on their amino groups to give *nitroaminopyrimidines*. Thus 6-methyl-4-pyrimidinamine with fuming nitric acid at 75° gave 4-methyl-6-nitroaminopyrimidine (~65%), which differed from its authentic isomer, 6-methyl-5-nitro-4-pyrimidinamine, and underwent reduction to 4-hydrazino-6-methylpyrimidine;[1932] 2-chloro-4-methyl-6-nitroaminopyrimidine was made rather similarly and confirmed in structure;[1932] but a subsequent claim[3217] to have made 6-methyl-2-nitramino-4(3*H*)-pyrimidinone was withdrawn later[1430] when the product proved to be the isomeric 2-amino-6-methyl-5-nitro-4(3*H*)-pyrimidinone. 6-Chloro-2,4-pyrimidinediamine in equal volumes of nitric acid and sulfuric acid at 20–40° gave 4-chloro-6-nitroamino-2-pyrimidinamine (**17**) 30–40%)[2294, cf. 2218] but when the proportion of sulfuric acid was increased 5-fold, 6-chloro-5-nitro-2,4-pyrimidinediamine (**18**) (62%) resulted, presumably by rearrangement.[2294,2308] Likewise, 6-methylamino- or 6-dimethylamino-4-pyrimidinamine gave 4-methylamino- (~50%) or 4-dimethylamino-6-nitroaminopyrimidine, respectively, when nitration was performed at 0° with too little sulfuric acid present;[2625] 6-amino- gave 6-nitroamino-2-trifluoromethyl-4(3*H*)-pyrimidinone (82%) on gentle nitration at 0°;[4131] and 2-dimethylamino-6-methoxy-4-pyrimidinamine (**19**, R = Y = H) with fuming nitric acid–sulfuric acid at 5° gave a separable mixture of its 5-nitro derivative (**19**, R = NO_2, Y = H), 2-dimethylamino-4-methoxy-5-nitro-6-nitroaminopyrimidine (**19**, R = Y = NO_2), and methyl 3-(*N'*,*N'*-dimethyl-*N''*-nitroguanidino)-2-nitro-3-nitroaminoacrylate (**20**) in an approximate ratio of 1 : 2 : 3.[638] Treatment of 6-methoxy-2-methylthio-4-pyrimidinamine (**21**) with an excess of fuming nitric acid at 0° induced *S*-oxidation and *N*-nitration to afford 4-methoxy-2-methylsulfinyl-6-nitroaminopyrimidine (**23**, *n* = 1) (53%); preoxidation of the thioether (**21**) to 6-



methoxy-2-methylsulfinyl-4-pyrimidinamine (**22**, $n = 1$) followed by a similar nitration gave the same nitroamine (**23**, $n = 1$) (68%); and more extensive oxidation of the thioether (**21**) to 6-methoxy-2-methylsulfonyl-4-pyrimidinamine (**22**, $n = 2$) followed by nitration gave 4-methoxy-6-methylsulfonyl-6-nitroaminopyrimidine (**23**, $n = 2$) (72%).[903] The nitroamines (**23**, $n = 1$ or 2) proved remarkably stable, while other groups underwent nucleophilic displacement to give, for example, 4-methoxy-6-nitroamino-2(1*H*)-pyrimidinone (**24**).[903]

Phenyl- and (rarely) alkylpyrimidines can undergo extranuclear *C*-nitration (with or without concomitant 5-nitration) to afford *nitrophenyl- or nitroalkylpyrimidines*. The nitration of 2- and 4-phenylpyrimidine has been discussed in Section 4.2.3.9. Nitrations of other phenylpyrimidine substrates have been reported frequently, but no logical rule as to the point(s) of entry has emerged as yet. Such nitrations are illustrated in the following examples.

5-Bromo- or 5-chloro-2-phenylpyrimidine with fuming nitric acid–sulfuric acid at 0° gave 92% of 5-bromo-2-*o*- and 5-bromo-2-*m*-nitrophenylpyrimidine (3 : 7) or 93% of 5-chloro-2-*o*- and 5-chloro-2-*m*-nitrophenylpyrimidine (1 : 2), respectively.[4711]

5-Phenyl-2-pyrimidinamine with potassium nitrate–sulfuric acid at 60° gave 5-*p*-nitrophenyl-2-pyrimidinamine (80%).[3072]

2-Methylsulfonyl- ($< 10°$) or 2-methylamino-5-phenylpyrimidine (30°) likewise afforded 2-methylsulfonyl- (82%) or 2-methylamino-5-*p*-nitrophenylpyrimidine (92%), respectively.[3072]

2-Methoxy-5-phenylpyrimidine likewise (20°) gave 2-methoxy-5-*p*-nitrophenylpyrimidine ($\sim 90\%$).[4023]

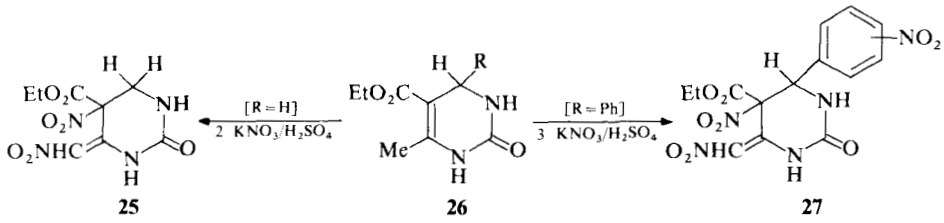
4,6-Dimethyl-5-phenyl-2(1*H*)-pyrimidinone with fuming nitric acid–sulfuric acid at 5° gave only 4,6-dimethyl-5-*p*-nitrophenyl-2(1*H*)-pyrimidinone (24%).[2114]

6-Phenyl-2,4(1*H*,3*H*)-pyrimidinedione gave, according to the conditions, 5-nitro-6-phenyl-, 6-*p*-nitrophenyl-, 5-nitro-6-*m*-nitrophenyl-, or 5-nitro-6-*p*-nitrophenyl-2,4(1*H*,3*H*)-pyrimidinedione, each in reasonable yield.[4652]

5-Ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with fuming nitric acid–sulfuric acid at 3° gave the *m*-nitro derivative ($\sim 37\%$ yield) plus the *p*-nitro isomer ($\sim 3\%$ yield);[4732,4733] the same substrate with nitronium tetrafluoroborate (O_2NBF_4) in acetonitrile at 0° gave only the *p*-isomer (96%).[244]

Ethyl 4-methyl-2-oxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (**26**, R = H) with potassium nitrate (2 mol) in sulfuric acid at 5° gave ethyl 5-nitro-4-nitromethylene-2-oxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxylate (**25**) (78%).[3941, cf. 4734]

Ethyl 4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (**26**, R = Ph) with potassium nitrate (3 mol) in sulfuric acid at 5° gave a



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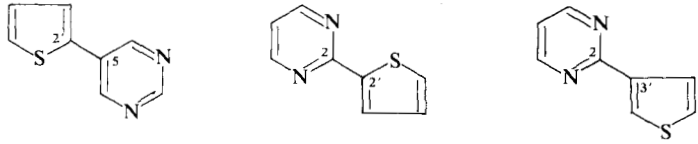
1 : 2 mixture (**27**) of ethyl 5-nitro-4-nitromethylene-6-*m*-nitrophenyl-2-oxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxylate and its *p*-isomer.[3941]

5-Nitro-2-phenylpyrimidine with nitric acid–sulfuric acid at 95° gave 5-nitro-2-*m*-nitrophenylpyrimidine (49%).[2305]

Also other examples.[462,3995]

Rather similarly, thienylpyrimidines undergo nitration readily in the thiophene ring. Thus 5-thien-2′-ylpyrimidine (**28**) with fuming nitric acid–sulfuric acid at 0° gave a separable mixture (80%) of 5-(4′-nitrothien-2′-yl)pyrimidine and its 5′-nitro isomer;[4427] 2-thien-2′-ylpyrimidine (**29**) with the same reagents gave 2-(4′-nitrothien-2′-yl)pyrimidine and its 5′-nitro isomer (total: 90%), but, with acetyl nitrate at 35°, some of the 3′-nitro isomer was formed also;[4008] while 2-(thien-3′-yl)pyrimidine (**30**) gave with either reagent a mixture of 2-(2′-nitrothien-3′-yl)pyrimidine, the 4′-nitro isomer, the 5′-nitro isomer, and 2-(2′,5′-dinitrothien-3′-yl)pyrimidine.[4008]



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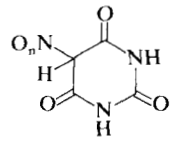
5.1.1.3. By Indirect Syntheses

Although the formation of 5-nitro- (**31**, $n = 2$) from 5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**31**, $n = 1$) on treatment with nitric acid[1657,2091] has long been considered as the *oxidation of a nitrosopyrimidine*,[2798] only in more recent years have unequivocal examples of such oxida-



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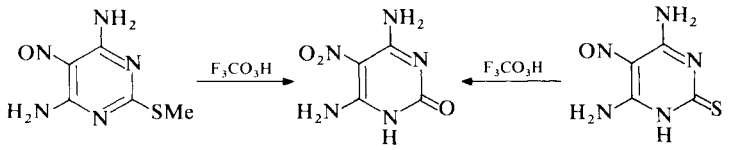
tions been reported. Thus hydrogen peroxide in trifluoroacetic acid at $< 35°$ gave the following 5-nitropyrimidines from the corresponding 5-nitrosopyrimidines.

5-Nitro-2-phenyl-4,6-pyrimidinediamine (87%).[1082]
2-Methyl-5-nitro-4,6-pyrimidinediamine (85%).[1082]
6-Amino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (97%).[1082]
2,6-Diamino-5-nitro-4(3*H*)-pyrimidinone (91%).[1082]
4,6-Diamino-5-nitro-2(1*H*)-pyrimidinone (85%).[1082]
6-Amino-2-methyl-5-nitro-4(3*H*)-pyrimidinone (82%).[1082]
2-Amino-6-ethylamino-5-nitro-4(3*H*)-pyrimidinone (96%).[1082]
6-Amino-2-methylamino-5-nitro-4(3*H*)-pyrimidinone (91%).[1082]
6-Amino-2-dimethylamino-5-nitro-4(3*H*)-pyrimidinone (81%).[1082]
6-Amino-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (92%).[1082]
1,3-Dimethyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (97%).[1082]
2,6-Diamino-1-methyl-5-nitro-4(1*H*)-pyrimidinone ($\sim 50\%$).[2407]
4-Methylamino-5-nitro-6-pentyloxy-2-pyrimidinamine (38%).[2217]
2-Dimethylamino-5-nitro-6-phenyl-4(3*H*)-pyrimidinone (52%).[47]

As might be expected, trifluoroperoxyacetic acid may induce additional oxidative reactions, especially if it is used in excess on an inappropriate substrate. Such incidental effects are illustrated in the following reactions, some of which are quite useful.

2-Methylthio-5-nitroso-4,6-pyrimidinediamine (**32**) or 4,6-diamino-5-nitroso-2(1*H*)-pyrimidinethione (**34**) gave 4,6-diamino-5-nitro-2(1*H*)-pyrimidinone (**33**) (84% or 92%, respectively).[1082]



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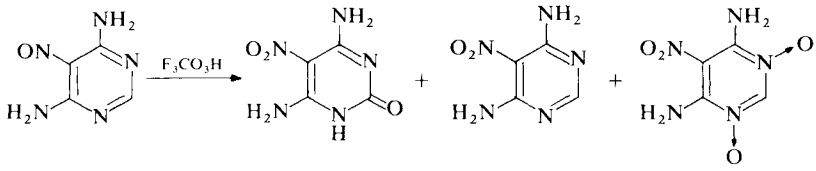
6-Amino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave 6-amino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (66%).[1082]

4,6-Diamino-5-nitrosopyrimidine (**35**) gave 4,6-diamino-5-nitro-2(1*H*)-pyrimidinone (**36**) ($\leqslant 60\%$), 5-nitro-4,6-pyrimidinediamine (**37**) ($\leqslant 39\%$), and its 1,3-dioxide (**38**) ($\leqslant 14\%$), according to the conditions.[1082,2426]

5-Nitroso-2,4,6-pyrimidinetriamine gave a separable mixture of 5-nitro-2,4,6-pyrimidinetriamine 1-oxide (28% yield) and the 1,3-dioxide (45% yield).[3549]



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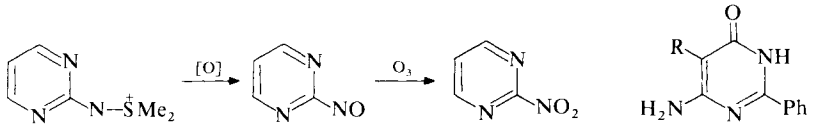
6-Anilino-5-nitroso-2,4-pyrimidinediamine gave 6-anilino-5-nitro-2,4-pyrimidinediamine 3-oxide (51%).[2176]

6-Imino-1-methyl-5-nitroso-1,6-dihydro-2,4-pyrimidinediamine gave 6-imino-1-methyl-5-nitro-1,6-dihydro-2,4-pyrimidinediamine 3-oxide (43%).[2176]

6-*p*-Bromoanilino-5-nitroso-2,4-pyrimidinediamine gave a single 6-*p*-bromoanilino-5-nitro-2,4-pyrimidinediamine *N*-oxide (73%).[2294]

Other oxidants have been used to convert 2-, 4-, or 5-nitrosopyrimidines into the corresponding nitropyrimidines. An important seminal example was the last step in the following sequence: 2-pyrimidinamine was converted[2830,2831] into 2-*S*,*S*-dimethylsulfimidopyrimidine (**39**) and thence by *m*-chloroperoxybenzoic acid oxidation into the unstable 2-nitrosopyrimidine (**40**), which underwent further oxidation by ozone to afford 2-nitropyrimidine (**41**) (last step: 33%).[3545] The following 2- or 4/6-nitropyrimidines were also made from their nitroso analogs: 4-methyl-6-nitro-2-phenylpyrimidine (peroxymaleic acid: ~12%; $KMnO_4$: ~35%; NaOCl: ~45%), 4-nitro-2,6-diphenylpyrimidine (NaOCl), 4-nitro-2-phenylpyrimidine ($KMnO_4$), 2-nitro-4,6-diphenylpyrimidine (KOCl: 55–75%), and 2-nitro-5-phenylpyrimidine (KOCl).[6013] Examples of such oxidation of 5-nitrosopyrimidines include the conversion of 2,6-diamino-5-nitroso-4(3*H*)-pyrimidinone into 2-amino-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione (82%) by treatment with an excess of sodium nitrite in 80% sulfuric acid at 5°;[1580] and of 6-amino-2-phenyl-4(3*H*)-pyrimidinone (**42**, R = H) or its 5-nitroso derivative (**42**, R = NO), by similar treatment, into 6-amino-5-nitro-2-phenyl-4(3*H*)-pyrimidinone (**42**, R = NO_2) (> 98% or 70%, respectively).[1580]



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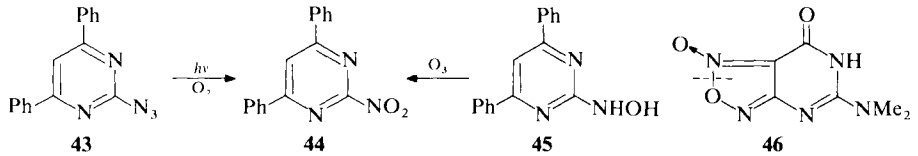
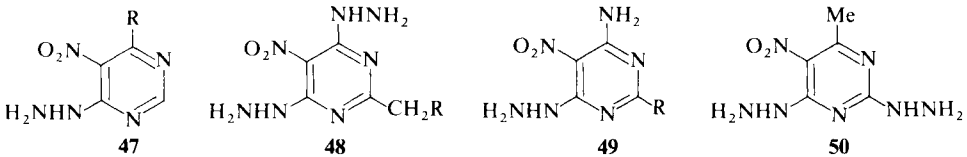
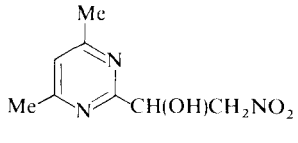
Several *other oxidative routes to nitropyrimidines* are represented in the following examples. Treatment of 4-chloro-6-hydroxyaminopyrimidine or its 2-methyl derivative in chloroform at 0° with a stream of ozone gave 4-chloro-5-nitropyrimidine (50%) or its 2-methyl derivative (> 90%), respectively;[6014] photolysis of a chloroform solution of 2-azido-4,6-diphenyl- (**43**) or 2-azido-4,6-

bis-*p*-chlorophenylpyrimidine in the presence of oxygen gave 2-nitro-4,6-diphenyl- (**44**) or 2-nitro-4,6-bis-*p*-chlorophenylpyrimidine, respectively, each in > 60% yield;[331] treatment of 2-hydroxyamino-4,6- (**45**) or 4-hydroxyamino-2,6-diphenylpyrimidine with ozone (3 mol) in methylene chloride gave 2-nitro-4,6- (**44**) (28%) or 4-nitro-2,6-diphenylpyrimidine (22%), respectively;[330] and treatment of 5-dimethylamino[1,2,5]oxadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one 1-oxide (**46**) with manganese dioxide in dimethylformamide gave 2-dimethylamino-5,6-dinitro-4(3*H*)-pyrimidinone (55–90%).[2615] In addition, several simple nitropyrimidines have been made from their easily obtained hydrazino derivatives by oxidation with silver oxide or silver acetate. Thus 5-nitropyrimidine was made from its 4,6-dihydrazino (**47**, R = $NHNH_2$) (Ag_2O: 31%; AgOAc: 70%)[2560,3546] or 4-hydrazino derivative (**47**, R = H) (Ag_2O: 24%);[946,3229,3230] 2-methyl- (Ag_2O: 25%) or 2-benzyl-5-nitropyrimidine (Ag_2O: 12%) from the respective 4,6-dihydrazino derivative (**48**, R = H or Ph);[2560] 4-methoxy-5-nitropyrimidine (Ag_2O: 62%) from 4-hydrazino-6-methoxy-5-nitropyrimidine (**47**, R = OMe);[684] 5-nitro- (AgOAc: 68%; $CuSO_4$: 5%), 2-methyl-5-nitro- (AgOAc: 20%), or 5-nitro-2-styryl-4-pyrimidinamine (AgOAc: 21%) from the respective 6-hydrazino derivative (**49**, R = H, Me, or CH:CHPh);[684] and 4-methyl-5-nitropyrimidine (AgOAc: 15%) from its 2,6-dihydrazino derivative (**50**).[231]





Many extranuclear nitropyrimidines have been made by *derivatization with nitro-bearing reagents*, processes of such little interest that a few random examples will suffice. 4,6-Dimethyl-2-pyrimidinecarbaldehyde with nitromethane gave 2-α-hydroxy-β-nitroethyl-4,6-dimethylpyrimidine (**51**) (68%) and thence, by dehydration in acetic anhydride, 4,6-dimethyl-2-β-nitrovinylpyrimidine (50%);[2037] also an analog.[682] 6-Ethylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione with *o*-fluoronitrobenzene and potassium carbonate in dimethylformamide at 160° gave the 5-*o*-nitrophenyl derivative (**52**) (59%).[310] 1,3-Dimethyl-2,4-6(1*H*,3*H*,5*H*)-pyrimidinetrione with *p*-nitrobenzaldehyde in refluxing ethanol gave the 5-*p*-nitrobenzylidene derivative (**53**) (90%) and thence, by borohydride reduction, the 5-*p*-nitrobenzyl analog (98%);[3733] also other analogs.[3732,4735] 2-Chloropyrimidine and *p*-nitrobenzenethiol, fused



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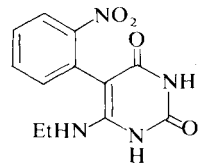

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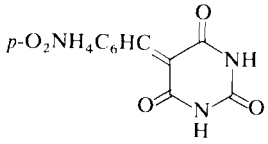

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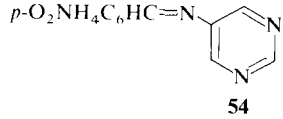

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without solvent for 5 min, gave 2-*p*-nitrophenylthiopyrimidine (75%).[4736] 2,4-Diamino-5-pyrimidinol with *p*-nitrobenzenediazonium chloride gave 2,4-diamino-6-*p*-nitrophenylazo-5-pyrimidinol (75%);[582] also analogs.[1493,1557] 5-Pyrimidinamine with *p*-nitrobenzaldehyde and a trace of acetic acid at 160° gave 5-*p*-nitrobenzylideneaminopyrimidine (**54**);[711] also analogs.[446] 4-Methyl-2-pyrimidinamine with *p*-nitrobenzaldehyde in sulfuric acid gave 4-*p*-nitrostyryl-2-pyrimidinamine (~90%);[4675] and analogs.[671,1911,2562,2694] 6-Methoxy-4-pyrimidinamine with *p*-nitrobenzenesulfonyl chloride in pyridine gave 4-methoxy-6-*p*-nitrobenzenesulfonamidopyrimidine (79%);[4737] also analogs.[1264] Other types of nitro-bearing derivatives have been made appropriately.[92,434,1391,2212,4200,4738,4739,6023]

5.1.2. Reactions of Nitropyrimidines

The only major reaction of nitropyrimidines is reduction to the corresponding pyrimidinamines. However, simple nitropyrimidines do undergo covalent additions, ring fissions with subsequent reactions, some intra- and intermolecular cyclizations involving the nitro group directly, and other minor reactions.

5.1.2.1. Reduction to Pyrimidinamines

The usual reason for introducing a nitro group is to afford an amino group at the same position. The choice of a reagent for any particular reduction may be restricted by the presence of labile groups in the molecule, but, as a rule, it is possible to choose from a large variety of reducing agents.

The use of reagents commonly employed for this purpose is illustrated in the reduction of the following nitropyrimidines (to the corresponding aminopyrimidines, except where indicated otherwise).

Hydrogenation over platinum

6-Chloro-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (in PhH at 3 atm: ~40%).[1000]

6-Chloro-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (in aqueous methanolic NH_3 at 2 atm; isolated as 5-NHCHO: 43%).[619,2170]

2-Dimethylamino-5-nitropyrimidine (in MeOH; isolated as 5-$NHSO_2Ph$: 60%).[2644]

6-Chloro-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (in Ac_2O–AcOH; isolated as 5-NHAc: 61%).[624]

Also other examples.[2309,4740]

Hydrogenation over palladium

5-Nitro-2-phenylpyrimidine (in EtOH: 88%).[4006]

2,4-Diethoxy- (in EtOH: 90%)[651] or 2,4-dimethoxy-5-nitropyrimidine (in MeOH: 91%).[1639]

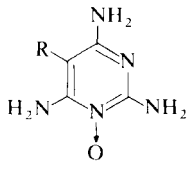
1-β-Ethoxycarbonylethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (in $MeOCH_2CH_2OH$: 92%).[2014]

2-Acetamido-5-nitro-4(3*H*)-pyrimidinone (in Me_2NCHO: > 95%).[603]

6-Hydrazino-5-nitro-4(3*H*)-pyrimidinone (in H_2O: 56%).[607]

5-Nitro-6-propylamino-4-pyrimidinamine (in EtOH at 4 atm: 62% as hydrochloride).[3544]

5-Nitro-2,4,6-pyrimidinetriamine 1-oxide (**55**, R = NO_2) [in H_2O: 2,4,5,6-pyrimidinetetramine 1-oxide (**55**, R = NH_2); in 90% HCO_2H: 5-(hydroxymethyl)amino-2,4,6-pyrimidinetriamine 1-oxide (**55**, R = $NHCH_2OH$) (49%)].[3549]



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2-Chloro-4-methyl-6-methylamino-5-nitropyrimidine [in aqueous ethanolic NH_3: 4-methyl-6-methylamino-5-pyrimidinamine (97%)].[3398]

Also other examples.[1021,1023,4724,4727,4741,4742,4806]

Hydrazine with palladium

5-Nitro-2-phenylpyrimidine (in boiling PhH: 67%).[2305]

5-Acetamido-2-*m*-nitrophenylpyrimidine (likewise; isolated as 5-acetamido-2-*m*-acetamidophenylpyrimidine).[2305]

1- or 3-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (in boiling EtOH: 78% or 81%, respectively).[1129,3904]

2-Morpholino-5-nitropyrimidine (in boiling EtOH: 42%).[3228]

Hydrogenation over Raney-nickel

5-Nitropyrimidine (in MeOH: 79%).[2560]

5-Nitro-2,4-pyrimidinediamine (suspended in MeOH: 89%).[1379,4743]

4-Methoxy-5-nitropyrimidine (in MeOH: 67%).[684]

6-Methylamino-5-nitro-4(3*H*)-pyrimidinone (suspended in MeOH: ~80%).[1383]

4-Diethylamino-6-methyl-5-nitropyrimidine (in $MeOCH_2CH_2OH$: 79%).[4747]

2-Chloro-4-methyl-6-methylthio-5-nitropyrimidine (in MeOH).[1157]

2,4-Dichloro- or 2,4,6-trichloro-5-nitropyrimidine (in MeOH or EtOH: 70–87% or >95%, respectively).[1038,2307,2503]

Ethyl 6-amino-2-chloro-5-nitro-4-pyrimidinecarboxylate (in MeOH: ~65%).[2959]

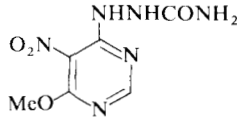
6-Fluoro-5-nitro-4-pyrimidinamine (in MeOH: 90%).[2556]

6-Butylamino-5-nitro-4-pyrimidinamine (in AcOEt: 69%).[4562]

2-Chloro-4-β-methoxycarbonylhydrazino-6-methyl-5-nitropyrimidine (in MeOH: 68%; use of Pd/H_2 gave 4-β-methoxycarbonylhydrazino-6-methyl-5-pyrimidinamine: 57%).[802]

2-Acetamido-4,6-dichloro-5-nitropyrimidine (in Me_2NAc: 44%).[620,630]

4-Methoxy-5-nitro-6-semicarbazidopyrimidine (**56**) (in MeOH: ~50%).[3227]



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5-*p*-Nitrophenyl-2-pyrimidinamine (in MeOH: 75%).[3072]

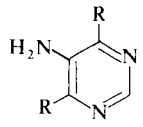
Also many other examples.[434,601,804,968,999,1022,1051,1076,1123,1372,1373,1380,1403,1428,1434,1581,1746,1747,1764,1766,2114,2625,2626,3046,3334,4023,4740,4744–4746,4748–4750]

Raney-nickel without hydrogen

2-Methylthio-5-nitropyrimidine [Raney-Ni (40 parts) in boiling EtOH: 5-pyrimidinamine (75%)].[2321]

6-Dimethylamino-2-methylthio-5-nitro-4-pyrimidinamine [likewise (15 parts): 6-dimethylamino-4,5-pyrimidinediamine (30%)].[2625]

4,6-Bismethylthio-5-nitropyrimidine [Raney-Ni (5 parts) in boiling aqueous NH_3: 5-pyrimidinamine (**57**, R = H) (56%) plus 4,6-bismethylthio-5-pyrimidinamine (**57**, R = SMe) (35%)].[1778]



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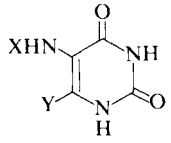
Sodium dithionite

5-Nitro-2,4(1*H*,3*H*)-pyrimidinedithione (in hot dilute alkali: ~ 60%).[626,1648]

5-Nitro-2,4-pyrimidinediamine (in hot H_2O: 77%).[2327]

5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione [in hot dilute NH_4OH followed by acidification and rebasification: 91%;[1639,4297] possibly via 5-sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione (**58**, X = SO_3H, Y = H)[1176] or 5-amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid (**58**, X = H, Y = SO_3H)[662]].



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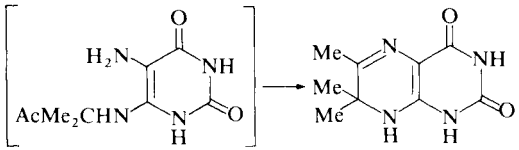
Ethyl 6-amino-5-nitro-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate (in aqueous $NaHCO_3$ at 50°: ~ 75%).[2959]

2-Dimethylamino-5-nitro-6-trifluoromethyl-4-pyrimidinamine (in aqueous acetonic $NaHCO_3$: > 80%).[4754]

5-Nitro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (in H_2O: 65%).[1689]

Methyl 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (in H_2O at 10°: 66%).[1123]

6-(α,α-Dimethylacetonyl)amino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione [in dilute alkali: 6,7,7-trimethyl-7,8-dihydro-2,4(1*H*,3*H*)-pteridinedione (**60**) (81%) by spontaneous cyclization of product (**59**)].[225]



59 **60**

5-Nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime (in aqueous alkali at 40°: ~ 45%).[1165]

5-Nitro-2,4,6-pyrimidinetriamine 1-oxide (**55**, R = NO_2) (in H_2O: 2,4,5,6-pyrimidinetetramine only).[3549]

2-Amino-6-hydrazino-5-nitro-4(3*H*)-pyrimidinone [in boiling H_2O: 2,5,6-triamino-4(3*H*)-pyrimidinone (20%)].[1301]

Also other cases.[243,1023,1038,1170,1187,1191,1231,1582,1596,2309,2973,2975,4751,4752,4755–4757]

Sodium hydrogen sulfide

2,4-Dichloro-5-nitropyrimidine [in H_2O–EtOH: 5-amino-2,4(1*H*,3*H*)-pyrimidinedithione (~75%)].[711]

2-Chloro-5-nitro-4-pyrimidinamine [in H_2O at > 70°: 4,5-diamino-2(1*H*)-pyrimidinethione (42%)].[2295,2442]

4-Chloro-6-methylamino-5-nitropyrimidine [in H_2O at 90°: 5-amino-6-methylamino-4(3*H*)-pyrimidinethione (65%)].[1379]

4,6-Dichloro-2-methyl-5-nitropyrimidine [in aqueous dioxane at 90°: 5-amino-2-methyl-4,6(1*H*,5*H*)-pyrimidinone (95%).[676]

2-Amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone [in MeOH at 20° followed by reduction of the nitro group by dithionite: 2,5-diamino-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone (59%)].[1565]

Also other examples.[1157,1191,1612,1981,2413,4652]

Tin or stannous chloride

5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione [Sn/HCl: ~10%; main product was 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione: 63%].[771,3275]

5-Nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Sn/HCl: 73%).[4759]

2,6-Dichloro-5-nitro-4-pyrimidinamine ($SnCl_2$/HCl: 70%).[1581]

4,6-Dichloro- or 4,6-dimethoxy-5-nitropyrimidine ($SnCl_2$/EtOH–HCl: 68% or 50%, respectively).[2208]

5-Nitro-2-styryl-4-pyrimidinamine ($SnCl_2$/HCl at 95°: ~55%).[684]

6-*t*-Butyl-2-chloro-5-nitro-4-pyrimidinamine ($SnCl_2$/HCl at 95°: 90%).[2184]

Also other examples.[617,2703,4676,4758]

Iron or ferrous hydroxide

2-Chloro-5-nitropyrimidine (Fe/AcOH–H_2O at 80°: ~ 55%).[704]

2,4-Dimethoxy-5-nitropyrimidine (Fe/AcOH–H_2O–EtOH at 100°: 92%).[1187,1639]

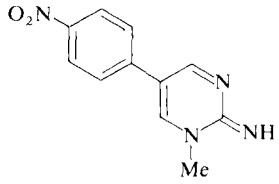
4-Ethoxy-5-nitro-2-pyrimidinamine (Fe/AcOH at 60°: ~ 70%).[1582]

2-Chloro-4-thiocyanato-5-nitropyrimidine (Fe/AcOH at 60°: ~ 80%).[633]

5-Nitro-2-trifluoromethyl-4,6-pyrimidinediamine (Fe/AcOH at 50°: 93%).[4090]

Ethyl 2,6-dichloro-5-nitro-4-pyrimidinecarboxylate (Fe/AcOH at 60°: 70%).[2957]

1-Methyl-5-*p*-nitrophenyl-2(1*H*)-pyrimidinimine (**61**) (Fe/HI–EtOH under reflux: 91%, as hydriodide).[3072]



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2,4- or 4,6-Dichloro-5-nitropyrimidine [$Fe(OH)_2/H_2O$ at 90°: 82% or 80%, respectively].[711,1648]

Also other cases.[243,1036,1195,1383,1585,2114,2846,3553,4760]

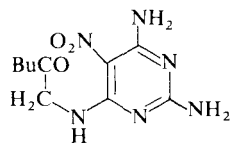
Zinc

5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione (Zn/HCl: poor yield;[1171] Zn/NH_4OH: poor yield[714]).

4-Chloro-6-methoxy-2-methyl-5-nitropyrimidine (Zn/H_2O at 100°: 53%).[651]

4-Amino-6-methyl-5-nitro-2(1*H*)-pyrimidinone (Zn/H_2O at 100°: 41%).[2418]

6-Methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione [Zn/98% HCO_2H at 90°: 5-formamido-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione (~ 75%)].[3177]



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5-Nitro-6-(β-oxohexyl)amino-2,4-pyrimidinediamine (**62**) [Zn/AcOH at 100°: isolated, after H_2O_2 oxidation, as 6-butyl-2,4-pteridinediamine (23%)].[4865]

Also other examples.[1279,1286,1353,4753,4761]

Other reducing agents

2-Chloro-4-(ethoxycarbonylmethyl)amino-5-nitropyrimidine [HI–red P under reflux: reduction, dechlorination, and cyclization occurred to give 7,8-dihydro-6(5*H*)-pteridinone (77%)].[4762]

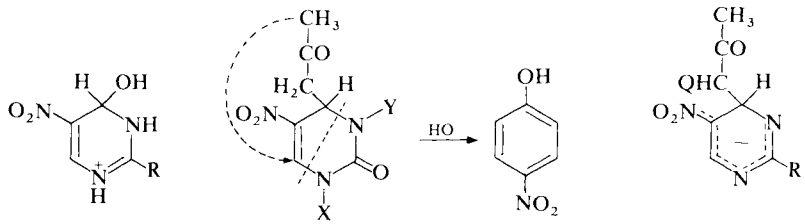
5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione (Al/Hg in NH_4OH: poor yield).[714,1637]

6-Methyl-2-nitroamino-4(3*H*)-pyrimidinone [80% hydrazine at 95°: 2-hydrazino-6-methyl-4(3*H*)-pyrimidinone (~ 60%)].[1429]

On treatment of 2-nitro-4,6-diphenyl- or 4-nitro-2,6-diphenylpyrimidine with phenylhydrazine in refluxing ethanol for 1 h, a peculiar reductive reaction took place to afford 2-hydroxyamino-4,6-diphenyl- (40%) or 4-hydroxyamino-2,6-diphenylpyrimidine (46%), respectively.[6013]

5.1.2.2. Other Reactions

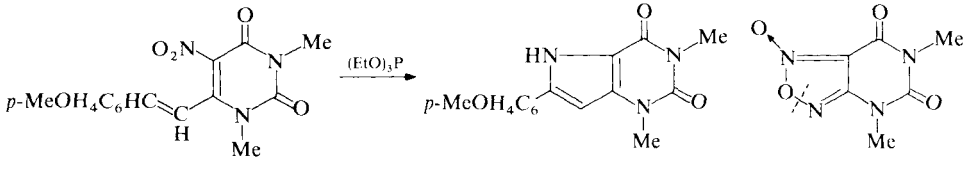
The cations of 5-nitropyrimidine and its 2-methyl and 2-benzyl derivatives clearly underwent immediate *covalent addition* of water in aqueous solution to give the 3,4-hydrates (**63**, R = H, Me, or CH_2Ph, respectively).[2560,4763] Likewise, 5-nitro-2(1*H*)-pyrimidinone underwent acid-catalyzed 3,4-addition by acetone to give the characterized adduct, 4-acetonyl-5-nitro-3,4-dihydro-2(1*H*)-pyrimidinone (**64**, X = Y = H) (82%), which cyclized in alkali with loss of urea to afford *p*-nitrophenol (**65**) (85%);[3414] 1-methyl-5-nitro-2(1*H*)-pyrimidinone gave a separable mixture of 4-acetonyl-1-methyl-5-nitro-3,4-dihydro-2(1*H*)-pyrimidinone (**64**, X = Me, Y = H) and its isomer (**64**, X = H, Y = Me), each of which gave *p*-nitrophenol on alkaline treatment;[3414] and several further-substituted *p*-nitrophenols were so made via appropriate adducts.[3414] Both 2-chloro- and 2-methoxy-5-nitropyrimidine reacted with acetylacetone under strongly alkaline conditions to afford, among other products, 2-acetyl-4-nitrophenol in low yield,[25] while 5-nitropyrimidine and its 2-methoxy or 2-diethylamino derivative reacted with acetone under similar conditions to give *p*-nitrophenol in 19–75% yield, according to the substrate's 2-substituent.[3755] These reactions undoubtedly proceeded via adducts similar to **64** but now formulated as the anionic σ-complexes (**66**, Q = Ac or H; R = Cl, OMe, H, or NEt_2). In a rather similar way, 1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione gave 4-nitroresorcinol (~ 10%) via an acetone adduct under alkaline conditions.[5873]

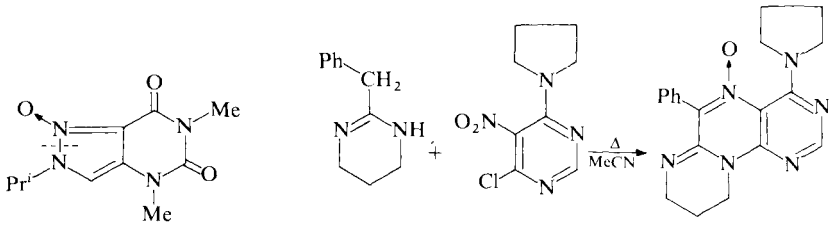


63 **64** **65** **66**

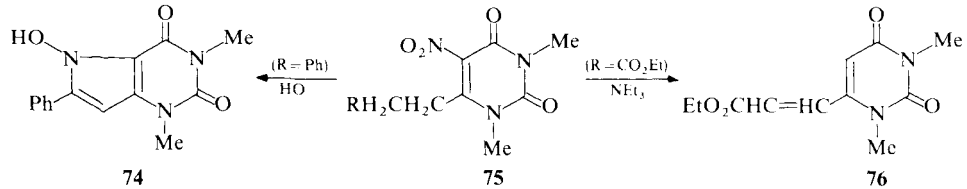
The direct *involvement of a nitro group in ring formation* is possible in various ways. Thus 6-*p*-methoxystyryl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**67**) in refluxing triethyl phosphite gave 6-*p*-methoxyphenyl-1,3-dimethyl-

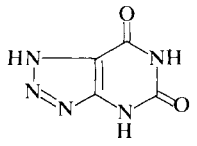
5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**68**) (40%);[4677] 6-azido-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione lost nitrogen in refluxing dimethylformamide to give 4,6-dimethyl[1,2,5]oxadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione 1-oxide (**69**) (45%);[1705] 6-isopropylaminomethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione in refluxing ethanol gave 2-isopropyl-4,6-dimethyl-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione 1-oxide (**70**) (63%);[2683] 4-chloro-5-nitro-6-pyrrolidinopyrimidine (**72**) with 2-benzyl-1,4,5,6-tetrahydropyrimidine (**71**) in refluxing acetonitrile under nitrogen gave 5-phenyl-7-pyrrolidino-2,3-dihydro-1*H*-pyrimido[2,1-*h*]pteridine 6-oxide (**73**) (40%);[178] and other such cyclizations have been reported.[4764–4766]





Although 1,3-dimethyl-5-nitro-6-phenethyl-2,4(1*H*,3*H*)-pyrimidinedione (**75**, R = Ph) underwent cyclization in ethanolic alkali to afford 5-hydroxy-1,3-dimethyl-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**74**) (93%) as expected, the analogous substrate, 6-*β*-ethoxycarbonylethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**75**, R = CO_2Et) in ethanolic triethylamine underwent an *elimination of the nitro group* to give only 6-*β*-ethoxycarbonylvinyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**76**) (90%).[148] Such elimination occurred when 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione lost nitrous acid on heating with sodium azide in dimethylformamide to give *v*-triazolo[4,5-*d*]-pyrimidine-5,7(4*H*,6*H*)-dione (**77**) (86%), a reaction of considerable





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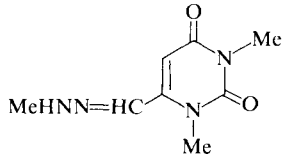

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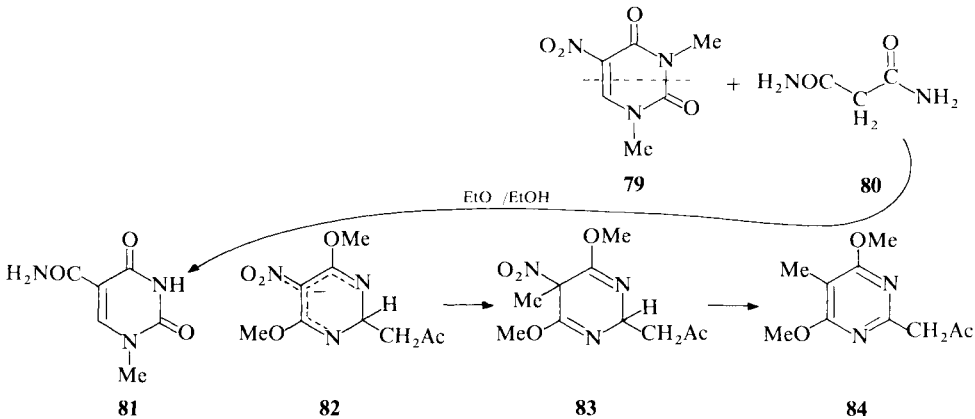
scope;[4767,4768] also when 6-bromomethyl-1,3-dimethyl- or 1,3-dimethyl-6-(α-methylhydrazino)methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione reacted with an excess of methylhydrazine to afford 1,3-dimethyl-6-methylhydrazonomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**78**) (83% or 38%, respectively).[1905]

Both *2- and 4/6-nitro substituents can act as leaving groups.* Thus appropriate nitro substrates gave 2-ethoxy-4,6-diphenyl- (EtOH, KOH, 20°, 18 h: 70%), 4,6-diphenyl-2-piperidino- (piperidine, EtOH, 20°, 36 h: 88%), and 2,4-diphenyl-6-piperidinopyrimidine (piperidine, EtOH, 20°, 2.5 h: > 90%).[6013] Likewise, 2,4-dimethoxy-6-nitro- gave 2,4,6-trimethoxy-5-pyrimidinamine (NaOMe, MeOH reflux: 73%).[6196]

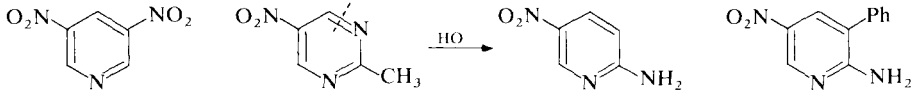
The *indirect replacement of a 5-nitro group* has been accomplished by treatment of 1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**79**) with malondiamide (**80**) in ethanolic ethoxide at 20° to afford 1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (**81**) (63%):[72,3390] also by 5-alkylation of the σ-complex (**82**) (derived from 4,6-dimethoxy-5-nitropyrimidine and acetone in alkaline solution [cf. 3355]) with methyl iodide in the presence of benzyltrimethylammonium chloride to give 2-acetonyl-4,6-dimethoxy-5-methyl-5-nitro-2,5-dihydropyrimidine (**83**) (40%), followed by treatment with methanolic alkali to afford 2-acetonyl-4,6-dimethoxy-5-methylpyrimidine (**84**) (72%).[3886]



79 80 81 82 83 84

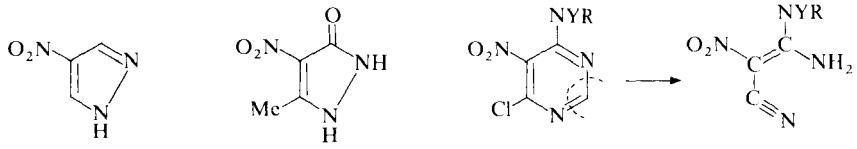
The conversion of *nitropyrimidines into pyridines* has been done in several ways: 5-nitropyrimidine in dilute acetic acid at 90° for 30 min gave 3,5-dinitropyridine (**85**) (50%) by a mechanism involving ring fission, partial degradation with loss of HCN, and recombination of fragments;[3546] 2-methyl-

5-nitropyrimidine (**86**) in aqueous alcoholic alkali gave 5-nitro-2-pyridinamine (**87**) in low yield, probably by a simple ring fission and recyclization mechanism;[3410] and 5-nitropyrimidine reacted with 2-phenylacetamidine in hot ethanol to afford 5-nitro-3-phenyl-2-pyridinamine (**88**) (86%), probably via intermediate cycloadducts.[4769] The nitromethane adduct of 1-benzoylmethyl-4-phenylpyrimidinium bromide in base gave 3-nitro-6-phenylpyridine.[16]



85 **86** **87** **88**

The conversion of *nitropyrimidines into pyrazoles* has also been done: 5-nitropyrimidine in aqueous hydrazine hydrate at 25° for 30 min gave 4-nitropyrazole (**89**) (90%);[3546] likewise, 1,3,6-trimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione in hot propanolic hydrazine gave 5-methyl-4-nitro-3(2*H*)-pyrazolone (**90**) (36%) with loss of *N*,*N*′-dimethylurea.[1905] Other examples have been reported.[3229,3230,5937]



89 **90** **91** **92**

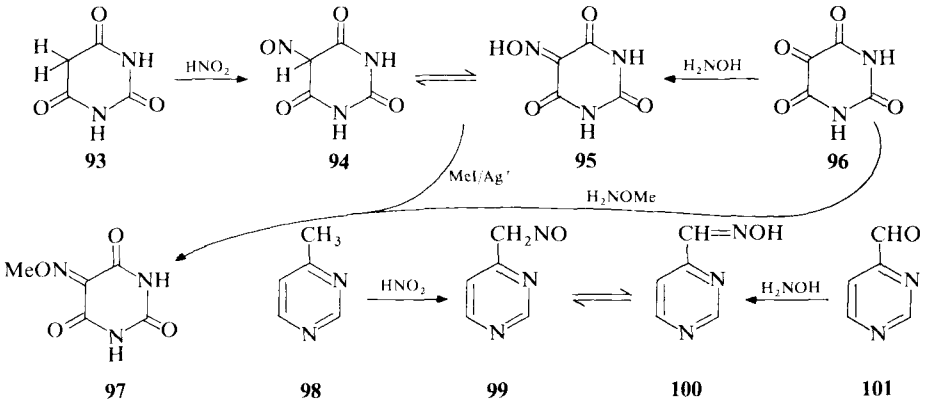
As might be expected, the *degradation of nitropyrimidines* to acyclic materials has been reported under hydrolytic or oxidative conditions.[4771] For example, on prolonged boiling in 60% acetic acid, 6-chloro-5-nitro-4-pyrimidinamine (**91**, R = Y = H) gave mainly 3,3-diamino-2-nitroacrylonitrile (**92**, R = Y = H), 4-chloro-6-ethylamino-5-nitropyrimidine (**91**, R = Et, Y = H) gave mainly 3-amino-3-ethylamino-2-nitroacrylonitrile (**92**, R = Et, Y = H), and 4-chloro-5-nitro-6-piperidinopyrimidine [**91**, R + Y = $(CH_2)_5$] gave only 3-amino-2-nitro-3-piperidinoacrylonitrile [**92**, R + Y = $(CH_2)_5$];[1589, cf. 6215] 4-benzylamino-6-chloro-5-nitropyrimidine (**91**, R = CH_2Ph, Y = H) in 50% aqueous dioxane at 25° for 2 weeks gave 3-amino-3-benzylamino-2-nitroacrylonitrile (**92**, R = CH_2Ph, Y = H) (~60%);[4770] and 6-*p*-nitrophenyl-2,4(1*H*,3*H*)-pyrimidinedione or its 5-nitro derivative with hot potassium permanganate gave *p*-nitrobenzoic acid as the sole isolable product in each case.[4652]

Nitropyrimidines have been reported to show cytotoxic[4772] and other biological activities of a low order.[4773]

5.2. NITROSOPYRIMIDINES

Although the nitroso group usually occupies the 5-position of pyrimidines, it can be accommodated occasionally at the 2- or 4/6-position or on an extracyclic

carbon or nitrogen atom. It is still uncertain whether 5-nitrosopyrimidines prefer to exist as such (—N=O) or as the tautomeric hydroxyiminopyrimidines (=N—OH) when the latter is possible by virtue of another appropriate group in the molecule.[1594,4797] For example, violuric acid may be formulated as 5-nitroso- (**94**) or 5-hydroxyimino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**95**), whether it is made by nitrosation[3553] of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**93**) or by the action of hydroxylamine[3561,3562] on the ketone, 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (alloxan) (**96**); moreover, 5-methoxyimino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**97**) was obtained either by methylation[3561,4774] of the tautomers (**94**/**95**) or by treatment of alloxan (**96**) with *O*-methylhydroxylamine.[4775] It is customary to formulate 2-, 4-, 5- or 6-nitrosopyrimidines as such.



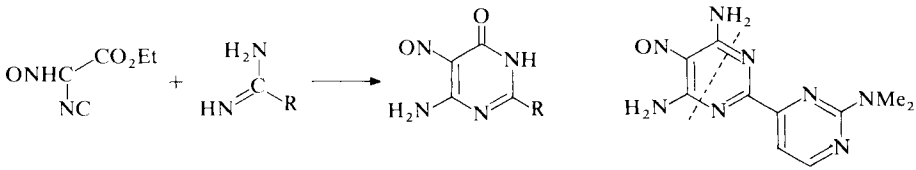
In a rather similar way, (nitrosoalkyl)pyrimidines are tautomeric with the oximes of pyrimidinecarbaldehydes (or ketones) [e.g., $-CH_2N{=}O \rightleftharpoons -CH{=}NOH$; $-CH_2CH(N{=}O)Me \rightleftharpoons -CH_2C(=NOH)Me$] but irrespective of the presence or absence of other groups in the molecule: thus, treatment of 4-methylpyrimidine (**98**) with nitrous acid[826] or treatment of 4-pyrimidinecarbaldehyde (**101**) with hydroxylamine[2758] gave the same product (**99**/**100**), usually formulated as 4-pyrimidinecarbaldehyde oxime rather than 4-nitrosomethylpyrimidine.

5.2.1. Preparation of Nitrosopyrimidines

Although most nuclear nitrosopyrimidines have been made by nitrosation with nitrous acid, some have been made by primary syntheses, and a few by indirect syntheses. The (extranuclear) nitrosoalkylpyrimidines have been made from alkylpyrimidines by nitrosation or a Claisen procedure (see Section 4.2.3.3) or from pyrimidinecarbaldehydes (or ketones) with hydroxylamine. A few *N*-nitrosopyrimidines have been made from secondary aminopyrimidines or from reduced pyrimidines with nitrous acid.

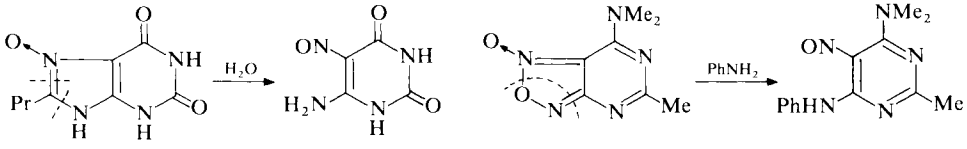
5.2.1.1. By Primary Syntheses

A variety of 5-nitrosopyrimidines has been made by the Principal Synthesis (Chapter 3) by employing appropriate prenitrosated three-carbon fragments. For example, condensation of ethyl 2-cyano-2-nitrosoacetate (**102**) with acetamidine gave 6-amino-2-methyl-5-nitroso-4(3*H*)-pyrimidinone (**103**, R = Me) (79%);[2421] with guanidine gave 2,6-diamino-5-nitroso-4(3*H*)-pyrimidinone (**103**, R = NH_2);[2421,2427] with urea gave 6-amino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione;[2421] and with thiourea gave 6-amino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (77%).[2421] Likewise, α-nitrosomalononitrile with *N*,*N*-dimethylguanidine gave 2-dimethylamino-5-nitroso-4,6-pyrimidinediamine (29%);[2645] the silver salt of α-nitrosomalononitrile with 2-dimethylamino-4-pyrimidinecarboxamidinium chloride gave 2′-dimethylamino-5-nitroso-2,4′-bipyrimidine-4,6-diamine (**104**) (84%);[57] and other such condensations have been reported.[1686,2431,2656]



102 **103** **104**

Several nitrosopyrimidines have been made by primary syntheses involving the degradation of bicyclic molecules (Section 2.6.3). For example, 8-propyl-2,6(1*H*,3*H*)-purinedione 7-oxide (**105**) in boiling aqueous buffer (pH 5) gave 6-amino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**106**) (~ 25%);[1593] and 7-dimethylamino-5-methyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxide (**107**) with aniline gave 4-anilino-6-dimethylamino-2-methyl-5-nitrosopyrimidine (**108**) (80%), perhaps with the loss of hyponitrous acid.[1733]



105 **106** **107** **108**

5.2.1.2. By Nitrosation

The presence of three electron-donating groups is necessary to ensure 5-nitrosation of a pyrimidine substrate, but two such groups are sometimes enough: for example, 4,6-pyrimidinediamine[1493,2441] and 4,6(1*H*,5*H*)-pyrimidinedione[1493] underwent nitrosation, but their respective isomers, 2,4-

pyrimidinediamine[4776] and 2,4(1*H*,3*H*)-pyrimidinedione,[1493] did not. The usual procedure is to treat the substrate in aqueous acetic acid at room temperature with sodium nitrite, followed by eventual pH adjustment if necessary; the use of dilute mineral acid has been recommended for less facile nitrosations, but there appears to be no hard evidence for its efficacy except for improving the solubility of weakly basic substrates. Extranuclear *C*- or *N*-nitrosations do not require the presence of electron-donating groups.

Appropriate substrates underwent *regular (acidic) nitrosation* under the conditions just outlined to afford the following products.

5-Nitrosopyrimidines

5-Nitroso-2,4,6-pyrimidinetriamine (99%).[1739]

4-Dimethylamino-6-methylamino-5-nitroso-2-pyrimidinamine (at 80°: 79%).[2626]

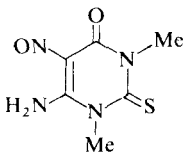
6-Amino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (> 90%).[1440,1594]

6-Amino-1-hydroxy-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (89%).[1278]

4-Amino-6-methylamino-5-nitroso-2(1*H*)-pyrimidinone (at 50–60°: > 95%).[1015]

6-Amino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (90%).[1298,1595]

6-Amino-1,3-dimethyl-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**109**) (96%).[1116]



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2-Amino-6-methylthio-5-nitroso-4(3*H*)-pyrimidinone (at 40°: 95%).[299]

5-Nitroso-6-pentyloxy-2,4-pyrimidinediamine (at 70°: 91%).[4777]

6-Methylthio-5-nitroso-2,4-pyrimidinediamine (at < 40°: > 95%).[1768]

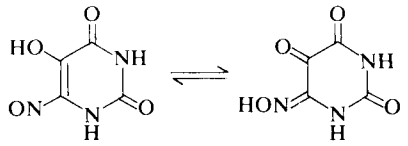
6-Benzylidenehydrazino-2-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (92%).[4764]

Also many other examples.[585,999,1051,1064,1073,1076,1280,1376, 1386,1397, 1444,1558,1595,1658,2079, 2182,2276,2309,2390,2419,2452,2625,3415, 3522, 3844, 3963, 4292, 4778–4782]

4/6-Nitrosopyrimidines

5-Hydroxy-6-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**110**) (85%).[1339]

2-Amino-5-hydroxy-6-nitroso-4(3*H*)-pyrimidinone (94%).[581,1341]



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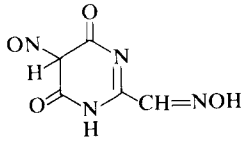
Extranuclear *C*-nitrosopyrimidines

Simple examples: see Section 4.2.3.3

5-Nitroso-4,6-dioxo-1,4,5,6-tetrahydro-2-pyrimidinecarbaldehyde oxime (**111**) [by dinitrosation of 2-methyl-4,6(1*H*,5*H*)-pyrimidinedione: 89%].[937]



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Extranuclear *N*-nitrosopyrimidines

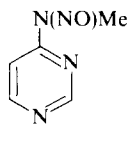
2-(*N*-Methyl-*N*-nitrosoamino)pyrimidine (30%) or its 4-isomer (**112**) (32%).[4783]

2-(*N*-Carboxymethyl-*N*-nitrosoamino)pyrimidine (65%).[4787]

6-Amino-5-(*N*-benzyl-*N*-nitrosoamino)-2,4(1*H*,3*H*)-pyrimidinedione (65%).[1398]

5-(*N*-Methyl-*N*-nitrosoamino)methyl-2,4(1*H*,3*H*)-pyrimidinedione (**113**) (> 20%).[4784]

2-Isopropylthio-6-(*N'*-methyl-*N'*-nitrosoureido)-4(3*H*)-pyrimidinone (**114**) (in 98% HCO_2H at < 5°: 90%);[156] also homologs.[250]



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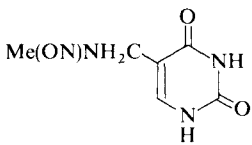

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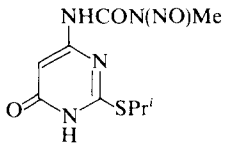

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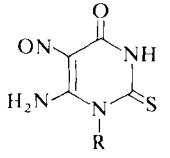
Nuclear *N*-nitrosopyrimidine

Methyl 4-methyl-2,6-bis-*o*-nitrophenyl-1-nitroso-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (preparation[4822] and structure[571]).

Some *variant nitrosation procedures* are evident in the nitrosation of 6-D-ribitylamino-2,4(1*H*,3*H*)-pyrimidinedione (barium nitrite, AcOH) followed by

isolation of the 5-nitroso derivative as its barium salt (> 58%);[1021] in the isolation of 5-nitroso-2-trifluoromethyl-4,6(1*H*,5*H*)-pyrimidinedione (83%) by extraction into ether;[4131] in the nitrosation of 2-amino-6-methyl-4(3*H*)-pyrimidinone in dimethylformamide containing sodium nitrite by the slow addition of formic acid at 30°;[1281] and in the nitrosation of appropriate water-insoluble substrates in an organic solvent by the addition of a nitrite ester with (sometimes) a trace of acid, to give 6-amino-1-benzyl-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**115**, R = CH_2Ph) (dioxane, isopentyl nitrite: < 95%),[4786] 6-amino-1-dibenzylamino-5-nitroso-2,4(1*H*,3*H*)pyrimidinedione (EtOH, isopentyl nitrite: ~50%),[585] 6-amino-1-dimethylamino-5-nitroso-2-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**115**, R = NMe_2) (EtOH, isopentyl nitrite: ~50%),[585] 6-cyclohexylamino-3-methyl-5-nitroso-1-piperidino-2,4(1*H*,3*H*)-pyrimidinedione (EtOH, isopentyl nitrite at 40°: > 95%),[2079] 6-(hydroxymethyl)amino-1, 3-dimethyl-5-nitroso-2, 4(1*H*, 3*H*)-pyrimidinedione (EtOH, pentyl nitrite: 78%),[2276,4785] 5-(*N*-methyl-*N*-nitrosoamino)-4-pyrimidinamine (EtOH, isopentyl nitrite at 80°: 95%),[4790] and other such products.[882,1317,6309] Extranuclear nitrosation by the Claisen procedure in the presence of a strong base has been discussed in Section 4.2.3.3. The use of *N*-nitrosodimethylamine as a nitrosating agent is exemplified at the end of the next paragraph, and the use of nitrosyl chloride/pyridine is illustrated in the conversion of 4-benzylamino-6-*p*-chlorophenyl-2-pyrimidinamine into its 5-nitroso derivative (NOCl, pyridine, $CHCl_3$, 5°, 30 min: 75%).[452]



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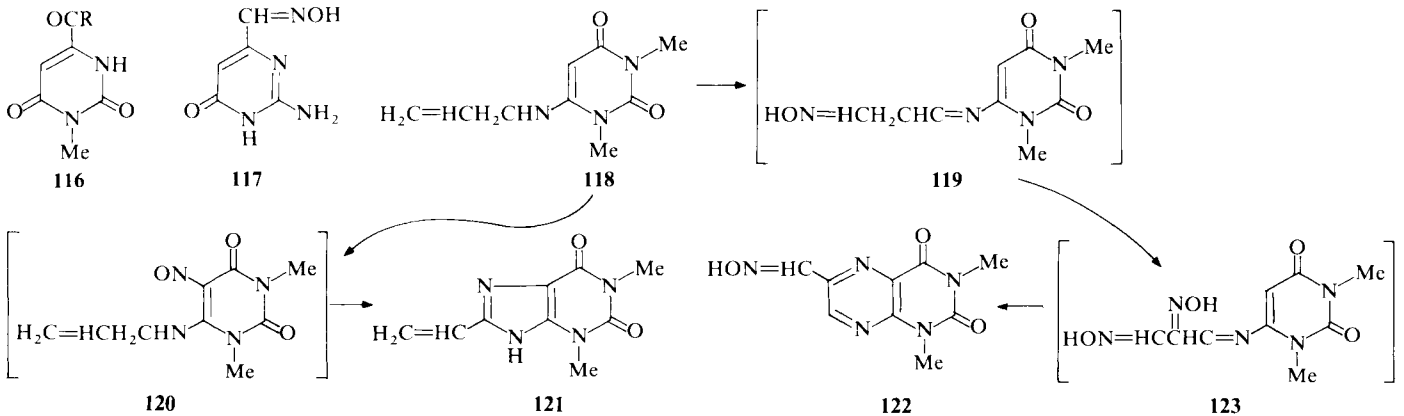
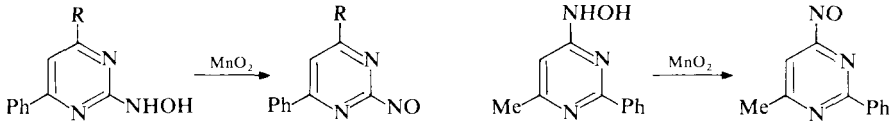
Occasionally, *complication of nitrosation reactions* may occur on account of concomitant or subsequent reactions. For example, 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbohydrazide (**116**, R = $NHNH_2$) with nitrous acid at 25° gave 6-amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione, perhaps via the azidocarbonyl analog (**116**, R = N_3), which was isolated if the reaction was done at 0°;[1114] 1-amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with nitrous acid at < 5° gave 5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (40%);[1518] 2-amino-6-carboxymethyl-4(3*H*)-pyrimidinone with warm aqueous nitrous acid gave 2-amino-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde oxime (**117**) (55%);[949] 6-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione likewise gave 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime;[701] and 2-(ethoxycarbonylmethyl)aminopyrimidine gave 2-(*N*-carboxymethyl-*N*-nitrosoamino)pyrimidine (65%).[4787] After nitrosation, spontaneous cyclization may ensue. For example, 6-allylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**118**) underwent nitrosation in aqueous solution at


OCR
NH
O
O
N
Me
116
CH=NOH
N
O
N
H
NH2
117
H2C=HCH2CHN
O
N
Me
O
N
Me
118
HON=HCH2CHC=N
O
N
Me
O
N
Me
119
ON
H2C=HCH2CHN
120
H2C=HC
N
N
H
121
HON=HC
122
NOH
HON=HCCHC=N
123

the allyl group to give the oxime (**119**), which then underwent a second nitrosation to afford the dioxime (**123**) and subsequent cyclization to 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pteridinecarbaldehyde oxime (**122**) (33%);[859] in contrast, the same substrate (**118**) underwent 5-nitrosation in hot ethyl acetate by isopentyl nitrite–*p*-toluenesulfonic acid to give a deeply colored solution of the intermediate (**120**), which gradually cyclized with loss of color to afford 1,3-dimethyl-8-vinyl-2,6(1*H*,3*H*)-purinedione (**121**) (54%).[859] Other such cyclizations have been reported.[859,4788] The use of *N*-nitrosodimethylamine–phosphoryl chloride as a nitrosating procedure for 6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave the 5-nitroso derivative, which then condensed with a second equivalent of substrate to afford 1,3,7,9-tetramethylpyrimido[5,4-*g*]pteridine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (30%);[2630] related reactions have been described.[2630,4789]

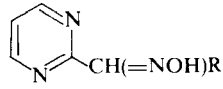
5.2.1.3. By Indirect Syntheses

The conversion of 2-pyrimidinamine into 2-*S*,*S*-dimethylsulfimidopyrimidine (**39**) and thence into 2-nitrosopyrimidine (**40**)[3545] has been mentioned in Section 5.1.1.3. Oxidation of 2-hydroxyamino-4-phenyl- (**124**, R = H), 2-hydroxyamino-4,6-diphenyl- (**124**, R = Ph), or 4-hydroxyamino-6-methyl-2-phenylpyrimidine (**126**) by (activated) manganese dioxide in chloroform at 20° gave 2-nitroso-4-phenyl- (**125**, R = H) (95%), 2-nitroso-4,6-diphenyl- (**125**, R = Ph) (89%), or 4-methyl-6-nitroso-2-phenylpyrimidine (**127**) (93%), respectively;[512,6016] analogs were made similarly[6014,6016] and proved reasonably stable.



124 **125** **126** **127**

As they are tautomeric with aldoximes or ketoximes, extranuclear and some nuclear nitrosopyrimidines may be made by the action of hydroxylamine on the appropriate carbonyl substrate. For example, 2-pyrimidinecarbaldehyde and 2-phenacylpyrimidine with aqueous or ethanolic hydroxylamine gave their respective "nitroso" derivatives, the aldoxime (**128**, R = H) (70%)[2753] and the ketoxime (**128**, R = Ph) (85%);[4702] similarly, 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (alloxan) with hydroxylamine gave 5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (violuric acid) (**94**), tautomeric with the ketoxime (**95**).[3561,3562]



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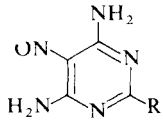
5.2.2. Properties of Nitrosopyrimidines

Although no kinetic measurements appear to have been reported, it is clear that a 5-nitroso group has a powerful electron-withdrawing effect, thereby activating leaving groups in the same molecule towards nucleophilic displacement. For example, the well-known resistance of 2-methylthiopyrimidines toward aminolysis (see Section 8.4.2.2) was reduced dramatically by the insertion of a 5-nitroso group: 2-methylthio-5-nitroso-4,6-pyrimidinediamine (**129**, R = SMe) with aqueous dimethylamine under reflux for a few minutes gave 2-dimethylamino-5-nitroso-4,6-pyrimidinediamine (**129**, R = NMe_2) (85%);[1310] 6-amino-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone (**130**, R = SMe) with aqueous hydroxylamine at 20° for 3 h gave 6-amino-2-hydroxyamino-5-nitroso-4(3*H*)-pyrimidinone (**130**, R = NHOH) (98%);[1310] and the same substrate (**130**, R = SMe) with aqueous dimethylamine under reflux for 20 min gave 6-amino-2-dimethylamino-5-nitroso-4(3*H*)-pyrimidinone (**130**, R = NMe_2) (> 60%).[1077] A similar effect was observed on the acidic hydrolysis of 4/6-amino groups: for example, 5,6-diamino-2,4(1*H*,3*H*)-pyrimidinedione was unaffected by boiling 6*M* hydrochloric acid, but its 5-nitroso analog (**131**) gave 5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (86%) in just 10 min.[1590]



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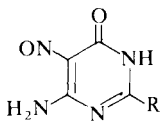

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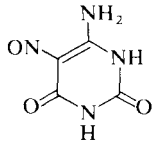

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The extraordinary range of colors shown by 5-nitrosopyrimidines (according to the other substituents present) has fascinated chemists since the earliest times, but extensive descriptive studies of such nitrosopyrimidines, their organic or metallic salts, and their metallic complexes have produced few meaningful attempts at correlation.[1060,1112,1594,3564,3883,4791–4795,4798–4801] However, practical analytical procedures for the quantitative determination of Fe^{2+}, Co^{2+}, Co^{3+}, Ni^{2+}, Cu^{2+}, and other metallic ions by colorimetric means have been based on the formation of uniquely colored complexes between each such ion and one of several nitrosopyrimidines; gravimetric methods have also been based on the formation of such complexes.[924,1113,2708,4796,4802,4803]

5.2.3. Reactions of Nitrosopyrimidines

The most useful reaction of nitrosopyrimidines is reduction to the corresponding pyrimidinamines. However, nitrosopyrimidines may undergo oxidation to the corresponding nitropyrimidines, cyclizations to heterobicyclic compounds, and several other minor reactions.

5.2.3.1. Reduction to Pyrimidinamines

Hydrogenation of nitrosopyrimidines was little used until recent years, perhaps for fear of chelation at the surface of the catalyst. Even now, sodium dithionite appears to be the reagent of choice, although ammonium hydrogen sulfide is still used from time to time and most of the other classical reducing agents have been employed occasionally.

The use of various reagents is illustrated in the reduction of the following nitrosopyrimidines to the corresponding aminopyrimidines (except where indicated otherwise).

Sodium dithionite (usually in dilute aqueous alkali)

6-Amino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (> 62% as sulfate).[2421, 2436,4297]

6-Amino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (at < 30°: 97%).[1595,2327]

6-Amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (in NH_4OH: 85%).[1107,2428]

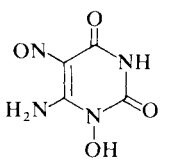
5-Nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (in H_2O: > 90%).[1658]

6-Dimethylamino-2-methylthio-5-nitroso-4-pyrimidinamine (in H_2O: > 89%).[1569]

6-Benzyloxy-5-nitroso-2,4-pyrimidinediamine (in H_2O: ~ 70%).[2452]

6-Amino-1-benzyl-5-nitroso-2-thioxo-1,2-dihydro-4(1*H*)-pyrimidinone (in boiling H_2O: 98%).[4786]

6-Amino-1-hydroxy-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**132**) (at 25°: 83%).[1278]



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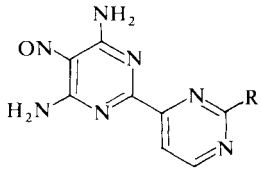

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2-Amino-6-methylamino-5-nitroso-4(3*H*)-pyrimidinone (in $HCONH_2$–HCO_2H at 110°: ~ 90% as 5-formamido analog).[1281]

5-Nitroso-2,4,6-pyrimidinetriamine (in H_2O at 80°: 82% as sulfate).[1739]

6-Amino-1-methyl-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (in boiling H_2O: 77%).[1444]

2′-Dimethylamino- (**133**, R = NMe_2) or 2′-methoxy-5-nitroso-2,4′-bipyrimidine-4,6-diamine (**133**, R = OMe) (respectively, in alkali: 82%; or in pyridine under reflux: 85%).[57]

Also other examples.[1103,1310,1317,1376,2343,2390,2419–2421,2625, 4290,4726, 4782,4804,4805]

Hydrogenation (catalyst given)

6-Amino-2-dimethylamino-5-nitroso-4(3*H*)-pyrimidinone (Ni in MeOH: ~ 90% as dihydrochloride).[1073]

6-Methoxy-5-nitroso-2,4-pyrimidinediamine (Ni in MeOH: ~ 60%).[2391]

4-Methoxy-6-methylamino-5-nitroso-2-pyrimidinamine (Ni in MeOH: ~ 85%).[2182]

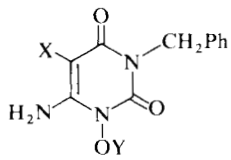
6-Acetamido-2-methylthio-5-nitroso-4-pyrimidinamine (Ni in tetrahydrofuran: ~ 60%; note survival of SMe group).[638]

4,6-Bisdimethylamino-5-nitroso-2-pyrimidinamine (Ni in EtOH: 71% as sulfate).[1739]

6-Amino-1-methyl-2-methylthio-5-nitroso-4(1*H*)-pyrimidinone (Ni in Me_2NCHO).[1116]

6-Amino-2-(ε-carboxypentyl)amino-5-nitroso-4(3*H*)-pyrimidinone (Pd in aqueous NaOH: 70%).[4807]

6-Amino-3-benzyl-1-benzyloxy-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**134**, X = NO, Y = CH_2Ph) [Pd *in* HCO_2H: 6-amino-5-formamido-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (**134**, X = NHCHO, Y = H) (87%)].[1280]



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6-Amino-2-methyl-5-nitroso-4(3*H*)-pyrimidinone (Pd at pH 8: > 95%).[3930]

6-Amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (Pd in HCO_2H: 5-NHCHO analog).[3721]

2-Methylthio-5-nitroso-4,6-pyrimidinediamine [Pt in EtOH: 34% as 4-amino-2-methylthio-7(8*H*)-pteridinone].[3532]

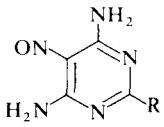
5-Nitroso-6-pentyloxy-2,4-pyrimidinediamine (Pt in MeOH).[4777]

Also other examples.[1021,1076,1104,2404,2428,2623,2626]

Hydrogen sulfide (as a salt)

6-Amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione;[1106,2428] 1,3-dialkyl homologs also.[586]

1-Carboxymethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (aqueous H_2S: 69%).[3963]



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2-Methyl- (**135**, R = Me) or 2-methylthio-5-nitroso-4,6-pyrimidinediamine (**135**, R = SMe) (at 0°: each > 50%).[1558]

6-Methylthio-5-nitroso-2,4-pyrimidinediamine (aqueous NaHS at 65°: 78% crude).[3522]

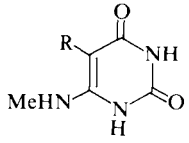
6-Amino-1-dimethylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (at 25°: > 50%).[585]

6-Methylamino-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone (at > 90°: 90%).[3872]

Also other examples.[1298]

Zinc/formic acid

6-Methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**136**, R = NO) [Zn dust in refluxing 98% HCO_2H: 5-NHCHO analog (**136**, R = NHCHO) (~ 85%)].[1376]



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1- or 3-Methyl-6-methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione [likewise: 5-NHCHO analog (~ 60%[1397] or ~ 65%,[1398] respectively)].

6-Benzylamino-3-ethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione [likewise: 5-NHCHO analog (> 70%)].[4808]

6-Amino-1-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione [Zn dust in 80% HCO_2H at 40°: 5-NHCHO analog (90%)].[1285]

Other reagents

6-Amino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (Zn/H_2SO_4).[2428]

1,3-Diethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (conc. aq. HI at − 20°: 95% as hydriodide).[1064]

1-Carboxymethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione ($SnCl_2$/HCl: 70%).[3963]

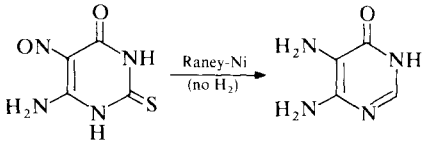
2,6-Diamino-5-nitroso-4(3*H*)-pyrimidinone (electrolytic in HCl with Pb or Zn cathode: 80%;[3672] $SnCl_2$/1*M* HCl: > 40% as sulfate[1592]).

6-Amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (Fe/HCl: 95%).[1271]

6-β-Hydroxyethylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione ($NaHSO_3$ in H_2O at 90°).[4779]

6-Amino-2-methyl-5-nitroso-4(3*H*)-pyrimidinone (excess Raney-Ni in H_2O at 70°: 72%).[2421]

6-Amino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**137**) [excess Raney-Ni in H_2O at 70°: 5,6-diamino-4(3*H*)-pyrimidinone (**138**) (63%)].[2421]



137 **138**

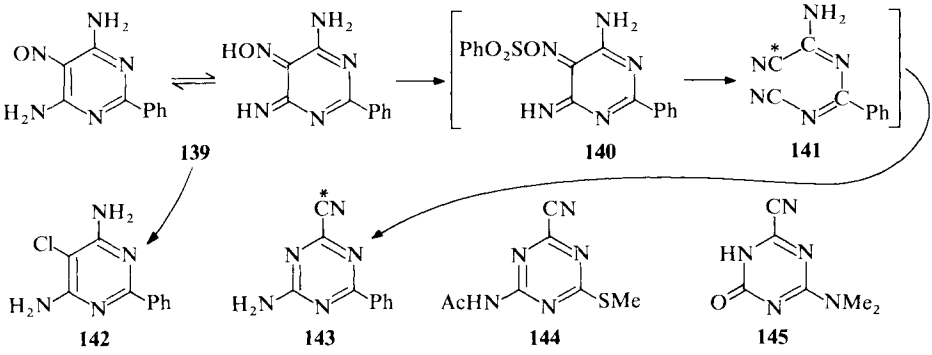
Representative 2- or 4-nitrosopyrimidines underwent a reductive reaction with phenylhydrazine in refluxing ethanol for 20 min to afford the corresponding 2- or 4-hydroxyaminopyrimidines: 2-hydroxyamino-4,6-diphenyl- (67%) and the isomeric 4-hydroxyamino-2,6-diphenylpyrimidine (50%) were so made.[6016]

5.2.3.2. Oxidation to Nitropyrimidines

The useful oxidation of 5-nitroso- into 5-nitropyrimidines has been discussed in Section 5.1.1.3.

5.2.3.3. Rearrangement to 1,3,5-Triazines

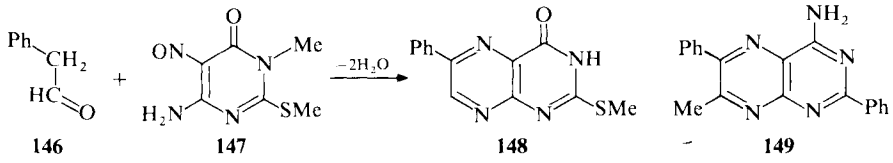
Rearrangement of 5-nitroso-4-pyrimidinamines into triazines occurs in the presence of benzenesulfonyl chloride–pyridine, thionyl chloride, phosphoryl chloride–pyridine, trifluoroacetic anhydride, or even acetic anhydride.[2645,4809] Thus 5-nitroso-2-phenyl-4,6-pyrimidinediamine (**139**) (in $PhSO_2Cl$–pyridine) afforded 4-amino-6-phenyl-1,3,5-triazine-2-carbonitrile (**143**) (30%) possibly via the intermediates (**140** and **141**),[2645] although an alternative mechanism was suggested subsequently.[4810] When such a rearrangement of the substrate (**139**) was attempted in neat phosphoryl chloride, 5-chloro-2-phenyl-4,6-pyrimidinediamine (**142**) (25%) was the only isolable product,[2645] whereas in the presence of pyridine only the triazinecarbonitrile (**143**) resulted;[4809] confusingly, both products (**142** and **143**) had virtually the same melting point.[2645] Likewise, 2-methylthio-5-nitroso-4,6-pyrimidinediamine gave 4-acetamido-6-methylthio-1,3,5-triazine-2-carbonitrile (**144**) (Ac_2O: 38%), 6-amino-2-dimethyl-



amino-5-nitroso-4(3*H*)-pyrimidinone gave 4-dimethylamino-6-oxo-1,6-dihydro-1,3-5-triazine-2-carbonitrile (**145**) (Ac_2O: 95%), and several other examples have been reported.[2645,4809]

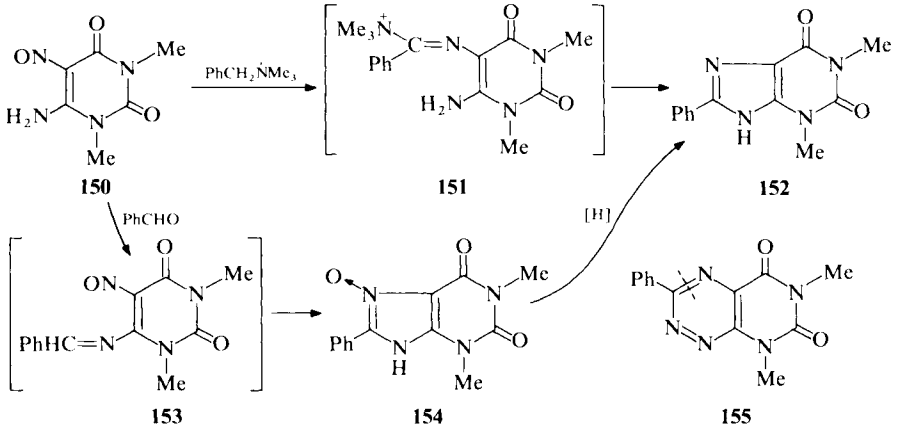
5.2.3.4. Conversion into Fused Pyrimidine Systems

Several heterobicyclic systems may be made directly from nitrosopyrimidines. The best known of such procedures in the (usually) unambiguous *Timmis synthesis of pteridines*,[4814] which involves the condensation of 5-nitroso-4-pyrimidinamines with α-carbonylmethylene and related compounds to give a single 6- and/or 7-substituted pteridine in each case.[4811] For example, boiling neat 6-amino-3-methyl-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone (**147**) and 2-phenylacetaldehyde (**146**) under a Dean–Stark water separator gave 3-methyl-2-methylthio-6-phenyl-4(3*H*)-pteridinone (**148**) (21%);[1286] 5-nitroso-2-phenyl-4,6-pyrimidinediamine with α-phenylacetone in boiling butanol containing sodium acetate gave 7-methyl-2,6-diphenyl-4-pteridinamine (**149**) (42%);[4812] and 5-nitroso-4,6-pyrimidinediamine with ethyl 2-phenylacetate in refluxing ethanolic ethoxide gave 4-amino-6-phenyl-7(8*H*)-pteridinone (41%).[4813] Hundreds of pteridines have been so made.[4811]



Somewhat analogous procedures have been used[4815] to convert 5-*nitroso*-4-*pyrimidinamines into purines*. For example, 6-amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**150**) with benzyltrimethylammonium iodide in refluxing dimethylformamide afforded 1,3-dimethyl-8-phenyl-2,6(1*H*,3*H*)-purinedione (**152**) (31%) by elimination of trimethylamine from the putative intermediate (**151**);[4816] the same substrate (**150**) with benzaldehyde in dimethyl-

formamide gave the Schiff base (**153**) and thence 1,3-dimethyl-8-phenyl-2,6(1*H*,3*H*)-purinedione 7-oxide (**154**), which was subsequently reduced to the purinedione (**152**) in moderate yield, especially in the presence of formic acid;[4817, cf. 2276,4818] and many other variations have been reported.[2276,4785,4817–4821] It is even possible to obtain an 8-unsubstituted purine: for example, 6-amino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione with formaldehyde in hot dimethyl sulfoxide gave 2,6(1*H*,3*H*)-purinedione 7-oxide (40%); while 6-methylamino-5-nitroso-1,3-diphenyl-2,4(1*H*,3*H*)-pyrimidinedione in boiling dimethylformamide gave 1,3-diphenyl-2,6(1*H*,3*H*)-purinedione (72%) directly.[882]



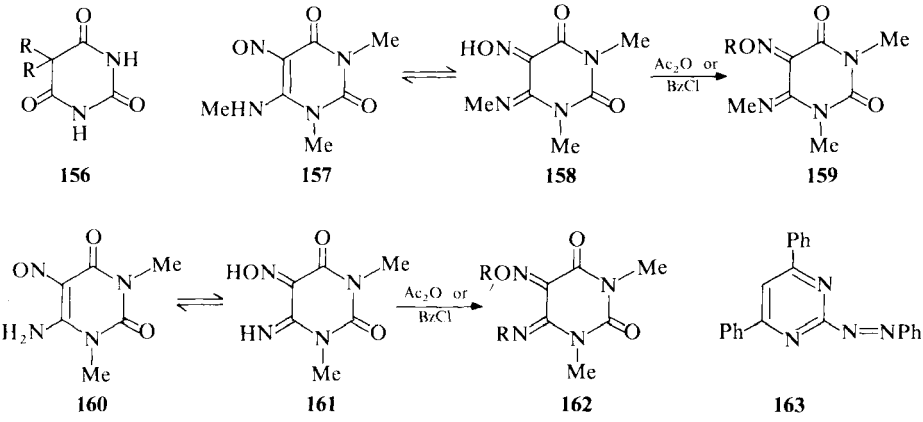
In a very similar way, the conversion of *4-hydrazino-5-nitrosopyrimidines into pyrimido[5,4-e]-as-triazines* is possible. For example, 6-hydrazino- was converted into 6-benzylidenehydrazino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione, which underwent cyclization in refluxing ethanolic hydrochloric acid to afford 6,8-dimethyl-3-phenylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**155**) (63%).[1277]

5.2.3.5. Other Reactions

Some other reactions of nitrosopyrimidines are illustrated in the following examples.

1. Treatment of 5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with aqueous chlorine at 30–40° or with aqueous bromine at 25° gave 5,5-dichloro- (**156**, R = Cl) (70%) or 5,5-dibromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**156**, R = Br) (80%), respectively.[1842]
2. 1,3-Dimethyl-6-methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**157**) underwent monoacylation on the hydroxyimino group of the tautomer

(**158**) to afford, for example, 5-acetoxyimino- (**159**, R = Ac) (55–70%) or 5-benzoyloxyimino-1,3-dimethyl-6-methylimino-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**159**, R = Bz) (72–75%);[2684,4820] in contrast, the primary amine, 6-amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (**160**), underwent diacylation of its tautomer (**161**) to afford, for example, 5-acetoxyimino-6-acetylimino- (**162**, R = Ac) (> 50%) or 6-benzoylimino-5-benzoyloxyimino-1,3-dimethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**162**, R = Bz) (> 67%).[641,4810] The foregoing products were powerful acylating agents.



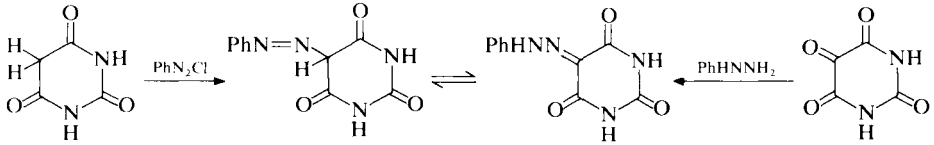
156 **157** **158** **159**

160 **161** **162** **163**

3. 2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime underwent *O*-acetylation in acetic anhydride to afford 6-acetoxyiminomethyl-2,4(1*H*,3*H*)-pyrimidinedione (67%).[701]
4. Treatment of 2-nitroso-4,6-diphenylpyrimidine with aniline, in acetic acid–chloroform, gave 4,6-diphenyl-2-phenylazopyrimidine (**163**) (60%).[512,6016] Other 2- and 4-phenylazopyrimidines were made similarly.[6014,6016]
5. Nucleophilic displacement of a 2- or 4/6-nitroso group is seen in the formation of 2-methoxy-4,6-diphenylpyrimidine (MaOMe, MeOH–$CHCl_3$, 20°, 10 min: 58%), 4-methoxy-2,6-diphenylpyrimidine (likewise: 39%), and 4,6-diphenyl-2(1*H*)-pyrimidinone (HCl, EtOH–H_2O, 20°?, briefly?: 35%), each from the corresponding nitroso substrate.[6016]
6. Stirring 4-hydroxyamino- with 4-nitroso-2,6-diphenylpyrimidine in chloroform (20°, 30 min) gave 2,2′,6,6′-tetraphenyl-4,4′-azoxypyrimidine (98%).[6016] Similar symmetrical azoxypyrimidines were obtained in quite good yield by treatment of 2- or 4/6-hydroxyaminopyrimidines with limited quantities of peroxymaleic acid or sodium hypochlorite under mild conditions, presumably by partial oxidation to a nitroso intermediate that promptly condensed with yet-unchanged hydroxyaminopyrimidine.[6013]

5.3. ARYLAZOPYRIMIDINES

An arylazo group can be attached to a pyrimidine under remarkably mild conditions that may not affect even quite labile substituents in the substrate. It is usually accommodated at the 5-position, but sometimes it can be attached at another nuclear carbon or at an extracyclic carbon or nitrogen. In the presence of a suitably placed tautomeric substituent, an arylazo group (—N=NAr) may exist at least partially as an arylhydrazono group (=N—NHAr): for example, 5-phenylazo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**165**) resulted from coupling 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione **(164)** with a benzenediazonium salt [519,4824,4840] or from treatment of 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione **(166)** with phenylhydrazine.[4823] Early evidence on such systems (obtained without benefit of modern spectral techniques) favored the arylhydrazono at the expense of the arylazo tautomers,[4213, cf. 519] but it is still customary to formulate all nuclear arylazopyrimidines as such. In contrast, extranuclear arylazo derivatives are usually formulated as arylhydrazones of the appropriate pyrimidine aldehydes or ketones, perhaps because they are often made from such carbonyl compounds.



164 **165** **166**

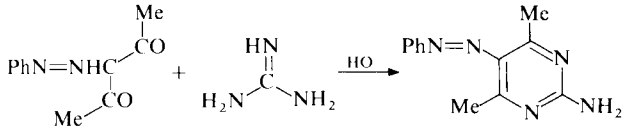
5.3.1. Preparation of Arylazopyrimidines

Most nuclear arylazopyrimidines are made by coupling an existing pyrimidine with a diazotized aromatic amine or occasionally by "reverse coupling" of a phenol or aromatic amine with a diazotized 5-pyrimidinamine; others may be made by primary syntheses or by indirect syntheses.

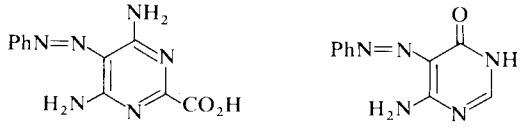
5.3.1.1. By Primary Syntheses

The formation of 5-arylazopyrimidines by the Principal Synthesis or by other primary syntheses has been covered in Chapters 3 and 2, respectively, but a few simple examples follow. 3-Phenylazopentane-2,4-dione (**167**) with guanidine in methanolic alkali at 50–70° gave 4,6-dimethyl-5-phenylazo-2-pyrimidinamine (**168**) (70%);[645,4050] α-phenylazomalononitrile with formamidine in ethanolic ethoxide gave 5-phenylazo-4,6-pyrimidinediamine (75%);[1619] ethyl 3-oxo-4-phenyl-2-phenylazobutyrate with thiourea in refluxing methanolic methoxide gave 6-benzyl-5-phenylazo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone

(60%);[4173] α-phenylazomalondiamidine with diethyl oxalate in ethanolic ethoxide at 25° gave 4,6-diamino-5-phenylazo-2-pyrimidinecarboxylic acid (**169**) (~ 20%);[1405] and 2-amidino-2-phenylazoacetamide hydrochloride with formamide at 150–170° gave 6-amino-5-phenylazo-4(3*H*)-pyrimidinone (**170**) (63%).[3185]



167 **168**



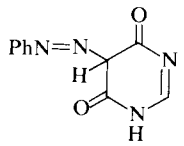
169 **170**

5.3.1.2. By Diazo-Coupling

Pyrimidines usually require the presence of at least two powerful electron-donating groups to permit *regular diazo coupling* at the 5-position or at a 4- or 6-position if the 5-position is occupied; when insufficient electron donation exists, attack may occur at an extracyclic carbon, nitrogen, or sulfur atom. Thus treatment of an appropriate substrate with a prediazotized aromatic amine, usually in mildly basic aqueous solution at or below room temperature, gave the following products.

5-Arylazopyrimidines

2-Methyl-5-phenylazo-4,6(1*H*,5*H*)-pyrimidinedione **(171)** (84%).[2637]



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6-Amino-5-phenylazo-2,4(1*H*,3*H*)-pyrimidinedione (~ 90%).[2437]

5-*p*-Chlorophenylazo-2,4-pyrimidinediamine (35%).[1650,4837]

5-*p*-Ethoxycarbonylphenylazo-2,4,6-pyrimidinetriamine (83%).[4826]

6-Chloro-5-phenylazo-2,4-pyrimidinediamine (72%).[1644]

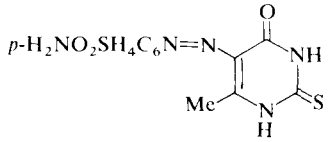
5-*p*-Nitrophenylazo-4,6-pyrimidinediamine (94%).[3615]

4-Ethylamino-2,6-dimethoxy-5-phenylazopyrimidine (36%).[2960]

5-(2′,4′-Dimethoxyphenylazo)-4-methyl-6-phenyl-2-pyrimidinamine (66%).[4052]

6-Methyl-5-*p*-sulfamoylphenylazo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone **(172)** (60%).[4830]

2-Amino-6-(3′-oxo-octyl)-5-phenylazo-4(3*H*)-pyrimidinone (73%).[635]



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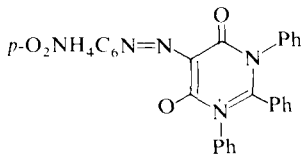

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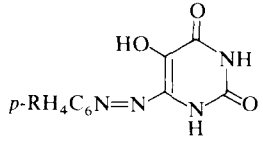
5-*p*-Nitrophenylazo-4-oxo-1,2,3-triphenyl-3,4-dihydropyrimidin-1-ium-6-olate **(173)** (*p*-nitrobenzenediazonium tetrafluoroborate in anhydrous MeCN followed by a tertiary amine: 66% yield overall).[233]

6-*β*-Hydroxyethylamino-5-phenylazo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (67%).[3872]

Also innumerable other examples in the foregoing references and elsewhere.[133,245,581,645,937,1042,1374,1484,1555,2137,2344,2441,2453,2474,3522,3635,3673,3686,3735,3869,3887,3959,3962,3965,4382,4805,4825, 4827–4829, 4831–4836, 4840,4859,7012]

4/6-Arylazopyrimidines

5-Hydroxy-6-*p*-sulfophenylazo-2,4(1*H*,3*H*)-pyrimidinedione (**174**, R = SO_3H).[4838,4839]



174

5-Hydroxy-6-phenylazo-2,4(1*H*,3*H*)-pyrimidinedione (**174**, R = H).[4839]

6-*p*-Chlorophenylazo-5-hydroxy-4(3*H*)-pyrimidinone (83%).[581]

2-Amino-5-hydroxy-6-*p*-sulfophenylazo-4(3*H*)-pyrimidinone.[581,1341]

4-*p*-Nitrophenylazo-5-pyrimidinol (22%).[1737]

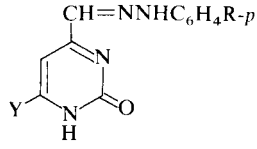
4-Amino-5-hydroxy-6-*p*-nitrophenylazo-2(1*H*)-pyrimidinone (78%).[582]

5-Methylamino-6-phenylazo-2,4(1*H*,3*H*)-pyrimidinedione (95%).[579]

2-Acetamido-5-hydroxy-6-*p*-nitrophenylazo-4(3*H*)-pyrimidinone [from 2-acetamido-5-acetoxy-4(3*H*)-pyrimidinone: 95%].[582]

Extranuclear *C*-arylazopyrimidines

2-Oxo-1,2-dihydro-4-pyrimidinecarbaldehyde *p*-chlorophenylhydrazone (**175**, R = Cl, Y = H) (> 95%) and its 6-methyl derivative (**175**, R = Cl, Y = Me);[4712] cf. the phenylhydrazones (**175**, R = H, Y = H or Me) formulated incorrectly.[2637]



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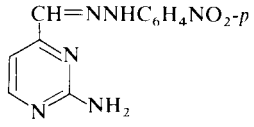
2-Methoxy-4-pyrimidinecarbaldehyde *p*-nitrophenylhydrazone (60%).[3328]

4-Oxo-3,4-dihydro-2-pyrimidinecarbaldehyde *p*-nitrophenylhydrazone (17%).[582]

Products from 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione or 4-amino-5-methyl-2(1*H*)-pyrimidinone with arenediazonium salts: still of indeterminate structure.[1493,4712,4841–4845]

Extranuclear attack by arenediazonium salts is further illustrated by the reaction of 4-methyl-2-pyrimidinamine, under mildly acidic conditions, with *p*-nitrobenzenediazonium chloride to give 2-amino-4-pyrimidinecarbaldehyde *p*-nitrophenylhydrazone (**176**) but with *p*-chlorobenzenediazonium chloride to give 4-methyl-2-(3′-*p*-chlorophenyl-2′-triazeno)pyrimidine (**177**);[4846] of 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone with *p*-chlorobenzenediazonium chloride to afford the thioether, 2-*p*-chlorophenylthio-4(3*H*)-pyrimidinone (> 70%), with loss of nitrogen;[4847] of 4,6-diamino-2(1*H*)-pyrimidinethione (**178**, R = H) with *p*-chlorobenzenediazonium chloride to give a separable mixture of 4,6-diamino-5-*p*-chlorophenylazo-2(1*H*)-pyrimidinethione (**178**, R = N:NC$_6$H$_4$Cl-*p*) and 5-*p*-chlorophenylazo-2-*p*-chlorophenylthio-4,6-pyrimidinediamine (**179**);[4837] of 2(1*H*)-pyrimidinethione (or simple derivatives) with *p*-chloro-



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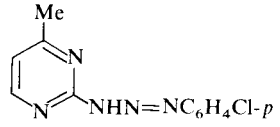

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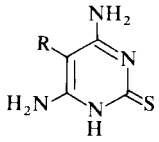

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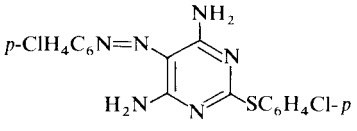

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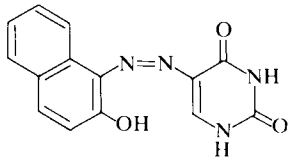
benzenediazonium chloride to give mainly 2-*p*-chlorophenylthiopyrimidine (or appropriate derivatives);[4846] of 4-phenacylpyrimidine with benzenediazonium chloride to qive 4-α-phenylhydrazonophenacylpyrimidine (66%), of proven fine structure;[503] and of other substrates with diazonium salts.[353,362]

The process of *reverse diazo-coupling* has rather limited use in the pyrimidine series. Although diazotized 5-pyrimidinamines were once reported not to couple with phenols or amines,[4848] this was later shown to be incorrect, first qualitatively[4849] and subsequently by isolation of 5-(2′-hydroxynaphthalen-1′-ylazo)-2,4(1*H*,3*H*)-pyrimidinedione (**180**) from diazotized 5-amino-2,4(1*H*,3*H*)-pyrimidinedione with β-naphthol.[4839] This type of reaction is further illustrated in the formation of the following azo compounds from diazotized 5-pyrimidinamines.



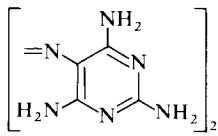
180

5-(2′-β-Diisopropylaminoethylaminonaphthalen-1′-ylazo)-2,4-dimethoxypyrimidine (in mildly acidic medium: 45%).[4850]

5-(2′,6′-Diaminopyridin-3′-ylazo)-2,4(1*H*,3*H*)-pyrimidinedione (89%).[4828]

5-(4′-Amino-6′-hydroxynaphthalen-1′-ylazo)-2,4(1*H*,3*H*)-pyrimidinedione (with 8-amino-2-naphthol in AcOH: 74%).[4828]

5,5′-Azopyrimidine-2,2′,4,4′,6,6′-hexamine (**181**) (from 2,4,6-triamino-5-pyrimidinediazonium chloride with 2,4,6-pyrimidinetriamine in acetate buffer: 63%).[2400]



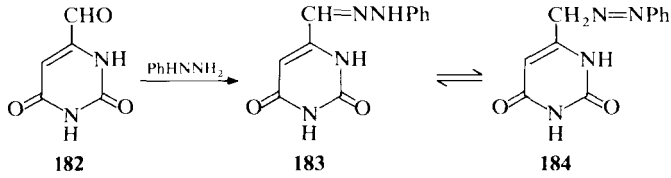
181

Also other examples in the foregoing references and elsewhere.[4839,4851] (See also Section 9.1.6.2).

5.3.1.3. By Other Means

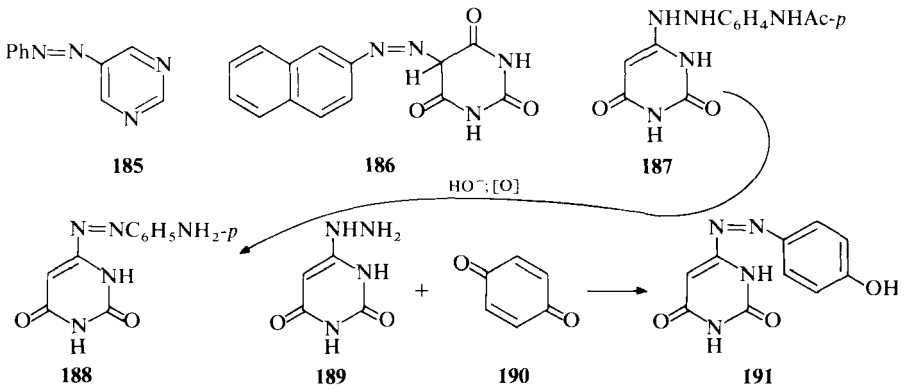
As mentioned at the beginning of Section 5.3, arylazopyrimidines can be made from *arylhydrazines with pyrimidine aldehydes or ketones.* Thus

alloxan (**166**) with phenylhydrazine gave 5-phenylazo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**165**);[4823,4852] 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde (**182**) with phenylhydrazine gave the phenylhydrazone (**183**) (74%), tautomeric with 6-phenylazomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**184**);[2858] and 2-acetyl-6-methyl-4(3*H*)-pyrimidinone with *p*-nitrophenylhydrazine gave the corresponding *p*-nitrophenylhydrazone.[671] This method for preparing such extranuclear arylhydrazones (covered fully in Sections 10.6.2, 10.7.2) has obvious advantages. Alkylhydrazones, e.g. 1,3,4-trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde dimethylhydrazone, must be made by this method.[3835]



The *remaining preparative routes*, which have been little developed in the pyrimidine series, are illustrated in the following examples.

1. 5-Pyrimidinamine reacted with nitrosobenzene in hot glacial acetic acid to give 5-phenylazopyrimidine (**185**) (~ 15%).[711]
2. 2-Nitroso-4,6-diphenylpyrimidine reacted with aniline to afford 4,6-diphenyl-2-phenylazopyrimidine (**163**) (60%).[512,6014,6016]
3. 5,5-Dichloro- or 5,5-dibromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione reacted with 2-naphthylhydrazine to furnish 5-naphthalen-2′-ylazo-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione (**186**).[4823]
4. 6-*N*′-(*p*-Acetamidophenyl)hydrazino-2,4(1*H*,3*H*)-pyrimidinedione (**187**) underwent oxidation and hydrolysis by boiling in dilute alkali to give 6-*p*-aminophenylazo-2,4(1*H*,3*H*)-pyrimidinedione (**188**) (42%).[4853]



5. 6-Hydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**189**) with *p*-benzoquinone (**190**) in ethanolic hydrochloric acid gave 6-*p*-hydroxyphenylazo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**191**) (85%);[4853] several analogs were made similarly.[4854]
6. The condensation of diazotized 4,5-dimethoxy-6-sulfanilamidopyrimidine with dimethylamine gave 4-*p*-(3,3′-dimethyltriazeno)benzene sulfonamido-5,6-dimethoxypyrimidine.[428]

5.3.2. Reactions of Arylazopyrimidines

As with nitro- and nitrosopyrimidines, the most useful reaction of arylazopyrimidines is their reductive cleavage to the corresponding pyrimidinamines (plus arylamines). However, they occasionally undergo cyclizations to fused pyrimidines.

5.3.2.1. Reduction to Pyrimidinamines

Hydrogenation, usually performed at atmospheric pressure over Raney-nickel, and the use of sodium dithionite appear to be the methods of choice for reducing arylazopyrimidines; other classical reagents have also been used. The processes are illustrated by the following transformations.

Hydrogenation (catalyst given)

5-Phenylazo- or 5-*p*-nitrophenylazo-4,6-pyrimidinediamine to 4,5,6-pyrimidinetriamine (Ni in EtOH at 100°/60 atm: > 90%).[1619,3615]

2-Guanidine-4,6-dimethyl-5-phenylazopyrimidine to 2-guanidino-4,6-dimethyl-5-pyrimidinamine [Ni in MeOH at n.t.p. (normal temperature and pressure: 20°, 1 atm.): ~60% as sulfate].[645]

5-*p*-Chlorophenylazo-6-methylamino-2,4-pyrimidinediamine to 6-methylamino-2,4,5-pyrimidinetriamine (Ni in EtOH at 90°/50 atm: 89% as sulfate).[1484]

6-Amino-5-phenylazo- to 5,6-diamino-2,4(1*H*,3*H*)-pyrimidinedione (Pd in AcOH at n.t.p.: ~ 75% as sulfate).[2437]

6-Benzylamino-5-phenylazo- to 5-amino-6-benzylamino-4(3*H*)-pyrimidinone (Pd in EtOH at n.t.p.: 70%).[4382]

2-Chloro-6-phenyl-5-phenylazo-4-pyrimidinamine to 2-chloro-6-phenyl-4,5-pyrimidinediamine (Ni in Me_2NCHO: 88%).[4855]

Also other examples.[1493,2246,2441,4856,4857]

Sodium dithionite

2,6-Diamino-5-phenylazo- to 2,5,6-triamino-4(3*H*)-pyrimidinone (boiling: isolated as sulfate).[3673]

2,6-Dimethyl-5-phenylazo- to 5-amino-2,6-dimethyl-4(3*H*)-pyrimidinone (40°).[750]

2-Amino-6-β-chloroethylamino-5-*p*-chlorophenylazo- to 2,5-diamino-6-β-chloroethylamino-4(3*H*)-pyrimidinethione (100°: 52%).[4827]

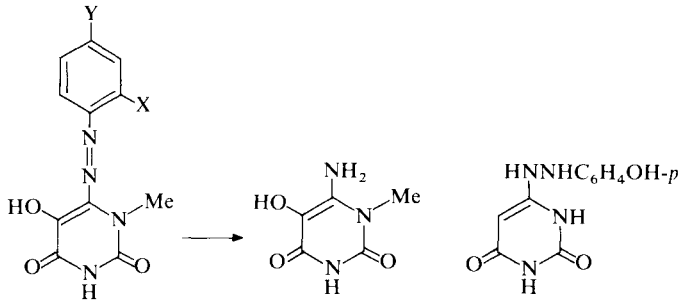
6-*p*-Chlorophenylazo- to 6-amino-5-hydroxy-4(3*H*)-pyrimidinone (boiling: 60%).[581]

6-Methyl-5-phenylazo- to 5-amino-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (in dilute alkali: 79%).[1038]

6-*o*-Carboxyphenylazo-5-hydroxy-1-methyl- (**192**, X = CO_2H, Y = H) or 5-hydroxy-1-methyl-6-*p*-sulfophenylazo- (**192**, X = H, Y = SO_3H) to 6-amino-5-hydroxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**193**) (at 65°: 56% or 52%, respectively).[579]

6-*p*-Hydroxyphenylazo- (**191**) to 6-*N'*-(*p*-hydroxyphenyl)hydrazino-2,4(1*H*,3*H*)-pyrimidinedione (**194**) (limited dithionite in alkali at 25° under nitrogen); also analogs.[4854]

Also other examples.[4831,4858,4859]



192 **193** **194**

Other reagents

6-Amino-5-phenylazo- (**195**, R = N:NPh) to 5,6-diamino- (**195**, R = NH_2) (Zn or Fe in dilute H_2SO_4: ~ 70% as sulfate)[2437] or to 6-amino-5-formamido-2,4(1*H*,3*H*)-pyrimidinedione (**195**, R = NHCHO) (Zn in 85% HCO_2H: ~ 80%).[2437]

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5-Phenylazo-2-*p*-tolyl-4,6-pyrimidinediamine to 2-*p*-tolyl-4,5,6-pyrimidinetriamine (Zn in AcOH: 58%).[2441]

5-Phenylazo- to 5-amino-6-ribitylamino-2,4(1*H*,3*H*)-pyrimidinedione (Zn in dilute H_2SO_4: used crude).[4825]

6-Chloro-5-phenylazo-2,4-pyrimidinediamine to 6-chloro-2,4,5-pyrimidinetriamine (Zn in aqueous ethanolic AcOH at 70°: 26%).[1644]

4-Chloro-5-*p*-chlorophenylazo-6-ethylamino-2-pyrimidinamine to 4-chloro-6-ethylamino-2,5-pyrimidinediamine (Zn in aqueous ethanolic AcOH at 70°: 74%; $SnCl_2$ in aqueous ethanolic HCl at 60°: 76%; Fe in HCl–AcOH; 71%).[2137]

6-Methylthio-5-phenylazo-2,4-pyrimidinediamine to 6-methylthio-2,4,5-pyrimidinetriamine (Sn in dilute HCl at 75°: 61%).[3522]

2,6-Diamino-5-phenylazo- to 2,5,6-triamino-4(3*H*)-pyrimidinone (Sn in ethanolic HCl at 80°: 37% as dihydrochloride;[1644] aqueous ethanolic NaHS at 65°: 53%).[3522]

6-Methyl-5-phenylazo-2-thioxo-1,2-dihydro- to 5-amino-6-methyl-4(3*H*)-pyrimidinone (reduction and desulfurization by Raney-Ni in aqueous NH_3 without H_2: 40%).[1401]

6-Amino-5-phenylazo- to 6-amino-5-formamido-4(3*H*)-pyrimidinone (electrolytic in HCO_2H).[4861]

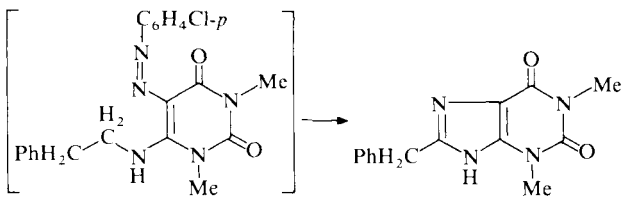
4-Ethylamino-2,6-dimethoxy-5-phenylazo- to 4-ethylamino-5-formamido-2,6-dimethoxypyrimidine (Zn in aqueous methanolic HCO_2H at 55°: 25%).[2960]

Also other examples in the foregoing references and elsewhere.[2344,4860]

5.3.2.2. Cyclization to Fused Pyrimidines

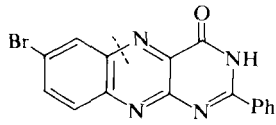
Two types of cyclization involving 5-arylazopyrimidines are illustrated in the following examples.

1. Treatment of 6-amino-5-*p*-chlorophenylazo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione with phenethylamine at 230° probably caused an initial transamination to the phenethylamino analog (**196**), which promptly lost *p*-chloroaniline to afford 8-benzyl-1,3-dimethyl-2,6(1*H*,3*H*)-purinedione (**197**) (44%).[4863, cf. 4862]



196 **197**

2. Heating 6-*p*-bromoanilino-5-*p*-nitrophenylazo-2-phenyl-4(3*H*)pyrimidinone in acetic acid–sulfuric acid (10 : 1) gave 7-bromo-2-phenylbenzo-[*g*]pteridin-4(3*H*)-one (**198**), presumably by scission of the azo grouping and loss of *p*-nitroaniline prior to cyclization.[4864]



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Chemistry of Heterocyclic Compounds, Volume 52
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CHAPTER 6

Halogenopyrimidines

Halogeno substituents in the 2- and 4/6-positions of pyrimidine have activities toward nucleophilic displacements (or other reactions) akin to those of aliphatic halogeno compounds or perhaps more nearly to that of the chloro substituent in chloro-2,4-dinitrobenzene. On the other hand, 5-halogeno substituents are broadly unreactive, almost in the sense of the chloro substituent in chlorobenzene. Extranuclear halogeno substituents are usually little affected by the pyrimidine nucleus and their reactions are reasonably predictable. On account of their high reactivities, 2- and 4/6-halogenopyrimidines have become the most useful intermediates for pyrimidine metatheses: since there is little practical difference between the reactivities of corresponding chloro-, bromo-, iodopyrimidines, the more easily obtained chloro derivatives are the ones usually employed for such purposes.

Pyrimidines with only halogeno substituents are colorless viscous liquids at room temperature or low-melting solids (see Table 6.1). Many such compounds have a characteristic musty or mouse-like odour and are at least mildly irritating to the skin and eyes: the *C*-alkylated derivatives have similar properties, as have also the extranuclear analogs such as 2-chloromethylpyrimidine.

6.1. PREPARATION OF 2- OR 4/6-CHLOROPYRIMIDINES

Most such chloropyrimidines have been made by the action of a phosphorus chloride on the corresponding (tautomeric) pyrimidinones, but other routes have been used occasionally.

6.1.1. Using Phosphoryl Chloride

It is usually sufficient to boil a simple pyrimidinone with phosphoryl chloride to convert it into a chloropyrimidine. However, for pyrimidinediones or pyrimidinetriones and for pyrimidinones bearing other functional groups, it is often necessary to add up to one equivalent of *N*,*N*-dimethyl- or (better) *N*,*N*-diethylaniline to assist the rate of conversion and to improve the yield very significantly.

TABLE 6.1. MELTING POINTS (°C) OF SIMPLE HALOGENOPYRIMIDINES

Pyrimidine	Cl	Br	I	F
2-Halogeno	66	57	32	25
4-Halogeno	Liquid	—	—	—
5-Halogeno	37	76	126	Liquid
2,4-Dihalogeno	62	67	—	Liquid
2,5-Dihalogeno	57	84	—	Liquid
4,5-Dihalogeno	Liquid	—	—	—
4,6-Dihalogeno	67	50	108	Liquid
2,4,5-Trihalogeno	Liquid	—	—	Liquid
2,4,6-Trihalogeno	25	Liquid	—	Liquid
4,5,6-Trihalogeno	51	—	—	Liquid
2,4,5,6-Tetrahalogeno	68	167	—	Liquid

The following chloropyrimidines were made by boiling the corresponding pyrimidinones with phosphoryl chloride for the time stated: an *N*,*N*-dialkylaniline or other tertiary base was added where indicated. Occasionally, selective partial chlorination of a pyrimidinedione or pyrimidinetrione occurred.

Without other substituents

2-Chloropyrimidine (6–12 h: 81%).[125,2322]

4-Chloropyrimidine (30 min: 25% as hydrochloride).[708,2321]

2,4-Dichloropyrimidine (2.5–5 h: 68–80%;[1675,2494] $PhNMe_2$, 2 h, 87%[711, cf. 2321]).

4,6-Dichloropyrimidine ($PhNMe_2$, 3 h, >90%;[2506, cf. 2507] pyridine, 3 h, 81%[2508]).

2,4,6-Trichloropyrimidine (140°, 1 h, sealed: 80%;[3596,3618] $PhNMe_2$, 0.5–3 h: 60–90%;[232,1040,1376,2341,3301] $PhPOCl_2$, 185°, 4 h: 67%[3687]).

With only alkyl substituents

2-Chloro-4,6-diethylpyrimidine (15 h: 83%).[2062]

4-Chloro-2-methylpyrimidine (30 min: > 90%).[689, cf. 678,2149,2259]

4-Chloro-6-ethyl-2-methylpyrimidine (2 h: 41%).[121]

5-Allyl-4-chloro-2,6-dimethylpyrimidine ($PhNMe_2$, 100°, 4 h: 70%).[878]

2-Chloro-4,6-dimethyl-5-prop-1′-ynylpyrimidine (10 h: 50%); also its 5-prop-2′-ynyl isomer (10 h: 46%).[843]

2,4-Dichloro-6-methylpyrimidine (30 min: > 90%).[1517,2249]

5-Butyl-4,6-dichloropyrimidine (40 min: 77%;[2186] $PhNMe_2$, 4 h: 82%[4362]).

5-Allyl-4,6-dichloropyrimidine ($PhNEt_2$, 5 h: 90%).[888]

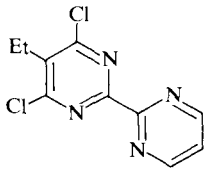
4,6-Dichloro-5-ethyl-2,2′-bipyrimidine (**1**) (1 h: 41%).[3693]

2,4,6-Trichloro-5-ethylpyrimidine (140°, sealed;[1228] $PhNMe_2$: 68–85%; [1219,4114] $PhNEt_2$: 75%[1219]).

2,4,6-Trichloro-5-isopropylpyrimidine (2,6-dimethylpyridine, 12 h: 89%).[3952]

2,2′,4′,6-Tetrachloro-4,5′-bipyrimidine (**2**) ($PhNMe_2$, 14 h: 72%).[4867]

6-Chloro-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione (**4**) [from Na salt of 5-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**3**) with $POCl_3 + H_3PO_4$, 1.5 h: 97%].[3760]



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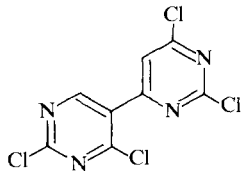

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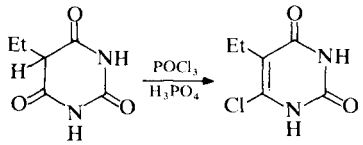

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6-Chloro-1,3-dimethyl-[644] or 6-chloro-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinetrione[855,1139] from 1,3-dimethyl- or 1,3,5-trimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, respectively ($POCl_3 + H_2O$, 1 h: 80%).

6-Chloro-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione [from 1-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with $POCl_3 + H_3PO_4$, 30 min: ~ 10% after purification].[876]

Also many other examples.[880,935,1219,1356,1509,1834,2076,2079,2098,2178,2238,2262,2264,2280,2358,2494,2614,3097,3105,3753,3754,3987,4866]

With only aryl or aryl + alkyl substituents

2-Chloro-4-phenylpyrimidine (45 min: 69%).[4039]

4-Chloro-2-phenylpyrimidine (2 h: > 67%).[846, cf. 2149]

2-Benzyl-4-chloro-6-methylpyrimidine (7 min: ~ 50%, plus a by-product).[3589,4123,6195]

4-Chloro-6-phenylpyrimidine (90 min: ~ 70%).[2264]

4-Chloro-2-naphthalen-2′-ylpyrimidine (2.5 h: 75%).[2084]

2-*p*-Bromophenyl-4-chloropyrimidine (4 h: 69%).[22]

2-Chloro-4,6-diphenylpyrimidine (8 h: 60%;[4868] 20 h: 42%[2258]).

4-Chloro-6-methyl-2-phenethylpyrimidine (15 min: 20%).[4123]

4-Chloro-2,6-dimethyl-5-styrylpyrimidine (90 min: 85%).[4656]

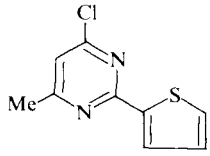
2-Chloro-4,6-dimethyl-5-*p*-nitrophenylpyrimidine (12 h: 91%).[2114]

4-Chloro-6-methyl-2-thien-2′-ylpyrimidine (**5**) (2 h: 91%).[4360]

2,4-Dichloro-6-phenylpyrimidine (1 h: 98%).[1834]

2,4-Dichloro-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine (2 h: 57%).[169]

4,6-Dichloro-5-phenylpyrimidine ($PhNMe_2$, 4 h, 84%).[4362]



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4,6-Dichloro-5-*p*-ethoxyphenyl-2-phenylpyrimidine ($PhNEt_2$, 30 h: 69%); also homologs.[4186]

2,4,6-Trichloro-5-(3′,4′-dimethoxybenzyl)pyrimidine ($PhNMe_2$, 2 h: 71%).[559]

6-Chloro-1,3-diphenyl-2,4(1*H*,3*H*)-pyrimidinedione ($POCl_3 + H_2O$, 45 min: 87%).[882]

Also other examples.[557,4130,4187,4188,4412,4420,4427,4869]

With nitro or arylazo substituents

2-Chloro-5-nitropyrimidine (30 min: 97%).[582,1012, cf. 704,2305]

2,4-Dichloro-5-nitropyrimidine ($PhNMe_2$, 1 h: 72%;[711,2295] an older method[2296] is dangerous).

4,6-Dichloro-5-nitropyrimidine ($PhNEt_2$, 2 h: 91%;[2503] $PhNMe_2$, 1 h: 70–85%[2246,2339,3547]).

2,4,6-Trichloro-5-nitropyrimidine ($PhNEt_2$, 50°, 30 min: 20%).[2063,2307]

2,4-Dichloro-5-nitro-6-propylpyrimidine ($PhNEt_2$, 1 h: 85%).[801]

2,4-Dichloro-5-nitro-6-phenylpyrimidine ($PhNEt_2$, 2 h: ~ 60%).[4652]

4,6-Dichloro-2-*m*-chlorostyryl-5-nitropyrimidine ($PhNEt_2$, 1 h: ~ 45%).[3451]

2,4-Dichloro-6-phenyl-5-phenylazopyrimidine (4 h: 65%).[4855]

Also other examples.[684,1401,2287,2413,4183]

With amino or acylamino substituents

4-Chloro-2-pyrimidinamine (20 min: 35%;[1663, cf. 1348] $POCl_3 + H_2SO_4$ or $ClSO_3H$: 93%[2313,3590]).

6-Chloro-4-pyrimidinamine ($PhNEt_2$, 4.5 h: 48–62%).[866]

2-Acetamido-4-chloro-6-methylpyrimidine (10 min: ~ 40%).[618]

2-Chloro-5,6-tetramethylene-4-pyrimidinamine ($PhNMe_2$, 6 h: 96%).[4870]

4-Chloro-6-methyl-5-pyrimidinamine ($PhNMe_2$: 13%).[1038]

4-Chloro-6-methylaminopyrimidine ($PhNEt_2$, 6 h: ~ 55%).[2625]

4-Chloro-2-diethylamino-6-methylpyrimidine (3 h: 81%).[520]

4-Chloro-6-phenethyl-2-pyrimidinamine (45 min: 68%).[4150]

6-Chloro-2,4-pyrimidinediamine (2 h: ~ 75%;[2452] $PhNMe_2$, 8 h: poor yield[2045]).

6-Chloro-4,5-pyrimidinediamine ($PhNMe_2$, 10 h: 15%).[2336]

2,6-Dichloro-4-pyrimidinamine ($PhNMe_2$, 3 h: 64–79%).[636,2504,4873, cf. 2513]

4,6-Dichloro-2-pyrimidinamine [neat $POCl_3$: 90% (?);[1349] $PhNMe_2$, 8 h: 80% (?);[2045] first way recommended[1644,3805]).

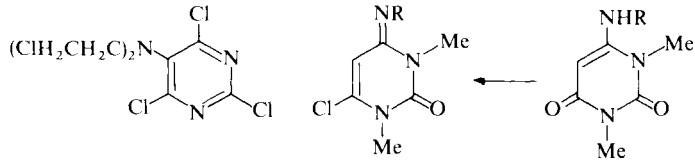
4,6-Dichloro-2′-dimethylamino-2,4′-bipyrimidine (2.5 h: 89%).[2653]

4,6-Dichloro-2-pyridin-2′-ylpyrimidine (1 h: 63%).[4030]

2-Acetamido-4,6-dichloro-5-(3′,4′-dimethoxybenzyl)pyrimidine ($PhNMe_2$,PhH, 2 h: 89%).[559]

2,4-Dichloro-6-phthalimidomethylpyrimidine (17 h: 67%).[311]

2,4,6-Trichloro-5-di(β-chloroethyl)aminopyrimidine (**6**) ($PhNEt_2$, 1 h: 71%).[4876,4877]



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6-Chloro-2-dimethylamino-4(3*H*)-pyrimidinone (10 min: 75% plus some 4,6-dichloro-2-dimethylaminopyrimidine).[1073]

4-Benzylimino- (**7**, R = CH_2Ph) (58%) or 4-benzylidenehydrazono-6-chloro-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone (**7**, R = N:CHPh) (97%) from 6-benzylamino- (**8**, R = CH_2Ph)[4788] or 6-benzylidenehydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**8**, R = N:CHPh),[4878] respectively, in boiling neat $POCl_3$ for 1–2 h.

Also other examples.[672,881,987,1066,1162,1241,1244,1356,1414,1520,1745,2017, 2084,2252,2473,3527,4121,4130,4142,4144,4358,4871,4872,4874,4875,4879,6943]

With alkoxy, alkylthio, or hydroxy substituents

4-Chloro-5-methoxypyrimidine (90 min: ~ 75%).[170,1343]

2-Chloro-4-mehoxy-6-methylpyrimidine (1 h: ~ 70%).[2762]

2-Chloro-5-*p*-nitrophenoxy-4,6-diphenylpyrimidine ($PhNMe_2$, 3 h: 80%).[4420]

2,4-Dichloro-5-methoxypyrimidine ($PhNMe_2$, 2–3 h: 61–85%).[1343,2198]

2,4-Dichloro-5-phenoxypyrimidine ($PhNEt_2$, 2 h: 96%).[1832]

4,6-Dichloro-2-methoxypyrimidine ($PhNMe_2$, ~ 2 h: 75%).[2484,2485]

2,4,6-Trichloro-5-methoxypyrimidine ($PhNMe_2$, 1 h: 52%).[2198]

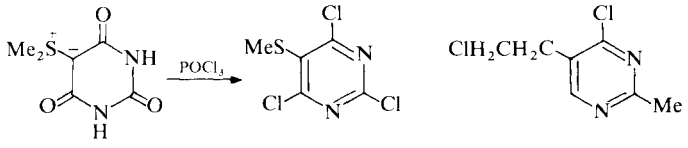
1-Benzyloxy-4-chloro-2(1*H*)-pyrimidinone ($PhNMe_2$, 18°, 53 h: 94%).[1681]

4-Chloro-2-methylthiopyrimidine (2 h: 75%).[2098]

2-Chloro-4-methylthiopyrimidine ($PhNEt_2$, 55°, 90 min).[2288]

5-Allyl-2-benzylthio-4-chloropyrimidine (3 h: 65%).[846]

2,4,6-Trichloro-5-methylthiopyrimidine (**10**) from 5-dimethylsulfonio-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrionide (**9**) ($PhNMe_2$, 24 h: 90%).[2471]



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6-Chloro-3-methyl-2-methylthio-4(3*H*)-pyrimidinone ($PhNMe_2$, 3 h: 57%).[619,2170]

2,4-Dichloro-5-pyrimidinol ($PhNMe_2$, 4 h: crude > 100%).[774]

2-Chloro-4,6-dimethyl-5-pyrimidinol ($PhNEt_2$, 3 h: ~ 70% as phosphate salt).[1012]

4-Chloro-2-chloromethylpyrimidine from 2-hydroxymethyl-4(3*H*)-pyrimidinone (80°, 15 min: 75%).[2057]

4-Chloro-5-β-chloroethyl-2-methylpyrimidine (**11**) from 5-β-hydroxyethyl-2-methyl-4(3*H*)-pyrimidinone (3 h: 88%).[2052]

Also other examples.[581,1821,1875,1934,2126,2162,2163,2187,2468,3143,3908,4089,4092,4880]

With preattached halogeno substituents

2,5-Dichloropyrimidine from 5-chloro-2(1*H*)-pyrimidinone (30 min: 56%).[1616]

5-Bromo-2-chloropyrimidine ($PhNMe_2$, 4 h: 75%).[1825]

2-Chloro-5-iodopyrimidine ($PhNEt_2$, 4 h: 60%).[1826]

2-Chloro-5-fluoropyrimidine ($PhNMe_2$, 2 h: 41%).[3765]

4,5-Dichloropyrimidine ($PhNMe_2$, 3 h: 48%).[1827, cf. 3743]

5-Bromo-4-chloropyrimidine ($PhNMe_2$, 3 h: 50–78%).[1827,1899]

4-Chloro-5-iodopyrimidine (< 3 h: 74%;[499] $PhNMe_2$, 1 h: 49%[2180]).

2,4,5-Trichloropyrimidine ($PhNMe_2$, 4 h: 86%).[2209, cf. 1827]

4,5,6-Trichloropyrimidine ($PhNMe_2$, 3 h: 77%).[1827]

5-Bromo-2,4-dichloropyrimidine ($PhNEt_2$, 2 h: 88%).[3598, cf. 1800,1838]

5-Bromo-4,6-dichloropyrimidine ($PhNMe_2$, 3 h: 46%).[1827]

2,4-Dichloro-5-fluoropyrimidine (pyridine, 1 h: 60%;[2479,2480] $PhNMe_2$, 40 min: > 67%;[3153] $PhNMe_2$, 2–3 h: ~ 90%[473,2269]).

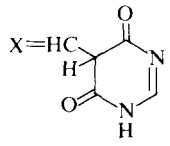
4,6-Dichloro-2-trifluoromethylpyrimidine ($PhNMe_2$, 2 h: 59%).[4090]

6-Chloro-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione from 5-fluoro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione ($PhNMe_2$, 100°, 10 min: 46%).[138]

Also other examples.[1788,1822,1833,1857,1958,2107,2117,2151,4124,4129,4882]

With carbonyl-based or cyano substituents

4,6-Dichloro-5-pyrimidinecarbaldehyde from 5-dimethyliminiomethyl-4,6(1*H*,5*H*)-pyrimidinedione (chloride) (**12**, X = $\overset{+}{N}Me_2$, equivalent to **12**, X = O) ($PhNMe_2$, 17 h: 63%).[1028]



12

5-Acetyl-4-chloro-6-methyl-2-phenylpyrimidine (30 min: 75–88%).[212,4883]

5-Acetyl-4-chloro-2,6-dimethylpyrimidine (1 h: 72%).[785]

5-Acetonyl-4-chloro-2,6-dimethylpyrimidine (15 min: 87%).[730]

5-Acetyl-2,4-dichloropyrimidine ($PhNEt_2$, 5 h: 78%).[2002]

Note: $PhNMe_2$, 20 h, produced exclusively 2,4-dichloro-5-α-chlorovinylpyrimidine in 57% yield[2361]).

6-Chloro-4-pyrimidinecarboxylic acid ($PhNMe_2$, 3 h: 50%).[2326]

2,4-Dichloro-5-pyrimidinecarboxylic acid ($PhNEt_2$, > 1 h: 70%).[2513, cf. 6036]

Ethyl 4-chloro-5-pyrimidinecarboxylate (NEt_3, 2.5 h: 64%).[1969]

Methyl 2-chloro-6-methyl-4-pyrimidinecarboxylate (15 min: 80%).[2266]

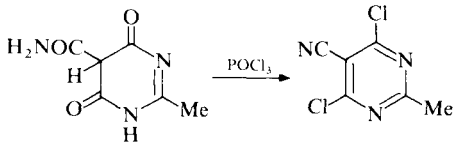
4-Chloro-2-methoxycarbonylmethylpyrimidine ($PhNEt_2$, 30 min: 42%).[1749]

Butyl 2,6-dichloro-4-pyrimidinecarboxylate (2 h: 83%).[374]

5-Acetoxy-2,4-dichloro-6-methylpyrimidine ($PhNMe_2$, 90 min: 71%).[751]

4-Chloro-2-phenyl-5-pyrimidinecarbonitrile from 4-oxo-2-phenyl-3,4-dihydro-5-pyrimidinecarboxamide (3.5 h: 90%).[4885]

4,6-Dichloro-2-methyl-5-pyrimidinecarbonitrile (**14**) from 2-methyl-4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxamide (**13**) ($PhNMe_2$, 1 h: 76%).[1010]

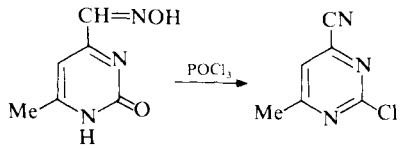


13 **14**

2-Chloro-5-pyrimidinecarbonitrile ($PhNMe_2$, 1 h: 65%).[1617]

2-Chloro-4-methyl-6-phenyl-5-pyrimidinecarbonitrile (30 min: 78%).[3942]

2,4-Dichloro-5-pyrimidinecarbonitrile ($PhNEt_2$, 2 h: ~ 75%).[2509]



15 **16**

2-Chloro-6-methyl-4-pyrimidinecarbonitrile (**16**) from 6-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde oxime (**15**) (2.5 h: 29%).[2267, cf. 1029]

Also other examples.[283,732,936,1745,1988,1997,2177,2990,4338,4884,4886]

With two or more different functional substituents

4-Chloro-2-dimethylamino-5-nitropyrimidine (? h: 55%).[1089]

4-Chloro-2-dimethylamino-5-pyrimidinecarbonitrile (2 h: ~ 85%).[2085]

6-Chloro-2-methylthio-4-pyrimidinamine ($PhNMe_2$, 1–8 h: 62–75%).[1015,1569, cf. 951,1357]

4,5-Dichloro-2-methylthiopyrimidine (2 h: 80%).[220]

2-Acetamido-4-chloro-5-phenoxypyrimidine (in $ClCH_2CH_2Cl$, 90 min: 81%).[3885]

2,4,6-Trichloro-5-trifluoromethylthiopyrimidine (120°, 4 h, sealed: 70%).[312]

4-Chloro-2-diethylamino-6-trifluoromethylpyrimidine (3 h: 53%).[477]

6-Chloro-2-chloromethyl-4-pyrimidinamine from 6-amino-2-hydroxymethyl-4(3*H*)-pyrimidinone (10 h: 51%).[1335]

4-Chloro-5-methoxy-2-methylthiopyrimidine (30–90 min: 60–86%).[718,2584,2586]

4,6-Dichloro-2-methoxy-5-nitropyrimidine ($PhNMe_2$, 2 h).[2484]

4,6-Dichloro-2-methylthio-5-nitropyrimidine ($PhNEt_2$, 1 h: 93%).[1764]

5-Anilino-4,6-dichloro-2-methylthiopyrimidine (18 h: 87%).[4200]

4,6-Dichloro-5-methoxy-2-pyrimidinamine (10 min: 24%).[1007]

4-Chloro-5-iodo-2-pyrimidinamine ($PhNMe_2$, 3 h: 48%).[1348]

Methyl 6-chloro-2-methylthio-4-pyrimidinecarboxylate (30 min: 84%).[1030]

Methyl 2,5,6-trichloro-4-pyrimidinecarboxylate ($PhNEt_2$, 2.5 h: 47%).[2121]

Ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate from the sodium salt of ethyl 2-methylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate (in $CHCl_3$, reflux, 3 h: ~ 90%).[1781,2992]

2,6-Dichloro-5-nitro-4-pyrimidinecarboxylic acid (3 h).[1035]

4-Amino-6-chloro-2-methyl-5-pyrimidinol (6 h: 44%).[1012]

4-Chloro-5-methoxy-6-methyl-2-pyrimidinamine (30 min: 60%).[1362]

4-Chloro-2-ethylthio-5-methoxypyrimidine (? h: 53%).[926]

4-Chloro-6-dimethoxymethyl-2-ethylthio-5-fluoropyrimidine ($PhNEt_2$, 55°, 90 min: 37%).[2066]

4-Chloro-2-methylthio-5-pyrimidinecarbonitrile (5 h: 90%).[1020]

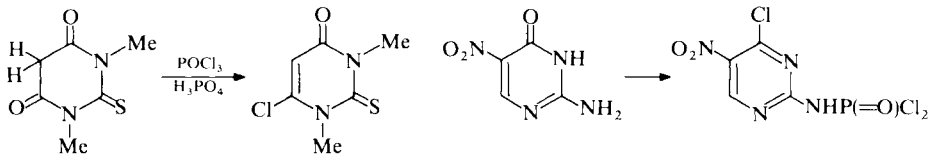
5-Acetonyl-4-chloro-6-methyl-2-methylthiopyrimidine (15 min: 86%).[730]

2-Acetamido-4,6-dichloro-5-nitropyrimidine (4 h: 67%).[620,630]

4-Chloro-2-cyanomethylthio-6-methylpyrimidine from 2-carbamoylmethylthio-6-methyl-4(3*H*)-pyrimidinone ($PhNMe_2$, 1 h: ~ 50%).[4888]

Also other examples.[774,1016,1220,1268,1357,1369,1370,1697,1816,1824,1958, 2046,2167,2192,2910,2989,3837,3976,4144,4887,6009]

As can be seen from the foregoing examples, chlorination with phosphoryl chloride usually converts all (tautomeric) oxo substituents on a molecule into chloro substituents but occasionally partial chlorination, at a 4/6- rather than the 2-position, is possible. During such chlorinations, passenger groups in the molecule may be affected: carbamoyl or hydroxyiminomethyl will become cyano, extranuclear but not 5-hydroxy groups will become chloro, carboxy may become chlorocarbonyl, acetyl may become α-chlorovinyl, and acid-labile groups may be hydrolyzed during the workup procedures if appropriate precautions are not taken. Tautomeric thioxo groups are usually affected adversely by phosphoryl chloride; for instance, 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave mainly bis(4-chloropyrimidin-2-yl) disulfide,[3805] but 1,3-dimethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**17**) with phosphoryl chloride plus phosphoric acid at 70°, for 5 h did give 6-chloro-1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**18**), albeit in only 27% yield.[1103] A rare complication in the presence of an amino group was the formation of *N*-(4-chloro-5-nitropyrmidin-2-yl)phosphoramidic dichloride (**20**) (~ 40%) from treatment of 2-amino-5-nitro-4(3*H*)-pyrimidinone (**19**) with boiling phosphoryl chloride for 5 h:[1766] the product (**20**) fortunately underwent successful aminolyses of its 2-substituent; another such dichlorophosphoramide has been reported.[1255] An interesting reaction is that of 4-phenylpyrimidine 1,3-dioxide with phosphoryl chloride at 20°, for 5 h to give 2-chloro-4-phenylpyrimidine 3-oxide (50%) and 2,4-dichloro-6-phenylpyrimidine (10%); at 70°, the reaction gave the same products but in 5% and 25%, respectively.[4893]



17 **18** **19** **20**

6.1.2. Using Phosphorus Pentachloride

Phosphorus pentachloride is a more powerful reagent than phosphoryl chloride but less convenient to use. It was employed widely in the early days of pyrimidine chemistry to convert tautomeric pyrimidinones (and occasionally other substrates) into chloropyrimidines, and it is still so used for difficult cases by employing phosphoryl chloride as a solvent for both substrate and reagent. The use of phosphorus pentachloride involves a real possibility of *C*-chlorination at the free 5-position of a substrate or at an attached methyl group. (Examples of the latter reaction have been given in Section 4.2.3.5.) Phosphorus pentachloride affects susceptible passenger groups much as does phosphoryl chloride (Section 6.1.1).

The following chloropyrimidines have been made, usually from the corresponding pyrimidinones by the use of phosphorus pentachloride.

2-Chloropyrimidine (PCl_5 + $POCl_3$, 140°, 45 min: 93%).[2098]

2-Chloro-5-phenylpyrimidine (PCl_5 + $POCl_3$, 120°, 3 h: 57%).[4890]

4-Chloro-2-phenylpyrimidine (PCl_5, 150°, 30 min: 65%).[4091,4889]

4-Chloro-6-phenylpyrimidine (PCl_5, 140°, 3 h: 90%).[1898]

4-Chloro-2,6-diphenylpyrimidine (PCl_5 + $POCl_3$, reflux, 3 h: 81%).[2656]

5-Bromo-2,4-dichloropyrimidine (PCl_5 + $POCl_3$, reflux, 41 h: 91%).[1838]

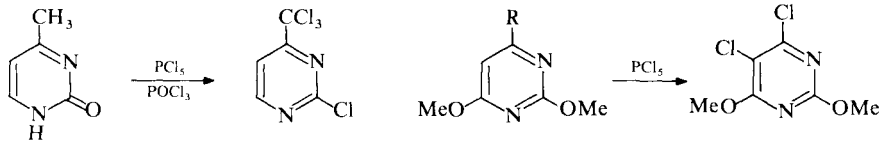
4,6-Dichloro-2-methylpyrimidine from 6-chloro-2-methyl-4(3*H*)-pyrimidinone (PCl_5, 140°, 3 h: > 90%).[2050]

2,4-Dichloro-6-ethylamino-5-phenylazopyrimidine (PCl_5 + $POCl_3$, reflux, 45 h: 55%).[2960]

2,2',4,4'-Tetrachloro-5,5'-bipyrimidine (PCl_5 + $POCl_3$, 120°, 2 h: 60%).[4892]

2,4-Dichloro-5-chloromethylpyrimidine from 5-chloromethyl- or 5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (PCl_5 + $POCl_3$, reflux, 2 h: 48% and 82%, respectively).[1699]

2-Chloro-4-trichloromethylpyrimidine (**22**) from 4-methyl-2(1*H*)-pyrimidinone (**21**) (PCl_5 + $POCl_3$, 135°, 6 h: 80%).[4891, cf. 2249]



21 **22** **23** **24**

2,6-Dichloro-4-pyrimidinecarbonyl chloride from 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (PCl_5 + $POCl_3$, reflux, 15 h: 64%);[2121] a stream of chlorine improved the yield to 98%.[2512]

2,4,5,6-Tetrachloropyrimidine from 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (PCl_5 + $POCl_3$, reflux, 15 h: 37%)[2350] or from 5-chloro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (PCl_5 + $POCl_3$, reflux, 8 h: 4%).[2121]

2,5-Dichloro-4,6-pyrimidinediamine from 4,6-diamino-2(1*H*)-pyrimidinone (PCl_5 + $POCl_3$, reflux, 2 h: 64%).[2514]

4,5-Dichloro-2,6-dimethoxypyrimidine (**24**) from 4-chloro-2,6-dimethoxypyrimidine (**23**, R = Cl) or from 2,6-dimethoxy-4-pyrimidinesulfonic acid (**23**, R = SO_3H) (PCl_5, 135°, 30–60 min: ~ 25% or ~ 50%, respectively).[2070]

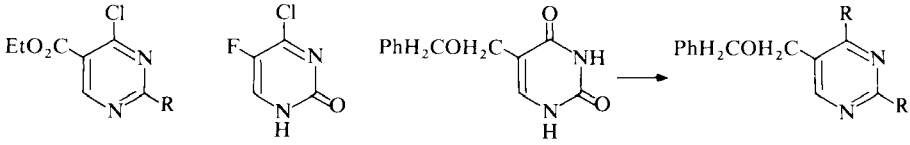
4,6-Dichloro-2,5-pyrimidinediamine from 2,5-diamino-4,6(1*H*,5*H*)-pyrimidinedione (PCl_5 + $POCl_3$, $PhCH_2Et_3NCl$, MeCN, reflux, 4 h: 32%).[6025]

2,4-Dichloropyrimidine from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (PCl_5, 100°, ? h: ~60%).[1242]

Also other examples.[574,1046,1637,2239,2248,2511,2516,4019,4093,4116,4120,4152,4869,4890,6226]

6.1.3. Using Thionyl Chloride or a Vilsmeier Reagent

The use of neat *thionyl chloride* to prepare 2- or 4/6-chloropyrimidines is rare: however, ethyl 4-oxo-2-phenyl-3,4-dihydro-5-pyrimidinecarboxylate with refluxing thionyl chloride for 30 h gave ethyl 4-chloro-2-phenyl-5-pyrimidinecarboxylate (**25**, R = Ph) (~90%);[4881] ethyl 2- methylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate in refluxing thionyl chloride for 3 h gave ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (**25**, R = SMe) (84%);[2991] and 5-fluoro-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone in thionyl chloride at 25° for 12 h gave 4-chloro-5-fluoro-2(1*H*)-pyrimidinone (**26**) (45%).[1267, cf. 1724]



25 **26** **27** **28**

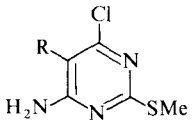
Tautomeric pyrimidinones may be converted into the corresponding chloropyrimidines under gentle conditions by treatment with a *Vilsmeier reagent*, such as chloromethylenedimethylammonium chloride ($ClHC{=}\overset{+}{N}Me_2Cl^-$), which may be made from dimethylformamide with phosgene, thionyl chloride, phosphoryl chloride, phosphorus pentachloride, or oxalyl chloride.[4894,4895] If the pyrimidinone substrate bears acid-sensitive groups, the reagent may be isolated prior to use in an inert solvent; if not, the reagent may be preformed and used in situ.[4896] For example, 5-benzyloxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (**27**) was shaken with a chloroform solution of chloromethylenedimethylammonium chloride at 20° for 48 h to give 5-benzyloxymethyl-2,4-dichloropyrimidine (**28**, R = Cl), which was converted immediately into 5-benzyloxymethyl-2,4-dimethoxypyrimidine (**28**, R = OMe) for isolation in 72% overall yield;[2922] in contrast, 2′,3′,5′-tri-*O*-benzoyluridine was converted into 4-chloro-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (> 95%) simply by refluxing with thionyl chloride plus dimethylformamide in chloroform for 6 h.[4897] Unfortunately, a Vilsmeier reagent often induces *C*-formylation of appropriate substrates (bearing electron-donating groups), either at the 5-position or on an appended alkyl group; moreover, it can form a Schiff base at a primary amino group. The use of such reagents for chlorinations is illustrated further in the formation of the following products from the corresponding pyrimidinones unless otherwise indicated.

4-Chloro-2-methoxy-6-methylpyrimidine ($SOCl_2$, Me_2NCHO, $CHCl_3$, reflux, 1 h, under N_2: 74%).[158]

4-Chloro-2-ethylthio-5-fluoropyrimidine ($SOCl_2$, Me_2NCHO, reflux, 3 h: 78%).[270]

4,6-Dichloro-5-pyrimidinecarbaldehyde from 4,6(1*H*,5*H*)-pyrimidinedione ($POCl_3$, Me_2NCHO, 100°, 3 h: 48%).[1019]

6-Chloro-2-methylthio-4-pyrimidinamine (**29**, R = H) and 4-amino-6-chloro-2-methylthio-5-pyrimidinecarbaldehyde (**29**, R = CHO) ($POCl_3$, Me_2NCHO, 100°, 2.5 h: 25% and 11%, respectively).[1019]



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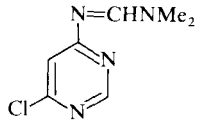

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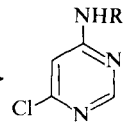

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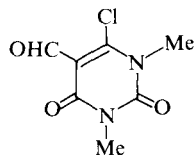

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4-Chloro-6-dimethylaminomethyleneaminopyrimidine (**30**) from 6-amino-4(3*H*)-pyrimidinone ($POCl_3$, Me_2NCHO, 100°, 1 h: ~50%);[1019] variations in workup gave 6-chloro-4-pyrimidinamine (**31**, R = H) or 4-chloro-6-formamidopyrimidine (**31**, R = CHO).[1570,2172]

4-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde (**32**) from 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione ($POCl_3$, Me_2NCHO, reflux, 45 min: 65%).[3770]

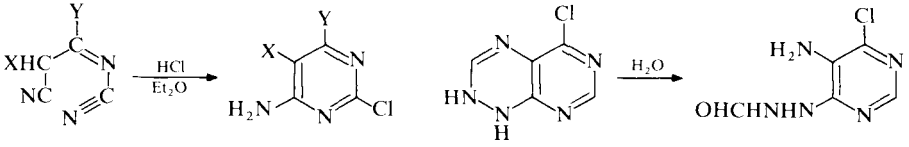
Also other examples.[2087,2223]

6.1.4. Using Diazotization of Pyrimidinamines

Although 2- or 4/6-pyrimidinamines are often made from chloropyrimidines, it is sometimes useful to do the reverse, particularly when an amino substrate is readily available by primary synthesis or other means. Diazotization of the primary amine in the presence of an excess of halide ion (e.g., in concentrated hydrochloric acid) often achieves this result, although the corresponding pyrimidinone is usually formed[1465,1780] as an easily separable by-product. Thus diazotization of 2-pyrimidinamine in 6*M* hydrochloric acid gave 2-chloropyrimidine in 26–33% yield,[2083,2255,2323] but the use of 5*M* lithium chloride in 4*M* hydrochloric acid as the reaction medium improved the yield to 50%.[752] Broadly similar procedures gave 2-chloro-4-methyl-,[2255] 2,5-dichloro- (~25%),[2255] 2-chloro-4-methoxy-6-methyl- (~25%),[1780,2126,2197] 2-chloro-4-ethylthio-6-methyl- (30%),[2126] 2-chloro-4,6-dimethoxy- (~25%),[1780] 4-*t*-butyl-2-chloro- (25%),[1465] 4-chloro-2,6-dimethyl- (42%),[1856] 4,6-dichloro- (3–4%),[1896] and 4-*t*-butyl-6-chloropyrimidine (9–17%);[4899] other examples have been reported.[4898]

6.1.5. Using Primary Syntheses

The formation of 2- or 4/6-chloropyrimidines is not possible by the Principal Synthesis, but a few other primary syntheses (Chapter 2) have been used occasionally. For example, α-(*N*-cyanoamidino)malononitrile (**33**, X = CN, Y = NH_2) in ethanolic hydrogen chloride gave 4,6-diamino-2-chloro-5-pyrimidinecarbonitrile (**34**, X = CN, Y = NH_2) (73%);[997] 3-cyanoimino-2-phenylsulfonylbutyronitrile (**33**, X = $PhSO_2$, Y = Me) likewise gave 2-chloro-6-methyl-5-phenylsulfonyl-4-pyrimidinamine (**34**, X = $PhSO_2$, Y = Me) (98%);[41] 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**35**) gave 4-chloro-6-*N'*-formylhydrazino-5-pyrimidinamine (**36**) (38%) by refluxing in aqueous ethanolic sodium chloride;[2173] 2-methylimidazole gave 4-chloro-2-methylpyrimidine (among other products) on heating above 500° with chloroform;[2104] and pyrazole with CCl_4 at 550° gave 2-chloropyrimidine.[3950]

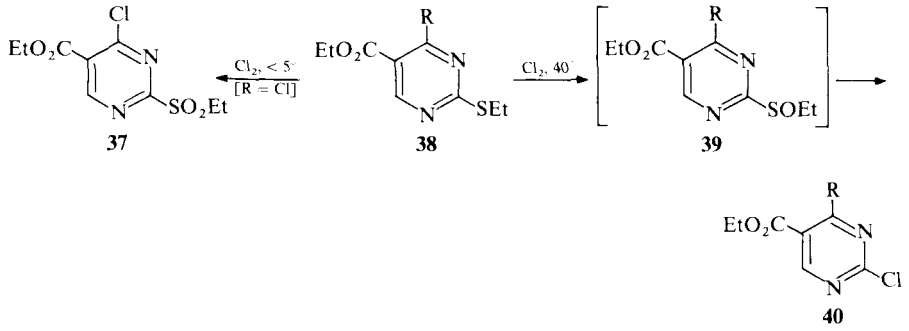


33 **34** **35** **36**

6.1.6. Using Other Routes

Several minor routes to 2- or 4/6-chloropyrimidines are best illustrated by the following examples.

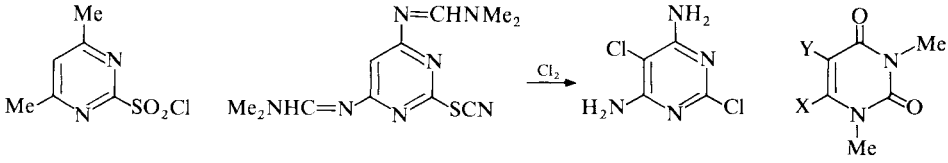
1. Treatment of an aqueous suspension of ethyl 4-chloro-2-ethylthio-5-pyrimidinecarboxylate (**38**, R = Cl) with chlorine at 0° gave ethyl 4-chloro-2-ethylsulfonyl-5-pyrimidinecarboxylate (**37**) (80%), but at 40° the same procedure gave ethyl 2,4-dichloro-5-pyrimidinecarboxylate (**40**, R = Cl) (72%), not via the sulfone (**37**), which was stable to toward chlorine



37 **38** **39** **40**

at 40°, but possibly via the sulfoxide (**39**, R = Cl);[1748] the analogous substrate, ethyl 2-ethylthio-5-pyrimidinecarboxylate (**38**, R = H), likewise afforded ethyl 2-chloro-5-pyrimidinecarboxylate (**40**, R = H) (79%) when treated at 45° with chlorine.[1631]

2. Oxidation of 4,6-dimethyl-2(1*H*)-pyrimidinethione with chlorine in dilute hydrochloric acid at 0° gave 4,6-dimethyl-2-pyrimidinesulfonyl chloride (**41**), which gradually lost sulfur dioxide at room temperature to furnish 2-chloro-4,6-dimethylpyrimidine.[2348]
3. Chlorination of 2,4-dichloro-5-fluoropyrimidine in carbon tetrachloride containing dibenzoyl peroxide in strong light gave 2,4,6-trichloro-5-fluoropyrimidine, presumably by a radical mechanism.[2153]
4. Treatment of 4,6-bis(dimethylaminomethyleneamino)-2-thiocyanatopyrimidine (**42**) in glacial acetic acid with a stream of chlorine for 1 h gave 2,5-dichloro-4,6-pyrimidinediamine (**43**) (71%).[135]
5. Dissolution of 6-iodo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**44**, X = I, Y = H) in a glacial acetic acid solution of chlorine at 50° for 2 min gave 5,6-dichloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**44**, X = Y = Cl) (~50%).[1812]



6.2. PREPARATION OF 2- OR 4/6-BROMOPYRIMIDINES

Methods used to make these bromopyrimidines are broadly analogous to those for their foregoing chloro analogs.

Unlike phosphoryl chloride, *phosphoryl bromide* is a solid and therefore is less convenient for converting tautomeric pyrimidinones into bromopyrimidines except when diluted with phosphorus tribromide, an inert solvent, or an appropriate tertiary amine. The use of phosphoryl bromide is illustrated in the formation of the following bromopyrimidines from the corresponding pyrimidinones.

2-Bromopyrimidine (PhMe, reflux, 2 h: 5%).[1967]

4-Bromo-6-*t*-butylpyrimidine (100°, 3 h: 40%).[4900]

2-Bromo-4-phenylpyrimidine (120°, 3 h: 37%).[4039]

4-Bromo-2,6-dimethylpyrimidine ($POBr_3$ + PBr_3, reflux, 2 h: ~80%).[1826]

2-Bromo-4,6-diphenylpyrimidine (130°, 4 h: 63%).[4901]

4-Bromo-2-pyrimidinamine (135°, 2h: 16%).[1928]

2,5-Dibromopyrimidine ($POBr_3$ + PBr_3, reflux, 90 min: ~50%).[1826]

2,4-Dibromopyrimidine ($PhNEt_2$, 120°, 1 h: 11%).[277, cf. 2464]

4-Bromo-2-methoxycarbonylmethylpyrimidine (PhMe, reflux, 90 min: 24%).[1749]

4,6-Dibromo-2-ethylpyrimidine (100–160°, isolated by sublimation: 79%).[1243]

4,6-Dibromo-2-isopropylaminopyrimidine (PhMe, reflux, 90 min: 50%).[2463]

6-Bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (130°, 30 min: ~40%).[1812]

2,4,6-Tribromopyrimidine (150°, 6 h: 61%;[1928] PhMe, $PhNMe_2$, ? h: 74%[788]).

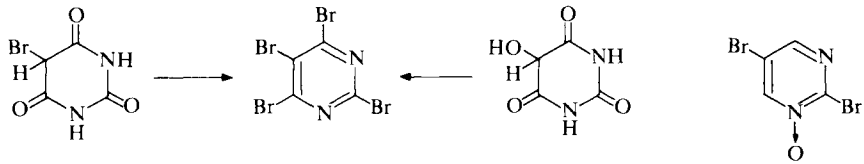
2,4,6-Tribromo-5-methylpyrimidine ($PhNMe_2$, PhMe, reflux, 5 h: 52%).[1839]

2,4,6-Tribromo-5-trifluoromethylpyrimidine (150°, 5 h: 80%).[312]

Ethyl 4-bromo-2-methylthio-5-pyrimidinecarboxylate (PhMe, reflux, 2 h: 63%).[1781]

2,4,5,6-Tetrabromopyrimidine (**46**) from 5-bromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**45**) (reflux, 30 min).[2153]

Also other examples.[4129,4174,4902]



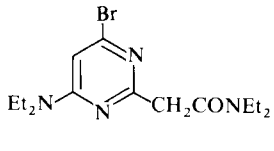
45 **46** **47** **48**

Heating 5-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (dialuric acid) (**47**) with *phosphorus pentabromide* diluted with phosphoryl chloride gave 2,4,5,6-tetrabromopyrimidine (**46**), purified by steam distillation.[3597]

The *diazotization* of appropriate 2- or 4/6-pyrimidinamines in an excess of bromide ion gave 2-bromo- (27–31%),[752,1967] 2-bromo-4,6-dimethyl- (24%),[1819] 2-bromo-4-chloro-6-methyl- (16%),[1819] and 2-bromo-5-dimethylaminomethyleneaminopyrimidine (48%),[752] as well as 2,5-dibromopyrimidine 1-oxide (**48**) (27%).[1966] Provided the 5-position was occupied to prevent 5-bromination, yields were usually better when a perbromide of the substrate amine was formed prior to diazotization: 2-bromo-4,5-diethoxy- (79%), 2-bromo-4-chloro-5-ethoxy- (67%), and 2-bromo-4-chloro-5-propylpyrimidine (9%) were so made.[1814]

The trimerization of 3-dimethylaminopropynenitrile in the presence of hydrogen bromide at 0° for 2 h provided a rather impractical *primary synthesis* of 4-bromo-6-dimethylamino-2-(*N*,*N*-diethylcarbamoyl)methylpyrimidine (**49**) (40%).[4422]

Although *bromination* of pyrimidine in the gas phase at 200–300° gave mainly 5-bromopyrimidine,[1965,1971] the main products at ~500° were 4,6-dibromo- and 2,4,6-tribromopyrimidine.[1971] It is interesting that 8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidinium bromide (**50**, R = H) underwent classical bromination by ethanolic bromine at its 7-position (equivalent to a 4/6-position in the pyrimidine ring) to afford the 7-bromo derivative (**50**, R = Br).[78]



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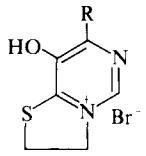

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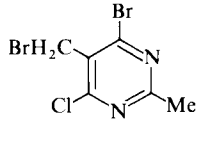

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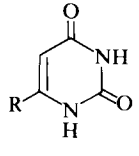

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A little-used method of considerable potential for making 2- or 4/6-bromopyrimidines is *transhalogenation* of the corresponding chloropyrimidines, which are usually much more readily available. Thus 2-chloropyrimidine in refluxing phosphorus tribromide for 2 h gave 2-bromopyrimidine (52%);[1856] 2-chloro- gave 2-bromo-4,6-dimethylpyrimidine (58%) likewise;[1856] and 4,6-dichloro-2,5-dimethylpyrimidine with bromine in chloroform has been reported to give 4-bromo-5-bromomethyl-6-chloro-2-methylpyrimidine (**51**) (35–50%).[1801] 6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione (**52**, R = H) has been converted into its 6-iodo analog (**52**, R = I) and thence into the 6-bromo analog (**52**, R = Br) (70%) by heating in dimethylformamide containing ammonium bromide at 150° for 1 h.[105]

6.3. PREPARATION OF 2-OR 4/6-IODOPYRIMIDINES

Almost all such iodopyrimidines have been made by *transhalogenation* of the corresponding chloro- or bromopyrimidines. Cold hydriodic acid is commonly used for this purpose: hot hydriodic acid tends to cause hydrolysis of 4/6-halogenopyrimidines and reductive dehalogenation of 2-halogenopyrimidines.[2258] The process of transhalogenation is illustrated in the formation of the following iodopyrimidines from their chloro analogs unless otherwise indicated.

2-Iodopyrimidine (HI, 5°, 30 min: 55%);[2258] from Br analog (HI, 5°, 30 min: 45%;[2258] KI, Me_2NCHO, reflux, 20 min: < 40%[3290]).

2-Iodo-4,6-dimethylpyrimidine (HI, 20°, 5 h: 60%).[1856]

4-Iodo-2,6-dimethylpyrimidine (HI, 20°, 30 min: 32%).[1856]

2-Iodo-4-phenylpyrimidine (HI, 25°, 6 days: 58%).[4903]

4-Iodo-5-phenylpyrimidine (HI, 20°, 11 h: 85%).[1856]

4-Iodo-2,6-diphenylpyrimidine (HI, AcOH, 25°, 24 h: 90%).[4905]

4-Iodo-6-phenylpyrimidine (HI, 20°, 20 h: 92%).[4904]

4-Iodo-2-methylthiopyrimidine (HI, 25°, 48 h: 76%;[3929] HI, 25°, 15 min: 60%[3043, cf.1745]).

5-Chloro-4-iodo-2-methylthiopyrimidine (HI, 25°, 60 h: 92%).[220]

4-Iodo-2,6-dimethoxypyrimidine (NaI, Me_2NCHO, reflux, 1 h: 42%).[1703]

6-Iodo-2,4-pyrimidinediamine (HI, reflux: ~ 80%; note survival of deactivated iodo substituent toward hydrolysis).[1349]

6-Iodo-2,4(1*H*,3*H*)-pyrimidinedione (NaI, Me_2NCHO, reflux, 1 h: 61–73%).[105,1703]

2,4-Di-*t*-butyl-6-iodopyrimidine (HI, 20°, 15 min: 51%); also analogs likewise.[3987]

Ethyl 4-iodo-2-methylthio-5-pyrimidinecarboxylate (NaI, AcOH, 100°, 30 min: ~50%;[1718] HI, 25°, 5 min: 79%[3043]).

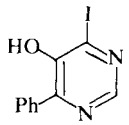
4-Iodo-2-methoxycarbonylmethylpyrimidine (HI, NaI, AcMe, reflux, 30 min: 70%).[1749]

4-Iodo-6-methylpyrimidine 1-oxide (HI, 20°, 7 days: 37%).[3287]

4,6-diiodopyrimidine (HI, NaI, AcMe, reflux, 5 h: 39%).[1784]

Also other examples.[1228,1509,1745,1812,1857,2178,2555,4906,4907]

At least one 4/6-iodopyrimidine has been made by classical *iodination*: 4-phenyl-5-pyrimidinol with iodine in aqueous potassium iodide containing ammonia at 45° for 4 h gave 4-iodo-6-phenyl-5-pyrimidinol (**53**) (72%).[23] The *cine-iodination* of 2-chloro-5-lithio-4-methoxy- to 2-chloro-4-iodo-6-methoxypyrimidine (I_2, THF: 85%) has been reported.[6873]



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6.4. PREPARATION OF 2- OR 4/6-FLUOROPYRIMIDINES

The transhalogenation of 2-or 4/6-chloropyrimidines into the corresponding fluoropyrimidines can be done more or less conveniently by treatment with silver fluoride, potassium fluoride (more recently assisted by an appropriate crown ether), cesium fluoride, or sulfur tetrafluoride. The conditions required are illustrated in the following examples.

2-Fluoropyrimidine (CsF, *N*-methylpyrrolidone, 150°, 3.5 h: 33%).[2558]

2-Fluoro-4,6-dimethylpyrimidine (CsF, Me_2NCHO, 150°, 7 h: 33%).[2558]

2,4-Difluoropyrimidine (CsF, 18-crown-6, tetraglyme, 150°, 8 h: 82%).[66]

4,6-Difluoropyrimidine (CsF, *N*-methylpyrrolidone, 100°, 6 h: 65%;[1730] SF_4, 150°, 3 h, sealed: ~ 70%[2064]).

2,4,6-Trifluoropyrimidine (CsF, Me_2NCHO, 150°, 2.5 h: 53%;[2558] neat AgF, reflux, 1 h, then retreated: 50–70%;[1040,1727,3656] KF + Sb_2O_3, 260°, 2 h, sealed: 48%;[1843,2454] KF, 310°, sealed: 90%[3690]).

2-Fluoro-4-methoxypyrimidine (KF, 18-crown-6, tetraglyme, 195°, 14 h: 55%).[66]

4,6-Difluoro-5-nitropyrimidine (AgF, $PhNO_2$, reflux, 45 min: ~80%).[2556]

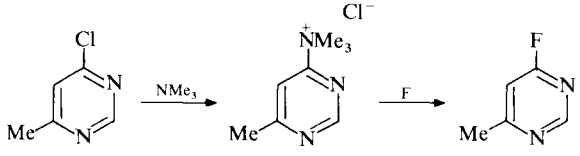
2,4,6-Trifluoro-5-methylpyrimidine (KF, Me_2NCHO, 140°, 10 h: 70%).[3164]

2,4,6-Trifluoro-5-isopropylpyrimidine (KF, 18-crown-6, MeCN, 40°, 15 h > 95%).[3952]

5-Chloro-2,4,6-trifluoropyrimidine (neat AgF, reflux, 1 h, then retreated ~75%;[1727] KF, 340°, 25 h: 35%[3657]).

Also other examples.[312,2063,2093]

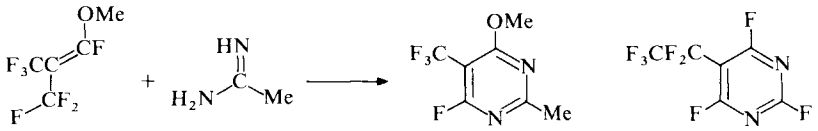
It is not at all clear why *displacement of trimethylammonio by fluoro* is so convenient in the pyrimidine series, thereby providing a good but rarely used indirect route from chloro- to 2- or 4/6-fluoropyrimidines. For example, 4-chloro-6-methylpyrimidine (**54**) with trimethylamine in benzene at 20° for 5 days gave 4-methyl-6-trimethylammoniopyrimidine chloride (**55**) (87%), which reacted with potassium hydrogen difluoride (KF.HF) in a gently stirred mixture of water and ether at 5° during 4–5 h to afford 4-fluoro-6-methylpyrimidine (**56**) (55%).[3154] The preparation of appropriate ammonio salts is discussed elsewhere (Section 6.7.2) and their conversion into fluoropyrimidines is illustrated in the formation of 4-fluoro-2,6-dimethyl- (H_2O–Et_2O: 95%),[3154] 4-fluoro-6-phenyl- (Me_2SO: 72%),[4904] 2-fluoro-4-phenyl- (Me_2SO: 55%),[4903] 2-fluoro-4,6-diphenyl- (Me_2SO: 58%),[4901] 4-fluoro-2,6-diphenyl- (Me_2SO: 80%),[4905] 4-fluoro-2-isopropyl- (H_2O–Et_2O: 81%),[1907] and 4-fluoro-2,6-dimethoxypyrimidine (diethylene glycol: 42%);[1703] also 2-fluoro-6-methyl-4-pyrimidinamine (BuOH: < 10%)[2093] and others.[1749]



54 **55** **56**

A few fluoropyrimidines have been made from appropriate pyrimidinamines by *diazotization* in aqueous hydrofluoric acid or tetrafluoroboric acid. These include 2-fluoro- (HF: 25%; HBF_4: 25–50%),[752,3154] 5-bromo-2-fluoro- (HBF_4: ~30%),[1749] and 4-fluoro-2-methoxypyrimidine (HBF_4: 10%);[66] also 3-ethyl-6-fluoro-4(3*H*)-pyrimidinone (HBF_4: 20%).[1245]

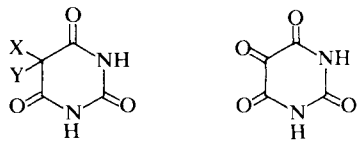
The formation of 4-fluoro-6-methoxy-2-methyl-5-trifluoromethylpyrimidine (**57**) by *primary synthesis*[176] has been discussed in Section 3.3.1; the rather non-specific rearrangements of perfluoropyridazines and perfluoropyrazines under pyrolytic conditions to give polyfluoropyrimidines:[4495,4496,4908] for example, 2,4,6-trifluoro-5-pentafluoroethylpyrimidine (**58**), has been mentioned in Section 2.6.2.



57 **58**

6.5. PREPARATION OF 5-HALOGENOPYRIMIDINES

Direct halogenation of a 5-unsubstituted pyrimidine usually gives its 5-halogeno derivative, especially if the substrate bears one or more electron-donating substituents. However, appropriate substrates may undergo extra-nuclear halogenation (with or without 5-halogenation), as indicated in Section 4.2.3.5, or even an occasional 4/6-halogenation as exemplified in Section 6.1.6. In practice, direct halogenation is the method of choice for making 5-chloro-, 5-bromo-, and 5-iodopyrimidines whereas other routes are more often employed for preparing 5-fluoropyrimidines. Molecules such as 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**59**, X = Y = H) will accommodate two halogen substituents at the 5-position to give, for example, the stable 5,5-dibromo derivative (**59**, X = Y = Br), akin to alloxan (**60**) or 5,5-diethylbarbituric acid (**59**, X = Y = Et) in structure: such dihalogeno derivatives undergo facile reductive monodebromination to afford regular 5-halogeno derivatives (e.g., **59**, X = Br, Y = H).



59 **60**

6.5.1. Using Direct Halogenation

The direct halogenations of pyrimidine (or its cation), simple alkylpyrimidines, and simple arylpyrimidines are discussed in Sections 4.1.3 and 4.2.3.5. The *5-monohalogenation* of other pyrimidines is illustrated in the formation of the following products, usually from their 5-unsubstituted analog (NCS, NBS, or NIS for *N*-chloro-, *N*-bromo-, or *N*-iodosuccinimide, respectively).

5-Chlorinations

5-Chloro-2-pyrimidinamine (Cl_2, H_2O, 70°: 41%;[894] same + $CaCO_3$: 60%;[1931] NCS, $CHCl_3$, reflux, 1 h: 60%[2258]).

5-Chloro-2,4-pyrimidinediamine (Cl_2, H_2O, 25°: < 30%).[2331]

5-Chloro-4(3*H*)-pyrimidinone (Cl_2, AcOH: ~30%).[1827,3743]

5-Chloro-2,6-dimethyl-4(3*H*)-pyrimidinone (NaOCl, H_2O, 25°, 1 h: 90%).[2117]

5-Chloro-2,4(1*H*,3*H*)-pyrimidinedione (NCS, AcOH, 55°: 52%;[2243] SO_2Cl_2, AcOH–Ac_2O, $AlCl_3$, reflux, 2 h: ~90%;[2341] $SOCl_2$, pyridine: 27%[1174]).

5-Chloro-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (SO_2Cl_2, AcOH, $FeCl_3$, reflux, 2 h: 98%).[1958]

5-Chloro-2-methylthio-4(3*H*)-pyrimidinone (NCS, AcOH, 55°: 63%;[2243] Cl_2 or SO_2Cl_2, AcOH: 20%).[1914,1957]

5-Chloro-2-dimethylamino-6-methyl-4(3*H*)-pyrimidinone (NCS, $CHCl_3$, reflux, 5 h: 25%; Pr^iSCl, CH_2Cl_2: 72%).[1732]

5-Chloro-4-methoxy-2-pyrimidinamine (Cl_2, dilute HCl, 10°: 49%).[2209]

5-Chloro-4-methoxy-6-methyl-2-pyrimidinamine (NCS, $CHCl_3$, reflux, 30 min: 75%).[1014]

5-Chloro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (SO_2Cl_2 H_2O, 100°, 5 min: 79%).[2354]

4-Amino-5-chloro-2(1*H*)-pyrimidinone (NCS, AcOH, 105°, 1 h: 69%).[1040]

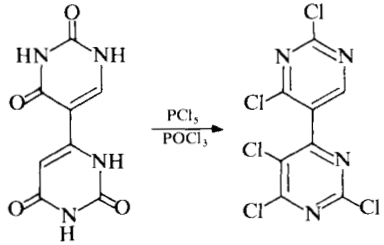
5-Chloro-6-methyl-2,4-pyrimidinediamine 3-oxide (NCS, $CHCl_3$–MeOH, reflux, 45 min: 66%).[3864]

5,6-Dichloro-2,4(1*H*,3*H*)-pyrimidinedione (Cl_2, H_2O, 80°: ~60%; Cl_2, AcOH, 70°: ~75%).[1812]

6-Amino-5-chloro-2-phenyl-4(3*H*)-pyrimidinone (neat $SOCl_2$, reflux, 2 h: 66%).[2491]

2,2′,4,5,6-Pentachloro-4,5′-bipyrimidine (**62**) from 4,5′-bipyrimidine-2,2′,4′,6(1*H*,1′*H*,3*H*,3′*H*)-tetrone (**61**) (PCl_5 + PCl_3, 115°, 16 h: 79%).[4867]

Also other examples.[210,318,610,909,1174,1265,1732,1788,1802,1803,1811,1813,1830,1940,1986,2088,2119,2151,2333,2341,3622,4882]



61 **62**

5-Brominations

5-Bromo-4-phenylpyrimidine (Br_2, $PhNO_2$, 150°, 7 h: 98%).[4911, cf. 23]

5-Bromo-4,6-dimethyl-2-pyrimidinamine (Br_2, EtOH–H_2O, 0°, 1 h, then SO_2 to reduce perbromide: 85%;[1118] Br_2, H_2O, 55°: 47%;[894] Br_2, H_2O, $CaCO_3$, 55°: 86%[1437]).

5-Bromo-2-piperidinopyrimidine (NBS, $CHCl_3$, reflux, 10 min: 96%).[4918]

5-Bromo-4,6-pyrimidinediamine (Br_2, H_2O, 25°, 30 min: ~90%).[968]

5-Bromo-2,4,6-pyrimidinetriamine (Br_2, AcOH–H_2O, 30°, 1 h: 77%;[837] Br_2, H_2O, 100°, 5 min: > 95%[1230]).

5-Bromo-2(1*H*)-pyrimidinone (Br_2, H_2O, 25°: 55%).[1986]

5-Bromo-4(3*H*)-pyrimidinone (Br_2, AcOH, 25°, 3 h: ~50%).[1827]

5-Bromo-2,6-di-*t*-butyl-4(3*H*)-pyrimidinone (Br_2, AcOH, 25°, 24 h: 58%; NBS, $CHCl_3$, reflux, 2 h: 82%).[4882]

5-Bromo-2,4(1*H*,3*H*)-pyrimidinedione (Br_2, H_2O, 95°, 30 min: 90%;[1861, cf. 1837,1936] dioxane.2Br, dioxane: > 98%[1873,4910]).

5-Bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (NBS, CCl_4, Bz_2O_2, reflux, 20 min: > 95%).[269]

5-Bromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Br_2, $HCONH_2$, 60°, 1 h: 78%;[954] enzymatic;[3932] Br_2, H_2O, 50°: 70%[1984]).

5-Bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde (Br_2, H_2O, 25°: 78%)[1869] or from substrate acetal (Br_2, $CHCl_3$, reflux, 30 min: 87%).[1868]

5-Bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (HBr, H_2O_2, 35°: 73%).[1872, cf. 1873,4910]

5-Bromo-2,-4-bisethylthio-6-methylpyrimidine (Br_2, CH_2Cl_2, 5°, 1 h: 94%).[68]

5-Bromo-6-phenylthio-2,4(1*H*,3*H*)-pyrimidinedione (Br_2, MeOH, 25°, 1 h: 83%).[4916]

5-Bromo-4-methoxy-6-methyl-2-methylthiopyrimidine (NBS, AcOH, 100°, 3 h: 50%; Br_2, AcOH, 20°, 2 h: 12%; likewise at 100°: isomeric product).[1788]

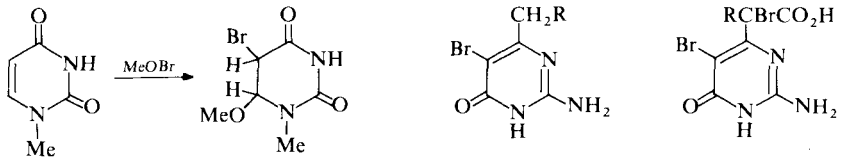
5-Bromo-2,4-dimethoxy-6-methylaminopyrimidine (NBS, AcOH–H_2O, 55°, 30 min: 58%).[675]

4-Amino-5-bromo-2(1*H*)-pyrimidinone (Br_2, H_2O, 25°, 2 h: 79%).[971]

2,6-Diamino-5-bromo-4(3*H*)-pyrimidinone (Br_2, H_2O, NaOH, 25°, 2 h: 78%).[2387]

1-β-Aminoethyl-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione (Br_2, AcOH, 25°, 12 h: 92%).[3775]

5-Bromo-6-methoxy-1-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**64**) from 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**63**) (MeOBr, MeOH, 0°, 1 h: 90%).[3452]



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2-Amino-5-bromo-6-carboxymethyl-4(3*H*)-pyrimidinone (**65**, R = CO_2H (Br_2, AcOH, 25°, 9 h: 87%); the 6-bromomethyl (**65**, R = Br), 6-α,-bromocarboxymethyl (**66**, R = H), and 6-α,α-dibromocarboxymethyl (**66**, R = Br) analogs were formed also, especially under more vigorous conditions.[949]

Also many other examples in the foregoing references and elsewhere.[32,112,226,367,610,719,909,951,955,961,967,1014,1133,1161,1265,1396,1465,1560,1616,1741,1742,1745,1802,1805,1808–1813,1816,1818,1821,1822,1828,1830,1841,1867,1874,1887,1895,1896,1914,1915,1946,1949,1952,1962,2218,2928,3622,3760,3903,4129,4172,4178,4394,4909,4912–4915,4917,6579]

5-Iodinations

5-Iodo-2-pyrimidinamine [I_2, $Hg(OAc)_2$, dioxane-H_2O, 70°, 30 min: 70%;[3289] I_2 + Cl_2, dioxane, 60°, 2 h: 52%[140]].

5-Iodo-4-pyrimidinamine (ICl, AcOH, 95°, 3 h: 50%;[1650] I_2, NaOH, H_2O, 80°, 19 h: 56%[499]).

5-Iodo-2-methylaminopyrimidine [I_2, $Hg(OAc)_2$, dioxane–H_2O, 95°, 30 min: 47%].[923]

5-Iodo-2,6-dimethyl-4-pyrimidinamine (ICl, AcOH, 25°, 2 days: 36%;[3748] I_2, H_2O_2, dilute H_2SO_4, CCl_4, reflux, 3 h: 97%[1347]).

5-Iodo-4,6-dimethyl-2-pyrimidinamine (NIS, $CHCl_3$, reflux, 45 min: 72%).[1014]

5-Iodo-2(1*H*)-pyrimidinone ($NaICl_2$, H_2O, 60°, 1 h: 35%;[44] neat ICl, 100°, 2.5 h: ~ 40%[1826]).

5-Iodo-4(3*H*)-pyrimidinone ($NaICl_2$, NaOH, H_2O, 65°, 2 h: 75%;[270] I_2, NaOH, H_2O, 55°, 2.5 h: 41%[1262]).

5-Iodo-2,4(1*H*,3*H*)-pyrimidinedione (I_2, NaOH, H_2O;[1234] NIS, $CHCl_3$, reflux, 1 h: 56%;[1014] ICl, *M* HCl, 70°, 30 min: 65–75%[4919]).

2-Amino-5-iodo-4(3*H*)-pyrimidinone [I_2, $Hg(OAc)_2$, dioxane–H_2O, 70°, 2 h: 90%].[1348]

4-Amino-5-iodo-2(1*H*)-pyrimidinone (I_2, NaOH, H_2O;[1234] I_2, HIO_3, AcOH–$CHCl_3$, 50°, 15 h: 86%[1352]).

2,6-Diamino-5-iodo-4(3*H*)-pyrimidinone (I_2, NaOH, H_2O, 50°, 5 min: 88%).[2384]

5-Iodo-6-methyl-2-methylthio-4(3*H*)-pyrimidinone (NIS, $CHCl_3$, reflux, 1 h: 83%).[3893]

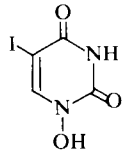
2-Ethylthio-5-iodo-4(3*H*)-pyrimidinone ($NaICl_2$, NaOH, dioxane–H_2O, 60°, 10 min: 48%).[270, cf. 1234]

6-Chloro-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione [I_2, $Hg(OAc)_2$, dioxane–H_2O, 85°, 1 h: ~ 80%].[1812]

5-Iodo-2,4-dimethoxy-6-methylpyrimidine (NCS + NaI, AcOH, 80°: 80%).[257]

1- (**67**) or 3-Hydroxy-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (I_2, NaOH, H_2O, 20°, 2–12 h: ~ 75% each).[1265]

Also other examples.[3,929,1265,1350,1616,1829,1857,1914,1962,2209,2928,4920,6077]



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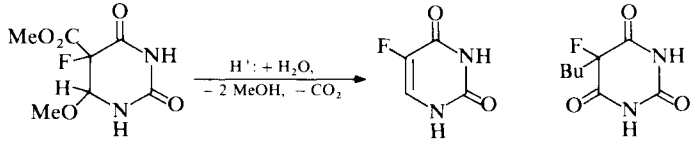
5-Fluorinations

5-Fluoro-2(1*H*)-pyrimidinone (F_2 + N_2, neat HF, 0°, 38%).[3165]

5-Fluoro-1-methyl-2(1*H*)-pyrimidinone (F_2, AcOH, 20°, 1 h: 61%).[3165]

5-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione (**69**) [F_2, H_2O, 25°: 55%;[3168] F_2 + Xe, AcOH, 20°: 70%;[3918] CF_3OF, $CFCl_3$–F_3CO_2H–H_2O, 25°, 15 h: 94%;[3168] XeF_2, HF, 0–20°: 10%;[3167] also from methyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate via methyl 5-fluoro-4-methoxy-2,6-dioxohexahydro-5-pyrimidinecarboxylate (**68**) (CF_3OF, $CFCl_3$, MeOH, 25°; then aqueous HCl, 100°: 90% overall);[1980, cf. 3171] AcOF has been used successfully also.[128,3738]].



68 **69** **70**

5-Fluoro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (neat CF_3OF, 25°, 4 h: > 90%).[3157]

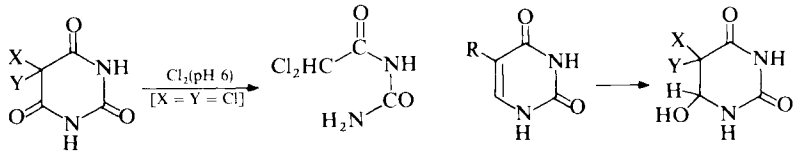
5-Butyl-5-fluoro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**70**) ($FClO_3$, MeOH, < 20°: 67%).[4921]

The *5,5-dihalogenation* of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione and related substrates (including most 5,6-dihydropyrimidines), each with two hydrogen atoms on C5, presents no problem. However, such dihalogenation of 2,4(1*H*,3*H*)-pyrimidinedione and related pyrimidines, in which C5 bears only one hydrogen

atom, can occur only after 5,6-addition of water, methanol, hypobromous acid or the like to these substrates.

Thus treatment of aqueous 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**71**, X = Y = H) with bromine (1 mol) at 50° gave the 5-bromo derivative (**71**, X = Br, Y = H) (70%), which underwent a second bromination under similar conditions to afford the 5,5-dibromo derivative (**71**, X = Y = Br),[1657,1984,4922] the same product has been made also from 5-nitroso- (**71**, X = NO, Y = H),[1842] 5-nitro- (**71**, X = NO_2, Y = H),[1657] 5-acetyl- (**71**, X = Ac, Y = H),[789] or 5-benzylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione:[1984] the original 5-substituent was displaced in each case. The dibromo product (**71**, X = Y = Br) reverted to the monobromo derivative (**71**, X = Br, Y = H) on treatment with ammonia[1842,1984] or by partial reduction with sodium amalgam,[3553] zinc,[3553] hydrazine,[1983] hydriodic acid,[4923] or cyclohexene.[4924] *N*-Alkylated 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones behaved similarly on bromination[789,1842] but 5-methyl-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione (**71**, X = Me, Y = H) predictably gave only its monobromo derivative (**71**, X = Me, Y = Br) (68%).[4925] Chlorination of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione likewise gave the 5-chloro (**71**, X = Cl, Y = H) or 5,5-dichloro derivative (**71**, X = Y = Cl) according to the conditions,[1983,2353] although the latter product was most easily made (80%) in hydrochloric acid with added hydrogen peroxide;[2354] excessive chlorination in water maintained at pH 6 gave only *N*-(dichloroacetyl)urea (**72**).[4926] The 1- and 3-alkylated substrates behaved similarly.[1064,1842] Treatment of 6-amino- or 6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione with sulfuryl chloride or chlorine in acetic acid gave 5,5-dichloro-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (>75%),[1813,4934] the same product as that obtained from tetramethylalloxantin with phosphorus pentachloride.[3706] The dichloro product (**71**, X = Y = Cl) gave the monochloro derivative (**71**, X = Cl, Y = H) on treatment with hydrazine,[1980] but stannous chloride caused complete dechlorination to the original substrate (**71**, X = Y = H).[1842] Chlorination of 5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**71**, X = NO_2, Y = H) in warm hydrochloric acid by the addition of hydrogen peroxide gave the 5-chloro-5-nitro derivative (**71**, X = NO_2, Y = Cl) (60–80%).[3571] Fluorination of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**71**, X = Y = H) with perfluoromethanol (CF_3OF) for 1 h gave the 5,5-difluoro derivative (**71**, X = Y = F) (~80%);[3157] fluorination of 5-butyl- (with perchloro fluoride, $FClO_3$) or of 5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (with perfluoromethanol) gave the 5-butyl-5-fluoro (**71**, X = Bu, Y = F) (67%)[4921] or the 5-fluoro-5-phenyl derivative (**71**, X = Ph, Y = F) (~80%),[3157] respectively. Dibromination of a 5,6-dihydropyrimidine is exemplified in the conversion of 2-methyl-5,6-dihydro-4-pyrimidinamine into its 5,5-dibromo derivative, which incidentally underwent dehydrobromination in triethylamine to afford 5-bromo-2-methyl-4-pyrimidinamine.[1929]

Treatment of 2,4(1*H*,3*H*)-pyrimidinedione (**73**, R = H) with sufficient bromine or chlorine in water gave, 5,5-dibromo- (**74**, X = Y = Br) or 5,5-dichloro-6-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**74**, X = Y = Cl), respectively;[2119,2321] the corresponding 5-bromo-5-chloro analog (**74**, X = Br, Y = Cl)



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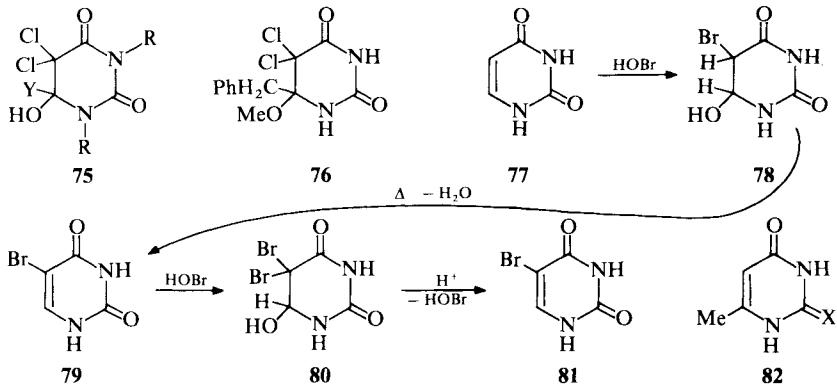
was obtained by treatment of 5-bromo- (**73**, R = Br) or 5-chloro-2,4(1*H*,3*H*)-pyrimidinedione (**73**, R = Cl) with aqueous chlorine or aqueous bromine, respectively.[2340] 6-Alkyl- or 1,3-dialkyl-2,4(1*H*,3*H*)-pyrimidinediones behaved similarly to afford, for example, 5,5-dibromo-6-hydroxy-6-methyl- (**75**, R = H, Y = Me)[1944,2060] or 5,5-dibromo-6-hydroxy-1,3-dimethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**75**, R = Me, Y = H),[963] respectively. When such dihalogenations were done in an alcohol, an appropriate alkoxy group replaced the hydroxy group in the product (**74**/**75**) to give, for example, 6-benzyl-5,5-dichloro-6-methoxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**76**);[4909] in other solvents, no dihalogenation occurred. When the substrate (**73**) already carried a 5-substituent, treatment with aqueous halogen simply inserted a single 5-halogeno or, if possible, displaced the first substituent and inserted two halogeno substituents. For example, 5-methyl- (**73**, R = Me) or 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**73**, R = NO_2) with aqueous chlorine gave 5-chloro-6-hydroxy-5-methyl- (**74**, X = Me, Y = Cl) or 5-chloro-6-hydroxy-5-nitro-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**74**, X = NO_2, Y = Cl), respectively, or with aqueous bromine the corresponding bromo derivatives;[2119,4927,4928,4933] likewise, 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (**73**, R = F) with methanolic bromine or aqueous chlorine gave 5-bromo-5-fluoro-6-methoxy- (82%) or 5-chloro-5-fluoro-6-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (66%), respectively;[4929] but, in contrast, both 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (**73**, R = CO_2H) and 5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (**73**, R = I) with aqueous chlorine gave 5,5-dichloro-6-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**74**, X = Y = Cl).[1980,2119] Most 1-, 3-, or 6-substituted 2,4(1*H*,3*H*)-pyrimidinediones appear to react similarly with halogens, as indicated in several of the foregoing examples and by the conversion of 1- or 3-benzyloxy-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione (with methanolic bromine) into 1- or 3-benzyloxy-5,5-dibromo-6-methoxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (~90% each).[1265] There seems to be a broad consensus of opinion as to the mechanism for such halogenation of uracils,[1858,1859,1861,1862,4929–4932,6576] as exemplified in formulae (**77**–**81**).[cf. 71,3744,3745]

Related substrates tend to react similarly with aqueous or alcoholic halogens, although susceptible substituents may be affected in the process. For example, both 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**82**, X = S) and 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**82**, X = O) with aqueous chlorine gave 5,5-dichloro-6-hydroxy-6-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**75**, R = H, Y = Me);[1944,3135] 2-ethylthio-4(3*H*)-pyrimidinone likewise



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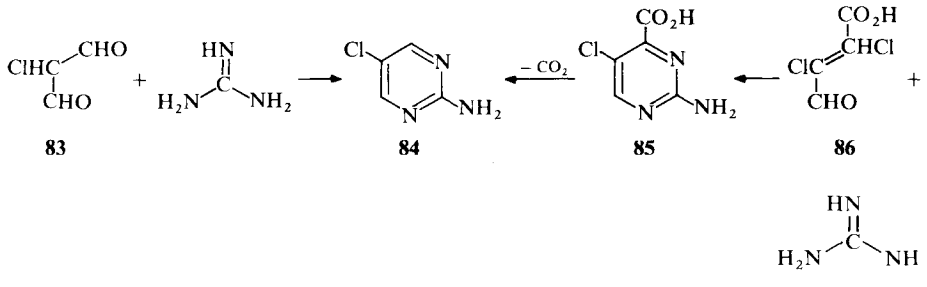
gave 5,5-dichloro-6-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**74**, X = Y = Cl);[2119] 4-amino-2(1*H*)-pyrimidinone with aqueous bromine gave 4-amino-5,5-dibromo-6-hydroxy-5,6-dihydro-2(1*H*)-pyrimidinone (gentle conditions)[1837] or 5,5-dibromo-6-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**74**, X = Y = Br) (less gentle conditions);[2312] 2-amino-4(3*H*)-pyrimidinone with aqueous chlorine gave 2-amino-5,5-dichloro-6-hydroxy-5,6-dihydro-4(3*H*)-pyrimidinone;[2119] 4,6(1*H*,5*H*)-pyrimidinedione with methanolic bromine gave the 5-bromo derivative and thence the 5,5-dibromo, isolated as a 2,3-methanol adduct;[1982] and analogous cases have been reported.[1803,1887,1952]

6.5.2. Using Primary Syntheses

Primary syntheses have been used quite extensively to make 5-halogenopyrimidines, especially for those lacking more than one electron-donating group (see Chapters 2 and 3). Such syntheses are exemplified briefly by the condensation of guanidine with α-chloromalondialdehyde (**83**) or chloromucic acid (**86**) to give 5-chloro-2-pyrimidinamine (**84**) directly (74%)[704] or (better) via decarboxylation of 2-amino-5-chloro-4-pyrimidinecarboxylic acid (**85**) (60% overall),[2316] respectively; of acetamidine with diethyl α-fluoromalonate to afford 5-fluoro-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione (83%);[272] of α-chloromalondialdehyde diacetal with formamide at 200° to give 5-chloropyrimidine (61%);[1970] and of 3-



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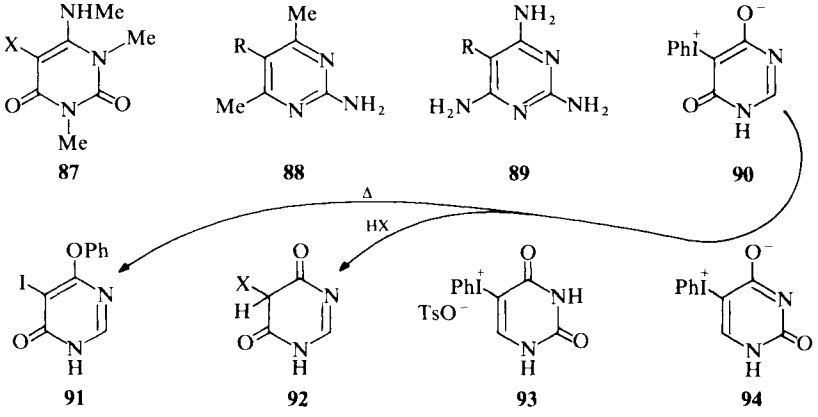
dimethylamino-2-fluoroacrylaldehyde with formamide at 190° to give 5-fluoropyrimidine (52%).[3161] Another type of primary synthesis is illustrated by the conversion of 5-oxo-4,5-dihydro[1,2,3]oxadiazolo[5,4-*d*]pyrimidine-7-carbaldehyde *p*-nitrophenylhydrazone into 5-iodo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde *p*-nitrophenylhydrazone (~90%) by heating with aqueous hydriodic acid.[4937]

6.5.3. Using Other Routes

Limited use has been made of several other routes to 5-halogenopyrimidines. Thus transhalogenation has been employed to convert 5-bromo- into 5-chloro-4,6(1*H*,5*H*)-pyrimidinedione (HCl, Me_2NCHO, 100°, 2 min: 82%),[2342] 5-bromo- into 5-chloro-1-ethyl-2,4,6(1*H*,3H,5*H*)-pyrimidinetrione (HCl, 100°, ~50%),[789] 2,6-diamino-5-bromo- into 2,6-diamino-5-iodo-4(3*H*)-pyrimidinone (KI, AcOH–H_2O, 100°, 10 min: 87%),[2384] 5-bromo- (**87**, X = Br) into 5-chloro-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione (**87**, X = Cl) (NH_4Cl, EtOH, reflux, 5 h: 83%),[675] and 2,4,5,6-tetrachloro- into 2,4,5,6-tetrafluoropyrimidine (KF, 410°, 22 h, sealed: 57%).[1728]

5-Pyrimidinamines have been converted into 5-halogenopyrimidines by diazotization and subsequent treatment with cuprous halide (Sandmeyer reaction) or with an excess of halide ion. Thus diazotized 4,6-dimethyl-2,5-pyrimidinediamine (**88**, R = NH_2) with potassium iodide at 85° gave 5-iodo-4,6-dimethyl-2-pyrimidinamine (**88**, R = I) (~60%);[645] diazotized 5-amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione with potassium iodide, cuprous chloride, or cuprous bromide gave 5-iodo- (75%), 5-chloro- (70%), or 5-bromo-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (80%), respectively;[4935] 2,4,5,6-pyrimidinetetramine (**89**, R = NH_2) was converted into 2,4,6-triamino-5-pyrimidinediazonium tetrafluoroborate (**89**, R = $\overset{+}{N}_2BF_4^-$) which on heating in paraffin oil to 225° gave 5-fluoro-2,4,6-pyrimidinetriamine (**89**, R = F) (65%);[2400] 2,6-diamino-5-fluoro-



4(3*H*)-pyrimidinone (60%) was made similarly;[2400] and diazotized 2-pyrimidinamine 1-oxide with hydrobromic acid gave several products including 5-bromo-2-pyrimidinamine 1-oxide and 2,5-dibromopyrimidine 1-oxide.[1966]

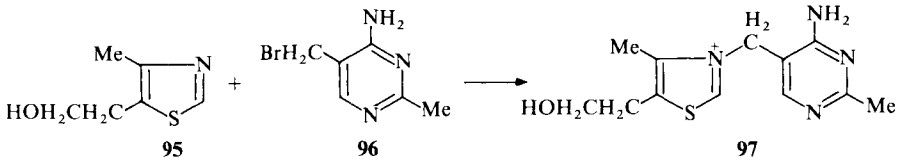
Treatment of 4,6(1*H*,5*H*)-pyrimidinedione with (diacetoxyiodo)- or (dichloroiodo)benzene in warm aqueous sodium carbonate gave the *phenyliodonio intermediate*, 6-oxo-5-phenyliodonio-1,6-dihydro-4-pyrimidinolate (**90**) (90%), which rearranged into 5-iodo-6-phenoxy-4(3*H*)-pyrimidinone (**91**) (69%) on heating in dimethylformamide but gave 5-bromo- (**92**, X = Br) (65%) or 5-chloro-4,6(1*H*,5*H*)-pyrimidinedione (**92**, X = Cl) (87%) on heating in ethanolic hydrobromic or hydrochloric acid;[76] several alkyl derivatives were made similarly;[76] and 5-phenyliodonio-2,4(1*H*,3*H*)-pyrimidinedione tosylate (**93**) (78%) as well as the betaine, 2-oxo-5-phenyliodonio-1,2-dihydro-4-pyrimidinolate (**94**), have been prepared but have seemingly remained unused.[4936]

Simple 5-halogenopyrimidines may be made by *removal* of unwanted groups: for example, conversion of 2-chloro-5-iodo- into 2-hydrazino-5-iodopyrimidine and subsequent oxidative removal of the hydrazino group by silver oxide gave 5-iodopyrimidine (50% overall).[2180]

The *metallation* of 4-chloro-2,6-dimethoxypyrimidine to its 5-lithio derivative and subsequent treatment with iodine in THF gave 4-chloro-5-iodo-2,5-dimethoxypyrimidine (86%).[6076]

6.6. PREPARATION OF EXTRANUCLEAR HALOGENOPYRIMIDINES

The necessity of making 5-bromomethyl-2-methyl-4-pyrimidinamine (**96**) for condensation with 5-β-hydroxyethyl-4-methylthiazole (**95**) to synthesize vitamin B_1 (thiamine) (**97**), probably provided the first real stimulation (1935–1940) to explore the synthesis and chemistry of extranuclear halogenopyrimidines.



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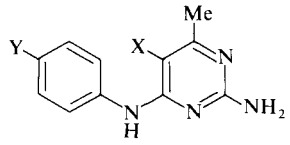
6.6.1. Using Direct Halogenation

Halogenation of simple alkyl or alkenyl groups attached directly to the pyrimidine nucleus has been discussed in Section 4.2.3.5. It is evident that the process is uncertain, especially as to the extent of halogenation, which varies with the reagent and conditions employed: troublesome mixtures often result. The less common halogenation of alkyl groups attached indirectly to the

nucleus, of functionally substituted alkyl groups, and of aryl groups is now illustrated by the following examples.

4-Anilino-6-methyl-2-pyrimidinamine (**98**, X = Y = H) into its 5-bromo derivative (**98**, X = Br, Y = H) (Br_2, AcONa, AcOH, 25° then 100°, 1 h: 98%) or 5-bromo-4-*p*-bromoanilino-6-methyl-2-pyrimidinamine (**98**, X = Y = Br) (2 Br_2 likewise: 98%).[4938]

5-Acetyl-2,4(1*H*,3*H*)-pyrimidinedione (**99**, X = Y = H) into its 5-α-bromoacetyl (**99**, X = Br, Y = H) (Br_2, MeOH, 25°: 60–73%;[831,833] Br_2, AcOH, warm: > 90%[795,2042]) and thence into its 5-α,α-dibromoacetyl analog (**99**, X = Y = Br) (Br_2, MeOH, reflux).[830]



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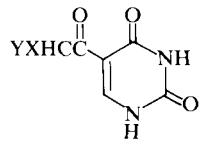

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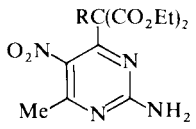
4-Di(ethoxycarbonyl)methyl- (**100**, R = H) into 4-bromodi(ethoxycarbonyl)methyl-6-methyl-5-nitro-2-pyrimidinamine (**100**, R = Br) (Br_2, PhH, 50°, 92%).[4939]

2-Methylthio-5-prop-2′-ynyloxy- (**101**, R = H) into 5-(3′-iodoprop-2′-ynyl)oxy-2-methylthiopyrimidine (**101**, R = I) (I_2, NaOH, MeOH–H_2O, 20°, 1 h: 94%).[926]



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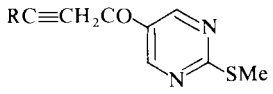

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5-Chloro-2-methylthio- into 5-chloro-2-chloromethylthiopyrimidine (SO_2Cl_2, CH_2Cl_2, reflux, 3 h: 82%).[3820]

4-Acetyl- into 4-α-bromoacetyl-2-pyrimidinamine (Br_2, HBr–AcOH, 25°, 20 h: 83%).[306]

4-Phenacyl- into 4-α-bromophenacylpyrimidine (Br_2, AcONa, AcOH, 20°, 30 min: 70%).[546]

2-Phenacyl- into 2-α-chlorophenacyl- (Cl_2, AcONa, AcOH, 20°, 30 min: 98%) or 2-α,α-dichlorophenacyl-5-phenylpyrimidine (2 Cl_2, AcONa, AcOH, 20°, 2.5 h: 95%).[546]

4-Amino- into a separable mixture of 4-amino-5-fluoro-, 4-difluoroamino-5-fluoro-, and 4-difluoroamino-2(1*H*)-pyrimidinone (F_2, H_2O, 0°, 1 h).[9]

Also other examples in the foregoing references.

6.6.2. Using Hydroxyalkylpyrimidine Intermediates

The conversion of an hydroxyalkyl into an halogenoalkyl substituent can be done with several reagents: good-quality thionyl chloride is the most selective and convenient, hydrohalide in acetic acid (or water) is usually effective but may produce hydrolysis of susceptible groups, and phosphorus halides or even Vilsmeier reagents are usable but prone to cause side reactions such as the conversion of any nuclear oxo/hydroxy substituent(s) into the corresponding halogeno substituent(s). The appropriate use of such reagents is illustrated in the formation of the following products, each from the corresponding hydroxyalkyl substrate unless indicated otherwise.

With thionyl chloride

5-Chloromethyl-2-ethylthio-4-pyrimidinamine ($CHCl_3$, reflux, 10 h: 77%).[1249]

5-Chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione ($CHCl_3$–pyridine, reflux, 30 min: > 95%;[1940] dioxane, reflux, 6 h: ~90%[1712]).

5-β-Chloroethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (neat, 20°, 24 h: 91%).[1319]

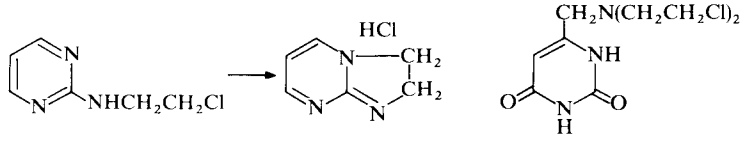
5-Chloromethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (digylme, 25°, 2 h: 76%).[760]

1-β-Chloroethyl-2,4(1*H*,3*H*)-pyrimidinedione (dioxane–pyridine reflux, 30 min: > 85%).[1323, cf. 1722]

2-β-Chloroethylaminopyrimidine (**102**) ($CHCl_3$, reflux, 15 min: 77%),[3524] which isomerized readily into the 2,3-dihydroimidazo[1,2-*a*]pyrimidine hydrochloride (**103**) (EtOH, reflux, 30 min: 92%);[3524] elsewhere, the hydrochloride (**103**) has been mistaken for the primary product (**102**).[4944]

2-β-Chloroethylamino-5-methyl-4(3*H*)-pyrimidinone (NEt_3, 50°, 30 min: > 95%).[3124]

6-[*N*,*N*-Di(β-chloroethyl)amino]methyl-2,4(1*H*,3*H*)-pyrimidinedione (**104**) (neat, 100°, 30 min: ~75%).[1498]



102 **103** **104**

Also many other such products.[701,911,1013,1721,1941,1946,3537,4940–4943,4945–4951] a few of which may, in fact, be their bicyclic isomers: for example, the product formulated as 4-di(β-chloroethyl)amino-2(1*H*)-pyrimidinethione[4951] was shown subsequently to be the isomeric

1-β-chloroethyl-2,3-dihydroimidazo[1,2-*c*]pyrimidine-5(1*H*)-thione hydrochloride.[4952]

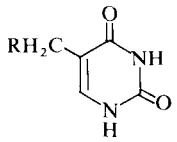
With hydrohalide solutions

5-Bromomethyl-2-methylpyrimidine (HBr, AcOH, 100°, 3 h: 80%).[1904,3062]

5-Bromomethyl-2-ethylthio-4-pyrimidinamine (HBr, AcOH, 100°, 2 h: 80%).[1249]

5-Bromomethyl-2-methyl-4-pyrimidinamine (HBr, AcOH, 60–100°, 2 h: 95%).[750,1918,1919]

5-Bromomethyl- (**105**, R = Br), 5-chloromethyl- (**105**, R = Cl), or 5-iodomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**105**, R = I) (HBr, AcOH, 95°, 8 h: 79%;[1940] 10*M* HCl, 25°, 30 min: 90%;[841,2271] or HI, H_2O, 25°, 10 min: 79%,[841] respectively).



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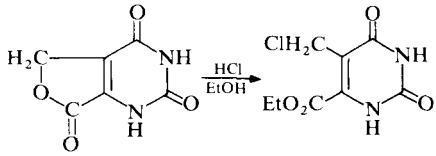
5-Bromomethyl- or 5-chloromethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (HBr, AcOH, reflux, 3 h: 83%;[1925] or 10*M* HCl, 20°, 30 min: 90%;[347] respectively).

5-Bromomethyl-2,4-pyrimidinediamine (HBr, AcOH; 100°, 2 h).[1937]

1-δ-Bromobutyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (HBr, H_2O, 100°: ~80%).[1881]

Ethyl 5-chloromethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (**107**) from the lactone (**106**) of 5-hydroxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (HCl, EtOH, 25° then reflux, 6 h: 70%).[2627]

Also other examples.[1182,1912,4124,4953,6579]



106 **107**

With phosphorus halides

2-Chloromethyl-4,6-dimethylpyrimidine ($POCl_3$, $CHCl_3$, reflux, 3 h: 90%).[2222]

4-α-Chloroethyl-2-methyl-6-phenylpyrimidine ($POCl_3$, reflux, 2 h: 80%).[4684]

5-Chloromethyl-2,6-dimethyl-4-pyrimidinamine ($POCl_3$, 80°: ~ 65%).[1119]

4-Chloro-5-chloromethyl-2-methylpyrimidine from 5-hydroxymethyl-2-methyl-4(3*H*)-pyrimidinone ($POCl_3$, reflux, 20 min: ~50%).[680]

6-Chloro-2-chloromethyl-4-pyrimidinamine from 6-amino-2-hydroxymethyl-4(3*H*)-pyrimidinone ($POCl_3$, reflux, 10 h: 51%).[1335]

4-Chloro- or 4, 6-dichloro-2-chloromethylpyrimidine from 2-hydroxymethyl-4(3*H*)-pyrimidinone ($POCl_3$, 80°, 15 min: 75%)[2057] or 2-hydroxymethyl-4,6(1*H*,5*H*)-pyrimidinedione ($POCl_3$, 100°, 5 h: 63%).[3468] respectively.

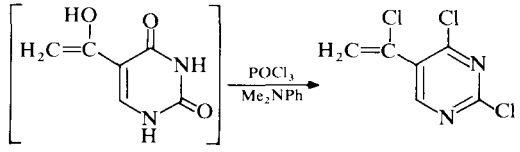
2,4-Dichloro-5-chloromethylpyrimidine from 5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (PCl_5 + $POCl_3$, reflux, 2 h: 82%).[1699]

5-Bromomethyl-4-methyl-2-methylthio-6-phenylpyrimidine from the 5-hydroxymethyl analog (PBr_3, PhH, NEt_3, 25°, 1 h: 65%).[14]

5-Benzyloxy-4-chloro-2-chloromethylpyrimidine from 5-benzyloxy-2-hydroxymethyl-4(3*H*)-pyrimidinone ($POCl_3$, reflux, 15 min: 68%).[4089]

2,4-Dichloro-5-α-chlorovinylpyrimidine (**109**) from the enol (**108**) of 5-acetyl-2,4(1*H*,3*H*)-pyrimidinedione ($POCl_3$, Me_2NPh, reflux, 20 h: 57%).[2361]

Also other examples.[1875,4953]



108 **109**

With Vilsmeier or other reagents

4-Amino-5-chloromethyl-2-cyclopropylpyrimidine ($SOCl_2$ + Me_2NCHO, 25°, 15 h: ~90%).[4242]

2-Amino-5-β-chloroethyl-4(3*H*)-pyrimidinone ($SOCl_2$ + Me_2NCHO, 40°, 2 h: ~60%).[1005]

6-Chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione ($SOCl_2$ + Me_2NCHO, reflux, 10 min: 93%).[1869]

5-Chloromethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($SOCl_2$ + Me_2NCHO, dioxane, 25°, 3 day, then reflux, 3 h: 78%).[698]

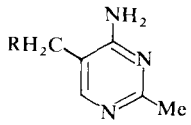
5-Fluoro-6-α-iodoethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione [$(PhO)_3\overset{+}{P}Me$ I^-, Me_2NCHO, 25°, 80%).[450]

Also other examples.[4954]

6.6.3. Using Alkoxyalkylpyrimidine Intermediates

The formation of halogenoalkylpyrimidines by fission of appropriate ethers (alkoxyalkylpyrimidines) with hydrohalide has almost fallen into disuse. The

process is exemplified in the conversion of 5-methoxymethyl- into 5-bromomethylpyrimidine (HBr, AcOH, 100°, 3 h: 84%);[1934] of 5-ethoxymethyl- (**110**, R = OEt) into 5-bromomethyl- (**110**, R = Br) (HBr, AcOH, 100°, 2 h: 90–96%),[1920,2914] 5-chloromethyl- (**110**, R = Cl) (HCl, EtOH, hot: 73%),[1670] or 5-iodomethyl-2-methyl-4-pyrimidinamine (**110**, R = I) (HI, AcOH, reflux, 2 h: ~60%);[3286] of 5-β-ethoxyethyl- into 5-β-bromoethyl-4-methyl-2-pyrimidinamine (as above: ~75%);[1149] and of 5-β-ethoxyethyl- into 5-β-chloroethyl-6-methyl-4(3*H*)-pyrimidinone (10*M* HCl, 150°, 3 h, sealed: 95%).[2145] Other such reactions have been reported.[1065,1532,4955] 1-Benzyloxymethyl- gave 1-iodomethyl-2,4(1*H*,3*H*)-pyrimidinedione (Me_3SiI, $CHCl_3$, reflux, 10 h: 88%).[6951]



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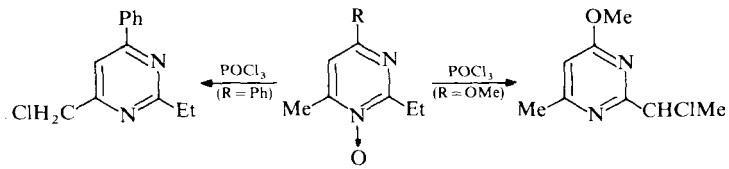
6.6.4. Using Other Indirect Syntheses

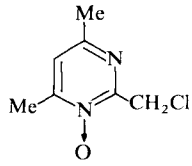
Several other indirect routes to extranuclear halogenopyrimidines can be quite useful, although their scopes are limited.

Treatment of a *pyrimidine N-oxide with phosphoryl chloride* can insert an α-chloro substituent into any alkyl group adjacent to the oxido substituent: if two such alkyl groups are available, chlorination appears to be site-specific, but there are too few examples to speculate on the controlling factor(s). Thus the simple substrates 2-methylpyrimidine 1-oxide and 4-methylpyrimidine 3-oxide in hot phosphoryl chloride–chloroform gave 2-chloromethyl- (34%) and 4-chloromethylpyrimidine (39%), respectively.[2226] However, 2-ethyl-4-methyl-6-phenylpyrimidine 3-oxide (**112**, R = Ph) with phosphoryl chloride in refluxing dioxane for several hours gave 4-chloromethyl-2-ethyl-6-phenylpyrimidine (**111**) (77%), while the isomeric 4-ethyl-2-methyl-6-phenylpyrimidine 3-oxide gave 4-α-chloroethyl-2-methyl-6-phenylpyrimidine (46%);[121] in contrast, 2-ethyl-4-methoxy-6-methylpyrimidine 1-oxide (**112**, R = OMe) gave 2-α-chloroethyl-4-methoxy-6-methylpyrimidine (**113**) (35%), while the isomeric



111 **112** **113**

4-ethyl-6-methoxy-2-methylpyrimidine 3-oxide gave 2-chloromethyl-4-ethyl-6-methoxypyrimidine (59%).[121] 2,4,6-Trimethylpyrimidine 1,3-dioxide with phosphoryl chloride in refluxing chloroform for 3 h gave only 2-chloromethyl-4,6-dimethylpyrimidine 1-oxide (**114**) (~25%).[763]



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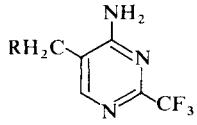

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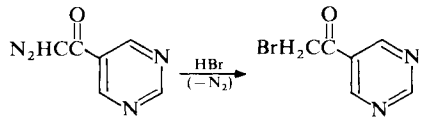
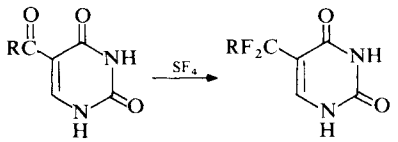


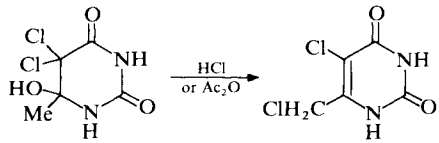
116 **117**

The diazotization of an extranuclear aminopyrimidine in the presence of halide ion can sometimes give the corresponding halogenopyrimidine. For example, treatment of 5-aminomethyl-2-trifluoromethyl-4-pyrimidinamine (**115**, R = NH_2), in hydrochloric acid–sodium chloride or in hydrobromic acid–sodium bromide at 60° with sodium nitrite, gave 5-chloromethyl- (**115**, R = Cl) (54%) or 5-bromomethyl-2-trifluoromethyl-4-pyrimidinamine (**115**, R = Br) (60%), respectively;[4241] in a rather similar way, preformed 5-diazoacetylpyrimidine (**116**) with hydrobromic acid at 0° gave 5-α-bromoacetylpyrimidine (**117**) (> 95%).[4956]

Difluoromethyl- or trifluoromethylpyrimidines may be made by treatment of the corresponding *carbaldehydes or carboxylic acids with sulfur tetrafluoride*. For example, 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde (**118**, R = H) or the corresponding 5-carboxylic acid (**118**, R = OH), with a little water and an excess of sulfur tetrafluoride in a bomb at 100° for >10 h, gave 5-difluoromethyl- (**119**, R = H) (60%) or 5-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione (**119**, R = F) (77%), respectively:[2849,4957,4958,4962] the latter reaction was reversed under alkaline conditions.[4959,4960]



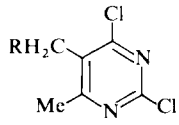
118 **119**



120 **121**

An interesting *relocation of a chloro substituent* occurred when 5,5-dichloro-6-hydroxy-6-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**120**) was boiled for more than 2 h in concentrated hydrochloric acid or acetic anhydride (less effective) to afford 5-chloro-6-chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione (**121**) (≤ 70%),[2060] a product previously formulated incorrectly.[2120,2272]

Occasional reports of extranuclear *transhalogenation* have appeared. Thus 2,4-dichloro-5-chloromethyl-6-methylpyrimidine (**122**, R = Cl) was converted into its 5-iodomethyl analog (**122**, R = I) (>95%) by simply mixing acetonic



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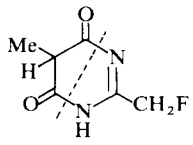
solutions of the substrate and sodium iodide for 2 h;[750,1699,2481] 5-chloro-2-chloromethylthio- gave 5-chloro-2-iodomethylthiopyrimidine (86%) similarly but under reflux for 4 h;[3820] 5-chloromethyl- gave 5-iodomethyl-2,4(1*H*,3*H*)-pyrimidinedione (89%) by dissolution in hydriodic acid at $< -5°$ for 3 h;[841] 3-*β*-chloroethyl- gave 3-*β*-iodoethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (81%) by refluxing with acetonic potassium iodide for 30 h;[1721] 2-chloro-5-trichloromethyl- gave 2-chloro-5-trifluoromethylpyrimidine (51%) by heating with antimony pentafluoride at 150° under nitrogen for 30 min;[117] and 5-trifluoromethylthio- gave 5-trichloromethylthio-2,4(1*H*,3*H*)-pyrimidinedione (crude: 80% yield) by heating in a bomb with boron trichloride in carbon disulfide at 100° for 1 week.[4961] Other examples have been reported.[6010]

6.6.5. Using Primary Syntheses

Several types of primary synthesis have been used to prepare extranuclear halogenopyrimidines, especially trifluoromethylpyrimidines (Chapters 2 and 3). A few random examples include the condensation of α-fluoroacetamidine with diethyl α-methylmalonate in cold methanolic methoxide for 3 days to afford 2-fluoromethyl-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione (**123**) (42%);[2910] the condensation of methyl 4-chlorobut-2-ynoate with *S*-methyl-*N*-phenylisothiourea in warm ethanol to give 6-chloromethyl-2-methylthio-1-phenyl-4(1*H*)-pyrimidinone (**124**) (70%);[3907] the condensation of 1-diethylaminopropyne with trifluoroacetonitrile (2 mol) in hexane at $-15°$ for 2 weeks (sealed tube) to give 4-diethylamino-5-methyl-2,6-bistrifluoromethylpyrimidine (**125**) (65%);[19] and the degradation of 5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine by bromine at 0° to afford 2-dibromomethyl-4,6-dimethylpyrimidine (90%).[4551] Primary syntheses proved to be the best way to make the antimalarial, pyrimethamine (5-*p*-chlorophenyl-6-ethyl-2,4-pyrimidinediamine),[4238] as well as innumerable analogs.[1367,4099,4238]



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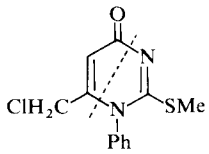

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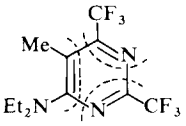

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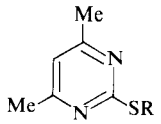
6.6.6. Using Derivatization Procedures

The formation of an extranuclear halogenopyrimidine by derivatization of an existing pyrimidine with a fragment already bearing a halogeno substituent is seldom interesting. A few such types of process are illustrated briefly by the following transformations.

6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione underwent *aminolysis* by *p*-chloroaniline at 205° for 3 h to give 6-*p*-chloroanilino-2,4(1*H*,3*H*)-pyrimidinedione (32%);[573] 4,6-dichloro-5-nitropyrimidine reacted similarly with di(β-chloroethyl)amine in methanol at 0° for 15 min to give 4-chloro-6-di(β-chloroethyl)amino-5-nitropyrimidine (89%).[24]

4,6-Dimethyl-2(1*H*)-pyrimidinethione underwent *S-alkylation* by trifluoromethyl iodide in liquid ammonia under irradiation for 1 h to give 4,6-dimethyl-2-trifluoromethylthiopyrimidine (**126**, R = CF_3) (82%);[194] the same substrate with perfluoropropene and triethylamine in dimethylformamide–dioxane at 100° for 72 h likewise gave 4,6-dimethyl-2-(perfluoroprop-1′-enyl)thiopyrimidine (**126**, R = CF:$CFCF_3$) (50%).[119]



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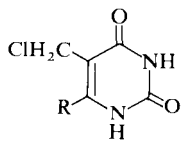

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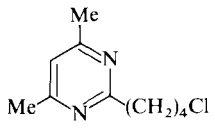
6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione underwent *direct C-alkylation* by neat chloromethyl methyl ether in a bomb at 100° to give 5-chloromethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**127**, R = Me) (> 80%);[2233] rather similarly, 2,4(1*H*,3*H*)-pyrimidinedione with formaldehyde, concentrated hydrochloric acid, and hydrogen chloride at 80° gave 5-chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione (**127**, R = H) (45–57%).[1490,2270,4963]

2-Bromo-4,6-dimethylpyrimidine underwent *indirect C-alkylation* by reaction with δ-chlorobutylzinc iodide in the presence of a palladium catalyst to afford 2-δ-chlorobutyl-4,6-dimethylpyrimidine (**128**) (95%).[3771]



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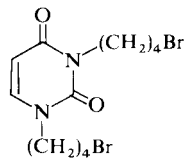

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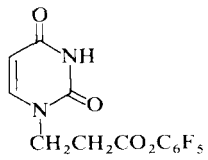
2,4(1*H*,3*H*)-Pyrimidinedione (as its disodium salt) underwent *N-alkylation* by an excess of 1,4-dibromobutane in dimethylformamide at ~ 60° for 8 h to give 1,3-bis(δ-bromobutyl)-2,4(1*H*,3*H*)-pyrimidinedione (**129**) (59%).[1720]

1-β-Carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione underwent *esterification* by pentafluorophenol (supplied as a complex) to afford 1-β-(pentafluorophenoxycarbonyl)ethyl-2,4(1*H*,3*H*)-pyrimidinedione (**130**) (90%).[110]

2-Pyrimidinamine underwent *N-acylation* by 4-chlorobutyryl chloride in chloroform–pyridine at 5° to give 2-(4′-chlorobutyramido)pyrimidine (72%);[2015] 4,5-pyrimidinediamine with 2,2-dichloropropionyl chloride in hot pyridine likewise gave a separable mixture of 5-(2′,2′-dichloropropionamido)-4-pyrimidinamine and 4,5-bis(2′,2′-dichloropropionamido)pyrimidine;[4964] and 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone gave its 5-(2′-bromopropionamido) analog (**131**) (67%) on treatment with 2-bromopropionyl bromide in methylene chloride at 0°.[33]



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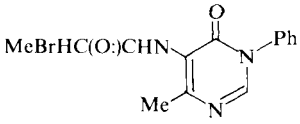
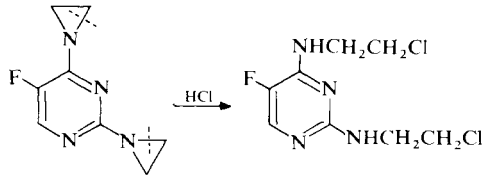


131

Pyrimidine underwent *addition* of perfluorohexyllithium in the presence of boron trifluoride to afford 4-perfluorohexyl-3,4-dihydropyrimidine (39%).[3936]

2,4,5,6-Tetrafluoropyrimidine underwent *alkanethiolysis* on treatment with "thiocarbonyl difluoride" (F_2CS) and cesium fluoride in acetonitrile to give 2,4,5-trifluoro-6-trifluoromethylthiopyrimidine and related compounds.[3740]

2,4-Diaziridino-5-fluoropyrimidine (**132**) underwent *ring fission* of its small rings, by treatment in ether at < 0° with hydrogen chloride, to give 2,4-bis(β-chloroethylamino)-5-fluoropyrimidine (**133**) (~ 85%).[2479]



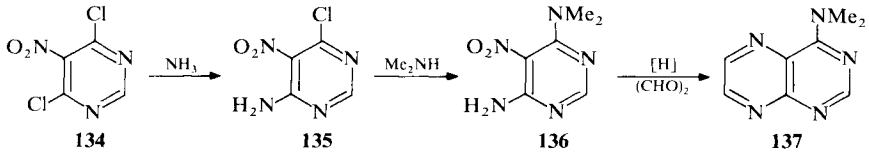
132 **133**

2,4,6-Pyrimidinetriamine underwent *diazo-coupling* to give 5-*m*-fluorophenylazo-2,4,6-pyrimidinetriamine (> 70%).[4832]

Many other examples have been reported in the foregoing references and elsewhere.[455,508,538,608,1291,1712,1723,2453,3806,3820,3989,4052,4709,4805,4833,4864,4961,4965–4968,4970–4975,4977]

6.7. REACTIONS OF 2- AND 4/6-HALOGENOPYRIMIDINES

Pyrimidines with halogeno substituents in the activated 2- or 4/6-positions undergo a great variety of reactions. Most of these have been done with the more readily available chloro derivatives. In the course of a multistage synthesis, it is often essential to have each halogeno substituent in a di- or trihalogenopyrimidine react separately and with a different reagent. For example, 4,6-dichloro-5-nitropyrimidine (**134**) was induced with care to undergo monoammonolysis to 6-chloro-5-nitro-4-pyrimidinamine (**135**);[2246] subsequent treatment with dimethylamine gave 6-dimethylamino-5-nitro-4-pyrimidinamine (**136**),[2334] which on reduction of its nitro group and condensation with glyoxal gave 4-dimethylaminopteridine (**137**).[2334]



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6.7.1. Dehalogenation of 2- or 4/6-Halogenopyrimidines

Halogeno substituents may be removed directly by reductive methods or indirectly by conversion into a thioxo, sulfo, alkylthio, or hydrazino substituent, which may then be removed by appropriate means.

Direct removal is usually done by (1) hydrogenolysis (or deuterolysis) over palladium–carbon or a similar catalyst, in the presence of a base if nuclear reduction is to be avoided; (2) treatment with zinc dust in water or aqueous ethanol; or (3) treatment with hydriodic acid. Other means have been employed occasionally. Hydrogenolysis shows little selectivity,[1833,2212,3598] either in respect of position or kind, if two or more halogeno substituents are present; zinc dust can be quite selective, as will appear in the examples; and hydriodic acid is applicable only to the removal of 2-halogeno substituents. The lability of other groups present is also relevant in choosing a removal procedure.

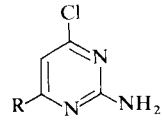
The formation of pyrimidine and of simple alkyl- or arylpyrimidines from their halogeno derivatives have been discussed in Sections 4.1.1 and 4.2.1.2, respectively. The formation of other pyrimidines from their 2- or 4/6-halogeno derivatives, by complete or selective removal of halogen, is illustrated in the following examples.

By catalytic hydrogenolysis

5-Ethylpyrimidine from its 4,6-dichloro derivative (Pd, AcONa, H_2O–EtOH: 80%).[3105]

2,5-Diphenylpyrimidine from its 4,6-dichloro derivative (Pd, MgO, H_2O–EtOH: 90%).[4187]

2-Pyrimidinamine from its 4-chloro (**138**, R = H) (Pd, BaO, H_2O)[4098] or 4,6-dichloro derivative (**138**, R = Cl) (Pd, KOH, MeOH: 88%;[3589] Pd, KOH, H_2O: 85%;[2207] Pd, KOH, H_2O–Et_2O: 88%[2513]).



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4-Pyrimidinamine from its 6-chloro (Pd, KOH, H_2O–Et_2O: 78%)[4976] or 2,6-dichloro derivative (Pd, KOH, MeOH;[3589] Pd, KOH, H_2O–Et_2O: 73%[2513]).

5-Pyrimidinamine from its 2,4-dichloro derivative (Pd, MgO, H_2O: 77%;[711] Pd, KOH, H_2O–Et_2O: 91%[2513]).

2-Dimethylamino-4-methyl- from 4-chloro-2-dimethylamino-6-methylpyrimidine (Pd, MgO, H_2O–EtOH: 82%).[2078]

5-(3′,4′,5′-Trimethoxybenzyl)-4-pyrimidinamine from its 2,6-dichloro derivative (Pd, NaOH, H_2O–EtOH: 98%).[361]

4-Dimethylamino-2-pyrimidinamine from 4-chloro-6-dimethylamino-2-pyrimidinamine (Pd, MgO, H_2O: 80%).[1741]

4-Hydrazino-5-pyrimidinamine from 4-chloro-6-hydrazino-5-pyrimidinamine (Pd, H_2O: 86% as hydrochloride).[1777]

2-*t*-Butyl-4,5-pyrimidinediamine from its 6-chloro derivative (Pd, MgO, H_2O: 62%).[2184]

2,4-Dimethoxy- from 4-chloro-2,6-dimethoxypyrimidine (Pd, NaOH, H_2O–Et_2O: 62%).[2513]

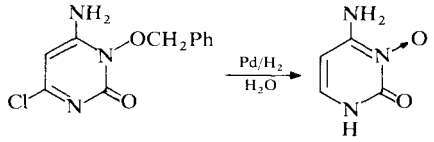
4-Methoxy-2-methyl-5-pyrimidinamine from 4-chloro-6-methoxy-2-methyl-5-pyrimidinamine (Pd, MgO, EtOH: 70%).[651]

2-Ethyl-4(3*H*)-pyrimidinone from its 6-chloro derivative (Pd, NaOH, EtOH: 89%).[2149]

4-Amino-5-pyrimidinecarbaldehyde from its 6-chloro derivative (Pd, MgO, MeOH: 90%).[1008]

4-Amino-2(1*H*)-pyrimidinone 3-oxide (**140**) from 4-amino-3-benzyloxy-6-chloro-2(3*H*)-pyrimidinone (**139**) (Pd, AcOH–H_2O: 61%).[1681]

5-Ethyl-2,4-pyrimidinediamine 3-oxide from its 6-chloro derivative (Pd, KOH, EtOH: 84%).[3684]



139 **140**

Ethyl 5-pyrimidinecarboxylate from its 4-chloro (Pd, MgO, EtOH: 75%)[1969] or 2,4-dichloro derivative (Pd, CaO, Pr^{i}OH: 63%).[2509]

5-Pyrimidinecarbaldehyde from its 4,6-dichloro derivative (Pd, MgO, MeOH: 79%).[3600]

4-Methyl-6-phenyl-5-pyrimidinecarbonitrile from its 2-chloro derivative (Pd, NEt_3, MeOH: 77%).[3942]

2-Amino-4(3*H*)-pyrimidinone from its 6-bromo or 6-iodo derivative (Pd, NH_3, MeOH: 50% in each case).[965]

5-Methoxy-2-methylsulfonylpyrimidine from its 4-chloro derivative (Pd, MeOH: 76%).[2114]

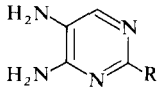
1,4,5,6-Tetrahydropyrimidine from 2,4-dichloropyrimidine (Pd, H_2O);[4980] see also analogs.[3612,4969]

Also many other examples.[559,670,785,987,1011,1012,1032,1089,1162,1232,1362,1374,1387,1400,1428,1479,1520,1648,1670,1731,1742,1743,1799,1833,1896,1934,1997,2002,2082,2083,2131,2138,2164,2167,2212,2219,2249,2280,2328,2473,2509,2600,3154,3342,3609,4114,4186,4188,4427,4878,4978,4979]

By catalytic deuterolysis

2-Deutero-4,5-pyrimidinediamine (**141**, R = D) from the 2-chloro analog (**141**, R = Cl) (Pd, D_2, NaOH, MeOH: 85%).[2269]

6-Deutero-2-methyl-4,5-pyrimidinediamine from its 6-chloro analog (likewise: 89%).[2269]



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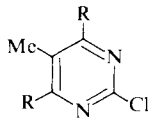
By zinc dust

2-Chloro- from 2,4-dichloropyrimidine (Zn, H_2O–EtOH: > 53%;[1834] Zn, NH_4Cl, H_2O: ~30%[1670,2321]).

2-Chloro-5-methyl- (**142**, R = H) from 2,4,6-trichloro-5-methylpyrimidine (**142**, R = Cl) (Zn, PhH, NaCl, NH_4OH: 85%).[1879]

2-Chloro-5-fluoro- from 2,4-dichloro-5-fluoropyrimidine (Zn, PhH, NH_4Cl, NH_4OH: 40%).[270]



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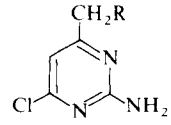

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4-Methyl-2-pyrimidinamine from 4-chloro-6-methyl-2-pyrimidinamine (**143**, R = H) (Zn, Raney-Ni, NH_4Cl, NaCl, H_2O: 80%)[4981] or 4-chloro-6-methoxycarbonylmethyl-2-pyrimidinamine (**143**, R = CO_2Me) (Zn, H_2O: 68%; note hydrolysis and decarboxylation).[670]

4-Pyrimidinamine or 2,4-pyrimidinediamine, each from its 5-iodo derivative (Zn, H_2O: 40–50%).[1349]

2-Methylthio- or 2-ethylthiopyrimidine, each from its 4-chloro derivative (Zn, H_2O–EtOH: 70%[3143] or 75%,[2133] respectively).

2(1*H*)-Pyrimidinone from its 4-chloro derivative (Zn, NH_4OH, EtOH).[1751]

2-Chloro-5-pyrimidinol from its 2,4-dichloro analog (Zn, H_2O: > 30%).[774]

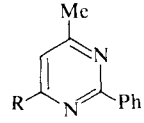
5-Fluoro-2-methylthiopyrimidine from its 4-chloro derivative (Zn, NaOH, H_2O: ~35%).[2160]

2-Methylthio-5-pyrimidinecarbonitrile from its 4-chloro derivative (Zn, AcOH, H_2O–EtOH: 67%).[43]

2-Ethylthio-5-methoxypyrimidine from its 4-chloro derivative (Zn, H_2O–EtOH: 60%).[926]

4-Methyl-2-phenyl- (**144**, R = H) from 4-chloro-6-methyl-2-phenylpyrimidine (**144**, R = Cl) (Zn, AcOH–H_2O, briefly); prolonged treatment gave a mixture of 2- and 4-methyl-5-phenylpyrrole.[4982]

Also other examples.[513,1007,1136,1219,1240,1509,1631,1663,1771,2192,3406,3430]



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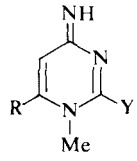
By hydriodic acid

4-Pyrimidinamine from its 2-chloro derivative (HI, red P).[710]

4(3*H*)-Pyrimidinone from 2,4-dichloropyrimidine (HI, red P).[710]

1-Methyl- (**145**, R = Y = H)[1154] or 1,6-dimethyl-4(1*H*)-pyrimidinimine (**145**, R = Me, Y = H),[1136] each from its 2-chloro derivative (**145**, R = H or Me, Y = Cl) (HI, red P: isolated as hydriodides).

4-Oxo-3,4-dihydro5-pyrimidinecarboxylic acid from ethyl 2,4-dichloro-5-pyrimidinecarboxylate (HI, AcOH, red P).[1631]



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Note: The necessity for red phosphorus in the foregoing reactions must be doubted from data in Section 4.2.1.2.

By other reagents

4-Amino-2(1*H*)-pyrimidinethione from 6-chloro-2-methylthio-4-pyrimidinamine (Na, liquid NH_3: 66%).[1653]

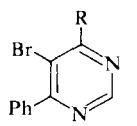
2-Methoxy-4-pyrimidinamine from its 6-chloro derivative (Ph_3P, then alkali: 9% overall; intermediate 2-methoxy-6-trimethylphosphonio-4-pyrimidinamine chloride uncharacterized).[3358]

2,4-Diethoxy-5-methylpyrimidine from 4-bromo-2,6-diethoxy-5-methylpyrimidine (BuLi, then NH_4Cl–H_2O: 53%).[1839]

2,4,5-Trifluoro- (35%), 2,5-difluoro- (17%), and other minor products from 2,4,5,6-tetrafluoropyrimidine ($LiAlH_4$, Et_2O).[2555]

The *indirect removal* of halogeno substituents becomes necessary in the presence of groups to which the foregoing reductive methods are inimical; indirect methods may also offer better selectivity or convenience. Sequences for the more usual indirect routes via hydrazino, thioxo, alkylthio, or sulfo intermediates can be devised logically from data for the preparation of such derivatives and for the subsequent removal of the relevant functional group. However, several integrated examples follow in order to illustrate such processes.

1. Condensation of 5-bromo-4-chloro-6-phenylpyrimidine (**146**, R = Cl) with *p*-toluenesulfonohydrazide in refluxing toluene for 12 h gave 5-bromo-4-phenyl-6-*N'*-tosylhydrazinopyrimidine (**146**, R = NHNHTs), which, in hot aqueous potassium carbonate for 30 min, afforded 5-bromo-4-phenylpyrimidine (**146**, R = H) (70% overall);[3743] likewise, 2,4-dichloropyrimidine gave 2,4-bis(*N'*-benzenesulfonylhydrazino)pyrimidine and thence pyrimidine (66% overall).[2566]



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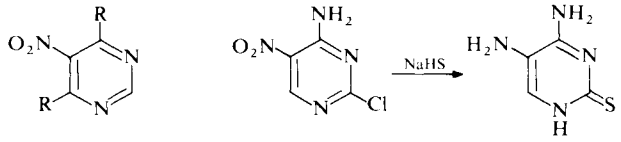
2. Treatment of 4,6-dichloro-5-nitropyrimidine (**147**, R = Cl) with hydrazine gave 4,6-dihydrazino-5-nitropyrimidine (**147**, R = $NHNH_2$),[2564] which underwent oxidation by silver oxide in methanol or by silver acetate in water to afford 5-nitropyrimidine (**147**, R = H) in 31%[2560] or 65–70% yield,[3546] respectively; analogous processes were used to prepare 2-methyl-5-nitro-,[2560] 2-benzyl-5-nitro-,[2560] 4-methoxy-5-nitro-,[684] 5-bromo-4-*t*-butyl-,[1822] 5-bromo-4-methyl-,[1822] 5-bromo-4-phenyl-,[1822] and 2,4-dimethylpyrimidine (cupric sulfate oxidation),[2149] as well as other products.[684,946,3211,3230] A general exploration in related series has been reported.[4983]



147 **148** **149**

3. 2-Chloro-5-nitro-4-pyrimidinamine (**148**) underwent thiolysis and reduction by aqueous sodium hydrogen sulfide to give 4,5-diamino-2(1*H*)-pyrimidinethione (**149**)[2295,2442] and subsequent desulfurization with Raney-nickel gave 4,5-pyrimidinediamine,[2295] the best route to this important intermediate; an analogous sequence gave 2-butyl-4,5-pyrimidinediamine.[1981]

6.7.2. Simple Aminolysis of 2- or 4/6-Halogenopyrimidines

The aminolysis of active halogenopyrimidines is probably the most used and most important reaction in pyrimidine chemistry. For that reason, the process is treated in some detail, especially in regard to the selective aminolysis of di- or trihalogenopyrimidines. The chief factors governing such selectivity are (1) the type(s) of halogeno substituent, (2) the position of each halogeno substituent, (3) the nature and position(s) of any other substituent(s) present, (4) the type of attacking amine, (5) steric factors associated with both reactants, and (6) the medium and conditions in use. Most of the know-how associated with aminolysis has been derived from a mass of preparative data in the literature,[4987] but it is interesting that such information is completely in line with conclusions from the few available *kinetic data on aminolyses* for halogenopyrimidines.[4721] Thus, without detailing the kinetic data, it is possible to conclude, for example, that (with all other factors equal) chloro, bromo, and iodo substituents undergo aminolysis at approximately the same rate,[1826] whereas a fluoro substituent reacts 60–200 times faster;[3154] 4(6)-halogeno substituents react up to 10 times faster than 2-halogeno substituents;[2260] the presence of each electron-donating group (e.g., Me, Ph, OMe, NMe_2) on the substrate decreases the rate of aminolysis, whereas each electron-withdrawing group (e.g., Cl, CF_3, NO_2) increases the rate profoundly;[2260,2954,4721,4990] the rate for aminolysis by an *n*-alkylamine is unaffected by increasing the chain length[1825,2101] or by

γ-branching, but a β-branch has a significant slowing effect, while one or two α-branches decrease the rate to ~ 5% or 0.1%, respectively, as compared with the *n*-alkylamine;[2101,3298,4721] the use of a secondary amine (i.e., a di-*n*-alkylamine) decreases the rate approximately to that observed for an α-branched alkylamine;[2101,3298] the insertion of a *C*-*t*-butyl group into the substrate reduces its rate of aminolysis, probably on account of steric hindrance to solvation of the ring-nitrogen atom(s);[2262] the nature of the solvent has a marked effect on the rate of aminolysis;[2262,2954] but the addition of copper or copper salts appears to have little, if any, effect on rate.[1825] Other important contributions to the kinetics of such aminolyses have been recorded.[3327,3685,4888,4889,4984–4986,4991]

It is quite evident that conditions for most of the reported preparative aminolyses were never optimized: this has often resulted in poor yields, either from incomplete reaction or from the formation of byproducts in a too vigorous reaction. However, a simple experimental *method for predicting optimal conditions* of temperature and time for such aminolyses has been available for some years.[1825] For a meaningful prediction it was clearly necessary to know in advance the order of the reaction, its rate constant, and its temperature coefficient. A pseudo-first-order reaction was assured by using a reasonable excess of amine; the rate constant could be read from an existing nomograph[4992] after determining the percentage completed at a given temperature and time by titration of halide ion; and for practical purposes the temperature coefficient proved to be constant within a defined framework.[1825] Hence prediction of optimal conditions in any particular case requires only a single small-scale experiment culminating in a simple titration of halide ion: the efficacy of this procedure has been tested in a variety of cases.[1405,1825,3298]

For pragmatic reasons, the following treatment is confined to aminolyses by ammonia, *N*-alkylated amines, or *N*-arylated amines; aminolyses by hydrazine, hydroxylamine, and other *N*-(functionally substituted) amines are collected in Section 6.7.3.

6.7.2.1. Aminolysis of Simple Halogenopyrimidines and Alkyl Derivatives

The following transformations illustrate the solvents and conditions used for such aminolyses with ammonia or appropriate amines.

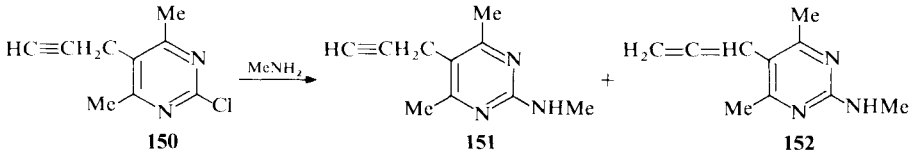
Monohalogenopyrimidines

2-Chloropyrimidine to 2-pyrimidinamine (EtOH, 130°, 6 h, sealed: 68%),[3376] 2-methylaminopyrimidine (EtOH, 80°, 5 h: 49%;[2083] EtOH, 120°, 1 h, sealed: 49%[708]), 2-dimethylaminopyrimidine (MeOH, 120°, 1 h, sealed: 46%),[708] 2-anilinopyrimidine (neat, K_2CO_3, 180°, 5 min: ~ 70%),[3337, cf. 2321] 2-butylaminopyrimidine (neat, 40°, 1 h: 82%, optimized),[1825] 2-*t*-butylaminopyrimidine (neat, 150°, 1 h: 70%, optimized),[3298]

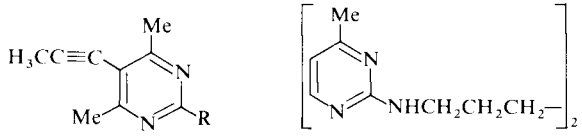
2-isopentylaminopyrimidine (neat, 40°, 90 min: > 50%),[1826] 2-diethylaminopyrimidine (neat, 130°, 24 h, sealed: 71%;[4993] EtOH, reflux, 1 h: 85%[1815]), and 2-trimethylammoniopyrimidine chloride (PhH, 20°: 90%).[3554,4866]

2-Chloro-4,6-dimethylpyrimidine to 4,6-dimethyl-2-pyrimidinamine (EtOH, 100°),[1874] 4,6-dimethyl-2-methylamino- (H_2O, 100°, 16 h, sealed: 90%),[2685] 2-hexylamino-4,6-dimethyl- (neat, 98°, 3 h: 75%),[1825] 2-*s*-butylamino-4,6-dimethyl- (neat, 100°, 3.5 h: 79%),[3298] 2-dipropylamino-4,6-dimethyl- (neat, 130°, 1 h: 83%),[3298] 4,6-dimethyl-2-morpholino- (H_2O, reflux, 90 min: ~ 95%),[1014] and 2-γ-hydroxypropylamino-4,6-dimethylpyrimidine (EtOH, reflux, 18 h: 85%).[3961]

2-Chloro-4,6-dimethyl-5-prop-2′-ynylpyrimidine (**150**) to a separable mixture of 4,6-dimethyl-2-methylamino-5-prop-2′-ynylpyrimidine (**151**) and 5-allenyl-4,6-dimethyl-2-methylaminopyrimidine (**152**) (EtOH, 100°, 1 h, sealed: ratio ~ 1 : 1; H_2O, pH 8.5, 1 h, sealed: ratio ~ 9 : 1);[843] in contrast, 2-chloro-4,6-dimethyl-5-prop-1′-ynylpyrimidine (**153**, R = Cl) gave only 4,6-dimethyl-2-methylamino-5-prop-1′-ynylpyrimidine (**153**, R = NHMe) (EtOH, 100°, 1 h, sealed: 69%).[843]



150 **151** **152**



153 **154**

4-Chloropyrimidine to 4-butylaminopyrimidine (EtOH, reflux, 3 h: ~90%),[3144] 4-phenethylaminopyrimidine (neat, 130°, 7 h: 35%),[1670] 4-diethylaminopyrimidine (neat, 130°, 60 h, sealed: 62%),[1970] and 4-trimethylammoniopyrimidine chloride (PhH, 5°, 12 h: ~50%).[3554]

4-Chloro-2-methylpyrimidine to 2-methyl-4-pyrimidinamine (EtOH, 100°, 3 h, sealed: ~40%),[2259] 4-dimethylamino-2-methylpyrimidine (EtOH, 100°, 3 h, sealed),[1462] 2-methyl-4-methylaminopyrimidine (PhH, reflux: 75%),[690] 2-methyl-4-trimethylammoniopyrimidine chloride (PhH, 20°, 2 days: 91%),[3154] and 1,6-bis(4′-methylpyrimidin-2′-ylamino)hexane (**154**) (hexamethylenediamine, EtOH, reflux, 2.5 h: 17%).[93]

4-Chloro-6-methyl-2-propylpyrimidine to 4-cyanoamino-6-methyl-2-propylpyrimidine (NaHNCN, Me_2NCHO, 100–110°, 42 h: ~15%).[683]

4-Iodo-6-methylpyrimidine to 6-methyl-4-pyrimidinamine (EtOH, 150°, 3 h, sealed).[1932]

4-Bromo-6-phenylpyrimidine to 4-isopropylamino-6-phenylpyrimidine (EtOH, 100°, 4 h, sealed: 95%).[4994]

Also many other examples.[1014,1135,1240,1405,1437,1465,1485,1509,1735,1741,1822,1856,1907,2084,2101,2105,2114,2127,2149,2150,2359,2764,3154,3327,3524,3876,4030,4037,4039,4093,4123,4129,4358,4360,4409,4869,4870,4889–4891,4903,4904,4944,4995–4998,5854,6850]

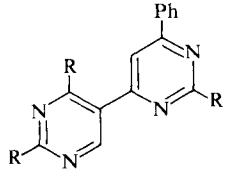
2,4-Dihalogenopyrimidines

2,4-Dichloropyrimidine to a mixture of 4-chloro-2-pyrimidinamine and 2-chloro-4-pyrimidinamine (EtOH, 25°, 18 h: 95%; separation by steam distillation gave pure products in 11% and 28% yields, respectively),[1675, cf. 2311] 2-chloro-4-pyrimidinamine only (BuOH–H_2O, 100°, 20 min, sealed: 63%),[1232] 2,4-pyrimidinediamine (PhOH, trace $CuSO_4$, 190°, 4 h: 80%),[1650] 2,4-bisdimethylaminopyrimidine (H_2O, 25°, 15 h: ~ 65%),[1743] 4-benzylamino-2-chloropyrimidine (BuOH–H_2O, 100°, 15 min: 75%),[1232] 4-*o*-carboxyanilino-2-chloropyrimidine (H_2O, trace HCl, 50°, 15 min: 78%) and thence 4-*o*-carboxyanilino-2-pyrimidinamine (EtOH, 120°, 3 h, sealed: 65%),[4999] and 2-chloro-4-piperidinopyrimidine ($CHCl_3$, reflux, 1 h: 61%) and thence 4-piperidino-2-pyrimidinamine (EtOH, ?°, 24 h, sealed: 88%).[1896, cf. 7034]

2,4-Dichloro-6-methylpyrimidine to a separable mixture of 2-chloro-6-methyl-4-pyrimidinamine and 4-chloro-6-methyl-2-pyrimidinamine (EtOH, 92°, 5 h, sealed: 47% and 40% yields, respectively),[2249, cf. 1509] 6-methyl-2,4-pyrimidinediamine (MeOH, 105°, 6 h, sealed: > 70%),[2249] 2,4-bisdiethylamino-6-methylpyrimidine (EtOH, 115°, 15 h, sealed: 65%),[520] 4-methyl-2,6-dipiperidinopyrimidine (EtOH, reflux, 3 h: 98%),[2127] a separable mixture of 4-benzylamino-2-chloro- and 2-benzylamino-4-chloro-6-methylpyrimidine (neat, 180°, 6 h: 49% and 23% yields, respectively),[3474] and 2,4-bis(3′,4′-dimethylanilino)-6-methylpyrimidine (HCl–H_2O, reflux, 5 h: 85%).[533]

2,2′,4′-Trichloro- (**155**, R = Cl) to 2,2′,4′-trisdimethylamino-6-phenyl-4,5′-bipyrimidine (**155**, R = NMe_2) (EtOH, reflux, 6 h: 60%).[5005]

Also the following second-stage aminolyses for which the substrates were not made by aminolytic means.



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4-Chloro-6-isopropyl-2-pyrimidinamine to 6-isopropyl-2,4-pyrimidinediamine (MeOH, 160°, 6 h, sealed).[1356]

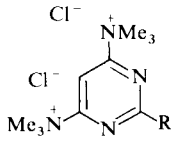
4-Chloro-2-methylaminopyrimidine to 2-methylamino-4-pyrimidinamine (PhOH, $CuSO_4$, ?°, 4 h: 69%).[2084]

2-Chloro-4-dimethylamino- to 4-dimethylamino-2-methylaminopyrimidine (EtOH, 100°, 2 h: 25%).[1741]

Also many other examples of all types.[397,557,615,618,682,1118,1135,1219,1239,1259,1356,1484,1520,1735,2076,2144,2248,2497,2896,3527,4116,4150,4152,4872,4879,4945,5000–5004,5006–5008,5011,6943,7034]

4,6-Dihalogenopyrimidines

4,6-Dichloropyrimidine to 4-chloro-6-methylaminopyrimidine (MeOH, 100°, 1 h, sealed: 80%) or 4,6-bismethylaminopyrimidine (H_2O, 170°, 4 h, sealed: ~ 60%),[1383] 4-chloro-6-piperidinopyrimidine (H_2O, 100°, 3 h: 93%;[866] AcMe, 25°, 30 min: 98%[5009]), 4-chloro-6-cyclohexylaminopyrimidine (EtOH, 100°, 1 h, sealed: 75%)[4382] 4-anilino-6-chloro- (H_2O–AcMe, HCl, reflux, 90 min: ~ 70%) and thence 4-anilino-6-methylaminopyrimidine (MeOH, 160°, 5 h, sealed),[2237] and 4,6-bistrimethylammoniopyrimidine dichloride (**156**, R = H) (PhH, 25°, 18 h: ~ 90% crude).[1791]



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4,6-Difluoropyrimidine to 6-fluoro-4-pyrimidinamine (EtOH, 5°: 50%) and 4-dimethylamino-6-fluoropyrimidine (EtOH, 25°: 97%).[1730]

4,6-Dichloro-2-methylpyrimidine to 6-chloro-2-methyl-4-pyrimidinamine (MeOH, 130°, 3 h, sealed: ~ 60%) or 2-methyl-4,6-pyrimidinediamine (MeOH, 200°, 4 h, sealed: 75%),[1558] 4,6-bisdimethylamino-2-methylpyrimidine (MeOH, reflux, 5 h),[1735] 4-chloro-2-methyl-6-piperidinopyrimidine (EtOH, 25°, 5 h: 84%),[57] 4,6-bisbenzylamino-2-methylpyrimidine (neat, 200°, 3 h, sealed: ~ 40%),[3533] and 2-methyl-4,6-bistrimethylammoniopyrimidine dichloride (**156**, R = Me) (PhH, 25°).[2522]

4,6-Dibromo-2-ethylpyrimidine to 6-bromo-2-ethyl-4-pyrimidinamine (H_2O, 70°, 12 h, sealed: 95%) or 2-ethyl-4,6-pyrimidinediamine (H_2O, 150°, 24 h, sealed: 81%).[1243]

Also the following second-stage aminolyses.

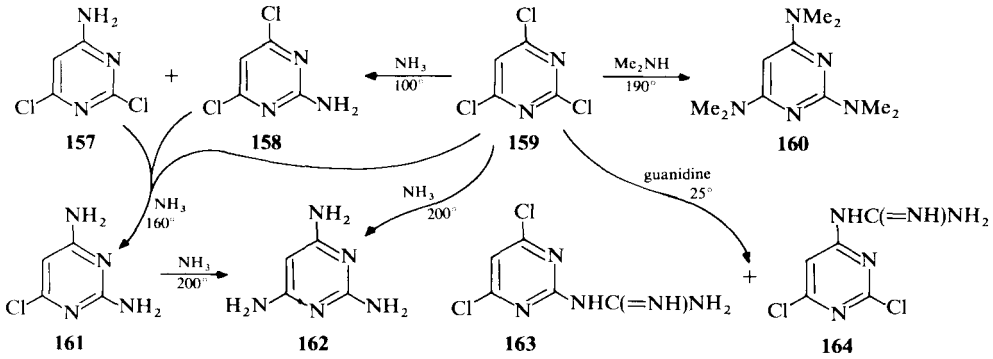
4-Chloro-6-methylamino- to 4-dimethylamino-6-methylaminopyrimidine (H_2O, 125°, 3 h, sealed: ~ 70%).[2625]

6-Chloro-2-methyl-4-pyrimidinamine to 2-methyl-6-pyrrolidino- (neat, 140°, 2 h: 89%)[1556,5010] and 6-dimethylamino-2-methyl-4-pyrimidinamine (no amine, Me_2NCHO, 185°, 5 h: 66%).[1740]

Also other examples.[1349,1580,2253,2507,3346,4362,5003]

2,4,6-Trihalogenopyrimidines

2,4,6-Trichloropyrimidine (**159**) to a separable mixture of 4,6-dichloro-2-pyrimidinamine (**158**) and 2,6-dichloro-4-pyrimidinamine (**157**) (EtOH, 20–100°, 3 h, sealed), thence to 6-chloro-2,4-pyrimidinediamine (**161**) (EtOH, 160°, 3 h, sealed), and thence to 2,4,6-pyrimidinetriamine (**162**) (EtOH, 200°, 90 min, sealed);[1349,2332, cf. 232] 4,6-dichloro-2-ethylamino- and 2,6-dichloro-4-ethylaminopyrimidine, thence to 4-chloro-2,6-bisethylaminopyrimidine, and thence to 2,4,6-trisethylaminopyrimidine (likewise but at 20°, 70°, and 170°, respectively);[1771] 4,6-dichloro-2-guanidino- (**163**) and 2,4-dichloro-6-guanidinopyrimidine (**164**) (H_2O–AcMe, 25°, 1 h: 35% and < 5%, respectively);[2174] 4-chloro-2,6-dipiperidinopyrimidine (EtOH, 50°, 2 h: 65%);[5012] and 2,4,6-trisdimethylaminopyrimidine (**160**) (Et_2O, 190°, 2 h, sealed: 95%).[1731]



2,4,6-Trifluoropyrimidine to a separable mixture of 4,6-difluoro-2-pyrimidinamine (mainly) and 2,6-difluoro-4-pyrimidinamine (EtOH, ? 20°, 1 h), thence to 6-fluoro-2,4-pyrimidinediamine (EtOH, 105°, 8 h, sealed: 98%), and thence to 2,4,6-pyrimidinetriamine (EtOH, 160°, 12 h, sealed: 57%).[1040]

2,4,6-Trichloro-5-ethylpyrimidine to 2,6-dichloro-5-ethyl-4-pyrimidinamine (EtOH, 25°), thence to 6-chloro-5-ethyl-2,4-pyrimidinediamine (EtOH, 160°, 3 h, sealed), and thence to 5-ethyl-2,4,6-pyrimidinetriamine (EtOH, 210°, 8 h, sealed).[1228]

Also the following second- and/or third-stage aminolyses.

4,6-Dichloro-2-dimethylaminopyrimidine to 6-chloro-2-dimethylamino-4-pyrimidinamine, 4-chloro-2-dimethylamino-6-methylaminopyrimidine, and 4-chloro-2,6-bisdimethylaminopyrimidine (EtOH, 110°, 18 h in each case).[2044]

4,6-Dichloro-2-pyrimidinamine to 4-chloro-6-methylamino-2-pyrimidinamine (MeOH–H_2O, 25°, 12 h: 70°;[2217] PrOH, 95°, 2 h: ~80% [2182]) and 4-butylamino-6-chloro-2-pyrimidinamine (EtOH, reflux, 6 h: 92%).[2137]

4-Chloro- to 4-dimethylamino-6-methylamino-2-pyrimidinamine (MeOH, 170°, 3 h, sealed: 23%).[2626]

6-Chloro- to 6-dimethylamino- (no amine, Me_2NCHO, reflux, 5 h: 54%)[1740] and 6-morpholino-2,4-pyrimidinediamine (neat, reflux, 3 h: 62%).[3869]

4,6-Dichloro- to 4,6-dipiperidino- (neat, reflux, 4 h: 88%)[2176] and 4,6-di-*o*-toluidino-2-pyrimidinamine (AcOH, HCl, reflux, 5 h: 56%).[5014]

Also other examples.[302,559,1356,1816 (cf. 4138),2081,2137,2474,3985,4907,5013, 5021,6213]

6.7.2.2. Aminolysis of Halogeno-5-nitropyrimidines and Related Substrates

Halogeno-5-nitropyrimidines undergo aminolysis much more readily than the corresponding unnitrated halogenopyrimidines; moreover, the preference for 4/6- rather than 2-aminolysis is more marked. Halogenonitroso- and arylazohalogenopyrimidines belong in this subsection, as do substrates bearing any functional group(s) additional to the nitro, nitroso, or arylazo group. The scope of such aminolyses and the required conditions are illustrated in the following examples, using an appropriate amine in each case.

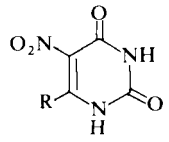
Monohalogeno substrates

2-Chloro-5-nitropyrimidine to 2-dimethylamino- (EtOH, reflux: 70%),[2643] 2-butylamino- (EtOH, 60°, 2 min: ~ 60%),[1951] and 2-*t*-butylamino-5-nitropyrimidine (EtOH, 60°, 2 min: 70%);[1951] also 5-nitro-2-trimethylammoniopyrimidine chloride (PhH, 20°, briefly: > 90%).[3554]

2-Chloro- to 2-dimethylamino-5-nitro-4,6-diphenylpyrimidine (EtOH, 25°, 15 h: 90%).[4758]

6-Chloro-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**165**, R = Cl) to 6-isopropylamino- (**165**, R = $NHPr^i$) (MeOH, reflux, 1 h: 76%),[1353] 6-β-hydroxyethylamino- (**165**, R = $NHCH_2CH_2OH$) (H_2O, reflux, 5 min: 80%),[1317] 6-*N*-ethylanilino- (**165**, R = NEtPh) (neat, 90°, 3 h: 85%),[4741] and 6-(carboxymethyl)amino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**165**, R = $NHCH_2CO_2H$) (H_2O, 90°, 2 h: 79%).[1233]

Also other examples.[466,2309,2407,3855,6231]



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2,4-Dihalogeno substrates

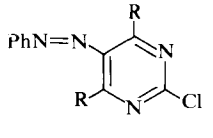
2,4-Dichloro-5-nitropyrimidine to 2-chloro-5-nitro-4-pyrimidinamine (EtOH or H_2O, 0°, 30 min: 72–92%)[2295] and thence (or directly) to 5-nitro-2,4-pyrimidinediamine (PhOH, 140°, 4 h: 85–91%;[2327] EtOH, reflux, 30 min: > 95%[1586,2296,2487]); 2-chloro-4-dimethylamino-5-nitropyrimidine (dioxane–H_2O–AcOH at pH 8, 15°, 2 h: ~ 65%) and thence to 4-dimethylamino-5-nitro-2-pyrimidinamine (EtOH, 140°, 6 h, sealed: ~ 30%);[1437] a separable mixture of 2-chloro-4-methylamino-5-nitropyrimidine (mainly), 4-chloro-2-methylamino-5-nitropyrimidine, and 2,4-bismethylamino-5-nitropyrimidine (dioxane–H_2O–AcOH at pH 8, 15°, 2 h)[2216, cf. 1379,1586] or only the last product (EtOH, 10°, 30 min: 84%;[1648] EtOH–H_2O, 20°, 30 min: 92%[1747]); and 4-anilino-2-chloro-5-nitropyrimidine (CH_2Cl_2, −5°: ~ 30%)[5015] or 2,4-dianilino-5-nitropyrimidine (CH_2Cl_2, 25°: 94%;[5015] PhH, 25°, 30 min: ~ 90%;[1374] EtOH, reflux, 1 h: 94%[1790]).

2,4-Dichloro-6-ethyl-5-nitropyrimidine to 2-chloro-4-ethyl-6-methylamino- (dioxane–H_2O–AcOH at pH 8, 0°: 75%) or 4-ethyl-2,6-bismethylamino-5-nitropyrimidine (EtOH, 25°, briefly ~ 60%).[1191]

2,4-Dichloro-6-phenyl-5-phenylazopyrimidine (**166**, R = Cl) to 2-chloro-6-phenyl-5-phenylazo-4-pyrimidinamine (**166**, R = NH_2) (Et_2O, < 5°, 1 h: 72%).[4855]

2,4-Dichloro-5-nitro-6-trifluoromethylpyrimidine to 2-chloro-5-nitro-6-trifluoromethyl-4-pyrimidinamine (EtOH–$CHCl_3$, 20°, 1 h: > 80%).[5019]

Methyl 2,6-dichloro-5-nitro-4-pyrimidinecarboxylate to methyl 2,6-diamino-5-nitro-4-pyrimidinecarboxylate (**167**, R = OMe) (H_2O, 25°, 1 h: 84%) or 2,6-diamino-5-nitro-4-pyrimidinecarboxamide (**167**, R = NH_2) (MeOH, 100°, 2 h, sealed: 22%).[1123]



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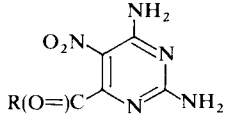

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Also many second-stage aminolyses, exemplified in the following conversions.

4-Chloro-2-dimethylamino- to 2-dimethylamino-4-ethylamino-5-nitropyrimidine (H_2O, reflux, 5 min: ~ 95%).[1746]

2-Amino-6-chloro- to 2-amino-6-(β-hydroxy-β-methylpropyl)amino- (**168**) (EtOH, reflux, 30 min: 90%)[27] and 2-amino-6-benzylamino-5-nitro-4(3*H*)-pyrimidinone (EtOH, reflux, 15 min: ~ 65%).[999]

2-Amino-6-chloro- to 2-amino-6-*t*-butylamino-3-methyl-5-nitro-4(3*H*)-pyrimidinone (neat, reflux, 10 min: ~ 85%).[1371]

4-Chloro-2-dimethylamino-6-methoxy- to 2-dimethylamino-4-methoxy-6-methylamino-5-nitropyrimidine (H_2O, 25°, 2 days: 94%).[2623]

4-β-Acetylhydrazino-2-chloro-5-nitro-6-trifluoromethylpyrimidine to 4-β-acetylhydrazino-5-nitro-6-trifluoromethyl-2-pyrimidinamine (EtOH, reflux, 3 h: ~ 65%).[5026]

Also other examples.[223,224,299,391,434,608,618,645,1023,1157,1196,1364,1371,1372,1401,1405,1427,1437,1581,1586,1714,1738,1746,1790,1836,1932,2080,2125,2148,2228,2243,2246,2297,2327,2334,2413,2418,2435,2624,2959,2994,3781,3785,4183,4671,4746,4750,4754,4762,4882,5000,5016–5018,5020,5022–5025,5027,5028,6242,6733]

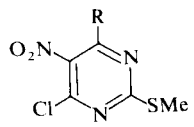
4,6-Dihalogeno substrates

4,6-Dichloro-5-nitropyrimidine to 6-chloro-5-nitro-4-pyrimidinamine (Et_2O–MeOH, 20°, 2 h: 54%;[2246] $AcONH_4$, dioxane–H_2O, 10°, 2 h: ~ 65%;[2300] THF–MeOH, $NaHCO_3$, 50°, 90 min: 82%[2301]), 5-nitro-4,6-pyrimidinediamine (EtOH, 60°, 5 min: 97%),[1434,3547] 4-chloro-6-methylamino-5-nitropyrimidine (dioxane–H_2O–AcOH at pH 8, 15°, 20 min),[1379] 4,6-bismethylamino-5-nitropyrimidine (MeOH, 10°, 10 min: 87%),[1648] 4-chloro-6-morpholino-5-nitropyrimidine (MeOH, 4°, 2 h: ~ 85%) and thence 4-furfurylamino-6-morpholino-5-nitropyrimidine (dioxane–NEt_3, 20°, 1 h: ~ 90%),[2500] 4-allylamino-6-chloro-5-nitropyrimidine (dioxane–H_2O–AcOH at pH 8, 15°, 2 h: 66%),[228] and 5-nitro-4,6-di-*p*-toluidinopyrimidine (Et_2O, 25°, 15 h: 60%).[5029]

4,6-Difluoro-5-nitropyrimidine to 6-fluoro-5-nitro-4-pyrimidinamine (Et_2O, – 60°: 24%).[2556]

4,6-Dichloro-5-nitro-2-phenylpyrimidine to 6-chloro-5-nitro-2-phenyl-4-pyrimidinamine (THF, 25°, ~ 90% crude;[4755] Et_2O–MeOH, 0°: 18%[4760]).

4,6-Dichloro-2-methylthio-5-nitropyrimidine (**169**, R = Cl) to 6-chloro-2-methylthio-5-nitro-4-pyrimidinamine (**169**, R = NH_2) (Et_2O–MeOH, 25°, 3 h: ~ 55%)[2286] and 4,6-bismethylamino-2-methylthio-5-nitropyrimidine (EtOH, 20°, 1 h: ~ 85%).[1764]



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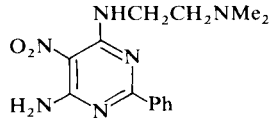
Also the following second-stage aminolyses.

4-Chloro-6-dimethylamino- to 4,6-bisdimethylamino-5-nitropyrimidine (MeOH–H_2O, 25°, 5 h: 95%).[243]

6-Chloro- to 6-guanidino-5-nitro-4-pyrimidinamine (EtOH, reflux, 1 h: 78%).[1579]



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6-Chloro- to 6-(β-dimethylaminoethyl)amino-5-nitro-2-phenyl-4-pyrimidinamine (**170**) (neat, reflux, 20 min: 86%).[236]

6-Chloro-2-methyl- to 2-methyl-6-methylamino-5-nitro-4-pyrimidinamine (MeOH, reflux, ? h: 90%).[3396]

6-Chloro-5-nitro-4-pyrimidinamine to 6-ethylamino-5-nitro- (H_2O, reflux, ? h: 89%)[2975] and 5-nitro-6-piperidino-4-pyrimidinamine (EtOH, reflux, 1 h: 92%).[4749]

Also other examples.[1118,1380,1382,1589,1612,1714,1747,1764,1981,1996,2125, 2135,2246,2287,2301,2303,2334,2500,2641,3334,3375,4090,4144,4183,4740,4742,4747, 4770,5016,5030–5035]

Trihalogeno substrates

2,4,6-Trichloro-5-nitropyrimidine to 2,6-dichloro-5-nitro-4-pyrimidinamine (Et_2O, 0°, 1 h: ~ 35%) or 2-chloro-5-nitro-4,6-pyrimidinediamine (EtOH, 25°, 1 h: ~ 80%),[2307, cf. 1581] 4,6-bis-*p*-bromoanilino-5-nitro-2-pyrimidinamine (probably) (Et_2O, *p*-bromoaniline, − 20°; then EtOH, NH_3, 140°, 12 h, sealed: 32% overall),[2294] and 2,4,6-triaziridino-5-nitropyrimidine (Et_2O–NEt_3, 25°, longstanding).[5038, cf. 2483,5036,5037]

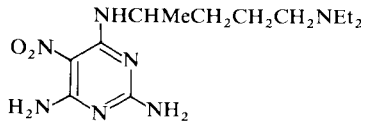
Also the following examples of second- and/or third-stage aminolyses.

2,6-Dichloro-5-nitro-4-pyrimidinamine to 6-benzylamino-2-chloro-5-nitro-4-pyrimidinamine (neat, 25°) or 2,6-bisbenzylamino-5-nitro-4-pyrimidinamine (neat, 25°, longer time?).[2499]

6-Chloro-5-nitro- to 5-nitro-6-piperidino- (neat, reflux, 30 min: 71%),[2176] 6-(δ-diethylamino-α-methylbutyl)amino-5-nitro-2,4-pyrimidinediamine (**171**) (MeOH, reflux, 2 h: 68%),[4742] and 6-*p*-bromoanilino-5-nitro-2,4-pyrimidinediamine (EtOH, reflux, 2 h: 59%).[2294, cf. 2218]

4-Chloro-5-*p*-chlorophenylazo-2,6-bisdimethylaminopyrimidine to 5-*p*-chlorophenylazo-2,4-bisdimethylamino-6-(ethoxycarbonylmethyl)aminopyrimidine (**172**) (Me_2NCHO, 70°, 90 min: 44%).[5039]

Also other examples.[225,2472,4826,4837,5049]



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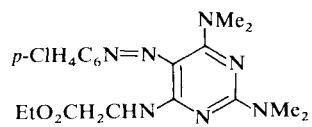

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6.7.2.3. Aminolysis of Halogeno-5-pyrimidinamines

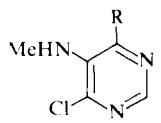
It will be realized that the aminolysis of halogeno substituents in the presence of 2- or 4/6-amino groups is covered throughout Section 6.7.2 in the second- and/or third-stage aminolyses of di- or trihalogeno substrates. The presence of a 5-amino group at the outset has much the same deactivating effect as such a group at other positions: this has been used to advantage in achieving mono-aminolysis of a 4,6-dihalogenopyrimidine, although the preference for 4-aminolysis in a 2,4-dihalogenopyrimidine is not as marked as in the presence of a nitro group. The following examples indicate the relative severity of the conditions required for aminolysis of halogenopyrimidines already bearing a 5-amino group.

2-Chloro-4-methyl-5-pyrimidinamine to 4-methyl-2,5-pyrimidinediamine (EtOH, 210°, 4 h, sealed: ~ 30%).[1932]

4,6-Dichloro-5-pyrimidinamine to 6-chloro-4,5-pyrimidinediamine (EtOH, 150°, 3 h, sealed: ~ 80%),[2337] 4-chloro-6-methylamino- (EtOH, 125°, 6 h, sealed: ~ 65%),[1648] 4-chloro-6-(β-hydroxyethyl)amino- (dioxane, reflux, 16 h: 67%),[5033] 4-chloro-6-(β-diethylaminoethyl)amino- (H_2O, reflux, 5 h: 90%),[5030] 4-benzylamino-6-chloro- (neat, 100°, 30 min: 83%;[1400] likewise, 2 h: 93%;[5042] H_2O, reflux, 30 min: 80%[4546]), 4-*t*-butylamino-6-chloro- (EtOH, 160°, 24 h, sealed: 70%),[2184] 4-chloro-6-*m*-fluorobenzylamino- (BuOH–NEt_3, reflux, 21 h: 75%),[561] and 4-anilino-6-chloro-5-pyrimidinamine (H_2O–EtOH–HCl, reflux, 8 h: 67%).[2300]

4,6-Dichloro- to 4-chloro-6-methylamino-2-trifluoromethyl-5-pyrimidinamine (MeOH, reflux, 2 h: 92%) and other 6-alkylamino analogs.[5046]

4,6-Dichloro-5-methylaminopyrimidine (**173**, R = Cl) to 6-chloro-5-methylamino-4-pyrimidinamine (**173**, R = NH_2) (EtOH, 175°, 4 h, sealed: 85%).[2219]



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2,4-Dichloro-5-pyrimidinamine to a separable mixture of 4-chloro-2,5- and 2-chloro-4,5-pyrimidinediamine (H_2O, 125°, 1 h, sealed: the second product in > 90% yield).[1035,2330]

5-Anilino-2,4-dichloropyrimidine to 5-anilino-2,4-pyrimidinediamine (EtOH, 140°, 16 h, sealed).[4874]

4-Benzylamino-6-chloro- to 4-benzylamino-6-piperidino-5-pyrimidinamine (EtOH, 180°, 7 h, sealed: 64%).[4546]

Also other examples.[190,851,2183,2184,5029,5034,5040,5041,5043–5045]

6.7.2.4. Aminolysis of Halogenopyrimidinones

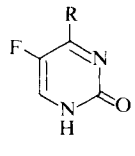
Although less deactivating than amino groups, oxo substituents do appreciably deactivate 2- or 4/6-halogeno substituents in the same molecule, especially in the case of tautomerizable pyrimidinones that will exist largely as anions during aminolysis. The aminolysis of halogeno-5-nitropyrimidinones has already been covered in Section 6.7.2.2, but halogenopyrimidines with any other additional functional group, such as formyl, are included in this section. The following examples illustrate the utility and required conditions for aminolysis of halogenopyrimidinones (and a few related substrates) using the appropriate amine in each case.

Tautomerizable substrates

6-Bromo- to 6-amino-2-ethyl-4(3*H*)-pyrimidinone (H_2O, 100°, 24 h, sealed: 86%).[1243]

6-Chloro- to 6-amino-2,5-dimethyl-4(3*H*)-pyrimidinone (H_2O, 175°, 9 h, sealed: 90%).[1159]

4-Chloro- (**174**, R = Cl) to 4-amino-5-fluoro-2(1*H*)-pyrimidinone (**174**, R = NH_2) (MeOH, reflux, 3 h: 80%).[1267]



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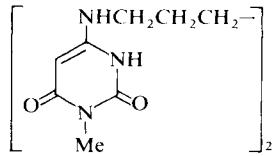

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6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione to 6-amino- (EtOH, 145°, 7 h, sealed),[3174] 6-methylamino- (H_2O, reflux, 3.5 h: 59%;[3174, cf. 2343] neat, 110°, 1 h, sealed: ~ 90%[1376]), 6-*p*-toluidino- (glycerol, 175°, briefly: 59%),[4200] and 6-di(β-hydroxyethyl)amino-2,4(1*H*,3*H*)-pyrimidinedione (neat, 170°, 10 min: 34%).[4947]

6-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione to 6-amino- (EtOH, 145°, 7 h, sealed)[3174] and 6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione (H_2O, reflux, 20 min: 65%);[3174] cf. preceding entry.

6-Chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione to 6-benzylamino- (neat, reflux, 1 h: ~ 70%)[1504] and 6-cyclohexylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (BuOH, reflux, 2 h: 76%);[2394] also 1,6-bis(1′-methyl-2′,6′-dioxo-1′,2′,3′,6′-tetrahydropyrimidin-4′-ylamino)hexane (**175**) (hexamethylenediamine, BuOH, reflux, 8 h: 58%)[6,20] and analogs.[345]

2-Amino-6-chloro-4(3*H*)-pyrimidinone to 2-amino-6-methylamino- (H_2O, 120°, 4 h, sealed: 80%),[1281] 2-amino-6-butylamino- ($EtOCH_2CH_2OH$, reflux: 64%),[850] 2-amino-6-(β-hydroxypropyl)amino (neat, reflux, 45 min: ~ 65%),[999] and 2-amino-6-anilino-4(3*H*)-pyrimidinone (AcOH–HCl, reflux, 4 h: 49%).[1279]

4-Amino-6-chloro-2(1*H*)-pyrimidinone to 4-amino-6-methylamino- (H_2O, reflux, 90 min: ~ 70%)[1015] and 4-amino-6-*p*-anisidino-2(1*H*)-pyrimidinone (glycol, 195°, 30 min: 76%).[4200]

Also other examples.[65,1073,2079,2118,2309,2659,3164,3853,3854,4651,4685,4808,5047,5048]

Nontautomerizable substrates

4-Chloro- to 4-amino-1-methyl-2(1*H*)-pyrimidinone (MeOH, 150°, 8 h).[696]

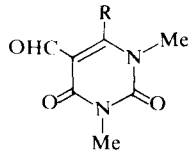
1-Benzyloxy-4-chloro- to 4-amino-1-benzyloxy-2(1*H*)-pyrimidinone (liquid NH_3, 20°, 48 h, sealed: 90%).[1681]

6-Chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione to 1,3-dimethyl-6-methylamino- (H_2O, hot, 5–10 min: ~ 75%),[644] 6-dimethylamino-1,3-dimethyl- (MeOH, reflux, briefly: 80%),[644] and 6-anilino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (neat, reflux, 3–6 h: ~ 90%).[1139,5050,5051]

6-Chloro- to 6-dimethylamino-1,3-diphenyl-2,4(1*H*,3*H*)-pyrimidinedione (MeOH, reflux, 30 min: 93%).[4458]

4-Chloro- (**176**, R = Cl) to 4-dimethylamino- (**176**, R = NMe_2) (EtOH, 85°, 2 h: 43%)[2087] and 4-(ethoxycarbonylmethyl)amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde (**176**, R = $NHCH_2CO_2Et$) (Me_2NCHO–NEt_3, 25°, 30 min: 48%).[5052]

Also other examples.[95,383,855,882,2614,3297,3739]



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Related substrates

6-Chloro-1,3-dimethyl- to 1,3-dimethyl-6-methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (H_2O, 25°, 2 h: 67%).[1103]

4-Chloro- to 4-amino-6-imino-1,3-dimethyl-3,6-dihydro-2(1*H*)-pyrimidinone (MeOH, 95°, 8 h: 56%).[1162]

4-Bromo- to 4-anilino-6-imino-1,3-dimethyl-3,6-dihydro-2(3*H*)-pyrimidinone (neat, trace HCl, 170°, 1 h).[1066]

Also other examples.[4788,5051]

6.7.2.5. Aminolysis of Halogenopyrimidine Ethers or Thioethers

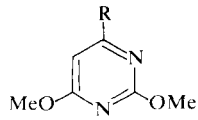
The aminolysis of halogenopyrimidines is not much affected by the presence of alkoxy or alkylthio groups in the molecule, although such groups may

themselves undergo aminolysis if conditions are sufficiently vigorous. The following examples illustrate the aminolysis of such halogenopyrimidine ethers and thioethers, with or without additional functional substituents (other than nitro, 5-amino, or oxo: already covered in the foregoing subsections).

Halogenopyrimidine ethers as substrates

4-Chloro-5-methoxy-2-phenylpyrimidine to 5-methoxy-2-phenyl-4-pyrimidinamine (EtOH, 150°, 10 h, sealed: 75%).[4092]

4-Chloro- (**177**, R = Cl) to 4-dimethylamino-2,6-dimethoxypyrimidine (**177**, R = NMe_2) (MeOH, 25°, 2 days: 94%)[1731] and 2,4-dimethoxy-6-(γ-morpholinopropyl)aminopyrimidine [**177**, R = $NH(CH_2)_3N(CH_2CH_2)_2O$] (EtOH, reflux, < 12 h: 63%).[5053]



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2,4-Dichloro-6-methoxypyrimidine to 4-chloro-6-methoxy-2-pyrimidinamine (MeOH, 100°, 90 min, sealed).[1663]

4-Chloro-5-methoxy-6-methylthiopyrimidine to 5-methoxy-6-methylthio-4-pyrimidinamine (EtOH, 135°, 6 h, sealed: 60%).[2203]

4-Chloro-5-methoxy-6-methoxymethyl-2-methylthiopyrimidine to 5-methoxy-6-methoxymethyl-2-methylthio-4-pyrimidinamine (liquid NH_3, 25°, 17 h, sealed: 93%).[2192]

5-Bromo-2-chloro-4-methoxypyrimidine to 5-bromo-4-methoxy-2-piperidinopyrimidine (Et_2O, reflux, 1 h: 78%).[1823]

2,5-Dichloro-4-methoxypyrimidine to 2,5-dichloro-4-pyrimidinamine (MeOH, 80°, 3 h, sealed; or neat, 15°, 15 h, sealed: note preferential replacement of OMe in contrast with preceding entry) but to 5-chloro-4-methoxy-2-trimethylammoniopyrimidine chloride (PhH, 20°, 3 h: 74%).[2209]

Also the following second-stage aminolyses.

2-Anilino-4-chloro-5-ethoxypyrimidine to 2-anilino-5-ethoxy-4-pyrimidinamine (EtOH, 180°, sealed).[2017]

2-Amino-4-chloro- to 2,4-diamino-6-ethoxy-5-pyrimidinecarbonitrile (EtOH, 120°, 6 h, sealed: 47°).[997]

Also other examples.[176,360,1264,1771,2477,4907]

Halogenopyrimidine thioethers as substrates

4-Chloro-2-methylthiopyrimidine to 4-dimethylamino- (EtOH, 25°, 30 min: ~ 75%),[1678] 4-benzylamino- (neat, 25°, 10 min: 70%),[1825] and 4-

(carboxymethyl)amino-2-methylthiopyrimidine (H_2O–EtOH, Na_2CO_3, reflux, 24 h: 75%);[5054] also to 2-methylthio-4-trimethylammoniopyrimidine chloride (PhH, 20°, 24 h: > 90%).[1628,1678,1681]

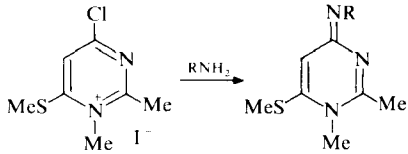
4-Chloro-5-methyl-2-methylthiopyrimidine to 5-methyl-2-methylthio-4-pyrimidinamine (EtOH, 140°, 7 h, sealed).[2239]

4-Chloro-2-*o*-chlorobenzylthio- to 2-*o*-chlorobenzylthio-4-dimethylamino-5-methylpyrimidine (H_2O–EtOH, 130°, 4 h, sealed: 67%).[2076]

4-Chloro-6-methyl-2-methylthiopyrimidine to 4-methyl-2-methylthio-6-trimethylammoniopyrimidine chloride (PhH, 20°, 3 days: ~ 55%).[1745]

4-Chloro-2-ethylthiopyrimidine to 2-ethylthio-4-methylaminopyrimidine (EtOH, 50°, 4 h: ~ 90%) or 2,4-bismethylaminopyrimidine (EtOH, 150°, 4 h, sealed);[1772, cf. 1384,1676] also analogous products.[718,951,1196]

4-Chloro-1,2-dimethyl-6-methylthiopyrimidinium iodide (**178**) to 1,2-dimethyl-6-methylthio-4(1*H*)-pyrimidinimine (**179**, R = H) (H_2O, 25°) and 1,2-dimethyl-6-methylthio-4-phenylimino-1,4-dihydropyrimidine (**179**, R = Ph) (H_2O, reflux, 30 min).[2237]



178 **179**

4,6-Dichloro-2-methylthiopyrimidine to 6-chloro-2-methylthio-4-pyrimidinamine (EtOH, 125°, sealed),[1046] 2-methylthio-4,6-pyrimidinediamine (H_2O, 185°, sealed),[951] or 2,4,6-pyrimidinetriamine (EtOH, 220°, sealed);[1046] also to 4,6-dianilino-2-methylthiopyrimidine (AcOH–HCl, reflux, 4 h: 75%).[2187]

2,4,6-Trichloro-5-trifluoromethylthiopyrimidine to a separable mixture of 4,6-dichloro-5-trifluoromethylthio-2-pyrimidinamine and 2,6-dichloro-5-trifluoromethylthio-4-pyrimidinamine (EtOH–H_2O, 0°, 2 h: 24% and 42%, respectively), to 6-chloro-5-trifluoromethylthio-2,4-pyrimidinediamine (EtOH–H_2O, reflux, 6 h: 80%), or to 5-trifluoromethylthio-2,4,6-pyrimidinetriamine (EtOH–H_2O, 200°, 3 h, sealed: 90%).[312]

5-Bromo-2-chloro- to 5-bromo-2-dimethylamino-4-methylthiopyrimidine (C_6H_{14}–EtOH, 25°, 1 h).[1823]

4,6-Dichloro- to 4,6-diamino-2-methylthio-5-pyrimidinecarbaldehyde (H_2O, 100°, 1 h, sealed: ~ 75%).[2423]

Ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate to ethyl 4-dimethylamino-2-methylthio-5-pyrimidinecarboxylate (EtOH, reflux, 1 h: 98%)[1781] and to analogs.[1816,2992,5060]

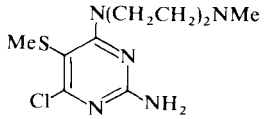
Methyl 6-chloro-2-methylthio-4-pyrimidinecarboxylate to 6-chloro-2-methylthio-4-pyrimidinecarboxamide (EtOH, 0°, 2 h: 66%) or 6-amino-2-methylthio-4-pyrimidinecarboxamide (H_2O, 100°, 8 h, sealed: 61%);[1030] and to *N*-methyl-6-methylamino-2-methylthio-4-pyrimidinecarboxamide (EtOH, 15°, 2 h: 65%).[1030]

Also the following second-stage aminolyses.

6-Chloro- to 6-dibenzylamino-2-methylthio-4-pyrimidinamine (neat, 180°, 4 h, sealed: ~ 50%).[3374]

4,6-Dichloro-5-methylthio-2-pyrimidinamine to 4-chloro-6-*N'*-methylpiperazino-5-methylthio-2-pyrimidinamine (**180**) (neat, reflux, 3 h).[2471]

Also other examples.[312,846,951,967,985,1156,1192,1218,1234,1242,1254,1264,1404,1543,1547,1599,1637,1781,2129,2159,4888,5055–5059]



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6.7.2.6. Aminolysis of Halogenopyrimidinecarboxylic Acids and Related Substrates

Halogeno substituents at the 2- or 4/6-position are activated appreciably toward aminolysis by the presence of a carboxy, alkoxycarbonyl, carbamoyl, cyano, formyl, or acyl group in the molecule: some of these groups also react with amines under appropriate conditions. The following examples illustrate the conditions required.

Halogenopyrimidinecarboxylic acids, esters, or amides as substrates

2,6-Dichloro- to 2,6-diamino- (EtOH, 130°, 7 h, sealed: 77%) and 2,6-bismethylamino-4-pyrimidinecarboxylic acid (H_2O, 0°, 3 h: 45%).[1030]

Ethyl 2-chloro- to ethyl 2-amino-5-pyrimidinecarboxylate (EtOH, 100°, 1 h, sealed: 62%).[1632]

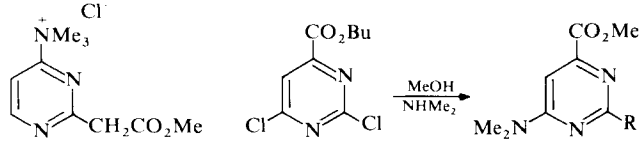
Ethyl 4-chloro- to ethyl 4-*o*-anisidino-5-pyrimidinecarboxylate (PhH, reflux, 30 min: 55%).[2990]

Ethyl 4-chloro- to ethyl 4-amino-2,6-dimethyl-5-pyrimidinecarboxylate (EtOH, 80–100°).[1466]

Ethyl 4-chloro- to ethyl 4-dimethylamino-2-methyl-5-pyrimidinecarboxylate (EtOH, 100°, 3 h, sealed).[1462]

4-Chloro-2-methoxycarbonylmethylpyrimidine to 2-methoxycarbonylmethyl-4-trimethylammoniopyrimidine chloride (**181**) (PhH, 20°, 3 days: ~ 50%).[1749]

Butyl 2,6-dichloro-4-pyrimidinecarboxylate (**182**) to methyl 2-chloro-6-dimethylamino-4-pyrimidinecarboxylate (**183**, R = Cl) (1 mol of Me_2NH, MeOH, Na_2CO_3, 25°, 2 h: 64%) or methyl 2,6-bisdimethylamino-4-pyrimidinecarboxylate (**182**, R = NMe_2) (5 mol of Me_2NH, likewise: 80%);[374] note the concomitant transesterification.



181 **182** **183**

Ethyl 6-chloro- to ethyl 6-amino-5-cyano-2-pyrrolidino-4-pyrimidinecarboxylate ($MeOCH_2CH_2OMe$, 20°, 15 h: 86%).[3764]

2,4-Dichloro- to 2,4-diamino-*N*-(3′,4′,5′-trimethoxyphenyl)-5-pyrimidinecarboxamide (H_2O, 180°, 8 h, sealed: ~70%).[2511]

Also other examples.[372,936,1988,2989,5061–5063]

Halogenopyrimidinecarbonitriles as substrates

2-Chloro- to 2-dimethylamino- (EtOH, 25°, 2 h: 66%),[2653] 2-diethylamino- (neat, reflux, 1 h: 79%),[3364] and 2-*p*-chloroanilino-4-pyrimidinecarbonitrile (EtOH, reflux, 1 h: 91%).[3364]

2-Chloro- to 2-amino-5-pyrimidinecarbonitrile (EtOH, 100°, 2 h, sealed: 70%).[1617]

4-Chloro- to 4-amino- (H_2O–MeOH, 50°, 15 min: 79%) and 4-benzylamino-5-pyrimidinecarbonitrile (EtOH, reflux, 30 min: 52%).[1614]

4-Chloro- to 4-dimethylamino-2-methyl-5-pyrimidinecarbonitrile (EtOH, reflux, 2 h: ~75%).[1462]

4-Chloro- to 4-amino- (EtOH, 100°, 36 h: 96%) and 4-morpholino-2,6-diphenyl-5-pyrimidinecarbonitrile (neat, 80°, 10 min: 85%).[4338]

2,4-Dichloro-5-pyrimidinecarbonitrile to 4-chloro-2-(ethoxycarbonylmethyl)amino-5-pyrimidinecarbonitrile ($CHCl_3$–H_2O, $NaHCO_3$, 20°, 30 min: 71%, note unusual orientation).[3911]

4,6-Dichloro- to 4-amino-6-chloro- (PhH, 25°, 3 h: ~ 70%) and 4-chloro-6-piperidino-5-pyrimidinecarbonitrile (dioxane–H_2O–AcOH, 20°, 3 h: ~ 80%).[787]

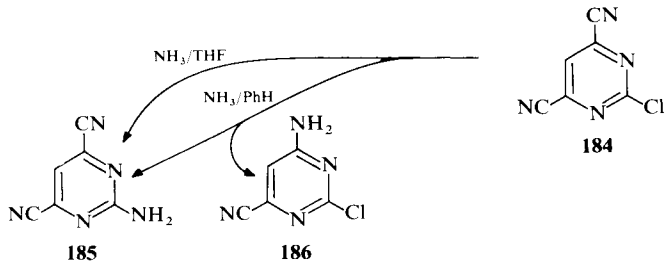
4,6-Dichloro-2-methyl-5-pyrimidinecarbonitrile to 4-chloro-6-dimethylamino- (dioxane, 10–20°, 3–4 h: 86%) or 4,6-bisdimethylamino-2-methyl-5-pyrimidinecarbonitrile (neat, 25°, 15 h: 97%).[1387]

2,4,6-Trifluoro-5-pyrimidinecarbonitrile to 2,4-diamino-6-fluoro-5-pyrimidinecarbonitrile (THF–H_2O, 30°, 90 min: 84%).[2063]

2,5,6-Trichloro-4-pyrimidinecarbonitrile to 2,6-diamino-5-chloro-4-pyrimidinecarboxamide (EtOH, 120°, 3 h, sealed: ~60%; note hydrolysis of the cyano group).[2046]

2-Chloro-4,6-pyrimidinedicarbonitrile (**184**) to 2-amino-4,6-pyrimidinedicarbonitrile (**185**) (THF, 20°, 24 h: 80%) or to 6-amino-2-chloro-4-pyrimidinecarbonitrile (**186**) (PhH, 20°, 3 days: 36% yield, by aminolytic displacement of CN rather than Cl) plus the preceding product (**185**) (38%).[1029]

Also other examples.[1010,2006,4886]



Halogenopyrimidinecarbaldehydes and related ketones as substrates

4,6-Dichloro-5-pyrimidinecarbaldehyde to 4-amino-6-chloro-5-pyrimidinecarbaldehyde (PhH, 25°, 12 h: 72%), 4-chloro-6-methylamino-5-pyrimidinecarbaldehyde (PhH–Et_2O, 25°, 14 h: 78%), and 4,6-bismethylamino-5-methyliminomethylpyrimidine (**187**) (excess amine in PhH, 10°, 3 h: 32%).[1027]

4,6-Dichloro-2-phenyl-5-pyrimidinecarbaldehyde to 4-amino-6-chloro- (PhH, 50°, 16 h: 71%)[1008] or 4,6-diamino-2-phenyl-5-pyrimidinecarbaldehyde (H_2O, 100°, 1 h, sealed: ~ 70%).[2423]

5-Benzoyl-4-chloro-2,6-dimethylpyrimidine to 5-benzoyl-2,6-dimethyl-4-pyrimidinamine (EtOH–H_2O, 180°, 24 h, sealed: 75%).[4883]

2,4-Dichloro- to 2,4-diazido-6-diazoacetylpyrimidine (NaN_3, AcMe–H_2O, 25°, 5 h: 80%).[6036]

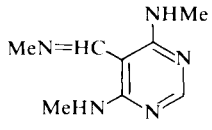
5-Acetyl-4,6-dichloropyrimidine to 5-acetyl-4-chloro-6-morpholinopyrimidine (dioxane, 20°, 3 h: ~ 50%).[787]

5-Acetonyl-4,6-dichloropyrimidine to 5-acetonyl-4-chloro-6-dimethylaminopyrimidine (H_2O, reflux, 1 h: 80%).[732]

Also the following second- or third-stage aminolyses.

4-Chloro- to 4-dimethylamino-6-*N*-ethylanilino-5-pyrimidinecarbaldehyde (EtOH–PhMe, 60°, 1 h: 70%).[852]

2-Amino-4,6-dichloro- to 2,4-diamino-6-chloro-5-pyrimidinecarbaldehyde (EtOH, 25°, 18 h: 83%) and thence to 2,4-diamino-6-*p*-bromoanilino-5-pyrimidinecarbaldehyde (**188**, X = O), isolated initially as its Schiff base,



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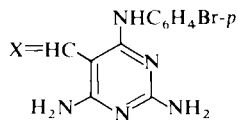

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4-*p*-bromoanilino-5-*p*-bromophenyliminomethyl-2,4-pyrimidinediamine (**188**, X = NC_6H_4Br-*p*) (EtOH–HCl, reflux, 3 h: 59%).[2388]

Also other examples in the foregoing references and elsewhere.[2611,6134]

6.7.2.7. Aminolysis of Halogenopyrimidines Bearing Miscellaneous Substituents

Although they show little tendency to undergo aminolytic displacement themselves, 5-halogeno and 5-trifluoromethyl substituents stimulate aminolysis of 2- or 4/6-halogenopyrimidines; so, too, do alkylsulfonyl and *N*-oxido substituents. The conditions required for aminolysis of such substrates are illustrated in the following examples.

5-Brominated substrates

5-Bromo-2-chloro- to 5-bromo-2-hexylamino- (neat, 25°, 5 min: 94%)[1825] and 5-bromo-2-isopentylaminopyrimidine (neat, 30°, 10 min: ~ 80%).[1826]

5-Bromo-4-chloro- to 5-bromo-4-methylamino- (EtOH, 0°, 15 h: 80%),[1901] 5-bromo-4-piperidino- (EtOH, 0°, 3 days: 54%),[1896] and 4-anilino-5-bromopyrimidine (EtOH, 0°, 3 days: 94%).[1896]

5-Bromo-2,4-dichloro- to 5-bromo-2-chloro-4-dimethylamino- (Et_2O, < 5°, then reflux, 20 min: 88%)[1799] and thence 5-bromo-2,4-bisdimethylaminopyrimidine (EtOH, reflux, 15 min: 94%).[1799]

Also the following second- or third-stage aminolyses.

5-Bromo-4-chloro- to 5-bromo-4-*p*-chloroanilino-6-methyl-2-pyrimidinamine (H_2O–HCl, reflux, 30 min: > 98%).[1818]

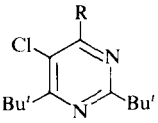
5-Bromo-6-chloro- to 6-anilino-5-bromo-2,4-pyrimidinediamine (H_2O–HCl, reflux, 3 h: ~ 40%).[1830]

Also other examples.[1787,1815,1836,5060]

5-Chlorinated substrates

2,4-Di-*t*-butyl-5,6-dichloropyrimidine (**189**, R = Cl) to 2,6-di-*t*-butyl-5-chloro-4-pyrimidinamine (**189**, R = NH_2) (EtOH, 130°, 20 h, sealed: 85%).[4882]

2,4,5-Trichloro-6-methylpyrimidine to 4-aziridino-2,5-dichloro-6-methylpyrimidine (Et_2O–PhH–NEt_2, < 10°, 1 h; then 25°, 15 h: 78%).[1836]



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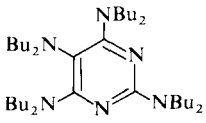

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2,4,5,6-Tetrachloropyrimidine to 4-anilino-2,5,6-trichloropyrimidine (H_2O–AcMe at pH 6–7, 50°, ? 30 min: 86%).[3685]

Also the following second- to fourth-stage aminolyses.

4,5-Dichloro-6-methyl-2-pyrimidinamine to 5-chloro-6-methyl-2,4-pyrimidinediamine (EtOH, 115°, 3 h, sealed: 73%).[2176]

4,5-Dichloro-2,6-bisdibutylaminopyrimidine to 2,4,5,6-tetrakisdibutylaminopyrimidine (**190**) (neat, 220°, 4 h: 69%; note displacement of a 5-chloro substituent).[1727]

Also other examples in the foregoing references and elsewhere.[4986]

5-Iodinated substrates

4-Chloro-5-iodo-6-methylpyrimidine to 5-iodo-6-methyl-4-pyrimidinamine (EtOH, 120°, 12 h, sealed: 80%).[2177]

2,4-Dichloro-5-iodopyrimidine to 4-(α-carboxy-γ-methylbutyl)amino-2-chloro-5-iodopyrimidine (Na salt of leucine, H_2O, reflux until homogeneous: 31%).[5060]

Also analogous examples.[2177]

5-Fluorinated substrates

2,4-Dichloro-5-fluoropyrimidine to 2-chloro-5-fluoro-4-pyrimidinamine (EtOH, 20°, 3 days: 39%;[1264] EtOH–H_2O, < 30°, 3 h; 79%;[621] neat, 20°, 1 h, sealed: 97%[1260]) and thence 5-fluoro-2,4-pyrimidinediamine (EtOH, NH_4Cl, 140°, 19 h, sealed: 36%);[1260] also to 4-aziridino-2-chloro-5-fluoro- (Et_2O–NEt_3, < 25°, 2 h: 50%) or 2,4-diaziridino-5-fluoropyrimidine (Et_2O–NEt_3, 25°, 36 h: 67%);[2479] and to 2-chloro-5-fluoro-4-piperidino- (Et_2O– NEt_3, 25°, 30 min) or 5-fluoro-2,4-dipiperidinopyrimidine (EtOH, reflux, 3 h: 62%).[2124]

2,4,5,6-Tetrafluoropyrimidine to 2,5,6-trifluoro-4-pyrimidinamine (Et_2O, 0°, 30 min: 36%), 2,4-bisdimethylamino-5,6-difluoropyrimidine (Et_2O, 30°, 12 h: 47%), and 2,4,5,6-tetrakisdibutylaminopyrimidine (**190**) (neat, 220°, 4 h; note the replacement of a 5-fluoro substituent).[1727,3656]

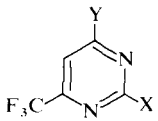
Also other examples.[2166,2480,5064]

Other substrates

2,4-Dichloro-6-trifluoromethylpyrimidine (**191**, X = Y = Cl) to 2-chloro-4-diethylamino- (**191**, X = Cl, Y = NEt_2) (EtOH, 20°, 3 h: 71%) or 2,4-

bisdiethylamino-6-trifluoromethylpyrimidine (**191**, X = Y = NEt_2) (EtOH, 70°, 15 h: 83%).[477]

2,4-Dichloro-5-trifluoromethylpyrimidine to 2-chloro-5-trifluoromethyl-4-pyrimidinamine (liquid NH_3, 20°, 2 h, sealed: 98%) and to a tlc (thin-layer-chromatography)-separable mixture of 4-benzylamino-2-chloro- and 2-benzylamino-4-chloro-5-trifluoromethylpyrimidine (EtOH, 40°, 15 min: 79% of the mixture).[5065]



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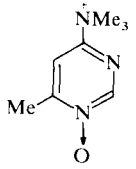

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4-Chloro-6-methylpyrimidine 1-oxide to 4-methyl-6-trimethylammonio-pyrimidine 3-oxide chloride (**192**) (PhH, 20°, 10 days).[3287]

4-Chloro-6-methylsulfonylpyrimidine to 4-aziridino- (EtOAc–NEt_3, 25°, 3 h: 75%) and 4-*p*-bromoanilino-6-methylsulfonylpyrimidine (EtOH, reflux, 6 h: 77%);[2289] note: methylsulfonyl is usually a better leaving group than chloro in a comparable position;[1332,4721,5066] but in this case, chloro was strongly activated by methylsulfonyl, whereas the reverse did not apply.

4-Chloro-2-ethylsulfonyl-5-methylpyrimidine to 2-ethylsulfonyl-5-methyl-4-pyrimidinamine (EtOH, 100°, 2 h, sealed: ~ 60%).[1544]

6.7.3. Aminolysis of 2- or 4/6-Halogenopyrimidines with Hydrazines, Hydroxylamine, or Hydrazoic Acid

Aminolyses with *N*-(functionally substituted) amines occasionally diverge from the lines for regular aminolyses just described: for example, hydrazine with an appropriate excess of halogenopyrimidine can furnish an hydrazo product. The conditions for regular and irregular aminolyses by such reagents are illustrated in the following transformations, divided according to the type of reagent and (when necessary) subdivided according to the type of substrate.

Using hydrazine on simple halogenopyrimidines

2-Chloro- to 2-hydrazinopyrimidine (EtOH, reflux, 2 h: ~20%).[2106, cf. 2197]

4-Chloro- to 4-hydrazino-2,6-dimethylpyrimidine (H_2O, reflux, 5 min: 75%).[880]

5-Allyl-4-chloro- to 5-allyl-4-hydrazino-2,6-dimethylpyrimidine (MeOH, reflux, 6 h: 83%).[365]

4,6-Dichloro- to 4-chloro-6-hydrazino- (EtOH, 25°, 3 h: 34%)[1827] or 4,6-dihydrazinopyrimidine (EtOH, reflux, 1 h: 89%).[2461]

2,4-Dichloro- to 2-chloro-4-hydrazino- (EtOH, 20°, 1 h: ~ 30%)[2147] or 2,4-dihydrazinopyrimidine (EtOH, reflux, 1 h: ~ 50%).[2459,2566]

2,4-Dichloro- to 2-chloro-4-hydrazino-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine (EtOH, reflux, 30 min: 61%).[169]

Also the following second- or third-stage aminolyses.

4-Chloro- to 4-hydrazino-6-methyl-2-pyrimidinamine (H_2O, K_2CO_3, 140°, 14 h, sealed: ~ 55%;[2197] MeOH, reflux, 5 h: 90%[3214]).

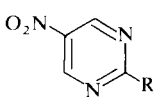
4,6-Dichloro-2-morpholino- to 4-chloro-6-hydrazino-2-morpholinopyrimidine (EtOH, reflux, 15 min: ~ 80%).[3527]

6-Chloro- to 6-hydrazino-2,4-pyrimidinediamine (neat, 50°, 16 h: 77%).[232]

Also other examples.[2062,2561,3194,3215–3217,4122,4130,4409,4890,5001]

Using hydrazine on halogeno-5-nitropyrimidines

2-Chloro- (**193**, R = Cl) to 2-hydrazino-5-nitropyrimidine (**193**, R = $NHNH_2$) (EtOH, 20°, 5 min: 97%)[2305] or *N*,*N*′-bis(5-nitropyrimidin-2-yl)hydrazine (**194**) (EtOH, 2 mol of substrate, reflux, 1 h: 37%).[2305,5067]



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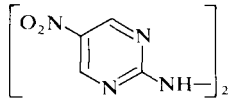

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2,4-Dichloro- to 2,4-dihydrazino-5-nitropyrimidine (Et_2O, 20°, 5 min: 75%).[1714]

6-Chloro- to 6-hydrazino-5-nitro-4(3*H*)-pyrimidinone (MeOH, 20°, 4 h: 88%).[607]

6-Chloro- to 6-hydrazino-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (MeOH, 0°, 1 h: > 95%;[3195] EtOH, reflux, 5 min: 86%[3753]) or to *N*,*N*′-bis(1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazine (MeOH, 2.5 mol of substrate, 0°, 1 h: 51%).[3753]

4-Chloro- to 4-hydrazino-6-methoxy-5-nitropyrimidine (EtOH, − 8°, 30 min: 73%).[684]

Also the following second-stage hydrazinolyses.

6-Chloro- to 6-hydrazino-5-nitro-4-pyrimidinamine (MeOH, 20°, 15 min: 91%;[607] EtOH, reflux, 2 h: 75%[684]).

2-Amino-6-chloro- to 2-amino-6-hydrazino-5-nitro-4(3*H*)-pyrimidinone (MeOH, 20°, 2.5 h: 93%).[1301]

Also other examples.[1552,2068,2560]

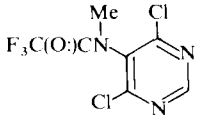
Using hydrazine on halogeno-5-pyrimidinamines

4-Chloro- to 4-hydrazino-6-methyl-5-pyrimidinamine (EtOH, reflux, 2 h: 85%).[1038]

4,6-Dichloro- to 4-chloro-6-hydrazino-2-phenyl-5-pyrimidinamine (EtOH, reflux, 30 min: 75%).[4760]

5-Acetamido-6-chloro- to 5-acetamido-6-hydrazino-2,4(1*H*,3*H*)-pyrimidinedione ($EtOH–NEt_3$, reflux, 3 h: > 90%; excess hydrazine was avoided by addition of tertiary base: hence acetamido group survived).[624]

4,6-Dichloro-5-α,α,α-trifluoro-*N*-methylacetamidopyrimidine (**195**) to 4-chloro-6-hydrazino-5-methylaminopyrimidine (H_2O, 20°, 3 days: 79%; note deacylation by excess hydrazine).[632]



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2-Acetamido-4,6-dichloro-5-pyrimidinamine to 4-chloro-6-hydrazino-2,5-pyrimidinediamine (EtOH, 20°, 3 days: > 53%; second-stage reaction: note deacylation).[620]

Also other examples.[1777,2957,5026]

Using hydrazine on halogenopyrimidinones

6-Chloro- to 6-hydrazino-4(3*H*)-pyrimidinone (EtOH, reflux, 30 min: 90%).[1680]

6-Chloro- to 6-hydrazino-2,4(1*H*,3*H*)-pyrimidinedione (H_2O, reflux, 1 h: > 98%).[3233]

6-Chloro- to 6-hydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (neat, reflux, 2 min: 80%).[644]

2-Amino-6-chloro- to 2-amino-6-hydrazino-4(3*H*)-pyrimidinone (BuOH, reflux, ? h: 86%; second-stage reaction).[1307]

Also other examples.[1139,3195]

Using hydrazine on halogenopyrimidine ethers or thioethers

4-Chloro- to 4-hydrazino-5-methoxypyrimidine (EtOH, reflux, 30 min: 60%).[1343]

4-Chloro- to 4-hydrazino-6-methoxypyrimidine (EtOH, K_2CO_3, reflux, 1 h: 88%).[3204]

5-Benzyloxy-4-chloro- to 5-benzyloxy-4-hydrazinopyrimidine (EtOH, 70°, 5 min: 88%).[718]

2,4-Dibenzyloxy-6-chloro- to 2,4-dibenzyloxy-6-hydrazinopyrimidine (neat, reflux, 20 min: 75%) plus a little 2,4,6-trihydrazinopyrimidine.[3301]

2-Chloro- to 2-hydrazino-4,6-dimethoxypyrimidine (H_2O, K_2CO_3, 85°, 2 h: > 90%;[1780] EtOH, K_2CO_3; reflux, 3 h: 86%[3204]).

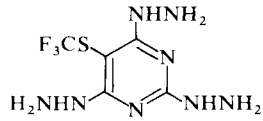
2-Chloro-4-methoxypyrimidine to *N*,*N*′-bis(4-methoxypyrimidin-2-yl)-hydrazine (EtOH, 2 mol of substrate, reflux, 10 h: 47%).[5067]

2,4-Dichloro- to 2-chloro-4-hydrazino-5-methoxypyrimidine (EtOH, reflux, 1 h: ~ 95%).[1343]

4-Chloro- to 4-hydrazino-5-methoxy-2-methylthiopyrimidine (EtOH, reflux, 5 min: 85%).[718]

2-Chloro- to 2-hydrazino-4-methyl-6-propylthiopyrimidine (EtOH, K_2CO_3, reflux, 30 min).[2126]

2,4,6-Trichloro- to 2,4,6-trihydrazino-5-trifluoromethylthiopyrimidine (**196**) (EtOH, 25°, 1 h: 84%).[312]



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4-Chloro- to 4-hydrazino-2-methylthio-6-phenyl-5-pyrimidinecarbonitrile (neat ?).[3955]

Also other examples.[751,2106,2126,2197]

Using hydrazine on other substituted halogenopyrimidines

Ethyl 4-chloro- to ethyl 4-hydrazino-2-trifluoromethyl-5-pyrimidinecarboxylate (EtOH, 0°, 15 h: 69%).[4131]

2-Chloro- to 2-hydrazino-6-methyl-4-pyrimidinecarbonitrile (EtOH, 25°, 10 min: 48%).[2267]

4-Chloro- to 4-hydrazino-2-propyl-6-trifluoromethylpyrimidine (EtOH, reflux, 2 h: ~ 85%).[880]

4,5-Dichloro- to 5-chloro-4-hydrazinopyrimidine (EtOH, 20°, 3 h: 38%).[1827]

5-Bromo-4-chloro- to 5-bromo-4-hydrazino-6-methylpyrimidine (EtOH, reflux, 1 h: 87%).[1822]

5-Bromo-2,4-di-*t*-butyl-6-chloro- to 5-bromo-2,4-di-*t*-butyl-6-hydrazinopyrimidine (EtOH, reflux, 3 h: 96%).[4882]

Also other examples.[1857]

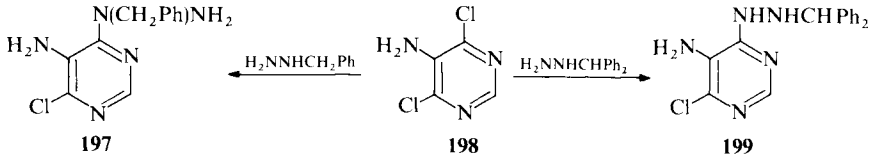
Using substituted hydrazines

Note: A monoalkylhydrazine normally reacts at its more basic secondary-amino center when attacking a halogenopyrimidine, to afford an α-alkylhydrazinopyrimidine; in contrast, a monoaryl- or monoacylhydrazine reacts at its primary-amino center; and there is seldom any ambiguity when a disubstituted hydrazine or an alkylidenehydrazine is used.

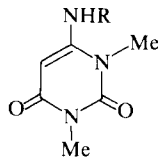
6-Chloro-1,3-dimethyl- to 1,3-dimethyl-6-α-methylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione (EtOH, 25°, 2 h: 85%).[2687]

4-Chloro- to 4-α-methylhydrazino-2-pyrimidinamine (MeOH, reflux, 2 h: 50%; second-stage reacton).[1203]

4,6-Dichloro- (**198**) to 4-α-benzylhydrazino-6-chloro-5-pyrimidinamine (**197**) (PhH, reflux, 2 h: 50%)[1777] but to 4-chloro-6-β-(diphenylmethyl)-hydrazino-5-pyrimidinamine (**199**) (PrOH, reflux, 4 h: 58%; exceptional orientation for steric and/or electronic reasons?).[5068]



197 **198** **199**



200

6-Chloro-1,3-dimethyl- to 1,3-dimethyl-6-β-phenylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione (**200**, R = NHPh) (EtOH, reflux, 2 h: 41%).[2089]

2-Amino-6-chloro-4(3*H*)-pyrimidinone to a mixture of 2-amino-6-β-phenylhydrazino- and 2-amino-6-α-phenylhydrazino-4(3*H*)-pyrimidinone, from which only the second (minor) product could be isolated in low yield (H_2O, reflux, 17 h).[5069]

2-Chloro- to 2-β-benzoylhydrazinopyrimidine (neat, K_2CO_3, 130°, 5 min: ~85%).[2197]

2,4-Dichloro-5-nitropyrimidine to a separable mixture of 2-chloro-4-β-formylhydrazino- and 2,4-bis-β-formylhydrazino-5-nitropyrimidine (EtOH–Et_2O, −10°, 1 h: ~60% and ~5%, respectively);[803] also to 4-β-acetylhydrazino-2-chloro- and 2,4-bis-β-acetylhydrazino-5-nitropyrimidine (likewise).[803]

4-Chloro-6-methoxy-5-nitropyrimidine to 4-methoxy-5-nitro-6-semicarbazidopyrimidine (EtOH–H_2O, $NaHCO_3$, 25°, 1 h: ~75%).[3227]

4-Chloro- to 4-benzenesulfonylhydrazino-5-methylthio-2-pyrimidinamine (MeOH, reflux, 6 h: > 56%, crude).[1567]

2-Acetamido-4,6-dichloro-5-nitropyrimidine to 2-acetamido-4-β-(benzyloxycarbonyl)hydrazino-6-chloro-5-nitropyrimidine (dioxane, 20°, 60 h: 37%).[620]

4,6-Dichloro- to 4-chloro-6-α,β-dimethylhydrazino-5-pyrimidinamine (H_2O, 70°, 2 h: 38%).[632]

2,4-Dichloro-5-nitropyrimidine to 2-chloro-4-β,β-diphenylhydrazino-5-nitropyrimidine ($CHCl_3$, 20°, 3 h: 93%).[5071]

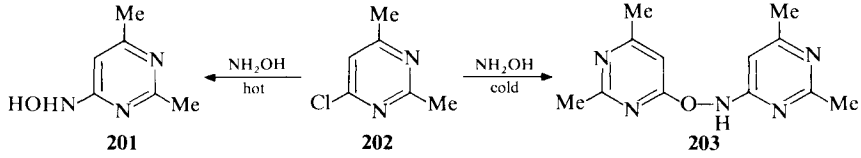
6-Chloro- to 6-ethylidenehydrazino-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (MeOH–$CHCl_3$, 20°, 5 min: > 75%); 6-benzylidenehydrazino analog similarly.[3037]

Also other examples.[17,340,619,801,802,1777,1844,2170,2566,3210,4142,5070]

Using hydroxylamine

2-Chloro- to 2-hydroxyaminopyrimidine (EtOH, reflux, 4 h: 42%).[1012]

2-Chloro-4,6-dimethylpyrimidine (**202**) to 2-hydroxyamino-4,6-dimethylpyrimidine (**201**) (EtOH–NEt_3, reflux, 1 h: 96%) or to *N*,*O*-bis(2,6-dimethylpyrimidin-4-yl)hydroxylamine (**203**) (EtOH, 20°, 4 weeks: 47%); also other products.[514]



201 **202** **203**

6-Chloro- to 6-hydroxyamino-2,4(1*H*,3*H*)-pyrimidinedione (EtOH, reflux, 1 h: 74%).[3241]

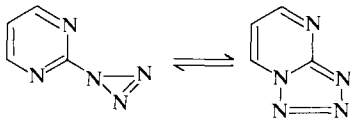
6-Chloro- to 6-hydroxyamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**200**, R = OH) (EtOH, reflux, 2 h: ~70%, plus two separable byproducts).[1139]

Also other examples.[776,1704]

Using azide ion (sodium azide)

Note: Although 2- and 4/6-azidopyrimidines appear to exist in equilibria with tetrazolopyrimidines., e.g., 2-azidopyrimidine (**204**) with tetrazolo[1,5-*a*]-pyrimidine (**205**), the azidopyrimidine nomenclature is retained in this book.

2-Chloro- to 2-azidopyrimidine (**204/205**) (H_2O–EtOH–HCl, reflux, 4 h: 59%).[1701]



204 **205**

2-Chloro- to 2-azido-4,6-diphenylpyrimidine (Me_2SO, 90°, 6 h: 91%).[150]

4-Chloro- to 4-azidopyrimidine (Me_2NCHO, 85°, 1 h: 21%).[607]

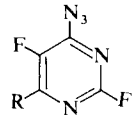
4-Chloro- to 4-azido-2,6-dimethyl-5-styrylpyrimidine (EtOH, reflux, 1 h: 90%).[4656]

6-Chloro- to 6-azido-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (THF, 20°, 5 h: 80%).[1704,1705]

4,6-Dichloro- to 4-azido-6-chloro-5-pyrimidinamine (Me_2NCHO, 95°, 1 h: 83%).[1702]

2,4,5,6-Tetrafluoropyrimidine to a separable mixture of 4-azido-2,5,6-trifluoro- (**206**, R = F) and 4,6-diazido-2,5-difluoropyrimidine (**206**, R = N_3) (MeCN, 0°, 7 h: 58% and 7%, respectively).[1700]

Also other examples.[22,644,1015,1714,2459,2984,3754,4412,5072,6237]



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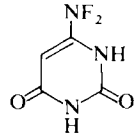


207

An interesting attempt to convert 6-chloro- into 6-difluoroamino-2,4-(1*H*,3*H*)-pyrimidinedione (**207**) with difluoroamine has been made.[9]

6.7.4. Alcoholysis of 2- or 4/6-Halogenopyrimidines

Nucleophilic displacement of 2- or 4/6-halogeno substituents by alkoxide ion occurs very easily except in cases of extreme deactivation, for example, by two or more amino groups. A few second-order rate constants and other quantitative data for the alcoholysis of chloropyrimidines have been reported,[739,2265,5073] but they convey little of interest and nothing surprising. From a preparative point of view, virtually all 2- or 4/6-halogenopyrimidines react quite easily with sodium alkoxide in the appropriate alcohol to afford the corresponding alkoxypyrimidines, although the conditions required do reflect to some extent the state of activation of the halogeno substituent and any major steric factors associated with either reactant. By carefully controlling the conditions and the proportion of alkoxide ion, it is usually possible to achieve selective stepwise alcoholysis of di- or trihalogenopyrimidines. Phenolyses are often done by warming the halogenopyrimidine and appropriate phenol in an inert solvent containing potassium carbonate.

The conditions and yields for such reactions are briefly illustrated in the formation of the following alkoxy- or aryloxypyrimidines, in each case from the corresponding chloropyrimidine by the appropriate general procedure just outlined for each category (except when indicated otherwise).

Simple alcoholysis

2-Methoxypyrimidine (reflux, 1 h: 78%;[2847, cf. 708,1968] MeOH–Ph_2O, NaH, 100°, 2 h: 89%[5074]).

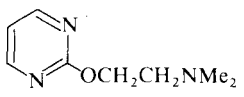
4-Methoxy-6-methylpyrimidine (reflux, 15 min: 79%).[2249]

4-Benzyloxy-2,6-dimethylpyrimidine (reflux, 15 min: 90%).[3345]

2-Methoxy-5-phenylpyrimidine (reflux, 1 h: > 90%).[4023]

2-(*β*-Dimethylaminoethoxy)pyrimidine (**208**) ($Me_2NCH_2CH_2OH$, THF, NaH, 25°, 10 h: 89%).[567]

2-Allyloxy-5-bromopyrimidine ($H_2C{=}CHCH_2OH$, THF, $KOBu^t$, 0°, 8 h: 82%).[3916]



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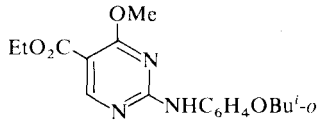

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5-Bromo-2-isopropoxypyrimidine (25°, 15 h: 76%).[3832]

4,5-Dibenzyloxy-2-methylpyrimidine (from the 4-chloro analog; $PhCH_2ONa$ in PhH, reflux, 4 h: 85%).[4089]

4-Ethoxy-2-methylthiopyrimidine (25°, 4 h; *then* reflux, 10 min: 88%).[828]

2-Anilino-4-ethoxy-6-methylpyrimidine (reflux, 2 h: 88%).[2896]

2-Ethoxy-5-nitropyrimidine (reflux, 90 min: 76%).[2941]

4-Methoxy-6-methylamino-5-nitropyrimidine (reflux, 1 h: 75%).[1379]

4-Ethoxy-2-pyrimidinamine (reflux, 3 h: 75%).[704]

4-Dimethylamino-2-methoxypyrimidine (reflux, 14 h: > 90%).[1678]

2-Methoxy-4-methylthiopyrimidine (25°, 8 h: 33%).[2941]

6-Methoxy-4-pyrimidinecarboxylic acid (reflux, 40 min: ~ 40%).[2326]

4-Amino-2-methoxy-5-pyrimidinecarbonitrile (MeOH – Me_2SO, KOH, 50°, 1 h: 65%).[400]

Ethyl 2-*o*-isobutoxyanilino-4-methoxy-5-pyrimidinecarboxylate (**209**) (neat MeOH, reflux, 3 h: 68% as hydrochloride).[3976]

6-Ethoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (reflux, 5 min: ~70%).[644]

Some unusually sluggish examples.

2,4-Bisdimethylamino-6-methoxypyrimidine (reflux, 24 h: 93%).[1731]

2-Dimethylamino-6-methoxy-4-pyrimidinamine (130°, 12 h, sealed: ~65%).[638]

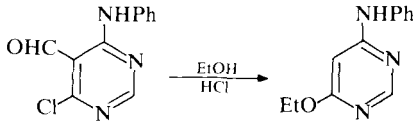
6-Benzyloxy-2,4-pyrimidinediamine (160°, 3 h: ~55%).[2452]

Some unusual procedures and/or results.

4-Anilino-6-ethoxypyrimidine (**211**) from 4-anilino-6-chloro-5-pyrimidinecarbaldehyde (**210**) (EtOH–HCl, 20°, 2 weeks: ~ 60%).[852]

5-Fluoro-4-methoxy-2(1*H*)-pyrimidinone from 4-chloro-5-fluoro-2(1*H*)-pyrimidinone (MeOH–HCl, 20°, 5 h: 65%).[1267]

4-Ethoxy-6-methoxy-5-nitropyrimidine from 4-chloro-6-methoxy-5-nitropyrimidine (EtOH, Ag_2O, reflux, 36 h: ~75%).[2559]



210 **211**

4-*t*-Butylperoxy-6-methylpyrimidine from 4-chloro-6-methylpyrimidine (Bu^tOOH, BaO, light petroleum, 25°, 3 h: 67%);[2136] analogous examples.[6199]

2-Ethoxy- from 2-chloro-5-nitro-6-trifluoromethyl-4-pyrimidinamine (EtOH–pyridine, reflux, 3 h: ~ 75%).[4754]

Also many other examples.[615,637,671,672,690,764,846, 872,883,903,1007, 1014,1030,1089,1139,1357,1362,1366,1369,1428,1462, 1520,1570,1586,1681,1701, 1732,1787,1818,1823,1874,1878,1879,1895,1899,1951,2106,2162,2167,2182,2187, 2194,2197,2209,2310,2334,2471,2477,2485,2523,2583,2588,2928,2940,2947,2959, 2989,3144,3324,3337,3348,3356,3827,3893,4019,4123,4633,4979,4999,5065,5075, 5076]

Selective alcoholysis of 2,4- or 4,6-dihalogenopyrimidines

4-Chloro-6-methoxypyrimidine (reflux, 30 min: 80%).[2600, cf. 1666]

2-Chloro-4-methyl-6-propoxypyrimidine (25°, 16 h: 91%).[2127]

4-Chloro-5-iodo-6-methoxy-2-methylpyrimidine (25°, 24 h: ~ 80%).[499]

5-Bromo-2-chloro-4-methoxy- and 5-bromo-4-chloro-2-methoxypyrimidine (20°, 30 min: 82% and 3%, respectively).[1799]

2-Chloro-4-ethoxy-5-fluoropyrimidine (20°, 1 h: 83–96%).[1260,2124]

4-Chloro-6-methoxy-5-pyrimidinamine (MeOH, NaOH, reflux, 1 h: 70%).[2208]

2-Chloro-4-methoxy-6-methyl-5-pyrimidinol (**213**) [from 5-acetoxy-2,4-dichloro-6-methylpyrimidine (**212**), reflux, 10 h: 90%].[751]

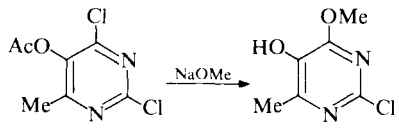
2-Chloro-4-ethoxy-6-trifluoromethylpyrimidine (5°, 3 h: 77%).[477]

4-Ethoxy-6-fluoro-2-pyrimidinamine (from 4,6-difluoro-2-pyrimidinamine, EtOH–PhMe, 60°, 1 h: 61%).[1040]

2-Bromo-4,5-diethoxypyrimidine (from 2-bromo-4-chloro-5-ethoxypyrimidine, reflux, 2 h: 95%).[1814]

4-Chloro-6-ethoxy-2-methyl-5-nitropyrimidine (20°, 1 h: ~ 85%).[2125]

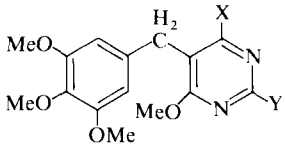
Also other examples.[473,615,696,1730,1743,1787,1801,1997, 2075,2131,2164,2208, 2209,2211,2521, 3685,4198]



212 **213**

Selective alcoholysis of 2,4,6-trihalogenopyrimidines

2,4-Dichloro-6-methoxy- (**214**, X = Y = Cl) (1 mol of NaOMe in MeOH, reflux, 1 h: 87%), 4-chloro-2,6-dimethoxy- (**214**, X = Cl, Y = OMe (2 mol NaOMe in MeOH, reflux, 1 h: 96%), or 2,4,6-trimethoxy 5-(3′,4′,5′-trimethoxybenzyl)pyrimidine (**214**, X = Y = OMe) (3 mol NaOMe in MeOH, 100°, 4 h, sealed: 98%).[361]



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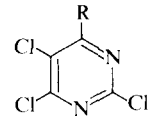

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4-Bromo-2,6-dimethoxypyrimidine (from 2,4,6-tribromopyrimidine, NaOMe in MeOH–PhH, 20°, 15 h: 80%).[1703]

2,4-Dibenzyloxy-6-chloropyrimidine (PhH, 50°, 1 h: 90%).[3301]

4-Butoxy-2,5,6-trichloropyrimidine (BuOH–H_2O, $NaHCO_3$, 20°, then 90°, 6 h: 40%).[1727]

2,4,5-Trifluoro-6-methoxy- (MeOH, Na_2CO_3, 20°, 30 min: 52%) and thence 2,5-difluoro-4,6-dimethoxypyrimidine (NaOMe in MeOH, reflux, 7 h: 87%);[1728] also 5-fluoro-2,4,6-trimethoxypyrimidine (from the tetrafluoro substrate, NaOMe in MeOH in excess, reflux, 6 h: 51%).[1728]

4-Allyloxy-2,5,6-trifluoro- (CH_2=$CHCH_2OH$ in THF, Na_2CO_3, 20°, 7 days: 61%) or 2,4,6-triallyloxy-5-fluoropyrimidine (CH_2=$CHCH_2ONa$ in CH_2=$CHCH_2OH$, reflux, 42 h: 63%).[293]

2,5-Difluoro-4-iodo-6-methoxypyrimidine (from 2,4,5-trifluoro-6-iodopyrimidine, 0–20°, 1 h: 74%; note the absolutely selective replacement of a fluoro, rather than the equivalent iodo substituent in the substrate).[2555]

2,4,5-Trichloro-6-ethoxypyrimidine (**215**, R = OEt) [from 2,5,6-trichloro-4-pyrimidinecarbonitrile (**215**, R = CN), EtOH–H_2O, NaOH, 20°, 5 min; note selective replacement of the cyano group] and subsequently 4,5-dichloro-2,6-diethoxypyrimidine (EtONa in EtOH, 20°, 3 days); also 5-chloro-2,4,6-triethoxypyrimidine (from original substrate, EtONa in EtOH, reflux, 12 h: ~ 70%).[2046]

Also other examples.[788,1040,1219,1228,1349,1376,1485,1663,1771,2063,2071,2110,2136,2343,2454,3164,4877]

Complete alcoholysis of 2,4- or 4,6-dihalogenopyrimidines

4,6-Dimethoxypyrimidine (reflux, 1 h: 55%).[2600,cf. 2526]

2,4-Diisopropoxypyrimidine (reflux, 1 h: 92%).[2569]

2,4-Di-*t*-butoxypyrimidine ($NaOBu^t$ in PhMe, reflux, 90 min: 93%).[2569]

2,4-Diethoxy-5-fluoropyrimidine (25°, 1 h: 82%).[2518]

2,6-Dimethoxy-4-pyrimidinamine (reflux, 2 h: ~70%;[636] 120°, 12 h, sealed: 81%[2504]).

Methyl 2,6-dimethoxy-4-pyrimidinecarboxylate (from 2,6-dichloro-4-pyrimidinecarbonyl chloride, reflux, 4 h: 65%).[2121]

4,6-Dimethoxy-5-nitropyrimidine (30°, 5 min: ~90%).[1016, cf. 2208]

2,4-Diethoxy-5-nitropyrimidine (25°, 2 h: 53%). [*Note*: If the ethanol contained a trace of water, a separable mixture of 2-ethoxy-5-nitro-4(3*H*)-pyrimidinone and 4-ethoxy-5-nitro-2(1*H*)-pyrimidinone was formed).[1584, cf. 1665]

5-Nitro-2,4-dipropoxypyrimidine (reflux, 30 min).[3227]

4,6-Dibenzyloxy-5-α-hydroxyethylpyrimidine ($PhCH_2ONa$ in $PhCH_2OH$–CH_2Cl_2, 25°, 3 h: 71%).[363]

5-Ethyl-4,6-dimethoxy-2,2′-bipyrimidine (reflux, 2 h: 85%).[3693]

Also other examples.[651, 868, 965, 1010, 1509, 1579, 1639, 1680, 1795, 1800, 1836, 1838, 2078, 2130, 2164, 2249, 2489, 2521, 2561, 3105, 3153, 4699, 4867, 4892, 5077, 6229]

Complete alcoholysis of 2,4,6-trihalogenopyrimidines

2,4,6-Trimethoxypyrimidine (reflux, 1 h: ~ 70%).[2110, cf. 1349, 2526]

2,4,6-Triallyloxypyrimidine (CH_2=$CHCH_2OH$, KOH, reflux, 1 h: > 90%).[3668]

2,4,6-Trimethoxy-5-nitropyrimidine (25°, 30 min: 66%).[3691]

2,4,6-Trichloro-5-di(β-chloroethyl)aminopyrimidine.[4876]

Also other examples.[1228, 1771, 2939, 5078]

Phenolysis

2-Phenoxypyrimidine (PhOH, K_2CO_3, 155°, 15 min: < 20%;[2930] PhOH, K_2CO_3, PhMe, reflux, 10 h: 82%[5079]).

4-Methyl-6-phenoxypyrimidine (PhOH, NaOEt, reflux, 30 min: 77%).[2585]

2-*p*-Tolyloxypyrimidine (neat, K_2CO_3, 175°, 1 h: ~ 75%).[1879]

4-(2′,4′-Dichlorophenoxy)-6-phenyl-2-pyrimidinamine (neat, KOH, 85°, 36 h: 77%).[4913]

2,4-Diphenoxypyrimidine (neat, K_2CO_3, 120°, 30 min: 95%).[5081]

4-Chloro-6-phenoxy-2-pyrimidinamine (PhONa, PhMe, reflux, 2.5 h: 60%)[3885] or 4,6-diphenoxy-2-pyrimidinamine (neat, K_2CO_3, 150°, 30 min: 62%).[5082]

5-Nitro-2,4-diphenoxypyrimidine (PhONa, xylene, 95°, 4 h: 83%).[1639]

2,4,6-Triphenoxypyrimidine (PhOH, KOH, 215°, 20 min: > 90%).[5083]

Also other examples.[1462, 1556, 1874, 2127, 2331, 4130, 5010, 5080, 6214]

6.7.5. Hydrolysis of 2- or 4/6-Halogenopyrimidines

The direct hydrolysis of 2- or 4/6-halogenopyrimidines to the corresponding pyrimidinones is usually possible by warming in acidic or alkaline aqueous media; moreover, selective hydrolysis of di- or trihalogenopyrimidines can usually be achieved, especially under alkaline conditions where the initial product forms an anion that tends to stabilize the remaining halogeno substituent(s). The choice of a medium is sometimes influenced by any incidental groups present: for example, alkoxy or alkylthio groups appear to survive better in alkali than in acid. The following examples illustrate the conditions required for such hydrolyses.

Acidic hydrolysis of monohalogeno substrates

2-Chloro-5-trifluoromethylpyrimidine to 5-trifluoromethyl-2(1*H*)-pyrimidinone (10*M* HCl, 50°, 40 min: 83%).[117]

2-Chloro-4-pyrimidinamine to 4-amino-2(1*H*)-pyrimidinone (H_2O, 140°, 2 h, sealed: 85%;[1675] 10*M* HCl, 100°, 2 h: ~ 80%[1664]).

4-Chloro-2-methyl-6-methylamino-5-nitropyrimidine to 2-methyl-6-methylamino-5-nitro-4(3*H*)-pyrimidinone (10*M* HCl, reflux, 15 min: ~55%).[1380]

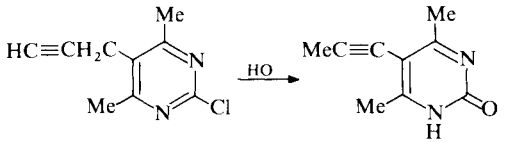
2-Chloro-5-fluoro-4-pyrimidinamine to 4-amino-5-fluoro-2(1*H*)-pyrimidinone (10*M* HCl, 95°, 2 h: 96%).[621]

6-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione to 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (*M* HCl, 100°, 30 min: 69%);[3174] kinetics.[407]

Also other examples.[1267,4999,5065]

Alkaline hydrolysis of monohalogeno substrates

2-Chloro-4,6-dimethyl-5-prop-2′-ynylpyrimidine (**216**) to 4,6-dimethyl-5-prop-1′-ynyl-2(1*H*)-pyrimidinone (**217**) (*M* NaOH, 100°, 2 h: 55%; note prototropic change in the 5-group).[843]



216 **217**

4-Chloro-5-fluoro-6-methyl-2-methylthiopyrimidine to 5-fluoro-6-methyl-2-methylthio-4(3*H*)pyrimidinone (*M* NaOH, reflux, 1 h: 31%).[2160]

4-Amino-6-chloro-1-methyl-2(1*H*)-pyrimidinone to 6-amino-3-methyl-2,4-(1*H*,3*H*)-pyrimidinedione (0.5*M* NaOH, reflux, 15 min: ~ 65%).[1015]

4-Ethoxy-6-fluoro-2-pyrimidinamine to 2-amino-6-ethoxy-4(3*H*)-pyrimidinone (*M* NaOH, reflux, 30 min: 86%).[1040]

2-Chloro-4-methylamino-5-nitropyrimidine to 4-methylamino-5-nitro-2(1*H*)-pyrimidinone (*M* NaOH, 95°, 1 h: 47%).[1586]

Also other examples.[2163,3398,5021,5084]

Selective acidic hydrolysis

4,6-Dichloropyrimidine to 6-chloro-4(3*H*)-pyrimidinone (3*M* HCl, 95°, 1 h: ~60%).[968]

4,6-Dichloro-2-methylpyrimidine to 6-chloro-2-methyl-4(3*H*)-pyrimidinone ($BuOH–H_2O$–HCl, reflux, 3 h: 60%).[2284, cf. 1159,1817]

5-Amino-4,6-dichloro-2-methylpyrimidine to 5-amino-6-chloro-2-methyl-4(3*H*)-pyrimidinone (6*M* HCl, reflux, 1 h: ~55%).[1016]

5-Amino-4,6-dichloropyrimidine to 5-amino-6-chloro-4(3*H*)-pyrimidinone (98% HCO_2H, reflux, 90 min: ~ 70% as hydrochloride;[607] 6*M* HCl, 95°, 30 min: 51%)[1017, cf. 1047]

2,4-Dichloro-6-methyl-5-nitropyrimidine to 2-chloro-6-methyl-5-nitro-4(3*H*)-pyrimidinone ($EtOH–H_2O$–AcOH–AcONa, 15°, 90 min: ~55% as hydrochloride).[2135]

2,4-Dichloro-6-ethylpyrimidine to 6-ethyl-4(3*H*)-pyrimidinone (HI, red P, reflux, 15 min: ~80%; note reductive removal of 2-chloro substituent).[2150]

2,4,5,6-Tetrafluoropyrimidine to 2,5,6-trifluoro-4(3*H*)-pyrimidinone (THF–H_2O, 25°, 2 h: 31%).[1727]

2,4-Dichloro-6-phenylpyrimidine to 6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (10*M* HCl, 160°, sealed).[5085]

Also other examples.[363,710,1135,1509,1517,1832,2118,2149,2237,2281]

Selective alkaline hydrolysis

4,6-Dibromo-2-ethylpyrimidine to 6-bromo-2-ethyl-4(3*H*)-pyrimidinone (1.3*M* NaOH, reflux, 12 h: < 50%).[1243]

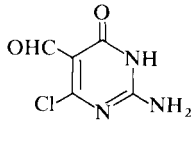
4,6-Dichloro-2-propylpyrimidine to 6-chloro-2-propyl-4(3*H*)-pyrimidinone (1.5*M* NaOH, reflux, 48 h: 72%).[1456]

2,4-Dichloro-5-fluoropyrimidine to 2-chloro-5-fluoro-4(3*H*)-pyrimidinone (2*M* NaOH, 45°, 1 h: 85–89%).[473,1260,2169]

4,6-Dichloro-5-phenoxypyrimidine to 6-chloro-5-phenoxy-4(3*H*)-pyrimidinone (1.25*M* NaOH + dioxane, 95°, 2 h: ~ 70%).[1832]

4,6-Dichloro-5-nitropyrimidine to 6-chloro-5-nitro-4(3*H*)-pyrimidinone (H_2O, Na_2CO_3, 40°, 5 h: 56%).[1832]

2-Amino-4,6-dichloro- to 2-amino-4-chloro-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde (**218**) (H_2O–NaOH–NEt_3, reflux, 90 min: 86%).[1026]



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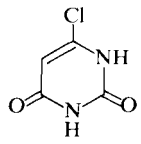

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2,4,6-Trifluoropyrimidine to 4,6-difluoro-2(1*H*)-pyrimidinone (H_2O–AcMe, KOH, 30°, briefly: 72%; structure authenticated) or 6-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (2.5*M* KOH, 80°, 1 h: 55%).[2454]

The catalytic effect of hydrogen peroxide on alkaline hydrolysis (hydroperoxy ion participation) is evident in the following examples.

2,4-Dichloro-6-methylpyrimidine to 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (*M* NaOH, H_2O_2, 20°, 5 min: 60%; cf. *M* NaOH, 20°, 24 h: 68%).[1045]

2,4,6-Trichloropyrimidine to 6-chloro-2,4(1*H*,3*H*)-pyrimidinedione (**219**) (*M* NaOH, H_2O_2, 20°, 5 min: 70%;[1045] cf. *M* NaOH, 20°, 24 h: 70%;[1045] and 2.5*M* KOH, 95°, 1 h: 82%[1021]).

Also other examples.[422,732,1159,1680,2186]

6.7.6. Alkanethiolysis of 2- or 4/6-Halogenopyrimidines

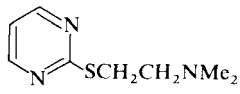
Although the preferred route to alkylthiopyrimidines is by *S*-alkylation of the corresponding pyrimidinethiones, both alkylthio- and arylthiopyrimidines may be made by treating halogenopyrimidines with alkanethiolate or arenethiolate ion, as appropriate, usually in an aqueous or alcoholic medium; reagents such as phenyl tributyltin sulfide may also be used effectively.[6851] Selective alkanethiolysis of di- or trihalogenopyrimidines is possible and often useful. This route to thioethers is illustrated in the formation of the following products, in each case from the corresponding chloropyrimidine unless indicated otherwise.

Simple alkanethiolysis

4-Methyl-6-methylthiopyrimidine (MeSNa, H_2O–EtOH, reflux, 3 h: ~90%).[2249]

2-Octadecylthiopyrimidine ($C_{18}H_{37}SNa$, tetraglyme, 100°, 2.5 h: 63%).[3839]

2-β-Dimethylaminoethylthiopyrimidine (**220**) ($Me_2NCH_2CH_2SNa$, EtOH, reflux, 10 h: 90%).[342]



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2-Methylthio-5-nitro-4-pyrimidinamine (MeSNa, EtOH, reflux, 15 min: ~80%).[681]

2-Ethylthio-5-iodopyrimidine (EtSK, EtOH, 25°, 24 h: 82%).[270]

2-Benzylthio-5-trifluoromethylpyrimidine ($PhCH_2SK$, Me_2NCHO, 25°, 1 h: 81%).[117]

4-Ethylthio-5-pyrimidinecarbonitrile (EtSNa, Pr^iOH, reflux, 4 h: 61%).[1614]

4-Methoxy-6-methylthiopyrimidine (MeSNa, MeOH, reflux, 30 min: ~60%).[2600]

4-Ethoxycarbonylmethylthio-6-methoxy-5-nitropyrimidine (EtO_2CCH_2SNa, H_2O, 5°, 5 h: 55%).[5086]

2-Methylthio-4-phenylpyrimidine (MeSNa, PhMe, 160°, 10 h, sealed: 65%).[5088]

4-β-Dimethylaminoethylthio-6-methyl-2-pyridin-2′-ylpyrimidine ($Me_2NCH_2CH_2SNa$, EtOH, reflux, 90 min: 64%).[4358]

Also other examples.[303,374,401,567,846,1020,1302,1520,1832,1951,2237,3120,3763,4360,4870,5087,5089]

Selective alkanethiolysis

4-Iodo-6-methylthiopyrimidine (from 4,6-di-iodopyrimidine, MeSNa, MeOH, 30–40°, 18 h: 70%).[1784]

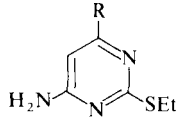
4-Carboxymethylthio-6-chloro-5-phenylpyrimidine (HO_2CCH_2SNa, EtOH, reflux, 5 h: 54%).[4362]

2-Chloro-4-ethylthio-5-fluoropyrimidine (EtSNa, dioxane, 15 h: 79%).[1267]

5-Bromo-2-chloro-4-methylthiopyrimidine (MeSK, Et_2O, −5°, 2 h: 66%).[1823]

2-Chloro-4-ethylthio-5-pyrimidinamine (EtSNa, EtOH, reflux, 15 min: ~75%).[633]

6-Chloro-2-ethylthio-4-pyrimidinamine (**221**, R = Cl) (EtSNa, MeOH, 50°, 1 h, sealed: 69%) or 2,6-bisethylthio-4-pyrimidinamine (**221**, R = SEt) (excess EtSNa, MeOH, 110°, 6 h, sealed: 78%).[2164]



221

2,4-Bisethylthio-6-methylpyrimidine (EtSNa, PhMe, reflux, 16 h: 88%).[68]

4,6-Bismethylthio-2-pyrimidinamine (MeSNa made in situ, H_2O–MeOH, reflux, 3 h: ~75%).[1780]

2,4-Bismethylthio-5-nitropyrimidine (MeSNa, MeOH, 0°, 2 h: ~75%).[804]

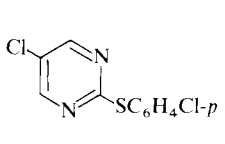
2,4,6-Tris-β-diethylaminoethylthio-5-nitropyrimidine ($Et_2NCH_2CH_2SNa$, 25°, 30 min).[5090]

Also other examples.[401,1748,1781,3740,6018]

Arenethiolysis

2-Phenylthiopyrimidine [PhSNa, EtOH, reflux, 2 h: ~60%;[1715] Bu_3SnSPh, $Pd(PPh_3)_4$, PhMe, ~100°, 24 h: 95%].[6851]

5-Chloro-2-*p*-chlorophenylthiopyrimidine (**222**) (*p*-ClC_6H_4SNa, $EtOCH_2CH_2OCH_2CH_2OH$, 120°, 4 h: 82%).[5091]



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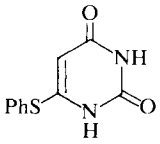

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5-Bromo-6-phenylthio-2,4-pyrimidinediamine (PhSH, NEt_3, EtOH, reflux, 2 h: ~45%).[1830]

2-Chloro-4-methyl-6-phenylthiopyrimidine (PhSH, KOH, EtOH, 0°, 2 h: 70%) or 4-methyl-2,6-bisphenylthiopyrimidine (likewise, reflux, 8 h: 82%).[5056]

Ethyl 2-methyl-4-*o*-nitrophenylthio-5-pyrimidinecarboxylate (*o*-$O_2NC_6H_4SNa$, EtOH, reflux 1 h: 73%).[2990]

6-Phenylthio-2,4(1*H*,3*H*)-pyrimidinedione (**223**) (PhSH, pyridine, reflux, 1 h: 92%;[5093] PhSNa, H_2O–$MeOCH_2CH_2OH$, reflux, 12 h: 90%[4685]).

Also other examples.[739,3120,4276,4736,5080,5088,5094,6070]

6.7.7. Thiolysis of 2- or 4/6-Halogenopyrimidines

The formation of pyrimidinethiones from the corresponding halogenopyrimidines is a valuable synthetic step that can be done directly by using reagents such as sodium hydrogen sulfide, or indirectly by the formation and subsequent alkaline degradation of a thiouroniopyrimidine. The direct route can be selective when a di- or trihalogenopyrimidine is used as a substrate; moreover, it is possible to reduce a 5-nitro group at the same time, a side reaction of considerable practical utility.

The *direct thiolytic route* is illustrated in the formation of the following pyrimidinethiones, in each case from the corresponding chloropyrimidine unless otherwise indicated.

Regular thiolysis of monohalogenopyrimidines

2(1*H*)-Pyrimidinethione (NaHS, MeOH, reflux, 30 min: 30%).[2348]

2-Amino-4(3*H*)-pyrimidinethione (NaHS, H_2O, reflux, 3 h: ~95%).[1507]

4-Dimethylamino-5-methyl-2(1*H*)-pyrimidinethione (NaHS, $EtOCH_2CH_2OH$, 135°, 30 min: 61%).[2076]

2,6-Diamino-4(3*H*)-pyrimidinethione (NaHS, H_2O–EtOH, reflux, 7 days: 74%;[1644] NaHS, $HOCH_2CH_2OH$, 140°, 1 h: ~70%[932]).

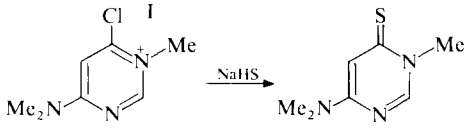
5-Amino-4(3*H*)-pyrimidinethione (KHS, H_2O, 60°, 2 h: ~80%).[1036]

6-Thioxo-5,6-dihydro-4(3*H*)-pyrimidinone (NaHS, $HOCH_2CH_2OH$, 130°, 2 h: 86%).[1666]

1,3-Dimethyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (NaHS, EtOH, 25°, 15 h: 64%).[2838]

6-Methoxy-4(3*H*)-pyrimidinethione (NaHS, EtOH, reflux, 2 h: ~50%).[3348]

6-Dimethylamino-3-methyl-4(3*H*)-pyrimidinethione (**225**) from 6-chloro-4-dimethylamino-1-methylpyrimidinium iodide (**224**) (NaHS, EtOH, reflux, 1 h: ~60%).[1507]



224 **225**

5-Bromo-2-methyl-4(3*H*)-pyrimidinethione (KHS, EtOH, reflux, 9 h: 84%).[1821]

5-Formamido-6-methylthio-4(3*H*)-pyrimidinethione (NaHS, MeOH, reflux, 30 min: 88%).[2171]

5-Amino-6-methylthio-4(3*H*)-pyrimidinethione (P_2S_5, pyridine, 95°, 2 h: 76%; mechanism unclear).[1565]

4-(*N*-Benzyl-*N*-methylamino)-6-methyl-5-nitro-2(1*H*)-pyrimidinethione (1 mol of NaHS, EtOH, 70°, 5 min: > 90%).[1157]

2-Amino-5-*p*-chlorophenylazo-6-*β*-hydroxyethylamino-4(3*H*)-pyrimidinethione (NaHS, EtOH, reflux, 20 h: 78%).[4827]

Also other examples.[802,850,958,1015,1135,1162,1215,1414,1509,1568,1874,2071,2129,2186,2237,2263,2321,2614,2940,2973,3134,3148]

Selective or complete thiolysis of di- or trihalogenopyrimidines

5-Amino-6-chloro-4(3*H*)-pyrimidinethione (1 mol KHS, H_2O–EtOH, 60°, 3 h: ~85%).[1036]

5-Amino-2-chloro-4(3*H*)-pyrimidinethione (1 mol KHS, H_2O–EtOH, 60°, 2 h; ~70%).[633]

2-Chloro-6-methyl-5-nitro-4(3*H*)-pyrimidinethione (Na_2S, H_2O–dioxane, 15°, 1 h: isolated after *S*-methylation in ~55% yield).[1157]

2,4 (1*H*,3*H*)-Pyrimidinedithione (NaHS, EtOH, reflux, 5 h: 48%).[3507,cf. 3148]

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrithione (KHS, EtOH, allowed to cool: ~55%).[1349]

2-Trifluoromethyl-4,6(1*H*,5*H*)-pyrimidinedithione (KHS, H_2O–MeOH, reflux, 30 min: 87%).[4090]

2,4(1*H*,3*H*)-Pyrimidinediselone (NaHSe, EtOH, reflux, 3 h: 31%).[3507]

5-Methyl-2,4 (1*H*,3*H*)-pyrimidinediselone (likewise: 49%).[1506]

Also other examples.[312,1035,6733]

Thiolysis with major side reactions

4,5-Diamino-2(1*H*)-pyrimidinethione from 2-chloro-5-nitro-4-pyrimidinamine (NaHS, H_2O, 90–95°, 2 h: 42%).[2295,2442]

5,6-Diamino-4(3*H*)-pyrimidinethione from 6-chloro-5-nitro-4-pyrimidinamine (NaHS, H_2O, reflux, 90 min: 80%).[2413]

5,6-Diamino-2-butyl-4(3*H*)-pyrimidinethione from 2-butyl-6-chloro-5-nitro-4-pyrimidinamine (NaHS, H_2O, 95°, 90 min: ~65%).[1981]

5-Amino-4-methyl-6-methylamino-2(1*H*)-pyrimidinethione from 2-chloro-4-methyl-6-methylamino-5-nitropyrimidine (NaHS, H_2O, 95°, 90 min: 78%).[1400,1401]

5-Amino-3-methyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione from 6-chloro-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (NaHS, H_2O, reflux, 3 h).[1047]

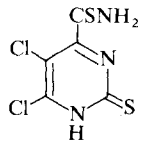
5-Amino-2,4(1*H*,3*H*)-pyrimidinedithione from 2,4-dichloro-5-nitropyrimidine (NaHS, H_2O–EtOH, reflux, 2 h: ~80%).[711]

5-Amino-2-methyl-4,6(1*H*,5*H*)-pyrimidinedithione from 4,6-dichloro-2-methyl-5-nitropyrimidine (NaHS, H_2O, 95°, 2 h: 95%).[676]

2,4(1*H*,3*H*)-Pyrimidinedithione from 4-chloro-2-methylthiopyrimidine (NaHS, $HOCH_2CH_2OH$, 150°, 30 min: ~70%).[958]

2,6-Dithioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid from methyl 6-chloro-2-methylthio-4-pyrimidinecarboxylate (NaHS, $HOCH_2CH_2OH$, 130°, 30 min: 69%).[1030]

5,6-Dichloro-2-thioxo-1,2-dihydro-4-pyrimidinecarbothioamide (**226**) (~80%) or 5-chloro-2,6-dithioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**227**) (~60%) from 2,5,6-trichloro-4-pyrimidinecarbonitrile (NaHS, H_2O, at 20° or 95° respectively).[2046]



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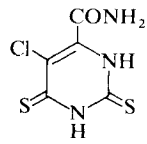

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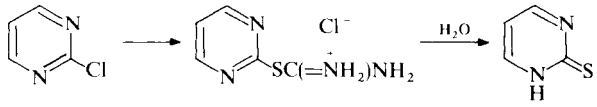
5-Amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedithione from 2-chloro-4-ethylamino-6-methyl-5-nitropyrimidine (NaHS, H_2O, 95°, 1 h: ~90%).[1191]

Also other examples.[1379,1382,1565,2435,4755,5019]

The *indirect thiolytic route* through a thiouronio intermediate is usually easier and frequently more effective than the foregoing direct metatheses; moreover, it induces no reductive side reactions. However, it offers no selectivity with di- or trihalogeno substrates, and it has been reported to fail completely in certain instances. The usual procedure is to heat the halogeno substrate e.g., (**228**) with alcoholic or acetonic thiourea to form the thiouronio intermediate (**229**) which may undergo spontaneous degradation on continued heating to afford the pyrimidinethione (**230**); alternatively, the reaction mixture or isolated intermediate may require cold or even hot alkaline treatment to furnish the pyrimidinethione. These possibilities are illustrated in the formation of the following products from the corresponding chloropyrimidines.



228 **229** **230**

With spontaneous degradation of intermediate

2(1*H*)-Pyrimidinethione (**230**) (EtOH, reflux, 11 h: 50–55%).[2321,5095]

4(3*H*)-Pyrimidinethione (EtOH, reflux, 2 h: 70%).[2321]

6-Methyl-4(3*H*)-pyrimidinethione (EtOH, reflux, 1 h: ~45%).[2249]

4-Amino-6-methyl-5-nitro-2(1*H*)-pyrimidinethione (EtOH, reflux, 30 min: >95%).[1428]

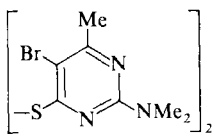
6-Methylamino-4(3*H*)-pyrimidinethione (PrOH, reflux, 4 h: ~20%).[2115]

6-Methyl-2-pyridin-2′-yl-4(3*H*)-pyrimidinethione (EtOH, reflux, 20 h: 74%).[4121]

5-Dimethylamino-2,4(1*H*,3*H*)-pyrimidinedithione (EtOH, reflux, 2 h: 82%).[2473]

2,6-Dithioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (EtOH, reflux, 3 h: 40%).[1030]

Bis(5-bromo-2-dimethylamino-6-methylpyrimidin-4-yl) disulfide (**231**) from



231

5-bromo-4-chloro-2-dimethylamino-6-methylpyrimidine (thiourea, EtOH, reflux, 6 h: 35%).[1745]

Also other examples.[3474,4870,6009]

With alkaline degradation of intermediate

4,6-Dimethyl-2(1*H*)-pyrimidinethione (EtOH, reflux, 6 h: intermediate; *M* NaOH, reflux, 45 min: ~40% overall).[2321]

5-Allyl-2,6-dimethyl-4(3*H*)-pyrimidinethione (AcMe, reflux, 2 h; EtONa, EtOH, reflux, 3 h: ~85% overall).[878]

5-Bromo-4(3*H*)-pyrimidinethione (EtOH, reflux, 10 min: intermediate; *M* NaOH, 60°, 5 min: > 80% overall).[1951, cf. 1899]

5-Nitro-2(1*H*)-pyrimidinethione (EtOH, reflux, 1 min: intermediate; *M* NaOH, 50°, 1 min: > 80% overall).[1951]

4-Methylthio-2(1*H*)-pyrimidinethione (EtOH, reflux, 1 h: intermediate; *M* NaOH, 25°, 1 min: > 70% overall).[2288]

5-Benzyl-6-methyl-2-phenyl-4(3*H*)-pyrimidinethione (EtOH, reflux, 3 h, then KOH: 83%).[4883]

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione (EtOH, reflux, 1 h: intermediate; *M* NaOH, reflux, 1 h: 76% overall).[1427]

5-Bromo-4,6(1*H*,5*H*)-pyrimidinedithione (EtOH, reflux, 15 min: intermediate; 2.5 *M* NaOH, reflux, 1 h: ~90% overall).[1787]

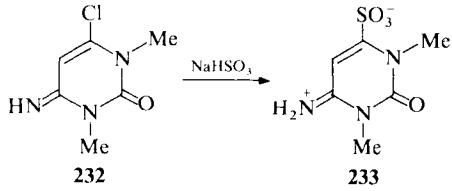
5-Nitro-2,4(1*H*,3*H*)-pyrimidinedithione (EtOH, reflux, 10 min: intermediate; *M* NaOH, 95°, 30 min: ~75% overall).[1648]

5-Nitro-4,6(1*H*,5*H*)-pyrimidinedithione (EtOH, reflux, 30 min, then NaOH).[1778]

Also other examples.[582,1011,1012,1080,1647,1782,1855,3988,5088,5096,5097]

6.7.8. Other Replacement Reactions of 2- or 4/6-Halogenopyrimidines

Pyrimidinesulfonic acids may be made from activated halogenopyrimidines by treatment with sodium or potassium sulfite. Thus 4-chloro-2,6-dimethylpyrimidine with aqueous sodium sulfite under reflux for 30 min gave 2,6-dimethyl-4-pyrimidinesulfonic acid, isolated as the dihydrate of its sodium salt in > 90% yield;[2763] crude sodium 2-pyrimidinesulfonate and its 4-methyl derivative were prepared similarly,[2763] as was 6-amino-2-oxo-1,2-dihydro-4-pyrimidinesulfonic acid (~30%).[1015] 4-Chloro-6-imino-1,3-dimethyl-1,6-dihydro-2(3*H*)-pyrimidinone (**232**) with aqueous sodium hydrogen sulfite at 25° for 30 min gave 6-imino-1,3-dimethyl-2-oxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid (> 95%), which proved easy to isolate as such because it existed as the relatively insoluble zwitterion (**233**).[1162] The less activated substrate, 6-chloro-2,4-pyrimidinediamine, required sodium sulfite in an autoclave at 145° for 25 h to afford sodium 2,6-diamino-4-pyrimidinesulfonate in reasonable



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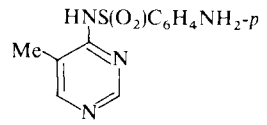
yield.[2331] 2,4,6-Trichloro-5-nitropyrimidine with sodium sulfite in aqueous dioxane at 20° for 8 h gave sodium 2,4,5,6-pyrimidinetetrasulfonate (16%) (note replacement of NO_2).[120] Especially for making simple pyrimidinesulfonates, freshly prepared potassium sulfite dihydrate[2263] proved superior to sodium sulfite. Thus 4-chloro-2,6-dimethylpyrimidine was boiled for 20 min in an equimolar aqueous solution of potassium sulfite, and the dry residue from evaporation was extracted with methanol to yield pure potassium 2,6-dimethyl-4-pyrimidinesulfonate (>70%).[2263] Similar procedures gave pure potassium salts of 4,6-dimethyl-2-, 5,6-dimethyl-4-, 5,6-dimethyl-2-, and 4-methyl-2-pyrimidinesulfonic acid as well as several analogs, including potassium 2-methyl-4-pyrimidinesulfonate, contaminated with a little potassium chloride from which they could not be purified.[2263] These latter products were subsequently prepared in a pure state by the oxidation of appropriate pyrimidinethiones with potassium permanganate[1711] (see Section 8.1.3.5).

Benzenesulfonamidopyrimidines for potential drug use are usually made by primary syntheses or acylation of pyrimidinamines (see Section 9.1.6.3), but they may also be prepared by treatment of appropriate halogenopyrimidines with sodiosulfanilamide or a related reagent. For instance, 4-chloro-5-methylpyrimidine and sodiosulfanilamide in dimethyl sulfoxide at 90° for 1 h gave 5-methyl-4-sulfanilamidopyrimidine (**234**) (> 60%);[1362] 4-chloro-6-methoxypyrimidine and sulfanilamide in acetamide containing potassium carbonate at 160° for 20 min gave 4-methoxy-6-sulfanilamidopyrimidine (25%) accompanied by other separable products;[2600] 2,4,5-trichloropyrimidine and sodio-*p*-acetamidobenzenesulfonamide in dimethylformamide at 25° for 15 h gave 4-*p*-acetamidobenzenesulfonamido-2,5-dichloropyrimidine (61%);[2209] and many other examples have been reported.[1616,1655,2109,2310,2485,4737,4979]



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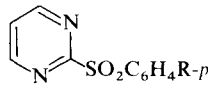
Phenylsulfonylpyrimidines have been made occasionally by treatment of a halogenopyrimidine with sodium benzenesulfinate or a related compound. Examples include the reaction of 2-chloropyrimidine with sodium benzenesulfinate in dimethyl sulfoxide at 95° for 4 h to give 2-phenylsulfonylpyrimidine

(**235**, R = H) (~50%);[1715] of 2-bromopyrimidine with sodium *p*-acetamidobenzenesulfinate in refluxing dimethylformamide for 3 h to give 2-*p*-acetamidophenylsulfonylpyrimidine (**235**, R = NHAc) (37%);[5098] and of 4-chloro-2,6-dimethoxypyrimidine with potassium benzenesulfinate in ethylene glycol at 140° for 5 h to give 2,4-dimethoxy-6-phenylsulfonylpyrimidine (35%).[3120] Yields are usually better by oxidation of the corresponding phenylthipyrimidines. Other examples have been reported.[1897,5727]



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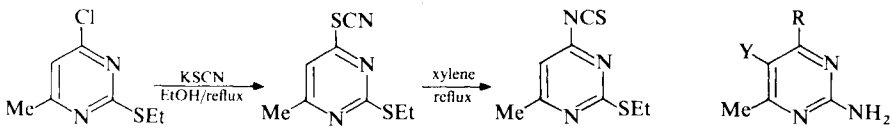
Thiocyanatopyrimidines may be made by warming halogenopyrimidines with potassium thiocyanate, but if the temperature is too high, subsequent isomerization to the isothiocyanatopyrimidines may occur. For example, 4-chloro-2-ethylthio-6-methylpyrimidine (**236**) and potassium thiocyanate in ethanol under reflux for 1 h gave 2-ethylthio-4-methyl-6-thiocyanatopyrimidine (**237**) (81%), which, in refluxing xylene for 8 h, isomerized into 2-ethylthio-4-isothiocyanato-6-methylpyrimidine (**238**) (67%).[3128] Quite similar procedures with potassium thiocyanate afforded 2-ethylthio-4-thiocyanatopyrimidine;[1886] a variety of its alkyl or aryl derivatives;[1886,2140,2157,5057,5100,5101] 5-carboxymethyl-,[1995] 5-ethoxy-,[2365] or 5-bromo-2-ethylthio-4-thiocyanatopyrimidine;[1886] and ethyl 2-ethylthio-4-thiocyanato-5-pyrimidinecarboxylate[3016] as well as some of the isomeric isothiocyanatopyrimidines. Some such isomeric products were made by simply prolonging the initial reaction or by performing it in a high-boiling solvent such as toluene.[969,1886] Although 4-chloro-6-methyl-2-pyrimidinamine (**239**, R = Cl, Y = H) failed to react with potassium thiocyanate even in refluxing xylene for 6 h,[3137] 4-chloro-5,6-dimethyl-2-pyrimidinamine (**239**, R = Cl, Y = Me) did give 4,5-dimethyl-6-thiocyanato-2-pyrimidinamine (**239**, R = SCN, Y = Me) (~50%) by essentially the same procedure.[2982] 2-Chloropyrimidine with ammonium thiocyanate gave 2-thiocyanatopyrimidine (25%),[2982] but 2-bromopyrimidine with potassium thiocyanate in refluxing dimethylformamide gave the same product in 41% yield.[3290] Selective replacement in dihalogeno substrates is clearly possible: 2,4-dichloropyrimidine with potassium thiocyanate in refluxing ethanol for 90 min gave 2-chloro-4-thiocyanatopyrimidine (40%),[2188] while 2,4-dichloro-5-nitropyrimidine with the



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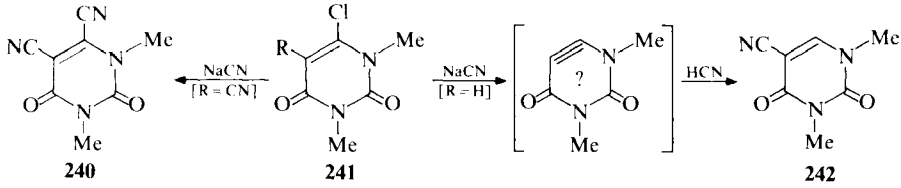
same reagent in glacial acetic acid at 10° for 15 min gave 2-chloro-5-nitro-4-thiocyanatopyrimidine (~80%).[1187]

The formation of ethyl 2-ethylthio-4-isocyanato-5-pyrimidinecarboxylate from the corresponding 4-chloro substrate (with potassium cyanate in refluxing benzene for 4 h) has been inferred by treatment with ammonia to give the 4-ureido analog.[3024]

Pyrimidinecarbonitriles are notoriously difficult to make by the reaction of halogenopyrimidines with cyanide ion. However, an occasional successful example has been reported: 4-iodo-2-methylthiopyrimidine with cuprous cyanide in refluxing pyridine for 4 h gave 2-methylthio-4-pyrimidinecarbonitrile (54%),[3043] 4-chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**241**, R = CN) with sodium cyanide in dimethyl sulfoxide at 25° for 3 h gave 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4,5-pyrimidinedicarbonitrile (**240**) (43%),[1987] but 6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**241**, R = H) with sodium cyanide in dimethyl sulfoxide at 120° for 15 min unexpectedly afforded 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**242**) (73%), probably via an initial dehydrochlorination of the substrate.[2670]



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(*Substituted-alkyl*)*pyrimidines* and related unsaturated products may be made from halogenopyrimidines in much the same ways as were their unsubstituted analogs (Section 4.2.1.6): a high proportion of reported examples have employed chloropyrimidines with carbanionic reagents. These and other replacements are illustrated in the following transformations (the predominant tautomeric form of some of the products may differ from that given[35]).

4-Chloro- to 4-di(methoxycarbonyl)methyl- [$(MeO_2C)_2CH_2$, NaOH, H_2O–AcMe, 25°, 1 h: 77%] and 4-(α-cyano-α-ethoxycarbonylmethyl)-6-methyl-5-nitro-2-pyrimidinamine (EtO_2CCH_2CN, NaOEt, EtOH, reflux, 10 min: 86%).[4939,5103]

4,6-Dichloro- (**244**, R = Me) to 4-chloro-6-di(ethoxycarbonyl)methyl-2-methyl-5-nitropyrimidine (**243**) [$(EtO_2C)_2CH_2$, 11*M* NaOH, light petroleum, 30°, 20 min: > 80%].[1157]

4,6-Dichloro-5-nitropyrimidine (**244**, R = H) to 4,6-dichloro-2-di(ethoxycarbonyl)methyl-5-pyrimidinamine (**245**) [$(EtO_2C)_2CH_2$, NaOH, H_2O, 30°, 15 min: ~40%; abnormal result by an initial attack at the electron-depleted 2-position by malonate anion with concomitant reduction by a logical mechanism].[1016,1157]

5-Bromo-2-fluoropyrimidine to 5-bromo-2-di(ethoxycarbonyl)methylpyrimidine [$(EtO_2C)CHK$, MeCN, 18-crown-6 ether, reflux, 10 h: 22%].[1749]

4-Chloro- to 4-dicyanomethyl-2,6-diphenylpyrimidine [$(CN)_2CH_2$, NaH, Me_2SO, 80°, 3 h: 67%].[5105]

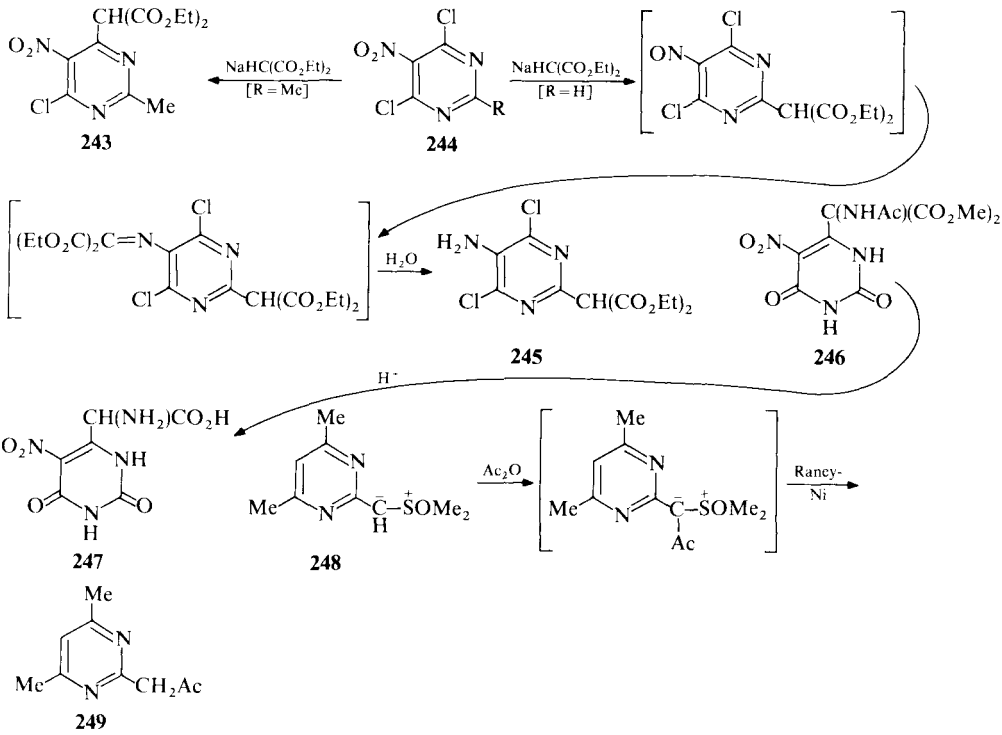
6-Chloro- to 6-(α-acetamido-α,α-dimethoxycarbonylmethyl)- (**246**) [$AcHNCH(CO_2Me)_2$, NaOMe, MeOH, reflux, 3 h: crude] and thence to 6-(α-amino-α-carboxymethyl)-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**247**) (HCl, reflux, 6 h: 74% overall).[1233]

4,6-Dichloro- to 4-chloro-6-β,β-diethoxyvinyl-5-nitropyrimidine [$(EtO)_2C{=}CH_2$, Et_2O, reflux, 4 h: 47%][5099] and 4-chloro-5-nitro-6-(α-phenyl-β-pyrrolidinovinyl)pyrimidine (β-pyrrolidinostyrene, NEt_3, CH_2Cl_2, 25°, 1 h: 41%).[5106]

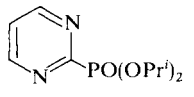
2-Iodo- to 2-(3′-hydroxyprop-1′-ynyl)-4,6-dimethylpyrimidine [$HC{\equiv}C\text{-}CH_2OH$, NEt_3, $Pd(PPh_3)_2Cl_2$, CuI, 25°, 3–4 h: 56%].[2724]

2-Chloro-4,6-dimethylpyrimidine to dimethyloxosulfonium 4,6-dimethylpyrimidin-2-ylmethylide (**248**) ($H_2\bar{C}\text{–}\overset{+}{S}OMe_2$, THF, reflux, 5 h: 70%) and thence by *C*-acylation and Raney-nickel desulfurization to products such as 2-acetonyl-4,6-dimethylpyrimidine (**249**).[737,738]

Also others.[25,356,372,739,1431,3987,4755,5102,5104,5107]



Pyrimidinephosphonic esters may be made from halogenopyrimidines with trialkyl phosphites,[1936] despite unpromising earlier reports.[3140,5108] Thus 2-chloropyrimidine with neat triisopropyl phosphite under reflux for 13 h afforded diisopropyl 2-pyrimidinephosphonate (**250**) (72%) with loss of isopropyl chloride; 2,4-dichloropyrimidine with limited triisopropyl phosphite at 170° for 20 min gave diisopropyl 2-chloro-4-pyrimidinephosphonate (71%); and 2-chloro-4,6-dimethylpyrimidine with diethyl sodium phosphite in refluxing toluene for 9 h gave diethyl 4,6-dimethyl-2-pyrimidinephosphonate (28%).[1936]



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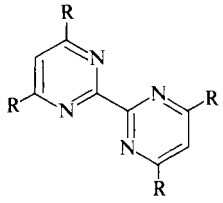

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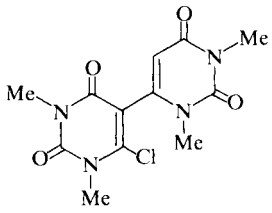

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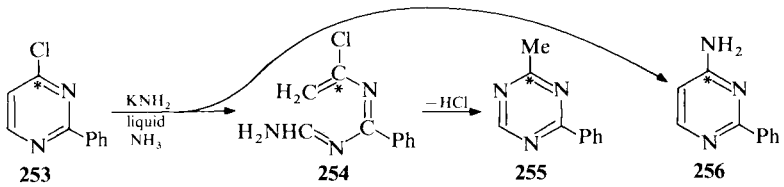
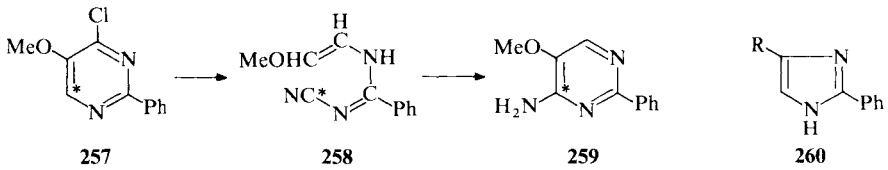
Bipyrimidines can be made from halogenopyrimidines under Ullmann or Busch conditions. Thus 2-bromopyrimidine (but not 2-chloropyrimidine) with copper in refluxing dimethylformamide for 8 h gave 2,2′-bipyrimidine (**251**, R = H) (35%);[1967] 2-bromo-4,6-dimethylpyrimidine likewise gave 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine (**251**, R = Me) (26%);[1819] 4-iodo-2-methylthiopyrimidine with copper in refluxing dimethylformamide for 2 h gave 2,2′-bismethylthio-4,4′-bipyrimidine (15%),[1745] but a better yield of product (38%) was obtained by heating the iodo substrate with hexamethylditin and a palladium catalyst in toluene for 20 h;[3929] 4-iodo-6-methyl-2-phenylpyrimidine with copper in refluxing *p*-cymene for 2.5 h gave 6,6′-dimethyl-2,2′-diphenyl-4,4′-bipyrimidine (28%);[1856] but 2-iodo-4,6-dimethyl pyrimidine on similar treatment gave 4,6-dimethylpyrimidine as the only isolable product.[1856] The alternative (Busch) procedure is exemplified in the conversion of 4-iodo-2,6-dimethylpyrimidine into 2,2′,6,6′-tetramethyl-4,4′-bipyrimidine (22%) by refluxing for 2 h in methanolic potassium hydroxide containing hydrazine hydrate and a palladium catalyst.[1856] A much better conversion of 2-chloropyrimidine into 2, 2′-bipyrimidine ($NiCl_2$, Ph_3P, Zn, Me_2NCHO, 50°, 6 h: 60%) was also applicable to bromo and alkylated analogs.[6138] An oddball reaction occurred on treatment of 6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione with diazomethane in THF–Et_2O for 2 weeks to afford 6′-chloro-1,1′,3,3′-tetramethyl-4,5′-bipyrimidine-2,2′,4′,6(1*H*,1′*H*,3*H*,3′*H*)-tetrone (**252**) (26%), the replacement of diazomethane by a tertiary amine, for example triethylamine, produced the same product.[5109]

Ring transformations (or other peculiar reactions[1366,2072,2597]) can occur on treatment of halogenopyrimidines with apparently bland reagents. The formation of *1,3,5-triazines* is exemplified in the reaction of 4-chloro-2-phenylpyrimidine (**253**) with potassium amide in liquid ammonia at − 33° for 2 h,

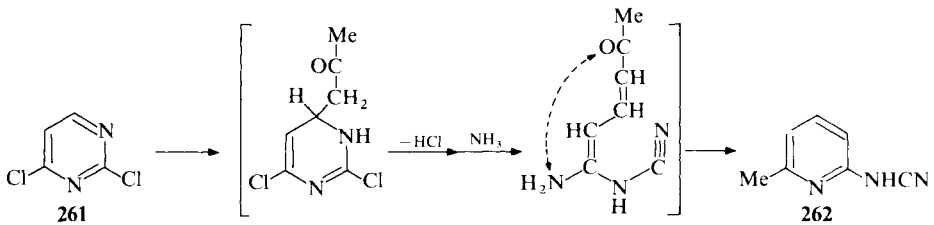


which afforded mainly 2-methyl-4-phenyl-1,3,5-triazine (**255**) and only a little 2-phenyl-4-pyrimidinamine (**256**).[2149] When a 4-^{14}C tag was introduced into the substrate (**253**), the tag appeared at the corresponding position in the triazine (**255**) suggesting that ring fission occurred at the 5,6-bond of the pyrimidine (**253**) to give the intermediate (**254**), which promptly recyclized to the triazine (**255**);[4091] the tag also appeared at C4 of the minor product (**256**), indicating that it was formed by a normal addition–elimination mechanism.[5110] Rather similarly, 4-chloro-2-ethyl- and 4-chloro-2,5-dimethylpyrimidine gave mainly 2-ethyl-4-methyl-1,3,5-triazine in each case,[2149] whereas 4-chloro-2,6-dimethylpyrimidine gave only 2,6-dimethyl-4-pyrimidinamine, demonstrating that a free 6-position is needed for the attack and fission necessary to produce a triazine.[2149] In contrast, similar treatment of C6-tagged 4-chloro-5-methoxy-2-phenylpyrimidine (**257**) gave an isolable acyclic product (**258**) that underwent thermal recyclization in boiling toluene to furnish 5-methoxy-2-phenyl-4-pyrimidinamine (**259**) bearing its amino group on the tagged carbon:[5110,5111] the mechanism of formation therefore differed from that just described for the analog (**256**).



Two interesting *imidazoles*, 2-phenyl-4-imidazolecarbonitrile (**260**, R = CN) and 4-ethynyl-2-phenylimidazole (**260**, R = C:CH), were formed by treatment of 4-chloro-2-phenyl-5-pyrimidinamine and 4-chloro-5-methyl-2-phenylpyrimidine, respectively, with an excess of sodium amide in liquid ammonia.[5111]

Treatment of 2,4-dichloropyrimidine with potassium enolates of simple ketones in liquid ammonia gave *pyridines*. For example, the substrate (**261**) with



acetone and potassium amide in liquid ammonia for 20 min gave 2-cyanoamino-6-methylpyridine (**262**) (43%), probably by the route shown.[206]

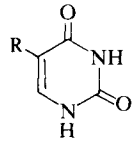
6.8. REACTIONS OF 5-HALOGENOPYRIMIDINES

Compared with 2- or 4/6-halogenopyrimidines, 5-halogenopyrimidines are markedly less reactive toward nucleophiles, simply because their halogeno substituent stands *meta* to both activating ring-nitrogen atoms. However, simple 5-halogenopyrimidines do react reasonably easily with reagents such as alkoxide or amines, and only in cases of extreme deactivation, for example, in 5-bromo-2,4-pyrimidinediamine, does the halogeno substituent assume the inert role familiar in chlorobenzene.

6.8.1. Dehalogenation of 5-Halogenopyrimidines

A 5-halogeno substituent is no more difficult to remove reductively than is a 2- or 4/6-halogeno substituent; indeed, if both types of substituent are present in the same molecule, selective removal of the activated halogen can seldom be attained by direct hydrogenolysis.[1833,3598, cf. 2212]

Hydrogenolysis, usually in the presence of a base, was used to remove a 5-halogeno substituent from the following substrates; 5-chloro-2-methyl-4-pyrimidinamine (Pd, H_2O: 37%),[1479] 5-chloro-2-phenylpyrimidine (Pd, MeOH–H_2O, NaOH: ~85%),[2212] 5-bromo-2-pyrimidinecarboxamide (Ni, EtOH–Et_2O, Na_2CO_3, 50°, 3 h: 50%),[729,1973] 5-bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (Pd, EtOH: 75%),[1860] 5-bromo-2,4-dichloro-6-methylpyrimidine (Pd, EtOH–H_2O, MgO: 43% of 4-methylpyrimidine),[1833] 1-benzyloxy-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (Pd, EtOH–H_2), 6 h: ~75%),[1265] 5-bromo-4-dimethylamino-2-methoxypyrimidine (Pd, EtOH, 10 min: 82%),[1799] and others.[1742,5127,5128] Deuterolysis of 5-bromo-2,4(1*H*,3*H*)-pyrimidinedione (**263**, R = Br) gave the 5-deutero analogue (**263**, R = D) (Pd, D_2, NaOD, D_2O, 20°, 1 h: 81%);[339] 5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (**263**, R = I) gave the same product (**263**, R = D) [$RuCl_2(Ph_3P)_3$, D_2, $AcNMe_2$, 25°: > 80%].[247]



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Other methods for 5-dehalogenation are illustrated by the formation of 5-unsubstituted pyrimidines from the following substrates.

5-Bromo-4(3*H*)-pyrimidinone (Zn, H_2O, reflux, 3 h).[1820]

5-Bromo-4-chloro-2-phenylpyrimidine (Zn, H_2O, reflux, 4 h: 46% of 2-phenylpyrimidine).[1820]

5-Bromo-2-methylthiopyrimidine (Raney-nickel, EtOH–NH_3, reflux, 2.5 h: 38% of pyrimidine).[1935]

5-Bromo-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione (neat $H_2NNH_2.H_2O$, 100°, briefly).[675]

5-Bromo-2-pyrimidinamine (Pd, H_2NNH_2, MeOH, KOH: 59%).[1856]

5-Bromo- or 5-iodo-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($HOCH_2CH_2$-OH, reflux, 8 h: 95% or ~ 75%, respectively).[3475,5112, cf. 4101]

5-Chloro-2,4(1*H*,3*H*)-pyrimidinedione (HI, 105°, 15 min: 60%).[2258]

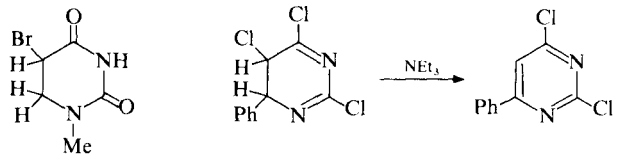
5-Iodo-1,3-dimethyl-6-phenoxy-2,4(1*H*,3*H*)-pyrimidinedione (photolysis, MeCN, 25°, 1 h: 14%).[5113]

5-Bromo-2-methylthio-4-pyrimidinecarboxylic acid (BuLi, C_6H_{14}–THF, – 90°, 90 min; then *M* HCl, 25°, 1 h: 78%).[502]

5-Bromo-2,4-bismethylthiopyrimidine (BuLi, C_6H_{14}–THF, – 60°, 10 min; then D_2O, 25°, 30 min: 92% of 5-deutero analog).[1782]

Also other examples.[76,1118,1616,1834,1935,3475,5129]

Dehydrohalogenation of 5-halogeno-5,6-dihydropyrimidines should not be overlooked. For example, 5-Bromo-1-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**264**) at 160° for a few minutes gave 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione;[1432] 4-amino-5-chloro-5,6-dihydro-2(1*H*)-pyrimidinone with triethylamine in refluxing ethanol for 15 h gave 4-amino-2(1*H*)-pyrimidinone (68%);[1006] 4-amino-5-bromo-1-phenyl-5,6-dihydro-2(1*H*)-pyrimidinone in refluxing ethanolic alkali for 2 min gave 4-amino-1-phenyl-2(1*H*)-pyrimidinone (89%);[1006] and 2,4,5-trichloro-6-phenyl-5,6-dihydropyrimidine (**265**) with triethylamine in refluxing toluene for 5 h gave 2,4-dichloro-6-phenylpyrimidine (**266**) (84%).[3821] The partial or complete dehalogenation of 5,5-dibromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione and related substrates has been exemplified in Section 6.5.1.



264 **265** **266**

6.8.2. Aminolysis of 5-Halogenopyrimidines

The conditions reported for *regular aminolyses* of 5-halogenopyrimidines vary considerably from reasonably mild to extremely vigorous. Unfortunately, such

recorded values do not necessarily reflect the true reactivities of the substrates toward the amines employed; indeed, some of the poor yields (or even outright failures[967,1932]) may well have arisen from decomposition of the products under the excessive conditions pertaining rather than from incomplete reactions. However, the following examples will give at least some idea of the temperatures and times usually considered necessary.

From simple 5-halogenopyrimidines

5-Bromo-4-methylpyrimidine to 4-methyl-5-pyrimidinamine (NH_4OH, 135°, 50 h, sealed: 75%).[1822]

5-Bromo- to 5-dimethylaminopyrimidine 1-oxide (Me_2NH, H_2O, 100°, 4 h, sealed: 20%).[1972]

5-Iodo-2,6-dimethyl- to 2,6-dimethyl-5-methylamino- ($MeNH_2$, EtOH–H_2O, reflux, 4 h: 39%), 5-dimethylamino-2,6-dimethyl- (Me_2NH, EtOH–H_2O, 25°, 2 weeks: 33%), and 2,6-dimethyl-5-trimethylammonio-4-pyrimidinamine (Me_3N, MeOH, 25°, 10 days: 71% as iodide).[1347]

2-Amino-5-bromo- to 2-amino-5-piperidino- (neat piperidine, reflux, 4 h: > 95%; morpholine likewise but butylamine failed to react)[5115] and 2-amino-5-anilino-4(3*H*)-pyrimidinone ($PhNH_2$, $HOCH_2CH_2OH$, NaOAC, reflux, 2 h: 43%).[4874]

5-Bromo- to 5-amino-2-methyl-4-pyrimidinecarboxylic acid (NH_4OH, Cu^{2+}, 100°, 2 h, sealed: 61%; no reaction without Cu^{2+}).[1479]

5-Bromo- to 5-amino-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide (NH_4OH, Cu, 100°, 3 h, sealed: 88%).[1560]

5-Bromo-2-dimethylamino-4-methoxypyrimidine to 2-dimethylamino-5-β-dimethylaminoethylamino-4(3*H*)-pyrimidinone (neat $Me_2NCH_2CH_2NH_2$, 140°, 4 h, sealed: 51%).[5114]

5-Bromo- to 5-azido-4-phenylpyrimidine 1-oxide (50%).[1710]

Also other examples.[1639,1822,2385,3877,4033,5116,5117]

From tautomeric 5-halogenopyrimidinediones

5-Bromo- to 5-methylamino- ($MeNH_2$, H_2O, 100°, 3.5 h: 71%),[1766, cf. 1125] 5-dimethylamino- (Me_2NH, H_2O, 100°, 3.5 h: 78%),[1766, cf. 1046] 5-butylamino- (neat $BuNH_2$, reflux, 2 h: > 95%),[2980] and 5-β-hydroxyethylamino-2,4(1*H*,3*H*)-pyrimidinedione ($HOCH_2CH_2NH_2$, H_2O, 160°, 5 h, sealed: 72%).[1941]

5-Bromo- to 5-anilino-2,4(1*H*,3*H*)-pyrimidinedione ($PhNH_2$, $HOCH_2CH_2OH$, reflux, 2 h: 76%).[4874]

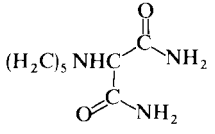
5-Bromo-6-carboxymethyl- to 6-methyl-5-morpholino-2,4(1*H*,3*H*)-pyrimidinedione (neat morpholine, reflux, 6 h: 42%; note concomitant decarboxylation).[1808]

5-Bromo-4,6(1*H*,5*H*)-pyrimidinedione to α-piperidinomalondiamide (**267**)

(neat piperidine, reflux, 2 h: ~70%; such 4,6-pyrimidinediones are unstable in base).[1981]

5-Bromo-6-ethyl- to 6-ethyl-5-piperidino-2,4(1*H*,3*H*)-pyrimidinedione (neat piperidine, KF as catalyst, 105°, 3 days: 77%).[126]

5,5-Dichloro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**268**) to 2,6-dioxo-5-pyridinio-1,2,3,6-tetrahydro-4-pyrimidinolate (**269**) (pyridine, reflux, 30 min: 89%);[81,5123] also some analogs.[81,545]



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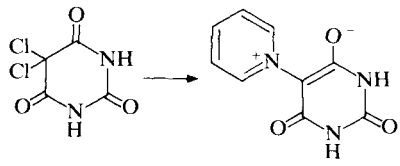


268 **269**

5-Bromo- to 5-diethylamino-5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Et_2NH, EtOH, 50°, 30 min: 36%).[5125]

6-Amino-5-bromo- to 6-amino-5-morpholino- and 6-amino-5-piperidino-2,4(1*H*,3*H*)-pyrimidinedione (neat secondary amine, reflux; primary amines behaved irregularly: see later examples).[5118,5119]

6-Amino-1-benzyl-5-bromo- to 6-amino-1-benzyl-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione ($MeNH_2$, H_2O, 25°, 15 h: 95%).[1396]

5-Bromo-6-(*p*-bromo-*N*-methylanilino)-3-methyl- to 6-*p*-bromo-*N*-methylanilino)-3-methyl-5-*p*-toluidino-2,4(1*H*,3*H*)-pyrimidinedione (*p*-toluidine, Me_2SO, 25° 4 h: 94%).[101]

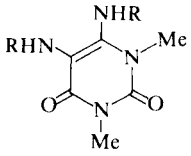
Also other examples.[579,1174,1230,1766,3219,5124,5126]

From nontautomeric pyrimidinediones

5-Bromo- to 5-allylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (neat $H_2C{=}CHCH_2NH_2$, reflux, 5 h: 70%).[854]

1-Allyl-5-bromo- to 1-allyl-5-dimethylamino-6-ethyl-3-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (Me_2NH, H_2O–Me_2NCHO, 100°, 8 h, sealed: 83%).[4172]

5,6-Dichloro- to 5,6-bis(β-hydroxyethylamino)-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**270**, R = CH_2CH_2OH) ($H_2NCH_2CH_2OH$, H_2O, 95°, 30 min: 39%).[2667]



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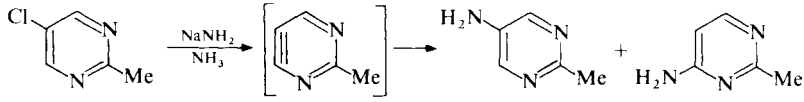
5-Bromo-1,3-dimethyl-6-methylamino- to 1,3-dimethyl-5,6-bismethylamino-2,4(1*H*,3*H*)-pyrimidinedione (**270**, R = Me) ($MeNH_2$, MeOH, reflux, 20 min: 70%).[675]

Also other examples.[1070]

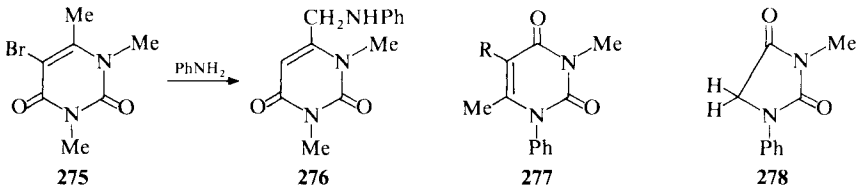
5-Halogenopyrimidines undergo several types of *irregular aminolysis* of which *cine*-substitution is the best represented. Thus 5-chloro-2-methylpyrimidine (**271**) in liquid ammonia containing sodium amide at $-33°$ for 2 h gave a mixed product in which were identified 2-methyl-5- (**273**) and 2-methyl-4-pyrimidinamine (**274**), a result consistent with a single 2-methyl-4,5-didehydropyrimidine intermediate (**272**);[5120] in this regard, it was later shown by appropriate isotopic labeling that the analogous transformation of 5-bromo-4-*t*-butylpyrimidine to 6-*t*-butyl-4-pyrimidinamine (~40%) took place to a large extent by the S_n (ANRORC) (substitution by addition of nucleophile, ring opening, ring closure) mechanism involving the initial addition of amide ion at the 2-position of the substrate.[4899, cf. 6227] Similar treatment of 5-bromo-4-phenylpyrimidine, 5-bromo-4-methoxypyrimidine, or 5-bromo-4(3*H*)-pyrimidinone afforded 6-phenyl-4-pyrimidinamine, 6-methoxy-4-pyrimidinamine, or 6-amino-4-(3*H*)-pyrimidinone, respectively, each as the sole reaction product.[1898] Such reactions also occur in organic bases that do not contain sodium amide or the like. For example, 5-chloropyrimidine and ethanolic piperidine at 130° in a bomb gave 4-piperidinopyrimidine (49%) along with other separable products, whereas 5-bromopyrimidine and neat diethylamine under similar conditions gave 4-diethylaminopyrimidine (24%) plus the isomeric 5-diethylaminopyrimidine, each identified as its picrate;[1970] 5-bromo-4(3*H*)-pyrimidinone or its 3-methyl derivative with neat piperidine under reflux for 4 h gave 6-piperidino-4(3*H*)-pyrimidinone (33%) or its 3-methyl derivative (62%), respectively, but 5-bromo-6-methyl-4(3*H*)-pyrimidinone was unaffected by piperidine under such conditions, possibly because it could not form a didehydro intermediate;[1953] and 5-bromo-1-*β*-(propylamino)ethyl-2,4(1*H*,3*H*)-pyrimidinedione with neat butylamine at 40° for 2 h gave 6-butylamino-1-*β*-(propylamino)ethyl-2,4(1*H*,3*H*)-pyrimidinedione (65%).[358]



271 **272** **273** **274**

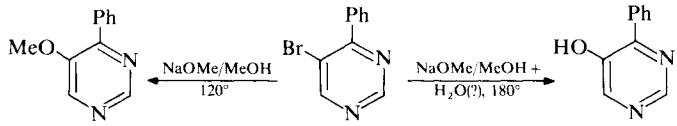
Other types of irregular aminolysis are represented by the transformations of 6-amino-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione to 6-anilino-, 6-benzylamino-, or 6-*p*-toluidino-2,4(1*H*,3*H*)-pyrimidinedione (neat primary amine under reflux; morpholine and piperidine reacted normally; see above);[5118,5119] 5-bromo-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**275**) to 6-anilinomethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione-(**276**) ($PhNH_2$, Me_2NCHO, reflux, 5 h:

85%);[762,5121,5122] the same substrate to 1,3,6-trimethyl-5-morpholino- (morpholine. Me_2NCHO, 100°, 8 h: 66%) or to 1,3-dimethyl-6-morpholinomethyl-2,4(1*H*,3*H*)-pyrimidinedione (morpholine, Me_2NCHO, 150°, 1 h: 27%);[762] and 5-bromo-3,6-dimethyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**277**, R = Br) to a separable mixture of 3,6-dimethyl-5-methylamino-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**277**, R = NHMe) and a ring-contraction product, 3-methyl-1-phenyl-1*H*-imidazole-2,4(3*H*,5*H*)-dione (**278**) ($MeNH_2$, H_2O–Me_2NCHO, 100°, 18 h, sealed: 21% and 30%, respectively).[202]



6.8.3. Other Reactions of 5-Halogenopyrimidines

Alcoholysis of 5-halogenopyrimidines is a rarely used reaction, exemplified in the transformation of 5-bromo- (**280**) to 5-methoxy-4-phenylpyrimidine (**279**) (NaOMe, MeOH, 120°, 20 h, sealed: 62%),[3743, cf 23] 5-chloro- to 5-ethoxy-2-hydroxymethyl-4,6(1*H*,5*H*)-pyrimidinedione (NaOEt, EtOH, reflux, 12 h: 80%),[1958] 5-iodo- to 5-methoxy-2,6-dimethyl-4-pyrimidinamine (NaOMe, MeOH, 25°, 10 days: 88%),[1347] and 5-bromo- to 5-methoxypyrimidine (as first example: 70%).[836]

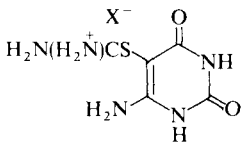


Hydrolysis of 5-halogenopyrimidinediones is not difficult, but little is known of the conditions needed for other 5-halogenopyrimidines. Thus 5-bromo- gave 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione ($NaHCO_3$, H_2O, reflux, 20 h: 50%),[3242] 5-bromo- gave 5-hydroxy-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaHCO_3$, H_2O, reflux, 12 h: 86%),[825] 5-bromo- gave 5-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaHCO_3$, H_2O, reflux, 6 h: 65%;[3242] PbO, H_2O, reflux, 1 h: 0%[3242, cf. 1860]), 3-benzyl-5-bromo- gave 3-benzyl-5-hydroxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaHCO_3$, H_2O–EtOH, CO_2, reflux, 22 h: 80%),[4912] 5-bromo- gave 5-hydroxyuridine (PbO, H_2O, 95°, 1 h: 38%),[5117,5130] but 5-bromo-4,6-dimethyl-2-pyrimidinamine gave 2-amino-4,6-dimethyl-5-pyrimidinol apparently only on heating with aqueous barium hydroxide and

copper at 180° in an autoclave.[5131] 5-Bromo-4-phenylpyrimidine (**280**) gave 4-phenyl-5-pyrimidinol (**281**) (72%) by heating with sodium methoxide in methanol (containing a little water?) at 180° for 8 h;[23] analogs likewise.[6005] A *cine*-substitution occurred when 5-bromo-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione was converted into 1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (54%) by heating in *M* sodium hydroxide at 60° for 6 h (optimal conditions);[3486] 2-*t*-butyl-4(3*H*)-pyrimidinone likewise.[3994]

Alkanethiolysis of 5-halogenopyrimidines is surprisingly well represented. Thus 5-bromo- gave 5-methylthio- (NaSMe, EtOH, reflux, 12 h: ~ 70%)[1715] or 5-ethylthiopyrimidine (NaSEt, EtOH, reflux, 4 h: 60%),[836] 2-amino-5-bromo- gave 2-amino-5-phenylthio-4(3*H*)-pyrimidinone (PhSH, K_2CO_3, $HOCH_2$-CH_2OH, 150°, 3 h),[4101] 5-chloro- or 5-bromo- gave 5-phenylthio-2,4(1*H*,3*H*)-pyrimidinedione (PhSH, K_2CO_3, $HOCH_2CH_2OH$, 140°, 2 h: 67% or only 11%, respectively),[5132] 6-amino-5-chloro- gave 6-amino-5-carboxymethylthio-3-ethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaSCH_2CO_2$-Na, H_2O, 90°, 30 min: 90%),[4581] 5-bromo- gave 5-phenylthio-2,4,6-pyrimidinetriamine (PhSH, NEt_3, BuOH, reflux, 2 days: 36%),[2176] 5-chloro-2-methylthio- gave 2-methylthio-5-phenylthio-4-pyrimidinecarboxylic acid (NaSPh, Me_2NCHO, reflux, 6 h: 82%),[2021] and other examples have been reported in the foregoing and other references.[160,491,1849,1956,2021,2358,2622,5133,7032] Some thioethers, for example, 5-carboxymethylthio-2,4,6-trimethoxypyrimidine, have been made via 5-lithio derivatives.[1788] Phenyl tributyltin sulfide with a palladium catalyst, appears to be remarkably effective.[6851]

Thiolysis of 5-halogenopyrimidines is unsatisfactory, mainly because 5-pyrimidinethiols are so prone to aerial or other oxidation to disulfides or sulfides. Thus attempted direct thiolysis of 5-bromo-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione by stirring with sodium hydrogen sulfide in dimethyl sulfoxide at 25° for 3 days gave only bis(1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) disulfide (54%);[3452] likewise, 2,6-diamino-5-bromo-4(3*H*)-pyrimidinone with aqueous sodium hydrogen sulfide gave a separable mixture of bis(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl) sulfide and disulfide.[2387] An indirect approach via a thiouronio intermediate has been successful occasionally. Thus 6-amino-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione with aqueous thiourea under reflux for 2 h gave 6-amino-5-thiouronio-2,4(1*H*,3*H*)-pyrimidinedione, characterized as its chloride (**282**, X = Cl) but isolated in bulk as the hydroxide (**282**, X = OH) (~25%); the latter underwent degradation by boiling for 5 min in deaerated aqueous alkali to afford 6-amino-5-mercapto-2,4(1*H*,3*H*)-



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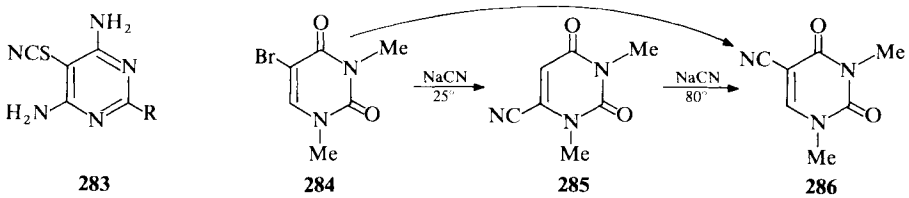
pyrimidinedione (~70%), but when the degradation was performed by boiling in regular aqueous sodium hydrogen carbonate for 1 h, only bis(4-amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) disulfide (~20%) was isolated.[837] Broadly similar treatment of 2,6-diamino-5-bromo- gave 2,6-diamino-5-thiouronio-4(3*H*)-pyrimidinone bromide, but alkaline degradation thereof under a variety of conditions gave only bis(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl) disulfide or sulfide.[2387] Other such results have been reported.[956,964,3321,5134,5135]

5-Thiocyanatopyrimidines can be made easily from their 5-halogeno analogs. For example, appropriate 5-bromopyrimidines afforded 5-thiocyanato-4,6-pyrimidinediamine (**283**, R = H) (KSCN, MeOH–HBr, 5°, 20 min: 42%),[837] 5-thiocyanato-2,4,6-pyrimidinetriamine (**283**, R = NH_2) (KSCN, EtOH–AcOH, reflux, 30 min: 72%),[837] 2,6-diamino-5-thiocyanato-4(3*H*)-pyrimidinone (KSCN, H_2O, reflux, 1 h: ~80%; KSCN, Me_2NCHO, 80°, 50 min ~90%),[2387] and 5-thiocyanato-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione.[3320]

5-Pyrimidinecarbonitriles may be made from their 5-halogeno analogs under vigorous conditions. Thus heating appropriate 5-bromopyrimidines with cuprous cyanide in refluxing quinoline for the stated times gave 5-pyrimidinecarbonitrile (40 min: 66%),[3290] 2-amino-5-pyrimidinecarbonitrile (40 min: 40%),[1616] 2-benzenesulfonamido-5-pyrimidinecarbonitrile (10 min: 63%),[1616] 2-methylamino-5-pyrimidinecarbonitrile (40 min: 42%),[1346] 4-oxo-6-phenyl-3,4-dihydro-5-pyrimidinecarbonitrile (45 min: 84%),[4886] and others.[923,960,1465] In a different way, bromo analogs afforded 2-butylamino- (~75%) and 2-dimethylamino-5-pyrimidinecarbonitrile (~60%) by irradiation in *t*-butanolic potassium cyanide.[5136] Cases of *cine*-substitution have been reported: when stirred with sodium cyanide (1 mol) in dimethylformamide at 25°, 5-bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**284**) gave 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**285**) (95%), but when this product (**285**) or the original substrate (**284**) was heated with an excess of sodium cyanide at 80°, the isomeric 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (**286**) resulted in good yield; the use of hot 50% aqueous ethanol as a reaction medium gave 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (86%), presumably by hydrolysis of the nitrile (**285**).[2671] A variety of 1- and/or 3-alkylated analogs behaved similarly, and the addition–elimination mechanism was explored by deuterium-exchange experiments.[1132,1883,2671]



283 **284** **285** **286**

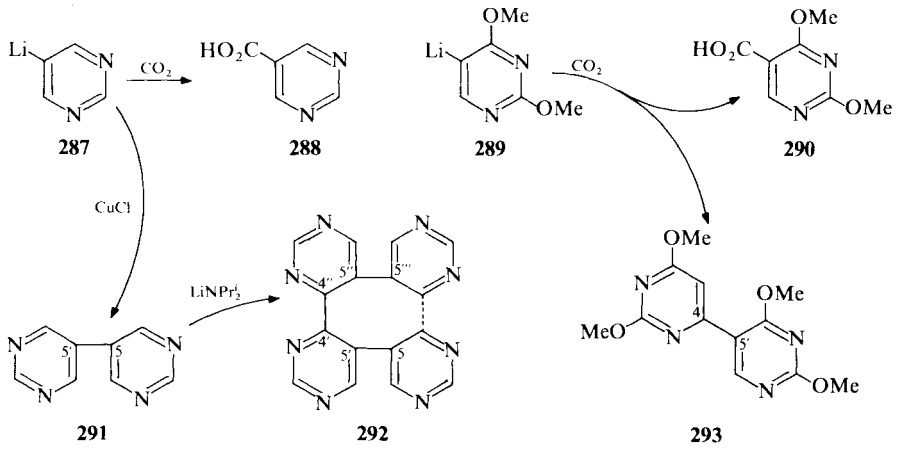
Other 5-(carbon-linked) substituents can seldom be introduced by direct replacement of 5-halogeno substituents, which are insufficiently activated to react with carbanionic reagents. However, exceptions exist,[6002] and direct procedures involving stimulation by irradiation or catalysts and other less direct procedures involving metalloorganic reagents are applicable. These are briefly illustrated in the following examples.

5-Iodopyrimidine with benzene, furan, or thiophene in acetonitrile under irradiation gave 5-phenyl- (74%), 5-furan-2′-yl- (62%), or 5-thien-2′-ylpyrimidine (58%), respectively.[2180]

5-Iodo-2-isopropyl-4-methylpyrimidine with neat ethyl acrylate, acrylonitrile, or styrene (in the presence of palladium acetate, triphenylphosphine, and triethylamine in each case) were heated in a sealed vessel (130°/1 h, 130°/ 2.5 h, or 150°/17 h, respectively) to afford 5-β-ethoxycarbonylvinyl-2-isopropyl-4-methyl- (69%), 5-β-cyanovinyl-2-isopropyl-4-methyl- (81%), or 2-isopropyl-4-methyl-5-styrylpyrimidine (59%).[2376, cf. 1890]

5-Bromopyrimidine was converted into 5-pyrimidinyl-lithium (**287**) (BuLi at − 110°) and thence into 5-pyrimidinecarboxylic acid (**288**) (solid CO_2, Et_2O: 68%).[3607]

2,4-Dimethoxy- (**290**) (75%),[788] 4,6-dimethoxy- (57%),[1788] and 4,6-bismethylthio-5-pyrimidinecarboxylic acid (25%),[1788] as well as other analogs[1788] were made likewise, but quite minor variations in conditions led to the alternative formation[1847,5114] of bipyrimidines, for example, 2,2′,4′,6-tetramethoxy-4,5′-bipyrimidine (**293**) in place of (**290**) from the substrate (**289**); see also the following paragraph.



5-Bromo-2,4,6-trimethoxypyrimidine was converted into 2,4,6-trimethoxypyrimidin-5-yl-lithium, which reacted with dimethylformamide to give 2,4,6-trimethoxy-5-pyrimidinecarbaldehyde (65%).[1788]

5-Bromo-2,4-diethoxypyrimidine gave 2,4-diethoxypyrimidin-5-yl-lithium and thence, by treatment with benzaldehyde, 2,4-diethoxy-5-α-hydroxybenzylpyrimidine (70% overall), which was readily oxidized (CrO_3–pyridine) to 5-benzoyl-2,4-diethoxypyrimidine.[5138]

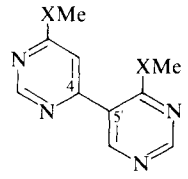
5-Bromo-2-methylthio-4-pyrimidinecarboxylic acid gave its 5-lithio analog and thence, with benzoyl chloride, 5-benzoyl-2-methylthio-4-pyrimidinecarboxylic acid (36%).[502]

5-Bromopyrimidine underwent a one-pot transformation to 5-(α,α-bis-*p*-chlorophenyl-α-hydroxymethyl)pyrimidine (*p,p'*-dichlorobenzophenone, BuLi, THF, − 95°: 55%).[304]

5-Bromo-2-methylthiopyrimidine was converted into 2-methylthio-5-tributylstannylpyrimidine (Bu_6Sn_2, Bu_4NF, Pd, THF, 25°, 4 h: 72%) and thence into 2-methylthio-5-thien-2'-ylpyrimidine [2-bromothiophene, $PdCl_2(PPh_3)_2$, THF, reflux, 10 h: 71%].[3970]

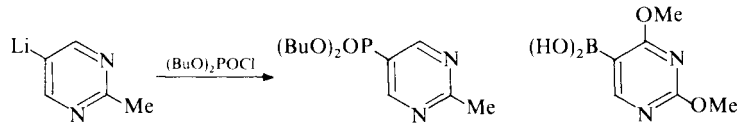
Also other examples in Sections 4.2.1.6 and 10.7.1 and elsewhere.[6004,6120]

Bipyrimidines may be made from 5-halogenopyrimidines in several ways. The Ullmann reaction converted 5-bromo-2-methylthio-4-pyrimidinecarboxylic acid into 2,2'-bismethylthio-5,5'-bipyrimidine (Cu, Me_2NCHO, reflux, 3 h: 40%; note concomitant decarboxylation) and 5-bromo-2-phenyl-4-pyrimidinecarboxylic acid into 2,2'-diphenyl-5,5'-bipyrimidine (likewise, 7 h: 70%);[1856] the last mentioned product was also made by the Busch reaction from 5-bromo-2-phenylpyrimidine (KOH, MeOH, H_2NNH_2, Pd, reflux, 2 h: 46%).[1856] Treatment of 5-bromopyrimidine with butyllithium in ether at − 90° followed by the addition of cuprous chloride to the initial product (**287**) and warming to 25° for several hours gave 5,5'-bipyrimidine (**291**) (57%), which on subsequent treatment with lithium di-isopropylamide afforded a separable mixture of 5,5': 4',4'': 5'',5'''-quarterpyrimidine (**292**) and its didehydro derivative (**292** cyclized at the dotted line).[5139] In contrast, 5-bromo-4-methoxy- or 5-bromo-4-methylthiopyrimidine with butyllithium in THF at approximately − 60° for 1 h gave 4',6-dimethoxy- (**294**, X = O) (43%) or 4',6-bismethylthio-2,5'-bipyrimidine (**294**, X = S) (56%), respectively,[1899] and other such examples have been reported.[1847,5114,5137]



294

5-Pyrimidinephosphonic and 5-pyrimidineboronic acid derivatives cannot be made directly from 5-halogenopyrimidines, but such products have been prepared via 5-lithio intermediates. Thus 5-bromo-2-methylpyrimidine with butyl-



295 296 297

lithium in ether gave a solution of 2-methylpyrimidin-5-yl-lithium (**295**), which reacted with dibutyl phosphorochloridate initially at $-40°$ to afford dibutyl 2-methyl-5-pyrimidinephosphonate (**296**) in low yield;[1936] rather similarly, 5-bromo-2,4-dimethoxypyrimidine was converted into its 5-lithio analog (**289**), which reacted with trimethyl or tributyl borate to give 2,4-dimethoxy-5-pyrimidineboronic acid (**297**) (not its ester);[2567] 2,4-dibenzyloxy-5-pyrimidineboronic acid was made similarly and then converted by hydrogenolysis into 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidineboronic acid.[2567] 5-Pyrimidineboronic acid was made via 5-lithiopyrimidine (52% overall).[277]

Thiazolo[4,5-d]pyrimidines have been reported to result from the condensation of 5-bromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with aliphatic thioamides[5140,5141] but this later proved to be incorrect.[1137,2351,3137,5142]

Acyloxylation of 5-fluoro- to 5-*m*-chlorobenzoyloxy-1,3-dimethyl-2,4-(1*H*,3*H*)-pyrimidinedione and oxidation to other products occurred on prolonged treatment with *m*-chloroperoxybenzoic acid.[13]

6.9. REACTIONS OF EXTRANUCLEAR HALOGENOPYRIMIDINES

The halogeno substituents in extranuclear halogenopyrimidines are insulated to a large extent from the powerful electronic influence of the pyrimidine nucleus, usually by at least one methylene group. Hence the reactivities of such halogenopyrimidines approximate in general to those of benzyl or phenethyl chloride and differ markedly from those of both types of nuclear halogenopyrimidine previously discussed.

Dehalogenation and dehydrohalogenation may be used to convert appropriate extranuclear halogenopyrimidines into alkyl-, alkenyl-, or alkynylpyrimidines: the processes have been discussed in Sections 4.2.1.2 and 4.2.1.4, respectively, but the following typical examples will serve to illustrate the procedures.

5-Chloromethyl- to 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (H_2, Pd, EtOH–H_2O: 90%;[1490] Sn, HCl, 60°, 3 h: 82%;[2270] Zn, HCl, 70°, 3 h: 26%[1978]).

5-Bromomethyl-2-ethyl- to 2-ethyl-5-methyl-4-pyrimidinamine (H_2, Pd, K_2CO_3: 80%).[1065]

2-Chloromethyl-6-methyl- to 2,6-dimethyl-4(3*H*)-pyrimidinone (H_2, Pd, MgO, MeOH: 52%).[2235]

6-Chloro-2-chloromethyl- or 6-chloro-2-fluoromethyl- to 2-methyl-4(3*H*)-pyrimidinone (H_2, Pd, EtOH–H_2O: 70%).[1802]

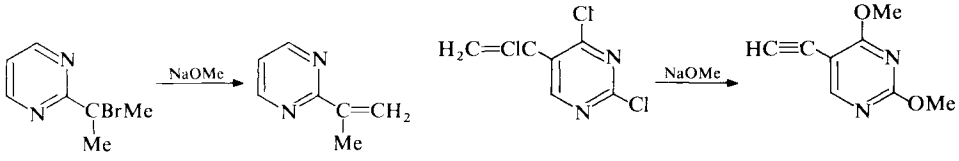
4-Trichloromethyl- to 4-dichloromethyl- (Sn, AcMe–HCl, 25°, 2 h: 65%) or to 4-methylpyrimidine (H_2, Pd, MgO, EtOH: 16% as picrate).[3605]

2-Phenyl-4-trichloromethyl- to 4-dichloromethyl-2-phenylpyrimidine (electrolytic reduction: 92%).[4695]

5-β-Benzoyl-α-iodovinyl- to 5-benzoylethynyl-2,4(1*H*,3*H*)-pyrimidinedione (KOH, H_2O–dioxane, 20°, 7 h: 46%).[6006]

2-(α-Bromo-α-methylethyl)pyrimidine (**298**) to 2-isopropenylpyrimidine (**299**) (NaOMe, MeOH, reflux, 24 h: 84%).[1908]

2,4-Dichloro-5-α-chlorovinyl- (**300**) to 5-ethynyl-2,4-dimethoxypyrimidine (**301**) (NaOMe, MeOH, reflux, 20 h: 87%).[832]



298 **299** **300** **301**

Aminolysis of extranuclear halogenopyrimidines proceeds very readily. The following examples illustrate the conditions required for regular aminolyses.

2-Bromomethylpyrimidine to 2-piperidinomethylpyrimidine (piperidine, EtOH, reflux, 3 min: 70%) and 2-pyridiniomethylpyrimidine bromide (pyridine, PhH, 25°, 12 h: 81%).[1933]

2-Chloromethylpyrimidine to 2-trimethylammoniomethylpyrimidine chloride (Me_3N, PhH, 25°, 12 h: 78%).[1933]

5-Bromomethyl- to 5-piperidinomethyl-2,4(1*H*,3*H*)-pyrimidinedione (piperidine, dioxane, reflux, 75 min: 44%).[1940, cf. 1490]

5-Chloromethyl- to 5-dimethylaminomethyl- [Me_2NH, $(MeOCH_2CH_2)_2O$, 20°, 2 h: ~75%],[1712] 5-azidomethyl- (NaN_3, MeCN, reflux, 5 h: 55%),[1712] and 5-*p*-nitroanilinomethyl-2,4(1*H*,3*H*)-pyrimidinedione (*p*-$O_2NC_6H_4NH_2$, AcMe, reflux, 2 h: 62%).[2632]

6-Chloromethyl- to 6-aminomethyl- (liquid NH_3, 25°, 18 h, sealed: 90%;[311] NH_4OH, 25°, 10 min: > 90%[1498]) and 6-anilinomethyl-2,4(1*H*,3*H*)-pyrimidinedione ($PhNH_2$, Me_2NCHO, 95°, 30 min: 35%).[762]

5-β-Bromoethyl- to 5-β-phthalimidoethyl- (K phthalimide, Me_2NCHO, reflux, 3 h) and thence to 5-β-aminoethyl-2,4(1*H*,3*H*)-pyrimidinedione (HBr, H_2O, reflux, 3.5 h: ~50% overall).[1005]

1-γ-Bromopropyl to 1-γ-azidopropyl-5-methyl-2,4(1*H*,3*H*)pyrimidinedione (NaN_3, MeCN, reflux, 18 h: 76%).[943]

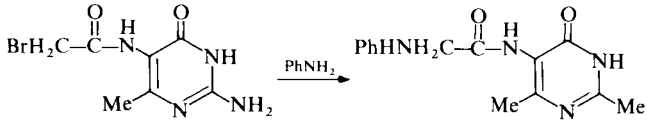
1-β-Bromoethyl- to 1-β-(benzylamino)ethyl-2,4(1*H*,3*H*)-pyrimidinedione ($PhCH_2NH_2$, NEt_3, 25°, 2 h: 65%).[3775]

2,4-Dichloro-5-chloromethyl- to 2,4-dichloro-5-phenethylaminomethyl- ($PhCH_2CH_2NH_2$, $C_6H_4Me_2$, 25°, 30 h: 70%) and 2,4-dichloro-5-morpholinomethylpyrimidine (morpholine, PhMe, 25°, 2 h: 90%).[1699]

6-Chloro-2-chloromethyl- to 6-morpholino-2-morpholinomethyl-4(3*H*)-pyrimidinone (neat morpholine, 25°, ? briefly: 77%).[1802]

6-Bromomethyl- to 6-allylaminomethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione ($H_2C{=}CHCH_2NH_2$, EtOAc, 0°, 30 min: 91%).[2683]

2-Amino-5-α-bromoacetamido- (**302**) to 2-amino-5-α-anilinoacetamido-6-methyl-4(3*H*)-pyrimidinone (**303**) ($PhNH_2$, Me_2SO, 25°, 2 days: 73%).[596]



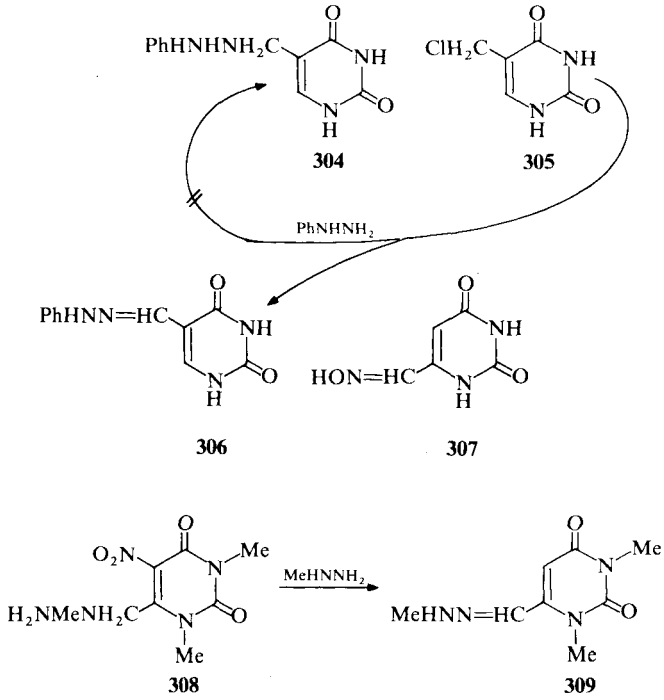
302 **303**

5-α-Bromopropionamido- to 5-α-dimethylaminopropionamido-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (Me_2NH, PhH–H_2O, 25°, 4 h: 51%).[33]

5-Bromoacetyl- to 5-(trimethylammonio)acetyl-2,4(1*H*,3*H*)-pyrimidinedione bromide (NMe_3, MeOH, 20°, 15 h: 31%)[2042] and to 5-azidoacetyl-2,4(1*H*,3*H*)-pyrimidinedione (NaN_3, $MeOCH_2CH_2OH$–H_2O, 25°, 2 h: 85%).[833]

Also other examples.[111,415,1074,1232,1670,1699,1937,3761,4124,4693,4963,4966,4967,5143,6462,6846]

Although extranuclear halogenopyrimidines can undergo normal aminolyses by hydrazine, hydroxylamine and their derivatives, unexpected reactions sometimes ensue. Thus 6-chloromethyl- simply gave 6-hydrazinomethyl-2,4(1*H*,3*H*)-pyrimidinedione (~95%) in warm methanolic hydrazine hydrate.[1498] However, 5-chloromethyl- (**305**) gave not 5-phenylhydrazinomethyl- (**304**), but 5-phenylhydrazonomethyl-2,4(1*H*,3*H*)-pyrimidinedione (i.e., 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde phenylhydrazone) (**306**) (39%) on comparable treatment with ethanolic phenylhydrazine;[2850] in a similar way, 6-chloro-2-chloromethyl- gave only 6-chloro-2-phenylhydrazonomethyl-4(3*H*)-pyrimidinone (~60%) in refluxing ethanolic phenylhydrazine.[1802] Likewise, 6-chloromethyl- gave 6-hydroxyiminomethyl-2,4(1*H*,3*H*)-pyrimidinedione (i.e., 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime) (**307**) (98%) in refluxing ethanolic hydroxylamine;[2850] also 4-bromomethyl-6-phenylpyrimidine 3-oxide so gave 6-phenyl-4-pyrimidinecarbaldehyde 3-oxide oxime.[5629] These dehydrogenative reactions appear to occur by intervention of a second molecule of phenylhydrazine or hydroxylamine that undergoes hydrogenolytic fission to aniline plus ammonia in one case and to water plus ammonia in the other.[2850] 6-Bromomethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione reacted normally with methylhydrazine (2 mol) in ethyl acetate



at 0° to afford the 6-α-methylhydrazinomethyl analog (**308**), but when this product (or the original substrate) was treated with an excess of methylhydrazine under similar conditions, a complicated sequence of reactions occurred with loss of nitrous acid to give 1,3-dimethyl-6-methylhydrazonomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**309**) (83% overall).[1905]

Alcoholysis of extranuclear halogenopyrimidines is usually even more facile than that of 2- or 4/6-halogeno substrates. The following examples illustrate the conditions employed for such reactions.

2-Chloromethyl- to 2-methoxymethyl-4,6-dimethylpyrimidine (NaOMe, MeOH, reflux, 1 h: 79%).[121]

2-Dibromomethyl- to 2-dimethoxymethyl-4,6-diphenylpyrimidine (i.e., 4,6-diphenyl-2-pyrimidinecarbaldehyde dimethyl acetal) (NaOMe, MeOH, reflux).[5144]

5-Chloromethyl-1,3-dimethyl- to 1,3-dimethyl-5-*p*-nitrophenoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaOC_6H_4NO_2$-*p*, NaI, Me_2NCHO, 25°, 6 h: 67%).[760]

Ethyl 5-chloromethyl- to ethyl 5-ethoxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (EtOH, reflux, 3 h: 76%).[2627]

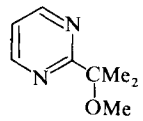
4-Chloro-2-chloromethyl- to 4-chloro-2-ethoxymethylpyrimidine (EtOH, ? hot: 88%).[2058]

2,4-Dichloro-5-chloromethylpyrimidine to 2,4-dichloro-5-ethoxymethyl- (1 mol NaOEt, EtOH, 25°, 1 h: 87%), 2-chloro-4-ethoxy-5-ethoxymethyl- (2 mol NaOEt, EtOH, 25°, 3 h: 86%), or 2,4-diethoxy-5-ethoxymethyl-pyrimidine (3 mol NaOEt, EtOH, reflux, 30 min: 88%).[1699]

5-(3′-Chloro-4′-nitrophenyl)- to 5-(3′-methoxy-4′-nitrophenyl)-6-methyl-2,4-pyrimidinediamine (NaOMe, MeOH, reflux, 18 h: 92%; chloro substituent activated by the nitro group).[462]

Also other examples.[1801,1925,1934,1940,3982]

The possibility of dehydrohalogenation in place of alcoholysis must be kept in mind for susceptible substrates. For example, 2-(α-bromo-α-methylethyl)-pyrimidine (**298**) in refluxing methanol for 2 days gave 2-(α-methoxy-α-methylethyl)pyrimidine (**310**) (80%), but similar treatment with methanolic sodium methoxide gave 2-isopropenylpyrimidine (**299**) (84%);[1908] other such cases have been reported.[832,1908]



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Hydrolysis of extranuclear monohalogenopyrimidines may be done directly in alkaline media, but the indirect route *via* an acyloxypyrimidine is still used sometimes. Both procedures are illustrated in the following examples.

Direct procedures

5-Bromomethyl- to 5-hydroxymethylpyrimidine (*M* NaOH, 40°, 8 h: 52%).[1933]

5-Bromomethyl- to 5-hydroxymethyl-2-methyl-4-pyrimidinamine ($NaHCO_3$, H_2O, reflux, briefly: 37%).[5145]

5-β-Chloroethyl- to 5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone (H_2O, 150°, 4 h, sealed: ~80%).[2145]

5-Bromoacetyl- to 5-glycollyl-2,4(1*H*,3*H*)-pyrimidinedione (KOH, MeOH $-H_2O$: ~70%).[830]

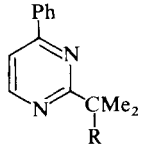
5-Chloromethyl- to 5-hydroxymethyl- (Ag_2CO_3, H_2O, 25°, ? many hours: 94%)[1490] and 5-hydroperoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (50% H_2O_2, H_2O, 25°, 30 min: 92%).[2853]

Also other examples.[1149,2274]

Indirect procedures

2-Bromomethyl- to 2-acetoxymethyl- (KOAc, EtOH, reflux, 4 h: 88%) and thence to 2-hydroxymethyl-4,6-dimethoxypyrimidine (K_2CO_3, MeOH, 25°, 12 h: 40%).[3974]

2-(α-Bromo-α-methylethyl)- (**311**, R = Br) to 2-(α-acetoxy-α-methylethyl)- (**311**, R = OAc) (AgOAc, AcOH, 100°, 10 min; 50%) and thence to 2-(α-hydroxy-α-methylethyl)-4-phenylpyrimidine (**311**, R = OH) (NaOH, H_2O, 95°, 24 h: 75%).[1908]



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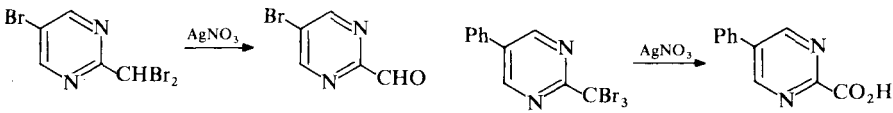
6-Chloromethyl- to 6-acetoxymethyl- (AgOAc, H_2O, reflux, 2 h: ~ 60%) and thence to 6-hydroxymethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione [$Ba(OH)_2$, H_2O, reflux, 1 h].[766,767]

5-Bromomethyl- to 5-acetoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (NaOAc, AcOH, reflux, 5 min: 63%) but no hydrolysis described.[1940]

Also other examples.[1801,2274,6462]

The hydrolysis of dihalogenomethyl- or trihalogenomethylpyrimidines is usually mediated by aqueous silver nitrate to afford the corresponding pyrimidinecarbaldehydes or pyrimidinecarboxylic acids, respectively, presumably by spontaneous dehydration of the intermediate dihydroxymethyl- or trihydroxymethylpyrimidines. Such reactions and some useful variations are illustrated in the following examples.

5-Bromo-2-dibromomethylpyrimidine (**312**) to 5-bromo-2-pyrimidinecarbaldehyde (**313**) ($AgNO_3$, EtOH–H_2O, reflux, 6 h: 47%, as its semicarbazone).[1788]



312 **313** **314** **315**

5-Bromo-2-tribromomethylpyrimidine to 5-bromo-2-pyrimidinecarboxylic acid ($AgNO_3$, AcOH–H_2O, 95°, 1 h: 70%).[729, cf. 1974]

5-Phenyl-2-tribromomethylpyrimidine (**314**) to 5-phenyl-2-pyrimidinecarboxylic acid (**315**) ($AgNO_3$, AcOH–H_2O, reflux, 90 min: 56%).[379]

2-β-Hydroxyphenethylamino-4-trichloromethylpyrimidine to 2-β-hydroxyphenethylamino-4-pyrimidinecarboxylic acid ($AgNO_3$, AcOH–H_2O, 95°, 2 h: 29%).[4891]

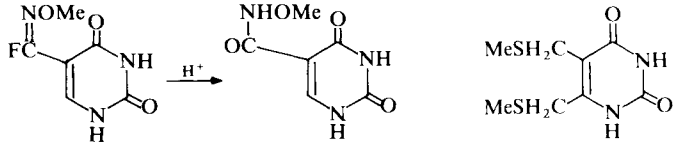
4,6-Bistribromomethylpyrimidine to 4,6-pyrimidinedicarboxylic acid ($AgNO_3$, AcOH, reflux, 3 h: 24%).[764]

5-Bromoacetyl-2,4(1*H*,3*H*)-pyrimidinedione to 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (pyridine, 75°, 30 min; then NaOH, H_2O, 75°, 1 h: 24%).[833]

Ethyl 5-methyl-6-oxo-2-tribromomethyl-1,6-dihydro-4-pyrimidinecarboxylate to diethyl 5-methyl-6-oxo-1,6-dihydro-2,4-pyrimidinedicarboxylate ($AgNO_3$, EtOH–EtOAc–H_2O, 25° 24 h: 51%).[2038]

5-Trifluoromethyl- to 5-(α-fluoro-α-methoxyiminomethyl)-2,4(1*H*,3*H*)-pyrimidinedione (**316**) ($MeONH_2$, H_2O, 90°, 1 h) and thence to *N*-methoxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (**317**) (0.1*M* HCl, 37°, 10 h).[461]

Also other examples.[1934,4959,4960]

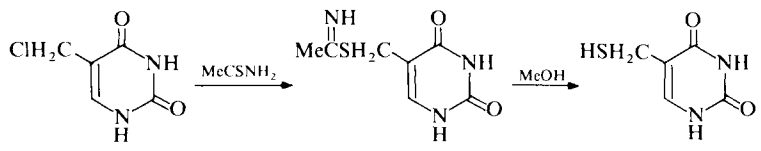


316 **317** **318**

Alkanethiolysis of extranuclear halogenopyrimidines can be done quite easily. Thus 5-chloromethyl- gave 5-ethylthiomethyl- (NaSEt, Me_2NCHO, 25°, briefly: 95%),[347] 5-benzylthiomethyl- (neat $PhCH_2SH$, 150°, 5 h: 98%),[841] 5-methylselenomethyl- (MeSeLi, THF, 20°, 2 h: 44%),[6125] and 5-carboxymethylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione (neat $HSCH_2CO_2H$, 150°, 3 h: 70%).[841] 2,4-Dichloro-5-chloromethylpyrimidine gave 2,4-dichloro-5-methylthiomethylpyrimidine (1 mol NaSMe, EtOH, 25°, 1 h: 85%) or 2,4-bismethylthio-5-methylthiomethylpyrimidine (3 mol NaSMe, EtOH, reflux, 30 min: 86%);[1699] 5,6-bis(chloromethyl)- gave 5,6-bis(methylthiomethyl)-2,4(1*H*,3*H*)-pyrimidinedione (**318**) (NaSMe, EtOH, reflux, 15 min: 65%);[1723] and other examples have been reported.[364,1326,3748]

Thiolysis of extranuclear halogenopyrimidines is usually unsatisfactory, mainly because the products are so prone to aerial oxidation. Thus no successful direct thiolyses have been reported but a few indirect procedures have given the desired mercaptoalkylpyrimidines; both direct and indirect routes have afforded sulfides or disulfides. Some such reactions are illustrated in the following examples.

5-Chloromethyl- (**319**) to 5-acetimidoylthiomethyl- (**320**) ($MeCSNH_2$, Me_2NCHO, 70°, 30 min: 62% as hydrochloride) and thence to 5-



319 **320** **321**

mercaptomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**321**) (MeOH, reflux, 2 h: 84%).[841,2271]

2-*β*-Chloroethylaminopyrimidine to bis[*β*-(pyrimidin-2-ylamino)ethyl] disulfide (Na_2S_2, EtOH–H_2O, 60°, 3 h: 40%).[4942]

5-Bromomethyl- to a separable mixture of 5-mercaptomethyl-2-methyl-4-pyrimidinamine and bis(4-amino-2-methylpyrimidin-5-ylmethyl) disulfide ($MeCS_2H$, pyridine, reflux, 7 h: ~25% and ~12%, respectively).[1326]

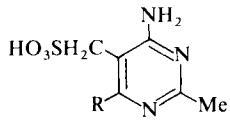
5-Bromomethyl- to 5-mercaptomethyl-2-methylthio-4-pyrimidinamine, bis-(4-amino-2-methylthiopyrimidin-5-ylmethyl) sulfide, or the corresponding disulfide ($MeCS_2H$, pyridine, reflux, 1 h: product according to workup method).[1326]

6-Chloromethyl- to 6-mercaptomethyl-5-phenoxy-2,4(1*H*,3*H*)-pyrimidinedione (KSCN, EtOH, reflux; mechanism?).[4955]

5-Chloromethyl-2-methyl-4-pyrimidinamine to bis(4-amino-2-methylpyrimidin-5-ylmethyl) sulfide (thiourea, THF, reflux, 15 min; then $NaHCO_3$).[5146]

Also other examples.[3984,4708]

Sulfonic acids, sulfones, and thiocyanates may be made directly from extranuclear halogenopyrimidines, but little use has been made of such reactions. For example, 5-chloromethyl-2-methyl- gave 2-methyl-5-sulfomethyl-4-pyrimidinamine (**322**, R = H) (~30%) on heating in aqueous sodium hydrogen sulfite into which sulfur dioxide was being passed;[584] the same product was obtained rather similarly from the 5-bromomethyl substrate[1466] and it proved to be identical with material from the sulfite degradation of vitamin B_1.[5147,5148] 2,6-Dimethyl-5-sulfomethyl-4-pyrimidinamine (**322**, R = Me) was made likewise from its 5-chloromethyl analogue.[584] Treatment of 4-bromomethyl-6-phenylpyrimidine with aqueous ethanolic sodium benzenesulfinate at 25° for 16 h gave 4-phenyl-6-phenylsulfonylmethylpyrimidine (**323**) (63%);[4641] and 5,6-bischloromethyl- gave 5,6-bis(methylsulfonylmethyl)-2,4(1*H*,3*H*)-pyrimidinedione (74%) by refluxing with ethanolic sodium methanesulfinate for 3 h.[1723] 5-Chloromethyl- gave 5-thiocyanatomethyl-2,4(1*H*,3*H*)-pyrimidinedione (KSCN, Me_2NCHO, 80°, 2 h: 69%);[841] 5-bromoacetyl- gave 5-thiocyanatoacetyl-2,4(1*H*,3*H*)-pyrimidinedione (KSCN, $MeOCH_2CH_2OH$, 60°, 5 min: 63%);[833] and 5-bromomethyl-2-methyl- gave 2-methyl-5-thiocyanatomethyl-4-pyrimidinamine (KSCN, THF, reflux, 2 h: ~45%).[1326]



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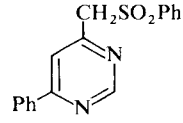

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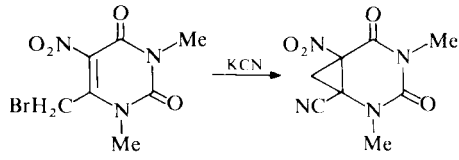
Carbonitriles may be made from the corresponding extranuclear halogenopyrimidines as exemplified in the conversion of 2-amino-6-bromomethyl- into 2-amino-6-cyanomethyl-5-δ-phenylbutyl-4(3*H*)-pyrimidinone (NaCN, Me_2NCHO, 100°, 2 h: 63%);[1182] of 2-chloromethyl into 2-cyanomethyl-4,6-dimethylpyrimidine (NaCN, EtOH–H_2O, reflux, 90 min: 84%);[2222] of 4-bromomethyl- into 4-cyanomethyl-2,6-dimethoxy-5-nitropyrimidine (NaCN, EtOH–H_2O, 0°: 55%);[1903] and of 2-*p*-bromophenyl-5-butyl- into 5-butyl-2-*p*-cyanophenylpyrimidine (CuCN, Me_2NCHO, heat).[3847] An interesting *cine*-type substitution occurred when 6-bromomethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**324**) was treated with potassium cyanide in aqueous dimethylformamide at 25° for 1 h to give 2,4-dimethyl-6-nitro-3,5-dioxo-2,4-diazabicyclo[4.1.0]heptane-1-carbonitrile (**325**) (40%), a so-called cyclothymine derivative.[1906]



324 **325**

Other carbon-linked groups may be introduced by replacement of extranuclear halogeno substituents, mainly by the use of carbanionic reagents, but occasionally by indirect means. These reactions are illustrated in the following examples.

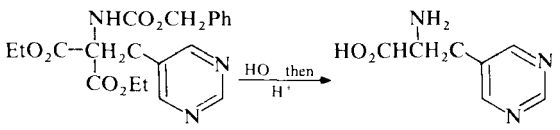
Using carbanionic reagents

4-Bromomethyl- to 4-β-cyanophenethylpyrimidine (PhCHNaCN, liquid NH_3–Et_2O, 3 h: 32%).[4538,4539]

5-Benzyloxy-4-chloro-2-chloromethyl- to 2-β-acetamido-β,β-di(ethoxycarbonyl)ethyl-5-benzyloxy-4-chloropyrimidine [$AcHNCHNa(CO_2Et)_2$, Me_2NCHO, 95°, 2 h: 74%].[4089]

5-Bromomethyl- to 5-β-benzyloxycarbonylamino-β,β-di(ethoxycarbonyl)-ethylpyrimidine (**326**) [$PhCH_2OCONHCH(CO_2Et)_2$, EtOH, reflux, 3 h: ~60% crude] and thence to 5-β-amino-β-carboxyethylpyrimidine (**327**) (saponification followed by monodecarboxylation in aqueous HCl: ~40%).[1934]

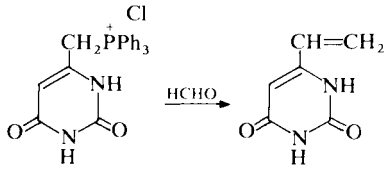
Also other examples akin to the last.[1335,1925,1926,2057,2058,2468,5149–5153]



326 **327**

Using indirect routes

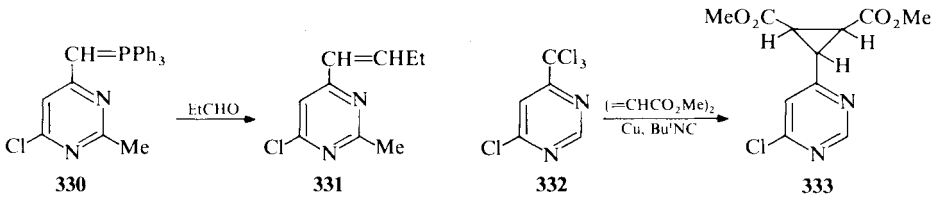
6-Chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione to 6-triphenylphosphoniomethyl-2,4(1*H*,3*H*)-pyrimidinedione chloride (**328**) (Ph_3P, EtOH, reflux, 16 h: 84%) and thence to 6-vinyl-2,4(1*H*,3*H*)-pyrimidinedione (**329**) (CH_2O, NaOEt, EtOH, 50°, 5 min: 83%; Wittig reaction).[1869]



328 **329**

2-Amino-6-bromomethyl-5-δ-phenylbutyl-4(3*H*)-pyrimidinone to 2-amino-5-δ-phenylbutyl-6-triphenylphosphoniomethyl-4(3*H*)-pyrimidinone bromide (Ph_3P, THF–PhH, reflux, 8 h: 95%) and thence to 2-amino-6-*p*-nitrostyryl-5-δ-phenylbutyl-4(3*H*)-pyrimidinone ($OHCC_6H_4NO_2$-*p*, NaOMe, Me_2NCHO, 100°, 1 h: 72%).[1182]

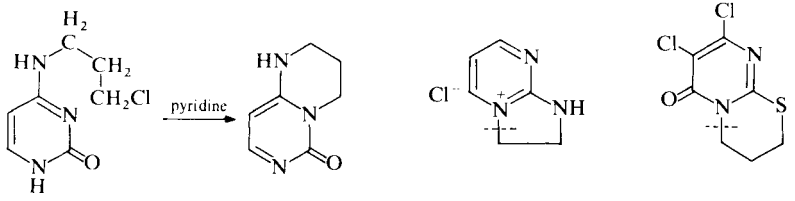
4-Chloro-2-methyl-6-trichloromethylpyrimidine to 4-chloro-2-methyl-6-triphenylphosphoranylidenemethylpyrimidine (**330**) (Ph_3P in excess, PhH, reflux, 8 h: 77%) and thence to 4-but-1′-enyl-6-chloro-2-methylpyrimidine (**331**) (EtCHO, 25°, ? 5 days: 77%; mechanism?).[99]



330 **331** **332** **333**

4-Chloro-6-trichloromethyl- (**332**) to 4-chloro-6-[1′-chloro-2′,3′-di(methoxycarbonyl)cyclopropyl]pyrimidine (**333**) (dimethyl fumarate, *t*-BuNC, Cu, PhH, reflux, 4 h: 25%; also analogs).[5154]

Intramolecular cyclization of appropriate extranuclear halogenopyrimidines can occur easily. For example, 4-γ-chloropropylamino-2(1*H*)-pyrimidinone



334 **335** **336** **337**

(**334**) in refluxing pyridine for 20 min gave 1,2,3,4-tetrahydro-6*H*-pyrimido[1,2-*c*]pyrimidin-6-one (**335**) (> 80%);[3537] 2-β-chloroethylaminopyrimidine in refluxing ethanol for 30 min gave 2,3-dihydroimidazo[1,2-*a*]pyrimidine hydrochloride (**336**) (92%);[3524] and whereas 2-γ-bromopropylthio-5,6-dichloro-4(3*H*)-pyrimidinone with neat diethylamine at 0° for 2 days gave 5,6-dichloro-2-γ-diethylaminolpropylthio-4(3*H*)-pyrimidinone (88%), the same reactants at reflux for a few minutes gave only 7,8-dichloro-3,4-dihydro-4*H*,6*H*-pyrimido-[2,3-*b*][1,3]thiazin-6-one (**337**).[2517] Other examples have been reported.[2517,3524,3537,5155]

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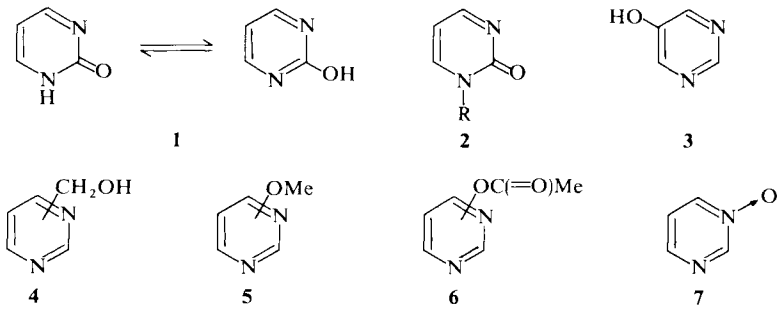
CHAPTER 7

Oxypyrimidines

The general category "oxypyrimidines" seems a conveniently imprecise term to embrace the cyclic amides [tautomeric (**1**) or nontautomeric (**2**) pyrimidinones], the phenolic 5-pyrimidinols (**3**), the alcoholic hydroxyalkylpyrimidines (**4**), the etherial alkoxypyrimidines (**5**), the ester-like acyloxypyrimidines (**6**), and the pyrimidine *N*-oxides (**7**). This group of pyrimidines is of particular interest in that several important natural products (e.g., uracil, thymine, vicine) and drugs (e.g., barbiturates) fall therein; moreover, at least half of all known pyrimidines bear some sort of oxy substituent.



7.1. TAUTOMERIC PYRIMIDINONES

Tautomeric 2- and 4/6-pyrimidinones are important, not only as such, but as primary intermediates for all manner of pyrimidine derivatives.

7.1.1. Preparation of Tautomeric Pyrimidinones

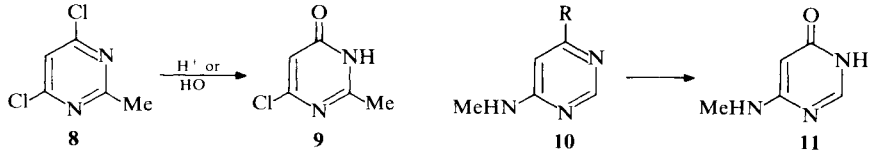
Although a high proportion of known tautomeric pyrimidinones may be made directly by primary syntheses, it is often more convenient or even necessary to prepare such pyrimidinones from other available pyrimidines.

7.1.1.1. By Primary Syntheses

Innumerable examples of the formation of tautomeric pyrimidinones by the Principal Synthesis (Chapter 3) or other primary syntheses (Chapter 2) have been given already.

7.1.1.2. From Halogenopyrimidines

The hydrolysis of 2- and 4/6-halogenopyrimidines to the corresponding pyrimidinones has been discussed in Section 6.7.5. The selective alkaline hydrolysis of di- or trihalogenopyrimidines appears to be the most useful aspect of the process: for example, the best route to 6-chloro-2-methyl-4(3*H*)-pyrimidinone (**9**) is by partial hydrolysis of the easily available 4,6-dichloro-2-methylpyrimidine (**8**);[1159,1817] and a good route to 4(3*H*)-pyrimidinone is by the concomitant 4-hydrolysis and reductive 2-dechlorination of 2,4-dichloropyrimidine in boiling hydriodic acid.[710,1670] Occasionally, it is better to convert a halogenopyrimidine into a pyrimidinone indirectly via an alkoxy intermediate. For example, direct hydrolysis of 4-chloro-6-methylaminopyrimidine (**10**, R = Cl) to 6-methylamino-4(3*H*)-pyrimidinone (**11**) proved unsatisfactory because of concomitant hydrolysis of the methyamino group, but the same substrate (**10**, R = Cl) could be converted into 4-methoxy-6-methylaminopyrimidine (**10**, R = OMe) and thence, by gentle acidic hydrolysis, into the required pyrimidinone (**11**).[1383]



8 **9** **10** **11**

7.1.1.3. From Pyrimidinamines

Acidic or alkaline hydrolysis may be used to convert most primary, secondary, or tertiary pyrimidinamines into the corresponding pyrimidinones; treatment with nitrous acid is also effective for primary pyrimidinamines. The choice between these methods is governed largely by the nature of any other group(s) attached to the molecule. Such procedures were used to prepare the following pyrimidinones, in each case from the corresponding primary pyrimidinamine unless otherwise indicated.

Acidic hydrolysis

6-Methyl-4(3*H*)-pyrimidinone (10*M* HCl, 150°, 10 h, sealed: 50%).[3503]

2-Methyl-4(*H*)-pyrimidinone (6*M* HCl, reflux, 4 h: 65%).[678]

2-Phenyl-4(3*H*)-pyrimidinone (10*M* HCl, 150°, 10 h, sealed: > 90%).[5110]

5-*p*-Methoxyphenyl-4(3*H*)-pyrimidinone (10*M* HCl + HCl gas, 90°, 12 h: 83%).[4412]

2-Methyl-6-phenyl-4(3*H*)-pyrimidinone (20% v/v H_2SO_4, reflux, 5 h).[665]

5,6-Diphenyl-2-thioxo-1,2-dihydro-4(3*H*)pyrimidinone (HCl, EtOH–H_2O, 25°, 24 h: 82%).[198]

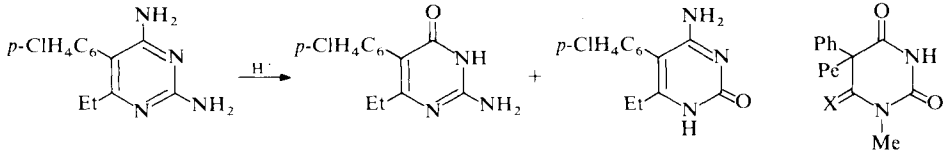
2(1*H*)-Pyrimidinone from 2-methylaminopyrimidine (*M* HCl, 160°, 6 h, sealed);[3378] 4,6-dimethyl-2(1*H*)-pyrimidinone (10*M* HCl, likewise).[861]

2-Amino-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione from 2-amino-6-*N*-benzyl-*N*-(β-hydroxy-β-methylpropyl)amino-5-nitro-4(3*H*)-pyrimidinone (48% HBr, 75°, 10 min; or 5*M* HCl, likewise).[27]

4-*o*-Hydroxyphenyl-5-methyl-2(1*H*)-pyrimidinone from its 2-cyanamino analog (10*M* HCl + dilute H_2SO_4, reflux, 3 days: 57%).[4570]

3-Benzyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione from 3-benzyl-2-hydrazino-6-methyl-4(3*H*)-pyrimidinone (6*M* HCl, reflux, 1 h: 75%).[5157]

2-Amino-5-*p*-chlorophenyl-6-ethyl-4(3*H*)-pyrimidinone (**13**) and 4-amino-5-*p*-chlorophenyl-6-ethyl-2(1*H*)-pyrimidinone (**14**) (isolated in ratio 3 : 5) from 5-*p*-chlorophenyl-6-ethyl-2,4-pyrimidinediamine (**12**) (6*M* HCl, reflux, 18h: ~85% of mixture).[289, cf. 5156,5160]



12 **13** **14** **15**

1,3-Dimethyl-2,4,6,(1*H*,3*H*,5*H*)-pyrimidinetrione from 6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (*M* HCl, reflux, 15 min: 80%).[644,1131]

2-Amino-5-nitroso-4,6(1*H*,5*H*)-pyrimidinedione from 2,6-diamino-5-nitroso-4(3*H*)-pyrimidinone or 5-nitroso-2,4,6-pyrimidinetriamine (6*M* HCl, reflux, 10 min: 67%).[1590]

1-Methyl-5-pentyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**15**, X = O) from 6-imino-1-methyl-5-pentyl-5-phenyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**15**, X = NH) (2*M* H_2SO_4, 100°, 1 h: 86%).[570]

Also other examples.[864,967,1105,1188,1289,1339,1402,1542,1602,1869,2114, 2814,3002,3011,3240,4389,4439,4441,4528,5085,5158,5159,5161]

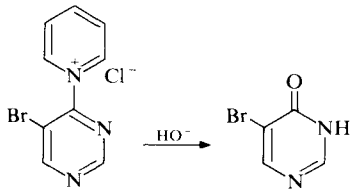
Alkaline hydrolysis

2(1*H*)-Pyrimidinone (10*M* NaOH, reflux, 12–16 h: 66–90%);[1534,1967, 2826,3380,3650,5162] from 2-methylaminopyrimidine (NaOH, MeOH–H_2O, 165°, 12 h, sealed: ~ 60%);[867] or from 2-trimethylammoniopyrimidine chloride (0.5*M* NaOH, 100°, 5 min: 40%).[3554]

5-Nitro-2(1*H*)-pyrimidinone (*M* NaOH, warm);[703] or from 5-nitro-2-trimethylammoniopyrimidine chloride (*M* NaOH, 20°, 5 min: > 90%).[3554]

5-Bromo-4-(3*H*)-pyrimidinone (**17**) from 5-bromo-4-pyridiniopyrimidine chloride (**16**) (2.5*M* NaOH, reflux, 2 h: low yield).[1965]

Also other examples,[1154,1383,1713,1791] including some kinetic studies of interest.[2826,5163,5164]



16 **17**

Nitrous acid treatment

4,6-Dimethyl-2(1*H*)-pyrimidinone ($NaNO_3$, 70% AcOH, 55°, 90 min: 60%).[1780]

4-*t*-Butyl-2(1*H*)-pyrimidinone ($NaNO_2$, 8*M* HCl, −10°, 1–2 h: > 30%).[1465,4037]

5-Ethoxy-2(1*H*)-pyrimidinone ($NaNO_2$, HCl, H_2O–dioxane, 0°, 2 h: 42%).[1086]

2-Benzylthio-6-chloro-4(3*H*)-pyrimidinone ($NaNO_2$, AcOH, 20°, 40 h: 99%).[2187]

6-Methoxy-2-methylthio-4(3*H*)-pyrimidinone ($NaNO_2$, AcOH, 20°, 40 h: 90%;[2187] $NaNO_2$, 40% AcOH, 5°, 1 h: 55%[903]).

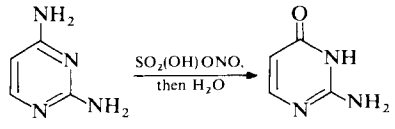
6-Chloro-4(3*H*)-pyrimidinone ($NaNO_2$, 20% AcOH, 10° then 55°, 3 h: 63%).[1568]

4,6-Dithien-2′-yl-2(1*H*)-pyrimidinone ($NaNO_2$, 60% AcOH, 20°, 30 min: ~60%).[3866]

4,6-Diphenyl-2(1*H*)-pyrimidinone ($NaNO_2$, 50% v/v H_2SO_4, −10° then 25°, 12 h: 70%).[2258]

5,5′-Bipyrimidine-2,2′(1*H*,1′*H*)-dione ($NaNO_2$, 2*M* H_2SO_4, 0°, 2 h: 80%).[4019]

2-Amino-4(3*H*)-pyrimidinone (**19**) from 2,5-pyrimidinediamine (**18**) [$SO_2(OH)ONO$, 20°, then H_2O: 40%; mechanism could involve H_2O



18 **19**

addition to the 4,5-bond of a diazonio intermediate]; also analogous cases.[752]

2-Acetoxypyrimidine ($NaNO_2$, glacial AcOH, 15°, 15 min: 60%).[752]

Also other examples.[289,1206,1511,1718,1852,1854,1902,4722,5156]

7.1.1.4. From Alkoxypyrimidines

Because so many alkoxypyrimidines are made from pyrimidinones (directly or via halogenopyrimidines), the reverse conversion of alkoxypyrimidines into pyrimidinones is of limited utility. However, there are four ways to carry out such reactions: acidic hydrolysis, alkaline hydrolysis, splitting by anhydrous hydrohalides, and reductive fission of benzyloxypyrimidines. These are illustrated in the following conversions.

Acidic hydrolysis

2(1*H*)-Pyrimidinone from 2-methoxypyrimidine (2*M* H_2SO_4, reflux, 6 h: 64%).[5074,6219]

2-Dimethylamino-4(3*H*)-pyrimidinone from 2-dimethylamino-4-methoxypyrimidine (10*M* HCl, 100°, 1 h: ~ 80%).[1743]

4,6-Dimethyl-2(1*H*)-pyrimidinone from 2-benzyloxy-4,6-dimethylpyrimidine (6*M* HCl, reflux, 20 min: 60%).[764]

6-Dimethylamino-4(3*H*)-pyrimidinone from 4-dimethylamino-6-methoxypyrimidine (6*M* HCl, reflux, 30 min: ~45%).[968]

5-Benzoyl-2,4(1*H*,3*H*)-pyrimidinedione from 5-benzoyl-2,4-diethoxypyrimidine (6*M* HCl, relux, 30 min: 35%).[5138]

5-Fluoro-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione from 5-fluoro-4-methoxy-1-methyl-2(1*H*)pyrimidinone (6*M* HCl, reflux, 30 min: 88%;[5166] 0.5*M* HCl, reflux, 10 min: 90%[3153]).

6-Amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione from 6-amino-2-methoxy-3-methyl-4(3*H*)-pyrimidinone (10*M* HCl, 25°, 12 h: > 80%).[1288]

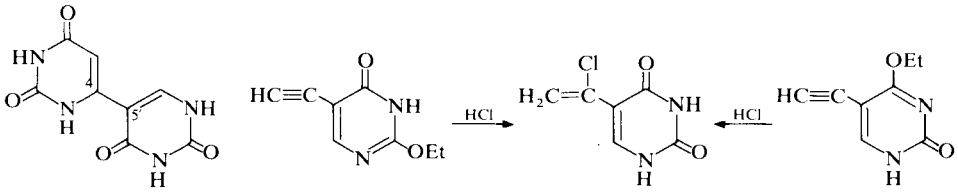
6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione from 4-chloro-2,6-dimethoxypyrimidine (HCl, AcOH–H_2O, reflux, 1 h, 55–75%;[105,1703,2049] 10*M* HCl, 20°, 15 min: 60%;[958] 6*M* HCl, 80°, 90 min: ~ 50%).[1376,4946]

6-Methoxy-4(3*H*)-pyrimidinone from 4,6-dimethoxypyrimidine (6*M* HCl, reflux, 20 min: ~ 95%).[3350]

4,5′-Bipyrimidine-2,2′,4′,6(1*H*,1′*H*,3*H*,3′*H*)-tetrone (**20**) from 2,2′,4′,6-tetramethoxy-4,5′-bipyrimidine (5*M* HBr, 110°, 50 min: 90%).[1847]

2-Amino-6-phenyl-4(3*H*)-pyrimidinone 1-oxide from 4-(2′,4′-dichlorophenoxy)-6-phenyl-2-pyrimidinamine 1-oxide (HCl, BuOH–H_2O, 75°, 2 days: 90%).[4913]

5-α-Chlorovinyl-2,4(1*H*,3*H*)-pyrimidinedione (**22**) from a mixture of 2-ethoxy-5-ethynyl-4(3*H*)-pyrimidinone (**21**) and 4-ethoxy-5-ethynyl-2(1*H*)-



20 **21** **22** **23**

pyrimidinone (**23**) (2*M* HCl, evaporated at 25°: 71%; note addition of HCl to triple bond).[2361]

6-Butyl-2-methoxy-5,6-dihydro-4(3*H*)-pyrimidinone from 2,4-dimethoxypyrimidine (BuLi, Et_2O, −20°; H_2O–THF, −10°; HCl, EtOH–H_2O, 25°, 24 h: 41%); also subsequent hydrolysis to 6-butyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (2*M* HCl, 60°, 90 min: 56%).[562]

Also other examples.[130,360,430,1219,1379 (cf. 1648),1383,1800,2495,2550,2582, 2960,3119,3455,4019,4382,4633,5065,5099,5167,5168]

Alkaline hydrolysis

(*Note*: Alkaline hydrolysis of alkoxypyrimidines appears to be slower and more selective than acidic hydrolysis.)

6-Methylthio-4(3*H*)-pyrimidinone from 4-methoxy-6-methylthiopyrimidine (*M* NaOH, 95°, until homogeneous: ~ 70%).[3350]

4-Amino-6-chloro-2(1*H*)-pyrimidinone from 6-chloro-2-methoxy-4-pyrimidinamine (2.5*M* NaOH, 95°, 2 h: 82%).[615]

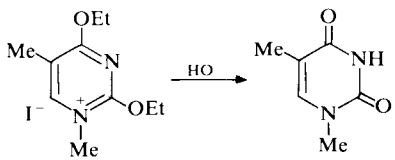
1-Methyl-6-thioxo-1,6-dihydro-4(5*H*)-pyrimidinone from 6-methoxy-3-methyl-4(3*H*)-pyrimidinethione (*M* NaOH, 100°, 15 min: ~ 80%).[3348]

2-Ethoxy-5-methyl-4(3*H*)-pyrimidinone from 2,4-diethoxy-5-methylpyrimidine (NaOH, EtOH–H_2O, reflux, 1 week: 68% cf. the following example).[2934]

2-Ethoxy-4-(3*H*)-pyrimidinone and 4-ethoxy-2(1*H*)-pyrimidinone from 2,4-diethoxypyrimidine (NaOH, EtOH–H_2O, reflux, 3 days: ~ 35% of each after separation).[2665]

1,5-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**25**) from 2,4-diethoxy-1,5-dimethylpyrimidinium iodide (**24**) (*M* NaOH, 20°, 1 h).[2520]

Also other examples.[812,3720]



24 **25**

Splitting by anhydrous hydrohalide

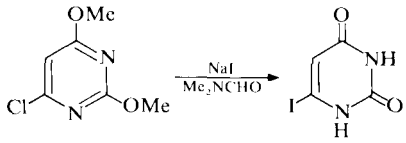
4-Amino-2(1*H*)-pyrimidinone from 2-methoxy-4-pyrimidinamine (pyridine–HCl, pyridine, 95°, 2 h).[2131]

4-Sulfanilamido-2(1*H*)-pyrimidinone from 2-methoxy-4-sulfanilamidopyrimidine (pyridine–HCl, pyridine, 95°, 2 h: > 90%; or 57% HI, 25°, 15 h).[2131]

6-Benzyloxy-5-methyl-4(3*H*)-pyrimidinone from 4,6-dibenzyloxy-5-methylpyrimidine (1 mol HCl in MeCN, 120°, 1 h, sealed: 87%); or 5-methyl-4,6(1*H*,5*H*)-pyrimidinedione from the same substrate (excess HCl in MeCN, 120°, 6 h, sealed: 82%).[2586,3470,5169]

5-Bromo-2,4(1*H*,3*H*)-pyrimidinedione from 5-bromo-2,4-dimethoxypyrimidine (50% HBr in AcOH, reflux, 30 min: 81%; NaI in AcOH, 95°, 4 h: 82%).[5165]

6-Iodo-2,4(1*H*,3*H*)-pyrimidinedione (**27**) from 4-chloro-2,6-dimethoxypyrimidine (**26**) (NaI, Me_2NCHO, reflux, 1 h: 73%; note concomitant transhalogenation).[1703]



26 **27**

5-Acetyl-4,6(1*H*,5*H*)-pyrimidinedione from 5-acetyl-4,6-dibenxyloxypyrimidine (HCl in BuOH, reflux, 2 h: 22%).[363]

2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid from 2,6-dimethoxy-4-pyrimidinesulfonic acid (Me_3SiI, sulfolane, 40°, 15 min: > 95%).[2346]

4,6-Dimethyl-2(1*H*)-one hydrochloride from 2-methoxy-4,6-dimethylpyrimidine hydrochloride (EtOH, reflux, briefly: 75%).[2532]

2-Isopropyl-4(3*H*)-pyrimidinone from 2-isopropyl-4-methoxypyrimidine (HBr in PhH, 50°, 24 h: 80%).[1907]

2-Methoxycarbonylmethyl-4(3*H*)-pyrimidinone from 4-methoxy-2-methoxycarbonylmethylpyrimidine (HBr in PhH, 50°, 16 h: 80%).[1749]

Also other examples.[965,1094,2346]

Reductive fission of benzyloxypyrimidines

4-Methyl-6-oxo-1,6-dihydro- from 4-benzyloxy-6-methyl-2-pyrimidinecarboxamide (H_2, Pd, MeOH: 85%).[3345]

6-Methyl-4(3*H*)-pyrimidinone or its 1-oxide from 4-benzyloxy-6-methylpyrimidine 1-oxide (H_2, Pd, MeOH: 80% or 64%, respectively, according to the volume of H_2 used).[3345]

2-Amino-6-fluoro-4(3*H*)-pyrimidinone from 4-benzyloxy-6-fluoro-2-pyrimidinamine (H_2, Pd, EtOH: 66%).[1040]

6-Fluoro-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione from 2,4-dibenzyloxy-6-fluoro-5-methylpyrimidine (H_2, Pd, MeOH: 95%).[3164]

Also other examples.[1838,2567,3174]

Such processes are most often of practical use because alkoxy groups are usually more easily hydrolyzed (or split) than are halogeno substituents in the same molecular environment, a fact evident in all categories of the foregoing examples.[105,615,1703,2049,3164] The same fact has made it convenient to use a two-step procedure for the conversion of 4-benzylamino-2-chloro- into 4-benzylamino-2-ethoxypyrimidine and thence (by warming briefly with concentrated hydrochloric acid) into 4-benzylamino-2(1*H*)-pyrimidinone;[1232] 2-chloro-4-pyrimidinamine into 2-methoxy-4-pyrimidinamine and thence into 4-amino-2(1*H*)-pyrimidinone;[1671] and for other such sequences.[1383,2057]

7.1.1.5. From Pyrimidinethiones or Derived Substrates

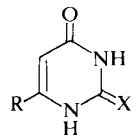
Pyrimidinethiones can sometimes be hydrolyzed directly into pyrimidinones, but it is usually better to convert such thiones into their alkylthio, alkylsulfinyl, or alkylsulfonyl derivatives or even into their derived sulfinic or sulfonic acids prior to hydrolysis. Such readily hydrolyzable intermediates need not necessarily be isolated; moreover, they may, of course, be prepared by other means. The following examples illustrate the hydrolytic step in such transformations.

From pyrimidinethiones directly

2,4(1*H*,3*H*)-Pyrimidinedione from 2-ethylthio-4(3*H*)-pyrimidinethione (5*M* HCl, reflux, prolonged).[3134]

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione (**28**, R = Me, X = O) from 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**28**, R = Me, X = S) (10*M* HCl, 150°, 3 h, sealed;[3135] PhIO, AcMe, 25°, 15 h, 58%[3727]).

2,4(1*H*,3*H*)-Pyrimidinedione (**28**, R = H, X = O) from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**28**, R = H, X = S) (PhIO, AcMe, 25°, 15 h: 62%).[3727]



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From isolated alkylthiopyrimidines

(*Note*: The conversion of pyrimidinethiones into alkylthiopyrimidines is discussed in Section 8.1.3.2.)

5-Phenylthio-2(1*H*)-pyrimidinone from 2-methylthio-5-phenylthiopyrimidine (HCl, MeOH–H_2O, 60°, 4 days: 95%).[3832]

4-Diethylamino-6-methyl-2(1*H*)-pyrimidinone from 4-diethylamino-6-methyl-2-methylthiopyrimidine (6*M* HCl, reflux, 15 h: 61%).[520]

1- or 3-Methyl-2,4(1*H*,3*H*)-pyrimidinedione from 1-methyl-2-methylthio-4(1*H*)- or 3-methyl-2-methylthio-4(3*H*)-pyrimidinone, respectively (6*M* HCl, reflux, 1–2.5 h: 72% or 83%, respectively).[1432, cf. 248]

1- or 3-Methyl-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione from 1-methyl-2-methylthio-6-phenyl-4(1*H*)- or 3-methyl-2-methylthio-6-phenyl-4(3*H*)-pyrimidinone, respectively (likewise: 65% or 72%, respectively).[301]

6-Chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione from 6-chloromethyl-2-methylthio-4(3*H*)-pyrimidinone (5*M* HCl, reflux, 3 h: 59%).[3907]

4-*o*-Hydroxyphenyl-6-methyl-5-nitro-2(1*H*)-pyrimidinone from 4-*o*-hydroxyphenyl-6-methyl-2-methylthio-5-nitropyrimidine (HCl, EtOH–H_2O, reflux, 6 h: 89%).[565]

4-Oxo-2,6-diphenyl-3,4-dihydro- from 4-methylthio-2,6-diphenyl-5-pyrimidinecarbonitrile (NaOH, EtOH–H_2O, 20°, 48 h: 30%).[48]

4-Morpholino-2(1*H*)-pyrimidinone from 2-benzylthio-4-morpholinopyrimidine (6*M* HCl, reflux, 5 h: 66% as hydrochloride).[4945]

1-Hydroxy-2,4(1*H*,3*H*)-pyrimidinedione from 1-benzyloxy-2-methylthio-4(1*H*)-pyrimidinone (6*M* HCl, reflux: 50%).[3274]

4-Amino-6-chloro-2(1*H*)-pyrimidinone from 6-chloro-2-methylthio-4-pyrimidinamine (5*M* HCl, reflux, 3 h: 90% as the hydrochloride).[1015, cf. 1568]

2,6-Dioxo-1,2,3,6-tetrahydro- from 2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (2*M* HCl, reflux, 3 h: 79%).[2889]

Ethyl 1,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro- from ethyl 1,6-dimethyl-4-methylthio-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate (2*M* HCl, reflux, 10 min: 61%; note survival of the ester).[796]

6-Amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione from 6-amino-3-methyl-2-methylthio-4-(3*H*)-pyrimidinone (*M* NaOH, reflux, 1 h: 79%).[1445]

5,5′-Bipyrimidine-2,2′(1*H*,1′*H*)-dione from 2,2′-bismethylthio-5,5′-bipyrimidine (3*M* HCl, reflux, 2 h: 80%).[4020, cf. 4019]

5-Bromo-2(1*H*)-pyrimidinone from 5-bromo-2-methylthiopyrimidine (TsNClNa, AcOH–THF–H_2O, 70°, 30 min: 74%; mechanism?).[3829]

5-Methyl-2(1*H*)-pyrimidinone from 2-carboxymethylthio-5-methylpyrimidine (2.5*M* HCl, reflux, 5 h: 80%).[1086]

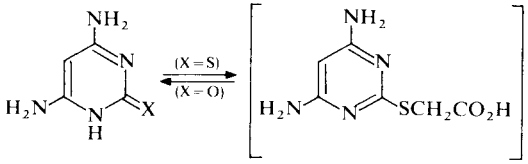
4-Amino-5-phenyl-2(1*H*)-pyrimidinone from 2-carboxymethylthio-5-phenyl-4-pyrimidinamine (6*M* HCl, reflux, 2 h: 83%).[4115]

Also other examples.[197,619,719,741,940,967,1046,1286,1321,1334,1678,1725,1782,1823,1899,2133 (cf. 3650),2192,2198,2888,3053,3148,4163,4262,4528,5114,5156]

Via unisolated alkylthiopyrimidines

(*Note*: The unisolated intermediate is commonly a carboxymethylthiopyrimidine, made in solution from the indicated pyrimidinethione by boiling with aqueous chloroacetic acid; only the subsequent hydrolytic step is shown here).

4,6-Diamino-2(1*H*)-pyrimidinone (**29**, X = O) from 4,6-diamino-2(1*H*)-pyrimidinethione (**29**, X = S) via the thioether (**30**) (*M* H_2SO_4, reflux, 1 h: 77%).[2404]



29 **30**

2,4(1*H*,3*H*)-Pyrimidinedione from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (2*M* HCl, reflux, 2 h: 95%);[2295, cf. 1650,3148] or from 4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (likewise: 70%).[3148]

4-Amino-2(1*H*)-pyrimidinone from 4-amino-2(1*H*)-pyrimidinethione (5*M* HCl, reflux, 2 h: 95%).[1652, cf. 1514,1650]

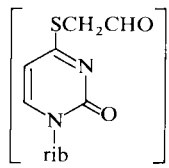
4-Amino-1-benzyl-2(1*H*)-pyrimidinone from 4-amino-1-benzyl-2(1*H*)-pyrimidinethione (5*M* HCl, reflux, 2 h: ~ 90%).[1511]

6-Cyclohexyl-2,4(1*H*,3*H*)-pyrimidinedinedione from 6-cyclohexyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone ($ClCH_2CO_2H$, H_2O, reflux, 6 h: 75%).[4175]

4-Acetyl-2-oxo-1,2-dihydro- from 4-acetyl-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylic acid ($ClCH_2CO_2H$, H_2O, reflux, 5 h: 50%).[823]

Also the following sequences using *S*-alkylating agents other than chloroacetic acid, as indicated.

6-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone to 2-(α-carboxy-α-methylethyl)thio-6-methyl-4(3*H*)-pyrimidinone (isolated), then to 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (3*M* HCl, reflux, 1 h: 95%).[3471]



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4-Thiouridine to uridine via unisolated 4-formylmethylthio-1-β-D-ribofuranosido-2(1*H*)-pyrimidinone (**31**) ($ClCH_2CHO$, pH 6, 37°, 24 h: > 90%).[5170]

Also other examples.[891,1152,1383,1482,1563,2123,2184,2413,2441,2698,2794,2898,3058,3083,3352,3385,3538,4053,4102,4117,4118]

From isolated alkylsulfonyl- or alkylsulfinylpyrimidines

(*Note*: The oxidation of alkylthio- to alkylsulfinyl- or alkylsulfonylpyrimidines is discussed in Section 8.4.2.4).

2(1*H*)- or 4(3*H*)-Pyrimidinone from 2-methylsulfonyl- or 4-methylsulfinylpyrimidine, respectively (2*M* NaOH, 25°, 2 h).[1715]

5-Methoxy-2(1*H*)-pyrimidinone from 5-methoxy-2-methylsulfonylpyrimidine (5*M* NaOH, 50°, 1 h: 89%).[2599]

5-Fluoro-2(1*H*)-pyrimidinone from 5-fluoro-2-methylsulfonylpyrimidine (5*M* NaOH, 80°, 15 min: 93%).[2160]

4,6-Dichloro-2(1*H*)-pyrimidinone from 4,6-dichloro-2-methylsulfonylpyrimidine (*M* NaOH, 40°, briefly: ~ 90% as Na salt).[958]

5-Chloro-2-oxo-1,2-dihydro- from 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid (5*M* NaOH, 40°, 30 min: 91%).[733]

5-Benzyl-2(1*H*)-pyrimidinone from 5-benzyl-2-methylsulfonylpyrimidine (NaOH, H_2O–dioxane, 25°, 15 min: 63%).[502]

5-Chloro-4-phenylethynyl-2(1*H*)-pyrimidinone from 5-chloro-2-methylsulfonyl-4-phenylethynylpyrimidine (*M* NaOH, 40°, 3 days: 63%).[220]

5-Trifluoromethyl-2(1*H*)-pyrimidinone from 2-ethylsulfonyl-5-trifluoromethylpyrimidine (*M* NaOH, 20°, 10 min: 67%).[117]

4-Amino-5-methyl-2(1*H*)-pyrimidinone from 2-ethylsulfonyl-5-methyl-4-pyrimidinamine (6*M* HCl, boil).[1544]

Also other examples.[43,724,774,1059,1155,1453,1454,1748,2162,2244,3741,5094]

Via unisolated sulfones or sulfoxides

(*Note*: Only the starting alkylthiopyrimidines and the resulting pyrimidinones are indicated, along with general conditions).

2,6-Dioxo-1,2,3,6-tetrahydro- from 2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (H_2SO_4–HNO_3, 20°, 1 h: 87%).[2889]

4-Methoxy-5,6-dimethyl-2(1*H*)-pyrimidinone from 4-methoxy-5,6-dimethyl-2-methylthiopyrimidine (25% H_2O_2, NaOMe–MeOH–H_2O, reflux, 1 h: 48%).[698,3324]

4-β-Hydroxyphenethylamino-2(1*H*)-pyrimidinone from 4-β-hydroxyphenethylamino-2-methylthiopyrimidine (30% H_2O_2, AcOH, 20°, 5 days: 20%).[4891]

4-Methoxy-2(1*H*)-pyrimidinone from 2-ethylthio-4-methoxypyrimidine (H_2O_2, EtOH;[1676,1751] the structure or melting point of this product appears to be incorrect[3285]).

Also other examples.[903,1543,2154–2156]

From isolated pyrimidinesulfonic acids or the like

4(3*H*)-Pyrimidinone from 4-pyrimidinesulfonic acid (kinetics in *M* NaOH).[1711]

2,6-Dimethyl-4(3*H*)-pyrimidinone from 2,6-dimethyl-4-pyrimidinesulfonic acid (2.5*M* HCl, 25°, 18 h: 80%; also kinetics in H^+ and HO^-).[2263]

4,6-Dimethyl-2(1*H*)-pyrimidinone from 4,6-dimethyl-2-pyrimidinesulfonyl fluoride (H_2O, reflux, 45 min: 47%).[1711]

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione from 4-methyl-6-oxo-1,6-dihydro-2-pyrimidinesulfonic acid (AcOH–H_2O, rapidly).[3224]

Also other examples.[1539,2071]

Via unisolated pyrimidinesulfonic acids or the like

(*Note*: The pyrimidinethione substrate, product, and general conditions are indicated in each case.)

6-Benzyl-5-phenylazo-2,4(1*H*,3*H*)-pyrimidinedione from 6-benzyl-5-phenylazo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (H_2O_2, 2*M* NaOH, 5°, 2 h: 58%).[4173]

6-Amino-5-ethyl-2-oxo-1,2-dihydro- from 6-amino-5-ethyl-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid (H_2O_2, NaOH, H_2O, boil, 3 min: 78%).[1183]

2,4(1*H*,3*H*)-Pyrimidinedione from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone, 4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone, or 2,4(1*H*,3*H*)-pyrimidinedithione (Me_2SO, H_2SO_4, 80°, 1.5–3 h: 75–80%).[1673]

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione from 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (KOBu^t, Bu^{t}OH, I, reflux, 30 h: 95%; sulfur is extruded as such).[3476]

1-Methyl-2,4(1*H*,3*H*)-pyrimidinedione from 1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone ($NaHSO_3$, H_2O, O_2, 20°, 7 h: 70%).[3418]

6-Ethyl-2,4(1*H*,3*H*)-pyrimidinedione from 6-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (2,5*M* HNO_3, ~50°, briefly: 55%).[2148]

5-β-Hydroxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione from 5-β-hydroxyethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (H_2O_2, NaOH, H_2O, 20°, 3 h: 60%).[3126]

2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid from ethyl 4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (10% HNO_3, reflux 30 min: 83%;[2873] H_2O_2, 10% H_2SO_4, 95°: ~ 50%[1631]).

Also other examples.[710,809,822,1183,2066,2178,2455,2855,6174]

7.1.1.6. By Other Means

Several minor routes to pyrimidinones are exemplified in the following paragraphs.

1. 2-Chloro-4-pyrimidinecarbonitrile gave 2,4(1*H*,3*H*)-pyrimidinedione (43%) by boiling in alkali;[1628] 2-methyl-4,5-pyrimidinedicarbonitrile gave 2-methyl-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile (39%) likewise;[1421] 1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinecarbonitrile gave 3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (43%) by refluxing in 50% sulfuric acid;[2522] and 2,5,6-trichloro-4-pyrimidinecarbonitrile gave 2,5,6-trichloro-4(3*H*)-pyrimidinone (~ 80%) by stirring with alkali at 0°.[2046]

2. 5-Nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime gave 5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (~ 50%) by boiling in alkali.[1165]

3. 4,6-Bis(dimethylaminomethyleneamino)-2-thiocyanatopyrimidine gave 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (60%) in refluxing hydrochloric acid;[1355] and 1-methyl-4-thiocyanato-2(1*H*)-pyrimidinone gave 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (~ 50%) by prolonged treatment at 20° with 0.1*M* acid or alkali.[3515]

4. 4-Methoxy-5,6-dimethylpyrimidine 1-oxide gave 4-methoxy-5,6-dimethyl-2(1*H*)-pyrimidinone (~ 30%) on treatment with tosyl chloride followed by base;[698] 5-nitroso-4,6-pyrimidinediamine gave 4,6-diamino-5-nitro-2(1*H*)-pyrimidinone (up to 50%, along with other separable products) on oxidation with peroxy acids;[2426] 5-bromopyrimidine gave 5-bromo-4(3*H*)-pyrimidinone (70%) on treatment with peroxyacetic acid in acetone containing sulfuric acid.[170]

5. 4,4′,6,6′-Tetraphenyl-2,2′-azoxypyrimidine underwent thermal rearrangement in refluxing glycol to afford 1-(4′,6′-diphenylpyrimidin-2′-yl)-4,6-diphenyl-2(1*H*)-pyrimidinone (97%).[511]

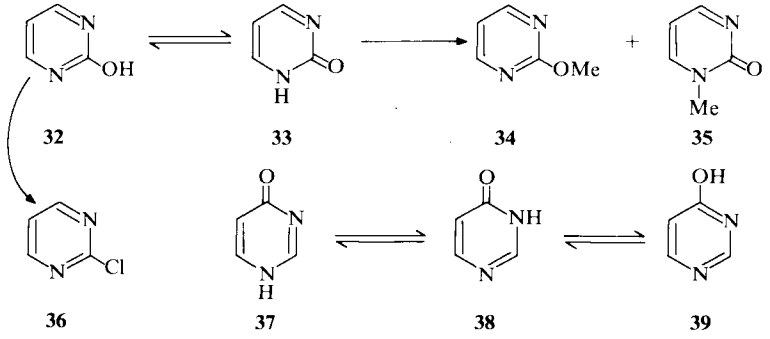
6. 5-Chloro-4-phenylethynyl-2-trimethylsiloxypyrimidine gave 5-chloro-5-phenylethynyl-2(1*H*)-pyrimidinone (90%) on dissolution in aqueous dioxane for 30 min.[220]

7. The formation of 5-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione from its 5,6-dihydro derivative was achieved in 76% yield by heating with cupric bromide in dimethylformamide–acetic acid for 14 h, whereas traditional oxidative methods gave little or no product.[139]

8. 1-Methyl-2,6-dioxo-3-phenyl-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide underwent rearrangement, by fission of its 2,3-bond and recyclization, to give 5-anilinomethylene-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (NaOEt, EtOH, reflux, 3 h: 61%).[6032]

7.1.2. Fine Structure of Tautomeric Pyrimidinones

The reactions of a tautomeric pyrimidinone clearly indicate that it exists in some sort of equilibrium between the hydroxypyrimidine and its cycloamidic form(s) in which the proton is attached to one or other ring nitrogen. For example, 2(1*H*)-pyrimidinone (**32**/**33**) reacts in its hydroxy form (**31**) with phosphoryl chloride to give 2-chloropyrimidine (**36**), whereas the same substrate undergoes methylation of both tautomeric forms to afford 2-methoxypyrimidine (**34**) and 1-methyl-2(1*H*)-pyrimidinone (**35**) in a ratio depending on the reagent and conditions. The relatively high melting points of 2(1*H*)- and 4(1*H*)-pyrimidinone (180° and 165°, respectively) compared with that of pyrimidine (22°) suggests that the former exist in the solid state as cyclic amides, a conclusion upheld by strong carbonyl-stretching bands in the 1600–1700 cm^{-1} region of their ir spectra,[437,708] and subsequently by an X-ray crystal structure of 2(1*H*)-pyrimidinone.[5175] Moreover, the uv spectrum of 2(1*H*)-pyrimidinone (**32**/**33**) in aqueous solution closely resembled that of the fixed amidic analog, 1-methyl-2(1*H*)-pyrimidinone (**35**), but differed profoundly from the other fixed analog, 2-methoxypyrimidine (**34**);[1432] similar studies of the isomeric 4-pyrimidinone (**37**/**38**/**39**) indicated that it existed in aqueous solution as a mixture of 4(1*H*)- (**37**) and 4(3*H*)-pyrimidinone (**38**) in which the latter predominated strongly.[1432] The first nmr examination of 2(1*H*)-pyrimidinone in dimethyl sulfoxide indicated equivalence of H4 and H6: hence, either the accepted formulation (**33**) was in error or there was a relatively fast *N*-proton exchange in the molecule (**33**);[4612] the latter explanation proved correct and would be accepted now as axiomatic.[5171–5173] A similar examination of 4(3*H*)-pyrimidinone in dimethyl sulfoxide and in water confirmed that it existed in each solvent, mainly as the 4(3*H*)-tautomer (**38**), probably with a small proportion of the 4(1*H*)-tautomer (**37**) present.[5174] However, both 2(1*H*)- and 4(3*H*)-pyrimidinone showed significant contributions from 2- and 4-pyrimidinol, respectively, in the vapor phase.[5224]



The fine structures of a great many pyrimidinones with or without one or more additional substituents have been examined in the solid state and/or in

solution. In fact, little of interest has emerged because virtually all pyrimidinones examined do exist in their oxo forms and only in a few instances do there appear to be significant contributions from the unusual tautomer. Most of these data have been reviewed adequately.[5172,5173] The following list includes typical pyrimidinones that have been so examined in the solid state and/or in solution; it also indicates a few examples in which the usual name may not reflect accurately the molecular species present.

X-Ray crystal structures

4-Amino-2(1*H*)-pyrimidinone (cytosine) as hydrate.[5178]

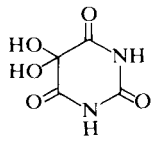
2,4(1*H*,3*H*)-Pyrimidinedione (uracil).[5182]

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione (barbituric acid),[5179] as dihydrate,[5180,5201] or as the ammonium salt.[5182] Structure is consistent with nmr.[5219]

5-Oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (alloxan)[3572,5183] and its so-called hydrate, 5,5-dihydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**40**).[3991,5184] Structures confirmed by nmr.[5219]

5-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (dialuric acid) as its hydrate, formulated as 5,6-dihydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione hydrate (**41**).[5185,5186] Anhydrous molecular structure confirmed by nmr.[5219]

5-Nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (dilituric acid), formulated as 6-hydroxy-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**42**);[5187,5220,5223] also its hydrate, formulated as the *aci*-nitropyrimidinetrione (**43**).[5188]



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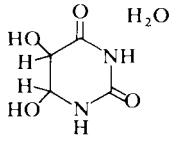

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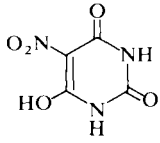

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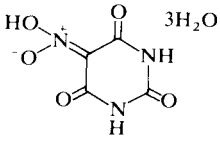

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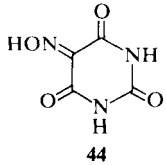

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5-Nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (violuric acid) as its hydrate, formulated as 5-hydroxyimino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**44**);[5189,5190] also its potassium and rubidium salts.[5191,5192]

5-Phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, formulated as 6-hydroxy-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (solid) but as a mixture of both forms in dimethyl sulfoxide (^{13}C nmr).[317]

5,5-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (barbital);[3029] also its sodium and potassium salts.[5195,5196]

Also related examples.[3116,3742,3971,3978,5193,5197–5201]

Structures based on solution spectra

4-Amino-2(1*H*)-pyrimidinone;[1534,1678,5171,5202,5203] a postulated zwitterionic form[5204] is no longer accepted.

2,4(1*H*,3*H*)-Pyrimidinedione;[3802,5204–5206] vapor likewise.[5224]

5-Methyl-2,4(1*H*,3*H*)-pyrimidinedione (thymine).[3162,5204,5205,5207]

2-Amino-4(3*H*)-pyrimidinone (isocytosine) as such with a small proportion of the 4(1*H*)-tautomer.[1507]

6-Amino-4(3*H*)-pyrimidinone (ψ-cytosine).[1507]

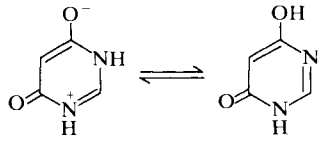
5-Halogeno-2,4(1*H*,3*H*)-pyrimidinediones.[2277,3162,5204,5205,5208]

5-Bromo-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione as such with a significant proportion of 5-bromo-4-hydroxy-1-methyl-2(1*H*)-pyrimidinone.[1894]

5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione.[1584,5205]

2-Thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (thiouracil).[3022,4612]

4,6(1*H*,5*H*)-Pyrimidinedione (ψ-uracil) probably exists mainly as the zwitterion (**45**) with a little 6-hydroxy-4(3*H*)-pyrimidinone (**46**);[5213] other data have been interpreted differently.[1216,1900,2777,3235,3278,3350,5174,5214–5216]

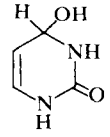


45 **46**

6-Thioxo-5,6-dihydro-4(3*H*)-pyrimidinone.[2186]

Also other examples.[1894 (cf. 1546),2277,2837,3802,5205,5207,5209–5212,5217,5218,6897]

There is good indirect evidence that 2(1*H*)-pyrimidinone may exist partly as the covalent hydrate, 4-hydroxy-3,4-dihydro-2(1*H*)-pyrimidinone (**47**), in aqueous solution.[5225] Association of 4(3*H*)-pyrimidinones by intermolecular hydrogen bonding has been suggested on the basis of concentration effects in their nmr spectra.[5226]



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7.1.3. Reactions of Tautomeric Pyrimidinones

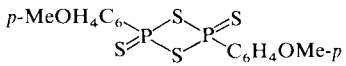
Pyrimidinones are the most commonly used starting molecules for the synthesis of many other types of pyrimidine. Hence, an understanding of their reactions is of the utmost importance.

7.1.3.1. Conversion into Halogenopyrimidines

The conversion of tautomeric pyrimidinones into the corresponding halogenopyrimidines, often by the action of phosphorus halides, has been discussed in Sections 6.1–6.4.

7.1.3.2. Conversion into Pyrimidinethiones

The traditional route from tautomeric pyrimidinones to pyrimidinethiones is by conversion into the chloropyrimidines (Section 7.1.3.1), followed by treatment with sodium hydrogen sulfide or thiourea (Section 6.7.7). However, direct thiation is less troublesome and usually more satisfactory. The process is carried out by heating with purified phosphorus pentasulfide[958] in an inert solvent or (usually better) in pyridine or another tertiary base; Lawesson's reagent (**48**), 2,4-bis-*p*-methoxyphenyl-1,3-dithia-2,4-diphosphetane-2,4-disulfide,[5227,5233] may be used in occasional difficult cases. 4/6-Oxo substituents undergo thiation much more readily than do 2-oxo substituents, so it is often possible to 4-monothiate a 2,4-pyrimidinedione selectively. Nontautomeric pyrimidinones also undergo thiation (see Section 7.5.2).



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The following products were made by direct thiation of the corresponding pyrimidinones, usually by heating under reflux with phosphorus pentasulfide in the indicated solvent.

Simple 4/6-monothiations

4(3*H*)-Pyrimidinethione (pyridine, 1 h: 58–74%).[958,3524,3637]

2,6-Dimethyl-4(3*H*)-pyrimidinethione (pyridine, 30 min: ~ 65%).[1951]

2-Methyl-4(3*H*)-pyrimidinethione (pyridine, 3 h: 60%).[690,3481]

2-Methyl-6-phenyl-4(3*H*)-pyrimidinethione (pyridine, 1 h: 62%).[234]

6-Methyl-2-phenyl-4(3*H*)-pyrimidinethione (Lawesson's reagent, hexamethylphosphoramide (?), 100°, 2 h: 67%).[3728]

5-Methoxy-4(3*H*)-pyrimidinethione (pyridine, 1 h: 54%).[1341,1343]

5-Amino-4(3*H*)-pyridinethione (xylene, 8 h: ~ 45%;[1036] pyridine: high yield[1654]).

5,6-Diamino-4(3*H*)-pyrimidinethione (*β*-picoline, 40 min: 68%;[5228] pyridine, 90 min: < 50%[2449,5228]).

5,6-Diamino-2-methyl-4(3*H*)-pyrimidinethione (pyridine, 6 h: 0%;[3058] *β*-picoline, 1 h: 49%;[593] NEt_3, 15 h: 51%[593]).

2-Amino-5-phenyl-4(3*H*)-pyrimidinethione (pyridine, 3 h: 78%).[4103]

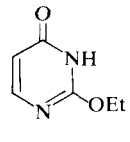
5-Hydroxy-2-methyl-4(3*H*)-pyrimidinethione (pyridine, 8 h: 86%).[1821]

2,5,6-Triamino-4(3*H*)-pyrimidinethione (quinoline, 170°, 7 h: 70%).[3671]

2,4(1*H*,3*H*)-Pyrimidinedithione from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (xylene, 8 h: 87% crude;[1650,2840] *α*-picoline, 15 min: 56% pure;[1652] diglyme, $NaHCO_3$, 110°, 1 h: 99%;[521] Lawesson's reagent, pyridine, 5 h: 78%[3874]).

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione from 6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (xylene, 8 h: 76% pure;[1221] *β*-picoline, 20 min: 63%[1752]).

4-Thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**50**, R = H) from 2-ethoxy-4(3*H*)-pyrimidinone (**49**) (pyridine + trace H_2O, 2 h: 50%).[3492]



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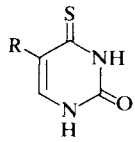

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5,6-Diamino-2,4(1*H*,3*H*)-pyrimidinedithione from 5,6-diamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (pyridine, 2.5 h: 55%).[1116]

Also other examples.[1038,1267,3129,3670,3868,3983,4163,4286,4874,5229]

Simple 2-monothiations

5-Bromo-2(1*H*)-pyrimidinethione (pyridine, 2 h: ~ 25%).[1951]

1-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione from 1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (tetralin, 180°, 4 h: 23%).[1513]

4-Methyl-6-phenyl-2(1*H*)-pyrimidinethione (Lawesson's reagent, PhH, 2 h: 69%).[3705]

4,6-Diphenyl-2(1*H*)-pyrimidinethione (Lawesson's reagent, hexamethylphosphoramide (?), 100°: 80%).[3728]

Selective thiations

4-Thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**50**, R = H) (pyridine hydrate, 3 h: 77%;[5231] pyridine, 20 h: 86%;[3226] Lawesson's reagent, hexamethylphosphoramide, 1 h: 78%;[3226] diglyme, $NaHCO_3$, 2 h: 92%[521]).

5-Ethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**50**, R = Et) (pyridine, 15 h: > 70%).[3760]

5-Fluoro-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**50**, R = F) (pyridine, 2 h: 76%;[2288] dioxane, 3 h: 86%;[2699] Lawesson's reagent, pyridine, 8 h: 69%[3874]).

1-Methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (pyridine, 3 h: 62%).[1533]

3-Methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (pyridine + trace H_2O, 5 h: ~ 35%).[3537]

5-Amino-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**50**, R = NH_2) (pyridine, 2 h: 50% as sulfate).[5086]

4,5-Diamino-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone (pyridine, 2.5 h: ~ 65%).[1443]

4-Amino-3-benzyl-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone (pyridine + trace H_2O, 5 h: 52%).[1058]

Methyl 1-methyl-2-oxo-6-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (dioxane, 2 h: > 90%).[3400]

Also other examples.[770,806,870,1550,4394,5232,5234]

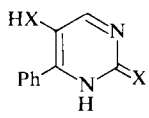
Di- and trithiations

2,4(1*H*,3*H*)-Pyrimidinedithione (sulfolane, 180°, 5 h: 97%;[3631] xylene, 90 min: 54% crude[2840]).

5-Butyl-2,4(1*H*,3*H*)-pyrimidinedithione (dioxane, 2 h: 72%).[4118]

1-Cyclohexyl-2,4(1*H*,3*H*)-pyrimidinedithione (pyridine, 8 h: 75%).[4394]

5-Mercapto-4,6-diphenyl-2(1*H*)-pyrimidinethione (**51**, X = S) from 5-hydroxy-4,6-diphenyl-2(1*H*)-pyrimidinone (**51**, X = O) (MeCN, NEt_3, 20°, 24 h: 46%; note unusual 5-thiation).[4054,5230]



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5-Phenyl-4,6(1*H*,5*H*)-pyrimidinedithione (pyridine, 3 h: 74%).[4362]

2-Phenyl-4,6(1*H*,5*H*)-pyrimidinedithione (likewise: 82%).[57]

6-Amino-2,4(1*H*,3*H*)-pyrimidinedithione (β-picoline, 2 h: 43%).[593]

2,5-Diamino-4,6(1*H*,5*H*)-pyrimidinedithione (pyridine, 6 h: 57%).[3988]

5-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione from 2-ethylthio-5-methyl-4(3*H*)-pyrimidinone (tetralin, 140–150°, 2 h: 75% crude; note thiation of the thioether group).[2840]

3-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione from 3-methyl-2,4(1*H*,3*H*)-pyrimidinedione or 3-methyl-2-methylthio-4(3*H*)-pyrimidinone (tetralin, 180°, 4 h: ~ 50% or 25%, respectively).[1221]

5,5-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrithione (PS_3, tetralin, reflux, 2 h: 56%;[5235] $P_2S_5 + K_2S$, xylene, reflux: ~50% plus 5,5-diethyl-2,6-dithioxo-1,2,3,6-tetrahydro-4(3*H*)-pyrimidinone, 25%).[5234] [*Note*: the similar use of PhMe gave a mixture of the last-mentioned product plus 5,5-diethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione[5234]].

Also other examples.[1515,2840]

7.1.3.3. *O*- or *N*-Acylation Reactions

The acylation of a tautomeric pyrimidinone, for example, with acetyl chloride or benzenesulfonyl chloride, may afford an acyloxypyrimidine, an *N*-acylpyrimidinone, or a mixture of both. Factors determining the site(s) of acylation are still unclear, and it is possible that some of the products described, especially in the pre-nmr era, may yet prove to be isomers. The formation of the following acylated products from the corresponding pyrimidinones will illustrate the conditions required.

1-Acetyl-4(1*H*)-pyrimidinone (Ac_2O, reflux, 1–6 h: 50–60%; proven structure).[314,836]

1-Acetyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, reflux, 4 h; proven structure).[815]

3(?)-Undecanoyl-2,4(1*H*,3*H*)-pyrimidinedione ($C_{10}H_{22}COCl$, tetralin, reflux, 2 h).[5256]

1,3-Dibenzoyl-2,4(1*H*,3*H*)-pyrimidinedione (BzCl, pyridine–MeCN, 20°, 16 h: 65%) and thence to 3-benzoyl-2,4(1*H*,3*H*)-pyrimidinedione (K_2CO_3, dioxane–H_2O, 20°: 65%).[51,5237, cf. 1726]

1-Benzoyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (BzCl, pyridine–MeCN, 20°, 2 h: 85%); the 3-benzoyl isomer (80%) was made via 1,3-dibenzoyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione, as in the previous example.[51,5237]

3-Acetyl-5-fluoro-1-*o*-nitrobenzyl-2,4(1*H*,3*H*)-pyrimidinedione (AcCl, NEt_3, dioxane, 20°, 1 h: 78%).[300]

4-Acetoxy-2-methoxy-6-methylpyrimidine (AcCl, pyridine–MeCN, 20°, 3 h: 78%); 4-benzoyloxy analog (BzCl, likewise: 95%).[3817]

4-Acetoxy-5-butyl-2-dimethylamino-6-methylpyrimidine (Ac_2O, reflux, 4 h: 86%).[672]

2-*t*-Butyl-4-methanesulfonyloxypyrimidine ($MeSO_2Cl$, NEt_3, PhH, 30 min).[5238]

4-Methanesulfonyloxy-6-methyl-2-methylthiopyrimidine ($MeSO_2Cl$, NEt_3, CH_2Cl_2, 30 min: > 70%).[2612]

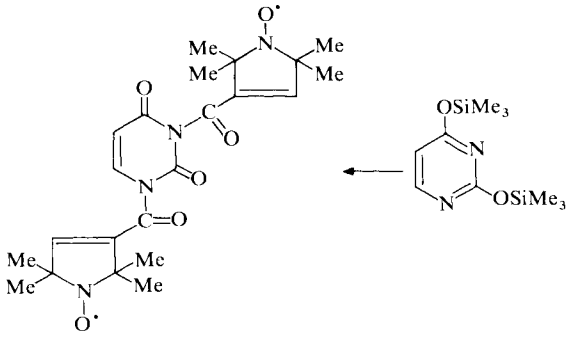
Ethyl 4-benzenesulfonyloxy-2-piperidino-5-pyrimidinecarboxylate ($PhSO_2Cl$, NaOH, H_2O, 50°, 40 min: 38%).[2989]

6-Toluenesulfonyloxy-5-(3′,4′,5′-trimethoxybenzyl)-2,4-pyrimidinediamine (TsCl, NaOH, AcMe–H_2O, 60°, 3 h: 78%).[558]

O,O-Diethyl *O*-(2-isopropyl-6-methylpyrimidin-4-yl)phosphorothioate from 2-isopropyl-6-methyl-4(3*H*)-pyrimidinone [ClP(:S)$(OEt)_2$, K_2CO_3, PhH, 50° (?)];[2905,5291] the product, "Diazinon," is a powerful insecticide.

Also other examples.[278,522,527,758,798,810,3011,4738,4941,5236,5237,5258,5271–5278,6019]

The *N*-acylation of a pyrimidinone may be assured by first converting the pyrimidinone into a trimethylsiloxy (see following Section 7.1.3.4) which then reacts with an acyl chloride under quite gentle conditions (cf. the Birkofer *N*-acylation procedure[5239,5240]) to afford an *N*-acylated pyrimidinone with loss of trimethylsilyl chloride. For example, 2,4-bistrimethylsiloxypyrimidine (**53**) reacted with the fairly stable radical, 2,2,5,5-tetramethyl-1-oxylpyrroline-3-carbonyl chloride, during 4 h in benzene under nitrogen at 20°, to yield 1,3-bis(2′,2′,5′,5′-tetramethyl-1′-oxylpyrroline-3′-carbonyl)-2,4(1*H*,3*H*)-pyrimidinedione (**52**) (69%), fully characterized.[135]



52 **53**

7.1.3.4. *O*-Silylation and *O*-Stannylation Reactions

Treatment of a pyrimidinone with chlorotrimethylsilane or "hexamethyldisilazane" (bistrimethylsilylamine) invariably gives the corresponding trimethylsiloxypyrimidine. Such a process may be used to characterize an otherwise nonmelting pyrimidinone, to provide a relatively volatile derivative for gc (gas chromatography) and so on, or to protect a potential hydroxy group from attack during other molecular modifications (see, for example, Section 7.1.3.3). It should be remembered that pyrimidinamines or tautomeric pyrimidinethiones will undergo respective *N*- or *S*-trimethylsilylation just as readily. The conditions required for silylations are illustrated in the formation of the following trialkylsiloxypyrimidines.

2,4-Bistrimethylsiloxypyrimidine (**53**) [$ClSiMe_3$, dioxane or PhH, NEt_3, 20°, 7 h: 72%;[1792,3387] $(Me_3Si)_2NH$, 150°, 11 h, sealed: 94–97%[828,1793]].

4-Ethoxy-2-trimethylsiloxypyrimidine [$(Me_3Si)_2NH$, 150°, 11 h, sealed: 85–98%].[828,1793]

5-Methyl-2,4-bistrimethylsiloxypyrimidine [$(Me_3Si)_2NH$, Me_2NCHO, 150°, 11 h: 92%].[1793,2786]

5-Chloro-2,4-bistrimethylsiloxypyrimidine [$(Me_3Si)_2NH$, $(NH_4)_2SO_4$, reflux, 5 h: 95%].[3822, cf. 5243]

5-Bromo-2,4-bistrimethylsiloxypyrimidine ($ClSiMe_3$, PhH, NEt_3, reflux, 2 h: 92%).[1800, cf. 5243]

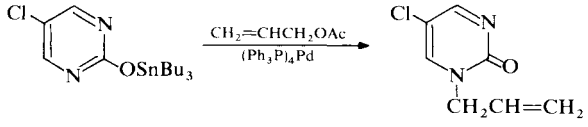
4-Fluoro-5-methyl-2,6-bistrimethylsiloxypyrimidine [$(Me_3Si)_2NH$, Me_2NCHO, reflux, 10 h: 62%].[3158]

4-Trimethylsiloxy-2-trimethylsilylthiopyrimidine [$(Me_3Si)_2NH$, $(NH_4)_2SO_4$, reflux, 2.5 h: 94%;[4118] $(Me_3Si)_2NH$ + $ClSiMe_3$, dioxane, reflux, 16 h: 89%[1689]].

2-Trimethylsiloxy-4-trimethylsilylaminopyrimidine ($ClSiMe_3$, NEt_3, 20°, 3 day: 69%).[3387]

Also other examples.[2933,3322,5098,5244]

In a similar way, appropriate tautomeric pyrimidinones react with bistributyltin oxide, $(Bu_3Sn)_2O$, in refluxing benzene during 2 h to afford 5-chloro-2-tributylstannyloxypyrimidine (**54**) (72%) and its 5-bromo (81%), 5-iodo (72%), or 5-phenylthio (68%) analogs.[3772] Like the trialkylsiloxy analogs, such stannyloxypyrimidines undergo facile *N*-alkylation with loss of the stannyl grouping to afford, for example, 1-allyl-5-chloro-2(1*H*)-pyrimidinone (**55**) (allyl acetate plus tetrakis(triphenylphosphine)palladium as a catalyst: 68%).[3772]



54 **55**

7.1.3.5. *O*- and/or *N*-Alkylation Reactions

Irrespective of the reagent and conditions, alkylation of a tautomeric pyrimidinone (e.g., **56**) usually gives an *N*-alkylpyrimidinone, sometimes accompanied by a smaller amount of the isomeric alkoxypyrimidine. Very occasionally, the ratio may be reversed, especially when diazomethane or a Meerwein reagent is used; moreover, steric and/or electronic effects associated with the reagent or passenger group(s) on the substrate can induce unexpected results.

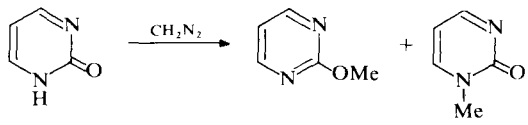
The formation of the following products exemplifies the results obtained on alkylation of various types of substrate with a variety of reagents. The examples are grouped according to the substrate type; within each such group, any

examples yielding an appreciable proportion on alkoxypyrimidine are usually placed first; given percentages represent isolated yields.

From simple (mono-)pyrimidinones

4-Ethoxy-2,6-dimethylpyrimidine (Et_3OBF_4, CH_2Cl, 20°, 15 h: 76%).[2534]

2-Methoxypyrimidine (**57**) (17%) and 1-methyl-2(1*H*)-pyrimidinone (**58**) (52%) (CH_2N_2, Et_2O, 2 days).[1432]



56 **57** **58**

4-Methoxypyrimidine (9%) and 3-methyl-4(3*H*)-pyrimidinone (51%) (CH_2N_2, Et_2O, 2 days);[1432] only the 1-methiodide of the latter (MeI, MeOH, 20°, 30 days: (17%);[1432] 1-methyl-4(1*H*)- (5%) and 3-methyl-4(3*H*)-pyrimidinone (25%) (MeI, KOH, EtOH, reflux, 30 min);[3117, cf. 1136] only the latter (Me_2SO_4, NaOMe, MeOH, reflux, 1 h: 47%; incorrect isomeric structure given in the original);[3496] and other data.[2551]

4-Methoxy-6-methylpyrimidine (~ 12%) and 3,6-dimethyl-4(3*H*)-pyrimidinone (~ 50%) (CH_2N_2, Et_2O, 24 h);[2249] only the latter (MeI, KOH, MeOH, reflux, 2 h: ~ 60%).[1879]

4-Methoxy-2,5-dimethylpyrimidine (17%) and 2,3,5-trimethyl-4(3*H*)-pyrimidinone (58%) (CH_2N_2, Et_2O–MeOH, 3 h).[3326]

4-Isopropoxy-2,6-dimethylpyrimidine from Na salt of 2,6-dimethyl-4(3*H*)-pyrimidinone (Pr^iI, EtOH, reflux, 9 h: 61%).[2701]

2,3-Diethyl-4(3*H*)- (52%) and 1,2-diethyl-4(1*H*)-pyrimidinone (27%) from Na salt of 2-ethyl-4(3*H*)-pyrimidinone (EtBr, Me_2NCHO, 20°, 2 days).[2551]

3-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4(3*H*)-pyrimidinone from Hg salt of 4(3*H*)-pyrimidinone (tetra-*O*-acetylglucopyranosyl bromide, PhMe, reflux, 1 h: 32%).[5245]

3-Methyl-2-phenyl-4(3*H*)-pyrimidinone (Me_2SO_4, "soda," H_2O (?): 90%).[690]

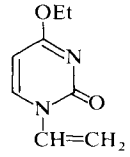
1-Allyl-2(1*H*)-pyrimidinone (CH_2=$CHCH_2Br$, NaOEt, EtOH, reflux: 74%).[919]

3-Diphenylmethyl-4(3*H*)-pyrimidinone (Ph_2CH_2OH + AcOH, reflux, 8 h: 51%).[4363]

1-Ethoxycarbonylmethyl-2(1*H*)-pyrimidinone ($BrCH_2CO_2Et$, K_2CO_3, MeCN, reflux, ~2 h: 30%).[355]

1-(3′,4′-Dichlorobenzyl)-2(1*H*)-pyrimidinone (3,4-dichlorobenzyl chloride, K_2CO_3, KI, MeOH, reflux, 24 h: 56%).[5246]

4-Ethoxy-1-vinyl-2(1*H*)-pyrimidinone (**59**) [CH_2=$CHOAc$, $Hg(OAc)_2$, H_2SO_4 (trace), 50°, 2 days, sealed: 55%].[1722]



59

Also other examples.[1312,1437,1735,1755,1951,2551,2941,2947,3165,4021,4178,4403,5247–5249,5253,6578]

[*Note*: Two limited studies[2551,5248] on the effect of solvent on alkylation of simple 4(3*H*)-pyrimidinones are rewarding to scan.]

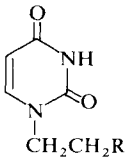
From simple pyrimidinediones: first-stage monoalkylations

(*Note*: No such *O*-alkylations appear to be known.)

1-Methyl-2,4(1*H*,3*H*)-pyrimidinedione from K salt of 2,4(1*H*,3*H*)-pyrimidinedione (MeI, dioxane or PhMe, reflux, 15 h: > 40%).[2769]

1-δ-Methoxybutyl-2,4(1*H*,3*H*)-pyrimidinedione [$MeO(CH_2)_4Br$, K_2CO_3, NaI, Me_2SO, 90°, 3 h: 49%).[4739]

1-β-Diethylaminoethyl-2,4(1*H*,3*H*)-pyrimidinedione (**60**, R = Et_2N) (Et_2N-CH_2CH_2Cl, NaH, dioxane, reflux, 6 h: 15%).[3616]



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1-β-Hydroxyethyl- (**60**, R = OH) (28%) and 1,3-bis-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione from Na salt of 2,4(1*H*,3*H*)-pyrimidinedione (ethylene carbonate, Me_2NCHO, reflux, 45 min).[1722,1756,1758]

1-Isopropyl- (25%) and 3-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (8%) from Na salt of substrate (Pr^iI, Me_2NCHO, 90°).[332]

5-Methyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione (PrBr, K_2CO_3, Me_2SO, 25°, 11 h: 44%).[608,1613]

1-Di(ethoxycarbonyl)methyl-2,4(1*H*,3*H*)-pyrimidinedione from K salt of substrate [$(EtO_2C)_2CHBr$, Me_2NCHO, 100°, 1 h: 70%].[5241]

1-Acetonyl-2,4(1*H*,3*H*)-pyrimidinedione from K salt of substrate ($BrCH_2Ac$, K_2CO_3, Me_2SO, 20°, 15 h: 56%).[742, cf. 745]

1,5-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (Me_3PO_4, $C_{10}H_8$, reflux, 5 h: 80%; excess Me_3PO_4 gave 1,3,5-trimethyl analog: 87%).[2770]

1-β-Cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione (**60**, R = CN) (CH_2=CHCN,

NaOH, NEt_3, H_2O, 60°, 8 h: 73%; excess reagents under reflux gave 1,3-bis-β-cyanoethyl analog: 77%).[1725]

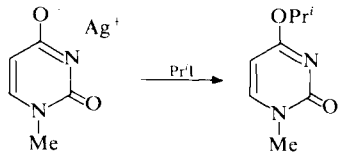
1-γ-Acetylthiopropyl- (**60**, R = CH_2CSAc) or 3-γ-acetylthiopropyl-2,4(1*H*,3*H*)-pyrimidinedione (*S*-γ-bromopropyl thioacetate, NaH, Me_2NCHO at 80–150° or Me_2SO at 20°, respectively).[940]

Also other examples.[378,488,742,875,983,994,1323,1722,1797,1864,1885,1943,2030,2489,2538,2540,2779,2781,2791,3196,3269,3700–3702,5223,5242,5254,5255,5265,6951]

[*Note*: Useful general spectrometric ways to distinguish 1- from 3-alkyl-2,4(1*H*,3*H*)-pyrimidinediones have been devised.[3099,5257]]

From simple pyrimidinediones: second-stage monoalkylations

4-Isopropoxy-1-methyl-2-(1*H*)-pyrimidinone (**62**) from 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**61**) silver salt (Pr^iI, PhMe, reflux, 11 h: 66%).[3045]



61 **62**

4-Isopropoxy-6-methyl-1-phenyl-2(1*H*)-pyrimidinone from 6-methyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione silver salt (Pr^iI, *n*-C_8H_{18}, reflux, 8 h: 50%, plus traces of the other two isomers).[5250,5251, cf. 2701,5264]

1-(3′,5′-Di-*O*-acetyl-2′-deoxyribofuranosyl)-4-ethoxy-5-methyl-2(1*H*)-pyrimidinone from 3′,5′-di-*O*-acetylthymidine silver salt (EtI, PhMe, 50°, 33 h: > 45%).[253]

3-Cyclohexyl-1,6-dimethyl- from 3-cyclohexyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Me_2SO_4, 2.5*M* NaOH, 25°: ~ 90%).[3425]

3-β-Hydroxyethyl-1-methyl- from 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (ethylene carbonate, K_2CO_3, Me_2NCHO, reflux, 75 min: 95%).[2143]

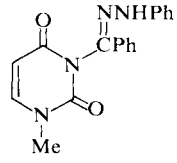
1-β-Hydroxyethyl-3,6-dimethyl- from 3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione ($ClCH_2CH_2OH$, 1.5*M* NaOH, reflux, 2 h: 76%).[3901]

3-Benzyl-1-methyl- from 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($PhCH_2Br$, KOH, EtOH, reflux, 7 h: 73%).[4912]

3-Amino-1-methyl- from 3-amino-2,4(1*H*,3*H*)-pyrimidinedione (CH_2N_2, MeOH–Et_2O, 20°, 1 h: ~ 40%).[1486]

3,6-Dimethyl- from 6-methyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione silver salt (MeI, Me_2NCHO, 20°, 24 h: 67%).[2701]

1-Methyl-3-(α-phenylhydrazonobenyzl)- (**63**) from 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione [PhC(Cl)=NNHPh, NaOH, EtOH–H_2O, 20°, 90 min: 70% plus an unexpected isomer].[375]



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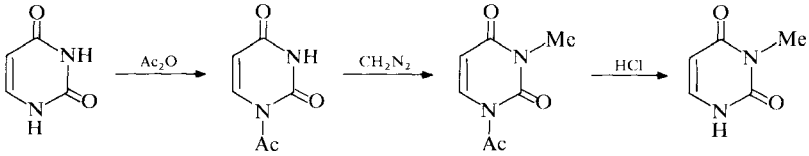
4-Benzyloxy-6-methoxy-5-methylpyrimidine (30%) and 6-benzyloxy-3,5-dimethyl-4(3*H*)-pyrimidinone (58%) from 6-benzyloxy-5-methyl-4(3*H*)-pyrimidinone (CH_2N_2, dioxane–Et_2O, 20°, 15 h).[5169]

Also other examples.[1483,1693,1722,1862,2700,3045,5092,5259–5263]

[*Note*: Second-stage alkylations may be used to produce a 3-monoalkylated-2,4(1*H*,3*H*)-pyrimidinedione by using a substrate bearing a 1-acyl or other removable group, which can be detached subsequently. This process is illustrated by the sequence 2,4(1*H*,3*H*)-pyrimidinedione (**64**) → its 1-acetyl (**65**) (Ac_2O) → its 1-acetyl-3-methyl (**66**) (CH_2N_2) → its 3-methyl derivative (**67**) (HCl, EtOH: 75% overall);[1722] also by others.[908,1797,2787,5237]]



64 **65** **66** **67**

From simple pyrimidinediones: dialkylations

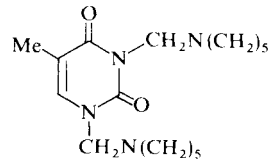
2,4-Diethoxypyrimidine (Et_3OBF_4, neat, 75°, 30 min: 43%).[2524]

1,3-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (CH_2N_2, Et_2O, 24 h: ~ 73% plus three minor isomeric products;[3329, cf. 2768] Me_2SO_4, 5*M* NaOH, 0–100°, 88–94%;[2401,2772, cf. 963,5279] Me_2SO_4, Bu_4NF, THF, 20°, 30 min: 99%;[2549] Me_2SO_4, KOH, Bu_4NBr, 20°, 3 h (no solvent): 96%;[266] MeBr or Me_3PO_4, Bu_4NF, THF, 25°, 1 h: > 97%;[1536] $Me_3\overset{+}{S}{=}O\ HO^-$, Me_2NCHO, 80°, 2 h: 81%;[1535] $C_6H_{11}N{=}C(OMe)NHC_6H_{11}$, Me_2NCHO, 100° 40 h: 77%[263]).

1,3,5-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (CH_2N_2, EtO_2, 24 h: high yield;[2768, cf. 963] Me_2SO_4, 3*M* NaOH, reflux, 30 min: 91%;[2786] Me_2SO_4, 5*M* NaOH, 0–100°: 61%;[2772] $Me_3\overset{+}{S}{=}O\ HO^-$, Me_2NCHO, 80°, 2 h: 77%[1535]).

1,3-Dibenzyl-2,4(1*H*,3*H*)-pyrimidinedione ($PhCH_2Br$, K_2CO_3, AcMe, reflux, 30 h: 82%;[5266] $PhCH_2Cl$, Bu_4NF, THF, 25°, 1 h: 96%[1536]).

5-Methyl-1,3-bis(piperidinomethyl)-2,4(1*H*,3*H*)-pyrimidinedione (**68**) (CH_2O, piperidine, EtOH–H_2O, reflux, 2 h: 90%; a double Mannich reaction !).[537]



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Also other examples.[1725,1755,1841,2024,2529,2997,3132,3245,4108,5247] including a general method.[2720]

From simple pyrimidinetriones

(*Note*: The alkylation of pyrimidinetriones is of little preparative use.)

6-Methoxy-2,4(1*H*,3*H*)-pyrimidinedione (~ 10%), 6-methoxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (~ 5%), and 2,6-dimethoxy-3-methyl-4(3*H*)-pyrimidinone (< 5%) from 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (CH_2N_2, Et_2O, 0°, 10 min);[2533, cf. 2804,3736,3756] 6-methoxy-2,4(1*H*,3*H*)-pyrimidinedione only (HCl gas, MeOH, 20°, 4 h: 77%).[3365]

6-Methoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (?) from 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, its 1-methyl-, or its 1,3-dimethyl derivative (CH_2N_2, Et_2O, 24–48 h: > 50%).[789,5267]

5-Ethyl-4,6-dimethoxy-2(1*H*)-pyrimidinone (CH_2N_2, Et_2O, 0°, 10 min: ~ 20%).[2533, cf. 2804]

2,6-Diethyl-3-methyl-5-phenyl-4(3*H*)-pyrimidinone (> 15%), and 2,4,6-trimethoxy-5-phenylpyrimidine (> 5%) from 5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (CH_2N_2, Et_2O, 0°, 24 h).[2533,2804]

1,3-Diethyl-6-methoxy-2,4(1*H*,3*H*)-pyrimidinedione from 1,3-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (3rd stage) (CH_2N_2, MeOH–Et_2O, 0°).[2533]

3,5-Diethyl-2,6-dimethoxy-4(3*H*)-pyrimidinone from 1,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (2nd and 3rd stages) (CH_2N_2, MeOH–Et_2O, 0°: 28% plus minor products).[2526]

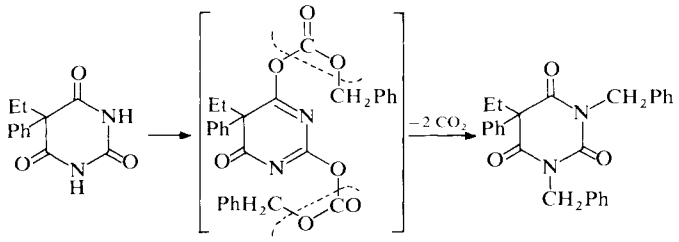
5,5-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (?) from Ag salt of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (MeI, MeOH, cold).[834,5269]

1,3-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Me_2SO_4, NaOH, H_2O).[5267]

5-Ethyl-1-(β-hydroxy-γ-methoxypropyl)-5-phenyl- from 5-ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione as Na salt ($ClCH_2CHOHCH_2OMe$, EtOH, reflux, 8 h: 85%).[5268]

1,3-Dibenzyl-5-ethyl-5-phenyl- (**71**) from 5-ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**69**) as Li_2 salt, possibly via the di-*O*-acylated intermediate (**70**) ($ClCO_2CH_2Ph$, Me_2NCHO, 60°, 30 min: 92%).[5270]

Also other examples.[106,350,569,3365,3485,5268,5270]



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From nitropyrimidinones

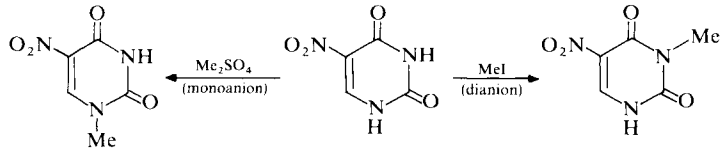
2-Isopropoxy-5-nitropyrimidine (14%) and 1-isopropyl-5-nitro-2(1*H*)-pyrimidinone (14%) (Pr^iI, KOH, Me_2NCHO–H_2O, 60°, 24 h).[2941]

1-Methyl-5-nitro-2(1*H*)-pyrimidinone from Na salt of substrate (MeI, EtOH, reflux, 2 h: poor yield;[703] initially formulated as 2-methoxy-5-nitropyrimidine but later corrected[4722] and confirmed in structure[1879]).

1-Ethyl-5-nitro-2(1*H*)-pyrimidinone (EtI, KOH, MeOH–H_2O, 55°, 24 h: 27%).[2941]

1-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**72**) (Me_2SO_4, NaOH, MeOH–H_2O, pH 8: 75%).[1126, cf. 1492,2779,3267]

3-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**74**) [MeI, Bu_4NOH, Me_2NCHO, 25°, 1 h: 47%; substrate (**73**) reacted as its dianion.][2706]



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1,3-Dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (excess Me_2SO_4, NaOH, H_2O, pH 8, 40°, 2 h: 85%);[1126] also from 1-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione.[1492,2703]

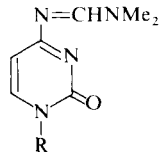
Also other examples.[904,1105,1130,1694,1887,4682]

From aminopyrimidinones

(*Note*: Aminopyrimidinones show little tendency to undergo *O*-alkylation.)

1. 4-Amino-2(1*H*)-pyrimidinones as substrates.

   4-Amino-1-methyl-2(1*H*)-pyrimidinone (MeI, KOH, EtOH: ~15%;[1511, cf. 963,1664] $Me_3S{=}O$ HO^-, Me_2NCHO, 80°, 2 h: 80%[1535]); less directly via 4-dimethylaminomethyleneamino-1-methyl-2(1*H*)-pyrimidinone (**75**, R = Me) [$Me_2NCH(OMe)_2$, trace F_3CCO_2H, reflux, 15 h: intermediate (98%); then 0.1*M* HCl, 20°, 12 h: 97%].[1540]



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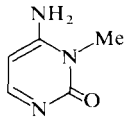
4-Amino-3-methyl-2(3*H*)-pyrimidinone (**76**) and 4-imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone (**77**) (excess Me_2SO_4, Me_2NCHO, 100°, 1 h: 25% and 5%, respectively;[3782] the major product (**76**) was confirmed in structure.[809,1383,1534,3577,3782]



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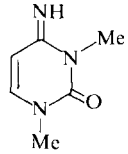

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4-Imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone (**77**) (MeBr, Bu_4NF, THF, 25°, 1 h: 85%;[1536] Me_2SO_4, Bu_4NF, THF, 25°, 30 min: 88% plus some 4-amino-1-methyl-2(1*H*)-pyrimidinone[2549]).

1-Allyl-4-amino-2-(1*H*)-pyrimidinone [$Me_2NCH(OCH_2CH{=}CH_2)_2$, Me_2N-CHO, 90°, 24 h: (**75**, $R = CH_2CH{:}CH_2$) (96%); then NH_4OH, 20°, 17 h: 99%].[871]

4,6-Diamino-1-methyl-2(1*H*)-pyrimidinone (Me_2SO_4, NaOH, H_2O, 40°, 4 h: ~55%;[2390] Me_2SO_4, pH 11.6, 100°, 2 h: 62%[2419]).

4-Amino-1-benzyl-2(1*H*)-pyrimidinone ($PhCH_2Cl$, KOH, EtOH, reflux, 2 h: ~75%).[1511]

6-Amino-3-benzyl-1-benzyloxy- from 6-amino-1-benzyloxy-2,4(1*H*,3*H*)-pyrimidinedione (2nd stage; $PhCH_2Cl$, Na_2CO_3, H_2O–EtOH, reflux, 4 h: 73% plus 7% of the 5-benzyl isomer).[1280]

Also other examples.[41,129,697,963,1396,1743,4115]

2. 2-Amino-4(3*H*)-pyrimidinones as substrates.

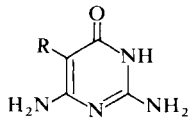
4-Ethoxy-6-methyl-2-pyrimidinamine (Et_3OBF_4, liquid SO_2, −40° to −20°, 4 h: 56%).[2524]

2-Amino-1-methyl-4(1*H*)- and 2-amino-3-methyl-4(3*H*)-pyrimidinone (Me_2SO_4, 5*M* NaOH, 40°, 2–5 h: 87% of mixture, separable with much loss;[982] MeI, NaOEt, EtOH, reflux, 90 min: ~ 50% of a mixture, also separable[1520]).

2-Amino-3,6-dimethyl-4(3*H*)-pyrimidinone (only?) (MeI, KOH, EtOH, 60°, 3 h: 50%).[657, cf. 861,959,1147]

2-Amino-3-β-hydroxyethyl-6-methyl-4(3*H*)- (25%) and 2-amino-1-β-hydroxyethyl-6-methyl-4(1*H*)-pyrimidinone (20%) ($ClCH_2CH_2OH$, NaOH, MeOH–H_2O, reflux, 4 h: easily separable mixture).[1312]

2,6-Diamino-5-methyl-4(3*H*)-pyrimidinone (**78**, R = Me) (only) from the 5-demethylpyrimidine (**78**, R = H) (MeI, NaOMe, MeOH, reflux, 1 h: 22%; quite unusual).[1520]



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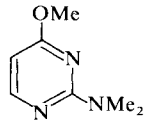

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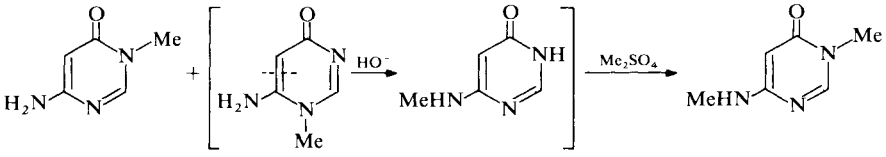
2-Dimethylamino-4-methoxypyrimidine (**79**) ($\sim$ 30%) and 2-dimethylamino-3-methyl-4(3*H*)-pyrimidinone ($\sim$ 15%) (MeI, NaOMe, MeOH, reflux, 2 h: both products of proven structure).[1743]

2-Amino-3-β-carboxyethyl-6-methyl-4(3*H*)-pyrimidinone (only?) (CH_2=CHCN, *M* NaOH, reflux, 10 h: 50%; note hydrolysis of CN to CO_2H).[979]

Also other examples.[41,301,333,984,1281,1282,1336,2017]

3. 6-Amino-4(3*H*)-pyrimidinones as substrates.

6-Amino-3-methyl-4(3*H*)-pyrimidinone (**80**) ($\sim$ 30%) and 3-methyl-6-methylamino-4(3*H*)-pyrimidinone (**83**) [Me_2SO_4, 2*M* NaOH, 40°;[659,968,1179] the second product probably arose from Dimroth rearrangement of 6-amino-1-methyl-4(1*H*)-pyrimidinone (**81**) and further methylation of the product (**82**)[1179]].



80 **81** **82** **83**

6-Amino-2,3-dimethyl-4(3*H*)-pyrimidinone (MeI, NaOEt, EtOH, reflux, 30 min: $\sim$ 50%).[1158]

6-Amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Me_2SO_4, NaOH, H_2O: as major product).[1213]

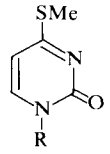
6-Amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione from 6-amino-2,4(1*H*,3*H*)-pyrimidinedione (excess Me_2SO_4, NaOH: 65%);[1131,2411] or from 6-amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (likewise: 80–85%).[1108,1131,1214]

Also other examples.[1062,1325]

From alkylthio- or thioxodihydropyrimidinones

(*Note*: Any such thioxodihydro substrate will undergo rapid and preferential *S*-alkylation to the corresponding alkylthio substrate, which may then undergo further *O*- or *N*-alkylation; unless otherwise stated, the appropriate alkylthio substrate may be assumed in the following examples.)

2-Isopropoxy-4-methylthiopyrimidine (**85**) (49%) and 1-isopropyl-4-methylthio-2(1*H*)-pyrimidinone (**84**, R = Pr^i) (35%) from Na salt of the substrate (**84**, R = H) (Pr^{i}I, Me_2NCHO, 20°).[2941]



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85

4-Allyloxy-2-methylthiopyrimidine (15%), 3-allyl-2-methylthio-4(3*H*)-pyrimidinone (26%), and 1-allyl-2-methylthio-4(1*H*)-pyrimidinone (8%) ($CH_2CH{=}CHBr$, KOH, EtOH–H_2O, reflux, 90 min).[846]

1-Methyl-4-methylthio-2(1*H*)-pyrimidinone (only) from Na salt of substrate (MeI, Me_2NCHO, 20°: 81%).[2941]

1-Benzyl-4-methylthio-2(1*H*)-pyrimidinone ($PhCH_2Br$, NaOMe, MeOH, reflux, 10 min: 91%).[870, cf. 3134]

1-Methyl-2-methylthio-4(1*H*)- (38%) and 3-methyl-2-methylthio-4(3*H*)-pyrimidinone (37%) from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (Me_2SO_4, 5*M* NaOH, 50–70°);[1432,3117] or only the second product [$Me_2NCH(OMe)_2$, PhMe, reflux, 1 h].[1783]

3-Benzyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone ($PhCH_2Cl$, KOH, EtOH, reflux ?, 5 h: ~ 40%; other isomer not observed).[5157]

3-β-Cyanoethyl-2-methylthio-4(3*H*)-pyrimidinone ($CH_2{=}CHCN$, pyridine–H_2O, reflux, 8 h: ~ 60%).[697]

1-Methyl-6-methylthio-3-propyl- from 6-methylthio-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione (2nd stage; MeI, NaOH, EtOH–H_2O, reflux, 2 h: 75%).[909]

4-Ethylthio-2(1*H*)-pyrimidinone (~ 30%) and 3-ethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (~ 20%) from 4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone [$EtC(OEt)_3$, $(EtCO)_2O$, reflux, 1 h; note unusually sluggish *S*-alkylation].[3146]

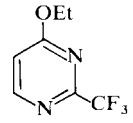
Also other examples.[112,182,321,525,891,911,929,1145,1806,1942,2241,2242,2698, 2700,2789,2904,3750,3751,5280,5285]

From halogenopyrimidinones

4-Chloro-6-methoxypyrimidine (3%) and 6-chloro-3-methyl-4(3*H*)-pyrimidinone (28%) (CH_2N_2, Et_2O, 20°, 15 h).[968]

5-Bromo-2-methoxypyrimidine (~ 17%) and 5-bromo-1-methyl-2(1*H*)-pyrimidinone (~ 40%) (CH_2N_2, Et_2O, 25°, 16 h).[1951]

4-Ethoxy-2-trifluoromethylpyrimidine (**86**) from Na salt of substrate (EtBr, Me_2NCHO, 20°, 5 h: ~ 98%).[2551]



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5-Bromo-1-ethyl-2(1*H*)-pyrimidinone (EtI, NaOH, EtOH, reflux, 3 h: ~ 60%).[1879]

5-Fluoro-1-methyl- (MeI, NaOMe, MeOH, 20°, 6 h: 67%)[3165] or 1-benzyl-5-fluoro-2(1*H*)-pyrimidinone ($PhCH_2Br$, NEt_3, CH_2Cl_2, 20°, 2 days: 50%).[294]

6-Chloro-1-methyl- (CH_2N_2, Et_2O–EtOH, 20°, 40 min: 52%); 6-chloro-3-methyl- (Me_2SO_4, 2.5*M* NaOH, 20°, 3 h: 51%); or 6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (CH_2N_2, Et_2O–EtOH, prolonged: > 90%; also by treatment of the 6-chloro-3-methyl product with Me_2SO_4/alkali: 68%).[2113]

1-Ethoxycarbonylmethyl- (57%) and 1,3-bis(ethoxycarbonylmethyl)-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (22%) ($BrCH_2CO_2Et$, K_2CO_3, Me_2NCHO, 100°, 10 h).[2023]

1-Allyl-6-chloro-3-methyl- from 6-chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($CH_2{=}CHCH_2Br$, K_2CO_3, Me_2NCHO, 20°, 2 h: 52%).[882]

5-Fluoro-1-tetrahydrofuran-2′-yl-2,4(1*H*,3*H*)-pyrimidinedione (2-*t*-butoxytetrahydrofuran, Me_2NCHO, 160°, 4 h: 67%; other 2-alkoxytetrahydrofurans gave much lower yields).[5282]

Also other examples.[44,113,117,191,327,328,429,516,741,800,875,899,1798,1962,2383,2911,3025,3048,3765,3827,3830,3850,4536,5281,6074,6171]

From alkoxy or hydroxypyrimidinones

2-Ethoxy-1-methyl-4(1*H*)- (18%) and 2-ethoxy-3-methyl-4(3*H*)-pyrimidinone (24%) (Me_2SO_4, 5*M* NaOH, 80°, 30 min).[1521]

4-Ethoxy-1-vinyl-2(1*H*)-pyrimidinone ($AcOCH{=}CH_2$, H^+, Hg^{2+}, 45°, 2 days, sealed: 55%).[1722]

5-Ethoxy-2,3-dimethyl-4(3*H*)-pyrimidinone (MeI, KOH, EtOH, reflux, 1 h: ~ 70%).[1821]

1,3-Dimethyl-5-trityloxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (MeI, BaO, Me_2NCHO, 20°, 24 h: 87%).[761]

5-Methoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione from 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (excess CH_2N_2, 24 h;[2576] Me_2SO_4[749]).

Also other examples.[901,2901,5283]

From other types of substituted pyrimidinones

(*Note*: These examples include some with two or more types of passenger group.)

2,3-Dimethyl-6-methylsulfonyl-4(3*H*)-pyrimidinone (MeI, NaOEt, EtOH, reflux, 3 h).[2142]

5-Acetyl-1-cyclohexyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Me_2SO_4, NaOH, H_2O, 20°, > 1 h: 80%).[794]

Methyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate from the corresponding acid (HCl, MeOH, 100°, 15 h: ~ 40%) or its Ag salt (MeI); 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (Me_2SO_4, NaOH, H_2O, 100°, 1 h); and 1,3-dimethyl- from 3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (Me_2SO_4, *M* NaOH, 30 min: ~ 50%).[2673] Much of the earlier literature is quite confusing.[2848,2875–2877,2879,2955,3139,3391,3576]

6-Ethoxy-1-methyl- and thence 6-ethoxy-3-ethyl-1-methyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione ($MeCHN_2$, Et_2O: product according to reagent excess and time).[2899]

6-Amino-3-methyl-2-methylthio- from 6-amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (Me_2SO_4, 2*M* NaOH, 40°, 6 h: ~ 75%).[659,1426]

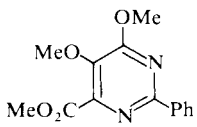
5-Dimethylamino-3-methyl-6-methylthio- from 5-dimethylamino-6-methylthio-4(3*H*)-pyrimidinone (MeI, KOH, EtOH, 20°, 28 h; or Me_2SO_4, K_2CO_3, AcMe, 20°, 25 h; ~ 60% by each way).[1017]

6-Benzyloxy-2-dimethylamino-5-nitro-6-pyrimidinamine from 6-amino-2-dimethylamino-5-nitro-4(3*H*)-pyrimidinone ($PhCH_2Cl$, K_2CO_3, Me_2NCHO, 80°, 2 h: 87%).[5284]

4-Amino-1-methyl-5-nitro-2(1*H*)-pyrimidinone (MeI, KOH, H_2O, 100°, 1 h, sealed: 70%;[1289] Me_2SO_4, KOH, H_2O, 20°: 70%[1433]).

5-Methoxy-6-methoxymethyl-3-methyl-2-methylthio- from 5-methoxy-6-methoxymethyl-2-methylthio-4(3*H*)-pyrimidinone (Me_2SO_4, 2*M* NaOH, < 30°, 4 h).[3268]

1-Benzyl-5-fluoro-4-methylthio-2(1*H*)-pyrimidinone [$Me_2NCH(OCH_2Ph)_2$,



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Me_2NCHO, 80°, 6 h: 48%; or $C_6H_{11}N{=}C(OCH_2Ph)NHC_6H_{11}$, $MeOCH_2CH_2OMe$, reflux, 70 min: 68%].[1895]

Methyl 5,6-dimethoxy-2-phenyl-4-pyrimidinecarboxylate (**87**) from methyl 5-hydroxy-6-oxo-2-phenyl-1,6-dihydro-4-pyrimidinecarboxylate (CH_2N_2, Et_2O–MeOH, 0°, 30 min: ~ 75% plus an unidentified isomer).[4137]

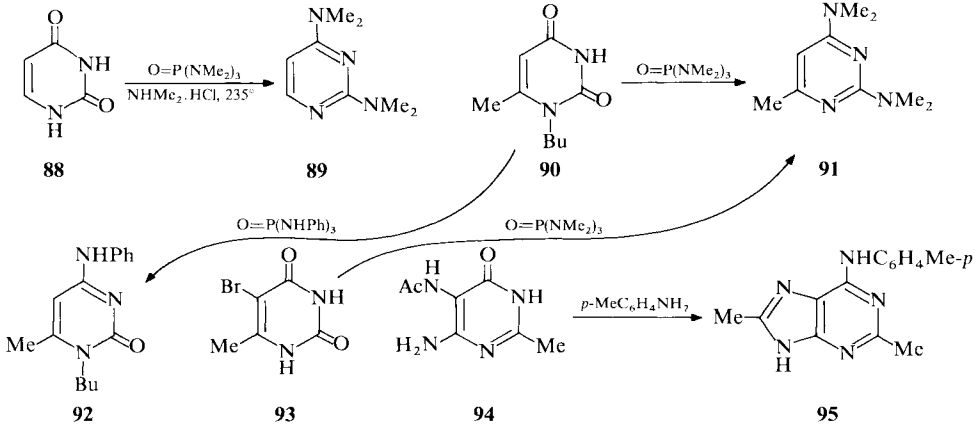
1,3-Dibenzyl-5-bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid ($PhCH_2Cl$, 0.5*M* NaOH, reflux, 5 h: 67%)[1797]

Also other examples.[202,369,502,524,568,777,933,1015,1076,1105,1289,1323,1402,1433,2894,3268,3924,3977,5280,5285]

7.1.3.6. Conversion into Pyrimidinamines

The conversion of tautomeric pyrimidinones into the corresponding pyrimidinamines is done usually via a chloropyrimidine, a pyrimidinethione, or such like intermediate. However, there exists a semidirect procedure for such a conversion,[5287] by heating with an amide of phosphoric or phosphorous acid: its use is limited by the vigorous conditions needed. Thus 2,4(1*H*,3*H*)-pyrimidinedione (**88**) and phosphoric trisdimethylamide [$O{=}P(NMe_2)_3$] at 235° for 1 h gave 2,4-bisdimethylaminopyrimidine (**89**) (75%);[1736] it proved important to use unpurified amide[5288] and the addition of a catalyst, for example, dimethylamine hydrochloride, improved the rate of reaction so that the same yield was achieved in 15 min.[1734] The same substrate (**88**) likewise gave 2.4-dianilinopyrimidine [$O{=}P(NHPh)_3$, 240°, 10 min: 46%];[1736] 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 2,4-bisdiethylamino-6-methylpyrimidine [$O{=}P(NEt_2)_3$, 220°, 25 min: 53%;[1736] or similarly, with a catalytic amount of $POCl_3$: 64%[1734]]; and 4,6(1*H*,5*H*)-pyrimidinedione gave 4,6-bisdimethylaminopyrimidine [$O{=}P(NMe_2)_3$, 210°, 1 h: 12%].[1736]

Selective aminolysis at the 4-position of 1-alkyl-2,4(1*H*,3*H*)-pyrimidinediones is possible. Thus, although 1-butyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**90**)



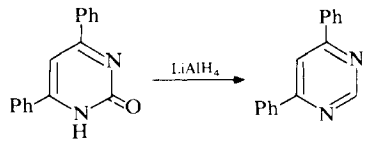
with phosphoric trisdimethylamide gave only 2,4-bisdimethylamino-6-methylpyrimidine (**91**) (47%) with loss of the butyl group,[1736] the same substrate (**90**) with phosphoric trisphenylamide gave 4-anilino-1-butyl-6-methyl-2(1*H*)-pyrimidinone (**92**) (82%),[2639] and 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione with phosphorous trisdimethylamide [$P(NMe_2)_3$] gave 4-dimethylamino-1-methyl-2(1*H*)-pyrimidinone (55%).[2639]

Other passenger groups may be lost or altered: for example, 5-bromo-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**93**) gave 2,4-bisdimethylamino-6-methylpyrimidine (**91**) as the sole isolable product (41%) on treatment with phosphoric trisdimethylamide;[1736] 4-amino-2(1*H*)-pyrimidinone with phosphoric trisphenylamide gave mainly 2,4-dianilinopyrimidine (20%);[1734] and 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid with phosphoric trisdimethylamide gave 2,6-bisdimethylamino-*N*,*N*-dimethyl-4-pyrimidinecarboxamide (28%).[1734]

Less predictable aminolyses have been reported occasionally. Thus 2-ethyl-6-methyl-4(3*H*)-pyrimidinone gave 2-ethyl-4-diformylmethyl-6-dimethylaminopyrimidine (Vilsmeier reagent from $Me_2NCHO + POCl_3$, 65°, 4 h: 28%);[2611] 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl fluoride gave 4-amino-2-oxo-1,2-dihydro-5-pyrimidinesulfonyl fluoride (NH_4OH, 25°, 10 min: 55%);[1608] 6-chloro-5-diphenylmethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 2,6-diamino-5-diphenylmethyl-4(3*H*)-pyrimidinone (NH_3, EtOH, 150°, 12 h, sealed: 70%);[4651] and 5-acetamido-6-amino-2-methyl-4(3*H*)-pyrimidinone (**94**) gave 2,8-dimethyl-6-*p*-toluidinopurine (**95**) (P_2O_5, NEt_3HCl, *p*-$MeC_6H_4NH_2$, 240°, 4 h: 94%), involving aminolysis before or after ring closure.[201]

7.1.3.7. Removal of Oxo Substituents

Removal of the oxo substituent(s) from a tautomeric pyrimidinone is usually done by conversion into the corresponding chloropyrimidine (Section 6.1) or pyrimidinethione (Section 7.1.3.2) followed by dechlorination (Section 6.7.1) or desulfurization (Section 8.1.3.1), respectively. However, the more direct reductive removal of an oxo substituent has proved successful occasionally. Thus the dry distillation of 2-ethyl-6-methyl-4(3*H*)-pyrimidinone with zinc dust gave 2-ethyl-4-methylpyrimidine in low yield;[2543] treatment of 2,4(1*H*,3*H*)-pyrimidinedione or its 5-methyl derivative in dilute acetic acid with sodium amalgam gave 2(1*H*)-pyrimidinone or 5-methyl-2(1*H*)-pyrimidinone, each in ~ 3% yield;[3497] 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione likewise gave 5-fluoro-2(1*H*)-pyrimidinone (~ 1% yield);[5289] and 4,6-diphenyl-2(1*H*)-pyrimidinone



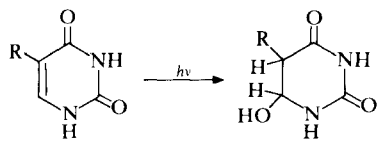
96 **97**

(**96**) was reduced by lithium aluminum hydride in dioxane at 100° during 5 h to afford 4,6-diphenylpyrimidine (**97**) (> 70%) plus a little of its dihydro derivative,[5290] a preparation subsequently modified to afford the latter in 78% yield and enabling it to be identified as the unusual 2,5-dihydro derivative.[137]

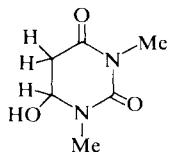
7.1.3.8. Photochemical Reactions

Pyrimidinones, both tautomeric and nontautomeric, undergo several types of photochemical reaction that essentially effect regions of the molecule other than the actual oxo substituent(s).[5292,6550] Chemical aspects of these are outlined briefly in the following paragraphs and in Section 11.1.9. The photoinduced formation of Dewar isomers of simple pyrimidinones appears to be confined in practice to nontautomeric substrates, so discussion of this phenomenon is located in Section 7.5.2. The standard abbreviations for photoproducts[5311] are not used here.

Photohydration of several biologically important pyrimidinones occurs on irradiating their solutions with ultraviolet light. Thus 2,4(1*H*,3*H*)-pyrimidinedione (**98**, R = H) gave its 5,6-hydrate, 6-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**99**, R = H), which reverted to the substrate (**98**, R = H) on treatment with acid;[5293,5299, cf. 5294,5295] likewise, 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 6-hydroxy-1,3-dimethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**100**),[5297,5298,5300] which was confirmed in structure,[1859,1860] reverted to the substrate in acid or alkali,[1860,5301] and underwent irreversible degradation on further irradiation.[5296] Most analogs with a 5-substituent resisted the formation of such hydrates, but 5-ethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**101**, R = Et) did appear to form a hydrate (**102**, R = Et), which subsequently lost ethanol to afford eventually a mixture of 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**101**, R = H) and its hydrate (**102**, R = H).[5302] A similar mixture resulted from 1-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (**103**), which seems to have undergone an initial hydration followed by photodecarboxylation of the product for the most part.[1807,5303] In contrast, 1-β-carboxyethyl-, 1-carbamoylmethyl-, and 1-ethoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione simply formed regular hydrates.[1807] Irradiation of 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione in isopropyl alcohol gave its 5,6-dihydro derivative (50% yield) with no sign of adduct formation.[6351] Other aspects of such photohydrates have been discussed,[5304–5309] and an extensive bibliography up to about 1975 has appeared.[5310a]



98 **99**



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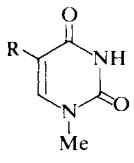

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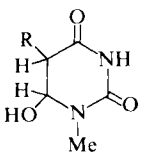

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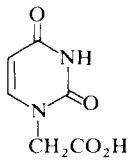
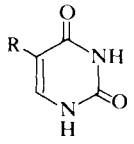


103

Photooxidation occurs when 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**104**, R = Me) is irradiated in aerated aqueous solution.[5322] Thus ultraviolet irradiation produced 5-hydroxymethyl- (**104**, R = CH_2OH), the aldehyde (**104**, R = CHO), and 5-unsubstituted-2,4(1*H*,3*H*)-pyrimidinedione (**104**, R = H).[5312] Although the 5-carboxy analog (**104**, R = CO_2H) could not be found, it was assumed to be a transitory product,[5312] an assumption strengthened by the identification of 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (**105**, R = CO_2H) among the products from an analogous oxidation of 1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**105**, R = Me).[2668] The formation of a "dithyminyl peroxide" molecule (**106**) has been postulated as the primary oxidative step in each of the foregoing photooxidations.[5313, cf. 5314] The uv irradiation of 5-bromo-6-hydroxy-5-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**107**) gave several products, of which at least one must have arisen by oxidation.[4933] In a quite different way, the benzil-sensitized photooxidation of 1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**105**, R = Me) in methylene chloride by oxygen in visible light (> 320 nm) gave mainly 5,6-dihydroxy-1,3,5-trimethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**109**) (60%), probably via hydration of the 5,6-epoxide (**108**).[5318]



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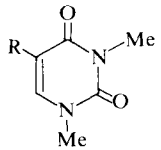

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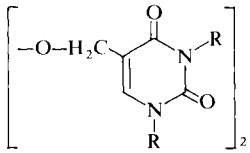

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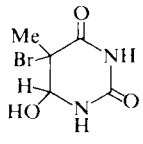

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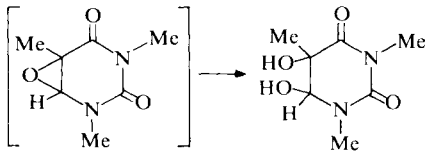
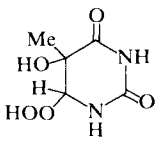


108 **109**

In contrast, γ-irradiation of 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**104**, R = Me) in aerated aqueous solution gave 6-hydroperoxy-5-hydroxy-5-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**110**),[5317] a product previously formulated as its isomer (**111**);[5306,5315,5319,5320] many other products have been identified after γ-irradiation of such pyrimidinones.[3574,5300,5316,5318,5321]



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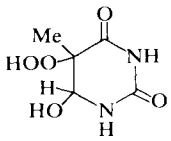


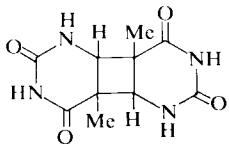
111

Photodimerization of 2,4(1*H*,3*H*)-pyrimidinedione and related compounds affords at least two types of dimeric product: the better-known type comprises the cyclobutane dimers in which two pyrimidine molecules are joined by two bonds so that a cyclobutane ring is formed from C5 and C6 of both parent molecules; the less well known type comprises simple bimolecular photoproducts, in most of which the two pyrimidine molecules are joined by a single bond between their respective 4- or 5-positions to afford a 4,4′- or 5,5′-bipyrimidine derivative. At least one phototrimer has been described,[5373,5374] in which both types of bonding are represented in the single product.

The formation of *cyclobutane dimers* can often be achieved effectively by uv irradiation of thin solid films or (better) of frozen aqueous solutions of the substrates: in the latter case, the formation of crystalline ice appears to force the solute into solid aggregates in which the substrate molecules are suitably arranged for dimerization, usually to a single dimer, during subsequent irradiation. Other frozen solvents are ineffective. Moreover, if the dimer is suspended later in (liquid) water and irradiated (even at the same wavelength), the equilibrium or steady state is reversed because the monomeric molecules are randomly distributed in the solution as they are formed and hence show relatively little tendency to redimerize.[5323,5324] The adverse biological effects produced by uv irradiation of living tissue appear to arise from the formation of such dimers from adjacent thymine residues in each polynucleotide strand: accordingly, photodimerization in such biopolymers has been studied extensively.[5292,5325-5328]

Cyclobutane dimers were first observed in 1958 when 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione was irradiated in frozen aqueous solution to mimic its immobile situation in a biopolymer helix:[5329] the product was tentatively formulated[5330] as the *anti*-dimer (**112**) without regard to the *cis* or *trans* relationship of the pyrimidine rings. However, it became evident in the course of later work,[5323,5325,5331-5337] that the main product was, in fact, the *cis–syn*-isomer (**113**) in which the head-by-head (*syn*) pyrimidine rings were disposed (*cis*) as are the front and back covers of a closed book, with the cyclobutane ring as the spine (unfortunately, this nomenclature is still not universally accepted[5310b]). The foregoing configuration was confirmed in four distinct ways.[5338-5341] Moreover, borohydride reduction of the *cis–syn*-dimer (**113**) gave mainly a single stereoisomer (**114**) of 1,2-bishydroxymethyl-1,2-dimethyl-3,4-diureidocyclobutane, whereas (for example) similar treatment of the *trans–anti*-dimer (isolated from a thymine solution irradiated in the presence of carbonyl sensitizers[5342]) gave 1,3-bishydroxymethyl-1,3-dimethyl-2,4-

diureidocyclobutane of the indicated configuration (**115**).[5343] Mixtures of all four isomeric dimers were formed by irradiation in various solvents, some containing sensitizers: each dimer was characterized by nmr and mass spectra; the conditions and solvent determined the ratio of isomers.[5364,5365] Broadly analogous cyclobutane dimers were also formed by irradiation of the following typical substrates as solid films, as frozen aqueous solutions, or as regular solutions in a variety of solvents.



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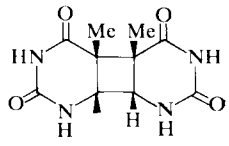

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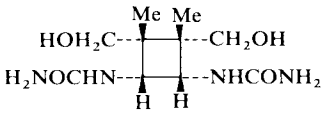

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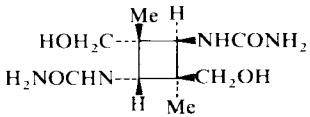
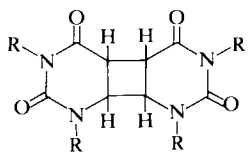


115

2,4(1*H*,3*H*)-Pyrimidinedione gave all four fundamental isomeric dimers (**116**, R = H), fully characterized.[5344-5351,5358] Each underwent complete *N*-methylation (MeI, Ag_2O, Me_2SO)[5353] to afford the appropriate dimer (**116**, R = Me) from 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione;[5352] some of these suffered a slow additional *C*-methylation to give, for example, the hexamethylated *trans–anti*-dimer (**117**) in 92% yield.[5354]



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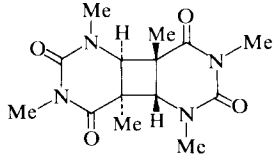


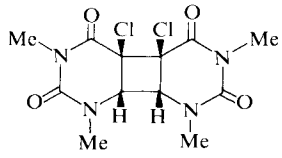
117

1,3-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave all four dimers (**116**, R = Me),[5355] each characterized subsequently.[5352,5356] Replacement of water by deuterium oxide during irradiation shifted the equilibrium, hydrate:dimer, dramatically in favor of the latter.[5357]

1,3,5-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave four isomeric dimers (e.g. **117**),[5135,5333,5339,5340] which were eventually characterized.[5359-5363]

6-Chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione, irradiated in aqueous solution, gave the crystalline *cis–syn*-dimer (**118**) in up to 40% yield.[3773]

1,5- and 3,5-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione.[5335,5366-5368]



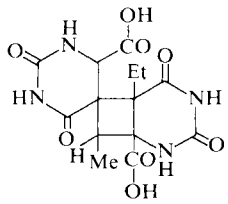
118

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione.[5358,5369]

1,3,5,6-Tetramethyl-2,4(1*H*,3*H*)-pyrimidinedione.[509,5370,5371]

2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid and its methyl ester, irradiated in aqueous solution, gave mainly the *trans–syn*-dimers.[5371,5372]

5-Ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (in contrast to the last example) gave the atypical and quite asymmetrical *anti*-dimer (**119**), in which the ethyl substituent of one substrate molecule formed part of the cyclobutane ring.[229,230]



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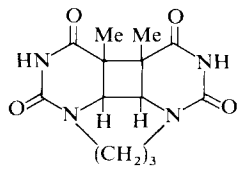

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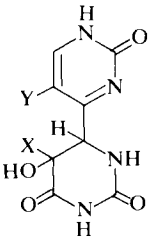
α,γ-Bis(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-propane and related substrates gave the 1,1′-propano-*syn*-dimer (**120**) and analogs.[402]

6-Methyl-2-methylthio-4(3*H*)-pyrimidinone.[5375]

4,6-Dimethyl-2(1*H*)-pyrimidinone gave an abnormal dimer with a cyclopentane "spine".[5377, cf. 5376]

Further information and references for some of the above and other such dimers have been collected.[5310b]

Irradiation of pyrimidinones can produce a variety of *simple bimolecular photoproducts* along with or instead of the foregoing cyclobutane dimers. For example, irradiation of 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione in frozen aqueous solution gave a substantial second product,[5378,5400] which was shown to be 5-hydroxy-5,5′-dimethyl-4,5-dihydro-4,4′-bipyrimidine-2,2′,6(1*H*,1′*H*,3*H*)-trione (**121**, X = Y = Me);[5379] 2,4(1*H*,3*H*)-pyrimidinedione formed a similar product, 5-hydroxy-4,5-dihydro-4,4′-bipyrimidine-2,2′,6(1*H*,1′*H*,3*H*)-trione (**121**, X = Y = H);[5380] and a mixture of both the foregoing substrates gave mainly 5-hydroxy-5-methyl-4,5-dihydro-4,4′-bipyrimidine-2,2′,6(1*H*,1′*H*,3*H*)-trione (**121**, X = Me, Y = H), which underwent facile dehydration to 5-methyl-4,4′-



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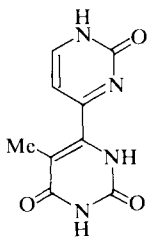

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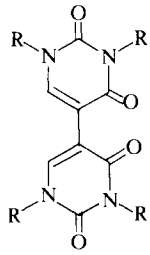

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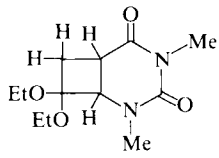

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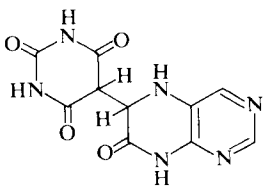
bipyrimidine-2,2',6(1*H*,1'*H*,3*H*)-trione (**122**).[5381] The last-mentioned product (**122**) and a related substance[5383] formed well-characterized macrocyclic tetramers on irradiation.[5382,5384] The irradiation of aqueous 5-bromo-2,4(1*H*,3*H*)-pyrimidinedione or its 1,3-dimethyl derivative gave 5,5'-bipyrimidine-2,2',4,4'(1*H*,1'*H*,3*H*,3'*H*)-tetrone (**123**, R = H) or its 1,1',3,3'-tetramethyl derivative (**123**, R = Me), respectively, in each case accompanied by other photoproducts.[5385, cf. 5386] Many other photoproducts have been reviewed.[5387]

Photoadditions of unrelated molecules to pyrimidinones are not uncommon. For example, ketene diethyl acetal added to 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione under irradiation to afford the adduct (**124**), which could be separated into two crystalline isomers, one with a *cis*- and the other with a *trans*-ring junction (in ratio ~ 6 : 1);[5390] other types of addition have been reported.[281,506,5266,5388,5389,5391]

7.1.3.9. Other Reactions

Both 4,6(1*H*,5*H*)-pyrimidinedione and 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione function as Michael reagents by *addition* to the 5,6-bond of 7(8*H*)-pteridinone to give 6-(4',6'-dioxo-1',4',5',6'-tetrahydropyrimidin-5'-yl)- (98%) and 6-(2',4',6'-trioxo-1',2',3',4',5',6'-hexahydropyrimidin-5'-yl)-5,6-dihydro-7(8*H*)-pteridinone (**125**) (90%), respectively;[5392] likewise, 2-methylthiopteridine with 2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione gave the 3,4-adduct, 4-(4',6'-dioxo-2'-thioxo-1',2',3',4',5',6'-hexahydropyrimidin-5'-yl)-2-methylthio-3,4-dihydropteridine (**126**) (83%).[5393] The conversion of 5-nitro-2(1*H*)-pyrimidinone into *p*-nitrophenol via an acetone adduct has been discussed in Section 5.1.2.2.



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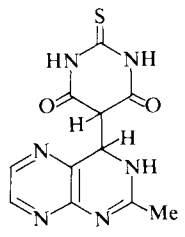

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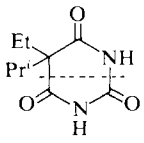

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Common pyrimidinones are included in a qualitative analytical compilation, *Komplexchemische Identifizierung von Pyrimidinderivaten im Mikromass-stab*, which lists the appearance in uv light as well as color reactions with sodium hydroxide, nitrous acid, alkaline cobalt sulfate, picric acid, ferrous ion, and some other test solutions.[3318] In an effort to develop a sensitive procedure for the identification of barbiturates in tissues, silver salts have been prepared therefrom in a form suitable for routine powder X-ray diffraction analysis;[5394] for the same reason, the degradation of barbiturates to simple identifiable amides has been investigated: for example, 5-ethyl-5-isopropyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**127**) in aqueous ammonia (200°, 10 min, sealed) gave 2-isopropylbutyramide (> 90%) by loss of CO_2 and NH_3 from obvious intermediates.[5395]

7.1.4. Some Naturally Occurring Pyrimidinones

No attempt will be made to discuss the pyrimidine nucleosides and nucleotides: an excellent introduction to this fast-moving area is available;[4004b] more detailed information can be gleaned from many books and reviews, especially of the annual-progress type. However, the following subsections do include brief outlines of those pyrimidines that occur naturally in nucleic acids or elsewhere.

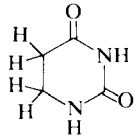
7.1.4.1. 2,4(1*H*,3*H*)-Pyrimidinedione (Uracil)

Uracil (**104**, R = H) was first isolated by the hydrolysis of yeast nuclein in 1900,[5396] and its structure was proved by synthesis in the following year;[3459] it was subsequently obtained from bovine thymus and spleen, herring sperm, and wheat germ.[5397–5399] Controlled hydrolysis of such materials containing polymeric ribonucleic acid(s) first gives several nucleotides, phosphate esters of uridine (1-β-D-ribofuranosidouracil), known under names such as uridylic acid a or b, uridine-5′-monophosphate, or the like; subsequent hydrolytic stages involve removal of the phosphate group(s) to afford uridine itself and then fission of the glycosidic link to furnish uracil.

Most of the synthetic routes to uracil have been outlined elsewhere (see Index). The best primary synthetic method is probably the classical condensation of malic acid with urea in fuming sulfuric acid,[2041] whereas the best metathetical method is still treatment of the readily available 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (thiouracil) with aqueous chloroacetic acid;[2295, cf. 1650,3148] numerous other methods are available for specific circumstances.[748,962,1483,1628,1673,1978,2258,2370,2868,3453,3475,3619,3622,3623,5112,5170, 5378,5401–5404,6898]

Uracil undergoes regular reactions, such as nitration or alkylation, which are covered elsewhere in appropriate sections (see Index). More specialized reactions include oxidative degradation to urea (H_2O_2/Fe^{2+},O_2/Fe^{2+}, or $I_2/NaHCO_3$);[5405,5406] ozonolysis to 1-formyl-5-hydroxy-2,4(3*H*,5*H*)-

imidazoledione (29%),[6118] production of a nonspecific purple color [Br_2/Ba(OH)$_2$];[2312] visualization of uracil and related chromatographic spots as blue areas in uv light (PhOH/NaOCl);[5407] reduction to 5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**128**) (H_2/Pt: > 90%);[5408, cf. 1978] conversion into 3-pyrazolone (**129**, X = Y = H) ($H_2NNH_2.H_2O$, 100°, 60 min: 90%),[5409,5411] 2-methyl-3-pyrazolone (**129**, X = Me, Y = H) (H_2NNHMe, H_2O, 80°, 15 h: 30%),[3236,5410] or 1,2-dimethyl-3-pyrazolone (**129**, X = Y = Me) (MeHNNHMe, likewise: 30%);[3236,5410] and the formation of a variety of photoproducts (see Section 7.1.3.8). In addition, the pattern of HO radical addition to uracil has been studied;[5412] evidence for the rather vague reactions between uracil and aqueous formaldehyde have been sought diligently;[5413] and a once-discarded idea,[1489] for 5-hydroxymethylation of uracil by formaldehyde in the presence of acid or alkali, has been developed as a preparative method for 5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (**104**, R = CH_2OH) in up to 81% yield.[1597] An attempt has been made to rationalize the dipole moments of uracil and a variety of derivatives.[3906]



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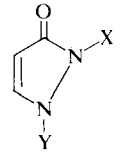

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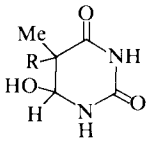
7.1.4.2. 5-Methyl-2,4(1*H*,3*H*)-pyrimidinedione (Thymine)

Thymine (**104**, R = Me) was first isolated in 1893, several years before uracil, from bovine thymus or spleen.[3460,3461] By 1901, its structure had been elucidated[3699,4928,5414] and confirmed by synthesis.[3459] Although thymine has been isolated occasionally from ribonucleic acids,[5415,5416] it has usually been obtained from deoxyribonucleic acids: the stagewise hydrolysis of such material is not easy, but the nucleoside, thymidine (1-β-D-2′-deoxyribofuranosidothymine), has been isolated satisfactorily.

The best primary synthesis of thymine is probably by the condensation of urea with β-methylmalic acid (α-hydroxy-β-methylsuccinic acid)[1522] or α-formylpropionic acid[2887] in fuming sulfuric acid (~ 50% yield in each case); the best metathetical procedure is the conversion of uracil into thymine via 5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (> 75% overall).[1597] Other methods of both types are available as required.[841,967,1152,1490,2270,2698,2852, 3463,3464,3469]

Thymine undergoes expected reactions with phosphorus halides, alkylating agents, and so on (see Index) but, having a 5-methyl group, it resists regular nitration and the like. However, thymine undergoes addition and other reac-

tions to afford, for example, 6-hydroxy-5-methyl-5-nitro-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**130**, R = NO_2) (fuming HNO_3);[2340,5417] 5-bromo-6-hydroxy-5-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**130**, R = Br) (Br_2, H_2O);[4927,5418] urea + hydroxyacetone + pyruvic acid (H_2O_2 + Fe^{2+}; O_2, Fe^{2+}, $NaHCO_3$; O_2, Fe^{2+}, *hv*);[5322,5419] 4-methyl-3-pyrazolone (**131**) or appropriate *N*-methyl derivatives (H_2NNH_2, H_2NNHMe, or MeHNNHMe);[3236,5409-5411] a separable mixture of 5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (*cis*-thyminyl glycol) (**130**, R = OH) and 5-hydroxy-5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**132**) ($KMnO_4$, pH 7, 15°, 2 min; the first product was not an intermediate for the second; the glycol epimerized in warm aqueous solution);[5420-5422] and a characteristic blue fluorescent solution as a color test [Br_2, $Ba(OH)_2$; then *o*-$O_2NC_6H_4CHO$, NH_4OH, Fe^{2+}].[5423] Two fascinating stable structural isomers (tautomers?) of thymine have been made. Thus 2-(bromomethyl) acrylamide and trichloroacetyl isocyanate gave *N*-2-(bromomethyl)acryloyl-*N'*-trichloroacetylurea (**133**), which underwent deacylation and loss of hydrogen bromide in warm sodium hydrogen carbonate solution to afford 5-methylene-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**134**) (26%); on melting (~ 215°), it rearranged partially into thymine (**104**, R = Me).[3468] The second isomer, cyclothymine (**135**) (~ 20%), was made from *cis*-cyclopropane-1,2-dicarboxamide with sodium hypochlorite.[3468] The photoproducts from thymine have been discussed (Section 7.1.3.8).



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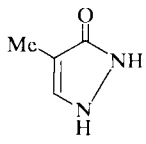

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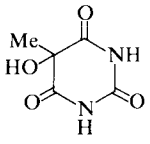

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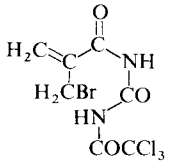

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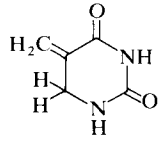

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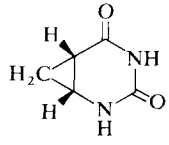

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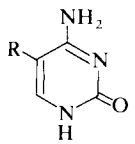
7.1.4.3. 4-Amino-2(1*H*)-pyrimidinone (Cytosine)

Cytosine (**136**, R = H) was first isolated in 1894 from the nucleic acids of calf thymus.[3461] Within a decade, it had been isolated from other sources and its structure had been elucidated;[5399,5424-5428] a synthesis had also been reported.[719] Cytosine occurs in both ribonucleic acid and deoxyribonucleic acid: acidic hydrolysis of the former gives the nucleotides, cytidylic acids a and b,

which are the 2′- and 3′- phosphate of cytidine (1-β-D-ribofuranosidocytosine); further hydrolysis gives cytidine itself and thence cytosine. Likewise, the deoxyribonucleic acids give sequentially deoxynucleotides, the deoxynucleoside (deoxyribosidocytosine), and cytosine.



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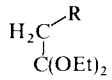

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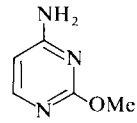

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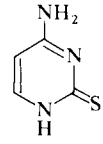

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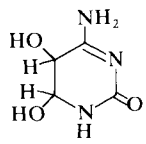
The least troublesome primary synthesis of cytosine is that involving the conversion of commerical 2-bromoacetaldehyde acetal (**137**, R = Br) into 3,3-diethoxypropionitrile (**137**, R = CN) (NaCN, Me_2SO, 70°, 4 h: 69%) followed by condensation with urea to afford cytosine (**136**, R = H) (NaOBu, BuOH, reflux, 2 h: 32%).[1677, cf. 1674,4259] The best metathetical route is probably that by the sequence 2,4(1*H*,3*H*)-pyrimidinedione → 2,4-dichloropyrimidine → a mixture of 2-chloro-4- and 4-chloro-2-pyrimidinamine → a separable mixture of 2-methoxy-4- (**138**) and 4-methoxy-2-pyrimidinamine → cytosine (**136**, R = H) (~ 50% based on the dichloropyrimidine) and isocytosine, respectively;[1671] another popular route involves the sequence 2,4(1*H*,3*H*)-pyrimidinedithione → 4-amino-2(1*H*)-pyrimidinethione (**139**) → cytosine (**139**, R = H) (~ 60% overall).[1652, cf. 1514,1650,2840] Several other methods are available.[811,967,1006,1568.1665,1673,1675,2131,3285.3585,3526,5231]

Cytosine undergoes the usual reactions associated with pyrimidinones and pyrimidinamines (see Index). In addition, oxidation by permanganate gave oxalic acid, biuret, formic acid, urea, and ammonia, probably via a "cytosine glycol," 4-amino-5,6-dihydroxy-5,6-dihydro-2(1*H*)-pyrimidinone (**140**);[1511,5426] oxidation with peroxyphthalic acid or (better) *m*-chloroperoxybenzoic acid gave 4-amino-2(1*H*)-pyrimidinone 3-oxide (**141**),[5429,5430] of confirmed orientation;[1681] treatment with hydrazine hydrate at 80° gave 4-hydrazino-2(1*H*)-pyrimidinone (**142**, X = Y = H) and 3-pyrazolamine (**143**), similar treatment at 90° gave the pyrazolamine (**143**) and α,β-bis(2-oxo-1,2-dihydropyrimidin-4-yl)hydrazine (**144**), and treatment with aqueous hydrazine at pH 6 gave the pyrimidine (**142**, X = Y = H) and α,β-di(pyrazol-3-yl)hydrazine (**145**);[3236,5411] in contrast, aqueous methylhydrazine or *N*,*N*′-dimethylhydrazine gave only 4-α-methylhydrazino- (**142**, X = Me, Y = H) or 4-α,β-dimethylhydrazino-2(1*H*)-pyrimidinone (**142**, X = Y = Me), respectively;[3236] treatment with hydroxylamine at pH 7 eventually gave the transamination product, 4-hydroxyamino-2(1*H*)-pyrimidinone (**146**) but in several steps via the adducts (**147**, R = H and OH);[1261,3225,3239,5431–5433] irradiation appeared to have little effect on cytosine[5310c] but irradiation of a mixture of cytosine and 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone did give 4′-amino-4,5′-bipyrimidine-2,2′(1*H*,1′*H*)-dione with loss of sulfur.[5434,5435]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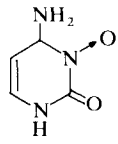
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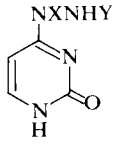
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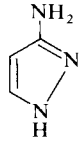
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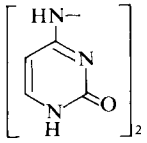
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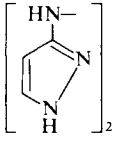
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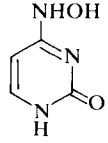
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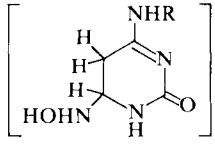
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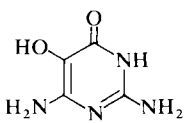
7.1.4.4. 2,6-Diamino-5-hydroxy-4(3*H*)-pyrimidinone (Divicine)

Victine was isolated from the seeds of the common tare (*Vicia sativa*) in 1870,[5436-5438] but only in 1896 was it recognized as the glycoside of a nitrogenous base, divicine,[5439] and only in 1911 was it even suggested that the base was a pyrimidine.[5440] In 1914, divicine was declared to be 5,6-diamino-2,4(1*H*,3*H*)-pyrimidinedione[5441,5442] but later in the same year this structure was revised[5443] and subsequently "confirmed" as 2,5-diamino-4,6(1*H*,5*H*)-pyrimidinedione.[1698] There the matter rested, apparently solved,[2421] for the next 40 years. In 1953, a brilliant review of existing and some new data led to the inescapable conclusion that divicine was, in fact, 2,6-diamino-5-hydroxy-4 (3*H*)-pyrimidinone (**148**) and that vicine was its 5-β-D-glucopyranoside.[2384] Three unequivocal syntheses of divicine have been reported subsequently: (1) ethyl α-cyano-α-(tetrahydropyran-2-yl)acetate with guanidine to give 2,6-diamino-5-tetrahydropyran-2′-yloxy-4(3*H*)-pyrimidinone, followed by gentle acidic hydrolysis;[1324,5444] (2) a primary synthesis of 2-amino-5-benzyloxy-4-(3*H*)-pyrimidinone, debenzylation, 6-nitrosation, and reduction;[581,1341] and, the best (3) an Elbs persulfate oxidation from commerical 2,6-diamino-4(3*H*)-pyrimidinone to give the sulfate ester, 2,6-diamino-5-sulfo-oxy-4(3*H*)-pyrimidinone (**149**),[1011,2403] followed by acidic hydrolysis to divicine (**148**) (50% overall).[2403] A fourth synthesis is outlined in Section 7.7.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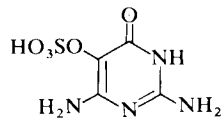
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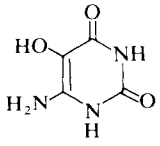
Divicine undergoes expected reactions[2384] and shows a number of positive colar tests.[1324,1340,1574,2384] It is one of the substances in fava beans (*Vicia fava*)

that cause favism (a sometimes fatal hemolysis) in people deficient in the glucose-6-phosphate dehydrogenase enzyme; it is highly active against the rodential malarial parasite *Plasmodium vinckei vinckei*, but apparently not against human parasites, such as *P. falsiparum* or *P. vivax*;[5445] and a divicine-induced free radical killing of tumor cells has been observed *in vitro*, especially when glutathione reductase is low or deliberately inhibited.[344, cf. 3933]

7.1.4.5. 6-Amino-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (Isouramil)

As the name suggests, convicine occurred with vicine in several species of vetch.[5438] A new specimen (from broad beans, *Vicia fava*) was reinvestigated in 1932, and it appeared to be a glycoside of isouramil (**150**):[5446] although the suspected aglycone was synthesized the same year[1339] and again subsequently,[1324] no effort was made to compare the synthetic and convicine-derived materials until 1968, when they were pronounced to be the same and convicine was identified as the 5-β-D-glucopyranoside of isouramil.[580]



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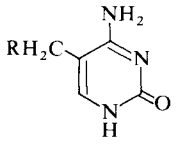
The best synthesis of isouramil involved 6-nitrosation of 5-hydroxy-2,4-(1*H*,3*H*)-pyrimidinedione (isobarbituric acid) and subsequent reduction by ammonium sulfide or sodium dithionite ($\leq$ 77% overall);[580,1339] the other used a primary synthesis of 6-amino-5-tetrahydropyran-2′-yloxy-2,4(1*H*,3*H*)-pyrimidinedione followed by acidic deprotection of the 5-hydroxy group (22% yield overall).[1324] Like divicine (Section 7.1.4.4), isouramil can induce favism in susceptible individuals;[5447] ironically, it may also induce some resistance to the human malarial parasite, *Plasmodium falciparum*, in such individuals.[2,5492]

7.1.4.6. 4-Amino-5-methyl-2(1*H*)-pyrimidinone (5-Methylcytosine)

When 5-methylcytosine (**151**, R = H) was first synthesized in 1904,[967] it was nominated as a likely constituent of nucleic acids. Sure enough, in 1925 the same group reported[5448] its isolation as a picrate from tubercle bacilli hydrolyzates, but in 1949 this discovery was shown to have been wishful thinking by a reexamination of the original specimen, which turned out to be only impure cytosine picrate.[5449] However, 5-methylcytosine was eventually found in the



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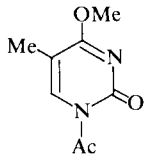
deoxyribonucleotide fractions from thymus, wheat germ, and other sources.[5450–5455]

Two improved syntheses of 5-methylcytosine have been reported: the first involved 4-ammonolysis of 5-methyl-2,4(1*H*,3*H*)-pyrimidinedithione followed by the replacement of the remaining 2-thioxo by a 2-oxo substituent ($ClCH_2CO_2H$);[1514] the second involved conversion of 2,4-dimethoxy-5-methylpyrimidine into 1-acetyl-4-methoxy-5-methyl-2(1*H*)-pyrimidinone (**152**) (neat AcCl) followed by 4-ammonolysis and deacetylation (NH_4OH, 110°, sealed: 57% overall).[811]



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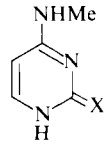
7.1.4.7. 4-Amino-5-hydroxymethyl-2(1*H*)-pyrimidinone (5-Hydroxymethylcytosine)

In 1952 5-hydroxymethylcytosine was isolated from T-even bacteriophages of *Escherichia coli* in which it occurred in place of cytosine.[5456,5457] The best synthetic route is probably that indicated in the following sequence: ethyl 4-amino-2-thioxo-1,2-dihydro- (primary synthesis) → ethyl 4-amino-2-methylthio-5-pyrimidinecarboxylate (MeI/KOH) → 5-hydroxymethyl-2-methylthio-4-pyrimidinamine ($LiAlH_4$) 4-amino-5-hydroxymethyl-2(1*H*)-pyrimidinone (HCl: 37% yield overall);[1331, cf. 1333,1334] other procedures employed an ethylthio intermediate and gave rather lower yields.[1249,1329,1330]

7.1.4.8. 4-Methylamino-2(1*H*)-pyrimidinone (*N*4-Methylcytosine)

Although it had been made as early as 1911,[1384] *N*4-methylcytosine (**153**, R′ = O) was found to be a minor component of ribosomal nucleic acids from *Escherichia coli* only in 1968.[5458] Of the several syntheses available, [1383–1385,1676,2638,2665,2768,3385] the best is probably that involving 4-methylaminolysis[1515] of 2,4(1*H*,3*H*)-pyrimidinedithione followed by conver-



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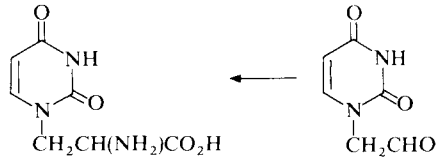
sion of the resulting thione (**153**, X = S) into the product (**153**, X = O) ($ClCH_2$-CO_2H: ~ 45% yield overall).[1383]

7.1.4.9. 1-(β-Amino-β-carboxyethyl)-2,4(1*H*,3*H*)-pyrimidinedione (Willardiine)

In 1959 a new nonprotein L-α-amino acid was isolated from the seeds of *Acacia willardiana*[5459] and subsequently from those of related subspecies.[5460] The new acid, willardiine, was formulated[5459] as the L-isomer of 1-β-amino-β-carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (**154**) and this was confirmed by three syntheses: (1) the acetal of 1-formylmethyl-2,4(1*H*,3*H*)-pyrimidinedione (**155**), prepared by an unambiguous primary synthesis, was converted into the free aldehyde (**155**) and thence by a Strecker reaction (KCN, NH_4OH, NH_4Cl) into DL-willardiine (**154**), which gave the L-isomer on resolution;[3197-3199] (2) 1-(β-carboxy-β-tosylaminoethyl)-2,4(1*H*,3*H*)-pyrimidinedione, made by an unambiguous primary synthesis, underwent acidic deacylation to afford DL-willardiine;[5461] and (3) condensation of ethyl formylacetate with *N*-(β-amino-β-carboxyethyl)urea gave the same product (**154**), albeit ambiguously.[4107]



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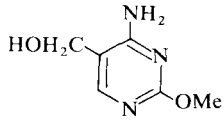
7.1.4.10. Some Pyrimidinone Antibiotics

Although not formally a pyrimidinone, *bacimethrin* in the *O*2-methyl derivative of 5-hydroxymethylcytosine (Section 7.1.4.7), specifically, 5-hydroxymethyl-2-methoxy-4-pyrimidinamine (**156**).[3262] It was isolated in 1961 from *Bacillus megatherium*[5462,5463] and proved active against a variety of microorganisms.[5464] The better of two syntheses involved the conversion of ethyl 4-amino-2-ethylsulfonyl- into ethyl 4-amino-2-methoxy-5-pyrimidinecarboxylate (NaOMe MeOH) followed by reduction of the ester grouping ($LiAlH_4$/THF: 52% overall).[2203,2966,2967]



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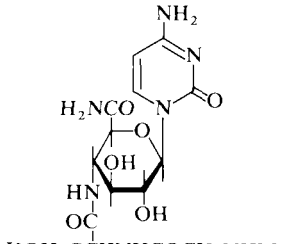
The complicated nucleoside, *gougerotin* (**157**), was isolated in 1962 from *Streptomyces gougerotin*;[5465] it showed a wide spectrum of antimicrobial activity.[5464] Structural studies continued for a decade,[3399,5467–5469] culminating in a total synthesis.[5470]



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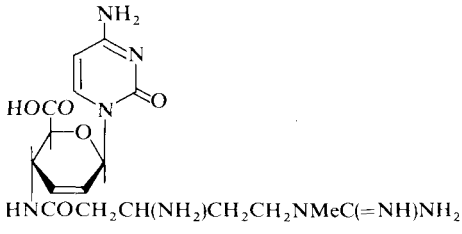

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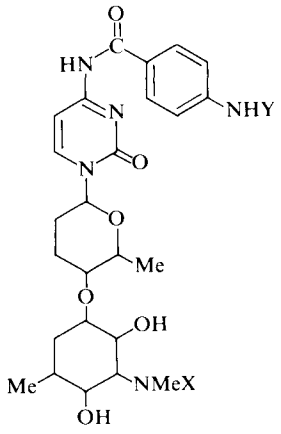
The structurally related *blasticidin S* (**158**) was isolated from *S. griseochromogenes* in 1958;[5471] it proved to be an excellent antifungal agent against *Piricularia oryzae*, the virulent fungus causing rice blast in Japan, and it was on the market by 1961. Its structure gradually emerged[5466,5472–5474] and a derivative of the deacylated molecule has been synthesized independently.[5475] Some quite simple 1-(2′-fluoroarabinofuranosyl)cytosines and related compounds (based on the foregoing natural structures) have shown significant activities against *Herpes simplex*-type viruses.[1352,5482]

Of three closely similar *N*4-acylated cytosines, *amicitin* (**159a**) was isolated first in 1953 from *S. vinaceusdrappus* and *S. fasciculatis*;[5476,5477] the same material (**159a**), *bamicitin* (**159b**), and *plicacetin* (**159c**) were later isolated from *S. plicatus*.[5478] Work on their structures and relationship continued[1531,5478–5480] culminating in the definitive formulations shown;[5481] a partial synthesis of plicacetin has been reported.[5480] The antibiotics exhibited a range of activities including some interesting antiviral properties.[5464]

The chiral antibiotic, *sparsomycin* (**160**), was isolated from the fermentation liquors of *S. sparsogenes* in 1962; it showed a wide spectrum of antimicrobial and antitumor activities but a rather high toxicity in mice (LD_{50} 2.4 mg/kg).[5483,5484] The structure was gradually elucidated,[2012,2040,5486–5488] and the natural material proved to be the S_C, R_S-enantiomer (**160**), a fact confirmed by an X-ray analysis.[5485] Synthetic analogs have not shown outstanding antitumor activities.[2179,5489–5491]

The cyclic peptide, *albomycin*, appears to have 3-methylcytosine as a small part of its structure.[3385]



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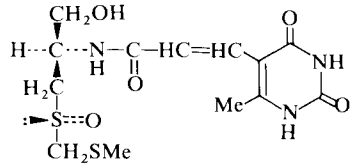
(a) X = Me, Y = $C(:O)CMe(NH_2)CH_2OH$
(b) X = H, Y = $C(:O)CMe(NH_2)CH_2OH$
(c) X = Me, Y = H



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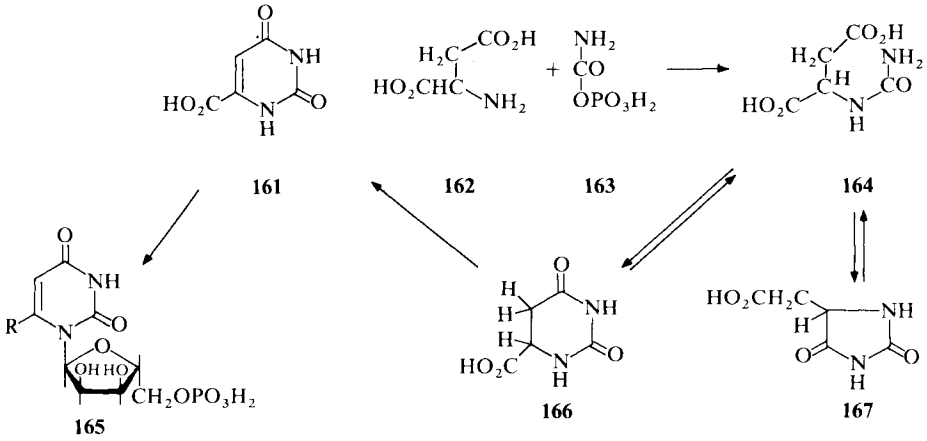
7.1.4.11. 2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic Acid (Orotic Acid)

Orotic aicd (**161**), isolated in a Milanese laboratory from the whey of cows' milk during 1904, was first formulated as a dihydrodiazepinetetrone.[2879] However, members of the Yale school found that it was probably an isomeric uracilcarboxylic acid, so they synthesized both 2,4-dioxo-1,2,3,4-tetrahydro-5-[2527] and 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid:[2876] they were discouraged by the apparent large differences in melting point between their products and that of the Italians, failed to make direct comparisions with the natural material, and remained ignorant that they had in fact synthesized orotic acid. To make matters worse, member of the same school later prepared 5-hydroxy-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid and, simply on the basis of similarity in melting points, virtually claimed the long-awaited synthesis of orotic aicd.[2123] Not until 1930 were proper comparisons made in Milan and orotic aicd emerged as the dioxopyrimidinecarboxylic acid (**161**).[3391] As a postscript, the original Yale synthesis of orotic acid[2876] was later shown to proceed, not directly as assumed, but by ring expansion of an intermediate hydantoin (Section 2.6.1):[2875,2877] this proved all the more ironic because the Yale author had begun his paper[2876] with criticism of an earlier worker for not considering that diethyl oxaloacetate with urea could give an hydantoin!

There are two good syntheses of orotic acid: (1) condensation of diethyl oxaloacetate with *S*-methylisothiourea in aqueous alkali to give 2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid, followed by acidic or oxidative hydrolysis (50% overall);[1030,2889] and (2) condensation of γ-chloroacetoacetyl chloride (made in situ from diketene and chlorine) with urea to give 6-chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione, followed by oxidative hydrolysis with alkaline peroxide (~ 40% overall).[2275] Several other syntheses have been reported.[788,915,937,1326,1592,1605, 2032,2678,2855,2859,2872,2876–2878,2880,2888, 2955,3392,5493, 6234]

Orotic acid undergoes many expected reactions (see Index). The chequered history of its methylation reactions has been rationalized;[2673] its metal complexes, metal salts, and amine salts have been studied;[3142,3792,5495–5497] photochemical reactions have been mentioned in Section 7.1.3.8; and several *S*-alkyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinethiocarboxylates have been made via the corresponding 4-pyrimidinecarbonyl chloride (orotyl chloride).[5498]

The biochemistry of orotic acid is very important,[2881,4004c,5538] as indicated in the following summary. It appears that orotic acid is the key substance in the biosynthesis of all biologically occurring pyrimidines. Thus union of ammonia and carbon dioxide in the presence of adenosine triphosphate gives carbamoyl dihydrogen phosphate (**163**),[5499,5500] which has been made synthetically.[5501] This substance combines enzymatically with L-aspartic acid (**162**) to lose phosphoric acid and afford ureidosuccinic acid (**164**);[5502,5503] which is in enzymatic equilibrium with 5-carboxymethylhydantoin (**167**) and with 4,5-dihydro-orotic acid (**166**);[5504] the latter is identical with synthetic material.[5505] The next step involves dehydrogenation by dihydro-orotate dehydrogenase to furnish the prime aromatic pyrimidine, orotic aicd (**161**).[5506,5507] This combines with ribose-5-phosphate-1-pyrophosphate in the presence of orotidylic pyrophosphorylase to give the nucleotide, orotidylic acid (**165**, R = CO_2H),[5508] which undergoes irreversible decarboxylation[5509] by orotidylic decarboxylase



to afford uridine-5′-phosphate (**165**, R = H) with subsequent elaboration, for example, to cytidine triphosphate.[5510] It is interesting that the critical enzymatic oxidation, (**166**) → (**161**), is inhibited by exogenous pyrimidines, for example, 5-bromo- or 5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, which anionize appreciably at the 4/6-position under the conditions of assay.[184]

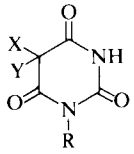
7.1.5. Pyrimidinones Used as Drugs or Agrochemicals

Several types of pyrimidinone include useful drugs or agrochemicals which are listed and discussed briefly in the following subsections. Many other pyrimidines and pyrimidinones of biological and/or potential medicinal interest have been reviewed elsewhere.[4773,5464,5538]

7.1.5.1. Substituted 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones (Barbiturates)

Unsubstituted barbituric acid (**168**, R = X = Y = H) was made first in 1864,[3553] but it does not occur naturally, nor has it any marked biological properties. The first sedative or hypnotic barbiturate, 5,5-diethylbarbituric acid (**168c**), was introduced in Germany about 1903 as Veronal[5511, cf. 3109] and later became known under the generic name of barbital/barbitone in English-speaking countries. Since that time, innumerable barbiturates have been prepared, and many have been used as sedatives: since the introduction of benzodiazepines soon after 1960, the use of barbiturates has decreased steadily, but as late as 1980 the following fifteen barbiturates and thiobarbiturates were still available from U.S. pharmacies for ethical use (minimal half-life given).[5512]

Amobarbital (**168a**)	8 h
Aprobarbital (**168b**)	—
Barbital (**168c**)	—
Butabarbital (**168d**)	34 h
Butalbital (**168e**)	—
Hexobarbital (**168f**)	3 h
Mephobarbital (**168g**)	—
Metharbital (**168h**)	—
Methohexital (**168i**)	—
Pentobarbital (**168j**)	15 h
Phenobarbital (**168k**)	24 h
Secobarbital (**168l**)	20 h
Talbutal (**168m**)	—
Thiamylal (**169**, X = $CH_2CH{:}CH_2$)	—
Thiopental (**169**, X = Et)	—



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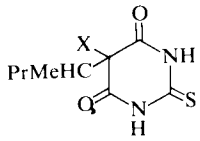

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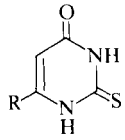
	R	X	Y
(a)	H	Et	Pe^{i}
(b)	H	Allyl	Pr^{i}
(c)	H	Et	Et
(d)	H	Et	Bu^{s}
(e)	H	Allyl	Bu^{i}
(f)	Me	Me	Cyclohex-1′-enyl
(g)	Me	Et	Ph
(h)	Me	Et	Et
(i)	Me	Allyl	CHMeC≡CEt
(j)	H	Et	CHMePr
(k)	H	Et	Ph
(l)	H	Allyl	CHMePr
(m)	H	Allyl	Bu^{s}

The main synthetic routes to the foregoing and other barbiturates are illustrated briefly in the following examples: (1) diethyl α,α-diethylmalonate with urea in ethanolic ethoxide at 105–110° (sealed) gave barbital (**168c**) in 70% yield;[3109,3642] (2) 5-α-methylbutyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (as Na salt) with allyl bromide in ethanol gave secobarbital (**168l**) without the partial rearrangement that occurred during a direct synthesis;[5513] and (3) ethyl α-cyano-α-cyclohex-1′-enylpropionate with *N*-methylurea gave 6-amino-5-cyclohex-1′-enyl-1,5 (or 3,5)-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione and thence, by acidic hydrolysis, hexobarbital (**168f**).[5514] Chiral barbiturates such as 5-ethyl-1-methyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione have been completely resolved on a cellulose triacetate column.[163]

The chemistry, pharmacology, and structure–activity relationships of barbiturates have been reviewed.[5512,5515] The only reported natural occurrence of a barbiturate is that of barbital (**168c**) in puffer fish, *Spaeroides oblongus*, caught in the Bay of Bengal during the breeding season.[3858]

7.1.5.2. 2-Thioxo-1,2-dihydro-4(3*H*)-pyrimidinones (Thiouracils)

Goitrogenic activity was first observed in 1928 when rabbits fed on cabbage developed thyroid hyperplasia;[5516] sulfur compounds and later thiourea-like compounds were gradually implicated.[5517–5520] In 1943, 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**170**, R = H) (thiouracil) was shown to be the most active of several cyclic thioureas, and it was introduced as a drug for human



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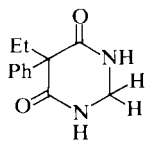
hyperthyroidism.[5512–5523] In 1945, it emerged that 6-methyl- (**170**, R = Me) and 6-propylthiouracil (**170**, R = Pr) were considerably better than unsubstituted thiouracil (**170**, R = H); for a decade or more, all three were available for use, but at the present time propylthiouracil (**170**, R = Pr) is the only such pyrimidine in most pharmacopoeial or similar listings.[5524] The pharmacology of thyroid and antithyroid drugs has been reviewed.[5525]

Thiouracils are made invariably from an appropriate β-oxoester with thiourea: for example, ethyl 3-oxohexanoate and thiourea in refluxing ethanolic sodium ethoxide for 6 h gave 6-propylthiouracil (**170**, R = Pr) (70%).[1684, cf. 6068]

7.1.5.3. 5-Ethyl-5-phenyl-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (Primidone)

In 1952 a new anticonvulsant, primidone (**171**), was introduced under the name Mysoline.[5526] To this day it remains a valuable drug for controlling grand mal, pyschomotor, and several other forms of epilepsy. On metabolism, it affords phenobarbital (**168k**) and α-ethyl-α-phenylmalondiamide (**172**), both of which have marked anticonvulsant properties; however, primidone does have an intrinsic effect because administration of an appropriate mixture of the metabolites has far less efficacy than the equivalent amount of primidone.[5527] Its pharmacology and role in treatment of the epilepsies have been reviewed.[5524,5528]



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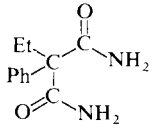

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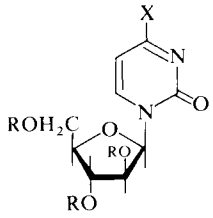
Of several routes to primidone, the most satisfactory appears to be desulfurization of 5-ethyl-5-phenyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione with Raney-nickel,[4368] photolysis of the same substrate in *s*-butanol (42% yield),[3857] or treatment of the diamide (**172**) with formic acid at 190° (sealed).[4368]

7.1.5.4. 4-Amino-1-β-D-arabinofuranosyl-2(1*H*)-pyrimidinone (Cytarabine)

In 1961 the arabinosylcytosine (**173**, R = H, X = NH_2) was shown to have antitumor activity,[5494] and it eventually became established as a valuable agent, especially for inducing initial remissions in some acute leukemias and lymphomas.[5529] It is also supplied in admixture with other agents (e.g., thioguanine) for multiple-drug therapy of leukemias.[5524] Even on continuous intravenous administration, much of the drug is converted into the corresponding (inactive) uracil derivative by a deaminase in the liver: accordingly, increasingly successful efforts have been made to administer cytarabine as various more stable prodrugs.[12] Cytarabine has an incidental antiviral activity against some herpes and vaccinia infections.[5529]



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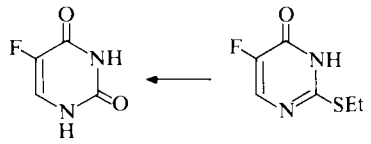
Cytarabine (**173**, R = H, X = NH_2) can be made by treatment of 2,4-dimethoxypyrimidine with 2,3,5-tri-*O*-benzyl-D-arabinosyl chloride to give the 4-methoxypyrimidinone (**173**, R = CH_2Ph, X = OMe), which reacts with ammonia to give the corresponding amine (**173**, R = CH_2Ph, X = NH_2) and thence, on hydrogenolysis, the required nucleoside (**173**, R = H, X = NH_2) in ~ 50% yield overall;[5530] also, in comparable yield, by epimerization of the glycosyl portion of cytidine or cytidylic acid in polyphosphoric acid, followed by hydrolysis and dephosphorylation of the initial product(s).[5531, cf. 5532] Other routes appear to be marginally less satisfactory.[5494,5533,5534]

7.1.5.5. 5-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione (Fluorouracil)

An apparent observation in 1954, that uracil was used more effectively in nucleic acid synthesis within a rat hepatoma than within normal rat liver,[5535, cf. 5536] seems to have stimulated the synthesis and testing of 5-fluorouracil (**174**) as an antimetabolite with potential antitumor activity.[2158] In the event, fluorouracil did have antineoplastic activity, and it is now considered a valuable drug, especially for the treatment of tumors of the breast, colon, rectum, and gential regions;[5464,5529] as with other inhibitors of DNA synthesis, the therapeutic index is low and great care is required during treatment.[5524] For this reason, a great many derivatives and prodrugs have been explored;[12,113,183,431] at least one of these, 5-fluoro-1-*N*-hexylcarbamoyl-2,4(1*H*,3*H*)-pyrimidinedione,[3025] is now used clinically.



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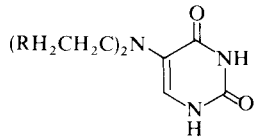
The original synthesis of fluorouracil involved the condensation of ethly α-fluoro-α-formylacetate with *S*-ethylisothiourea to give 2-ethylthio-5-fluoro-4(3*H*)-pyrimidinone (**175**) followed by acidic hydrolysis to the product (**174**);[2158] rather similar primary syntheses with subsequent elaborations have also been used.[138,430,3169,3170] Much better yields have been obtained by direct fluorination of uracil under a variety of conditions.[128,3167,3168,3171,3918,5537] A few other routes have been reported.[1262,3157,3172,3173]

7.1.5.6. 5-Di(β-chloroethyl)amino-2,4(1*H*,3*H*)-pyrimidinedione (Uracil Mustard)

Uracil mustard (**176**, R = Cl) was made initially in 1958 on the hunch that it might be advantageous to attach the active alkylating portion of a nitrogen mustard to a substantial natural carrier group, such as uracil: the product (**176**) proved active as a carcinostatic and carcinolytic agent in animals,[4940] and it has become a favored drug for chronic lymphocytic leukemia, Hodgkin's disease, and some other lymphomas.[5529] Its LD_{50} is < 4 mg/kg in mice, but it is reasonably well tolerated in appropriate oral dosage.[4773]

The synthesis of uracil mustard involved treatment of 5-amino-2,4(1*H*,3*H*)-pyrimidinedione with ethylene oxide to give 5-di(β-hydroxyethyl)amino-2,4(1*H*,3*H*)-pyrimidinedione (**176**, R = OH), which reacted with thionyl chloride to give the dichloro compound (**176**, R = Cl).[4940]

5-(β-Chloroethyl-β-fluoroethylamino)-2,4(1*H*,3*H*)-pyrimidinedione and related analogs proved disappointing in activity.[6243]



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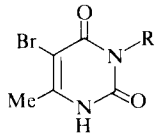
7.1.5.7. 5-Bromo-3-*s*-butyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Bromacil)

In 1962, bromacil (**177**, R = Bu^s) and its 3-alkyl homologs, including isocil (**177**, R = Pr^i), were shown to have valuable selective phytotoxic properties and



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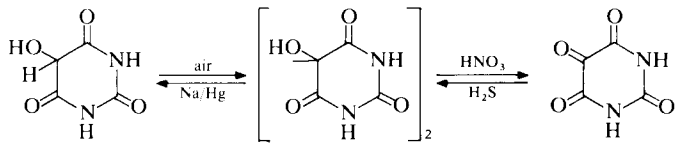
minimal mammalian toxicity.[1891] Thus bromacil achieves a complete kill of most broad-leaf annuals or perennials as well as many grasses without any appreciable effect on the food crop(s);[5540] it does this by inhibiting photosynthesis only in the unwanted species.[5539,6217] The reported route to bromacil comprises condensation of *s*-butyl isocyanate with methyl 3-aminocrotonate to afford methyl 3-(3′-s-butylureido)crotonate, cyclization in alkali, and a final bromination.[1891]

7.1.6. The Alloxan Group of Pyrimidinones

The relationship of alloxan, alloxantin, and dialuric acid is best shown by their oxidative–reductive interconversion. Thus gentle oxidation (air) of 5-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (*dialuric acid*) (**178**) gave 5,5′-dihydroxy-5,5′-bipyrimidine-2,2′,4,4′,6,6′(1*H*,1′*H*,3*H*,3′*H*,5*H*,5′*H*)-hexone (*alloxantin*) (**179**) and more vigorous oxidation (nitric acid), 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (*alloxan*) (**180**);[3569,5541] in reverse, alloxan (**180**) was reduced (hydrogen sulfide) to alloxantin (**179**) and thence (sodium amalgam, excess hydrogen sulfide, or stannous chloride) to dialuric acid (**178**).[1138,3279,3568,3717,5542] In addition, alloxantin (**179**) was made by simply mixing equimolar portions of dialuric acid (**178**) and alloxan (**180**).[3279] The redox potentials of the foregoing system have been studied,[3811] as well as those of related systems.[2715,3575,5543–5548]



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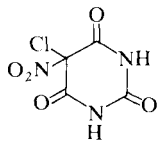
7.1.6.1. 5-Oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Alloxan)

In 1818 Gaspard Brugnatelli oxidized 2,6,8(1*H*,3*H*,7*H*)-purinetrione (uric acid) with nitric acid, chlorine, or iodine to afford alloxan (**180**),[5549] the first synthesis of any pyrimidine; this method was modified subsequently to improve yields to ~ 35%.[1138,1656,3280,3568,3569,4542,4543,5550,5551,5554] Alloxan has been made also by (1) oxidation of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, directly

(CrO_3: ~75%)[3570] or via 5-benzylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (CrO_3: ~70% overall);[3573,5552,5553] (2) chlorination of 5-nitro- to 5-chloro-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**181**) ($HCl + H_2O_2$: 60–80%) followed by dry thermal decomposition (110–180°: 78%);[3571] (3) treatment of 5-chloro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with fuming nitric acid followed by decomposition of the unisolated intermediate (**181**) by boiling the reaction mixture (76% overall);[3571] (4) oxidation of 2,4(1*H*,3*H*)-pyrimidinedione at pH 3.5 ($KMnO_4$: suitable for small-scale working);[3574] (5) oxidation of 2,6(1*H*,3*H*)-purinedione (xanthine) ($KClO_3$/HCl);[2712] (6) evaporation of 5,5-diethoxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with nitric acid (> 95% yield);[5556] and some other less useful procedures.



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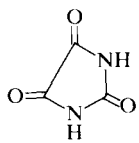
Alloxan crystallizes from water as a tetrahydrate but it also forms other hydrates and alcoholates. The existence of anhydrous alloxan in a flat tetraoxo form has been confirmed by X-ray crystal analysis.[3572,5565] Alloxan decomposes slowly in storage, and this has led to explosions due to the accumulation of carbon dioxide in toowell-sealed bottles.[5557–5564] In its elevated oxidation state, alloxan resembles the less well known quinonoid pyrimidines (Section 7.7).

Besides the reductions already mentioned, alloxan undergoes many reactions to give, for example, the following products.

5-Oxo-5*H*-imidazole-2,4(1*H*,3*H*)-dione (parabanic acid) (**182**) (oxidative ring contraction; HNO_3).[5566]

4-Hydroxy-2,5-dioxo-1,2,3,5-tetrahydro-4*H*-imidazole-4-carboxylic acid (**183**) (alloxanic acid) and subsequently to aliphatic products (hydrolytic ring contraction, etc.; Na_2CO_3);[4542,5555,5566,5567] the mechanism has been studied.[2713,3811,5568,5569]



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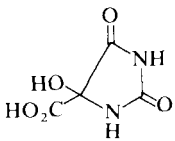

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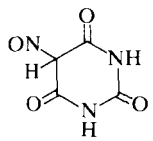

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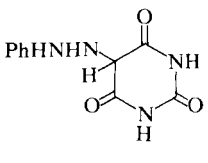
5-Nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**184**) (violuric acid) (oxime formation and prototropy; H_2NOH). [2798,3561,3562, cf. 3553]

5-Phenylhydrazino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**185**) (phenylhydrazone formation and prototropy; $PhNHNH_2$).[4823,4852, cf. 4824]

1-Hydroxymethyl- (**186**, R = H) or 1,3-bishydroxymethyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (*N*-alkylation; limited or excess of CH_2O in acidic medium).[1760]

Benzo[*g*]pteridine-2,4(1*H*,3*H*)-dione (**187**) (alloxazine) (condensation) with *o*-phenylenediamine).[5570,5571]



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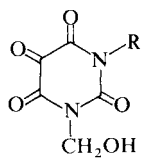

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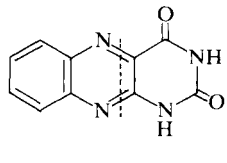

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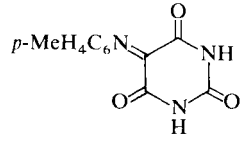

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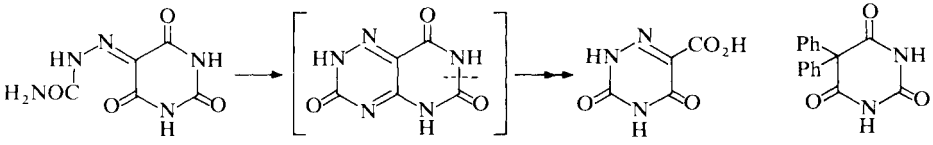
5-*p*-Tolylimino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**188**) (Schiff base formation; *p*-toluidine, AcOH) and thence other products;[5572] alloxanic acid (**183**) and other products were formed under different conditions [5573]

5-Semicarbazono-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**189**) (H_2NCONH-NH_2) and thence to the unisolated pyrimido[4,5-*e*]-*as*-triazinetrione (**190**); finally to 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (**191**) (2*M* NaOH).[2714, cf. 5574] Analogous reactions have also been reported.[649,5575,5576]



189 **190** **191** **192**

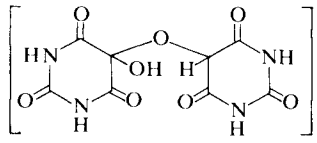
5,5-Diphenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**192**) (PhH, H_2SO_4),[5551] a product unavailable by the obvious Principal Synthesis.[5577,5578]

Also other reactions.[5579,5580]

Although alloxan was identified in intestinal mucus as early as 1852,[5588] it has not been found elsewhere as a natural product. However, it has an interesting diabetogenic action, apparently associated with the removal of essential zinc from insulin by chelation: such irreversible diabetes can be induced in many species of animal with intrinsically low glutathione levels but not in humans, owls, or guinea-pigs.[4773,5589–5593] A single injection of alloxan brought about a dramatic reduction in the malarial parasitemia within mice infected with *Plasmodium vinckei vinckei*; the mechanism appears to have involved a reactive oxygen species, such as hydroxyl radicals, produced in situ within the host red cells.[5594]

7.1.6.2. 5,5′-Dihydroxy-5,5′-bipyrimidine-2,2′,4,4′,6,6′(1*H*,1′*H*,3*H*,3′*H*,5*H*,5′*H*)-hexone (Alloxantin)

Alloxantin is a strangely labile compound, probably best formulated as the bipyrimidine (**179**), although an unsymmetrical ether form (**193**) has been favored by some.[2576,2981,3280,5552,5581–5587]



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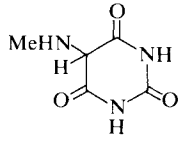

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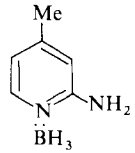
Alloxantin (**179**) has been made by controlled reduction (hydrogen sulfide) of alloxan (**180**);[3281,3568] by the aerial oxidation of dialuric acid (**178**);[3717,5541] by admixture of equimolar portions of aqueous dialuric acid and alloxan, whereupon the relatively insoluble (0.3% at 25°) product (**179**) crystallized;[3279] and by less practical procedures. Redox measurements of alloxantin have been recorded,[5595,5596] and it has been reported that an aqueous solution is > 80% dissociated into alloxan and dialuric acid.[5584] An acetyl and a benzoyl derivative have been made,[772] treatment of alloxantin with methylamine in aqueous acetic acid gave 5-methylamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**194**) (46%),[3384] and other rather mundane reactions have been reviewed.[5597]

7.1.6.3. 5-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Dialuric Acid) and Isodialuric Acid

Dialuric acid (**178**) has been made by the reduction of alloxan (**180**) with stannous chloride,[1138] an excess of hydrogen sulfide (88% yield),[3279, cf. 3281] or 2-amino-4-methylpyridine borane (**195**) (in F_3CCO_2H at 20° for 3 h: 58%);[336] by hydrolysis of 5-amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (6*M* HCl, reflux, 30 min: 55%);[1590, cf. 3280] or by primary synthesis of 5-tetrahydropyran-2′-yloxy-or 5-benzyloxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**196**) followed by alkaline hydrolysis[1324] or hydrogenolytic debenzylation,[1337] respectively. Dialuric acid undergoes some expected reactions: for example, treatment in phosphoryl



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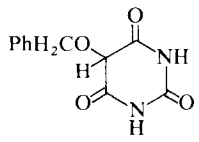

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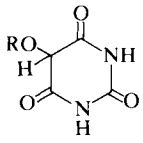
chloride with phosphorus pentachloride or pentabromide at 120° gave 2,4,5,6-tetrachloro- or 2,4,5,6-tetrabromopyrimidine, respectively;[3597,3653] and treatment with boiling acetic anhydride or benzoyl chloride gave 5-acetoxy- (**197**, R = Ac) or 5-benzoyloxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**197**, R = Bz), respectively.[772]



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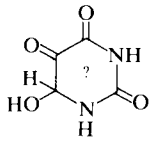

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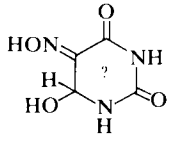

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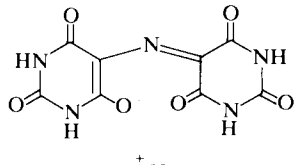
Isodialuric acid, from 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione with aqueous bromine,[771] has been formulated as the 5-oxo compound (**198**) mainly on the grounds that it is isomeric with dialuric acid; it is converted into dialuric acid (**178**) by alkali;[5541] and it gives an oxime (**199**), methyl ether, and a phenylhydrazone.[749,4839] Pending reinvestigation, the formulation of isodialuric acid must be considered doubtful.

7.1.6.4. Bis(2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl)amine (Purpuric Acid) and Its Ammonium Salt (Murexide)

Although not a member of the alloxan family, purpuric acid and its ammonium salt, murexide, have long been associated with such pyrimidinones. Murexide was made first in 1819 by oxidation of uric acid followed by treatment with ammonia,[1656,5598] a preparation later modified to afford a > 90% yield by boiling alloxantin in glacial acetic acid containing ammonium acetate for 2 min.[5599] It is usually formulated as the salt (**200**) to account for its deep color (solid—red by transmitted light, green by reflected light; solutions—usually red-purple) in comparison with that of its parent.[5586, cf. 2981,5600,5601] The long-known murexide test, for detecting uric acid or other purines,[5602] simply amounts to a crudely executed preparation of murexide.



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7.2. 5-PYRIMIDINOLS

Unlike 2- or 4/6-pyrimidinols, which exist and react as the tautomeric 2- or 4/6-pyrimidinones (Section 7.1), 5-pyrimidinols are phenolic in nature and

resemble *m*-nitrophenol or 3,5-dinitrophenol in most of their properties and reactions.

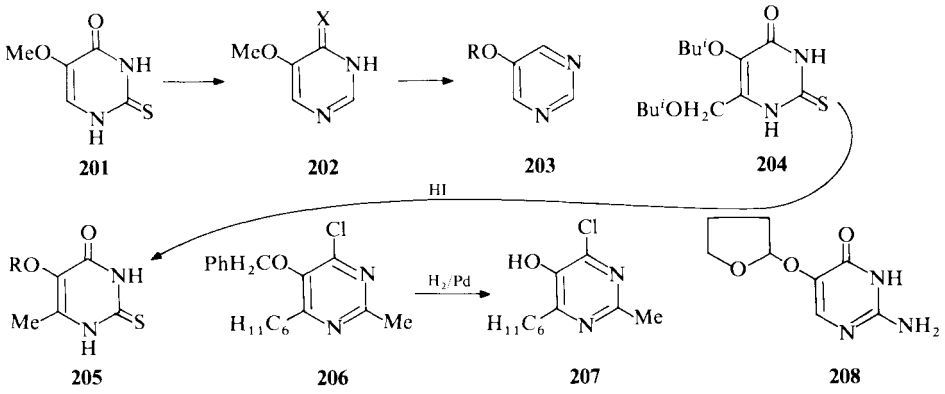
7.2.1. Preparation of 5-Pyrimidinols

Most 5-pyrimidinols have been made by indirect primary syntheses, by indirect oxidative hydroxylation of an existing pyrimidine with a free 5-position, or by metathesis from a 5-substituted pyrimidine.

7.2.1.1. Via 5-Alkoxypyrimidines

The traditional route to 5-pyrimidinols is by primary synthesis (with or without subsequent steps) of a 5-alkoxypyrimidine, followed by hydrolysis or hydrogenolysis. For example, condensation of methyl α-formyl-α-methoxyacetate with thiourea gave 5-methoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**201**), which was converted subsequently into 5-methoxy-4(3*H*)-pyrimidinone (**202**, X = O) (Raney-nickel), 5-methoxy-4(3*H*)-pyrimidinethione (**202**, X = S) (P_2S_5), 5-methoxypyrimidine (**203**, R = Me) (Raney-nickel), and 5-pyrimidinol (**203**, R = H) (KOH in glycol under reflux);[1343] an alternative route involved the formation of 5-bromopyrimidine followed by methanolysis and hydrolysis to the product (**203**, R = H).[836,1969]

Without detailing the route(s) to each substrate, methods for the conversion of 5-alkoxypyrimidines into 5-pyrimidinols are illustrated in the following examples.



5-Methoxy-2-phenlypyrimidine to 2-phenyl-5-pyrimidinol (KOH, glycol, reflux, 10 h: 61%).[1343]

5-Isobutoxy-6-isobutoxymethyl- (**204**) to 5-isobutoxy-6-methyl- (**205**, R = Bu^i) (HI, reflux, 40 min: 48%) or to 5-hydroxy-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**205**, R = H) (HI, reflux, 4 h: 59%).[2898]

5-Methoxy-4(3*H*)-pyrimidinone or 5-methoxy-4-pyrimidinamine to **5-hydroxy-4(3*H*)-pyrimidinone** (HBr, reflux, 2 h: 73% or 80%, respectively).[718]

5-Benzyloxy- to 5-hydroxy-4(3*H*)-pyrimidinone (6*M* HCl, reflux, 20 min: 68%;[718] H_2, Pd, *M* NaOH or HCO_2H: > 90%[1340]).

5-Benzyloxy-2-pyrimidinamine to 2-amino-5-pyrimidinol (H_2, Pd: 72%).[718]

5-Benzyloxy-to 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (6*M* HCl, reflux, 1 h: 75%).[581]

5-Methoxy-2,4,6-triphenylpyrimidine to 2,4,6-triphenyl-5-pyrimidinol (HBr + AcOH, reflux, 1 h: 84%).[4479]

2-Dimethylamino-5,5-diethoxy-5,6-dihydro- to 2-dimethylamino-5-hydroxy-4(3*H*)-pyrimidinone (HCO_2H, reflux, 19 h: 62%).[3818]

5-Benzyloxy-4-chloro-6-cyclohexyl-2-methylpyrimidine (**206**) to 4-chloro-6-cyclohexyl-2-methyl-5-pyrimidinol (**207**) (H_2, Pd, AcOH: 64%).[3908]

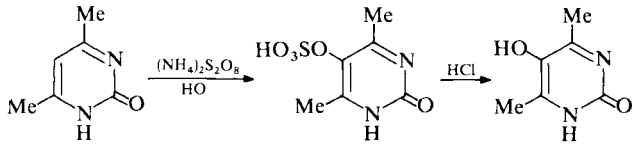
2-Amino-5-benzyloxy- to 2-amino-5-hydroxy-4(3*H*)-pyrimidinone (H_2, Pd, H_2O–AcOH: 76% as sulfate;[1324] similarly in HCO_2H: > 90%[1340]).

2-Amino-5-tetrahydropyran-2′-yloxy- (**208**) to 2-amino-5-hydroxy-4(3*H*)-pyrimidinone *M*H_2SO_4, 20°, 1 h: 92%).[1324]

Also other examples.[774,926,1086,1188,1337,2904,3268,4838]

7.2.1.2. Via 5-Sulfooxypyrimidines or 5-Acyloxypyrimidines

Pyrimidines with electron-donating substituents and a free 5-position usually undergo the Elbs persulfate oxidation to afford their 5-sulfo-oxy derivatives, which may be converted into the corresponding 5-pyrimidinols by acidic hydrolysis. Thus treatment of 4,6-dimethyl-2(1*H*)-pyrimidinone (**209**) with cold alkaline persulfate gave 4,6-dimethyl-5-sulfo-oxy-2(1*H*)-pyrimidinone (**210**) (50%), which, on boiling in 5*M* HCl for 20 min, gave 5-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**211**) (60%).[578,1011] Broadly similar treatment of appropriate substrates gave, for example, the following products.



209 **210** **211**

2-Amino-5-hydroxy-4(3*H*)-pyrimidinone.[578]

5-Hydroxy-6-methyl-2-piperidino-4(3*H*)-pyrimidinone.[578]

2,4-Diamino-5-pyrimidinol.[578]

6-Amino-5-hydroxy-4(3*H*)-pyrimidinone (hydrolysis: 65%).[581]

5-Hydroxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (50% yield overall).[751,1011,6017]

2,4-Diamino-6-methyl-5-pyrimidinol (gentle acidic hydrolysis: 72%) or 2-amino-5-hydroxy-6-methyl-4(3*H*)-pyrimidinone (vigorous acidic hydrolysis: 58%), both from 6-methyl-2,4-pyrimidinediamine.[1328]

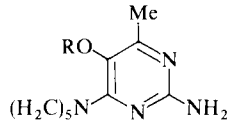
2,6-Diamino-5-hydroxy-4(3*H*)-pyrimidinone (divicine; 50% overall).[2403]

5-Hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (hydrolysis: 64%).[1345]

2,4-Bisdimethylamino-5-pyrimidinol.[1011]

Also other examples from the foregoing references.

In very much the same way, 6-piperidino-2,4-pyrimidinediamine with dibenzoyl peroxide gave its 5-benzoyloxy derivative (**212**, R = Bz), which was converted by dimethylamine at 0° into 2,4-diamino-5-pyrimidinol (**212**, R = H) in 30% overall yield;[5604] 6-amino-5-benzyloxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione was made similarly but hydrolysis was unsuccessful.[5611]



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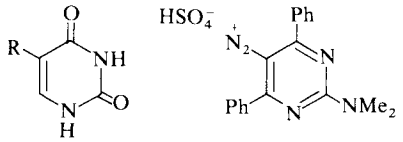
7.2.1.3. From 5-Pyrimidinamines

The conversion of 5-pyrimidinamines into 5-pyrimidinols may be done by vigorous hydrolysis or (for primary amines only) by diazotization. Thus 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**213**, R = NO_2) underwent reduction and subsequent *hydrolysis* on treatment with tin is hot hydrochloric acid to afford 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (**213**, R = OH) (63%);[3275, cf. 771,1943] 5-amino-4(3*H*)-pyrimidinone or 4,5-pyrimidinediamine underwent hydrolysis in boiling 6*M* HCl during 4 h to afford 5-hydroxy-4(3*H*)-pyrimidinone (75% or 95%, respectively);[718] 5-ethoxycarbonylamino- gave 5-hydroxy-2-methyl-4(3*H*)-pyrimidinone (10*M* HCl, 125°, 1 h, sealed: 41%);[1118] 5-ethylamino-4-pyrimidinamine gave 5-hydroxy-4(3*H*)-pyrimidinone (10*M* HCl, 100°, 6 h, sealed: 83%);[1774] and other examples have been reported.[1342,1585,6193]



213 **214**

Although *diazotization* failed to convert 5-pyrimidinamine into 5-pyrimidinol,[711] warming a diazotized solution of 2-ε-carboxypentylamino-5-pyrimidinamine gave 2-ε-carboxypentylamino-5-pyrimidinol (60%).[5153] In a similar way, 5-amino- gave 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (80%)[5605] and 2-dimethylamino-4,6-diphenyl-5-pyrimidinamine gave 2-dimethylamino-4,6-diphenyl-5-pyrimidinol (55%) by diazotization in concentrated sulfuric acid followed by treatment of the solid diazonium sulfate (**214**) in hot 60% sulfuric acid.[4758]

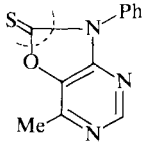
7.2.1.4. From 5-Halogenopyrimidines

Although the conversion of a few 5-halogenopyrimidines into 5-pyrimidinols has been done under extremely vigorous conditions, at least two such reactions were successful under quite mild conditions. For example, 4-anilino-5-bromo-6-methylpyrimidine gave 4-anilino-6-methyl-5-pyrimidinol (12%) by heating in a sealed vessel with aqueous barium hydroxide containing copper powder at 190° for 10 h,[2896] whereas 5-bromo- gave 5-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (> 65%) by refluxing with aqueous sodium hydrogen carbonate for 5 h.[3242] Other examples have been quoted in Section 6.8.3. The abnormal hydrolysis of 5-bromo-1,5-dialkyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones has been studied.[5609]

7.2.1.5. By Other Means

The formation of 5-pyrimidinols by *primary syntheses* without isolation of an intermediate 5-protected-hydroxy species is unusual. However, condensation of 3-acetoxy-2,4-pentanedione with thiourea in ethanolic hydrochloric acid under reflux for 5 h gave 5-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinethione (47%) without a separate deacetylation;[1343] treatment of the easily made 7-methyl-3-phenyl-1,3-oxazolo[4,5-*d*]pyrimidin-2(3*H*)-thione (**215**) with Raney-nickel or alkali gave 4-anilino-6-methyl-5-pyrimidinol (44% or 84%, respectively);[2896] and other examples have been given in Chapters 2 and 3.

The *addition* of *m*-chloroperoxybenzoic acid to 1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 6-*m*-chlorobenzoyloxy-5-hydroxy-1,3,5-trimethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione [**216**, R=C(:O)C_6H_4Cl-*m* (76%), which



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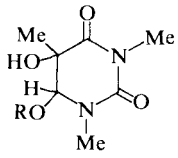

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underwent hydrolysis in aqueous ammonia at 20° to afford 5,6-dihydroxy-1,3,5-trimethyl-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**216**, R = H) (55%).[3757]

The direct *oxidation* of 5-alkyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones with warm alkaline hydrogen peroxide or with chromic oxide in acetic acid gave, for example, 5-benzyl-5-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione;[5606,6739] however, rather similar treatment of 2,6-diamino-4(3*H*)-pyrimidinone gave 6-amino-1,3,5-triazine-2,4(1*H*,3*H*)-dione (80%) or related triazines, probably by a Dimroth-like rearrangement.[5607]

The *acylative rearrangement* of 4-phenylpyrimidine 1,3-dioxide by acetic anhydride in refluxing chloroform for 10 h, followed by treatment of the crude product (a 5-acetoxy intermediate?) in water for 24 h, gave 4-phenyl-5-pyrimidinol 3-oxide (40%);[5608] similar treatment of 2,4,6-trimethylpyrimidine 1,3-dioxide, but without the water stage, gave a separable mixture of 5-acetoxy-2,4,6-trimethylpyrimidine 1-oxide and 2-acetoxymethyl-4,6-dimethylpyrimidine 1-oxide: no hydrolysis was reported.[763]

7.2.2. Reactions of 5-Pyrimidinols

5-Pyrimidinols undergo few reactions apart from the *O*-acylations and *O*-alkylations to be expected of such phenolic substances. Many give a red to violet color with ferric chloride.[578,1324,1341]

7.2.2.1. *O*-Acylation

Treatment with appropriate acylating reagents produce the following 5-acyloxypyrimidines, usually from the corresponding 5-pyrimidinols.

5-Acetoxy-4(3*H*)-pyrimidinone (Ac_2O, pyridine, 25°, 1 h: 81%).[314]

5-Acetoxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, Soxlet, 10 h: 81%; [6017] Ac_2O, reflux, 3 h: 86%[751, cf. 769]).

5-Acetoxy-4,6-dimethyl-2(1*H*)-pyrimidinone (Ac_2O, reflux, 30 min: > 90%)[578]

2-Acetamido-5-acetoxy- or 2-amino-5-benzoyloxy- from 2-amino-5-hydroxy-6-methyl-4(3*H*)-pyrimidinone (refluxing Ac_2O or BzCl/alkali, respectively).[578]

5-Acetoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O), pyridine, 50°, 12 h: ~ 70%) or from 5-hydroxy-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, Me_2SO as oxidant, 25°, 24 h: ~ 45%).[754]

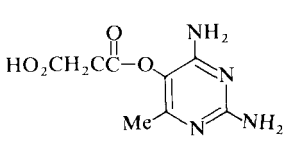
5-Benzoyloxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (BzCl, pyridine, 60°, 77%). [1328]

5-α-Carboxyacetoxy-6-methyl-2,4-pyrimidinediamine (**217**) [$CH_2(COCl)_2$, 1.5*M* NaOH, 25°, 30 min: 45%].[5610]

O,O-Bis(2-methylthiopyrimidin-5-yl) thiocarbonate (**218**) from 2-methylthio-5-pyrimidinol ($SCCl_2$, NaOH, H_2O + $CHCl_3$, reflux, 3 min: 48%).[2834]

4-Benzoyl-6-methyl-5-mesyloxy-2-phenylpyrimidine (**219**) ($MeSO_2Cl$, pyridine, 0°, 4 h: 50%) [136]

Also other examples.[579,718,771,772,774,1328]



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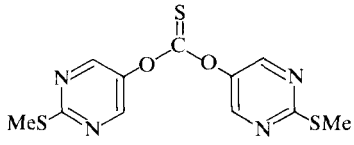

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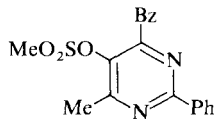

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7.2.2.2. *O*-Alkylation

Appropriate reagents and conditions for the *O*-alkylation of 5-pyrimidinols are illustrated in the formation of the following 5-alkoxypyrimidines.

4-Anilino-5-methoxy-6-methylpyrimidine (CH_2N_2, Et_2O).[2896]

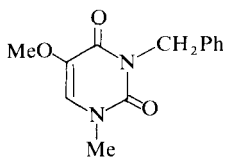
5-Methoxy-4-phenylpyrimidine 3-oxide (CH_2N_2, Et_2O–$CHCl_3$ 20°, 5 h).[5608]

2-Methylthio-5-prop-2′-ynyloxypyrimidine ($HC{\equiv}CCH_2Cl$, K_2CO_3, Me_2SO, 50°, 4 h: 81%).[3523]

5-Allyloxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione ($H_2C{=}CHCH_2Br$, NaOMe, MeOH, reflux, 1 h: 82%).[854]

5-Methoxy-2-methylthio-6-propyl-4(3*H*)-pyrimidinone from 5-hydroxy-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (Me_2SO_4, 2.5*M* NaOH, 25°, 10 min: 70%).[825]

3-Benzyl-5-methoxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**220**) (CH_2N_2, Et_2O–MeOH, 12 h: 85%).[4912]



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4-Benzoyl-5-methoxy-6-methyl-2-phenylpyrimidine (Me_2SO_4, Na_2CO_3, H_2O–AcMe, 25°, 3 h: 50%).[136]

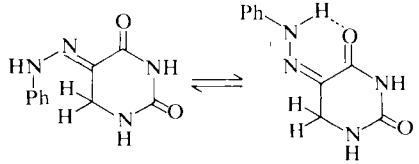
Also other examples.[749,926,2576,2723]

7.2.2.3. Other Reactions

The few reported examples of other reactions of 5-pyrimidinols are of little use in themselves, but they may indicate possibilities.

To 5-Halogenopyrimidines. 5-Pyrimidinols appear to be unresponsive to treatment with phosphorous halides or the like. However, 5-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione has been converted into 2,4,5,6-tetrachloro- or 2,4,5,6-tetrabromopyrimidine by heating at 120°with the appropriate phosphorous pentahalide in phosphoryl chloride.[3597]

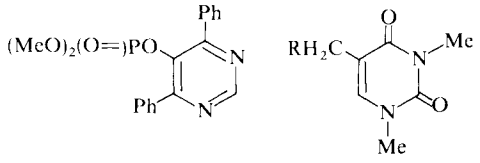
Aminolysis. Although 5-pyrimidinols do not normally react with amines, 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione with phenylhydrazine in acetate buffer at 95° for 2 h gave 5-phenylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione (60%),[5613] on nmr evidence existing initially in the *anti*-hydrazono form (**221a**) but converted into the isomeric *syn*-form (**221b**) on prolonged heating in methoxyethanol.[5612] 5-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione also reacts with hydrazine derivatives rather similarly.[757]



221a **221b**

Oxidation. Although oxidation of 5-pyrimidinols is usually impossible, the special circumstances pertaining in 5-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**178**) allowed it to be oxidized to 5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (alloxan) (**180**), probably via alloxantin (**179**), as described in Section 7.1.6.

Dehydroxylation. No direct way to dehydroxylate 5-pyrimidinols has been developed. However, an indirect route has been indicated in the conversion of 4,6-diphenyl-5-pyrimidinol into 5-dimethoxyphosphinyloxy-4,6-diphenylpyrimidine (**222**) ($POCl_3$, reflux, 1 h; evaporation, MeOH, 25°) and thence into 4,6-diphenylpyrimidine (Na, NH_3–THF: 57%).[4488]



222 **223**

To 5-(Substituted-alkyl)pyrimidines. Replacement of the 5-hydroxy group by a substituted-alkyl group is possible by using an appropriate Wittig reagent. For example, 5-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione with (ethoxycarbonylmethylene)triphenylphosphorane ($Ph_3P{=}CHCO_2Et$) in refluxing acetonitrile for 9 h gave 5-ethoxycarbonylmethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**223**, R = CO_2Et) (93%); the 5-methoxycarbonylmethyl, 5-cyanomethyl, and other analogues were made similarly.[1994]

Cyclizations. A 5-hydroxy group can be incorporated into a new ring: for example, 4-amino-5-pyrimidinol and neat triethyl orthoformate gave oxazolo[4,5-*d*]pyrimidine (trace TsOH, > 140°: 45%).[6031]

7.3. EXTRANUCLEAR HYDROXYPYRIMIDINES

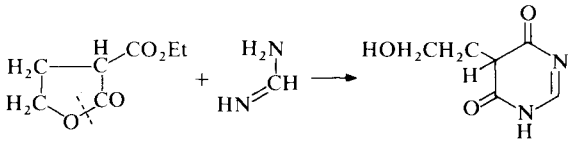
Extranuclear hydroxypyrimidines are simply alcohols in which those reactions and properties associated with the hydroxy group(s) are only mildly affected by the presence of the pyrimidine ring or by the position at which the hydroxyalkyl substituent is attached thereto. In such respects, the hydroxymethylpyrimidines might be likened to the corresponding dinitrobenzyl alcohols.

7.3.1. Preparation of Extranuclear Hydroxypyrimidines

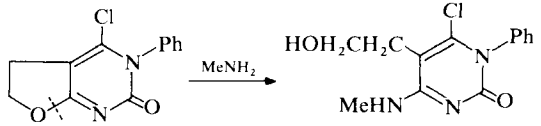
Of the many ways to make pyrimidinyl alcohols, most are mundane and well known in other heterocyclic and carbocyclic series: accordingly, discussion of each such method will be brief.

7.3.1.1. By Primary Syntheses

Some primary syntheses of pyrimidines bearing hydroxyalkyl groups, especially in the 2- and/or 5-positions, have been discussed in Chapters 2 and 3. For example, 2-hydroxyacetamidine with ethyl acetoacetate gave 2-hydroxymethyl-6-methyl-4(3*H*)-pyrimidinone (H_2O, 25°, 3 h: 48%),[1759] α-ethoxycarbonyl-γ-butyrolactone (**224**) with formamidine gave 5-β-hydroxyethyl-4,6(1*H*,5*H*)-pyrimidinedione (**225**) (NaOEt, EtOH, 45°, 24 h: 68%),[3035] 4-chloro-3-phenyl-5,6-dihydrofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**226**) with ethanolic methylamine gave 4-chloro-5-β-hydroxyethyl-6-methylamino-3-phenyl-2(3*H*)-pyrimidinone



224 **225**

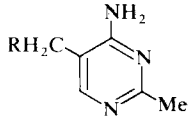


226 **227**

(**227**) ($MeNH_2$, EtOH, 50°, 1 h, sealed: 75%),[4536, cf. 4535] and other such cases have been reported.[936,986,1684,4289]

7.3.1.2. From Aminoalkylpyrimidines

The conversion of aminoalkyl- into hydroxyalkylpyrimidines has been done invariably by treatment with warm aqueous nitrous acid. Thus 5-aminomethyl- (**228**, R = NH_2) gave 5-hydroxymethyl-2-methyl-4-pyrimidinamine (**228**, R = OH) by slowly treating an aqueous solution of the substrate dihydrochloride with sodium nitrite at 60° and maintaining the temperature there for 60 min.[678,750,3517] The following products were made rather similarly unless indicated otherwise.



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2-Ethyl-5-hydroxymethyl-4-pyrimidinamine (80%).[1065]

5-Hydroxymethyl-2,4-dimethylpyrimidine (15 h: 39%).[2761]

2-Cyclopropylmethyl-5-hydroxymethyl-4-pyrimidinamine (5 h: 79%).[4242]

6-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (67%).[701]

5-Hydroxymethyl-1-methyl-4(3*H*)-pyrimidinone (95°, 6 h: 40%).[680,1418,1419]

Also other examples.[1119,1489]

7.3.1.3. From Halogenoalkylpyrimidines

These metatheses have been discussed fully in Section 6.9.

7.3.1.4. From Pyrimidinecarboxylic Esters or the Like

The reduction of pyrimidinecarboxylic esters with lithium aluminum hydride or a related reagent has been used extensively to prepare the corresponding hydroxyalkylpyrimidines. This is illustrated in the formation of the following products, in each case from the corresponding ethyl ester with lithium aluminum hydride in ether or THF, unless indicated otherwise.

5-Hydroxymethyl-2-methylpyrimidine (21%).[3062]

2-Hydroxymethyl-4,6-dimethylpyrimidine (from methyl 4,6-dimethyl-2-pyrimidinecarboxylate: 45%).[1933]

5-Hydroxymethyl-2,4-dimethylpyrimidine (54%).[2761,3259]

5-Hydroxymethyl-2-methoxy-4-pyrimidinamine (69%).[2203,2967]

4-Hydrazino-5-hydroxymethyl-2-methylthiopyrimidine (67%).[2695]

6-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione [from butyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate: 52%].[770]

6-*β*-Hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione [from 6-ethoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione: 62%].[1232]

4-Dimethylamino-5-hydroxymethyl-2-methylpyrimidine (74%).[1904,2621]

4-Chloro-5-hydroxymethyl-2-methylpyrimidine (49%).[1904]

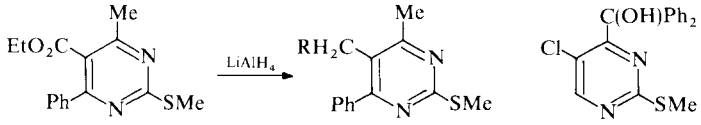
5-Hydroxymethyl-2-trifluoromethyl-4-pyrimidinamine (59%).[5614]

5-Hydroxymethyl-2,6-bistrifluoromethyl-4(3*H*)-pyrimidinone [from 4-oxo-2,6-bistrifluoromethyl-3,4-dihydro-5-pyrimidinecarboxylic acid; BH_3.THF, THF, 20°, 15 h: 59%].[3921]

4-Hydroxymethyl-2-methylthiopyrimidine [from 2-methylthio-4-pyrimidinecarboxylic acid with $ClHC{=}\overset{+}{N}Me_2$ Cl^- and then $NaBH_4$ in MeCN–THF below −20°: 68%).[3931]

Also other examples.[1249,1326,1329–1331,1629,1912,2812]

Occasionally such reductions can go too far by reducing hydroxymethyl products to their methyl analogs: for example, ethyl 4-methyl-2-methylthio-6-phenyl-5-pyrimidinecarboxylate (**229**) with lithium aluminum hydride in ether at 5° for 30 min gave a separable mixture of 5-hydroxymethyl-4-methyl- (**230**, R = OH) (25% yield) and 4,5-dimethyl-2-methylthio-6-phenylpyrimidine (**230**, R = H) (30%);[14] another such example has been reported.[2695]



229 **230** **231**

A potential route from pyrimidinecarboxylic esters to less simple hydroxyalkylpyrimidines has been exemplified in the treatment of ethyl 5-chloro-2-methylthio-4-pyrimidinecarboxylate with phenylmagnesium bromide followed by acidification to afford 5-chloro-4-α-hydroxydiphenylmethyl-2-methylthiopyrimidine (**231**) (55%).[2291] An unusual but logical reaction sequence was that of 5-hydrazinocarbonylmethyl- to 5-hydroxymethyl-2-methylpyrimidine (31%) by treatment with nitrous acid (twice).[3062]

7.3.1.5. By *C*-Hydroxymethylation, Mainly with Formaldehyde

Although formaldehyde usually attacks the 5-position of an appropriate pyrimidine to give a 5-hydroxymethyl derivative, in suitable cases such attack

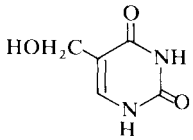
may occur at the 2- or 4/6-position or even on an activated methyl group. These reactions are illustrated in the formation of the following products, in each case from the obvious substrate.

5-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (**232**) (CH_2O, 0.4*M* KOH, 50°, 3 days: 81%; CH_2O, 0.5*M* HCl, reflux, 24 h: 27%.[1597, cf. 1489]

5-Hydroxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (CH_2O, HO^-: 90%; CH_2O, H^+: 76%).[2792]

5-Hydroxymethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (CH_2O, HCl, 70°, 90 min: 56%).[2776]

5-Hydroxy-6-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (CH_2O, *M* NaOH, 50°, 3 h: 73%).[747]



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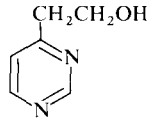

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4-β-Hydroxyethylpyrimidine (**233**) (from 4-methylpyrimidine with neat paraformaldehyde, 165°, 3–5 h, sealed: 81–87%).[2078,4678]

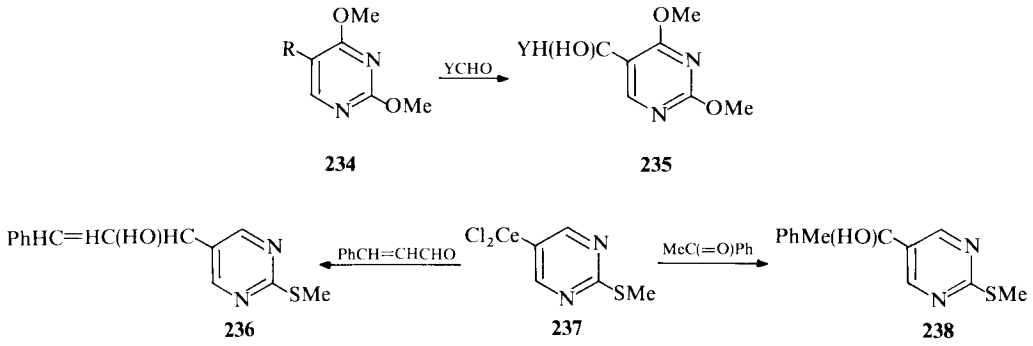
4-β-Hydroxyethyl-2,6-diphenylpyrimidine (neat paraformaldehyde, 160°, 20 h, sealed: 24%).[4678]

Also other examples.[854,3260]

The use of a different reagent is exemplified in the treatment of 4,6-dimethylpyrimidine in methanolic sulfuric acid with ammonium persulfate (under reflux for 5 h) to afford 2-hydroxymethyl-4,6-dimethylpyrimidine (93%);[2222] 4-hydroxymethyl- (54%), 4-hydroxymethyl-2-isopropyl-6-methyl- (53%), and 4-hydroxymethyl-2-methyl-6-phenylpyrimidine (65%) were made similarly.[2222,3258]

7.3.1.6. From *C*-Metallopyrimidines with Aldehydes or Ketones

Apart from formaldehyde (see preceding subsection), aldehydes and ketones appear to require a metallated substrate with which to form appropriate *C*-hydroxyalkylpyrimidines. Thus treatment of 2,4-dimethoxypyrimidine (**234**, R = H) with lithium 2,2,6,6-tetramethylpiperidide in ether at 0° gave the 5-lithio derivative (**234**, R = Li), which reacted with acetaldehyde or benzaldehyde to afford 5-α-hydroxyethyl- (**235**, Y = Me) (44%) or 5-α-hydroxybenzyl-2,4-dimethoxypyrimidine (**235**, Y = Ph) (65%), respectively;[474] rather similarly, treatment of 5-bromopyrimidine with lithium diisopropylamide and benzaldehyde



gave 5-bromo-4-α-hydroxybenzylpyrimidine (36%).[5620] A second procedure has been typified by the treatment of 5-bromo-2-methylthiopyrimidine in THF at −90°, first with butyllithium to give the 5-lithio analog, then with cerous chloride to give (2-methylthiopyrimidin-5-yl)cerous chloride (**237**), and finally with cinnamaldehyde or acetophenone to yield 5-(α-hydroxycinnamyl)-2-methylthiopyrimidine (**236**) (97%) or 5-(1′-hydroxy-1′-phenylethyl)-2-methylthiopyrimidine (**238**) (83%), respectively.[6004] A third procedure involved side-chain metallation of 4-allyl-2-chloropyrimidine and subsequent treatment with aldehydes to afford several types of hydroxyalkylpyrimidine.[3909] Lithiation and subsequent treatment with acetaldehyde converted 2,4-dichloropyrimidine into 2,4-dichloro-5- (20%) and 2,4-dichloro-6-α-hydroxyethylpyrimidine (19%).[6124]

7.3.1.7. From Pyrimidinecarbaldehydes or Pyrimidinyl Ketones

Such substrates may be converted into hydroxyalkylpyrimidines by reduction, by treatment with Grignard reagents, or by minor procedures such as the Cannizzaro reaction.

By reduction. Several reagents have been employed to produce hydroxyalkylpyrimidines from the corresponding aldehydes or ketones, as illustrated in the formation of the following products.

5-Hydroxymethyl-2-methyl-4-pyrimidinamine (H_2, Pt, EtOH: 70%;[1458] H_2, Pd or Ni;[1409] Al/Hg[1409]).

2-Amino-6-hydroxymethyl-5-δ-phenylbutyl-4(3*H*)-pyrimidinone (H_2, Pd, EtOH–$MeOCH_2CH_2OH$: 80%).[1182]

2-Cyclopentyl-5-hydroxymethyl-4-pyrimidinamine from 4-amino-2-cyclopentyl-5-pyrimidinecarbonitrile (H_2, Pd, 3*M* HCl, pressure: 65%; via unisolated 5-CH:NH and 5-CHO analogs).[4242]

5-Hydroxymethylpyrimidine ($LiAlH_4$, THF, 4 h: 78%).[1028]

6-Hydroxymethyl-4(3*H*)-pyrimidinone ($NaBH_4$. MeOH–H_2O, 25°, 90 min: 73%).[2856]

4,5-Bishydroxymethyl-2-methylthiopyrimidine from 5-hydroxymethyl-2-methylthio-4-pyrimidinecarbaldehyde ($NaBH_4$, MeOH, 25°, 30 min: 62%).[768]

4-Hydroxymethyl-2-methyl-6-phenylpyrimidine ($NaBH_4$, MeOH, 25°, 5 min: 93%).[4683]

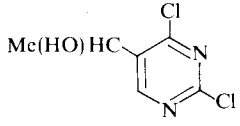
4-α-Hydroxymethyl-6-methyl-2-phenylpyrimidine ($NaBH_4$, EtOH, reflux, 1 h: 83%).[4684]

5-α-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaBH_4$, 0.1*M* NaOH, 20°, 22 h: 75%).[252]

5- or 6-α-Hydroxybenzyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaBH_4$, H_2O, 20° → 100°, 20 min: 40% or 96%, respectively).[788,5138]

Also other examples.[419,795,974,1868,3446,3967,5978]

By Grignard treatments. This route is exemplified in the reaction of 4,6-dichloro-5-pyrimidinecarbaldehyde with methylmagnesium iodide to give 4,6-dichloro-5-α-hydroxyethylpyrimidine (**239**) (85%);[787] of 5-acetyl-2,4-dimethylpyrimidine with ethylmagnesium or phenylmagnesium bromide to give 5-α-hydroxy-α-methylpropyl- (**240**, R = Et) (69%)[3048] or 5-α-hydroxy-α-phenylethyl-2,4-dimethylpyrimidine (**240**, R = Ph) (68%),[3048, cf. 2291] respectively; of 2-phenacylpyrimidine with phenylmagnesium bromide or phenyllithium under appropriate conditions to give 2-β-hydroxy-β,β-diphenylethylpyrimidine (81% or ~ 50%, respectively);[5615] and of 5-β-formylethynyl-2,4-dimethoxypyrimidine with methylmagnesium iodide to give 2-3′-hydroxybut-1′-ynyl-2,4-dimethoxypyrimidine (90%).[3934] Lithio reagents may be used.[6130]



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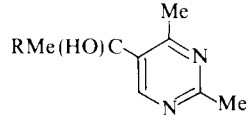

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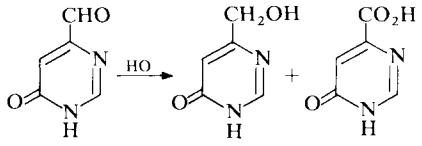
By minor procedures. These methods are illustrated by the examples that follow.

1. 6-Oxo-1,6-dihydro-4-pyrimidinecarbaldehyde (**241**) in 6*M* sodium hydroxide at 95° for 15 min gave a separable mixture of 6-hydroxymethyl-4(3*H*)-pyrimidinone (**242**) (15%) and 6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (**243**) (20%);[2856] other such Cannizzaro reactions gave 6-hydroxymethyl-2-methylthio-4(3*H*)-pyrimidinone (~ 30%),[2856] 6-hydroxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (~ 30%),[3139] and 6-hydroxymethyl-2,4(1*H*,3*H*)-



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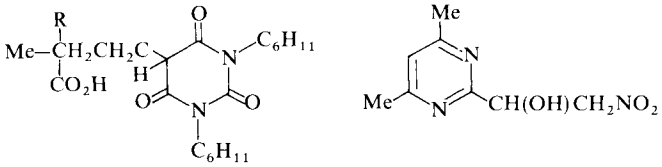
pyrimidinedione (~ 35%),[3139] in each case accompanied by the corresponding carboxylic acid.

2. 5-β-Acetylethyl-1,3-dicyclohexyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione reacted with ammonium cyanide/ammonium hydroxide under Strecker reaction conditions to give 5-γ-carboxy-γ-hydroxybutyl-1,3-dicyclohexyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**244**, R = OH) (~ 40%) instead of the expected amine (**244**, R = NH_2).[5616]



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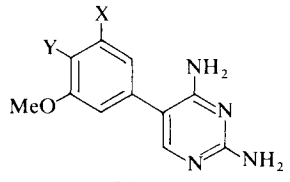
3. 4,6-Dimethyl-2-pyrimidinecarbaldehyde reacted with nitromethane to give 2-α-hydroxy-β-nitroethyl-4,6-dimethylpyrimidine (**245**) (68%), and only on dehydration in acetic anhydride did this afford the expected 4,6-dimethyl-2-β-nitrovinylpyrimidine (50%).[2037]

4. Polymerization of 4,6-pyrimidinedicarbaldehyde gave poly[α,β-dihydroxy-α,β-bis(4,6-pyrimidinediyl)ethylene], in which each pyrimidine ring was joined to its neighbours by —C(OH)=C(OH)— links.[535]

7.3.1.8. From Alkoxyalkyl- or Acyloxyalkylpyrimidines

This route to hydroxyalkylpyrimidines is seldom used. However, 5-ethoxymethyl-2-methyl-4-pyrimidinamine gave 5-hydroxymethyl-2-methyl-4(3*H*)-pyrimidinone (6*M* HCl, reflux, 14 h: ~ 90%),[2813] 1,3-dimethyl-5-trityloxymethyl- gave 5-hydroxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (80% AcOH, 80°, 5 min: 71%),[761] 5-(3′,4′,5′-trimethoxybenzyl)-(**246**, X = Y = OMe) gave 5-(4′-hydroxy-3′,5′-dimethoxybenzyl)-2,4-pyrimidinediamine (**246**, X = OMe, Y = OH) (10*M* HCl, reflux, 6 h: 50%),[5617, cf. 4686] 5-(4′-bromo-3′,5′-dimethoxybenzyl)- (**246**, X = OMe, Y = Br) gave 5-(4′-bromo-3′-hydroxy-5′-methoxybenzyl)-2,4-pyrimidinediamine (**246**, X = OH, Y = Br) (NaSEt, Me_2NCHO, 75°, 24 h: ~ 85%),[164] 2-acetoxymethyl- gave 2-hydroxymethyl-4,6-dimethoxypyrimidine (K_2CO_3, MeOH, 25°, 12 h: 40%),[3974] 2-α-acetoxy-α-methylethyl- gave 2-α-hydroxy-α-methylethyl-4-



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phenylpyrimidine (0.04*M* NaOH, 95°, 24 h: 75%),[1908] and other examples have been reported.[544,3929]

7.3.1.9. By Derivatization or Other Minor Routes

The direct or indirect attachment (derivatization) of an hydroxyalkyl group to an existing pyrimidine can be done in several ways. The following conversions briefly illustrate some of these.

2,4-Dichloro- to 2-chloro-4-β-hydroxyethylamino- ($HOCH_2CH_2NH_2$, MeOH, − 10°, 2 h: 80%)[5020] or 2,4-bis(β-hydroxyethylamino)-6-methyl-5-nitropyrimidine ($HOCH_2CH_2NH_2$, EtOH, reflux, 1 h).[5018]

5-Ethyl-2-methoxy-5-phenyl-4,6(1*H*,5*H*)-pyrimidinedione to 5-ethyl-1,3-bishydroxymethyl-2-methoxy-5-phenyl-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**247**) (CH_2O, K_2CO_3, H_2O, 40°, 10 min: pure but unstable).[4368]

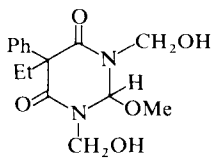
4,6-Dimethyl-2(1*H*)-pyrimidinethione to 2-β-hydroxyethylthio-4,6-dimethylpyrimidine ($ClCH_2CH_2OH$, NaOH, H_2O–PrOH, 20°, then 95°, 2 h: 74%).[1312]

4,6-Dimethyl-2(1*H*)-pyrimidinone to 1-β-hydroxyethyl-4,6-dimethyl-2(1*H*)-pyrimidinone (likewise: 57%).[1312]

2-Pyrimidinamine to 1-β-hydroxyethyl-2(1*H*)-pyrimidinimine ($BrCH_2CH_2OH$, EtOH, 100°, 5 h, sealed: 94% as hydrochloride).[923]

5-Ethylamino- to 5-*N*-ethyl-*N*-(β-hydroxyethyl)amino- (**248**, R = H) (ethylene oxide, AcOH–H_2O,25°, 15 h: 44%) or 5-*N*-ethyl-*N*-(β-hydroxyethyl)amino-3-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (**248**, R = CH_2CH_2OH) (likewise, 6 days: 44%).[1941]

Also other examples.[585,1317,1323,1755,1757,1758,1850,1941,2014,2135,3247,3249,4739,4877,4949,5003,5033,5168]



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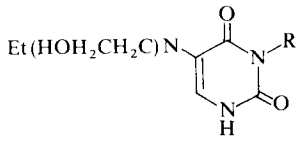

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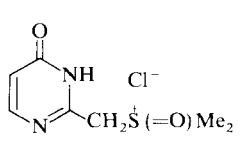
Other minor routes are exemplified by the irradiation of aqueous 2-dimethyloxosulfoniomethyl-4(3*H*)-pyrimidinone chloride (**249**) to give 2-hydroxymethyl-4(3*H*)-pyrimidinone (~ 40%);[2635] by the hydration of 5-benzylidene- to 5-α-hydroxybenzyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**250**) (80%) in dilute alkali at 20° for 20 min;[4649] by hydration of the double bond and hydrolysis of 5-isobutenyl-2-phthalimidopyrimidine (**251**) during treatment in hot aqueous acid to give 5-β-hydroxy-β-methylpropyl-2-pyrimidinamine (**252**) (~ 50%);[4687] and by the conversion of 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid into its 5-(β-hydroxyethyl)aminomethyl derivative (**253**) (~ 30%), using a Mannich reaction with formalin and β-aminoethanol.[5619]



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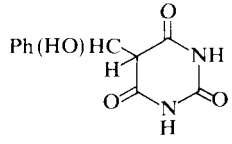

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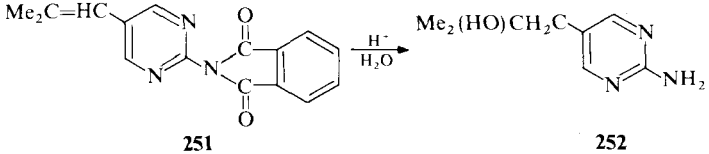

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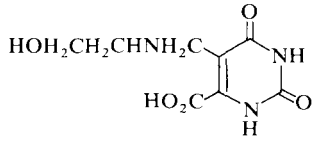

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7.3.2. Reactions of Extranuclear Hydroxypyrimidines

The hydroxyalkyl- and hydroxyarylpyrimidines undergo the few useful reactions to be expected of alcohols and phenols, respectively.

7.3.2.1. *O*-Acylation

Despite an earlier tendency to convert hydroxyalkyl- into chloroalkyl- and thence into acetoxyalkylpyrimidines (using silver acetate),[766,767,1801,2233] hydroxyalkyl- and hydroxyarylpyrimidines are, in fact, easily acylated directly, as indicated in the formation of the following acyloxy derivatives.

4-Acetoxymethyl-2,6-dimethylpyrimidine (Ac_2O, AcONa, 80°, 6 h: 88%).[118]

5-Acetoxymethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, AcOH, 75°, 12 h: 90%).[760]

5-β-Acetoxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, pyridine, 20°, 1 h: 83%).[1321]

5-Acetoxymethyl-2-methylthio-4-pyrimidinamine (limited Ac_2O, EtOAc, reflux, 2 h: 94%) or 4-acetamido-5-acetoxymethyl-2-methylthiopyrimidine (excess Ac_2O, EtOAc, reflux, 15 h: 58%).[577]

5-Benzoyloxymethyl-4-methyl-2-methylthiopyrimidine (BzCl, pyridine, 20°, 16 h: 55%).[2695]

4-Benzoyloxymethyl-2-methoxypyrimidine (BzCl, NEt_3, etc., CH_2Cl_2, 20°, 12 h: 98%).[3931]

3-β-(Chloroacetoxy)ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($ClCH_2$-COCl, pyridine, $CHCl_3$, reflux, 7 h: 66%).[1721]

5-Acetoxy-6-acetoxymethyl- from 5-hydroxy-6-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, pyridine, 25°, 1 h: 83%). [747]

5-Hexyl-2-*p*-propionyloxyphenylpyrimidine (EtCOCl, pyridine, 60°, 30 min: 53%; also many homologs).[4009]

5-β-Mesyloxyethyl-2,4(1*H*,3*H*)-pyrimidinedione ($MeSO_2Cl$, pyridine, 20° ?, 15 h: 87%).[2039, cf. 3719]

5-β-Tosyloxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (TsCl, pyridine, − 10°, 3 days: 80%).[2039]

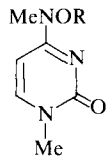
4-Acetoxyamino-5-fluoro- from 5-fluoro-4-hydroxyamino-2(1*H*)-pyrimidinone (Ac_2O, AcOH, reflux, 2 min: ~ 90%).[1365]

6-Ethylcarbamoyloxyamino- from 6-hydroxyamino-1,3-dimethyl-2,4(1*H*, 3*H*)-pyrimidinedione (EtNCO, pyridine, reflux, 2 h: 29%).[776, cf. 173]

Also other examples.[761,770,911,1597,1889,2143,4108,4683,5623,6003,6579]

7.3.2.2. *O*-Alkylation

Perhaps in order to avoid concomitant *N*-alkylation by conventional reagents, *O*-alkylation of hydroxyalkylpyrimidines is usually done by heating in the appropriate alcohol containing a little hydrochloric acid for several hours. In this way, 5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 5-methoxymethyl- (98%), 5-ethoxymethyl- (97%), 5-propoxymethyl- (95%), 5-butoxymethyl- (94%), and 5-benzyloxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (95%);[2933. cf. 758,1597,2922,5258] likewise, 5-hydroxymethyl- gave 5-methoxymethyl- (74%)[760] or 5-allyloxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (65%).[901] More usual reagents have been used to convert 5-hydroxymethyl- into 5-trityloxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (Ph_3CCl, pyridine, reflux, 6 h: 60%);[761] 4-*N*-hydroxy-*N*-methylamino- (**254**, R = H) into 4-*N*-methoxy-*N*-methylamino-1-methyl-2(1*H*)-pyrimidinone (**254**, R = Me) (CH_2N_2,



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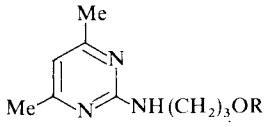

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Et_2O–EtOH, 20°, 15 h: ~ 40%);[3225] and 2-γ-hydroxypropylamino- (**255**, R = H) into 2-γ-benzyloxypropylamino-4,6-dimethylpyrimidine (**255**, R = CH_2Ph) (NaH, $PhCH_2Br$, PhMe, reflux, 1 h: 51% and two separable by-products).[3961]

7.3.2.3. Reductive Dehydroxylation

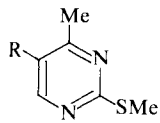
Although it is not often needed, dehydroxylation of hydroxyalkylpyrimidines can be effected by several reducing agents. The following conversions typify such reactions.

5-Hydroxymethyl- into 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (H_2, Pt, AcOH–H_2O: 95%).[1597]

5-Hydroxymethyl-2-methyl- into 2,5-dimethyl-4(3*H*)-pyrimidinone (H_2, Pd, AcOH–EtOH: 60%).[2812]

5-Hydroperoxymethyl- into 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (H_2, Pd, H_2O: 93%).[2853]

Ethyl 4-methyl-2-methylthio-5-pyrimidinecarboxylate (**256**, R = CO_2Et) into 5-hydroxymethyl-4-methyl- (**256**, R = CH_2OH) and thence into 4,5-dimethyl-2-methylthiopyrimidine (**356**, R = Me) (LiH, THF?, − 70°: low yields).[2695]



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6-Hydroxymethyl- into 6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (HI, P, reflux, 4 h).[2274]

5-Hydroxymethyl-6-methyl- into 5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (Sn, HCl: 38%).[2792]

Also other examples.[766,767,2695]

7.3.2.4. Oxidation

The oxidation of hydroxyalkylpyrimidines can give aldehydes, carboxylic acids, or ketones according to the substrate and conditions used. Such oxidative

reactions are illustrated in the formation of the following products, in each case from the corresponding hydroxyalkyl substrate except where otherwise indicated.

To aldehydes

4-Amino-2-methylthio-5-pyrimidinecarbaldehyde ($Na_2Cr_2O_7$, AcOH, 25°, 2 h: 60%).[1326]

4,6-Dimethoxy-2-pyrimidinecarbaldehyde (pyridinium chlorochromate, CH_2Cl_2, 25°, 75 min: 71%).[3974]

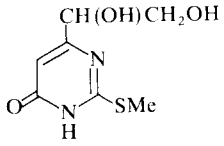
4-Methyl-2-methylthio-6-phenyl-5-pyrimidincarbaldehyde (likewise, 40 min: 60%).[14]

2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde [MnO_2, H_2O, 100°, 15 min: 40–60%;[2851] MnO_2, Me_2SO, 100°, 15 min: 85%;[2851] $Ce(SO_4)_2$: 70%;[2851] $Ce(NO_3)_4(NH_4NO_3)_2$, H_2O, 60°, 5 min: 44%;[2042,2590] $K_2S_2O_8$, Ag^+, H_2O, 35°, 15 min: 70–90%;[2851] MnO_2, HCl: 50%;[1697] O_2, Pt, AcOH–H_2O, 25°, 18 h: unisolated[1597]].

2-Isopropyl-6-methyl-4-pyrimidinecarbaldehyde (SeO_2, dioxane, 25°, 3 h: 55%).[2222]

4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde $K_2S_2O_8$, Ag^+, H_2O, 40°, 15 min ?: 63%).[2852]

2-Methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde from 6-α,β-dihydroxyethyl-2-methylthio-4(3*H*)-pyrimidinone (**257**) ($NaIO_4$, H_2O, 25°, 4 h: 77%).[2859]



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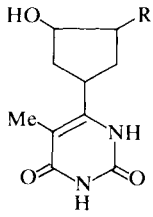
5-β-Formylethynyl- from 5-3′-hydroxyprop-1′-ynyl-2,4-dimethoxypyrimidine [Swern's reagent (Me_2SO, ClOCCOCl, Et_3N), −78°: 76%].[3934]

Also other examples.[2222,2776]

To carboxylic acids

2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid ($K_2Cr_2O_7$, 5*M* H_2SO_4, 20°, then 95°, 5 min: 65%;[1490] O_2, Pt, H_2O, 25°, 18 h: ~ 80% but not isolated[1597]).

1-(3′-Carboxy-4′-hydroxycyclopentyl)- (**258**, R = CO_2H) from 1-(3′-hydroxy-4′-hydroxymethylcyclopentyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**258**, R = CH_2OH) (O_2, Pt, H_2O, pH 9, 90°, 24 h, sealed: very low yield).[5618]



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2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (fresh NiO_2, dilute NaOH, 25°, 15 h: 33%); also its 3-methyl (likewise: 73%) and 3-ethyl derivative (likewise: 78%).[2888]

6-Oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (limited fresh NiO_2, dilute NaOH, 25°, 4 h: 72%; excess NiO_2 for 15 h gave the foregoing 2,6-dioxo analog: 67%).[2888]

4-Amino-2-methyl-5-pyrimidinecarboxylic acid ($KMnO_4$, Na_2CO_3, H_2O, 20°, 15 h: 50%).[678]

To ketones

5-Acetyl-4,6-dichloropyrimidine (MnO_2, CH_2Cl_2, 20°, 3 days: ~ 90%).[787]

5-Acetylpyrimidine (MnO_2, CH_2Cl_2, 20°, 3 h: 73%).[793]

4-Acetyl-2,6-diethoxypyrimidine (MnO_2, PhH, 20°, 24 h: 85%).[788]

5-Benzoyl-2,4-diethoxypyrimidine (CrO_3, pyridine, 10–20°, 15 h: 60%).[5138]

4-Benzoyl-2,6-diethoxypyrimidine (likewise: 91%).[788]

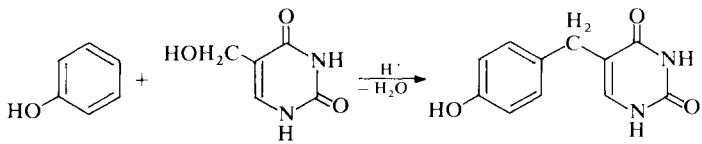
5-*o*-Anisoyl-4-chloro-2,6-dimethoxypyrimidine (MnO_2, PhMe, boil beneath a Dean–Stark trap, 1 h: 75%).[6076]

6-Benzoyl-2,4(1*H*,3*H*)-pyrimidinedione (MnO_2, AcOH, reflux, briefly: 61%).[788]

Also other examples.[6873]

7.3.2.5. Reaction with Aromatic Compounds

Phenols and other such aromatic, heteroaromatic, and other compounds that can undergo electrophilic substitution may react with cations derived from appropriate hydroxymethylpyrimidines to afford carbon-to-carbon linked products. For example, 5-hydroxymethyl- (**259**) gave 5-*p*-hydroxybenzyl-2,4(1*H*,3*H*)-pyrimidinedione (95%) (**260**) by heating in neat phenol containing



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hydrochloric or trifluoroacetic acid at 100° for 30 min.[5621] The presently known scope of this useful reaction is indicated by the following transformations.

5-Hydroxymethyl- to 5-(3′-chloro-6′-hydroxybenzyl)-2,4(1*H*,3*H*)-pyrimidinedione (*p*-chlorophenol, 100°, 30 min: 90%); also analogs.[5621]

5-Hydroxymethyl- to 5-*p*-hydroxybenzyl-3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2,4(1*H*,3*H*)-pyrimidinedione (PhOH, 100°, 1 h: 71%).[5621]

5-Hydroxymethyl- to 5-(3′,5′-di-*t*-butyl-4′-hydroxybenzyl)-2,4(1*H*,3*H*)-pyrimidinedione (2,6-di-*t*-butylphenol, AcOH, HCl, reflux, 6 h: 38%).[557]

5-Hydroxymethyl- to 5-*p*-hydroxybenzyl- (PhOH, 100°, 1 h: 55%) or 5-(2′,3′,4′-trimethoxybenzyl)-2,4-pyrimidinediamine (1,2,3-trimethoxybenzene, AcOH–H_2O, 100°, 3 h: 34%).[5622]

5-Hydroxymethyl- to 5-(4′-amino-3′-methoxybenzyl)- (*o*-anisidine, glycol or AcOH, HCl, 110°, 6 h: ~30%),[555,3925] or 5-(3′-allyl-4′-hydroxy-5′-methoxybenzyl)-2,4-pyrimidinediamine (2-allyl-6-methoxyphenol, AcOH, HCl, 100°, 6 h: ~3%).[3928]

5-Hydroxymethyl-2,4-pyrimidinediamine with 8-methoxy-2,2,4-trimethyl-1,2-dihydroquinoline gave 6-(2′,4′-diaminopyrimidin-5′-yl)methyl-8-methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (AcOH, HCl, reflux, 2 h: 79%).[3927]

5-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione with 6-amino-2,4(1*H*,3*H*)-pyrimidinedione gave 6-amino-5-(2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)methyl-2,4(1*H*,3*H*)-pyrimidinedione (F_3CCO_2H, reflux, 5 h: 70%).[5623]

5-Hydroxymethyl- gave 5-benzyl- (PhH, neat HF, 0°, 2 h: 52%), 5-*p*-methylbenzyl- (PhMe, likewise: 59%), or 5-(*m*-trifluoromethylbenzyl)-2,4(1*H*,3*H*)-pyrimidinedione ($PhCF_3$, likewise).[4658]

5-Hydroxymethyl- gave 5-γ,γ-difluoropropyl- ($H_2C{=}CHF$, neat HF, 0°: 44%) or 5-β,β,γ,γ,γ-pentafluoropropyl-2,4(1*H*,3*H*)-pyrimidinedione ($F_2C{=}CF_2$, HF, 20°, 4 h, sealed: low yield).[4975]

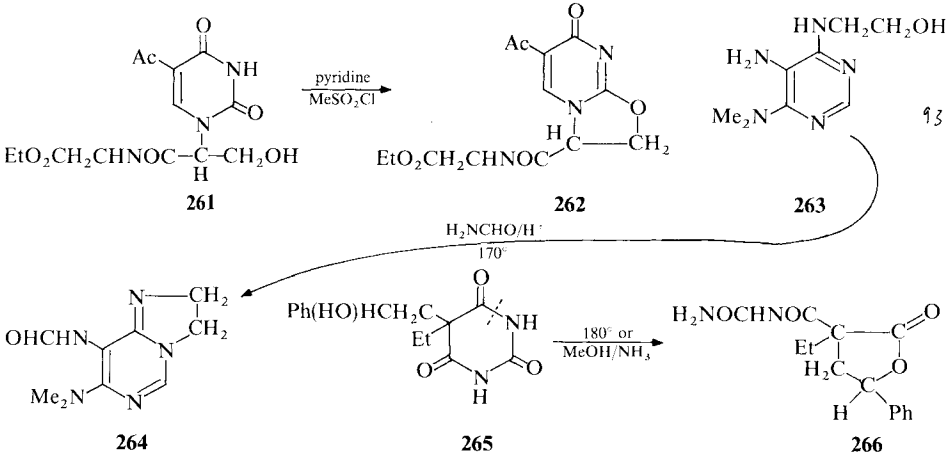
Also other examples in the foregoing references.

7.3.2.6. Other Reactions

A few other reactions of hydroxyalkylpyrimidines are illustrated briefly in the following examples.

1. 5-Acetyl-1-α-[*N*-(ethoxycarbonylmethyl)carbamoyl]-β-hydroxyethyl-2,4-(1*H*,3*H*)-pyrimidinedione (**261**) underwent cyclization in pyridine containing methanesulfonyl chloride (~20°, 15 h) to give 6-acetyl-3-*N*-(ethoxycarbonylmethyl)carbamoyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (**262**) (~20%),[4557] useful for reconversion into other pyrimidines.

2. A different type of cyclization occurred on heating 4-dimethylamino-6-(β-hydroxyethyl)amino-5-pyrimidinamine (**263**) in formamide containing a little HCl at 170° for 30 min: instead of the expected purine, the only isolable product was 7-dimethylamino-8-formamido-2,3-dihydroimidazo[1,2-*c*]pyrimidine (**264**) as its hydrochloride (~12%), subsequently identified by an unambiguous synthesis.[5624]
3. 5-Ethyl-5-β-hydroxyphenethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**265**) underwent an interesting rearrangement, either by heating at 180–215° for 30 min or by dissolution in refluxing methanolic ammonia for 30 min, to afford α-ethyl-γ-phenyl-α-ureidocarbonyl-γ-butyrolactone (**266**) (> 90%, allowing for substrate recovery).[5625]



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7.4. ALKOXY- AND ARYLOXYPYRIMIDINES

For the sake of brevity, the term "alkoxypyrimidine" is deemed to include aryloxypyrimidines in this section. Because of their inherent differences, 2- or 4/6-alkoxy-, 5-alkoxy-, and extranuclear alkoxypyrimidines are treated in that order within each subsection of the discussion hereafter.

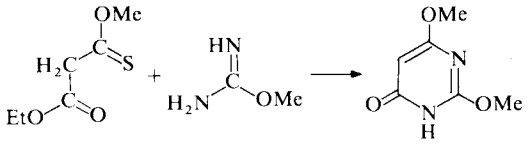
7.4.1. Preparation of Alkoxypyrimidines

Most alkoxypyrimidines have been made by primary syntheses or from their chloro analogs, but several other routes have sometimes proved both successful and more convenient.

7.4.1.1. By Primary Syntheses

Primary syntheses have been used extensively to produce all types of alkoxypyrimidines (see Chapters 2 and 3). Random examples include the condensation

of *O*-methylisourea with ethyl α-(methoxythiocarbonyl)acetate (**267**) in refluxing methanolic methoxide to give 2,6-dimethoxy-4(3*H*)-pyrimidinone (**268**) (71%);[972] of guanidine with ethyl α-cyano-α-ethoxyacetate in ethanolic ethoxide to give 2,4-diamino-5-ethoxy-4(3*H*)-pyrimidinone (58%);[2384] and of neat guanidine carbonate with 1-methoxy-2,4-pentanedione at 100° to give 4-methoxy-6-methoxymethyl-2-pyrimidinamine (93%).[2193]



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7.4.1.2. By Alcoholysis of Halogenopyrimidines

The avid nucleophilic displacement of 2- or 4/6-halogeno substituents by alkoxide ion has been discussed in Section 6.7.4; the analogous but less ready formation of 5-alkoxypyrimidines is covered in Section 6.8.3; and the facile but sometimes complicated transformation of (extranuclear) halogenoalkyl- to alkoxyalkylpyrimidines is illustrated in Section 6.9.

7.4.1.3. By Alcoholysis of Other Substrates

Because it is such a good nucleophile, alkoxide ion will displace almost any leaving group, especially if it is located at an activated site on the pyrimidine ring. The conditions required for such alcoholyses of various substrates are illustrated succinctly in the following examples: relatively vigorous conditions are required and yields tend to be low when any substrate exists as an anion in the reaction mixture.

From alkylthiopyrimidines

4-Hydroxymethyl-2-methylthio- to 4-hydroxymethyl-2-methoxypyrimidine (NaOMe, MeOH, reflux, 12 h: 71%).[3931]

2-Methylthio- to 2-methoxy-5-styrylpyrimidine (chloramine T, MeOH, AcOH, reflux, 15 h: 90%).[3829]

5-Fluoro-1-methyl-4-methylthio- to 5-fluoro-4-methoxy-1-methyl-2(1*H*)-pyrimidinone (NaOMe, MeOH, 20°, 24 h: 58%).[1895]

2-Methylthio- to 2-butoxy-4(3*H*)-pyrimidinone (BuOH, pyridine, Hg^{2+}, reflux, 6 h: 12%).[5626]

1-Methyl-4-methylthio- to 4-*t*-butoxy-1-methyl-2(1*H*)-pyrimidinone (*t*-butanol, *hv*: 40%).[2938]

Also other examples in the foregoing references.

From alkylsulfinylpyrimidines

4-Methylsulfinyl- to 4-propoxypyrimidine (NaOPr, PrOH, 90°, 2 h: characterized as picrate).[1715]

2-Methylsulfinyl- to 2-ethoxy-5-prop-2′-ynyloxypyrimidine (EtOH, NaOH, 70–100°: 24%, as its 3′-iodo derivative).[926]

4-Methoxy-2-methylsulfinyl- to 2,4-dimethoxy-6-nitroaminopyrimidine (NaOMe, MeOH, 25°, 3 h: 22%).[903]

Also other examples in the foregoing references.

From alkylsulfonylpyrimidines

2-Methylsulfonyl- to 2-ethoxypyrimidine (NaOEt, EtOH, reflux, 1 h: ~30%).[1715]

5-Methyl-2-methylsulfonyl- to 2-methoxy-5-methylpyrimidine (NaOMe, MeOH, reflux, 1 h: 79%).[1897]

5-Methoxy-2-methylsulfonyl- to 2,5-dimethoxypyrimidine (NaOMe, MeOH, reflux, 30 min: 38%).[2599]

5-Methoxy-2-methylsulfonyl- to 2,5-dimethoxy-4-pyrimidinamine (NaOMe, MeOH, 140°, 8 h, sealed: 60%).[2203]

Ethyl 4-amino-2-methylsulfonyl- to ethyl 4-amino-2-methoxy-5-pyrimidinecarboxylate (NaOMe, MeOH, 10°, 1 h: 76%).[2967]

Also other examples in the foregoing references and elsewhere.[1059,1544,1748,3603]

From alkoxypyrimidines (transalkoxylation)

2-Methoxy- to 2-ethoxy-5-nitropyrimidine (EtOH, NEt_3, reflux, 3 h: > 90%)[2942] or 5-nitro-2-propoxypyrimidine (PrOH, Ag_2O, reflux, 16 h: ~60%[2559]).

2,4-Dimethoxy-5-nitro- to 5-nitro-2,4-dipropoxypyrimidine (PrOH, Ag_2O, reflux, 20 h: 30%).[2559]

2-Methoxy- to 2-ethoxy- (NaOEt, EtOH, reflux, 2 days: 85%) or 2-cyclohexyloxy-6-methyl-4(3*H*)-pyrimidinone ($NaOC_6H_{11}$, $C_6H_{11}OH$, reflux, 24 h: 81%).[130]

4-Methyl-6-phenoxy- to 4-methoxy-6-methylpyrimidine (NaOMe, MeOH, reflux, 1 h: 75%).[5627]

Also other examples in the foregoing references and elsewhere.[2130,2268]

From pyrimidinecarbonitriles

2,6-Dimethyl-4-pyrimidinecarbonitrile to 4-methoxy-2,6-dimethylpyrimidine (NaOMe, MeOH, reflux, 2 h: 50%, plus a separable byproduct).[2268, cf. 2766]

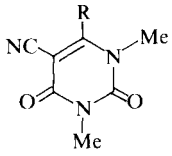
4-Methoxy-2-pyrimidinecarbonitrile to 2,4-dimethoxypyrimidine (NaOMe, MeOH, reflux, 1 h: ~ 70%).[2211]

4-Butoxy-6-methyl-2-pyrimidinecarbonitrile to 2,4-dibutoxy-6-methylpyrimidine (NaOBu, BuOH, reflux, 1 h: 90%).[2268]

6-Ethoxy-2-methyl-4-pyrimidinecarbonitrile to 4,6-diethoxy-2-methylpyrimidine (NaOEt, EtOH, reflux, 2 h: 33%).[2522]

1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4,5-pyrimidinedicarbonitrile (**269**, R = CN) to 4-methoxy-l,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile (**269**, R = OMe) (NaOMe, MeOH, reflux, 30 min: 41%).[1987]

Also other examples in the foregoing references and elsewhere.[1133,1421,2585]



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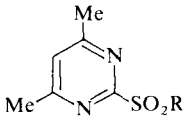
From miscellaneous substrates

2- or 4-Trimethylammoniopyrimidine chloride to 2- (90%) or 4-methoxypyrimidine (74%), respectively (NaOMe, MeOH, 20°, 5 min); 2-methoxy-5-nitropyrimidine (70%) similarly.[3232]

5,5-Diethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione to 2-ethoxy-5,5-diethyl-4,6(1*H*,5*H*)-pyrimidinedione (EtOH, Ag_2O, reflux, 24 h: ~ 90%).[5628]

4,6-Dimethyl-2-pyrimidinesulfonyl fluoride (**270**, R = F) to 2-methoxy-4,6-dimethylpyrimidine [NaOMe, MeOH, reflux, 90 min: 60%, probably via the methyl ester (**270**, R = OMe); kinetics of this and related reactions were measured].[1711]



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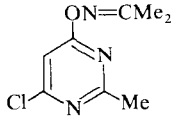

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4-Chloro-6-isopropylideneaminooxy- (**271**) to 4,6-diethoxy-2-methylpyrimidine (NaOEt, EtOH, reflux, 6 h: 55%).[3884]

5-β-Tosyloxyethyl- to 5-β-ethoxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (EtOH, reflux, > 3 h).[2039]

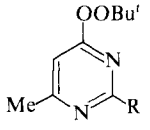
2-Dimethyloxosulfoniomethyl-4(3*H*)-pyrimidinone chloride (**249**) to 2-methoxymethyl-4(3*H*)-pyrimidinone (MeOH, *hv*).[2635]

7.4.1.4. By *O*-Alkylation

The rather fickle route to 2- or 4/6-alkoxypyrimidines by *O*-alkylation of the corresponding 2- or 4/6-pyrimidinones is outlined in Section 7.1.3.5; the more reliable *O*-alkylation of 5-pyrimidinols and extranuclear hydroxypyrimidines is discussed in Sections 7.2.2.2 and 7.3.2.2, respectively; and the analogous *O*-trialkylsilylation of tautomeric pyrimidinones is exemplified in Section 7.1.3.4.

7.4.1.5. By Other Routes

An interesting preparation of several *t*-butoxypyrimidines involves the rearrangement of 4-*t*-butylperoxypyrimidines, easily available from the corresponding 4-chloropyrimidines with barium *t*-butyl peroxide:[2136] for example, 4-*t*-butylperoxy-6-methylpyrimidine (**272**, R = H) or its 2-chloro derivative (**272**, R = Cl) gave 5-*t*-butoxy-6-methyl-4(3*H*)-pyrimidinone (**273**, R = H) (80%) or its 2-chloro derivative (**273**, R = Cl) (85%), respectively, on standing in light petroleum solution for 3 weeks.[2136]



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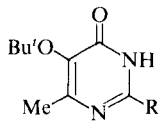

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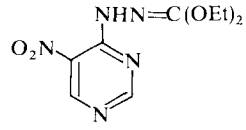

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The formation of some extranuclear dialkoxypyrimidines, seldom considered as such, is exemplified briefly in the conversion of 4-hydrazino- into 4-diethoxymethylenehydrazino-5-nitropyrimidine (**274**) [$(EtO)_4C$, EtOH, reflux, 6 h: ~ 30%];[3227] of 4-hydrazino- into 4-dipropoxymethylenehydrazino-6-methoxy-5-nitropyrimidine [neat $(PrO)_4C$, 160°, 15 min: ~ 40%];[3237] of 4-dibromomethyl- into 4-dimethoxymethyl-6-phenylpyrimidine 1-oxide (NaOMe, MeOH, 20°, 10 min: 26%);[5629] and of 4,6-dichloro-5-formylmethyl- into 4,6-dichloro-5-*β*,*β*-diethoxyethylpyrimidine (EtOH, NH_4Cl, reflux, 3.5 h: 90%).[888]

The direct introduction of extranuclear alkoxy groups occurred on condensation of 2,4,6-pyrimidinetriamine with 2-formyl-3-(3′,4′,5′-trimethoxyphenyl)-acrylonitrile (in refluxing ethanol for 30 min) to afford 5-*β*-cyano-*β*-formyl-*α*-(3′,4′,5′-trimethoxyphenyl)ethyl-2,4,6-pyrimidinetriamine (78%).[77]

7.4.2. Reactions of Alkoxypyrimidines

Some of the reactions of alkoxypyrimidines depend on the considerable efficacy of alkoxy substituents as leaving groups, especially when they are located at the (activated) 2- or 4/6-position. Although they fall far short of

halogeno or alkylsulfonyl substituents in this respect, alkoxy groups are significantly better than their alkylthio counterparts.[4721]

7.4.2.1. Aminolysis

The rates for butylaminolysis of simple 2- or 4/6-alkoxypyrimidines have been measured under preparative conditions.[3144] The rate constants indicated that 4-methoxy- reacted more rapidly than did 2-methoxypyrimidine by a factor of 10, that the higher alkoxypyrimidines underwent aminolysis more slowly than the corresponding methoxy homologs (e.g., 2-methoxy- reacted 90 times faster than did 2-isopropoxypyrimidine), and that 2-chloro- was aminolysed about 40,000 times faster than was 2-methoxypyrimidine under comparable conditions.[3144] Although the last fact might discourage the use of alkoxypyrimidines as intermediates for pyrimidinamines, suitable increases in time and temperature can easily overcome the intrinsic disadvantage: for example, 4-methoxypyrimidine plus neat butylamine at 150° for 3 h gave 4-butylaminopyrimidine in 75% isolated yield,[3144] without any risk of appreciable rearrangement.[1879] Moreover, like halogeno substituents, alkoxy groups were activated toward aminolysis by the presence of electron-withdrawing groups, but deactivated by electron-donating groups, effects evident in the conditions used in the following preparative examples.

Using simple substrates

4-Methoxypyrimidine to 4-pyrimidinamine (NH_3, MeOH, 170°, 7 h, sealed: > 50%, characterized as 4-acetamidopyrimidine)[696] or 4-hydrazinopyrimidine (H_2NNH_2, MeOH, reflux, 2 h: 55%).[1827]

4-Methoxy- to 4-amino- (NH_3, MeOH, 95°, 24 h, sealed: ~ 55%),[1531, cf. 1537] 4-dimethylamino- ($HNMe_2$, H_2O, 150°, 8 h, sealed:[696] $HNMe_2$, MeOH, 180°, 7 h, sealed: 62%[1534, cf. 2638]), or 4-methoxyamino-1-methyl-2(1*H*)-pyrimidinone ($MeONH_2$, EtOH, reflux, 2 h: ~ 70%).[3225]

4-Ethoxy- to 4-amino- (NH_3, EtOH, 120°, 8 h, sealed: 75%),[1665] 4-dimethylamino- ($HNMe_2$, MeOH, 120°, 16 h, sealed: 93%)[2664, cf. 2638,2665] or 4-hydrazino-2(1*H*)-pyrimidinone (H_2NNH_2, EtOH, reflux, 2 h: > 90%).[1533]

4-Methyl-2-phenoxy- to 2-hydrazino-4-methylpyrimidine (H_2NNH_2, H_2O, reflux: ~75%).[3215]

2-Methoxy- to 2-butylamino-6-methyl-4(3*H*)-pyrimidinone ($BuNH_2$, NaH, tetralin, reflux, 5 h: 77%).[158]

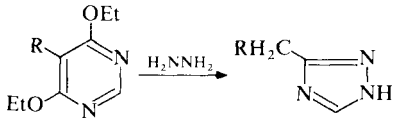
4-Chloro-2-methoxy-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine to 5-(3′,4′,5′-trimethoxybenzyl)-2,4-pyrimidinediamine (NH_4OH, Me_2NCHO, reflux, 12 h with NH_3 passing: 82%).[3944]

4,6-Dimethoxypyrimidine to 6-methoxy-4-pyrimidinamine ($NaNH_2$, NH_3, 10°, 24 h, sealed: 85%).[1366]

2-Methoxy-5-phenylpyrimidine to 5-phenyl-2-pyrimidinamine (23%) and 3,5-diphenylpyridine (27%) (NH_3, EtOH, 200°, 4 days; mechanism is obscure).[5631]

4,6-Diethoxypyrimidine (**275**, R = H) or its 5-methyl derivative (**275**, R = Me) to 3-methyl- (**276**, R = H) (60%) or 3-ethyl-1,2,4-triazole (**276**, R = Me) (70%), respectively (H_2NNH_2, H_2O, 210°, 5 h; mechanism discussed).[2521,4630]

Also other examples.[1153,1219,1521,1549,2829,2912,3945,5080,5167,5630]



275 **276**

Using substrates bearing electron-withdrawing substituents

4-Ethoxy-5-fluoro-1-methyl- to 5-fluoro-1-methyl-4-methylamino-2(1*H*)-pyrimidinone ($MeNH_2$, MeOH, 115°, 15 h, sealed: > 95%).[2619]

5-Bromo-4,6-dimethoxypyrimidine to 5-bromo-6-methoxy-4-pyrimidinamine (KNH_2, NH_3, − 33°, 24 h: abnormal mechanism).[4898]

4-Ethoxy-1-ethylpyrimidinium tetrafluoroborate to 1-ethyl-4(1*H*)-pyrimidinimine (liquid NH_3, − 33°, 30 min: 68%).[1245]

4-Methoxy- to 4-hydrazino-6-methyl-2-methylthiopyrimidine (H_2NNH_2, EtOH, reflux, 3 days: 66% net yield).[1701, cf. 2562]

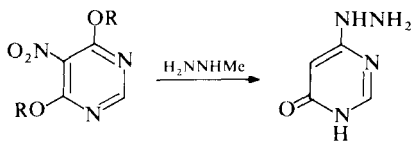
4-Methoxy- to 4-*t*-butylamino- (Bu^tNH_2, MeOH, reflux, 3 h: 90%)[684] or 4-hydrazino-5-nitropyrimidine (H_2NNH_2, MeOH, − 4°, 15 min: 62%).[3229,3230]

5-Nitro-2,4-dipropoxy- to 4-hydrazino-5-nitro-2-propoxypyrimidine (H_2NNH_2, EtOH, 25°, 12 h: ~80%).[3227]

4,6-Dimethoxy- to 4-hydrazino-6-methoxy-2-methyl-5-nitropyrimidine (H_2NNH_2, EtOH, < 0°, 1 h: 85%).[1552]

4-Ethoxy- to 4-amino-5-nitro-2(1*H*)-pyrimidinone (NH_3, EtOH, 100°, 1 h, sealed: 85%).[1584]

4,6-Dimethoxy- (**277**, R = Me) or 4,6-diethoxy-5-nitropyrimidine (**277**, R = Et) to 6-hydrazino-4(3*H*)-pyrimidinone (**278**) (H_2NNHMe, pyridine, reflux, 1 h: 65%; by a complex mechanism).[1680]



277 **278**

2,4-Diethoxy-1-methylpyrimidinium iodide to 4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine hydriodide (NH_3, MeOH, gentle conditions).[5638]

Also other examples.[2559,3211,3285,5167,5638]

Using substrates bearing electron-donating substituents

4-Methoxy-2-pyrimidinamine to 2,4-pyrimidinediamine (NH_3, MeOH, 200°, 4 h, sealed: no reaction at 110°).[2912]

5-Amino-6-methoxy- to 5-amino-6-hydrazino-4(3*H*)-pyrimidinethione (neat $H_2NNH_2.H_2O$, reflux, 1 h: 89%).[1038]

2-Methoxy- to 2-anilino-6-methyl-4-pyrimidinamine (neat $PhNH_2$, 180°, 6 h: 53%, plus a separable by-product).[1148]

Also other examples.[213]

7.4.2.2. Conversion into *N*- or *C*-Alkylpyrimidinones

Most 2- or 4/6-alkoxypyrimidines may be converted into *N*-alkylpyrimidinones by thermal rearrangement or by the classical Hilbert–Johnson reaction (treatment with an alkyl or acyl halide and involving a quaternary intermediate). The related trialkylsiloxypyrimidines, very easily made from tautomeric pyrimidinones, undergo the so-called Silyl–Hilbert–Johnson reaction in a similar way. The *ortho*-Claisen rearrangement of alkoxypyrimidines to *C*-alkylpyrimidinones is also discussed here.

Thermal rearrangement. The thermal rearrangement of alkoxypyrimidines was first observed in 1929 when 2,4-dimethoxypyrimidine was heated at 240° under reflux for 4 h to give 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (~90%).[1841,2937] Likewise, 2- or 4-methoxypyrimidine in a sealed tube at 195° for 2–3 h gave 1-methyl-2(1*H*)- or 3-methyl-4(3*H*)-pyrimidinone (45%), respectively,[1432] whereas 2,4-diethoxypyrimidine required similar treatment at 260° for 24 h to afford 1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione (~80%).[1841] It was later realized that such reactions could be catalyzed significantly by tertiary bases, the efficiency of which varied according to their basic strength;[2947,3144] catalysis by an acid or Lewis acid has also been used,[1148,5165] especially in *O*- to *N*-glycosyl rearrangements;[5651] and catalysis by palladium complexes has been found effective.[3916] The rather limited scope of this thermal rearrangement as a preparative method is illustrated further by the following examples.

2,4-Dimethoxy-6-methyl-5-propylpyrimidine gave 1,3,6-trimethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione (280°, 3 h: 90%).[2489]

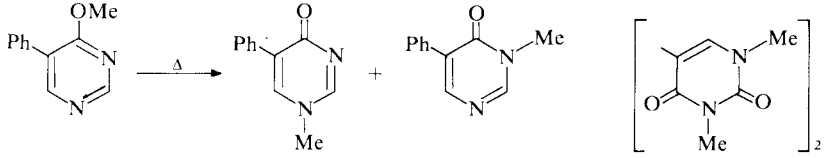
2-Methoxypyrimidine gave 1-methyl-2(1*H*)-pyrimidinone (NEt_3, 160°, 4 h, sealed: 10% after purification).[2947]

4-Methoxy-5-nitropyrimidine gave 3-methyl-5-nitro-4(3*H*)-pyrimidinone (98°, 1 week: 16% after purification).[1879]

1-Allyl-4-allyloxy-2(1*H*)-pyrimidinone gave 1,3-diallyl-2,4(1*H*,3*H*)-pyrimidinedione (240°, 2 h: 62%.[846] (*Note*: 4-Alkenyloxy derivatives may undergo an additional or alternative thermal *ortho*-Claisen rearrangement to give 5-alkenyl derivatives,[5632] as outlined later.)

2-Allyloxy-5-bromopyrimidine gave 1-allyl-5-bromo-2(1*H*)-pyrimidinone [THF, $(PhCN)_2PdCl_2$, reflux, 16 h: 94%].[3916]

4-Methoxy-5-phenylpyrimidine (**279**) gave 1-methyl-5-phenyl-4(1*H*)- (**280**) and 3-methyl-5-phenyl-4(3*H*)-pyrimidinone (**281**) (200°, 3 h, sealed: 90% of a 1 : 3-mixture as indicated by nmr;[5248] NEt_3, 170°, 4 h, sealed: 5% and 60%, respectively, after separation[4023]).



279 **280** **281** **282**

2,2′,4,4′-Tetramethoxy-5,5′-bipyrimidine gave 1,1′3,3′-tetramethyl-5,5′-bipyrimidine-2,2′4,4′(1*H*,1′*H*,3*H*,3′*H*)-tetrone (**282**) (230°, briefly?: 80%).[4892]

2,4-Dimethoxy-6-methylpyrimidine gave 1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (340°, 5 h, sealed: 44%;[2495] 180°, trace *p*-$MeC_6H_4SO_3H$, 3 min: 80%[1148]).

5-Bromo-2,4-dimethoxypyrimidine to 5-bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (NaI, $AcCH_2CH_2Ac$, 100°, 6 h: 75%; no reaction under similar conditions without NaI).[5165]

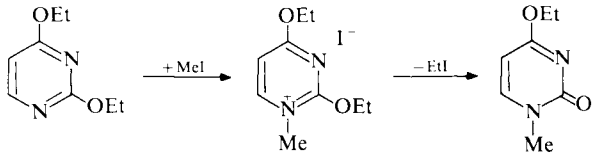
Also other examples.[293,1664,1680,1841,2024,2240 (cf. 2249), 2492,3132,3339,5633,5634]

In kinetic studies, the thermal rearrangements of 2- and 4-methoxypyrimidine proved to be first-order reactions; of the higher 2-alkoxypyrimidines, only the ethoxy, isopropoxy, and *s*-butoxy homologs showed any measurable rearrangement, even in the presence of a tertiary base above 200°.[2947] The *C*-methyl derivatives of such substrates rearranged more slowly than did the parent alkoxypyrimidines, but 5-bromo and especially 5-nitro derivatives did so quite rapidly.[1879] For example, at 190° in the presence of triethylamine (5 mol), the first-order rate constants (10^6 *k*, s^{-1}) were: 2-methoxy-, 25; 2-methoxy-4-methyl-, 3.4; 2-methoxy-5-methyl-, 7.4; 5-bromo-2-methoxy-, 200; 2-methoxy-5-nitro-, 50,000; 4-methoxy-, 14; 4-methoxy-2-methyl-, 3.0; 4-methoxy-6-methyl-, 3.0; 4-methoxy-5-methyl-, 7.1; 5-bromo-4-methoxy-, 6000; and 4-methoxy-5-nitropyrimidine, 30,000.[1879] These rate constants had an evident qualitative relationship to electron donation or electron withdrawal by the passenger

groups. This was placed on a more quantitative basis by rate measurements for the rearrangement of 2-methoxy-5-*p*-substituted-phenylpyrimidines (170°, NEt_3): the plot of log *k* versus modified Hammett *para-sigma* constants for substituted (NMe_2, Me, H, OMe, Cl, Br, NO_2) phenyl groups, proved pleasingly rectilinear.[4023]

A radical mechanism for the thermal rearrangement was precluded by quite negligible changes in rate following the addition of dibenzoyl peroxide or benzoquinone.[2947] An intramolecular mechanism, suggested by the predominantly α- rather than γ-migration of the alkyl group (cf. the *ortho*-Claisen rearrangement),[2947] was also proved wrong:[4023] a "crossover" experiment using 2-ethoxy-5-nitropyrimidine and 4-methoxypyridine [which in isolation gives 1-methyl-4(1*H*)-pyridinone[5635] at a rate comparable with that for rearrangement of the ethoxynitropyrimidine[4023]] gave all four possible rearranged products, thus showing that the rearrangement was at least intermolecular,[5637] in line with a similar conclusion[5636] in the pyridine series.

Hilbert–Johnson reaction. The Hilbert–Johnson reaction is more versatile than the foregoing thermal rearrangement of alkoxypyrimidines, and it usually requires only gentle conditions. Thus, as reported in the original paper,[1841] dissolution of 2,4-dimethoxypyrimidine in neat methyl iodide for 12 h gave 4-methoxy-1-methyl-2(1*H*)-pyrimidinone (> 95%); similar treatment of 2,4-diethoxypyrimidine (**283**) with methyl iodide gave 4-ethoxy-1-methyl-2(1*H*)-pyrimidinone (**285**), indicating that the *N*-alkyl substituent arose from the alkyl halide rather than from the alkoxy group; and treatment of the same substrate with refluxing ethyl iodide for 1 week completed both stages to afford 1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione (80%). Although these reactions clearly proceeded through quaternary intermediates, only a few such compounds have been isolated and then converted into the appropriate final products: for example, 2,4-diethoxypyrimidine (**283**) with methyl iodide in acetonitrile at 25° for 5 h gave the 1-methiodide (**284**) (35%), but any prolongation of the reaction time steadily decreased the yield of **284** and increased that of 4-ethoxy-1-methyl-2(1*H*)-pyrimidinone (**284**);[5638] other such characterized intermediates have been reported occasionally.[1219,1664,2115,2588,3074,3456,5623]



283 **284** **285**

Although the main use of the Hilbert–Johnson reaction has been to prepare new pyrimidine nucleosides (a topic beyond the scope of this book),[5639] its use in simple pyrimidine chemistry has been by no means minor, as indicated in the following typical transformations.

Using alkyl halides

2,6-Dimethoxy- to 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (MeI, 120°, 16 h, sealed: > 95%).[2603]

4-Chloro-2,6-dimethoxypyrimidine to 6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (MeI, 100°, 30 h, sealed: 60%).[2110, cf. 2111]

2,4,6-Trimethoxypyrimidine to 2,6-dimethoxy-3-methyl-4(3*H*)-pyrimidinone (MeI, reflux, 30 h: major product).[2533, cf. 2110]

2,4-Dimethoxy-6-methylpyrimidine to a separable mixture of 4-methoxy-1,6-dimethyl-2(1*H*)-pyrimidinone and 1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (MeI, 20°, 60 h: 63% and 4%, respectively; the addition of a little pyridine made virtually no difference).[698, cf. 2024]

4-Methoxy-5-phenylpyrimidine to its 1-methiodide (MeI, MeOH, pyridine, 20°, 12 h: 75%) and thence to 1-methyl-5-phenyl-4(1*H*)-pyrimidinone (Ag_2SO_4, H_2O, 90°: 44%);[5640] compare with the thermal rearrangement discussed previously.

2,4-Diethoxypyrimidine to 4-ethoxy-1-*β*-hydroxyethyl-2(1*H*)-pyrimidinone (*β*-bromoethanol, 55°, 5 days: 20%).[1323]

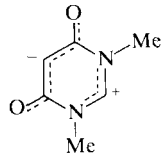
5-Fluoro-2,4-dimethoxypyrimidine to 5-fluoro-4-methoxy-1-methyl-2(1*H*)-pyrimidinone (MeI, 65°, 18 h, sealed: 78%;[5166] MeI, 20°, 10 days: 67%[3153]).

2,4-Dibenzyloxypyrimidine to 1-benzyl-4-benzyloxy- ($PhCH_2Cl$, 25°, 15 days: 35%) or 4-benzyloxy-1-methyl-2(1*H*)-pyrimidinone (MeI, 25°, 4 days: 65%).[2569]

4-Dimethylamino-6-methoxypyrimidine to 6-dimethylamino-3-methyl-4(3*H*)-pyrimidinone (MeI, reflux, 2 h: 90%).[1743]

4,6-Dimethoxypyrimidine to 6-methoxy-3-methyl-4(3*H*)-pyrimidinone (~70%) and an isomeric product (~20%) (MeI, reflux, 10 h);[3350] the minor product was ultimately formulated as the betaine (**286**).[2587, cf. 2586,3351,5215]

Also other examples.[812,846,1260,1551,1602,1743,1894,2024,2030,2587,2903,2922,3285,5167,6077]



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Using acyl halides

2,4-Dimethoxy-5-methylpyrimidine to 1-acetyl-4-methoxy-5-methyl-2(1*H*)-pyrimidinone (AcCl, 20°, 2 days: 82% after deacetylation with MeOH).[3324]

2,4-Dimethoxypyrimidine to 1-acetyl-4-methoxy- (AcCl, 20°: > 90%) or 4-methoxy-1-methanesulfonyl-2(1*H*)-pyrimidinone ($MeSO_2Cl$, 20°: > 80%).[811]

Using sugar halides

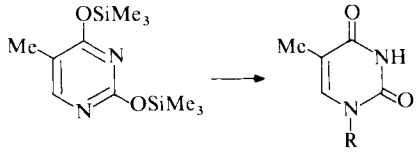
The original example involved condensation of 2,4-dimethoxypyrimidine with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide to give 4-methoxy-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-2(1*H*)-pyrimidinone (50°, 2 days: 30%) and thence 1-β-D-glucopyranosyl-2,4(1*H*,3*H*)-pyrimidinedione (HCl, EtOH, 20°, 1 day: > 95%).[2937,5641]

This extensive subject has been reviewed:[5639] scope and conditions may be gleaned from typical papers, some describing genuine Hilbert–Johnson reactions and some outlining Lewis acid catalyzed rearrangements.[698,920,1602,2024,2569,2586,2902,2922,2939,2951,3153,5166,5169,5642–5653]

Silyl–Hilbert–Johnson reaction. The use of 2- and/or 4/6-trialkylsiloxypyrimidines as substrates for the Hilbert–Johnson reaction has proven very useful, mainly because tautomeric pyrimidinones can be converted directly and easily into trialkylsiloxypyrimidines (see Section 7.1.3.4) and partly because the subsequent *N*-alkylation or acylation is usually facile. The scope and conditions for the second step are illustrated in the following transformations.

4-Methyl-2,6-bistrimethylsiloxypyrimidine to 1,6-dimethyl- and 1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (MeI, reflux, 2 h: 76% and "a small amount," respectively).[1829]

5-Methyl-2,4-bistrimethylsiloxypyrimidine (**287**) to 1,5-dimethyl- (**288**, R = Me) (MeI, reflux, 2 h: 93%),[5654] 1-α-bromopropyl-5-methyl- (**288**, R = $CH_2CH_2CH_2Br$) (excess $BrCH_2CH_2CH_2Br$, 110°, 3 h; or 20°, 10 days: ~80%),[608,611,1961, cf. 1959,5655] or 5-methyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione (**288**, R = Pr) (PrBr, 20°, 10 days: 48%).[608]



287 **288**

2,4-Bistrimethylsiloxypyrimidine to 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (substrate made in situ; MeI, reflux, 38 h: 76% overall).[3971, cf. 828]

5-Fluoro-2,4-bistrimethylsiloxypyrimidine to 5-fluoro-1-γ-hydroxypropyl- ($BrCH_2CH_2CH_2OSiMe_3$, MeCN, 125°, 3 days, sealed: 44%)[237] or 5-fluoro-1-tetrahydrothien-2′-yl-2,4(1*H*,3*H*)-pyrimidinedione (2-acetoxytetrahydrothiophene, NaI, MeCN, reflux, 7 h: 45%).[59]

2-Trimethylsiloxy-4-*N*-(trimethylsilyl)acetamidopyrimidine to 4-acetamido-1-γ-bromopropyl-2(1*H*)-pyrimidinone ($BrCH_2CH_2CH_2Br$, 25°, > 10 days: 43%).[611]

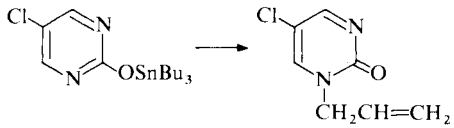
2-Trimethylsiloxy-4-trimethylsilylaminopyrimidine to 4-amino-1-tetrahydrofuran-2′-yl-2(1*H*)-pyrimidinone (2-acetoxytetrahydrofuran, $SnCl_4$, CH_2Cl_2, 0–20°, 3 h: 33%)[5656] or 4-acetamido-1-vinyl-2(1*H*)-pyrimidinone [$AcOCH{=}CH_2$, $Hg(OAc)_2$, H_2SO_4, reflux, 2 days: 14% after purification].[726]

2,4-Bistrimethylsiloxypyrimidine to 1-acetyl- (AcCl, PhH, 20°, 10 h: 43%)[828] or 1-tosyl-2,4(1*H*,3*H*)-pyrimidinedione (TsCl, *o*-xylene, reflux, 5 h: 46%).[3457]

5-Methyl-2,4-bistrimethylsiloxypyrimidine (**287**) to 1-(*t*-butyldimethylsiloxy)methyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**288**, R = $CH_2OSiMe_2Bu^t$) ($Bu^tMe_2SiOCH_2Cl$, MeCN, 20°, 20 h: > 36%).[3830]

Also other examples.[135,538,724,1689,3304,5657, 5658]

Analogous trialkylstannyloxy substrates may be used rather similarly in what might be called a Stannyl–Hilbert–Johnson type of reaction: for example, 5-chloro-2-ributylstannyloxypyrimidine (**289**) [made in situ from 5-chloro-2(1*H*)-pyrimidinone and bis(tributyltin)oxide] reacted with allyl acetate in the presence of tetrakis(triphenylphosphine)palladium in THF at 20° during 18 h to afford 1-allyl-5-chloro-2(1*H*)-pyrimidinone (**290**) (68%).[3772]



289 **290**

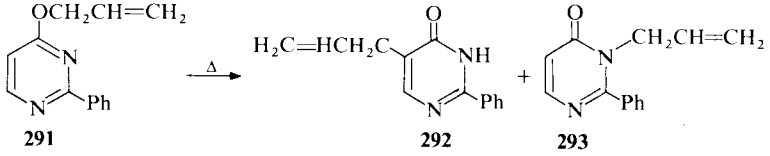
Ortho-Claisen rearrangement. 4-Alkenyloxypyrimidines are prone to *ortho*-Claisen rearrangement into 5-alkenylpyrimidinones with inversion of the migrating group; this may occur concomitantly with the more usual thermal rearrangement to *N*-alkenylpyrimidinones just discussed. Saturated alkoxy substituents also occasionally undergo such rearrangement into *C*-alkyl isomers. These phenomena are illustrated in the following transformations.

4-Allyloxy-2-phenylpyrimidine (**291**) to 5-allyl- (**292**) and 3-allyl-2-phenyl-4(3*H*)-pyrimidinone (**293**) ($Et_2C_6H_4Me$-*m*, reflux, 16 h: 36% and 14%, respectively).[846]

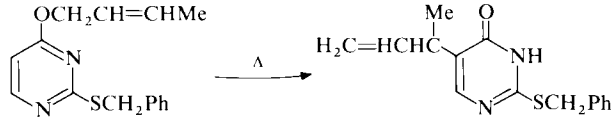
4-Allyloxy-2-pyrimidinamine to 5-allyl-2-amino-4(3*H*)-pyrimidinone (Et_2NPh, reflux, 4 h: ~15%).[872]

4-Allyloxy-2-methylthiopyrimidine to 5-allyl- and 3-allyl-2-methylthio-4(3*H*)-pyrimidinone ($Et_2NC_6H_4Me$-*m*, reflux, 6h: 32% and 19%, respectively).[846,872]

2-Benzylthio-4-but-2′-enyloxypyrimidine (**294**) to 2-benzylthio-5-α-methylallyl-4(3*H*)-pyrimidinone (**295**) ($Et_2NC_6H_4Me$-*m*, reflux, 6h: 32% as sole isolable product).[910]



291 **292** **293**



294 **295**

5-Benzyloxy-1,3-dimethyl- to 6-benzyl-5-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (tetralin, reflux, 16 h: 31%).[854]

Also other examples.[846]

(*Note*: A "crossover" rearrangement with a mixture of 4-but-2′-enyloxy-2-methylthio- and 4-allyloxy-2-benzylthiopyrimidine confirmed the intramolecular nature of such *ortho*-Claisen rearrangements.[910])

7.4.2.3. Conversion into Halogenopyrimidines

Both nuclear and extranuclear alkoxypyrimidines may be converted into the corresponding halogenopyrimidines by hydrolysis to the corresponding tautomeric pyrimidinone, pyrimidinol, or hydroxyalkylpyrimidine (Section 7.1.1.4, 7.2.1.1, or 7.3.1.8) followed by treatment with a phosphorus halide or other appropriate reagent (Sections 6.1.1–6.1.3, 6.2–6.4, 7.2.2.3, or 6.6.2). However, extranuclear halogenoalkylpyrimidines may also be made directly from alkoxyalkylpyrimidines by vigorous treatment with a hydrohalide acid (Section 6.3.3).

7.4.2.4. Hydrolysis

The direct hydrolysis of 2- or 4/6-, 5-, or extranuclear alkoxypyrimidines is discussed in Sections 7.1.1.4, 7.2.1.1, and 7.3.1.8, respectively.

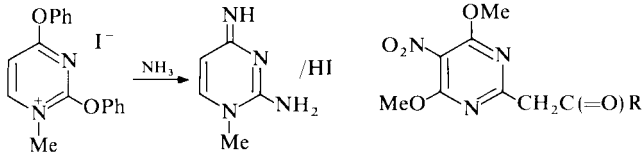
7.4.2.5. Transalkoxylation

The direct conversion of one 2- or 4/6-alkoxypyrimidine into another such alkoxypyrimidine is possible when the substrate is sufficiently activated, such as by a nitro group; see Section 7.4.1.3.

7.4.2.6. Other Reactions

The activated diaryloxy substrate, 1-methyl-2,4-diphenoxypyrimidinium iodide (**296**) with methanolic sodium hydrogen sulfide at 25° for 3 h gave 1-methyl-2,4(1*H*,3*H*)-pyrimidinedithione (**297**) (85%).[2520]

4,6-Dimethoxy-5-nitropyrimidine reacted with acetone or acetophenone in the presence of potassium hydroxide to give appropriate characterized Meisenheimer complexes, which underwent oxidation by ferric chloride to afford 2-acetonyl-4,6-dimethoxy-5-nitro- (**298**, R = Me) (~60% overall) or 4,6-dimethoxy-5-nitro-2-phenacylpyrimidine (**298**, R = Ph) (low yield), respectively.[735]

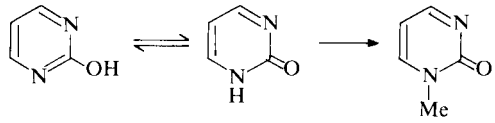


296 **297** **298**

5-Ethoxymethyl-2-methyl- gave 2-methyl-5-sulfomethyl-4(3*H*)-pyrimidinone on heating with aqueous sodium hydrogen sulfite at 145° for 18 h in a sealed vessel.[3098]

7.5. NONTAUTOMERIC PYRIMIDINONES

When the structure of a tautomeric pyrimidinone (e.g., **299**) is immobilized by *N*-substitution, the product (e.g., **300**) is a nontautomeric or fixed pyrimidinone, no longer exhibiting acidic properties.



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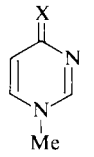
7.5.1. Preparation of Nontautomeric Pyrimidinones

The three major routes to nontautomeric pyrimidinones have been discussed already: for *primary syntheses*, see Chapters 2 and 3; for the *N-acylation or N-alkylation of tautomeric pyrimidinones*, see Section 7.1.3.3 or 7.1.3.5, respectively; and for the routes *from alkoxy- or trialkylsiloxypyrimidines*, see Section 7.4.2.2.

Hydrolysis of fixed pyrimidinimines. Pyrimidinimines may undergo two reactions in alkali. If the alkyl or other substituent occupies a ring nitrogen

opposite the imino group, only hydrolysis to the corresponding *N*-alkylpyrimidinone will occur; if the alkyl group is adjacent to the imino group, Dimroth rearrangement to the isomeric alkylaminopyrimidine (see Section 9.3.2) may well occur more rapidly than hydrolysis. The scope of the hydrolytic reaction for preparing nontautomeric pyrimidinones is illustrated in the following transformations.

1-Methyl-4(1*H*)-pyrimidinimine (**301**, X=NH) to 1-methyl-4(1*H*)-pyrimidinone (0.1*M* NaOH, 25°, 10 h: 55% isolated as the picrate).[3377, cf. 1136]



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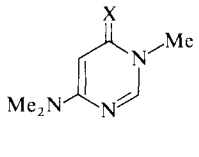

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1,2-Dimethyl- or 1,6-dimethyl-4(1*H*)-pyrimidinimine to 1,2-dimethyl- or 1,6-dimethyl-4(1*H*)-pyrimidinone, respectively (dilute KOH, reflux, 1 h: each isolated as picrate).[1136]

1-Methyl-5-phenyl-4(1*H*)-pyrimidinimine to 1-methyl-5-phenyl-4(1*H*)-pyrimidinone (0.1*M* NaOH, 20°, 10 h: 37%).[5640,5659,5660, cf. 4403]

1-Methyl-5-naphthalen-1′-yl-4(1*H*)-pyrimidinimine to 1-methyl-5-naphthalen-1′-yl-4(1*H*)-pyrimidinone (0.1*M* NaOH, 20°, 24 h: 85%).[5661]

1-Ethyl-2-phenyl-4(1*H*)-pyrimidinimine to 1-ethyl-2-phenyl-4(1*H*)-pyrimidinone (dilute KOH, reflux, 30 min: 55%).[1245]

Substrates in the following examples underwent Dimroth rearrangement so slowly (on account of electron-donating substituents) that hydrolysis became the dominant reaction.

4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinimine to 4-dimethylamino-1-methyl-2(1*H*)-pyrimidinone (2.5*M* NaOH, 95°, 1 h); mother liquors contained a trace of 4-dimethylamino-2-methylaminopyrimidine.[1741]

1,4-Dimethyl-2(1*H*)-pyrimidinimine to 1,4-dimethyl-2(1*H*)-pyrimidinone (1.8*M* NaOH, 25°, 2 days: 55%; 2*M* NaOH, 100°, 15 min: 25% plus an equal amount of 4-methyl-2-methylaminopyrimidine).[1465]

4-Dimethylamino-1-methyl-6-methylimino-1,6-dihydropyrimidine (**302**, X =NMe) to 6-dimethylamino-3-methyl-4(3*H*)-pyrimidinone (**302**, X=O) (3*M* NaOH).[1507]

1-Amino-2-hydrazono-4,6-dimethyl-1,2-dihydropyrimidine to 1-amino-4,6-dimethyl-2(1*H*)-pyrimidinone (H_2O, 80°, 4 days: 15% plus other separable products).[1142]

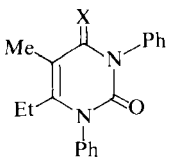
Also other examples.[1465,1664]

From fixed pyrimidinethiones. Although the conversion of a tautomeric pyrimidinethione into the corresponding pyrimidinone is commonplace, the apparently similar route from a nontautomeric pyrimidinethione to a nontautomeric pyrimidinone is quite unusual, mainly because direct hydrolyses are inapplicable. However, some other ways to achieve such conversions are illustrated by the following examples.

4-Ethyl-5-methyl-1,3-diphenyl-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone (**303**, X=S) gave 6-ethyl-5-methyl-1,3-diphenyl-2,4(1*H*,3*H*)-pyrimidinedione (**303**, X=O) (H_2O_2, AcOH, NaOAc, 35°, 3 h: 80%); also analogs likewise.[4393]

Ethyl 4-methyl-2,3-diphenyl-6-thioxo-3,6-dihydro- (**304**, X=S) gave ethyl 4-methyl-6-oxo-2,3-diphenyl-3,6-dihydro-5-pyrimidinecarboxylate (**304**, X=O) [$Hg(OAc)_2$, AcOH, reflux, 5 h: 34%].[3150]

5-Benzoyl-1-(α-methylbenzylidene)amino-4-phenyl-2(1*H*)-pyrimidinethione (**305**, X=S) gave 5-benzoyl-1-α-(methylbenzylidene)amino-4-phenyl-2(1*H*)-pyrimidinone (**305**, X=O) (HgO, dioxane, 25°, 1 week: 10%).[6007]



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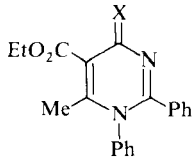

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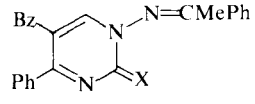

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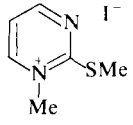
1,4,6-Trimethyl-2(1*H*)-pyrimidinethione gave the corresponding pyrimidinone ($ClCH_2CO_2H$, H_2O, reflux, 5 h; clearly via acidic hydrolysis of 2-carboxymethylthio-1,4,6-trimethylpyrimidinium chloride).[2697]

By miscellaneous minor procedures. Some other seldom-used procedures are illustrated by the following transformations.

1-Methyl-2-methylthiopyrimidinium iodide (**306**) to 1-methyl-2(1*H*)-pyrimidinone (5 *M* NaOH, 20°, 20 min).[3493]



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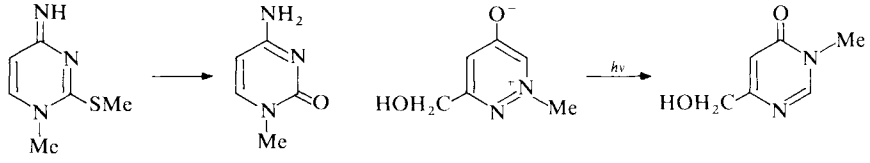
4-Methyl-2-methylthio-1,6-diphenylpyrimidinium iodide to 4-methyl-1,6-diphenyl-2(1*H*)-pyrimidinone (NaOMe, MeOH, H_2O?, 20°, 3 h).[4082]

1-Methyl-2,6-bismethylthiopyrimidinium iodide to 3-methyl-2-methylthio-4(3*H*)-pyrimidinone (*M* NaOH, 25°, 6 h: 80%).[1508]

1-Methyl-2-methylthio-4(1*H*)-pyrimidinimine (**307**) to 4-amino-1-methyl-2(1*H*)-pyrimidinone (**308**) ($HSCH_2CH_2OH$, $Et_3N.H_2CO_3$, H_2O, 40°, 3 h: 92%).[1512]

6-Hydroxymethyl-2-methylpyridazinium-4-olate (**309**) to 6-hydroxymethyl-3-methyl-4(3*H*)-pyrimidinone (**310**) (*hv*, EtOH, 25°: 75%); also homologs.[2498]

Also other examples.[1513,5662]



307 **308** **309** **310**

7.5.2. Reactions of Nontautomeric Pyrimidinones

The nontautomeric pyrimidinones undergo few reactions apart from thiation, *N*-dealkylation, and the interesting but practically unimportant isomerization into Dewar forms.

The *thiation* of fixed pyrimidinones to the corresponding thiones is no more difficult than the thiation of tautomeric pyrimidinones. The reagents and conditions required are illustrated in the formation of the following fixed pyrimidinethiones.

1-Methyl-4(1*H*)- and 3-methyl-4(3*H*)-pyrimidinethione (P_2S_5, pyridine, reflux, 60–90 min: 53% and 71%, respectively).[3480]

1,3-Dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (P_2S_5, pyridine or toluene, reflux, 3–4 h: > 65%)[968,2840] or 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedithione (P_2S_5, tetralin, 180°, 4 h;[968] P_2S_5, pyridine–PhMe, 190°, 6 h, sealed: 63%[806]).

6-Methoxy-3-methyl-4(3*H*)-pyrimidinethione (P_2S_5, pyridine, reflux, 3 h: ~ 40%).[3348]

2-Amino-3-methyl-4(3*H*)-pyrimidinethione (P_2S_5, pyridine, reflux, 3 h: ~35%).[1507]

1-Methyl-2-methylthio-4(1*H*)- and 3-methyl-2-methylthio-4(3*H*)-pyrimidinethione (P_2S_5, α-picoline, reflux, 6 h: 71% and 87%, respectively).[1508]

1-Methyl-6-methylthio-2(1*H*)-pyrimidinethione (P_2S_5, α-picoline, reflux, 1 h: 15%).[1508]

5-Fluoro-1,3-dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (P_2S_5, dioxane, reflux, 30 min: 60%).[2619]

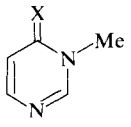
1-Benzyl-4,6-diphenyl-2(1*H*)-pyrimidinethione [Lawesson's reagent (**48**), PhH, reflux, 3 h: 86%].[3705]

3,6-Dimethyl-2-phenyl-4(3*H*)-pyrimidinethione [Lawesson's reagent (**48**), PhH, reflux, 10 h: 84%].[3728]

Also other examples.[456,968,1221,1533,3867]

The *N-dealkylation* of fixed pyrimidinones is possible but seldom useful. For example, 1-*β*-cyanoethyl- or 1,3-bis-*β*-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 2,4(1*H*,3*H*)-pyrimidinedione (> 80%) by refluxing in ethanolic sodium ethoxide for 6 h;[2370] 3-cyclohexyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide gave 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (98% H_2SO_4, 90°, 30 min: 89%) or 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (48% HBr, reflux, 1 h: 98%);[2676] 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 2,4(1*H*,3*H*)-pyrimidinedione (65%) by refluxing with urea in ethanolic ethoxide for 15 h (replacement of the whole N—C—N portion of the molecule);[962,5402] and related transformations.[242]

Although regular *aminolysis* of fixed pyrimidinones has not been reported, an indirect hydrazinolysis has been devised: treatment of 3-methyl-4(3*H*)-pyrimidinone (**311**, X = O) with triethyloxonium tetrafluoroborate gave the quaternary salt (**312**), which reacted with formylhydrazine to give the formylhydrazono derivative (**311**, X = NNHCHO) and thence, by acidic hydrolysis, 4-hydrazono-3-methyl-3,4-dihydropyrimidine (**311**, X = NNH_2).[3496] (*Note*: The substrate, intermediates, and product were all described incorrectly as their 1-methyl isomers.)



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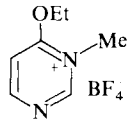

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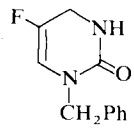

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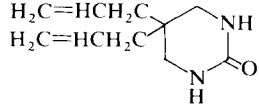

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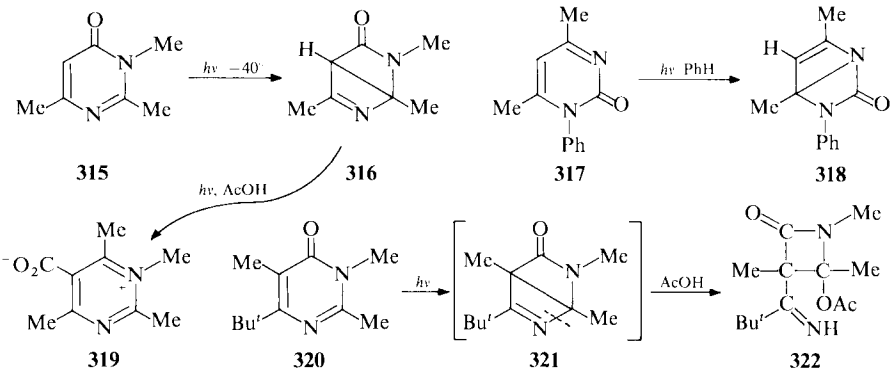
The *reduction* of fixed pyrimidinones seems quite regular (see Section 11.1.8); for example, 1-benzyl-5-fluoro-2(1*H*)-pyrimidinone with tetraisopropoxyzirconium in isopropyl alcohol at 90° for 2 days gave the 3,4-dihydro derivative (**313**) (49%); triisopropoxyaluminum was less effective.[294] Partial deoxygenation occurred on reduction of 5,5-diallyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione by lithium aluminum hydride in refluxing ether for 2 days to afford 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**314**) (~ 50%).[249]

A *dehydrogenation* of 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione occurred, on treating it with 2-methylfuranyllithium at − 78°, to afford 1,1′,3,3′-tetramethyl-4,4′-bipyrimidine-2,2′,6,6′(1*H*,1′*H*,3*H*,3′*H*)-tetrone (70%).[10]

The formation of *fixed Dewar pyrimidinones* from their regular isomers occurred on irradiation in an appropriate solvent. The resulting equilibrium mixtures, containing substantial proportions (⩽ 80%) of the Dewar isomers, were used to spectrally characterize the latter before their eventual degradation

to monocyclic and acyclic products; occasionally, Dewar isomers could be actually isolated. For example, 2,3,6-trimethyl-4(3*H*)-pyrimidinone (**315**) developed a 2,5-bond on irradiation in MeOH–NH_3 or Et_2O–NH_3 at $-40°$ to give its Dewar isomer, 1,3,6-trimethyl-2,6-diazabicyclo[2,2,0]hex-2-en-5-one (**316**);[5663,6204] in contrast, 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinone (**317**) developed a 3,6-bond on irradiation in benzene to afford 4,6-dimethyl-3-phenyl-1,3-diazabicyclo[2,2,0]hex-5-en-2-one (**318**) (isolated yield: 67%).[5664] Irradiation under different conditions led to a variety of products, most of which appeared to be formed via the Dewar isomers.[114,279,295,335,3881,3935] For example, the substrate (**315**) gave 1,2,4,6-tetramethylpyrimidinium-5-carboxylate (**319**) by a complicated mechanism via **316** (*hv*, AcOH–MeCN, 25°, 7 h: 55% overall),[335] whereas 6-*t*-butyl-2,3,5-trimethyl-4(3*H*)-pyrimidinone (**320**) gave **321** and thence 4-acetoxy-3-(α-imino-β,β-dimethylpropyl)-1,3,4-trimethylazetidin-2-one (**322**) as the chief product (*hv*, AcOH–MeCN, 0°: 32%).[3881]



Rather similar substrates undergo facile 2,5-cycloaddition by a variety of reagents such as dimethyl maleate or phenyl isocyanate.[287,288]

7.6. THE PYRIMIDINE *N*-OXIDES*

The first pyrimidine *N*-oxides were prepared by Ochiai in 1945 by the action of peroxyacetic acid on 4-methylpyrimidine[4688] to give what was then believed to be a single mono-*N*-oxide product. Later, with the advent of improved separation and instrumental methods, it was shown to be a separable mixture of the 1- and 3-oxide.[3443] Until more recent times, structural ambiguity has been a problem when unsymmetrical pyrimidines have been oxidized by direct means.

The chemistry of the pyrimidine *N*-oxides is not as well represented in the literature as that of pyridine or quinoline *N*-oxides. This may be explained in

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part by the fact that pyrimidine *N*-oxides generally are less easily prepared by direct oxidation than are their pyridine and quinoline counterparts. With the plethora of novel ring closure and rearrangement methods currently available for preparing *N*-oxides, they are now more readily accessible. An excellent comprehensive review has recently appeared,[6050] complementing two earlier works.[5890,5891]

7.6.1. Preparation of Pyrimidine *N*-Oxides

7.6.1.1. By Direct Oxidation

The oxidizing agent most commonly used in the early days of *N*-oxide chemistry, peroxyacetic acid, is still often used despite having marked drawbacks.[4691,6050] The convenience of preparation probably accounts for its continued popularity. It is generally prepared in situ by the addition of required amounts of the appropriate concentration of hydrogen peroxide to glacial acetic acid. A principal disadvantage of this reagent is its potential for causing hydrolysis of labile functional groups.[2107,2333] The advantages and disadvantages of various peroxycarboxylic acid reagents have been outlined previously.[5891] Table 7.1 gives some typical examples of the use of peroxyacetic acid to form pyrimidine *N*-oxides.

TABLE 7.1. THE *N*-OXIDATION OF PYRIMIDINES BY PEROXYACETIC ACID

Substituents				Yield(s) of Oxide(s)		
2-	4-	5-	6-	N1	N3	Ref.
Me	Et	—	Me	30	25	5893
i-Pr	Et	—	Me	28	18	5893
Ph	Me	—	Me	45	—	5893
Me	CH_2Ph	—	Me	18	15	5893
Me	Ph	—	Me	40	0.6	5893
Me	Me	—	*i*-Pr	18	28	3001
—	OMe	Me	Me	78	0	698
Me	Me	—	Me	33	—	3439
NHMe	—	—	—	30	—	36
OMe	—	—	—	18	—	36
—	NHMe	—	—	11	—	36
—	$NHMe_2$	—	—	10	—	36
—	OMe	—	—	29	—	36
—	OMe	—	Me	70	—	36
—	Ph	—	—	25	—	4691
—	Ph	Me	—	76	—	4691
—	NH_2	Ph	—	—	43	515
NH_2	Me	—	Me	60	—	291

When anhydrous conditions are called for, as when hydrolytically labile substituents such as halogeno or phenoxy are present, the use of peroxymaleic acid in aprotic solvents has proved very useful:[2107] Table 7.2 gives typical examples. Peroxyphthalic acid, although effective,[2211,4688] appears to have not been used in recent times. *m*-Chloroperoxybenzoic acid is also useful where anhydrous conditions are required, and it has been used in both protic and aprotic solvents. It is commercially available, reasonably stable, and very effective, all factors that contribute to its popularity. Several recent studies have utilized this reagent to prepare a large number of pyrimidine *N*-oxides.[36,170,515,3743,4691] Table 7.3 lists some typical examples.

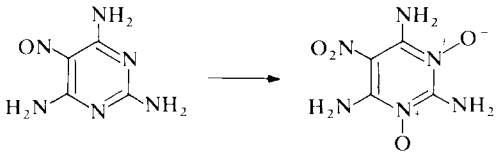
TABLE 7.2. THE *N*-OXIDATION OF PYRIMIDINES BY PEROXYMALEIC ACID

Substituents				Yield(s) of Oxide(s)		
2-	4-	5-	6-	N1	N3	Ref.
Me	Cl	—	Me	34	0	2107
Et	Cl	—	Me	57	0	2107
i-Pr	Cl	—	Me	74	0	2107
Cl	Me	—	Me	34	—	5892
—	OPh	—	Me	50	0	3503
—	Cl	—	Me	30	0	5894
—	Cl	—	Ph	26	0	5894
—	OPh	—	Ph	52	0	3287

TABLE 7.3. THE *N*-OXIDATION OF PYRIMIDINES BY *m*-CHLOROPEROXYBENZOIC ACID

Substituents				Yield(s) of Oxide(s)		
2-	4-	5-	6-	N1	N3	Ref.
OH	NH_2	F	—	0	34	1265
Cl	NH_2	F	—	0	20	1265
NH_2	NH_2	TMB[a]	—	38.5	22.8	5895
NH_2	NH_2	—	Cl	0	44.7	5897
NH_2	Me	—	Cl	0	8	5897
NH_2	Me	—	DCP[b]	0	64	5896
NH_2	OTs	—	MCA[c]	73	0	4296
NH_2	—	—	—	30	—	36
—	NH_2	—	—	25	Trace	36
—	—	Ph	—	37	—	3743
Me	OPh	—	NH_2	31	—	515
Me	Me	—	—	35	32	4691
Me	Ph	—	—	52	0	4691

[a] TMB = 3′,4′,5′-trimethoxybenzyl-.
[b] DCP = 2′,4′-dichlorophenoxy-.
[c] MCA = methoxycarbonylamino-.



323 324

The powerful oxidizing nature of trifluoroperoxyacetic acid is clearly demonstrated in its ability to bring about multiple oxidations. Thus only three examples of pyrimidine di-*N*-oxide formation by direct oxidation have appeared in the literature,[2176,2426,3549] and trifluoroperoxyacetic acid was the oxidizing agent used in each of these cases. This reagent will also oxidize susceptible functional groups, for example the oxidation of the nitroso substrate (**323**) to the nitro product (**324**)[2426,3549] or a phenylthio to a phenylsulfonyl group,[2176] has been reported in conjunction with *N*-oxide formation. Table 7.4 lists some examples of the use of trifluoroperoxyacetic acid for preparing *N*-oxides, and Table 7.5 illustrates its use in preparing some pyrimidine di-*N*-oxides.

TABLE 7.4. THE *N*-OXIDATION OF PYRIMIDINES BY TRIFLUOROPEROXYACETIC ACID

Substituents				Yield(s) of Oxide(s)		
2-	4-	5-	6-	N1	N3	Ref.
NH_2	NH_2	NO_2	NH_2	28[a]	—	3549
NH_2	NHEt	NO_2	NH_2	68(58)[a]	—	2176
NH_2	NMePh	NO_2	NH_2	7	—	2176
NH_2	NHPh	NO_2	NH_2	51[a]	—	2176
NH_2	NH_2	H	Cl	—	65	2333
NH_2	NH_2	Cl	Cl	—	80	2333
NH_2	NH_2	Et	—	—	69	3864
NH_2	SO_2Ph	—	NH_2	60[b]	—	2176
Me	NH_2	NO_2	NH_2	51[a]	—	2426

[a] From 5-NO starting material.
[b] From 4-SPh starting material.

TABLE 7.5. THE DI-*N*-OXIDATION OF PYRIMIDINES BY TRIFLUOROPEROXYACETIC ACID

Substituents					
2-	4-	5-	6-	Yield of di-*N*-Oxide	Ref.
NH_2	NH_2	NO_2	NH_2	48[a]	3549
H	NH_2	NO_2	NH_2	13[a]	2426
NH_2	Me	Cl	NH_2	25	2176

[a] From 5-NO starting material.

TABLE 7.6. THE *N*-OXIDATION OF PYRIMIDINES BY HYDROGEN PEROXIDE AND Na_2WO_4

Substituents				Yield(s) of Oxide(s)		
2-	4-	5-	6-	N1	N3	Ref.
–	—	–	—	17	–	5899
–	—	Br	–	19	—	1972
–	—	OMe	—	61	—	1972
–	Ph	–	—	70	0	4694
Me	Ph	—	—	60	0	4694
–	NH_2	–	Ph	–	30	515
NH_2	–	Ph	—	27	—	515

TABLE 7.7. THE *N*-OXIDATION OF PYRIMIDINES BY HYDROGEN PEROXIDE AND MoO_3

Substituents				Yield(s) of Oxide(s)		
2-	4-	5-	6-	N1	N3	Ref.
—	–	Cl	–	13	–	3743
	Me	Cl	—	22	34	3743
—	OMe	Cl	—	37	0	3743

Other peroxy acid reagents have also been used to form pyrimidine *N*-oxides, for example, *p*-methoxycarbonylperoxybenzoic acid.[515] Some recent work comparing the activities of various peroxy acid reagents on pyrimidine substrates has appeared.[36,170,515,4691]

Other methods of direct *N*-oxidation include the use of hydrogen peroxide in the presence of sodium tungstate[515] or molybdic anhydride and acetic acid:[3743] examples are shown in Tables 7.6 and 7.7. 4,6-Dimethylpyrimidine 1-oxide and 4-methyl-6-phenylpyrimidine 3-oxide have been prepared by the action of hydroxylamine-*O*-sulfonate on the parent compounds.[5898]

7.6.1.2. By Primary Synthesis

Early methods of pyrimidine *N*-oxide formation by the Principal Synthesis involved the incorporation of the N—O moiety into the ring as part of the one-carbon fragment. In most cases, but not all,[2783] the oxygen atom of the N—O grouping was protected and this was removed subsequent to cyclization.[1265,3036,4191,4194,4196,5900] This method has also been applied in preparing di-*N*-oxides.[4226] Variations on the theme have been used to make *N*-hydroxylated reduced pyrimidines.[4361,5901–5903] Oxidation with manganese dioxide of the 1-hydroxytetrahydropyrimidine 3-oxides, formed by cyclizing 1,3-hydroxyaminooximes with aldehydes, gives the corresponding pyrimidine di-*N*-

oxides.[3626,3627,4386] Recent examples of cyclizing unprotected amidoximes with three-carbon fragments have been reported.[6940] Pyrimidinetriamine *N*-oxides, of which the antihypertensive drug minoxidil (6-piperidino-2,4-pyrimidinediamine 3-oxide) is prototypical, can be formed readily by treating 3-amino-3-cyanoiminopropanenitriles with hydroxylamine.[2979,4351]

Primary syntheses yielding pyrimidine *N*-oxides through ring transformations of other heterocycles continue to appear in the literature. Early examples include the action of hydroxylamine on 1,3-oxazinones[5904] or of benzyloxyamine on 6-hydroxymethyl-2-thioxo-2*H*-1,3-thiazin-4(3*H*)-one (with subsequent cleavage of the protecting benzyl group[2888]) to eventually produce various derivatives of 1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione. More recently, 3-(substituted-amino)-1,2,4-oxadiazole has been transformed to 2-amino-6-phenyl-4(1*H*)-pyrimidinone 3-oxide by heating in the presence of toluenesulfonic acid under anhydrous conditions.[1672] Neutralization of the fused pyrimidinium reaction product from acetyl- or benzoylacetone with 3,5-isoxazolediamine, gives 2-cyanomethyl-4,6-dimethylpyrimidine 1-oxide and 2-cyanomethyl-4-methyl-6-phenylpyrimidine 1-oxide, respectively.[6051] Similarly, 4-methyl-6-phenyl-2-pyrimidinamine 1-oxide is formed from the fused pyrimidinium reaction product of benzoylacetone and 5-phenyl-1,2,4-oxadiazol-3-amine; the 4,6-dimethyl analog is formed likewise from acetylacetone and the same oxadiazole.[313] These same pyrimidine *N*-oxides can be formed directly from 3-(substituted-amino)-5-phenyl (or methyl)-1,2,4-oxadiazole.[291]

Pyrimidinium compounds can also undergo transformations and rearrangements to give *N*-oxides. For example, 1-aminopyrimidinium mesitylenesulfonates react with excess hydroxylamine to give pyrimidine *N*-oxides in good yield. 4,6-Dimethyl-, 4,6-diphenyl-, and 2,4,6-trimethylpyrimidine 1-oxide have been prepared in this manner.[5905] 6-Substituted-4-methyl-2-methylthio-1-phenylpyrimidinium iodides also react with hydroxylamine to give 2-anilino-4,6-dimethyl- or 2-anilino-4-methyl-6-phenylpyrimidine 1-oxide.[2686] In a similar fashion, a series of 4,6-disubstituted-1-phenylpyrimidine-2(1*H*)-thiones reacted with excess of hydroxylamine to give 2-anilino-4,6-disubstituted-pyrimidine 1-oxides in good yields,[2686] along with isoxazole byproducts. 2-Chloropyrimidine reacts with excess hydroxylamine to give 2-pyrimidinamine 1-oxide, but 4,6-dichloropyrimidine reacts more normally to give the corresponding 4-chloro-6-hydroxyaminopyrimidine.[6052]

5,6-Diamino-4(1*H*)-pyrimidinone 3-oxide and its 2-methyl derivative are prepared by the reaction of 4(1*H*)-pteridinone 3-oxide and its 2-methyl derivative with an excess of hydroxylamine.[2422] Base-catalysed ring opening of a purine *N*-oxide to give a 5-formamidopyrimidine *N*-oxide has been reported.[3257]

7.6.2. Properties of Pyrimidine *N*-Oxides

Electron-spin resonance (esr), dipole moment, and molecular orbital studies. Electronic structures[4689] and dipole moments for various pyrimidine *N*-oxides

have been published.[3443,4690,5906] Some esr and polarographic studies,[5907] half-wave redox potentials,[5708,5709] ionization energies, and photoelectronic spectra[5910] of pyrimidine *N*-oxides have been reported and compared with those of other heterocyclic *N*-oxides. Appropriate mo (molecular orbital) studies and their relationship with ^{1}H nmr[5911] and ^{15}N nmr chemical shifts[5912] have appeared. Other mo studies of methylpyrimidine *N*-oxides found a correlation between the change-transfer ability and the chemical reactivity of the methyl groups towards nitrosation and deuterium exchange reactions.[5913]

Nuclear magnetic resonance studies. Some early ^{1}H nmr studies of the effects of *N*-oxidation on pyrimidines are still relevant.[5893,5914–5916] The acidity of hydrogen atoms on methyl groups of pyrimidine *N*-oxides have been compared by studying deuterium exchange reactions using ^{1}H nmr techniques.[6053] A ^{1}H nmr procedure using lanthanide shift reagents on appropriately substituted pyrimidines has proved to be a powerful tool in identifying or confirming the site of *N*-oxidation where structural ambiguity is problematic.[3001]

Several studies involving ^{15}N[3346,3609,6054,6055] and ^{14}N[5917,6055] nmr measurements have appeared. The utility of ^{15}N nmr techniques for structural determinations has been claimed[3346] and questioned[3609] for 2,4-pyrimidinediamine *N*-oxides. The ^{17}O chemical shift for pyrimidine *N*-oxide has been determined and is in line with the predicted value.[6056]

A recent study has correlated the ^{1}H nmr chemical shifts for pyrimidine *N*-oxides with their pK_a values.[6057] On the basis of earlier work[6054] showing that a relationship exists between ^{15}N chemical shifts and ir absorption frequencies of the N—O grouping, a quantitative measure of the π-deficiency of diazine *N*-oxides indicates that pyrimidine *N*-oxide is less π-deficient than either pyrazine or pyridazine *N*-oxide;[6058] in this study, relationships between ^{13}C and ^{15}N nmr chemical shifts and ir N—O absorption frequencies were examined.

Infrared and ultraviolet spectra; X-ray crystallography. The ir spectra of pyrimidine *N*-oxides were studied earlier.[2828,3439,3633] The tautomeric structures of *N*-alkoxy- and *N*-hydroxy-4,6-dimethyl-2-pyrimidinones were determined using ir and uv spectra in conjunction with ionization constants.[2828] Using ir spectroscopy, it has been suggested that the oxygen atom of pyrimidine *N*-oxide is the basic center of the molecule.[5918] A detailed account of the uv spectra of pyrimidine *N*-oxides appeared earlier.[5919] A relationship was shown to exist between ^{15}N chemical shifts and the N—O ir absorption frequencies of pyrimidine *N*-oxides.[6054] The relationship between ir absorption frequencies of the N—O grouping and ^{13}C nmr have been examined in studies on the nature of π-deficiency in pyrimidine *N*-oxides.[6058]

The crystal structures of the 1-oxide of the antibacterial drug trimethoprim[5920] and the potassium and rubidum salts of 5-bromo-3-hydroxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione[1950] have been determined.

Ionization constants. In most cases, *N*-oxidation in the pyrimidine series causes a base-weakening and/or an acid-strengthening effect,[2828,3864,6057] although in the case of 4-amino-2(1*H*)-pyrimidinone 3-oxide a slight increase in

basic strength was observed, even though this compound was a much stronger acid than 4-amino-2(1*H*)-pyrimidinone.[5430] The *N*-hydroxy and *N,N'*-dihydroxy derivatives of the barbiturate drugs, barbital and phenobarbital among others, are much stronger acids than are the parent compounds.[5921]

Other physical properties. Deuterium exchange reactions of pyrimidine *N*-oxides have been reported.[1972,5913,5921] Hydrogen atoms on positions adjacent to the *N*-oxide moiety exchange more readily than those on corresponding positions of the parent pyrimidine.[1972] Partition coefficients for several 6-(disubstituted-amino)-2,4-pyrimidinediamine 3-oxides have been reported.[2040]

7.6.3. Reactions of Pyrimidine *N*-Oxides

Reduction. The pyrimidine *N*-oxides are generally susceptible to catalytic reduction,[1587,2426,2686,3257,5013,5922] although exceptions have been noted.[3036] Choice of catalyst and conditions can allow reductions of other functional groups to take place in the presence of an *N*-oxide grouping. For example, reductive dehalogenations in the presence of an *N*-oxide grouping have been reported.[3609,5894]

Several of the usual chemical agents such as dithionite[5893,5895] or phosphorus trichloride[3705] will reduce the *N*-oxide grouping. Titanium trichloride[5923] and triethyl phosphite[4386] as well as the older agents such as zinc[1681] or iron[3503] in acid are also effective. Apparently, other functional groups can be reduced by chemical means without reducing the *N*-oxide.[1587]

Halogenation. Halogenation at C5 of pyrimidine *N*-oxides is well represented in the literature.[3705,3864,4694 6059,6060] Diazotization of various 2-pyrimidinamine *N*-oxides in the presence of acetic acid and lithium chloride gives the corresponding 2-chloropyrimidine *N*-oxides.[6066] Under different conditions, using sodium nitrite in the presence of hydrochloric or hydrobromic acid, 5-halogenated and other products are isolated instead.[1966,6066] Chlorination of pyrimidinone *N*-oxides by phosphorus halides requires the *N*-oxide grouping to be protected.[1681]

Nitrosation and nitration. Nitrosation of pyrimidine *N*-oxides possessing three electron-donating groups is easily accomplished.[1280,1325,5924] Nitration has been less frequently reported.[1587]

Acylation. Acylations of pyrimidine *N*-oxides can give molecular rearrangements[836,5430] including side-chain acyloxylation with concomitant loss of the *N*-oxide grouping in pyrimidine *N*-oxides containing methyl substituents,[118,764] although some exceptions, such as 5-acetoxylation, have been noted.[763] Reaction with acid chlorides gives chloromethylpyrimidines,[764] but again an exception has been noted.[763] The reaction with phosphoryl chloride has been improved.[121,2226] The base-catalyzed reaction between ethyl benzoate and 4,6-dimethylpyrimidine *N*-oxide gave only 4-methyl-6-phenacylpyrimidine

1-oxide and none of the isomeric 3-oxide: this is indicative of the increased acidity of methyl groups that are adjacent to the *N*-oxide function.[6053]

With pyrimidinamine *N*-oxides, the normal *N*- and/or *O*-acylation products are isolated.[654,5762] The reaction of 2,4-pyrimidinediamine 3-oxides with chloroformates gives oxadiazolopyrimidinecarbamates.[5925]

The reaction of a methylpyrimidine *N*-oxide with benzaldehyde to give a styrylpyrimidine *N*-oxide has been reported.[4657] A Mannich reaction on such a methyl *N*-oxide has also been described.[4657]

Alkylation. Alkylations of pyrimidine *N*-oxides are usually catalyzed by base, where the *N*-oxide grouping is sometimes masked by a protecting group.[1047,1325] *O*-Methylation, without the use of base catalysis, of a pyrimidinamine *N*-oxide has recently been described.[515] Base-catalyzed alkylations of 5,5-diethyl-*N*-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione gave separable mixtures of *N*- and *O*-alkylated products.[3036]

Reissert–Henze-type reactions. In this reaction, a pyrimidine *N*-oxide with an unsubstituted 2-, 4-, or 6-position is allowed to react with cyanide in the presence of benzoyl chloride to give a pyrimidinecarbonitrile. Early examples[2211,2762] often reported poor yields. A much improved method using trimethylsilyl cyanide has been reported recently.[142]

Photochemical reactions. Photochemical reactions of simple pyrimidine *N*-oxides have been reported.[5922,5926] The photolyses of 2- and 5-methoxypyrimidine *N*-oxides have been described in detail.[5927] 4,6-Disubstituted-pyrimidine *N*-oxides undergo molecular rearrangement: the products of these reactions are dependent on the bulk of the 4- and 6-substituents and on the solvent system used.[4633,5662] Photolysis of 2,4,6-trisubstituted-pyrimidine *N*-oxides has also been studied.[5928]

Miscellaneous reaction types. 2,4-Pyrimidinediamine 3-oxides react with sulfur trioxide to give the corresponding *O*-sulfates.[5930] Diazotization of 2-pyrimidinamine *N*-oxide in the presence of hydrofluoric acid gives 5-hydroxypyrimidine-2-diazohydroxide.[5929]

Molecular rearrangements. The observed acid-catalyzed rearrangement of 4-phenylpyrimidine 1-oxide to 5-phenylisoxazole[5931] has been employed for determination of other pyrimidine *N*-oxides.[3001] The action of potassium amide in liquid ammonia on 4-chloro-6-methyl (or phenyl)pyrimidine 1-oxide gives 6-methyl (or phenyl)-4-pyrimidinamine 1-oxide (as a minor product) and 3-methyl (or phenyl)-5-isoxazolamine (as the major product).[5894] Further studies on these reactions have been reported.[3287,3503]

The 1-oxides of 4-phenylpyrimidine[5933] and 4,6-dimethylpyrimidine[3013] react with reactive methylene compounds to give ring-open products. The latter *N*-oxide, however, reacts with 3-methyl-5-isoxazolamine to give 2-(5′-amino-3′-methylisoxazol-4′-yl)-4,6-dimethylpyrimidine.[3013] 4-Phenylpyrimidine 1,3-dioxide reacts with ethyl cyanoacetate in the presence of acetic anhydride to give

5-acetoxy-4-(α-cyano-α-ethoxycarbonylmethyl)-6-phenylpyrimidine, formulated as ethyl α-(5-accetoxy-6-phenyl-3,4-dihydropyrimidin-4-ylidene)-α-cyanoacetate.[5608] 5-Methylpyrimidine *N*-oxide reacts with perfluoropropene to give a mixture of 5-methyl-4- and 5-methyl-2-(α,β,β,β-tetrafluoroethyl)pyrimidine.[5932]

The 1,3-dipolar cycloaddition reaction between phenyl isocyanate and 4-ethoxy-6-methylpyrimidine 1-oxide gives 2-anilino-4-ethoxy-6-methylpyrimidine, but when phenylisothiocyanate is used, 7-methyl-3-phenyloxazolo[4,5-*d*]pyrimidine-2(3*H*)-thione is formed instead.[2896,3333] The reaction of 4-alkoxy-6-methylpyrimidine 1-oxides with dimethyl acetylenedicarboxylate to give ultimately methyl 4-alkoxy-2-methoxycarbonylmethyl-6-methylpyrimidine has been described.[1878,3333] 4-Methyl-6-piperidinopyrimidine 3-oxide reacts differently: betaine formation and loss of oxygen from N3 takes place instead.[1878] The 4-alkoxy-6-methylpyrimidine 1-oxides react with 1-morpholinoisobut-1-ene in the presence of benzoyl chloride to give 4-alkoxy-2-α-formyl-α-methylethyl-6-methylpyrimidines in good yields.[5934] If the 4-alkoxy group is replaced by methyl, the corresponding aldehydes are formed in low yields.[5934] Reaction of the 4-alkoxy-6-methylpyrimidine 1-oxides with a different eneamine, 1-morpholinocyclohexene, gives 4-alkoxy-6-methyl-2-α-oxocyclohexylpyrimidines in good yields, while replacement of the alkoxy group by methyl or phenyl gives similar products but in lower yields.[5934] The reaction of a 4-alkoxy-6-methylpyrimidine 1-oxide with diketene has been reported to give a mixture of an isoxazole and an oxazolopyridine.[5930]

4-Methylpyrimidine 3-oxide or 4,6-dimethylpyrimidine *N*-oxide reacts with *N*-phenylbenzimidoyl chloride to give 2-*N*-benzoylanilino- and 2-anilino-4-methylpyrimidine or their 4,6-dimethyl analogs, respectively.[5729] When this reaction with 4-methylpyrimidine 3-oxide is carried out in the presence of triethylamine, 4-benzoylanilinomethylpyrimidine and 4-*p*-benzamidobenzylpyrimidine are formed instead.[5935]

Simple pyrimidine *N*-oxides react with hydroxylamine to give isoxazoles. ^{15}N-Labeling shows that the N—O portion of the isoxazole was derived from hydroxylamine and not from the *N*-oxide portion of the original pyrimidine.[5936] Hydrazine reacts with 5,5-diethyl-1-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione to give 4,4-diethylpyrazolidine-3,5-dione.[3036]

7.6.4. Biological Properties of Pyrimidine *N*-Oxides

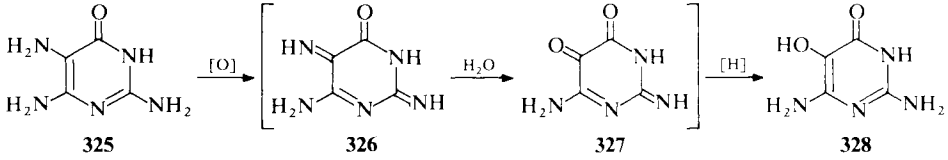
The biological properties of the pyrimidine *N*-oxides seem to be rather unremarkable with one exception. The biological activities of the triaminopyrimidine *N*-oxides appear to be myraid in nature. Many claims for these compounds exist, including antihypertensive,[6061] hair growth stimulant,[6062] and animal growth-promoting properties.[6063] During the 5-year period to 1986, there were 19 patents filed on these compounds: of these, 6 were for hypertensive use and 7 were for hair growth stimulants. During the 4-year period up to 1990,

there were 101 patents filed on such compounds, 67 of which dealt with hair growth.

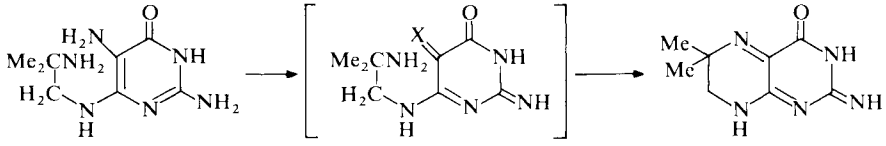
Some 5-pyrimidinecarboxanilide *N*-oxides are claimed to have herbicidal properties.[6064] Some arylsulfonylhydrazones of 4-pyrimidinecarbaldehyde 3-oxide display some activity against a murine tumor.[6065] *N*-Aralkoxydihydro-2,4(1*H*,3*H*)-pyrimidinediones are claimed to have antiinflammatory activity.[5901]

7.7. THE QUINONOID PYRIMIDINES

As the name implies, a quinonoid (or quinoid) pyrimidine is related to a regular pyrimidine (at least in respect of structure and elevated oxidation state) much as is benzoquinone to hydroquinone. Although quinonoid pyrimidines have not been purified, characterized, or as extensively studied as their pteridine counterparts,[6935] they have been implicated clearly in several synthetic and biosynthetic processes. For example, 2,5,6-triamino-4(3*H*)-pyrimidinone (**325**) underwent oxidation by iodine in methanolic methoxide under anaerobic conditions to give the quinonoid diimine (**326**), isolable and then reasonably stable as a dry solid; this material rapidly hydrolyzed in mildly acidic media to its 5-oxo analog (**327**), which was immediately reduced with dithionite to afford 2,6-diamino-5-hydroxy-4(3*H*)-pyrimidinone (divicine) (**328**) in 74% yield overall.[6936] In a rather analogous way, 2,5-diamino-6-(*β*-amino-*β*-methylpropyl)amino-4(3*H*)-pyrimidinone (**329**) succesively underwent oxidation to the quinonoid diimine (**330**, R = NH), hydrolysis to the oxo analog (**330**, X = O), and spontaneous cyclization to the isolable quinonoid 6,6-dimethyldihydropterin (**331**), an unnatural substrate for dihydropteridine reductase.[6937]



325 **326** **327** **328**



329 **330** **331**

The formation of other such useful enzyme substrates or cofactors has been facilitated by quinonoid pyrimidine intermediates.[6938,6939]

The quinonoid pyrimidines have much in common with alloxan (see Section 7.1.6.1).

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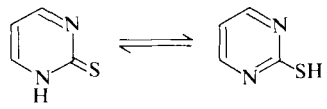
CHAPTER 8

Thiopyrimidines

The term "thiopyrimidine" covers any pyrimidine with a sulfur-containing substituent that is attached directly or indirectly to the pyrimidine ring through its sulfur atom. The thiopyrimidines form a closely knit family. Thus the parent tautomeric pyrimidinethione, 5-pyrimidinethiol, or (extranuclear) mercaptoalkylpyrimidine may be *S*-alkylated to an alkylthiopyrimidine (thioether, RSR′), which may then be oxidized to an alkylsulfinyl- [sulfoxide, RS(=O)R′] or alkylsulfonylpyrimidine [sulfone, $RS(=O)_2R'$]; alternatively, the parent may be oxidized directly to a dipyrimidinyl disulfide (RSSR), to pyrimidinesulfinic acid (RSO_2H), or to a pyrimidinesulfonic acid (RSO_3H). Nontautomeric pyrimidinethiones, the few known selenium-containing pyrimidines, dipyrimidinyl sulfides (RSR), and minor entities such as pyrimidinesulfenic acids (RSOH) are included in this chapter, but, for pragmatic reasons, treatment of the thiocyanatopyrimidines (RSC≡N) is deferred to be with isothiocyanato- (RN=C=S) and thioureidopyrimidines [$RNHC(=S)NH_2$] in Chapter 9.

8.1. TAUTOMERIC PYRIMIDINETHIONES

The tautomeric pyrimidinethiones are typified by 2(1*H*)-pyrimidinethione (**1**). Although this cyclic thioamide (**1**) exists in equilibrium with only a minute proportion of its tautomer, 2-pyrimidinethiol (**2**), the latter is so reactive that *S*-alkylation and oxidative reactions proceed readily.



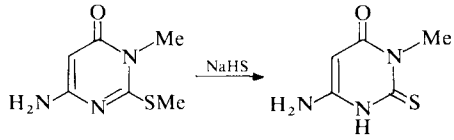
1 **2**

8.1.1. Preparation of Tautomeric Pyrimidinethiones

The three chief methods for making tautomeric pyrimidinethiones have been discussed already: by *primary syntheses* (Chapters 2 and 3), by *thiolysis of halogenopyrimidines* (Section 6.7.7), and by *thiation of pyrimidinones* (Section

7.1.3.2). The less important routes to tautomeric pyrimidinethiones are summarized in the following paragraphs.

From alkylthiopyrimidines. Such thioethers may be converted into pyrimidinethiones by thiolysis, thiation, or splitting. Thus *thiolysis* is represented in the conversion of 6-amino-3-methyl-2-methylthio-4(3*H*)-pyrimidinone (**3**) into 6-amino-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**4**) (*M* NaHS, 115°, 3 h, sealed: 83%).[1445] *Thiation* has been used to convert 2-ethylthio-5-methyl-4(3*H*)-pyrimidinone into 5-methyl-2,4(1*H*,3*H*)-pyrimidinedithione (P_2S_5, tetralin, 145°, 2 h: 75%);[2840] also 3-methyl-2-methylthio-4(3*H*)-pyrimidinone into 3-methyl-2,4(1*H*,3*H*)-pyrimidinedithione (P_2S_5, tetralin, 180°, 4 h: 21%).[1221] The *splitting* of thioethers may be achieved with several reagents, as illustrated in the following examples.



3 **4**

2-Ethylthio-4(3*H*)-pyrimidinethione to 2,4(1*H*,3*H*)-pyrimidinedithione (molten substrate, dry HCl, 170°).[3148]

5-Chloro-2-methylthio- to 5-chloro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (50% HI, AcOH–Ac_2O, reflux, 90 min: 72%).[1914]

2-Benzylthio-5-iodo- to 5-iodo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (likewise, 95°: 57%;[1914] $AlBr_3$, PhMe, 60°, 6 h: 82%[3044]).

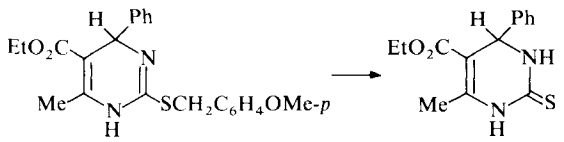
6-Benzylthio-5-formamido-4-pyrimidinamine to 6-amino-5-formamido-4(3*H*)-pyrimidinethione (liquid NH_3, Na, reflux: 61%).[1649]

6-Methylthio-4-pyrimidinamine to 6-amino-4(3*H*)-pyrimidinethione (liquid NH_3, $NaNH_2$, slowly: 69%).[1653]

1-Benzyl-2-benzylthio-4(1*H*)- to 1-benzyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (10*M* HCl, 95°, 15 min: 86%).[3117]

Ethyl 2-*p*-methoxybenzylthio-4-methyl-6-phenyl-1,4-dihydro- (**5**) to ethyl 4-methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (**6**) (F_3CO_2H–EtSH: > 54%).[531]

Also other examples.[531,593,1653]

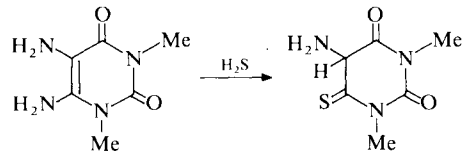


5 **6**

From acylthiopyrimidines. The deacylation of acylthiopyrimidines is illustrated in the conversion of 2-benzoylthio-4,6-dimethylpyrimidine into 4,6-dimethyl-2(1*H*)-pyrimidinethione (Et_2NH, PhH, 25°, 15 min: > 95%) and of 2-benzoylthio-4,6-pyrimidinediamine into 4,6-diamino-2(1*H*)-pyrimidinethione (H_2O, reflux, 3 min: > 95%).[5665]

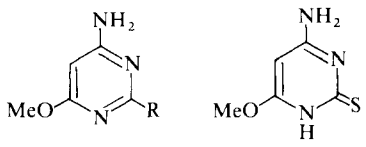
From acyloxypyrimidines. Displacement of an acyloxy group occurred on stirring 2,4-dimethyl-6-tosyloxypyrimidine with ethanolic thiourea for 20 h (followed by aqueous alkaline treatment) to give 2,6-dimethyl-4(3*H*)-pyrimidinethione (68%).[2612]

From pyrimidinamines. The direct conversion of a pyrimidinamine into the corresponding pyrimidinethione is illustrated by the transformation of 5,6-diamino-1,3-dimethyl- (**7**) to 5-amino-1,3-dimethyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**8**) (H_2S, pyridine, 60°, 20 h, sealed: 81%),[3998] of 6-amino-5,5-diethyl-2,4(3*H*,5*H*)-pyrimidinedione to 5,5-diethyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (H_2S, EtOH, 150°, 12 h, sealed: 46%),[5666] and of 5-*p*-chlorophenyl-6-ethyl-2,4-pyrimidinediamine or 2-amino-5-*p*-chlorophenyl-6-ethyl-5,6-dihydro-4(3*H*)-pyrimidinone to 5-*p*-chlorophenyl-6-ethyl-2,4(1*H*,3*H*)-pyrimidinedithione (P_2S_5, tetralin, 190°, 2 h: 5% or 25%, respectively).[5160]



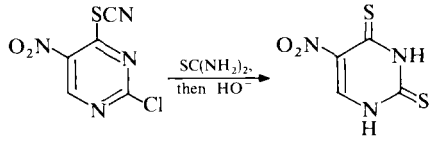
7 **8**

From alkylsulfonyl- or alkylsulfinylpyrimidines. The thiolysis of a pyrimidine sulfone occurred when 6-methoxy-2-methylsulfonyl-4-pyrimidinamine (**9**, R = SO_2Me) was boiled with *M* sodium hydrogen sulfide for 90 min to afford 4-amino-6-methoxy-2(1*H*)-pyrimidinethione (**10**) (38%), accompanied by a little 6-methoxy-2-methylthio-4-pyrimidinamine (**9**, R = SMe) (formed by reduction of the sulfone);[903] likewise, 5-methoxy-2-methylsulfonylpyrimidine gave 5-methoxy-2(1*H*)-pyrimidinethione (74%),[1897] and 4-methoxy-2-methylsulfinyl-6-nitroaminopyrimidine gave 4-methoxy-6-nitroamino-2(1*H*)-pyrimidinethione, isolated after *S*-methylation to 4-methoxy-2-methylthio-6-nitroaminopyrimidine (34% overall).[903]



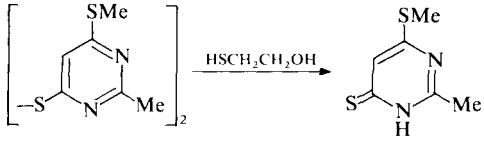
9 **10**

From thiocyanatopyrimidines. The ways to convert thiocyanatopyrimidines into pyrimidinethiones are represented in the following conversions. 2-Chloro-5-nitro-4-thiocyanatopyrimidine (**11**) gave 5-nitro-2,4(1*H*,3*H*)-pyrimidinedithione (**12**) (H_2NCSNH_2, H_2O, hot, 30 min, then alkali);[1582] 5-nitro-4-thiocyanato-2-pyrimidinamine gave a separable mixture of 2-amino-5-nitro-4(3*H*)-pyrimidinethione and 4-ethoxy-5-nitro-2-pyrimidinamine (NaOEt, EtOH, 0°, 2 h);[1582] 2-ethylthio-4,5-dimethyl-6-thiocyanatopyrimidine gave 2-ethylthio-5,6-dimethyl-4(3*H*)-pyrimidinethione (neat AcSH, reflux, 3 h: > 80%);[2157] and other such examples have been reported.[1886,2157,2387,3320,5101,5667,5700, cf. 2140,2188,5995]



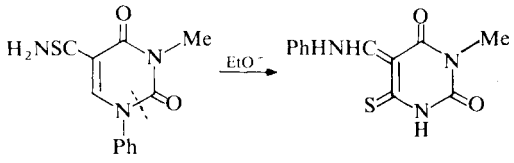
11 **12**

From dipyrimidinyl disulfides. The reduction of disulfides to thiones is illustrated by the following examples. Bis(4,6-diphenylpyrimidin-2-yl) disulfide was reduced by tin in hot hydrochloric acid to give 4,6-diphenyl-2(1*H*)-pyrimidinethione (70%);[4053] bis(2-methyl-6-methylthiopyrimidin-4-yl) disulfide (**13**) in ethanolic β-mercaptoethanol at 20° gave 2-methyl-6-methylthio-4(3*H*)-pyrimidinethione (**14**) (90%);[1778] bis(2,6-dimethoxypyrimidin-4-yl) disulfide with lithium aluminum hydride in ether gave 2,6-dimethoxy-4(3*H*)-pyrimidinethione (76%);[2071] and sodium hydrogen sulfite has also been used for such reduction.[5696]



13 **14**

Minor routes. Several minor routes to pyrimidinethiones have been used in the following examples: (1) treatment of 2-chloro-4-methylamino-5-nitropyrimidine with hot aqueous sodium hydrogen sulfide gave, not only the expected 5-amino-4-methylamino-2,4(1*H*)-pyrimidinethione, but also 5-amino-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedithione (5%) into which the second thioxo group had been introduced directly;[1379] (2) 4-methyl-6-phenyl-3,6-dihydro-2(1*H*)-pyrimidinethione underwent dehydrogenation on refluxing with sulfur in xylene for 15 h to afford 4-methyl-6-phenyl-2(1*H*)-pyrimidinethione (75%);[5668] (3) 1-methyl-2,6-dioxo-3-phenyl-1,2,3,6-tetrahydro-5-pyrimidinecarbothioamide (**15**) rearranged in refluxing ethanolic ethoxide during 6 h to

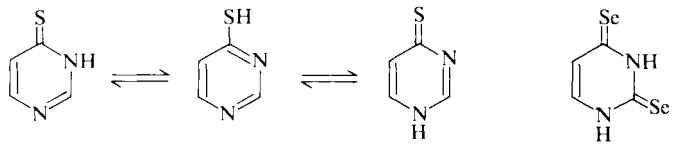


15 16

furnish 5-anilinomethylene-3-methyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**16**) (92%);[6032] (4) 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione underwent replacement of its whole N—C—N portion on refluxing with thiourea in ethanolic ethoxide during 15 h, to give 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (91%);[962,5402] and (5) treatment of 4,6-dimethyl-2-methylthiopyrimidine in refluxing ethanolic sodium hydrogen selenide (NaHSe) gave 4,6-dimethyl-2(1*H*)-pyrimidineselone (63%).[3986]

8.1.2. Fine Structure of Tautomeric Pyrimidinethiones

Although the fine structure of tautomeric pyrimidinethiones has not been investigated in the depth accorded to the corresponding pyrimidinones (Section 7.1.2), it is evident that such pyrimidinethiones exist as such and not as pyrimidinethiols. Thus, by comparing the uv spectra and ionization constants of 2(1*H*)- and 4(3*H*)-pyrimidinethione with those of their *N*- and *S*-methyl derivatives, it was concluded that the 2-thione (**1**) existed in aqueous solution as such with only a minute contribution from the 2-thiol (**2**) and that the isomeric 4-thione existed as a 2 : 1 mixture of 4(3*H*)- (**17**) and 4(1*H*)-pyrimidinethione (**19**) with practically no contribution from 4-pyrimidinethiol (**18**).[3480] The following fine structures for pyrimidinethiones are based on experimental evidence, sometimes not entirely conclusive: 4-amino-2(1*H*)- and 4-amino-2(3*H*)-pyrimidinethione (uv);[1507] 4-dimethylamino-2(1*H*)-pyrimidinethione (uv);[1507] 6-dimethylamino-4(3*H*)-pyrimidinethione (uv);[1507] 2-amino-4(3*H*)-pyrimidinethione (uv);[1507] 2,4(1*H*,3*H*)-pyrimidinedithione (X-ray);[3630] 2,4(1*H*,3*H*)-pyrimidinediselone (**20**) (X-ray);[3628] 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone and its derivatives (spectra);[3022,3581,4612,5669] 6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone (uv);[2186, cf. 3348] and other pyrimidinethiones.[3581,5670]



17 18 19 20

8.1.3. Reactions of Tautomeric Pyrimidinethiones

Most of the reactions of pyrimidinethiones occur by virtue of the small proportion of pyrimidinethiol present.

8.1.3.1. Desulfurization

The removal of sulfur from a tautomeric pyrimidinethione to give the corresponding pyrimidine (desulfurization) is usually done by stirring in hot aqueous or alcoholic solution (often containing ammonia to improve substrate solubility) with 3–5 parts of wet *Raney-nickel catalyst* for 1–3 h. Although the quality of Raney-nickel can be important in this process,[3498,5671,5672] it is generally satisfactory to use a quickly prepared grade[1650] rather than the high grades sometimes used for catalytic hydrogenations. Some nuclear reduction can take place under such desulfurization conditions,[188,764,2566,3492,3857,4368,5673] but this is seldom troublesome. The process is illustrated in the formation of the following products, each from the appropriate pyrimidinethione using the outlined general procedure, unless indicated otherwise.

From simple 2-pyrimidinethiones

Pyrimidine (25–27%).[764,2566,5674]

4,6-Dimethylpyrimidine (in HCl–EtOH: 55%).[764,2566]

4-Isopropyl-6-methylpyrimidine (64%).[3302]

4,5,6-Trimethylpyrimidine (in HCl–EtOH: 25%).[3302]

Also other examples.[4638]

From simple 4/6-pyrimidinethiones

Pyrimidine (from the 2,4-dithione: 17%).[2566]

4,5-Trimethylenepyrimidine (from the 6-thione: 58%,[5675] from the 2,6-dithione: 38%[3526]).

From 2-pyrimidinethiones bearing one amino group

4-Pyrimidinamine (61%).[1650]

4-Methylaminopyrimidine (54%).[708]

4-Pentylaminopyrimidine (67%).[5676]

4-Dimethylaminopyrimidine (50%).[708]

4-Methyl-6-piperidinopyrimidine (65%).[5676]

1-Methyl-4(1*H*)-pyrimidinimine (in EtOH + NH_4Cl: 30% as hydrochloride).[1508]

Also other examples.[1136,3474,5677]

From 4/6-pyrimidinethiones bearing one amino group

4,5-Trimethylene-2-pyrimidinamine (55%).[5675]

Also other examples.[3526]

From 2-pyrimidinethiones bearing two amino groups

4,5-Pyrimidinediamine (65%);[2295,5674] *cf.* by nickel boride (45%).[5674]

4,6-Pyrimidinediamine (85%).[1650, cf. 1297,3615]

4,5,6-Pyrimidinetriamine (78%).[3186]

6-Phenyl-4,5-pyrimidinediamine (~ 80%).[4652]

Also other examples.[1400,2413]

From 4/6-pyrimidinethiones bearing two amino groups

2,4-Pyrimidinediamine (65%).[3526]

4,5-Pyrimidinediamine (from the 6-thione: 77%;[3526] from the 2,6-dithione: 84%[3613]).

2-Methyl-4,5-pyrimidinediamine (80%).[2413]

2-Butyl-4,5-pyrimidinediamine (87%).[1981]

5-γ-Anilinopropyl-4-methyl-2-pyrimidinamine (77%).[3193]

Also other examples.[1612,4286,4755,4760]

From 2-pyrimidinethiones bearing oxy substituents

4(3*H*)-Pyrimidinone (82%).[1650,5674]

6-*t*-Butyl-4(3*H*)-pyrimidinone (97%).[1822,5678]

5-Benzyl-4,6(1*H*,5*H*)-pyrimidinedione (69%).[3104]

5-Benzyloxy-4(3*H*)-pyrimidinone (62%).[1343]

4,6-Dimethyl-5-pyrimidinol (25%).[1343]

5-β-Hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone (82%).[3126]

1-Ethyl-4(1*H*)-pyrimidinone (52%).[3117]

6-Methyl-3-phenyl-4(3*H*)-pyrimidinone (79%).[4178]

5-Methoxy-6-methoxymethyl-4(3*H*)-pyrimidinone (~ 55%).[2192]

Also other examples.[659,698,1319,1341,1787,1822,2200,2264,3193,3498,3499,3526, 4184,4567,5096]

From 4/6-pyrimidinethiones bearing oxy substituents

2-Methyl-4(3*H*)-pyrimidinone (93%).[2263]

5-Methyl-2(1*H*)-pyrimidinone (66%).[2062]

5-Benzyloxypyrimidine (42%).[1343]

Also other examples.[1341]

From 2-pyrimidinethiones bearing amino and oxy substituents

6-Amino-4(3*H*)-pyrimidinone (87%).[1650, cf. 659,1036,1570,3526,5674]

5,6-Diamino-4(3*H*)-pyrimidinone (> 75%).[2327,2455]

6-Methyl-5-piperidinomethyl-4(3*H*)-pyrimidinone (83%).[3498]

5-Amino-6-methyl-4(3*H*)-pyrimidinone (73%).[1038]

5-(3′,4′,5′-Trimethoxybenzyl)-2-pyrimidinamine (40%).[3346]

Also other examples.[659,973,1880,2420]

From 4/6-pyrimidinethiones bearing amino and oxy substituents

2-Amino-4(3*H*)-pyrimidinone (80%).[1666]

4-Amino-2(1*H*)-pyrimidinone (43%).[1568,3526]

From 2-pyrimidinethiones bearing other substituents

5-Fluoro-4(3*H*)-pyrimidinone (56%).[1262]

6-Trifluoromethyl-4,5-pyrimidinediamine (~ 60%).[5019]

4-Amino-5-pyrimidinecarboxylic acid (47%).[809]

4-Oxo-3,4-dihydro-5-pyrimidinecarboxylic acid (14%).[2873]

6-Amino-5-*β*,*β*-diethoxyethyl-4(3*H*)-pyrimidinone (75%).[3859]

Ethyl 5,6-diamino-4-pyrimidinecarboxylate (80%).[2435]

Ethyl 4-methyl-3,6-diphenyl-3,6-dihydro-5-pyrimidinecarboxylate (in AcMe: 67%).[370]

Also other examples.[1030,1641,2856,3140,3416,3859]

From 4/6-pyrimidinethiones bearing other substituents

4-Chloro-5-pyrimidinamine (~ 30%).[1036]

5-*p*-Chlorophenyl-4-methyl-2-pyrimidinamine (72%).[5096]

5-Benzamidomethyl-2-methylpyrimidine (82%).[1414]

5-Benzamido-4-pyrimidinamine (~ 20%).[5679]

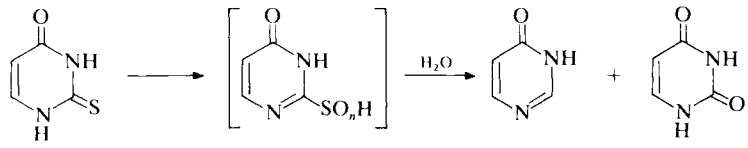
Ethyl 2-methyl-5-pyrimidinecarboxylate (30%).[3062]

Also other examples.[3400]

The alternative, and usually less satisfactory, *oxidative desulfurization* is essentially an indirect process, often carried out as a one-pot procedure. The action of alkaline, neutral, or acidic hydrogen peroxide on a tautomeric pyrimidinethione may remove sulfur in favor of hydrogen (desulfurization) or in favor of oxygen (oxidative hydrolysis): these reactions usually occur simultaneously but one or other may predominate, as indicated in the following transformations.

2-Thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**21**) gave 4(3*H*)-pyrimidinone (**23**) (40%) and 2,4(1*H*,3*H*)-pyrimidinedione (**24**) (44%), probably by loss of H_2SO_3 from the sulfinic acid (**22**, $n = 2$) and the sulfonic acid (**22**, $n = 3$), respectively.[710]

5-Acetyl-6-methyl-2-naphthalen-1′-yl-4(3*H*)-pyrimidinethione gave 5-acetyl-4-methyl-2-naphthalen-1′-ylpyrimidine (H_2O_2, AcOH, reflux, 5 min:



25%) or 5-acetyl-6-methyl-2-naphthalen-1′-yl-4(3*H*)-pyrimidinone (H_2O_2, NaOH, H_2O, reflux, 3 min: 30%).[3990]

2(1*H*)-Pyrimidinethione gave pyrimidine (39% as picrate).[764]

5-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave 5-methyl-4(3*H*)-pyrimidinone (~ 60%).[2108]

5,6-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave 5,6-dimethyl-4(3*H*)-pyrimidinone (~ 45%).[2108]

6-Ethoxymethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave 6-ethoxymethyl-5-methyl-4(3*H*)-pyrimidinone (~ 50%).[1532]

6-Pentyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave 6-pentyl-2,4(1*H*,3*H*)-pyrimidinedione.[2178]

6-Diethoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave 6-diethoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (> 90%).[2855]

Also other examples.[2108,2145]

Other oxidants proved equally unpredictable: 5-ethoxycarbonylmethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone underwent desulfurization to 5-ethoxycarbonylmethyl-4(3*H*)-pyrimidinone (64%) by treatment with lead acetate and hydrogen peroxide in warm acetic acid,[2002] but 6-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone gave only 6-ethyl-2,4(1*H*,3*H*)-pyrimidinedione (55%) on treatment with warm dilute nitric acid.[2148] For desulfurization via isolated sulfinic acids, see Section 8.7.3.

8.1.3.2. *S*-Alkylation and Acylation

The *alkylation* of a tautomeric pyrimidinethione invariably proceeds readily to give an *S*-alkyl derivative; any possible *N*-, *O*-, or *C*-alkylation of the same molecule is less rapid and hence easily avoided. However, at least one dihydropyrimidinethione has been reported to undergo preferential *N*-alkylation under certain conditions.[14] Many pyrimidinethiones can be *S*-methylated simply by dissolving in *M* sodium hydroxide, adding methyl iodide or sulfate (1.1 mol), and shaking briefly at room temperature: the methylthiopyrimidine usually precipitates, but it may be extracted if it is water-soluble; other *S*-alkylations are not quite so ready and are often done with the appropriate alkyl halide in warm alcoholic alkoxide. Such general procedures, as well as certain variations thereon, are illustrated in the formation of the following alkylthiopyrimidines, in each case from the corresponding pyrimidinethione unless otherwise indicated.

Simple methylthiopyrimidines

2-Methylthiopyrimidine (Me_2SO_4, $NaHCO_3$, H_2O, 20°: 62–83%).[1968,3496]

2-Methyl-4-methylthiopyrimidine (MeI, NaOH, H_2O, 20°: 95%).[690]

4-Methyl-6-methylthio-2-phenylpyrimidine (MeI, K_2CO_3, AcMe, 60°, 15 h, sealed: 99%).[3728]

2-Methyl-4,6-bismethylthiopyrimidine [MeI, 2*M* NaOH, 20°, 15 h: 80%; limited MeI for 15 min gave 2-methyl-6-methylthio-4(3*H*)-pyrimidinethione: 46%].[1778]

2,4-Bismethylthiopyrimidine [MeI, *M* KOH, 20°, 1 h;[968] $Me_2NCH(OMe)_2$, PhMe, reflux, 30 min: 73%[1783]].

5,5-Diethyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedithione (Me_2SO_4, *M* NaOH, 20°, 2 h: > 35%).[5234]

4-Methyl-2-methylthio-1,6-diphenylpyrimidinium iodide (MeI, 120°, 8 h, sealed: 85%).[4082]

Also other examples.[108,764,958,1508,1951,2114,2697,2702,4053]

Methylthiopyrimidinamines

4-Dimethylamino-2-methylthiopyrimidine (MeI, *M* NaOH, 20°, 30 min: ~ 70%).[1678]

4-Hydrazino-6-methyl-2-methylthiopyrimidine (MeI, *M* NaOH, 20°, 5 min: 88%).[1752]

4-Methyl-6-methylthio-5-pyrimidinamine (MeI, NaOH, H_2O: 72%).[1038]

2-Methylthio-4,6-pyrimidinediamine (Me_2SO_4, 4*M* NaOH, 95°, 1 h: ~ 80%).[2625, cf. 250]

2-Methylthio-6-phenyl-4,5-pyrimidinediamine (MeI, *M* NaOH, 25°, 2 h: 69%).[236]

5-Dimethylaminomethyleneamino-2-methylthiopyrimidine [$Me_2NC(OMe)_2$, PhH, reflux, 30 min: 96%].[3603]

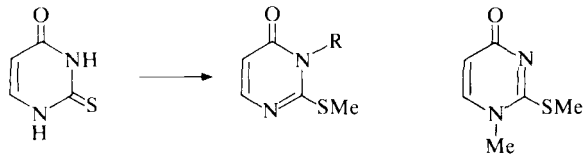
Also other examples.[681,932,958,1046,1379,1400,1507,1508,1520,1743,2115,2413,3373,4286]

Methylthiopyrimidinones

2-Methylthio-4(3*H*)-pyrimidinone (**26**, R = H) (MeI, NaOH, H_2O–EtOH, 60°, 30 min: 63–80%;[1914,3837, cf. 2700] MeI, Me_2NCHO, 25°, 15 h: 82%[1689, cf. 5680]).

3-Methyl-2-methylthio-4(3*H*)- (**26**, R = Me) plus 1-methyl-2-methylthio-4(1*H*)-pyrimidinone (**27**) from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**25**) (Me_2SO_4, 5*M* NaOH, 50–70°, 1 h: ~ 37% each);[1432] or only the first product [$Me_2NCH(OMe)_2$, PhMe, reflux, 1 h].[1783]

2-Butyl-6-methylthio-4(3*H*)-pyrimidinone (MeI, 0.4*M* NaOH, 25°, 2 h: 93%).[2186]



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5-Methyl-2-methylthio-4(3*H*)-pyrimidinone (MeI, NaOMe, MeOH, reflux, 16 h: 61%).[2106]

2,5-Bismethylthio- from 5-methylthio-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (MeI, NaOMe, MeOH, 20°, 2 h: 88%).[1789]

5-(6′-Methylpyridin-3′-yl)methyl-2-methylthio-4(3*H*)-pyrimidinone (MeI, NaOH, H_2O–EtOH, 50°, 3 h: ~ 70%).[322]

3-Methyl-6-methylthio-4(3*H*)-pyrimidinone (MeI, 0.2*M* NaOH, 20°, 1 h: ~ 90%).[3348]

2-Methylthio-4,6(1*H*,5*H*)-pyrimidinedione (Me_2SO_4, 2*M* NaOH, 25°, 3 h: ~ 70%).[958, cf. 1764]

Also other examples.[89,227,544,806,930,958,1046,1058,1167,1319,1508,1550,2147, 2237,2702,2888,3148,3528,3837,4108,4163,4178,5430,6173]

Amino(methylthio)pyrimidinones

2-Amino-6-methylthio-4(3*H*)-pyrimidinone (MeI, *M* NaOH, 25°, 3 h: > 80%).[958]

4-Amino-6-methylthio-2(1*H*)-pyrimidinone (Me_2SO_4, 1.5*M* NaOH, 95°, 1 h: > 95%).[1568]

6-Methylamino-2-methylthio-4(3*H*)-pyrimidinone (Me_2SO_4, KOH, H_2O, 25°, 2 h: 83%).[3872]

5-Amino-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione (MeI, 2.5*M* NaOH, 25°, 1 h: 73%).[3988]

6-Amino-1-methyl-2-methylthio-4(1*H*)-pyrimidinone (MeI, K_2CO_3, AcMe, 25°, 66 h: 42%;[1116] MeI, *M* NaOH, reflux, 3 h: 88%[1425]).

Also other examples.[1015,1038,1358,1570,6944]

Methylthiopyrimidinecarboxylic acids and derivatives

2-Methylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid (Me_2SO_4, NaOH, H_2O, 25°, 2.5 h: 48%).[2873]

2-Amino-6-methylthio-4-pyrimidinecarboxylic acid (MeI, *M* NaOH, 20°, 5 h: 69%).[1030]

2-Amino-4-methylthio-5-pyrimidinecarbonitrile (MeI, NaOMe, MeOH, 20°, 2 h: 73%).[1223]

4-Benzyl-6-methylthio-2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile (MeI, NaOMe, MeOH, 20°, 6 h: 70%).[31]

Ethyl 4-amino-2-methylthio-5-pyrimidinecarboxylate (Me_2SO_4, KOH, H_2O, 70°, 2 h: 77%).[2974]

5-Ethoxycarbonylmethyl-2-methylthio-4(3*H*)-pyrimidinone (MeI, 0.5*M* NaOH, 5°, 15 h: 90%).[2007]

Also other examples.[370,796,958,1030,2973,3875,3942,4423,6009]

Halogeno(methylthio)pyrimidines and derivatives

5-Bromo-2-methylthiopyrimidine (MeI, $NaHCO_3$, H_2O, 20°, 6 h: ~ 90%).[1951]

4-Chloro-6-methylthio-2-pyrimidinamine (MeI, *M* NaOH, 25°, 3 h: > 80%).[958]

4-Chloro-2-dimethylamino-6-methylthiopyrimidine (MeI, 0.5*M* NaOH, 20°, 10 min: ~ 90%).[1507]

5-Fluoro-4-methylthio-2(1'*H*)-pyrimidinone (MeI, NaOMe, MeOH, 20°, 4 h: 79%).[2699]

5-Bromo-4,6-bismethylthiopyrimidine (MeI, *M* NaOH, 25°, 3 h: > 80%).[958]

Also other examples.[958,1782,2699]

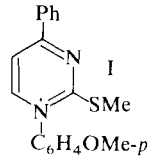
Other substituted methylthiopyrimidines

5-Acetyl-2,4-dimethyl-6-methylthiopyrimidine (MeI, NaOH, H_2O, 20°, 2 h: 86%).[4423]

5-Acetyl-4-methyl-6-methylthio-2-naphthalen-1'-ylpyrimidine (MeI, Na_2CO_3, H_2O, reflux, 10 min: 90%).[3990]

4-Methoxy-6-methylthiopyrimidine (MeI, 0.2*M* NaOH, 20°, 90 min: ~ 70%).[3348]

1-*p*-Methoxyphenyl-2-methylthio-4-phenylpyrimidinium iodide (**28**) (MeI, MeCN, reflux, 3 min: 94%).[6026]



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2-Methylthio-5-nitropyrimidine (MeI, NaOH, H_2O, 20°, 90 min: > 46%).[582, cf. 1951]

4,6-Bismethylthio-5-nitropyrimidine (MeI, *M* NaOH, 20°, 15 min: ~ 40%).[1778]

5-Acetamido-4-methyl-2,6-bismethylthiopyrimidine (MeI, $NaHCO_3$, H_2O, 25°, 30 min: 79%).[676]

4-Methoxy-6-methylthio-5-pyrimidinamine (Me_2SO_4, K_2CO_3, AcMe, 20°, 20 h: 78%).[1017]

2-Methylthio-6-trifluoromethyl-4,5-pyrimidinediamine (MeI, 2*M* NaOH, 20°, 15 min: ~ 90%).[4754]

Also other examples.[903,1191,1319,2973,3958,4102,4121,4887,4891,6015,6733]

Ethylthiopyrimidines and derivatives

4-Ethylthiopyrimidine (EtI, *M* NaOH, 20°, 4 h: ~ 70%).[3144]

2-Ethylthio-5-methoxy-4(3*H*)-pyrimidinone (Et_2SO_4, 4*M* NaOH, 86°, 3 h: 79%).[926]

4-Ethylthio-2-pyrimidinamine (EtI, *M* NaOH, 20°, 3 h: > 80%).[958]

2-Ethylthio-1-methyl-4-pyrimidinimine hydriodide (EtI, MeOH, reflux, 3 h: 81%).[1713]

2-Ethylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (EtI, *M* NaOH, 20°, 5 h: 79%).[1030]

4-Ethylthio-6-methylamino-5-pyrimidinamine (EtI, *M* KOH, 20°, 3 h: > 90%).[3130]

Also other examples.[633,925,932,958, 1030,1218,1358,1515,2133,2157,2700,2854, 2939,3126,3129,3148,4036,5055,5681]

Other alkylthiopyrimidines and derivatives

2-Isopropylthiopyrimidine (Pr^iI, $NaHCO_3$, H_2O, 25°, 24 h: ~50%).[3144]

6-Propylthio-2,4-pyrimidinediamine (PrI, KOH, H_2O–dioxane, 80°, 1 h: ~90%).[932]

2-Isopropylthio-4,6-pyrimidinediamine (Pr^iI, KOH, H_2O–dioxane, 80°, 4 h: 76%).[156]

2-Butylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (BuI, *M* NaOH, 20°, 5 h: 53%).[1030]

6-α-Phenylacetamido-2-propylthio-4-pyrimidinamine (PrI, NaOEt, Me_2NCHO, 60°, 30 min: 56%).[5665]

Also other examples.[925,958,1358]

Benzylthiopyrimidines and derivatives

2-Benzylthio-1,6-dimethyl-4(1*H*)-pyrimidinone ($PhCH_2Cl$, NaOEt, EtOH, reflux, 3 h: 67%).[1915]

2-Benzylthio-4-di(β-hydroxyethyl)aminopyrimidine ($PhCH_2Cl$, NaOH, H_2O–EtOH, 65°, 2 h: 86%).[4945]

2-Amino-6-benzylthio-4-pyrimidinecarboxylic acid ($PhCH_2Cl$, *M* NaOH, 20°, 5 h: 69%).[1030]

6-Amino-2-benzylthio-4(3*H*)-pyrimidinone ($PhCH_2Cl$, NaOH, H_2O–EtOH, reflux, 15 min: 75%).[4804]

2-*o*-Chlorobenzylthio-4-dimethylamino-5-methylpyrimidine (ClH_2C-C_6H_4Cl-*o*, NaOH, H_2O–dioxane, 70°, 3 h: 46%).[2076]

6-Benzylthio-2,4-pyrimidinediamine ($PhCH_2Cl$, K_2CO_3, Me_2NCHO, 60°, 1 h: > 90%).[932]

5-Amino-6-benzylthio-4(3*H*)-pyrimidinethione (limited $PhCH_2Cl$, KOH, H_2O–EtOH, reflux, 15 min: ~80%).[5682]

2-Diphenylmethylthiopyrimidine (Ph_2CHOH, AcOH, reflux, 8 h: 63%).[4363]

Also other examples.[958,961,1218,1301,1305,2698,2700,3139,3148,3615,4827]

Alkenylthio-, alkynylthio-, or arylthiopyrimidines

4-Allylthio-2-amino-6-methylthio-5-pyrimidinecarbonitrile ($CH_2{=}CHCH_2Br$, KOH, Me_2NCHO–H_2O, 25°, 30 min: 69%).[3752,3879]

4,6-Dimethyl-2-(perfluoroprop-1′-enyl)thiopyrimidine ($F_3CCF{=}CF_2$, NEt_3, Me_2NCHO–dioxane, 100°, 7 h, sealed: 50%).[119]

2-Methyl-4-(prop-1′-enyl)thio-5-pyrimidinol ($MeCHBrCH_2Br$, Na_2CO_3, Me_2NCHO, 60°, 4 h: 53%; note the concomitant loss of HBr to afford the alkenylthio product).[42]

2-(Prop-2′-ynyl)thio-4(3*H*)-pyrimidinone ($HC{\equiv}CCH_2Br$, KOH, H_2O, 55°, 2 h: 87%).[6415]

4,6-Bis-*p*-methoxyphenyl-2-thien-2′-ylthiopyrimidine (2-iodothiophene, NaH, Me_2NCHO, Cu, reflux, 12 h: 24%).[5684]

4-(2′,4′-Dinitrophenyl)thio-2,6-dimethoxypyrimidine (1-chloro-2,4-dinitrobenzene, NaOH, EtOH, reflux: ?%).[2071]

2-Vinylthiopyrimidine ($HC{\equiv}CH$, KOH, H_2O–dioxane, 180°, 90 min, sealed: 80%).[3145]

6-(β-Methoxycarbonylvinyl)thio-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione ($HC{\equiv}CCO_2Me$, $CHCl_3$, 25°, 15 h: 85%).[5683]

Also other examples.[917,932,3145,3747,5685]

(Carboxyalkylthio)pyrimidines and derivatives

[*Note*: Although not always necessary, these reactions are best done in the presence of base so that the product does not undergo acidic hydrolysis to the corresponding pyrimidinone (see Section 7.1.1.5).]

2-Carboxymethylthiopyrimidine ($ClCH_2CO_2H$, H_2O, reflux, 30 min: 60%).[764]

2-Carboxymethylthio-4,6-pyrimidinediamine ($ClCH_2CO_2H$, H_2O, reflux, 1 h: 75%).[2402]

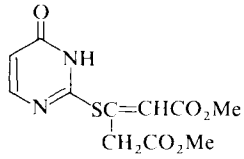
2-Carboxymethylthio-4-oxo-6-phenyl-3,4-dihydro-5-pyrimidinecarbonitrile (K salt of substrate, $ClCH_2CO_2K$, H_2O, reflux, 2 h: 80%).[3875]

2,4,6-Tris(carboxymethylthio)-5-phenylpyrimidine ($ClCH_2CO_2Me$, NaOMe, MeOH, reflux, 30 min; then saponification: 42%).[4362]

6-Amino-2-ethoxycarbonylmethylthio-4-(3*H*)-pyrimidinone ($BrCH_2CO_2Et$, NaOEt, EtOH–Me_2SO, reflux, 4 h: < 95%).[724]

6-Amino-2-di(ethoxycarbonyl)methylthio-4(3*H*)-pyrimidinone [$BrHC(CO_2Et)_2$, NaOH, H_2O, 25°, 10 min: ~55%].[1091]

2-β-Methoxycarbonyl-α-(methoxycarbonylmethyl)vinylthio-4(3*H*)-pyrimidinone (**29**) [$C(=CHCO_2Me)_2$, MeOH, reflux, 13 h: 90% as a separable mixture of *E*- and *Z*-isomers].[3889]



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4-α-Carbamoylethylthiopyrimidine ($MeCHBrCONH_2$, $NaHCO_3$, H_2O, 1 h: 80%).[5687]

4-Carbamoylmethylthio-2-methyl-6-phenylpyrimidine ($ClCH_2CONH_2$, 0.25*M* NaOH, reflux, 1 h: 71%).[234]

2-Cyanomethylthiopyrimidine ($ClCH_2CN$, $NaHCO_3$, H_2O, reflux, 1 h: 82%).[5687]

Also other examples.[96,359,453,1455,1514,2133,2566,2799,3148,3498,4142,4362,4951,5156,5676,5677,5686,5687,6206]

Other (substituted-alkyl)thiopyrimidines

2-Chloromethylthiopyrimidine (neat $ClCH_2Br$, powdered KOH, trace of $PhCH_2Et_3NBr$, 30 min: 58%).[4972, cf, 4971]

4,6-Dimethyl-2 -trifluoromethylthiopyrimidine (F_3Cl, liquid NH_3, reflux, *hv*, 1 h: 82%).[194]

2-β-Aminoethylthiopyrimidine ($BrCH_2CH_2NH_2$, H_2O–Pr^iOH, reflux , 20 h: 40% as dihydrobromide).[3147]

5-Bromo-4-β-dimethylaminoethylthiopyrimidine ($Me_2NCH_2CH_2Cl$, 2*M* NaOH, 25°, 15 h: 53%).[2653]

2-β-Hydroxyethylthio-4,6-dimethylpyrimidine ($ClCH_2CH_2OH$, NaOH, H_2O–PrOH, 95°, 2 h: 74%).[1312]

6-Acetonylthio-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione ($AcCH_2Br$, EtOH, 25°, 30 min: 93% note apparent lack of base).[2838]

6-Methyl-2-phenacylthio-4(3*H*)-pyrimidinone ($BzCH_2Cl$, NaOH, H_2O–EtOH, 95°, 20 min: 70%); also analogs.[3860]

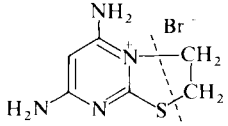
Also other examples.[406,1312,1821,2517,4971,5688]

Bis(pyrimidinylthio)alkanes and fused bicyclic products

Bis(pyrimidin-2-ylthio)methane [Na salt of substrate (2 mol), CH_2Br_2, Me_2NCHO, 20°, 30 min: 95%].[5689]

1,7-Bis(4′,6′-dimethylpyrimidin-2′-ylthio)heptane [Na salt of substrate (2 mol), $Br(CH_2)_7Br$, Me_2NCHO, 30°, 2 h: 90%].[159]

5,7-Diamino-2,3-dihydrothiazolo[3,2-*a*]pyrimidinium bromide (**30**) from sodium 4,6-diaminopyrimidine-2-thiolate [$BrCH_2CH_2Br$ (1 mol), Me_2NCHO, 40°, 1 h: 88%].[159]



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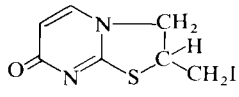

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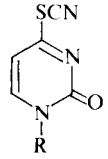
2-Iodomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]-pyrimidin-7-one (**31**) from 1-allyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (I_2, CH_2Cl_2: 79%, presumably via the 1-β,γ-diiodopropyl analog of the substrate).[107]

Also other examples.[107,159,377,906,5689,5690]

Tautomeric pyrimidinethiones also undergo the closely related process of *S-cyanation* to afford thiocyanatopyrimidines. For example, 2(1*H*)-pyrimidinethione gave 2-thiocyanatopyrimidine (BrCN, NaOH, H_2O–EtOH, 10°, 5 min: 82%),[2982] 4-amino-2(1*H*)-pyrimidinethione gave 2-thiocyanato-4-pyrimidinamine (BrCN, NaOH, H_2O–EtOH, 20°, 6 h: 13%),[1713] 4-thioxo-3,4-dihydro- gave 4-thiocyanato-2(1*H*)-pyrimidinone (**32**, R = H) (BrCN, EtOH + pH 9 buffer, 20°, 15 min; ~70%),[3515] and 1-methyl-4-thioxo-3,4-dihydro- gave 1-methyl-4-thiocyanato-2(1*H*)-pyrimidinone (**32**, R = Me) (BrCN, NaOH, H_2O–EtOH, 25°, 1 h: 66%).[3514,3515] Rather similarly, 2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione reacted with phenylcarbamimidoyl chloride [PhNHC(=NH)Cl] to give 2-phenylthiouronio-4,6(1*H*,5*H*)-pyrimidinedione chloride (**33**) (> 70%).[427]



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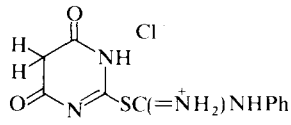

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Pyrimidinethiones also undergo *S-acylation* under gentle conditions, but at higher temperatures they appear to afford *N*-acylpyrimidinethiones. For example, 4,6-diamino-2(1*H*)-pyrimidinethione with benzoyl chloride in dimethylformamide or acetonitrile containing triethylamine at 20° gave 2-benzoylthio-4,6-pyrimidinediamine (80%), whereas the same reactants at 80° gave 4,6-diamino-1-benzoyl-2(1*H*)-pyrimidinethione (93%) and at 120° gave 4-amino-

6-benzamido-2(1*H*)-pyrimidinethione (61%);[5695] 5-amino-2,4(1*H*,3*H*)-pyrimidinedithione with hot acetic anhydride for a few minutes gave 5-acetamido-2,4-bisacetylthiopyrimidine (> 95%), but continued heating for 5 h caused cyclization to 5-acetylthio-2-methylthiazolo[5,4-*d*]pyrimidine (~80%);[626] 2-amino-6-methyl-4(3*H*)-pyrimidinethione gave 4-benzoylthio-6-methyl-2-pyrimidinamine by benzoylation under Schotten–Baumann conditions;[1509] 4,6-dimethyl-2(1*H*)-pyrimidinethione gave *S*,*S*-bis(4,6-dimethylpyrimidin-2-yl)dithiocarbonate ($COCl_2$, NEt_3, CH_2Cl_2, 0°, 1 h: 72%), a good reagent for stimulating the direct esterification of carboxylic acids by alcohols;[259] and 2(1*H*)-pyrimidinethione gave 2-*o*-nitrobenzenesulfenylthiopyrimidine (i.e., 2-*o*-nitrophenyldithiopyrimidine) ($O_2NC_6H_4SCl$-*o*, NaOMe, MeOH: 37%).[4942] Several arsenic and antimony acids have been used to *S*-acylate pyrimidinethiones.[3388]

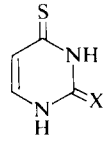
The *S-trialkylsilylation* of pyrimidinethiones occurs readily, although the products have seldom, if ever, been characterized properly. For example, 5-butyl-2,4(1*H*,3*H*)-pyrimidinedithione with hexamethylenedisilazane and ammonium sulfate under reflux for 5 h gave 5-butyl-2,4-bis(trimethylsilylthio)pyrimidine (50% after distillation).[4118]

8.1.3.3. Aminolysis

Tautomeric 4/6-pyrimidinethiones undergo aminolysis much more readily than do the corresponding 2-pyrimidinethiones: the resulting capacity for selective 4-aminolysis of 2,4(1*H*,3*H*)-pyrimidinethiones has proved of great use in synthetic sequences. Like other leaving groups, thioxo substituents are activated by electron-withdrawing substituents and deactivated by electron-donating substituents in the same molecule. The process of aminolysis is illustrated by the following transformations.

From substrates with one thioxo substituent

4-Thioxo-3,4-dihydro- (**34**, X = O) gave 4-methylamino- (**35**, R = NHMe) ($MeNH_2$, MeOH, 105°, 20 h, sealed: 90%),[1542] 4-hydrozino- (**35**, R = $NHNH_2$) (H_2NNH_2, EtOH, reflux, 1 h: 67%),[3226] or 4-β-carboxyethylamino-2(1*H*)-pyrimidinone (**35**, R = $NHCH_2CH_2CO_2H$) [$H_2NCH_2CH_2CO_2H$, H_2O, reflux, 34 h: ~70%; cf. 90% in 2 h from the 4-methylthio substrate (**35**, R = SMe)].[2288]



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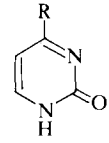

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1-Cyclohexyl-4-thioxo-3,4-dihydro- gave 4-amino-1-cyclohexyl-2(1*H*)-pyrimidinone (NH_3, EtOH, 120°, 20 h, sealed: 76%).[4394, cf. 3622]

4-Methyl-2-oxo-6-thioxo-1,2,3,6-tetrahydro- gave 4-(β-hydroxyethyl)amino-6-methyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxanilide ($HOCH_2CH_2NH_2$, pyridine, reflux, 4 h: 60%).[39]

Ethyl 4-amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate gave 4-amino-2-hydrazino-5-pyrimidinecarbohydrazide (H_2NNH_2, EtOH, reflux, 5 h: 53%; note additional conversion of ester to hydrazide).[447]

5-Hexyl-6-methyl-2-thioxo-1,2-dihydro- gave 5-hexyl-2-hydrazino-6-methyl-4(3*H*)-pyrimidinone (H_2NNH_2, PrOH, reflux, 6 h: 63%).[4171]

5-Ethoxycarbonylmethyl-2-thioxo-1,2-dihydro- gave 2-amino-5-carbamoylmethyl-4(3*H*)-pyrimidinone (NH_3, EtOH, 120°, 15 h, sealed: 54%; note additional conversion of ester to amide).[2007]

Also other examples.[166,770,1533,2147,2686,3537,4108,5231,5232,5691,5692,6201]

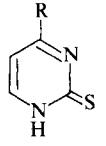
From substrates with two or three thioxo substituents

2,4(1*H*,3*H*)-Pyrimidinedithione (**34**, X = S) gave 4-amino- (**36**, R = NH_2) (NH_4OH, 100°, 16 h, sealed: 91%;[1514] NH_4OH, 100°, 24 h: 66%[1652]), 4-methylamino- (**36**, R = NHMe) ($MeNH_2$, H_2O, 100°, 3.5 h, sealed: 60%),[1515] 4-dimethylamino- (**36**, R = NMe_2) (Me_2NH, H_2O–EtOH, 130°, sealed: ~70%),[708, cf. 1515] 4-butylamino- (**36**, R = NHBu) (neat $BuNH_2$, reflux, 5 h: ~70%),[5677] 4-benzylamino- (**36**, R = $NHCH_2Ph$) (neat $PhCH_2NH_2$, ~95°, 3 days: ~95%),[5694; cf. 1515,5677,5693] or 4-anilino-2(1*H*)-pyrimidinethione (**36**, R = NHPh) (neat $PhNH_2$, reflux, 3 h: 90%);[1515] also analogous products.[1515,3234,4891,4945,4951,5677,5693]

6-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione gave 4-hydrazino-6-methyl-2(1*H*)-pyrimidinethione (H_2NNH_2, EtOH, reflux, 1 h: 80%)[3220, cf. 1752] or α,β-bis(6-methyl-2-thioxo-1,2-dihydropyrimidin-4-ylamino)ethane (H_2N-$CH_2CH_2NH_2$, PhOH, reflux, 2 h: 71%);[618] also analogous products.[1515,3474,4163]

5-Amino-2,4(1*H*,3*H*)-pyrimidinedithione gave 5-amino-4-methylamino-2(1*H*)-pyrimidinethione ($MeNH_2$, H_2O, 130°, 15 h, sealed: 63%);[1380] similar ammonolysis proved unsatisfactory.[1648]

5-Nitro-2,4(1*H*,3*H*)-pyrimidinedithione gave only 2,4-bismethylamino-5-nitropyrimidine (**37**) ($MeNH_2$, H_2O, 100°, 16 h: 50%).[1648]



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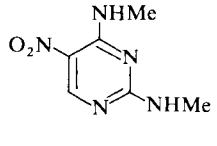

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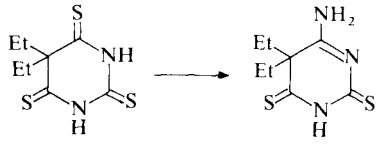
5-*p*-Chlorophenyl-6-ethyl-2,4(1*H*,3*H*)-pyrimidinedithione gave (exceptionally) a separable mixture of 4-amino-5-*p*-chlorophenyl-6-ethyl-2(1*H*)- and 2-amino-5-*p*-chlorophenyl-6-ethyl-4(3*H*)-pyrimidinethione (NH_4OH, 155°, 15 h, sealed: 80% and 20% crude yield, respectively).[5160]

5,5-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrithione (**38**) gave 6-amino-5,5-diethyl-2,4(3*H*,5*H*)-pyrimidinedithione (**39**) (NH_4OH, 95°, 30 min: 60%).[5234]

2,4(1*H*,3*H*)-Pyrimidinediselone gave 4-amino-2(1*H*)-pyrimidineselone (NH_4OH, 100°, 17 h, sealed: 50%).[1506]



38 **39**

8.1.3.4. Hydrolysis

The direct and indirect hydrolysis of pyrimidinethiones to pyrimidinones have been discussed in Section 7.1.1.5.

8.1.3.5. Oxidation

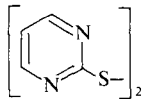
Unlike 5- or extranuclear-pyrimidinethiols, 2- or 4/6-pyrimidinethiones are quite stable in air. However, they can be oxidized to disulfides or to sulfinic or sulfonic acids: in the latter case, hydrolytic conditions must be avoided to obviate subsequent conversion into pyrimidinones as discussed in Section 7.1.1.5.

The conditions for such oxidations are illustrated in the formation of the following products, in each case from the corresponding thione.

To dipyrimidinyl disulfides

Dipyrimidin-2-yl disulfide (**40**) (I_2/KI, $NaHCO_3$, H_2O, 25°: 85%).[1711]

Bis(4-oxo-3,4-dihydropyrimidin-2-yl) disulfide (I_2/KI, NaOH or $NaHCO_3$, H_2O, 5°: ~90%).[5696]



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Bis(2,6-dimethoxypyrimidin-4-yl) disulfide (3% H_2O_2, dioxane, 20°, 30 min: 73%).[2071]

Bis(5-ethoxycarbonyl-6-methyl-2-phenylpyrimidin-4-yl) disulfide (air, NH_4OH, 20°, 24 h:[3150] Br_2, AcOH;[822] note: the products differed appreciably in melting point).

Bis(2,6-diaminopyrimidin-4-yl) disulfide (I_2/KI, pH 6–8, 7°: 80%; HNO_2, AcOH: ?%).[1644]

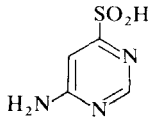
Bis(4,6-diphenylpyrimidin-2-yl) disulfide (HNO_2, AcOH, 25°: > 95%).[4053]

Bis(5-dimethylaminomethyleneaminopyrimidin-2-yl) disulfide (Me_2SO, H^+, 25°, 4 days: 69%).[3603]

Also other examples.[837,841,1509,1533,1568,1778,3417,3514,4423,4588]

To pyrimidinesulfinic acids

6-Amino-4-pyrimidinesulfinic acid (**41**) (H_2O_2, *M* NaOH, 5°, 30 min: 49%).[1568]



41

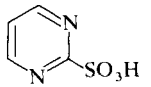
2,6-Diamino-4-pyrimidinesulfinic acid (H_2O_2, *M* NaOH, 5°, 10 min: 45%).[1644]

4,5-Diamino-6-oxo-1,6-dihydro-2-pyrimidinesulfinic acid (H_2O_2, NaOH, H_2O, < 0°, 1 h: 87%;[1692] longer stirring decreased the yield progressively[1595,3870]).

4,6-Diamino- and 4,5,6-triamino-2-pyrimidinesulfinic acid (H_2O_2, 2*M* NaOH, < 20°, 30 min: 95% and 85%, respectively).[2442, cf. 2444]

To pyrimidinesulfonic acids

2-Pyrimidinesulfonic acid (**42**) ($KMnO_4$, H_2O–EtOH, 5°, 10 min: 74% as K salt).[1711]



42

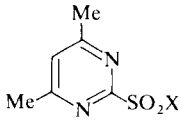
4-Oxo-3,4-dihydro-2-pyrimidinesulfonic acid ($KMnO_4$, pH 7 buffer, 20°, 20 min: ~60%).[3567]

4-Amino-6-oxo-1,6-dihydro-2-pyrimidinesulfonic acid ($KMnO_4$, KOH, H_2O, 25°, 30 min: 73%).[3870]

4-Amino-5-phenyl-2-pyrimidinesulfonic acid (H_2O_2, NaOH, H_2O, 25°, 3 h: 46%).[4262]

6-Imino-1,3-dimethyl-2-oxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid (H_2O_2, AcOH, 25°, 90 min: 85%, probably existing in a zwitterionic form).[1162]

4,6-Dimethyl-2-pyrimidinesulfonyl chloride (**43**, X = Cl) (Cl_2, *M* HCl, 5°, 20 min: 46% as the derived sulfonamide).[2348]



43

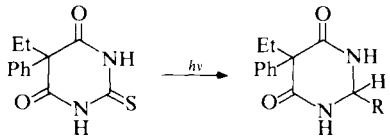
4,6-Dimethyl-2-pyrimidinesulfonyl fluoride (**43**, X = F) (Cl_2, KHF_2, H_2O–MeOH, < −10°, 30 min: 78%).[1711]

Also other examples.[1365,1538,1539,1711,3224,5697]

8.1.3.6. Other Reactions

Pyrimidinethiones form a wide variety of *metal complexes*, exemplified in the Cu, Ni, Co, Fe, Rh, Pd, and Pt chelates from 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone;[5698,5699] Fe, Mo, W, Co, and Ni chelates from 2(1*H*)-pyrimidinethione;[482,492] and a Cd chelate from 4,6-diamino-2(1*H*)-pyrimidinethione.[483]

Prolonged *irradiation* of 5-ethyl-5-phenyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**44**) in propyl alcohol gave 5-ethyl-5-phenyl-2-propoxy-2,3-dihydro- (**45**, R = OPr) (52%), but similar treatment in isopropyl alcohol gave only 5-ethyl-5-phenyl-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**45**, R = H) (32%).[3857]

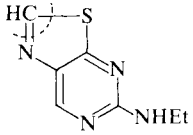


44 **45**

The rarely possible direct conversion of a *pyrimidinethione into a chloropyrimidine* has been exemplified in Section 6.1.2.

The formation of a *dipyrimidinyl sulfide* occurred when 4-methyl-6-phenyl-2(1*H*)-pyrimidinethione was treated with aniline in refluxing butanol for 14 h to give bis(4-methyl-6-phenylpyrimidin-2-yl) sulfide (~40% plus some unchanged thione).[108]

The conversion of pyrimidinethiones into *thiabicyclic products* is possible. For example, 5-amino-2-ethylamino-4(3*H*)-pyrimidinethione in refluxing triethyl orthoformate for 2 h gave 5-ethylaminothiazolo[5,4-*d*]pyrimidine (**46**) (86%);[1195] 3-formamido-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone underwent dehydrative cyclization in refluxing phosphoryl chloride during 30 min to furnish 7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**47**) (66%);[1573] and other such cyclizations have been reported.[476,5046,5679]



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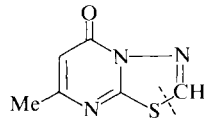


47

The conversion of a pyrimidinethione into a *pyrimidinesulfenamide* (Pym-SNH_2) occurred when 4,6-dimethyl-2(1*H*)-pyrimidinethione was treated with alkaline chloramine at $< 0°$ for 15 min to give 4,6-dimethyl-2-pyrimidinesulfenamide (25%).[1711]

8.2. 5-PYRIMIDINETHIOLS

Few 5-pyrimidinethiols are known; however, like true (nitro) thiophenols, they appear to be moderately acidic and quite easily oxidized in air, even as solids.

8.2.1. Preparation of 5-Pyrimidinethiols

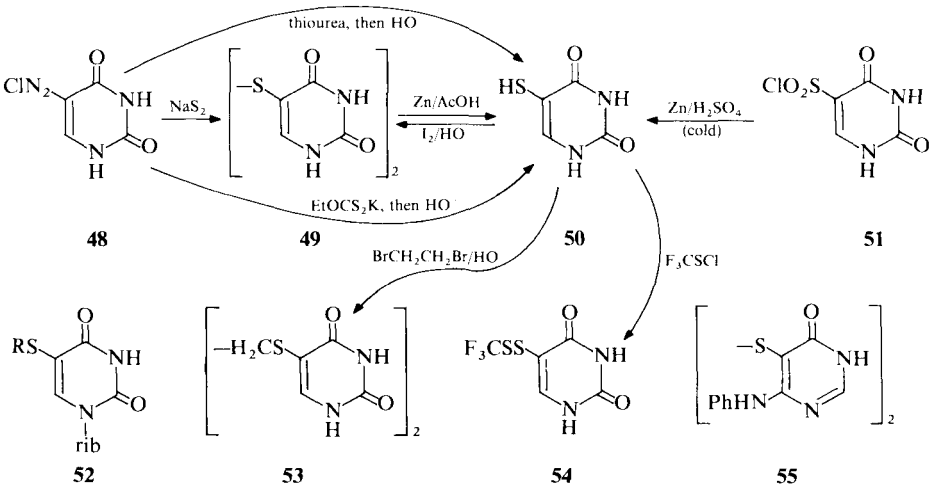
Most of the known 5-pyrimidinethiols have been made either from a diazotized 5-pyrimidinamine or by reduction of a appropriate 5-substituted pyrimidine.

Thus *diazotization* of 5-amino-2,4(1*H*,3*H*)-pyrimidinedione gave a solution of the diazonium chloride (**48**), which was converted into 5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**50**) in one of three ways: (1) treatment with thiourea followed by alkaline hydrolysis of the isothiouronium salt (13% overall), (2) treatment with sodium disulfide followed by reduction of the dipyrimidinyl disulfide (**49**) with Zn/AcOH (25% overall); or (3) treatment with potassium ethyl xanthate followed by alkaline hydrolysis of the product (22% overall).[3319]

The *reductive route* is exemplified by the conversion of bis(2-aminopyrimidin-5-yl) disulfide into 2-amino-5-pyrimidinethiol ($Na_2S_2O_4$, NaOH, H_2O, 60°: 81% after *S*-methylation);[840] of bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) disulfide (**49**) into 5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**50**) (Zn, AcOH, reflux, 3 h: 63%);[3319] of bis(4-anilino-6-oxo-1,6-dihydropyrimidin-5-yl) disulfide

into 6-anilino-5-mercapto-4(3*H*)-pyrimidinone ($NaBH_4$, NaOH, H_2O, warm);[4558] of 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride (**51**) into 5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**50**) (Zn, 20% H_2SO_4, 5°, then warmed: ~50% as Zn salt);[2679, cf. 964] and of 5-thiocyanatouridine (**52**, R = CN) into 5-mercaptouridine (**52**, R = H) ($Na_2S_2O_4$, $HSCH_2CH_2OH$, H_2O, 15 min).[5700]

An oddball reaction was that of bis(1,3-dimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl) sulfide with refluxing acetic anhydride to afford 5-acetylthio-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (71%), not apparently deacylated subsequently.[840]



8.2.2. Reactions of 5-Pyrimidinethiols

5-Pyrimidinethiols undergo reactions to be expected of thiophenols, as indicated briefly in the following paragraphs.

S-Alkylation and acylation. 5-Mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**50**) gave 5-methylthio- (MeI, NaOH, H_2O, 20°, 2–5 h: 69%),[839,3119] 5-butylthio- (BuBr, NaOH, H_2O–EtOH, 20°, 18 h: 73%),[839] 5-prop-2′-ynylthio- ($HC{\equiv}CCH_2Br$, NaOMe, MeOH, 20°, 15 h: 80%),[931] 5-carbamoylmethylthio- (ICH_2CONH_2, *M* NaOH, 20°, 15 h: 89%),[931] and 5-acetylthio2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, pyridine, reflux, 2 h: 72%);[839] the same substrate (**50**) gave α,β-bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylthio)ethane (**53**) [$BrCH_2CH_2Br$ (0.5 mol), NaOH, H_2O, reflux: ~60%];[5701] 6-amino-5-mercapto- gave 5-acetylthio-6-amino-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, reflux, 6 h: < 20%);[837] and 5-mercapto- (**50**) gave the disulfide, 5-trifluoromethanesulfenylthio-2,4(1*H*,3*H*)-pyrimidinedione (**54**) (F_3CSCl, THF, 20°), 15 h: 54%).[4961]

Oxidation. 5-Mercapto-2,4(1*H*,3*H*)-pyrimidinedione (**50**) gave bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) disulfide (**49**) (I_2, *M* NaOH, reflux, 2 h);[3319] 6-anilino-5-mercapto-4-(3*H*)-pyrimidinone gave bis(4-anilino-6-oxo-1,6-dihydropyrimidin-5-yl) disulfide (**55**) (I_2/KI, air, NaOH, H_2O, 25°).[4558]

8.3. EXTRANUCLEAR MERCAPTOPYRIMIDINES

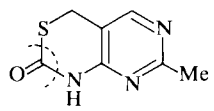
Although relatively little work on mercaptoalkylpyrimidines and the like has been reported, such compounds clearly resemble aliphatic thiols in their preparative methods and reactions.

8.3.1. Preparation of Extranuclear Mercaptopyrimidines

The various methods so far used to make mercaptoalkylpyrimidines are exemplified, albeit inadequately, in the following paragraphs.

By thiolysis. The direct thiolysis of halogenoalkylpyrimidines has proved unsatisfactory, but a few indirect procedures have been used successfully: see Section 6.9.

By primary syntheses. Alkaline degradation of 7-methyl-1,4-dihydro-2*H*-pyrimido[4,5-*d*][1,3]thiazin-2-one (**56**) gave 5-mercaptomethyl-2-methyl-4-pyrimidinamine (~60%);[584] similar treatment of 6-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**57**) gave 1-β-mercaptoethyl-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (> 95%);[4548] and other examples have been given in Chapters 2 and 3.



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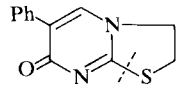

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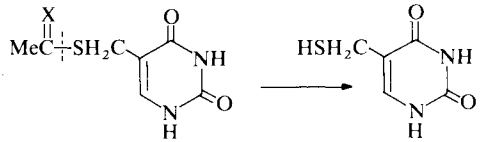
From S-acylated derivatives. The easily made hydrochloride of 5-acetimidoylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**58**, X = NH) underwent deacylation in refluxing methanol during 2 h to give 5-mercaptomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**59**) (84%);[841] alternatively, dissolution of the same hydrochloride of (**58**) in water for a few minutes gave 5-acetylthiomethyl-2,4(1*H*,



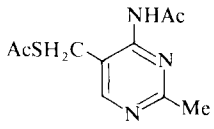
58 **59**

3*H*)-pyrimidinedione (**58**, X = O) (88%) and thence (in aqueous ammonia) the deacylated product (**59**) (51%).[841]

8.3.2. Reactions of Extranuclear Mercaptopyrimidines

Mercaptoalkylpyrimidines appear to undergo reactions expected of aliphatic thiols, as exemplified in the following paragraphs.

S-Alkylation and acylation. 5-Mercaptomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**59**) with methyl iodide in 0.25*M* alkali at 5° for 15 h gave 5-methylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione (64%); similar treatment with ethyl iodide for 48 h gave the 5-ethylthiomethyl homolog (74%).[841] 5-Mercaptomethyl-2-methyl-4-pyrimidinamine with acetic anhydride/sodium acetate gave 4-acetamido-5-acetylthio-2-methylpyrimidine (**60**) (~45%).[584]



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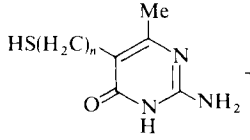
Desulfurization. Treatment of 5-mercaptomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**59**) with 3 parts of Raney-nickel catalyst in boiling aqueous suspension for 3 h gave 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (72%).[841]

To thiabicyclic products. 2-Amino-5-β-mercaptoethyl- (**61**, $n = 2$) or 2-amino-5-γ-mercaptopropyl-6-methyl-4(3*H*)-pyrimidinone (**61**, $n = 3$) underwent dehydrative cyclization in polyphosphoric acid at 95° to give 4-methyl-5,6-dihydrothieno[2,3-*d*]pyrimidin-2-amine (**62**, $n = 2$) (77%) or 4-methyl-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-2-amine (**62**, $n = 3$) (82%), respectively; other analogs were made also.[1359]



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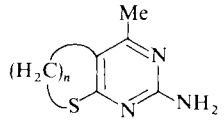

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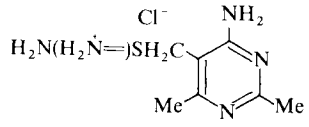

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Oxidation. Several mercaptoalkylpyrimidines (already free or liberated in situ from appropriate derivatives) had been oxidized immediately to the corresponding disulfides. For example, 5-acetylthiomethyl- or 5-mercaptomethyl-2,4(1*H*,3*H*)-pyrimidinedione was aerated in aqueous ammonia for 24 h to give bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylmethyl) disulfide (84% or 78%, respectively);[841] 2,6-dimethyl-5-thiouroniomethyl-4-pyrimidinamine chloride (**63**) was heated for 5 min in *M* alkali and then allowed to stand for 2

days while aerial oxidation occurred to give bis(4-amino-2,6-dimethylpyrimidin-5-ylmethyl) disulfide (83%);[1119] and rather similar sequences (some with H_2O_2 as an additional oxidant) have been reported.[1326,5146]

8.4. ALKYLTHIO- AND ARYLTHIOPYRIMIDINES

Broadly speaking, the position of attachment to the pyrimidine ring makes little difference to the preparation or reactions of alkylthiopyrimidines. However, there is an unique electrophilic preparative route to 5-alkylthiopyrimidines, and the nucleophilic displacement of an alkylthio group occurs more readily from the 2- or 4/6-position than from an extranuclear position or the 5-position. Although dipyrimidinyl sulfides logically belong here, for pragmatic reasons they are discussed with the disulfides in Section 8.6. In this section, the term "alkylthiopyrimidines" is deemed to include arylthiopyrimidines.

8.4.1. Preparation of Alkylthiopyrimidines

The three main ways to prepare such thioethers have been covered already: cross-references to such coverage and discussions of the remaining preparative methods appear in the following subsections.

8.4.1.1. By Primary Syntheses

Extensive use has been made of the Principal Synthesis (Chapter 3) to prepare all types of 2-alkylthiopyrimidines; other primary synthesis (Chapter 2) have also been used to make a variety of these thioethers.

8.4.1.2. By *S*-Alkylation

The *S*-alkylation of 2- or 4/6-pyrimidinethiones has been covered in Section 8.1.3.2; of 5-pyrimidinethiols, in Section 8.2.2; and of (extranuclear) mercaptoalkylpyrimidines, in Section 8.3.2.

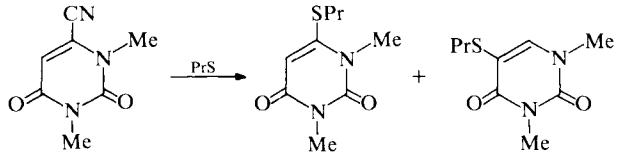
8.4.1.3. By Alkanethiolysis of Halogenopyrimidines

Such alkanethiolysis of 2- or 4/6-halogeno substrates has been discussed in Section 6.7.7; of 5-halogeno substrates, in Section 6.8.3; and of extranuclear halogeno substrates, in Section 6.9.

8.4.1.4. By Other Displacement Reactions

Pyrimidine substrates bearing several other types of leaving group may be used to make thioethers, as illustrated in the following examples.

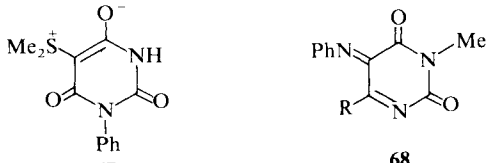
From pyrimidinecarbonitriles. Ethyl 4-cyano-2-methylthio- gave ethyl 2,4-bismethylthio-5-pyrimidinecarboxylate (NaCN, Me_2SO, 90°, 30 min: 32%);[1781] 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**64**) with propanethiolate anion under phase-transfer conditions gave the regular substitution product, 1,3-dimethyl-6-propylthio-2,4(1*H*,3*H*)-pyrimidinedione (**65**) (5%), accompanied by the isomeric *cine*-substitution product (**66**) (38%);[3898] and other examples have been reported.[3898]



64 **65** **66**

From a trimethylammoniopyrimidine. Ethyl 2-methylthio-4-trimethylammonio-5-pyrimidinecarboxylate chloride gave ethyl 2,4-bismethylthio-5-pyrimidinecarboxylate (KCN, $AcNH_2$, 90°, 30 min: 6%, clearly by an unimaginable mechanism).[1781]

From a pyrimidinecarbaldehyde. 4-Chloro-2,6-dioxo-1-phenyl-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde gave 5-dimethylsulfonio-2,6-dioxo-1-phenyl-1,2,3,6-tetrahydro-4-pyrimidinolate (**67**) (Me_2SO, 70°, 7 h: 30%, by a logical mechanism).[181]



67 **68**

From a dialkylaminopyrimidine. 6-(*N*-*p*-bromophenyl-*N*-methylamino)- (**68**, R = $NMeC_6H_4Br$-*p*) gave 6-benzylthio-3-methyl-5-phenylimino-2,4(3*H*,5*H*)-pyrimidinedione (**68**, R = SCH_2Ph) ($PhCH_2SH$, MeCN, 20°, 15 h: 40%; also two minor products).[329]

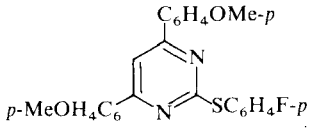
From other alkylthiopyrimidines (transalkanethiolysis). This useful process has been used occasionally. For example, 1-methyl-2-methylthio- gave 2-ethylthio-1-methyl-4-(1*H*)-pyrimidinimine hydriodide (EtSH, 20°, 4 h: 82%);[1713] 2-methylthio- gave 2-octylthio- ($C_8H_{17}SH$, NEt_3, reflux, 3–4 h: 88%)

or 2-phenylthio-4(3*H*)-pyrimidinone (PhSH, likewise: 50%);[933] and 6-methyl-2-methylthio-4(3*H*)-pyrimidinone gave not only the expected 4-acetonyloxy-6-methyl-2-methylthio- (81%) but also 4-acetonyloxy-2-acetonylthio-6-methylpyrimidine (10%), the latter by an obscure mechanism (Na salt of substrate, $ClCH_2Ac$, Me_2NCHO, 30°, 10 h).[5253]

From an alkylsulfonylpyrimidine (by displacement). 2-Ethylsulfonyl-5-fluoropyrimidine gave 2-benzylthio-5-fluoropyrimidine ($PhCH_2SK$, $MeOCH_2CH_2OMe$, 20°, 2 h: 70%).[270]

8.4.1.5. By a Grignard Reaction

A dipyrimidinyl disulfide may be converted into two molecules of an alkylthiopyrimidine by a Grignard reagent. This potentially useful reaction seems to have been used only to transform bis[4,6-bis(*p*-methoxyphenyl)pyrimidin-2-yl] disulfide to 2-*p*-fluorophenylthio-4,6-bis(*p*-methoxyphenyl)pyrimidine (**69**) (*p*-FC_6H_4MgBr, Et_2O, reflux, 1 h: 47%).[5684]



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8.4.1.6. By Reduction of a Sulfone or Sulfoxide

2-Methylsulfonylpyrimidine with hydriodic acid at 95° for 10 min gave 2-methylthiopyrimidine, isolated in ~30% yield; 2-methylsulfinylpyrimidine was also so reduced.[1715]

8.4.1.7. By Attack with Alkanesulfenyl Chlorides

Pyrimidines bearing two or more electron-donating groups are prone to electrophilic attack at their 5-positions by sulfenyl chlorides. The reaction was discovered fortuitously during an attempt to chloromethylate 2,4(1*H*,3*H*)-pyrimidinedione with chloromethyl methyl ether in dimethyl sulfoxide at 20° for 24 h: 5-methylthio-2,4(1*H*,3*H*)-pyrimidinedione (70%) resulted,[2832] clearly due to the formation in situ of methanesulfenyl chloride (MeSCl).[2832] This reaction was improved subsequently,[3133,3509] and the general procedures are further illustrated in the formation of the following products.

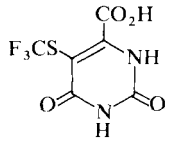
2-Dimethylamino-6-methyl-5-methylthio-4(3*H*)-pyrimidinone (Me_2SO, AcCl, 20°, 15 h: 40%; Me_2SO, $ClCH_2OMe$, 20°, 15 h: 74%; Na salt of substrate, MeSSMe, SO_2Cl_2, CH_2Cl_2, 20°?, 15 h: 91%).[1732]

2,4-Bisdimethylamino-6-methyl-5-methylthiopyrimidine (MeSSMe, SO_2Cl_2, CH_2Cl_2, 20°, 15 h: 93%).[1732]

1,3-Dimethyl-5-trifluoromethylthio-2,4(1*H*,3*H*)-pyrimidinedione (F_3CSCl, pyridine, 20°, 12 h, sealed: 47%).[4973]

4-Amino-5-trifluoromethylthio-4-(3*H*)-pyrimidinone (F_3CSCl, pyridine, 20°, 3 h, sealed: 36%).[4961]

2,6-Dioxo-5-trifluoromethylthio-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (**70**) (F_3CSCl, pyridine, −25°, 40 min: 51%).[4961]



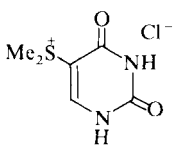
70

5-Isobutylthio-2,4(1*H*,3*H*)-pyrimidinedione (Bu^tSCl, Me_2NCHO, 20°, 15 h: 90%).[3133]

5-Phenylthio-2,4(1*H*,3*H*)-pyrimidinedione (PhSSPh, SO_2Cl_2, $Cl_2CHCHCl_2$, 20°, 15 h: 73%).[3133]

5-Phenylseleno-2,4(1*H*,3*H*)-pyrimidinedione (PhSeSePh, SO_2Cl_2, Cl_2CH-$CHCl_2$–Me_2NCHO, 20°, 1 h: 76%).[3133]

In appropriate circumstances, some sulfenyl chlorides may induce *S*- or *N*-acylations rather than the foregoing *C*5-acylations. Products so formed include, for example, 1,3-bis(trichloromethylthio)-2,4(1*H*,3*H*)-pyrimidinedione (Cl_3CSCl, pyridine, −20°, 30 min: 50%) or 2,4-dimethoxy-6-(*o*-nitrophenyldithio)pyrimidine (*o*-$O_2NC_6H_4SCl$, MeO^-, MeOH–AcMe, 20°, 15 min: 46%).[4942] Another type of exceptional behavior was noticed in the transformation of 2,4(1*H*,3*H*)-pyrimidinedione into 5-dimethylsulfonio-2,4(1*H*,3*H*)-pyrimidinedione chloride (**71**) (~30%) by dimethyl sulfoxide and hydrogen chloride at 70°;[2832] also of 1-phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione into 5-dimethylsulfonio-2,6-dioxo-1-phenyl-1,2,3,6-tetrahydro-4-pyrimidinolate (**67**) (35%) by dimethyl sulfoxide and phosphoryl chloride at 60°.[181]



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8.4.2. Reactions of Alkylthiopyrimidines

Like their oxygen analogs, 2- and 4/6-alkylthiopyrimidines undergo nucleophilic displacement reactions at satisfactory rates, intermediate between those for halogenopyrimidines and pyrimidinethiones; 2-, 4/6-, 5-, and ω-alkylthiopyrimidines all undergo desulfurization and oxidative reactions.

8.4.2.1. Desulfurization

The total removal of alkylthio groups in favor of hydrogen is usually done by stirring with 3–6 parts of Raney-nickel catalyst in refluxing alcohol or water for several hours. For illustration, the following products were so obtained from their indicated alkylthio derivatives.

Pyrimidine (2-SCH_2CO_2H, Na_2CO_3, EtOH–H_2O, 2 h: 14%;[764] 5-Br-2-SMe, NH_3, EtOH, 2.5 h: 38%[1935]).

6-Acetamido-3-methyl-4(3*H*)-pyrimidinone (2-SMe, H_2O, 4 h: ~70%).[659]

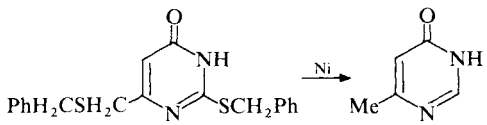
5-Pyrimidinamine from 2-methylthio-5-nitropyrimidine (EtOH, 3 h: 75%).[2321]

5-Amino-4(3*H*)-pyrimidinone (2-SEt, H_2O, 3 h: ~50%).[702]

4-Diethylamino-5-methylpyrimidine [2,6-$(SMe)_2$, dioxane–H_2O, 20 h: 46%].[3840]

1-Methyl-4(1*H*)-pyrimidinone (2-SMe, H_2O, 90 min: 57%).[1432]

6-Methyl-4(3*H*)-pyrimidinone (**73**) from 2-benzylthio-6-benzylthiomethyl-4-(3*H*)-pyrimidinone (**72**) (14 parts Ni, 0.25*M* NaOH, 80°, 1 h: 48%).[3500]



72 **73**

4-Pyrimidinecarboxylic acid (5-Br-2-SMe, H_2O, 2 h: 48% as Ni salt).[1935]

6-Chloro-4-pyrimidinamine (2-SMe, EtOH, 2 h: 51%).[1568,3526]

4-Imino-1-methyl-1,4-dihydro-2-pyrimidinamine (6-SMe/HCl, NH_4Cl, H_2O, 5 h: 64% as hydrochloride).[1520]

4-Benzylaminopyrimidine (2-SCH_2CO_2H, EtOH, 9 h: ~70%).[5677]

4,6-Pyrimidinediamine (2-SMe, EtOH, 3 h: 63%;[3526] 2-$SCH_2CH_2NEt_2$, NH_4OH, 1 h: ~50%[3616]).

6-Methoxy-4-pyrimidinamine (2-SMe, EtOH: 80%;[1570] 2-SMe, H_2O, 3 h: ~35%[659]).

5-Methyl-4-phenyl-2-pyrimidinamine from its 5-CH_2SMe, CH_2SEt, or CH_2SCH_2Ph analog (EtOH, 5 h: > 80% in each case).[4056]

Also other examples.[1090,1101,1136,1262,1292,1379,1383,1400,1764,1879,2264,2625,2756,3117,3126,3409,3498,4178,4804,4891,5160,5676]

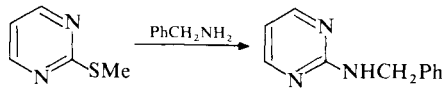
8.4.2.2. Aminolysis

Despite popular belief, alkylthiopyrimidines undergo aminolysis appreciably less readily than do the corresponding alkoxypyrimidines.[4721] Nevertheless, alkylthiopyrimidines are often valuable intermediates for the preparation of pyrimidinamines. The aminolysis of typical simple alkythiopyrimidines has been studied kinetically.[1951,3144] Like the corresponding chloropyrimidines, 4-methylthio- and 4-ethylthiopyrimidine underwent butylaminolysis more rapidly than their respective 2-isomers at several convenient temperatures. However, at 150° 4-methylthiopyrimidine behaved exceptionally in reacting marginally more slowly than did its 2-isomer, simply because the plots of rate constant versus temperature crossed at 163° (isokinetic temperature), and only above that point were the relative rates normal.[3144] Each ethylthiopyrimidine reacted more slowly than did the corresponding methylthio homolog.[3144] The usual substituent effects were evident: electron donation by *C*-methyl groups progressively decreased the rate of aminolysis, but electron withdrawal by a 5-bromo or 5-nitro substituent increased the rate of reaction very markedly.[1951] This was quite impressive on a preparative scale: 4-methyl-2-methylthiopyrimidine with neat butylamine at 180° for 65 h gave a 42% yield of 2-butylamino-4-methylpyrimidine, whereas 2-methylthio-5-nitropyrimidine with butylamine at 20° for 1 min gave a 95% yield of 2-butylamine-5-nitropyrimidine; both figures were in full agreement with calculations using predetermined rate constants.[1951]

An idea of the conditions usually employed (but not necessarily optimal) for aminolyses of alkylthiopyrimidines can be gleaned from the following typical transformations.

Using regular 2-alkylthio substrates

2-Methylthio- (**74**) to 2-benzylaminopyrimidine (**75**) (neat $PhCH_2NH_2$, 215°, 14 h: ~25%).[5705]



74 **75**

2-Methylthio- to 2-morpholino-4(3*H*)-pyrimidinone (neat morpholine, 140°, 2 h: 89%);[3527] 2-ethylthio- to 2-anilino-4(3*H*)-pyrimidinone (neat $PhNH_2$, 100°, 12 h: 66%).[2084]

2-Benzylthio-1,6-dimethyl- to 1,6-dimethyl-2-methylamino-4(1*H*)-pyrimidinone ($MeNH_2$, EtOH, 150°, 12 h, sealed: 98%).[911]

6-Amino-2-methylthio- to 6-amino-2-piperidino- (piperidine.AcOH, 115°, 6 h: 61%)[254] or 6-amino-2-dimethylamino-4-(3*H*)-pyrimidinone (Me_2NH.AcOH, 160°, 1 h: 62%).[1093]

5-Benzamido-2-benzylthio- to 2-anilino-5-benzamido-4(3*H*)-pyrimidinone ($PhNH_2$, AcOH, 170°, 1 h: 98%).[451]

4-Methyl-2-methylthio- to 2-hydrazino-4-methylpyrimidine (H_2NNH_2, EtOH, reflux, 50 h: 20%).[2106]

4-Amino-*N*-methyl-2-methylthio- to 4-amino-2-hydrazino-*N*-methyl-5-pyrimidinecarboxamide ($H_2NNH_2.H_2O$, EtOH, reflux, 15 h: 38%).[447]

5-Methyl-2-methylthio- to 2-amino-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (NH_4OH, 120°, 16 h, sealed: 89%).[1224]

4-Anilino-2-carboxymethylthio- to 4-anilino-2-benzylaminopyrimidine ($PhCH_2NH_2$, reflux, 20 h: 75%).[5676]

5,6-Dimethyl-2-methylthio- to 2-β-diethylaminoethylamino-5,6-dimethyl-4(3*H*)-pyrimidinone (neat $Et_2NCH_2CH_2NH_2$, reflux, 3 h: 98%).[614]

Also other examples.[162,301,322,349,544,847,860,951,1046,1254,1303,1637,1772,1915,2017,2025,2126,2229,2562,2636,2702,2743,2970,3234,4292,4875,4879,5053,5702–5704,5706,6170]

Using regular 4/6-alkylthio substrates

4-Methylthio- to 4-amino- (NH_3, EtOH, 150°, 22 h, sealed: 89%;[721] NH_3, MeOH, 20°, 1 week: >95%[5231]), 4-β-carboxyethylamino- ($H_2NCH_2CH_2CO_2H$, Na_2CO_3, H_2O, reflux, 2 h: 90%),[2288] or 4-hydroxyamino-2(1*H*)-pyrimidinone (H_2NOH.HCl, EtOH, reflux, 5 h: ~30% as hydrochloride).[5430]

4-Methyl-6-methylthio- to 4-*p*-chloroanilino-6-methyl-2(1*H*)-pyrimidinone (neat $H_2NC_6H_4Cl$-*p*, 160°, 3 h: ~75%).[5704]

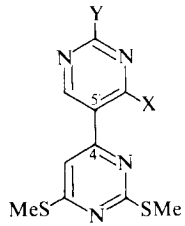
5-Methyl-4-methylthio- to 4-benzylamino-5-methyl- ($PhCH_2NH_2$, BuOH, reflux, 10 h: 85%)[1232] or 4-carboxymethylamino-5-methyl-2(1*H*)-pyrimidinone ($H_2NCH_2CO_2H$, Na_2CO_3, H_2O, reflux, 3 h: 77%).[5708]

5-Fluoro-4-methylthio- to 5-fluoro-4-hydrazino-2(1*H*)-pyrimidinone (H_2NNH_2, H_2O, reflux, 3 h: 67%).[2699]

1-(β-Hydroxyethoxy)methyl-4-methylthio- to 4-amino-1-(β-hydroxyethoxy)methyl-2(1*H*)-pyrimidinone (NH_3, MeOH, 110°, 24 h, sealed: 85%).[5711]

2,2′,4′,6-Tetrakismethylthio- (**76**, X = Y = SMe) to 4′-(β-dimethylaminoethyl)amino-2,2′,6-trismethylthio- (**76**, X = $Me_2NCH_2CH_2NH$, Y = SMe) ($Me_2NCH_2CH_2NH_2$, EtOH, 120°, 4 h, sealed: 51%) or 2′,4′-bis[(β-dimethylaminoethyl)amino]-2,6-bismethylthio-4,5′-bipyrimidine (**76**, X = Y = $Me_2NCH_2CH_2NH$) (similarly but at 140° for 8 h: 38%).[5114]

Also other examples.[1058,5707,5709,5710]



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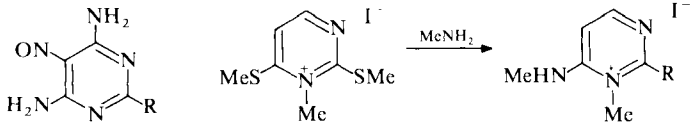
Using activated alkylthio substrates

6-Amino-2-methylthio- to 6-amino-2-morpholino- (morpholine, H_2O, 25°, 90 min: 87%)[1310] or 6-amino-2-(γ-carboxypropyl)amino-5-nitroso-4(3*H*)-pyrimidinone ($H_2NCH_2CH_2CH_2CO_2H$, H_2O, reflux, 1 h: 77%).[4807]

2-Methylthio- (**77**, R = SMe) to 2-dimethylamino-5-nitroso-4,6-pyrimidinediamine (**77**, R = NMe_2) (Me_2NH, H_2O, reflux, 2 min: 85%).[1310]

6-Methylthio- to 6-anilino-5-nitroso-2,4-pyrimidinediamine ($PhNH_2$, $PhNH_2$.HCl, BuOH, reflux, 1 h: 94%).[1768]



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4-*o*-Hydroxyphenyl-6-methyl-2-methylthio- to 2-ethylamino-4-*o*-hydroxyphenyl-6-methyl-5-nitropyrimidine ($EtNH_2$, H_2O, reflux, 2 h: 94%).[565]

4-*m*-Methoxyphenyl-2,6-bismethylthio- to 2,4-dihydrazino-6-*m*-methoxyphenyl-5-pyrimidinecarbonitrile (H_2NNH_2, pyridine, reflux, 3 h: 75%).[6009]

5-Acetyl-4-methyl-2-methylthio- to 5-acetyl-4-methyl-2-piperidinopyrimidine (neat piperidine, reflux, 4 h: 54%).[3031]

1-Benzyl-6-methylthio-2,4-diphenyl- to 1-benzyl-2,4-diphenyl-6-piperidinopyrimidinium tetrafluoroborate (piperidine, MeCN, 20°, 24 h: 98%); debenzylation to 2,4-diphenyl-6-piperidinopyrimidine (61%) occurred in warm piperidine.[3746]

4-Amino-1-methyl-2-methylthio- to 2,4-diamino-1-methylpyrimidinium-iodide (NH_3, MeOH, 20°, 3 h: 87%).[1713]

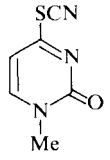
1-Methyl-2,6-bismethylthio- (**78**) to 1-methyl-6-methylamino-2-methylthio- (**79**, R = SMe) ($MeNH_2$, EtOH, 0°, 2 min: 95%) or 1-methyl-2,6-bismethylaminopyrimidinium iodide (**79**, R = NHMe) ($MeNH_2$, EtOH, 60°, 1 h: 91%).[1508]

Also other examples.[88,182,690,806,1077,1512,3046,3496,3955,4163,5712,6008,6026,6143]

8.4.2.3. Other Displacement Reactions

The *hydrolysis* of 2- or 4/6-alkylthiopyrimidines has been discussed in Section 7.1.1.5; the conversion of alkylthiopyrimidines into pyrimidinethiones by *thiolysis*, *thiation*, or *splitting* is covered in Section 8.1.1.

The process of *displacement by thiocyanate ion* has been used to convert 1-methyl-4-methylthio- into 1-methyl-4-thiocyanato-2(1*H*)-pyrimidinone (**80**) (KSCN, MeCN, reflux, 20 h: ~40%).[3515]



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8.4.2.4. Oxidation to Alkylsulfinyl- and Alkylsulfonylpyrimidines

Because both sulfoxides and sulfones arise from oxidation of 2-, 4/6-, 5-, or extranuclear-thioethers, it is understandably easier to make a pure sulfone (by employing slightly over 2 eq of oxidant) than to make the corresponding sulfoxide (by employing 1 eq of oxidant): in the latter case, the product inevitably contains some sulfone and some thioether from which the sulfoxide must be separated, sometimes with appreciable loss. Accordingly, the sulfone is usually preferred to the sulfoxide as a useful intermediate, a fact reflected in the number of each type of product reported.

The reagents, conditions, and yields for oxidation to alkylsulfinyl- and/or alkylsulfonylpyrimidines are illustrated in the formation of the following products.

To sulfoxides

2-Methylsulfinylpyrimidine (0.5*M* $NaIO_4$, 20°, 16 h: ~50%).[1715]

4-Methylsulfinylpyrimidine (*m*-$ClC_6H_4CO_3H$, $CHCl_3$, 0°, 15 h: ~65%).[1715]

5-Phenylsulfinylpyrimidine (*m*-$ClC_6H_4CO_3H$, $CHCl_3$, 0°, 15 h: ~45%).[1715]

5-Methylsulfinyl-2,4(1*H*,3*H*)-pyrimidinedione (H_2O_2, AcOH, 25°, 15 h: 59%;[3119] neat fuming HNO_3: > 50%;[3119] H_2O_2, AcOH–AcMe, < 0°, 15 h: 83%[1789]).

2-Ethylsulfinyl-5-iodopyrimidine (*m*-$ClC_6H_4CO_3H$, CH_2Cl_2, < 0°, 6 h: 92%).[270]

5-Chloro-2-chloromethylsulfinylpyrimidine (*m*-$ClC_6H_4CO_3H$, $CHCl_3$, < 0°, then 20°, 15 h: 73%).[3820]

4,6-Dichloro-2-methylsulfinyl-5-nitropyrimidine (m-$ClC_6H_4CO_3H$, $CHCl_3$, 20°, 15 h: 88%).[3988]

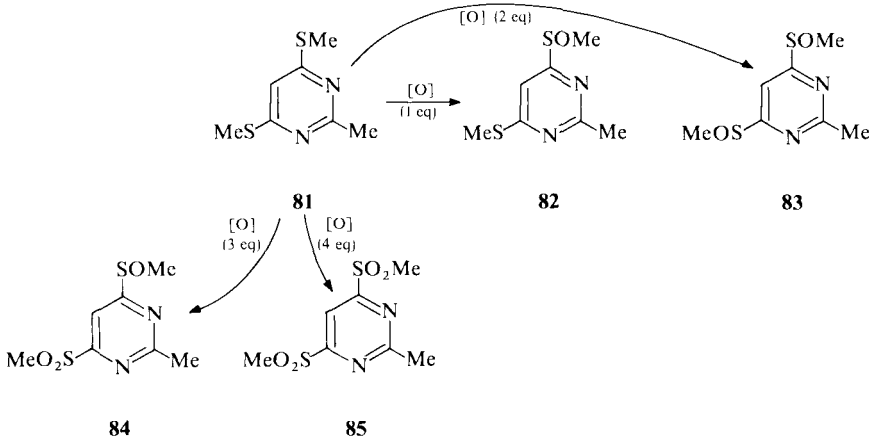
4,6-Dimethyl-2-trifluoromethylsulfinylpyrimidine (m-$ClC_6H_4CO_3H$, $CHCl_3$, 20°, 16 h: 94%).[194]

5-Phenylseleninyl-2,4(1*H*,3*H*)-pyrimidinedione from its 5-phenylseleno analog (m-$ClC_6H_4CO_3H$, F_3CO_2H, − 15° then 20°, 15 h: 66%).[3133]

5-Dimethylaminomethyleneamino-2-methylsulfinylpyrimidine (NaOCl, $NaHCO_3$, H_2O, 15°, 20 min: 76%).[3603]

2-Methyl-4-methylsulfinyl-6-methylthio- (**82**) (97%), 2-methyl-4,6-bismethylsulfinyl- (**83**) (60%), 2-methyl-4-methylsulfinyl-6-methylsulfonyl- (**84**) (80%), or 2-methyl-4,6-bismethylsulfonylpyrimidine (**85**) (60%) [each from substrate **81** with m-$ClC_6H_4CO_3H$ (1,2,3, or 4 eq, respectively), 20°, 48 h].[1778]

Also other examples.[844,903,1732,2291,4581,4961,5094,6133]



To sulfones

2-Methylsulfonylpyrimidine (Cl_2, H_2O, < 5°, 2 h: ~55%);[1715] NaOCl, H_2O, 40°, 90 min: 86%[1897]).

2-Phenylsulfonylpyrimidine (Cl_2, H_2O, < 5°, 2 h: ~70%).[1715]

5-Chloro-2-chloromethylsulfonylpyrimidine [m-$ClC_6H_4CO_3H$, $CHCl_3$, 20°, 15 h: 63%; $MoO_5.(Me_2N)_3PO$, CH_2Cl_2, 20°, 2 h: 53%).[3820]

5-Chloro-4-iodo-2-methylsulfonylpyrimidine (m-$ClC_6H_4CO_3H$, CH_2Cl_2, 4°, 20 h: 87%).[220]

5-Acetyl-2-methylsulfonylpyrimidine (Cl_2, H_2O, 5°, 30 min: 84%).[3741]

5-Benzoyl-2-methylsulfonylpyrimidine (m-$ClC_6H_4CO_3H$, CH_2Cl_2, 20°, 3 h: 90%).[502]

2-Methylsulfonyl-4-phenyl-5-pyrimidinecarbonitrile (Cl_2, H_2O–dioxane, 0°, 15 min: 81%).[43]

5-Bromo-2-methylsulfonyl-4-pyrimidinecarboxylic acid (H_2O_2, AcOH, 20°, 4 days: 75%;[1897] H_2O_2, AcOH, 95°, 2 h: 50%[1954]).

2-Methylsulfonyl-4-tributylstannylpyrimidine (*m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0°, 24 h: 96%).[3929]

4,6-Bismethylsulfonyl-5-pyrimidinamine (*m*-$ClC_6H_4CO_3H$, $CHCl_3$, 20°, 24 h: > 95%).[1778]

5-Methylsulfonylmethyl-4-phenyl-2-pyrimidinamine (H_2O_2, AcOH, 95°, 3 h: 65%).[4056]

6-Phenylsulfonyl-2,4-pyrimidinediamine 3-oxide (**86**) from 6-phenylthio-2,4-pyrimidinediamine or its 3-oxide (H_2O_2, F_3CCO_2H, 20°, 24 h: 60% or 48%, respectively).[2176]

5-Methylsulfonyl-2,4(1*H*,3*H*)-pyrimidinedione (*m*-$ClC_6H_4CO_3H$, F_3CCO_2H, 20°, 15 h: > 90%;[3509] AcO_2H, AcOH, 5–20°, 12 h: 88%;[1789] $KMnO_4$, AcOH–H_2O, 25°, 10 min: 45%[3119]).

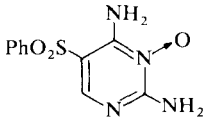
5-Trifluoromethylsulfonyl-2,4(1*H*,3*H*)-pyrimidinedione (CrO_3, 66% H_2SO_4, 150°, 2 h: 58%).[4961]

2-Dimethylamino-6-methyl-5-methylsulfonyl-4(3*H*)-pyrimidinone ($KMnO_4$, AcOH–H_2O, 25°, 1 h?: 58%).[1732]

4-Ethoxy-2-ethylsulfonylpyrimidine (NaOCl, H_2O, < 0°, then 20°, 30 min: 65%).[828, cf. 2162]

2-Methylsulfonyl-5-nitropyrimidine (Cl_2, H_2O, < 5°, 2 h: 48%).[3228]

6-Amino-5-carboxymethylsulfonyl-3-ethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione (**87**) (AcO_2H, AcOH, H_2O, 15°, 1 h: 76%).[4581]



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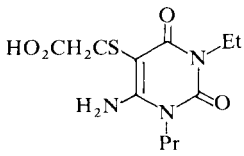

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4-Benzylsulfonyl-2,6-dimethoxypyrimidine (H_2O_2, HCO_2H, 20°, 3 h: 73%).[5087]

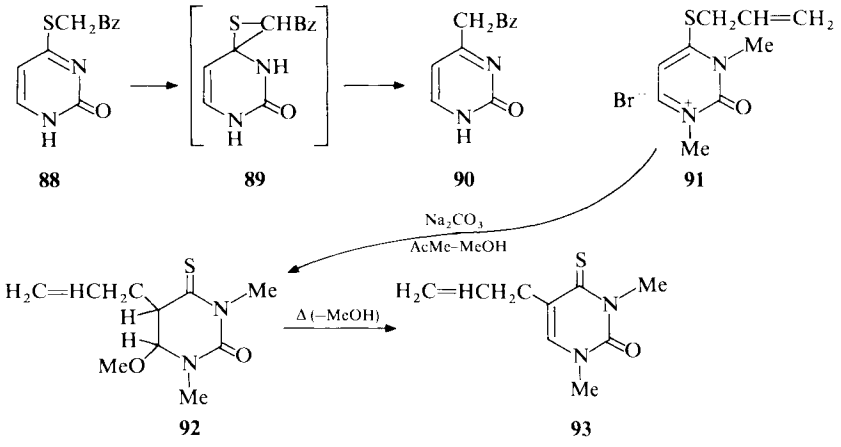
2-Methylsulfonyl-5-pyrimidinol (H_2O_2, H_2O, 20°, briefly: 69%).[2599]

Also many other examples.[194,379,577,724,739,774,844,903,958,1059,1091,1155,1567,1631,1676,1715,1748,1749,1778,1784,1816,2043,2070,2114,2142,2156,2160,2162,2192,2203,2240,2289,2600,3119,3120,3268,3603,3988,4027,4249,4322,5056,5088,5094,5098,5713,5714,6133]

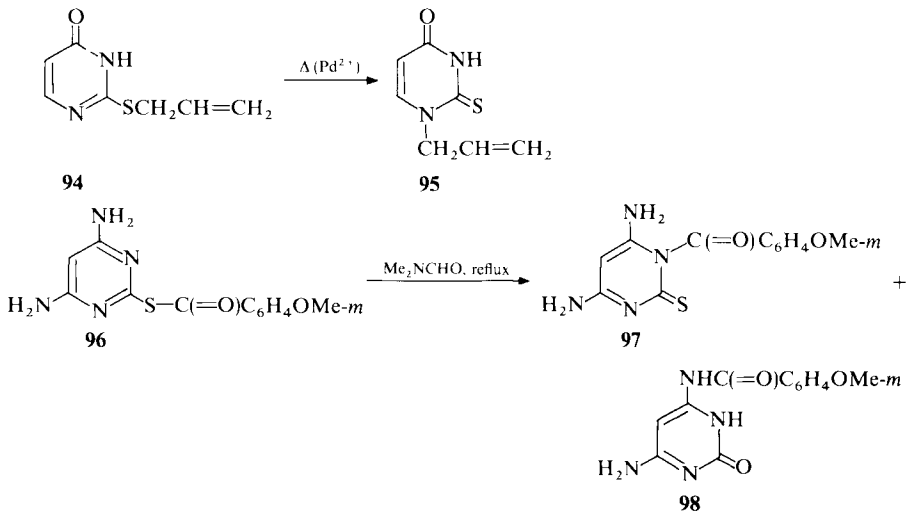
8.4.2.5. Miscellaneous Reactions

Alkylthiopyrimidines undergo several other reactions, illustrated briefly in the following paragraphs.

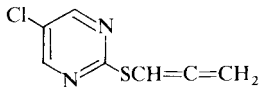
Sulfur extrusion. 4-Phenacylthio-2(1*H*)-pyrimidinone (**88**) gave 4-phenacyl-2(1*H*)-pyrimidinone (**90**) (64%) by refluxing in β-methoxyethanol for 30 min, probably via the episulfide (**89**);[744] other phenacylthio and substituted-phenacylthio substrates behaved similarly.[472,744]



Isomerizations. 4-Allylthio-1,3-dimethyl-2-oxo-2,3-dihydropyrimidinium bromide (**91**) underwent a sulfur–Claisen rearrangement at 25° in acetone–methanol containing sodium carbonate to give the methanol adduct (**92**), which lost methanol in refluxing chloroform to afford 5-allyl-1,3-dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidnone (**93**) (75% overall).[896] In contrast, 2-allylthio-4 (3*H*)-pyrimidinone (**94**) underwent an *S* → *N*-allylic rearrangement on refluxing for 4 h in tetrahydrofuran containing a Pd^{2+} catalyst



$[PdCl_2(PdCN)_2]$, to give a mixture (96%) containing mainly 1-allyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**95**) with < 10% of its 3-allyl isomer.[89] Rather similarly, 2-*m*-methoxybenzoylthio-4,6-pyrimidinediamine (**96**) underwent successive (?) isomerizations on refluxing in dimethylformamide for 5 min to give a separable mixture of 4,6-diamino-1-*m*-methoxybenzoyl-2(1*H*)-pyrimidinethione (**97**) (30%) and 4-amino-6-*m*-methoxybenzamido-2(1*H*)-pyrimidinethione (**98**) (63%). [5665] Quite differently, 5-chloro-2-prop-2′-enylthio- gave its isomer, 2-allenylthio-5-chloropyrimidine (**99**) (54%), on treatment with potassium *t*-butoxide in *t*-butyl alcohol at 20° for 90 min.[844]



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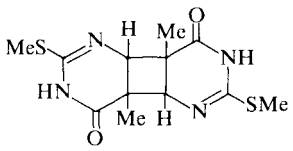

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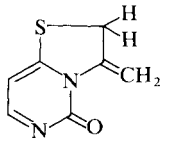

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Photodimerization. Photoylsis of 5-methyl-2-methylthio-4(3*H*)-pyrimidinone in acetone gave the "cyclobutane" dimer (**100**), identified by acidic hydrolysis to a known dimer of thymine.[5715]

Cyclizations. 4-Prop-2′-ynylthio-2(1*H*)-pyrimidinone underwent cyclization in refluxing α,β-dimethoxyethane containing a catalyst $[PdCl_2.(PdCN)_2]$ to give 3-methyl-5*H*-thiazolo[3,2-*c*]pyrimidin-5-one (88% net yield), formulated as its methylene tautomer (**101**); analogs behaved similarly.[276]

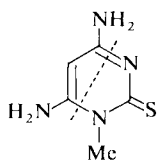
8.5. NONTAUTOMERIC (FIXED) PYRIMIDINETHIONES

Alkylation or acylation of a tautomeric pyrimidinethione almost invariably gives an *S*-alkyl or *S*-acyl derivative rather than a fixed *N*-alkyl- or *N*-acylpyrimidinethione. Fortunately, *N*-alkylated 4/6-pyrimidinethiones may be made by thiation and *N*-alkylated 2-pyrimidinethiones are available quite readily by the Principal Synthesis; otherwise, fixed pyrimidinethiones would indeed be rare.

8.5.1. Preparation of Fixed Pyrimidinethiones

By the Principal Synthesis. The condensation of *N*-alkylated thioureas with a range of C—C—C fragments to give 1-alkyl-2(1*H*)-pyrimidinethiones has been covered in Chapter 3. For example, malononitrile and *N*-methylisothiourea in refluxing ethanolic ethoxide for 6 h gave 4,6-diamino-1-methyl-2(1*H*)-pyrimidinethione (**102**) (23%).[1575]

By other primary syntheses. A few fixed pyrimidinethiones have been made by the primary syntheses discussed in Chapter 2. For example, 1-anilino-2-benzimidoyl-1-phenylpropene (**103**) with carbon disulfide at 70° for 7 h in a



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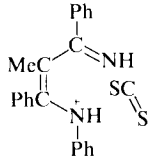

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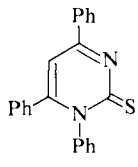

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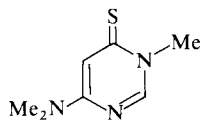
sealed vessel gave a separable mixture of 5-methyl-1,4,6-triphenyl-2(1*H*)-pyrimidinethione (**104**) (64%) and a triazine by-product.[5716]

By thiation of fixed pyrimidinones. This useful process has been discussed in Section 7.5.2. For example, 3-methyl-4(3*H*)-pyrimidinone with phosphorus pentasulfide in refluxing pyridine for 90 min gave the corresponding thione (71%).[3480]

By (exceptional) N-alkylation/acylation. This unusual route to fixed pyrimidinethiones is illustrated in the conversion of 4-dimethylamino-1-methyl-6-methylthiopyrimidinium iodide into 6-dimethylamino-3-methyl-4(3*H*)-pyrimidinethione (**105**) (NaHS, EtOH, reflux, 90 min: ~30%);[1743] in the condensation of thiourea with an excess of ethyl acrylate in ethanolic ethoxide to afford 2-thioxo-1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone (**106**, R = H) (unisolated) and thence (by *N*-alkylation with a second molecule of ethyl acrylate) 1-*β*-ethoxycarbonylethyl-2-thioxo-1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone (**106**, R = $CH_2CH_2CO_2Et$) in good overall yield;[349] and in the conversion of 4,6-diamino-2(1*H*)-pyrimidinethione into 4,6-diamino-1-benzoyl-2(1*H*)-pyrimidinethione (**107**) (BzCl, MeCN, 80°: 93%; possibly via the *S*-benzoyl isomer: see Section 8.1.3.2).[5695]



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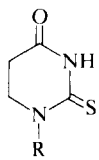

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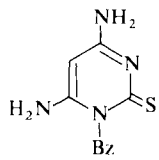

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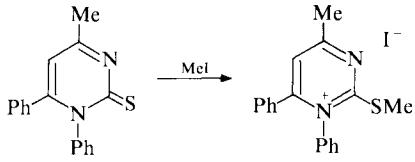
By S → N rearrangement. The palladium-catalyzed thermal conversion of an alkylthio- or acylthiopyrimidine into the isomeric *N*-alkyl- or *N*-acylpyrimidinethione has been exemplified in Section 8.4.2.5. The reported uncatalyzed isomerization of 2-methylthio-4(3*H*)-pyrimidinone to 1-methyl- and 3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone at 200° cannot be classed as preparative.[1689]

8.5.2. Reactions of Fixed Pyrimidinethiones

Only a few reactions of nontautomeric pyrimidinethiones have been reported, as illustrated in the following paragraphs.

S-Alkylation. It is quite possible to *S*-alkylate a fixed pyrimidinethione in order to provide an alkylthiopyrimidinium halide or other such product. For example, 4-methyl-1,6-diphenyl-2(1*H*)-pyrimidinethione (**108**) gave 4-methyl-2-methylthio-1,6-diphenylpyrimidinium iodide (**109**) (MeI, 120°, 8 h, sealed: 85%);[4082] 1,5-diphenyl-4(1*H*)-pyrimidinethione gave 4-methylthio-1,5-diphenylpyrimidinium sulfate (Me_2SO_4, MeCN, reflux, 2 min: 46%, isolated as perchlorate);[387] and 1-anilino-4-phenyl-2(1*H*)-pyrimidinethione gave 1-anilino-2-methylthio-4-phenylpyrimidinium iodide (MeI, MeCN, reflux until clear: 95%).[6008]

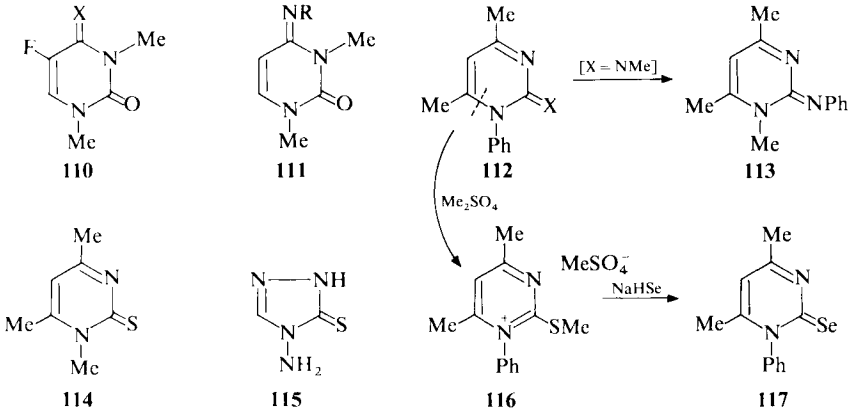


108 **109**

To fixed pyrimidinones. Although direct hydrolysis is inapplicable, indirect hydrolysis via an isolated or unisolated alkylthiopyrimidinium intermediate is possible. This procedure and some other specialized processes are exemplified in Section 7.5.1.

To (fixed) pyrimidinimines. This little-used route to pyrimidinimines is illustrated by the conversion of 5-fluoro-1,3-dimethyl-4-thioxo- (**110**, X = S) into 5-fluoro-4-imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone (**110**, X = NH) (NH_3, EtOH, 115°, 40 h, sealed: 60%);[2619] of 1,3-dimethyl-4-thioxo- into 4-hydrazono-1,3-dimethyl- (**111**, R = NH_2) or 4-hydroxyimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone (**111**, R = OH) (H_2NNH_2 or H_2NOH, EtOH, reflux, 90 min or 4 h: 65% or 70%, respectively);[3225] and of 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinethione (**112**, X = S) into 1,4,6-trimethyl-2-phenylimino-1,2-dihydropyrimidine (**113**), via Dimroth rearrangement of the unisolated primary product (**112**, X = NMe) ($MeNH_2$, MeOH, $AgClO_4$, 25°, 15 h: 48% as perchlorate).[5717] Hydrazinolysis of 1,4,6-trimethyl-2(1*H*)-pyrimidinethione (**114**) proved to be an even more complicated reaction by affording at least 2-hydrazono-4,6-dimethyl-1,2-dihydro-1-pyrimidinamine, 3,5-dimethylpyrazole, and 4-amino-5-hydrazino-3*H*-1,2,4-triazole-3(2*H*)-thione (**115**) by rational mechanisms;[3238] such reactions have been explored further,[1575] and the formation of the triazolethione (**115**) has been developed into a practical general method for detecting acyclic or heterocyclic thioureido groupings.[5718]

To fixed pyrimidineselones. Like the fixed pyrimidinones just mentioned, fixed pyrimidineselones may be obtained from the corresponding pyrimidinethiones by indirect means. For example, treatment 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinethione (**112**, X = S) with warm dimethyl sulfate gave the crude 4,6-dimethyl-2-methylthio-l-phenylpyrimidinium salt (**116**), which was then allowed



to react with refluxing ethanolic sodium hydrogen selenide for 1 h to give 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidineselone (**117**) (89% overall); several analogs were made similarly.[3986]

Reductions. Ring reduction of fixed pyrimidinethiones has been achieved without affecting the sulfur substituent: for example, reduction of 4,6-dimethyl-1-*o*-tolyl-2(1*H*)-pyrimidinethione with $LiAlH_4$, $LiBH_4$, or $NaBH_4$ gave a mixture (83–95%) consisting of approximately equal parts of its 3,4-dihydro, 3,6-dihydro, and 3,4,5,6-tetrahydro derivatives; the ratio of products was affected by the nature of the substituent on the phenyl ring and sometimes by the reagent used.[566] However, Raney-nickel desulfurization of ethyl 1-benzyl-2,6-dimethyl-4-thioxo-1,4-dihydro-5-pyrimidinecarboxylate necessarily involved nuclear reduction to afford ethyl 1-benzyl-2,6-dimethyl-1,4-dihydro-5-pyrimidinecarboxylate (44%),[320] whereas Raney-nickel (under the usual conditions) was able to desulfurize the dihydro substrate, ethyl 4-methyl-3,6-diphenyl-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate, to ethyl 4-methyl-3,6-diphenyl-3,6-dihydro-5-pyrimidinecarboxylate with no further nuclear reduction; several analogs behaved similarly.[370,6292]

8.6. DIPYRIMIDINYL DISULFIDES AND SULFIDES

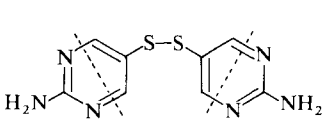
Most known examples of such disulfides and sulfides are symmetrical, but naturally it is possible to make unsymmetrical analogs, at least by some of the methods available. As will be seen, some methods that lead logically to disulfides occasionally afford sulfides and vice versa.

8.6.1. Preparation of Dipyrimidinyl Disulfides

Most of the reported disulfides have been made by oxidation, but several other methods are available, as indicated in the following paragraphs.

By oxidation. The oxidation of tautomeric pyrimidinethiones, 5-pyrimidinethiols, and (extranuclear) mercaptoalkylpyrimidines to their respective disulfides has been discussed in Sections 8.1.3.5, 8.2.2, and 8.3.2, respectively.

By primary syntheses. Primary syntheses have been used to make a few disulfides (see Chapters 2 and 3). For example, bis(β-diethylamino-α-formylvinyl) disulfide and guanidine in methanolic methoxide at 20° for 15 h gave bis(2-aminopyrimidin-5-yl) disulfide (**118**) (76%);[840] and irradiation of 4,6-dimethyl-1,2,3-thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**119**) gave bis(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) disulfide (50%).[1134]



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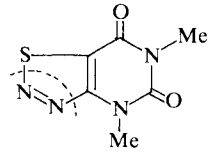

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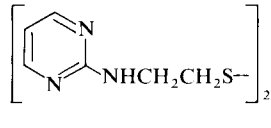

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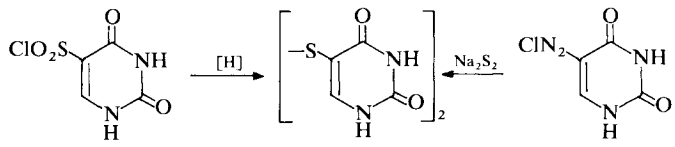
From halogenopyrimidines. The transformation of a halogenopyrimidine to a dipyrimidinyl disulfide is best done by formation of the corresponding thione or thiol, followed by oxidation. However, a direct route is available, as in the conversion of 2-(β-chloroethyl)aminopyrimidine into bis[β-(pyrimidin-2-ylamino)ethyl] disulfide (**120**) (Na_2S_2, EtOH–H_2O, 60°, 3 h: 40%)[4942] or of 6-amino-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione into bis(4-amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) disulfide (Na_2S_2, EtOH, reflux, 8 h: >100%!).[956] An unreliable semidirect route is illustrated in the conversion of 5-bromo- or 5,5-dibromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione into 5-amidinothio-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione [$(H_2N)_2CS$, EtOH, 95°, 30 min: ~90%], which underwent rapid alkaline hydrolysis to bis(2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl) disulfide;[964] attempts to use this procedure on similar substrates often gave a sulfide rather than a disulfide.[961,964,1427]

By reduction. Pyrimidinesulfonyl chlorides have been reduced to disulfides. Thus 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride (**121**) gave bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) disulfide (**122**) (limited Zn, dilute H_2SO_2, reflux, 4 h: 82%),[2679, cf. 964] but a similar reductive process affording bis(4-amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) disulfide was never optimized.[964]

From thiocyanatopyrimidines. Dissolution of 2-amino-6-phenyl-5-thiocyanato-4(3*H*)-pyrimidinone in 2.5*M* sodium hydroxide for 15 h gave bis-

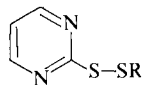


121 **122** **123**

(2-amino-4-oxo-6-phenyl-3,4-dihydropyrimidin-5-yl) disulfide (> 95%);[3137] rather similar processes gave bis(2-amino-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl) disulfide (90%),[5719] bis(4-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) disulfide (51%),[5719] and bis(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl) disulfide (~50%).[2387]

From a pyrimidinediazonium salt. The diazonium salt (**123**) from 5-amino-2,4(1*H*,3*H*)-pyrimidinedione reacted with alkaline sodium disulfide at 0–20° to give bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) disulfide (**122**) (39%).[3319]

By appropriate S-acylation of pyrimidinethiones. This procedure has considerable potential for the formation of unsymmetrical disulfides. As illustration, 2(1*H*)-pyrimidinethione with *o*-nitrobenzenesulfenyl chloride in methanolic methoxide at 25° gave 2-*o*-nitrophenyldithiopyrimidine (**124**, R = $C_6H_4NO_2$-*o*) (37%);[4942] the same thione with dimethyl-*S*-methylthiosulfonium tetrafluoroborate ($Me_2\overset{+}{S}$–SMe BF_4^-) in nitromethane containing a tertiary base at 30° gave 2-methyldithiopyrimidine (**124**, R = Me) (71%).[5720]



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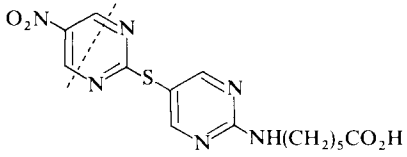
8.6.2. Preparation of Dipyrimidinyl Sulfides

The preparative methods appropriate to alkylthiopyrimidines (Section 8.4.1) can naturally be used to make both symmetrical and unsymmetrical dipyrimidinyl sulfides. The following paragraphs illustrate those commonly used as well as a more specialized procedure.

By primary syntheses. Relevant primary syntheses (covered in Chapters 2 and 3) include, for example, the condensation of 5-amidinothio-2-ε-carboxypentylaminopyrimidine with α-nitromalonaldehyde in aqueous piperidine to give the unsymmetrical product, 2-ε-carboxypentylaminopyrimidin-5-yl 5-nitropyrimidin-2-yl sulfide (**125**) (70%);[5135] also the condensation of bis(β-diethylamino-α-formylvinyl) sulfide with guanidine (2 mol) in methanolic methoxide to give the symmetrical product, bis(2-aminopyrimidin-5-yl) sulfide (78%).[840]



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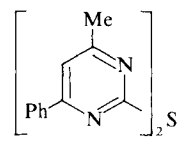

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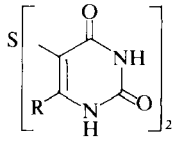
From a halogenopyrimidine with a pyrimidinethione (or thiol). This route is not used often, but it is probably the best for both symmetrical and unsymmetrical sulfides. For example, 2-chloro-4-methyl-6-phenylpyrimidine with 4-methyl-6-phenyl-2(1*H*)-pyrimidinethione in refluxing ethanol for 5 h gave bis(4-methyl-6-phenylpyrimidin-2-yl) sulfide (**126**) (94%);[1856] and 5-chloromethyl- with 5-mercaptomethyl-2,4(1*H*,3*H*)-pyrimidinedione in dimethylformamide at 100° for 3 h gave bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylmethyl) sulfide (> 95%).[841,2271]

By electrophilic attack with sulfur chlorides. Treatment of 2,4(1*H*,3*H*)-pyrimidinedione (or one of a restricted range of its derivatives), usually in boiling formic or glacial acetic acid, with sulfur chloride (S_2Cl_2), sulfur dichloride (SCl_2), or occasionally even thionyl chloride ($SOCl_2$), induces attack at the vacant 5-position with the formation of the corresponding sulfide. The following products were made in this way.

Bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) sulfide (**127**, R = H) (S_2Cl_2: 70%; SCl_2: 35%).[5721]



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Bis(4-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) sulfide (**127**, R = Me) (S_2Cl_2: > 95%).[840]

Bis(2,4-dioxo-6-propyl-1,2,3,4-tetrahydropyrimidin-5-yl) sulfide (**127**, R = Pr) (S_2Cl_2 or SCl_2: ~55%).[5721]

Bis(1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) sulfide S_2Cl_2: 53%; SCl_2: 58%).[5721]

Bis(1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) sulfide S_2Cl_2: 59%; SCl_2: 42%).[5721]

Bis(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) sulfide (S_2Cl_2, PhH, 70°: 38%; SCl_2, PhH, 50°: 75%).[5721]

Bis(4-chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) sulfide (neat S_2Cl_2: 50%).[840]

Bis[4-amino (or 4-anilino)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl] sulfide (S_2Cl_2 in AcOH or light petroleum, respectively: > 90% each).[840]

Bis(1,3-dimethyl-4-methylamino-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl) sulfide (neat $SOCl_2$: 60%; also other products).[2088]

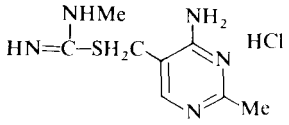
Bis(2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl) sulfide (S_2Cl_2: 33% SCl_2: 48%).[5721]

Bis(1,3-dimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl) sulfide (S_2Cl_2: 94%; neat $SOCl_2$: 60%).[840]

Bis(1,3-diethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl) sulfide (S_2Cl_2 in light petroleum: 93%).[840]

By other routes. Minor routes to dipyrimidinyl sulfides have been used in the following examples.

1. Treatment of 5-chloromethyl-2-methyl- with *N*-methylthiourea gave 2-methyl-5-*N*-methylamidinothiomethyl-4-pyrimidinamine hydrochloride (**128**), which was converted into bis(4-amino-2-methylpyrimidin-5-ylmethyl) sulfide (95%) on treatment in warm aqueous sodium hydrogen carbonate; other *N*-alkylthioureas and thiosemicarbazide proved equally effective in this reaction.[5146] The related bis(2-amino-6-methylpyrimidin-4-yl) sulfide was made rather similarly using unsubstituted thiourea.[961]



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2. 4,6-Dichloro-5-*p*-nitrophenylpyrimidine reacted with ethanolic potassium hydrogen sulfide to afford bis(5-*p*-nitrophenyl-6-thioxo-1,6-dihydropyrimidin-4-yl) sulfide as the only isolable product.[4362]

3. Thermolysis of bis(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) disulfide (in Dowtherm A at 270° for 5 h) gave the corresponding sulfide (32%).[1134]

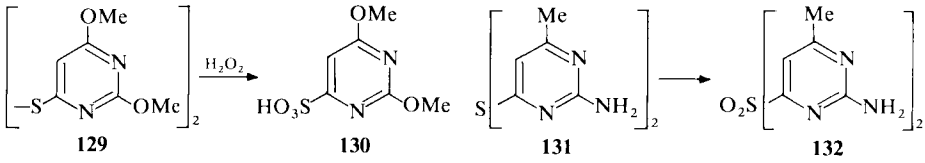
8.6.3. Reactions of Dipyrimidinyl Disulfides and Sulfides

The few reported reactions of disulfides and sulfides are illustrated in the following paragraphs.

Reduction. Although of little practical use, dipyrimidinyl disulfides may be reduced to the corresponding thiones/thiols: see Sections 8.1.1 and 8.2.2. The reported desulfurization of bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylmethyl) disulfide to 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Raney-nickel, H_2O, reflux, 3 h: 71%) probably involved an initial reduction to the 5-mercaptomethyl analog.[841]

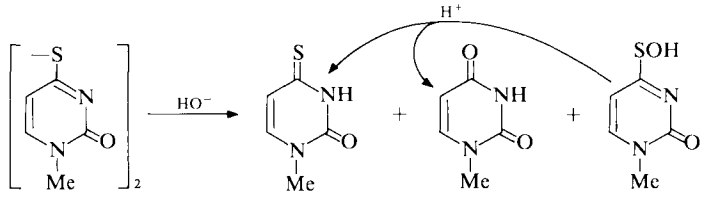
Oxidation. Disulfides are oxidized to pyrimidinesulfonic acids (via sulfinic acids?), but sulfides are oxidized to dipyrimidinyl sulfones (via sulfoxides?). Thus, bis(2,6-dimethoxypyrimidin-4-yl) disulfide (**129**) gave 2,6-dimethoxy-4-pyrimidinesulfonic acid (**130**) (H_2O_2, HCO_2H, 25°, 3 h: 78%);[2071] bis(4-amino-2,6-dimethylpyrimidin-5-ylmethyl) disulfide gave 2,6-dimethyl-5-sulfomethyl-4-

pyrimidinamine (H_2O_2, AcOH, 60°, 8 h: ~75%);[584] bis(2-amino-6-methylpyrimidin-4-yl) sulfide (**131**) gave the corresponding sulfone (**132**) ($KMnO_4$, dilute H_2SO_4);[1427] bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylmethyl) sulfide gave the corresponding sulfone (H_2O_2, F_3CCO_2H, 60°, 30 min: 46%);[841,2271] and 2-ε-carboxypentylaminopyrimidin-5-yl 5-nitropyrimidin-2-yl sulfide (**125**) gave the corresponding sulfone ($KMnO_4$, AcOH: ~60%).[5135]



129 **130** **131** **132**

Cleavage (hydrolysis). The hydrolytic cleavage of a disulfide in alkali has been used to make a pyrimidinesulfenic acid: bis(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl) disulfide (**133**) in 0.1*M* sodium hydroxide at 25° for 1 h gave a separable mixture of 1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**134**), 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**135**), and 1-methyl-2-oxo-1,2-dihydro-4-pyrimidinesulfenic acid (**136**) (isolated in 30% yield as its silver salt and then converted into the free acid).[3417]



133 **134** **135** **136**

8.7. PYRIMIDINESULFONIC AND RELATED ACIDS

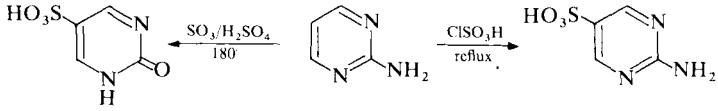
This section outlines the meagre existing knowledge of sulfonic, sulfinic, and sulfenic acids of pyrimidine and of their derived chlorides, esters, amides, and so on.

8.7.1. Preparation of Pyrimidinesulfonic Acids and Some Derivatives

As well as the direct routes to pyrimidinesulfonic acids, this section includes direct preparations of sulfonic acid derivatives from nonsulfonated substrates; the formation of such derivatives from sulfonic acids and their metatheses are considered as reactions (Section 8.7.2).

By sulfonation or halogenosulfonation. The direct sulfonation of pyrimidines with sulfuric acid is virtually unknown apart from the conversion of 2-pyrimi-

dinamine (**138**) into 2-oxo-1,2-dihydro-5-pyrimidinesulfonic acid (**137**) (fuming H_2SO_4, 180°, 5 h: 24%).[845] In contrast, the same substrate (**138**) reacted with an excess of chlorosulfonic acid under reflux during 8 h to afford 2-amino-5-pyrimidinesulfonic acid (**139**) (58%).[869, cf. 845] The rather similar use of chloro- or fluorosulfonic acid (100–160°, 15 min–8 h) to afford pyrimidinesulfonic acids or their halides is illustrated in the formation of the following products.



137 **138** **139**

4,6-Diamino-2-methylthio-5-pyrimidinesulfonic acid (33%).[1101]

2,4-Diamino-6-oxo-1,6-dihydro-5-pyrimidinesulfonic acid (34%).[1101]

2,4-Diamino-6-chloro-5-pyrimidinesulfonic acid (31%).[1101]

2-Amino-4-oxo-3,4-dihydro-5-pyrimidinesulfonic acid (34%).[1449]

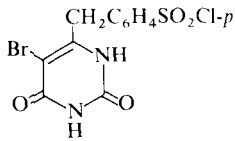
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinesulfonic acid (44%).[1450]

2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride (25–70%).[1450,2679, cf. 964,2516]

2,4-Diamino-6-methyl-5-pyrimidinesulfonyl chloride (36%).[1449]

4-Amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonyl chloride.[1101]

5-Bromo-6-*p*-chlorosulfonylbenzyl-2,4(1*H*,3*H*)-pyrimidinedione (**140**) (63%; *note*—an occupied 5-position induced extranuclear chlorosulfonation).[1962]



140

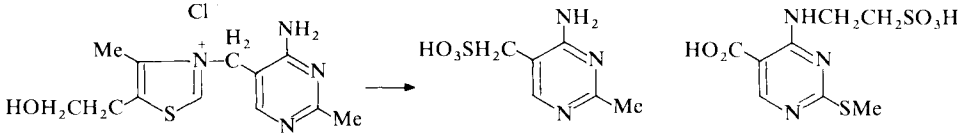
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl fluoride (92%).[1608]

Also other examples in the foregoing references and elsewhere.[249,1348]

By oxidation. The oxidation of pyrimidinethiones and dipyrimidinyl disulfides to the corresponding pyrimidinesulfonic acids or their halides has been covered in Sections 8.1.3.5 and 8.6.3. In addition, 2,6-dimethoxy-4-pyrimidinesulfenamide underwent permanganate oxidation at 30° during 15 min to give the corresponding sulfonamide (64%).[2070]

By displacement reactions. The formation of pyrimidinesulfonic acids from 2- or 4/6-halogenopyrimidines, from extranuclear halogenopyrimidines, or from an extranuclear alkoxypyrimidine has been discussed in Sections 6.7.8, 6.9, and

7.4.2.6, respectively. In addition, the displacement of a substantial tertiary amino grouping by sulfite ion occurred during the fission of vitamin B_1, 5-(5′-β-hydroxyethyl-4′-methylthiazolio)methyl-2-methyl-4-pyrimidinamine chloride (**141**), by aqueous sodium hydrogen sulfite at 25° for 1–4 days, to give 2-methyl-5-sulfomethyl-4-pyrimidinamine (**142**) (> 90%).[3511,5148]



141 **142** **143**

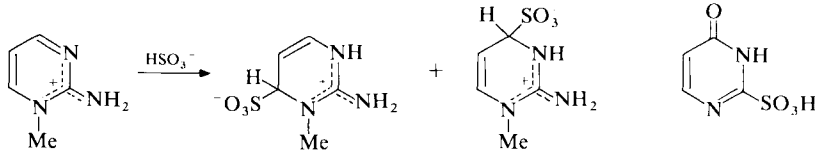
By derivatization. The formation of extranuclear pyrimidinesulfonic acids, amides, and so on by derivatization is typified by the selective aminolysis of ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate with the sodium salt of taurine (in acetone at 25° for 12 h) to give 2-methylthio-4-β-sulfoethylamino-5-pyrimidinecarboxylic acid (**143**) (43%),[1302] by the coupling of 6-methyl-2,4-pyrimidinediamine with diazotized sulfanilic acid to afford 6-methyl-5-*p*-sulfophenylazo-2,4-pyrimidinediamine (~50%),[3635] or by the coupling of 4,6-dimethyl-2(1*H*)-pyrimidinethione with *p*-(*N*-acetylsulfamoyl)benzenediazonium chloride to furnish 5-*p*-(*N*-acetylsulfamoyl)phenylazo-4,6-dimethyl-2-(1*H*)-pyrimidinethione (40%).[133]

By other procedures. Pyrimidinesulfonic acids have been formed in several other ways.

1. During reduction of 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione with dithionite, an isolable intermediate sulfonic acid of indeterminate structure[662,1176] was observed (see Section 5.1.2.1).

2. A product formulated as 5-sulfoamino-2,4,6-pyrimidinetriamine has been formed in three ways: by reduction of 5-nitroso-2,4,6-pyrimidinetriamine with hot aqueous sodium hydrogen sulfite; by treatment of 2,4,5,6-pyrimidinetetramine with etherial sulfuryl chloride (SO_2Cl_2); and by fusion at 150° of the same tetramine substrate with sulfamide (H_2NSO_3H).[3530]

3. The addition of bisulfite anion to several pyrimidine substrates has been studied. Thus 1-methyl-2(1*H*)-pyrimidinimine cation (**144**) gave the zwitterionic dihydro adducts **145** and **146**,[5722] reactions subsequently explored in depth;[5722,5723] the analogous additions of bisulfite anion to 2(1*H*)-



144 **145** **146** **147**

pyrimidinones, 2,4(1*H*,3*H*)-pyrimidinedione, and some derivatives have been studied.[3729,5724,5725] It is interesting that aeration of an aqueous solution of 2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone containing bisulfite anion gave 4-oxo-3,4-dihydro-2-pyrimidinesulfonic acid (**147**) quantitatively, whereas no reaction occurred without bisulfite.[3567]

4. The addition of sodium β-mercaptoethanesulfonate to 1-benzyl-5-fluoro-2(1*H*)-pyrimidinone gave an approximately 1 : 1 mixture of 1-benzyl-5-fluoro-4-(β-sulfoethylthio)-3,4-dihydro- and 1-benzyl-5-fluoro-6-(β-sulfoethylthio)-3,6-dihydro-2(1*H*)-pyrimidinone; analogous substrates behaved rather similarly.[3969]

8.7.2. Reactions of Pyrimidinesulfonic Acids and Some Derivatives

When situated in the 2- or 4/6-position, sulfo or derived groups can undergo either modification or complete displacement on treatment with nucleophiles; the same groups in the 5-position can undergo only modification.

Reduction. The reduction of 5-pyrimidinesulfonyl chlorides to 5-pyrimidinethiols has been covered in Section 8.2.1.

Hydrolysis. The hydrolysis of 2- or 4/6-pyrimidinesulfonic acids or the like (isolated or made in situ) to pyrimidinones has been discussed in Section 7.1.1.5. 2,4-Diamino-6-methyl-5-pyrimidinesulfonyl chloride has a more firmly attached sulfonyl grouping, so that hydrolysis in boiling water gave only the free sulfonic acid.[1450]

Other displacement reactions. Other reactions, in which the whole sulfonyl-containing group is displaced, are illustrated in the following transformations.

2,6-Dimethoxy-4-pyrimidinesulfonic acid to 4-chloro-2,6-dimethoxy- (PCl_5–$POCl_3$, reflux, 30 min: ~50%) or 4,5-dichloro-2,6-dimethoxypyrimidine (neat PCl_5, 130°, 30 min: ~55%).[2070]

Sodium 2,6-dimethyl-4-pyrimidinesulfonate to 2,6-dimethyl-4-pyrimidinecarbonitrile (KCN, distillation diminished pressure, 260°: ~30%); also analogs.[2763]

Sodium 1-methyl-2-oxo-1,2-dihydro-4-pyrimidinesulfonate to 4-amino- (7*M* NH_4OH, 20°, 30 min: 93%) or 4-dimethylamino-1-methyl-2(1*H*)-pyrimidinone ($HNMe_2$, H_2O, 20°, 4 h: 84%).[1538,1539]

Potassium 2,6-dimethyl-4-pyrimidinesulfonate to 4-hydrazino-2,6-dimethylpyrimidine (H_2NNH_2, EtOH–H_2O, reflux, 1 h: 56%).[1711]

4,6-Dimethyl-2-pyrimidinesulfonohydrazide (or the corresponding sulfonamide or sulfonyl fluoride) to 2-hydrazino-4,6-dimethylpyrimidine (H_2NNH_2, MeOH, reflux, 1 h: > 95%).[1711]

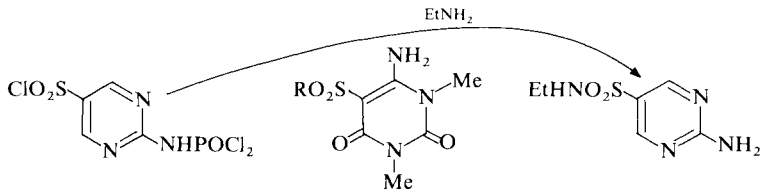
4,6-Dimethyl-2-pyrimidinesulfonyl fluoride to 2-methoxy-4,6-dimethylpyrimidine (NaOMe, MeOH, reflux, 90 min: 60%).[1711]

Sodium 1-methyl-2-oxo-1,2-dihydro-4-pyrimidinesulfonate to 1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (H_2S, H_2O, 20°, 30 min: 91%).[1539]

5-Methyl-2-pyrimidinesulfonyl fluoride to 2-azido-5-methylpyrimidine (NaN_3, MeOH–H_2O, 25°, 1 day: 55%).[1711] Also other examples.[729,1608,3120,3224]

To pyrimidinylsulfonyl halides. Although pyrimidinylsulfonyl halides can be prepared more directly (Sections 8.1.3.5, 8.7.1), they may also be obtained from the corresponding sulfonic acids. For example, sodium 2-amino-5-pyrimidinesulfonate with neat phosphorus pentachloride at 150° for 90 min gave 2-dichlorophosphinylamino-5-pyrimidinesulfonyl chloride (**148**) (71%);[869] 4,6-diamino-2-methylthio-5-pyrimidinesulfonic acid in refluxing phosphoryl chloride for 1 h gave the corresponding sulfonyl chloride (crude: > 60%);[1101] and 2-oxo-1,2-dihydro-5-pyrimidinesulfonic acid with neat phosphorus pentachloride at 180° for 2 h gave 2-chloro-5-pyrimidinesulfonyl chloride (87%).[845]

To pyrimidinesulfonic esters. Such esters are best made from pyrimidinesulfonic acids via the pyrimidinesulfonyl halides (which may, of course, be made otherwise). Thus 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride with aqueous sodium phenoxide at 25° for 10 min gave phenyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonate (< 20%);[2679] also 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonyl chloride (**149**, R = Cl) in methanol for 15 h gave methyl 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonate (**149**, R = OMe) (46%).[1101]



148 **149** **150**

To pyrimidinesulfonamides. Like the foregoing esters, pyrimidinesulfonamides are usually made via pyrimidinesulfonyl halides. [*Note*: It is essential to distinguish such true pyrimidinesulfonamides from the "pyrimidine sulfonamide" drugs (such as sulfadiazine), which are *N*-sulfanilyl derivatives of pyrimidinamines (see Section 9.4.4).] The conditions required to make pyrimidinesulfonamides, in each case from the corresponding sulfonyl chloride unless otherwise indicated, are illustrated in the formation of the following products.

2-Pyrimidinesulfonamide (liquid NH_3: > 10%).[2348]

4,6-Dimethyl-2-pyrimidinesulfonamide (liquid NH_3: > 46%;[2348] from the sulfonyl fluoride in liquid NH_3, 5 min: 82%[1711]).

N,*N*-Diethyl-4,6-dimethyl-2-pyrimidinesulfonamide (from 4,6-dimethyl-2-pyrimidinesulfonyl fluoride; neat Et_2NH, reflux, 5 min: > 90%).[1711]

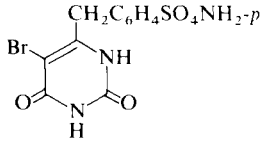
2-Amino-*N*,*N*-diethyl-5-pyrimidinesulfonamide (**150**) [from 2-dichlorophosphinylamino-5-pyrimidinesulfonyl chloride (**148**); Et_2NH, Et_2O, reflux, 12 h: 71%].[869]

2,4-Dioxo-*N*-phenyl-1,2,3,4-tetrahydro-5-pyrimidinesulfonamide ($PhNH_2$, 2.5*M* NaOH, 20°, 15 min: ~20%).[2679]

4-Amino-*N*-ethyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonamide (neat $EtNH_2$, – 50°, until homogeneous: 26%).[1101]

5-Bromo-6-*p*-sulfamoylbenzyl-2,4(1*H*,3*H*)-pyrimidinedione (**151**) (NH_4OH, 20°, 18 h: 53%).[1962]

Also other examples in the foregoing references and elsewhere.[1450,2347,5726]



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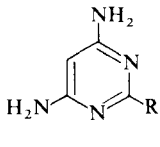
8.7.3. Pyrimidinesulfinic Acids

The few known pyrimidinesulfinic acids have been made by controlled oxidation of the corresponding pyrimidinethiones, as outlined in Section 8.1.3.5.

Pyrimidinesulfinic acids are reasonably stable as their anions in alkaki, but in acidic media they usually lose sulfur dioxide to afford pyrimidines unsubstituted at the position that carried the sulfino group; however, the corresponding pyrimidinone may also be formed by normal hydrolysis. For example, 4,5,6-triamino-2-pyrimidinesulfinic acid in refluxing 0.5*M* sulfuric acid for 2 h gave 4,5,6-pyrimidinetriamine sulfate (~ 75%);[2441,2444] similar treatment of 4,6-diamino-2-pyrimidinesulfinic acid (**152**, $R=SO_2H$) gave a separable mixture of 4,6-pyrimidinediamine (**152**, R = H) and 4,6-diamino-2(1*H*)-pyrimidinone (**153**), but when 10*M* sulfuric acid at 20° was used, only 4,6-pyrimidinediamine (**152**, R = H) (98% as sulfate) resulted.[2441] In a rather different way, 4,5-diamino-6-oxo-1,6-dihydro-2-pyrimidinesulfinic acid in ethanolic hydrogen chloride at 20° for 20 h gave 5,6-diamino-4(3*H*)-pyrimidinone



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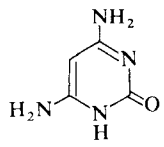

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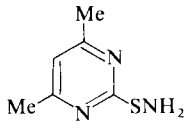
hydrochloride (~85%), whereas the use of regular hydrochloric acid gave only 5,6-diamino-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride.[1595] Examples of such reactions using unisolated pyrimidinesulfinic acids as substrates have been given toward the end of Section 8.1.3.1.

8.7.4. Pyrimidinesulfenic Acids

Pyrimidinesulfenic acids and their derivatives are very poorly represented to date. The formation (and characterization) of 1-methyl-2-oxo-1,2-dihydro-4-pyrimidinesulfenic acid (**136**) by hydrolytic cleavage of the corresponding disulfide has been covered in Section 8.6.3: in hot dilute hydrochloric acid it gave 1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone (**134**) and 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**135**).[3417] Treatment of 4,6-dimethyl-2(1*H*)-pyrimidinethione in cold dilute alkali with a freshly made solution of chloramine gave 4,6-dimethyl-2-pyrimidinesulfenamide (**154**) (25%);[1711] 2,6-dimethoxy-4-pyrimidinesulfenamide (**155**) (67%) was made similarly and subsequently oxidized by aqueous permanganate to afford 2,6-dimethoxy-4-pyrimidinesulfonamide (64%).[2070]



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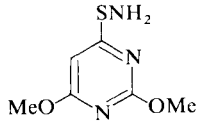

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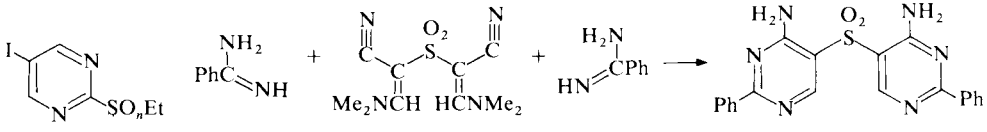
8.8. PYRIMIDINE SULFONES AND SULFOXIDES

Pyrimidine sulfones and sulfoxides are important mainly because 2- and 4/6-alkylsulfonyl and alkylsulfinyl groups undergo nucleophilic replacement even more easily than do corresponding halogeno substituents.[4721] Moreover, sulfones in particular are easily made in good yield from the ubiquitous alkylthiopyrimidines.

8.8.1. Preparation of Alkylsulfonyl- and Alkylsulfinylpyrimidines

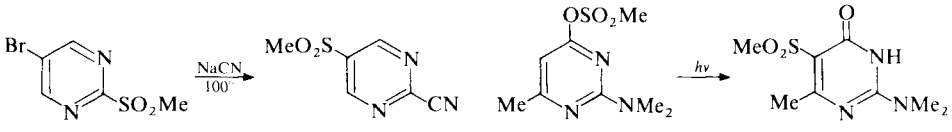
Oxidation of thioethers. Most sulfones and sulfoxides have been made by stagewise oxidation of the corresponding thioethers, as discussed in Section 8.4.2.4. Isolated sulfoxides can, of course, be oxidized further to sulfones: for example, 2-ethylsulfinyl- (**156**, $n=1$) gave 2-ethylsulfonyl-5-iodopyrimidine (**156**, $n=2$) (m-$ClC_6H_4CO_3H$, CH_2Cl_2, 20°, 5 h: 90%).[270] The oxidation of dipyrimidinyl sulfides to the corresponding sulfones has been exemplified in Section 8.6.3.

Primary syntheses. A few 5-alkylsulfonylpyrimidines and dipyrimidin-5-yl sulfones have been made by primary syntheses (Chapters 2 and 3). For example, bis(β-dimethylamino-α-cyanovinyl) sulfone (**157**) with benzamidine (2 mol) in refluxing aqueous methanol for 4 h gave bis(4-amino-2-phenylpyrimidin-5-yl) sulfone (**158**) (80%);[319] likewise, ethyl β-ethoxy-α-methylsulfonylacrylate with acetamidine in boiling ethanolic ethoxide for 2 h gave 2-methyl-5-methylsulfonyl-4(3*H*)-pyrimidinone (~20%).[3075]



156 **157** **158**

From halogenopyrimidines. The treatment of 2- or 4/6-halogenopyrimidines with arenesulfonate salts to afford arylsulfonylpyrimidines has been covered in Section 6.7.8. Such a displacement probably accounts for the peculiar reaction of 5-bromo-2-methylsulfonylpyrimidine (**159**) with sodium cyanide in dimethyl sulfoxide at 100° for 1 h to give 5-methylsulfonyl-2-pyrimidinecarbonitrile (**160**) (71%) because the initially displaced sodium methanesulfonate subsequently reacted with the 5-bromo substituent.[1897]



159 **160** **161** **162**

By rearrangement. Irradiation of the acyloxy substrate, 2-dimethylamino-4-methanesulfonyloxy-6-methylpyrimidine (**161**), induced rearrangement to 2-dimethylamino-6-methyl-5-methylsulfonyl-4(3*H*)-pyrimidinone (**162**) (60%); a number of analogs behaved similarly.[2622]

8.8.2. Reactions of Alkylsulfonyl- and Alkylsulfinylpyrimidines

Because alkylsulfonyl and alkylsulfinyl substituents are such good leaving groups, most of the reported reactions of these sulfones and sulfoxides are nucleophilic displacements.

Hydrolysis. Some kinetic measurements for the alkaline hydrolysis of several 2-*p*-substituted-phenylsulfonyl- and the corresponding phenylsulfinylpyrimidines have indicated that electron-withdrawing substituents hasten the hydrolysis and that each sulfone reacts marginally more rapidly than the corresponding sulfoxide.[5094] The preparatively useful hydrolysis of 2- or 4/6-alkylsulfonyl- and alkylsulfinylpyrimidines is covered in Section 7.1.1.5.

Alcoholysis. The formation of 2- or 4/6-alkoxypyrimidines from the corresponding sulfones or sulfoxides is covered in Section 7.4.1.3.

Thiolysis and alkanethiolysis. The thiolysis of sulfones or sulfoxides to pyrimidinethiones is seldom useful but existing examples have been given in Section 8.1.1. The even more rare alkanethiolysis of a sulfone has been illustrated at the end of Section 8.4.1.4.

Aminolysis. Rates for aminolyses of 2- and 4-methylsulfonyl-, 2- and 4-methylsulfinyl-, and 2-phenylsulfonylpyrimidine by pentylamine and cyclohexylamine in dimethyl sulfoxide have been measured: such substrates reacted appreciably faster than 2-chloropyrimidine under similar conditions.[1715] The conditions usually employed for preparative aminolyses of this type are illustrated in the formation of the following products, in each case from the corresponding methylsulfonyl or methylsulfinyl substrate unless indicated otherwise.

From sulfone substrates

2-Cyclohexylaminopyrimidine ($C_6H_{11}NH_2$, EtOH, reflux, 4 h: ~40%).[1715]

4,6-Dimethyl-2-methylamino-5-phenylpyrimidine ($MeNH_2$, EtOH, 100°, 2 h, sealed: 90%).[2114]

4,6-Dimethyl-5-phenyl-2-pyrimidinamine (NH_4OH, NH_4Cl, 120°, 18 h, sealed: 81%).[2114]

6-Ethylamino-2,4-pyrimidinediamine 3-oxide from the 6-phenylsulfonyl substrate ($EtNH_2$, EtOH, 130°, 4 h, sealed: 53%).[2176]

2-Hydrazino-5-nitropyrimidine (H_2NNH_2, EtOH, reflux, 1 h: > 95%).[3228]

2-Hydrazino-5-methoxypyrimidine ($H_2NNH_2.H_2O$, Me_2SO, 100°, 3 h: 71%).[1897]

Ethyl 4-amino-2-aziridino-5-pyrimidinecarboxylate from the 2-ethylsulfonyl substrate (aziridine, NEt_3, EtOAc–AcMe, 50°, 1 h: 44%).[2203]

Also other examples in the foregoing references and elsewhere.[577,1544]

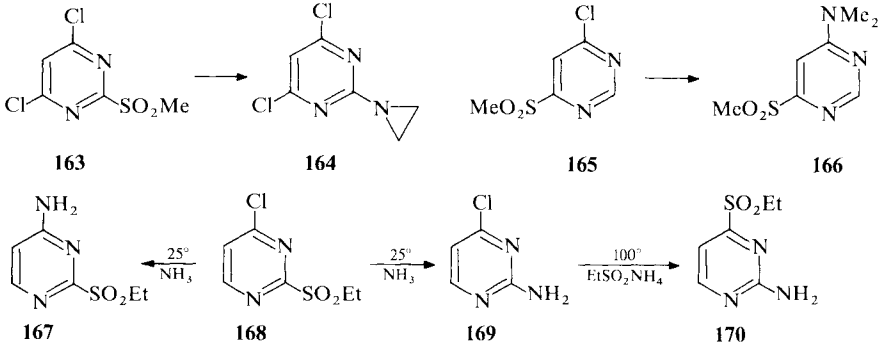
From sulfoxide substrates

2-Pentylaminopyrimidine (neat $C_5H_{11}NH_2$, 100°, 10 h: ~40% as picrate).[1715]

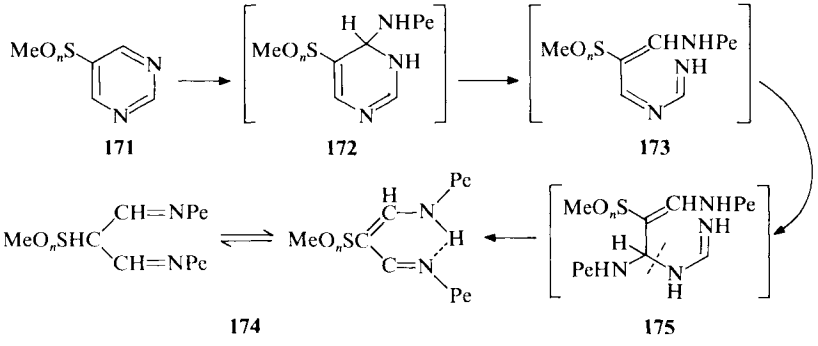
2-Dimethylamino-4-methoxy-6-nitroaminopyrimidine (Me_2NH, EtOH, 25°, 1 day: 70%).[903]

The aminolysis of a substrate bearing both halogeno and alkylsulfonyl groups is not totally predictable. For example, 4,6-dichloro-2-methylsulfonylpyrimidine (**163**) with aziridine in benzene containing triethylamine at 40° gave only 2-aziridino-4,6-dichloropyrimidine (**164**) (~50%),[1816] whereas 4-chloro-6-methylsulfonylpyrimidine (**165**) with ethanolic dimethylamine at 70° gave 4-dimethylamino-6-methylsulfonylpyrimidine (**166**) (72%)[2289] and even 5-fluoro-2-methylsulfonylpyrimidine with ethanolic hydrazine hydrate under reflux gave

5-hydrazino-2-methylsulfonylpyrimidine (85%). Furthermore, 4-chloro-2-ethylsulfonylpyrimidine (**168**) with ammonia at 25° gave 2-ethylsulfonyl-4-pyrimidinamine (**167**) (2%) plus 4-chloro-2-pyrimidinamine (**169**) (61%), whereas at 100° most of the latter product appeared to react with the eliminated ammonium ethanesulfonate to afford a third product, 4-ethylsulfonyl-2-pyrimidinamine (**170**) (35%).[5713] Most of the foregoing results can be rationalized, albeit without total conviction.

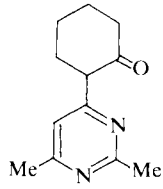


When attempts were made to pentylaminolyse 5-methylsulfonyl- (**171**, $n=2$) or 5-methylsulfinylpyrimidine (**171**, $n=1$), a reaction more facile than the expected displacement occurred with loss of ammonia.[5728] The products, identified as 2-methylsulfonyl- (**174**, $n=2$) and 2-methylsulfinyl-1,3-bispentyliminopropane (**174**, $n=1$), respectively, probably arose via the intermediates (**172** → **173** → **175**); likewise benzylamine gave 1,3-bisbenzylimino-2-methylsulfonyl- and 1,3-bisbenzylimino-2-methylsulfinylpropane.[5728] In such behavior and in the covalent hydration of their cations, the sulfone (**171**, $n=2$) and the sulfoxide (**171**, $n=1$) resembled 5-nitropyrimidine in which acute localization of the π-electrons also caused facile ring fissions and covalent hydration.[2560]



Displacement by carbanions. Such reactions are illustrated in the conversion of 4-benzyloxy-2-methylsulfonyl- into 4-benzyloxy-2-di(ethoxycarbonyl)-

methylpyrimidine [$(EtO_2C)_2CHNa$, EtOH?: 38%];[5714] also of 2,4-dimethyl-6-phenylsulfonyl- into 4-dicyanomethyl-2,6-dimethyl- [$(NC)_2CHNa$, THF, reflux, 1 h: 78%] or 2,4-dimethyl-6-2′-oxocyclohexylpyrimidine (**176**) [$(CH_2)_5CO$, NaH, THF, 40°, 90 min: 32%].[739]



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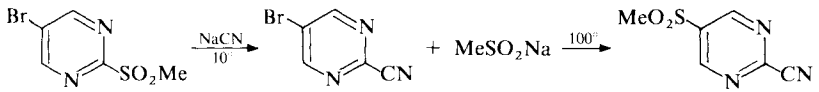
Displacement by cyanide ion. Several pyrimidinecarbonitriles have been made from the corresponding sulfones. For example, 2-methylsulfonylpyrimidine gave 2-pyrimidinecarbonitrile (KCN, Me_2NCHO, 100°, 4 h: ~40%);[1715] 5-*p*-heptyloxyphenyl-2-methylsulfonylpyrimidine gave 5-*p*-heptyloxyphenyl-2-pyrimidinecarbonitrile (NaCN, Me_2SO, 50°, 5 h; 79%);[4027] 5-chloro-2-methylsulfonylpyrimidine gave 5-chloro-2-pyrimidinecarbonitrile (NaCN, Me_2SO, 10°, 30 min: 78%);[1897] 5-bromo-2-methylsulfonylpyrimidine (**177**) gave 5-bromo-2-pyrimidinecarbonitrile (**178**) (NaCN, Me_2SO, 10°, 30 min: 75%) or 5-methylsulfonyl-2-pyrimidinecarbonitrile (**179**) (likewise but at 100° for 1 h: 71%; by replacement of the bromo substituent with the initially eliminated sodium methanesulfinate);[1897] and other instances have been reported.[379,3603]

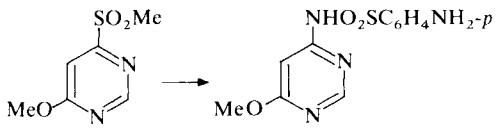


177 **178** **179**

Displacement by azide or sulfanilamide anions. Such azanions react quite readily with pyrimidine sulfones: the usual conditions are illustrated in the following transformations.

2-Methylsulfonyl- to 2-azidopyrimidine (NaN_3, Me_2NCHO, 95°, 3 h: ~ 60%).[1715]

4-Methoxy-6-methylsulfonyl- (**180**) to 4-methoxy-6-sulfanilamidopyrimidine (**181**) (*p*-$H_2NC_6H_4SO_2NHNa$, Me_2SO, 60°, 1 h: 48%).[2600]



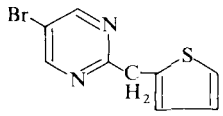
180 **181**

5-Methoxy-2-methylsulfonyl- to 5-methoxy-2-sulfanilamidopyrimidine (p-$H_2NC_6H_4SO_2NH_2$, K_2CO_3, no solvent, 150°, 2 h: 79%).[3268]

4,6-Dimethyl-2-phenylsulfonyl- to 4,6-dimethyl-2-sulfanilamidopyrimidine (p-$H_2NC_6H_4SO_2NHNa$, no solvent, 120°, 8 h: 97%).[3120]

Also other examples.[1784,2192,3120,5087]

Reduction or oxidation. Both 2-methylsulfonyl- and 2-methylsulfinylpyrimidine underwent reduction by hydriodic acid to 2-methylthiopyrimidine.[1715] Pyrimidine sulfoxides clearly undergo oxidation to the corresponding sulfones (see Sections 8.4.2.4 and 8.8.1), which resist further oxidation.



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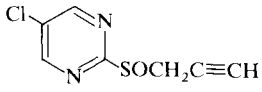

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Biological effects. Certain pyrimidine sulfones and sulfoxides have shown inactivating effects on selected human cancer cell lines *in vitro*. For example, 5-bromo-2-(thien-2′-ylmethyl)sulfonylpyrimidine (**182**) completely blocked one such type of cell in metaphase;[3825] and 5-chloro-2-prop-2′-ynylsulfinylpyrimidine (**183**) showed a significant synergistic effect with cisplatin when used to inactivate cells of another line.[3851]

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CHAPTER 9

Aminopyrimidines

The title of this chapter is used in a generic sense to include pyrimidines bearing primary, secondary, tertiary, or quaternary amino groups at the 2-, 4/6-, 5-, 1/3-, or ω-positions or imino groups at any of the possible positions. The number of such aminopyrimidines known is second only to that of oxypyrimidines. Aminopyrimidines occur as natural products (e.g., cytosine) and are the essential intermediates in the most important synthetic routes to purines, pteridines, and other such bicyclic systems. To avoid confusion, the specific terms, pyrimidinamine and pyrimidinimine, are reserved in the present work for those pyrimidines bearing a primary amino or an unsubstituted fixed imino group attached directly to the ring.

9.1. THE REGULAR AMINOPYRIMIDINES

Regular aminopyrimidines are considered to be those in which the amino or hydrazino group(s) is (are) unsubstituted or bear only nonfunctional alkyl or aryl substituents.

9.1.1. Preparation of 2- or 4/6-Aminopyrimidines

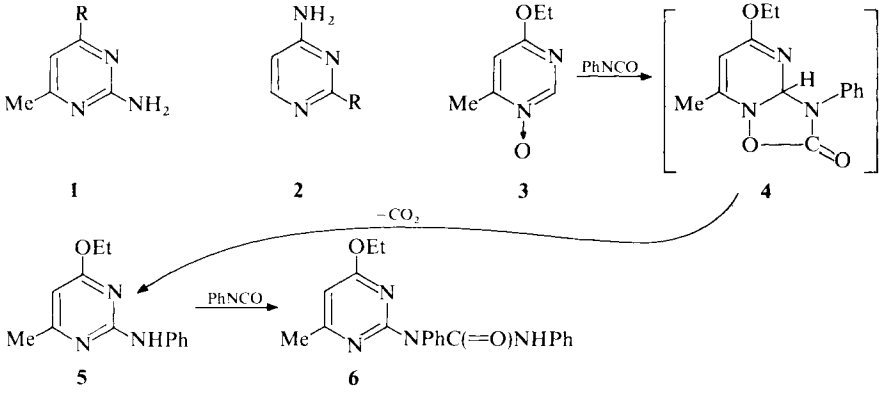
Most of the important routes to such aminopyrimidines have already been discussed elsewhere but cross-references, sometimes with a brief indication of the scope of each method, are included in this section for convenience.

9.1.1.1. By Primary Syntheses

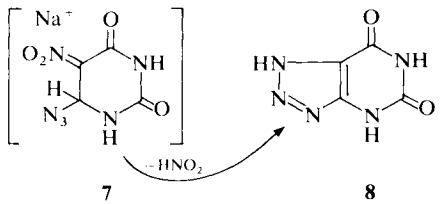
Many of the primary syntheses described in Chapter 2 afford a variety of aminopyrimidines with ease but the Principal Synthesis (Chapter 3) is even more useful: a primary, secondary, or tertiary amino group at the 2-position of the resulting pyrimidine may be achieved by using guanidine or substituted guanidine as the N—C—N fragment; a primary amino group at the 4- and/or 6-position results from using a nitrile or dinitrile as the C—C—C fragment.

9.1.1.2. By Direct or Indirect Amination

The pyrimidine nucleus usually resists direct amination, but treatment of 4-methylpyrimidine with sodium amide in tetralin at 150° for 9 h gave a mixture of products from which 4-methyl-2-pyrimidinamine (**1**, R = H) and 6-methyl-2,4-pyrimidinediamine (**1**, R = NH_2) were isolated.[3449] In a different way, 2-methyl- or 2-*t*-butylpyrimidine with sodium amide in liquid ammonia at − 33° for 3 h, followed by treatment with permanganate, gave 2-methyl- (**2**, R = Me) (10%) or 2-*t*-butyl-4-pyrimidinamine (**2**, R = Bu^t) (60%);[479] in much the same way, 4-phenylpyrimidine gave 6-phenyl-4- and 4-phenyl-2-pyrimidinamine;[4713,4714] 4-*t*-butylpyrimidine gave 6-*t*-butyl-4- and 4-*t*-butyl-2-pyrimidinamine,[4714] and 5-phenylpyrimidine gave 5-phenyl-2- and 5-phenyl-4-pyrimidinamine (2% and 80%, respectively).[534] 5-Nitro-2-pyrimidinamine was made similarly.[6448]



Some reactions, which amount to aminations in effect, are illustrated by the conversion of 4-ethoxy-6-methylpyrimidine 1-oxide (**3**) successively into the (unisolated) adduct (**4**), 2-anilino-4-ethoxy-6-methylpyrimidine (**5**) (12%), and 2-*N*,*N*′-diphenylureido-4-ethoxy-6-methylpyrimidine (**6**) (40%) (PhNCO, 100°, 5 h);[3333] of 4,6-dimethylpyrimidine 1-oxide into 2-anilino- (9%) and 2-*N*-benzoylanilino-4,6-dimethylpyrimidine (22%) [PhC(Cl)=NPh, PhCl, reflux, 10 h];[5729] of 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione into *v*-triazolo[4,5-*d*]-pyrimidine-5,7(4*H*,6*H*)-dione (**8**), probably by loss of nitrous acid from an



amination product (**7**) (NaN_3, NH_4Cl, Me_2NCHO, 70°, 6 days: 86%);[4767,4768] and of 1-methyl-4-phenylpyrimidinium iodide into 4-phenyl-2-pyrimidinamine by a rational mechanism involving ring fission of the initial product followed by transamination and reclosure (H_2NCN, KOH, EtOH, 115°, 3 h, sealed?: 60%).[4639]

9.1.1.3. By Aminolysis

The aminolysis of pyrimidines bearing almost a dozen types of leaving group has been used extensively to make all manner of aminopyrimidines. Many such reactions have been covered already.

From halogenopyrimidines. See Sections 6.7.2 and 6.7.3.

From pyrimidinethiones. See Section 8.1.3.3.

From alkylthiopyrimidines. See Section 8.4.2.2.

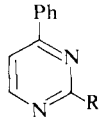
From pyrimidinones. See Section 7.1.3.6.

From alkoxypyrimidines. See Section 7.4.2.1.

From nitropyrimidines. See Section 5.1.2.2.

From pyrimidine sulfones or sulfoxides. See Section 8.2.2.

From thiocyanatopyrimidines. This route is probably of little practical utility. However, it has been used for the conversion of 4-phenyl-2-thiocyanatopyrimidine (**9**, R = SCN) into a separable mixture of 4-phenyl-2-pyrimidinamine (**9**, R = NH_2) (32%) and bis(4-phenylpyrimidin-2-yl) disulfide (46%) (KNH_2, liquid NH_3, −33°, 1 h);[5088] of 2-chloro-5-nitro-4-thiocyanatopyrimidine into 5-nitro-2,4-pyrimidinediamine (NH_4OH, 15°, 30 min) or 2,4-bisdiethylamino-5-nitropyrimidine (Et_2NH, PhH–EtOH, 20°, 20 min);[1582] and of ethyl 2-ethylthio-4-thiocyanato- into ethyl 4-amino-2-ethylthio-5-pyrimidinecarboxylate (EtOH, 150°, 5 h, sealed: 90%; this apparent aminolysis proceeded via isothiocyanato and thiourethane intermediates).[3016]



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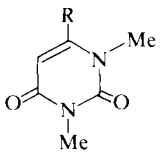

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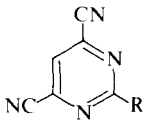

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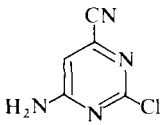
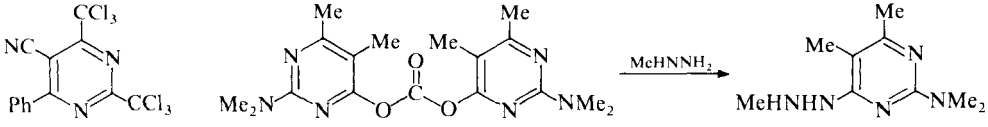


12

From pyrimidinecarbonitriles. Cyano groups can be displaced from the 2- or 4/6-position by amines under appropriate conditions. Thus 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**10**, R = CN) gave 6-butylamino- (**10**, R = NHBu) (neat $BuNH_2$, reflux, 3 h: 76%) or 6-hydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**10**, R = $NHNH_2$) (neat H_2NNH_2, 100°,

30 h: 51%);[1133] 2-chloro-4,6-pyrimidinedicarbonitrile (**11**, R = Cl) gave a separable mixture of 6-amino-2-chloro-4-pyrimidinecarbonitrile (**12**) and 2-amino-4,6-pyrimidinedicarbonitrile (**11**, R = NH_2) (NH_3, PhH, 25°, 3 days: 36% and 38%, respectively; in THF, only the second product was formed: 80%);[1029] 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4,5-pyrimidinedicarbonitrile gave 4-anilino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile ($PhNH_2$, Me_2NCHO, reflux, 15 h: 88%);[1987] the nitrile precursor, 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde oxime, gave 6-ethylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione ($EtNH_2$, H_2O, reflux, 5 h: ?%);[1165] the trinitrile equivalent, 4-phenyl-2,6-bistrichloromethyl-5-pyrimidinecarbonitrile (**13**), gave 2-hydrazino-4-phenyl-6-trichloromethyl-($H_2NNH_2.H_2O$, 100°, 3 h: 70%) and thence 2,4-dihydrazino-6-phenyl-5-pyrimidinecarbonitrile ($H_2NNH_2.H_2O$, 120°, 3 h: 50%);[4466] and 4-diethoxycarbonylmethyl-6-methyl-5-nitro-2-pyrimidinamine has been reported to give 6-methyl-5-nitro-2,4-pyrimidinediamine (88%) by heating in aqueous ammonia.[3412]



13 **14** **15**

From acyloxypyrimidines. This rare aminolysis is typified by the conversion of bis(2-dimethylamino-5,6-dimethylpyrimidin-4-yl) carbonate (**14**) into 2-dimethylamino-4,5-dimethyl-6-β-methylhydrazinopyrimidine (**15**) with loss of carbon dioxide ($MeHNNH_2$, PhH, 25°, 15 h: 54%).[2609]

From other aminopyrimidines (transamination). Transamination has been used extensively since 1960,[3788] usually to convert easily prepared aminopyrimidines into their less accessible analogs; it is more easily applicable to 4/6- than to 2-aminopyrimidines. The recommended procedure is to heat the aminopyrimidine substrate (as its hydrochloride or acetate) with a modest excess of the reagent amine as free base; however, it is quite satisfactory to use the substrate as base with the reagent as its salt, or sometimes to use both substrate and reagent as free bases. The process is illustrated by the following transformations.

2,6-Dimethyl-4-pyrimidinamine hydrochloride to 4-butylamino-2,6-dimethylpyrimidine ($BuNH_2$, 170°, 20 h, sealed: 91%).[3788]

4,6-Dimethyl-2-pyrimidinamine to 2-benzylamino-4,6-dimethylpyrimidine ($PhCH_2NH_2.HCl$, 160°, 5 h: ~15%).[3788]

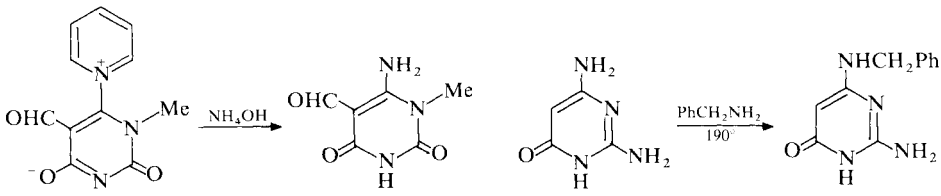
4-Amino- to 4-anilino-2(1*H*)-pyrimidinone ($PhNH_2.HCl$, 165°, 6 h: 64%).[3788]

6-Amino- to 6-*p*-ethylanilino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (*p*-$EtC_6H_4NH_2.HCl$ and base, 170°, 7 h: 63%).[298]

6-Amino- to 6-methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone ($MeNH_2$.HCl, $MeNH_2$, MeNHCHO, reflux, 2 h: 76%; note survival of the thioxo substituent).[3872]

4-Trimethylammoniopyrimidine chloride to 4-hydrazino ($H_2NNH_2.H_2O$, 20°, 15 min: 98%) or 4-propylaminopyrimidine ($PrNH_2$, 50°, 3 h: 71% as picrate).[3232]

5-Formyl-1-methyl-2-oxo-6-pyridinio-1,2-dihydro-4-pyrimidinolate (**16**) to 4-amino-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde (**17**) (NH_4OH, reflux, 40 h: 68%).[548]



16 **17** **18** **19**

2,6-Diamino- (**18**) to 2-amino-6-piperidino- (piperidine.AcOH, 170°, 6 h: 20%)[254] or 2-amino-6-benzylamino-4(3*H*)-pyrimidinone (**19**) ($PhCH_2NH_2$, $HOCH_2CH_2OH$, 190°, 90 h: 73%).[5731]

2,4-Bisdimethylamino- to 2-dimethylamino-4-hydrazino-5-nitropyrimidine ($H_2NNH_2.H_2O$, H_2O, reflux, 5 h: 30%).[1714]

2,6-Bismethylamino- to 6-amino-2-methylamino-4(3*H*)-pyrimidinone (neat $AcONH_4$, reflux!, 2 h: 24%).[1093]

6-Amino- to 6-furfurylamino- (furfurylamine.AcOH, fused, 3 h: 55%)[1093] or 6-hydrazino-2,4(1*H*,3*H*)-pyrimidinedione (H_2NNH_2, AcOH–H_2O, reflux, 1 h: 82%).[3233]

4-Amino-5-methyl-2(1*H*)-pyrimidinone hydrochloride to 4-hydroxyamino-5-methyl-2(1*H*)-pyrimidinone (H_2NOH, H_2O, 25°, 18 h: 70%).[1549, cf. 3239]

6-Methyl-2-nitroamino- to 2-anilino-6-methyl-4(3*H*)-pyrimidinone ($PhNH_2$, 145°, 85%);[2790] also analogs likewise.[2790,5739]

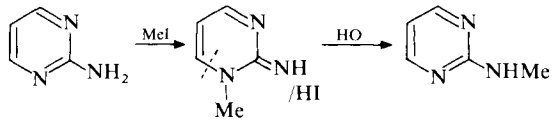
Also other examples.[47,724,1093,1279,1282,1507,1549,1580,2079,2680,3232,3239,3788,3846,4292,5730,5732,5733]

9.1.1.4. By Modification of Existing Aminopyrimidines

Modification of the amino group(s) on an existing aminopyrimidine to afford a different aminopyrimidine can be quite useful and may be done in several ways, as exemplified in the following paragraphs.

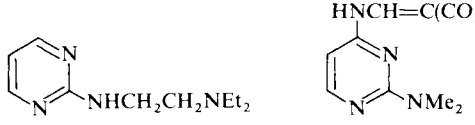
Using alkylation. Alkylation of a primary or secondary 2- or 4/6-aminopyrimidine usually occurs on a ring nitrogen to afford an imine that may

undergo Dimroth rearrangement to the corresponding alkylaminopyrimidine: for example, 2-pyrimidinamine (**20**) with methyl iodide gave 1-methyl-2-(1*H*)-pyrimidinimine hydriodide (**21**), which in alkali underwent ring fission and reclosure to give 2-methylaminopyrimidine (**22**).[3377] Such indirect alkylations are discussed in Sections 9.3.1.1 (alkylation step) and 9.3.2 (rearrangement step).



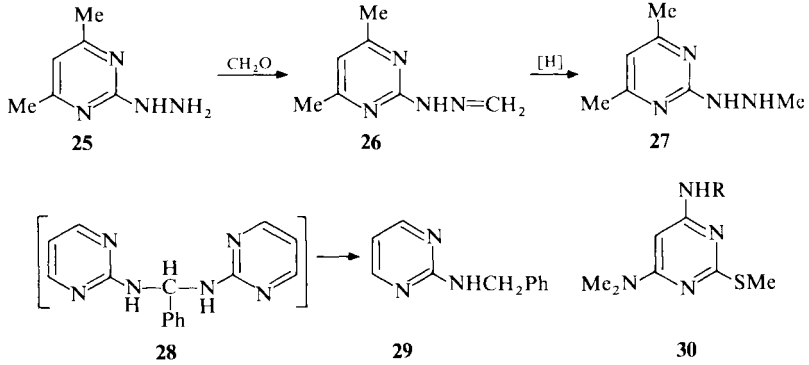
20 **21** **22**

However, the direct alkylation of such an amino group is possible sometimes. Thus 2-pyrimidinamine gave 2-β-diethylaminoethylaminopyrimidine (**23**) ($NaNH_2$, PhMe, reflux, 12 h; then $Et_2NCH_2CH_2Cl$, PhMe, reflux, 18 h: 64%);[3359] 2-methylamino- gave 2-dimethylaminopyrimidine ($LiNH_2$, PhH, reflux, 90 min; then MeI, PhH, reflux, 15 h: 31%);[2083] 2-pyrimidinamine gave 2-β-hydroxyethylaminopyrimidine [$(CH_2)_2O$, H_2O, 30°: 36%][6218] or 2-β-hydroxyphenethylaminopyrimidine (styrene oxide, HCl, EtOH, reflux, 30 h: > 32% as hydrochloride);[4891] 2-dimethylamino-4-pyrimidinamine gave 4-β,β-diethoxycarbonylvinylamino-2-dimethylaminopyrimidine (**24**) [EtOCH=C$(CO_2Et)_2$140°, 3 h: 90%];[2648,5734] 5-phenyl-4-pyrimidinamine gave bis(5-phenylpyrimidin-4-ylamino)methane (Me_2SO, 155°, 24 h: 15%);[5789] 2-benzylidenehydrazino-4,6-dimethyl- gave 2-β-benzylidene-α-propylhydrazino-4,6-dimethyl- (NaH, THF, PrI, reflux, > 2 h: 62%) and thence 4,6-dimethyl-2-α-propylhydrazinopyrimidine (2*M* HCl, reflux, 4 h: 84%);[3769] and other such examples have been reported.[305,308,3359,5734,5735,5790,5791] In addition, ethyl chloroformate and like reagents, invariably alkylate/acylate primary or secondary 2- or 4/6-aminopyrimidines directly on their amino group, as reported in Section 9.2.1.1.



23 **24**

Two-stage alkylations are also possible. Thus 2-hydrazino-4,6-dimethylpyrimidine (**25**) gave 4,6-dimethyl-2-methylenehydrazinopyrimidine (**26**) (CH_2O, EtOH, 70°, 15 min) and thence 4,6-dimethyl-2-β-methylhydrazinopyrimidine (**27**) (H_2, Pd, EtOH: 70%);[2689] 2-pyrimidinamine with benzaldehyde in refluxing formic acid for > 17 h gave an intermediate, probably **28**, and thence 2-benzylaminopyrimidine (**29**) (56%);[5736,5737, cf. 695,1627] and 6-dimethylamino-2-methylthio-4-pyrimidinamine (**30**, R = H) gave 4-acetamido-6-dimethylamino-2-methylthiopyrimidine



(**30**, R = Ac) (Ac_2O, pyridine, 95°, 1 h: 90%) and thence 4-dimethylamino-6-ethylamino-2-methylthiopyrimidine (**30**, R = Et) ($LiAlH_4$, Et_2O–pyridine, reflux, 2–5 h: 75%).[640]

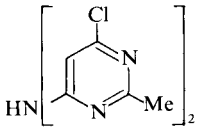
Using reductive splitting. Hydrazino- or azidopyrimidines may be converted into aminopyrimidines by reduction. For example, 6-hydrazino- gave 6-amino-4(3*H*)-pyrimidinone (Raney-Ni, NH_4OH, reflux, 30 min: 79%);[1680] 4-hydrazino-6-methyl-2-pyridin-4′-ylpyrimidine gave 6-methyl-2-pyridin-4′-yl-4-pyrimidinamine (H_2, Ni, EtOH, 60°: 81%);[4122] 2,4-dimethoxy-6-α-methylhydrazino- (**31**, R = NH_2) gave 2,4-dimethoxy-6-methylamino-pyrimidine (**31**, R = H) (Raney-Ni, EtOH: 91%);[2577] ethyl 6-azido- gave ethyl 6-amino-2,5-dimethyl-4-pyrimidinecarboxylate (H_2, Pd, EtOH, 10 h: 97%);[2038] and other such reactions have been reported.[2577] A related and confirmed oddball reaction was that of 4-β,β-diphenylhydrazino-2-hydrazino-5-nitropyrimidine with aqueous silver acetate at 25° to afford 4-β,β-diphenylhydrazino-5-nitro-2-pyrimidinamine (48%).[5071]

31

Using dealkylation. The thermal monodealkylation of a trialkylammoniopyrimidine is not unusual. Thus 4-phenyl-6-trimethylammoniopyrimidine chloride lost methyl chloride on warming in dimethyl sulfoxide to give 4-dimethylamino-6-phenylpyrimidine;[4904] and 2-chloro-4-methyl-6-triethylammoniopyrimidine chloride lost ethyl chloride, during attempted isolation, to give 2-chloro-4-diethylamino-6-methylpyrimidine.[2136] However, the dealkylation of a dialkylamino- or alkylaminopyrimidine is seldom possible except in the special circumstances represented by the reductive debenzylation of 6-benzylamino- to 6-amino-2,4(1*H*,3*H*)-pyrimidinedione (H_2, Pd, EtOH, 38°,

17 h: ~80%)[1504] or the conversion of 4-*t*-butylamino-2-chloro-5-fluoropyrimidine into 4-amino-5-fluoro-2(1*H*)-pyrimidinone with concomitant formation of *t*-butyl chloride (10*M* HCl, reflux, 30 min).[1269]

Using miscellaneous procedures. 2,5,6-Triphenyl-4-pyrimidinamine gave 4-hydroxyamino-2,5,6-triphenylpyrimidine (H_2O_2, AcOH, reflux, 3 h)[4350] (possibly via an *N*-oxide?). Treatment of 6-amino-2-methyl-4(3*H*)-pyrimidinone or 6-chloro-2-methyl-4-pyrimidinamine with phosphoryl chloride at 230° (sealed?) for 5 h gave bis(6-chloro-2-methylpyrimidin-4-yl)amine (**32**) (65%) (also analogs similarly).[5010,5738] The conversion of hydrazino- into azidopyrimidines is discussed toward the end of Section 9.1.6.8.



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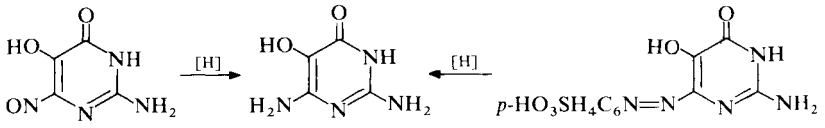
9.1.1.5. By Other Means

Reduction

1. Some of the few known pyrimidines with a nitro, nitroso, or arylazo group in the 2- or 4/6-position have been used as substrates for reduction to the corresponding pyrimidinamines (Sections 5.2.3.1 and 5.3.2.1); for example, 2,6-diamino-5-hydroxy-4(3*H*)-pyrimidinone (**34**) was made by dithionite reduction of 2-amino-5-hydroxy-6-nitroso- (**33**) or 2-amino-5-hydroxy-6-*p*-sulfophenylazo-4(3*H*)-pyrimidinone (**35**) in 94% or 7% yield, respectively.[581]

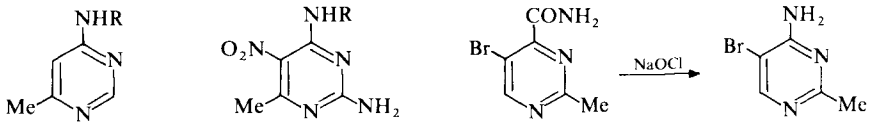


33 **34** **35**

2. Rather similarly, 4-methyl-6-nitroaminopyrimidine (**36**, R = NO_2) gave either 4-hydrazino-6-methylpyrimidine (**36**, R = NH_2) (Zn, AcOH–H_2O, 0°: 20%) or under more vigorous conditions, 6-methyl-4-pyrimidinamine (**35**, R = H) (Sn, HCl; presumably by reductive splitting of the hydrazino product);[1932] 4-methoxy-6-nitroamino- gave 4-amino-6-methoxy-2(1*H*)-pyrimidinone (H_2, Pd, MeOH–H_2O, 20°, 5 days: 83%);[903] 6-methyl-2-nitroamino- gave 2-hydrazino-6-methyl-4(3*H*)-pyrimidinone (H_2NNH_2, H_2O, 95°, 30 min: 79%; reduction or transamination?).[1429,3032, cf. 1430,3217]

3. In a quite different way, 4-benzyloxyamino-6-methyl-5-nitro-2-pyrimidinamine (**37**, R = OCH_2Ph) gave either 6-methyl-5-nitro-2,4-

pyrimidinediamine (**37**, R = H) (NH_2SH, EtOH, reflux, 30 min: 73%) or 6-methyl-2,4,5-pyrimidinetriamine [$Fe(OH)_2$, H_2O, 100°, 20 min: 80%; Raney-Ni, H_2NNH_2, EtOH, reflux, 20 min: 64%].[3411]



Hofmann reaction. 5-Bromo-2-methyl-4-pyrimidinecarboxamide (**38**) gave 5-bromo-2-methyl-4-pyrimidinamine (**39**) under classical Hofmann conditions (NaOCl, NaOH, H_2O, 0° then 80°: 70%);[1479] the 5-chloro analog (72%) was obtained similarly.[1479]

Hydrolysis. Aminopyrimidines may be made by hydrolysis of some of their derivatives. For example, 4-chloro-6-formamidopyrimidine underwent deacylation without aminolysis in warm aqueous ammonia during 1 h to afford 6-chloro-4-pyrimidinamine;[2172] 2-acetamidopyrimidine in methanolic hydrogen chloride gave 2-pyrimidinamine hydrochloride;[709] 2-acetamido-5-pyrimidinamine in *M* alkali gave 2,5-pyrimidinediamine;[705] and other cases have been noted.[696,1542,5826]

The Schiff base, 4-chloro-6-dimethylaminomethyleneaminopyrimidine, in *M* alkali at 95° for 2 h, gave 6-dimethylamino-4-pyrimidinamine (70%) by initial hydrolysis followed by deformylation of the dimethylformamide produced and a final dimethylaminolysis.[2172] Likewise, treatment of 4-ethoxymethyleneamino-2-methylthio-5-pyrimidinecarbonitrile with methanolic ammonia at 20° for 24 h afforded 4-amino-2-methylthio-5-pyrimidinecarbonitrile (30%).[351]

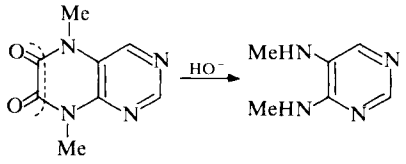
9.1.2. Preparation of 5-Aminopyrimidines

Almost all the known (primary) 5-pyrimidinamines have been made by reduction of nitro-, nitroso-, or arylazopyrimidines, whereas most of the few known secondary or tertiary 5-aminopyrimidines have been made by modification of the primary amines. However, a few other routes have been used also.

9.1.2.1. By Primary Syntheses

Although the Principal Synthesis (Chapter 3) is generally unsuited to the production of 5-aminopyrimidines, several other primary syntheses (Chapter 2) have been used. For example, condensation of α-(methylamino)malondiamide with ethyl formate or formamide in ethanolic ethoxide gave 5-methylamino-4,6(1*H*,5*H*)-pyrimidinedione (40–60%);[1981] degradation of 2(3*H*)-purinone in

refluxing 0.5*M* sulfuric acid for 2 h gave 4,5-diamino-2(1*H*)-pyrimidinone (25% as sulfate);[681] and treatment of 5,8-dimethyl-6,7(5*H*,8*H*)-pteridinedione (**40**) in boiling *M* alkali for 90 min gave the otherwise inaccessible 4,5-bismethylamino-pyrimidine (**41**).[1773]



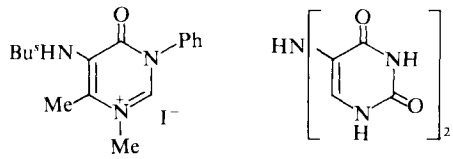
40 **41**

9.1.2.2. By Reduction

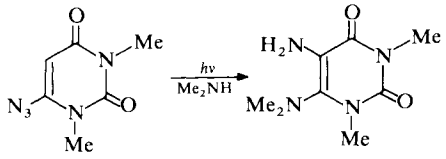
The very important reduction of 5-nitro-, 5-nitroso-, or 5-arylazopyrimidines to the corresponding 5-pyrimidinamines has been discussed fully in Sections 5.1.2.1, 5.2.3.1, and 5.3.2.1, respectively.

9.1.2.3. By Aminolyses

The considerable scope for aminolysis of *5-halogenopyrimidines* has been outlined in Section 6.8.2. The use of other 5-substituted substrates is usually unsatisfactory or very limited (e.g., see Section 7.2.2.3), but *transamination* has been reported in the conversion of 5-dimethylamino- into 5-*s*-butylyamino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone methiodide (**42**) (Bu^sNH_2, MeCN, reflux, 3 h: 49%; also some analogs);[33] and of 5-amino-2,4(1*H*,3*H*)-pyrimidinedione into bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)amine (**43**) (half cation, $HOCH_2CH_2OH$, 160°: 90%).[3968] The peculiar conversion of 6-azido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**44**) into 5-amino-6-dimethylamino-1,3-



42 **43**



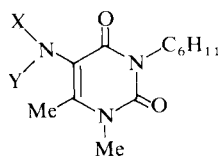
44 **45**

dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**45**) (Me_2NH, THF, *hv*, 3 h: 59%) probably involved a formal transamination at some stage.[1069]

9.1.2.4. By Alkylation of Existing 5-Aminopyrimidines

5-Amino groups may be modified by alkylation in several ways.

Direct alkylation. Direct alkylation of a 5-amino or 5-alkylamino group is sometimes possible, especially when preferential 1/3-alkylation is precluded by lack of a suitably placed tautomeric substituent. For example, 5-amino-3-cyclohexyl-1,6-dimethyl- (**46**, X = Y = H) gave 3-cyclohexyl-5-ethylamino-1,6-dimethyl- (**46**, X = Et, Y = H) (limited Et_2SO_4, CaO, MeOH, reflux, 2 h: 79%) and thence 3-cyclohexyl-5-(*N*-ethyl-*N*-methylamino)-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**46**, X = Et, Y = Me) (Me_2SO_4, CaO, MeOH, reflux, 3 h: ~70%);[5740] the original substrate (**46**, X = Y = H) also gave 3-cyclohexyl-5-dimethylamino-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (excess Me_2SO_4, CaO, MeOH, reflux, 8 h: 85%) and some related 5-dialkylamino homologs;[5740] 4,6-bismethylamino-5-pyrimidinamine gave 4,5,6-trismethylaminopyrimidine (MeI, MeOH, reflux, 4 h: > 50%);[1764] 5-amino- gave 5-β-fluoroethylamino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($BrCH_2CH_2F$, NEt_3, Me_2NCHO, 90°, 8 h: 70%);[2658] and 5-ethylamino- gave 5-(*N*-ethyl-*N*-β-hydroxyethylamino)-2,4(1*H*,3*H*)-pyrimidinedione (ethylene oxide, AcOH–H_2O, 20°, 15 h: 44%).[1941] Rather similarly, 2-methoxy-5-pyrimidinamine gave 5-(2′-carboxy-5′-chloroanilino)-2-methoxypyrimidine (2,4-dichlorobenzoic acid, K_2CO_3, Cu, PeOH, reflux, 3 h: ~20%);[1639] likewise, 5-amino- gave 5-(2′,4′-dinitroanilino)-2,4(1*H*,3*H*)-pyrimidinedione (1-fluoro-2,4-dinitrobenzene, $HOCH_2CH_2OH$, 175°, 90 min: 83%).[4874]



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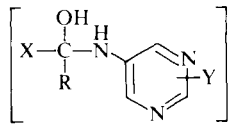

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Reductive alkylation. This process usually involves the one-pot catalytic hydrogenation of a mixture of a 5-pyrimidinamine and an aldehyde or ketone, so that the 5-alkylideneaminopyrimidine [or perhaps its hydrated precursor (**47**)] formed in situ is immediately reduced to the corresponding 5-alkylamino- or 5-dialkylaminopyrimidine, according to the ratio of reactants; the two steps may, of course, be done separately. The following transformations illustrated such alkylations.

4-Methyl-5-pyrimidinamine to 5-ethylamino-4-methylpyrimidine (MeCHO, H_2, Pd, EtOH, 50°, 5 h: 86%).[1833]

2,4,5-Pyrimidinetriamine to 5-isopropylamino-2,4-pyrimidinediamine (AcMe, H_2, Pt, MeOH–H_2O, 25°, 12 h: 80% as hydrochloride).[373]

5-Amino- to a difficulty separable mixture of 5-ethylamino- and 5-diethylamino-2,4(1*H*,3*H*)-pyrimidinedione (MeCHO, H_2, Ni, EtOH, 25°, 8 h: ~80% of mixture).[1941]

5,6-Diamino- to 6-amino-5-benzylamino- (PhCHO, H_2, Ni, EtOH: 48%) and thence to 6-amino-5-(*N*-benzyl-*N*-ethylamino)-4(3*H*)-pyrimidinone (MeCHO, H_2, Ni, EtOH: 48%), which was subsequently debenzylated reductively to afford 6-amino-5-ethylamino-4(3*H*)-pyrimidinone (H_2, Pd, H_2O: ~40%).[1094]

4,5-Diamino- to 4-amino-5-ethylamino- [MeCHO (2 mol), H_2, Ni, EtOH: 32%] or 4-amino-5-diethylamino-2(1*H*)-pyrimidinone [MeCHO (6 mol), likewise: 45%].[1094]

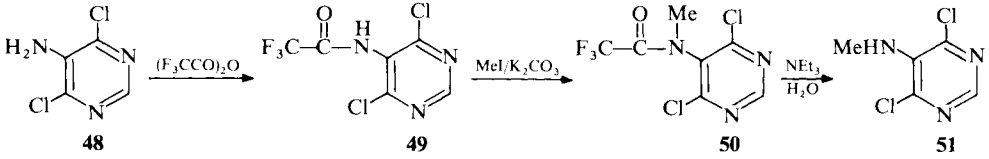
5-Amino-6-ethylamino- to 5,6-bisethylamino- [MeCHO (1 mol), H_2, Ni, EtOH: 25%] or 5-diethylamino-6-ethylamino-4(3*H*)-pyrimidinone [MeCHO (2 mol), likewise: 36%].[1094]

5,6-Diamino- to 6-amino-5-benzylideneamino- (substrate hydrochloride, PhCHO, H_2O, 1 h: ~65%) and thence to 6-amino-5-benzylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (H_2, Ni, *M* NaOH: 67%).[5741]

Also other examples.[1094,3797]

α-Cyanoalkylation. A related process involves treatment of a 5-aminopyrimidine with an aldehyde and cyanide ion to afford the corresponding 5-α-cyanoalkylaminopyrimidine, presumably by initial formation of a Schiff base followed by addition of HCN to the double bond. For example, 2,4,5,6-pyrimidinetetramine hydrochloride gave 5-α-cyanoethylamino-2,4,6-pyrimidinetriamine (MeCHO, KCN, AcOH, MeOH–H_2O, 50°, 15 min: 95%);[5822] 2-phenyl-4,5,6-pyrimidinetriamine gave 5-α-cyanobenzylamino-2-phenyl-4,6-pyrimidinediamine (PhCHO, likewise: > 95%);[5822] and 5-amino- gave 5-α-cyanomethylamino-6-methylamino-4(3*H*)-pyrimidinone (HCHO, KCN, MeOH, reflux, 1 h: 81%).[2420] Such products are the substrates for a useful synthesis of 7-pteridinamines.[5823]

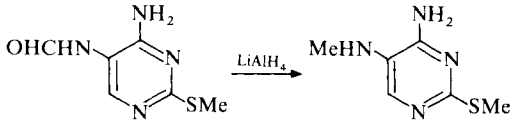
Alkylation of a 5-acylamino substrate. The monoalkylation of a 5-amino group is facilitated greatly by initial acylation followed by alkylation and deacylation. For example, 4,6-dichloro-5-pyrimidinamine (**48**) was converted successively into 4,6-dichloro-5-trifluoroacetamidopyrimidine (**49**) [neat $(F_3CO)_2O$, 20°, 3 h], 4,6-dichloro-5-α,α,α-trifluoro-*N*-methylacetamido-pyrimidine (**50**) (MeI, K_2CO_3, Me_2NCHO, 20°, 18 h), and 4,6-dichloro-5-methylaminopyrimidine (**51**) (NEt_3, H_2O, 20°, 16 h: 60% overall);[632] rather similarly, 5,6-diamino-1,3-dimethyl- successively gave 6-amino-1,3-dimethyl-5-*p*-toluenesulfonamido- (TsCl, pyridine, reflux, 30 min: 80%), 6-amino-5-*N*-ethyl-*p*-toluenesulfonamido-1,3-dimethyl- ($EtSO_4$, 2*M* NaOH, 80°, 1 h: 57%), and 6-amino-5-ethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidine-



48 49 50 51

dione (liquid NH_3, Na: 80% as picrate initially).[1102] Such alkylations without deacylation can be useful.[6236,6241]

Alkylation by reduction of a 5-acylamino substrate. It is sometimes convenient to acylate a 5-pyrimidinamine and then reduce the acyl to an alkyl group with a metal hydride. For example, 2-methylthio-4,5-pyrimidinediamine gave 5-formamido-2-methylthio-4-pyrimidinamine (**52**) (HCO_2H, reflux, 1 h: 80%) and thence 5-methylamino-2-methylthio-4-pyrimidinamine (**53**) ($LiAlH_4$, Et_2O–pyridine, reflux, 2 h: 63%);[1383] 6-dimethylamino-5-formamido- gave 6-dimethylamino-5-methylamino-2-methylthio-4-pyrimidinamine ($LiAlH_4$, Et_2O–pyridine, reflux, 2 h: 79%);[640] and other examples have been reported.[1400,1764] The reductive step fails with some acylamino substrates, probably for lack of solubility in appropriate solvents.[1383,1764]



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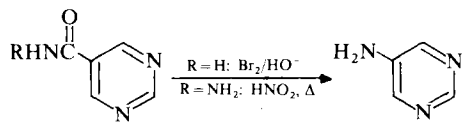
9.1.2.5. By Hofmann or Curtius Reactions

5-Pyrimidinecarboxamides have been converted into 5-pyrimidinamines by employing partial Hofmann or Curtius reactions. Thus 2,4-dimethyl-5-pyrimidinecarboxamide gave 5-methoxycarbonylamino-2,4-dimethylpyrimidine (Br_2, NaOMe, MeOH, reflux: 94%) and thence 2,4-dimethyl-5-pyrimidinamine [$Ba(OH)_2$, H_2O, reflux, 4 h: 86%];[651] 2-ethyl-4-methyl-5-pyrimidinamine (85% overall) was made similarly;[651] 5-pyrimidinecarboxamide (**54**, R = H) gave 5-pyrimidinamine (**55**) (NaOCl, KOH, H_2O, 0° then 100°, 30 min: 61%);[1969] 5-pyrimidinecarbohydrazide (**54**, R = NH_2) gave the same product (**55**) (HNO_2, AcOH–H_2O, 5°; solid intermediate, PhH, reflux, briefly:



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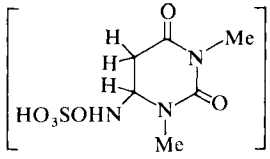
58%);[1969] and 2,4,6-trimethyl-5-pyrimidinecarbohydrazide gave 2,4,6-trimethyl-5-pyrimidinamine (Pe^{i}ONO, HCl, 0° then 60°, 2 h; urethane intermediate dry distilled from CaO: 40%).[651]

9.1.2.6. By Other Means

Several other procedures of minor utility may be used to furnish 5-aminopyrimidines, as illustrated in the following examples.

1. The *deacylation* of 5-formamido- gave 5-amino-6-isopropylamino-2,4(1*H*,3*H*)-pyrimidinedione (HCl, MeOH, reflux, 2 h: 80% as hydrochloride);[1353] 5-acetamido- gave 5-amino-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione (HCl, EtOH, reflux, 5 h: 80%);[369] 2-amino-6-benzylamino-5-formamido- gave 2,5-diamino-6-benzylamino-4(3*H*)-pyrimidinone (HCl gas, MeOH, 25°, 90 min: 77% as dihydrochloride);[90,1279] 5-acetamido-2-amino- gave 2,5-diamino-6-methyl-4(3*H*)-pyrimidinone (6*M* HCl, reflux, 30 min: 83% as hydrochloride);[596] and other cases have been noted.[632,1281,1288,1679,2391,5824,5825]
2. The *self-transamination* of 5-amino-2,4(1*H*,3*H*)-pyrimidinedione gave bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)amine [HCl (0.5 mol) in glycol, 20°, 12 h: 95%].[6872]
3. The *hydrolysis of a Schiff base*, 2-butoxy-5-dimethylaminomethyleneaminopyrimidine, gave 2-butoxy-5-pyrimidinamine (0.4*M* K_2CO_3, 110°, 8 h, sealed ?: 55%);[3428] 5-dimethylaminomethyleneamino-2-pyrimidinamine gave 2,5-pyrimidinediamine (0.4*M* K_2CO_3, 100°, 1 h: 85%).[1623]
4. Treatment with *nitrous acid* converted 5-hydrazino- into 5-azido-2-methylsulfonylpyrimidine (55%).[1710]
5. The *thermal rearrangement* of 5-allylamino- gave 6-allyl-5-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (tetralin, reflux, 12 h: 24%).[854]
6. The *covalent adduct* (**56**?) from hydroxylamine-*O*-sulfonic acid and 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**57**) gradually underwent complicated changes to afford 5-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (pH 2, 37°, 40 h: > 95%).[1128]
7. 5-*Diazo*- gave 5-morpholino-2,4(1*H*,3*H*)-pyrimidinedione [morpholine, $Rh(OAc)_3$, PhH, reflux, ? h: 95%].[6127]



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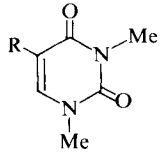

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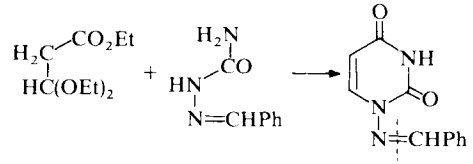
9.1.3. Preparation of *N*1- or *N*3-Aminopyrimidines

Most such aminopyrimidines have been made by *primary syntheses* (see Chapters 2 and 3). For example, diethyl malonate with *N*-piperidinourea gave 1-piperidino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (NaOEt, EtOH, reflux, 5 h: 90%);[2079] ethyl *β*,*β*-diethoxypropionate (**58**) with benzaldehyde semicarbazone (**59**) gave 1-benzylideneamino-2,4(1*H*,3*H*)-pyrimidinedione (**60**) (NaOEt, EtOH, reflux, 16 h: ~60%) and thence 1-amino-2,4(1*H*,3*H*)-pyrimidinedione (1.5*M* HCl, steam distillation until all PhCHO gone: > 90%);[1483] *β*-(methoxycarbonylamino)acryloyl chloride with benzaldehyde hydrazone gave successively the intermediate (**61**) (PhH, 20°, 24 h: ~70% crude), 3-benzylideneamino-2,4(1*H*,3*H*)-pyrimidinedione (**62**) (NaOEt, EtOH, reflux, 3 h: ~65%), and 3-amino-2,4(1*H*,3*H*)-pyrimidinedione (dilute HCl, steam distillation: ~80%).[1486]



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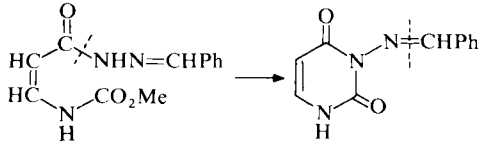
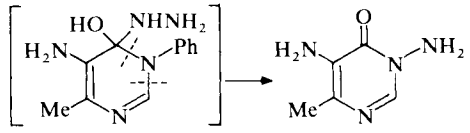


61 **62**

A few *N*-aminopyrimidines have been made by *other means*. For example, 5-amino-6-methyl-3-phenyl-4-(3*H*)-pyrimidinone gave 3,5-diamino-6-methyl-4(3*H*)-pyrimidinone (**64**) ($H_2NNH_2.H_2O$, reflux, 3 h: 71%), possibly by loss of aniline from the intermediate adduct (**63**);[2416,2417] treatment of 2,4(1*H*,3*H*)-pyrimidinedione with hydroxylamine-*O*-sulfonic acid gave a mixture of 1- and 3-amino-2,4(1*H*,3*H*)-pyrimidinedione plus a little 1,3-diamino-2,4(1*H*,3*H*)-pyrimidinedione, each isolated initially as a benzylidene derivative (*M* NaOH, 35°, 7 h: then PhCHO, 2 h);[1483,1486] and 3-amino-6-methyl-4(3*H*)-pyrimidinone was so made.[5898]



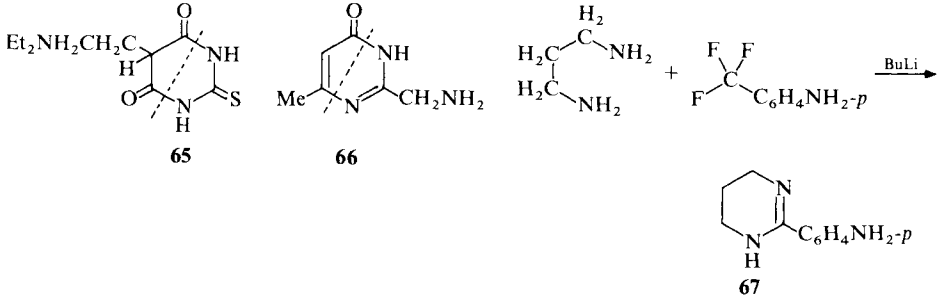
63 **64**

9.1.4. Preparation of Extranuclear Aminopyrimidines

Extranuclear aminopyrimidines have been made by a variety of methods, summarized briefly in the following subsections.

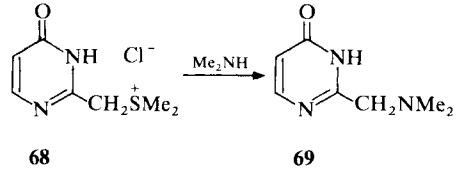
9.1.4.1. By Primary Syntheses

Only a few ω-aminopyrimidines have been made by direct primary syntheses; a few more have been made with an initially protected amino group (see Chapters 2 and 3). Such syntheses are exemplified in the condensation of diethyl α-(β-diethylaminoethyl)malonate with thiourea in ethanolic ethoxide to give 5-β-diethylaminoethyl-2-thioxo-1,2-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**65**) in poor yield;[980] of ethyl acetoacetate with 2-phthalimidoacetamidine to give 6-methyl-2-phthalimidomethyl-4(3*H*)-pyrimidinone (NaOMe, MeOH, reflux, 1 h: 67%) and thence 2-aminomethyl-6-methyl-4(3*H*)-pyrimidinone (**66**) (H_2NNH_2, EtOH, reflux, 1 h; then HBr: isolated as hydrobromide);[1416] and of 1,3-diaminopropane with *p*-trifluoromethylaniline to give 2-*p*-aminophenyl-1,4,5,6-tetrahydropyrimidine (**67**) (BuLi, Et_2O, $-5°$, 90 min: 72%).[6028]



9.1.4.2. By Aminolyses

Aminolysis of ω-halogenopyrimidines is facile and useful: it has been discussed in Section 6.9. Leaving groups other than halogeno substituents have been employed occasionally: for example, 2-dimethylsulfoniomethyl-4(3*H*)-pyrimidinone chloride (**68**) gave 2-dimethylamino-4(3*H*)-pyrimidinone (**69**) (Me_2NH, MeOH, 25°, 15 h: 73%).[2635]



9.1.4.3. By Reductive Processes

Extensive use has been made of reduction to convert a variety of substrate types into ω-aminopyrimidines.

With nitriles as substrates. The reduction of pyrimidinecarbonitriles to the corresponding aminomethylpyrimidines is usually done by catalytic hydrogenation, in alcoholic ammonia to minimize the formation of secondary amines as by-products;[1408] however, other reducing agents have been used, especially when hydrogenation was precluded. The processes are illustrated in the formation of the following products.

5-Aminomethyl-4-pyrimidinamine (H_2, Ni, MeOH–NH_3, 100°, 125 atm, 6 h: > 95% as dihydrochloride;[1457] H_2, Pd, AcOH–HCl–H_2O, 25°, 1 atm: 70% as dihydrochloride).[1414]

5-Aminomethyl-2-methyl-4-pyrimidinamine (H_2, Ni, MeOH–NH_3, 25°, 125 atm, 1 h: 93% as dihydrochloride; plus bis(4-amino-2-methylpyrimidin-5-ylmethyl)amine: 4%).[1408, cf. 409,1466,1472]

5-Aminomethyl-2,4-pyrimidinediamine (H_2, Ni, MeOH–NH_3, 25°, 125 atm, 1 h: 94% with no secondary amine; similarly at 3 atm: 81%).[1408,1480]

5-Aminomethyl-4-methoxy-2-methylpyrimidine (H_2, Ni, Pr^iOH, 4 h: 80%).[1387]

2-Amino-5-γ-aminopropyl-6-methyl-4(3*H*)-pyrimidinone (H_2, Pt, HCl–H_2O–EtOH, 18 h: 75% as dihydrochloride).[942]

5-Aminomethyl-1-cyclohexyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (H_2, Co, EtOH–NH_3, 80°, 50 atm, 8 h: 95% as dihydrochloride); also analogs.[5143]

5-Aminomethyl-2-butyl-4-pyrimidinamine (electrolytic in HCl: ~65% as dihydrochloride).[5742]

5-Aminomethyl-2-ethylthio-4-pyrimidinamine ($LiAlH_4$, Et_2O, 90 min: ~74%).[1249]

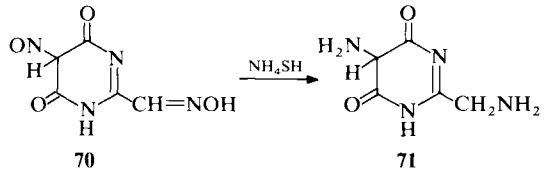
5-Aminomethyl-4-chloro-2-ethylthiopyrimidine ($LiAlH_4$, Et_2O, 1 h: 89%).[1249]

Also other examples.[417,1010,1118,1120,1387,1412,1421,3614]

With oximes as substrates. Appropriate aldoximes and ketoximes may be reduced to aminoalkylpyrimidines, as illustrated in the following transformations.

4-Pyrimidinecarbaldehyde oxime to 4-aminomethylpyrimidine (H_2, Pd, MeOH, 1 h: 72%).[826]

5-Nitroso-4,6-dioxo-1,4,5,6-tetrahydro-2-pyrimidinecarbaldehyde oxime (**70**) to 5-amino-2-aminomethyl-4,6(1*H*,5*H*)-pyrimidinedione (**71**) (NH_4SH, H_2O, 25°, 5 min: 43%).[937]



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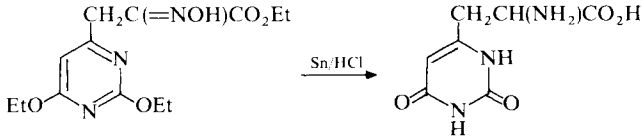
4-Acetonyl-2,6-dimethylpyrimidine oxime to 4-β-aminopropyl-2,6-dimethylpyrimidine (H_2, Ni, EtOH, 25°, 36 h: 18% as maleate salt).[1611]

4-Ethoxalylmethyl-2,6-diethoxypyrimidine oxime (**72**) to 6-β-amino-β-carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione (**73**) (Sn, HCl, reflux, 30 min: 51%).[4699]



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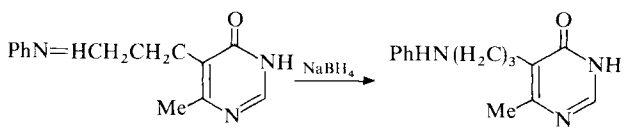
2-Oxalomethyl-4,6(1*H*,5*H*)-pyrimidinedione oxime to 2-β-amino-β-carboxyethyl-4,6(1*H*,5*H*)-pyrimidinedione (H_2, Ni, NH_4OH, 25°, 18 h: 66%).[4699]

5-Ethyl-6-oxalomethyl-2-thioxo-1,2-dihydro-4-(3*H*)-pyrimidinone oxime to 6-β-amino-β-carboxyethyl-5-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (Na/Hg, EtOH–H_2O, reflux, 30 min: 33%).[3422]

Also other examples.[686,1611,3140,5979,5993]

With Schiff bases as substrates. In much the same way, Schiff bases (from pyrimidine aldehydes or ketones with primary amines) may be reduced to aminoalkylpyrimidines. For example, 5-β-formylethyl-6-methyl-4(3*H*)-pyrimidinone reacted with aniline to give crude 6-methyl-5-γ-phenyliminopropyl-4(3*H*)-pyrimidinone (**74**), which underwent borohydride reduction to 5-γ-anilinopropyl-6-methyl-4(3*H*)-pyrimidinone (**75**) (20% overall).[3193] Rather similarly, 2-acetamido-5-β-formylethyl-6-methyl- gave 2-acetamido-6-methyl-5-γ-(pyridin-3′-ylamino)propyl-4(3*H*)-pyrimidinone (3-pyridinamine, H_2, Pd, EtOH, 3 days: 62%; one pot reaction);[5743] and many other examples have been reported.[881,4784,5743,5984]



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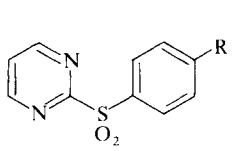
With nitro or azido substrates. It is obvious that extranuclear nitro- or azidopyrimidines may be reduced to their amino analogs. For example, 5-ethyl-5-*p*-nitrophenyl- gave 5-*p*-aminophenyl-5-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (H_2, Pd, EtOH–AcOH, 60°, 40 min: 94%),[244] 6-*p*-nitrostyryl- gave 6-*p*-aminophenethyl-5-δ-phenylbutyl-2,4-pyrimidinediamine (H_2 Pt, EtOH, 25°, 24 h: 92%).[4280] 2-*p*-nitrophenylsulfonylpyrimidine (**76**, R = NO_2) gave 2-*p*-aminophenylsulfonylpyrimidine (**76**, R = NH_2) (Fe, AcOH–H_2O, reflux, 2 h: 72%),[5098] and other examples have been cited in Section 5.1.2.1. Likewise, 5-(3′-azido-4′-chlorophenyl)- gave 5-(3′-amino-4′-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine (NaHS, H_2O, 65°: 84%),[462] and 4-β-azidoethyl- (**77**, R = N_3) gave 4-β-aminoethylpyrimidine (**77**, R = NH_2) (H_2, Pt, MeOH, 8 h: < 22%).[1226]



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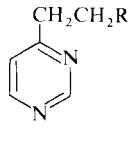

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9.1.4.4. By Aminoalkylation Reactions

The replacement of a hydrogen atom by an aminoalkyl group or of geminate hydrogen atoms by an aminoalkylidene group has been used quite widely to prepare such extranuclear aminopyrimidines.

Using the Mannich reaction. Application of the Mannich reaction (CH_2O, RNH_2 or R_2NH, H^+, H_2O) to *C*-methylpyrimidines, with or without additional electron-donating substituents, has been discussed in Section 4.2.3.7. Its application to other substrates is illustrated in the following reactions, some of which provided 1- or 3-aminoalkylated products.

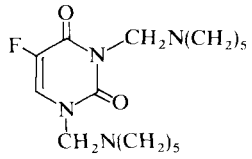
3-Methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 5-diethylaminomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($Et_2NH.HCl$, CH_2O, AcOH, reflux, 48 h: 34%).[251]

1-(2′,4′-Dimethylbenzyl)-3-phenyl-2-thioxo-2,3-dihydro- gave 1-(2′,4′-dimethylbenzyl)-3-phenyl-5-piperidinomethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (piperidine, CH_2O, EtOH, reflux, 2 h: > 50%).[179]

4-Methyl-5-pyrimidinol gave 4-dimethylaminomethyl-6-methyl-5-pyrimidinol (neat $Me_2NCH_2NMe_2$ in place of Me_2NH + CH_2O, reflux, 2 h: 60%).[6017]

4,6-Dimethyl-5-pyrimidinol 1-oxide gave 2-dimethylaminomethyl-4,6-dimethyl-5-pyrimidinol 1-oxide ($Me_2NCH_2NMe_2$, PhH, reflux, 40 min: 85%).[21]

5-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione gave 5-fluoro-1,3-bispiperidinomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**78**) (piperidine, CH_2O, EtOH–H_2O, reflux, 2 h: 65%).[537]



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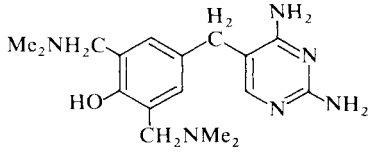
3,4,5,6-Tetrahydro-2(1*H*)-pyrimidinone gave 1-morpholinomethyl- and 1,3-bis(morpholinomethyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (morpholine, CH_2O, EtOH–H_2O, reflux: 60% and 25%, respectively).[3914]

4-Amino-2(1*H*)-pyrimidinone gave 1-diethylaminomethyl-4-diethylaminomethylamino-2(1*H*)-pyrimidinone (Et_2NH, CH_2O, H_2O–THF, 25°, 15 h: 75%).[129]

5-Ethyl-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione gave 5-ethyl-1-methyl-3,5-bismorpholinomethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (morpholine, CH_2O, EtOH–H_2O, reflux, 30 min: 86%).[5745]

5-*p*-Hydroxybenzyl- gave 5-(3′,5′-bisdimethylaminomethyl-4′-hydroxybenzyl)-2,4-pyrimidinediamine (**79**) (Me_2NH, CH_2O, EtOH?, reflux, 2 h: 71% as phosphate salt).[419]

Also other examples.[21,69,419,3913,5744,5745,6017]

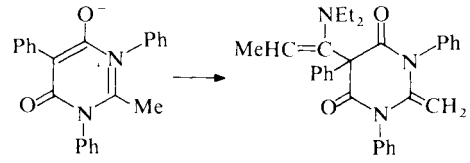


79

Using direct aminoalkylation. A substrate may be aminoalkylated at any site susceptible to regular alkylation: indeed, a few examples of aminoalkyl ation are included with those for the regular *O*-, *N*-, or *S*-alkylations of appropriate substrates (e.g., in Sections 7.1.3.5 and 8.1.3.2). Less obvious aminoalkylations are illustrated by the following transformations.

5-Pyrimidinol to 4-dimethylaminomethyl- (26%) or 4,6-bis(dimethylaminomethyl)-5-pyrimidinol (53%) (neat $Me_2NCH_2NMe_2$, reflux, for 30 min or 3 h, respectively).[1737]

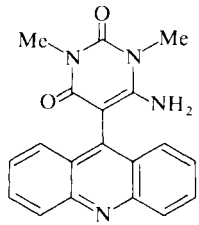
2-Methyl-6-oxo-1,3,5-triphenyl-1,6-dihydropyrimidinium-4-olate (**80**) to 5-(1′-diethylaminoprop-1′-enyl)-2-methylene-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (**81**) ($Et_2NC{\equiv}CMe$, PhMe, reflux, 8 h: 66%).[286]



80 **81**

6-Methyl-4(3*H*)-pyrimidinone to 6-methyl-2-pyridin-2′-yl-4(3*H*)-pyrimidinone (pyridine 1-oxide, Pd + Pt, pyridine, reflux, 30 min: ~35% plus other products);[5746] analogs likewise.[3975]

6-Amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione to its 5-acridin-9′-yl derivative (**82**) (9-chloroacridine, EtOH, 20°, 20 h: 85%; structure confirmed by X-ray).[315]



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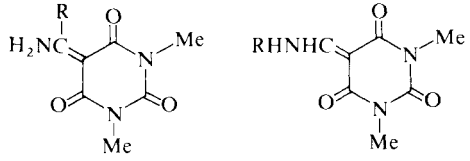
Using direct aminoalkylidenation. Aminoalkylidenation may occur by attack of a simple amide or its derived Vilsmeier reagent at the 5-position of appropriate pyrimidine substrates, at an activated methyl group, or even at a primary amino group. Such processes are clarified in the following specific reactions.

1,3-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione gave 5-aminomethylene- (**83**, R = H) (neat H_2NCHO, 195°, 1 h: 92%; H_2NCHS, Et_2O–MeOH, 40°, 30 min: 90%) or 5-α-aminoethylidene-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**83**, R = Me) (neat $AcNH_2$, 200°, 1 h: 55%); also 1,3-dimethyl-5-methylaminomethylene- (**84**, R = Me) (neat MeHNCHO, 205°, 2 h: 93%; MeHNCHS, NEt_3, EtOH, reflux, 4 h: 26%) or 5-anilinomethylene-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**84**, R = Ph) (neat PhHNCHO, 180°, 2 h: 76%; PhHNCHS, NEt_3, EtOH, reflux, 3 h: 89%).[1207]



83 **84**

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione gave its 5-dimethylaminomethylene derivative [$Me_2NCHO + POCl_3$ (Vilsmeier reagent: $Me_2\overset{+}{N}{=}CHCl$, Cl^-), 20°, 3 h: 88%].[83]

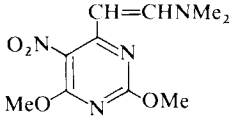
1,3-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione gave its 5-dimethylaminomethylene derivative (Me_2NCHO, $COCl_2$, PhH, 40°, 30 min: 81%).[2843]

1,3-Dibutyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione gave its 5-aminomethylene derivative [1,3,5-triazine (≡HCHO), EtOH, reflux, 30 min: > 95%; neat HCHO, reflux, 3 h: 68%].[389]

4,6(1*H*,5*H*)-Pyrimidinedione gave its 5-dimethylaminomethylene derivative (Me_2NCHO, $COCl_2$, $CHCl_3$, 50°, 3 h: 93%).[1027,1028,3600]

2,4-Dimethoxy-6-methyl-5-nitropyrimidine gave 4-β-dimethylaminovinyl-2,6-dimethoxy-5-nitropyrimidine (**85**) [$Me_2NCH(OMe)_2$, Me_2NCHO, 20°, 3 h: 98%].[2086]

6-Chloro-4,5-pyrimidinediamine gave 4-chloro-5,6-bis(dimethylaminomethyleneamino)pyrimidine (**86**) (Me_2NCHO, $POCl_3$, 90°, 1 h: ~40%).[2556]



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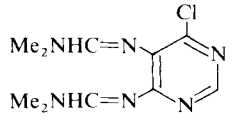

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9.1.4.5. By the Hofmann or Curtius Reaction

A few extranuclear aminopyrimidines have been made by the degradation of appropriate amides or hydrazides. Thus the Hofmann reaction was used to convert 5-carbamoylmethyl- into 5-aminomethyl-2-methyl-4-pyrimidinamine (Br_2, 2.5*M* KOH, 95°, 3 h: isolated via a Schiff base);[750,1388] 2-β-carbamoylethyl- into 2-β-aminoethylpyrimidine (Cl_2, 2.5*M* NaOH, 20°, 1 h, then 95°, 1 h: 60% as dihydrochloride);[1225] and related products were made similarly.[750,1225,1388] Several rather complicated and ill-described variations of the Curtius reaction were employed to convert 5-hydrazinocarbonylmethyl- into 5-aminomethyl-2-methyl-4(3*H*)-pyrimidinone,[1388] 2-ethylthio-5-hydrazinocarbonylmethyl-4(3*H*)-pyrimidinone, or 5-hydrazinocarbonylmethyl-2,4-(1*H*,3*H*)-pyrimidinedione, into 5-aminomethyl-2,4(1*H*,3*H*)-pyrimidinedione,[1395,1489] and the homologous 5-aminomethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione was made rather similarly.[1415] In addition, 1-β-carboxyethyl- was converted into 1-β-aminoethyl- (40%) via 1-β-azidocarbonylethyl-2,4(1*H*,3*H*)-pyrimidinedione.[3775]

9.1.4.6. By other Means

Several minor routes to extranuclear aminopyrimidines are illustrated in the following paragraphs.

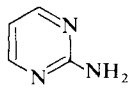
From ω-acylaminopyrimidines. 2-Chloro-6-methylamino-5-*N*-methylformamido-4(3*H*)-pyrimidinone gave 5,6-bismethylamino-2,4(1*H*,3*H*)-pyrimidinedione (HCl, EtOH, reflux: 82%);[1776] 1-δ-phthamimidobutyl- gave 1-δ-aminobutyl-2,4(1*H*,3*H*)-pyrimidinedione (6*M* HCl, reflux, 12 h: 76%);[5747] 6-*p*-acetamidobenzylamino- gave 6-*p*-aminobenzylamino-2,4(1*H*, 3*H*)-pyrimidinedione (2.5*M* NaOH, reflux, 1 h: 54%);[5748] 2,4-bismethylthio-6-phthalimidomethyl- gave 4-aminomethyl-2,6-bismethylthiopyrimidine ($H_2NNH_2.H_2O$, EtOH–dioxane, reflux, 3 days: 88%;[311] and other examples have been reported.[1335,1389,1451,1567,1915,2208,4344]

Transamination. Although regular ω-transaminations are unknown in the pyrimidine series, a rather specialized example has been described: quaternization of the Mannich base, 5-dimethylaminomethyl-2-methyl-4-pyrimidinamine, with acetonic methyl iodide at 20° gave 2-methyl-5-trimethylammoniomethyl-4-pyrimidinamine iodide, which underwent transamination in aqueous ammonia (170°, 8 h, sealed) to give 5-aminomethyl-2-methyl-4-pyrimidinamine (~40% as dihydrochloride).[1074]

Derivatization. The attachment of an amino-bearing portion by aminoalkylation has been discussed in Section 9.1.4.4, but other rather mundane derivatizations are possible: for example, 6-chloro- gave 6-β-dimethylaminoethoxy-2,4-pyrimidinediamine ($Me_2NCH_2CH_2ONa$, xylene, reflux, 6 h: 74%);[1768] irradiation of 1-methyl-4,6-diphenyl-2(1*H*)-pyrimidinone and triethylamine in benzene gave 6-α-diethylaminoethyl-1-methyl-4,6-diphenyl-3,6-dihydro-2(1*H*)-pyrimidinone (40%).[3923]

9.1.5. Fine Structure of Aminopyrimidines

Apart from poorly based suggestions to the contrary before 1950, there has never been any real doubt that all primary or secondary 2- and 4/6-aminopyrimidines (like their 5- or ω-isomers) exist as such, rather than as their iminodihydro tautomers. As early as 1955, a uv spectral comparison of 2-pyrimidinamine (**87**), 2-methylaminopyrimidine (**88**), 2-dimethylaminopyrimidine (**89**), and 1-methyl-2(1*H*)-pyrimidinimine (**90**) under carefully controlled conditions of pH showed that the tautomeric amines (**87**, **88**) did exist almost entirely as such, at least in aqueous solution.[708,3377] A similar comparison[708,3377] of 4-pyrimidinamine (**91**), 4-dimethylaminopyrimidine (**92**), 1-methyl-4(1*H*)-pyrimidinimine (**93**), and 3-methyl-4(3*H*)-pyrimidinimine (**94**) was completed in 1971 when the final "fixed" imine (**94**) at last became available: it



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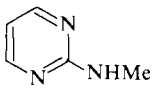

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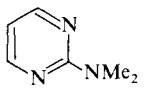

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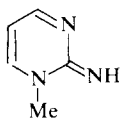

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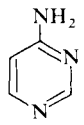

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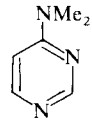

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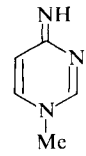

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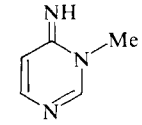

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emerged that 4-pyrimidinamine (**91**) did, in fact, exist predominantly as such;[1508] meanwhile, nmr spectra had proved consistent with such formulation of simple aminopyrimidines.[3290,4612] The many experimental studies on tautomerism in aminopyrimidines and other susceptible entities have been reviewed authoritatively.[5172,5173]

Two rules -of -thumb are relevant and applicable to the spectral correlation of tautomeric pyrimidinamines and pyrimidinones. In this context,[3348] the Jones rule[5749,5750] indicates that the neutral species of a 2-, 4/6-, or 5-pyrimidinamine has an uv spectrum similar to that of the corresponding 2-pyrimidinone, 4/6-pyrimidinone, or 5-pyrimidinol as the anion; the Albert–Taguchi rule[5751] further indicates that the cation of a 2-pyrimidinamine has a uv spectrum similar to tnat of the corresponding 2-pyrimidinone as the neutral species, but this correlation is inapplicable at the 4-, 5-, or 6-position.

9.1.6. Reactions of Aminopyrimidines

Although a few reactions are particulary suited or even unique to one or other type of aminopyrimidine, the majority of reactions are common to 2-, 4/6-, 5-, *N*-, and ω-aminopyrimidines: accordingly, this major section is not divided according to such types of substrate.

9.1.6.1. Hydrolysis

The direct (H^+, HO^-) and indirect (HNO_2) hydrolysis of 2/4/6-, 5-, and ω-aminopyrimidines have been discussed in Sections 7.1.1.3, 7.2.1.3, and 7.3.1.2, respectively.

9.1.6.2. Diazotization and Subsequent Reactions

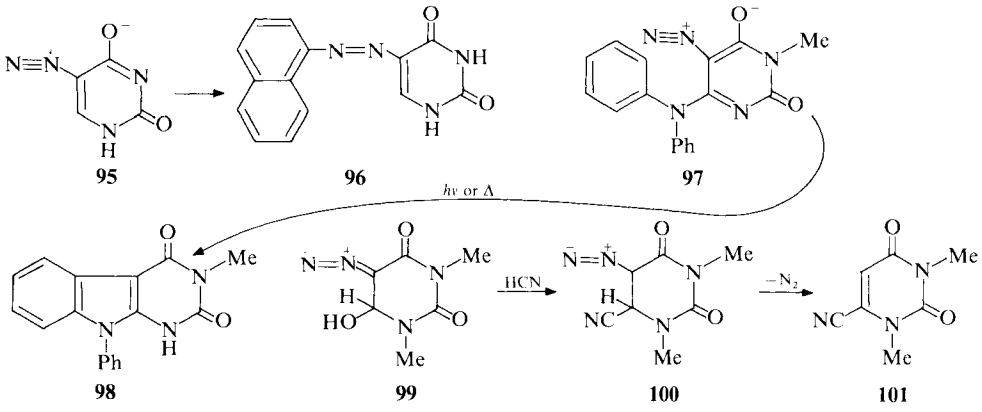
Although any primary pyrimidinamine may be converted into its transient diazonio analog by treatment with nitrous acid, only from 5-pyrimidinamines are such products sufficiently stable for isolation or even short-term preservation in solution; other diazoniopyrimidines must be used in subsequent reactions as they are being formed.

The formation of such diazoniopyrimidines (transient or otherwise) and their conversion into the corresponding *pyrimidinones or pyrimidinols* have just been

cross-referenced in the preceding subsection; their conversion into 2-, 4/6-, 5-, or *ω-halogenopyrimidines* has been discussed in Sections 6.1.4, 6.5.3, and 6.6.4, respectively; and some of their coupling reactions have been mentioned toward the end of Section 5.3.1.2.

The formation of (sometimes isolable) 5-diazoniopyrimidines, usually from the corresponding 5-pyrimidinamines, and some of their typical subsequent reactions are illustrated in the following examples.

5-Diazonio-2-oxo-1,2-dihydro-4-pyrimidinolate (**95**) ($NaNO_2$, *M* HCl, − 5°, 1 h: then neutralized and dried at 100°/20 mm)[4849, cf. 4839,5752] and thence to 5-(2′-aminonaphthalen-1′-ylazo)-2,4(1*H*,3*H*)-pyrimidinedione (**96**) (β-naphthylamine, HCl, 0°, 1 h),[711] 5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione (see Section 8.2.1), 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (CuCN, KCN, H_2O, 20° then 95°, 1 h: 64% overall),[1175, cf. 2869] or 5,5′-bipyrimidine-2,2′,4,4′(1*H*,1′*H*,3*H*,3′*H*)-tetrone (Cu powder, H_2O, 5°, 40 min: 48% overall).[4892]



5-Diazonio-($NaNO_2$, 2*M* HCl, 10°: chloride, in solution) and thence to 5-*p*-dimethylaminophenylazo-4,6-dimethyl-2-pyrimidinamine (*N*,*N*-dimethylaniline.HCl, NaAc, 10°, 2 days).[645]

5-Diazonio- $NaNO_2$, dilute H_2SO_4, 0°, 10 min: sulfate in solution) and thence to 5-azido-2-methoxy-4,6-diphenylpyrimidine (KN_3, H_2O, 20°, 30 min: ~40% overall).[4758]

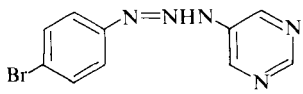
2-Amino-5-diazonio-6-diisopropylamino-4(3*H*)-pyrimidinone chloride (HCl, MeOH, Pe^{i}ONO, 0°: 76%) and thence to 2-amino-5-diazonio-6-diisopropylamino-4-pyrimidinolate [H_2O, pH 8 (ion exchange): 44% overall].[1051]

5-Diazonio-6-diphenylamino-3-methyl-2-oxo-2,3-dihydro-4-pyrimidinolate (**97**) ($NaNO_2$, AcOH, then H_2O: 90%) and thence to 3-methyl-9-phenylindolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**98**) (EtOH, *hv*, 5 h: > 95%; or Me_2NCHO, reflux, 5 h: 60%).[575]

A diazo-hydrate, formulated as **99**, from 5-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaNO_2$ HCl, 0°, 40 min, to pH 7, 60°, 10 min: 82%);[1129] thence to the corresponding diazonitrile (**100**?) (HCN, H_2O, 5°, 2 days: 82%);[2672] and finally to 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**101**) ($NaHCO_3$ H_2O, 20°, 24 h: 52%).[2672]

Also a variety of other examples.[243,248,380,645,711,1032,1051,1129,1424,2068,3209,5135,5754]

In this context, an interesting reaction is that of 5-pyrimidinamine with *p*-bromobenzenediazonium chloride to afford 5-(3′-*p*-bromophenyl-2′-triazeno)-pyrimidine (**102**) (63%) and two minor products.[5755]



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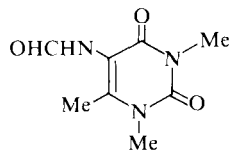
9.1.6.3. Acylation

All primary or secondary aminopyrimidines undergo acylation at their amino group(s). However, 5- or ω-amino groups acylate more easily than do 2- or 4/6-amino groups: for example, a 4,5-diaminopyrimidine invariably acylates first at the 5-position and only more slowly (or under more vigorous conditions) at the 4-position. Diacylation of a primary amino group has been reported occasionally. Formylations usually occur satisfactorily in hot 90–98% formic acid, but most other acylations proceed best with an acyl halide or acid anhydride as the reagent, sometimes in the presence of a base such as pyridine. The reagents and conditions required for various acylations of diverse aminopyrimidine substrates are illustrated in the formation of the following acylaminopyrimidines.

5-Formylations

5-Formamido-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**103**) (HCO_2H, reflux, 2 h: 89%).[3189]



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4-Chloro-5-formamido-6-methylthiopyrimidine (HCO_2H, Ac_2O, 100°, 30 min: 93%).[2171]

5-Formamido-4-pyrimidinamine (HCO_2H, reflux, 1 h: 80%).[1383,2296]

5-Formamido-4,6-bismethylaminopyrimidine (HCO_2H, 95°, 1 h: > 90%).[1764]

2-Dimethylamino-5-formamido-4-methyl-6-methylaminopyrimidine (HCO_2H, reflux, 2 h: < 90%).[601]

6-Amino-1-methyl-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione (HCO_2H, reflux, 10 min: 27%).[1104]

6-Amino-5-formamido-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione (HCO_2H, reflux: 75%).[1278]

5-Thioformamido-4,6-pyrimidinediamine (HCS_2Na, H_2O, 25°, 12 h: ~80%).[1619]

Also other examples.[116,676,681,805,1080,1179,1202,1239,1282,1288,1379,1400, 1434, 1451,1557,1558,1569,1649,2307,3176,3177,4804,4857,5756,5757,6241]

2-, 4/6 or ω-Formylations

6-Formamido-2,4(1*H*,3*H*)-pyrimidinedione (HCO_2H, $HCONH_2$, reflux, 1 h: 80%).[1126]

4,5-Diformamido-2-methyoxypyrimidine (AcOCHO, 50°, 1 h).[681]

6-β-Formylhydrazino-5-nitro-4(3*H*)-pyrimidinone (HCO_2H, reflux, 30 min: 78%).[2173]

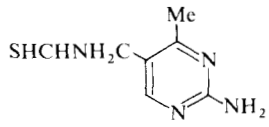
2-β-Formylhydrazino-5-hexyl-6-methyl-4-(3*H*)-pyrimidinone (HCO_2H, 60°, 90 min: 89%).[4171]

4-Chloro-6-β-formylhydrazino-5-pyrimidinamine (HCO_2Bu, reflux, 2.5 h: 57%).[632]

5-Formamidomethyl-2-methyl-4-pyrimidinamine ($H_2NCH{=}NH$, EtOH, reflux, 1 h: 45%;[685] HCO_2H, reflux, 4 h: > 90%;[3178] $HCONH_2$, 100°, 10 h).[3179,3180]

4-Methyl-5-thioformamidomethyl-2-pyrimidinamine (**104**) (HCS_2Na, H_2O, 20°, 4 h: 71%).[960]

Also other examples.[619,1406,1457,1480,1752,2170,3027,3195,3220]



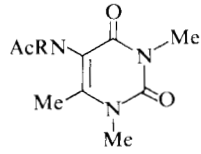
104

5-Acetylations

5-Acetamidopyrimidine (Ac_2O, PhH, reflux, 2 h).[711]

5-Acetamido-2,4-dimethoxypyrimidine (Ac_2O, PhH, reflux, 2 h: 91%).[1602]

5-Acetamido-6-methyl-2,4(1*H*,3*H*)-pyrimidinedithione (Ac_2O, reflux, 30 min: 61%).[676]



105

5-Acetamido- (**105**, R = H) (Ac_2O, 20°, 3 h: ~80%) or 5-diacetylamino-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**105**, R = Ac) (Ac_2O, reflux, 30 min: ~75%).[1127]

5-Acetamido-6-amino-4(3*H*)-pyrimidinone (Ac_2O, NaOAc, AcOH, reflux, 6 h: > 90% crude).[604]

6-Methyl-5-thioacetamido-2,4(1*H*,3*H*)-pyrimidinedione ($MeCS_2H$, dioxane, 95°, 4 h: > 95%).[1239]

5-α-Chloroacetamido-2,4,6-pyrimidinetriamine (neat $ClCH_2CO_2H$, 95°, 1 h: 51%).[5758]

4-Amino-5-trifluoroacetamido-2(1*H*)-pyrimidinone (F_3CCO_2H, reflux, 1 h: 88%).[1291]

6-Amino-5-α-cyanoacetamido-4(3*H*)-pyrimidinone (neat $NCCH_2CONH_2$, 190°, 15 min: ~70%).[1679]

6-Benzylamino-5-trifluoroacetamido-4-pyrimidinamine [$(F_3CCO)_2O$, PhH, reflux, 2 h: > 90%).[5759]

Also other examples.[628,645,651,2620,4006,5760,5778,5779]

2-, 4/6-, or ω-Acetylations

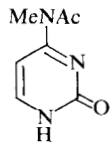
2-Acetamido- (Ac_2O, reflux, 1 h: 56–90%)[708,709] or 4-acetamidopyrimidine (likewise: 77%).[708, cf. 696,710]

2-Acetamido-5-nitropyrimidine (Ac_2O, reflux: 83%).[704, cf. 703,705]

6-Acetamido-4-pyrimidinamine (Ac_2O, dioxane, reflux, 4 h: 87%)[612] or 4,6-bisacetamidopyrimidine (excess Ac_2O likewise: 78%).[612, cf. 1379]

6-Acetamido-2-methylthio-4-pyrimidinamine (AcCl, AcOEt, reflux, 1 h: 90% as hydrochloride; or Ac_2O, pyridine, 20°, 15 h).[699]

4-*N*-Methylacetamido-2(1*H*)-pyrimidinone (**106**) (Ac_2O, AcOH, reflux, 3 h: > 90%).[1542]



106

2-Diacetylamino-4-methylpyrimidine (neat Ac_2O, reflux, 2 h: > 50% plus some 2-acetamido-4-methylpyrimidine).[686]

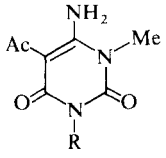
4-β-Acetylhydrazino-6-chloro-5-pyrimidinamine (Ac_2O, 20°, 2.5 h: 48%).[632]

2,4-Bisacetamido-6-piperidinopyrimidine 3-oxide (neat Ac_2O, 25°, 30 min: 70%).[5762]

5-Butyl-2-α-chloroacetamido-6-methyl-4(3*H*)-pyrimidinone ($ClCH_2COCl$, Me_2NCHO, 25°, 2 h: 70%).[672]

6-Acetamido-2,4(1*H*,3*H*)- or 6-acetamido-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O, AcOH, reflux, 1 h: 76% or 50%, respectively).[694]

5-Acetyl-6-amino-1-methyl- (**107**, R = H) or 5-acetyl-6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**107**, R = Me) (each from its 5-deacetyl substrate; Ac_2O, AcOH, reflux: 99% or 83%, respectively; note *C*-acylation!).[694]



107

5-Acetamido-2,6-diamino- (AcOH, reflux, 3 h: ~90%) or 2,5,6-trisacetamido-4(3*H*)-pyrimidinone (Ac_2O, reflux, 6 h: ~20%).[629]

5-Acetamidomethyl-2-methyl-4-methylaminopyrimidine (Ac_2O, NEt_3: > 95%).[1406]

2-Acetamido-5-γ-acetamidopropyl-6-methyl-4(3*H*)-pyrimidinone (Ac_2O, AcMe–H_2O, 20°, 18 h: ~50%).[942]

2-*p*-Acetamidophenylsulfonylpyrimidine (Ac_2O, pyridine: 89%).[5098]

4-*N*-Acetoxyacetamido- from 4-hydroxyamino-6-methyl-2-phenylpyrimidine (Ac_2O, dioxane, 20°, 18 h: 98%).[3910, cf. 6014]

Also other examples.[386,580,581,603,610,618,630,635,638,640,646,653,659,664,670,693,718–720,723,805,1328,1462,2025,2038,2377,2577,3368,4279,4280,4411,4967,5096,5756,5761,5763–5767]

Benzoylations

5-Benzamido- (BzCl, pyridine, 25°, 15 h: 65%)[711] or 2-benzamidopyrimidine (BzOPh, tetralin, 180°, 2 h: 26%).[5768]

4-Benzamido-1-methyl-2(1*H*)-pyrimidinone (BzCl, pyridine, 100°, 90 min: ~60%).[696, cf. 720,1531]

5-Benzamido-4-pyrimidinamine and 4,5-bisbenzamidopyrimidine (BzCl, pyridine, reflux, briefly: 45% and 10%, respectively).[681,5679]

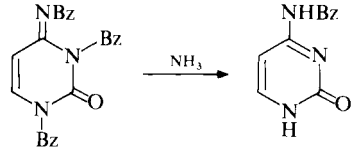
4-Amino-5-benzamido-2(1*H*)-pyrimidinone (BzCl, *M* NaOH, 25°, 30 min: 87%).[236]

4-*p*-Chlorobenzamido-2,6-dimethoxypyrimidine (*p*-ClC_6H_4COCl, pyridine, 25°: ~80%); also many analogs.[4968]

4-Benzamido-5-pyrimidinol and 4-benzamido-5-benzoyloxypyrimidine from 4-amino-5-pyrimidinol (BzCl, pyridine, 70°, 1 h: 31% and 23%, respectively).[718]

1,3-Dibenzoyl-4-benzoylimino-3,4-dihydro-2(1*H*)-pyrimidinone (**108**) (BzCl, pyridine, 25°, 3 days: ~40%) and thence 4-benzamido-2(1*H*)-pyrimidinone (**109**) (NH_3, EtOH, 0°, 15 h).[720]

Also other examples.[594,628,646,2577,5769,5770]



108 **109**

Other acylations

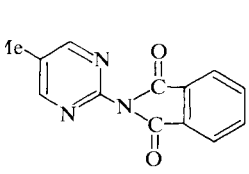
4-Octanamido-2(1*H*)-pyrimidinone ($C_7H_{15}COCl$, pyridine, reflux, 2 h: 78%).[5771]

5,6-Bisisobutyramido-4(3*H*)-pyrimidinone (Pr^iCOCl, pyridine, 25°, 1 h: 71%).[605]

5-Methyl-2-phthalimidopyrimidine (**110**) (neat phthalic anhydride, 190°, 2 h: 56%).[4687]

6-Amino-1,3-dimethyl-5-phthalimido- (phthalic acid, 180°, 10 min: 78%) or 1,3-dimethyl-5,6-diphthalimido-2,4(1*H*,3*H*)-pyrimidinedione (phthaloyl chloride, 160°, 1 h: 55%).[5772]

N,*N*′-Dipyrimidin-5-yloxamide (**111**) [$(COCl)_2$, $CHCl_3$, reflux, 2.5 h: 84%].[5773]



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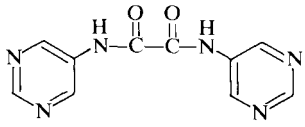

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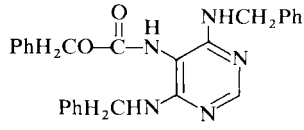


112

4,6-Bisbenzylamino-5-benzyloxycarbonylaminopyrimidine (**112**) ($PhCH_2O$-COCl, KOAc, EtOAc–H_2O: 51%);[4546] see also Section 9.2.1.1.

2-Acetoacetamidopyrimidine [$(H_2C{=}CO)_2$, $CHCl_3$, 25°, 2.5 h: 80%].[3361]

5-Acetoacetamido-4-pyrimidinamine (neat $AcCH_2CO_2Et$, reflux, 5 min: 84%).[2183]

5-3′-Bromopropionamido-6-methoxy-4(3*H*)-pyrimidinethione ($BrCH_2CH_2$-COCl, K_2CO_3, AcMe, 20°, 2.5 h: 70%).[1365]

6-Amino-5-3′-carboxypropionamido-4(3*H*)-pyrimidinone [$(CH_2CO_2H)_2$, 210°, 10 min: ~60%].[1679]

2,4-Dimethoxy-6-nicotinamidopyrimidine (nicotinoyl chloride, pyridine, 60°, 5 min: ~75%).[4968]

Also other examples.[316,628,676,1451,1996,2015,3004,3899,4964,4968,5256,5774–5777,6765]

Alkane- or arenesulfonylations (see also Section 9.4.4)

2-Benzenesulfonamidopyrimidine ($PhSO_2Cl$, pyridine, warm briefly: > 50%).[5780–5782]

4,6-Dimethyl-2-*p*-toluenesulfonamidopyrimidine (TsCl, pyridine, 100°, 1 h: ~50%).[646]

2,4-Dimethoxy-6-*p*-nitrobenzenesulfonamidopyrimidine (*p*-$O_2NC_6H_4SO_2Cl$, pyridine, 60°, 30 min: 60%).[5087]

1-Allyl-6-amino-5-benzenesulfonamido-3-ethyl-2,4(1*H*,3*H*)-pyrimidinedione ($PhSO_2Cl$, pyridine, 95°, 90 min: 93%).[5783]

4-*p*-Acetamidobenzenesulfonamido-6-methoxy-2-methylthio- (*p*-$AcHNC_6H_4SO_2Cl$, pyridine, 25°, 15 h) and thence to 4-methoxy-2-methylthio-6-sulfanilamidopyrimidine (2.5*M* NaOH, 95°, 5 h).[1358]

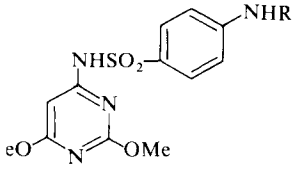
4-*p*-Ethoxycarbonylaminobenzenesulfonamido-2,6-dimethoxy- (**113**, R = CO_2Et) (*p*-$EtO_2CHNC_6H_4SO_2Cl$, pyridine, 60°, 1 h: 88%) and thence to 2,4-dimethoxy-6-sulfanilamidopyrimidine (**113**, R = H) (*M* NaOH, 90°, 1 h: 89%).[2504]

2-Butanesulfonamido-4-(3*H*)-pyrimidinone and a major by-product, 4-pyridinio-2-pyrimidinamine chloride ($BuSO_2Cl$, pyridine, 40°, 15 h: 16% and 39%, respectively).[5786]

4-Bis(*p*-nitrobenzenesulfonyl)amino-5,6-dimethoxypyrimidine (*p*-$O_2NC_6H_4SO_2Cl$, pyridine, 20°, 14 h: > 95%) and thence to 4,5-dimethoxy-6-*p*-nitrobenzenesulfonamidopyrimidine (NaOH, MeOH, reflux, 15 min: > 95%).[916]

N,*N*′-(Dipyrimidin-2-yl)methanedisulfonamide (**114**) [2-pyrimidinamine with $CH_2(SO_2Cl)_2$, dioxane: 20%].[490]

5-(4′-Bromo-3′,5′-dimethoxybenzyl)-2,4-bistrifluoromethanesulfenamidopyrimidine (**115**) (F_3CSCl, pyridine, THF, −200° then 25°, 24 h: 82%).[3905]



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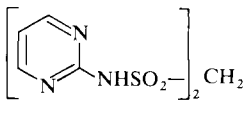

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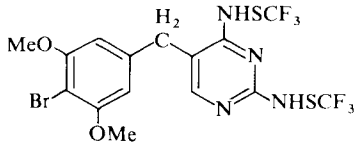
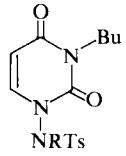


115

3-Butyl-1-*p*-toluenesulfonamido- (**116**, R = H) and 3-butyl-1-ditosylamino-2,4(1*H*,3*H*)-pyrimidinedione (**116**, R = Ts) (TsCl, pyridine 20°, 20 h: ~75% and ~5%, respectively); the second gave the first product (0.5*M* NaOH, EtOH, reflux, 5 h: 89%).[1483]

Also other examples.[560,593,615,1007,1358,1567,1616,1811,2109,2131,2164,2193,2208,2209,2504,2946,2970,3358,4045,4737,5783–5788,6208]



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9.1.6.4. Alkylation

Unlike acylation, alkylation of a primary or secondary 2- or 4/6-aminopyrimidine usually takes place initially on a ring nitrogen to afford a 1- or 3-alkylated iminopyrimidine, which may subsequently undergo Dimroth rearrangement to its alkylamino isomer: these processes are discussed fully in Sections 9.3.1.1 and 9.3.2, and the exceptional direct alkylations of such aminopyrimidines on extranuclear nitrogen are covered in Section 9.1.1.4. Naturally, a 5-aminopyrimidine undergoes quite regular alkylations at its amino group, as described in Section 9.1.2.4.

9.1.6.5. Alkylidenation (Schiff Base Formation)

Most primary aminopyrimidines undergo alkylidenation by aldehydes, ketones, or their acetals to afford Schiff bases. These alkylideneamino- or alkylidenehydrazinopyrimidines must be distinguished from the Schiff bases derived from pyrimidinecarbaldehydes or ketones with arylamines or arylhydrazines, usually described as anils or hydrazones of the parent pyrimidines (see Section 10.6.2).

The formation of the following Schiff bases, in each case from the corresponding amino- or hydrazinopyrimidine, illustrates the usual conditions employed.

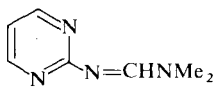
From 2- or 4/6-pyrimidinamines

2-Dimethylaminomethyleneaminopyrimidine (**117**) ($ClHC{=}\overset{+}{N}Me_2$ Cl^-, PhMe, reflux, 1 h: 88%).[74]

4-Chloro-2-dimethylaminomethyleneamino-6-methylpyrimidine [neat $Me_2NCH(OMe)_2$, reflux, 2 h: 22%].[496]

4-Dimethylaminomethyleneamino-1-methyl-2(1*H*)-pyrimidinone [from 4-amino-2(1*H*)-pyrimidinone, $Me_2NCH(OMe)_2$, trace of F_3CCO_2H, reflux, 15 h: 98%; note unexpected methylation] and thence to 4-amino-1-methyl-2(1*H*)-pyrimidinone (0.1*M* HCl, 20°, 12 h: 97%).[1540]

Ethyl 2,2-bis(pyrimidin-2′-ylamino)acetate (**118**) (from 2-pyrimidinamine, EtO_2CCHO, AcOH–H_2O, 25°, 15 h: 69%; abnormal product).[4787]



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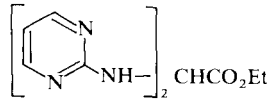

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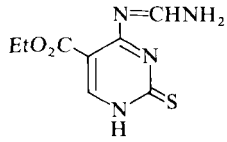


119

2-*p*-Nitrobenzylideneaminopyrimidine (from 2-phosphoranylideneaminopyrimidine, *p*-$O_2NC_6H_4CHO$, PhH, reflux, 15 h: 63%).[5794]

Ethyl 4-aminomethyleneamino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate (**119**) ($HCONH_2$, 130°, 40 h).[1651]

6-*p*-Bromobenzylideneamino-2,4(1*H*,3*H*)-pyrimidinedione (*p*-BrC_6H_4CHO, EtOH–H_2O, reflux, 4 h: 75%).[325, cf. 1]

Also other examples.[1,1019,1342,2134,3175,5792,5793,6941]

(*Note*: Formaldehyde often behaves abnormally, as illustrated in the formation of the following products from the corresponding aminopyrimidines.)

2-Hydroxymethylaminopyrimidine [CH_2O (1 mol), H_2O, 20°, 30 min: 67%] or bis(pyrimidin-2-ylamino)methane [CH_2O (0.5 mol), H_2O, 20°, 1 h: 42%].[5808]

2-Bis(hydroxymethyl)amino-4-*β*-(5′-nitrofuran-2′-yl)vinylpyrimidine (excess CH_2O, H_2O, reflux, 1 h: ~20%).[5809]

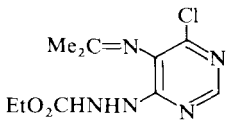
Bis(4-amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-5-yl)methane (CH_2O, H_2O, 95°, briefly: > 90%; amino group unattacked!).[2659]

From 5-pyrimidinamines

5-*p*-Nitrobenzylideneaminopyrimidine (*p*-$O_2NC_6H_4CHO$, trace of AcOH, 160°, 5 min: > 90%).[711]

5-Benzylideneamino-2,4(1*H*,3*H*)-pyrimidinedione (PhCHO, H_2O–EtOH, reflux, 4 h: 98%).[5795]

4-Chloro-6-*β*-ethoxycarbonylhydrazino-5-isopropylideneaminopyrimidine (**120**) (AcMe, $NaHCO_3$, 25°, 4 h: 59%).[5801]



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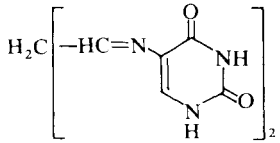


121

1,3-Bis(2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5-ylimino)propane (**121**) ($OHCCH_2CHO$, HCl–H_2O, 20°, 1 h: 48% as hydrochloride).[652]

2,6-Diamino-5-benzylideneamino-4(3*H*)-pyrimidinone (PhCHO, EtOH–H_2O, 0°, 15 h: 82%).[5796]

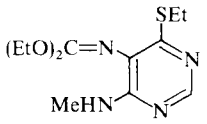
5-Ethoxymethyleneamino-4-pyrimidinamine [neat $HC(OEt)_3$, reflux, 5 min: 66%].[622]

6-Chloro-5-α-ethoxypropylideneamino-4-pyrimidinamine [$EtC(OEt)_3$, 95°, 2 h: 75%] or 4-chloro-5,6-bis(α-ethoxypropylideneamino)pyrimidine [$EtC(OEt)_3$, trace of HCO_2H, 100°, 2 h: 64%].[622]

5-Diethoxymethyleneamino-4-ethylthio-6-methylaminopyrimidine (**122**) [$C(OEt)_4$, AcOH, 25°, 18 h: 75%].[3130]

5-Ethoxycarbonylmethyleneamino-6-methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone [$EtO_2CCH(OH)OEt$, H_2O, 50°, 40 min: 98%].[3871]

5-Dimethylaminomethyleneamino-2,6-dimethyl-4(3*H*)-pyrimidinone [$Me_2NCH(OMe)_2$, EtOH, reflux, 6 h: 50%].[58]



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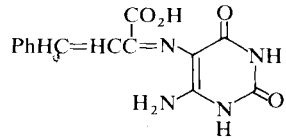


123

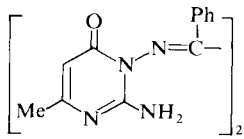
6-Amino-5- (**123**) [$PhCH{=}CHC(=O)CO_2H$, H_2O, mild HO^-, 25°, 2 h: 70%] or 5-amino-6-(1′-carboxy-3′-phenylprop-2′-enylideneamino)-2,4(1*H*,3*H*)-pyrimidinedione (likewise but mild H^+: 80%).[563]

Also other examples.[594,601,652,684,1103,1398,3189,3522,4279,4836,5797–5800, 5802–5805,6239–6944]

From 1/3- or ω-aminopyrimidines

1-Diphenylmethyleneamino-2,4(1*H*,3*H*)-pyrimidinedione (Ph_2CO, NH_4Cl, 200°, 20 h: ~40%).[1483]

1,2-Bis(2′-amino-4′-methyl-6′-oxo-1′,6′-dihydropyrimidin-1′-ylimino)-1,2-diphenylethane (**124**) [from 2,3-diamino-6-methyl-4(3*H*)-pyrimidinone, PhCOCOPh, 230°, 10 min: 84%].[1573]



124

4-Benzylideneamino-5-benzylideneaminomethyl-2-methylpyrimidine? (PhCHO, Et_2O, 20°, product uncharacterized but dilute HCl at 50° gave back the starting material).[750]

From hydrazinopyrimidines

2-Benzylidenehydrazinopyrimidine (PhCHO, Me_2NCHO, reflux 1 h: 74%).[2062]

4-Ethylidenehydrazino-6-methylpyrimidine (MeCHO, EtOH, 95°, 90 min).[5807]

2-Benzylidenehydrazino-6-methyl-4(3*H*)-pyrimidinone (PhCHO, H_2O–Et_2O, warm: ~75%).[1429,5807, cf. 5159]

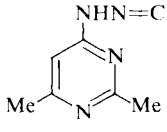
4-Benzylidenehydrazino-2,6-dimethoxypyrimidine (PhCHO, EtOH, warm: 83%).[2577]

4-Benzylidenehydrazino-6-chloro-5-pyrimidinamine (PhCHO, EtOH, 20°, 15 h: ~50%; note preferential attack on hydrazino group).[1777]

2,4-Dimethyl-6-(1′-methylpropylidene)hydrazinopyrimidine (**125**) (neat AcEt, reflux, 20 min: 43%).[2718]

6-β-Ethylidene-α-methylhydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (MeCHO, AcOH, 5°, 15 min: 92%).[3040]

4-Dimethylaminomethylenehydrazinopyrimidine [neat $Me_2NCH(OMe)_2$, 25°, 30 min: 48%].[5812]



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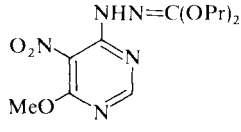

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4-(Dipropoxymethylene)hydrazino-6-methoxy-5-nitropyrimidine (**126**) [$C(OPr)_4$, 160°, 20 min: ~55%].[3237]

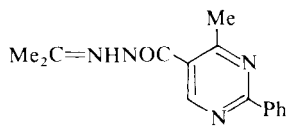
4-α-Ethoxyethylidenehydrazino-2-methoxy-5-nitropyrimidine [$MeC(OEt)_3$, EtOH, reflux, 1 h: ~65%].[2559]

4-Chloro-6-methyl-2-(5′-nitrofurfurylidenehydrazino)pyrimidine from 2-benzylidenehydrazino-4-chloro-6-methylpyrimidine (5-nitro-2-furaldehyde, *M* HCl, 55°, 90 min: ~90%).[2562,5820]

Also other examples.[1277,1552,2197,2562,2691,2716,2717,3039,3041,3194,3210,3211, 3216,3227,3301,4764,5806,5810–5819]

(*Note*: Pyrimidinecarbohydrazides also form such Schiff bases, as indicated in the following examples.)

N-Isopropylidene- (**127**) (AcMe, reflux, 5 h: 67%) or *N*-(4′-hydroxy-3′-methoxybenzylidene)-4-methyl-2-phenyl-5-pyrimidinecarbohydrazide (vanillin, EtOH, reflux, 5 h: 60%).[5821]



127

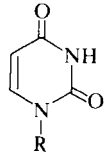
4,5-Pyrimidinediamine underwent an interesting reaction with hexane-2,5-dione in refluxing alcoholic acetic acid to give 5-(2′,5′-dimethylpyrrol-1′-yl)-4-pyrimidinamine (53%).[6225]

9.1.6.6. Conversion into Heterobicyclic Products

Amino- and hydrazinopyrimidines are used widely in the synthesis of several bicycle fused-pyrimidine systems. Appropriate volumes in this *Heterocyclic Compounds* series should be consulted for details of such synthetic routes to pteridines, purines, thiazolopyrimidines, *v*-triazolopyrimidines, pyrimidopyrimidines, pyrazolopyrimidines, and related systems. Unexpected results have been noted occasionally.[15,17,22,150,177,280,371,398,410,426,464,475,481,3737]

9.1.6.7. Removal of Amino or Hydrazino Groups

The *removal of an amino group* in favor of hydrogen is poorly represented by the conversion of 1-amino-2,4(1*H*,3*H*)-pyrimidinedione (**128**, R = NH_2) into 2,4(1*H*,3*H*)-pyrimidinedione (**128**, R = H) ($NaNO_2$, AcOH, 20°: 88%),[1483] 3-amino-1-methyl- into 1-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($NaNO_2$, 3*M* HCl, 5°: ~50%),[1486] 1-amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**129**, X = NH_2, Y = H) into 5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**129**, X = H, Y = NO) ($NaNO_2$, HCl–AcOH, 0°, 2 h: 40%),[1518] 1-amino-2-thioxo-2,3-dihydro- into 5-nitroso-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione (likewise: 17%),[1518] 4-amino-2(1*H*)-pyrimidinone into 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (H_2, Pt, 0.1*M* HCl: isolated as picrate),[721,3399] and 6-amino-2,4(1*H*,3*H*)-pyrimidinedione or its 5-methyl derivative into 2,4(1*H*,3*H*)-pyrimidinedione or its 5-methyl derivative, respectively (H_2, Pt, H_2O, warm: there appears to be some confusion whether the substrates were authentic or not).[3463]



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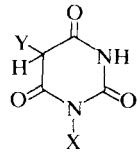

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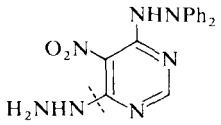
In contrast, *oxidative dehydrazinolysis* of 2- or 4/6-hydrazinopyrimidines is a facile reaction. Examples of its use in the indirect removal of halogeno substituents have been given in Section 6.7.1; the reagents and conditions required for the oxidative process are illustrated further in the dehydrazinolysis of the following substrates.

4-Hydrazino-2-methyl-6-phenylpyrimidine ($CuSO_4$, H_2O, reflux, 2.5 h: > 75%).[4130]

4-β,β-Diphenylhydrazino-6-hydrazino-5-nitropyrimidine (**130**) (AgOAc, H_2O, 20°, 5 min: 65%; note survival of the $NHNPh_2$ group).[5071]

4-Hydrazino-2-methyl-5-nitropyrimidine (Ag_2O, MeOH, 50°, 2 h: ~65%).[1552]

4-Hydrazino-2(1*H*)-pyrimidinone (Ag_2O, H_2O, 25°, 24 h: 79%).[2699]



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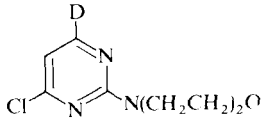

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4-Chloro-6-hydrazino-2-morpholinopyrimidine (AgOAc, H_2O, 70°, 3 h: 30%; product **131** was 96% specifically deuterated).[3527]

Also other examples.[746,1857,2084,3355,3546]

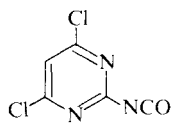
The *reductive splitting* of a hydrazino- to the corresponding aminopyrimidine has been covered in Section 9.1.1.4.

9.1.6.8. Other Reactions

The remaining reactions of aminopyrimidines are exemplified briefly in the following paragraphs.

1. The direct *fluorination* of 6-amino-2,4(1*H*,3*H*)-pyrimidinedione in water at 0° gave a mixture of 6-difluoroamino-, 6-amino-5-fluoro-, and 6-difluoroamino-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione, of which the first was identified by unambiguous synthesis from 6-chloro-2,4(1*H*,3*H*)-pyrimidinedione with difluoroamine (HNF_2);[9] likewise, 4-amino-2(1*H*)-pyrimidinone gave 4-difluoroamino-, 4-amino-5-fluoro-, and 4-difluoroamino-5-fluoro-2(1*H*)-pyrimidinone.[9]

2. The conversion of *amino into isocyanato/isothiocyanato* groups occurred on treatment of 4,6-dichloro-2-pyrimidinamine with oxalyl chloride in refluxing benzene for 2 h to give 4,6-dichloro-2-isocyanatopyrimidine (**132**) (95%) with loss of hydrogen chloride and carbon monoxide;[2482] on treatment of 5-amino-2,4(1*H*,3*H*)-pyrimidinedione with aqueous thiophosgene at 25° for 3 h to give



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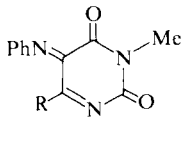
5-isothiocyanato-2,4(1*H*,3*H*)-pyrimidinedione (77%);[3315] and on treatment of 2-trimethylsilylaminopyrimidine with ethereal thiophosgene at − 60° for 5 h to give 2-isothiocyanatopyrimidine (48%).[3314]

3. The rarely used conversion of *aminopyrimidines into pyrimidinethiones* has been covered in Section 8.1.1. Rather similarly, treatment of the tertiary amine, 6-(*N*-*p*-bromophenyl-*N*-methylamino)-3-methyl-5-phenylimino-2,4(3*H*,5*H*)-pyrimidinedione (**133**, R = $NMeC_6H_4Br$-*p*), with phenylmethanethiol in acetonitrile at 25° for 15 h gave a separable mixture of the corresponding 6-benzylthio compound (**133**, R = SCH_2Ph) (40%), its reduction product 5-anilino-6-benzylthio-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**134**, R = SCH_2Ph) (25%), and some reduced starting material (**134**, R = $NMeC_6H_4Br$-*p*).[329]



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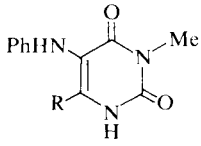

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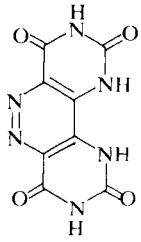
4. The action of *nitrosobenzene* in glacial acetic acid converted 5-pyrimidinamine into 5-phenylazopyrimidine (15%).[711]

5. The *oxidation* of hydroxyamino- to nitrosopyrimidines has been discussed in Section 5.2.1.3. The troublesome aerial oxidation of many di- and triaminopyrimidines to highly colored products has been little investigated,[1503] probably because it has little effect on their performance as intermediates and, in any case, can be largely obviated by storing such amines as their reasonably air-stable salts; moreover, even the highly susceptible base, 4,6-bismethylamino-5-pyrimidinamine, has been obtained as a white solid by preparing, isolating, and storing it under strictly anaerobic conditions.[1770] The oxidation of 5-amino-2,4(1*H*,3*H*)-pyrimidinedione with potassium ferricyanide appeared to give the interesting tricyclic product, dipyrimido[5,4-*c*,4,5-*e*]pyridazine-2,4,7,9(1*H*,3*H*,8*H*,10*H*)-tetrone (**135**);[5827] the same substrate was also oxidized by bromine or permanganate to afford some mundane products.[771,5828]



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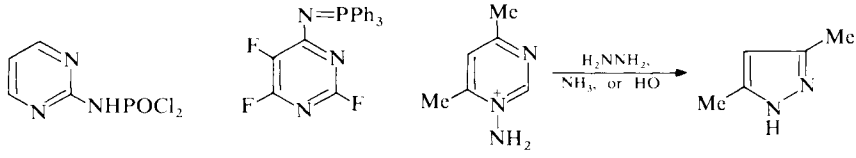
6. The reactions of *phosphorus reagents with aminopyrimidines* are typified by the transformation of 2-pyrimidinamine to 2-dichlorophosphinylaminopyrimi-

dine (**136**) ($POCl_3$, reflux, 6 h: 90%),[5829] 4-methoxy-5-methyl-2-pyrimidinamine to 2-dichlorophosphinylamino-4-methoxy-5-methylpyrimidine ($POCl_3$, PhH, 50°, 3 h: 69%),[5830] sodium 2-amino-5-pyrimidinesulfonate to 2-dichlorophosphinylamino-5-pyrimidinesulfonyl chloride (neat PCl_5, reflux, 5 h: ~50%),[1766] 2-amino-5-methylthio-4(3*H*)-pyrimidinone to 4-chloro-2-dichlorophosphinylamino-5-methylthiopyrimidine ($POCl_3$, Me_2NPh, reflux, 2 h: 71%),[1567] and 4-azido-2,5,6-trifluoropyrimidine to 2,4,5-trifluoro-6-triphenylphosphoranylideneaminopyrimidine (**137**) with loss of nitrogen (Ph_3P, Et_2O, reflux, 4 h: 81%).[1700]

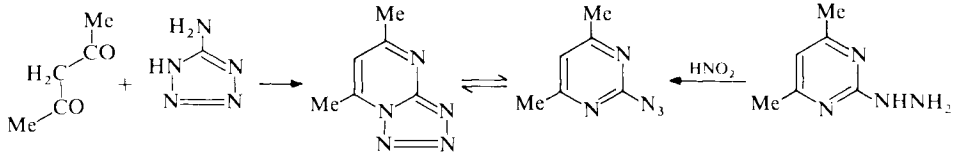


136 **137** **138** **139**

7. An *apparent ring contraction* occurred when 1-amino-4,6-dimethylpyrimidinium salt (**138**) reacted with liquid ammonia, cold aqueous alkali, or (best) with hydrazine in THF at 25° for 3 h to give 3,5-dimethylpyrazole (**139**) (80%); the mechanism proved complicated.[5831]

8. Data on the *metallic complexes of aminopyrimidines* are typified by measurements of the stability constants for silver complexes of several 2-pyrimidinamines[395] and by the X-ray structure of a complex involving 2-pyrimidinamine, 2-(*p*-chlorophenoxy)-2-methylpropionic acid, and copper ion.[484]

9. Conversion of *hydrazino- to azidopyrimidines* may be done with nitrous acid: for example, 4,6-dihydrazino- gave 4,6-diazidopyrimidine (HNO_2, H_2O, 25°, briefly: 77%).[2461] Although invariably written as azidopyrimidines in this book (see Section 6.7.3), it should be noted that 2- or 4/6-azidopyrimidines may (and usually do) exist largely as the corresponding isomeric tetrazolopyrimidines: thus condensation of 5-tetrazolamine (**140**) with acetylacetone or the treatment of 2-hydrazino-4,6-dimethylpyrimidine (**142**) with nitrous acid gave the same product, formulated as 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine (**141a**) $\rightleftharpoons$ 2-azido-4,6-dimethylpyrimidine (**141b**).[3206,5832] Such equilibria were subsequently examined in detail by physical means (nmr, ir, ms): the ratio of monocyclic to bicyclic form is affected profoundly by the position(s) of the azido group(s), the type of solvent, the state of ionization, and the nature and position(s) of any other substituent(s).[607,1701,1702,1706,1716, cf. 5833,5834]



140 **141a** **141b** **142**

10. Methods for making several other types of (*substituted-amino*)- *from aminopyrimidines* are covered in the sections indicated: alkoxycarbonylaminopyrimidines (urethanes), Section 9.2.1.1; ureidopyrimidines, Section 9.2.2.1; nitrosoaminopyrimidines, Section 5.2.1.2; sulfoaminopyrimidines, Section 9.2.5; and guanidinopyrimidines, Section 9.2.8.

9.2. *N*-(FUNCTIONALLY SUBSTITUTED) AMINOPYRIMIDINES

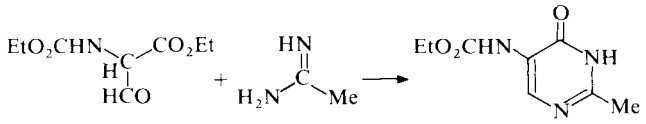
This category includes the pyrimidine urethanes (alkoxycarbonylaminopyrimidines), the pyrimidine ureides (ureidopyrimidines), the sulfonamidopyrimidines, the trialkylammoniopyrimidine halides, and several less important types.

9.2.1. Alkoxycarbonylaminopyrimidines (Urethanes)

Pyrimidine urethanes and thiourethanes have been studied more widely than their uses appear to justify.

9.2.1.1. Preparation of Urethanes

By primary syntheses. A few 2- and 5-alkoxycarbonylaminopyrimidines have been made by primary syntheses (see Chapters 2 and 3): for example, ethyl 2-ethoxycarbonylamino-2-formylacetate (**143**) and acetamidine in very dilute alkali at 25° for 2 days gave 5-ethoxycarbonylamino-2-methyl-4(3*H*)-pyrimidinone (**144**) (30%).[1118]



143 **144**

By alkoxyacylation of aminopyrimidines. Nearly all primary or secondary aminopyrimidines can be alkoxyacylated directly on their amino groups by using ethyl chloroformate or similar reagents, thereby affording urethanes. Reagents and conditions are illustrated in the formation of the following products.

2-Ethoxycarbonylaminopyrimidine (EtO_2CCl, pyridine, < 10°, 1 h: 25%;[5835] EtO_2CCl, NaOH–H_2O, 40°: 42%).[2893]

5-Ethoxycarbonylamino-4-methyl-6-*p*-nitrobenzylidenehydrazinopyrimidine (EtO_2CCl, pyridine, 25°, 10 min: 79%).[1038]

4-Methoxycarbonylaminopyrimidine [MeO_2CCl (0.5 mol), PhH, reflux: 36%].[2893]

4-Hexyloxycarbonylamino-2(1*H*)-pyrimidinone (HxO_2CCl, pyridine, 95°, 2 h: > 45%).[723]

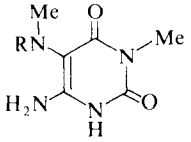
5-Ethoxycarbonylamino-4,6-pyrimidinediamine (EtO_2CCl, pyridine, < 5°, 2 h: 58%).[3544]

6-Amino-5-(*N*-ethoxycarbonyl-*N*-methylamino)-3-methyl- (**145**, R = CO_2Et) from 6-amino-3-methyl-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione (**145**, R = H) (EtO_2CCl, $NaOH–H_2O$, 25°, 1 h: 60%).[5824]

4,6-Bis(ethoxycarbonylamino)pyrimidine [EtO_2CCl, $NaOH–H_2O$, 25°, 1 h: 25%; $(EtO_2C)_2O$ (2 mol), EtOH, 25°, briefly: 95%].[3004]

2-(Ethylthio)carbonylaminopyrimidine (EtSOCCl, EtOH, 12°, 1 h: 55%).[3004]

4,6-Bis[(ethylthio)carbonylamino]pyrimidine (EtSOCCl, pyridine, 25°, 90 min: 26%) and thence to 4,6-bis(ethoxycarbonylamino)pyrimidine ($HgCl_2$, EtOH, NEt_3, reflux, 1 h: 83%).[3004]



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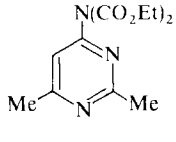

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4-Ethoxycarbonylamino- (ethoxycarbonylpyridinium chloride, pyridine, 80°, 24 h: 80%) or 4-di(ethoxycarbonyl)amino-2,6-dimethylpyrimidine (**146**) [$(EtO_2C)_2O$, EtOH, reflux, 1 h: 38%].[5836]

4-Chloro-6-β-ethoxycarbonylhydrazino-5-pyrimidinamine (EtO_2CCl, dioxane, 25°, 20 h: 70%).[5801]

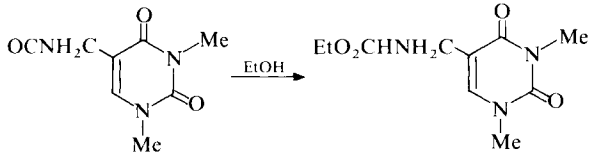
Also other examples in the foregoing references and elsewhere.[341,634,655,1106,1222,1775,2682,5068,6049]

By partial Hofmann or Curtius reactions. Without being pedantic about classifications, investigators have used certain stages of the Hofmann or Curtius reactions to advantage in preparing urethanes. The following sequences illustrate such procedures but see also Section 10.8.2.

2,4-Dimethyl-5-pyrimidinecarboxamide to 5-methoxycarbonylamino-2,4-dimethylpyrimidine (NaOMe, MeOH, Br_2, reflux: 94%).[651]

5-Chloromethyl- to 5-isocyanatomethyl- (**147**) (AgOCN, PhH, reflux, 5 h: 52%) to 5-ethoxycarbonylaminomethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**148**) (EtOH, reflux, ? h: 91%).[1114]

Butyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate to 2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbohydrazide ($H_2NNH_2.H_2O$, MeOH, reflux, 20 min: 66%) to 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl



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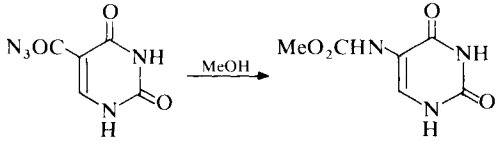


149 150

azide (**149**) ($NaNO_2$, dilute HCl, $< 10°$, 20 min: 56%) to 6-methoxycarbonylamino-2,4(1*H*,3*H*)-pyrimidinedione (**150**) (MeOH, reflux, 3 h: ~80%; likewise for homologs).[1645,5837]

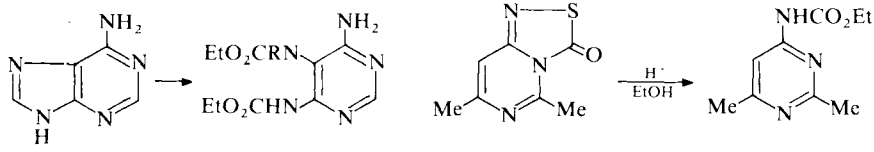
4-Pyrimidinecarbohydrazide[1604] to 4-pyrimidinecarbonyl azide (AcOH, $NaNO_2$, cold: 67%)[2893, cf. 5838] to 4-ethoxycarbonylaminopyrimidine (EtOH, reflux).[2893]

2,4,6-Trimethyl-5-pyrimidinecarbohydrazide to 5-ethoxycarbonylamino-2,4,6-trimethylpyrimidine (PeONO, HCl–EtOH, 0° then 50°, 2 h: > 40% as hydrochloride).[651]

4-Chloro-2-ethylthio-5-phenyl- to 2-ethylthio-5-phenyl-4-thiocyanato- (KSCN, EtOH, reflux, 30 min: 97%) to 2-ethylthio-4-isothiocyanato-5-phenyl- (xylene, reflux, 30 h: 70%) to 4-ethoxy(thiocarbonyl)amino-2-ethylthio-5-phenylpyrimidine (EtOH, reflux, briefly: ~75%).[5667]

Also other examples.[969,1395,1415,1645,1995,2365,3016,5101]

From heterobicyclic substrates. The formation of pyrimidine urethanes by degradation of bicyclic systems in the presence of suitable reagents might almost be considered primary syntheses. For example, 6-purinamine (**151**) gave 6-ethoxycarbonylamino-5-*N*-ethoxycarbonylformamido-4-pyrimidinamine (**152**, R = CHO) (EtO_2CCl, EtOH–H_2O, KOAc, 14°, 90 min: 25%) and thence 5,6-bis(ethoxycarbonylamino)-4-pyrimidinamine (**152**, R = H) (H_2O, reflux, 5 min: 36%);[4545] 5,7-dimethyl-3*H*-[1,2,4]thiadiazolo[4,3-*c*]pyrimidin-3-one (**153**) gave 4-ethoxycarbonylamino-2,6-dimethylpyrimidine (**154**) (63%) simply by dissolu-



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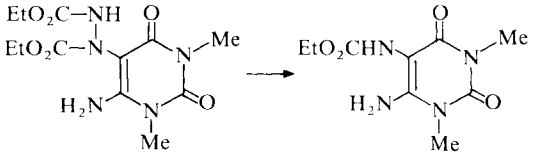
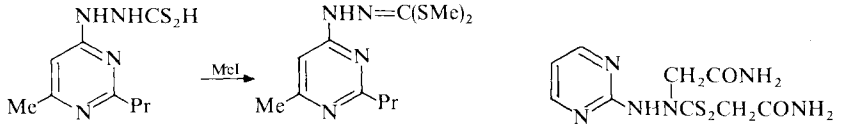
tion in hot ethanolic hydrochloric acid for 5 min;[2069] and other such procedures have been reported.[3544]

By a semidirect amination. Treatment of a 5-unsubstituted pyrimidine bearing electron-donating substituents with diethyl azodicarboxylate ($EtO_2CN{=}NCO_2Et$) affords a 5-α,β-diethoxycarbonylhydrazino derivative that may be split by Raney-nickel to give the corresponding 5-ethoxycarbonylamino derivative.[5839] For example, 6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione so gave a 5-α,β-dimethoxycarbonylhydrazino derivative (**155**) (77%) and thence the corresponding 5-ethoxycarbonylamino derivative (**156**) (74%);[5839] 6-benzylamino-1,3-dimethyl- gave 6-benzylamino-5-α,β-diethoxycarbonylhydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (neat EtO_2CNNCO_2Et, 160°, 1 h: 85%);[5840,5841] and many analogs were made similarly.[5839-5841] The products proved useful for the synthesis of purines and pyrimidotriazines.



155 **156**

By dithiocarbonation and S-alkylation. Carbon disulfide is sufficiently reactive to attack the more basic nitrogen of hydrazinopyrimidines. Thus 4-hydrazino- gave 4-β-(dithiocarboxy)hydrazino-6-methyl-2-propylpyrimidine (**157**) (CS_2, K_2CO_3, H_2O, 20°, 90 min: ~80%) and thence (reportedly) 4-bis(methylthio)methylenehydrazino-6-methyl-2-propylpyrimidine (**158**) (MeI, K_2CO_3, H_2O, 20°, 1 h: ~65% as hydrochloride);[5842] 2-hydrazinopyrimidine behaved similarly with carbon disulfide to give 2-β-(dithiocarboxy)-hydrazinopyrimidine (CS_2, NaOH, $RtOH–H_2O$, reflux, 2 h: 72% as Na salt), but on alkylation with 2-chloroacetamide this gave 2-β-carbamoylmethyl-β-carbamoylmethylthio(thiocarbonyl)hydrazinopyrimidine (**159**) ($ClCH_2CONH_2$, EtOH, reflux, 4 h: 47%), confirmed in structure by its nmr spectrum.[5843]



157 **158** **159**

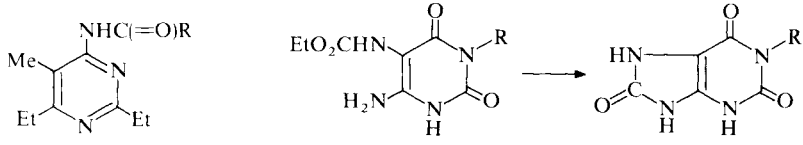
9.2.1.2. Reactions of Urethanes

The *saponification and decarboxylation* of urethanes are exemplified in the conversion of 5-methoxycarbonylamino-2,4-dimethylpyrimidine into

2,4-dimethyl-5-pyrimidinamine [$Ba(OH)_2$, H_2O, reflux, 4 h: 86%],[651] of 5-ethoxycarbonylamino-2,4,6-trimethylpyrimidine hydrochloride into 2,4,6-trimethyl-5-pyrimidinamine (CaO, dry distillation in vacuo: 40%),[651] and other examples have been reported.[634,1255] Acidic hydrolysis appear to be unsatisfactory.[1395,1415]

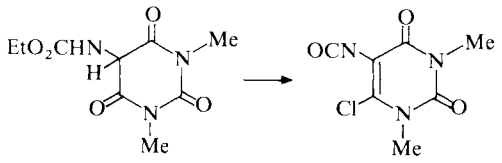
A related *hydrogenolysis and decarboxylation* sequence has been used to make 6-amino-2,4(1*H*,3*H*)-pyrimidinedione from its 6-benzyloxycarbonylamino derivative (H_2, Pd, AcOH–EtOH, 3 atm, 3 h).[1645]

Urethanes undergo *aminolysis* to afford the corresponding ureidopyrimidines: for example, 4-ethoxycarbonylamino-2,6-diethyl-5-methyl- (**160**, R = OEt) gave 2,4-diethyl-5-methyl-6-ureido- (**160**, R = NH_2) or 2,4-diethyl-5-methyl-6-*N'*-phenylureidopyrimidine (**160**, R = NHPh) (NH_3/PhH or neat $PhNH_2$, warm, briefly).[634] An *internal aminolysis* (cyclization) can occur when there is an amino group adjacent to the alkoxycarbonylamino group: for example, 6-amino-5-ethoxycarbonylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**161**, R = Me) in boiling 5*M* alkali for 30 min gave 1-methyl-2,6,8(1*H*,3*H*,7*H*)-purinetrione (**162**, R = Me) (52%);[5824] 6-amino-5-ethoxycarbonylamino-2,4(1*H*,3*H*)-pyrimidinedione (**161**, R = H) gave 2,6,8(1*H*,3*H*,7*H*)-purinetrione (**162**, R = H) (40–50%) by heating the dry sodium salt of the substrate at 180° for several hours;[1106] and other examples have been reported.[1222,1775]



160 **161** **162**

The conversion of *urethanes into isocyanates* by loss of ethanol has proved possible: thus 5-ethoxycarbonylamino-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**163**), in phosphoryl chloride containing ~4% added water, gave 6-chloro-5-isocyanato-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**164**) (65%).[2181]



163 **164**

9.2.2. Ureidopyrimidines

Ureido- and thioureidopyrimidines have been used as convenient derivatives of aminopyrimidines and as intermediates, mainly for 8-purinones and 8-purinethiones.

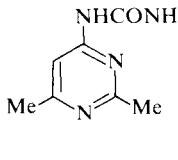
9.2.2.1. Preparation of Ureido- and Thioureidopyrimidines

From aminopyrimidines with isocyanates. A great variety of ureido-, thioureido-, semicarbazido-, and thiosemicarbazidopyrimidines may be made from primary or secondary aminopyrimidines or hydrazinopyrimidines with isocyanates or isothiocyanates. The scope of such reactions and the required conditions are illustrated in the following transformations.

Ureidopyrimidines

2,6-Dimethyl-4-pyrimidinamine to 4-*N'*-ethylureido-2,6-dimethylpyrimidine (**165**) (EtNCO, dioxane, reflux, 3 h: 81%).[5844]

4-Amino- to 4-*N'*-phenylureido-2(1*H*)-pyrimidinone (neat PhNCO, 150°, 10 min: ~75%).[5845, cf. 2893]



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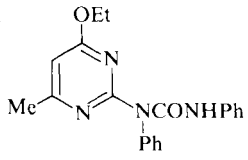

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2-Anilino- to 2-*N*,*N'*-diphenylureido-4-ethoxy-6-methylpyrimidine (**166**) (neat PhNCO, 100°, 2 h: 60%).[2896]

2-Methylthio-4,6-pyrimidinediamine to 6-*N'*-benzylureido-2-methylthio-4-pyrimidinamine ($PhCH_2NCO$, THF, reflux, 5 h: 35%).[3861]

2-Benzylthio-4,6-pyrimidinediamine to 2-benzylthio-6-*N'*-methylureido-4-pyrimidinamine (MeNCO, THF, 25°, > 8 h: 82%).[156]

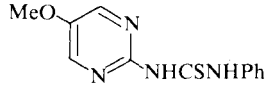
5,6-Diamino-1-phenyl- to 6-amino-1-phenyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione (KOCN, dilute HCl, 20°, 1 h: 90%).[5847]

1-Amino-3-butyl- to 3-butyl-1-*N'*-tosylureido-2,4(1*H*,3*H*)-pyrimidinedione (TsNCO, PhH, 25°, 14 h: ~80%).[1483]

Also other examples.[100,250,612,654,692,885,1171,1441,1492, 1651,1943,2340,2846, 3717,4122,5846,6012,6129]

Thioureidopyrimidines

5-Methoxy-2-pyrimidinamine to 5-methoxy-2-*N'*-phenyl(thioureido)pyrimidine (**167**) (PhNCS, PhH, reflux, 1 h: ~90%).[5848]



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2,6-Dimethyl-4-pyrimidinamine to 4-*N'*-butyl(thioureido)-2,6-dimethylpyrimidine (neat BuNCS, 170°, 2 h: ~50%).[683]

2-Chloro-6-methyl-4-pyrimidinamine to 2-chloro-4-methyl-6-*N'*-phenyl(thioureido)pyrimidine (PhNCS, dioxane, reflux, 16 h: 70%; neat PhNCS, 120°, 3 h: 60%).[533]

2-Methylthio-4,5,6-pyrimidinetriamine to 5-*N'*-ethyl(thioureido)-2-methylthio-4,6-pyrimidinediamine (EtNCS, EtOH, reflux, 30 min: ~65%).[3374]

4.6-Dimethyl-5-phenylazo-2-pyrimidinamine to 4,6-dimethyl-5-phenylazo-2-*N'*-phenyl(thioureido)pyrimidine (PhNCS, PhH, reflux, 12 h: 78%).[274]

5-Ethylamino- to 5-*N*-ethyl-*N'*-phenyl(thioureido)-4-pyrimidinamine (PhNCS, dioxane, reflux, 3 h: 69%).[1774]

5-Amino-6-methyl- to 6-methyl-5-thioureido-2,4(1*H*,3*H*)-pyrimidinedione (substrate.HCl, KSCN, H_2O, warm: ?%).[3534]

2-Methylthio-4,6-pyrimidinediamine to 6-*N'*-ethoxycarbonyl(thioureido)-2-methylthio-4-pyrimidinamine (**168**) (EtO_2CNCS, $CHCl_3$, reflux, 30 min: 83%).[497]

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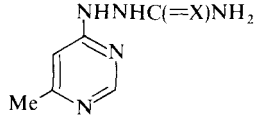
5-Amino- to 5-*N'*-methoxycarbonyl(thioureido)-2,4(1*H*,3*H*)-pyrimidinedione [MeO_2CNCS (made in situ), MeCN, reflux, 2 h: 94%].[384,3845]

2-Pyrimidinamine to 2-*N'*-benzoyl(thioureido)pyrimidine [BzNCS (made in situ), AcMe, reflux, 3 h: 79%].[6000]

Also other examples.[90,438,612,885,1441,2842,3863,6731]

Semicarbazido- and thiosemicarbazidopyrimidines

4-Hydrazino-6-methyl- to 4-methyl-6-semicarbazido- (**169**, X = O) (substrate.HCl, KOCN, H_2O, 95°, 1 h: ?%) or 4-methyl-6-thiosemicarbazidopyrimidine (**169**, X = S) (KSCN, likewise: ~75%).[5807]



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2-Hydrazino-4-methyl- to 4-methyl-2-thiosemicarbazidopyrimidine (substrate.HCl, KSCN, H_2O, reflux, 5 h: ~30%).[3216, cf. 3217]

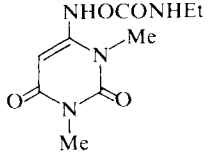
4-Hydrazino-6-methyl-2-propyl- to 4-methyl-2-propyl-6-semicarbazido- (NaOCN, dilute HCl, 95°, 30 min: ~75%) or 4-methyl-6-(4'-

methylsemicarbazido)-2-propylpyrimidine (MeNCO, PhH, reflux, 7 min: 80%).[683]

2-Hydrazino- to 2-4′-allyl(thiosemicarbazido)-4(3*H*)-pyrimidinone ($H_2C{=}CHCH_2NCS$, reflux?, 2 h: > 95%).[5850]

Also other examples.[683,5850]

Exceptional behavior was observed when 6-hydroxyamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione reacted with ethyl isocyanate in refluxing pyridine during 2 h to afford 6-(*N*-ethylcarbamoyl)oxyamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**170**) (29%);[776] in contrast, the same substrate with *o*-nitrophenyl isothiocyanate in refluxing ethanolic triethylamine gave 1,3-dimethyl-7-*o*-nitrophenyl-8-thioxo-8,9-dihydro-2,6(1*H*,3*H*)-purinedione (95%).[173]



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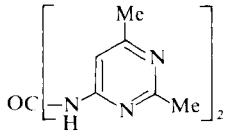

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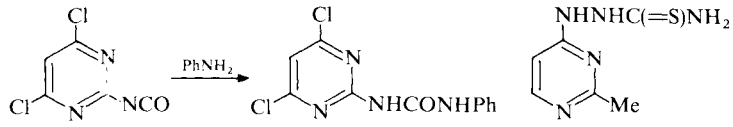
From aminopyrimidines with other reagents. Isocyanates or isothiocyanates may be replaced by other reagents to give ureidopyrimidines and related products. Thus 5-aminomethyl- gave 5-ureidomethyl-2,4(1*H*,3*H*)-pyrimidinedione ($H_2NCONHNO_2$, K_2CO_3, H_2O, reflux: 56%);[701] 2-pyrimidinamine gave 2-*N*′-pyridin-2′-yl(thioureido)pyrimidine [2-methylthio(thiocarbonyl)aminopyridine, PhMe, reflux, 18 h: 49%];[5849] 4,6-dimethyl-2-pyrimidinamine gave 4,6-dimethyl-2-ureidopyrimidine (EtO_2CNH_2, 190°, 1 h: ?%);[2362] 2,6-dimethyl-4-pyrimidinamine gave *N*,*N*′-bis(2,6-dimethylpyrimidin-4-yl)urea (**171**) ($COCl_2$, CCl_4, 25°, 3 h: 82%);[6012] and other examples have been reported.[1179,1810,3718] Although fusion of 6-amino-2,4(1*H*,3*H*)-pyrimidinedione or 2,6-diamino-4(3*H*)-pyrimidinone with urea was first thought to afford 6-ureido-2,4(1*H*,3*H*)-pyrimidinedione or 2-amino-6-ureido-4(3*H*)-pyrimidinone, respectively,[1093] each product was later shown to be an isomeric amide (viz., 4-amino-2,6-dioxo-1,2,3,6-tetrahydro- or 2,4-diamino-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide).[5851]

From isocyanatopyrimidines. Isocyanato- and isothiocyanatopyrimidines react with ammonia or amines to furnish ureido- or thioureidopyrimidines. For example, 4,6-dichloro-2-isocyanato- (**172**) gave 4,6-dichloro-2-*N*′-phenylureidopyrimidine (**173**) ($PhNH_2$, PhH, 20°, 18 h: 97%),[2482] 2-ethylthio-4-isothiocyanato-6-methyl- gave 2-ethylthio-4-methyl-6-thioureidopyrimidine (NH_4OH, Et_2O or xylene, shaken: > 50%),[3128,3137] 5-isothiocyanato- gave 5-*N*′-β-fluoroethyl(thioureido)-2,4(1*H*,3*H*)-pyrimidinedione ($FCH_2CH_2NH_2.HCl$, NEt_3, Me_2NCHO, 60°, 2 h, sealed: 71%),[3315] and other examples have been published.[969,1114,1395,2157,2188,5101,5667]



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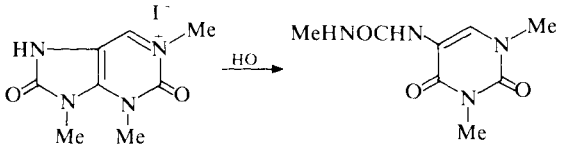
By aminolytic reactions. The aminolysis of pyrimidine urethanes to give ureidopyrimidines has been exemplified in Section 9.2.1.2. Unlike urea and thiourea, semicarbazide and thiosemicarbazide retain appreciable basic character and are capable of displacing activated halogeno or other leaving groups: for example, 4-chloro-2-methylpyrimidine with thiosemicarbazide gave 2-methyl-4-thiosemicarbazidopyrimidine (**174**) (~75%),[3216] and 4-ethoxy-2(1*H*)-pyrimidinone with aqueous semicarbazide (pH 4.2, warm?, 48 h) gave 4-semicarbazido-2(1*H*)-pyrimidinone (82%).[2829]

From cyanoaminopyrimidines. The few known cyanoaminopyrimidines undergo controlled hydrolysis or thiolysis to afford ureido- or thioureidopyrimidines. Thus 6-cyanoamino-2-methyl- gave 2-methyl-6-ureido-4(3*H*)-pyrimidinone (6*M* HCl, 95°, 30 min: ?%),[4140] 4-cyanoamino-2,6-dimethyl- gave 2,4-dimethyl-6-thioureidopyrimidine (NH_4HS, H_2O, 100°, 16 h, sealed: ~70%),[683] 2-cyanoamino-4,6-dimethyl- gave 4,6-dimethyl-2-ureidopyrimidine (3*M* H_2SO_4, boil, 8 min: ~90%),[2362] and other examples have been reported.[1150]

By primary syntheses. A few ureidopyrimidines have been made by primary syntheses (see Chapters 2 and 3). For example, condensation of diethyl α-(*N'*-methylureido)malonate with guanidine carbonate in refluxing ethanol for 2 days gave 2-amino-5-*N'*-methylureido-4,6(1*H*,5*H*)-pyrimidinedione (73%);[1697] condensation of carbamoylguanidine with 4,4-dimethoxybutan-2-one in aqueous ethanol at 80° for 2 h gave 4-methyl-2-ureidopyrimidine (15%);[2554] and alkaline hydrolysis of 1,3,9-trimethyl-2,8-dioxo-2,3,7,8-tetrahydropurinium iodide (**175**) gave 1,3-dimethyl-5-*N'*-methylureido-2,4(1*H*,3*H*)-pyrimidinedione (**176**).[4550]



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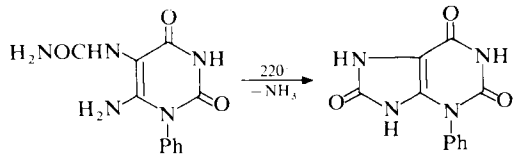
9.2.2.2. Reactions of Ureido- and Thioureidopyrimidines

Although ureidopyrimidines and the like undergo few useful reactions apart from cyclizations, several such reactions are exemplified briefly here. 6-Amino-1-phenyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione (**177**) (as its sodium salt) slowly



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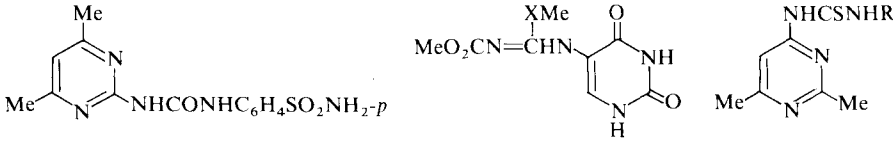
underwent *cyclization* by loss of ammonia at 220° to afford 3-phenyl-2,6,8(1*H*,3*H*,7*H*)-purinetrione (**178**),[5847] and 2,6-diamino-5-*N'*-methoxycarbonyl(thioureido)-4(3*H*)-pyrimidinone lost hydrogen sulfide on treatment with dicyclohexylcarbodiimide in dimethylformamide to give 2-methoxycarbonylamino-oxazolo[5,4-*d*]pyrimidine-5,7-diamine (84%);[90] 2-methyl-6-ureido-4(3*H*)-pyrimidinone suffered partial *hydrolysis and decarboxylation* in aqueous alkali (90°, 2 h) to give 6-amino-2-methyl-4(3*H*)-pyrimidinone;[4140] 4,6-dimethyl-2-ureidopyrimidine underwent complete *hydrolysis* in dilute sulfuric acid (reflux, 3 h) to furnish 4,6-dimethyl-2(1*H*)-pyrimidinone (~50%);[2362] the same substrate was involved in *transamination* with neat sulfanilamide at 160° during 15 min to give 4,6-dimethyl-2-*N'*-(*p*-sulfamoylphenyl)ureidopyrimidine (**179**) (~65%);[2362] 5-*N'*-methoxycarbonyl(thioureido)-2,4(1*H*,3*H*)-pyrimidinedione underwent regular *S-methylation* by methyl iodide (K_2CO_3, Me_2NCHO, 20°, 12 h) to give 5-(*N'*-methoxycarbonyl-*S*-methylisothioureido)-2,4(1*H*,3*H*)-pyrimidinedione (**180**, X = S) (40%), whereas the same substrate with methanolic dicyclohexylcarbodiimide gave the oxygen analog, 5-(*N'*-methoxycarbonyl-*O*-methylisoureido)-2,4(1*H*,3*H*)-pyrimidinedione (**180**, X = O);[384] and a similar substrate, 4-*N'*-ethoxycarbonyl(thioureido)-2,6-dimethylpyrimidine (**181**, R = CO_2Et), underwent *saponification and decarboxylation* of its terminal ester grouping in *M* alkali at 20° for 10 h to give 2,4-dimethyl-6-thioureidopyrimidine (**181**), R = H.[3863]



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9.2.3. Nitroaminopyrimidines

The *preparation* of nitroaminopyrimidines may be done by the Prinicipal Synthesis (see Chapter 3 and Section 5.1.1.1) or by nitration of appropriate aminopyrimidines (Section 5.1.1.2).

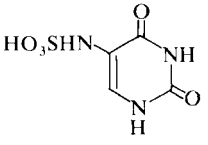
Useful *reactions* of nitroaminopyrimidines are virtually confined to transamination (see Section 9.1.1.3) and reduction to the corresponding hydrazino- or aminopyrimidine, according to the reagent used (see Section 9.1.1.5).

9.2.4. Nitrosoaminopyrimidines

Secondary aminopyrimidines undergo *N*-nitrosation, either in aqueous nitrous acid or by treatment with an alcoholic nitrite ester: examples have been given in Section 5.2.1.2. Although such nitrosoamines should undergo reduction to the corresponding α-alkylhydrazinopyrimidines, 5-*N*-methyl-*N*-nitrosoamino-4-pyrimidinamine failed to do so.[3789]

9.2.5. Sulfoaminopyrimidines

As pointed out in Section 5.1.2.1, reduction of 5-nitro-2,4(1*H*,3*H*)-pyrimidinedione with alkaline sodium dithionite initially gave a well-defined and stable product (> 85%), formulated as 5-sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione (**182**): on vigorous acid treatment followed by neutralization, this substance gave 5-amino- or 5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione, according to the severity of conditions.[1176, cf. 1126] The initial product (**182**) was later reformulated as the isomeric 5-amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid (**183**),[662] but its exact structure must be considered unresolved until an nmr spectrum is reported. Likewise, the structure of 6-sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione (from the 6-amino analog with chlorosulfonic acid)[1126] must be viewed with some reserve. However, there seems to be no reason to doubt the structure of 5-sulfoamino-2,4,6-pyrimidinetriamine (**184**) [from the 5-nitroso analog with $NaHSO_3$ or from the tetramine with $SO_2(NH_2)_2$ or SO_2Cl_2][3530] or of 5-sulfoamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (from the 5-nitroso or 5-oxo analog with NH_4HS).[1656,1657] The conversion of 6-hydrazino-2,4(1*H*,3*H*)-pyrimidinedione into 1,2,3-selenadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**185**) H_2SeO_3, H_2O–EtOH, 25°, 30 min: 61%)[371] may have involved a β-seleninohydrazino intermediate.



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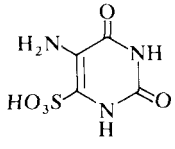

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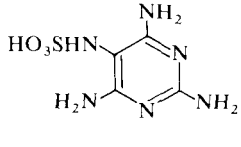

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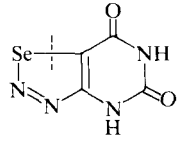

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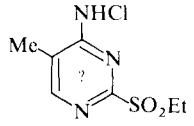
9.2.6. Halogenoaminopyrimidines

Halogenoaminopyrimidines have been reported occasionally. The formation of several difluoroaminopyrimidines by direct fluorination has been discussed in Section 9.1.6.8; the formation of 4-chloroamino-2-ethylsulfonyl-5-methylpyrimidine (**186**) and its 6-methyl isomer (by concomitant oxidation and *N*-chlorination of 2-ethylthio-5- and 2-ethylthio-6-methyl-4-pyrimidinamine,



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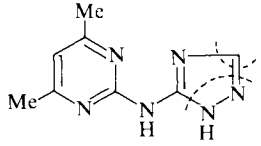
respectively, with chlorine) has been reported,[2043] albeit without adequate structural confirmation; and the formation of 6-difluoroamino- from 6-chloro-2,4(1*H*,3*H*)-pyrimidinedione, by treatment with difluoroamine in trifluoroacetic acid, failed as a preparative procedure.[9]

9.2.7. Cyanoaminopyrimidines

2-Cyanoaminopyrimidines have been *prepared* by the Principal Synthesis using cyanoguanidine (dicyandiamide) as the N—C—N— fragment (see Chapter 3): whether the product from such a synthesis bore the cyano group on its amino group or on a ring nitrogen led to early polemics,[1150,2362,2363,2531,2736,5852] but it now seems to be accepted that such products are cyanoaminopyrimidines. Some 2- or 4-cyanoaminopyrimidines have been made from the corresponding halogenopyrimidines by treatment with the cyanamide anion (see Section 6.7.2): for example, 4-chloro- gave 4-cyanoamino-6-methyl-2-propylpyrimidine (NaHNCN, Me_2NCHO, 100–110°, 40 h: ~18%).[683]

The useful *reactions* of cyanoaminopyrimidines include conversion into ureido- or thioureidopyrimidines (see Section 9.2.2.1); conversion into guanidinopyrimidines, as exemplified in the treatment of 2-cyanoamino-6-trifluoromethyl-4(3*H*)-pyrimidinone with *p*-aminobenzophenone to give 2-*N*′-(*p*-benzoylphenyl)guanidino-6-trifluoromethyl-4(3*H*)-pyrimidinone (Na salt of substrate, HCl, $EtOCH_2CH_2OH$, reflux, 24 h: 70%);[5853] and conversion into triazolylaminopyrimidines and related systems, as typified by the reaction of 2-cyanoamino-4,6-dimethylpyrimidine with hydrazine and formaldehyde (in aqueous methanol at 25° for 2 days) to give 4,6-dimethyl-2-(1′,2′,4′-triazol-5′-yl)aminopyrimidine (**187**) (39%).[2364]



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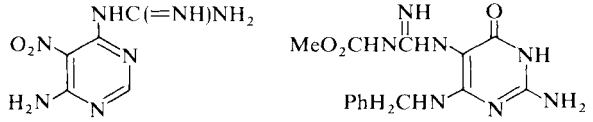
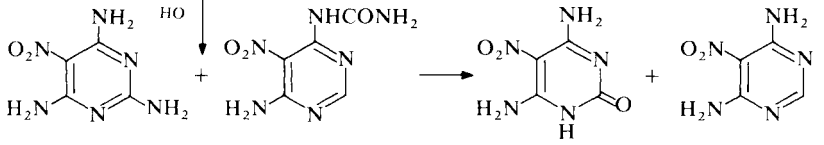
9.2.8. 2-Guanidinopyrimidines

2-Guanidinopyrimidines have sometimes been *prepared* by the Principal Synthesis (see Chapter 3) using biguanide as the N—C—N fragment: for

example, 3-phenylazopentane-2,4-dione and biguanide in aqueous methanol at 45° for 16 h gave 2-guanidino-4,6-dimethyl-5-phenylazopyrimidine.[645] However, 2- or 4/6-guanidinopyrimidines have usually been made by aminolysis of appropriate halogenopyrimidines (or similar substrates) with guanidine or substituted guanidines (see Section 6.7.2), as typified by the conversion of 6-chloro- into 6-guanidino-5-nitro-4-pyrimidinamine (**188**) (guanidine, EtOH, reflux, 1 h: 78%)[1579] or of 2,4,5,6-tetrachloropyrimidine into a difficulty separable mixture of 4,5,6-trichloro-2-guanidino- and 2,4,5-trichloro-6-guanidinopyrimidine (guanidine, AcMe–H_2O, 25°, 90 min: 17% and 3%, respectively, after separation).[2174] Guanidinopyrimidines have also been made by treatment of cyanoaminopyrimidines with amines (see Section 9.2.7) or by treatment of primary pyrimidinamines with *S*-alkylisothioureas, as exemplified by the conversion of 2,5-diamino-6-benzylamino- into 2-amino-6-benzylamino-5-*N'*-methoxycarbonylguanidino-4(3*H*)-pyrimidinone (**189**) [MeSC(=NH)$NHCO_2Me$, NaOAc, H_2O, 80°, 4 h: 36%].[3844]



188 **189**



190 **191** **192** **193**

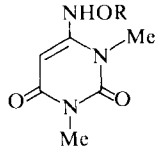
The *reactions* of guanidinopyrimidines include condensation with α-dicarbonyl compounds to afford dipyrimidinylamines, but of more interest is treatment with alkali or acid: for example, 6-guanidino-5-nitro-4-pyrimidinamine (**188**) with alkali gave 5-nitro-6-ureido-4-pyrimidinamine (**191**) and 5-nitro-2,4,6-pyrimidinetriamine (**190**), the latter by 1,2- or 2,3-fission, loss of C2 as formic acid, and reformation of a ring involving the guanidino group; the ureidopyrimidine (**191**) underwent a similar rearrangement to give 4,6-diamino-5-nitro-2(1*H*)-pyrimidinone (**192**), accompanied by the hydrolytic product, 5-nitro-4,6-pyrimidinediamine (**193**).[1579] Acid treatment of the original substrate (**188**) induced rather similar reactions, during which an aliphatic intermediate, 3-guanidino-3-imino-2-nitropropionamide, was isolated.[1579]

9.2.9. Hydroxyaminopyrimidines

Hydroxyaminopyrimidines have been *prepared* almost invariably by the action of hydroxylamine on (activated) halogenopyrimidines (see Section 6.7.3);

however, the transmination of 4,6-dimethyl-2-nitroamino- into 2-hydroxyamino-4,6-dimethylpyrimidine (58%) occurred readily in aqueous hydroxylamine at 90° for 15 min,[2790] and acidic hydrolysis of 4-benzyloxyamino-2-methylthiopyrimidine gave 4-hydroxyamino-2(1*H*)-pyrimidinone (75%).[1681]

Hydroxyaminopyrimidines tend to *react* as alcohols rather than as amines, at least in respect of the acylation or alkylation processes. For example, 6-hydroxyamino- (**194**, R = H) gave 6-acetoxyamino- (**194**, R = Ac) (Ac_2O, 50°, briefly: ~90°) or 6-methoxyamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**194**, R = Me) (CH_2N_2, Et_2O–EtOH, 20°, 1 day: 60%).[1139]



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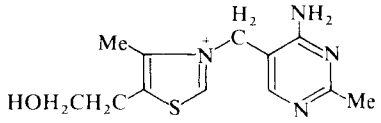
9.2.10. Trialkylammonio- and Pyridiniopyrimidine Halides

Most known examples in this category are, in fact, trimethylammoniopyrimidine chlorides. They are made invariably by treatment at room temperature of an activated halogenopyrimidine with a tertiary base, usually in an inert solvent such as benzene: accordingly, the quaternary amino group may be so located at a 2-, 4/6- or ω-position in the product but seldom, if ever, at the 5-position. The *preparation* of such compounds has been included in Sections 6.7.2, 6.8.2, and 6.9. It is important that gentle conditions are maintained during the aminolysis: otherwise, dealkylation by spontaneous loss of alkyl halide from the product may occur, thus affording the corresponding tertiary aminopyrimidine (see Section 9.1.1.4); naturally, pyridiniopyrimidines are not prone to this complication. A well-known preparation of this type was the aminolysis of 5-bromomethyl-2-methyl-4-pyrimidinamine with 5-β-hydroxyethyl-4-methylthiazole to give 5-(5′-β-hydroxyethyl-4′-methylthiazolio)methyl-2-methyl-4-pyrimidinamine (**195**) (thiamine; vitamin B_1);[750,1920,5857] the desamino analog was made similarly;[3062] and an interesting but odd preparation involved treatment of 4-methylpyrimidine with iodine in refluxing pyridine for 2–3 h to give 4-pyridiniomethylpyrimidine iodide (58%).[3446,5856]



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The most useful *reaction* of such quaternary amino substituents is their ability to act as good leaving groups for displacement by anionic reagents, such as

HO^-, NC^-, RO^-, $H_2NC_6H_4SO_2NH^-$, F^-, or N_3^-, but conditions and reagents must be chosen to avoid or minimize the thermal dealkylation just mentioned. The displacement reactions of these ammoniopyrimidines are illustrated in the following transformations.

Hydrolysis (see also Section 7.1.1.3)

4,6-Dimethyl-2-trimethylammoniopyrimidine chloride to 4,6-dimethyl-2(1*H*)-pyrimidinone (*M* NaOH, 80°, 15 min: 80%).[2602]

2-Amino-5-nitro-6-pyridinio-4(3*H*)-pyrimidinone chloride to 2-amino-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione (H_2O, reflux, 10 min: ~ 60%).[1364]

Alcoholysis or phenolysis (see also Section 7.1.4.3)

4,6-Dimethyl-2-trimethylammoniopyrimidine chloride to 2-methoxy-4,6-dimethyl- (NaOMe, MeOH, reflux, 1 h: ~ 75%) or 4,6-dimethyl-2-phenoxypyrimidine (neat NaOPh, 100°, 1 h: ~ 90%).[2602]

Ethyl 2-methylthio-4-trimethylammonio-5-pyrimidinecarboxylate chloride to methyl 4-methoxy-2-methylthio-5-pyrimidinecarboxylate (KCN, MeOH, 55°, 1 h: 79%; note transesterification and failure to form a nitrile).[1781]

Displacement by fluoride ion (see also Section 6.4)

2,4-Dimethoxy-6-trimethylammoniopyrimidine chloride to 4-fluoro-2,6-dimethoxypyrimidine (KF, $HOCH_2CH_2OH$, 80°, 1 h: 42%).[1703]

2-Methoxycarbonylmethyl-4-trimethylammoniopyrimidine chloride to 4-fluoro-2-methoxycarbonylmethylpyrimidine (KHF_2, H_2O–Et_2O, 5°, 20 min: 12%).[1749]

Displacement by azide ion

2,4-Dimethoxy-6-trimethylammoniopyrimidine chloride to 4-azido-2,6-dimethoxypyrimidine (NaN_3, H_2O, 80°, 30 min: 76%).[1703]

Displacement by cyanide ion

4,6-Dimethyl-2-trimethylammoniopyrimidine chloride to 4,6-dimethyl-2-pyrimidinecarbonitrile (KCN, $AcNH_2$, 80°, 30 min: ~ 70%).[2602]

4-Phenyl-2-trimethylammoniopyrimidine chloride to 4-phenyl-2-pyrimidinecarbonitrile (KCN, Me_2SO, 25°, 15 h: 58%).[5088]

2-Methylthio-4-trimethylammoniopyrimidine chloride to 2-methylthio-4-pyrimidinecarbonitrile (KCN, $AcNH_2$, 85°, 1 h: 44%).[1628]

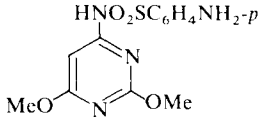
4-Methyl-2-phenyl-6-trimethylammoniopyrimidine chloride to 6-methyl-2-phenyl-4-pyrimidinecarbonitrile (KCN, $AcNH_2$, 95°, 1 h: 68%).[1856]

4,6-Diphenyl-2-trimethylammoniopyrimidine chloride to 4,6-diphenyl-2-pyrimidinecarbonitrile (KCN, $AcNH_2$, 100°, 40 min: 97%).[5854]

Also other examples.[1745,1749,2603,2764,3290,3602]

Displacement by sulfanilamide anion

2,4-Dimethyl- or 2,4-dimethoxy-6-trimethylammoniopyrimidine chloride to 2,4-dimethyl- or 2,4-dimethoxy-6-sulfanilamidopyrimidine (**196**) ($H_2NC_6H_4SO_2NHNa$, $AcNH_2$, 95° then 180°/25 m: 76% or 62%, respectively).[2466, cf. 2600]



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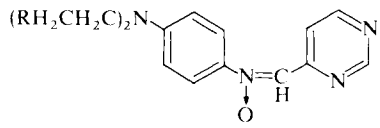
4-Methyl-2-trifluoromethyl-6-trimethylammoniopyrimidine chloride to 4-methyl-6-sulfanilamido-2-trifluoromethylpyrimidine ($H_2NC_6H_4SO_2NHNa$, $AcNH_2$, 100°, 30 min: 53%).[4124]

5-Fluoro-2-methoxy-4-trimethylammoniopyrimidine chloride to 5-fluoro-2-methoxy-4-sulfanilamidopyrimidine ($H_2NC_6H_4SO_2NHNa$, $AcNH_2$, 135°, 20 h: 36%).[1264]

Also other examples.[2198,2209,5855]

Displacement by nitrosobenzenes

4-Pyridiniomethylpyrimidine chloride to the nitrones (**197**, R = Cl or OH) [(Cl— or HO—$CH_2CH_2)_2NC_6H_4NO$-*p*, KOH, MeOH–H_2O, 20°: ~ 70%;[5856] $Me_2NC_6H_4NO$-*p* failed to react![3446]].



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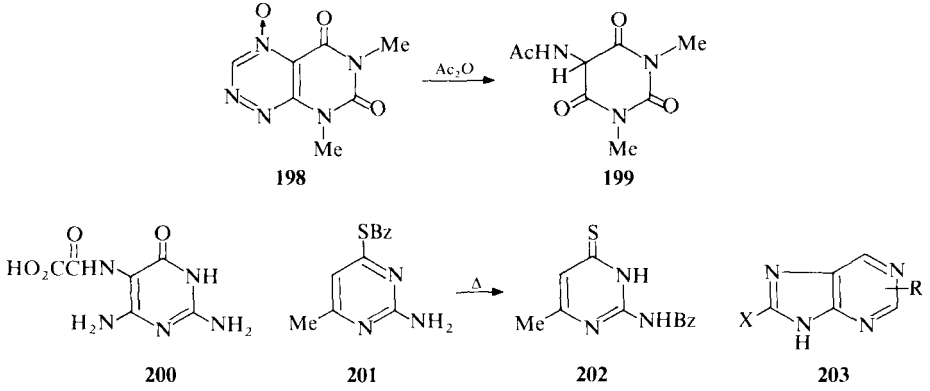
9.2.11. Acylaminopyrimidines

Preparation. Most acylaminopyrimidines have been made by *acylation* of aminopyrimidines (see Section 9.1.6.3), including the one-pot reduction and acylation of appropriate nitro-, nitroso-, phenylazo-, or cyanopyrimidines: for example, 6-amino-3-methyl-5-nitro- gave 6-amino-5-formamido-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Zn, HCO_2H, 80–100°, 3 h: 72%),[1286] 6-amino-5-phenylazo- gave 6-amino-5-formamido-2,4(1*H*,3*H*)-pyrimidinedione (Zn, 90% HCO_2H, 95°, ? h: ~ 65%),[2437] and 2,4-dimethyl-5-pyrimidinecarbonitrile gave

5-acetamidomethyl-2,4-dimethylpyrimidine (H_2, Ni, NaOAc, Ac_2O, 20°, 24 h: 40%).[2761] A second approach is by *primary synthesis* (see Chapters 2 and 3): for example, neat ethyl acetoacetate and *p*-nitrobenzenesulfonylguanidine under reflux for 90 min gave 6-methyl-2-*p*-nitrobenzenesulfonamido-4(3*H*)-pyrimidinone (~ 35%),[4057] and degradation of 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-oxide (**198**) in refluxing Ac_2O–AcOH for 1 h gave 5-acetamido-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**199**) (50%).[656] Some other minor synthetic routes are illustrated in the *transacylation* of 2,6-diamino-5-formamido- into 2,6-diamino-5-oxaloamino-4(3*H*)-pyrimidinone (**200**) [$(HO_2C)_2$, H_2O, reflux, 1 h: ~ 80%][5826] or of 5-benzamido- into 5-acetamido-2-methylthio-4(3*H*)-pyrimidinone (Ac_2O, reflux, 1 h: ~ 60%);[702] in the thermal *isomerization* of 4-benzoylthio-6-methyl-2-pyrimidinamine (**201**) to 2-benzamido-6-methyl-4(3*H*)-pyrimidinethione (**202**) (180°, 30 min);[1509] and in the *displacement reactions* of arenesulfonamide anions with substrates bearing several types of leaving group [see Sections 6.7.8 (halogens), 9.2.10 (trimethylammonio), and 8.8.2 (alkylsulfonyl)].



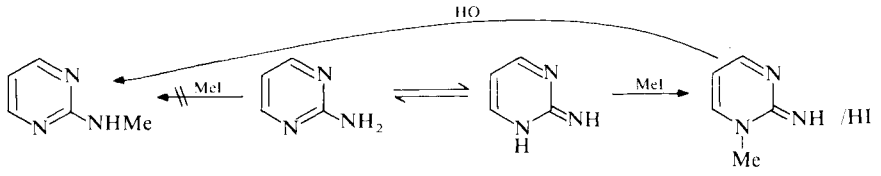
198 199 200 201 202 203

Reactions. The most important reaction 2/4/6-, 5-, and ω-acylaminopyrimidines is deacylation (deprotection), as discussed in Sections 9.1.1.5, 9.1.2.6, and 9.1.4.6, respectively; the selective monodeacylation of (diacylamino)pyrimidines has been exemplified at the end of Section 9.1.6.3. 5-Acylaminopyrimidines may be converted into 5-alkylaminopyrimidines by either direct reduction or alkylation to 5-(*N*-acyl-*N*-alkylamino)pyrimidines followed by deacylation (see Section 9.1.2.4). 5-Acylamino-4/6-aminopyrimidines have been used extensively for the synthesis of 8-unsubstituted-, 8-alkyl-, or 8-arylpurines (**203**, X = H, alkyl, or aryl).[5858]

9.3. NONTAUTOMERIC IMINOPYRIMIDINES

Although the iminodihydro form of a (tautomeric) 2- or 4/6-aminopyrimidine is normally present in only minute amount, alkylation of such as amine usually

occurs exclusively on a ring nitrogen, thus fixing the product in the imino form. For example, 2-pyrimidinamine (**205**) with methyl iodide gave one product, 1-methyl-2(1*H*)-pyrimidinimine hydriodide (**206**), from which 2-methylaminopyrimidine (**204**) could be formed subsequently only by Dimroth rearrangement (see Section 9.3.2) during prolonged alkaline treatment.[3377] Such fixed imines are much stronger bases ($pK_a > 10$ as a rule) than their amino precursors or the isomeric alkylaminopyrimidines (pK_a 3–5).



204 **205** **206**

9.3.1. Preparation of Nontautomeric Iminopyrimidines

Most fixed iminopyrimidines have been made by alkylation of the corresponding amino- or alkylaminopyrimidines, but a few have been made by primary syntheses or other means.

9.3.1.1. By Alkylation of Aminopyrimidines

Treatment of a primary or secondary 2- or 4/6-aminopyrimidine with an alkyl halide (or related reagent) gives a 1- or 3-alkylated iminodihydropyrimidine, usually as the appropriate hydrohalide. The following imines were so made and isolated unless otherwise indicated.

From 2-pyrimidinamine

1-Methyl-2(1*H*)-pyrimidinimine.HI (**206**) (MeI, MeOH, 25°, 5 days: 88%;[3377] MeI, EtOH, reflux, 5 h: 91%).[867,5808]

1-Ethyl-2(1*H*)-pyrimidinimine.HI (EtI, EtOH, reflux 28 h: ~ 80%).[867,1741]

1-Propyl-2(1*H*)-pyrimidinimine.HBr (PrBr, PrOH, reflux, 10 h: 73%)[867, cf. 923] of the hydriodide (PrI, MeOH, reflux, 12 h: 67%).[923]

1-Heptyl-2(1*H*)-pyrimidinimine.HI (neat $C_7H_{15}I$, stirred, 95°, 16 h: ~ 30%).[1741]

1-*p*-Nitrobenzyl-2(1*H*)-pyrimidinimine.HBr ($BrH_2CC_6H_4NO_2$-*p*, EtOH, reflux, 24 h: 75%).[923]

1-Prop-2′-ynyl-2(1*H*)-pyrimidinimine.HBr ($BrCH_2C{\equiv}CH$, EtOH, reflux, 36 h: ~ 50%).[3583]

1-β-Hydroxyethyl-2(1*H*)-pyrimidinimine.HBr ($BrCH_2CH_2OH$, BuOH–Me_2N-CHO, reflux, 9 h: 80%).[3249]

1-Methoxycarbonylmethyl-2(1*H*)-pyrimidinimine.HBr ($BrCH_2CO_2Me$, Me_2N-CHO, 25°, 24 h: 80%).[984]

Also other examples in the foregoing references and elsewhere.[3490]

From 2-pyrimidinamine bearing nuclear substituents

5-Ethyl-1-methyl-2(1*H*)-pyrimidinimine.HI (neat MeI, reflux, 24 h: 90%).[1741]

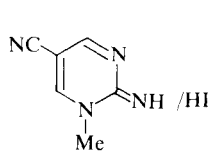
4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinimine.HI (MeI, MeOH, reflux, 1 h: 95%).[1741]

4-Methyl-1-*p*-nitrobenzyl-2(1*H*)-pyrimidinimine picrate ($BrCH_2C_6H_4NO_2$-*p*, $MeOCH_2CH_2OH$, 100°, 6 h: isolated as picrate).[1465]

1,4,6-Trimethyl-5-prop-1′-ynyl- or 1,4,6-trimethyl-5-prop-2′-ynyl-2(1*H*)-pyrimidinimine.HI (MeI, 100°, 15 h, sealed: 23% or 33%, respectively).[843]

5-Bromo-1-ethyl-2(1*H*)-pyrimidinimine.HI (neat EtI, 125°, 40 h, sealed: ~ 60%).[1437]

2-Imino-1-methyl-1,2-dihydro-5-pyrimidinecarbonitrile.HI (**207**) (MeI, $MeOCH_2OH$, 98°, 24 h, sealed: 83%).[1346]



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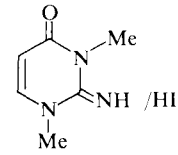

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4-Dimethylamino-1-methyl-5-nitro-2(1*H*)-pyrimidinimine.HI (MeI, PrOH, reflux, 18 h: ~ 65%).[1437]

5-Methoxy-1-methyl-2(1*H*)-pyrimidinimine.HI (MeI, MeOH, 25°, 3 days: ~ 60%).[2114]

2-Imino-1,3-dimethyl-1,2-dihydro-4(3*H*)-pyrimidinone.HI (**208**) from 2-amino-3-methyl-4(3*H*)-pyrimidinone (MeI, MeOH, reflux, 24 h: 68%).[2636]

Also other examples in the foregoing references and elsewhere.[923,1465,2144,3072,4729]

From 4-pyrimidinamines

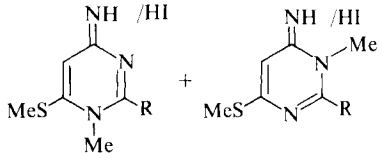
1-Methyl-4(1*H*)-pyrimidinimine.HI (MeI, MeOH, reflux, 1 h: 80%).[1136,3377]

1-Ethyl-2-phenyl-4(1*H*)-pyrimidinimine.HBF_4 (Et_3OBF_4, $C_2H_4Cl_2$, reflux, ? h: 66%).[1245]

2-Chloro-1-methyl-4(1*H*)-pyrimidinimine.HI (MeI, $EtOCH_2CH_2OH$ reflux, 5 h).[1154]

2-Methoxy-1-methyl- (MeI, MeOH, 20°, 24 h: 75%)[1664,1678] or 1-methyl-2-methylthio-4(1*H*)-pyrimidinimine.HI (MeI, MeOH, reflux, 3 h: 91%).[1520]

1-Methyl-6-methylthio-4(1*H*)- (**209**, R = H) and 3-methyl-6-methylthio-4(3*H*)-pyrimidinimine.HI (**210**, R = H) (MeI, MeOH, reflux, 4 h, ~ 30% each after separation).[2115]



209 **210**

1-β-Hydroxyethyl-6-imino-3-methyl-3,6-dihydro-2(1*H*)-pyrimidinone (base) from 4-amino-1-methyl-2(1*H*)-pyrimidinone (ethylene oxide, MeOH, 38°, 48 h: 32%).[3247]

1-Methyl-5-*p*-nitrophenyl-4(1*H*)-pyrimidinimine.HI (MeI, MeOH, reflux, 2 h: 79%).[5661]

2-Dimethylamino-1-methyl-4(1*H*)-pyrimidinimine.HI (MeI, EtOH, reflux, 3 h: 35%).[1742]

4-Imino-1-methyl-1,4-dihydro-5-pyrimidinamine.HI (MeI, MeOH, reflux, 3 h: 77%).[1520]

Also other examples in the foregoing and other references.[696,941, 1536,1996,2549,4403,5659,7033]

From 2,4- or 4,6-pyrimidinediamines

(*Note*: Both 2,4- and 4,6-pyrimidinediamines give iminodihydropyrimidinamines of yet indeterminate fine structure, although names have been chosen to give the suffixed amine group the lowest possible number.)

4-Imino-1-methyl-1,4-dihydro-2-pyrimidinamine.HI (MeI, MeOH, reflux, 1 h: 76%).[1520, cf. 3377]

4-Imino-1-methyl-6-methylthio-1,4-dihydro- (**209**), R = NH_2) and 4-imino-3-methyl-6-methylthio-3,4-dihydro-2-pyrimidinamine.HI (**210**, R = NH_2) (MeI, MeOH, reflux, 24 h: 39% and 22% after separation).[1520]

5-Bromo-4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine.HI (MeI, EtOH, reflux, 8 h: 68%).[1742]

6-Imino-1-methyl-1,6-dihydro-4-pyrimidinamine.HI (MeI, MeOH, reflux, 3 h: 89%).[1770]

6-Imino-1-methyl-1,6-dihydro-4,5-pyrimidinediamine.HI (MeI, MeOH, reflux, 3 h: ~ 50%).[1764]

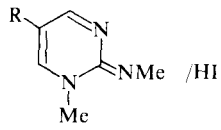
4-Imino-1-methyl-1,4-dihydro-2,5-pyrimidinediamine (MeI, MeOH, reflux, 4 h: ~ 60%).[1764]

6-Imino-1-methyl-1,6-dihydro-2,4-pyrimidinediamine.HI (MeI, MeOH, reflux, 6 h: 47%).[1520]

Also other examples in the foregoing references.

From 2- or 4-alkylaminopyrimidines

1-Methyl-2-methylimino-1,2-dihydropyrimidine.HI (**211**, R = H) (neat MeI, reflux, 18 h: 90%).[1741]



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1-Allyl-2-*propylimino*-1,2-dihydropyrimidine.HBr (neat CH_2=CH-CH_2Br, reflux, 18 h: 89%).[902]

2-Allylimino-1-propyl-1,2-dihydropyrimidine.HI (neat PrI, reflux, 18 h: 42%).[902]

1-Benzyl-2-benzylimino-1,2-dihydropyrimidine.HCl (neat $PhCH_2Cl$, 95°, 24 h: ~ 60%).[1437]

5-Bromo-1-methyl-2-methylimino-1,2-dihydropyrimidine.HI (**211**, R = Br) (MeI, MeOH, 100°, 4 h, sealed).[1741]

1-Methyl-2-methylimino-1,2-dihydro-5-pyrimidinecarbonitrile.HI (MeI, $MeOCH_2CH_2OH$, 98°, 24 h: 81%).[1346]

1-Methyl-4-methylimino-1,4-dihydro-2-methylthiopyrimidine.HI neat MeI, 25°, 2.5 h: > 90%).[1508]

Also other examples in the foregoing references and elsewhere.[696,867,923,1143,2115,2237,3247,3788]

From alkylaminopyrimidinamines or bis(alkylamino)pyrimidines

(*Note*: The fine structures of these products have not been investigated.)

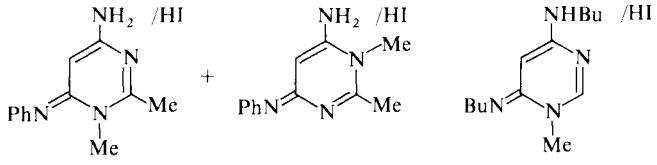
1-Methyl-2-methylimino-1,2-dihydro-4-pyrimidinamine.HI (MeI, EtOH, reflux, 3 h: 81%).[1520]

1-Methyl-4-methylimino-1,4-dihydro-2-pyrimidinamine.HI (MeI, EtOH, reflux, 3 h: 95%).[1742]

4-Chloro-3-methyl-6-methylimino-3,6-dihydro-2-pyrimidinamine.HI (MeI, EtOH, reflux, 24 h: 52%).[1742]

1,6-Dimethyl-4-phenylimino-1,4-dihydro-2-pyrimidinamine.HI (neat MeI, reflux, 18 h: ~ 60%).[1143]

1,6-Dimethyl-2-phenylimino-1,2-dihydro-4-pyrimidinamine.HI (MeI, EtOH, reflux, 4 h).[1154]



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1,2-Dimethyl-6-phenylimino-1,6-dihydro- (**212**) and 2,3-dimethyl-6-phenylimino-3,6-dihydro-4-pyrimidinamine.HI (**213**) (MeI, MeOH, reflux, 4 h: separated by solubilities in EtOH–EtOAc).[1136]

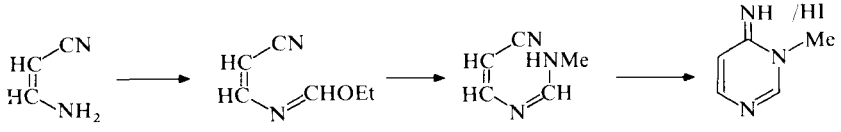
4-Butylamino-6-butylimino-1-methyl-1,6-dihydropyrimidine.HI (**214**) (MeI, EtOAc, reflux, 1 h: 43%).[866]

Also other examples in most of the foregoing references.

9.3.1.2. By Other Means

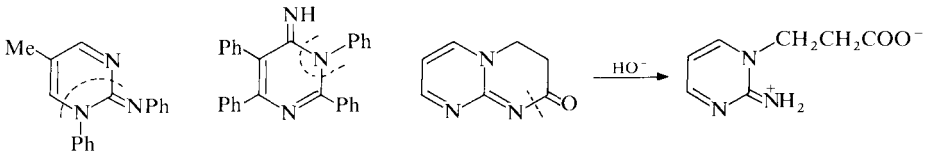
Several less used but quite important routes to pyrimidinimines are illustrated in the following paragraphs.

Primary syntheses. The best route to simple 3-alkyl-4(3*H*)-pyrimidinimines (unavailable by alkylation) is exemplified in the sequence: malononitrile → 3-aminoacrylonitrile (**215**) ($LiAlH_4$) → 3-(ethoxymethyleneamino)acrylonitrile (**216**) [$(EtO)_3CH$, Ac_2O] → 3-(methylaminomethyleneamino)acrylonitrile (**217**) ($MeNH_2$, EtOH, 25°) → 3-methyl-4(3*H*)-pyrimidinimine.HI (**218**) (EtOH, reflux, 1 h, then HI: 70%);[2570] several homologs and anologs were made similarly.[1571,2570]



215 216 217 218

Less versatile routes are exemplified in the condensation of 3-aminomethacrylaldehyde with diphenylcarbodiimide at 120° to give 5-methyl-1-phenyl-2-phenylimino-1,2-dihydropyrimidine (**219**) (47%);[4406] in related condensations;[5859] in the condensation of 3-(α-chlorobenzylidene)-amino-2,3-diphenylacrylonitrile with aniline to give 2,3,5,6-tetraphenyl-4(3*H*)-pyrimidinimine (**220**) (EtOH, reflux, 48 h);[4349] in the degradation of 3,4-dihydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-one (**221**) in mild alkali to give 1-β-carboxyethyl-2(1*H*)-pyrimidinimine, probably existing as the zwitterion (**222**);[2015] and in other instances (Chapter 2). Most reported uses of the Principal Synthesis to make iminopyrimidines have not been confirmed (see, e.g., Section 3.3.2) but condensations, such as that of α,α-diethylmalononitrile with guanidine

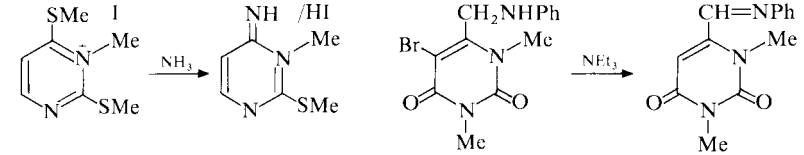


219 **220** **221** **222**

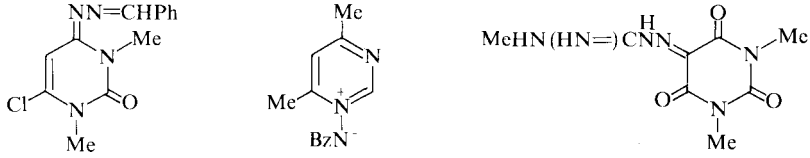
to afford 5,5-diethyl-6-imino-5,6-dihydro-2,4-pyrimidinediamine or a tautomer,[3107] cannot be disputed.

By aminolysis of fixed pyrimidinethiones. This route to pyrimidinimines has been discussed in Section 8.5.2.

Miscellaneous routes. The following examples illustrate some occasionally used procedures to obtain pyrimidinimines: (1) 1-methyl-2,6-bismethylthiopyrimidinium iodide (**223**) in ethanolic ammonia at 25° for 90 min gave 3-methyl-2-methylthio-4(3*H*)-pyrimidinimine.HI (**224**) (92%);[1508] (2) 6-anilinomethyl-5-bromo-1,3-dimethyl- (**225**) in refluxing ethanolic triethylamine for 24 h lost HBr to afford 1,3-dimethyl-6-phenyliminomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**226**) (65%),[762] an extranuclear iminopyrimidine of the type readily available as the Schiff bases or hydrazones from pyrimidineacarbaldehydes; (3) 6-benzylidenehydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione in refluxing phosphoryl chloride for 1 h gave 4-benzylidenehydrazono-6-chloro-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone (**227**) (97%);[4878] (4) 1-amino-4,6-dimethylpyrimidinium mesitylenesulfonate in benzoyl chloride at 25° for 15 h gave the isoelectronic equivalent (78%) of the corresponding *N*-benzoylimino derivative, formulated as the zwitterion (**228**);[5860] (5) 5-nitroso- or 5,5-dibromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones with *N*-aminoguanidines gave several products that appeared to exist as 5-guanidinoimino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones (e.g., **229**);[5861] and (6) pyrimidine methiodide with potassium permanganate in liquid ammonia gave 3-methyl-4-(3*H*)-pyrimidinimine, isolated as its hydriodide (> 80%).[479]



223 **224** **225** **226**

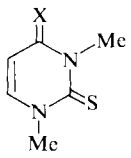


227 **228** **229**

9.3.2. Reactions of Nontautomeric Iminopyrimidines

Hydrolysis. The hydrolysis of fixed pyrimidinimines to fixed pyrimidinones has been discussed in Section 7.5.1.

Thiation. The direct conversion of a fixed pyrimidinimine into a fixed pyrimidinethione seems to have occurred on treatment of 2-imino-1,3-dimethyl-1,2-dihydro-4(3*H*)-pyrimidinone with phosphorus pentasulfide in pyridine at 95° for 3 h to give a separable mixture of 1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (**230**, X = O (~ 20%) and 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedithione (**230**, X = S) (~ 5%).[2636]



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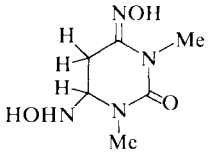

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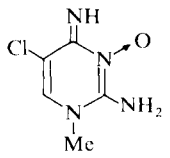

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Transamination. The de facto transamination of 4-imino-1,3-dimethyl-3,4-dihydro- to 4-hydroxyimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone occurred in anhydrous hydroxylamine at 37° during 36 h followed by hot hydrochloric acid, probably via the adduct (**231**).[3225]

Stability to oxidation. Provided concomitant hydrolysis can be precluded, pyrimidinimines appear to survive oxidative conditions: for example, 5-chloro-4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine with 30% aqueous hydrogen peroxide in trifluoroacetic acid at 20° for 6 h gave its 3-oxide (**232**) (77%).[2176]

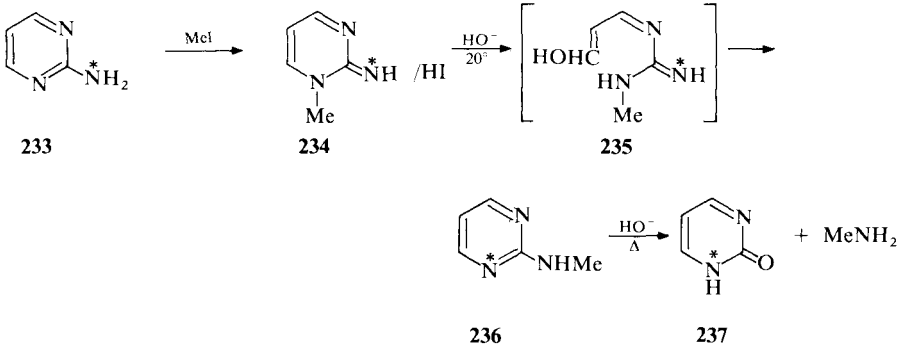
Ring contraction. Treatment of 6-*p*-bromo-*N*-methylanilino-3-methyl-5-phenylimino-2,4(3*H*,5*H*)-pyrimidinedione with methanolic methoxide at 25° gradually gave a single product, methyl 4-anilino-5-*p*-bromo-*N*-methylanilino-3-methyl-2-oxo-3,4-dihydro-2*H*-imidazole-4-carboxylate (> 95%), by a rational mechanism.[28]

Deuteration. The reasonably facile deuteration of the *C*-methyl groups of representative pyrimidinimines[2742] has been mentioned in Section 4.2.3.1.

Dimroth rearrangement. Although the first examples in the pyrimidine series were reported in 1954–1955,[2083,2237,3377] the term "Dimroth rearrangement" was coined[1741] only in 1963 to cover an isomerization proceeded by ring fission and subsequent recyclization, whereby a ring-nitrogen and its attached substituent exchanged places with an imino (or potential imino group) in the α-position. It is simply illustrated by the rearrangement of 1-methyl-2(1*H*)-pyrimidinimine (**206**) to 2-methylaminopyrimidine (**204**) in aqueous alkali at room temperature.[1741,3377] Several other examples in the pyrimidine series,[809,864,1221,1383,1770] as well as a number in related heterocyclic systems,[2237,3669,5862,5863,5865,5866] were reported prior to experimental elu-

cidation of the mechanism (for other historical references; see reviews elsewhere[5864,5867,6221]). It should be distinguished carefully from the Dimroth reaction,[6222] a preparative route to 1,2,3-triazoles!

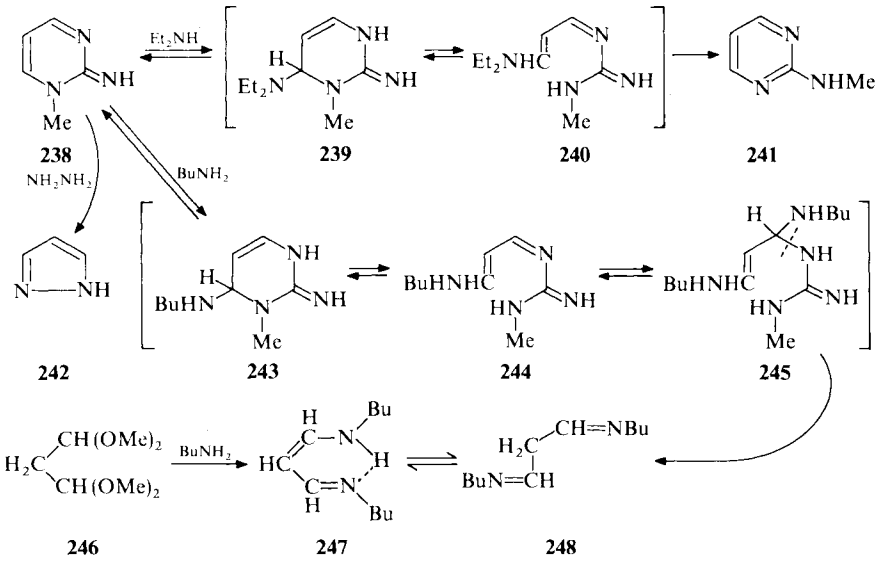
The gross *mechanism* of the Dimroth rearrangement was proved independently in two laboratories.[867,3378] Thus aminolysis of 2-chloropyrimidine by [^{15}N]-ammonia gave 2-pyrimidinamine labeled isotopically on the extracyclic nitrogen; its methylated derivative (**234**) was then rearranged in cold alkali to give an (unisolated) intermediate (**235**) and thence 2-methylaminopyrimidine (**236**), which underwent a vigorous alkaline hydrolysis to afford 2(1*H*)-pyrimidinone (**237**) and methylamine: only the first of these products showed ^{15}N-enrichment on mass spectral examination, indicating that the extracyclic nitrogen of the imine (**234**) had been incorporated into the ring during rearrangement. The mechanism was discussed subsequently in terms of the kinetics of its several steps, and the essential role of water under normal conditions was confirmed.[3791] However, anhydrous secondary amines also provided a satisfactory medium for rearrangement. Thus when the hydriodide of 1-methyl-2(1*H*)-pyrimidinimine (**238**) was warmed with diethylamine, the adduct (**239**) underwent ring fission to the acyclic intermediate (**240**), which recyclized to 2-methylaminopyrimidine (**241**) (60%);[5728] the same imine was unaffected by triethylamine,[5728] but with the primary amine, butylamine, an unexpected reaction took place to give 1,3-bisbutyliminopropane (**248**), probably via the intermediates (**243**–**245**).[5728, cf. 1256] The product (**248**) was stabilized in its cyclic form (**247**), which was made unambiguously from 1,1,3,3-tetramethoxypropane (**246**) and butylamine.[5728] The imine (**238**) reacted rather similarly with hydrazine to furnish pyrazole (**242**) (60%).[5728]



233 **234** **235**

236 **237**

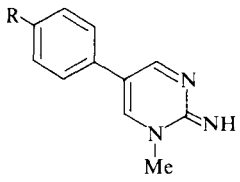
The first *rate studies* on Dimroth rearrangement were done with known pteridines.[2391,3669,5868] These indicated two successive reactions (ring fission and reclosure) that were slowed by electron-donating substituents and accelerated by electron-withdrawing substituents.[4583,5969–5871] This immediately explained most existing qualitative data in the pyrimidine series, including some puzzling failures to rearrange.[982,1520,3782] A spectral study of the rearrangement of 1-methyl-2(1*H*)-pyrimidinimine (**234**) indicated that ring fission to **235**



was the rate determining step (half-life $t_{1/2}$ = 114 min at 25° and pH 14.0) and that no buildup of the intermediate (**235**) occurred on the way to the final product (**236**).[1741,4583] However, when the reaction was performed in the presence of hydroxylamine, the acyclic intermediate (**235**) was trapped and characterized as its oxime;[3791] in addition, a hydrolytic by-product, malondialdehyde, was identified[3791] and partial hydrolytic removal of methylamine from the intermediate was shown to occur under some conditions to give a little 2(1*H*)-pyrimidinone (**237**) on recyclization.[3379] This picture proved general for the rearrangement of most pyrimidinimines.

The retarding effect of electron-donating substituents on rearrangement is typified by that of 4-dimethylamino-1-methyl-2(1*H*)-pyrimidinimine ($t_{1/2}$ = 2000 min at 25° and pH 14);[923,1346,1741] the hastening effect of electron-withdrawing substituents is even more marked under similar conditions: for example, 5-iodo-1-methyl-2(1*H*)-pyrimidinimine ($t_{1/2}$ = 31 min) or 4-dimethylamino-1-methyl-5-nitro-2(1*H*)-pyrimidinimine ($t_{1/2}$ = < 0.1 min);[843,923,1346,1437,3791,4583,5870] and some steric and electronic effects of variations in the *N*-alkyl, alkenyl, or alkynyl group also affects the rate of rearrangement quite appreciably.[843,923,1741,4583] All such rates have been tabulated and discussed.[5864] In addition, rearrangement rates have been measured for a compact series of 1-methyl-5-(*p*-substituted-phenyl)-2(1*H*)-pyrimidinimines (**249**): although the mesomeric effects of the *p*-substituents were severely attenuated by a considerable interplanar angle between the benzene and pyrimidine rings (confirmed independently[3072] by pK_a and spectral measurements), rates decreased significantly in the order $NO_2 > F > Cl > Br > Me > OMe > NH_2 > NMe_2$, thus following qualitatively the σ_p values for the substituents.[2114] Rearrangement rates have also been reported[2570] for a less compact

series of 3-methyl-4(3*H*)-pyrimidinimines (**250**), additionally *C*-alkylated in the 2-, 5-, and/or 6-position(s): a 5-alkyl group slowed rearrangement 25- to 190-fold, a 2- or 6-alkyl group caused only a 5-fold slowing, and in the 5- but not in the 2- or 6- position, the relative effects of different alkyl groups lay in the order $Pr^i > Et > Me$.[2570]



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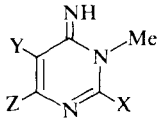

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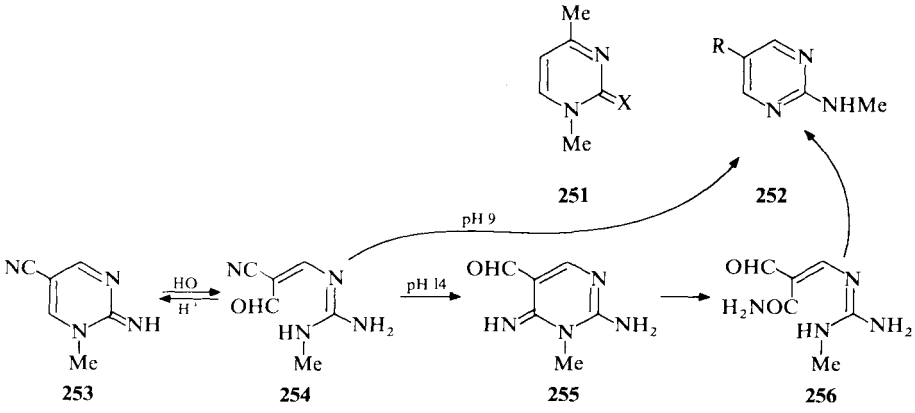
Several *abnormal rearrangements* have been reported.

1. 1,4-Dimethyl-2(1*H*)-pyrimidinimine (**251**, X = NH) rearranged so very slowly that the product contained only 10% of 4-methyl-2-methylaminopyrimidine along with 80% of 1,4-dimethyl-2(1*H*)-pyrimidinone (**251**, X = O) and 10% of 4-methyl-2(1*H*)-pyrimidinone;[1465] 4-*t*-butyl-1-methyl-2(1*H*)-pyrimidinimine behaved rather similarly, but no satisfactory explanation has emerged.[1465]

2. 2-Imino-1-methyl-1,2-dihyro-5-pyrimidinecarbonitrile **253** in alkali rapidly gave the (characterized) intermediate (**254**). In acid this reverted to the salt of the parent imine (**253**); in aqueous ammonia (pH 9) it gave the normal rearranged product, 2-methylamino-5-pyrimidinecarbonitrile (**252**, R = CN); but in alkali (pH 14) it gave 2-amino-4-imino-3-methyl-3,4-dihydro-5-pyrimidinecarbaldehyde (**255**) by an alternative ring closure involving the cyano group. The last product (**255**) then slowly underwent a second abnormal rearrangement to afford 2-methylamino-5-pyrimidinecarboxamide (**252**, R = $CONH_2$), presumably via the unisolated intermediate (**256**).[1346] It seems

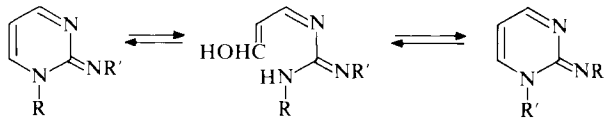


251 **252**

253 **254** **255** **256**

likely that the abnormal cyclization (**254** → **255**) occurred because the formyl group in **254** was deactivated by hydration in strong alkali: this hypothesis was strengthened by the completely normal rearrangement of 2-imino-1,4,6-trimethyl-1,2-dihydro-5-pyrimidinecarbonitrile, involving a ketonic intermediate not prone to such hydration.[923]

Rearrangement of *secondary iminopyrimidines*, such as 1-alkyl-2-alkylimino-1,2-dihydropyrimidines, takes place quite readily. However, whereas a regular 1-alkyl-2(1*H*)-pyrimidinimine gains formal aromaticity on rearrangement, this driving force is absent when a secondary iminopyrimidine (**257**) rearranges into its isomer (**259**) via the intermediate (**258**). In the latter case, an equilibrium mixture of the isomers (**257** and **259**) was attained, independent of the isomer used as starting material and controlled by steric and electronic factors associated with the groups R and R′.[902,1437] Thus equilibrium favored the isomer with the bulkier and/or more electron-withdrawing group attached to the exocyclic nitrogen atom. For example, 1-ethyl-2-methylimino- (**257**, R = Et, R′ = Me) or 2-ethylimino-1-methyl-1,2-dihydropyrimidine- (**259**, R = Et, R = Me) gave in alkali the same equilibrium mixture containing 2 parts of the former and 3 parts of the latter (steric control); and 1-allyl-2-propylimino- (**257**, R = $CH_2CH{:}CH_2$, R′ = Pr) or 2-allylimino-1-propyl-1,2-dihydropyrimidine (**259**, R = $CH_2CH{:}CH_2$, R′ = Pr) attained an equilibrium mixture containing 1 part of the former and 3 parts of the latter (electronic control).[902,1437]



257 **258** **259**

As a *preparative procedure*, Dimroth rearrangement can be quite useful. The preparation of 1/3-alkyl-2/4(1/3*H*)-pyrimidinimines has been discussed in Section 9.3.1, and the preparative-scale rearrangement of such imines to their 2/4-alkylamino isomers is illustrated briefly in the following isomerizations.

Under the usual conditions

1-Ethyl-2(1*H*)-pyrimidinimine.HI to 2-ethylaminopyrimidine (*M* NaOH, 95°, 10 min: 70%, isolated as picrate).[1741]

1,4,6-Trimethyl-5-phenyl-2(1*H*)-pyrimidinimine.HI to 4,6-dimethyl-2-methylamino-5-phenylpyrimidine (2*M* NaOH, 95°, 4 h: 84%).[2114]

3-Methyl-4(3*H*)-pyrimidinimine.HI to 4-methylaminopyrimidine (2*M* NaOH, 60°, 2 h: ~ 90%).[1508]

3-Ethyl-6-phenyl-4(3*H*)-pyrimidinimine.HBF_4 to 4-ethylamino-6-phenylpyrimidine (dilute KOH, reflux, 15 min: 65%).[1245]

1-Methyl-5-*p*-tolyl-2(1*H*)-pyrimidinimine.HI to 2-methylamino-5-*p*-tolylpyrimidine (*M* KOH, 25°, 12 h: 81%).[3072]

Also many other examples in most of the references throughout this section.

Under unusual conditions

4-Imino-3-methyl-2-methylthio-3,4-dihydro-5-pyrimidinecarbonitrile.HI to 4-methylamino-5-pyrimidinecarbonitrile (during desulfurization; Ni, NH_4I, EtOH, reflux, 15 h: 62%).[1571]

4-Amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acid to 4-methylamino-2(1*H*)-pyrimidinone (during decarboxylation; 260°, 5 min). 1383, cf. 809,864

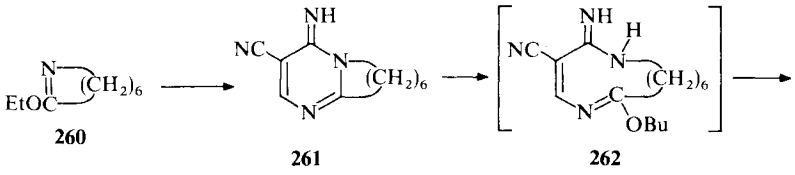
6-Imino-l-methyl-1,6-dihydro-4-pyrimidinamine.HCl to 6-methylamino-5-nitro-4-pyrimidamine (during nitration; HNO_3–H_2SO_4, 40°, 30 min: 85%). [1770]

Also other preparative examples[4318,4319] and during electron bombard ment.[5872]

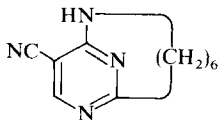
Treatment with *acetic anhydride* induced 4-amino-,[721] 4-methylamino-,[1542] and 4-*β*-carboxyethylamino-2-(1*H*)-pyrimidinone,[697] as well as 4-amino-2(1*H*)-pyrimidinone 3-oxide,[5430] to undergo complicated reaction sequences all involving Dimroth-like rearrangements.

At least one example of a Dimroth rearrangement within a *reduced pyrimidine system* has been reported.[6244]

The rearrangement of some (bicyclic) *polymethylenepyrimidinimines* have been studied in some detail.[1571,2570,5872, cf. 6039a,6039b] For example, 2-ethoxy-3,4,5,6,7,8-hexahydroazocine (**260**) condensed with α-(aminomethylene)malononitrile to give 4-imino-6,7,8,9,10,11-hexahydro-4*H*-pyrimido[1,2-a]azocine-3-carbonitrile (**261**), which underwent rearrangement in boiling butanol to give 2,10,13-triazabicyclo[7,3,1]trideca-1(13),9,11-triene-12-carbonitrile (**263**), probably via the intermediate (**262**).[1571]



260 **261** **262**



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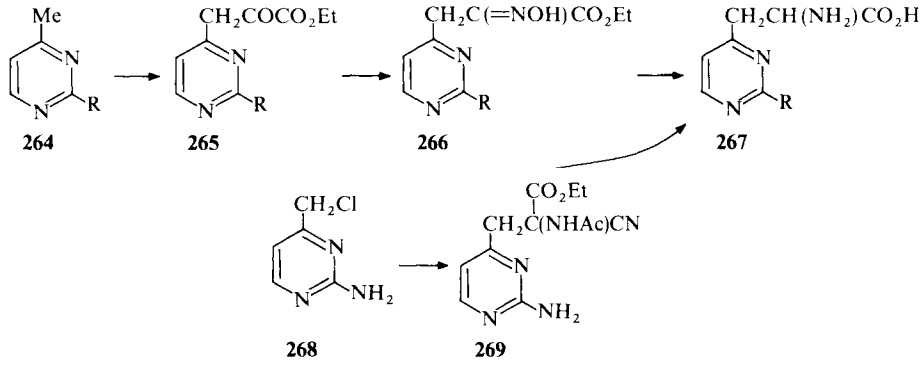
9.4. NATURALLY OCCURRING OR MEDICINAL AMINOPYRIMIDINES

Any such aminopyrimidines that also bear an oxo group have been discussed in Sections 7.1.4 and 7.1.5.

9.4.1. 4-β-Amino-β-carboxyethyl-2-pyrimidinamine (Lathyrine, Tingitanin)

Lathyrine was isolated from the seeds of the Tangier pea (*Lathyrus tingitanus*) in 1961.[5874,5875] Its structure (**267**, R = NH_2) rested at first on spectral data, [5876] but later it was confirmed by oxidation to 2-amino-5-pyrimidinecarboxylic acid,[686] and by no less than four syntheses: the first involved the sequence (**264**, R = NAc_2) → (**265**, R = NH_2) → (**266**, R = NH_2) → (**267**, R = NH_2);[686] the second and third were alike, involving the sequences **264** (R = OMe or SEt) → **265** (R = OMe or SEt → **266** (R = OMe or SEt) → **267** (R = OMe or SEt) → **267** (R = NH_2);[4703] and in the fourth synthesis, 4-methyl-2-pyrimidinamine was converted by several steps into its chloro derivative (**268**), which was condensed with ethyl α-acetamido-α-cyanoacetate to give the pyrimidine (**269**) and thence, by treatment with acid, the product (**267**, R = NH_2).[1629]

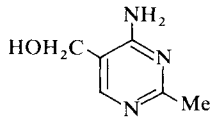


9.4.2. 5-(5′-β-Hydroxyethyl-4′-methylthiazolio)methyl-2-methyl-4-pyrimidinamine Chloride Hydrochloride (Thiamine, Vitamin B_1)

The chemistry and biology of thiamine are so well known and have been so extensively reviewed, even within a decade of its synthesis,[6040] that the present coverage can be quite brief. Although it had been known for at least half a century that a diet of polished rice led to beriberi and that the disease could be prevented or cured by a more varied diet, only in 1926 was the vitamin isolated

(from rice bran) in crystalline form[6041,6042] within 10 years, the structure of thiamine (**195**) had been elucidated and total syntheses accomplished [750,1472,1920,5857,6220] (see also Section 9.2.10); because of its pharmaceutical importance, many variations on the syntheses,[37] as well as procedures for extraction of thiamine from rice bran or other sources, have been reported in great detail, especially in patents.[6040] The practical pharmacology of thiamine has been summarized in the context of other vitamins.[6043]

Acidic hydrolysis of thiamine afforded 5-hydroxymethyl-2-methyl-4-pyrimidinamine (*toxopyrimidine, pyramine*) (**270**),[5877] a substance exceptionally toxic to vitamin B_6-deficient rodents in which it induces fatal convulsions.[5878] The marked effects of toxopyrimidine and its homologs, e.g. 2-ethyl-5-hydroxymethyl-4-pyrimidinamine[1065] or 5-hydroxymethyl-2-methyl-4-methyl-aminopyrimidine,[5145] on humans have been reviewed.[5464] The 2-trifluoromethyl analog of thiamine is also toxic.[6207]



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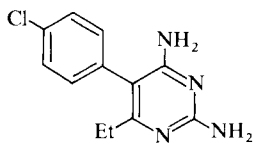
9.4.3. The Antimicrobial 2,4-Pyrimidinediamines

At least three 2,4-pyrimidinediamines are still widely used as antimicrobial agents.[5524,5886,6045]

5-*p*-Chlorophenyl-6-ethyl-2,4-pyrimidinediamine (*pyrimethamine*) (**271**) is usually made by a Principal Synthesis (see Section 3.8.2).[4238,4270,4272] It is a powerful inhibitor of the enzyme, dihydrofolate reductase (essential to protein synthesis *in vivo*), but it has much stronger affinity for the protozal than for the mammalian enzyme: accordingly, in appropriate dosage, pyrimethamine is a useful prophylactic agent against the common human malarial parasites, *Plasmodium falciparum* and *P. vivax*. It appears to protonate at N1 on nmr evidence.[463]



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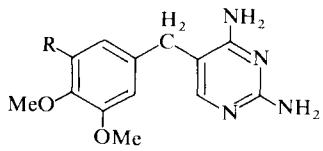

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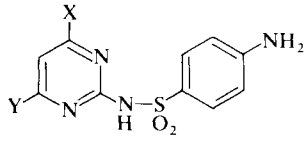
Although 5-(3′,4′,5′-trimethoxybenzyl)-2,4-pyrimidinediamine (*trimethoprim*) (**272**, R = OMe) was envisaged originally as an antimalarial drug,[5879,5881] it proved to be a much better agent against human bacterial infections, especially

in synergistic combination with an antibacterial sulfonamide,[5880,5882] in practice 5-methyl-3-sulfanilamidoisoxazole (sulfamethoxazole), under the name Bactrim or Septrin. Trimethoprim has usually been made by a Principal Synthesis (see Section 3.7.2): its success as a drug led to much work on improved preparative procedures and the synthesis of diverse analogs.[2633,4248,4253–4257, 4281,4294,5883–5886,6037]

The closely related substance, 5-(3′,4′-dimethoxybenzyl)-2,4-pyrimidinediamine (*diaveridine*) (**272**, R = H), proved an effective synergist to sulfonamides for coccidial infections in birds.[5887–5889] The best-known preparation of diaveridine[4251] follows that of trimethoprim (see Section 3.7.2).

9.4.4. Sulfanilamidopyrimidines

From more than 5000 sulfonamides prepared and tested for antibacterial activity mainly in the period 1935–1955, at least a dozen sulfanilamidopyrimidines were introduced into clinical use. However most of these fell into disuse as the antibiotics became progressively more available: at the present time, 2-sulfanilamidopyrimidine (*sulfadiazine*) (**273**, X = Y = H) is probably the only such pyrimidine used to any extent in most countries, although mixtures containing sulfadiazine, 4-methyl-2-sulfanilamidopyrimidine (*sulfamerazine*) (**273**, X = Me, Y = H), and 4,6-dimethyl-2-sulfanilamidopyrimidine (*sulfamethazine*) (**273**, X = Y = Me) remain available simply because the overall solubility of their acetylated metabolites in urine is high enough to minimize any risk of precipitation and kidney blockage.[6044] 2,6-Dimethyl-4-sulfanilamidopyrimidine (*sulfisomidine*)[494] appeared in the *European Pharmacopoeia* (1990).



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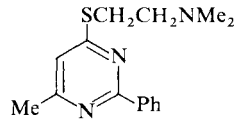
Common synthetic routes to sulfanilamidopyrimidines are illustrated in the formation of 4,6-dimethyl-2-sulfanilamidopyrimidine (**273**, X = Y = Me) by (1) condensation of acetylacetone with *p*-nitrobenzenesulfonylguanidine to give 4,6-dimethyl-2-*p*-nitrobenzenesulfonamidopyrimidin, followed by reduction;[4057] (2) condensation of acetylacetone with *p*-aminobenzenesulfonylguanidine to give the product (**273**, X = Y = Me) directly;[4057] and (3) acylation of 4,6-dimethyl-2-pyrimidinamine with *p*-acetamidobenzenesulfonyl chloride to give 2-*p*-acetamidobenzenesulfonamido-4,6-dimethylpyrimidine, followed by deacetylation.[704,1217,4036] Another useful route, involving the treatment of an (activated) halogenopyrimidine with sodiosulfanilamide or a related reagent, has been discussed in Section 6.7.8.

9.4.5. Bleomycin and Phleomycin

The closely related antibiotics, bleomycin (**275**)* and phleomycin (**275**), were first isolated from cultures of *Streptomyces verticillus* in 1956.[6046] Both showed powerful antimicrobial and anticancer properties, and despite their significantly toxic side effects, bleomycin is used routinely for treatment of some carcinomas of the head and genitalia, as well as for some lymphomas. The activities of these antibiotics may be amplified significantly, both *in vitro* and *in vivo*, by the



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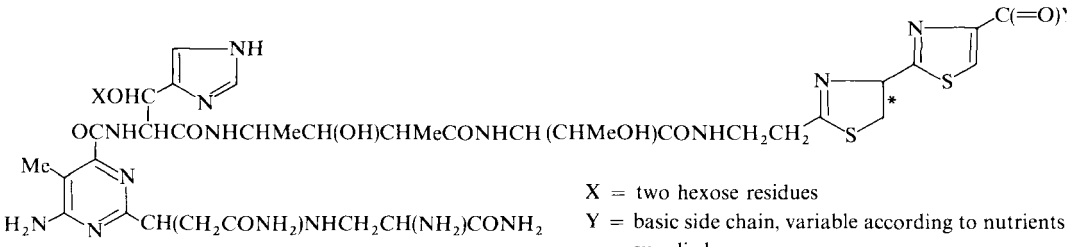

X = two hexose residues
Y = basic side chain, variable according to nutrients supplied
* Double bond in bleomycin

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addition of certain small heterocyclic molecules, such as 2,6,7-trimethyl-2,6(1*H*,3*H*)-purinedione (caffeine) or 4-β-dimethylaminoethylthio-6-methyl-2-phenylpyrimidine (**274**).[343,6047] By so using an amplifier, the amount and hence the toxicity of the antibiotic may be reduced without compromising its efficacy,[6048] but this advance has not been adopted clinically. The molecular basis of such amplification has been investigated.[340]

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CHAPTER 10

Pyrimidinecarboxylic Acids and Related Derivatives

This chapter covers the pyrimidinecarboxylic acids and their extended family of esters, amides, nitriles, aldehydes, ketones, isocyanates, thiocyanates, isothiocyanates, nitrile oxides, and related compounds. In using this chapter, it should be remembered that a given interconversion is discussed only at the first logical opportunity: for example, the formation of esters from carboxylic acids is covered as a reaction of acids rather than as a preparative method for esters, simply because acids are discussed prior to esters. Nevertheless, extensive cross-references have been inserted.

10.1. PYRIMIDINECARBOXYLIC ACIDS

10.1.1. Preparation of Pyrimidinecarboxylic Acids

By primary syntheses. Many primary synthetic methods have been used to make pyrimidinecarboxylic acids directly (see Chapters 2 and 3). The oxidation of quinazoline to 4,5-pyrimidinedicarboxylic acid and thence 5-pyrimidinecarboxylic acid,[3603] and of 2-methylquinazoline to 2,5-pyrimidinedicarboxylic acid,[6069] should not be overlooked.

By hydrolysis of esters. Although alkaline hydrolysis (saponification) is normally preferred for the conversion of esters into acids, acidic hydrolysis is also effective and the choice may depend on other groups in the molecule. Both methods are illustrated in the hydrolysis of the following esters to the corresponding carboxylic acids, except where otherwise indicated.

Ethyl 5-pyrimidinecarboxylate (2*M* NaOH, 50°, 10 min: 88%).[2509]

Ethyl 2-methyl-5-pyrimidinecarboxylate (2*M* NaOH, 25°, 1 h: 88%).[3996]

Ethyl 2-ethyl-5-pyrimidinecarboxylate (HO^-: 42%).[3097]

2-Ethoxycarbonylmethylpyrimidine (0.3*M* NaOH, reflux, 30 min: 60%).[1997]

Methyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (*M* HCl, reflux, 16 h: 96%).[1980]

Ethyl 5,6-diamino-4-pyrimidinecarboxylate (0.5*M* Na_2CO_3, reflux, 20 min: > 90%).[2435]

Ethyl 2,4-diamino-5-pyrimidinecarboxylate (NaOH, H_2O–EtOH, reflux, 30 min: > 90%).[2331]

Ethyl 2,4-bistrifluoromethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylate (0.5*M* NaOH, reflux, 1 h: 84%).[3921]

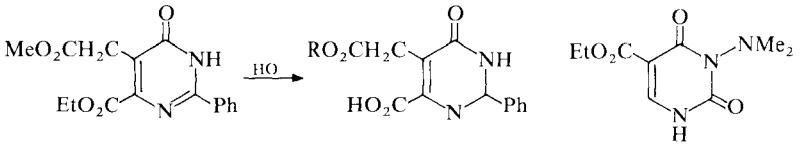
Methyl 6-acetonyl-5-chloro-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate (*M* NaOH, 25°, 1 h: 67%).[733]

Ethyl 4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (2*M* H_2SO_4, boil, 90 min: > 90%).[2873]

Diethyl 2-phenyl-4,5-pyrimidinedicarboxylate (2*M* KOH, reflux, 16 h: 98%).[5939]

1-Ethoxycarbonylmethoxy-2(1*H*)-pyrimidinone (HBr, AcOH, boil, 15 min: 99% as hydrobromide).[3366]

Ethyl 5-methoxycarbonylmethyl-6-oxo-2-phenyl-1,6-dihydro-4-pyrimidinecarboxylate (**1**) to 5-methoxycarbonylmethyl- (**2**, R = Me) [NaOH, H_2O–MeOH (**1** : **2**), 25°, 24 h: 41%] or 5-carboxymethyl-6-oxo-2-phenyl-1,6-dihydro-4-pyrimidinecarboxylic acid (**2**, R = H) [NaOH, H_2O-MeOH (1 : 1), 25°, 5 h: 75%].[3849]



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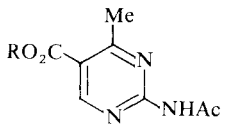
Ethyl 2-methylthio-5-pyrimidinecarboxylate to 2-oxo-1,2-dihydro-5-pyrimidinecarboxylic acid (KOH, EtOH, reflux, 1 h: 72%).[381]

Ethyl 1-dimethylamino-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (**3**) (6*M* HCl, reflux, 15 min: 30%).[1071]

Also many other examples.[32,110,166, 809,864,1032,1086,1254,1262,1338,1462, 1474,1475,1534,1628,1632,1749,1876,1988,2002,2031,2517,2673,2970,3020,3780,3840, 3894,4089,4151,4274,4637,4826,4870,4890,5938,5940,5941]

By hydrogenolysis of esters. Benzyl esters are especially useful as substrates when there is another hydrolysis-prone substituent present, because such esters may be converted into the corresponding carboxylic acids by hydrogenolysis: for example, benzyl 2-acetamido-4-methyl-5-pyrimidinecarboxylate (**4**, R = CH_2Ph) gave the carboxylic acid (**4**, R = H) (24%) on hydrogenation in



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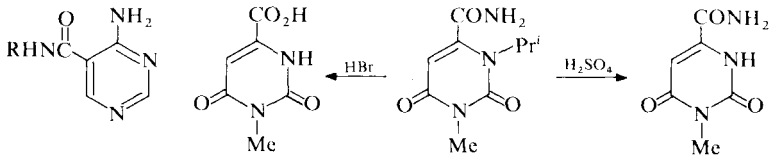
methanol over palladium;[691] and benzyl 1-ethyl-2,6-dioxo-1,2,3,4,5,6-hexahydro-4-pyrimidinecarboxylate gave the corresponding carboxylic acid (H_2, Pd, EtOH?, 25°, 2 h: 93%).[3977]

By hydrolysis of amides. Amides may be converted into carboxylic acids under acidic or alkaline conditions, as illustrated in the hydrolysis of the following amides.

4-Amino-5-pyrimidinecarboxamide (**5**, R = H)[708] or 4-amino-5-pyrimidinecarboxanilide (**5**, R = Ph)[1634] (2*M* NaOH, 100°, 30 min: 89% or 62%, respectively).

1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (48% HBr, reflux, 1 h: 75%).[2676]

4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide (BuONO, AcOH, HCl gas, 100°, 3 h: 47%).[3003]



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3-Isopropyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**7**) to 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (**6**) (48% HBr, reflux, 2 h: > 80%) or to 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**8**) (98% H_2SO_4, 90°: ~ 75%); note removal of the *s*-alkyl group in each case.[2675]

Also other examples.[990,1626,1628,2872,5965]

By hydrolysis of nitriles. Likewise, pyrimidinecarboxylic acids may be obtained from the corresponding nitriles by hydrolysis, usually in alkali. The reactions probably proceed via intermediate (unisolated) amides. The required conditions are illustrated by hydrolysis of the following pyrimidinecarbonitriles.

2-Pyrimidinecarbonitrile (2*M* NaOH, reflux, 2 h: 70%).[3290]

4,6-Dimethyl-2-pyrimidinecarbonitrile (*M* NaOH, 60°, 1 h: 75%).[2603]

5-Phenyl-2-pyrimidinecarbonitrile (4*M* NaOH, reflux, 30 min: 71%).[379]

2,6-Dimethoxy-4-pyrimidinecarbonitrile (*M* NaOH, 70°, 1 h: 42%).[2603]

4-Amino-5-pyrimidinecarbonitrile (2.5*M* NaOH, 95°, 1 h: 78%).[708]

5-Chloro-2-pyrimidinecarbonitrile (2*M* NaOH, reflux, 5h: 61%).[1897]

2-Methylthio-4-pyrimidinecarbonitrile (2*M* NaOH, reflux, 2 h: 43%); longer heating (4 h) gave 2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid.[1628]

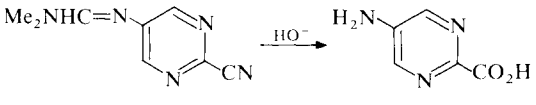
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (50% H_2SO_4, reflux, 1 h: 65%).[1175]

5-*p*-Cyanophenyl-6-methyl-2,4-pyrimidinediamine (KOH, $HOCH_2CH_2OH$, reflux, 5 h: > 95%).[4274]

2-Amino-5-*β*-cyanoethyl-6-methyl-4(3*H*)-pyrimidinone (6*M* HCl, reflux, 2 h: 86%).[981]

5-Dimethylaminomethyleneamino-2-pyrimidinecarbonitrile (**9**) to 5-amino-2-pyrimidinecarboxylic acid (**10**) (2*M* NaOH, reflux, 20 min: 79%).[1623]

Also other examples.[974,979,1485,1632,2222,2670,3622,5942]



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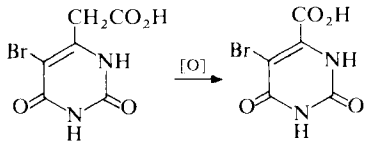
If such hydrolyses are done under sufficiently vigorous conditions, concomitant decarboxylation may occur. For example, 1-ethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile gave 1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione (48% HBr, reflux, 1 h), isolated as its 5-bromo derivative (Br_2, $CHCl_3$: 78% overall);[1883] rather similarly, 4-benzylamino-2,6-diphenyl-5-pyrimidinecarbonitrile gave 2,6-diphenyl-4(3*H*)-pyrimidinone (H_3PO_4, 160°, 3 h: ?%).[4314]

By hydrolysis of trihalogenomethylpyrimidines (Ag^+). Treatment of some trihalogenomethylpyrimidines with aqueous silver nitrate induces hydrolysis to the corresponding pyrimidinecarboxylic acid with the formation of silver halide. The process has been discussed toward the end of Section 6.9.

By oxidation of alkyl- or oxoalkylpyrimidines. The direct oxidation of alkyl-, alkenyl-, or styrylpyrimidines to pyrimidinecarboxylic acids has been discussed in Section 4.2.3.3; and the oxidation of hydroxymethylpyrimidines to pyrimidinecarboxylic acids has been covered in Section 7.3.1.4. The oxidation of other (substituted-alkyl)pyrimidines to pyrimidinecarboxylic acids is exemplified in the conversion of 5-bromo-6-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione (**11**) into 5-bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (**12**) ($Na_2Cr_2O_7$, dilute H_2SO_4, 80°, 1 h: ~ 65%);[1809] 4-acetamido-6-(*β*-furan-2′-ylvinyl)-2-methylpyrimidine (**13**) into 6-acetamido-2-methyl-4-pyrimidinecarboxylic acid (**14**) (O_3, AcOH, then H_2O, 100°, 10 min: good yield);[671] 5-acetyl-4-methyl-2-phenylpyrimidine into 4-methyl-2-phenyl-5-pyrimidine-



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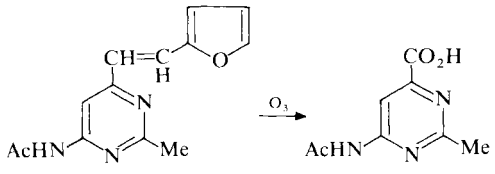

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carboxylic acid ($KMnO_4$, H_2O, 25°, 4 h, then 100°: 60%);[1688] and less clear cases.[817,2603]

By oxidation of pyrimidinecarbaldehydes. Although pyrimidinecarbaldehydes or their acetals are oxidized easily to pyrimidinecarboxylic acids, the poor availability of aldehydes (compared with acids) ensures that the process is little used save as confirmation of structure. The customary reagents and conditions are illustrated in the formation of the following acids, in each case from the corresponding aldehyde unless indicated otherwise.

5-Pyrimidinecarboxylic acid ($KMnO_4$, NaOH, H_2O, 0°, then 20°, 90 min: 72%).[1028]

6-Phenyl-4-pyrimidinecarboxylic acid from 4-diformylmethyl-6-phenylpyrimidine ($KMnO_4$, H_2O, 3 h: > 95%).[2611]

6-Oxo-1,6-dihydro-4-pyrimidinecarboxylic acid ($KMnO_4$, NaOH, H_2O, 25°, 2 h: 35%).[2856]

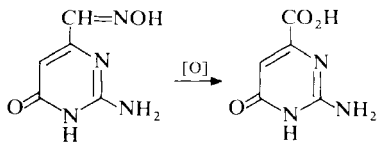
2-Amino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylic acid ($KMnO_4$, NaOH, H_2O, 50°, 5 min: ~ 60%).[682]

2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (H_2O_2, KOH, H_2O, 20°, 1 h: 30%);[2861] also from 2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde (Ag_2O, H_2O–EtOH, 20°, 20 h: ~ 60%)[2859] or from 6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde ($Na_2Cr_2O_7$, H_2SO_4, H_2O, 60°, 10 min: 76%).[1592,2855]

1,3,4-Trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid ($K_2S_2O_8$, trace Ag^+, H_2O, 40°, 2 h: 87%).[3894]

2-Amino-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid (**16**) from the corresponding carbaldehyde oxime (**15**) (KNO_3, H_2SO_4, 100°, 30 min: ~ 25%).[949]

Also other examples.[3640]



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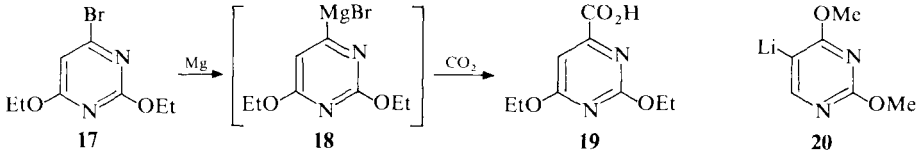
The disproportionation of pyrimidinecarbaldehydes into pyrimidinecarboxylic acids and hydroxymethylpyrimidines by the Cannizzaro reaction[2856,3139] has been discussed in Section 7.3.1.7.

From metallopyrimidines made in situ. Pyrimidinecarboxylic acids have been made occasionally by carbonation of metallopyrimidines, prepared in situ from halogenopyrimidines or by direct metallation. Such processes are illustrated in the following sequences.

4-Bromo-2,6-diethoxypyrimidine (**17**) → 2,6-diethoxypyrimidin-4-ylmagnesium bromide (**18**) (Mg, trace I, THF, − 30°, 1 h) → 2,6-diethoxy-4-pyrimidinecarboxylic acid (**19**) (solid CO_2, − 80°: 35% overall).[788]

5-Bromo-2,4-dimethoxypyrimidine → 5-lithio-2,4-dimethoxypyrimidine (**20**) (BuLi, THF, − 80°, 5 min) → 2,4-dimethoxy-5-pyrimidinecarboxylic acid (solid CO_2, − 80°: 75% overall).[788]

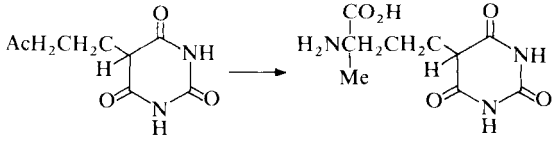


5-Bromo-4-chloro-6-methoxypyrimidine → 4-chloro-5-lithio-6-methoxypyrimidine (BuLi, Et_2O, − 40°, 10 min) → 4-chloro-6-methoxy-5-pyrimidinecarboxylic acid (solid CO_2, − 45°: 53% overall);[1787] also several analogs likewise.[1787]

5-Bromo-2,4-dimethoxy-6-methylpyrimidine → 5-lithio-2,4-dimethoxy-6-methylpyrimidine (BuLi, Et_2O, − 70°, 15 min) → 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylic acid (solid CO_2, Et_2O, − 60°: 90%).[3894]

2,4-Dimethoxypyrimidine → 5-lithio-2,4-dimethoxypyrimidine (**20**) (lithium 2,2,6,6-tetramethylpiperidide, Et_2O, 0°, 5 min) → 2,4-dimethoxy-5-pyrimidinecarboxylic acid (CO_2, ?°: 30% after esterification).[474]

By the Strecker reaction. A classical Strecker reaction has been used to convert 5-β-acetylethyl- (**21**) into 5-γ-amino-γ-carboxybutyl-1-cyclohexyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**22**) (NaCN, NH_4OH, NH_4Cl, MeOH–H_2O: ~ 30%);[5616] another example has been outlined in Section 7.1.4.9.



By derivatization. Many ω-carboxypyrimidines have been made by mundane derivatizations, as illustrated briefly in the following transformations.

5-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione to its 1-carboxymethyl derivative ($ClCH_2CO_2H$, pH 10, 25°, then reflux, 2 h: 66%).[2023]

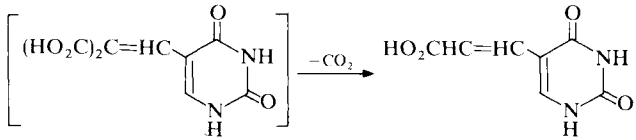
6-Chloro- to 6-ε-carboxypentylamino-5-nitro-4-pyrimidinamine (6-aminohexanoic acid, H_2O–BuOH, pH 8.5, 20°, 6 h: 90%).[5035]

2,4-Dichloro- to 4-*o*-carboxyanilino-2-chloropyrimidine (*o*-$ClC_6H_4CO_2H$, HCl–H_2O, 50°, 15 min, then 20°, 1 h: 78%).[4999]

2-Ethylthio- to 2-carboxymethylamino-6-methyl-4(3*H*)-pyrimidinone ($H_2NCH_2CO_2H$, Na_2CO_3, H_2O, reflux, 14 h: 29%).[2743]

2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde to 5-β,β-dicarboxyvinyl- (**23**) (unisolated) and thence to 5-β-carboxyvinyl-2,4(1*H*,3*H*)-pyrimidinedione (**24**) ($HO_2CCH_2CO_2H$, piperidine, pyridine, reflux, 90 min: 84%).[2042]

Also other examples.[411,697,983,1807,1961,1989,2003,2612,4703,5006–5008,5023,5024,5045,5060]



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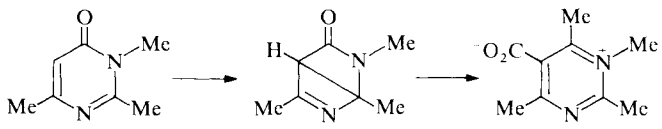
By photolysis. Irradiation of fixed 4(3*H*)-pyrimidinones in alkanoic acids has been reported[335] to afford reasonable yields of 5-pyrimidinecarboxylic acids via the Dewar-pyrimidinones. For example, irradiation of 2,3,6-trimethyl-4(3*H*)-pyrimidinone (**25**) in acetic acid at 25° for 7 h gave 1,2,4,6-tetramethylpyrimidinium-5-carboxylate (**27**) (69% net); the same product (**27**) (54%) was formed on irradiation of the Dewar-pyrimidinone (**26**) in acetic acid–acetonitrile.[335] Analogs were made similarly.[335]



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10.1.2. Reactions of Pyrimidinecarboxylic Acids

Decarboxylation. Decarboxylation of carboxypyrimidines has been used widely, especially for the removal of unwanted alkyl or related carbon-linked substituents that can be converted into carboxy groups by oxidation or other

means. Decarboxylation of the following substrates will serve to illustrate the required conditions and the yields to be expected.

4-Pyrimidinecarboxylic acid (slow dry distillation);[1517] cupric 4-pyrimidinecarboxylate gave 4,4′-bipyrimidine (likewise: 5%).[4030]

4,6-Pyrimidinedicarboxylic acid (Ph_2O, 240°: 60%).[764]

5-Bromo-2-pyrimidinecarboxylic acid (250°, 90 min: 85%).[1935, cf. 1974]

2-Amino-5-pyrimidinecarboxylic acid (dry, 300°. 3 h: 74%).[3996]

4-Amino-5-pyrimidinecarboxylic acid (Ph_2CO, 280°, 5 min: ~ 25%).[708]

5-Benzoyl-2-methylthio-4-pyrimidinecarboxylic acid (PhOMe, reflux, 2.5 h: 98%).[502]

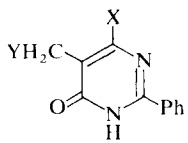
2-Methylthio-5-phenylthio-4-pyrimidinecarboxylic acid (200°, 20 min: 90%).[2021]

5-Butyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (quinoline, Cu, reflux, 1 h: 80%).[2677]

5-Benzoyl-2-phenyl-4,6-pyrimidinedicarboxylic acid (Ac_2O–AcOH, reflux, 5 h: 91%).[4478]

6-Dibenzylamino-5-methyl-2,4-pyrimidinedicarboxylic acid (Ac_2O–AcOH, reflux, 30 h: 52%).[3840]

5-Carboxymethyl-6-oxo-2-phenyl-1,6-dihydro-4-pyrimidinecarboxylic acid (**28**, X = Y = CO_2H) to 5-methyl-6-oxo-2-phenyl-1,6-dihydro-4-pyrimidinecarboxylic acid (**28**, X = CO_2H, Y = H) ($AcNMe_2$, 120°, 3 h: 85%) or to 5-methyl-2-phenyl-4(3*H*)-pyrimidinone (**28**, X = Y = H) (dry, 250°, 5 min: 82%).[3849]



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4-Amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acid to 4-amino-3-methyl-2(3*H*)-pyrimidinone (255°, 0.01 mm: 32%)[1534] or to 4-methylamino-2(1*H*)-pyrimidinone (260°, 760 mm, 5 min: ~ 50%).[809,864,1383]

Also several simple examples in Section 4.2.1.3 and less simple examples elsewhere.[671,904,1808,1856,1874,1934,1978,2039,2222,2673,3392,3622,3765,4137,4418,4517,5104,5303a,5943]

Esterification. Most of the usual procedures have been used for the *direct* esterification of pyrimidinecarboxylic acids, as illustrated in the formation of the following esters.

Methyl 2-pyrimidinecarboxylate (from Ag salt of acid, MeI, $CHCl_3$, reflux, 2 h: 54%).[3290]

Methyl 4-pyrimidinecarboxylate (MeOH, H_2SO_4, reflux, 8 h: 47%;[729] MeOH, HCl gas, reflux, 4 h: 52%;[729] MeOH, HCl, reflux, 8 h: 86%;[3446] CH_2N_2, Et_2O, 20 h: > 95%).[729].

Methyl 5-pyrimidinecarboxylate (MeOH, HCl gas, 20°, 3 days: 48%).[2321]

Methyl 5-bromo-2-pyrimidinecarboxylate (CH_2N_2, Et_2O, 0°, 15 h: > 95%).[729,1973]

Methyl 4-*m*-trifluoromethylanilino-5-pyrimidinecarboxylate (CH_2N_2, Et_2O, 20°, 15 h?: 67%).[5940]

Methyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (MeOH, HCl gas, reflux, 15 h: ~ 45%).[2673, cf. 2879,3082,3391]

Methyl 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (MeOH, H_2SO_4, reflux, 8 h: ~ 85%).[2994]

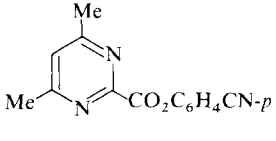
Methyl 4-amino-2-methyl-5-pyrimidinecarboxylate (MeOH, H_2SO_2, reflux, 2.5 h: 76%).[1458]

5-Ethoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione (EtOH, trace H_2SO_4, reflux, 20 h: 96%).[2007]

p-Cyanophenyl 4,6-dimethyl-2-pyrimidinecarboxylate (**29**) (HOC_6H_4CN-*p*, Ph_3P, NEt_3, CCl_4, MeCN, 20°, 6 h: 66%).[379]

Benzyl 2,6-dioxo-1,2,3,4,5,6-hexahydro-4-pyrimidinecarboxylate ($PhCH_2Br$, NEt_3, Me_2NCHO, 20°, 2 days: 59%).[3977]

5-*β*-Methoxycarbonylvinyl-2,4(1*H*,3*H*)-pyrimidinedione (MeOH, trace H_2SO_4, reflux, 3 days: > 90%).[2039]



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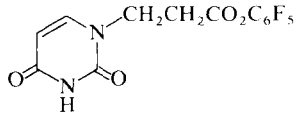

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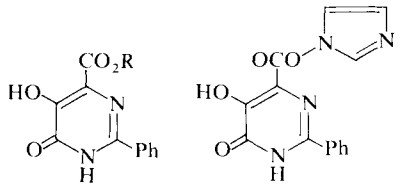
1-*β*-(Pentafluorophenoxycarbonyl)ethyl-2,4(1*H*,3*H*)-pyrimidinedione (**30**) (C_6F_5OH, dicyclohexylcarbodiimide, Me_2NCHO, 0°, 15 h: 90%).[110]

2,5-Bis(*p*-ethoxycarbonylanilino)pyrimidine (EtOH, H_2SO_4, reflux, 10 h: 75%).[5944]

Methyl 5-hydroxy-6-oxo-2-phenyl-1,6-dihydro-4-pyrimidinecarboxylate (**31**, R = Me) [from the acid (**31**, R = H) via the characterized intermediate (**32**); carbonyldi(1-imidazole), Me_2NCHO, 20°, 15 h, then MeOH, reflux, 10 min: ~ 60% overall].[4137]

Also many other examples.[733,949,979,1030,1086,1225,1479,1856,1881,1933, 2003,2004,2197,2264,2291,2331,2745,2871,2882,3095,3323,3446,4274,5496,5837,5945,6849]



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Esterification is sometimes done *indirectly* through an acid chloride or acid anhydride intermediate, usually as a one-pot procedure. Such reactions are illustrated in the following transformations.

5-Pyrimidinecarboxylic acid to 5-pyrimidinecarbonyl chloride ($SOCl_2$, reflux, ? h: 86%) and thence to ethyl 5-pyrimidinecarboxylate (EtOH, Et_2O, reflux, 2 h: 56%).[1028]

2-Methyl-5-pyrimidinecarboxylic acid to methyl 2-methyl-5-pyrimidinecarboxylate ($SOCl_2$, MeOH, 20°, 10 h: > 65%).[2692]

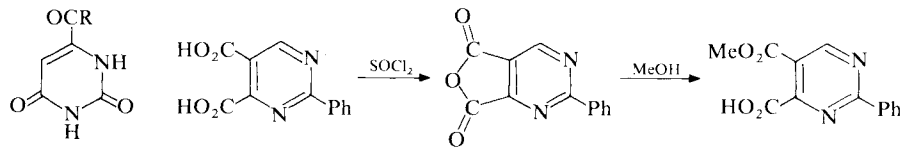
2-Amino-5-carboxymethyl- to 2-amino-5-butoxycarbonylmethyl-4(3*H*)-pyrimidinone ($SOCl_2$, BuOH, −40°, then 40°, then reflux, 2 h each: 88%).[992]

2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (**33**, R = OH) to the 4-carbonyl chloride (**33**, R = Cl) ($SOCl_2$) and thence to *S*-propyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinethiocarboxylate (**33**, R = SPr) (neat PrSH, reflux, 1 h: < 30%).[5498]

4,6-Diphenyl-2-pyrimidinecarboxylic acid to the crude carbonyl chloride ($SOCl_2$, Me_2NCHO, PhH, reflux, 24 h) and thence to *p*-cyanophenyl 4,6-diphenyl-2-pyrimidinecarboxylate (HOC_6H_4CN-*p*, pyridine, 20°, 5 days: ~50%).[379]

2-Phenyl-4,5-pyrimidinedicarboxylic acid (**34**) to the corresponding anhydride (**35**) (neat $SOCl_2$, reflux, 2 h: 75%) and thence to 5-methoxycarbonyl-2-phenyl-4-pyrimidinecarboxylic acid (**36**) (MeOH, reflux, 3 h: 76%).[5939]

Also other examples.[256,2038,2669,3096,3954,5946]



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Conversion into acid halides. Although many pyrimidinecarboxylic acids have been converted into their crude acid chlorides for the preparation of esters (see preceeding paragraph) or amides (see Section 10.2.2), few such chlorides

have been purified and characterized properly. The preparations of the following (pure) acid chlorides serve to illustrate further the customary procedures and conditions.

2-Methylthio-5-pyrimidinecarbonyl chloride (neat $SOCl_2$, reflux, 2 h: 76%).[381]

2-Methylthio-5-phenylthio-4-pyrimidinecarbonyl chloride (neat $SOCl_2$, reflux, 30 min: 75%).[2021]

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl chloride (neat $SOCl_2$, trace Me_2NCHO, reflux, 90 min: 82%).[2670]

2,6-Dichloro-4-pyrimidinecarbonyl chloride from 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid ($POCl_3$, reflux, 15 h, the PCl_5 added, reflux, 15 h: 64%;[2121] or $POCl_3$, reflux, 8 h, then $SOCl_2$ added, reflux, 6 h: 40%).[6036]

2,4-Dichloro-5-pyrimidinecarbonyl chloride ($POCl_3/PCl_5$ as for preceeding isomer: > 50%).[2511,2512]

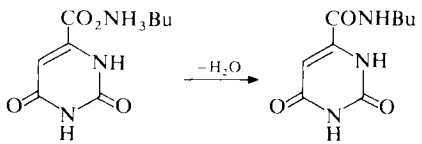
1,3,5-Trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl chloride ($SOCl_2$, trace Me_2NCHO, PhH, reflux, 15 h: 91%).[2669]

Ethyl 4-chlorocarbonyl-2-oxo-6-phenyl-1,2-dihydro-5-pyrimidinecarboxylate (neat $SOCl_2$, reflux, 15 min: 35%).[5947]

6-Chloro-5-methyl-2-phenyl-4-pyrimidinecarbonyl chloride (neat PCl_5, 130°, 1 h: 86%).[5948]

2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl chloride ($SOCl_2$, trace Me_2NCHO, PhH, reflux, 1 h: 96%);[5949] the use of $SOCl_2$/pyridine apparently gave a product rich in the anhydride but satisfactory for making esters or amides.[2121,2882]

Conversion into amides. Conversions of pyrimidinecarboxylic acids into amides are usually done via esters (see Section 10.2.2) or acid chlorides (see Section 10.3.1), but a semidirect route appears to be possible also. Thus butylammonium 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (**37**) in boiling toluene containing a little phosphoryl chloride (for dehydration ?) gave *N*-butyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**38**) (> 80%);[3005] several *N*-alkyl or *N*,*N*-dialkyl analogs were made similarly.[3005]



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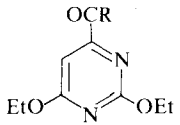
Reduction. The reduction of a pyrimidinecarboxylic acid to the corresponding hydroxymethylpyrimidine is done usually via the ester. However, two

examples of the direct borohydride reduction of acids have been given in Section 7.3.1.4.

Other conversions. Several other reactions of pyrimidinecarboxylic acids are indicated in the following specific examples: (1) 2-phenyl-[5939] and 2,6-diphenyl-4,5-pyrimidinedicarboxylic acid[4418] have been converted into their respective anhydrides ($SOCl_2$); (2) 2,6-diethoxy-4-pyrimidinecarboxylic acid (**39**, R = OH) with methyllithium in ether–THF at 0–5° for 15 min gave 4-acetyl-2,6-diethoxypyrimidine (**39**, R = Me) (~60%)[788]—in a different way, 1-carboxymethyl- gave 1-acetonyl-2,4(1*H*,3*H*)-pyrimidinedione (25%) by heating in pyridine–acetyl chloride at 100° for 4 h;[745] (3) 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid with neat sulfur tetrafluoride at 100° in an autoclave for 16 h gave 5-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione (**40**) (77%);[4957] (4) formation constants (stability constants) for complexes of some heavy metals and pyrimidinecarboxylic acids have been measured;[436] and (5) the polymerization of 4,5-pyrimidinedicarboxylic acid in refluxing pyridine/acetic anhydride for 10 h has been reported.[3774]



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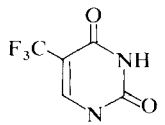

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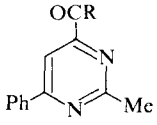
10.2. PYRIMIDINECARBOXYLIC ESTERS

10.2.1. Preparation of Pyrimidinecarboxylic Esters

By primary syntheses. Several types of primary synthesis (Chapters 2 and 3) have been used extensively to make pyrimidine esters.

By esterification of acids. The conversion of pyrimidinecarboxylic acids into the corresponding esters, either directly or via acid chlorides, has been discussed in Section 10.1.2.

By alcoholysis of amides. Although many amides are made from esters, it is convenient sometimes to do the reverse. For example, 2-methyl-6-phenyl-4-pyrimidinecarboxamide (**41**, R = NH_2) gave methyl 2-methyl-6-phenyl-4-pyrimidinecarboxylate (**41**, R = OMe) (MeOH, $Et_2O.BF_3$, reflux: 94%);[2692]



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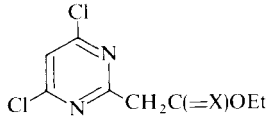
several analogs were made similarly;[2692] and 4-carbamoylmethyl-2-*p*-chlorophenyl- gave 2-*p*-chlorophenyl-4-methoxycarbonylmethylpyrimidine (MeOH, HCl gas, reflux, 20 min).[5950]

From nitriles. Nitriles afford esters in two stages, alcoholysis to the imidic ester followed by hydrolysis to the regular ester. Thus 4,6-dichloro-2-cyanomethyl- gave the hydrochloride of 4,6-dichloro-2-(*C*-ethoxyformimidoyl)methylpyrimidine (**42**, X = NH) (EtOH, Et_2O, PhH, HCl gas, 5°, 15 h: 90%) and thence 4,6-dichloro-2-ethoxycarbonylmethylpyrimidine (42, X = O) (H_2O, 40°, 2 h: ~60%);[1997] 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile gave methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboximidate (**43**, R = NH) (KOH, MeOH, reflux, 1 h: 80%) and thence methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (**43**, R = O) (10% HCl, reflux, 15 min: 61%);[1133] and other examples have been reported.[2603,5950]



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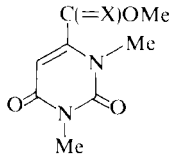

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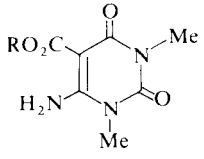
By transesterification. Although the process is seldom used, one ester can be transformed into another fairly readily. Thus ethyl gave methyl or propyl 5-*p*-fluorophenylthiomethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate by refluxing in methanolic methoxide for 2 h (63% yield) or by refluxing in propanolic potassium cyanide for 12 h (77% yield), respectively;[5951] other examples have been reported.[5950]

By direct attachment. An alkoxycarbonyl grouping may sometimes be attached directly to the pyrimidine nucleus or to a methyl group thereon. For example, 6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave ethyl (**44**, R = Et) or phenyl 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate (**44**, R = Ph) ($ClCO_2Et$ or $ClCO_2Ph$, pyridine, reflux, 3 h: ~80% each);[775,2961,2962] 5-*p*-chlorophenyl-2-methylpyrimidine gave 5-*p*-chlorophenyl-2-di(ethoxycarbonyl)methylpyrimidine (**45**) [$(EtO)_2CO$, NaH, reflux: 70%];[5950] 2,4-dimethoxypyrimidine gave ethyl 2,4-dimethoxy-5-pyrimidinecarboxylate ($ClCO_2Et$, $LiMe_4$–piperidide, Et_2O, 0–20°: 6%);[6071]



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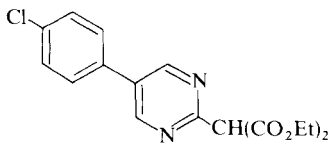

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5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione with *p*-nitrobenzyl chloroformate gave its 1-*p*-nitrobenzyloxycarbonyl, 3-*p*-nitrobenzyloxycarbonyl, or 1,3-bis-*p*-nitrobenzyloxycarbonyl derivative, according to conditions;[300] and rather similar attachments to ring nitrogens of dihydropyrimidines have been recorded.[3836] The conversion of 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione into methyl 1,3-dimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxylate via a tricyclic intermediate has been observed.[2843]

By derivatization. Derivatization processes have been used widely to make pyrimidines in each of which an ester grouping is attached to the nucleus by one of a variety of linkages. Some such processes are illustrated in the following transformations.

4-Methylpyrimidine to 4-*β*-butoxycarbonylvinylpyrimidine (**46**) (BuO_2CCHO, pyridine 100°, 70 h: 14%).[3446]

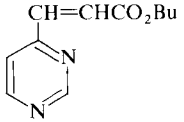
1,3-Dimethyl- to 5-*β*-ethoxycarbonylvinyl-1,3-dimethyl-6-(triphenylphosphoranylidene)amino-2,4(1*H*,3*H*)-pyrimidinedione ($EtO_2CC{\equiv}CH$, EtOH, reflux, 19 h: 66%.[268]

5-Iodo-2,4-dimethoxy-6-methyl- to 2,4-dimethoxy-5-*β*-methoxycarbonylvinyl-6-methylpyrimidine [$MeO_2CCH{=}CH_2$, $Pd(OAc)_2$, Ph_3P, NEt_3, 140°, 7 h, sealed: 91%].[257]

2-Chloro- to 2-ethoxycarbonylmethyl-4,6-dimethylpyrimidine [$(EtO_2C)_2CH_2$, Na, PhMe, reflux, 90 min: 20%; reactions must include partial hydrolysis and decarboxylation during workup].[1933]

4,6-Dichloro- to 4-chloro-6-*β*,*β*-diethoxyvinyl- [$H_2C{=}C(OEt)_2$, Et_2O, reflux, 4 h: 47%] and thence to 4-chloro-6-ethoxycarbonylmethyl-5-nitropyrimidine ($EtOH{-}H_2O$, 20°, 12 h: crude, > 55%).[5099]

2-Amino-6-*N*-methylhydrazino- to 2-amino-6-*N'*-*α*-methoxycarbonylethylidene-*N*-methylhydrazino-4(3*H*)-pyrimidinethione (**47**) ($AcCO_2Me$, MeOH, reflux, 19 h: 77%).[1203]



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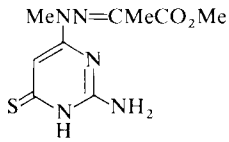

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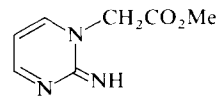

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2-Phenyl-5-vinyl- to 5-*α*-ethoxycarbonylethyl-2-phenylpyrimidine (EtOH, HCl gas, CO, $PdCl_2$, Ph_3P, 300 atm, 90°, 2.5 h: > 95%).[6202]

4,6-Dimethyl-2(1*H*)-pyrimidinethione to 2-ethoxycarbonylmethylthio-4,6-dimethylpyrimidine (Na salt of substrate, $ClCH_2CO_2Et$, EtOH, reflux, 2 h: 96%).[2799]

2-Pyrimidinamine to 1-methoxycarbonylmethyl-2(1*H*)-pyrimidinimine (**48**) ($BrCH_2CO_2Me$, Me_2NCHO, 20°, 24 h: 80% as hydrobromide).[984]

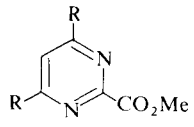
5-Hydroxy- to 5-ethoxycarbonylmethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione ($Ph_3P{=}CHCO_2Et$, MeCN, reflux, 9 h: 93%).[1994]

Also many other examples.[124,1335,1878,1925,1989,2023,2042,2057,2374,2376,2468,2648,2838,2894,3333,3771,4107,4151,4304,4755,4870,4939,5099,5153,5283,5608,5687,5952–5954,6038,6202]

10.2.2. Reactions of Pyrimidinecarboxylic Esters

Hydrolysis. The hydrolytic conversion of esters into the corresponding pyrimidinecarboxylic acids has been discussed in Section 10.1.1.

Reduction. The hydrogenolytic conversion of benzyl esters into the corresponding acids has been covered in Section 10.1.1; the hydride reduction of esters to hydroxymethylpyrimidines has been discussed in Section 7.3.1.4; and the partial reduction of esters to aldehydes is exemplified in the conversion of methyl 4-pyrimidinecarboxylate into 4-pyrimidinecarbaldehyde ($LiAlH_4$, THF, −70°, 45 min: 15%),[3446] of methyl 2-pyrimidinecarboxylate (**49**, R = H) into 2-pyrimidinecarbaldehyde (**50**, R = H) (limited $LiAlH_4$, THF, −70°, 15 min: 50%),[2760] and of appropriate substrates into 4,6-dimethyl- (**50**, R = Me) (52%) or 4,6-diphenyl-2-pyrimidinecarbaldehyde (**50**, R = Ph) (58%) by similar means.[2760]



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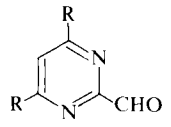

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Aminolysis. The aminolysis of esters to afford pyrimidinecarboxamides has been used extensively, although a few unexpected failures have been reported.[1249,2970,5614,5955] The usual conditions and efficiencies are exemplified in the following transformations.

Simple pyrimidinecarboxamides

Methyl 4-pyrimidinecarboxylate to 4-pyrimidinecarboxamide (NH_3, MeOH, 20°, 2 days: > 95%).[729]

Methyl 5-pyrimidinecarboxylate to 5-pyrimidinecarboxamide (NH_3, MeOH, 20°, 4–6 days: 64–84%; NH_4OH, 20°, 2 days: 34%);[729,2321] from ethyl ester (liquid NH_3, 60°, 8 h, sealed: > 95%).[1969]

Ethyl 2,4-dimethyl-5-pyrimidinecarboxylate to 2,4-dimethyl-5-pyrimidinecarboxamide (NH_3, MeOH, 100°, 16 h, sealed: 82%;[651] NH_4OH, 20°, 24 h: > 95%).[2761]

Methyl 6-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate to 6-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxamide (NH_4OH, 20°, 1 day: 90%).[2266]

Diethyl 4,5-pyrimidinedicarboxylate to 4,5-pyrimidinedicarboxamide (NH_4OH, 25°, 3 h: 78%).[2548]

Methyl 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (NH_3, MeOH, 100°, 6 h, sealed: 60%).[1123]

Also other examples.[449,1030,1250,1421,1472,2003,2264,2266,2396,2627,3764,4274,4362,4885]

Carbamoylalkylpyrimidines

5-Ethoxycarbonylmethyl- to 5-carbamoylmethylpyrimidine (NH_3, EtOH, 100°, 2 days, sealed: 87%).[2002]

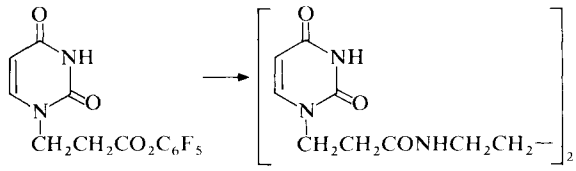
6-Ethoxycarbonylmethyl- to 6-carbamoylmethyl-2,4(1*H*,3*H*)-pyrimidinedione (NH_3, NaOMe, MeOH, 25°: 89% as Na salt).[2006]

2- or 4-β-Methoxycarbonylethyl- to 2- or 4-β-carbamoylethylpyrimidine (NH_3, EtOH, 20°, 3 days: 84% or 75%, respectively).[1225]

4,6-Diethoxy-2-ethoxycarbonylmethyl- to 2-carbamoylmethyl-4,6-diethoxypyrimidine (NH_4OH, 20°, 2 weeks: 89%).[1991]

1-β-(Pentafluorophenoxycarbonyl)ethyl-2,4(1*H*,3*H*)-pyrimidinedione (**51**) to *N*,*N*′-bis[β-(2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-1′-yl)propionyl]-1,4-butanediamine (**52**) [$H_2N(CH_2)_4NH_2$, Me_2NCHO, EtOAc, 20°, 30 min: 56%].[110]

Also other examples.[750,1388,1685,1918]



51 **52**

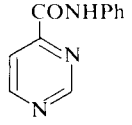
N-Alkyl- or *N*-arylpyrimidinecarboxamides

Ethyl 4-pyrimidinecarboxylate to 4-pyrimidinecarboxanilide (**53**) ($PhNH_2$, $PhNH_2.HCl$, reflux, 2 h: 42%).[4682]

Butyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate to *N*-butyl- ($BuNH_2$, 170°, 15 h, sealed: 63%) or *N*-(β-hydroxyethyl)-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide ($H_2NCH_2CH_2OH$, EtOH, 150°, 15 h, sealed: 48%).[5837]

Phenyl 4-amino-1,3-dimethyl-2,6-dioxo,1,2,3,6-tetrahydro-5-pyrimidinecarboxylate to 4-amino-*N*-ethyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide ($EtNH_2$, pyridine, reflux, 3 h: 82%).[1197]

Ethyl 4-amino-2-methylthio-5-pyrimidinecarboxylate to 4-amino-*N*-methyl-2-methylthio-5-pyrimidinecarboxamide ($MeNH_2$, H_2O, reflux, 5 h: 34%).[447]



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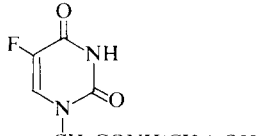

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5-Fluoro-1-(*p*-nitrophenoxycarbonyl)methyl- to 5-fluoro-1-*N*-(γ-hydroxypropyl)carbamoylmethyl-2,4(1*H*,3*H*)-pyrimidinedione (**54**) [$H_2N(CH_2)_3OH$, MeOH, 20°, 15 h: 80%].[564]

Also other examples.[1030,2882]

Pyrimidinecarbohydrazides

Ethyl 5-pyrimidinecarboxylate to 5-pyrimidinecarbohydrazide (**55**) (H_2NNH_2, EtOH, reflux, 2 h: 54%);[1969] from the methyl ester similarly.[2264]

5-Ethoxycarbonylmethyl- to 5-hydrazinocarbonylmethylpyrimidine (H_2NNH_2, EtOH, reflux, 2 h: 93%).[2002]

Methyl 6-ethyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate to 6-ethyl-2-oxo-1,2-dihydro-4-pyrimidinecarbohydrazide (H_2NNH_2, MeOH, 25°, 1 day: 71%).[2266]

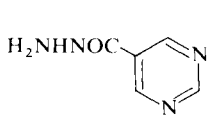
Ethyl 2,4-diamino-5-pyrimidinecarboxylate to 2,4-diamino-5-pyrimidinecarbohydrazide (neat $H_2NNH_2.H_2O$, reflux, 2 h: 87%).[1471]

2-Ethoxycarbonylmethylthio- to 2-hydrazinocarbonylmethylthio-6-methyl-4(3*H*)-pyrimidinone ($H_2NNH_2.H_2O$, EtOH, 60°, 15 min: 95%).[96]

2-Acetamido-5-β-ethoxycarbonylethyl- to 2-amino-5-β-hydrazinocarbonylethyl-6-methyl-4(3*H*)-pyrimidinone ($H_2NNH_2.H_2O$, EtOH, reflux, 1 h: 73%; note concomitant deacylation).[1300]

Diethyl 4,5-pyrimidinedicarboxylate to pyrimido[4,5-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**56**) ($H_2NNH_2.H_2O$, MeOH, reflux, 4 h: 62%).[2530]

Also other examples.[275,651,661,1114,1300,1395,1415,1458,1473,1604,2003,2018, 2197,2766,2970,3028,3095,4274,4362, 4491,5837,5951



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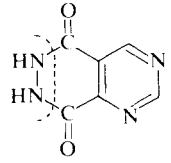

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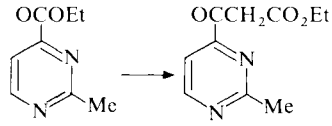
Removal. The removal of an unwanted ester grouping is done usually by hydrolysis and subsequent decarboxylation. Indeed, such a sequence may account for the apparently direct removal of the ester grouping from ethyl 4-

amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate to give 4-amino-2(1*H*)-pyrimidinethione (~70%) by heating in formamide for 2 days.[1651]

Claisen reaction. Pyrimidine esters can take part in classical Claisen reactions to afford pyrimidine ketones. For example, methyl 2-methyl-4-pyrimidinecarboxylate (**57**) gave 4-ethoxymalonyl-2-methylpyrimidine (**58**) (EtOAc, NaOEt, PhMe, reflux, 1 h: 73%),[5956] methyl 4,6-diphenyl-2-pyrimidinecarboxylate gave 2-cyanoacetyl-4,6-diphenylpyrimidine (MeCN, NaH, Me_2NCHO, 20°, 3 h: 67%),[5957] and some analogs were made similarly.[5956,5957]



57 **58**

10.3. PYRIMIDINECARBOXAMIDES

For pragmatic reasons, the corresponding carbohydrazides and carbonyl azides are treated separately in Section 10.4.

10.3.1. Preparation of Pyrimidinecarboxamides

By primary syntheses. Although not used extensively, several types of primary synthesis have been employed to afford pyrimidinecarboxamides (see Chapters 2 and 3).

By aminolyses. The conversion of *carboxylic acids* or their *esters* into carboxamides is discussed in Sections 10.1.2 and 10.2.2, respectively. The conversion of *pyrimidinecarbonyl chlorides* into amides occurs even more readily, as illustrated in the following examples.

5-Pyrimidinecarbonyl chloride (crude) to 5-pyrimidinecarboxamide (NH_3, PhH, reflux, 2 h: 62%;[1028] NH_3, Et_2O, 20°, 1 h: > 67%[2509, cf. 2321]) or to *N,N*-diethyl-5-pyrimidinecarboxamide (Et_2NH, Et_2O, 20°, 1 h: >52%).[2509]

5-Bromo-2-methyl-4-pyrimidinecarbonyl chloride (crude) to 5-bromo-2-methyl-4-pyrimidinecarboxamide (NH_4OH, PhH, shaken, 5 min: >86%).[1479]

2-Amino-5-β-chlorocarbonylethyl-6-methyl- to 2-amino-6-methyl-5-β-(phenylcarbamoyl)ethyl-4(3*H*)-pyrimidinone ($PhNH_2$, pyridine, 20°, 30 min: 81%).[981]

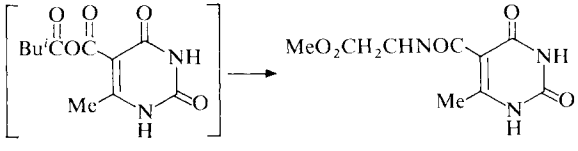
2-Amino-5-δ-chlorocarbonylbutyl- (crude) to 2-amino-5-δ-carbamoylbutyl-4,6-(1*H*,5*H*)-pyrimidinedione (NH_3, Me_2NCHO, 20°, 5 h: 46%).[256]

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl chloride to 1,3-dimethyl-2,4-dioxo,1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (NH_3, PhH, reflux, 30 min: 71%).[2670]

2,4-Dichloro-5-pyrimidinecarbonyl chloride to 2,4-dichloro-*N*-(3′,4′,5′-trimethoxyphenyl)-5-pyrimidinecarboxamide [3,4,5-$(OMe)_3C_6H_2NH_2$, Et_3N, THF, 20°, 15 h].[2511]

Also other examples.[168,510,1564,1787,2331,2870,2871,5949,5958,5959]

The formation of amides by aminolysis of less usual substrates has been reported also. Thus (1) 4-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid was converted into its (unisolated) mixed *anhydride* (**59**) ($ClCO_2Bu^i$, Et_3N, Me_2NCHO, −10°, 15 min), which was then allowed to react (−5°, 1 h) with the methyl ester of glycine to afford *N*-(methoxycarbonylmethyl)-4-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide (**60**) (73% overall);[5491] (2) the *lactone* (**61**) from 5-hydroxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid gave 5-aminomethyl-2,6-dioxo-1,2,3,6-tetrahydro- (**62**, R = H) or 5-anilinomethyl-2,6-dioxo-*N*-phenyl-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**62**, R = Ph) (NH_3 or $PhNH_2$, EtOH, reflux: 56% or 76%, respectively).[5619]



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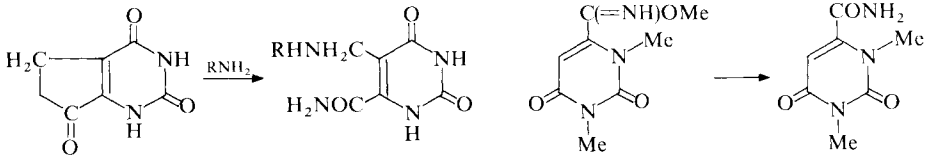


61 **62** **63** **64**

From a carboximidic ester. Although the mechanism may be debatable, methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboximidate (**63**) gave 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**64**) (NH_4Cl or $MeNH_3Cl$, Me_2NCHO, reflux, 1 h: 60–65%; neat $PhNH_2.HCl$, 150–200°, 20 min: 76%; SO_2Cl_2 or $POCl_3$, 20°, 1 h: 52–55%; neat PCl_5, 100–150°, 30 min: 60%).[1133]

By hydrolysis of nitriles. The controlled hydrolysis of pyrimidinecarbonitriles to pyrimidinecarboxamides is done usually in fairly concentrated sulfuric

acid (naturally of limited hydrolytic capacity), in alkali containing hydrogen peroxide (the Radziszewski reaction[5960–5962]), or simply in mildly basic media such as aqueous ammonia. These procedures are illustrated in the formation of the following amides from the corresponding nitriles.

Acidic hydrolysis

2-Chloro-4-pyrimidinecarboxamide (98% H_2SO_4, 15–20°, 4 h: 47%).[1628]

2-Amino-4-methyl-5-pyrimidinecarboxamide (96% H_2SO_4, 25°, 32 h: 75%).[1465]

2-Amino-4,6-dimethyl-5-pyrimidinecarboxamide (98% H_2SO_4, 95°, 30 min: 62%).[923]

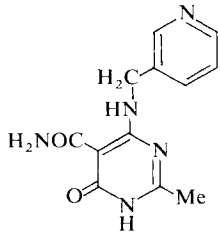
4-Amino-2-methylamino-5-pyrimidinecarboxamide (98% H_2SO_4, < 30°, 2 h: 68%); also analogs.[847]

4-Methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide (90% H_2SO_4, 95°, 5 h: > 95%; note survival of thioether group).[3212]

2,4-Diamino-6-phenyl-5-pyrimidinecarboxamide (98% H_2SO_4, < 30°, then 95°, 90 min: 96%).[1123]

2-Methyl-4-oxo-6-(pyridin-3′-ylmethyl)amino-3,4-dihydro-5-pyrimidinecarboxamide (**65**) (98% H_2SO_4, 70°, 4 h: 85%).[572]

Also other examples.[72,682,1086,1250,1304,1471,2675,3003,4332,5942]



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Radziszewski conditions

5-Chloro-2-pyrimidinecarboxamide (KOH, H_2O_2, H_2O–EtOH, 50°, 3 h: 82%); without H_2O_2, only the acid resulted (2*M* NaOH, reflux, 5 h: 62%).[1897]

4-Amino-5-pyrimidinecarboxamide (0.2*M* KOH, H_2O_2, 50°, 1 h: 66%).[708]

4-Methoxy-6-methyl-2-pyrimidinecarboxamide (Na_2CO_3, H_2O_2, H_2O–AcMe, 20°, 3 days: ~70%).[2762]

2,6-Dimethyl-4-pyrimidinecarboxamide ($NaHCO_3$, H_2O_2, H_2O–AcMe, 20°, 2 h: 82%).[2766]

4-Methyl-6-phenoxy-2-pyrimidinecarboxamide (Na_2CO_3, H_2O_2, H_2O–AcMe, 20°, 3 h: 69%).[2585]

Also other examples.[1250,2585]

In mildly basic media

4,6-Dimethyl-2-pyrimidinecarboxamide (dilute NH_4OH, 95°, 3 h: 75%).[2603]

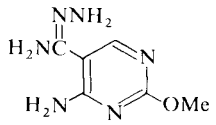
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (dilute NH_4OH, 95°, 2 h: 63%).[2603]

4-Amino-2-methylthio-5-pyrimidinecarboxamide (0.1*M* NaOH, reflux, 15 min: 80%).[577, cf. 447]

5-Amino-2-pyrimidinecarboxamide from 5-dimethylaminomethyleneamino-2-pyrimidinecarbonitrile (0.2*M* NaOH, 95°, 1 h: 90%).[1623]

4-Amino-2-methoxy-5-pyrimidinecarboxamidrazone (**66**) from 4-dimethylaminomethyleneamino-2-methoxy-5-pyrimidinecarbonitrile (H_2NNH_2, 20°, 18 h: 40%).[351]

4-Amino-2-methylthio-5-pyrimidinecarboxamide oxime (**67**) (NH_2OH, EtOH, 20°, 12 h: 74%).[386]



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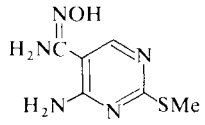

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1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (AcMe, NaOEt, reflux, 2 h; or MeCN, NaOEt, reflux, 20 h: 15%; mechanisms?).[4]

Also other examples.[386,768,6899]

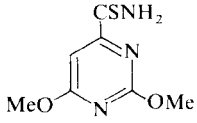
Analogous thiolyses

2-, 4-, or 5-pyrimidinecarbothioamide (NH_4HS, EtOH, 20°, 16 h: 78–91%).[729]

4,6-Dimethyl-2-pyrimidinecarbothioamide (H_2S, NEt_3, Et_2O, 25°, 48 h, sealed: 95%).[2603]

2,6-Dimethoxy-4-pyrimidinecarbothioamide (**68**) (likewise: 90%).[2603]

4,6-Dimethyl-2-thiocarbamoylmethylpyrimidine (H_2S, pyridine, NEt_3, 100°, 15 h, sealed: 60%?).[2833]



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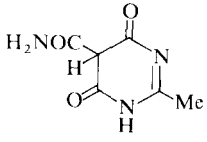
By direct insertion. A carbamoyl group may be inserted sometimes into a vacant nuclear position, especially in the presence of elctron-donating groups. For example, 2-methyl-4,6(1*H*,5*H*)-pyrimidinedione with potassium cyanate

and urea at 150° for 3 h gave 2-methyl-4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxamide (**69**) (54%); the same yield was obtained with urea alone, provided the reaction time was doubled.[1010] Likewise, 6-amino-2,4(1*H*,3*H*)-pyrimidinedione with urea at 150–160° for 3 h gave 2,4-dioxo-6-ureido-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (**70**) (~ 50%)[5963] but when the reaction time was reduced to 1 h, the single isolable product was 4-amino-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide (75%) (**71**),[5851] initially reported incorrectly as the isomeric 6-ureido-2,4(1*H*,3*H*)-pyrimidinedione;[1093] similar treatment of 2,6-diamino-4(3*H*)-pyrimidinone (for 1 h) gave 2,4-diamino-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide (43%)[5851] rather than its isomer,[1093] 2-amino-6-ureido-4(3*H*)-pyrimidinone. Some more satisfactory examples are provided by the formation of the following amides or thioamides.



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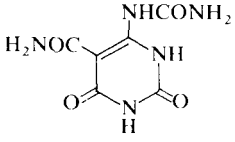

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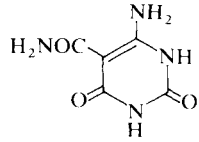

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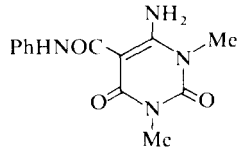

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4-Amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxanilide (**72**) (PhNCO, pyridine, reflux, 6 h: 63%).[775]

4-Dimethylamino-2,6-dioxo-1,3-diphenyl-1,2,3,6-tetrahydro-5-pyrimidinecarbothioanilide (neat PhNCS, 145°, 2 h: 80%).[4458]

5-Fluoro-*N*-hexyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxanilide (HxNCO, pyridine, 90°, 1 h: > 95%).[3025]

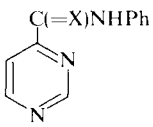
4-Amino-*N*-*p*-chlorophenyl-3-ethyl-6-oxo-3,6-dihydro-5-pyrimidinecarbothioamide (*p*-ClC_6H_4NCS, pyridine, reflux, > 3 h).[1055]

4,6-Dimethyl-2-pyrimidinecarboxamide (H_2NCHO, H_2SO_4, $FeSO_4$, Bu^tOOH, H_2O, < 20°, 1 h: 43%).[792]

6,*N*,*N*-Trimethyl-2-phenyl-4-pyrimidinecarboxamide (Me_2NCHO, likewise: 71%).[792]

Also many other examples in the foregoing references and elsewhere.[362,449,5914]

From methylpyrimidines. The ferricyanide oxidation of *C*-methylpyrimidines in aqueous ammonia at 60° for 7 h has been used to afford amides: 1-methyl- (~ 40%) and 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (~ 50%),[2673] as well as the parent 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide were also made this way.[2872] In an essentially similar way, 4-methylpyrimidine with sulfur in refluxing aniline for 35 h gave 4-pyrimidinecarbothioanilide (**73**, X = S) (57%), which was converted easily into the corresponding carboxanilide (**73**, X = O) (SeO_2, dioxane, reflux, 1 h: 70%).[4682]



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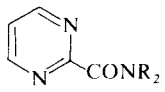

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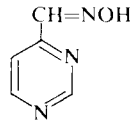

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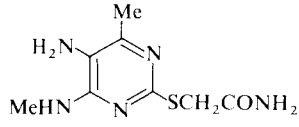

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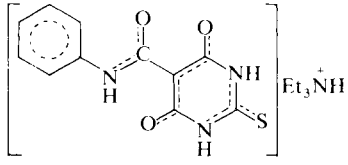
Miscellaneous procedures. Several other rarely used routes to amides are illustrated in the following examples: (1) treatment of 2-pyrimidinecarbonitrile in refluxing ether–benzene with the *Grignard* reagent, diethylaminomagnesium bromide (from ethylmagnesium bromide and diethylamine), gave a separable mixture of 2-pyrimidinecarboxamide (**74**, R = H) (~20%) and its *N*,*N*-diethyl derivative (**74**, R = Et) (~ 15%);[729] 4-pyrimidinecarbonitrile likewise gave 4-pyrimidinecarboxamide (~35%) and its *N*,*N*-diethyl derivative (~20%);[729] (2) 4-pyrimidinecarbaldehyde oxime (**75**) underwent *Beckmann* rearrangement to 4-pyrimidinecarboxamide (HCO_2Na, HCO_2H, reflux, 3 h: 75%);[826] (3) the hydroxy group in 5-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione was displaced by an appropriate *Wittig* reagent to afford the corresponding 5-carbamoylmethyl derivative ($Ph_3P{=}CHCONH_2$, MeCN, reflux, 9 h: 55%);[1994] (4) the conversion[3390] of 1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione into 1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide by *ring fission* with malondiamide has been discussed in Section 5.1.2.2; and (5) a few *derivatizations* have been used to make, for example, 2-carbamoylmethylthio-4-methyl-6-methylamino-5-pyrimidinamine (**76**) ($ClCH_2CONH_2$, $NaHCO_3$, H_2O, 95°, 40 min: 85%);[5686] also other types.[234,1683,4121]

10.3.2. Reactions of Pyrimidinecarboxamides

Although the fine structures of simple pyrimidinecarboxamides have not been investigated, the X-ray results for the triethylammonium salt of a typical amide, 4,6-dioxo-2-thioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxanilide, appeared to indicate maximal delocalization of the negative charge and of the C=S and three C=O portions of the molecule (**77**).[493]



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Dehydration to nitriles. The conversion of *N*-unsubstituted amides into nitriles is done usually (but not always) with a phosphorus halide as the

dehydrating agent. Such reactions are illustrated in the formation of the following nitriles.

2-, 4-, or 5-Pyrimidinecarbonitrile ($POCl_3$, reflux, 1 h: 70%, 77%, or 8%, respectively);[729,1973] 5-pyrimidinecarbonitrile (P_2O_5, dry distillation, 250°/88 mm: 77%).[2509]

2-Methyl-5-pyrimidinecarbonitrile [$POCl_3$, pyridine (exothermic), 2 h: 44%].[1387]

2-Methyl-4,5-pyrimidinedicarbonitrile ($POCl_3$, xylene, reflux, 24 h: 57%).[1421]

5-Bromo-2-methyl-4-pyrimidinecarbonitrile ($POCl_3$, PhMe, reflux, 2 h: 90%].[1479]

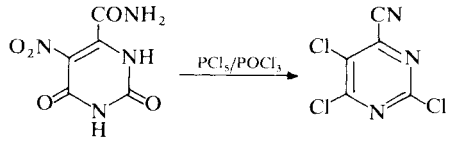
4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile ($POCl_3$, xylene, reflux, 1 h: 80%).[198]

4,6-Dichloro-5-cyanomethylpyrimidine from 5-carbamoylmethyl-4,6(5*H*, 1*H*)-pyrimidinedione ($POCl_3$, $PhNMe_2$, reflux, 10 min: 76%).[1991]

4-Chloro-2-phenyl-5-pyrimidinecarbonitrile from 4-oxo-2-phenyl-3,4-dihydro-5-pyrimidinecarboxamide ($POCl_3$, reflux, 3.5 h: > 90%).[4885]

2,5,6-Trichloro-4-pyrimidinecarbonitrile (**79**) from 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (**78**) (PCl_5, $POCl_3$, reflux, 3 h: ~20%).[2046]

Also other examples.[1010,1988,2006,2268]

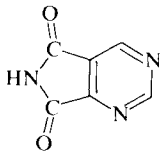


78 **79**

Hydrolysis. The hydrolysis of amides to pyrimidinecarboxylic acids has been discussed in Section 10.1.1.

Degradation to pyrimidinamines. Hofmann degradations of pyrimidinecarboxamides to 2-, 4/6-, 5-, or ω-aminopyrimidines have been discussed in Sections 9.1.1.5, 9.1.2.5, and 9.1.4.5, respectively.

Other reactions. Some other reactions of amides are illustrated in the following examples: (1) 4,5-pyrimidinedicarboxamide underwent thermal *cyclization* with loss of ammonia at 200° during 2 h to afford 4,5-pyrimidinedicarboximide (**80**) (18%);[2548] (2) 4,6-diamino-2-phenyl-5-pyrimidinecarboxamide suffered *removal* of its amide grouping, by heating with thiourea at 180° for 5 h followed by warm aqueous alkali, to give 2-phenyl-4,6-pyrimidinediamine (~20%) by an obscure mechanism;[1123] and (3) treatment of 2-, 4-, or 5-



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pyrimidinecarbothioamide in refluxing ethanolic hydroxylamine for 8 h caused *sulfur displacement* with the formation of 2- (74%), 4- (92%), or 5-pyrimidinecarboxamideoxime (23%), respectively.[729]

10.4. PYRIMIDINECARBOHYDRAZIDES AND PYRIMIDINECARBONYL AZIDES

Preparation of hydrazides. The usual route to hydrazides is the hydrazinolysis of esters, discussed in Section 10.2.2.

Preparation of azides. The carbonyl azides are made from hydrazides by treatment with nitrous acid, as illustrated in the formation of the following products.

4-Amino-2-methyl-5-pyrimidinecarbonyl azide ($NaNO_2$, 10% AcOH, 5°, brief time: 95%).[1471]

2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl azide ($NaNO_2$, 0.3*M* HCl, 8°, 20 min: 56%).[5837]

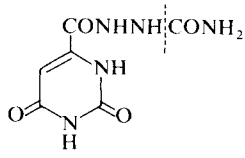
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl azide ($NaNO_2$, dilute HCl, 80%).[1114]

5-β-Azidocarbonylethyl-6-methyl-2-thioxo-1,2-dihydro-4 (3*H*)-pyrimidinone ($NaNO_2$, dilute HCl, < 5°, 30 min: 76%).[1300]

5-Azidocarbonylmethyl-2-ethylthio-4(3*H*)-pyrimidinone (KNO_2, *M* HCl, < 5°, 10 min: 60%).[1395]

Also other examples.[1114,1300,1395,1415,1441, cf. 651,1388,5966]

Reactions of hydrazides. The conversion of hydrazides into azides has just been discussed. Other reactions are illustrated in the formation of the following derivatives: 6-semicarbazidocarbonyl-2,4(1*H*,3*H*)-pyrimidinedione (**81**)



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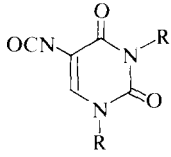
(KOCN, dilute HCl: ~80%),[3028] 5-bromo-2-methylthio-4-[4′-phenyl(thiosemicarbazido)carbonyl]pyrimidine (PhNCS, EtOH, reflux: 58%),[5967] 6-β-formylhydrazinocarbonyl-2,4(1*H*,3*H*)-pyrimidinedione (HCO_2H, 95°, 10 min),[3006] 6-isopropylidenehydrazinocarbonyl-2,4(1*H*,3*H*)-pyrimidinedione (AcMe, EtOH–H_2O, reflux, 3 h: 85%),[3006] 4-benzylidenehydrazinocarbonyl-2,6-dimethylpyrimidine (PhCHO, EtOH, reflux, 1 h: 82%),[2766] and related products.[1458,2766,3006]

Reactions of azides. Most pyrimidinecarbonyl azides undergo *thermolysis* (with loss of nitrogen) to give the corresponding isocyanatopyrimidines, such as 5-isocyanato-2,4(1*H*,3*H*)-pyrimidinedione (**82**, R = H) (xylene, reflux, 4 h: 98%),[1114] its 1,3-dimethyl derivative (**82**, R = Me) (PhH, reflux, 2 h: 95%),[1114] 4-isocyanato-2-methylthio-5-phenylthiopyrimidine (PhMe, reflux, 8 h: > 72%; from the azide substrate made in situ),[2021] 5-β-isocyanatoethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (PhMe, reflux, 6 h: 76%),[1300] 2-ethylthio-5-isocyanatomethyl-4(3*H*)-pyrimidinone (PhMe, 80°, then reflux, 30 min: > 90%),[1395] and others.[1300,1395,1415] However, 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl azide failed to so react satisfactorily in boiling toluene.[3006] In contrast, 4-amino-2-methyl-5-pyrimidinecarbonyl azide gave only a transitory isocyanate that cyclized swiftly to afford 2-methyl-8(7*H*)-purinone (**83**) (xylene, 95°, 30 min, then reflux, 10 min: > 95%).[1471] When such thermolyses are done in alcohols, the resulting isocyanates react at once therewith to give urethanes (see Section 9.2.1.1).



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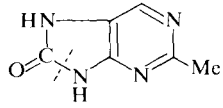

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As might be expected, 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl azide underwent *hydrolysis* in boiling water to give the corresponding carboxylic acid[3006] or *aminolysis* in toluene containing ethylamine (or a homolog) at 60° to give *N*-ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide (90%) or an *N*-alkyl homolog, respectively.[3006]

10.5. PYRIMIDINECARBONITRILES

10.5.1. Preparation of Pyrimidinecarbonitriles

By primary syntheses. Primary synthetic routes to nitriles have been covered in Chapters 2 and 3: the products from most such syntheses are 5- or ω-cyanopyrimidines.

By dehydration of amides. This method has been discussed in Section 10.3.2.

By dehydration of aldoximes. Some pyrimidine aldoximes are readily available, either from pyrimidinecarbaldehydes or by nitrosation of (activated) methylpyrimidines, so that this route has proved quite useful. The reagents and conditions are illustrated in the formation of the following nitriles.

5-Pyrimidinecarbonitrile ($SOCl_2$ or Ac_2O, reflux, 30 min: 79% or 15%, respectively).[1028]

2-Methyl- or 2,6-dimethyl-4-pyrimidinecarbonitrile ($POCl_3$, $CHCl_3$, reflux, 1 h: 67% or 56%, respectively).[3762]

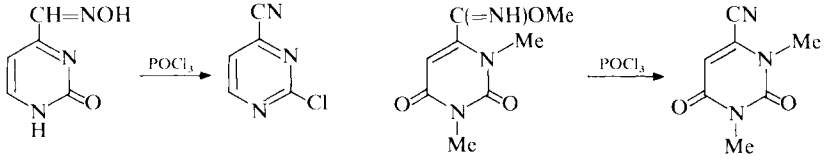
4,6-Dichloro-2-methylthio-5-pyrimidinecarbonitrile ($SOCl_2$, reflux, 3 h: 43%).[1020]

4,6-Diamino-5-pyrimidinecarbonitrile (neat Ac_2O, reflux, 14 h: 88%).[443]

Ethyl 4-cyano-2-methylthio-5-pyrimidinecarboxylate (Ac_2O, reflux, 3 h: 90%).[1781]

2-Chloro-4-pyrimidinecarbonitrile (**85**) from 2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde oxime (**84**) ($POCl_2$ $PhNMe_2$, reflux, 30 min: 60%).[1628]

Also other examples.[682,1026,1029,1073,2267]



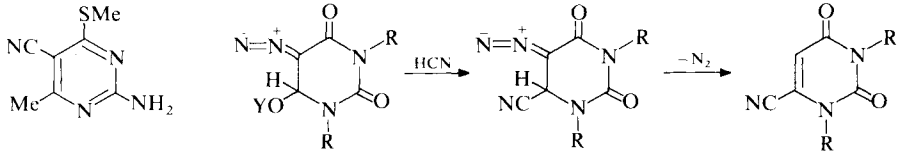
84 **85** **86** **87**

By dealcoholation of a carboximidic ester. Treatment of methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboximidate (**86**) in refluxing phosphoryl chloride for 30 min gave 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**87**) (83%);[1133] Such reactions are usually of little use because imidic esters are made, as a rule, from the nitriles!

By displacement reactions. The displacement of several leaving groups by cyanide ion has been discussed already under each such group: *2/4/6-halogeno*, Section 6.7.8; *5-halogeno*, Section 6.8.3; *ω-halogeno*, Section 6.9; *trimethylammonio*, Section 9.2.10; *sulfo*, Section 8.7.2; and *alkylsulfonyl*, Section 8.8.2.

From 5-diazoniopyrimidine halides. Diazotized 5-aminopyrimidines with cuprous and/or potassium cyanide usually give the corresponding 5-pyrimidinecarbonitriles. Such procedures gave, for example, 2-amino-4-methyl-6-methylthio- (**88**) (NaCN),[1424] 2,4-dioxo-1,2,3,4-tetrahydro- (CuCN, KCN, H_2O, 5°, 2 h, then 95°, 1 h: 64%),[1175, cf. 2869] 2-amino-4,6-dioxo-1,4,5,6-tetrahydro- (likewise: 65%),[1175] 4-oxo-2-thioxo-1,2,3,4-tetrahydro- (likewise: 62%),[1175] and 2-amino-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile (likewise: 62%).[1175] However, *cine*-substitution can occur: for example, treatment of the performed

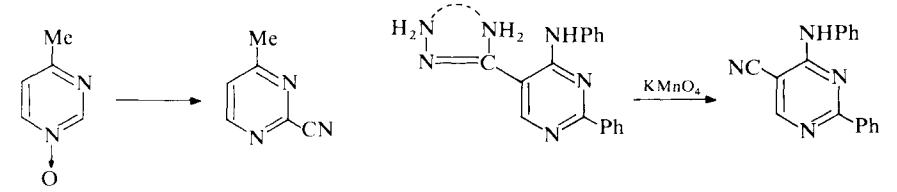
methanol adduct (**89**, R = H, Y = OMe) of 5-diazo-2,4(1*H*,3*H*)-pyrimidinedione or the hydrate (**89**, R = Me, Y = H) of its 1,3-dimethyl derivative with aqueous potassium cyanide at 20° gave 2,6-dioxo- (**91**, R = H) (62%) 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**91**, R = Me) (~40%) with or without isolation of an intermediate HCN adduct (**90**, R = H or Me) in each case.[2672]



88 **89** **90** **91**

Direct introduction. Treatment of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with the mercuric fulminate–potassium cyanide complex in water under reflux for 90 min gave 2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbonitrile (~80%), in which the cyano group had been derived from the fulminate because the same product was formed by using a fulminate–potassium iodide complex.[3712]

From simple pyrimidine N-oxides. Simple pyrimidine *N*-oxides with a vacant 2- or 4/6-position undergo the classical Reissert–Henze reaction (aqueous cyanide ion plus benzoyl chloride, shaken at 20° for 1–15 h) to afford very variable yields of pyrimidinecarbonitriles. For example, 4-methylpyrimidine 1-oxide (**92**) gave 4-methyl-2-pyrimidinecarbonitrile (**93**) (~2%),[2762] 4-methoxypyrimidine 1-oxide gave 4-methoxy-2-pyrimidinecarbonitrile (~80%),[2210] 4-ethoxy-6-methylpyrimidine 1-oxide gave 4-ethoxy-6-methyl-2-pyrimidinecarbonitrile (85%),[2585] and 2,4-dimethylpyrimidine 1-oxide gave 2,6-dimethyl-4-pyrimidinecarbonitrile (< 2%).[2762] A modified Reissert–Henze procedure (Me_3SiCN, NEt_3, MeCN, reflux, 1–24 h) proved more satisfactory: for example, the above-mentioned 4-methyl-2-pyrimidinecarbonitrile (**93**) and 2,6-dimethyl-4-pyrimidinecarbonitrile were obtained in yields of 71% and 81%, respectively.[142]



92 **93** **94** **95**

By oxidation of amidinopyrimidines. 4-Anilino-2-phenyl-5-pyrimidinecarboxamidrazone (**94**) and several cyclized (dihydrotriazolyl) analogs have been reported to undergo permanganate oxidation to afford 4-anilino-2-phenyl-5-pyrimidinecarbonitrile (**95**).[413]

By derivatization. Many extranuclear cyanopyrimidines have been made in a variety of ways using reagents already bearing a cyano group. Some such processes are illustrated briefly in the following transformations.

5-Iodo- to 5-β-cyanovinyl-2-isopropyl-4-methylpyrimidine [CH_2=CHCN, Et_3N, $Pd(OAc)_2$, Ph_2P, 125°, 2.5 h: 81%].[2376]

5,6-Diamino- to 4-amino-5-cyanomethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (HCN, H_2O–MeOH, then CH_2O, 30–40°, 1 h: 72%).[1107]

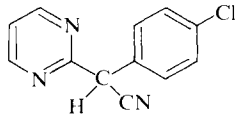
2-Chloro- to 2-*p*-chloro-α-cyanobenzylpyrimidine (**96**) (*p*-$ClC_6H_4CH_2CN$, NaH, THF, reflux, 2.5 h: 64%).[5970]

5-Bromo-2,4(1*H*,3*H*)-pyrimidinedione to 5-bromo-1-β-cyanoethyl- (**97**, R = H) [CH_2=CHCN, NaOH (1 mol), Et_3N, H_2O, 20°, 6 h: 78%] or 5-bromo-1,3-bis-β-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione (**97**), R = CH_2CH_2CN) (likewise but without NaOH: 75%).[1798]

5-Amino-6-methoxy-4(3*H*)-pyrimidinethione to 4-cyanomethylthio-6-methoxy-5-pyrimidinamine ($ClCH_2CN$, KOH, MeOH, reflux, 5 h: 78%).[1565]

4-Methoxy- to 4-α-cyanobenzylpyrimidine (NaH, $PhCH_2CN$, THF, reflux, ? h: 62%).[6119]

5-Hydroxy- to 5-cyanomethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (Ph_3P=CHCN, MeCN, 20°, 9 h: > 95%).[1994]



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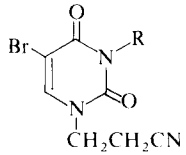

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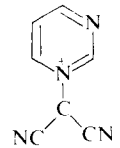

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Pyrimidine to pyrimidinium dicyanomethylide (**98**) (tetracyanoethylene oxide, Et_2O, 20°, 1 day: 60%).[445]

Also other examples.[268,1725,1797,4868,5763,5971,5972,6203]

10.5.2. Reactions of Pyrimidinecarbonitriles

Most of the reactions of nitriles have been discussed already, as indicated by the cross-references in the following paragraphs.

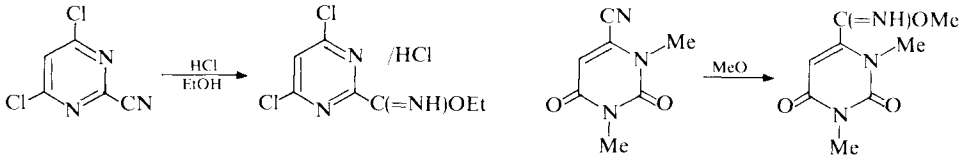
Hydrolysis to carboxylic acids. See Section 10.1.1.

Hydrolysis to carboxamides. See Section 10.3.1.

Hydrolysis to pyrimidinones. See Section 7.1.1.6.

Alcoholysis to alkoxypyrimidines. See Section 7.4.1.3.

Alcoholysis to carboximidic esters. Although many such imidic esters (traditionally known as "imino ethers") have been made as intermediates for the preparation of pyrimidinecarboxamidines, few have been characterized. Two approaches are available: treatment with alcoholic hydrogen chloride or with alcoholic sodium alkoxide. Thus 2-, 4-, or 5-pyrimidinecarbonitrile gave ethyl 2-, 4-, or 5-pyrimidinecarboximidate, respectively (EtOH, HCl gas, 0°: each in ~50% yield as hydrochloride);[729] 4,6-dichloro-2-cyanomethyl- (**99**) gave 4,6-dichloro-2-(*C*-ethoxyformimidoyl)methylpyrimidine (**100**) (EtOH, HCl gas, Et_2O–PhH, 0–5°, 12 h: 90% as hydrochloride);[1997] and 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile (**101**) gave methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboximidate (**102**) (NaOMe or KOH, MeOH, reflux, 1 h: 66% or 80%, respectively).[1133]

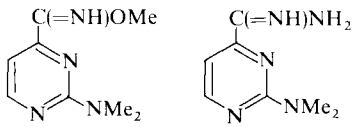


99 **100** **101** **102**

Alcoholysis to carboxylic esters. This metathesis is done indirectly via a carboximidic ester (see Section 10.2.1). Even the apparently direct conversion of 2-methyl-4,5-pyrimidinedicarbonitrile into methyl 5-cyano-2-methyl-4-pyrimidinecarboxylate (under peculiar conditions) probably so proceeded.[1421]

Aminolysis to pyrimidinamines. See Section 9.1.1.3.

Aminolysis to pyrimidinecarboxamidines. The classical *indirect* route from nitriles to amidines is via carboximidic esters (usually crude). The first step in this process has been covered earlier in this section; the second step is illustrated in the conversion of methyl 2-dimethylamino-4-pyrimidinecarboximidate (**103**) into 2-dimethylamino-4-pyrimidinecarboxamidine (**104**) (crude substrate, NaOMe, NH_4Cl, MeOH, 20°, 2 h: 81% as hydrochloride, based on the nitrile precursor);[2656] also of ethyl 2-pyrimidinecarboximidate into 2-pyrimidinecarboxamidine (NH_3 gas, EtOH: ?%).[729]



103 **104**

The more convenient *direct* route from nitriles to amidines is illustrated in the formation of the following carboxamidines, in each case from the corresponding carbonitrile.

2-Pyrimidinecarboxamidine (neat $PhSO_3NH_4$, 240°, 45 min: 42% as $PhSO_3H$ salt).[1856]

2-Dimethylamino-4-pyrimidinecarboxamidine (**104**) (neat $PhSO_3NH_4$, 265°, 20 min: 56% as $PhSO_3H$ salt).[2653]

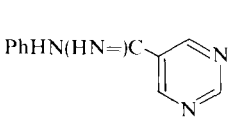
N-Phenyl-2- or *N*-phenyl-4-pyrimidinecarboxamidine (neat $PhNH_2$, $AlCl_3$, 175°: 67% or 36%, respectively).[729]

N-Phenyl-5-pyrimidinecarboxamidine (**105**) ($PhNH_2$, $AlCl_3$, CS_2, reflux, 3 h: 38%).[729]

4-Anilino-*N*-γ-dimethylaminopropyl-2-phenyl-5-pyrimidinecarboxamidine ($H_2NCH_2CH_2CH_2NMe_2$: 53%).[3846]

4-*p*-Chlorobenzylamino-2-*N*-hydroxyamidinomethylthio-6-phenylpyrimidine (**106**) (H_2NOH, Me_2NCHO, 100°, 3 h: 50% as hydrochloride).[4888]

Also other examples in the foregoing references and elsewhere.[4466]



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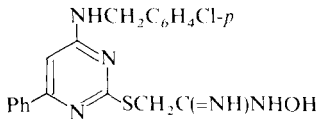
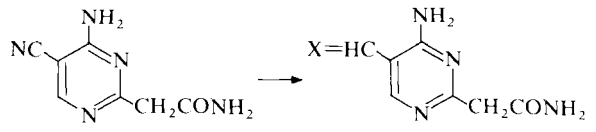


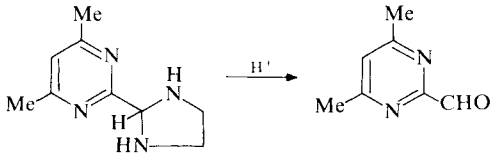
106

Reduction to aminomethylpyrimidines. See Section 9.1.4.3.

Reductive hydrolysis to pyrimidinecarbaldehydes. Occasionally it is possible to convert pyrimidinecarbonitriles into the corresponding pyrimidinecarbaldehydes by partial reduction to iminomethylpyrimidines, which usually undergo hydrolysis (without isolation) to afford the aldehydes. For example, 4-amino-2-carbamoylmethyl-5-pyrimidinecarbonitrile (**107**) gave 4-amino-2-carbamoylmethyl-5-pyrimidinecarbaldehyde (**108**, X = O) via the unisolated imino intermediate (**108**, X = NH) (H_2, Pd, dilute HCl, 16 h: 46%);[974] 4,6-dimethyl-2-pyrimidinecarbonitrile gave 2-(1′,3′-diphenylimidazolidin-2′-yl)-4,6-dimethylpyrimidine (**109**) (H_2, Ni, $PhNHCH_2CH_2NHPh$, MeOH–AcOH, 20°: 45%) and thence 4,6-dimethyl-2-pyrimidinecarbaldehyde (**110**) (6*M* HCl, 20°, 10 min: 66%);[2759] 4-amino-5-pyrimidinecarbonitrile gave 4-amino-5-pyrimidinecarbaldehyde (H_2, Pd, dilute H_2SO_4, 35°, ~ 4 h: 49%);[1614] 4-oxo-3,4-dihydro-5-pyrimidinecarbaldehyde (60%) was made similarly;[1614] and 4-amino-2-methyl-5-pyrimidinecarbonitrile gave 4-amino-2-methyl-5-pyrimidinecarbaldehyde (H_2, Pd, 4*M* HCl, 22°, 30 h: ~ 50% after purification through a Ni complex).[1460] Other procedures for reducing the last-mentioned



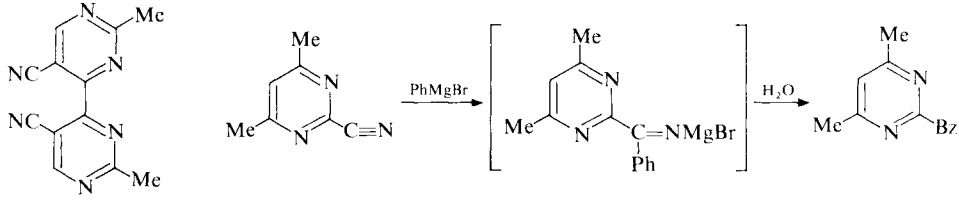
107 **108**



109 110

substrate, 4-amino-2-methyl-5-pyrimidinecarbonitrile, to a variety of products have been investigated extensively.[1227,1409,1410,1458,1459,3190,5973] An isolated second step of such a process involves the alkaline hydrolysis of 5-iminomethyl-1-*m*-(trifluoromethyl)phenyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione to 2,4,6-trioxo-1-*m*-(trifluoromethyl)phenyl-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde (84%).[3370]

Naturally, overly vigorous reductive hydrolysis of pyrimidinecarbonitriles leads to the isolation of hydroxymethylpyrimidines instead of the pyrimidinecarbaldehydes. For example, 4-amino-2-cyclopentyl-5-pyrimidinecarbonitrile gave 2-cyclopentyl-5-hydroxymethyl-4-pyrimidinamine (H_2, Pd, 3*M* HCl, 5 h: 80%).[4242] An unexpected reduction was that of 2-methyl-4,5-pyrimidinedicarbonitrile to 2,2′-dimethyl-4,4′-bipyrimidine-5,5′-dicarbonitrile (**111**) (H_2, Ni, Me_2NCHO, 20 h: 50%);[1421] also of 5-acetoxymethyl-2-methylthio-4-pyrimidinecarbonitrile to 5-hydroxymethyl-2-methylthiopyrimidine [$Cr(OAC)_2$, NaOH, EtOH–H_2O, reflux, 1 h: 33%].[768]



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To pyramidine ketones by Grignard reagents. A few pyrimidinecarbonitriles have been converted into pyrimidine ketones by using Grignard reagents. For example, 4-pyrimidinecarbonitrile gave 4-acetylpyrimidine (MeMgBr, Et_2O, 0°, 3 h: 20%),[729] and 4,6-dimethyl-2-pyrimidinecarbonitrile (**112**) gave 2-benzoyl-4,6-dimethylpyrimidine (**113**) (PhMgBr, Et_2O, 2 h, 0°, then reflux, 3 h: ~ 25%),[2603] but 2-pyrimidinecarbonitrile behaved differently.[729]

10.6. PYRIMIDINECARBALDEHYDES

Pyrimidinecarbaldehydes and their acetals are probably more important as intermediates or substrates than in their own right.

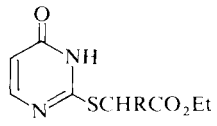
10.6.1. Preparation of Pyrimidinecarbaldehydes

A great variety of routes have been used for the preparation of nuclear and extranuclear aldehydes.

By primary syntheses. Although free aldehydes are seldom, if ever, made by primary syntheses, many of their acetals have been so made; see Chapters 2 and 3.

By semidirect C-formylation. There are several ways to attach a *C*-formyl group to the nucleus or the side chain of appropriate pyrimidines.

Substrates with sufficient electron-donating substituents undergo such formylation by *derivatives of formic acid.* For example, 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione gave 2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde [neat $HC(OEt)_3$, reflux, 90 min: 88%];[3541] its 1-methyl (75%)[3541] and 1,3-dimethyl derivative (71%)[1391, cf. 3541] were made similarly. The analogous substrate, 6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione, gave 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde (neat AcOCHO, 95°, 2 h: ~ 45%).[653] Side-chain *C*-formylation occurred on treatment of 2-ethoxycarbonylmethylthio-4(3*H*)-pyrimidinone (**114**, R = H) with ethyl formate–sodium ethoxide to afford 2-(α-ethoxycarbonyl-α-formylmethyl)thio-4(3*H*)-pyrimidinone (**114**, R = CHO).[5975]



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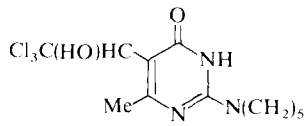

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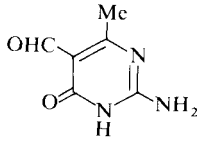
Appropriate substrates are attacked by *chloral* to give adducts, which lose chloroform on alkaline hydrolysis to afford pyrimidinecarbaldehydes. Thus 6-methyl-2-piperidino-4(3*H*)-pyrimidinone gave its 5-β,β,β-trichloro-α-hydroxyethyl derivative (**115**) (Cl_3CCHO, pyridine, 95°, 2 h) and thence 4-methyl-6-oxo-2-piperidino-1,6-dihydro-5-pyrimidinecarbaldehyde (KOH, H_2O–EtOH, 95°, 30 min: ~ 67% overall);[682] several analogs were made similarly, but chloral also reacted at primary amino or methyl substituents to give adducts from which no apparent aldehydes were obtained.[682]

Some use has been made of the *Reimer–Tiemann synthesis* (chloroform–concentrated alkali) to convert 5-unsubstituted substrates bearing electron-donating groups into 5-pyrimidinecarbaldehydes. For example, 2-amino-6-methyl-4(3*H*)-pyrimidinone so gave 2-amino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde (**116**) ($CHCl_3$, 15*M* KOH, some EtOH, 60–70°, then 5°, 4 h: 65%);[1233, cf. 682] rather similar procedures gave 2,4-dioxo-1,2,3,4-tetrahydro- ($CHCl_3$, 4*M* NaOH, reflux, 4 h: ~ 40%),[4963, cf. 2128] 2,4,6-trioxo-1,2,3,4,5,6-hexahydro- ($CHCl_3$, 15*M* KOH, little EtOH, reflux,



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1 h: 42%),[2128] and 4-methyl-6-oxo-2-thioxo-1,2,3, 6-tetrahydro-5- pyrimidinecarbaldehyde (likewise: 17%);[2128] and other examples have been reported.[682,2128,2681,2891,5976]

The application of *Vilsmeier reagents* (Me_2NCHO–phosphoryl chloride or the like) to 5-unsubstituted pyrimidines gives much better and more consistent yields of 5-pyrimidinecarbaldehydes, although any tautomeric oxo substituent may be converted concomitantly into a chloro substituent, any primary amino group may become a dimethylaminomethyleneamino group, and any activated *C*-methyl group may be formylated instead of the vacant 5-position. The reagents, conditions, and yields are illustrated by the formation of the following products, in each case from the corresponding 5-unsubstituted or *C*-methyl substrate unless otherwise indicated.

Without isolation of the intermediate

4-Chloro-2-dimethylamino-6-methoxy-5-pyrimidinecarbaldehyde (Me_2NCHO, $POCl_3$, 0°, then 75°, 1 h: 88%).[2075]

2,4-Dioxo-6-phenylthio-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde (Me_2NCHO, $POCl_3$, 90°, 2 h: 96%).[5093]

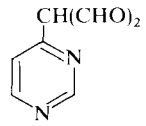
1-Cyclohexyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5- pyrimidinecarbaldehyde (Me_2NCHO, $POCl_3$, 110°, 40 min: 60%).[2087]

4-Amino-3-ethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde (Me_2NCHO, $SOCl_2$, 0°, then reflux, 1 h: 75%).[1058]

2-Amino-4,6-dichloro-5-pyrimidinecarbaldehyde from 2-amino-4,6(1*H*,5*H*)-pyrimidinedione (Me_2NCHO, $POCl_3$, 5°, then 100°, 5 h: 28–51%).[1019, 1026]

4-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde from 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Me_2NCHO, $POCl_3$, 0°, then reflux, 45 min: 65%).[3739,3770]

4-α,α-Diformylmethylpyrimidine (**117**) (Me_2NCHO, $COCl_2$, $CHCl_3$, 5°, then 35°, 1 h: 47%).[4679]



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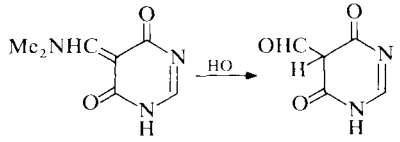
Also other examples in Section 4.2.3.8 and elsewhere.[83,1019,2075,2087,2611,4576,5052,5093]

With isolation of the intermediate

5-Dimethylaminomethylene-4,6(1*H*,5*H*)-pyrimidinedione (**118**) (Me_2NCHO, $COCl_2$, $CHCl_3$, 5°, then 55°, 3 h: 93% as hydrochloride) and thence 4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarbaldehyde (**119**) (H_2O, 20°, 5 h: 63%).[1027,1028,cf.2681,3600]

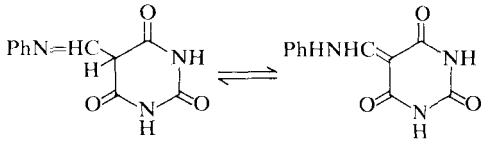
5-Dimethylaminomethylene-2-phenyl-4,6(1*H*,5*H*)-pyrimidinedione (likewise: 93%) and thence 4,6-dioxo-2-phenyl-1,4,5,6-tetrahydro-5-pyrimidinecarbaldehyde (likewise: 71%).[1028]

5-Dimethylaminomethylene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (Me_2NCHO, $POCl_3$, 20°, 3 h: 88%) but not hydrolyzed to the aldehyde.[83]



118 **119**

Another route to aldehydes involving the foregoing type of *5-aminomethylene intermediate* is illustrated by the fusion of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione with *N*,*N*′-diphenylformamidine at 150–180° to give 5-anilinomethylene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**120**), which underwent alkaline hydrolysis to 2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde;[5977] analogs were made similarly.[2890,5977]



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The process of 5-formylation is facilitated by using a *5-lithiopyrimidine* as substrate. Thus, 2,4-dimethoxypyrimidine gave 2,4-dimethoxy-5-pyrimidinecarbaldehyde [$LiN(CHMeCHMe)_2CH_2$, Et_2O, 0°, 5 min; then Me_2NCHO, 20°, 10 min: 24%];[474,6071] 4-chloro-2,6-dimethoxypyrimidine gave 4-chloro-2,6-dimethoxy-5-pyrimidinecarbaldehyde [$LiN(CHMeCHMe)_2CH_2$ (?) or BuLi, THF, −25°; then HCO_2Et, −70°, 1 h; then HCl–EtOH: 86%];[6076] and 2-chloro-4-methoxypyrimidine gave 4-methoxy-2-morpholino-5-pyrimidinecarbaldehyde [$LiN(CHMeCHMe)_2CH_2$, THF, −70°, 1 h; then $O(CH_2CH_2)_2NCHO$, −70°, 1 h; 30%].[6873]

By reductive hydrolysis of pyrimidinecarbonitriles. See Section 10.5.2.

By oxidation of methylpyrimidines. See Section 4.2.3.3.

By oxidation of hydroxymethylpyrimidines. See Section 7.3.2.4.

From derivatives. The recovery of free aldehydes from their derivatives (acetals, oximes, Schiff bases, etc.) is necessary when such derivatives are used as intermediates or to facilitate isolation of aldehydes from reaction mixtures.

Thus, for obvious reasons, primary syntheses and other procedures are often designed to afford pyrimidinecarbaldehyde acetals as the initial products. The conversion of such *acetals to aldehydes* is illustrated in the formation of the following products, in each case from the diethyl acetal unless otherwise indicated.

4-Pyrimidinecarbaldehyde (1% H_2SO_4, 60°, 3 h: 47%).[2756]

2-Phenyl-4-pyrimidinecarbaldehyde (0.5% HCl, EtOH–H_2O, reflux, 40 min: 43%).[2756]

2-Acetamido-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde from its dimethyl acetal (88% HCO_2H, 95°, 1 h: 94%).[635]

5-Fluoro-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde from its dimethyl acetal (50% AcOH, 95°, 40 min: 89%).[2066]

6-Oxo-1,6-dihydro-4-pyrimidinecarbaldehyde (50% AcOH, 95°, > 2 h: 70%).[3140]

2,6-Diamino-5-*p*-chlorophenyl-4-pyrimidinecarbaldehyde (0.4*M* HCl, reflux, 1 h: 93%).[4280]

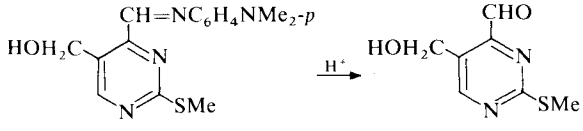
2-Acetamido-5-β-formylethyl-6-phenyl-4(3*H*)-pyrimidinone (H_2O, reflux, 1 h: 91%).[668]

4-(Formylmethyl)amino-5-nitro-2(1*H*)-pyrimidinone (*M* HCl, reflux, 20 min: 82%).[5084]

1-Formylmethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (Dowex 50-X 8(H), $EtOCH_2CH_2OEt$–H_2O, 95°, 5 h: 91%).[1887]

Also other examples.[667,1299,1870,1871,2578,2855,2856,3193,3196,3199,4280,4665,9978,5979]

Although many pyrimidine aldoximes are best made by nitrosation of (activated) methylpyrimidines (Section 4.2.3.3) or by other indirect means, the conversion of such *oximes into aldehydes* has seldom, if ever, been reported formally! However, the conversion of a *Schiff base into an aldehyde* has been detailed in that of 4-*p*-dimethylaminophenyliminomethyl-5-hydroxymethyl-2-methylthio-

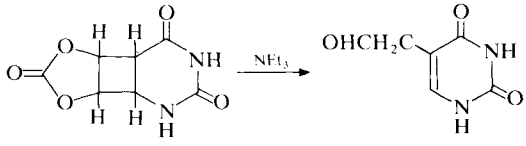


121 **122**

pyrimidine (**121**) into 5-hydroxymethyl-2-methylthio-4-pyrimidinecarbaldehyde (**122**) (*M* HCl, EtOAc, 20°, 5 min: 75%)[768] and in like reactions.[2388,3601]

By controlled reduction of esters. See Section 10.2.2.

By derivatization. ω-Formylpyrimidines have been made by derivatizing pyrimidine substrates with reagents bearing an aldehydo or potential aldehydo group. For example, 2-amino-6-chloro- gave 2-amino-6-β,β-diethoxyethylamino- [$H_2NCH_2CH(OEt)_2$, EtOH, reflux, 20 min: 67%] and thence 2-amino-6-(formylmethyl)amino-5-nitro-4(3*H*)-pyrimidinone (10*M* HCl, 95°, 20 min: 86%);[5022] 4,5-diamino- gave 4-amino-5-β,β-diethoxyethylideneamino- [$OHCCH(OEt)_2$, H_2O, 95°, 10 min: crude] and thence 4-amino-5-β,β-diethoxyethylamino-2(1*H*)-pyrimidinone (H_2, Ni, EtOH: 10% overall);[5084] 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 5-methyl-2,4-bistrimethylsiloxypyrimidine [neat $F_3CC(=NSiMe_3)OSiMe_3$, 120°, 2 h: crude] and thence 1-β-formylvinyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (HC≡CCHO, 20°, 1 h; then H_2O: 77% overall);[5980] 2,4(1*H*,3*H*)-pyrimidinedione gave an adduct (**123**) (vinylene carbonate, H_2O–AcMe, *hv*, 15 h: ~ 80%) and thence 5-fomylmethyl-2,4(1*H*,3*H*)-pyrimidinedione (**124**) (Et_3N, Me_2NCHO: 40%);[3200, cf. 3980] and 2-dimethylamino-4,6-diphenylpyrimidine gave its 5-β-formylvinyl derivative [3-(*N*-methylanilino)acrylaldehyde, $POCl_3$, MeCN, 2,3,5,6-tetramethylpyrazine (as proton acceptor), reflux, 15 h: 56%].[6858]



123 **124**

By miscellaneous methods. Several little-used routes to pyrimidinecarbaldehydes are illustrated in the following examples: (1) diazotized 4-methyl-6-methylthio-2,5-pyrimidinediamine gave 2-amino-4-methyl-6-methylthio-5-pyrimidinecarbaldehyde (CH_2O, H_2NOH, H_2O; then NaOAc, $CuSO_4$);[1424] (2) 4-amino-2-methyl-5-pyrimidinecarbohydrazide gave its *N'*-benzenesulfonyl derivative ($PhSO_2Cl$, pyridine, 20°, 4 h: 73%) and thence 4-amino-2-methyl-5-pyrimidinecarbaldehyde (Na_2CO_3, glycol, 160°, 5 min: 44%),[1458] an example of the McFadyan–Stevens prcedure; (3) 6-amino-1-benzyloxy-3-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione gave 4-amino-3-benzyloxy-l-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde (Ni, 97% HCO_2H, 20°, 15 min; then Ac_2O, reflux, 1 h: ~ 55%, by a complicated mechanism);[1325] (4) 2-imino-1-methyl-1,2-dihydro-5-pyrimidinecarbonitrile gave 2-amino-4-imino-3-methyl-3,4-dihydro-5-pyrimidinecarbaldehyde (by an abnormal Dimroth rearrangement: for details, see Section 9.3.2);[1346] (5) 5-chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde oxime or phenylhydrazone on aminolysis with hydroxylamine or phenylhydrazine, respectively,[2850] as indicated in Section 6.9; and (6) 5-bromo-2-

dibromethylpyrimidine gave 5-bromo-2-pyrimidinecarbaldehyde ($AgNO_3$: see Section 6.9).[1788]

10.6.2. Reactions of Pyrimidinecarbaldehydes

Although pyrimidinecarbaldehydes are very reactive species, relatively few useful reactions (apart from oxidations and reductions) have been reported.

Oxidation. See Section 10.1.1.

Reduction. See Section 7.3.1.7.

Conversion into acetals. Acetals are usually made from aldehydes by warming with an anhydrous acid in an alcohol and/or an orthoester, as in the formation of 5-bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde diethyl acetal (**125**) (EtOH, HBr gas, reflux: 87%),[1868] 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde dimethyl acetal (MeOH, $MeC_6H_4SO_3H$-*p*, reflux, 15 h: 67%),[2589,2590] 4-amino-5-pyrimidinecarbaldehyde dimethyl acetal [MeOH, $MeC_6H_4SO_3H$-*p*, $HC(OMe)_3$, reflux, 8 h: 87%],[1008] 5-pyrimidinecarbaldehyde diethyl acetal [$MeC_6H_4SO_3H$-*p*, $HC(OEt)_3$, reflux, 4 h: 58%],[1028] and 4,6-dichloro-5-β,β-diethoxyethylpyrimidine (EtOH, NH_4Cl, reflux, 3.5 h: 90%);[888] some kinetic measurements for the first stage of such acetal formation—hemiacetal formation—have been reported.[2759]

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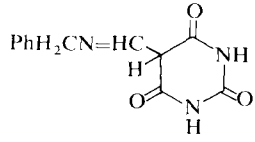

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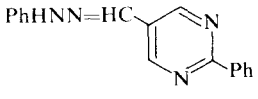
Conversion into Schiff bases. This type of Schiff base, produced by warming a pyrimidinecarbaldehyde with a primary amine and often known as "anils", must be distinguished from those produced from a pyrimidinamine with an aromatic aldehyde (Section 9.1.6.5). Preparative conditions are illustrated by the formation of 5-benzyliminomethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**126**) ($PhCH_2NH_2$, EtOH–H_2O, NEt_3, 65°, 5 min: 84%),[3541] 5-*p*-chlorophenyl-6-β-dimethylaminoethyliminomethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone ($Me_2NCH_2CH_2NH_2$, EtOH, reflux, 30 min: 81%),[1870] 2,4,6-trimethoxy-5-phenyliminomethylpyrimidine ($PhNH_2$, EtOH, reflux, > 24 h: 80%),[3688] and other such compounds.[881,1097,2578,2891,2987,3131,5936,5966,5981]

Conversion into hydrazones. Conditions for making pyrimidinecarbaldehyde phenylhydrazones and the like are typified in the formation of 2-phenyl-5-pyrimidinecarbaldehyde phenylhydrazone (**127**) ($PhNHH_2$, trace HCl, MeOH, 20°, 18 h: 88%),[6021] 5-bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecar-

baldehyde hydrazone (H_2NNH_2, H_2O, 20°, 1 h: 79%) or azine (limited H_2NNH_2, H_2O, 60°: 69%),[1868] 5-pyrimidinecarbaldehyde 2,4-dinitrophenylhydrazone [$H_2NHNC_6H_3(NO_2)_2$-2,4, H_2SO_4, MeOH, 25°, 5 h: ~ 80%],[1028] 4-chloro-1, 3-dimethyl-2, 6-dioxo-1,2,3, 6-tetrahydro-5-pyrimidinecarbaldehyde methylhydrazone ($MeNHNH_2$, $CHCl_3$, < 10°, 1 h: ~ 50%),[2089] 4,6-dioxo-2-thioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde dimethylhydrazone (Me_2NNH_2, AcOH–H_2O, 10 min),[2891] 5-ethyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde *p*-chlorophenylhydrazone (*p*-$ClC_6H_4NHNH_2$, EtOH or AcOH, reflux, 10 min: 74%),[2578] and many other such compounds.[682,1027,1599,2584,2681,2757,2858,2861,3131,3140,3640,5982,5983,6461]



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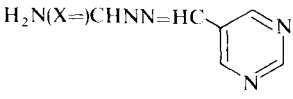

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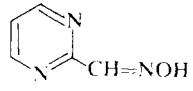
Conversion into semicarbazones. semicarbazones and thiosemicarbazones are usually made by treating an aldehyde with the reagent hydrochloride in aqueous sodium acetate. Thus were made 5-pyrimidinecarbaldehyde semicarbazone (**128**, X = O) (20°, 3 h: ~ 70%) or thiosemicarbazone (**128**, X = S) (MeOH–H_2O, 20°, 15 h: ~ 70%),[1028] 5-benzyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde thiosemicarbazone (EtOH–H_2O, reflux, 20 min: 63%),[1870] 6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde semicarbazone (EtOH, reflux, 10 min: 88%).[2578] 4-methyl-6-oxo-2-piperidino-1,6-dihydro-5-pyrimidinecarbaldehyde thiosemicarbazone ($EtOCH_2CH_2OH$, 100°, 30 min: ~ 70%),[682] and other such compounds.[1753,1868,2681,2858,2891]

Conversion into oximes. Treatment of a pyrimidinecarbaldehyde with aqueous or alcoholic (freed) hydroxylamine usually affords the corresponding oxime. Conditions are indicated in the formation of 2-pyrimidinecarbaldehyde oxime (**129**) (H_2O, 20°, 15 h: 70%),[2758] 5-pyrimidinecarbaldehyde oxime (H_2O, 60°, 2 h: ~ 80%),[1028] 4,6-diamino-5-pyrimidinecarbaldehyde oxime (H_2O, reflux, 1 h: 69%),[443] 4-α-formyl-α-(*p*-nitrophenylazo)methylpyrimidine (**130**) ($H_2NOH.HCl$, pyridine, EtOH, reflux, 2 min: > 95%),[362] 2-amino-6-(formylmethyl)amino-5-nitro-4(3*H*)-pyrimidinone oxime ($H_2NOH.HCl$, NaOEt, EtOH–H_2O, 95°, 20 min: 89%),[5022] and other such compounds.[682,1020,1703,2075,3131,3739,5979] Aldoximes undergo reduction to aminomethylpyrimidines (see Section 9.1.4.3), dehydration to pyrimidinecarbonitriles



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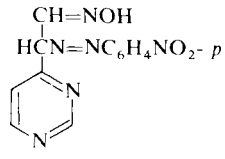

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(see Section 10.5.1) and dehydrogenation to pyrimidinecarbonitrile oxides (see Section 10.8.6).

Other reactions. Although not used to any extent, several other reactions of pyrimidinecarbaldehydes have been reported, as typified in the following examples.

1. 4-Amino-6-dimethylamino-5-pyrimidinecarbaldehyde underwent *decarbonylation* to 6-dimethylamino-4-pyrimidinamine (2*M* HCl, reflux, 3 h: ~ 70%);[852,2445] and 2,4,6-triamino-5-pyrimidinecarbaldehyde gave 2,4,6-pyramidinetriamine (H_2SO_4, MeOH, 20°, 5 h: reaction followed by uv spectra).[3897]

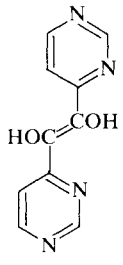
2. Appropriate pyrimidinecarbaldehydes condensed with reagents bearing an *activated methylene grouping* to afford 6-acetonylidenemethyl-2-ethylthio-5-fluoro-4(3*H*)-pyrimidinone (AcMe, dilute NaOH, 20°, 2.5 h: 75%),[2066] 5-acetonylidenemethyl-2,4(1*H*,3*H*)-pyrimidinedione (AcMe, piperidine, AcOH, reflux, 40 h: 65%),[2042] 5-β-benzoylvinyl-6-methyl-2-piperidino-4(3*H*)-pyrimidinone (BzMe, NaOH, H_2O–EtOH, 20°, 7 days: ~ 35%),[682] 2-α-hydroxy-β-nitroethyl-4,6-dimethylpyrimidine ($MeNO_2$: 68%) followed by dehydration to 4,6-dimethyl-2-β-nitrovinylpyrimidine (Ac_2O: 50%),[2037] 5-β-ethoxycarbonylvinyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione ($Ph_3P{=}CHCO_2Et$, Me_2NCHO: 41%),[2040] and ethyl 2-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]-pyrimidine-6-carboxylate via the obvious unisolated intermediate.[1929]

3. 2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde underwent *formyl → dihalogenomethyl* modification on prolonged treatment with aqueous sulfur tetrafluoride at 50–100° (sealed) to give 5-difluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione (60%).[4957]

4. 4-Pyrimidinecarbaldehyde hydrate underwent a *benzoin-type reaction* to give a product formulated in its enediol form, α,β-bispyrimidin-4-ylethylene-α,β-diol (**131**) (KCN, EtOH–H_2O, 20°: 60%).[2756]

5. 2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde gave the *nitrone*, 6-phenyliminomethyl-2,4(1*H*,3*H*)-pyrimidinedione 2′-oxide (**132**) (PhNHOH, EtOH, reflux, 2 h);[5985] cf. analogs.[5856]

6. 5-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde gave 6-bis(*p*-dimethylaminophenyl)methyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione, a *triphenylmethane-like* product ($PhNMe_2$, $ZnCl_2$, 100°, 4 h: ~ 60%).[5986]



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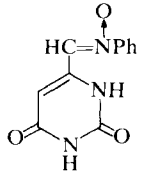

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7. Appropriate ω-formylpyrimidines or their derivatives can undergo intramolecular *cyclization*: for example, 4-chloro-2-(formylmethyl)amino-6-methylaminopyrimidine diethyl acetal gave 5-chloro-7-methylaminoimidazo[1,2-*a*]pyrimidine (H_2SO_4, 95°, 4 h: > 80%).[412]

10.7. PYRIMIDINE KETONES

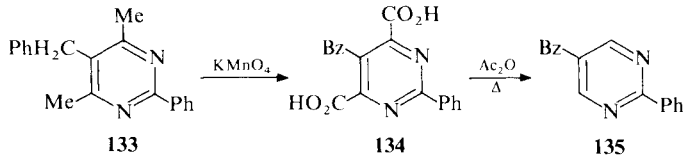
Unlike aldehydes, pyrimidine ketones are seldom used as intermediates. Nevertheless, a good number of such ketones have been made, usually with biological activity in mind.

10.7.1. Preparation of Pyrimidine Ketones

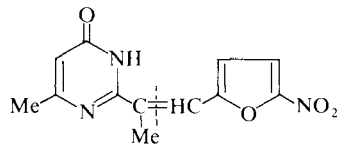
Pyrimidine ketones have been made by a surprisingly large number of routes, outlined in the following subsections.

By primary syntheses. Primary syntheses have been used widely to make ketones directly or via derivatives such as their acetals: see Chapters 2 and 3.

By oxidation. The formation of pyrimidine ketones from the corresponding *secondary alcohols* has been discussed in Section 7.3.2.4. The oxidation of *C-alkylpyrimidines* to ketones has been mentioned briefly in Section 4.2.3.3, but further examples include the transformation of 2-benzyl- to 2-benzoyl-4-methoxy-6-methylpyrimidine (SeO_2, EtOH, reflux, 4 h: 83%);[2525] the sequence 5-benzyl-4,6-dimethyl-2-phenylpyrimidine (**133**) to 5-benzoyl-2-phenyl-4,6-pyrimidinedicarboxylic acid (**134**) ($KMnO_4$, H_2O, reflux, 10 h: 53%) and thence to 5-benzoyl-2-phenylpyrimidine (**135**) (AcOH–Ac_2O, reflux, 5 h: 91%);[4478] and other such reactions.[5970] The rare *oxidative scission* of an unsaturated to a ketonic substituent occurred in the conversion of 6-methyl-2-α-(5′-nitrofurfurylidene)ethyl- (**136**) into 2-acetyl-6-methyl-4(3*H*)-pyrimidinone (O_3, AcOH, 0°, then H_2O_2–H_2O, 95°, 10 min).[671]



133 **134** **135**



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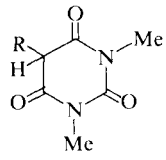
By C-acylation. There are several ways to achieve *C*-acylation of pyrimidine substrates. Regular acylating agents attack the 5-position or an (activated) methyl group; homolytic acylation occurs only at the 4/6-position; the Claisen reaction attacks only activated methyl substituents; and indirect acylation may occur at the 5- or an ω-position. The reagents and conditions for such *C*-acylations are illustrated in the following transformations.

Regular 5-acylations

1,3-Dimethyl- (**137**, R = H) to 5-acetyl-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**137**, R = Ac) (neat Ac_2O, reflux, 4 h: > 95%).[653,789, cf. 4576]



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6-Dimethylamino- to 5-acetyl-6-dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (neat Ac_2O, reflux, 3 h: ~ 40%).[653]

6-Amino- to 5-acetyl-6-amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Ac_2O–AcOH, reflux, 1 h: > 95%).[694] [*Note*: The isomeric 3-methyl substrate gave 6-acetamido-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione on similar treatment![694]]

6-Amino-1,3-dimethyl- gave 6-amino-5-benzoyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (BzCl, pyridine, reflux, 3 h: 65%).[775]

Also other examples.[694 (cf. 6238),775,2801,6203]

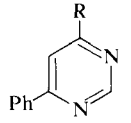
Regular and Claisen ω-acylations

See Section 4.2.3.6.

Homolytic 4/6-acylations

[Procedure A: RCHO, H_2SO_4, Bu^tOOH, $FeSO_4$, H_2O, 15°, 1 h. Procedure B: $AcCO_2H$, $(NH_4)_2S_2O_8$, $AgNO_3$, H_2SO_4, H_2O, 50°, 1 h.]

4-Phenyl- (**138**, R = H) to 4-acetyl-6-phenylpyrimidine (**138**, R= Ac) [A (R = Me): 45%; B: 25%].[814]



138

4-Methyl- to 4-acetyl-6-methylpyrimidine [A (R = Me): 34%; B: 25%].[814]

2,4-Dimethyl- to 4-acetyl-2,6-dimethylpyrimidine (B: 29%).[792]

2-Methyl-4-phenyl- to 4-acetyl-2-methyl-6-phenylpyrimidine [A (R = Me): 75%; B: 52%].[792]

2-Methyl-4-phenyl- to 2-methyl-4-phenyl-6-propionylpyrimidine [A (R = Et): 78%].[792]

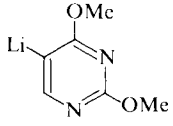
2-Methyl-4-phenyl- to 4-benzoyl-2-methyl-6-phenylpyrimidine [A (R = Ph): 12%].[792]

Also other examples.[792,814, cf. 5988]

Indirect 5- or ω-acylations

2,4-Dimethoxy- to 5-lithio-2,4-dimethoxy- (**139**) [$LiN(CHMeCHMe)_2CH_2$, Et_2O, 0°, 10 min: unisolated] and thence to 5-acetyl-2,4-dimethoxypyrimidine (EtOAc, Et_2O, 20°, 30 min: 4% overall).[474,6071]

1,3-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione to 5-benzoyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione benzoylhydrazone (2,5-diphenyl-1,3,4-oxadiazole, Et_2O, *hv*, 3 days: 45%) and thence to 5-benzoyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (HCl, MeOH–H_2O, 20°, 5 h: 89%).[5992]



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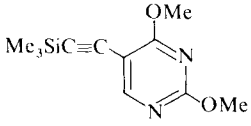

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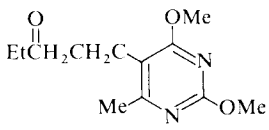
5-Ethynyl-2,4-dimethoxy- to 2,4-dimethoxy-5-trimethylsilylethynyl- (**140**) (Bu^{t}Li, THF, −50°, 15 min; then $ClSiMe_3$, −50°, 2 h: 80%)[832] and thence to 5-acetylethynyl-2,4-dimethoxy- ($AlCl_3$, AcCl, CH_2Cl_2, 0–25°, 6 h: > 95%) or 5-benzoylethynyl-2,4-dimethoxypyrimidine (likewise, BzCl: 82%);[3730,6006] also via an ethynylboron intermediate.[6126]

From halogenopyrimidines. The replacement of a halogeno substituent by a ketonic group has been used only rarely in the pyrimidine series. However, the following examples indicate potential utility.

5-Iodo-2,4-dimethoxy-6-methyl- gave 2,4-dimethoxy-6-methyl-5-β-propionylethylpyrimidine (**141**) [$EtCOCH{=}CH_2$, Et_3N, $Pd(OAc)_2$, Ph_3P, 120°, 2 h, sealed: 60%].[6077]



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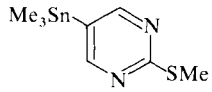
5-Iodo- gave a separable mixture of 5-β-acetylethyl- and 5-β-acetylvinyl-3-methyl-2-methylthio-4(3*H*)-pyrimidinone ($AcCH{=}CH_2$, likewise: 41% and 23%, respectively).[6077]

5-Iodo- gave a separable mixture of 5-β-acetylethyl- and 5-β-acetylvinyl-4-methoxy-2-methylthiopyrimidine ($AcCH{=}CH_2$, likewise, 4 h: 70% and 13%, respectively).[3893]

5-Bromo-2-methylthio- gave 2-methylthio-5-trimethylstannyl- (**142**) (BuLi, THF, −95°, 60 min, then $ClMe_3Sn$, THF, −90°, 30 min, 0°, 20 h: 82%) and thence 5-benzoyl-2-methylthiopyrimidine [BzCl, $(Ph_3P)_2PdCl_2$, $ClCH_2CH_2Cl$, reflux, 4 h: 97%].[3833]



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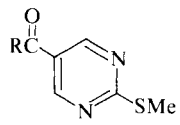
4-Iodo- gave 4-β-benzoylvinyl-6-methyl-2-methylthiopyrimidine [PhCH(OH)C≡CH, $(Ph_3P)_2PdCl_2$, CuI, NEt_3, 20°, 20 h: 44%].[6067]

Also other examples in the foregoing references.

From pyrimidinecarbonyl chlorides. The formation of ketones from acid chlorides is illustrated by the treatment of 2-methylthio-5-pyrimidinecarbonyl chloride (**143**, R = Cl) with methylmanganese iodide (MeMnI; made in situ) in THF–Et_2O to give 5-acetyl-2-methylthiopyrimidine (**143**, R = Me) (73%);[3811] 5-benzoyl-2-chloropyrimidine (29%) and other analogs were made with appropriate alkyl- or arylmanganese iodides in a similar way,[3811] and 2-methylthio-5-pyrimidinecarbonyl chloride with 3-(hexyldimethylsiloxy)methyl-5-(trimethylstannyl)furan gave 5-[4′-(hexyldimethylsiloxy)methyl-2′-furoyl]-2-methylthiopyrimidine [THF, $(PPh_3)_2PdCl_2$, reflux, 30 min: 73%].[53] In a different way, 2,6-dichloro-4-pyrimidinecarbonyl chloride reacted with an excess of diazomethane in ether to afford 2,4-dichloro-6-diazoacetylpyrimidine (**144**) (80%).[6036]



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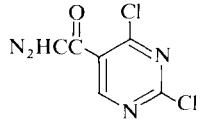

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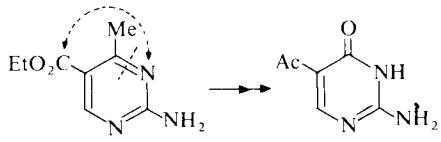
From pyrimidinecarboxylic acids or pyrimidinecarbonitriles. See Section 10.1.2 or 10.5.2, respectively.

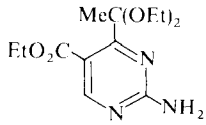
From pyrimidinecarboxylic esters. Esters can take part in Claisen reactions to afford ketones: see the end of Section 10.2.2. In addition, several esters have undergone ring fission and recyclization to ketones. For example, ethyl 2-amino-4-methyl-5-pyrimidinecarboxylate (**145**) gave 5-acetyl-2-amino-4(3*H*)-



145 146

pyrimidinone (**146**) with loss of ethanol (NaOEt, EtOH, evaporated at 95%, acidified: 79%);[778,779] likewise, ethyl 4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate gave 5-acetyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone (87%).[779]

From pyrimidine ketone acetals. It is sometimes convenient to isolate a pyrimidine ketone initially as an acetal: subsequent recovery of the free ketone is exemplified in the formation of ethyl 4-acetyl-2-amino-5-pyrimidinecarboxylate from its diethyl acetal (**147**) (10*M* HCl, 20°, 1 h: 90°);[823] 6-acetyl-5-*p*-chlorophenyl-2,4-pyrimidinediamine from its dimethyl acetal (HCl, MeOH–H_2O, reflux, 2 h: 95%),[4281] and 4-acetyl-2-pyrimidinamine from its dimethyl acetal (88% H_2SO_4, 25°, 2 h: 78%).[306]



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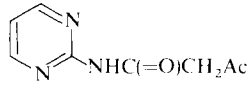
By derivatization. The attachment of a preformed ketonic grouping to an existing pyrimidine is exemplified by the following transformations.

6-Chloro- to 6-acetonylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione ($AcCH_2NH_2$, EtOH, 20°, briefly: 96%).[4744]

2-Pyrimidinamine to 2-acetoacetamidopyrimidine (**148**) (diketene, $CHCl_3$, 2.5 h: 80%).[3361]



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6-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone to 6-methyl-2-phenacylthio-4(3*H*)-pyrimidinone ($BzCH_2Cl$, NaOH, H_2O–EtOH, 95°, 20 min: 70°).[3860]

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione to its 5-β-benzoyl-α-phenylethyl derivative (PhCH=CHBz, MeOH–H_2O, reflux, 5 h: 90%).[5989]

5-Fluoro-4-methylthio-2(1*H*)-pyrimidinone to its 1-acetonyl derivative (substrate K salt, $AcCH_2Cl$, Me_2SO, 20°, 2 h: 85%).[741]

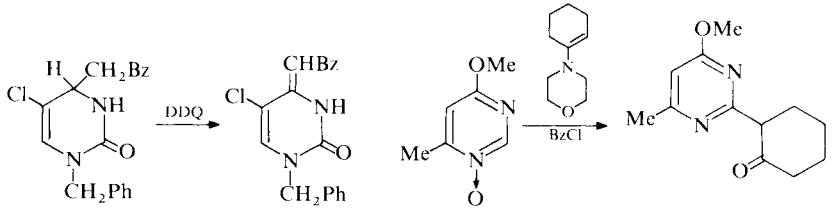
6-Methyl-2-methylthio-4(3*H*)-pyrimidinone to 4-acetonyloxy-6-methyl-2-methylthiopyrimidine (substrate Na salt, $AcCH_2Cl$, Me_2NCHO, 20°, 10 h: 81%).[5253]

Also other examples.[3785,3860,3940,4254,5688,5990,5991]

From pyrimidinecarbaldehydes with methylene reagents. See Section 10.6.2.

By other routes. Several little-used routes to pyrimidine ketones are typified in the following examples.

1. 2-Hex-1′-ynyl-4,6-dimethyl- gave 4,6-dimethyl-2-valerylmethylpyrimidine by a net *hydration* of the triple bond [$HgSO_4$, H_2SO_4, AcMe–H_2O, reflux, 6 h: 68%; piperidine, PhMe, reflux, 60 h, then $(CO_2H)_2.2H_2O$, Et_2O–EtOH, reflux, 6 h: 73%].[4655]
2. 1-Benzyl-5-chloro-2(1*H*)-pyrimidinone formed the isolable *adduct*, 1-benzyl-5-chloro-4-phenacyl-3,4-dihydro-2(1*H*)-pyrimidinone (**149**) ($BzCH_2Li$, PhMe–C_6H_{13}, 0°, 1 h: 54%), which underwent oxidation to 1-benzyl-5-chloro-4-phenacyl-2(1*H*)-pyrimidinone, formulated on spectral evidence as the tautomer (**150**) [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), PhH, 20°, 1 h: 95%];[218] see also some rather analogous reactions.[736,3755,3886]
3. 2,4-Dimethyl-6-phenacylthiopyrimidine underwent thermal *sulfur extrusion* to give 2,4-dimethyl-6-phenacylpyrimidine (Me_2NCHO, reflux, ? h: 50%);[472] analogs behaved similarly.[472]



149 **150** **151** **152**

4. 4-Methoxy-6-methylpyrimidine 1-oxide (**151**) reacted with *eneamines and benzoyl chloride* to give, for example, 4-methoxy-6-methyl-2-2′-oxocyclohexylpyrimidine (**152**) (*N*-cyclohex-1-enylmorpholine, BzCl, $CHCl_3$, < 40°, 2 h; then HCl, 20°: 80%).[5934]

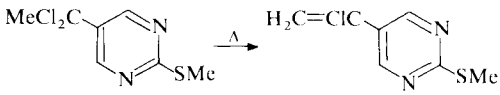
10.7.2. Reactions of Pyrimidine Ketones

Remarkably few reactions have been reported for pyrimidine ketones during the last hundred years.

Reduction. The conversion of ketones into secondary alcohols is exemplified in Section 7.3.1.7.

Oxidation. The conversion of ketones into carboxylic acids has been covered in Section 10.1.1.

Action of phosphorus chlorides. Treatment of an acetylpyrimidine with a phosphorus chloride gives the corresponding α,α-dichloroethyl derivative, which may lose 1 or 2 molecules of hydrogen chloride to afford an α-chlorovinyl- or an ethynylpyrimidine, respectively. For example, 5-acetyl- gave 5-α,α-dichloroethyl- (**153**) (PCl_5, PhH, reflux, 3 h: crude), which gave 5-α-chlorovinyl- (**154**) (trace $AlBr_3$, distillation, 0.1 mm: 59% overall) and thence 5-ethynyl-4-methyl-2-methylthiopyrimidine ($KOBu^t$, Me_2NCHO, 20°, 4 h: 85%);[3741] rather similarly, 5-acetyl-2,4(1*H*,3*H*)-pyrimidinedione gave 2,4-dichloro-5-α-chlorovinylpyrimidine ($POCl_3$, $PhNMe_3$, reflux, 20 h, distillation, 20 mm: 57%) and thence 5-ethynyl-2,4(1*H*,3*H*)-pyrimidinedione (KOH, H_2O–dioxane, reflux, 1 h: 56%).[2361]



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Formation of derivatives. The formation of the following derivatives, in each case from the corresponding ketone, illustrates the usual reagents and conditions employed.

Oximes

5-Benzoyl-2,4(1*H*,3*H*)-pyrimidinedione oxime ($HONH_2$.HCl, pyridine, warm).[788]

4,6-Dibenzyloxy-2-ethoxalylmethylpyrimidine oxime ($HONH_2$.HCl, NaOAc, MeOH, reflux, briefly, then 20°, 15 h: 84%).[4699]

4,6-Diphenacylpyrimidine dioxime ($HONH_2$.HCl, pyridine, EtOH, 20°, 3 day: 70%).[5987]

Also other examples.[789,3422,4478,5991,5993]

Hydrazones

6-Acetonylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione hydrazone (H_2N-$NH_2.H_2O$, EtOH, 95°, 1 h: 83% as hydrazinium salt).[4744]

Ethyl 4-acetyl-2-methyl-5-pyrimidinecarboxylate phenylhydrazone ($PhNHNH_2$, EtOH–H_2O, reflux, 3 h: 80%).[824]

2-Acetyl-6-methyl-4(3*H*)-pyrimidinone *p*-nitrophenylhydrazone.[671]

5-Acetyl-2,4(1*H*,3*H*)-pyrimidinedione 2,4-dinitrophenylhydrazone [2,4-$(NO_2)_2C_6H_3NHNH_2$, 2*M* HCl, warm].[788]

Also other examples.[784,788,789,6121]

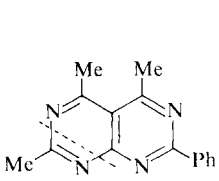
Semicarbazones

5-Acetyl-2,4-dimethylpyrimidine semicarbazone.[785]

5-Acetyl-1-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione semicarbazone ($H_2NCONHNH_2$.HCl, KOAc, NH_3, H_2O–EtOH, 95°, 20 min: ~85%).[789]

Also other examples.[789]

Cyclization reactions. The role of pyrimidine ketones as synthones for bi- or tricyclic systems may be illustrated briefly by the condensation of 5-acetyl-4-chloro-6-methyl-2-phenylpyrimidine with acetamidine to give 2,4,5-trimethyl-7-phenylpyrimido[4,5-*d*]pyrimidine (**155**) [fresh neat MeC(=NH)NH_2, 130°, 30 min: 63%],[4883] or by the cyclization of 1-acetonyl-4,6-dimethyl-2(1*H*)-pyrimidinone to 3,6-dimethylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one (**156**) (NaOMe, MeOH, reflux, 15 min: 93%).[209]



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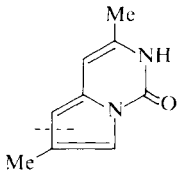

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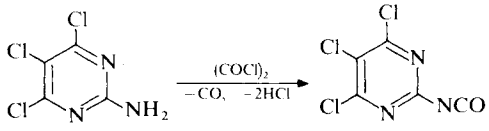
10.8. PYRIMIDINE ISOCYANATES, THIOCYANATES, ISOTHIOCYANATES, AND NITRILE OXIDES

Although isocyanato-, thiocyanato-, and isothiocyanatopyrimidines are reasonably well represented in the literature, pyrimidinecarbonitrile oxides are still considered as novelties and cyanatopyrimidines are still unknown.

10.8.1. Preparation of Pyrimidine Isocyanates

From halogenopyrimidines. Treatment of chloropyrimidines with cyanate ion has been used to make isocyanatopyrimidines. Thus ethyl 4-chloro-2-ethylthio- gave ethyl 2-ethylthio-4-isocyanato-5-pyrimidinecarboxylate (KOCN, PhH, reflux, 4 h: isolated after aminolysis, as the 4-ureido anlaog);[3024] and 5-chloro- gave 5-isocyanato-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (AgOCN, PhH, reflux, 5 h: ~50%).[1114]

From pyrimidinamines. Treatment of primary pyrimidinamines with oxalyl chloride affords isocyanatopyrimidines. For example, 4,5,6-trichloro-2-pyrimidinamine (**157**) gave 4,5,6-trichloro-2-isocyanatopyrimidine (**158**) [$(COCl)_2$, PhH, reflux, > 2 h: 90%];[1530] analogs, such as 4,5-dichloro-6-



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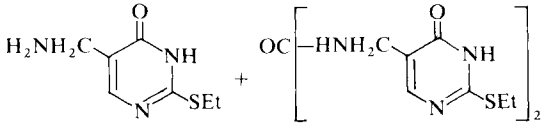
isocyanato-2-phenyl- (95%)[1530] or 4,6-dichloro-2-isocyanatopyrimidine (95%),[2482] were made similarly.

From pyrimidinecarbonyl azides. Thermal decomposition of pyrimidinecarbonyl azides furnishes the isocyanate analogs, as discussed in Section 10.4.

From a urethane. For an example, see Section 9.2.1.

10.8.2. Reactions of Pyrimidine Isocyanates

Hydrolysis. The hydrolysis of an isocyanatopyrimidine gives a carboxyaminopyrimidine, which usually loses carbon dioxide to afford a pyrimidinamine. For example, 4,6-dichloro-2-isocyanatopyrimidine gave 4,6-dichloro-2-pyrimidinamine (H_2O–AcMe, 2°, 18 h: > 95%);[2482] 2-ethylthio-5-isocyanatomethyl-4(3*H*)-pyrimidinone gave 5-aminomethyl-2,4(1*H*,3*H*)-pyrimidinedione (10*M* HCl, 95°) or, under milder conditions, a separable mixture of 5-aminomethyl-2-ethylthio-4(3*H*)-pyrimidinone (**159**) and *N*,*N*′-bis(2-ethylthio-4-oxo-3,4-dihydropyrimidin-5-ylmethyl)urea (**160**) (H_2O, 95°, 20 min: 10% and 65%, respectively);[1395] 5-isocyanato-2,4(1*H*,3*H*)-pyrimidinedione behaved rather similarly.[1395]



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Alcoholysis. Treatment of an isocyanatopyrimidine with an alcohol gives the corresponding urethane. Thus 4,6-dichloro-2-isocyanato- gave 4,6-dichloro-2-methoxycarbonylaminopyrimidine (MeOH, PhH, 20°, 15 h: > 95%);[2482] 2-ethylthio-5-isocyanatomethyl- gave 5-ethoxycarbonylaminomethyl-2-ethylthio-4(3*H*)-pyrimidinone (inferred details: EtOH, reflux, 1 h: 75%);[1395] 5-β-isocyanatoethyl- gave 5-β-(isobutoxycarbonylamino)ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Bu^iOH, reflux, 6 h: 45%);[1300] and other such reactions have been reported.[1114]

Aminolysis. The aminolysis of an isocyanatopyrimidine furnishes the corresponding ureido- or (substituted-ureido)pyrimidine, as illustrated in Section 9.2.2.1.

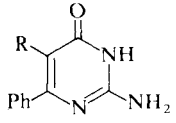
10.8.3. Preparation of Pyrimidine Thiocyanates

Thiocyanatopyrimidines must be made under reasonably mild conditions in order to avoid thermal isomerization into the corresponding isothiocyanatopyrimidines.

By primary syntheses. Several [1,3,4]thiadiazolo[3,2-*a*]pyrimidines have been degraded[3516,4565] to thiocyanatopyrimidines: see Section 2.6.3.

From tautomeric pyrimidinethiones. Such thiones undergo *S*-cyanation by cyanogen bromide: see Section 8.1.3.2.

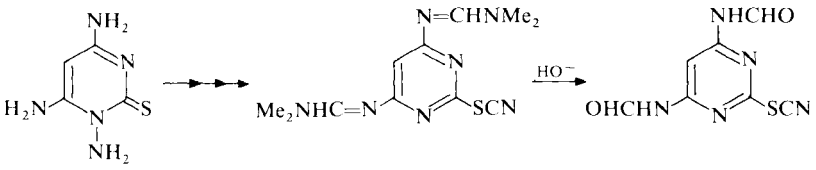
From halogenopyrimidines. The displacement of a 2/4/6- or 5-halogeno substituent by thiocyanate ion has been discussed in Sections 6.7.8 and 6.8.3, respectively. Although the conversion of 2-amino-6-phenyl-4(3*H*)-pyrimidinone (**161**, R = H) into its 5-thiocyanato derivative (**161**, R = SCN) (by treatment of the substrate plus potassium thiocyanate with bromine in glacial acetic acid) has been presented as a direct introduction of a thiocyanato group,[3137,5719] the possibility of a 5-bromo intermediate (**161**, R = Br) does not appear to have been excluded entirely.



161

From alkylthiopyrimidines. An example of the displacement of an activated methylthio group by thiocyanate ion[3515] has been given in Section 8.4.2.3.

By rearrangement. 1,4,6-Triamino-2(1*H*)-pyrimidinethione (**162**) in dimethylformamide–phosphoryl chloride underwent rearrangement, involving the participation of doubly bound sulfur as a neighboring group, to give eventually, 4,6-bisdimethylaminomethyleneamino-2-thiocyanatopyrimidine (**163**) (65%) and thence (on standing in dilute acetic acid for 1 day) 4,6-diformamido-2-thiocyanatopyrimidine (**164**) (> 95%); the mechanism has been discussed.[1355,5994]

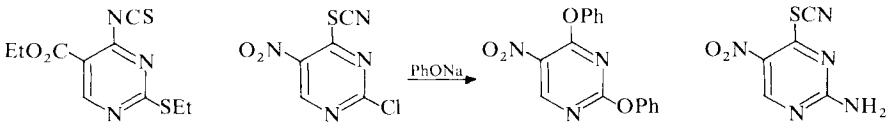


162 **163** **164**

10.8.4. Reactions of Pyrimidine Thiocyanates

Much of the information on reactions of thiocyanates was reported many years ago, and some of it is decidedly vague.

Thermal isomerization. Thiocyanatopyrimidines isomerize into isothiocyanatopyrimidines on prolonged heating at 110–190° in an inert solvent, if necessary within a sealed vessel. Such a procedure gave ethyl 2-ethylthio-4-isothiocyanato-5-pyrimidinecarboxylate (**165**) (PhH, 190°, 8 h, sealed: 75%),[3016] 2-ethylthio-4-isothiocyanato-5,6-dimethylpyrimidine (xylene, reflux, 2 h: 55%),[2157] 5-ethyl-2-ethylthio-4-isothiocyanatopyrimidine (PhMe, reflux, 6 h: 85%),[2140] and other such products.[1886,2188,2365,3128,5101,5667] The formation and isomerization of the thiocyanatopyrimidine have been done rather ineffectively as a one-pot reaction: for example, 4-chloro-2-ethylthio- so gave 2-ethylthio-4-isothiocyanatopyrimidine (KSCN, PhMe, reflux, prolonged)[969] and 4-chloro-5-ethoxycarbonylmethyl-2-ethylthio- so gave 5-ethoxycarbonylmethyl-2-ethylthio-4-isothiocyanatopyrimidine.[1995,3023]

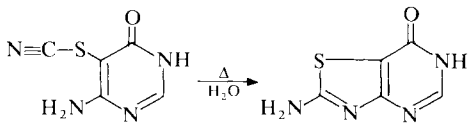


165 **166** **167** **168**

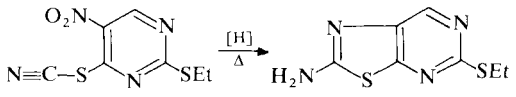
Displacement reactions. A suitably activated thiocyanato substituent can act as a leaving group: such aminolysis has been discussed in Section 9.1.1.3; *hydrolysis* has been illustrated briefly in Section 7.1.1.6; and *alcoholysis–phenolysis* has been exemplified, albeit inadequately, by the conversion of 2-chloro-5-nitro-4-thiocyanato- (**166**) into 5-nitro-2,4-diphenoxypyrimidine (**167**) (PhONa, EtOH, 0°, 1 h) and of 5-nitro-4-thicyanato- (**168**) into 4-ethoxy-5-nitro-2-pyrimidinamine (EtONa, EtOH, 0°, 2 h: ~55% plus a separable byproduct).[1582]

Conversion into thiones and thiols. Thiocyanatopyrimidines may be converted into the corresponding thiones or thiols in several rather unsatisfactory ways, already covered in Section 8.1.1.

Cyclization to thiazolopyrimidines. A useful route to two systems of thiazolopyrimidines involves intramolecular cyclization of thiocyanatopyrimidines. For example, 6-amino-5-thiocyanato-4(3*H*)-pyrimidinone (**169**) gave 2-amino-



169 **170**



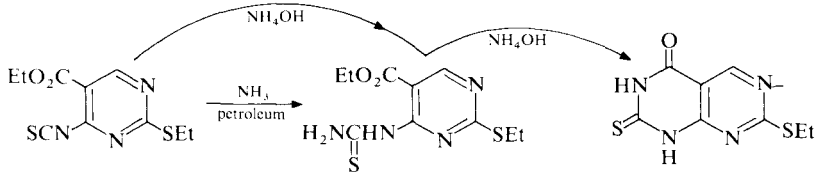
171 172

thiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (**170**) (H_2O, reflux, 5 h: 70%);[837] 2-ethylthio-5-nitro-4-thiocyanatopyrimidine (**171**) gave 5-ethylthiothiazolo[5,4-*d*]pyrimidin-2-amine (**172**) (Fe, AcOH, 60°, 2 h: ~85%);[1187] and other examples have been reported.[837,1187,3137]

10.8.5. Preparation and Reactions of Pyrimidine Isothiocyanates

The usual way to make isothiocyanates has been by *thermal rearrangement* of thiocyanatopyrimidines: see Section 10.8.4. However, the classical route from pyrimidinamines with *thiophosgene* has been used occasionally: see Section 9.1.6.8.

Isocyanatopyrimidines react with alcohols to give thiourethanes (see Section 9.2.1.1) or with ammonia or amines to afford thioureido- or (substituted-thioureido)pyrimidines, respectively (see Section 9.2.2.1). If conditions are inappropriate during such aminolyses, cyclization may occur. Thus ethyl 2-ethylthio-4-isothiocyanato-5-pyrimidinecarboxylate (**173**) with ammonia gas in light petroleum gave the 4-thioureido analog (**174**), but with concentrated aqueous ammonia, even at 20°, it gave 7-ethylthio-2-thioxo-1,2-dihydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**175**) (79%).[3017]



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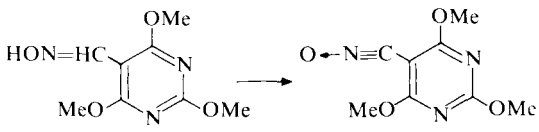
10.8.6. Preparation and Reactions of Pyrimidine Nitrile Oxides

The dehydrogenation of pyrimidinecarbaldehyde oximes (e.g., **176**) has been used to prepare the corresponding nitrile oxides: in practice, aldoximes with



176 177

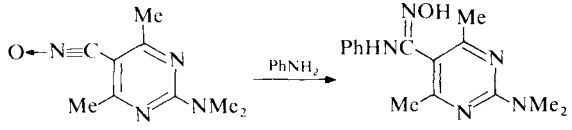
appropriate flanking groups were chosen as substrates in order to inhibit dimerization to which nitrile oxides are apparently prone.[5996] The formation of the following products illustrates the reagents and conditions employed.

2,4,6-Trimethoxy-5-pyrimidinecarbonitrile oxide (**177**) (NaOH, Br_2, H_2O, pyridine, 0°, 30 min: 19%;[2075, cf. 5997] NBS, NEt_3, Me_2NCHO, 10–15°, 45 min: 80%).[2476]

2-Dimethylamino-4,6-dimethyl-5-pyrimidinecarbonitrile oxide (**178**) (NaOBr, H_2O–pyridine, 0°, 30 min: 34%).[2075, cf. 5997]

4-Chloro-2-dimethylamino-6-methoxy-5-pyrimidinecarbonitrile oxide (NaOBr, H_2O–pyridine, 0°, 30 min: 22%).[2075, cf. 5997]

4,6-Dichloro-2-dimethylamino-5-pyrimidinecarbonitrile oxide (NBS, NEt_3, Me_2NCHO, 15°, 45 min: 73%).[2476]



178 **179**

Such nitrile oxides appear to be quite reactive: for examples, the oxide (**178**) with neat aniline at 110° for 45 min gave 2-dimethylamino-4,6-dimethyl-5-pyrimidinecarboxanilide oxime (**179**) (40%).[2075]

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D. J. Brown
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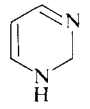
CHAPTER 11

The Reduced Pyrimidines*

Formally there is a total of nine hydrogenated derivatives (**1**–**9**) of pyrimidine: five dihydro, three tetrahydro, and one hexahydro when no allowance is made for the complications due to tautomerism or for the possible existence of ring-conformational isomers. Thus the mobile nature of hydrogen atoms attached to ring nitrogen atoms ensures that 1,4- and 1,6-dihydropyrimidines (**2** and **3**) will be in tautomeric equilibrium with each other, as will the 1,2,3,4- and 1,2,5,6-tetrahydropyrimidines (**6** and **7**), respectively. Since the tetrahydro and hexahydro compounds are formally derivatives of cyclohexene or cyclohexane in which CH or CH_2 groups have been replaced by N or NH groups, isomerism resulting from chair–boat or other conformational interconversions is at least another possibility. On structural grounds, the dihydropyrimidines have been subdivided further into two groups.[6175] The 1,2-, 1,4-, and 1,6-dihydro compounds (**1**–**3**) are cyclic enamines, in which the lone pair of the sp^3-hybridized nitrogen atom can conjugate with the four π-electrons of the C=C and C=N double bonds. The two remaining dihydro compounds (**4** and **5**) are cyclic imines in which such conjugation is absent.[185] Theoretical calculations have also been performed on a hypothetical isomer, the 1,3-dihydro-1,3-diazine (**10**) structure. These indicate that its C_s structure will have lower energy and singlet stability compared with the alternative C_{2v} structure.[6176]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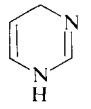
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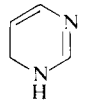
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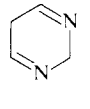
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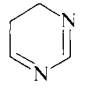
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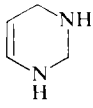
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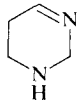
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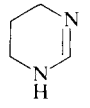
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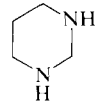
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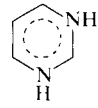

10

* By Dr R. F. Evans, Department of Chemistry, The University of Queensland, Brisbane, Australia 4072. This chapter is dedicated to Professor Herbert C. Brown, Nobel Laureate 1979, on the occasion of his eightieth birthday and in commemoration of two exhilarating postdoctoral years 1954–1956 with him.

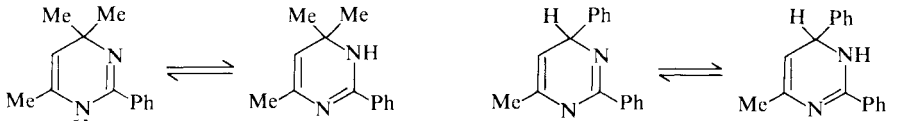
Methods of preparing reduced pyrimidines fall broadly into two groups: those that involve the cyclization of appropriate acyclic precursors (and therefore in many cases parallel the synthesis of the parent heteroaromatic pyrimidine) and those that involve the modification of preexisting pyrimidine rings by addition of hydrogen or, to a less extent, other reagents. In the latter category belong derivatives of short lives postulated and sometimes identified as reactive intermediates in various overall substitution reactions of the pyrimidine ring. Lack of space precludes more than a brief mention of such intermediates and also of those reactions where the final reduced pyrimidine is unstable and its existence has had to be deduced from decomposition products. This applies regardless of whether the instability was intrinsic to the molecule or resulted from inappropriate methods of isolation.

11.1. PREPARATION OF DIHYDROPYRIMIDINES

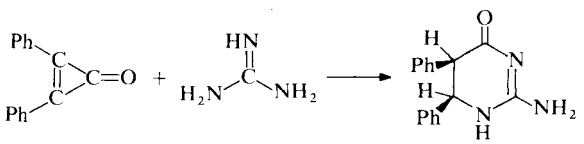
11.1.1. By a Modified Principal Synthesis (Method A)

Of the methods currently available, the condensation of a three-carbon entity, especially an α,β-unsaturated carbonyl compound, with an N—C—N containing compound is probably the one most widely described in the literature. This is particularly so when the N—C—N moiety belongs to the urea, thiourea, or guanidine molecule, to their *N*, *S*, or *O*-substituted derivatives, as well as to an amidine molecule. See also appropriate sections of Chapter 3.

A popular provider of the three-carbon entity was the α,β-unsaturated system of mesityl oxide or phorone, either used directly or produced in situ from the self-condensation of acetone in the reaction medium. Thus the reaction of benzamidine with mesityl oxide affords a solution containing a tautomeric mixture of the 1,4- and 1,6-dihydro compounds (**11** and **12**) from which only the solid 1,6-isomer (**12**) can be obtained.[6177, cf. 6303] By contrast, the solid product from an analogous condensation of benzylideneacetone with benzamidine has



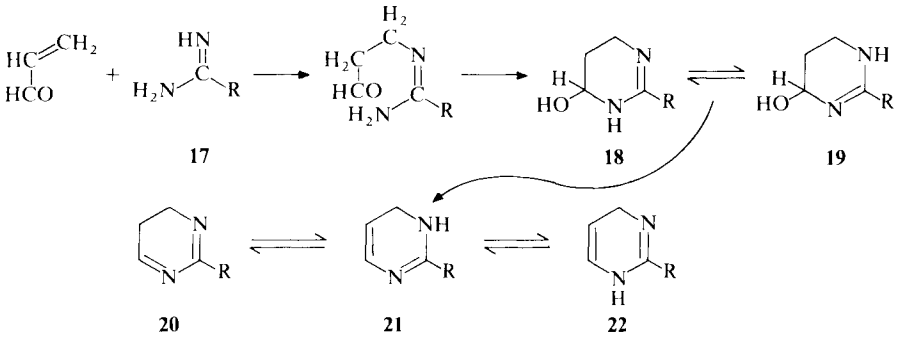
11 **12** **13** **14**



15 **16**

the alternative 1,4-arrangement (**13**), although in solution it is in tautomeric equilibrium with (**14**).[6178] The three-membered ring of diphenylcyclopropenone provides the three-carbon fragment in a cycloaddition process with amidines and guanidine itself (**15**), affording a 5,6-dihydro-4-(1*H*)-pyrimidinone (**16**) with a *cis* arrangement of the two phenyl substituents.[6179] The 6-phenyl group inverts its position when **16** is heated.[6179]

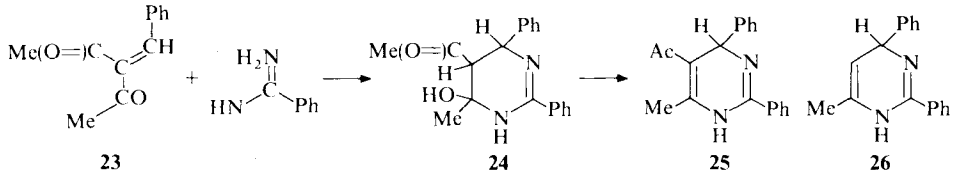
Only relatively recently has the simplest α,β-unsaturated carbonyl compound, acrolein, been used successfully in these condensation reactions.[102,267,290,334] The overall reaction was broken down into its individual steps and the intermediate tautomeric hydroxytetrahydropyrimidine (**18** ⇌ **19**) isolated. This resulted from nucleophilic attack of the amidine (**17**, R = H, Me or Ph) on the activated double bond followed by ring closure. Mild dehydration, effected thermally or by using acid catalysis or acetic acid as the solvent, produced high yields of the relevant dihydropyrimidine tautomers (**21** ⇌ **22**) possibly through the initial formation of the unstable 4,5-dihydro isomer (**20**) following the dehydration process.[6180,6181] The parent compounds (**21**, **22**, R = H) were stable only in solution and could not be isolated in the pure state.



17 **18** **19**

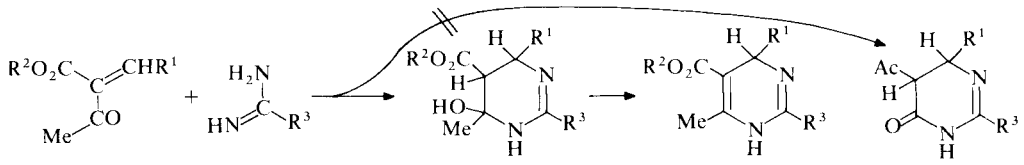
20 **21** **22**

The importance of first isolating the tetrahydro intermediate is also exemplified when there are two different α,β-unsaturated carbonyl regions in the molecule producing the three-carbon fragment. Thus **23** cyclized with benzamidine in acetone at −5°C to give **24**, which, on heating in benzene, dehydrated to the 1,4-dihydro compound (**25**). By contrast in ethanol, solvent participation under base catalysis brought about loss of the acetyl group to give **26**. In the case of the benzylideneacetoacetic esters (**27**), the usual participation of



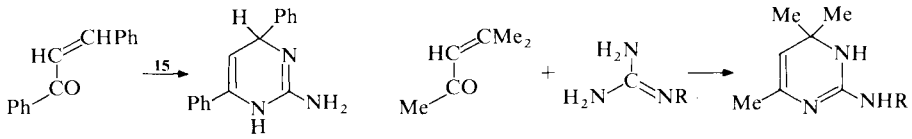
23 **24** **25** **26**

the more reactive ester function in the cyclization process can be avoided. Low-temperature cyclization and separate dehydration of the isolated hydroxy-tetrahydro compounds (**28**) leads to high yields of the physiologically active 5-functionalized 1,4-dihydro compounds (**29**) that are analogs of the calcium antagonist nifedipine.[500]

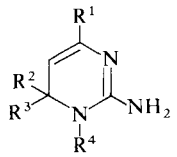


27 **28** **29**

Guanidine cyclocondenses with both aromatic and aliphatic α,β-unsaturated ketones. Chalcone itself[4054] gives **30**, while mesityl oxide[4072] with a selection of *N*-substituted guanidines gives products (**31**, R = Me, $PhCH_2$, or Ph) in which the substituent ends up on the exocyclic nitrogen atom.[441,470] A low reaction temperature (25°) and the avoidance of protic solvents for crystallization of the products is essential to avoid thermal isomerization and dimerization to give a mixture of products.[4071,4073] In this way pure solids comprising solely the 2-amino-1,6-dihydro compounds (e.g., **32**, $R^1 = R^2 = R^3 = Me$, R^4 = H, Me, or Et; or $R^1 = R^2 = Ph$, $R^3 = R^4 = H$) are obtained. In some reactions, exclusion of atmospheric oxygen[3866] is necessary to prevent aromatization of the product to the parent pyrimidine; in others, oxygen introduction has been done deliberately for this purpose.[6182]



30 **31**



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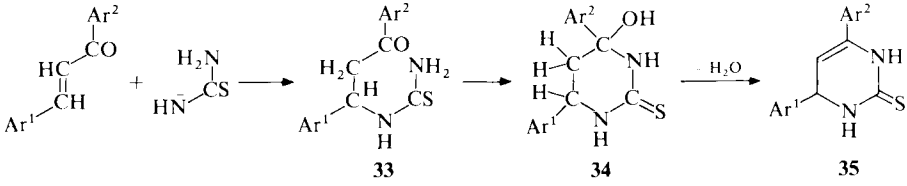
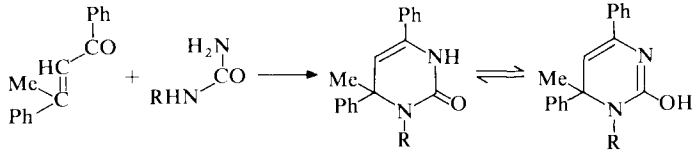
The chalcones, 1,3-diarylprop-2-en-1-ones, also condense with thiourea under strongly alkaline conditions (sodium ethoxide) to give 1,6(3,4)-dihydro products (**35**).[6183] The thiourea anion probably adds to the activated double bond, and the Michael addition product (**33**) may then cyclize to a tetrahydropyrimidine derivative (**34**), which readily loses a molecule of water to give the 1,6-dihydro compound (**35**) directly. Support for this mechanism comes from the condensation of dypnone (**36**) with urea or *N*-methylurea to form the appropriate



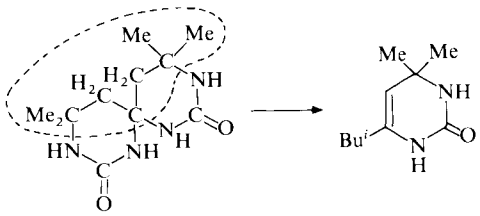
33 34 35



36 37 38

dihydropyrimidinone (**37**, R = H or Me).[6184] Assuming that the NHMe is the more nucleophilic end of the *N*-methylurea molecule, structure **37** (R = Me) fits in with such a scheme involving initial Michael addition to the activated ethylenic double bond; ^{1}H nmr evidence suggests that **37** (R = H) tautomerizes in solution with structure **38** (R = H), in which the dihydro level of reduction is now plainly evident.

Urea and acetone under acid catalysis at 40–50° give the spiran (**39**). An initial self-condensation between three molecules of acetone seems to be involved since this condensation product, phorone, also reacts with urea at higher temperatures to give one and the same spiro compound, in which the phorone carbon skeleton is outlined by the dotted fence in formula **39**.[6185] Under acidic conditions (phosphoric acid), hydrogen at high temperatures and pressures in the presence of rhodium causes hydrogenolysis of the spiro compound to the 1,4(1,6)-dihydro derivative (**40**). A related molecule is formed by the ammonium-chloride-catalyzed Michael addition of urea to the olefinic double bond of mesityl oxide, followed by cyclization to **41** and dehydration to the final product (**42**).[6185]



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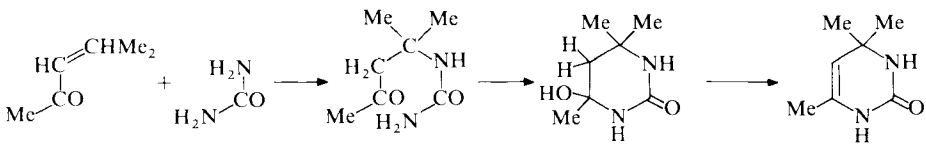
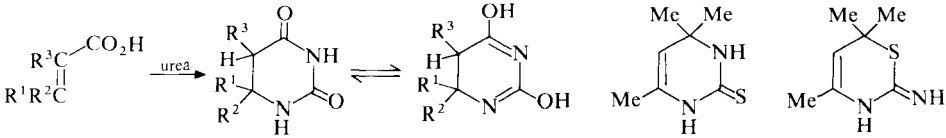


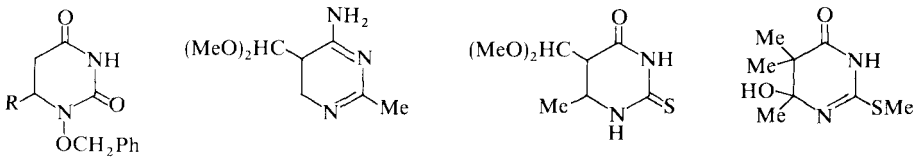
41 42

In these condensations involving urea and thiourea, one double bond in the resulting hydropyrimidine must be associated with C2, thereby excluding the preparation of the series represented by **1**. If the C—C—C fragment also contains an unsaturated CO or CN entity, C4 in the resulting hydropyrimidine must also be associated with a double bond, leading to the availability of the 5,6-dihydro species (**5**) only by this procedure. Thus the long-known condensation of urea with acrylic acid (**43**, $R^1 = R^2 = R^3 = H$)[3459] or its esters[4112] affords the dihydrouracil compound (**44**, $R^1 = R^2 = R^3 = H$), which is the more stable dioxo tautomer of the 5,6-dihydro-2,4-dihydroxy species (**45**, $R^1 = R^2 = R^3 = H$). Both *C*-methyl derivatives of acrylic acid such as crotonic acid[3459,4112] and *C*-phenyl derivatives such as cinnamic acid[3459,5259] behave in an analogous manner (**43** → **44** → **45**, R^1 = Me or Ph, $R^2 = R^3 = H$) and so on.[6186] In similar condensations with thiourea (or ammonium thiocyanate acting as its precursor[6187,6188]) the desired dihydropyrimidine may be only a minor product. Thus mesityl oxide affords the 1,3-thiazine (**47**) as the major product but only 10% of the isomeric dihydropyrimidine (**46**).[6189]



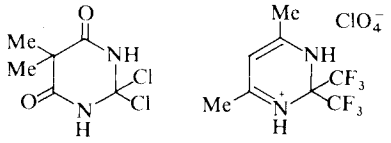
43 **44** **45** **46** **47**

5,6-Dihydropyrimidines are important intermediates in the biosynthesis and degradation of pyrimidines while 5,6-dihydrouracil is a constituent of transfer RNA. It is not surprising, therefore, that the 5,6-dihydro series is well represented in the products arising from the use of unusual C—C—C and/or N—C—N combinations. Thus α,β-unsaturated carboxamides,[5901] α-dimethoxymethyl-β-methoxypropionitrile,[337] a concealed β-keto ester,[3332] and a nonenolized one[4177] react separately with *N*-benzyloxyurea,[5901] an amidine,[337] thiourea,[3332] and its *S*-methyl derivative[4177] to give the 5,6-dihydro compounds (**48**–**51**), respectively.



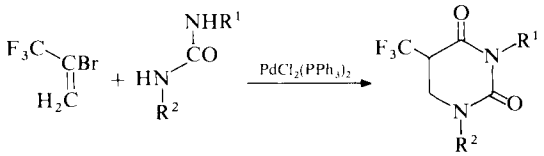
48 **49** **50** **51**

Cyanamide furnishes the N—C—N region of a chlorinated 2,5-dihydropyrimidine (**52**) with dimethylmalonyl chloride,[4229] while a geminal fluorinated diamine reacts with acetylacetone to give the salt of the 1,2-dihydro derivative (**53**), which, as a vinylogous amidinium system, possesses resonance stability.[418]



52 53

A fluorinated alkene in the presence of carbon monoxide under pressure acts as the equivalent of a C—C—C fragment in the reaction with urea and its *N*-methylated derivatives (catalyzed by a palladium complex) and results in a fluorinated dihydrouracil (**54** → **55**, R^1 = H or Me, R^2 = H or Me).[444] When the bromine atom in the fluorinated alkene is replaced by the carboxyl group, the substituted acrylic acid readily undergoes the more general reaction with urea or thiourea and their *N*-alkyl derivatives. The occasional implication of the intermediate 3-ureidopropionic acids in this process leads to the use of acetic anhydride or dicyclohexylcarbodiimide for their cyclization to the dihydrouracils.[460]



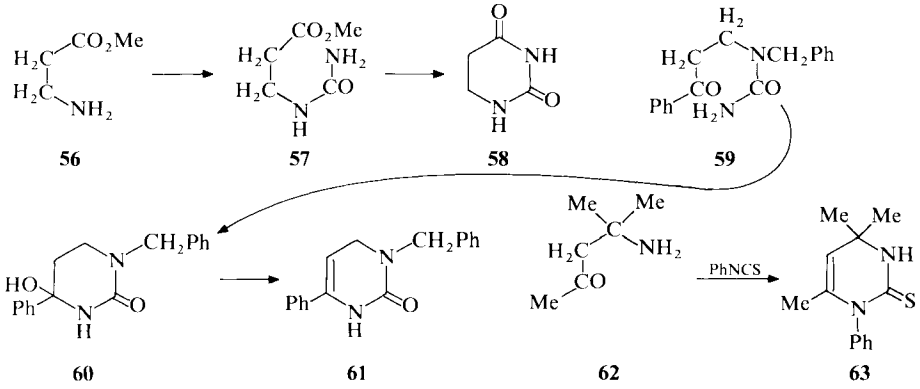
54 55

11.1.2. From an Aminopropane Derivative and an Isocyanate (Method B)

This reaction, which is nearly 100 years old,[480] involves the reaction of a three-carbon fragment already carrying a primary or secondary amino group with cyanic acid and its metal salts,[495] an alkyl isocyanate, or their thio analogs.[547] Thus the combination of methyl 3-aminopropionate (**56**) with cyanic acid gives methyl 3-ureidopropionate (**57**), which, with its C—C—C—N—C—N backbone, contains all the atoms required to form a pyrimidine ring. Thermal cyclization[480,6246] is enough to cause N1—C6 (or N3—C4) bond formation to give 5,6-dihydrouracil (**58**). Cyclization may occur under mild conditions as with 3-ureidopropionic acid itself (**57**, H for Me) (formed from β-alanine and urea) in the presence of a clay mineral, montmorillonite,[6247,6248] to give dihydrouracil again. 3-Alkylamino- and 3-arylaminopropionic acids, the latter prepared by the direct addition of aniline (for example) to the activated double bond of acrylic acids, leads to *N*1-substituted dihydrouracils. *N*3-Alkylated derivatives may be made by using an alkyl or aryl isocyanate in place of cyanic acid.[6249,6250] A 1,3-disubstituted dihydrouracil results from the combination of a secondary β-amino acid with an alkyl or aryl isocyanate.[6250]

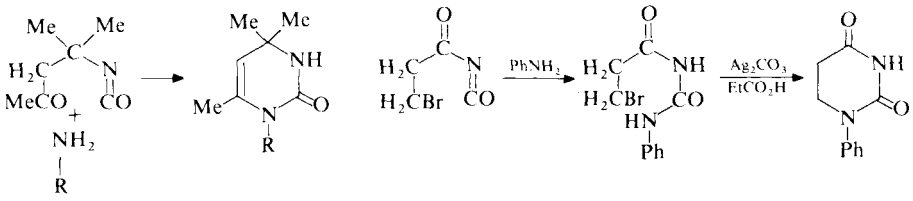
Optically active β-amino acids lead to substituted 5,6-dihydrouracils still retaining this activity at C6.[6251]

β-Ureido ketones may replace the propionic acids in this reaction. Thus the Mannich product from acetophenone, formaldehyde, and benzylamine (or other primary amine) reacts with potassium cyanate to give the β-ureido ketone (**59**). This readily cyclizes at room temperature to the tetrahydropyrimidine (**60**), which can be easily dehydrated thermally or by a trace of acid to give the dihydropyrimidine (**61**).[6252] Diacetonamine (**62**) reacts with cyanic acid,[6253] thiocyanic acid,[6253] or phenyl isothiocyanate[6253,6254] to give, for example, the analog (**63**). 3-Aminopropionitriles react with isothiocyanates, and the readily isolated intermediate β-thioureidopropionitriles cyclize under acidic catalysis to give 5,6-dihydro-2-thiouracils.[191]



11.1.3. From an Isocyanatopropane Derivative and an Amine (Method C)

This synthesis, a reversal of Method B, is illustrated by the reaction of 4-isocyanato-4-methylpentan-2-one (**64**) with appropriate simple primary amines to give the hydropyrimidine (**65**, R = Me or Ph).[6255] The sulfur analog of **64**, obtained directly from the reaction of mesityl oxide and ammonium thiocyanate in 50% sulfuric acid, also reacts with alkylamines but via an isolable thioureido intermediate.[4347,6256] Both of these reactions therefore probably proceed through cyclization of the same C—C—C—N—C—N entity obtained in Method B (Section 11.1.2). The intermediate is also of the same type as that involved in the reaction of mesityl oxide and urea to give **42** by Method A (Section 11.1.1). In another example, an *acyl isocyanate* (**66**), as distinct from an alkyl one, is converted by an aromatic amine into the acylurea (**67**). Treatment with silver carbonate in propionic acid causes cyclization to the 5,6-dihydrouracil (**68**).[4113] Alternatively, **67** can be dehydrobrominated and the unsaturated acylurea slowly cyclized in acidic media[6257] in an intramolecular analog

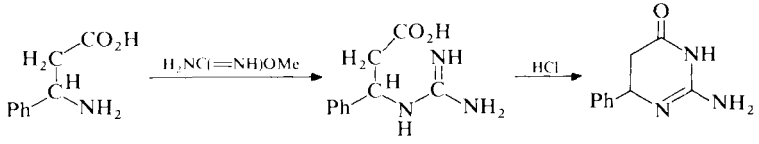


64 65 66 67 68

of the addition of ureas to the activated olefinic double bonds of acrylic acids and the like in Method A (Section 11.1.1).

11.1.4. From an Aminopropane Derivative and *O*-Methylurea (Method D)

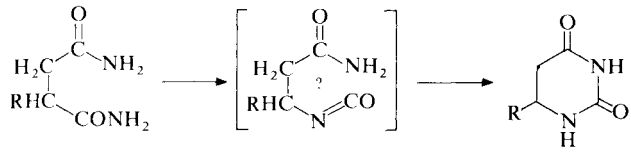
This potentially useful synthesis is exemplified by the condensation of 3-amino-3-phenylpropionic acid (**69**) with *O*-methylurea to give the 3-guanidino compound (**70**). This contains the complete C—C—C—N—C—N framework for the pyrimidine nucleus, and cyclization to the hydropyrimidine derivative (**71**) occurs in boiling hydrochloric acid;[6258] the intermediate (**70**) is of the type to be expected when guanidine adds to the activated olefinic double bond of cinnamic acid as in Method A (Section 11.1.1). The substrate (**69**) also reacts with ethyl benzimidate, regarded as a distant relative of *O*-methylurea, to give the 5,6-dihydro derivative (**71**, Ph for NH_2).[6259]



69 70 71

11.1.5. Syntheses Involving Amide Intermediates (Method E)

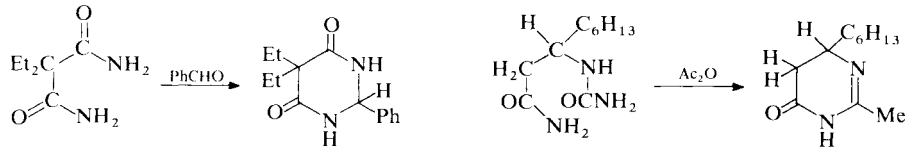
These include the intramolecular equivalent to the attack of an isocyanatopropane derivative by a separate primary amine (Method B, Section 11.1.2). Succinamide (**72**, R = H) is partly degraded by the Hofmann reaction, presumably to 3-isocyanatopropionamide (**73**, R = H), which then cyclizes to the 5,6-dihydrouracil (**74**, R = H).[4328,6246] A similar sequence of reactions occurs with 2-methylsuccinamide (**72** → **73** → **74**, R = Me).[4328] The lead tetraacetate oxidation of some succinamides to dihydrouracils probably involves a similar isocyanato intermediate.[3477,6260] This intermediate has a different six-atom backbone, N—C—C—C—N—C from the one common to Methods A–D



72 73 74

(Sections 11.1.1–11.1.4) and the ring formation involves bonding between the C2 and N3 atoms.

In theory, there are four ways in which the hydropyrimidine ring can be completed from a precursor molecule containing a five-atom backbone arranged in the appropriate order: by addition of the N1, C2, C4, or C5 ring atoms, respectively. The second possibility is the one most represented in dihydropyrimidine ring formation and in this section is represented firstly by the ready condensation of nonenolizable diamides such as 2,2-diethylmalonamide (**75**) with benzaldehyde or benzal chloride[6261,6262] to give the 2-phenyl derivative of a 2,5-dihydro species (**76**). The unsubstituted molecule (**76**, H for Ph) does not form with formaldehyde,[4368,6263,6264] but formamide and sometimes formic acid are more successful. It is suspected that an *N*-formyl derivative is formed that then cyclizes to the pyrimidine, which is, in turn, reduced to the dihydro state by the excess of formamide or formic acid. In a more recent example, the carbonyl carbon atoms of aromatic and heteroaromatic aldehydes furnish the missing carbon atom to the N—C—C—C—N backbone of diethyl malondiimidate.[6265]



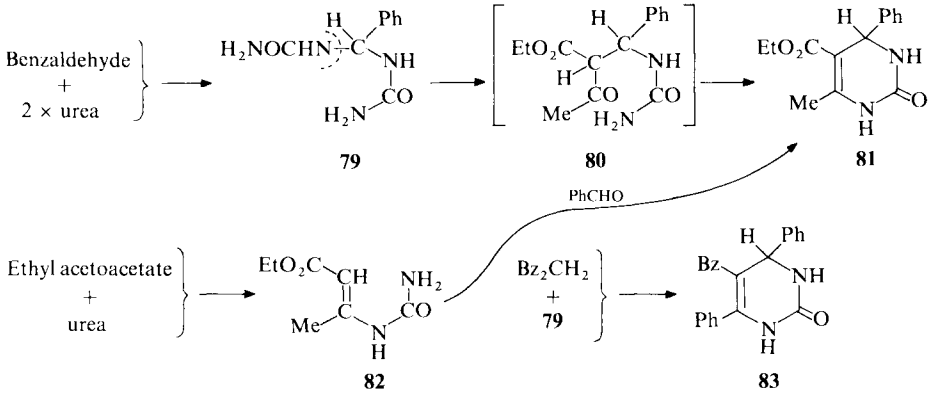
75 76 77 78

Certain acylated β-amino acids containing an N—C—C—C—N—C backbone can be cyclized under the influence of dehydrating agents such as phosphorus pentachloride (or pentoxide) and acetic anhydride. This involves N1—C2 bond completion and formation of a dihydropyrimidine (e.g., **77** → **78**).[6266]

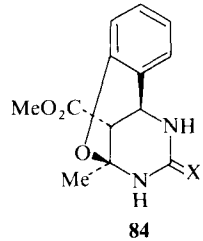
11.1.6. The Biginelli Reaction

This is another reaction that is almost 100 years old[4460] but has recently taken on a new lease on life[3942] because the products, when properly substituted, can act as cardiovascular agents; they can be regarded as aza-analogs of the dihydropyridine heart drug (coronary vasodilator), nifedipine. In the ori-

ginal one-pot reaction, which was later shown to be strongly catalyzed by acid,[6267] a mixture of benzaldehyde, urea, and ethyl acetoacetate in alcohol gave the 1,6-dihydropyrimidine (**81**). The urea reacts with benzaldehyde to give α,α-diureidotoluene (**79**) and with the ester to give ethyl 3-ureidocrotonate (**82**).[6268] Each of these then further reacts with the third component (ethyl acetoacetate or benzaldehyde, respectively) giving the dihydropyrimidine (**81**), in one case via **80**.

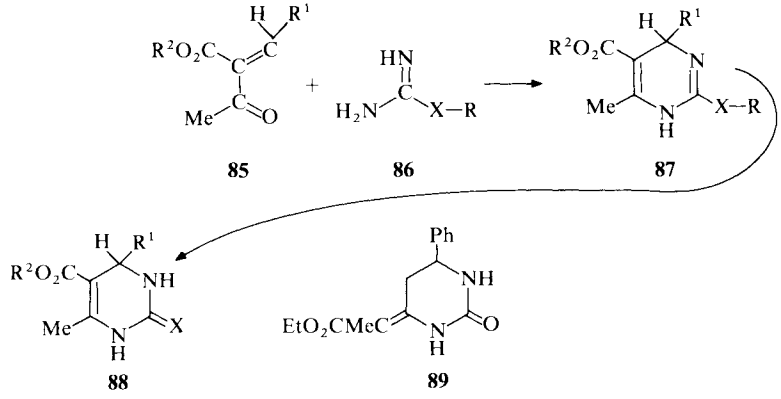


All these components in the Biginelli reaction can be varied widely. The aldehyde component includes both aliphatic and aromatic aldehydes,[6269-6271] α,β-unsaturated aldehydes,[6269,6285] as well as more complex examples drawn from the carbohydrate field,[6286,6287] while α,β-dichloroethyl ethyl ether functions as an effective precursor for chloroacetaldehyde[6288] in both the orthodox Biginelli reaction and its reaction with 3-ureidocrotonic esters such as **82**[6272] in the Folkers–Johnson modification of this reaction.[6268] Although doubt has been cast on whether α,α-diureidotoluene (**79**) is a key intermediate in the Biginelli reaction,[3402] it can be used independently to form Biginelli-type products such as (**83**) with β-diketones such as dibenzoylmethane,[6273] and other ketones.[4696] However, the Biginelli product from salicylaldehyde, urea or thiourea, and methyl acetoacetate is not isolable: the hydroxy group undergoes a nuclephilic addition to the 5,6-double bond of the heterocyclic ring to form an annelated oxygen-bridged pyrimidine (**84**, X = O or S).[6274]



84

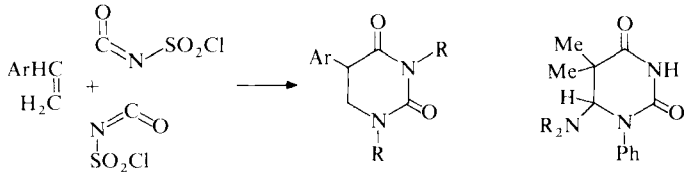
Primary, secondary, or tertiary amide derivatives [5947,6275–6277,7035] have been used in place of the ester to produce (**81**; NH_2, NHR, or NR_2 in place of EtO in EtO_2C). Substituted ureas and thioureas can replace the urea component.[6275,6277] Ethyl trifluoroacetate has been used as the ester component.[6278] However, acid-sensitive groups are lost in the Biginelli condensation, the yields are often low, and the reaction is inapplicable for the synthesis of *N*3-alkylated derivatives since *N*-alkylureas afford *N*1-alkylated isomers.[6270] Consequently, effective alternatives to the Biginelli reaction have been developed recently.[530,531,3945] The ester was first reacted with the aldehyde under standard Knoevenagel condensation conditions, and the unsaturated β-keto ester (**85**) reacted with *O*-methylurea[530] (**86**, X = O, R = Me) or *S*-*p*-methoxybenzylthiourea[531] (**86**, X = S, R = $CH_2C_6H_4OMe$-*p*) under mild alkaline conditions. The product (**87**) consists predominantly of the 1,4-dihydro tautomer, which on acid treatment gives the Biginelli compound (**88**, X = O or S), or it can be reacted with a variety of electrophilic alkylating agents to give *N*3-derivatives,[3945,6279] as was found earlier with analogs (**87**: Me, Ph, NH_2, or NMe_2 for X—R).[205] Oxycarbonylation with alkyl chloroformates also occurs at N3 to give compounds serving as novel calcium antagonists.[6280]



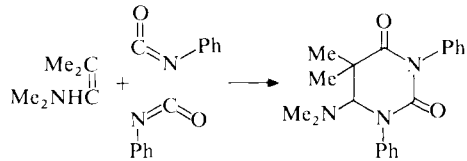
The crucial step in the alternative to the Biginelli reaction is actually an example of Method A (Section 11.1.1). This overlap between the two methods reflects the continuing interest in the Biginelli products with potentially beneficial biological activity. It also seems that the α,β-unsaturated condensation products between aldehydes and alkyl acetoacetates as well as *N*-aryl acetoacetamides[6281] serve as almost ideal C—C—C counterparts to their N—C—N reaction partners, forming isolable hydroxytetrahydro compounds that can be dehydrated in good yields. An alkyl group on C2 of the β-keto ester hinders aldol condensation at that site and deflects it to the unhindered terminal methyl group of the molecule. Hence ethyl 2-methylacetoacetate gives (**89**) with benzaldehyde and urea in an orthodox Biginelli reaction.[3402]

11.1.7. Other Primary Syntheses

Although chlorosulfonyl isocyanate is one isocyanate that does not seem to have been investigated under Method B (Section 11.1.2), its mixed cycloaddition reactions with a variety of unsaturated molecules also give dihydropyrimidines. Two moles of chlorosulfonyl isocyanate (**90**) cycloadd to the side-chain double bond of an *ortho*-(dialkylamino)styrene to give an *N,N'*-disubstituted dihydrouracil (**91**, R = SO_2Cl, Ar = $C_6H_4NR_2$-*o*), which loses its chlorosulfonyl substituents on mild hydrolysis to give the final product (**91**, R = H, Ar = $C_6H_4NR_2$-*o*).[6282,6283] Chloroformyl isocyanate also adds to the double bond of Schiff bases[6284] and to one of the olefinic double bonds of phorone[6289] in other mixed cyclotrimerization reactions. The addition of certain enamines gives isolable intermediates containing a C—C—C—N—C backbone that undergo ring closure with aniline to form dihydrouracils such as **92** (NR_2 = morpholino or piperidino).[6290] Organic isocyanates[4227] and their sulfur counterparts[6291] also take part in mixed cycloaddition reactions with an enamine (**93** → **94**) and even a vinylidene phosphorane.[7036]

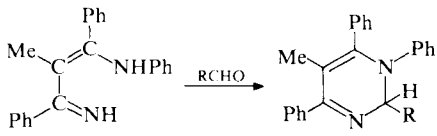


90 **91** **92**



93 **94**

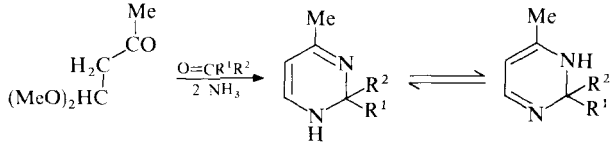
Reactions in which the hydropyrimidine ring is completed by insertion of the missing C2 atom into an N—C—C—C—N precursor include the aluminum chloride catalyzed reaction of the amino imine (**95**) (which can be regarded as a derivative of a β-dicarbonyl compound) with aldehydes, and sometimes ketones



95 **96**

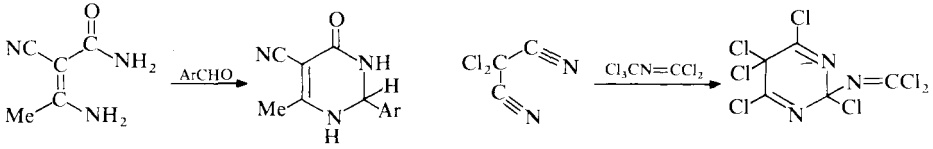
in the form of their ketals, to give dihydropyrimidines (**95** → **96**).[6293,6294] In a later extension of this reaction,[3843] (*S*)-(−)-2-benzyloxypropionaldehyde was used in the presence of the milder zinc chloride to form a chiral 1,2-dihydropyrimidine (**96**, R = $CHMeOCH_2Ph$).

Another derivative of β-dicarbonyl compounds, such as the oxoacetal (**97**), undergoes a similar condensation with a ketone and ammonia in the presence of ammonium nitrate to give a tautomeric mixture of dihydro compounds (**98** ⇌ **99**, $R^1 = R^2$ = Et).[6295,6296] The monoacetal of acetylacetone with diethyl ketone gave the symmetrical 2,2-diethyl-4,6-dimethyl analog of **98**/**99**.[6297] Other examples are known[4479,6298] but aromatic β-dicarbonyl compounds tend to give the dehydrogenated parent heterocycle from the expected dihydro product.[4479]



97 **98** **99**

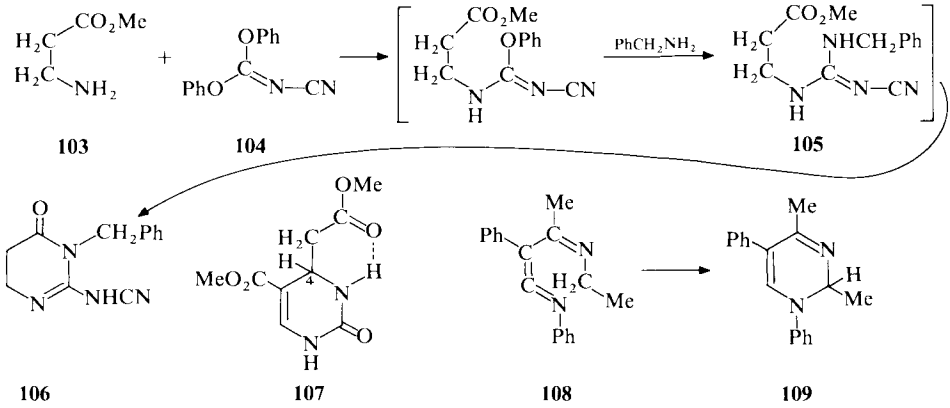
However, the carbonyl carbon atom of aromatic aldehydes is alone capable of furnishing the missing carbon atom to the N—C—C—C—N backbone of enamino amides (e.g., **100** → **101**).[6299] Another example of an N—C—C—C—N plus C cyclization strategy starts with dichloromalononitrile. The missing carbon atom is provided by reaction with trichloromethyl isocyanide dichloride to give the highly chlorinated 2,5-dihydropyrimidine (**102**).[6300]



100 **101** **102**

Another approach starts with the C2 fragment and builds on separately the N—C—C—C and N fragments required to achieve the six-atom backbone for cyclization. The carbon fragment is a double-bonded carbon atom, that of the cyano imine (**104**). Sequential replacement of each phenoxy group by the amino groups of methyl 3-aminopropionate (**103**) and benzylamine, respectively, gave a nonisolable intermediate (**105**) that cyclized to the 5,6-dihydropyrimidine (**106**).[523] The procedure has been adapted for the preparation of optically active (**106**) bearing groups such as CO_2Bu^t at C6.[6301] It was pointed out that this approach had close analogies to the biosynthetic formation of orotic acid via dihydroorotic acid.[6302] Certain free or protected β-dialdehydes and β-aldehydo esters do not react as such in attempted Principal Synthesis reactions with urea.[3332,3402] Instead, they undergo a series of reactions that may include

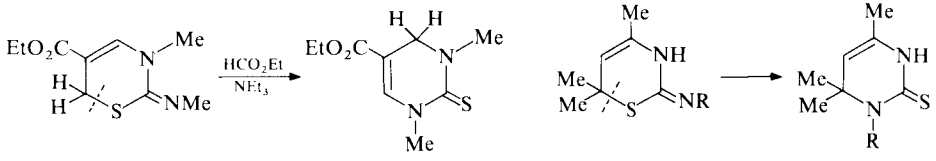
hydrolysis, keto-enol tautomerism, and aldol condensations to yield intermediates that will. Thus, methyl 3-methoxyacrylate with urea finally affords the H-bonded product (**107**) accompanied by hydrolysis and decarboxylation products involving the group on C4.[3402]



103 **104** **105** **106** **107** **108** **109**

An instance where an aliphatic precursor contains all the requisite atoms to form the six-membered hydropyrimidine ring is the imidoyl ketene (**108**). This rearranges readily at ambient temperature through a 1,5-H shift to give **109**.[6308]

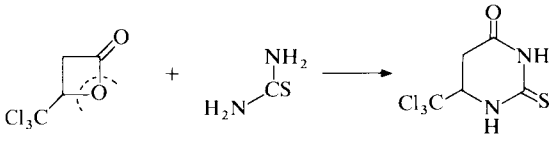
There are several examples of the conversion of other heterocycles into hydropyrimidines. In particular, the chemistry of reduced pyrimidines and 1,3-thiazines intertwine as in the conversion of **110** into **111**[913,4521,6189,6304,6305] and the Dimroth-like rearrangement of **112** into **113**, which can also be obtained from the deamination of a 4-aminotetrahydropyrimidine-2-thione, itself a rearrangement product of a 6-amino-1,3-thiazine.[6306,6307]



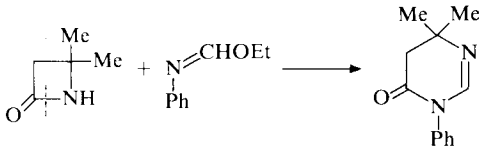
110 **111** **112** **113**

From heteromonocyclic systems with ring sizes below six-membered can be drawn the example of the β-propiolactone/oxetanone (**114**). The three carbon atoms of its strained ring become the C—C—C backbone of the dihydropyrimidine compound (**115**), which is formed by ring expansion and concomitant relief of strain on fusion with thiourea;[6310,6311] similar reactions occur with other N—C—N partners.[6312] The four-membered azetidin-2-one (**116**) likewise ring-expands with an imidic ester (**117**) to give the product **118**.[6313] The related thioamide derivative (**119**), one of the four products isolable from the reaction of *N*-substituted thioureas with β-halogenoacyl halides, also converts into the

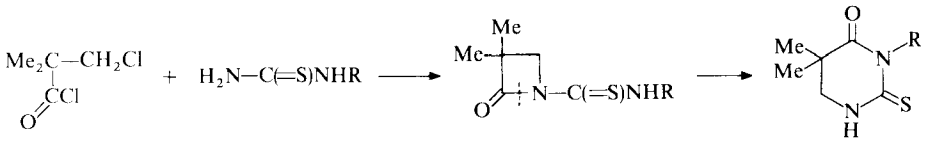
hydropyrimidine ring (**120**) on acid treatment.[6314] However, a less complex reaction with *N*,*N*′-disubstituted thioureas still offers a choice of product between a hydropyrimidine and a 1,3-thiazine derivative, depending on the judicious selection of substituents along the C—C—C backbone of the *β*-halogenoacyl halide.[6315]



114 **115**

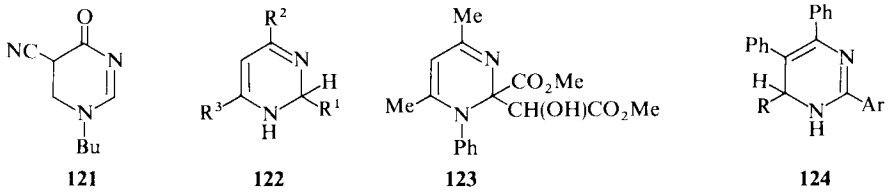


116 **117** **118**

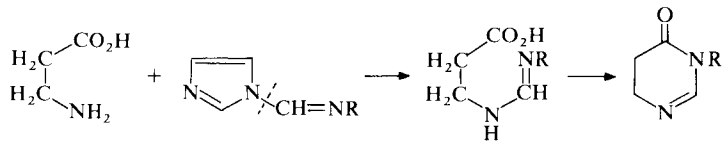


119 **120**

The ring expansion of the five-membered ring in aminopyrrolines,[6316] *N*-substituted pyrazoles,[6317,6318] and 2-vinylpyrazolium salts,[6319] as well as the rearrangement of certain diazabicyclic systems,[6320,6321] leads to dihydropyrimidine molecules such as **121**,[6316] **122** (R^1 = Ph, R^2 = R^3 = Me),[6317,6318] **123**,[6319] **122** (R^1 = CH:CHPh, R^2 = R^3 = Ph),[6320] and **124** (Ar = $C_6H_4NO_2$-



121 **122** **123** **124**



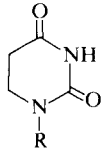
125 **126**

p, R = H or Ph),[6321] respectively. An imidazole ring acts as a carrier for an *N*-alkyliminoformyl group that is transferred to a *β*-alanine molecule, thereby converting it into an R—N—C—N—C—C—C type intermediate that is cyclized by hot acetic anhydride (**125** → **126**, R = Bu^t or C_6H_{11}).[6322]

11.1.8. By Reduction of Pyrimidines

Catalytic reduction is one of almost a dozen methods of reduction,[6323] which for a long time has continued to be a convenient means of obtaining some reduced pyrimidines. This applies especially to the 5,6-dihydro derivatives of the three biologically important pyrimidine bases (uracil, cytosine, and thymine) either free or combined as the related nucleosides and nucleotides or in other naturally occurring molecules such as some of the streptovirudins,[6324] transfer-RNA,[6325] or in chromosomal RNA of a rat ascites tumor.[6326]

What is believed to be the first example goes back to the days of Sabatier[6327] and Senderens (1897–1919), the pioneers of organic catalytic hydrogenation involving finely divided metals, and represents an early contemporary application of what was undoubtedly then a modern technique. In 1912, Levene and La Forge[5130] reduced uridine to dihydrouridine (**127**, R = ribos-1′-yl) with hydrogen and colloidal palladium. This was a step of great significance for future nucleoside/nucleotide chemistry because there followed the observation that the sugar entity could be removed from the reduced nucleoside, to give dihydrouracil (**127**, R = H), under hydrolytic conditions much gentler than normally possible with the parent nucleoside. This was subsequently made standard practice for the routine identification of the sugar component of the nucleoside, albeit with a different mode of reduction[6328,6329] of the nitrogenous heterocyclic component. Over the next 40 or so years, platinum in its various finely divided forms was the catalyst of choice for the reduction of the 5,6-double bond of free uracil, its 1-methyl derivative, and other such substrates in a number of solvents over a range of temperatures at 1–4 atm of pressure of hydrogen.[829,1638,2032,5408,6330] Although platinum was to be overtaken by other Group VIII metals such as palladium, rhodium, and nickel, it still remained the catalyst of choice for the addition of deuterium to uracil to produce [5,6-$^2H_2$]5,6-dihydrouracil (**128**)[1978] and for the production of the 3,6-dihydro species[5162] when the hydrogenation of 2(1*H*)-pyrimidinone or its 1-methyl derivative was deliberately interrupted at the dihydro stage (**129**, R = H or Me).



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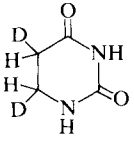

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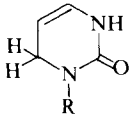
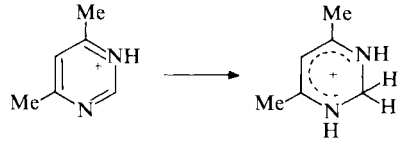
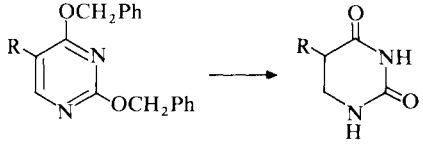


129

Although there were early isolated instances of the use of palladium in the hydrogenation of uracil and other oxopyrimidine derivatives,[1638,2032,6331] Smith and Christensen[2513] were the first to undertake a systematic investigation of the palladium-catalyzed hydrogenation of pyrimidine compounds, concentrating on a number of pyrimidinamines. In most cases, reduction stopped at the dihydro level. The configuration of the dihydro derivatives was not determined, and the investigators probably had separation problems due to hydrolytic replacement of some amino groups during the course of reduction or workup, as well as irreversible ring opening and hydrolytic decomposition in other cases. These problems were either identified or avoided in a slightly later systematic investigation with a wider range of pyrimidine compounds that were largely reduced to the 1,4,5,6-tetrahydro stage (see Section 11.2.4).[6332] However, a dihydro derivative was detected[6333] during the palladium-on-charcoal-catalyzed reduction of 2-pyrimidinamine en route to the 1,4,5,6-tetrahydro level and actually isolated[6334] with 4,6-dimethylpyrimidine as substrate, where the rate of addition of the second mole of hydrogen was practically zero. The protonated molecule was hydrolytically stable in aqueous acidic media and exhibited a singlet for the methyl groups in its ^{1}H nmr spectrum. This suggested that the cation had a symmetrical structure probably following 1,2(2,3)-addition of hydrogen to the protonated starting material (**130** → **131**). The 1,6-addition of 1 mol of hydrogen to the rings of both 5-pyrimidinamine and 5-pyrimidinol is the start of a complex sequence of reactions, described more fully in Section 11.2.4. A much later and again isolated example was the palladium-on-charcoal-catalyzed combined hydrogenolysis–hydrogenation of the *O*,*O*-dibenzylated ether (**132**, R = Me_3Si) to the reduced 5-trimethylsilyluracil (**133**, R = Me_3Si).[6335]



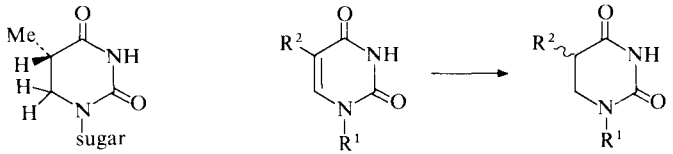
130 **131**



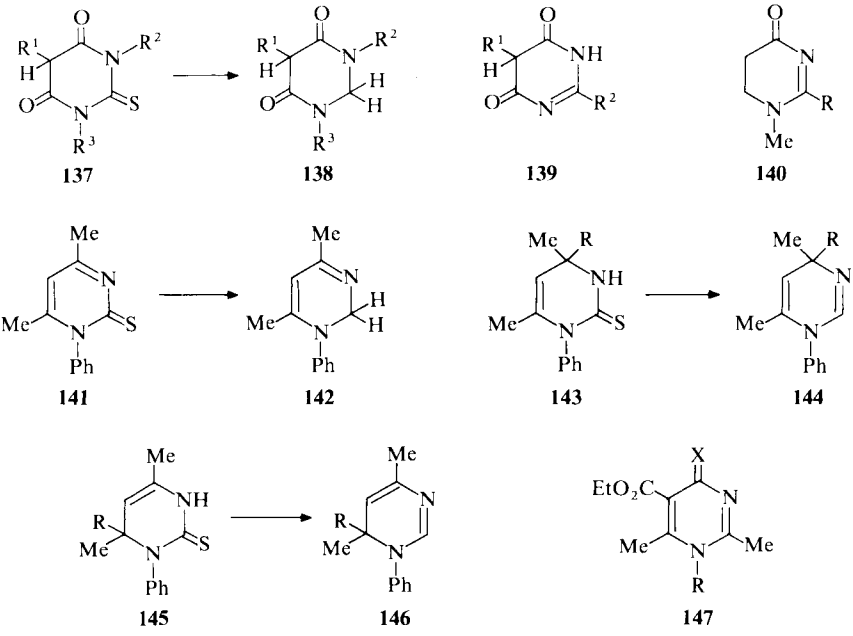
132 **133**

Following an earlier experiment with uracil and 1-methyl uracil,[3492] rhodium-on-alumina attracted attention in 1968 when it was claimed that it catalyzed the stereospecific addition of hydrogen to the 5,6-double bond of thymidine to give the *S*(−)-isomer (**134**) only.[6336] With 1-β-D-ribofuranosylthy-

mine, both diastereomers of the corresponding dihydrouridine derivative were generated (**135** → **136**, R^1 = β-ribofuranosyl, R^2 = Me).[6337] Other substrates investigated ranged from simple 5-aminouracils (**135** → **136**, R^1 = H, R^2 = NH_2 or $NMeCH_2Ph$)[6338] to the uracil component of more complex molecules such as α- and β-uridine 3′,5′-cyclic monophosphate.[6339,6340] A change in catalytic support from alumina to charcoal led to a change in diastereomeric ratio from 3 : 2 to 1 : 1 during the reduction of the 2′,3′-*O*,*O*-isopropylidene derivative of 1-β-D-ribofuranosylthymine.[6341] Rhodium-on-charcoal was also used in the hydrogenation of the 5,6-double bond of the pyrimidine ring in derivatives of uridine,[6342] isocytosine,[6343] and uracil.[6344]

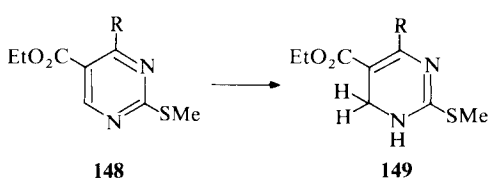


In the light of the previous emphasis in this section on the biologically important pyrimidine bases, it is not surprising that the fourth Group VIII metal, nickel (as Raney-nickel), was also used to hydrogenate the easily reduced 5,6-double bond of uracil and 1-methyluracil (**135** → **136**, R^1 = H or Me, R^2 = H).[3492] A hydrogen atmosphere was not required for this purpose, as the hydrogen adsorbed on the finely divided metal was sufficient for reduction. In more recent times, however, recognition of the affinity of Raney-nickel for sulfur has led to its widespread use for the removal of this element when it is part of the heterocyclic ring or a substituent.[6345] Thus it smoothly dethiates *and* reduces the C2 thiocarbonyl part of various 2-thiobarbiturates to CH_2, thereby giving the corresponding 1,2-dihydropyrimidine derivatives: for example (**137** → **138**, R^1 = Bu, R^2 = R^3 = Ph).[6346,6347] The same type of compound resulted from catalytic hydrogenation under pressure of the 1,2-double bond in 5-substituted 4,6-pyrimidinediones (**139**, R^1 = Et or Ph, R^2 = H; or R^1 = H, R^2 = Et).[6348] Dethiation alone occurred with 5,6-dihydro derivatives of both 4-thio- and 2-thiouracils [e.g., (**140**, R = SH) → (**140**, R = H)].[6349] Various simpler 2-pyrimidinethiones gave specific specimens of 1,2-, 1,4-, and 1,6-dihydropyrimidines of unequivocal structure. Thus reductive dethiation of **141** with Raney-nickel under methanol *and* hydrogen gave the 1,2-dihydro compound (**142**); in the *absence* of hydrogen gas, dethiation alone occurred with a number of 2-pyrimidinethiones to give the isomeric 1,4- and 1,6-dihyropyrimidines [**143** → **144** and **145** → **146** (R = H or Me)].[3922,6292,6350] Reductive dethiation of the 4-thione group in **147** (X = S, R = $PhCH_2$ or aryl) was also brought about in the presence of hydrogen to give a 1,4-dihydropyrimidine containing an electron-withdrawing group in the 5-position (**147**, X = H_2, R = $PhCH_2$ or aryl) that was the aza-analog of a dihydropyridine that served as a model compound for NAD(P)H.[320]



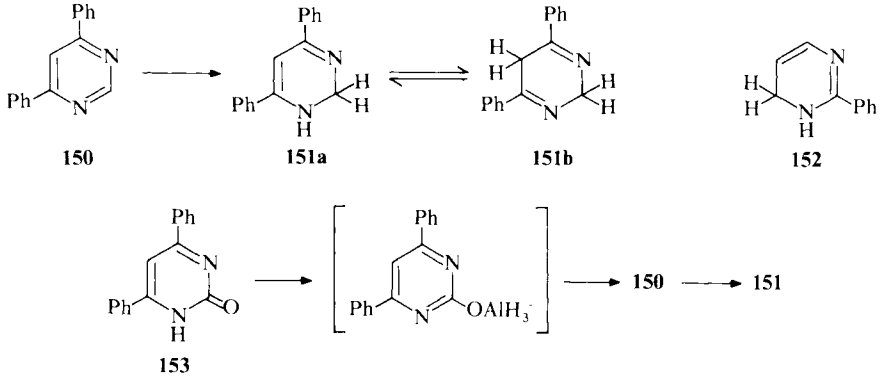
Complex metal hydrides, which in effect act as a source of hydride ions, represent another large group of reducing agents.[6323] Over the past four decades they have given mixed results with a relatively limited range of pyrimidine compounds compared with their counterparts in the pyridine series. The reagents have been overwhelmingly the nucleophilic and basic anions of lithium aluminum hydride (LAH) and lithium, potassium, or sodium borohydrides (LBH, KBH, or NaBH, respectively) with the occasional alkyl or other derivative of the latter. Until relatively recently, there was a pronounced tendency to concentrate on the biologically important pyrimidine bases and the medically important barbiturates as substrates.

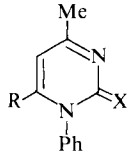
Early work showed that a variety of ethyl 4-substituted-2-methylthio-5-pyrimidinecarboxylates were reduced to the 1,6-dihydro compounds by LAH, NaBH, and LBH (**148** → **149**, R = Cl, CN, Me, OH, CH:NOH).[2695] Sometimes at lower temperatures (− 70°) preferential reduction of the 5-ester grouping to an hydroxymethyl group occurred.



The level of electron deficiency of the pyrimidine ring is crucial to reduction by these negatively charged reagents. Thus NaBH does not reduce pyrimidine

itself nor its 4,6-dimethyl derivative, but it does attack the corresponding methiodides (affording unidentified products), the positive charge now taking the electron deficiency in the ring beyond the critical level. The more powerful LAH (in refluxing ether) reduces pyrimidine readily (possibly to the 1,2,3,4-tetrahydro stage)[6332] but leaves 4,6-dimethylpyrimidine substantially unchanged,[6352] probably because of deprotonation of a methyl group by the basic LAH to form an anion that resists attack by the negatively charged reducing agent on account of the electrostatic repulsion involved. A similar rationalization explains the ability of KBH to reduce 1,3-dimethyluracil to its 5,6-dihydro derivative (**135** → **136**, R^1 = Me, R^2 = H, NMe for NH) but to leave uracil itself unchanged. However, derivatives of uracil like uridine, when simultaneously irradiated with uv light, undergo reduction at the 5,6-double bond by NaBH[6353] because the double bond has now assumed some free-radical character. The vacant 2-position in 4,6-diphenylpyrimidine (**150**) is attacked by LAH to give the 1,2-dihydro compound (**151a**), which in solution exhibited enamine–imine tautomerism (**151a** ⇌ **151b**).[137,6354] In 2-phenylpyrimidine, the 2-position was blocked and reduction occurred at the vacant, and therefore less hindered, 4(6)-position to give a 1,6-dihydro compound (**152**).[137,145] The acidic nature of the NH proton in 4,6-diphenyl-2(1*H*)-pyrimidinone (**153**) did not prevent its reduction by LAH to the 1,2-dihydro derivative probably through the intermediacy of 4,6-diphenylpyrimidine. Similarly, deoxygenation probably was the first step in LAH reduction of 2-phenyl-4(3*H*)-pyrimidinone to the 1,6-dihydro compound (**152**). The *N*-phenyl derivatives of the 2-pyrimidinones and their sulfur analogs, in which complications due to the relatively acidic NH grouping had been eliminated, proved to be a fertile set of substances for investigation. Thus treatment of 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinone and its sulfur analog (**154**, R = Me, X = O or S) with ethanolic NaBH gave the 3,6(1,4)-dihydro compound (**155**, R = Me, X = O or S). When the solvent was switched to methanol, the oxo compound gave two more products, the isomeric 3,4-dihydro compound (**156**, R = Me, X = O) and the 3,4,5,6(1,4,5,6)-tetrahydro derivative (**157**, R = Me, X = O), the latter as the major product.[6355] In acetic acid, however, NaBH is converted into sodium acetoxyborohydride, a more powerful

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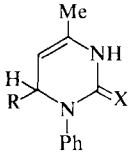
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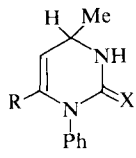
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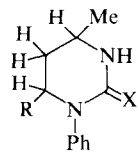
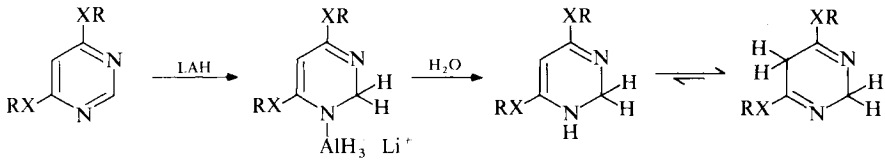
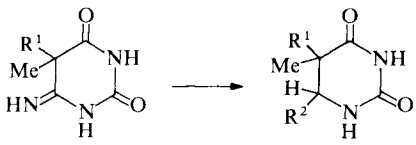

157

reducing agent.[6366] In this solvent, the reagent then reduces compounds of type **154** to the tetrahydro stage in the majority of cases, although in the reduction of the substrate (**154**, R = Ph, X = O), the 3,4-dihydro compound predominated heavily over the tetrahydro product. Both LAH and NaBH were used in the production of the 3,4- and 1,6-dihydrothiones, subsequently subjected to Raney-nickel dethiation as described earlier. Ethereal LAH with the same group of compounds based on **154** (X = O or S) frequently gave mixtures of either 3,6- and 3,4-dihydro compounds or of the tetrahydro derivative with some of the 3,4-dihydro compound.

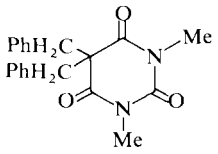
A different pattern of reduction emerged when electron-donating alkoxy and alkylthio groups were placed at the 4- and 6-positions of the pyrimidine ring (**158**). Thus LAH reduction first occurred at the unprotected 2-position to give **159** and thence after aqueous workup the 1,2-dihydro compound (**160**). In solution, this underwent rapid imine–enamine rearrangement to the significantly more stable 2,5-isomer, the double cyclic imine form (**161**), which in some cases was isolated in solid form (e.g., **161**, RX = MeO, EtO, Bu^{t}O, EtS, or PhS).[6354]


158 159 160 161

The substituted borohydride, sodium cyanoborohydride and its deuterium counterpart, reductively deaminated 6-imino-5-(α-thyminyl)-5,6-dihydrothymine (**162**, R^1 = α-thyminyl) to **163** (R^1 = α-thyminyl, R^2 = H or D). The protio product proved to be identical with the principal photoproduct obtained from uv irradiation of calf thymus DNA.[5623] Both methanol and water adducts (**163**, R^1 = α-thyminyl, R^2 = OMe or OH) could also be isolated.


162 163

With the pharmacologically and medically important barbiturates, preferential reduction of the 4- and 6-oxo substituents over the 2-oxo substituent occurred but to a CHOH entity and not to a CH_2 grouping.[6356-6361,6367] Thus **164** with methanolic NaBH gave the 6-hydroxydihydrouracil (**165**) and the *trans*-4,6-dihydroxy derivative of a tetrahydropyrimidine (**166**). The product (**165**) could be reduced separately to **166**, which isomerized to the more stable *cis*-form in the presence of strong base or dilute mineral acid.[6356]



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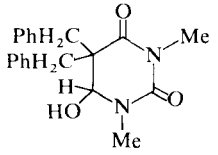

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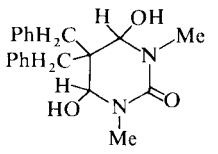

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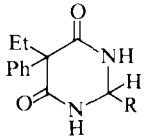
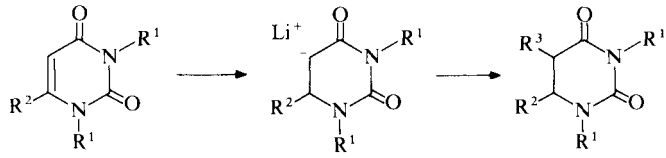


167

The CH_2 grouping in the 2-position of the important anticonvulsant, pyrimidone (**167**, R = H), resulted from NaBH reduction of certain 2-alkoxy derivatives (**167**, R = MeO to $C_6H_{13}O$) but not a 2-oxo substituent.[6362]

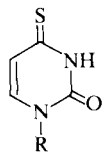
The 5,6-double bond of the *N*,*N*′-disubstituted uracils (**168**, R^1 = Me, CH_2Ph, CH_2OCH_2Ph; R^2 = H) (but not uracil itself) and of methyl orotates (**168**, R^1 = Me etc., $R^2 = CO_2Me$) is specifically reduced by lithium tri-*s*-butylborohydride, "L-Selectride," to give the corresponding derivatives of **169** and **170** (R^1 = Me etc., $R^2 = R^3$ = H).[6363] This reagent gave better yields than the potassium equivalent[6364] and substituents like F or $C{\equiv}CSiMe_3$ in the 5-position, which might not survive alternative hydrogenation methods like catalytic reduction,[2158] remained unaffected. An additional advantage was that alkylating agents such as ethyl or benzyl bromide could be used to trap the intermediate anion with formation of the 5-substituted dihydrouracil (**170**, R^2 = H, R^3 = Et or CH_2Ph).



168 **169** **170**

Aqueous NaBH, aided by simultaneous irradiation with uv light, now rapidly reduced the 5,6-double bond of certain 4-thiouracils (**171**, R = H or ribosyl).[6365] The NaBH reduction of the highly electron deficient ring in the cation of **172** (X = Br or I) was accompanied by one of the rare "thio-Claisen" rearrangements of pyrimidine chemistry to give the product **173** (R = H).[896]

Reductions using *electrophilic* hydride reagents are definitely in a minority. One isolated example is the borane–THF (tetrahydrofuran) reduction of uracil derivatives with electron-withdrawing CO_2H or CO_2Et groups in the 5-position: 5,6-dihydro compounds resulted, accompanied by decarboxylation in the



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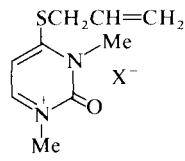

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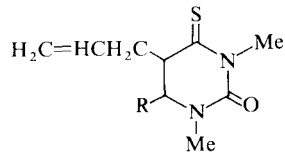

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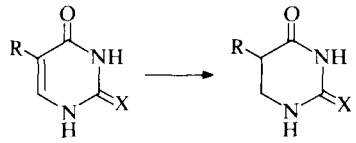

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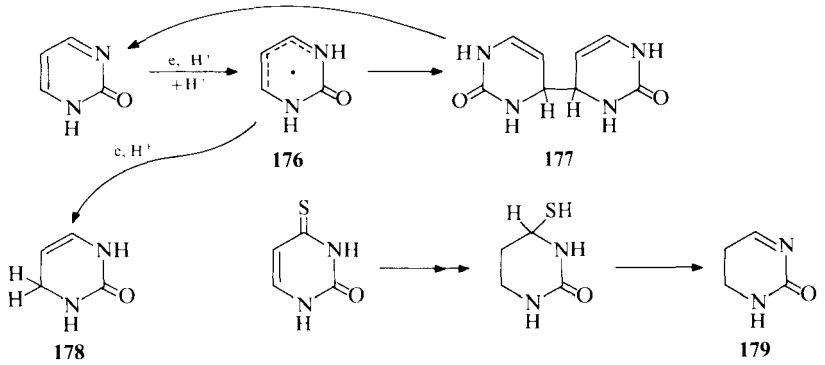
case of the free carboxylic acid [(**174**, R = CO_2H, X = O or S) → (**175**, R = H, X = O or S); (**174**, R = CO_2Et, X = S) → (**175**, R = CO_2Et, X = S)].[6368] Uracil or thiouracil could not be reduced by borane.

Electrochemical methods of reduction constitute the third set of techniques that have been applied, with mixed results, to pyrimidine and a lopsided selection of its derivatives, especially the biologically important bases, whether free or combined in nucleosides and nucleotides.[6369]

The behavior of pyrimidine itself during polarographic reduction depends on the pH of the aqueous solution. In acidic solution, two 1-electron waves are observed while in a neutral medium, two 2-electron waves are observed. In alkaline solution, a 4-electron reduction is effected via 1,6-dihydropyrimidine,[6370] to give a tetrahydropyrimidine,[6370-6376] whose structure could not be deduced unequivocally from its uv spectrum, probably the only spectroscopic technique readily available at the time to the investigators.

2(1*H*)-Pyrimidinone, the stable tautomer of 2-hydroxypyrimidine, is almost unique among substituted pyrimidines. It is one of the few pyrimidine compounds with which, in addition to the elucidation of electrochemical parameters such as the number of electrons participating in the reduction process, macroelectrolysis has also been carried out with a view to identification of products. In aqueous tetramethylammonium bromide, 2(1*H*)-pyrimidinone exhibits two reduction waves. Preparative electrolysis at the potential of the first wave gave a solid dimeric reduction product consisting of two molecules of reduced pyrimidinone. On the other hand, electrolysis on wave 2 led to the formation of two products, one of which was identical with that formed on wave 1. The other was identified as 3,6-dihydro-2(1*H*)-pyrimidinone,[6369] identical with the product from the interrupted catalytic hydrogenation of 2(1*H*)-pyrimidinone (viz., **129**, R = H).[5162] The pathway for the electrochemical reduction of 2(1*H*)-pyrimidinone can consequently be formulated as involving first the addition of one electron and a proton to the substrate forming a resonance-stabilized free radical (**176**). This has a choice of dimerizing to give **177**, a structure in accord

with both ^{1}H nmr and X-ray spectral data, or of accepting a second electron and a second proton to give **178**. 1,3-Dimethyl-2(1*H*)-pyrimidinone (cation) duplicated the behavior of the parent molecule by forming both a dihydro derivative (**178**, NMe for NH) and a dimeric product (**177**, NMe for NH).[6377] 4,6-Dimethyl-2(1*H*)-pyrimidinone afforded only a crystalline dimer, confirmed as a tetramethylated derivative of **177** by X-ray diffraction studies.[5377] These dimers revert to the monomers on uv irradiation; they may also undergo acid-catalyzed covalent hydration.[5376] These two extra factors, in addition to the instability of some reduced pyrimidines toward atmospheric oxygen, illustrate some of the difficulties inherent in the isolation of such compounds.

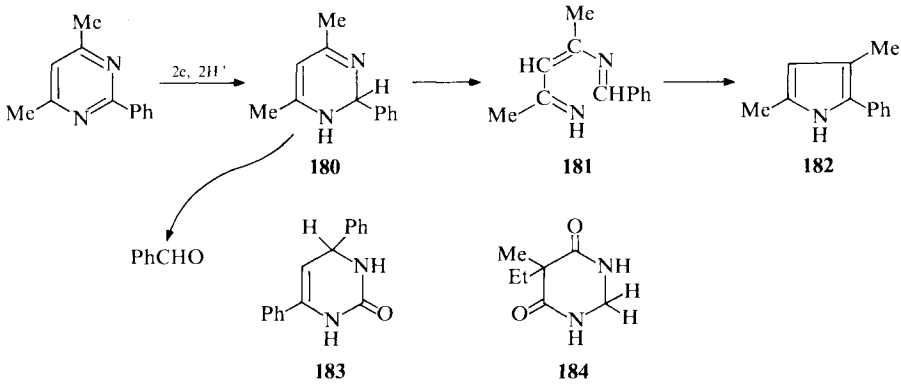


Cytosine in acidic media undergoes a three-electron reduction that involves the elimination of ammonia. The resulting 2(1*H*)-pyrimidinone then undergoes a one-electron reduction as described earlier. In neutral media, deamination of the intermediate is only partial, and it is possible to detect both 5,6-dihydro- and a tetrahydrocytosine as minor products.[6369] The reductions of 4-pyrimidinamine and its 2,6-dimethyl derivative also involve deamination, but the reduction of 2-pyrimidinamine does not. Depending on the conditions, 3,4-dihydro-2-pyrimidinamine is formed as well as an unstable photodissociable dimer. The latter is readily isolable when 1-methyl-2(1*H*)-pyrimidinimine is reduced, and it has a structure analogous to that of **177**.[6378]

2(1*H*)-Pyrimidinethione, together with its 4,6-dimethyl and 1,4,6-trimethyl derivatives, are reduced to dimers (e.g., **177**, S for O), but only it gives a 3,4(6)-dihydro compound on further reduction.[6379,6380] While 2-thiouracil does not undergo electroreduction in an aqueous medium, its *S*-methyl derivative undergoes a two-step reduction with elimination of methanethiol. The intermediate 4(3*H*)-pyrimidinone is then reduced to the 1,2,5,6-tetrahydro stage.[6381] The *S*-methyl derivative of 4-thiouracil first undergoes a two-electron reduction leading to elimination of methanethiol. Further reduction leads to formation of the radical (**176**), which proceeds to form the same products obtained from both 2(1*H*)-pyrimidinone and cytosine.[6382] 4-Thiouracil itself undergoes a reduction process involving the overall addition of four electrons and four protons. The

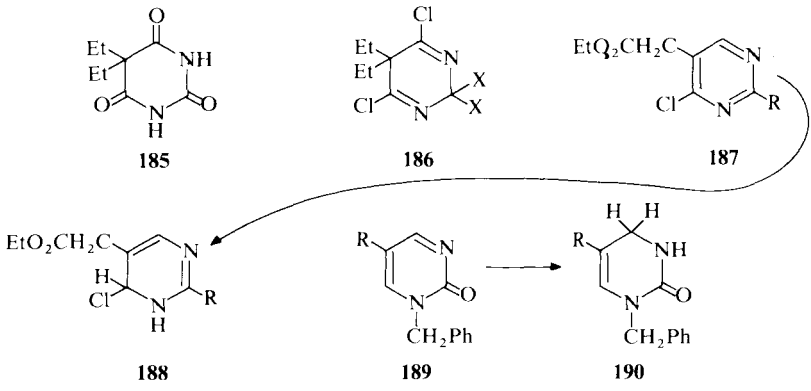
product, 4-mercapto-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, subsequently loses hydrogen sulfide to give 5,6-dihydro-2(1*H*)-pyrimidinone (**179**).[6383]

4,6-Dimethyl-2-phenylpyrimidine undergoes a two-electron reduction in an acetate buffer to give an unstable 1,2-dihydro compound (**180**) since it is readily hydrolyzed to benzaldehyde. When the reduction proceeds until four electrons are consumed, the dihydro derivative is believed to ring-open to a tautomer (**181**), which undergoes further reduction and cyclization to a pyrrole (**182**).[4695] In the absence of a 2-phenyl substituent, the initial reduction of an alkylpyrimidine is directed toward the 1,6-rather than the 1,2-double bond, leading eventually to a dimer in which each pyrimidine ring is at the dihydro level. In contrast to the results with LAH, electrolytic reduction of 4,6-diphenyl-2(1*H*)-pyrimidinone does not deoxygenate the molecule but gives the dihydro derivative (**183**).[6384] The relative ease of hydrogenolytic splitting of an exocyclic C—N bond is again exemplified by the reduction at a lead cathode of the appropriate 2-iminobarbituric acid derivative to the 2,5-dihydro compound (**184**).[6385]



A useful summary of the experimental data incorporates some generalizations regarding the ease of electrochemical reduction of substituted pyrimidines, especially tautomerizable compounds.[6386]

Dissolving metal is a reduction method remarkably underrepresented in the hydropyrimidine field, and it seems to be confined to only one metal. The earliest mention is probably the reductive removal by zinc dust and water[6387] of two chlorine atoms from a tetrachlorinated compound prepared in turn from 5,5-diethylbarbituric acid [(**185**) → (**186**, X = Cl) → (**186**, X = H)]. It is a pity that no attempt was made to confirm the structure even with the limited resources then available by, for example, hydrolytic degradation to the stable tautomer of **186** (X = H, OH for Cl), which could then be synthesized from α,α-diethylmalondiamide and formamide or formic acid (see Section 11.1.5).[6262] Zinc and acetic acid reduced both 5-methyl-2-phenyl- and 5-*p*-chlorophenyl-2-methylpyrimidine to their unstable 1,6-dihydro derivatives.[4982,6388] In the presence of a 4-chloro substituent, some 1,6-dihydropyrimidines were produced as by-products (**187** → **188**, R = C_6H_4Cl-*p*). The major reaction pathway in-



volved ring contraction to pyrroles,[6388] as was observed previously with some electrochemical reductions.[4695]

Hydrogen-transfer reduction[6389] is especially important with molecules involved in the chemistry of life, such as uracil, thymine, cytosine, and orotic acid. 5,6-Dihydro derivatives are the major metabolites of these substances as well as of others such as the antitumor derivative, 5-fluorouracil.[6390] Thus in a variety of organisms, uracil is first metabolized to 5,6-dihydrouracil by the enzyme, dihydrothymine dehydrogenase (EC 1.3.1.2; formerly known as dihydrouracil dehydrogenase), which involves the transfer of the equivalent of a hydride ion from the 4-position of the dihydropyridine ring in NADPH to the substrate in question.[6393] In the case of uracil,[6394] as well as of 5-fluorouracil and thymine,[6400] the reduction leads to overall *trans*(*anti*)-addition of hydrogen at the *Si* faces of both the *C*6- and *C*5-positions. Impure L-dihydroorotate dehydrogenase catalyzed the NADH reduction of [carboxyl-^{14}C]orotic acid to dihydroorotic acid, which was accompanied by its ring-opened hydrolysis product, *N*-carbamoyl-L-[^{14}C]aspartic acid.[6395]

Meerwein–Ponndorf–Verley reductions of 2(1*H*)-pyrimidinones with tetraisopropoxyzirconium (or much less effectively with triisopropoxyaluminum) led to exclusive formation of the 3,4-dihydro derivatives (**189** → **190**, R = H, F, Cl, Br, or I).[294]

Photochemical reduction was observed as far back as 1968 during the preparation of 5,6-dihydrouracil by irradiation of uracil.[6351] The same product was observed subsequently with 5-bromouracil, the reaction first involving reductive dehalogenation.[6396–6398] 5,6-Dihydro derivatives were obtained also from both uracil and thymine following irradiation of their aqueous solutions, which contained tryptophan and other indole derivatives as sensitizers.[6399]

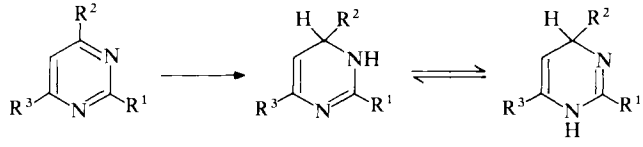
Other reductive methods are almost unrepresented. Thus the 5,6-double bonds of pyrimidinones such as uracil and its derivatives are an obvious target for the application of the many missing reduction methods, particularly for specific hydrogenation with the heavier isotopes (D_2, T_2). There seem to be no examples of reduction by diimide (the active reducing agent in a hydrazine–oxidizing agent combination), homogeneous hydrogenation, reduction by free-radical

producing agents such as the silanes, nor by electrophilic hydride agents such as derivatives of borane or alane. Hydrogen transfer, involving sources of hydrogen other than the gas, in both the presence and absence of metal catalysts, has been barely investigated outside the confines of the biologically important bases (as described earlier), nor has the effect of uv stimulation. The product of finely divided metals by the Rieke process and the effects of ultrasonication on heterogeneous reduction reactions remain to be exploited. The value of "cross-reduction," involving the use of a different type of reducing system on the product obtained from a particular reduction process, is also to be emphasized for the purpose of increasing the level of reduction of the pyrimidine substrate.

11.1.9. By Addition of Reagents Other than Hydrogen to a Double Bond

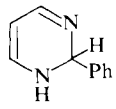
A variety of nucleophiles attack the C4-, C6-, and to a lesser extent the C2-position of the electron-deficient nucleus in pyrimidine and some of its derivatives.

Carbon nucleophiles are represented mainly by organometallic reagents based on lithium and magnesium, although copper and titanium compounds have been investigated recently. The early work was aimed at preparing the substituted (usually alkylated and arylated) pyrimidines and the dihydropyrimidine intermediates in the reactions of pyrimidines with the organometallics *at the time* were usually never isolated and seldom identified unequivocally. Instead, they were dehydrogenated in situ to the parent pyrimidines.[836,3607,4642,6401] Consequently, the reaction of the Grignard reagent, *t*-butylmagnesium chloride, with pyrimidine was assumed to occur in the 4(6)-position since subsequent oxidation with potassium permanganate afforded 4-*t*-butylpyrimidine: (**191**, $R^1 = R^2 = R^3 = H$) → (**192**, $R^1 = R^3 = H$, $R^2 = Bu^t$) → (**191**, $R^1 = R^3 = H$, $R^2 = Bu^t$).[6333] Similarly, the reaction of 4-methyl-2-phenylpyrimidine with phenyllithium was assumed to occur in the vacant 4-position (**192**, $R^1 = R^2 = Ph$, $R^3 = Me$) since subsequent oxidation yielded 4-methyl-2,6-diphenylpyrimidine (**191**, $R^1 = R^2 = Ph$, $R^3 = Me$).[4642] However, much later work[6177,6178,6402] made use of the wide variety of spectroscopic techniques not readily available to workers before 1960 to confirm the structure of the product, not as **192** ($R^1 = R^2 = Ph$, $R^3 = Me$) but as **193** ($R^1 = R^2 = Ph$, $R^3 = Me$) in the *solid* state;[6178] the existence of a tautomeric equilibrium in *solution* (viz., **192** ⇌ **193**, $R^1 = R^2 = Ph$, $R^3 = Me$), was deduced from spectroscopic examination.[6402] Ethereal phenyl-



191 **192** **193**

lithium reacts with pyrimidine (**191**, $R^1 = R^2 = R^3 = H$) to give a similar 1,6 ⇌ 1,4-dihydro tautomeric mixture, which, however, may contain at least 4% of the 1,2-dihydro isomer (**194**). In the case of 4-phenylpyrimidine, nucleophilic attack at C2 at the expense of the tautomeric mixture could be enhanced to 40% by precoupling the phenyllithium with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.[6403] The tautomeric mixture (**192** ⇌ **193**, $R^1 = H$, $R^2 = R^3 = Ph$) or its lithio derivative reacted with electrophilic reagents such as methyl iodide or methyl chloroformate to form largely *N*-substituted derivatives of the 1,6-dihydro tautomer (**193**, $R^1 = H$, $R^2 = R^3 = Ph$ with NMe or NCO_2Me in place of NH) of fixed structures.[6404] Even when all reactive positions are occupied by phenyl groups, reaction still occurs with alkyllithiums to give, for example, **195** (R = Me or Bu).[4504,4505] Heteroaryllithium reagents have also been used to form a variety of 6-heteroaryl-1,6-dihydro compounds. These isomerized on acetone-sensitized photolysis to the corresponding 5-substituted-1,2-dihydropyrimidines.[6405,6406]



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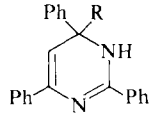

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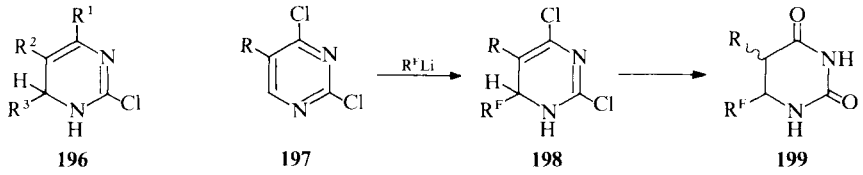
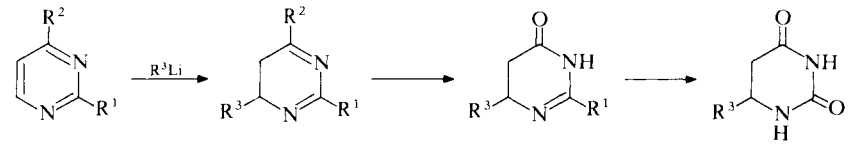
In halogenated pyrimidines, the halogen atom(s) increase the electron deficiency of the ring even further than in the parent pyrimidine. Addition of both lithium and Grignard reagents competes successfully with halogen–metal exchange, addition occurring in a vacant 4/6-position. Thus phenylmagnesium bromide, aided by a nickel chloride–phosphine complex, added to the unsubstituted position in 2,4,5-trihalogenated pyrimidines to give compounds such as **196** ($R^1 = R^2 = Cl$, $R^3 = Ph$).[3821] 2-Chloropyrimidine and a 5-aryl derivative also afforded 1,6-dihydro derivatives with the appropriate lithium reagent,[4890,6407] as did 5-chloropyrimidine with butyllithium.[6408] An investigation into the value of these reactions for the preparation of alkyl-, aryl-, and heteroarylpyrimidines from polyhalogenopyrimidines employed immediate dehydrogenation of each intermediate 1,6-dihydro compound without isolation or characterization.[3734] It was concluded that addition of the nucleophile occurred preferentially at a vacant 4/6-position; if the 2-, 4-, and 6-position were all occupied, addition to a C4/6-position still occurred, but it was followed by chloride elimination with aromatization of the product. Perfluoroalkyllithiums also reacted at the vacant 6-position of 2,4-dichloropyrimidine and its 5-methyl derivative to give 1,6(3,4)-dihydro compounds that, because of their instability on exposure to moisture, were isolated as the 5,6-dihydrouracils following acid hydrolysis in methanol (**197** → **198** → **199**; R = H or Me; $R^F = C_2F_5$, *n*-C_4F_9, *n*-C_6F_{13}, or *n*-C_8F_{17}). Only in the case of **198** (R = Me, R^F = *n*-C_6F_{13}) was the dihydro compound sufficiently stable for isolation and for its structure to be established by nmr examination.[3936] With one exception, unstable dihydro



196 197 198 199

derivatives were also isolated from the reaction of organolithiums with both 2,4-bismethylthio- and 2,4-dimethoxypyrimidines. They possessed nmr spectra very similar to that of the stable adduct from the thio compound and 2-thiazolyllithium. This featured an ABX pattern that fitted in with the two hydrogen atoms at C5 [AB] and one hydrogen atom at C6 [X] of a 5,6-dihydro species (**200** → **201**, $R^1 = R^2 =$ SMe, R^3 = thiazol-2-yl).[562] The 5,6-dihydro intermediates could be regioselectively hydrolyzed to the respective 2-methylthio- and 2-methoxy-6-substituted-5,6-dihydro-4(3*H*)-pyrimidinones (**202**; R^1 = SMe or OMe; R^3 = alkyl, aryl, or heteroaryl). The methoxy compounds were hydrolyzed further on stronger acid treatment to the 6-substituted dihydrouracils (**203**, R^3 = alkyl, aryl, or heteroaryl). 5-Bromo-2,4-bismethylthiopyrimidines also reacted with a variety of organolithiums, but the intermediate 6-substituted-5,6-dihydropyrimidines underwent spontaneous dehydrobromination to the heteroaromatic 6-substituted pyrimidines.[6409] By contrast with 5-chloropyrimidine,[6408] 5-bromopyrimidine and butyllithium formed 5-lithiopyrimidine because, on quenching with deuterium oxide, 5-deuteropyrimidine was formed.[6410] In certain circumstances, such 5-lithio compounds add to the 6-position of the substrate from which they were formed to give dihydro derivatives of various 4,5′-bipyrimidines.[6411] This was also the case with 5-bromo-4-lithiopyrimidine, obtained by direct metalation of 5-bromopyrimidine with the very strongly basic lithium diisopropylamide, which then added to the 1,6-double bond of unreacted bromo compound.[5620]



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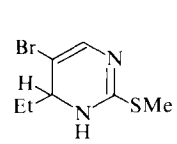
The bromine atom in 5-bromo-2-methylthiopyrimidine denudes the ring of electrons to such an extent that it now adds the more weakly nucleophilic Grignard reagent, ethylmagnesium bromide, to form the 6-ethyl-1,6-dihydropyrimidine (**204**).[1890] The 5-ethoxycarbonyl group in ethyl 4-methyl-2-methylthio-5-pyrimidinecarboxylate also fulfilled a similar electron-withdrawing function. Reaction with phenylmagnesium bromide gave the 6-phenyl-1,6-dihydro adduct (**205**).[2291] Grignard reagents react with the cyano group in 2- and 4-pyrimidinecarbonitriles, but the 5-pyrimidinecarbonitrile (**206**, R = H) reacted at its vacant 6-position with ethylmagnesium bromide to give **207**.[3048]

The dimethoxy compound (**206**, R = OMe), on the other hand, reacted at its already substituted 2-position to give **208**. Unsubstituted 4,6-dialkoxypyrimidines require the more powerfully nucleophilic alkyllithiums to react,[1787,6412] each giving as a final product the 2,5-dihydro derivative, perhaps by tautomeric isomerization of an initial and less stable 1,2-dihydro compound resulting from attack at the unoccupied 2-position (**209** → **210** → **211**).[6412]



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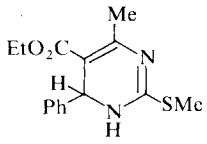

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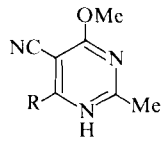

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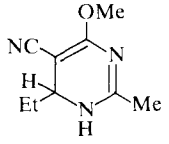

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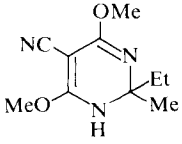

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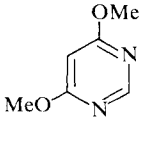

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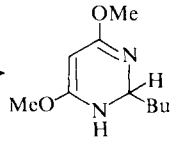

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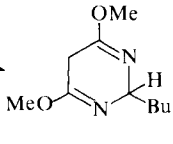

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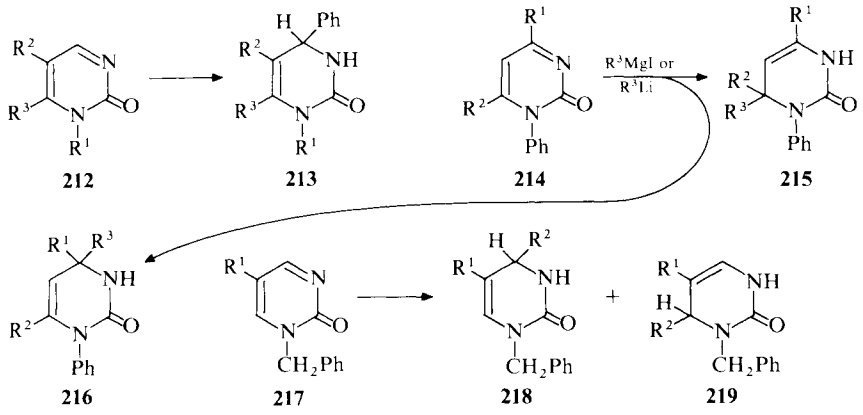
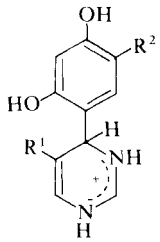
The relatively acidic proton of the NH grouping of 2(1*H*)-pyrimidinones is incompatible with the strongly basic organometallics, causing decomposition of the latter reagents to the parent hydrocarbons. Consequently it must be replaced by an nonacidic alkyl or aryl group before nucleophilic attack by the reagent can take place successfully. Early work concentrated on the reaction of phenyllithium with 1-alkyl-2(1*H*)-pyrimidinones that gave the 3,4-adduct regardless of whether a phenyl group was absent[6413] or present at the 5-position[4024,6414] or the 6-position[6416] of the ring (**212** → **213**; R^1 = alkyl, R^2 = R^3 = H; R^1 = alkyl, R^2 = Ph, R^3 = H; R^1 = alkyl, R^2 = H, R^3 = Ph). A later and more extensive investigation[4645] involved the reaction of both Grignard reagents and their lithium counterparts with various 1-phenyl-2(1*H*)-pyrimidinones and their sulfur analogs. Thus 1-phenyl-2(1*H*)-pyrimidinone (**214**, R^1 = R^2 = H) reacted with methylmagnesium iodide to give only the 3,6-dihydro derivative (**215**, R^1 = R^2 = H, R^3 = Me). By contrast, methyllithium gave exclusively the regio 3,4-isomer (**216**, R^1 = R^2 = H, R^3 = Me). When the pyrimidinone contained methyl groups (**214**, R^1 = R^2 = Me), reaction with methylmagnesium iodide afforded a mixture of two isomers in which **215** (R^1 = R^2 = R^3 = Me) predominated by 19 : 1. Methyllithium also produced a mixture, but one in which the other isomer (**216**, R^1 = R^2 = R^3 = Me) predominated by a like margin. This reversal in behavior was also noted in the 2-thio analogs reaction with methylmetallics. However, ethyl- and isopropyllithium gave exclusively the 3,4-dihydro isomer (**216**, R^1 = R^2 = Me, R^3 = Et or Pr^i). It was concluded that alkyl Grignard reagents attack the 6-position in preference to the 4-position of such pyrimidinones, while alkyllithiums attack predominantly the 4-position.



The size of the alkyl group of the Grignard reagent influenced the ratio of the two dihydro derivatives (**215** : **216**).[4645,6417] The discovery that 1-substituted-2(1*H*)-pyrimidinones inhibited mitosis prompted a second and slightly later look at this reaction. 1-Benzyl-2(1*H*)-pyrimidinone and its 5-chloro, 5-bromo, and 5-iodo derivatives were the substrates, and the organometallics included methyl and phenyl Grignard reagents, lithiums, and lithium cuprates.[219] Methyllithium was the only reagent that exhibited complete regioselectivity, and that only with the parent compound (**217** → **218**, R^1 = H, R^2 = Me). The percentage of **218** (R^1 = H, R^2 = Me or Ph) dropped off and that of **219** (R^1 = H, R^2 = Me or Ph) steadily increased with the use of lithium diphenylcuprate (85% of **218**), lithium dimethylcuprate (60%), methylmagnesium iodide (43%), until with both phenyllithium and phenylmagnesium bromide, isomer **218** (R^1 = H, R^2 = Ph) was very much the minor component (8%) in the mixture with **219** (R^1 = H, R^2 = Ph). The 5-chloro and 5-bromo compounds gave mixtures of the two adducts, with isomer **218** (R^1 = Cl or Br, R^2 = Me or Ph) predominating in half of the reactions. The 5-iodo derivative reacted with only two of the six organometallics investigated (viz., methylmagnesium iodide and lithium dimethylcuprate), a result attributed to the bulkiness of the iodine substituent and its relatively low electronegativity. However, complete regioselectivity was achieved when phenyl-, *p*-methoxyphenyl-, and *p*-chlorophenyltriisopropoxytitanium reagents[222] were used with the foregoing 1-benzylpyrimidinone substrates as well as some 1-methyl, 1-benzyloxymethyl, and 1-*p*-chlorobenzylthio analogs. The new carbon–carbon bond was formed at C4 with exclusive formation of the 3,4-isomer (**218**; R^1 = H, Cl, Br, or I; R^2 = aryl). The only other organometallic reagent investigated in this field seems to be zinc. Certain 1-aryl-2(1*H*)-pyrimidinones were found to react with α-halogenoesters in the presence of zinc (the Reformatsky reaction). A mixture of the 3,4- and 3,6-adduct was formed, in which the former predominated (e.g., **214** → **215** mainly + **216**, R^1 = R^2 = H, R^3 = CO_2Et or $CHMeCO_2Et$).[61]

Pyrimidine and 5-methylpyrimidine exist as the protonated species in trifluoroacetic acid. The electron density in the ring of these species is again

markedly reduced, and these species can function as effective electrophiles. They can bring about monosubstitution (and in some cases, disubstitution) in the electron-rich rings of phenols such as resorcinol to form salts containing the cations of dihydropyrimidines like (**220**, R^1 = H or Me, R^2 = H).[4635]



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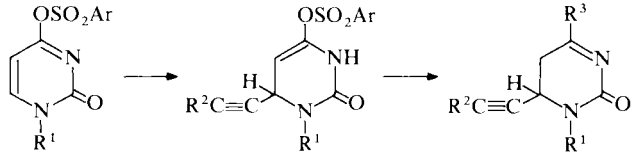
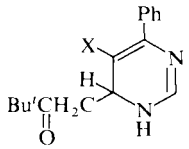
Other examples of carbanionic attack on pyrimidines include the attachment of acetylide anions at C6 of 3′,5′-bis-*t*-butyldimethyl-silylated derivatives of triisopropylphenylsulfonyluridine, followed by treatment of the adduct with other nucleophiles such as methanol or diethylamine to give 5,6-dihydro derivatives (**221** → **222** → **223**; R^1 = protected sugar; R^2 = Ph, R^3 = OMe; R^2 = $SiMe_3$, R^3 = NEt_2).[6420] There are also a few examples of reactions involving carbanions derived from carbonyl compounds. Thus the enolate anion of pinacolone in liquid ammonia not only replaces the halogen atom in electron-deficient 5-halogeno-2-phenylpyrimidines by an $S_{RN}1$ mechanism but also adds to the 1,6-bond in the ring to give isolable adducts (e.g., **224**, X = Cl or Br).[5991] The 1,6-bonds in the highly electron-deficient rings of nitropyrimidinones[3414] and chloropyrimidinecarboxylates[733] also add acetone and other carbonyl compounds to give crystalline adducts (e.g., **225**, R^1 = R^2 = H, R^3 = NO_2; **225**, R^1 = Me, R^2 = CO_2Me, R^3 = Cl).



221 **222** **223**



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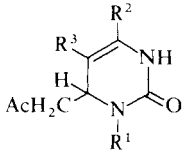

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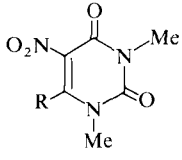
Because of the biological importance of the parent molecules, nucleophilic addition to the C5—C6 enaminic double bond of uracil and thymine is a topic

that has generated a wealth of literature. Most additions to uracils, especially those catalyzed by base, are reversible unless the uracil derivative possesses an electron-withdrawing group at C5.[476] Hence cyanide ion adds to C6 of the 5-nitrouracils (**226**, R = Me or Et) to give isolable stable adducts of one diastereomeric configuration (**227**, R = Me or Et).[1906] Similar dihydro intermediates are involved in the transformation by cyanide ion of 5-bromouracils into 6-cyanouracils,[2671] and of certain 5-nitrouracils into nitroresorcinols.[5873] The conversion of 5-cyano-1,3-dimethyluracil into bicyclic products starts with nucleophilic attack at C6 by a variety of carbanions.[6421] Potassium cyanide causes extra ring formation with the 6-bromomethyl compound (**226**, R = CH_2Br) yielding the cyclothymine derivative (**228**). Dimethyloxosulfonium *methylide*,[112,5266] metal carbenes,[6422,6423] and dichlorocarbene[6422] are also reagents that construct a fused three-membered ring on to the 5,6-bond of uracils and other pyrimidinones. Trichlorogermane (Cl_3GeH) does not function as a source of the germanium analog (Cl_2Ge:) of dichlorocarbene. Instead, it adds to the 5,6-double bond of *N*-acetylated uracil and 5-fluorouracil, giving the Michael-addition products (**229**, R = H or F).[6424] The borane reduction of uracils mentioned earlier[6368] probably proceeds by initial hydroboration, specifically, the addition of the elements of borane across the 5,6-double bond. As might be expected,[6333] a 5-nitro group in 1,3-disubstituted uracils also facilitates reduction of this double bond by nucleophilic attack of borohydride ion with the formation of products such as **230**.[3995]



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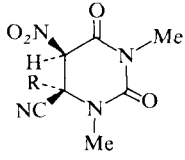

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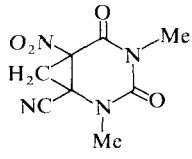

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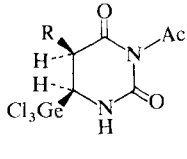

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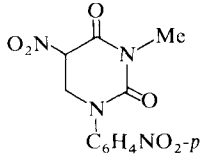

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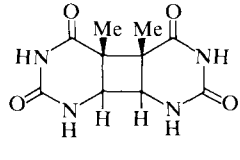
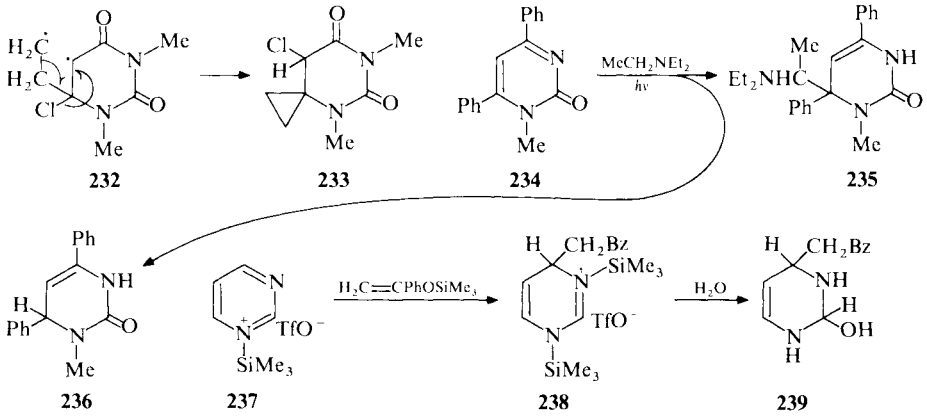


231

The formation of cyclobutane dimeric products, in which each of the two pyrimidine rings has attained the dihydro level of reduction, is considered to be one of the major classes of DNA lesions involved in the cytotoxicity of uv radiation, especially below 300 nm.[6425,6426] Such photodimers, especially of the *cis–syn* variety (**231**) derived from thymine, exist in nucleosomal DNA after uv irradiation[6427] and form the major type of cyclobutane dimer following γ-radiolysis of aqueous solutions of thymine itself at 77 K.[6428] Photodimerization

reactions have also been observed with 5-fluorouracil,[6429] methylcytosines,[6430] a pyrimidinone derivative,[6431] and 1,3-dimethylthymine.[6432] Four-membered carbocyclic rings fused onto the 5,6-bond of uracil and of its cogeners, also result from photocycloaddition reactions with alkynes or alkenes.[5389,6433-6439] Sometimes an intermediate in these reactions is deflected down a reaction path that leads to a ring that is not four-membered. Thus one of the products obtained from acetone-sensitized irradiation of 6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione with ethylene is **233**, formed by a rearrangement in the biradical intermediate (**232**); its chlorine atom can be removed subsequently by zinc and acetic acid.[6433] Of biological significance is the cyclobutane ring formation that results from the photocycloaddition of thymidine residues to the activated olefinic double bonds of the photosensitizing drugs known as *psoralens*,[6440-6443] other coumarins,[5388] and deaminated metabolites of histidine.[6445]

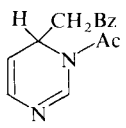
Another C—C bond formation reaction occurs during the irradiation of 2(1*H*)-pyrimidinones in the presence of hydrogen donors such as ethers,[3842] sulfides,[3842] and amines.[3923] Thus the compound (**234**) with aliphatic amines gave mainly the 1 : 1 3,6-adduct (**235**). A minor product was the 3,6-dihydro derivative (**236**), identical with the NaBH-reduction product from **234**.[3923] Aromatic amines gave only the analogous 1 : 1 adducts. The quaternary salt (**237**) derived from pyrimidine and trimethylsilyl triflate adds silylated enol ethers to give a charged 1,4-dihydropyrimidine intermediate (e.g., **238**). Aqueous workup afforded a covalent hydrate of the dihydropyrimidine species (**239**), which was now formally at the tetrahydro level of reduction.[6444] *N*-Acylpyrimidinium tetrafluoroborates undergo analogous reactions, and some dihydropyrimidines such as **240** were isolated in almost pure form.[6446]



232 **233** **234** **235**

236 **237** **238** **239**

Nitrogen nucleophiles are also well represented. Thus, when pyrimidine is added to potassium amide in liquid ammonia, the solution is stable for several days at $-70°$ and contains the anion (**241**, R = X = Y = H) of 1,4 (or 1,6)-dihydro-4-pyrimidinamine.[6447] However, no spectroscopic indication of these



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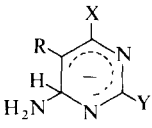

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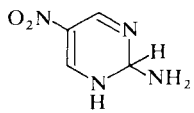

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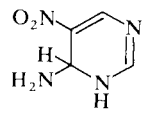

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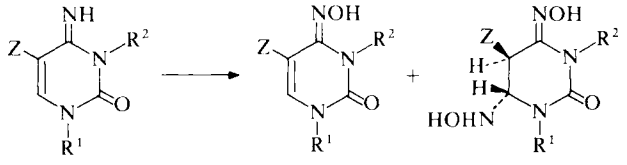
σ-adducts was obtained starting with 2-alkylpyrimidines. They were undoubtedly present since, in the presence of potassium permanganate in the liquid ammonia solution, dehydrogenation to the corresponding aromatic 2-alkyl-4-pyrimidinamine occurred.[479] 5-Phenylpyrimidine gives a similar intermediate (**241**, X = Y = H, R = Ph), some of which is involved in a ring opening–ring closing sequence leading to the 5-phenyl-2-pyrimidinamine accompanying the 4-isomer in this traditional Chichibabin amination occurring in the absence of permanganate.[534] Ammonia itself, a much weaker base than the amide ion, initially adds across the N1—C2 azomethine bond of the highly electron-deficient ring of 5-nitropyrimidine to give 5-nitro-1,2-dihydro-2-pyrimidinamine (**242**). With time, this kinetically controlled adduct is converted into the more stable isomer (**243**) following addition of ammonia at C4(6).[6448] Other Group V nucleophiles, known to add to the 4(6)-position of the electron-denuded ring of 5-nitropyrimidine, are azide ion[4768] and dialkyl phosphites.[6449,6450] The ring of certain quaternized pyrimidine derivatives is also sufficiently electrophilic that ammonia (free of amide ion) adds to the 6-position or, if the latter is blocked, to the 2-position.[3441,4584,4918] Anions similar to **241** and related types of σ-adducts[6451] play a part in the indirect substitution of the halogen atoms in halogenated pyrimidines. They also are implicated in various ring transformations of pyrimidines[6452] such as the change of various *N*-substituted pyrimidinium salts into pyrazoles[5831,6453] (brought about by hydrazine) or into pyrimidine 1-oxides[5905] (brought about by hydroxylamine), as well as the rearrangement of quaternized 2-alkylpyrimidines into 2-alkylaminopyridines (brought about by methylamine).[4717] Other transformation reactions of the pyrimidine ring, that involve initial addition at the *C*2- or *C*6-position, make use of ambident nucleophiles such as amidines,[2942,4639,4769] guanidine, and thiourea derivatives.[6454] The physical isolation of most, if not all, σ-adducts formed between pyrimidine and nitrogen-containing nucleophiles is most difficult since it is now firmly established that such adducts readily undergo ring-opening.[6451,6455] However, there are hopes that the addition of amines and hydrazine to the 5,6-double bond of certain 1,3-disubstituted 5-nitrouracils may be exceptional in this respect.[3995,4768] (footnotes!)

The reactions of the biologically important pyrimidine bases with certain nitrogen nucleophiles, particularly hydroxylamine, have attracted attention. Cytosine and its derivatives (**244**) undergo replacement of the 4-amino or imino group to give **245** accompanied by a predominantly *trans*-addition of hydroxylamine across the 5,6-enamine double bond to give a second product (**246**, Z = H or F); the ratio of these products is dependent on the pH of the reaction



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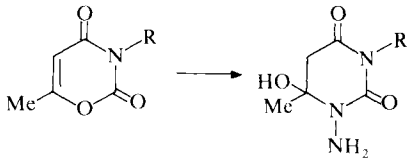
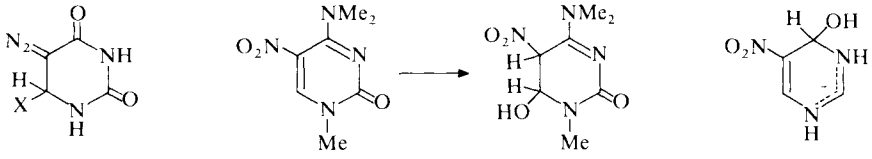


247 248

medium.[1261] Solvent plays a part in the process since reaction of the methylcytosines in heavy water is accompanied by partial deuteration at C5.[6456] Strongly acidic conditions cause elimination of hydroxylamine from **246**.[6457,6458] The addition of hydroxylamine to uracil and 5-halogenated uracils also proved reversible[6459] and was an intermediate stage in the dehalogenation of the 5-bromo and 5-iodo compounds.[6460] Other instances of the probable initial attack of a nitrogen nucleophile at C6 of a uracil derivative are known,[1128,6461,6462] while the reaction of the ε-amino group of lysine with the photoexcited thymidine molecule has important biological implications.[6463] Finally in this subsection, nucleophilic attack at the *C*2-carbonyl grouping of a different heterocylic system, the oxazine (**247**), by hydrazine constitutes a synthesis of the 5,6-dihydropyrimidine molecule (**248**).[6183]

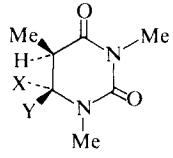
Oxygen nucleophiles require a ring or double bond severely denuded of electrons by electron-withdrawing groups before attachment by actual covalent bonds will occur although water easily forms crystalline hydrates[6464] or hydrogen bonds in solution to entities such as carbonyl groupings that are part of the pyrimidine ring.[6465] Thus 5-diazouracil readily forms a 1,6-hydrate (**249**, X = OH) in water as well as a similar adduct with methanol (**249**, X = OMe).[2672,6466] Although there is no apparent ionizable proton in the 5-nitro compound (**250**), it does have an acidic pK_a of 9.04. This has been ascribed to the hydroxyl proton of the covalent hydrate (**251**), formed by hydration of the electron-poor 5,6-double bond.[4768] The positive charge in the pyrimidinium cation obviously enhances the electron deficiency of the ring, rendering it an even more attractive target for nucleophiles, even weak ones like water. Hence



249 250 251 252

5-nitro-, 5-methylsulfonyl-, and 5-methylsulfinylpyrimidine in aqueous acid are completely converted into the hydrated cations such as **252**.[2560,5728] The presence of even a small percentage of hydrated species in aqueous solution can play a vital role in the reactions of pyrimidine derivatives, for example, in the rapid acid-catalyzed deuteration of 2(1*H*)-pyrimidinone[5225] and in various halogenation reactions (described later) that proceed through such hydrated molecules. A 5-nitro group also renders the ring in pyrimidine or 2-methoxypyrimidine susceptible to attack by methoxide ion at C2 and C4, respectively.[946,6467] Similarly, the *C*6-position in 1,3-dimethyl-5-nitrouracil is vulnerable to attack by a whole series of nucleophiles including the hydroxyl ion[5724] and the ethoxide ion; the latter gives rise to a stable crystalline sodium salt of the Meisenheimer type.[1735]

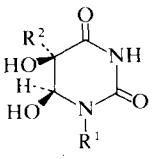
The formation of dihydropyrimidine compounds by *photohydration* has accumulated a large literature over the past decade or so. This particularly applies to the biologically important pyrimidine bases and their *N*-alkyl derivatives whose photoexcited molecules undergo additions to their 5,6-double bonds. Thus radiation of 1,3-dimethylthymine with long-wavelength light gave both stereoisomeric forms (**253** and **254**) of the photohydrate.[6468] The analogous photohydration of aqueous 1,3-dimethyluracil has been suggested as the basis for a chemical actinometer, both for photoreactions with low efficiency and for irradiation between 240 and 280 nm.[6469–6471] Other photohydrates are known from uracil and 5-fluorouracil,[5310a,6466,6472–6474] cytidine,[6475] cytidylic acid,[6475,6476] and 1,N^4-dimethylcytosine.[6477] With alcohols, α-hydroxyalkyl radicals are involved so that 1,3-dimethylthymine in ethanol gives *cis*- and *trans*-6-α-hydroxyethyl-1,3-dimethyl-5,6-dihydrothymine (**255** + **256**) as the major products.[6478] Similar adducts were noted with the 1,3-dimethyl derivatives of both uracil and thymine in 2-propanol solution[6396,6479] and with the former in both ethanol and 2-propanol.[6480] Analogous adducts also arose from treatment of pyrimidine bases with alcoholic solutions of free-radical initiators such as di-*t*-butyl peroxide,[6479,6481] supporting the intervention of α-hydroxyalkyl radicals in the photochemical experiments. Photoreduction of the 5,6-double bond sometimes accompanied the photoaddition,[6351,6477,6482] as did photodimerization,[5352,6477] as distinct from the photolysis of various pyrimidinones in the presence of a tertiary amine[6483] or C—C bond formation in the presence of primary amines[6484] or of ethers[6485,6486] mentioned earlier in another connexion.[3842,3923]



253: X = H, Y = OH
254: X = OH, Y = H
255: X = H, Y = CH(OH)Me
256: X = CH(OH)Me, Y = H

Further oxygenated derivatives of dihydropyrimidines arise from the (theoretical) addition of hydrogen peroxide to the 5,6-double bonds of the biologically important pyrimidine bases to give *5,6-dihydroxy adducts* (or *glycols*). These

form an important component of the extensive literature on dihydropyrimidines, which has been enhanced by the discovery that the *cis*-isomers of thymine and thymidine glycols are released in both human and rat urine as the result of the repair of oxidatively damaged DNA.[6487,6488] The latter, brought about by active oxygen species such as the hydroxyl radical, superoxide anion, hydrogen peroxide, and singlet oxygen, may be related to mutagenesis, carcinogenesis, and aging.[6489] In the laboratory, the 5,6-double bonds of uracil and of various 5- and 6-substituted derivatives,[6490] have been subjected to the action of potassium permanganate, probably the oldest and best-known classical reagent for the detection of olefinic double bonds in an organic molecule. The reaction involved a concerted (3 + 2) cycloaddition by the permanganate anion across 5,6-double bond to form a cyclic ester that was subsequently hydrolyzed to the *cis*-glycol and a soluble Mn(IV) species.[5422,6492] This resulted in various yields of *cis*-diols (e.g., **257**, R^1 = H, R^2 = Me;[5421,6493] **257**, R^1 = deoxyribose, R^2 = Me).[6491,6494,6495] In certain cases, the *cis*-glycols isomerized to *cis* + *trans* mixtures from which the *trans*-glycols were separated by chromatography.[6496] Osmium tetroxide, another reagent for olefinic double bonds, gave cyclic osmic esters when it added across the 5,6-bond of cytosine,[6497] 5-methylcytosine,[6497] and 1-methylthymine.[6498] The monomer of the osmium (VI) species, Os_2O_6(pyridine)$_4$, reacted with both *cis*- and *trans*-glycols in the thymine series to form the corresponding bis(pyridine) *cis*-osmate (VI) esters (**258**, L-pyridino).[6496] Potassium peroxomonosulfate is another oxidizing agent that converts both thymine and its 1,3-dimethyl derivative into the *cis*-5,6-glycols,[6499] possibly through a 5,6-epoxide (**259**) whose protonated molecule (**260**) ring-opened to a carbocation (**261**) that was trapped by water and other nucleophiles (e.g., hydrogen peroxide and methanol) to give the product (**262**).[6499] The absence of the *trans*-isomer in the product from water was rationalized in terms of an energetically favorable *gauche* stereochemistry.[5318,6500–6502] By contrast, thymidine was claimed to give a mixture of glycols in which the *cis*-isomer predominated.[6503] The same oxidizing agent converted 5-bromo-1,3-dimethyluracil into a mixture of 5,5-dibromo-6-hydroxy- (**263**) and 5,5,6-trihydroxy-1,3-dimethyl-5,6-dihydrouracil (**264**).[6504]



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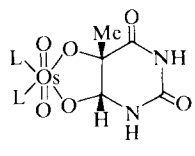

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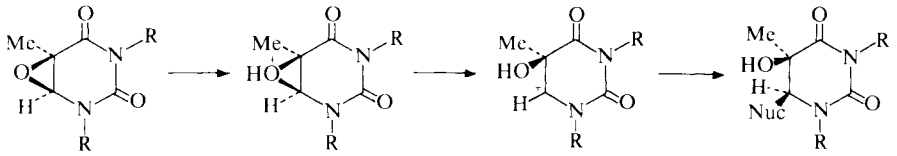
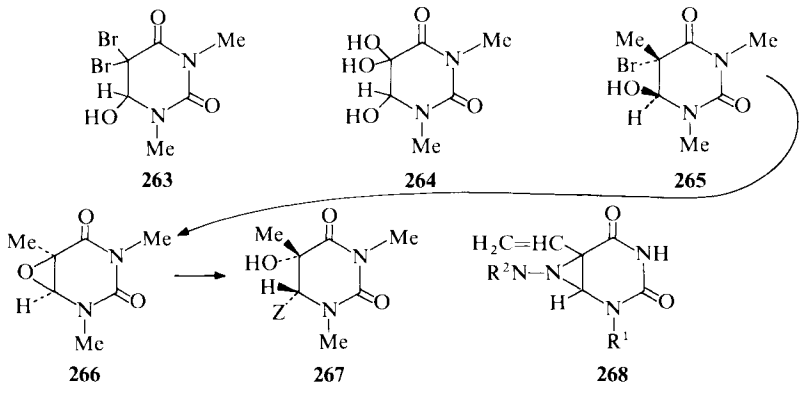
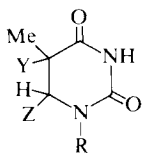


259 **260** **261** **262**

The behavior of these proposed 5,6-epoxide intermediates seems to be related to their mode of production. Thus, that produced in situ during the tertiary-amine-induced hydrolysis of the *trans*-1,3-dimethylthymine bromohydrin (**265** → **266**) gives a mixture of *cis*- and *trans*-5,6-glycols (**267**, Z = OH; **267**, Z = OH, then H and OH on C6 interchanged).[6500] This contrasts with the behavior of the 5,6-epoxide that is produced during the α-diketone-sensitized photooxidation of 1,3-dimethylthymine: when intercepted by water, acetic acid, or thiophenol molecules, this gave only the *cis*-adducts (**267**, Z = OH, OAc, or SPh)[5318] or with phenol, the carbon–carbon-coupled products (**267**, Z = C_6H_4OH-*o* and *p*).[6501] However, the intermediate again produced in situ from the reaction of the racemic form of **265** with triethylamine, reacted with primary and secondary amines to give a mixture of *cis*- and *trans*-forms of the 6-amino adducts (e.g., **267**, Z = NHPh or $NHCH_2Bu^t$).[6505] The proportion of *cis*-adduct increased with polarity of the solvent, suggesting that the solvent was stabilizing an ionic intermediate[6505] like a zwitterion formed on ring opening of the epoxide ring.[6489] In the case of the thymidine epoxide derived from (5*R*,6*R*)-*trans*-(+)-5-bromo-6-hydroxy-5,6-dihydrothymidine, reaction with both amines and L-amino acid ethyl esters afforded the *cis*-adduct only. Use of the diastereomeric (5*S*,6*S*) compound led to the isolation of both *cis*- and *trans*-adducts.[6489] In earlier experiments designed as models for nucleic acid–protein interactions, racemic **266** had reacted with the ethyl esters of L-amino acids to give four optically active diastereomeric adducts.[6506,6507] It would be worthwhile to attempt detection and characterization of the epoxide intermediate (or its equivalent) by ^1H, ^{13}C, and ^{17}O nmr spectroscopic techniques and by actual isolation—if not from base-induced dehydrobrominations, then by the use of epoxidation reagents such as dimethyl dioxirane,[6508] or even molecular oxygen and alcohol catalyzed by transition metal–diketone complexes.[6509] Further, direct aziridination of the 5,6-double bond is attracting attention (**268**, R^1 = protected sugar, R^2 = phthaloyl).[6510] Reaction of such fused aziridines with alcohols would complement the reactions of the epoxide with amines. The corresponding 5,6-episulfides also need investigation.



Some dihydropyrimidines are also produced by *radiolysis*[6511,6512] and *sonolytic*[6513,6514] or *photolytic reactions*[6515] in aqueous solutions. The first two processes involve the formation[6515,6516] and the subsequent addition of hydroxyl radicals to the 5,6-double bonds of the biologically important pyrimidine bases, free or combined in nucleosides. The addition occurs preferentially at the 5-position.[5412,6517,6518] The major 5-hydroxypyrimidin-6-yl radicals are ultimately converted, inter alia, into a mixture of *cis*- and *trans*-5,6-glycols.[6519] With thymidine, however, the presence of dissolved oxygen leads to entrapment of both free radicals as the peroxides, 6(5)-hydroperoxy-5(6)-hydroxy-5,6-dihydrothymidine (**269**, R = sugar, Y = OH or OOH, Z = OOH or OH), and all eight possible isomers were isolated.[6520] In the absence of oxygen, the photohydrate, 6-hydroxy-5,6-dihydrothymidine (**269**, Y = H, Z = OH), is formed, presumably by reduction of the 6-hydroxythymidin-5-yl radical: all four diastereomers were isolated.[6521] A significant product formed on γ-irradiation of thymidine in frozen aqueous solution was 5,6-dihydrothymidine (**269**, R = sugar, Y = Z = H).[6512] Hydrogen fluoride, stabilized in pyridine containing ethanol, was particularly useful for the quantitative hydrolytic release of *cis*-thymine glycol from the (5*S*,6*R*) diastereomer of 5,6-dihydroxy-5,6-dihydrothymidine (**269**, Y = Z = H), although *cis*-6-ethoxy-5-hydroxy-5,6-dihydrothymine was sometimes a by-product.[6522] It has been suggested that the 5-hydroxypyrimidin-6-yl radicals in these radiolysis processes are the exclusive precursors of the glycols.[6523] By contrast with derivatives of uracil, radiolysis of its 4,6-dioxo isomer leads to the formation of a 5-dihydropyrimidin-2-yl radical.[6524] The intermediate free radicals were trapped by nitro compounds,[6525] 2-methyl-2-nitrosopropane,[6526,6527] and 2,2,6,6-tetramethylpiperidin-4-one 1-oxyl.[6488,6528,6529] The nitro compounds,[6525,6530] as well as another free radical (2,2,6,6-tetramethylpiperidine 1-oxyl),[6531,6532] enhanced the yield of glycols with thymine.[6533] The former free radical formed dihydro adducts with the free radicals formed during γ-irradiation of thymine.[6528] The major products were **270a** and **270b**,[6528] formed by combination with the thymin-5-yl and thymin-6-yl radicals, respectively. With thymidine, no less than eight adducts were isolated and characterized by nmr spectroscopy; in these, the trap moiety was



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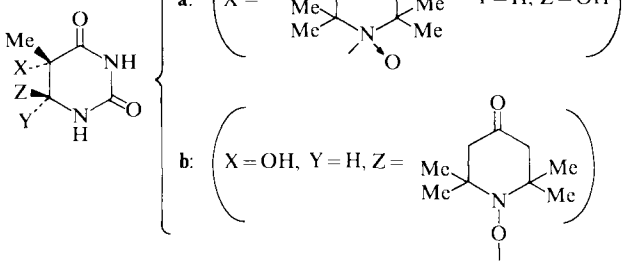

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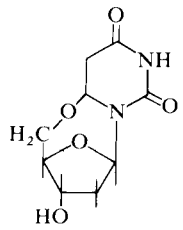
linked to the *C*5- or *C*6-position of a 5,6-saturated thymine ring, the nitrosyl nitrogen atom, or the oxygen atom, respectively.[6488,6529] The minor 6-hydroxypyrimidin-5-yl radicals are also intermediates in the radiolytic reduction[6534] of 5-bromo-6-hydroxy-5,6-dihydrothymine in aqueous solution as well as in the radiation-induced reduction of *cis*-thymine glycol in aqueous sodium formate.[6535] In the latter investigation, the main products were thymine, 5,6-dihydrothymine (**270**, X = Y = Z = H), and 6-hydroxy-5,6-dihydrothymine (**269**, R = Y = H, Z = OH). The last substance was also a product from the uv photolytic ($\lambda > 280$ nm) reduction of the *cis*-thymine glycol in the presence of aromatic amine sensitizers.[6515]

Sonolysis of aqueous solutions of thymine leads mainly to 5-(hydroxymethyl)uracil and 5,6-dihydroxy-5,6-dihydrothymine, again (as with γ-radiolysis) involving the addition of hydroxyl radicals to the molecule.[6513,6536,6537] Although similar processes occur with both cytosine[6538] and uracil, they lead to ring-cleavage and ring-contraction products.[6539]

The photohydration of uracil derivatives, mentioned earlier, is brought about by irradiation in the near-uv range (say, 240–290 nm).[5310a,6468–6474] Far-uv light (say, 180–240 nm) has effects paralleling those of γ-radiation,[6540] although in 2′-deoxynucleosides and 2′-deoxynucleotides, ionization took place preferentially at purine rather than pyrimidine moieties under the influence of pulses of 193-nm laser light.[6541] Photohydration and the formation of cyclobutane pyrimidine dimers are associated with DNA lesions involved in the cytotoxicity of uv radiation. Analogous to photohydration is the formation of cyclonucleosides when, for example, deoxyuridine is irradiated with 254-nm light. The 5′-hyroxy group of the sugar moiety adds to the 5,6-double bond of the pyrimidine ring to give the O^6:5′-cyclo-5,6-dihdro-2′-deoxyuridine (**271**).[5309] Other photo-induced additions to the 5,6-double bond have been mentioned earlier with respect to alcohols. Another example occurs during the photolyis of thymidine in aqueous acetone, to give, inter alia, both diastereomers of the acetone adduct, 5-acetonyl-5,6-dihydrothymidine.[6542] The major class of lesions caused in DNA by the absorption of uv light are the cyclobutane pyrimidine dimers that are formed between adjacent pyrimidine moieties on the same DNA strand.[6543] The next, still biologically important, class of photoproduct is the (6-4)pyrimidine photoadduct type, formed usually to the extent of about 10% of the dimers[6544,6545] but in calf thymus DNA in a ratio dependent on the wavelength of



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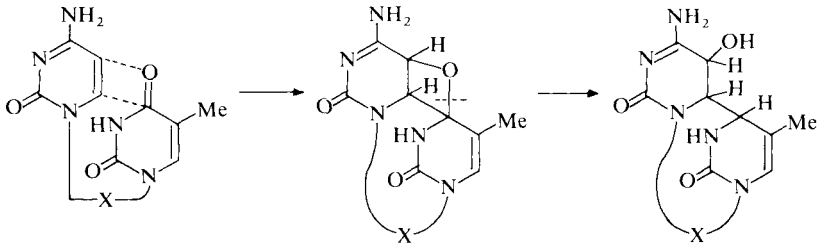
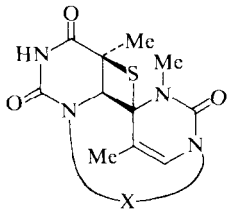
the uv light over the 150–365-nm range.[6546] Such photoaddition is illustrated by the uv irradiation of 2′-deoxycytidyl-(3′ → 5′)-thymine (**272**) in which it is believed that the *C*4-carbonyl grouping of the thymine ring adds to the 5,6-double bond of the cytosine moiety to form a compound with a four-membered oxetane ring (**273**). This opens spontaneously to a product (**274**) in which the cytosine ring still retains a 5,6-dihydro level of reduction.[6547] A second product arose from **274** by conversion of the thymine ring into its Dewar valence bond isomer, while a third product resulted from deamination of the cytosine ring in **274** to give a 5,6-dihydrouracil derivative.[6547] A similar four-membered azetidine ring is believed to be involved when the *C*4-imino group of a cytosine tautomer adds to the 5,6-double bond of a thymine ring.[5387b] This (2 + 2) cycloaddition reaction was attempted with a model system based on the dinucleoside phosphate, thymidyl(3′-5′)-4-thiothymidine. Addition between the 5,6-double bond of the 5′-pyrimidine base and the *C*4-thiocarbonyl functional grouping of the 3′-pyrimidine base did occur, and the stable four-membered thietane intermediate (**275**) was isolated.[6548] Molecular modeling studies have been carried out on some of these photoadducts.[6549]



272 **273** **274**



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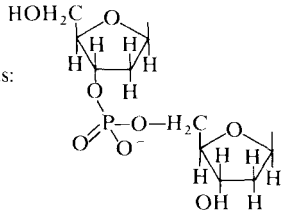
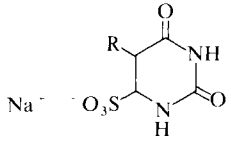
In formulas **272**–**275**, X represents:



Sulfur nucleophiles, based on another Group VI element, are represented mainly by the action of the hydrogen sulfite anion and thiolate anions on the biologically important pyrimidine bases and, to a lesser extent, on those pyrimidines containing powerful electron-withdrawing groups. The first class derives its importance from its widespread use in the chemical modification of nucleic acids: this has also raised the question of a potential genetic hazard from atmospheric sulfur dioxide and bisulfite toward living organisms.[6557]

Thus the 5,6-bond of uracil underwent nucleophilic attack from sodium sulfite or bisulfite to give the 5,6-dihydrouracil salt (**276**, R = H), which is isolable

as a crystalline product.[6552] Similar behavior was observed with 5-fluorouracil,[6553,6554] *N*-alkyluracils,[6555] thiouracils,[6555,6556] 1,3-dimethylorotaldehyde,[2669] and uracil nucleosides.[6557-6559] The bisulfite addition to cytidine[6552] and other cytosine derivatives[6557-6561] was frequently complicated by the replacement of the 4-amino group by other nucleophiles such as water,[6558] hydroxylamine,[6562,6563] hydrazine,[6559] or analogous nitrogen bases.[6562,6563] Thus 5-methylcytosine[6564] gave a mixture of the *cis*- and *trans*-isomer of sodium 5,6-dihydrothymine-6-sulfonate (**276**, R = Me), as distinct from the direct (and reversible) addition of sodium hydrogen sulfite to the 5,6-bond of thymine itself, a reaction that gives the *trans*-isomer.[6565]



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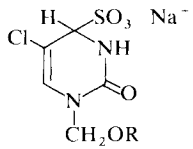

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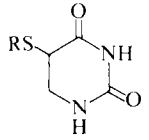
Electron-deficient pyrimidine molecules that are attacked by bisulfite ion at the *C*6-position include 1,3-dimethyl-5-nitrouracil,[5724] 2-amino-1-methylpyrimidinium ion[5722] (not bearing methyl groups at the *C*4- or *C*6-position[5723]), and 1-substituted-5-chloro-2(1*H*)-pyrimidinones.[3729,6074] The latter two types of substrate also undergo addition at the *C*4-position to give, for example, the products **277**.[6074] Similar behavior occurs on treatment of the pyrimidinones with phosphite esters,[3729] alcohols,[3827] and Grignard compounds,[3830] but not with vinyltitanium reagents.[3828] Addition of bisulfite ion to the 5,6-double bond is also implicated in the bisulfite-mediated dehalogenation of various 5-halogenated uracils[6580-6583] and some 5-halogenated cytosines[6584] as well as in the replacement of the 4-amino group of cytidine by hydrazine.[6559] The sulfite anion, through its sulfur atom, acts at C6 of the molecules concerned, where calculations have shown that the lowest unoccupied molecular orbital has its lowest electron density.[6585] It has been observed that photoaddition of bisulfite ion to the 5,6-bond of 5-deuterouracil occurs at a concentration much lower than that required for the thermal addition and that it is stereochemically random.[6586]

The suggestion that the cross-linking of proteins to DNA under the influence of uv light might be responsible for yet another biological lesion, led to model experiments that demonstrated that cysteine did indeed cross-link to uracil or thymine through its sulfur atom to form 1 : 1-adducts such as **278**, [R = $CH_2CH(\overset{+}{N}H_3)CO_2^-$].[6566,6567] The same uracil adduct results from the acetone-sensitized photochemical reaction between cytosine and cysteine in water.[6568]

As with bisulfite, cysteine addition across the 5,6-bond seems to be involved in the dehalogenation of 5-halogenated 2′-deoxyuridines[6569] and 5-iodouracil[6570] in the presence of the α-amino acid. Alkane- and arenethiols act similarly in the



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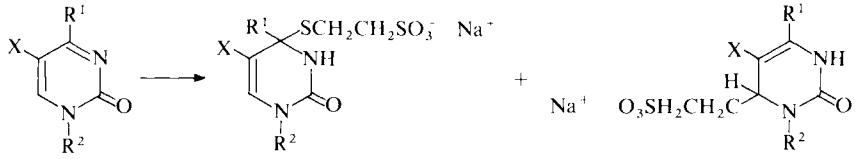
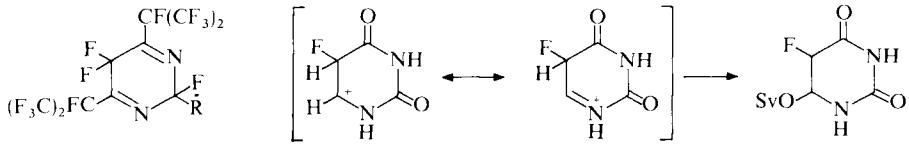
debromination of 5-bromo-1,3-dimethyluracil,[6571] as do sodium hydrogen sulfide[3452] and β-mercaptoethanol[6572] in the dehalogenation of 5-halogenated uracils. Reversible addition of β-mercaptoethanol to the 5,6-bond of 1,3-dimethyl-5-nitrouracil seems to be free of complications, and 76% of the adduct with the sulfur atom linked to the *C*6-position is present at equilibrium in solution.[5724] Intramolecular attack by the 5′-mercapto group of 2′,3′-*O*-isopropylideneuridine-5′-thiol on C6 of the uracil system to form a cyclonucleoside is one of the few examples of the actual isolation of a mercaptodihydropyrimidine system.[6573] The anion in sodium 2-mercaptoethanesulfonate prefers to react via the thiol end of the anion and adds to the electron-deficient nuclei of 5-chloro-2(1*H*)-pyrimidinones, giving both 3,6- and 3,4-adducts (**279** → **280** → **281**: R^1 = H or CO_2Me; R^2 = H, Ph, or CH_2Ph; X = Cl).[3969]



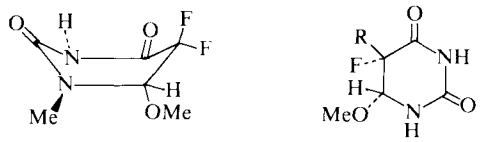
279 **280** **281**

Electrophilic halogenation reactions, involving the four lighter elements of Group VII, also give rise to dihydropyrimidine derivatives. Thus direct *fluorination* by cobalt trifluoride of perfluoroisopropylated pyrimidines leads to both replacement of nuclear hydrogen atoms and addition to form perfluorinated 2,5-dihydropyrimidine derivatives (e.g., **282**, R = F or *i*-C_3F_7).[6574] In view of the antitumor importance of 5-fluorouracil, it is not surprising to find that its preparation by direct fluorination of uracil represents a significant proportion of these reactions reported in the literature, especially in the patent section thereof. The reagents used have included elemental fluorine diluted with an inert gas such as nitrogen[6575] or argon,[3171] trifluoromethyl hypofluorite,[3168] cesium fluorooxysulfate,[6576] or acetyl hypofluorite.[3738,6577,6587] The electrophilic fluorination of uracil in acetic acid probably proceeds through an intermediate resonance-stabilized carbocation (**283**), produced either directly or through a radical cation species.[3738] In **283**, the extra electron-deficiency due to the *C*5-fluorine substituent (the most electronegative element in the Periodic Table) results in the capture of a nucleophilic solvent molecule (SvOH) to give the 5,6-adduct (**284**, Sv = Ac)[3171,6575,6588] or (**284**, Sv = Ac, F = ^{18}F).[6589] This loses acetic acid on sublimation in a vacuum to give 5-fluorouracil but also solvolyzes

with various alcohols to give the corresponding alkoxy compounds (**284**, Sv = Me, Et, or Bu).[3171] The covalent hydrate (**284**, Sv = H) was formed in water[6590,6591] or in aqueous trifluoroacetic acid as the reaction medium.[3168] Adducts with fluorinated alcohols and with thiols were obtained from the solvolysis of the trifluoroacetyl analog (**284**, Sv = CF_3CO).[6592] An alkyl substituent at N1 of the uracil molecule (or the sugar moiety in uridine) heavily stabilized these adducts[3738] and *cis*-addition was preferred to *trans*-addition.[3738] *gem*-Difluorination at C5 was also observed.[6502,6593] Thus, with 1-methyluracil, a stereoselective reaction with methanolic trifluoromethyl hypofluorite afforded (±) *cis*-5,5-difluoro-6-methoxy-5,6-dihydrouracil, which existed in the boat conformation (**285**) in both the solid state and in solution.[6502] The reaction of 1,3-dimethyluracils with cesium trifluorooxysulfate in a range of alcohols was less stereoselective, although *cis*-addition predominated in the formation of each pair of diastereomeric 6-alkoxy-5-fluoro-1,3-dimethyldihydrouracils.[6576] The Lewis acid, ferric chloride, in acetonitrile converted 6-acetoxy-5-fluoro adducts of the uracil nucleosides into the corresponding diastereomeric O^6-cyclonucleosides with the oxygen bridge involving both the 5′- and the 2′-hydroxyl substituents of the sugar moiety.[6587] *gem*-Difluorination at the *C*5-position occurs with 6-*O*-cyclouracil nucleosides,[6594] with the extra oxygen bridge involving other hydroxyl groups on the sugar moiety. A sequence of events similar to that found for uracil can be related in respect of the fluorination of 5-substituted uracils.[1980,3509,6595–6598] However, unstable 5,6-difluoro-5,6-dihydro compounds have been claimed as intermediates in the fluorination of pyrimidinones.[3165,6599,6600] Fluorination of cytosine or cytidine was complicated by a strong tendency to deamination, thus affording the corresponding uracil analogs.[3738,6587,6592]



282 **283** **284**

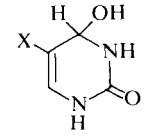


285 **286**

The *chlorination* of 5-fluorouracil in various hydroxylic solvents gave adducts such as **286** (R = Cl); expect for that with long-chain alcohols, some of the alternative isomers were formed also.[6601]

The *bromination* of 5-fluorouracil in methanol gave the *trans*-adduct (**286**, R = Br): subsequent catalytic hydrogenolysis (Pd/C) replaced the bromo substituent

to give **286** (R = H), in which the original *cis*-arrangement of the fluoro and methoxy substituents was retained and that was identical with the product obtained by direct fluorination of uracil.[6502] The kinetics of the fast bromination at the *C*5-position of 2(1*H*)- and 4(3*H*)-pyrimidinones have been explained in terms of electrophilic attack on the activated enamine systems of the extremely reactive covalent hydrates (e.g., **287**, X = H; **288**) present in minute amounts (0.05% and 0.0003%, respectively) in equilibrium with the anhydrous molecules.[6602,6603] Unlike fluorination, therefore, solvent involvement had preceded electrophilic halogen attack. In these systems, the majority of the hydrated species were too labile to be isolated, but they could be detected in solution by uv and/or ^{1}H nmr spectroscopy:[1952,6604] for example, the dihydro- (**287**, X = Br) and tetrahydro species (**289**, $R^1 = R^2 = H$) were evident during the bromination of 2(1*H*)-pyrimidinone to its 5-bromo derivative. However, the quaternary cation (**290**, R = Me), which is known to add a variety of nucleophiles,[1803] reacted with excess bromine to afford a solid 5,5-dibromo derivate analogous to **289** (R^2 = Me) from an aqueous reaction mixture and the 4,6-dimethoxy analog from a methanolic medium.[1952] More stable intermediates can be isolated with the uracils, so that *N*1-substituted uracils, for example, brominated in an aqueous medium at pH 7 to give the appropriate adduct comparable to **289**.[6605] Formally these adducts can be regarded as bromohydrins resulting from the addition of hypobromous acid to the 5,6-double bond. Reaction in methanol produced the analogous crystalline methanol adducts.[3452] The hypobromite adduct of thymine **291** (R = H, Z = OH) has been known since 1925,[5418] but only relatively recently has a series of *trans*-alkoxy and acyloxy adducts of thymidine (**291**; R = deoxyribose; Z = OMe, OEt, OBu, OC_5H_{11}, OAc, or OBz) been described.[6606] Mild reduction (Zn/AcOH) of the two enantiomers of **291** (R = deoxyribose, Z = OH) was instrumental in fixing the absolute configuration of the *cis*-6-hydroxy-5,6-dihydrothymidine obtained.[6607] Again it is only relatively recently[6604] that the 6-methyl isomer of thymine has been (di)brominated to give crystalline 5,5-dibromo-6-hydroxy-6-methyl-5,6-dihydrouracil. An intriguing example of an



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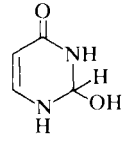

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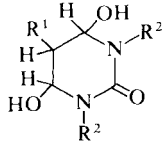

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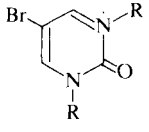

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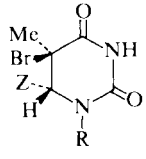

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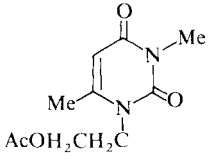

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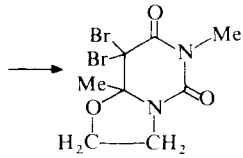


293

intramolecular nucleophilic addition at C6, which leads to the entrapment of an intermediate electron-deficient brominated cation, is the conversion **292** → **293**. This is brought about by bromine dissolved in glacial acetic acid.[6579] Bromination of cytosine and its derivatives also involves an addition–elimination sequence. The isolation of the 5-bromo-6-hydroxy adducts required careful work in order to avoid the easy hydrolysis of the exocyclic amino group to give the corresponding uracil derivatives.[971,1541]

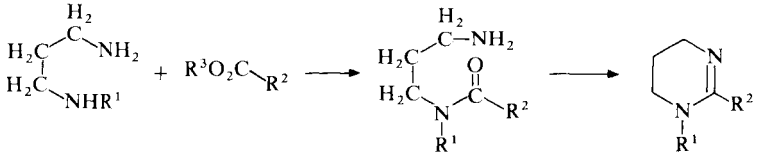
Direct *iodination* is the underrepresented in this area. One of the few examples is the conversion of *N*1-substituted uracils by ethanolic *N*-iodosuccinimide into the 6-ethoxy-5-iodo-5,6-dihydro adducts.[6605]

11.2. PREPARATION OF TETRAHYDROPYRIMIDINES

Of the three isomeric possibilities, the 1,4,5,6-tetrahydro system (**8**) still remains the most investigated. It is easily prepared, and there is great stability associated with the cyclic amidinium resonance of the protonated molecule. Such resonance possibilities in protonated 1,4,5,6-tetrahydro-2-pyrimidinamine are even greater, which may have a bearing on the occurrence of this system in natural products such as antibiotics belonging to the viomycin, capreomycin, and tuberactinomycin families.[6621,6622]

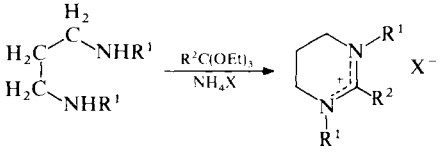
11.2.1. From 1,3-Propanediamine or a Related Substrate

The condensation of 1,3-propanediamine (PDA: **294**, $R^1 = H$) with a carboxylic acid (**295**, $R^3 = H$) (or much later, a derivative thereof), followed by dehydration of the resulting mono- (**296**) or diacylated material, has been a versatile method for the preparation of compounds based on the 1,4,5,6-tetrahydropyrimidine nucleus (**8**) ever since the initial century-old observation that 1,3-diacetamidopropane, on heating in a hydrogen chloride stream, afforded 2-methyl-1,4,5,6-tetrahydropyrimidine (**297**, $R^1 = H$, $R^2 = Me$).[6623] Although there were improvements in experimental techniques,[4355] renewed interest in the reaction had to await the discovery that markedly improved yields resulted when PDA was first allowed to react with, not an acid, but its ester (**295**, R^3 = alkyl) to give the monoacyl compound (**296**, $R^1 = H$) only. This derivative was then actually isolated prior to its thermal dehydration alone, or sometimes over calcium oxide, to give the cyclic product (**297**, $R^1 = H$, $R^2 = Me$



294 **295** **296** **297**

or Ph).[6624] In the preparation of analogs, the carbon backbone of PDA can bear C-methyl substituents[6625-6627] or a 2-hydroxy group;[6628,6629] the acyl group of the ester has reached octadecanoyl.[6626,6628,6629] Although the ethyl esters (**295**, $R^3 = Et$) have been employed as a rule, the alkyl group (R^2) of the acyl group in **295** has been further varied considerably from the more usual hydrogen,[4980,6625] alkyl,[6625] phenylalkyl,[6625] or phenyl[6625,6630] to groups such as trifluoromethyl,[6631] ethoxymethyl,[6632,6633] diethoxymethyl,[6633] and diethylaminomethyl.[6634] With β-keto esters, only the short acyl portion is incorporated into the tetrahydropyrimidine ring (**297**, $R^1 = Et$, $R^2 = Me$; $R^1 = CF_3$).[6635,6636] Orthoesters such as triethyl orthoacetate, triethyl orthopropionate, and triethyl orthobenzoate have replaced ordinary carboxyl esters in the preparation of 2-substituted 1,4,5,6-tetrahydropyrimidines (**297**: $R^1 = H$; $R^2 = Me$, Et, or Ph) from PDA.[6637] *N*,*N*′-Dialkyl derivatives of PDA reacted with triethyl orthoesters in the presence of ammonium fluoroborate or ammonium hexafluorophosphate to give the corresponding 2-substituted 1,4,5,6-tetrahydropyrimidinium salts (**298**: $R^1 = H$, Me, Et, Pr^i, Bu^t, or Ph: $R^2 = H$, Me, Et, or Ph; $X = BF_4$ or PF_6).[6638]



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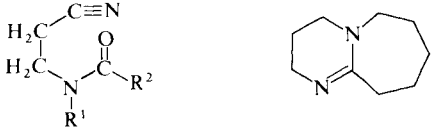


299 **300**

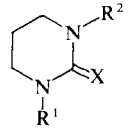
The intermediate aminoamide (**296**, $R^2 = Me$) has also been produced in situ when the acetyl derivative (**299**, $R^2 = Me$) of the product from addition of a primary amine to acrylonitrile was reduced with hydrogen over Raney-nickel; the vigorous reaction conditions caused cyclization of the intermediate acetamide to the hydropyrimidine (**297**: $R^1 = Me$, Et, Pr, Bu, or $C_{12}H_{25}$; $R^2 = Me$).[6639,6640] In a similar approach, the first stage in the preparation of the synthetically useful[6685,6686] reagent BDU (**300**) (which can be regarded as an N1:C2-polymethylene derivative of 1,4,5,6-tetrahydropyrimidine) involved the addition of caprolactam to the activated double bond of acrylonitrile.[6687]

Formamide and other amides[6632,6641] have sometimes replaced an ester in the reaction with PDA and its derivatives. However, the use of free carboxylic acids has, with few exceptions such as oxalic[6642] or phenylacetic acid,[6643] been largely neglected presumably as a result of losses of the PDA as the diamide under the somewhat extreme experimental conditions required. This may be a

mistake since, in one recent example, the best yields of **297** ($R^1 = H$, $R^2 = Bu^t$) arose with the acid (pivalic) rather than its methyl ester while the butyl ester did not react at all with PDA.[3890] The introduction of phenyl phosphorodiamidate as a rapid-cyclization agent also avoids complications with the use of carboxylic acids and affords, via a phosphate polymer, good yields of **297** [$R^1 = H$, $R^2 = n$-alkyl (C_9–C_{17})].[6644] Both polyphosphoric acid and its ethyl ester similarly aided the cyclization of 1-aroylamino-3-arylaminopropanes to the 1,2-diaryl compounds (**297**, $R^1 = R^2 = Ar$).[6645,6646]

Other carboxylic acid derivatives, which have been used as sources of C2 for 1,4,5,6-tetrahydropyrimidines, are the nitriles ($R^2C{\equiv}N$) whose cyano group furnishes C2 for the ring in **297**. Thus PDA reacts with hydrocyanic acid (H—C≡N) to afford the parent 1,4,5,6-tetrahydropyrimidine (**297**, $R^1 = R^2 = H$) with concomitant evolution of ammonia.[6647,6648] Structural additions to the diamine component include *N*- and *C*-alkyl or aryl groups[6647–6649] as well as a 2-hydroxy substituent.[6649] There are many more variations in the nitrile component illustrating the generality of this reaction between nitriles and 1,3-diamines. Thus R^2 in R^2—C≡N can be an alkyl (e.g., nonyl),[6650] aryl,[6651] substituted benzyl,[6649] α-naphthyl,[6652] 9-xanthenyl,[6653] its 10-thia analog,[6653] γ-(*t*-butylamino)propyl,[6654] trichloromethyl,[6688] trifluoromethyl,[6689] polyvinyl,[6690] amino,[6691] substituted amino,[6691] cyano,[6632] or a β-cyanoethyl group;[6692] the last two afford products, each of which contains two 1,4,5,6-tetrahydropyrimidine rings. The nitrile group in both aliphatic and aromatic carbonitriles can be activated toward cyclization with PDA by prior conversion, either into an *N*-methylnitrilium salt with methyl trifluoromethanesulfonate[6693] or into the imidate.[6655,6656,6694,6695] Thus the latter modification with the cyanohydrins of aromatic aldehydes and ketones led to the isolation of optical isomers of the protonated molecules [**297**, $R^1 = H$, $R^2 = CH(OH)Ar$].[6657] The isomeric isocyanide group, when linked to a *t*-butyl group, reacted with PDA in a silver-cyanide-catalyzed reaction to give the parent compound (**8**).[6658]

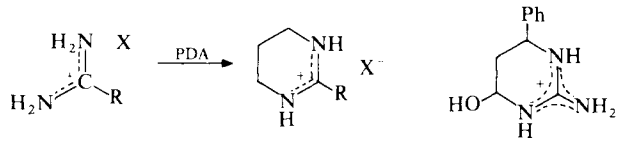
PDA and its derivatives can also be condensed with carbonic acid derivatives like dimethyl carbonate,[6659] diethyl carbonate,[6660,6661] diphenyl carbonate,[3492] phosgene,[6662–6665] urea,[6666–6670] or carbon dioxide[6671] to produce 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**301**, $R^1 = R^2 = H$, X = O) and analogs such as its 1,3-dimethyl derivative (**301**, $R^1 = R^2 = Me$, X = O), which is an important modern aprotic solvent.[6672] Carbon monoxide can also furnish the missing carbonyl group of **301** (X = O) provided the reaction with PDA is carried out in the presence of nickel carbonyl.[6673] Thiourea[6674] and carbon disulfide[6675–6679] can also supply a missing thiocarbonyl group to connect both



301

nitrogen atoms of PDA to form the thio analogs (**301**, X=S). The parent compound (**301**, $R^1=R^2=H$, X=S) also results from attemped dehydrogenation of **8** with sulfur.[4980] The sulfur atom in these molecules can be replaced by oxygen following oxidation with hydrogen peroxide; the hydrogen of their NH groupings can be replaced by alkyl.[6680] Carbonyl oxime[6681] and thiophosgene,[6682,6704] produced in situ from suitable precursors, lead to **301** with R^1 = Me, $R^2=CH_2Ph$, X=NOH and **301** with $R^1=R^2=H$, X=S, respectively, while carbon diselenide with PDA gives **301** with $R^1=R^2=H$, X=Se.[6705]

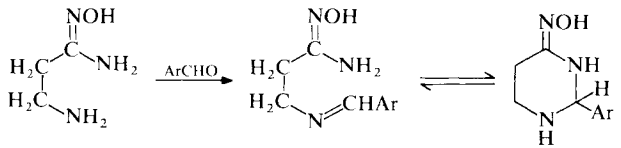
Condensations between PDA and its derivatives with amidine or guanidine salts have also turned out to be generally applicable to the preparation of the salts of 2-substituted 1,4,5,6-tetrahydropyrimidines (**302** → **303**: R=H, alkyl, Ph, CH_2Ph, or NH_2; X=halide, usually Cl).[4980,6706] Formamidine salts, for example, gave the salt of the parent compound (**302**, R=H, X=OAc, Cl, or $HgCl_3$).[4980] 1,3,5-Triazine, serving as a source of formamidine, also reacted with PDA to give the parent tetrahydropyrimidine.[4980,6707] It should be noted here that the dihydropyrimidines, mentioned earlier as being formed by the condensation of amidines with α,β-unsaturated aldehydes and ketones, result from the dehydration of an initially-formed 2-substituted 4(6)-hydroxy-1,4,5,6-tetrahydropyrimidine (**18** ⇌ **19**), which has actually been isolated in many reactions.[102,267,290,334] They include the optically active diastereomers from a (+)-pulegone–acetamide reaction,[6708] the product from entrapment of an unstable perfluoroalkyl ketone with amidines or thiouronium salts,[6709] the solid product from an acrolein–benzamidine reaction (**18** ⇌ **19**, R=Ph) that was sufficiently stable for an X-ray examination,[102] and some plant growth inhibitors arising from the reaction of acetamidine with 2-alkylideneacetoacetamides.[6710] Occasionally, α,β-unsaturated aldehydes have reacted with guanidine hydrochloride so that an intermediate hydrate such as **304** can be isolated.[6711] Similar hydrates are known from the intramolecular cyclization of β-ureidopropiophenones [e.g., $BzCH_2CH_2N(CH_2Ph)CONH_2$].[6252] The reaction between the trichloromethyl group in (trichloromethyl)benzene and PDA to give the 2-phenyl compound (**297**, $R^1=H$, $R^2=Ph$)[6712] is paralleled in the activated trifluoromethyl group of *o*- and *p*-(trifluoromethyl)aniline reacting with PDA (in the form of its lithio salt) to give **297** ($R^1=H$, $R^2=C_6H_4NH_2$-*o*/*p*).[6028] However, with (trifluoromethyl)phenyl isocyanide dichlorides, it is the isocyanide region that is built into the hydropyrimidine ring to give, for example **301** ($R^1=R^2=H$, X=: $NC_6H_4CF_3$-*m*).[6713] An intermediate carbodiimide might be implicated in this reaction following an earlier precedent with the benzyl



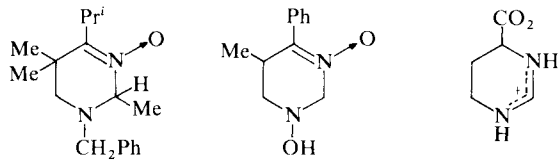
302 **303** **304**

analog, which was claimed by contrast to give a product with the tautomeric 2-benzylamino structure (**297**, $R^1 = H$, $R^2 = NHCH_2Ph$).[6714]

When one or both of the nitrogenous 1,3-substituents on a propane chain is (are) derived from hydroxylamine, the molecule still contains an N—C—C—C—N backbone that will require only one carbon atom to complete the hydropyrimidine ring. The carbonyl carbon of an aromatic aldehyde fulfils this purpose when it condenses with 3-aminopropionamide oxime (**305**) to give a benzylideneamino compound (**306**). In solution, **306** is in ring-chain equilibrium with the tetrahydropyrimidine derivative (**307**), which sometimes crystallizes out when the reaction is performed in ethanol.[6715] The exocyclic C=N bond in (**307**) contrasts with the endocyclic ones within the heterocyclic ring of compounds such as **308** and **309**, which were prepared much earlier from the reaction of aldehydes with 3-benzylaminopropionaldehyde oximes[6716] or β-hydroxylamino oximes,[4386] respectively. 2,4-Diaminoalkanoic acids contain an N—C—C—C—N skeleton that enables them also to function as substitutes for PDA. Thus 2,4-diaminobutyric acid and formamidine acetate give the zwitterion (**310**).[6706] Diethoxymethyl acetate functioned as an aldehyde equivalent in cyclizing a diaminopropane bearing both a phosphonate and carboxylic ester grouping to give the hydropyrimidine salt (**311**).[6738] 2,4-Diaminobutyric acid also condenses with the carboxyl group of serine or glutamine to afford the tetrahydropyrimidines (**312**, $R = CH_2OH$ or $CH_2CH_2CONH_2$, respectively), which are contained in certain bacterial siderophores called *pyoverdins*.[6741] The 1,3-arrangement of the amino groups in the essential α-amino acid, asparagine,



305 **306** **307**



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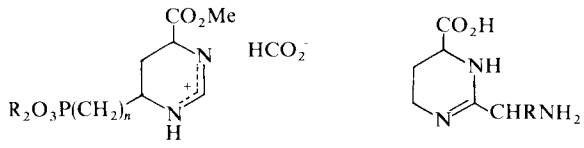


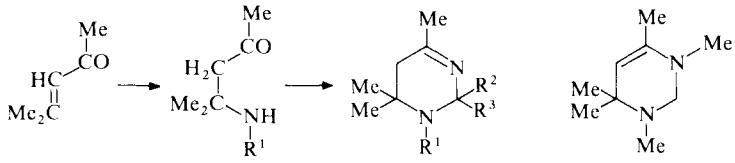
311 **312**

has ensured its use as a PDA-type substrate in reactions with formaldehyde[6742,6743] and acetone.[6744] Certain α-amino-ω-guanidino acids with the appropriate arrangement of groups have also been cyclized to tetrahydropyrimidinecarboxylic acids.[6745]

11.2.2. From Carbonyl Compounds with Ammonia, Amines, or Ureas

Following investigations spanning many decades,[6746–6750] the "acetonin,"[6746] isolated from the reaction of acetone and ammonia, was finally identified as 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine (**314**, $R^1 = H$, $R^2 = R^3 = Me$).[6666,6751,6752] Excellent yields resulted when acetone and liquid ammonia, in the presence of calcium or ammonium chloride as a catalyst, were kept at 20° for 24 h;[6666] the presence of promoters, such as alkali metal or other ammonium salts, also improved the yields.[6753,6754] Acetonin forms a crystalline monohydrate in which the C=N grouping is still extant.[4356] The mechanism is seen as involving the initial condensation of two molecules of acetone to give mesityl oxide, followed by addition of ammonia to give diacetonamine (**313**, $R^1 = H$). Further reaction with ammonia and acetone furnishes the missing N—C atoms to supplement the N—C—C—C skeleton in diacetonamine and thus produce the hydropyrimidine ring of the product (**314**, $R^1 = H$, $R^2 = R^3 = Me$).

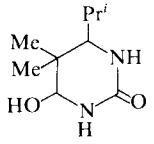
Exploitation of this basic reaction has demonstrated its versatility. Thus diacetonamine and formaldehyde yield (**314**, $R^1 = R^2 = R^3 = H$) while other aldehydes and other ketones besides acetone can be used.[6755] Going back one stage to mesityl oxide, this, in turn, can be allowed to react with primary amines like methylamine to form (**313**, $R^1 = Me$), which subsequently reacts with benzaldehyde and ammonia to yield **314** ($R^1 = Me$, $R^2 = H$, $R^3 = Ph$).[6755] Cyclocondensation of mesityl oxide, methylamine, and formaldehyde in the presence of alkali gives a 1,2,3,4-tetrahydropyrimidine compound (**315**);[6756] ammonia can replace the amine.[6757] Mesityl oxide also reacts with urea or thiourea under alkaline conditions to afford 4-hydroxy-4,6,6-trimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**41**) or the thione, both of which then failed to eliminate water to give the expected dihydro derivatives.[6758–6760]



313 **314** **315**

Mesityl oxide can be replaced in its reactions with urea and *N*-alkylureas by acrolein[6761,6762] by other α,β-unsaturated aldehydes and ketones,[6758,6763] or by suitable precursors. Thus 2 mol of isobutyraldehyde or its hemiacetal chloride[6766,6767] with urea form the hydropyrimidine derivative (**316**) under

acidic conditions. This ureidoalkylation of aldehydes and ketones has been thoroughly exploited.[6768] The reaction proceeds through an intermediate oxadiazine like **317**, formed from *N*,*N*′-dimethylurea, formaldehyde, and acetaldehyde. Ring opening at the ring oxygen atom is followed by recyclization so that the activated methyl group (formerly part of the acetaldehyde molecule) becomes the 5-methylene portion of the hydropyrimidine (**318**). Such α-ureidoalkylation of olefins is also possible, either with strongly polarized alkenes or in the presence of complex metallic catalysts.[6769] More complex reactions between ureas and saturated or unsaturated ketones are known: these give rise to products such as spiro compounds,[6770] bicyclic ureas,[6771] and dimeric molecules,[6772] in all of which one pyrimidine ring has a tetrahydro level of oxidation.



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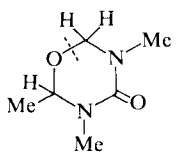

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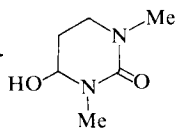

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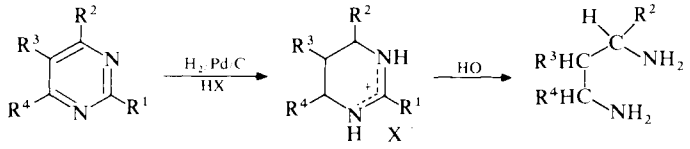
11.2.3. From 1,3-Dihalogenopropane Derivatives

This reaction has been largely neglected since publication of the original[4000] and improved[6773] versions of the condensation of 1,3-dibromopropane with benzamidine to give 2-phenyl-1,4,5,6-tetrahydropyrimidine (**297**, R^1 = H, R^2 = Ph). The most recent example appears to be the reaction of 1,3-dihalogenopropanes with 2,6-dichloro-*N*-phenylbenzamidine to give the salt of **297** (R^1 = Ph, R^2 = $C_6H_3Cl_2$-2′,6′),[6774] although the alkaline cyclization of a γ-chloroalkylurea (a likely intermediate from the reaction of a 1,3-dihalogenopropane with urea) may be noted.[6775]

11.2.4. By Reduction of Pyrimidines or Dihydropyrimidines

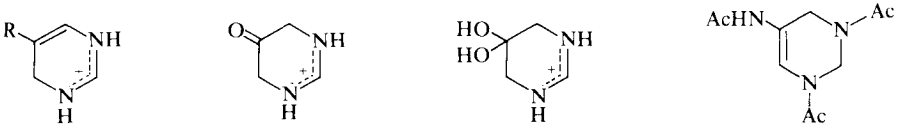
Although a number of catalysts has been used to prepare tetrahydropyrimidines by reductive methods, palladium (especially in the form of palladized charcoal) seems to have been the one most widely used,[712,2513,3612,4969] even from an early date.[6331] The pyrimidines (**319a–j**) absorb two moles of hydrogen when reduced in acidic media with hydrogen and palladized charcoal. Each product (**320a–j**) is a salt of the 1,4,5,6-tetrahydropyrimidine derivative, confirmed in structure by alkaline hydrolysis to a 1,3-propanediamine (**321a–j**). The acid protonates each pyrimidine substrate prior to its reduction and also each product, which as a neutral molecule would poison the catalyst. Moreover, the products (**320**) are salts containing the resonating amidinium system and



319 320 321

Product	R^1	R^2	R^3	R^4	X
a	H	H	H	H	Cl
b	Me	Me	H	Me	Cl
c	NH_2	H	H	H	Cl or AcO
d	NHAc	H	H	H	Cl or AcO
e	NHBz	H	H	H	Cl
f	NH_2	Me	H	Me	Cl
g	H	H	NHAc	H	Cl
h	OMe	H	H	H	AcO
i	H	H	OMe	H	Br
j	OH	H	H	H	Cl

consequently more stable than the free bases. The parent 1,4,5,6-tetrahydropyrimidine hydrochloride is obtained both from the reduction of pyrimidine in aqueous hydrochloric acid and from the reductive dehalogenation of 2,4-dichloropyrimidine in water. Three pyrimidine derivatives were found not to follow this 1,4,5,6-reduction pattern. Thus 5-pyrimidinamine, on reduction in acidic solution, absorbs only 1 mol of hydrogen to form the salt of the enamine (**322**, R = NH_2), which is rapidly hydrolyzed to the pyrimidinol (**322**, R = OH) existing as the keto tautomer (**323**); a hydration of the carbonyl grouping follows to give the isolated product, a salt of the *gem*-diol (**324**).[3612] 5-Pyrimidinol also absorbs only 1 mol of hydrogen to give ultimately the same product (**324**).[712] Catalytic reduction of 5-acetamidopyrimidine in hot acetic anhydride at 100° yields the triacetyltetrahydropyrimidine (**325**).[712]

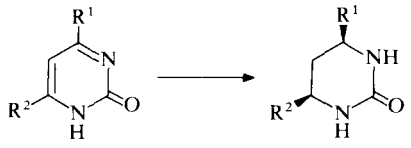


322 323 324 325

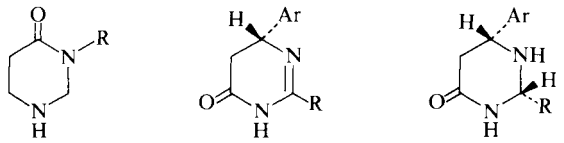
Catalytic reduction of 4,6-dimethyl-2(1*H*)-pyrimidinone (**326**, $R^1 = R^2$ = Me) over palladium at ambient temperature led to saturation of both double bonds in the ring and the formation of the *cis*-stereoisomer (**327**, $R^1 = R^2$ = Me).[2827,6776] A series of 1-benzyl-2(1*H*)-pyrimidinones,[5246] *N*-alkylated pyrimidinimines,[5788] *N*-alkylated 2(1*H*)-pyrimidinethiones,[6777] and a 4-α-hydroxyiminomethylpyrimidine precursor of capreomycidine[670] were also catalytically reduced to the tetrahydro stage. Raney-nickel is another metallic catalyst which has been used in this area, either alone or in the presence of hydrogen. Thus the

ring in 2(1*H*)-pyrimidinone or its 1-methyl derivative is saturated by Raney-nickel alone (e.g., **326** → **327**, $R^1 = R^2 = H$),[3492] but the reduction of 4,6-dichloro-2-propylpyrimidine to the 1,4,5,6-tetrahydro compound (**297**, $R^1 = H$, $R^2 = Pr$) involved hydrogen.[1456] Reductive dethiation is also possible with this catalyst, so that 4-thiouracil also afforded a tetrahydro derivative (**327**, $R^1 = R^2 = H$), as did both 4-thiothymine and 4-thiothymidine.[3492] Platinum resembles palladium in its catalytic activity and 1,4,5,6-tetrahydropyrimidines have been so obtained, inter alia, from 4-methyl-2-pyrimidinamine,[686] 2(1*H*)-pyrimidinone,[5162] and its 4,6-dimethyl or 1,4,6-trimethyl derivative;[6352] 2-methyl- or 2,6-dimethyl-4(3*H*)-pyrimidinone afforded 1,2,5,6-tetrahydro compounds.[3305] However, rhodium was a better catalyst than platinum for the reduction of the parent 4(3*H*)-pyrimidinone or its 3-methyl derivative to the 1,2,5,6-tetrahydro stage (**328**, R = H or Me).[5162] It also gave a better yield of the tetrahydro-2(1*H*)-pyrimidinone (**327**, $R^1 = R^2 = H$) compared to Raney-nickel.[3492] Both platinum and rhodium catalysts were too active during the reduction of cytosine and cytidine, hydrogenolytic splitting of the 4-amino group accompanying 1,4,5,6-tetrahydrogenation of the pyrimidine ring.[6778]

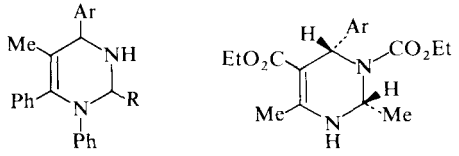
Metal hydrides are the only other class of reducing agents that have played a significant role. The sodium borohydride reduction of the 4- and 6-carbonyl groupings of various barbituric acids to a mixture of tetrahydro *cis*- and *trans*-diols has already been mentioned.[6356] It has also been used recently to reduce the endocyclic C=N bonds of various dihydropyrimidines. Thus even the hindered bond in **329** (R = Bu^t, Ar = C_6H_4OMe-*p*, a compound that stemmed from an initial condensation of pivalaldehyde with asparagine[6744]) could



326 **327**



328 **329** **330**

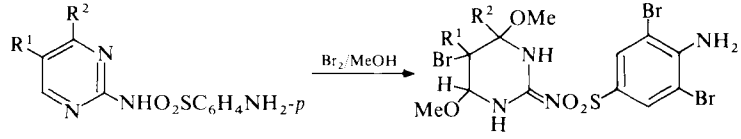


331 **332**

be reduced to give the 1,2,5,6-tetrahydro compound (**330**, R = Bu^t, Ar = C_6H_4OMe-*p*).[6779,6780] Similarly, the 3,4-double bond in various chiral 1,2-dihydropyrimidines (e.g., **96**, R = Ph or $CHMeOCH_2Ph$) was also reduced affording chiral 1,2,3,4-tetrahydropyrimidines (e.g., **331**, Ar = C_6H_4Me-*p*, R = $CHMeOCH_2Ph$).[3843] Compound **332** (Ar = $C_6H_4NO_2$-*o*) resulted from a stereoselective NBH reduction of its 1,6-dihydro precursor.[205] The more powerful LAH has been preeminent in selectively reducing one C4/6 carbonyl grouping to CH_2 before reducing a C2 carbonyl or another C4/6 carbonyl grouping in 1-methyl-5,6-diphenyl-5,6-dihydrouracil,[6781] and in other 4,6-dioxo[6782] or 4-oxo-2-thioxo substrates.[6783] The substituent as well as the 2-oxo part in ethyl 2-oxo-1,2-dihydro-5-pyrimidinecarboxylate undergo reduction to give 5-hydroxymethyl-1,2,3,4-tetrahydropyrimidine.[6784]

11.2.5. By Addition of Reagents Other than Hydrogen to Nuclear Double Bonds

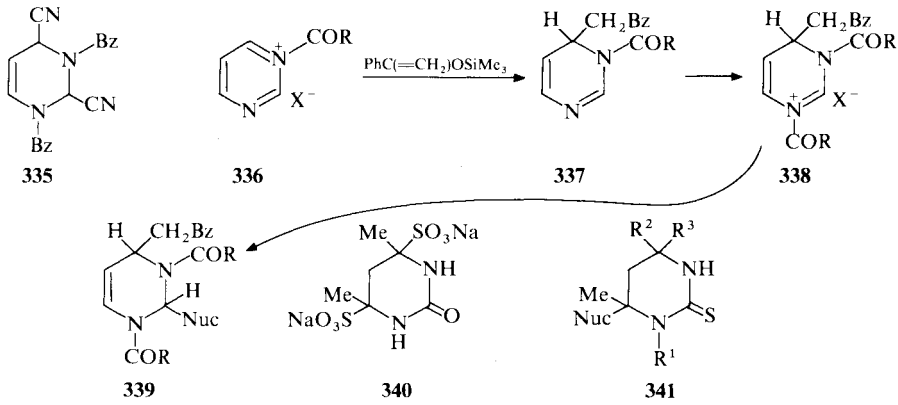
The initial attack of an electrophile on the 5-position of the pyrimidine ring gives a heavily electron-deficient carbonium ion that is sometimes intercepted and captured by nucleophilic solvent molecules. Thus, while bromination occurs in both rings of the sulfanilamidopyrimidines (**333**, R = H or Me), the final product is one in which two methanolic solvent molecules have added to the brominated ring to give **334** (R^1 = H or Me, R^2 = H)[2886,6785] or a tautomer thereof. Under similar circumstances, a 4-methylated substrate was monobrominated on its methyl group as well,[1828] so affording the analogous disolvate (**334**, R^1 = H, R^2 = CH_2Br). Similar disolvates were formed during the fluorination of certain *N*-alkylated 2(1*H*)-pyrimidinones.[3165]



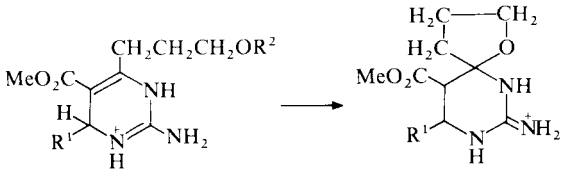
333 **334**

Carbon nucleophiles also add to *N*-alkyldihydropyrimidines. Thus 1-methyl-4,6-diphenyl-1,6-dihydropyrimidine reacts with methyllithium to form a 1,2,5,6-tetrahydro product.[6404] Pyrimidine itself reacts with trimethylsilyl cyanide, benzoyl chloride, and some aluminum chloride as catalyst to give the Reissert-type compound (**335**).[4634] The intermediate quaternary acyl pyrimidinium cations in this reaction have been exploited to form other 1,2,3,4-tetrahydropyrimidine derivatives. Thus the *N*-acylpyrimidinium salt (**336**, R = Me or OEt) reacted with soft nucleophiles such as the (enolic) silyl ether of acetophenone to give the initial adduct (**337**). This extremely rapidly undergoes a second *N*-quaternization to **338**, followed by nucleophilic attack to give a final isolated

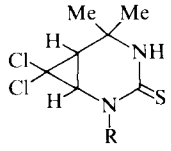
product like **339** (Nuc = CH_2Bz, R = Me or OEt).[6786] In some cases it is possible to generate **338** momentarily in situ and to allow it to react with other nucleophiles to afford products like **339** (Nuc = SPh, OMe, or OEt; R = CH_2CCl_3).[6444,6786]



Another example of nucleophilic attack on a pyrimidine ring so that it attains a tetrahydro level of reduction is the addition of two molecules of sodium hydrogen sulfite to 4,6-dimethyl-2(1*H*)-pyrimidinone to give **340**.[6787] This is paralleled by the addition of nucleophiles such as methanol and hydroxylamine to the 5,6-double bond of 1,4-dihydropyrimidines to give compounds such as **341** with Nuc = OMe, $R^2 = R^3 = H$[80,6787] and **341** with Nuc = NHOH, $R^2 = R^3$ = Me.[6789] Intramolecular nucleophilic addition has also been observed, as in the dihydropyrimidine ester [**342**, $R^1 = (CH_2)_{10}Me$, R^2 = H or Me], which is an intermediate in the biomimetic synthesis of the bicyclic guanidine moieties in the alkaloids, crambines A and B.[6788] This cyclizes to a stereoisomeric spiroaminal mixture containing tetrahydropyrimidine rings [**343**, $R^1 = (CH_2)_{10}Me$].



Dichlorocarbene adds to the 5,6-double bond of some 1,4-dihydro-2(1*H*)-pyrimidinethiones, thereby fusing a three-membered ring on to the six-membered one, which accordingly attains a tetrahydro level of reduction as in **344** (R = Me, Et, or Ph).[6790] Some *C*-protonated dihydro-2(1*H*)-pyrimidinones can act as electrophiles in substituting the rings of hindered phenols like 2,6-xylenol to give tetrahydropyrimidine compounds such as **345**.[4088,4705,6792]



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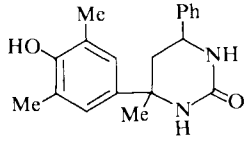

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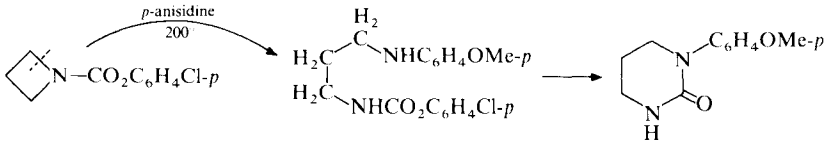
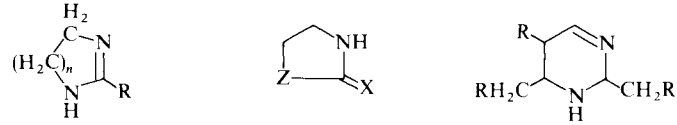
11.2.6. From Other Heterocyclic Substances

An early example is the apparent ring expansion of the four-membered azetidine derivative (**346**), brought about by heating with primary aromatic amines such as *p*-anisidine; nucleophilic attack on the carbon next to the ring nitrogen atom causes fission to an intermediate carbamic acid ester (**347**), which recyclizes with expulsion of *p*-chlorophenol to form the tetrahydropyrimidine (**348**).[6791]



346 347 348

Many more examples involve ring expansion of five-membered heterocycles such as fluorinated pyrazolines,[6793] 5-oxazolinones,[6794] reduced oxazoles,[6795,6796] and 4,5-dihydroimidazoles.[6644] The last-mentioned substrates with PDA incorporates C2 plus its attached alkyl or aryl group as the corresponding feature of the resulting 1,4,5,6-tetrahydropyrimidine molecule [(**349**, $n = 1$) → (**349**, $n = 2$)].[3920] The ring enlargement of 2-pyrrolidinimine (**350**, X = NH, Z = CH_2) to 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**350**, X = O, Z = CH_2NH), brought about by alkaline hypochlorite, is another recent example.[6797]

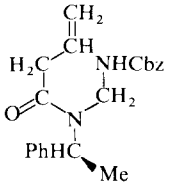


349 350 351

Modifications to six-membered rings include the thermal rearrangement of a perhydro-1,3-oxazine to a reduced 1-benzoyl-3-phenyl-2(1*H*)-pyrimidinone,[6798] the facile deammoniation of 2,4,6,-trialkylhexahydro-1,3,5-triazines to mixtures rich in tetrahydropyrimidines (**351**, R = Me, Et, or Pr),[6799] and the rearrangement of the oxadiazine (**317**), mentioned earlier in Section 11.2.2.

11.2.7. Miscellaneous Preparations

The hexahydro-1,3,5-triazine formed from (*S*)-(α-phenylethyl)amine and formaldehyde provides a link with the previous subsection. It reacts with β,γ-unsaturated acyl chlorides to give *N*-chloromethyl adducts (e.g., **352**, Cl for NHCbz). These react in turn with ammonia followed by benzyloxycarbonyl chloride to give the protected amidal (**352**, Cbz = $PhCH_2OCO$), which is an excellent substrate for a mercury trifluoroacetate-promoted cyclization to the hydropyrimidine (**353**, X = $HgOCOCF_3$, Cbz = $PhCH_2OCO$).[6800] Subsequent sequential treatment with sodium bromide and lithium borohydride yielded a separable 63 : 37 mixture of two 4-methyl diastereomers (**353**, X = H, Cbz = $PhCH_2OCO$). The initial use of α,β-unsaturated acyl chlorides led to the synthesis of 6-phenyl- and 6,6-dimethyl analogs of **353** (X = H, Cbz = $PhCH_2OCO$).[6801]



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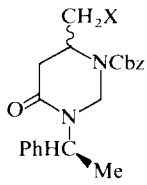

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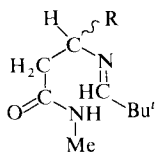
In another approach to cyclofunctionalization, the Schiff bases from each enantiomer of 3-(substituted-amino)butyric acid *N*-methylamide (**354**, R = Me) underwent cyclization on treatment with benzoyl chloride in the presence of 4-dimethylaminopyridine to give a mixture of hydropyrimidines (**355**) in which the *cis*- heavily predominated over the *trans*-stereoisomer (95 : 5).[6802] Intermediates based on 3-aminopropionic acid have also been used in this process [(**354**, R = H) → (**355**, R = H)].[6803] Another example of cyclofunctionalization was furnished by the bromocyclization of the allylamidine (**356**) by *N*-bromosuccinimide to give the 5-bromo-1,4,5,6-tetrahydropyrimidine (**357**).[6804]



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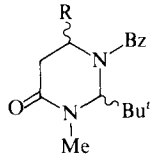

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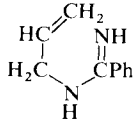

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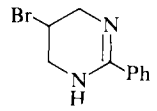

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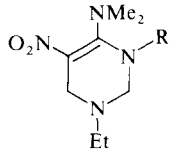
A number of recent multicomponent cyclocondensations may also be mentioned here. A series of nitroenamines such as $O_2NCH = C(NMe_2)NHR$ were allowed to react with primary amines (such as ethylamine) and formaldehyde to give hydropyrimidines like the potential pesticide [**358**, R = (pyridin-3′-yl)methyl].[6805] Methyl and ethyl 3-aminocrotonate, $Me(H_2N)C = CHCO_2R$,

with 2 mol of an aromatic aldehyde in the presence of ammonium acetate, give other 1,2,3,4-tetrahydropyrimidine compounds (**359**).[6806] Similar reduced compounds arise when *N*,*N*′-di(arylmethylene)arylmethanediamines [(ArCH = N)$_2$CHAr] condense with 1,3-dicarbonyl compounds to give **359** (Ac for CO_2R).[144]



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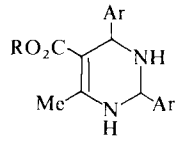

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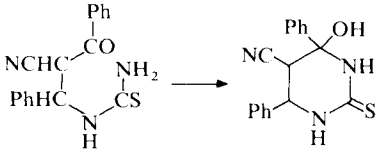
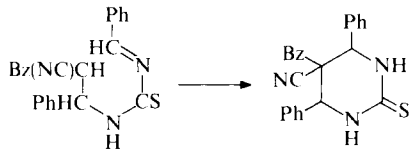
This subsection is completed by reference to a one-pot synthesis in which an α,β-unsaturated nitrile such as α-benzoylcinnamonitrile [PhCH=C(CN)Bz] is allowed to react with thiourea. In the presence of triethylamine, the adduct (**360**) from the initial nucleophilic attack by thiourea on the β-carbon atom of the chain cyclizes to give (**361**). In solution, **361** may still be in tautomeric equilibrium with open chain (**360**) since reaction with a second molecule of benzaldehyde gives another product (**363**), possibly through cyclization of the benzylidene-condensation intermediate (**362**).[127] However, only **360** crystallizes from solution when equimolar amounts of the nitrile, benzaldehyde, and thiourea or 2 mol of the nitrile and 1 mol of thiourea are refluxed in ethanol containing potassium acetate as a (weaker) base. Urea can also form the oxygenated equivalent of **363**.[127]



360 **361**



362 **363**

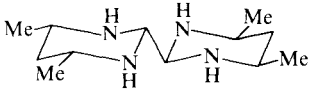
11.3. PREPARATION OF HEXAHYDROPYRIMIDINES

These compounds have been prepared almost exclusively by the *condensation of various 1,3-diamino substituted compounds* based on PDA *with aldehydes and ketones*, which supply to the N—C—C—C—N framework the missing C2, required to complete the hexahydropyrimidine ring.

There are examples in which the carbon backbone of the PDA derivative carries methyl,[6666,6751] phenyl,[6808] hydroxy,[6807] and nitro substituents,[6809–6812] but exploitation of the basic reaction has concentrated mainly on the use of substituents on one or both nitrogen atoms of PDA: for example, alkyl,[4356,6334,6665,6814,6815] aryl,[6816,6817] aralkyl,[6818–6826] sulfonyl,[6827] nitro,[6827] and acyl groups containing up to 18 carbon atoms.[6828]

However, there have always been examples where the use of both *C*- and *N*-substituents in the one diamine has occurred.[6808,6829–6831]

A bias in favor of aldehydes (rather than ketones) is apparent;[6832] the use of formaldehyde is predominant among the former. Even a dialdehyde, glyoxal, has been used in a condensation with PDA and some of its *C*-methyl derivatives to give perhydro-2,2′-bipyrimidines such as **364**, with a bridging bond between the two chair-shaped nuclei equatorially disposed.[6833–6835] The parent hexahydropyrimidine (**365**, R^1–R^6 = H) results from the condensation of aqueous PDA monohydrochloride with formaldehyde,[4356] via a Schiff base at the unprotonated amino group [$H_3\overset{+}{N}(CH_2)_3N{=}CH_2$] and subsequent tautomerization to the cyclic hydropyrimidine salt: basification thereof yields free hexahydropyrimidine, which, contrary to previous belief,[1109,6836] does exist in the neat liquid state as a cyclic molecule. When unprotonated. PDA condenses with 2 mol of formaldehyde to give a tetramer (**366**) consisting of four hexahydropyrimidine rings joined through their nitrogen atoms by methylene groups.[6837] This tetramer, in turn, can react with a third molecule of formaldehyde (or, alternatively, an initial reaction of PDA with three molecules of formaldehyde can be used) to give 1-formyl-3-methylhexahydropyrimidine (**365**, R^1 = CHO, R^2 = R^3 = R^5 = R^6 = H, R^4 = Me).[501] Formaldehyde and PDA, in a gas-phase reactor packed with an alumina catalyst, yielded a mixture of 1-methyl- and 1,3-dimethylhexahydropyrimidine.[6839] Hexahydropyrimidine itself and its 2-methyl and 2-ethyl derivatives were other high-temperature products from PDA alone,[6840] or mixed with ethylene glycol[6841] or allylamine[6842] that involved other metallic oxide[6841] or palladium[6842] catalysts. The hexahydropyrimidine produced in situ from 1,3-diamine–formaldehyde mixtures can be treated further with more formaldehyde and another reagent such as hydrogen cyanide,[6843] glycollonitrile (2-hydroxyacetonitrile),[6844] or 2,6-di-*t*-butylphenol[6845] to give *N*,*N*′-disubstituted hexahydropyrimidines [e.g., **365**, R^1 = R^4 = CH_2CN, R^2 = R^3 = R^5 = H, R^6 = H or OH or **365**, R^1 = R^4 = ($CH_2C_6H_2$-3′,5′-Bu^t_2-4′-OH), R^2 = R^3 = R^5 = R^6 = H], respectively.



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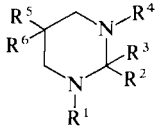

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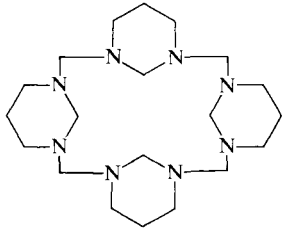

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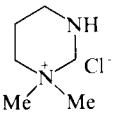
Formaldehyde is also capable of bringing about ring closure even when one of the nitrogen atoms in the PDA derivative is tertiary. Thus ^{1}H nmr evidence indicated that an aqueous solution of 3-dimethylaminopropylamine monohydrochloride was converted by formaldehyde into the hexahydropyrimidine



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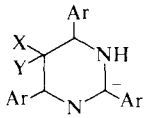
quaternary ammonium salt (**367**).[6838] More simply, formaldehyde condenses with an *N*-alkylated 1,3-propanediamine to furnish the corresponding *N*-alkylated hexahydropyrimidine (e.g., **365**, R^1 = Me or Pr^i, R^2–R^6 = H).[6815,6853] Even a polyamine like spermidine, which is 4-(γ-aminopropylamino)butylamine, gives a six- rather than a seven-membered ring with formaldehyde[6813,6854] and with its ^{14}C-[6855] and perdeutero-[6856] counterparts, as well as with acetaldehyde[6729,6857] [**365**, $R^1 = (CH_2)_4NH_2$, R^2 = H or Me, R^3–R^6 = H]. Other aldehydes, such as isobutyraldehyde, react with 3-methylaminopropylamine to give the hexahydropyrimidine (**365**, R^1 = Me, $R^2 = Pr^i$, R^3–R^6 = H),[6815] yet the product reacts with isocyanates to give exclusively the urea aldimine [$Pr^iCH{=}N(CH_2)_3$–NMeCONHR, where R = Bu or Ph] as if there was a small amount, undetectable by spectroscopic means, of a much more reactive open-chain tautomer [$MeNH(CH_2)_3N{=}CHPr^i$] present in equilibrium with the cyclic molecule. The ketone, cyclohexanone, behaved analogously.[6815] When 3-*t*-butylaminopropylamine was condensed with benzaldehyde or acetone, strain in the molecule helped to destabilize the cyclic structure so that the product was the open-chain tautomer, either the aldimine, $Bu^tNH(CH_2)_3N{=}CHPh$, or the ketimine, $Bu^tNH(CH_2)_3N{=}CMe_2$, respectively. Other diamines, which gave exclusively ketimines with ketones, include 1,3-dimethyl-3-methylamino- and 3-dimethylamino-1,3-dimethylbutylamine.[6832] Another aliphatic aldehyde of note is pivalaldehyde, which condenses with an appropriate diamine, $Me_2C(CH_2NHMe)_2$, to give the sterically hindered molecule (**365**, $R^1 = R^4 = R^5 = R^6$ = Me, R^2 = H, $R^3 = Bu^t$).[6829–6831,3859] A wide range of aliphatic,[6799,6860] aromatic,[6799,6861] and heterocyclic aldehydes[6862] cause no problems in these condensation reactions, even although some quite crowded molecules result.[6829–6831] It is surprising that a nearly century-old observation, that formaldehyde does not cause cyclization of the hindered diamine, 1,3-di-*o*-toluidinopropane,[6816] has never been confirmed, particularly with the availability of modern high-pressure techniques to "squeeze" reactant molecules.[6863] Other crowded molecular candidates for synthesis would be *t*-butylated products such as **365** ($R^1 = R^2 = R^4 = Bu^t$, $R^3 = R^5 = R^6$ = H) or even those with a 4,5,6-tri-*t*-butylated backbone in view of the recent availability of an aliphatic intermediate with such a feature.[6864]

Another direction, in which formaldehyde reveals itself as a special case, is in its ability to condense with primary nitroalkanes. In the presence of primary amines and an excess of formaldehyde,[6812] an intermediate 1,3-diol, for example, $O_2NCH(CH_2OH)_2$, is formed and then undergoes cyclocondensation to give 5-nitrohexahydropyrimidines such as **365** ($R^1 = R^4$ = Ph, $R^2 = R^3 = R^5$

= H, $R^6 = NO_2$).[6865] 1,1-Dinitroalkanes,[6866,6867] leading to 5,5-dinitro products, as well as 1,4-dinitrobutane,[6868] have been investigated in this type of reaction. The α-amino acids can also provide nitrogen atoms for the hydropyrimidine ring in such cyclocondensations, giving molecules such as **365** ($R^1 = R^4 = CH_2CO_2H$, $R^2 = R^3 = H$, $R^5 = CH_2OH$, Me, or Et);[6869] so can ammonia, but the NH groupings are then further alkylated with one or more molecules of the nitroalkane.[6870,6871] Compounds with CH_2 or CH groups activated by other electron-withdrawing groups (CO, SO_2, etc.) also take part in these cyclocondensation reactions with primary amines and formaldehyde: thus another aldehyde (like isobutyraldehyde) furnishes a series of 1,3-dialkyl-4-hydroxy-5,5-dimethylhexahydropyrimidines,[6874] while ethyl methyl ketone leads to compounds such as **365** ($R^1 = R^4 = Pr^i$, $R^2 = R^3 = H$, $R^5 = Me$, $R^6 = Ac$).[6875] Hexahydrotriazines can function, in effect, as a source of both formaldehyde and primary amine residues when they condense with acetates (XCH_2CO_2Et) activated by electron-withdrawing groups (X) on the α-carbon atom. So, diethyl malonate ($X = CO_2Et$) heated with 1,3,5-tribenzylhexahydro-1,3,5-triazine in the presence of trifluoroacetic acid gives **365** ($R^1 = R^4 = CH_2Ph$, $R^2 = R^3 = H$, $R^5 = R^6 = CO_2Et$).[6876]

The 1,3-arrangement of nitrogen atoms in *N,N'*-dibenzylidenephenylmethanediamine, $PhCH(N{=}CHPh)_2$, enables it to function as a precursor of hexahydropyrimidines. Various active methylene compounds, CH_2XY, undergo Michael addition to the N=C bonds to give 2,4,6-triarylhexahydropyrimidines (**368**, Ar = Ph, X = CN, Y = CO_2Me or $CONH_2$).[6877]



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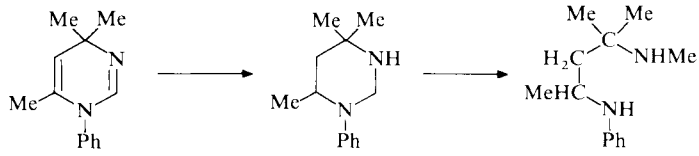
Only a few hexahydropyrimidines are reported to arise from the *reduction of a pyrimidine or of a di- or tetrahydropyrimidine*, and only three types of reductive method seem to have been used. One of the few examples involves the hydrogenation (over platinum) of the 5,6-double bonds in some *N,N'*-dialkyl- or diaryl-5-nitro-1,2,3,4-tetrahydropyrimidines to afford the corresponding 5-nitrohexahydro products: in these reactions, the electron-withdrawing nitro group has clearly activated the C=C double bond.[6878,6879] However, the nitro group in many 1,3-dialkyl-5-nitrohexahydropyrimidines is reduced to an amino group by using Raney-nickel and hydrogen at 70°/1000 psi, but without causing any ring fission even under such vigorous conditions.[6880] Similar conditions do not seem to have been applied yet to the reduction of the amidine C=N double bond of 1,4,5,6-tetrahydropyrimidines or of their salts, in which the problem will be compounded by the need to overcome a powerful stabilizing resonance of the amidinium system. This latter factor probably ensured that 4,6-dichloro-2-pyrimidinamine gave 1,4,5,6-tetrahydro-2-pyrimidinamine (as its salt)[6333,6881]

and not the hexahydro derivative as originally claimed.[2207] For the same reason, a report,[2051] claiming that catalytic hydrogenation over palladium of some chlorinated methylaminopyrimidines reduced the ring to the hexahydro stage while leaving untouched chlorine atoms elsewhere in the molecule, needs checking. No other claim for the direct catalytic reduction of the pyrimidine ring to its hexahydro derivative has been discovered in the literature.

A dissolving metal reduction (sodium/ethanol) successfully saturates the solitary C=N bond in 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine by sequential addition of electrons and protons to the double bond.[6666,6751]

The third group of reducing agents has had a significant though mixed impact in this area. Thus sodium borohydride reduces the C=N bond in various 1,2,5,6-tetrahydropyrimidines[6757,6799] and even the activated C=C bond in *N*,*N*′-disubstituted-5-nitro-1,2,3,4-tetrahydropyrimidines.[6878] However, the more powerful (at least in aprotic solvents) LAH is required to accomplish the reduction of ring-carbonyl groupings (usually in an amide or urea environment) to CH_2 groupings in tetrahydro-2(1*H*)-pyrimidinones,[6882] tetrahydro-4(3*H*)-pyrimidinones,[6883] dihydrouracils,[6781] and barbituric acids.[6885] Unlike LAH, sodium borohydride can be used in protic solvents such as ethanol, which aids the reduction process by enabling the formation of more reactive positively charged intermediates. These can frequently complicate the reduction process, leading to overreduction and formation of an open-chain 1,3-diamine. Hence, it is important to use the correct quantity of sodium borohydride needed to achieve the required stage of reduction: thus 3 mol of sodium borohydride reduced both double bonds, including the amidine C=N in an *N*-substituted dihydropyrimidine (e.g., **369**) to give the fully saturated molecule (**370**), which was converted by an excess of the reducing agent into the *N*-methylated open-chain diamine (**371**).[6884] Overreduction also occurs with another hydride reducing agent, diisobutyl aluminum hydride, which attacks the amidine C=N bond in 1-isopropyl-2-methyl-1,2,3,4-tetrahydropyrimidine leading to *N*-ethyl-*N*′-isopropyl-1,3-propanediamine.[6692]



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11.4. REACTIONS OF REDUCED PYRIMIDINES

Because of space constraints, this chapter is deliberately structured to emphasize the synthetic aspects of reduced pyrimidines at the expense of their reactions, properties, and applications. Thus information in the remainder of this chapter is heavily slanted toward material published since that reviewed in

1985[188,6886] or the following year.[6175,6887] The volume of material to be considered seems to have declined since the apparent golden age of this topic in the early 1980s, no doubt reflecting redirection of scarce financial resources to other areas. However, the sustained interest in certain 1,4-dihydropyrimidines, stemming from their potential medicinal use as calcium-channel blockers and antihypertensive agents, has ensured continuing exploration in at least one aspect of hydropyrimidines.[3941,3942,6888–6890]

11.4.1. Reductions

Many reductions of di- and tetrahydropyrimidines have been mentioned in Sections 11.2.4 and 11.3, so this section deals only with a selection of cases of overreduction leading to fission of the hydropyrimidine ring. This is particularly evident when the cyclic structure is in dynamic equilibrium with an open-chain tautomer containing a C=N bond. The latter grouping is very easily reduced, thereby causing the continual disappearance of the open-chain form and displacement of the equilibrium, so that the final result is the apparent hydrogenolysis of the hexahydropyrimidine ring. Thus 2,2-dimethylhexahydropyrimidine (**365**, $R^2 = R^3 = Me$, $R^1 = R^4 = R^5 = R^6 = H$), in equilibrium with γ-isopropylidenepropylamine [$H_2N(CH_2)_3N{=}CMe_2$], affords γ-isopropylaminopropylamine [$H_2N(CH_2)_3NHPr^i$] on shaking with hydrogen and Adams's catalyst under ambient conditions.[4356] Sodium borohydride is also proficient at this task, as mentioned previously, even when no open-chain tautomer can be present: a small yield of γ-methylaminopropylamine is so obtained from hexahydropyrimidine itself, probably by reduction of the double bond of a ring-opened immonium ion produced by interaction of one ring nitrogen atom's lone pair of electrons with a solvent alcohol molecule.[4356,6334] 1,2,3-Trialkylhexahydropyrimidines give much better yields of the diamine. Sodium borohydride also causes ring fission at the amide bond of dihydrouracils, 5,6-dihydrouracil itself giving γ-ureidopropanol [$H_2NCONH(CH_2)_3OH$] in methanolic solution,[6336,6353] whereas dihydro-2-thiouracil requires ultraviolet stimulus to give the thioureido counterpart.[6891] By contrast, it is the malonyl portion of the ring of some barbiturate drugs that is cleaved to give 2,2-disubstituted-1,3-diols[6353,6892] unless two benzyl groups are present at C5, when the ring fission product is β-benzyl-γ-phenylpropanol.[6356] Other reductive ring openings to 1,3-diamines have been observed with LAH and 1-aryl-4,6-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinones,[6893, cf. 6665] with NaBH and 1-alkyl-1,2-dihydropyrimidines (presumably after reduction to the hexahydro stage),[6808] and in a catalytic hydrogenolysis of an *N*,*N*′-dibenzylated hexahydropyrimidine over palladium.[6894]

The reductive repair of various models (representing damaged nucleic acids) is a significant contemporary research topic. Thus repair of 1,3-dimethylthymine bromohydrin, causing reversion to the original 1,3-dimethylthymine, is brought about by a one-electron transfer system consisting of 1,5-dihydro-5-deazaflavin

and a flavinium perchlorate in the presence of magnesium perchlorate.[6900] Ascorbic acid, in the presence of a catalytic amount of cupric ion, regenerated the original thymine and thymidine derivatives from the corresponding bromohydrins.[6901] Alternatively, the deazaflavin may be used alone in the presence of trifluoroacetic acid or, in turn, may be replaced by 1-benzyl-1,4-dihydro-3-quinolinecarboxamide to function as another NADH model.[6902] Another approach to the repair problem involves the application of sunlight, of heat alone, or of heat in the presence of sulfhydryl-containing compounds to the bromohydrins of thymine,[6903] thymidine,[6903] and thymidine phosphate.[6904] In the case of the 5,6-diols of thymine and thymidine, used as another set of models for oxidatively damaged nucleic acids, only trivalent phosphorus compounds from a number of reducing agents proved effective for reductive repair.[6905] However, the photoreduction of thymine glycol to thymine is sensitized by aromatic amines in aqueous solution,[6515] while the analogous γ-irradiation-induced transformation is promoted both by aromatic amines and by low-valence transition-metal salts.[6535]

The formation of pyrimidine dimers is the other main source of damage to nucleic acids, a situation remedied in situ by a class of enzymes known as *photolases.* These probably transfer an electron to the dimer and split the cyclobutane ring, so regenerating the 5,6-double bonds of the two original pyrimidine molecules in the process. The photolytic effect of these enzymes can be mimicked by the use, either of a methoxyindole bound to a dimer-recognizing macrocycle,[6906] or of the monoanion derived from 2′,3′,4′,5′-tetraacetyl-1,5-dihydroriboflavin.[6907] The enthalpy of the exothermic cleavage of a model uracil photodimer has been measured.[6908]

11.4.2. Oxidations

This subsection concentrates on recent research experience involving the removal of hydrogen from, rather than the addition of oxygen to, a substrate; the removal of hydrogen from a dihydropyrimidine should be aided by the gain in stability associated with ring aromatization. The oxidation potentials of certain 1,4-dihydropyrimidines containing stabilizing electron-withdrawing ethoxycarbonyl groups are much higher than those of their 1,4-dihydropyridine counterparts, which are model compounds of NAD(P)H. It was concluded from molecular-orbital calculations that aromatization of this particular small group of compounds to the pyrimidinium cations would not be easy and that they would have weaker reducing abilities than the pyridine analogs.[320] Not surprisingly, it was found separately than an electron-donating dimethylamino substituent in the 2-position of both 1,4- and 1,6-dihydro compounds lowered their oxidation potentials.[3922] Experience shows that the foregoing small group of compounds (unlike some other 1,4-dihydro compounds with electron-donating amino groups,[75] or some 1,6-dihydropyrimidines, both of which underwent spontaneous oxidative dehydrogenation with atmospheric oxygen[4982]) required

more powerful oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for their effective aromatization.[283,2695,3936,6033,6320,6409,6411] Even DDQ sometimes proved inferior to activated manganese dioxide in the aromatization of certain dihydro-2(1*H*)-pyrimidinones;[61,219,222] in turn, manganese dioxide gave way to the tetrachloro-*p*-benzoquinone (chloranil) for the effective dehydrogenation of *N*-arylated dihydro-2(1*H*)-pyrimidinones.[6909]

Potassium permanganate, usually dissolved in acetone, was an early dehydrogenating agent applied in this area[4642,6333] and is still so used.[102,3734,6405,6406] Latterly, dissolved in liquid ammonia, it has facilitated the in situ dehydrogenation of the aminodihydro intermediates involved in the Chichibabin amination reactions of pyrimidines, which result in the apparent nucleophilic displacement of a nuclear hydrogen atom by an amino group.[479,6448]

Other recently used oxidants have included DMSO,[6298,6402] potassium hexacyanoferrate,[4635] and even malachite green.[6350] A cation radical was involved in the first step of the dehydrogenation of 4,6-dimethyl-2-phenyl-1,2-dihydropyrimidine in the presence of silver nitrate, ferric perchlorate, or phenothiazine cation radical perchlorate. Hydrogen evolution occurred subsequently.[6910] Hydrogen transference, between some 1,4-dihydropyrimidines and α,β-unsaturated carbonyl compounds (e.g., chalcone and maleic anhydride) or the activated carbonyl groups of trifluoroacetone and pyruvic acid, has been noted.[188]

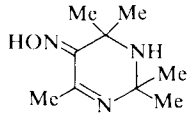
A mixture of 1,3-propanediamine and a carboxylic acid such as pivalic acid forms a 2-alkyl-1,4,5,6-tetrahydropyrimidine on passage over an alumina catalyst at 250–290°. Subsequent passage of the product over a palladium dehydrogenation catalyst at the much higher temperature of 300–340° affords the 2-alkylpyrimidine.[6641,6848] Vanadium phosphate can also be used for the aromatization step.[6911] The reluctance of the hydropyrimidine ring to dehydrogenate, except under these vigorous conditions, is also supported by the treatment of the parent 1,4,5,6-tetrahydropyrimidine with palladized charcoal, which led to dehydrogenative coupling and formation of 1,1′,4,4′,5,5′,6,6′-octahydro-2,2′-bipyrimidine.[4980] Similarly, an attempted dehydrogenation with sulfur led to the insertion of a sulfur atom at C2 in the molecule followed by tautomerization to give 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethione.[4980] Lead tetraacetate plus a catalytic amount of cupric acetate effected dehydrogenation of a 1,2,5,6-tetrahydro-4(3*H*)-pyrimidinone to its 1,2-dihydro analog.[6780]

A mixture of 1,3-propanediamine and an aldehyde, passed over a palladium, platinum, or rhodium catalyst at high temperatures, cyclizes to give a 2-alkylhexahydropyrimidine, which then dehydrogenates to the heteroaromatic 2-alkylpyrimidine.[3090] Milder dehydrogenation of hexahydropyrimidines to, for example, 1,3-dialkyl-1,4,5,6-tetrahydropyrimidinium salts, is effected by mercuric acetate[6831] or by air in the presence of palladium black;[6894] a nickel-on-kieselguhr catalyst is used in the production of the free 1,4,5,6-tetrahydropyrimidine bases.[6757] 2-Methylhexahydropyrimidine is unusual, in that when shaken with platinum and hydrogen under ambient conditions, hydrogen is not ab-

sorbed but evolved to give 2-methyl-1,2,5,6-tetrahydropyrimidine, an example of an oxidation under reducing conditions.[4356]

11.4.3. Nitrosations and Nitrations

These processes continue to be underrepresented in the chemistry of hydropyrimidines, perhaps reflecting an unease at working with potential carcinogens such as the *N*-nitroso compounds. One of the few nuclear *C*-nitrosations of a hydropyrimidine on record results from nitrous acid treatment of 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine. In preference to attack at the NH grouping, nitrosation occurs at C5 followed by tautomerization to the oximino derivative (**372**) with its conjugated double bonds.[6912] After an interval of almost two decades, interest in the direct nitrosation[4356] of hexahydropyrimidine itself to give the 1,3-dinitroso derivative (**373**, $R^1 = R^2 = NO$, $R^3 = H$) has been renewed because of its cancer-producing properties,[6913] which made it a candidate for inclusion in a computerized pattern-recognition project on structure–carcinogenicity relationships.[6914] Another reason was the use of these compounds as intermediates for the production of potentially explosive 1,3-dinitramines: for the first time by a process of nitrolysis rather than of oxidation, nitric acid or a solution of nitrogen pentoxide in nitric acid was used to convert a series of 1,3-dinitrosohexahydropyrimidines (**373**, $R^1 = R^2 = NO$, $R^3 = H$ or Me) into the corresponding 1,3-dinitro compounds (**373**, $R^1 = R^2 = NO_2$, $R^3 = H$ or Me);[6915,6916] some 1-nitro-3-nitroso compounds could also be isolated, as well as the spirocyclic compounds (**374**, R = NO and **374**, $R = NO_2$). The crowded tetranitroso compound (**375**, R = NO) was obtained by direct nitrous acid treatment of the tetramine (**375**, R = H),[6917] but the corresponding tetranitro compound was obtained by adding the tetramine to a solution of fuming nitric acid in trifluoroacetic anhydride.[6833]



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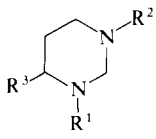

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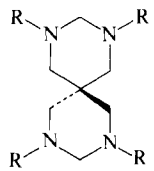

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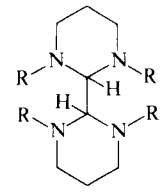

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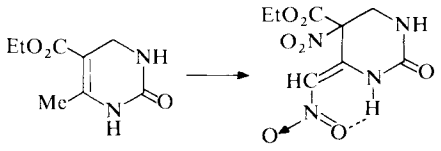
The nitroso and nitro compounds were subjected to a ^1H, ^{13}C, and ^{15}N nmr study to determine the types of rotational isomer in solution.[6917] An X-ray examination of the nitramine (**373**, $R^1 = R^2 = NO_2$, $R^3 = H$) revealed that the ring was dish-shaped with both nitro groups on the same side thereof.[6918] This contrasts with the situation in the tetranitro compound (**375**, $R = NO_2$), where the usual chair conformation of both rings was maintained.[6833]

Extranuclear nitration is represented by the nitration of the exocyclic 6-methyl group of the Biginelli compound (**376**) that accompanied nitronium ion

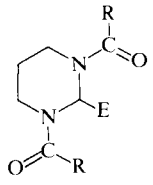
attack at C5 and that finally afforded the *Z*-6-nitromethylene compound (**377**). This exists as such in the solid state but in solution a dynamic equilibrium with the *E*-stereoisomer was established.[3941]



376 **377**

11.4.4. Acylations

There are five parent hydropyrimidines that contain one ring–NH grouping and two others that also contain a second NH grouping. If primary or secondary amino groups or hydroxy groups are attached to the ring as substituents, or if tautomerizable carobonyl or thiocarbonyl groupings are part of the hydropyrimidine ring, there are many obvious sites for attack by acylating (or alkylating) agents. Ring acylation is frequently complicated by ring opening, even when there is little or no likelihood of an open-chain tautomer being present in the substrate. Thus benzoylation of 1,4,5,6-tetrahydropyrimidine, its 2-phenyl derivative, and 4,4,6-trimethylhexahydropyrimidine gives in each case a di- or tribenzoyl derivative of the open-chain 1,3-diamine.[6666,6773] However, benzoylation at the exocyclic amino group of 1,2,3,4-tetrahydro-2-pyrimidinamine leaves the ring intact as a tetrahydropyrimidinium salt.[3612] Hexahydropyrimidine, assumed to be produced quantitatively in situ from a 1,3-propanediamine–formaldehyde reaction, was acylated by acid chlorides under Schotten–Baumann conditions to give moderate yields of the 1,3-diacyl compounds (**378**, E = H, R = Bu^t or Ph).[6919] Strong bases, such as lithium diisopropylamide or even *t*-butyllithium, removed a proton from C2. The anion from the dibenzoyl compound subsequently underwent self-condensation to afford the triphenyl compound (**378**, E = Bz, R = Ph) or, like the anion derived from 1,3-dinitrosohexahydropyrimidine under similar circumstances,[6920] could be trapped by electrophilic reagents, such as benzaldehyde, to give the benzyl alcohol (**378**, E = CHOHPh, R = Ph). Conformational equilibria in solution were investigated by ^{1}H and ^{13}C nmr spectroscopy and revealed, inter alia, that in the



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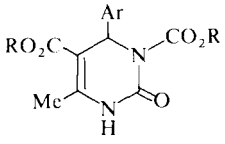
1,3-dipivaloyl case (**378**, E = H, R = Bu^t) 92% of the molecules in fully deuterated acetone at −103° existed in the *syn–anti* arrangement depicted.[6921] Acetyl chloride in benzene acetylates the NH groupings of 1- and 2-methylhexahydropyrimidine and the NH grouping of 2-methyl-1,4,5,6-tetrahydropyrimidine, where ring opening was observed.[6922] This latter observation may explain the modest yields of 1-acyl derivatives when the same tetrahydro compound was subjected to acetylation, benzoylation, benzenesulfonation, and methanesulfonation processes.[6923]

The related process of alkoxycarbonylation, planned to take place stereoselectively at the *N*3-position in preference to the *N*1-position, was an important step in improving the vasodilative action of certain 3,4-dihydropyrimidines of the Biginelli type, which led to the production of compounds such as **379**[6280] and their 2-thioxo analogs.[6279] Other 4-aryl-6-methyldihydro-5-pyrimidinecarboxylates, which also underwent preferential *N*3-acylation or alkoxycarbonylation, included the 2-oxo,[3924] the 2-thioxo,[3942] the 2-methoxy,[3945] and the 2-methylthio ones.[3942] A group of 6-chloro-2-substituted (methyl, phenyl, or dimethylamino)-4-aryldihydro-5-pyrimidinecarboxylates behaved similarly.[283] Acetylation of 4(3*H*)-pyrimidinone, as well as of its 5-acetoxy and 5-methoxy derivatives, occurs exclusively at the *N*1-position but in the presence of water covalent addition of water occurs at the C2-position: the 1,2-dihydropyrimidine ring then opens to give crystalline *cis*-3-acetamido-*N*-formylacrylamides, H(O=)C—HN—(O=)C—RC=HC=HNAc (R = H, OMe, or OAc), as isolable final products.[314]



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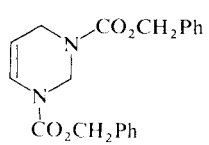

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A Vilsmeier formylation at *N*1 in a 4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate was effected by a mixture of phosphoryl chloride and *N*,*N*-dimethylformamide;[3942] acetyl chloride under Friedel–Craft conditions on the same substrate caused intramoleuclar acylation between the ester group and an *ortho*-position of the 6-phenyl substituent, so leading to a tricyclic indeno[1,2-*d*] pyrimidine derivative.[3942] *N*-Acylation also plays a valuable part in the in situ trapping and stabilization of partially reduced pyrimidines, for example the product (**380**) from the reduction of pyrimidine with sodium cyanoborohydride in the presence of benzyl chloroformate.[6924]

An *S*-acylation occurred inadvertently when acetic anhydride was used as the dehydrative cyclization agent in the preparation of 5-trifluoromethyl-5,6-dihydro-2-thiouracil from an open-chain precursor.[460] A *C*-acylation is exemplified by the acetylation of the 6-methyl groups in both 4,4,6-trimethyl-3,4-dihydro-2(1*H*)-pyrimidinone and the corresponding thione to give 6-acetonyl derivatives.[6925]

11.4.5. Halogenations

During the 1900s through the early 1950s, the ready monobromination[1432,1893,2774,3459,5259,6246,6257] and sometimes dibromination[1893] at the 5-position of 5,6-dihydrouracils and 5,6-dihydrothymines, together with various *C*6- and *N*1-alkyl or phenyl derivatives, played a significant role in their aromatization to the parent 2,4(1*H*,3*H*)-pyrimidinediones. Dehydrobromination and formation of the required 5,6-double bond occurred in basic,[3459] acidic,[2774] and aprotic solvents[1893,6257] or simply on heating above their melting points.[5259]

In the case of various 3,4-dihydro-2(1*H*)-pyrimidinones, bromination in water (or other hydroxylic solvents) caused addition of the elements of hypobromous acid to an unsubstituted 5,6-double bond to give a 5-bromo-6-hydroxy (or alkoxy)-tetrahydro derivative.[6926] However, the presence of a 6-methyl substituent deflected bromination (but not chlorination) away from the 5,6-double bond in favor of mono-, di-, or tribromination of the methyl group.[6927] In turn, the simultaneous presence of a *C*5-ethoxycarbonyl group led to easy cyclization with the 6-bromomethyl substituent and the formation of a fused furo-[3,4-*d*]pyrimidine.[6792]

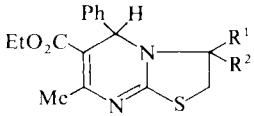
Only isolated examples of *N*-halogenation seem to be known, such as that of 6-methyl-5,6-dihydrouracil in the presence of sodium hydroxide[6928] or that of the NH groupings in the cyclic urea, 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, and its 4,4,6,6-tetramethyl derivative.[6929]

11.4.6. Metatheses of Reduced Pyrimidinones and Pyrimidinethiones

When situated alpha (α-) to a pyrimidinic nitrogen atom, hydroxy and mercapto groups tautomerize to the more stable oxo and thioxo structures, respectively. At both the pyrimidine and reduced pyrimidine levels, the conversion of carbonyl to thiocarbonyl is effected by phosphorous pentasulfide.[5230,6930] The reverse process can be brought about by oxidation with hydrogen peroxide in dimethyl sulfoxide.[127] As with the parent pyrimidines, in the hydropyrimidine series transformation of the cyclic amide grouping (—CO—NH—) to a *C*-chloro derivative (—CCl=N—) can be effected with phosphoryl chloride,[283] without altering the level of reduction of the ring. Raney-nickel dethiation (desulfurization) of the thiones to dihydropyrimidines has been mentioned previously.[3492,3922,6292]

Methyl iodide and other alkyl halides alkylate at the sulfur atom of Biginelli 2-thiones[3942] and of 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethiones,[6931-6933] and it is the ready displacement of these 2-alkylthio groups, and to a lesser extent their 2-methoxy analogs, by nucleophiles that is a significant step in these metatheses. Thus the 2-alkylthio groups in *N*1-unsubstituted Biginelli compounds are replaced by alkoxy groups by the use of a sodium alkoxide in the

appropriate alkanol. However, the reaction was retarded by large groups such as phenyl on N1. If this phenyl group possessed an *ortho*-substituent, like OH or CMe_2OH, which had nucleophilic properties, intramolecular displacement of the alkylthio group became possible with the formation of a third ring in products such as pyrimidobenzoxazole.[6934] Biginelli thioxo compounds behaved as cyclic thioureas and reacted with various dielectrophiles, such as 1,2-dibromoethane or bromoacetic acid, first at the sulfur atom and then at N3 to form fused pyrimidines (e.g., **381**, $R^1 = R^2 = H$; or $R^1 + R^2 = O$).[3942] An aliphatic acylamino substituent attached at N1 not only aided in the nucleophilic displacement of a methylthio group by hydrazine in a trimethyl-1,4-dihydropyrimidine but also caused ring expansion to give a triazolotriazepine (**382**).[6946] Triazole and triazepine rings were also fused on to the 1,2-bond of 4,6-diaryl-4,5-dihydro-2(1*H*)-pyrimidinethiones with the aid of acethydrazide and acetylacetone.[6947]



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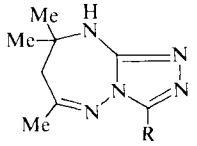

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O-Methylation in 4,4,6-trimethyl-3,4-dihydro-2(1*H*)-pyrimidinones can be accomplished with triethyloxonium tetrafluoroborate, a Meerwein reagent. Direct replacement of the 2-methoxy substituent by a *p*-methoxybenzylthio group was catalyzed by oxalic acid.[6279]

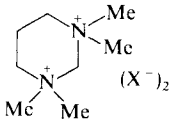
In the 5,6-dihydrouracil series, acid hydrolysis converts both methylthio and methoxy derivatives back to the parent dihydrouracils. However, a 4-methylthio was hydrolyzed before a 2-methylthio group.[562]

11.4.7. *N*-Alkylations

N-Alkylations can be carried out by a variety of reagents, although, as noted previously,[3942] the sulfur atom of a C=S/C—SH tautomer (as in the Biginelli compounds) will usually compete successfully for the reagent.[6948] This has led to the use of bifunctional electrophilic alkylating or acylating agents, which ensured that both the sulfur and a ring-nitrogen atom become substituted, thus forming bicyclic compounds.[6206,6949,6950] In the oxygenated analogs, the carbonyl oxygen atom does not compete with the ring-nitrogen atoms as a site for alkylation, so that the disodio salt of the cyclic urea (**301**, $R^1 = R^2 = H$, X = O) reacts with quite complex alkyl halides such as benzyloxymethyl chloride[6951] or *β*-dimethylaminoethyl chloride[6952] to substitute both nitrogen atoms with the respective alkyl group (**301**, $R^1 = R^2 = CH_2OCH_2Ph$ or $CH_2CH_2NMe_2$, X = O). The *β*-dimethylamino side chains can be degraded subsequently to vinyl groups suitable for polymerization.[6952] The 2-*S*- and 2-*O*-methyl derivatives of

Biginelli compounds are valuable intermediates. Even when they exist in solution as a mixture of 1,4- and 3,4-dihydro tautomers, reaction with alkyl or acyl halides gives only a single product in each case, namely, the *N*3-alkyl-3,4-dihydropyrimidine derivative.[205,3945]

1,3-Dimethylhexahydropyrimidine reacts rapidly with methyl iodide to form the monomethiodide.[4356] The very reagent trimethyloxonium borofluoride is required to quaternate both nitrogen atoms to form the salt (**383**), which has to cope with the Coulombic repulsion between the two very near positive charges as well as adverse axial methyl–methyl interactions if the ring has a chair conformation.[6953] Axial methylation was the preferred approach for further methylation of *N*,*N*′-dialkylhexahydropyrimidines containing axial 5-nitro groups, while large alkyl groups such as *t*-butyl or cyclohexyl on the nitrogen atom totally prevented quaternization.[6954] The *N*-alkylation of a 3-NH grouping remaining in a series of 1-alkylhexahydropyrimidines was accomplished by β-anilinoethyl bromide.[6955] Other complex halides used for *N*-alkylation purposes included 3-chloro-1-cyclohexyl-1-phenylpropanol, which substituted the NH grouping of 1,4,5,6-tetrahydropyrimidine giving **298** [one, $R^1 = CH_2CH_2C(OH)(C_6H_{11})Ph$; the other, $R^1 = R^2 = H$, X = Cl],[6956] while 2-bromo-1-phenylethylidenemalononitrile alkylated one NH grouping rather than the sulfur substituent in 3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinethione, with subsequent ring opening to give an isothiocyanate, $S{=}C{=}N(CH_2)_3NHCH_2CPh{=}C(CN)_2$.[6957]



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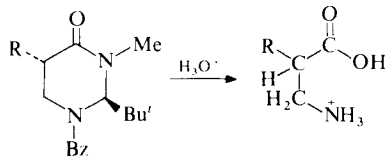
11.4.8. Other Reactions

Nonhydorgenolytic ring openings. Reduced derivatives of 2- and 4-pyrimidinones are cyclic ureas or amides, which can therefore be hydrolyzed with destruction of the hydropyrimidine ring. The *C*4-carbonyl grouping in the reduced 4-pyrimidinones has an electron-withdrawing effect that ensures that the hydrogen atom(s) on the neighbouring α-carbon atom (C5) are relatively acidic. These can be removed by strong bases like lithium diisopropylamide (LDA) forming an enolate anion which can be alkylated. In **384** (R = H), produced by benzoic anhydride-assisted cyclization of a derivative of β-alanine (**354**, R = H), the 2-*t*-butyl group occupies a rare axial position. Alkylation of its enolate occurs almost entirely from the side opposite to the bulky *t*-butyl substituent to give (**384**, R = Me, Bu, C_6H_{13}, CH_2Ph, or $CH_2CH{=}CH_2$).[6803] Acidic hydrolysis of compounds (**384**) under drastic conditions gave the desired α-substituted-β-amino acids (**385**), such as (*R*)-α-methyl-β-alanine.[6958] Using enantiomerically pure derivatives of type **384**, optically pure diastereomers of β-



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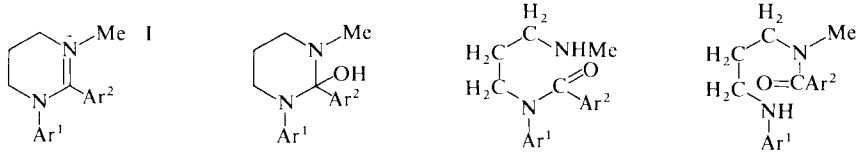
amino-α-methyl (or benzyl)-butyric acids were prepared subsequently.[6802] An analogous strategy was followed for the asymmetric synthesis of β-amino-β-aryl acids from enantiomerically pure dihydro-4-pyrimidinones.[6780,6959] The two diastereomers of the hydropyrimidinone (**353**, X = H) were readily separated and exhibited high *trans*-selectivity when their enolates were alkylated at C5. Subsequent hydrolysis led to more α-substituted β-amino acids.[6800,6801,6960] Some 1-aryl-6-methyl-5,6-dihydrouracils have been investigated for methylation (as well as for benzylation and oximination reactions), but no data were given about the site of methylation or about any stereoselectivity.[6961] The acidic ring-opening hydrolysis of chiral 1,2,3,4-tetrahydropyrimidines has also been exploited for the asymmetric synthesis of β-aminoketones and their subsequent LAH reduction products, the corresponding aminoalcohols.[3843]

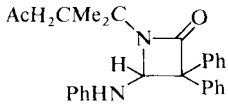
The methiodides (**386**) derived from various 1,2-diaryl-1,4,5,6-tetrahydropyrimidines in neutral or alkaline solutions form pseudobases (**387**), which can be detected by hplc (high-performance liquid chromatography).[6646] Initially, these ring-open to form the 1,3-diamines with the aroyl group on the arylamino nitrogen atom (**388**), which subsequently rearrange to the isomeric compounds (**389**) with the aroyl group on the methylated, and presumably more basic, nitrogen atom.[6646] Ring opening can also be brought about by nitrogen nucleophiles. Thus hydroxylamine converts 4,4,6-trimethyl-3-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone into an amino oxime, $PhNHCMe_2CH_2CMe{=}NOH$.[6962] Sometimes the hydropyrimidine ring in the initial product from a reaction undergoes fission readily. In this category falls the condensation of 1-substituted-4,4,6-trimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione with α-halogenated carboxylic acid or ketones. This starts with *S*-alkylation, which is followed by sequential ring opening of the hydropyrimidine ring and a new recylcization to afford a 2,4-dioxathiazolidine or 2-oxa-4-thiazoline derivative, respectively.[6964]



386 387 388 389

As a result of the [2 + 2] cycloaddition reaction between the 2,3-double bond of 4,4,6-trimethyl-1-phenyl-1,4-dihydropyrimidine and the olefinic double bond of diphenylketene, a fused pyrimidine is formed. During aqueous workup,

hydration of the pyrimidine ring is followed by its fission to give **390** as the final isolated product.[6963] The facile ring opening of dihydrouracils to β-ureido carboxylic acids and the ring closure of the latter back to the hydropyrimidines in sulfuric acid solution are topics that have proven suitable for kinetic and mechanistic investigation.[6965]



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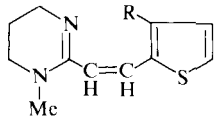
Reactions with aldehydes. Two categories of reaction with aldehydes have been noted, depending on whether the site of reaction is an activated methyl group or an NH grouping. The first case is represented by the industrially important condensation of the 2-methyl group of 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine with 2-thiophenecarbaldehyde or its 3-methyl derivative to give products [pyrantel: (**391**, R = H); morantel: (**391**, R = Me)][6966–6971] still of interest today.[6972,6973] A variant on such reactions involves condensation with an aromatic aldehyde in the presence of sulfur to give in most cases, a thioacylketene aminal [**301**, R^1 = Me, Et, or C_6H_{11}; R^2 = H; X = ArC(:S)CH:].[6974] However, salicylaldehyde gives betaines (e.g., **392**).[6975] The 4-methyl group in 4-methyl-6-phenyl-3,6-dihydro-2(1*H*)-pyrimidinethione undergoes a similar condensation with benzaldehyde to form a corresponding styryl derivative, which dimerizes in acid;[4088] it also undergoes a Mannich reaction with formaldehyde and secondary amines.[6976]



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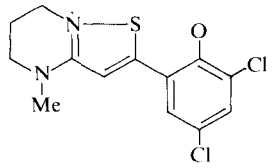

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Reactions at an NH site are exemplified by additions to the carbonyl grouping of formaldehyde to form *N*-hydroxymethyl compounds from, for example, hexahydropyrimidine (using an excess of reagent)[6977] or 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (which, in the presence of secondary amines such as morpholine, proceeds further to form Mannich bases).[6978] Formaldehyde can also form a cyclic tetramer (**366**) via the nitrogen atoms of hexahydropyrimidine[4356,6837] and can join the nitrogen atoms belonging to different rings in dodecahydro-2,2′-bipyrimidine.[6979]

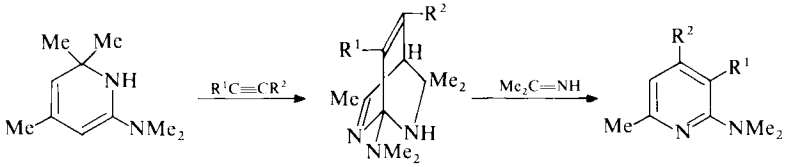
Miscellaneous reactions

1. It was noted previously that lithium tri-*s*-butylborohydride was an efficient reagent for the reduction of the 5,6-double bond of *N*-alkylated uracils. Before

hydrolytic workup of the reduction mixture, the initial carbanion can be *C*-alkylated by methyl, allyl, or benzyl halides to form the corresponding 5-alkyl-5,6-dihydrouracils.[6363,6364]

2. A rare case of direct *N*-phenylation is observed when 2,4,4,6-tetramethyl-1,4-dihydropyridimidine reacts with diphenyliodonium chloride to give 2,4,4,6-tetramethyl-1-phenyl-1,4-dihydropyrimidine.[3922]

3. Some conversions of hydropyrimidines into hydropyridines have been discovered. Thus the benzoate salts of 2,4-diaryl-6-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylates (**359**) are transformed on heating into 2,6-diaryl-1,2,3,6-tetrahydro-5-pyridinecarboxylates.[6806] The thermally induced transformation at the melting point of 1-substituted-4,4,6-trimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione into a 4-(substituted-amino)-6,6-dimethyl-5,6-dihydro-2(1*H*)-pyridinethione[6980] probably proceeded by a ring fission–ring closure sequence,[6981] so constituting a unique Dimroth-type rearrangement. The conjugated double bonds in 2-dimethylamino-4,4,6-trimethyl-3,4-dihydropyrimidine undergo a [4 + 2] cycloaddition with acetylenic compounds containing electron-withdrawing groups to yield an heteroaromatic pyridine derivative (**393** → **394** → **395**, $R^1 = R^2 = CO_2Me$ or Ac).[6982]

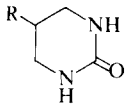


393 **394** **395**

4. Manipulation of substituents on the hydropyrimidine ring is frequently possible without altering the level of reduction of that ring. Thus a 6-amino group, being part of an enamino system, underwent acidic hydrolysis to a 6-oxo substituent (the stable tautomeric form of the enol produced initially),[198,6983] while phosphoryl chloride dehydrated a primary amido group to a nitrile in preference to chlorination of a ring carbonyl grouping.[198] In Biginelli compounds, the benzyl group of 5-benzyl ester could be hydrogenolyzed off without affecting the dihydropyrimidine ring;[6890] the resulting 5-carboxyl group could be manipulated, via Curtius rearrangement of the azide and production of the isocyanate and urethane, to give an example of the little-reported dihydro-5-pyrimidinamines.[6890] Both bromine atoms in the dibromomethyl group of ethyl 4-dibromomethyl-3-methyl-2-oxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate were replaced by azido groups using sodium azide.[6888] In the absence of the *N*-methyl group, the 6-dibromomethyl group was degraded to a cyano group.[6888] Photochemical treatment of the geminal diazide (produced in the first example) in the presence of oxygen leads to loss of the whole diazidomethyl function and oxidation to ethyl 1-methyluracil-5-carboxylate.[6889]

5. The displacement of the 5-tosyloxy group in (**396**, R = TsO) by the *p*-methoxyphenylmethanethiolate anion gives both the 5-thio ether (**396**, R

= $SCH_2C_6H_4OMe$-*p*) and its 4-isomer, as well as a ring-contraction product (**397**, R = $CH_2SCH_2C_6H_4OMe$-*p*) arising through the intermediacy of an aziridine intermediate (**398**), which can be produced separately by the action of sodium hydride on **396** (R = TsO).[6984] Another fused three-membered ring, this time in the form of a fused cyclopropanopyrimidine intermediate, is believed to be involved in a ring expansion (coupled with addition of Grignard compounds) of ethyl 4-alkyl-6-chloromethyl-2-oxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylates to ethyl 2,7-dialkyl-2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylates.[6985]



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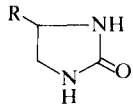

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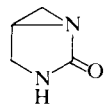
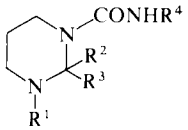


398

6. Strong bases bring about the elimination of nitrous acid (and consequent aromatization of the ring) from 2-acetonyl-5-alkyl-4,6-dimethoxy-5-nitro-2,5-dihydropyrimidines, although hydrochloric acids splits the ring in two places.[6986]

7. There is a competition between the H of the NH grouping and that of the OH group in 4-hydroxy-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethiones for replacement by various sulfur nucleophiles such as arylsulfinic acids, dithiocarbamates, or *O*-ethyldithiocarbonates.[6987]

8. Hexahydropyrimidines are cyclic aminals. [*Note*: This work closely resembles its anagram, *animals*, a fact that still leads to light-hearted confusion,[6815] over a quarter of a century after the original (?) precedent[6988] was brought to the attention of chemists repeatedly.[6989–6991]] Thus 1-methylhexahydropyrimidine reacts with butyl and phenyl isocyanates at the free NH grouping to give urea derivatives in which the ring is still intact as **399** (R^1 = Me, R^2 = R^3 = H, R^4 = Bu of Ph).[6815] However, the presence of electron-donating isopropyl or pentamethylene groups at C2 causes ring opening and formation of the ureido derivative of the open-chain tautomer, (e.g., **400**, R^1 = Me, R^2 = H, R^3 = Pr^i, R^4 = Bu or Ph). Phenyl and *p*-nitrophenyl substituents at C2 give mixtures of the appropriate **399** and **400** derivatives. 1-Isopropylhexahydropyrimidine also reacted with sterically hindered 2,6-dimeth-



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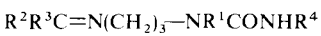


400

ylphenyl isocyanate to afford the cyclic urea aminal (**399**, $R^1 = Pr^i$, $R^2 = R^3 = H$, $R^4 = C_6H_3Me_2$-2,6). Subsequent hydrolytic treatment with sodium metabisulfite and hydrochloric acid furnished the ring-opened urea derivative, (2,6-$Me_2C_6H_3$)NHCONH$(CH_2)_3NHPr^i$.[6853] The hydropyrimidine ring in the aroyl substituted ketene aminal (**301**, $R^1 = R^2 = H$, X = ArCOCH:) remains unaltered when the hydrogen on the carbon atom alpha to the carbonyl grouping is substituted by benzyl (using benzyl chloride)[6992] or by 2,4-dinitrophenyl (in a radical nucleophilic substitution process using 1-bromo-2,4-dinitrobenzene).[6993] However, when the ketene aminal undergoes a [2 + 3] cyclocondensation with an aromatic nitrile oxide, which incorporates the COCH portion into a five-membered oxazole ring, one of the secondary amino group's hydrogen atoms migrates, thus changing the ring to a 1,4,5,6-tetrahydropyrimidine arrangement.[6994] A similar tautomeric shift was observed in the tetrahydropyimidine ring when a new insecticide, hydramethylnon, decomposed above 210°.[6995]

9. The reversible intermolecular addition of nitrogen- and oxygen-nucleophiles to the 5,6-double bonds of uracil derivatives and of 1,4-dihydropyrimidines has been mentioned above in connection with the synthesis of di- and tetrahydropyrimidines. The kinetics of regeneration of the original 5,6-double bond have been examined in connection with the elimination of hydroxylamine and its derivatives from their 5,6-adducts with cytosine.[1261,6457] Intramolecular addition has also been known for some time, as with the fusion of pyrazolo and isoxazolo rings onto the 5,6-double bonds of a hydropyrimidine ring by using the appropriate hydrazone or oxime derivatives of a 5-acetylhydropyrimidine.[6996] There seems to have been little attempt to reverse such processes, particularly under hydrolytic conditions, to see whether the adduct might function as a physiologically useful pro-drug. Some complex recent examples include the degradation of a bicylic oxazolidinone (derived originally from aspartic acid) to a dihydroorotic acid derivative,[6998] or the isolation of a 1,3-disubstituted-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethione from the acid-catalyzed ring opening of tricyclic tetraazapentalene derivatives containing a hypervalent sulfur atom.[6997]

10. In 4,4,6-trimethyl-3,4-dihydro-2(1*H*)-pyrimidinone, the *gem*-dimethyl groups hindered dehydrogenation and hence aromatization of the ring. Consequently, on heating with sulfur (which could otherwise act as a dehydrogenating agent) in the presence of morpholine, the 6-methyl group is converted into the 6-carboxylic acid morpholide. In the absence of base, sulfur fuses a 3-thioxo-1,2-thiolo ring on to the 5,6-double bond.[5668]

11. Hexahydropyrimidine plays an unknown role as an intermediate in the fragmentation–methylation series of reactions with macrocyclic polyamines, which occurs during the Eschweiler–Clarke methylation process.[6999]

12. 4,4,6-Trimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione behaves as a cyclic urea and forms an analytically useful yellow complex with metals such as palladium.[7000]

11.5. PROPERTIES OF REDUCED PYRIMIDINES

11.5.1. Ionization

There have been few attempts at systematic determination of pK_a values in recent years.[7001,7002] This is regrettable because, for example, the aerial oxidation of some dihydro-2-pyrimidinamines seems to be bound up with their basic strength:[75] the stronger the base, the more easily oxidized. It would be interesting to discover any critical pK_a value conferring stability toward oxidation.

Although not as strongly basic as 1,4,5,6-tetrahydropyrimidines, various 4- and 6-methylated 1-phenyl-1,4-dihydropyrimidines all proved quite basic, with pK_a values in the narrow range, 8.43 to 8.68.[6292] This reflected the fact that protonation occurred at the unsubstituted nitrogen atom, giving a cation stabilized by amidinium resonance. Substituents in the phenyl ring had only minor effects. The presence of an electron-withdrawing group at C5, coupled with a switch of a methyl group from C4 to C2, reduced basicity by about 1 unit.[320] The highest pK_a recorded (9.66) was that of 4,6-dimethyl-1-phenyl-1,2-dihydropyrimidine, which was understandable in the light of protonation on the unsubstituted nitrogen atom to give a cation with vinamidinium resonance.[6292,6297,7003]

The acidity of *C*2-H in 2-benzoyl-1,3-dimethylhexahydropyrimidine has aroused interest.[7004] It is a weaker acid than acetophenone because the anion is destabilized by the orbital bearing the negative charge adversely interacting with an axial orbital containing the lone pair of electrons of a ring-nitrogen atom.[7004]

11.5.2. Tautomerism

The tendency for 1,2,2-trialkylhexahydropyrimidines to prefer (on account of ring strain, inter alia) the tautomeric open-chain alkyliminopropylamine structure has been known for some time.[4356] Similar ring-chain tautomerism has been confirmed in 2-aryl-4-hydroxyiminohexahydropyrimidines, and, in the case of the 2-phenyl compound, actual crystalline specimens of both the cyclic and open-chain tautomers have been isolated.[6715]

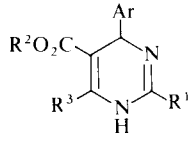
Data from X-ray crystallography (which seems to be acquiring rapidly the status of a daily routine laboratory technique) are invaluable for solving questions of tautomerism in the solid state. Thus it has been shown that in crystalline 2-phenyl-3,4,5,6-tetrahydro-4-pyrimidinol, the ring-nitrogen atom of the amidine system that carries an hydrogen atom is the one nearer to the ring-carbon atom bearing the hydroxyl substituent.[102]

4,6-Diethoxy-2,5-dihydropyrimidine exists as such in the solid state,[6354] the molecule possessing a flat ring: no enamine–imine tautomerism took place in solution. In contrast, 4,6-diphenyl-1,2-dihydropyrimidine had that structure in

the solid state but, in solution, exhibited extra peaks in the ^{13}C nmr spectrum, ascribed to its 2,5-dihydro tautomer.[137] The solid 1,2-dihydro tautomer had a molecule in which C2 and C5 were out of the ring plane; the distance between the two nitrogen atoms also precluded the existence of N–N interaction, and the ring did not possess the structure of an homoaromatic species, even in solution down to $-60°$.[188] Deviations from ring planarity in the solid state were also found for 4,4,6-trimethyl-2-phenyl-3,4-dihydropyrimidine[6177] and 4-methyl-2,6-diphenyl-3,6-dihydropyrimidine.[6178] In dilute solutions of carefully purified solvents, the latter molecule was in equilibrium with its 3,4-dihydro tautomer, the equilibrium distribution, [3,4]/[3,6], diminishing from 1.27 ($CDCl_3$, $-60°$) to 0.67 [$(CD_3)_2SO$, 25°].[7005]

An extra complication was encountered with 2-substituted-4,4,6-trimethyldihydropyrimidines. When the substituent was linked to C2 via a heteroatom, besides the 1,6 ⇌ 1,4 equilibrium, bands due to a third tautomer (the 4,5-dihydro one) were observed in both the ^1H and ^{13}C nmr spectra. The proportion of this tautomer rose as high as 45% in the 2-dimethylamino case.[7006]

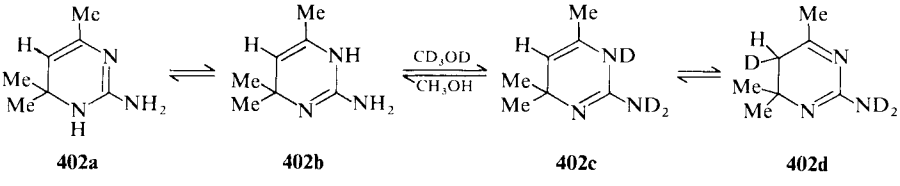
In respect of the Biginelli-related type of compound **401**, it was found that, in addition to the electron-withdrawing 5-ester group, the presence of a second electron-withdrawing substituent at the 2-position was essential for any detectable tautomeric equilibrium within the ring in solution. Thus in solutions of **401** ($R^1 = CF_3$, $R^2 = Pr^i$, $R^3 = Me$, $Ar = C_6H_4NO_2$-*o*) proton exchange between the 1,4-tautomer (as drawn) and the 3,4(1,6)-tautomer became slow enough to be detected by nmr spectroscopy at ambient temperature. In dilute deuterated benzene solution, the ratio of 1,4- to 1,6-tautomer was approximately 2 : 1, and this increased as the concentration increased. When the trifluoromethyl substituent was replaced by methylthio, the 1,4- and 1,6-tautomers were present in approximately equal amounts. When R was H or alkyl, only an averaged broad spectrum was observed, even at 270 MHz.[7007] An ethyl 4-*o*-chlorophenyl-2,6-dimethyldihydro-5-pyrimidinecarboxylate (**401**, $R^1 = R^3 = Me$, $R^2 = Et$, $Ar = C_6H_4Cl$-*o*) was shown to exist exclusively in the 1,4-dihydro tautomeric form with a rather flat boat-shaped ring in the crystalline state.[7008] When the 6-methyl group was replaced by a chloro substituent, the compound formed a hemihydrochloride, in which only half the molecules were in the electron-localized 1,4-dihydro form.[7008] An electron-withdrawing acetyl group in the 5-position had a similar effect to the alkoxycarbonyl substituent. A number of 5-acetyldihydropyrimidines, which existed in the solid state completely as their



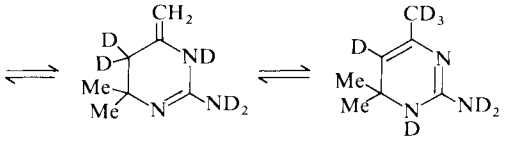
401

1,4-dihydro tautomers, underwent amidinic tautomerism with their 1,6-dihydro forms in solution.[290]

The 5-proton and protons belonging to the 2- and/or the 4-methyl groups in 4,4,6-trimethyl-3,4-dihydro-2-pyrimidinamine and in 2,4,4,6-tetramethyl-3,4-dihydropyrimidine were readily exchanged for deuterium by dissolution in CD_3OD in the absence of a base.[7009] In 1,4,4,6-tetramethyl-2-methylthio-1,4-dihydropyrimidine, where tautomeric shifts were blocked, no such H/D-exchange occurred, although the methylthio substituent was replaced by a tri deuteromethoxy group. The exchanges were rationalized in terms of a series of equilibria involving enamine tautomeric shifts (e.g., **402a–f**).[7009]



402a **402b** **402c** **402d**



402e **402f**

11.5.3. Nuclear Magnetic Resonance

The results of access to the more powerful 270–500 MHz nmr instruments have been seen in the preceding subsection. These instruments are clearly capable of results far beyond those from the mundane 60–100-MHz spectrometers that still give useful results liable to burial without comment in experimental sections of papers. Thus on a 500-MHz instrument, the use of a selective saturation technique confirmed that the two dihydro compounds in a solution of **401** ($R^1 = CF_3$, $R^2 = Pr^i$, $R^3 = Me$, $Ar = C_6H_4NO_2$-*o*) were definitely tautomers and that the NH proton was slowly transferred from the 1- to the 3-position of the hydropyrimidine ring.[7007] A spectacular demonstration of the power of a 400-MHz instrument involved the condensation of spermidine with acetaldehyde to afford 1-(δ-ethylideneaminobutyl)-2-methylhexahydropyrimidine, which possessed a chair conformation and two equatorial substituents. The 400-MHz spectrum was amenable to first-order analysis yielding chemical shifts and coupling constants for 20 out of the 23 protons in the molecule.[6729,6857]

The use of ^{13}C spectra has been decisive in settling the thione–thiol equilibrium in dihydropyrimidines, usually in favor of the thione structure,[7010] as well

as in elucidating the tautomeric equilibria in *N*-alkylated and *N,N'*-dialkylated 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethiones.[7011] The *cis*- and *trans*-stereoisomers of 5-acetyl-2,4-diphenyl-1,2,3,4-tetrahydropyrimidine were distinguished by their ^{13}C spectra,[144] as were the 1,4- and 1,6-tautomers of 2-methylthio, 2-methoxy, and 2-dimethylamino derivatives of a Biginelli-type compound.[531,3945,6948]

Records of ^{15}N nmr data continue to be sparse in the hydropyrimidine field. A recent example involves the 1,3-dinitroso derivative of hexahydropyrimidine and its 4-methyl counterpart.[6917] One notable ^{15}N shielding effect became apparent: the 10–12-ppm deshielding of the ring-nitrogen atom when the adjacent 4-position carried the methyl substituent. It was pointed out that this deshielding effect was comparable with the 9-ppm effect observed in the ^{13}C nmr spectra and arose from the same net displacement of electron density when a proton was replaced by a methyl group. Rotamer populations were estimated from ^{1}H nmr results supplemented by ^{13}C nmr data. It was confirmed that the rotamer with both nitroso groups pointing away from the *C*2-methylene grouping (*anti–anti*) had the greatest population and the rotamer with the two nitroso groups pointing toward this methylene grouping (*syn–syn*) had the least. The third *syn–anti* (and the *anti–syn*, in the case of the 4-methyl compound) had an intermediate population.[6917]

The stereochemical arrangement of the substituents in *cis*- and *trans*-6-alkoxy-5-fluoro-5,6-dihydrouracils were deduced from the magnitude of the proton–fluorine coupling constants ($J_{H6,F}$) in the ^{1}H nmr spectra and were confirmed subsequently by a single-crystal X-ray analysis of the *cis*-6-ethoxy-5-fluoro compound.[6601]

11.5.4. Conformations

There is a clear overlap between this and the preceding subsection in view of the utility of coupling constants in elucidating conformation(s), but this is another area where (at least in the solid state) X-ray crystallography has again made a decided impact at all three levels of reduction of the pyrimidine ring.

At the dihydro level, the ring in 4,6-diethoxy-2,5-dihydropyrimidine has already been mentioned as flat,[6354] while others seem to be described as boat-shaped with varying degrees of shallowness. Thus in the Biginelli-type compound (**401**, $R^1 = SCH_2Ph$, $R^2 = Et$, $R^3 = Me$, $Ar = C_6H_4NO_2$-*m*) the reduced pyrimidine ring was described as boat-shaped with the 4-aryl substituent occupying a pseudoaxial position.[6948] A related 2-methoxy compound (**401**, $R^1 = OMe$, $R^2 = Pr^i$, $R^3 = Me$, $Ar = C_6H_4NO_2$-*m*) has also been examined[6279] as well as an optically stable Biginelli compound.[6890]

A 1,4,5,6-tetrahydropyrimidine derivative (as the free base) has been mentioned earlier.[102] The rings in two 1,2,3,4-tetrahydropyrimidine derivatives seem to be nonplanar.[205,3843] The heterocyclic ring in 1,4,5,6-tetrahydropyrimidine tribromomercurate is flat at the resonating amidinium end, but the 5-CH_2

grouping projects out of the plane of the rest of the molecule.[7013] The rings in a variety of *N*-benzoyl-2-*t*-butyltetrahydro-4-pyrimidinones exhibit a range of shapes from half-chair to twist-boat conformations, and the *t*-butyl group is forced into axial or flagpole positions, respectively.[7014]

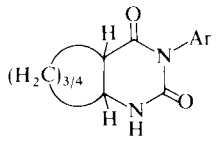
At the hexahydro level, 5-hydroxy-2-methyl-2-pyridin-2′-ylhexahydro-5-pyrimidinol has the conventional chair-shaped ring with equatorial hydroxyl and methyl groups but an axial pyridinyl substituent.[6807] Other chair conformations exist in various crystalline dodecahydro-2,2′-bipyrimidines.[6833–6835] However, the ring in **373** ($R^1 = R^2 = NO_2$, $R^3 = H$) is dish-shaped.[6918] In solution, the conformation of hexahydropyrimidines at a particular temperature is governed by two factors, the rate for ring inversion and the rates for inversion of the nitrogen atoms.[7015] The barrier for ring inversion is significantly higher than that for nitrogen inversion. The complexity of the situation is illustrated by the fact that in discussions of variable temperature ^1H and ^{13}C nmr data for 1,3-diethyl-2-methylhexahydropyrimidine, equilibria involving no less than eight conformers (all with chair-shaped rings) were taken into account.[7016] In considering the various inversion barriers, it became important to clearly define the ground state.[7017] According to molecular mechanics calculations, the structure of the most stable conformer of hexahydropyrimidine and its *N*-alkyl derivatives is a flattened chair, with the ring being flatter in the C—C—C region than in the N—C—N region.[7018] In hexahydropyrimidine itself, about half the molecules exist in a conformation in which one *N*-hydrogen atom occupies an axial position and the other an equatorial (the A–E situation), slightly greater than the E–E population (43%), and vastly in excess of the A–A population (both *N*—H atoms in the axial positions) of around 7.5%. In the other nine molecules examined, the A–A population was calculated to be zero in eight and amounted to ~2.5% in 2-*t*-butyl-1,3-dimethylhexahydropyrimidine. In 1,3-dimethylhexahydropyrimidine, the calculations suggested that about 66% of the molecular population had the E–E conformation, closer to the figure (55%) suggested by dipole moment measurements[7019] than that (89%) indicated by ^{13}C nmr results.[7020] The calculations predict that a methyl substituent at C2 should stabilize A–E conformers relative to E–E ones because of the greater intersubstituent van der Waal's repulsions in the latter, in agreement with experimental data.[7016] The calculations further reveal that in 1,2,3-trimethylhexahydropyrimidine, the proportion of the molecular population with an axial 2-methyl group was around 15%, compared with the 9–11% according to ^{13}C nmr studies.[7020] In 1,3-diethyl-2-methylhexahydropyrimidine, the substantial buttressing effect of the ethyl groups[7016] ensured that the 2-methyl group occupies predominantly an axial position, about 57% according to these calculations. Such calculations also suggest for the crowded (but still unknown) 1,2,3-tri-*t*-butylhexahydropyrimidine that the molecule should exist overwhelmingly (> 99.9%) in the A–E conformer with the *t*-butyl group also mainly axial (> 99.9%).

The introduction of a 5-hydroxy substituent into the unsubstituted hexahydropyrimidine molecule causes complications. It occupies an equatorial

position in D_2O where intermolecular hydrogen bonding prevails but largely (> 95%) with an axial position in $CDCl_3$ because of internal hydrogen bonding. The 2-methyl and 2,2-dimethyl homologs also seemed to have significant axial hydroxyl groups, but the investigation was rendered difficult because of the number of diastereoisomers, facile solvolysis, or ring opening.[7021,7022] The effect of more complex substituents on the conformations of various hexahydropyrimidines has also been discussed.[7023]

11.5.5. Mass Spectra

As with other spectroscopic data, much mass-spectral information is listed in the experimental sections of papers, largely without comments.[6292,6364,6951] In Biginelli compounds, the mass spectra include peaks due to ions resulting from a cyclization process between the 5-ethoxycarbonyl group and a 4-methyl or 4-phenyl substituent.[7024] In molecules such as **403** (which can be regarded as 5,6-dialkyl-5,6-dihydrouracils), *cis*- and *trans*-fusion of the two rings can be distinguished readily from the mass spectra, which also contain prominent ions of the composition $[ArN{=}C{=}O]^{+\cdot}$ and $ArNH_2^{+\cdot}$.[7025] The mass spectra of substituted 1,4-dihydropyridines have recently attracted attention.[7026,7027] In view of the repeated stress on the azalog (aza-analog) relationship with 1,4-dihydropyrimidines like the Biginelli compounds, it is to be hoped that systematic mass-spectrometric investigations, using all the modern techniques [EI, CI, FAB (electron ionization, configuration interaction, fast atom bombardment), etc.] will be undertaken shortly. Compared with the parent heteroaromatic pyrimidines, reduced pyrimidines have fared badly in this area.



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11.5.6. Applications of Hydropyrimidines

Reference to even a recent semiannual index of *Chemical Abstracts* will reveal that hydropyrimidines continue to have multitudinous uses, although it is unlikely that the claim for a 4-methyldihydro-2(1*H*)-pyrimidinone as both an hypnotic and a fertilizer will be bettered as an example of broad-spectrum activity.[7028] Constraints of space prevent even a brief survey, but perhaps the prominence of dihydropyrimidines in medically important areas such as neoplasm inhibitors,[7029] antiparasitic agents,[7030] vasodilative and hypertensive activity,[6280] and platlet activating factor antagonists[7031] is worthy of mention.

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CHAPTER 12

The Ionization and Spectra of Pyrimidines

Although the ionization, uv spectral, and ir/Raman spectral properties of pyrimidine and its simple derivatives are notable, in that they reflect the fundamental state of a biologically important π-deficient diazine system (**1**), such aspects have been discussed adequately elsewhere in the context of related systems.[5998,5999,6078,6079,6080,6081] For additional earlier (but still valid) experimental and correlative work, see the first edition of this book (Chapter 13 and references cited therein). Even the roles of such data in elucidating the gross and/or fine structures of individual pyrimidines (see, e.g., Section 7.1.2) have been assumed largely in recent years by various forms of nmr spectra: very few modern papers report ionization or absorption data for new compounds, except when such material is of potential use for quantitative analytical or kinetic purposes. Accordingly, any discussion in this chapter is confined to nmr spectra (by Dr. M. David Fenn); other relevant topics are represented only by tabulated data for selected pyrimidines or by listing a few typical examples with references.

1

12.1. IONIZATION CONSTANTS

Modern procedures for determining ionization constants have been described in considerable detail.[6082] Monumental critical compilations of ionization constants for organic bases and acids have appeared:[6083–6085] naturally, these invaluable works include data for pyrimidines, but the relatively modest Table 12.1 presented here has been compiled independently from original papers and is intended to include all known pK_a values for those pyrimidines defined as "simple" in the introduction to the Appendix. In addition, the prediction of ionization constants has reached a moderate level of reliability[6086–6088,6116] and such values may be used where reasonable latitude is acceptable for the purpose in hand. See also Section 12.5 for nmr-determined pK_a values.

TABLE 12.1. MEASURED pK_a VALUES[a] FOR SIMPLE PYRIMIDINES IN WATER AT 20–25°

Pyrimidine	pK_a Acidic	pK_a Basic	Ref.
5-Acetamido-2,6-diamino-4(3*H*)-pyrimidinone	9.9	3.1	629
4-Acetamidopyrimidine		2.8	1400
4-Acetylimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione		3.2	806
4-Acetylimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone		3.7	806
5-Allenyl-4,6-dimethyl-2-methylaminopyrimidine		4.9	843
2-Allylamino-4,6-dimethylpyrimidine		5.0	843
2-Allylaminopyrimidine		3.6	1405
5-Allyl-2-chloro-4,6-dimethylpyrimidine		− 0.5	843
5-Allyl-4,6-dimethyl-2-methylaminopyrimidine		5.4	843
5-Allyl-4,6-dimethyl-2-pyrimidinamine		5.2	843
1-Allyl-4,6-dimethyl-2(1*H*)-pyrimidinimine		11.2	843
5-Allyl-4,6-dimethyl-2(1*H*)-pyrimidinone	10.7	4.0	843
2-Allylimino-1,2-dihydro-1-propylpyrimidine		11.5	902
1-Allyl-4-methoxy-6-nitroamino-2(1*H*)-pyrimidinone	3.52		903
1-Allyl-2-propylimino-1,2-dihydropyrimidine		12.3	902
1-Allyl-2(1*H*)-pyrimidinimine		10.5	923
5-Allyl-1,4,6-trimethyl-2(1*H*)-pyrimidinimine		12.0	843
2-Amino-5-bromo-4(3*H*)-pyrimidinone	8.1	2.6	1040
4-Amino-5-bromo-2(1*H*)-pyrimidinone	10.3	3.0	1040,2277
2-Amino-5-chloro-4(3*H*)-pyrimidinone	8.0	2.5	1040
2-Amino-6-chloro-4(3*H*)-pyrimidinone	8.1	0.5	1040
4-Amino-5-chloro-2(1*H*)-pyrimidinone	10.4	2.9	1040
4-Amino-6-chloro-2(1*H*)-pyrimidinone	8.6	3.3	1040
2-Amino-5-diazonio-6-dimethylamino-4-pyrimininolate[b]		5.1	1051

6-Amino-5-dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione		3.8	2667
2-Amino-6-dimethylamino-3-methyl-5-nitro-4(3*H*)-pyrimidinone		− 0.4	2407
2-Amino-6-dimethylamino-5-nitro-4(3*H*)-pyrimidinone	8.5	− 0.6	1051,2407
6-Amino-5-dimethylamino-4(3*H*)-pyrimidinone	10.4	4.2	1094
2-Amino-4,6-dimethyl-5-pyrimidinecarbonitrile		1.7	923
2-Amino-4,6-dimethyl-5-pyrimidinecarboxamide		3.4	923
6-Amino-2,5-dimethyl-4(3*H*)-pyrimidinone	11.4	2.6	3783
5-Amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	2.6, 8.7		3792
5-Amino-6-ethylamino-4(3*H*)-pyrimidinone	10.1	3.5	1094
6-Amino-5-ethylamino-4(3*H*)-pyrimidinone	9.8	4.8	1094
4-Amino-5-ethyl-1-methyl-2(1*H*)-pyrimidinone		5.0	1219
4-Amino-5-fluoro-1-methyl-2(1*H*)-pyrimidinone		2.8	2619
2-Amino-5-fluoro-4(3*H*)-pyrimidinone	8.0	2.6	1040
2-Amino-6-fluoro-4(3*H*)-pyrimidinone	8.4	< 0.0	1040
4-Amino-5-fluoro-2(1*H*)-pyrimidinone	10.9	2.8 or 2.9	1040,2664
4-Amino-6-fluoro-2(1*H*)-pyrimidinone	9.1	1.5	1040,2277
2-Amino-5-formamido-6-methylamino-4(3*H*)-pyrimidinone	10.8	1.9	3785
4-Amino-5-formamido-6-methyl-2(1*H*)-pyrimidinone	11.4	3.9	1291
4-Amino-5-formamido-2(1*H*)-pyrimidinone	10.9	3.6	1291
2-Amino-5-hydroxy-6-hydroxymethyl-4(3*H*)-pyrimidinone	9.8[c]	4.0[c]	1324
2-Amino-5-hydroxy-4,6(1*H*,5*H*)-pyrimidinedione		2.9[c]	1324
6-Amino-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	9.0[c]		1324
2-Amino-5-hydroxy-4(3*H*)-pyrimidinone	9.6[c]	4.1[c]	1324
2-Amino-4-imino-3-methyl-3,4-dihydro-5-pyrimidinecarbaldehyde	12.6(?)	8.5	923,1346
2-Amino-6-methoxy-5-nitro-4(3*H*)-pyrimidinone	7.4		1364
4-Amino-6-methoxy-2(1*H*)-pyrimidinethione	8.9	3.2	903
4-Amino-6-methoxy-2(1*H*)-pyrimidinone	10.9	4.6	903
2-Amino-6-methylamino-5-nitro-4(3*H*)-pyrimidinone	8.7	− 0.4	2407,3781
6-Amino-2-methylamino-4(3*H*)-pyrimidinone	11.0	3.2	1520

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
2-Amino-3-methyl-6-methylamino-5-nitro-4(3*H*)-pyrimidinone		− 0.2	2407,2624,3781
5-Amino-2-methyl-6-methylamino-4(3*H*)-pyrimidinethione	10.4	2.3	1400
4-Amino-3-methyl-2-methylimino-2,3-dihydro-5-pyrimidinecarbaldehyde	13.4(?)	8.7	923,1346
2-Amino-1-methyl-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	5.6		1346
4-Amino-1-methyl-5-nitro-2(1*H*)-pyrimidinone	10.6	< 1.0	1221
4-Amino-2-methyl-5-pyrimidinecarbaldehyde		4.5	1462
2-Amino-4-methyl-5-pyrimidinecarbonitrile		1.1	1465
4-Amino-2-methyl-5-pyrimidinecarbonitrile		3.5	1462
2-Amino-4-methyl-5-pyrimidinecarboxamide		2.7	1465
4-Amino-2-methyl-5-pyrimidinecarboxamide		5.0	1462
4-Amino-2-methyl-5-pyrimidinecarboxylic acid[b]	6.3	2.1	1462,3780
2-Amino-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione	7.4		3783
5-Amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	9.8		3904
5-Amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	10.5		3904
6-Amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	11.0		3814
6-Amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	8.6		3814
6-Amino-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	9.2	0.0	3783
2-Amino-3-methyl-4(3*H*)-pyrimidinethione		2.9	1507
4-Amino-1-methyl-2(1*H*)-pyrimidinone		4.6	696,2664
4-Amino-3-methyl-2(3*H*)-pyrimidinone	13.0	7.4 or 7.5	806,1534,3537,3782
4-Amino-5-methyl-2(1*H*)-pyrimidinone	12.4	4.6	1546
5-Amino-2-methyl-4(3*H*)-pyrimidinone	10.0	3.9, − 1.1	1551
6-Amino-3-methyl-4(3*H*)-pyrimidinone		1.0	968
6-Amino-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	9.8	0.0	968

2-Amino-5-nitro-4(3*H*)-pyrimidinone	6.7		1584
4-Amino-5-nitro-2(1*H*)-pyrimidinone	7.3 or 7.4	< 3.0	1221,1584
2-Amino-5-pyrimidinecarbonitrile		0.7, − 1.5	1346
4-Amino-5-pyrimidinecarbonitrile		2.5	1346
2-Amino-5-pyrimidinecarboxamide		2.1	1346
4-Amino-5-pyrimidinecarboxamide		4.2	1346
2-Amino-5-pyrimidinecarboxylic acid	4.5		3579
4-Amino-5-pyrimidinecarboxylic acid[b]	5.6		3579
6-Amino-4-pyrimidinecarboxylic acid[b]	6.3		3579
2-Amino-4,6(1*H*,5*H*)-pyrimidinedione	7.0–7.4[c]	1.3	1324,3783,3794
5-Amino-2,4(1*H*,3*H*)-pyrimidinedione	9.5	3.2	1640
6-Amino-2,4(1*H*,3*H*)-pyrimidinedione	8.4 or 8.7, 15.3	0.0 or 0.8	1640,3783,3814
2-Amino-4(3*H*)-pyrimidinethione	8.0	2.9	1507
4-Amino-2(1*H*)-pyrimidinethione	10.6	3.3	1221,1507
6-Amino-4(3*H*)-pyrimidinethione	9.3	− 0.2	1507
2-Amino-4(3*H*)-pyrimidinone	9.4 or 9.6 (10.8[d])	4.0 (3.9[d])	1520,3786,3788
4-Amino-2(1*H*)-pyrimidinone	12.2 (> 13.0[d])	4.5 or 4.6 (4.8[d])	1546,2664, 3786–3788
6-Amino-4(3*H*)-pyrimidinone	10.1 (11.3[d])	1.4 (< 2.5[d])	968,3788
6-Amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	7.3	0.3	3783
2,6-Bisdimethylamino-5-nitro-4(3*H*)-pyrimidinone	8.5	1.6	2407
4,6-Bisdimethylamino-2-pyrimidinamine		7.2, 0.8	3779
4,6-Bisdimethylaminopyrimidine		6.4, < 1.0	968
5,6-Bisethylamino-4(3*H*)-pyrimidinone	10.1	4.8	1094
4,6-Bisethylthio-2-methoxycarbonylmethylpyrimidine		1.1[e]	1749
4,6-Bismethylamino-2-methylthio-5-nitropyrimidine		1.6	1764
4,6-Bismethylamino-5-nitropyrimidine		2.6	1764
4,5-Bismethylaminopyrimidine		6.0	3789
4,6-Bismethylaminopyrimidine		6.4	968
4,6-Bismethylthiopyrimidine		1.6, − 5.6	3581

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
5-Bromo-2-carboxymethylpyrimidine	3.7		1749
5-Bromo-6-chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	4.9		1812
5-Bromo-6-chloro-2,4(1*H*,3*H*)-pyrimidinedione	4.9		1812
6-Bromo-5-chloro-2,4(1*H*,3*H*)-pyrimidinedione	4.8		1812
5-Bromo-4,5-dimethyl-2-methylaminopyrimidine		3.6	1437
5-Bromo-4,6-diemthyl-2-pyrimidinamine		3.4	1437
5-Bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione		− 6.4	1894
5-Bromo-1,4-dimethyl-2(1*H*)-pyrimidinimine		10.3	1465
5-Bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	2.2 or 2.4, 7.3 or 7.6		1872,3792
5-Bromo-2-ethoxypyrimidine		− 0.4	1879
5-Bromo-2-ethylaminopyrimidine		2.1	1437
5-Bromo-1-ethyl-2(1*H*)-pyrimidinimine		10.2	1437,3791
5-Bromo-1-ethyl-2(1*H*)-pyrimidinone		− 0.6	1879
5-Bromo-6-iodo-2,4(1*H*,3*H*)-pyrimidinedione	5.9		1812
6-Bromo-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	5.3		1812
5-Bromo-4-methoxy-1-methyl-2(1*H*)-pyrimidinone		− 3.3	1894
5-Bromo-2-methoxypyrimidine		− 0.8	1951
5-Bromo-4-methoxypyrimidine		1.4	1951
5-Bromo-2-methylaminopyrimidine		2.1	1741
5-Bromo-4-methyl-2-methylaminopyrimidine		2.9	1465
5-Bromo-1-methyl-2-methylimino-1,2-dihydropyrimidine		10.7 or 10.8	1741,3791
5-Bromo-4-methyl-2-pyrimidinamine		2.7	1465
5-Bromo-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	7.8–8.4	− 6.6	1894,3058,3904

5-Bromo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	8.3		3904
6-Bromo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	6.1		1812
5-Bromo-1-methyl-2(1*H*)-pyrimidinimine		10.0–10.2	1741,3791
5-Bromo-1-methyl-2(1*H*)-pyrimidinone		0.6	1879
5-Bromo-3-methyl-4(3*H*)-pyrimidinone		0.1	1879
5-Bromo-2-methylthiopyrimidine		0.9	1951
5-Bromo-4-methylthiopyrimidine		1.0	1951
5-Bromo-2-pyrimidinamine		2.0	1741
5-Bromo-4-pyrimidinamine		4.0	2826
2-Bromopyrimidine		1.6	1826
5-Bromo-2-pyrimidinecarboxylic acid	2.8		3579
5-Bromo-2,4-pyrimidinediamine		5.6	2331
5-Bromo-4,6-pyrimidinediamine		4.2	968
5-Bromo-2,4(1*H*,3*H*)-pyrimidinedione	7.8–8.6,13.0	− 7.3	1894,2277,2341,3904
6-Bromo-2,4(1*H*,3*H*)-pyrimidinedione	6.9		1812
5-Bromo-2(1*H*)-pyrimidinethione	5.5	− 0.4	1879
5-Bromo-4(3*H*)-pyrimidinethione	5.6	− 0.5	1879
5-Bromo-2,4,6-pyrimidinetriamine		5.2, − 0.3	3779
5-Bromo-2(1*H*)-pyrimidinone	7.4	0.4	1741,1879
5-Bromo-4(3*H*)-pyrimidinone	7.2	0.4	1879
5-Bromo-1,4,6-trimethyl-2(1*H*)-pyrimidinimine		11.0	1437,3791
2-Carboxymethyl-4,6-bisethylthiopyrimidine	4.0	1.2	1749
2-Carboxymethyl-4-chloro-6-methoxypyrimidine	3.7		1749
2-Carboxymethyl-4-chloro-6-methylpyrimidine	3.8		1749
2-Carboxymethyl-4-chloropyrimidine	3.6		1749
2-Carboxymethyl-4,6-dichloropyrimidine	3.3		1749
2-Carboxymethyl-4,6-dimethoxypyrimidine	3.9	1.2	1749
2-Carboxymethyl-4-ethylsulfonylpyrimidine	3.5		1749
2-Carboxymethyl-4-ethylthiopyrimidine	4.2	2.0	1749

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
2-Carboxymethyl-4-fluoropyrimidine	3.6		1749
2-Carboxymethyl-4-iodopyrimidine	3.7	− 0.4	1749
2-Carboxymethyl-4-isopropylpyrimidine	3.9	1.6	1749
2-Carboxymethyl-4-methoxypyrimidine	4.2	1.8	1749
2-Carboxymethyl-4-methylpyrimidine	3.9	1.4	1749
2-Carboxymethylpyrimidine	3.7	0.6	1749
5-Chloro-4,6-dimethoxy-2-pyrimidinamine		0.6	2069
4-Chloro-6-dimethylaminopyrimidine		2.4	968
2-Chloro-4,6-dimethyl-5-propylpyrimidine		0.3	843
2-Chloro-4,6-dimethylpyrimidine		− 0.7	843
6-Chloro-5-ethyl-2,4-pyrimidinediamine		4.0	3864
6-Chloro-5-ethyl-2,4-pyrimidinediamine 3-oxide		2.3	3864
4-Chloro-6-imino-1-methyl-1,6-dihydro-2-pyrimidinamine		9.9	1520
6-Chloro-5-iodo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	5.2		1812
6-Chloro-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	5.0		1812
6-Chloro-5-isopropyl-4(3*H*)-pyrimidinone	8.1	− 0.9	2186
4-Chloro-2-methoxycarbonylmethylpyrimidine		− 0.8[e]	1749
4-Chloro-6-methoxy-2-methoxycarbonylmethylpyrimidine		~ − 1.4[e]	1749
6-Chloro-2-methylamino-4-pyrimidinamine		3.8	1520
2-Chloro-4-methylaminopyrimidine		2.8	1520
4-Chloro-2-methylaminopyrimidine		2.6	1520
4-Chloro-6-methylaminopyrimidine		2.2	968
5-Chloro-2-methylaminopyrimidine		2.0	923

4-Chloro-2-methyl-6-methylamino-5-nitropyrimidine		< 1.0	1400
2-Chloro-4-methyl-6-methylamino-5-pyrimidinamine		3.5	1405
4-Chloro-1-methyl-6-methylimino-1,6-dihydropyrimidine		~ 9.0	2115
5-Chloro-6-methyl-2,4-pyrimidinediamine		6.0	3864
5-Chloro-6-methyl-2,4-pyrimidinediamine 3-oxide		2.5	3864
6-Chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	5.8 or 6.0		1812,2277
6-Chloro-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	6.5		3164
5-Chloro-1-methyl-2(1*H*)-pyrimidinimine		10.2	3791
6-Chloro-3-methyl-4(3*H*)-pyrimidinimine		~ 9.0	2115
6-Chloro-5-methyl-4(3*H*)-pyrimidinone	7.8	− 1.1	2186
5-Chloro-2-pyrimidinamine		1.7	923
6-Chloro-4-pyrimidinamine		2.1	968
2-Chloropyrimidine		− 1.9	1826
6-Chloro-4-pyrimidinecarboxylic acid	2.8		2326
5-Chloro-2,4-pyrimidinediamine		5.5 or 5.6	2331,3864
6-Chloro-2,4-pyrimidinediamine		3.6	1520,2331,3864
5-Chloro-2,4-pyrimidinediamine 3-oxide		2.0	3864
6-Chloro-2,4-pyrimidinediamine 3-oxide		2.3	3864
5-Chloro-2,4(1*H*,3*H*)-pyrimidinedione	7.9 or 8.0, ~ 13.0		2277,2341
6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione	5.7 or 5.8, ~ 13.0		1812,2277
5-Chloro-2,4,6-pyrimidinetriamine		5.2, − 0.4	3779
6-Chloro-4(3*H*)-pyrimidinone	7.4		968
5,6-Diamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione		4.4	1640
2,6-Diamino-5-formamido-4(3*H*)-pyrimidinone	9.9	2.5	3796
2,6-Diamino-5-hydroxy-4(3*H*)-pyrimidinone	9.2[c]	3.8[c]	1324
2,5-Diamino-6-methylamino-4(3*H*)-pyrimidinone	10.9	5.3, 1.2	3797
5,6-Diamino-2-methylamino-4(3*H*)-pyrimidinone	10.6	5.4	1520
2,6-Diamino-1-methyl-5-nitro-4(1*H*)-pyrimidinone		2.8	2407
2,6-Diamino-5-methyl-4(3*H*)-pyrimidinone	11.1 or 11.3	3.6	1520,3783

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a Acidic	pK_a Basic	Ref.
4,6-Diamino-5-methyl-2(1*H*)-pyrimidinone	11.8	6.7	3783
5,6-Diamino-1-methyl-4(1*H*)-pyrimidinone	> 14.0	3.6	2420
4,5-Diamino-6-oxo-1,6-dihydro-2-pyrimidinesulfonic acid	3.7, 9.2	2.4	3870
2,6-Diamino-5-propionamido-4(3*H*)-pyrimidinone	10.2	2.6	629
2,4-Diamino-5-pyrimidinecarbonitrile		3.8	2331
2,6-Diamino-4-pyrimidinecarboxamide		4.9	2331
2,4-Diamino-5-pyrimidinecarboxylic acid	6.8[b]	2.9[b]	2331
2,6-Diamino-4-pyrimidinecarboxylic acid	7.8[b]	1.4[b]	2331
5,6-Diamino-4-pyrimidinecarboxylic acid	7.2[b]	1.5[b]	2435
2,5-Diamino-4,6(1*H*,5*H*)-pyrimidinedione	~ 8.9	~ 3.6	3794
5,6-Diamino-2,4(1*H*,3*H*)-pyrimidinedione		4.6, 1.7	1640,3795
2,4-Diamino-6-pyrimidinesulfonic acid	4.7[b]		2331
2,6-Diamino-4(3*H*)-pyrimidinethione	10.2	1.7	2331
4,5-Diamino-2(1*H*)-pyrimidinethione	10.4	3.0	2443
4,6-Diamino-2(1*H*)-pyrimidinethione	10.5	5.0	3783
5,6-Diamino-4(3*H*)-pyrimidinethione	9.3 or 9.4	2.2 or 2.3	3798
2,6-Diamino-4(3*H*)-pyrimidinone	10.8 (10.2?)	3.3 (4.2?)	1520,3783,3794
4,5-Diamino-2(1*H*)-pyrimidinone	11.5	4.4	2443
4,6-Diamino-2(1*H*)-pyrimidinone	12.0	6.5 or 6.6	1741,3783
5,6-Diamino-4(3*H*)-pyrimidinone	9.9	3.6, 1.3 (?)	2443
5,6-Dibromo-2,4(1*H*,3*H*)-pyrimidinedione	5.0		1812
4,6-Dichloro-2-methoxycarbonylmethylpyrimidine		− 2.6[e]	1749
5,6-Dichloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	4.8		1812
2,4-Dichloro-5-pyrimidinecarboxylic acid	3.1		3579

2,6-Dichloro-4-pyrimidinecarboxylic acid	2.8		2326
5,6-Dichloro-2,4-pyrimidinediamine		2.1	3864
5,6-Dichloro-2,4-pyrimidinediamine 3-oxide		1.7	3864
5,6-Dichloro-2,4(1*H*,3*H*)-pyrimidinedione	4.7		1812
5,6-Diethoxy-2,4(1*H*,3*H*)-pyrimidinedione	10.5		2550
4,6-Dihydrazino-2-methyl-5-nitropyrimidine		4.5	684
5,6-Di-iodo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	6.2		1812
5,6-Di-iodo-2,4(1*H*,3*H*)-pyrimidinedione	6.1		1812
4,5-Di-isopropyl-6-methylaminopyrimidine		7.1	2570
5,6-Di-isopropyl-3-methyl-4(3*H*)-pyrimidinimine		10.4	2570
4,6-Dimethoxy-2-methoxycarbonylmethylpyrimidine		1.1	1749
4,5-Dimethoxy-2-methylpyrimidine		4.1	1462,1551
2,4-Dimethoxy-6-nitroaminopyrimidine	3.8 (?)		903
4,6-Dimethoxy-2-pyrimidinamine		3.4	2069
4,6-Dimethoxypyrimidine		1.5	3350
4-Dimethylamino-2,6-dimethylpyrimidine		7.7	1405
2-Dimethylamino-4-ethoxy-5-nitropyrimidine		1.3	1364
4-Dimethylamino-5-fluoro-1-methyl-2(1*H*)-pyrimidinone		2.2	2619
2-Dimethylamino-4-methoxy-6-nitroaminopyrimidine	5.7	0.0	903
2-Dimethylamino-4-methoxypyrimidine		5.9	1507
4-Dimethylamino-2-methoxypyrimidine		6.2	1678
4-Dimethylamino-6-methoxypyrimidine		4.2 or 4.3	968,3806
2-Dimethylamino-4-methylamino-5-nitropyrimidine		3.7	2624,3781
4-Dimethylamino-6-methylamino-5-nitropyrimidine		2.9	1764
4-Dimethylamino-6-methylamino-5-pyrimidinamine		5.4	1764
4-Dimethylamino-2-methylaminopyrimidine		8.1	1741
4-Dimethylamino-6-methylaminopyrimidine		6.4	968
6-Dimethylamino-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	5.0		2407
4-Dimethylamino-2-methylpyrimidine		7.5	1462

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
4-Dimethylamino-2-methyl-5-pyrimidinecarbonitrile		4.4	1462
4-Dimethylamino-2-methyl-5-pyrimidinecarboxamide		5.9	1462
4-Dimethylamino-2-methyl-5-pyrimidinecarboxylic acid		1.9[b]	1462
2-Dimethylamino-3-methyl-4(3*H*)-pyrimidinethione		2.0	1507
4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinethione		2.6	1507
6-Dimethylamino-3-methyl-4(3*H*)-pyrimidinethione		− 0.8	1507
4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinimine		13.7	1741
2-Dimethylamino-3-methyl-4(3*H*)-pyrimidinone		3.5	1507
4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinone		4.2	696
4-Dimethylamino-3-methyl-2(3*H*)-pyrimidinone		6.0	1743
6-Dimethylamino-3-methyl-4(3*H*)-pyrimidinone		< 1.0	1507
2-Dimethylamino-4-methylthiopyrimidine		5.0	1507
4-Dimethylamino-2-methylthiopyrimidine		5.7	1507
4-Dimethylamino-6-methylthiopyrimidine		4.6	1507
4-Dimethylamino-5-nitro-2-pyrimidinamine		3.5	1437
6-Dimethylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	4.8, 13.1		2407
4-Dimethylamino-2-pyrimidinamine		8.0	1741
2-Dimethylaminopyrimidine		4.0 or 4.2	708,1405,3778
4-Dimethylaminopyrimidine		6.3 or 6.4	708,3778
6-Dimethylamino-2,4-pyrimidinediamine		7.2, 0.7	3779
2-Dimethylamino-4,6(1*H*,5*H*)-pyrimidinedione	~ 6.7	1.5	3805
2-Dimethylamino-4(3*H*)-pyrimidinethione	8.0	2.2	1507
4-Dimethylamino-2(1*H*)-pyrimidinethione	11.2	2.4	1507
6-Dimethylamino-4(3*H*)-pyrimidinethione	~ 9.5	− 0.3	1507

2-Dimethylamino-4(3*H*)-pyrimidinone	9.9	3.7	1507
4-Dimethylamino-2(1*H*)-pyrimidinone	12.3	4.3	2664
6-Dimethylamino-4(3*H*)-pyrimidinone	10.4	1.2	968
1,3-Dimethyl-5,6-bismethylamino-2,4(1*H*,3*H*)-pyrimidinedione		4.9	2667
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	0.8		2673
1,3-Dimethyl-6-methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	9.2		2624,3781
4,6-Dimethyl-2-methylamino-5-propylpyrimidine		5.6	843
4,6-Dimethyl-2-methylamino-5-prop-1′-ynylpyrimidine		4.1	843
4,6-Dimethyl-2-methylamino-5-prop-2′-ynylpyrimidine		4.9	843
2,4-Dimethyl-6-methylaminopyrimidine		7.6	1405
2,5-Dimethyl-4-methylaminopyrimidine		7.6	2570
4,5-Dimethyl-6-methylaminopyrimidine		7.0	2570
4,6-Dimethyl-2-methylaminopyrimidine		5.3	1741
4,6-Dimethyl-2-methylamino-5-pyrimidinecarbonitrile		1.7	923
4,6-Dimethyl-2-methylamino-5-pyrimidinecarboxamide		3.6	923
1,3-Dimethyl-4-methylimino-3,4-dihydro-2(1*H*)-pyrimidinone		9.8	806
2,4-Dimethyl-6-methylthiopyrimidine		4.1	1715
4,6-Dimethyl-2-methylthiopyrimidine		2.1	1715
3,6-Dimethyl-2-methylthio-4(3*H*)-pyrimidinone		0.9	2553
1,6-Dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	7.4		2706
3,6-Dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	6.8		2706
1,3-Dimethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	4.7		3810
1,2-Dimethyl-4-oxo-1,4-dihydro-5-pyrimidinecarbonitrile		0.0	1551
1,2-Dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile		− 0.1	1551
1,2-Dimethyl-4-oxo-1,4-dihydro-5-pyrimidinecarboxamide		1.4	1551
1,2-Dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide		1.5	1551
1,4-Dimethyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxamide		1.8	1465
4,6-Dimethyl-2-propylaminopyrimidine		5.2	1405
4,6-Dimethyl-5-propyl-2-pyrimidinamine		5.5	843

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a Acidic	pK_a Basic	Ref.
4,6-Dimethyl-5-propyl-2(1*H*)-pyrimidinone	10.8	4.2	843
4,6-Dimethyl-2-prop-2′-ynylaminopyrimidine		4.4	843
4,6-Dimethyl-5-prop-1′-ynyl-2-pyrimidinamine		4.0	843
4,6-Dimethyl-5-prop-2′-ynyl-2-pyrimidinamine		4.5	843
4,6-Dimethyl-1-prop-2′-ynyl-2(1*H*)-pyrimidinimine		10.4	843
4,6-Dimethyl-5-prop-1′-ynyl-2(1*H*)-pyrimidinone	9.4	2.7	843
4,6-Dimethyl-5-prop-2′-ynyl-2(1*H*)-pyrimidinone	10.2	3.6	843
2,6-Dimethyl-4-pyrimidinamine		7.0 or 6.3[f]	1405,2069
4,6-Dimethyl-2-pyrimidinamine		4.9 or 5.0	1405,3777,3784
4,6-Dimethylpyrimidine		2.7	1855
2,5-Dimethyl-4,6-pyrimidinediamine		7.1, 0.2	3783
5,6-Dimethyl-2,4-pyrimidinediamine		8.1	2331
1,3-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione		− 3.3	1894
1,5-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	10.3		3904
3,5-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	10.7		3904
5,6-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	10.3		2550
2,6-Dimethyl-4-pyrimidinesulfonic acid	1.6		2263
4,5-Dimethyl-2-pyrimidinesulfonic acid	− 0.3		2263
4,6-Dimethyl-2-pyrimidinesulfonic acid	− 0.1		2263
5,6-Dimethyl-4-pyrimidinesulfonic acid	1.2		2263
2,6-Dimethyl-4(3*H*)-pyrimidinethione	8.1	1.8	1879
4,6-Dimethyl-2(1*H*)-pyrimidinethione	8.5	2.8	1855
1,3-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	4.6		2802
1,4-Dimethyl-2(1*H*)-pyrimidinimine		11.1	1465

1,6-Dimethyl-2(1*H*)-pyrimidinimine		10.9	2114
2,3-Dimethyl-4(3*H*)-pyrimidinimine		10.4	2570
3,5-Dimethyl-4(3*H*)-pyrimidinimine		9.8	2570
3,6-Dimethyl-4(3*H*)-pyrimidinimine		10.1	2570
4,6-Dimethyl-5-pyrimidinol	7.3 or 8.3[c]	3.1 or 3.8,[i] −4.8	3758,3951
4,6-Dimethyl-5-pyrimidinol-1-oxide	6.0[c]	5.5(?)[i]	3758
1,2-Dimethyl-4(1*H*)-pyrimidinone		2.7	1551
1,4-Dimethyl-2(1*H*)-pyrimidinone		3.2[g]	1879
1,5-Dimethyl-4(1*H*)-pyrimidinone		2.5	1879
1,6-Dimethyl-2(1*H*)-pyrimidinone		3.4	1879
2,3-Dimethyl-4(3*H*)-pyrimidinone		2.7	1551
2,5-Dimethyl-4(3*H*)-pyrimidinone	9.6	3.2	1551
2,6-Dimethyl-4(3*H*)-pyrimidinone	9.8	3.1	843
3,5-Dimethyl-4(3*H*)-pyrimidinone		2.2	1879
4,5-Dimethyl-2(1*H*)-pyrimidinone		3.4	2263
4,6-Dimethyl-2(1*H*)-pyrimidinone	9.9 or 10.5	3.8	843,2828
4,6-Dimethyl-2(1*H*)-pyrimidinone 3-oxide	6.1	2.9	2828
1,3-Dimethyl-4-semicarbazono-3,4-dihydro-2(1*H*)-pyrimidinethione	13.7(?)	3.3	806
1,3-Dimethyl-4-semicarbazono-3,4-dihydro-2(1*H*)-pyrimidinone	14.1(?)	4.0	806
1,3-Dimethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	2.6		2837
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	4.2 or 4.3, 8.9		3142,3579
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	2.1–2.8, 9.5, >13.0		1546,2326,2856,3142
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonamide	5.4		3804
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid	7.3[h]		3804
5-Ethoxycarbonylamino-2-methyl-4(3*H*)-pyrimidinone	8.1	2.7	1551
2-Ethoxy-5-methylpyrimidine		1.8	1879
2-Ethoxy-5-nitro-4(3*H*)-pyrimidinone	4.9		1584
4-Ethoxy-5-nitro-2(1*H*)-pyrimidinone	6.6		1584
2-Ethoxypyrimidine		1.3	3144

TABLE 12.1. *(Continued)*

Pyrimidine	pK_a Acidic	pK_a Basic	Ref.
2-Ethoxy-4(3*H*)-pyrimidinone	8.2		1546
4-Ethoxy-2(1*H*)-pyrimidinone	10.7	1.0	1546,1894
Ethyl 4-acetamido-2-methyl-5-pyrimidinecarboxylate		1.4	1462
Ethyl 4-amino-2-methyl-5-pyrimidinecarboxylate		4.5	1462,3780
4-Ethylamino-5-nitro-2(1*H*)-pyrimidinone	7.7		1221
Ethyl 4-amino-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	9.9	3.3	3783
2-Ethylaminopyrimidine		4.0	1741
6-Ethylamino-2,4-pyrimidinediamine		7.2	3864
6-Ethylamino-2,4-pyrimidinediamine 3-oxide		4.6	3864
4-Ethylamino-2(1*H*)-pyrimidinethione	11.1	3.1	1221
4-Ethylamino-2(1*H*)-pyrimidinone	> 13.0	4.6	1221
Ethyl 4-amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate	7.6	0.6	3783
Ethyl 2,4-diamino-5-pyrimidinecarboxylate		5.1	2331
Ethyl 5,6-diamino-5-pyrimidinecarboxylate		4.8	2435
Ethyl 4-dimethylamino-2-methyl-5-pyrimidinecarboxylate		5.5	1462
Ethyl 1,2-dimethyl-4-oxo-1,4-dihydro-5-pyrimidinecarboxylate		1.5	1551
Ethyl 1,2-dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylate		1.4	1551
Ethyl 4-ethoxy-2-methyl-5-pyrimidinecarboxylate		2.7	1462
5-Ethyl-4-ethylamino-1-methyl-2(1*H*)-pyrimidinone		4.7	1219
2-Ethylimino-1-methyl-1,2-dihydropyrimidine		12.0	902
Ethyl 4-methoxy-2-methyl-5-pyrimidinecarboxylate		2.4	1551
2-Ethyl-4-methylaminopyrimidine		7.3	2570
5-Ethyl-2-methylaminopyrimidine		4.3	1741
5-Ethyl-4-methylaminopyrimidine		6.7	2570

Ethyl 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	8.2		3347
1-Ethyl-2-methylimino-1,2-dihydropyrimidine		11.9	902
5-Ethyl-1-methyl-4-methylamino-2(1*H*)-pyrimidinone		4.7	1219
Ethyl 2-methyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	7.8	1.3	1551
5-Ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	10.4		2550
6-Ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	10.4		2550
2-Ethyl-3-methyl-4(3*H*)-pyrimidinimine		10.1	2570
5-Ethyl-1-methyl-2(1*H*)-pyrimidinimine		11.5	1741
5-Ethyl-3-methyl-4(3*H*)-pyrimidinimine		9.9	2570
1-Ethyl-6-methyl-2(1*H*)-pyrimidinone		3.5	1879
5-Ethyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	10.3		2550
5-Ethyl-2,4-pyrimidinediamine		7.6	3864
5-Ethyl-2,4-pyrimidinediamine 3-oxide		3.5	3864
5-Ethyl-2,4,6-pyrimidinetriamine		6.8, 1.6	3779
1-Ethyl-2(1*H*)-pyrimidinimine		10.9	1741
1-Ethyl-2(1*H*)-pyrimidinone		2.7	1879
2-Ethylthio-5-fluoro-4-hydrazinopyrimidine		4.8	3029
2-Ethylthio-4-hydrazinopyrimidine		4.8	3029
4-Ethylthio-2-methoxycarbonylmethylpyrimidine		2.0	1749
2-Ethylthio-3-methyl-4(3*H*)-pyrimidinone		0.9	2553
2-Ethylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	6.0, 10.5		3142
1-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	8.7		2553
3-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	8.7		2553
5-Fluoro-4-imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone		7.2	2619
5-Fluoro-4-methylamino-2(1*H*)-pyrimidinone		2.7	2664
5-Fluoro-1-methyl-4-methylamino-2(1*H*)-pyrimidinone		2.4	2619
6-Fluoro-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	4.8		3164
5-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione	8.0 or 8.2		2664,3347,3807
6-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione	4.0, ~ 13.0		2277

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
5-Formamido-4,6-bismethylamino-2-methylthiopyrimidine		4.2	1764
5-Formamido-4,6-bismethylaminopyrimidine		5.0	1764
5-Formamido-2-methylamino-4-pyrimidinamine		6.1	1764
5-Formamido-2-methyl-4-methylamino-6-methylthiopyrimidine		3.9	1400
5-Formamido-2-methylthio-4-pyrimidinamine		3.7	1400
5-Formamido-2,4-pyrimidinediamine		6.0	2331
5-Formamido-2,4,6-pyrimidinetriamine		5.6 or 5.7	1739,3779
2-Hydrazino-3,6-dimethyl-4(3*H*)-pyrimidinone		5.5	2106
2-Hydrazino-4-methoxy-6-methylpyrimidine		6.2	2106
4-Hydrazino-6-methoxy-5-nitropyrimidine		2.8	684
6-Hydrazino-2-methyl-5-nitro-4-pyrimidinamine		4.1	684
2-Hydrazino-6-methyl-4(3*H*)-pyrimidinone		3.8	2106
6-Hydrazino-5-nitro-4-pyrimidinamine		3.7	684
4-Hydrazino-5-nitropyrimidine		2.6	3229
2-Hydrazinopyrimidine		4.6, −0.5	1715
1-β-Hydroxyethyl-2(1*H*)-pyrimidinamine		10.5	923
4-Hydroxyimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone		2.7(?)	806,3225
5-Hydroxymethyl-2-methyl-4(3*H*)-pyrimidinone	9.2	2.7	1551
5-Hydroxy-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	6.4[c]		1324
5-Hydroxy-2-methyl-4(3*H*)-pyrimidinone	7.6, 12.7	2.9	1551, cf. 1324
5-Hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	8.1, 11.5		3801
5-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	2.8 (3.2[c]), 11.0		1324,3801,3811
5-Hydroxy-4(3*H*)-pyrimidinone	7.5, 11.6	2.0	3801

5-Hydroxy-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	2.6[c]		1324
2-Imino-1,4-dimethyl-1,2-dihydro-5-pyrimidinecarboxamide		9.5	1465
4-Imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione		8.6	806
4-Imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone		9.3 or 9.4	696,806,3782
4-Imino-1-methyl-1,4-dihydro-2-pyrimidinamine		12.9	1520
4-Imino-1-methyl-1,4-dihydro-5-pyrimidinamine		> 12.5	1520
6-Imino-1-methyl-1,6-dihydro-4-pyrimidinamine		12.7	1437
2-Imino-1-methyl-1,2-dihydro-5-pyrimidinecarboxamide		9.1	1346
4-Imino-1-methyl-1,4-dihydro-2,5-pyrimidinediamine		13.7	1764
6-Imino-1-methyl-1,6-dihydro-2,4-pyrimidinediamine		> 12.7	1520
6-Imino-1-methyl-1,6-dihydro-4,5-pyrimidinediamine		12.1	1764
4-Imino-1-methyl-2-methylthio-1,4-dihydro-5-pyrimidinamine		> 12.6	1520
4-Imino-1-methyl-6-methylthio-1,4-dihydro-2-pyrimidinamine		> 12.0	1520
4-Imino-3-methyl-6-methylthio-3,4-dihydro-2-pyrimidinamine		> 11.2	1520
6-Imino-1-methyl-5-nitro-1,6-dihydro-4-pyrimidinamine		~ 7.6	1437
2-Imino-1,4,6-trimethyl-1,2-dihydro-5-pyrimidinecarboxamide		~ 10.2	923
5-Iodo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	1.9, 7.6		3792
4-Iodo-2-methoxycarbonylmethylpyrimidine		− 0.6	1749
5-Iodo-2-methylaminopyrimidine		2.4	923
6-Iodo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	6.9		1812
5-Iodo-1-methyl-2(1*H*)-pyrimidinimine		10.2	3799
5-Iodo-2-pyrimidinamine		2.2	923
5-Iodo-2,4(1*H*,3*H*)-pyrimidinedione	8.3 or 8.4, ~13.0		2277,2341
6-Iodo-2,4(1*H*,3*H*)-pyrimidinedione	6.6		1812
4-Isopropoxy-2-methylpyrimidine		4.5	1462
2-Isopropoxypyrimidine		1.6	3144
2-Isopropylamino-4,6-dimethylpyrimidine		5.2	1405
2-Isopropylaminopyrimidine		4.1	1437
4-Isopropyl-2-methoxycarbonylmethylpyrimidine		1.6	1749

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
2-Isopropyl-4-methylaminopyrimidine		7.4	2570
4-Isopropyl-6-methylaminopyrimidine		6.5	2570
5-Isopropyl-4-methylaminopyrimidine		6.8	2570
2-Isopropyl-3-methyl-4(3*H*)-pyrimidinimine		10.3	2570
5-Isopropyl-3-methyl-4(3*H*)-pyrimidinimine		9.9	2570
6-Isopropyl-3-methyl-4(3*H*)-pyrimidinimine		10.6	2570
5-Isopropyl-4,6(1*H*,5*H*)-pyrimidinedione	6.4	− 0.6	2186
1-Isopropyl-2(1*H*)-pyrimidinone		2.9	1879
5-Isopropyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	5.1, 12.3	− 0.7	2186
2-Methoxycarbonylmethylpyrimidine		0.5	1749
2-Methoxy-4,6-dimethylpyrimidine		2.8	1951
4-Methoxy-2,5-dimethylpyrimidine		4.8	1551
4-Methoxy-2,6-dimethylpyrimidine		4.8	1951
1-Methoxy-4,6-dimethyl-2(1*H*)-pyrimidinone		3.1	2828
5-Methoxy-1,2-dimethyl-4(1*H*)-pyrimidinone		2.8	1551
5-Methoxy-2,3-dimethyl-4(3*H*)-pyrimidinone		2.7	1551
4-Methoxy-2-methoxycarbonylmethylpyrimidine		2.1	1749
4-Methoxy-2-methylaminopyrimidine		5.8	1741
4-Methoxy-6-methylaminopyrimidine		4.2	968
5-Methoxy-2-methylaminopyrimidine		3.4	2114
4-Methoxy-3-methyl-6-methylimino-3,6-dihydropyrimidine		~ 11.0	2115
4-Methoxy-1-methyl-6-nitroamino-2(1*H*)-pyrimidinone	3.8		903
2-Methoxy-4-methylpyrimidine		2.1	2249

2-Methoxy-5-methylpyrimidine		1.7	1879
4-Methoxy-2-methylpyrimidine		4.0	1462,1551
4-Methoxy-5-methylpyrimidine		3.6	1879
4-Methoxy-6-methylpyrimidine		3.7	2249
4-Methoxy-2-methyl-5-pyrimidinecarbonitrile		0.8	1551
4-Methoxy-2-methyl-5-pyrimidinecarboxamide		2.5	1551
6-Methoxy-5-methyl-4(3*H*)-pyrimidinethione	7.9	− 1.6	2186
2-Methoxy-1-methyl-4(1*H*)-pyrimidinimine		> 12.0	1678
5-Methoxy-1-methyl-2(1*H*)-pyrimidinimine		11.4	2114,3072
6-Methoxy-3-methyl-4(3*H*)-pyrimidinimine		~ 11.0	2115
2-Methoxy-6-methyl-4(3*H*)-pyrimidinone	8.4	~ 1.6	2249
4-Methoxy-1-methyl-2(1*H*)-pyrimidinone		0.7	1894
5-Methoxy-2-methyl-4(3*H*)-pyrimidinone	9.1	2.6	1551
6-Methoxy-3-methyl-4(3*H*)-pyrimidinone		− 0.4	3348
4-Methoxy-2-methylthio-6-nitroaminopyrimidine	3.7		903
4-Methoxy-6-methylthiopyrimidine		1.6	3348
4-Methoxy-6-nitroamino-2(1*H*)-pyrimidinone	3.6, 11.0		903
2-Methoxy-4-pyrimidinamine		5.3	1546
4-Methoxy-2-pyrimidinamine		5.5	1507
4-Methoxy-5-pyrimidinamine		4.3	1879
6-Methoxy-4-pyrimidinamine		4.0	968
2-Methoxypyrimidine		0.5 or 1.0	3144,3778, cf. 3801
4-Methoxypyrimidine		2.5	708,1432,3778
6-Methoxy-4-pyrimidinecarboxylic acid	3.7		2326
5-Methoxy-2,4-pyrimidinediamine		7.2	2331
6-Methoxy-4(3*H*)-pyrimidinethione	7.5	− 2.0	3348
5-Methoxy-4(3*H*)-pyrimidinone	8.6	1.8	3801
6-Methoxy-4(3*H*)-pyrimidinone	8.5	− 0.2	3350
6-Methylamino-5-nitro-4-pyrimidinamine		2.8	1770

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
6-Methoxy-2,4-pyrimidinediamine		5.5	2331
1-Methoxy-2(1*H*)-pyrimidinone		0.5	3366
4-Methylamino-6-methylthiopyrimidine		4.4	2115
6-Methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	5.1, 13.2		2407,3781
4-Methylamino-5-nitro-2(1*H*)-pyrimidinone	7.8	< 1.0	1221
2-Methylamino-4-pyrimidinamine		7.6	1520
6-Methylamino-4-pyrimidinamine		6.3	1770
2-Methylaminopyrimidine		3.8 or 4.0	708,1741
4-Methylaminopyrimidine		6.1	708
2-Methylamino-5-pyrimidinecarbonitrile		0.8	1346
2-Methylamino-5-pyrimidinecarboxamide		2.1	1346
6-Methylamino-2,4-pyrimidinediamine		7.2, 1.1	3779
6-Methylamino-4,5-pyrimidinediamine		5.9	1520
4-Methylamino-2(1*H*)-pyrimidinethione	11.1	3.1	1221
6-Methylamino-4(3*H*)-pyrimidinethione	9.6	− 0.3	2115
2-Methylamino-4(3*H*)-pyrimidinone	9.8	3.9	1520
4-Methylamino-2(1*H*)-pyrimidinone	> 13.0	4.6	1221
6-Methylamino-4(3*H*)-pyrimidinone	10.5	< 1.7	968
6-Methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	6.9		3872
2-Methyl-4,6-bismethylamino-5-nitropyrimidine		3.4	1764
2-Methyl-4,6-bismethylamino-5-pyrimidinamine		6.9	1764
Methyl 2,6-diamino-4-pyrimidinecarboxylate		5.3	2331
3-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	9.1		2673
Methyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	7.9		3347

1-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	< 1.0, 10.5		2673
3-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	0.7, 9.8		2673
1-Methyl-2-methylamino-6-methylimino-1,6-dihydropyrimidine		11.6	1508
2-Methyl-4-methylamino-6-methylthio-5-pyrimidinamine		6.0	1400
6-Methyl-5-methylamino-2-methylthio-4-pyrimidinamine		5.4	1400
1-Methyl-6-methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	8.5, 12.0		2407,3781
3-Methyl-6-methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	5.3		2407,3781
2-Methyl-4-methylamino-5-pyrimidinamine		7.5	1400
4-Methyl-6-methylamino-5-pyrimidinamine		6.8	1400
6-Methyl-4-methylamino-4-pyrimidinamine		6.1	1400
2-Methyl-4-methylaminopyrimidine		7.2	2570
4-Methyl-2-methylaminopyrimidine		4.6	1465
4-Methyl-6-methylaminopyrimidine		6.7	2570
5-Methyl-4-methylaminopyrimidine		6.6	2570
4-Methyl-2-methylamino-5-pyrimidinecarboxamide		2.9	1465
3-Methyl-6-methylamino-4(3*H*)-pyrimidinethione		− 0.5	1507
1-Methyl-4-methylamino-2(1*H*)-pyrimidinone		4.5	696
1-Methyl-6-methylamino-2(1*H*)-pyrimidinone	14.3	7.4	806
3-Methyl-6-methylamino-4(3*H*)-pyrimidinone		0.8	1507, cf. 968,2115
6-Methyl-5-*N*-methylformamido-2-methylthio-4-pyrimidinamine		4.0	1400
6-Methyl-5-*N*-methylformamido-4-pyrimidinamine		4.6	1400
1-Methyl-2-methylimino-1,2-dihydro-4-pyrimidinamine		14.0	1520
1-Methyl-2-methylimino-1,2-dihydropyrimidine		11.7	1437
1-Methyl-4-methylimino-6-methylthio-1,4-dihydropyrimidine		~ 11.0	2115
1-Methyl-6-methylimino-2-methylthio-1,6-dihydropyrimidine		10.3	1508
4-Methyl-2-methylthiopyrimidine		2.0	2249
4-Methyl-6-methylthiopyrimidine		3.3	2249
3-Methyl-2-methylthio-4(3*H*)-pyrimidinethione		− 0.3	806
1-Methyl-2-methylthio-4(1*H*)-pyrimidinimine		> 12.5	1520

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
1-Methyl-6-methylthio-4(1*H*)-pyrimidinimine		~11.0	2115
3-Methyl-2-methylthio-4(3*H*)-pyrimidinimine		9.9	1508
1-Methyl-6-methylthio-2(1*H*)-pyrimidinone		4.1(?)	806
1-Methyl-6-methylthio-4(1*H*)-pyrimidinone		1.8	3348
3-Methyl-2-methylthio-4(3*H*)-pyrimidinone		1.1	806
3-Methyl-6-methylthio-4(3*H*)-pyrimidinone		0.1	3348
5-Methyl-6-methylthio-4(3*H*)-pyrimidinone	9.1	0.0	2186
6-Methyl-2-methylthio-4(3*H*)-pyrimidinone	7.9		2553
2-Methyl-5-nitro-4-pyrimidinamine		2.7	684
2-Methyl-5-nitropyrimidine		1.5	2560
1-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	7.2 or 7.4		1432,2706,3347,3904
3-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	5.7		2706,3347,3904
6-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	6.4		2706
2-Methyl-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	6.2	− 0.2	1551
2-Methyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxamide	7.6	1.3	1551
2-Methyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	4.4, 9.9	0.8	1551
2-Methyl-4-pyrimidinamine		6.5	1462
4-Methyl-2-pyrimidinamine		4.2	3777
4-Methyl-5-pyrimidinamine		3.2	2249
6-Methyl-4-pyrimidinamine		6.3	2249
2-Methylpyrimidine		2.3	3778
4-Methylpyrimidine		2.0 or 2.1, − 6.1	3777,3778,3951
Methyl 2-pyrimidinecarboxylate		− 0.7	3791
6-Methyl-4-pyrimidinecarboxylic acid	3.1		2326

5-Methyl-2,4-pyrimidinediamine		7.7	2331
6-Methyl-2,4-pyrimidinediamine		7.5–7.7	2331,3784,3864
6-Methyl-2,4-pyrimidinediamine 1-oxide		4.5	3864
6-Methyl-2,4-pyrimidinediamine 3-oxide		3.4	3864
1-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	9.7 or 9.8	− 3.4	1546,1894,2277,3347,3786,3802,3904
2-Methyl-4,6(1*H*,5*H*)-pyrimidinedione	6.4 (6.6[c])	0.2	1324,3350
3-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	10.0		2277,3347,3802,3904
5-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	9.9, > 13.0		1221,1546,3347,3787,3802,3904
5-Methyl-4,6(1*H*,5*H*)-pyrimidinedione	6.0	− 0.5	2186
6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	9.6 or 9.7	~1.2	2249,3347,3786
3-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione	7.0		1221
6-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione	6.9, 12.0		1221
2-Methyl-4-pyrimidinesulfonic acid	0.8		2263
4-Methyl-2-pyrimidinesulfonic acid	− 0.8		2263
5-Methyl-2-pyrimidinesulfonic acid	− 1.2		2263
6-Methyl-4-pyrimidinesulfonic acid	0.2		2263
1-Methyl-2(1*H*)-pyrimidinethione		1.7	3480
1-Methyl-4(1*H*)-pyrimidinethione		1.2	3480
3-Methyl-4(3*H*)-pyrimidinethione		0.6	3480
4-Methyl-2(1*H*)-pyrimidinethione	8.0	2.2	2249
6-Methyl-4(3*H*)-pyrimidinethione	7.3	1.8	2249
1-Methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	4.2, 12.8		2802
1-Methyl-2(1*H*)-pyrimidinimine		10.8	3377
1-Methyl-4(1*H*)-pyrimidinimine		12.2	3377
3-Methyl-4(3*H*)-pyrimidinimine		10.0	1508
4-Methyl-5-pyrimidinol	7.1	2.5, − 4.8	3951
1-Methyl-2(1*H*)-pyrimidinone		2.5	1432
1-Methyl-4(1*H*)-pyrimidinone		2.0	3800
2-Methyl-4(3*H*)-pyrimidinone	9.1	2.5 or 2.7	1551,2263

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
3-Methyl-4(3*H*)-pyrimidinone		1.8	1432
4-Methyl-2(1*H*)-pyrimidinone	9.8	3.2	2249
5-Methyl-4(3*H*)-pyrimidinone	9.1	2.3	1879
6-Methyl-4(3*H*)-pyrimidinone	9.0	2.1	2249
2-Methylsulfinylpyrimidine		< -3.0	1715
4-Methylsulfinylpyrimidine		< 0.0	1715
5-Methylsulfinylpyrimidine		0.4	1715
2-Methylsulfonylpyrimidine		< -3.0	1715
4-Methylsulfonylpyrimidine		< 0.0	1715
5-Methylsulfonylpyrimidine		1.0	1715
6-Methylsulfonyl-2,4(1*H*,3*H*)-pyrimidinedione	4.7		3347,3804
2-Methylthio-5-nitropyrimidine		-2.7	1951
2-Methylthio-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	2.0		1764
2-Methylthio-4-pyrimidinamine		4.9	1507
4-Methylthio-2-pyrimidinamine		4.8	1507
6-Methylthio-2-pyrimidinamine		3.9	2115
2-Methylthiopyrimidine		0.6	3480
4-Methylthiopyrimidine		2.5	3480
2-Methylthio-2-pyrimidinecarboxylic acid	3.4		3579
2-Methylthio-4,5-pyrimidinediamine		5.1	1520
6-Methylthio-2,4-pyrimidinediamine		5.5	1520
2-Methylthio-4,6(1*H*,5*H*)-pyrimidinedione	5.1		1764
6-Methylthio-4(3*H*)-pyrimidinone	8.5	$-0.1, -7.0$	968,3348,3581
2-Methylthio-4-trimethylammoniopyrimidine chloride		> 11.9	1678

1-Methyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	2.5, 11.4		2837
1-Methyl-6-thioxo-1,6-dihydro-4(5*H*)-pyrimidinone	4.4	− 2.2	3348
3-Methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	8.2		806
3-Methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	5.1	− 1.1	3348
5-Methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	4.9, 11.6	− 1.2	2186
6-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	8.1		2553
6-Nitroamino-2,4(1*H*,3*H*)-pyrimidinedione	5.5, 12.9		903
5-Nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	< 1.5, 4.9		3142,3792
5-Nitro-2-pyrimidinamine		0.4	1741
5-Nitro-4-pyrimidinamine		2.0	684
5-Nitropyrimidine		0.7	2560
5-Nitro-2,4-pyrimidinediamine		2.6	2331
5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione	5.5 or 5.6 (5.3?)	11.5 or 11.7 (11.3?)	1546,1584,2706,3347,3904
5-Nitro-2,4,6-pyrimidinetriamine		3.2	3779,3864
5-Nitro-2,4,6-pyrimidinetriamine 1-oxide		2.0	3864
5-Nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	10.3[h]		3810
5-Nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	4.4, 9.7		3810
2-Oxo-1,2-dihydro-5-pyrimidinecarboxylic acid	3.5		3579
6-Oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	2.8, 8.4		2326,2856
4-Oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	3.9		3579
6-Oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	2.7		2326
2-Propoxypyrimidine		1.3	3144
2-Propylaminopyrimidine		4.1	1741
1-Propyl-2(1*H*)-pyrimidinimine		11.0	923
1-Propyl-2(1*H*)-pyrimidinone		2.8	1879
6-Propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	8.3, > 12.0	− 4.2, − 6.5	3581
2-Prop-2′-ynylaminopyrimidine		2.9	843
1-Prop-2′-ynyl-2(1*H*)-pyrimidinimine		10.0	843
2-Pyrimidinamine		3.5 or 3.7	1405,3777,3778

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a Acidic	pK_a Basic	Ref.
4-Pyrimidinamine		5.7	3777,3778
5-Pyrimidinamine		2.6 or 2.8	711,3777
Pyrimidine		1.3, − 6.9 or − 7.1	3777,3812, cf. 3813,3951
2-Pyrimidinecarboxylic acid	2.9 or 3.0	− 1.1	2579,3791
4-Pyrimidinecarboxylic acid	3.0		2326
5-Pyrimidinecarboxylic acid	3.2		3579
2,4-Pyrimidinediamine		7.3 or 7.4, − 1.0	1640,2331,3777,3864
2,5-Pyrimidinediamine		~4.0, ~1.0	1741
4,5-Pyrimidinediamine		6.0, − 1.0	1640,3793
4,6-Pyrimidinediamine		6.0	968
2,4-Pyrimidinediamine 3-oxide		3.2	3864
2,4(1*H*,3*H*)-Pyrimidinedione	9.4 or 9.5, 13.0 or 13.2	− 3.4	1894,2277,3347,3787,3801,3802,3904
4,6(1*H*,5*H*)-Pyrimidinedione	5.4	0.3	1324,3350,3801
2,4(1*H*,3*H*)-Pyrimidinediselone	5.5		3507
2,4(1*H*,3*H*)-Pyrimidinedithione	6.4 or 6.5, 11.2 or 12.6		1221,3507,3581
4,6(1*H*,5*H*)-Pyrimidinedithione	3.6, 9.7	− 2.3, − 7.2	3581
2-Pyrimidinesulfonic acid	− 1.7		2263
4-Pyrimidinesulfonic acid	− 0.5		1711
2,4,5,6-Pyrimidinetetramine		6.8	1739
2(1*H*)-Pyrimidinethione	7.0 or 7.1	1.4, − 8.3	1968,3480,3581

4(3*H*)-Pyrimidinethione	6.9	0.7 or − 0.7, − 6.6	1968,3480,3581
2,4,5-Pyrimidinetriamine		7.6, 2.6	2443
2,4,6-Pyrimidinetriamine		6.7–7.2, 1.1 or 1.3	3331,3777,3779,3783
4,5,6-Pyrimidinetriamine		5.8, 1.5	2443
2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione	3.9, 12.5		2802,3801
5-Pyrimidinol	6.8	1.8 or 1.9	3800, cf. 3758,3951
2(1*H*)-Pyrimidinone	9.2	2.2	3650
4(3*H*)-Pyrimidinone	8.6	1.7 or 1.9	1432,2327
2(1*H*)-Pyrimidinone 3-oxide	5.1	0.5	3366
2-Selenoxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	3.7		3652
2-Selenoxo-1,2-dihydro-4(3*H*)-pyrimidinone	7.2		3507
2,3,5,6-Tetramethyl-4(3*H*)-pyrimidinimine		10.9	2570
6-Thioxo-1,6-dihydro-4-pyrimidinecarboxylic acid	3.0		2326
2-Thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	3.7, 7.9, > 13.0	− 4.4, − 6.7	3581, cf. 2837,3803
2-Thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	7.7, 12.7, or > 13.0	− 4.2 or − 6.6	2553,3581,3809
6-Thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	4.3, 10.5	− 1.7	968,3348
2,5,6-Triamino-4(3*H*)-pyrimidinone	10.1	5.1, 2.0	3796
2,4,5-Trimethyl-6-methylaminopyrimidine		8.1	2570
1,4,6-Trimethyl-2-methylimino-1,2-dihydro-5-pyrimidinecarbonitrile		9.4	923
1,4,6-Trimethyl-5-propyl-2(1*H*)-pyrimidinimine		12.2	843
1,4,6-Trimethyl-5-prop-1′-ynyl-2(1*H*)-pyrimidinimine		11.0	843
1,4,6-Trimethyl-5-prop-2′-ynyl-2(1*H*)-pyrimidinimine		11.6	843
2,4,6-Trimethylpyrimidine		3.7	3951
2,5,6-Trimethyl-4-pyrimidinesulfonic acid	2.3		2263
1,4,6-Trimethyl-2(1*H*)-pyrimidinethione		3.2	2249
1,4,6-Trimethyl-2(1*H*)-pyrimidinimine		11.6	1741
2,3,5-Trimethyl-4(3*H*)-pyrimidinimine		10.1	2570

TABLE 12.1. (*Continued*)

Pyrimidine	pK_a		Ref.
	Acidic	Basic	
2,3,6-Trimethyl-4(3*H*)-pyrimidinimine		11.0	2570
3,5,6-Trimethyl-4(3*H*)-pyrimidinimine		10.8	2570
2,4,6-Trimethyl-5-pyrimidinol	7.6	3.8, −2.8	3951
1,2,5-Trimethyl-4(1*H*)-pyrimidinone		3.5	1551
1,4,6-Trimethyl-2(1*H*)-pyrimidinone		4.0	2249
2,3,5-Trimethyl-4(3*H*)-pyrimidinone		3.4	1551
2,5,6-Trisacetamido-4(3*H*)-pyrimidinone	7.7	−0.1	629
4,5,6-Trismethylaminopyrimidine		1.0	1764

[a] The term "simple pyrimidine" is defined at the head of the Appendix table. Each value is rounded to the first decimal place because long acquaintance with ionization constants in the pyrimidine series suggests that many reported pK_a values are reliable only thus far. This is partly because some workers pay little attention to the temperature of measurement, partly to significant variations in the buffers or titrants used, and partly to whether the constants are *mixed* (concentration-dependent) or *thermodynamic* (corrected to infinite dilution), a point frequently unreported.

[b] Neutral molecule zwitterionic.

[c] In 50% aqueous ethanol.

[d] In aqueous dimethylformamide.

[e] In aqueous methanol.

[f] In 50% aqueous acetone.

[g] Data omitted in error from original publication.

[h] Second acidic constant.

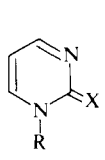
[i] In nitromethane.

12.2. ULTRAVIOLET SPECTRA

The ultraviolet spectra of pyrimidine and some typical simple derivatives are given briefly in Table 12.2. Care has been taken to present data representing a single ionic species in each case, a criterion not always observed, especially in the pre-1950 literature. Although full absorption curves for pyrimidines are seldom published nowadays, the literature does contain enough examples to make them familiar.[708,1432,1741,1968,3377,6078,6089]

12.3. INFRARED AND RAMAN SPECTRA

Although a great many ir spectra of pyrimidines must have been measured in order to confirm the presence of a carbonyl or other such entity in the molecule, very few complete spectra have been published, and even fewer have been analyzed to any extent. However, the ir and Raman spectra of pyrimidine itself (**1**) have been reported, and all bands therein have been assigned to one or more of the 24 possible vibration modes;[4606] the bands arising from pyrimidine hydrochloride (within the range 680–1800 cm^{-1}) have been assigned;[6092] such spectra from 2(1*H*)- (**2**, R = H, X = O) and 4(3*H*)-pyrimidinone (**3**, R = H, X = O), as well as from their hydrochlorides and sodium salts, have been analyzed in detail;[437,6091–6093] and some of the bands from 2(1*H*)- (**2**, R = H, X = S) and 4(3*H*)-pyrimidinethione (**3**, R = H, X = S), from 2- (**5**) and 4-methylthiopyrimidine (**6**), and from 1-methyl-2(1*H*)- (**2**, R = Me, X = S), 3-methyl-4(3*H*)- (**3**, R = Me, X = S), and 1-methyl-4(1*H*)-pyrimidinethione (**4**, R = Me, X = S) have been assigned in connection with tautomerism in the parent thiones.[6094] Relevant bands in the ir spectra of 2-, 4-, and 5-pyrimidinamine and related compounds have been studied, also in connection with tautomerism.[3377,6099, cf. 6100] The availabililty of ir, Raman, and other spectral data for simple pyrimidines is usually indicated under individual entries in the appendixed "Table of Simple Pyrimidines".



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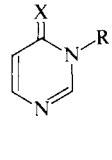

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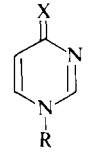

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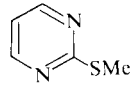

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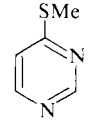

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TABLE 12.2. ULTRAVIOLET SPECTRA OF TYPICAL SIMPLE PYRIMIDINES

Pyrimidine	Solvent or Species[a]	λ_{max}(log ε)[b]	Ref.
Pyrimidine (unsubstituted)	0	271(2.63), 243(3.51)	3791
	+	242(3.74)	
	EtOH	280(2.58), 343(3.47)	
	C_6H_{12}	298(2.51), 243(3.31)	
2-Methylpyrimidine	0	248(3.46)	1968
	+	251(3.87)	
4-Methylpyrimidine	0	244(3.53)	1968
	+	244(3.70)	
5-Phenylpyrimidine	EtOH	256(4.08)	4638
5-Nitropyrimidine	C_6H_{12}	293(2.72), 255(3.54), 249(3.74), 241(3.88), 235(3.92), 232(3.91), 224(3.88)	2560
	0	237(3.90)	
	+	305(3.83)	
2-Chloropyrimidine	0	251(3.43), 209(3.75)	1968
	EtOH	282(2.23), 252(3.19)	
5-Chloropyrimidine	0	258(3.38), 211(3.85)	1968
	EtOH	293(2.52), 258(3.34)	
5-Bromopyrimidine	0	261(3.46), 216(4.02)	1968
	EtOH	294(2.53), 261(3.33), 217(3.87)	
2(1*H*)-Pyrimidinone	0	298(3.68), 212(4.03)	1432
	+	309(3.76)	
	−	292(3.66), 220(4.07)	

4(3*H*)-Pyrimidinone	0	260(3.57), 223(3.86)	708
	+	251(3.47), 224(3.99)	
	–	263(3.52), 227(4.05)	
5-Pyrimidinol	0	325(2.03), 271(3.68), 214(3.99)	3791,6090
	+	285(3.67), 223(3.84)	
	–	304(3.65), 238(4.05)	
	EtOH	276(3.73), 218(4.00)	
2-Methoxypyrimidine	0	267(3.66)	1968,3791,6090
	+	273(3.70)	
	C_6H_{12}	295(2.60), 264(3.62)	
4-Methoxypyrimidine	0	248(3.53)	708,3791,6090
	+	240(3.83), 227(3.88)	
	C_6H_{12}	270(2.44), 248(3.49)	
1-Methyl-2(1*H*)-pyrimidinone	0	302(2.73), 215(4.00)	1432
	+	313(3.85)	
1-Methyl-4(1*H*)-pyrimidinone	0	240(4.16)	1432,3791,6090
	+	250(3.42), 229(4.01)	
3-Methyl-4(3*H*)-pyrimidinone	0	269(3.59), 221(3.83)	1432
	+	258(3.47), 226(3.96)	
2(1*H*)-Pyrimidinethione	0	346(3.42), 278(4.33)	3480, cf. 1968
	+	378(3.18), 285(4.51), 208(3.87)	
	–	270(4.23), 231(3.69)	
4(3*H*)-Pyrimidinethione	0	327(3.91), 285(4.03)	3480
	+	305(4.22)	
	–	293(4.04)	
2-Methylthiopyrimidine	0	285(3.25), 250(4.11)	3480
	+	313(3.51), 255(4.10), 214(3.48)	
4-Methylthiopyrimidine	0	279(3.91), 257(3.85)	3480
	+	302(4.23), 221(3.47)	

TABLE 12.2. (*Continued*)

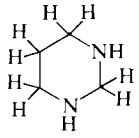
Pyrimidine	Solvent or Species[a]	λ_{max}(log ε)[b]	Ref.
1-Methyl-2(1*H*)-pyrimidinethione	0	344(3.45), 279(4.26)	3480
	+	378(3.14), 283(4.34)	
1-Methyl-4(1*H*)-pyrimidinethione	0	328(4.33)	3480
	+	304(4.24)	
3-Methyl-4(3*H*)-pyrimidinethione	0	322(3.91), 287(4.03)	3480
	+	304(4.23)	
2-Methylsulfinylpyrimidine	0	247(3.57)	1715
2-Methylsulfonylpyrimidine	0	265(2.41), 243(3.23), 239(3.21)	1715
4-Methylsulfonylpyrimidine	0	286(2.89), 277(2.93), 250(3.42), 229(3.90)	1715
5-Methylsulfonylpyrimidine	0	277(2.63), 243(3.06), 240(3.06)	1715
4-Methyl-2-pyrimidinesulfonic acid	–	248(3.43)	2263
6-Methyl-4-pyrimidinesulfonic acid	–	252(3.65)	2263
2-Pyrimidinamine	0	292(3.50), 224(4.13)	708
	+	302(3.60), 221(4.17)	
4-Pyrimidinamine	0	268(3.55), 234(4.08)	1968
	+	246(4.27)	
	EtOH	272(3.71), 236(4.30)	

5-Pyrimidinamine	0	298(3.49), 236(4.04)	711
	+	332(3.57), 253(4.16)	
2-Dimethylaminopyrimidine	0	318(3.35), 243(4.26)	708
	+	324(3.47), 235(4.24)	
4-Dimethylaminopyrimidine	0	286(3.56), 250(4.22)	708
	+	262(4.21)	
1-Methyl-2(1*H*)-pyrimidinimine	0	345(3.46), 236(4.19)	3377
	+	301(3.63), 222(4.17)	
1-Methyl-4(1*H*)-pyrimidinimine	0	315(2.79), 253(4.21)	3377
	+	250(4.21)	
3-Methyl-4(3*H*)-pyrimidinimine	0	293(3.39), 249(3.77), 243(3.93)	1508
	+	277(3.48), 238(3.59)	
2-Pyrimidinecarboxylic acid	0	270(2.64), 240(3.43)	3791
	−	275(2.61), 246(3.42)	
Methyl 2-pyrimidinecarboxylate	0	270(2.58), 245(3.36)	3791
	+	245(3.64)	
2-Acetylpyrimidine	EtOH	290(2.50), 218(4.02)	793
4-Acetylpyrimidine	EtOH	264(3.60), 202(3.98)	793
5-Acetylpyrimidine	EtOH	289(2.75), 222(4.11)	793
4-Methylpyrimidine 1-oxide[c]	0	300(3.10), 248(3.90)	5919
	C_7H_{16}	350(3.10), 342(3.33), 278(4.04)	

[a] Indicated species are all in aqueous buffer of appropriate pH; 0 = neutral molecule.
[b] Because of widespread variations in interpretation, shoulders and inflections are included without distinction from maxima.
[c] Approximate values taken from small published curves.

12.4. MASS SPECTRA

Apart from an occasional molecular ion value, given to supplement (or in lieu of) an elemental analysis, there is a marked paucity of mass spectral data for pyrimidines in the literature. This is probably because such spectra are quite simple as a rule and hence of little intrinsic interest.[6101] For example, the dominant fragmentation mode of pyrimidine (**1**) is loss of HCN twice, first involving C4 + N3 and then C2 + N1, to give ionized acetylene (*m/z* 26) as the base peak of the spectrum.[4626,6098,6102,6103] Fragmentation patterns for other simple pyrimidines are exemplified in those of hexahydropyrimidine (**7**),[4356] 2-methylpyrimidine,[6104] 4-methylpyrimidine,[6105] 2-pyrimidinamine,[4626] 4,6-dimethyl-2-pyrimidinamine,[2928] 4,6-dichloro-2-pyrimidinamine,[6095] 2,6-dimethyl-4-pyrimidinamine,[2928] 6-methyl-4-pyrimidinone,[2928] 2,4(1*H*,3*H*)-pyrimidinedione,[4626,6108,6109] 4-amino-2(1*H*)-pyrimidinone,[4626] 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione,[6096] 2,3-dimethyl-4(3*H*)-pyrimidinone,[6104] 2-methyl-5-pyrimidinol (**8**),[6104] and others.[712,1907,2363,6097,6106,6107,6110–6115] The relatively extensive mass spectral work on barbiturates (mainly for analytical purposes) and on pyrimidine nucleotides and nucleosides has been summarized succinctly with a full bibliography.[6101] For remarks on the mass spectra of hydropyrimidines, see Section 11.5.5.



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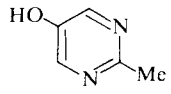

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12.5. NUCLEAR MAGNETIC RESONANCE SPECTRA*

Nuclear magnetic resonance spectroscopy is now so universally used to solve structural problems in all areas of heterocyclic chemistry[6683,6684] that it seems quite unnecessary to discuss such generalities of spectra in the pyrimidine series. However, appropriate data for a range of simple pyrimidines are presented in the next six pages within Table 12.3 (^{1}H nmr spectra), Table 12.4 (^{13}C nmr), and Table 12.5 (^{14}N and ^{15}N nmr). Moreover, the applications of nmr work to several specialized topics in pyrimidine chemistry, including tautomerism, are discussed briefly.

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TABLE 12.3. SELECTED ^{1}H NMR SPECTRA OF SIMPLE PYRIMIDINES[a]

Pyrimidine	H2	H4	H5	H6	Other	Solvent[b]	Ref.
Unsubstituted	9.26 $J_{2,5}$ 1.5	8.78 $J_{4,5}$ 5.0 $J_{4,6}$ 2.5	7.36 $J_{5,6}$ 5.0	8.78		$CDCl_3$	4611,4612
4-Pyrimidinamine	8.39 $J_{2,5}$ 1.25		6.44 $J_{5,6}$ 6.15	8.04		DMSO	3290
2-Bromopyrimidine		8.72 $J_{4,5}$ 4.8	7.57	8.72		AcMe	3290
5-Bromopyrimidine	9.15	8.96		8.96		AcMe	3290
2-Chloropyrimidine		8.78 $J_{4,5}$ 4.9	7.55	8.78		AcMe	3290
2-Pyrimidinecarbonitrile		9.04 $J_{4,5}$ 5.1	7.86	9.04		AcMe	3290
5-Pyrimidinecarbonitrile	9.44	9.00		9.00		DMSO	3290
1-Methyl-2(1*H*)-pyrimidinone		8.52 $J_{4,5}$ 4.15 $J_{4,6}$ 2.93	6.39 $J_{5,6}$ 6.47	8.18	1-Me: 3.43	DMSO	6617
1-Methyl-4(1*H*)-pyrimidinone	8.25 $J_{2,6}$ 2.69 $J_{2,5}$ 0.73		5.98 $J_{5,6}$ 7.57	7.67	1-Me: 3.56	DMSO	6616
3-Methyl-4(3*H*)-pyrimidinone	8.45 $J_{2,5}$ 0.85		6.38 $J_{5,6}$ 6.59	7.90	3-Me: 3.42	DMSO	6616
1-Methyl-4(1*H*)-pyrimidinethione	8.31 $J_{2,6}$ 2.20 $J_{2,5}$ 0.85		7.07 $J_{5,6}$ 7.20	7.54	1-Me: 3.62	DMSO	6616
3-Methyl-4(3*H*)-pyrimidinethione	8.76 $J_{2,5}$ 0.98		7.35 $J_{5,6}$ 5.98	7.84	3-Me: 3.76	DMSO	6616

TABLE 12.3. (*Continued*)

Pyrimidine	H2	H4	H5	H6	Other	Solvent[b]	Ref.
2-Iodopyrimidine		8.58 $J_{4,5}$ 4.9	7.57	8.58		AcMe	3290
4-Methoxypyrimidine	8.80 $J_{2,6}$ 0.5		6.93 $J_{5,6}$ 5.9	8.52	OMe: 3.93	DMSO	6616
2-Methylpyrimidine		8.63 $J_{4,5}$ 4.9	7.12 $J_{5,6}$ 4.9	8.63	2-Me: 2.62	$CDCl_3$	4611,4612
5-Methylpyrimidine	8.99	8.65		8.65	5-Me: 2.32	AcMe	4611,4612
2-Methylthiopyrimidine		8.64 $J_{4,5}$ 4.9	7.21 $J_{5,6}$ 4.9	8.64	SMe: 2.53	DMSO	6617
4-Methylthiopyrimidine	8.93 $J_{2,5}$ 1.40		7.45 $J_{5,6}$ 5.61	8.49	SMe: 2.57	DMSO	6616
5-Nitropyrimidine	9.64 $J_{2,4}$ 0.3	9.67		9.67		CCl_4	2560
2(1*H*)-Pyrimidinone		8.28 $J_{4,5}$ 5.1	6.36 $J_{5,6}$ 5.1	8.28		DMSO	6617
4(3*H*)-Pyrimidinone	8.15 $J_{2,5}$ 1.1		6.31 $J_{5,6}$ 6.7	7.89		DMSO	6616
2(1*H*)-Pyrimidinethione		8.26 $J_{4,5}$ 5.2	6.83 $J_{5,6}$ 5.2	8.26		DMSO	6617
4(3*H*)-Pyrimidinethione	8.29		7.19 $J_{5,6}$ 6.2	7.87		DMSO	6616

[a] Chemical shifts in ppm from Me_4Si; coupling constants in hertz.
[b] Solvents fully deuterated where possible.

TABLE 12.4. SELECTED ^{13}C NMR SPECTRA OF SIMPLE PYRIMIDINES[a]

Pyrimidine	C2	C4	C5	C6	Other	Solvent[b]	Ref.
Unsubstituted	158.39	156.90	121.86	156.90		DMSO	4614
	158.60	159.40	123.65	158.40		D_2O	4616
	159.06	156.78	121.42	156.78		$CDCl_3$	5893
	159.20	157.60	122.60	157.60		neat	6618
2-Pyrimidinamine	164.90	159.30	111.50	159.30		DMSO	4616
4-Pyrimidinamine	158.27	163.10	105.06	154.62		DMSO	4614
4,6-Dimethyl-2-pyrimidinamine	163.17	166.61	108.59	166.61	Me_2: 23.33	DMSO	4614
2,6-Dimethyl-4-pyrimidinamine	165.90	163.61	99.93	163.61	2-Me: 23.59 6-Me: 23.36	DMSO	4614
2-Bromopyrimidine	153.60	159.40	120.20	159.40		$CDCl_3$	4613
2-Chloropyrimidine	160.30	160.50	120.80	160.50		DMSO	4613
4-Chloropyrimidine	159.10	158.30	122.30	161.40		$CDCl_3$	4918
2-Pyrimidinecarbonitrile	145.50	159.60	125.20	159.60	CN: 116.50	AcMe	4613
2,4-Pyrimidinediamine	163.05	163.85	95.00	155.50		DMSO	6594
4,6-Pyrimidinediamine	157.70	163.35	82.60	163.35		DMSO	6594
1-Methyl-2(1*H*)-pyrimidinone	159.89	165.99	103.96	148.55	1-Me: 39.33	$CDCl_3$	235, cf. 6617
1-Methyl-4(1*H*)-pyrimidinone	142.04	169.76	112.82	152.45	1-Me: 40.55	$CDCl_3$	235, cf. 6617
3-Methyl-4(3*H*)-pyrimidinone	151.53	151.44	115.66	153.58	3-Me: 34.29	$CDCl_3$	235, cf. 6617
1-Methyl-2(1*H*)-pyrimidinethione	183.38	159.22	109.00	148.65	1-Me: 46.86	$CDCl_3$	235, cf. 6617
1-Methyl-4(1*H*)-pyrimidinethione	148.38	197.78	125.15	137.83	1-Me: 39.74	DMSO	235, cf. 6617
3-Methyl-4(3*H*)-pyrimidinethione	152.69	183.29	128.50	147.49	3-Me: 40.97	DMSO	235, cf. 6617
2,4-Dimethylpyrimidine	166.64	166.29	117.73	156.47	2-Me: 25.54 4-Me: 23.54	DMSO	4614
4,6-Dimethylpyrimidine	157.56	165.89	120.02	165.89	Me_2: 23.39	DMSO	4614
2-Fluoropyrimidine	163.20	161.60	120.10	161.60		$CDCl_3$	4613
2(1*H*)-Pyrimidinone	159.25	156.78	105.07	156.78		$CDCl_3$	235, cf. 6617

TABLE 12.4. (*Continued*)

Pyrimidine	C2	C4	C5	C6	Other	Solvent[b]	Ref.
4(3*H*)-Pyrimidinone	149.98	163.88	116.42	155.72		$CDCl_3$	235, cf. 6617
2-Iodopyrimidine	129.50	158.40	120.80	158.40		$CDCl_3$	4613
2(1*H*)-Pyrimidinethione	181.20	154.00	109.20	154.00		DMSO	4613, cf. 6617
4(3*H*)-Pyrimidinethione	149.86	182.82	126.32	149.73		DMSO	235, cf. 6617
2-Methoxypyrimidine	185.70	159.30	115.00	159.30	OMe: 54.70	$CDCl_3$	4613, cf. 6617
4-Methoxypyrimidine	158.51	169.51	106.70	156.89	OMe: 53.71	$CDCl_3$	235, cf. 6617
2-Methylthiopyrimidine	170.03	157.11	116.20	157.11	SMe: 14.03	$CDCl_3$	235, cf. 6617
4-Methylthiopyrimidine	158.24	170.70	118.86	154.02	SMe: 12.35	$CDCl_3$	235, cf. 6617
5-Nitropyrimidine	162.50	152.50	142.70	152.50		$CDCl_3$	6619
2,4,6-Pyrimidinetriamine	162.80	164.30	74.80	164.30		DMSO	6594

[a] Chemical shifts in ppm from Me_4Si.
[b] Solvents fully deuterated.

TABLE 12.5. SELECTED ^{14}N AND ^{15}N NMR SPECTRA OF SIMPLE PYRIMIDINES[a]

Pyrimidine	1-^{15}N	3-^{15}N	Other ^{15}N	1-^{14}N + 3-^{14}N	Strength	Solvent[b]	Ref.
Unsubstituted	− 84.8	− 84.8			0.5*M*	DMSO	3346
				− 92 ± 2	0.5*M*	H_2O	4622
Pyrimidine 1-oxide	− 80.3	− 90.0				DMSO	3346
2-Pyrimidinamine	− 129.9	− 129.9	NH_2: − 297		0.5*M*	DMSO	3346
2-Pyrimidinamine 1-oxide	− 134.0	− 130.1	NH_2: − 304.8			DMSO	3346
4,6-Dimethyl-2-pyrimidinamine	− 138.0	− 138.0	NH_2: − 300.4		0.5*M*	DMSO	4624
2,6-Dimethyl-4-pyrimidinamine	− 121.02	− 139.2	NH_2: − 299.0			DMSO	4624
4-Methyl-2-pyrimidinamine	− 138.2	− 130.3	NH_2: − 299.5			DMSO	4624
2-Bromopyrimidine				− 86 ± 4	5%	AcMe	4623
2-Chloropyrimidine	− 88.2	− 88.2			0.5*M*	DMSO	3346
2,4-Pyrimidinediamine	− 164.5	− 173.4	2-NH_2: − 301.6 4-NH_2: − 299.6		0.5*M*	DMSO	3346
2,4-Pyrimidinediamine 3-oxide	− 166.8	− 167.8	2-NH_2: − 306.2 4-NH_2: − 307.4			DMSO	3346
4,6-Pyrimidinediamine	− 149.4	− 149.4	$(NH_2)_2$: − 309.1		0.5*M*	DMSO	3346
2,4-Dichloropyrimidine	− 92.6	− 94.5			0.5*M*	DMSO	4624
4,6-Dichloropyrimidine	− 93.7	− 93.7			0.5*M*	DMSO	4624
2,4-Dimethoxypyrimidine	− 150.0	− 160.9			0.5*M*	DMSO	4624
2-Dimethylaminopyrimidine	− 132.0	− 132.0	NMe_2: − 311.9		0.5*M*	DMSO	3346

TABLE 12.5. (*Continued*)

Pyrimidine	1-^{15}N	3-^{15}N	Other ^{15}N	1-^{14}N + 3-^{14}N	Strength	Solvent[b]	Ref.
2-Fluoropyrimidine				-113.4 ± 4	5%	AcMe	4623
2-Iodopyrimidine				-69 ± 4	5%	AcMe	4623
2-Methoxypyrimidine				-127 ± 4	5%	AcMe	4623
2-Methylsulfonylpyrimidine				-101 ± 4	5%	AcMe	4623
4-Methylpyrimidine	−93.1	−84.7			0.5*M*	DMSO	4624
5-Methylpyrimidine	−85.9	−85.9			0.5*M*	DMSO	4624
2-Methylthiopyrimidine				−101 ± 4	5%	AcMe	4623
2,4,6-Pyrimidinetriamine	−189.5	−189.5	2-NH_2: −304.0 4,6-$(NH_2)_2$: −306.0		0.5*M*	DMSO	3346

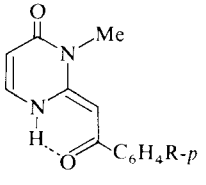
[a] Chemical shifts in ppm from external neat $MeNO_2$.

[b] Undeuterated solvents; DMSO contained 0.1*M* concentration of $Cr(acac)_3$.

12.5.1. Tautomerism

There is no doubt that nmr spectroscopy is now the method of choice for detecting and evaluating tautomeric equilibria in pyrimidine derivatives. While ^{1}H, ^{13}C, and ^{17}O studies are indeed useful, the large shifts seen in ^{15}N nmr spectroscopy appear to offer the most useful form of nmr in the examination of tautomerism.

Keto–enol tautomerism in appropriate pyrimidinones and pyrimidinethiones is well known and has been discussed briefly in Sections 7.1.2 and 8.1.2, respectively: almost invariably, such 2- and 4-pyrimidinones and pyrimidinethiones exist predominantly as their quinoidal tautomers. However, groups other than an oxo or thioxo substituent may also stabilize quinoidal tautomers, usually by hydrogen bonding to ring nitrogen. Hence, 3-methyl-2-phenacyl-4(3*H*)-pyrimidinone (**9**, R = H) and its *p*-bromo analog (**9**, R = Br) both exist almost exclusively as the quinoidal enaminoketone tautomers shown, at least in DMSO or $CDCl_3$ solution.[6608] The ^{1}H nmr spectra clearly display coupling between the pyrimidine NH and both H6 (5.2 Hz) and H5 (1.2 Hz). The ^{15}N chemical shifts for N1 and N3 (− 234.6 and − 251.9 ppm) are large compared with that of 2-methoxypyridine (− 112 ppm) or 2-methoxypyrimidine (− 127 ppm).[4623] Thus the tautomer appears to be stabilized by hydrogen bonding between the phenacyl carbonyl and N1. α-Halogeno derivatives of 2- and 4-phenacylpyrimidine (e.g., **10**, X = Br) also exist as quinoidal tautomers,[546] again apparently stabilized by hydrogen bonding: an estimate of the relative amounts of the two tautomers has been obtained by integration of the ^{1}H nmr spectrum. In contrast, the closely related (*o*-hydroxyaryl)pyrimidines (e.g., **11**) have been shown by ^{17}O studies to have little, if any, of the keto tautomers in DMSO or $CDCl_3$,[6609] with the ^{17}O chemical shift (90–95 ppm) cited as indicative of aromaticity.[6615] 4,6-Diphenacylpyrimidine in $CDCl_3$ exists as several tautomers:[6610] the ^{14}N, ^{1}H, and ^{17}O nmr spectra were used to calculate the relative amounts of each of the five tautomers present. A ^{14}N chemical shift of − 143 ppm and ^{17}O shifts of 95–125 ppm are indicative of aromatic tautomers, and it is calculated that the proportion of quinoidal tautomers is only 10%. Cyano esters, typified by the pyrimidine (**12**), do favor the quinoidal form shown.[6611] Upfield shifts of H4 and H6 in the order of 0.2–1.0 ppm are reported as indicative of the presence of quinoidal tautomers. The introduction of either an electron-withdrawing or an electron-donating group into the 5-position results in a shift toward the aromatic tautomer: in the



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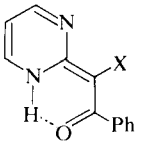

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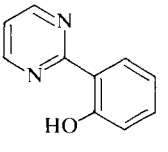
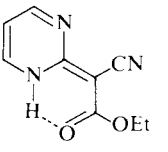


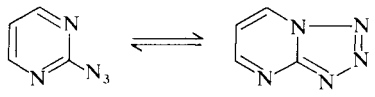
11



12

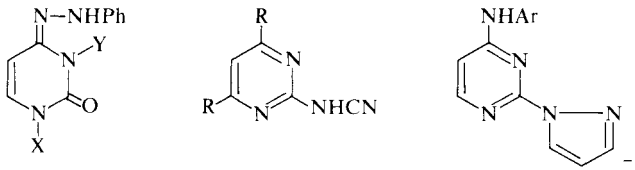
first case, the quinoidal tautomer is destabilized, whereas, in the second case, the aromatic tautomer is stabilized.

2-Azido- and 2,4-diazidopyrimidine have been investigated by ^{1}H and ^{13}C nmr spectroscopy.[6612] In $CDCl_3$, both molecules exist predominantly in their azido forms (e.g., **13**), but dissolution in the more polar solvent, DMSO, moved each equilibrium toward a fused bicyclic form (e.g., tetrazolo[1,5-*a*]-pyrimidine, **14**). An upfield shift of 26 ppm for C6 and an increase of 14 Hz for $^{1}J_{C6,H6}$ were noted on formation of the cyclic tetrazolo tautomer. The same tautomeric system has also been investigated by ^{15}N nmr spectroscopy: significant downfield shifts of up to 200 ppm were observed on formation of the tetrazolo tautomer.[6613]



13 **14**

4-Phenylhydrazino-2(1*H*)-pyrimidinone (**15**, X = Y = H) and its 1-methyl analog (**15**, X = Me, Y = H) exist predominantly as their indicated hydrazono tautomers in DMSO; the 3-methyl derivative (**15**, X = H, Y = Me) occurs almost exclusively as the hydrazone shown.[6614] These facts were determined by comparison of the ^{1}H nmr spectra with that of the 1,3-dimethyl derivative (**15**, X = Y = Me), which must exist only in the hydrazone form.



15 **16** **17**

Although primary and secondary aminopyrimidines usually exist exclusively in their amino forms (see Section 9.1.5), a ^{13}C nmr study of 2-cyanoamino-4, 6-dialkylpyrimidines (**16**, R = alkyl) revealed that such compounds are in equilibrium with their 2-cyanoiminodihydro tautomers.[161] However, a study of 4-arylamino-2-(pyrazol-1′-yl)pyrimidinones (**17**) in $CDCl_3$, DMSO, and CCl_4 by ^{1}H nmr indicated that the molecules do not exist to any appreciable extent as their imino tautomers.[6620]

12.5.2. Protonation Studies

Nuclear magnetic resonance is also a useful technique in protonation studies. Not only may pK_a figures be evaluated, but the site of protonation may often be determined. Chemical shifts for *all* isotopes giving rise to nmr spectra are

dependent on pH (or pD), and this relationship may be used to estimate pK_a values. A standard chemical shift–pH plot is developed and analyzed by the usual techniques. Only ^1H and ^{13}C nmr have been used for this purpose in the pyrimidine series, a fact probably influenced by the original work on protonation by Pugmire and Grant.[4618,6696] However, it must be remembered that ^{15}N, ^{17}O, and ^{31}P nuclei also offer possibilities. The potential for ^{15}N nmr is illustrated by the large change in chemical shift ($\sim$ 50 ppm) for N7 on protonation of inosine, with little or no change recorded for N1, N3, or N9;[6697] similar changes have been noted for adenine.[6698] The ^{31}P nucleus offers a method for the study of protonation in nucleosides: it is more sensitive than ^{13}C, exhibiting a large chemical-shift dependence on pH. However, ^{17}O is unlikely to be of general practical use without isotopic enrichment because of its low natural abundance (0.04%), low sensitivity (0.003 compared with protons), and large quadrupole moment. Nevertheless, it may be the nucleus of choice for some oxygenated pyrimidines, in which the possibility of protonation on oxygen exists.

Table 12.6 (located on the next page) lists some pK_a values for pyrimidines, as determined by nmr spectroscopy. The values should be considered only as estimates for several reasons. The working rule, pD = pH meter reading + 0.4, may be used to determine pD, but this rule applies only to solutions of ionic strengths < 0.1. Ionic strengths encountered in nmr spectroscopy are usually much greater than 0.1, so that ambiguity will exist between true and measured pD values. A far more serious problem arises from activity coefficients of the acid and conjugate base, which are unlikely to be known and may well differ significantly from unity. The situation is made even more complex by the necessity (in the case of ^1H nmr spectra) of using deuterated solvents. It is known that pK_a (D_2O) and pK_a (H_2O) may differ by as much as 0.6 units.[6699] As nmr is sensitive to stereochemical and intermolecular effects, factors such as unfolding a complex molecule or disaggregation may give rise to misleading results. Hence, at this time pK_a values determined by nmr should be considered only as estimates.

As a general rule in ^1H nmr work, resonances nearest to the site of protonation shift downfield by a value significantly greater than those resonances remote therefrom. However, this behavior is not universal, and in some cases ^1H nmr may not be decisive in establishing the site of protonation.[3951] The ^{13}C spectra are more informative, in that carbon adjacent to the site of protonation moves to higher field, while that remote therefrom moves to lower field. In ^{15}N spectra, large shifts occur at the site of protonation.[6697,6698] The magnitude of the vicinal ^{13}C, ^1H coupling constant ($^3J_{C2,H6}$) across the protonated nitrogen has been reported[6700] as indicative of the relative percentages of the monoprotonated forms in pyrimidines,[6700] but this ratio should be corrected for substituent effects.[6701] Thus 4-methyl-2-pyrimidinamine has an *N*1- to *N*3-protonation ratio of approximately 2 : 1.

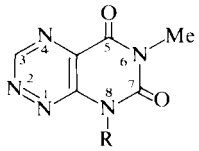
Benoit and Frechette[6702] have examined the biologically important pyrimidines (cytosine, uracil, and thymine) as well as a simple model compound, 2,6-

TABLE 12.6. SOME pK_a VALUES DETERMINED BY NMR SPECTROSCOPY

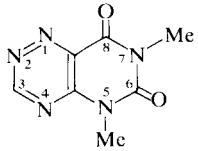
Pyrimidine	Dication	Monocation	Anion	Ref.
Unsubstituted	− 7.1	1.3		3951
Pyrimidine 1-oxide	− 7.9	− 0.5		6057
4-Amino-2(1*H*)-pyrimidinone	− 6.4			6702
2,6-Dimethyl-4-pyrimidinamine	− 1.58			6702
5-Pyrimidinol		1.8	6.8	3951
5-Pyrimidinol 1-oxide	< − 7.5	− 0.1	4.8	6057
4-Methyl-5-pyrimidinol	− 4.8	2.5	7.1	3951
4-Methyl-5-pyrimidinol 1-oxide		0.4	4.8	6057
4,6-Dimethyl-5-pyrimidinol	− 4.8	3.1	7.3	3951
4,6-Dimethyl-5-pyrimidinol 1-oxide	− 6.4	0.6	5.1	6057
2,4,6-Trimethyl-5-pyrimidinol	− 2.8	3.8	7.6	3951
2,4,6-Trimethyl-5-pyrimidinol 1-oxide	− 4.3	0.9	5.7	6057
4-Methylpyrimidine	− 6.1	2.1		3951
4-Methylpyrimidine 1-oxide	− 8.1	0.2		6057
4-Methylpyrimidine 3-oxide	− 6.3	0.3		6057
6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione		− 3.08		6702
2,4-Dimethylpyrimidine		3.7		3951
2,4,6-Trimethylpyrimidine		0.4		6057
2,4(1*H*,3*H*)-Pyrimidinedione		− 2.35		6702
Pyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**18**)		2.92		6703
6-Methylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**19**)		2.91		6703
5,7-Dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,8*H*)-dione (**20**)		3.21		6703

dimethyl-4-pyrimidinamine. Both ^{1}H and ^{13}C nmr spectra were recorded in sulfuric acid–water mixtures. From the chemical-shift data were obtained pK_a values of -2.35 for uracil, -3.08 for thymine, and -1.58 for 2,6-dimethyl-4-pyrimidinamine (second basic pK_a): these values proved closely comparable with the respective values (-2.38, -3.02, and -1.73) obtained by conventional measurements of uv spectral changes. Examination of the ^{13}C spectra supported the premise that the first protonation for cytosine was at N3 and that the second occurred at O2; protonation of both uracil and thymine occurred initially at O4 and then at O2. It was also pointed out that dissolving a polyfunctional base in an acidic solvent such as trifluoroacetic acid (TFA) and then attributing the observed changes in chemical shift to only one species, can be misleading. For example, 2,6-dimethyl-4-pyrimidinamine in TFA exists as a mixture of mono- and dication in a ratio of 3 : 1. Such observations confirm that any determination of pK_a by nmr in nonaqueous solvents will be subject to error.

Turning for a moment to fused pyrimidines, the preferred protonation site for each biologically important pyrimidotriazinedione [rheumycin (**18**), fervenulin (**19**), and isofervenulin (**20**)] has been examined in $CDCl_3$–TFA mixtures by using ^{1}H and ^{13}C spectra.[6703] It was established that protonation of both **18** and **19** takes place at N2, whereas protonation of **20** occurs competitively at N1, N2, and O6; pK_a values of 2.92, 2.91, and 3.21 were reported for **18**, **19**, and **20**, respectively, but in view of the reservations expressed,[6702] these values must be considered tentative.



18: R = H
19: R = Me



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Using chemical-shift data, Lezina and coworkers have estimated pK_a values for a series of methylpyrimidines,[3951] methyl-5-pyrimidinols,[3951] and corresponding *N*-oxides[6057] in D_2O–D_2SO_4 solutions using ^{1}H nmr. The *N*-oxidation significantly decreased the basicity of the second nitrogen atom, whereas the introduction of methyl substituents generally increased the ionization constants of all ring nitrogens. The data are consistent with all nonoxidized pyrimidines being *N*1-protonated but the *N*-oxides being protonated initially at the oxygen atom of the N → O grouping, irrespective of the presence or absence of an hydroxyl group.

Threadgill et al.[463] have investigated the site of protonation in three 2,4-pyrimidinediamines of pharmaceutical interest: the 5-*p*-chlorophenyl, 5-(3′-azido-4′-chlorophenyl), and 5-(3′-amino-4′-chlorophenyl) derivatives of 6-ethyl-2,4-pyrimidinediamine. On comparing the spectra of the free bases with

those of the corresponding ethanesulfonate salts in deuterated DMSO, significant upfield shifts were recorded for C2 and C6 on conversion into the salts. This was interpreted as indicating *N*1-protonation.

12.5.3. Some Recent Topics

The most important developments to occur in nmr techniques over the last 10 years have been the introduction of multipulse sequences and two-dimensional nmr: unfortunately, pyrimidines have been virtually absent from studies involving such techniques. It should be borne in mind that assignment of resonances is often simplified by the use of multipulse sequences or of homo and hetero cross-correlation spectroscopy.

In the first instance, nmr parameters are governed by intramolecular properties. Hence, conformations and stereochemistry of pyrimidine nucleosides[6722–6726] and hydropyrimidines[523,571,6729,6730] have been investigated by making use of $J_{C,H}$ coupling constants. A Karplus relationship for the glycosidic bond conformation in uridine has been reported.[6724] The use of nmr spectroscopy in studies of the restricted rotation of exocyclic dimethylamino groups in substituted pyrimidines[397,6732–6734] and pyrimidinethiones[6732] has been reported. Rotation of the pyrimidine ring itself in 10-*S*-3-sulfuranes[6735] has been studied and two liquid crystal investigations have been carried out on 4-dimethylaminopyrimidine[6736] and unsubstituted pyrimidine.[6737] The foregoing studies have resulted in useful information on π-electron deficiencies and activation energies in pyrimidines and the effect of substituents thereon.

Intermolecular effects also influence nmr parameters. This dependence has been utilized to study the association of pyrimidines in aqueous solution[6717–6721] and the interaction between pyrimidines and a model receptor.[6727] Kinetic studies, such as hydrolysis of the antimalarial pyrimethamine and its derivatives,[289] or the reaction of formaldehyde with pyrimidine,[6728] have been reported. Evidence for the formation of adducts between ammonia and 5-nitropyrimidine or between borane and pyrimidine has been provided by nmr data.[6448,6764]

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D. J. Brown
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APPENDIX

Table of Simple Pyrimidines

This table aims to be a complete list of simple pyrimidines described up to the end of 1991. For each compound is recorded (1) melting and/or boiling point; (2) an indication of reported spectra or other physical properties (apart from ionization constants, which are collected in Table 12.1); (3) any reported salts or simple derivatives, especially when the parent compound is ill-characterized; and (4) references(s) to the original literature. For an outline of the nomenclature employed, see Section 2.1.

To keep the table within manageable proportions, the following categories of pyrimidine have been *excluded* on the grounds that they are not simple.

Fused or nucleus-reduced pyrimidines

Pyrimidines with any cyclic substituent

Pyrimidines bearing a substituent with > 3 carbon atoms

Pyrimidines with two substituents at any position

Pyrimidines with two or more independent functional groups on a single substituent

The following conventions and abbreviations have been used in the table.

Melting point. This term covers not only a regular melting point or melting range but also such variations as "decomposing at," "melting with decomposition at," and so on. The use of the symbol $>$ before a melting point indicates that the substance melts or decomposes above that temperature or that it does not melt or decompose below that temperature. When two differing melting points are given in the literature, they appear in the table as, for example, "254 or 273"; when more than two melting points are given, they are recorded in a form such as "208 to 221" in order to distinguish them from the single melting range "208–221."

Boiling point. Boiling points are distinguished from melting points by the presence of a pressure in millimeters of mercury (mmHg) after the temperature: for example, 112–113/0.01.

Abbreviations. Abbreviations for physical data are as follows.

anal	analytical data (usually assumed)
crude	compound not purified
dip	dipole moment
fl-sp	fluorescence spectrum
ir	infrared spectrum
ms	mass spectrum
nmr	nuclear magnetic resonance spectrum (nuclei other than ^1H are given)
pol	polarographic data
uv	ultraviolet spectrum
xl-st	crystal structure (X-ray data)

Abbreviations. For salts or solvates are as follows.

AcOH	acetate salt
$(CO_2H)_2$	oxalate salt
EtOH	ethanolate
HBr, etc.	appropriate hydrohalide salt
Hg, etc.	appropriate heavy-metal salt
H_2O	hydrate
H_2SO_4	sulfate salt
$\overset{+}{H}N(CH)_5$	pyridinium salt
NH_4	ammonium salt
K, etc.	appropriate alkali metal salt
pic	picrate salt
TsOH	*p*-toluenesulfonate salt

Abbreviations. For derivatives are as follows.

Ac	acetyl derivatives
acetal	diethyl acetal
dnp	2,4-dinitrophenylhydrazone
$H_2NN=$	hydrazone
$HON=$	oxime
MeI, etc.	methiodide, etc.
np	*p*-nitrophenylhydrazone
$PhHNN=$	phenylhydrazone
sc	semicarbazone

tfa	trifluoroacetyl derivative
Ts	*p*-toluenesulfonyl derivative
tsc	thiosemicarbazone

Other notes. The use of "cf." before a reference number indicates incorrect, suspect, or mildly relevant information therein. A query mark (?) indicates an anomaly, apparent anomaly, or reasonable doubt associated with a datum or reference. The chromatographic retardation factor is symbolized as R_F.

Pyrimidine	m.p. (°C), etc.	Ref.
6-Acetamido-5-acetonyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	> 300	575
5-Acetamido-6-acetoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	180	576
4-Acetamido-5-acetoxymethyl-2-methylthiopyrimidine	141–142	577
2-Acetamido-5-acetoxy-6-methyl-4(3*H*)-pyrimidinone	232–233	578
6-Acetamido-5-acetoxy-2,4(1*H*,3*H*)-pyrimidinedione	> 260 or > 300	579,580
2-Acetamido-5-acetoxy-4(3*H*)-pyrimidinone	~ 200 or 269–270	581,582
2-Acetamido-5-acetyl-4-methylpyrimidine	152–153	583
4-Acetamido-5-acetylthiomethyl-2-methylpyrimidine	116	584
5-Acetamido-6-amino-1-dimethylamino-2,4(1*H*,3*H*)-pyrimidinedione	260	585
5-Acetamido-6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	275 to 281	586–590
5-Acetamido-6-amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	285 to 305	587(?),588–591
5-Acetamido-6-amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 350, uv	592
5-Acetamido-6-amino-2-methyl-4(3*H*)-pyrimidinethione	—	593
2-Acetamido-5-amino-6-methyl-4(3*H*)-pyrimidinone	246	594
5-Acetamido-2-amino-6-methyl-4(3*H*)-pyrimidinone	295–298 or 305–308	595,596
5-Acetamido-6-amino-2-methyl-4(3*H*)-pyrimidinone		597
5-Acetamido-6-amino-2-methylthio-4(3*H*)-pyrimidinone	> 270	6075
5-Acetamido-6-amino-2,4(1*H*,3*H*)-pyrimidinedione	205–207 or > 320	587,588,590,591,597–600
5-Acetamido-4-amino-2(1*H*)-pyrimidinethione	> 260	601
5-Acetamido-6-amino-4(3*H*)-pyrimidinethione	280	602
2-Acetamido-5-amino-4(3*H*)-pyrimidinone	230–234	603
5-Acetamido-6-amino-4(3*H*)-pyrimidinone	> 300	604,605
5-Acetamido-6-amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	> 260	606,6075
5-Acetamido-4-azido-6-chloropyrimidine	176–177	607
4-Acetamido-1-γ-azidopropyl-2(1*H*)-pyrimidinone	133–134	608

5-Acetamido-6-azido-4-pyrimidinamine	uv	607
4-Acetamido-2,4-bisacetoxymethyl-5-pyrimidinol	115–117	609
2-Acetamido-5-bromo-6-methoxycarbonylmethyl-4(3*H*)-pyrimidinone	198–200	610
4-Acetamido-1-γ-bromopropyl-2(1*H*)-pyrimidinone	139–142	608,611
6-Acetamido-5-bromo-4-pyrimidinamine	181	612
2-Acetamido-4-chloro-5-β-cyanoethyl-6-methylpyrimidine	140–145	613
5-Acetamido-4-chloro-2,6-dimethylpyrimidine	141–142	614
4-Acetamido-2-chloro-6-ethoxypyrimidine	215–216	615
4-Acetamido-6-chloro-2-ethoxypyrimidine	193 or 194–196	615,616
5-Acetamido-6-chloro-2-methylthio-4(3*H*)-pyrimidinone	262–264	6075
4-Acetamido-2-chloro-6-methoxypyrimidine	216–217	615
4-Acetamido-6-chloro-2-methoxypyrimidine	195–196 or 197–198	615,616
5-Acetamido-4-chloro-6-methylaminopyrimidine	232–234	617
2-Acetamido-4-chloro-6-methylpyrimidine	137	618
5-Acetamido-6-chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	217–218	619
2-Acetamido-6-chloro-5-nitro-4(3*H*)-pyrimidinone	260	620,621
5-Acetamido-2-chloro-4-pyrimidinamine	209–211	622
5-Acetamido-6-chloro-4-pyrimidinamine	232–233	607
2-Acetamido-5-chloropyrimidine	188–189	623
4-Acetamido-6-chloropyrimidine	156	612
5-Acetamido-6-chloro-2,4(1*H*,3*H*)-pyrimidinedione	241–242	624
5-Acetamido-6-chloro-4(3*H*)-pyrimidinone	212–213	625
2-Acetamido-5-β-cyanoethyl-6-methyl-4(3*H*)-pyrimidinone	202–203	613
5-Acetamido-2,4-diacetylthiopyrimidine	> 300	626
5-Acetamido-2,6-diamino-4(3*H*)-pyrimidinone	> 320 or 343–344	627–629,597
5-Acetamido-4,6-diazidopyrimidine	uv	607
2-Acetamido-4,6-dichloro-5-nitropyrimidine	224	620,630
2-Acetamido-4,6-dichloro-5-pyrimidinamine	135–138	620,630

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Acetamido-2,6-dichloropyrimidine	184–185	631
5-Acetamido-4,6-dichloropyrimidine	149–150	632
5-Acetamido-2,4-diethoxypyrimidine	136	633
4-Acetamido-2,6-diethyl-5-methylpyrimidine	59	634
2-Acetamido-6-dimethoxymethyl-4(3*H*)-pyrimidinone	163–166	635
4-Acetamido-2,6-dimethoxypyrimidine	183–185	636
4-Acetamido-2-dimethylamino-6-ethoxypyrimidine	166–167	615
4-Acetamido-2-dimethylamino-6-ethylthiopyrimidine	155–156	615,637
4-Acetamido-2-dimethylamino-6-isopropoxypyrimidine	156–157	615,637
4-Acetamido-2-dimethylamino-6-isopropylthiopyrimidine	186–187	615
4-Acetamido-2-dimethylamino-6-methoxy-5-nitropyrimidine	160	638
4-Acetamido-2-dimethylamino-6-methoxypyrimidine	187–188 or 189	615,638
5-Acetamido-2-dimethylamino-6-methyl-4(3*H*)-pyrimidinone	225–227	639
4-Acetamido-6-dimethylamino-2-methylthiopyrimidine	219–220	640
4-Acetamido-2-dimethylamino-5-nitropyrimidine	168	638
6-Acetamido-2-dimethylamino-5-nitro-4(3*H*)-pyrimidinone	273–275	638
6-Acetamido-2-dimethylamino-5-nitroso-4(3*H*)-pyrimidinone	~ 175	641
4-Acetamido-2-dimethylamino-6-propoxypyrimidine	165–166	615
4-Acetamido-2-dimethylamino-6-propylthiopyrimidine	165–167	615
6-Acetamido-2-dimethylamino-4(3*H*)-pyrimidinone	293–295	638
5-Acetamido-1,3-dimethyl-6-*N*-methylacetamido-2,4(1*H*,3*H*)-pyrimidinedione	186–189 or 192–193	588,642,643
5-Acetamido-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	247–249	644
5-Acetamido-4,6-dimethyl-2-pyrimidinamine	246–247	645
2-Acetamido-4,6-dimethylpyrimidine	123 or 124	646,647
4-Acetamido-2,6-dimethylpyrimidine	182–183 or 188–189	648–650

5-Acetamido-2,4-dimethylpyrimidine	114–115	651
5-Acetamido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	221–222	652
6-Acetamido-3,5-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	230–232	653
2-Acetamido-4,6-dimethylpyrimidine 1-oxide	148	654
5-Acetamido-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	208 or 230–231	655,656
2-Acetamido-3,6-dimethyl-4(3*H*)-pyrimidinone	130–132	657
5-Acetamido-2,6-dimethyl-4(3*H*)-pyrimidinone	275–277	595,614,658
6-Acetamido-1,5-dimethyl-4(1*H*)-pyrimidinone	273–274	659
6-Acetamido-3,5-dimethyl-4(3*H*)-pyrimidinone	189–190	659
6-Acetamido-1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	660
5-Acetamido-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbohydrazide	> 330	661
5-Acetamido-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	anal	661
5-Acetamido-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid		662
4-Acetamido-6-ethoxypyrimidine	130–131	615
6-Acetamido-2-ethoxy-4(3*H*)-pyrimidinone	258–259	616,663
5-Acetamido-4-ethylamino-6-methyl-2-methylthiopyrimidine	218–219	664
4-Acetamido-6-ethyl-2-methylpyrimidine	163–164	665
5-Acetamido-2-ethylthio-4-thiocyanatopyrimidine	185–186	633
4-Acetamido-5-fluoro-2(1*H*)-pyrimidinone	235–237	666
2-Acetamido-5-β-formylethyl-6-methyl-4(3*H*)-pyrimidinone	158–160	667–669
5-Acetamido-6-hydrazino-2,4(1*H*,3*H*)-pyrimidinedione	324–325	624
2-Acetamido-4-hydroxyiminomethylpyrimidine	228–229	670
6-Acetamido-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	> 300	580
4-Acetamido-6-isopropoxy-5-nitroso-2-pyrimidinamine	177–180	638
4-Acetamido-6-isopropoxypyrimidine	105–106	615
4-Acetamido-2-isopropyl-6-methylpyrimidine	122–124	671
2-Acetamido-4-methoxycarbonylmethylpyrimidine	118–120	670
2-Acetamido-6-methoxycarbonylmethyl-4(3*H*)-pyrimidinone	185–186	610

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Acetamido-4-methoxy-6-methoxycarbonylmethylpyrimidine	89–91	670
2-Acetamido-4-methoxy-6-methylpyrimidine	98–99	672
4-Acetamido-6-methoxy-2-methylthiopyrimidine	164–165	659
6-Acetamido-2-methoxy-5-nitro-4-pyrimidinamine	185–190	638
4-Acetamido-6-methoxy-5-nitroso-2-pyrimidinamine	220	638
2-Acetamido-5-methoxypyrimidine	160	673
4-Acetamido-6-methoxypyrimidine	138–139	615
5-Acetamido-4-methoxypyrimidine	162–164	674
4-Acetamido-6-methoxy-2,5-pyrimidinediamine	122	638
6-Acetamido-5-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	> 300	580
6-Acetamido-2-methoxy-4(3*H*)-pyrimidinone	275–280	616
5-Acetamido-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	> 280	675
4-Acetamidomethyl-2,6-bismethylthiopyrimidine	145–146, nmr	311
5-Acetamido-4-methyl-2,6-bismethylthiopyrimidine	171–173	676
4-Acetamidomethyl-2,6-dimethoxypyrimidine	97–102, nmr	311
5-Acetamidomethyl-2-ethyl-4-pyrimidinamine	206–207	677
6-Acetamido-1-methyl-2-methylamino-4(1*H*)-pyrimidinone	247–250, ir, ms, nmr	517
5-Acetamidomethyl-2-methyl-4-pyrimidinamine	204–205 or 208–209	677,678,3263,3865
2-Acetamidomethyl-6-methyl-4(3*H*)-pyrimidinone	196–197	679
5-Acetamidomethyl-2-methyl-4(3*H*)-pyrimidinone	219–220	680
6-Acetamido-3-methyl-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone	168	641
5-Acetamido-6-methyl-2-methylthio-4-pyrimidinamine	239–240	664
5-Acetamido-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	248–252	595
6-Acetamido-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	251	659
2-Acetamido-6-methyl-5-nitro-4(3*H*)-pyrimidinone	254–255	594

2-Acetamido-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	240	682
2-Acetamido-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	285–286	682
4-Acetamido-2-methyl-6-propylpyrimidine	132–133	665
4-Acetamido-6-methyl-2-pyrimidinamine	261–262	683
5-Acetamido-2-methyl-4-pyrimidinamine	208–210	684,685
2-Acetamido-4-methylpyrimidine	148 to 154	686–688
4-Acetamido-2-methylpyrimidine	140 or 141–142	671,689,690
4-Acetamido-6-methylpyrimidine	124–125	671
2-Acetamido-4-methyl-5-pyrimidinecarboxylic acid	247–249	691
6-Acetamido-2-methyl-4-pyrimidinecarboxylic acid	247–249	671
5-Acetamido-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	200–220	692
6-Acetamidomethyl-2,4(1*H*,3*H*)-pyrimidinedione	276–281, nmr	311,701
6-Acetamido-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	254–255	693
6-Acetamido-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	280–281	694
5-Acetamido-6-methyl-2,4(1*H*,3*H*)-pyrimidinedithione	344–347	676
2-Acetamido-6-methyl-4(3*H*)-pyrimidinone	218 to 222	618,647,695
4-Acetamido-1-methyl-2(1*H*)-pyrimidinone	268 or 273–274	696,697
4-Acetamido-6-methyl-2(1*H*)-pyrimidinone	> 300	698
6-Acetamido-3-methyl-4(3*H*)-pyrimidinone	303–304	659
6-Acetamido-5-methyl-4(3*H*)-pyrimidinone	303	659
6-Acetamido-2-methylthio-5-nitroso-4-pyrimidinamine	184–185	638
6-Acetamido-2-methylthio-4-pyrimidinamine	225–226	658,699,700
6-Acetamido-2-methylthio-4,5-pyrimidinediamine	210, then 285–290	638
5-Acetamido-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	> 226, nmr	3988,6075
5-Acetamido-2-methylthio-4(3*H*)-pyrimidinone	220–221	702
2-Acetamido-5-nitropyrimidine	187–188	703–705
2-Acetamido-5-nitro-4(3*H*)-pyrimidinone	294–296	603
2-Acetamido-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	> 300	635

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Acetamido-6-oxo-1,6-dihydro-2-pyrimidinesulfonamide	—	706
2-Acetamido-4-propoxypyrimidine	135–136	615
2-Acetamido-5-pyrimidinamine	—	705
6-Acetamido-4-pyrimidinamine	325	612,707
2-Acetamidopyrimidine	145–146 or 146–147	688,708,709
4-Acetamidopyrimidine	198–200	696,708,710
5-Acetamidopyrimidine	248–149, ir, uv; EtI: 165	711,712
4-Acetamido-5-pyrimidinecarbonitrile	124–125	713
2-Acetamido-4,6(1*H*,5*H*)-pyrimidinedione	crude: > 325	709
5-Acetamido-2,4(1*H*,3*H*)-pyrimidinedione	—	714
6-Acetamido-2,4(1*H*,3*H*)-pyrimidinedione	> 350	694
5-Acetamido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	> 280	715–717,6075
4-Acetamido-5-pyrimidinol	179–180	718
2-Acetamido-4(3*H*)-pyrimidinone	249–250	709,719
4-Acetamido-2(1*H*)-pyrimidinone	304 to 328	720–724
6-Acetamido-4(3*H*)-pyrimidinone	288–290	612,659
5-Acetamido-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	284 or > 300, nmr	725,3988,6075
5-Acetamido-2,4,6-trimethylpyrimidine	171–172	651
6-Acetamido-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	221–223	653
4-Acetamido-1-vinyl-2(1*H*)-pyrimidinone	240–242	726
4-Acetimidoylamino-2,6-dimethylpyrimidine	148	727
5-Acetimidoylamino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	360	728
5-Acetimidoylaminomethyl-2-methyl-4-pyrimidinamine	HCl: 246–250	677
5-Acetimidoylaminomethyl-2-methyl-4(3*H*)-pyrimidinone	HCl: 197–202	677
5-Acetimidoylpyrimidine	180–181	729

5-Acetonyl-2-amino-6-methyl-4(3*H*)-pyrimidinone	234	730
5-Acetonyl-2-amino-4,6(1*H*,5*H*)-pyrimidinedione	> 280	731
5-Acetonyl-4-chloro-6-dimethylamino-2-methylpyrimidine	52	732
5-Acetonyl-4-chloro-6-dimethylaminopyrimidine	78	732
5-Acetonyl-4-chloro-2,6-dimethylpyrimidine	80–81	730
5-Acetonyl-4-chloro-6-methyl-2-methylthiopyrimidine	94–95	730
5-Acetonyl-6-chloro-2-methyl-4(3*H*)-pyrimidinone	188–189	732
6-Acetonyl-5-chloro-2-oxo-1,2-dihydro-3-pyrimidinecarboxylic acid	192	733
4-Acetonyl-5-chloro-2(1*H*)-pyrimidinone	197	733
5-Acetonyl-6-chloro-4(3*H*)-pyrimidinone	170–171	732
4-Acetonyl-2-cyanoamino-6-methylpyrimidine	207–209	734
5-Acetonyl-4,6-dichloropyrimidine	76–77	732
2-Acetonyl-4,6-dimethoxy-5-methylpyrimidine	101–102 or 110–112, nmr	3886
2-Acetonyl-4,6-dimethoxy-5-nitropyrimidine	84–86 or 99–100; K: anal, nmr	25,735,736
4-Acetonyl-2,6-dimethoxy-5-nitropyrimidine	122–124	736
2-Acetonyl-4,6-dimethylpyrimidine	95/4	737,738
4-Acetonyl-2,6-dimethylpyrimidine	72–74/1 or 73–74/0.5	738,739
5-Acetonyl-2,6-dimethyl-4(3*H*)-pyrimidinone	199–200 or 202	730,740
5-Acetonyl-2-ethylthio-6-methyl-4(3*H*)-pyrimidinone	172–173	730
1-Acetonyl-5-fluoro-4-methylthio-2(1*H*)-pyrimidinone	195–196	741
1-Acetonyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	220	741
1-Acetonyl-5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	217	742
4-Acetonyl-2-methoxy-5-nitropyrimidine	118–120	736
5-Acetonyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	206–208	730,740
4-Acetonyl-6-methyl-2-nitroaminopyrimidine	232–233	734
4-Acetonyl-6-methyl-2-pyrimidinamine	136	743
1-Acetonyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	197	742
5-Acetonyl-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	321	732

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Acetonyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	258–259	730
4-Acetonyl-6-methyl-2(1*H*)-pyrimidinethione	249	743
4-Acetonyl-5-methyl-2(1*H*)-pyrimidinone	202	744
4-Acetonyl-6-methyl-2(1*H*)-pyrimidinone	250	734
5-Acetonyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	257–260	730
1-Acetonyl-2,4(1*H*,3*H*)-pyrimidinedione	203–205 or 209–210	742,745
5-Acetonyl-4,6(1*H*,5*H*)-pyrimidinedione	265–266	732
6-Acetonyl-2,4(1*H*,3*H*)-pyrimidinedione	218; oxime: 283	746
5-Acetonyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	220	731
6-Acetonyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	190	746
5-Acetoxy-6-acetoxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	114–115	747
5-Acetoxy-6-acetoxymethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	204–205	747
5-Acetoxy-6-acetoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	255–258	747
3-Acetoxy-1-acetyl-2,4(1*H*,3*H*)-pyrimidinedione (?)	142–144	748
5-Acetoxy-6-amino-2,4(1*H*,3*H*)-pyrimidinedione	> 195	580
5-Acetoxy-6-chloro-2,4(1*H*,3*H*)-pyrimidinedione	260	749
5-Acetoxy-2,4-dichloro-6-methylpyrimidine	55 or 78–80	750,751
4-Acetoxy-2-dimethylamino-6-methyl-5-propylpyrimidine	69	753
5-Acetoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	151–152	754
5-Acetoxy-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	209–210	755
5-Acetoxy-3-ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	189	756
5-Acetoxy-2-hydroxyamino-4,6(1*H*,5*H*)-pyrimidinedione	168	757
4-Acetoxy-2-methoxy-6-methylpyrimidine	121–122, ir, nmr	278,3817
5-Acetoxymethyl-1-acetyl-2,4(1*H*,3*H*)-pyrimidinedione	113–114	758
2-Acetoxymethyl-5,6-dichloro-4(3*H*)-pyrimidinone	203–208	759

2-Acetoxymethyl-4,6-dimethoxypyrimidine	liquid, anal, nmr	3974
6-Acetoxymethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	89, nmr	6462
2-Acetoxymethyl-4,6-dimethylpyrimidine	136–137/20, ir, nmr	118
4-Acetoxymethyl-2,6-dimethylpyrimidine	134–137/26, ir, nmr	118
5-Acetoxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	99–100	760,761
6-Acetoxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	128	762
4-Acetoxymethyl-2,6-dimethylpyrimidine 1,3-dioxide	H_2O: 56	763
2-Acetoxymethyl-4,6-dimethylpyrimidine 1-oxide	100	763
1-Acetoxymethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	127–128, nmr	113
2-Acetoxymethyl-4-methoxy-6-methoxymethylpyrimidine	125–128/3, ir, nmr	118
2-Acetoxymethyl-4-methoxy-6-methylpyrimidine	136–137/21, 162–163/48, ir, nmr	118
2-Acetoxymethyl-4-methoxypyrimidine	130–132/19, ir, nmr	118
4-Acetoxymethyl-6-methoxypyrimidine	135–138/22, ir, nmr	118
2-Acetoxymethyl-6-methoxy-4(3*H*)-pyrimidinone	96–98, nmr	3974
4-Acetoxymethyl-6-methylpyrimidine	100–110/15, 125–128/22; pic: 136	118,764
5-Acetoxymethyl-l-methyl-2,4(1*H*,3*H*)-pyrimidinedione	155–157 or 162–164	760,765
5-Acetoxymethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	144–145	760,765
6-Acetoxymethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	260–261	766,767
5-Acetoxymethyl-2-methylthio-4-pyrimidinamine	137–138; HCl: 155–159	577
5-Acetoxymethyl-2-methylthio-4-pyrimidinecarbonitrile	37–38	768
5-Acetoxymethyl-2-methylthio-4-pyrimidinecarboxamide	138–139	768
5-Acetoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	217–223	1940
5-Acetoxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 230 or 295	751,769,6017
6-Acetoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	240–242	770
5-Acetoxy-6-methyl-4(3*H*)-pyrimidinone	150–152, nmr, uv	314
4-Acetoxymethyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	206–208	770
5-Acetoxymethyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	97–98, ir, ms, nmr, uv	260
2-Acetoxypyrimidine	75–80/0.4	752

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Acetoxy-2,4(1*H*,3*H*)-pyrimidinedione	—	771
5-Acetoxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	210–212	772,773
5-Acetoxy-2(1*H*)-pyrimidinone	179–180	774
5-Acetoxy-4(3*H*)-pyrimidinone	158, then 177–178, nmr, uv	314
2-Acetoxy-4(3*H*)-pyrimidinone 1-oxide	175–177	748
5-Acetoxy-2-semicarbazido-4,6(1*H*,5*H*)-pyrimidinedione	200	757
5-Acetoxy-2-thiosemicarbazido-4,6(1*H*,5*H*)-pyrimidinedione	300	757
5-Acetoxy-2,4,6-trimethylpyrimidine 1-oxide	106	763
5-Acetyl-6-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	202 to 214	653,694,775,776
5-Acetyl-6-amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	308–310	694
5-Acetyl-6-amino-3-methyl-4(3*H*)-pyrimidinone	214–215	777
5-Acetyl-2-amino-4(3*H*)-pyrimidinone	301–302	778,779
1-Acetyl-5-bromo-3-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	69–70	780
1-Acetyl-5-bromomethyl-2,4(1*H*,3*H*)-pyrimidinedione	168	781
1-Acetyl-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione	175–177	782
5-Acetyl-2-carbamoylmethyl-4-methylpyrimidine	125–127	783
5-Acetyl-1-α-carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	174	784
5-Acetyl-1-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	200	784
5-Acetyl-4-chloro-2,6-dimethylpyrimidine	104/8	785
4-Acetyl-5-chloro-2-methylthiopyrimidine	46, ms, nmr	3831
5-Acetyl-2-chloropyrimidine	90 or 92, ir, ms, nmr	381,3831
5-Acetyl-6-chloro-2,4(1*H*,3*H*)-pyrimidinedione	> 300	786
5-Acetyl-6-chloro-4(3*H*)-pyrimidinone	150–160, ir, nmr, uv	363
5-Acetyl-4,6-dichloropyrimidine	90–91	787
4-Acetyl-2,6-diethoxypyrimidine	37	788

5-Acetyl-1,3-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	61–62, 168–170/18	789
5-Acetyl-2,4-dimethoxypyrimidine	78–79 or 82–83, ir, ms, nmr	474,6071
5-Acetyl-4,6-dimethoxypyrimidine	63–65, ir, nmr, uv	363
5-Acetyl-6-dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	121–122	653
5-Acetyl-2-dimethylamino-4-methylpyrimidine	56–57	790
5-Acetyl-1,3-dimethyl-6-*N*-methylacetamido-2,4(1*H*,3*H*)-pyrimidinedione	113–114	653
5-Acetyl-2,4-dimethyl-6-methylthiopyrimidine	47	791
5-Acetyl-2,6-dimethyl-4-pyrimidinamine	120–121, ir, ms, nmr	6029
2-Acetyl-4,6-dimethylpyrimidine	39–41, 70–72/3	792,793
4-Acetyl-2,6-dimethylpyrimidine	96–98/20	792
5-Acetyl-2,4-dimethylpyrimidine	62–64/3, 96/15	583,785
5-Acetyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	170 or 175	794,795
5-Acetyl-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	211–212	796
5-Acetyl-2,6-dimethyl-4(3*H*)-pyrimidinethione	149	791
5-Acetyl-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	95–97; oxime: 159	653,789
5-Acetyl-2,6-dimethyl-4(3*H*)-pyrimidinone	207	785
5-Acetyl-6-ethylamino-2-methyl-4(3*H*)-pyrimidinone	241–243, ir, nmr, uv	572
5-Acetyl-2-ethyl-6-methyl-4(3*H*)-pyrimidinethione	137 or 154	791,797
1-Acetyl-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	142–145	798
5-Acetyl-1-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	789
1-Acetyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	126–127 or 128–129	799,800
4-Acetyl-2-guanidinopyrimidine	173–176, nmr; dimethyl ketal: 213, nmr	306
4-β-Acetylhydrazino-2-chloro-5-nitro-6-propylpyrimidine	156–157	801
4-β-Acetylhydrazino-2-chloro-5-nitropyrimidine	135 or 137	802,803
6-β-Acetylhydrazino-5-nitro-4(3*H*)-pyrimidinone	223	804
6-β-Acetylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione	274–275	805
5-Acetyl-1-β-hydroxyethyl-2-methoxy-4(1*H*)-pyrimidinone	154–156	165

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Acetyl-1-β-hydroxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	229–231	165
4-Acetylimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione	180	806
4-Acetylimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	156	696,720,806
1-Acetyl-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	167–168	807,808
5-Acetyl-3-isopropyl-2-methylthio-4(3*H*)-pyrimidinone	anal	809
5-Acetyl-3-isopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	144	809
5-Acetyl-3-β-methoxyethyl-2-methylthio-4(3*H*)-pyrimidinone	94	809
5-Acetyl-3-β-methoxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	137	809
4-Acetyl-2-methoxy-6-methylpyrimidine	61–62	792
1-Acetyl-5-methoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	164 or 165–166	758,810
1-Acetyl-4-methoxy-5-methyl-2(1*H*)-pyrimidinone	107	811,812
1-Acetyl-5-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	205–206	813
1-Acetyl-4-methoxy-2(1*H*)-pyrimidinone	93–94	811
5-Acetyl-6-methyl-2-propyl-4(3*H*)-pyrimidinethione	152	791
5-Acetyl-4-methyl-2-pyrimidinamine	227; pic: 195	583
2-Acetyl-5-methylpyrimidine	49, ms, nmr	3831
4-Acetyl-2-methylpyrimidine	100/17, ir, nmr; oxime: 191–192, ir, nmr; sc: 222–223	122
4-Acetyl-6-methylpyrimidine	74–76	814
1-Acetyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	193–195 or 196–197	815,816
5-Acetyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	234 or 243	784,794
5-Acetyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	197	817
5-Acetyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	226–227	448,796
5-Acetyl-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	205–208	789,818
5-Acetyl-4-methyl-2(1*H*)-pyrimidinone	204–205, nmr, uv	439

5-Acetyl-2-methylsulfonylpyrimidine	132–134, ir, ms, nmr	381,3741,3833
5-Acetyl-2-methylthiopyrimidine	128–134, ir, ms, nmr	381,819,3833
5-Acetyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	333, ir, nmr, uv	6143
5-Acetyl-1-methyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	210	820
5-Acetyl-1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	215–216	821
5-Acetyl-4-methyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	262	822
4-Acetyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxylic acid	236; PhNHN=: 258	823,824
1-Acetyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	230–232	825
1-Acetyl-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	225–227	825
4-Acetyl-2-pyrimidinamine	148–149, nmr; dimethyl ketal: 150–151, nmr	306
2-Acetylpyrimidine	52	793
4-Acetylpyrimidine	65–67; oxime: 184–185	729,793,826
5-Acetylpyrimidine	87–88	793
1-Acetyl-2,4(1*H*,3*H*)-pyrimidinedione	187 to 191	815,827,828
5-Acetyl-2,4(1*H*,3*H*)-pyrimidinedione	283 to 295	784,786,829–832
5-Acetyl-4,6(1*H*,5*H*)-pyrimidinedione	300, ir, nmr, uv	363
6-Acetyl-2,4(1*H*,3*H*)-pyrimidinedione	255–260 or 265–266	788,833
5-Acetyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	295–297	789,834,835
1-Acetyl-4(1*H*)-pyrimidinone	116–118 or 117–120, nmr	314,836(?)
5-Acetyl-2(1*H*)-pyrimidinone	169–171, ir, ms, nmr	381,3741
5-Acetylthio-6-amino-2,4(1*H*,3*H*)-pyrimidinedione	> 300	837
5-Acetylthio-2,4-bistrimethylsiloxypyrimidine	53–55, 110–111/0.4	838,839
5-Acetylthio-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	157–161	840
5-Acetylthio-2,4(1*H*,3*H*)-pyrimidinedione	253–255	838,839
4-Acetyl-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylic acid	246; PhNHN=: 238	823,824
5-Acetyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	285	820
1-Acetyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	242–243	842

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Acetyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	310–311	778,779
6-Acetyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	274–276	833
5-Acetyl-2,3,6-trimethyl-4(3*H*)-pyrimidinone	89–90 or 93–94	335,785
4-Allenyl-2-chloropyrimidine	liquid, nmr	3943
5-Allenyl-4,6-dimethyl-2-methylaminopyrimidine	101	843
5-Allenyl-4,6-dimethyl-2-pyrimidinamine	142	843
2-Allenylsulfonyl-5-chloropyrimidine	130	844
2-Allenylthio-5-chloropyrimidine	32–34	844
Alloxan; *see* 5-Oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione		
N-Allyl-2-allylamino-5-pyrimidinesulfonamide	165–167	845
1-Allyl-4-allyloxy-2(1*H*)-pyrimidinone	anal, uv	846
2-Allylamino-4-amino-5-pyrimidinecarbonitrile	171–172	847
2-Allylamino-4-amino-5-pyrimidinecarboxamide	222–223	848
1-Allyl-6-amino-3,5-bis-β-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	151	849
4-Allylamino-6-chloro-5-nitropyrimidine	46–47, ir, ms, nmr	228
4-Allylamino-6-chloro-2-pyrimidinamine	120	850
4-Allylamino-6-chloro-5-pyrimidinamine	113	851
4-Allylamino-6-chloro-5-pyrimidinecarbaldehyde	50–51	852
1-Allyl-6-amino-6-β-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	260–263	849
1-Allyl-6-amino-3,5-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	166–167	853
2-Allylamino-4,6-dimethylpyrimidine	73	843
1-Allyl-6-amino-3,5-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	171–172	853
5-Allylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	107–109	854
6-Allylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	163–165	855
6-Allyl-5-amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	pic: 159–161	854

1-Allyl-6-amino-3-ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	83–86	853
1-Allyl-6-amino-5-ethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	133–134	853
1-Allyl-6-amino-3-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	-	856
3-Allyl-6-amino-1-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	-	856
1-Allyl-6-amino-3-*β*-hydroxypropyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	216–218	857
1-Allyl-6-amino-3-*β*-hydroxypropyl-2,4(1*H*,3*H*)-pyrimidinedione	170–172	857
1-Allyl-6-amino-5-isopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	217–220	858
6-Allylamino-3-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	190	859
4-Allylamino-2-methylpyrimidine	109/1.6	846
6-Allylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	252–255	859
2-Allylamino-5-methyl-4(3*H*)-pyrimidinone	182–183	860
2-Allylamino-6-methyl-4(3*H*)-pyrimidinone	149	861
5-Allyl-2-amino-6-methyl-4(3*H*)-pyrimidinone	266–267	862,863
4-Allylamino-2-methylthiopyrimidine	83–84	846
1-Allyl-6-amino-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	233–234	858
4-Allylamino-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	194–195	852
1-Allyl-6-amino-2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile	210	864
2-Allylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxamide	278	865
2-Allylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	197	865
4-Allylamino-2-pyrimidinamine	117–119	846
6-Allylamino-4-pyrimidinamine	146	866
2-Allylaminopyrimidine	pic: 156–157	867
1-Allyl-5-amino-2,4(1*H*,3*H*)-pyrimidinedione	225–230	868
5-Allyl-2-amino-4,6(1*H*,5*H*)-pyrimidinedione	272, nmr	203
N-Allyl-2-amino-5-pyrimidinesulfonamide	225–226	869
1-Allyl-4-amino-2(1*H*)-pyrimidinone	232–236 or 250–252	870,871
1-Allyl-6-amino-2(1*H*)-pyrimidinone	240	868
5-Allyl-2-amino-4(3*H*)-pyrimidinone	202–206	872

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-Allyl-6-amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	230–231	856,873
5-Allyl-2,4-bistrimethylsiloxypyrimidine	140–142/12	874
1-Allyl-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione	170	875
1-Allyl-5-bromo-2(1*H*)-pyrimidinone	144, ms, nmr	3916
1-Allyl-6-chloro-3,5-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	120/0.1	876,877
5-Allyl-2-chloro-4,6-dimethylpyrimidine	115/4, uv	843
5-Allyl-4-chloro-2,6-dimethylpyrimidine	93–95/vacuum	878
1-Allyl-6-chloro-5-ethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	140–141/0.3	877
1-Allyl-6-chloro-3-ethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	162–163/14	879
5-Allyl-4-chloro-6-methyl-2-propylpyrimidine	145–146/30	880
1-Allyl-6-chloro-3-methyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	190/16	879
5-Allyl-4-chloro-6-methyl-2-pyrimidinamine	145–146	881
4-Allyl-2-chloro-6-methylpyrimidine	liquid, nmr	3943
3-Allyl-6-chloro-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	50	882
4-Allyl-2-chloropyrimidine	liquid, nmr	3943
1-Allyl-5-chloro-2(1*H*)-pyrimidinone	130–131	883,3772,3916
1-Allyl-5,6-diamino-3-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	138–141 or 143–145	857,884–886
5-Allyl-4,6-dichloro-2-pyrimidinamine	182, nmr, uv	203
5-Allyl-4,6-dichloropyrimidine	74–76/0.8, 96–98/8	887,888
1-Allyl-3,5-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	138/0.3	877
3-Allyl-2,5-difluoro-6-methoxy-4(3*H*)-pyrimidinone	72, nmr	293
3-Allyl-5,6-difluoro-2-methoxy-4(3*H*)-pyrimidinone	liquid, M^+, nmr	293
3-Allyl-5,6-difluoro-2,4(1*H*,3*H*)-pyrimidinedione	95–96, nmr	293
3-Allyl-2,5-difluoro-4(3*H*)-pyrimidinone	37–39, nmr	293
5-Allyl-2-dimethylamino-6-methyl-4(3*H*)-pyrimidinone	96 or 174	672,863

5-Allyl-2-dimethylamino-4(3*H*)-pyrimidinone	94	863
5-Allyl-2,4-dimethyl-6-methylaminopyrimidine	90–91	889
5-Allyl-4,6-dimethyl-2-methylaminopyrimidine	92	843
3-Allyl-5,6-dimethyl-2-methylthio-4-(3*H*)-pyrimidinone	83	890
5-Allyl-3,6-dimethyl-2-methylthio-4(3*H*)-pyrimidinone	86	891–893
5-Allyl-2,6-dimethyl-4-pyrimidinamine	190–191	889
5-Allyl-4,6-dimethyl-2-pyrimidinamine	131–134	843,894
1-Allyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	45–47	895
3-Allyl-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	59–61	895
5-Allyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	214	891
5-Allyl-2,6-dimethyl-4(3*H*)-pyrimidinethione	140–141	878
1-Allyl-4,6-dimethyl-2-pyrimidinimine	HI: 184–186	843
5-Allyl-2,6-dimethyl-4(3*H*)-pyrimidinone	151–152	862
5-Allyl-4,6-dimethyl-2(1*H*)-pyrimidinone	176	843
5-Allyl-1,3-dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	liquid, nmr, uv	896
1-Allyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	149–152	870
1-Allyl-3-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	897
3-Allyl-5-fluoro-2,6-dimethoxy-4(3*H*)-pyrimidinone	71–72, nmr	293
3-Allyl-5-fluoro-6-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	149–151, nmr	293
1-Allyl-5-fluoro-4-methylthio-2(1*H*)-pyrimidinone	117	741
1-Allyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	125 or 126–127	741,898,899
3-Allyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	78–80, nmr	293
5-Allyl-4-hydrazino-2,6-dimethylpyrimidine	63-65	365
5-Allyl-4-hydrazino-6-methyl-2-propylpyrimidine	pic: 143	880,900
6-Allyl-5-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	104–106	854
1-Allyl-5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	118–120	901
2-Allylimino-1-propyl-1,2-dihydropyrimidine	HI: 92; pic: 104	902
3-Allyl-6-isopropyl-2-methylthio-4(3*H*)-pyrimidinone	118–120/0.3, nmr, uv	89

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
3-Allyl-6-isopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	159, nmr	89
1-Allyl-4-methoxy-6-nitroamino-2(1*H*)-pyrimidinone	163–164	903
1-Allyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	161–162	904
1-Allyl-3-methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	179–180	882
1-Allyl-5-methyl-2-methylthio-4(1*H*)-pyrimidinone	111, nmr, uv	89
1-Allyl-6-methyl-2-methylthio-4(1*H*)-pyrimidinone	111, nmr, uv	89
3-Allyl-5-methyl-2-methylthio-4(3*H*)-pyrimidinone	55, nmr, uv	89
3-Allyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	48–50, 125–130/1.1 nmr, uv	89,905
5-Allyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	84 or 189–191	905,906
3-Allyl-1-methyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	265/360(?)	907
5-Allyl-6-methyl-2-propyl-4(3*H*)-pyrimidinone	112–113	880
1-Allyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	—	846
1-Allyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	168–169	895
3-Allyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	175–177	908
3-Allyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	184	890,895,905
5-Allyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	130–132 or 230, ir, nmr	130,905
5-Allyl-2-methyl-4(3*H*)-pyrimidinone	153–154	872
3-Allyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	176–178	909
1-Allyl-2-methylthio-4(1*H*)-pyrimidinone	80 or 95–97, nmr, uv	89,846
1-Allyl-4-methylthio-2(1*H*)-pyrimidinone	76, nmr	89
3-Allyl-2-methylthio-4(3*H*)-pyrimidinone	52–55, 110–112/0.4, nmr, uv	89,846
3-Allyl-6-methylthio-4(3*H*)-pyrimidinone	69–71	909
5-Allyl-2-methylthio-4(3*H*)-pyrimidinone	152–154	872,910
1-Allyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	150, nmr	89
1-Allyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	167, nmr	89,911

3-Allyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	155, nmr	89
3-Allyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	189 or 190–191, nmr	89,905,912
5-Allyl-1-methyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	155–157	896
5-Allyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	188	905,906
1-Allyl-2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile	147–148	913,914
1-Allyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	151–152	915
2-Allyloxy-5-bromopyrimidine	28–30, ms, nmr	3916
2-Allyloxy-5-chloropyrimidine	25	883,3916
4-Allyloxy-2,5-difluoro-6-methoxypyrimidine	25, nmr	293
4-Allyloxy-5,6-difluoro-2-methoxypyrimidine	liquid, M^+, nmr	293
6-Allyloxy-2,5-difluoro-3-methyl-4(3*H*)-pyrimidinone	42–44, nmr, uv	293
4-Allyloxy-2,5-difluoropyrimidine	crude: nmr	293
4-Allyloxy-5,6-difluoropyrimidine	crude: nmr	293
6-Allyloxy-2,5-difluoro-4(3*H*)-pyrimidinone	123–124, nmr	293
4-Allyloxy-2-dimethylaminopyrimidine	63–65/0.1, n_D^{23} 1.5305	672,863
5-Allyloxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	103–104	854
2-Allyloxy-5-fluoro-4,6-dimethoxypyrimidine	41–42, nmr	293
4-Allyloxy-5-fluoro-2,6-dimethoxypyrimidine	42–43, nmr	293
6-Allyloxy-5-methoxy-4-pyrimidinamine	41–42	916
4-Allyloxy-6-methyl-2-methylthiopyrimidine	160–164/17	917
6-Allyloxy-5-methyl-4-pyrimidinamine	98–103	868
4-Allyloxy-2-methylpyrimidine	47/0.5	872
4-Allyloxy-1-methyl-2(1*H*)-pyrimidinone	110–112	846
2-Allyloxy-6-methyl-4(3*H*)-pyrimidinone	164	918
4-Allyloxy-2-methylthiopyrimidine	88/0.5	846,972
4-Allyloxy-5-nitro-2(1*H*)-pyrimidinone	230	868
4-Allyloxy-2-pyrimidinamine	85–87	872
2-Allyloxypyrimidine	50–52/0.5	919

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Allyloxy-4,6(1*H*,5*H*)-pyrimidinedione	171	918
4-Allyloxy-2,5,6-trifluoropyrimidine	74–76/17, nmr	293
1-Allyl-2-propylimino-1,2-dihydropyrimidine	HBr: 115; pic: 93	902
1-Allyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	112–114	875
1-Allyl-2,4(1*H*,3*H*)-pyrimidinedione	105–108 or 110, nmr	89,870,875,6073
3-Allyl-2,4(1*H*,3*H*)-pyrimidinedione	133–134	908
5-Allyl-2,4(1*H*,3*H*)-pyrimidinedione	280–281	872,920
5-Allyl-4,6(1*H*,5*H*)-pyrimidinedione	240 to 272	887,888,921
5-Allyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	167	922
1-Allyl-2(1*H*)-pyrimidinimine	HBr: 214, uv; pic: 149–150	867,923
1-Allyl-2(1*H*)-pyrimidinone	62–64	919
2-Allylsulfinyl-5-chloropyrimidine	82	844
2-Allylsulfonyl-5-chloropyrimidine	84	844
4-Allylthio-2-amino-6-methylthio-5-pyrimidinecarbonitrile	160–162 or 162–163, ir, nmr	3747,3752
2-Allylthio-6-amino-5-nitroso-4(3*H*)-pyrimidinone	191	924
2-Allylthio-6-amino-4(3*H*)-pyrimidinone	201–203	925
2-Allylthio-4-chloro-5-methoxypyrimidine	30	926
2-Allylthio-5-chloropyrimidine	62–63/0.1	844
2-Allylthio-5,6-dichloro-4(3*H*)-pyrimidinone	172–174	927
5-Allylthio-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	liquid: anal, nmr	3898
2-Allylthio-3,6-dimethyl-4(3*H*)-pyrimidinone	43	917
2-Allylthio-5-hydroxymethyl-4-pyrimidinamine	98	928
2-Allylthio-5-iodo-6-methyl-4(3*H*)-pyrimidinone	159	929
2-Allylthio-5-isopropyl-4,6(1*H*,5*H*)-pyrimidinedione	224–225	930
2-Allylthio-6-isopropyl-4(3*H*)-pyrimidinone	101, nmr	89

2-Allylthio-5-methoxypyrimidine	140/20	926
2-Allylthio-5-methoxy-4(3*H*)-pyrimidinone	132–133	926
2-Allylthio-4-methylpyrimidine	95/5, n_D^{20} 1.5650	193
4-Allylthio-2-methylpyrimidine	67/0.1	846
2-Allylthio-5-methyl-4(3*H*)-pyrimidinone	165, nmr	89
2-Allylthio-6-methyl-4(3*H*)-pyrimidinone	131 to 140, nmr	89,905,917,925,929
4-Allylthio-1-methyl-2(1*H*)-pyrimidinone	121–123	896
6-Allylthio-1-methyl-2(1*H*)-pyrimidinone	88–89	896
4-Allylthio-2-methylthiopyrimidine	126/1.3	846
2-Allylthio-6-propyl-4(3*H*)-pyrimidinone	101	925
4-Allylthio-2-pyrimidinamine	133–135	846
5-Allylthio-2,4(1*H*,3*H*)-pyrimidinedione	231–234	931
6-Allylthio-2,4,5-pyrimidinetriamine	149–151	932
2-Allylthio-5-pyrimidinol	100	926
2-Allylthio-4(3*H*)-pyrimidinone	135 to 140, ir, ms, nmr	89,925,933,6415
1-Allyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	136–137(?), 184 to 198, ir, ms, nmr	89,107,258,910,6415
1-Allyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	122–125	870
3-Allyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	119, nmr	89
3-Allyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	135–137	909
5-Allyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	185–186	934
5-Allyl-2,4,6-trichloropyrimidine	38–39, 96–98/3	935
3-Allyl-2,5,6-trifluoro-4(3*H*)-pyrimidinone	33–34, nmr	293
5-Allyl-1,4,6-trimethyl-2(1*H*)-pyrimidinimine	HCl: 231; HI: 203; pic: 146	843
6-Amino-5-aminomethyl-2-chloro-4-pyrimidinecarboxylic acid	237	936
5-Amino-2-aminomethyl-4,6(1*H*,5*H*)-pyrimidinedione	HCl: 200	937
4-Amino-5-aminomethyl-2(1*H*)-pyrimidinethione	220	938
4-Amino-5-aminomethyl-2(1*H*)-pyrimidinone	264–267	938,939

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Amino-1-β-amino-oxyethyl-2(1*H*)-pyrimidinone	HCl: 209–210	940,941
4-Amino-1-γ-amino-oxypropyl-2(1*H*)-pyrimidinone	HCl: 106–108	940
2-Amino-5-γ-aminopropyl-6-methyl-4(3*H*)-pyrimidinone	HCl: 298–300	942
4-Amino-1-γ-aminopropyl-2(1*H*)-pyrimidinone	138–140 or 159–162; HCl: 293	608,940,943
6-Amino-3,5-bis-β-cyanoethyl-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	170–171	849
6-Amino-3,5-bis-β-cyanoethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	145	849
4-Amino-2,6-biscyanomethyl-5-pyrimidinecarbonitrile	220–224(?)	944,945,947,5969
6-Amino-1,5-bisdimethylamino-2,4(1*H*,3*H*)-pyrimidinedione	248–250	585
4-Amino-2,6-bishydroxymethyl-5-pyrimidinol	90–95	609
2-Amino-4,6-bismethylthio-5-pyrimidinecarbonitrile	208–209, ir, nmr	3752
4-Amino-2,6-bismethylthio-5-pyrimidinecarbonitrile	231–232	948
2-Amino-5-bromo-6-bromomethyl-4(3*H*)-pyrimidinone	200–201	949
2-Amino-5-bromo-6-carboxymethyl-4(3*H*)-pyrimidinone	HBr: 230–232	949,950
4-Amino-5-bromo-6-chloro-2(1*H*)-pyrimidinone	230	951
6-Amino-5-bromo-2-dimethylamino-4(3*H*)-pyrimidinone	232–234	952
6-Amino-5-bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	210 or 214–216	953,954
2-Amino-5-bromo-3,6-dimethyl-4(3*H*)-pyrimidinone	262	911
2-Amino-5-bromo-3-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	HBr: 171–173	955
2-Amino-5-bromo-3-β-hydroxypropyl-6-methyl-4(3*H*)-pyrimidinone	HBr: 192–193	955
6-Amino-5-bromo-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	265 or 278–280	956,957
2-Amino-5-bromo-6-methyl-4-(3*H*)-pyrimidinethione	207	958
2-Amino-5-bromo-6-methyl-4(3*H*)-pyrimidinone	249–250	614,959–962
4-Amino-5-bromo-1-methyl-2(1*H*)-pyrimidinone	—	963
6-Amino-5-bromo-2-methylthio-4(3*H*)-pyrimidinone	> 200	951,961
4-Amino-2-bromo-5-pyrimidinecarbonitrile	> 300, ir, nmr	478

6-Amino-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione	306 or > 350	837,953,954,964
2-Amino-5-bromo-4(3*H*)-pyrimidinone	273 or 275	719,961
2-Amino-6-bromo-4(3*H*)-pyrimidinone	233–234	965,966
4-Amino-5-bromo-2(1*H*)-pyrimidinone	170–171 or 240–242; HBr: 255–256	967–971
6-Amino-2-bromo-4(3*H*)-pyrimidinone	> 280	972,973
6-Amino-5-bromo-4(3*H*)-pyrimidinone	268 or 281	837,968
6-Amino-5-bromo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	> 300	951
4-Amino-2-carbamoylmethyl-5-pyrimidinecarbaldehyde	249–250	974
4-Amino-2-carbamoylmethyl-5-pyrimidinecarbonitrile	258	974,975
2-Amino-5-carbamoylmethyl-4(3*H*)-pyrimidinone	280 or 295	976
2-Amino-6-carbamoylmethyl-4(3*H*)-pyrimidinone	> 285	950
2-Amino-3-α-carboxyethyl-5-ethyl-6-methyl-4(3*H*)-pyrimidinone	215	977
2-Amino-5-β-carboxyethyl-6-methyl-4(3*H*)-pyrimidinethione	222–225	613
2-Amino-3-α-carboxyethyl-6-methyl-4(3*H*)-pyrimidinone	227	978
2-Amino-3-β-carboxyethyl-6-methyl-4(3*H*)-pyrimidinone	244–245	979
2-Amino-5-β-carboxyethyl-6-methyl-4(3*H*)-pyrimidinone	237–239 or 301–303	980,981
2-Amino-1-β-carboxyethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	299–302	982
2-Amino-1-β-carboxyethyl-4(1*H*)-pyrimidinone	anal, uv	982
2-Amino-3-β-carboxyethyl-4(3*H*)-pyrimidinone	—	982
4-Amino-1-β-carboxyethyl-2(1*H*)-pyrimidinone	266–268	940
4-Amino-3-β-carboxyethyl-2(3*H*)-pyrimidinone	255–259 or > 290	697,983
2-Amino-3-carboxymethyl-5,6-dimethyl-4(3*H*)-pyrimidinone	233	977
2-Amino-3-carboxymethyl-5-ethyl-6-methyl-4(3*H*)-pyrimidinone	245	977
2-Amino-1-carboxymethyl-5-ethyl-4,6(1*H*,5*H*)-pyrimidinedione	213	977
2-Amino-1-carboxymethyl-6-methyl-4(1*H*)-pyrimidinone	228–230	984
2-Amino-3-carboxymethyl-6-methyl-4-(3*H*)-pyrimidinone	240–241	978,984
2-Amino-5-carboxymethyl-6-methyl-4(3*H*)-pyrimidinone	315–320 or 322	985,986

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Amino-6-carboxymethyl-3-methyl-4(3*H*)-pyrimidinone	256–258	950
6-Amino-5-carboxymethyl-2-methyl-4(3*H*)-pyrimidinone	anal	987
2-Amino-6-carboxymethyl-5-nitro-4(3*H*)-pyrimidinone	309–310	988
4-Amino-2-carboxymethyl-5-pyrimidinecarboxylic acid	258	974
6-Amino-1-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	-	989
6-Amino-5-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	> 338	990,991
5-Amino-1-carboxymethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	260, ir, nmr, uv	3963
2-Amino-5-carboxymethyl-4(3*H*)-pyrimidinone	317–319	992
2-Amino-6-carboxymethyl-4(3*H*)-pyrimidinone	185–190, then 295–300	949,950,988,993
4-Amino-1-carboxymethyl-2(1*H*)-pyrimidinone	280	994
4-Amino-3-carboxymethyl-2(3*H*)-pyrimidinone	HCl: > 300	995
4-Amino-5-carboxymethyl-2(1*H*)-pyrimidinone	> 290; pic: 217–218	996
2-Amino-5-β-chlorocarbonylethyl-6-methyl-4(3*H*)-pyrimidinone	crude: > 150	981
2-Amino-4-chloro-6-dimethylamino-5-pyrimidinecarbonitrile	219–221	997
4-Amino-6-chloro-2-dimethylamino-5-pyrimidinecarbonitrile	—	998
5-Amino-6-chloro-2-dimethylamino-4(3*H*)-pyrimidinone	233–235	999
5-Amino-6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	120–121	1000
6-Amino-5-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	239–240	953
2-Amino-4-chloro-6-ethoxy-5-pyrimidinecarbonitrile	191	1001
2-Amino-5-chloro-6-ethoxy-4(3*H*)-pyrimidinone	216–218	1002
4-Amino-2-β-chloroethyl-5-pyrimidinecarbonitrile	> 230	1003
4-Amino-2-chloro-6-ethyl-5-pyrimidinecarbonitrile	232	1004
2-Amino-5-β-chloroethyl-4(3*H*)-pyrimidinone	HCl: 214–215	1005
4-Amino-5-chloro-1-ethyl-2(1*H*)-pyrimidinone	194–196	1006
6-Amino-2-chloro-5-hydroxymethyl-4-pyrimidinecarboxamide	237	936

4-Amino-2-chloro-6-isopropyl-5-pyrimidinecarbonitrile	199	1004
2-Amino-6-chloro-5-methoxy-4(3*H*)-pyrimidinone	280–281	1007
2-Amino-4-chloro-6-methylamino-5-pyrimidinecarbonitrile	279	997
2-Amino-6-chloro-3-methyl-5-nitro-4(3*H*)-pyrimidinone	275–276	999
4-Amino-6-chloro-2-methyl-5-pyrimidinecarbaldehyde	192–193	1008
2-Amino-4-chloro-6-methyl-5-pyrimidinecarbonitrile	258–259	682
4-Amino-2-chloro-6-methyl-5-pyrimidinecarbonitrile	253 or 254	1004,1009
4-Amino-6-chloro-2-methyl-5-pyrimidinecarbonitrile	245–246	1010
5-Amino-6-chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	243	1000
4-Amino-6-chloro-2-methyl-5-pyrimidinol	212–220	1011,1012
4-Amino-5-chloromethyl-2(1*H*)-pyrimidinone	HCl: > 300	1013
2-Amino-5-chloro-6-methyl-4(3*H*)-pyrimidinone	260	1014
2-Amino-6-chloro-3-methyl-4(3*H*)-pyrimidinone	305	999
4-Amino-5-chloro-1-methyl-2(1*H*)-pyrimidinone	H_2O: anal, nmr, uv; HCl: anal, nmr, uv	318
4-Amino-6-chloro-1-methyl-2(1*H*)-pyrimidinone	220–225	1015
5-Amino-6-chloro-2-methyl-4(3*H*)-pyrimidinone	231–233 or 233–234	269,1016
5-Amino-6-chloro-3-methyl-4(3*H*)-pyrimidinone	139	1017
6-Amino-2-chloro-5-methyl-4(3*H*)-pyrimidinone	220	972,973
4-Amino-6-chloro-5-methyl-2(1*H*)-pyrimidinone 3-oxide	232–235	1018
4-Amino-6-chloro-2-methylthio-5-pyrimidinecarbaldehyde	189–190	1019
2-Amino-4-chloro-6-methylthio-5-pyrimidinecarbonitrile	crude	1004
4-Amino-2-chloro-6-methylthio-5-pyrimidinecarbonitrile	crude	1004
4-Amino-6-chloro-2-methylthio-5-pyrimidinecarbonitrile	223–226	1020
2-Amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone	275 to 365, ir, uv	223,608,999,1021–1025,6937
2-Amino-4-chloro-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	> 190	1026
2-Amino-4-chloro-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	> 350	1026
4-Amino-6-chloro-5-pyrimidinecarbaldehyde	163–165	1027,1028

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Amino-2-chloro-5-pyrimidinecarbonitrile	243–244, ir, nmr	478
4-Amino-6-chloro-5-pyrimidinecarbonitrile	200	787
6-Amino-2-chloro-4-pyrimidinecarbonitrile	232–234	1029
6-Amino-2-chloro-4-pyrimidinecarboxamide	333–335	1030
2-Amino-5-chloro-4-pyrimidinecarboxylic acid	sp	1031
5-Amino-2-chloro-4-pyrimidinecarboxylic acid	155	1032
2-Amino-5-chloro-4,6(1*H*,5*H*)-pyrimidinedione	-	1033
6-Amino-5-chloro-2,4(1*H*,3*H*)-pyrimidinedione	325	1034
2-Amino-6-chloro-4(3*H*)-pyrimidinethione	> 360	958
5-Amino-2-chloro-4(3*H*)-pyrimidinethione	> 300	633,1035
5-Amino-6-chloro-4(3*H*)-pyrimidinethione	196–200 or > 300	1036–1039
2-Amino-5-chloro-4(3*H*)-pyrimidinone	306–307	1040
2-Amino-6-chloro-4(3*H*)-pyrimidinone	257–259 or 261	863,1041–1045
4-Amino-5-chloro-2(1*H*)-pyrimidinone	291–292	1040
4-Amino-6-chloro-2(1*H*)-pyrimidinone	> 300; HCl: > 360	615,1015,1040,1046
5-Amino-6-chloro-4(3*H*)-pyrimidinone	235–236 or 241; HCl: 240–242, ir, uv	607,1017,1047
6-Amino-2-chloro-4(3*H*)-pyrimidinone	> 300	972,973
6-Amino-2-cyanoamino-5-nitroso-4(3*H*)-pyrimidinone	—	1048,1049
6-Amino-2-cyanoamino-4(3*H*)-pyrimidinone	-	1050
6-Amino-5-β-cyanoethyl-1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	147	849
6-Amino-5-β-cyanoethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	232–235	849
6-Amino-5-β-cyanoethyl-3-ethyl-1-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	171–173	849
6-Amino-3-β-cyanoethyl-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	243–244	849
2-Amino-5-β-cyanoethyl-6-methyl-4(3*H*)-pyrimidinethione	242–244	613

2-Amino-5-β-cyanoethyl-6-methyl-4(3*H*)-pyrimidinone	266–267	981
6-Amino-3-β-cyanoethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	202–203	849
6-Amino-5-β-cyanoethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	250–252	849
4-Amino-1-β-cyanoethyl-2(1*H*)-pyrimidinone	249–250	697
2-Amino-5-diazonio-6-dimethylamino-4-pyrimidinolate	178; HCl: 159	1051
2-Amino-4,6-dichloro-5-pyrimidinecarbaldehyde	> 130 or 240–245	1019,1026
4-Amino-2,6-dichloro-5-pyrimidinecarbaldehyde	185–186	1019
6-Amino-1,3-diethyl-5-formamido-2,4(1*H*,3*H*)-pyrimidinedione	235 to 261	586,1052–1054
4-Amino-1,3-diethyl-*N*-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidine-carbothioamide	185–190	1055
4-Amino-1,3-diethyl-*N*-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidine-carbothioamide	190–193	1055
5-Amino-1,3-diethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	95–96	1056
6-Amino-1,3-diethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	155–157; H_2O: 100	1057,1058
4-Amino-5,*N*-diethyl-6-methyl-2-pyrimidinesulfonamide	108–109	1059
6-Amino-1,3-diethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	204–206	586,1052,1060,1061
6-Amino-1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	195 to 200	586,1052,1058,1060,1062
6-Amino-1,5-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1063
5-Amino-1,3-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	200	1064
6-Amino-2,5-diethyl-4(3*H*)-pyrimidinone	202–204	1065
4-Amino-1,3-diethyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	174–175	1066
6-Amino-1,3-diethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	178–182	1067,1068
2-Amino-6-dimethoxymethyl-4(3*H*)-pyrimidinone	202–206	635
2-Amino-2,6-dimethoxy-5-pyrimidinecarbaldehyde	224–228	1019
4-Amino-2,6-dimethoxy-5-pyrimidinecarbaldehyde	189–190; tsc: > 335	1019
5-Amino-6-dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	142–143	1069
6-Amino-5-dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	194	1070
2-Amino-4-dimethylamino-6-ethoxy-5-pyrimidinecarbonitrile	113	997
6-Amino-1-dimethylamino-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	276–278	1071

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Amino-1-dimethylamino-5-formamido-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	198–199	585
6-Amino-1-dimethylamino-5-formamido-2,4(1*H*,3*H*)-pyrimidinedione	275	585,1072
6-Amino-1-dimethylamino-3-β-hydroxyethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	201–203	585
6-Amino-1-dimethylamino-3-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	192–193	585
5-Amino-2-dimethylamino-6-methylamino-4(3*H*)-pyrimidinone	HCl: 265	1073
6-Amino-5-dimethylaminomethyl-2-methyl-4(3*H*)-pyrimidinone	286 or > 300	1074,1075
2-Amino-6-dimethylamino-3-methyl-5-nitro-4(3*H*)-pyrimidinone	208–211	999
6-Amino-2-dimethylamino-3-methyl-5-nitro-4(3*H*)-pyrimidinone	259–260	1076
6-Amino-1-dimethylamino-3-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	288–289	585,1072
6-Amino-2-dimethylamino-3-methyl-5-nitroso-4(3*H*)-pyrimidinone	206 or 258–259	1076,1077
4-Amino-2-dimethylamino-6-methyl-5-pyrimidinecarbonitrile	202	1078
4-Amino-2-dimethylamino-*N*-methyl-5-pyrimidinecarboxamide	245–246, nmr, uv	6454
6-Amino-1-dimethylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	219–220	585
6-Amino-1-dimethylamino-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	296–299	1071
6-Amino-5-dimethylamino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	240–241	1079
5-Amino-4-dimethylamino-6-methyl-2(1*H*)-pyrimidinethione	250	1080
4-Amino-6-dimethylamino-1-methyl-2(1*H*)-pyrimidinone	265–268	1015
5-Amino-2-dimethylamino-6-methyl-4(3*H*)-pyrimidinone	202–204	1081
6-Amino-1-dimethylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	221–222	585
2-Amino-6-dimethylamino-5-nitro-4(3*H*)-pyrimidinone	250–251	999
6-Amino-2-dimethylamino-5-nitro-4(3*H*)-pyrimidinone	287 to 306	638,999,1076,1082
2-Amino-6-dimethylamino-5-nitroso-4(3*H*)-pyrimidinone	205	1051
4-Amino-6-dimethylamino-5-nitroso-2(1*H*)-pyrimidinone	> 360	1015
6-Amino-2-dimethylamino-5-nitroso-4(3*H*)-pyrimidinone	259 to 263	1077,1083,1084
6-Amino-1-dimethylamino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	198–200	585

4-Amino-6-dimethylamino-5-pyrimidinecarbaldehyde	201–202	852
4-Amino-2-dimethylamino-5-pyrimidinecarbohydrazide	–	1085
2-Amino-4-dimethylamino-5-pyrimidinecarbonitrile	161–162	1086
4-Amino-2-dimethylamino-5-pyrimidinecarbonitrile	233–235 or 239; HCl: 253–255	939,1087,1088
2-Amino-4-dimethylamino-5-pyrimidinecarboxamide	246–248	1086
4-Amino-2-dimethylamino-5-pyrimidinecarboxamide	289–290; HCl: 293	847,1078,1088
2-Amino-4-dimethylamino-5-pyrimidinecarboxylic acid	> 250	1086
6-Amino-1-dimethylamino-2,4(1*H*,3*H*)-pyrimidinedione	291–293	585
2-Amino-4-dimethylamino-5-pyrimidinol	pic: 200–203	1011
2-Amino-6-dimethylamino-4(3*H*)-pyrimidinone	> 350 or 351	1001,1051
4-Amino-6-dimethylamino-2(1*H*)-pyrimidinone	324–326	615,1015
5-Amino-2-dimethylamino-4(3*H*)-pyrimidinone	HCl: > 310	1089
5-Amino-6-dimethylamino-4(3*H*)-pyrimidinone	162–163	1090
6-Amino-2-dimethylamino-4(3*H*)-pyrimidinone	285–293	1083,1084,1091–1093
6-Amino-5-dimethylamino-4(3*H*)-pyrimidinone	219–224	1094
6-Amino-2-dimethylamino-5-sulfo-oxy-4(3*H*)-pyrimidinone	208–212	1011
6-Amino-1-dimethylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	202–203 or 216–218	585,1095,1096
4-Amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	194–196; oxime: 248–249; $H_2NN{=}$: > 300	653,1097
5-Amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	> 180, ir, ms, nmr	3731
4-Amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide	257–259 or 267–268	449,1098
5-Amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	225	1099,1100
4-Amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonamide	218–220; H_2O: 117–119	1101
5-Amino-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	143; pic: 189–190	644,794
6-Amino-1,3-dimethyl-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	177–178; HCl: 259–261; pic: 194	1102
5-Amino-1,3-dimethyl-6-methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	120–124	1103
6-Amino-1,3-dimethyl-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	222	1104

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Amino-3,5-dimethyl-2-methylthio-4(3*H*)-pyrimidinone	173	659
6-Amino-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	232–235	1082
4-Amino-1,6-dimethyl-5-nitro-2(1*H*)-pyrimidinone	190–195	1105
6-Amino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	251–252 or 252–260; H_2O: 233	1048,1106–1114
6-Amino-1,3-dimethyl-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	215 to 222	660,1113,1115,1116
6-Amino-1,3-dimethyl-5-propionamido-2,4(1*H*,3*H*)-pyrimidinedione	257–258	586
6-Amino-1,3-dimethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	164–165	653
2-Amino-4,6-dimethyl-5-pyrimidinecarbonitrile	247–248 or 250	442,923
4-Amino-2,6-dimethyl-5-pyrimidinecarbonitrile	220–225 or 227; pic: 195	1117–1122
2-Amino-4,6-dimethyl-5-pyrimidinecarboxamide	281–282	923
4-Amino-2,6-dimethyl-5-pyrimidinecarboxamide	212–214	1123
1-Amino-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	151–152	1124
5-Amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	136–138 or 233–235 (275?), ir, nmr, uv; HCl: 289–290	1125–1129,3904
5-Amino-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	281–282	1130
5-Amino-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	256–257	1130
6-Amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	285–307; HCl: 246–250	653,1062,1107,1108,1111, 1131–1134
6-Amino-1,5-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	327	653
6-Amino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedithione	273–275	660
2-Amino-*N*,*N*-dimethyl-5-pyrimidinesulfonamide	240–241	869
2-Amino-5,6-dimethyl-4(3*H*)-pyrimidinethione	270	1135
4-Amino-1,6-dimethyl-2(1*H*)-pyrimidinethione	322	1136
4-Amino-5,6-dimethyl-2(1*H*)-pyrimidinethione	> 300	1135
5-Amino-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	200	655,715,1137–1141

1-Amino-4,6-dimethyl-2(1*H*)-pyrimidinone	HCl: 250–252	1142
2-Amino-1,6-dimethyl-4(1*H*)-pyrimidinone	284–285	1143,1144
2-Amino-3,6-dimethyl-4(3*H*)-pyrimidinone	310 or 318 (172–174?)	657,861,959,1143,1145–1148
2-Amino-5,6-dimethyl-4(3*H*)-pyrimidinone	303–306, 330	863,959,1149–1152
3-Amino-2,6-dimethyl-4(3*H*)-pyrimidinone	120–125, nmr	167
4-Amino-1,5-dimethyl-2(1*H*)-pyrimidinone	308–310	963,1153
4-Amino-1,6-dimethyl-2(1*H*)-pyrimidinone	340–342	1154
4-Amino-5,6-dimethyl-2(1*H*)-pyrimidinone	332–334; HBr: 291	698,1155,1156
5-Amino-2,6-dimethyl-4(3*H*)-pyrimidinone	194 or 200	750,1042,1157
6-Amino-1,5-dimethyl-4(1*H*)-pyrimidinone	277–278	659
6-Amino-2,3-dimethyl-4(3*H*)-pyrimidinone	242	1158
6-Amino-2,5-dimethyl-4(3*H*)-pyrimidinone	283	1159,1160
6-Amino-3,5-dimethyl-4(3*H*)-pyrimidinone	190–191	659
6-Amino-1,3-dimethyl-5-thiocyanato-2,4(1*H*,3*H*)-pyrimidinedione	> 200	1161
4-Amino-3,*N*-dimethyl-2-thioxo-2,3-dihydro-5-pyrimidinecarboxamide	264–265, nmr	6454
5-Amino-1,3-dimethyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione	278–280 or 280–282	1137,1163,3998
4-Amino-1,3-dimethyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	260 or 283–286	660,1066,1162
6-Amino-1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	286–293	660,1068,1115
6-Amino-1,5-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	302	659
4-Amino-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	> 300, uv	1164,3897
5-Amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	oxime: > 300	1165
1-Amino-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	228	1166
2-Amino-4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarbonitrile	268–270	1167
2-Amino-4,6-dioxo-1,4,5,6-tetrahydro-1-pyrimidinecarboxamide	—	1168
2-Amino-4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxylic acid	270–275	1175
3-Amino-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	215–216	1169
5-Amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	anal; HCl: > 220	1170–1174
4-Amino-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonamide	268	964

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid	anal; Na: anal	662 (cf. 1176),1177–1179
4-Amino-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonyl chloride	265	1180
6-Amino-1,3-dipropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	1067,1181
2-Amino-5-ethoxy-6-ethoxymethyl-4(3*H*)-pyrimidinone	221 or 224–225	1149,1182
2-Amino-4-ethoxy-6-methylamino-5-pyrimidinecarbonitrile	176	997
6-Amino-5-ethoxymethyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	> 200	1183
4-Amino-6-ethoxy-2-methyl-5-pyrimidinecarbonitrile	232 or 233–235	1010,1184
2-Amino-4-ethoxy-6-methylthio-5-pyrimidinecarbonitrile	174, ir, nmr	6139
6-Amino-5-ethoxymethyl-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid	> 200	1183
4-Amino-2-ethoxy-5-pyrimidinecarbonitrile	182–184, ir, nmr	400,478
2-Amino-5-ethoxy-4,6(1*H*,5*H*)-pyrimidinedione	> 320	1149,1185
4-Amino-5-ethoxy-2(1*H*)-pyrimidinethione	244	1186
5-Amino-2-ethoxy-4(3*H*)-pyrimidinethione	127	1187
5-Amino-6-ethoxy-4(3*H*)-pyrimidinethione	193–195	1047
2-Amino-5-ethoxy-4(3*H*)-pyrimidinone	245–246 or 248	1149,1188
2-Amino-6-ethoxy-4(3*H*)-pyrimidinone	292–294 or > 300	1040,1189
4-Amino-5-ethoxy-2(1*H*)-pyrimidinone	300	1188
6-Amino-2-ethoxy-4(3*H*)-pyrimidinone	245–246 or 247	972,973,1190
5-Amino-6-ethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	pic: 245–246	1069
6-Amino-5-ethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	193–194	1102
2-Amino-6-ethylamino-3-methyl-5-nitro-4(3*H*)-pyrimidinone	257–259	999
5-Amino-4-ethylamino-6-methyl-2(1*H*)-pyrimidinethione	> 300	1191
5-Amino-4-ethylamino-6-methyl-2(1*H*)-pyrimidinone	anal	1192,1193
2-Amino-6-ethylamino-5-nitro-4(3*H*)-pyrimidinone	342–344	1082
2-Amino-6-ethylamino-5-nitroso-4(3*H*)-pyrimidinone	265–266 or 269	299,1042

6-Amino-2-ethylamino-5-nitroso-4(3*H*)-pyrimidinone	—	1194
6-Amino-5-ethylamino-2,4(1*H*,3*H*)-pyrimidinedione	—	1054
2-Amino-6-ethylamino-4(3*H*)-pyrimidinethione	224	850
5-Amino-2-ethylamino-4(3*H*)-pyrimidinethione	156	1195
2-Amino-6-ethylamino-4(3*H*)-pyrimidinone	229–230	1042
4-Amino-5-ethylamino-2(1*H*)-pyrimidinone	254–256	1094
4-Amino-6-ethylamino-2(1*H*)-pyrimidinone	336–337	1015
5-Amino-4-ethylamino-2(1*H*)-pyrimidinone	240	1196
5-Amino-6-ethylamino-4(3*H*)-pyrimidinone	194–196	1094
6-Amino-2-ethylamino-4(3*H*)-pyrimidinone	—	1194
6-Amino-5-ethylamino-4(3*H*)-pyrimidinone	207–210	1094
1-β-Aminoethyl-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione	HBr: 279–280, nmr, uv	3775
4-Amino-*N*-ethyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide	172	775,1197
6-Amino-5-ethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	196–198 or 208–209	653,853
5-β-Aminoethyl-2,6-dimethyl-4(3*H*)-pyrimidinone	HCl: 240	1198
4-Amino-3-ethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	295–300	1058
1-Amino-6-ethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	202–203	1199
4-Amino-*N*-ethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbothioamide	> 300	1055
1-β-Aminoethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	287–288	1200
2-Amino-6-ethyl-5-fluoro-4(3*H*)-pyrimidinone	—	1201
6-Amino-5-*N*-ethylformamido-2,4(1*H*,3*H*)-pyrimidinedione	340	1054,1202
3-Amino-5-ethyl-2-hydrazino-6-methyl-4(3*H*)-pyrimidinone	175–177	32
2-Amino-6-α-ethylhydrazino-4(3*H*)-pyrimidinone	349–350	1203
3-Amino-6-ethyl-2-hydrazino-4(3*H*)-pyrimidinone	144–145	32
6-Amino-3-ethyl-1-β-hydroxyethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	172–173	1204
6-Amino-1-ethyl-3-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1205
6-Amino-3-ethyl-1-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	180–181	1062,1205

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Amino-6-ethyl-5-β-hydroxyethyl-4(3*H*)-pyrimidinone	239–240	1206
6-Amino-5-ethylideneamino-2,4(1*H*,3*H*)-pyrimidinedione	275–300	1054
5-α-Aminoethylidene-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	248–250	1207
4-Amino-2-ethyl-6-isopropyl-5-pyrimidinecarbonitrile	—	1208
4-Amino-6-ethyl-3-isopropyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile	254	809
4-Amino-6-ethyl-3-β-methoxyethyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile	202	809
6-Amino-5-ethyl-2-methoxy-4(3*H*)-pyrimidinone	226	972,973
5-Amino-5-ethyl-6-methylamino-2(1*H*)-pyrimidinethione	310	1191
5-Amino-1-ethyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	> 175, ir, ms, nmr	3731
5-α-Aminoethyl-2-methyl-4-pyrimidinamine	103	1209
5-β-Aminoethyl-2-methyl-4-pyrimidinamine	101	1209
5-β-Aminoethyl-1-4-methylpyrimidine	165/2 or 132/16; pic: 184–185	1210,1211
4-Amino-2-ethyl-6-methyl-5-pyrimidinecarbonitrile	—	1212
4-Amino-6-ethyl-2-methyl-5-pyrimidinecarbonitrile	—	1212
5-β-Aminoethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	HBr: 312	1005
5-Amino-1-ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	234–236	895
5-Amino-3-ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	203–205	895
6-Amino-1-ethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	232–233	1062
6-Amino-3-ethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	208–209	1062,1213,1214
6-Amino-5-ethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	284–285	653
2-Amino-5-ethyl-6-methyl-4(3*H*)-pyrimidinethione	230–245	1215
2-Amino-1-ethyl-6-methyl-4(1*H*)-pyrimidinone	289–290	1144
2-Amino-3-ethyl-6-methyl-4(3*H*)-pyrimidinone	ir	1216
2-Amino-5-ethyl-6-methyl-4(3*H*)-pyrimidinone	280 to 289	863,1151,1152,1215,1217,1218

4-Amino-5-ethyl-1-methyl-2(1*H*)-pyrimidinone	246	1219
4-Amino-5-ethyl-6-methyl-2(1*H*)-pyrimidinone	295 or 296–298	1059,1218
6-Amino-5-ethyl-2-methyl-4(3*H*)-pyrimidinone	272–273	1159
6-Amino-5-ethyl-2-methylthio-4(3*H*)-pyrimidinone	215–217	1220
4-Amino-6-ethyl-5-nitro-2(*H*)-pyrimidinethione	225	1191
4-Amino-3-ethyl-5-nitro-2(3*H*)-pyrimidinone	crude	1221
6-Amino-1-ethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	249	1222
2-Amino-4-ethyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	316–317	1223
4-Amino-3-ethyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	252	864
2-Amino-5-ethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	275–276	1224
4-Amino-3-ethyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acid	240	864
6-Amino-5-ethyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	247–248	1183
6-Amino-3-ethyl-1-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	1067,1181
2-β-Aminoethylpyrimidine	HCl: 167–168	1225
4-α-Aminoethylpyrimidine	92–93/12, 96–100/18, $[\alpha]_D^{20}$ − 10.65° (EtOH)	1226
4-β-Aminoethylpyrimidine	HCl: 180–182	1225
5-α-Aminoethylpyrimidine	90–95/15, nmr, $[\alpha]_D^{20}$ − 37.3 (EtOH)	1226
4-Amino-2-ethyl-5-pyrimidinecarbaldehyde	dnp: 290	1227
4-Amino-2-ethyl-5-pyrimidinecarbonitrile	198 or 202	975,1118
4-Amino-6-ethyl-5-pyrimidinecarbonitrile	—	1208
2-Amino-4-ethyl-5-pyrimidinecarboxylic acid	> 300, ir, nmr, uv	3996
1-β-Aminoethyl-2,4(1*H*,3*H*)-pyrimidinedione	160–162, nmr	3775
2-Amino-5-ethyl-4,6(1*H*,5*H*)-pyrimidinedione	320 or 340	1228–1230
5-β-Aminoethyl-2,4(1*H*,3*H*)-pyrimidinedione	HBr: 307–309	1005
5-Amino-3-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	171–172	895
5-Amino-6-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	206–207	1231
6-β-Aminoethyl-2,4(1*H*,3*H*)-pyrimidinedione	256–257 or 258	1232,1233

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Amino-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	288–290	1062
6-Amino-3-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	286	532
6-Amino-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	321–323 or 339	1219,1234,1235
4-Amino-5-ethyl-2(1*H*)-pyrimidinethione	273–274	1236,1237
1-Amino-5-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	149–153	1238
5-Amino-1-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	225 or 230	789,818
2-Amino-5-ethyl-4(3*H*)-pyrimidinone	227–228 or 230–232	1152,1219
2-Amino-6-ethyl-4(3*H*)-pyrimidinone	247–248 or 249–251 (217?)	1118,1239–1241
4-Amino-1-ethyl-2(1*H*)-pyrimidinone	244–247; HBr: 207	870,871,1006
4-Amino-5-ethyl-2(1*H*)-pyrimidinone	277 or 282–283; HCl: 236–237	1219,1242
6-Amino-1-ethyl-4(3*H*)-pyrimidinone	215–217	1055
6-Amino-2-ethyl-4(3*H*)-pyrimidinone	245	1243,1244
6-Amino-3-ethyl-4(3*H*)-pyrimidinone	pic: 176–177	1245
6-Amino-2-ethylthio-3-methyl-5-nitroso-4(3*H*)-pyrimidinone	—	1246
4-Amino-2-ethylthio-6-methyl-5-pyrimidinecarbonitrile	214–215	1247
6-Amino-2-ethylthio-3-methyl-4(3*H*)-pyrimidinone	203–204	1246
2-Amino-4-ethylthio-6-methylthio-5-pyrimidinecarbonitrile	161–162, ir, nmr	3752
6-Amino-2-ethylthio-5-nitroso-4(3*H*)-pyrimidinone	222	924,1248
4-Amino-2-ethylthio-5-pyrimidinecarbonitrile	140 to 147	938,1118,1249–1252
4-Amino-2-ethylthio-5-pyrimidinecarbothioamide	184	939
4-Amino-2-ethylthio-5-pyrimidinecarboxamide	218–219 or 220	1253
4-Amino-2-ethylthio-5-pyrimidinecarboxylic acid	230	1254
5-Amino-2-ethylthio-4(3*H*)-pyrimidinethione	—	626
2-Amino-6-ethylthio-4(3*H*)-pyrimidinone	248	958

5-Amino-2-ethylthio-4(3*H*)-pyrimidinone	159	702,1255
6-Amino-2-ethylthio-4(3*H*)-pyrimidinone	213 to 219	925,951,1256,1257
6-Amino-5-ethyl-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid	238–239	1183
5-Aminoethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	298–300	1258
6-Amino-1-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	249–250	849
6-Amino-3-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	294	532
6-Amino-5-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	283–284	1220
4-Amino-5-ethynyl-2(1*H*)-pyrimidinone	> 225	1259
2-Amino-5-fluoro-6-methyl-4(3*H*)-pyrimidinone	> 300	1201
2-Amino-6-fluoromethyl-4(3*H*)-pyrimidinone	250–260	1201
4-Amino-5-fluoro-1-methyl-2(1*H*)-pyrimidinone	297–299 or > 300, nmr	1260,1261,3738
6-Amino-5-fluoro-2-methyl-4(3*H*)-pyrimidinone	322–325	1262
2-Amino-5-fluoro-4,6(1*H*,5*H*)-pyrimidinedione	—	1201
6-Amino-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	> 300, ms	9,1263
2-Amino-5-fluoro-4(3*H*)-pyrimidinone	271–274 or 274–276	962,1040,1264
2-Amino-6-fluoro-4(3*H*)-pyrimidinone	> 280	1040
4-Amino-5-fluoro-2(1*H*)-pyrimidinone	295 to 300, ms	9,360,621,1040,1265–1269
4-Amino-6-fluoro-2(1*H*)-pyrimidinone	> 300	1040
6-Amino-5-fluoro-4(3*H*)-pyrimidinone	> 290	1262
4-Amino-5-fluoro-2(1*H*)-pyrimidinone 3-oxide	255	1265
5-Amino-6-formamido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1270
6-Amino-5-formamido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	250 to 253	1053,1106,1126,1270–1277
6-Amino-5-formamido-1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	304–305	660
6-Amino-5-formamido-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	295–300	1278
2-Amino-5-formamido-6-isopropylamino-3-methyl-4(3*H*)-pyrimidinone	238–240	1279
2-Amino-5-formamido-6-isopropylamino-4(3*H*)-pyrimidinone	265–267	1279
6-Amino-5-formamido-1-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	215	1280
2-Amino-5-formamido-6-methylamino-4(3*H*)-pyrimidinone	> 350	850,1281,1282

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Amino-5-formamido-2-methylamino-4(3*H*)-pyrimidinone	> 300	1282
2-Amino-5-formamido-3-methyl-6-methylamino-4(3*H*)-pyrimidinone	> 300	1282
6-Amino-5-formamido-3-methyl-2-methylamino-4(3*H*)-pyrimidinone	300–302	1282
6-Amino-5-formamido-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	256–257	1283
6-Amino-5-formamido-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 340	591,1053,1284–1286
6-Amino-6-formamido-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 360	1286–1288
4-Amino-5-formamido-1-methyl-2(1*H*)-pyrimidinethione	270–275	1179
2-Amino-5-formamido-3-methyl-4(3*H*)-pyrimidinone	264–266	1281
4-Amino-5-formamido-1-methyl-2(1*H*)-pyrimidinone	—	1289
4-Amino-5-formamido-6-methyl-2(1*H*)-pyrimidinone	> 345	1290,1291
6-Amino-5-formamido-1-methyl-2(1*H*)-pyrimidinone	275–278	1283
6-Amino-5-formamido-3-methyl-4(3*H*)-pyrimidinone	245–247 or 266–267	1283,1292
2-Amino-5-formamido-6-propylamino-4(3*H*)-pyrimidinone	277–279	850
6-Amino-5-formamido-2,4(1*H*,3*H*)-pyrimidinedione	> 330	591,1106,1276,1293
6-Amino-5-formamido-2,4(1*H*,3*H*)-pyrimidinedithione	crude	1294
6-Amino-5-formamido-4(3*H*)-pyrimidinethione	255	1295
2-Amino-5-formamido-4(3*H*)-pyrimidinone	> 300, ir, uv	243
4-Amino-5-formamido-2(1*H*)-pyrimidinone	anal	1291,1296
6-Amino-5-formamido-4(3*H*)-pyrimidinone	287–288	1283,1297
6-Amino-5-formamido-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	1298
2-Amino-5-β-formylethyl-6-methyl-4(3*H*)-pyrimidinone	acetal: 179–180	669,881
5-Amino-6-β-formylhydrazino-4(3*H*)-pyrimidinone	225	804
4-Amino-1-formylmethyl-2(1*H*)-pyrimidinone	HCl: anal, sp	1299
4-Amino-1-β-formylvinyl-2(1*H*)-pyrimidinone	255–257, nmr	5980
2-Amino-5-β-hydrazinocarbonylethyl-6-methyl-4(3*H*)-pyrimidinone	> 270	1300

3-Amino-2-hydrazino-5,6-dimethyl-4(3*H*)-pyrimidinone	137–140	32
2-Amino-6-hydrazino-3-methyl-5-nitro-4(3*H*)-pyrimidinone	189	999
3-Amino-2-hydrazino-6-methyl-5-propyl-4(3*H*)-pyrimidinone	166–168	32
4-Amino-2-hydrazino-*N*-methyl-5-pyrmidinecarboxamide	234–237, ms, nmr	447
5-Amino-6-hydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 170	3753
3-Amino-2-hydrazino-6-methyl-4(3*H*)-pyrimidinone	207–210	32
2-Amino-6-hydrazino-5-nitro-4(3*H*)-pyrimidinone	> 264	1301
3-Amino-2-hydrazino-6-propyl-4(3*H*)-pyrimidinone	155–157	32
4-Amino-2-hydrazino-5-pyrimidinecarbohydrazide	236–238 or 247–248, nmr	447,1302
4-Amino-2-hydrazino-5-pyrimidinecarbonitrile	234–236	1303
4-Amino-2-hydrazino-5-pyrimidinecarboxamide	280–282	1304
5-Amino-6-hydrazino-4(3*H*)-pyrimidinethione	222–224	1038,1305
2-Amino-6-hydrazino-4(3*H*)-pyrimidinone	297 or > 300	1306,1307
3-Amino-6-hydrazino-4(3*H*)-pyrimidinone	193–195, ms	167
5-Amino-6-hydrazino-4(3*H*)-pyrimidinone	245–248	607
6-Amino-2-hydrazino-4(3*H*)-pyrimidinone	253 to 264 (310?)	1257,1303,1308,1309
6-Amino-2-hydroxyamino-5-nitroso-4(3*H*)-pyrimidinone	262	1310
6-Amino-1-β-hydroxyethyl-3-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	—	1204
6-Amino-3-β-hydroxyethyl-1-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	—	1204
6-Amino-1-β-hydroxyethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	216–217 or 219–221	1062,1205
6-Amino-3-β-hydroxyethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	213–215 or 270–272	1205,1311
2-Amino-1-β-hydroxyethyl-6-methyl-4(1*H*)-pyrimidinone	194–195	1312
2-Amino-3-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	182	1312
2-Amino-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	265–270	986,1313
6-Amino-5-β-hydroxyethyl-2-methyl-4(3*H*)-pyrimidinone	265–268	1314
6-Amino-1-β-hydroxyethyl-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	240	1068
6-Amino-1-β-hydroxyethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	> 250	1315–1317
2-Amino-1-β-hydroxyethyl-4-oxo-1,4-dihydro-5-pyrimidinecarbonitrile	248	1318

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Amino-5-β-hydroxyethyl-6-propyl-4(3*H*)-pyrimidinone	245–246	1206
4-Amino-2-β-hydroxyethyl-5-pyrimidinecarbaldehyde	162–163	974
4-Amino-2-α-hydroxyethyl-5-pyrimidinecarbonitrile	197	975
4-Amino-2-β-hydroxyethyl-5-pyrimidinecarbonitrile	189–190	1003
4-Amino-2-β-hydroxyethyl-5-pyrimidinecarboxylic acid	270–272	974
2-Amino-5-β-hydroxyethyl-4,6(1*H*,5*H*)-pyrimidinedione	280–281	1319
6-Amino-1-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	253 to 262	1062,1316,1317,1320
6-Amino-5-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	308–310	1321
2-Amino-5-β-hydroxyethyl-4(1*H*)-pyrimidinone	211–212	1322
2-Amino-5-β-hydroxyethyl-4(3*H*)-pyrimidinone	260–262 or 268–270	1005,1321
4-Amino-1-β-hydroxyethyl-2(1*H*)-pyrimidinone	228–229	1323
4-Amino-5-β-hydroxyethyl-2(1*H*)-pyrimidinone	275	1321
6-Amino-5-β-hydroxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	299–300	1321
2-Amino-5-hydroxy-6-hydroxymethyl-4(3*H*)-pyrimidinone	H_2SO_4: anal, uv	1324
6-Amino-1-hydroxy-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidine-carbaldehyde	250	1325
4-Amino-2-hydroxymethyl-5-pyrimidinecarbonitrile	222	975
6-Amino-1-hydroxy-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	252–258	1018
6-Amino-5-hydroxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	anal, uv	579
4-Amino-5-hydroxymethyl-2(1*H*)-pyrimidinethione	229–232	1326
2-Amino-5-hydroxy-6-methyl-4(3*H*)-pyrimidinone	> 310	578,1327,1328
4-Amino-5-hydroxymethyl-2(1*H*)-pyrimidinone	295	1249,1329–1331,1333,1334
4-Amino-5-hydroxy-6-methyl-2(1*H*)-pyrimidinone	> 300	1011
4-Amino-6-hydroxymethyl-2(1*H*)-pyrimidinone	> 210	770
6-Amino-2-hydroxymethyl-4(3*H*)-pyrimidinone	265	1335

6-Amino-5-hydroxy-2-methyl-4(3*H*)-pyrimidinone	> 203	1011
6-Amino-1-hydroxy-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	224	1278
2-Amino-5-hydroxy-6-nitroso-4(3*H*)-pyrimidinone	> 300	581
2-Amino-3-β-hydroxypropyl-6-methyl-4(3*H*)-pyrimidinone	198–199	1336
6-Amino-5-β-hydroxypropyl-2,4(1*H*,3*H*)-pyrimidinedione	252–253	1321
4-Amino-1-γ-hydroxypropyl-2(1*H*)-pyrimidinone	HCl: 165–167	940
6-Amino-5-β-hydroxypropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	262	1321
2-Amino-5-hydroxy-4,6(1*H*,5*H*)-pyrimidinedione	> 320	1324,1337
6-Amino-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	315	1278,1338
6-Amino-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	> 300	580,1011,1324,1339
2-Amino-5-hydroxy-4(3*H*)-pyrimidinone	> 340	578,1324,1327,1340–1343
4-Amino-5-hydroxy-2(1*H*)-pyrimidinone	> 300	1011,1188,1344,1345
6-Amino-5-hydroxy-4(3*H*)-pyrimidinone	> 290	581
4-Amino-6-imino-1,3-dimethyl-1,6-dihydro-2(3*H*)-pyrimidinone	HCl: 310	1162
2-Amino-4-imino-3-methyl-3,4-dihydro-5-pyrimidinecarbaldehyde	202–203; pic: 195	1346
2-Amino-5-iodo-3,6-dimethyl-4(3*H*)-pyrimidinone	223–224	1347
2-Amino-5-iodo-6-methyl-4(3*H*)-pyrimidinone	225–226	1347
2-Amino-5-iodo-4,6(1*H*,5*H*)-pyrimidinedione	anal	1033
2-Amino-5-iodo-4(3*H*)-pyrimidinone	anal	1348
2-Amino-6-iodo-4(3*H*)-pyrimidinone	241 or 243–244	965,1349
4-Amino-5-iodo-2(1*H*)-pyrimidinone	225–245 or 248	1234,1350–1352
4-Amino-2-isopropoxy-5-pyrimidinecarbonitrile	160–162, ir, nmr	400
5-Amino-6-isopropylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	121–122	1069
2-Amino-6-isopropylamino-3-methyl-5-nitro-4(3*H*)-pyrimidinone	H_2O: 189–194	1279
5-Amino-6-isopropylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	HCl: > 280	1353
2-Amino-6-isopropylamino-5-nitro-4(3*H*)-pyrimidinone	300	1279
2-Amino-6-isopropylamino-5-nitroso-4(3*H*)-pyrimidinone	> 360	299
5-Amino-6-isopropylamino-2,4(1*H*,3*H*)-pyrimidinedione	HCl: > 300	1353

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Amino-5-isopropyl-1,3-dimethyl-2,4(2*H*,3*H*)-pyrimidinedione	174–176	653
5-Amino-1-isopropyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidine-carbonitrile	129–132, ir, ms, nmr	3731
6-Amino-5-isopropyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	248–250	653
4-Amino-3-isopropyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	252	864
2-Amino-5-isopropyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	241–242	1224
4-Amino-2-isopropyl-5-pyrimidinecarbonitrile	150–151	1354
4-Amino-6-isopropyl-5-pyrimidinecarbonitrile	—	1208
2-Amino-4-isopropyl-5-pyrimidinecarboxylic acid	285–287, ir, nmr, uv	3996
2-Amino-6-isopropyl-4(3*H*)-pyrimidinone	246–248	1356
4-Amino-1-isopropyl-2(1*H*)-pyrimidinone	201–203	870
6-Amino-2-isopropylthio-5-nitroso-4(3*H*)-pyrimidinone	219–221	924
6-Amino-2-isopropylthio-4(3*H*)-pyrimidinone	218–219 or 300	1357,1358
4-Amino-3-isopropyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile	178	809
6-Amino-5-isothiouronio-2,4(1*H*,3*H*)-pyrimidinedione	chloride: > 340	837
2-Amino-5-β-mercaptoethyl-6-methyl-4(3*H*)-pyrimidinone	288–292	1359
2-Amino-5-β-mercaptoethyl-4(3*H*)-pyrimidinone	272–273	1359
2-Amino-5-γ-mercaptopropyl-6-methyl-4(3*H*)-pyrimidinone	256–258	1359
6-Amino-5-γ-mercaptopropyl-2,4(1*H*,3*H*)-pyrimidinedione	320–325	1359
6-Amino-5-γ-mercaptopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	1359
6-Amino-5-mercapto-2,4(1*H*,3*H*)-pyrimidinedione	> 320	837
2-Amino-6-methoxycarbonylmethyl-4(3*H*)-pyrimidinone	87–89(?), 192–193, 194–197, ir, ms, nmr	670,950,3889
6-Amino-2-methoxy-3,5-dimethyl-4(3*H*)-pyrimidinone	208–210	653
2-Amino-5-β-methoxyethyl-6-methyl-4(3*H*)-pyrimidinone	230–232	1149

4-Amino-3-β-methoxyethyl-6-methyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile	233	809
4-Amino-3-β-methoxyethyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	228	864
4-Amino-3-β-methoxyethyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile	198	809
2-Amino-5-methoxy-6-methoxymethyl-4(3*H*)-pyrimidinone	196	1149
6-Amino-5-methoxy-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	206–207	1360
2-Amino-6-methoxy-3-methyl-5-nitro-4(3*H*)-pyrimidinone	215–218	999
6-Amino-2-methoxy-3-methyl-5-nitroso-4(3*H*)-pyrimidinone	145	1060,1287
2-Amino-4-methoxy-6-methyl-5-pyrimidinecarbonitrile	254–255	1009
2-Amino-4-methoxymethyl-5-pyrimidinecarboxylic acid	267, ir, nmr, uv	3996
5-Amino-6-methoxy-2-methyl-4(3*H*)-pyrimidinethione	crude: 192–193	676
2-Amino-5-methoxy-6-methyl-4(3*H*)-pyrimidinone	223–224	1361,1362
2-Amino-6-methoxymethyl-4(3*H*)-pyrimidinone	266–267	1149
4-Amino-6-methoxy-1-methyl-2(1*H*)-pyrimidinone	273–283	1015
6-Amino-2-methoxy-3-methyl-4(3*H*)-pyrimidinone	216 or 233–235	1060,1287,1288,1363
6-Amino-2-methoxy-5-methyl-4(3*H*)-pyrimidinone	237–238 or 243	653,972,973
6-Amino-5-methoxy-2-methylthio-4(3*H*)-pyrimidinone	203	1360
2-Amino-6-methoxy-5-nitro-4(3*H*)-pyrimidinone	> 274	1364
6-Amino-1-methoxy-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	194	1280
6-Amino-2-methoxy-5-nitroso-4(3*H*)-pyrimidinone	anal	1060,1288
2-Amino-4-methoxy-5-pyrimidinecarbonitrile	207–208	1009
4-Amino-2-methoxy-5-pyrimidinecarbonitrile	218 to 222, ir, nmr	351,400,478,847,938,1009
4-Amino-2-methoxy-5-pyrimidinecarboxamide	228–231, nmr	386
4-Amino-2-methoxy-5-pyrimidinecarboxamidrazone	192–195, nmr	351
2-Amino-5-methoxy-4,6(1*H*,5*H*)-pyrimidinedione	> 350	1007,1185
6-Amino-1-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	248–249	1280
5-Amino-6-methoxy-4-pyrimidinesulfonic acid	212–214	1365
2-Amino-6-methoxy-4(3*H*)-pyrimidinethione	263	1366

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Amino-6-methoxy-2(1*H*)-pyrimidinethione	219	903
5-Amino-6-methoxy-4(3*H*)-pyrimidinethione	214–215	1038
2-Amino-5-methoxy-4(3*H*)-pyrimidinone	266–267; H_2SO_4: 262–264	1007,1093,1367,1368
3-Amino-6-methoxy-4(3*H*)-pyrimidinone	140–141, ir, ms, nmr	5898
4-Amino-6-methoxy-2(1*H*)-pyrimidinone	220 or 227–233	903,1369
6-Amino-2-methoxy-4(3*H*)-pyrimidinone	221 or 228–229	972,973,1287
6-Amino-5-methoxy-4(3*H*)-pyrimidinone	219–220 or 230–231	1360,1370
6-Amino-5-methoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	275–280	1360
5-Amino-6-methylamino-2-methylthio-4(3*H*)-pyrimidinone	273, uv	3872
2-Amino-6-methylamino-5-nitro-4(3*H*)-pyrimidinone	360 or > 360	999,1371,1372
6-Amino-2-methylamino-5-nitro-4(3*H*)-pyrimidinone	348–350 or 350–352	1082,1373
2-Amino-6-methylamino-5-nitroso-4(3*H*)-pyrimidinone	> 300 or > 360	299,1374
4-Amino-6-methylamino-5-nitroso-2(1*H*)-pyrimidinone	> 360	1015
6-Amino-2-methylamino-5-nitroso-4(3*H*)-pyrimidinone	> 320	1084
2-Amino-4-methylamino-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	350	299
4-Amino-2-methylamino-5-pyrimidinecarbonitrile	225	847,939
4-Amino-2-methylamino-5-pyrimidinecarboxamide	268–270	847
2-Amino-5-methylamino-4.6(1*H*,5*H*)-pyrimidinedione	HCl: anal	1375
5-Amino-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	250–260 or > 280; HCl: > 350	675,1376,1377
6-Amino-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	HCl: 268–272	1378
5-Amino-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedithione	> 300	1379
2-Amino-6-methylamino-4(3*H*)-pyrimidinethione	295	850
5-Amino-4-methylamino-2(1*H*)-pyrimidinethione	255	1379,1380

5-Amino-6-methylamino-4(3*H*)-pyrimidinethione	265–270	1379,1381,1382
2-Amino-6-methylamino-4(3*H*)-pyrimidinone	255 to 266	299,1093,1281,1374
4-Amino-6-methylamino-2(1*H*)-pyrimidinone	> 360	1015
5-Amino-4-methylamino-2(1*H*)-pyrimidinone	217 or 220	1383–1385
5-Amino-6-methylamino-4(3*H*)-pyrimidinone	210–215	1383,1386
6-Amino-2-methylamino-4(3*H*)-pyrimidinone	227–230 or 232–234 ir, ms, nmr	517,1083,1084,1093
5-Amino-6-methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	234–235	3872
4-Aminomethyl-2,6-bismethylthiopyrimidine	83–84, nmr	311
6-Aminomethyl-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione	HCl: anal	701
5-Aminomethyl-2-carbamoylmethyl-4-pyrimidinamine	pic: 197	975
5-Aminomethyl-4-chloro-2-ethylthiopyrimidine	112	1249
5-Aminomethyl-4,6-dimethoxy-2-methylpyrimidine	54	1387
4-Aminomethyl-2,6-dimethoxypyrimidine	49–53, nmr	311
5-Aminomethyl-4-dimethylamino-2-methylpyrimidine	132/3; HCl: 260	1387,1388
5-Aminomethyl-2,6-dimethyl-4-pyrimidinamine	194; HCl: 292 or 198; pic: 218	1119–1121
2-Aminomethyl-4,6-dimethylpyrimidine	168	1389
4-Amino-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	> 330	548
1-Amino-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	128	1166
1-Amino-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	244–245	1199
5-Amino-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	250–300	1100
5-Aminomethylene-1,3-diethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	250–251	1390
5-Aminomethylene-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	228 to 233	1207,1391,1392
5-Aminomethylene-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	> 320	1393
5-Aminomethyl-4-ethylamino-2-methylpyrimidine	135/3	1388
5-Aminomethyl-2-ethyl-4-pyrimidinamine	HCl: 229 or 248–250; pic: 228–229	975,1118,1388,1394
5-Aminomethyl-2-ethylthio-4-pyrimidinamine	148	1249

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Aminomethyl-2-ethylthio-4(3*H*)-pyrimidinone	221–222	1395
6-Amino-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	310 or 314–326	1378,1396
2-Amino-6-α-methylhydrazino-4(3*H*)-pyrimidinethione	244–247	1203
2-Amino-6-α-methylhydrazino-4(3*H*)-pyrimidinone	274–280	1203
5-Aminomethyl-2-α-hydroxyethyl-4-pyrimidinamine	HCl: 255	975
5-Aminomethyl-2-β-hydroxyethyl-4-pyrimidinamine	270; pic: 216–217	1003
5-Aminomethyl-2-hydroxymethyl-4-pyrimidinamine	HCl: 246; pic: 207	975
5-Aminomethyl-2-isopropyl-4-pyrimidinamine	HCl: 257–260	1354
5-Aminomethyl-4-methoxy-2-methylpyrimidine	46; HCl: 150–151; pic: 188	750,1387
6-Amino-2-methyl-5-methylaminomethyl-4(3*H*)-pyrimidinone	HCl: 278 or 281	1074,1075
2-Amino-3-methyl-6-methylamino-5-nitro-4(3*H*)-pyrimidinone	269–270 or 270–272	999,1371
5-Amino-1-methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	HCl: 238	1397
5-Amino-3-methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	HCl: > 350	1398
6-Amino-1-methyl-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	183–185 or 210	957,1399
5-Amino-2-methyl-6-methylamino-4(3*H*)-pyrimidinone	272	1400
5-Amino-4-methyl-6-methylamino-2(1*H*)-pyrimidinethione	243–244 or 280–285	1400,1401
4-Amino-1-methyl-6-methylamino-2(1*H*)-pyrimidinone	273–275	1015
5-Amino-1-methyl-4-methylamino-2(1*H*)-pyrimidinone	180; pic: 210	1383,1402
5-Amino-2-methyl-6-methylamino-4(3*H*)-pyrimidinone	221	1403
5-Amino-4-methyl-6-methylamino-2(1*H*)-pyrimidinone	295	1404,1405
5-Amino-6-methyl-2-methylamino-4(3*H*)-pyrimidinone	208–210	1081
6-Amino-1-methyl-2-methylamino-4(1*H*)-pyrimidinone	281–282, ir, ms, nmr	517
5-Aminomethyl-2-methyl-4,6-bismethylaminopyrimidine	HCl: 250	1387
6-Amino-1-methyl-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	338–340	1104
6-Amino-3-methyl-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	335–341	1396

4-Amino-3-methyl-2-methylimino-2,3-dihydro-5-pyrimidinecarbaldehyde	205; HI: 241	1346
5-Aminomethyl-2-methyl-4-methylaminopyrimidine	130/3; HCl: 273	975,1388,1406
4-Aminomethyl-6-methyl-2-pyrimidinamine	HCl: 265	1407
5-Aminomethyl-2-methyl-4-pyrimidinamine	132; HCl: 248 to 268	409,417,678,1388,1408–1412
5-Aminomethyl-6-methyl-4-pyrimidineamine	140–141; HCl: 277; pic: 238	750
5-Aminomethyl-2-methylpyrimidine	77–78 or 81	1387,1413,1414
5-Aminomethyl-2-methyl-4,6-pyrimidinediamine	201–202	1387
5-Aminomethyl-6-methyl-2,4-pyrimidinediamine	HCl: 255	938
5-Aminomethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 335	1415
2-Aminomethyl-6-methyl-4(3*H*)-pyrimidinone	HBr: 265–266; HCl: 273–274	1416,1417
5-Aminomethyl-2-methyl-4(3*H*)-pyrimidinone	HCl: 280 or 283 (167?); pic: 157–158	678,680,975,1418–1421
6-Amino-3-methyl-2-methylthio-5-nitro-4(3*H*)-pyrimidinone	208	1076
6-Amino-1-methyl-2-methylthio-5-nitroso-4(1*H*)-pyrimidinone	225 or > 300	924,1116
6-Amino-3-methyl-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone	234 or 235	1116,1422
2-Amino-4-methyl-2-methylthio-5-pyrimidinecarbaldehyde	—	1423
2-Amino-4-methyl-6-methylthio-5-pyrimidinecarbonitrile	241–243	1424
4-Amino-6-methyl-2-methylthio-5-pyrimidinecarbonitrile	237 or 238–240	847,1078
4-Amino-*N*-methyl-2-methylthio-5-pyrimidinecarboxamide	185–190, ms, nmr	447
6-Amino-1-methyl-2-methylthio-4(1*H*)-pyrimidinone	272 or 286	968,1425
6-Amino-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	255 or 257	659,1426
2-Amino-6-methyl-5-nitro-4-pyrimidinecarbaldehyde	*p*-$ClC_6H_4NHN{=}$: 246	1157
2-Amino-1-methyl-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	300–302	1364
6-Amino-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	354	1286
4-Amino-6-methyl-5-nitro-2(1*H*)-pyrimidinethione	220–221, 240–250, or 250	442,1427,1428
2-Amino-6-methyl-5-nitro-4(3*H*)-pyrimidinone	> 300; H_2O: > 300	949,1429–1431
4-Amino-1-methyl-5-nitro-2(1*H*)-pyrimidinone	271–273 or 274	1289,1385,1432,1433
4-Amino-3-methyl-5-nitro-2(1*H*)-pyrimidinone	> 235	1221

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Amino-6-methyl-5-nitro-2(1*H*)-pyrimidinone	280–285	1290,1434
6-Amino-2-methyl-5-nitro-4(3*H*)-pyrimidinone	250–260 or > 333	1082,1435,1436
6-Amino-3-methyl-5-nitro-4(3*H*)-pyrimidinone	284	968,1437
6-Amino-1-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	> 340	1048,1106,1113,1213,1286 1438,1439
6-Amino-3-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	> 350	1288,1440
6-Amino-2-methyl-5-nitroso-4(3H)-pyrimidinone	anal	1441,1442
6-Amino-1-methyl-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	217–220 or 225 (> 300?)	1113,1116,1284,1443,1444
6-Amino-3-methyl-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	221–223	1445
2-Amino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	269–270 or 340	682,1233,1446
2-Amino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	~265 or > 300	1175,1223,1447
4-Amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarbonitrile	> 270	864
2-Amino-1-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	290–292	982
2-Amino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylic acid	245–246 or 263–265	682,1175
2-Amino-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	300–301 or 311–313	1224,1448
4-Amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylic acid	240 or 251	864,1383
6-Amino-5-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	258–260	1183
2-Amino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinesulfonic acid	> 300; Na: 278–280	1449
4-Amino-2-methyl-6-oxo-1,6-dihydro-5-pyrimidinesulfonic acid	305–306	1101
4-Amino-6-methyl-2-oxo-1,2-dihydro-5-pyrimidinesulfonic acid	290–291	1450
5-Aminomethyl-2-propyl-4-pyrimidinamine	HCl: 243 or 257–260	1354,1394,1451
6-Amino-1-methyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	278–282	653
2-Amino-6-methyl-5-propyl-4(3*H*)-pyrimidinone	268–270 or 271–274 (293–294?)	1151,1152,1452
4-Amino-6-methyl-5-propyl-2(1*H*)-pyrimidinone	218–219 or 317–318	1453–1455

6-Amino-5-methyl-2-propyl-2(3*H*)-pyrimidinone	209–210	1456
5-Aminomethyl-4-pyrimidinamine	134; HCl: 270 to 298	939,1414,1451,1457
4-Aminomethylpyrimidine	pic: 156–157	826
4-Amino-2-methyl-5-pyrimidinecarbaldehyde	195–196 or 197–198	1008,1409,1458–1463
4-Amino-2-methyl-5-pyrimidinecarbohydrazide	220–221	1464
2-Amino-4-methyl-5-pyrimidinecarbonitrile	269–270	960,1465
2-Amino-6-methyl-4-pyrimidinecarbonitrile	199–200	1029,1216
4-Amino-2-methyl-5-pyrimidinecarbonitrile	249 to 258	975,1010,1250,1251,1408,1412, 1459,1466–1470
4-Amino-6-methyl-5-pyrimidinecarbonitrile	217–219	847
4-Amino-2-methyl-5-pyrimidinecarbonyl azide	140	1471
2-Amino-4-methyl-5-pyrimidinecarboxamide	287	1465
2-Amino-6-methyl-4-pyrimidinecarboxamide	ir	1216
4-Amino-2-methyl-5-pyrimidinecarboxamide	260 or 264–265	1471–1473
2-Aminomethyl-5-pyrimidinecarboxylic acid	291–293	1474
2-Amino-4-methyl-5-pyrimidinecarboxylic acid	256–316	1475,1476,3996
2-Amino-6-methyl-4-pyrimidinecarboxylic acid	300–302	1476
4-Amino-2-methyl-5-pyrimidinecarboxylic acid	270–280	678,974,1458,1470,1473,1477, 1478
4-Amino-6-methyl-2-pyrimidinecarboxylic acid	245–246	671
5-Aminomethyl-2-pyrimidinecarboxylic acid	280–281	1474
5-Amino-2-methyl-4-pyrimidinecarboxylic acid	191–192	1479
5-Aminomethyl-2,4-pyrimidinediamine	HCl: 278–280, uv	975,1408,1480,1481
3-Amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedithione	174–177	1482
1-Amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	158–159	1483
1-Amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	242–244	1124
2-Amino-1-methyl-4,6(1*H*,5*H*)-pyrimidinedione	> 360	1484
2-Amino-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione	> 300	1485
3-Amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	164–165	1486

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
3-Amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	269–272 or 275–279	1169,1482,1487,1488
5-Aminomethyl-2,4(1*H*,3*H*)-pyrimidinedione	265; HCl: 250–254; H_2SO_4: 245–246; pic: 222–223	1395,1489–1491
5-Amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	242–244 or 248–250, ir, nmr, uv	1129,1492,3904
5-Amino-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	270; HCl: 273–274	369
5-Amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	200–202 or 202–204, ir, nmr, uv	1129,3904
5-Amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	270 or 272–274	692,1493–1497
6-Aminomethyl-2,4(1*H*,3*H*)-pyrimidinedione	295–297, ~ 296–298; HCl: 328, ir, nmr	311,701,1498
6-Amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	305	1062,1106,1213,1284,1499, 1500–1503
6-Amino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	327 or 330	532,1288,1445,1504
6-Amino-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	310–312 or 353–355	1505
5-Amino-2-methyl-4,6(1*H*,5*H*)-pyrimidinedithione	crude: > 360	676
5-Amino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedithione	> 300	1157,1191
4-Amino-5-methyl-2(1*H*)-pyrimidineselone	227–229	1506
2-Amino-4-methyl-5-pyrimidinesulfonic acid	230	1449
2-Amino-3-methyl-4(3*H*)-pyrimidinethione	232 or 233–234	1507,1508
2-Amino-6-methyl-4(3*H*)-pyrimidinethione	321	958,1509,1510
4-Amino-1-methyl-2(1*H*)-pyrimidinethione	268 to 271	1508,1511–1513
4-Amino-5-methyl-2(1*H*)-pyrimidinethione	273–274	1514,1515
4-Amino-6-methyl-2(1*H*)-pyrimidinethione	> 280	1509,1515–1517
5-Amino-6-methyl-4(3*H*)-pyrimidinethione	305–306	1038
6-Amino-2-methyl-4(3*H*)-pyrimidinethione	298	593
1-Amino-5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	153–155	1518

5-Amino-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	253–256	773,818,1137,1138,1519
2-Amino-4-methyl-5-pyrimidinol	202–204	7
4-Amino-2-methyl-5-pyrimidinol	HCl: 270–273	1011,1012
2-Amino-1-methyl-4(1*H*)-pyrimidinone	275 to 285	962,982,1520,1521
2-Amino-3-methyl-4(3*H*)-pyrimidinone	257 to 266	982,1508,1520,1521
2-Amino-5-methyl-4(3*H*)-pyrimidinone	274 to 283	614,962,1152,1522
2-Amino-6-methyl-4(3*H*)-pyrimidinone	270 to 298, nmr	158,959,1145,1147,1233,1509, 1523–1530,4141
3-Amino-6-methyl-4(3*H*)-pyrimidinone	111 or 115–117, ir, ms, nmr	167,5898
4-Amino-1-methyl-2(1*H*)-pyrimidinone	296–303; HCl: 285–300	871,1261,1512,1520,1531–1541
4-Amino-3-methyl-2(3*H*)-pyrimidinone	HCl: 242–245; HI: 274–277; pic: 231–246	806,809,1534,1542
4-Amino-5-methyl-2(1*H*)-pyrimidinone	270 or 287–292; HCl: 290; pic: 290–291	811,967,1018,1514,1543–1546
4-Amino-6-methyl-2(1*H*)-pyrimidinone	361–363	1122,1547–1550
5-Amino-2-methyl-4(3*H*)-pyrimidinone	237; HCl: 258	1551
5-Amino-6-methyl-4(3*H*)-pyrimidinone	218–219 or 221–222	1038,1401,1552
6-Amino-2-methyl-4(3*H*)-pyrimidinone	293 to 301	650,987,1159,1160,1441, 1553–1556
6-Amino-3-methyl-4(3*H*)-pyrimidinone	184–185	659,1179
6-Amino-5-methyl-4(3*H*)-pyrimidinone	243	659
4-Amino-5-methyl-2(1*H*)-pyrimidinone 3-oxide	262–266	1018
4-Amino-2-methylsulfonyl-5-pyrimidinecarbonitrile	211–214	577
4-Amino-2-methylsulfonyl-5-pyrimidinecarboxamide	216–218	577
4-Amino-6-methyl-5-sulfooxy-2(1*H*)-pyrimidinone	265–267	1011
6-Amino-2-methyl-5-sulfooxy-4(3*H*)-pyrimidinone	265–267	1011
6-Amino-2-methyl-5-thioformamido-4(3*H*)-pyrimidinone	> 260	1557,1558
6-Amino-2-methylthio-5-nitro-4(3*H*)-pyrimidinone	299	1091
2-Amino-6-methylthio-5-nitroso-4(3*H*)-pyrimidinone	> 225	299

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Amino-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone	245 to 255	924,970,1116,1559
5-Amino-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide	278–279 or 280	1560,1561
5-Amino-2-methythio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	247–249; NH_4: 237–239	1561
6-Amino-2-methythio-5-propyl-4(3*H*)-pyrimidinone	193–194	1220
4-Amino-2-methylthio-5-pyrimidinecarbaldehyde	183–184; oxime: 201–202	1326
2-Amino-4-methylthio-5-pyrimidinecarbonitrile	263–264	1223
4-Amino-2-methythio-5-pyrimidinecarbonitrile	232–235 or 235–237	865,1088
4-Amino-2-methylthio-5-pyrimidinecarboxamide	262–263 or 280–281	577,998,1562
6-Amino-2-methylthio-4-pyrimidinecarboxamide	294	1030
4-Amino-2-methylthio-5-pyrimidinecarboxamide oxime	227–229, nmr	386
2-Amino-6-methylthio-4-pyrimidinecarboxylic acid	255	1030
4-Amino-2-methylthio-5-pyrimidinecarboxylic acid	251–252	1331,1563
5-Amino-2-methythio-4-pyrimidinecarboxylic acid	190–191	1564
5-Amino-2-methythio-4,6(1*H*,5*H*)-pyrimidinedione	> 301	1046,3988
5-Amino-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	252–253	1163
5-Amino-6-methylthio-4(3*H*)-pyrimidinethione	241–243	1565
2-Amino-5-methylthio-4(3*H*)-pyrimidinone	248–252	1566,1567
2-Amino-6-methylthio-4(3*H*)-pyrimidinone	271–273 or 274–276	299,958
4-Amino-6-methylthio-2(1*H*)-pyrimidinone	294	958,1568
6-Amino-2-methylthio-4(3*H*)-pyrimidinone	261 to 278	724,925,1015,1358,1569,1570
2-Amino-4-methylthio-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile	273–275, ir, nmr; Na: > 350, ir, nmr; urea complex: ir, xl st	3747,3752,3879
2-Amino-4-methyl-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile	> 260	1223
4-Amino-3-methyl-2-thioxo-2,3-dihydro-5-pyrimidinecarbonitrile	255	1571
4-Amino-*N*-methyl-2-thioxo-1,2-dihydro-5-pyrimidinecarboxamide	276–277, nmr	6454

4-Amino-3-methyl-2-thioxo-2,3-dihydro-5-pyrimidinecarboxylic acid	306	1508
6-Amino-5-methyl-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid	241–243	1183
5-Amino-1-methyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	266	1572
5-Amino-3-methyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione	> 300	1047
1-Amino-4-methyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	176–178	1482
3-Amino-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	236–237 or 247–248	1482,1573
5-Amino-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	320–322	1038,1574
6-Amino-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	271–272	873,1284,1575
6-Amino-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	308 or > 315	532,1445
6-Amino-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	1576
6-Amino-3-methyl-1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione	—	897
4-Amino-5-methyl-1-vinyl-2(1*H*)-pyrimidinone	220–221	1577
6-Amino-2-nitroamino-4(3*H*)-pyrimidinone	270	1309
2-Amino-5-nitro-6-propylamino-4(3*H*)-pyrimidinone	325	608
2-Amino-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	> 400, ir, nmr	27,1578–1580
6-Amino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	> 420	1082,1581
2-Amino-5-nitro-4(3*H*)-pyrimidinethione	—	1582
6-Amino-5-nitro-4(3*H*)-pyrimidinethione	223	1583
2-Amino-5-nitro-4(3*H*)-pyrimidinone	280 or 300; guanidinium salt: 248	239,1342,1584
4-Amino-5-nitro-2(1*H*)-pyrimidinone	360 or > 360	967,970,1584–1587
6-Amino-5-nitro-4(3*H*)-pyrimidinone	> 300	1588,1589
4-Amino-5-nitro-2(1*H*)-pyrimidinone 3-oxide	220	1587
6-Amino-5-nitroso-2-propylthio-4(3*H*)-pyrimidinone	221	924
2-Amino-5-nitroso-4,6(1*H*,5*H*)-pyrimidinedione	Na_2: > 300	299,1578,1590,1591
6-Amino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	> 300	1048,1106,1293,1440,1442, 1592–1594
6-Amino-5-nitroso-4(3*H*)-pyrimidinone	anal	1588
6-Amino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	1113,1298,1442,1588,1595

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Amino-5-nitro-6-thioxo-1,6-dihydro-4(3*H*)-pyrimidinone	crude	1596
6-Amino-5-nitro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	1588
2-Amino-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	oxime: sp	949
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinecarbaldehyde	tsc: anal	1597,1598
6-Amino-2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde	255	1599
2-Amino-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	> 300	1600,1601
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile	270 or 340; H_2O: 225, ir, nmr	400,938,1250,1251,1602,1603
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinecarbonyl azide	165	1604
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinecarboxamide	> 320	1250,1253,1254,6035
2-Amino-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide	320	1605
2-Amino-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	> 300 or 320	949,982,1606
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinecarboxylic acid	256 to 263	1250,1253,1254,1331,1607
4-Amino-6-oxo-1,6-dihydro-2-pyrimidinecarboxylic acid	> 350	1405
6-Amino-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	292–294	1030
2-Amino-4-oxo-3,4-dihydro-5-pyrimidinesulfonic acid	Na: 288–290	1449
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinesulfonic acid	—	1450
4-Amino-6-oxo-1,6-dihydro-2-pyrimidinesulfonic acid	K: > 300	3872
5-Amino-6-oxo-1,6-dihydro-4-pyrimidinesulfonic acid	250–251	1365
6-Amino-2-oxo-1,2-dihydro-4-pyrimidinesulfonic acid	> 360	1015
4-Amino-2-oxo-1,2-dihydro-5-pyrimidinesulfonyl fluoride	H_2O: 209–210	1608
4-Amino-2-oxo-3-propyl-2,3-dihydro-5-pyrimidinecarbonitrile	225	864
4-Amino-2-oxo-3-propyl-2,3-dihydro-5-pyrimidinecarboxamide	265	864
2-Amino-6-oxo-5-propyl-1,6-dihydro-4-pyrimidinecarboxylic acid	278–279	1224
6-Amino-2-oxo-5-propyl-1,2-dihydro-4-pyrimidinecarboxylic acid	219–221	1183
2-Amino-5-oxo-4,6(1*H*,5*H*)-pyrimidinedione	—	1609

1-β-Amino-oxyethyl-4-imino-3-methyl-3,4-dihydro-2(1*H*)-pyrimidinone	HCl: 214	941
1-β-Amino-oxyethyl-4-methylamino-2(1*H*)-pyrimidinone	200	941
1-β-Amino-oxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	HCl: 183–184	940
1-γ-Amino-oxypropyl-2,4(1*H*,3*H*)-pyrimidinedione	HCl: 190–192	940
6-Amino-5-propionamido-2,4(1*H*,3*H*)-pyrimidinedione	anal	589
2-Amino-5-propoxy-4,6(1*H*,5*H*)-pyrimidinedione	> 300	1610
2-Amino-5-propoxy-4(3*H*)-pyrimidinone	236–238	1007
4-Amino-2-propylamino-5-pyrimidinecarbonitrile	167–169	847
2-Amino-6-propylamino-4(3*H*)-pyrimidinethione	268	850
2-Amino-6-propylamino-4(3*H*)-pyrimidinone	257	850
1-γ-Aminopropyl-5-bromo-2,4(1*H*,3*H*)-pyrimidinedione	HBr: 254, nmr, uv	3775
4-β-Aminopropyl-2,6-dimethylpyrimidine	130–131	1611
1-γ-Aminopropyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	296–297	1200
1-γ-Aminopropyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	234–236, nmr, uv	237
1-γ-Aminopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	119–120; HCO_2H: 157–160	608,943
4-Amino-2-propyl-5-pyrimidinecarbonitrile	165	939
4-Amino-2-propyl-5-pyrimidinecarboxamide	204–205	1612
2-Amino-4-propyl-5-pyrimidinecarboxylic acid	279–280, ir, nmr, uv	3996
1-γ-Aminopropyl-2,4(1*H*,3*H*)-pyrimidinedione	164–166, nmr	943,3775
6-Amino-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	283	532
6-Amino-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	> 300	1499
2-Amino-*N*-propyl-5-pyrimidinesulfonamide	235–236	869
2-Amino-5-propyl-4(3*H*)-pyrimidinone	238–239	1152
2-Amino-6-propyl-4(3*H*)-pyrimidinone	209	672
4-Amino-1-propyl-2(1*H*)-pyrimidinone	256–259	608,724,870,871,1613
6-Amino-2-propyl-4(3*H*)-pyrimidinone	290 or 293–294	1244,1456
2-Amino-6-propylthio-4(3*H*)-pyrimidinone	228–232	958
6-Amino-2-propylthio-4(3*H*)-pyrimidinone	207 to 213	925,1357,1358

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Amino-5-propyl-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid	233–234	1183
6-Amino-5-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	247–248	1220
2-Amino-5-pyrimidinecarbaldehyde	190–195 or 208–210, ir, ms, nmr; PhNHN=: 242, nmr	6021,6122,6170
4-Amino-5-pyrimidinecarbaldehyde	181 or 192–193; PhNHN=: 182–185	1008,1614
4-Amino-5-pyrimidinecarbohydrazide	197	1615
2-Amino-5-pyrimidinecarbonitrile	250–260 or 300–310	1086,1616–1618
4-Amino-5-pyrimidinecarbonitrile	250 to 258; pic: 189	478,708,713,1117,1251,1414, 1468,1614,1619–1622
5-Amino-2-pyrimidinecarbonitrile	230–231	1623
2-Amino-5-pyrimidinecarbonyl azide	133–135	1624
2-Amino-5-pyrimidinecarboxamide	317	1346
4-Amino-5-pyrimidinecarboxamide	254 to 261	708,713,1615,1621,1625
5-Amino-2-pyrimidinecarboxamide	233–235	1623
6-Amino-4-pyrimidinecarboxamide	$HClO_4$: 216–217; pic: 273	1626
2-Amino-4-pyrimidinecarboxylic acid	275 or 285	686,1627–1630
2-Amino-5-pyrimidinecarboxylic acid	> 300, ir, nmr, uv	1631,1632,3996
4-Amino-5-pyrimidinecarboxylic acid	275 to 284	708,809,1633,1634
5-Amino-2-pyrimidinecarboxylic acid	270–274	1623
5-Amino-4-pyrimidinecarboxylic acid	256–258	1032
6-Amino-4-pyrimidinecarboxylic acid	256–257	1628
2-Amino-4,6-pyrimidinedicarbonitrile	195–196	1029
2-Amino-4,5-pyrimidinedicarboxylic acid	> 300	1635
1-Amino-2,4(1*H*,3*H*)-pyrimidinedione	244–245	1483

2-Amino-4,6(1*H*,5*H*)-pyrimidinedione	> 330	407,1001,1149,1499,1525, 1578,1634
3-Amino-2,4(1*H*,3*H*)-pyrimidinedione	190–200; HBr: 230–235	1486
5-Amino-2,4(1*H*,3*H*)-pyrimidinedione	anal	967,1125,1172,1176,1637–1639
5-Amino-4,6(1*H*,5*H*)-pyrimidinedione	208; HCl: 247–249	625,1037,1641
6-Amino-2,4(1*H*,3*H*)-pyrimidinedione	275 or > 350	709,1106,1111,1293,1499–1502, 1592,1640,1642–1646
2-Amino-4,6(1*H*,5*H*)-pyrimidinedithione	250 or 267	958,1427,1647
5-Amino-2,4(1*H*,3*H*)-pyrimidinedithione	> 270	626,711,1035,1648
5-Amino-4,6(1*H*,5*H*)-pyrimidinedithione	> 330	1036,1037,1641,1649
6-Amino-2,4(1*H*,3*H*)-pyrimidinedithione	309 or > 360	593,958
6-Amino-4-pyrimidinesulfinic acid	> 360	1568
2-Amino-5-pyrimidinesulfonamide	283–285	845,869
2-Amino-5-pyrimidinesulfonic acid	305–307 or 326–328	845,869
2-Amino-4(3*H*)-pyrimidinethione	231–233	958,1507
4-Amino-2(1*H*)-pyrimidinethione	273 to 279	1514,1515,1650–1653
5-Amino-4(3*H*)-pyrimidinethione	207	1036,1654
6-Amino-4(3*H*)-pyrimidinethione	300 to 306	958,1568,1653,1655
1-Amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	135–138	1518
5-Amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	310–312	1138,1656–1660
5-Amino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrithione	> 300	1661
4-Amino-5-pyrimidinol	> 250	718
2-Amino-4(3*H*)-pyrimidinone	272 to 278	719,962,1526,1662–1673,6740
4-Amino-2(1*H*)-pyrimidinone	305 to 325; HCl: 267–268	339,719,722,967,1006,1514, 1650,1652,1664,1671,1673–1678
5-Amino-4(3*H*)-pyrimidinone	206 to 216; HCl: 213–217	243,702,1037,1654
6-Amino-4(3*H*)-pyrimidinone	263 to 274	659,1297,1570,1588,1650,1679, 1680
2-Amino-4(3*H*)-pyrimidinone 1-oxide	292	1672

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Amino-2(1*H*)-pyrimidinone 3-oxide	265–275	1681
4-Amino-2(3*H*)-pyrimidinone 1-oxide	265–270	1681
6-Amino-5-sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione	—	1682
4-Amino-5-sulfo-oxy-2(1*H*)-pyrimidinone	anal; K: anal	1345
4-Amino-1,3,*N*,*N*-tetramethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidine-carboxamide	182–184	1683
6-Amino-5-thiocyanato-2,4(1*H*,3*H*)-pyrimidinedione	> 300	837,1161
6-Amino-5-thiocyanato-4(3*H*)-pyrimidinone	260–262	837
2-Amino-4-thioxo-3,4-dihydro-5-pyrimidinecarbonitrile	> 260	1223
4-Amino-2-thioxo-1,2-dihydro-5-pyrimidinecarbonitrile	> 270 to 320	938,1250–1252
4-Amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxamide	> 320	1250
2-Amino-6-thioxo-1,6-dihydro-4-pyrimidinecarboxylic acid	291–293	1030
4-Amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylic acid	276–279	1684,1685
6-Amino-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid	272–274	1030
1-Amino-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	208–209	1518
5-Amino-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	> 300	1258,1641,1686,1687,3988
5-Amino-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione	250	1137,1163
2-Amino-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	250 or > 360	958,1189,1688
3-Amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	217–218	1573
4-Amino-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	355	958,1644
5-Amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	1689
6-Amino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	300 or > 360	958,1298,1499,1570,1595, 1690–1692
6-Amino-1,3,5-triethyl-2,4(1*H*,3*H*)-pyrimidinedione	169–170	853,1063
4-Amino-1,3,*N*-trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide	230	775,1197

4-Amino-1,3,*N*-trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonamide	203–204	1101
5-Amino-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	165 to 171	1056,1693–1696
6-Amino-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	244–246 or 251–252	653,853
2-Amino-5-ureido-4,6(1*H*,5*H*)-pyrimidinedione	> 400	1578,1697
6-Amino-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	anal	1441,1698
4-Amino-2-vinyl-5-pyrimidinecarbonitrile	219–220	1003
4-Amino-1-vinyl-2(1*H*)-pyrimidinone	217–218	726,1577
4-Azido-5-azidomethyl-2-chloropyrimidine	< 200	1699
5-β-Azidocarbonylethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	100–110	1300
5-β-Azidocarbonylethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	100–110	1300
5-Azidocarbonylmethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1415
5-Azidocarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	75–78	1395
4-Azido-5-chloro-2,6-difluoropyrimidine	24–26	1700
2-Azido-4-chloro-6-methylpyrimidine	58–60	1701
4-Azido-6-chloro-5-pyrimidinamine	171–173	607,1702
4-Azido-2,6-dimethoxypyrimidine	41–42	1701,1703
6-Azido-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	148–149	1704,1705
2-Azido-4,6-dimethylpyrimidine	153–154	1701,1706–1709
4-Azido-2,6-dimethylpyrimidine	84–85	1701
6-Azido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	149–151	644
4-α-Azidoethylpyrimidine	crude: 95–98/15	1226
5-α-Azidoethylpyrimidine	crude: 75–83/15	1226
2-Azido-4-methoxy-6-methylpyrimidine	163–164	1701
5-Azido-2-methoxypyrimidine	42–43	1710
5-Azidomethyl-2,4-dichloropyrimidine	-	1699
2-Azido-4-methyl-6-methylthiopyrimidine	151–152	1701
4-Azido-6-methyl-2-methylthiopyrimidine	66–67	1701
2-Azido-5-methylpyrimidine	123	1711

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Azidomethyl-2,4(1*H*,3*H*)-pyrimidinedione	197–201	1712
6-Azido-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	268–270	1263
2-Azido-1-methyl-4(1*H*)-pyrimidinimine	HI: sp	1713
5-Azido-2-methylsulfonylpyrimidine	142–145	1710
2-Azido-5-nitro-4-pyrimidinamine	181–182	1714
1-γ-Azidopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	98–100	943
1-γ-Azidopropyl-2,4(1*H*,3*H*)-pyrimidinedione	75–76	943
2-Azidopyrimidine	120 to 125	1701,1706,1707,1715,1716
4-Azidopyrimidine	77–79	607
2-Azido-4,6(1*H*,5*H*)-pyrimidinedione	250	1717
4-Azido-2,5,6-trifluoropyrimidine	55/18	1700
4-Azido-2,5,6-trimethylpyrimidine	96–97	1701
1,3-Bisacetoxymethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	110–111, nmr	113
4,6-Bisacetoxymethyl-2-methylpyrimidine 1,3-dioxide	86	763
2,4-Bis-β-acetylhydrazino-5-nitropyrimidine	266–267	803
4,6-Bisallylaminopyrimidine	163	866
2,6-Bis-α-bromoethyl-5-bromomethyl-4-pyrimidinamine	126	1718,1719
2,6-Bis-α-bromoethyl-5-bromomethyl-4(3*H*)-pyrimidinone	149	1718
4,6-Bisbromomethyl-2-ethylpyrimidine 1,3-dioxide	154	763
4,6-Bisbromomethyl-5-methyl-2-methylthiopyrimidine	124–125, nmr	6133
2,4-Bisbromomethyl-6-methylpyrimidine 1,3-dioxide	157	763
4,6-Bisbromomethyl-2-methylpyrimidine 1,3-dioxide	146	763
4,5-Bisbromomethyl-2-methylthiopyrimidine	liquid, nmr	6133
1,3-Bis-γ-bromopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	anal, n_D^{20} 1.5720	1720

1,3-Bis-γ-bromopropyl-2,4(1*H*,3*H*)-pyrimidinedione	anal, n_D^{20} 1.5657	1720
2,4-Bis-α-chloroethyl-5-chloromethyl-4-pyrimidinamine	110	1718,1719
2,6-Bis-α-chloroethyl-5-chloromethyl-4(3*H*)-pyrimidinone	132	1718
1,3-Bis-β-chloroethyl-6-chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione	71–72	1721
1,3-Bis-β-chloroethyl-2,4(1*H*,3*H*)-pyrimidinedione	160/0.1	1722
5,6-Bischloromethyl-2,4(1*H*,3*H*)-pyrimidinedione	190–194	1723
1,3-Bis-β-cyanoethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	105–108	1724
1,3-Bis-β-cyanoethyl-5-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	96–98	1725
1,3-Bis-β-cyanoethyl-5-methoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	143–145	1725
1,3-Bis-β-cyanoethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	107–109	1725
1,3-Bis-β-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	78–79 or 108–109	1725,1726
1,3-Bis-β-cyanoethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	113–115	1725
2,4-Bisdimethylamino-5,6-difluoropyrimidine	96–97	1727
4,6-Bisdimethylamino-2,5-difluoropyrimidine	93–94	1728
5,6-Bisdimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1729
2,4-Bisdimethylamino-5-ethoxymethylpyrimidine	161; pic: 205	853
2,4-Bisdimethylamino-6-ethyl-5-nitropyrimidine	74–75	6733
2,4-Bisdimethylamino-6-fluoropyrimidine	23–25, 102–103/5	1730
2,4-Bisdimethylamino-6-methoxypyrimidine	42–43	1731
4,6-Bisdimethylamino-2-methoxypyrimidine	53–55	1731
2,4-Bisdimethylaminomethyl-6-methyl-5-pyrimidinol	179–180, nmr	6017
2,4-Bisdimethylamino-6-methyl-5-methylthiopyrimidine	100–102/0.06, n_D^{20} 1.5830	1732
2,4-Bisdimethylamino-6-methyl-5-nitropyrimidine	122–123	1157
4,6-Bisdimethylamino-2-methyl-5-nitrosopyrimidine	125	1733
2,4-Bisdimethylamino-6-methyl-5-pyrimidinamine	75	1157
2,4-Bisdimethylamino-5-methylpyrimidine	46 or 47, nmr; pic: 176–177	397,1734
2,4-Bisdimethylamino-6-methylpyrimidine	84–85/2, 120–123/6, 132/11; pic: 181–182 or 184–185	1734–1736

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,6-Bisdimethylamino-2-methylpyrimidine	88–89	1735
4,6-Bisdimethylamino-2-methyl-5-pyrimidinecarbonitrile	123	1387
4,6-Bisdimethylaminomethyl-5-pyrimidinol	105–107	1737
2,4-Bisdimethylamino-5-nitropyrimidine	83–84 or 88–92	1714,1738
4,6-Bisdimethylamino-5-nitropyrimidine	159–161	243
2,6-Bisdimethylamino-5-nitro-4(3*H*)-pyrimidinone	265–267	999
2,6-Bisdimethylamino-5-nitro-4-pyrimidinamine	225–228	1739
2,4-Bisdimethylamino-5-pyrimidinamine	92–96	1738
2,6-Bisdimethylamino-4-pyrimidinamine	103 to 117	615,1739,1740
4,6-Bisdimethylamino-2-pyrimidinamine	200	1741
4,6-Bisdimethylamino-5-pyrimidinamine	80–81	243
2,4-Bisdimethylaminopyrimidine	38 to 55, 98/0.9	1736,1742–1744
4,6-Bisdimethylaminopyrimidine	105 to 108	968,1736,1745
2,4-Bisdimethylamino-5-pyrimidinecarbonitrile	92–93; HCl: 192–195	1078
2,6-Bisdimethylamino-4,5-pyrimidinediamine	182; H_2SO_4: 203–205	1484,1739
2,4-Bisdimethylamino-5-pyrimidinol	Na: anal, ms	1011
2,4-Bisdimethylamino-5-sulfo-oxypyrimidine	214–220	1011
1,3-Bisethoxymethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	54	1724
2,4-Bisethylamino-6-methyl-5-nitropyrimidine	124–125 or 128	1746,1747
2,4-Bisethylamino-6-methyl-5-pyrimidinamine	H_2SO_4: 185	1746
2,4-Bisethylamino-5-nitropyrimidine	171–172 or 175	1746, 1747
4,6-Bisethylamino-5-nitropyrimidine	83–84 or 87–88	47,1747
2,4-Bisethylamino-5-pyrimidinamine	210; H_2SO_4: 217	1746,1747
4,6-Bisethylamino-2-pyrimidinamine	136	1042
4,6-Bisethylamino-5-pyrimidinamine	210–211	1747

4,6-Bisethylaminopyrimidine	187	866
5,6-Bisethylamino-4(3*H*)-pyrimidinone	152–154	1094
2,4-Bisethylsulfonyl-5-fluoropyrimidine	132–134, nmr	270
2,4-Bisethylsulfonylpyrimidine	87–88	1748
2,4-Bisethylthio-5-ethylthiomethyl-6-methylpyrimidine	131–134/0/004, nmr	347
2,4-Bisethylthio-5-fluoropyrimidine	142–144/14, nmr	270
4,6-Bisethylthio-2-methoxycarbonylmethylpyrimidine	204–206/2	1749
2,4-Bisethylthio-6-methyl-5-pyrimidinamine	75	1157
2,4-Bisethylthio-6-methylpyrimidine	crude: liquid, nmr	68
2,6-Bisethylthio-4-pyrimidinamine	78–80	616,1750
4,6-Bisethylthio-2-pyrimidinamine	52–53 or 54	958,1149
2,4-Bisethylthiopyrimidine	135–140/6	1676,1748,1751
4,5-Bisformamido-2-methoxypyrimidine	180–181	681
4,6-Bisformamido-2-thiocyanatopyrimidine	249	1355
2,4-Bis-β-formylhydrazino-6-methylpyrimidine	225–227	1752
2,4-Bis-β-formylhydrazino-5-nitropyrimidine	209–210	803
4,6-Bis-β-formylhydrazinopyrimidine	285–287	1752
1,3-Bisformylmethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	MeHNC(S)NHN═: 227	1753
1,3-Bisformylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	sc: 230; tsc: 227	1753
2,4-Bisguanidinoamino-5-methylpyrimidine	220	1754
2,4-Bisguanidinoamino-6-methylpyrimidine	235	1754
2,4-Bisguanidinoaminopyrimidine	192	1754
1,3-Bis-β-hydroxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	111–112	1755
1,3-Bis-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	152–153 or 154	1722,1755–1758
2,6-Bishydroxymethyl-5-methyl-4(3*H*)-pyrimidinone	HCl: 167–169	1759
4,5-Bishydroxymethyl-2-methylthiopyrimidine	72–73	768
1,3-Bishydroxymethyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	1760
2,4-Bisisopropylamino-6-methyl-5-nitropyrimidine	75–76	1747

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,4-Bisisopropylamino-6-methyl-5-pyrimidinamine	H_2SO_4: 189–190	1747
2,4-Bisisopropylamino-5-nitropyrimidine	160–161	1747
4,6-Bisisopropylamino-5-nitropyrimidine	127–128	1747
2,4-Bisisopropylamino-5-pyrimidinamine	H_2SO_4: 208–209	1747
4,6-Bisisopropylamino-5-pyrimidinamine	236	1747
2,4-Bisisopropylidenehydrazino-6-methylpyrimidine	170–171	1754
2,4-Bis-β-methoxyethyl-6-methylpyrimidine	170–175/11, ir, nmr	3893
2,6-Bismethoxymethyl-5-methyl-4(3*H*)-pyrimidinone	105–106	1761
2,5-Bismethoxymethyl-4-pyrimidinamine	86–88	1762
4,6-Bismethoxymethyl-2-pyrimidinamine	133–134	1149
2,6-Bismethoxymethyl-4(3*H*)-pyrimidinone	98–99	1763
2,6-Bismethylamino-5-methylaminomethyl-4-pyrimidinecarboxylic acid	163	936
4,6-Bismethylamino-5-methylaminomethylpyrimidine	162–164	1027
4,6-Bismethylamino-2-methylthio-5-nitropyrimidine	190	1764
4,6-Bismethylamino-2-methylthiopyrimidine	152–153	1765
2,4-Bismethylamino-5-nitropyrimidine	251 to 263	1586,1648,1738,1747,1766
4,6-Bismethylamino-5-nitropyrimidine	192–195	1648,1747
4,6-Bismethylamino-5-nitroso-2-pyrimidinamine	264–266	1767,1768
2,4-Bismethylamino-5-pyrimidinamine	H_2SO_4: 220	1766
4,6-Bismethylamino-2-pyrimidinamine	crude HCl: 326	1767,1769
4,6-Bismethylamino-5-pyrimidinamine	150 or 178–180	1738,1770
2,4-Bismethylaminopyrimidine	130–132	1771,1772
4,5-Bismethylaminopyrimidine	140–142	1773,1774
4,6-Bismethylaminopyrimidine	207–209	1383
2,6-Bismethylamino-4-pyrimidinecarboxylic acid	314	1030

2,6-Bismethylamino-4,5-pyrimidinediamine	259	1484
4,6-Bismethylamino-2,5-pyrimidinediamine	crude: uv	1769
5,6-Bismethylamino-2,4(1*H*,3*H*)-pyrimidinedione	246–247; HCl: 259 or 261	1775,1776
2,6-Bismethylamino-4(3*H*)-pyrimidinone	241–244 or 242–245	1093,1282
4,6-Bis-α-methylhydrazino-5-nitropyrimidine	175–177	1680
4,6-Bis-α-methylhydrazino-5-pyrimidinamine	180	1777
5,6-Bismethylsulfonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	288–289	1723
4,6-Bismethylsulfonyl-2-pyrimidinamine	240–249, nmr	3988
4,6-Bismethylsulfonyl-5-pyrimidinamine	182–187	1778
5,6-Bismethylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione	193–195	1723
2,6-Bismethylthio-5-nitro-4-pyrimidinamine	220–221	1294
2,4-Bismethylthio-5-nitropyrimidine	129–130	804
4,6-Bismethylthio-5-nitropyrimidine	148–152	1778
2,6-Bismethylthio-4-pyrimidinamine	121–123	958,1779
4,6-Bismethylthio-2-pyrimidinamine	114–116 or 116–118, nmr	958,1780,3988
4,6-Bismethylthio-5-pyrimidinamine	79 or 90–92	958,1778
2,4-Bismethylthiopyrimidine	9–10, 98/0.25, 110/1, 139–140/6; 1-MeI: 144–145; 3-MeI: 157	968,1508,1513,1702,1781–1783
4,6-Bismethylthiopyrimidine	52–54 (119?)	958,1784–1786
4,6-Bismethylthio-5-pyrimidinecarboxamide	214–215	1787
2,4-Bismethylthio-5-pyrimidinecarboxylic acid	201–203 or 206–209	958,1782
2,6-Bismethylthio-4-pyrimidinecarboxylic acid	145–146	1030
4,6-Bismethylthio-5-pyrimidinecarboxylic acid	225 or 229–230	1787,1788
2,6-Bismethylthio-4,5-pyrimidinediamine	192–193	1294
4,6-Bismethylthio-2,5-pyrimidinediamine	122–125. nmr	3988
2,5-Bismethylthio-4(3*H*)-pyrimidinone	206–208	1789
2,6-Bismethylthio-4(3*H*)-pyrimidinone	197	958
4,6-Bismethylthio-2(1*H*)-pyrimidinone	208–210 or 212–213	1780,1786

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,4-Bispropylamino-5-pyrimidinamine	H_2SO_4: 210–212	1747,1790
4,6-Bispropylamino-5-pyrimidinamine	208–209	1747
2,4-Bispropylaminopyrimidine	160–170/0.02, ms, nmr, uv	66
4,6-Bispropylthio-2-pyrimidinamine	85–87	958
4,6-Bistrimethylammoniopyrimidine	crude dichloride: nmr	1791
2,4-Bistrimethylsiloxypyrimidine	31–33, 112/13, 116/12(?), 120/18	135,828,1792–1795
3-β-Bromoallyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	89	890
3-β-Bromoallyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	191	890
5-Bromo-4,6-bisbromomethyl-2-pyrimidinamine	182–184	1796
5-Bromo-1,3-bis-β-cyanoethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidine-carboxylic acid	167–168	1797
5-Bromo-1,3-bis-β-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	167–168	1798
5-Bromo-2,4-bisdimethylaminopyrimidine	25–26	1799
5-Bromo-2,4-bisdimethylsiloxypyrimidine	crude: ir	1800
5-Bromo-2,4-bisethylthio-6-methylpyrimidine	crude: 43–45	68
5-Bromo-1,3-bis-β-hydroxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	174–175	955
5-Bromo-2,4-bismethylthiopyrimidine	65–66	1782
5-Bromo-4,6-bismethylthiopyrimidine	155	958,1787
5-Bromo-4,6-bispropylthiopyrimidine	44–46	958
4-Bromo-2,6-bistrimethylsiloxypyrimidine	60/vacuum	1800
5-Bromo-2,4-bistrimethylsiloxypyrimidine	80/vacuum	277,1800
5-Bromo-2-β-bromoethyl-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	126–127, ir, ms, nmr, uv	3895
5-Bromo-1-β-bromoethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	198–200, nmr	6579
5-Bromo-6-bromomethyl-1-β-bromopropyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	liquid: ir, ms, nmr, uv	3895
5-Bromo-6-bromomethyl-1-γ-bromopropyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	104–105, nmr	6579

4-Bromo-2-bromomethyl-6-chloro-2-methylpyrimidine	135–137	1801
5-Bromo-2-bromomethyl-6-chloro-4(3*H*)-pyrimidinone	260–261	1802
5-Bromo-6-bromomethyl-l-β-hydroxyethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	161–162, nmr	6579
5-Bromo-6-bromomethyl-l-γ-hydroxypropyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	93–95, nmr	6579
5-Bromo-2-bromomethyl-6-methyl-4-pyrimidinamine	168–170, nmr	6010
5-Bromo-4-bromomethyl-1-methyl-2(1*H*)-pyrimidinone	3-MeBr: 205	1803
5-Bromo-4-bromomethyl-2-methylthiopyrimidine	62–64, nmr	6133
5-Bromo-1-β-bromopropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	107–108, nmr	6579
5-Bromo-1-γ-bromopropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	116–117, nmr	6579
5-Bromo-1-β-carbamoylethyl-2,4(1*H*,3*H*)-pyrimidinedione	281	1804
5-Bromo-6-carbamoylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	anal	1805
5-Bromo-1-β-carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	250	1804
4-Bromo-2-carboxymethylpyrimidine	Na: > 300	1749
5-Bromo-1-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	244 or 280	1806,1807
5-Bromo-6-carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	278–280	1808,1809
5-Bromo-4-chloro-2,6-dimethoxypyrimidine	96–98	675
5-Bromo-4-chloro-2-dimethylamino-6-methylpyrimidine	79–80	1745
5-Bromo-2-chloro-4-dimethylaminopyrimidine	62–64	1799
5-Bromo-2-chloro-4,6-dimethylpyrimidine	81	1787
5-Bromo-2-chloro-2,6-dimethylpyrimidine	45	1810,1811
5-Bromo-6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	161–163	1812,1813
2-Bromo-4-chloro-5-ethoxypyrimidine	43–46	1814
5-Bromo-2-chloro-4-*N*-ethyl-*N*-methylaminopyrimidine	22–26	1815
5-Bromo-4-chloro-2-ethylsulfonylpyrimidine	81–82	1748
5-Bromo-4-chloro-2-ethylthiopyrimidine	27, 168/25	967,969
5-Bromo-6-chloro-2-fluoromethyl-4(3*H*)-pyrimidinone	220	1802
5-Bromo-2-chloro-4-methoxypyrimidine	73–75	1799
5-Bromo-4-chloro-2-methoxypyrimidine	anal, nmr	1799

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Bromo-4-chloro-6-methoxypyrimidine	67–70 or 77	1787,1788
5-Bromo-2-chloromethyl-6-methyl-4-pyrimidinamine	150–152, nmr	6010
5-Bromo-4-chloro-6-methyl-2-methylsulfonylpyrimidine	140–142	1816
5-Bromo-4-chloro-6-methyl-2-methylthiopyrimidine	69–70 or 72–73	1811,1816,1817
5-Bromo-4-chloro-6-methyl-2-pyrimidinamine	207–208	614,960,1818
2-Bromo-4-chloro-6-methylpyrimidine	33–34	1819
5-Bromo-4-chloro-2-methylpyrimidine	107/27	1820,1821
5-Bromo-4-chloro-6-methylpyrimidine	53–56	1811,1822
5-Bromo-6-chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	232–233	1812
5-Bromo-6-chloro-2-methylthio-4-pyrimidinamine	164–165	951,1707
5-Bromo-2-chloro-4-methylthiopyrimidine	56–58	1823
5-Bromo-4-chloro-2-methylthiopyrimidine	44	1824
2-Bromo-4-chloro-5-propylpyrimidine	130/18	1814
5-Bromo-2-chloropyrimidine	79	1825,1826
5-Bromo-4-chloropyrimidine	87/16 or 100/10	1820,1827,1828
5-Bromo-6-chloro-2,4-pyrimidinediamine	217	1830,1831
5-Bromo-6-chloro-2,4(1*H*,3*H*)-pyrimidinedione	303–305	1812
6-Bromo-5-chloro-2,4(1*H*,3*H*)-pyrimidinedione	305–306	1812
5-Bromo-6-chloro-4(3*H*)-pyrimidinone	249	1832
5-Bromo-4-cyanoamino-2-ethylthiopyrimidine	310	969
5-Bromo-3-β-cyanoethyl-2-methylthio-4(3*H*)-pyrimidinone	127–129	1798
5-Bromo-1-β-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	232–234	1798
5-Bromo-3-β-cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	176–178	1798
5-Bromo-2,4-dichloro-6-methylpyrimidine	42–43, 114/0.03	1811,1833–1836
5-Bromo-4,6-dichloro-2-methylsulfonylpyrimidine	169–171	1816

5-Bromo-4,6-dichloro-2-methylthiopyrimidine	83–85	1816
5-Bromo-2,6-dichloro-4-pyrimidinamine	155–157	1707
5-Bromo-4,6-dichloro-2-pyrimidinamine	235–236	1707
5-Bromo-2,4-dichloropyrimidine	~ 20, 92–93/5, 103–104/6, 112–113/12	951,1637,1800,1811,1837,1838
5-Bromo-4,6-dichloropyrimidine	75–76	1827
4-Bromo-2,6-diethoxy-5-methylpyrimidine	75–76	1839
2-Bromo-4,5-diethoxypyrimidine	49; HCl; 135	1814
4-Bromo-2,6-diethoxypyrimidine	17–19, 132–133/10	788
5-Bromo-2,4-diethoxypyrimidine	72–74	1544.1837
5-Bromo-4,6-diethoxypyrimidine	34–35	1788
4-Bromo-1,3-diethyl-6-imino-1,6-dihydro-2(3*H*)-pyrimidinone	97–98	1066
5-Bromo-1,3-diethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	139–141	1808
5-Bromo-2,6-diethyl-4-pyrimidinamine	155	1840
5-Bromo-1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	80–81	1841
5-Bromo-1,3-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	81–82	1842
5-Bromo-2,4-difluoro-6-methylpyrimidine	74/20	1843
5-Bromo-4,6-dihydrazinopyrimidine	150	1844
5-Bromo-1,3-di-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1845
5-Bromo-2,4-dimethoxy-6-methylaminopyrimidine	104–106	675
5-Bromo-4,6-dimethoxy-2-methylpyrimidine	116–117	1788
5-Bromo-2,6-dimethoxy-4-pyrimidinamine	170–172	636,1846
4-Bromo-2,6-dimethoxypyrimidine	90–91	1703
5-Bromo-2,4-dimethoxypyrimidine	63–64 or 65–66 (51–52?), 125/17	1814,1837,1847
5-Bromo-4,6-dimethoxypyrimidine	148–150	1787,1788
5-Bromo-6-dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	98	675
5-Bromo-2-dimethylamino-4-methoxypyrimidine	65–67	1799
5-Bromo-4-dimethylamino-2-methoxypyrimidine	29–31	1799

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Bromo-2-dimethylamino-4-methylaminopyrimidine	70–71	1742
5-Bromo-4-dimethylamino-2-methylaminopyrimidine	121–122	1742
5-Bromo-4-dimethylamino-1-methyl-2-methylimino-1,2-dihydropyrimidine	HCl: 208–209; HI: 185–186	1742
2-Bromo-4-dimethylamino-6-methylpyrimidine	93	1848
5-Bromo-4-dimethylamino-1-methyl-2(1*H*)-pyrimidinimine	HCl: 227–230; HI: 248–250	1742
5-Bromo-2-dimethylamino-6-methyl-4(3*H*)-pyrimidinone	229–233	863,952,1745,1849
5-Bromo-2-dimethylamino-4-methylthiopyrimidine	58–60	1823
5-Bromo-2-dimethylamino-4-pyrimidinamine	139–140	1742
5-Bromo-4-dimethylamino-2-pyrimidinamine	114–115	1742
5-Bromo-2-dimethylaminopyrimidine	81–82	1850
5-Bromo-2-dimethylamino-4(3*H*)-pyrimidinone	246–247	1799,1823
5-Bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	125	1132,1133
5-Bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	299	1133
5-Bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	211	1851
5-Bromo-4,6-dimethyl-2-methylaminopyrimidine	130; pic: 164	1437
5-Bromo-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	152	675
5-Bromo-1,3-dimethyl-6-methylhydrazonomethyl-2,4(1*H*,3*H*)-pyrimidinedione	104–106	762
4-Bromo-1,3-dimethyl-6-propylimino-1,6-dihydro-2(3*H*)-pyrimidinone	68	1066
5-Bromo-2,6-dimethyl-4-pyrimidinamine	141–143	1818,1852–1854
5-Bromo-4,6-dimethyl-2-pyrimidinamine	174–188, ir, ms, nmr	894,961,1118,1796,1811,1846, 1855,6138
2-Bromo-4,6-dimethylpyrimidine	71–72	1819,1826,1856
4-Bromo-2,6-dimethylpyrimidine	54–55	1826
5-Bromo-2,4-dimethylpyrimidine	41–42 (136–137?), 78–81/18, nmr	140,1810,1857
5-Bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	181–185, ir, nmr, uv	269,323,1664,1858–1862,3904

5-Bromo-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	264	1863
5-Bromo-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	231–233 or 243	1864,1865
6-Bromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	132–133	1812
5-Bromo-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	97–99	1842
5-Bromo-1,4-dimethyl-2(1*H*)-pyrimidinimine	HI: 220; pic: 203	1465
5-Bromo-2,6-dimethyl-4(3*H*)-pyrimidinone	195	1810,1852,1854,1866
5-Bromo-4,6-dimethyl-2(1*H*)-pyrimidinone	223 or 228–231; HBr: > 300	1014,1867
5-Bromo-2,4-dimethyl-6-thioureidopyrimidine	205	1810
5-Bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	268–270 or 273–275; tsc: 280 or > 300	1868–1871
5-Bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	314–316; H_2O: 286–288	1171,1797,1808,1809,1872,1873
5-Bromo-2-ethoxy-4,6-dimethylpyrimidine	40–41, 254/760	1874,1876
5-Bromo-4-ethoxy-2-ethylsulfonylpyrimidine	90–91	1748
5-Bromo-4-ethoxy-2-ethylthiopyrimidine	140/6	1748
5-Bromo-6-ethoxymethyl-2-methyl-4(3*H*)-pyrimidinone	136–138	1877
5-Bromo-4-ethoxy-6-methyl-2-methylthiopyrimidine	122–125/3	1014
5-Bromo-4-ethoxy-6-methyl-2-pyrimidinamine	108–109	1014
5-Bromo-4-ethoxy-6-methylpyrimidine	112–113/15	1878
5-Bromo-4-ethoxy-2-methylpyrimidine 1-oxide	96–97	1878
5-Bromo-2-ethoxypyrimidine	56–57	1879
5-Bromo-2-ethoxy-4(3*H*)-pyrimidinone	163	1837
5-Bromo-4-ethoxy-2(1*H*)-pyrimidinone	–	1837
5-Bromo-6-ethylamino-2-methyl-4(3*H*)-pyrimidinone	201–202, ir, nmr, uv	572
5-Bromo-2-ethylaminopyrimidine	122; pic: 158	1437
2-α-Bromoethyl-6-chloro-4(3*H*)-pyrimidinone	178–180	1802
5-α-Bromoethyl-4,6-dichloropyrimidine	102/0.25	1880
5-α-Bromoethyl-4,6-dimethoxypyrimidine	crude	1880
5-Bromo-2-ethyl-4,6-dimethoxypyrimidine	67–69	1788

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-β-Bromoethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	96–97, nmr	6579
5-Bromo-6-ethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	115–116, nmr, uv	269
1-β-Bromoethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	220–222	1881
5-Bromo-6-ethyl-2-ethylthio-4(3*H*)-pyrimidinone	172–173	1637
5-Bromo-4-*N*-ethyl-*N*-methylamino-2-methoxypyrimidine	ms, nmr	1815
5-β-Bromoethyl-4-methyl-2-pyrimidinamine	159–160	1149
5-β-Bromoethyl-6-methyl-2,4-pyrimidinediamine	HBr: anal	1882
1-β-Bromoethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	209–210	1322
5-β-Bromoethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	268–270	1005
5-Bromo-1-ethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	148–149	1883
5-Bromo-1-ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	234–235	895
5-Bromo-3-ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	203–206	895
5-Bromo-2-ethyl-6-methyl-4(3*H*)-pyrimidinone	194–196	1866
5-Bromo-3-ethyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	216	909
5-Bromo-3-ethyl-6-methylthio-4(3*H*)-pyrimidinone	130–132	909
6-Bromo-2-ethyl-4-pyrimidinamine	142–145	1243
4-α-Bromoethylpyrimidine	crude: nmr	1226
5-α-Bromoethylpyrimidine	crude: nmr	1226
1-β-Bromoethyl-2,4(1*H*,3*H*)-pyrimidinedione	145–146, nmr	3775
2-Bromo-5-ethyl-4,6-pyrimidinediamine	241–244	972,1884
3-β-Bromoethyl-2,4(1*H*,3*H*)-pyrimidinedione	159–160	1885
5-β-Bromoethyl-2,4(1*H*,3*H*)-pyrimidinedione	262–263	1005
5-Bromo-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	250–253	1883
5-Bromo-2-ethyl-4,6(1*H*,5*H*)-pyrimidinedione	223–224	1788
5-Bromo-6-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	230–231 or 233–234	126,969

5-Bromo-1-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	103–104	789
5-Bromo-1-ethyl-2(1*H*)-pyrimidinimine	HCl: 258; pic: 195	1437
5-Bromo-1-ethyl-2(1*H*)-pyrimidinone	149–150	1879
6-Bromo-2-ethyl-4(3*H*)-pyrimidinone	157–158	1243
5-Bromo-2-ethylthio-4-isothiocyanatopyrimidine	78–80	969,1886
5-Bromo-2-ethylthio-6-methyl-4-pyrimidinamine	113–114	1818
5-Bromo-2-ethylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	183–185	1871
5-Bromo-2-ethylthio-4-pyrimidinamine	124–125	951,967,1637
5-Bromo-2-ethylthiopyrimidine	43–45	1824
5-Bromo-2-ethylthio-4(3*H*)-pyrimidinethione	198	969,1886
5-Bromo-2-ethylthio-4(3*H*)-pyrimidinone	189	967,1014
5-Bromo-2-ethylthio-4-thiocyanatopyrimidine	81–82	1886
5-Bromo-2-ethylthio-4-thioureidopyrimidine	219–220	969,1886
5-Bromo-2-ethylthio-4-ureidopyrimidine	—	969
5-Bromo-2-fluoropyrimidine	92–93	1749
5-Bromo-6-formamidomethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	701
2-Bromo-5-formamidopyrimidine	130–131	1623
5-Bromo-1-formylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	230–233; acetal: 121–122	1887
5-Bromo-4-hydrazino-2,6-dimethylpyrimidine	145–146	1857
5-Bromo-4-hydrazino-6-methyl-2-propylpyrimidine	89–90	900
5-Bromo-4-hydrazino-6-methylpyrimidine	194–195	1822
5-Bromo-4-hydrazino-2-methylthiopyrimidine	148–150	1844
5-Bromo-2-hydrazinopyrimidine	205–206	1888
5-Bromo-4-hydrazinopyrimidine	185–187	1827
5-Bromo-1-β-hydroxyethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	147–148, nmr	6579
5-Bromo-3-β-hydroxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	213–214	955
5-Bromo-4-hydroxymethyl-2-methoxypyrimidine	crude: 123–124, nmr	1850
5-Bromo-2-hydroxymethylpyrimidine	93–94	1889

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Bromo-2-hydroxymethyl-4-pyrimidinecarboxylic acid	152–153; K: 251–252	1889
5-Bromo-6-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	173–174	1868
5-Bromo-1-β-hydroxypropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	140–141, nmr	6579
5-Bromo-1-γ-hydroxypropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	145–146, nmr	6579
5-Bromo-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	240	1265
6-Bromo-5-hydroxy-3-vinyl-4(3*H*)-pyrimidinethione	118, ms, nmr, uv	60
4-Bromo-6-imino-1,3-dimethyl-1,6-dihydro-2(3*H*)-pyrimidinone	190	1066
5-Bromo-4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine	HCl: 289; HI: 234–236	1742
6-Bromo-5-iodo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	170–171	1812
5-Bromo-4-iodo-2-isopropyl-6-methylpyrimidine	78	1890
5-Bromo-2-iodomethyl-6-methyl-4-pyrimidinamine	167–170, nmr	3748,6010
5-Bromo-4-iodo-2-methylthiopyrimidine	130–131	1745
5-Bromo-6-iodo-2,4(1*H*,3*H*)-pyrimidinedione	284–286	1812
6-Bromo-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	260–261	1812
5-Bromo-2-isopropoxypyrimidine	44–46/0.08, ms, nmr	3832
5-Bromo-2-isopropylamino-6-methylpyrimidine	200–201	1765
5-Bromo-4-isopropylamino-4-pyrimidinamine	138	612
5-Bromo-1-isopropyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	115–120	1883
5-Bromo-3-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	158–159	1891,1892
5-Bromo-3-isopropyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	220	909
5-Bromo-1-isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	203–205 or 214–215	1883,1893
4-Bromo-2-methoxycarbonylmethylpyrimidine	50–53	1749
5-Bromo-6-methoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1805
5-Bromo-2-methoxy-4,6-dimethylpyrimidine	61–62	1787
5-Bromo-4-methoxy-3,6-dimethyl-2(3*H*)-pyrimidinethione (?)	237–238	1788

5-Bromo-4-methoxy-6-methyl-2-methylthiopyrimidine	70–71	1788
5-Bromo-4-methoxy-6-methyl-2-pyrimidinamine	153–155 or 245–248	1014,1811
5-Bromo-2-methoxy-4-methylpyrimidine	crude: nmr	1850
5-Bromo-4-methoxy-6-methylpyrimidine	79–80	1788
5-Bromo-4-methoxy-1-methyl-2(1*H*)-pyrimidininone	148–149	1894
5-Bromo-6-methoxy-2-methylthio-4-pyrimidinamine	135–136 or 138–140	1331,1818
5-Bromo-2-methoxy-4-methylthiopyrimidine	68–70	1823
5-Bromo-4-methoxy-2-methylthiopyrimidine	86	1895
2-Bromo-6-methoxy-4-pyrimidinamine	186–188	965,966
4-Bromo-6-methoxy-2-pyrimidinamine	161–163	965,966
5-Bromo-2-methoxy-4-pyrimidinamine	134–136	1837
5-Bromo-4-methoxy-2-pyrimidinamine	118 or 125–126	1811,1814
5-Bromo-6-methoxy-4-pyrimidinamine	158–160	1896
5-Bromo-2-methoxypyrimidine	57 or 90, ms, nmr	1897,3765,3829
5-Bromo-4-methoxypyrimidine	66 to 74	1788,1898,1899
5-Bromo-4-methoxy-2-pyrimidinecarbonitrile	147–149, nmr	3743
5-Bromo-2-methoxy-4-pyrimidinecarboxylic acid	171–173	1897
5-Bromo-4-methoxypyrimidine 1-oxide	158, nmr	3743
5-Bromo-2-methoxy-4(3*H*)-pyrimidinone	190	1837
5-Bromo-6-methoxy-4(3*H*)-pyrimidinone	234–235	1900
5-Bromo-2-methylamino-4-pyrimidinamine	120–121	1742
5-Bromo-4-methylamino-2-pyrimidinamine	145–146	1742
5-Bromo-2-methylaminopyrimidine	121; pic: 181	1741,1850
5-Bromo-4-methylaminopyrimidine	128–129	1901
5-Bromo-6-methylamino-2,4(1*H*,2*H*)-pyrimidinedione	> 320	675
5-Bromo-4-methyl-2,6-bistrimethylsiloxypyrimidine	121–124/2.5	1829
2-Bromomethyl-5-chloro-6-methyl-4-pyrimidinamine	158–160, nmr	6010
2-Bromomethyl-2-chloro-4-pyrimidinamine	210	1249

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Bromomethyl-6-chloro-4(3*H*)-pyrimidinone	194–195	1802
5-Bromomethyl-4,6-dichloro-2-chloromethylpyrimidine	127–129	1875
5-Bromomethyl-2,4-dichloro-6-ethylthiopyrimidine	liquid, anal, nmr	347
5-Bromomethyl-4,6-dichloro-2-methylpyrimidine	109–110	1801
5-Bromomethyl-2,6-diethyl-4-pyrimidinamine	153	1718,1719
5-Bromomethyl-2,6-diethyl-4(3*H*)-pyrimidinone	172	1718,1902
4-Bromomethyl-2,6-dimethoxy-5-nitropyrimidine	liquid, anal	1903
2-Bromomethyl-4,6-dimethoxypyrimidine	38–39, nmr	3974
5-Bromomethyl-4-dimethylamino-2-methylpyrimidine	HBr: 221	1904
5-Bromomethyl-4,6-dimethyl-2-methylthiopyrimidine	70–71, nmr	6133
6-Bromomethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	143–144	1905,1906
4-Bromomethyl-2,6-dimethylpyrimidine 1,3-dioxide	150	763
2-α-Bromo-α-methylethyl-4-chloropyrimidine	80–82/1.5	1907
2-α-Bromo-α-methylethyl-4-fluoropyrimidine	65–68/22	1907
2-α-Bromo-α-methylethyl-4-methoxypyrimidine	72–74/0.3	1908
4-Bromomethyl-2-ethyl-6-methylpyrimidine 1,3-dioxide	124	763
5-Bromomethyl-2-ethyl-4-pyrimidinamine	HBr: 175 to 185	1065,1394,1532,1909,1910
2-α-Bromo-α-methylethylpyrimidine	85–86	1908
5-Bromomethyl-2-ethylthio-4-pyrimidinamine	HBr: 283–285	1249
5-Bromo-4-methyl-2-methylaminopyrimidine	87–88; pic: 153	1465,1911
5-Bromo-1-methyl-4-methylamino-2(1*H*)-pyrimidinone	175–176; HBr: > 256	971
5-Bromo-1-methyl-2-methylimino-1,2-dihydro-4-pyrimidinamine	HCl: 209–210; HI: 249–250	1742
5-Bromo-1-methyl-4-methylimino-1,4-dihydro-2-pyrimidinamine	HCl: 280–281; HI: 255	1742
5-Bromo-1-methyl-2-methylimino-1,2-dihydropyrimidine	HI: 238; pic: 210–212	1741
5-Bromomethyl-2-methyl-4-methylaminopyrimidine	HBr: 215–220	1912

4-Bromomethyl-5-methyl-2-methylthiopyrimidine	71–72, nmr	6133
5-Bromomethyl-2-methyl-4-methylthiopyrimidine	HBr: 275	1904
5-Bromomethyl-4-methyl-2-methylthiopyrimidine	54–56, nmr	6133
4-Bromomethyl-5-methylpyrimidine	liquid, M^+, nmr	6133
5-Bromomethyl-4-methylpyrimidine	liquid, M^+, nmr	6133
4-Bromomethyl-2-methylthiopyrimidine	liquid, M^+, nmr	6133
5-Bromo-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	250–252 or 255–260 (246?)	961,1834,1913–1915
3-Bromo-6-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	170–171	1916
5-Bromomethyl-2-methyl-4-pyrimidinamine	HBr: 192 to 213	750,987,1388,1917–1924
5-Bromomethyl-6-methyl-4-pyrimidinamine	—	750
5-Bromomethyl-2-methylpyrimidine	HBr: > 200	1904
5-Bromomethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 350	1925,1926
5-Bromomethyl-2-methyl-4(3*H*)-pyrimidinethione	HBr: > 260	1904
5-Bromomethyl-2-methyl-4(3*H*)-pyrimidinone	198–200	1419
5-Bromo-1-methyl-6-methylthio-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	28–30	909
5-Bromomethyl-2-methylthio-4-pyrimidinamine	HBr: > 280 or 300	1326,1331,1927
5-Bromo-4-methyl-6-methylthio-2-pyrimidinamine	138–140 or 140–142	958,1811
5-Bromo-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	130	1895
5-Bromo-3-methyl-6-methylthio-4(3*H*)-pyrimidinone	120–122	909
5-Bromo-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	209–210	1820
5-Bromomethyl-2-propyl-4-pyrimidinamine	HBr: 244–245	1394
5-Bromo-4-methyl-6-propyl-2-pyrimidinamine	95–97	958
5-Bromo-3-methyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	97–99	1883
5-Bromo-4-methyl-6-prop-2′-ynyl-2(1*H*)-pyrimidinone	197–200, ir, nmr	276
4-Bromo-6-methyl-2-pyrimidinamine	152–154	1241,1928
5-Bromomethyl-4-pyrimidinamine	—	1909
5-Bromo-2-methyl-4-pyrimidinamine	137–138 or 138–140; H_2O: 103–104; HCl: 263–264	1479,1929

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Bromo-4-methyl-2-pyrimidinamine	192–195	1811,1930,1931
5-Bromo-6-methyl-4-pyrimidinamine	194 or 197	1818,1932
2-Bromomethylpyrimidine	liquid, anal	1933
4-Bromomethylpyrimidine	anal	1933
5-Bromomethylpyrimidine	HBr: 108–113	1934
5-Bromo-2-methylpyrimidine	83–84	1479,1855,1935
5-Bromo-4-methylpyrimidine	72–73/14, 90/23	1822,3743
5-Bromo-2-methyl-4-pyrimidinecarbonitrile	40, 115–117/13	1479
5-Bromo-4-methyl-2-pyrimidinecarbonitrile	67, nmr	3743
5-Bromo-6-methyl-4-pyrimidinecarbonitrile	84–85, nmr	3743
5-Bromo-2-methyl-4-pyrimidinecarboxamide	157–158	1479
5-Bromo-2-methyl-4-pyrimidinecarboxylic acid	170–172 or 172–173	1479,1936
2-Bromo-5-methyl-4,6-pyrimidinediamine	208–210	972,1884
5-Bromomethyl-2,4-pyrimidinediamine	crude; HBr: > 280	1937,1938
5-Bromo-6-methyl-2,4-pyrimidinediamine	188–189	1939
5-Bromomethyl-2,4(1*H*,3*H*)-pyrimidinedione	> 330	841,1940
5-Bromo-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	266 or 267–272	963,1125,1432,1664,1941
5-Bromo-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	218 or 240, ir	76,1788
5-Bromo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	227 to 241	1432,1531,1941,1942,3904
5-Bromo-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	241 to 250 (270 to 278?)	692,925,961,1808,1829,1833, 1835,1836,1915,1943–1950
6-Bromo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	281–282	1812
5-Bromo-4-methylpyrimidine 1-oxide	133. nmr	3743
5-Bromo-4-methylpyrimidine 3-oxide(?)	106–107, nmr	3743
5-Bromo-2-methyl-4(3*H*)-pyrimidinethione	200–204	1821

5-Bromo-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	H_2O: 105–106	1842
5-Bromo-1-methyl-2(1*H*)-pyrimidinimine	HCl: 261; pic: 184–185	1741
5-Bromo-1-methyl-2(1*H*)-pyrimidinone	236 or 237–239 (210?), ms, nmr; 3-MeBr: 268 or 275; 3-MeCl: 257	1803,1951,1952,3765
5-Bromo-2-methyl-4(3*H*)-pyrimidinone	226 or 231–232	1820,1821
5-Bromo-3-methyl-4(3*H*)-pyrimidinone	153–154 or 158–159	112,1879,1951,1953
5-Bromo-6-methyl-4(3*H*)-pyrimidinone	227–229 or 232–233 (212–214?)	1014,1788,1822
5-Bromo-2-methylsulfonylpyrimidine	132–133	1897
5-Bromo-2-methylsulfonyl-4-pyrimidinecarboxylic acid	192–193	1897,1954
5-Bromo-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	231–232	1871
5-Bromo-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide	244–245	1560
5-Bromo-6-methylthio-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	241	909
5-Bromo-6-methylthio-3-propyl-4(3*H*)-pyrimidinone	120–121	909
5-Bromo-2-methylthiopyrimidine	67–68	1824,1855,1935,1951
5-Bromo-4-methylthiopyrimidine	71–73 or 78	1899,1951
5-Bromo-2-methylthio-4-pyrimidinecarboxylic acid	176–177, nmr; HCl: 135–136; K: anal	502,1564,1935,1955,1956
5-Bromo-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	> 360	1816
5-Bromo-2-methylthio-4(3*H*)-pyrimidinone	219 to 255	1824,1895,1914
5-Bromo-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	256 or 268–272	1835,1914,1957
4-Bromomethyl-2,5,6-trichloropyrimidine	56–57	1958
5-Bromomethyl-2,4,6-trichloropyrimidine	134–135	1801,1958
5-Bromo-2-nitroaminopyrimidine	189	1888
5-Bromo-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	140–143, nmr	3765
5-Bromo-2-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	206–207	1820
4-Bromo-6-propoxy-2-pyrimidinamine	81–82	965
1-β-Bromopropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	98–99, nmr	6579
1-γ-Bromopropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	102–103 or 104–105, nmr	1720,6579

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
3-γ-Bromopropyl-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	73–74	1720
1-γ-Bromopropyl-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	106–110	1959,1960
1-γ-Bromopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	136–138	608,611,1961
3-γ-Bromopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	204–206	1720
1-γ-Bromopropyl-2,4(1*H*,3*H*)-pyrimidinedione	85–87 or 87–96	608,1961
5-Bromo-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	189–190	1883
5-Bromo-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	221–222 or 235–236	126,1962
5-Bromo-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	226–227	825
2-Bromo-5-pyrimidinamine	182–183	1623
4-Bromo-2-pyrimidinamine	> 130	1928
5-Bromo-2-pyrimidinamine	235 to 244	894,1811,1855,1931,1963
5-Bromo-4-pyrimidinamine	208–211	1827,1964,1965
5-Bromo-2-pyrimidinamine 1-oxide	236	1966
2-Bromopyrimidine	53 or 56–57, sp	505,752,1856,1967
5-Bromopyrimidine	73–74 or 75–76	836,1935,1965,1968–1972
5-Bromo-2-pyrimidinecarbaldehyde	dnp: 225–227; tsc: 229–230	1788
5-Bromo-2-pyrimidinecarbonitrile	116–117 or 120–121, nmr	1897,3743
5-Bromo-4-pyrimidinecarbonitrile	35–36, 135/19, ir, nmr	3743
5-Bromo-2-pyrimidinecarboxamide	208–210	729,1897,1973
5-Bromo-2-pyrimidinecarboxylic acid	191 to 198	1897,1935,1974
2-Bromo-4,6-pyrimidinediamine	255	972,1884
5-Bromo-2,4-pyrimidinediamine	217	894,1742
5-Bromo-4,6-pyrimidinediamine	213, xl st	968,1975
5-Bromo-2,4(1*H*,3*H*)-pyrimidinedione	295 to 318	782,925,1265,1798,1837,1858, 1861,1862,1872,1873,1949, 1975–1980

5-Bromo-4,6(1*H*,5*H*)-pyrimidinedione	20(?), 261–263 or 263–264	76,961,1827,1981,1982
6-Bromo-2,4(1*H*,3*H*)-pyrimidinedione	> 260 or > 340, nmr	105,422,1703,1812
5-Bromo-2,4(1*H*,3*H*)-pyrimidinedithione	253–255	1782
5-Bromo-4,6(1*H*,5*H*)-pyrimidinedithione	213	958
5-Bromopyrimidine 1-oxide	161–167, nmr	170,1972,3743
5-Bromo-2(1*H*)-pyrimidinethione	180 or 214–215	1086,1951
5-Bromo-4(3*H*)-pyrimidinethione	185	1951
5-Bromo-2,4,6-pyrimidinetriamine	200–202 or 206–208	837,1230
5-Bromo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	200 or 212–215	954,1842,1983–1985,3932
5-Bromo-2(1*H*)-pyrimidinone	234–235 or 241–243, ms	1827,1855,1986,3765,3829
5-Bromo-4(3*H*)-pyrimidinone	197–200 (252–255?), nmr; pic: 150–151; H_2SO_4: 163–164	170,1262,1820,1827,1971
5-Bromo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	270	1914,1957
5-Bromo-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	244–245, nmr, uv	521,3760
5-Bromo-2,4,6-triethoxypyrimidine	52–54	1788
5-Bromo-2,4,6-trimethoxypyrimidine	144–145	1788
5-Bromo-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione.	126 to 142, nmr, uv	269,1343,1695,1808,1863,1864
5-Bromo-1,2,6-trimethyl-4(1*H*)-pyrimidinimine	HI: anal, nmr, X-ray	7033
5-Bromo-1,4,6-trimethyl-2(1*H*)-pyrimidinimine	HCl: 250; pic: 191–192	1437,1465
5-Bromo-2-trimethylsiloxypyrimidine	62/0.01	44
5-Bromo-2,4,6-tripropoxypyrimidine	130–140/0.1	1788
5-α-Bromovinyl-2,6-dimethoxypyrimidine	107–108	1880
5-β-Bromovinyl-2,4(1*H*,3*H*)-pyrimidinedione	220	831
5-Bromo-6-vinyl-2,4(1*H*,3*H*)-pyrimidinedione	> 250	1869
5-Carbamoyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	164–166	1987
5-β-Carbamoylethyl-4-chloro-2-methylpyrimidine	134, then 180–196	1988
1-β-Carbamoylethyl-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	230	1804

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-α-Carbamoylethyl-2-methyl-4-pyrimidinamine	231	1209
5-β-Carbamoylethyl-2-methyl-4-pyrimidinamine	195–200	1388
2-β-Carbamoylethylpyrimidine	135–136	1225
4-β-Carbamoylethylpyrimidine	117–118	1225
1-β-Carbamoylethyl-2,4(1*H*,3*H*)-pyrimidinedione	222	1989
5-Carbamoylmethyl-6-chloro-2-ethylthio-4-pyrimidinamine	167	985
5-Carbamoylmethyl-4-chloro-2-methylpyrimidine	228–230	1990
5-Carbamoylmethyl-4-chloro-2-methylthiopyrimidine	168–170	1302
2-Carbamoylmethyl-4,6-diethoxypyrimidine	139–140	1991
2-Carbamoylmethyl-4,5-dimethylpyrimidine	182	1992
2-Carbamoylmethyl-4,6-dimethylpyrimidine	129–130	1993
5-Carbomoylmethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	255–256	1994
5-Carbamoylmethyl-2,6-dimethyl-4(3*H*)-pyrimidinone	258–260	1990
5-Carbamoylmethyl-2-ethyl-4-pyrimidinamine	233–234 or 236	1388,1394
2-Carbamoylmethyl-6-ethyl-4(3*H*)-pyrimidinone	196–197	1749
5-Carbamoylmethyl-2-ethylthio-4(3*H*)-pyrimidinone	214	976
5-Carbamoylmethyl-2-ethylthio-4-thioureidopyrimidine	230	1995
2-Carbamoylmethyl-5-hydroxymethyl-4-pyrimidinamine	230–231	974
1-Carbamoylmethyl-4-imino-1,4-dihydro-5-pyrimidinamine	HI: anal	1996
2-Carbamoylmethyl-6-isopropyl-4(3*H*)-pyrimidinone	164–165	1997
5-Carbamoylmethyl-4-methoxy-2-methylpyrimidine	201	750
5-Carbamoylmethyl-2-methyl-4-methylaminopyrimidine	156	1388
3-Carbamoylmethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	241	911
5-Carbamoylmethyl-2-methyl-4-pyrimidinamine	228 or 250	750,1388,1918,1924,1998
5-Carbamoylmethyl-6-methyl-4-pyrimidinamine	223	750

5-Carbamoylmethyl-2-methylpyrimidine	183–185 or 186	1413,1990
2-Carbamoylmethyl-4-methyl-5-pyrimidinecarboxylic acid	222–224	783
2-Carbamoylmethyl-6-methyl-4(3*H*)-pyrimidinone	235 to 252	1997,1999–2001
5-Carbamoylmethyl-2-methyl-4(3*H*)-pyrimidinone	242	1418,1419
5-Carbamoylmethyl-2-propyl-4-pyrimidinamine	215	1394
2-Carbamoylmethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	248–250	1749
5-Carbamoylmethylpyrimidine	170 or 172–173	1990,2002
1-Carbamoylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	288–290 or 298	1807,2003,2004
2-Carbamoylmethyl-4,6(1*H*,5*H*)-pyrimidinedione	-	1981,1991
5-Carbamoylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	-	1685
6-Carbamoylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	282 to 295	1232,1805,2005,2006
5-Carbamoylmethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	258–261	990
5-Carbamoylmethyl-4(3*H*)-pyrimidinone	257–259	1990
5-Carbamoylmethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	272	990
5-Carbamoylmethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	269–270 or 277–280	1990,2007
5-β-Carboxyethyl-4-dimethylamino-2-methylpyrimidine	HCl: 190–192	1988
5-β-Carboxyethyl-2,6-dimethyl-4(3*H*)-pyrimidinone	K: > 300	2008
1-α-Carboxyethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	202; cyclohexylamine salt: 246–250	552,1166
1-β-Carboxyethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	218–219	2009
3-α-Carboxyethyl-5-ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	231–232	2010
1-β-Carboxyethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	185	2011
5-β-Carboxyethyl-5-β-hydroxyethyl-2-methylthio-4(3*H*)-pyrimidinone	174–175	911
6-β-Carboxyethyl-5-β-hydroxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	245	911
1-β-Carboxyethyl-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	180–181	1804
5-β-Carboxyethyl-2-methyl-4-pyrimidinamine	233; HCl: > 300	1209,1988
1-β-Carboxyethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	170–175 or 180	983,2011
5-β-Carboxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	302–304	2012

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-β-Carboxyethyl-6-methyl-4(3*H*)-pyrimidinone	193–194	2013
5-β-Carboxyethyl-2-methyl-4(3*H*)-pyrimidinone	210–211	1988
6-β-Carboxyethyl-2-methylthio-4(3*H*)-pyrimidinone	174–175	911
5-β-Carboxyethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	305–306	613
1-β-Carboxyethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	268–270	2014
2-β-Carboxyethylpyrimidine	179–180	1225
4-β-Carboxyethylpyrimidine	198–199	1225
1-β-Carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	174 to 189	110,697,983,1807,1989
3-β-Carboxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	169–174	697
1-β-Carboxyethyl-2(1*H*)-pyrimidinimine	betaine: 171–172	2015
5-β-Carboxyethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	235–236	980
1-β-Carboxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	192–193	2016
6-β-Carboxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	272–274 or 282–284	825,911
2-Carboxymethyl-4,6-bisethylthiopyrimidine	Na: 165–166	1749
5-Carboxymethyl-4-chloro-2-ethylthio-6-methylpyrimidine	118–119	2017
5-Carboxymethyl-4-chloro-2-ethylthiopyrimidine	132	976
2-Carboxymethyl-4-chloro-6-methoxypyrimidine	Na: > 305	1749
2-Carboxymethyl-4-chloro-6-methylpyrimidine	Na: > 310	1749
5-Carboxymethyl-4-chloro-2-methylpyrimidine	122–125	1990
2-Carboxymethyl-4-chloropyrimidine	Na: > 300	1749
5-Carboxymethyl-2-cyanoamino-4(3*H*)-pyrimidinone	247–250	2018
5-Carboxymethyl-2,4-dichloro-6-methylpyrimidine	156–157	1415
2-Carboxymethyl-4,6-dichloropyrimidine	Na: > 320	1997
2-Carboxymethyl-4,6-dimethoxypyrimidine	Na: 241–243	1749
5-Carboxymethyl-4,6-dimethoxypyrimidine	177–179	1788

2-Carboxymethyl-4,5-dimethylpyrimidine	258	1992
1-Carboxymethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	200–201	657
5-Carboxymethyl-2,6-dimethyl-4(3*H*)-pyrimidinone	232–233 or 240–241	1529,2019,2020
1-Carboxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	233	1166
1-Carboxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	275	1166
1-Carboxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	250–275	1166
5-Carboxymethyl-4-ethoxy-2-methylthiopyrimidine	144–146	2021
6-Carboxymethyl-2-ethoxy-4(3*H*)-pyrimidinone	—	1876
2-Carboxymethyl-4-ethylsulfonylpyrimidine	Na: > 295	1749
5-Carboxymethyl-2-ethylthio-6-methyl-4-pyrimidinamine	221	985
5-Carboxymethyl-2-ethylthio-6-methyl-4(3*H*)-pyrimidinone	255	985
2-Carboxymethyl-4-ethylthiopyrimidine	Na: > 290	1749
1-Carboxymethyl-2-ethylthio-4-(1*H*)-pyrimidinone	208–209	1806
5-Carboxymethyl-2-ethylthio-4(3*H*)-pyrimidinone	184	976
6-Carboxymethyl-2-ethylthio-4(3*H*)-pyrimidinone	155	1806
5-Carboxymethyl-2-ethylthio-4-thioureidopyrimidine	220–221	1995
2-Carboxymethyl-4-fluoropyrimidine	Na: > 310	1749
1-Carboxymethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	273–276 or 276–277; NH_4: 225–227	2022,2023
2-Carboxymethyl-5-hydroxymethyl-4-pyrimidinamine	167, then 193	974
1-Carboxymethyl-4-imino-1,4-dihydro-5-pyrimidinamine	300	1996
2-Carboxymethyl-4-iodopyrimidine	Na: > 300	1749
1-Carboxymethyl-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	248–249	2022
2-Carboxymethyl-4-isopropylpyrimidine	Na: 220–222	1997
2-Carboxymethyl-4-methoxypyrimidine	Na: > 300	1997
1-Carboxymethyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	110	1166
1-Carboxymethyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	277–279	1199
5-Carboxymethyl-2-methyl-4-methylaminopyrimidine	217	1388,1406

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Carboxymethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	270–272	985
4-Carboxymethyl-6-methyl-5-nitro-2(1*H*)-pyrimidinone	anal	1157
2-Carboxymethyl-4-methylpyrimidine	Na: 257–261	1997
5-Carboxymethyl-2-methylpyrimidine	183–185	1990
5-Carboxymethyl-4-methylpyrimidine	189–190	575
2-Carboxymethyl-6-methyl-4-pyrimidinecarboxylic acid	218–220	1416
5-Carboxymethyl-6-methyl-2,4-pyrimidinediamine	279–280	985
1-Carboxymethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	239–240	1806
1-Carboxymethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	260–261 or 270	994,2024
1-Carboxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	263–264	2025
3-Carboxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	244–246 or 254–255, uv	911,3751
5-Carboxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	340, xl st	985,2026
4-Carboxymethyl-6-methyl-2(1*H*)-pyrimidinethione	Na: > 300	743
5-Carboxymethyl-2-methyl-4(3*H*)-pyrimidinone	245–246	1418
5-Carboxymethyl-6-methyl-4(3*H*)-pyrimidinone	147–149	1415
1-Carboxymethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	246–247	2027
1-Carboxymethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	263–265	2025
5-Carboxymethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	295	750
1-Carboxymethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	264–265	1806
6-Carboxymethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	153	2028
1-Carboxymethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	210–212, ir, uv	3963
5-Carboxymethyl-2-propyl-4(3*H*)-pyrimidinone	180	2029
2-Carboxymethylpyrimidine	Na: 220	1997
5-Carboxymethylpyrimidine	165–168 or 172–173	1990,2002
1-Carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	285 to 296	994,2003,2028,2030

3-Carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	220–222 or 222–224, uv	995,3751
5-Carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	311 to 320	976,1685,2007,2031
6-Carboxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	322 to 340	1806,2031–2034
1-Carboxymethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	160–170, ir, uv	3963
5-Carboxymethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	250	990
2-Carboxymethyl-4-(3*H*)-pyrimidinone	Na: > 300	1749
5-Carboxymethyl-4-(3*H*)-pyrimidinone	209–210	1990
5-Carboxymethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	> 230	990
1-Carboxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	265	2035
5-Carboxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	260 or 275–279	996,2007
6-Carboxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	2036
5-Carboxymethyl-2,4,6-trimethoxypyrimidine	161–163	1788
5-β-Carboxyvinyl-2,4-dimethoxy-6-methylpyrimidine	208–209, ir, nmr	3894
2-β-Carboxyvinyl-4,6-dimethylpyrimidine	194–197	2037
5-β-Carboxyvinyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	281–282, ir, nmr	95
2-β-Carboxyvinyl-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	257–258	2038
5-β-Carboxyvinyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	284–286	2039
5-β-Carboxyvinyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	265–270	257,2012,2040
5-β-Carboxyvinyl-2-methyl-4(3*H*)-pyrimidinone	243, nmr	3888
2-β-Carboxyvinylpyrimidine	235–237	1225
4-β-Carboxyvinylpyrimidine	265–267	1225
5-β-Carboxyvinylpyrimidine	crude	1028
5-β-Carboxyvinyl-2,4(1*H*,3*H*)-pyrimidinedione	283–284 or 285	2039,2041,2042
5-β-Carboxyvinyl-4(3*H*)-pyrimidinone	240, nmr	3888
5-β-Carboxyvinyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	263-266, ir, nmr	3894
4-Chloroamino-2-ethylsulfonyl-5-methylpyrimidine (?)	125–126	2043
4-Chloroamino-2-ethylsulfonyl-6-methylpyrimidine (?)	133–134	2043
4-Chloro-2,6-bis-α-chloroethyl-5-chloromethylpyrimidine (?)	–	1718

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Chloro-2,6-bisdimethylaminopyrimidine	45–46 or 52	1742,2044,2045
5-Chloro-4,6-bisdimethylaminopyrimidine	61	1791
5-Chloro-2,6-bisdimethylamino-4-pyrimidinecarbonitrile	80–82	2046
4-Chloro-2,6-bisethylaminopyrimidine	64–66 or 66–68	2047,2048
5-Chloro-4,6-bisethylthiopyrimidine	58–59	958
4-Chloro-2,6-bisisopropylaminopyrimidine	78–83	2048
4-Chloro-2,6-bismethoxymethyl-5-methylpyrimidine	83/0.025	1761
4-Chloro-2,6-bismethoxymethylpyrimidine	77–78/0.15	1763
2-Chloro-4,6-bismethylaminopyrimidine	258–259	1742
4-Chloro-2,6-bismethylaminopyrimidine	133 or 134	1742,1765,1771
2-Chloro-4,6-bismethylthiopyrimidine	67	1780
5-Chloro-4,6-bismethylthiopyrimidine	118–120	958
4-Chloro-2,6-bistrimethylsiloxypyrimidine	crude	2049
5-Chloro-2,4-bistrimethylsiloxypyrimidine	92/1, nmr	3822
5-β-Chlorocarbonylethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	613
6-Chloro-5-β-chloroethyl-2-γ-chloropropyl-4(3*H*)-pyrimidinone	122–123	2050
2-Chloro-5-β-chloroethyl-4-methylaminopyrimidine	132–133	2051
4-Chloro-5-β-chloroethyl-6-methyl-2-pyrimidinamine	165–190	986
4-Chloro-5-β-chloroethyl-2-methylpyrimidine	93–94/2.5; HCl: 123–125	2052
4-Chloro-5-β-chloroethyl-6-methylpyrimidine	100–110/2	2053
4-Chloro-5-β-chloroethyl-2-pyrimidinamine	170–171	2052
4-Chloro-5-β-chloroethylpyrimidine	92–94/2; HCl: 140	2051
5-Chloro-6-chloromethyl-3-isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	—	2054
5-Chloro-2-chloromethyl-6-methyl-2-pyrimidinamine	150–152, nmr	6010
4-Chloro-2-chloromethyl-6-methylpyrimidine	29; HCl: 126	2055,2056

4-Chloro-5-chloromethyl-2-methylpyrimidine	54	680
6-Chloro-2-chloromethyl-5-methyl-4(3*H*)-pyrimidinone	209–212	759
2-Chloro-5-chloromethyl-4-pyrimidinamine	HCl: 215	1249
6-Chloro-2-chloromethyl-4-pyrimidinamine	112	1335
4-Chloro-2-chloromethylpyrimidine	95/10	2057–2059
5-Chloro-6-chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione	270–275	2060
6-Chloro-2-chloromethyl-4(3*H*)-pyrimidinone	173	1802
6-Chloro-2-γ-chloropropyl-5-methyl-4(3*H*)-pyrimidinone	180–230	759
5-Chloro-1-(3′-chloroprop-2′-ynyl)-2(1*H*)-pyrimidinone	135, ms, nmr	6171
2-Chloro-5-α-chlorovinyl-4-pyrimidinamine	159–160	1259
4-Chloro-5-α-chlorovinyl-2-pyrimidinamine	178–179	1259
4-Chloro-5-β-cyanoethyl-6-methyl-2-pyrimidinamine	215–216	613
4-Chloro-2-cyanomethyl-6-isopropylpyrimidine	liquid, anal	1997
4-Chloro-2-cyanomethyl-6-methylpyrimidine	78–79	1997
2-Chloro-6-cyano-4-pyrimidinecarboxamide	185–186	1029
4-Chloro-2,6-diethoxy-5-ethylpyrimidine	159/26	1219
5-Chloro-2,4-diethoxy-6-fluoropyrimidine	71–73	1727
4-Chloro-2,6-diethoxypyrimidine	248/760	1771
4-Chloro-1,3-diethyl-6-imino-1,6-dihydro-2(3*H*)-pyrimidinone	105–106	1066
4-Chloro-2,6-diethyl-5-methylpyrimidine		1719,2061
6-Chloro-1,3-diethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	25	855
6-Chloro-2,5-diethyl-4-pyrimidinamine	213–214	1065
2-Chloro-4,6-diethylpyrimidine	66/0.3	2062
5-Chloro-2,4-diethylpyrimidine	liquid, anal, ms, nmr	3822
6-Chloro-1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	67–68 or 86–88	855,1813
5-Chloro-2,4-difluoro-6-methoxypyrimidine	crude	2063
5-Chloro-4,6-difluoro-2-methoxypyrimidine	crude	2063
5-Chloro-2,6-difluoro-4-pyrimidinamine	crude	2063

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Chloro-4,6-difluoro-2-pyrimidinamine	crude	2063
4-Chloro-2,6-difluoropyrimidine	—	2064
5-Chloro-2,4-difluoropyrimidine	72–73/90, n_D^{25} 1.4628	1730
4-Chloro-2,6-difluoro-5-pyrimidinecarbonitrile	108–110/40	2063
4-Chloro-2,6-dihydrazinopyrimidine	> 280	2065
6-Chloro-1,3-di-isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	75–78	882
4-Chloro-6-dimethoxymethyl-2-ethylthio-5-fluoropyrimidine	102–103/0.2	2066
4-Chloro-2,6-dimethoxy-5-methylpyrimidine	76–77	1485
5-Chloro-2,4-dimethoxy-6-methylpyrimidine	67–69	1014
5-Chloro-2,4-dimethoxy-6-methylsulfonylpyrimidine	180–182	2067
5-Chloro-2,4-dimethoxy-6-methylthiopyrimidine	92–94	2067
4-Chloro-2,6-dimethoxy-5-nitropyrimidine	67–69	2068
5-Chloro-2,6-dimethoxy-4-pyrimidinamine	163–165	2067
5-Chloro-4,6-dimethoxy-2-pyrimidinamine	176	2069
2-Chloro-4,6-dimethoxypyrimidine	101	1780
4-Chloro-2,6-dimethoxypyrimidine	73–74	1233,1349,1663.1750,2070–2072
4-Chloro-5,6-dimethoxypyrimidine	53–55	1360,2073
5-Chloro-2,4-dimethoxypyrimidine	72–73	1827
4-Chloro-2,6-dimethoxy-5-pyrimidinecarbaldehyde	97, nmr	6076
4-Chloro-2,6-dimethoxy-5-trimethylstannylpyrimidine	57, nmr	6076
2-Chloro-4-dimethylamino-5,6-dimethylpyrimidine	92–93	1848
4-Chloro-2-dimethylamino-5,6-dimethylpyrimidine	40–41	1745
2-Chloro-4-dimethylamino-6-ethylpyrimidine	128/2	1848
4-Chloro-6-dimethylamino-2-formamido-5-pyrimidinecarbaldehyde	190–193	1026
4-Chloro-5-dimethylamino-6-formylimino-3-methyl-3,6-dihydropyrimidine	125	2074

4-Chloro-2-dimethylamino-6-methoxy-5-nitropyrimidine	114–116	1364
4-Chloro-2-dimethylamino-6-methoxypyrimidine	56 or 62	1484,2075
4-Chloro-6-dimethylamino-2-methoxypyrimidine	88–89	1743
4-Chloro-2-dimethylamino-6-methoxy-5-pyrimidinecarbaldehyde	128; oxime: 225	2075
4-Chloro-2-dimethylamino-6-methoxy-5-pyrimidinecarbonitrile oxide	154–155	2075
2-Chloro-4-dimethylamino-6-methylaminopyrimidine	206–207	1742
4-Chloro-2-dimethylamino-6-methylaminopyrimidine	71 or 78, 122–125/1; HCl: 219–221; HI: 218	903,1484,1742,2044
4-Chloro-6-dimethylamino-2-methylaminopyrimidine	181–182	1742
4-Chloro-6-dimethylamino-3-methyl-2-methylimino-2,3-dihydropyrimidine	HCl: 200–201; HI: 195–197	1742
6-Chloro-5-dimethylaminomethyl-2-methyl-4-pyrimidinamine	115–116	1074
2-Chloro-4-dimethylamino-6-methyl-5-nitropyrimidine	97–98	645,1157
2-Chloro-4-dimethylamino-6-methyl-5-pyrimidinamine	63	1157
2-Chloro-4-dimethylamino-5-methylpyrimidine	68–70 or 69–71	1219,2076
2-Chloro-4-dimethylamino-6-methylpyrimidine	87, nmr	397,1848,2077
4-Chloro-2-dimethylamino-6-methylpyrimidine	35–36; pic: 128–129	1241,2078
4-Chloro-6-dimethylamino-2-methyl-5-pyrimidinecarbonitrile	104–105	1387
6-Chloro-1-dimethylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	127–128	2079
4-Chloro-6-dimethylamino-3-methyl-2(3*H*)-pyrimidinimine	HCl: 232–233; HI: 203–204	1742
5-Chloro-2-dimethylamino-6-methyl-4(3*H*)-pyrimidinone	246	1732
4-Chloro-2-dimethylamino-6-methylthiopyrimidine	51–52	1507
6-Chloro-2-dimethylamino-5-nitro-4-pyrimidinamine	132	1484
2-Chloro-4-dimethylamino-5-nitropyrimidine	116–117	1437,1714
4-Chloro-2-dimethylamino-5-nitropyrimidine	140 or 143	1089,1746
4-Chloro-6-dimethylamino-5-nitropyrimidine	104	1157
6-Chloro-2-dimethylamino-5-nitro-4(3*H*)-pyrimidinone	252–253	2080
4-Chloro-6-dimethylamino-2-pyrimidinamine	164–165	1484,1742,2045
6-Chloro-2-dimethylamino-4-pyrimidinamine	142–156; HCl: 226; HI: 251	615,1742,2044,2045,2081

Pyrimidine	m.p. (°C), etc.	Ref.
2-Chloro-4-dimethylaminopyrimidine	81	1848,2082
4-Chloro-2-dimethylaminopyrimidine	38 or 41–42; pic: 144–145	2083,2084
4-Chloro-6-dimethylaminopyrimidine	102–103	968
4-Chloro-6-dimethylamino-5-pyrimidinecarbaldehyde	139–141	852,1027
4-Chloro-2-dimethylamino-5-pyrimidinecarbonitrile	147–149 or 149–150	1020,1078,2085
4-Chloro-6-dimethylamino-5-pyrimidinecarbonitrile	107–108	787
6-Chloro-2-dimethylamino-4(3*H*)-pyrimidinethione	304	1507
5-Chloro-6-dimethylamino-4(3*H*)-pyrimidinone	215	1791
6-Chloro-2-dimethylamino-4(3*H*)-pyrimidinone	217	1073,1484
2-Chloro-6-β-dimethylaminovinyl-4-pyrimidinecarbonitrile	161–163	2086
4-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	150 or 156–158; oxime: 134–135	1987,2087,3739,3770
4-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	171–172	1987
4-Chloro-6-α,β-dimethylhydrazino-5-pyrimidinamine	79–81	1251
5-Chloro-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	181 or 190–192	675,2088
6-Chloro-1,3-dimethyl-5-methylhydrazonomethyl-2,4(1*H*,3*H*)-pyrimidinedione	crude: 170–180	2089
4-Chloro-5,6-dimethyl-2-methylthiopyrimidine	35–36	614,2090
4-Chloro-2,6-dimethyl-5-nitropyrimidine	35, 106–108/12	601,651,1552
6-Chloro-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	65 to 87, ir	1000,1047,1233,1364,3753
5-Chloro-1,3-dimethyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	> 150	2091,2092
4-Chloro-1,3-dimethyl-6-propylimino-1,6-dihydro-2(3*H*)-pyrimidinone	63	1162
2-Chloro-4,6-dimethyl-5-propylpyrimidine	56–58	843
4-Chloro-5,6-dimethyl-2-propylpyrimidine	122–126/22	880
6-Chloro-1,3-dimethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	48–50	855
2-Chloro-4,6-dimethyl-5-prop-1′-ynylpyrimidine	127	843

2-Chloro-4,6-dimethyl-5-prop-2′-ynylpyrimidine	114	843
2-Chloro-5,6-dimethyl-4-pyrimidinamine	182–183	1135,2093
4-Chloro-2,6-dimethyl-5-pyrimidinamine	73 or 80; pic: 169	614,750,1042
4-Chloro-5,6-dimethyl-2-pyrimidinamine	215–216	1135,1149
5-Chloro-2,6-dimethyl-4-pyrimidinamine	164–168	1014,1853,1854,2094,2095
5-Chloro-4,6-dimethyl-2-pyrimidinamine	182–184 or 192–193	1014,2096
6-Chloro-2,5-dimethyl-4-pyrimidinamine	196–197 or 199	1118,1159
2-Chloro-4,5-dimethylpyrimidine	23–26, 88/3	2097
2-Chloro-4,6-dimethylpyrimidine	38–39, 223/760	843,1874,1936,2098–2102
4-Chloro-2,5-dimethylpyrimidine	anal, nmr	2103,2104
4-Chloro-2,6-dimethylpyrimidine	39–40, 82/15, 182/760	727,739,1810,1856,2101, 2104–2107
4-Chloro-5,6-dimethylpyrimidine	48 or 51–52, 206/760	698,1135,2104,2108,2109
5-Chloro-2,4-dimethylpyrimidine	M^+, nmr	2104
5-Chloro-4,6-dimethylpyrimidine	M^+, nmr	2104
6-Chloro-2,5-dimethyl-4-pyrimidinecarboxamide	nmr	2038
2-Chloro-4,6-dimethyl-5-pyrimidinecarboxylic acid	152	1787
5-Chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	150 or 150–152, ir, nmr	323,3757,3773
6-Chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	109–113, ir	644,2110–2113,3753
2-Chloro-4,6-dimethylpyrimidine 1-oxide	97, ir, nmr	5892
4-Chloro-2,6-dimethylpyrimidine 1-oxide	99–101 or 102	739,2107
5-Chloro-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	130–132	953,1842
4-Chloro-1,6-dimethyl-2(1*H*)-pyrimidinimine	HI: 257	2114
6-Chloro-1,2-dimethyl-4(1*H*)-pyrimidinimine	HI: 244–246	1136,2115
6-Chloro-2,3-dimethyl-4(3*H*)-pyrimidinimine	HI: 232–234	1136
2-Chloro-4,6-dimethyl-5-pyrimidinol	H_3PO_4: 169, nmr	1011,1012
5-Chloro-2,6-dimethyl-4(3*H*)-pyrimidinone	191–193 or 199	1854,2107,2116,2117
5-Chloro-4,6-dimethyl-2(1*H*)-pyrimidinone	241–245	2117

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Chloro-2,5-dimethyl-4(3*H*)-pyrimidinone	225–229	759,1159,2118
6-Chloro-1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	122–123 or 189–190	1103, 1134
4-Chloro-2,6-dimethyl-5-vinylpyrimidine	110/3, nmr	3999
5-Chloro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	251 to 296	1174,2119–2121
4-Chloro-2,6-dipropylpyrimidine	122–125/18	880
5-Chloro-2,6-dithioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	190	2046
5-Chloro-1,3-divinyl-2,4(1*H*,3*H*)-pyrimidinedione	77–79, ir, nmr	516
4-Chloro-6-ethoxycarbonylmethyl-2-pyrimidinamine	83–84	2122
4-Chloro-5-ethoxy-6-ethoxymethyl-2-ethylthiopyrimidine	165–166/10	2123
4-Chloro-5-ethoxy-6-ethoxymethyl-2-pyrimidinamine	79–80	1149
2-Chloro-4-ethoxy-5-ethoxymethylpyrimidine	32–33	1699
4-Chloro-5-ethoxy-2-ethylthiopyrimidine	46, 185/25	1188
2-Chloro-4-ethoxy-5-fluoropyrimidine	35–36, 82/3	1260,2124
4-Chloro-2-ethoxy-5-fluoropyrimidine	—	1268
2(4?)-Chloro-4(2?)-ethoxy-6-methylaminopyrimidine	134	1771
4-Chloro-6-ethoxy-2-methylaminopyrimidine	95	1771
4-Chloro-5-ethoxymethyl-2-methylpyrimidine	72–73/0.5	1920
4-Chloro-6-ethoxy-5-methyl-2-methylthiopyrimidine	85	1046
4-Chloro-6-ethoxy-2-methyl-5-nitropyrimidine	81	2125
5-Chloro-4-ethoxy-6-methyl-2-pyrimidinamine	123–125	1811
5-Chloro-6-ethoxy-2-methyl-4-pyrimidinamine	161	1002
6-Chloro-2-ethoxymethyl-4-pyrimidinamine	—	1763
2-Chloro-4-ethoxy-6-methylpyrimidine	39–41, 80–81/4; HCl: 148–149	2106,2126,2127
4-Chloro-2-ethoxymethylpyrimidine	HCl: 118	2058
4-Chloro-5-ethoxy-2-methylpyrimidine	46–47	1821

2(4?)-Chloro-4(2?)-ethoxy-6-methyl-5-pyrimidinecarbonitrile	134–136	2128
4-Chloro-6-ethoxy-2-methyl-5-pyrimidinecarbonitrile	63–64	1010
5-Chloro-1-ethoxymethyl-2(1*H*)-pyrimidinone	89, ms, nmr	44
5-Chloro-6-ethoxy-2-methyl-4-pyrimidinone	216–218	1002
4-Chloro-5-ethoxy-2-methylthiopyrimidine	75	2129
4-Chloro-6-ethoxy-5-nitropyrimidine	42, 134–136/16	2125
2-Chloro-6-ethoxy-4-pyrimidinamine	132–133 or 133–134	615,965,966
4-Chloro-5-ethoxy-2-pyrimidinamine	166–167	1149
4-Chloro-6-ethoxy-2-pyrimidinamine	87	2130
4-Chloro-6-ethoxy-5-pyrimidinamine	54–55	1017,1365
6-Chloro-2-ethoxy-4-pyrimidinamine	128–129	615,616,2131,2132
6-Chloro-5-ethoxy-4-pyrimidinamine	119–120	916
2-Chloro-5-ethoxypyrimidine	70	2133
4-Chloro-6-ethoxypyrimidine	anal	2134
5-Chloro-6-ethoxy-2,4-pyrimidinediamine	132	1002
4-Chloro-2-ethylamino-6-methoxypyrimidine	70–73	2048
4-Chloro-2-ethylamino-6-methylaminopyrimidine	H_2SO_4: 148	1484
4-Chloro-6-ethylamino-2-methylaminopyrimidine	85–88	2048
2-Chloro-4-ethylamino-6-methyl-5-nitropyrimidine	66 or 71–72	1191,2135
4-Chloro-2-ethylamino-6-methylpyrimidine	92–94, nmr	1241,2136
4-Chloro-6-ethylamino-2-methylpyrimidine	73–75	2047
4-Chloro-6-ethylamino-5-nitropyrimidine	114	1589
4-Chloro-6-ethylamino-2-pyrimidinamine	152–153 or 154	850,1042,2137
4-Chloro-6-ethylamino-5-pyrimidinamine	148–149	2138
6-Chloro-2-ethylamino-4-pyrimidinamine	113–114	1765
4-Chloro-6-ethylaminopyrimidine	124–126	1094
4-Chloro-6-ethylamino-5-pyrimidinecarbaldehyde	76–77	852
4-Chloro-6-ethylamino-2,5-pyrimidinediamine	208–209	2137

2-Chloro-4-methylthiopyrimidine	66–68, 125–126/15	1765,2288
4-Chloro-2-methylthiopyrimidine	– 2–0; 112/12, 122/18	828,1637,2098
4-Chloro-6-methylthiopyrimidine	50–51 or 52–54	1037,2289
5-Chloro-2-methylthiopyrimidine	55–57	1897
4-Chloro-2-methylthio-5-pyrimidinecarbonitrile	61–63 or 67–68	1020,2290
6-Chloro-2-methylthio-4-pyrimidinecarboxamide	204–205	1030
5-Chloro-2-methylthio-4-pyrimidinecarboxylic acid	169–170 or 181–184	1564,1955,2291
5-Chloro-2-methylthio-4,6-pyrimidinediamine	192	951
5-Chloro-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	255–259	2292
5-Chloro-2-methylthio-4(3*H*)-pyrimidinedione	259–260	1914,2243
6-Chloro-2-methylthio-4(3*H*)-pyrimidinone	208 or 215–216	958,1568,2187
5-Chloro-2-methylthio-4-vinylpyrimidine	65/0.03, ms, nmr	3826
5-Chloro-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	262–263 or 265–270	1174,1914
4-Chloro-6-methyl-2-vinylpyrimidine	67/5	2293
4-Chloro-6-nitroamino-2-pyrimidinamine	228	1364,2294 (cf. 2218)
5-Chloro-2-nitroaminopyrimidine	173	1888
6-Chloro-5-nitro-2-propyl-4-pyrimidinamine	143	1612
2-Chloro-5-nitro-4-pyrimidinamine	217 to 221	2295–2299
6-Chloro-5-nitro-4-pyrimidinamine	152 to 157	228,2246,2300–2303
2-Chloro-5-nitropyrimidine	106–111	582,704,1012,2304–2306
4-Chloro-6-nitropyrimidine	73–76, nmr, uv	6014
2-Chloro-5-nitro-4,6-pyrimidinediamine	> 300	1581,2307
6-Chloro-5-nitro-2,4-pyrimidinediamine	220–222	2294,2308
6-Chloro-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	218 or 220–222 (244–246?)	624,1233,2309
6-Chloro-5-nitro-4(3*H*)-pyrimidinone	198–199	607,1832
4-Chloro-6-nitrosopyrimidine	crude	6014
2-Chloro-5-nitro-4-thiocyanatopyrimidine	141	1187
4-Chloro-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	210–215	2310

4-Chloro-5-ethyl-6-methyl-2-pyrimidinamine	156–157	1215,1217
6-Chloro-5-ethyl-2-methyl-4-pyrimidinamine	229–231	1159
4-Chloro-2-ethyl-6-methylpyrimidine	93/20	880,2107
4-Chloro-6-ethyl-2-methylpyrimidine	70–75/2	121
5-β-Chloroethyl-4-methylpyrimidine	32, 112/8	1211
1-β-Chloroethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	88–89	1722
1-β-Chloroethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	203–205	1323
3-β-Chloroethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	93–94	2143
3-β-Chloroethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	196–197	1721
5-β-Chloroethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	265–270	986
6-Chloro-1-ethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	80–85	882
4-Chloro-2-ethyl-6-methylpyrimidine 1-oxide	76	2107
4-Chloro-1-ethyl-6-methyl-2(1*H*)-pyrimidinimine	HI: 234–235	2144
5-β-Chloroethyl-6-methyl-4(3*H*)-pyrimidinone	HCl: 168–169	2145
5-Chloro-2-ethyl-6-methyl-4(3*H*)-pyrimidinone	168	2107
6-Chloro-2-ethyl-5-methyl-4(3*H*)-pyrimidinone	197–201 or 203–204	759,2050,2146
6-Chloro-5-ethyl-2-methyl-4(3*H*)-pyrimidinone	198–205 or 209	759,1159,2118
6-Chloro-5-ethyl-2-methylthio-4-pyrimidinamine	HCl: 215–216	1220
4-Chloro-6-ethyl-2-methylthiopyrimidine	136–137/14	2147
5-α-Chloroethyl-2-methylthiopyrimidine	90–91/0.1, ms, nmr	3829
5-Chloro-3-ethyl-6-methylthio-4(3*H*)-pyrimidinone	126–128	909
5-β-Chloroethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	205–206	1319
2-Chloro-6-ethyl-5-nitro-4-pyrimidinamine	140–141	2148
6-Chloro-5-ethyl-2-propyl-4(3*H*)-pyrimidinone	156–157	2050
2-Chloro-5-ethyl-4-pyrimidinamine	146–147	1219
4-Chloro-5-ethyl-2-pyrimidinamine	178–179	1219
4-Chloro-6-ethyl-2-pyrimidinamine	120 to 130	1118,1239–1241
6-Chloro-2-ethyl-4-pyrimidinamine	133	1244

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Chloro-4-ethylpyrimidine	89–91/7	1240
2-Chloro-5-ethylpyrimidine	90–101/11, ms, nmr	513
4-Chloro-2-ethylpyrimidine	– 5, 75/18	2149
4-Chloro-6-ethylpyrimidine	193/760	2150
2-Chloro-5-ethyl-4,6-pyrimidinediamine	238–240	972,1884
2-Chloro-6-ethyl-4,5-pyrimidinediamine	203	2148
6-Chloro-2-ethyl-4,5-pyrimidinediamine	262	2139
6-Chloro-5-ethyl-2,4-pyrimidinediamine	183	1228
6-Chloro-5-ethyl-2,4-pyrimidinediamine 3-oxide	222	3864
1-β-Chloroethyl-2,4(1*H*,3*H*)-pyrimidinedione	162 to 167	1322,1323,1722,1756
5-Chloro-2-ethyl-4,6(1*H*,5*H*)-pyrimidinedione	318–319	1875
5-Chloro-6-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	260–261	2151
6-Chloro-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	165	876
6-Chloro-3-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	215–217 or 220	876,2152
6-Chloro-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	213–215	1219,3760
5-Chloro-1-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	146–151	789
6-Chloro-2-ethyl-4(3*H*)-pyrimidinone	161 or 162	1802,2149
4-Chloro-2-ethylsulfonyl-5,6-dimethylpyrimidine	78	1155
4-Chloro-2-ethylsulfonyl-5-fluoropyrimidine	96	2153
2-Chloro-5-ethylsulfonylmethyl-4-isopropylaminopyrimidine	187, nmr	347
4-Chloro-5-ethylsulfonylmethyl-2-isopropylaminopyrimidine	135, nmr	347
4-Chloro-2-ethylsulfonyl-6-methyl-5-propylpyrimidine	99–100	1453,1454
4-Chloro-2-ethylsulfonyl-5-methylpyrimidine	65–66 or 67–68	1543,1748,2154–2156
4-Chloro-2-ethylsulfonyl-6-methylpyrimidine	189–191/3.5	2043
4-Chloro-2-ethylsulfonylpyrimidine	57–58	1676,1748,1751

4-Chloro-2-ethylthio-5,6-dimethylpyrimidine	142–144/10	2157
2-Chloro-2-ethylthio-5-ethylthiomethyl-6-methylpyrimidine	112–114/0.004, nmr	347
2-Chloro-4-ethylthio-5-ethylthiomethylpyrimidine	liquid, anal, nmr	347
2-Chloro-4-ethylthio-5-fluoropyrimidine	47, 90/0.5, nmr	270,1267
4-Chloro-2-ethylthio-5-fluoropyrimidine	100–101 or 108/12, 122–124/14, 235/760, nmr	270,2153,2158–2160
4-Chloro-2-ethylthio-5-iodopyrimidine	67 or 69, nmr	270,1234
4-Chloro-6-ethylthio-2-methoxycarbonylmethylpyrimidine	142–144/2	1749
4-Chloro-2-ethylthio-5-methoxypyrimidine	71	926
2-Chloro-5-ethylthiomethyl-4-isopropylamino-6-methylpyrimidine	90–91, nmr	347
4-Chloro-5-ethylthiomethyl-2-isopropylamino-6-methylpyrimidine	liquid, anal, nmr	347
2-Chloro-5-ethylthiomethyl-4-isopropylaminopyrimidine	111, nmr	347
2-Chloro-5-ethylthiomethyl-4-methoxypyrimidine	liquid, anal, nmr	347
4-Chloro-2-ethylthio-6-methyl-5-propylpyrimidine	140–142/4, 165–166/11	1453,1455
2-Chloro-5-ethylthiomethyl-4-pyrimidinamine	116, nmr	347
5-Chloro-4-ethylthio-6-methyl-2-pyrimidinamine	125–127	1811
2-Chloro-4-ethylthio-6-methylpyrimidine	96–97/3	2126
4-Chloro-2-ethylthio-5-methylpyrimidine	136–137/12, 146–147/17	967,2162
4-Chloro-2-ethylthio-6-methylpyrimidine	87/3, 89–90/0.5, 142/15	1547,2043,2126,2163
5-Chloro-2-ethylthio-6-methyl-4(3*H*)-pyrimidinone	185 or 188–190	1914,1957
2-Chloro-4-ethylthio-5-pyrimidinamine	94	633
4-Chloro-6-ethylthio-2-pyrimidinamine	109–110	958
6-Chloro-2-ethylthio-4-pyrimidinamine	78–79	2164
4-Chloro-2-ethylthiopyrimidine	131/18, 135/24, n_D^{20} 1.5808	719,828,967,1676
6-Chloro-2-ethylthio-4-pyrimidinecarbaldehyde	138–139/10	1599
4-Chloro-2-ethylthio-5-pyrimidinecarbonitrile	35–36, 163/13	1249
4-Chloro-2-ethylthio-5-pyrimidinecarbonyl chloride	38–40	1253

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Chloro-2-ethylthio-5-pyrimidinecarboxamide	134	1253
5-Chloro-2-ethylthio-4(3*H*)-pyrimidinone	196–199	2165
5-Chloro-4-ethynyl-2-methylsulfonylpyrimidine	123, ms, nmr	220
6-Chloro-5-ethynyl-2,4(1*H*,3*H*)-pyrimidinedione	> 300	786
4-Chloro-5-fluoro-6-fluoromethyl-2-methylthiopyrimidine	125–128/16	2160
2-Chloro-5-fluoro-4-hydroxyaminopyrimidine	165	1265
2-Chloro-5-fluoro-4-isopropylaminopyrimidine	60–61	2166
2-Chloro-5-fluoro-4-methoxypyrimidine	30, 67/5, nmr	270,2124
4-Chloro-5-fluoro-2-methoxypyrimidine	86–87/21	1264
4-Chloro-2-fluoromethyl-6-methylpyrimidine	114/22	2167
4-Chloro-5-fluoro-6-methyl-2-methylthiopyrimidine	73	2160
4-Chloro-6-fluoromethyl-2-methylthiopyrimidine	67–70	2167
2-Chloro-6-fluoromethyl-4-pyrimidinamine	201–203	2167
4-Chloro-6-fluoromethyl-2-pyrimidinamine	162	2167
6-Chloro-2-fluoromethyl-4-pyrimidinamine	180–181	2167
6-Chloro-5-fluoro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	215–217	138,2141
6-Chloro-2-fluoromethyl-4(3*H*)-pyrimidinone	192–193	1802
4-Chloro-5-fluoro-2-methylsulfonylpyrimidine	103	2153
4-Chloro-5-fluoro-2-methylthiopyrimidine	108–112/15, 221/760	2153,2160
2-Chloro-5-fluoro-4-propoxypyrimidine	85–86/5	2124
2-Chloro-5-fluoro-4-pyrimidinamine	190 to 197	621,1260,1264,1265, 1268,1269
4-Chloro-5-fluoro-2-pyrimidinamine	110	1264
2-Chloro-5-fluoro-4-pyrimidinamine 3-oxide	208–210	1265
2-Chloro-5-fluoropyrimidine	46/10, nmr	270,3765

6-Chloro-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	232	138,2141
2-Chloro-5-fluoro-4(3*H*)-pyrimidinone	170–171 or 176–177, then 228–243	473,1260,2169
4-Chloro-5-fluoro-2(1*H*)-pyrimidinone	173–176	1267
4-Chloro-5-formamido-2,6-dimethylpyrimidine	158–159	614
4-Chloro-5-formamido-6-methylpyrimidine	90	1552
6-Chloro-5-formamido-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	225–226	619,2170
4-Chloro-5-formamido-6-methylthiopyrimidine	163–164	2171
6-Chloro-5-formamido-4-pyrimidinamine	254	1202
2-Chloro-5-formamidopyrimidine	120–122	1623
4-Chloro-6-formamidopyrimidine	143–145	2172
2-Chloro-4-β-formylhydrazino-6-methyl-5-nitropyrimidine	crude	801
2-Chloro-4-β-formylhydrazino-5-nitropyrimidine	130–131	803
4-Chloro-6-β-formylhydrazino-5-pyrimidinamine	crude	2173
4-Chloro-2-guanidino-6-methylaminopyrimidine	HCl: 260–264, nmr	2174
4-Chloro-6-guanidino-2-pyrimidinamine	220, nmr	2174
4-Chloro-6-guanidino-5-pyrimidinamine	HCl: 230, ms	2174
6-Chloro-2-guanidino-4-pyrimidinamine	HCl: 241–245	2174
2-Chloro-4-guanidinopyrimidine	crude(?), 160–165, nmr	306
2-Chloro-4-hydrazino-5-methoxypyrimidine	148–150	1343
4-Chloro-4-hydrazino-5-methylaminopyrimidine	159	632
2-Chloro-4-hydrazino-6-methyl-5-pyrimidinamine	crude	803
2-Chloro-4-hydrazino-6-methylpyrimidine	> 320	1752
4-Chloro-6-hydrazino-2-methylpyrimidine	170–172	900
4-Chloro-6-hydrazino-2-methylthiopyrimidine	157	2065
4-Chloro-6-hydrazino-2-propylpyrimidine	90–92	900
2-Chloro-4-hydrazino-5-pyrimidinamine	172	803
4-Chloro-6-hydrazino-2-pyrimidinamine	196–197	2065

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Chloro-6-hydrazino-5-pyrimidinamine	184	1777
2-Chloro-4-hydrazinopyrimidine	290–291	2147
4-Chloro-6-hydrazinopyrimidine	164–165 or 177	1827,2175
5-Chloro-2-hydrazinopyrimidine	181–182	1888
5-Chloro-4-hydrazinopyrimidine	190–192	1827
4-Chloro-6-hydrazino-2,5-pyrimidinediamine	> 260	620
4-Chloro-6-hydroxyamino-2-methylpyrimidine	170–173	6014
4-Chloro-6-hydroxyaminopyrimidine	162–165 or 172–174, nmr	1012,6014,6052
4-Chloro-5-α-hydroxyethyl-2,6-dimethoxypyrimidine	78, nmr	6076
2-Chloro-5-β-hydroxyethyl-4-methoxypyrimidine	109–110, ir, nmr	6873
4-Chloro-5-β-hydroxyethyl-6-methyl-2-pyrimidinamine	189–192	986
4-Chloro-5-hydroxymethyl-2,6-dimethoxypyrimidine	96, nmr	6076
2-Chloro-5-α-hydroxy-α-methylethylpyrimidine	anal, ms, nmr	381
2-Chloro-5-hydroxymethyl-6-methyl-4-pyrimidinamine	179	750
4-Chloro-5-hydroxymethyl-6-methyl-2-pyrimidinamine	pic: 283	750
4-Chloro-5-hydroxymethyl-2-methylpyrimidine	82–83	1904
2-Chloro-5-hydroxymethyl-4-pyrimidinamine	206	1249
5-Chloro-2-hydroxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	> 360	1958
6-Chloro-3-hydroxy-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	215–220	1018
2-Chloro-5-hydroxy-6-methyl-4(3*H*)-pyrimidinone	> 300	2136
5-Chloro-4-(3′-hydroxyprop-1′-ynyl)-2-methylthiopyrimidine	114–116, ms, nmr	220
6-Chloro-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	300	749
4-Chloro-6-imino-1,3-dimethyl-1,6-dihydro-2(3*H*)-pyrimidinone	150	1162
4-Chloro-6-imino-1-methyl-1,6-dihydro-2-pyrimidinamine	192	1520
4-Chloro-6-imino-3-methyl-3,6-dihydro-2-pyrimidinamine	HCl: 272–273; HI: 268–270	1742

5-Chloro-4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine	HI: 268; CF_3CO_2H: 267–268	2176
5-Chloro-4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine 3-oxide	235–236; CF_3CO_2H: 184–185	2176
4-Chloro-5-iodo-2,6-dimethoxypyrimidine	127, nmr	6076
4-Chloro-5-iodo-2,6-dimethylpyrimidine	92–94	2177
6-Chloro-5-iodo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	170–171	1812
4-Chloro-5-iodo-2-ethylthiopyrimidine	69	1234
4-Chloro-5-iodo-2-isopropyl-6-methylpyrimidine	118/3	1857
5-Chloro-4-iodo-2-isopropyl-6-methylpyrimidine	83–85	1890
4-Chloro-5-iodo-6-methoxy-2-methylpyrimidine	82–83, nmr	499
2-Chloro-4-iodo-6-methoxypyrimidine	109–111, ir, nmr	6873
5-Chloro-2-iodomethyl-6-methyl-4-pyrimidinamine	174–175, nmr	3748
4-Chloro-5-iodo-6-methyl-2-methylthiopyrimidine	93–94, nmr	499
2(4?)-Chloro-4(2?)-iodo-6-methylpyrimidine	161	2178
4-Chloro-5-iodo-2-methylpyrimidine	77, nmr	499
4-Chloro-5-iodo-6-methylpyrimidine	117–118	2177
6-Chloro-5-iodo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	247–248	1812
6-Chloro-2-iodomethyl-4(3*H*)-pyrimidinone	205–207	1802
6-Chloro-5-iodo-2-methyl-4(3*H*)-pyrimidinone	251–252, ir, nmr	499
5-Chloro-4-iodo-2-methylsulfonylpyrimidine	136–138, ms, nmr	220
4-Chloro-5-iodo-2-methylthiopyrimidine	63–64, nmr	499
5-Chloro-4-iodo-2-methylthiopyrimidine	106, ms, nmr	220
4-Chloro-5-iodo-2-pyrimidinamine	anal	1348
2-Chloro-5-iodopyrimidine	129–130	270,2179
4-Chloro-5-iodopyrimidine	61–62 or 63–65, nmr	499,2180
6-Chloro-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	266–267	1812
5-Chloro-4-iodo-2(1*H*)-pyrimidinone	crude, ms, nmr	220

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Chloro-4-iodo-2-trimethylsiloxypyrimidine	crude, ms, nmr	220
6-Chloro-5-isocyanato-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	145–146	2181
2-Chloro-4-isopropoxy-6-methylpyrimidine	79/3 or 95/2, 110–112/4 HCl: 150–160	2106,2126,2127
2-Chloro-6-isopropoxy-4-pyrimidinamine	119–120	965,966
4-Chloro-6-isopropoxy-2-pyrimidinamine	85–86	2182
6-Chloro-2-isopropoxy-4-pyrimidinamine	134–135	615
6-Chloro-5-isopropoxy-4-pyrimidinamine	139–141	916
4-Chloro-2-isopropylamino-6-methoxypyrimidine	—	2048
4-Chloro-2-isopropylamino-6-methylpyrimidine	HCl: 100–102	1241
4-Chloro-6-isopropylamino-5-nitropyrimidine	73–75	1589
4-Chloro-6-isopropylamino-2-pyrimidinamine	—	2185
4-Chloro-6-isopropylamino-5-pyrimidinamine	180–182 or 182–183	2183,2184
6-Chloro-5-isopropyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	52–53	855
4-Chloro-6-isopropylimino-1,3-dimethyl-1,6-dihydro-2(3*H*)-pyrimidinone	52	1162
4-Chloro-6-isopropyl-2-methoxycarbonylmethylpyrimidine	110–112/1	1997
4-Chloro-6-isopropyl-2-(*C*-methoxyformimidoyl)methylpyrimidine	HCl: 106–108	1997
4-Chloro-2-isopropyl-6-methoxypyrimidine	59–61/0.6	1908
4-Chloro-2-isopropyl-6-methylpyrimidine	91–92/10	671
5-Chloro-3-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1892
4-Chloro-2-isopropyl-6-methylpyrimidine 1-oxide	94–95	2107
4-Chloro-6-isopropyl-2-methyl-5-pyrimidinol	99–102, nmr	3908
5-Chloro-2-isopropyl-6-methyl-4(3*H*)-pyrimidinone	160	2107
4-Chloro-6-isopropyl-2-pyrimidinamine	99–102	1356
4-Chloro-2-isopropylpyrimidine	39–41/1	1907

5-Chloro-2-isopropyl-4,6(1*H*,5*H*)-pyrimidinedione	> 365	1875
5-Chloro-6-isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	260	2151
6-Chloro-5-isopropyl-4(3*H*)-pyrimidinone	174–175	2186
2-Chloro-4-isopropylthio-6-methylpyrimidine	77–79/3	2126
4-Chloro-2-isopropylthio-6-methylpyrimidine	102–104/0.5	2126
5-Chloro-2-isopropylthio-6-methyl-4(3*H*)-pyrimidinone	162–163	1914
6-Chloro-2-isopropylthio-4-pyrimidinamine	98	2187
6-Chloro-2-isopropylthio-4(3*H*)-pyrimidinone	159	1357
2-Chloro-4-isothiocyanatopyrimidine	—	2188
4-Chloro-2-methoxycarbonylmethyl-6-methylpyrimidine	crude, 105–107/1.5	1749
4-Chloro-6-methoxycarbonylmethyl-2-pyrimidinamine	103–104 or 104–106	670,2122
4-Chloro-2-methoxycarbonylmethylpyrimidine	86–88/0.4	1749
6-Chloro-3-methoxycarbonylmethyl-4(3*H*)-pyrimidinone	HBr: anal	2189
2-Chloro-4-methoxy-5,6-dimethylpyrimidine	65–66	1155
4-Chloro-2-methoxy-5,6-dimethylpyrimidine	35–36, nmr	158
4-Chloro-6-methoxy-2,5-dimethylpyrimidine	70/4	2190
4-Chloro-5-β-methoxyethyl-6-methyl-2-pyrimidinamine	134–135	1149
6-Chloro-5-β-methoxyethyl-4-pyrimidinamine	113–114	2191
4-Chloro-2-(*C*-methoxyformimidoyl)methyl-6-methylpyrimidine	HCl: 105–106	1997
4-Chloro-6-methoxy-2-methoxycarbonylmethylpyrimidine	116–118/1.5	1997
4-Chloro-5-methoxy-6-methoxymethyl-2-methylpyrimidine	70–72/0.1	1761
4-Chloro-6-methoxy-5-methoxymethyl-2-methylpyrimidine	51–53	1801
4-Chloro-5-methoxy-6-methoxymethyl-2-methylthiopyrimidine	44–45	2192
4-Chloro-5-methoxy-6-methoxymethyl-2-pyrimidinamine	99–100	1149
4-Chloro-5-methoxy-2-methoxymethylpyrimidine	73–74	1761
4-Chloro-5-methoxy-6-methoxymethylpyrimidine	115–116/11	1761,2192
4-Chloro-6-methoxy-2-methylaminopyrimidine	153	1484
4-Chloro-6-methoxymethyl-2,5-dimethylpyrimidine	56–57/0.2	1761

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Chloro-2-methoxymethyl-5-methyl-4-pyrimidinamine	150–151	1761
2-Chloro-4-methoxymethyl-6-methylpyrimidine	19–20, 125/15	2193
4-Chloro-2-methoxymethyl-5-methylpyrimidine	59/0.025	1761
4-Chloro-2-methoxymethyl-6-methylpyrimidine	73/0.6, 115/15, nmr	121,1763
4-Chloro-6-methoxymethyl-2-methylpyrimidine	90–100/11, 105–106/16, nmr	1763
4-Chloro-6-methoxymethyl-5-methylpyrimidine	36–37	1761
4-Chloro-5-methoxy-6-methyl-2-methylthiopyrimidine	58–59	2192
2-Chloro-4-methoxy-6-methyl-5-nitropyrimidine	60–63	1362,2194
4-Chloro-6-methoxy-2-methyl-5-nitropyrimidine	51–52	651
4-Chloro-5-methoxymethyl-2-propylpyrimidine	—	2195
2-Chloro-4-methoxy-6-methyl-5-pyrimidinamine	71–75 or 72–77	1362,2194
2-Chloro-6-methoxy-5-methyl-4-pyrimidinamine	168–169	965,966
4-Chloro-5-methoxy-6-methyl-2-pyrimidinamine	124–125	1361,1362
4-Chloro-6-methoxymethyl-2-pyrimidinamine	131–132	1149
4-Chloro-6-methoxy-2-methyl-5-pyrimidinamine	60–61	651
4-Chloro-6-methoxy-5-methyl-2-pyrimidinamine	187–189	965
5-Chloro-4-methoxy-6-methyl-2-pyrimidinamine	138–141 or 142–144	1014,1811
6-Chloro-2-methoxymethyl-4-pyrimidinamine	102	2196
2-Chloro-4-methoxy-6-methylpyrimidine	32–35, 100/14, 112/26; HCl: 164	2106,2126,2127,2197
4-Chloro-2-methoxy-6-methylpyrimidine	71–73, nmr	158
4-Chloro-5-methoxy-2-methylpyrimidine	84–86 or 98–99	2198,2199
4-Chloro-5-methoxy-6-methylpyrimidine	55–56/7	1362,2200
4-Chloro-6-methoxymethylpyrimidine	90–93/12	1763
4-Chloro-6-methoxy-2-methylpyrimidine	77–78/8	2201

4-Chloro-6-methoxy-2-methyl-5-pyrimidinecarbonitrile	87	1010
5-Chloro-2-methoxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	300	1761
2-Chloro-4-methoxy-6-methyl-5-pyrimidinol	149–150	751
5-Chloro-2-methoxymethyl-4(3*H*)-pyrimidinone	153	1761
4-Chloro-5-methoxy-2-methylsulfonylpyrimidine	148	2114
4-Chloro-6-methoxy-2-methylsulfonylpyrimidine	90–91	2202
4-Chloro-5-methoxy-2-methylthiopyrimidine	72 to 82	718,2198,2203,2204
4-Chloro-6-methoxy-2-methylthiopyrimidine	39–40	2202
4-Chloro-6-methoxy-2-nitroaminopyrimidine	120–122	1364
4-Chloro-6-methoxy-5-nitro-2-pyrimidinamine	177–179	1364
4-Chloro-6-methoxy-5-nitropyrimidine	65–66	1038,2205
4-Chloro-5-methoxy-2-propylthiopyrimidine	119/0.4	926
2-Chloro-5-methoxy-4-pyrimidinamine	181–182 or 189–190	1343,2198
2-Chloro-6-methoxy-4-pyrimidinamine	184–185 or 187–188 (234–238?)	615,965,966,1369,2206
4-Chloro-5-methoxy-2-pyrimidinamine	146–148	1007
4-Chloro-6-methoxy-2-pyrimidinamine	164 to 174	965,1241,1663,2072,2130,2207
4-Chloro-6-methoxy-5-pyrimidinamine	62–64 or 79–80	1037,2205,2208
5-Chloro-4-methoxy-2-pyrimidinamine	118–120	2209
6-Chloro-2-methoxy-4-pyrimidinamine	127–130	615,616,2164
6-Chloro-5-methoxy-4-pyrimidinamine	171 to 181	1360,1370,2210
2-Chloro-4-methoxypyrimidine	55	696,2211
2-Chloro-5-methoxypyrimidine	51 or 75–77	1343,2212,2213
4-Chloro-5-methoxypyrimidine	60–71, ir, nmr, uv	170,1343,2198,2214
4-Chloro-6-methoxypyrimidine	31–32, 80/18	968,1666
5-Chloro-2-methoxypyrimidine	51–52, ms	1897,2215,3765
5-Chloro-4-methoxypyrimidine	39–40, 77–78/17, nmr	3743
2-Chloro-4-methoxy-5-pyrimidinecarbaldehyde	94–95, ir, nmr	6873
5-Chloro-4-methoxy-2-pyrimidinecarbonitrile	45–46, nmr	5743

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Chloro-6-methoxy-5-pyrimidinecarboxamide	145	1787
4-Chloro-6-methoxy-5-pyrimidinecarboxylic acid	140–141 or 145	1787,1788
5-Chloro-2-methoxy-4-pyrimidinecarboxylic acid	170–172	1897
5-Chloro-4-methoxypyrimidine 1-oxide	165, nmr	3743
5-Chloro-6-methoxy-4(3*H*)-pyrimidinone	244–245	1900
2-Chloro-4-methoxy-5-trimethylsilylpyrimidine	oil, anal, ir, nmr	474,6071,6873
2-Chloro-6-methylamino-5-*N*-methylformamido-4(3*H*)-pyrimidinone	271–272	1776
4-Chloro-5-methylamino-6-α-methylhydrazinopyrimidine	119–121	632
4-Chloro-5-methylamino-6-methylthiopyrimidine	48–50	1017
4-Chloro-6-methylamino-2-methylthiopyrimidine	130–131	1765
2-Chloro-4-methylamino-5-nitropyrimidine	80 to 91	1379,1586,2216
4-Chloro-2-methylamino-5-nitropyrimidine	172–173 (122?)	1586,2216
4-Chloro-6-methylamino-5-nitropyrimidine	147–148 or 150–151	1379,1381,1382
2-Chloro-4-methylamino-5-pyrimidinamine	145–146	2216
4-Chloro-6-methylamino-2-pyrimidinamine	161 to 164	850,1742,1765,2182,2217
4-Chloro-6-methylamino-5-pyrimidinamine	162 or 166–167	1381,1648,1777
6-Chloro-5-methylamino-4-pyrimidinamine	138–140	2219
2-Chloro-4-methylaminopyrimidine	128–129	1520
4-Chloro-2-methylaminopyrimidine	123–124	1520,2084
4-Chloro-6-methylaminopyrimidine	137–138	1383,1765
5-Chloro-2-methylaminopyrimidine	122–124; pic: 174–175	923,1616
4-Chloro-6-methylamino-5-pyrimidinecarbaldehyde	158–159	1027
6-Chloro-5-methylamino-4(3*H*)-pyrimidinethione	215–217	2220
6-Chloro-2-methylamino-4(3*H*)-pyrimidinone	265	1484
6-Chloro-5-methylamino-4(3*H*)-pyrimidinone	HCl: 247–248	632

2-Chloromethyl-4,6-diethoxypyrimidine	81–85/0.1	1786
5-Chloromethyl-2,6-dimethyl-4-pyrimidinamine	HCl: 253	1119
2-Chloromethyl-4,6-dimethylpyrimidine	33 or 65–66	763,2221,2222
4-Chloromethyl-2,6-dimethylpyrimidine	94/15, nmr	121
5-Chloromethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	147–148 or 148–149	760,1114
5-Chloromethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	238–240	1864
2-Chloromethyl-4,6-dimethylpyrimidine 1-oxide	116–118	763
4-Chloro-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	crude, 183	2223,2224
4-Chloro-6-methyl-2,5-dipropylpyrimidine	131–137/10	880
2-Chloromethyl-4-ethyl-6-methoxypyrimidine	76–78/2, nmr	121
5-Chloromethyl-2-ethyl-4-pyrimidinamine	HCl: 176–178	2225
5-Chloromethyl-2-ethylthio-4-pyrimidinamine	HCl: 202–204	1249
6-Chloromethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	240–241	2158
4-Chloro-6-α-methylhydrazino-2-pyrimidinamine	196–198	1203
4-Chloro-6-α-methylhydrazino-5-pyrimidinamine	203–204	1777
2-Chloromethyl-5-iodo-6-methyl-4-pyrimidinamine	125–128, nmr	6010
4-Chloromethyl-2-isopropyl-6-methoxypyrimidine	101–102/23	2226
4-Chloromethyl-2-isopropyl-6-methylpyrimidine	118–120/20	2222
5-Chloromethyl-3-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	—	1916
5-Chloromethyl-2-methoxymethyl-4-pyrimidinamine	HCl: 201–202	1762
5-Chloromethyl-2-methoxy-4-pyrimidinamine	HCl: anal	2227
2-Chloromethyl-4-methoxypyrimidine	69–70/2	2226
2-Chloro-4-methyl-6-methylamino-5-nitropyrimidine	102–104 or 110–111	1401,1405,2228
4-Chloro-2-methyl-6-methylamino-5-nitropyrimidine	138–139	1400
2-Chloro-4-methyl-6-methylamino-5-pyrimidinamine	133	1405
4-Chloro-2-methyl-6-methylamino-5-pyrimidinamine	127–128	1648
2-Chloro-5-methyl-4-methylaminopyrimidine	180–182	2076
4-Chloro-5-methyl-2-methylaminopyrimidine	131	2229

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Chloro-6-methyl-2-methylaminopyrimidine	135 or 136	1241,2229
4-Chloro-3-methyl-6-methylimino-3,6-dihydro-2-pyrimidinamine	HCl: 239; HI: 222	1742
6-Chloro-1-methyl-2-methylimino-1,2-dihydro-4-pyrimidinamine	HCl: 272–273; HI: 245–247	1742
4-Chloro-3-methyl-6-methylimino-3,6-dihydropyrimidine	HCl: 238; HI: 223	2115
2-Chloromethyl-6-methyl-4-pyrimidinamine	138–140, nmr	6010
5-Chloromethyl-2-methyl-4-pyrimidinamine	163; HCl: 214–215	1388,1670,2230–2232
4-Chloromethyl-6-methylpyrimidine	60–61/2; pic: 115	764,2226
5-Chloromethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	239–241	760
5-Chloromethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	300 to 338 (225?)	347,698,2233,2234
6-Chloromethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	244–245	766,767
2-Chloromethyl-6-methyl-4(3*H*)-pyrimidinone	164–165	2235
2-Chloro-4-methyl-6-methylthio-5-nitropyrimidine	—	1157
2-Chloro-4-methyl-6-methylthio-5-pyrimidinamine	110	1157
5-Chloromethyl-2-methylthio-4-pyrimidinamine	HCl: > 300	2236
5-Chloro-4-methyl-5-methylthio-2-pyrimidinamine	137–139	1811
6-Chloro-5-methyl-2-methylthio-4-pyrimidinamine	157; HCl: 242	1046,1220
2-Chloro-4-methyl-6-methylthiopyrimidine	107–110/5, 166–168/70	1765,2126
4-Chloro-2-methyl-6-methylthiopyrimidine	126–128/19	2237
4-Chloro-6-methyl-2-methylthiopyrimidine	20–23 or 38, 97–99/2, 132/15, 147/32	2126,2238–2242
5-Chloro-4-methyl-2-methylthiopyrimidine	150/8, ms, nmr	3826
4-Chloro-2-methyl-6-methylthio-5-pyrimidinecarbonitrile	112, ir, nmr, uv	3882
5-Chloro-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	269–270	1940,2243
6-Chloromethyl-2-methylthio-4(3*H*)-pyrimidinone	180–181 or 183–185 (235?), ir, nmr	2244 (cf. 2243), 3907

6-Chloro-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	111–112	619
2-Chloro-6-methyl-4-nitroaminopyrimidine	—	1932
2-Chloro-6-methyl-5-nitro-4-pyrimidinamine	171 or 172–173	1427,1581,1932,2245
4-Chloro-6-methyl-5-nitro-2-pyrimidinamine	160 or 225	1157,2246,2247
6-Chloro-2-methyl-5-nitro-4-pyrimidinamine	183	2246
4-Chloro-2-methyl-6-nitropyrimidine	108–109, nmr, uv	6014
6-Chloro-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	195–197	619,999,2170,3753
2-Chloro-6-methyl-5-nitro-4(3*H*)-pyrimidinone	HCl: > 200	2135
4-Chloro-2-methyl-6-nitrosopyrimidine	crude	6014
5-Chloro-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	185	1262
2-Chloro-4-methyl-6-propoxypyrimidine	81–83/2, 122–123/13; HCl: 130–132	2126,2127
4-Chloro-6-methyl-2-propylaminopyrimidine	49–50	1241
4-Chloro-6-methyl-5-propyl-2-pyrimidinamine	175–176; HCl: anal	1452,2248
6-Chloro-5-methyl-2-propyl-4-pyrimidinamine	171–172	1456
4-Chloro-2-methyl-6-propylpyrimidine	91–100/16, nmr	122
4-Chloro-6-methyl-2-propylpyrimidine	95–100/3	880
6-Chloro-3-methyl-l-propyl-2,4(1*H*,3*H*)-pyrimidinedione	44–47	882
6-Chloro-2-methyl-5-propyl-4(3*H*)-pyrimidinone	220–221	1159
6-Chloro-5-methyl-2-propyl-4(3*H*)-pyrimidinone	170–171	1456
2-Chloro-4-methyl-6-propylthiopyrimidine	103–105/2	2126
4-Chloro-6-methyl-2-propylthiopyrimidine	106–107/0.5	2126
2-Chloro-4-methyl-5-pyrimidinamine	93–95	1932,1964,2264,2250
2-Chloro-5-methyl-4-pyrimidinamine	—	2251
2-Chloro-6-methyl-4-pyrimidinamine	215–216	1509,1932,2249,2250
4-Chloro-2-methyl-5-pyrimidinamine	—	2250
4-Chloro-5-methyl-2-pyrimidinamine	184–185	614,2250
4-Chloro-6-methyl-2-pyrimidinamine	182–183	682,1509,1510,1932,2043,2249, 2250

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Chloro-6-methyl-5-pyrimidinamine	98–99	1038
5-Chloro-2-methyl-4-pyrimidinamine	145–146	1479
5-Chloro-4-methyl-2-pyrimidinamine	189–191	1931
5-Chloro-6-methyl-4-pyrimidinamine	196–197 or 197–198	1014,1932
6-Chloro-2-methyl-4-pyrimidinamine	189 or 190–191	987,1158,1159,1556,1558,2250, 2252,2253
6-Chloro-5-methyl-4-pyrimidinamine	237–238	614,2093,2254
2-Chloromethylpyrimidine	101–103/26	1933,2226
2-Chloro-4-methylpyrimidine	48, 65/0.01, 101/23	1834,2238,2249,2255–2257,3734
2-Chloro-5-methylpyrimidine	91–92	1485,1879,2062,2258
4-Chloromethylpyrimidine	50–51/6	1933,2226
4-Chloro-2-methylpyrimidine	54 to 60	678,689,2104,2259–2263
4-Chloro-5-methylpyrimidine	25–27, 62–64/7-8	1543,2264
4-Chloro-6-methylpyrimidine	34–35 or 35–36, 59–60/22 or 66/12	1509,1822,2104,2249,2262,2264, 2265
5-Chloro-2-methylpyrimidine	54–55 or 56–57	1479,1933,2104
5-Chloro-4-methylpyrimidine	49–50, 90/19, nmr; pic: 110–111	1933,2104,3743
2-Chloro-6-methyl-4-pyrimidinecarbohydrazide	156–157	2266
2-Chloro-6-methyl-4-pyrimidinecarbonitrile	45–47	1029,2267
4-Chloro-2-methyl-5-pyrimidinecarbonitrile	64–65	1406,1472
4-Chloro-6-methyl-2-pyrimidinecarbonitrile	65	2268
5-Chloro-2-methyl-4-pyrimidinecarbonitrile	100–102/13	1479
5-Chloro-4-methyl-2-pyrimidinecarbonitrile	110/24, nmr	3743
5-Chloro-6-methyl-4-pyrimidinecarbontrile	57–58, ir, nmr	3743
2-Chloro-6-methyl-4-pyrimidinecarboxamide	181–182	1029,2266

4-Chloro-6-methyl-2-pyrimidinecarboxamide	177–178	2268
5-Chloro-2-methyl-4-pyrimidinecarboxamide	165–166	1479
2-Chloro-6-methyl-4-pyrimidinecarboxylic acid	182	2266
5-Chloro-2-methyl-4-pyrimidinecarboxylic acid	160	1479
2-Chloro-5-methyl-4,6-pyrimidinediamine	244–245	972,1884
2-Chloro-6-methyl-4,5-pyrimidinediamine	250 to 265	1428,1581,1932
4-Chloro-6-methyl-2,5-pyrimidinediamine	198	645
5-Chloro-6-methyl-2,4-pyrimidinediamine	175–176	2176
6-Chloro-2-methyl-4,5-pyrimidinediamine	239–243	2269
6-Chloro-5-methyl-2,4-pyrimidinediamine	199–200	1485
5-Chloro-6-methyl-2,4-pyrimidinediamine 1,3-dioxide	237, uv	2176
5-Chloro-6-methyl-2,4-pyrimidinediamine 3-oxide	264–266	3864
5-Chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione	268 to 355	841,1233,1490 (cf. 2243), 1712,1940,2270
5-Chloro-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	260 or > 305, ir	76,1958
5-Chloro-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	325 or 330–332	1940,1944,2043,2060,2163, 2272,2273
6-Chloromethyl-2,4(1*H*,3*H*)-pyrimidinedione	240 to 253 (209), ir, ms, nmr	701,1869,2243,2274,2275,3907
6-Chloro-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	196–197	2113
6-Chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	267 to 282	619,876,1504,2113,2152,2170, 2276–2278,3753
6-Chloro-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	266–267	876,2279,2280
4-Chloro-6-methylpyrimidine 1-oxide	110, ir, nmr	5894
5-Chloro-4-methylpyrimidine 1-oxide	141–142, nmr	3743
5-Chloro-4-methylpyrimidine 3-oxide (?)	70–72, nmr	3743
5-Chloro-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	137	1842
5-Chloro-l-methyl-2(1*H*)-pyrimidinimine	HCl: 276–277; HI: 260; pic: 181–182	923

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Chloro-3-methyl-4(3*H*)-pyrimidinimine	HI: 207	2115
2-Chloro-6-methyl-4(3*H*)-pyrimidinone	123–125; HCl: > 275	2136,2281
4-Chloro-1-methyl-2(1*H*)-pyrimidinone	207–208	696
4-Chloro-5-methyl-2(1*H*)-pyrimidinone	—	1543
5-Chloro-1-methyl-2(1*H*)-pyrimidinone	210, ms, nmr; 3-MeCl: 244	1803,3765
5-Chloro-2-methyl-4(3*H*)-pyrimidinone	227–228	2282,2283
5-Chloro-6-methyl-4(3*H*)-pyrimidinone	209–211	1014
6-Chloro-2-methyl-4(3*H*)-pyrimidinone	231 to 236; HCl: > 240	1159,1262,1817,2050,2142, 2146,2284
6-Chloro-3-methyl-4(3*H*)-pyrimidinone	87–88	968
6-Chloro-5-methyl-4(3*H*)-pyrimidinone	198 to 203	1832,2093,2186
6-Chloro-2-methysulfinyl-4-pyrimidinamine	242–243	903
5-Chloro-2-methylsulfonylpyrimidine	123–125	1897
5-Chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid	178–180	1897
6-Chloro-2-methylthio-5-nitro-4-pyrimidinamine	179–180	2286
5-Chloro-2-methylthio-4-prop-1′-enylpyrimidine	*cis* + *trans*: 100/0.01, ms, nm; *trans*: 77	3826
6-Chloro-2-methylthio-5-propyl-4-pyrimidinamine	204–205	1220
4-Chloro-2-methylthio-6-propylpyrimidine	153–154/17	2147
5-Chloro-6-methylthio-3-propyl-4(3*H*)-pyrimidinone	126–127	909
4-Chloro-5-methylthio-2-pyrimidinamine	199–200	1566,1567
4-Chloro-6-methylthio-2-pyrimidinamine	106–108	958
4-Chloro-6-methylthio-5-pyrimidinamine	93–95 or 95–96	1037,1039,1565
6-Chloro-2-methylthio-4-pyrimidinamine	131 or 132–135	951,1015,1046,1357,1569,1570, 2287

2-Chloro-4-methylthiopyrimidine	66–68, 125–126/15	1765,2288
4-Chloro-2-methylthiopyrimidine	– 2–0; 112/12, 122/18	828,1637,2098
4-Chloro-6-methylthiopyrimidine	50–51 or 52–54	1037,2289
5-Chloro-2-methylthiopyrimidine	55–57	1897
4-Chloro-2-methylthio-5-pyrimidinecarbonitrile	61–63 or 67–68	1020,2290
6-Chloro-2-methylthio-4-pyrimidinecarboxamide	204–205	1030
5-Chloro-2-methylthio-4-pyrimidinecarboxylic acid	169–170 or 181–184	1564,1955,2291
5-Chloro-2-methylthio-4,6-pyrimidinediamine	192	951
5-Chloro-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	255–259	2292
5-Chloro-2-methylthio-4(3*H*)-pyrimidinedione	259–260	1914,2243
6-Chloro-2-methylthio-4(3*H*)-pyrimidinone	208 or 215–216	958,1568,2187
5-Chloro-2-methylthio-4-vinylpyrimidine	65/0.03, ms, nmr	3826
5-Chloro-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	262–263 or 265–270	1174,1914
4-Chloro-6-methyl-2-vinylpyrimidine	67/5	2293
4-Chloro-6-nitroamino-2-pyrimidinamine	228	1364,2294 (cf. 2218)
5-Chloro-2-nitroaminopyrimidine	173	1888
6-Chloro-5-nitro-2-propyl-4-pyrimidinamine	143	1612
2-Chloro-5-nitro-4-pyrimidinamine	217 to 221	2295–2299
6-Chloro-5-nitro-4-pyrimidinamine	152 to 157	228,2246,2300–2303
2-Chloro-5-nitropyrimidine	106–111	582,704,1012,2304–2306
4-Chloro-6-nitropyrimidine	73–76, nmr, uv	6014
2-Chloro-5-nitro-4,6-pyrimidinediamine	> 300	1581,2307
6-Chloro-5-nitro-2,4-pyrimidinediamine	220–222	2294,2308
6-Chloro-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	218 or 220–222 (244–246?)	624,1233,2309
6-Chloro-5-nitro-4(3*H*)-pyrimidinone	198–199	607,1832
4-Chloro-6-nitrosopyrimidine	crude	6014
2-Chloro-5-nitro-4-thiocyanatopyrimidine	141	1187
4-Chloro-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	210–215	2310

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Chloro-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	145–147	733,3765
2-Chloro-6-propoxy-4-pyrimidinamine	104–105	965,966
6-Chloro-2-propoxy-4-pyrimidinamine	114–115	615
4-Chloro-6-propylamino-2-pyrimidinamine	105	850
4-α-Chloropropyl-2,6-diethoxypyrimidine	146/8	788
3-β-Chloropropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	208–209	861
5-β-Chloropropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	233	906
5-β-Chloropropyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	218–220	906
6-Chloro-2-propyl-4-pyrimidinamine	126 or 127–129	1244,1456
2-Chloro-4-propylpyrimidine	35–66/125, ms, nmr	513
5-Chloro-2-propyl-4,6(1*H*,5*H*)-pyrimidinedione	294	1875
5-Chloro-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	242–244	2151
6-Chloro-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	194	876
6-Chloro-2-propyl-4(3*H*)-pyrimidinone	168–169 or 171	1456,1802
4-Chloro-6-propylthio-2-pyrimidinamine	105–106	958
6-Chloro-2-propylthio-4-pyrimidinamine	97	2187
5-Chloro-2-prop-2′-ynyloxypyrimidine	66	883
2-Chloro-4-prop-2′-ynylpyrimidine	liquid, nmr	3943
5-Chloro-1-prop-2′-ynyl-2(1*H*)-pyrimidinone	130	883,3824
5-Chloro-2-prop-2′-ynylsulfinylpyrimidine	92	844
5-Chloro-2-prop-2′-ynylsulfonylpyrimidine	70	844
5-Chloro-2-prop-2′-ynylthiopyrimidine	66	844
2-Chloro-4-pyrimidinamine	200 or 206–207	710,1232,1675,2299,2311,2312
2-Chloro-5-pyrimidinamine	196–198 or 198–199	704,1623
4-Chloro-2-pyrimidinamine	168	1663,1675,2311,2313,2314

4-Chloro-5-pyrimidinamine	110 or 123	1036,1037
5-Chloro-2-pyrimidinamine	232 to 238	623,704,894,1931,1963,1966, 2114,2258,2315–2318
5-Chloro-4-pyrimidinamine	192–194	1827
6-Chloro-4-pyrimidinamine	215 or 218–220	866,968,972,1019,1568,1570, 2172,2319,2320
5-Chloro-2-pyrimidinamine 1-oxide	219	1966
2-Chloropyrimidine	65–66, 91/26	125,752,1834,1936,1967,1968, 2083,2098,2255,2256,2321–2325
4-Chloropyrimidine	HCl: 193–194	708,1968,1970,2321,2325
5-Chloropyrimidine	36–37	1968,1970,2204,2212
2-Chloro-4-pyrimidinecarbonitrile	50–51	1628,1630
2-Chloro-5-pyrimidinecarbonitrile	130–132	1617
4-Chloro-5-pyrimidinecarbonitrile	45–47	1614
5-Chloro-2-pyrimidinecarbonitrile	78 to 86, ir, nmr	1745,1897,3743
5-Chloro-4-pyrimidinecarbonitrile	120/24, ir, nmr	3743
2-Chloro-5-pyrimidinecarbonyl chloride	52, ir, ms. nmr	381
2-Chloro-4-pyrimidinecarboxamide	151–153	1630
5-Chloro-2-pyrimidinecarboxamide	207–208	1897
6-Chloro-4-pyrimidinecarboxamide	162–163	2326
5-Chloro-2-pyrimidinecarboxylic acid	206–207	1897
6-Chloro-4-pyrimidinecarboxylic acid	132–133	2326
2-Chloro-4,5-pyrimidinediamine	220 to 232	1035,2307,2327–2330
2-Chloro-4,6-pyrimidinediamine	273–274	972,1884
4-Chloro-2,5-pyrimidinediamine	> 260	1035
5-Chloro-2,4-pyrimidinediamine	215–216	2331
6-Chloro-2,4-pyrimidinediamine	198 or 200–201, nmr	232,614,1349,1769,2332,2333
6-Chloro-4,5-pyrimidinediamine	247 to 254	1434,2303,2329,2334–2339
5-Chloro-2,4-pyrimidinediamine 3-oxide	222–224	3864

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Chloro-2,4-pyrimidinediamine 3-oxide	190, nmr, uv	2333
2-Chloro-4,6-pyrimidinedicarbonitrile	93–95 or 115–116	1029,1745
5-Chloro-4,6-pyrimidinedicarbonitrile	99–100, ir, nmr	3743
2-Chloro-4,6-pyrimidinedicarboxamide	288–289	1029
5-Chloro-2,4-pyrimidinedicarboxylic acid	168–169	1479
5-Chloro-2,4(1*H*,3*H*)-pyrimidinedione	300 to 325	323,1174,1827,1979,1980,2043, 2165,2243,2340,2341
5-Chloro-4,6(1*H*,5*H*)-pyrimidinedione	> 230 or 260 (300?), ir	76,1827,2342
6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione	294 to 307	105,876,1021,1045,1233,1703, 2049,2277,2309,2343–2346
5-Chloro-4,6(1*H*,5*H*)-pyrimidinedithione	215–217	958
5-Chloropyrimidine 1-oxide	155–156, nmr	3743
5-Chloro-2-pyrimidinesulfonamide	135–140	2347
2-Chloro-5-pyrimidinesulfonyl chloride	66–67	845
5-Chloro-2-pyrimidinesulfonyl chloride	—	2348
5-Chloro-2(1*H*)-pyrimidinethione	221–222	1086,1855,1897,2318,2349
5-Chloro-4(3*H*)-pyrimidinethione	212	1827
6-Chloro-4(3*H*)-pyrimidinethione	crude	1037
2-Chloro-4,5,6-pyrimidinetriamine	250–260	1581
5-Chloro-2,4,6-pyrimidinetriamine	201–203	2176,2350,2351
6-Chloro-2,4,5-pyrimidinetriamine	227	1574,1644,2352
5-Chloro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	280 to 300	1842,1983,1985,2353,2354
2-Chloro-5-pyrimidinol	195–196	774
4-Chloro-2(1*H*)-pyrimidinone	152–154	1676
5-Chloro-2(1*H*)-pyrimidinone	236 or 237–238, ms	1616,1855,1986,3765,3830

5-Chloro-4(3*H*)-pyrimidinone	177–179 or 180–182	1262,1827,2355
6-Chloro-4(3*H*)-pyrimidinone	192–193	968,1568,1666,1832
2-Chloro-4-thiocyanato-5-pyrimidinamine	> 300	633
2-Chloro-4-thiocyanatopyrimidine	125–126	2188,2356
6-Chloro-2-thioureido-4-pyrimidinamine	350, nmr	3861
2-Chloro-4-thioureidopyrimidine	316–318	2188
5-Chloro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	262–266 or 264–270	1914,2357
5-Chloro-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	305–306, nmr	521
5-Chloro-2,4,6-triethoxypyrimidine	44–48 or 57	1788,2046
5-Chloro-2,4,6-trifluoropyrimidine	115/760	1727,1728,2063
4-Chloro-2,5,6-trimethoxypyrimidine	73	2198
5-Chloro-2,4,6-trimethoxypyrimidine	130–132	1788
2-Chloro-4,5,6-trimethylpyrimidine	91	2358
4-Chloro-2,5,6-trimethylpyrimidine	215/760; pic: 132	2104,2359
5-Chloro-2,4,6-trimethylpyrimidine	84/17	2104,2358
5-Chloro-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	151	1695,1863
6-Chloro-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	134–135 or 135–136	1139,2360
5-Chloro-1,2,6-trimethyl-4(1*H*)-pyrimidinimine	HI: anal, nmr	7033
5-Chloro-2-trimethylsiloxypyrimidine	90/8–9	44
5-α-Chlorovinyl-2-dimethylamino-4-methylpyrimidine	100/0.08	790
5-α-Chlorovinyl-4-methyl-2-methylsulfonylpyrimidine	67–68, ir, ms, nmr	3741
5-α-Chlorovinyl-4-methyl-2-methylthiopyrimidine	129–131/0.2, ir, ms, nmr	3741
5-α-Chlorovinyl-2-methylsulfonylpyrimidine	111–114, ir, ms, nmr	3741
5-α-Chlorovinyl-2-methylthiopyrimidine	73–75, ir, ms, nmr	3741
5-α-Chlorovinyl-2,4(1*H*,3*H*)-pyrimidinedione	275–278	2361
5-α-Chlorovinyl-2(1*H*)-pyrimidinone	130–140, ir, ms, nmr	3741
2-Cyanoamino-4,6-diethylpyrimidine	164, ir, ms, nmr	241
2-Cyanoamino-4,6-di-isopropylpyrimidine	94, ir, ms, nmr	388

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Cyanoamino-4,6-dimethylpyrimidine	225 or 224–233, ir, ms, nmr	241,2362–2364
4-Cyanoamino-2,6-dimethylpyrimidine	251–252	683
2-Cyanoamino-5,6-dimethyl-4(3*H*)-pyrimidinone	280	1150
2-Cyanoamino-4,6-dipropylpyrimidine	76, ir, ms, nmr	241
4-Cyanoamino-5-ethoxy-2-ethylthiopyrimidine	—	2365
2-Cyanoamino-4-ethyl-6-methylpyrimidine	138, ir, ms, nmr	161
2-Cyanoamino-5-ethyl-6-methyl-4(3*H*)-pyrimidinone	257	1150
4-Cyanoamino-6-methyl-2-propylpyrimidine	196–198	683
2-Cyanoamino-4-methylpyrimidine	200	2366
2-Cyanoamino-5-methyl-4(3*H*)-pyrimidinone	293	1150
2-Cyanoamino-6-methyl-4(3*H*)-pyrimidinone	285	1150
6-Cyanoamino-2-methylthio-4-pyrimidinamine	250, ms, nmr	497
2-Cyanoamino-4-propylpyrimidine	200	2366
2-Cyanoaminopyrimidine	261	2367
2-Cyanoamino-4,6(1*H*,5*H*)-pyrimidinedione	—	1050
5-Cyanoamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	2368,2369
2-Cyanoamino-4(3*H*)-pyrimidinone	295–300	962
6-β-Cyanoethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	224–228, nmr	148
1-α-Cyanoethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	233–234	2011
1-β-Cyanoethyl-5-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	226–228	1725
3-β-Cyanoethyl-5-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	220–221	2370
1-β-Cyanoethyl-5-methoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	240–242	1725
3-β-Cyanoethyl-5-methoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	242–244	2370
1-β-Cyanoethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	195–196 or 204–206	1725,2011
3-β-Cyanoethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	137–139	2370

3-β-Cyanoethyl-2-methylthio-4(3*H*)-pyrimidinone	100–102	697,1725
1-β-Cyanoethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	192–194	1725
5-β-Cyanoethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	258–260, ir, uv	613
1-β-Cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	219, then 229–230 or 235–237	1725,1726,1989
3-β-Cyanoethyl-2,4(1*H*,3*H*)-pyrimidinedione	140–142	1725,2370
5-β-Cyanoethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	183–186	2371
1-β-Cyanoethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	215–217 or 231–232	1725,2016
3-β-Cyanoethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	152–154	2370
4-Cyanomethyl-2,6-dimethoxy-5-nitropyrimidine	75–77	1903
2-Cyanomethyl-4,6-dimethylpyrimidine	78–79	2222
5-Cyanomethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	116–118	1994
2-Cyanomethyl-4,6-dimethylpyrimidine-1-oxide	65, ir, ms, nmr, uv	6051
4-Cyanomethyl-2-isopropyl-6-methylpyrimidine	120–123/20	2222
5-Cyanomethyl-2-methyl-4-pyrimidinamine	255	2372
2-Cyanomethyl-6-methyl-4(3*H*)-pyrimidinone	320	2373
2-Cyanomethyl-5-nitroso-4,6-pyrimidinediamine	> 300	1768
2-Cyanomethyl-4,6-pyrimidinediamine	241–243	1991
6-Cyanomethyl-2,4-pyrimidinediamine	crude, 295	2006
2-β-Cyanovinyl-4,6-dimethylpyrimidine	*trans*: 75; *cis*: 83	2374,2375
4-β-Cyanovinyl-2,6-dimethylpyrimidine	70–72	2374,2375
5-β-Cyanovinyl-2,4-dimethylpyrimidine	*trans*: 92	2374,2375
5-β-Cyanovinyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	165–166	440
6-β-Cyanovinyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	144, nmr	148
5-β-Cyanovinyl-2-isopropyl-4-methylpyrimidine	87–89 (*E*: 83–85)	2375,2376
1-β-Cyanovinyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	198–200, ir, nmr	5980
2,4-Diacetamido-5-acetoxy-6-methylpyrimidine	228–229	1328
2,5-Diacetamido-6-amino-4(3*H*)-pyrimidinone	> 300, ir, nmr, uv	403
4,6-Diacetamido-2-dimethylaminopyrimidine	205–206	638

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5,6-Diacetamido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	235 (208–209?)	588,589
2,4-Diacetamido-6-isopropoxy-5-nitrosopyrimidine	211–212	638
4,5-Diacetamido-6-methyl-2-methylthiopyrimidine	204–205	664
2,4-Diacetamido-6-methylpyrimidine	231	1328
4,6-Diacetamido-2-methylpyrimidine	H_2O: 232	2377
2,4-Diacetamido-6-methyl-5-pyrimidinol	215–216	1328
4,6-Diacetamido-5-nitroso-2-pyrimidinamine	199–200	638,2378,2379
2,5-Diacetamidopyrimidine	294–295	1623
4,5-Diacetamidopyrimidine	162–164	1379
4,6-Diacetamidopyrimidine	276	612
2,4-Diacetamido-5-pyrimidinecarbonitrile	197–198	1480
5,6-Diacetamido-2,4(1*H*,3*H*)-pyrimidinedione	> 300	588,590,598,599,643, 2380–2382
2,6-Diacetamido-4(3*H*)-pyrimidinone	> 340	709,1331
1,3-Diacetonyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	130 or 132	741,2383
2,5-Diacetyl-4,6-dimethylpyrimidine	110–112/3	792
4,6-Diallyl-2-chloropyrimidine	liquid, nmr	3943
1,3-Diallyl-5,6-difluoro-2,4(1*H*,3*H*)-pyrimidinedione	liquid, M^+, nmr	293
1,3-Diallyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	38	899
1,3-Diallyl-5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	35–38	901
2,4-Diallyloxy-5-fluoro-6-methoxypyrimidine	23–25, nmr	293
2,4-Diallyloxy-5-methylpyrimidine	42–43	868
2,4-Diallyloxy-5-nitropyrimidine	108–110/8	868
2,6-Diallyloxy-4-pyrimidinamine	48–53	2164
2,4-Diallyloxypyrimidine	85/0.5, 122/7	846,868

1,3-Diallyl-2,4(1*H*,3*H*)-pyrimidinedione	anal, uv	846
2,6-Diamino-5-bromomethyl-4(3*H*)-pyrimidinone	HBr(?): > 300	1938
2,6-Diamino-5-bromo-4(3*H*)-pyrimidinone	243 to 265	954,1331,1975,2384–2387
2,6-Diamino-5-bromo-4(3*H*)-pyrimidinone 1-oxide	> 300, ir	27
2,3-Diamino-5-*β*-carboxyethyl-6-methyl-4(3*H*)-pyrimidinone	121–122	32
2,5-Diamino-6-carboxymethyl-4(3*H*)-pyrimidinone	anal	950
2,6-Diamino-5-carboxymethyl-4(3*H*)-pyrimidinone	> 350	992
2,3-Diamino-5-chloro-6-methyl-4(3*H*)-pyrimidinone	302–305	32
2,5-Diamino-6-chloro-3-methyl-4(3*H*)-pyrimidinone	244	999
2,4-Diamino-6-chloro-5-pyrimidinecarbaldehyde	240	2388
4,6-Diamino-2-chloro-5-pyrimidinecarbonitrile	> 360	997
2,6-Diamino-5-chloro-4-pyrimidinecarboxamide	253	2046
2,4-Diamino-6-chloro-5-pyrimidinesulfonic acid	> 330	1101
2,6-Diamino-5-chloro-4(3*H*)-pyrimidinone	305 or 341–342	1002,2350
4,6-Diamino-5-chloro-2(1*H*)-pyrimidinone	> 360; pic: 325	2350
5,6-Diamino-2-cyanoamino-4(3*H*)-pyrimidinone	—	1049
5,6-Diamino-1,3-diethyl-2,4(1*H*,3*H*)-pyrimidinedione	103–104	586,1052,1054
5,6-Diamino-1-dimethylamino-3-*β*-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	anal	585
5,6-Diamino-1-dimethylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	157–159	585
5,6-Diamino-1-dimethylamino-2,4(1*H*,3*H*)-pyrimidinedione	220	585,1072
4,6-Diamino-5-dimethylamino-2(1*H*)-pyrimidinethione	277–279	2389
2,5-Diamino-6-dimethylamino-4(3*H*)-pyrimidinone	230	1051
2,6-Diamino-5-dimethylamino-4(3*H*)-pyrimidinone	HCl: 210–213	1094
4,5-Diamino-6-dimethylamino-2(1*H*)-pyrimidinone	HCl: 211–213 (mono-), 258 (di-)	2390
5,6-Diamino-2-dimethylamino-4(3*H*)-pyrimidinone	HCl: 286–287	1073,1083,1084,1092,2391
5,6-Diamino-1-dimethylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	220	585
5,6-Diamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	208 to 210 (183?), ir; HCl: 310 or > 350	1102,1106,1107,1111,1126,1276, 1286,2392–2394,3721,3753

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5,6-Diamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedithione	anal	660
4,5-Diamino-1,6-dimethyl-2(1*H*)-pyrimidinone	230	1105
4,5-Diamino-1,3-dimethyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	anal	660
5,6-Diamino-1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	230–240 or 240–243	660,1115
2,4-Diamino-6-ethoxy-5-pyrimidinecarbonitrile	220 to 222	948,997,2395
4,6-Diamino-2-ethoxy-5-pyrimidinecarbonitrile	262	997
2,6-Diamino-5-ethoxy-4(3*H*)-pyrimidinone	260–261	2384
2,5-Diamino-6-ethylamino-4(3*H*)-pyrimidinone	236–237	1042
2,6-Diamino-5-ethylamino-4(3*H*)-pyrimidinone	HCl: 190–195	1094
5,6-Diamino-*N*-ethyl-4-pyrimidinecarboxamide	168	2396
2,6-Diamino-5-ethyl-4-pyrimidinecarboxylic acid	252–253	1183
5,6-Diamino-1-ethyl-2,4(1*H*,3*H*)-pyrimidinedione	270	1222
4,6-Diamino-5-ethyl-2(1*H*)-pyrimidinethione	292	2397
2,6-Diamino-5-ethyl-4(3*H*)-pyrimidinone	265–267 or 289–291	1151,2398
5,6-Diamino-2-ethylthio-3-methyl-4(3*H*)-pyrimidinone	H_2O: 97–98	1246
5,6-Diamino-2-ethylthio-4(3*H*)-pyrimidinone	194–195 or 202–203	1248,2399
2,4-Diamino-6-fluoro-5-pyrimidinecarbonitrile	> 300	2063
2,6-Diamino-5-fluoro-4(3*H*)-pyrimidinone	anal, uv	2400
2,6-Diamino-5-formamido-3-methyl-4(3*H*)-pyrimidinone	294–295 or > 350	1282,2391,2401
2,6-Diamino-5-formamido-4(3*H*)-pyrimidinethione	275	1649
4,6-Diamino-5-formamido-2(1*H*)-pyrimidinethione	anal, uv	1298,2402
2,6-Diamino-5-formamido-4(3*H*)-pyrimidinone	> 350	1279,1297,2401
4,6-Diamino-5-formamido-2(1*H*)-pyrimidinone	> 350	1288,1297
2,6-Diamino-5-formylmethyl-4(3*H*)-pyrimidinone	acetal: 156–158	3859
2,3-Diamino-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	109–111	32

5,6-Diamino-1-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	253–254 or 255	1317,1320
2,6-Diamino-5-β-hydroxyethyl-4(3*H*)-pyrimidinone	295–300	986,1314
2,6-Diamino-5-hydroxymethyl-4(3*H*)-pyrimidinone	> 290	1001
5,6-Diamino-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	> 300	1278
2,6-Diamino-5-hydroxy-4(3*H*)-pyrimidinone	> 300	581,1324,1341,2384,2403,6936
4,6-Diamino-5-hydroxy-2(1*H*)-pyrimidinone	> 300	1011
2,6-Diamino-5-iodo-3-methyl-4(3*H*)-pyrimidinone	224–225, ir, nmr	27
2,6-Diamino-5-iodo-4(3*H*)-pyrimidinone	233–236	2384
2,5-Diamino-6-isopropylamino-3-methyl-4(3*H*)-pyrimidinone	230–234	1279
2,5-Diamino-6-isopropylamino-4(3*H*)-pyrimidinone	HCl: > 320	1279
2,6-Diamino-5-isopropylamino-4(3*H*)-pyrimidinone	HCl: > 300	373
2,3-Diamino-6-isopropyl-4(3*H*)-pyrimidinone	165–167	32
2,6-Diamino-5-isothiouronio-4(3*H*)-pyrimidinone	bromide: 273–274; bromide/HBr: > 350	2387
2,6-Diamino-5-γ-mercaptopropyl-4(3*H*)-pyrimidinone	256–258	1359
2,5-Diamino-6-methoxy-3-methyl-4(3*H*)-pyrimidinone	195–200	999
5,6-Diamino-2-methoxy-3-methyl-4(3*H*)-pyrimidinone	160	1287,1288
2,5-Diamino-6-methylamino-4(3*H*)-pyrimidinone	204–210; HCl: 236 or 237–238	1281,1372–1374,2404
2,6-Diamino-5-methylamino-4(3*H*)-pyrimidinone	HCl: 259–262 (mono-), 242–252 (di-)	1094,1378,2405
4,5-Diamino-6-methylamino-2(1*H*)-pyrimidinone	206–210; HCl: 303	2390
5,6-Diamino-2-methylamino-4(3*H*)-pyrimidinone	HCl: 275–277	1083,1373,2404
2,6-Diamino-5-*N*-methylformamido-4(3*H*)-pyrimidinone	> 360	1378,2406
2,5-Diamino-3-methyl-6-methylamino-4(3*H*)-pyrimidinone	HCl: anal	1281
2,6-Diamino-1-methyl-5-methylamino-4(3*H*)-pyrimidinone	HCl: 303–304	1094
2,6-Diamino-3-methyl-5-methylamino-4(3*H*)-pyrimidinone	HCl: > 300	1094
5,6-Diamino-1-methyl-2-methylthio-4(3*H*)-pyrimidinone	crude	1116
5,6-Diamino-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	212	1116,1422,1426
2,6-Diamino-1-methyl-5-nitro-4(1*H*)-pyrimidinone	262	2407

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,6-Diamino-3-methyl-5-nitro-4(3*H*)-pyrimidinone	342–343 or 346–347	999,1076,1371
2,6-Diamino-1-methyl-5-nitroso-4(1*H*)-pyrimidinone	anal	2408, cf. 1083
2,6-Diamino-3-methyl-5-nitroso-4(3*H*)-pyrimidinone	> 320	1076,1084
4,6-Diamino-1-methyl-5-nitroso-2(1*H*)-pyrimidinone	320	2390
2,5-Diamino-6-methyl-4-pyrimidinecarbaldehyde	*p*-$ClC_6H_4NHN{=}$: 228	1157
2,4-Diamino-6-methyl-5-pyrimidinecarbonitrile	285–287 or 292; HCl: > 300	1122,1123,2409
4,6-Diamino-2-methyl-5-pyrimidinecarbonitrile	397–398	1010,2410
2,4-Diamino-6-methyl-5-pyrimidinecarboxamide	240–241	847
2,4-Diamino-*N*-methyl-5-pyrimidinecarboxamide	275, nmr, uv	6454
2,6-Diamino-5-methyl-4-pyrimdinecarboxylic acid	260–261	1183
5,6-Diamino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 330; HCl: > 300	589,1106,1276,1286,1503,2393, 2411,2412
5,6-Diamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	246–248 or > 340; HCl: > 350	587,1287,1288
5,6-Diamino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedithione	> 300	1443
2,4-Diamino-6-methyl-5-pyrimidinesulfonic acid	270–272	1449
2,4-Diamino-6-methyl-5-pyrimidinesulfonyl chloride	228–230	1449
2,5-Diamino-6-methyl-4(3*H*)-pyrimidinethione	210	645
4,5-Diamino-1-methyl-2(1*H*)-pyrimidinethione	266–267	1179
4,5-Diamino-6-methyl-2(1*H*)-pyrimidinethione	H_2O: 250	2413,2414
4,6-Diamino-1-methyl-2(1*H*)-pyrimidinethione	249–251	1575
4,6-Diamino-5-methyl-2(1*H*)-pyrimidinethione	318–320	2415
5,6-Diamino-2-methyl-4(3*H*)-pyrimidinethione	285	593,2413
2,4-Diamino-6-methyl-5-pyrimidinol	154–155; H_2SO_4: 278–280	1328
2,3-Diamino-6-methyl-4(3*H*)-pyrimidinone	282–285 or 283	32,1573
2,5-Diamino-6-methyl-4(3*H*)-pyrimidinone	275 or 281–282; HCl: 255–260	596,639,959,1081,1429,1430

2,6-Diamino-1-methyl-4(1*H*)-pyrimidinone	265–272 or 275–280, ir, ms, nmr, uv; H_2SO_4: anal, xl st	517,2408
2,6-Diamino-3-methyl-4(3*H*)-pyrimidinone	275–277, ir, nmr, uv; H_2O: 245; H_2SO_4: 237	27,1076,1084
2,6-Diamino-5-methyl-4(3*H*)-pyrimidinone	280 to 324	1230,1520,2398
3,5-Diamino-6-methyl-4(3*H*)-pyrimidinone	145–146	2416,2417
4,5-Diamino-1-methyl-2(1*H*)-pyrimidinone	250; pic: 239	1289,1383,1385,1520
4,5-Diamino-3-methyl-2(3*H*)-pyrimidinone	crude	1221
4,5-Diamino-6-methyl-2(1*H*)-pyrimidinone	280	1290,1402,1434,2418
4,6-Diamino-1-methyl-2(1*H*)-pyrimidinone	H_2SO_4: 324–327	2390,2419
5,6-Diamino-1-methyl-4(1*H*)-pyrimidinone	222–223	2420
5,6-Diamino-2-methyl-4(3*H*)-pyrimidinone	255 or > 280; H_2SO_4: 265	1434,1441,1503,1555,2421, 2422,3930
5,6-Diamino-3-methyl-4(3*H*)-pyrimidinone	193 or 195; H_2SO_4: 249	968,1090,1422
5,6-Diamino-2-*methyl*-4(1*H*)-pyrimidinone 3-oxide	245–246	2422
4,6-Diamino-2-methylsulfonly-5-pyrimidinesulfonamide	238–239	1101
4,6-Diamino-2-methylthio-5-pyrimidinecarbaldehyde	228–230	2423
4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide	198–199	1101
5,6-Diamino-2-methylthio-4(3*H*)-pyrimidinethione	239	1116
4,5-Diamino-6-methylthio-2(1*H*)-pyrimidinone	260	2424
5,6-Diamino-2-methylthio-4(3*H*)-pyrimidinone	215–216	970,1559
4,5-Diamino-3-methyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	> 300	1443,2425
5,6-Diamino-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	258–259 or 265–268	1284,1443,1444,2420
5,6-Diamino-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	292–293	1445
5,6-Diamino-3-methyl-1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione	—	897
2,6-Diamino-5-nitro-4-pyrimidinecarboxamide	> 285	1123
2,6-Diamino-5-nitro-4(3*H*)-pyrimidinone	> 360	1082,1371,1579
4,6-Diamino-5-nitro-2(1*H*)-pyrimidinone	> 360	1579,2426
4,6-Diamino-5-nitroso-2(1*H*)-pyrimidinethione	crude	1298,1355,2402

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,6-Diamino-5-nitroso-4(3*H*)-pyrimidinone	> 360	299,1057,1293,1310,2401,2421, 2427–2430
4,6-Diamino-5-nitroso-2(1*H*)-pyrimidinone	300 or > 360	2390,2431–2433
2,4-Diamino-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	> 300, nmr, uv	5,1164,3897
4,5-Diamino-6-oxo-1,6-dihydro-2-pyrimidinesulfinic acid	188–190 or 192	1595,1692,3870
2,4-Diamino-6-oxo-1,6-dihydro-2-pyrimidinesulfonic acid	> 330	1101
4,6-Diamino-2-oxo-1,2-dihydro-5-pyrimidinesulfonic acid	> 330	1101
2,6-Diamino-5-propionamido-4(3*H*)-pyrimidinone	H_2O: 280	629
2,6-Diamino-5-propylamino-4(3*H*)-pyrimidinone	HCl: 176–182	1094
2,6-Diamino-5-propyl-4-pyrimidinecarboxylic acid	243–244	1183
5,6-Diamino-2-propyl-4-(3*H*)-pyrimidinethione	184–185	1612
2,6-Diamino-5-propyl-4(3*H*)-pyrimidinone	238–240	1151
4,6-Diamino-5-propyl-2(1*H*)-pyrimidinone	300	2434
2,4-Diamino-5-pyrimidinecarbaldehyde	263 to 275; oxime: 290–291	419,1481,1937
4,6-Diamino-5-pyrimidinecarbaldehyde	253, ir, nmr; oxime: 283, ir, nmr	443
2,4-Diamino-5-pyrimidinecarbohydrazide	266–268	1471
2,4-Diamino-5-pyrimidinecarbonitrile	> 270 or 322	419,478,1118,1250,1251,1480
4,6-Diamino-5-pyrimidinecarbonitrile	345, ir, nmr, uv	443
2,4-Diamino-5-pyrimidinecarbonyl azide	155	1471
2,4-Diamino-5-pyrimidinecarboxamide	> 320	1250
2,6-Diamino-4-pyrimidinecarboxamide	> 300	2331
5,6-Diamino-4-pyrimidinecarboxamide	300	2396
2,4-Diamino-5-pyrimidinecarboxylic acid	295–305	1600,2331
2,6-Diamino-4-pyrimidinecarboxylic acid	345	1030
4,6-Diamino-2-pyrimidinecarboxylic acid	> 360	2377

5,6-Diamino-4-pyrimidinecarboxylic acid	> 25(!)	2435
1,3-Diamino-2,4(1*H*,3*H*)-pyrimidinedione	185–186	1483
2,5-Diamino-4,6(1*H*,5*H*)-pyrimidinedione	anal	1578,1658,2421
5,6-Diamino-2,4(1*H*,3*H*)-pyrimidinedione	H_2SO_4: anal	1054,1272,1293,1339,1503,1640, 2421,2436–2440
2,5-Diamino-4,6(1*H*,5*H*)-pyrimidinedithione	ms	1661,3988
5,6-Diamino-2,4(1*H*,3*H*)-pyrimidinedithione	310	1116,1294,1443
2,6-Diamino-4-pyrimidinesulfinic acid	> 360	1644
4,6-Diamino-5-pyrimidinesulfinic acid	168–170	2441
4,6-Diamino-5-pyrimidinesulfonamide	217–218	1101
2,6-Diamino-4-pyrimidinesulfonic acid	Na: anal, uv	2331
2,5-Diamino-4(3*H*)-pyrimidinethione	217 or 235	1035,1195,1582
2,6-Diamino-4(3*H*)-pyrimidinethione	300 to > 360	932,958,1520,1644,1649
4,5-Diamino-2(1*H*)-pyrimidinethione	250	1035,2295,2442,2444
4,6-Diamino-2(1*H*)-pyrimidinethione	> 360	852,958,1298,1355,2402,2444, 2445
5,6-Diamino-4(3*H*)-pyrimidinone	257	2413,2446–2449
2,4-Diamino-5-pyrimidinol	> 300; pic: 250	1327
4,6-Diamino-5-pyrimidinol	265–268	1011
2,3-Diamino-4(3*H*)-pyrimidinone	178–180	1573
2,5-Diamino-4(3*H*)-pyrimidinone	245	1342
2,6-Diamino-4(3*H*)-pyrimidinone	260 to 283, ir, ms, nmr	517,1001,1293,2137,2401, 2450–2453
4,5-Diamino-2(1*H*)-pyrimidinone	> 230; HCl: *205–210*; H_2SO_4: > 300	*681,970,1379,1385,1585,* 1587,2418,2424,2443
4,6-Diamino-2(1*H*)-pyrimidinone	> 360	1040,1297,2377,2390,2402, 2441,2454
5,6-Diamino-4(3*H*)-pyrimidinone	HCl: 251–252	1595,2327,2421,2422, 2455–2457

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,5-Diamino-2(1*H*)-pyrimidinone 3-oxide	HCl: crude	1587
5,6-Diamino-4(1*H*)-pyrimidinone 3-oxide	203–204	2422
2,6-Diamino-5-sulfo-oxy-4(3*H*)-pyrimidinone	> 300	1011,2403
4,6-Diamino-5-sulfo-oxy-2(1*H*)-pyrimidinone	> 300	1011
2,6-Diamino-5-thiocyanato-4(3*H*)-pyrimidinone	258	2387
5,6-Diamino-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid	234	2435
2,5-Diamino-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	> 300	1565,1596
4,5-Diamino-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	H_2SO_4: > 270	1443
5,6-Diamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	1298,1588,1595,1692,2327, 2457,2458
2,4-Diazido-5-azidomethylpyrimidine	liquid, anal, ir, uv	1699
4,6-Diazido-5-chloro-2-fluoropyrimidine	121–122	1700
4,6-Diazido-2,5-difluoropyrimidine	106	1700
2,4-Diazido-5-methylpyrimidine	104–105, ir, ms	1701
2,4-Diazido-6-methylpyrimidine	126 to 128, ir, ms	1701,2459,2460
2,4-Diazidopyrimidine	92	2459
4,6-Diazidopyrimidine	106–107	2461
5-Diazo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	H_2O: 101–102; MeOH: 37–38	1129
5-Diazo-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	H_2O: 155–158; MeOH: 121–123	1129
5-Diazo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	123–124; MeOH: 95–97	1129
5-Diazo-2,4(1*H*,3*H*)-pyrimidinedione	H_2O: 210	2462
5,6-Dibromo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	166–167	1813
4,6-Dibromo-2-ethylpyrimidine	53	1243

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,6-Diethyl-5-methyl-4-pyrimidinamine	188–189 or 193	727,2116,2534–2537
2,4-Diethyl-5-methylpyrimidine	204–205/760	1719,1902,2061
2,4-Diethyl-6-methylpyrimidine	125/100	2293
4,6-Diethyl-2-methylpyrimidine	132–135/15	2293
Diethyl 2-methyl-4,5-pyrimidinedicarboxylate	118/0.09	1421
1,3-Diethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	56–67 or 65–67, 140–143/7	2024,2529,2538
1,3-Diethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	52 or 50–53	895,2024,2539–2542
1,3-Diethyl-5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	35	855
1,5-Diethyl-3-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	104/0.01, ir, nmr	69
2,5-Diethyl-6-methyl-4(3*H*)-pyrimidinone	135	2543
2,6-Diethyl-5-methyl-4(3*H*)-pyrimidinone	156–157	1719,2061,2544
4,6-Diethyl-2-methylthiopyrimidine	68/0.05, n_D^{25} 1.4832	2532
1,3-Diethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	97–98	1145
1,3-Diethyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	116–117	2091
1,3-Diethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	107	1064
2,4-Diethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylic acid	249	1719
Diethyl 2-oxo-1,2-dihydro-4,5-pyrimidinedicarboxylate	161–162	1635
1,3-Diethyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	1064
2,5-Diethyl-4-pyrimidinamine	151–153	1065
2,6-Diethyl-4-pyrimidinamine	166	1719,1840,2545
2,4-Diethylpyrimidine	68–72/15, 85–86/28	2546
4,6-Diethyl-2,5-pyrimidinediamine	98	645
Diethyl 4,5-pyrimidinedicarboxylate	154	2530,2547,2548
1,3-Diethyl-2,4(1*H*,3*H*)-pyrimidinedione	14–15, 135/4	1536,1841,2529,2549
5,6-Diethyl-2,4(1*H*,3*H*)-pyrimidinedione	245	2550

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,4-Dichloro-5-dimethylamino-6-methylpyrimidine	—	2251
4,6-Dichloro-2-dimethylamino-5-methylpyrimidine	60–61	2470
2,4-Dichloro-6-dimethylamino-5-methylthiopyrimidine	—	2471
4,6-Dichloro-2-dimethylamino-5-methylthiopyrimidine	—	2471
4,6-Dichloro-2-dimethylamino-5-nitropyrimidine	117–120	1484,2472
2,4-Dichloro-5-dimethylaminopyrimidine	90–91	1766,2473
2,4-Dichloro-6-dimethylaminopyrimidine	113	2474
4,6-Dichloro-2-dimethylaminopyrimidine	53–56	1241,2044,2470,2475
4,6-Dichloro-2-dimethylamino-5-pyrimidinecarbaldehyde	142; oxime: 165	2476
5,6-Dichloro-2-dimethylamino-4-pyrimidinecarbonitrile	147–150	2046
4,6-Dichloro-2-dimethylamino-5-pyrimidinecarbonitrile oxide	159–162	2476
2,4-Dichloro-5,6-dimethylpyrimidine	70–71, 250/760	1135
2,5-Dichloro-4,6-dimethylpyrimidine	63–64	2117
4,6-Dichloro-2,5-dimethylpyrimidine	39	1118,1159
5,6-Dichloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	155–157	1812
2,4-Dichloro-5-ethoxymethylpyrimidine	86–90/0.001	1699
4,6-Dichloro-2-ethoxymethylpyrimidine	49/0.03	1763
4,6-Dichloro-5-ethoxy-2-pyrimidinamine	181–182 or 188–189	1149,1185
2,4-Dichloro-5-ethoxypyrimidine	41–42	2129
2,4-Dichloro-6-ethoxypyrimidine	~ 25, 235/760	1771
4,6-Dichloro-5-ethoxypyrimidine	102–107/12	916
2,4-Dichloro-6-ethylaminopyrimidine	74–75 or 98–100	412,2047
4,6-Dichloro-2-ethylaminopyrimidine	61–64	2048
2,6-Dichloro-5-*N*-ethylformamido-4-pyrimidinamine	221	1202
4,6-Dichloro-5-ethyl-2-methoxymethylpyrimidine	69/0.07	1761

4,6-Dichloro-2-ethyl-5-methoxypyrimidine	—	2477
2,4-Dichloro-5-ethyl-6-methylpyrimidine	25–27 or 39, 130–131/6	1215,2478
4,6-Dichloro-2-ethyl-5-methylpyrimidine	111/21	2465
4,6-Dichloro-5-ethyl-2-methypyrimidine	100–101/10, 212–214/760	1159,2118
2,4-Dichloro-6-ethyl-5-nitropyrimidine	31	2148
4,6-Dichloro-2-ethyl-5-nitropyrimidine	78/0.1	2139
4,6-Dichloro-5-ethyl-2-propylpyrimidine	84–85/3, 115–116/7	1456,2465
2,6-Dichloro-5-ethyl-4-pyrimidinamine	214–216	1228
4,6-Dichloro-2-ethyl-5-pyrimidinamine	86/0.3	2139
4,6-Dichloro-5-ethyl-2-pyrimidinamine	191–192	1228
2,4-Dichloro-5-ethylpyrimidine	51	1219
2,4-Dichloro-6-ethylpyrimidine	90–95/4	2150,2151
4,6-Dichloro-2-ethylpyrimidine	86–87/14	1118,1243,1875
4,6-Dichloro-5-ethylpyrimidine	106–110/20	1880
5,6-Dichloro-2-ethyl-4(3*H*)-pyrimidinone	217–223	759
4,6-Dichloro-2-ethylsulfonyl-5-fluoropyrimidine	80	2153
2,4-Dichloro-5-ethylsulfonylmethyl-6-methylpyrimidine	160	347
2,4-Dichloro-5-ethylsulfonylmethylpyrimidine	130	347
2,4-Dichloro-6-ethylthio-5-ethylthiomethylpyrimidine	liquid, anal, nmr	347
4,6-Dichloro-2-ethylthio-5-fluoropyrimidine	103–106/4	2153
2,4-Dichloro-5-ethylthiomethyl-6-methylpyrimidine	41–42	347
2,4-Dichloro-5-ethylthiomethylpyrimidine	114–118/0.2	347
4,5-Dichloro-2-ethylthiopyrimidine	199	1249
5,6-Dichloro-2-ethylthio-4(3*H*)-pyrimidinone	204–205	927
2,4-Dichloro-6-fluoromethylpyrimidine	61–64	2167
4,6-Dichloro-2-fluoromethylpyrimidine	56 or 58–59	1802,2167
5,6-Dichloro-2-fluoromethyl-4(3*H*)-pyrimidinone	195–196	1802
4,6-Dichloro-5-fluoro-2-methylsulfonylpyrimidine	106–107	2153

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,6-Dichloro-5-fluoro-2-methylthiopyrimidine	56	2153
2,4-Dichloro-5-fluoropyrimidine	35 to 43	473,1264,2168,2169,2479,2480
2,4-Dichloro-6-fluoropyrimidine	crude	2064
4,6-Dichloro-2-fluoropyrimidine	crude	2064
2,4-Dichloro-6-fluoro-5-pyrimidinecarbonitrile	crude	2063
4,6-Dichloro-2-fluoro-5-pyrimidinecarbonitrile	crude	2063
2,6-Dichloro-5-formamido-4-pyrimidinamine	216–217 or 224	1202,2307
4,6-Dichloro-5-formylmethyl-2-pyrimidinamine	180–182, nmr, uv; acetal: 146–149, nmr, uv	203
4,6-Dichloro-5-formylmethylpyrimidine	84–86	888
5,6-Dichloro-2-guanidino-4-pyrimidinamine	HCl: 319	2174
2,4-Dichloro-6-guanidinopyrimidine	225, then 360	2174
4,6-Dichloro-2-guanidinopyrimidine	> 360	2174
2,5-Dichloro-4-hydrazinopyrimidine	220	1827
2,4-Dichloro-5-α-hydroxyethylpyrimidine	liquid, anal, ir, nmr	6124
2,4-Dichloro-6-α-hydroxyethylpyrimidine	liquid, anal, ir, nmr	6124
4,6-Dichloro-5-α-hydroxyethylpyrimidine	111–112	787
4,6-Dichloro-5-hydroxyiminomethyl-2-pyrimidinamine	150	1026
4,5-Dichloro-6-imino-1,6-dihydro-2-pyrimidinamine	173; HCl: 269–270	1520
2,4-Dichloro-5-iodomethyl-6-methylpyrimidine	93–94	750,2481
2,4-Dichloro-5-iodomethylpyrimidine	52–53	1699
4,6-Dichloro-5-iodo-2-methylpyrimidine	90–91, nmr	499
2,4-Dichloro-5-iodopyrimidine	71–72	807
2,4-Dichloro-5-β-iodovinylpyrimidine	72–73, ms, nmr	6198
4,6-Dichloro-2-isocyanatopyrimidine	37–38, 48–50/0.03	2482

4,6-Dichloro-5-isopropoxypyrimidine	108–113	916
4,5-Dichloro-6-isopropylamino-2-pyrimidinamine	—	2185
2,4-Dichloro-6-isopropylaminopyrimidine	61–62	412,2185
4,6-Dichloro-2-isopropylaminopyrimidine	liquid	2048
2,4-Dichloro-6-isopropyl-5-nitropyrimidine	37, 134–136/12	617
2,4-Dichloro-6-isopropylpyrimidine	83/5	2151
4,6-Dichloro-2-isopropylpyrimidine	47–48/0.6, 50–53/1	1875,1908
4,6-Dichloro-5-isopropylpyrimidine	112/71	2186
5,6-Dichloro-2-isopropyl-4(3*H*)-pyrimidinone	227–230	759
5,6-Dichloro-2-isopropylthio-4(3*H*)-pyrimidinone	192–194	927
4,6-Dichloro-2-methoxycarbonylmethylpyrimidine	62–63	1997
4,6-Dichloro-2-(*C*-methoxyformimidoyl)methylpyrimidine	HCl: 136–137	1997
4,5-Dichloro-6-methoxy-2-methoxymethylpyrimidine	59–60	1761
4,6-Dichloro-5-methoxy-2-methoxymethylpyrimidine	40	1761
4,6-Dichloro-2-methoxymethyl-5-methylpyrimidine	31	1761
2,4-Dichloro-5-methoxymethylpyrimidine	95–97/1.5	1934
4,5-Dichloro-2-methoxymethylpyrimidine	40	1761
4,6-Dichloro-2-methoxymethylpyrimidine	41	1763,2196
5,6-Dichloro-2-methoxymethyl-4(3*H*)-pyrimidinone	196–201	759
2,4-Dichloro-6-methoxy-5-nitropyrimidine	48–50	2483
4,6-Dichloro-2-methoxy-5-nitropyrimidine	73–75	2484
4,6-Dichloro-5-methoxy-2-pyrimidinamine	216–217	1007,1185
2,4-Dichloro-5-methoxypyrimidine	66–68 or 74	1343,2198
2,4-Dichloro-6-methoxypyrimidine	51	1349,1663,2047
2,5-Dichloro-4-methoxypyrimidine	51–53	2209
4,6-Dichloro-2-methoxypyrimidine	59–60	2484-2486
4,6-Dichloro-5-methoxypyrimidine	57–58	916,1360,2206
4,6-Dichloro-5-*N*-methylacetamidopyrimidine	149–150	632

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,6-Dichloro-2-methylamino-5-methylthiopyrimidine	158	2471
2,4-Dichloro-5-methylaminopyrimidine	139 or 148–149	1766,2473
2,4-Dichloro-6-methylaminopyrimidine	186 or 188–190	412,1771
4,6-Dichloro-2-methylaminopyrimidine	155–158 or 164	1484,1771,2048
4,6-Dichloro-5-methylaminopyrimidine	78–79	632
4,6-Dichloro-5-methyl-2-methylthiopyrimidine	64	1046
2,4-Dichloro-6-methyl-5-nitropyrimidine	50–52, 53–54, 125/10, 132/17	1427,1581,1746,1932,2249,2413, 2487,2488
4,6-Dichloro-2-methyl-5-nitropyrimidine	54–55, 106–107/12, 115/20	1118,2287,2413
2,4-Dichloro-6-methyl-5-propylpyrimidine	31–33, 145–146/20	2489
4,6-Dichloro-2-methyl-5-propylpyrimidine	114–115/11	1159,2490
4,6-Dichloro-5-methyl-2-propylpyrimidine	24–26, 100–101/5	1456
2,4-Dichloro-6-methyl-5-pyrimidinamine	115–116	1833,1964
2,6-Dichloro-5-methyl-4-pyrimidinamine	201	1485
4,5-Dichloro-6-methyl-2-pyrimidinamine	211–212	1014
4,6-Dichloro-2-methyl-5-pyrimidinamine	70–72	1016,2413
4,6-Dichloro-5-methyl-2-pyrimidinamine	249	614,1485
5,6-Dichloro-2-methyl-4-pyrimidinamine	145	2491
2,4-Dichloro-5-methylpyrimidine	25–26 or 27–29, 108–109/11	1219,1485,2076,2492–2494
2,4-Dichloro-6-methylpyrimidine	46–47, 99/10	68,1517,1834,1855,2495–2497
4,5-Dichloro-2-methylpyrimidine	185/0.3	2283
4,5-Dichloro-6-methylpyrimidine	100/18, nmr	3743
4,6-Dichloro-2-methylpyrimidine	45–46 or 48–49	1159,1558,1855,3734
4,6-Dichloro-5-methylpyrimidine	56–57	1832,2254
4,6-Dichloro-2-methyl-5-pyrimidinecarbaldehyde	103–105	1027,1028

2,4-Dichloro-6-methyl-5-pyrimidinecarbonitrile	93–94	2128
4,6-Dichloro-2-methyl-5-pyrimidinecarbonitrile	114–115	1010
5,6-Dichloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	231–233	1812
2,4-Dichloro-6-methyl-5-pyrimidinol	78–80, 108/2	6017
5,6-Dichloro-2-methyl-4(3*H*)-pyrimidinone	245–251	759
5,6-Dichloro-3-methyl-4(3*H*)-pyrimidinone	108	2498
4,6-Dichloro-2-methylsulfinyl-5-nitropyrimidine	130–134, ms, nmr	3988
4,6-Dichloro-2-methylsulfonyl-5-nitropyrimidine	154–156, ms, nmr	3988
4,6-Dichloro-2-methylsulfonylpyrimidine	119	958
2,4-Dichloro-5-methylthiomethylpyrimidine	80–100/0.001	1699
4,6-Dichloro-2-methylthio-5-nitropyrimidine	61–63	1764,2153
4,5-Dichloro-2-methylthiopyrimidine	121–122/8, ms, nmr	220
4,6-Dichloro-2-methylthiopyrimidine	39 to 43, 135–136/14	958,1046,2187,2198
4,6-Dichloro-2-methylthio-5-pyrimidinecarbaldehyde	82–84; oxime: 110–112	1020
4,6-Dichloro-2-methylthio-5-pyrimidinecarbonitrile	103–104	1020
5,6-Dichloro-2-methylthio-4(3*H*)-pyrimidinone	271	927
2,4-Dichloro-5-nitro-6-propylpyrimidine	43–44	801
4,6-Dichloro-5-nitro-2-propylpyrimidine	39, 107/4	1612
2,6-Dichloro-5-nitro-4-pyrimidinamine	162–164	1581,2307,2499
2,4-Dichloro-5-nitropyrimidine	135/17	711,1582,1746,2247,2295, 2296,2327
4,6-Dichloro-5-nitropyrimidine	100 to 104 (219–220?), ms, nmr	228,2246,2339,2500–2503
2,6-Dichloro-5-nitro-4-pyrimidinecarboxamide	190	2046
2,6-Dichloro-5-nitro-4-pyrimidinecarboxylic acid	—	1035
2,4-Dichloro-6-propylaminopyrimidine	86–88	412
4,6-Dichloro-2-propylpyrimidine	98–99/12	1456,1875
4,6-Dichloro-5-propylpyrimidine	liquid, anal, nmr	2490
5,6-Dichloro-2-propyl-4(3*H*)-pyrimidinone	185–192	759

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5,6-Dichloro-2-propylthio-4(3*H*)-pyrimidinone	165–166	927
2,4-Dichloro-5-pyrimidinamine	121–122	633,711,1766
2,5-Dichloro-4-pyrimidinamine	191–193	2209
2,6-Dichloro-4-pyrimidinamine	265 to 271	616,636,1349,1657,2093,2466, 2504
4,6-Dichloro-2-pyrimidinamine	218–221	1014,1349,1644,2045,2207, 2350,2482
4,6-Dichloro-5-pyrimidinamine	142 to 148	602,1036,1038,1648,2208,2307, 2503
2,4-Dichloropyrimidine	58–60 or 61–62, 80/10, 100/19	277,711,1675,1834,1855, 1936,2494
2,5-Dichloropyrimidine	57, 190/760	1616,1855,2255,2505
4,5-Dichloropyrimidine	83/34	1827
4,6-Dichloropyrimidine	67	1855,1896,2506–2508
4,6-Dichloro-5-pyrimidinecarbaldehyde	59 to 70, oxime: 100	1019,1027,1028,2310
2,4-Dichloro-5-pyrimidinecarbonitrile	62–63, 110–112/2	2509
2,6-Dichloro-4-pyrimidinecarbonitrile	—	2510
4,6-Dichloro-5-pyrimidinecarbonitrile	145	2310
2,4-Dichloro-5-pyrimidinecarbonyl chloride	90–91/0.3, 130/12, n_D^{20} 1.5932	2511,2512
2,6-Dichloro-4-pyrimidinecarbonyl chloride	109/5	2121,6036
2,6-Dichloro-4-pyrimidinecarboxamide	170	1030
2,4-Dichloro-5-pyrimidinecarboxylic acid	96–97	2513
2,6-Dichloro-4-pyrimidinecarboxylic acid	115–117	1030
2,5-Dichloro-4,6-pyrimidinediamine	300–301 or 302–304	1355,2350,2351,2514
2,6-Dichloro-4,5-pyrimidinediamine	268	1581

4,6-Dichloro-2,5-pyrimidinediamine	188–198 or 261(?), ms, uv; HCl: > 264	620,630,2307,6025
5,6-Dichloro-2,4-pyrimidinediamine	217–218 or 218–220	1830,1831,2333,2350,3864
5,6-Dichloro-2,4-pyrimidinediamine 3-oxide	185	2333
5,6 Dichloro-2,4(1*H*,3*H*)-pyrimidinedione	200 or 299–301	1812,2046
2,5-Dichloropyrimidine 1-oxide	102	1966
2,4-Dichloro-5-pyrimidinesulfonic acid	Na: —	2515,2516
2,4-Dichloro-5-pyrimidinesulfonyl chloride	97–99, 140–142/12	2515,2516
4,5-Dichloro-2(1*H*)-pyrimidinone	206	1249
4,6-Dichloro-2(1*H*)-pyrimidinone	262	958
5,6-Dichloro-4(3*H*)-pyrimidinone	212–213	1832
5,6-Dichloro-2-thioxo-1,2-dihydro-4-pyrimidinecarbothioamide	> 80	2046
5,6-Dichloro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	236–238	2517
2,4-Dichloro-5-trimethylsilylpyrimidine	30–35, nmr	6134
4,6-Dichloro-5-trimethylsilylpyrimidine	48–49, ms, nmr	6134
2,4-Dichloro-5-vinylpyrimidine	crude liquid, nmr	6198
2,4-Diethoxy-5,6-difluoropyrimidine	43	1727
2,4-Diethoxy-5-ethoxymethylpyrimidine	90–100/0.001	1699
2,4-Diethoxy-5-ethyl-6-methylpyrimidine	130/8, 138–139/17	1059,2478
2,4-Diethyoxy-5-ethylpyrimidine	110/5	1219
4,5-Diethoxy-2-ethylthiopyrimidine	HCl: 129–130	2017
2,4-Diethoxy-5-fluoropyrimidine	18–19, 148–150/88	2124,2518
2,4-Diethoxy-6-fluoropyrimidine	59/0.25	1727
2,4-Diethoxy-6-α-hydroxyethylpyrimidine	72	788
2,4-Diethoxy-6-α-hydroxypropylpyrimidine	49	788
2,4-Diethoxy-5-iodo-6-methylpyrimidine	47–48, ir, nmr	3893
2,4-Diethoxy-6-methylaminopyrimidine	—	1771
2,4-Diethoxy-6-methyl-5-nitropyrimidine	38	2024

Pyrimidine	m.p. (°C), etc.	Ref.
4,6-Diethoxy-2-methyl-5-nitropyrimidine	74	2125
2,4-Diethoxy-6-methyl-5-propylpyrimidine	145–148/18	2489
2,4-Diethoxy-5-methylpyrimidine	25–26 or 36–37; 1-MeI: 77–78	1544,1839,2492,2494,2519,2520
2,4-Diethoxy-6-methylpyrimidine	118–119/15, 142–143/70, ir, nmr	2127,2495,3893
4,6-Diethoxy-2-methylpyrimidine	63–65/2.5, 104–105/31 or 107/20, n_D^{24} 1.4820	2521,2522,3884
4,6-Diethoxy-5-methylpyrimidine	41	2521
4,6-Diethoxy-2-methyl-5-pyrimidinecarbonitrile	111	1010
2,4-Diethoxy-6-nitro-5-pyrimidinamine	128–130, nmr, uv	6196
2,4-Diethoxy-5-nitropyrimidine	42–44 or 45	651,1187,1584,2024
4,6-Diethoxy-5-nitropyrimidine	61–62 or 62–63	1579,1680
2,4-Diethoxy-5-pyrimidinamine	64–66	633,651,1187
2,6-Diethoxy-4-pyrimidinamine	107–108 or 111–112	616,2523
4,5-Diethoxy-2-pyrimidinamine	94–95	1149
4,6-Diethoxy-2-pyrimidinamine	101, 265–266/760	1149,2130
5,6-Diethoxy-4-pyrimidinamine	83–84	916
2,4-Diethoxypyrimidine	19–20, 224–225/760; 1-MeI: 56–58	812,1216,1546,1771,1841,2494, 2520,2524
2,5-Diethoxypyrimidine	19, 124/24	2133
4,6-Diethoxypyrimidine	25, 109/15; $EtBF_4$: 97–98	2521
2,6-Diethoxy-4-pyrimidinecarbaldehyde	oxime: 125–126	2525
2,6-Diethoxy-4-pyrimidinecarboxylic acid	115–117	788
4,6-Diethoxy-5-pyrimidinecarboxylic acid	107–109	1788
4,6-Diethoxy-2(1*H*)-pyrimidinone	196–198	1786
Diethyl 2-amino-4,5-pyrimidinedicarboxylate	151–152	1635

Diethyl 2-chloro-4,5-pyrimidinedicarboxylate	31–32	2102
3,5-Diethyl-2,6-dimethoxy-4(3*H*)-pyrimidinone	86–87	2526
4,6-Diethyl-2,5-dimethylpyrimidine	pic: 106–107	1159
1,3-Diethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	162–163	2527
1,3-Diethyl-4,6-dioxo-2-thioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde	—	2528
2,4-Diethyl-6-ethylamino-5-methylpyrimidine	45, 260/760	1902,2061
1,3-Diethyl-4-ethylimino-3,4-dihydro-2(1*H*)-pyrimidinone	pic: 168–170	2529
Diethyl 2-ethyl-4,5-pyrimidinedicarboxylate	128–129/0.1	2530
2,4-Diethyl-5-fluoropyrimidine	liquid, anal, ms, nmr	3822
2,4-Diethyl-6-hydrazinopyrimidine	86–87	880,900
4,6-Diethyl-2-hydrazinopyrimidine	77–79	2062
1,3-Diethyl-6-hydrazino-2,4(1*H*,3*H*)-pyrimidinedione	183–185	855
1,3-Diethyl-6-hydroxyamino-2,4(1*H*,3*H*)-pyrimidinedione	112–113	776
2,6-Diethyl-5-β-hydroxyethyl-4(3*H*)-pyrimidinone	151	1718
3,5-Diethyl-2-imino-4,6-dioxo-1,2,3,4,5,6-hexahydro-1-pyrimidinecarbonitrile	168–170	2531
2,6-Diethyl-5-iodomethyl-4-pyrimidinamine	152	1718
2,6-Diethyl-5-iodomethyl-4(3*H*)-pyrimidinone	157	1718
2,6-Diethyl-5-methoxymethyl-4-pyrimidinamine	130	1718
2,4-Diethyl-6-methoxy-5-methylpyrimidine	225/760	1902
4,6-Diethyl-2-methoxypyrimidine	60/0.1, n_D^{20} 1.4720	2532
1,3-Diethyl-6-methoxy-2,4(1*H*,3*H*)-pyrimidinedione	68–69	2533
1,3-Diethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	170–171	855
1,3-Diethyl-6-α-methylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione	102–104	1134
2,4-Deithyl-5-methyl-6-methylaminopyrimidine	74, 258/760	1902
1,3-Diethyl-5-methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	103–104	855
1,3-Diethyl-6-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	85–86	1056
Diethyl 5-methyl-6-oxo-1,6-dihydro-2,4-pyrimidinedicarboxylate	120–122	2038
4,6-Diethyl-2-methyl-5-propylpyrimidine	pic: 124–125	1159

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,6-Diethyl-5-methyl-4-pyrimidinamine	188–189 or 193	727,2116,2534–2537
2,4-Diethyl-5-methylpyrimidine	204–205/760	1719,1902,2061
2,4-Diethyl-6-methylpyrimidine	125/100	2293
4,6-Diethyl-2-methylpyrimidine	132–135/15	2293
Diethyl 2-methyl-4,5-pyrimidinedicarboxylate	118/0.09	1421
1,3-Diethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	56–67 or 65–67, 140–143/7	2024,2529,2538
1,3-Diethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	52 or 50–53	895,2024,2539–2542
1,3-Diethyl-5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	35	855
1,5-Diethyl-3-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	104/0.01, ir, nmr	69
2,5-Diethyl-6-methyl-4(3*H*)-pyrimidinone	135	2543
2,6-Diethyl-5-methyl-4(3*H*)-pyrimidinone	156–157	1719,2061,2544
4,6-Diethyl-2-methylthiopyrimidine	68/0.05, n_D^{25} 1.4832	2532
1,3-Diethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	97–98	1145
1,3-Diethyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	116–117	2091
1,3-Diethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	107	1064
2,4-Diethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylic acid	249	1719
Diethyl 2-oxo-1,2-dihydro-4,5-pyrimidinedicarboxylate	161–162	1635
1,3-Diethyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	1064
2,5-Diethyl-4-pyrimidinamine	151–153	1065
2,6-Diethyl-4-pyrimidinamine	166	1719,1840,2545
2,4-Diethylpyrimidine	68–72/15, 85–86/28	2546
4,6-Diethyl-2,5-pyrimidinediamine	98	645
Diethyl 4,5-pyrimidinedicarboxylate	154	2530,2547,2548
1,3-Diethyl-2,4(1*H*,3*H*)-pyrimidinedione	14–15, 135/4	1536,1841,2529,2549
5,6-Diethyl-2,4(1*H*,3*H*)-pyrimidinedione	245	2550

1,3-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	52–53, 167/19	789,1064,1842,2533
1,5-Diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	90–91 or 115–116	2526,2531
1,2-Diethyl-4(1*H*)-pyrimidinone	108–111	2551
2,3-Diethyl-4(3*H*)-pyrimidinone	liquid, anal	2551
2,6-Diethyl-4(3*H*)-pyrimidinone	89–90	880
4,6-Diethyl-2(1*H*)-pyrimidinone	HCl: 205–207	2062
1,3-Diethyl-2-thioxo-2,3-dihydro-4,6((1*H*,5*H*)-pyrimidinedione	103–105	2552
1,3-Diethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	66, uv	2035,2553
5,6-Diethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	214–215 or 220	1684,2550
1,3-Diethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde	—	2528
4,6-Diethyl-2-ureidopyrimidine	190	2554
1,3-Diethyl-5-ureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	196	1064
2,5-Difluoro-4,6-bismethylaminopyrimidine	180–182	1728
2,5-Difluoro-4,6-diiodopyrimidine	185	2555
2,5-Difluoro-4,6-dimethoxypyrimidine	106–108	1728
2,4-Difluoro-5,6-dimethylpyrimidine	167/760	2093
4,6-Difluoro-2,5-dimethylpyrimidine	148–150/760	2093
2,5-Difluoro-4-iodo-6-methoxypyrimidine	109–110	2555
2,5-Difluoro-6-iodo-4-pyrimidinamine	195–197	2555
2,4-Difluoro-6-methoxypyrimidine	crude	2063
4,6-Difluoro-2-methoxypyrimidine	crude	2063
2,6-Difluoro-5-methyl-4-pyrimidinamine	183–184	2093
4,6-Difluoro-5-methyl-2-pyrimidinamine	220–223	2093
2,4-Difluoro-5-methylpyrimidine	27–28/1–2, nmr	66
2,4-Difluoro-6-methylpyrimidine	27–28/1–2, 135–137/760 (or 145/760), nmr	66,1843,2093
4,6-Difluoro-2-methylpyrimidine	120–122/760	2093
4,6-Difluoro-5-methylpyrimidine	132–134/760	2093

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,6-Difluoro-5-nitropyrimidine	crude: 188–195/760	2556
2,6-Difluoro-4-pyrimidinamine	206 to 216	1040,2063,2093,2557
4,6-Difluoro-2-pyrimidinamine	230	1040,2063,2093
4,6-Difluoro-5-pyrimidinamine	157–159	2556
2,4-Difluoropyrimidine	20–22/1-2, 68–70/135, nmr	66,2064,2558
2,5-Difluoropyrimidine	100–102/760	2555
4,6-Difluoropyrimidine	112–114/760	1730
2,5-Difluoro-4,6-pyrimidinediamine	232–233	1728
4,6-Difluoro-2(1*H*)-pyrimidinone	K: >280	2454
4,6-Dihydrazino-5-*N*-methylacetamidopyrimidine	240–245	632
2,4-Dihydrazino-6-methyl-5-nitropyrimidine	198	2559
4,6-Dihydrazino-2-methyl-5-nitropyrimidine	198, uv	684,2560
2,4-Dihydrazino-5-methylpyrimidine	200–201	1754
2,4-Dihydrazino-6-methylpyrimidine	208 to 216; HCl: 200	1701,1754,2106,2561–2563
2,4-Dihydrazino-5-nitropyrimidine	270	1714
4,6-Dihydrazino-5-nitropyrimidine	200 to 206	684,1714,2564
2,6-Dihydrazino-4-pyrimidinamine	143	2565
2,4-Dihydrazinopyrimidine	211–212 or 216	1754,2459,2566
4,6-Dihydrazinopyrimidine	223–224	2461
5-Dihydroxyboryl-2,4-dimethoxypyrimidine	115–117	2567
5-Dihydroxyboryl-2,4(1*H*,3*H*)-pyrimidinedione	330	2567
3,5-Dihydroxy-2,4(1*H*,3*H*)-pyrimidinedione	anal, nmr. uv	1587
5,6-Diiodo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	213–215	1812
4,6-Diiodo-2-isopropyl-6-methylpyrimidine	78–79	1890
2,4-Diiodo-6-methylpyrimidine	90	2178

4,6-Diiodo-2-methylpyrimidine	195–197	1857
5,6-Diiodo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	265	1812
4,6-Diiodo-2-pyrimidinamine	--	2568
4,6-Diiodopyrimidine	107–108	1784
5,6-Diiodo-2,4(1*H*,3*H*)-pyrimidinedione	269–270	1812
2,4-Di-isopropoxy-5-methylpyrimidine	76/0.3; 1-MeI: 79–81	2520
2,4-Di-isopropoxy-6-methylpyrimidine	105–110/9, 132–134/25, ir, nmr; pic: 137	698, 2495, 2561, 3893
2,6-Di-isopropoxy-4-pyrimidinamine	65	2523
4,6-Di-isopropoxy-2-pyrimidinamine	90, 160/30	2130
2,4-Di-isopropoxypyrimidine	111/11	2569
4,5-Di-isopropyl-6-methylaminopyrimidine	130	2570
1,3-Di-isopropyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	181–182	882
2,4-Di-isopropyl-6-methylpyrimidine	anal	2571
1,3-Di-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	93–94	2572
5,6-Di-isopropyl-3-methyl-4(3*H*)-pyrimidinimine	HI: 252	2570
4,6-Di-isopropyl-2-pyrimidinamine	80	2573
2,4-Di-isopropylpyrimidine	77–84/15	2546,2574
2,6-Di-isopropyl-4(3*H*)-pyrimidinone	109–110	2575
2,4-Dimethoxy-5,6-dimethylpyrimidine	39–40, 229/760	1135
5,6-Dimethoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	anal	2576
4,6-Dimethoxy-2-methoxycarbonylmethylpyrimidine	100–104/0.5	1749
2,6-Dimethoxy-3-methoxycarbonylmethyl-4(3*H*)-pyrimidinimine	HBr: anal	2189
4,6-Dimethoxy-5-methoxymethyl-2-methylpyrimidine	83–84	1801
4,5-Dimethoxy-6-methoxymethyl-2-pyrimidinamine	132–133	1149
2,4-Dimethoxy-6-methylaminopyrimidine	136–138 or 144–145	675,2577
2-Dimethoxymethyl-4,6-dimethylpyrimidine	118–120/7	2222
6-Dimethoxymethyl-3,5-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	93–94	2578

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Dimethoxymethyl-3-ethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	98–100	2578
6-Dimethoxymethyl-2-ethylthio-5-fluoro-4(3*H*)-pyrimidinone	105–106	2066
6-Dimethoxymethyl-2-ethylthio-4(3*H*)-pyrimidinone	121–122	1871
6-Dimethoxymethyl-3-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	103–104	2578
6-Dimethoxymethyl-5-ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	135–136	2578
6-Dimethoxymethyl-5-fluoro-2-propylthio-4(3*H*)-pyrimidinone	77–79	2066
6-Dimethoxymethyl-5-fluoro-2-methylthio-4(3*H*)-pyrimidinone	135–137	2066
6-Dimethoxymethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	215–216	2066
6-Dimethoxymethyl-5-fluoro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	201–202	2066
2,4-Dimethoxy-6-α-methylhydrazinopyrimidine	105–106	2577,2579
6-Dimethoxymethyl-5-methyl-3-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	88–90	2578
4-Dimethoxymethyl-6-methyl-2-pyrimidinamine	74–75	1149
5-Dimethoxymethyl-2-methyl-4-pyrimidinamine	105 to 109	677,1008,2580
6-Dimethoxymethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	137	2578
6-Dimethoxymethyl-2-methylthio-4(3*H*)-pyrimidinone	154–155	1871
6-Dimethoxymethyl-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	148–149	2578
6-Dimethoxymethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	155–156	2578
2,4-Dimethoxy-6-methyl-5-nitropyrimidine	81 or 83	2559,2581,2582
4,6-Dimethoxy-2-methyl-5-nitropyrimidine	116–117 or 123–124	651,1216,1680
2,4-Dimethoxy-6-methyl-5-propylpyrimidine	135–140/20	2489
6-Dimethoxymethyl-3-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	106–107	2578
2,4-Dimethoxy-6-methyl-5-pyrimidinamine	70–72 or 73	1964,2581
2,6-Dimethoxy-5-methyl-4-pyrimidinamine	125–126	965
4,5-Dimethoxy-6-methyl-2-pyrimidinamine	117–118	1362,2583
4,6-Dimethoxy-2-methyl-5-pyrimidinamine	97–98	651,1216

4,6-Dimethoxy-5-methyl-2-pyrimidinamine	112–114 or 116	2093,2130
5-Dimethoxymethyl-4-pyrimidinamine	78–79	1008
2,4-Dimethoxy-5-methylpyrimidine	60–61, 322/760, ir, nmr	812,1485,2492,2494,6117
2,4-Dimethoxy-6-methylpyrimidine	66–68 or 69–70; pic: 149	1148,1509,2078,2268,2561,2585, 3893
4-Dimethoxymethylpyrimidine	45–50/0.2	2584
4,5-Dimethoxy-2-methylpyrimidine	54	1462,1551
4,6-Dimethoxy-2-methylpyrimidine	52–53; $EtBF_4$: 173–174	1735,2586–2588
4,6-Dimethoxy-5-methylpyrimidine	87 or 90–91, ir nmr	2586,2587,6117
4,6-Dimethoxy-2-methyl-5-pyrimidinecarbonitrile	135	1387
2,4-Dimethoxy-6-methyl-5-pyrimidinecarboxylic acid	142–144, ir, nmr	3894
4,6-Dimethoxy-2-methyl-5-pyrimidinecarboxylic acid	209–210	1788
5-Dimethoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	194–195 or 199–200	2589,2590
6-Dimethoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	182–183	1871
2,6-Dimethoxy-3-methyl-4(3*H*)-pyrimidinone	85–94, nmr	2533,3736,3756
2,6-Dimethoxy-5-methyl-4(3*H*)-pyrimidinone	224–226	972,973
4,6-Dimethoxy-1-methyl-2(1*H*)-pyrimidinone	96–97, nmr	2110,3736,3756
2,4-Dimethoxy-6-methylsulfonylpyrimidine	122–123	2070
5,6-Dimethoxy-2-methylthio-4-pyrimidinamine	115–117	1360
2,4-Dimethoxy-6-methylthiopyrimidine	45–46	2070
6-Dimethoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	180–181	2578
2,4-Dimethoxy-6-nitroaminopyrimidine	118	903
2,4-Dimethoxy-6-nitro-5-pyrimidinamine	170–171, nmr, uv	6196
2,6-Dimethoxy-5-nitro-4-pyrimidinamine	180–182	1294,2591
2,4-Dimethoxy-5-nitropyrimidine	92–93 or 94–96	1379,1639,2559
4,6-Dimethoxy-5-nitropyrimidine	170–171 or 173–174	1016,2208
2,6-Dimethoxy-5-nitroso-4-pyrimidinamine	178–181	2591
2,6-Dimethoxy-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	217–218	2592
4,6-Dimethoxy-2-propylpyrimidine	93–94/9	1456

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,4-Dimethoxy-5-pyrimidinamine	86–88 or 88–89	651,1187,1602,1639
2,5-Dimethoxy-4-pyrimidinamine	176 or 180–181	2198,2203
2,6-Dimethoxy-4-pyrimidinamine	145–152 (110 or 188–191?)	616,636,1019,1369,2466,2504, 2523,2577,2593–2595
4,5-Dimethoxy-2-pyrimidinamine	88	1007
4,6-Dimethoxy-2-pyrimidinamine	92 to 98, 252/760; pic: 198–199	1366,2072,2110,2130,2596,2597
4,6-Dimethoxy-5-pyrimidinamine	92 to 102	243,1362,2208,2564
5,6-Dimethoxy-4-pyrimidinamine	88–89	916,2206,2598
2,4-Dimethoxypyrimidine	18, 95–98/22, 202–204/760; pic: 129–130	812,1663,2211,2494,2513,3893
2,5-Dimethoxypyrimidine	70–71	1897,2599
4,6-Dimethoxypyrimidine	30–31 or 76–77, 36–40/0.2, 85/16	968,2526,2600,3743
2,4-Dimethoxy-5-pyrimidinecarbaldehyde	120–122 or 123, nmr	474,2601,6071,6198
2,6-Dimethoxy-4-pyrimidinecarbaldehyde	107	2601
4,6-Dimethoxy-2-pyrimidinecarbaldehyde	70–72, nmr	3974
4,6-Dimethoxy-5-pyrimidinecarbaldehyde	135–137 or 142–143; tsc: 221–223	1788,2310
2,4-Dimethoxy-5-pyrimidinecarbonitrile	143	1602
2,6-Dimethoxy-4-pyrimidinecarbonitrile	109	2602–2604
4,5-Dimethoxy-2-pyrimidinecarbonitrile	86–87, nmr	3743
4,6-Dimethoxy-5-pyrimidinecarbonitrile	208–210	1788
2,6-Dimethoxy-4-pyrimidinecarboxamide	186	2603
4,6-Dimethoxy-5-pyrimidinecarboxamide	242–244	1787,1788
2,4-Dimethoxy-5-pyrimidinecarboxylic acid	167–168, nmr	474,788
2,6-Dimethoxy-4-pyrimidinecarboxylic acid	H_2O: 165	2603
4,6-Dimethoxy-5-pyrimidinecarboxylic acid	196–197 or 200–201	1787,1788

2,6-Dimethoxy-4,5-pyrimidinediamine	177–178	1294
4,5-Dimethoxypyrimidine 1-oxide	204–205, nmr	3743
2,6-Dimethoxy-4-pyrimidinesulfonamide	189–190	2070
2,6-Dimethoxy-4-pyrimidinesulfonic acid	208–209, *uv*	2071
2,6-Dimethoxy-4(3*H*)-pyrimidinethione	282–285	2070,2071,2605
2,6-Dimethoxy-4(3*H*)-pyrimidinone	192–193 or 195, nmr	972,973,3736,3756
4,6-Dimethoxy-2(1*H*)-pyrimidinone	193–194, nmr	1780,3736,3756
2,4-Dimethoxy-5-trimethylsilylpyrimidine	liquid, anal, ir, nmr	474,6117
4,6-Dimethoxy-5-trimethylsilylpyrimidine	liquid, anal, ir, nmr	6117
2,4-Dimethoxy-5-vinylpyrimidine	crude liquid, ms, nmr	6198
4,6-Dimethoxy-5-vinylpyrimidine	54–56/0.3	1880
4-Dimethylamino-2,6-difluoropyrimidine	85–86	1727
2-Dimethylamino-4,6-dimethoxypyrimidine	68	1731
4-Dimethylamino-2,6-dimethoxypyrimidine	42	1731
2-Dimethylamino-4-*N*,*N*-dimethylcarbamoyloxy-5,6-dimethylpyrimidine	91	2606
4-Dimethylamino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidine-carbaldehyde	184	2087
5-Dimethylamino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidine-sulfonic acid	264	2607
5-Dimethylamino-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	nmr, uv	551,2608
2-Dimethylamino-4,5-dimethyl-6-β-methylhydrazinopyrimidine	141	2609
2-Dimethylamino-4,6-dimethyl-5-pyrimidinamine	122	645
5-Dimethylamino-2,6-dimethyl-4-pyrimidinamine	161–162	1347
2-Dimethylamino-4,6-dimethylpyrimidine	90–91/15; pic: 158 or 160–163	2075,2602,2610
4-Dimethylamino-2,6-dimethylpyrimidine	105–107/13, 120 to 130/ ~ 25, 226/760, n_D^{20} 1.5355; pic: 168 to 177	1405,1734,2602,2611,2612
2-Dimethylamino-4,6-dimethyl-5-pyrimidinecarbaldehyde	151; oxime: 144–145	2075
2-Dimethylamino-4,6-dimethyl-5-pyrimidinecarbonitrile oxide	180	2075
5-Dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	81–83, nmr, uv	551,2608

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Dimethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	79–80 or 81, nmr, uv	551,644,2608
4-Dimethylamino-2,6-dimethylpyrimidine 1-oxide	97–99 ir, nmr; pic: 153–154	121
2-Dimethylamino-*N*,*N*-dimethyl-5-pyrimidinesulfonamide	200–201	845
2-Dimethylamino-5,6-dimethyl-4(3*H*)-pyrimidinethione	162–163	863
5-Dimethylamino-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	225	2613
2-Dimethylamino-1,6-dimethyl-4(1*H*)-pyrimidinone	77–78	911
2-Dimethylamino-5,6-dimethyl-4(3*H*)-pyrimidinone	174–175	2609
4-Dimethylamino-1,5-dimethyl-2(1*H*)-pyrimidinone	194–197	1219
4-Dimethylamino-1,3-dimethyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	122–124	2614
2-Dimethylamino-5,6-dinitro-4(3*H*)-pyrimidinone	190	2615
1-Dimethylamino-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	235–243	1071
2-Dimethylamino-4-ethoxycarbonyloxy-5,6-dimethylpyrimidine	106–109/0.01	753
2-Dimethylamino-5-β-ethoxyethyl-6-methyl-4(3*H*)-pyrimidinone	104–105	863
4-Dimethylamino-2-ethoxy-5-methylpyrimidine	20–21	1219
2-Dimethylamino-4-ethoxy-5-nitropyrimidine	104–106	1364
2-Dimethylamino-6-ethoxy-4-pyrimidinamine	68 or 86–87	615,637
4-Dimethylamino-6-ethoxy-2-pyrimidinamine	145–147	2045
6-Dimethylamino-2-ethoxy-4-pyrimidinamine	136–137	615,2616
2-Dimethylamino-5-ethoxypyrimidine	1(?)-MeI: 120	673
4-Dimethylamino-6-ethylamino-5-formamido-2-methylthiopyrimidine	137–138	2617
2-Dimethylamino-4-ethylamino-6-methyl-5-nitropyrimidine	117–118	1191
4-Dimethylamino-6-ethylamino-2-methyl-5-nitrosopyrimidine	68	1733
2-Dimethylamino-4-ethylamino-6-methyl-5-pyrimidinamine	94–96	1191
4-Dimethylamino-6-ethylamino-2-methylthio-5-nitrosopyrimidine	119–120	640
4-Dimethylamino-6-ethylamino-2-methylthio-5-pyrimidinamine	crude	640,2617

4-Dimethylamino-6-ethylamino-2-methylthiopyrimidine	126–127	640
2-Dimethylamino-4-ethylamino-5-nitropyrimidine	98	1746
2-Dimethylamino-6-ethylamino-5-nitro-4(3*H*)-pyrimidinone	282	999
2-Dimethylamino-4-ethylamino-5-pyrimidinamine	H_2SO_4: 195–198	1746
2-Dimethylamino-6-ethylamino-4,5-pyrimidinediamine	H_2SO_4: 239	2618
4-Dimethylamino-5-*N*-ethylformamido-6-methyl-2-methylthiopyrimidine	109–110	1080
6-Dimethylamino-5-*N*-ethyl-*N*-methylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	64–65	1729
2-Dimethylamino-4-ethyl-6-methylamino-5-nitropyrimidine	145–146	1191
2-Dimethylamino-4-ethyl-6-methylamino-5-pyrimidinamine	69–71	1191
2-Dimethylamino-5-ethyl-6-methyl-4(3*H*)-pyrimidinethione	140–141	863
2-Dimethylamino-5-ethyl-6-methyl-4(3*H*)-pyrimidinone	141 or 143	672,863
2-Dimethylamino-6-ethyl-5-nitro-4-pyrimidinamine	132–133	1191
2-Dimethylamino-5-ethyl-6-propyl-4(3*H*)-pyrimidinone	103–104	672,863
2-Dimethylamino-4-ethylpyrimidine	91–92/15; pic: 110–111	2078
2-Dimethylamino-6-ethyl-4,5-pyrimidinediamine	116–117	1191
2-Dimethylamino-5-ethyl-4(3*H*)-pyrimidinone	124–125	863
2-Dimethylamino-6-ethyl-4(3*H*)-pyrimidinone	140	863
2-Dimethylamino-5-ethylthio-6-methyl-4(3*H*)-pyrimidinone	117	1732
2-Dimethylamino-6-ethylthiomethyl-4(3*H*)-pyrimidinone	118	672,863
2-Dimethylamino-5-ethynyl-4-methylpyrimidine	80–84/0.1	790
4-Dimethylamino-5-fluoro-1-methyl-2(1*H*)-pyrimidinone	152–153	2619
2-Dimethylamino-4-fluoropyrimidine	25–27, 68–69/70	1730
4-Dimethylamino-2-fluoropyrimidine	63–64	2558
4-Dimethylamino-6-fluoropyrimidine	105–107	1730
2-Dimethylamino-5-formamido-4-methyl-6-methylaminopyrimidine	229	601
4-Dimethylamino-5-formamido-6-methyl-2-methylthiopyrimidine	179–181	1080
6-Dimethylamino-5-formamido-2-methylthio-4-pyrimidinamine	225–226	1569

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Dimethylamino-5-formamido-4-pyrimidinamine	235	681
6-Dimethylamino-5-formamido-4-pyrimidinamine	185–187	1569
2-Dimethylamino-6-formamido-4,5-pyrimidinediamine	285–287	2620
2-Dimethylamino-4-hydrazino-5-nitropyrimidine	221	1714
4-Dimethylamino-2-hydrazino-5-nitropyrimidine	182–183	1714
2-Dimethylamino-6-hydrazino-5-nitro-4(3*H*)-pyrimidinone	215–216	999
2-Dimethylamino-4-hydrazinopyrimidine	106, nmr	397
2-Dimethylamino-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	165–167	1319
2-Dimethylamino-4-β-hydroxyethylpyrimidine	123–125/1.5, n_D^{25}1.5539	2078
2-Dimethylamino-5-β-hydroxyethyl-4,6(1*H*,5*H*)-pyrimidinedione	anal	1319
4-Dimethylamino-5-hydroxymethyl-2-methylpyrimidine	125–126	2621
2-Dimethylamino-4-hydroxymethylpyrimidine	crude: nmr	1850
2-Dimethylamino-5-hydroxy-4(3*H*)-pyrimidinone	166–168, nmr	3818
2-Dimethylamino-4-iodo-5,6-dimethylpyrimidine	45	1745
2-Dimethylamino-6-isopropoxy-4-pyrimidinamine	104	637
6-Dimethylamino-2-isopropoxy-4-pyrimidinamine	105–106	615,2616
1-Dimethylamino-6-isopropylamino-3-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	167–168	2079
1-Dimethylamino-6-isopropylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	126–127	2079
2-Dimethylamino-6-isopropylamino-4,5-pyrimidinediamine	235	2618
2-Dimethylamino-5-isopropyl-6-methyl-4(3*H*)-pyrimidinone	181–183	863
2-Dimethylamino-6-isopropylthio-4-pyrimidinamine	100	637
2-Dimethylamino-4-mesyloxy-6-methyl-5-propylpyrimidine	71	672,753
2-Dimethylamino-4-mesyloxy-6-methylpyrimidine	87	672,753,2622
2-Dimethylamino-4-mesyloxypyrimidine	76	672,753,2622

2-Dimethylamino-4-methoxy-6-*N*-methylacetamido-5-nitropyrimidine	136–137	638
2-Dimethylamino-4-methoxy-6-methylamino-5-nitropyrimidine	180	2623
2-Dimethylamino-4-methoxy-6-methylaminopyrimidine	45	903
4-Dimethylamino-2-methoxymethyl-6-methylpyrimidine	145–150/25, nmr	121
4-Dimethylamino-6-methoxymethyl-2-methylpyrimidine	136–137/15, nmr	121
2-Dimethylamino-4-methoxy-6-methyl-5-methylthiopyrimidine	140/14, n_D^{23}1.5583	1732
2-Dimethylamino-4-methoxy-6-methylpyrimidine	112/13, n_D^{23}1.5223	1732
2-Dimethylamino-4-methoxy-6-nitroaminopyrimidine	147–148	903
2-Dimethylamino-6-methoxy-5-nitro-4-pyrimidinamine	187–188 or 192–193	638,1076
2-Dimethylamino-4-methoxy-5-nitropyrimidine	178–179	1089
4-Dimethylamino-6-methoxy-5-nitropyrimidine	79–80, ir	243
2-Dimethylamino-6-methoxy-5-nitroso-4-pyrimidinamine	214	1076
2-Dimethylamino-4-methoxy-5-pyrimidinamine	HCl: > 300	1089
2-Dimethylamino-6-methoxy-4-pyrimidinamine	89 or 93–94	615,637,638
4-Dimethylamino-6-methoxy-5-pyrimidinamine	69–70, ir	243
6-Dimethylamino-2-methoxy-4-pyrimidinamine	158–159	615
2-Dimethylamino-4-methoxypyrimidine	14, 49/0.5	1731,1743
4-Dimethylamino-2-methoxypyrimidine	154/18; HBr: 135–140	1678,1799
4-Dimethylamino-6-methoxypyrimidine	136/20	968
2-Dimethylamino-4-methoxy-5-pyrimidinecarbonitrile	154–155	1078
4-Dimethylamino-6-*N*-methylacetamido-5-nitropyrimidine	100–101	638
6-Dimethylamino-5-methylamino-2-methylthio-4-pyrimidinamine	166–167	640
2-Dimethylamino-4-methylamino-5-nitropyrimidine	179–181	2624
4-Dimethylamino-6-methylamino-5-nitropyrimidine	96–97 or 101	47,1764,2625
2-Dimethylamino-6-methylamino-5-nitro-4(3*H*)-pyrimidinone	310–312	999
4-Dimethylamino-6-methylamino-5-nitroso-2-pyrimidinamine	206	2626
2-Dimethylamino-6-methylamino-5-nitroso-4(3*H*)-pyrimidinone	255	1073
2-Dimethylamino-4-methylamino-5-pyrimidinamine	194–196	2624

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Dimethylamino-6-methylamino-2-pyrimidinamine	175–185	2626
4-Dimethylamino-6-methylamino-5-pyrimidinamine	151–154	1764,2625
2-Dimethylamino-4-methylaminopyrimidine	77–78	1742
4-Dimethylamino-2-methylaminopyrimidine	98	1741
4-Dimethylamino-6-methylaminopyrimidine	138–141 or 146–148	968,2625
2-Dimethylamino-6-methylamino-4,5-pyrimidinediamine	H_2SO_4: 273	1484
4-Dimethylamino-6-methylamino-2,5-pyrimidinediamine	crude	2626
6-Dimethylamino-2-methylamino-4,5-pyrimidinediamine	H_2SO_4: 193	1484
5-Dimethylamino-6-methylamino-4(3*H*)-pyrimidinone	194–200	1094
6-Dimethylaminomethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	116–118	6462
2-Dimethylaminomethyl-4,6-dimethyl-5-pyrimidinol 1-oxide	109–111, nmr	21
5-Dimethylaminomethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	214–217	2627
5-Dimethylaminomethylene-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	109	2087
5-Dimethylaminomethylene-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	208–209, nmr	83
5-Dimethylaminomethylene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	250–252, nmr	83
6-Dimethylaminomethyl-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	180–182	2628
2-Dimethylamino-4-methyl-6-methylamino-5-nitropyrimidine	147	601
1-Dimethylamino-3-methyl-6-methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	228–229	2079
2-Dimethylamino-4-methyl-6-methylamino-5-pyrimidinamine	109–110	601
2-Dimethylamino-1-methyl-6-methylimino-1,6-dihydropyrimidine	HCl: 194–197; HI: 146–148; pic: 167–169	1742
4-Dimethylamino-1-methyl-2-methylimino-1,2-dihydropyrimidine	HCl: 267; HI: 221	1742
4-Dimethylamino-1-methyl-6-methylimino-1,6-dihydropyrimidine	HI: 268	1507
5-Dimethylaminomethyl-2-methyl-4-pyrimidinamine	74–75	1074
4-Dimethylaminomethyl-6-methyl-5-pyrimidinol	149–151, nmr	6017

2-Dimethylamino-6-methyl-5-methylsulfinyl-4(3*H*)-pyrimidinone	175	1732
2-Dimethylamino-6-methyl-5-methylsulfonyl-4(3*H*)-pyrimidinone	229 to 235	863,1732,2622
4-Dimethylamino-6-methyl-2-methythio-5-nitropyrimidine	78	645
4-Dimethylamino-6-methyl-2-methylthio-5-pyrimidinamine	70 or 71–72	645,1080
4-Dimethylamino-6-methyl-2-methylthiopyrimidine	39–41 or 43–44, 138/4; pic: 187–188 or 189–190	1736,2612,2629
2-Dimethylamino-6-methyl-5-methylthio-4(3*H*)-pyrimidinone	181–182	1732
5-Dimethylamino-3-methyl-6-methylthio-4(3*H*)-pyrimidinone	78–79	1017
5-Dimethylaminomethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	185	2036
2-Dimethylamino-6-methyl-5-nitro-4-pyrimidinamine	148–149	1191
4-Dimethylamino-6-methyl-5-nitro-2-pyrimidinamine	192–193	645
6-Dimethylamino-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	218–220	999
4-Dimethylamino-6-methyl-5-nitro-2(1*H*)-pyrimidinethione	224	645
4-Dimethylamino-1-methyl-5-nitro-2(1*H*)-pyrimidinimine	HI: 236	1437
6-Dimethylamino-2-methyl-5-nitroso-4-pyrimidinamine	187	1733
2-Dimethylamino-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	> 300	682
2-Dimethylamino-6-methyl-5-propyl-4(3*H*)-pyrimidinone	120	672,863
2-Dimethylamino-6-methyl-4-pyrimidinamine	132	2093
4-Dimethylamino-6-methyl-2-pyrimidinamine	166–172	1149,1484,1736
6-Dimethylamino-2-methyl-4-pyrimidinamine	185–191	1556,1740,2252,2630,2631
2-Dimethylamino-4-methylpyrimidine	103–106/40	2078
4-Dimethylamino-2-methylpyrimidine	103–105/23; pic: 209–211 or 215–217	671,1462
4-Dimethylamino-5-methylpyrimidine	—	2251
4-Dimethylamino-6-methylpyrimidine	46–47, 120/19	1735
6-Dimethylamino-2-methyl-4-pyrimidinecarbaldehyde	oxime: 227–228	2522
4-Dimethylamino-2-methyl-5-pyrimidinecarbonitrile	132–134	1387,1462
6-Dimethylamino-2-methyl-4-pyrimidinecarbonitrile	140–141	2522
4-Dimethylamino-2-methyl-5-pyrimidinecarboxamide	244–245	1462

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Dimethylamino-2-methyl-5-pyrimidinecarboxylic acid	182–184	1462
2-Dimethylamino-6-methyl-4,5-pyrimidinediamine	153	1191
4-Dimethylamino-6-methyl-2,5-pyrimidinediamine	117–119	645
5-Dimethylaminomethyl-2,4(1*H*,3*H*)-pyrimidinedione	HBr: 270–273; pic: 247–248	1491,2632,2633
5-Dimethylamino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	295–298	1948
6-Dimethylaminomethyl-2,4(1*H*,3*H*)-pyrimidinedione	322–324	1498
2-Dimethylamino-3-methyl-4(3*H*)-pyrimidinethione	75–76	1507
2-Dimethylamino-6-methyl-4(3*H*)-pyrimidinethione	154–155	863
4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinethione	203–204	1507,1743
4-Dimethylamino-5-methyl-2(1*H*)-pyrimidinethione	242–245	2076
4-Dimethylamino-6-methyl-2(1*H*)-pyrimidinethione	292–296	2076,2634
6-Dimethylamino-3-methyl-4(3*H*)-pyrimidinethione	181–182 or 182–183	1507,1743
1-Dimethylamino-3-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	92–93	2079
1-Dimethylamino-5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	145–146	1071
2-Dimethylamino-1-methyl-4(1*H*)-pyrimidinimine	HCl: 287; HI: 280–281	1742
4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinimine	HCl: 298; HI: 286; pic: 186–187	1741,1742
2-Dimethylamino-4-methyl-5-pyrimidinol	114–116	7
4-Dimethylaminomethyl-5-pyrimidinol	199–200	1737
2-Dimethylaminomethyl-4(3*H*)-pyrimidinone	152–155	2635
2-Dimethylamino-3-methyl-4(3*H*)-pyrimidinone	95–96	1507,1743,2636
2-Dimethylamino-5-methyl-4(3*H*)-pyrimidinone	186–187	672
2-Dimethylamino-6-methyl-4(3*H*)-pyrimidinone	175 to 203 (106?)	863,1073,1081,1093,2078,2637
4-Dimethylamino-1-methyl-2(1*H*)-pyrimidinone	176 to 183; HCl: 191–199	696,1537–1539,2638,2639
4-Dimethylamino-3-methyl-2(3*H*)-pyrimidinone	116–117	1743

4-Dimethylamino-5-methyl-2(1*H*)-pyrimidinone	156–159	1219
4-Dimethylamino-6-methyl-2(1*H*)-pyrimidinone	264–265	6035
6-Dimethylamino-3-methyl-4(3*H*)-pyrimidinone	156–157 or 160	968,1507,1743
4-Dimethylamino-6-methylsulfonylpyrimidine	142–143	2289
2-Dimethylamino-5-methylsulfonyl-4(3*H*)-pyrimidinone	259–261	2622
6-Dimethylamino-2-methylthio-5-nitroso-4-pyrimidinamine	219–220	1569
4-Dimethylamino-5-methylthio-2-pyrimidinamine	102–105	1567
6-Dimethylamino-2-methylthio-4-pyrimidinamine	162–164	1569
2-Dimethylamino-4-methylthiopyrimidine	29–30; pic: 184–185	1507
4-Dimethylamino-2-methylthiopyrimidine	39–40, 168/18	1507,1678
4-Dimethylamino-6-methylthiopyrimidine	54–56	1743
6-Dimethylamino-2-methylthio-4,5-pyrimidinediamine	154–155	1569
5-Dimethylamino-6-methylthio-4(3*H*)-pyrimidinone	203–205	1017
5-Dimethylaminomethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	194	2036
4-Dimethylamino-6-nitroaminopyrimidine	241	2625
2-Dimethylamino-5-nitro-6-nitroamino-4(3*H*)-pyrimidinone	219	638
2-Dimethylamino-5-nitro-6-propylamino-4(3*H*)-pyrimidinone	257–259	2640
2-Dimethylamino-5-nitro-4-pyrimidinamine	210–211 or 213–215	1089,1766,2327
4-Dimethylamino-5-nitro-2-pyrimidinamine	142–143	1437,1766
6-Dimethylamino-5-nitro-4-pyrimidinamine	159–161 or 162–163 (135?)	2334,2641,2642
2-Dimethylamino-5-nitropyrimidine	222	2643,2644
2-Dimethylamino-5-nitro-4,6-pyrimidinediamine	249–250	1484
6-Dimethylamino-5-nitro-2,4-pyrimidinediamine	234	2217
2-Dimethylamino-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	anal	1484
6-Dimethylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	247	2407
6-Dimethylamino-5-nitro-4(3*H*)-pyrimidinethione	182–185	1583
2-Dimethylamino-5-nitro-4(3*H*)-pyrimidinone	301 or 304–311	863,1089
6-Dimethylamino-5-nitro-4(3*H*)-pyrimidinone	207–208 or 216–217	1090,1589

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Dimethylamino-5-nitroso-4,6-pyrimidinediamine	282 or 283	1083,1091,1092,1768,2645
6-Dimethylamino-5-nitroso-2,4-pyrimidinediamine	252–254 or 258–259	1092,1739,1768,2646
2-Dimethylamino-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	294–296	2085,2647
2-Dimethylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxamide	> 300	2647
2-Dimethylamino-6-propoxy-4-pyrimidinamine	64	637
6-Dimethylamino-2-propoxy-4-pyrimidinamine	182–183	615
2-Dimethylamino-6-propylamino-4,5-pyrimidinediamine	H_2SO_4: 240	2618
2-Dimethylamino-6-propyl-4(3*H*)-pyrimidinone	127	863
2-Dimethylamino-4-pyrimidinamine	148 to 155	615,1742,2084,2648
2-Dimethylamino-5-pyrimidinamine	crude	1089
4-Dimethylamino-2-pyrimidinamine	155–156	1741,1742
4-Dimethylamino-5-pyrimidinamine	103–109	1583
5-Dimethylamino-4-pyrimidinamine	121–124	2649
6-Dimethylamino-4-pyrimidinamine	202 to 213 (178?)	852,866,2172,2650
2-Dimethylaminopyrimidine	78–81/17, sp; pic: 170–171	708,2083,2651,6852
4-Dimethylaminopyrimidine	40, 60/0.1, 131–132/50, nmr	36,708,1744,2652
5-Dimethylaminopyrimidine	79–80; pic: 172	1972,2473
2-Dimethylamino-5-pyrimidinecarbaldehyde	267–268, ir, ms, nmr	6170
2-Dimethylamino-4-pyrimidinecarbonitrile	112–113 (116–118?)	1745,2653
2-Dimethylamino-5-pyrimidinecarbonitrile	133–134	2654
4-Dimethylamino-5-pyrimidinecarbonitrile	109–111 or 114	1614,2655
6-Dimethylamino-4-pyrimidinecarbonitrile	88–90	1745
2-Dimethylamino-4-pyrimidinecarboxamidine	HCl: 286; $PhSO_3H$: 228–230	2653,2656

2-Dimethylamino-4,5-pyrimidinediamine	crude: 121; HCl: 260; H_2SO_4: 216	1089,1766,2327,2626
2-Dimethylamino-4,6-pyrimidinediamine	261–263	1083,1091
4-Dimethylamino-2,5-pyrimidinediamine	H_2SO_4: 198–199	1766
5-Dimethylamino-2,4-pyrimidinediamine	159–160; HCl: 242	1766,2649
6-Dimethylamino-2,4-pyrimidinediamine	180–181 or 193–194	1092,1740,2646
6-Dimethylamino-4,5-pyrimidinediamine	157–159; H_2SO_4: 165	2641,2642,2650,2657
2-Dimethylamino-4,6(1*H*,5*H*)-pyrimidinedione	320 or 356	1241,2044,2472,2474,2475
5-Dimethylamino-2,4(1*H*,3*H*)-pyrimidinedione	297 to 308	1046,1766,2473,2658
6-Dimethylamino-2,4(1*H*,3*H*)-pyrimidinedione	312–314 or 317–320	2309,2454,2474,2659,2660
5-Dimethylamino-2,4(1*H*,3*H*)-pyrimidinedithione	256	2473
4-Dimethylaminopyrimidine 1-oxide	52–54/0.05, nmr	36
5-Dimethylaminopyrimidine 1-oxide	154	1972
2-Dimethylamino-4(3*H*)-pyrimidinethione	149 or 161–162	863,1507
4-Dimethylamino-2(1*H*)-pyrimidinethione	265–270 or 281–283	708,1086,1515,2661,2662
6-Dimethylamino-4(3*H*)-pyrimidinethione	276–280	1743
2-Dimethylamino-4,5,6-pyrimidinetriamine	H_2SO_4: 314	1484
6-Dimethylamino-2,4,5-pyrimidinetriamine	209	1092,1484,2626,2646
1-Dimethylamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	183–184	2079
5-Dimethylamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	283–285	2663
2-Dimethylamino-4(3*H*)-pyrimidinone	170 or 174–176	863,1089,1799,2083,2084
4-Dimethylamino-2(1*H*)-pyrimidinone	248 to 259	1678,1743,2662,2664,2665
6-Dimethylamino-4(3*H*)-pyrimidinone	271 to 289, nmr	167,968,1743,1791
4-Dimethylamino-5-sulfo-oxy-2-pyrimidinamine	254–258	1011
2-Dimethylamino-5-thioformamido-4,6-pyrimidinediamine	180	1091
4-Dimethylamino-2-thioxo-1,2-dihydro-5-pyrimidinecarbonitrile	230–231	1086
4-Dimethylamino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylic acid	—	1086
5-Dimethylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	228–230	2649

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Dimethylamino-2,5,6-trifluoropyrimidine	45–47	1728
5-Dimethylamino-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	94	1863
6-Dimethylamino-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	78–79	855
4-Dimethylamino-1,2,6-trimethylpyrimidinium iodide	anal, nmr, X-ray	7033
2-Dimethylamino-4-vinylpyrimidine	95–98/14; dimer: 109–110; pic: 130–133	2078,2666
2-Dimethylamino-5-vinylpyrimidine	67, nmr	261
1,3-Dimethyl-5,6-bis-*N*-methylacetamido-2,4(1*H*,3*H*)-pyrimidinedione	222–224	588,643
1,3-Dimethyl-5,6-bismethylamino-2,4(1*H*,3*H*)-pyrimidinedione	144, uv; pic: 165	675,2667
4,5-Dimethyl-2,6-bistrimethylsiloxypyrimidine	83–85	1829
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde	PhNHN=: 215–216, nmr; dnp: 318–320	323,2668,6461
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	76–77; H_2NN=: 232–233; MeHNN=: 216–217	1905,2669
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbohydrazide	202–203	1114
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbohydrazide	212–213	1114
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	153 to 165	794,1132,1133,1166,2670,2671
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	166–168 or 168–170	1132,1133,2671,2672
1,6-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	297–298	1199,3995
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl azide	105	1114
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl azide	58–59	1114
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl chloride	155	2670
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	216–218 or 219–220	4,282,1987,2670,3995
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	238–240	1133,1851,2671
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	180–182 or 183	904,2527,2670

1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	145 to 153	1851,2669,2673–2676
1,5-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	288	2677,2678
1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4,5-pyrimidinedicarbonitrile	182–185	1987
N,*N*-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonamide	340–342	1180,2679
6-*β*,*β*-Dimethylhydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	218–219	2680
5-Dimethylimmoniomethyl-4,6(1*H*,5*H*)-pyrimidinedione	chloride: 231–232	2681
1,3-Dimethyl-5-*N*-methylacetamido-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	153–154	675,1070
1,6-Dimethyl-2-*N*-methylacetamido-4(1*H*)-pyrimidinone	196	2025
3,6-Dimethyl-2-*N*-methylacetamido-4(3*H*)-pyrimidinone	129–130	2025
1,3-Dimethyl-5-methylaminomethylene-2,4,6(1*H*,3*H*,5*H*))-pyrimidinetrione	230–231	1391
1,3-Dimethyl-6-methylamino-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	259–260	2682
1,3-Dimethyl-6-methylaminomethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	99–100	2683
2,4-Dimethyl-6-methylamino-5-nitropyrimidine	107–108	601
1,3-Dimethyl-6-methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	147 to 153, then 260	644,2276,2684
1,3-Dimethyl-6-methylamino-5-nitroso-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	120	1103
4,6-Dimethyl-2-methylamino-5-propylpyrimidine	114	843
1,3-Dimethyl-6-methylamino-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	110–111	855
4,6-Dimethyl-2-methylamino-5-prop-1′-ynylpyrimidine	161	843
4,6-Dimethyl-2-methylamino-5-prop-2′-ynylpyrimidine	132	843
2,4-Dimethyl-6-methylamino-5-pyrimidinamine	185–186	601
2,6-Dimethyl-5-methylamino-4-pyrimidinamine	261–262	1347
4,6-Dimethyl-2-methylamino-5-pyrimidinamine	113	645
2,4-Dimethyl-6-methylaminopyrimidine	126	1405
2,5-Dimethyl-4-methylaminopyrimidine	114	2570
4,5-Dimethyl-6-methylaminopyrimidine	127	2570
4,6-Dimethyl-2-methylaminopyrimidine	98 to 100; pic: 201	861,1741,2685,2686
4,6-Dimethyl-2-methylamino-5-pyrimidinecarbonitrile	195–196 or 198; pic: 152	442,923
2,*N*-Dimethyl-4-methylamino-5-pyrimidinecarboxamide	189	1912

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,6-Dimethyl-2-methylamino-5-pyrimidinecarboxamide	222; pic: 241	923
1,3-Dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	244–245	644,2276,2687
4,6-Dimethyl-2-methylaminopyrimidine 1-oxide	144	2686
1,3-Dimethyl-5-methylamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	200 or 220, uv	551,1138,2688
1,5-Dimethyl-4-methylamino-2(1*H*)-pyrimidinone	177–179	1153
1,6-Dimethyl-2-methylamino-4(1*H*)-pyrimidinone	241–242	911
3,6-Dimethyl-2-methylamino-4(3*H*)-pyrimidinone	213–214	2025
1,3-Dimethyl-6-methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	238–239	1103
2,6-Dimethyl-5-*N*-methylcarbamoylmethyl-4(3*H*)-pyrimidinone	272–275	2019,2020
1,3-Dimethyl-6-(α-methylhydrazino)methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	126–127, ir, nmr	1905,6462
4,6-Dimethyl-2-α-methylhydrazinopyrimidine	59–60	2689
4,6-Dimethyl-2-β-methylhydrazinopyrimidine	86–89	2689
1,3-Dimethyl-6-α-methylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione	122 or 135–137	2687,2690,2691
4,6-Dimethyl-2-methylimino-1,2-dihydro-1-pyrimidinecarbonitrile	120–122	2363
1,3-Dimethyl-4-methylimino-3,4-dihydro-2(1*H*)-pyrimidinone	79; HI: 180	696,806
Dimethyl 2-methyl-4,6-pyrimidinedicarboxylate	150–152	2692
4,6-Dimethyl-2-methylsulfinylmethylpyrimidine	73–75	2222
2,3-Dimethyl-6-methylsulfonyl-4(3*H*)-pyrimidinone	151–152	2142
4,6-Dimethyl-2-methylthiomethylpyrimidine	111/4	2222
3,6-Dimethyl-2-methylthio-5-propyl-4(3*H*)-pyrimidinone	85–68	891,892
5,6-Dimethyl-2-methylthio-4-pyrimidinamine	157–159	614,2090,2693
2,4-Dimethyl-6-methylthiopyrimidine	26–28, 100–101/15, nmr; pic: 150	167,1951
4,5-Dimethyl-2-methylthiopyrimidine	66–70/20 or 80/0.2	2694,2695
4,6-Dimethyl-2-methylthiopyrimidine	24 or 27, 47/0.05, 120–122/17; pic: 109	1046,1951,2099,2532,2696,2697

Dimethyl 2-methylthio-4,5-pyrimidinedicarboxylate	87–88, ir, nmr	6072
4,6-Dimethyl-2-methylthio-5-pyrimidinol	225–229	1011,1012
1,5-Dimethyl-4-methylthio-2(1*H*)-pyrimidinone	83 or 104–106	2698,2699
1,6-Dimethyl-2-methylthio-4(1*H*)-pyrimidinone	207 or 224–225; HI: 210–212	911,2242
1,6-Dimethyl-4-methylthio-2(1*H*)-pyrimidinone	170–171 or 173	911, 2241
3,6-Dimethyl-2-methylthio-4(3*H*)-pyrimidinone	89 to 94	1145,1146,2106,2242, 2553,2700,2701
5,6-Dimethyl-2-methylthio-4(3*H*)-pyrimidinone	216 to 237	1529,2157,2702,3837
1,3-Dimethyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	139–140	755,1099
2,6-Dimethyl-5-nitro-4-pyrimidinamine	159–160	601,1428
4,6-Dimethyl-5-nitro-2-pyrimidinamine	220 or 225	1157,1431
1,3-Dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	154 to 161, ir, nmr, uv	282,1099,1432,1492, 1584,2703–2705,3904,3995
1,6-Dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	249–250 (191?)	1105,1130
3,6-Dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	229–230 or 231–233 (149?)	1130,1492,2706
1,3-Dimethyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	146 to 152	1082,1099,1140,2091,2707
2,6-Dimethyl-5-nitro-4(3*H*)-pyrimidinone	222	1157
1,3-Dimethyl-5-nitroso-6-propylamino-2,4(1*H*,3*H*)-pyrimidinedione	224–226	2276
4,6-Dimethyl-2-nitrosopyrimidine	111–112, nmr	6016
1,3-Dimethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	141 or 144–147	1141,2707–2709
4,6-Dimethyl-5-nitroso-2(1*H*)-pyrimidinone (?)	—	861
4,6-Dimethyl-2-β-nitrovinylpyrimidine	123–124	2037
1,4-Dimethyl-6-oxo-1,6-dihydro-2-pyrimidinecarbaldehyde	oxime: 193–194	2522
2,4-Dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	dnp: 305; oxime: 238–240	2128
4,6-Dimethyl-2-oxo-1,2-dihydro-5-pyrimidinecarbaldehyde	PhHNN=: 229–230	2128
1,2-Dimethyl-4-oxo-1,4-dihydro-5-pyrimidinecarbonitrile	201–202	1551
1,2-Dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	83	1551
1,4-Dimethyl-6-oxo-1,6-dihydro-2-pyrimidinecarbonitrile	70–72	2522
1,2-Dimethyl-4-oxo-1,4-dihydro-5-pyrimidinecarboxamide	248–249	1551

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1,2-Dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	251	1551
1,4-Dimethyl-2-oxo-1,2-djhydro-5-pyrimidinecarboxamide	223	1465
2,5-Dimethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	260–261	2038
1,3-Dimethyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	270–272	655,1140,2710–2715
1,5-Dimethyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	213–215	2578
1,4-Dimethyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	280	809
4,6-Dimethyl-2-propylamino-5-pyrimidinamine	101	645
2,4-Dimethyl-6-propylaminopyrimidine	HCl: 205	1825
4,6-Dimethyl-2-propylaminopyrimidine	130/11; pic: 125	1825
1,3-Dimethyl-6-propylamino-2,4(1*H*,3*H*)-pyrimidinedione	170	2276
4,6-Dimethyl-2-α-propylhydrazinopyrimidine	95/0.2; PhCH=: 111–112	3769
1,3-Dimethyl-6-propylidenehydrazino-2,4(1*H*,3*H*)-pyrimidinedione	196–197 or 203	2716–2718
4,6-Dimethyl-5-propyl-2-pyrimidinamine	165–167	843
2,4-Dimethyl-6-propylpyrimidine	75/10; pic: 85–86	2719
1,3-Dimethyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	60–61, 173–176/4.5	854,2720
1,6-Dimethyl-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	85–87	895
1,6-Dimethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	148–150	2489
3,6-Dimethyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	52–54	895
3,6-Dimethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	193–194 or 198	891,892.2489
4,6-Dimethyl-*N*-propyl-2-pyrimidinesulfonamide	111–112	2347
2,6-Dimethyl-5-propyl-4(3*H*)-pyrimidinone	157–159	2721
4,6-Dimethyl-1-propyl-2(1*H*)-pyrimidinone	92–94, ir, nmr	295
4,6-Dimethyl-5-propyl-2(1*H*)-pyrimidinone	181	843
5,6-Dimethyl-2-propyl-4(3*H*)-pyrimidinone	127 or 132–133	880,2722
1,3-Dimethyl-5-propylthio-2,4(1*H*,3*H*)-pyrimidinedione	66–68, nmr	3898

1,3-Dimethyl-6-propylthio-2,4(1*H*,3*H*)-pyrimidinedione	106–108, nmr	3898
4,6-Dimethyl-2-prop-2′-ynylaminopyrimidine	119	843
1,3-Dimethyl-5-prop-2′-ynyloxy-2,4(1*H*,3*H*)-pyrimidinedione	140–142	2723
4,6-Dimethyl-5-prop-1′-ynyl-2-pyrimidinamine	214	843
4,6-Dimethyl-5-prop-2′-ynyl-2-pyrimidinamine	153	843
2,4-Dimethyl-6-prop-1′-ynylpyrimidine	58–60, 110/3	1857,2724
4,6-Dimethyl-2-prop-1′-ynylpyrimidine	105–106, 140/18	1857,2724
4,6-Dimethyl-1-prop-2′-ynyl-2(1*H*)-pyrimidinimine	HBr: 203	843
2,6-Dimethyl-5-prop-2′-ynyl-4(3*H*)-pyrimidinone	223–224	2721
4,6-Dimethyl-5-propyl-1′-ynyl-2(1*H*)-pyrimidinone	257	843
4,6-Dimethyl-5-prop-2′ynyl-2(1*H*)-pyrimidinone	231	843
2,4-Dimethyl-5-pyrimidinamine	107–108	651
2,5-Dimethyl-4-pyrimidinamine	202 to 206; pic: 222 or 224–225	1159,2725–2729
2,6-Dimethyl-4-pyrimidinamine	184–185 or 190, ir, uv, xl, st	420,648,727,967, 1122,1212,1216,1405, 1855,2105,2577,2730–2733
4,5-Dimethyl-2-pyrimidinamine	215–217 (159?)	1135,1930,2097,2734,2735
4,6-Dimethyl-2-pyrimidinamine	149 to 158, sp	79,238,291,647,1874,2318,2363, 2735–2743,3723
5,6-Dimethyl-4-pyrimidinamine	229–231	1135,2108
4,6-Dimethyl-2-pyrimidinamine 1-oxide	252 or 254–255, ms	291,313,654
2,4-Dimethylpyrimidine	– 4, 37–41/13, 150/760, ir, nmr, uv; pic: 136–138 or 137–140	2105,2149,2328,2546,2574, 2744,3996
2,5-Dimethylpyrimidine	19, 59–60/13, 64–65/15, 75–77/25	2745–2748
4,5-Dimethylpyrimidine	25, 71/21, 102/9, 159/760 (or 175/760); pic: 160–161	575,1135,2749–2751

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,6-Dimethylpyrimidine	24–26, 155–156/720, 157–161/760; 1-MeI: 247–250; pic: 141–142	764,1517,1855,1874,2099,2258, 2566,2603,2744,2752–2755
2,6-Dimethyl-4-pyrimidinecarbaldehyde	oxime: 200 or 213, ir, nmr; oxime/H_2O: 195	763,1745,2756,3762
4,6-Dimethyl-2-pyrimidinecarbaldehyde	88–90; oxime: 75–78 (*anti*), 196–198 (*syn*)	2222,2757–2760
2,6-Dimethyl-4-pyrimidinecarbohydrazide	194–195	2266
2,4-Dimethyl-5-pyrimidinecarbonitrile	51–53	2761
2,6-Dimethyl-4-pyrimidinecarbonitrile	51 to 57, 110/21, 113–115/29, nmr	142,2268,2603,2604, 2762,2763,3762
4,5-Dimethyl-2-pyrimidinecarbonitrile	70, ir, nmr	3743
4,6-Dimethyl-2-pyrimidinecarbonitrile	81–82 or 85, 135/20, nmr	142,2268,2466,2603,2604,2764
5,6-Dimethyl-4-pyrimidinecarbonitrile	56–57, ir, nmr	3743
2,4-Dimethyl-5-pyrimidinecarboxamide	188–189 or 191–192	651,2765
2,6-Dimethyl-4-pyrimidinecarboxamide	185	2266,2268,2603,2766
4,6-Dimethyl-2-pyrimidinecarboxamide	183–184 or 190–191	792,2603
4,6-Dimethyl-2-pyrimidinecarboxamidine	155–156; $PhSO_3H$: 226	1856,2696
2,4-Dimethyl-5-pyrimidinecarboxylic acid	154–155 or 188–189, ir, nmr, uv	2767,3996
2,6-Dimethyl-4-pyrimidinecarboxylic acid	191–192 or 198–200	2266,2603
4,6-Dimethyl-2-pyrimidinecarboxylic acid	145–146	1517,2603,2757
2,5-Dimethyl-4,6-pyrimidinediamine	225–226 or 234–235	1118,1159
2,6-Dimethyl-4,5-pyrimidinediamine	248 or 252–254	750,1428
4,6-Dimethyl-2,5-pyrimidinediamine	183–184	614,1574
5,6-Dimethyl-2,4-pyrimidinediamine	192; pic: > 300	1118,1135

Dimethyl 4,6-pyrimidinedicarboxylate	81–82	2692
1,3-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	120 to 124, sp	263,266,435,644,812,963,1507, 1535,1536,1546,1841,2041,2519, 2549,2720,2768–2772
1,5-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	280–293 (255–257?), nmr, uv	812,1153,1807,2296,2492, 2698,2770,2773–2776,3904,5654
1,5-Dimethyl-4,6(1*H*,5*H*)-pyrimidinedione	298–300 or 307–310	1900,2587,2777
1,6-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	220 to 227	698,1100,1143,1145,1154, 1829,2240,2242,2778–2783
2,5-Dimethyl-4,6(1*H*,5*H*)-pyrimidinedione	anal	1159,1801,2784
3,5-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	202 to 218, nmr, uv	760,765,812,963,965,2775, 2785–2787,3904
3,6-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	259 to 265, ir, nmr	130,278,1100,1124,1143,1152, 1864,1942,2240,2242,2522,2539, 2779,2782,2788–2791
5,6-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	294 to 307, ir, nmr	130,698,766,767,1135,1673, 2157,2359,2550,2792–2794
1,3-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedithione	121	806,968,2636
5,6-Dimethyl-2,4(1*H*,3*H*)-pyrimidinedithione	> 300	1035,1135
2,4-Dimethylpyrimidine 1-oxide	83–85, 85–88/3, ir, nmr; pic: 112	121,2744
2,4-Dimethylpyrimidine 3-oxide	49–52, 76–77/3, ir, nmr	121
4,5-Dimethylpyrimidine 1-oxide	139–140, nmr	3743
4,5-Dimethylpyrimidine 3-oxide (?)	semisolid, nmr; pic: 124–126	3743
4,6-Dimethylpyrimidine 1-oxide	115, ir, nmr	2744,5898
4,6-Dimethyl-2(1*H*)-pyrimidineselone	166–167, ir, uv	3986
4,6-Dimethyl-2-pyrimidinesulfenamide	99–100	1711
4,6-Dimethyl-2-pyrimidinesulfonamide	198–199 or 200–201	1711,2347,2348,2795,2796
2,6-Dimethyl-4-pyrimidinesulfonic acid	K: 326; Na: 285	2263,2763
4,6-Dimethyl-2-pyrimidinesulfonic acid	K: 292–293 or 295	1711,2263

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5,6-Dimethyl-4-pyrimidinesulfonic acid	K: 314	2263
4,6-Dimethyl-2-pyrimidinesulfonohydrazide	124–125	1711
4,6-Dimethyl-2-pyrimidinesulfonyl chloride	crude	2347,2348
4,6-Dimethyl-2-pyrimidinesulfonyl fluoride	58	1711
1,2-Dimethyl-4(1*H*)-pyrimidinethione	244–246, uv	690
1,4-Dimethyl-2(1*H*)-pyrimidinethione	3-$MeHSO_4$: 156; 3-$MeClO_4$: 91	1803
2,3-Dimethyl-4(3*H*)-pyrimidinethione	108–109	690
2,6-Dimethyl-4(3*H*)-pyrimidinethione	221–230 (200?), nmr	167,1427,2612,2733,2797
4,6-Dimethyl-2(1*H*)-pyrimidinethione	210 or 218; Na: > 300	133,764,2099,2321,2797–2799
5,6-Dimethyl-4(3*H*)-pyrimidinethione	240–265	1135
1,3-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	118 to 124, nmr, uv	143,644,789,1134,2453,2708, 2800–2805,3736,3739,3753,3756
1,5-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	169–170 or 172–173	2806–2808
1,2-Dimethyl-4(1*H*)-pyrimidinimine	HI: 248	690
1,4-Dimethyl-2(1*H*)-pyrimidinimine	HCl: 222; HI: 253–254; pic: 204	1465,2742
1,6-Dimethyl-2(1*H*)-pyrimidinimine	HI: 220	2114
2,3-Dimethyl-4(3*H*)-pyrimidinimine	M^+, nmr; HI: 242–245 or 246, nmr	479,2570
3,5-Dimethyl-4(3*H*)-pyrimidinimine	HI: 224	2570
3,6-Dimethyl-4(3*H*)-pyrimidinimine	HI: 216	2570
4,6-Dimethyl-5-pyrimidinol	138, nmr; H_2O: 90; pic: 176–177	2809,3758,3951
4,6-Dimethyl-5-pyrimidinol 1-oxide	187–189, nmr	21,3758
1,2-Dimethyl-4(1*H*)-pyrimidinone	180–182 or 190; HI: 118; pic: 178–180	690(?),1136,1551,2551

1,4-Dimethyl-2(1*H*)-pyrimidinone	156–157; pic: 159; 3-$MeHSO_4$: 159; 3-$MeClO_4$: 128	1465,1803,1879,1951, 2742,2810,2811
1,5-Dimethyl-2(1*H*)-pyrimidinone	132–134; HCl: > 230	1879,2699
1,5-Dimethyl-4(1*H*)-pyrimidinone	140–144	1879
1,6-Dimethyl-2(1*H*)-pyrimidinone	88–89; HCl: 229; pic: 213	1465,1879
1,6-Dimethyl-4(1*H*)-pyrimidinone	pic: 174–176	1136
2,3-Dimethyl-4(3*H*)-pyrimidinone	62–66, nmr; pic: 172	112,297,479,690(?),1136,1735, 2551,3726
2,5-Dimethyl-4(3*H*)-pyrimidinone	174 or 175–176	1420,2103,2108,2728,2812, 2813
2,6-Dimethyl-4(3*H*)-pyrimidinone	190 to 206, nmr	167,1146,1852,2000, 2106,2107,2235,2263,2543, 2612,2814–2822,4334
3,5-Dimethyl-4(3*H*)-pyrimidinone	59	1879
3,6-Dimethyl-4(3*H*)-pyrimidinone	80–82; pic: 188–190	1136,1879,2249
4,5-Dimethyl-2(1*H*)-pyrimidinone	196, ms; HCl: 250 or 264	56,2097,2823
4,6-Dimethyl-2(1*H*)-pyrimidinone	190 to 199, ms; HCl: 260 or 281	56,79,861,1711,1936,2098,2348, 2532,2602,2736,2824–2827
5,6-Dimethyl-4(3*H*)-pyrimidinone	205–206 or 208–209	698,1135,2108,2359,2815
4,6-Dimethyl-2(1*H*)-pyrimidinone 3-oxide	HBr: 235–240	2828
1,5-Dimethyl-4-semicarbazido-2(1*H*)-pyrimidinone	< 360(!)	2829
1,3-Dimethyl-4-semicarbazono-3,4-dihydro-2(1*H*)-pyrimidinethione	263	806
1,3-Dimethyl-4-semicarbazono-3,4-dihydro-2(1*H*)-pyrimidinone	268	806
2-*S*,*S*-Dimethylsulfimido-4,6-dimethylpyrimidine	120; pic: 180	2830
4-*S*,*S*-Dimethylsulfimido-2,6-dimethylpyrimidine	101–106	2830
4-*S*,*S*-Dimethysulfimido-2-methoxypyrimidine	71–75	2830
4-*S*,*S*-Dimethylsulfimido-6-methoxypyrimidine	115–118	2830
2-*S*,*S*-Dimethylsulfimido-4-methylpyrimidine	95	2830,2831
4-*S*,*S*-Dimethylsulfimido-2-methylthiopyrimidine	67; pic: 175–180	2830

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-*S*,*S*-Dimethylsulfimidopyrimidine	40, nmr	2830,2831
4-*S*,*S*-Dimethylsulfimidopyrimidine	100–105, nmr	2830
1,3-Dimethyl-5-sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione	253	1126
2,6-Dimethyl-5-sulfomethyl-4-pyrimidinamine	> 310	584
2-Dimethylsulfoniomethyl-6-methyl-4-pyrimidinamine	iodide: 138–140, nmr	3748
5-Dimethylsulfonio-2,4(1*H*,3*H*)-pyrimidinedione	chloride: 190	2832
2-Dimethylsulfoxoniomethyl-3-methyl-4(3*H*)-pyrimidinone	iodide: 181, ms, nmr; methylide: 190, ms, nmr	112
4,6-Dimethyl-2-thiocarbamoylmethylpyrimidine	149–150	2833
5-*N*,*N*-Dimethyl(thiocarbamoyloxy)-2-methylthiopyrimidine	100–101	2834
2,4-Dimethyl-6-thioureidopyrimidine	223 to 235, nmr	2842,3861,3863
4,6-Dimethyl-2-thioureidopyrimidine	262–264 or 270–275, nmr	3861,3862
2,4-Dimethyl-6-thioxo-1,6-dihydro-5-pyrimidinecarbonitrile	210–211 or 212	791,2835
4,6-Dimethyl-2-thioxo-1,2-dihydro-5-pyrimidinecarbonitrile	204–205, ir, nmr	442
1,3-Dimethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	183 or 184–186	2836,2837
1,3-Dimethyl-6-thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione	126	2838
1,3-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	107 to 111, nmr	258,962,2035,2636,2839
1,3-Dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	131–132 or 132–133	968,2840
1,5-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	226 to 232	963,2027,2775
1,5-Dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	211–213	1153
1,6-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	235–245 or 268–270	1145,1915
1,6-Dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	241	911
3,5-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	207–208	2775
3,6-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	265 or 271–273	2788,2841
5,6-Dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	279 to 290	1155,1684,2108,2157,2359,2550, 2793,2794

2,4-Dimethyl-5-trimethylammonio-4-pyrimidinamine	iodide: 217–218	1347
1,3-Dimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxamide	217 to 221	2843–2845
4,6-Dimethyl-2-ureidopyrimidine	209 or 211	2362,2554
1,3-Dimethyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	> 290	600,2846
1,3-Dimethyl-5-ureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	210	1140,2847
5,6-Dimethyl-2-ureido-4(3*H*)-pyrimidinone	269	1150
2,4-Dimethyl-5-vinylpyrimidine	90–100/30, nmr	3999
2,4-Dimethyl-6-vinylpyrimidine	110–120/3, nmr	3999
4,6-Dimethyl-2-vinylpyrimidine	90–100/3, nmr	3999
2,4-Dioxo-1-propyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	165 or 172–174	1166,1883
2,6-Dioxo-3-propyl-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	181–183	1883
2,4-Dioxo-3-propyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	172–173	904
2,6-Dioxo-1-propyl-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	204–205	2848
2,6-Dioxo-3-propyl-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (?)	206–207	2673 (cf. 2848)
2,6-Dioxo-5-propyl-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	302–303	1224
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde	302–303 or 303–304; $H_2NN{=}$: 298; oxime: anal; tsc: 275 or 320	323,1597,1598,2042,2128, 2590,2849–2853
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	H_2O: 268 to 275; MeHNN=: 274–275; oxime: anal; PhHNN=: 354–356; tsc: 320	701,2854–2862
4,6-Dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarbaldehyde	245–250 or 250–252; PhHNN=: 254–257	1027,1028,2681
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbohydrazide	245	1844
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	280 to 295 (320?)	1175,1249,1602,2863–2869
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	> 260	2672
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl azide	176	1114
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl chloride	crude	2870
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl chloride	–	2871

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbothioamide	310–312	1491
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	> 300	1980,2863,2868
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	- -	2872
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	278 to 297	788,1175,1490,1631, 1980,2864,2873,2874
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	324 to 345 (245?)	1592,2034,2275,2673,2855,2859, 2861,2871,2875–2885,2887–2889
4,6-Dioxo-1,4,5,6-tetrahydro-2-pyrimidinecarboxylic acid	220	1405
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonamide	305	964,1450
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonamide	> 235	2070,2346
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonic acid	Na: anal	1450
2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid	248–250	2070,2071,2346
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride	> 300	2679
2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl fluoride	255–256	1608
4,6-Dioxo-2-thioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde	dnp: 295	2890,2891
2,6-Dipropoxy-4-pyrimidinamine	42	2523
4,6-Dipropoxy-2-pyrimidinamine	72, 184/42	2130
2,6-Dipropyl-4-pyrimidinamine	186–189	2892
2,6-Dipropyl-4(3*H*)-pyrimidinone	71–73	880
4,6-Dipropyl-2-ureidopyrimidine	134	2554
4,6-Dithiocyanato-5-pyrimidinamine	> 250	602
2,4-Dithioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	261–263	958
2,6-Dithioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	281–282	1030
2,6-Dithioxo-1,2,3,6-tetrahydro-4(3*H*)-pyrimidinone	262–264	958
4,6-Dithioxo-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone	266–267	958

1,3-Divinyl-2,4(1*H*,3*H*)-pyrimidinedione	60, ir, nmr	378
2-Ethoxycarbonylaminopyrimidine	116–117; pic: 157–159	2893
4-Ethoxycarbonylaminopyrimidine	167–168; pic: 196–200	2893
5-Ethoxycarbonylamino-2,4(1*H*,3*H*)-pyrimidinedione	223–224	2893
4-Ethoxycarbonylamino-2(1*H*)-pyrimidinone	> 290	2894
4-Ethoxycarbonyl-5-methyl-6-oxo-1,6-dihydro-2-pyrimidinecarboxylic acid	223–225	2038
5-Ethoxycarbonyloxy-6-methyl-2,4-pyrimidinediamine	135–136	1328
4-Ethoxy-2,6-diethyl-5-methylpyrimidine	229–231/760	2061
2-Ethoxy-4,6-diethylpyrimidine	57–58/0.01	2895
2-Ethoxy-4,6-dimethylpyrimidine	162(?), 22/760; HCl: anal	1874,1876
4-Ethoxy-2,6-dimethylpyrimidine	68/2.7, 92–94/35, 98/45; pic: 119 or 125	671,739,2524,2896,3884
6-Ethoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	133	644
4-Ethoxy-2,6-dimethylpyrimidine 1-oxide	102–104	739
2-Ethoxy-5,6-dimethyl-4(3*H*)-pyrimidinone	129–131, ir, nmr	130
4-Ethoxy-1,5-dimethyl-2(1*H*)-pyrimidinone	108–110 or 111	2024,2492,2786
5-Ethoxy-2,3-dimethyl-4(3*H*)-pyrimidinone	100	1821
5-Ethoxy-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	260 or 272	2123,2897
5-Ethoxy-4-ethoxymethyl-2-ethylthiopyrimidine	167	2123
5-Ethoxy-6-ethoxymethyl-2-ethylthio-4(3*H*)-pyrimidinone	123	2123
4-Ethoxy-6-ethoxymethyl-2-methylpyrimidine	liquid, crude; pic: 91–93	1877
5-Ethoxy-4-ethoxymethyl-2-pyrimidinamine	106–107	1149
5-Ethoxy-6-ethoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	168–170	2123,2898
5-Ethoxy-6-ethoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	174–176 or 178	2123,2898
4-Ethoxy-6-ethylaminopyrimidine	88–89	1245
4-Ethoxy-5-ethyl-2-ethylsulfonyl-6-methylpyrimidine	212–215/10	1059
4-Ethoxy-5-ethyl-2-ethylthio-6-methylpyrimidine	139–140/5	1059
4-Ethoxy-l-ethyl-5-methyl-2(1*H*)-pyrimidinone	78	2492

Pyrimidine	m.p. (°C), etc.	Ref.
4-Ethoxy-5-ethyl-1-methyl-2(1*H*)-pyrimidinone	91, uv	1219
4-Ethoxy-5-ethyl-6-methyl-2(1*H*)-pyrimidinone	179–180	1059
6-Ethoxy-3-ethyl-2-methyl-4(3*H*)-pyrimidinone	1-EtBF_4: 227–228	2588
6-Ethoxy-3-ethyl-1-methyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	230–234	2899
2-Ethoxy-5-ethyl-4-pyrimidinamine	51–52	1208
4-Ethoxy-5-ethyl-2-pyrimidinamine	57–58	1208
4-Ethoxy-2-ethylpyrimidine	liquid, anal	2551
2-Ethoxy-5-ethyl-4,6(1*H*,5*H*)-pyrimidinedione	211	2900
6-Ethoxy-1-ethyl-4(1*H*)-pyrimidinimine	HBF_4: 197–198	1245
2-Ethoxy-1-ethyl-4(1*H*)-pyrimidinone	crude, 94–97	2901
2-Ethoxy-5-ethyl-4(3*H*)-pyrimidinone	109–110	1219
4-Ethoxy-1-ethyl-2(1*H*)-pyrimidinone	88	812,2024,2902,2903
4-Ethoxy-5-ethyl-2(1*H*)-pyrimidinone	158–160	1219
6-Ethoxy-3-ethyl-4(3*H*)-pyrimidinone	1-EtBF_4: 181–182	2588
4-Ethoxy-2-ethylsulfonyl-6-methyl-5-propylpyrimidine	crude	1453,1454
4-Ethoxy-2-ethylsulfonyl-5-methylpyrimidine	67–68	1543,1748,2156
4-Ethoxy-2-ethylsulfonylpyrimidine	194/4.5	828,1748
5-Ethoxy-2-ethylthio-4-isocyanatopyrimidine	45–50, 228–235/23	2365
4-Ethoxy-2-ethylthio-6-methyl-5-propylpyrimidine	147/4	1453,1454
4-Ethoxy-2-ethylthio-5-methylpyrimidine	135–136/12	1748,2155
4-Ethoxy-2-ethylthio-6-methylpyrimidine	105–106/1, 154/20	1547,2788
5-Ethoxy-2-ethylthio-1-methyl-4(1*H*)-pyrimidinone	149–151	2904
5-Ethoxy-2-ethylthio-3-methyl-4(3*H*)-pyrimidinone	50	2904
2-Ethoxy-6-ethylthio-4-pyrimidinamine	165–169/1.5	616
5-Ethoxy-2-ethylthio-4-pyrimidinamine	105	1188

4-Ethoxy-2-ethylthiopyrimidine	31–32, 124/11, 138/18; HCl: 120–121	828,967,1676
4-Ethoxy-2-ethylthio-5-pyrimidinecarboxamide	134	1253
5-Ethoxy-2-ethylthio-4(3*H*)-pyrimidinethione	144–145	2365
5-Ethoxy-2-ethylthio-4(3*H*)-pyrimidinone	169	1188
5-Ethoxy-2-ethylthio-4-thiocyanatopyrimidine	66–67	2365
5-Ethoxy-2-ethylthio-4-ureidopyrimidine	166–167	2365
2-Ethoxy-5-ethynyl-4(3*H*)-pyrimidinone	178–180	2361
4-Ethoxy-5-ethynyl-2(1*H*)-pyrimidinone	198–201	1259,2361
4-Ethoxy-5-fluoro-2-methoxypyrimidine	45–47	2124
4-Ethoxy-5-fluoro-1-methyl-2(1*H*)-pyrimidinone	135–136	1260
2-Ethoxy-5-fluoro-4-pyrimidinamine	—	1268
4-Ethoxy-6-fluoro-2-pyrimidinamine	120–123	1040
2-Ethoxy-5-fluoro-4(3*H*)-pyrimidinone	182–183	1724
4-Ethoxy-5-fluoro-2(1*H*)-pyrimidinone	165–167	1267
4-Ethoxy-2-hydrazino-6-methylpyrimidine	70–73 or 82–83	2106,2126
4-Ethoxy-6-hydrazinopyrimidine	118–119 or 200	167,2521
2-Ethoxy-1-β-hydroxyethyl-5-methyl-4(1*H*)-pyrimidinone	133–135	1322
4-Ethoxy-1-β-hydroxyethyl-2(1*H*)-pyrimidinone	82–83	1323
2-Ethoxy-5-hydroxymethyl-4-pyrimidinamine	148–150	2203,2227
5-Ethoxy-2-hydroxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	209–210	1958
6-Ethoxy-4-imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	141–142	1066
5-Ethoxy-4-iodo-2-isopropylpyrimidine	145/20	1890
2-Ethoxy-6-isopropoxy-4-pyrimidinamine	130–131	2523
4-Ethoxy-2-isopropyl-6-methylpyrimidine	89–90/12	456,2905
6-Ethoxy-2-isopropylthio-4-pyrimidinamine	74–75	615,2906
4-Ethoxy-2-methoxycarbonylmethyl-6-methylpyrimidine	92–95/3	1878
4-Ethoxy-5-methoxy-6-methoxymethyl-2-pyrimidinamine	113–114	1149
4-Ethoxy-6-methoxymethyl-2-pyrimidinamine	90–91	1149

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Ethoxy-2-methoxymethyl-4-pyrimidinamine	99	1763
5-Ethoxy-4-methoxy-2-methylpyrimidine	110/14	1821
4-Ethoxy-6-methoxy-5-nitropyrimidine	69–71	2559
2-Ethoxy-6-methoxy-4-pyrimidinamine	144–145	615,2906,2907 (cf. 616,2593)
4-Ethoxy-6-methoxy-2-pyrimidinamine	98, 226–228/760	2130
5-Ethoxy-4-methoxy-2-pyrimidinamine	110 or 122	1007,2908
6-Ethoxy-2-methoxy-4-pyrimidinamine	112–113	615,2906,2907 (cf. 616)
6-Ethoxy-5-methoxy-4-pyrimidinamine	64–65	916,2210
2-Ethoxy-4-methoxypyrimidine	80/10	2901
2-Ethoxy-6-methoxy-4(3*H*)-pyrimidinone	150–152	972,973
6-Ethoxy-2-methoxy-4(3*H*)-pyrimidinone	184–185	972,973
4-Ethoxy-6-methylamino-2-pyrimidinamine	123–126	1374
5-Ethoxymethyl-2,6-diethyl-4-pyrimidinamine	115	1718
5-Ethoxymethyl-2,6-diethyl-4(3*H*)-pyrimidinone	—	1718
6-Ethoxymethyl-2,5-diethyl-4(3*H*)-pyrimidinone	157–158	2815,2818
2-Ethoxymethyl-1,6-dimethyl-4(1*H*)-pyrimidinimine	HI: anal, nmr, X-ray	7033
5-Ethoxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	223–228	2627
5-Ethoxymethyl-2-ethyl-6-methyl-4(3*H*)-pyrimidinone	51	1718
5-Ethoxymethyl-2-ethyl-4-pyrimidinamine	64–65; pic: 158–160	1532,1910
5-Ethoxymethyl-2-ethyl-4(3*H*)-pyrimidinone	146–147	1532
5-Ethoxymethyl-2-fluoromethyl-4(3*H*)-pyrimidinone	180	2910
1-Ethoxymethyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	129–130	1724,2911
6-Ethoxymethyl-2-hydroxymethyl-5-methyl-4(3*H*)-pyrimidinone	124–126	1759
5-Ethoxymethyl-2-methoxymethyl-4-pyrimidinamine	63–65	1762
2-Ethoxymethyl-6-methyl-4-pyrimidinamine	140–146, nmr	3748

4-Ethoxymethyl-6-methyl-2-pyrimidinamine	106–108	2912,2913
5-Ethoxymethyl-2-methyl-4-pyrimidinamine	85 to 91; pic: 187 to 190	678,1801,1910,1920,1922,1924, 2813,2914–2921
6-Ethoxymethyl-2-methyl-4-pyrimidinamine	89–90 or 95–96	1160,1532
6-Ethoxymethyl-5-methyl-4-pyrimidinamine	137–138	1532
5-Ethoxymethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	126–129	2922
5-Ethoxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	312–315	2233
6-Ethoxymethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	220	767
2-Ethoxymethyl-6-methyl-4(3*H*)-pyrimidinone	69–72	2235
5-Ethoxymethyl-2-methyl-4(3*H*)-pyrimidinone	177 to 184	1420,1801,1920,2230,2919,2923, 2924
6-Ethoxymethyl-2-methyl-4(3*H*)-pyrimidinone	155–157	1877
6-Ethoxymethyl-5-methyl-4(3*H*)-pyrimidinone	118	1532
5-Ethoxymethyl-2-methylthio-4-pyrimidinamine	101–105	1331
4-Ethoxy-6-methyl-2-methylthiopyrimidine	40 or 41; pic: 84	1014,2242,2925
6-Ethoxymethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	190–192	766,767
2-Ethoxy-6-methyl-5-nitro-4-pyrimidinamine	165–166 or 168	1428,2926
5-Ethoxymethyl-2-propyl-4-pyrimidinamine	42	1451
4-Ethoxy-6-methyl-5-propyl-2(1*H*)-pyrimidinone	178–179	1453,1454
5-Ethoxymethyl-2-propyl-4(3*H*)-pyrimidinone	131	1451
2-Ethoxy-6-methyl-4-pyrimidinamine	109–110	1217
4-Ethoxy-6-methyl-2-pyrimidinamine	86 to 100; H_2O: 36–38	1014,1144,1217,2126,2524, 2927,2928
5-Ethoxymethyl-2-pyrimidinamine	130–132	2929
5-Ethoxymethyl-4-pyrimidinamine	79; pic: 186	1451
5-Ethoxy-2-methyl-4-pyrimidinamine	144	1186
6-Ethoxy-2-methyl-4-pyrimidinamine	122 or 123; pic: 177	1556,2252
2-Ethoxy-4-methylpyrimidine	203–205/760, nmr; pic: 104–106	1879,2930
2-Ethoxy-5-methylpyrimidine	78–79/2; pic: 106	1879

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Ethoxy-2-methylpyrimidine	liquid, anal, nmr, uv	2551
4-Ethoxy-6-methylpyrimidine	85/3, 182/760; pic: 101–104 or 105–106	671,2585
6-Ethoxy-2-methyl-4-pyrimidinecarbaldehyde	oxime: 216–217	2522
4-Ethoxy-2-methyl-5-pyrimidinecarbonitrile	35	1010
4-Ethoxy-6-methyl-2-pyrimidinecarbonitrile	59–61	2585
6-Ethoxy-2-methyl-4-pyrimidinecarbonitrile	52–53	2522
4-Ethoxy-6-methyl-2-pyrimidinecarboxamide	122–123	2585
2-Ethoxy-6-methyl-4,5-pyrimidinediamine	136–137	2926
5-Ethoxymethyl-2,4-pyrimidinediamine	162 or 165–166; pic: 204	1938,2931
2-Ethoxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	219	1763
3-Ethoxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	154–156	2932
5-Ethoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	212–213 or 217–218	1597,1940,2933
5-Ethoxy-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	240	2904
6-Ethoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	175	2274
4-Ethoxy-6-methylpyrimidine 1(or 3)-oxide	121	2585
4-Ethoxy-1-methyl-2(1*H*)-pyrimidinethione	134–135	2520
5-Ethoxy-2-methyl-4(3*H*)-pyrimidinethione	177–181	1821
2-Ethoxy-1-methyl-4(1*H*)-pyrimidinone	112–115	1521
2-Ethoxy-3-methyl-4(3*H*)-pyrimidinone	55–60 or 59–60	1521,2901
2-Ethoxy-5-methyl-4(3*H*)-pyrimidinone	147–148	2934
2-Ethoxy-6-methyl-4(3*H*)-pyrimidinone	197 to 210, ir, nmr; HCl: 312–314	1876,2281,2935,2936
4-Ethoxy-1-methyl-2(1*H*)-pyrimidinone	136	812,1537,2937,2938
4-Ethoxy-5-methyl-2(1*H*)-pyrimidinone	212–213	1543,1544,2156
4-Ethoxy-6-methyl-2(1*H*)-pyrimidinone	196	2939

5-Ethoxymethyl-4(3*H*)-pyrimidinone	98	1451
5-Ethoxy-2-methyl-4(3*H*)-pyrimidinone	163–164 and 169–171 (two crystal forms)	1821
6-Ethoxy-2-methyl-4(3*H*)-pyrimidinone	191	1189,1667
5-Ethoxy-2-methyl-3-β-sulfoethyl-4(3*H*)-pyrimidinone	193–194	1821
4-Ethoxy-2-methylsulfonylpyrimidine	crude, 182/4	828
6-Ethoxy-2-methylthio-4-pyrimidinamine	92 to 96	615,1357,1358,2198
2-Ethoxy-4-methylthiopyrimidine	liquid, anal, uv; 1-MeI: anal	2520,2940
4-Ethoxy-2-methylthiopyrimidine	116/11 or 117/10; 1-MeI: anal	828,2520
5-Ethoxy-2-methylthio-4(3*H*)-pyrimidinethione	190	2129
5-Ethoxy-2-methylthio-4(3*H*)-pyrimidinone	190	1188
5-Ethoxy-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	210–211	2904
6-Ethoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	180–181	2274
4-Ethoxy-5-methyl-2-trimethylsiloxypyrimidine	53–54	1793
6-Ethoxy-1-methyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	205	2899
4-Ethoxy-5-nitro-2-pyrimidinamine	227	1582
6-Ethoxy-5-nitro-4-pyrimidinamine	180	1579
2-Ethoxy-5-nitropyrimidine	51–53 or 52–54	2941,2942
2-Ethoxy-5-nitro-4(3*H*)-pyrimidinethione	133	1187
2-Ethoxy-5-nitro-4(3*H*)-pyrimidinone	165–166	1584
4-Ethoxy-5-nitro-2(1*H*)-pyrimidinone	198–199	1584
6-Ethoxy-5-nitroso-2,4-pyrimidinediamine	crude	2943
2-Ethoxy-6-propoxy-4-pyrimidinamine	135–136/1	2523
2-Ethoxy-4-pyrimidinamine	82–83; HCl: 168	615,1217,2131
4-Ethoxy-2-pyrimidinamine	154–156	704
4-Ethoxy-5-pyrimidinamine	—	2944
5-Ethoxy-2-pyrimidinamine	107 to 115	1007,1086,1368,2945,2946
6-Ethoxy-4-pyrimidinamine	145–146 or 151–152	615,1655
2-Ethoxypyrimidine	77–78/20	1715,2947

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Ethoxypyrimidine	63/15; $EtBF_4$: anal	2551,2588,2948
4-Ethoxy-5-pyrimidinecarboxamide	138–140	1633
4-Ethoxy-2,5-pyrimidinediamine	128–129	1582
5-Ethoxy-2,4-pyrimidinediamine	148–149	1367
6-Ethoxy-2,4-pyrimidinediamine	167–169	2943,2949
2-Ethoxy-4,6(1*H*,5*H*)-pyrimidinedione		2950
5-Ethoxy-2,4(1*H*,3*H*)-pyrimidinedione	275	1188,2129,2133,2365,2897
5-Ethoxy-2,4(1*H*,3*H*)-pyrimidinedithione	255–268	2129
5-Ethoxy-2(1*H*)-pyrimidinethione	192–193 or 203–205	1086,2133
6-Ethoxy-4(3*H*)-pyrimidinethione	196–199	2605
6-Ethoxy-2,4,5-pyrimidinetriamine	130–133	2943,2949
2-Ethoxy-4(3*H*)-pyrimidinone	127–129	812,1546,1665,2665
4-Ethoxy-2(1*H*)-pyrimidinone	167 to 170	812,828,1544,1546,1665,1676, 2665,2902,2951
5-Ethoxy-2(1*H*)-pyrimidinone	108–109	1086
5-Ethoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	2952
6-Ethoxy-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	124–125	1139
4-Ethoxy-2-trimethylsiloxypyrimidine	115–117/17	828,1793
2-Ethoxy-1-vinyl-4(1*H*)-pyrimidinone	97–99	1722
4-Ethoxy-1-vinyl-2(1*H*)-pyrimidinone	77–78	1722
Ethyl 3-acetamido-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	221–227	1169
Ethyl 5-acetamido-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	277	2954
Ethyl 2-acetamido-4-methyl-5-pyrimidinecarboxylate	177–179	691
Ethyl 4-acetamido-2-methyl-5-pyrimidinecarboxylate	94–95	1462
Ethyl 4-acetamido-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	217	2695

Ethyl 4-acetamido-5-pyrimidinecarboxylate	100–101	1615
Ethyl 4-acetyl-2-amino-5-pyrimidinecarboxylate	160; PhHNN=: 211	823,824
Ethyl 3-acetyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	139	2955
Ethyl 4-acetyl-2-methyl-5-pyrimidinecarboxylate	98/0.03; PhHNN=: 176	823,824
Ethyl 5-acetyl-4-methyl-6-thioxo-1,6-dihydro-2-pyrimidinecarboxylate	173	791
Ethyl 5-acetyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	206–208	1635
Ethyl 4-acetyl-5-pyrimidinecarboxylate	85/0.05	823
Ethyl 4-allylamino-2-methylthio-5-pyrimidinecarboxylate	44–45	1302
Ethyl 1-allyl-6-amino-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	202	864
Ethyl 2-allylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	218–219	865
Ethyl 3-allyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	174	904
Ethyl 1-allyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	90	2956
Ethyl 1-allyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	115–118 or 119–122	913,914
Ethyl 3-allyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	221	809
Ethyl 2-allylthio-4-amino-5-pyrimidinecarboxylate	92–94	928
Ethyl 5-amino-2-chloro-6-hydrazino-4-pyrimidinecarboxylate	274–276	2957
Ethyl 5-amino-2-chloro-6-isopropylidenehydrazino-4-pyrimidinecarboxylate	197–198	2957
Ethyl 2-amino-4-chloro-6-methyl-5-pyrimidinecarboxylate	crude	2958
Ethyl 4-amino-2-chloro-6-methyl-5-pyrimidinecarboxylate	crude	2958
Ethyl 6-amino-2-chloro-5-nitro-4-pyrimidinecarboxylate	171–172 or 173–174	2435,2959
Ethyl 4-amino-2-chloro-5-pyrimidinecarboxylate	156	1249
Ethyl 2-amino-4-cyano-5-pyrimidinecarboxylate	230–231	1781
Ethyl 4-amino-2-cyano-5-pyrimidinecarboxylate	136–138	1781
Ethyl 5-amino-2,6-dichloro-4-pyrimidinecarboxylate	114	2957
4-Ethylamino-2,6-dimethoxypyrimidine	96–97	2960
Ethyl 6-amino-2-dimethylamino-5-nitro-4-pyrimidinecarboxylate	183	2959
Ethyl 2-amino-4-dimethylamino-5-pyrimidinecarboxylate	106–107	1086
Ethyl 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	207–108	775,2961,2962

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Ethylamino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	270–315	2276
6-Ethylamino-1,3-dimethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	96	855
2-Ethylamino-4,6-dimethyl-5-pyrimidinamine	72; H_2SO_4: 145	645,2963
2-Ethylamino-4,6-dimethylpyrimidine	66–68, 85/8; pic: 156	1825,2964
4-Ethylamino-2,6-dimethylpyrimidine	136/10; HCl: 198	1825
Ethyl 4-amino-2,6-dimethyl-5-pyrimidinecarboxylate	128–129, ir, ms, nmr	1466,6029
Ethyl 6-amino-2,5-dimethyl-4-pyrimidinecarboxylate	148	2038
6-Ethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	165	644
4-Ethylamino-1,5-dimethyl-2(1*H*)-pyrimidinone	144	1153
Ethyl 5-amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	260 or 284	1172
2-Ethylamino-4,6-dipropylpyrimidine	78/0.01, n_D^{20} 1.5142	2964
Ethyl 6-amino-2-ethoxy-5-nitro-4-pyrimidinecarboxylate	120	2959
Ethyl 4-amino-2-ethoxy-5-pyrimidinecarboxylate	105–106	1544
4-Ethylamino-5-*N*-ethylformamido-6-methyl-2-methylthiopyrimidine	122–123	1080
6-Ethylamino-5-*N*-ethylformamido-2,4(1*H*,3*H*)-pyrimidinedione	268	2965
Ethyl 2-amino-4-ethyl-5-pyrimidinecarboxylate	164–165, ir, nmr, uv	3996
Ethyl 4-amino-2-ethylsulfonyl-5-pyrimidinecarboxylate	67–68	1544,1748
4-Ethylamino-2-ethylthio-6-methylpyrimidine	70	1192
4-Ethylamino-6-ethylthio-2-pyrimidinamine	120	850
4-Ethylamino-2-ethylthiopyrimidine	200/11	1196
Ethyl 4-amino-2-ethylthio-5-pyrimidinecarboxylate	102 or 103	928,1249,1254,1326,2863
Ethyl 4-amino-3-ethyl-2-thioxo-2,3-dihydro-5-pyrimidinecarboxylate	252	809
4-Ethylamino-5-formamido-2,6-dimethoxypyrimidine	145–146	2960
6-Ethylamino-5-formamido-2,4(1*H*,3*H*)-pyrimidinedione	326	1376
Ethyl 4-amino-2-hydrazino-5-pyrimidinecarboxylate	172–174	2790

Ethyl 4-amino-3-β-hydroxyethyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	212	864
4-Ethylamino-5-hydroxymethyl-2-methylpyrimidine	161–162	2621
Ethyl 4-amino-5-hydroxymethyl-2-oxo-1,2-dihydro-1-pyrimidinecarboxylate	crude	2894
2-Ethylamino-5-hydroxymethyl-4-pyrimidinamine	133–136	577
Ethyl 2-amino-4-isopropyl-5-pyrimidinecarboxylate	74–75, ir, nmr, uv	3996
Ethyl 4-amino-3-β-methoxyethyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	178	864
Ethyl 4-amino-3-β-methoxyethyl-2-thioxo-2,3-dihydro-5-pyrimidinecarboxylate	206	809
4-Ethylamino-6-methoxy-2-methylpyrimidine	liquid, anal, nmr	1245
4-Ethylamino-6-methoxy-2-pyrimidinamine	137–138	1042
Ethyl 4-amino-2-methoxy-5-pyrimidinecarboxylate	151–153	2203,2966,2967
5-Ethylamino-4-methylaminopyrimidine	154–155	1774
2-Ethylamino-6-methylamino-4,5-pyrimidinediamine	H_2SO_4: 293	2618
5-Ethylamino-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	235	2682
4-Ethylamino-6-methyl-2-methylamino-5-nitropyrimidine	107–108	1191
6-Ethylamino-1-methyl-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	>225	2968
4-Ethylamino-6-methyl-2-methylthio-5-pyrimidinamine	143–144	1191
2-Ethylamino-4-methyl-6-methylthiopyrimidine	62	1765
4-Ethylamino-6-methyl-5-nitro-2(1*H*)-pyrimidinethione	198	1191
4-Ethylamino-6-methyl-5-nitro-2(1*H*)-pyrimidinone	260–265	1192
6-Ethylamino-2-methyl-5-nitro-4(3*H*)-pyrimidinone	279–280, ir, nmr, uv	572
4-Ethylamino-2-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	>290, ir, nmr, uv	572
Ethyl 2-amino-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	anal	2969
Ethyl 4-amino-3-methyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	230	864
6-Ethylamino-2-methyl-4-pyrimidinamine	185	2253
5-Ethylamino-4-methylpyrimidine	55–56, 123–125/7	1833
Ethyl 2-amino-4-methyl-5-pyrimidinecarboxylate	212 to 226, ir, nmr, uv	779,1475,1476,2970,3996
Ethyl 2-amino-6-methyl-4-pyrimidinecarboxylate	151	1476
Ethyl 4-amino-2-methyl-5-pyrimidinecarboxylate	120 or 124	1117,1472,2231,2971

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Ethylamino-4-methyl-5-pyrimidinol	100–103	7
2-Ethylamino-6-methyl-4(3*H*)-pyrimidinone	170–174	1241
4-Ethylamino-1-methyl-2(1*H*)-pyrimidinone	—	2972
4-Ethylamino-6-methyl-2(1*H*)-pyrimidinone	245–250	1192
6-Ethylamino-2-methyl-4(3*H*)-pyrimidinone	224–228, ir, nmr	572
Ethyl 4-amino-2-methylsulfonyl-5-pyrimidinecarboxylate	163–164	1302
Ethyl 6-amino-2-methylthio-5-nitro-4-pyrimidinecarboxylate	130	2973
4-Ethylamino-6-methylthio-2-pyrimidinamine	168	850
Ethyl 2-amino-4-methylthio-5-pyrimidinecarboxylate	153–154	1781
Ethyl 4-amino-2-methylthio-5-pyrimidinecarboxylate	128–130, 130–131	447,1331,1563,2974
4-Ethylamino-6-methylthio-2,5-pyrimidinediamine	crude	850
Ethyl 4-amino-3-methyl-2-thioxo-2,3-dihydro-5-pyrimidinecarboxylate	235–237 or 238	809,1508
Ethyl 6-amino-5-nitro-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	240	2959
2-Ethylamino-5-nitro-4-pyrimidinamine	179	1746
6-Ethylamino-5-nitro-4-pyrimidinamine	185–186	2975
2-Ethylamino-5-nitropyrimidine	175	2643
6-Ethylamino-5-nitro-2,4-pyrimidinediamine	crude, 218–220	2176
6-Ethylamino-5-nitro-2,4-pyrimidinediamine 3-oxide	258–259	2176
6-Ethylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	299–301	1165
4-Ethylamino-5-nitro-2(1*H*)-pyrimidinone	273 or 275	1196,1221
6-Ethylamino-5-nitro-4(3*H*)-pyrimidinone	215–217 or 226–229	1094,1589
6-Ethylamino-5-nitroso-2,4-pyrimidinediamine 3-oxide	264	2176
6-Ethylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	253 or 360	1376,2276
2-Ethylamino-5-nitro-4-thiocyanatopyrimidine	166–167	1195
Ethyl 6-amino-5-nitro-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylate	202–204	2959

4-Ethylamino-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	244–245	852
2-Ethylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboamide	308	2647
Ethyl 2-amino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	303–304	1475,1781,2873
Ethyl 2-amino-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	220	1606
Ethyl 4-amino-2-oxo-1,2-dihydro-1-pyrimidinecarboxylate	>280	2894
Ethyl 4-amino-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	260–270 or 278–286	723,1249,1254,1330,1331,1544, 1673,1781,2976
2-Ethylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	205	865
Ethyl 4-amino-2-oxo-3-propyl-2,3-dihydro-5-pyrimidinecarboxylate	215	864
Ethyl 2-amino-4-propyl-5-pyrimidinecarboxylate	124–125, ir, nmr, uv	3996
Ethyl 4-amino-2-propylthio-5-pyrimidinecarboxylate	97–99	928
4-Ethylamino-5-pyrimidinamine	195–198	2138
5-Ethylamino-4-pyrimidinamine	213	2977
6-Ethylamino-4-pyrimidinamine	193	866
2-Ethylaminopyrimidine	58–60; HI: 119; pic: 167–168	867,1741,2978
2-Ethylamino-5-pyrimidinecarbaldehyde	131–133, ir, ms, nmr	6170
Ethyl 2-amino-5-pyrimidinecarboxylate	141 to 149, ir, nmr, uv	1631,1632,3996
Ethyl 4-amino-5-pyrimidinecarboxylate	102–104	1615,1633
Ethyl 5-amino-4-pyrimidinecarboxylate	148	1032
2-Ethylamino-4,5-pyrimidinediamine	178	1746
6-Ethylamino-2,4-pyrimidinediamine	155–156	3864
6-Ethylamino-2,4-pyrimidinediamine 3-oxide	273 or 275	2176,2979
5-Ethylamino-2,4(1*H*,3*H*)-pyrimidinedione	243–245 or 268–274; pic: 192–193	1941,2980
6-Ethylamino-2,4(1*H*,3*H*)-pyrimidinedione	288–289 or 302–304	1376,2276,2960
4-Ethylamino-2(1*H*)-pyrimidinethione	226	1221
5-Ethylamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	297	2663,2981
4-Ethylamino-2(1*H*)-pyrimidinone	214	1221
6-Ethylamino-4(3*H*)-pyrimidinone	217–220	1094

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
Ethyl 4-amino-2-thiocyanato-5-pyrimidinecarboxylate	152–154	2982
Ethyl 4-amino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate	260–265 or 281; HCl: 209–211	1331,1685,2983,6454
2-Ethylamino-4,5,6-trimethylpyrimidine	82; pic: 177	2964
6-Ethylamino-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	102–103	855
Ethyl 6-azido-2-β-carbamoylethyl-5-methyl-4-pyrimidinecarboxylate	149	2984
Ethyl 6-azido-2-β-carboxyethyl-5-methyl-4-pyrimidinecarboxylate	144	2984
Ethyl 6-azido-2,5-dimethyl-4-pyrimidinecarboxylate	104–105	2038
Ethyl 2,4-bisallylamino-6-methyl-5-pyrimidinecarboxylate	94–95	2958
Ethyl 2,4-bisdimethylamino-6-methyl-5-pyrimidinecarboxylate	121–123/0.1	2958
5-Ethyl-2,6-bismethoxymethyl-4(3*H*)-pyrimidinone	81–82	1761
4-Ethyl-2,6-bismethylamino-5-nitropyrimidine	147	1191
4-Ethyl-2,6-bismethylamino-5-pyrimidinamine	133–134	1191
Ethyl 2,4-bisethylthio-5-pyrimidinecarboxylate	82–83 or 86–88	1302,1781,2985
5-Ethyl-2,4-bistrimethylsiloxypyrimidine	19	1959
Ethyl 5-bromo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	264–265	1949
Ethyl 1-β-bromoethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	196–197	1881
Ethyl 4-bromo-2-methylthio-5-pyrimidinecarboxylate	63	1781
Ethyl 5-bromo-2-methylthio-4-pyrimidinecarboxylate	33–34, 122–123/0.3	2291
Ethyl 2-carbamoylmethyl-4-methyl-5-pyrimidinecarboxylate	143	783
Ethyl 2-carbamoylmethyl-6-methyl-4-pyrimidinecarboxylate	202	783
Ethyl 2-carbamoyl-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	180–181	2038
Ethyl 1-α-carboxyethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	159–161	2986
Ethyl 1-β-carboxyethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	183	2986
Ethyl 1-carboxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	181–182	2986
Ethyl 6-chloro-5-cyano-2-dimethylamino-4-pyrimidinecarboxylate	118–120	3763

Ethyl 6-chloro-2-cyano-5-methyl-4-pyrimidinecarboxylate	crude, nmr	2038
Ethyl 4-chloro-2,6-dimethyl-5-pyrimidinecarboxylate	-	1466
Ethyl 6-chloro-2,5-dimethyl-4-pyrimidinecarboxylate	liquid, nmr	2038
Ethyl 2-chloro-4-ethylamino-6-methyl-5-pyrimidinecarboxylate	66–67	2958
Ethyl 2-β-chloroethyl-4-methyl-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylate	128	791
Ethyl 4-chloro-2-ethylthio-5-pyrimidinecarboxylate	203/20	1254,1631
Ethyl 6-chloro-5-fluoro-2-methyl-4-pyrimidinecarboxylate	45–46	1262
Ethyl 6-chloro-2-formyl-5-methyl-4-pyrimidinecarboxylate	63, ir, ms, nmr; dnp: 214–215	171,2987
Ethyl 5-chloromethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	210–211	2627
Ethyl 2-chloro-4-methyl-6-methylamino-5-pyrimidinecarboxylate	78–80	2958
Ethyl 5-chloro-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	156	1262
Ethyl 2-chloro-4-methyl-6-propylamino-5-pyrimidinecarboxylate	126–127/0.1, n_D^{20} 1.5378	2958
Ethyl 4-chloro-2-methyl-5-pyrimidinecarboxylate	89–91/0.4, 100/1, 102–106/?	1302,2988–2990
Ethyl 5-chloro-2-methyl-4-pyrimidinecarboxylate	88/1, n_D^{20} 1.5062	2291
Ethyl 4-chloro-2-methylsulfonyl-5-pyrimidinecarboxylate	129–130	577
Ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate	58–59 or 59–60	1781,2985,2989,2991,2992
Ethyl 5-chloro-2-methylthio-5-pyrimidinecarboxylate	120–122/0.5, n_D^{22} 1.5630	2291
Ethyl 2-chloro-5-pyrimidinecarboxylate	45 or 61	1631,1632
Ethyl 4-chloro-5-pyrimidinecarboxylate	74–75/0.05	1969,2990
Ethyl 4-cyano-2-methylthio-5-pyrimidinecarboxylate	46–47	1781,2695
Ethyl 5,6-diamino-2-chloro-4-pyrimidinecarboxylate	270	2959
Ethyl 5,6-diamino-2-dimethylamino-4-pyrimidinecarboxylate	165	2959
Ethyl 5,6-diamino-2-ethoxy-4-pyrimidinecarboxylate	201	2959
Ethyl 2,4-diamino-6-methyl-5-pyrimidinecarboxylate	165–166	2958
Ethyl 5,6-diamino-2-methylthio-4-pyrimidinecarboxylate	227	2973
Ethyl 2,6-diamino-5-nitro-4-pyrimidinecarboxylate	186	2959
Ethyl 5,6-diamino-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	234	2959
Ethyl 2,4-diamino-5-pyrimidinecarboxylate	207 or 215–217	1249,1254,1302,1544,1600,1601, 1781,2993

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
Ethyl 5,6-diamino-4-pyrimidinecarboxylate	243	2435
Ethyl 5,6-diamino-2-thioxo-1,2-dihydro-4-pyrimidinecarboxylate	202 or 206–208	2435,2959
Ethyl 2,4-dichloro-6-methyl-5-pyrimidinecarboxylate	118–120/0.5, n_D^{20} 1.5188	2958
Ethyl 2,6-dichloro-5-nitro-4-pyrimidinecarboxylate	37–38	2994
Ethyl 2,4-dichloro-5-pyrimidinecarboxylate	36–37, 145/11	1249,1544,1748
Ethyl 2,4-diethoxy-6-methyl-5-pyrimidinecarboxylate	118–120/0.5	2958
Ethyl 4,6-diethoxy-2-pyrimidinecarboxylate	116–120/0.1	1786
5-Ethyl-2,4-dimethoxy-6-methylpyrimidine	113–115/11 or 118/7	1059,2478
3-Ethyl-2,6-dimethoxy-5-methyl-4(3*H*)-pyrimidinone	81–82	2526
5-Ethyl-4,6-dimethoxy-1-methyl-2(1*H*)-pyrimidinone	77	2804
5-Ethyl-4,6-dimethoxy-2-propylpyrimidine	106–107/7	1456
2-Ethyl-5,6-dimethoxy-4-pyrimidinamine	98–100	2477
5-Ethyl-4,6-dimethoxy-2-pyrimidinamine	92–94	2130
5-Ethyl-2,4-dimethoxypyrimidine	234–236/760	1228
5-Ethyl-4,6-dimethoxypyrimidine	34–35	1880
Ethyl 2,4-dimethoxy-5-pyrimidinecarboxylate	60–61, ir, nmr	474,6071
2-Ethyl-4,6-dimethoxy-5-pyrimidinecarboxylic acid	148–151	1788
5-Ethyl-2,6-dimethoxy-4(3*H*)-pyrimidinone	221	972,973
5-Ethyl-4,6-dimethoxy-2(1*H*)-pyrimidinone	203–213 or 215	2533,2804
Ethyl 1-dimethylamino-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	203–205	1071
Ethyl 5-dimethylaminomethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidine-carboxylate	190–198	2627
Ethyl 4-dimethylamino-2-methyl-5-pyrimidinecarboxylate	124–126/6	1462
Ethyl 4-dimethylamino-2-methylthio-5-pyrimidinecarboxylate	50	1781
Ethyl 2-dimethylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	165–167	2647

Ethyl 4-dimethylamino-5-pyrimidinecarboxylate	90/0.65	1615
Ethyl 4-dimethylamino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate	186–188	1086
N-Ethyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	158	904
Ethyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboximidate	98–100	1133,2671
Ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	112	904
Ethyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	60	2669
Ethyl 1,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	200–201	796
5-Ethyl-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	164–165	855
Ethyl 1,6-dimethyl-4-methylthio-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	76–78	796
5-Ethyl-4,6-dimethyl-2-methylthiopyrimidine	95/0.05, n_D^{20} 1.5558	2995
5-Ethyl-3,6-dimethyl-2-methylthio-4(3*H*)-pyrimidinone	114–116	891,892
6-Ethyl-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	119–120, nmr	148,2996
Ethyl 1,2-dimethyl-4-oxo-1,4-dihydro-5-pyrimidinecarboxylate	187–188; HI: 163	1551
Ethyl 1,2-dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylate	61–62	1551
Ethyl 2,4-dimethyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylate	160–162	1466
Ethyl 2,5-dimethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	171–172	2038
Ethyl 1,6-dimethyl-2-oxo-4-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	214–215	796,821
5-Ethyl-1,3-dimethyl-6-propylamino-2,4(1*H*,3*H*)-pyrimidinedione	95	855
5-Ethyl-1,3-dimethyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	77–78	2997
2-Ethyl-5,6-dimethyl-4-pyrimidinamine	197–198 or 204	665,2998
6-Ethyl-2,5-dimethyl-4-pyrimidinamine	—	2999
2-Ethyl-4,6-dimethylpyrimidine	85/27	763,2293
4-Ethyl-2,6-dimethylpyrimidine	72–76/11, 85/28; pic: 86–87	2293,3000,3001
Ethyl 2,4-dimethyl-5-pyrimidinecarboxylate	80–81/0.6, 113–115/12	651,2767,3996
2-Ethyl-4,6-dimethyl-5-pyrimidinecarboxylic acid	148–149, ir, ms, nmr	335
4-Ethyl-2,6-dimethyl-5-pyrimidinecarboxylic acid	172–174, ir, ms, nmr, uv	335
1-Ethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	99 or 110–112	756,2779,2788
3-Ethyl-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	106–108 or 112–114	756,2779

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Ethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	81–82	2720
5-Ethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	229	891,892
2-Ethyl-4,6-dimethylpyrimidine 1,3-dioxide	135	763
4-Ethyl-2,6-dimethylpyrimidine 1-oxide	96/2	3001
4-Ethyl-2,6-dimethylpyrimidine 3-oxide	79–80	3001
N-Ethyl-4,6-dimethyl-2-pyrimidinesulfonamide	130–131	1711
1-Ethyl-3,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	77 or 78–79, ir, nmr	69,2805
1-Ethyl-2,6-dimethyl-4(1*H*)-pyrimidinimine	HI: anal, nmr	7033
2-Ethyl-5,6-dimethyl-4(3*H*)-pyrimidinone	165 or 172–174	2543,3881
5-Ethyl-2,6-dimethyl-4(3*H*)-pyrimidinone	140–141	2543,2815
6-Ethyl-2,5-dimethyl-4(3*H*)-pyrimidinone	168–169	2545,2815,3002
Ethyl 2,4-dimethyl-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylate	142	791
Ethyl 1,3-dimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxylate	138	2909
Ethyl 2,6-dioxo-1(or 3)-propyl-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	97	2848
1-Ethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	208–209 or 212–213	1166,1883
3-Ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	178–180	1883
4-Ethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	280–281 or 284–285, ir, nmr	31,1199,3003
S-Ethyl 2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarbothioate	194	3004
N-Ethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	280–285	3005
N-Ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	280–290	3006
Ethyl 2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxylate	120 or 130–132	2893,2894
Ethyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	234 to 242	1980,2527,2867,3007
Ethyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	210–211	2673,3008
1-Ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid (?)	228–231 or 235	2848,3009
1-Ethyl-2,6-dioxo-1,2,3,6-hexahydro-5-pyrimidinecarboxylic acid	179	904

3-Ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	250–251	2888
5-Ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	304 or 311–313	1224,3010
5-Ethyl-2,6-dipropyl-4-pyrimidinamine	109–111 or 115	683,3011,3012
5-Ethyl-2,6-dipropyl-4(3*H*)-pyrimidinone	97–98	3012
Ethyl 5-ethoxy-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	203–212 or 230	2123,2897
Ethyl 5-ethoxy-2-ethylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	82–83	2123
Ethyl 4-ethoxy-2-ethylthio-5-pyrimidinecarboxylate	175/8	1748
Ethyl 5-ethoxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	199–201	2627
Ethyl 4-ethoxy-2-methyl-5-pyrimidinecarboxylate	52 or 53–55	1462,2524,3013
Ethyl 2-ethoxy-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	185–186	1544
Ethyl 4-ethoxy-2-oxo-6-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	195–203 or 240	2605,2953
Ethyl 4-ethoxy-5-pyrimidinecarboxylate	28–30, 82–85/0.1	1615,1633,3014
5-Ethyl-6-ethylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	117–118	855
4-Ethyl-2-ethylamino-6-methylpyrimidine	69/0.01, n_D^{20} 1.5268; pic: 112	2964
Ethyl 2-ethylamino-4-methyl-5-pyrimidinecarboxylate	102–104	2970
5-Ethyl-4-ethylamino-1-methyl-2(1*H*)-pyrimidinone	99–101	1219
Ethyl 2-ethylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	205–206	2647
N-Ethyl-2-ethylamino-5-pyrimidinesulfonamide	191–192	845
3-Ethyl-6-ethylamino-4(3*H*)-pyrimidinone	134–135 or 139–140, nmr	167,3074
Ethyl 1-ethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	86	2848
Ethyl 1-ethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	219	904
Ethyl 5-ethyl-2-formyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	acetal: 61–63, ir, nmr	171
Ethyl 2-*N*-ethyl-*N*-methylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	137–138	2647
Ethyl 1-ethyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	116	904
Ethyl 2-ethyl-4-methyl-5-pyrimidinecarboxylate	118–120/10	651
Ethyl 4-ethyl-2-methyl-5-pyrimidinecarboxylate	84–85/0.4, ir, nmr, uv	3996
Ethyl 2-ethyl-4-methyl-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylate	155	797
Ethyl 3-ethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	257	809

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Ethyl-2-ethylsulfonyl-4-methoxy-6-methylpyrimidine	45–47	1059
Ethyl 4-ethylthio-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	203–204	2605
Ethyl 2-ethylthio-5-fluoro-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	164 or 168–169	2161,3015
5-Ethyl-2-ethylthio-4-isothiocyanatopyrimidine	146–149/8	2140
Ethyl 2-ethylthio-4-isothiocyanato-5-pyrimidinecarboxylate	32–33	3016,3017
5-Ethyl-2-ethylthio-4-methoxy-6-methylpyrimidine	162/22	1059
Ethyl 2-ethylthio-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	172–173	2229
5-Ethyl-2-ethylthio-6-methyl-4-pyrimidinamine	89–91	1218
3-Ethyl-2-ethylthio-6-methyl-4(3*H*)-pyrimidinone	106/1	2788
5-Ethyl-2-ethylthio-6-methyl-4(3*H*)-pyrimidinone	138 or 141	1059,1216,1218
Ethyl 4-ethylthio-2-methylthio-5-pyrimidinecarboxylate	168/0.8	1302
Ethyl 2-ethylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	131	3018
5-Ethyl-2-ethylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	208–209	1224
5-Ethyl-2-ethylthio-4-pyrimidinamine	74–76	1242
4-Ethyl-2-ethylthiopyrimidine	105–107/4	1240
5-Ethyl-2-ethylthiopyrimidine	82–84	3019
Ethyl 2-ethylthio-5-pyrimidinecarboxylate	49–51, 172/14	1631,3020
Ethyl 4-ethylthio-5-pyrimidinecarboxylate	25, 108/0.4	1615
6-Ethyl-5-ethylthio-2,4-pyrimidinediamine	156	3021
3-Ethyl-2-ethylthio-4(3*H*)-pyrimidinone	29–30	3022
5-Ethyl-2-ethylthio-4(3*H*)-pyrimidinone	117–120	1242
6-Ethyl-2-ethylthio-4(3*H*)-pyrimidinone	89	2150
5-Ethyl-2-ethylthio-4-thiocyanatopyrimidine	46–47, 158–160/5	2140
Ethyl 2-ethylthio-4-thiocyanato-5-pyrimidinecarboxylate	104–105, 204–205/4	3016,3017,3023
5-Ethyl-2-ethylthio-4-thioureidopyrimidine	143–144	2140

Ethyl 2-ethylthio-4-thioureido-5-pyrimidinecarboxylate	165–168	3016
Ethyl 2-ethylthio-4-ureido-5-pyrimidinecarboxylate	140–141	3024
S-Ethyl 5-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarbothioate	175–176, nmr	327
N-Ethyl-5-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxamide	165	3025
Ethyl 5-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxylate	128–130	1724
Ethyl 5-fluoro-2-isopropylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	155–158	3015
Ethyl 5-fluoro-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	289	1262
Ethyl 5-fluoro-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	183–184	3026
Ethyl 4-fluoro-2-methylthio-5-pyrimidinecarboxylate	48–49	1781
Ethyl 5-fluoro-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	235	2282
Ethyl 5-fluoro-6-oxo-2-propylthio-1,6-dihydro-4-pyrimidinecarboxylate	154–156	3015
3-Ethyl-6-fluoro-4(3*H*)-pyrimidinone	86–88	1245
4-Ethyl-5-formamido-2,6-bismethylaminopyrimidine	151	1191
5-*N*-Ethylformamido-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	262	2682
5-*N*-Ethylformamido-6-methyl-2-methylthio-4-pyrimidinamine	137–138	664
2-Ethyl-5-formamidomethyl-4-pyrimidinamine	185; HCl: 103–104	975,3027
Ethyl 2-formyl-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	acetal: 109–110, nmr	171
Ethyl 4-formyl-2-methyl-5-pyrimidinecarboxylate	88–89/0.1	823
Ethyl 4-formyl-2-methylthio-5-pyrimidinecarboxylate	oxime: 191	1781
Ethyl 2-formyl-6-oxo-5-propyl-1,6-dihydro-4-pyrimidinecarboxylate	acetal: 57–59, ir, nmr	171
Ethyl 4-formyl-5-pyrimidinecarboxylate	76/0.02	823
Ethyl 5-hydrazino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	237–239	3028
5-Ethyl-4-hydrazino-6-methyl-2-propylpyrimidine	62–65	880,900
2-Ethyl-4-hydrazino-6-methylpyrimidine	150	880,900,3030
4-Ethyl-6-hydrazino-2-methylpyrimidine	127–128	880,900
Ethyl 2-hydrazino-4-methyl-5-pyrimidinecarboxylate	173–174 or 185	2790,2970,3031
5-Ethyl-2-hydrazino-6-methyl-4(3*H*)-pyrimidinone	232, then 320	1529,3032
Ethyl 4-hydrazino-2-methylthio-5-pyrimidinecarboxylate	100–101	3033

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
Ethyl 2-hydrazino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	235–238	1302,2065
2-Ethyl-4-hydrazino-6-propylpyrimidine	188/20	880,900
4-Ethyl-6-hydrazino-2-propylpyrimidine	186/25	880,900
4-Ethyl-6-hydrazino-2(1*H*)-pyrimidinone	300	2147
6-Ethyl-2-hydrazino-4(3*H*)-pyrimidinone	202	2562
1-Ethyl-6-hydroxyamino-2,4(1*H*,3*H*)-pyrimidinedione	205–227	776
Ethyl 5-hydroxy-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	260	1172
N-Ethyl-1-β-hydroxyethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide	222	904
Ethyl 1-β-hydroxyethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	175–176	904
Ethyl 1-β-hydroxyethyl-6-methyl-2-oxo-4-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	147–148	3034
2-Ethyl-5-β-hydroxyethyl-4,6(1*H*,5*H*)-pyrimidinedione	267–268	3035
5-Ethyl-1-β-hydroxyethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	213–215	3034
Ethyl 5-hydroxy-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	218	1262
2-Ethyl-5-hydroxymethyl-4-pyrimidinamine	113–114; HCl: 174	1065,1394
1-Ethyl-6-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	211–212	2888
3-Ethyl-5-hydroxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	230	756
1-Ethyl-6-hydroxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	193–194	2888
1-Ethyl-5-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	250	1492,2779
5-Ethyl-1-hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	191	3036
6-Ethylidenehydrazino-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	135–136	3037
6-Ethylidenehydrazino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	148–150 or 152	1277,3038
2-Ethylidenehydrazino-4,6-dimethylpyrimidine	122–123	3039
6-Ethylidenehydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	210–212	2717
6-β-Ethylidene-α-methylhydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	131	2687,2691

6-β-Ethylidene-α-methylhydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	182–183 or 202	3040,3041
5-Ethylidene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	223	3042
Ethyl 4-imino-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	178	864
5-Ethyl-4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine	HI: 286–288; CF_3CO_2H: 216–217	2176
5-Ethyl-4-imino-1-methyl-1,4-dihydro-2-pyrimidinamine 3-oxide	> 110	2176
2-Ethylimino-1-methyl-1,2-dihydropyrimidine	HI: 160–161	902,1741
5-Ethyl-2-imino-3-methyl-4,6-dioxo-1,2,3,4,5,6-hexahydro-1-pyrimidinecarbonitrile	177	2531
5-Ethyl-4-iodo-2-isopropyl-6-methylpyrimidine	45–47	1890
Ethyl 4-iodo-2-methylthio-5-pyrimidinecarboxylate	72–74	1781,3043
5-Ethyl-6-iodo-4-pyrimidinamine	191–193	1228
6-Ethyl-5-iodo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	Na: 234–235	3044
2-Ethyl-4-isopropoxy-6-methylpyrimidine 1-oxide	94–95	2744
1-Ethyl-4-isopropoxy-6-methyl-2(1*H*)-pyrimidinone	70–71	3045
5-Ethyl-6-isopropylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	137–139	855
Ethyl 4-isopropylamino-2-methylthio-5-pyrimidinecarboxylate	50	3046
Ethyl 2-isopropylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	193–195	2647
Ethyl 4-isopropylamino-5-pyrimidinecarboxylate	90/0.07	1615
Ethyl 4-isopropylidenehydrazino-2-methylthio-5-pyrimidinecarboxylate	164–166	3033
Ethyl 1-isopropyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	98	904
4-Ethyl-2-isopropyl-6-methylpyrimidine	91–92/15, ir, nmr	3001,5893
Ethyl 4-isopropyl-2-methyl-5-pyrimidinecarboxylate	80–82/0.5, ir, nmr, uv	3996
4-Ethyl-2-isopropyl-6-methylpyrimidine 1-oxide	94/3 or 101/1, ir, nmr	3001,5893
4-Ethyl-2-isopropyl-6-methylpyrimidine 3-oxide	90–94/3 or 93/1, ir, nmr	3001,5893
3-Ethyl-2-isopropyl-6-methyl-4(3*H*)-pyrimidinone	—	456
5-Ethyl-2-isopropyl-6-methyl-4(3*H*)-pyrimidinone	153	2722
2-Ethyl-6-isopropyl-4(3*H*)-pyrimidinone	62–63, 130/2	2575
Ethyl 4-isopropylthio-2-methylthio-5-pyrimidinecarboxylate	161/0.8	1302

Pyrimidine	m.p. (°C), etc.	Ref.
5-Ethyl-3-methoxycarbonylmethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	94–95, ir, nmr, uv	3750
5-Ethyl-2-methoxy-4,6-dimethylpyrimidine	74/0.05, n_D^{20} 1.4810	2995
5-Ethyl-6-methoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	84	3047
Ethyl 3-β-methoxyethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidine-carboxylate	202	809
5-Ethyl-6-methoxy-2-methoxymethyl-4-pyrimidinamine	83–84	1761
Ethyl 5-methoxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	166–167	2627
2-Ethyl-5-methoxymethyl-6-methyl-4(3*H*)-pyrimidinone	anal	1718
4-Ethyl-2-methoxy-6-methylpyrimidine	47–48/0.05, n_D^{20} 1.4952; HCl: 150	2532
4-Ethyl-6-methoxy-2-methylpyrimidine	57–58/2, nmr	121
4-Ethyl-6-methoxy-2-methyl-5-pyrimidinecarbonitrile	31–32	3048
Ethyl 4-methoxy-2-methyl-5-pyrimidinecarboxylate	47–48 or 48–49	1551,1904
5-Ethyl-2-methoxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	281–282	1761
2-Ethyl-4-methoxy-6-methylpyrimidine 1-oxide	61–63	2107,2744
4-Ethyl-6-methoxy-2-methylpyrimidine 3-oxide	100–104/2, ir, nmr; pic: 100–101	121
1-Ethyl-6-methoxy-2-methyl-4(1*H*)-pyrimidinimine	HBF_4: 208–209	1245
5-Ethyl-2-methoxy-6-methyl-4(3*H*)-pyrimidinone	210	2935
5-Ethyl-4-methoxy-6-methyl-2(1*H*)-pyrimidinone	194–195	1059
6-Ethyl-2-methoxy-4-pyrimidinamine	82	663
5-Ethyl-4-methoxypyrimidine	114–116/65	1880
Ethyl 4-methoxy-5-pyrimidinecarboxylate	86/0.45	1615
1-Ethyl-4-methoxy-2(1*H*)-pyrimidinone	91–92	812
6-Ethyl-2-methoxy-4(3*H*)-pyrimidinone	210, ir, nmr	130

5-*N*-Ethyl-*N*-methylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	crude, uv; pic 206–207	1729
2-*N*-Ethyl-*N*-methylamino-6-methyl-5-propyl-4(3*H*)-pyrimidinone	116–117	863
2-*N*-Ethyl-*N*-methylamino-6-methyl-4(3*H*)-pteridinone	152–155	1241
4-Ethyl-6-methylamino-2-methylthio-5-nitropyrimidine	84–85	1191
4-Ethyl-6-methylamino-2-methylthio-5-pyrimidinamine	154–155	1191
Ethyl 4-methylamino-2-methylthio-5-pyrimidinecarboxylate	93–94	1302
4-Ethyl-6-methylamino-5-nitro-2(1*H*)-pyrimidinethione	210–211	1191
2-*N*-Ethyl-*N*-methylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxamide	265	2647
Ethyl 2-methylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	242	2647
5-Ethyl-4-methylamino-6-propyl-2(1*H*)-pyrimidinethione	—	3049
2-Ethyl-4-methylaminopyrimidine	HCl: 247	2570
4-*N*-Ethyl-*N*-methylaminopyrimidine	ms, nmr	1815
5-Ethyl-2-methylaminopyrimidine	51; pic: 168	1741
5-Ethyl-4-methylaminopyrimidine	148	2570
Ethyl 4-methylamino-5-pyrimidinecarboxylate	63	1615
6-Ethyl-2-methylamino-4(3*H*)-pyrimidinone	162–163	1765
Ethyl 4-methyl-2,6-bismethylamino-5-pyrimidinecarboxylate	124–125	2958
1-Ethyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	133	1166
3-Ethyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	114–115	1883
4-Ethyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	239–240	1199
S-Ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarbothioate	103	3004
3-Ethyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	225	1883
Ethyl 1(or 3)-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	139	2848,2955
Ethyl 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	221	904
Ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxylate	70–72	2894
Ethyl 5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxylate	180	2894
Ethyl 5-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	255	3050,3051
Ethyl 6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	224–226 or 233–234	796,2958

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-Ethyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	172	904
5-Ethyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	287	2677
Ethyl 4-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonate	176	3052
Ethyl 4-methyl-2,6-dithioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	270	2958
Ethyl 4-α-methylhydrazino-2-methylthio-5-pyrimidinecarboxylate	107–109	3033
1-Ethyl-2-methylimino-1,2-dihydropyrimidine	HI: 156–157	1741
1-Ethyl-3-methyl-6-methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	270–275	882
Ethyl 2-methyl-4-methylamino-5-pyrimidinecarboxylate	67–68	1912
Ethyl 4-methyl-2-methylamino-5-pyrimidinecarboxylate	95–96	2970
1-Ethyl-3-methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	208–211	882
5-Ethyl-1-methyl-4-methylamino-2(1*H*)-pyrimidinone	128–130	1219
Ethyl 4-methyl-6-methylamino-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate	215	2958
Ethyl 2-methyl-4-α-methylhydrazino-5-pyrimidinecarboxylate	crude	3007
Ethyl 5-methyl-2-(methylthio)carbonyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	anal, nmr	2038
Ethyl 5-methyl-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	201–202	3050
6-Ethyl-5-methyl-2-methylthio-4-pyrimidinamine	122–123	2693
4-Ethyl-6-methyl-2-methylthiopyrimidine	67/0.05, n_D^{20} 1.5491	2532
Ethyl 2-methyl-4-methylthio-5-pyrimidinecarboxylate	57–58	1904
Ethyl 4-methyl-2-methylthio-5-pyrimidinecarboxylate	53–54 or 59–60	1781,2970,3031
3-Ethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	54–55	2242
5-Ethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	203 or 210–211	1529,3053
1-Ethyl-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	103–105 or 106, nmr	282,1492,2779,3995
3-Ethyl-1-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	124	1492,2779
1-Ethyl-3-methyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	95–96	3054

4-Ethyl-2-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	acetamidinium salt: 199–200	3048
Ethyl 1-methyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	HBr: 187–189	914,3055
Ethyl 2-methyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	190 or 191	1469,1472,2915,3056
Ethyl 4-methyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	248–250 or 250–252	779,829,830
Ethyl 4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxylate	–	3057
Ethyl 5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	160–162	2038
1-Ethyl-3-methyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	124; H_2O: 82	3054
1-Ethyl-5-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	180–182	2578
1-Ethyl-4-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	268	809
Ethyl 1-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	205	809
Ethyl 4-methyl-2-oxo-6-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	251	791
1-Ethyl-6-methyl-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	63–65	895
3-Ethyl-6-methyl-1-propyl-2,4(1*H*,3H)-pyrimidinedione	38–40	895
5-Ethyl-1-methyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	197–199	3058
5-Ethyl-3-methyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	125–127	3058
5-Ethyl-6-methyl-2-propyl-4(3*H*)-pyrimidinone	121	880,2722
2-Ethyl-4-methyl-5-pyrimidinamine	70–71, 133/12	651
2-Ethyl-5-methyl-4-pyrimidinamine	175–177	1065,2999
2-Ethyl-6-methyl-4-pyrimidinamine	166–167	650
4-Ethyl-5-methyl-2-pyrimidinamine	200	3059,3060
4-Ethyl-6-methyl-2-pyrimidinamine	116–118, ir, ms, nmr	3723
5-Ethyl-2-methyl-4-pyrimidinamine	158–160	1159
5-Ethyl-4-methyl-2-pyrimidinamine	166–167	1217
6-Ethyl-2-methyl-4-pyrimidinamine	148–149	665
2-Ethyl-4-methylpyrimidine	160/760	2543
4-Ethyl-2-methylpyrimidine	60–65/18, 89/60, ir, nmr, uv; pic: 113–115	122,3996
4-Ethyl-5-methylpyrimidine	72/11, 75–78/13; pic: 111	2750,2751

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Ethyl-2-methylpyrimidine	65–66/13, 80–82/25; pic 143	2747,2748
5-Ethyl-4-methylpyrimidine	193/760 or 194/760; HCl: 100	1215,3061
2-Ethyl-4-methyl-5-pyrimidinecarboxamide	167–169	651
Ethyl 2-methyl-5-pyrimidinecarboxylate	70–71/0.45, 110–115/20, ir, nmr, uv	1387,3062,3996
4-Ethyl-2-methyl-5-pyrimidinecarboxylic acid	163–164, ir, nmr, uv	3996
4-Ethyl-6-methyl-2,5-pyrimidinediamine	132	645
5-Ethyl-2-methyl-4,6-pyrimidinediamine	232–233	1159
5-Ethyl-6-methyl-2,4-pyrimidinediamine	161–162	1215
6-Ethyl-5-methyl-2,4-pyrimidinediamine	168–170	3063
1-Ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	222–223 or 233	2492,2538,2770
1-Ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	194–196 or 197–198	756,895,1695,2540,2778,2939, 3064,3065
2-Ethyl-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione	> 300	3066
3-Ethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	60–61 or 73–75, 140–141/4	1841,3067
3-Ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	202	2538
3-Ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	195 to 206	1152,2242,2539,2541,2788,3064
5-Ethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	162	1219
5-Ethyl-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	anal	1159,2784
5-Ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	147 or 153	2677,2785
5-Ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	237–238 or 246–248	1215,1218,2550,3053
6-Ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	258–260 or 263	2550,3068
5-Ethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedithione	250–280	1215
6-Ethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedithione	—	3069,3070
1-Ethyl-3-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	108–109	2805

1-Ethyl-5-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	147	2807
5-Ethyl-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	102–103 or 104	2531,3071
2-Ethyl-3-methyl-4(3*H*)-pyrimidinimine	HI: 215	2570
5-Ethyl-1-methyl-2(1*H*)-pyrimidinimine	HCl: 255; HI: 205–206; pic: 148	1741,3072
5-Ethyl-3-methyl-4(3*H*)-pyrimidinimine	HI: 240	2570
1-Ethyl-2-methyl-4(1*H*)-pyrimidinone	129–130	2551
1-Ethyl-4-methyl-2(1*H*)-pyrimidinone	hygroscopic, anal	1879
1-Ethyl-5-methyl-2(1*H*)-pyrimidinone	85	1879
1-Ethyl-6-methyl-2(1*H*)-pyrimidinone	98–99; HCl: 203	1879
2-Ethyl-6-methyl-4(3*H*)-pyrimidinone	156 to 164	880,2107,2819–2822,3073
3-Ethyl-2-methyl-4(3*H*)-pyrimidinone	44–45	2551
3-Ethyl-6-methyl-4(3*H*)-pyrimidinone	1-$EtBF_4$: 126	3074
4-Ethyl-6-methyl-2(1*H*)-pyrimidinone	HCl: 220	2532
6-Ethyl-2-methyl-4(3*H*)-pyrimidinone	122–123 or 125–126, ir, nmr	121,880
6-Ethyl-5-methyl-4(3*H*)-pyrimidinone	161–162	2815
2-Ethyl-5-methylsulfonyl-4(3*H*)-pyrimidinone	192–195	3075
6-Ethyl-2-methylthio-5-nitro-4-pyrimidinamine	122	1191
4-Ethyl-2-methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	240, ms, nmr	6173
Ethyl 2-methylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	132–133 or 134–136	2527,2873,2991
5-Ethyl-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	232–233	1224
Ethyl 2-methylthio-4-propylthio-5-pyrimidinecarboxylate	187/2.5	1302
6-Ethyl-2-methylthio-4-pyrimidinecarboxamide	126	2266
Ethyl 2-methylthio-5-pyrimidinecarboxylate	104/0.001, ir, ms, nmr	381
6-Ethyl-2-methylthio-4,5-pyrimidinediamine	193–194	1191
3-Ethyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	236–240	909
5-Ethyl-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	257	1046
6-Ethyl-2-methylthio-4(3*H*)-pyrimidinethione	189	2147
1-Ethyl-4-methylthio-2(1*H*)-pyrimidinone	66–67 (227?)	870,2941

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
3-Ethyl-6-methylthio-4(3*H*)-pyrimidinone	86–88	909
5-Ethyl-2-methylthio-4(3*H*)-pyrimidinone	187–189	3022
6-Ethyl-2-methylthio-4(3*H*)-pyrimidinone	153 or 157	1765,2147,3076
Ethyl 2-methylthio-4-thiocyanato-5-pyrimidinecarboxylate	161	2985
Ethyl 2-methylthio-4-trimethylammonio-5-pyrimidinecarboxylate	chloride: 109–111	1781
Ethyl 2-methylthio-4-trimethylhydrazino-5-pyrimidinecarboxylate	92–93	1302
Ethyl 2-methyl-4-thioxo-3,4-dihydro-5-pyrimidinecarboxylate	154 or 157–158	2988,3062
Ethyl 4-methyl-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate	160 or 188–189	779,3077
1-Ethyl-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	52–53 or 56, nmr	258,2035
3-Ethyl-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	72–73, nmr	258,2035
3-Ethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	202–203	2788
5-Ethyl-1-methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	171–172	3034
5-Ethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	208 to 218	1218,1684,2550
6-Ethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	218 to 227	1684,2550,3078
4-Ethyl-6-methyl-2-ureidopyrimidine	168	2554
5-Ethyl-6-methyl-2-ureido-4(3*H*)-pyrimidinone	235	1150
Ethyl 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	250	1172,2994
1-Ethyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	H_2O: 189	895
2-Ethyl-5-nitropyrimidine	liquid, anal, ms, nmr	2942
6-Ethyl-5-nitro-2,4-pyrimidinediamine	179, then 191	2441
1-Ethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	194–195	895,1492,2779
2-Ethyl-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	> 260	2139
3-Ethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	159–161	895
6-Ethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	230	2148
1-Ethyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	H_2O: 132–133	2091

1-Ethyl-5-nitro-2(1*H*)-pyrimidinone	111–113, nmr	1879,2941
2-Ethyl-5-nitroso-4,6-pyrimidinediamine	254	2431
1-Ethyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	H_2O: 183	789,3079
6-Ethyl-2-oxo-1,2-dihydro-4-pyrimidinecarbohydrazide	237	2266
6-Ethyl-2-oxo-1,2,dihydro-4-pyrimidinecarboxamide	310	2266
Ethyl 2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	163–164; HBr: 184–186	1632,3020
Ethyl 4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	185 to 192	713,1625,1631,1969
2-Ethyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	216	3080
Ethyl 4-oxo-2-propylamino-3,4-dihydro-5-pyrimidinecarboxylate	212	2647
Ethyl 4-oxo-3-propyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	212	809
1-Ethyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	H_2O: 103	3079
1-Ethyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	155–157	2578
5-Ethyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	148–150	2578
4-Ethyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	250 or 258–259, ir, ms, nmr	6173,6174
Ethyl 4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	243–244 or 245	1631,2870,3081
Ethyl 6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	196–198	3082
4-Ethyl-6-propylamino-2(1*H*)-pyrimidinethione	-	3049
1-Ethyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	162–163	2720
5-Ethyl-2-propyl-4,6(1*H*,5*H*)-pyrimidinedione	> 300	1456,3066
5-Ethyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	223 to 232	2550,2997,3068,3083,3084
2-Ethyl-6-propyl-4(3*H*)-pyrimidinone	67–68	880
6-Ethyl-2-propyl-4(3*H*)-pyrimidinone	82–84	880
5-Ethyl-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	209 or 215–216	2550,2997,3083,3084
2-Ethyl-4-pyrimidinamine	180 to 185	479,2149,3085
4-Ethyl-2-pyrimidinamine	135–141, ir, nmr, uv; pic: 193–195	1240,2366,2734, 3086,3087,3996
5-Ethyl-2-pyrimidinamine	141–142 or 142–143	1228,1963,3019,3088
5-Ethyl-4-pyrimidinamine	160–162 or 163	1228,2652,3089

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Ethyl-4-pyrimidinamine	H_2O: 48. pic: 204–205	2150
2-Ethylpyrimidine	107/200, 147–150/760; 1-EtBF_4: 109–110. nmr	479,3090,3890,3891,6848
4-Ethylpyrimidine	85/70, 89–90/75; pic: 85–87	2752,3091,3092
5-Ethylpyrimidine	– 13, 84–86/60 or 96/60; pic: 136	2749,3093,3105
2-Ethyl-4-pyrimidinecarbaldehyde	oxime: 116–118	2525
Ethyl 2-pyrimidinecarboximidate	crude	729
Ethyl 4-pyrimidinecarboximidate	29–30	729,3094
Ethyl 5-pyrimidinecarboximidate	87	729,3094
Ethyl 2-pyrimidinecarboxylate	64–65	729
Ethyl 4-pyrimidinecarboxylate	37–39 or 38–42, 115–116/6, 155–160/88	3095,3096
Ethyl 5-pyrimidinecarboxylate	16 or 38–39, 103/12, 106–108/13	1028,1969,2509
2-Ethyl-5-pyrimidinecarboxylic acid	182–183	3097
2-Ethyl-4,6-pyrimidinediamine	223	1243
5-Ethyl-2,4-pyrimidinediamine	149–151; pic: 273–275	1118,1228
5-Ethyl-4,6-pyrimidinediamine	235 or 245; HCl: 284	1118,1228,3098
6-Ethyl-2,4-pyrimidinediamine	160–161; pic: 248–249	1118,1239
6-Ethyl-4,5-pyrimidinediamine	159–161	2148
5-Ethyl-2,4-pyrimidinediamine 3-oxide	298	3864
1-Ethyl-2,4(1*H*,3*H*)-pyrimidinedione	144 to 148, nmr	258,870,1536,2549,2770,2902, 2903,3099
2-Ethyl-4,6(1*H*,5*H*)-pyrimidinedione	294 or 299	1118,1243,1981,3100
3-Ethyl-2,4(1*H*,3*H*)-pyrimidinedione	173–174 or 174–175	1152,1942,2549,3099

5-Ethyl-2,4(1*H*,3*H*)-pyrimidinedione	298–300 or 300–303 (< 280?), ir, Hg: > 360	229,798,831,1152,1219, 1228,1242,2677,2720,2887, 3101–3103,3760, 6118(?)
5-Ethyl-4,6(1*H*,5*H*)-pyrimidinedione	330	2506,3100,3104,3105
6-Ethyl-2,4(1*H*,3*H*)-pyrimidinedione	201–203 or 204–207 (310?), ir, nmr	130,1233,1637,1869, 2148,2150,2441
4-Ethyl-2(1*H*)-pyrimidinethione	217–218; HCl: 244	3106
5-Ethyl-2(1*H*)-pyrimidinethione	201 to 228	1086,2748,3019
2-Ethyl-4,5,6-pyrimidinetriamine	272	2441
5-Ethyl-2,4,6-pyrimidinetriamine	190	1228,3107,3108
6-Ethyl-2,4,5-pyrimidinetriamine	244–248	2441
1-Ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	789
5-Ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	193–194 or 197, xl st; Na: —	834,1219,2533,2804,3036, 3109–3116,3760,4114
1-Ethyl-2(1*H*)-pyrimidinimine	HCl: 232–233; HI: 189; pic: 178–179	867,1741
1-Ethyl-4(1*H*)-pyrimidinimine	HBF_4: 127–128	1245
1-Ethyl-2(1*H*)-pyrimidinone	3-EtI: 212; 3-MeCl: 219; 3-MeI: 213	2810
1-Ethyl-4(1*H*)-pyrimidinone	64-66; HCl: 232–234	2551,3117
2-Ethyl-4(3*H*)-pyrimidinone	112 to 120, ir, nmr	421,487,2149,2551,2821
3-Ethyl-4(3*H*)-pyrimidinone	60–64 or 70–71; 1-EtBF_4: 116–117	2551,2588,3117
4-Ethyl-2(1*H*)-pyrimidinone	HCl: 211–213	1240
5-Ethyl-2(1*H*)-pyrimidinone	167; HCl: 217–220	2748,3019
5-Ethyl-4(3*H*)-pyrimidinone	83–85	3118
6-Ethyl-4(3*H*)-pyrimidinone	170–171	2150
2-Ethylsulfinyl-5-fluoropyrimidine	132–134/0.1, nmr	270
2-Ethylsulfinyl-5-iodopyrimidine	96, nmr	270

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Ethylsulfinyl-2,4(1*H*,3*H*)-pyrimidinedione	222	3119
4-Ethylsulfonyl-2,6-dimethoxypyrimidine	108–111	1750,3120
4-Ethylsulfonyl-5,6-dimethoxypyrimidine	87–88	1360,2073
2-Ethylsulfonyl-5,6-dimethyl-4-pyrimidinamine	134–135	1155
2-Ethylsulfonyl-5-fluoropyrimidine	60–61, 145/0.3, nmr	270,2160
1-Ethylsulfonyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione	214–215	800
2-Ethylsulfonyl-5-iodopyrimidine	138, nmr	270
4-Ethylsulfonyl-2-methoxycarbonylmethylpyrimidine	165–166/0.7	1749
2-Ethylsulfonyl-4-methoxy-5,6-dimethylpyrimidine	65–66	1155
2-Ethylsulfonyl-4-methoxy-6-methyl-5-propylpyrimidine	232/7	1453,1454
2-Ethylsulfonyl-4-methoxy-5-methylpyrimidine	67–68	1543,2156
2-Ethylsulfonyl-5-methoxypyrimidine	75–76	3121
2-Ethylsulfonyl-5-methyl-4-methylaminopyrimidine	138–140	1543
2-Ethylsulfonyl-6-methyl-5-propyl-4-pyrimidinamine	101–102	1453,1454
2-Ethylsulfonyl-5-methyl-4-pyrimidinamine	135–137	1543,1544,2043,2156
5-Ethylsulfonyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	223	3122
5-Ethylsulfonyl-2-pyrimidinamine	226–228	869
5-Ethylsulfonyl-2,4(1*H*,3*H*)-pyrimidinedione	282 or 284	3119,3122
5-Ethylthio-2,4-bistrimethylsiloxypyrimidine	96–97/0.2	839
4-Ethylthio-2,6-dimethoxypyrimidine	145/12	3120
4-Ethylthio-5,6-dimethoxypyrimidine	84/0.05	1360,2073
6-Ethylthio-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	110–111	3123
2-Ethylthio-1,3-dimethyl-6-oxo-3,6-dihydro-1-pyrimidinium-4-olate	98–100, ir, nmr, uv	285
2-Ethylthio-5,6-dimethyl-4-pyrimidinamine	91 or 92–93	1155,1156
6-Ethylthio-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	127–128	1066

2-Ethylthio-5,6-dimethyl-4(3*H*)-pyrimidinethione	187–188	2157
2-Ethylthio-1,5-dimethyl-4(1*H*)-pyrimidinone	154–160	963,2786,3124
2-Ethylthio-3,5-dimethyl-4(3*H*)-pyrimidinone	60–62 or 65	963,2786,3124
2-Ethylthio-3,6-dimethyl-4(3*H*)-pyrimidinone	63–64	1942,2789
2-Ethylthio-5,6-dimethyl-4(3*H*)-pyrimidinone	155–156	1155,2157,3053
2-Ethylthio-4,5-dimethyl-6-thiocyanatopyrimidine	65–66, 160/1.5	2157
2-Ethylthio-4,5-dimethyl-6-thioureidopyrimidine	209–210	2157
4-Ethylthio-5-ethylthiomethyl-2-isopropylamino-6-methylpyrimidine	liquid, anal, nmr	347
2-Ethylthio-5-fluoro-6-β-formylvinyl-4(3*H*)-pyrimidinone	136–138	2066
2-Ethylthio-5-fluoro-4-hydrazinopyrimidine	55	3029
2-Ethylthio-5-fluoro-6-hydroxymethyl-4(3*H*)-pyrimidinone	136–138	2066
2-Ethylthio-5-fluoro-4-methoxypyrimidine	104–107/10, nmr	270
2-Ethylthio-5-fluoro-1-methyl-4(1*H*)-pyrimidinone	152–153	933
2-Ethylthio-5-fluoro-3-methyl-4(3*H*)-pyrimidinone	95–96	933
2-Ethylthio-5-fluoro-6-methyl-4(3*H*)-pyrimidinone	190–192	1201
2-Ethylthio-5-fluoro-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	180–182; oxime: 240	2066
2-Ethylthio-5-fluoro-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	168–169	1266
2-Ethylthio-5-fluoro-4-pyrimidinamine	94–95	1266,2158,2161
2-Ethylthio-5-fluoropyrimidine	92/11, 94/14, nmr	270,2160
2-Ethylthio-5-fluoro-4(3*H*)-pyrimidinone	190 to 194	270,1266,1895,2161
2-Ethyl-5-thioformamidomethyl-4-pyrimidinamine	145 or 160	975,1457
6-Ethyl-5-thioformamido-4-pyrimidinamine	178	1239
2-Ethylthio-5-formamido-4(3*H*)-pyrimidinone	266–268 or 269–270, ir, uv	243,702
2-Ethylthio-5-hydrazinocarbonylmethyl-4(3*H*)-pyrimidinone	207–208	1395
2-Ethylthio-4-hydrazino-6-methylpyrimidine	91 to 96	2106,2126,3125
4-Ethylthio-2-hydrazino-6-methylpyrimidine	96–97	2126
2-Ethylthio-4-hydrazinopyrimidine	75	3029
2-Ethylthio-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	156–157	3126

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Ethylthio-5-hydroxymethyl-4-pyrimidinamine	151 to 157 (170?)	928,1249,1326,1329,3127
4-Ethylthio-6-imino-1,3-dimethyl-3,6-dihydro-2(1*H*)-pyrimidinone	66	1066
2-Ethylthio-6-iminomethyl-4-pyrimidinamine	182	1599
2-Ethylthio-5-iodo-4-pyrimidinamine	127	1234
2-Ethylthio-5-iodopyrimidine	66, nmr	270
2-Ethylthio-5-iodo-4(3*H*)-pyrimidinone	196 or 199–200	270,1234
2-Ethylthio-5-isocyanatomethyl-4(3*H*)-pyrimidinone	189–191	1395
2-Ethylthio-5-isopropyl-3-methoxycarbonylmethyl-6-methyl-4(3*H*)-pyrimidinone	135/1, ir, nmr, uv	3750
4-Ethylthio-2-isopropyl-6-methylpyrimidine	115–116/11	2905
2-Ethylthio-5-isopropyl-6-methyl-4(3*H*)-pyrimidinone	128–130	3750
2-Ethylthio-5-isopropyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	206–207	1224
5-Ethylthio-6-isopropyl-2,4-pyrimidinediamine	118–119	3021
2-Ethylthio-4-isothiocyanato-5,6-dimethylpyrimidine	29–30, 150–152/1.5	2157
2-Ethylthio-4-isothiocyanato-6-methylpyrimidine	146–148/1	3128
2-Ethylthio-4-isothiocyanatopyrimidine	200–205/45; polymer: 175–177	969
2-Ethylthio-3-methoxycarbonylmethyl-6-methyl-4(3*H*)-pyrimidinone	50–51, ir, nmr, uv	3750
4-Ethylthio-2-methoxycarbonylmethylpyrimidine	114–116/0.5	1749
2-Ethylthio-4-methoxy-5,6-dimethylpyrimidine	138/5	1155
2-Ethylthio-4-methoxy-6-methyl-5-propylpyrimidine	147/4	1453,1454
2-Ethylthio-4-methoxy-5-methylpyrimidine	104–105/4, 145–147/17	1543,2786
2-Ethylthio-4-methoxy-6-methylpyrimidine (?)	—	3125
4-Ethylthio-5-methoxy-2-methylpyrimidine	53–54	3129
2-Ethylthio-6-methoxy-4-pyrimidinamine	115 to 118	615,1358,2164,2906
6-Ethylthio-2-methoxy-4-pyrimidinamine	78–80 or 83–84	616,2164
2-Ethylthio-4-methoxypyrimidine	anal	1676

2-Ethylthio-5-methoxypyrimidine	86/0.4	926
2-Ethylthio-5-methoxy-4(3*H*)-pyrimidinone	140	926
4-Ethylthio-6-methylamino-2-pyrimidinamine	118	850
4-Ethylthio-6-methylamino-5-pyrimidinamine	91	3130
2-Ethylthio-4-methylaminopyrimidine	58; HCl: 216	1348,1676,1772
2-Ethylthio-5-(*N*-methylcarbamoyl)methyl-4(3*H*)-pyrimidinone	203–206	2020
2-Ethylthio-4-methyl-6-methylaminopyrimidine	87	1404
2-Ethylthio-5-methyl-4-methylaminopyrimidine	58–60; HCl: 228–229	1543,2155
2-Ethylthio-6-methyl-5-(*N*-methylcarbamoyl)methyl-4(3*H*)-pyrimidinone	243–245	2020
5-Ethylthiomethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	215–216, nmr	347
2-Ethylthio-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	186; oxime: 235	3131
2-Ethylthio-4-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	182–183	1247
2-Ethylthio-5-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	220	2229
2-Ethylthio-6-methyl-5-propyl-4-pyrimidinamine	86–87	3132
2-Ethylthio-6-methyl-5-propyl-4(3*H*)-pyrimidinone	92–93	1453,1455
2-Ethylthio-5-methyl-4-pyrimidinamine	96–97	967,2043
2-Ethylthio-6-methyl-4-pyrimidinamine	104	1516,1547,2043
4-Ethylthio-6-methyl-2-pyrimidinamine	122–125	958,2126
2-Ethylthio-4-methylpyrimidine	91–93/6, 123–124/18, n_D^{20} 1.5514; HCl: 141–142	193,2133,2694
2-Ethylthio-5-methylpyrimidine	78–79/0.02	2747
5-Ethylthio-6-methyl-2,4-pyrimidinediamine	138	3021
5-Ethylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione	244–246, nmr	347,841
5-Ethylthio-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	253–256	3133
2-Ethylthio-5-methyl-4(3*H*)-pyrimidinethione	181	1886,2698
2-Ethylthio-6-methyl-4(3*H*)-pyrimidinethione	205	1427,1647
2-Ethylthio-1-methyl-4(1*H*)-pyrimidinimine	HI: 184–185	1713
2-Ethylthio-1-methyl-4(1*H*)-pyrimidinone	133–134(?), uv	1942,2553,3022(?),3134

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Ethylthio-3-methyl-4(3*H*)-pyrimidinone	76–77 or 79–80(?), uv	1942,2553,3022(?),3134
2-Ethylthio-5-methyl-4(3*H*)-pyrimidinone	159–161	967,2162,2229,2698
2-Ethylthio-6-methyl-4(3*H*)-pyrimidinone	143–145 or 154–156	227,925,1806,2043,2939,3135, 3136
2-Ethylthio-4-methyl-6-thiocyanatopyrimidine	69–70, 155–158/5	3128
2-Ethylthio-5-methyl-4-thiocyanatopyrimidine	95	1886
6-Ethylthio-2-methylthio-4-pyrimidinamine	crude	1358
2-Ethylthio-4-methyl-6-thioureidopyrimidine	235–236	3128,3137
2-Ethylthio-5-methyl-4-thioureidopyrimidine	192	969
4-Ethylthio-5-methyl-1-vinyl-2(1*H*)-pyrimidinone	115–117	3138
6-Ethylthio-5-nitro-4(3*H*)-pyrimidinone	214	1832
2-Ethylthio-5-nitroso-4,6-pyrimidinediamine	crude	1246
2-Ethylthio-5-nitro-4-thiocyanatopyrimidine	131	1187
2-Ethylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	145 to 168; oxime: 254–256	1703,2854,2855,3139–3141
2-Ethylthio-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	220–222	1249,1600,2863
2-Ethylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbonitrile	210–211	1703
2-Ethylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	167	2527,3142
2-Ethylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	247–248	1030,3139
2-Ethylthio-6-propyl-4(3*H*)-pyrimidinone	91	925
2-Ethylthio-4-pyrimidinamine	85–86	719,951,1676
4-Ethylthio-2-pyrimidinamine	155 or 156–157	958,1149
5-Ethylthio-2-pyrimidinamine	116	2946
6-Ethylthio-4-pyrimidinamine	145 or 147–149	958,1655
2-Ethylthiopyrimidine	77/2.5, 106/14, 115/20, nmr; HCl: 98–99	270,2133,3143–3145

4-Ethylthiopyrimidine	89–90/12; pic: 105–106	3144
5-Ethylthiopyrimidine	96–98/10; pic: 98	836
4-Ethylthio-5-pyrimidinecarbonitrile	61–63	1614
2-Ethylthio-5-pyrimidinecarboxylic acid	182–183	3020
2-Ethylthio-4,5-pyrimidinediamine	155–157	3146
2-Ethylthio-4,6-pyrimidinediamine	146–147, ir, nmr; HBr: 169–173	250,1246,3147
4-Ethylthio-2,5-pyrimidinediamine	87	1582
5-Ethylthio-2,4(1*H*,3*H*)-pyrimidinedione	255–257 or 258	839,3119,3133
6-Ethylthio-2,4(1*H*,3*H*)-pyrimidinedione	230–233	2605
2-Ethylthio-4(3*H*)-pyrimidinethione	149	3134,3148
2-Ethylthio-4,5,6-pyrimidinetriamine	129	1246
6-Ethylthio-2,4,5-pyrimidinetriamine	150–151	932
2-Ethylthio-5-pyrimidinol	120	926
2-Ethylthio-4(3*H*)-pyrimidinone	151 to 156	828,925,3053,3146,3148
4-Ethylthio-2(1*H*)-pyrimidinone	176–178	3146
2-Ethylthio-4-thiocyanato-5-pyrimidinamine	234	633
2-Ethylthio-4-thiocyanatopyrimidine	82	1886
2-Ethylthio-4-thioureidopyrimidine	214	969
2-Ethylthio-1,3,5-trimethyl-6-oxo-3,6-dihydro-1-pyrimidinium-4-olate	197–198, ir, ms, nmr, uv	285
Ethyl 2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate	214–216	3020
Ethyl 4-thioxo-3,4-dihydro-5-pyrimidinecarboxylate	149–150	1615
5-Ethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	190–192	1046,3149
1-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	239–241 or 242–243, nmr	258,2035,2553,3146
1-Ethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	156–157	870
1-Ethyl-6-thioxo-3,6-dihydro-2(1*H*)-pyrimidinone	160–162	3146
3-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	177 or 189–190, nmr	424,425,2035,2553
3-Ethyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	148–150	909
4-Ethyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	223	2147

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	190–193	1219,1684,2720
5-Ethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	> 250 or > 275, ir, uv	3034,3760
6-Ethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	228–230	1684,2148,3076
Ethyl 2,5,6-triamino-4-pyrimidinecarboxylate	H_2O: 205–206	2959
5-Ethyl-2,4,6-trimethoxypyrimidine	67–68	1228
4-Ethyl-2,5,6-trimethylpyrimidine	52–54/2.5, ir, ms, nmr	3896,6419
5-Ethyl-2,4,6-trimethylpyrimidine	crude: ir, ms, nmr	3896
Ethyl 2,4,6-trimethyl-5-pyrimidinecarboxylate	MeI: 116–118, ir, ms, nmr	335
6-Ethyl-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	116–118	2542
4-Ethyl-1,2,6-trimethylpyrimidinium-5-carboxylate	226–227, M^+, ms	335
4-Ethyl-2,3,6-trimethylpyrimidinium-5-carboxylate	229–231, M^+, ms	335
Ethyl 1,2,6-trimethyl-4-thioxo-1,4-dihydro-5-pyrimidinecarboxylate	165 or 167	821,3150
3-Ethyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	> 300	895
1-Ethyl-5-ureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	218	789
5-Ethynyl-2,4-dimethoxypyrimidine	83–84	832
5-Ethynyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	NH_4: nmr	3151
5-Ethynyl-4-methyl-2-methylsulfonylpyrimidine	97–98, ir, ms, nmr	3741
5-Ethynyl-4-methyl-2-methylthiopyrimidine	75–76, ir, ms, nmr	3741
5-Ethynyl-4-methyl-2(1*H*)-pyrimidinone	180, ir, ms, nmr	3741
5-Ethynyl-2-methylthiopyrimidine	46–47, ir, ms, nmr	3741
2-Ethynylpyrimidine	95–96	3152
5-Ethynyl-2,4(1*H*,3*H*)-pyrimidinedione	320	786,832,2361,6126
5-Fluoro-1,3-bis-β-formylethyl-2,4(1*H*,3*H*)-pyrimidinedione	liquid, anal	2383
5-Fluoro-1,3-bis-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	liquid, anal	429,2383
5-Fluoro-1,3-bishydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	429

5-Fluoro-1,3-bis-γ-hydroxypropyl-2,4(1*H*,3*H*)-pyrimidinedione	liquid, anal	429,2383
5-Fluoro-1,3-bismethoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	liquid, anal	2383
5-Fluoro-2,4-bismethylthiopyrimidine	39	741
4-Fluoro-2,6-dimethoxypyrimidine	51 or 54–55	1040,1703,2454
5-Fluoro-2,4-dimethoxypyrimidine	48–50 or 50–51	2124,3153
2-Fluoro-4,6-dimethoxy-5-pyrimidinecarbonitrile	crude	2063
4-Fluoro-2,6-dimethoxy-5-pyrimidinecarbonitrile	crude	2063
5-Fluoro-4,6-dimethoxy-2(1*H*)-pyrimidinone	183–185, nmr	293
5-Fluoro-*N*,*N*-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxamide	194–196	3025
2-Fluoro-5,6-dimethyl-4-pyrimidinamine	226–228	2093
6-Fluoro-2,5-dimethyl-4-pyrimidinamine	195–196	2093
2-Fluoro-4,6-dimethylpyrimidine	12–14, 70/20, 74–75/18	2558,3154
4-Fluoro-2,6-dimethylpyrimidine	72/21 or 73–74/120, n_D^{25} 1.4618	1730,3154
5-Fluoro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	128 to 141, nmr, uv x1 st	899,2619,3155,3738,3978,6576
5-Fluoro-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	138
5-Fluoro-2,6-dimethyl-4(3*H*)-pyrimidinone	177–178	1201
6-Fluoro-2,5-dimethyl-4(3*H*)-pyrimidinone	222–223	2093
5-Fluoro-1,3-dimethyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	171–172	2619
5-Fluoro-2,6,dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	262–263	2066
5-Fluoro-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarbonyl chloride	crude	522
5-Fluoro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	250 to 259	1266,2158,2871,3015,3026, 3156,3157
5-Fluoro-2,4-dioxo-*N*-vinyl-1,2,3,4-tetrahydro-1-pyrimidinecarboxamide	150–160	3025
5-Fluoro-2,4-dipropoxypyrimidine	117/8, n_D^{20} 1.4750	2124
5-Fluoro-1,3-diprop-2′-ynyl-2,4(1*H*,3*H*)-pyrimidinedione	98	899
5-Fluoro-1,3-divinyl-2,4(1*H*,3*H*)-pyrimidinedione	120–121, ir, nmr	516
5-α-Fluoroethyl-2-methylthiopyrimidine	liquid, ms, nmr	3829
5-Fluoro-6-fluoromethyl-2-methylthio-4(3*H*)-pyrimidinone	199–200 or 221–222, nmr, uv	326,2158

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Fluoro-5-formamidopyrimidine	116–118	1623
5-Fluoro-1-β-formylethyl-2,4(1*H*,3*H*)-pyrimidinedione	140–141, nmr	237
5-Fluoro-1-formylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	292; acetal: 114–115	1299
5-Fluoro-1-β-formylvinyl-2,4(1*H*,3*H*)-pyrimidinedione	240–242, ir, nmr	5980
5-Fluoro-4-hydrazino-2(1*H*)-pyrimidinone	> 250	2699
5-Fluoro-4-hydroxyamino-2(1*H*)-pyrimidinone	260	1265
5-Fluoro-6-α-hydroxyethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	151–160, ir, nmr; *O*-Ts: —	450
5-Fluoro-1-β-hydroxyethyl-4-methylthio-2(1*H*)-pyrimidinone	161–162	741
5-Fluoro-1-β-hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	159–160	741
5-Fluoro-1-γ-hydroxypropyl-2,4(1*H*,3*H*)-pyrimidinedione	148–149, nmr, uv	237
5-Fluoro-1-hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	240	1265
5-Fluoro-4-imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	114–115	2619
4-Fluoro-2-isopropylpyrimidine	141–142/760	1907
4-Fluoro-2-methoxycarbonylmethylpyrimidine	liquid, anal	1749
5-Fluoro-1-methoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	185–186	2023
5-Fluoro-1-methoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	132–134	2911
5-Fluoro-4-methoxy-1-methyl-2(1*H*)-pyrimidinone	193–194, nmr	1895,3153
5-Fluoro-2-methoxy-4-pyrimidinamine	190–191	1264
5-Fluoro-4-methoxy-2-pyrimidinamine	139–141	1264
2-Fluoro-4-methoxypyrimidine	28–30/10, 76–79/135, nmr	66,2558
4-Fluoro-2-methoxypyrimidine	25–26/10, 65–66/135, ms	66,1730
4-Fluoro-6-methoxypyrimidine	6–7, 73–74/135	1730
5-Fluoro-2-methoxypyrimidine	52/12, 163–165/760, ms, n_D^{20} 1.4785, nmr	1897,3765
5-Fluoro-2-methoxy-4(3*H*)-pyrimidinone	195–197 or 206–207	430,1266,1267,1724,2158,2161

5-Fluoro-4-methoxy-2(1*H*)-pyrimidinone	189–190	1267
4-Fluoro-6-methylamino-5-pyrimidinamine	142–144	2556
5-Fluoro-4-methylamino-2(1*H*)-pyrimidinone	267–268	2664
4-Fluoro-5-methyl-2,6-bistrimethylsiloxypyrimidine	125/15	3158
5-Fluoro-*N*-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxamide	170	3025
2-Fluoromethyl-6-methoxy-4-pyrimidinamine	156–158	2167
4-Fluoromethyl-6-methoxy-2-pyrimidinamine	121–122	2167
6-Fluoromethyl-2-methoxy-4-pyrimidinamine	141–143	2167
5-Fluoro-1-methyl-4-methylamino-2(1*H*)-pyrimidinone	129–130	2619
2-Fluoromethyl-5-methyl-4-pyrimidinamine	158–160	2910
2-Fluoromethyl-6-methyl-4-pyrimidinamine	161–163	2167
2-Fluoromethyl-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione	> 300	2910
2-Fluoromethyl-5-methyl-4(3*H*)-pyrimidinone	anal	2910
2-Fluoromethyl-6-methyl-4(3*H*)-pyrimidinone	166–168	2910
6-Fluoromethyl-2-methyl-4(3*H*)-pyrimidinone	204–207	1201
5-Fluoro-4-methyl-2-methylsulfonylpyrimidine	71	2160
6-Fluoromethyl-2-methylthio-4-pyrimidinamine	103–104	2167
5-Fluoro-4-methyl-2-methylthiopyrimidine	97–100/17	2160
5-Fluoro-1-methyl-4-methylthio-2(1*H*)-pyrimidinone	154	741,1895
5-Fluoro-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	126–128	741
5-Fluoro-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	269–270	2160
6-Fluoromethyl-2-methylthio-4(3*H*)-pyrimidinone	226–227 or 230–231	2167,3159
5-Fluoro-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide	308–309	1262
5-Fluoro-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	183 or 214–215	1262,2282
2-Fluoromethyl-4-pyrimidinamine	151–153	2167
2-Fluoro-6-methyl-4-pyrimidinamine	209–210	2093
4-Fluoro-6-methyl-2-pyrimidinamine	198	2093
6-Fluoro-2-methyl-4-pyrimidinamine	175–176	2093

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Fluoro-5-methyl-4-pyrimidinamine	232–233	2093
2-Fluoro-4-methylpyrimidine	56/17, 67–68/120	2558,3154
4-Fluoro-2-methylpyrimidine	30–32/20, 65–66/140, n_D^{25} 1.4587	1730,3154
4-Fluoro-6-methylpyrimidine	19–20, 43/20, 59–60/187	1730,3154
5-Fluoro-2-methylpyrimidine	118–119/760, n_D^{20} 1.4637	3160,3161
2-Fluoromethyl-4,6(1*H*,5*H*)-pyrimidinedione	> 250	2910
5-Fluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione	270–272	1201
5-Fluoro-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	263–264 or 264–265, nmr	741,1260,2776,3162,3738
5-Fluoro-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	> 300 or 310, ir	272,3163
5-Fluoro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	190–191, nmr	138,741,3738
5-Fluoro-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 300	1201
6-Fluoro-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	210	3164
5-Fluoro-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	138
5-Fluoro-1-methyl-2(1*H*)-pyrimidinone	177–178, ms, nmr	3165,3765
5-Fluoro-2-methyl-4(3*H*)-pyrimidinone	215–217 or 218–220	1262,2282
5-Fluoro-4-methyl-2(1*H*)-pyrimidinone	198–200	2160
5-Fluoro-6-methyl-4(3*H*)-pyrimidinone	143–144; HCl: 177–178	2355
6-Fluoromethyl-4(3*H*)-pyrimidinone	anal	3159
6-Fluoro-2-methyl-4(3*H*)-pyrimidinone	229–230	2093
6-Fluoro-5-methyl-4(3*H*)-pyrimidinone	199–200	2093
5-Fluoro-2-methylsulfonylpyrimidine	80	2160
5-Fluoro-1-methylsulfonyl-2,4(1*H*,3*H*)-pyrimidinedione	223–224	800
5-Fluoro-2-methylthio-6-methylthiomethyl-4(3*H*)-pyrimidinone	168–170, nmr, uv	326
5-Fluoro-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	220–222; oxime: 262	2066
5-Fluoro-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	199–201	1266,2161

5-Fluoro-4-methylthio-1-prop-2′-ynyl-2(1*H*)-pyrimidinone	141–142	741
5-Fluoro-2-methylthiopyrimidine	87/13	2160
5-Fluoro-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	219–220	2292
5-Fluoro-2-methylthio-4(3*H*)-pyrimidinone	230 to 243, nmr, uv	326,1266,2160,2161,3166
5-Fluoro-4-methylthio-2(1*H*)-pyrimidinone	221–223 or 222–224	2288,2699
5-Fluoro-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	294–297	2355
6-Fluoro-5-nitro-4-pyrimidinamine	161–163	2556
2-Fluoro-5-nitro-4,6-pyrimidinediamine	> 250	2063
5-Fluoro-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide	> 360	1262
5-Fluoro-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	214–215 or 221	1262,2282
5-Fluoro-6-oxo-2-propylthio-1,6-dihydro-4-pyrimidinecarbaldehyde	129–131	2066
5-Fluoro-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	> 300	2066
5-Fluoro-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	—	1266
5-Fluoro-1-propionyl-2,4(1*H*,3*H*)-pyrimidinedione	124–125	800
5-Fluoro-2-propoxy-4(3*H*)-pyrimidinone	154	1724
2-Fluoro-4-propylaminopyrimidine	liquid, ms, nmr, uv	66
4-Fluoro-2-propylaminopyrimidine	56–57, ms, nmr, uv	66
5-Fluoro-1-prop-2′-ynyl-2,4(1*H*,3*H*)-pyrimidinedione	150–151	741
5-Fluoro-4-prop-2′-ynylthio-2(1*H*)-pyrimidinone	166, ir, nmr	276
2-Fluoro-4-pyrimidinamine	212, ms, nmr, uv	66
2-Fluoro-5-pyrimidinamine	178–179	1623
4-Fluoro-2-pyrimidinamine	158, ms, nmr, uv	66
5-Fluoro-2-pyrimidinamine	192–193 or 196–198	1264,3160,3161
6-Fluoro-4-pyrimidinamine	154–155	1730
2-Fluoropyrimidine	17–25, 75/20, 85–86/135	752,2558,3154
5-Fluoropyrimidine	101–102/733, n_D^{19} 1.4693, nmr	3160, 3161
5-Fluoro-2-pyrimidinecarbonitrile	44–45	1897
5-Fluoro-2,4-pyrimidinediamine	166–167	1260

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Fluoro-2,4-pyrimidinediamine	198–199	1040
6-Fluoro-4,5-pyrimidinediamine	218–220	2556
5-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione	272–287	128,138,430,1262,1265–1267, 2158,2161,3157,3166–3173,3918
6-Fluoro-2,4(1*H*,3*H*)-pyrimidinedione	240 or 245; K: > 300	2346,2454,3174
5-Fluoro-2(1*H*)-pyrimidinethione	160–161	3160,3161
5-Fluoro-2,4,6-pyrimidinetriamine	anal, uv	2400
5-Fluoro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	–	138
5-Fluoro-2(1*H*)-pyrimidinone	169 to 173, ms	270,1267,2160,2699,3161, 3165,3763
5-Fluoro-4(3*H*)-pyrimidinone	200–205	1262,2282,2355
5-Fluoro-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	Na: > 300	2292
5-Fluoro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	225–226	1262,2158,2161
5-Fluoro-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	275 to 281, ir, ms, nmr, uv	1267,2288,2699
5-Fluoro-2,4,6-trimethoxypyrimidine	98–99	1728
5-Fluoro-1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione	197–199	741
5-Formamido-2,6-bismethylamino-4(3*H*)-pyrimidinone	282–283	1282,2404
5-Formamido-2,4-bis-*N*-methylformamidopyrimidine	> 300	3175
5-Formamido-2,6-bismethylthio-4-pyrimidinamine	260	1202
5-Formamido-2,4-bispropylaminopyrimidine	159–160	1790
4-Formamido-2,6-dimethoxypyrimidine	205	1019
5-Formamido-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	250, then 285	1104
5-Formamido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	204	1126
6-Formamido-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	anal	1126
5-Formamido-2,6-dimethyl-4(3*H*)-pyrimidinone	245–248	614,639

4-Formamido-6-isopropoxy-5-nitroso-2-pyrimidinamine	190	638
5-Formamido-6-isopropylamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	235	1353
5-Formamido-6-isopropylamino-2,4(1*H*,3*H*)-pyrimidinedione	264	1353
4-Formamido-6-methoxy-5-nitroso-2-pyrimidinamine	190	638
5-Formamido-2-methoxypyrimidine	181–182	1623
5-Formamido-2-methoxy-4(3*H*)-pyrimidinone	185–187, ir, uv	243
5-Formamido-4-methylamino-6-methylthiopyrimidine	204–205	3176
5-Formamido-2-methylamino-4-pyrimidinamine	202; HCO_2H: 195	1764
5-Formamido-4-methylaminopyrimidine	142	1379
5-Formamido-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	> 350	1376,3177
5-Formamido-3-methyl-2,6-bismethylamino-4(3*H*)-pyrimidinone	291–292	1282,2404
4-Formamidomethyl-2,6-bismethylthiopyrimidine	130–131, nmr	311
5-Formamido-4-methyl-2,6-bismethylthiopyrimidine	180–181	676
6-Formamidomethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	anal	701
5-Formamido-2-methyl-4-methylamino-6-methylthiopyrimidine	222–223	1400
5-Formamido-3-methyl-6-methylamino-2-methylthio-4(3*H*)-pyrimidinone	273–275	619
5-Formamido-3-methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	350–352 or > 360	619,1398
5-Formamidomethyl-2-methyl-4-methylaminopyrimidine	152–153	1406
5-Formamidomethyl-2-methyl-4-pyrimidinamine	222–225; HCl: 214; pic: 191–193	685,975,3178–3180
5-Formamidomethyl-2-methyl-4(3*H*)-pyrimidinone	213	3178
6-Formamido-3-methyl-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone	169–170	641
5-Formamido-6-methyl-2-methylthio-4-pyrimidinamine	235	1400
5-Formamido-6-methyl-2-methylthio-4(3*H*)-pyrimidinethione	248–250	676
5-Formamidomethyl-4-pyrimidinamine	171–172; pic: 205 or 265	1451,3181
5-Formamido-6-methyl-4-pyrimidinamine	205–209	1932
5-Formamido-6-methyl-2,4-pyrimidinediamine	300	645,1932
5-Formamido-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	290	3182
6-Formamidomethyl-2,4(1*H*,3*H*)-pyrimidinedione	261–264, nmr	311,701

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Formamido-6-methyl-2,4(1*H*,3*H*)-pyrimidinedithione	285–287	676
5-Formamido-2-methyl-4(3*H*)-pyrimidinone	> 300, ir, uv	243
5-Formamido-6-methyl-4(3*H*)-pyrimidinone	190–191	1552
5-Formamido-2-methylsulfonylpyrimidine	161–162	1623
5-Formamido-2-methylthio-4-pyrimidinamine	180–190	681
5-Formamido-6-methylthio-4-pyrimidinamine	222	3183
5-Formamido-2-methylthiopyrimidine	122–123	1623
5-Formamido-2-methylthio-4,6-pyrimidinediamine	254	700
5-Formamido-6-methylthio-4(3*H*)-pyrimidinethione	213–214	2171
3-Formamido-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	219–220	1573
5-Formamido-2-pyrimidinamine	221–222	1623
5-Formamido-4-pyrimidinamine	185 to 198	1053,1383,1400,2296,3184
6-Formamido-4-pyrimidinamine	276 or 285	612,3185
5-Formamidopyrimidine	186–187	1623
5-Formamido-2-pyrimidinecarbonitrile	192–193	1623
5-Formamido-2,4-pyrimidinediamine	224	2296
5-Formamido-4,6-pyrimidinediamine	anal, uv	1297,2740,3186,3187
5-Formamido-2,4(1*H*,3*H*)-pyrimidinedione	310 to 313	243,1170,1176,3182
5-Formamido-4,6(1*H*,5*H*)-pyrimidinedione	> 240	1641
6-Formamido-2,4(1*H*,3*H*)-pyrimidinedione	anal	1126
5-Formamido-2(1*H*)-pyrimidinethione	295–298	1623
5-Formamido-2,4,6-pyrimidinetriamine	152–155	1297,3188
5-Formamido-2(1*H*)-pyrimidinone	> 360	1623
5-Formamido-4(3*H*)-pyrimidinone	260–264, ir, uv	243
3-Formamido-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	196–198	1573

5-Formamido-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	> 350, ir, uv	243
5-Formamido-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	152	3189
6-Formamido-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	174–176	653
5-Formimidoyl-2-methyl-4-pyrimidinamine	—	3190
5-Formimidoyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	anal	3191,3192
5-Formyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	crude	1597
5-β-Formylethyl-4-methyl-2-pyrimidinamine	acetal: —	3193
5-β-Formylethyl-6-methyl-4(3*H*)-pyrimidinone	H_2O (?): anal; acetal: 76–77	3193
5-Formylethynyl-2,4-dimethoxypyrimidine	130	3934
4-β-Formylhydrazino-2,6-dimethyl-5-nitropyrimidine	157–158	1552
4-β-Formylhydrazino-6-methoxy-2,5-dimethylpyrimidine	181	2190
4-β-Formylhydrazino-6-methyl-2-methylthiopyrimidine	190–191 or 198–200	1752,3194
6-β-Formylhydrazino-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	210, then 251	3195
2-β-Formylhydrazino-4-methylpyrimidine	158–159	6209
6-β-Formylhydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	222–223	3195
6-β-Formylhydrazino-5-nitro-4(3*H*)-pyrimidinone	241–242 or 263–264	804,2173
6-β-Formylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione	> 230	805
5-Formylmethyl-2-methoxy-4,6-pyrimidinediamine	acetal: 149–151	3859
1-Formylmethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	300; H_2O: > 300; acetal: 76–78	1299,3196
1-Formylmethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	236–237; acetal: 91; sc: 250; tsc: 240	1753,1887
1-Formylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	207; H_2O: 213–214; acetal: 89 to 93; sc: 225; tsc: 223–228	1753,3196–3199
5-Formylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	uv; dnp: 257	3200
5-Formyl-2-methylthio-4-pyrimidinecarboxylic acid	171, nmr	502
1-β-Formylvinyl-5-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	212–214, ir, nmr	5980
1-β-Formylvinyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	215–218, ir, nmr	5980
1-β-Formylvinyl-2,4(1*H*,3*H*)-pyrimidinedione	210–212, ir, nmr	5980
4-Guanidinoamino-6-methyl-2-pyrimidinamine	250	1754

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Guanidino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	HCl: 162–163	1174
2-Guanidino-6-methyl-5-propyl-4(3*H*)-pyrimidinone	291–292	863
2-Guanidino-5-nitro-4-pyrimidinamine	HCl: 303	2174
6-Guanidino-5-nitro-2,4-pyrimidinediamine	HCl: 324	2174
4-Guanidino-2-pyrimidinamine	HCl: 290	2174
2-Guanidino-4,5-pyrimidinediamine	HCl: 225	2174
2-Guanidino-4,6-pyrimidinediamine	HCl: 274	2174
6-Guanidino-4,5-pyrimidinediamine	H_2SO_4: 305	2174
2-Guanidino-4,6(1*H*,5*H*)-pyrimidinedione	anal; HCl: anal; H_2SO_4: anal	3201
6-Guanidino-2,4(1*H*,3*H*)-pyrimidinedione	300	2474
2-Hydrazino-4,6-bismethylthiopyrimidine	106	1780
5-α-Hydrazinocarbonylethyl-2-methyl-4-pyrimidinamine	263	1209
5-β-Hydrazinocarbonylethyl-2-methyl-4-pyrimidinamine	201	1209
5-β-Hydrazinocarbonylethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	268–270	1300
5-β-Hydrazinocarbonylethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	276–280	1300
5-Hydrazinocarbonylmethyl-2-methyl-4-pyrimidinamine	235	1406
5-Hydrazinocarbonylmethyl-2-methylpyrimidine	158 or 161	1413,3202
5-Hydrazinocarbonylmethyl-4-methylpyrimidine	141–142	575
5-Hydrazinocarbonylmethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 375	1415
5-Hydrazinocarbonylmethylpyrimidine	141–142	2002
1-Hydrazinocarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	241	2003
6-Hydrazinocarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	326	1395,2005,3028,3203
4-Hydrazino-2,6-dimethoxy-5-nitropyrimidine	155–156	2068
2-Hydrazino-4,6-dimethoxypyrimidine	97–98 or 101–104	1780,3204
4-Hydrazino-2,6-dimethoxypyrimidine	120–122; HCl: 143	2577,2579

4-Hydrazino-2,6-dimethyl-5-nitropyrimidine	127–128	1552,2068
6-Hydrazino-1,3-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	128–130, ir	3753
6-Hydrazino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	168	3205
4-Hydrazino-5,6-dimethyl-2-propylpyrimidine	78–80	880,900
4-Hydrazino-2,6-dimethyl-5-pyrimidinamine	HCl: 218–220	1552
4-Hydrazino-5,6-dimethyl-2-pyrimidinamine	220	1754
2-Hydrazino-4,6-dimethylpyrimidine	162–166	1529,1711,2363,2566,3206
4-Hydrazino-2,5-dimethylpyrimidine	198–200	3207
4-Hydrazino-2,6-dimethylpyrimidine	180–181 or 186–187	1711,2149,2577
4-Hydrazino-5,6-dimethylpyrimidine	215–217	2106
6-Hydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	212 to 229	644,1132,1133,2112
2-Hydrazino-3,6-dimethyl-4(3*H*)-pyrimidinone	201–203 or 206–207; pic: 196–197	2106,3208
2-Hydrazino-5,6-dimethyl-4(3*H*)-pyrimidinone	245–300 or 333	1303,1529
4-Hydrazino-1,5-dimethyl-2(1*H*)-pyrimidinone	169–172	2699
6-Hydrazino-1,3-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	223–224	1134
5-Hydrazino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	120; hydrazinium salt: 213–214	1174,3209
4-Hyrazino-2,6-dipropylpyrimidine	48–50	880,900
4-Hydrazino-5-β-hydrazinocarbonylethyl-2-methylpyrimidine	182	1209
2-Hydrazino-5-β-hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	227–228	1303
4-Hydrazino-5-hydroxymethyl-2-methylthiopyrimidine	145–146	2695
2-Hydrazino-6-hydroxymethyl-4(3*H*)-pyrimidinone	230	2106
4-Hydrazino-6-hydroxymethyl-2(1*H*)-pyrimidinone	> 250	770
4-Hydrazino-5-iodo-2-isopropyl-6-methylpyrimidine	108–109	1857
2-Hydrazino-5-iodopyrimidine	196–197	2180
2-Hydrazino-4-isopropoxy-6-methylpyrimidine	50–51 or 135–136	2106,2126
4-Hydrazino-2-isopropyl-6-methylpyrimidine	86	880,900

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Hydrazino-4-isopropylthio-6-methylpyrimidine	62–65	2126
4-Hydrazino-2-isopropylthio-6-methylpyrimidine	103–104	2126
4-Hydrazino-6-methoxy-2,5-dimethylpyrimidine	142	2190
4-Hydrazino-2-methoxy-6-methyl-5-nitropyrimidine	136–138	2559
4-Hydrazino-6-methoxy-2-methyl-5-nitropyrimidine	144–145	1552
2-Hydrazino-4-methoxy-6-methylpyrimidine	112–114 or 114–116 (199–201?)	2065,2106,2126,2197, 3125(?),3204
4-Hydrazino-2-methoxy-6-methylpyrimidine	154–156	3204
4-Hydrazino-6-methoxy-2-methylpyrimidine	148–149	3204
4-Hydrazino-5-methoxy-2-methylthiopyrimidine	72–73	718
4-Hydrazino-2-methoxy-5-nitropyrimidine	135–136	2559
4-Hydrazino-6-methoxy-5-nitropyrimidine	154–155	684
2-Hydrazino-4-methoxypyrimidine	120–121	2106
2-Hydrazino-5-methoxypyrimidine	141–142	1897
4-Hydrazino-5-methoxypyrimidine	184–185	1343
4-Hydrazino-6-methoxypyrimidine	148–149	3204
4-Hydrazino-6-methyl-2,5-dipropylpyrimidine	109–111	880
2-Hydrazino-4-methyl-6-methylthiopyrimidine	120–122 or 123–124	2126,2562
4-Hydrazino-6-methyl-2-methylthiopyrimidine	138 to 145	1701,1752,2065,2106,2126,2562, 3194,3210
4-Hydrazino-6-methyl-5-nitro-2-propoxypyrimidine	107–109	2559
4-Hydrazino-6-methyl-5-nitro-2-pyrimidinamine	184–185	1754
6-Hydrazino-2-methyl-5-nitro-4-pyrimidinamine	252	684
4-Hydrazino-2-methyl-5-nitropyrimidine	152	1552,3211
6-Hydrazino-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	212 to 217	999,3195,3753

4-Hydrazino-6-methyl-5-nitro-2(1*H*)-pyrimidinone	228–229	2559
4-Hydrazino-2-methyl-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	275	3212
2-Hydrazino-4-methyl-6-propoxypyrimidine	70–71	2126
4-Hydrazino-2-methyl-6-propylpyrimidine	100–102	880,900
4-Hydrazino-6-methyl-2-propylpyrimidine	93–95	880
2-Hydrazino-6-methyl-5-propyl-4(3*H*)-pyrimidinone	215–216 or 216–218	863,1529
2-Hydrazino-4-methyl-6-propylthiopyrimidine	64–65	2126
4-Hydrazino-6-methyl-2-propylthiopyrimidine	104–105	2126
2-Hydrazino-6-methyl-4-pyrimidinamine	184–186	2106,3213
4-Hydrazino-5-methyl-2-pyrimidinamine	230–234	1754
4-Hydrazino-6-methyl-2-pyrimidinamine	236–238	1754,2106,2197,3214
4-Hydrazino-6-methyl-5-pyrimidinamine	215	1038
6-Hydrazino-2-methyl-4-pyrimidinamine	240–242	1556
2-Hydrazino-4-methylpyrimidine	87–89 or 89–91 (141?); HCl: 194–198	2106,2936,3215,3216,3217(?)
2-Hydrazino-5-methylpyrimidine	137 to 144	1711,1897,2062
4-Hydrazino-2-methylpyrimidine	122–124; HCl: 213–214	880,2106
4-Hydrazino-5-methylpyrimidine	205–206	2106
4-Hydrazino-6-methylpyrimidine	140 to 144	880,1932,2106,3214,3218
2-Hydrazino-6-methyl-4-pyrimidinecarbonitrile	195	2267
4-Hydrazino-2-methyl-5-pyrimidinecarboxylic acid	340	3007
5-Hydrazino-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	267	3219
6-Hydrazinomethyl-2,4(1*H*,3*H*)-pyrimidinedione	288–290	1498
6-Hydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	223 or 236–238	2690,3195
6-Hydrazino-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	275–276	2279
4-Hydrazino-6-methyl-2(1*H*)-pyrimidinethione	272–275 or 280	1752,3220
2-Hydrazino-5-methyl-4(3*H*)-pyrimidinone	224 or 225	2106,3221,3222
2-Hydrazino-6-methyl-4(3*H*)-pyrimidinone	240 to 252	1429,1529,2065,2106,2126, 2571,3218,3221,3223,3224

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Hydrazino-1-methyl-2(1*H*)-pyrimidinone	173 or 177–179	2106,2699,3225
4-Hydrazino-6-methyl-2(1*H*)-pyrimidinone	235 or 285; H_2O: 251	2106,3215,3226
6-Hydrazino-2-methyl-4(3*H*)-pyrimidinone	155–156	1680
5-Hydrazino-2-methylsulfonylpyrimidine	186–189	1897
4-Hydrazino-2-methylthio-5-nitropyrimidine	198	804
4-Hydrazino-5-nitro-2-propoxypyrimidine	83–84	3227
2-Hydrazino-5-nitro-4-pyrimidinamine	> 225	1714
6-Hydrazino-5-nitro-4-pyrimidinamine	199 or > 264; HCl: > 300	607,684
2-Hydrazino-5-nitropyrimidine	168–169 or 173–175	2305,3228
4-Hydrazino-5-nitropyrimidine	148 or 151	3227,3229,3230
4-Hydrazino-5-nitro-2(1*H*)-pyrimidinone	208–209	804
6-Hydrazino-5-nitro-4(3*H*)-pyrimidinone	> 250	607
2-Hydrazino-4-oxo-3,4-dihydro-5-pyrimidinecarbohydrazide	275	3046
2-Hydrazino-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	> 320	3231
6-Hydrazino-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	242–243	1134
2-Hydrazino-6-propyl-4(3*H*)-pyrimidinone	185–186	3221,3222
4-Hydrazino-6-propyl-2(1*H*)-pyrimidinone	245	2147
4-Hydrazino-5-pyrimidinamine	159–160; HCl: 234	1777
2-Hydrazinopyrimidine	108 to 113	1715,1827,2106,2197(?),3232
4-Hydrazinopyrimidine	132–134	1827,3232
4-Hydrazino-5-pyrimidinecarbohydrazide	183	1615
2-Hydrazino-5-pyrimidinecarbonitrile	163–164	1897
4-Hydrazino-5-pyrimidinecarbonitrile	260	1614
6-Hydrazino-2,4-pyrimidinediamine	233–235, nmr	232
6-Hydrazino-4,5-pyrimidinediamine	HCl: > 200	607

5-Hydrazino-2,4(1*H*,3*H*)-pyrimidinedione	anal	3209
6-Hydrazino-2,4(1*H*,3*H*)-pyrimidinedione	290	1306,2279,3233
4-Hydrazino-2(1*H*)-pyrimidinethione	276–279	2147,3221,3234
2-Hydrazino-4(3*H*)-pyrimidinone	190–191 or 194–195	2970,3234
4-Hydrazino-2(1*H*)-pyrimidinone	305–310 or > 350	1533,2699,3226,3236
6-Hydrazino-4(3*H*)-pyrimidinone	> 230 or 245–255	1680,3237
4-Hydrazino-2,5,6-trimethylpyrimidine	164–166	880
6-Hydrazino-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	162–163 or 174–176	855,1139
2-Hydrazono-4,6-dimethyl-1,2-dihydro-1-pyrimidinamine	122–123	3238
4-Hydrazono-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	129	3225
5-Hydrazono-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	anal	2462
5-Hydrazono-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	> 300	2462
5-Hydroperoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	> 230	2853
2-Hydroxyamino-4,6-dimethylpyrimidine	207–210 or 209–211	1012,2790
4-Hydroxyamino-2,6-dimethylpyrimidine	198–200, nmr, uv	514,1012
6-Hydroxyamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	146–148 or 148–150	776,1139
4-Hydroxyamino-1,5-dimethyl-2(1*H*)-pyrimidinone	214–215; HCl: 208–210	1549
4-Hydroxyamino-1,6-dimethyl-2(1*H*)-pyrimidinone	260–261	1549
4-Hydroxyamino-5-hydroxymethyl-2(1*H*)-pyrimidinone	HCl: 260	3239
4-Hydroxyamino-6-methyl-2-pyrimidinamine	> 200	1012
2-Hydroxyamino-4-methylpyrimidine	105	1012
6-Hydroxyamino-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	248–250	776
6-Hydroxyamino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	190 or 203–206	776,1704
2-Hydroxyamino-1-methyl-4(1*H*)-pyrimidinimine	HI: 258	1713
2-Hydroxyamino-6-methyl-4(3*H*)-pyrimidinone	225–228 or 233	2790,3240
4-Hydroxyamino-1-methyl-2(1*H*)-pyrimidinone	224–225; HCl: 218–219	1549,3239
4-Hydroxyamino-5-methyl-2(1*H*)-pyrimidinone	261–262 or 270	1549,3239
6-Hydroxyamino-2-methyl-4(3*H*)-pyrimidinone	338	3212

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Hydroxyamino-5-nitroso-4,6-pyrimidinediamine	> 300	1310
2-Hydroxyaminopyrimidine	180	1012
6-Hydroxyamino-2,4(1*H*,3*H*)-pyrimidinedione	280	3241
5-Hydroxyamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	208	757
4-Hydroxyamino-2(1*H*)-pyrimidinone	243–244; HCl: 214–215 or 220–221	1549,3239
5-Hydroxy-1,3-dimethyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	95–97	854
3-Hydroxy-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	171	2783
5-Hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	198–199 or 201	749,754,1859,1860,2703,3242
5-Hydroxy-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	335	3243,3244
5-Hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinethione	> 230	1343
5-Hydroxy-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	170 to 229	1138,1140,2703
5-Hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone	> 300	578,1011,1343
1-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	205–207	1338
3-Hydroxy-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	261	2888
5-α-Hydroxyethyl-2,4-dimethoxypyrimidine	oil, ir, nmr	6071
1-β-Hydroxyethyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	134–136 or 136–137, ir, nmr	3895,3901,3902
3-β-Hydroxyethyl-1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	112–115	1721
5-β-Hydroxyethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	140–142	3245
1-β-Hydroxyethyl-4,6-dimethyl-2(1*H*)-pyrimidinone	134–135; HCl: 231–232	1312
5-β-Hydroxyethyl-2,6-dimethyl-4(3*H*)-pyrimidinone	192–195	1198
1-β-Hydroxyethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	194	1318
1-β-Hydroxyethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	231–232	1881
4-β-Hydroxyethyl-2,6-dipropoxypyrimidine	128–132/0.4	3246
2-β-Hydroxyethyl-5-hydroxymethyl-4-pyrimidinamine	167–168	974

1-β-Hydroxyethyl-6-imino-3-methyl-3,6-dihydro-2(1*H*)-pyrimidinone	194–196	3247
1-β-Hydroxyethyl-6-isopropylimino-3-methyl-3,6-dihydro-2(1*H*)-pyrimidinone	57–60	2143
5-β-Hydroxyethyl-3-isopropyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	3248
1-β-Hydroxyethyl-2-methoxy-5-methyl-4(1*H*)-pyrimidinone	128–130	1322
3-β-Hydroxyethyl-6-methoxy-4(3*H*)-pyrimidinimine	HBr: 122–124	3249
1-β-Hydroxyethyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	123–124, nmr	3995
3-β-Hydroxyethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	109–110, ir, nmr	525
5-β-Hydroxyethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	198–199; HCl: 194–195	3126,3250
1-β-Hydroxyethyl-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	215, nmr	3995
4-β-Hydroxyethyl-6-methyl-2-propoxypyrimidine	148–183/12(!)	3246
5-β-Hydroxyethyl-2-methyl-4-pyrimidinamine	193–194	3251
5-β-Hydroxyethyl-4-methyl-2-pyrimidinamine	159–160	1149
5-β-Hydroxyethyl-4-methylpyrimidine	155–156/8	1211
1-β-Hydroxyethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	179–181	1323
3-β-Hydroxyethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	136–138 or 138–140	2143,3247,3252
3-β-Hydroxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	205–207	1755
5-β-Hydroxyethyl-1(or 3)-methyl-2,4(1*H*,3*H*)-pyrimidinedione	255–256	1005
5-β-Hydroxyethyl-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	275–276	3035
5-β-Hydroxyethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	263 to 270	1206,2053,3126
6-α-Hydroxyethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	219–220	3253
2-α-Hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	134–135	2820
2-β-Hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	163–165	3254
5-β-Hydroxyethyl-2-methyl-4(3*H*)-pyrimidinone	172–173	1005
5-β-Hydroxyethyl-6-methyl-4(3*H*)-pyrimidinone	154–155 or 155–156	2053,2145,3126
5-α-Hydroxyethyl-2-methylthiopyrimidine	liquid, anal, ms, nmr	3829
5-β-Hydroxyethyl-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	218–220	1319
3-β-Hydroxyethyl-2-methylthio-4(3*H*)-pyrimidinone	121–122, ir, nmr	525
5-β-Hydroxyethyl-2-methylthio-4(3*H*)-pyrimidinone	184–185	1321

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-β-Hydroxyethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	204	1318
5-β-Hydroxyethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	250 to 267	1206,1684,2053,3126,3255
5-β-Hydroxyethyl-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	267–268	1206
4-β-Hydroxyethylpyrimidine	125–127/9 or 130–135/10, n_D^{25} 1.5323	2078,3246
1-β-Hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	136–138	1323,1722,1756–1758
3-β-Hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	172–173	1757,1758
5-α-Hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	anal, nmr, uv	252
5-β-Hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	264–265	831,2039
5-β-Hydroxyethyl-4,6(1*H*,5*H*)-pyrimidinedione	239–240 or 247–248	1319,3035
6-β-Hydroxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	208–210	1232
5-β-Hydroxyethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	193–194(?) or > 300	1258,1319
1-β-Hydroxyethyl-2(1*H*)-pyrimidinimine	HBr: 186; pic: 163–164	923,3249
1-β-Hydroxyethyl-2(1*H*)-pyrimidinone	138–139	1755
5-β-Hydroxyethyl-4(3*H*)-pyrimidinone	153–155	2051
5-Hydroxyethyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	181 or 196–197	1319,3256
5-β-Hydroxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	248–249	1005,2051
5-Hydroxy-6-hydroxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	187–188	747
5-Hydroxy-6-hydroxymethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	195–196	854
5-Hydroxy-6-hydroxymethyl-2,4(1*H*.3*H*)-pyrimidinedione	> 320	747,2123
5-Hydroxy-6-hydroxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	268–269	2628
4-Hydroxyimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	169–170 or 180; HCl: 212–215	806,3225
4-Hydroxyiminomethyl-2,6-dimethylpyrimidine 1,3-dioxide	220	763
1-Hydroxy-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	205–210	1265
3-Hydroxy-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione	225–235	1265

5-Hydroxy-6-isopropyl-2-methyl-4(3*H*)-pyrimidinone	189–191, nmr	3908
1-Hydroxy-6-methylamino-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	242–249	3257
2-Hydroxymethyl-4,6-dimethoxypyrimidine	60–62, nmr	3974
5-Hydroxymethyl-2,4-dimethoxypyrimidine	123, ir, nmr	6076
5-Hydroxymethyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidine-carboxylic acid	lactone: 155–156	1851
5-Hydroxymethyl-2,6-dimethyl-4-pyrimidinamine	185	1119
2-Hydroxymethyl-4,6-dimethylpyrimidine	87–88 or 88–89	1933,2222,3258
4-Hydroxymethyl-2,6-dimethylpyrimidine	109–110	1933,2222
5-Hydroxymethyl-2,4-dimethylpyrimidine	60–61	3259
5-Hydroxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	136 to 142	323,760,761,3245
5-Hydroxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	212–213	3260
5-Hydroxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	lactone: 310–312	1597,3261
5-Hydroxymethylene-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	Na: > 350	1207
2-α-Hydroxy-α-methylethyl-6-methyl-4(3*H*)-pyrimidinone	98	2722
5-α-Hydroxy-α-methylethyl-2-methylthiopyrimidine	anal, ir, nmr	381
5-Hydroxymethyl-4-isopropylamino-2-methylpyrimidine	161–162	2621
4-Hydroxymethyl-2-isopropyl-6-methylpyrimidine	135–138/20	2222
5-Hydroxymethyl-3-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione		1916
5-Hydroxymethyl-2-methoxymethyl-4-pyrimidinamine	128–130	1762
2-Hydroxymethyl-4-methoxy-6-methylpyrimidine	55–56 or 56–57	64,3258
4-Hydroxymethyl-2-methoxy-6-methylpyrimidine	146–147	3258
4-Hydroxymethyl-6-methoxy-2-methylpyrimidine	116	3258
5-Hydroxymethyl-4-methoxy-2-methylpyrimidine	101–102	1904
5-Hydroxymethyl-2-methoxy-4-pyrimidinamine	170–171 or 173–174	2203,2227,2966,2967,3262
4-Hydroxymethyl-2-methoxypyrimidine	115–116 (104–105?), ir, nmr	1850,3931
2-Hydroxymethyl-6-methoxy-4(3*H*)-pyrimidinone	168–170, nmr	3974
5-Hydroxymethyl-4-methylamino-2-methylthiopyrimidine	157–158	2695

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Hydroxymethyl-2-methylamino-4-pyrimidinamine	142–144	577
5-Hydroxymethyl-*N*-methyl-2,6-bismethylamino-4-pyrimidinecarboxamide	163	936
5-Hydroxymethyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	lactone: 267	3261
5-Hydroxymethyl-2-methyl-4-methylaminopyrimidine	171–172	1912,2621
5-Hydroxymethyl-4-methyl-2-methylthiopyrimidine	48–49, nmr; *p*-$O_2NC_6H_4CO$: 149–150	2695,6133
5-Hydroxymethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	220–221	2793
6-Hydroxymethyl-1-methyl-2-methylthio-4(1*H*)-pyrimidinone	237–238	2888
5-Hydroxymethyl-2-methyl-4-propylaminopyrimidine	111–112	2621
5-Hydroxymethyl-2-methyl-4-pyrimidinamine	194–200	750,1409,1410,1458,1918, 1919,2231,3263–3265
5-Hydroxymethyl-6-methyl-4-pyrimidinamine	166	678,750
5-Hydroxymethyl-2-methylpyrimidine	105	1904,3202
2-Hydroxymethyl-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione	289	1875
5-Hydroxymethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	239–242	323,765,2776
5-Hydroxymethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	170–171	323,760,765
5-Hydroxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	314–315	1597,2233,2212,2792
6-Hydroxymethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	225–226	2888
6-Hydroxymethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	224–225	766,767
5-Hydroxymethyl-2-methyl-4(3*H*)-pyrimidinethione	193–195	1904
4-Hydroxymethyl-6-methyl-5-pyrimidinol	134–135, ms, nmr, uv	458
2-Hydroxymethyl-6-methyl-4(3*H*)-pyrimidinone	200–203	2056
5-Hydroxymethyl-2-methyl-4(3*H*)-pyrimidinone	207 or 215–216	680,1418,1419,2812,2813
6-Hydroxymethyl-2-methyl-4(3*H*)-pyrimidinone	HCl: 248–250	1877
6-Hydroxymethyl-3-methyl-4(3*H*)-pyrimidinone	118	2498

5-Hydroxymethyl-2-methylsulfonyl-4-pyrimidinamine	172–173	577
5-Hydroxymethyl-2-methylthio-4-pyrimidinamine	126–128	577,928,1331,2974,3266
4-Hydroxymethyl-2-methylthiopyrimidine	120–121, ir, nmr	3931
5-Hydroxymethyl-2-methylthiopyrimidine	63–64	768
5-Hydroxymethyl-2-methylthio-4-pyrimidinecarbaldehyde	135–136; oxime: 178	768,6133
5-Hydroxymethyl-2-methylthio-4-pyrimidinecarboxamide	177–179	768
6-Hydroxymethyl-2-methylthio-4(3*H*)-pyrimidinone	219–220 or 221–222	2856,2888
5-Hydroxymethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	280–290	2793
6-Hydroxymethyl-1-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	226–227	2888
5-Hydroxy-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	> 250	1262
5-Hydroxymethyl-1-prop-1′-enyl-2,4(1*H*,3*H*)-pyrimidinedione	167–169	901
5-Hydroxymethyl-2-propylamino-4-pyrimidinamine	114–117	577
5-Hydroxymethyl-2-propyl-4-pyrimidinamine	115–116; HCl: 168	1354,1394
5-Hydroxymethyl-2-propylthio-4-pyrimidinamine	138–139	928
4-Hydroxymethyl-2-pyrimidinamine	145	1629
4-Hydroxymethylpyrimidine	67–68	1933
5-Hydroxymethylpyrimidine	60	1028
5-Hydroxymethyl-2,4-pyrimidinediamine	230–232 or 231–234 (265?); HCl: 327	419,577,1480,1481
1-Hydroxy-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	231–235	1018
2-Hydroxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	207 or > 305	1958,2468
3-Hydroxy-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	226–228	1018
5-Hydroxymethyl-2,4(*H*,3*H*)-pyrimidinedione	260–300	323,1321,1344,1490,1597, 2243(?),3967
5-Hydroxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	299	1492,2779,3267,3268
5-Hydroxy-2-methyl-4,6(1*H*,5*H*)-pyrimidinedione	> 290	1324,1337
5-Hydroxy-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	247 or 250–252	2703,2904,3268
5-Hydroxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	> 300	751,769,1011,1495,1943,2898, 3269,6020

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	254 or 260–261	701,770,2274,2888
6-Hydroxymethyl-2,4,5-pyrimidinetriamine	-	3270
5-Hydroxy-1-methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	184–185; H_2O: 167–168	1138
2-Hydroxymethyl-4(3*H*)-pyrimidinone	194 or 196–197	2057,2058,2635
5-Hydroxy-2-methyl-4(3*H*)-pyrimidinone	280 to 317	42,581,1118,1262,1324,1340, 1551,1821
5-Hydroxy-6-methyl-4(3*H*)-pyrimidinone	230–231	2416
6-Hydroxymethyl-4(3*H*)-pyrimidinone	179–181; HCl: 198–200	2856
5-Hydroxy-2-methylsulfinyl-4-pyrimidinecarboxylic acid	182–184	2291
2-Hydroxymethyl-5-thioformamidomethyl-4-pyrimidinamine	157	975
4-Hydroxymethyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	226–227	770
5-Hydroxy-3-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	2904
5-Hydroxy-6-methyl-2-thioxo-1,2,-dihydro-4(3*H*)-pyrimidinone	> 310	2898
6-Hydroxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	259 or 263–264	2888,3139
5-Hydroxymethyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	127–128, ir, ms, nmr, uv	260
5-Hydroxy-2-methyl-3-vinyl-4(3*H*)-pyrimidinethione	150–152, ms, nmr, uv	60
5-Hydroxy-6-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	250	1339,3271
1-β-Hydroxyprop-1′-enyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	152–154, ir, nmr	5980
5-β-Hydroxypropyl-2,4-dimethoxypyrimidine	nmr	474
1-β-Hydroxypropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	103–104, ir, nmr, uv	3895
1-γ-Hydroxypropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	94–96, nmr	6579
1-β-Hydroxypropyl-4,6-dimethyl-2(1*H*)-pyrimidinone	122–123	1312
1-β-Hydroxypropyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	223	1318
3-γ-Hydroxypropyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	67–69, nmr	525
3-β-Hydroxypropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	162–163	1755

3-γ-Hydroxypropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	156–157	3272
3-γ-Hydroxypropyl-2-methylthio-4(3*H*)-pyrimidinone	92–93, nmr	525
1-β-Hydroxypropyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	191	1318
3-Hydroxy-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	178–179, ms	2783
5-β-Hydroxypropyl-2,4(1*H*,3*H*)-pyrimidinedione	258–260	3273
5-Hydroxy-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	232–234	825
5-Hydroxy-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	249–252	825
6-γ-Hydroxypropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	247–249	825
5-3′-Hydroxyprop-1′-ynyl-2,4-dimethoxypyrimidine	122	3934
2-3′-Hydroxyprop-1′-ynyl-4,6-dimethylpyrimidine	155–157	1857,2724
4-3′-Hydroxyprop-1′-ynyl-2,6-dimethylpyrimidine	121–123	1857,2724
5-3′-Hydroxyprop-1′-ynyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	201–203	440
4-3′-Hydroxyprop-1′-ynyl-2-isopropyl-6-methylpyrimidine	145/2	1857
5-3′-Hydroxyprop-1′-ynyl-2-isopropyl-4-methylpyrimidine	155/1	1857
2-3′-Hydroxyprop-1′-ynyl-4-methoxy-6-methylpyrimidine	158–160	1857
4-3′-Hydroxyprop-1′-ynyl-6-methyl-2-methylthiopyrimidine	102–103	1857
1-Hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	280–286	748,3274
3-Hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	290–293	748
6-Hydroxy-2,4(1*H*,3*H*)-pyrimidinedione	330	581,1011,1344,1345,1585,1587, 1667,3275–3277
5-Hydroxy-4,6(1*H*,5*H*)-pyrimidinedione	anal	1324,3278
5-Hydroxy-4(3*H*)-pyrimidinethione	212, ms, nmr	42
1-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	408
5-Hydroxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	154–155, 213–214, > 350, xl st	2,336,1324,1337,1590, 3278–3282
5-Hydroxy-2(1*H*)-pyrimidinone	> 300	774,1086,2599
5-Hydroxy-4(3*H*)-pyrimidinone	260–300 or 300; HCl: > 270; HBr: > 270	718,1340,1774
5-Hydroxysulfonyloxy-2,4(1*H*,3*H*)-pyrimidinedione	K: anal	1345

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Hydroxy-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	> 200	1324
1-Hydroxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	203, then 277	3274
5-Hydroxy-3-vinyl-4(3*H*)-pyrimidinethione	143, ms, nmr, uv	60
2-Imino-1,4-dimethyl-1,2-dihydro-5-pyrimidinecarbonitrile	crude, nmr	1465
2-Imino-4,6-dimethyl-1,2-dihydro-1-pyrimidinecarbonitrile (?)	227–229	2363
2-Imino-1,4-dimethyl-1,2-dihydro-5-pyrimidinecarboxamide	HI: 247; pic: 200	1465
4-Imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinethione	162; HI: 206	806
2-Imino-1,3-dimethyl-1,2-dihydro-4(3*H*)-pyrimidinone	139–140; HI: 262–263	2636
4-Imino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	143–147; HI: 260	696,806,1162,1536,1664,1678, 2549
4-Imino-1,3-dimethyl-5-nitroso-3,4-dihydro-2(1*H*)-pyrimidinone		3283
6-Imino-1,3-dimethyl-2-oxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid	> 360	1162
4-Imino-6-methoxy-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	156	1162
4-Imino-6-methoxy-3-methyl-3,4-dihydro-2,5-pyrimidinediamine	HCl: anal	1375
4-Imino-1-methyl-1,4-dihydro-2-pyrimidinamine	HCl: 276; HI: 274 or 280; pic: 255	1520,1713,1742
6-Imino-l-methyl-1,6-dihydro-4-pyrimidinamine	HCl: 268–269	1770
2-Imino-1-methyl-1,2-dihydro-5-pyrimidinecarbonitrile	HCl: 228; HI: 231	923,1346
2-Imino-1-methyl-1,2-dihydro-5-pyrimidinecarboxamide	HI: 240; pic: 257	923,1346
4-Imino-1-methyl-1,4-dihydro-2,5-pyrimidinediamine	HI: 264	1764
6-Imino-1-methyl-1,6-dihydro-2,4-pyrimidinediamine	HI: 309–310	1520
6-Imino-1-methyl-1,6-dihydro-4,5-pyrimidinediamine	HI: 260	1764
4-Imino-1-methyl-2-methylthio-1,4-dihydro-5-pyrimidinamine	HCl: 227; HI: 235	1520
4-Imino-1-methyl-6-methylthio-1,4-dihydro-2-pyrimidinamine	HCl: 287–288; HI: 281–282	1520
4-Imino-3-methyl-6-methylthio-3,4-dihydro-2-pyrimidinamine	191–192; HCl: 281–282; HI: 250	1520
6-Imino-1-methyl-5-nitro-1,6-dihydro-4-pyrimidinamine	HI: 223; pic: 212–214	1437

6-Imino-l-methyl-5-nitro-1,6-dihydro-2,4-pyrimidinediamine 3-oxide	202; CF_3CO_2H: 183–184	2176
6-Imino-l-methyl-5-nitroso-1,6-dihydro-2,4-pyrimidinediamine	CF_3CO_2H: 238	2176
2-Imino-1,4,6-trimethyl-1,2-dihydro-5-pyrimidinecarbonitrile	HI: 238–239; pic: 183	923
2-Imino-1,4,6-trimethyl-1,2-dihydro-5-pyrimidinecarboxamide	HI: 254–255; pic: 215	923
2-Imino-1,3,6-trimethyl-1,2-dihydro-4(3*H*)-pyrimidinone	> 300; HI: 219–220	1523
2-Iodoamino-4,6-dimethylpyrimidine	crude	3284
5-Iodo-2,4-bis-β-methoxyethyl-6-methylpyrimidine	135–140/6, ir, nmr	3893
5-Iodo-2,4-di-isopropoxy-6-methylpyrimidine	135–140/7, ir, nmr	3893
5-Iodo-2,4-dimethoxy-6-methylpyrimidine	82–84, ir, nmr	257,3893
4-Iodo-2,6-dimethoxypyrimidine	173–175	1703
5-Iodo-2,4-dimethoxypyrimidine	63–64 or 71, ir, nmr	807, 3893
5-Iodo-2,4-dimethyl-6-methlaminopyrimidine	137–138	1347
5-Iodo-3,6-dimethyl-2-methylthio-4(3*H*)-pyrimidinone	104–106 or 219, ir, nmr	929,6077
5-Iodo-2,6-dimethyl-4-pyrimidinamine	140 to 155, ir, nmr	140,1347,2116,2177,3284
5-Iodo-4,6-dimethyl-2-pyrimidinamine	182 to 192, ir, nmr	140,645,1014,3284
2-Iodo-4,6-dimethylpyrimdine	127–129	1856
4-Iodo-2,6-dimethylpyrimidine	111 or 112	1856,2258
5-Iodo-2,4-dimethylpyrimidine	81–82 or 86–87, nmr	140,2375
5-Iodo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	184–187, ir, nmr	323,6077
6-Iodo-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	174–175	1812
5-Iodo-1,6-dimethyl-4(1*H*)-pyrimidinimine	HI: anal, nmr	7033
5-Iodo-2,6-dimethyl-4(3*H*)-pyrimidinone	198–203, ir, nmr	140
5-Iodo-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	—	1764
1-β-Iodoethyl-3,5-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	114–115	1322
1-β-Iodoethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	94–96	1322
3-β-Iodoethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	201–203	1721
5-β-Iodoethyl-2,4(1*H*,3*H*)-pyrimidinedione	265	2039
5-Iodo-2-isopropyl-6-methyl-4-pyrimidinamine	145–147	140,2177

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Iodo-2-isopropyl-6-methylpyrimidine	135/18	1857
5-Iodo-2-isopropyl-4-methylpyrimidine	115–120/16, 125/18, nmr	140,1857
5-Iodo-3-isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	—	2054
5-Iodo-2-isopropyl-6-methyl-4(3*H*)-pyrimidinone	185–186 or 188–189, ir, nmr	140,1857
4-Iodo-2-methoxycarbonylmethylpyrimidine	59–61	1749
5-Iodo-4-methoxy-1,6-dimethyl-2(1*H*)-pyrimidinone	105–106, ir, nmr	6077
5-Iodo-4-methoxy-6-methyl-2-methylthiopyrimidine	72–73, ir, ms, nmr	3893
5-Iodo-4-methoxy-6-methyl-2-pyrimidinamine	155–156	1347
2-Iodo-4-methoxy-6-methylpyrimidine	74–75, 137–140/18	1857
5-Iodo-4-methoxy-2-methylthiopyrimidine	85–87, ir, ms, nmr	3893
5-Iodo-4-methoxy-2-pyrimidinamine	155–157	2209
5-Iodo-4-methoxy-2(1*H*)-pyrimidinone	228–229	3285
5-Iodo-2-methylaminopyrimidine	136–137; pic: 208–209	923
6-Iodo-2-methylamino-4(3*H*)-pyrimidinone	230	1771
5-Iodo-4-methyl-2,6-bistrimethylsiloxypyrimidine	135–139/3.5	1829
5-Iodo-4-methyl-2,6-dipropoxypyrimidine	140–145/6, ir, nmr	3893
2-Iodomethyl-6-methyl-4-pyrimidinamine	156–158, nmr	3748
5-Iodomethyl-2-methyl-4-pyrimidinamine	HI: 212	3286
4-Iodo-6-methyl-2-methylthiopyrimidine	100–101	1856
5-Iodo-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	126–128, ir, nmr	6077
5-Iodo-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	186–188 or 198–199, ir, nmr	499,3893
5-Iodo-4-methyl-2-pyrimidinamine	154–155	1347
5-Iodo-6-methyl-4-pyrimidinamine	164–165 or 170–173, nmr	140,2177,6010
6-Iodo-5-methyl-4-pyrimidinamine	238	1485
2-Iodo-4-methylpyrimidine	87–89	2375

4-Iodo-6-methylpyrimidine	20; pic: 120–121	1509,1517,3287
5-Iodo-4-methylpyrimidine	69–70, nmr	140
1-Iodomethyl-2,4(1*H*,3*H*)-pyrimidinedione	218–220, ms, nmr	6951
5-Iodomethyl-2,4(1*H*,3*H*)-pyrimidinedione	252	841
5-Iodo-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	238 to 283	1014,1829,3288
6-Iodo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	289–291	1812
4-Iodo-6-methylpyrimidine 1-oxide	89–91, nmr	3287
5-Iodo-1-methyl-2(1*H*)-pyrimidinimine	HI: 239; pic: 204–205	923
5-Iodo-2-methyl-4(3*H*)-pyrimidinone	200–202, ir, nmr	499
5-Iodo-6-methyl-4(3*H*)-pyrimidinone	238–239, ir, nmr	1014,2928
4-Iodo-6-methylsulfonylpyrimidine	124–127	1784
4-Iodo-2-methylthiopyrimidine	45 to 53, nmr; HI: 140–142	1745,3043,3929
4-Iodo-6-methylthiopyrimidine	50–51	1784
5-Iodo-2-methylthio-4(3*H*)-pyrimidinone	189–191 or 212–213, ir, nmr	499,3893
5-Iodo-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	270 or 285–290	1914,1957,3044
5-Iodo-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	Na: 215–216	3044
5-Iodo-2-pyrimidinamine	223–225, ir, nmr	140,3289
5-Iodo-4-pyrimidinamine	230–231	1650
6-Iodo-4-pyrimidinamine	207–210	972
2-Iodopyrimidine	29 or 30–32	2258,3290
5-Iodopyrimidine	126	2180
5-Iodo-2,4(1*H*,3*H*)-pyrimidinedione	270–273	1014,1234,1265,1979,3291
6-Iodo-2,4(1*H*,3*H*)-pyrimidinedione	278–279 or 279–280, nmr	105,1703,2258
5-Iodo-2(1*H*)-pyrimidinone	> 200 or > 280; K: anal	44,270,1826
5-Iodo-4(3*H*)-pyrimidinone	240 or 254–265, ir, nmr	499,2355
5-Iodo-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	214–215 or 220	1914,2357,3044
5-Iodo-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	152–153, ir, nmr	6077
5-Iodo-2-trimethylsiloxypyrimidine	65–69/0.01	44

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-β-Iodovinyl-2,4-dimethoxypyrimidine	89–90, ms, nmr	6198
5-Isocyanato-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	150–151	1114
5-β-Isocyanatoethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	240–244	1300
5-β-Isocyanatoethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	207–209	1300
5-Isocyanatomethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	81–82	1114
5-Isocyanatomethyl-2,4(1*H*,3*H*)-pyrimidinedione	273–275	1395
5-Isocyanato-2,4(1*H*,3*H*)-pyrimidinedione	318	1114
2-Isopropenyl-4-methoxypyrimidine	85–87/18	1908
2-Isopropenyl-6-methyl-4(3*H*)-pyrimidinone	147–148	3292
2-Isopropenylpyrimidine	35–37/0.05	1908
4-Isopropoxy-2,6-dimethylpyrimidine	58–61/2	2701,2744
4-Isopropoxy-2,6-dimethylpyrimidine 1-oxide	85	2744
6-Isopropoxy-5-isopropyl-2-isopropylthio-4(3*H*)-pyrimidinone	177–178	3293
4-Isopropoxy-2-isopropyl-6-methylpyrimidine	—	456
4-Isopropoxy-2-isopropyl-6-methylpyrimidine 1-oxide	164/28	2744
6-Isopropoxy-5-isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	—	3294
6-Isopropoxy-5-isopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	196–197	3293
6-Isopropoxy-2-methoxymethyl-4-pyrimidinamine	84	1763
2-Isopropoxy-6-methoxy-4-pyrimidinamine	98–99	615,2906
6-Isopropoxy-2-methoxy-4-pyrimidinamine	154–156/3	2523
6-Isopropoxy-5-methoxy-4-pyrimidinamine	111–112	916,2210,2598
4-Isopropoxy-6-methylamino-5-nitroso-2-pyrimidinamine	180–181	2182
4-Isopropoxy-6-methylamino-2-pyrimidinamine	105–107	2182
4-Isopropoxy-6-methylamino-2,5-pyrimidinediamine	96–98	2182
4-Isopropoxy-6-methyl-2-methylthiopyrimidine	100–105/2	2701

4-Isopropoxy-6-methyl-2-propylpyrimidine 1-oxide	78–79	2744
4-Isopropoxy-6-methyl-2-pyrimidinamine	67–68	2126
4-Isopropoxy-2-methylpyrimidine	pic: 146–148	1462
4-Isopropoxy-1-methyl-2(1*H*)-pyrimidinone	83–85	2938,3045
4-Isopropoxy-6-methyl-2(1*H*)-pyrimidinone	142–143	698
6-Isopropoxy-2-methylthio-4-pyrimidinamine	123–126/0.15; pic: 177–178	2198
2-Isopropoxy-4-methylthiopyrimidine	liquid, anal	2941
2-Isopropoxy-5-nitropyrimidine	45–47	2941
6-Isopropoxy-5-nitroso-2,4-pyrimidinediamine	244–246	2452
2-Isopropoxy-4-pyrimidinamine	75–76	615
5-Isopropoxy-2-pyrimidinamine	67 or 74–75	673,2945,2946
6-Isopropoxy-4-pyrimidinamine	89 or 93–94	615,1655
2-Isopropoxypyrimidine	90–91/18	2947
6-Isopropoxy-2,4-pyrimidinediamine	105–107	2452
2-Isopropoxy-4,6(1*H*,5*H*)-pyrimidinedione	anal	3295
5-Isopropoxy-2,4(1*H*,3*H*)-pyrimidinedione	anal	2952
6-Isopropoxy-2,4,5-pyrimidinetriamine	149–150	2452
5-Isopropoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	anal	2952
4-*Isopropoxy-2,5,6-tristrimethylsilylaminopyrimidine*	*105/0.001*	3296
6-Isopropylamino-1,3-dimethyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	120 or 128–130	2394,3297
2-Isopropylamino-4,6-dimethyl-5-pyrimidinamine	101	645,2963
2-Isopropylamino-4,6-dimethylpyrimidine	112/12; pic: 173	3298
4-Isopropylamino-2,6-dimethylpyrimidine	100, 137/12; HCl: 249	3298
6-Isopropylamino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	121–122	3297
6-Isopropylamino-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	260–263	1353
6-Isopropylamino-2-methyl-4-pyrimidinamine	110	2253
2-Isopropylamino-5-methyl-4(3*H*)-pyrimidinone	170–171	860
2-Isopropylamino-6-methyl-4(3*H*)-pyrimidinone	-	1241

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Isopropylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	291–293	1353
6-Isopropylamino-5-nitro-4(3*H*)-pyrimidinone	208–209	1589
2-Isopropylamino-5-nitroso-4,6-pyrimidinediamine	204–208	1768
6-Isopropylamino-5-nitroso-2,4-pyrimidinediamine	193–194	1768
2-Isopropylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxamide	215–218	2647
2-Isopropylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	188	865
4-Isopropylamino-5-pyrimidinamine	182–186 or 188–189	2183,2184
6-Isopropylamino-4-pyrimidinamine	177	866
2-Isopropylaminopyrimidine	27–28, 93/12; pic: 174 or 175	923,1437,2463
2-Isopropylamino-4,6(1*H*,5*H*)-pyrimidinedione	anal	2463
6-Isopropylamino-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	122–123	855
5-Isopropyl-1,3-dimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	86–88	855
1-Isopropyl-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	162	3299
3-Isopropyl-5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	—	3300
2-Isopropyl-3,6-dimethyl-4(3*H*)-pyrimidinethione	—	456
2-Isopropyl-4,6-dimethyl-5-pyrimidinol 1-oxide	159–161, nmr	21
2-Isopropyl-1,6-dimethyl-4(1*H*)-pyrimidinone	—	456
2-Isopropyl-3,6-dimethyl-4(3*H*)-pyrimidinone	—	456
2-Isopropyl-5,6-dimethyl-4(3*H*)-pyrimidinone	145	2722
3-Isopropyl-5,6-dimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	1916
1-Isopropyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	227–228 or 274	1166,1883
3-Isopropyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	178–180	1883
1-Isopropyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	192	904
5-Isopropyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	282–283	1224
6-Isopropylidenehydrazino-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	144 to 148	2716,2717,3301

5-Isopropyl-2-isopropylthio-4,6(1*H*,3*H*)-pyrimidinedione	271–272	3293
4-Isopropyl-2-methoxycarbonylmethylpyrimidine	120–122/6	1997
3-Isopropyl-5-methoxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	117–118	2054
2-Isopropyl-4-methoxy-6-methylpyrimidine	—	456
2-Isopropyl-4-methoxy-6-methylpyrimidine 1-oxide	51	2744
2-Isopropyl-4-methoxypyrimidine	42–43/0.3	1908
2-Isopropyl-6-methoxy-4-pyrimidinecarbaldehyde	oxime: 146–147	2525
2-Isopropyl-4-methylaminopyrimidine	HCl: 195	2570
4-Isopropyl-6-methylaminopyrimidine	HCl: 257	2570
5-Isopropyl-4-methylaminopyrimidine	121	2570
3-Isopropyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	128–130	1883
3-Isopropyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	171–172	1883
3-Isopropyl-6-methyl-5-methylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione		1916
5-Isopropyl-4-methyl-2-methylthiopyrimidine	100–107/4.5	2694
3-Isopropyl-1-methyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	57–58	909
1-Isopropyl-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	151–152, nmr	3995
2-Isopropyl-4-methyl-6-propoxypyrimidine	—	456
2-Isopropyl-6-methyl-3-propyl-4(3*H*)-pyrimidinone	—	456
2-Isopropyl-4-methyl-6-prop-1′-ynylpyrimidine	118/18	1857
2-Isopropyl-6-methyl-4-pyrimidinamine	212	671
4-Isopropyl-5-methyl-2-pyrimidinamine	—	3060
4-Isopropyl-6-methyl-2-pyrimidinamine	126–127, ir, ms, nmr	3723
6-Isopropyl-2-methyl-4-pyrimidinamine	96, uv	29
4-Isopropyl-2-methylpyrimidine	60–65/16, ir, nmr, uv	3996
4-Isopropyl-5-methylpyrimidine	71–72/20	3302
5-Isopropyl-2-methylpyrimidine	81–83/20	2748
2-Isopropyl-6-methyl-4-pyrimidinecarbaldehyde	100–102/20	2222
4-Isopropyl-2-methyl-5-pyrimidinecarboxylic acid	170–171, ir, nmr, uv	3996

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-Isopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	213–216	2774
1-Isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	160–162	332
3-Isopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	134–135	2787
3-Isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	186–188 or 193	332,2572
5-Isopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	289–292	3303,3304
6-Isopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	250–251	3303
2-Isopropyl-6-methyl-4(3*H*)-pyrimidinethione	160–161	2905
4-Isopropyl-5-methyl-2(1*H*)-pyrimidinethione	176–177	3302
2-Isopropyl-3-methyl-4(3*H*)-pyrimidinimine	HI: 204	2570
5-Isopropyl-3-methyl-4(3*H*)-pyrimidinimine	HI: 222	2570
6-Isopropyl-3-methyl-4(3*H*)-pyrimidinimine	HI: 216	2570
2-Isopropyl-5-methyl-4(3*H*)-pyrimidinone	160–162	3305
2-Isopropyl-6-methyl-4(3*H*)-pyrimidinone	170–174	880,2722,2819,2820,2822, 3292,3306
6-Isopropyl-2-methyl-4(3*H*)-pyrimidinone	138–139	2575
6-Isopropyl-5-methylthio-2,4-pyrimidinediamine	145	3021
3-Isopropyl-6-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	210	909
5-Isopropyl-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	247–248	930
1-Isopropyl-4-methylthio-2(1*H*)-pyrimidinone	143–145	2941
5-Isopropyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	257–258	3303,3307
6-Isopropyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	179–180	3303
6-Isopropyl-5-nitro-2,4-pyrimidinediamine	152–154	2441
6-Isopropyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	> 230	617
1-Isopropyl-5-nitro-2(1*H*)-pyrimidinone	109–110	2941
6-Isopropyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	193–195	3308

3-Isopropyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	84–85	809
6-Isopropyl-2-propyl-4(3*H*)-pyrimidinone	55–56, 181/2	2575
2-Isopropyl-4-pyrimidinamine	159–160, nmr	479
4-Isopropyl-2-pyrimidinamine	116–119, ir, nmr, uv	2414,3309,3310,3996
5-Isopropyl-2-pyrimidinamine	72–73	1963
5-Isopropyl-4-pyrimidinamine	140–141	3311,3312
2-Isopropylpyrimidine	46–47/2, 115/200, 153–154/760; 1-$EtBF_4$: 69–71, nmr	479,1908,3090,3890
5-Isopropylpyrimidine	96–97/40, 185/730; pic: 116 and 124 (two x1 forms)	2749,3093
6-Isopropyl-2,4-pyrimidinediamine	134, uv; HCl: 181–184	29,1356
1-Isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	131–133 or 132–134, nmr	258,870,3099
2-Isopropyl-4,6(1*H*,5*H*)-pyrimidinedione	296–297 or 313–315	1875,1908
3-Isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	126–127	3099
5-Isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	283 to 290	1833,3083,3084,3313
5-Isopropyl-4,6(1*H*,5*H*)-pyrimidinedione	> 310	2186
6-Isopropyl-2,4(1*H*,3*H*)-pyrimidinedione	199–200	2441
5-Isopropyl-2(1*H*)-pyrimidinethione	239–242	2748,3019
6-Isopropyl-2,4,5-pyrimidinetriamine	158–160	2441
1-Isopropyl-2(1*H*)-pyrimidinimine	pic: 182–183	923
1-Isopropyl-2(1*H*)-pyrimidinone	90; $MeHSO_4$: 137; pic: 166–167	2810,2941,2947
2-Isopropyl-4(3*H*)-pyrimidinone	143–144	1907
5-Isopropyl-2(1*H*)-pyrimidinone	94	2748
2-Isopropylthio-3-methoxycarbonylmethyl-6-methyl-4(3*H*)-pyrimidinone	54–55, ir, nmr, uv	3750
2-Isopropylthio-6-methoxy-4-pyrimidinamine	116–117	615,2906
4-Isopropylthio-6-methyl-2-pyrimidinamine	108–109	2126
2-Isopropylthio-6-methyl-4(3*H*)-pyrimidinone	152–153	227,3570

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Isopropylthiopyrimidine	106–107/12	3144
2-Isopropylthio-4,6-pyrimidinediamine	121–123, ms, nmr	156
5-Isopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	237 to 245	1684,3083,3084,3303
5-Isopropyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	272–273	2186
6-Isopropyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	179–180	1684,2151
2-Isopropyl-4-trimethylammoniopyrimidine	chloride: 124–125	1907
2-Isothiocyanatopyrimidine	34, 58/0.005	3314
5-Isothiocyanato-2,4(1*H*,3*H*)-pyrimidinedione	> 300	3315
2-Isothiouroniomethyl-6-methyl-4-pyrimidinamine	iodide: 180–182, nmr	3748
5-β-Mercaptoethyl-2,6-dimethyl-4(3*H*)-pyrimidinone	276	1359
1-β-Mercaptoethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	220–221	3316
5-β-Mercaptoethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	310	1359
5-β-Mercaptoethyl-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	224–227	1359
3-β-Mercaptoethyl-2,4(1*H*,3*H*)-pyrimidinedione	197–198	3316
5-Mercaptomethyl-2-methyl-4-pyrimidinamine	161–163; HCl: 212; pic: 203 or 210	584,1326,3317
5-Mercaptomethyl-2-methylthio-4-pyrimidinamine	138–139	1326
5-Mercaptomethyl-2,4(1*H*,3*H*)-pyrimidinedione	270 or 272–274	841,2271
2-Mercaptomethyl-4(3*H*)-pyrimidinone	anal	3318
5-γ-Mercaptopropyl-2,6-dimethyl-4(3*H*)-pyrimidinone	215–218	1359
1-β-Mercaptopropyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	158	1318
5-γ-Mercaptopropyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	283–285	1359
5-Mercapto-2,4(1*H*,3*H*)-pyrimidinedione	anal	1180,2679,3319
5-Mercapto-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	H_2O: anal; K: anal;	3320,3321
5-β-Mesyloxyethyl-2,4(1*H*,3*H*)-pyrimidinedione	180–182	2039

4-Methoxyamino-1-methyl-2(1*H*)-pyrimidinone	127	3225
4-Methoxyamino-2(1*H*)-pyrimidinone	HCl: 195–196	3239
5-Methoxy-2,6-bismethoxymethyl-4-pyrimidinamine	80–81	1761
5-Methoxy-2,4-bistrimethylsiloxypyrimidine	103–104/0.6	3322
2-Methoxycarbonylaminopyrimidine	134–136	2893
4-Methoxycarbonylaminopyrimidine	181–182; pic: 195–197	2893
5-Methoxycarbonylamino-2,4(1*H*,3*H*)-pyrimidinedione	293–294	2893
5-Methoxycarbonylmethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	99–100	1994
3-Methoxycarbonylmethyl-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	76–77, ir, nmr, uv	3750,3751
2-Methoxycarbonylmethyl-6-methyl-4-pyrimidinecarbonitrile	55–56	1749
5-Methoxycarbonylmethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	280–282	985
3-Methoxycarbonylmethyl-2-methylthio-4(3*H*)-pyrimidinone	95–96, ir, nmr, uv	3750,3751
2-Methoxycarbonylmethyl-4-methyl-6-trimethylammoniopyrimidine	chloride: 134–137	1749
4-Methoxycarbonylmethyl-2-pyrimidinamine	120–142 (!), anal	670
2-Methoxycarbonylmethylpyrimidine	90–93/4	1749
1-Methoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	> 177	1806
5-Methoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	236–237	2007
6-Methoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedione	216–218 or 220	2028,3028,3323
5-Methoxycarbonylmethyl-2,4(1*H*,3*H*)-pyrimidinedithione	232–233, nmr	521
1-Methoxycarbonylmethyl-2(1*H*)-pyrimidinimine	HBr: > 280	984
2-Methoxycarbonylmethyl-4(3*H*)-pyrimidinone	180–181	1749
5-Methoxycarbonylmethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	211	2007
2-Methoxycarbonylmethyl-4-trimethylammoniopyrimidine	chloride: 150–152	1749
4-Methoxy-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	165–167	1987
4-Methoxy-5,6-dimethyl-2-methylthiopyrimidine	40–41	698,3324
4-Methoxy-2,6-dimethyl-5-nitropyrimidine	42–43	651
4-Methoxy-1,6-dimethyl-5-propyl-2(1*H*)-pyrimidinone	180–182/4.5	2489
2-Methoxy-5,6-dimethyl-4-pyrimidinamine	178 or 180–181	2093,2504

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Methoxy-2,6-dimethyl-5-pyrimidinamine	86–87	651
4-Methoxy-5,6-dimethyl-2-pyrimidinamine	154–155	1149,2581
5-Methoxy-2,6-dimethyl-4-pyrimidinamine	148–150	1347
6-Methoxy-2,5-dimethyl-4-pyrimidinamine	110	1362,3325
2-Methoxy-4,6-dimethylpyrimidine	34–37, 208–209/760; HCl: 224; H_2SO_4: > 350; pic: 137–139	1465,1711,1874,2268,2532,2602
4-Methoxy-2,5-dimethylpyrimidine	35/0.5, 89–90/30	1551,3326
4-Methoxy-2,6-dimethylpyrimidine	72/15 or 78/11; pic: 124	1951,2107,2268,2744,3327,3328
4-Methoxy-5,6-dimethylpyrimidine	118/40	698
2-Methoxy-4,6-dimethyl-5-pyrimidinecarboxamide	237–238	1787
2-Methoxy-4,6-dimethyl-5-pyrimidinecarboxylic acid	152–153	1787
5-Methoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	191	749,2576
6-Methoxy-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	156 to 166, nmr	789,1133,2110,2533,2802, 2804,3736,3756
4-Methoxy-2,6-dimethylpyrimidine 1-oxide	84–85 or 87–88	2107,2744
4-Methoxy-5,6-dimethylpyrimidine 1-oxide	158–159	698
1-Methoxy-4,6-dimethyl-2(1*H*)-pyrimidinone	− 5	2828
2-Methoxy-3,5-dimethyl-4(3*H*)-pyrimidinone	106–108	3329
2-Methoxy-3,6-dimethyl-4(3*H*)-pyrimidinone	M^+, ir, nmr	130
2-Methoxy-5,6-dimethyl-4(3*H*)-pyrimidinone	198, ir, nmr	130
4-Methoxy-1,5-dimethyl-2(1*H*)-pyrimidinone	144	812,2492,3330
4-Methoxy-1,6-dimethyl-2(1*H*)-pyrimidinone	134–135 or 139–140 (112–113?)	698,2024,2495
4-Methoxy-5,6-dimethyl-2(1*H*)-pyrimidinone	230–231 or 249–250	698,1155,3324
5-Methoxy-1,2-dimethyl-4(1*H*)-pyrimidinone	214; HI: 211	1551
5-Methoxy-2,3-dimethyl-4(3*H*)-pyrimidinone	113	1551

6-Methoxy-2,3-dimethyl-4(3*H*)-pyrimidinone	84–86; HCl: 175	2586,2587
6-Methoxy-3,5-dimethyl-4(3*H*)-pyrimidinone	89–90	1900,2586,2587
6-Methoxy-1,3-dimethyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	210	2899
1-β-Methoxyethyl-4-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidine-carbonitrile	207	809
2-β-Methoxyethyl-6-methyl-4-pyrimidinamine	254–255	1763
5-β-Methoxyethyl-2-methyl-4-pyrimidinamine	108–113; pic: 208–209	2917
3-β-Methoxyethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	96–97 or 97–98	2143,2932
6-α-Methoxyethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	217	3253
2-β-Methoxyethyl-6-methyl-4(3*H*)-pyrimidinone	133–135	3331
6-α-Methoxyethyl-5-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	207	3253
5-α-Methoxyethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	168–169	3332
4-Methoxyimino-1,3-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone	77	3225
4-Methoxy-2-methoxycarbonylmethyl-6-methylpyrimidine	101–102/2, 110–111/4	1878,3333
4-Methoxy-6-methoxycarbonylmethyl-2-pyrimidinamine	107–109	670
4-Methoxy-2-methoxycarbonylmethylpyrimidine	100–102/1.5	1997
6-Methoxy-3-methoxycarbonylmethyl-4(3*H*)-pyrimidinimine	HBr: anal	2189
4-Methoxy-5-β-methoxyethyl-6-methyl-2-pyrimidinamine	82–83	1149
5-Methoxy-6-methoxymethyl-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	46–47	3268
5-Methoxy-4-methoxymethyl-6-methyl-2-pyrimidinamine	—	432
4-Methoxy-2-methoxymethyl-6-methylpyrimidine	110–114/20, nmr	121
4-Methoxy-6-methoxymethyl-2-methylpyrimidine	110/19, nmr; pic: 105	121
4-Methoxy-2-methoxymethyl-6-methylpyrimidine 1-oxide	90, ir, nmr	118
4-Methoxy-6-methoxymethyl-2-methylpyrimidine 1-oxide	107–108, ir, nmr	118
5-Methoxy-6-methoxymethyl-2-methyl-4(3*H*)-pyrimidinone	165–167	1761
5-Methoxy-4-methoxymethyl-2-methylsulfonylpyrimidine	95–97	2192
5-Methoxy-6-methoxymethyl-2-methylthio-4-pyrimidinamine	94–95	2192
5-Methoxy-4-methoxymethyl-2-methylthiopyrimidine	32–33, 168/10	2192

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Methoxy-6-methoxymethyl-2-methylthio-4(3*H*)-pyrimidinone	153–154	3268
4-Methoxy-6-methoxymethyl-2-pyrimidinamine	116–117	1149
5-Methoxy-4-methoxymethyl-2-pyrimidinamine	137–138	1149
6-Methoxy-2-methoxymethyl-4-pyrimidinamine	93–94	1763,2196
5-Methoxy-4-methoxymethylpyrimidine	118–120/10	2192
5-Methoxy-2-methoxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	213–214	1761
5-Methoxy-6-methoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	188	2898
5-Methoxy-2-methoxymethyl-4(3*H*)-pyrimidinone	112–113	1761
5-Methoxy-6-methoxymethyl-4(3*H*)-pyrimidinone	147–151	1761,2192
5-Methoxy-6-methoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	187–188 or 189–190	2898,3268
2-Methoxy-4-methylamino-4-nitropyrimidine	135–137	1379,1648
4-Methoxy-2-methylamino-5-nitropyrimidine	206–207 or 207–208	1586,2216
4-Methoxy-6-methylamino-5-nitropyrimidine	148–150	1379
4-Methoxy-6-methylamino-5-nitroso-2-pyrimidinamine	210–211	2182
4-Methoxy-6-methylamino-2-pyrimidinamine	135–137	2182
4-Methoxy-6-methylamino-5-pyrimidinamine	139–140	3334
4-Methoxy-2-methylaminopyrimidine	55–57	1520
4-Methoxy-6-methylaminopyrimidine	84–86	1383
5-Methoxy-2-methylaminopyrimidine	96	2114
4-Methoxy-6-methylamino-2,5-pyrimidinediamine	171–173	2182
2-Methoxymethyl-4,6-dimethylpyrimidine	102–103/13, nmr	121
4-Methoxymethyl-2,6-dimethylpyrimidine	96/17, nmr	121
5-Methoxymethyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione	273–275	760,3245
6-Methoxymethyl-2,5-dimethyl-4(3*H*)-pyrimidinone	159–160	1761,2815,2818
5-Methoxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	220	2627

4-Methoxy-6-α-methylhydrazino-5-nitropyrimidine	201–202	1680
4-Methoxy-6-α-methylhydrazino-2-pyrimidinamine	150–152	1203
2-Methoxy-4-methyl-6-methylamino-5-nitropyrimidine	130–131	601
2-Methoxy-4-methyl-6-methylamino-5-pyrimidinamine	134–135	601
4-Methoxy-3-methyl-6-methylimino-3,6-dihydropyrimidine	HI: 215–217	2115
2-Methoxymethyl-5-methyl-4-pyrimidinamine	124–125	1762
2-Methoxymethyl-6-methyl-4-pyrimidinamine	150–153, nmr	3748
4-Methoxymethyl-6-methyl-2-pyrimidinamine	114–116	2193,2913
5-Methoxymethyl-2-methyl-4-pyrimidinamine	116 or 118–120	677,2918,3335
2-Methoxymethyl-4-methylpyrimidine	99/15, nmr	121
4-Methoxymethyl-2-methylpyrimidine	75–80/18 or 82–83/15, ir, nmr, uv; pic: 126	121,3996
4-Methoxymethyl-2-methyl-5-pyrimidinecarboxylic acid	149–150, ir, nmr, uv	3996
2-Methoxymethyl-5-methyl-4,6(1*H*,5*H*)-pyrimidinedione	290	1761
5-Methoxymethyl-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	142–143 or 146–147	760,765
5-Methoxymethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	144–146	760,765
5-Methoxymethyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	239 or > 330	1925,1926,2233
4-Methoxymethyl-6-methyl-5-pyrimidinol	55–57, ms, nmr, uv	458
2-Methoxymethyl-5-methyl-4(3*H*)-pyrimidinone	140–141	1761
2-Methoxymethyl-6-methyl-4(3*H*)-pyrimidinone	96–98 or 103, ir, nmr	121,1763
4-Methoxymethyl-6-methyl-2(1*H*)-pyrimidinone	HCl: 162–172; pic: 154–155	2193
5-Methoxymethyl-2-methyl-4(3*H*)-pyrimidinone	202–203	2923,3336
6-Methoxymethyl-2-methyl-4(3*H*)-pyrimidinone	169 or 173–174, ir, nmr	121,1763
6-Methoxymethyl-5-methyl-4(3*H*)-pyrimidinone	140–141	1761
4-Methoxy-6-methyl-2-methylsulfonylpyrimidine	80	2240
5-Methoxy-4-methyl-2-methylsulfonylpyrimidine	106–107	2192
5-Methoxymethyl-2-methylthio-4-pyrimidinamine	104–106	1326,2236
4-Methoxymethyl-2-methylthiopyrimidine	liquid, ms, nmr	3929

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Methoxy-6-methyl-2-methylthiopyrimidine	35, 104–112/5,126–130/12–18; pic: 137–139	1701,2106,2240,2242,3337
5-Methoxy-2-methyl-4-methylthiopyrimidine	90	3129
5-Methoxy-4-methyl-2-methylthiopyrimidine	53–54	2192
4-Methoxymethyl-2-methylthio-5-pyrimidinol	190–191	3338
5-Methoxy-1-methyl-2-methylthio-4(1*H*)-pyrimidinone	180–181	3268
5-Methoxy-3-methyl-2-methylthio-4(3*H*)-pyrimidinone	140–141	3268
5-Methoxy-6-methyl-2-methylthio-4(3*H*)-pyrimidinone	202–203	2192
4-Methoxy-1-methyl-6-nitroamino-2(1*H*)-pyrimidinone	178–179	903
4-Methoxy-6-methyl-5-nitro-2-propoxypyrimidine	104–106/0.3	2559
4-Methoxy-6-methyl-5-nitro-2-pyrimidinamine	185 or 199	645,3328
4-Methoxy-2-methyl-5-nitropyrimidine	48	1552,3211
4-Methoxy-1-methyl-5-nitro-2(1*H*)-pyrimidinone	151–152	1602
6-Methoxy-3-methyl-5-nitro-4(3*H*)-pyrimidinone	149	3339
4-Methoxy-2-methyl-6-propionylpyrimidine	47–48, 65/1	3048
4-Methoxy-6-methyl-2-propionylpyrimidine	47–48; sc: 193–195	3048
5-Methoxymethyl-2-propyl-4-pyrimidinamine	—	3340,3341
4-Methoxy-6-methyl-2-propylpyrimidine 1-oxide	75	2744
4-Methoxy-6-methyl-5-propyl-2(1*H*)-pyrimidinone	178–179	1454
5-Methoxymethyl-2-propyl-4(3*H*)-pyrimidinone	—	2195
4-Methoxy-6-methyl-2-prop-1′-ynylpyrimidine	140/18	1857
2-Methoxymethyl-4-pyrimidinamine	111–112	1763
2-Methoxy-4-methyl-5-pyrimidinamine	88–89	1932
2-Methoxy-6-methyl-4-pyrimidinamine	130–132 or 144–146, nmr	158,1148,3342
4-Methoxymethyl-2-pyrimidinamine	120–121 or 123–124, ir, nmr, uv	1149,3996

4-Methoxy-2-methyl-5-pyrimidinamine	55–57	651
4-Methoxy-6-methyl-2-pyrimidinamine	156–157 or 158	672,1149,2126,2197,2927, 3342,3343
4-Methoxy-6-methyl-5-pyrimidinamine	69–72	1362,2194
5-Methoxymethyl-2-pyrimidinamine	124–126	2929,3344
5-Methoxy-2-methyl-4-pyrimidinamine	93–99	2199
5-Methoxy-4-methyl-2-pyrimidinamine	121–122	1362
5-Methoxy-6-methyl-4-pyrimidinamine	122–123	1362,2200
6-Methoxy-2-methyl-4-pyrimidinamine	164–165	1158,1556
2-Methoxy-4-methylpyrimidine	89/21, nmr; pic: 119–120	186,1850,1951,2249
2-Methoxy-5-methylpyrimidine	78–79/8, 96/10, n_D^{18} 1.5040; pic: 120	1879,1897
4-Methoxy-2-methylpyrimidine	60/17,157–158/760; pic: 159 to 168	1462,1551,1735,2551,2744,3328
4-Methoxy-5-methylpyrimidine	93–94/35; pic: 175	1879
4-Methoxy-6-methylpyrimidine	69/2, nmr; pic: 117	36,186,671,2249,2585,2744,3345
5-Methoxy-4-methylpyrimidine	90–92/15, 100/20, ir, nmr	2192,3743,6117
4-Methoxy-6-methyl-2-pyrimidinecarbaldehyde	crude, 110–115, ir, nmr; crude oxime: –	64
6-Methoxy-2-methyl-4-pyrimidinecarbaldehyde	oxime: 230–231	3048
4-Methoxy-2-methyl-5-pyrimidinecarbonitrile	73–76 or 79–80	1421,1551
4-Methoxy-5-methyl-2-pyrimidinecarbonitrile	50, ir, nmr	3743
4-Methoxy-6-methyl-2-pyrimidinecarbonitrile	95–99, 145/15, nmr	64,142,2585,2762
5-Methoxy-4-methyl-2-pyrimidinecarbonitrile	67, ir, nmr	3743
5-Methoxy-6-methyl-4-pyrimidinecarbonitrile	52–53, ir, nmr	3743
6-Methoxy-2-methyl-4-pyrimidinecarbonitrile	65–66, 120/15	3048
4-Methoxy-2-methyl-5-pyrimidinecarboxamide	175	1551
4-Methoxy-6-methyl-2-pyrimidinecarboxamide	170–171	2585,2762
4-Methoxy-6-methyl-2,5-pyrimidinediamine	H_2SO_4: 167–169	645
5-Methoxymethyl-2,4-pyrimidinediamine 1-oxide	236	3346
5-Methoxymethyl-2,4-pyrimidinediamine 3-oxide	240	3346

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Methoxymethyl-4,6(1*H*,5*H*)-pyrimidinedione	210	1763,2196
5-Methoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	203–204	1597,2933
5-Methoxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	244–245	3268
5-Methoxy-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	229	3268
5-Methoxy-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione	240–241	3347
6-Methoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione	203–205, nmr	6118
6-Methoxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione	229–230 (?) or 235–239, nmr	2533,2804,3736,3756
6-Methoxy-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione	224–225 (?), nmr	2804,3736,3756
4-Methoxy-2-methylpyrimidine 1-oxide	113–114	2744
4-Methoxy-5-methylpyrimidine 1-oxide	156–157, nmr	3743
4-Methoxy-6-methylpyrimidine 1-oxide	135–136, nmr	36,2744
5-Methoxy-4-methylpyrimidine 1-oxide	206–209, nmr	3743
5-Methoxy-4-methylpyrimidine 3-oxide (?)	139, nmr	3743
6-Methoxy-2-methyl-4-pyrimidinesulfonic acid	Na: 279–280	2047
5-Methoxy-2-methyl-4(3*H*)-pyrimidinethione	206–208	3129
6-Methoxy-3-methyl-4(3*H*)-pyrimidinethione	138–139	3348
6-Methoxy-5-methyl-4(3*H*)-pyrimidinethione	220–222	2186
2-Methoxy-1-methyl-4(1*H*)-pyrimidinimine	HI: 128	1664
4-Methoxy-1-methyl-2(1*H*)-pyrimidinimine	HI: crude	2520
5-Methoxy-1-methyl-2(1*H*)-pyrimidinimine	HI: 190	2114
6-Methoxy-3-methyl-4(3*H*)-pyrimidinimine	HI: 143–144	2115
2-Methoxymethyl-4(3*H*)-pyrimidinone	HCl: 228–231	2635
2-Methoxy-3-methyl-4(3*H*)-pyrimidinone	93–95	3329
2-Methoxy-5-methyl-4(3*H*)-pyrimidinone	198–199	812
2-Methoxy-6-methyl-4(3*H*)-pyrimidinone	207, ir, nmr	130,1855,2240,2249,2935

4-Methoxy-1-methyl-2(1*H*)-pyrimidinone	140 or 149–150	812,1513,1841,2937,2938
4-Methoxy-5-methyl-2(1*H*)-pyrimidinone	220–221 or 225–227 (182–183?)	812,1543,3324
4-Methoxy-6-methyl-2(1*H*)-pyrimidinone	209–211 or 211–213 (194–196?)	2240,2762,3349
5-Methoxy-2-methyl-4(3*H*)-pyrimidinone	212–215	2198,3129
5-Methoxy-6-methyl-4(3*H*)-pyrimidinone	158–159	1362,2200
6-Methoxymethyl-4(3*H*)-pyrimidinone	155	1763
6-Methoxy-1-methyl-4(1*H*)-pyrimidinone (?)	267–269	2586,3350,3351
6-Methoxy-3-methyl-4(3*H*)-pyrimidinone	144–145 or 146–147, ir, ms, nmr; 3-MeI: 130–135	1900,2587,3235,3348,3350,5898
6-Methoxy-5-methyl-4(3*H*)-pyrimidinone	234–235	1900
4-Methoxy-2-methylsulfinyl-6-nitroaminopyrimidine	164–165	903
6-Methoxy-2-methylsulfinyl-4-pyrimidinamine	187–189	903
4-Methoxy-2-methylsulfonyl-6-nitroaminopyrimidine	167–168	903
5-Methoxy-2-methylsulfonyl-4-pyrimidinamine	168–169	2203
6-Methoxy-2-methylsulfonyl-4-pyrimidinamine	217–218	903
2-Methoxy-5-methylsulfonylpyrimidine	160–161	1897
4-Methoxy-6-methylsulfonylpyrimidine	98–99	2600
5-Methoxy-2-methylsulfonylpyrimidine	113–115 or 118–119	2114,3121,3268
4-Methoxy-1-methylsulfonyl-2(1*H*)-pyrimidinone	172–173	811
5-Methoxy-2-methylsulfonyl-4(3*H*)-pyrimidinone	220–222	813
5-Methoxy-6-methylsulfonyl-4(3*H*)-pyrimidinone	232–233	2203
4-Methoxy-2-methylthio-6-nitroaminopyrimidine	112–113	903
5-Methoxy-2-methylthio-6-propyl-4(3*H*)-pyrimidinone	90–92	825
2-Methoxy-6-methylthio-4-pyrimidinamine	94–95	616,3353
4-Methoxy-6-methylthio-2-pyrimidinamine	89	1366
4-Methoxy-6-methylthio-5-pyrimidinamine	70–71	1017
5-Methoxy-2-methylthio-4-pyrimidinamine	134–136	2198,2203
6-Methoxy-2-methylthio-4-pyrimidinamine	138 to 144; HNO_3: 172; H_2SO_4: 190–192	615,903,1358,1570,2187,2906

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Methoxy-4-methylthiopyrimidine	liquid, anal	2941
4-Methoxy-2-methylthiopyrimidine	35	1895
4-Methoxy-6-methylthiopyrimidine	60/0.3; pic: 117–118	1784,2600,3348
5-Methoxy-2-methylthiopyrimidine	69	2198
5-Methoxy-4-methylthiopyrimidine	75	1343
4-Methoxy-2-methylthió-5-pyrimidinecarboxamidine	HCl: 230–240	4563
6-Methoxy-2-methylthio-4-pyrimidinecarboxylic acid	233–234	1030
2-Methoxy-5-methylthio-4(3*H*)-pyrimidinone	170–171	3119
5-Methoxy-2-methylthio-4(3*H*)-pyrimidinone	196–197 or 197–198	2198,2204,3268
6-Methoxy-2-methylthio-4(3*H*)-pyrimidinone	191 or 198–199	903,2187
1-Methoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	167–169	1689
5-Methoxy-6-methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	215 or 290–291	1362,2192,2200
6-Methoxymethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	221–222	3354
4-Methoxy-6-nitroamino-2(1*H*)-pyrimidinone	181	903
2-Methoxy-5-nitro-4-pyrimidinamine	203–204	2334
4-Methoxy-5-nitro-2-pyrimidinamine	225–227, nmr	1582,6448
6-Methoxy-5-nitro-4-pyrimidinamine	238–240	2334
2-Methoxy-5-nitropyrimidine	66–68 or 69–70	703(?),1951,2449,2942,3232
4-Methoxy-5-nitropyrimidine	39–40	684,946,3355
2-Methoxy-5-nitro-4,6-pyrimidinediamine	crude, 263	2441
6-Methoxy-5-nitro-2,4-pyrimidinediamine	240	3356
2-Methoxy-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	185	2484
6-Methoxy-5-nitro-4(3*H*)-pyrimidinethione	165–166	1038
6-Methoxy-5-nitro-4(3*H*)-pyrimidinone	242–243	1680,1900
4-Methoxy-5-nitro-6-semicarbazidopyrimidine	211	3227

6-Methoxy-5-nitroso-2,4-pyrimidinediamine	217–224	2452,2943,3357
4-Methoxy-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	218–222	2310
2-Methoxy-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	199–201	2203
2-Methoxy-6-propoxy-4-pyrimidinamine	161–165/3	2523
5-Methoxy-6-propoxy-4-pyrimidinamine	70–71	916,2210
6-Methoxy-2-propylthio-4-pyrimidinamine	96–100	615,2906
5-Methoxy-2-propylthiopyrimidine	34, 100/0.6	926
5-Methoxy-2-propylthio-4(3*H*)-pyrimidinone	143–144	926
2-Methoxy-4-pyrimidinamine	165 to 174	615,1366,1546,1664,1671,1675, 2131,2164,3358
2-Methoxy-5-pyrimidinamine	119–120	1623
4-Methoxy-2-pyrimidinamine	118–120	1366,1663,1671,1675,2207,2520, 2596,3359,3360
4-Methoxy-5-pyrimidinamine	61 to 77	684,1037,2205
5-Methoxy-2-pyrimidinamine	70 to 88	1007,1086,1185,1368,2929,2945
5-Methoxy-4-pyrimidinamine	118	718
6-Methoxy-4-pyrimidinamine	150 to 160; pic: 202	615,968,1366,1570,3361
2-Methoxypyrimidine	69–70/22 or 70–71/15, ms, nmr; pic: 105–106 or 106–108	36,235,708,1432,1856,3232, 3362,3765
4-Methoxypyrimidine	69–70/30, nmr; $EtBF_4$: 77–79; pic: 123–124 or 126	36,235,696,708,1432,2513,2588, 2744,3232
5-Methoxypyrimidine	47, 76/10; pic: 127	1341,1343,1972,3363
2-Methoxy-5-pyrimidinecarbaldehyde	89–90, ir, ms, nmr	6170
2-Methoxy-5-pyrimidinecarbonitrile	81	1897
4-Methoxy-2-pyrimidinecarbonitrile	51–52 or 53, 115/20, nmr	142,2211
4-Methoxy-5-pyrimidinecarbonitrile	93–96	1614
5-Methoxy-4-pyrimidinecarbonitrile	83–84, ir, nmr	3743
6-Methoxy-4-pyrimidinecarboxamide	181–182	2820
2-Methoxy-4-pyrimidinecarboxamidine	HCl: 210	2656

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Methoxy-4-pyrimidinecarboxylic acid	235–237	3364
6-Methoxy-4-pyrimidinecarboxylic acid	198	2326
2-Methoxy-4,6-pyrimidinediamine	pic: 212	2072
5-Methoxy-2,4-pyrimidinediamine	138–140	1367
6-Methoxy-2,4-pyrimidinediamine	161–162 or 162–163; pic: 242	2072,2452,2943,2949
1-Methoxy-2,4(1*H*,3*H*)-pyrimidinedione	200–202	748
2-Methoxy-4,6(1*H*,5*H*)-pyrimidinedione	193–195	2484–2486
3-Methoxy-2,4(1*H*,3*H*)-pyrimidinedione	205–207	748
5-Methoxy-2,4(1*H*,3*H*)-pyrimidinedione	341–345	1343,2198,2370
5-Methoxy-4,6(1*H*,5*H*)-pyrimidinedione	275–278	1360,2206
6-Methoxy-2,4(1*H*,3*H*)-pyrimidinedione	257–259 or 264–269, nmr	2533,3365,3736,3756
2-Methoxypyrimidine 1-oxide	100–101, nmr	36
4-Methoxypyrimidine 1-oxide	132–134, nmr	36,2744
5-Methoxypyrimidine 1-oxide	160–161 or 162, ir, ms, nmr, uv	170,1972
4-Methoxy-2(1*H*)-pyrimidinethione	> 250	2605
5-Methoxy-2(1*H*)-pyrimidinethione	174–176 or 179–181	1086,1897
5-Methoxy-4(3*H*)-pyrimidinethione	209–211	1341,1343
6-Methoxy-4(3*H*)-pyrimidinethione	193–194	2605,3348
6-Methoxy-2,4,5-pyrimidinetriamine	176–178	2391,2943
1-Methoxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	185–187	1338
5-Methoxy-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	> 360	2198
1-Methoxy-2(1*H*)-pyrimidinone	HCl:145	3366
2-Methoxy-4(3*H*)-pyrimidinone	167–168	812
4-Methoxy-2(1*H*)-pyrimidinone	203 to 216	812,1676(?),3285,3324
5-Methoxy-2(1*H*)-pyrimidinone	187–189	2599

5-Methoxy-4(3*H*)-pyrimidinone	207 to 220, ir, ms, nmr, uv	170,1341,1343,2214,3367
6-Methoxy-4(3*H*)-pyrimidinone	211–212	1900,3350
4-Methoxy-6-semicarbazido-5-pyrimidinamine	236	3227
5-Methoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	280 to 302	1341,1343,2214,2370
6-Methoxy-1,3,*N*-trimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	106	2909
2-Methoxy-4,5,6-trimethylpyrimidine	38–40, 62/0.05, ms	56,2995
6-Methoxy-1,3,5-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	107–108	1139
2-Methoxy-3,5,6-trimethyl-4(3*H*)-pyrimidinone	M^+, ir, nmr	130
4-Methoxy-5-trimethylsilylpyrimidine	oil, ir, nmr	474,6071
5-Methoxy-4-trimethylsilylpyrimidine	liquid, anal, ir, nmr	6117
4-Methoxy-2,5,6-tristrimethylsilylaminopyrimidine	111/0.001	3296
2-Methoxy-5-vinylpyrimidine	30/0.02, ms, nmr	3829
Methyl 6-acetamido-2,5-dimethyl-4-pyrimidinecarboxylate	crude, ir, nmr	2038
5-*N*-Methylacetamido-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	AcOH: 270–280	675
5-*N*-Methylacetamido-2-methylthio-4-pyrimidinamine	250–251	2228
Methyl 2-acetamido-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	196–201 or 206–207	3368,3369
4-*N*-Methylacetamidopyrimidine	125–130/10	690
4-*N*-Methylacetamido-2(1*H*)-pyrimidinone	193–194	1542
Methyl 6-acetonyl-5-chloro-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	225–226	733
Methyl 2-amino-6-chloro-4-pyrimidinecarboxylate	135–137	1030
Methyl 4-amino-2-chloro-5-pyrimidinecarboxylate	159–161	1631
Methyl 2-amino-4-dimethylamino-5-pyrimidinecarboxylate	136–137	1086
Methyl 4-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonate	206–208	1101
Methyl 6-amino-2,5-dimethyl-4-pyrimidinecarboxylate	crude, nmr	2038
Methyl 5-amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	254–255 or 270	661,1123
Methyl 4-amino-3-β-hydroxyethyl-2-oxo-2,3-dihydro-5-pyrimidinecarboxylate	195	2547
Methyl 2-amino-4-methoxymethyl-5-pyrimidinecarboxylate	144–145, ir, nmr, uv	3996
Methyl 4-amino-2-methoxy-5-pyrimidinecarboxylate	208–210	2203
5-Methylaminomethylene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	> 330	3370

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Methylaminomethylene-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	> 330	3370
4-Methylamino-5-*N*-methylformamido-6-methylthiopyrimidine	169–171	3371
6-Methylamino-5-*N*-methylformamido-2,4(1*H*,5*H*)-pyrimidinedione	anal	1775,3257
Methyl 4-amino-2-methyl-5-pyrimidinecarboxylate	184; HCl: 181	1458,1470
5-Methylaminomethyl-2,4(1*H*,3*H*)-pyrimidinedione	HCl: 230–232	3372
Methyl 4-amino-2-methyl-5-pyrimidinesulfonate	350	1315
6-Methylamino-2-methylthio-5-nitroso-4-pyrimidinamine	—	658,2657
6-Methylamino-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone	254	3872
5-Methylamino-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	209–210	1561
4-Methylamino-2-methylthio-5-pyrimidinamine	108–110	1179,3373
4-Methylamino-6-methylthio-2-pyrimidinamine	134	850
4-Methylamino-6-methylthio-5-pyrimidinamine	116	1379
5-Methylamino-2-methylthio-4-pyrimidinamine	202–204	1383
6-Methylamino-2-methylthio-4-pyrimidinamine	143–144	1558
2-Methylamino-4-methylthiopyrimidine	80	1765
4-Methylamino-2-methylthiopyrimidine	76–78	1508
4-Methylamino-6-methylthiopyrimidine	117–118; pic: 199–201	2115
4-Methylamino-6-methylthio-2,5-pyrimidinediamine	crude	850
5-Methylamino-2-methylthio-4,6-pyrimidinediamine	172	3374
6-Methylamino-2-methylthio-4,5-pyrimidinediamine	pic: 195–208	2657,3374
2-Methylamino-5-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	> 250	2471
6-Methylamino-2-methylthio-4(3*H*)-pyrimidinone	239–240, nmr, uv	3872
2-Methylamino-5-nitro-4-pyrimidinamine	226–228	1766,2334
4-Methylamino-5-nitro-2-pyrimidinamine	245–247 or 249–250	1586,1766
6-Methylamino-5-nitro-4-pyrimidinamine	241 to 248; pic: 265	1437,1770,2975,3375

2-Methylamino-5-nitropyrimidine	227–229	2643
6-Methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	> 300	2309
6-Methylamino-5-nitro-4(3*H*)-pyrimidinethione	202	1583
2-Methylamino-5-nitro-4(3*H*)-pyrimidinone	326	1586
4-Methylamino-5-nitro-2(1*H*)-pyrimidinone	310–315 or 325	1383,1384,1586
6-Methylamino-5-nitro-4(3*H*)-pyrimidinone	298 or > 300	1383,1589
2-Methylamino-5-nitroso-4,6-pyrimidinediamine	288–290	1768
6-Methylamino-5-nitroso-2,4-pyrimidinediamine	240–241 or 245–247	1092,1768,2646
6-Methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	> 280 or > 350	675,1376,2343,3872
6-Methylamino-5-nitroso-4(3*H*)-pyrimidinone	229–231	1386
2-Methylamino-5-nitro-4-thiocyanatopyrimidine	191–192	1195
2-Methylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxamide	156	2647
Methyl 2-amino-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	281 to 294	949,1030,1605,3368,3369
2-Methylamino-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	217	865
2-Methylamino-4-pyrimidinamine	131–133	1520,2084
4-Methylamino-2-pyrimidinamine	163	1374,1742
4-Methylamino-5-pyrimidinamine	207–210 or 211–213	1583,1648
5-Methylamino-4-pyrimidinamine	191 to 197	1383,2219,2977
6-Methylamino-4-pyrimidinamine	205 or 209–211; HCl: 214	866,1770
2-Methylaminopyrimidine	58–59 or 59–61, 91–92/14, nmr	36,708,867,2083,3376–3380
4-Methylaminopyrimidine	69 to 72, 142–144/16, nmr; pic: 162–163	36,479,708,1508,1771,2115
5-Methylaminopyrimidine	96	2473
2-Methylamino-5-pyrimidinecarbonitrile	203; pic: 172	1346
4-Methylamino-5-pyrimidinecarbonitrile	222–223	1571,1614
2-Methylamino-5-pyrimidinecarboxamide	249–250; pic: 229	1346
Methyl 2-amino-4-pyrimidinecarboxylate	230	1629
2-Methylamino-5-pyrimidinecarboxylic acid	308–309	1346

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Methylamino-4,5-pyrimidinediamine	H_2SO_4: 202–204; pic: 215–216	1764,1766,2334,3381
4-Methylamino-2,5-pyrimidinediamine	H_2SO_4: 213–215	1766
5-Methylamino-2,4-pyrimidinediamine	HCl: 225–226	1766
6-Methylamino-2,4-pyrimidinediamine	192–194	1769,2646,2979
6-Methylamino-4,5-pyrimidinediamine	187–189; H_2SO_4: > 300	1770,2657,3375
6-Methylamino-2,4-pyrimidinediamine 3-oxide	188	2979
2-Methylamino-4,6(1*H*,5*H*)-pyrimidinedione	> 310	1484,2474
5-Methylamino-2,4(1*H*,3*H*)-pyrimidinedione	242 to 313	968,1766,2473,2980
5-Methylamino-4,6(1*H*,5*H*)-pyrimidinedione	240	1981,3100,3382
6-Methylamino-2,4(1*H*,3*H*)-pyrimidinedione	290 to 302	675,1376,2343,2474,3174
2-Methylaminopyrimidine 1-oxide	124–126, nmr	36
4-Methylaminopyrimidine 1-oxide	137–139, nmr	36
4-Methylamino-2(1*H*)-pyrimidinethione	236–237	1515,3049
6-Methylamino-4(3*H*)-pyrimidinethione	258–265	2115
2-Methylamino-4,5,6-pyrimidinetriamine	H_2SO_4: 255	1484
6-Methylamino-2,4,5-pyrimidinetriamine	H_2SO_4: 250	1484,1769,2646
5-Methylamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	250	1138,2663,2688,2981,3383,3384
2-Methylamino-4(3*H*)-pyrimidinone	214–215 or 217–218	962,1520,2084
4-Methylamino-2(1*H*)-pyrimidinone	271–272 or 275–278	1383–1385,1676,2638,2665, 2768,3385
6-Methylamino-4(3*H*)-pyrimidinone	250–256 or 251	968,1383
2-Methylamino-5-sulfo-oxy-4-pyrimidinamine	254–258	1011
6-Methylamino-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	299–300, nmr, uv	3872
4-Methylamino-5-vinylpyrimidine	- -	2051
Methyl 2,6-bisdimethylamino-4-pyrimidinecarboxylate	79–81, nmr	374

2-Methyl-4,6-bismethylamino-5-nitropyrimidine	200–201	1764
4-Methyl-2,6-bismethylamino-5-nitropyrimidine	228 to 252	47,1747,2228,3386
2-Methyl-4,6-bismethylamino-5-nitrosopyrimidine	204	1733
2-Methyl-4,6-bismethylamino-5-pyrimidinamine	145–146; HI: 215–217	1764
4-Methyl-2,6-bismethylamino-5-pyrimidinamine	H_2SO_4: 218–220	1747
2-Methyl-4,6-bismethylamino-5-pyrimidinecarbonitrile	196	1387
2-Methyl-4,6-bismethylsulfinylpyrimidine	122–126	1778
2-Methyl-4,6-bismethylsulfonylpyrimidine	192–196	1778
4-Methyl-2,6-bismethylthio-5-nitropyrimidine	84–85 or 88–89	804,6733
4-Methyl-2,6-bismethylthio-5-pyrimidinamine	75	1157
2-Methyl-4,6-bismethylthiopyrimidine	31–32	1778
4-Methyl-2,6-bismethylthiopyrimidine	43–44	958
5-Methyl-2,4-bismethylthiopyrimidine	35–36	2695
4-Methyl-2,6-bispropylamino-5-pyrimidinamine	H_2SO_4: 195	1747
4-Methyl-2,6-bistrimethylsiloxypyrimidine	75–78	698,1829
5-Methyl-2,4-bistrimethylsiloxypyrimidine	63–65 or 74–75, 94–96/4, 121–123/12	135,839,1792–1795,2786,3387
Methyl 2,6-bistrimethylsiloxy-4-pyrimidinecarboxylate	138–140/4	1829
Methyl 5-bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidine-carboximidate	137	1133
Methyl 5-bromomethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	206–210	2627
Methyl 5-bromo-1-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	140–141, nmr	3765
Methyl 5-bromomethyl-2-pyrimidinecarboxylate	121–123	1474
Methyl 5-bromo-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	207–208	1560
Methyl 5-bromo-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	174–175, nmr	3765
Methyl 5-bromo-2-pyrimidinecarboxylate	148–149	729,1973
5-*N*-Methylcarbamoylmethyl-2-methylthio-4(3*H*)-pyrimidinone	213–216	2019,2020
5-*N*-Methylcarbamoylmethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	310–315	2019,2020
Methyl 2-chloro-6-dimethylamino-4-pyrimidinecarboxylate	137–138, nmr	374

Pyrimidine	m.p. (°C), etc.	Ref.
Methyl 5-chloro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	255–256	2121
Methyl 2-chloromethyl-4-methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarboxylate	184, ir, nmr, uv	3882
Methyl 5-chloro-1-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	135	733,3765
Methyl 2-chloro-6-methyl-4-pyrimidinecarboxylate	111–113	2266
Methyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate	76–78	1897
Methyl 6-chloro-2-methylthio-4-pyrimidinecarboxylate	118–119	1030
Methyl 5-chloro-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	160–161	733,3765
Methyl 6-chloro-4-pyrimidinecarboxylate	60–61	1628
Methyl 5-cyano-2-methyl-4-pyrimidinecarboxylate	74–76	1421
Methyl 2,6-diamino-5-nitro-4-pyrimidinecarboxylate	> 300	1123
Methyl 2,6-diamino-4-pyrimidinecarboxylate	HCl: anal, uv	2331
Methyl 2,4-dichloro-6-methyl-5-pyrimidinecarboxylate	79–81, 149–151/14	2958
Methyl 2,6-dichloro-5-nitro-4-pyrimidinecarboxylate	90–91	2994
Methyl 2,4-dimethoxy-5-pyrimidinecarboxylate	91–93 or 96–97, ir, nmr	1781,6071
Methyl 2,6-dimethoxy-4-pyrimidinecarboxylate	108–109	2121
Methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboximidate	120	1133
Methyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	70–74 or 76–77	1114,1133,1851,2669
O-Methyl 4,6-dimethyl-2-pyrimidinecarbothioate (?)	215	3388
Methyl 2,6-dimethyl-4-pyrimidinecarboxylate	53–55 or 55–56	1933,2266,2692
Methyl 4,6-dimethyl-2-pyrimidinecarboxylate	122–123/7, 142/11, 150–155/16	2603,2692,2760
Methyl 1,3-dimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxylate	152–155	2843
1-Methyl-2,6-dioxo-4-propylamino-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	194–195, nmr	83
1-Methyl-2,6-dioxo-3-propyl-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	70–71	1883
1-Methyl-2,6-dioxo-3-propyl-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide	166–167, nmr	282,3995
Methyl 2,4-dioxo-3-propyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	205	904

1-Methyl-2,6-dioxo-3-propyl-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	164–168	2675,2676
1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde	227–229	323,2776
1-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	202–205, ir, ms, nmr	323
2-Methyl-4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarbaldehyde	230–240 (or 300?); PhHNN=: 215–220	1027,1028,2128
5-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	209–211 or 212–213; MeHNN=: 261–262; oxime: 257; PhHNN=: 320–321	2858,3131
6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde	220–223; dnp: > 300; oxime: 260	682,2012,2128,2852
1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	256 or 267	794,2864
1-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	223	3389
3-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonitrile	228–229	2671
4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	350 or 352	1004,1199,2128,2867,3003
1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	> 300, nmr	72,3390
1-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	> 300	2675,2676
2-Methyl-4,6-dioxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxamide	280–285	1010
3-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	> 300	2676
4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxamide	> 300	3003
N-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	> 300	3005
Methyl 2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinecarboxylate	192–195	2893
Methyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate	233 or 253–256	1980,2527
Methyl 2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	243–245 or 248–250 (230?)	1605,2121,2673,2876,2879,3391
1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	266	3392
1-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	> 300	2673,2675,2676,2848,3392
1-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	242	904,1383
3-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	257 and 273–275 (two x1 forms)	2673,2888
4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	242	3003
5-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	325–327	1224,3010,3051,3393
4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonic acid	+ dmf: 150–151; Na: 250–260	3052

Pyrimidine	m.p. (°C), etc.	Ref.
4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonohydrazide	221–222	3052
4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonyl azide	193	3052
4-Methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonyl chloride	255–256	3052
4-Methyl-2,6-dipropoxypyrimidine	151/22 or 165–170/7, ir, nmr; pic: 101	2127,2495,2561,3893
6-Methyl-2,5-dipropyl-4(3*H*)-pyrimidinone	101–102	880
5-Methylene-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	NH_4: anal	3394
Methyl 4-ethoxycarbonyl-5-methyl-6-oxo-1,6-dihydro-2-pyrimidinecarboxylate	154–155	2038
Methyl 6-ethyl-2-methylthio-4-pyrimidinecarboxylate	74	2266
Methyl 5-ethynyl-2,6-dimethoxy-4-pyrimidinecarboxylate	135–137	3151
Methyl 5-fluoro-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	199–201	2282
5-*N*-Methylformamido-4,6-pyrimidinediamine	285	3183
Methyl 5-β-formylethynyl-2,6-dimethoxy-4-pyrimidinecaboxylate	156–158	3151
4-α-Methylhydrazino-5-nitropyrimidine	127–128	3230
6-α-Methylhydrazino-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	119–120	1134
4-α-Methylhydrazino-2-pyrimidinamine	241–243	1203
4-α-Methylhydrazino-5-pyrimidinamine	136	1777
Methyl 2-hydrazino-5-pyrimidinecarboxylate	224–226	1897
6-α-Methylhydrazino-2,4-pyrimidinediamine	194 or 214–217, nmr	232,1203
6-α-Methylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione	284–285	2279
4-α-Methylhydrazino-2(1*H*)-pyrimidinone	240	3236
Methyl 5-3′-hydroxyprop-1′-ynyl-2,6-dimethoxy-4-pyrimidinecarboxylate	136–137	3151
2-Methyl-5-hydroxy-4(3*H*)-pyrimidinethione	226–228	1821
Methyl 5-iodo-2,6-dimethoxy-4-pyrimidinecarboxylate	112–113	3151
4-Methyl-6-mesyloxy-2-methylthiopyrimidine	74–75	2612

Methyl 5-methoxymethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	174	2627
Methyl 4-methoxymethyl-2-methyl-5-pyrimidinecarboxylate	80–85/0.1, ir, nmr, uv	3996
Methyl 4-methoxy-6-methyl-2-pyrimidinecarboxylate	70–71, ir, nmr	64
Methyl 4-methoxy-2-methylthio-5-pyrimidinecarboxylate	66–68	1781
Methyl 6-methoxy-2-methylthio-4-pyrimidinecarboxylate	100–102	1030
Methyl 2-methoxy-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	199–201	2203
Methyl 2-methoxy-4-pyrimidinecarboxylate	46–50, 178–185/13	3364
Methyl 2-methoxy-5-pyrimidinecarboxylate	128–129	1897
2-Methyl-4-*N*-methylacetamidopyrimidine	28–29, 130/10	690
1-Methyl-4-*N*-methylacetamido-2(1*H*)-pyrimidinone	268	696
1-Methyl-4-methylamino-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	> 300, nmr	83
3-Methyl-6-methylamino-5-*N*-methylformamido-2,4(1*H*,3*H*)-pyrimidinedione	267	3395
1-Methyl-2-methylamino-6-methylimino-1,6-dihydropyrimidine	HI: 255	1508
3-Methyl-6-methylamino-2-methylthio-5-nitroso-4(3*H*)-pyrimidinone	247–248	619
2-Methyl-4-methylamino-6-methylthio-5-pyrimidinamine	108	1400
4-Methyl-6-methylamino-2-methylthio-5-pyrimidinamine	160	601
6-Methyl-5-methylamino-2-methylthio-4-pyrimidinamine	120–121	1400
4-Methyl-6-methylamino-2-methylthiopyrimidine	112–113	2637
N-Methyl-6-methylamino-2-methylthio-4-pyrimidinecarboxamide	191–192	1030
2-Methyl-6-methylamino-5-nitro-4-pyrimidinamine	242–243	3396
6-Methyl-2-methylamino-5-nitro-4-pyrimidinamine	198–199	1428
1-Methyl-6-methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	260	2407
3-Methyl-6-methylamino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	329–330	999
4-Methyl-6-methylamino-5-nitro-2(1*H*)-pyrimidinethione	217–218	1191
1-Methyl-4-methylamino-5-nitro-2(1*H*)-pyrimidinone	203	1402,1433
2-Methyl-6-methylamino-5-nitro-4(3*H*)-pyrimidinone	288–289 or 301–302	47,1380
4-Methyl-6-methylamino-5-nitro-2(1*H*)-pyrimidinone	246–249 or 250 (280?)	1404,1405,3398
1-Methyl-6-methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	> 320	1397

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
3-Methyl-6-methylamino-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione	262–263, 267, or 292–294	619,1504,2276,3397
4-Methyl-2-methylamino-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	290	682,1446
5-Methyl-2-methylamino-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	270–280	2229
3-Methyl-6-methylamino-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	182–185	882
2-Methyl-4-methylamino-5-pyrimidinamine	103–105	1400
2-Methyl-5-methylamino-4-pyrimidinamine	pic: 225	1466
2-Methyl-6-methylamino-4-pyrimidinamine	239–240 or 250	658,1557,2253
4-Methyl-6-methylamino-5-pyrimidinamine	165–167	1400,1401,3398
6-Methyl-5-methylamino-4-pyrimidinamine	133–135	1400
2-Methyl-4-methylaminopyrimidine	80 to 90	479,690,2570
4-Methyl-2-methylaminopyrimidine	55–56, nmr; pic: 183–184	36,1465,2114
4-Methyl-6-methylaminopyrimidine	115, nmr	36,2570
5-Methyl-2-methylaminopyrimidine	102	2229
5-Methyl-4-methylaminopyrimidine	124	2570
2-Methyl-4-methylamino-5-pyrimidinecarbonitrile	151–152 or 153–154	1406,1571
4-Methyl-2-methylamino-5-pyrimidinecarbonitrile	171	1465
4-Methyl-2-methylamino-5-pyrimidinecarboxamide	238; pic: 225	1465
2-Methyl-4-methylamino-5-pyrimidinecarboxylic acid	HCl: 127–130	1912
6-Methyl-2-methylamino-4,5-pyrimidinediamine	HCl: 250	1428
1-Methyl-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	206	1125
1-Methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	276	1397
2-Methyl-5-methylamino-4,6(1*H*,5*H*)-pyrimidinedione	242	3100
3-Methyl-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	209	1125
3-Methyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	290 or 300–302	1504,2276
6-Methyl-5-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	anal	1046

4-Methyl-2-methylaminopyrimidine 1-oxide	169–171	36
4-Methyl-6-methylaminopyrimidine 3-oxide	146–147, nmr	36
N-Methyl-2-methylamino-5-pyrimidinesulfonamide	194–195	845
3-Methyl-6-methylamino-4(3*H*)-pyrimidinethione	167–168	1507
5-Methyl-4-methylamino-2(1*H*)-pyrimidinethione	237–241	2076,3049
1-Methyl-5-methylamino-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	276	1138
1-Methyl-2-methylamino-4(1*H*)-pyrimidinone	200–201	2636
1-Methyl-4-methylamino-2(1*H*)-pyrimidinone	177 to 183; HCl: 215–225; HI: 233	696,1534,1537–1539,2619,3225
1-Methyl-6-methylamino-2(1*H*)-pyrimidinone	HI: 273–274; pic: 212	806,3399
2-Methyl-6-methylamino-4(3*H*)-pyrimidinone	279–281 or 282	47,1158
3-Methyl-2-methylamino-4(3*H*)-pyrimidinone	101–102	2636
3-Methyl-6-methylamino-4(3*H*)-pyrimidinone	187–188, uv	968,1179,1507,2115
5-Methyl-2-methylamino-4(3*H*)-pyrimidinone	213	2229
5-Methyl-4-methylamino-2(1*H*)-pyrimidinone	235	1543
6-Methyl-2-methylamino-4(3*H*)-pyrimidinone	201–202	861,2229
1-Methyl-4-methylamino-2(1*H*)-pyrimidinone 3-oxide	> 300	3225
2-Methyl-4-methylamino-5-thioformamidomethylpyrimidine	132	1406
4-Methyl-6-methylamino-5-thioformamido-2(1*H*)-pyrimidinone	> 300	1558
5-Methyl-4-methylamino-1-vinyl-2(1*H*)-pyrimidinone	154–156	3138
Methyl 2-methyl-4,6-bismethylthio-5-pyrimidinecarboxylate	90, ir, nmr, uv	3882
6-Methyl-5-*N*-methylcarbamoylmethyl-2-methylthio-4(3*H*)-pyrimidinone	266–269	2019,2020
2-Methyl-5-*N*-methylcarbamoylmethyl-4(3*H*)-pyrimidinone	215–217	2019,2020
6-Methyl-5-*N*-methylcarbamoylmethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	299–303	2019,2020
Methyl 1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	203–210 (140–141?)	2848(?),3400
Methyl 5-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	242	2627
Methyl 4-methyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinesulfonate	204–205	3052
6-Methyl-5-*N*-methylformamido-2-methylthio-4-pyrimidinamine	166–167	1400
6-Methyl-5-methylformamido-4-pyrimidinamine	178–179	1400

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
3-Methyl-6-α-methylhydrazino-2-methylthio-4(3*H*)-pyrimidinone	190–191	619
3-Methyl-6-α-methylhydrazino-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	180 or 199–200	999,3401
3-Methyl-6-α-methylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione	207–209	619
1-Methyl-4-α-methylhydrazino-2(1*H*)-pyrimidinone	189	3225
6-Methyl-2-α-methylhydrazino-4(3*H*)-pyrimidinone	187–189	2106
1-Methyl-2-methylimino-1,2-dihydro-4-pyrimidinamine	HCl: 289: HI: 228–231	1520,1713
1-Methyl-4-methylimino-1,4-dihydro-2-pyrimidinamine	HCl: 301; HI: 217	1742
1-Methyl-2-methylimino-1,2-dihydropyrimidine	HI: 218; pic: 147	1437,1741
1-Methyl-2-methylimino-1,2-dihydro-5-pyrimidinecarbonitrile	HCl: 242; HI: 208–209	923,1346
1-Methyl-4-methylimino-2-methylthio-1,4-dihydropyrimidine	HI: 184	1508
1-Methyl-4-methylimino-6-methylthio-1,4-dihydropyrimidine	HI: 200	2115
1-Methyl-6-methylimino-2-methylthio-1,6-dihydropyrimidine	HI: 198	1508
Methyl 2-methyl-4-methylamino-5-pyrimidinecarboxylate	93–94	1912
Methyl 6-methyl-2-methylthio-4-pyrimidinecarboxylate	111–112	2266
Methyl 2-methyl-4-methylthio-6-thioxo-1,6-dihydro-5-pyrimidinecarboxylate	212, ir, nmr, uv	3882
Methyl 1-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	241–245	3400
Methyl 1-methyl-2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	204; HBr: 186	3402
Methyl 2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	226–228 or 242–243	1605,3403
Methyl 6-methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylate	176–178	2266
Methyl 1-methyl-2-oxo-6-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	234–235	3400
Methyl 1-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	188	3404
Methyl 2-methyl-4-pyrimidinecarboxylate	54–55	2692
Methyl 2-methyl-5-pyrimidinecarboxylate	78	1387
Methyl 5-methyl-2-pyrimidinecarboxylate	99–100	2745,2746
Methyl 6-methyl-4-pyrimidinecarboxylate	66–68	2692

2-Methyl-4-methylsulfinyl-6-methylsulfonylpyrimidine	135–141	1778
2-Methyl-4-methylsulfinyl-6-methylthiopyrimidine	79–81	1778
4-Methyl-2-methylsulfinylpyrimidine	liquid, nmr	6133
4-Methyl-2-methylsulfonylpyrimidine	liquid, nmr	6133
5-Methyl-2-methylsulfonylpyrimidine	79–81	1897
4-Methyl-2-methylsulfonyl-5-pyrimidinecarbonitrile	115, nmr	43
Methyl 2-methylsulfonyl-5-pyrimidinecarboxylate	129–131	1897
2-Methyl-6-methylsulfonyl-4(3*H*)-pyrimidinethione	172–174	1778
2-Methyl-5-methylsulfonyl-4(3*H*)-pyrimidinone	220–223	3075
2-Methyl-6-methylsulfonyl-4(3*H*)-pyrimidinone	215–216	2142
Methyl 4-methylthio-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylate	277, ir, nmr, uv	6143
6-Methyl-3-β-methylthioethyl-2,4(1*H*,3*H*)-pyrimidinedione	169–171, ir, nmr	525
2-Methyl-5-methylthiomethyl-4-pyrimidinamine	176–178	1326
4-Methyl-6-methylthio-5-nitro-2-pyrimidinamine	219	645
6-Methyl-2-methylthio-5-nitro-4-pyrimidinamine	155	1428
4-Methyl-2-methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarbaldehyde	300	2128
2-Methyl-4-methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	> 280 to 307, ir, nmr, uv	88,572,3212,3882
2-Methyl-4-methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	333	3212
Methyl 2-methylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	207–209	1897
Methyl 2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	253–254	1030
1-Methyl-2-methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarboxylic acid	153	809
5-Methyl-2-methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	234–235 or 243–244	1224,3050
4-Methyl-2-methylthio-6-propoxypyrimidine	130–137/9	2242
Methyl 2-methylthio-6-propyl-4-pyrimidinecarboxylate	61–62	2266
1-Methyl-6-methylthio-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	100–101	909
1-Methyl-2-methylthio-6-propyl-4(1*H*)-pyrimidinone	40–42	825
6-Methyl-2-methylthio-3-propyl-4(3*H*)-pyrimidinone	crude	2242
6-Methyl-2-methylthio-5-propyl-4(3*H*)-pyrimidinone	180–181 or 181–182	1455,1529,2702

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Methyl-2-methylthio-6-prop-1′-ynylpyrimidine	76–77, 120/3	1857
4-Methyl-2-methylthio-5-pyrimidinamine	141–142	2581
4-Methyl-6-methylthio-2-pyrimidinamine	147 to 154	958,2126,3342
4-Methyl-6-methylthio-5-pyrimidinamine	85–86	1038
5-Methyl-2-methylthio-4-pyrimidinamine	130–131	2239
6-Methyl-2-methylthio-4-pyrimidinamine	135–137	614,1516,1855,2581,2629
2-Methyl-4-methylthiopyrimidine	88–90/15	690
4-Methyl-2-methylthiopyrimidine	75–76/4, 101–102/20 or 111/15, n_D^{20} 1.5640; pic: 106–108	193,1951,2238,2249,3406
4-Methyl-6-methylthiopyrimidine	25–28, 104/17	2249,3407
5-Methyl-2-methylthiopyrimidine	118–120/16	2747
4-Methyl-2-methylthio-5-pyrimidinecarbaldehyde	63–64 or 67–69, nmr	819,6133
5-Methyl-2-methylthio-4-pyrimidinecarbaldehyde	56–57, nmr; oxime: 178	768,6133
6-Methyl-2-methylthio-4-pyrimidinecarbaldehyde	87; oxime: 219	2756
6-Methyl-2-methylthio-4-pyrimidinecarbohydrazide	176–177	2266
4-Methyl-2-methylthio-5-pyrimidinecarbonitrile	52–53, nmr	43
5-Methyl-2-methylthio-4-pyrimidinecarbonitrile	56–57	768
6-Methyl-2-methylthio-4-pyrimidinecarbonitrile	65–66	1745
5-Methyl-2-methylthio-4-pyrimidinecarboxamide	151–152	768
6-Methyl-2-methylthio-4-pyrimidinecarboxamide	183–184	2266
Methyl 2-methylthio-5-pyrimidinecarboxylate	95–96	1897
4-Methyl-2-methylthio-5-pyrimidinecarboxylic acid	169–171	2970
4-Methyl-6-methylthio-2,5-pyrimidinediamine	141–142	645
6-Methyl-2-methylthio-4,5-pyrimidinediamine	194–195	1428
1-Methyl-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	195–197	619,2170

5-Methyl-2-methylthio-4,6(1*H*,5*H*)-pyrimidinedione	303	1046
6-Methyl-5-methylthio-2,4(1*H*,3*H*)-pyrimidinedione	298–305	3133
1-Methyl-2-methylthio-4(1*H*)-pyrimidinethione	148	1508
1-Methyl-4-methylthio-2(1*H*)-pyrimidinethione	150	1513
1-Methyl-6-methylthio-2(1*H*)-pyrimidinethione	125; 3-MeI: 145–146	806,1508
2-Methyl-6-methylthio-4(3*H*)-pyrimidinethione	228–230	1778
3-Methyl-2-methylthio-4(3*H*)-pyrimidinethione	128 or 136–138	806,1508
6-Methyl-2-methylthio-4(3*H*)-pyrimidinethione	214 to 248	958,1427,2241,2612
1-Methyl-2-methylthio-4(1*H*)-pyrimidinimine	HCl: 237–238; HI: 224–225	1520,2520
1-Methyl-6-methylthio-4(1*H*)-pyrimidinimine	HCl: 250–251; HI: 234–235; pic: 241–243	2115
3-Methyl-2-methylthio-4(3*H*)-pyrimidinimine	57; HI: 231	1508
3-Methyl-6-methylthio-4(3*H*)-pyrimidinimine	HI: 186–187	2115
1-Methyl-2-methylthio-4(1*H*)-pyrimidinone	168–169 or 182–183	1432,1689
1-Methyl-4-methylthio-2(1*H*)-pyrimidinone	121–122 or 123–124	1513,3134,3408
1-Methyl-6-methylthio-2(1*H*)-pyrimidinone	142; HI: 189–191; 3-MeI: 219	806,1508
1-Methyl-6-methylthio-4(1*H*)-pyrimidinone	196–197; pic: 190–191	3348
2-Methyl-6-methylthio-4(3*H*)-pyrimidinone	222–224	2142,2237
3-Methyl-2-methylthio-4(3*H*)-pyrimidinone	122 to 127	112,806,1432,1508,1783,1895
3-Methyl-6-methylthio-4(3*H*)-pyrimidinone	169 to 175	909,968,3348
4-Methyl-6-methylthio-2(1*H*)-pyrimidinone	174–175 or 178–180	1550,2241,3226
5-Methyl-2-methylthio-4(3*H*)-pyrimidinone	232–234	2106,3050,3053
5-Methyl-4-methylthio-2(1*H*)-pyrimidinone	205–211 or 214–215	2288,2698
5-Methyl-6-methylthio-4(3*H*)-pyrimidinone	236–237	2186
6-Methyl-2-methylthio-4(3*H*)-pyrimidinone	218 to 225	227,321,925,1145,1516,1529, 2700,2925,3076,3135,3409,3837
4-Methyl-2-methylthio-5-vinylpyrimidine	40–41, ms, nmr	3829
4-Methyl-6-nitroaminopyrimidine	190–200	1932
6-Methyl-2-nitroamino-4(3*H*)-pyrimidinone	224	1429

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4-Methyl-5-nitro-2,6-bispropylaminopyrimidine	98–99	1747
Methyl 5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	199–200	2994
1-Methyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	anal	2779
3-Methyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	anal	1100,3269
3-Methyl-5-nitro-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	—	282,3995
2-Methyl-5-nitro-4-pyrimidinamine	> 230 or 277–278, nmr	684,6448
2-Methyl-5-nitropyrimidine	57–59 or 59–60	2560,2942,3410
4-Methyl-5-nitropyrimidine	liquid, M^+, nmr	231
2-Methyl-5-nitro-4,6-pyrimidinediamine	> 360	1082,2287,2426
6-Methyl-5-nitro-2,4-pyrimidinediamine	235–236	1434,1932,2487,3411,3412
2-Methyl-5-nitro-4,6-pyrimidinediamine 1-oxide	241–243	2426
1-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	256 to 265, ir, nmr, uv	1105,1126,1289,1402,1432,2705, 3267,3269,3347,3904
1-Methyl-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	265–269	1680
2-Methyl-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	270–280	1118,2413
3-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	263 to 280, ir, nmr, uv	282,1432,2703,2704,2706,2779, 3347,3904,3995
6-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	290	1290,1494,1496,1497,1932,2228, 2413,2559,2582,3304
6-Methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedithione	240 or 241	1427,1647,6733
1-Methyl-5-nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	142–143	2091,3271,3413
1-Methyl-5-nitro-2(1*H*)-pyrimidinone	169–170 or 170–171	3414
2-Methyl-5-nitro-4(3*H*)-pyrimidinone	161; acetamidinium salt: 176–177	239
3-Methyl-5-nitro-4(3*H*)-pyrimidinone	101–102	1879
6-Methyl-5-nitro-4(3*H*)-pyrimidinone	228–229	1552

3-Methyl-5-nitroso-6-propylamino-2,4(1*H*,3*H*)-pyrimidinedione	242	3397,3415
2-Methyl-5-nitroso-4,6-pyrimidinediamine	306	658,1558,2431,2432
1-Methyl-5-nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	202–203	1842,3271
1-Methyl-2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde	oxime: 240	3400
1-Methyl-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	oxime: 257	3416
6-Methyl-2-oxo-1,2-dihydro-4-pyrimidinecarbaldehyde	oxime: 272–274 or 286	1628,2267
2-Methyl-4-oxo-3,4-dihydro-5-pyrimidinecarbohydrazide	242–243 or 248	3056,3215
6-Methyl-2-oxo-1,2-dihydro-4-pyrimidinecarbohydrazide	235–236	2266
1-Methyl-2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile	233–234	914,1617,3055
2-Methyl-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	235 or 243–245	975,1406,1469,1472,1473,1600, 2864
4-Methyl-2-oxo-1,2-dihydro-5-pyrimidinecarbonitrile	258–260, nmr	43
2-Methyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxamide	253–254	1551
2-Methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide	> 300	1605
4-Methyl-6-oxo-1,6-dihydro-2-pyrimidinecarboxamide	285–286	3345
6-Methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxamide	> 360	2266
Methyl 2-oxo-1,2-dihydro-5-pyrimidinecarboxylate	192, uv; HBr: 177–178	3402
Methyl 4-oxo-3,4-dihydro-5-pyrimidinecarboxylate	209–210	1625,1969
Methyl 6-oxo-1,6-dihydro-4-pyrimidinecarboxylate	226–228	1628
1-Methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	209–210	3400
2-Methyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	201	1551
2-Methyl-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	261 or 284–285 (> 300?)	1605,1820,3080
6-Methyl-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	214–215	2266
1-Methyl-2-oxo-1,2-dihydro-4-pyrimidinesulfenic acid	sp; Ag: anal	3417
1-Methyl-2-oxo-1,2-dihydro-4-pyrimidinesulfonic acid	K: 248–252	1538,1539,3418
4-Methyl-6-oxo-1,6-dihydro-2-pyrimidinesulfonic acid	K: 300	3224
2-Methyl-4-oxo-6-propylamino-3,4-dihydro-5-pyrimidinecarbonitrile	> 270	572
5-Methyl-6-oxo-1-propyl-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	152–153	2578

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-Methyl-5-oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	154–156	2710,2713–2715,3419–3421
1-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	215–216; acetal: 122–125	2578,3416
4-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	300; np: 322; PhHNN=: 276–277	2128,2891
5-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	232–233 or 233–234; oxime: 233 or 245	2578,3131,3422
1-Methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	295	3423
1-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	257	1508
4-Methyl-2-oxo-6-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	245–250 or > 300, ir, nmr	791,821,3960
Methyl 6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	255	1605
1-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	298	1508
3-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	231–232	2888
6-Methyl-5-phosphonomethyl-2,4(1*H*,3*H*)-pyrimidinedione	282–284	2234
6-Methyl-2-prop-1′-enyl-4(3*H*)-pyrimidinone	185–187	3292
2-Methyl-4-prop-1′-enylthio-5-pyrimidinol	anal, ms, nmr	42
2-Methyl-4-propionylpyrimidine	43–44, ir, nmr; oxime: 162–163, ir, nmr	122
4-Methyl-6-propoxy-2-pyrimidinamine	59–61 or 61–62	1149,2126
2-Methyl-6-propylamino-4-pyrimidinamine	122	2253
3-Methyl-6-propylamino-2,4(1*H*,3*H*)-pyrimidinedione	243	3415,3424
2-Methyl-6-propylamino-4(3*H*)-pyrimidinone	198	2284
1-Methyl-3-propyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	165–168	1883
6-Methyl-5-propyl-2-propylthio-4(3*H*)-pyrimidinone	89–90	1455
2-Methyl-6-propyl-4-pyrimidinamine	134–135	665
4-Methyl-6-propyl-2-pyrimidinamine	75–76, ir, ms, nmr	3723
5-Methyl-2-propyl-4-pyrimidinamine	129–130	1456

2-Methyl-4-propylpyrimidine	75–80/16, 98/50, ir, nmr, uv: pic: 90–92	122,3996
2-Methyl-5-propylpyrimidine	82–84/17	2748
2-Methyl-4-propyl-5-pyrimidinecarboxylic acid	100–101, ir, nmr, uv	3996
4-Methyl-6-propyl-2,5-pyrimidinediamine	114–116	645
5-Methyl-2-propyl-4,6-pyrimidinediamine	181–182	1159
6-Methyl-5-propyl-2,4-pyrimidinediamine	195–197	2248
1-Methyl-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	192–193	825
2-Methyl-5-propyl-4,6(1*H*,5*H*)-pyrimidinedione	> 300	1159,2784,3066
5-Methyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	134 to 138	608,1318,1613
5-Methyl-2-propyl-4,6(1*H*,5*H*)-pyrimidinedione	anal	1456
6-Methyl-1-propyl-2,4(1*H*,3*H*)-pyrimidinedione	170–172 or 173	895,2778,3099
6-Methyl-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	183 to 190	895,1152,3099,3425
6-Methyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	247–248	1455
2-Methyl-6-propyl-4(3*H*)-pyrimidinone	89–91 or 99–101, ir, nmr	122,880
5-Methyl-2-propyl-4(3*H*)-pyrimidinone	145–146	1456
6-Methyl-2-propyl-4(3*H*)-pyrimidinone	142–143 or 148–149	2722,2819,2820,3292
6-Methyl-5-propyl-4(3*H*)-pyrimidinone	115–116	3426
4-Methyl-6-propylthio-2-pyrimidinamine	107	2126
4-Methyl-2-propylthiopyrimidine	125–128/17	2694
6-Methyl-5-propylthio-2,4(1*H*,3*H*)-pyrimidinedione	229–231	3133
6-Methyl-2-propylthio-4(3*H*)-pyrimidinone	123	227,925
1-Methyl-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	170–172	825
5-Methyl-1-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	200	1318
5-Methyl-6-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	204–205	3078
6-Methyl-5-propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	209–210	1453,1455,3307,3426
4-Methyl-6-prop-2′-ynylthio-2(1*H*)-pyrimidinone	199–202, ir, nmr	276
5-Methyl-4-prop-2′-ynylthio-2(1*H*)-pyrimidinone	199–202, ir, nmr	276
4-Methyl-5-prop-2′-ynyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	248–250, ir, ms, nmr	6415

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Methyl-4-pyrimidinamine	202 to 206; pic: 167	479,671,678,689,987,1159, 1477–1479,1556,1855,2259,3427
2-Methyl-5-pyrimidinamine	158–161	651,3428
4-Methyl-2-pyrimidinamine	155 to 160, ir, nmr, uv; pic: 230–232	36,670,1475,1509,1855,1930, 2366,2742,3086,3087,3405,3406, 3429–3436,3996
4-Methyl-5-pyrimidinamine	151–152	1833,1932,1964,2249,3342
5-Methyl-2-pyrimidinamine	192–196	1963,2367,2743
5-Methyl-4-pyrimidinamine	170–179	1485,2108,2652,3089,3437
6-Methyl-4-pyrimidinamine	190–196 or 197, nmr	1509,1655,1818,1822,1932,2108, 2249,6010
4-Methyl-2-pyrimidinamine 1-oxide	233–235, nmr	36
6-Methyl-4-pyrimidinamine 1-oxide	232–234, nmr	36
2-Methylpyrimidine	− 5 or − 6, 90/200, 127–129/720, 129 to 138/760; pic: 105–106 or 112–114; 1-MeI: 173–174	671,1225,1933,1968,2259,2513, 2744–2746,3090,3439–3441, 3890,3891
4-Methylpyrimidine	60/27, 138–139/720–728, 139–141/760, nmr; pic: 131 or 132; 1-MeI: 111–112	764,1225,1517,1735,1834,1933, 1968,2078,2258,2264,2513,2744, 2752,3061,3091,3096,3216,3439, 3442–3445,3951
5-Methylpyrimidine	28–30 or 32, 152/725 or 151 to 155/760; pic: 140–142	1735,2258,2264,2318,2513,2744, 2747,2749,2750,3093,3439
2-Methyl-4-pyrimidinecarbaldehyde	H_2O: 66; oxime: 147–150(?) or 170, ir, nmr	2525,2756,3762
2-Methyl-5-pyrimidinecarbaldehyde	68–69, ir, ms, nmr	6170
4-Methyl-2-pyrimidinecarbaldehyde	oxime(?): 147–150	2525
5-Methyl-4-pyrimidinecarbaldehyde	oxime: 155	826

6-Methyl-4-pyrimidinecarbaldehyde	53; oxime: 150 or 180(?)	1745,2525,2756
2-Methyl-4-pyrimidinecarbonitrile	27–29 or 29–30, 92/15, 100/20, nmr	142,3762
2-Methyl-5-pyrimidinecarbonitrile	72	1387
4-Methyl-2-pyrimidinecarbonitrile	49–50 or 52–57, 115/20, nmr	142,2762,2763
5-Methyl-2-pyrimidinecarbonitrile	66–67	1897
5-Methyl-4-pyrimidinecarbonitrile	120/20, ir, nmr	3743
6-Methyl-4-pyrimidinecarbonitrile	92–94/10	2525
2-Methyl-5-pyrimidinecarboxamide	218–219	1387
Methyl 2-pyrimidinecarboxylate	103–104 or 104–105	2746,2760
Methyl 4-pyrimidinecarboxylate	63–68 or 70–71	729,3446,3447
Methyl 5-pyrimidinecarboxylate	84	729,2321
2-Methyl-4-pyrimidinecarboxylic acid	204–206	3448
2-Methyl-5-pyrimidinecarboxylic acid	195 to 198, ir, nmr, uv	1387,3097,3996
5-Methyl-2-pyrimidinecarboxylic acid	146–147	2745,2746
5-Methyl-4-pyrimidinecarboxylic acid	190	1135
6-Methyl-4-pyrimidinecarboxylic acid	165–166	1874
2-Methyl-4,5-pyrimidinediamine	246–248, nmr	684,2269,2413
2-Methyl-4,6-pyrimidinediamine	294–303	1159,1556,1558,2507
4-Methyl-2,5-pyrimidinediamine	182–183	645,1932
5-Methyl-2,4-pyrimidinediamine	188–189	1485
5-Methyl-4,6-pyrimidinediamine	243	1485
6-Methyl-2,4-pyrimidinediamine	178 to 186; pic: 287	1447,1509,1734,1736,1932,2249, 3449–3451,3864
6-Methyl-4,5-pyrimidinediamine	208–209	1428,1932,2269,2413,2488
6-Methyl-2,4-pyrimidinediamine 1-oxide	HCl: 265, uv	3864
6-Methyl-2,4-pyrimidinediamine 3-oxide	273, uv	3864
2-Methyl-4,5-pyrimidinedicarbonitrile	36–38	1421
2-Methyl-4,5-pyrimidinedicarboxamide	234–236	1421

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	230 to 237 (224?), sp, xl st	248,437,812,828,1432,1486, 1546,1807,1841,1893,1941, 2370,2769,2770,2773,2776, 2778,2781,3099,3134,3352, 3392,3405,3452–3454,3971, 6118(?),6951
1-Methyl-4,6(1*H*,5*H*)-pyrimidinedione	151–152 or 155–156	2777,3235,3455,3456
2-Methyl-4,6(1*H*,5*H*)-pyrimidinedione	anal	1159,2784,3278,3350,3382
3-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	174 to 184, sp	437,696,809,812,904,1152,1432, 1546,1722,1941,1942,2538,2677, 3099,3453,3457,6118(?)
5-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	312 to 340, sp	51,841,1152,1522,1978,2280, 2492,2677,2887,3053,3101, 3103,3458–3469
5-Methyl-4,6(1*H*,5*H*)-pyrimidinedione	312 to > 330, sp	614,1832,2587,3470
6-Methyl-2,4(1*H*,3*H*)-pyrimidinedione	300 to 334, sp	130,771,911,925,1045,1124, 1673,1943,1947,2346,2413, 2788,2958,3065,3224,3267, 3438,3453,3471–3477, 3727,6020
5-Methyl-2,4(1*H*,3*H*)-pyrimidinediselone	186	1506
2-Methyl-4,6-pyrimidinedisulfonic acid	Na_2: > 320	2047
1-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione	255 to 261	968,1511,1513,2520
2-Methyl-4,6(1*H*,5*H*)-pyrimidinedithione	> 300	1778
3-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione	213	1221
5-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione	281 to 285, nmr	521,1035,2840,3070,3464,3478
6-Methyl-2,4(1*H*,3*H*)-pyrimidinedithione	240 to > 360, nmr	521,958,1221,1427,1509,1647, 1752,2241,3069,3479

2-Methylpyrimidine 1-oxide	50	2744,6940
4-Methylpyrimidine 1-oxide	45–47, nmr, uv; pic: 104–105	3443
4-Methylpyrimidine 3-oxide	82–83, nmr, uv; pic: 137–138	3443,5894
5-Methylpyrimidine 1-oxide	113–116 or 114–115, nmr, $HgCl_2$: 170	2744,3439,3743
4-Methyl-2-pyrimidinesulfonamide	163	1711
5-Methyl-2-pyrimidinesulfonamide	151–152	1711
2-Methyl-4-pyrimidinesulfonic acid	K: anal	2263
4-Methyl-2-pyrimidinesulfonic acid	K: 290–295	2263,2763
4-Methyl-6-pyrimidinesulfonic acid	K: 259–260	1711,2263
5-Methyl-2-pyrimidinesulfonic acid	K: > 310	1711,2263
4-Methyl-2-pyrimidinesulfonyl fluoride	101–102/0.3	1711
5-Methyl-2-pyrimidinesulfonyl fluoride	76–77	1711
1-Methyl-2(1*H*)-pyrimidinethione	189–191, nmr; 3-MeBr: 201; 3-$MeHSO_4$: 154	235,1803,3480
1-Methyl-4(1*H*)-pyrimidinethione	235–236 or 246	3445,3480
2-Methyl-4(3*H*)-pyrimidinethione	145–146 or 151	690,3481
3-Methyl-4(3*H*)-pyrimidinethione	97–98 or 98–99	3445,3480
4-Methyl-2(1*H*)-pyrimidinethione	196 to 221; HCl: 250	193,405,764,1086,1855,2249, 3106,3431,3432,3482,3483
5-Methyl-2(1*H*)-pyrimidinethione	217 to 252	1086,2747,2748,3019
6-Methyl-4(3*H*)-pyrimidinethione	231 or 255–260, nmr	167,1509,2249
2-Methyl-4,5,6-pyrimidinetriamine	250	1434,2287,2448,3484
5-Methyl-2,4,6-pyrimidinetriamine	227–228	1485
6-Methyl-2,4,5-pyrimidinetriamine	242–244	1581,1932,1964,2487,3411
1-Methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	130 to 133, nmr	789,818,1499,1842,2533,2802, 2804,3485,3486,3736,3753,3756
5-Methyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	202–203, nmr	407,1485,3109,3383,3486–3489, 3736

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1-Methyl-2(1*H*)-pyrimidinimine	102–104; HCl: 265 or 278; HI: 247–248	1741,3377,3378,3490
1-Methyl-4(1*H*)-pyrimidinimine	HCl: 207; HI: 205–206; pic: 175	1508,2115,3377
3-Methyl-4(3*H*)-pyrimidinimine	ms, nmr; HI: 218–220	479,1508,2570
2-Methyl-5-pyrimidinol	175–179	6005
4-Methyl-5-pyrimidinol	187–189 or 190, nmr	3491,3951,6017
4-Methyl-5-pyrimidinol 1-oxide	175–177, nmr	6017
4-Methyl-5-pyrimidinol 3-oxide	256–260, nmr	6017
1-Methyl-2(1*H*)-pyrimidinone	125 to 132, sp; 3-MeBr: 268; 3-MeCl: 250; 3-MeI: 232–234; 3-$MeHSO_4$: 205; pic: 162–164	235,1432,1803,1952,2699, 2810,2947,3492,3493,3765
1-Methyl-4(1*H*)-pyrimidinone	155–156, sp; pic: 164–166	235,1136,1432,1743,2551,3377
2-Methyl-4(3*H*)-pyrimidinone	210 to 214, ir, nmr; HCl: 259–260	112,421,487,678,689,1802,1820, 2259,2263,2635,2821,3494,3495
3-Methyl-4(3*H*)-pyrimidinone	121 to 129, sp; 1-$EtBF_4$: 101–102; pic: 175–176 or 178–179, xl st	112,235,297,479,1136,1432, 2551,3117,3496,3726,3742
4-Methyl-2(1*H*)-pyrimidinone	150, ms; HCl: 237 to 246; pic: 192	56,1465,2238,2249,2637,2742, 2817,3432,3482
5-Methyl-2(1*H*)-pyrimidinone	209 to 218, ms	56,1086,2062,2748,3496
5-Methyl-4(3*H*)-pyrimidinone	149 to 156	2108,2264,3118,3154
6-Methyl-4(3*H*)-pyrimidinone	142 to 153, nmr	167,671,1429,1509,1517,1822, 2136,2249,2264,2762,2815,3345, 3409,3498–3506
5-Methylselenomethyl-2,4(1*H*,3*H*)-pyrimidinedione	239–241, nmr	6125
5-Methyl-2-selenoxo-1,2-dihydro-4(3*H*)-pyrimidinone	228–229	3507

6-Methyl-2-selenoxo-1,2-dihydro-4(3*H*)-pyrimidinone	315–320	3508
4-Methyl-6-semicarbazido-2-pyrimidinamine	280–281	533
1-Methyl-4-semicarbazido-2(1*H*)-pyrimidinone	172–173	2829
4-Methylsulfinyl-6-methylthio-2-pyrimidinamine	158–159, nmr	3988
2-Methylsulfinylpyrimidine	152–154/0.5	1715
4-Methylsulfinylpyrimidine	47–49	1715
5-Methylsulfinylpyrimidine	84–86	1715
5-Methylsulfinyl-2,4(1*H*,3*H*)-pyrimidinedione	228 or 230–240	1789,3119,3509
2-Methylsulfinyl-5-pyrimidinol	148–149	926
1-Methyl-5-sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione	264	1126
2-Methyl-5-sulfomethyl-4-pyrimidinamine	> 310 or > 440	584,1466,3510–3513; see also 2729
2-Methyl-5-sulfomethyl-4(3*H*)-pyrimidinone	325	3098,3510,3512
2-Methylsulfonyl-5-nitropyrimidine	157–158	3228
2-Methylsulfonyl-5-pyrimidinamine	140–141	1623
2-Methylsulfonylpyrimidine	72–74	1715,1897
4-Methylsulfonylpyrimidine	53–54	1715
5-Methylsulfonylpyrimidine	135–136	1715
2-Methylsulfonyl-5-pyrimidinecarbonitrile	172–173	43,1897
5-Methylsulfonyl-2-pyrimidinecarbonitrile	191–192	1897
2-Methylsulfonyl-4,6-pyrimidinediamine	197–198	1091
5-Methylsulfonyl-2,4(1*H*,3*H*)-pyrimidinedione	309 or 342	1789,3119,3509
6-Methylsulfonyl-2,4(1*H*,3*H*)-pyrimidinedione	307–308	2070,3347
2-Methylsulfonyl-5-pyrimidinol	180–182	2599
6-Methylsulfonyl-4(3*H*)-pyrimidinone	223–224	2289
2-Methylsulfonyl-5-trimethylstannylpyrimidine	108, ir, ms, nmr	3833,3970
6-Methyl-5-sulfo-oxy-2,4(1*H*,3*H*)-pyrimidinedione	> 320	6017
2-Methyl-5-thioacetamidomethyl-4-pyrimidinamine	187	1472

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Methyl-5-thioacetamido-2,4(1*H*,3*H*)-pyrimidinedione	265–267	1239
5-Methylthio-2,4-bistrimethylsiloxypyrimidine	36–37	839
2-Methyl-5-thiocyanatomethyl-4-pyrimidinamine	> 150	1326
4-Methyl-2-thiocyanato-5-pyrimidinecarboxylic acid	127–129	2982
1-Methyl-2-thiocyanato-4(1*H*)-pyrimidinimine	HBr: 185	1713
1-Methyl-4-thiocyanato-2(1*H*)-pyrimidinone	145–146 or 148–149	3514,3515
6-Methyl-2-thiocyanato-4(3*H*)-pyrimidinone	168–169	3516
4-Methylthio-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	293 to 305, ir nmr, uv	1004,3882,6143
3-*β*-Methylthioethyl-2,4(1*H*,3*H*)-pyrimidinedione	180–183, ir, nmr	525
2-Methyl-5-thioformamidomethyl-4-pyrimidinamine	174 to 193; pic: 166	685,939,975,1010,2481, 3517–3519
4-Methyl-5-thioformamidomethyl-2-pyrimidinamine	212–213	960
2-Methyl-5-thioformamidomethyl-4(3*H*)-pyrimidinone	199–200	680,3520
6-Methyl-5-thioformamido-4-pyrimidinamine	168	1239
2-Methyl-5-thioformamido-4,6-pyrimidinediamine	anal	1558
6-Methyl-5-thioformamido-2,4-pyrimidinediamine	255	1239
6-Methyl-5-thioformamido-2,4(1*H*,3*H*)-pyrimidinedione	260–262	1239
5-Methylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione	258–260	841
6-Methylthiomethyl-2,4(1*H*,3*H*)-pyrimidinedione	221–222	3500
2-Methylthio-5-methylthiomethyl-4-pyrimidinamine	139–140	1326
2-Methylthio-6-methylthiomethyl-4(3*H*)-pyrimidinone	149–150	3500
6-Methylthiomethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	284–286	3521
2-Methylthio-5-nitro-4-pyrimidinamine	181–183 or 183–184, nmr	681,6448
2-Methylthio-5-nitropyrimidine	80 to 85	582,1012,1951,2321,3228
2-Methylthio-5-nitro-4,6(1*H*,5*H*)-pyrimidinedione	223 to 245	1764,2292,3988

2-Methylthio-5-nitroso-4,6-pyrimidinediamine	261–262	2431,2625
6-Methylthio-5-nitroso-2,4-pyrimidinediamine	> 260	1768,3522
2-Methylthio-5-nitroso-4,6(1*H*,5*H*)-pyrimidinedione	180–200	1046
2-Methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	133	2856
2-Methylthio-4-oxo-3,4-dihydro-5-pyrimidinecarbonitrile	220–223	1078,2085
4-Methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile	239	3212
2-Methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide	275–276	1560
4-Methylthio-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	340	3212
2-Methylthio-4-oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	234–235	2527,2873
2-Methylthio-6-oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	250 to 255	1030,2856,2889,3082,3139
6-Methylthio-2-oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	228–230	1030
2-Methylthio-6-oxo-5-propyl-1,6-dihydro-4-pyrimidinecarboxylic acid	219–220	1224
2-Methylthio-5-prop-1′-enylpyrimidine	0, ms, nmr	3829
2-Methylthio-6-propoxy-4-pyrimidinamine	crude	1358
4-Methylthio-2-propoxypyrimidine	liquid, anal, uv	2941
2-Methylthio-6-propyl-4-pyrimidinecarbohydrazide	114–115	2266
2-Methylthio-6-propyl-4-pyrimidinecarboxamide	138–139	2266
6-Methylthio-3-propyl-2,4(1*H*,3*H*)-pyrimidinedione	171	909
2-Methylthio-6-propyl-4(3*H*)-pyrimidinethione	193	2147
2-Methylthio-5-propyl-4(3*H*)-pyrimidinone	153	162
2-Methylthio-6-propyl-4(3*H*)-pyrimidinone	154 to 158 (116–119?)	825,925(?),2147,3076,3837
4-Methylthio-1-propyl-2(1*H*)-pyrimidinone	101–103	2941
6-Methylthio-3-propyl-4(3*H*)-pyrimidinone	79	909
2-Methylthio-5-prop-2′-ynyloxypyrimidine	85–86	3523
2-Methylthio-4-pyrimidinamine	123–125 or 125–126	1520,1637,1855
2-Methylthio-5-pyrimidinamine	105 or 110–111	1623,2198
4-Methylthio-2-pyrimidinamine	150–153 or 152–154	958,1507
5-Methylthio-2-pyrimidinamine	156 or 160–161	840,1566,1567

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
6-Methylthio-4-pyrimidinamine	167 to 170; pic: 213–215	958,1653,1655,2115
2-Methylthiopyrimidine	99/14, sp; HCl: 142–144; MeI: 155–156; pic: 89–91	235,1824,1968,2098,3143,3406, 3440,3480,3493
4-Methylthiopyrimidine	68/0.9, 86–87/12, sp; 1-MeI: 141–143 or 144–146; 3-MeI: 134–135	235,3445,3480,3493,3524
5-Methylthiopyrimidine	42–43, 70–71/2	1715
2-Methylthio-4-pyrimidinecarbaldehyde	68; oxime: 165	2756
2-Methylthio-5-pyrimidinecarbaldehyde	79–83 or 84, ir, ms, nmr; PhNHN=: 189–190, nmr	502,6021,6122,6170
2-Methylthio-4-pyrimidinecarbonitrile	76 to 84	1628,1745,3043
2-Methylthio-5-pyrimidinecarbonitrile	79–80 or 81, nmr	43,1897
4-Methylthio-5-pyrimidinecarbonitrile	92–93 or 94–96	713,1633
2-Methylthio-5-pyrimidinecarbonyl chloride	170, ir, nmr	381
2-Methylthio-4-pyrimidinecarboxylic acid	208–210 or 213–215, ir, nmr	502,1935,3043,3931
2-Methylthio-5-pyrimidinecarboxylic acid	267, ms, nmr	381
2-Methylthio-4,5-pyrimidinediamine	157–159	681
2-Methylthio-4,6-pyrimidinediamine	185 or 188–189, ir, nmr; pic: 212	250,699,1046,2625,3525,3526
6-Methylthio-2,4-pyrimidinediamine	202–204	932,1520,3522
6-Methylthio-4,5-pyrimidinediamine	155–157	2413,3183
2-Methylthio-4,6(1*H*,5*H*)-pyrimidinedione	> 300 or > 360	958,1764,2474,3527
5-Methylthio-2,4(1*H*,3*H*)-pyrimidinedione	300 to 308	839,1789,2832,3119,3133,3509
6-Methylthio-2,4(1*H*,3*H*)-pyrimidinedione	328–330	2605,3528
2-Methylthio-4,6(1*H*,5*H*)-pyrimidinedithione	> 360	958
2-Methylthio-4(3*H*)-pyrimidinethione	201 or 203	958,3022,3529
4-Methylthio-2(1*H*)-pyrimidinethione	190–192	2288

2-Methylthio-4,5,6-pyrimidinetriamine	182 or 185–186	1558,2448,3525,3530–3532
6-Methylthio-2,4,5-pyrimidinetriamine	191–192	932,3522
2-Methylthio-5-pyrimidinol	168–169 or 176–177	774,2198,6193
2-Methylthio-4(3*H*)-pyrimidinone	198 to 201	112,321,925,1689,2098,3053, 3234,3837
4-Methylthio-2(1*H*)-pyrimidinone	205; Na: 290	2941,3134
6-Methylthio-4(3*H*)-pyrimidinone	229–234	958,1666,2605,3348
4-Methyl-6-thiosemicarbazido-2-pyrimidinamine	HCl: 255–256	533
2-Methylthio-5-thiocyanato-4,6-pyrimidinediamine	211–214	837
2-Methylthio-5-thioformamido-4,6-pyrimidinediamine	235	1558,3533
2-Methylthio-6-thioureido-4-pyrimidinamine	207–210 or 238–240, ms, nmr	497,3861
6-Methylthio-5-thioureido-2,4(1*H*,3*H*)-pyrimidinedione	350	1163
2-Methylthio-6-thioxo-1,6-dihydro-4-pyrimidinecarboxylic acid	235	1030
5-Methylthio-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	271–273	1789
2-Methylthio-5-trimethylstannylpyrimidine	liquid, anal, ir, ms, nmr	3833,3970
2-Methylthio-6-ureido-4-pyrimidinamine	203–208, nmr	3861
6-Methyl-5-thioureido-2,4(1*H*,3*H*)-pyrimidinedione	278–279	3534
6-Methyl-2-thioureido-4(3*H*)-pyrimidinone	232	3535
2-Methylthio-5-vinylpyrimidine	48–49, ms, nmr	3829
4-Methylthio-1-vinyl-2(1*H*)-pyrimidinone	145–146	3138
2-Methyl-4-thioxo-3,4-dihydro-5-pyrimidinecarboxylic acid (?)	184–185	2988
1-Methyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	195 to 202	1572,1575,3536
5-Methyl-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	244	1046
1-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	220 to 230	962,1689,1713,2027,2035, 2839,3352
1-Methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	193–194 or 195–197	1513,1533,1538,1539
1-Methyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	183–184 or 185–187	806,1508,3537
1-Methyl-6-thioxo-1,6-dihydro-4(5*H*)-pyrimidinone	209–210	3348
2-Methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	295–297 or 301	1189,2237,2263

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
3-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	283 or 292–294 (207?), nmr	424,425,2035,3538
3-Methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	209–211 or 210–212	909,3348
4-Methyl-6-thioxo-1,6-dihydro-2(3*H*)-pyrimidinone	339–341 or 341–342	521,2241,3226,3508
5-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	264 to 280	962,1689,2698,3458,3467
5-Methyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	255–330, ir, ms, nmr, uv	521,1232,2698,3034,3760,3874
5-Methyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	200	2186
6-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	290 to 330	227,1145,1170,1684,1787,1806, 2700,2765,2816,3076,3135,3539, 3540
Methyl 2,5,6-triamino-4-pyrimidinecarboxylate	217	1123
Methyl 2,5,6-trichloro-4-pyrimidinecarboxylate	56–58	2121
2-Methyl-6-trimethylammonio-4-pyrimidinamine	chloride: 210	2093
6-Methyl-2-trimethylammonio-4-pyrimidinamine	chloride: 190	2093
2-Methyl-4-trimethylammoniopyrimidine	chloride: 155–157	3154
4-Methyl-6-trimethylammoniopyrimidine	chloride: 169–172	3154,3287
5-Methyl-4-trimethylammoniopyrimidine	chloride: 186–187	3154
4-Methyl-6-trimethylammoniopyrimidine 3-oxide	crude chloride: nmr	3287
Methyl 1,3,5-trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate	125–126	2669
Methyl 2,4,6-trimethyl-5-pyrimidinecarboxylate	56–58, ir, ms, nmr	335
1-Methyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde	197–199	3541
4-Methyl-2-ureidopyrimidine	229	2554
6-Methyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	anal	692,1492
1-Methyl-5-ureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	220	1519,2847
5-Methyl-2-ureido-4(3*H*)-pyrimidinone	245	1150
6-Methyl-2-ureido-4(3*H*)-pyrimidinone	229	1150

3-Methyl-1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione	95–97	1722
5-Methyl-1-vinyl-2,4(1*H*,3*H*)-pyrimidinedione	205–207	1323
5-Nitroamino-2,4(1*H*,3*H*)-pyrimidinedione	> 330	903
5-Nitro-2,4-bispropylaminopyrimidine	121–122	1747,1790
5-Nitro-4,6-bispropylaminopyrimidine	62–63	1747
5-Nitro-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde	oxime: 218–220	1165
5-Nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxamide	285 or > 300	1123,2046
5-Nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	> 230	771,1170,1172,1764,1943,2994
5-Nitro-2,4-dipropoxypyrimidine	32–33, 115–117/0.25, nmr, uv	2559, 3227
5-Nitro-2,6-dithioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	–	1035
4-Nitromethylpyrimidine	125, nmr, uv	3542
5-Nitro-2-propoxypyrimidine	37–38, 91/0.4	2559
5-Nitro-4-propoxypyrimidine	20, 116/5	2559
5-Nitro-2-propylamino-4-pyrimidinamine	—	3543
5-Nitro-6-propylamino-4-pyrimidinamine	163–164	3544
5-Nitro-2-propylaminopyrimidine	116 or 119	2643,3232
5-Nitro-6-propylamino-2,4(1*H*,3*H*)-pyrimidinedione	274–275	1165
5-Nitro-2-propylamino-4-thiocyanatopyrimidine	134–135	1195
5-Nitro-2-propyl-4,6-pyrimidinediamine	198	1612
5-Nitro-6-propyl-2,4-pyrimidinediamine	162–164	2441
5-Nitro-2-propyl-4,6(1*H*,5*H*)-pyrimidinedione	301–302	1612
5-Nitro-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione	226–227	1962
5-Nitro-2-pyrimidinamine	233 to 238, nmr	703–705,2304,2318,2942, 3232,6448
5-Nitro-4-pyrimidinamine	212–214	684
2-Nitropyrimidine	57–58	3545
5-Nitropyrimidine	56–58 or 59–60	946,2560,3546
5-Nitro-2,4-pyrimidinediamine	245–250(?) or 345–350	1582,1586,2297,2308,2327,2487

Pyrimidine	m.p. (°C), etc.	Ref.
5-Nitro-4,6-pyrimidinediamine	> 400	1434,1579,1650,2246,2303,2426, 2441,2501,2502,3547,3548
5-Nitro-4,6-pyrimidinediamine 1,3-dioxide	> 240	2426
5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione	295 to 311	711,1125,1187,1584,1637,2295, 2298,2340,2704,2705,3153
5-Nitro-4,6(1*H*,5*H*)-pyrimidinedione	> 300	2246,2501–2503,3375,3547,3548
5-Nitro-2,4(1*H*,3*H*)-pyrimidinedithione	200 or 213–215	626,1035,1582,1648
5-Nitro-4,6(1*H*,5*H*)-pyrimidinedithione	> 300	1778
5-Nitro-2(1*H*)-pyrimidinethione	217	1951
5-Nitro-2,4,6-pyrimidinetriamine	> 350	1579,2332,3549
5-Nitro-2,4,6-pyrimidinetriamine 1,3-dioxide	anal, uv	3549
5-Nitro-2,4,6-pyrimidinetriamine 1-oxide	anal, uv	3549
5-Nitro-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	H_2O: 176 to 183, xl st	2091,2798,3413,3550–3553
5-Nitro-2(1*H*)-pyrimidinone	199 to 203; EtOH: 205–208	582,703,2304,3554,3555
5-Nitro-4(3*H*)-pyrimidinone	190–192	1654,3555,3556
5-Nitroso-4,6-dioxo-1,4,5,6-tetrahydro-2-pyrimidinecarbaldehyde	oxime: > 310	937
5-Nitroso-2-propyl-4,6-pyrimidinediamine	228 or 231	3557,3558
2-Nitrosopyrimidine	127–129, nmr	6016
5-Nitroso-4,6-pyrimidinediamine	—	2441 (cf. 2431)
5-Nitroso-2,4,6-pyrimidinetriamine	345–346	1739,2431,2432,3188,3559,3560
5-Nitroso-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	245–246	1518,1590,3271,3553,3561,3562
5-Nitroso-1-β-sulfoethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	Na; pyridinium: anal, nmr	6309
5-Nitroso-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	210 or > 300	1518,1686,3563,3564
5-Nitro-2-sulfoaminopyrimidine	Na: —	3565
5-Nitro-4-thiocyanato-2-pyrimidinamine	209–210	1582

5-Nitro-2-thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	Na: > 300	3988
5-Nitro-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	243–245 or 255–257	1689,2704
5-Nitro-2-trimethylammoniopyrimidine	chloride: 204; picrate: 132–133	3554
5-Nitro-4-trimethylsiloxy-2-trimethylsilylthiopyrimidine	140/0.1	1689
5-Nitro-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-1-pyrimidinecarboxamidine	HCl: —	1168
5-Nitro-6-ureido-4-pyrimidinamine	> 400	1579
2-Oxo-1,2-dihydro-4-pyrimidinecarbaldehyde	oxime: 226, uv	1628,1630
4-Oxo-3,4-dihydro-5-pyrimidinecarbaldehyde	245–247; PhHNN=: 250–253	1614
6-Oxo-1,6-dihydro-4-pyrimidinecarbaldehyde	> 330; acetal: 122–124	2856,3140
4-Oxo-3,4-dihydro-5-pyrimidinecarbohydrazide	208	1615
2-Oxo-1,2-dihydro-5-pyrimidinecarbonitrile	260–262 or 266–268, nmr	43,1617,1618
4-Oxo-3,4-dihydro-5-pyrimidinecarbonitrile	244–245 or 247	1571,1625
4-Oxo-3,4-dihydro-5-pyrimidinecarboxamide	266–268 or 276–278	713,1615,1625
6-Oxo-1,6-dihydro-4-pyrimidinecarboxamide	> 400	2856
2-Oxo-1,2-dihydro-4-pyrimidinecarboxylic acid	> 180 or 225	1628,1630
2-Oxo-1,2-dihydro-5-pyrimidinecarboxylic acid	> 220 or 290, ms, nmr	381,3020
4-Oxo-3,4-dihydro-5-pyrimidinecarboxylic acid	236–237 or 238	713,1631,2873
6-Oxo-1,6-dihydro-4-pyrimidinecarboxylic acid	264 or 268–270	1030,1626,1820,2856
2-Oxo-1,2-dihydro-4,6-pyrimidinedicarbaldehyde	dioxime: –	2257
2-Oxo-1,2-dihydro-4,5-pyrimidinedicarboxamide	> 300	3566
2-Oxo-1,2-dihydro-5-pyrimidinesulfonic acid	> 300	845
4-Oxo-3,4-dihydro-2-pyrimidinesulfonic acid	K_2: anal	3567
4-Oxo-2-propylamino-3,4-dihydro-5-pyrimidinecarboxamide	296	2647
4-Oxo-2-propylamino-3,4-dihydro-5-pyrimidinecarboxylic acid	20(?)	865
2-Oxo-6-propyl-1,2-dihydro-4-pyrimidinecarbohydrazide	187–189	2266
2-Oxo-6-propyl-1,2-dihydro-4-pyrimidinecarboxamide	286–287	2266
6-Oxo-2-propylthio-1,6-dihydro-4-pyrimidinecarboxylic acid	236–237	1030
4-Oxo-6-propyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde	dnp: 319	2891

Pyrimidine	m.p. (°C), etc.	Ref.
6-Oxo-1-propyl-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	134–135	2578
4-Oxo-6-propyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	260–261, ir, ms, nmr	6174
5-Oxo-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	x1 st; PhNHN=: nmr	192,519,3568–3575,3991
4-Oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbaldehyde	dnp: 305	2891
6-Oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbaldehyde	249 to 251	2578,2854–2856,2862,3141
4-Oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile	265 to 283	1175,1331,1684,2983,3423
4-Oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbonyl chloride	crude	2870
2-Oxo-6-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	307–308	1030
4-Oxo-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid	284–287 or 288–289 (246–247?)	1175,1685,2873
6-Oxo-2-thioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	319 to 322	1605,3081,3082,3139,3576,3577
5,*N*,*N*,*N*′,*N*′-Pentamethyl-6-oxo-1,6-dihydro-2,4-pyrimidinedicarboxamide	crude, nmr	2038
6-Prop-1′-enylidenehydrazino-2,4(1*H*,3*H*)-pyrimidinedione	249–250	3233
5-Prop-1′-enyl-2,4(1*H*,3*H*)-pyrimidinedione	232–236, nmr	6125
6-β-Propionylhydrazino-2,4(1*H*,3*H*)-pyrimidinedione	257–258	805
5-Propionyloxy-2,4(1*H*,3*H*)-pyrimidinedione	242–245	3578
2-Propoxy-4-pyrimidinamine	76–78	615,724
5-Propoxy-2-pyrimidinamine	73–75 or 82–84	673,1007,1368,2945
6-Propoxy-4-pyrimidinamine	132–133	615
2-Propoxypyrimidine	92–93/22	2947
4-Propoxypyrimidine	pic: 92–93	1715
2-Propoxy-4,6(1*H*,5*H*)-pyrimidinedione	anal; 2-propyluronium salt: 173	3295
5-Propoxy-2,4(1*H*,3*H*)-pyrimidinedione	—	2952
6-Propoxy-4(3*H*)-pyrimidinethione	160–162	2605
5-Propoxy-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	—	2952
6-Propylamino-4-pyrimidinamine	140	866

2-Propylaminopyrimidine	19.5, 115/20; pic: 150–151 or 151–152	867,1741,3232
4-Propylaminopyrimidine	pic: 160–161	3232
6-Propylamino-4,5-pyrimidinediamine	HCl: 198–199	3544
5-Propylamino-2,4(1*H*,3*H*)-pyrimidinedione	HCl: 264–265	2980
Propyl 6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonate	188–190	3052
N-Propyl-2-propylamino-5-pyrimidinesulfonamide	162–163	845
6-Propyl-2-propylthio-4(3*H*)-pyrimidinone	66	925
2-Propyl-4-pyrimidinamine	78–79	1456
4-Propyl-2-pyrimidinamine	121 to 125, ir, nmr, uv	1217,2366,3086,3087,3434, 3435,3996
5-Propyl-4-pyrimidinamine	162	2652,3089
2-Propylpyrimidine	126/200	3090
4-Propylpyrimidine	71/11, 94–95/50; pic: 88–89	2752,3091,3092
5-Propylpyrimidine	68–69/11	3093
2-Propyl-5-pyrimidinecarboxylic acid	108–109	3097
5-Propyl-2-pyrimidinecarboxylic acid	103	3097
2-Propyl-4,5-pyrimidinediamine	148–150	1612
2-Propyl-4,6-pyrimidinediamine	202–203	1456
6-Propyl-2,4-pyrimidinediamine	HCl: 190–194	1356
1-Propyl-2,4(1*H*,3*H*)-pyrimidinedione	119–121 or 121–123	608,870,3099,6073
2-Propyl-4,6(1*H*,5*H*)-pyrimidinedione	296 or 309–310	1456,1612,1981,2819
3-Propyl-2,4(1*H*,3*H*)-pyrimidinedione	157–158	908,3099
5-Propyl-2,4(1*H*,3*H*)-pyrimidinedione	292 or 293–294	1152,1673
5-Propyl-4,6(1*H*,5*H*)-pyrimidinedione	> 300	921
6-Propyl-2,4(1*H*,3*H*)-pyrimidinedione	217–219 or 219–221	825,2151,2441,2783
4-Propyl-2(1*H*)-pyrimidinethione	213–215; HCl: 239	3579
5-Propyl-2(1*H*)-pyrimidinethione	208 or 219	2748,3019
2-Propyl-4,5,6-pyrimidinetriamine	171–172	2441

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Propyl-2,4,6-pyrimidinetriamine	185–186	1151
6-Propyl-2,4,5-pyrimidinetriamine	183–186	2441
1-Propyl-2(1*H*)-pyrimidinimine	HBr: 147 or 152; HI: 163; pic:124	867,923
1-Propyl-2(1*H*)-pyrimidinone	36	2947
2-Propyl-4(3*H*)-pyrimidinone	106–107	1456
5-Propyl-2(1*H*)-pyrimidinone	116	2748
6-Propyl-4(3*H*)-pyrimidinone	110–112	3501,3506
6-Propylthio-2,4-pyrimidinediamine	107–109	932
5-Propylthio-2,4(1*H*,3*H*)-pyrimidinedione	253 or 261	3119,3133
6-Propylthio-2,4,5-pyrimidinetriamine	145–146	932
2-Propylthio-5-pyrimidinol	102	926
2-Propylthio-4(3*H*)-pyrimidinone	102–104 or 117	925,1637
1-Propyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	89–90	870
3-Propyl-6-thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	153–156	909
5-Propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	159–161	1684,3084,3303
6-Propyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	218–219	1684,3076,3580–3582,6068
6-Propyl-4-thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	193	2147
2-Prop-2′-ynylaminopyrimidine	108–109, nmr	843,3583
5-Prop-2′-ynyl-2,4(1*H*,3*H*)-pyrimidinedione	256–260, nmr	6125
1-Prop-2′-ynyl-2(1*H*)-pyrimidinimine	HBr: 195–196	843,3583
5-Prop-2′-ynylthio-2,4(1*H*,3*H*)-pyrimidinedione	215–217	931
2-Prop-2′-ynylthio-4(3*H*)-pyrimidinone	155–160, ir, ms, nmr	6415
4-Prop-2′-ynylthio-2(1*H*)-pyrimidinone	171, ir, nmr	276

2-Pyrimidinamine	125–126, sp: pic: 235–237	36,708,1349,1653,1671,1856, 2513,3061,3088,3232,3377,3431, 3433,3584–3595,3891,3996,4017
4-Pyrimidinamine	149–151, sp; HI: 180; pic: 225	708,1349,1626,1650,1653,2258, 2513,2652,3232,3290,3377,3589
5-Pyrimidinamine	164–170 or 171–172	704,711,1037,1623,1778,1968, 1969,2321,2513
2-Pyrimidinamine 1-oxide	186–188 or 193, ms, nmr	36,6052
4-Pyrimidinamine 1-oxide	196–197, nmr	36
Pyrimidine	22.5, 122–123/720, 124–126/760, n_D^{20} 1.4960, nmr; HCl: 163–165; MeI: 135–136 or 137; pic: 153–156	658,711,764,836,1297,1517, 1874,1935,1965,2212,2258, 2513,2566,2752,3093,3363, 3439,3596–3598,3951,4585
2-Pyrimidinecarbaldehyde	78–82/9; dnp: 273; *syn*-oxime: 237–240	2758,2760
4-Pyrimidinecarbaldehyde	42–44/0.7, 51/0.8; $H_2NN{=}$: 117–118; dnp: 279; oxime: 152–154 or 155–156	826,2584,2756,3446,3599,3601
5-Pyrimidinecarbaldehyde	38–41; acetal: 113/12	1028,3600
4-Pyrimidinecarbohydrazide	144–145 or 147	1604,3096
5-Pyrimidinecarbohydrazide	124	1969
2-Pyrimidinecarbonitrile	42–44	729,1715,2763,3602,3603
4-Pyrimidinecarbonitrile	31–32	729,793
5-Pyrimidinecarbonitrile	85–86 or 86–88	729,1219,2509
4-Pyrimidinecarbonyl azide	89–90	2893
2-Pyrimidinecarbothioamide	225	729
4-Pyrimidinecarbothioamide	236	729
5-Pyrimidinecarbothioamide	170	729,2509
2-Pyrimidinecarboxamide	167	729,1973,6899
4-Pyrimidinecarboxamide	191 to 197	729,826,2893

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
5-Pyrimidinecarboxamide	211 to 214	729,1969,2321,2509
2-Pyrimidinecarboxamidine	125–126; $PhSO_3H$: 190	729,1856,1973
5-Pyrimidinecarboxamidine	HCl: 213	729
2-Pyrimidinecarboxamidrazone	109–110	3604
2-Pyrimidinecarboxylic acid	199	2745,2746
4-Pyrimidinecarboxylic acid	226–230 or 238–240	1517,1935,1968,2264,3096,3447, 3605
5-Pyrimidinecarboxylic acid	260 to 270	1028,1968,2264,2509,3606,3607
2,4-Pyrimidinediamine	145–146 or 149–150, sp	292,596,951,1297,1349,1650, 1653,1678,1743,2912,3346,3608, 3609
2,5-Pyrimidinediamine	200 to 213	1623,1624,3059.3610,3611
4,5-Pyrimidinediamine	201–203 or 205; HCl: 241 (mono-), 231 (di-)	2295,2296,2443,3612,3613
4,6-Pyrimidinediamine	268–270 or 270–271; pic: 300	972,1216,1297,1650,2507, 3614–3616
2,4-Pyrimidinediamine 1-oxide	289	3346
2,4-Pyrimidinediamine 3-oxide	219–220; H_2O: 183 or 192–193	3346,3609
4,6-Pyrimidinedicarbaldehyde	dioxime: 220; $(PhHNN{=})_2$: 184	826,3617
2,5-Pyrimidinedicarbonitrile	127–128	1897
4,5-Pyrimidinedicarboxamide	224–225	2548
4,5-Pyrimidinedicarboximide	255, ir, nmr	2548
4,5-Pyrimidinedicarboxylic acid	225	2548,3606,3774
4,6-Pyrimidinedicarboxylic acid	218 or 222	764,1874

2,4(1*H*,3*H*)-Pyrimidinedione	320 to 335, sp	57,247,339,422,435,962,1673, 1676,1978,2041,2295,2346,2771, 2868,3053,3148,3453,3475,3477, 3619–3623,3727,6898,6951
4,6(1*H*,5*H*)-Pyrimidinedione	230 or > 300; HCl: > 225	1117,1981,2339,2501,2502,2506, 2508,2587,3382,3547,3548,3624, 3625
Pyrimidine 1,3-dioxide	226–228, nmr	3626,3627
2,4(1*H*,3*H*)-Pyrimidinediselone	208–209	3507,3628
2,4(1*H*,3*H*)-Pyrimidinedithione	231 to 300, ir, ms, nmr, uv, x1 st	521,958,1035,1650,1652,2321, 2473,2840,3069,3148,3507, 3629–3631,3874
4,6(1*H*,5*H*)-Pyrimidinedithione	245–246 or 250–252	958,1785
Pyrimidine 1-oxide	92–95 or 95–96	2744,3632,3633,5899
2-Pyrimidinesulfonamide	180–181	1711,2347,2348
2-Pyrimidinesulfonic acid	K: 328	1711,2263,2763
4-Pyrimidinesulfonic acid	K: 330	1711
2-Pyrimidinesulfonyl chloride	crude	2348
2-Pyrimidinesulfonyl fluoride	57	1711
2,4,5,6-Pyrimidinetetramine	205; H_2SO_4: 255 or > 360	426,1739,1769,2243,2332,2448, 3188,3530,3559,3634,3635
2,4,5,6-Pyrimidinetetrasulfonic acid	Na_4: anal, ir; Ag_4: —	120
2(1*H*)-Pyrimidinethione	217 to 230, sp	235,764,958,1086,1968,2321, 2348,3480,3496,3595,3636
4(3*H*)-Pyrimidinethione	188 or 190–192; HCl: 220	958,1968,2321,3480,3524,3637
2,4,5-Pyrimidinetriamine	179; H_2SO_4: —	1379,2296,2327,2443,2487,3638
2,4,6-Pyrimidinetriamine	246 or 252; pic: > 300	1040,1046,1349,1769,2332, 3188,3559
4,5,6-Pyrimidinetriamine	257	1434,1619,2441,2443,2444,2448, 2456,2501,2502,3615,3639

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2,4,6-Pyrimidinetricarbaldehyde	np (mono-): > 320	3640
2,4,6-Pyrimidinetricarboxylic acid	> 320	3000,3640
2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione	243–245 or 245–247, sp	192,407,789,834,2804,3111, 3112,3550,3641–3648,3736, 3756,6897
2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrithione	> 360	958,1349,3649
5-Pyrimidinol	209–211 or 211–212, nmr	1341,1343,1969,3758,3951
5-Pyrimidinol 1-oxide	202–204, nmr	21,3758
2(1*H*)-Pyrimidinone	176 or 178–180 and 161 (metastable x1 form), sp; HCl: 203 or 210	125,235,708,764,1676,1967, 1986,2098,2699,3366,3380, 3554,3595,3650,3765
4(3*H*)-Pyrimidinone	162 to 166, ir, ms, nmr, uv	170,235,437,708,710,1032,1650, 1820,2325,2821,3554,3651
2(1*H*)-Pyrimidinone 3-oxide	HBr: 220, ir	3366
2-Selenoxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	193–210	3652 (cf. 172)
2-Selenoxo-1,2-dihydro-4(3*H*)-pyrimidinone	235–236	3507,3652
5-Semicarbazido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	> 290	749
4-Semicarbazido-2(1*H*)-pyrimidinone	uv	2829
5-Sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione; *see* 5-Amino-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinesulfonic acid		
6-Sulfoamino-2,4(1*H*,3*H*)-pyrimidinedione	280; Na: > 320	1126
5-Sulfoamino-2,4,6-pyrimidinetriamine	anal, uv	3530
6-β-Sulfoethyl-2,4(1*H*,3*H*)-pyrimidinedione	Na: 318–321	1869
1-β-Sulfoethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	Na; pyridinium: anal, nmr	6309
5-Sulfooxy-4,6-pyrimidinediamine	> 300	1011
5-Sulfooxy-2,4,6-pyrimidinetriamine	> 300	1011

2,4,5,6-Tetrabromopyrimidine	165–166 or 167	2153,3597
2,4,5,6-Tetrachloropyrimidine	66–68	1855,2121,2350,3597,3653–3655
2,4,5,6-Tetrafluoropyrimidine	82–83/760 or 89/760	1727,1728,3656–3658
2,4,5,6-Tetramethylpyrimidine	29–30/0.2, 82–122/20, or 196–197/750, ir, nmr, uv; pic: 129–130	382,3000,6419
1,3,5,6-Tetramethyl-2,4(1*H*,3*H*)-pyrimidinedione	123–125 or 131–132	1735,2792
1,3,5,6-Tetramethyl-2,4(1*H*,3*H*)-pyrimidinedithione	199	3659
2,3,5,6-Tetramethyl-4(3*H*)-pyrimidinimine	HI: 249	2570
1,2,4,6-Tetramethylpyrimidinium-5-carboxylate	223–225, M^+, ms	335
1,4,5,6-Tetramethyl-2(1*H*)-pyrimidinone	88–89, ms	56,3660
1,3,*N*,*N*-Tetramethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxamide	113–130	1055
2-Thiocyanato-4-pyrimidinamine	169	1713
2-Thiocyanatopyrimidine	107–109	3290
5-Thiocyanato-4,6-pyrimidinediamine	184–185	837
5-Thiocyanato-2,4,6-pyrimidinetriamine	219–220	837
5-Thiocyanato-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	NH_4: anal; K: anal	3320
4-Thiocyanato-2(1*H*)-pyrimidinone	225–227	3515
5-Thioformamidomethyl-4-pyrimidinamine	174	939,1457
5-Thioformamidomethyl-2,4-pyrimidinediamine	181–182	1480
5-Thioformamido-4,6-pyrimidinediamine	> 200	1619
5-Thioformamido-4,6(1*H*,5*H*)-pyrimidinedithione	250	1641
2-Thiosemicarbazido-4,6-pyrimidinediamine	—	3661
6-Thioureido-2,4-pyrimidinediamine		3662
5-Thioureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	NH_4: 255	2368,3663
2-Thioxo-1,2-dihydro-5-pyrimidinecarbonitrile	175–176	1086
4-Thioxo-3,4-dihydro-5-pyrimidinecarbonitrile	205–206 or > 300	713,1614
2-Thioxo-1,2-dihydro-4-pyrimidinecarboxylic acid	201–202	1628,1630
6-Thioxo-1,6-dihydro-4-pyrimidinecarboxylic acid	247–248	1628

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
2-Thioxo-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	> 235	958,1499,1525,1787,3664,3665
6-Thioxo-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione	245	958
2-Thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	300 to 340, nmr	258,958,962,2035,3148,3494, 3666,3667
4-Thioxo-3,4-dihydro-2(1*H*)-pyrimidinone	289 to 328, ir, ms, nmr, uv	521,958,3134,3148,3226, 3492,3874
6-Thioxo-5,6-dihydro-4(3*H*)-pyrimidinone	240–242 or 247	958,1666,2186,3348
2-Thioxo-5-ureido-2,3-dihydro-4,6(1*H*,5*H*)-pyrimidinedione	300	1686
6-Thioxo-5-ureido-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione	anal	1163
2-Thioxo-5-vinyl-1,2-dihydro-4(3*H*)-pyrimidinone	> 170	3332
4,5,6-Triacetamido-2-dimethylaminopyrimidine	231–232	2620
2,4,6-Triacetamido-5-nitrosopyrimidine	214 or 217–218	638,2378,2379
2,4,6-Triacetamidopyrimidine	304–305	709
2,5,6-Triacetamido-4(3*H*)-pyrimidinone	244–248	629
2,4,6-Triallyloxy-5-fluoropyrimidine	96–98/0.01, nmr	293
2,4,6-Triallyloxypyrimidine	liquid, anal	3668
2,5,6-Triamino-1-methyl-4(1*H*)-pyrimidinone	H_2SO_4: anal	1375
2,5,6-Triamino-3-methyl-4(3*H*)-pyrimidinone	HCl: > 300	2391,3669
4,5,6-Triamino-1-methyl-2(1*H*)-pyrimidinone	H_2SO_4: > 360	2390,2419
2,4,6-Triamino-5-pyrimidinecarbaldehye	> 250, ms, nmr, uv	5,1164,3897
2,4,6-Triamino-5-pyrimidinecarboxamide	211–213	1123
2,5,6-Triamino-4-pyrimidinecarboxamide	286–288	1123
4,5,6-Triamino-2-pyrimidinesulfinic acid	> 300	2441,2444
2,4,6-Triamino-5-pyrimidinesulfonic acid	> 310	1101
1,4,6-Triamino-2(1*H*)-pyrimidinethione	265	1355

2,5,6-Triamino-4(3*H*)-pyrimidinethione	270	1644,1649,3670,3671
4,5,6-Triamino-2(1*H*)-pyrimidinethione	anal	1298,2402,2444,3531
2,4,6-Triamino-5-pyrimidinol	> 300	1011
2,5,6-Triamino-4(3*H*)-pyrimidinone	HCl: > 340 (mono-), > 300 (di-); H_2SO_4: > 320	1057,1094,1288,1293,1301,1331, 2401,2427–2429,2436, 3672–3681
4,5,6-Triamino-2(1*H*)-pyrimidinone	> 360	1288,2390,2402,2433
2,4,5-Tribromo-6-ethoxypryimidine	—	3682
2,4,6-Tribromo-5-methylpyrimidine	136–137	1839
2,4,6-Tribromopyrimidine	112–113 or 113–115,124/5	1928,1971
2,4,6-Tribromo-5-pyrimidinecarbonitrile	212–214	3683
2,4,5-Trichloro-6-chloromethylpyrimidine	130–145/0.5	3655
2,4,6-Trichloro-5-chloromethylpyrimidine	112	3655
4,5,6-Trichloro-2-chloromethylpyrimidine	28–30	1958,2465
2,4,6-Trichloro-5-α-chlorovinylpyrimidine	39	786
2,4,6-Trichloro-5-cyanomethylpyrimidine	125	3655
2,4,5-Trichloro-6-ethoxypyrimidine	66	1727,2046
2,4,5-Trichloro-6-ethylpyrimidine	88/5	2151
2,4,6-Trichloro-5-ethylpyrimidine	74–76 or 75–77	1219,1228
2,4,6-Trichloro-5-ethylthiomethylpyrimidine	61–62	347
2,4,6-Trichloro-5-fluoropyrimidine	81/15	2153
2,4,5-Trichloro-6-guanidinopyrimidine	> 300	2174
4,5,6-Trichloro-2-guanidinopyrimidine	> 360	2174
2,4,5-Trichloro-6-isocyanatopyrimidine	81–82/0.1	1530
4,5,6-Trichloro-2-isocyanatopyrimidine	90–91/0.06	1530
2,4,5-Trichloro-6-isopropylpyrimidine	89/5	2151
2,4,6-Trichloro-5-isopropylpyrimidine	69–71	1875
4,5,6-Trichloro-2-isopropylpyrimidine	39	1875

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
4,5,6-Trichloro-2-methoxymethylpyrimidine	41–42	1761
2,4,6-Trichloro-5-methoxypyrimidine	67–68	2198
2,4,5-Trichloro-6-methylpyrimidine	20–21, 115–120/12, 245–247/760	1836,1943,1958,2273
2,4,6-Trichloro-5-methylpyrimidine	67–68, 136/25	1485,1735,3655
4,5,6-Trichloro-2-methylpyrimidine	68	1958
4,5,6-Trichloro-2-methylsulfonylpyrimidine	141	2153
2,4,6-Trichloro-5-methylthiopyrimidine	105–107/2	2471
4,5,6-Trichloro-2-methythiopyrimidine	60	2153
2,4,6-Trichloro-5-nitropyrimidine	56 or 57–58	2063,2307,3684
2,4,5-Trichloro-6-propylpyrimidine	98/5	2151
2,4,6-Trichloro-5-propylpyrimidine	30–32	1875
4,5,6-Trichloro-2-propylpyrimidine	65/0.75	1875
2,4,6-Trichloro-5-pyrimidinamine	116–117	2307
2,5,6-Trichloro-4-pyrimidinamine	161 to 171	2351,2491,3685
4,5,6-Trichloro-2-pyrimidinamine	236–237	2350
2,4,5-Trichloropyrimidine	73–74/3, 94–95/12	1827,1855,2209
2,4,6-Trichloropyrimidine	21–23 or 23–25 (89–93?), 94–95/10, 102/18	232,1213,1233,1855,2045,2287, 3301,3655(?),3686–3688
4,5,6-Trichloropyrimidine	49–51	1827
2,4,6-Trichloro-5-pyrimidinecarbaldehyde	186	2224
2,4,6-Trichloro-5-pyrimidinecarbonitrile	119 or 122–123	2063,2592,3689
2,5,6-Trichloro-4-pyrimidinecarbonitrile	80	2046
2,5,6-Trichloro-4-pyrimidinecarboxylic acid	120	2121
2,5,6-Trichloro-4(3*H*)-pyrimidinone	197	2046

2,4,6-Trichloro-5-trimethylsilylpyrimidine	41–42, M^+, nmr	6134
4,5,6-Triethoxy-2-pyrimidinamine	75–76	1149
2,4,5-Triethoxypyrimidine	33–34; HCl: 104	1814
2,4,6-Triethoxypyrimidine	10, 255–256/760	1771,2939,2948
2,4,6-Triethoxy-5-pyrimidinecarboxylic acid	138–140	1788
2,4,5-Triethyl-6-methylpyrimidine	crude: ir, ms, nmr	3896
2,4,6-Triethyl-5-methylpyrimidine	crude: ir, ms, nmr	3896
4,5,6-Triethyl-2-methylpyrimidine	pic: 101–102	1159
1,3,6-Triethyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione	81–82	2542
2,5,6-Triethyl-4-pyrimidinamine	183–184	3011
2,4,6-Triethylpyrimidine	120/80	2293
1,3,5-Triethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	liquid, anal, n_D^{25} 1.4855	2807
2,5,6-Triethyl-4(3*H*)-pyrimidinone	144	3011
2,4,5-Trifluoro-6-iodopyrimidine	25–25, 66–68/18	2555
2,4,5-Trifluoro-6-methoxypyrimidine	55–56/20	1728
2,4,5-Trifluoro-6-methylaminopyrimidine	122–123	1728
2,4,6-Trifluoro-5-methylpyrimidine	132–133/760	2093,3164
2,4,6-Trifluoro-5-nitropyrimidine	36–38	2063
2,4,5-Trifluoro-6-prop-2′-ynyloxypyrimidine	39–40, nmr	293
2,5,6-Trifluoro-4-pyrimidinamine	156–157 or 158	1727,1728
2,4,5-Trifluoropyrimidine	89–91/760	2555
2,4,6-Trifluoropyrimidine	59–60/180, 98–102/760	1727,1728,1843,2093,2454, 2558,3656,3690
4,5,6-Trifluoropyrimidine	crude	2555
2,4,6-Trifluoro-5-pyrimidinecarbonitrile	33–34	2063
2,5,6-Trifluoro-4(3*H*)-pyrimidinone	121 or 125–126	1727,1728
2,4,6-Trihydrazinopyrimidine	217–218	1754
2,4,6-Trimethoxy-5-methylpyrimidine	99–100, ir, nmr	6117

Pyrimidine	m.p. (°C), etc.	Ref.
2,4,6-Trimethoxy-5-nitropyrimidine	122–123	3691
2,4,6-Trimethoxy-5-pyrimidinamine	104–106, nmr, uv	1362,6196
4,5,6-Trimethoxy-2-pyrimidinamine	110 or 113–115	1007,3692
2,4,6-Trimethoxypyrimidine	50–52, or 53, 232/760, nmr	1349,2072,2526,2533,2802, 3688,3736,3756
4,5,6-Trimethoxypyrimidine	56–58	1360
2,4,6-Trimethoxy-5-pyrimidinecarbaldehyde	130–133, uv; oxime: 248–249; tsc: 223	1788,2075,3688,3897
2,4,6-Trimethoxy-5-pyrimidinecarbonitrile oxide	142 or 145–147	2075,2476
2,4,6-Trimethoxy-5-pyrimidinecarboxylic acid	207–209	1788
2,4,6-Trimethoxy-5-trimethylsilylpyrimidine	liquid, anal, ir, nmr	6117
2-Trimethylammoniopyrimidine	bromide: anal; chloride: 204–205; pic: 175–176	3554,3693
4-Trimethylammoniopyrimidine	chloride: 138; pic: 159–160	3554
1,3,4-Trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbaldehyde	121–122; $Me_2NN{=}$: 131–132, nmr; PhHNN=: 227–229, ir, nmr	2087,3835
1,3,4-Trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarbonitrile	—	794,3995
1,3,5-Trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonyl chloride	54–56	2669
1,3,*N*-Trimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide	196	904
1,3,4-Trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-5-pyrimidinecarboxylic acid	218–220, ir, nmr	3894
1,3,5-Trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarboxylic acid	212; H_2O: 203–205	1851,2669
2,4,5-Trimethyl-6-methylaminopyrimidine	94–96	2570
1,3,5-Trimethyl-6-methylamino-2,4(1*H*,3*H*)-pyrimidinedione	162–163	855,1139
1,2,6-Trimethyl-4-methylimino-1,4-dihydropyrimidine	pic: 166	3694
1,4,6-Trimethyl-2-methylimino-1,2-dihydro-5-pyrimidinecarbonitrile	HI: 203; pic: 161–162	923
4,5,6-Trimethyl-2-methylthiopyrimidine	51–52, 74/0.05	2995

3,5,6-Trimethyl-2-methylthio-4(3*H*)-pyrimidinone	85–86	891,892
1,3,6-Trimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione	149–150 or 153–154	1056,1693,1694,3995
1,4,6-Trimethyl-2-oxo-1,2-dihydro-5-pyrimidinesulfonic acid	221–223	3695
1,3,5-Trimethyl-6-propylamino-2,4(1*H*,3*H*)-pyrimidinedione	91	855
1,3,6-Trimethyl-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione	74–75	2489
1,4,6-Trimethyl-5-propyl-2(1*H*)-pyrimidinimine	HCl: 243; HI: 191; pic: 197	843
1,4,6-Trimethyl-5-prop-1′-ynyl-2(1*H*)-pyrimidinimine	HCl: 257; HI: 224	843
1,4,6-Trimethyl-5-prop-2′-ynyl-2(1*H*)-pyrimidinimine	HI: 195–196	843
2,4,6-Trimethyl-5-pyrimidinamine	116–118	651,3696, (cf. 3697)
4,5,6-Trimethyl-2-pyrimidinamine	206–207 or 208, ir, ms, nmr	2735,2912,3698,3723
2,4,5-Trimethylpyrimidine	107/12; pic: 198	1992
2,4,6-Trimethylpyrimidine	60/11, 68–72/12, 83/33, 84–87/45; 166/760 or 167–168/750, uv, nmr; $2H_2O$: 45 or 47; MeI: 257–258; pic: 145–146	238,382,1855,2099,2222,2467, 2571,2719,3439,3441,3626,3951
4,5,6-Trimethylpyrimidine	76/12	3302
2,4,6-Trimethyl-5-pyrimidinecarboxylic acid	205; NH_4: 162–165, ir, ms, nmr, uv	651
1,3,5-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	151–153 or 153–155, nmr, uv	812,963,1535,2492,2538,2768, 2770,2772,3699,3904
1,3,6-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	111 to 115 (106–107?)	698,1100,1148, 1863,1864,1943, 2495,2539–2542,2669,2779, 2791,3475,3700–3703
1,5,6-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	256–258 or 261–262 (172–174?)	1829,2792(?),3058
3,5,6-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedione	217 to 228, ir, nmr	130,891,1864,3058
2,4,6-Trimethylpyrimidine 1,3-dioxide	206–209	3626
1,3,6-Trimethyl-2,4(1*H*,3*H*)-pyrimidinedithione	127	3659,3704
2,5,6-Trimethyl-4-pyrimidinesulfonic acid	K: anal	2263

ALPHABETICAL LIST OF SIMPLE PYRIMIDINES (*Continued*)

Pyrimidine	m.p. (°C), etc.	Ref.
1,4,5-Trimethyl-2(1*H*)-pyrimidinethione	3-$MeHSO_4$: 198	1803
1,4,6-Trimethyl-2(1*H*)-pyrimidinethione	156 or 157	2697,3705
1,3,5-Trimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	88 or 89–90	1139,1391,2805,3706
1,2,6-Trimethyl-4(1*H*)-pyrimidinimine	HI: anal, nmr	7033
1,4,6-Trimethyl-2(1*H*)-pyrimidinimine	HCl: 244; HI: 274–275; pic: 169	1741,2114
2,3,5-Trimethyl-4(3*H*)-pyrimidinimine	HI: 244	2570
2,3,6-Trimethyl-4(3*H*)-pyrimidinimine	HI: 246	2570
3,5,6-Trimethyl-4(3*H*)-pyrimidinimine	HI: 244	2570
2,4,6-Trimethyl-5-pyrimidinol	152–154, nmr; H_2O: 90–94; pic: 160–161	7,2809,3758,3951
2,4,6-Trimethyl-5-pyrimidinol 1-oxide	193–195, nmr	21,3758
1,2,5-Trimethyl-4(1*H*)-pyrimidinone	175–176; HI: 114	1551
1,4,6-Trimethyl-2(1*H*)-pyrimidinone	63; 3-$MeHSO_4$: 147	1803,2249,2697,2811,2825
2,3,5-Trimethyl-4(3*H*)-pyrimidinone	28–30, 150–157/32; HCl: anal; HI: 180	1551,3326
2,3,6-Trimethyl-4(3*H*)-pyrimidinone	53–54 or 58–61; HI: 215	2701,3707,3708
2,5,6-Trimethyl-4(3*H*)-pyrimidinone	174 to 178	880,2359,2543,2722,2815,3709
4,5,6-Trimethyl-2(1*H*)-pyrimidinone	243, ms; H_2O: 243; HCl: 278	56,2358,2824,3660
2-Trimethylsiloxy-4-trimethylsilylaminopyrimidine	122–123	1792,3387
4-Trimethylsiloxy-2-trimethylsilylthiopyrimidine	crude	1689
3,5,6-Trimethyl-2-thioxo-1,2-dihydro-4(3*H*)-pyrimidinone	255–256 or 268–269	3058,3710,3711
1,3,*N*-Trimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxamide	174 or 178	2844,2909
1,3,6-Trimethyl-5-ureido-2,4(1*H*,3*H*)-pyrimidinedione	300	1695
2,4,6-Trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbaldehyde	330 or 340 (230?); dnp: 300–302	2128,2681,2862,2890,3541

2,4,6-Trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarbonitrile	> 360	2592,3712
2,4,6-Trioxo-1,2,3,4,5,6-hexahydro-5-pyrimidinecarboxamide	> 360	2592,2845,3713–3715
2,4,6-Tripropoxypyrimidine	178–180/20	1788
2,4,6-Trisacetoxymethylpyrimidine 1,3-dioxide	108	763
4,5,6-Trisbromomethyl-2-methylthiopyrimidine	106–107, nmr	6133
2,4,6-Trisbromomethylpyrimidine 1,3-dioxide	188	763
2,4,6-Trisdimethylaminopyrimidine	142–143	1731
2,4,6-Trissemicarbazidopyrimidine	—	3662
2,4,6-Trisethylthio-5-ethylthiomethylpyrimidine	42–43, nmr	347
2,4,6-Trismethylaminopyrimidine	pic: 232–235	1771
4,5,6-Trismethylaminopyrimidine	148–149; HI: 191–192	1764
2,4,6-Trismethylthio-5-nitropyrimidine	177–178, nmr	3988
2,4,6-Trismethylthiopyrimidine	114–116	958
2,4,6-Tristrimethylammoniopyrimidine	trichloride: —	3716
2,4,6-Tristrimethylsiloxypyrimidine	38–41	1829
2,4,6-Triureidopyrimidine	–	3662
6-Ureidomethyl-2,4(1*H*,3*H*)-pyrimidinedione	anal	701
6-Ureido-2,4-pyrimidinediamine	—	3662
5-Ureido-2,4(1*H*,3*H*)-pyrimidinedione	210 or 310	1171,1176,1943,2340,2846,
5-Ureido-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione	—	717,2663,3717,3718
5-Vinyl-2-pyrimidinamine	136, nmr	261
4-Vinylpyrimidine	56–58/10; pic: 125–130	2078
5-Vinylpyrimidine	86/45	1880
1-Vinyl-2,4(1*H*,3*H*)-pyrimidinedione	180–182 or 188–189, ir, nmr	378,726,1323,1722
5-Vinyl-2,4(1*H*,3*H*)-pyrimidinedione	> 230, nmr, uv	252,2039,3332,3719
6-Vinyl-2,4(1*H*,3*H*)-pyrimidinedione	> 350	1869
2-Vinylthiopyrimidine	62–63/1; MeI: 143	3145

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D. J. Brown
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Index

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