

THE PYRIMIDINES

SUPPLEMENT II

This is the sixteenth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Consulting Editors



THE PYRIMIDINES

Supplement II

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To
My Research Students
Past and Present
who taught me far more about pyrimidine
chemistry than I ever taught them:

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry "as readily accessible as possible", new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

The original volume, entitled *The Pyrimidines*, covered the literature published through 1957 and, subsequently, *The Pyrimidines, Supplement I* updated this coverage to 1967. The present volume, *The Pyrimidines, Supplement II*, continues this review process for the period 1968–1983, inclusive.

It is important to realize that *Supplement II* does not contain any information already recorded in the original volume or in *Supplement I*. Thus all three volumes must be used together in order to cover all the literature on any aspect of pyrimidine chemistry. Unfortunately, the two earlier volumes are now out of print but both can be obtained (at least for the present) as reprints from the Krieger Publishing Co., Inc., P.O. Box 9542, Melbourne, Florida, U.S.A., 32901.

To facilitate combined use of the three volumes, all section headings and tables in *Supplement II* include back references to the page numbers for corresponding sections or tables (if any) in the previous volumes; in such back references (as in *Beilstein*), page numbers of the original volume are preceded by *H* (for *Hauptwerk*) and those of *Supplement I* by *E* (for *Ergänzungswerk*).

Because of numerous complaints from users that the classified appendix tables of simple pyrimidines in the original volume and *Supplement I* were difficult to use effectively, such tables have been replaced in *Supplement II* by a single rather massive alphabetical table of simple pyrimidines described from 1968 to 1983. Although old fashioned in minor respects, the original nomenclature conventions (*H* 3) have been retained to assist in the combined use of all three volumes: In particular, it should be noted that all substituents are rendered as prefixes, the common tautomeric groups are rendered in their hydroxy or mercapto form, and “hydro” is considered as an alphabetically placed substituent. The original definition of a “simple pyrimidine” (*H* 501) has also been retained to regulate inclusion in the appendix table of pyrimidines; as before, references in that table are preceded by the letter(s) *H* and/or *E* when earlier information has also appeared in appropriate tables of the original volume and/or *Supplement I*, respectively. Except in a very few cases (indicated by inclusion of a *Chemical Abstracts* citation in the reference), all information in both text and tables has been gleaned from original publications, as flagged periodically in *Chemischer Informationsdienst*

and/or *Chemical Abstracts*. For obvious pragmatic reasons, patents have been ignored in general. As in *Supplement I*, references are given in a single list for simplicity. References prior to 4329 will be found in one or the other of the earlier volumes. The indexing conventions are similar to those outlined previously (*H* 677) and are summarized again immediately prior to the Index of this volume.

The origins of papers on pyrimidine chemistry are given below for the period 1968–1983. When compared with the figures for the previous decade, 1958–1967 (*E* ix), it is evident that the marked decrease in papers from the United States, the British Commonwealth, and to a lesser extent Germany, has been balanced by a phenomenal increase in papers from Japan and Russia, while other regional contributions have remained more or less static. Indeed, Japan now stands a very close second to the United States, and Russia is only just behind Germany.

United States of America	20.17%
Japan	18.60%
British Commonwealth (and India)	14.44%
Germany (East and West)	11.72%
Russia	11.21%
Eastern Europe	7.59%
France and Switzerland	5.78%
Netherlands and Belgium	3.72%
Austria	1.86%
Italy, Spain, and South America	1.76%
Scandinavia	1.32%
Others (Israel, China, Korea, etc.)	1.86%.

Many friends have assisted enormously in the preparation of this supplementary volume. Foremost are Drs. Bill Cowden, Russell Evans (kindly assisted by Mr. H. K. Edwards), and David Fenn, who completed appropriate sections on pyrimidine *N*-oxides, reduced pyrimidines, and the nmr spectra of pyrimidines, respectively. My colleagues, Drs. Wilf Armarego, Gordon Barlin, Doug Perrin, and Ernest Spinner never failed to proffer excellent advice. Kenya Mori assisted frequently in the translation of Japanese papers. Kerry McAndrew, Abira Hassan, and Barbara Cronin gave invaluable assistance in the library, in checking the typescript, and in other ways. Despite ill health, Janice White cheerfully prepared the greater part of the typescript from my appalling handwriting, a task to which

Diane Dick, Rosemary Enge, and Caroline Cobban also contributed as time permitted. To the above good people and to my wife for her patience during the years of weekend writing, I offer my sincere thanks.

D. J. BROWN

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Canberra, Australia
April 1985*

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CHAPTER I

Introduction to the Pyrimidines (*H 1, E 1*)

Some important and useful advances made in pyrimidine chemistry since 1970 are included in this chapter. Hence it is broadly supplementary only to the fourth section of the original Ch. I. Moreover, no attempt is made herein to cover new or improved primary syntheses, which are highlighted in Ch. II and III of this supplement. Several brief but general reviews of pyrimidine chemistry have appeared recently in English,^{6326, 6330} Italian,⁶¹⁸² and German.⁶¹⁸³

4. General Summary of Pyrimidine Chemistry (*H 9, E 2*)

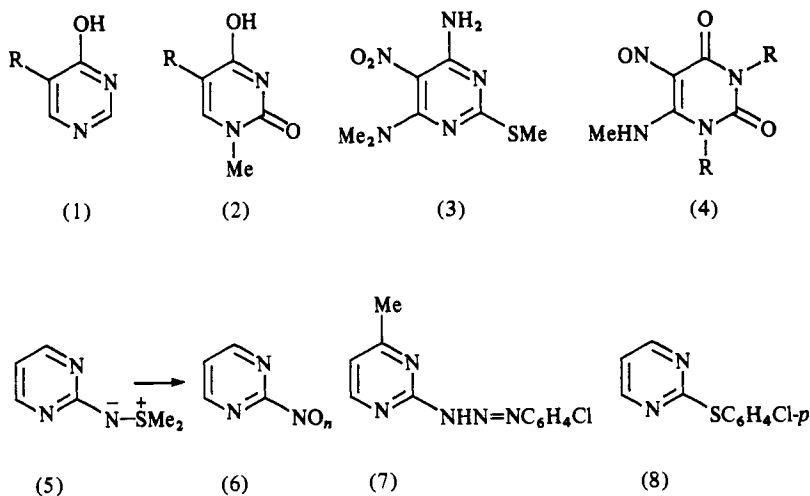
A. Electrophilic Substitution (*H 10, E 2*)

(1) Nitration and Nitrosation (*H 10, E 2*)

(Ch. V, Sects. 1 and 2)

The successful nitration of 2-hydroxypyrimidine by potassium nitrate in sulfuric acid at 100°, previously reported (*E 96*) from preliminary communications, has now been confirmed and extended to 4-hydroxypyrimidine (1, R = H),⁵⁴¹¹ from which 4-hydroxy-5-nitropyrimidine (1, R = Me; 40% yield) was so made. In less difficult cases, a novel and effective procedure has been reported; the action of nitronium tetrafluoroborate in sulfolane at 20° converted 1-methyluracil (2, R = H) into its 5-nitro derivative (2, R = NO₂) in excellent yield, and analogues were made similarly.⁵⁵¹⁶ More and more examples of nitration in the presence of labile groups have emerged, as exemplified in the direct formation of 4-amino-6-dimethylamino-2-methylthio-5-nitropyrimidine (3) by using potassium nitrate/sulfuric acid at 0° (42%),⁴⁶¹⁷ or of 4-chloro-2,6-dimethoxy-5-nitropyrimidine (76%) by using fuming nitric

acid/sulfuric acid, initially at 5° and then at 80°. ⁵⁹⁹⁴ Work has continued on the nitration of phenylpyrimidines in the benzene ring, ^{5441, 5662, 5663, 6155} but it is still impossible to forecast the position(s) of nitration.



The poor yields obtained by regular nitrosation in aqueous media to afford 1,3-dialkyl-1,2,3,4-tetrahydro-6-methylamino-5-nitroso-2,4-dioxypyrimidines (4) have been improved dramatically by using isoamyl nitrite/ethanol; in this way, the 1,3-dicyclohexyl homologue (4, R = C₆H₁₁) was obtained in 42% yield. The oxidation of nitroso- to nitropyrimidines has continued to prove valuable. Indeed, the conversion of 2-amino- into 2-*S,S*-sulfimidopyrimidine (5) followed by oxidation to 2-nitrosopyrimidine (6, *n* = 1) and further oxidation by ozone to 2-nitropyrimidine (6, *n* = 2) has represented a landmark in pyrimidine chemistry, being the first 2/4-nitropyrimidine ever made. ⁶²⁶⁷

(2) Diazo Coupling (*H* 11)

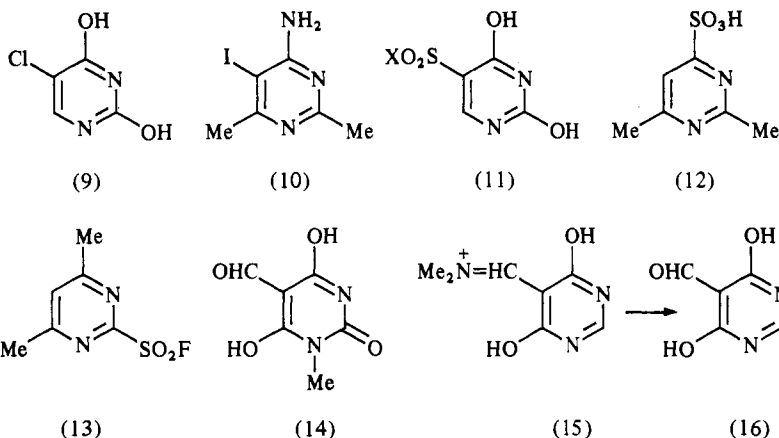
(Ch. V, Sect. 3.A)

Besides innumerable examples of diazo coupling at the 5-position and a few at the 4-position or on an activated methyl substituent, it has been pointed out that diazonium salts can attack amino or mercapto groups if the normal sites are insufficiently activated. This is seen in the formation of 2-*p*-chlorophenyldiazoamino-4-methylpyrimidine (7) or 2-*p*-chlorophenylthiopyrimidine (8). ⁶⁰⁹⁰

(3) *Halogenation (H 11, E 2)*

(Ch. VI, Sect. 2.A)

The use of sulfuryl chloride and even thionyl chloride for 5-chlorinations has been expanded greatly to give excellent yields, for example, 5-chloro-2,4-dihydroxypyrimidine (9) by sulfuryl chloride/aluminum chloride in acetic acid/acetic anhydride (>90%),⁴⁷³⁶ or 4-amino-5-chloro-6-hydroxy-2-phenylpyrimidine (neat thionyl chloride at 130°; 66%).⁴⁹⁶³ Iodination by iodine in the presence of hydrogen peroxide (to reoxidize the hyriodic acid formed) has been effective in preparing 4-amino-5-iodo-2,6-dimethylpyrimidine (10) (97%) and analogues.⁴⁵⁰⁶

(4) *Sulfonation (H 11, E 2)*

(Ch. VIII, Sect. 4.A)

The process of 5-sulfonation has fallen into disuse, although 5-chlorosulfonyl- (11, X = Cl) and 5-fluorosulfonyl-2,4-dihydroxypyrimidine (11, X = F) have been made by treating uracil with the appropriate halogenosulfonic acid at 160°.^{4798, 6074} The 2/4-sulfo-pyrimidines can be made either by displacement of a chloro substituent with sodium sulfite to give, for example, 2,4-dimethyl-6-sulfo-pyrimidine (12),⁵⁶⁶⁷ or by permanganate oxidation of a mercaptopyrimidine to give, for example, 5-methyl-2-sulfo-pyrimidine (65%).⁵⁶⁶⁹ Such oxidation with chlorine in the presence of potassium hydrogen difluoride gives directly 2-fluorosulfonyl-4,6-dimethylpyrimidine (13) and related compounds.⁵⁶⁶⁹

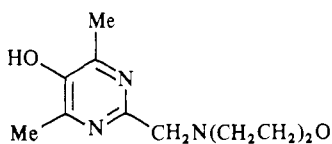
(5) *Attack by Chloroform (H 11)*

(Ch. XI, Sect. 5.A)

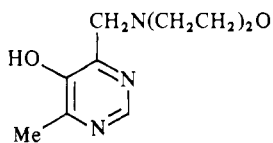
The Reimer–Tiemann synthesis has been used successfully to make 2-amino-5-formyl-4-hydroxy-6-methylpyrimidine (63%).⁴⁵¹¹

(6) *Other Electrophilic Attacks (H 11, E 3)*

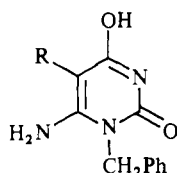
Direct 5-formylation (Ch. XI, Sect. 5.A) by boiling in triethyl orthoformate has been used to make 5-formyl-1-methylbarbituric acid (14).⁵⁹⁰⁰ Vilsmeier reagents have been used more extensively in this regard to give, for example, 5-dimethylimmoniomethyl-4,6-dihydroxypyrimidine (15) and thence, by hydrolysis, 5-formyl-4,6-dihydroxypyrimidine (16).⁵⁸¹⁹ The same reagent is equally applicable to the formylation of active methyl groups [Ch. IV, Sect. 2.C(8)]. The Mannich reaction may also occur at either a nuclear position or at a methyl substituent [Ch. IV, Sect. 2.C(7)] to convert, for example, 5-hydroxy-4,6-dimethylpyrimidine into 5-hydroxy-4,6-dimethyl-2-morpholinomethyl- (17) or 5-hydroxy-4-methyl-6- β -morpholinoethylpyrimidine (18) according to conditions.⁶¹⁵⁰



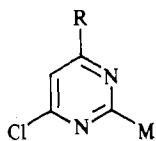
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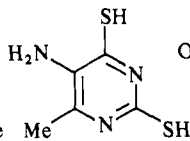
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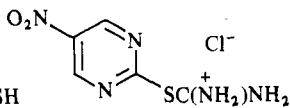
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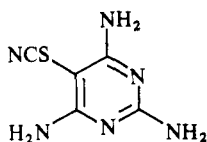
(20)



(21)



(22)



(23)

C. Nucleophilic Metatheses (*H* 12, *E* 3)(1) Replacement of Halogens (*H* 13, *E* 3)

(Ch. VI, Sects. 5 and 6)

(a) *By Amino or Substituted-Amino Groups* (*H* 13, *E* 4). Two kinetic studies of such aminolyses have been reported. The first involved piperidinolysis of a variety of substituted chloropyrimidines, the rates for which showed good correlations with σ_I and σ_R constants derived from the benzene series,⁴⁷⁶² the second presented data for the aminolysis of corresponding chloro-, bromo-, iodo-, and fluoropyrimidines indicating that the fluoropyrimidines reacted 60–200 times faster than the others, which differed less than threefold among themselves.^{5664, 5676} A great many novel preparative aminolyses have been reported but they have revealed little new in principle or technique. Although aminolysis of 5-halogenopyrimidines usually needs vigorous conditions, this is not always so; 6-amino-1-benzyl-5-bromouracil (19, R = Br) reacted with aqueous methylamine at 20° to give the 5-methylamino analogue (19, R = NHMe) in 95% yield.⁴⁹¹⁴ Moreover, in some cases the amino group may enter the ring *adjacent* to the position of the leaving halogen. For example, 5-chloropyrimidine with diethylamine at greater than 100° gave 4-diethylaminopyrimidine and other products,⁴⁴⁸³ probably *via* a dehydropyrimidine intermediate.⁶⁰⁹⁴

(b) *By Alkoxy Groups* (*H* 13, *E* 4). Rates have been measured for the methoxylation of several 4-chloropyrimidines; 4,6-dichloropyrimidine reacted 16 times faster than 4-chloropyrimidine because of electron-withdrawal by the second substituent. In contrast, 4-chloro-6-methyl- and 4-chloro-6-methoxypyrimidine reacted, respectively, at 0.6 and 0.03 times the rate for 4-chloropyrimidine, because of electron-release by the additional substituent.⁴⁶⁰³ The many preparative alkoxylation with alcoholic alkoxides have added little new, but alkoxylation can also be carried out under acidic conditions. Thus, 4-chloro-5-fluoro-2-hydroxy- gave 5-fluoro-2-hydroxy-4-methoxypyrimidine on treatment with methanolic hydrogen chloride at 20°.⁴⁸⁹⁵ Work has continued on the preferential alkoxylation of di- and trihalogenopyrimidines with moderate success, but surprises still occur as in the gentle ethoxylation of 2,4,5-trichloro-6-cyanopyrimidine, which gave 2,4,5-trichloro-6-ethoxypyrimidine by preferential displacement of the cyano group.⁵⁹⁷¹

(c) *By Hydroxy Groups* (*H* 14, *E* 5). Direct acidic hydrolysis of di- and trihalogenopyrimidines can often be selective, as in the formation of 4-chloro-6-hydroxy-2-methylpyrimidine (20, R = OH) from the di-

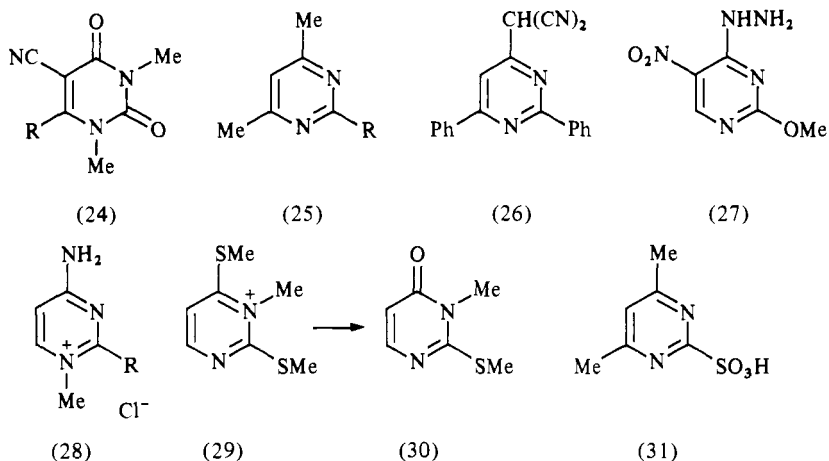
chloro analogue (20, R = Cl) with hot 3 M hydrochloric acid.⁵⁰¹⁵ Alkaline hydrolysis can also be selective but more interesting is the catalytic effect of added hydrogen peroxide. For example, complete hydrolysis of 2,4-dichloro-6-methylpyrimidine by aqueous sodium hydroxide at 20° took about 27 h but, under comparable conditions with the addition of hydrogen peroxide, the reaction was complete in 5 min, presumably because of participation by the highly nucleophilic hydroperoxy ion.⁴⁸⁵⁵

(d) *By Alkylthio or Arylthio Groups (H 14, E 5).* Preferential alkylthioxylation of 5-bromo-2,4-dichloropyrimidine has been achieved by using sodium methanethioxide (1 mol) in ether at 0°. ⁴⁷⁰⁶ More important are numerous examples of 2-, 4/6-, and 5-arylthioxylation because arylthiopyrimidines are not readily available by other means.

(e) *By Mercapto Groups (H 14, E 5).* Sodium hydrogen sulfide has been widely used to convert chloro- into mercaptopyrimidines, especially when reduction of a nitro or other substituent can be done at the same time, as in the formation of 5-amino-4,6-dimercapto-2-methylpyrimidine (21) from the dichloronitro analogue in 95% yield.⁵⁶⁸⁹ Use of the indirect route *via* a thiouronio intermediate has shown a strong revival of recent years; it is capable of several variations, as in the transformation of 2-chloro-5-nitropyrimidine by thiourea into 5-nitro-2-thiouroniopyrimidine chloride (22) and thence, by treatment with methyl iodide/alkali, into 2-methylthio-5-nitropyrimidine directly.^{6372, 6423} Both methods are applicable to 5-halogenopyrimidines under appropriately enhanced conditions.

(f) *By Sulfo and Related Groups (H 15, E 6).* New work on the displacement of chloro by sulfo substituents using sodium sulfite is mentioned in Sect. A(4) above. Even quite deactivated bromo substituents can be replaced by a thiocyanato group; 2,4,6-triamino-5-bromopyrimidine and ethanolic potassium thiocyanate under reflux gave 2,4,6-triamino-5-thiocyanatopyrimidine (23),⁵²⁴⁴ but too vigorous conditions must be avoided to preclude rearrangement into the corresponding isothiocyanates (Ch. XI, Sect. 7.B).

(g) *By Other Groups (E 6).* Although a cyano group may sometimes be introduced by the reaction of cyanide ion with an active halogenopyrimidine, as in the formation of 4,5-dicyano- (24, R = CN) from 4-chloro-5-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (24, R = Cl) by stirring with sodium cyanide in dimethyl sulfoxide,⁴⁹⁹⁷ it is usually better to employ another leaving group, such as trimethylammonio or sulfo; 5-halogenopyrimidines with cuprous or potassium cyanide are often more successful, but occasionally *cine*-substitution can occur.⁴⁹³⁷ The important replacement of an halogeno substituent



by an alkyl, alkenyl, or alkynyl group (which may or may not bear an additional substituent) is discussed in Ch. IV, Sect. 2.A and in Ch. VI, Sect. 5.I. Thus, the reaction of ethyl magnesium bromide with 2-chloro-4,6-dimethylpyrimidine (25, R = Cl) to give 2-ethyl-4,6-dimethylpyrimidine (25, R = Et) was improved greatly by the addition of a nickel phosphine complex;⁵⁰⁹⁶ 2-iodo-4,6-dimethylpyrimidine (25, R = I) and styrene (in the presence of triethylamine and palladium) gave 4,6-dimethyl-2-styrylpyrimidine (25, R = CH:CHPh),⁶³⁰¹ and the 2-chloro substrate (25, R = Cl) with hexyne gave 2-hex-1'-ynyl-4,6-dimethylpyrimidine (25, R = C:CBu);⁶³⁵³ and 4-chloro-2,6-diphenylpyrimidine with sodiummalononitrile gave 4-dicyanomethyl-2,6-diphenylpyrimidine (26).⁴⁸¹⁵ Some of these reactions were applicable to 5-halogenopyrimidines.

(2) Replacement of Alkoxy, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, and Sulfo Groups (H 15, E 6)

The relatively sluggish replacement of alkoxy groups can be advantageous, for example when preferential aminolysis of a dialkoxy-pyrimidine is desired. Thus, 2,4-dimethoxy- gave 4-hydrazino-2-methoxy-5-nitropyrimidine (27) in greater than 80% yield by refluxing in ethanolic hydrazine⁵⁶⁶⁰ (Ch. VII, Sect. 7.C). Alkaline hydrolysis of dialkoxy-pyrimidines is also useful in a similar respect (Ch. VII, Sect. 1.E).

Under similar conditions, alkylthio groups are displaced more slowly than alkoxy groups. However, on activation by a nitro group or by quaternization at a ring nitrogen, alkylthio becomes a highly active

leaving group. For example, 4-amino-1-methyl-2-methylthiopyrimidinium chloride (28, $R = SMe$) underwent ammonolysis to 2,4-diamino-1-methylpyrimidinium chloride (28, $R = NH_2$) by stirring with methanolic ammonia at 25° ⁴⁴⁹⁰ (see also Ch. VIII, Sect. 2.C). Likewise, preferential 6-hydrolysis of 1-methyl-2,6-bismethylthiopyrimidinium iodide (29) occurred in dilute alkali at 25° to give 1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine (30), which was no longer quaternized and therefore relatively stable to further hydrolysis.⁵⁶⁶⁵

Pyrimidine sulfones and sulfoxides undergo displacement reactions at rates comparable with those for the corresponding chloropyrimidines. They have been so used mainly in the formation of hydroxy- and alkoxy-pyrimidines (Ch. VII, Sects. 1.F and 4.C), but also as substrates for aminolyses, in the formation of nitriles, and for several other displacement reactions (Ch. VIII, Sect. 5.B).

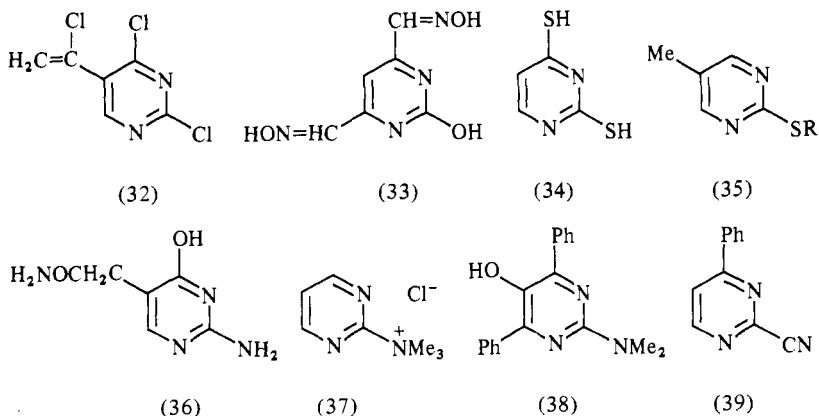
Now that 2- and 4/6-sulfopyrimidines can be made with ease (Ch. VIII, Sect. 4.A) from chloro- to mercaptopyrimidines, their use as substrates will probably increase quite dramatically. Examples are the *hydrolysis* of 2,4-dimethyl-6-sulfo- to 4-hydroxy-2,6-dimethylpyrimidine (80%);⁵⁶⁶⁷ the *aminolysis* of 1,2-dihydro-1-methyl-2-oxo-4-sulfo- to 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (93%) at 25° ;^{6098, 6099} and the *hydrazinolysis* of 4,6-dimethyl-2-sulfopyrimidine (31) (or its 2-fluorosulfonyl, 2-sulfamoyl, or 2-*N*-aminosulfamoyl analogue) to 2-hydrazino-4,6-dimethylpyrimidine under mild conditions;⁵⁶⁶⁹ and other reactions such as that of 2-fluorosulfonyl-5-methylpyrimidine with methanolic *sodium azide* at 25° to give 2-azido-5-methylpyrimidine (55%)⁵⁶⁶⁹ (Ch. VIII, Sect. 4.B).

D. Other Metatheses (*H* 16, *E* 7)

(1) *Hydroxy- to Chloropyrimidines* (*H* 16, *E* 7)

(Ch. VI, Sect. 1)

Most conversions of 2- or 4/6-hydroxypyrimidines into the corresponding chloropyrimidines continue to be done in an excess of phosphoryl chloride, if necessary with the addition of *N,N*-diethylaniline in molar or submolar ratio to the substrate. For many years the addition of phosphorus pentachloride has been considered a last resort, but recently it has proven advantageous in several quite simple cases.⁶³⁷⁷ Although the presence of amino groups is no longer considered any bar to the use of phosphoryl chloride, some other groups can be affected. For example, 5-acetyl-2,4-dihydroxypyrimidine gave 2,4-dichloro-5-



α -chlorovinylpyrimidine (32);⁵³²⁹ 5-carboxy-2,4-dihydropyrimidine gave 2,4-dichloro-5-chlorocarbonylpyrimidine;⁵⁴⁶² 5-carbamoyl-4-hydroxy- gave 4-chloro-5-cyano-2-phenylpyrimidine;⁵⁵⁸² and the dioxime, 2-hydroxy-4,6-bishydroxyiminomethylpyrimidine (33), gave 2-chloro-4,6-dicyanopyrimidine.^{4820, 5284}

Phosphoryl bromide, with or without a diluent such as phosphorus tribromide or toluene,⁵⁶⁶⁴ has been used quite widely to make 2- or 4/6-bromopyrimidines, but there is no way to produce fluoro or iodo analogues by similar means.

(2) *Hydroxy- to Mercaptopyrimidines (H 16, E 8)*

(Ch. VII, Sect. 6.B)

Direct thiation of 2- or 4/6-hydroxypyrimidines with pure phosphorus pentasulfide in pyridine or a picoline is now widely applicable, although 2-hydroxypyrimidines are more resistant. The presence of an amino group no longer appears to be disadvantageous since the advent of pyridine in place of xylene or tetralin as the usual medium. Complete thiation of uracil to 2,4-dimercaptopyrimidine (34) is best carried out with phosphorus pentasulfide in tetramethylene sulfone (sulfolane) to give a 97% yield.⁴⁸⁴² Lawesson's reagent offers an excellent means to thiate 2-hydroxy- or 2-oxypyrimidines.⁶⁴⁵⁹

(3) *Mercapto- to Hydroxypyrimidines (H 17, E 8)*

Although direct hydrolysis of mercaptopyrimidines is seldom possible, three indirect routes may be used: (1) *S*-alkylation followed

by hydrolysis, (2) oxidation to a sulfopyrimidine followed by hydrolysis, and (3) *S*-alkylation followed by oxidation to a sulfone followed by hydrolysis. All three methods have been used recently but the first most extensively, as in the conversion of 2-mercapto- (35, R = H) into 2-carboxymethylthio- (35, R = CH₂CO₂H) into 2-hydroxy-5-methylpyrimidine (65%).⁴³⁸⁴

(4) *Mercapto- to Aminopyrimidines* (H 17, E 8)

(Ch. VIII, Sect. 1.D)

Although it is usually better to convert a mercapto- into an alkylthio- or alkylsulfonylpyrimidine prior to aminolysis, direct aminolysis of most 4-mercaptopyrimidines is relatively easy and offers a facility for preferential aminolysis of 2,4-dimercapto- to 4-amino-2-mercaptopyrimidines, a most useful process. However, in appropriate cases and under sufficiently vigorous conditions, 2-mercapto groups may also be displaced by amines as illustrated in the conversion of 5-ethoxycarbonylmethyl-4-hydroxy-2-mercaptopyrimidine into 2-amino-5-carbamoylmethyl-4-hydroxypyrimidine (36) by heating in ethanolic ammonia at 120°. ⁵⁹⁷³

(5) *Amino- to Hydroxypyrimidines* (H 17, E 9)

(Ch. VII, Sects. 1.D and 2)

The direct hydrolysis of a 2- or 4/6-aminopyrimidine requires quite vigorous acidic or alkaline conditions, except for trimethylammoniopyrimidines, which need only mild conditions, as indicated in the conversion of 2-trimethylammoniopyrimidine chloride (37) into 2-hydroxypyrimidine by dilute alkali at 20° for 5 min;⁵³⁴² the alternative procedure is treatment with nitrous acid, which may also be used with 5-aminopyrimidines to make, for example, 2-dimethylamino-5-hydroxy-4,6-diphenylpyrimidine (38).⁶¹⁴⁷

(6) *Amino- to Halogenopyrimidines* (H 18, E 9)

(Ch. VI, Sects. 1.C, D, F)

The conversion of 2-amino- into 2-chloropyrimidine by hydrochloric acid/sodium nitrite has been improved by adding an excess of chloride ion as lithium chloride;⁴³⁸² although 4-amino groups have not

been found amenable to such treatment in the past, the use of nitrous acid/cuprous chloride converted 4,6-diamino- into 4,6-dichloropyrimidine.⁴⁶⁶³ The nitrous acid/halide ion method has now been used to make 2-bromo- and 2-fluoropyrimidines. The latter preparation is particularly effective when fluoroboric acid is used instead of sodium fluoride as a source of fluoride ion.⁵⁶⁷⁶

(7) *Replacement of Trimethylammonio Groups (H 18, E 9)*

(Ch. IX, Sect. 8)

Although the trimethylammonio substituent acts as a good leaving group for all manner of nucleophiles, relatively little use has been made of it recently except for making fluoropyrimidines (Ch. VI, Sect. 1.F) or cyanopyrimidines, for example, 2-cyano-4-phenylpyrimidine (39) by using potassium cyanide in dimethyl sulfoxide at room temperature.⁶⁰⁴⁰ It is important in all such replacements to avoid high temperatures, which induce loss of methyl chloride from the quaternary group with the formation of the corresponding dimethylamino derivative, useless as a substrate.⁵³⁹³

(8) *Interchange of Halogen Substituents (E 10)*

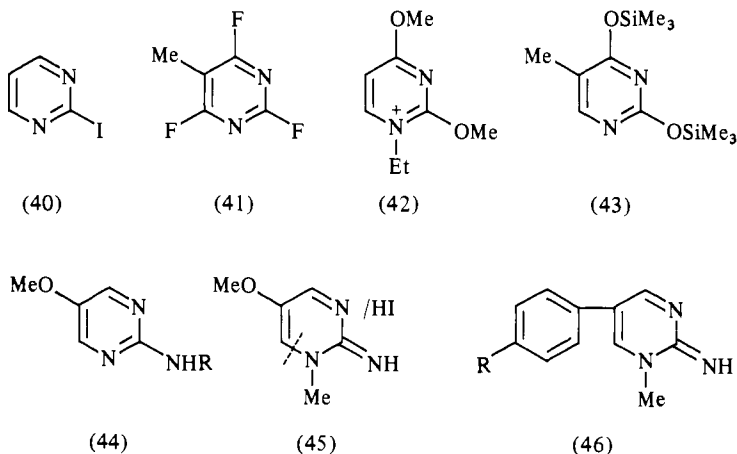
(Ch. VI, Sects. E and F)

All 2- or 4/6-iodopyrimidines are still made only from their chloro or bromo analogues. Thus, treatment of 2-chloro- or 2-bromopyrimidine with hydriodic acid at 5° gave 2-iodopyrimidine (40);⁵⁶⁷³ variations suited to analogous interchanges include hydriodic acid at 25°,⁶⁰⁴¹ hydriodic acid in aqueous acetic acid,⁵⁷⁶¹ hydriodic acid/sodium iodide in refluxing acetone,⁵⁶⁹³ and sodium iodide/dimethylformamide on the steam bath.⁴⁶⁵⁰ In contrast, the conversion of chloro- into fluoropyrimidines requires much more vigorous conditions, as illustrated in the formation of 2,4,6-trifluoro-5-methylpyrimidine (41) using potassium fluoride in dimethylformamide at 140°.⁴⁵²⁶

(9) *Hydroxy- to Aminopyrimidines (New)*

(Ch. VII, Sect. 6.E)

The conversion of hydroxy- into aminopyrimidines is usually done *via* a derived chloro-, alkylthio-, or alkoxy pyrimidine. However, the semi-direct aminolysis of hydroxypyrimidines is now possible, providing



the substrate and product can withstand the required conditions. For example, uracil and phosphoric trisdimethylamide at 235° gave 2,4-bisdimethylaminopyrimidine (78%) and several other phosphoric and phosphorous amides have been used successfully.^{4844, 4850}

E. Addition Reactions (*H* 18, *E* 10)

(1) *Quaternization; Dimroth Rearrangement* (*H* 18, *E* 10) (Ch. X, Sects. 1.A and 2)

The "quaternization" of an hydroxypyrimidine to eventually give an *N*-alkylated oxypyrimidine, has continued to be used extensively. Much of the work being reported is mundane and repetitive, especially in respect of uracil derivatives. Indeed, in some cases the site of alkylation has been assumed by analogy, instead of being proven experimentally. The classical Hilbert–Johnson reaction, illustrated in the conversion of 2,4-dimethoxypyrimidine by ethyl iodide into 1-ethyl-1,2-dihydro-4-methoxy-2-oxypyrimidine *via* the (unisolated) quaternary intermediate (42),⁵⁴⁹⁰ has been extended. Thus, the "Silyl Hilbert–Johnson" reaction is based on the ability to *O*-trimethylsilylate hydroxypyrimidines to give trimethylsilyloxypyrimidines, which act as admirable substrates. For example, 2,4-dihydroxy-5-methylpyrimidine was converted easily into 5-methyl-2,4-bistrimethylsilyloxypyrimidine (43), which reacted with propyl bromide at room temperature to give 5-methyl-1-propyluracil in good yield.⁵⁶⁴⁶

The quaternization of 2- or 4/6-aminopyrimidines gives *N*1- or *N*3-alkylated iminopyrimidines, some of which undergo Dimroth rearrange-

ment in alkali to give the corresponding 2- or 4/6-alkylaminopyrimidines. For example, 2-amino-5-methoxypyrimidine (44, R = H) gave 1,2-dihydro-2-imino-5-methoxy-1-methylpyrimidine hydriodide (45) which rearranged into 5-methoxy-2-methylaminopyrimidine (44, R = Me).⁵⁶⁶² A second review of Dimroth rearrangement appeared in 1970;⁴⁴⁹⁶ subsequently, rate studies on the rearrangement of a series of 1,2-dihydro-2-imino-1-methyl-5-(*p*-substituted-phenyl)pyrimidines (46) showed good correlation with σ_p values for the substituents.⁵⁶⁶² Similar rate studies on a series of *C*-alkylated 1,6-dihydro-6-imino-1-methylpyrimidines revealed considerable and logical differences according to the nature and position(s) of the *C*-alkyl group(s).⁵⁶⁷⁹

(2) Formation of *N*-Oxides (*H* 19, *E* 11)

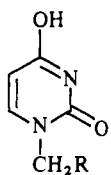
(Ch. X, Sect. 4)

A steady trickle of reports on pyrimidine *N*-oxides has continued. A good general method for determining the position of *N*-oxidation in unsymmetrical pyrimidine *N*-oxides is still outstanding but continuing efforts to use ¹H-, ¹³C-, and ¹⁵N-nmr techniques for this purpose (see also Ch. XIII, Sect. 3.E) are promising.

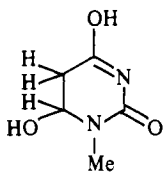
(4) Photohydrates and Photodimers (*H* 20, *E* 11)

(Ch. VII, Sect. 8)

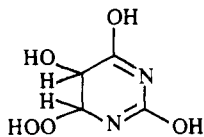
The photochemistry of thymine, uracil, and other natural pyrimidines was reviewed in great detail in 1976;⁵²²⁸ much of the work appearing currently deals with unnatural pyrimidines related thereto. For example, irradiation of 1-carboxymethyluracil (47, R = CO₂H) in aqueous solution caused both *photohydration* and *photodecarboxylation* to afford 5,6-dihydro-6-hydroxy-1-methyluracil (48) and 1-methyluracil (47, R = H), respectively.⁵²⁰⁴ The γ -irradiation of thymine in aerated aqueous solution is now known to give 4,5-dihydro-4-hydroperoxy-2,5,6-trihydroxy-5-methylpyrimidine (49),⁵²⁰⁹ a substance that is highly mutagenic in a bacterial system. In addition to the well-known cyclobutane-dimers, irradiation of thymine in frozen aqueous solution is now known to produce several "nose-to-tail" dimers of biological importance,⁵¹⁹⁹ which are substituted bipyrimidines; many new cyclobutane dimers from unnatural pyrimidines have been described.



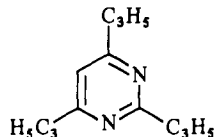
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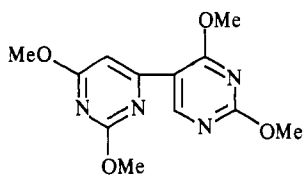
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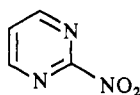
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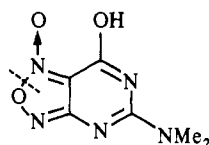
(50)



(51)



(52)



(53)

(5) Addition of Metal Alkyls (*H* 20, *E* 12)

Cyclopropyllithium underwent addition to pyrimidine to afford, after permanganate oxidation, a mixture of 2- and 4-cyclopropylpyrimidine; repetitions of the treatment eventually produced 2,4,6-tricyclopropylpyrimidine (50).⁶⁰⁵¹ A complicated but useful type of reaction is illustrated in the treatment of 5-bromo-2,4-dimethoxypyrimidine with butyllithium followed by carbon dioxide to give the unsymmetrical 2,2',4',6-tetramethoxy-4,5'-bipyrimidine (51).⁴⁷⁰⁰ Analogous examples have been reported (see Ch. VI, Sect. 6.B).⁶¹⁸⁰

(6) Addition of Amines (*E* 13)

Relatively little has been reported in the addition of amines to pyrimidines, but the reaction of pyrimidine and alkylpyrimidines with hydrazine and methylhydrazine to afford pyrazole and appropriate alkylated pyrazoles has now been fully documented.⁴⁶⁶⁸

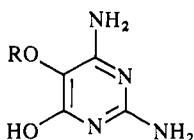
F. Oxidative Reactions (*H* 20, *E* 13)

The oxidation of nitroso- to nitropyrimidines (Ch. V, Sect. 1.A) has been used quite widely; besides the oxidation of 2-nitroso- to 2-

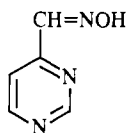
nitropyrimidine (52) by ozone,⁶²⁶⁷ other nitrosopyrimidines have been oxidized successfully by hydrogen peroxide/trifluoroacetic acid,⁵⁶⁴⁷ and by nitrous acid/sulfuric acid.⁴⁹⁷² An "oxidative primary synthesis" is represented in the oxidation of 5-dimethylamino-7-hydroxy[1,2,5]-oxadiazolo[3,4-*d*]pyrimidine 1-oxide (53) to 2-dimethylamino-4-hydroxy-5,6-dinitropyrimidine by manganese dioxide/dimethylformamide.⁶²⁹³ The useful oxidation of mercapto- to sulphopyrimidines is mentioned in Sect. 4.A(4) above. Oxidation of alkylthio- to alkylsulfonylpyrimidines (usually by peroxy acids) is even more useful because it converts a sluggish into an excellent leaving group for nucleophilic displacements (Ch. VIII, Sect. 2.C).

The oxidation of alkyl-, hydroxyalkyl-, alkenyl-, and alkynylpyrimidines to pyrimidine aldehydes, ketones, and carboxylic acids (by selenium dioxide, permanganate, ozone, etc.) is covered in Ch. IV, Sect. 2.C.

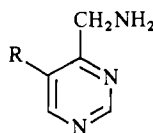
The introduction of a 5-hydroxy group by the Elbs persulfate oxidation has been studied again after many years of neglect (Ch. VII, Sect. 2); 2,4-diamino-5,6-dihydroxypyrimidine (divicine; 54, R = H) was so made *via* the isolated sulfo-oxy intermediate (54, R = SO₃H),⁴⁸⁶⁰ and the substituent requirements in the substrate for such oxidation have been studied carefully.⁶³⁷³



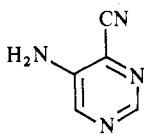
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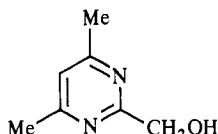
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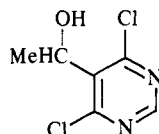
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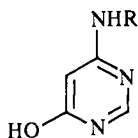
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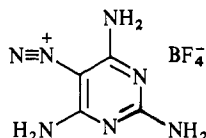
(58)



(59)



(60)



(61)

G. Reductive Reactions (*H* 21, *E* 13)(1) *Nuclear Reduction* (*H* 21, *E* 13)

The relatively small amount of material on nuclear reduction of pyrimidines is covered in Ch. XII, Sects. 1–3.

(2) *Reductive Removal of Groups* (*H* 22, *E* 14)

The classical reductive methods of dehalogenation and desulfurization have been used very widely. Dehalogenation by hydrogenolysis over palladium (in the presence of a base) is convenient and effective but shows no selectivity in respect of the kind or position of the halogen(s). Zinc dust does show selectivity towards 4-halogeno groups, and hydriodic acid is applicable only to 2-halogen removal⁵⁶⁸³ (Ch. VI, Sect. 5.A).

Desulfurization of mercapto- or alkylthiopyrimidines by Raney nickel in aqueous ammonia or ethanol (Ch. VIII, Sects. 1.D, 2.C) has been widely used without any new techniques emerging.

(3) *Reductive Modification of Groups* (*H* 23, *E* 14)

The reduction of 5-nitroso-, 5-nitro-, or 5-arylazopyrimidines continues to be the preferred route to 5-aminopyrimidines (Ch. V, Sects. 1.B, 2.B, 3.B). Nowadays, catalytic hydrogenation is usual but sodium dithionite or classical reagents like zinc or stannous chloride still have their devotees. Some (extranuclear) aminomethylpyrimidines (Ch. IX, Sect. 3.A) have been made by reduction of corresponding nitrosomethylpyrimidines, usually formulated as the oximes of aldehydes. For example, 4-hydroxyiminomethyl- (55) gave 4-aminomethylpyrimidine (56, R = H).⁵⁸⁶² However, most such aminomethyl derivatives are still made by reduction of nitriles. For example, 4-amino-5-cyano- (57) gave 4-amino-5-aminomethylpyrimidine (56, R = NH₂) by hydrogenation.⁵⁷⁹³

Lithium aluminum hydride may be used conveniently to reduce esters to their hydroxymethyl analogues, such as 2-hydroxymethyl-4,6-dimethylpyrimidine (58).⁵⁶⁸² Aldehydes and ketones may be reduced similarly or with borohydride to primary or secondary alcohols, respectively. Aldehydes and ketones also react with Grignard reagents to give secondary or tertiary alcohols, respectively. For example, 4,6-dichloro-5-formylpyrimidine with methyl magnesium iodide gave 4,6-dichloro-5-

α -hydroxyethylpyrimidine (59).⁵⁷⁶⁸ Other examples are given in Ch. VII, Sects. D and F.

H. Modification of Substituents (*H* 24, *E* 15)

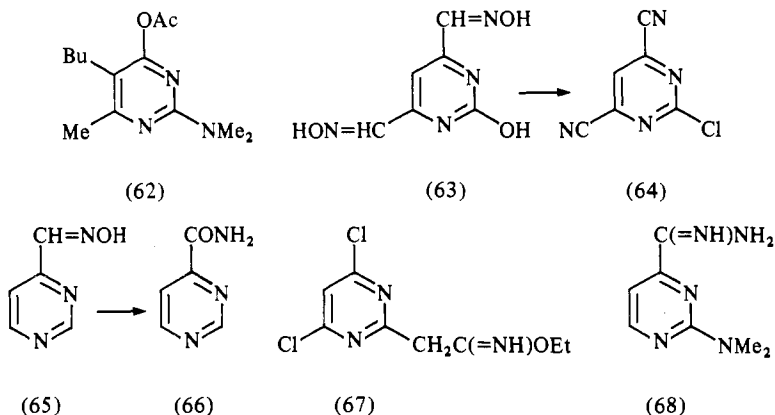
(1) *Amino Groups* (*H* 24, *E* 15) (Ch. IX)

Transamination occurs more readily with 4- than with 2-aminopyrimidines; 4-amino-6-hydroxy- gave 4-hydroxy-6-morpholino-2-phenylpyrimidine with morpholine at 125°,⁴⁹⁷² but 2-amino-4-chloro- gave 2,4-dianilino-6-hydroxypyrimidine with aniline, only at 185°. ⁴⁶³⁵ Transamination of a trimethylammoniopyrimidine is very much easier. 2-Trimethylammonio-5-nitropyrimidine gave 5-nitro-2-propylaminopyrimidine (>72%) by standing in propylamine at 20° for just 5 min.⁵³⁴⁰ The reductive splitting of an hydrazino group is seen in the conversion of 4-hydrazino- (60, R = NH₂) into 4-amino-6-hydroxypyrimidine (60, R = H) by boiling with Raney nickel in aqueous ammonia.⁶²⁹⁸

Most (primary) aminopyrimidines readily form Schiff bases, for example, 2,4,5-tris(dimethylaminomethyleneamino)pyrimidine from 2,4,5-triaminopyrimidine with dimethylformamide dimethyl acetal.⁶²⁸⁹ All primary or secondary aminopyrimidines undergo normal acylations and the known products are legion; primary 5-aminopyrimidines can be converted in diazonium salts which are sometimes isolable, for example, 2,4,6-triamino-5-diazoniopyrimidine tetrafluoroborate (61).⁴⁷⁴⁴ The conversion of 2- or 4/6-aminopyrimidines into 1- or 3-alkyldihydro-2 (or 4/6)-iminopyrimidines and thence in some cases by rearrangement into 2- or 4/6-alkylaminopyrimidines is mentioned in Sect. 4.E(1) above.

(2) *Hydroxy and Alkoxy Groups* (*H* 25, *E* 16) (Ch. VII; Ch. X)

The conversion of hydroxy- into oxo-pyrimidines by *N*-alkylation is covered in Sect. 4.E(1) above. Conversion into *O*-alkyl derivatives (i.e., alkoxy-pyrimidines) by alkylation is dependent on position; 5- and extranuclear-hydroxypyrimidines undergo *O*-alkylation by alkyl halide/alkali or other regular alkylating procedures, but 2- and 4/6-hydroxypyrimidines usually need quite specialized procedures to give an appreciable proportion of *O*-alkyl derivatives in the products, as discussed



in Ch. VII, Sect. D. In contrast, *O*-acylation to give, for example, 4-acetoxy-5-butyl-2-dimethylamino-6-methylpyrimidine (62), usually proceeds quite normally in acetic anhydride or the like, whatever the position of the hydroxy group (Ch. VII, Sect. 6.C).

The Hilbert–Johnson conversion of 2- or 4-alkoxypyrimidines into *N*-alkylated oxypyrimidines is covered in Sect. 4.E(1) above; the thermal rearrangement of alkoxyprymidines occurs only at high temperatures, preferably with base catalysis. For example, 4-methoxy-5-phenylpyrimidine at 170° in the presence of triethylamine gave a 1:1 mixture of 1,4-dihydro-1-methyl-4-oxo- and 1,6-dihydro-1-methyl-6-oxo-5-phenylpyrimidine, kinetic measurements have been made^{5635, 6036} [see Ch. X, Sect. 1.A(4)]. Such reactions have little preparative potential.

(3) *Mercapto Groups* (H 25)

Mercaptopyrimidines undergo alkylation almost exclusively and very easily on sulfur. This and the oxidative and reductive reactions of mercaptopyrimidines are mentioned elsewhere in this summary section.

(4) *Alkyl and Related Groups* (H 26, E 17)

Apart from oxidative reactions (Sect. 4.F) to aldehydes, carboxylic acids, and so on, 2- and 4/6-methylpyrimidines will undergo nitrosation of their methyl group(s) to give the oximes of aldehydes [Ch. IV, Sect. 2.C(4)], which may be dehydrated to nitriles [Ch. XI, Sect. 4.A(3)]. Thus 2-amino-4,6-dimethylpyrimidine with nitrous acid gave 2-hydroxy-

4,6-bishydroxyiminomethylpyrimidine (63) and thence with phosphoryl chloride, 2-chloro-4,6-dicyanopyrimidine (64).⁴⁸²⁰

(5) *Carboxy and Related Groups (E 17)*

(Ch. XI)

Most of the transformation procedures within the carboxylic acid/ester/nitrile and related areas differ little from those in any other series. However, of note is the rarely used Beckmann rearrangement of the oxime, 4-hydroxyiminomethylpyrimidine (65), in buffered formic acid to afford 4-carbamoylpyrimidine (66);⁵⁸⁶² the conversion of nitriles into "imino-ethers" by the ethanolic hydrogen chloride route, giving for example 4,6-dichloro-2-(*C*-ethoxyformimidoyl)methylpyrimidine (67),⁵⁶⁸⁸ or by the more modern ethanolic sodium ethoxide;⁴⁹³⁹ the direct conversion of nitriles into amidines by fusion with ammonium benzenesulfonate, as in the formation of 4-amidino-2-dimethylaminopyrimidine (68);⁶¹⁸¹ and the unusual *C*-acetylation of 6-amino-1-substituted-uracils to give, for example, 5-acetyl-6-amino-1-methyluracil (> 95%).⁵⁴⁴⁶

CHAPTER II

The Principal Synthetic Method (*H* 31, *E* 20)

1. General Scope (*H* 31, *E* 20)

The linking of a C—C—C fragment with an N—C—N fragment still remains the principal synthetic method for making pyrimidines. All 10 divisions of the Principal Synthesis have been used widely in the 13–14 year period under review for new or improved syntheses, sometimes in quite ingenuous ways. Indeed some of the intermediates bore little superficial resemblance to the prototypes (β -dialdehydes, etc.) although they continued to act as such in the Principal Synthesis. For example, the so-called bisdimethylaminotrimethinium salts (17) or the doubled version (21) reacted avidly as “ β -dialdehydes” with N—C—N fragments to give a variety of 2,5-disubstituted pyrimidines and some 2,2'-disubstituted 5,5'-bipyrimidines, mostly in good yield; by pre-substitution of the 1- and/or 3-carbon, the resulting trimethinium salts (43 and 57) became “aldehydo-ketone” and “diketone” equivalents, thus leading respectively to 2,4-disubstituted or 2,4,6-trisubstituted pyrimidines.

The condensation of unsymmetrical C—C—C with unsymmetrical N—C—N fragments gives products of ambiguous structure. So much information has been gathered over the years on the preferred configurations of such products that an alarming tendency to assume structures by real or imaginary analogy has emerged, especially in certain countries. The absolute necessity for proper structural proof is underlined by the condensation of α -ethoxymethyleneacetonitrile (173) with *N*-methylthiourea to give, against all precedent, 4-amino-1,2-dihydro-1-methyl-2-thiopyrimidine (174) instead of the expected 2,3-dihydro-3-methyl isomer.

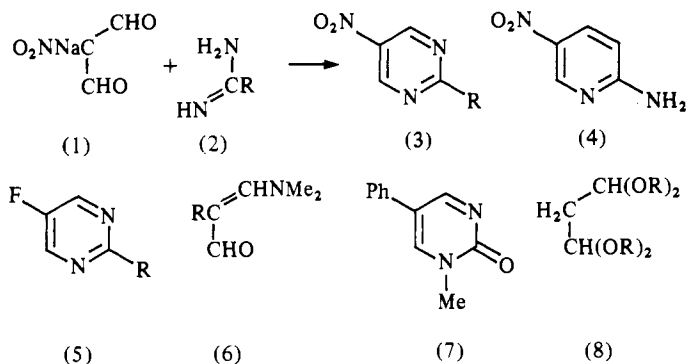
A fairly comprehensive review⁶³³⁰ and several brief reviews^{6182, 6183, 6326} of the Principal Synthesis and other primary syntheses have

appeared. A useful review of the use of lactones, lactams, and thiol-lactones in the synthesis of pyrimidines and other heterocycles has become available.⁴⁴⁵⁷

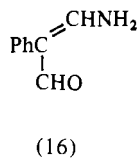
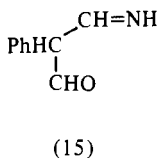
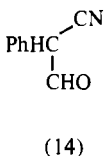
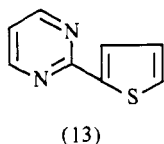
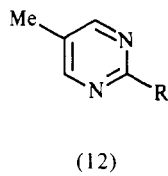
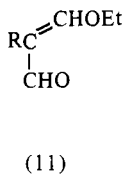
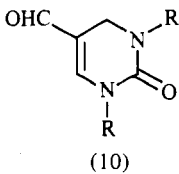
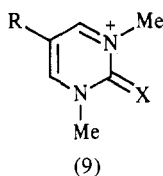
2. Use of β -Dialdehydes (*H* 32, *E* 20)

As might be expected, only a few actual dialdehydo intermediates have been used recently in the Principal Synthesis. However, sodio nitromalondialdehyde (1) has been shown to react with the hydrochloride of furan-2-carboxamide (2, $R = \text{fur-2-yl}$) in aqueous piperidine to give 2-fur-2'-yl-5-nitropyrimidine (3, $R = \text{fur-2-yl}$) in excellent yield;⁵²⁸⁵ the use of acetic anhydride in pyridine or of benzyltrimethylammonium hydroxide in methanol as a condensing medium gave less desirable yields.⁴⁵⁶⁴ The analogous reaction of nitromalondialdehyde with *S*-methylthiourea (2, $R = \text{SMe}$) in aqueous *N*-ethylpiperidine has been improved to give a better yield of 2-methylthio-5-nitropyrimidine (3, $R = \text{SMe}$), but when morpholine was used as the base, subsequent nucleophilic displacement of the methylthio group occurred to yield 2-morpholino-5-nitropyrimidine [3, $R = \text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$].⁵²⁸⁵ The same substrate (1) and phenylguanidine (2, $R = \text{NHPh}$) in aqueous benzyltrimethylammonium hydroxide gave 2-anilino-5-nitropyrimidine (3, $R = \text{NHPh}$).⁵⁷³⁸ The condensation of nitromalondialdehyde with acetamide has been shown⁴⁸¹² to give, not 2-methyl-5-nitropyrimidine (3, $R = \text{Me}$) as previously described (*H* 32), but the isomeric 2-amino-5-nitropyrimidine (4); the authentic pyrimidine (3, $R = \text{Me}$) had been prepared meanwhile by other means.^{2688, 6123} The formation of α -fluoromalondialdehyde and its subsequent conversion into 5-fluoropyrimidine (5, $R = \text{H}$) and the 2-substituted derivatives (5, $R = \text{Me, Ph, OH, SH, NH}_2$) have been mentioned,⁵⁸⁵⁷ but details are available only for the preparation of 5-fluoro-2-hydroxypyrimidine (5, $R = \text{OH}$).⁵⁸⁵⁸ However, analogous preparations for 5-fluoro-2-methyl- (5, $R = \text{Me}$), 5-fluoro-2-phenyl- (5, $R = \text{Ph}$), 5-fluoro-2-mercapto- (5, $R = \text{SH}$), and 2-amino-5-fluoropyrimidine (5, $R = \text{NH}_2$) directly from the fluoromalondialdehyde equivalent 3-dimethylamino-2-fluoroacrolein (6, $R = \text{F}$) are available.⁵⁸⁵⁸ Furan-2-carboxamide has been condensed with the same intermediate (6, $R = \text{F}$) to give 5-fluoro-2-fur-2'-ylpyrimidine (5, $R = \text{furyl}$) or with α -chloromalondialdehyde to give the 5-chloro analogue.⁴⁵⁶⁴ α -Ethoxycarbonylmalondialdehyde and *C*-benzyloxycarbonylaminoacetamide gave (in boiling acetic acid) 2-benzyloxycarbonylaminoethyl-5-ethoxycarbonylpyrimidine (31%).⁶⁰⁹¹ Similarly, 1,2-dihydro-1-methyl-2-oxo-5-phenylpyrimidine (7) has been made by

condensing *N*-methylurea with either α -phenylmalondialdehyde or 3-dimethylamino-2-phenylacrolein (6, R = Ph) in boiling toluene containing *p*-toluenesulfonic acid. Several 1-alkyl homologues and substituted-phenyl analogues were made similarly. The free dialdehydes gave better yields than the equivalent acrolein.⁶⁰⁷⁹

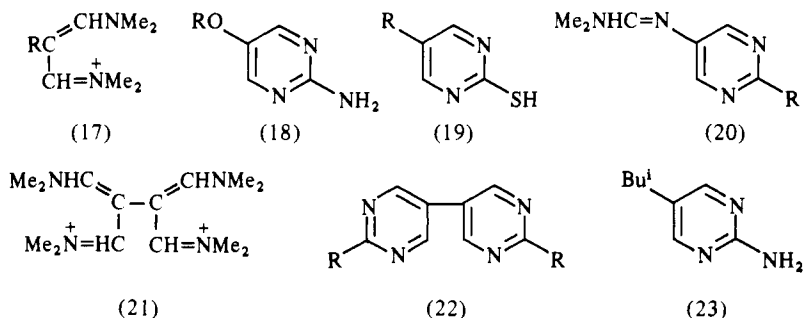


The use of malondialdehyde diacetals is exemplified in the condensation of 1,1,3,3-tetraethoxypropane (8, R = Et) with *N*-(ethoxycarbonylmethoxy)urea in ethanolic hydrogen chloride to give 1-ethoxycarbonylmethoxy-1,2-dihydro-2-oxopyrimidine;⁴⁵⁸³ in the similar preparation of 1-benzyloxy-1,2-dihydro-2-oxopyrimidine or its 1-methoxy analogue;⁴⁵⁸³ in the reaction of 1,1,2,3,3-pentamethoxypropane with guanidine in ethanolic hydrochloric acid to give 2-amino-5-chloropyrimidine (rather than the 5-methoxy analogue);⁵⁶⁶² in the reaction of tetramethoxypropane (8, R = Me) with pyridine-4-carboxamide without solvent at 130° to give 2-pyrid-4'-ylpyrimidine;⁵⁹⁹¹ in the condensation of *N,N'*-dimethylurea (or homologues) with the tetraalkoxypropane (8, R = Me or Et) in alcoholic hydrochloric, hydriodic, or sulfuric acid to give the appropriate dihydro-1,3-dimethyl-2-oxopyrimidinium salt (9, X = O) or homologues in excellent yield;^{5324, 5326} and in the similar formation of dihydro-1,3-dimethyl-2-thiopyrimidinium salts (9, R = H, X = S).⁵²⁶⁶ The closely akin, dihydro-1,3-dimethyl-2-oxo-5-phenylpyrimidinium salt (9, R = Ph, X = O) and its thio analogue (9, R = Ph, X = S) were formed similarly from 2-phenylmalondialdehyde, rather than its diacetal, in the presence of perchloric acid.⁵²⁶⁶ In contrast, α -hydroxymethylmalondialdehyde diacetal reacted under similar conditions with *N,N'*-dimethylurea, not as a dialdehyde but as an aldehydo alcohol, to give 1,2,3,4-tetrahydro-5-formyl-1,3-dimethyl-2-oxopyrimidine (10, R = Me); urea gave the analogous reduced pyrimidine (10, R = H).⁵⁴³⁰



The use of 3-alkoxyacroleins in place of β -dialdehydes is well documented. Thus, 3-ethoxy-2-methylacrolein (11, $R = \text{Me}$) with acetamidine (in ethanolic sodium ethoxide), urea (in ethanolic hydrochloric acid), thiourea (in ethanolic sodium ethoxide), or *N*-carboxymethyl-*N*-methylguanidine (in ethanolic sodium ethoxide) gave 2,5-dimethyl- (12, $R = \text{Me}$), 2-hydroxy-5-methyl- (12, $R = \text{OH}$), 2-mercapto-5-methyl- (12, $R = \text{SH}$), or 2-*N*-carboxymethyl-*N*-methylamino-5-methylpyrimidine (12, $R = \text{NMe CH}_2\text{CO}_2\text{H}$), respectively; most of the 5-ethyl, 5-propyl, and 5-isopropyl homologues were made similarly.⁴⁴⁶³ Likewise, 2-*p*-bromophenyl-3-ethoxyacrolein (11, $R = \text{C}_6\text{H}_4\text{Br}$) and *p*-hexylbenzamidine gave 5-*p*-bromophenyl-2-*p*-hexylphenylpyrimidine. Other homologues are also described.⁴⁹⁰⁶

Of all the equivalents of β -dialdehydes, the most extensively used have been the 3-aminoacroleins, of which one, type (6), has been mentioned already. Other examples of its use include the condensation of 3-dimethylaminoacrolein (6, $R = \text{H}$) with free thiophene-2-(and 3)-carboxamide in methanol to give 2-thien-2'-ylpyrimidine (13) and its thien-3'-yl isomer respectively,⁴⁸⁹¹ 3-dimethylamino-2-piperidinoacrolein [6, $R = \text{N}(\text{CH}_2)_5$] with thiourea to give 2-mercapto-5-piperidino-pyrimidine,⁶²⁸¹ and 3-dimethylamino-2-octylacrolein with *p*-hydroxybenzamidine to give 2-*p*-hydroxyphenyl-5-octylpyrimidine.⁴⁵⁴² Aminoacroleins without *N*-substituents may also be used conveniently. Thus, catalytic hydrogenation of α -formylphenylacetonitrile (14) gave 3-iminopropionaldehyde (15), tautomeric with 3-amino-2-phenylacrolein (16). This reacted with urea or thiourea in ethanolic hydrochloric acid to give 2-hydroxy-⁵⁶³⁵ and 2-mercapto-5-phenylpyrimidine,⁵⁶⁶³ respectively. Several *N*-methylated and substituted-phenyl analogues were made similarly,^{5635, 5663} and 3-amino-2-methylacrolein with *N*-(δ -amino- δ -carboxybutyl)guanidine gave 2-(δ -amino- δ -carboxybutyl)amino-5-methylpyrimidine.⁴⁴⁷⁶

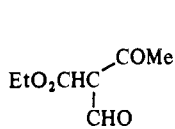


Another useful type of β -dialdehyde equivalent is represented in the so-called bisdimethylaminotrimethinium salts (17). Thus, the unsubstituted intermediate (17, $\text{R} = \text{H}$) and benzamidine in ethanolic sodium methoxide gave 2-phenylpyrimidine, the intermediate (17, $\text{R} = \text{Me}$) and formamidine gave 5-methylpyrimidine, the chloro derivative (17, $\text{R} = \text{Cl}$) and benzamidine or guanidine gave 5-chloro-2-phenyl- or 2-amino-5-chloropyrimidine respectively, and the nitro intermediate (17, $\text{R} = \text{NO}_2$) with guanidine or thiourea gave 2-amino- or 2-mercapto-5-nitropyrimidine respectively, all in excellent yield.⁴⁴⁸⁸ Further examples are provided in the formation of 2-amino-5-cyano- and the 2-amino-5-alkoxypyrimidines (18, $\text{R} = \text{CH}_2\text{Ph}$, Me , and Et);⁴³⁸⁴ in the formation of 2-mercaptopyrimidine (19, $\text{R} = \text{H}$) and its 5-chloro (19, $\text{R} = \text{Cl}$), 5-bromo (19, $\text{R} = \text{Br}$), 5-cyano (19, $\text{R} = \text{CN}$), and other such derivatives;^{4384, 5435} and in the condensation of the intermediate (17, $\text{R} = \text{N}:\text{CHNMe}_2$) with formamidine to give 5-dimethylaminomethyleneaminopyrimidine (20, $\text{R} = \text{H}$) or with guanidine, thiourea, or *S*-methylthiourea to give the respective 2-amino (20, $\text{R} = \text{NH}_2$), 2-mercapto (20, $\text{R} = \text{SH}$), or 2-methylthio (20, $\text{R} = \text{SMe}$) derivatives.⁴³⁸³ Likewise, acetamidine gave the 2-methyl analogue (20, $\text{R} = \text{Me}$).⁶⁵¹⁰ Condensation of the intermediate (17, $\text{R} = \text{C}_6\text{H}_4\text{OBu}$) with *S*-methylthiourea in pyridine gave 5-*p*-butoxyphenyl-2-methylthiopyrimidine in good yield;⁴⁵⁴⁵ the intermediate (17, $\text{R} = 5'$ -chlorothien-2'-yl) and formamidine gave 5-5'-chlorothien-2'-ylpyrimidine;⁵²²⁰ and the intermediate (21) with guanidine, thiourea, or *S*-methylthiourea gave 2,2'-diamino- (22, $\text{R} = \text{NH}_2$), 2,2'-dimercapto- (22, $\text{R} = \text{SH}$), or 2,2'-bismethylthio-5,5'-bipyrimidine (22, $\text{R} = \text{SMe}$), respectively.^{4386, 5580} Formamidine failed to yield a bipyrimidine.⁴³⁸⁶

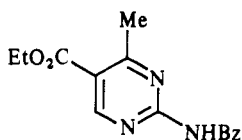
2-Amino-5-isobutylpyrimidine (23) has been made from 2-isobutylmalondialdehyde or its monoacetal and guanidine. Both intermediates were made *in situ* by unusual routes,⁴⁵³² as was that for an analogous condensation yielding 2-amino-5-methoxypyrimidine.⁵⁸¹³

3. Use of β -Aldehydo Ketones (*H* 34, *E* 22)

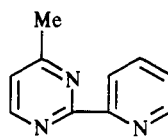
A few free aldehydo ketones have been used to prepare 4-substituted-6-unsubstituted-pyrimidines, but their acetals have been more widely employed. Ethyl α -formylacetoacetate (24) reacts as an aldehydo ketone (rather than an aldehydo ester or keto ester) with benzoylguanidine in ethanol to give 2-benzamido-5-ethoxycarbonyl-4-methylpyrimidine (25); the 2-*p*-nitrobenzamido analogue was made similarly, albeit in only 21% yield.⁵²⁴⁸ Benzyl α -formylacetoacetate and guanidine carbonate in benzyl alcohol at 100° gave 2-amino-5-benzyloxycarbonyl-4-methylpyrimidine,⁵²⁴⁸ and α -formylbenzyl phenyl ketone (so-called hydroxymethylenedeoxybenzoin) with urea in *N,N*-dimethylacetamide at 150° gave 2-hydroxy-4,5-diphenylpyrimidine.⁶⁰⁷⁹ The use of acetals is exemplified in the condensation of formylacetone dimethyl acetal with pyridine-2-carboxamide to give 4-methyl-2-pyrid-2'-ylpyrimidine (26) in good yield,⁵⁹⁵⁹ of 1,1-dimethoxy-2-methylpentan-3-one (27, R = Et) or its 2,4-dimethyl homologue (27, R = Prⁱ) with guanidine to give 2-amino-4-ethyl(or isopropyl)-5-methylpyrimidine (28, R = Et or Prⁱ),⁶³²² and of 4,4-dimethoxybutan-2-one with *N,N'*-dimethylurea under acidic conditions to give the dihydro-1,3,4-trimethyl-2-oxopyrimidinium salt (29).



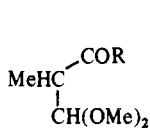
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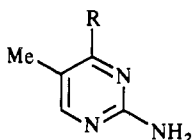
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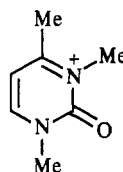
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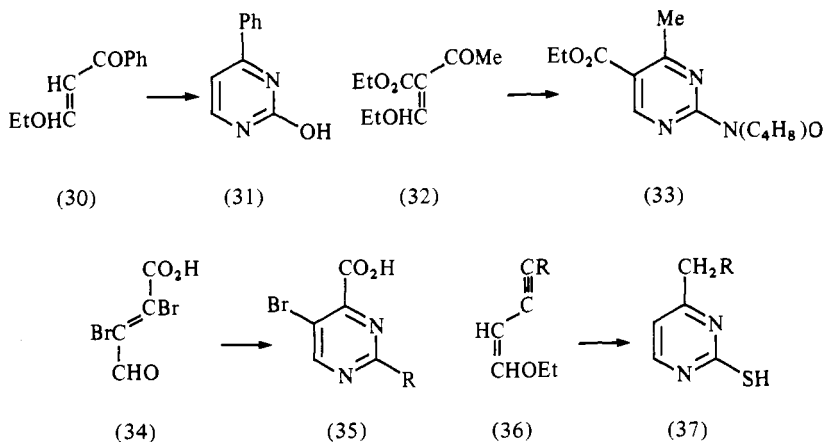
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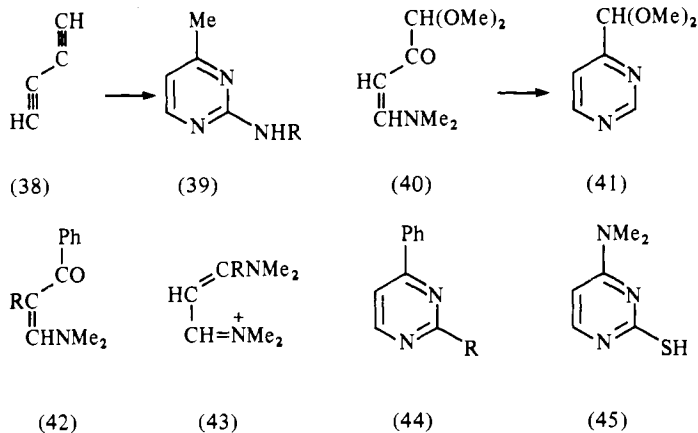
(29)

The use of α -methoxymethylene ketones as β -aldehydo ketones is quite common. For example, α -ethoxymethyleneacetophenone (30) and urea in ethanolic sodium ethoxide gave 2-hydroxy-4-phenylpyrimidine (31),⁶⁰⁴² ethyl ethoxymethyleneacetoacetate (32) and *C*-morpholinoformamidine gave only 5-ethoxycarbonyl-4-methyl-2-morpholinopyrimidine (33) despite the other possibilities,⁶²⁸² ethoxy-

methyleneacetylacetone and ethanolic guanidine or benzamidine gave 5-acetyl-2-amino-4-methylpyrimidine or 5-acetyl-4-methyl-2-phenylpyrimidine respectively,⁵³⁷⁸ diethyl ethoxymethyleneoxalylacetate and formamidine (or other amidines) gave 4,5-diethoxycarbonylpyrimidine^{4453, 6329} or its 2-alkyl/aryl derivatives,⁶³²⁹ and there are more complicated condensations.^{4416, 4438}



Mucochloric and mucobromic acid (34) are still proving useful as β -aldehyde ketones. Thus, with pivalamidide was formed 5-bromo-2-*t*-butyl-4-carboxypyrimidine (35, R = Bu^t),⁴³⁶⁴ with *S*-methylthiourea in aqueous triethylamine was formed 5-bromo-4-carboxy-2-methylthiopyrimidine (35, R = SMe) or its 5-chloro analogue,⁵⁸⁵⁵ and with glycolamidide (*C*-hydroxyacetamidide) was formed 5-bromo-4-carboxy-2-hydroxymethylpyrimidine (35, R = CH₂OH).⁵⁹³² Appropriate acetylenes (see H 35) may also be used as β -aldehyde ketones. Thus, ethoxymethylenepropyne (36, R = H) (or its ethylthiomethylene, piperidinomethylene, or diethylaminomethylene analogue) reacted with thiourea to give 2-mercapto-4-methylpyrimidine (37, R = H), ethoxymethylenebut-2-yne (36, R = Me) and thiourea gave 4-ethyl-2-mercaptopyrimidine (37, R = Me), and the 4-propyl and butyl homologues were made similarly.⁴⁷⁷⁷ Formamide or guanidine reacted with similar substrates to give 4-methyl-, 4-ethyl-, 2-amino-4-methyl-, and 2-amino-4-ethylpyrimidine as well as other homologues.^{5757, 5758} In addition, diacetylene (butadiyne: 38, R = H) and guanidine or dicyandiamide (cyanoguanidine) gave 2-amino- (39, R = H) or 2-cyanoamino-4-methylpyrimidine (39, R = CN) respectively, and appropriate monalkyldiacetylenes (38, R = Me or Et) gave the 4-ethyl or 4-propyl homologues.⁶⁰⁵⁰

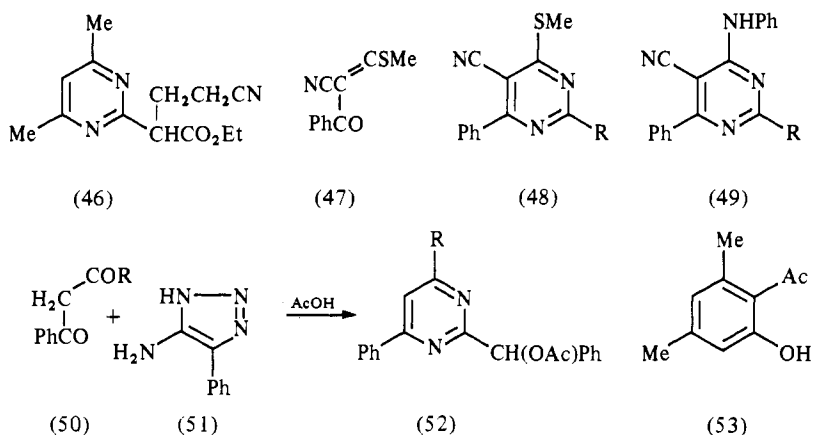


Another type of aldehydo ketone equivalent is represented in 4-dimethylamino-1,1-dimethoxybut-3-en-2-one (40), which reacted with formamidine acetate at 120° without solvent to afford 4-dimethoxymethylpyrimidine (41) in excellent yield.⁴⁴⁴⁸ Similarly, from a large number of examples, 2-benzoyl-1-dimethylaminopropene (42, R = Me) and alcoholic guanidine gave 2-amino-5-methyl-4-phenylpyrimidine,⁵⁴⁸⁴ ethyl 2-benzoyl-3-dimethylaminoacrylate (42, R = CO₂Et) and *S*-methylthiourea gave 5-ethoxycarbonyl-2-methylthio-4-phenylpyrimidine,⁶¹⁶⁶ and 1-benzoyl-1,2-bisdimethylaminoethylene (42, R = NMe₂) and benzamidine gave 5-dimethylamino-2,4-diphenylpyrimidine.⁶¹⁰⁷ Appropriately substituted bisdimethylaminotrimethinium salts have been used too; for example, the phenyl derivative (43, R = Ph) and guanidine or benzamidine gave 2-amino-4-phenyl (44, R = NH₂) or 2,4-diphenylpyrimidine (44, R = Ph) respectively,⁴⁴⁸⁸ while the trisdimethylamino intermediate (43, R = NMe₂) and thiourea gave 4-dimethylamino-2-mercaptopyrimidine (45).⁴³⁸⁴ Other interesting examples have been reported.⁶³⁹⁹

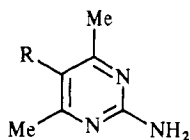
4. Use of β -Diketones (*H* 36, *E* 23)

The condensation of glycolamidine (*C*-hydroxyacetamidine) with acetylacetone proceeded so slowly in aqueous potassium carbonate at room temperature to give 2-hydroxymethyl-4,6-dimethylpyrimidine, that it proved better to prepare it indirectly;⁵⁶⁸² the reaction of *p*-chlorobenzamidine hydrochloride with *p*-chlorobenzoylacetone without solvent at 250° to give 2,4-bis-*p*-chlorophenyl-6-methylpyrimidine also proved unsatisfactory and another synthesis was used.⁵⁵⁹⁰ However,

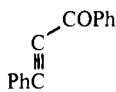
acetylacetone did condense with 4-cyano-2-ethoxycarbonylbutyramidine in ethanol containing piperidine to give 2-(γ -cyano- α -ethoxycarbonylpropyl)-4,6-dimethylpyrimidine (46) in reasonable yield.⁵⁰⁹⁸ Much better results were obtained using the acylketene thioacetals as diketone equivalents. Thus, 2-benzoyl-3,3-bismethylthioacrylonitrile (47, R = SMe) and acetamidine in refluxing dimethylformamide containing triethylamine gave 5-cyano-2-methyl-4-methylthio-6-phenylpyrimidine (48, R = Me) in 90% yield. The same thioacetal (47, R = SMe) with guanidine or *S*-methylthiourea gave 2-amino-5-cyano-4-methylthio- (48, R = NH₂) and 5-cyano-2,4-bismethylthio-6-phenylpyrimidine (48, R = SMe), respectively.⁴⁵⁵⁷ Likewise, 3-anilino-2-benzoyl-3-methylthioacrylonitrile (47, R = NHPh) gave the analogous 4-anilino-5-cyano-2-methyl- (49, R = Me), 2-amino-4-anilino-5-cyano- (49, R = NH₂), and 4-anilino-5-cyano-2-methylthio-6-phenylpyrimidine (49, R = SMe).⁴⁵⁵⁷ An unusual (composite) reaction is that of benzoylacetone (50, R = Me) or dibenzoylmethane (50, R = Ph) with 4-amino-5-phenyl-1,2,3-triazole (51) in boiling glacial acetic acid to give 2-acetoxybenzyl-4-methyl-6-phenyl- (52, R = Me) or 2-acetoxybenzyl-4,6-diphenylpyrimidine (52, R = Ph), respectively, in good yield.⁵²⁴¹



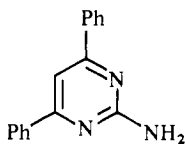
Guanidines react very readily with diketones or their equivalents. Recent examples employing unsubstituted guanidine include condensation of its hydrochloride with acetylacetone in aqueous ethanolic sodium hydrogen carbonate to give 2-amino-4,6-dimethylpyrimidine (54, R = H) along with 2-acetyl-3,5-dimethylphenol (53) as an easily separated byproduct from self-condensation of the diketone;⁴⁴⁷⁶ of guanidine carbonate with 3-phenylacetylacetone at 150° to give 2-amino-4,6-dimethyl-5-phenylpyrimidine (54, R = Ph);⁵⁶⁶² of guanidine



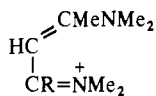
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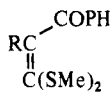
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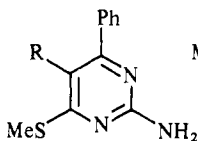
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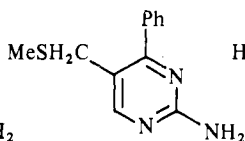
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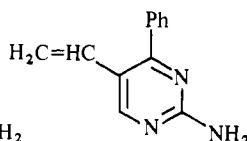
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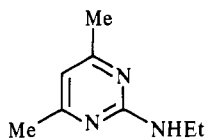


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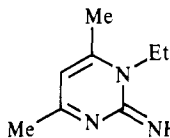


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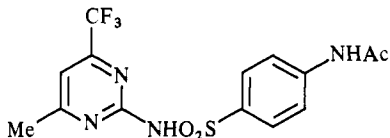
carbonate with 1-benzoyl-3,3,3-trifluoroacetone at 150° to give 2-amino-4-phenyl-6-trifluoromethylpyrimidine;⁵⁸⁶⁵ of guanidine nitrate with 3-methylacetylacetone in ethanolic sodium ethoxide to give 2-amino-4,5,6-trimethylpyrimidine (54, R = Me);⁶³²⁰ of guanidine carbonate with *p*-methylselenobenzoylacetone at 150° to give 2-amino-4-methyl-6-*p*-methylselenophenylpyrimidine;⁴⁵⁰⁵ of guanidine carbonate with 2-acetoacetylthiophene at 150° to give 2-amino-4-methyl-6-thien-2'-ylpyrimidine;⁵¹¹¹ of guanidine nitrate with 3-phenylhydrazonoacetylacetone in methanolic sodium hydroxide to give 2-amino-4,6-dimethyl-5-phenylazopyrimidine (54, R = N:NPh);⁵³⁶³ and of guanidine nitrate with α -benzoyl- α -phenylhydrazonoacetone in methanolic sodium hydroxide to give 2-amino-4-methyl-6-phenyl-5-phenylazopyrimidine.⁵⁸⁶⁹ In addition, guanidine condensed with benzoylphenylacetylene (55) to give 2-amino-4,6-diphenylpyrimidine (56),^{6210, 6542} with the dimethyl-bisdimethylaminotrimethinium salt (57) to give 2-amino-4,6-dimethylpyrimidine (54, R = H),⁴⁴⁸⁸ and with 1-benzoyl-2,2-bismethylthioethylene (58, R = H) in dimethylformamide containing sodium hydride to give 2-amino-4-methylthio-6-phenylpyrimidine (59, R = H).^{5371, 5381} It should be noted that if the last condensation was done in ethanolic sodium ethoxide, the methylthio substituent in the product (59, R = H) was replaced to afford 2-amino-4-ethoxy-6-phenylpyrimidine in good yield.^{5371, 5381} Moreover, when the "diketone" (58, R = H) was replaced by its homologue, 2-benzoyl-1,1-bismethylthiopropene (58, R = Me), the latter no longer acted like a diketone to give the expected product (59, R = Me), but instead gave 2-amino-5-methylthiomethyl-4-phenylpyrimidine (60) by a complicated but plausible mechanism.⁵³⁸² When the butene (58, R = Et) is used, one of the products is 2-amino-4-phenyl-5-vinylpyrimidine (61).⁵³⁸²



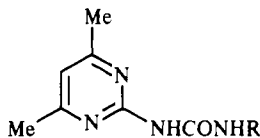
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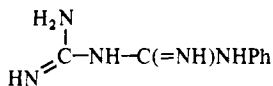
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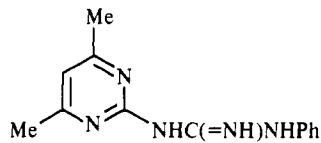
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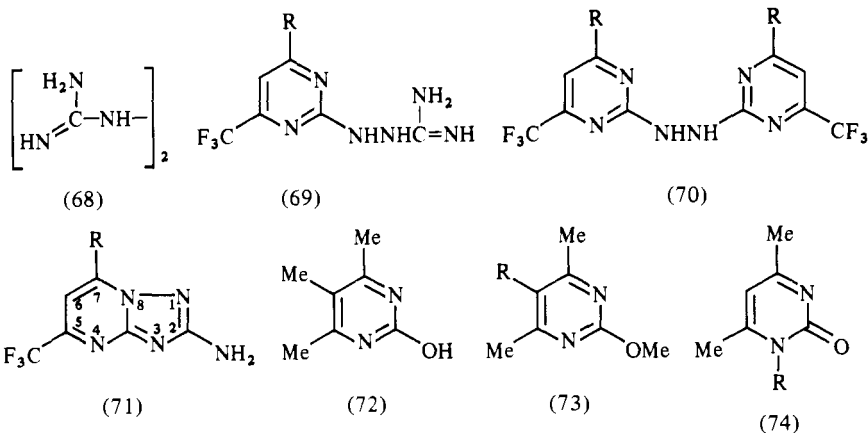


(66)



(67)

Substituted guanidines have been condensed extensively with β -diketones. Thus, ethyl guanidine and acetylacetone gave 2-ethylamino-4,6-dimethylpyrimidine (62);⁴⁵⁵¹ although the yield was poor, this was probably not due to the alternative formation of the strongly basic isomer (63), which would have undoubtedly undergone Dimroth rearrangement to the ethylaminopyrimidine (62) under the reaction conditions. Other such condensations led to 2-ethylamino-4-methyl-6-thien-2'-ylpyrimidine,⁴⁵⁵¹ 2-ethylamino-4-methyl-6-trifluoromethylpyrimidine,⁴⁵⁵⁸ 2-dimethylamino-4,6-diphenylpyrimidine,⁶²⁹⁰ 2-diethylamino-4,6-dimethylpyrimidine,⁴⁵⁶² 2-diethylamino-4-methyl-6-trifluoromethylpyrimidine,⁴⁵⁵⁹ 4,6-dimethyl-2-*p*-nitroanilinopyrimidine,⁶²⁷² 4,5,6-trimethyl-2-*p*-nitroanilinopyrimidine,⁶²⁷² 4-benzyl-6-methyl-2-*p*-nitroanilinopyrimidine,⁵⁸³¹ 2-carboxymethylamino-4,6-dimethylpyrimidine,⁴⁴⁷⁶ 2-*p*-acetamidobenzenesulphonoamido-4-methyl-6-trifluoromethylpyrimidine (64),⁵⁷⁸⁵ and many other such pyrimidines.⁴³³³ Carbamoylguanidine reacted with acetylacetone and its unbranched homologues at room temperature to give 4,6-dimethyl-2-ureidopyrimidine (65, R = H) and its 4,6-di-*n*-alkyl homologues;⁶⁰¹⁵ when the reaction was attempted with branched diketones, higher temperatures were required and the expected products were degraded to simple 2-amino derivatives such as 2-amino-4,6-di-isopropylpyrimidine.⁶¹³⁷ The use of (*N*-phenylcarbamoyl)guanidines led to the more stable products such as 4,6-dimethyl-2-*N'*-phenylureidopyrimidine (65, R = Ph).⁶²⁰⁵ Similarly, phenylbiguanides (66) gave 4,6-dimethyl-2-*N'*-phenylguanidinopyrimidine (67) and related compounds.^{4975, 6205} In contrast, biguanidine (68) and trifluoroacetylacetone gave a separable mixture of 2-guanidinoamino-4-methyl-6-trifluoromethylpyrimidine (69, R = Me) and *N,N'*-bis(4-methyl-6-trifluoromethylpyrimidin-2-yl)-



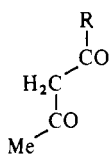
hydrazine (70, R = Me).⁵⁷¹³ In some such condensations, the (intermediate) guanidinoaminopyrimidine underwent intramolecular cyclization (in part or completely) to give a triazolopyrimidine. From the available data it is not possible to predict the products. For example, 1,1,1-trifluoro-4-phenylbutane-2,4-dione and biguanidine in refluxing ethanol gave 2-guanidinoamino-4-phenyl-6-trifluoromethylpyrimidine (69, R = Ph) and 2-amino-7-phenyl-5-trifluoromethyl-s-triazolo[1,5-a]pyrimidine (71, R = Ph),⁶⁰¹⁰ whereas 1,1,1-trifluorohexane-2,4-dione and biguanidine under similar conditions gave *N,N'*-bis(4-ethyl-6-trifluoromethylpyrimidin-2-yl)hydrazine (70, R = Et) and 2-amino-7-ethyl-5-trifluoromethyl-s-triazolo[1,5-a]pyrimidine (71, R = Et);⁵⁷¹³ analogous condensations gave one or other type of mixture.⁶⁰⁰⁹

The condensation of urea with 3-methylacetylacetone in ethanolic hydrochloric acid at room temperature took 30 days to give 2-hydroxy-4,5,6-trimethylpyrimidine (72) (as hydrochloride) in 50% yield.⁵²⁴⁷ This process was speeded up by heating under reflux, but isolation of the free base (from its urea complex*) by continuous chloroform extraction gave only 33% yield.⁶³²⁵ The conversion of 2-acetoacetylthiophene into 2-hydroxy-4-methyl-6-thien-2'-ylpyrimidine was also done in ethanolic hydrochloric acid at room temperature.⁵¹¹¹ However, the condensation of *O*-methylurea with a variety of β -diketones has been done in aqueous potassium carbonate. In this way were obtained 2-methoxy-4,6-dimethyl- (73, R = H),⁴⁴⁶⁷ 2-methoxy-4,5,6-trimethyl- (73, R = Me),⁴⁵⁵⁴ 5-ethyl-2-methoxy-4,6-dimethyl- (73, R = Et),⁴⁵⁵⁴ 2-methoxy-4-methyl-6-trifluoromethyl-,⁴⁵⁴⁶ 2-methoxy-4,6-bistrifluoro-

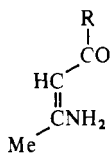
*The structure of the related complex between 2-hydroxy-4,6-dimethylpyrimidine and urea has been investigated in some detail,⁶⁷²¹ but it can be avoided in practice.⁶⁹³²

methyl-,⁴⁵⁴⁶ and 2-methoxy-4-phenyl-6-trifluoromethylpyrimidine,⁴⁵⁵⁵ as well as other analogues.

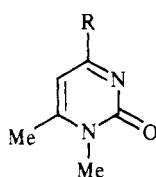
At least some *N*-substituted ureas condense with simple β -diketones in boiling ethanol. In this way were prepared 1-benzoyl- (74, R = Bz), 1-benzyl- (74, R = CH₂Ph), and 1-cyclohexyl-1,2-dihydro-4,6-dimethyl-2-oxopyrimidine (74, R = C₆H₁₁) in good yield.⁴³⁹² However, 1-benzyl-1,2-dihydro-2-oxo-4,6-diphenylpyrimidine was made⁶²⁹⁰ from dibenzoylmethane and *N*-benzylurea in refluxing glacial acetic acid containing toluene-*p*-sulfonic acid, while 1,2-dihydro-1,4,5,6-tetramethyl-2-oxopyrimidine was prepared in ethanolic hydrochloric acid.⁶³²⁵ Likewise *N,N'*-dimethylurea and acetylacetone condensed in concentrated hydrochloric acid to give dihydro-1,3,4,6-tetramethyl-2-oxopyrimidinium chloride,⁵³²⁴ and the hydrogen sulfate was made similarly.^{5266, 5324} The condensation of *N*-alkylureas with unsymmetrical β -diketones can, of course, lead to two isomers, but little was published on possible selectivity until the significant note of Otsuka and Tsuda.⁵¹⁵²



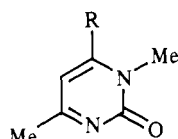
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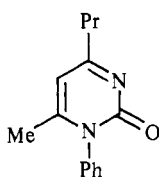
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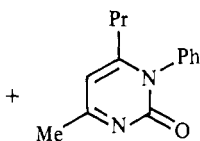
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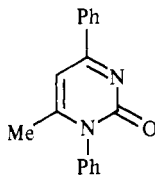
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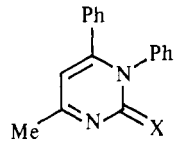
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(80)



(81)



(82)

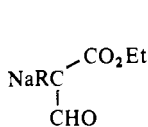
Heptane-2,4-dione (75, R = Pr) and methylurea gave almost equal amounts of 1,2-dihydro-1,6-dimethyl-2-oxo-4-propyl (77, R = Pr) and 1,2-dihydro-1,4-dimethyl-2-oxo-6-propylpyrimidine (78, R = Pr), whereas from the diketone equivalent, 2-aminohept-2-en-4-one (76, R = Pr), the ratio (77, R = Pr):(78, R = Pr) was 2:1. Benzoylacetone (75, R = Ph) gave 1,2-dihydro-1,6-dimethyl-2-oxo-4-phenyl- (77, R = Ph) and 1,2-dihydro-1,4-dimethyl-2-oxo-6-phenylpyrimidine (78, R = Ph) in 1:10 ratio, but 2-amino-1-benzoylpropene (76, R = Ph) gave (77, R = Ph) and (78, R = Ph) in 1:2 ratio. In contrast, intermediate (75, R = Pr) and *N*-phenylurea gave 1,2-dihydro-6-methyl-2-oxo-1-phenyl-4-propyl- (79) and 1,2-dihydro-4-methyl-2-oxo-1-phenyl-6-

propylpyrimidine (80) in 2:1 ratio, whereas the intermediate (76, R = Ph) gave the products (79 and 80) in almost equal quantities. From such limited information the necessarily vague conclusion⁵¹⁵² was that the reaction of β -diketones with *N*-alkylureas was "controlled by the enol form of the diketones and the basicity of the ureas." More recently it was noted⁶⁰⁸⁵ that benzoylacetone (75, R = Ph) and *N*-phenylurea gave predominantly 1,2-dihydro-6-methyl-2-oxo-1,4-diphenylpyrimidine (81), whereas a similar condensation with *N*-phenylthiourea gave predominantly 1,2-dihydro-4-methyl-1,6-diphenyl-2-thiopyrimidine (82, X = S), which could be converted easily into its oxo analogue, 1,2-dihydro-4-methyl-2-oxo-1,6-diphenylpyrimidine (82, X = O). A practical route was thus provided to each of the isomers (81) and (82, X = O).⁶⁰⁸⁵

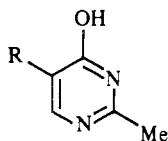
Apart from the above example, few recent condensations of thiourea and diketones have been described. However, 3-methylacetylacetone and thiourea in ethanolic hydrochloric acid did give 2-mercapto-4,5,6-trimethylpyrimidine as hydrochloride,⁶³¹⁹ and there are a few related examples.^{4349, 6377} In addition, many examples using *S*-alkylthioureas have been described, albeit from one laboratory and sometimes recording very low yields. Among the products so formed were 4,6-dimethyl-2-methylthiopyrimidine (aqueous potassium carbonate),⁴⁴⁶⁷ 4,5,6-trimethyl-2-methylthiopyrimidine,⁴⁵⁵⁴ 2-methylthio-4-phenyl-6-trifluoromethylpyrimidine,⁴⁵⁵⁵ 2-methylthio-4,6-bistrifluoromethylpyrimidine,⁴⁵⁴⁶ 2-benzylthio-4,6-dimethylpyrimidine (ethanolic pyridine containing potassium carbonate),⁶²⁷¹ 2-benzylthio-4,6-diethylpyrimidine (potassium carbonate in dimethylformamide),⁶²⁷¹ 2-benzylthio-4,6-bistrifluoromethylpyrimidine (aqueous ethanolic potassium carbonate plus ether),⁵⁹⁴⁷ and many others.⁴⁵⁴⁷ Condensation of thiourea with chalcone (benzylideneacetophenone) (1 or 2 mol) gave 4,5-dihydro-2-mercapto-4,6-diphenyl- or 2-mercapto-4,6-diphenylpyrimidine, respectively.⁶⁵³¹

5. Use of β -Aldehyde Esters (*H* 38, *E* 25)

The condensation of aldehyde esters and their equivalents with amidines is well represented. Thus, ethyl sodioformylpropionate (83, R = Me) and acetamidine hydrochloride in ethanol containing sodium ethoxide (0.5 mol) gave 4-hydroxy-2,5-dimethylpyrimidine (84, R = Me),⁵⁶⁹⁵ ethyl α -benzyloxy- α -formylacetate (83, R = OCH₂Ph) and acetamidine or *C*-hydroxyacetamidine under similar conditions gave 5-benzyloxy-4-hydroxy-2-methyl- (84, R = OCH₂Ph) or 5-benzyloxy-4-hydroxy-2-hydroxymethylpyrimidine.⁵³⁴⁵ Analogues so prepared



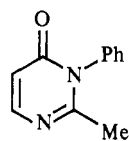
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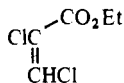
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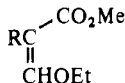
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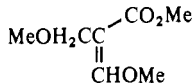
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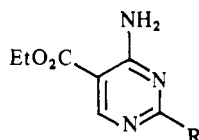
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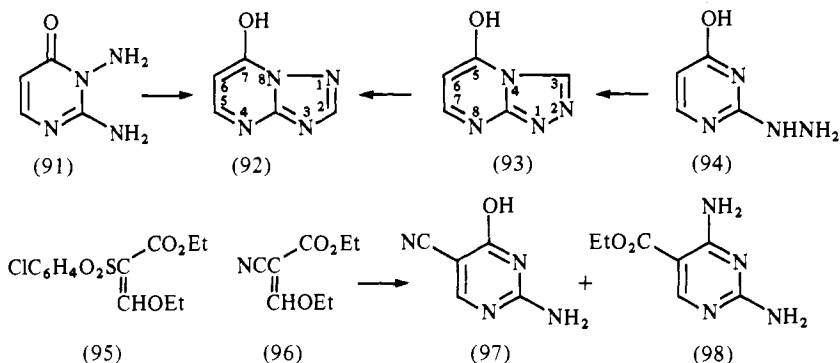


(89)



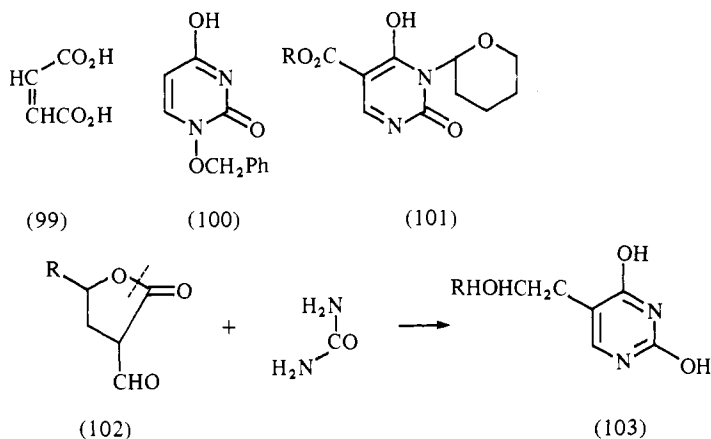
(90)

include 2-ethyl-4-hydroxypyrimidine,⁵²⁹⁴ 4-hydroxy-2-phenylpyrimidine,⁶⁰³⁸ 4-hydroxy-5-methoxy-2-phenylpyrimidine,⁴⁶⁷⁴ 2-benzyl-4-hydroxypyrimidine,⁴⁶⁷⁰ 4-hydroxy-2- β -naphthylpyrimidine,⁴⁶⁷⁰ 4-hydroxy-5-methyl-2-phenylpyrimidine,⁴⁴⁷⁸ and 5-benzamidomethyl-4-hydroxy-2-methylpyrimidine (84, R = CH₂Bz).⁵⁷⁹³ Turning to aldehyde ester equivalents, ethyl propynoate (85, R = Et) and *N*-phenylacetamide gave a single product said to be 1,6-dihydro-2-methyl-6-oxo-1-phenylpyrimidine (86), rather than its isomer, by a rather shaky analogy;⁶²⁴⁶ ethyl 2,3-dichloroacrylate (87) and benzamide gave 5-chloro-4-hydroxy-2-phenylpyrimidine;⁵⁷⁵⁵ dimethyl ethoxymethylenemalonate (88, R = CO₂Me) and pyridine-3-carboxamide gave only 5-ethoxycarbonyl-4-hydroxy-2-pyrid-3'-ylpyrimidine, despite the possibility of the intermediate (88, R = CO₂Me) reacting as a diester;⁴⁹⁷⁶ methyl 3-methoxy-2-methoxymethylenepropionate (89) and acetamide gave 4-hydroxy-5-methoxymethyl-2-methylpyrimidine (84, R = CH₂OMe);⁶¹⁹⁸ methyl α -ethoxymethylene- α -nitroacetate (88, R = NO₂) and formamide gave 4-hydroxy-5-nitropyrimidine;⁴³⁵⁷ and dimethyl α -methoxymethyleneglutarate and acetamide gave 4-hydroxy-5- β -methoxycarbonyl-ethyl-2-methylpyrimidine (84, R = CH₂CH₂CO₂Me).⁶²⁰⁰ An interesting study⁴⁹⁶⁰ of the condensation of ethyl α -cyano- α -ethoxymethyleneacetate with an excess of acetamide showed that the former reacted mainly as an aldehyde ester rather than as an aldehyde nitrile; thus at 5°, 5-cyano-4-hydroxy-2-methylpyrimidine (84, R = CN) was obtained as its acetamidinium salt in 85% yield, whereas the alternative product, 4-amino-5-ethoxycarbonyl-2-methylpyrimidine (90, R = Me), was formed in only 8% yield. However, with benzamide little cyclization occurred at 5°, while at 25° the chief cyclized product was 4-amino-5-ethoxycarbonyl-2-phenylpyrimidine (90, R = Ph) with only a little 5-cyano-4-hydroxy-2-phenylpyrimidine.⁴⁹⁶⁰

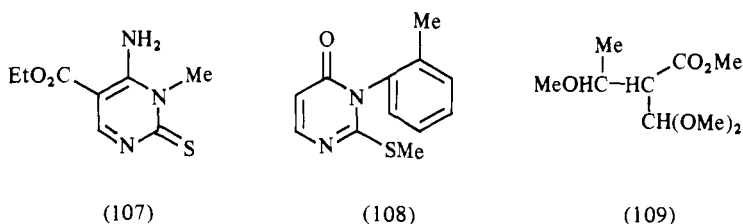
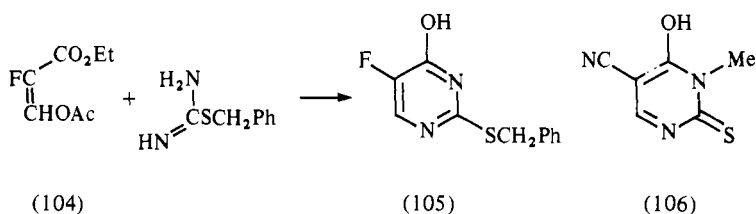


Condensation of methyl α -formyl- α -(methylthio)acetate with guanidine gave an acyclic intermediate which on heating at 130° in a vacuum gave 2-amino-4-hydroxy-5-methylthiopyrimidine.⁴³³² However, no such complication occurred when ethyl α -adamantyl- α -formylacetate was condensed with guanidine in boiling ethanol to give 5-adamantyl-2-amino-4-hydroxypyrimidine,⁵²⁹⁶ or when ethyl 2-formylbutyrate was condensed with guanidine in ethanol to give 2-amino-5-ethyl-4-hydroxypyrimidine.⁵⁷⁵⁴ The reaction of ethyl formylacetate (preparation⁵²⁹⁴) with aminoguanidine gave a single product formulated as 1,2-diamino-1,6-dihydro-6-oxypyrimidine (91), mainly because prolonged boiling in formic acid gave 7-hydroxy-*s*-triazolo[1,5-*a*]pyrimidine (92).⁵¹⁴⁰ It is worth pointing out that had the initial product been the isomeric 2-hydrazino-4-hydroxypyrimidine (94) (which indeed has an m.p. close to that recorded for the product), subsequent treatment with formic acid could well have given the same triazolo[1,5-*a*]pyrimidine (92) by initial cyclization to 5-hydroxy-*s*-triazolo[4,3-*a*]pyrimidine (93) followed by a Dimroth-like rearrangement to the [1,5-*a*] isomer.⁵⁶⁹¹ Aldehyde ester equivalents have been condensed with guanidines. Thus, diethyl α -ethoxymethylenemalonate reacted with *N*-amidinomorpholine to give 5-ethoxycarbonyl-4-hydroxy-2-morpholinopyrimidine,⁶²⁸² ethyl α -ethoxymethylene- α -phenylacetate and guanidine gave 2-amino-4-hydroxy-5-phenylpyrimidine,³⁵³² ethyl α -*p*-chlorophenylsulphonyl- α -ethoxymethyleneacetate (95) and guanidine gave 2-amino-5-*p*-chlorophenylsulfonyl-4-hydroxypyrimidine,⁵⁵⁸³ ethyl α -cyano- α -ethoxymethyleneacetate (96) and guanidine in molar proportions gave a little 2-amino-5-cyano-4-hydroxypyrimidine (97) but mainly the alternative product 2,4-diamino-5-ethoxycarbonylpyrimidine (98),^{4960, 4961} and malic acid with *N*-amidinomorpholine in concentrated sulfuric acid at room temperature gave 4-hydroxy-2-morpholinopyrimidine in 67% yield (a Davidson-Baudisch synthesis; see *H* 38).⁴⁹⁸⁰

The condensation of free aldehyde esters with urea is still rare, but aldehyde ester equivalents have been used frequently. Ethyl α -formylpropionate and urea in oleum at 100° gave 2,4-dihydroxy-5-methylpyrimidine in 50% yield,⁴⁸⁵⁶ ethyl α -formylbutyrate similarly gave 5-ethyl-2,4-dihydroxypyrimidine,⁴⁸⁵⁶ ethyl α -formyl- α -(methylthio)acetate and urea gave only an acyclic product so that the expected 2,4-dihydroxy-5-trifluoromethylthiopyrimidine had to be made indirectly,⁴⁴⁸⁷ propynoic acid (85, R = H) and urea or *N,N'*-dimethylurea in boiling benzene containing a little sulfuric acid (or in polyphosphoric acid) gave 2,4-dihydroxypyrimidine or 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine respectively,^{5123, 5513} maleic acid (99) and urea in hot polyphosphoric acid gave 2,4-dihydroxypyrimidine in low yield,⁵⁰³⁰ ethyl α -fluoro- α -methoxymethyleneacetate and *N*-benzyloxyurea gave 1-benzyloxy-5-fluorouracil (100) confirmed in orientation by unambiguous synthesis,³⁴⁶⁴ diethyl α -ethoxymethylenemalonate and *N*-(tetrahydropyran-2-yl)urea in ethanolic sodium ethoxide at 25° or 75° gave 5-ethoxycarbonyl- (101, R = Et) or 5-carboxy-3-(tetrahydropyran-2'-yl)uracil (101, R = H) respectively,⁶⁰¹¹ methyl 2-methoxymethylenepropionate and *N*-isopropylurea in aqueous acid at 25° gave an acyclic intermediate (*E* and *Z* forms) which in methanolic sodium methoxide at 95° gave 3-isopropyl-5-methyluracil,⁶²⁹² α -formyl- γ -valerolactone (102, R = Me) and urea gave 2,4-dihydroxy-5-2'-hydroxypropylpyrimidine (103, R = Me),⁵⁴⁷⁸ α -formyl- γ -butyrolactone (102, R = H) and urea gave 2,4-dihydroxy-5-2'-hydroxyethylpyrimidine (103, R = H),⁵⁴²⁷ and other examples are recorded,^{3763, 5429} including a modified procedure (see *H* 42) for making 5-ethoxycarbonyl-2,4-dihydroxypyrimidine from diethyl ethoxymethylenemalonate and urea *via* diethyl ureidomethylenemalonate.⁶²⁷⁷



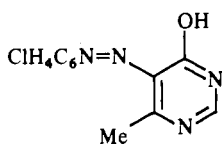
The condensation of thioureas with free aldehydo esters is exemplified in the formation of 5-ethoxycarbonylmethyl-4-hydroxy-2-mercaptopyrimidine (from methyl α -formylsuccinate/ethanolic sodium ethoxide; note transesterification),⁵⁹⁷³ 4-hydroxy-5-isopropyl-2-mercaptopyrimidine (from ethyl 2-formyl-3-methylbutyrate),^{5890, 5964} 4-hydroxy-2-mercapto-5-methylpyrimidine (from ethyl 2-formylpropionate)⁵⁴¹⁸ 5-adamant-1'-yl-4-hydroxy-2-mercaptopyrimidine (from ethyl α -adamant-1-yl- α -formylacetate),⁵²⁹⁷ 5-cyclopropyl-4-hydroxy-2-mercaptopyrimidine,⁴³⁷⁶ and others.^{5140, 5431, 5754, 5856, 5963} Similar preparations from aldehydo ester equivalents are seen in the conversion of ethyl α -ethoxymethylene- α -nitroacetate by thiourea (in aqueous dioxan containing sodium hydroxide) into 4-hydroxy-2-mercapto-5-nitropyrimidine,⁵⁴¹⁸ of isopropyl 2-ethoxymethylene-6-phenylhexanoate into 4-hydroxy-2-mercapto-5-4'-phenylbutylpyrimidine,⁵⁸⁶¹ of ethyl 3-acetoxy-2-fluoroacrylate (104) by *S*-benzylthiourea into 2-benzylthio-5-fluoro-4-hydroxypyrimidine (105), of ethyl α -cyano- α -ethoxymethyleneacetate by *N*-methylthiourea (in ethanolic sodium ethoxide at reflux) into 5-cyano-3-methyl-2-thiouracil (106) plus a little 4-amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-thiopyrimidine (107) (when done at 25°, the condensation gave mainly the latter product),⁵⁶⁶⁵ of ethyl propynoate by *S*-methyl-*N*-*o*-tolylthiourea into 1,6-dihydro-2-methylthio-1-*o*-tolyl-6-oxopyrimidine (108),⁶²⁴⁶ and of methyl 2-dimethoxymethyl-3-methoxypropionate (109) into several pyrimidines.⁵⁴²⁸ Other examples have been reported.⁶³⁴⁸



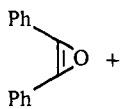
6. Use of β -Keto Esters (*H* 48, *E* 31)

Many recent examples of the use of β -keto esters in the Principal Synthesis are quite routine, and for this reason they are relegated to Table III. Unusual or interesting examples are discussed below.

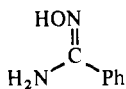
Ethyl α -*p*-chlorophenylazoacetoacetate and formamidine in methanolic sodium methoxide gave 5-*p*-chlorophenylazo-4-hydroxy-6-methylpyrimidine (110) in 80% yield,⁵⁶³⁴ ethyl acetoacetate and trichloroacetamidine without solvent at 25° for 24 h gave 4-hydroxy-6-methyl-2-trichloromethylpyrimidine,⁶⁰³³ ethyl acetoacetate and 3,3-dichloro-2,2-difluoroacetamidine in water at 25° gave 2- β -dichloro- α -difluoroethyl-4-hydroxy-6-methylpyrimidine,⁵⁹⁹⁵ ethyl acetoacetate and pyridin-2(or 4)-carboxamidine in methanolic sodium methoxide under reflux for 24 h gave 4-hydroxy-6-methyl-2-pyrid-2'(or 4')-yl-pyrimidine respectively,^{6087, 6298} diphenylcyclopropenone (111) and benzamide oxime (112) in refluxing toluene gave 4-hydroxy-2,5,6-triphenylpyrimidine (113),⁵⁹⁴⁴ the same cyclopropenone (111) and *S,S*-dimethyl-*N*- α -(phenylimino)benzylsulfimide [$\text{Me}_2\text{S}=\text{NC}(=\text{NPh})\text{Ph}$] in refluxing toluene gave 1,6-dihydro-6-oxo-1,2,4,5-tetraphenylpyrimidine which is the *N*-phenyl derivative of (113),⁵²⁵⁹ dimethyl acetylenedicarboxylate and benzamide oxime in refluxing toluene (for water removal) gave 4,5-dihydroxy-6-methoxycarbonyl-2-phenylpyrimidine (114) in good yield by an unusual mechanism,⁵⁸⁰⁰ dimethyl acetylenedicarboxylate and trichloroacetamidine gave 4-hydroxy-6-methoxycarbonyl-2-trichloromethylpyrimidine in poor yield,⁴⁸²¹ and α -acetyl- γ -butyrolactone (115) and aromatic amidines gave 2-*p*-chlorophenyl-4-hydroxy-5- β -hydroxyethyl-6-methylpyrimidine (116) and 24 analogues;⁶³⁰⁵ similarly, 3-ethoxyethylidene-2,3-dihydro-5-methyl-2-



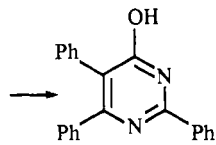
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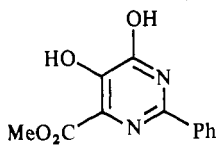
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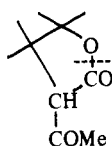
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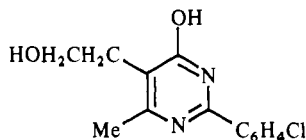
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(114)

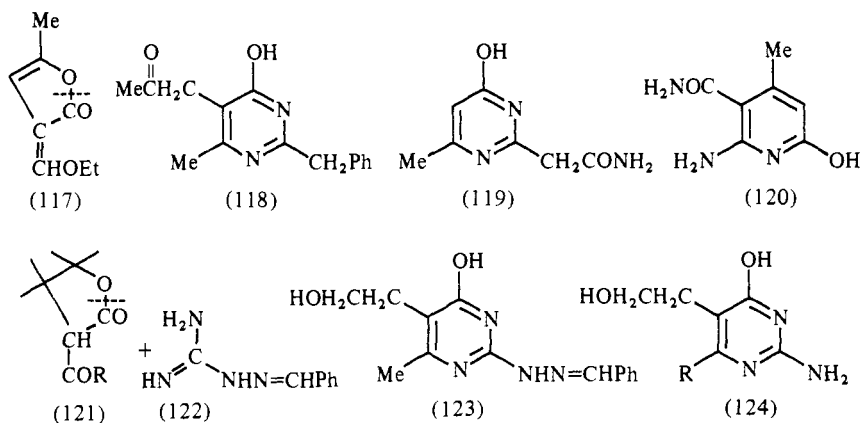


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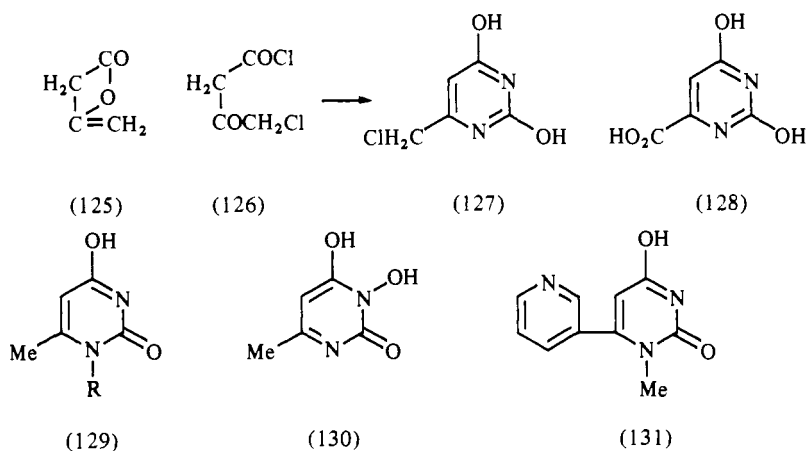
(116)

oxofuran (117) and phenylacetamidine gave 5-acetyl-2-benzyl-4-hydroxy-6-methylpyrimidine (118).⁴⁴⁵⁹ When *C*-carbamoylacetylamidine was condensed with ethyl acetoacetate in ethanolic sodium hydroxide at 25°, the expected 2-carbamoylmethyl-4-hydroxy-6-methylpyrimidine (119) was formed in good yield along with a separable isomeric by-product, 2-amino-3-carbamoyl-6-hydroxy-4-methylpyridine (120), formed in low yield by an alternative cyclization; when hot ethanolic sodium ethoxide was used as a condensation medium the ratio of products was reversed.^{5640, 5688} It would appear that an *N*-alkylbenzamidine condenses with ethyl acetoacetate or with diketene to give only one product, 1-alkyl-1,6-dihydro-4-methyl-6-oxo-2-phenylpyrimidine, as exemplified in 1,6-dihydro-1,4-dimethyl-6-oxo-2-phenylpyrimidine and analogues.^{4484, 4510}



The condensation of benzylideneaminoguanidine (122) with 2-acetyl- γ -butyrolactone (121, R = Me) at 130° without solvent gave 2-benzylidenehydrazino-4-hydroxy-5- β -hydroxyethyl-6-methylpyrimidine (123) and thence, by treatment with ethanolic hydrazine hydrate, the 2-hydrazino analogue;⁵⁰⁵³ the similar lactone, 2-propionyl- γ -butyrolactone (121, R = Et) and its higher homologues (121, R = Pr, Hx, etc.) reacted with guanidine to yield 2-amino-4-ethyl-6-hydroxy-5-hydroxyethylpyrimidine (124, R = Et) and homologues;⁵³⁶¹ diketene reacted with biguanide or 1-phenylbiguanide to give 2-guanidino-4-hydroxy-6-methylpyrimidine^{5394, 6194} or 4-hydroxy-6-methyl-2-*N'*-phenylguanidinopyrimidine,^{4951, 6205, 6328} respectively; diethyl acetone-dicarboxylate and guanidine carbonate (1 or 2 mol) gave respectively 2-amino-4-ethoxycarbonyl- or 2-amino-4-carboxy-6-hydroxypyrimidine,⁵⁷⁶³ and other related but more complicated reactions have been reported.^{5709, 5879}

The reaction of diketene (125) with urea was found to be catalysed by mercuric sulfate in glacial acetic acid to yield 2,4-dihydroxy-6-methylpyrimidine.^{4787, 4849} Diketene (125) has also been used to make γ -chloroacetoacetyl chloride (126), which on treatment with urea in pyridine-acetic anhydride at 20° gave 4-chloromethyl-2,6-dihydroxypyrimidine (127), a good substrate for oxidative hydrolysis to 4-carboxy-2,6-dihydroxypyrimidine (orotic acid: 128).⁴⁵¹² The latter was also made by the condensation of diethyl oxalylacetate with urea in oleum at 100°; the same conditions gave a small yield of 2,4-dihydroxy-6-methylpyrimidine from ethyl acetoacetate and urea.⁴⁸⁵⁶ The condensation of diketene (125) with *N*-phenylurea or other *N*-substituted analogues has been claimed⁴⁹²⁵ to give entirely 6-methyl-1-phenyluracil (129) or analogues, whereas ethyl acetoacetate and similarly substituted ureas give 6-methyl-3-substituted uracils. There does not seem to be any rigorous proof for this; on the one hand, *N*-hydroxyurea and ethyl acetoacetate certainly gave 3-hydroxy-6-methyluracil (2,4-dihydroxy-6-methylpyrimidine 3-oxide: 130),⁵³⁵⁰ but on the other, ethyl nicotinoylacetate and *N*-methylurea were said to give 1-methyl-6-pyrid-3'-yluracil (131) on apparently sound mass spectral evidence.⁴⁵²³ Propiophenone semicarbazone and diketene gave 1- α -ethylbenzylideneamino-6-methyluracil of proven structure.⁵⁰⁷⁰



Most of the condensations of keto esters with thiourea and its derivatives are covered in Table III. In addition, ethyl $\gamma\gamma$ -diethoxyacetoacetate and *N*-methylthiourea under the usual alkaline conditions gave in good yield only one isomer, 6-diethoxymethyl-3-methyl-2-thiouracil (132);⁶⁰⁶⁹ ethyl α -trifluoromethyl- (133, R = F) or α -fluoromethylacetoacetate (133, R = H) with *S*-methylthiourea gave 4-hydroxy-2-

TABLE III. Additional Examples of the Use of β -Keto Esters in the Principal Synthesis (*H* 44, *E* 32)

Three-Carbon Fragment	One-Carbon Fragment	Solvent and Conditions	Pyrimidine (Yield)	Ref.
Ethyl acetoacetate	3-Phenylpropionamidine	Aq. ethanolic sodium hydroxide; 25°; many h	4-Hydroxy-6-methyl-2-phenethyl- (c. 15%)	6018
Ethyl acetoacetate	3-Methoxypropionamidine	Aq. ethanol; 25°	4-Hydroxy-2- β -methoxyethyl-6-methyl ^a (39%)	4513
Ethyl acetoacetate	3-Ethoxypropionamidine	Ethanolic sodium ethoxide; 25°; 3 h	2- β -Ethoxyethyl-4-hydroxy-6-methyl- (67%)	5096
Ethyl α -isopropylacetoacetate	Benzamidine	Ethanolic sodium ethoxide; reflux; 24 h	4-Hydroxy-5-isopropyl-6-methyl-2-phenyl- ^b (c. 40%)	4348
Ethyl 2-bromocrotonate	Benzamidine	Trimethylamine in benzene; 20°; 6 h. Also: ethanolic sodium ethoxide; reflux	4-Hydroxy-6-methyl-2-phenyl- ^b (23%; 81%)	6339, 6377
Ethyl 2-acetylhept-6-enoate	Acetamidine	Ethanolic sodium hydroxide; 25°; 24 h	4-Hydroxy-2,6-dimethyl-5-pent-4'-enyl- ^c	5290
Diethyl 2-acetylglutarate	Benzamidine	Ethanol; reflux; 12 h	5- β -Ethoxycarbonyl-4-hydroxy-6-methyl-2-phenyl- ^d (38%)	5766
Ethyl benzoylacetate	Isobutyramidine	Ethanolic sodium ethoxide; reflux; 6 h	4-Hydroxy-2-isopropyl-6-phenyl- (55%)	5690
Ethyl <i>o</i> -toluoylacetate	Benzamidine	Ethanol; 120°; sealed; 24 h	4-Hydroxy-2-phenyl-4- <i>o</i> -tolyl- (30%)	5352
Ethyl benzoylacetate	<i>p</i> -Chlorobenzamidine	Aq. ethanolic sodium carbonate; 25°; 16 h	2- <i>o</i> -Chlorophenyl-4-hydroxy-6-phenyl- (30%)	5590
Ethyl benzoylacetate	Benzamidine	Aq. ethanolic sodium hydroxide; 25°; 100 h. Better: ethanolic sodium ethoxide; reflux; 24 h	4-Hydroxy-2,6-diphenyl- (26%, 70%)	5760, 6377

Ethyl propionylacetate	2-Amidinoacetamide	Ethanol sodium hydroxide; 25°; 16 h	2-Acetamidomethyl-4-ethyl-6-hydroxy- (18%)	5693
Ethyl picolinoylacetate	Acetamidine	Aq. potassium hydroxide; 25°; 72 h	4-Hydroxy-2-methyl-6-pyrid-2'-yl- (c. 40%)	6039
Diethyl oxalylpropionate	Acetamidine	Ethanol potassium hydroxide; reflux; 12 h	4-Carboxy-6-hydroxy-2,5-dimethyl- (65%)	6140
Ethyl α -(adamant-1'-yl)acetoacetate	Guanidine	Ethanol sodium ethoxide; reflux; 60 h	5-Adamant-1'-yl-2-amino-4-hydroxy-6-methyl- (55%)	5296
Ethyl 2-adamant-1'-yl-3-oxohexanoate	Guanidine	Ethanol sodium ethoxide; reflux; 120 h	5-Adamant-1'-yl-2-amino-4-ethyl-6-hydroxy- ^e (31%)	5298
Ethyl acetoacetate	1-Phenylbiguanide	Aq. ethanolic sodium hydroxide; 25°; 170 h	4-Hydroxy-6-methyl-2- <i>N'</i> -phenylguanidino- <i>f</i> (74%)	6205
Ethyl acetoacetate	<i>N</i> -carboxymethyl-guanidine	—	2-Carboxymethylamino-4-hydroxy-6-methyl- ^g (40%)	4476
t-Butyl α -cyanoacetoacetate	Guanidine	Ethanol sodium ethoxide; reflux; 1 h	2-Amino-5-cyano-4-hydroxy-6-methyl- (68%)	5788
Ethyl 2-benzoyl-3-methoxypropionate	Guanidine	Sodium methoxide in t-butyl alcohol; reflux; 18 h	2-Amino-4-hydroxy-5-methoxymethyl-6-phenyl-	5725
Ethyl α - <i>p</i> -chlorobenzyl- $\gamma\gamma$ -dimethoxyacetoacetate	Guanidine	Ethanol sodium ethoxide; reflux; 6 h	2-Amino-5- <i>p</i> -chlorobenzyl-4-dimethoxymethyl-6-hydroxy- ^b (46%)	5743
Ethyl α -propylacetoacetate	<i>N,N</i> -dimethylguanidine	Methanolic sodium methoxide; reflux; 20 h	2-Dimethylamino-4-hydroxy-6-methyl-5-propyl- ^f (54%)	5722
Ethyl acetoacetate	Biguanide	Aq. ethanolic sodium hydroxide; 25°; 18 h	2-Guanidino-4-hydroxy-6-methyl- (c. 80%)	5394
Ethyl isobutyroacetate	Guanidine	Ethanol sodium ethoxide; reflux; 2 h	2-Amino-4-hydroxy-6-isopropyl- (72%)	5807
Ethyl $\gamma\gamma$ -dimethoxyacetoacetate	Guanidine carbonate	Ethanol; reflux; 48 h	2-Amino-4-dimethoxymethyl-6-hydroxy- (73%)	5300

TABLE III (Continued)

Three-Carbon Fragment	One-Carbon Fragment	Solvent and Conditions	Pyrimidine (Yield)	Ref.
Ethyl α -octylacetoacetate	Guanidine	Ethanol; sodium ethoxide; reflux; 3 h	2-Amino-4-hydroxy-6-methyl-5-octyl- <i>f</i> (46%)	5453
Ethyl γ, γ, γ -trifluoroacetoacetate	Cyanoguanidine	Ethanol; sodium ethoxide; reflux; 60 h	2-Cyanoamino-4-hydroxy-6-trifluoromethyl- (69%)	6507
Methyl 2-cyano-3-methoxy-3-phenylpropenoate	Guanidine	Ethanol; reflux; 2 h	2-Amino-5-cyano-4-hydroxy-6-phenyl- (54%)	6286
Methyl 4,5-isopropylidenedioxy-3-oxopentanoate	Guanidine carbonate	Ethanol; 100°; 4 h	2-Amino-4,2',2'-dimethyl-1',3'-dioxolan-4'-yl-6-hydroxy- (70%)	4604
Ethyl isonicotinoylacetate	Urea	120°; 17 h	2,4-Dihydroxy-6-pyrid-4'-yl- (38%)	4523
Ethyl oxalylacetate	<i>N</i> - β -hydroxyethylurea	(See <i>E</i> 31)	6-Carboxy-3- β -hydroxyethyluracil	4778
Ethyl adamant-1-ylcarbonylacetate	Urea	Ethanol; sodium ethoxide; reflux; 24 h	4-Adamant-1'-yl-2,6-dihydroxy- (22%)	4389
Ethyl propionylacetate	<i>N</i> -phenylurea	Dimethylformamide + acetic anhydride; 25°; 4 days; then sodium hydroxide at 25°	6-Ethyl-3-phenyluracil (95%)	4931
Ethyl α -adamant-1-ylacetoacetate	Thiourea	Ethanol; reflux; 8 h	5-Adamant-1'-yl-4-hydroxy-2-mercapto-6-methyl-	5297
Methyl 2-isopropyl-5-methyl-3-oxohexanoate ^h	Thiourea	Methanol; reflux; 12 h	4-Hydroxy-6-isobutyl-5-isopropyl-2-mercapto- (11%)	5890
Diethyl 2-acetylglutarate	Thiourea	Ethanol; sodium ethoxide; reflux; 2 h	5- β -Ethoxycarbonyl-4-hydroxy-2-mercapto-6-methyl- (35%)	5707
Ethyl α -methoxyacetoacetate	Thiourea	Ethanol; sodium ethoxide; reflux; 5.5 h	4-Hydroxy-2-mercapto-5-methoxy-6-methyl- (c. 45%)	5786
Isopropyl $\gamma\gamma$ -dimethoxy- α -3'-phenylpropylacetoacetate	Thiourea	Ethanol; sodium ethoxide; reflux; 12 h	4-Dimethoxymethyl-6-hydroxy-2-mercapto-5- γ -phenylpropyl- ^g (12%)	5526

Ethyl α -benzyl- $\gamma\gamma$ -dimethoxyacetate	Thiourea	Ethanol sodium ethoxide; reflux; 9 h	5-Benzyl-4-dimethoxymethyl-6-hydroxy-2-mercapto- <i>f</i> (30%)	5743
Isopropyl α -benzyl- $\gamma\gamma\gamma$ -trifluoroacetate	Thiourea	Sodium methoxide in <i>t</i> -butyl alcohol; reflux; 18 h	5-Benzyl-4-hydroxy-2-mercapto-6-trifluoromethyl- <i>d</i> (25%)	5874
Ethyl benzoylacetate	Thiourea	Ethanol sodium ethoxide; reflux; 72 h	4-Hydroxy-2-mercapto-6-phenyl- (61%)	4675
Ethyl α -methylacetate	Thiourea	Ethanol sodium ethoxide; reflux; 8 h	4-Hydroxy-2-mercapto-5,6-dimethyl-	4725
Ethyl $\gamma\gamma$ -diethoxy-acetoacetate	Thiourea	Ethanol sodium ethoxide; 25°; 24 h	4-Diethoxymethyl-6-hydroxy-2-mercapto-	6069
Ethyl 3-oxohept-6-enoate	Thiourea	Ethanol sodium ethoxide; reflux; 4 h	4-But-3'-enyl-6-hydroxy-2-mercapto- <i>f</i> (87%)	4569
Ethyl α -adamant-1-ylcarbonylacetate	Thiourea	Ethanol sodium ethoxide; reflux; 24 h	4-Adamant-1'-yl-6-hydroxy-2-mercapto- (60%)	4389
2-Acetyl- γ -butyrolactone	Thiourea	Methanol sodium methoxide; reflux; 15 h	4-Hydroxy-5- β -hydroxyethyl-2-mercapto-6-methyl- <i>f</i> (32%)	5361
Ethyl α -cyclohexyl-carbonylacetate	Thiourea	Ethanol sodium ethoxide; reflux; 7 h	4-Cyclohexyl-6-hydroxy-2-mercapto- (71%)	6052
Ethyl $\gamma\gamma$ -dimethoxy- α -fluoroacetate	<i>S</i> -propylthiourea	Methanol sodium methoxide; 25°; 24 h	4-Dimethoxymethyl-5-fluoro-6-hydroxy-2-propylthio- <i>d</i> (7%)	5525
Diethyl oxalylacetate	<i>S</i> -methylthiourea	Aq. sodium hydroxide; 25°; 8 h	4-carboxy-6-hydroxy-2-methylthio- (60%)	5618
Ethyl methyl oxalylacetate	<i>S</i> -methylthiourea	Aq. ammonia; 5°; 3 h	4-carbamoyl-6-hydroxy-2-methylthio- (70–80%)	5151
Ethyl α -methoxy-acetoacetate	<i>S</i> -methylthiourea	Aq. alkali; <i>c</i> . 5°; 24 h	4-Hydroxy-5-methoxy-6-methyl-2-methylthio- (16%)	4397
Ethyl 4- <i>o</i> -nitrophenyl-acetoacetate	<i>S</i> -ethylthiourea	Carbon tetrachloride + water emulsion; 25°; 48 h	2-Ethylthio-4-hydroxy-6- <i>o</i> -nitrobenzyl- <i>f</i> (82%)	4560

^a And nine 2- β -alkoxyethyl homologues.

^b And four analogues.

^c And 5-hex-5'-enyl homologue.

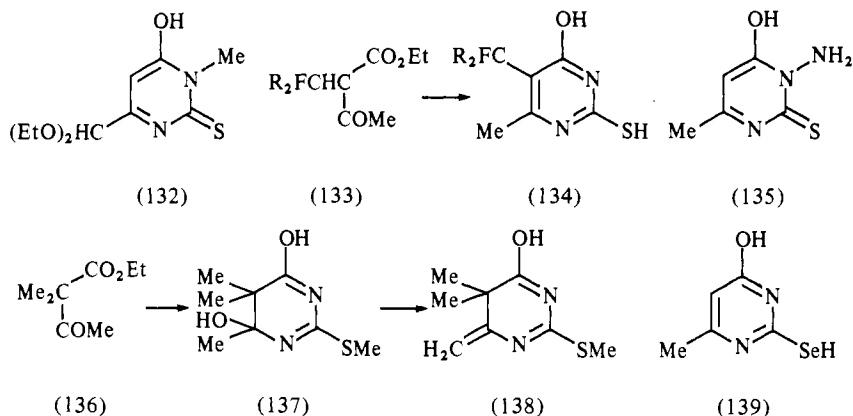
^d And three analogues.

^e And the 4-butyl homologue

^f And analogues.

^g And nine homologues.

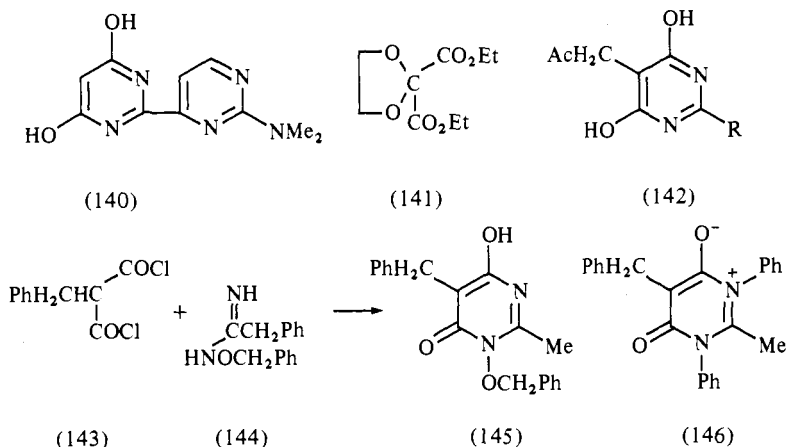
^h From self-condensation of methyl isovalerate.



mercapto-6-methyl-5-trifluoromethyl- (134, R = F) or 5-fluoromethyl-4-hydroxy-2-mercapto-6-methylpyrimidine (134, R = H), respectively;⁵⁷⁸⁵ ethyl acetoacetate and thiosemicarbazide appeared to give only one isomer, 3-amino-6-methyl-2-thiouracil (135);⁵¹⁴⁰ diketene and thiosemicarbazide (supplied as its isopropylidene derivative) in acid gave the same product (135);⁵¹⁶⁶ ethyl $\alpha\alpha$ -dimethylacetoacetate (136) and *S*-methylthiourea gave initially 4,5-dihydro-4,6-dihydroxy-4,5,5-trimethyl-2-methylthiopyrimidine (137) which lost water on sublimation to give 4,5-dihydro-6-hydroxy-5,5-dimethyl-4-methylene-2-methylthiopyrimidine (138) at the same oxidation state as a normal pyrimidine;⁵²⁸⁰ ethyl acetoacetate and selenourea gave 4-hydroxy-2-hydroseleno-6-methylpyrimidine (139) in good yield;⁶²⁰⁴ diketene and *N*-phenylthiourea gave a separable mixture of 6-methyl-1(and 3)-phenyl-2-thiouracil with the latter predominating;⁴⁹³⁰ and other complicated examples are known.^{4547, 4604, 4716, 4726, 5701, 5774, 5812, 5917, 5923, 5940, 5999, 6053, 6358}

7. Use of β -Diesters (Malonic Esters) (H 51, E 38)

The condensation of malonic esters with amidines has been extensively used recently. In addition to the examples in Table IV, 4-amidino-2-dimethylaminopyrimidine and dimethyl malonate in methanolic sodium methoxide gave 2'-dimethylamino-4,6-dihydroxy-2,4'-bipyrimidine (140) in 71% yield;⁶¹⁸¹ diethyl α -acetylmalonate as its cyclic acetal (141) with acetamidine or benzamidine gave 5-acetyl-4,6-dihydroxy-2-methylpyrimidine (142, R = Me) or its 2-phenyl analogue (142, R = Ph);^{5702, 5703} α -benzylmalonyl chloride (143) and *N*-benzyloxyacetamidine (144) in refluxing xylene gave 5-benzyl-1-



benzyloxy-1,6-dihydro-4-hydroxy-2-methyl-6-oxopyrimidine (145), but the yield was improved by replacing the chloride by bis(2,4,6-trichlorophenyl) α -benzylmalonate and heating without solvent at 190° .⁴³⁵³ The last-mentioned ester also reacted with *N,N'*-diphenylacetamide to give the betaine (146);^{4340, 4354} carbon suboxide (147) and *N*-benzyloxyacetamide (148) in ether, initially at -20° and then at 25° , gave 1-benzyloxy-1,6-dihydro-4-hydroxy-2-methyl-6-oxopyrimidine (149) in 52% yield;⁴³³⁷ carbon suboxide (147) and *N,N'*-diphenylbenzamidinium under similar conditions gave *anhydro*-4-hydroxy-6-oxo-1,2,3-triphenylpyrimidinium hydroxide, akin to (146);⁵⁴⁹⁷ and other examples are known.^{5882, 5993} In contrast to some of the above reactions, α -benzylmalonyl chloride (143) reacted with (free) benzamide oxime (150) in boiling xylene to give simply 5-benzyl-4,6-dihydroxy-2-phenylpyrimidine (151), whereas the same starting materials in boiling chlorobenzene

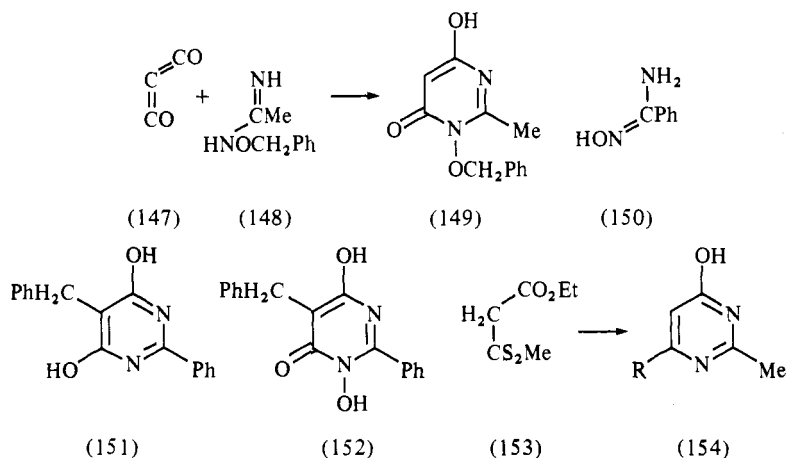


TABLE IV. Additional Examples of the Use of Malonic Esters in the Principal Synthesis (*H* 56, *E* 40)

Three-Carbon Fragment	One-Carbon Fragment	Solvent and Conditions	Pyrimidine (Yield)	Ref.
Diethyl malonate	1, 1, 1-trichloroacetamidine	Ethanolic sodium ethoxide; reflux; 4 h	4, 6-Dihydroxy-2-trichloromethyl- (55%)	5785
Diethyl malonate	Isobutyramidine	Ethanolic sodium ethoxide; reflux; 6 h	4, 6-Dihydroxy-2-isopropyl- (61%)	5690
Diethyl malonate	Pyridine-2-carboxamidine	Ethanolic sodium ethoxide; reflux; 3 h	4, 6-Dihydroxy-2-pyrid-2'-yl- ^a (62%)	5959
Diethyl malonate	Pyridine-3-carboxamidine	Ethanolic sodium ethoxide; 25°; 24 h	4, 6-Dihydroxy-2-pyrid-3'-yl- ^b	4715
Dimethyl malonate	Pivalamidine	Methanolic sodium methoxide; 25°; 2 h (?)	2- <i>t</i> -Butyl-4, 6-dihydroxy- (62%)	5753
Diethyl malonate	<i>C</i> -phenylacetamidine	Ethanolic sodium ethoxide; 25°; 24 h	2-Benzyl-4, 6-dihydroxy- ^c	4917
Diethyl malonate	Valeramidine	Methanolic sodium methoxide; 25° then reflux; 30 h total	2-Butyl-4, 6-dihydroxy- (60%)	4570
Diethyl α -ethylmalonate	Formamidine	Ethanolic sodium ethoxide; 25°; 24 h	5-Ethyl-4, 6-dihydroxy- (87%)	4577
Diethyl α -allylmalonate	Formamidine	Methanolic sodium methoxide; 25°; 18 h	5-Allyl-4, 6-dihydroxy- (54%)	6064
Diethyl α -ethylmalonate	2-Amidinopyrimidine	Ethanolic sodium ethoxide; 25°; 24 h	5-Ethyl-4, 6-dihydroxy-2, 2'-bipyrimidine (40%)	4580
Diethyl α -pent-4-enylmalonate	Acetamidine	Ethanolic sodium ethoxide; reflux; 6 h	4, 6-Dihydroxy-2-methyl-5-pent-4'-enyl- ^d (83%)	5290
Diethyl α - <i>o</i> -tolylmalonate	Benzamidine	Ethanolic sodium ethoxide; 110° (sealed); 5 h	4, 6-Dihydroxy-2-phenyl-5- <i>o</i> -tolyl- (17%)	5352
Diethyl α - <i>p</i> -methoxyphenylmalonate	Benzamidine	Methanolic sodium methoxide; reflux; 8 h	4, 6-Dihydroxy-5- <i>p</i> -methoxyphenyl-2-phenyl- ^e (98%)	4529

TABLE IV. (Continued)

Three-Carbon Fragment	One-Carbon Fragment	Solvent and Conditions	Pyrimidine (Yield)	Ref.
Diethyl α -phenylmalonate	<i>p</i> -Hexylbenzamidine	Methanolic sodium methoxide; reflux; 8 h	2- <i>p</i> -hexylphenyl-4, 6-dihydroxy-5-phenyl- <i>f</i> (89%)	4529
Diethyl α - <i>p</i> -ethoxyphenylmalonate	<i>p</i> -Ethoxybenzamidine	Methanolic sodium methoxide; 80°; 8 h	2, 5-Bis- <i>p</i> -ethoxyphenyl-4, 6-dihydroxy- <i>f</i> (72%)	4497
Diethyl α -butylmalonate	<i>p</i> -Butoxybenzamidine	Methanolic sodium methoxide; reflux; 5 h	2- <i>p</i> -Butoxyphenyl-5-butyl-4, 6-dihydroxy- <i>g</i> (79%)	4539
Diethyl α - <i>o</i> -methoxycarbonylbenzylmalonate	Formamidine	Methanolic sodium methoxide; 25° then reflux; 22 h total	4, 6-Dihydroxy-5- <i>p</i> -methoxycarbonylbenzyl- (58%)	4443
Diethyl α -(3-methoxycarbonylfur-2-yl)methylmalonate	Formamidine	Methanolic sodium methoxide; 25° then reflux; 19 h total	4, 6-Dihydroxy-5-(3'-methoxycarbonylfur-2'-yl)methylpyrimidine	4444
Diethyl α -ethylmalonate	Guanidine	Ethanol; reflux; 8 h	2-Amino-5-ethyl-4, 6-dihydroxy- (55%)	5296
Diethyl α -adamant-1-ylmalonate	Guanidine carbonate	Ethanol; reflux; 24 h	5-Adamant-1'-yl-2-amino-4, 6-dihydroxy- (76%)	5296
Diethyl malonate	Biguanide	Methanolic sodium methoxide; reflux; 16 h	Bis(4, 6-dihydroxypyrimidin-2-yl)amine (c. 70%)	5394
Diethyl α -ureidomalonate	Guanidine	Methanolic sodium methoxide; 80°; under nitrogen; 3 h	2-Amino-4, 6-dihydroxy-5-ureido- <i>d</i> (c. 54%)	5295
Diethyl α -(4-ethoxycarbonyl-4-cyclohexylbutyl)malonate	Guanidine	Methanolic sodium methoxide	2-Amino-5-(4'-cyclohexyl-4'-ethoxycarbonyl)butyl-4, 6-dihydroxy- <i>h</i>	6161
Diethyl α - <i>p</i> -ethoxycarbonylphenethylmalonate	Guanidine	Methanolic sodium methoxide; 25°; 4 h	2-Amino-5- <i>p</i> -carboxyphenethyl-4, 6-dihydroxy- <i>i</i> (40%)	6186
Diethyl α - <i>o</i> -dimethylaminoanilomalonate	Urea	Ethanol; sodium ethoxide; reflux; 7 h	5- <i>o</i> -Dimethylaminoanilino-2, 4, 6-trihydroxy- <i>h</i> (98%)	5177

Diethyl α -phenylmalonate	Urea	Ethanollic sodium ethoxide; reflux; 2 h	2, 4, 6-Trihydroxy-5-phenyl- ^d	5321
Dimethyl α , α -dimethoxymalonate	Urea	Methanollic sodium methoxide; reflux; 8 h	5, 5-Dimethoxybarbituric acid ^d (48%)	5901
Malonic acid	<i>N</i> , <i>N'</i> -diethylurea	Acetic anhydride; 60°; 6 h	1, 3-Diethyl-1, 2, 3, 4-tetrahydro-6-hydroxy-2, 4-dioxo- (<i>c</i> . 15%)	5321
Malonic acid	<i>N</i> , <i>N'</i> -bis- β -methoxycarbonyl ethylurea	Acetic anhydride; 60°; 8 h	1, 3-Bis- β -methoxycarbonyl ethyl-1, 2, 3, 4-tetrahydro-6-hydroxy-2, 4-dioxo- (63%)	6219
Diethyl α -ethylmalonate	<i>N</i> -ethylurea	Ethanollic sodium ethoxide; reflux; 3 h	1, 5-Diethylbarbituric acid (50%)	5323
Diethyl α -ethylmalonate	<i>N</i> -benzyl oxyurea	Propanollic sodium propoxide; reflux; 36 h	1-Benzyl oxy-5-ethylbarbituric acid (33%)	5218
α -Ethyl- α -phenylmalonyl dichloride	<i>N</i> , <i>N'</i> -dibenzyl oxyurea	Toluene; reflux; 22 h	1, 3-Dibenzyl oxy-5-ethylhexahydro-2, 4, 6-trioxo-5-phenyl- ^j (25%)	6268
Diethyl α , α -dimethylmalonate	<i>N</i> -ethylurea	Ethanollic sodium ethoxide; reflux; 6 h	1-Ethyl-5, 5-dimethylbarbituric acid ^d (55%)	5898
Diethyl α -amylmalonate	Thiourea	Ethanollic sodium ethoxide; reflux; 8 h	5-Amyl-4, 6-dihydroxy-2-mercapto- (30%)	5882
Diethyl α -adamant-1-ylmalonate	Thiourea	Ethanollic sodium ethoxide; reflux; 7 h	5-Adamant-1'-yl-4, 6-dihydroxy-2-mercapto- (68%)	5297
Diethyl malonate	Acetone thiosemicarbazone	Ethanollic sodium ethoxide; reflux; 48 h	1-Amino-2-thioarbituric acid (39%)	5186

^a And 5-methyl and 5-phenyl derivatives.

^b And 5-substituted or other analogues.

^c And many 5-mono- and 5, 5-di-substituted analogues.

^d And three analogues.

^e And 15 analogues.

^f And 11 analogues.

^g And 41 analogues.

^h And five analogues.

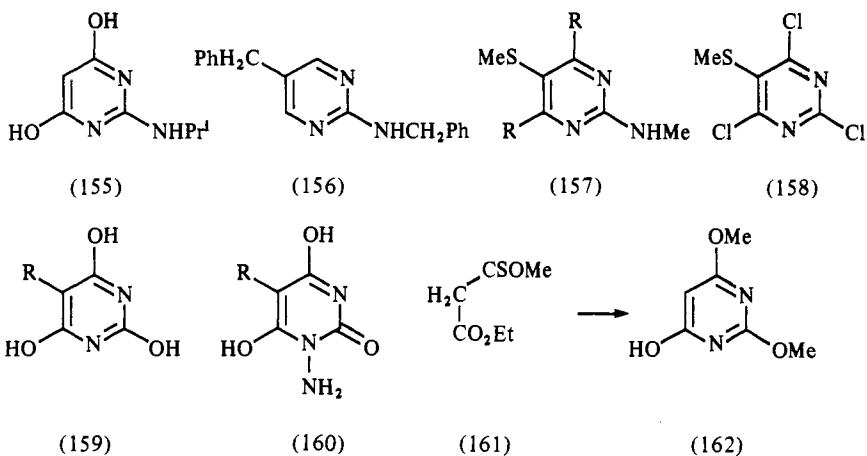
ⁱ Ester hydrolysed during work up; and four analogues.

^j And the 5, 5-diethyl analogue.

containing triethylamine gave the corresponding *N*-oxide, usually written as 5-benzyl-1,6-dihydro-1,4-dihydroxy-6-oxo-2-phenylpyrimidine (152).⁴⁹¹⁶ When methyl 2-ethoxycarbonyldithioacetate (153) was allowed to react with acetamidine in ethanolic sodium ethoxide, a separable mixture of 4-hydroxy-6-mercapto-2-methylpyrimidine (154, R = SH) and the ethoxy analogue (154, R = OEt) was obtained (in poor yield), but when the reaction was carried out in boiling dioxane under nitrogen, only the required mercaptopyrimidine (154, R = SH) was obtained in 70% yield;⁴³⁶¹ 4-hydroxy-6-mercapto-2-phenylpyrimidine and 2-amino-4-hydroxy-6-mercaptopyrimidine were obtained similarly from free benzamidine and guanidine, respectively.⁴³⁶¹

Substituted guanidines appear to react with diesters to give only 2-substituted-aminopyrimidines. Thus, diethyl malonate and isopropylguanidine in methanolic sodium methoxide gave 4,6-dihydroxy-2-isopropylaminopyrimidine (155) in 70% yield;⁶³²⁷ diethyl α -benzylmalonate and benzylguanidine gave 5-benzyl-2-benzylamino-4,6-dihoxypyrimidine (156);⁶²⁷⁹ and diethyl α -(methylthio)malonate and methylguanidine gave a product identified as 4,6-dihydroxy-2-methylamino-5-methylthiopyrimidine (157, R = OH) by conversion into 4,6-dichloro-2-methylamino-5-methylthiopyrimidine (157, R = Cl), which was identical with the mono-methylaminolysis product from 2,4,6-trichloro-5-methylthiopyrimidine (158).⁶⁰⁶¹ The reaction of 5-aminotetrazole with diethyl malonate at 180° was nothing more than a Principal Synthesis which gave 2-azido-4,6-dihydroxypyrimidine in low yield.⁵⁸⁸⁶ More complicated examples have been reported.⁶⁵¹⁸

Barbituric acid derivatives have continued to be made from diesters and ureas. Some of the simple examples are in Table IV. Preparation

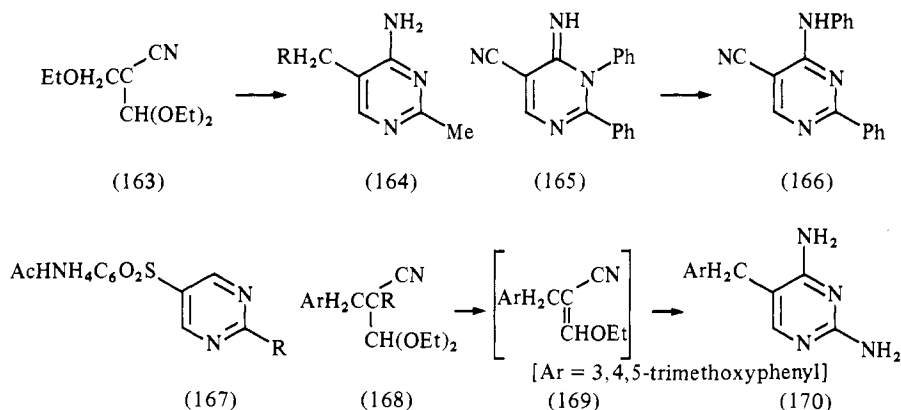


of the parent compound, 2,4,6-trihydroxypyrimidine (159, R = H) from malonic acid and urea in acetic acid–acetic anhydride, as well as its subsequent 5-nitration to dilituric acid (159, R = NO₂), have been described in some detail;⁴⁷⁴⁸ the latter compound has also been made directly, and in better overall yield, from diethyl α -nitromalonate and urea in ethanolic sodium ethoxide, while 1-methyl-5-nitrobarbituric acid was made by substituting *N*-methylurea for urea in the same preparation.⁴⁷⁴⁸ Condensation of diethyl malonate with the semicarbazone of acetone or benzaldehyde in a medium of ethanolic sodium ethoxide gave 1-aminobarbituric acid (160, R = H) in 6 or 25% yield respectively;⁵¹⁸⁶ 1-amino-5-methylbarbituric acid (160, R = Me) was made similarly,⁵¹⁸⁶ as were the 5-ethyl, 5-propyl, and 5-butyl homologues,⁵¹⁸⁵ using acetone semicarbazone in each case. When ethyl 2-methoxy(thiocarbonyl)acetate (161) reacted with *O*-methylurea in methanolic sodium methoxide, 4-hydroxy-2,6-dimethoxypyrimidine (162) resulted;⁵¹⁵³ several analogues were made similarly.⁵¹⁵³ The unusual boron-containing compound, “5-barenylmethylbarbituric acid” has been made from the corresponding malonic ester and urea.⁴⁷⁸⁸

Condensations of malonic esters with thioureas have been poorly represented recently. Of note was the reaction of malonic acid with *N,N'*-diphenylthiourea in chloroform containing phosphoryl chloride to give 1,2,3,4-tetrahydro-6-hydroxy-4-oxo-1,3-diphenyl-2-thiopyrimidine.⁵⁸⁷⁰ The reaction of diethyl malonate with *N*-methylthiourea under normal alkaline conditions to give 1-methyl-2-thiobarbituric acid in 82% yield was also of note.⁵¹⁸¹

8. Use of β -Aldehyde Nitriles (*H* 59, *E* 44)

Amidines undergo ready condensation with β -aldehyde nitriles or their equivalents to yield 4-aminopyrimidines; some regular examples are summarized in Table IVa. Of more interest is the reaction of 3-ethoxy-2-diethoxymethylpropionitrile (163) with acetamidine, which gives a separable mixture of 4-amino-5-ethoxymethyl-2-methylpyrimidine (164, R = OEt) and mainly 5-acetamidomethyl-4-amino-2-methylpyrimidine (164, R = NHAc); the latter appeared to be formed *via* an intermediate pyrimidopyrimidine.⁵⁸²⁹ α -Ethoxymethylenemalononitrile condensed with *N*-phenylbenzamidine in ethanol at -10° to give 5-cyano-1,6-dihydro-6-imino-1,2-diphenylpyrimidine (165), but when this product was melted or the original reaction was done at 25° , Dimroth rearrangement ensued to furnish the isomeric product, 4-anilino-5-cyano-2-phenylpyrimidine (166), thus incidentally proving the



position of the *N*-phenyl grouping in (165); several analogues of the rearranged material (166) were made similarly.⁵⁹⁴² As mentioned in Sect. II.5, ethyl α -cyano- α -ethoxymethyleneacetate reacted with acetamidine both as an aldehydo ester and an aldehydo nitrile, although the product from the latter, 4-amino-5-ethoxycarbonyl-2-methylpyrimidine, was but minor in quantity;⁴⁹⁶⁰ in contrast, guanidine gave predominantly 2,4-diamino-5-ethoxycarbonylpyrimidine (95%).^{4960, 4961} An unusual condensation is that of α -*p*-acetamidophenylsulphonyl- β -ethoxyacrylonitrile with benzamidine to afford 5-*p*-acetamidophenylsulphonyl-4-amino-2-phenylpyrimidine (167, R = Ph); guanidine gave the corresponding 5-*p*-acetamidophenylsulphonyl-2,4-diaminopyrimidine (167, R = NH₂).⁵⁵⁸³ Some fascinating condensations of 2-dimethoxymethyl-3-methoxypropionitrile with amidines have been studied closely.⁵¹⁰⁰⁻⁵¹⁰⁵

Some guanidine and aldehydo nitrile condensations appear in Table IVa but most have been aimed at improved syntheses of trimethoprim (2,4-diamino-5-3',4',5'-trimethoxybenzylpyrimidine: an antibacterial, widely used in combination with sulphonamides) and related compounds. The various general routes to such compounds were reviewed in 1976,⁴⁵⁴⁴ but the following condensations will serve as examples in the present context. Thus, ethanolic guanidine reacted with 2-diethoxymethyl-2-formyl-3-(3',4',5'-trimethoxyphenyl)propionitrile (168, R = CHO) or with 2-diethoxymethyl-2-ethoxycarbonyl-3-(3',4',5'-trimethoxyphenyl)propionitrile (168, R = CO₂Et) to give trimethoprim (170); both reactions appeared to utilize the intermediate enol ether (169).⁵⁸⁹² Similarly, 2-anilinomethylene-3-(4'-methoxycarbonyl-3',5'-dimethylphenyl)propionitrile gave 2,4-diamino-5-(4'-methoxycarbonyl-3',5'-dimethoxybenzyl)pyrimidine, and many ana-

TABLE IVa. Additional Examples of the Use of Aldehyde Nitriles in the Principal Synthesis (E 46)

Three-Carbon Fragment	One-Carbon Fragment	Solvent and Conditions	Pyrimidine (Yield)	Ref.
2,3-Bisdimethylamino-acrylonitrile	Formamidine acetate	120° without solvent; 1 h	4-Amino-5-dimethylamino- (28%)	6107
3-Ethoxyacrylonitrile	Pyridine-4-carboxamidine	100–160° without solvent; 3 h	4-Amino-2-pyrid-4'-yl- ^a (73%)	5605
2-Chloroacrylonitrile	Pyridine-4-carboxamidine	Methanolic sodium methoxide; 25°; 3 h	4-Amino-2-pyrid-4'-yl- (70%)	5605
α-Ethoxymethylene-malononitrile	Cyclopropylacetamidine	Ethanol; 0°; 6 h	4-Amino-5-cyano-2-cyclopropylmethyl- ^b (c. 75%)	5469
α-Ethoxymethylene-phenylacetoneitrile	Acetamidine	Ethanol; sodium ethoxide; reflux; 12 h	4-Amino-2-methyl-5-phenyl- (29%)	5309
3-Ethoxy-2-methoxymethylenepropionitrile	Acetamidine	Ethanol; 50°; 2 h or reflux; 2 h	4-Amino-5-ethoxymethyl-2-methyl- (55%)	4428, 6201
N-p-Chlorophenyl-2-cyano-2-ethoxymethylene-acetamide	Formamidine	—	4-Amino-5-N-p-chlorophenyl-carbamoyl-	6369
Dimethylaminomethylene-malononitrile	Formamidine	Methanolic sodium methoxide; 25°; 3 h	4-Amino-5-cyano- ^c (c. 60%)	3752
3-Methoxy-2-methoxymethylenepropionitrile	Benzamidine	Methanol	4-Amino-5-methoxymethyl-2-phenyl-	5100
4,4-Diethoxy-2-methoxymethylenebutyronitrile	Acetamidine	Ethanol	4-Amino-5-β-ethoxyvinyl-2-methyl-	5830
3-Anilino-2-(3',4',5'-trimethoxybenzyl)-acrylonitrile	Benzamidine	Ethanol; reflux; 100 h	4-Amino-2-phenyl-5-(3',4',5'-trimethoxybenzyl)- (77%)	6113
α-Bismethylthiomethylene-malononitrile	C-morpholinoformamidine	Ethanol; reflux; 3 h	4-Amino-5-cyano-6-methylthio-2-morpholino- (43%)	6282

α -Butoxymethylene- α -phenylacetone nitrile	Guanidine	Ethanol	2, 4-Diamino-5-phenyl- (78%)	4833
2, 3-Bisdimethylamino-acrylonitrile	Guanidine	80° without solvent (?); 2 h	2, 4-Diamino-5-dimethylamino- (30%)	6107
3-Methoxy-2-then-2'-ylacrylonitrile	Guanidine	Methanol; reflux; 24 h	2, 4-Diamino-5-then-2'-yl- ^d (36%)	5388
3-Anilino-2-pyrid-2'-ylmethylacrylonitrile	Guanidine	Ethanol; reflux; 18 h	2, 4-Diamino-5-pyrid-2'-ylmethyl- ^e (66%)	4896
α -Formyl-(3, 4, 5-trimethoxyphenyl)acetone nitrile	Guanidine	—	2, 4-Diamino-5-3', 4', 5'-trimethoxyphenyl-	5400
3-Isobutoxy-2-(<i>p</i> -naphthylthiophenyl)acrylonitrile	Guanidine	Ethanol; sodium ethoxide; reflux; 2 h	2, 4-Diamino-5- <i>p</i> -(naphth-2'-ylthio)phenyl- (51%)	5479
2-Ethoxymethylene-3-pyrid-3'-ylpropionitrile	Guanidine	Methanol; reflux; 18 h	2, 4-Diamino-5-pyrid-3'-yl- ^d (c. 30%)	5597
3-Methoxy-2-phenylacrylonitrile	Urea or thiourea	Ethanol; sodium ethoxide; reflux; 3 h	4-Amino-2-hydroxy(or mercapto)-5-phenyl- (48, 63%)	6081

^a And three closely related compounds.

^b Named incorrectly in original paper; and four analogues.

^c And the 2-methyl derivative.

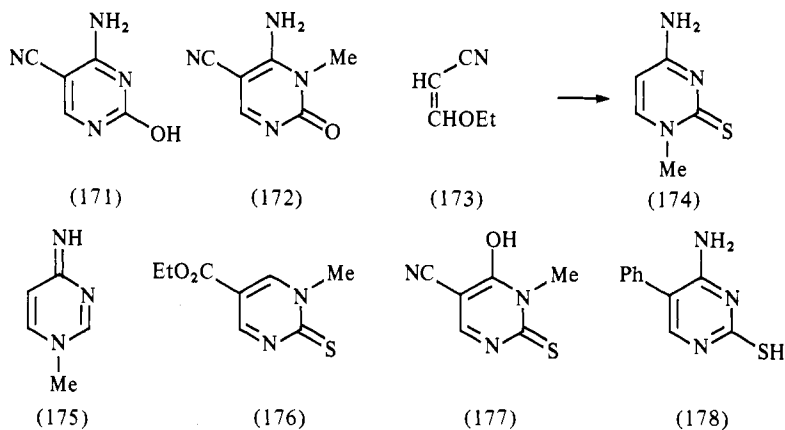
^d And two analogues.

^e Also the pyrid-3'-yl and pyrid-4'-yl isomers.

logues with different 4'-substituents were made likewise;⁵⁹³⁹ 2-diethoxymethyl-3-(3',4'-dimethoxy-2'-methylphenyl)propionitrile gave 2,4-diamino-5-(3',4'-dimethoxy-2'-methylbenzyl)pyrimidine;⁵⁴⁶⁷ 2-ethoxymethylene-3-(3'-trifluoromethoxyphenyl)propionitrile gave 2,4-diamino-5-(3'-trifluoromethoxybenzyl)pyrimidine;⁵⁴⁵⁹ 3-methoxy-2-(3',4',5'-trimethoxyphenoxy)acrylonitrile gave 2,4-diamino-5-(3',4',5'-trimethoxyphenoxy)pyrimidine;⁵⁴⁶² and many analogues were made similarly.^{4905, 5459, 5462, 5467, 6514}

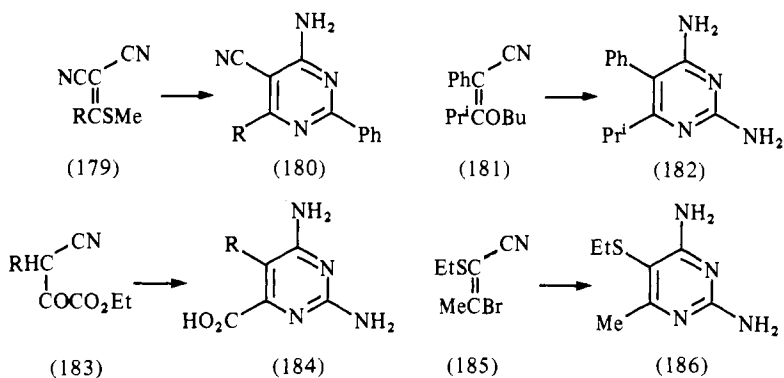
The condensation of urea with aldehydo nitriles has continued to be useful, especially in the form of the Whitehead synthesis for cytosine derivatives (see *H* 62). For example, malononitrile, triethyl orthoformate, and urea at 120° gave the acyclic intermediate, ureidomethylene-malononitrile, which in methanolic sodium methoxide gave 4-amino-5-cyano-2-hydroxypyrimidine (171);⁵⁷⁸¹ likewise, ethyl cyanoacetate, triethyl orthoformate, and *N*-cyclohexylurea gave initially ethyl α -cyano- α -(cyclohexylureidomethylene)acetate and thence 4-amino-3-cyclohexyl-5-ethoxycarbonyl-2,3-dihydro-2-oxypyrimidine (172).⁴⁹⁴¹

Similar preparations using thioureas are exemplified in the reaction of α -ethoxymethyleneacetoneitrile (173) with *N*-methylthiourea to give (against all precedent) 4-amino-1,2-dihydro-1-methyl-2-thiopyrimidine (174), confirmed in structure by desulfurization to the known 1,4-dihydro-4-imino-1-methylpyrimidine (175);⁵⁶⁶⁵ of ethyl α -cyano- α -ethoxymethyleneacetate with *N*-methylthiourea in ethanolic sodium ethoxide at 25° to give mainly 4-amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-thiopyrimidine (176) and a little 5-cyano-3-methyl-2-thiouracil (177), although the ratio was reversed if the reaction was done under reflux;⁵⁶⁶⁵ and of 3-ethoxy-2-phenylacrylonitrile with thiourea to give 4-amino-2-mercapto-5-phenylpyrimidine (178).⁵⁸⁶¹



9. Use of β -Keto Nitriles (*H* 65, *E* 47)

Keto nitriles have not been used to any great extent in recent Principal Syntheses. However, appropriate amidines have been used to convert 2-cyano-3-(methylthio)crotononitrile (179, $R = \text{Me}$) into 4-amino-5-cyano-6-methyl-2-phenylpyrimidine (180, $R = \text{Me}$),⁴⁵⁰⁸ 2-cyano-3-methylthio-3-phenylacrylonitrile (179, $R = \text{Ph}$) into 4-amino-5-cyano-2,6-diphenylpyrimidine (180, $R = \text{Ph}$),⁴⁵⁰⁸ 2-cyano-4-methyl-3-methylthiopent-2-enenitrile (179, $R = \text{Pr}^i$) into 4-amino-5-cyano-2-ethyl-6-isopropylpyrimidine,⁵⁸¹⁰ and 2-cyano-3,3-bismethylthioacrylonitrile (179, $R = \text{SMe}$) into 4-amino-5-cyano-6-methylthio-2-phenylpyrimidine (180, $R = \text{SMe}$) (using aqueous benzamidine at 100°).⁵⁷⁶⁷ Other regular examples are also known,^{5945, 6341} as well as a few cases in which partly reduced substrates have been used with subsequent oxidation; for example, *N*-*m*-tolylbenzamidine and α -*p*-chlorobenzylidene-malononitrile gave, after aerial oxidation and Dimroth rearrangement, 4-*p*-chlorophenyl-5-cyano-2-phenyl-6-*m*-toluidinopyrimidine in 43% yield.^{4372, 6179, 6337}



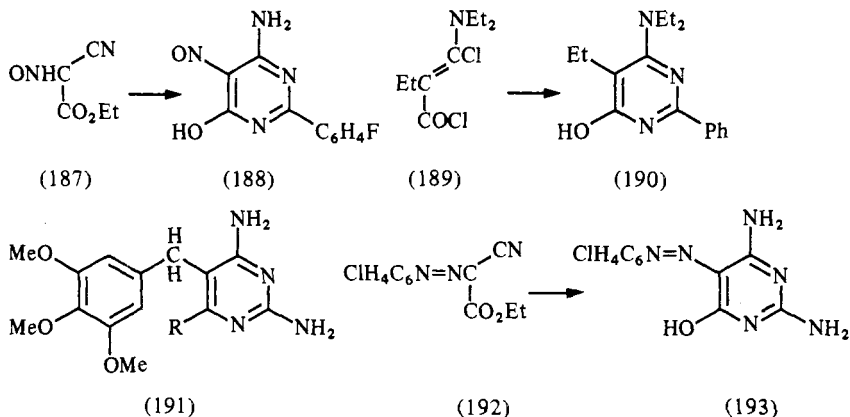
Likewise, guanidine has been used to convert 3-butoxy-3-isopropyl-2-phenylacrylonitrile (181) into 2,4-diamino-6-isopropyl-5-phenylpyrimidine (182),⁴⁸³⁴ 2-cyano-3-ethoxy- or 2-cyano-3-methylthio-crotononitrile (179, $R = \text{Me}$) into 2,4-diamino-5-cyano-6-methylpyrimidine,^{4508, 5767} ethyl 3-cyano-3-methylpyruvate (183, $R = \text{Me}$) into 2,4-diamino-6-carboxy-5-methylpyrimidine (184, $R = \text{Me}$) (the aqueous alcoholic alkaline medium accounted for the hydrolysis of the ester group),⁵⁷⁴⁵ the homologous pyruvates (183, $R = \text{Et}$, Pr , Bu , etc.) into the pyrimidines (184, $R = \text{Et}$, Pr , Bu , etc.),⁵⁷⁴⁵ 2-*p*-chlorophenyl-3,4,4-trimethoxypent-2-enenitrile into 2,4-diamino-5-*p*-chlorophenyl-6-1',1'-dimethoxyethylpyrimidine,⁵⁴⁷⁴ 3-bromo-2-ethylthiocrotononitrile (185) into 2,4-diamino-5-ethylthio-6-methylpyrimidine (186)

(and several homologues similarly),⁶⁰¹² and other such keto nitriles into appropriate 2,4-diamino pyrimidines.^{4833, 5400, 5479, 5526, 5743, 5788}

The condensation of keto nitriles with ureas and thioureas is represented in the conversion of 3-adamant-1'-yl-3-isobutoxyacrylonitrile by urea into 4-adamant-1'-yl-6-amino-2-hydroxypyrimidine,⁴³⁸⁹ of 2-cyano-3-methoxy-3-phenylacrylonitrile by *O*-methylurea into 4-amino-5-cyano-2-methoxy-6-phenylpyrimidine,⁶²⁸⁶ of ethyl 3-cyano-3-ethylpyruvate (183, R = Et) by thiourea into 4-amino-6-carboxy-5-ethyl-2-mercaptopyrimidine,⁵⁷⁴⁵ of α -levulinoyl- α -phenylacetonitrile by thiourea into 4-acetonilylmethyl-6-amino-2-mercapto-5-phenylpyrimidine,⁵⁹⁸² and of 2-cyano-3,3-bismethylthioacrylonitrile (179, R = SMe) by *S*-(*N,N*-dimethyl-*N'*-phenylamidino)thiourea into 4-amino-5-cyano-2-(*N,N*-dimethyl-*N'*-phenylamidino)thio-6-methylthiopyrimidine.⁵⁹⁴⁰ Other examples are known also.⁴⁶⁸⁵

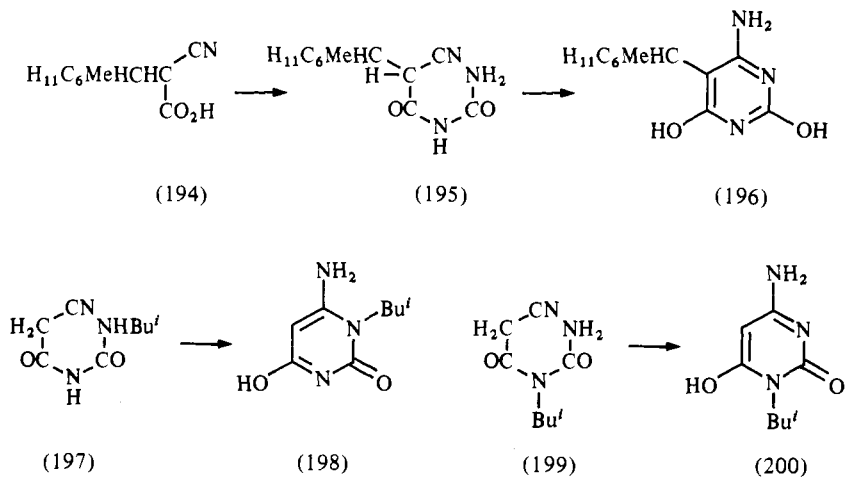
10. Use of β -Ester Nitriles (*H* 67, *E* 48)

Ethyl α -cyano- α -nitrosoacetate (187) has been condensed with a variety of *o*-substituted-benzamidines to give, for example, 4-amino-2-*o*-fluorophenyl-6-hydroxy-5-nitrosopyrimidine (188) in good yield;⁵²⁷⁹ methyl α -cyano- α -methoxyacetate and formamidine in refluxing methanolic sodium methoxide gave 4-amino-6-hydroxy-5-methoxypyrimidine;⁵⁷⁸² and 3-chloro-3-diethylamino-2-ethylacryloyl chloride (189) with benzamidine gave 4-diethylamino-5-ethyl-6-hydroxy-2-phenylpyrimidine (190).⁶⁰⁷² Although the last reaction should be classified as that of a keto ester with an amidine, it has been mentioned here because a 4-(substituted-amino)pyrimidine was formed. There are other good examples.^{6377, 6536}



A novel route to trimethoprim and related antibacterials made use of the initial condensation of an ester nitrile with guanidine; for example, ethyl 2-cyano-3-(3',4',5'-trimethoxyphenyl)propionate and guanidine gave 2,4-diamino-6-hydroxy-5-(3',4',5'-trimethoxybenzyl)pyrimidine (191, R = OH) which was converted into its 6-chloro analogue (191, R = Cl) and thence, by dechlorination, to trimethoprim (191, R = H).⁴⁵⁶⁵ Both methyl and ethyl α -cyanoacetate have been condensed with guanidine under comparable conditions to give 2,4-diamino-6-hydroxypyrimidine in good yield.^{5339, 5365} Ethyl α -*p*-chlorophenylhydrazono- α -cyanoacetate (192) reacted with guanidine in ethanolic sodium ethoxide to give 2,4-diamino-5-*p*-chlorophenylazo-6-hydroxypyrimidine (193) in 70% yield,⁵³⁶⁵ and ethyl 2-cyano-4,4-diethoxybutyrate with guanidine to give 2,4-diamino-5- β , β -diethoxyethyl-6-hydroxypyrimidine.⁴⁴⁹² The formation of 2,4-diamino-6-hydroxypyrimidine has been redescribed in detail.⁶⁴⁰⁵

The condensations of α -cyanoacetic acid or ethyl α -cyanoacetate with urea have been studied comparatively; the latter appears to give 4-amino-2,6-dihydroxypyrimidine with least trouble.⁴⁴³¹ Likewise, ethyl α -cyanopropionate and urea gave 4-amino-2,6-dihydroxy-5-methylpyrimidine satisfactorily.⁵⁸⁴⁰ However, a two-step process has been used to condense 2-cyano-3-cyclohexylbutyric acid (194) with urea in acetic anhydride to give initially 2-cyano-3-cyclohexylbutyrylurea (195) followed by cyclization in ethanolic sodium ethoxide to afford 4-amino-5- α -cyclohexylethyl-2,6-dihydroxypyrimidine (196).⁶⁰⁵² Condensations with substituted ureas are illustrated by the reaction of *O*-methylurea with methyl α -cyanoacetate to give 4-amino-6-hydroxy-2-methoxypyrimidine;⁴⁵⁷⁴ of *N*-methoxyurea with ethyl α -cyanoacetate to give 6-amino-1-methoxyuracil;⁵⁴²⁵ of *N*-benzyloxyurea with ethyl 2-cyano-4,4-diethoxybutyrate in ethanolic sodium ethoxide under reflux for 24 h to give 6-amino-1-benzyloxy-5- β , β -diethoxyethylpyrimidine;⁵⁴²² of *N*-benzylurea with methyl α -cyanoacetate to give 6-amino-1-benzyluracil in 65% yield;⁴⁹¹⁴ of *N*-phenethylurea with ethyl cyanoacetate to give 6-amino-1-phenethyluracil;⁵²⁸¹ of *N,N'*-dimethylurea with α -cyanoacetic acid in acetic acid-acetic anhydride, followed by cyclization of the intermediate in alkali, to give 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (72%);⁴⁴³¹ and of *N*-isobutylurea with cyanoacetic acid to give initially the intermediate *N*-cyanoacetyl-*N'*-isobutylurea (197) [or its isomer (199)] followed by cyclization to 6-amino-1-isobutyluracil (198) [or its isomer (200)].⁴⁴⁰⁵ In the last case, the 1-alkyluracil (198) rather than the 3-alkyluracil (200) structure was proven correct once again, this time by nmr examination of the

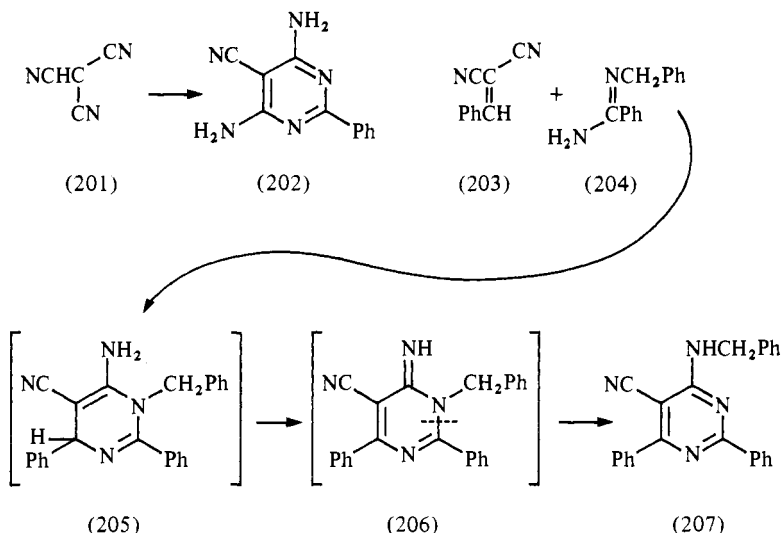


intermediate which turned out to have structure (197) rather than (199); the method appeared to be generally applicable to such molecules.⁴⁴⁰⁵

The condensation of ethyl α -cyanoacetate with thiourea in ethanolic sodium ethoxide gave excellent yields of 4-amino-6-hydroxy-2-mercaptopyrimidine;^{5059, 5853} ethyl α -cyano- α -phenylazoacetate and thiourea also gave 4-amino-6-hydroxy-2-mercapto-5-phenylazopyrimidine in good yield;⁵⁸⁶⁴ but for no apparent reason, ethyl α -cyano- α -phenylacetate and thiourea gave only a 7% yield of 4-amino-6-hydroxy-2-mercapto-5-phenylpyrimidine under reasonably comparable conditions.⁵¹⁵³ Ethyl α -cyanoacetate and *N*-methylthiourea gave 6-amino-1-methyl-2-thiouracil in good yield.⁵¹⁸¹ Methyl 2-cyano-3-dibutoxyborylpropionate and thiourea gave 4-amino-6-hydroxy-2-mercapto-5-methylpyrimidine *via* a bicyclic(?) boron-containing intermediate.⁵⁵²³

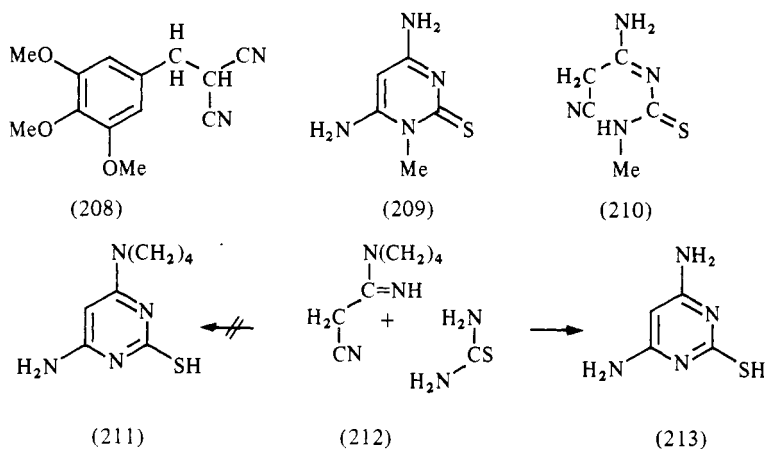
11. Use of β -Dinitriles; Malononitriles (H 72, E 49)

Being an α -substituted malononitrile, tricyanomethane (201) reacted normally with benzamidine to give a salt which on heating in dimethylformamide yielded 4,6-diamino-5-cyano-2-phenylpyrimidine (202).⁵⁷⁶⁷ In contrast, α -benzylidenemalononitrile (203) reacted with *N*-benzylbenzamidine (204), not as a dinitrile but as a β -alcohol nitrile, to give initially 4-amino-3-benzyl-5-cyano-3,6-dihydro-2,6-diphenylpyrimidine (205) (unisolated) which underwent aerial oxidation to 1-benzyl-5-cyano-1,6-dihydro-6-imino-2,4-diphenylpyrimidine (206) (also unisolated) and subsequent Dimroth rearrangement into 4-benzyl-



amino-5-cyano-2,6-diphenylpyrimidine (207).⁵⁹⁴¹ This sequence proved reasonably general⁴³⁶⁶ in preparing, for example, 4-benzylamino-5-cyano-6-naphth-2'-yl-2-phenyl-,⁵⁹⁴¹ 4-biphenyl-2'-ylamino-5-cyano-6-phenyl-2-*p*-tolyl-,⁵⁹⁴³ 4-anilino-6-biphenyl-4'-yl-5-cyano-2-phenyl-,⁴³⁶⁹ and 4-biphenyl-4'-yl-6-biphenyl-4'-ylamino-5-cyano-2-phenylpyrimidine,⁴³⁶⁹ as well as other analogues.

However, 3,4,5-trimethoxybenzylmalononitrile (208) reacted with guanidine quite normally to give 2,4,6-triamino-5-3',4',5'-trimethoxybenzylpyrimidine (191, R = NH₂) and malononitrile with *N*-methylthiourea gave 4,6-diamino-1,2-dihydro-1-methyl-2-thiopyrimidine (209);⁵¹⁸¹ the latter reaction was also done stepwise by isolating



the acyclic intermediate. *N*-(1'-amino-2'-cyanoethylidene)-*N*'-methylthiourea (210), and then heating at about its melting point to complete cyclization.⁵¹⁸¹ An unusual condensation was that of the β -amidino nitrile, 3-imino-3-pyrrolidinopropiononitrile (212) with thiourea to give 4,6-diamino-2-mercaptopyrimidine (213) rather than the expected 4-amino-2-mercapto-6-pyrrolidinopyrimidine (211); possible mechanisms have been discussed.^{5444, 5730}

CHAPTER III

Other Methods of Primary Synthesis (*H* 82, *E* 53)

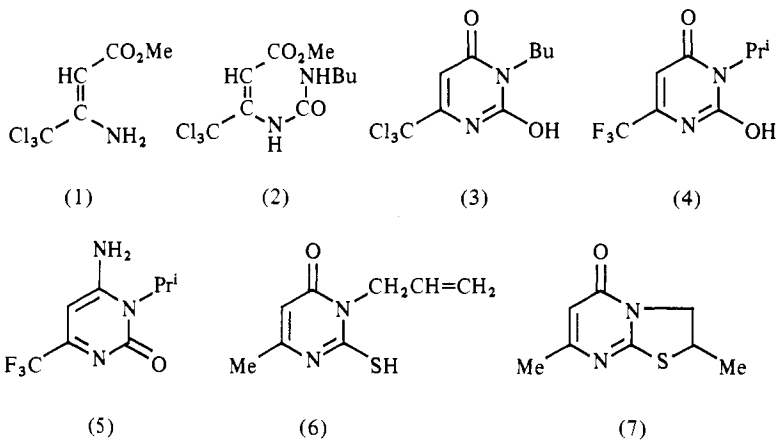
1. General Remarks (*H* 82, *E* 53)

There has been a considerable expansion in the numbers and types of primary synthesis used for pyrimidines. Indeed the classification originally adopted (*H* 82) has been stretched to its limit to accommodate the new material. However, retention of the system was essential in order to facilitate back reference to the earlier volumes.

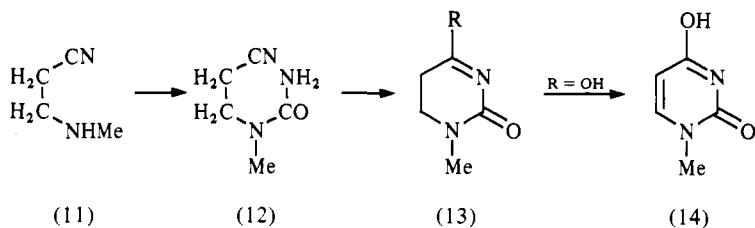
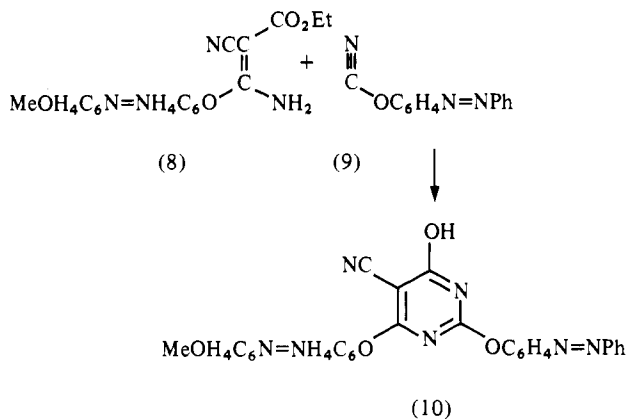
2. Syntheses Involving Preformed Aminomethylene Groups (*H* 82, *E* 53)

A. Aminomethylene Derivatives with Isocyanates (*H* 82, *E* 53)

Several recent examples illustrate this type of synthesis in its classical form. Thus, methyl 3-amino-4,4,4-trichlorocrotonate (1) reacted with butyl isocyanate in dimethyl sulfoxide containing potassium *t*-butoxide to give the (unisolated) intermediate urea (2) and thence 3-butyl-6-trichloromethyluracil (3) in low yield;⁵⁸⁸ later the experimental procedures were improved so that, for example, ethyl 3-amino-4,4,4-trifluorocrotonate and isopropyl isocyanate gave 3-isopropyl-6-trifluoromethyluracil (4) in greater than 70% yield.^{589, 593} Likewise, 3-amino-4,4,4-trifluorocrotononitrile and isopropyl isocyanate gave 4-amino-2,3-dihydro-3-isopropyl-2-oxo-6-trifluoromethylpyrimidine (5).⁵⁸⁹ Similarly, ethyl 3-aminocrotonate and allyl isothiocyanate at 100° without a condensing agent gave 3-allyl-6-methyl-2-thiouracil (6), which underwent cyclization in acid to 2,3-dihydro-2,7-dimethyl-5-oxo-[5*H*]-thiazolo[3,2-*a*]pyrimidine (7).⁵³⁷³ The use of a cyanate in place of an isocyanate in such reactions appeared to lead to a 2-*O*-substituted urea. Thus, ethyl 3-amino-2-cyano-3-(4'-*p*-methoxyphenyl-



azophenoxy)crotonate (8) and *p*-phenylazophenyl cyanate (9) gave 5-cyano-4-hydroxy-6-(4'-*p*-methoxyphenylazophenoxy)-2-*p*-phenylazophenoxypyrimidine (10) in reasonable yield.⁴⁴¹¹

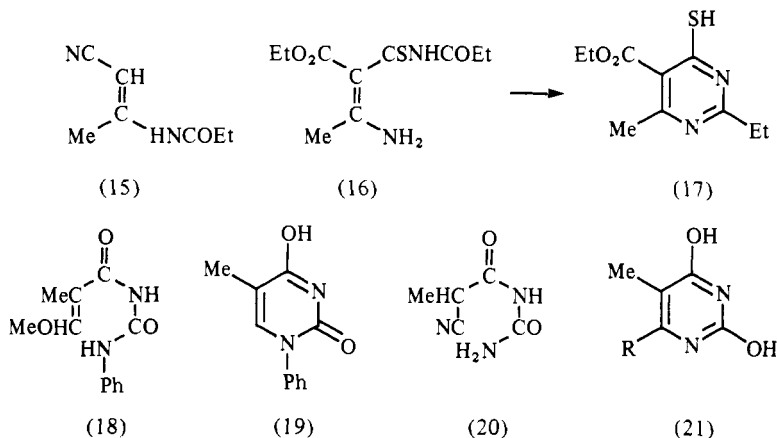


The use of such classical reactions with intermediates lacking the double bond (see *H* 83) led initially to dihydropyrimidines. A recent example was the condensation of ethyl acrylate with cyclohexylamine and ring closure with cyanic acid, followed by oxidation by 5-bromi-

nation/dehydrobromination to yield 1-cyclohexyluracil.⁶¹¹⁴ A useful extension of this procedure is exemplified in the treatment of acrylonitrile with methylamine to give 3-methylaminopropionitrile (11) followed by treatment with cyanic acid to give 3-(*N*-methylureido)-propionitrile (12) and subsequent cyclization by methanolic sodium methoxide, to give 4-amino-1,2,5,6-tetrahydro-1-methyl-2-oxopyrimidine (13, R = NH₂), or by methanolic hydrochloric acid to give 5,6-dihydro-1-methyluracil (13, R = OH).^{5614, 5630} The latter was converted into 1-methyluracil (14) by 5-bromination and subsequent (thermal?) dehydrobromination in boiling dimethylformamide.⁵⁶³⁰ Another good example involved condensation of 3-anilinopropionitrile with benzoyl isocyanate, ring closure to 4-amino-1,2,5,6-tetrahydro-2-oxo-1-phenylpyrimidine, 5-bromination and subsequent dehydrobromination to afford 4-amino-1,2-dihydro-2-oxo-1-phenylpyrimidine.⁵⁷⁹⁸ Such dehydrogenations have been used in other contexts too.^{6516, 6590}

The condensation of acyl isothiocyanates with ethyl 3-amino-crotonate and related enamines can go in two ways, neither of which involves formation of a urea. Thus, the acyl isothiocyanate may simply acylate the amino group to give, for example, 3-propionamidopropionitrile (15), which reacts no further, or it may attack the 2-position to give, for example, ethyl 3-amino-2-[*N*-propionyl(thiocarbamoyl)]-crotonate (16), which can and does undergo cyclization to 5-ethoxycarbonyl-2-ethyl-4-mercapto-6-methylpyrimidine (17). Although good preliminary data have appeared,⁶²⁹¹ further rationalization of these reactions is urgently needed.

As before (*E* 54), several nonclassical syntheses are mentioned here because they proceed through ureido intermediates which, however, are obtained in different ways. For example, 2-methoxymethylene-

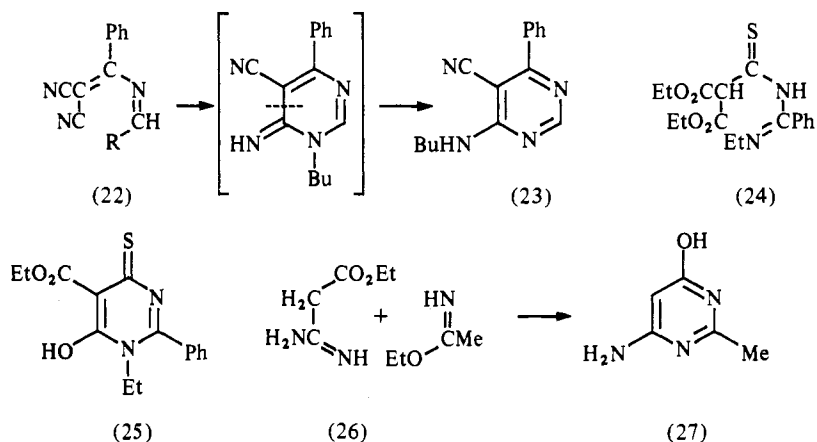


propionyl isocyanate with aniline gave *N*-(2-methoxymethylene-propionyl)-*N'*-phenylurea (18) which underwent cyclization to 5-methyl-1-phenyluracil (19) in a variety of acidic media of which fusion with *p*-toluenesulfonic acid at 150° resulted in excellent yields.⁵²³⁶

The intermediate *N*-(2-cyanopropionyl)urea (20), easily made from urea and 2-cyanopropionic acid, will be recognized as a typical intermediate in the condensation of a β -ester nitrile with urea by the Principal Synthesis that would undergo cyclization to 4-amino-2,6-dihydroxy-5-methylpyrimidine (21, R = NH₂). However, by isolating the intermediate (20) and reducing the cyano group (presumably to the iminomethyl, i.e. aldehyde, stage) subsequent cyclization gave 2,4-dihydroxy-5-methylpyrimidine (21, R = H); the procedure proved effective in making the 2,6-¹³C₂ molecule.⁵⁵⁶⁹

When the enamine, α -amino- β,β -dicyanostyrene was allowed to react with *N,N*-dimethylformamide dimethyl acetal, β,β -dicyano- α -dimethylaminomethyleneaminostyrene (22, R = NMe₂) resulted. On heating with a primary amine, for example, butylamine, this underwent transamination to the intermediate (22, R = NHBu), cyclization, and immediate Dimroth rearrangement to yield 4-butylamino-5-cyano-6-phenylpyrimidine (23); the 4-amino and other 4-alkylamino analogues were made similarly.⁶¹²⁹

A useful synthesis, resembling some of the above, began with condensation of α -ethyliminobenzyl isothiocyanate with diethyl malonate to give the intermediate (24), which underwent cyclization to yield 5-ethoxycarbonyl-1-ethyl-1,4-dihydro-6-hydroxy-2-phenyl-4-thiopyrimidine (25; or tautomer); the reaction was versatile in that the ester group was replacable by a nitrile or acyl group, the hydroxy by an alkyl group, and the alkyl or aryl groups could be varied.⁴⁵³³

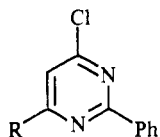


B. Aminomethylene Compounds with Imino Ethers or Imidoyl Chlorides (H 84, E 56)

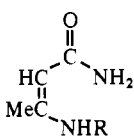
This type of synthesis is represented in the condensation of ethyl α -amidinoacetate (26) with ethyl acetimidate in methanol at room temperature to give an 86% yield of 4-amino-6-hydroxy-2-methylpyrimidine (27).⁵⁰⁹⁸

C. Aminomethylene Derivatives with Thioamides (H 85)

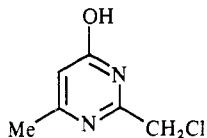
The only example of such a reaction is frankly of doubtful mechanism, although a thiocarbamoyl intermediate might be involved. Thus, condensation of 3-aminocrotononitrile with *N,N*-dimethylbenzamide in phosphoryl chloride gave an intermediate nitrile which, on successive treatment with aqueous sodium hydrogen sulfide and iodine in benzene, cyclized to give 4-chloro-6-methyl-2-phenylpyrimidine (28, R = Me); 4-chloro-2,6-diphenylpyrimidine (28, R = Ph) was made similarly.⁵⁵⁷⁷



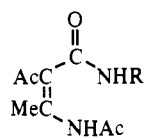
(28)



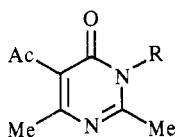
(29)



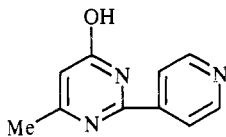
(30)



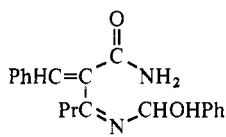
(31)



(32)



(33)



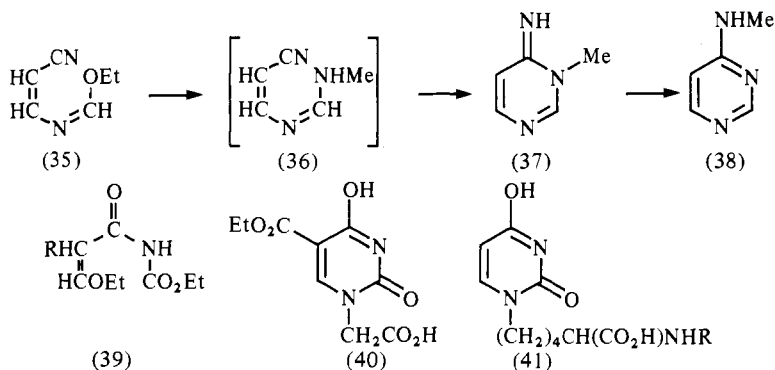
(34)

D. Use of Acylated Aminomethylene Derivatives (H 85)

After long neglect, this reaction has been developed considerably by workers in Sendai and has found considerable use elsewhere too. For example, acylation of 3-aminocrotonamide (29, R = H) with monochloroacetic anhydride afforded 3-chloroacetamidocrotonamide (29, R = COCH₂Cl), which on heating in tetralin at 220° gave 2-chloromethyl-4-hydroxy-6-methylpyrimidine (30) in 78% yield;⁵⁰⁷⁹ the 2-dichloromethyl and 2-trichloromethyl analogues were made similarly,⁵⁰⁷⁹ an

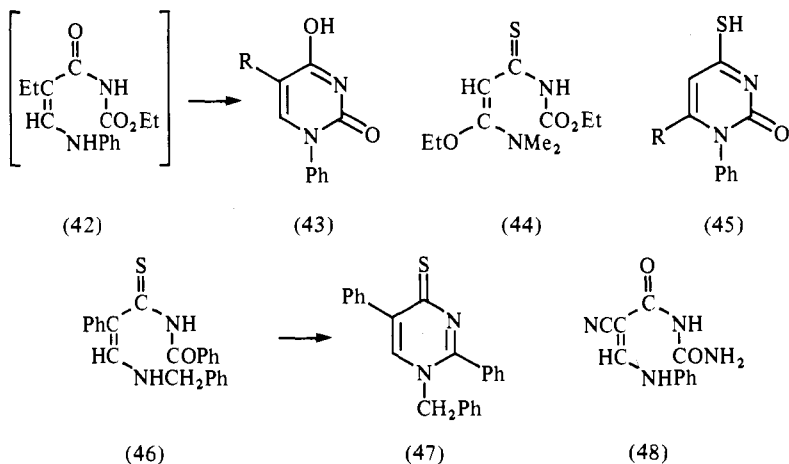
extraordinarily useful route to such labile products. When initial acylation was carried out with ketene, both *C*- and *N*-acetylation occurred to give the intermediate, 3-acetamido-2-acetylcrotonamide (31, R = H), which underwent cyclization in hot aqueous alkali to give 5-acetyl-4-hydroxy-2,6-dimethylpyrimidine (32, R = H);⁵⁰⁷⁷ by using 3-amino-*N*-methylcrotonamide as substrate, 5-acetyl-1,6-dihydro-1,2,4-trimethyl-6-oxopyrimidine (32, R = Me) resulted *via* the intermediate 3-acetamido-2-acetyl-*N*-methylcrotonamide (31, R = Me).⁵⁰⁷⁷ Naturally, esters could be used for *N*-acylation of 3-aminocrotonamide prior to cyclization in alcoholic alkoxide. In this way, for example, ethyl lactate gave 4-hydroxy-2- α -hydroxyethyl-6-methylpyrimidine;⁵⁰⁷⁵ ethyl benzoate gave 4-hydroxy-6-methyl-2-phenylpyrimidine;⁵⁰⁷⁵ ethyl cinnamate gave (with potassium *t*-butoxide but not with sodium ethoxide) 4-hydroxy-6-methyl-2-styrylpyrimidine;⁵⁰⁸⁰ the ethyl ester of *N*-acetylglycine gave 2-acetamidomethyl-4-hydroxy-6-methylpyrimidine;⁶²⁷⁵ ethyl isonicotinate gave 4-hydroxy-6-methyl-2-pyrid-4'-ylpyrimidine (33),^{6005, 6288} also made in better yield from pyridine-4-carboxamide and ethyl acetoacetate;⁶²⁸⁸ ethyl thiophen-2-carboxylate gave 4-hydroxy-6-methyl-2-thien-2'-ylpyrimidine;⁶²⁸⁸ ethyl 2-methylthiazole-4-carboxylate gave 4-hydroxy-6-methyl-2-(2'-methylthiazol-4'-yl)pyrimidine;⁶²⁸⁷ ethyl ethoxymethyleneacetoacetate gave (indirectly) 4-hydroxy-6-methylpyrimidine;⁵⁰⁸⁴ and benzyloxycarbonylglycine ethyl ester gave 2-ethoxycarbonylaminomethyl-4-hydroxy-6-methylpyrimidine (by transesterification of the intermediate benzyloxycarbonylaminomethyl analogue).⁵¹²⁹ Aminocrotonamide and succinic anhydride gave 2- β -carboxyethyl-4-hydroxy-6-methylpyrimidine (66%).⁶⁵²⁶

Some closely related reactions include the condensation of 3-amino-4-methylpent-2-enamide with acetic anhydride followed by treatment with ethanolic sodium ethoxide to give 4-hydroxy-6-isopropyl-2-methylpyrimidine;⁵⁹⁰⁹ of the same substrate with two molecules of benzaldehyde to give an (unisolated) intermediate (34) and thence 5-benzyl-4-hydroxy-6-isopropyl-2-phenylpyrimidine;⁵⁹⁰⁹ of 3-aminocrotonamide with an excess of acetonitrile in methanolic sodium methoxide to give, by an unknown mechanism, 4-hydroxy-2,6-dimethylpyrimidine;⁶¹⁶⁹ of 3-aminoacrylonitrile with triethyl orthoformate to give 3-ethoxymethyleneaminoacrylonitrile (35), which reacted with methylamine to give, *via* the (unisolated) amidine (36), 1,6-dihydro-6-imino-1-methylpyrimidine (37) which was isolated as a salt or converted by a Dimroth rearrangement in alkali into 4-methylaminopyrimidine (38);⁵⁶⁷⁹ and of *C*-mono-, di-, or trialkylated substrates akin to (35) with methylamine to give 2-, 4-, and/or 5-substituted analogues of (37) and (38).^{5679, 5683}

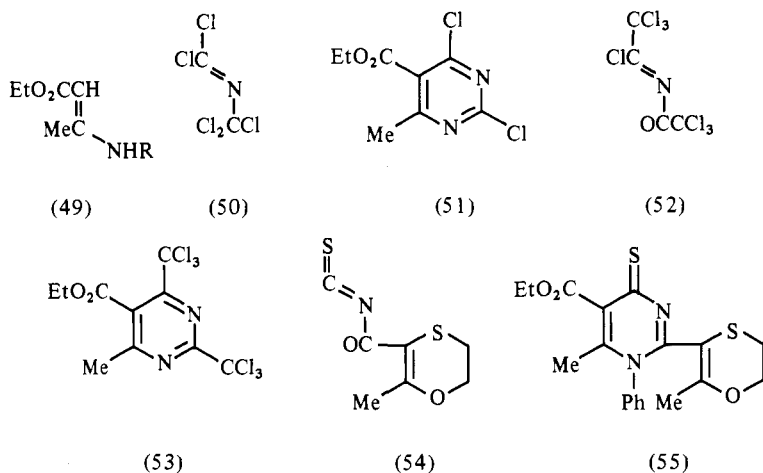


E. The Shaw Synthesis from Aminomethyleneacrylurethanes (H 87, E 56)

Several forms of the Shaw synthesis have been employed recently.⁴⁹⁴¹ The acylurethane, 3-ethoxy-2-*N*-diethoxycarbonylacrylamide (39, R = CO₂Et), with glycine in alkali gave 1-carboxymethyl-5-ethoxycarbonyluracil (40) in good yield;⁵¹²⁹ 2-cyano-3-ethoxy-*N*-ethoxycarbonylacrylamide (39, R = CN) and 3-aminopropionic acid similarly gave 1-β-carboxyethyl-5-ethoxycarbonyluracil,⁵⁹²⁰ 3-ethoxy-*N*-ethoxycarbonylacrylamide (39, R = H) and *N*(α)-benzyloxycarbonyllysine gave 1-(5'-benzyloxycarbonylamino-5'-carboxypentyl)uracil (41, R = CO₂CH₂Ph) and thence, by acid hydrolysis, 1-(5'-amino-5'-carboxypentyl)uracil (41, R = H);⁴⁶⁷³ hydrogenation of *N*-(2-cyanobutyl)urethane in the presence of aniline hydrochloride afforded an unisolated intermediate (42) which in alkali gave 5-ethyl-1-phenyluracil (43, R = Et);⁴⁸⁰² 3-dimethylamino-3-ethoxy-*N*-ethoxycarbonyl(thioacrylamide) (44) reacted with aniline to give 6-ethoxy-1-phenyl-4-thiouracil (45, R = OEt) rather than the 6-dimethylamino analogue (45, R = NMe₂);⁵⁵³⁶ 3-amino-2-benzoyl-3-ethoxy-*N*-ethoxycarbonyl(thioacrylamide), in which both N-atoms were already in place, underwent cyclization in triethylamine to give 5-benzoyl-4-ethoxy-2-hydroxy-4-mercaptopyrimidine;⁵⁵³⁶ *N*-benzoyl-3-benzylamino-2-phenyl(thioacrylamide) (46) in alkali gave 1-benzyl-1,4-dihydro-2,5-diphenyl-4-thiopyrimidine (47);⁵⁵⁷² *N*-ethoxycarbonyl-2-methyl-3-piperidino(thioacrylamide) and ethanolic ammonia gave 2-hydroxy-4-mercapto-5-methylpyrimidine in 86% yield;⁵⁵⁷³ and 2-acetyl-*N*-ethoxycarbonyl-3-methylaminocrotonamide in aqueous trimethylamine gave 5-acetyl-1,6-dimethyluracil.⁵⁶⁰¹ Somewhat similarly, 3-anilino-*N*-carbamoyl-*N*-cyanoacrylamide (48), easily made from *N*-cyanoacetylurea with trimethyl orthoformate and aniline, cyclized on heating to give 5-cyano-1-phenyluracil (43, R = CN).⁶²⁷⁰



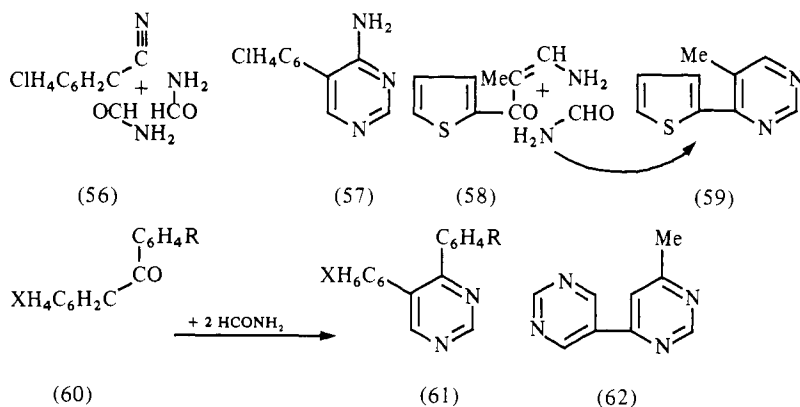
Two useful syntheses are best classified here. Condensation of ethyl 3-aminocrotonate (49, R = H) with *N*-(dichloromethylene)trichloromethylamine (50) gave 2,4-dichloro-5-ethoxycarbonyl-6-methylpyrimidine (51). The reaction was carried out in benzene containing calcium carbonate and gave good yields. Moreover, it was capable of many variations; for example, the same ester (49) with *N*-(tetrachloroethylidene)trichloroacetamide (52) gave 5-ethoxycarbonyl-4-methyl-2,6-bistrichloromethylpyrimidine (53).⁴⁴⁷⁰ The second synthesis involved condensation of ethyl 3-anilincrotonate (49, R = Ph) with 5,6-dihydro-2-methyl-1,4-oxathiin-3-carbonyl isothiocyanate (54) in acetone to give 2-(5,6-dihydro-2-methyl-1,4-oxathiin-3-yl)-5-ethoxycarbonyl-1,4-dihydro-6-methyl-1-phenyl-4-thio-pyrimidine (55).⁶⁰⁰⁴



3. Syntheses Involving an Aminomethylene Group Formed *in Situ* (H 90, E 59)

B. Formamide with Components Containing an Active Methylene Group (H 91, E 59)

A great many variations in this category have appeared. A series of substituted phenylacetonitriles were heated at *c.* 180° with an excess of formamide with or without added ammonia or trisformamidomethane, to give 4-amino-5-arylpyrimidines.⁵⁴⁷⁷ For example, *p*-chlorophenylacetonitrile (56) and formamide at 190° for 8 h gave 4-amino-5-*p*-chlorophenylpyrimidine (57) in 30% yield.⁵⁴⁷⁷ Similarly, pyrid-4-ylacetonitrile with a mixture of trisformamidomethane, formamide, and *p*-toluenesulfonic acid at 170° for 7 h gave 4-amino-5-pyrid-4'-ylpyrimidine in 52% yield.⁴⁶⁰¹ Likewise, 2-(pyrid-4'-yl)-acetamide gave 4-hydroxy-5-pyrid-4'-ylpyrimidine,⁴⁶⁰¹ thien-2-ylacetonitrile gave 4-amino-5-thien-2'-ylpyrimidine,⁴⁴⁰⁶ *p*-tolylacetonitrile gave 4-amino-5-*p*-tolylpyrimidine,⁵⁴⁸⁷ and ethyl *p*-nitrophenylacetate gave 4-hydroxy-5-*p*-nitrophenylpyrimidine.⁴⁵⁰¹ Although superficially similar, the reaction of 2-propionylthiophene with formamide at 180–190° to give 5-methyl-4-thien-2'-ylpyrimidine (59) probably proceeds through the intermediate (58).⁵⁵⁰¹ See also Sect. 5.E.(7) for similar reactions using 1,3,5-triazine (virtually formamidine) in place of formamide.



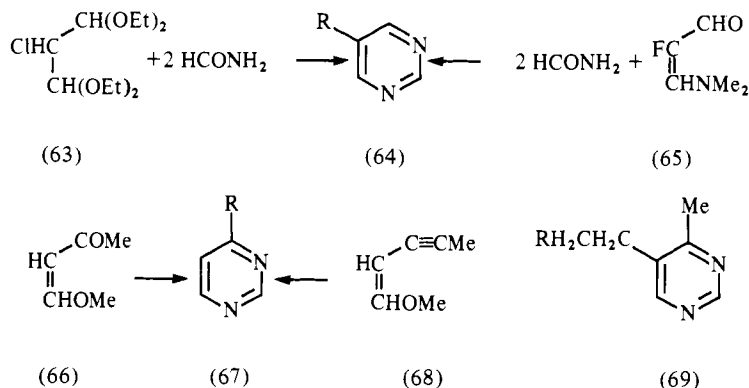
Such condensations appear to be improved by the presence of phosphoryl chloride; desoxybenzoin (60, R = X = H) with formamide and phosphoryl chloride at 140° for 4 h gave 4,5-diphenylpyrimidine (61, R = X = H);⁴⁹⁷⁹ α -(*p*-methoxybenzoyl)-*p*-nitrotoluene (60, R = OMe, X = NO₂) gave 4-*p*-benzoylphenyl-5-*p*-nitrophenylpyrimidine;⁴⁹⁵⁸ phenylacetone gave 4-methyl-5-phenylpyrimidine (*p*-toluenesulphonic acid or phosphoryl chloride);^{5118, 5119} acetamide, formamide, and phosphoryl chloride at 120° gave 4-aminopyrimidine in 32%

yield,⁵⁷⁵² and many 5-alkyl-4-aminopyrimidines were made from higher homologues of acetamide.⁵⁰³⁴

Heterocycles with active methyl groups can act as substrates in this reaction, 2-methylpyridine and formamide at 180° for 27 h gave a small yield of 5-pyrid-2'-ylpyrimidine;⁵¹¹⁵ the same substrate with trisformamidomethane and formamide gave the same product in slightly better yield;⁵¹¹⁴ 4,6-dimethylpyrimidine with formamide and phosphoryl chloride gave 6-methyl-4,5'-bipyrimidine (62), albeit in poor yield,⁵¹²⁰ and 2-methylpyrazine gave 5-pyrazine-2'-ylpyrimidine.⁵¹¹⁴

C. Formamide with β -Dicarbonyl and Related Compounds (*H* 92, *E* 61)

It is worth repeating that β -dicarbonyl compounds or their equivalents will usually react with formamide to give the same products as might be expected from their reaction with formamidine in the Principal Synthesis. Thus, the dialdehyde equivalent, 2-chloro-1,1,3,3-tetraethoxypropane (63, R = Cl) with formamide and ammonium chloride at 200° gave 5-chloropyrimidine in 61% yield;⁴⁴⁸³ 3-dimethylamino-2-fluoroacrolein (65) gave 5-fluoropyrimidine in 52% yield;⁵⁸⁵⁸ 3-amino-2-thien-2' or 3'-ylacrolein gave 5-(thien-2' or 3'-yl)pyrimidine;⁵²²⁰ 3-aminoacrolein gave pyrimidine (64, R = H);⁴⁵¹⁵ and several 2-alkyl-3-aminoacroleins gave 5-methylpyrimidine (64, R = Me) or higher homologues.⁴⁵¹⁵ The aldehydo ketone equivalent, methoxymethyleneacetone (66) gave 4-methylpyrimidine (67, R = Me);⁶²²⁰ 1-methoxybut-1-en-3-yne (68) gave 4-ethylpyrimidine (67, R = Et);⁶²²⁰ and 3-chloro-2- β -chloroethylcrotonaldehyde (69) gave a mixture of 5- β -hydroxy- (69, R = OH) and 5- β -amino-ethyl-4-methylpyrimidine (69, R = NH₂) by displacement of the β -chloro substituent during the reaction.⁵⁸³⁴ The

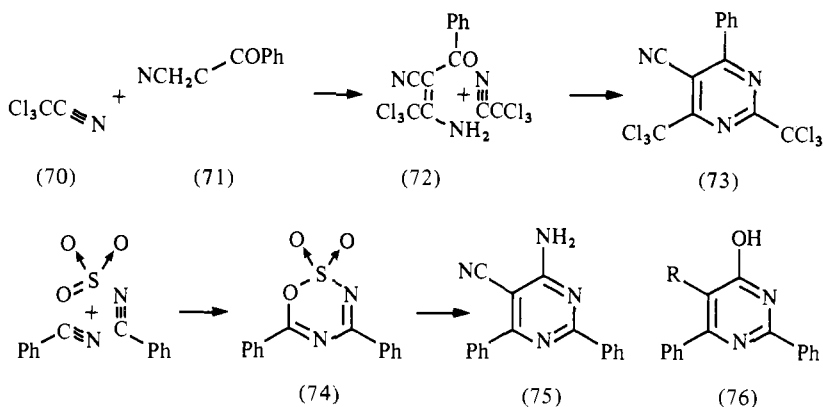


aldehydo nitrile 2-*p*-fluorophenyl-2-formylacetonitrile gave 4-amino-5-*p*-fluorophenylpyrimidine;⁵⁴⁷⁷ 2-formyl-2-*m*-methoxyphenylacetonitrile (with formamide and phosphoryl chloride) gave 4-amino-5-*m*-methoxyphenylpyrimidine;⁴⁹⁵⁷ and 2-formyl-2- α -naphthylacetonitrile gave, under similar conditions, 4-amino-5- α -naphthylpyrimidine.⁵¹⁰⁹ Appropriate keto nitriles with formamide and phosphoryl chloride gave 4-amino-6-benzyl-5-*m*-methoxyphenylpyrimidine,⁴⁹⁵⁷ 4-amino-6-methyl-5-(5',6',7',8'-tetrahydro- β -naphthyl)pyrimidine.⁵¹¹⁰ 4-amino-6-methyl-5- α -naphthylpyrimidine,⁵¹⁰⁹ 4-amino-6-methyl-5-*m*-tolylpyrimidine,⁴⁹⁸¹ and 4-amino-5-(3',4'-methylenedioxyphenyl)-6-phenylpyrimidine.⁴⁹⁷⁷

A somewhat different technique was used to convert several aldehydo and keto ester intermediates into 4-hydroxypyrimidines; for example, ethyl 3-ethoxyacrylate, triethyl orthoformate and (liquid) ammonia were heated at 120° for 12 h to give 4-hydroxypyrimidine;⁵⁵⁵⁰ likewise, ethyl 3-ethoxycrotonate, triethyl orthopropionate and ammonia gave 2-ethyl-4-hydroxy-6-methylpyrimidine.⁵⁵⁵⁰

D. The Frankland–Kolbe and Related Syntheses from Nitriles (*H* 93, *E* 61)

Traditional Frankland–Kolbe syntheses have been used to trimerize acetonitrile in the presence of sodium methoxide at 150° to give 4-amino-2,6-dimethylpyrimidine;⁵¹³⁵ to condense trichloroacetonitrile (70) with benzoylacetonitrile (71) in ether containing finely divided sodium to give 3-amino-2-benzoyl-4,4,4-trichlorocrotononitrile (72), which then underwent condensation with a third nitrile, trichloroacetonitrile, to give 5-cyano-4-phenyl-2,6-bistrichloromethylpyrimidine (73);⁵⁹⁵³ and to trimerize phenylacetonitrile in the presence of methyl aluminum dichloride to give 4-amino-2,6-dibenzyl-5-phenylpyrimidine.⁵⁸¹⁴

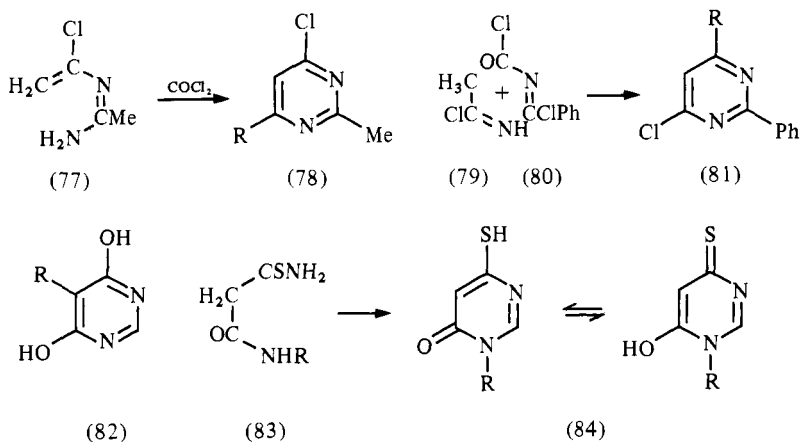


A related procedure is seen in the condensation of two molecules of benzonitrile with sulfur trioxide to give the cyclic crystalline complex, 4,6-diphenyl-1,2,3,5-oxathiadiazine 2,2-dioxide (74), which then reacted with malononitrile to yield 4-amino-5-cyano-2,6-diphenylpyrimidine (75).⁴⁴⁸⁵ The complex (74) also underwent reaction with other methylene compounds; thus, diethyl sodiomalonate gave 5-ethoxycarbonyl-4-hydroxy-2,6-diphenylpyrimidine (76, R = CO₂Et), ethyl cyanoacetate gave 5-cyano-4-hydroxy-2,6-diphenylpyrimidine (76, R = CN), ethyl acetoacetate gave 5-acetyl-4-hydroxy-2,6-diphenylpyrimidine (76, R = Ac), ethyl nitroacetate gave 4-hydroxy-5-nitro-2,6-diphenylpyrimidine (76, R = NO₂), and acetylacetone gave 5-acetyl-4-methyl-2,6-diphenylpyrimidine.⁴⁴⁸⁵ See also Sect. 5.F(6)(d)(xi).

The reaction of three molecules of acetonitrile with one of piperidine or morpholine in the presence of lanthanum perchlorate gave 2,4-dimethyl-6-piperidinopyrimidine or its 6-morpholino analogue respectively. A mechanism has been suggested that appears to be unproven.⁵⁵⁵⁶

The self-condensation of nitriles under acidic conditions, with or without other reagents such as phosgene, has been studied widely by Yanagida, Komori, and their colleagues in Osaka. Since much of the work has been reviewed,⁵⁰³³ the present treatment simply exemplifies its utility in pyrimidine synthesis. Thus, warming acetonitrile with dry hydrogen chloride initially gave the isolable *N*- α -chlorovinylacetamidine (77) (as hydrochloride),⁶³³¹ which was treated with phosgene to give (probably) 4-chloro-6-hydroxy-2-methylpyrimidine (78, R = OH) and thence, by reaction with more phosgene, 4,6-dichloro-2-methylpyrimidine (78, R = Cl) in a greater than 70% yield;⁵⁰²¹ by beginning with propionitrile 4,6-dichloro-2-ethyl-5-methylpyrimidine resulted and other homologues were made similarly.⁵⁰²¹ The reaction can be done without isolating the intermediate (77) and by adjusting the proportions of acetonitrile, hydrogen chloride, and phosgene correctly, 4-chloro-6-hydroxy-2-methylpyrimidine (78, R = OH) was isolated in 55% yield.^{5027, 5028} Several homologues, such as 4-chloro-2-heptyl-5-hexyl-6-hydroxypyrimidine, were made similarly,⁵⁰²⁸ but arylacetonitriles tended to give mainly isoquinolines,⁵⁰²⁶ while α -branched aliphatic nitriles gave only traces of pyrimidines.⁵⁰²⁰

The reaction of simple amides with hydrogen chloride and phosgene leads also, *inter alia*, to pyrimidines. Thus acetamide, like acetonitrile, gave 4,6-dichloro-2-methylpyrimidine (78, R = Cl) in 83% yield, but with increasing chain-length yields of pyrimidines decreased and yields of the corresponding aliphatic nitriles increased; for example,

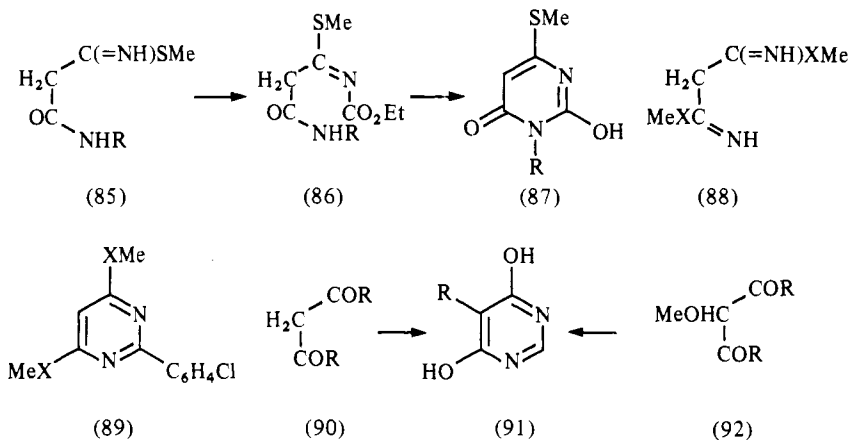


lauramide yielded 22% of 4,6-dichloro-5-decyl-2-undecylpyrimidine and 78% of lauronitrile.⁵⁰²⁹ The reactive intermediate α -chlorobenzylidenecarbamoyl chloride (80) condensed with acetonitrile plus hydrogen chloride, that is, acetimidoyl chloride (79), to give both 4-chloro-6-hydroxy- (81, R = OH) and 4,6-dichloro-2-phenylpyrimidine (81, R = Cl) in small yield.⁵⁰²⁵

4. Syntheses from Malondiamides, Malondiamidines, and Related Compounds (H 97, E 63)

A. Malondiamides with Esters: Remfry-Hull Syntheses (H 97, E 63)

The condensation of appropriate α -substituted malondiamides with ethyl formate in ethanolic sodium ethoxide has been used to prepare 4,6-dihydroxy-5-phenylpyrimidine (82, R = Ph) and its 5-propyl (82, R = Pr), 5-allyl (82, R = $\text{CH}_2\text{CH}=\text{CH}_2$), and 5-amyl (82, R = C_5H_{11}) analogues.⁵⁸⁸² *N*-Substituted malondiamides have also been used. For example, treatment of 2-cyano-*N*-methylacetamide with hydrogen sulfide in the presence of triethylamine gave *N*-methyl- α -thiocarbamoylacetamide (83, R = Me), which reacted with ethyl formate as above to afford 1,6-dihydro-4-mercapto-1-methyl-6-oxo-pyrimidine (84, R = Me); by starting with appropriately *N*-substituted cyanoacetamides, the substrates (83, R = Et, Pr, Bu, Ph, etc) and the corresponding pyrimidines (84) were made also.⁴⁸⁰⁶ The *S*-methylated thioamide, 3-imino-*N*-methyl-3-(methylthio)propionamide (85, R = Me), reacted with ethyl chloroacetate to give 3-ethoxycarbonylimino-*N*-methyl-3-(methylthio)propionamide (86, R = Me), which underwent



cyclization in alcoholic alkali to give 3-methyl-6-methylthiouracil (87, R = Me).⁴⁸⁰⁶ Analogous intermediates and products (85–87; R = Et, Pr, Bu, Ph, etc) were made similarly.⁴⁸⁰⁶

In much the same way, the *O,O*-dimethylated malondiamide, 1,3-diimino-1,3-dimethoxypropane (88, X = O), was treated with *p*-chlorobenzoyl chloride in methylene chloride at -40° in the presence of a tertiary base to give 2-*p*-chlorophenyl-4,6-dimethoxypyrimidine (89, X = O) in 82% yield;⁴⁹⁴⁹ similarly 1,3-diimino-1,3-bismethylthio- propane (88, X = S) gave 2-*p*-chlorophenyl-4,6-bismethylthiopyrimidine (89, X = S), while the same substrate with ethyl chloroformate (this time in acetone/trimethylamine at room temperature) gave 2-hydroxy-4,6-bismethylthiopyrimidine.⁴⁹⁴⁹

B. Malondiamides with Amides (H 98, E 63)

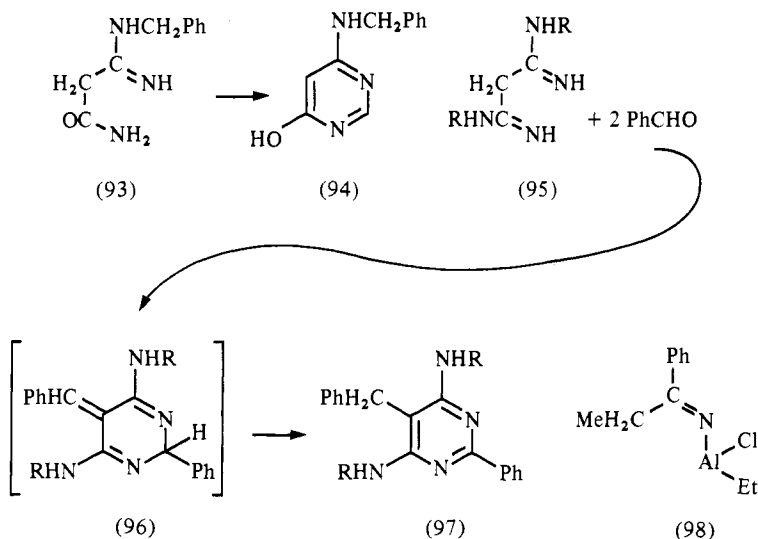
By treatment of diethyl malonate (90, R = OEt) with formamide in ethanolic sodium ethoxide under reflux, malondiamide (90, R = NH₂) is formed and then converted by more formamide into 4,6-dihydroxypyrimidine (91, R = H).^{3529, 4722} Likewise, dimethyl α -methoxymalonate (92, R = OMe) was converted by ammonia into α -methoxymalon- diamide (92, R = NH₂), which was then treated with formamide in ethanolic sodium ethoxide to give 4,6-dihydroxy-5-methoxypyrimidine (91, R = OMe).⁵⁸²⁸ α -(diphenylmethyl)malondiamide also reacted with formamide to give 5-diphenylmethyl-4,6-dihydroxypyrimidine (91, R = Ph₂CH), but the best yields were obtained in dimethyl sulfoxide containing potassium *t*-butoxide.⁵⁵⁰³

C. Malondiamides with Carbonic Acid Derivatives (*H* 99)

A simple example of this unusual category is provided by the reaction of α -nitromalondiamide with phosgene in toluene in a sealed tube at 120° to give dilituric acid (2,4,6-trihydroxy-5-nitropyrimidine) in 50% yield.⁴⁷⁴⁸

D. The Use of Malondiamidines (*H* 100, *E* 63)

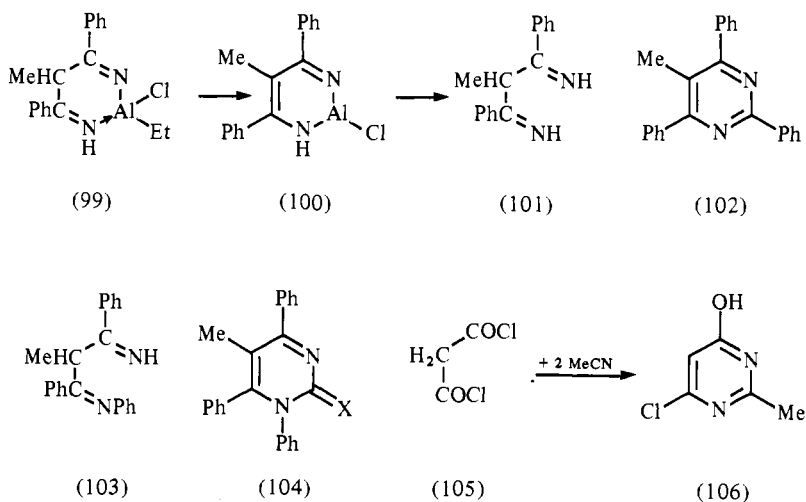
A good route to 4-alkylamino-6-hydroxypyrimidines is exemplified in the condensation of 2-(*N*-benzylamidino)acetamide (93) with formaldehyde in ethanolic sodium ethoxide to give 4-benzylamino-6-hydroxypyrimidine (94) in 90% yield.⁵³⁵⁷



Malondiamidine (95, $R = H$) might be expected to react with benzaldehyde to give a 4,6-diamino-2-phenyldihydropyrimidine but, in fact, it reacts with two molecules of benzaldehyde in pyridine to give 4,6-diamino-5-benzylidene-2,5-dihydro-2-phenylpyrimidine (96, $R = H$), which undergoes facile rearrangement into 4,6-diamino-5-benzyl-2-phenylpyrimidine (97, $R = H$).⁵¹³¹ The reaction is versatile; for example, *N*-methyl-2-(*N*-methylamidino)acetamide (95, $R = \text{Me}$) and benzaldehyde gave 5-benzyl-4,6-bismethylamino-5-phenylpyrimidine (97, $R = \text{Me}$), and benzaldehyde may be replaced by other aromatic or heteroaromatic aldehydes.⁵¹³¹

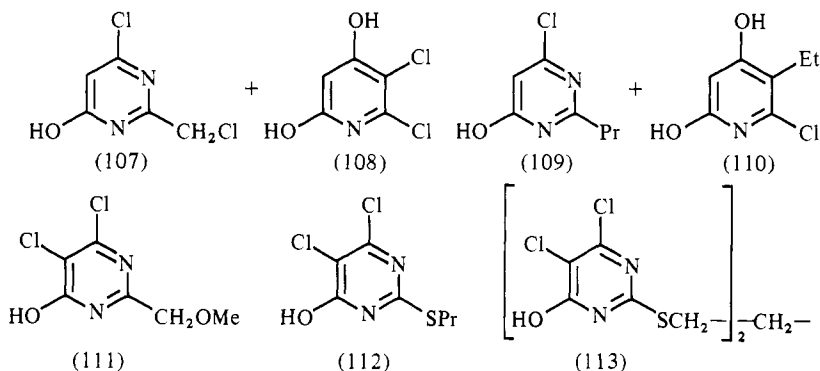
E. The Use of 1,3-Diiminopropanes of Related Components (New)

Treatment of ethyl(α -ethylbenzylideneamino)aluminum chloride (98) with benzonitrile gave the aluminum complex (99), which lost ethane at 160° to give the cyclic aluminum compound (100), or underwent alkaline hydrolysis to 1,3-diimino-2-methyl-1,3-diphenylpropane (101). On heating the last-mentioned compound (101) with benzonitrile at 130° for 20 h, a small yield of 5-methyl-2,4,6-triphenylpyrimidine (102) resulted, but on repeating the reaction with added aluminum chloride a good yield of the pyrimidine (102) was obtained. Comparable yields were also obtained by using either of the aluminum-containing compounds (99) or (100) as substrate with benzonitrile;⁴⁴⁹⁹ variations were possible and gave, for example, 5-ethyl-2-phenyl-4-propyl- or 5-ethyl-4-phenyl-2-propylpyrimidine.⁴⁴⁹⁹ Diimines like (101) have also been condensed with carbonic or thiocarbonic acid derivatives to give 2-oxo- or 2-thiopyrimidines.⁵⁷⁶⁴ Thus, 1-imino-2-methyl-1,3-diphenyl-3-phenyliminopropane (103) and ethyl chloroformate in pyridine at $0-20^\circ$ gave 1,2-dihydro-5-methyl-2-oxo-1,4,6-triphenylpyrimidine (104, X = O), while with carbon disulfide at 70° for several hours the product was 1,2-dihydro-5-methyl-1,4,6-triphenyl-2-thiopyrimidine (104, X = S), both in 90% yield; several variations were also successful.⁵⁷⁶⁴ 3-Aminocrotonamide reacted with benzaldehyde to give 2-benzylidene-3-iminobutyramide, which reacted with another benzaldehyde molecule to give 5-benzyl-4-hydroxy-6-methyl-2-phenylpyrimidine, the oxidation state imbalance having been rectified by the benzylidene double bond.⁵⁰⁷⁶



F. The Use of Malonyl Dichlorides with Cyano Compounds (New)

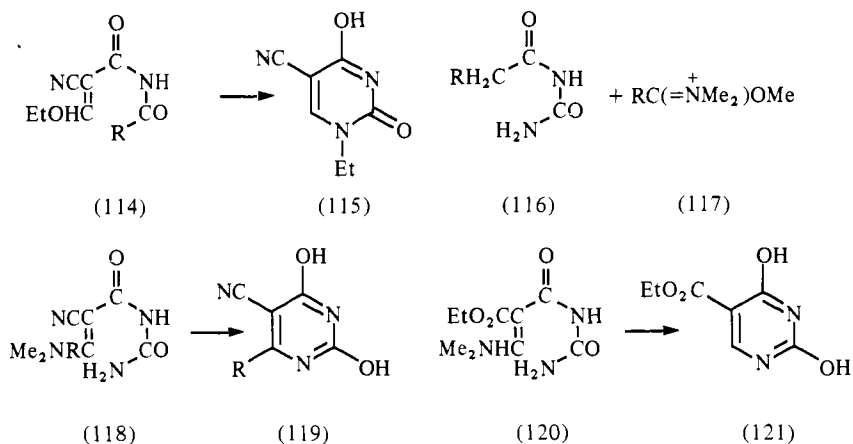
It was revealed in 1968 that malonyl dichloride (105) and nitriles gave pyrimidines under some conditions; for example, acetonitrile gave 4-chloro-6-hydroxy-2-methylpyrimidine (106).⁶³³² Unfortunately, pyridines may also be formed so, as a synthesis of pyrimidines, the reaction is limited; moreover, its mechanism is still obscure despite considerable work and some suggestions.⁵²⁵³ Some other examples of its successful use include the synthesis of 4-chloro-2-chloromethyl-6-hydroxypyrimidine (107), along with 2,3-dichloro-4,6-dihydroxypyridine (108), by the action of malonyl dichloride and chloroacetonitrile at 20°;⁵²⁵³ 4-chloro-2-fluoromethyl-6-hydroxypyrimidine with no pyridine by-product;⁵²⁵³ 4-chloro-6-hydroxy-2-propylpyrimidine (109) in small yield and 2-chloro-3-ethyl-4,6-dihydroxypyridine (110) in better yield (using butyronitrile);⁵²⁵³ and 4-chloro-2-cyclohexylmethyl-6-hydroxypyrimidine.⁵⁷³¹ α -Substituted malonyl dichlorides have also been used with appropriate nitriles to give 4,5-dichloro-6-hydroxy-2-methoxymethylpyrimidine (111),⁵⁷³¹ 4-chloro-6-hydroxy-2,5-dimethylpyrimidine,⁵⁷³¹ 5-benzyl-4-chloro-2-chloromethyl-6-hydroxypyrimidine,⁵⁷³¹ 4,5-dichloro-2-fluoromethyl-6-hydroxypyrimidine,⁵²⁵³ and many other such derivatives mainly in low yield.^{5253, 5731}



The reaction has been extended to alkyl thiocyanates, which give 2-alkylthio analogues. Thus, propyl thiocyanate (2 molecules) and α -chloromalonyl dichloride at 25° for 12 days gave 4,5-dichloro-6-hydroxy-2-propylthiopyrimidine (112) in 40% yield;⁴⁸⁹⁴ similarly prepared were 4-chloro-2-ethylthio-6-hydroxy-5-phenylpyrimidine, 5-benzyl-2-benzylthio-4-chloro-6-hydroxypyrimidine, and a dozen other analogues.⁴⁸⁹⁹ Trimethylene bithiocyanate and chloromalonyl dichloride gave 1,3-bis-(4',5'-dichloro-6'-hydroxypyrimidin-2'-ylthio)propane (113).⁴⁸⁹⁴

5. Other Syntheses of Pyrimidines (*H* 101, *E* 64)A. Ethoxymethyleneacetic Acid to Uracil Derivatives (*H* 101, *E* 64)

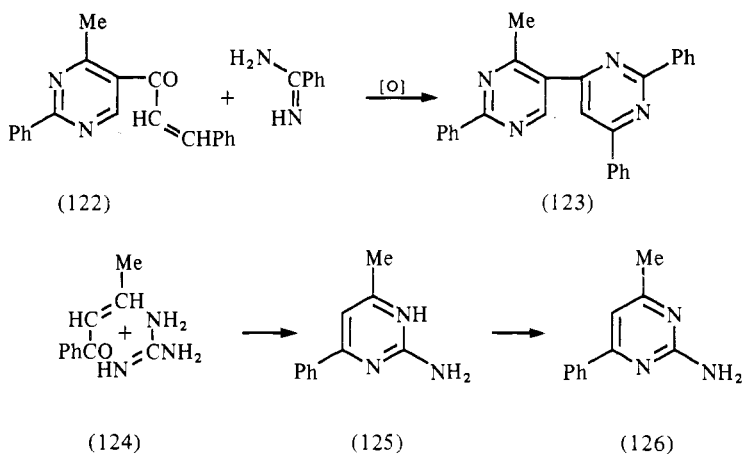
There have been no recent classical examples of this synthesis. However, there are several in which typical intermediates have been used, even if they were obtained by atypical routes. For example, 2-cyano-3-ethoxy-*N*-ethoxycarbonylacrylamide (114, $R = \text{OEt}$) reacted with ethanolic ethylamine to give 5-cyano-1-ethyluracil (115), probably *via* the unisolated urea derivative (114, $R = \text{NHEt}$); six other 1-alkyl homologues were made similarly, all in excellent yield.⁴⁹⁴⁰



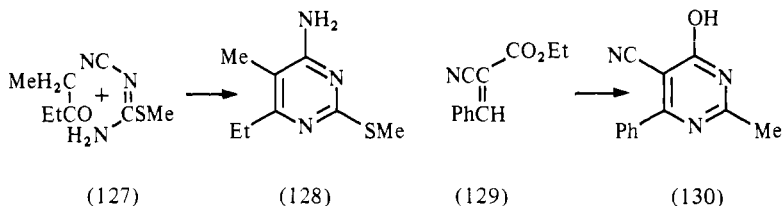
A different approach is evident in the condensation of cyanoacetylurea (116, $R = \text{CN}$) with the quaternary trimethylated acetamide (117, $R = \text{Me}$) to give *N*-(2-cyano-3-dimethylaminocrotonoyl)urea (118, $R = \text{Me}$), which underwent cyclization in alkali to 5-cyano-2,4-dihydroxy-6-methyluracil (119, $R = \text{Me}$);⁴⁹⁰² also in the analogous conversion of ethoxycarbonylacetylurea (116, $R = \text{CO}_2\text{Et}$) by the formamide derivative (117, $R = \text{H}$) into *N*-(3-dimethylamino-2-ethoxycarbonylcrotonoyl)urea (120) and thence 5-ethoxycarbonyl-2,4-dihydroxypyrimidine (121).⁴⁹⁰² Similarly, α -cyanoacetic acid reacted with *N*-methylurea in acetic anhydride to give *N*-cyanoacetyl-*N'*-methylurea which, in turn, reacted with the trimethylated formamide (117, $R = \text{H}$) to give *N*-(2-cyano-3-dimethylaminoacryloyl)urea (118, $R = \text{H}$) and thence 5-cyano-2,4-dihydroxypyrimidine (119, $R = \text{H}$);⁴⁹⁴¹ some comparative data with alternative Shaw syntheses (III, 2, *E*) are available.⁴⁹⁴¹

D. Amidines and Others with Unsaturated Carbonyl Compounds (*H* 102, *E* 65)

The original form of this synthesis, from unsaturated ketones and amidines, has been exemplified recently in the condensation of two molecules of 5-cinnamoyl-4-methyl-2-phenylpyrimidine (122) with one molecule of benzamidine to give 4'-methyl-2,2',6-triphenyl-4,5'-bipyrimidine (123), the necessary dehydrogenation being provided by the second molecule of the substrate (122),⁶²⁵⁸ as well as in the reaction of 4-*p*-chlorophenylbut-3-en-2-one with *p*-chlorobenzamidine to give 2,4-bis-*p*-chlorophenyl-6-methylpyrimidine,⁵⁵⁹⁰ and in several valuable procedures using air as oxidant.^{4817, 6263} However, guanidine behaves similarly with unsaturated ketones; guanidine and 1-benzoylpropene (124) gave 2-amino-1,6-dihydro-6-methyl-4-phenylpyrimidine (125), which could be isolated as the picrate but was converted in ethanolic sodium ethoxide into the fully aromatic product 2-amino-4-methyl-6-phenylpyrimidine (126) by a postulated "base catalyzed elimination of H₂";⁵⁸²¹ several other examples have been given.⁵⁸²¹



The synthesis of pyrimidines from dicyanodiamide and ketones (*E* 66) has been extended to the use of *N*-cyano-*S*-methylthiourea. Thus, the latter reagent (127) and a tenfold excess of diethyl ketone were heated with a small amount of organic base (pyrrolidine or undefined "DBU") at 150° to give 4-amino-6-ethyl-5-methyl-2-methylthiopyrimidine (128) in low yield. Cyclic ketones, such as cyclohexanone, underwent a similar reaction to give, for example, 4-amino-5,6,7,8-tetrahydro-2-methylthioquinazoline in quite good yield.⁶¹⁴¹ No dehydrogenation is required in this reaction.



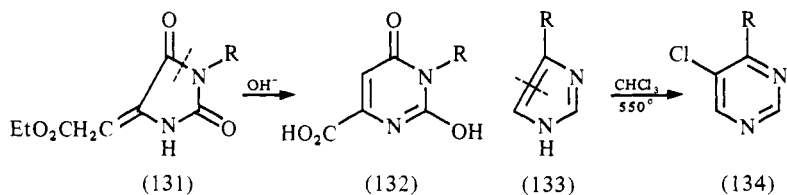
Unsaturated esters have been used in place of unsaturated ketones – ethyl 2-cyano-3-phenylacrylate (129) and acetamidine gave 5-cyano-4-hydroxy-2-methyl-6-phenylpyrimidine (130) in reasonable yield, presumably *via* a dihydro derivative.⁶³⁰²

E. Syntheses of Pyrimidines from Other Ring Systems (*H* 103, *E* 66)

With the considerable increase in the number of heterocyclic systems which have been converted into pyrimidines, the classification within this section has become somewhat illogical in order; however, it has been retained on the grounds of ease in back reference to earlier volumes. Where such syntheses are more of interest than utility, treatment is brief.

(1) *Pyrimidines from Imidazoles* (*H* 103, *E* 66)

Although hydantoin intermediates (131) have long been implicated in the formation of orotic acids (4-carboxy-2,6-dihydroxypyrimidines) from diethyl oxalacetate and ureas, it has been shown that when that condensation was done in oleum, no hydantoin intermediate was involved. Thus, in 96% sulfuric acid, the same reagents did form 5-ethoxycarbonylmethylenhydantoin (131, *R* = *H*), which was found to be stable in oleum and hence not an intermediate in the reaction; the hydantoin (131, *R* = *H*) was, of course, converted by alkali into orotic acid (132, *R* = *H*).⁴⁸⁵⁶ A traditional route to substituted orotic acids *via* hydantoins is illustrated by the condensation of diethyl oxalacetate with *N*-phthalimidourea in acetic acid containing hydrogen chloride at

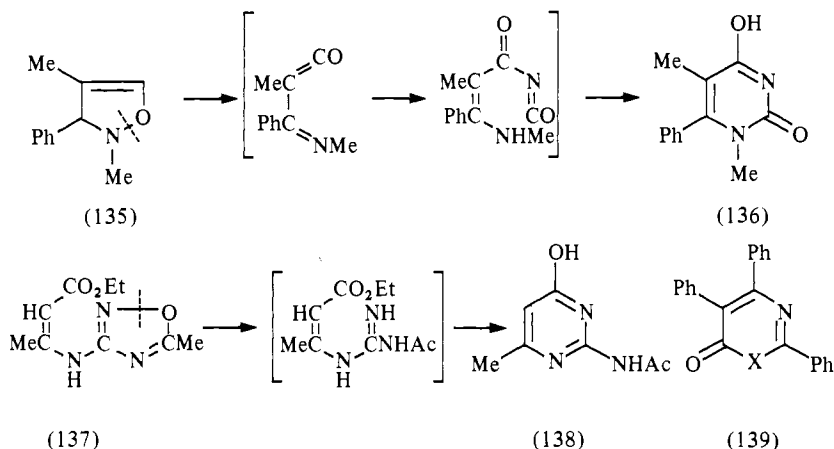


106° to give 5-ethoxycarbonylmethylene-3-phthalimidomethylhydantoin [131, $R = CH_2N(CO)_2C_6H_4$], and its subsequent treatment by hot alkali followed by hot acid to give 1-aminomethyl-4-carboxy-1,6-dihydro-2-hydroxy-6-oxypyrimidine (132, $R = CH_2NH_2$: 3-amino-methylorotic acid).⁴⁷⁸²

Imidazole (33, $R = H$) and an excess of chloroform at 550° gave up to 35% yield of 5-chloropyrimidine (134, $R = H$); 4-methylimidazole (133, $R = Me$) gave a mixture of 5-chloro-4-methylpyrimidine (134, $R = Me$) (20% yield) and 4-chloro-6-methylpyrimidine (15%); and di- and trimethylimidazoles gave similar results.⁶⁰⁰³ The reaction is of no preparative value.

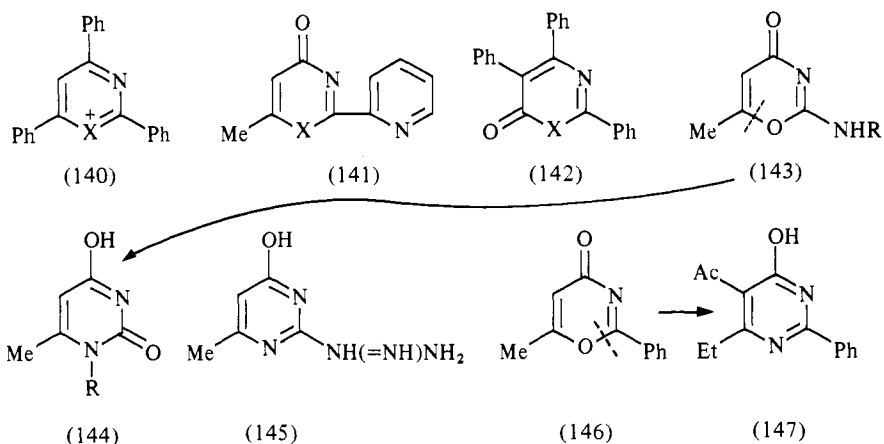
(2) *Pyrimidines from Mixed 5- or 6-Membered Heterocycles*
(H 104, E 68)

2,4-Dimethyl-3-phenylisoxazolium perchlorate (135) and potassium cyanate in aqueous methanol gave 1,5-dimethyl-6-phenyluracil (136) in low yield, possibly by the route indicated.⁶²⁴⁴ Isothiazoles have given pyrimidines.⁴⁷²³



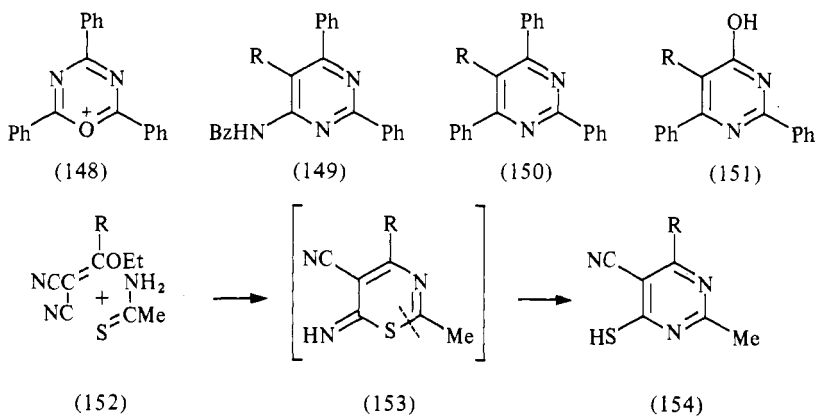
Hydrogenolytic ring fission of a 1,2,4-oxadiazole bearing a suitable side chain can lead to pyrimidines. For example, 3-(2'-ethoxycarbonyl-1'-methylvinyl)amino-5-methyl-1,2,4-oxadiazole (137) with hydrogen over palladium-charcoal gave 2-acetamido-4-hydroxy-6-methylpyrimidine (138), probably *via* the intermediate shown,⁴⁵⁹² by using a ketonic in place of an ester group at the end of the side chain, 2-acetamido-4,6-dialkyl/arylpyrimidines resulted.⁴⁵⁹² The trouble with the method is formation of appropriate oxadiazoles as substrates.

Treatment of 6-oxo-2,4,5-triphenyl-1,3-oxazine (139, $X = O$) with aqueous ammonia at 20° gave 4-hydroxy-2,5,6-triphenylpyrimidine (139, $X = NH$) in good yield; although of minor preparative value, this reaction did constitute confirmation of the structure (139, $X = NH$) for the same compound produced by a less predictable Principal Synthesis.⁵⁹⁴⁴ Similarly, 2,4,6-triphenyl-1,3-oxazinium salts (140, $X = O$) with methylamine, aniline, or semicarbazide gave the corresponding 1-methyl-2,4,6-triphenyl- (140, $R = NMe$), 1,2,4,6-tetraphenyl- (140, $R = NPh$), and 2,4,6-triphenyl-1-ureidopyrimidinium salt (141, $R = NNHCONH_2$), respectively.⁵¹⁴⁷ Such reactions have been used effectively to prepare 2-substituted-4-hydroxy-6-methylpyrimidines. Ethyl pyridine-2'-carboximidate reacted with diketene to give 6-methyl-4-oxo-2-pyrid-2'-yl-1,3-oxazine (141, $X = O$), which with aqueous ethanolic ammonia at 90° in a sealed tube gave 4-hydroxy-6-methyl-2-pyrid-2'-ylpyrimidine (141, $R = NH$) in 67% yield;⁶⁰⁰⁵ the pyrid-3' and 4'-yl isomers and the pyrid-2'-ylmethyl analogue were made similarly.⁶⁰⁰⁵ Likewise 6-oxo-2,4,5-triphenyl-1,3-oxazine (142, $X = O$) reacted with appropriate primary amines to give 1,6-dihydro-1-methyl-6-oxo-2,4,5-triphenylpyrimidine (142, $X = NMe$);⁵⁸²⁷ several homologues were made similarly,^{4589, 5827} and 6-chloro-3,4-dihydro-3-methyl-2,4-dioxo-1,3-oxazine with methylamine gave 1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxypyrimidine, probably by initial methylaminolysis of the chloro substituent followed by rearrangement.⁶²⁵⁰ In a quite different way, ethyl cyanamide (*N*-cyanoethylamine) and diketene gave 6-methyl-2-methylamino-4-oxo-1,3-oxazine (143, $R = Me$), which rearranged in boiling glacial acetic acid to give 1,6-dimethyluracil (144, $R = Me$), and by appropriate variations in the alkylcyanamide, the *N*-alkyl substituent was changed in the oxazine (143) and the pyrimidine

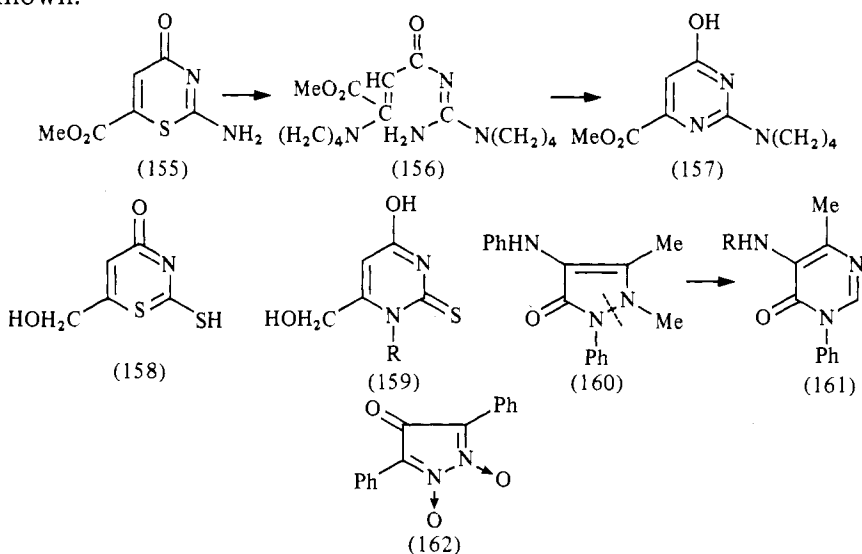


(144).⁶¹⁹⁴ In contrast, the product from dicyandiamide and diketene, 2-guanidino-6-methyl-4-oxo-1,3-oxazine [143, $R = C(\cdot NH)NH_2$], was converted by ammonia into 2-guanidino-4-hydroxy-6-methylpyrimidine (145).⁶¹⁹⁴ Another type of oxazine to pyrimidine conversion is exemplified in the treatment of 6-methyl-4-oxo-2-phenyl-1,3-oxazine (146) with thiopropionamide to give 5-acetyl-4-ethyl-6-hydroxy-2-phenylpyrimidine (147).⁵⁰⁹² It is evident that ring fission of the oxazine occurred at the 1,2-bond, followed by insertion of the thiopropionamide with loss of hydrogen sulfide and final ring closure so that the original $O1 + C6 + 6-Me$ fragment appeared in the pyrimidine as a 5-acetyl group; the reaction was capable of variation and yields were quite good.⁵⁰⁹² Although of no importance, 2,4-dimethyl-6-oxo-1,3-oxazine was converted into 2,4,6-trimethylpyrimidine in low yield by prolonged heating at $300-320^\circ$; several analogues were made similarly.⁶¹⁰⁸

The oxadiazine, 2,4,6-triphenyl-1,3,5-oxadiazinium chloride (148) as its stannic chloride complex was easily prepared from benzonitrile (2 mol) with benzoyl chloride and stannic chloride. It reacted with malononitrile in the presence of triethylamine to give 4-benzamido-5-cyano-2,6-diphenylpyrimidine (149, $R = CN$),⁵¹³³ with methyl α -cyanoacetate to give the 5-methoxycarbonyl analogue (149, $R = CO_2Me$), and with benzoylacetonitrile to give the 5-benzoyl analogue (149, $R = Bz$).⁵¹³³ Similarly, ethyl benzoylacetate gave 5-ethoxycarbonyl-2,4,6-triphenylpyrimidine (150, $R = CO_2Et$), while dibenzoylmethane gave the 5-benzoyl analogue (150, $R = Bz$)⁵¹³⁴ and cyanoacetamide or benzoylacetamide gave 5-cyano-4-hydroxy-2,6-diphenylpyrimidine (151, $R = CN$) or its 5-benzoyl analogue (151, $R = Bz$), respectively.⁵¹³⁴ The mechanism clearly involves ring fission, addition of the methylene compound, recyclization, and rearrangement, but it does not appear to have been worked out in detail.



The formation of pyrimidines *via* 1,3-thiazines is a useful route; thus, condensation of thioacetamide with 2-cyano-3-ethoxycrotononitrile (152, R = Me) under alkaline conditions gave (presumably) 5-cyano-6-imino-2,4-dimethyl-1,3-thiazine (153, R = Me), which rearranged without isolation to 5-cyano-4-mercapto-2,6-dimethylpyrimidine (154, R = Me) in good yield.⁶³⁰² Likewise, 2-cyano-3-ethoxy-3-phenylacrylonitrile (152, R = Ph) gave the intermediate (153, R = Ph) and thence 5-cyano-4-mercapto-2-methyl-6-phenylpyrimidine (154, R = Ph); other variations were also successful.⁶³⁰² Another sequence, in which the sulfur atom of the thiazine is not represented in the final pyrimidine, is exemplified in the condensation of thiourea with dimethyl acetylenedicarboxylate to give 2-amino-6-methoxycarbonyl-4-oxo-1,3-thiazine (155), which underwent aminolytic cleavage by pyrrolidine at 20° to give methyl 4-oxo-2-pyrrolidino-4-(*N'*-tetramethyleneguanidino)crotonate (156) and subsequent cyclization in acetic anhydride to afford 4-hydroxy-6-methoxycarbonyl-2-pyrrolidino-pyrimidine (157) in a greater than 60% overall yield.⁶²²⁷ A sequence, in which a sulfur atom in the thiazine does survive into the pyrimidine, involved condensation of dithiocarbamic acid with ethyl 4-hydroxybut-2-ynoate to give 6-hydroxymethyl-2-mercapto-4-oxo-1,3-thiazine (158), which in aqueous ammonia, methylamine, or benzylamine gave 4-hydroxy-6-hydroxymethyl-2-mercaptopyrimidine (159, R = H), 1,2-dihydro-4-hydroxy-6-hydroxymethyl-1-methyl-2-thiopyrimidine (159, R = Me), or 1-benzyl-1,2-dihydro-4-hydroxy-6-hydroxymethyl-2-thiopyrimidine (159), respectively.⁵¹⁷⁵ Other useful examples are known.⁵³⁵³



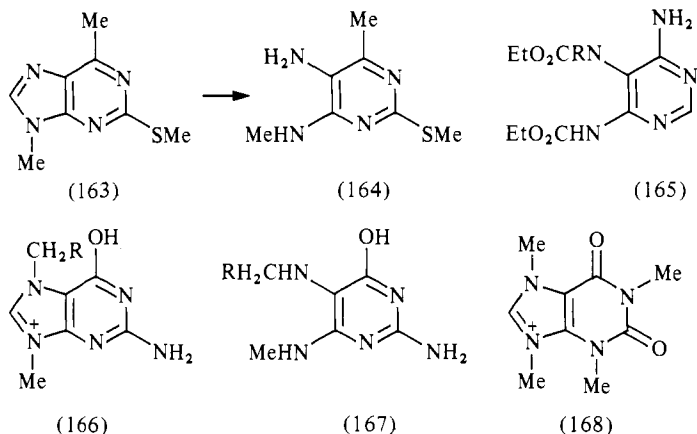
(3) *Pyrimidines from Azoles (H 105, E 69)*

In attempting to methylate 4-anilino-1,5-dihydro-2,3-dimethyl-5-oxo-1-phenylpyrazole (160, R = Ph) by methyl iodide/sodium hydride in xylene no alkylation occurred. but the product was 5-anilino-1,6-dihydro-4-methyl-6-oxo-1-phenylpyrimidine (161, R = Ph) (40%), in which the *N*-methyl group from the pyrazole had provided the extra carbon atom for the pyrimidine ring.^{5049,6076} The simpler analogue 2-amino-1,5-dihydro-2,3-dimethyl-5-oxo-1-phenylpyrazole (160, R = H) behaved similarly in xylene/sodium hydride (or other strong base) to give 5-amino-1,6-dihydro-4-methyl-6-oxo-1-phenylpyrimidine (161, R = H).⁶⁰⁷⁶

An interesting ring expansion of 4-oxo-3,5-diphenyl-(4*H*)-pyrazole 1,2-dioxide (162) occurred with ethyl propiolate to give 2-ethoxycarbonyl-5-hydroxy-4,6-diphenylpyrimidine 1-oxide in 20% yield, but the reaction has not been developed.⁵⁴⁹⁹

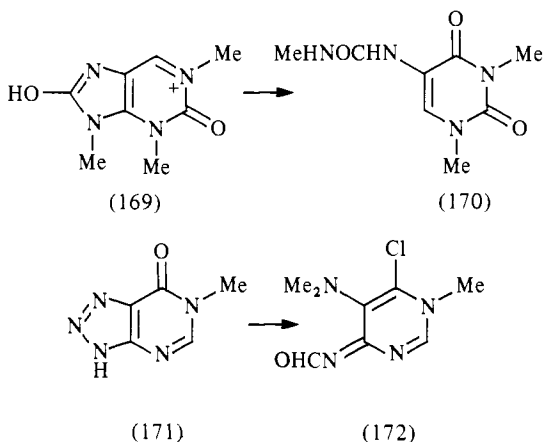
(4) *Pyrimidines from Purines and Related Heterobicycles (H 105, E 69)*

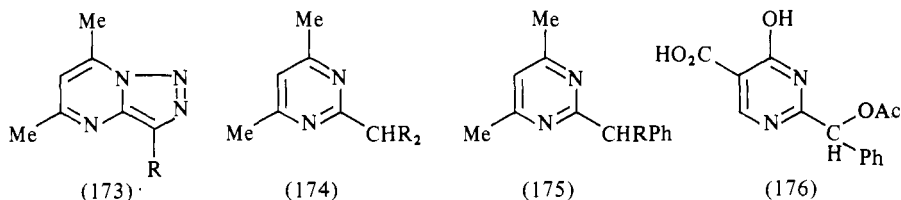
Although of little preparative value, 6,9-dimethyl-2-methylthiopurine (163) was converted by hot alkali into 5-amino-4-methyl-6-methylamino-2-methylthiopyrimidine (164) in 94% yield;⁵⁶⁷⁰ 6-amino-9- β,β,β -trifluoroethylpurine in alkali gave 4,5-diamino-6- β,β,β -trifluoroethylaminopyrimidine;⁵²⁵⁷ 7,8-dihydro-7,9-dimethyl-8-thiopurine in alkali gave 4,5-bismethylaminopyrimidine (other 7,9-dimethyl analogues behaved similarly);⁵⁸⁷³ 6-aminopurine and ethyl chloroformate in ethyl acetate containing potassium acetate gave 4-amino-6-ethoxycarbonylamino-5-*N*-ethoxycarbonylformamidopyrimidine (165, R = CHO), which in hot water lost the formyl group to give 4-amino-5,6-bisethoxycarbonylamino-2-methylthiopyrimidine (165, R = H);⁵⁵⁹⁶ 6-amino-9-propylpurine and diethyl pyrocarbonate gave a separable mixture of 4-amino-5-ethoxycarbonylamino-6-*N*-propylformamido-, 4,5-bisethoxycarbonylamino-6-propylamino-, and 4,5-bisethoxycarbonylamino-6-*N*-propylformamidopyrimidine;⁵⁸⁷¹ guanosine similarly gave 2-amino-5-ethoxycarbonylamino-4-hydroxy-6-ribofuranosylaminopyrimidine.⁴⁵⁷⁹ Other examples have been reported.⁵⁷⁴⁷ Quaternized purines are clearly susceptible to degradation to pyrimidines; 2-amino-7-ethoxycarbonyl-(or cyano)methyl-6-hydroxy-9-methylpurinium halide (166, R = CO₂Et or CN) in mildly alkaline solution gave 2-amino-5-*N*-[ethoxycarbonyl-(or cyano)methyl] formamido-4-hydroxy-6-methylaminopyrimidine



(167, R = CO₂Et or CN),⁴⁶²⁵ 1,2,3,6-tetrahydro-1,3,7,9-tetramethyl-2,6-dioxapurinium halide (168) was reduced by sodium borohydride to an hexahdropurine with an appreciable byproduct of 5-dimethylamino-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxypyrimidine,^{4786, 5735} 2,6-dihydroxy-7,9-dimethylpurinium 3-oxide methosulfate (or the corresponding zwitterion) was degraded by aqueous ammonia to give 2,4-dihydroxy-6-methylamino-5-*N*-methylformamidopyrimidine 1-oxide,⁵⁴²⁴ and 2,3-dihydro-8-hydroxy-1,3,9-trimethylpurinium iodide (169) underwent alkaline hydrolysis to afford 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-*N'*-methylureidopyrimidine (170).⁵³³⁶

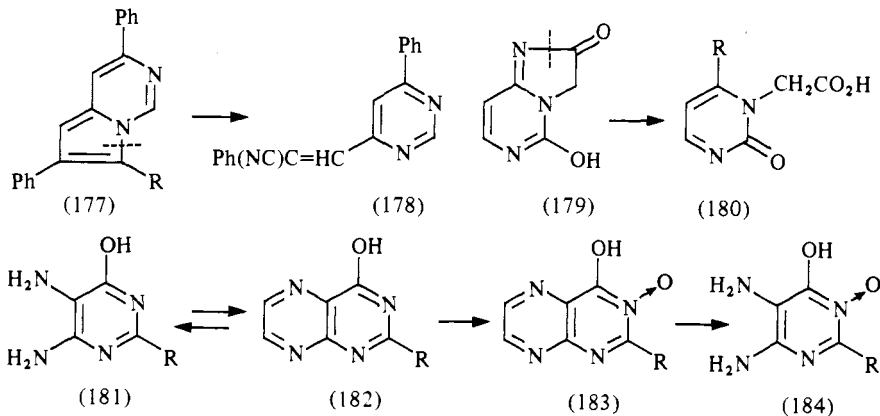
Two types of triazolopyrimidine may be broken down to pyrimidines. Treatment of 6,7-dihydro-6-methyl-7-oxo-*v*-triazolo[5,4-*d*]-pyrimidine (171) with thionyl chloride and dimethylformamide probably produced the unusual structure, 4-chloro-5-dimethylamino-6-formylimino-3,6-dihydro-3-methylpyrimidine (172); photolysis of





3-phenyl-, 7-chloro-3-phenyl-, and 7-cyano-3-phenyl-*v*-triazolo[5,4-*d*]-pyrimidine in benzene gave as minor products in low yield, 4-anilino-, 4-anilino-6-chloro-, and 4-anilino-6-cyano-5-phenylpyrimidine, respectively.⁶⁰⁸⁸ Bromination of 5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (173, R = H) gave 2-dibromomethyl-4,6-dimethylpyrimidine (174, R = Br) in 90% yield and thence 2-diethoxymethyl-4,6-dimethylpyrimidine (174, R = OEt);⁵⁴⁴⁹ since the starting material was easily made, the procedure has potential. So too has the conversion of 5,7-dimethyl-3-phenyl-*v*-triazolo[1,5-*a*]pyrimidine (173, R = Ph) by glacial acetic acid into 2- α -acetoxybenzyl-4,6-dimethylpyrimidine (175, R = OAc),^{5241, 5249} of the same substrate (173, R = Ph) by acetyl chloride into 2- α -chlorobenzyl-4,6-dimethylpyrimidine (175, R = Cl);⁵²⁴¹ and of several related triazolopyrimidines into useful 2-substituted pyrimidines such as 2-acetoxybenzyl-5-carboxy-4-hydroxypyrimidine (176).⁵²⁴¹

A few pyrrolopyrimidines have been degraded to pyrimidines. Thus, 7-nitroso-3,6-diphenylpyrrolo[1,2-*c*]pyrimidine (177, R = NO) underwent reductive cleavage by cyclohexene/palladium-charcoal under reflux to give 4- β -cyanostyryl-6-phenylpyrimidine (178). Paradoxically, the 7-amino analogue (177, R = NH₂) was oxidized by lead tetracetate or dehydrogenated by palladium-charcoal (without hydrogen) to give the same pyrimidine (178), and yields were comparable by all three methods.⁵²⁴⁶ Other examples are known.^{5239, 5246, 5544}

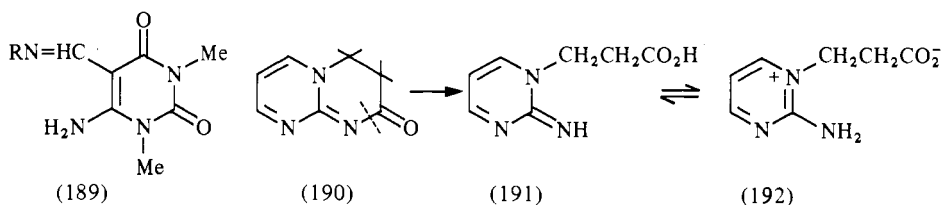
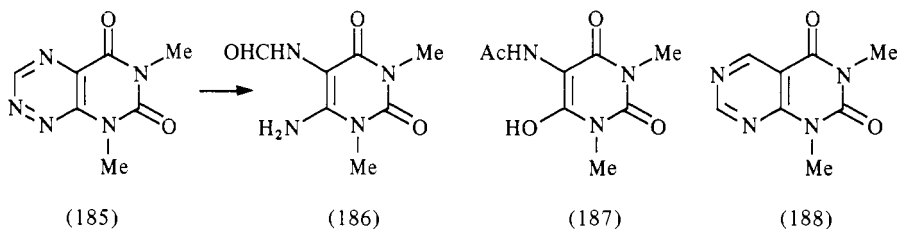


The imidazopyrimidine, 2,3-dihydro-5-hydroxy-2-oxoimidazo-[1,2-*c*]pyrimidine (179), which was made from 4-chloroacetyl-amino-2-hydroxypyrimidine, underwent ring fission in dilute hydrochloric acid to give 4-amino-3-carboxymethyl-2,3-dihydro-2-oxypyrimidine (180, R = NH₂); alkaline treatment of the substrate (179) gave 3-carboxymethyluracil (180, R = OH).⁵⁷⁷¹

(5) *Pyrimidines from Pteridines and Other Azanaphthalenes*
(H 106, E 71)

When 4-hydroxypteridine (182, R = H) was treated with aqueous hydroxylamine, some was converted into 4,5-diamino-6-hydroxypyrimidine (181, R = H) (from which the pteridine was made originally!) and some was converted *via* an hydroxylamine addition intermediate into 4-hydroxypteridine 3-oxide (183, R = H), which gradually gave 4,5-diamino-6-hydroxypyrimidine 1-oxide (184, R = H);⁵⁶⁵⁰ 4-hydroxy-2-methylpteridine (182, R = Me) behaved similarly to give a separable mixture of its 3-oxide (183, R = Me), 4,5-diamino-6-hydroxy-2-methylpyrimidine (181, R = Me) and its 1-oxide (184, R = Me).⁵⁶⁵⁰ The reaction provides a useful route at least to the *N*-oxides.

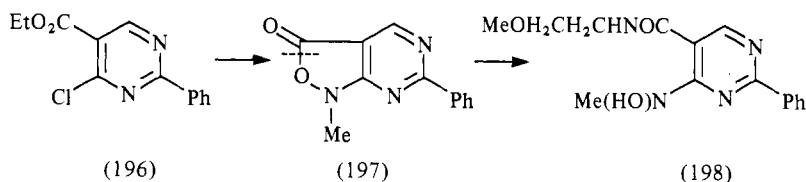
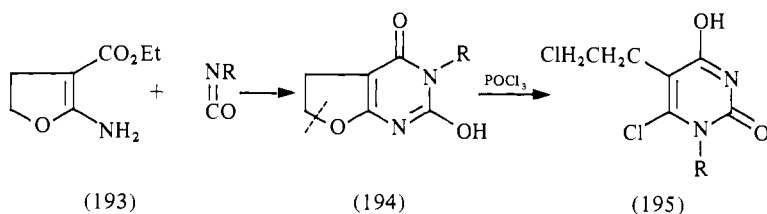
Fervenuin, 5,6,7,8-tetrahydro-6,8-dimethyl-5,7-dioxopyrimido-[5,4-*e*]-*as*-triazine (185), underwent hydrogenation over Raney nickel to give 4-amino-5-formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (186), a compound made more easily in other ways.⁴⁶²⁶ Fervenuin 4-oxide with hot acetic anhydride gave 5-acetamido-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine (187), also made more easily otherwise.⁶⁰¹³



The pyrimidopyrimidine, 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimido[4,5-*d*]pyrimidine (188), reacted with hydrazine or aqueous hydroxylamine to give the hydrazone, 4-amino-5-hydrazonomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (189, $R = NH_2$), or the oxime, 4-amino-1,2,3,6-tetrahydroxy-5-hydroxyiminomethyl-1,3-dimethyl-2,6-dioxypyrimidine (189, $R = OH$), respectively.⁵⁴³⁴ 2-Hydroxy-4,6-diphenylpyrimidine was obtained by treatment of 3,4,4a,5,6,8a-hexahydro-2,7-dihydroxy-4,5,8a-triphenylpyrimido[4,5-*d*]pyrimidine with butanolic hydrochloric acid.⁵⁹¹¹ 3,4-Dihydro-2-oxo-2*H*-pyrimido[1,2-*a*]pyrimidine (190) has been reported to afford 1- β -carboxyethyl-1,2-dihydro-2-iminopyrimidine (191) as its betaine (192) by alkaline hydrolysis, but the possibility of Dimroth rearrangement to 2- β -carboxyethylaminopyrimidine does not appear to have been considered.⁵⁴⁹²

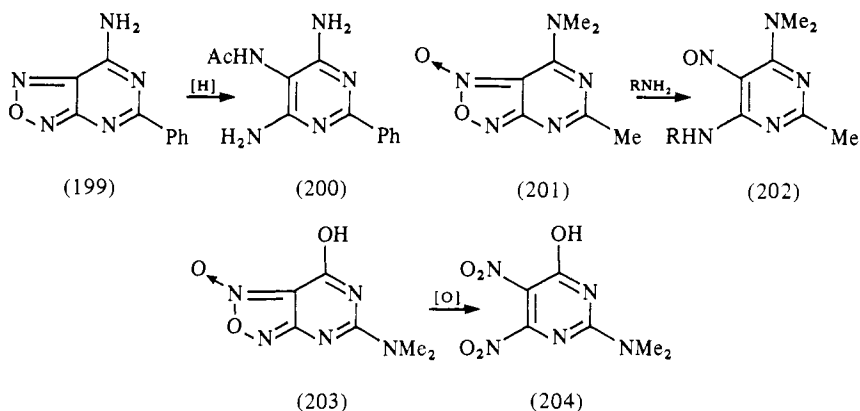
(6) *Pyrimidines from Oxaza and Thiaza Bicyclic Systems (E 72)*

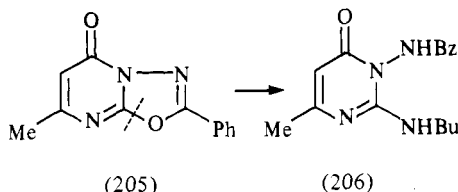
A rather specialized route to some pyrimidines *via* furopyrimidines is exemplified in the conversion of 2-amino-3-ethoxycarbonyl-4,5-dihydrofuran (193) by *p*-chlorophenyl isocyanate into 3-*p*-chlorophenyl-3,4,5,6-tetrahydro-2-hydroxy-4-oxofuro[2,3-*d*]pyrimidine (194, $R = ClC_6H_4$), which on treatment with phosphoryl chloride gave 6-chloro-5- β -chloroethyl-1-*p*-chlorophenyluracil (195, $R = ClC_6H_4$)⁴⁴⁵² rather than the 3-*p*-chlorophenyl isomer as was expected from earlier reports.⁶³³³ The synthesis proved reasonably versatile, and a rational explanation of the apparently anomalous configuration in the uracils (195) has been given.⁴⁴⁵²



The isoxazolopyrimidine, 1,3-dihydro-1-methyl-3-oxo-6-phenyl-isoxazolo[3,4-*d*]pyrimidine (197), was easily made from 4-chloro-5-ethoxycarbonyl-2-phenylpyrimidine (196) with *N*-methylhydroxylamine, and subsequent treatment with neat β -methoxyethylamine under reflux gave 4-*N*-hydroxymethylamino-5-*N*- β -methoxyethylcarbamoyl-2-phenylpyrimidine (198).⁵⁵³⁹ The use of different amines gave several *N*-substituted-carbamoyl analogues.⁵⁵³⁹

Several oxadiazolopyrimidines can furnish pyrimidines. As part of a general procedure for preparing substituted adenines,^{5398, 5399} 4-amino-5-nitrosopyrimidines were readily transformed by lead tetracetate into 1,2,5-oxadiazolo[3,4-*d*]pyrimidines which, after modification, were reconverted into pyrimidines and thence to the required adenines. The relevant step in the present context is exemplified in the conversion of 7-amino-5-phenyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine (199) by zinc/acetic acid reduction into 5-acetamido-4,6-diamino-2-phenylpyrimidine (200), in the hydrogenation of 5-dimethylamino-7-formamido[1,2,5]oxadiazolo[3,4-*d*]pyrimidine to give 4,5-diamino-2-dimethylamino-6-formamidopyrimidine in 80% yield,⁵³⁹⁹ and in other such procedures that gave pyrimidines of particular use as pteridine intermediates.⁵³⁹⁸ The same bicyclic system has proved invaluable in making certain nitroso- and nitro-pyrimidines not otherwise available easily. Thus, 7-dimethylamino-5-methyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxide (201) reacted with ammonia or aniline to give 4-amino(or anilino)-6-dimethylamino-2-methyl-5-nitrosopyrimidine (202, R = H or Ph), respectively, by a complicated but plausible mechanism.⁶²⁹⁴ The related substrate, 5-dimethylamino-7-hydroxy[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxide (203) underwent oxidation by manganese dioxide in dimethylformamide to give a quite unprecedented product, 2-dimethylamino-4-hydroxy-5,6-dinitroypyrimidine (204).⁶²⁹³

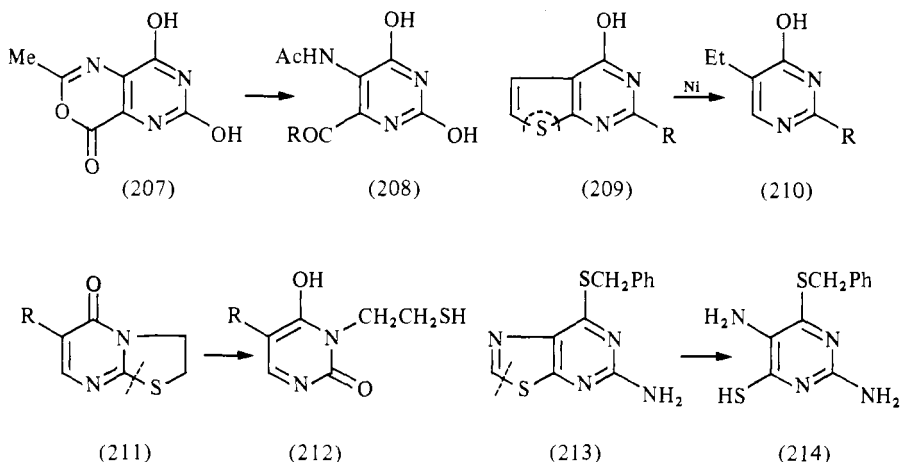




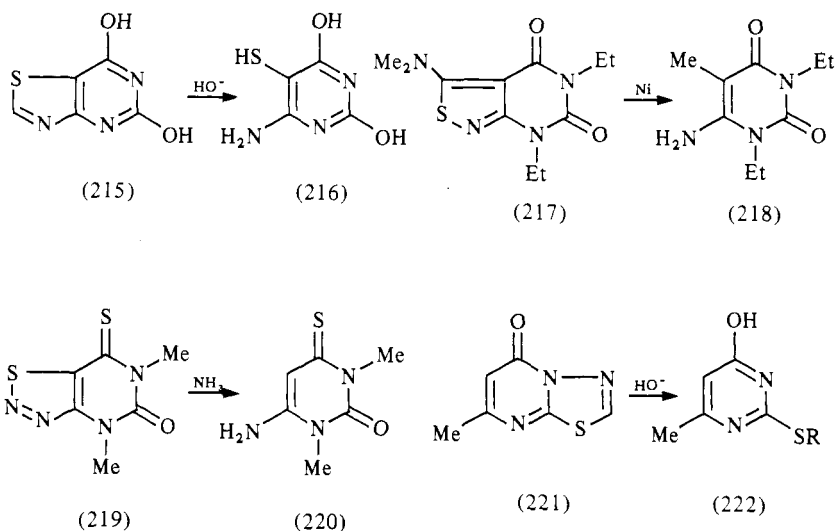
The formation of pyrimidines from another such system is illustrated in the treatment of 7-methyl-5-oxo-2-phenyl-5*H*-1,3,4-oxadiazolo[3,2-*a*]-pyrimidine (205) with neat butylamine to give 1-benzamido-2-butylamino-1,6-dihydro-4-methyl-6-oxopyrimidine (206) in 70% yield. Several other examples were reported.⁴⁵¹⁴

6,8-Dihydroxy-2-methyl-4-oxo-4*H*-pyrimido[5,4-*d*][1,3]oxazine (207) was easily made, and it was converted by ethanolic ammonia or ethanolic sodium ethoxide into 5-acetamido-4-carbamoyl- (208, R = NH₂) or 5-acetamido-4-ethoxycarbonyl-2,6-dihydroxypyrimidine (208, R = OEt), respectively.⁴⁷⁹²

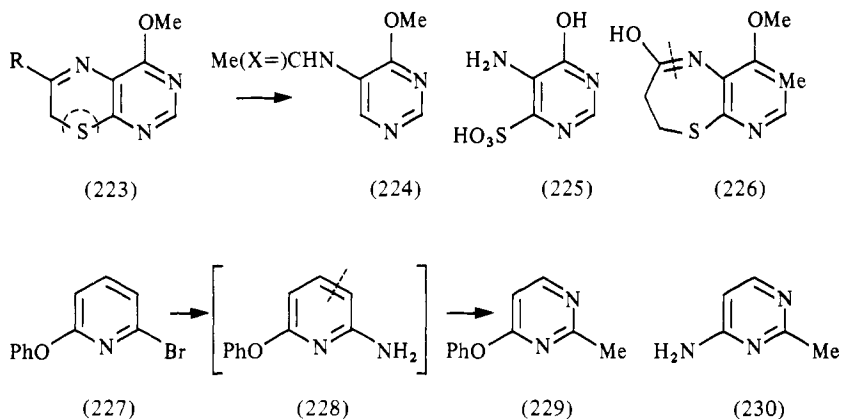
Turning to thiazabicyclic systems, the degradation of thieno[2,3-*d*]pyrimidines is exemplified in the desulfurization of 4-hydroxy-2-*p*-methoxyphenylthieno[2,3-*d*]pyrimidine (209, R = C₆H₄OMe) by Raney nickel in ethanol to give 5-ethyl-4-hydroxy-2-*p*-methoxyphenylpyrimidine (210, R = C₆H₄OMe).⁴³⁴⁸ When the phenyl group lacked a substituent, it was reduced to cyclohexyl during desulfurization, thus, 4-hydroxy-2-phenylthieno[2,3-*d*]pyrimidine (209, R = H) gave 2-cyclohexyl-5-ethyl-4-hydroxypyrimidine (210, R = C₆H₁₁).⁴³⁴⁸ Other examples, leading to 5-cyclohexyl-4-hydroxy-2-piperidinomethylpyrimidine and related products, have been reported.⁴³⁴⁴



A variety of thiazolopyrimidines have been converted into pyrimidines. Thus, 2,3-dihydro-5-oxo-6-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine (211, R = Ph) or its 7-phenyl isomer was converted by alkaline or acid hydrolysis into 3- β -mercaptoethyl-5-phenyluracil (212, R = Ph) or its 6-phenyl isomer, respectively.⁶²⁴¹ Likewise, 2,3-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine (211, R = H) or its 6-ethoxycarbonyl derivative (211, R = CO₂Et) gave 3- β -mercaptoethyluracil (212, R = H) or its 5-carboxy derivative (212, R = CO₂H), respectively,⁵³⁹⁵ while oxidation of 8-ethoxy-2,3-dihydro-5-methylthiazolo[3,2-*c*]pyrimidinium bromide with hot alcoholic bromine gave 5-ethoxy-1,6-dihydro-2-methyl-6-oxo-1- β -sulfoethylpyrimidine in 40% yield.⁵⁹⁵⁸ Treatment of 5-amino-7-benzylthiothiazolo[5,4-*d*]pyrimidine (213) with hydrazine in hot dioxane rather surprisingly gave 2,5-diamino-4-benzylthio-6-mercaptopyrimidine (214),⁵²³⁴ 2-amino-5-ethylaminothiazolo[5,4-*d*]pyrimidine underwent alkaline hydrolysis to give 5-amino-2-ethylamino-4-mercaptopyrimidine in 98% yield.⁵⁷⁴² Rather similarly, 5,7-dihydroxythiazolo[4,5-*d*]pyrimidine (215) in hot alkali gave 4-amino-2,6-dihydroxy-5-mercaptopyrimidine (216).⁵²⁴⁴ The use of isothiazolopyrimidines in pyrimidine synthesis has been confined to desulfurizations. Thus, 3-dimethylamino-5,7-diethyl-4,5,6,7-tetrahydro-4,6-dioxoisothiazolo[3,4-*d*]pyrimidine (217) with Raney nickel gave 4-amino-1,3-diethyl-1,2,3,6-tetrahydro-5-methyl-2,6-dioxopyrimidine (218) in good yield,⁵⁰³⁶ and 7-benzyl-3-ethylamino-6,7-dihydro-4-hydroxy-6-oxoisothiazolo[3,4-*d*]pyrimidine likewise gave 6-amino-1-benzyl-5-methyluracil.⁵⁰³⁷



Two types of thiadiazolopyrimidines have been converted into pyrimidines, but the processes have limited potential as syntheses. 4,5,6,7-Tetrahydro-4,6-dimethyl-5-oxo-7-thio-1,2,3-thiadiazolo[4,5-*d*]-pyrimidine (219) was heated in ethanolic ammonia to give an almost quantitative yield of 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-thiopyrimidine (220).⁶⁰¹⁴ Using a different system, 7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (221) in cold alkali gave 4-hydroxy-6-methyl-2-thiocyanatopyrimidine (222, R = CN), which under less gentle conditions or in methanolic hydrochloric acid went one stage further to 4-hydroxy-2-mercapto-6-methylpyrimidine (222, R = H).^{5146, 5950, 6334} The same products were obtained from the isomeric 5-methyl-7-oxo-7*H*-[1,3,4] thiadiazolo[3,2-*a*] pyrimidine,⁶³³⁴ but the presence of a 2-substituent in the substrate altered the degradation; for example, 2,7-dimethyl- and 7-methyl-2-methylthio-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*] pyrimidine in dilute hydrochloric acid gave 3-amino-6-methyluracil and 6-methyl-3-methylthio(thiocarbonyl)aminouracil, respectively.⁵⁹⁵⁰

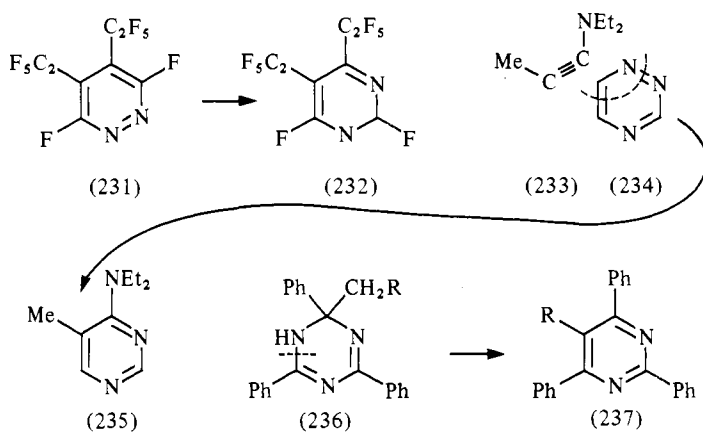


Several interesting pyrimidines have been made from pyrimido[4,5-*b*]thiazines. Thus, 6-amino-4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]-thiazine (223, R = NH₂) and Raney nickel gave 5-acetimidoylamino-4-methoxypyrimidine (224, X = NH), and similar treatment of 6-hydroxy-4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazine (223, R = OH) gave 5-acetamido-4-methoxypyrimidine (224, X = O).⁴⁷⁸¹ In contrast, the same substrate (223, R = OH) was oxidized by peroxyacetic acid to give 5-amino-4-hydroxy-6-sulphopyrimidine (225), while oxidation of 7,8-dihydro-6-hydroxy-4-methoxypyrimido[4,5-*b*][1,4]thiazepine (226) gave 5-amino-4-β-carboxyethylsulfonyl-6-methoxypyrimidine.⁴⁸²⁵

(7) *Pyrimidines from Other Azines (E 74 and 76)*

The amination of certain pyridines in potassium amide/liquid ammonia affords, among other products, pyrimidines which require isolation by glc techniques. For example, 2-bromo-6-phenoxy pyridine (227) gave 2-methyl-4-phenoxy pyrimidine (229), presumably by aminolysis to 2-amino-6-phenoxy pyridine (228) (also present in the products), followed by 3,4-bond scission and recyclization so that C3 appeared as the 2-Me group in the pyrimidine (229). Other 2-halogeno-6-substituted-pyridines behaved similarly, including 2,6-dichloropyridine which gave 4-amino-2-methylpyrimidine (230) *inter alia*.⁶⁰³⁹

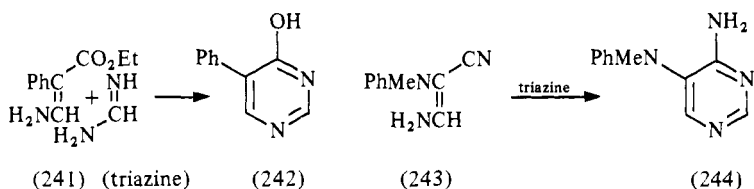
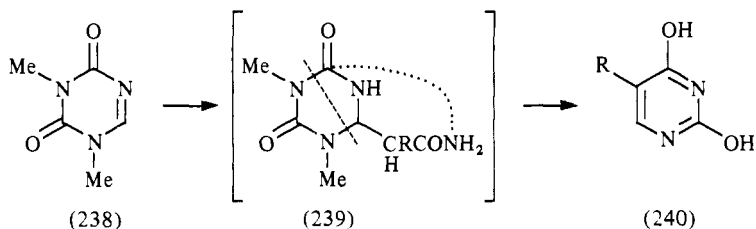
The pyrolysis of perfluoro-4,5-diethylpyridazine, that is, 3,6-difluoro-4,5-bis(pentafluoroethyl)pyridazine (231), in dry nitrogen over platinum at 650° gave, among other products, 2,4-difluoro-5,6-bis(pentafluoroethyl)pyrimidine (232);^{5268, 5922} perfluoro-4,5-diisopropylpyridazine behaved similarly, either under the above conditions or on static pyrolysis in a sealed nickel tube at 370° to give 2,4-difluoro-5,6-bis(heptafluoroisopropyl)pyrimidine,⁵⁹²² earlier described incorrectly⁵²⁹¹ as an isomer. Tetrafluoropyridazine at 800° gave tetrafluoropyrimidine (46%) and other products.⁵²⁹¹ The same transformation also was possible under milder conditions.⁵⁶⁴⁵ A review of some aspects of "transformations of pyridazine compounds into pyrimidine derivatives" has appeared.⁴⁵⁹⁸



When 1,2,4-triazine (234) and *N,N*-diethylprop-1-ynylamine (233) were mixed in pure chloroform, 4-diethylamino-5-methylpyrimidine (235) resulted in reasonable yield by replacement of the N4 + C5 fragment (HCN!) in the ring. Several substituted triazines behaved similarly, any 5-substituent not appearing in the product.⁴⁴⁷⁸

The thermolysis of 1,2-dihydro-2-methyl-2,4,6-triphenyl-1,3,5-triazine (236, R = H) gave 2,4,6-triphenylpyrimidine (237, R = H) with loss of ammonia. The homologue, 2-ethyl-1,2-dihydro-2,4,6-triphenyl-1,3,5-triazine (236, R = Me), behaved similarly to give 5-methyl-2,4,6-triphenylpyrimidine (237, R = Me) in good yield.^{5804, 6746} Treatment of dihydro-2,4,6-triphenyl-1,3,5-triazine with hexafluorobut-2-yne gave 2,4-diphenyl-5,6-bistrifluoromethylpyrimidine.⁴⁸¹³

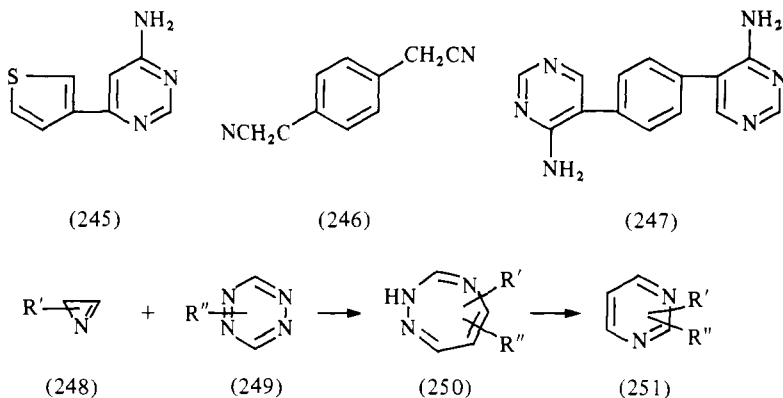
When 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-1,3,5-triazine (238) was treated with malondiamide or cyanoacetamide in ethanolic sodium ethoxide, nucleophilic attack of the 6-position ensued to give the intermediate (239, R = CONH₂ or CN), which then rearranged as shown to give 5-carbamoyl- (240, R = CONH₂) and 5-cyano-2,4-dihydroxypyrimidine (240, R = CN), respectively.^{5421, 6386} Fluoroacetamide likewise gave 5-fluorouracil (240, R = F).⁶⁵⁰⁵ Such ring changes with amines, nitriles and so forth under high pressures have been reported.^{5135, 5136}



It has been pointed out that 1,3,5-triazine acts exactly like formamidine in some hydroxypyrimidine syntheses (*H* 446). So too does it in some pyrimidine syntheses, which would be classified with the Principal Synthesis (III.3.B.) if triazine was simply a source of formamidine. Whatever the mechanism, the use of triazine is exemplified in the condensation of ethyl phenylacetate with triazine in pyridine/piperidine to give first the aminomethylene intermediate (241) and then, by a pseudo Principal Synthesis, 4-hydroxy-5-phenylpyrimidine (242);⁴⁵⁰¹ of 2-*N*-methylanilinoacetonitrile with triazine in ethanolic sodium ethoxide to give first 3-amino-2-*N*-methylanilinoacrylonitrile (243) and thence 4-amino-5-*N*-methylanilinoacrylonitrile (244);⁴⁵²¹ of

thien-2-ylacetonitrile with triazine to give 4-amino-5-thien-2'-ylpyrimidine (245);⁴⁴⁸⁹ and of 1,4-biscyanomethylbenzene (246) with triazine to give 4-amino-5-*p*-(4'-aminopyrimidin-5'-yl)phenylpyrimidine (247).⁴⁴⁸⁹

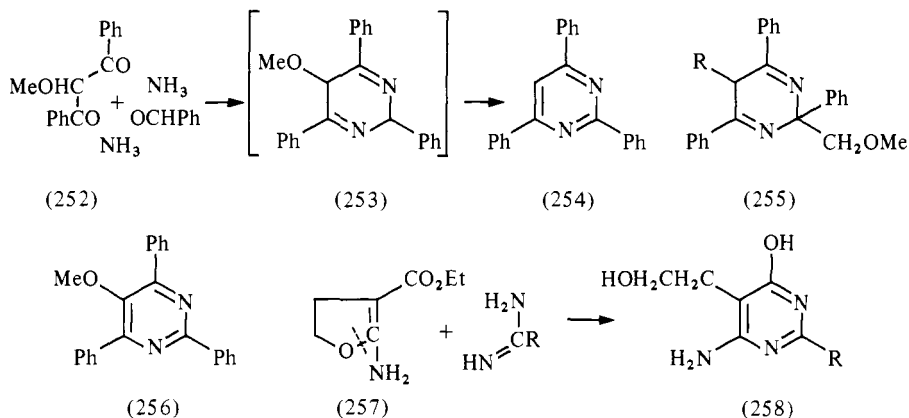
The condensation of 1-azirines (248) with 1,2,4,5-tetrazines (249) in refluxing toluene to give initially triazepines (250) and subsequently pyrimidines (251) has been reported briefly.⁶²⁰⁹



F. Miscellaneous Sequences (E 76)

(2) Syntheses from Fragments with In-Built Oxidation Capacity (E 77)

The second type of this reaction, in which a dihydropyrimidine is formed initially followed by oxidation through elimination of methanol, acetone, and so forth, has been developed further. Thus, heating benzaldehyde, ammonium acetate, and α -methoxydibenzoylmethane (252) in glacial acetic acid probably gave a dihydro intermediate (253), from which methanol was eliminated as methyl acetate under the conditions of the reaction, to give 2,4,6-triphenylpyrimidine (254) in good yield.⁴⁴⁷⁷ However, when an analogous mixture of α -methoxydibenzoylmethane, ω -methoxyacetophenone, and ammonium acetate was heated in acetic acid, the intermediate, 1,5-dihydro-5-methoxy-2-methoxymethyl-2,4,6-triphenylpyrimidine (255, R = OMe) (or its 1,2-dihydro tautomer), could be isolated and characterized as its hydrochloride prior to mild alkaline treatment, which caused elimination of dimethyl ether to give 5-methoxy-2,4,6-triphenylpyrimidine (256). A similar mixture using unsubstituted dibenzoylmethane likewise gave the intermediate, 1,5-dihydro-2-methoxymethyl-2,4,6-triphenylpyrimidine (255, R = H), or tautomer which could not be aromatized without decomposition.⁴⁴⁷⁷



(3) *Syntheses Involving Pyrimidine Rearrangements (E 79)*

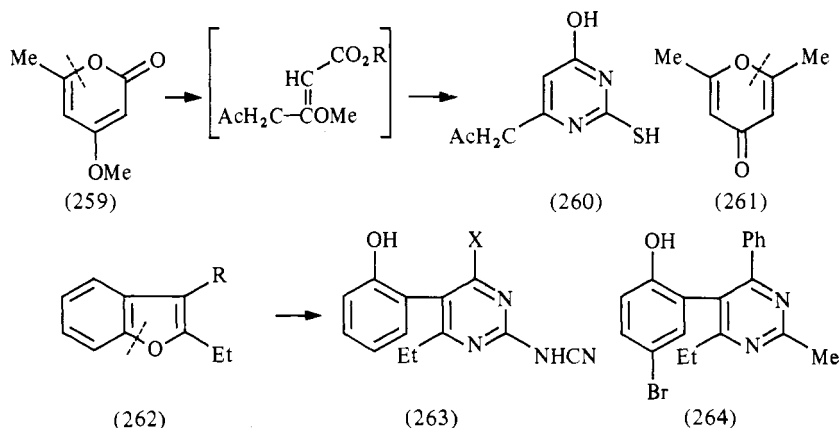
The Dimroth rearrangement has continued to be useful. It is treated in Ch. X, Sect. 2B.

(4) *Syntheses Involving Benzofurans and Related Compounds (E 80)*

This French synthesis has been developed considerably in the last decade. It is really a Principal Synthesis in which the three-carbon fragment is supplied by ring-fission of an oxygen heterocycle. Because of its inherent limitations, treatment will be brief, especially since a review is available covering much of the literature through 1975.⁴⁴⁴⁷

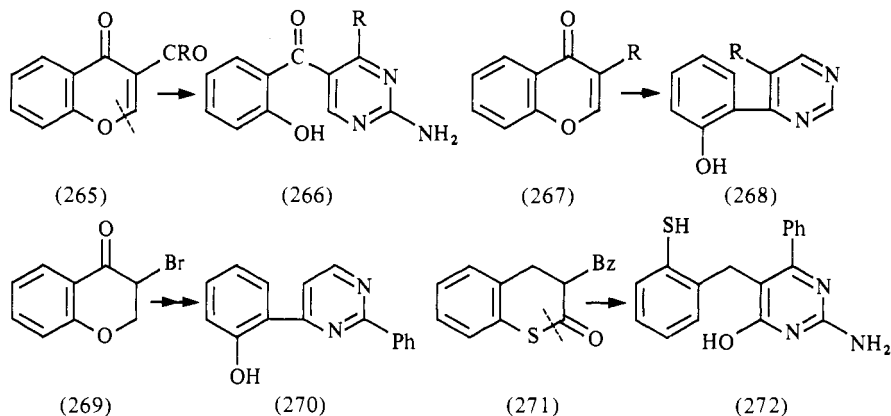
Furans and pyrans offer the simplest cases. Thus, 2-amino-3-ethoxycarbonylfuran (257) and free acetamidine or guanidine in refluxing ethanol gave 4-amino-6-hydroxy-5- β -hydroxyethyl-2-methyl- (258, R = Me) or 2,4-diamino-6-hydroxy-5- β -hydroxyethylpyrimidine (258, R = NH_2), respectively.⁴⁴⁶⁵ 4-Methoxy-2-methyl-6-oxopyran (259) and thiourea in ethanolic sodium ethoxide gave 4-acetyl-6-hydroxy-2-mercaptopyrimidine (260) in good yield;⁴⁴⁴⁰ 2,6-dimethyl-4-oxopyran (261) and guanidine gave 4-acetyl-2-amino-6-methylpyrimidine;⁴⁴¹⁷ and the same substrate (261) with urea gave 4-acetyl-2-hydroxy-6-methylpyrimidine, although only in low yield.⁴⁴¹⁴ Pyrylium salts have been used to furnish pyrimidines.⁴⁸⁶⁹

Examples of benzofurans as intermediates include the transformation of 2-ethyl-3-formylbenzofuran (262, R = CHO) by cyano-guanidine (dicyandiamide) into 2-cyanoamino-4-ethyl-5-*o*-hydroxyphenylpyrimidine (263, X = H);⁴⁴³⁶ 3-cyano-2-ethylbenzofuran (262,



R = CN) into 4-amino-2-cyanoamino-6-ethyl-5-*o*-hydroxyphenylpyrimidine (263, X = NH₂);⁴⁴³⁶ 3-acetyl-2-ethyl-6-nitrobenzofuran by thiourea into 4-ethyl-5-(2'-hydroxy-5'-nitrophenyl)-2-mercapto-6-methylpyrimidine (80%);⁴⁴¹⁸ 3-benzoyl-5-bromo-2-ethylbenzofuran by acetamidine into 5-(3'-bromo-6'-hydroxyphenyl)-4-ethyl-2-methyl-6-phenylpyrimidine (264),⁵¹⁴⁸ and many others.^{4409, 4418, 4434, 5148}

Chromones (oxochromenes) have been used similarly. 3-Formyl- (265, R = CHO) or 3-acetyl-4-oxochromene (265, R = Ac) reacted with guanidine to give 2-amino-5-*o*-hydroxybenzoylpyrimidine (266, R = H) or its 4-methyl derivative (266, R = Me), respectively (the latter compound was previously described⁴⁴¹⁵ as the isomeric 5-acetyl-2-amino-4-*o*-hydroxyphenylpyrimidine);⁴⁴⁹¹ the same substrate (265, R = H) with thiourea gave 5-*o*-hydroxybenzoyl-2-mercaptopyrimidine;⁵⁹⁹⁰ 3-methyl-4-oxochromene (267, R = Me) reacted rather differently with formamide (in place of formamidine; Sect. 3.C.) to give 4-*o*-hydroxyphenyl-5-methylpyrimidine (268, R = Me) in good

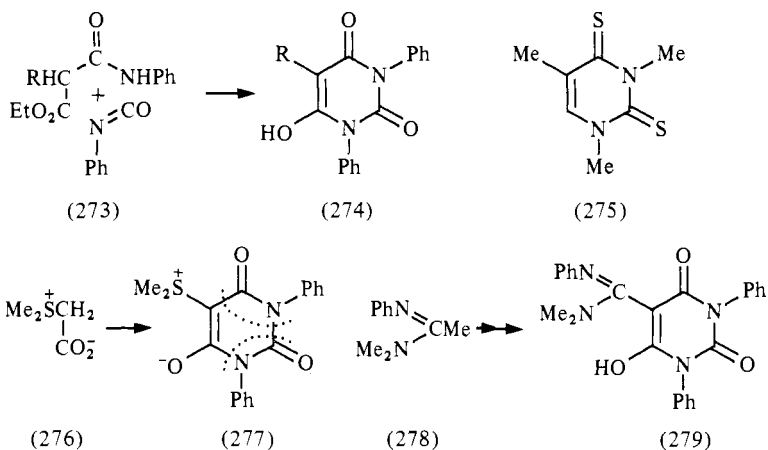


yield,⁴⁴⁵⁰ the reduced substrate, 3-bromo-4-oxochroman (269) was also useable because with benzamidine it underwent immediate dehydrobromination to the chromene (267, R = H) and subsequent condensation to yield 4-*o*-hydroxyphenyl-2-phenylpyrimidine (270).⁴⁴⁴⁵ Other examples have been given.^{4408, 4409, 4413, 4419, 4435, 4461}

Likewise, 3-benzoyl-2-oxo(thiochroman) (271) and guanidine in ethanolic ethoxide gave 2-amino-4-hydroxy-5-*o*-mercaptobenzyl-6-phenylpyrimidine (272).⁴⁴⁶⁰

(5) *Syntheses from Isocyanates or Isothiocyanates and Active Methylene Compounds (E 81)*

These rather ill-defined reactions have been of considerable, if limited, use. They are illustrated by the condensation of diethyl malonate with phenyl isocyanate to give diethyl α -phenylcarbamoylmalonate (273, R = CO₂Et), which then reacted with a second molecule of phenyl isocyanate to afford 5-ethoxycarbonyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenylpyrimidine (274, R = CO₂Et); the intermediate need not be isolated except when two different isocyanates are to be used.⁴⁴⁸⁰ Similarly, ethyl cyanoacetate reacted with phenyl isocyanate in pyridine to give ethyl α -cyano- α -phenylcarbamoylacetate (273, R = CN) and thence 5-cyano-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenylpyrimidine (274, R = CN);⁶⁰⁴⁹ propionaldehyde and methyl isothiocyanate gave 1,2,3,4-tetrahydro-1,3,5-trimethyl-2,4-dithiopyrimidine (275);⁶¹⁸⁸ and α -dimethylsulfonioacetate ("thetine") (276) with phenyl isocyanate gave 5-dimethylsulfonio-1,2,3,4-tetrahydro-2,4-dioxo-1,3-diphenylpyrimidin-6-olate (277) in

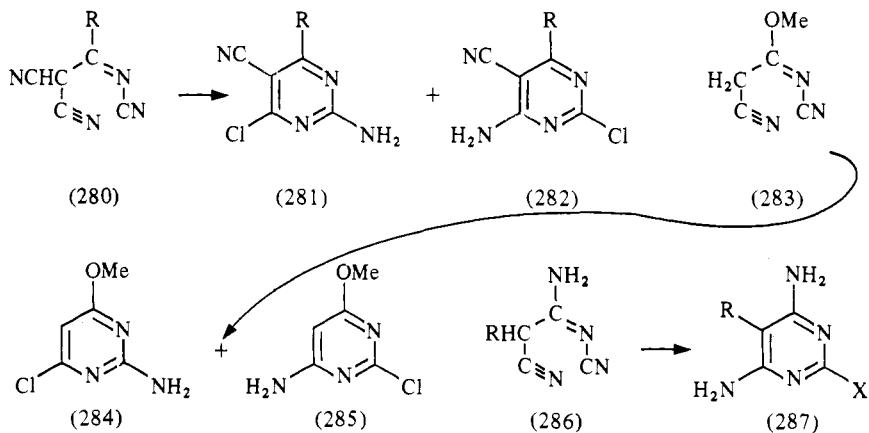


good yield.⁴³³¹ Other examples have been described,^{4331, 6188} including the reaction of *N,N*-dimethylacetamide with one molecule of phenyl isocyanate to give (with elimination of carbon dioxide) an intermediate amidine (278), which then cyclized with several more molecules of phenyl isocyanate to give 5-(*N,N*-dimethyl-*N'*-phenylamidino)-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenylpyrimidine (279).⁵⁵⁸⁷

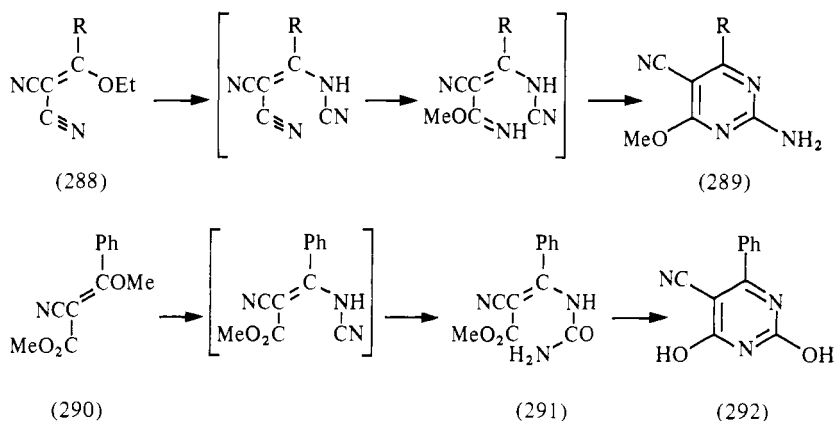
(6) Some Other Syntheses (E 81)

Several unrelated and hitherto unused syntheses are collected here.

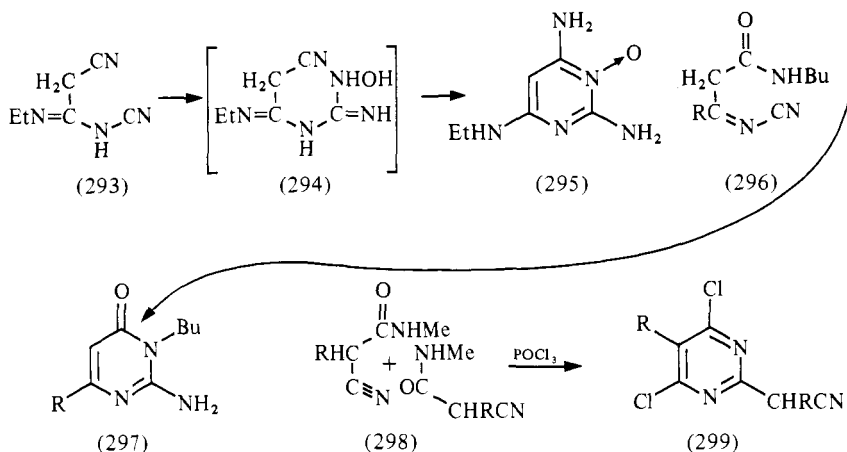
(a) *Synthesis via Cyanoamino Intermediates (New)*. When ethyl 2,2-*N*-tricyanoacetimidate (280, R = OEt) was treated with ethereal hydrogen chloride, cyclization occurred to give a mixture(?) of 2-amino-4-chloro- (281, R = OEt) and 4-amino-2-chloro-5-cyano-6-ethoxy-pyrimidine (282, R = OEt) from which the former was isolated.⁴⁴⁸⁶ However, the analogous intermediate (280, R = Me), which was made *in situ* from ethyl *N*-cyanoacetimidate and malononitrile, gave exclusively 4-amino-2-chloro-5-cyano-6-methylpyrimidine (282, R = Me) while its analogue (280, R = SMe) again gave a mixture of 2-amino-4-chloro- (281, R = SMe) and 4-amino-2-chloro-5-cyano-6-methylthiopyrimidine (282, R = SMe).⁴⁹⁰¹ It was later shown that the simple analogue methyl 2,2-dicyanoacetimidate (283) with hydrogen chloride indeed gave a mixture of 2-amino-4-chloro- (284) and 4-amino-2-chloro-6-methoxy-pyrimidine (285), but when a Lewis acid (e.g., boron trifluoride etherate) was also present, only the latter product (285) was formed.^{5154, 5158} The related intermediates 2,2-dicyanoacetamidine (286, R = H) and 2,2-dicyanobutyramidine (286, R = Et) cyclized with hydrogen chloride or hydrogen bromide (but not with hydrogen iodide) to give exclusively



4,6-diamino-2-chloro(or bromo)pyrimidine (287, R = H, X = Cl or Br) or their 5-ethyl derivatives (287, R = Et, X = Cl or Br), respectively.^{5153, 5157} Related cyclizations were also investigated.^{5153, 5156} Some alkaline cyclizations have been successful. For example, treatment of α -ethoxymethylenemalononitrile (288, R = H) with cyanamide in methanolic sodium methoxide gave 2-amino-5-cyano-4-methoxypyrimidine (289, R = H), and by starting with alkylated substrates (288, R = alkyl), products such as 2-amino-5-cyano-4-methoxy-6-phenylpyrimidine (289, R = Ph) were made; the alcoholic alkoxide determined the 4-alkoxy group.⁶²⁸⁶ An extension of this reaction is seen in the treatment of methyl 2-cyano-3-methoxycinnamate (290) with cyanamide and subsequently with aqueous hydrochloric acid to give methyl 2-cyano-3-ureidocinnamate (291), which underwent cyclization to 5-cyano-2,4-dihydroxy-6-phenylpyrimidine (292) in good overall yield.⁶²⁹⁶



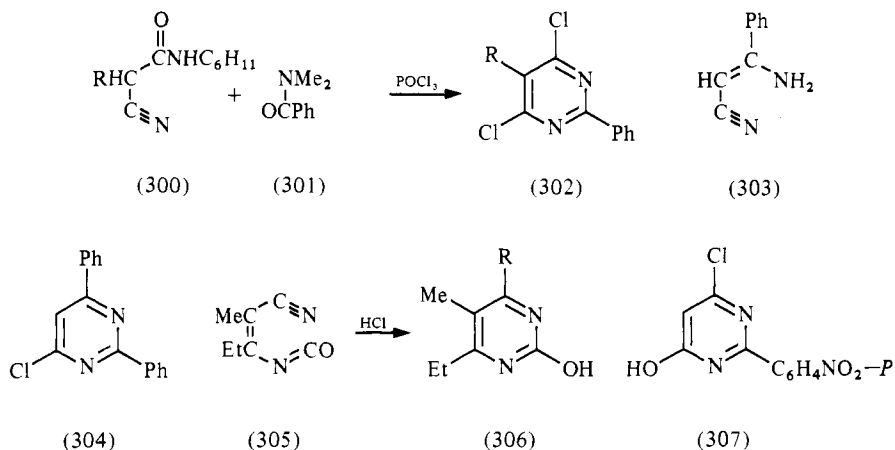
Other aspects of this type of synthesis have been investigated. Treatment of the easily made 2,N-dicyano-N'-ethylacetamidine (293) with ethanolic hydroxylamine hydrochloride gave 2,4-diamino-6-ethylaminopyrimidine 3-oxide (295), probably *via* the unisolated intermediate (294);⁵⁵⁰⁸ an improved method for preparing intermediates such as (293) was developed, and one of these, N,N-diallyl-2,N-dicyanoacetamidine, reacted with hydrogen chloride in glacial acetic acid to give exclusively 4-amino-2-chloro-6-diallylaminopyrimidine.⁵⁵⁶⁶ Another development involved the synthesis of ethyl 2-butylcarbamoyl-N-cyanoacetimidate (296, R = OEt) and its conversion by potassium t-butoxide into 2-amino-1-butyl-4-ethoxy-1,6-dihydro-6-oxopyrimidine (297, R = OEt) in good yield;⁵⁵²¹ alternatively, the intermediate (296, R = OEt) was treated with diethylamine to give the amidine (296,



R = NEt₂), which then afforded 2-amino-1-butyl-4-diethylamino-1,6-dihydro-6-oxopyrimidine (297, R = NEt₂).⁵⁵²¹ Other adaptations led to such products as 2,4-dihydroxy-5-piperidino- and 4-hydroxy-2,6-dipiperidinopyrimidine.⁵⁹⁴⁶

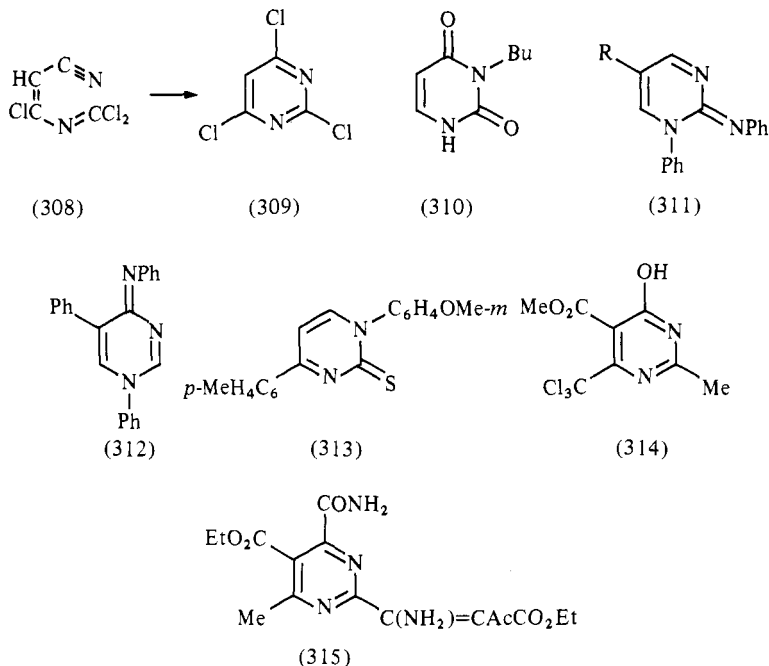
(b) *The Harris and Huppertz Synthesis (New)*. When 2-amino-*N*-methylpropionamide (298, R = Me) was heated in phosphoryl chloride, self-condensation occurred to give 4,6-dichloro-2-α-cyanoethyl-5-methylpyrimidine (299, R = Me) with loss of the *N*-methyl group;⁵³⁴⁷ similar treatment of 2-cyano-*N*-methylbutyramide (298, R = Et) or its *N*-ethyl homologue gave a single product, 4,6-dichloro-2-α-cyanopropyl-5-ethylpyrimidine (299, R = Et).⁵³⁴⁷ In seeking to elucidate the complicated mechanism of this condensation, it became evident that two different amides could be used to advantage. Thus, 2-cyano-*N*-cyclohexylvalerate (300, R = Pr) and *N,N*-dimethylbenzamide (301) in phosphoryl chloride gave 4,6-dichloro-2-phenyl-5-propylpyrimidine (302, R = Pr);⁵³⁵¹ 2-cyano-*N*-cyclohexyl-2-phenylacetamide (300, R = Ph) and *N,N*-dimethylbenzamide (301) gave 4,6-dichloro-2,5-diphenylpyrimidine (302, R = Ph) in 80% yield.⁵³⁵² Several other examples were recorded.^{5351, 5352} In addition, the synthesis was extended to the condensation of the analogous 3-aminocinnamionitrile (303) with *N,N*-dimethylbenzamide (301) to give 4-chloro-2,6-diphenylpyrimidine (304).⁵³⁵²

(c) *Syntheses from Unsaturated Isocyanates (New)*. 3-Amino-2-methylpent-2-enenitrile was converted by phosgene into 3-isocyanato-2-methylpent-2-enenitrile (305), which on heating in dioxane containing hydrogen chloride gave 4-ethyl-2,6-dihydroxy-5-methylpyrimidine (306, R = OH), probably *via* the corresponding chloro compound (306,

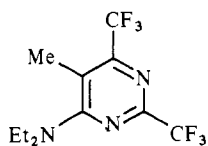


R = Cl).⁵⁰²² β -Chloro- β -isocyanato-*p*-nitrostyrene, acetonitrile, and hydrogen chloride at 60° for 7 days gave 4-chloro-6-hydroxy-2-*p*-nitrophenylpyrimidine (307), but the reaction is of little value.⁵⁰²⁴ In contrast, trichloromethyl isocyanide dichloride (the equivalent of trichloromethyl isocyanate) reacted with acetonitrile in the presence of ferric chloride to give 1-chloro-2-cyanovinyl isocyanide dichloride (308), which underwent cyclizations to afford 2,4,6-trichloropyrimidine (309) in excellent yield. Several analogues were made similarly.⁴⁵⁰⁰

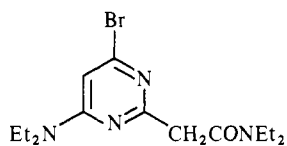
(d) *Miscellaneous Sequences (New)*. The following sequences will probably be of very limited use and will be treated briefly; the original papers should be consulted for possible mechanisms. (1) Treatment of *N*-butylisomaleimide with trimethylsilyl azide gave 1-butyl-1,2,3,6-tetrahydro-2,4-dioxo-3-trimethylsilylpyrimidine (310, R = SiMe₃), which in ethereal hydrogen chloride gave 3-butyluracil (310, R = H).⁵⁴⁸⁸ (2) 3-Amino-2-methylacrolein reacted with diphenylcarbodiimide to give 1,2-dihydro-5-methyl-1-phenyl-2-phenyliminopyrimidine (311, R = Me). Several homologues (311, R = Et, Pr, or Prⁱ) were made similarly.⁴⁴⁶⁴ (3) Treatment of 2-aza-3-chloro-1,5-bisdimethylamino-4-phenylpentamethinium perchlorate with aniline gave 1,4-dihydro-1,5-diphenyl-4-phenyliminopyrimidine (312),⁴⁵⁵⁶ treatment of 3-isothiocyanato-*N,N*-dimethyl-3-*p*-tolylprop-2-eniminium perchlorate with *m*-anisidine gave 1,2-dihydro-1-*m*-methoxyphenyl-2-thio-4-*p*-tolylpyrimidine (313),⁴⁵⁶³ and 1,3,5-trisdimethylamino-2-azapentamethinium perchlorate with ammonium acetate gave 4-dimethylaminopyrimidine.⁶⁰⁹³ (4) Treatment of methyl 3-amino-2-cyano-3-trichloromethylacrylate with acetic anhydride in the presence of a Lewis acid has been reported to give 4-hydroxy-5-methoxycarbonyl-2-methyl-6-trichloromethyl-



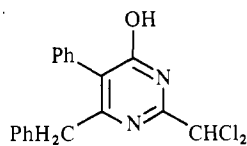
pyrimidine (314).⁵⁹¹³ (5) Ethyl acetoacetate (2 mol) reacted with cyanogen (2 mol) in the presence of a little acetylaceton-nickel complex under mild conditions to give 2-(2'-acetyl-1'-amino-2'-ethoxycarbonylvinyl)-4-carbamoyl-5-ethoxycarbonyl-6-methylpyrimidine (315) in good yield. Several analogues were made similarly.⁶¹⁸⁷ (6) Prolonged treatment of *N,N*-diethylprop-1-ynylamine with trifluoroacetonitrile (2 mol) gave 4-diethylamino-5-methyl-2,6-bistrifluoromethylpyrimidine (316). Several related reactions were reported.⁶²⁸⁵ (7) Passing dry hydrogen bromide through dimethylaminopropyne nitrile gave a mixture from which 4-bromo-6-diethylamino-2-(diethylcarbamoyl)methylpyrimidine (317) was separated in 40% yield.⁵⁹³⁶ (8) 1,1,1-Trichloro-2,2-bis(*C*-phenylacetamido)ethane underwent an unusual reaction in ethanolic potassium hydroxide to give 4-benzyl-2-dichloromethyl-6-hydroxy-5-phenylpyrimidine (318) by loss of water and hydrogen chloride. Analogues were formed similarly, and most yields were quite good.⁴⁷⁴⁰ (9) 3- α -Chlorobenzylideneamino-2,3-diphenylacrylonitrile reacted with propylamine to afford 1,6-dihydro-6-imino-2,4,5-triphenyl-1-propylpyrimidine (319, X = NH, R = Pr), proven in structure by conversion with nitrous acid into the corresponding 6-oxo derivative (319, X = O, R = Pr).⁴⁵⁸⁹ Other primary (but not secondary or tertiary) amines gave appropriate 1-alkyl or aryl



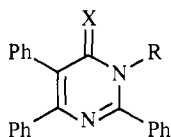
(316)



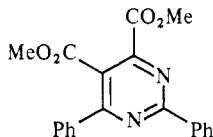
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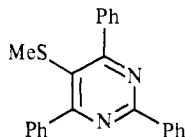
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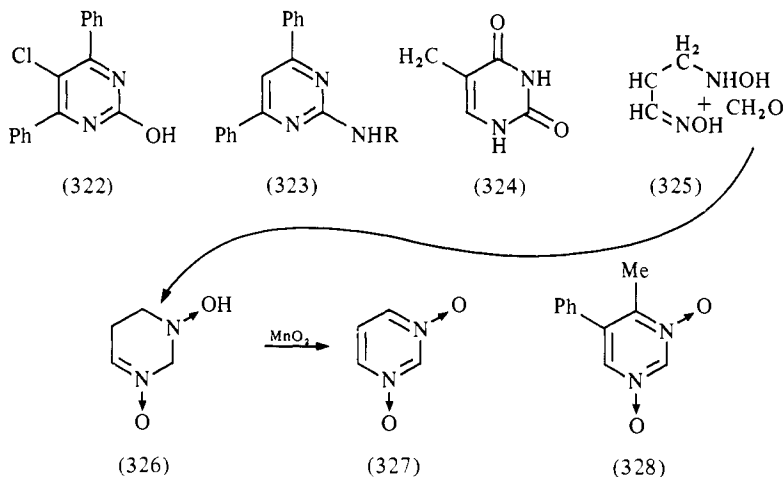


(320)



(321)

analogues,⁴⁵⁸⁹ although hydroxylamine gave, not the analogous 1-hydroxy derivative (319, X = NH, R = OH), but 4-hydroxyamino-2,5,6-triphenylpyrimidine isomeric with the oxime (319, X = NOH, R = H).⁴⁶¹⁴ (10) An interesting condensation occurred between dimethyl acetylenedicarboxylate (supplying C4 + C5) and *N*-benzylidenebenzamidine to give 4,5-dimethoxycarbonyl-2,6-diphenylpyrimidine (320).⁵⁹⁷² (11) The available substrate, 4,6-diphenyl-1,2,3,5-oxathiadiazine 2,2-dioxide (74) (Sect. 3.D), reacted with sulfur ylides to give, after treating the initial product in aqueous potassium chloride, 5-methylthio-2,4,6-triphenylpyrimidine (321) and related compounds.⁵⁰⁶⁸ (12) The condensation of ω -chloroacetophenone with α,α -diureidotoluene ("benzylidenebisurea") gave 5-chloro-1,6-dihydro-2-hydroxy-4,6-diphenylpyrimidine, which was readily dehydrogenated by tetrachloroquinone ("chloranil") to give 5-chloro-2-hydroxy-4,6-diphenylpyrimidine (322), a synthesis of some versatility.⁴⁷⁵⁶ Another route, involving oxidation of an (unisolated) dihydropyrimidine with a stream of air, led to 2-amino- (323, R = H) or 2-acetamido-4,6-diphenylpyrimidine (323, R = Ac) as well as analogues.⁴⁷⁶⁰ (13) The action of urea on 2-(dimethylaminomethyl)acrylic acid gave 5-dimethylaminomethyl-4,5-dihydro-2,6-dihydroxypyrimidine, which was reported to undergo oxidation by *m*-chloroperoxybenzoic acid to yield a (stable) isomer of thymine, formulated as hexahydro-5-methylene-2,4-dioxopyrimidine (324).⁴³³⁸ (14) Treatment of *N*-hydroxy-3-hydroxyimino-propylamine (325) with formaldehyde gave 1,2,5,6-tetrahydro-1-hydroxypyrimidine 3-oxide (326), which underwent oxidation by manganese dioxide to give pyrimidine 1,3-dioxide (327) in low yield. The reactions were more effective when substituents were present as in the preparation of 5-methyl-4-phenylpyrimidine 1,3-dioxide (328).^{4757, 4814, 4861} (15) Condensation of 2-cyanoacetamide or 2-cyano-



(thioacetamide) with methyl *N*-cyanoacetimidate gave 2-amino-5-cyano-4-hydroxy(or mercapto)-6-methylpyrimidine in good yield.⁶⁵²⁷ (16) The thermal cyclization of 2,4,6-trichloro-1,3,7-triazaheptatrienium chlorides gave, for example, 4,6-dichloro-2-dimethylaminopyrimidine directly.⁶⁶¹⁰ (17) The reaction of appropriate enamidines with isocyanates gave intermediates, for example, *N*- α,β -diphenylvinyl-*N'*-methylcarbamoylbenzamidine ($\text{PhCH}=\text{CPhNHCPH}=\text{NCONHMe}$), which on dehydration with tosyl chloride/pyridine completed the 4,5-bond of a pyrimidine ring to afford (in the above example) 4-methylamino-2,5,6-triphenylpyrimidine. Several analogues were made similarly.⁶⁷³⁰

6. Formation of the Pyrimidine Ring in Fused Heterocycles (*H* 107, *E* 82)

There seems little point in a supplementary treatment of this marginally relevant section, especially in view of the appearance of dedicated volumes on quinazolines,³¹⁹⁷ purines,⁶³³⁵ and condensed pyrazines (including some pyrimidopyrazines),⁶³³⁶ as well as a recent excellent review, "Annellation of a pyrimidine ring on to an existing ring".⁶³³⁸

CHAPTER IV

Pyrimidine and Its *C*-Alkyl and *C*-Aryl Derivatives (*H* 116, *E* 86)

Little work has appeared on the parent heterocycle but its alkyl and aryl derivatives have been the subjects of many publications.

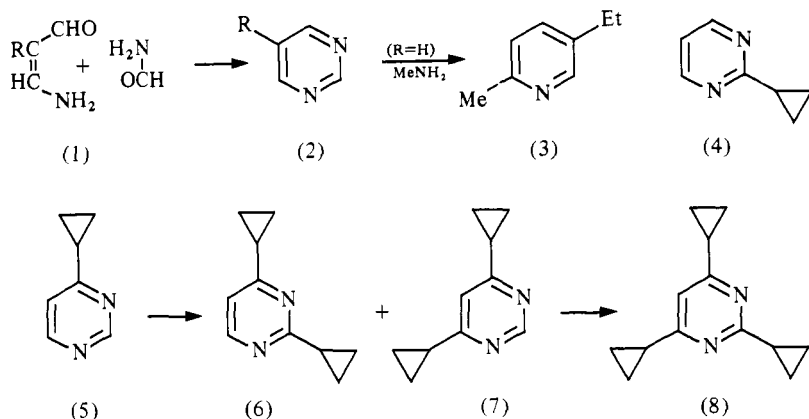
1. Pyrimidine (Unsubstituted) (*H* 116, *E* 86)

A. Preparation of Pyrimidine (*H* 116, *E* 86)

Although pyrimidine is available commercially in small quantities, two convenient syntheses have proved useful recently. The first involved heating 3-aminoacrolein (1, *R* = H), formamide, and piperidinium acetate at 140° followed by a simple workup to give pyrimidine (2, *R* = H) in 60% yield; 2-alkylated analogues, for example, 2-aminomethylenebutyraldehyde (1, *R* = Et), similarly gave the corresponding 5-alkylpyrimidines, for example, 5-ethylpyrimidine (2, *R* = Et).⁴⁵¹⁵ The other route involved heating 2-chloro-, 2-bromo-, or 2-iodopyrimidine with hydriodic acid for a few minutes to achieve dehalogenation to pyrimidine (2, *R* = H) in *c.* 40% yield. The method was also applicable to 2-chloro-4,6-dimethyl- or 2-chloro-4,6-diphenylpyrimidine to give 4,6-dimethyl- or 4,6-diphenylpyrimidine, respectively.⁵⁶⁷³ Precise details for converting pyrimidine into its hydrochloride have been reported.⁵⁵⁹⁴

B. Properties of Pyrimidine (*H* 117, *E* 86)

The infrared spectrum of solid crystalline pyrimidine has been studied in some detail and compared with spectra in nonpolar sol-



vents.⁶³⁰⁸ The influence of protonation and of complexation with mercuric halides and so forth on the infrared and Raman spectra of pyrimidine have been investigated, and assignments for the observed bands have been proposed.⁶³⁰⁹

The prediction of ring proton shifts in the nmr spectrum of pyrimidine in CDCl_3 has been attempted,⁶³⁶⁰ and the ^1H nmr of neat pyrimidine at 60 MHz has been reported.⁵⁶⁷³

The ^{13}C nmr spectra and $J_{\text{C,H}}$ values for pyrimidine,^{5282, 6312, 6313, 6317} its cation,^{6314, 6318} and a variety of alkyl or other simple derivatives^{5282, 5696, 6312-6318} have been recorded and discussed. The chemical shifts,⁶³⁶² short-range J values,⁶³⁶³ and long-range J values⁶³⁶⁴ for pyrimidine in perdeuteroacetone are collected in the following summary: 122.3 (p.p.m. *ex* TMS), $J_{\text{C}_5, \text{H}_2}$ 1.9 Hz, $J_{\text{C}_5, \text{H}_4}$ 9.5, $J_{\text{C}_5, \text{H}_5}$ 169, C5; 157.7, $J_{\text{C}_4, \text{H}_2}$ 9.1, $J_{\text{C}_4, \text{H}_4}$ 183, $J_{\text{C}_4, \text{H}_5}$ 1.9, $J_{\text{C}_4, \text{H}_6}$ 5.3, C4 + C6; 159.7, $J_{\text{C}_2, \text{H}_2}$ 203, $J_{\text{C}_2, \text{H}_4}$ 10.3, $J_{\text{C}_2, \text{H}_5}$ 0.0, C2.

Although ^{14}N nmr spectra are not easy to obtain because of inherently low detection sensitivity (*c.* 10^{-3} that of ^1H), the use of wide tubes, long accumulation times, and (if possible) a ^1H – ^{14}N double resonance technique has given reasonable data for pyrimidine⁶³⁶¹ and some simple derivatives.⁶³⁶⁵ The acquisition of ^{15}N nmr spectra suffers the same difficulties which are further exaggerated if natural abundance rather than ^{15}N -tagged samples are to be used; spectra are quite complicated because of both ^{15}N – ^1H and ^{15}N – ^{13}C couplings. Pyrimidine as free base showed a single peak at –85 p.p.m. (relative to nitromethane); as monocation, at –135; and as dication, at –183.⁶¹¹³ Such spectra for simple derivatives have also been measured.^{6092, 6113, 6366-6368}

The second basic $\text{p}K_a$ value for pyrimidine has been redetermined as –6.92.⁶³⁵⁹ Detailed MO calculations have revealed that the definition

of pyrimidine as a π -deficient system does not necessarily represent the actual π -electronic charge distribution in fused pyrimidines such as purine or pteridine.⁴⁵⁷⁶

C. Reactions of Pyrimidine (*H* 118, *E* 87)

Heating pyrimidine (2, R = H) with aqueous methylamine at 190° induced rearrangement into 3-ethyl-6-methylpyridine (3) in 25% yield.⁴⁶⁹⁸ By repeating the experiment with [1,3-¹⁵N]-, [4,6-¹⁴C]- and [5-¹⁴C]-pyrimidine, the mechanism was shown to involve initial fragmentation to hydrogen cyanide (2 mol) and *N*-methylacetalimine followed by reaction of 4 molecules of the latter to give the pyridine.⁴⁶⁹⁸

The 5-bromination of pyrimidine has been reinvestigated.⁵⁵⁹⁴ Pyrimidine hydrochloride in nitrobenzene reacted with bromine at 130° to yield up to 88% of 5-bromopyrimidine (2, R = Br); pyrimidine hydrochloride perbromide underwent pyrolysis at 120° to give 70% of 5-bromopyrimidine; and direct vapor phase bromination of pyrimidine at 230° gave up to 62% of 5-bromopyrimidine hydrobromide.⁵⁵⁹⁴

Pyrimidine reacted with cyclopropyllithium to give a mixture which on treatment with water and subsequent permanganate oxidation gave a separable mixture of 2-cyclopropylpyrimidine (4) and 4-cyclopropylpyrimidine (5). The latter reacted similarly with cyclopropyllithium to give 2,4- (6) and 4,6-dicyclopropylpyrimidine (7) as an unseparated mixture, which reacted yet again to yield 2,4,6-tricyclopropylpyrimidine (8).⁶⁰⁵¹

The reaction of pyrimidine with hydrazine, previously mentioned (*E* 87) from a short communication,³²⁴⁶ has been reported fully.⁴⁶⁶⁸ Thus, pyrimidine, 4-methylpyrimidine, and 4,6-dimethylpyrimidine reacted with hydrazine to give pyrazole, 3-methylpyrazole, and 3,5-dimethylpyrazole, respectively, in good yield; the same substrates with methylhydrazine gave 1-methyl-, a mixture of 1,3- and 1,5-dimethyl-, and 1,3,5-trimethylpyrazole, respectively; and pyrimidine methiodide and hydrazine gave pyrazole. A rational mechanism was proposed.⁴⁶⁶⁸

Pyrimidine reacted with pivalic acid, by treatment in aqueous sulfuric acid (containing silver nitrate) with ammonium persulfate, to give 4,5-di-*t*-butylpyrimidine in good yield.⁶¹⁰⁵ A semi-direct 4-arylation of pyrimidine is discussed in Sect. 2.A(5) below.

Pyrimidine with a mixture of trimethylsilyl cyanide, benzoyl chloride, and aluminum chloride gave the double Reissert compound, 1,3-dibenzoyl-2,4-dicyano-1,2,3,4-tetrahydropyrimidine, in 59% yield.⁶¹⁵¹

Some interesting dehydrogenations of pyrimidine to give 4,4'-bipyrimidine and so forth, have been investigated.⁵¹⁰⁷

2. C-Alkyl and C-Aryl Pyrimidines (*H* 119, *E* 87)

More attention has been paid recently to the reactivity of alkyl/aryl groups attached to pyrimidine and also to the electronic and steric effects of such groups. This has been reflected in an increased amount of literature on the preparation and reactions of alkylpyrimidines with or without additional functional groups.

A. Preparation of Alkyl Pyrimidines (*H* 119, *E* 87)

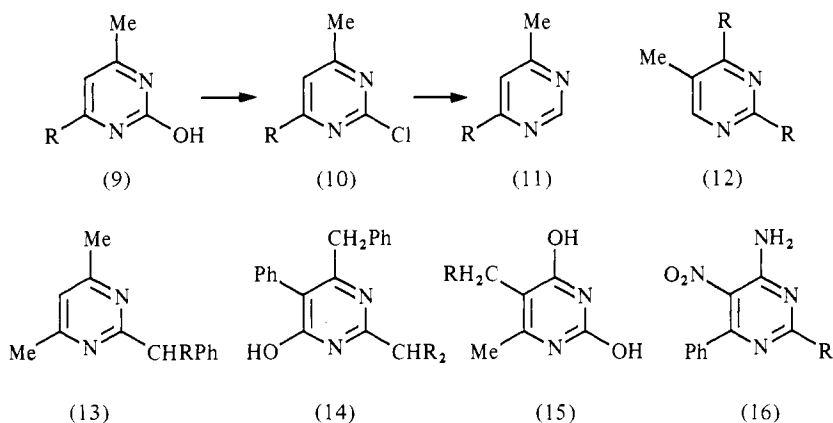
(1) *Direct Syntheses of Alkylpyrimidines* (*H* 119, *E* 87)

Innumerable examples of Principal Syntheses (Ch. II) and other direct syntheses (Ch. III) leading to C- and N-alkylated pyrimidines have been given.

(2) *Alkylpyrimidines from Chlorinated Alkylpyrimidines* (*H* 120, *E* 88)

The traditional use of dechlorination was to prepare C-alkylated hydroxy- or aminopyrimidines by primary syntheses and then remove the unwanted functional groups by conversion into chloro substituents followed by reductive dehalogenation. Such a process has been exemplified recently in the conversion of 2-hydroxy-4-methyl- (9, R = H) and 2-hydroxy-4,6-dimethylpyrimidine (9, R = Me) into the corresponding 2-chloropyrimidines (10, R = H or Me) and thence by treatment with hydriodic acid into 4-methyl- (11, R = H) and 4,6-dimethylpyrimidine (11, R = Me); 4,6-diphenylpyrimidine was made similarly.⁵⁶⁷³ Because 4-chloro substituents cannot be removed conveniently by hydriodic acid, the conversion of thymine (12, R = OH) into 5-methylpyrimidine (12, R = H) required three steps: dichlorination to 2,4-dichloro-5-methylpyrimidine (12, R = Cl), removal of the 4-chloro substituent by treatment with zinc dust in aqueous ammonia to give 2-chloro-5-methylpyrimidine, and final removal of the 2-chloro substituent with hydriodic acid.⁵⁶⁷³ Hydrogenolysis of 2,4-dichloro-6-methylpyrimidine over palladium in ether containing sodium hydroxide gave 4-methylpyrimidine in 80% yield.⁵⁶⁸²

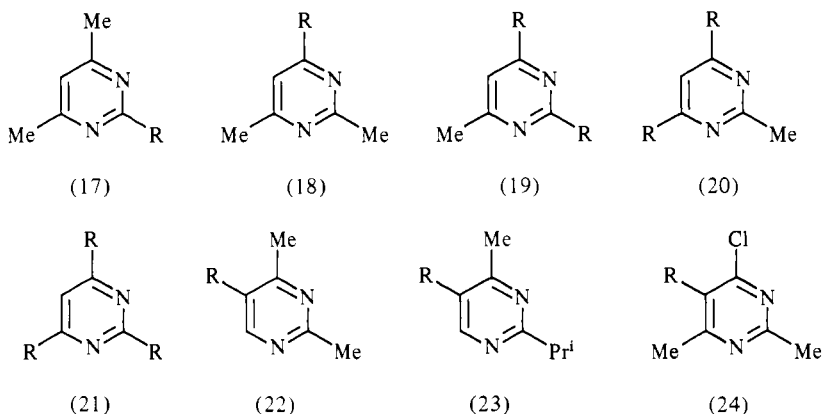
A less traditional use of dechlorination in making alkylpyrimidines was illustrated by the primary synthesis of 2- α -chlorobenzyl-4,6-dimethylpyrimidine (13, R = Cl) followed by hydrogenolysis over palladium to give 2-benzyl-4,6-dimethylpyrimidine (13, R = H) in 80% yield;⁵²⁴¹ by the primary synthesis of 4-benzyl-2-dichloromethyl-6-hydroxy-5-phenylpyrimidine (14, R = Cl) followed by zinc dehalogenation to 4-benzyl-6-hydroxy-2-methyl-5-phenylpyrimidine (14, R = H);⁴⁷⁴⁰ and by conversion of 2,4-dihydroxy-5-hydroxymethyl-6-methylpyrimidine (15, R = OH) into the 5-chloromethyl analogue (15, R = Cl) and thence by hydrogenolysis over palladium in dimethylformamide into 2,4-dihydroxy-5,6-dimethylpyrimidine (15, R = H) in greater than 90% yield.⁴³⁸⁷



The conversion of a chloro into an alkyl, alkenyl, or alkynyl substituent has been done in several ways. The first method was illustrated in the treatment of 4-amino-2-chloro-5-nitro-6-phenylpyrimidine (16, R = Cl) and diethyl malonate in tetrahydrofuran with strong alkali to afford 4-amino-2-di(ethoxycarbonyl)methyl-5-nitro-6-phenylpyrimidine [16, R = CH(CO₂Et)₂], which on boiling in concentrated hydrochloric acid underwent both hydrolysis and double decarboxylation to give the required 4-amino-2-methyl-5-nitro-6-phenylpyrimidine (16, R = Me).⁵⁴⁴¹ It will be evident that the original chloro substituent must occupy an activated position to undergo such a reaction.

The second (well-known) method, involving the action of Grignard reagent on chloropyrimidines, has been improved greatly by carrying out the reaction in the presence of nickel phosphine complexes such as Ni(Ph₂PCH₂CH₂PPh₂)Cl₂.⁵⁰⁹⁶ In this way 2-chloro-4,6-dimethylpyrimidine (17, R = Cl) was converted by the appropriate alkyl magnesium bromide into 2-ethyl- (74%), 2-butyl- (67%), 2-amyl- (64%),

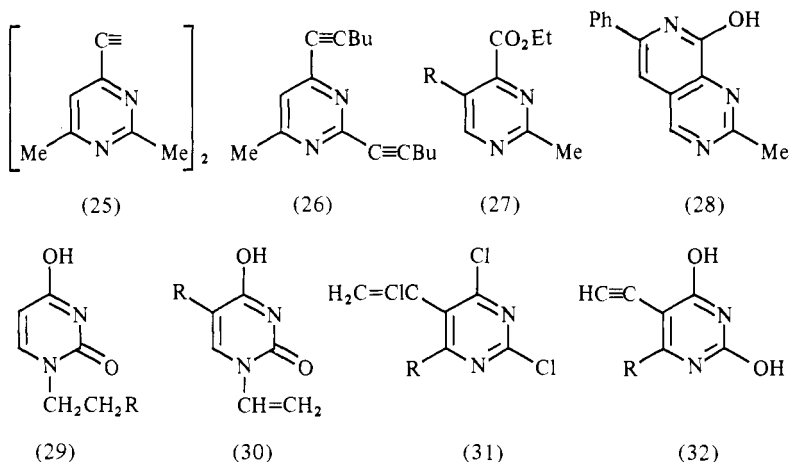
2-hexyl- (54%), and 2-benzyl-4,6-dimethylpyrimidine (17, R = alkyl) as well as into 4,6-dimethyl-2-phenylpyrimidine (17, R = Ph); 4-chloro-2,6-dimethylpyrimidine gave 4-ethyl-2,6-dimethyl- (18, R = Et) and 2,4-dimethyl-6-phenylpyrimidine (18, R = Ph), both in 60–80% yield; 2,4-dichloro-6-methyl- (19, R = Cl) and 4,6-dichloro-2-methylpyrimidine (20, R = Cl), with an excess of ethyl magnesium bromide, gave 2,4-diethyl-6-methyl- (19, R = Et) and 4,6-diethyl-2-methylpyrimidine (20, R = Et), respectively; and 2,4,6-trichloropyrimidine (21, R = Cl) likewise gave 2,4,6-triethylpyrimidine (21, R = Et) in 40% yield.⁵⁰⁹⁶ It is interesting that the dichloro (19 and 20, R = Cl) and the trichloro (21) substrates each reacted with a single molecule of alkyl magnesium bromide to give a mixture of the possible products along with unchanged substrate; no preference for reaction with the more reactive 4(6)-chloro substituent was observed.⁵⁰⁹⁶ 2,4,6-Triphenylpyrimidine has been so made in 95% yield.⁶⁵⁷⁵



The third method has been developed in Sendai to introduce unsaturated alkyl groups in place of an halogeno substituent.⁵⁹⁹² Thus, 2-iodo-4,6-dimethyl- (17, R = I), 4-iodo-2,6-dimethyl- (18, R = I), and 5-iodo-2,4-dimethylpyrimidine (22, R = I) all reacted with styrene in the presence of palladium (as acetate, chloride or "black") and triethylamine at 90° to give reasonable yields of 4,6-dimethyl-2- (17, R = CH:CHPh), 2,4-dimethyl-6- (18, R = CH:CHPh), and 2,4-dimethyl-5-styrylpyrimidine (22, R = CH:CHPh), respectively.⁶³⁰¹ Similar reactions with ethyl acrylate or acrylonitrile gave products like 2- β -ethoxycarbonylvinyl-4,6-dimethylpyrimidine (17, R = CH:CHCO₂Et) or 5- β -cyanovinyl-2,4-dimethylpyrimidine (22, R = CH:CHCN).⁶³⁰¹ Likewise, 5-iodo-2-isopropyl-4-methylpyrimidine (23, R = I) reacted with styrene in the presence of the palladium acetate/triphenylphosphine

complex* and triethylamine to give (*trans*) 2-isopropyl-4-methyl-5-styrylpyrimidine (23, R = CH:CHPh);^{5654, 5655} 4-iodo-2-methyl-6-phenylpyrimidine gave 2-methyl-4-phenyl-6-styrylpyrimidine;⁶⁰⁸⁹ 5-bromo-2,4-dimethylpyrimidine (22, R = Br) gave 2,4-dimethyl-5-styrylpyrimidine (22, R = CH:CHPh);⁵⁶⁵⁴ 4-chloro-5-iodo-2,6-dimethylpyrimidine (24, R = I) gave 4-chloro-2,6-dimethyl-5-styrylpyrimidine (24, R = CH:CHPh), despite the more reactive chloro substituent in the substrate;⁶³⁵² and 4-amino-, 4-hydroxy-, and 4-chloro-5-iodo-2,6-dimethylpyrimidine all reacted with ethyl acrylate similarly to give 4-amino-5- β -ethoxycarbonylvinyl-, 5- β -ethoxycarbonylvinyl-4-hydroxy-, and 4-chloro-5- β -ethoxycarbonylvinyl-2,6-dimethylpyrimidine, respectively.⁶³⁵¹ These methods have also been used to introduce acetylenic substituents. For example, treatment of 4-iodo-2,6-dimethylpyrimidine (18, R = I) and propyne in the presence of the palladium chloride/triphenylphosphine complex, cuprous iodide, and triethylamine gave 2,4-dimethyl-6-prop-1'-ynylpyrimidine (18, R = C:CMe) in 80% yield; 2-iodo-4,6-dimethylpyrimidine (17, R = I) with hexyne gave 2-hex-1'-ynyl-4,6-dimethylpyrimidine (17, R = C:CBu); 5-bromo-2,4-dimethylpyrimidine (23, R = Br) with phenylacetylene gave 2,4-dimethyl-5-phenylethynylpyrimidine (22, R = C:CPh). Many other compounds were made similarly.^{5093, 5094} It should be noted that when 4-iodo-2,6-dimethylpyrimidine was allowed to react with unsubstituted acetylene under similar conditions, 1,2-bis(2',6'-dimethylpyrimidin-4'-yl)acetylene (25) was formed in 37% yield.⁵⁰⁹⁴ The regular reaction with substituted acetylenes proved applicable to 2,4-di-iodo-6-methylpyrimidine (19, R = I), which with hexyne gave 2,4-dihex-1'-ynyl-6-methylpyrimidine (26);^{5093, 5094} in addition, 5-bromo-4-ethoxy-2-methylpyrimidine (27, R = Br) or 4-chloro-5-ethoxycarbonyl-2-methylpyrimidine with phenylacetylene gave the isomeric 4-ethoxycarbonyl-2-methyl-5-phenylethynyl- (27, R = C:CPh) and 5-ethoxycarbonyl-2-methyl-4-phenylethynylpyrimidine, both of which underwent aminolytic cyclization in ethanolic ammonia to give 8-hydroxy-2-methyl-6-phenylpyrido[3,4-*d*]pyrimidine (28) and the analogous 5-hydroxy-2-methyl-7-phenylpyrido[4,3-*d*]pyrimidine, respectively.⁶³⁵¹ Although chloropyrimidines proved inferior to iodopyrimidines as substrates, 2-chloro-4,6-dimethylpyrimidine (17, R = Cl) did react with hexyne and phenylacetylene to give 2-hex-1'-ynyl-4,6-dimethyl- (17, R = C:CBu) and 4,6-dimethyl-2-phenylethynylpyrimidine (17, R = C:CPh), respectively, in *c.* 40%

*It was concluded subsequently that the addition of triphenylphosphine actually retarded the reaction in the pyrimidine series, as judged from many examples using acrylonitrile, ethyl acrylate, and styrene with iodopyrimidines.⁶³⁹⁰



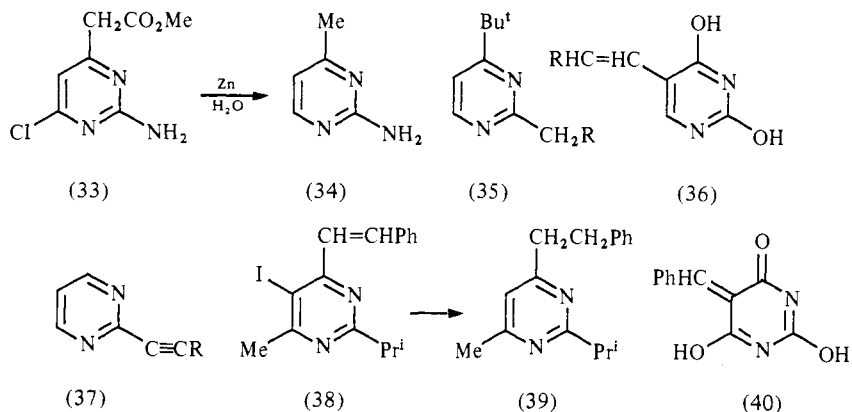
yield.⁶³⁵³ Like its reaction with styrene (*v.s.*), 4-chloro-5-iodo-2,6-dimethylpyrimidine (24, R = I) reacted at its iodo substituent with phenylacetylene under the usual conditions, to afford 4-chloro-2,6-dimethyl-5-phenylethynylpyrimidine (24, R = C:CPh). The same product was prepared by a similar conversion of 4-hydroxy-5-iodo-2,6-dimethylpyrimidine into 4-hydroxy-2,6-dimethyl-5-phenylethynylpyrimidine followed by treatment with phosphoryl chloride.⁶³⁵²

Alkenyl- and alkynylpyrimidines have been made conveniently by dehydrohalogenation (specifically, removal of HCl) from a chloroalkyl- or chloroalkenylpyrimidine, respectively. For example, 1- β -hydroxyethyluracil (29, R = OH) was converted by thionyl chloride into 1- β -chloroethyluracil (29, R = Cl), which was treated with potassium *t*-butoxide in dimethyl sulfoxide to give 1-vinyluracil (30, R = H) in good yield;⁵⁴⁹⁵ 1- β -chloroethyluracil (29, R = Cl) and its 5-methyl derivative, 1- β -chloroethylthymine, were both dehydrochlorinated by sodium methoxide in dioxane to give 1-vinyluracil (30, R = H) and 5-methyl-1-vinyluracil (30, R = Me), respectively;⁵⁸¹⁸ and 1- β -chloroethyl-5-fluorouracil behaved similarly to give 5-fluoro-1-vinyluracil (30, R = F) in 40% yield.⁴⁸⁸⁹ Similarly, treatment of 5-acetyl-2,4-dihydroxypyrimidine with phosphoryl chloride gave 2,4-dichloro-5- α -chlorovinylpyrimidine (31, R = H), which underwent dehydrochlorination and hydrolysis in boiling alkali to afford 5-ethynyl-2,4-dihydroxypyrimidine (32, R = H);⁵³²⁹ 5-acetyl-2,4,6-trihydroxypyrimidine likewise gave 2,4,6-trichloro-5- α -chlorovinylpyrimidine (31, R = Cl) and thence 4-chloro-5-ethynyl-2,6-dihydroxypyrimidine (32, R = Cl) in which the third nuclear chloro substituent had survived hydrolysis.⁶⁰¹⁷ When the intermediate 2,4-dichloro-5- α -chlorovinyl-

pyrimidine (31, R = H) was treated with ethanolic ammonia, a separable mixture of 2-amino-4-chloro- and 4-amino-2-chloro-5- α -chlorovinylpyrimidine was obtained; subsequent treatment of the latter with alkali gave 4-amino-5-ethynyl-2-hydroxypyrimidine.⁵²⁸⁷ An indirect route from 2,4-dichloro-5- α -chlorovinylpyrimidine (31, R = H) to 5-ethynyl-2,4-dihydroxypyrimidine (32, R = H), *via* 5-ethynyl-2,4-dimethoxy- and 2,4-dimethoxy-5-trimethylsilylethynylpyrimidine, was reported to be advantageous for large scale working.⁶³⁴⁹

(3) Alkylpyrimidines from Their Carboxy and Other Derivatives (H 120)

The simple removal of nuclear groups (apart from the chloro substituent, discussed above) to leave behind simple alkylpyrimidines, has been neglected recently. However, the removal of groups from an existing side chain to leave a plain alkyl side chain has been used. For example, prolonged boiling of 2-amino-4-chloro-6-methoxycarbonylmethylpyrimidine (33) with zinc dust in water produced dechlorination, hydrolysis of the ester, and subsequent decarboxylation to afford 2-amino-4-methylpyrimidine (34) in 68% yield;⁵²⁴³ 4-*t*-butyl-2-methoxycarbonylmethyl- (35, R = CO₂Me) in warm alkali gave 4-*t*-butyl-2-carboxymethylpyrimidine (35, R = CO₂H), which underwent quantitative decarboxylation on heating at 90° for a few minutes to yield 4-*t*-butyl-2-methylpyrimidine (35, R = H);⁵⁶⁹³ heating 5- β -carboxyvinyl-2,4-dihydroxypyrimidine (36, R = CO₂H) in quinoline at 220° gave a small yield of 2,4-dihydroxy-5-vinylpyrimidine (36, R = H);⁵⁴²⁷ 2,4-dihydroxy-5- α -hydroxyethylpyrimidine and methanesulfonyl chloride in a tertiary base gave the ester, 2,4-dihydroxy-5- α -methane-

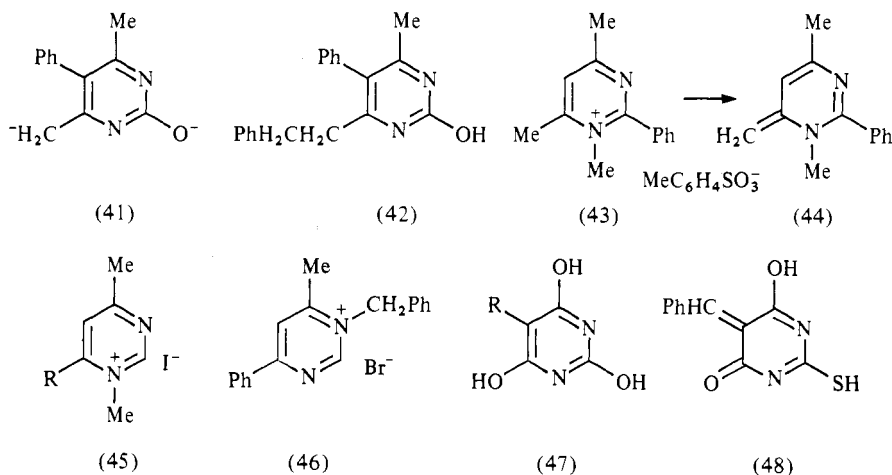


sulfonyloxyethylpyrimidine, which on heating in the same base afforded 2,4-dihydroxy-5-vinylpyrimidine (36, R = H) in 85% yield;⁶⁰⁴³ and when 2-(3'-hydroxy-3'-methylbut-1'-ynyl)pyrimidine (37, R = CMe₂OH) was heated with potassium hydroxide at 110°, 2-ethynylpyrimidine (37, R = H) resulted (with loss of acetone).⁶²⁶⁵

(4) *Interconversion of Alkyl Groups (H 122, E 87)*

Irrespective of their method of formation, alkenyl- and alkynylpyrimidines may be reduced to the corresponding alkylpyrimidines. For example, hydrogenation of 5-iodo-2-isopropyl-4-methyl-6-stryrylpyrimidine (38) over palladium removed the iodo substituent and reduced the styryl group to give 2-isopropyl-4-methyl-6-phenethylpyrimidine (39);⁵⁶⁵⁵ hydrogenation of 4-allyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine gave 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-propylpyrimidine in greater than 90% yield;⁵⁴¹⁵ triethylammonium formate conveniently reduced 5-benzylidenearbituric acid (40) to 5-benzyl-2,4,6-trihydroxypyrimidine in greater than 90% yield;⁵⁸⁹⁹ both 2,4-dimethyl-6- and 4,6-dimethyl-2-phenylethynylpyrimidine underwent hydrogenation to give 2,4-dimethyl-6- and 4,6-dimethyl-2-phenethylpyrimidine, respectively;⁵⁰⁹⁴ hydrogenation of 2,4-dihydroxy-6-vinylpyrimidine gave 4-ethyl-2,6-dihydroxypyrimidine in excellent yield;⁵⁴⁰³ and 2,4-dihydroxy-6-styryl- similarly gave 2,4-dihydroxy-6-phenethylpyrimidine.⁵⁴⁰³ Other examples have been reported.^{5122, 5306}

Other ways to modify existing alkyl groups attached to the pyrimidine nucleus are exemplified in the treatment of 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine with two molecules of butyllithium or sodium amide to give the dianion (41) followed by treatment with benzyl chloride to afford 2-hydroxy-4-methyl-6-phenethyl-5-phenylpyrimidine (42) in good yield,^{5504, 5547} as well as in the perfectly normal quaternization of 4,6-dimethyl-2-phenylpyrimidine to give the 1,4,6-trimethyl-2-phenylpyrimidinium *p*-toluenesulphonate (43) followed by a most unusual removal of *p*-toluenesulphonic acid, by treatment with potassium *t*-butoxide in an aprotic medium, to give 1,6-dihydro-1,4-dimethyl-6-methylene-2-phenylpyrimidine (44), a stable distillable liquid.⁵⁷⁰⁶ The conversion of (activated) methylpyrimidines into styrylpyrimidines by aromatic aldehydes is discussed in Sect. 2.C(1) below. Highly activated methyl groups can be alkylated normally; 1,2,3,4-tetrahydro-1,3,6-trimethyl-5-nitro-2,4-dioxypyrimidine with benzyl bromide in dimethylformamide at 80° gave the 6-phenethyl analogue (93%).⁶⁵¹²



(5) Direct Introduction of Alkyl Groups (H 123)

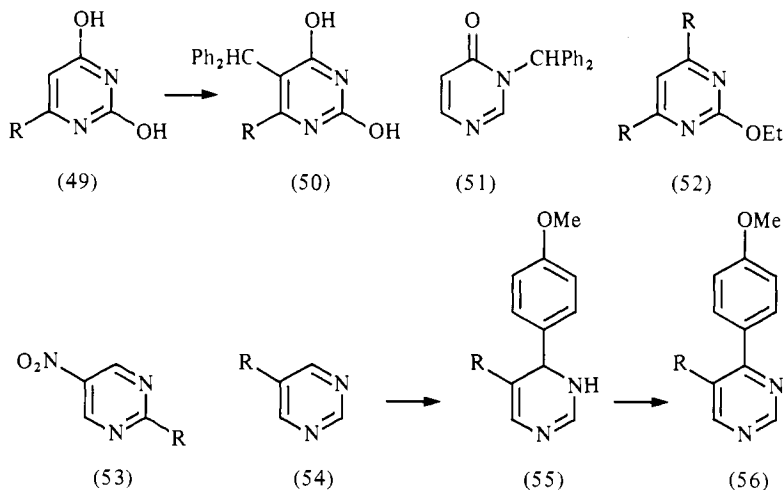
The *N*-alkylation of pyrimidines lacking tautomeric groups has usually been done by quaternization with an alkyl halide. For example, 4-methylpyrimidine and methyl iodide at room temperature for several days gave a single product, which proved to be 1,4-dimethylpyrimidinium iodide (45, R = H);⁴⁸³⁸ 4,6-dimethylpyrimidine gave 1,4,6-trimethylpyrimidinium iodide (45, R = Me);⁴⁶⁶⁸ 4- or 5-phenylpyrimidine in refluxing methyl iodide gave 1-methyl-4(or 5)-phenylpyrimidinium iodide, respectively;⁴⁶⁸³ 2-methyl- or 2,4,6-trimethylpyrimidine gave 1,2-dimethyl- or 1,2,4,6-tetramethylpyrimidinium iodide, respectively;⁴⁶⁸⁹ pyrimidine gave 1-methylpyrimidinium iodide;⁴⁶⁹⁰ and 4-methyl-6-phenylpyrimidine and benzyl bromide gave 1-benzyl-6-methyl-4-phenylpyrimidinium bromide (46).⁵²⁵⁵ Many less simple examples have also been reported.^{5058, 5061, 5343}

Several *C*-methylations have been done by irradiation in methanolic hydrogen chloride, for example, 2,4-diamino-5-cyano-6-methylpyrimidine was so prepared in 57% yield.⁴⁹⁷⁸

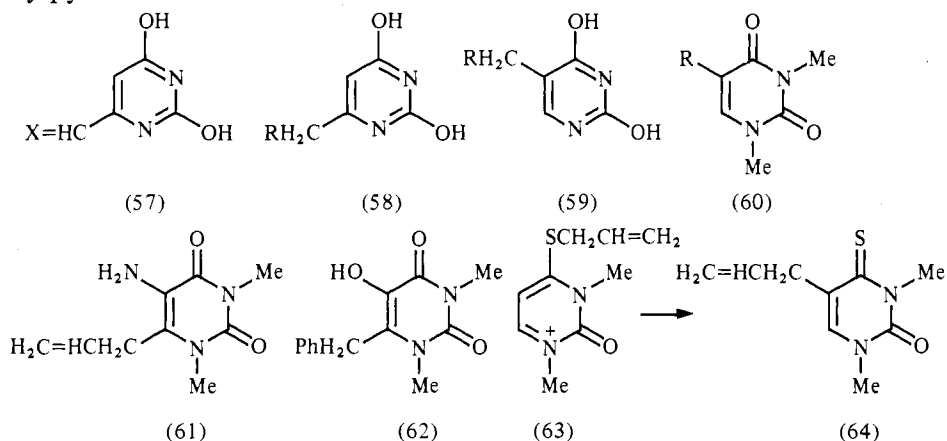
Other nuclear *C*-alkylations are also possible. Thus, heating 2,4,6-trihydroxypyrimidine (47, R = H) with trimethylammonium formate at 135° gave the trimethylammonium salt of 2,4,6-trihydroxy-5-methylpyrimidine (47, R = Me) in 80% yield. In the same way, from appropriate substrates were obtained 1,5-dimethylbarbituric acid, 1,2,3,4-tetrahydro-6-hydroxy-1,3,5-trimethyl-2,4-dioxypyrimidine, and 4,6-dihydroxy-2-mercapto-5-methylpyrimidine.⁵⁸⁹⁹ Barbituric acid, 2,4,6-trihydroxypyrimidine, also reacted with aromatic aldehydes in hot

aqueous suspension to afford, for example, 5-*o*-nitrobenzylidenebarbituric acid,⁵³⁸⁵ 5-*p*-chlorobenzylidenebarbituric acid,⁵⁸⁹⁷ 5-*p*-dimethylaminobenzylidenebarbituric acid,⁵⁸⁹⁷ and other such compounds;⁴⁸⁸⁷ 4,6-dihydroxy-2-mercaptopyrimidine reacted similarly to give 5-benzylidene-2-thiobarbituric acid (48) and several derivatives.⁴⁸⁶⁶

5-Diarylmethylation has been found possible for pyrimidine substrates which have at least two strongly electron-donating groups. Thus, 2,4-dihydroxypyrimidine (49, R = H), diphenylmethanol, and boron trifluoride etherate (or stannic chloride) in refluxing acetic acid furnished 5-diphenylmethyl-2,4-dihydroxypyrimidine (50, R = H) in 96% yield;⁵⁵⁰³ 2,4,6-trihydroxypyrimidine (49, R = OH) similarly gave 5-diphenylmethyl-2,4,6-trihydroxypyrimidine (50, R = OH);⁵⁵⁰³ and appropriate substrates gave 4-amino-5-diphenylmethyl-6-hydroxy-2-mercapto-, 5-diphenylmethyl-4,6-dihydroxy-, 4-amino-5-diphenylmethyl-2-hydroxy- (poor yield), and 5-diphenylmethyl-4-hydroxy-2-mercaptopyrimidine as well as other analogues with one of the phenyl groups substituted.⁵⁵⁰³ Application of the reaction to 2- or 4-hydroxypyrimidine led to *N*-alkylation, giving 1-diphenylmethyl-1,2-dihydro-2-oxo- or 1-diphenylmethyl-1,6-dihydro-6-oxopyrimidine (51), respectively.⁵⁵⁰³ The relative reactivities of amino substituents and the 5-position in a variety of pyrimidines, towards the diphenylmethyl cation, have been determined preparatively.⁵⁵⁰² Treatment of 2-ethoxypyrimidine (52, R = H), pivalic acid, and silver nitrate in dilute sulfuric acid with ammonium persulfate gave 4,6-di-*t*-butyl-2-ethoxypyrimidine (52, R = Bu^t), which was hydrolyzed without isolation to 4,6-di-*t*-butyl-2-hydroxypyrimidine.⁶¹⁰⁵ Some photochemical alkylations and arylations have been reported.^{4359, 5271}



Semidirect alkylations and arylations are illustrated in the reaction of 5-nitropyrimidine (53, R = H) and benzamidine to give 5-nitro-2-phenylpyrimidine (53, R = Ph) in excellent yield;⁶¹²³ pivalamidine behaved similarly to give 2-*t*-butyl-5-nitropyrimidine (52, R = Bu^t), but amidines and other such nucleophiles with an active methylene group gave more than one product and this gives a clue to the mechanism which has been discussed.⁶¹²³ Another such reaction involved the addition of anisole to pyrimidine (54, R = H) or 5-methylpyrimidine (54, R = Me) in trifluoroacetic acid to give 1,6-dihydro-6-*p*-methoxyphenylpyrimidine (55, R = H) and its 5-methyl derivative (55, R = Me), which underwent oxidation by alkaline ferricyanide to yield 4-*p*-methoxyphenylpyrimidine (56, R = H) and the 5-methyl derivative (56, R = Me), respectively, both in good yield.⁴⁴⁹⁵ Similarly, 5-thien-2'-yl- and 5-thien-3'-yl-pyrimidine reacted with butyllithium to give (after hydrolysis) 4-butyl-3,4-dihydro-5-thien-2'(and 3')-ylpyrimidine, which underwent ferricyanide oxidation to 4-butyl-5-thien-2'(and 3')-ylpyrimidine.⁴⁴⁰⁶



Alkyl groups have been introduced even less directly. Thus, a mixture of 4-formyl-2,6-dihydroxypyrimidine (57, X = O) and benzyltriphenylphosphonium chloride was treated with butyllithium to give 2,4-dihydroxy-6-styrylpyrimidine (57, X = CHPh) in 50% yield;⁵⁴⁰³ 4-chloromethyl-2,6-dihydroxypyrimidine (58, R = Cl) was treated with triphenylphosphine to give the chloride of 2,4-dihydroxy-6-triphenylphosphoniomethylpyrimidine (58, R = P⁺Ph₃), which reacted with paraformaldehyde to afford 2,4-dihydroxy-6-vinylpyrimidine (57, X = CH₂) in greater than 80% yield;⁵⁴⁰³ and treatment of 2,4-dihydroxy-5-hydroxymethylpyrimidine (59, R = OH) in anhydrous hydrogen fluoride with benzene or toluene gave 5-benzyl-2,4-dihydroxypyrimidine

(59, R = Ph) or its *p*-methylbenzyl analogue (59, R = C₆H₄Me), respectively, in good yield.⁴⁸⁰¹ The conversion of 1,2-dihydro-4,6-dimethyl-2-oxo-1-phenyl- into 1,2,3,4-tetrahydro-4,4,6-trimethyl-2-oxo-1-phenylpyrimidine by methyl magnesium iodide or methyllithium, has been reported, along with analogues.⁶⁴²²

(6) *Ethynylpyrimidines* (H 124)

The formation of ethynyl- and other alkynylpyrimidines has been included in the above sections.

(7) *C-Alkylpyrimidines by Rearrangement* (New)

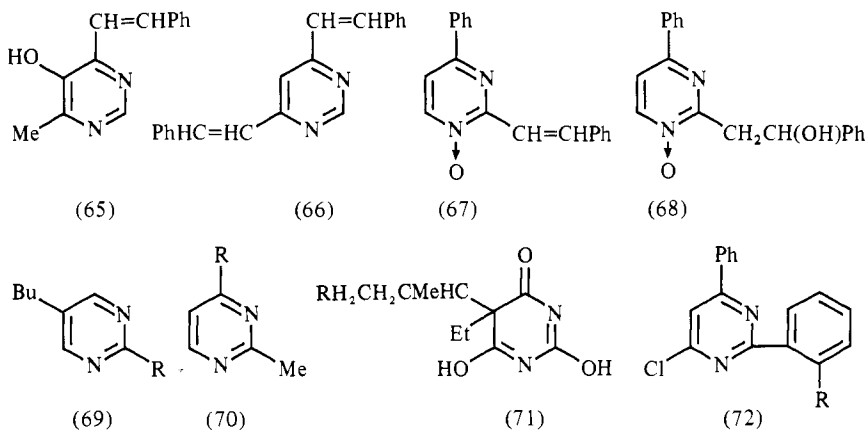
5-Allylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (60, R = NHCH₂CH:CH₂) underwent a thermal (Claisen) rearrangement at greater than 200° to give 4-allyl-5-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (61) in low yield,⁵⁴¹⁵ 5-benzyloxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (60, R = OCH₂Ph) behaved similarly to give 4-benzyl-1,2,3,6-tetrahydro-5-hydroxy-1,3-dimethyl-2,6-dioxypyrimidine (62),⁵⁴¹⁵ and 4-allylthio-2,3-dihydro-1,3-dimethyl-2-oxypyrimidin-1-ium bromide (63) rearranged in methanolic sodium carbonate to an intermediate methanol adduct, which lost methanol on refluxing in chloroform to give 5-allyl-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thiopyrimidine (64) in excellent yield.⁴⁴²¹ A variety of photochemical and thermal rearrangements of *S*-benzyl- to 5-benzylpyrimidines has been described;⁴⁴⁴¹ for example irradiation of 4-benzylthio-2,3-dihydro-3-methyl-2-oxypyrimidine in *t*-butanol gave, among other products, 5-benzyl-3-methyl-4-thiouracil (45%).⁴⁴⁴¹

C. Reactions of Alkyl and Aryl Pyrimidines (H 124, E 89)

The reactions summarized below are those of the actual alkyl or aryl substituents on the pyrimidine ring, irrespective of other attached groups.

(1) *Methyl- to Styrylpyrimidines* (H 125, E 89)

The conversion of methyl- into styryl- and substituted styrylpyrimidines has continued to be widely used. The processes are exempli-



fied in the formation, from the corresponding methylpyrimidines with an appropriate benzaldehyde, of 4,6-distyryl- (zinc chloride or acetic anhydride: 70%),⁴⁹¹⁸ 2-phenyl-4,6-distyryl- (zinc chloride),⁴⁹¹⁸ 4-*m*-chlorostyryl- (acetic anhydride: 44%),⁵³⁰⁹ 2-amino-4-*m*-chlorostyryl- (formic acid: 63%),⁵³⁰⁹ 4-amino-6-*m*-chlorostyryl- (acetic acid + sulfuric acid: 20%),⁵³⁰⁹ 4-*m*-cyanostyryl-2-dimethylamino- (acetic anhydride: 60%),⁵³⁰⁹ 5-hydroxy-4-methyl-6-styryl- (65) plus 5-hydroxy-4,6-distyryl- (66) (5% hydrochloric acid: 24%, 18%),⁶³⁷⁰ 2-hydroxy-4-styryl- (95%),⁴⁸³² 4-*p*-dimethylaminostyryl-2-mercapto- (75%),⁴⁸³² and 4-hydroxy-6-methyl-2-styrylpyrimidine (80%).⁴⁸³¹ Alkylpyrimidine *N*-oxides have also reacted successfully with aldehydes. Thus, 2-methyl-4-phenylpyrimidine 1-oxide and benzaldehyde in aqueous ethanolic potassium hydroxide gave 4-phenyl-2-styrylpyrimidine 1-oxide (67) in low yield along with an equal quantity of the "hydrate," 2-(2'-hydroxy-2'-phenylethyl)-4-phenylpyrimidine 1-oxide (68),⁶⁰⁸⁹ under similar conditions, 4,6-dimethylpyrimidine *N*-oxide gave (crude) 4,6-distyrylpyrimidine *N*-oxide, which was deoxygenated by phosphorus trichloride to give 4,6-distyrylpyrimidine in 53% overall yield. It thus appeared that 4/6-methyl groups were much more reactive than a 2-methyl group, even in the presence of an *N*-oxide substituent.⁶⁰⁸⁹

(3) Alkyl- to Carboxypyrimidines (H 126, E 89)

The traditional use of permanganate to convert methyl- into carboxy-pyrimidines appears to have fallen into disuse. However, the same transformation has been done with selenium dioxide under appropriately vigorous conditions. Thus, 4-methyl- gave 4-carboxy-

pyrimidine in 80% yield by heating with selenium dioxide in pyridine for 6 h;⁵⁴⁸⁰ 5-butyl- (69, R = Me) or 5-amyl-2-methylpyrimidine similarly gave 5-butyl- (69, R = CO₂H) or 5-amyl-2-carboxypyrimidine in *c.* 30% yield;⁵⁷¹⁵ and 2,4-dimethylpyrimidine (70, R = Me) gave 4-carboxy-2-methylpyrimidine, isolated as its ester, 4-methoxycarbonyl-2-methylpyrimidine (70, R = CO₂Me), in 60% yield.⁵⁶⁵²

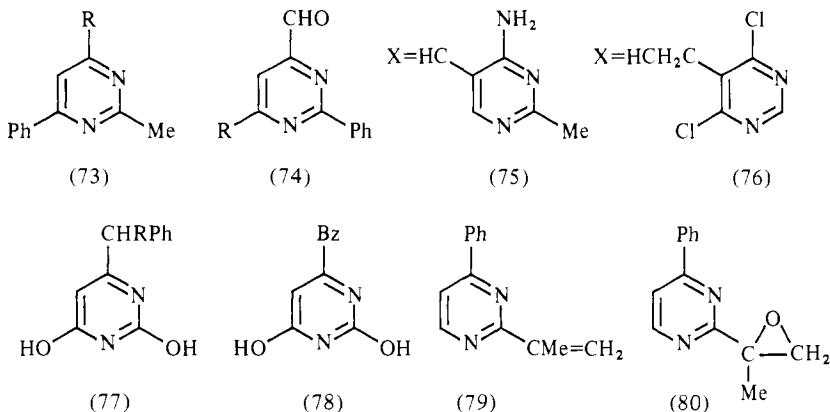
The oxidation of part of an alkyl or aryl group has been reported; 5-ethyl-5-(1'-methylpent-4'-enyl)barbituric acid (71, R = CH:CH₂) and ruthenium tetroxide (prepared *in situ* from the expensive dioxide) gave 5-(3'-carboxy-1'-methylpropyl)-5-ethylbarbituric acid (71, R = CO₂H) in 81% yield,⁵⁵³⁷ and 4-chloro-6-phenyl-2-*o*-tolylpyrimidine (72, R = Me) with sodium dichromate in acetic acid + sulfuric acid gave 2-*o*-carboxy-phenyl-4-chloro-6-phenylpyrimidine (72, R = CO₂H) in 45% yield along with the corresponding 4-hydroxy analogue in 22% yield.⁵³⁵²

(4) Other Oxidations of Alkylpyrimidines (H 128, E 89)

By using a single molar equivalent of selenium dioxide in dioxane or acetic acid, controlled oxidations of methyl- to formylpyrimidines have been achieved. In this way, 2,4-dimethyl- (73, R = Me) gave a 90% yield of 4-formyl-2-methyl-6-phenylpyrimidine (73, R = CHO);⁶¹³⁶ 4,6-dimethyl-2-phenylpyrimidine gave (with 1 equivalent of selenium dioxide) 4-formyl-6-methyl-2-phenylpyrimidine (74, R = Me) or (with 2 equivalents of reagent) 4,6-diformyl-2-phenylpyrimidine (74, R = CHO);⁶¹³⁶ 4-methyl-2-phenylpyrimidine gave 4-formyl-2-phenylpyrimidine (74, R = H);⁶²⁹⁹ and 2,4-dihydroxy-6-methylpyrimidine gave 4-formyl-2,6-dihydroxypyrimidine ("orotaldehyde"), a very useful synthesis despite a mediocre yield.^{5617, 5876} 4-Formyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine was made similarly, *via* its diethyl acetal.⁶⁸⁵³

Oxidation of alkenylpyrimidines with ozone has proved useful. For example, ozonolysis of 4-amino-5- β -ethoxyvinyl-2-methylpyrimidine (75, X = CHOEt) gave 4-amino-5-formyl-2-methylpyrimidine (75, X = O),⁵⁸³⁰ and 5-allyl-4,6-dichloropyrimidine (76, R = CH₂) gave 4,6-dichloro-5-formylmethylpyrimidine (76, R = O) in 60% yield.⁶⁰⁶⁴

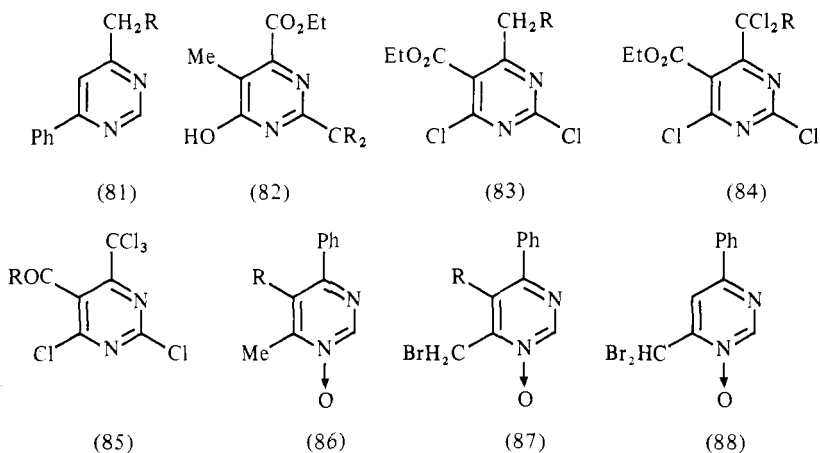
Other partial side-chain oxidations have been reported. 4-Benzyl-2,6-dihydroxypyrimidine (77, R = H) with selenium dioxide (1 mol) gave 2,4-dihydroxy-6- α -hydroxybenzylpyrimidine (77, R = OH), but with 2 mol of reagent gave 4-benzoyl-2,6-dihydroxypyrimidine (78);⁵⁸⁷⁷ 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine ("trimethoprim") with manganese dioxide in glacial acetic acid gave 2,4-diamino-5-



(3',4',5'-trimethoxybenzoyl)pyrimidine in good yield;⁵⁴⁶⁸ 2-isopropenyl-4-phenylpyrimidine (79) with *m*-chloroperoxybenzoic acid gave 2-(1',2'-epoxy-1'-methylethyl)-4-phenylpyrimidine (80) in 85% yield;⁵⁶⁹⁰ 5-(2'-methylprop-1'-enyl)-2-phthalimidopyrimidine with *m*-chloroperoxybenzoic acid gave 5-(1',2'-epoxy-2'-methylpropyl)-2-phthalimidopyrimidine (51%);⁵⁷⁶² and the same substrate with mercuric acetate gave 5-(2'-hydroxy-2'-methylpropyl)-2-phthalimidopyrimidine, isolated as the free 2-amino analogue.⁵⁷⁶²

(5) Alkyl- to Halogenoalkylpyrimidines (H 130)

The direct halogenation of a methylpyrimidine with elemental bromine or chlorine has but seldom given a single product. However, 4-methyl-6-phenylpyrimidine (81, R = H) with bromine (1 mol) in acetic acid did give 4-bromomethyl-6-phenylpyrimidine (81, R = Br) in good yield;⁵²⁵⁵ 4-ethoxycarbonyl-6-hydroxy-2,5-dimethylpyrimidine (82, R = H) with bromine (3 mol) in acetic acid/sodium acetate resulted only in complete bromination of the 2-methyl group, to give 4-ethoxycarbonyl-6-hydroxy-5-methyl-2-tribromomethylpyrimidine (82, R = Br) in 92% yield;⁶¹⁴⁰ and dropwise addition of bromine to a benzene solution of 2,4-dihydroxy-6-methoxycarbonyl-5-methylpyrimidine under irradiation gave the 5-bromomethyl analogue.⁶¹⁹³ More commonly, several products resulted. For example, 2,4-dichloro-5-ethoxycarbonyl-6-methylpyrimidine (83, R = H) with chlorine or sulfuryl chloride at 100° gave 2,4-dichloro-6-chloromethyl-5-ethoxycarbonylpyrimidine (83, R = Cl) and its 6-dichloromethyl analogue (84, R = H) in comparable yields; at 130–140°, the latter (84, R = H) predominated in 84% yield. At 180–190° in ultraviolet light, a mixture

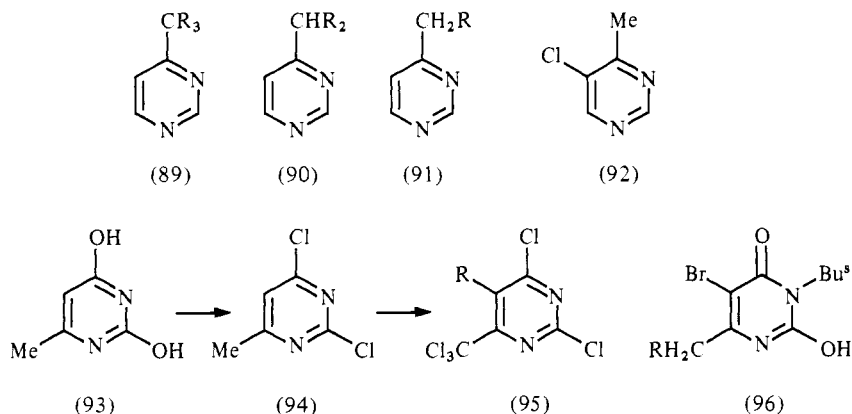


of 2,4-dichloro-5-chlorocarbonyl-6-trichloromethylpyrimidine (85, $R = Cl$) and 2,4-dichloro-5-pentachloroethoxycarbonyl-6-trichloromethylpyrimidine (85, $R = OC_2Cl_5$) resulted.⁴⁴⁷⁰ Likewise, bromination of 4-methyl-6-phenylpyrimidine 3-oxide (86, $R = H$) by bromine in acetic anhydride/sodium acetate at 20–25° gave its 5-bromo derivative (86, $R = Br$), 4-bromomethyl-6-phenylpyrimidine 3-oxide (87, $R = H$), its 5-bromo derivative (87, $R = Br$), and 4-dibromomethyl-6-phenylpyrimidine 3-oxide (88); under other conditions, the same products were isolated but in different proportions.⁴⁸¹⁰ 3-Isopropyl-6-methyluracil and sulfuryl chloride gave mainly 3-isopropyl-6-trichloromethyluracil or 5-chloro-6-dichloromethyl-3-isopropyluracil, according to conditions.⁵⁵⁸⁸ Other examples have been reported in detail.⁶⁵¹⁷

The use of *N*-bromo- or *N*-chloro-succinimide to halogenate methylpyrimidines also led to mixtures; thus, 4-methylpyrimidine (89, $R = H$) with *N*-bromosuccinimide in carbon tetrachloride gave a separable mixture of 4-tribromomethyl- (89, $R = Br$), 4-dibromomethyl- (90, $R = Br$), and 4-bromomethylpyrimidine (91, $R = Br$). The same substrate with *N*-chlorosuccinimide gave 4-trichloro- (89, $R = Cl$), 4-dichloro- (90, $R = Cl$), and 4-chloromethylpyrimidine (91, $R = Cl$) as well as some 5-chloro-4-methylpyrimidine (92). 2-Methylpyrimidine gave similar mixtures with both reagents.⁵⁶⁸²

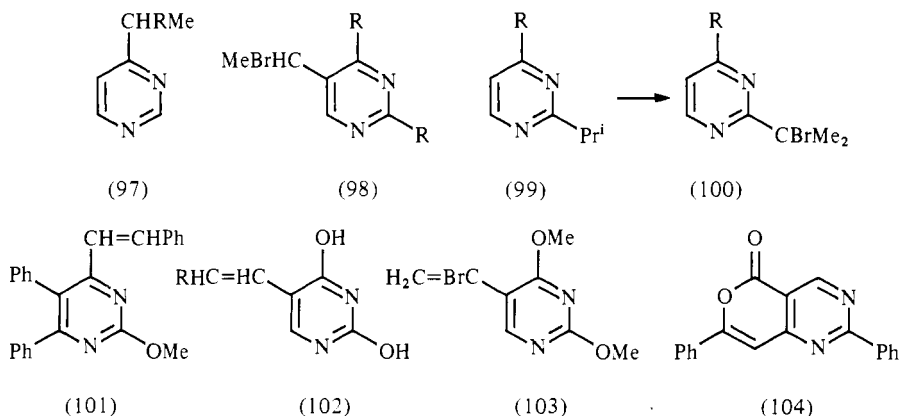
The use of phosphoryl chloride containing phosphorus pentachloride to convert 2- and/or 4/6-hydroxy groups into chloro substituents has sometimes led to chlorination of methyl groups as well. This has proven useful, even in the absence of any requirement for nuclear chloro substituents. The process is illustrated by treatment of 4-methylpyrimidine (89, $R = H$) with the above mixture at 125° for 5 h, which gave 4-trichloromethylpyrimidine (89, $R = Cl$) as the sole

product in greater than 50% yield;⁵⁹⁵⁴ 2,4-dimethylpyrimidine reacted similarly only at its 4-methyl group to give 2-methyl-4-trichloromethylpyrimidine,⁵⁹⁵⁴ 4,6-dimethylpyrimidine gave some 4,6-bis-trichloromethylpyrimidine but also two partially chlorinated products, 4,6-bis-dichloromethyl- and 4-dichloromethyl-6-trichloromethylpyrimidine;⁵⁰⁷² 4-hydroxy-6-methyl- or 4-chloro-6-methylpyrimidine gave 4-chloro-6-trichloromethylpyrimidine in 60% yield;⁵⁰⁷² 4-hydroxy-6-methyl-2-phenyl- gave 4-chloro-2-phenyl-6-trichloromethylpyrimidine;⁶⁷³⁴ 4-methyl-2-phenyl gave 2-phenyl-4-trichloromethylpyrimidine;⁶⁷³⁴ and 4-hydroxy-2-isopropyl-6-methylpyrimidine gave 4-chloro-2-isopropyl-6-trichloromethylpyrimidine in 84% yield.⁵⁰⁷² Uracil derivatives reacted similarly. 2,4-Dihydroxy-6-methylpyrimidine (93) gave a separable mixture of 2,4-dichloro-6-methylpyrimidine (94), 2,4-dichloro-6-trichloromethylpyrimidine (95, R = H), and 2,4,5-trichloro-6-trichloromethylpyrimidine (95, R = Cl);⁵⁹⁵⁴ and 4-bromo-3-*s*-butyl-6-methyluracil (96, R = H) under mild conditions gave the 6-chloromethyl analogue (96, R = Cl).⁵⁵⁸⁸



Higher alkylpyrimidines α -halogenate less readily than the corresponding methylpyrimidines, but the process has been found possible and useful. Thus, 4-ethylpyrimidine (97, R = H) with *N*-bromosuccinimide and benzoyl peroxide in boiling carbon tetrachloride gave 4- α -bromoethylpyrimidine (97, R = Br) in good yield; 5-ethylpyrimidine likewise gave 5- α -bromoethylpyrimidine under similar conditions but including quartz/mercury vapor lamp irradiation;⁴³⁷⁹ 4,6-dichloro-5-ethyl- and 5-ethyl-4,6-dimethoxypyrimidine both underwent similar bromination to give 5- α -bromoethyl-4,6-dichloropyrimidine (98, R = Cl) and its 4,6-dimethoxy analogue (98, R = OMe), respectively;⁴⁵⁷⁷

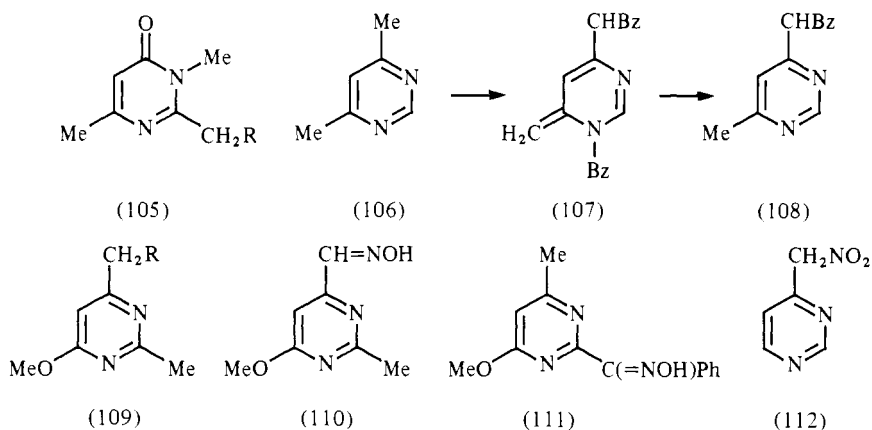
2-isopropylpyrimidine (99, R = H) and its 4-phenyl derivative (99, R = Ph) gave 2- α -bromo- α -methylethylpyrimidine (100, R = H) and its 4-phenyl derivative (100, R = Ph), respectively;⁵⁶⁹⁰ 4-fluoro- (99, R = F) and 4-chloro-2-isopropylpyrimidine (99, R = Cl) gave 2- α -bromo- α -methylethyl-4-fluoropyrimidine (100, R = F) and its 4-chloro analogue (100, R = Cl), respectively;⁵⁶⁹⁴ and 5-isobutyl-2-phthalimidopyrimidine gave 5- α -bromo- β -methylpropyl-2-phthalimidopyrimidine.⁵⁷⁶²



The halogenation of alkenylpyrimidines had proven less simple than might be expected. Thus, while 2-methoxy-4,5-diphenyl-6-styrylpyrimidine (101) simply added bromine to give 4- α,β -dibromophenethyl-2-methoxy-5,6-diphenylpyrimidine,⁵⁹⁸⁴ 2,4-dihydroxy-5-vinylpyrimidine (102, R = H) underwent apparent substitution by bromine in dimethylformamide to give 5- β -bromovinyl-2,4-dihydroxypyrimidine (102, R = Br) in good yield. However, it seemed reasonable to postulate that the reaction proceeded by initial addition of bromine to give the 5- α,β -dibromoethyl analogue followed by spontaneous dehydrobromination to the product (102, R = Br).⁵⁸⁴⁹ In contrast, dibromination of 5-ethyl-2,6-dimethoxypyrimidine, followed by dehydrobromination of the reaction mixture by adding potassium *t*-butoxide, gave 5- α -bromo-vinyl-2,4-dimethoxypyrimidine (103).⁴⁵⁷⁷ The product from addition of bromine to 5-carboxy-2-phenyl-4-styrylpyrimidine could not be isolated because it rapidly cyclized to give 5-oxo-2,7-diphenylpyrano-[4,3-*d*]pyrimidine (104).⁵⁹⁸³ However, 5-allyl- gave 5- β,γ -dibromopropyl-4- β -hydroxyethylamino-2,6-dimethylpyrimidine (67%) in a quite regular way, using bromine in chloroform.⁶⁵⁰⁸

(6) *Claisen Reactions of Alkylpyrimidines* (*H* 131, *E* 90)

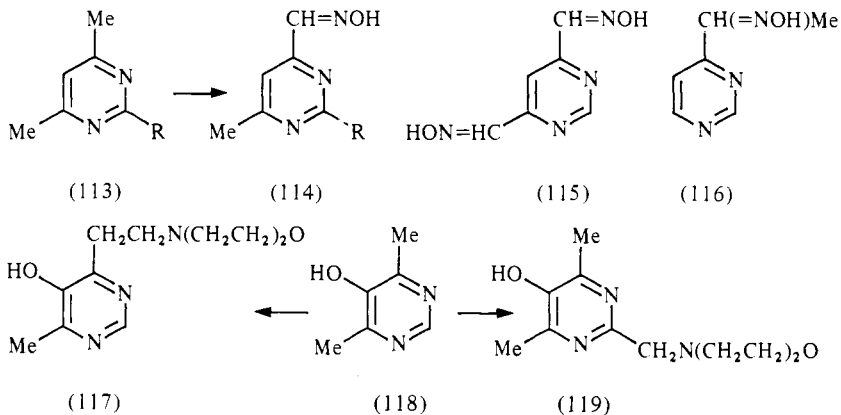
There have been few recent examples of the regular Claisen acylation of methylpyrimidines. However, the reaction is represented in the treatment of 1,6-dihydro-1,2,4-trimethyl-6-oxopyrimidine (105, $R = H$) with diethyl oxalate or ethyl benzoate in benzene containing sodium ethoxide to give 2-ethoxalylmethyl-1,6-dihydro-1,4-dimethyl-6-oxo- (105, $R = COCO_2Et$) or 1,6-dihydro-1,4-dimethyl-6-oxo-2-phenacylpyrimidine (105, $R = Bz$), respectively.⁵⁰⁹⁰ A variation of the reaction has also been reported in which an acyl chloride has been used in place of an ester; 4,6-dimethylpyrimidine (106) reacted with benzoyl chloride in benzene containing triethylamine to give 1-benzoyl-1,6-dihydro-6-methylene-4-phenacylpyrimidine (107) which, on boiling in butanol, was *N*-debenzoylated to give 4-methyl-6-phenacylpyrimidine (108). The *p*-chloro- and *p*-methoxyphenacyl analogues were obtained similarly,⁴⁸⁰³ as were other analogues.^{4808, 6380}



The use of nitrite or nitrate esters in alkaline media for "nitrosation" or nitration of methylpyrimidines is, of course, a Claisen reaction. For example, treatment of 4-methoxy-2,6-dimethylpyrimidine (109, $R = H$) with sodium amide in liquid ammonia followed by ethyl nitrite gave the nitroso derivative (109, $R = NO$), best written as 4-hydroxyiminomethyl-6-methoxy-2-methylpyrimidine (110);⁵⁰⁸⁹ 4,6-dimethylpyrimidine likewise gave 4-hydroxyiminomethyl-6-methylpyrimidine;⁵⁰⁷⁴ 2-benzyl-4-methoxy-6-methylpyrimidine reacted similarly, but at the more activated benzyl group, to give 2- α -hydroxyiminobenzyl-4-methoxy-6-methylpyrimidine (111);⁵⁰⁷⁴ 1,6-dihydro-1,2,4-trimethyl-6-oxopyrimidine (105, $R = H$) gave 1,6-dihydro-2-hydroxyiminomethyl-1,4-dimethyl-6-oxopyrimidine (rather than the

expected isomer, by attack at the 4-methyl group of the substrate);⁵⁰⁹⁰ and 4-methylpyrimidine in liquid ammonia containing sodium amide, reacted with propyl nitrate to give 4-nitromethylpyrimidine (112) in 71% yield.⁶²¹⁷

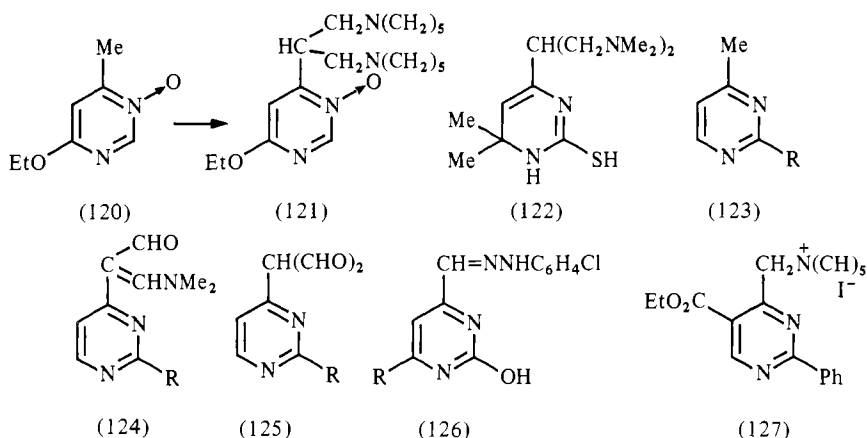
Methylpyrimidines have also been nitrosated by a completely different process involving treatment of their hydrochlorides with amyl nitrite in anhydrous ethanol. In this way, 4,6-dimethyl- (113, R = H) and 2,4,6-trimethylpyrimidine (113, R = Me) gave 4-hydroxyiminomethyl-6-methylpyrimidine (114, R = H) and its 2,6-dimethyl homologue (114, R = Me), respectively.⁵²⁸⁴ With an excess of reagent, 4,6-dimethylpyrimidine (114, R = H) gave 4,6-bishydroxyimino-methylpyrimidine (115) in 40% yield.⁵⁸⁶² 4-Ethylpyrimidine, under similar conditions, gave 4- α -hydroxyiminoethylpyrimidine (116).⁵⁸⁶² In addition, some such nitrosations have been carried out in aqueous nitrous acid. For example, 1,2-dihydro-1,4-dimethyl-2-oxopyrimidine with nitrous acid in 50% aqueous acetic acid at 0° gave 1,2-dihydro-4-hydroxyiminomethyl-1-methyl-2-oxopyrimidine,⁵⁴¹⁴ 2,4-dihydroxy-6-methyl-5-nitropyrimidine and aqueous acetic acid containing nitrous acid at 70° gave 2,4-dihydroxy-6-hydroxyiminomethyl-5-nitropyrimidine.⁵⁵⁷⁶ Other cases have been reported briefly.⁵²⁷⁸



(7) Mannich Reactions of Methylpyrimidines (H 132, E 91)

Although the Mannich reaction usually occurs at an activated methyl group attached to pyrimidine, it may also occur at the 5- or even the 2-position. Thus, treatment of 5-hydroxy-4,6-dimethylpyrimidine (118) with morpholine and *aqueous* formaldehyde gave only 5-hydroxy-4-methyl-6- β -morpholinoethylpyrimidine (117), whereas with morpholine and *anhydrous* paraformaldehyde it gave only 5-

hydroxy-4,6-dimethyl-2-morpholinomethylpyrimidine (119).⁶¹⁵⁰ The Mannich reaction may also attach *two* aminomethyl groupings on to a single methyl substituent. 4-Ethoxy-6-methylpyrimidine 1-oxide (120) with paraformaldehyde and piperidine hydrochloride in ethanol gave 4-ethoxy-6- β -piperidino- α -(piperidinomethyl)ethylpyrimidine 1-oxide (121) in reasonable yield,⁶⁰⁸⁹ and 1,6-dihydro-2-mercapto-4,6,6-trimethylpyrimidine with paraformaldehyde and dimethylamine hydrochloride in ethanol gave 4- β -dimethylamino- α -(dimethylaminomethyl)-ethyl-1,6-dihydro-2-mercapto-6,6-dimethylpyrimidine (122).⁴³⁵¹ Other such reactions have also been reported.^{4351, 4352}



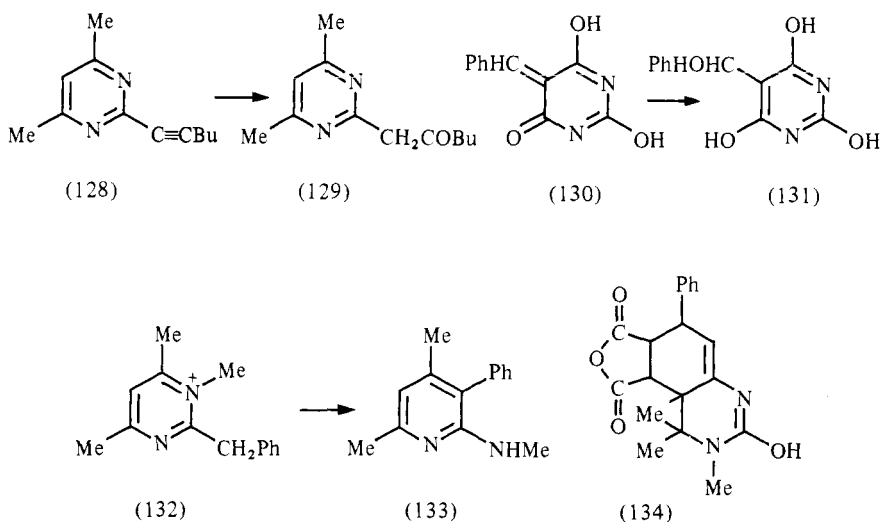
(8) Other Reactions of Alkyl and Aryl Pyrimidines (H 134, E 91)

Methylpyrimidines undergo the *Vilsmeier reaction* on treatment with dimethylformamide and phosphoryl chloride or phosgene. This has been illustrated in the conversion of 4-methylpyrimidine (123, R = H) by such means into the intermediate 4- β -dimethylamino- α -formylvinylpyrimidine (124, R = H) and thence, by treatment with sodium hydroxide, into 4-diformylmethylpyrimidine (125, R = H);^{5073, 5863} 4-methyl-2-phenylpyrimidine (123, R = Ph) likewise gave 4- β -dimethylamino- α -formylvinyl-2-phenylpyrimidine (124, R = Ph) and thence 4-diformylmethyl-2-phenylpyrimidine (125, R = Ph);⁵⁰⁷³ and 4-methyl-2-methylthiopyrimidine (123, R = SMe) gave 4-diformylmethyl-2-methylthiopyrimidine (125, R = SMe) in 35% yield without isolation of the intermediate (124, R = SMe).⁶⁰⁸⁷

The *formation of a C,N-bond* from methylpyrimidines has been done in several other ways. Thus, 2-hydroxy-4-methyl- and 2-hydroxy-4,6-dimethylpyrimidine with diazotized *p*-chloroaniline gave 4-*p*-chlorophenylhydrazonomethyl-2-hydroxypyrimidine (126, R = H) or its 6-methyl derivative (126, R = Me), respectively, in quantitative yield;⁵²⁶⁴ 5-ethoxycarbonyl-4-methyl-2-phenylpyrimidine with pyridine containing iodine gave 5-ethoxycarbonyl-2-phenyl-4-pyridiniopyrimidine iodide (127);⁵³⁷⁹ and 2,4-dihydroxy-5,6-dimethylpyrimidine was attacked by 3,5-dioxo-4-phenyl-1,2,4-triazoline in dimethyl sulfoxide to give 2,4-dihydroxy-5-methyl-6-(3',5'-dioxo-4'-phenyl-1',2',4'-triazolidin-1'-yl)methylpyrimidine.⁴⁴⁵¹

The "*hydration*" of an *alkynylpyrimidine* to the corresponding ketone has been illustrated in the treatment of 2-hex-1'-ynyl-4,6-dimethylpyrimidine (128) in refluxing aqueous acetone containing mercuric sulfate and sulfuric acid (or by a less direct method) to give 2-butyrylmethyl-4,6-dimethylpyrimidine (129); several analogous reactions were described.⁶³⁵³ The analogous "*hydration*" of 5-benzylidene barbituric acid and related derivatives occurred in two stages: after standing in dilute alkali at 15° for 20 min, the benzylidene compound (130) had been converted into the secondary alcohol, 2,4,6-trihydroxy-5- α -hydroxybenzylpyrimidine (131); after 2 h at 30°, however, the 5-substituent had been eliminated and only barbituric acid remained.⁴⁸⁸⁷

Kinetic and preparative data on the *deuteration* of methylpyrimidines have been reported.^{5184, 6274, 6321, 6322, 6325}



Transformations of *alkylpyrimidines into pyridines* have been reported; heating 2-benzyl-1,4,6-trimethylpyrimidinium iodide (132) in aqueous ethanolic triethylamine gave 2,4-dimethyl-6-methylamino-5-phenylpyridine (133).⁴⁸⁴¹ Other such transformations by quite different routes have been described.^{5263, 5290} A classical *Diels–Alder addition* of maleic anhydride to 1,6-dihydro-1,6,6-trimethyl-4-styrylpyrimidine gave the product (134) in excellent yield.⁴³³⁵ The *polymerization* of 1-vinyluracil in dioxane containing a little *N,N'*-azobisisobutyronitrile gave poly-1-vinyluracil conveniently.⁵⁵²⁸ Other examples have been mentioned.⁵⁰³¹ The *nitration* of 4-phenylpyrimidine in nitric acid and sulfuric acid at 0° gave a mixture of 4-*o*- and 4-*m*-nitrophenylpyrimidine. Similar nitration of 5-bromo-2-phenylpyrimidine gave a mixture of 5-bromo-4-*o*- and 5-bromo-4-*m*-nitrophenylpyrimidine.⁶¹⁵⁵

CHAPTER V

Nitro-, Nitroso-, and Arylazopyrimidines (*H* 138, *E* 94)

Although several 4/6-nitroso- and arylazopyrimidines have been known for some time, the first 2- and 4/6-nitropyrimidines have been made only recently.^{6267, 6293} This represents a milestone in pyrimidine chemistry.

1. The Nitropyrimidines (*H* 138, *E* 94)

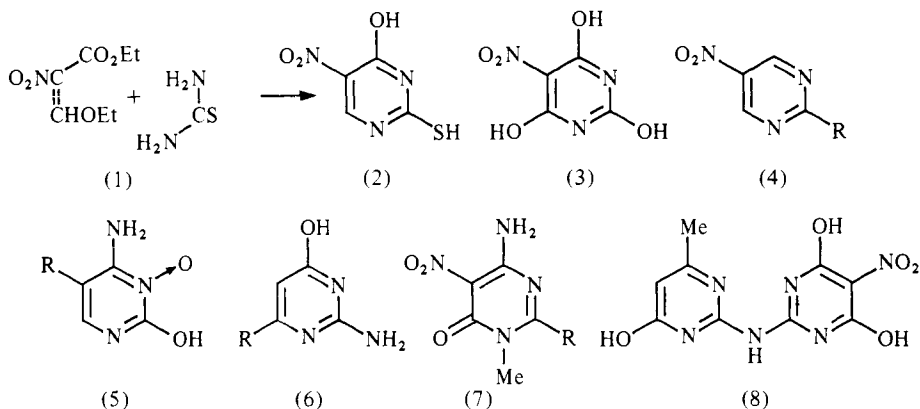
A. Preparation of Nitropyrimidines (*H* 138, *E* 95)

(1) *Nitropyrimidines by Primary Synthesis* (*H* 139, *E* 95)

Instances of the primary synthesis of nitropyrimidines from fragments already bearing a nitro group have been given in Ch. II and III. Typical examples could include the condensation of ethyl 3-ethoxy-2-nitroacrylate (1) with thiourea in aqueous dioxane containing alkali to give 4-hydroxy-2-mercapto-5-nitropyrimidine (2) in 71% yield;⁵⁴¹⁸ of diethyl α -nitromalonate with urea in ethanolic sodium ethoxide to give 2,4,6-trihydroxy-5-nitropyrimidine (dilituric acid: 3) in greater than 80% yield;⁴⁷⁴⁸ of α -nitromalondiamide with phosgene in toluene to give also dilituric acid (3);⁴⁷⁴⁸ and of 1,3-bisdimethylamino-2-nitrotrimethinium perchlorate with guanidine to give 2-amino-5-nitropyrimidine (4, R = NH₂).

(2) *Nitropyrimidines by Nitration* (*H* 139, *E* 95)

Some interesting data on the kinetics for nitration of 2-hydroxy- and 2,4-dihydroxypyrimidine and some of their *N*-methyl derivatives

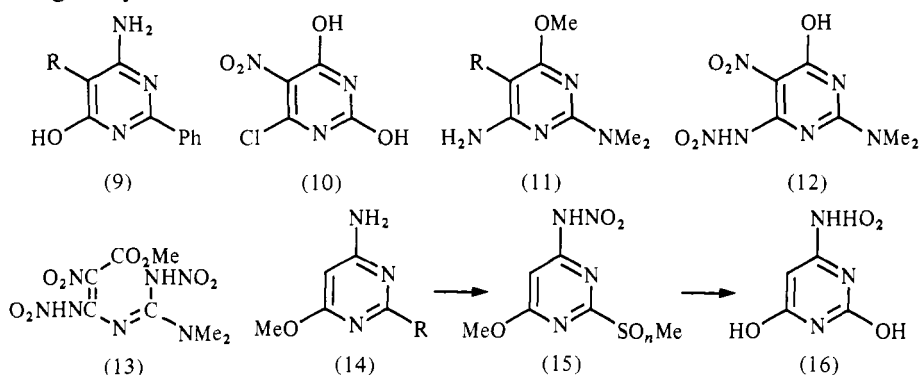


in sulfuric acid have been reported. It was concluded that such pyrimidines underwent nitration as above in their oxo/dioxo forms and as free bases, despite the high acidities involved.⁵³¹⁵

The successful nitration of 2-hydroxypyrimidine, previously reported (*E* 96) from preliminary communications has now been developed and extended to 4-hydroxypyrimidine.⁵⁴¹¹ Thus, both hydroxypyrimidines were dissolved in concentrated sulfuric acid and treated with solid potassium nitrate followed by heating at 95° for 20 h, to give 2-hydroxy-5-nitropyrimidine (4, R = OH) (50%) and 4-hydroxy-5-nitropyrimidine (40%), respectively. The former crystallized from ethanol as a stable ethanol adduct, which required prolonged heating in a vacuum to remove the solvent molecule.^{5411, 6372} The same vigorous process was adopted for the difficult nitration of 4-amino-2-hydroxypyrimidine 3-oxide (5, R = H) to its 5-nitro derivative (5, R = NO₂) in 86% yield.⁵⁴²⁶ It was also successful in converting 2-amino-4-hydroxy-6-methylpyrimidine (6, R = Me) into its 5-nitro derivative, but when applied to 2-amino-4-carboxymethyl-6-hydroxypyrimidine (6, R = CH₂CO₂H) only oxidation occurred to give 2-amino-4-carboxy-6-hydroxypyrimidine (6, R = CO₂H).⁵⁷⁶³

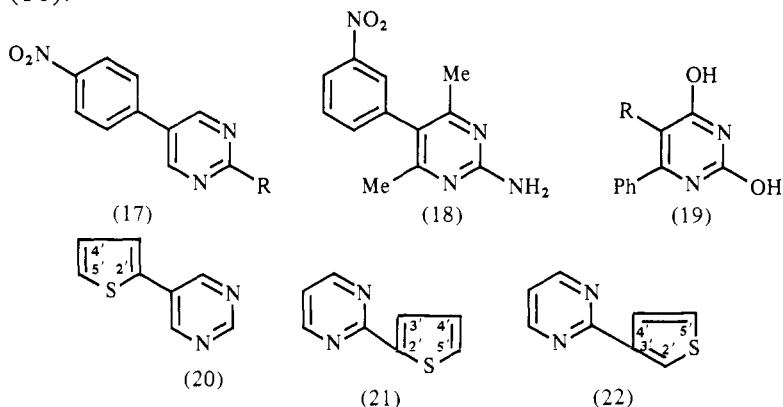
Less vigorous conditions were sufficient to convert appropriate substrates into 4,6-dihydroxy-5-nitropyrimidine (fuming nitric acid in acetic acid at 20°),⁵⁶¹⁹ 2-*t*-butyl-4,6-dihydroxy-5-nitropyrimidine (as above; 94% yield),⁵⁷⁵³ 4-*t*-butyl-2,6-dihydroxy-5-nitropyrimidine (fuming nitric acid in sulfuric acid at 30°),⁵⁷⁵³ 4-amino-2-dimethylamino-6-hydroxy-5-nitropyrimidine (fuming nitric acid in sulfuric acid at 0–5°),⁴⁶³² 2,4-diamino-1,6-dihydro-1-methyl-5-nitro-6-oxopyrimidine (7, R = NH₂, as above),⁴⁶³² 1-cyclohexyl-6-methyl-5-nitrouracil (nitric acid in sulfuric acid at 5°),⁴⁹²⁵ 5-nitro-2-picrylamino- and 5-nitro-2,4,6-trispiroaminopyrimidine (fuming nitric acid at 110° and

75°, respectively),⁵⁵⁹³ 4',6,6'-trihydroxy-4-methyl-5'-nitrodiprimidin-2-ylamine (8) (nitric acid in sulfuric acid at 25°),⁵³⁹⁴ and related products.^{4570, 4925} An unusual and effective procedure has been reported: treatment of 2,4-dihydroxypyrimidine, 1-methyluracil, or 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine with nitronium tetrafluoroborate in sulfolane at 20° gave the corresponding 5-nitro derivatives in excellent yield.⁵⁵¹⁶ Although the method was unsuccessful in producing nitrated nucleosides, at least one nitrated nucleotide was so produced.⁵⁵¹⁶ Another unusual reagent for nitration was nitrous acid, but it appeared that the mechanism involved initial formation of a nitroso derivative followed by oxidation.⁴⁹⁷² For example, treatment of 4-amino-6-hydroxy-2-phenylpyrimidine (9, R = H) or its preformed 5-nitroso derivative (9, R = NO) in 80% sulfuric acid with 4 equivalents of sodium nitrite gave the corresponding 5-nitro derivative (9, R = NO₂) in good yield.⁴⁹⁷²



Successful nitrations in the presence of labile groups have been well represented in the direct formation of 4-amino-6-dimethylamino-2-methylthio-5-nitropyrimidine (potassium nitrate in sulfuric acid at 0°, 42%),⁴⁶¹⁷ 4-amino-1,6-dihydro-1-methyl-2-methylthio-5-nitro-6-oxopyrimidine (7, R = SMe) (fuming nitric acid in sulfuric acid at 5°, 51%),⁴⁶³² 4-amino-2,6-dimethoxy-5-nitropyrimidine (as above),⁵⁷¹⁰ 4-acetamido-2-dimethylamino-6-methoxy-5-nitropyrimidine (as above),⁴⁶³³ 4-chloro-2,6-dimethoxy-5-nitropyrimidine (as above, but finally at 80°, 76%),⁵⁹⁹⁴ 4-chloro-2,6-dihydroxy-5-nitropyrimidine (10) (fuming nitric acid in sulfuric acid at 4°, 70%),^{4511, 5387} 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine (as above).^{4511, 5435} 2-amino-4-chloro-6-hydroxy-5-nitropyrimidine (nitrate salt of substrate in sulfuric acid at 0°,^{5627, 5646} or fuming nitric acid in sulfuric acid at 35°),^{5229, 5637, 5646} and 2,4-diamino-6-chloro-5-nitropyrimidine (fuming nitric acid in sulfuric acid at 30°, 62%).⁵⁶²⁰

An interesting nitration is that of 4-amino-2-dimethylamino-6-methoxypyrimidine (11, R = H), which on treatment with fuming nitric acid in sulfuric acid at 5° gave a separable mixture of the expected 5-nitro derivative (11, R = NO₂), 2-dimethylamino-4-hydroxy-5-nitro-6-nitroaminopyrimidine (12), and the acyclic ester (13).⁴⁶³³ Treatment of 4-amino-6-methoxy-2-methylthiopyrimidine (14, R = SMe) with an excess of fuming nitric acid at 0° induced *S*-oxidation and *N*-nitration to give 4-methoxy-2-methylsulfinyl-6-nitroaminopyrimidine (15, *n* = 1). As might be expected, preoxidation of the thioether (14, R = SMe) to 4-amino-6-methoxy-2-methylsulfonylpyrimidine (14, R = SOME) followed by similar nitration gave a better yield of the same nitroamine (15, *n* = 1), and more extensive oxidation of the thioether (14, R = SMe) to 4-amino-6-methoxy-6-methylsulfonylpyrimidine (14, R = SO₂Me) followed by nitration gave 4-methoxy-2-methylsulfonyl-6-nitroaminopyrimidine (15, *n* = 2).⁴⁶⁵⁶ The nitroamines proved remarkably stable and survived a number of nucleophilic replacements performed on the other groups to give, for example, 2,4-dihydroxy-6-nitroaminopyrimidine (16).⁴⁶⁵⁶

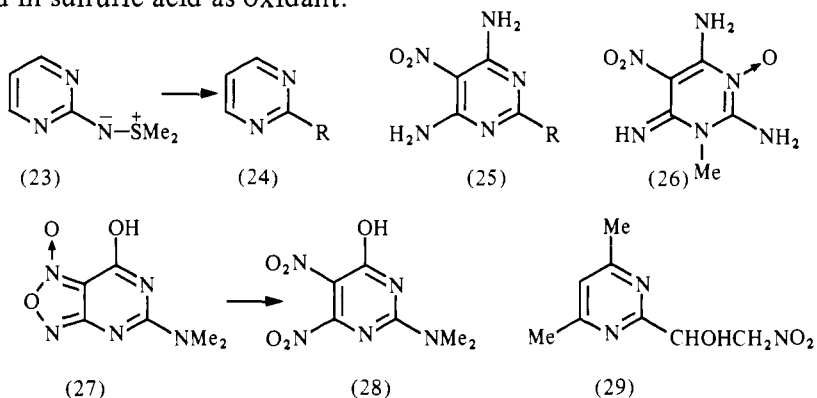


The nitration of phenylpyrimidines in the phenyl ring has been reported quite frequently, but it is still impossible to forecast the position of entry. Thus, 4-phenylpyrimidine gave a mixture of 4-*o*- and 4-*m*-nitrophenylpyrimidine, and 5-chloro-4-phenylpyrimidine behaved similarly to give 5-chloro-4-*o*- and 5-chloro-4-*m*-nitrophenylpyrimidine, albeit in different ratios.⁶¹⁵⁵ In contrast, 2-amino-, 2-methylamino-, and 2-methylsulfonyl-5-phenylpyrimidine gave only their respective *p*-nitro derivatives (17, R = NH₂, NHMe, or SO₂Me),⁵⁶⁶³ whereas 2-amino-4,6-dimethyl-5-phenylpyrimidine gave its *m*-nitro derivative (18) with a trace of the *p*-isomer, but 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine gave only the *p*-nitro derivative.⁵⁶⁶² 2,4-Dihydroxy-6-phenylpyrimidine

(19, R = H) gave, according to conditions, its 5-nitro (19, R = NO₂), its *p*-nitro, its 5,*m*-dinitro, or its 5,*p*-dinitro derivative, each in reasonable yield.⁵⁴⁴¹ The nitration of thienylpyrimidines takes place readily in the thiophene ring. Thus, 5-thien-2'-ylpyrimidine (20) gave (nitric acid/sulfuric acid at 0°) as separable mixture of 5-4'(and 5')-nitrothien-2'-lypyrimidine in 80% overall yield;⁴⁴⁰⁶ 2-thien-2'-ylpyrimidine (21) likewise gave 2-4'(and 5')-nitrothien-2'-ylpyrimidine, but acetyl nitrate at 35° gave, in addition, some 2-3'-nitrothien-2'-ylpyrimidine;⁴⁸⁹¹ and 2-thien-3'-ylpyrimidine (22) gave, with either reagent, 2-2'(and 4', and 5')-nitrothien-3'-ylpyrimidine as well as 2-2',5'-dinitrothien-3'-ylpyrimidine.⁴⁸⁹¹

(3) Nitropyrimidines by Indirect Syntheses (*H* 142, *E* 97)

The oxidation of nitroso- to nitro-pyrimidines has proven of great value. Thus, 2-aminopyrimidine was converted^{5261, 6375} into 2-*S,S*-dimethylsulfimidopyrimidine (23) and thence by oxidation into 2-nitrosopyrimidine (24, R = NO), which underwent oxidation by ozone to give 2-nitropyrimidine (24, R = NO₂), the first such compound ever prepared.⁶²⁶⁷ Less spectacular examples include the preparation, from the corresponding 5-nitroso derivatives, of 4,6-diamino-5-nitropyrimidine (25, R = H) and its 2-methyl derivative (25, R = Me) using hydrogen peroxide in trifluoroacetic acid;⁵⁶⁴⁷ 2,4-diamino-6-anilino-5-nitropyrimidine;⁵¹⁸⁸ 2,4-diamino-1,6-dihydro-6-imino-1-methyl-5-nitropyrimidine 3-oxide (26) (from the nitroso analogue lacking the *N*-oxide substituent);⁵¹⁸⁸ 2-amino-4-amyloxy-6-methylamino-5-nitropyrimidine;⁴⁶⁵⁵ a separable mixture of 2,4,6-triamino-5-nitropyrimidine 1-oxide and 1,3-dioxide (from 2,4,6-triamino-5-nitrosopyrimidine, as above);⁶²³⁵ and 2-amino-4,6-dihydroxy-5-nitropyrimidine, using nitrous acid in sulfuric acid as oxidant.⁴⁹⁷²



Another interesting but specialized oxidative route has led to a 4,5-dinitropyrimidine. A longish synthesis gave 5-dimethylamino-7-hydroxy[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxide (27), which reacted with manganese dioxide in dimethylformamide to give 2-dimethylamino-4-hydroxy-5,6-dinitropyrimidine (28) in excellent yield.⁶²⁹³

Naturally it is possible to add a group already bearing a nitro substituent to a pyrimidine in all sorts of ways. Such a process is exemplified in the condensation of 4-methylamino-3-nitrobenzaldehyde with 1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxypyrimidine to give hexahydro-1,3-dimethyl-5-(4'-methyl-3'-nitrobenzylidene)-2,4,6-trioxypyrimidine;⁵¹⁸³ of 2-formyl-4,6-dimethylpyrimidine with nitromethane to give 2- α -hydroxy- β -nitroethyl-4,6-dimethylpyrimidine (20);⁴⁸³⁶ of 2-chloropyrimidine with *p*-nitrobenzenethiol to give 2-*p*-nitrophenylthiopyrimidine;⁶⁰⁴⁵ and of 4-amino-2,5-dihydroxypyrimidine with diazotized *p*-nitroaniline to give 4-amino-2,5-dihydroxy-6-*p*-nitrophenylazopyrimidine.⁶³⁷²

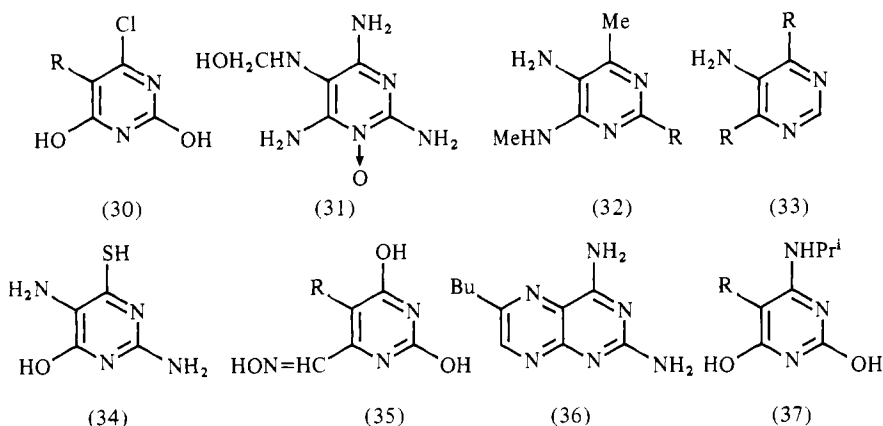
B. Reactions of Nitropyrimidines: Mainly Reduction (*H* 143, *E* 99)

The usual reason for introducing a nitro group is to afford an amino group at the same position. Many and varied have been the means employed to reduce nitro groups. Although the presence of other groups sometimes influences the choice of reagent, personal preference and experience seem to have played a large part.

The use of *hydrogenation over platinum* is infrequent but is exemplified in the reduction of 4-chloro-2,6-dihydroxy-5-nitro- (30, R = NO₂) in acetic anhydride under pressure to 5-acetamido-4-chloro-2,6-dihydroxypyrimidine (30, R = NHAc) in 61% yield,⁵³⁸⁷ and of 4-amino-6-dimethylamino-2-methylthio-5-nitro- to 4,5-diamino-6-dimethylamino-2-methylthiopyrimidine followed by immediate conversion into a pteridine to avoid isolation of the unstable triamine. Other examples have been described.⁴⁷⁹⁵

Hydrogenation over palladium has been used to convert the corresponding 5-nitropyrimidines into 4,5-diamino-6-propylaminopyrimidine (isolated as hydrochloride, 62%),⁵⁸⁷¹ 4,5-diamino-6-(4'-diethylamino-1'-methylbutyl)aminopyrimidine (as hydrochloride, 74%),⁵²³⁰ 5-amino-6-*N*-ethyl-*p*-toluidino-3-methyluracil (in ethanolic acetic acid, 90% yield; also 10 analogous examples),⁵⁰¹⁶ and 2,4,5,6-tetra-aminopyrimidine 1-oxide (in water under 5 atmospheres).⁶²³⁵ Similar hydrogenation of 2,4,6-triamino-5-nitropyrimidine 1-oxide in

formic acid gave 2,4,6-triamino-5-*N*-(hydroxymethyl)aminopyrimidine 1-oxide (31).⁶²³⁵ Such reduction of 2-chloro-4-methyl-6-methylamino-5-nitropyrimidine in ethanolic ammonia additionally removed the chloro substituent to give 5-amino-4-methyl-6-methylaminopyrimidine (97%).⁵⁴³² A palladium catalyst with hydrazine has also been used to reduce 5-nitro- to 5-aminopyrimidines. 5-Amino-1 (and 3)-methyluracil (>89%)⁵⁴⁴⁸ as well as 5-amino-2-morpholinopyrimidine⁵²⁸⁵ were obtained in this way.



Hydrogenation over Raney nickel has remained the most popular way to reduce nitropyrimidines. In this way were formed 2-acetamido-5-amino-4,6-dichloropyrimidine,^{5229, 5637} 5-amino-4,6-dichloropyrimidine (in anhydrous methanol, 83%),⁵⁶¹⁹ 4,5-diamino-2-dimethylamino-1,6-dihydro-1-methyl-6-oxopyrimidine (in aqueous ethanol; used crude),⁴⁶³² 4,5-diamino-2-chloro-6-trifluoromethylpyrimidine (in methanol, 70%), 2,5-diamino-4-hydroxy-6-methylaminopyrimidine (in aqueous alkali, 88% as hydrochloride;⁵⁸⁴² in ethanol, 45% as dihydrochloride⁴⁶²⁸), 5-amino-4-methyl-6-methylamino-2-piperidinopyrimidine (73%),⁵⁶⁸⁵ 5-amino-4-hydroxy-2-methyl-6-methylaminopyrimidine (69%),⁵⁶⁸⁰ 4,5-diamino-6-benzylaminopyrimidine,⁴⁷⁹⁵ 5-amino-4-methoxy-6-semicarbazidopyrimidine (in methanol; 50%),⁵⁶⁷⁴ 4,5-diamino-6-piperidinopyrimidine,⁴⁷⁸⁹ 5-amino-2,4-dimethyl-6-methylaminopyrimidine (32, R = Me) (96%),⁵⁶⁷⁰ 5-amino-2-methoxy-4-methyl-6-methylaminopyrimidine (32, R = OMe),⁵⁶⁷⁰ and other 5-aminopyrimidines.^{4623, 5356, 5661, 5767} Nickel-catalyzed reductions of extranuclear nitropyrimidines has been found convenient to give, for example, 5-*p*-aminophenyl-2-methoxy-,⁵⁶³⁵ 2-amino-5-*p*-aminophenyl-,⁵⁶⁶³ and 2-amino-5-*p*-aminophenyl-4,6-dimethylpyrimidine.⁵⁶⁶² Treatment of 4,6-

bismethylthio-5-nitropyrimidine with a massive amount of Raney nickel catalyst (without a hydrogen atmosphere) gave a separable mixture of 5-amino-4,6-bismethylthiopyrimidine (33, R = SMe) and its desulfurized product 5-aminopyrimidine (33, R = H).⁶³⁷⁴

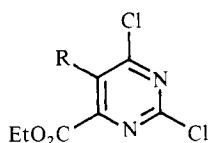
The traditional reducing agent, *sodium hydrogen sulfide*, has continued to be used for reducing nitropyrimidines, especially if a chloro is to be converted into a mercapto substituent at the same time. Thus, 2-amino-4-chloro-6-hydroxy-5-nitropyrimidine with methanolic sodium hydrogen sulfide gave 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (34) in good yield,⁴⁷⁶⁶ and 4,6-dichloro-2-methyl-5-nitropyrimidine and aqueous sodium hydrogen sulfide gave 5-amino-4,6-dimercapto-2-methylpyrimidine (95%).⁵⁶⁸⁹ Other examples have also been reported.^{4570, 5441, 5677}

The rapid and convenient reduction of 5-nitropyrimidines by *sodium dithionite* (sodium hydrosulfite) has been used extensively in the absence of labile groups. Such reduction has given 4,5-diamino-2-dimethylamino-6-trifluoromethylpyrimidine (in aqueous acetone, > 80%),⁵⁸²³ 5-amino-4-hydroxy-2-mercaptopyrimidine (in water, 58%),⁵⁴¹⁸ 5-amino-4-ethyl-2-mercapto-6-methylaminopyrimidine (in dilute alkali, *c.* 50%),⁵⁶⁷⁷ 4,5-diamino-6-methyl-2-phenylpyrimidine (in aqueous sodium hydrogen carbonate, *c.* 40%),⁵⁴³⁹ 5-amino-2,4-dihydroxy-6-methoxycarbonylpyrimidine (about 10°, 66%),⁵⁷⁶⁷ and other amines.^{4630, 4985, 5078, 5443, 6134} However, sodium dithionite sometimes has untoward (or desirable) effects; 2,4,6-triamino-5-nitropyrimidine *N*-oxide gave 2,4,5,6-tetra-aminopyrimidine,⁶²³⁵ 2-amino-4-hydrazino-6-hydroxy-5-nitropyrimidine gave 2,4,5-triamino-6-hydroxypyrimidine,⁵²³⁴ and 2,4-dihydroxy-6-hydroxyiminomethyl-5-nitropyrimidine (35, R = NO₂) gave 5-amino-2,4-dihydroxy-6-hydroxyiminomethylpyrimidine (35, R = NH₂; with the oxime intact!).⁵⁵⁷⁶

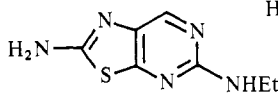
Although sometimes considered archaic, reduction of nitropyrimidines by *tin* (*stannous chloride*), *zinc*, or *iron* has given good results. Thus, stannous chloride reduction of the corresponding nitropyrimidines gave 4,5-diamino-6-*t*-butyl-2-chloropyrimidine (90%),⁵⁷⁵³ 5-amino-2-diethylamino-4,6-diphenylpyrimidine (in poor yield),⁶¹⁴⁷ 5-amino-4,6-dichloropyrimidine (*c.* 60%),⁵⁷⁸⁴ and other such amines.^{5784, 6147} Zinc reductions have been used in two specialized ways. Reduction of 2,4-diamino-5-nitro-6-*N*-(valeryl-methyl)aminopyrimidine in glacial acetic acid with zinc dust was followed by spontaneous cyclization to a dihydropteridine, which was aromatized by the addition of hydrogen peroxide to give 2,4-diamino-6-butylpteridine (36) as product.⁵³⁰⁷ Several analogous reductive cyclizations have been reported.^{5304, 5307}

The well-known use of zinc in formic acid to convert nitro- into formamidopyrimidines prior to cyclization to purines has been neglected recently. However, such a reduction has been used in one laboratory as a method of choice, with subsequent removal of the unwanted *N*-formyl groups in methanolic hydrogen chloride. Thus, 2,4-dihydroxy-6-isopropylamino-5-nitropyrimidine (37, $R = \text{NO}_2$) gave 5-formamido-2,4-dihydroxy-6-isopropylaminopyrimidine (37, $R = \text{NHCHO}$) and thence 5-amino-2,4-dihydroxy-6-isopropylaminopyrimidine (37, $R = \text{NH}_2$).⁴⁶²⁷ Similar procedures gave 2,5-diamino-4-anilino-6-hydroxypyrimidine,⁴⁶³⁵ 2,5-diamino-4-hydroxy-6-isopropylaminopyrimidine,⁴⁶³⁵ and analogues.^{4620, 4627, 4635} Iron reduction of nitropyrimidines has been represented in the conversions of 2,4-dichloro-6-ethoxycarbonyl-5-nitropyrimidine (38, $R = \text{NO}_2$), by iron powder in glacial acetic acid, into 5-amino-2,4-dichloro-6-ethoxycarbonylpyrimidine (38, $R = \text{NH}_2$) in c. 80% yield;⁵²⁶⁰ of 4,6-dichloro-5-nitro- similarly into 5-amino-4,6-dichloro-2-phenylpyrimidine (90%);⁵⁷⁹² of 2-ethylamino-5-nitro-4-thiocyanatopyrimidine similarly into 5-amino-2-ethylamino-4-thiocyanatopyrimidine, which cyclized spontaneously to 2-amino-5-ethylaminothiazolo[5,4-*d*]pyrimidine (39);⁵⁷⁴² and of 1,2-dihydro-2-imino-1-methyl (or 1,4,6-trimethyl)-5-*p*-nitrophenylpyrimidine hydroiodide, by iron powder in ethanol containing a little hydriodic acid and a trace of ferrous sulfate, into 5-*p*-aminophenyl-1,2-dihydro-2-imino-1-methylpyrimidine hydriodide (40, $R = \text{H}$) or its 1,4,6-trimethyl homologue (40, $R = \text{Me}$), respectively, in greater than 70% yield, without the risk of Dimroth rearrangement.^{5662, 5663}

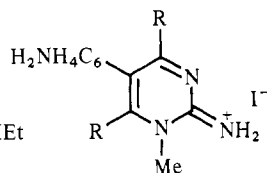
Nitropyrimidines undergo several *other reactions*, outlined briefly below. Treatment of 1,2,3,4-tetrahydro-1,3-dimethyl-5-nitro-2,4-dioxypyrimidine (41) with malondiamide and sodium ethoxide at



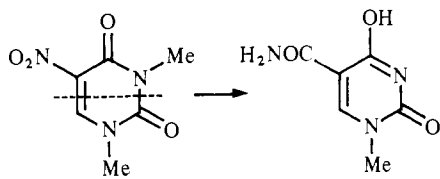
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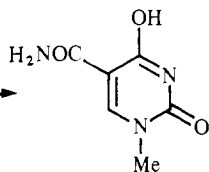
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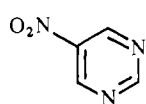
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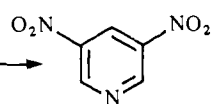
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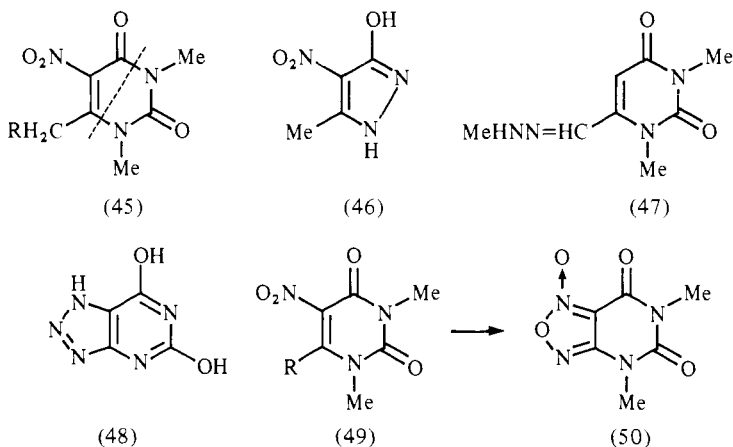


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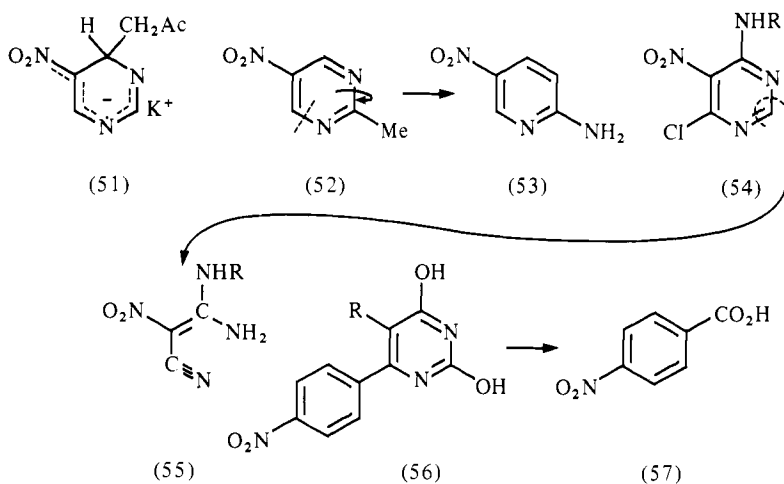


(44)

reflux gave 5-carbamoyl-1-methyluracil (42) and *N*-methyl-2-nitroacetamide. Several other 1,3-disubstituted nitrofuracils behaved similarly.⁶⁰³⁴ 5-Nitropyrimidine (43) in boiling dilute acetic acid gave 3,5-dinitropyridine (44) in almost 50% yield by a plausible mechanism involving covalent hydration, ring fission, partial degradation with loss of hydrogen cyanide, and recombination of fragments.⁵⁹³⁸ 1,2,3,4-Tetrahydro-1,3,6-trimethyl-5-nitro-2,4-dioxypyrimidine (45, R = H) reacted with hydrazine in refluxing propanol to give 3-hydroxy-5-methyl-4-nitropyrzole (46), but 4-bromomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine (45, R = Br) reacted with methylhydrazine to give 1,2,3,4-tetrahydro-1,3-dimethyl-6-*N'*-methylhydrazonomethyl-2,4-dioxypyrimidine (47) in which the nitro group had been eliminated.⁴⁹⁴³ Another elimination of a nitro group, probably as nitrous acid, occurred when 2,4-dihydroxy-5-nitropyrimidine reacted with sodium azide in dimethylformamide to give 5,7-dihydroxy-*v*-triazolo[4,5-*d*]pyrimidine ("8-azaxanthine"; 48) in 86% yield. This reaction was developed considerably to be a useful synthesis for a variety of such triazolopyrimidines.^{5406, 5408} In contrast, 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine (49, R = Cl) with sodium azide in tetrahydrofuran gave the corresponding 4-azido derivative (49, R = N₃) which, on refluxing in dimethylformamide, lost nitrogen to give 4,5,6,7-tetrahydro-4,6-dimethyl-5,7-dioxo[1,2,5]oxadiazolo[4,5-*d*]pyrimidine 1-oxide (50) in which the nitro group had been incorporated.⁴⁹⁹³ Similarly 4-bromomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine and methylamine under vigorous conditions gave 4,5,6,7-tetrahydro-2,4,6-trimethyl-5,7-dioxopyrazolo[4,3-*d*]pyrimidine 1-oxide.⁴⁹⁴⁵ Other complicated cyclizations, involving a nitro group attached to pyrimi-



dines, have been described.^{4988, 4989, 5014} *Sigma* complexes of 5-nitropyrimidine and its methoxy derivatives have been obtained by treatment with potassium hydroxide in acetone; the complex (51) and related entities have been isolated and characterized.⁶¹⁴⁴ Unlike 5-nitropyrimidine in acetic acid (see above), 2-methyl-5-nitropyrimidine (52) in aqueous alcoholic alkali gave 2-amino-5-nitropyridine (53) in good yield by a ring-fission mechanism.⁴⁸¹² Similar conversions, especially of pyrimidinium salts into pyridines, were described.⁴⁸¹² As might be expected from the above, nitropyrimidines are also prone to ring-fission without recyclization, that is, degradation. For example, on prolonged boiling in 60% acetic acid, 4-amino-6-chloro-5-nitropyrimidine (54, R = H) gave 3,3-diamino-2-nitroacrylonitrile (55, R = H) and some 4-amino-6-hydroxy-5-nitropyrimidine; 4-chloro-6-ethylamino-5-nitropyrimidine (54, R = Et) gave mainly 3-amino-3-ethylamino-5-nitroacrylonitrile (55, R = Et) and a little of the same hydroxypyrimidine; and tertiary amines, such as 4-chloro-5-nitro-6-piperidinopyrimidine, gave only the acyclic products, 3-amino-2-nitro-3-piperidinoacrylonitrile or analogues.⁵⁴⁴² The reaction was further exemplified by the degradation of 4-benzylamino-6-chloro-5-nitropyrimidine (54, R = CH₂Ph) in 50% aqueous dioxane (without acid) to give, after 14 days, 3-amino-3-benzylamino-2-nitroacrylonitrile (55, R = CH₂Ph) in *c.* 60% yield.⁵⁴³³ Oxidative degradation of 2,4-dihydroxy-6-*p*-nitrophenylpyrimidine (56, R = H) or its 5-nitro derivative (56, R = NO₂) by permanganate gave *p*-nitrobenzoic acid (57) as the sole isolable product.⁵⁴⁴¹ The above and other ring-cleavage reactions of pyrimidines have been reviewed.⁵⁸⁰³



Sundry biological activities of a low order have been attributed to nitropyrimidines.^{6046, 6376}

5-Nitropyrimidine underwent inverse Diels–Alder cycloadditions with ketene acetals and so forth to give 3-nitropyridine derivatives.⁶³⁸⁹ It also reacted with 2-phenylacetamides to give eventually 2-amino-5-nitro-3-phenylpyridine and other products.⁶⁵²⁵

2. Nitrosopyrimidines (*H* 146, *E* 102)

Little fundamental work has appeared recently on nitrosopyrimidines. Indeed, it is still true that the tautomeric structure and/or cis-trans configuration of 5-nitrosopyrimidines has not been determined beyond doubt, for example in respect of 4-amino-2,6-dihydroxy-5-nitrosopyrimidine⁵⁴²³ or 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine.⁴⁶⁰⁸ Physical properties of the latter and of the complex it forms with cupric nitrate have been studied extensively.^{4608–4612} After screening a dozen nitrosopyrimidines, a useful method was developed for determining Fe^{2+} spectrophotometrically by its blue complex with 2-dimethylamino-4,6-dihydroxy-5-nitrosopyrimidine.⁵¹⁶⁵ 4-Amino-2-dimethylamino-6-hydroxy-5-nitrosopyrimidine likewise formed a blue complex with Fe^{2+} and a yellow one with Co^{3+} , so that both ions could be determined in the same solution by absorption measurements at appropriate wavelengths.⁵¹³⁰ Other useful reagents for Fe^{2+} and Co^{2+} were 6-amino-1-methyl-5-nitroso-2-thiouracil and 6-amino-5-nitroso-1-phenyl-2-thiouracil.⁵¹²⁷ *S*-Alkylation of the above and other nitroso-2-thiouracils produced another set of useful reagents for Fe^{2+} , Co^{2+} , and Co^{3+} , and the structure of the isolated complexes were examined by spectral and magnetic susceptibility measurements.⁶¹⁶⁸

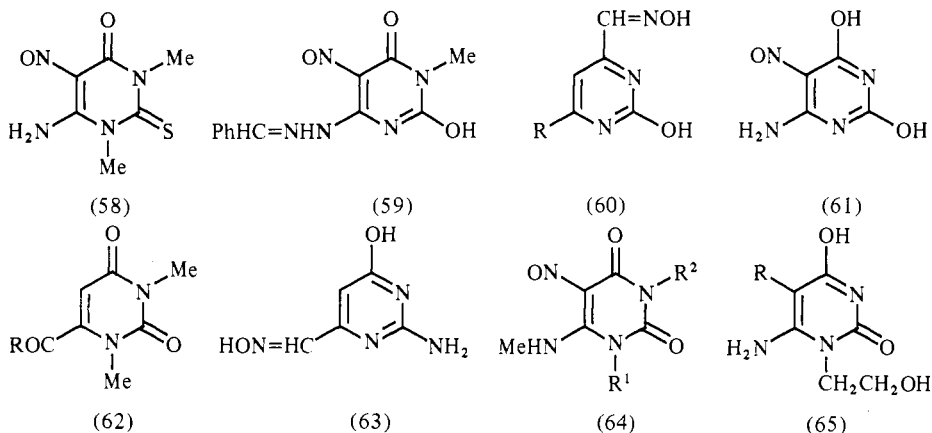
The activation of leaving groups by a nitroso group has been demonstrated dramatically by the conversion of 4-amino-6-hydroxy-2-methylthio- into 4-amino-2-dimethylamino-6-hydroxy-5-nitrosopyrimidine by boiling with aqueous dimethylamine for 20 min.⁵⁸²⁰

A. Preparation of Nitrosopyrimidines (*H* 147, *E* 102)

Most nitrosopyrimidines are still made by nitrosation of an existing pyrimidine but a few have been made by primary synthesis or other indirect means.

(1) *Nitrosopyrimidines by Nitrosation* (*H* 148, *E* 102)

Many nitrosations have been carried out by the addition of aqueous sodium nitrite to a solution of the pyrimidine in dilute acetic acid; however, the concentrations, order of addition, reaction temperature, and time have been varied widely and apparently without logic. The process is illustrated in the formation of the following compounds: 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-6-oxo-2-thiopyrimidine (58),⁴⁶¹⁶ 3-methyl-5-nitroso-6-propylaminouracil (86%),⁵⁰⁰² 4-hydroxy-6-methylamino-5-nitroso-2-phenylpyrimidine (96%),⁵⁰⁰² 2,4-diamino-6-amyloxy-5-nitrosopyrimidine,⁴⁶²⁴ 4,6-diamino-1,2-dihydro-1-methyl-5-nitroso-2-oxopyrimidine,⁵²⁴⁵ 2,4-diamino-6-methylthio-5-nitrosopyrimidine,⁵⁷⁴⁴ 2,4,6-triamino-5-nitrosopyrimidine (99%),⁴⁶⁴³ 2-amino-4-dimethylamino-6-methylamino-5-nitrosopyrimidine,⁴⁶²³ 6-benzylidenediazino-3-methyl-5-nitrosouracil (59),⁴⁹⁸⁹ 4-amino-2-dimethylamino-6-methoxy-5-nitrosopyrimidine,⁴⁶³² and others.^{4628, 5182} A similar process has caused nitrosation of an activated methyl substituent. As well as examples already given [Ch. IV, Sect. 2.C. (6)], the conversion of 4-carboxymethyl-2,6-dihydroxypyrimidine into 2,4-dihydroxy-6-hydroxyiminomethylpyrimidine (60, *R* = OH),⁵⁸⁶⁸ and of 2-hydroxy-4-methyl- into 2-hydroxy-4-hydroxyiminomethylpyrimidine (60, *R* = H) should be mentioned.⁵⁶²¹



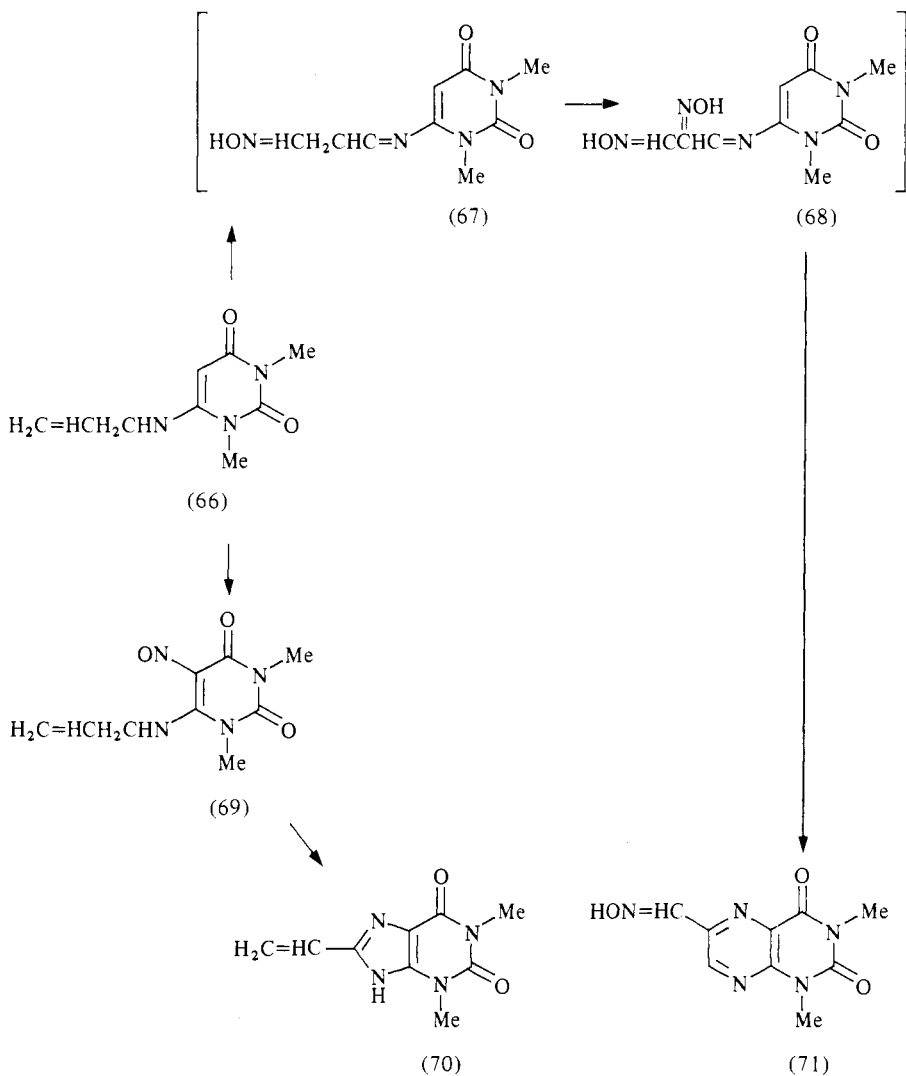
Hydrochloric or other mineral acid has been used in place of acetic acid for nitrosations, perhaps for improved solubility of weakly basic substrates or simply as a personal preference. This variation has been used to make 4-amino-2,6-dihydroxy-5-nitrosopyrimidine (61)^{4574, 5423} and 6-amino-1-methoxy-5-nitrosouracil (>95%),⁵⁴²⁵ to convert (with an additional reaction in each case) 4-hydrazinocarbonyl-1,2,3,6-tetra-

hydro-1,3-dimethyl-2,6-dioxypyrimidine (62, $R = \text{NHNH}_2$) into 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxypyrimidine, perhaps *via* the corresponding 4-azidocarbonyl analogue (62, $R = \text{N}_3$), which was isolated if the reaction was carried out at 0° instead of $20\text{--}25^\circ$; 1-aminobarbituric acid into 2,4,6-trihydroxy-5-nitrosopyrimidine;⁵¹⁸⁶ and 2-amino-4-carboxymethyl-6-hydroxy- into 2-amino-4-hydroxy-6-hydroxyiminomethylpyrimidine (63).⁵⁷⁶³

It has been reported⁴⁶⁵⁷ that 1,3-dialkyl-1,2,3,4-tetrahydro-6-methylamino-5-nitroso-2,4-dioxypyrimidines (64) are particularly difficult to prepare in good yield by regular nitrosation as above. For example, the 1-ethyl-3-methyl compound (64, $R^1 = \text{Et}$, $R^2 = \text{Me}$) was so formed only in 12% yield. However, by treating the appropriate substrate in ethanol with isoamyl nitrite at $20\text{--}25^\circ$, yields were improved appreciably to give, for example, the 1-benzyl-3-methyl homologue (64, $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Me}$) in 29% yield and the 1,3-dicyclohexyl homologue (64, $R^1 = R^2 = \text{C}_6\text{H}_{11}$) in 42% yield.⁴⁶⁵⁷ By treating 6-amino-1- β -hydroxyethyluracil (65, $R = \text{H}$) in aqueous ethanol with isoamyl nitrite, its 5-nitroso derivative (65, $R = \text{NO}$) resulted in 71% yield.⁶⁰²⁰

Some nitrosations are followed spontaneously by cyclization. For example, 4-allylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (66) underwent nitrosation in aqueous solution at the allyl group to give (after a proton shift) the oxime intermediate (67), which promptly underwent a second nitrosation to afford the dioxime (68) and subsequent ring closure to 1,2,3,4-tetrahydro-6-hydroxyimino-methyl-1,3-dimethyl-2,4-dioxopterin (71). In contrast, the same substrate (66) underwent nitrosation in an aprotic solvent (ethyl acetate) by isoamyl nitrite/toluene sulfonic acid to give initially the 5-nitroso compound (69) (recognized by the deep color of the reaction mixture), which then cyclized (with loss of color) to give 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-8-vinylpurine (70).⁴⁶⁶⁰ Other such cyclizations have been described.^{4660, 4994} The use of *N*-nitrosodimethylamine as a nitrosating agent for 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (72, $R = \text{H}$) in the presence of phosphoryl chloride gave initially the 5-nitroso derivative (72, $R = \text{NO}$), which then condensed with starting material (72, $R = \text{H}$) to afford 1,2,3,4,6,7,8,9-octahydro-1,3,7,9-tetramethyl-2,4,6,8-tetraoxopyrimido[5,4-*g*]pteridine (73).⁴⁹⁵⁵ Many related reactions have been described for this versatile nitrosating agent.^{4955, 5008}

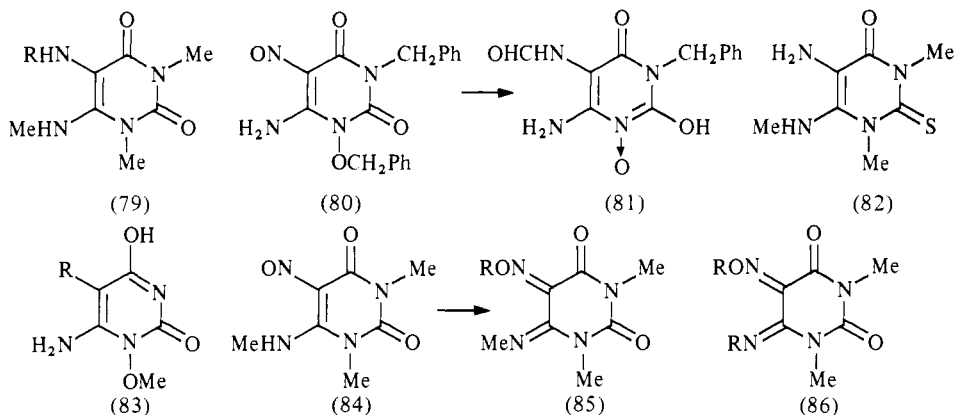
Nitrosation of 2-ethoxycarbonylmethylaminopyrimidine in dilute hydrochloric acid has been reported to give one *N*-nitroso derivative of



the corresponding acid, presumably 2-(N-carboxymethyl-N-nitroso)-aminopyrimidine (74).⁵⁵³⁸

(2) Nitrosopyrimidines by Other Means (H 149, E 103)

Preparations for several nitrosopyrimidines by the Principal Synthesis have been mentioned in Ch. II. A further example is the condensation of 4-amidino-2-dimethylaminopyrimidine with ethyl 2-cyano-2-hydroxyiminoacetate to give 4-amino-2'-dimethylamino-6-



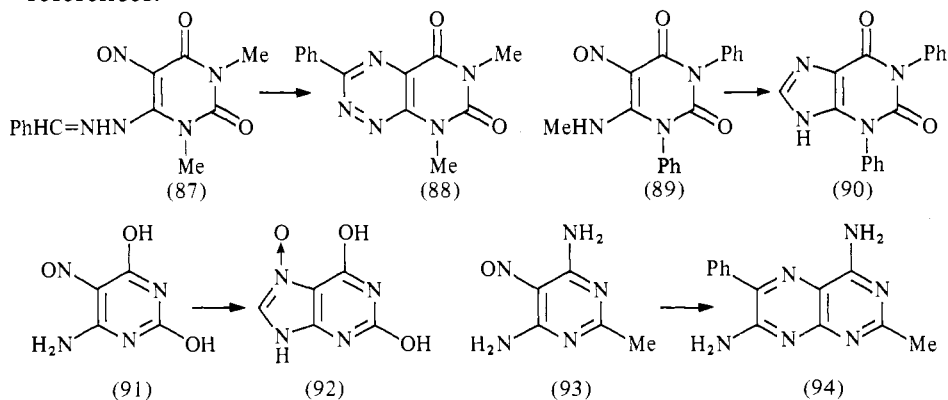
(Raney nickel/tetrahydrofuran; note survival of methylthio group),⁴⁶³³ 2,5-diamino-4-benzamido-6-methoxypyrimidine (Raney nickel/tetrahydrofuran),⁴⁶³³ 4,5,6-triamino-2-methylthiopyrimidine (platinum/ethanol; not isolated),⁴⁶¹⁷ 5-amino-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxypyrimidine (79, R = H) (Raney nickel/ethanol suspension; isolated as the 5-formamido analogue),⁶²³¹ 6-amino-3-benzyl-5-formamidouracil 1-oxide (81) [palladium/98% formic acid; from 4-amino-1-benzyl-3-benzyloxy-1,2,3,6-tetrahydro-5-nitroso-2,6-dioxypyrimidine (80) in 87% yield],⁵⁴²⁵ 4,5-diamino-2,6-bisdimethylaminopyrimidine (Raney nickel/ethanol suspension, isolated as sulfate),⁴⁶⁴³ 4,5-diamino-3,6-dihydro-3-methyl-2-methylthio-6-oxopyrimidine (Raney nickel/dimethylformamide, note methylthio group),⁴⁶¹⁶ 2,4,5-triamino-6-amyloxypyrimidine (platinum/methanol; not isolated as such),⁴⁶²⁴ and others.^{4623, 4632, 5004, 5048}

A correspondingly lower percentage of nitrosopyrimidines have been reduced with dithionite. Among the products so produced were 2,4,5,6-tetra-aminopyrimidine (82% as sulfate),⁴⁶⁴³ 2,4,5-triamino-6-hydroxypyrimidine (78% as sulfate),⁶⁴⁰⁵ 5-amino-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-4-oxo-2-thiopyrimidine (82),⁴⁶⁶¹ 2,4,5-triamino-6-*p*-iodoanilinopyrimidine (and analogues),⁵³⁶⁸ 4,5,6-triamino-1,2-dihydro-1-methyl-2-oxypyrimidine (64% as sulfate),⁵²⁴⁵ 5,6-diamino-1- β -hydroxyethyluracil,⁶⁰²⁰ and 5,6-diamino-1-methyl-2-thiouracil.⁵¹⁸² Zinc and formic acid have been used to convert 6-amino-1-methoxy-5-nitrosouracil (83, R = NO) into 6-amino-5-formamido-1-methoxyuracil (83, R = NHCHO) for subsequent cyclization to 3-methoxyxanthine,⁵⁴²⁵ 6-amino-1-methyl-5-nitrosouracil into 6-amino-5-formamido-1-methyluracil,⁴⁶²⁰ and 2-amino-4-anilino-6-hydroxy-5-nitrosopyrimidine into 2-amino-4-anilino-5-formamido-6-hydroxypyrimidine.⁴⁶³⁵

(2) Other Reactions of Nitrosopyrimidines (*H* 151, *E* 104)

Acylation of a 5-nitroso group is possible providing there is a handy tautomeric group to provide a proton to permit it to react in its "isonitroso form." Thus, 1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-5-nitroso-2,4-dioxopyrimidine (84) reacted in its isonitroso form (85, *R* = *H*) with acetic anhydride in tetrahydrofuran to give 5-acetoxyiminohexahydro-1,3-dimethyl-6-methylimino-2,4-dioxopyrimidine (85, *R* = *Ac*);⁴⁶⁴⁵ the 5-benzoyloxyimino analogue was made similarly, using benzoyl chloride and triethylamine;⁴⁶⁴⁵ but 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine (isonitroso form; 86, *R* = *H*) reacted with acetic anhydride to give the diacetyl derivative, 5-acetoxyimino-4-acetylimino-hexahydro-1,3-dimethyl-2,6-dioxopyrimidine (86, *R* = *Ac*).⁴⁶⁴⁴

Intramolecular cyclizations involving a 5-nitroso group have been exemplified in the transformation of 4-benzylidenedihydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine (87), in ethanolic hydrochloric acid, to 5,6,7,8-tetrahydro-6,8-dimethyl-5,7-dioxo-3-phenylpyrimido[5,4-*e*]-*as*-triazine (88);⁴⁶²⁶ of 1,2,3,4-tetrahydro-6-methylamino-5-nitroso-2,4-dioxo-1,3-diphenylpyrimidine (89), by boiling in dimethylformamide, to 1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenylpurine (90);⁴⁶⁵⁷ of 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine, by treatment with phosphoryl chloride/dimethylformamide, to 8-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurine;⁴⁹⁷³ of 4-amino-2,6-dihydroxy-5-nitrosopyrimidine (91), with formaldehyde in hot dimethyl sulfoxide, to 2,6-dihydroxypurine 7-oxide (92);^{4574, 5423} of 4,6-diamino-2-methyl-5-nitrosopyrimidine (93), by treatment with phenylacetone nitrile, to 4,7-diamino-2-methyl-6-phenylpteridine (94);⁵⁷⁴⁴ and many others in the above references.



3. The Arylazopyrimidines (*H* 152, *E* 108)

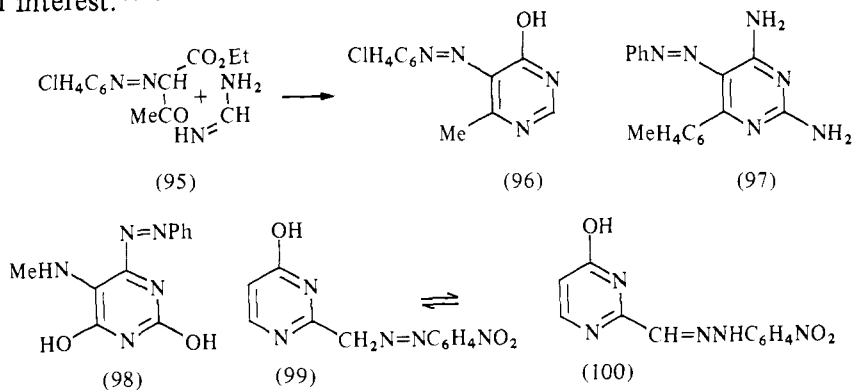
A large number of 5-phenylazopyrimidines has been prepared, some as intermediates for 5-aminopyrimidines, some as substrates for cyclization, and some for biological testing in their own right. Several 4/6-phenylazo- and α -phenylazoalkylpyrimidines have been made and examined.

A. Preparation of Arylazopyrimidines (*H* 152, *E* 108)

Most of the arylazopyrimidines described of late have been made by coupling, but other routes have been represented.

(1) Arylazopyrimidines by Primary Synthesis (*H* 152, *E* 108)

Examples of the primary synthesis of phenylazopyrimidines have been given in Ch. I and II. Typical procedures were the condensation of ethyl 2-*p*-chlorophenylazoacetoacetate (95) with formamide in methanolic sodium methoxide to give 5-*p*-chlorophenylazo-4-hydroxy-6-methylpyrimidine (96);⁵⁶³⁴ of ethyl 2-benzoyl-2-phenylazoacetate with thiourea to give 4-hydroxy-2-mercapto-6-phenyl-5-phenylazopyrimidine;⁵⁸⁷⁴ and of 3-phenylazoacetylacetone with guanidine to give 2-amino-4,6-dimethyl-5-phenylazopyrimidine.⁵³⁶³ Another type is also of interest.⁴⁴¹¹



(2) Arylazopyrimidines by Coupling (*H* 153, *E* 108)

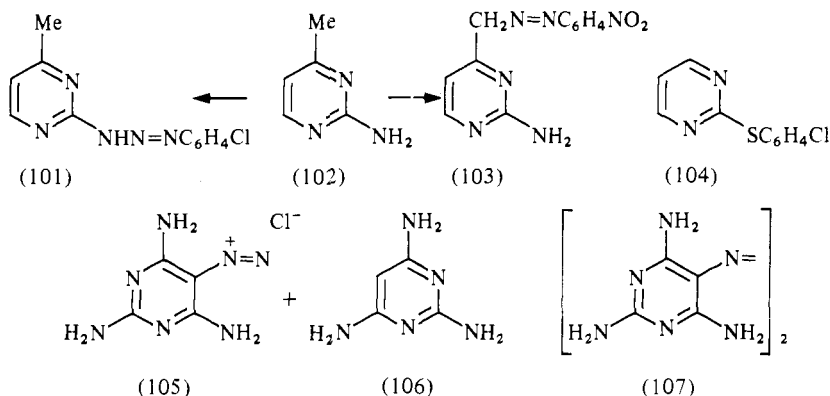
Coupling of 2,4-diamino-6-*p*-toluidinopyrimidine with benzenediazonium chloride was initiated in acid solution and completed at pH 8–9

to give the 5-phenylazo derivative (97).⁵³⁶⁸ Similar couplings gave 4-ethylamino-2,6-dimethoxy-5-phenylazopyrimidine (at pH 5–6),⁵⁵⁴¹ 2,4-dihydroxy-6-phenyl-5-phenylazopyrimidine (at pH 8–9), 2-amino-5-2',4'-dimethoxyphenylazo-4-methyl-6-phenylpyrimidine (at pH 6–7; 66%),⁵⁸⁶⁹ 4-hydroxy-2-mercapto-6-methyl-5-*p*-sulfamoylphenylazopyrimidine (in aqueous dimethylformamide at pH c. 6),⁵³⁶⁹ 2,4-diamino-6-hydroxy-5-*m*-nitrophenylazopyrimidine (73%),⁵³⁶⁵ 2-amino-4-*p*-anisidino-6-hydroxy-5-phenylazopyrimidine (at pH 6; 84%),⁵³⁵⁹ 4-benzylamino-6-hydroxy-5-phenylazopyrimidine (in "alkaline solution"; 65%),⁵³⁵⁷ 2,4,6-triamino-5- α -naphthylazopyrimidine (at pH 6),⁵²⁹³ and innumerable analogues in the above reference and elsewhere.^{5300, 5358, 5463, 5465, 6030}

As has been pointed out previously, diazo coupling is possible at the 4/6-position or on a methyl substituent, provided the 5-position is unavailable and the other site is sufficiently activated. The required conditions do not differ from those for 5-coupling. Some typical examples reported are 2,4-dihydroxy-5-methylamino-6-phenylazopyrimidine (98) (in "bufferized" solution; 95%),⁵⁰⁶⁰ 5-hydroxy-4-*o*-nitrophenylazopyrimidine [in mild alkali(?); 22%],⁶³⁴⁷ 4-amino-6-*p*-chlorophenylazo-2,5-dihydroxypyrimidine (46%),⁶³⁷² 2-methoxy-4-*p*-nitrophenylazomethylpyrimidine (in sodium acetate buffered solution; 60%),⁴⁷⁶³ and 4-hydroxy-2-*p*-nitrophenylazomethylpyrimidine (99) [probably better formulated as 4-hydroxy-2-*p*-nitrophenylhydrazonomethylpyrimidine (100) but the "azo" formulation is retained here].⁶³⁷²

It must be remembered that diazonium salts may react with primary amino groups to give diazoamino products or may arylate mercapto substituents, especially if there is no other sufficiently activated site for attack. Thus, with *p*-chlorobenzenediazonium chloride, 2-amino-4-methylpyrimidine (102) gave 2-*p*-chlorophenyldiazoamino-4-methylpyrimidine (101) (in acetic acid), but with *p*-nitrobenzenediazonium chloride in dilute acid, attack occurred at the methyl group to give 2-amino-4-*p*-nitrophenylazomethylpyrimidine (103);⁶⁰⁹⁰ 2-mercaptopyrimidine (and some simple derivatives) with *p*-chlorobenzenediazonium chloride gave 2-*p*-chlorophenylthiopyrimidine (104) (and analogues).⁶⁰⁹⁰

Reverse coupling has been represented in the diazotisation of 2,4,5,6-tetra-aminopyrimidine to give 2,4,6-triaminopyrimidine-5-diazonium chloride (105), which coupled with 2,4,6-triaminopyrimidine (106) in acetate buffer to afford 2,2',4,4',6,6'-hexa-amino(azopyrimidine) (107) in 63% yield.⁴⁷⁴⁴

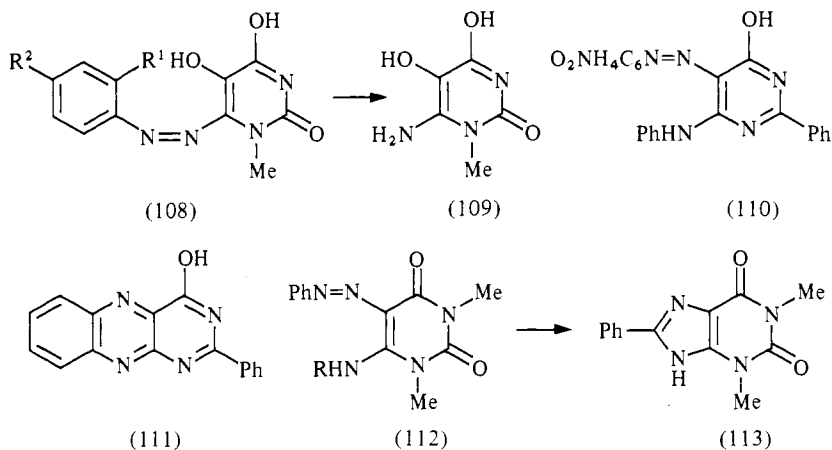


(3) Other Preparations of Arylazopyrimidines (H 155)

4-(*N'*-*p*-Acetamidophenylhydrazino)-2,6-dihydroxypyrimidine underwent hydrolysis and aerial oxidation on boiling in alkali to give 4-*p*-aminophenylazo-2,6-dihydroxypyrimidine in 40% yield.⁵⁴⁸² In a different way, 6-hydrazino-3-methyluracil reacted with *p*-benzoquinone to give 6-*p*-hydroxyphenylazo-3-methyluracil in 85% yield.⁵⁴⁸² Analogues were made similarly.⁵⁴⁵⁸

B. Reactions of Arylazopyrimidines (H 156, E 109)

Arylazopyrimidines undergo few reactions apart from reduction to the corresponding aminopyrimidine, a convenient and useful process. Such *reductions* are typified as the formation of 5-amino-4-benzylamino-6-hydroxypyrimidine (palladium/ethanol; 70%),⁵³⁵⁷ 4,5-diamino-2-chloro-6-phenylpyrimidine (Raney nickel/dimethylformamide at 10 atmospheres; 88%),⁶⁰⁶⁷ and the like (palladium/methanol);⁵³⁰² also in the reduction of 2-amino-4-*p*-anisidino-6-methyl-5-phenylazopyrimidine by dithionite to 2,5-diamino-4-*p*-anisidino-6-methylpyrimidine,⁵³⁵⁹ and either 6-*o*-carboxyphenylazo-5-hydroxy-1-methyl- (108, $\text{R}^1 = \text{CO}_2\text{H}$, $\text{R}^2 = \text{H}$) or 5-hydroxy-1-methyl-6-*p*-sulphophenylazouracil (108, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{SO}_3\text{H}$) by dithionite to a common product, 6-amino-5-hydroxy-1-methyluracil (109).⁵⁰⁶⁰ An unusual dithionite (partial) reduction is that of 2,4-dihydroxy-6-*p*-hydroxyphenylazopyrimidine to 2,4-dihydroxy-6-*N'*-(*p*-hydroxyphenyl)hydrazinopyrimidine.⁵⁴⁵⁸ The zinc/formic acid reduction of 4-ethylamino-2,6-dimethoxy-5-phenylazopyrimidine gave, as might be expected, 4-ethylamino-5-formamido-2,6-dimethoxypyrimidine, but in poor yield.⁵⁵⁴¹



Two *cyclizations* involving arylazopyrimidines are of interest. Heating 4-anilino-6-hydroxy-2-phenyl-5-*p*-nitrophenylazopyrimidine (110) in acetic acid containing sulfuric acid at 140° gave 4-hydroxy-2-phenylbenzo[*g*]pteridine (111), presumably with loss of *p*-nitroaniline.⁴⁹⁶⁶ The second cyclization involved initial transamination of 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-phenylazopyrimidine (112, $R = H$) by benzylamine to give the benzylamino analogue (112, $R = CH_2Ph$) followed by cyclization to give 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-6-phenylpurine (113) with loss of aniline.⁵⁰¹¹ Both cyclizations have been extended to the formation of analogues.

CHAPTER VI

Halogenopyrimidines (*H* 162, *E* 110)

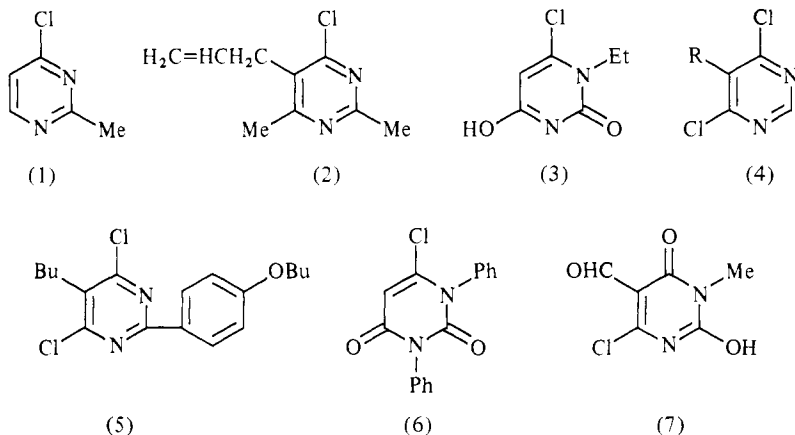
The spate of new biological uses for halogenopyrimidines, so evident prior to 1970, has now dwindled to a trickle. However, chemical work in the area has continued unabated, mainly in respect of halogenopyrimidines as intermediates, for which they are uniquely qualified. In particular, fluoropyrimidines have attracted much (biologically fruitless) attention, probably on account of the interest generated by fluorouracil and "Fluoropan" as antineoplastic agents in the 1960s.⁵⁸¹⁷ In addition, fluoro derivatives have shown good metaphase arresting activity in a series of "metahalones" (halogenated 2-hydroxypyrimidines) still being investigated.⁶¹⁷⁷ Other general aspects of halogenopyrimidines recently noted include mass spectra of aminohalogenopyrimidines,⁴⁸⁰⁴ ¹³C nmr spectra of 2-halogenopyrimidines,⁵²⁸² and the crystal structures for salts of 5-bromo-6-methyluracil 3-oxide.⁶²³⁷

1. Preparation of 2-, 4-, and 6-Halogenopyrimidines (*H* 162, *E* 110)

A. Chloropyrimidines from Hydroxypyrimidines with Phosphoryl Chloride (*H* 162, *E* 110)

(1) *Simple Cases* (*H* 162, *E* 110)

Although most simple cases of the conversion of such hydroxy- into chloropyrimidines have been described previously, the following monochloropyrimidines lacking other functional groups have been made recently by treatment of the corresponding hydroxypyrimidines with boiling phosphoryl chloride: 4-chloro-2-methylpyrimidine (1),⁵⁸²⁹ 4-chloro-6-cyclopropylpyrimidine (with *N,N*-diethylaniline as "catalyst"),⁵⁸¹² 2-chloro-4,6-diethylpyrimidine (15 h under reflux; 83%), 2-chloro-4,5,6-trimethylpyrimidine (12 h; 78%),⁵²⁴⁷ 5-allyl-4-chloro-



2,6-dimethylpyrimidine (2),⁶³⁴⁶ 6-chloro-1-ethyluracil (3) (from *N*-ethylbarbituric acid with phosphoryl chloride pretreated with a little dilute phosphoric acid; the 3-ethyl isomer was removed during work up),⁴⁵²⁷ and 5-butyl-4-chloro-2,6-dihydroxypyrimidine (phosphoryl chloride plus phosphoric acid).⁵⁹¹⁵

Simple dichloropyrimidines made similarly include 2,4-dichloropyrimidine,⁵⁶²² 2,4-dichloro-5-methylpyrimidine,⁵⁶²² 4,6-dichloro-5-ethylpyrimidine (4, R = Et) (65%),⁴⁵⁷⁷ 5-allyl-4,6-dichloropyrimidine (4, R = CH₂CH:CH₂),⁶⁰⁶⁴ 4,6-dichloro-5-ethyl-2,2'-bipyrimidine,⁴⁵⁸⁰ 2,4-dichloro-6-propylpyrimidine,⁵⁸⁰⁷ 2,4-dichloro-5-ethylpyrimidine (80%),⁵⁷⁹⁷ and others.⁵⁷¹⁵ Tri- and tetra-chloro examples include 2,4,6-trichloro-5-ethylpyrimidine (dimethylaniline, 68%; diethylaniline, 75% yield)⁵⁷⁹⁷ and 2,2',4',6-tetrachloro-4,5'-bipyrimidine.⁴⁷⁰⁴

Simple chloropyrimidines bearing substituted or unsubstituted aromatic groups have been made similarly, and the products include 2-chloro-4-phenylpyrimidines,⁶⁰⁴² 4-chloro-2-methyl-6-phenylpyrimidine (95%),⁶⁰³⁹ 4-chloro-5-methyl-2-phenylpyrimidine,⁵⁷⁹² 2-benzyl-4-chloropyrimidine (75%),⁴⁶⁷⁰ 4-chloro-2- β -naphthylpyrimidine,⁴⁶⁷⁰ 2-*p*-butoxyphenyl-5-butyl-4,6-dichloropyrimidine (5) (diethylaniline, 20 h reflux; also about 40 homologues),⁴⁵³⁹ 4,6-dichloro-5-*p*-methoxyphenyl-2-phenylpyrimidine (diethylaniline, 30 h; also about 30 related compounds),⁴⁵²⁹ 4,6-dichloro-2,5-di-*p*-tolylpyrimidine (diethylaniline, 40 h; also 12 analogues),⁴⁴⁹⁷ 4-chloro-6-methyl-2-phenethylpyrimidine (15 min; poor yield),⁶⁰¹⁸ 2-chloro-4,6-diphenylpyrimidine (8 h; 60%),^{4818, 5673, 5836} 2-chloro-5-methyl-4,6-diphenylpyrimidine,⁴⁷⁵⁶ 4-chloro-2,6-dimethyl-5-styrylpyrimidine (85%),⁶³⁵² 2-chloro-4,6-dimethyl-5-*p*-nitrophenylpyrimidine (91%),⁵⁶⁶² 4-chloro-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenylpyrimidine (6) (phosphoryl chloride plus

a little water; 87%),⁴⁶⁵⁷ 4-chloro-5-*p*-tolylpyrimidine,⁵⁴⁸⁷ 4-chloro-6-methyl-2-thien-2'-ylpyrimidine,⁶²⁸⁷ and 4-chloro-5-thien-3'-ylpyrimidine.⁴⁴⁰⁶

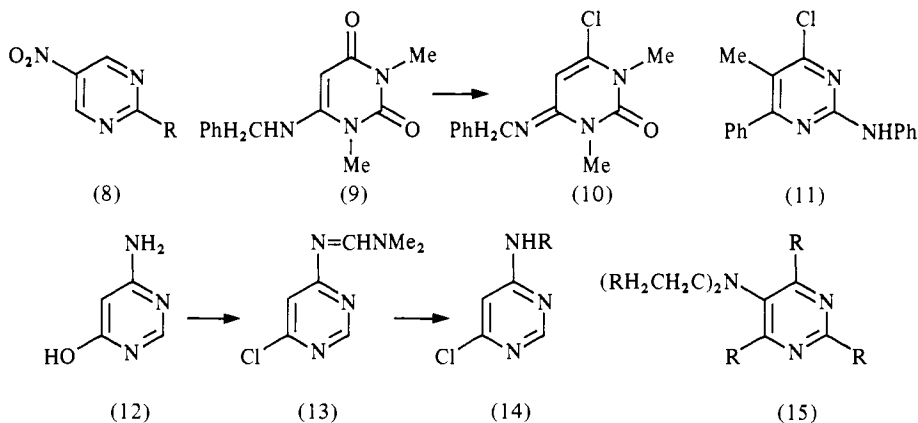
A 5-hydroxy group is unaffected by phosphoryl chloride so that 2,5-dihydroxy-4,6-dimethylpyrimidine with phosphoryl chloride/diethylaniline gave only 2-chloro-5-hydroxy-4,6-dimethylpyrimidine, isolated as its phosphate salt.⁶³⁷³ The use of phosphoryl chloride with dimethylformamide can bring about additional formylation. Thus, *N*-methylbarbituric acid gave 6-chloro-5-formyl-3-methyluracil (7).^{4984, 5000} 2,4,6 trihydroxy- gave 2,4,6-trichloro-5-formylpyrimidine,⁵⁰⁰⁰ and 1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenylpyrimidine gave 4-chloro-5-formyl-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenylpyrimidine.⁴⁹²³ 4-Hydroxy-5- β -hydroxyethyl-2-methylpyrimidine, not unnaturally gave 4-chloro-5- β -chloroethyl-2-methylpyrimidine.⁵⁷⁴¹

(2) *In the Presence of a Nitro Group (H 163, E 111)*

Several procedures for converting hydroxynitro- into chloronitropyrimidines have been revised with advantage. Thus, boiling 2-hydroxy-5-nitropyrimidine (8, R = OH) ethanolate in phosphoryl chloride for just 30 min gave 2-chloro-5-nitropyrimidine (8, R = Cl) in 97% yield;⁶³⁷² conversion of 4,6-dihydroxy- into 4,6-dichloro-5-nitropyrimidine by the original method (phosphoryl chloride/dialkylaniline) with steam distillation of the product from the reaction mixture gave a 70% yield,⁴⁷²² but slow addition of diethylaniline to a gently refluxing solution of substrate in phosphoryl chloride, followed by a traditional work-up procedure, gave an even better 91% yield.⁵⁶¹⁹ The latter procedure also converted 2,4-dihydroxy- into 2,4-dichloro-5-nitro-6-propylpyrimidine in excellent yield.⁵⁶⁶⁸ Other modern examples include the preparation of 2,4-dichloro-5-nitro-6-phenylpyrimidine (diethylaniline) in *c.* 60% yield,⁵⁴⁴¹ 4,6-dichloro-2-*m*-chlorostyryl-5-nitropyrimidine (diethylaniline), 45%,⁵³⁰⁹ and 2,4,6-trichloro-5-nitropyrimidine.⁵⁷⁷⁰

(3) *In the Presence of Amino Groups (H 163, E 112)*

The reservations about using phosphoryl chloride in the presence of amino-type substituents have largely disappeared with time as more and more successful examples have emerged. Current procedures are illustrated in the formation of 2-amino-4-chloro-6-isopropylpyrimidine



(phosphoryl chloride; worked up in ice/ammonia);⁵⁸⁰⁷ 4-chloro-2-dimethylamino-5,6-dimethylpyrimidine (usual method; final sublimation);⁵²⁸⁴ 5-butyl-4-chloro-2-dimethylamino-6-methylpyrimidine (ice/ammonia; 96%);⁵³⁹² 4-benzylimino-6-chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxypyrimidine (10) from 4-benzylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (9) and phosphoryl chloride, which were “violently refluxed at 240° in an oil bath for 3 h” to give a 60% yield;⁴⁹⁹⁴ several homologues of the last example done similarly;^{4969, 4971} 4-benzylidenehydrazono-6-chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxypyrimidine (97%, and related compounds);⁵¹⁶² 2,4-dichloro-5-methylaminopyrimidine (phosphoryl chloride/triethylamine; complicated work-up to give 23%);⁶⁰⁶² 4,6-dichloro-2'-dimethylamino-2,4'-bipyrimidine (89%);⁶¹⁸¹ bis-(4,6-dichloropyrimidin-2-yl)amine;⁵³⁹⁴ and 4,6-dichloro-2-dimethylamino-5-phenylpyrimidine.⁶⁵⁷⁸

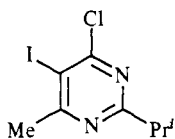
Less simple examples include the preparation of 2-anilino-4-chloro-5-methyl-6-phenylpyrimidine (11),⁵⁷³⁷ 4-chloro-2-(3',5'-dibromo-4'-ethoxyanilino)-6-methylpyrimidine (phosphoryl chloride under reflux for 3 h, 65%),⁶³⁰⁴ 2-anilino-4-chloropyrimidine (85%),⁴⁶⁷⁰ 4,6-dichloro-2-pyridin-2'-ylpyrimidine (worked up by extraction from alkaline solution; 62%),⁵⁹⁵⁹ 4-chloro-6-methyl-2-pyridin-3'-ylpyrimidine and related compounds,^{6087, 6288} 4-chloro-2-piperidino (or morpholino)-pyrimidine,⁵⁸⁶⁶ and 4-chloro-2-methyl-6-pyridin-2'-ylpyrimidine.⁶⁰³⁹ The use of phosphoryl chloride with dimethylformamide converted 4-amino-6-hydroxypyrimidine (12) into 4-chloro-6-dimethylamino-methyleneaminopyrimidine (13), 4-chloro-6-formamidopyrimidine (14, R = CHO), or 4-amino-6-chloropyrimidine (14, R = H) according to the conditions of work-up (dilute ammonia was best for the last-mentioned product).^{5852, 5853} Phosphoryl chloride and plenty of diethyl-

aniline transformed 5-di(β -hydroxyethyl)amino-2,4,6-trihydroxypyrimidine (15, R = OH) into 2,4,6-trichloro-5-di(β -chloroethyl)aminopyrimidine (15, R = Cl) in *c.* 70% yield.^{4774, 5905} However, 4-amino-5,6-dihydroxy-2-methylpyrimidine gave only 4-amino-6-chloro-5-hydroxy-2-methylpyrimidine.^{6373, 6423}

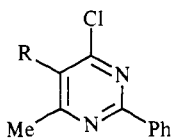
(4) In the Presence of Any Other Groups (H 164, E 113)

The presence of a *pre-attached halogeno* substituent on the hydroxy substrate has no appreciable effect on its reaction with phosphoryl chloride. Thus, 4-hydroxy- gave 4-chloro-5-iodo-2-isopropyl-6-methylpyrimidine (16) in 94% yield under the usual conditions.⁵⁰⁹⁴ Other chloropyrimidines so formed include 4,5-dichloro-6-phenyl-,⁵⁰⁷¹ 2,4-dichloro-5-fluoro- (using pyridine or dimethylaniline),^{4783, 5626} 5-bromo-2,4-dichloro- (80%; better yield with added phosphorus pentachloride),^{5592, 5935} 4-*t*-butyl-5,6-dichloro- (88%),⁴⁶⁶⁴ 5-bromo-4-chloro-2,6-diphenyl- (97%),⁵⁷⁶⁰ 5-bromo-4-chloro- (improved procedure; 78%),⁴⁷⁰⁵ 2,5-dichloro-4,6-dimethyl- (diethylaniline),⁶⁰³³ 4-chloro-5-iodo- (dimethylaniline; 49%),⁵²⁶² and 2-chloro-5-iodopyrimidine (diethylaniline).⁵⁶⁶⁴

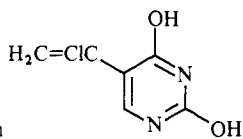
Alkoxy or *aryloxy* groups have no noticeable effect on the use of phosphoryl chloride, except for the necessity to avoid prolonged acid conditions, which could cause hydrolysis of 2- or 4/6- alkoxy groups. Examples include 4-chloro-5-methoxy-2-phenyl- (using "wet" phosphoryl chloride),⁴⁶⁷⁴ 4-chloro-5-ethoxy-2-methyl-,⁵⁹⁵⁸ 4-chloro-6-cyclopropyl-5-methoxy- (dimethylaniline),⁵⁹⁹⁹ 5-benzyloxy-4-chloro-2-methyl-,⁵³⁴⁵ and 2-chloro-5-*p*-nitrophenoxy-4,6-diphenylpyrimidine (dimethylaniline).⁴⁷⁵⁶



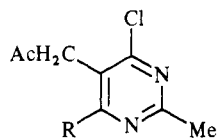
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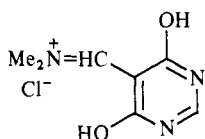
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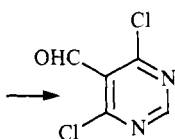
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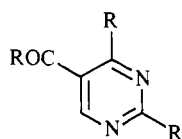
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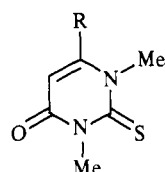
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Ketonic or (potential) *aldehyde groups* are also compatible with phosphoryl chloride, although they are sometimes modified. Thus, treatment of 5-acetyl (or benzoyl)-4-hydroxy-6-methyl-2-phenylpyrimidine with phosphoryl chloride gave 5-acetyl (or benzoyl)-4-chloro-6-methyl-2-phenylpyrimidine (17, R = Ac or Bz),⁴⁴⁵⁶ and 5-acetyl-4-chloro-2,6-dimethylpyrimidine was made similarly.⁵⁰⁷⁷ In contrast, treatment of 5-acetyl-2,4-dihydroxypyrimidine with phosphoryl chloride/dimethylaniline gave exclusively 2,4-dichloro-5- α -chlorovinylpyrimidine (18).⁵³²⁹ The following chloropyrimidines were made similarly: 5-acetonyl-4-chloro-6-ethyl-2-phenylpyrimidine,⁴⁴⁶² 5-acetonyl-4-chloro-2,6-dimethylpyrimidine,⁵⁷⁰¹ and 5-acetonyl-4,6-dichloro-2-methylpyrimidine (19, R = Cl) with a byproduct of the monochloro analogue (19, R = OH).⁵⁷⁰³ The aldehyde precursor 5-dimethylimminiomethyl-4,6-dihydroxypyrimidine chloride (20) reacted with phosphoryl chloride/dimethylaniline to give 4,6-dichloro-5-formylpyrimidine (21) in good yield; the 2-methyl- and 2-phenyl derivatives were made similarly.⁵⁷⁹⁴

Modification of *carboxy* and related groups may also occur during the use of phosphoryl chloride. For example, 5-carboxy-2,4-dihydroxypyrimidine (22, R = OH) gave 2,4-dichloro-5-chlorocarbonylpyrimidine (22, R = Cl) on prolonged treatment with phosphoryl chloride followed by the addition of phosphorus pentachloride (to complete the reaction?).⁵⁴⁶² In contrast, 4-carboxy-6-hydroxypyrimidine in phosphoryl chloride/dimethylaniline gave only 4-carboxy-6-chloropyrimidine.⁴⁷⁷⁰ Esters withstand phosphoryl chloride, but prolonged strongly acidic conditions during work-up should be avoided. Products from such processes include 4-chloro-5-ethoxycarbonyl-2-methylpyrimidine (phosphoryl chloride/diethylaniline),⁵²⁵² 4-chloro-2-methoxycarbonyl-methylpyrimidine (diethylaniline),⁴⁶⁹³ 4-chloro-5- β -ethoxycarbonyl-vinyl-2,6-dimethylpyrimidine (83),⁶³⁵¹ 4-chloro-5- β -ethoxycarbonyl-ethyl-2,6-dimethylpyrimidine (68%),⁵⁷⁶⁶ and the "reverse ester" 5-acetoxy-2,4-dichloro-6-methylpyrimidine (dimethylaniline).⁵⁷²⁹

Although *cyano* groups withstand phosphoryl chloride, *carbamoyl*- and *hydroxyiminomethyl-pyrimidines* normally yield the corresponding cyanopyrimidine by dehydration under such treatment. Thus, 5-cyano-4-hydroxy- gave 4-chloro-5-cyano-6-phenylpyrimidine (84%),⁵⁸¹⁶ 5-carbamoyl-4-hydroxy- gave 4-chloro-5-cyano-2-phenylpyrimidine (>90%),⁵⁵⁸² 2-carbamoylmethyl-4-hydroxy- gave 4-chloro-2-cyano-methyl-6-phenylpyrimidine;⁵⁶⁸⁸ 2-hydroxy-4-hydroxyiminomethyl- gave 2-chloro-4-cyano-6-methylpyrimidine,⁴⁸²⁰ and 2-hydroxy-4,6-bis-hydroxyiminomethyl- gave 2-chloro-4,6-dicyanopyrimidine,^{4820, 5284} although samples differed in melting point by more than 20°.

Although *mercapto groups* are normally affected by phosphoryl chloride, 1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-4-oxo-2-thiopyrimidine (23, R = OH), in which the 2-substituent was all but fixed in the thio-form, was converted by "wet" phosphoryl chloride at 70° into 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-6-oxo-2-thiopyrimidine (23, R = Cl), albeit in only 27% yield.⁴⁶⁶¹ *Alkylthio groups* are compatible with phosphoryl chloride, as indicated by the formation of 4-chloro-2-ethylthio-6-methylpyrimidine,⁴⁸⁸⁵ but other attached groups may be affected as in the treatment of 2-carbamoylmethylthio-4-hydroxy-6-methylpyrimidine with phosphoryl chloride/dimethylaniline to give 4-chloro-2-cyanomethylthio-6-methylpyrimidine.⁵⁴⁷⁶ 5-Dimethylsulfonio-2,4,6-trihydroxypyrimidine acetate reacted with phosphoryl chloride/dimethylaniline to give 2,4,6-trichloro-5-methylthiopyrimidine in 90% yield.⁶⁰⁶¹

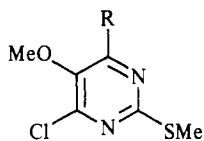
5-Benzamidomethyl-4-chloro-2-methylpyrimidine⁵⁷⁹³ and 2,4-dichloro-6-phenyl-5-phenylazopyrimidine⁶⁰⁶⁷ were both made in good yield from the respective hydroxy analogues.

(5) In the Presence of Two Different Groups (E 114)

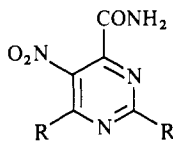
Examples of the use of phosphoryl chloride in the presence of two different groups are divided for convenience into amino + another group, alkylthio + another group, and amide + a nitro group. The first category is exemplified in the formation of 4-chloro-5-ethoxycarbonyl-2-pyrrolidinopyrimidine (93%),⁴⁹⁷⁶ 4-amino-2-chloro-6-methoxypyrimidine,⁵⁸²⁶ 2-amino-4-chloro-5-methoxy-6-methylpyrimidine,⁵⁷⁸⁶ 4-amino-6-chloro-5-methoxypyrimidine,⁵⁷⁸² 4-chloro-2-ethoxy-5-fluoropyrimidine,⁵⁸³³ 2-amino-4-chloro-6-trifluoromethylpyrimidine,⁵⁷⁸⁵ 2-amino-5-*N'*-butylureido-4,6-dichloropyrimidine,⁵²⁹⁵ and bis(4,6-dichloro-5-nitropyrimidin-2-yl)amine ("wet" phosphoryl chloride/dimethylaniline).⁵³⁹⁴

The second category is illustrated in the preparation of 4-chloro-6-cyclopropyl-5-methoxy-2-methylthiopyrimidine (24, R = C₃H₅) (diethylaniline),⁶⁰⁰⁰ 4-chloro-2-ethylthio-5-methoxypyrimidine,⁴³⁹⁵ 4-chloro-5-methoxy-6-methoxymethyl-2-methylthiopyrimidine (24, R = MeOCH₂),⁴³⁹⁷ 4-chloro-6-dimethoxymethyl-2-ethylthio-5-fluoropyrimidine (37%),⁵⁵²⁵ 4-chloro-5-cyano-2-methylthiopyrimidine (90%),⁵⁵⁸¹ and 5-acetonyl-4-chloro-6-methyl-2-methylthiopyrimidine.⁵⁷⁰¹

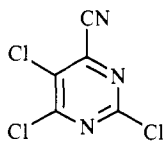
The third category includes the formation of 2-acetamido-4,6-dichloro-5-nitropyrimidine (67%),^{5229, 5637} and the treatment of 4-carbamoyl-2,6-dihydroxy-5-nitropyrimidine (25, R = OH) with phos-



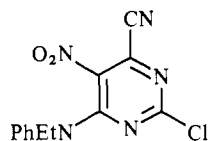
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phoryl chloride/diethylaniline to give a separable mixture of 4-carbamoyl-2,6-dichloro-5-nitropyrimidine (25, $R = Cl$), 2,4,5-trichloro-6-cyanopyrimidine (26), and a little 2-chloro-4-cyano-6-*N*-ethylanilino-5-nitropyrimidine (27).⁵⁹⁷¹

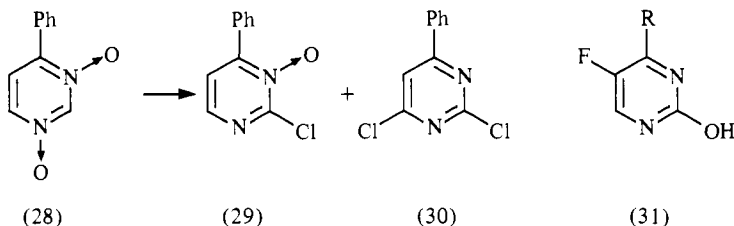
B. Use of Phosphorus Pentachloride to Produce Chloropyrimidines (*H* 165, *E* 115)

Phosphorus pentachloride, usually dissolved in phosphoryl chloride, is still used to convert even quite simple hydroxypyrimidines into chloropyrimidines. In most cases, there is no evident advantage over the use of phosphoryl chloride alone. The process is illustrated in the preparation of 4,6-dichloro-2-methylpyrimidine (phosphorus pentachloride alone; >90%),⁵⁰²⁸ 2,2'-dichloro-5,5'-bipyrimidine,⁵⁵⁸⁰ 2,2',4,4'-tetrachloro-5,5'-bipyrimidine (60%),⁴³⁷⁵ 4-chloro-2-phenylpyrimidine (phosphorus pentachloride alone; 65%),⁶⁰³⁸ 4-chloro-6-methyl-2-phenylpyrimidine (and isomers, all in >80% yield),⁶³⁷⁷ 4-chloro-2,6-diphenylpyrimidine,⁶³⁷⁷ 4-chloro-5-methyl-2-*p*-tolylpyrimidine (61%),⁴⁴⁷⁸ 2-chloro-5-phenylpyrimidine,⁶⁰⁸⁰ and related compounds,^{4818, 6080} as well as in the conversion of 5-carboxy-2,4-dihydroxy- into 2,4-dichloro-5-chlorocarbonylpyrimidine⁵⁹¹⁹ and in the formation of 5-bromo-2,4-dichloropyrimidine,⁵⁵⁹² 4-chloro-2- β,β -dichloro- α,α -difluoroethyl-6-methylpyrimidine (the halogenated ethyl substituent was present at the outset),⁵⁹⁹⁵ 5-adamantyl-2-amino-4-chloropyrimidine,⁵²⁹⁷ the 6-ethyl⁵⁴⁵³ or 6-propyl⁵²⁹⁸ derivative, 2,4-dichloro-6-ethylamino-5-phenylazopyrimidine,⁵⁵⁴¹ and 2,4-dichloro-5-chloro-sulfonylpyrimidine (the 5-substituent was in the same substrate).⁶⁰⁷⁴

C. Other Ways of Preparing 2-, 4-, and 6-Chloropyrimidines (*H* 166, *E* 116)

The few primary syntheses of chloropyrimidines have been covered in Ch. III. Some of the more interesting include the conversion of α -(*N*-cyanoamidino)malononitrile by etherial hydrogen chloride into 4,6-diamino-2-chloro-5-cyanopyrimidine,⁴⁴⁸⁶ of 2-cyano-*N*-cyclohexyl-2-*o*-tolylacetamide by *N,N*-dimethylbenzamide and phosphoryl chloride

into 4,6-dichloro-2-phenyl-5-*o*-tolylpyrimidine;⁵³⁵² of nitriles and phosgene into a variety of 4-chloropyrimidines;⁵⁰²⁸ of 5-chloro-1,2-dihydropyrimido[5,4-*e*]as-triazine by boiling aqueous ethanolic sodium chloride into 5-amino-4-chloro-6-*N*'-formylhydrazinopyrimidine;⁵²³¹ and of 2-methylimidazole by chloroform at a high temperature into 4-chloro-2-methylpyrimidine *inter alia*.⁶⁰⁰³



Conversion of an amino- into a chloro-pyrimidine can be convenient when the aminopyrimidine is readily available. Thus, an improved procedure for converting 2-amino- into 2-chloropyrimidine, by treatment with nitrous acid in the presence of an excess of chloride ion (hydrochloric acid and lithium chloride), has been reported.⁴³⁸² Although 4/6-aminopyrimidines have not proven amenable to such change in the past, 4,6-diamino- has now been converted (nitrous acid/cuprous chloride) into 4,6-dichloropyrimidine, albeit in poor yield.⁴⁶⁶³ In addition, 4-amino- and 4-amino-5-bromo- have been so converted (no details) into 4-chloro- and 5-bromo-4-chloro-6-methoxypyrimidine, respectively,⁴⁶⁹⁶ as well as 4-amino-6-*t*-butyl- into 4-*t*-butyl-6-chloropyrimidine in low yield.⁶⁶⁶⁷

Other possible routes to chloropyrimidines are exemplified in the treatment of 4-phenylpyrimidine 1,3-dioxide (28) with phosphoryl chloride to give a separable mixture of 2-chloro-4-phenylpyrimidine 3-oxide (29), 2,4-dichloro-6-phenylpyrimidine (30), and two minor products;⁶³⁴⁵ in the highly unusual conversion of 5-ethoxycarbonyl-4-hydroxy-2-phenylpyrimidine into 4-chloro-5-ethoxycarbonyl-2-phenylpyrimidine by prolonged boiling in thionyl chloride;⁵⁶⁴⁹ in the equally unusual conversion of 5-fluoro-2-hydroxy-4-mercaptopyrimidine (31, R = SH) into 4-chloro-5-fluoro-2-hydroxypyrimidine (31, R = Cl) in 45% yield by standing in thionyl chloride at 25°;⁴⁸⁹⁵ and in the replacement of the iodo substituent of 1,2,3,4-tetrahydro-6-iodo-1,3-dimethyl-2,4-dioxypyrimidine during treatment with chlorine to give 4,5-dichloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine.⁴⁶⁵⁰

D. Preparation of 2-, 4-, and 6-Bromopyrimidines (*H* 167, *E* 117)

Compared with 2- and 4/6-chloropyrimidines, very few such bromopyrimidines have been made, probably because they offer little if any advantage and because phosphoryl bromide is less convenient to use (being a solid) and much more expensive than phosphoryl chloride.

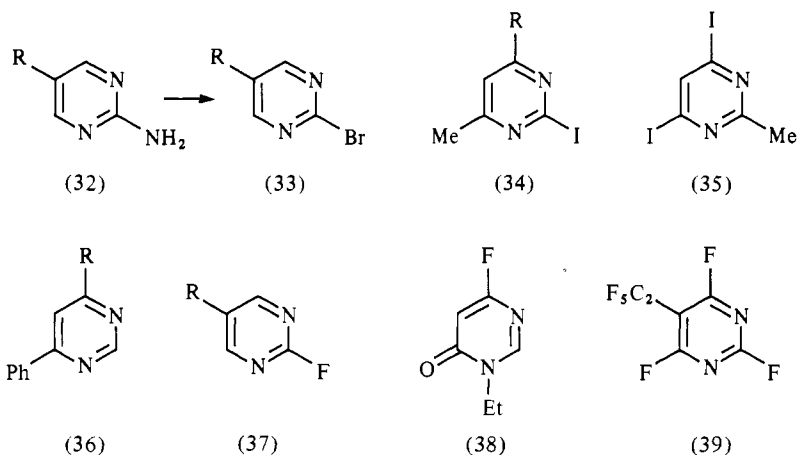
The use of phosphoryl bromide alone is illustrated in the preparation of 4-bromo-6-*t*-butylpyrimidine (100° for 3 h; 40%),⁵⁹²⁹ 2-bromo-4,6-diphenylpyrimidine (130° for 4 h; 63%), 4-bromo-6-phenylpyrimidine (120° for 4 h; 60%),⁴⁶⁷⁵ 2-bromo-4-phenylpyrimidine (37%),⁶⁰⁴² 4-bromo-2,6-diphenylpyrimidine (92%), 6-bromo-3-methyluracil (c. 55%),⁴⁶⁵⁰ 4,6-dibromo-2-isopropylaminopyrimidine,⁶³²⁷ and 4,5-dibromo-2,6-diphenylpyrimidine (83%).⁵⁷⁶⁰ Just as (solid) phosphorus pentachloride may be diluted with phosphoryl chloride for convenience, so phosphoryl bromide has been used with a diluent to give 4-bromo-2-methoxycarbonylmethylpyrimidine (toluene; 24%),⁵⁶⁹³ 2,5-dibromopyrimidine (5-bromo-2-hydroxypyrimidine in phosphorus tribromide containing phosphoryl bromide; c. 55% yield),⁵⁶⁶⁴ or 4-bromo-2,6-dimethylpyrimidine (similarly; c. 80%).⁵⁶⁶⁴ The use of phosphoryl bromide/dimethylaniline/toluene converted 5-methylbarbituric acid into 2,4,6-tribromo-5-methylpyrimidine in 52% yield.⁵⁵¹⁷

Other routes to such bromopyrimidines have been used only seldom. However, 2-aminopyrimidine (32, R = H) and its 5-dimethylaminomethyleneamino derivative (32, R = Me₂NCH:N) with nitrous acid in an excess of bromide ion gave 2-bromopyrimidine (33, R = H) and the derivative (33, R = MeNCH:N), respectively, in reasonable yield.⁴³⁸² Several 2-bromopyrimidines have been made by primary syntheses, but in low yield.⁵⁹³⁶ Direct bromination of pyrimidine in the gas phase at 500° gave mainly 4,6-dibromo- and 2,4,6-tribromopyrimidine, at lower temperatures appreciable amounts of 5-bromopyrimidine were formed.⁴⁶⁷⁷ Treatment of 2-amino-5-bromopyrimidine *N*-oxide with nitrous acid/bromide ion gave 2,5-dibromopyrimidine *N*-oxide.⁶⁷²⁹

E. Preparation of 2-, 4-, and 6-Iodopyrimidines (*H* 168, *E* 118)

Such iodopyrimidines are still made only from other halogenopyrimidines, as detailed for 2-iodopyrimidine (hydriodic acid at 5° on 2-chloro- or 2-bromopyrimidine; 45–55% yield),⁵⁶⁷³ 2-iodo-4-phenylpyrimidine (hydriodic acid at 25° for 6 days; 58%),⁶⁰⁴¹ 4-iodo-6-phenylpyrimidine (hydriodic acid at 25°; 92%),⁶¹¹⁷ 4-iodo-2,6-diphenylpyrimidine (hydriodic acid in aqueous acetic acid at 25°; 98%),⁵⁷⁶¹ 4-

iodo-2-methoxycarbonylmethylpyrimidine (hydriodic acid and sodium iodide in acetone under reflux; 70%),⁵⁶⁹³ 4-iodo-2-methylthiopyrimidine and its 5-bromo derivative (hydriodic acid at 25°; *c.* 50%),⁵²⁸⁴ 2-iodo-4-methoxy-6-methylpyrimidine (34, R = OMe),⁵⁰⁹⁴ 2-dimethylamino-4-iodo-5,6-dimethylpyrimidine,⁵²⁸⁴ 2-iodo-4-methyl-6-piperidinopyrimidine [34, R = N(CH₂)₅],⁵⁰⁹⁴ 4-iodo-6-methylpyrimidine 1-oxide (hydriodic acid),⁴⁶⁸⁵ 4,6-di-iodo-2-methylpyrimidine (35) (55%),⁵⁰⁹⁴ 6-iodo-3-methyluracil (sodium iodide/hot dimethylformamide; *c.* 80%),⁴⁶⁵⁰ and 2,4,5-trifluoro-6-iodopyrimidine (from the tetrafluoro analogue in sodium iodide/dimethylformamide).⁵⁷⁷⁹



F. Preparation of 2-, 4-, and 6-Fluoropyrimidines (*E* 118)

These fluoropyrimidines have been made by several routes. The rather esoteric methods (*E* 118) for converting chloro- into fluoropyrimidines are no longer used, although 2,4,6-trichloro- has been converted into 2,4,6-trifluoro-5-methylpyrimidine (63%) by heating with potassium fluoride in dimethylformamide at 140°,⁴⁵²⁶ and 2 (and 4)-fluoropyrimidine as well as several derivatives of each were prepared from their chloro analogues by heating with caesium fluoride in dimethylformamide or methylpyrrolidone.^{4752, 4755} In addition, 2,4,6-trichloro-5-cyanopyrimidine, 2,4,6-trichloro-5-nitropyrimidine, and 2,4,5,6-tetrachloropyrimidine have all been heated with potassium fluoride at more than 250° to give their 2,4,6-trifluoro analogues along with other products.⁵⁷⁷⁰

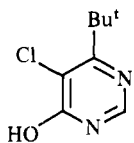
Of much more practical use was the treatment of (chloropyrimidine-derived) trimethylammonioypyrimidines, for example (36, R = N⁺Me₃)

with fluoride ion in dimethylsulfoxide to give 4-fluoro-6-phenylpyrimidine (36, R = F) (72%), with a byproduct of 4-dimethylamino-6-phenylpyrimidine (36, R = NMe₂);⁶¹¹⁷ 2-fluoro-4-phenylpyrimidine (53%);⁶⁰⁴¹ 4-fluoro-2,6-dimethylpyrimidine (95%);⁵⁶⁷⁶ 4-fluoro-6-methylpyrimidine (55%);⁵⁶⁷⁶ 4-fluoro-2,6-diphenylpyrimidine (80%);⁵⁷⁶¹ 4-fluoro-2-isopropylpyrimidine (81%);⁵⁶⁹⁴ and 2-fluoro-4,6-diphenylpyrimidine (58%).⁴⁶⁸¹ Primary aminopyrimidines were also converted into fluoropyrimidines, but by treatment with nitrous acid and fluoride ion. In this way were obtained 2-fluoropyrimidine (37, R = H) (25%),⁴³⁸² 5-bromo-2-fluoropyrimidine (37, R = Br) (*c.* 40%),⁵⁶⁹³ and 1-ethyl-4-fluoro-1,6-dihydro-6-oxopyrimidine (38).⁴⁶⁹⁷ The use of fluoroboric acid instead of hydrogen or sodium fluoride led to improved yields; for example 2-fluoropyrimidine (37, R = H) in up to 50% yield, 2-fluoro-4-methylpyrimidine in 31% yield, and 2-fluoro-4,6-dimethylpyrimidine in 26% yield.⁵⁶⁷⁶ The rather nonspecific rearrangement of perfluoropyridazines and perfluoropyrazines into polyfluoropyrimidines, for example, 2,4,6-trifluoro-5-pentafluoroethylpyrimidine (39), under pyrolytic conditions^{5250, 5291, 5922} have been covered in Ch. III.

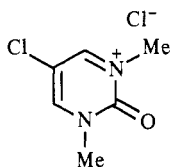
2. Preparation of 5-Halogenopyrimidines (*H* 168, *E* 119)

A. 5-Halogenopyrimidines by Direct Halogenation (*H* 169, *E* 119)

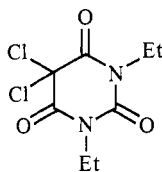
The *5-chlorination of pyrimidines* has been more widely used of late, and several procedures have been employed. The use of elemental chlorine is illustrated in the formation of 4-*t*-butyl-5-chloro-6-hydroxypyrimidine (40) (in glacial acetic acid at 20°; 50%),⁴⁶⁶⁴ 2,4-diamino-5,6-dichloropyrimidine (in dilute hydrochloric acid; 42%),⁵⁵⁸⁵ 2,4-diamino-5-chloropyrimidine (in water at 25°; *c.* 30%),⁵⁴⁰⁰ 5-chloro-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium chloride (41) (methanolic chlorine; 90%),⁵²⁶⁶ 4,5-dichloro-2,6-dihydroxypyrimidine (in water at 80°; *c.* 60%; in acetic acid at 70°; *c.* 75%),⁴⁶⁵⁰ 5,6-dichloro-3-methyluracil (in acetic acid/acetic anhydride at 70°; *c.* 70%),⁴⁶⁵⁰ 4,5-dichloro-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxypyrimidine (in acetic acid/acetic anhydride at 50° with limited chlorine), 5,5-dichloro-1,3-diethylhexahydro-2,4,6-trioxypyrimidine (42) (under similar conditions with an excess of chlorine),^{6110, 4650} 1-benzyloxy-5-chlorouracil (in acetic acid; >80% yield),³⁴⁶⁴ and 5-chloro-2,4-dihydroxypyrimidine (from 2,4-dihydroxy-5-methoxycarbonylpyrimidine with chlorine in hydrochloric acid under reflux; 63% yield).⁶²⁷⁷ In addition, treatment of 5-fluoro-2,6-dihydroxypyrimidine with chlorine, generated *in situ*



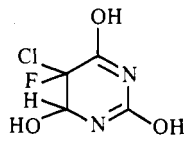
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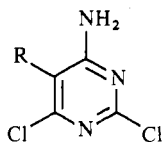
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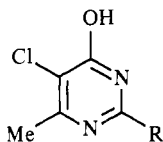
(42)



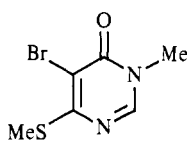
(43)



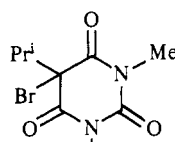
(44)



(45)



(46)



(47)

from hydrochloric acid with hydrogen peroxide, resulted in the addition of hypochlorous acid to give 5-chloro-5-fluoro-4,5-dihydro-2,6-dihydroxypyrimidine (43), which proved to be reasonably stable.⁵⁴¹³

The use of sulfuryl chloride, or (strangely enough) thionyl chloride, is often more convenient than chlorine, for obvious reasons. Some examples are the preparation of 5-chloro-3-isopropyl-6-trifluoromethylpyrimidine (sulfuryl chloride in acetic acid/acetic anhydride at 50°; *c.* 70%), 5-chloro-2,4-dihydroxypyrimidine (as above with aluminum chloride as catalyst, >90%;⁴⁷³⁶ thionyl chloride in pyridine, 28%⁵¹³⁷), 5-chloro-1-cyclohexyluracil (as above with a ferric chloride catalyst; 47%),⁴⁷²⁰ 5-chloro-1-ethyl-1,6-dihydro-4-methylthio-6-oxypyrimidine (sulfuryl chloride in dioxane or carbon tetrachloride at 50°, 50%; also several homologues),⁴⁸⁰⁶ 5,5-dichloro-1,3-diethylhexahydro-2,4,6-trioxypyrimidine (42) (from 4-amino-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxypyrimidine with neat sulfuryl chloride at 25°, 89%;⁵¹⁶³ *m.p.* differs from specimen described above⁶¹¹⁰), 5-chloro-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxypyrimidine (thionyl chloride under reflux; also other products),⁶⁰³⁷ 5-chloro-4-hydroxy-2-mercapto-6-methylpyrimidine (thionyl chloride in pyridine; 11%),⁵¹³⁷ 4-amino-5-chloro-6-hydroxy-2-phenylpyrimidine (neat thionyl chloride at 130°; 66%),⁴⁹⁶³ and 4-amino-2,5,6-trichloropyrimidine (44, R = Cl) (75%) from 4-amino-2,6-dichloropyrimidine (44, R = H) as above.⁴⁹⁶³

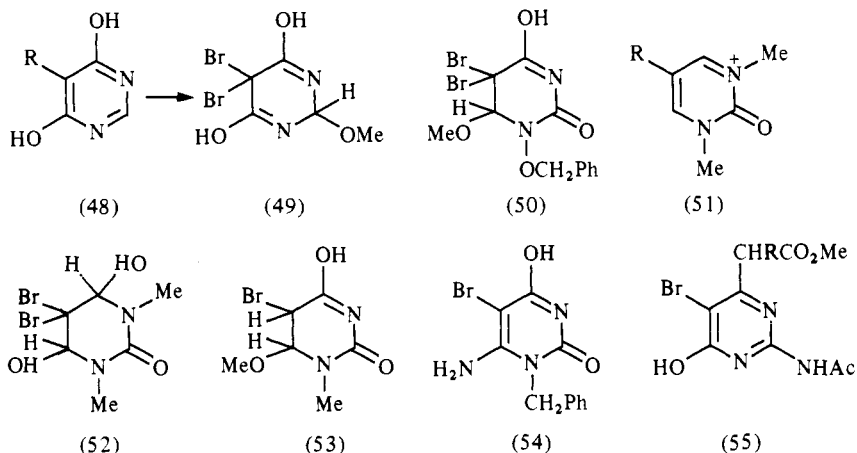
The use of *N*-chlorosuccinimide has proven very convenient to make 4-bromo-5-chloro-2,6-dihydroxypyrimidine (in acetic acid/acetic anhydride at 50°),⁴⁶⁵⁰ 2,4-di-*t*-butyl-5-chloro-6-hydroxypyrimidine (in chloroform under reflux; 73%),⁴⁶⁶⁴ 2-amino-5-chloropyrimidine (as above; 60%),⁵⁶⁷³ 4,5-dichloro-2-chloromethyl-6-hydroxypyrimidine

(as above, from the 5-dechloro analogue; c. 90%),⁵²⁵³ 2-amino-5-chloro-4-ethoxy (or ethylthio)-6-methylpyrimidine (as above),⁵¹⁶¹ and others.^{5390, 5704} Sodium hypochlorite in water was used to make 5-chloro-4-hydroxy-2,6-dimethylpyrimidine (45, R = Me) (90%) and the isomeric 5-chloro-2-hydroxy-4,6-dimethylpyrimidine (68%);⁶⁰³³ propane-2-sulphenyl chloride (ClSPrⁱ) in dichloromethane converted 2-dimethylamino-4-hydroxy-6-methylpyrimidine into its 5-chloro derivative (45, R = NMe₂) in 72% yield, as compared with 25% using *N*-chlorosuccinimide;⁵³⁹⁰ and phosphorus pentachloride/phosphoryl chloride converted 2,2',4',6-tetrahydroxy-4,5'-bipyrimidine into 2,2',4',5,6-pentachloro-4,5'-bipyrimidine.⁴⁷⁰⁴

The *5-bromination of pyrimidines* is nearly always done by elemental bromine, but a variety of solvents have been used with no apparent logic. The most popular medium of late has been acetic acid (glacial or aqueous) in which were made 1-benzyloxy-5-bromouracil,³⁴⁶⁴ 5-bromo-1,6-dihydro-1-methyl-4-methylthio-6-oxopyrimidine (46),⁴⁸⁰⁶ 5-bromo-4-chloro-2,6-dihydroxypyrimidine (and related compounds),⁴⁶⁵⁰ 5-bromo-2,4-di-*t*-butyl-6-hydroxypyrimidine (58%; use of *N*-bromosuccinimide gave 82%),⁴⁶⁶⁴ 5-bromo-6-ethyl-3-phenyluracil,⁴⁹³¹ 5-bromo-1,4-dihydro-6-methyl-4-oxo-1-phenylpyrimidine and its 1,6-dihydro-4-methyl-6-oxo isomer,⁴⁹³⁰ 5-bromo-1-cyclohexyluracil⁶¹¹⁴ 5-bromo-4-carbamoyl-6-hydroxy-2-methylthiopyrimidine (86%),⁵¹⁵¹ 5-bromohexahydro-5-isopropyl-1,3-dimethyl-2,4,6-trioxypyrimidine (47),⁵⁸⁶⁷ 2,4,6-triamino-5-bromopyrimidine (77%; better yield in water, see below),⁵²⁴⁴ 1-benzyl-5-bromo-1,2,3,6-tetrahydro-3-methyl-2,6-dioxypyrimidine,⁵⁴¹⁰ 2-amino-5-bromo-4-hydroxy-6-phenylpyrimidine 1-oxide,⁶¹⁹⁵ 5-bromo-4-hydroxy-2,6-diphenylpyrimidine (93%),⁵⁷⁶⁰ 5-bromo-2-dimethylamino-4-hydroxy-6-methylpyrimidine,⁵²⁸⁴ 4,5-dibromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine,⁶¹¹⁰ and others.^{5032, 5930, 5934, 5937, 6609}

Direct bromination in water has been represented in the formation of 5-bromo-4-formyl-2,6-dihydroxypyrimidine (78%),⁵⁴⁰³ 2,4,6-triamino-5-bromopyrimidine (c. 100%),⁵²⁹⁶ 4-amino-5-bromo-2-hydroxypyrimidine,⁵²²⁷ 5-bromo-4-hydroxy-2-methylpyrimidine,⁵⁹⁵⁸ and 5-bromo-1,2-dihydro-1-methyl-2-oxopyrimidine.⁵³²⁶ Bromination in base gave 5-bromo-4-hydroxy-2-methylthiopyrimidine (aqueous alkali),⁶¹¹¹ 2,4-diamino-5-bromo-6-hydroxypyrimidine (aqueous alkali),⁵²⁵¹ and 5-bromo-1- β,β -diethoxyethyluracil (pyridine).⁶²³⁶ Bromination in alcoholic media gave 5-bromo-1-cyclohexyluracil (aqueous ethanol, 70%; see the use of acetic acid above),⁴⁷²⁰ 5-bromo-3-methyl-6-(phenylthio)uracil (methanol; >90%),⁶²⁷³ 5-bromo-3-methyl-6-phenoxyuracil

(methanol),⁶²⁷³ 5-bromo-4-chloro-2-fluoromethyl-6-hydroxypyrimidine (ethanol),⁵²⁵³ 5-bromo-1,2,3,4-tetrahydro-1,3-bis- β -hydroxyethyl-6-methyl-2,4-dioxypyrimidine (butanol at 100°; 90%),⁴⁷⁸⁴ and others.⁶⁰²² Some such brominations can go further. Thus, 4,6-dihydroxypyrimidine (48, R = H) reacted with methanolic bromine (1 mol) to give 5-bromo-4,6-dihydroxypyrimidine (48, R = Br), which reacted more slowly with an excess of methanolic bromine to give 5,5-dibromo-2,5-dihydro-4,6-dihydroxy-2-methoxypyrimidine (49 or tautomer);⁵³¹⁶ 1-benzyloxy-5-bromouracil (see above) and methanolic bromine gave 1-benzyloxy-5,5-dibromo-5,6-dihydro-6-methoxyuracil (50 or tautomer);³⁴⁶⁴ and other examples are known.⁵²⁶⁶ Aqueous bromine behaved similarly by converting the 1,2-dihydro-1,3-dimethyl-2-oxypyrimidinium halide (51, R = H) into the 5-bromo derivative (51, R = Br) and thence into 5,5-dibromohexahydro-4,6-dihydroxy-1,3-dimethyl-2-oxypyrimidine (52);⁵³²⁶ other such reactions have been reported⁶²³⁶ and discussed mechanistically.^{5317, 5325, 5413}



Bromination in aprotic solvents has become quite rare, although it has been used to make 5-bromo-4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (chloroform 83%),⁴⁹³⁹ 5-bromo-4-formyl-2,6-dihydroxypyrimidine (chloroform 87% on the substrate acetal),⁴⁵⁰⁷ 5-bromo-2,4-dihydroxy-6-methylpyrimidine (initially without solvent, then carbon tetrachloride),⁵⁹⁵⁷ 5-bromo-4-phenylpyrimidine (nitrobenzene),⁵⁵⁹⁵ and 5-bromopyrimidine (nitrobenzene, chlorobenzene, and so forth).⁵⁵⁹⁴ Other 5-brominations of interest are the gas-phase bromination of pyrimidine, which gave, *inter alia*, 5-bromopyrimidine,⁵⁵⁹⁴ the addition of methyl hypobromite (MeOBr) to

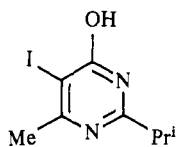
1-methyluracil to give 5-bromo-5,6-dihydro-6-methoxy-1-methyluracil (53) in 90% yield;⁵²⁹² the formation of 5-bromohexahydro-1,3,5-trimethyl-2,4,6-trioxypyrimidine,⁵⁹²⁸ and the dibromination of 4-amino-5,6-dihydro-2-methylpyrimidine followed by dehydrobromination by triethylamine to give 4-amino-5-bromo-2-methylpyrimidine.⁵¹⁰¹

A few 5-brominations have been carried out with *N*-bromosuccinimide to give, for example, 4-amino-5-bromo-6-methoxypyrimidine (in carbon tetrachloride; 25% yield),⁴⁶⁶³ 5-bromo-2-piperidinopyrimidine (96%),⁴⁶⁸⁸ 6-amino-1-benzyl-5-bromouracil (54) (in acetic acid/acetic anhydride; 88%),⁴⁹¹⁴ 5-bromo-4-hydroxy-6-methyl-2-methylthiopyrimidine (aqueous dioxane; 60%),⁴⁵⁶⁸ 5-bromo-2,4-dihydroxy-6-methylpyrimidine (in ethanol; benzoyl peroxide did not improve the yield of 55%),⁵⁰⁴⁶ and others.⁵¹⁶¹ It must be remembered that *N*-bromosuccinimide (and, indeed, bromine under vigorous conditions) can brominate alkyl groups too. Thus, 2-acetamido-4-hydroxy-6-methoxycarbonylmethylpyrimidine and *N*-bromosuccinimide in dimethylformamide gave its 5-bromo derivative (55, R = H) and/or 2-acetamido-5-bromo-4-(*C*-bromo-*C*-methoxycarbonylmethyl)-6-hydroxypyrimidine (55, R = Br), according to conditions.⁵⁷⁰⁴ Likewise, 2-amino-4-carboxymethyl-6-hydroxypyrimidine and bromine gave the 5-bromo derivative, 2-amino-5-bromo-4-*C*-bromo-*C*-carboxymethyl-6-hydroxypyrimidine, or even 2-amino-5-bromo-4-dibromomethyl-6-hydroxypyrimidine (tribromination/decarboxylation), according to the ratio of bromine and severity of conditions.⁵⁷⁶³

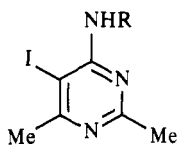
The *5-iodination of pyrimidines* has been done with elemental iodine in several ways: the simplest is iodine in aqueous alkali, but only when other groups present are stable to such treatment, as in the formations of 4-hydroxy-5-iodo-2-isopropyl-6-methylpyrimidine (56) (86%),⁵⁰⁹⁴ 2,4-dihydroxy-5-iodo-6-methylpyrimidine (80%),⁵⁹⁵⁷ and 2,4-dihydroxy-5-iodopyrimidine 1-oxide.³⁴⁶⁴ A related procedure used iodine and a little carbon tetrachloride in aqueous acid with the addition of hydrogen peroxide to use up the hydriodic acid formed during iodination by reoxidizing it to iodine. In this way were made 4-amino-5-iodo-2,6-dimethylpyrimidine (57, R = H) in 97% yield, 4-butylamino-5-iodo-2,6-dimethylpyrimidine (57, R = Bu), several homologues, 2-amino-5-iodo-4-methylpyrimidine (45%), and 2-amino-1,6-dihydro-5-iodo-1,4-dimethyl-6-oxypyrimidine (87%).⁴⁵⁰⁶ Another variation involved adding iodine in dioxane to the substrate in hot water containing mercuric acetate to give, for example, 4-chloro-2,6-dihydroxy-5-iodopyrimidine (*c.* 80%), 2,4-dihydroxy-5,6-di-iodopyrimidine (from

the 6-iodo substrate), and 4-bromo-1,2,3,6-tetrahydro-5-iodo-1,3-dimethyl-2,6-dioxypyrimidine (c. 45%).⁴⁶⁵⁰

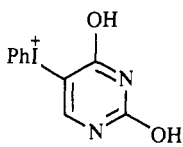
Although *N*-iodosuccinimide has been all but unused recently,⁶⁰⁴⁷ the classical reagent, iodine monochloride, has been employed to give both 1- and 3-benzyloxy-5-iodouracil in greater than 75% yield³⁴⁶⁴ and to make 2-hydroxy-5-iodopyrimidine (c. 70%).⁵⁶⁶⁴ Treatment of uracil with phenyl iodosoacetate in the presence of *p*-toluenesulfonic acid gave the tosylate of 2,4-dihydroxy-5-phenyliodiniopyrimidine (58), which was converted easily into the chloride, bromide, or betaine.⁴⁸⁴³



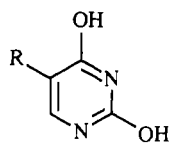
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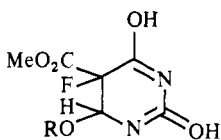
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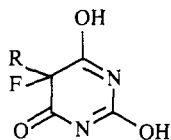
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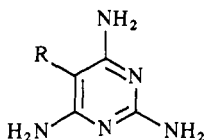
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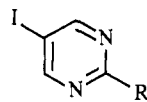
(60)



(61)



(62)



(63)

The *5-fluorination of pyrimidines* has not been carried out widely. However, the process has been explored to some extent, mainly in connection with possible preparations of the antitumor agent, 5-fluorouracil (59, R = F). Thus, treatment of uracil in aqueous trifluoroacetic acid with perfluoromethanol in trichlorofluoromethane at 25° gave 5-fluoro-2,4-dihydroxypyrimidine (59, R = F) in greater than 90% yield.⁵⁴⁸⁹ The same product was obtained by fluorination of uracil with fluorine gas (55%)⁵⁴⁸⁹ or with xenon difluoride (10% yield on XeF₂),⁴⁸⁷⁰ as well as by fluorination of 2,4-dihydroxy-5-methoxycarbonylpyrimidine (59, R = CO₂Me) with perfluoromethanol to give (in water) 5-fluoro-4,5-dihydro-2,4,6-trihydroxy-5-methoxycarbonylpyrimidine (60, R = H) or (in methanol) 5-fluoro-4,5-dihydro-2,6-dihydroxy-6-methoxy-5-methoxycarbonylpyrimidine (60, R = Me), both of which were converted by acid or alkali into 5-fluoro-2,4-dihydroxypyrimidine (59, R = F) in excellent yield.⁶²⁷⁷ Vacuum sublimation of the intermediate (60, R = Me) achieved the same end.⁶¹⁶³ Fluorination of other substrates has given 5-butyl-5-fluorobarbituric acid (61, R = Bu) (by "perchloryl fluoride" FClO₃),⁴⁷⁹⁹ 5-fluoro-2-hydroxypyrimidine (fluorine gas; 38%),⁴³⁹⁸ 5-fluoro-1,2-dihydro-1-methyl-2-oxypyrimidine (as above;

61%),⁴³⁹⁸ 4-carboxy-5-fluoro-2,6-dihydroxypyrimidine (perfluoromethanol; >90%),⁵⁵⁵² 5-fluoro-5-phenylbarbituric acid (61, R = Ph) (perfluoromethanol),⁵⁵⁵² 5,5-difluorobarbituric acid (61, R = F) (perfluoromethanol),⁵⁵⁵² and others.^{4398, 5552, 6277}

C. Other Methods for Preparing 5-Halogenopyrimidines (*H* 175, *E* 122)

The primary synthesis of 5-halogenopyrimidines has been covered in Ch. II and III. Simple examples would include the condensation of 2-chloro-1,1,3,3-tetraethoxypropane with formamide at 200° to give 5-chloropyrimidine in 61% yield;⁴⁴⁸³ the condensation of 3-dimethylamino-2-fluoroacrolein with formamide to give 5-fluoropyrimidine;⁵⁸⁵⁸ and the conversion of 2,4,5-trimethylimidazole by dichlorocarbene into 5-chloro-2,4,6-trimethylpyrimidine in low yield.⁵²⁴⁷ Other than such syntheses, 2,4,5,6-tetra-aminopyrimidine (62, R = NH₂) has been converted into 2,4,6-triaminopyrimidine-5-diazonium tetrafluoroborate (62, R = N₂⁺BF₄⁻), which on heating to 225° in paraffin oil gave 2,4,6-triamino-5-fluoropyrimidine (62, R = F) in 65% yield.⁴⁷⁴⁴ 2,4-Diamino-5-fluoro 6-hydroxypyrimidine has been made similarly,⁴⁷⁴⁴ and 5-iodopyrimidine (63, R = H) has been made by converting 2-chloro-5-iodo- (63, R = Cl) into 2-hydrazino-5-iodopyrimidine (63, R = NHNH₂) and then oxidatively removing the hydrazino group by treatment with silver oxide.⁵²⁶² Other examples involving diazonium salts are known.⁶⁷²⁹

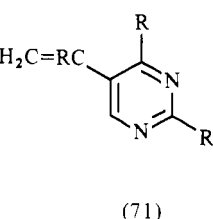
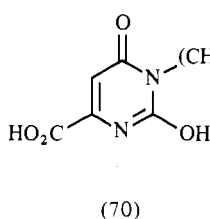
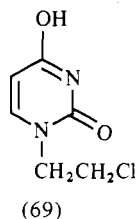
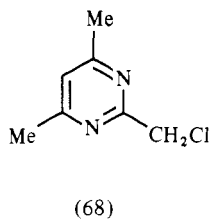
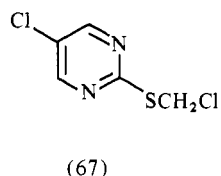
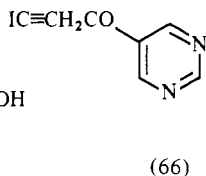
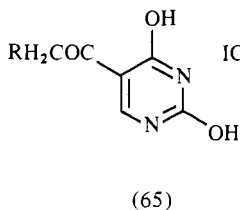
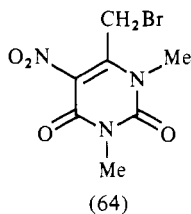
3. Preparation of Extranuclear Halogenopyrimidines (*H* 176, *E* 122)

The treatment below is somewhat subjective. The chloro substituent on 5-chloromethyluracil is very much part of a pyrimidine but that on 4,6-dihydroxy-5-*p*-chlorophenylazopyrimidine is not, for practical purposes.

A. By Direct Halogenation (*H* 176, *E* 122)

The direct halogenation of *C*-alkyl groups attached directly to the pyrimidine nucleus has been detailed in Ch. IV. Sect. 2.C (5). Selected examples include the conversion of 4-methylpyrimidine by *N*-bromosuccinimide into a separable mixture of 4-mono-, 4-di-, and 4-tribromomethylpyrimidine;⁵⁶⁸² of 2-isopropyl- into 2- α -bromo- α -methylethylpyrimidine;⁵⁶⁹⁰ of 1,2,3,4-tetrahydro-1,3,6-trimethyl-5-nitro-2,4-dioxo- into 4-bromomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-

2,6-dioxypyrimidine (64) by bromine in acetic acid;⁶¹³⁸ of 3-isopropyl-6-methyl- into 3-isopropyl-6-trichloromethyluracil by sulfonyl chloride in acetic acid/acetic anhydride;⁵⁵⁸⁸ and of 2-thien-2'-ylpyrimidine into 2-5'-bromothien-2'-ylpyrimidine by bromine in acetic acid/sodium acetate.⁴⁸⁹¹



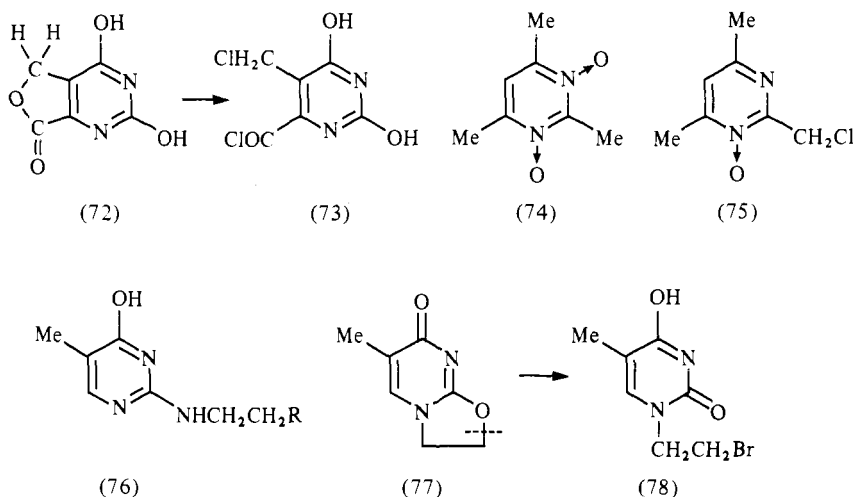
Extranuclear halogenations of other than directly attached alkyl or aryl groups are exemplified in the transformation of 5-acetyl- into 5-chloro(or bromo)acetyl-2,4-dihydroxypyrimidine (65, R = Cl or Br) by chlorine (or bromine) in acetic acid or methanol;^{5238, 5473, 5849} of 5-prop-2'-ynoxy- into 5-3'-iodoprop-2'-ynoxypyrimidine (66) by treatment with iodine/sodium hydroxide;⁴³⁹⁵ and of 5-chloro-2-methylthio- into 5-chloro-2-chloromethylthiopyrimidine (67) by treatment with sulfonyl chloride.⁶³⁷⁸

B. From the Corresponding Hydroxyalkylpyrimidines (H 178, E 123)

A variety of reagents have been used to convert hydroxyalkyl- into halogenoalkyl-pyrimidines, as indicated in the preparation of 4-chloromethyl-2,6-dihydroxypyrimidine (thionyl chloride/dimethylformamide; 93%), 5-chloromethyl-2,4-dihydroxypyrimidine (10 M hydrochloric acid; 90%);⁵⁶⁴¹ 5-chloromethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (thionyl chloride; 76%);⁶²³⁹ 4-amino-5-chloromethyl-2-cyclopropylpyrimidine (thionyl chloride/dimethylformamide; > 85%), 5-chloromethyl-2,4-dihydroxy-6-methylpyrimidine (thionyl chloride/dimethylformamide; 78%);⁴³⁸⁷ 2-chloromethyl-4,6-dimethylpyrimidine (68) (phosphoryl chloride; 90%);⁶⁰⁰⁸ 2,4-diamino-5-bromomethyl-

pyrimidine (hydrogen bromide in acetic acid),⁵³⁸⁴ and 5-benzyloxy-4-chloro-2-chloromethylpyrimidine (from 5-benzyloxy-4-hydroxy-2-hydroxymethylpyrimidine with phosphoryl chloride).⁵³⁴⁵ It is evident from the above that phosphoryl chloride replaces each 2-, 4/6- and extranuclear hydroxy group by a chloro substituent, whereas thionyl chloride or hydrohalides are selective in replacing only extranuclear hydroxy groups.

Less simple examples are provided by the formation of 4- α -chloroethyl-2-methyl-6-phenylpyrimidine (phosphoryl chloride 80%),⁶²⁹⁹ 5- β -chloroethyl-4-hydroxy-6-methyl-2-(3',4',5'-trimethoxyphenyl)pyrimidine (thionyl chloride and hydrogen chloride; crude material cyclized in base to 5,6-dihydro-4-methyl-2-(3',4',5'-trimethoxyphenyl)furo[2,3-*d*]pyrimidine),⁶³⁰⁶ 1- β -chloroethyluracil (69) (thionyl chloride/pyridine; 90%),^{5495, 5818} 3- β -chloroethyl-6-methyluracil (thionyl chloride/pyridine),⁶²¹⁸ 1,3-bis- β -chloroethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxypyrimidine (as above; 49%),⁶²¹⁸ 3- δ -bromobutyl-6-carboxyuracil (70) (48% hydrobromic acid at 100°),⁴⁷⁷⁸ and 2,4-dichloro-5- α -chlorovinylpyrimidine (71, R = Cl) [from the enolic form (71, R = OH) of 5-acetyluracil with phosphoryl chloride; 57%],⁵³²⁹ as well as by the ring fission of the lactone (72) of 4-carboxy-2,6-dihydroxy-5-hydroxymethylpyrimidine by treatment with ethanolic hydrogen chloride to give 4-chlorocarbonyl-5-chloromethyl-2,6-dihydroxypyrimidine (73)⁶¹⁹³ and by the treatment of 2,4,6-trimethylpyrimidine 1,3-dioxide (74) with phosphoryl chloride to give 2-chloromethyl-4,6-dimethylpyrimidine *N*-oxide (75), a structure beyond reasonable doubt.⁶¹⁶⁰



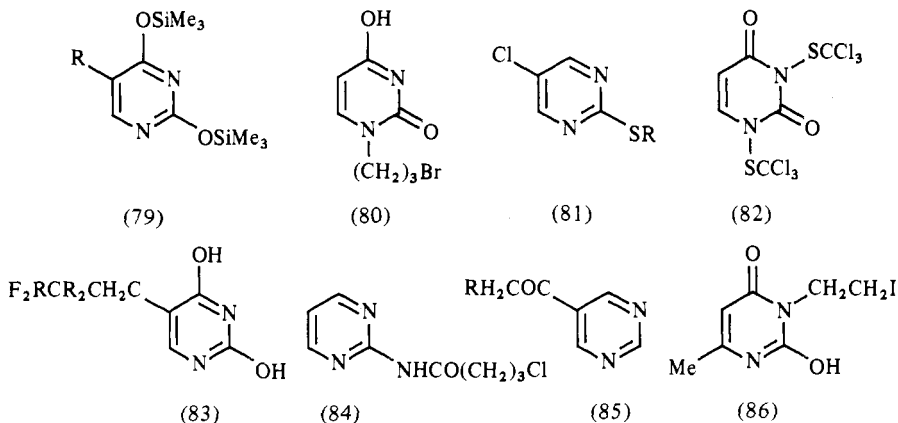
This route has also been used to make halogenoalkylaminopyrimidines, in which the chloroalkyl moiety is attached indirectly to the pyrimidine nucleus. Thus, 4-hydroxy-2- β -hydroxyethylamino-5-methylpyrimidine (76, R = OH) with thionyl chloride gave 2- β -chloroethylamino-4-hydroxy-5-methylpyrimidine (76, R = Cl) in 99% yield.⁴⁵⁷¹ The homologous 2- γ -chloropropyl derivative (76, R = CH₂Cl) was made similarly,⁴⁵⁷¹ as were 2- β -chloroethylamino-1,2-dihydro-1,6-dimethyl-2-oxopyrimidine,⁴⁵⁶⁹ 4-[N,N-di(β -chloroethyl)amino]methyl-2,6-dihydroxypyrimidine,⁵⁸⁵⁴ 4- β -chloroethylamino-2,6-dimethoxypyrimidine,⁴⁷¹⁴ and other such compounds.⁴⁷⁷⁵

D. By Direct Primary Synthesis (*H* 179, *E* 124)

Some primary syntheses leading to extranuclear halogenopyrimidines have been discussed in Ch. II and III. A few random examples include the formation by the Principal Synthesis of 5-*p*-chlorophenyl-2-mercaptopyrimidine,⁵⁶⁶³ the condensation of α -chloromalonyl chloride with fluoroacetonitrile to give 4,5-dichloro-2-fluoromethyl-6-hydroxypyrimidine,⁵²⁵³ the degradation of 5,7-dimethyl-*v*-triazolo-[1,5-*a*]pyrimidine by bromine to give 2-dibromomethyl-4,6-dimethylpyrimidine,⁵⁴⁴⁹ and the ring fission of 2,3-dihydro-6-methyl-7-oxo-7*H*-[1,3]oxazolo[3,2-*a*]pyrimidine (77) by methanolic hydrobromic acid to give 1- β -bromoethyl-5-methyluracil (78).⁶⁰⁷⁷

E. By Other Means (*H* 180, *E* 125)

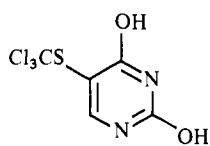
Halogenoalkylation may be applied to ring-nitrogen or to substituents such as mercapto or amino groups. This process is illustrated in the treatment of 2,4-bis(trimethylsilyloxy)pyrimidine (79, R = H) with 1,3-dibromopropane at 25° for 7 days to give 1- γ -bromopropyluracil (80, R = H);⁵⁶⁴⁶ the similar conversion of the thymine derivative (79, R = Me) into 1- γ -bromopropyl-5-methyluracil (80, R = Me);⁵⁶⁴⁶ the reaction of the disodium salt of uracil with an excess of 1,4-dibromobutane in dimethylformamide at *c.* 50° to give 1,3-bis(δ -bromobutyl)-1,2,3,4-tetrahydro-2,4-dioxypyrimidine;⁴⁸²⁸ and other such reactions which, naturally, can give rise to oligomers under inappropriate conditions.⁴⁸²⁸ Halogenoalkylation is easier at sulfur. Treatment of 5-chloro-2-mercaptopyrimidine (81, R = H) with bromochloromethane in acetonitrile/chloroform containing triethylamine at 5° gave 5-chloro-2-chloromethylthiopyrimidine (81, R = ClCH₂).⁶³⁷⁸



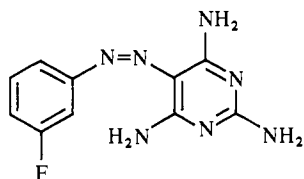
In a broadly similar way, 2-mercapto- gave 2-chloromethylthiopyrimidine,^{4873, 5519} but 2-mercapto-4,6-dimethylpyrimidine gave a separable mixture of 2-chloromethylthio-4,6-dimethylpyrimidine and bis(4,6-dimethylpyrimidin-2-ylthio)methane;⁴⁸⁷³ 2-mercaptopyrimidine with 1-bromo-2-fluoroethane gave 2- β -fluoroethylthiopyrimidine.⁴⁸⁷³ Such results suggest that a bromo is more reactive than a chloro or fluoro substituent in the above context. A sort of combination, in effect, of the above processes is seen in the *N,N*-dialkylation of uracil with perchloromethanethiol (Cl_3CSCl) to give 1,2,3,4-tetrahydro-2,4-dioxo-1,3-bis(trichloromethylthio)pyrimidine (82).⁴⁴⁸⁷ Halogenoalkylation of an amino group is represented, likewise, in the reaction of 2-aminopyrimidine with perchloromethanethiol to give 2-trichloromethylthio-aminopyrimidine.⁵⁴⁸⁵ A somewhat similar reaction is that of 2,4-dihydroxy-5-hydroxymethylpyrimidine in anhydrous hydrogen fluoride with vinyl fluoride or tetrafluoroethylene to give 5- γ,γ -difluoropropyl-2,4-dihydroxypyrimidine (83, $\text{R} = \text{H}$) or 2,4-dihydroxy-5- $\beta,\beta,\gamma,\gamma,\gamma$ -pentafluoropropylpyrimidine (83, $\text{R} = \text{F}$).⁴⁸⁰⁰

Halogenoacylation has wide potential but appears to have been little used, apart from the conversion of 2-aminopyrimidine into 2- γ -chloropropionamidopyrimidine (84) and related compounds.⁵⁴⁹² *Haloaminolysis* is represented in the reaction of 2,4,6-trichloropyrimidine with *N,N*-bis(β -chloroethyl)hydrazine to give mainly 2,4-dichloro-6-[*N,N*-di-(β -chloroethyl)hydrazino]pyrimidine, and in related reactions.⁴⁷⁹¹ The conversion of an extracyclic *diazo* to *halogeno* substituent has been used to convert 5-diazoacetyl- (85, $\text{R} = \text{N}_2$) into 5-bromoacetylpyrimidine (85, $\text{R} = \text{Br}$) by cold hydrobromic acid.⁴⁴⁷³ Extranuclear *transhalogenation* of 5-chloro-2-chloromethylthio- to 5-chloro-2-iodomethylthiopyrimidine has been achieved by boiling with

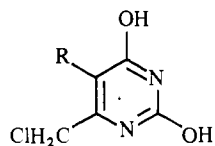
sodium iodide in acetone;⁶³⁷⁸ of 3- β -chloroethyl- to 3- β -iodoethyl-6-methyluracil (86) by potassium iodide in acetone;⁶²¹⁸ and of 2,4-dihydroxy-5-trifluoromethylthio- to 2,4-dihydroxy-5-trichloromethylthiopyrimidine (87) by prolonged treatment with boron trichloride.⁴⁴⁶⁹ The introduction of extranuclear *halogenoarylazo* groups has been widely carried out by diazo coupling reactions (Ch. V., Sect. 3.A) which gave, for example, 2,4,6-triamino-5-*m*-fluorophenylazopyrimidine (88),⁵²⁹³ 2-amino-5-*o*-bromophenylazo-4,6-dimethylpyrimidine,⁵³⁶³ and many other such compounds.^{4966, 5358, 5365, 5368, 5869} *Miscellaneous routes* to extranuclear halogenopyrimidines are exemplified in the treatment of 4-chloromethyl-2,6-dihydroxypyrimidine (89, R = H) with paraformaldehyde in formalin containing hydrochloric acid to give 4,5-bischloromethyl-2,6-dihydroxypyrimidine (89, R = CH₂Cl);⁵⁶⁰³ in the conversion of 4-hydroxy-2-mercapto-6-methylpyrimidine, by paraformaldehyde and di(β -chloroethyl)amine in dimethylformamide, into 5-[di-*N,N*-(β -chloroethyl)amino] methyl-4-hydroxy-2-mercapto-6-methylpyrimidine (90);⁴⁵⁹³ in the treatment of 4-amino-2-hydroxypyrimidine with *S*-chloro-*C,C,C*-trifluoromethanethiol (F₃CSCl) in pyridine to give 4-amino-2-hydroxy-5-trifluoromethylthiopyrimidine (91);⁴⁴⁶⁹ in the *S*-alkylation of 2,4-dihydroxy-5-mercaptopyrimidine by the same reagent (F₃CSCl) to give the disulfide, 2,4-dihydroxy-5-trifluoromethyldithiopyrimidine (92);⁴⁴⁶⁹ and in the treatment of 5-carboxy- and 5-formyl-2,4-dihydroxypyrimidine with sulfur tetrafluoride at 100° to give 2,4-dihydroxy-5-trifluoromethylpyrimidine (77%) and 5-difluoromethyl-2,4-dihydroxypyrimidine (60%), respectively.⁵⁶³¹ The reaction of 2- and 4-methylpyrimidine 1-oxides with phosphoryl chloride gave only 2- and 4-chloromethylpyrimidine, respectively, both in reasonable yield.⁶⁶⁰⁸



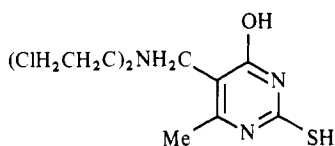
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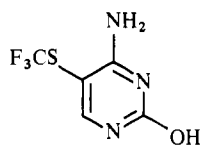
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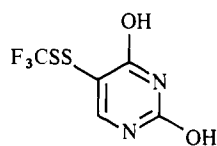
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(92)

5. Reactions of 2-, 4-, and 6-Halogenopyrimidines (*H* 183, *E* 126)

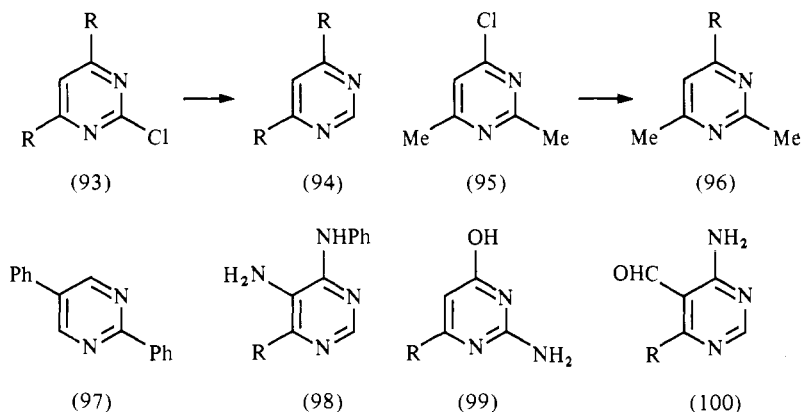
Active halogenopyrimidines have retained their place as the most valuable substrates for preparing all manner of other pyrimidines.

A. Removal of 2-, 4-, and 6-Halogens (*H* 183, *E* 126)

The direct removal of halogeno substituents is usually done by hydrogenolysis over palladium or some other catalyst, in the presence of a base if nuclear reduction is to be avoided. Zinc dust or hydriodic acid dehalogenations are sometimes convenient, and a few minor methods are also represented below. Hydrogenolysis shows but little selectivity, either for position or kind, if several halogen substituents are present. Zinc can be more selective, as will appear in some examples. Hydriodic acid is applicable only to 2-chloropyrimidines.

(1) *In the Presence of Only Alkyl or Aryl Groups* (*H* 183, *E* 127)

Pyrimidine has been made conveniently by dehalogenation of 2-chloro- (93, *R* = H), 2-bromo-, or 2-iodopyrimidine with hot hydriodic acid. The mediocre yield, *c.* 40%, was probably due to isolation difficulties because 4,6-dimethyl- (94, *R* = Me) and 4,6-diphenylpyrimidine (94, *R* = Ph) were made likewise from their respective 2-chloro derivatives (93, *R* = Me or Ph) in nearly 80% yield.⁵⁶⁷³ Attempts to dehalogenate 4-chloro-2,6-dimethylpyrimidine (95) with hydriodic acid resulted in 4-iodo- (96, *R* = I) or 4-hydroxy-2,6-dimethylpyrimidine (96, *R* = OH), according to conditions.⁵⁶⁷³ In contrast, zinc dust in hot aqueous ammonia completely dehalogenated 2,4-dichloro-5-methylpyrimidine to give 5-methylpyrimidine (75%).⁵⁶⁷³ Hydrogenolysis over palladium in ethanol or aqueous ethanol containing magnesium oxide or sodium acetate has been used to dehalogenate the 4,6-dichloro derivatives of 5-ethylpyrimidine (80% yield),⁴⁴⁹⁷ 2,5-diphenylpyrimidine (97) (95% yield),⁴⁴⁹⁷ 2,5-bis-*p*-ethoxyphenylpyrimidine (61%),⁴⁴⁹⁷ 2-phenyl-5-*p*-tolylpyrimidine (60%),⁴⁵²⁹ 2-*p*-hexylphenyl-5-phenylpyrimidine (43%),⁴⁵²⁹ 5-butyl-2-*p*-propoxyphenylpyrimidine (92%),⁴⁵³⁹ and about 100 homologues/analogues.^{4497, 4529, 4539} The action of lithium aluminum hydride in ether on 2,4,5,6-tetrafluoropyrimidine proved selective only in not attacking the 5-fluoro substituent; by using 2.5 mol of reagent, a mixture of 2,4,5-tri-, 4,5,6-tri-, and 2,5-difluoropyrimidine resulted.⁵⁷⁷⁹



(2) In the Presence of Amino Groups (H 185, E 127)

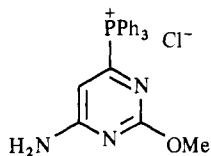
The hydrogenolytic removal of chloro in the presence of only amino group(s) is exemplified in the conversion of 2,4-dichloro-5-methylaminopyrimidine, by hydrogenation over palladium in water containing magnesium oxide, into 5-methylaminopyrimidine (10% yield; probably so poor because the magnesium chloride/amine complex was not broken by alkali prior to isolation by sublimation);⁶⁰⁶² 4,6-dibromo-2-isopropylaminopyrimidine (palladium in ethanolic sodium carbonate) into 2-isopropylaminopyrimidine;⁶³²⁷ 4-amino-6-chloro- into 4-aminopyrimidine (78%);⁴⁵⁰⁹ 2-chloro-4-piperidino- (palladium in methanol with magnesium oxide) into 4-piperidinopyrimidine (37%; no alkaline treatment before isolation);⁴⁶⁶³ 2-chloro-4-pyrrolidino- (palladium in methanol containing sodium acetate) into 4-pyrrolidinopyrimidine (98%);⁴⁵⁸¹ 5-amino-4-anilino-6-chloro- (98, R = Cl) (palladium in methanol containing magnesium oxide) into 5-amino-4-anilino-pyrimidine (98, R = H) (60%);⁵¹²⁸ 4,5-diamino-2-t-butyl-6-chloro- (palladium in water with magnesium oxide) into 4,5-diamino-2-t-butyl-pyrimidine (62%; after treatment with sodium carbonate);⁵⁷⁵³ and 5-amino-4-chloro-6-isopropylamino- (as above) into 5-amino-4-isopropylaminopyrimidine.⁵⁷⁵³

Similar palladium-catalyzed hydrogenolyses in the presence of both amino and other functional groups are illustrated in the formation of 2-amino-4-hydroxypyrimidine (99, R = H) from its 6-iodo or bromo derivative (99, R = I or Br) (methanolic ammonia);⁵¹⁵⁴ 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine (68%) from its 6-chloro derivative (as above);⁴⁹⁶⁹ 4-benzylidenehydrazono-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxopyrimidine (37%) from its 6-chloro derivative

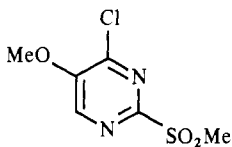
(ethanol),⁵¹⁶² 4-amino-5-hydroxy-2-methylpyrimidine (83%) from its 6-chloro derivative (ethanol; magnesium oxide),⁶³⁷³ 2,4-diaminopyrimidine 3-oxide (69%) from its 6-chloro derivative (ethanolic potassium hydroxide),⁶⁰⁹² 5-amino-4-methoxy-6-methylpyrimidine from its 2-chloro derivative (methanol; potassium hydroxide),⁵⁷⁸⁶ 2-dimethylamino-4-methoxypyrimidine (98%) from its 6-chloro derivative (aqueous methanol; magnesium oxide),⁶¹⁰⁶ 4-dimethylamino-2-methoxypyrimidine (82%) from its 6-chloro derivative (ethanol),⁴⁷⁰³ 4-amino-5-formylpyrimidine (100, R = H) from its 6-chloro derivative (100, R = Cl) (methanol; magnesium oxide; note survival of aldehyde group as such),⁴⁴⁷¹ 2-amino-4-trifluoromethylpyrimidine from its 6-chloro derivative (ethanolic ammonia);⁵⁷⁸⁵ and 2-amino-4-methoxycarbonylmethylpyrimidine from its 6-chloro derivative (methanol; magnesium oxide).⁵²⁴³ The last conversion was done more effectively (68% yield) by boiling in water with zinc dust.⁵²⁴³ The use of reagents other than hydrogenolysis is further illustrated in the dehalogenation of 4-amino-6-chloro-2-methoxypyrimidine by treatment with triphenylphosphine to give 4-amino-2-methoxy-6-triphenylphosphoniopyrimidine chloride (101), which in alkali gave 4-amino-2-methoxypyrimidine in low yield,⁵⁰⁶⁹ as well as in the treatment of 4-amino-6-chloro-2-methylthiopyrimidine in liquid ammonia with sodium to give 4-amino-2-mercaptopyrimidine (66%) (the product was named incorrectly as the 6-mercapto isomer in the experimental section of the original paper).⁴³⁵⁶ Other dechlorinations have been reported.⁶⁴²³

(3) *In the Presence of Other Groups (H 185, E 127)*

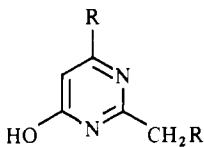
Hydrogenolysis over palladium has been used to dehalogenate the following substrates: 5-acetyl-4,6-dichloropyrimidine (ethanol; magnesium oxide; 34%),⁶²⁴³ 4-chloro-5-methoxy-2-methylsulfonylpyrimidine (102) (76%, without affecting the sulfone group),⁵⁶⁶² 5-butyl-4-chloro-2,6-dihydroxypyrimidine,⁵⁹¹⁵ 4-chloro-5-thien-2'-(or 3')-ylpyrimidine,⁴⁴⁰⁶ 5-acetyl-4-chloro-2,6-dimethylpyrimidine (methanol).⁵⁰⁷⁷ 4-chloro-2-methoxycarbonylmethyl-6-phenylpyrimidine (>80%; methanol; sodium carbonate),⁵⁶⁸⁸ 4,6-dichloro-2-ethoxycarbonylmethylpyrimidine (68%) (water; sodium carbonate),⁵⁶⁸⁸ and 4-chloro-6-hydroxy-2-methylpyrimidine (ethanol; sodium hydroxide; 90%).⁵⁶⁷⁶ The same procedure converted 2,4-dichloro-6-ethoxycarbonyl-5-nitropyrimidine into 5-amino-2-chloro-4-ethoxycarbonylpyrimidine and thence into 5-amino-4-ethoxycarbonylpyrimidine,⁴³⁶⁴ while 4-chloro-2-chloromethyl-6-hydroxypyrimidine (103, R = Cl) or its



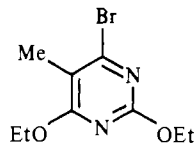
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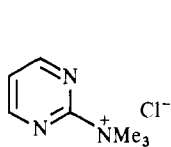
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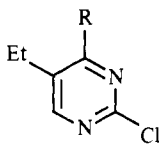
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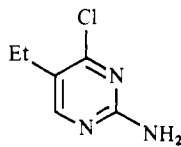
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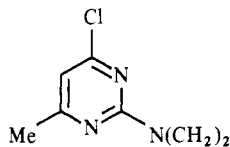
(105)



(106)



(107)



(108)

2-fluoromethyl analogue gave 4-hydroxy-2-methylpyrimidine (103, R = H) in 70% yield.⁵²⁵³

Other reagents are illustrated in the dehalogenation of 4-chloro-2,6-diethoxy-5-ethylpyrimidine (zinc dust/ethanol; 76%),⁵⁷⁹⁷ 4-chloro-5-methoxy-6-methoxymethylpyrimidine (zinc dust/aqueous sodium hydroxide at 20°) or hydrogenolysis over palladium gave 5-methoxy-4-methoxymethylpyrimidine (in 84% yield, but zinc dust/aqueous sodium hydroxide at 95° gave mainly 5-methoxy-4-methylpyrimidine),⁴³⁹⁷ 4-chloro-2-ethylthio-5-methoxypyrimidine (zinc/aqueous ethanol; 60%; also several alkylthio homologues),⁴³⁹⁵ and 4-bromo-2,6-diethoxy-5-methylpyrimidine (104) (butyllithium followed by ammonium chloride).⁵⁵¹⁷

(4) Indirect Removal of Halogeno Substituents (*H* 187, *E* 128)

The removal of a chloro substituent, by conversion into a triphenylphosphonio group followed by alkaline treatment, has been mentioned in Sect. 2 above. Examples of the more usual indirect removals of chloro substituents by initial conversion into a hydrazino, mercapto, or methylthio group, followed by oxidative or reductive removal as appropriate, will be found logically under the preparation of such intermediates and under their removal.

B. Replacement of 2-, 4-, and 6-Halogens by Amino Groups (*H* 187, *E* 129)

As well as a wide review of nucleophilic substitution in azines,⁴⁷⁵⁸ two practical kinetic studies of the aminolysis of halogenopyrimidines have extended existing knowledge (see *E* 129 *et seq*). The first of these

(from Novosibirsk), presented second-order rate constants for the piperidinolysis in isooctane of 2-chloro-, 4-chloro-, 2-chloro-4-substituted-, 4-chloro-2-substituted-, and 4-chloro-6-substitutedpyrimidine in which the substituents were methyl, phenyl, methoxy, dimethyl-amino, chloro, and trifluoromethyl. It emerged that rate constants showed good correlation using σ_I and σ_R Taft/Lewis constants derived from the benzene series, and a comparison of ρ_I and ρ_R coefficients in both series indicated the relative conductance of electronic effects in the pyrimidine system.⁴⁷⁶² This work followed naturally from earlier results for the piperidinolysis of 2-chloropyrimidines in a variety of solvents, which emphasized the importance of solvation in such aminolysis.⁴⁷⁹⁰

The second study (from Canberra) initially presented $t_{1/2}$ values for the isopentyl- and 1,4-dimethylpentylaminolysis of simple 2(and 4)-chloro-, 2(and 4)-bromo-, and 2(and 4)-iodopyrimidines without additional solvent.⁵⁶⁶⁴ The study was later extended to include comparable 2- and 4-fluoropyrimidines, and relative rates were confirmed by measuring second-order rate constants using ethanolic piperidine under classical conditions.⁵⁶⁷⁶ The fluoropyrimidines reacted 60–200-fold faster than other corresponding halogenopyrimidines, which varied but three-fold between themselves.^{5664, 5676}

Sad to say, many of the examples of preparative aminolyses recorded in the following pages, will be recognized as classical cases of the use of “overkill” conditions to achieve a desired target.

(1) *Aminolysis of Simple Halogenopyrimidines (H 188, E 129)*

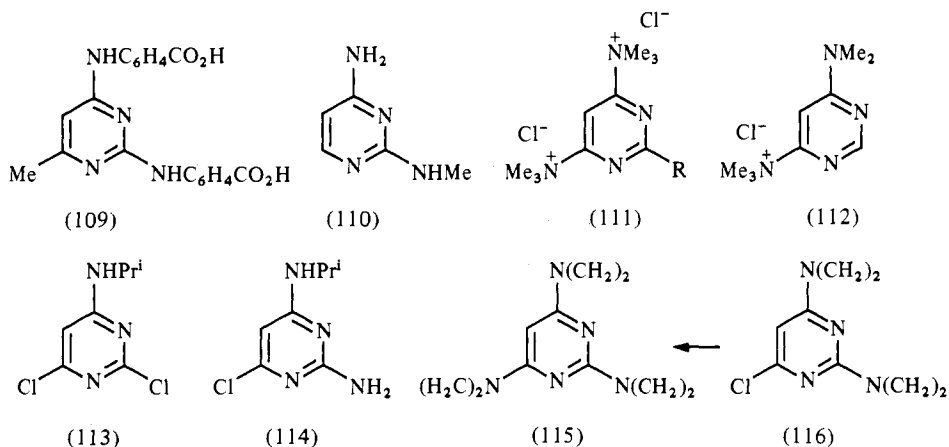
(a) *With One Active Halogen.* Preparative conditions used for the aminolysis of simple halogenopyrimidines are illustrated by the following conversions using *ammonia*: 2-chloro- to 2-amino-4-phenylpyrimidine (ethanolic ammonia; 120°; 10 h; 70%),⁶⁰⁴² 2-benzyl-4-chloro- to 4-amino-2-benzylpyrimidine (ethanolic ammonia; 145°; 6 h; 76%),⁴⁶⁷⁰ 4-chloro- to 4-amino-2,6-diphenylpyrimidine (ethanolic ammonia; 130°; 20 h; *c.* 100%),⁵⁷⁶⁰ and 2-chloro- to 2-amino-4,6-dimethyl-5-*p*-nitrophenylpyrimidine (ethanolic ammonia; 150°; 17 h; >90%);⁵⁶⁶² *primary amines*: 4-chloro-2-methyl- to 2-methyl-4-methylaminopyrimidine (methylamine in benzene under reflux; 75%),⁴⁴⁴⁹ 2-chloro-4,6-dimethyl- to 4,6-dimethyl-2-methylaminopyrimidine (aqueous methylamine; 100°; 16 h; 90%),⁵⁴⁸⁶ 2-chloro- to 2-isoamyl-amino- (no solvent; 40°; 1.5 h; *c.* 80%) or 2-(1,4-dimethylpentylamino)-pyrimidine (no solvent; 95°; 2 h),⁵⁶⁶⁴ 4-bromo- to 4-isopropylamino-6-

phenylpyrimidine (ethanolic isopropylamine; 100°; 4 h; 95%),⁴⁶⁷⁹ 4-t-butyl-2-chloro- to 2-benzylamino-4-t-butylpyrimidine (refluxing benzylamine; 18 h; 54%),⁵⁴⁸⁴ 2-benzyl-4-chloro- to 4-anilino-2-benzyl-6-methylpyrimidine (aniline; 130°; 1.5 h),⁶⁰¹⁸ 4-chloro- to 4-benzylamino-2,6-dimethylpyrimidine (benzylamine in dimethyl sulfoxide; 50°; > 24 h; 74%),⁵⁸⁸³ 2-chloro- to 2-*o*-carboxyanilino-4,6-diphenylpyrimidine (anthranilic acid; 150°; 2 h; 80%),⁴⁸¹⁸ 4-chloro- to 4- β -dimethylaminoethylamino-6-methyl-2-thien-2'-ylpyrimidine (β -dimethylaminoethylamine; reflux; 1.5 h),⁶²⁸⁷ and other such compounds;^{5662, 6288} *secondary amines*: 2-chloro- to 2-diethylamino- (no solvent at 130° for 24 h; 71%;⁶⁰⁷³ or ethanolic amine under reflux for 1 h, 85%)⁶¹⁷² or 2-piperidinopyrimidine (ethanolic piperidine; reflux; 1 h; 60%),⁵⁶⁷⁶ 2-chloro-5-phenyl- to 5-phenyl-2-piperazinopyrimidine (ethanolic piperazine at 60°; 81%),⁶⁰⁸⁰ 4-chloro- to 4-diethylamino- (no solvent; 130°, 60 h; 62%) or 4-piperidinopyrimidine (no solvent; 200°; 48 h; 62%),⁴⁴⁸³ 4-chloro- to 4-diethylamino-2,5-dimethylpyrimidine (diethylamine in chloroform under reflux for 60 h; 38%),⁴⁴⁷⁸ 4-chloro-5- β -chloroethyl- to 5- β -chloroethyl-4-*N*-ethylanilinopyrimidine (*N*-ethylaniline in refluxing ethanol for 7 h; 68%; note β -chloro substituent unaffected),⁴⁸⁷⁶ and others;⁵⁹⁵⁹ *tertiary amines*: 2-chloropyrimidine to 2-trimethylammoniopyrimidine chloride (105) (trimethylamine in benzene at 20°),⁵³⁴² 4-chloropyrimidine to 4-trimethylammoniopyrimidine chloride (as above *c.* 60%),⁵³⁴² 4-chloro-2-isopropylpyrimidine to 2-isopropyl-4-trimethylammoniopyrimidine chloride (in benzene at 25° for 3 days),⁵⁶⁹⁴ 2-chloro-4-phenylpyrimidine to 4-phenyl-2-trimethylammoniopyrimidine chloride (in benzene; 12 h; 99%),^{5839, 6041} 4-chloro-2(or 5)-methylpyrimidine to 2(or 5)-methyl-4-trimethylammoniopyrimidine chloride (in benzene; 2 days or 18 weeks, respectively),⁵⁶⁷⁶ and 4-chloro-6-phenylpyrimidine to 4-phenyl-6-trimethylammoniopyrimidine chloride (in benzene; 20 h; 96%).⁶¹¹⁷

(b) *With Two or Three Active Halogens.* The aminolysis of a 2,4-dihalogenopyrimidine under sufficiently gentle conditions usually gives a mixture of two aminohalogenopyrimidines in which the 4-amino-2-chloropyrimidine normally predominates, but when conditions are more vigorous a diaminopyrimidine results. Thus, treatment of 2,4-dichloro-5-ethylpyrimidine (106, R = Cl) with ethanolic ammonia at 90° gave 4-amino-2-chloro- (106, R = NH₂) in 72% yield and the isomeric 2-amino-4-chloro-5-ethylpyrimidine (107) in 7% yield after separation; treatment of 2,4-dichloro-6-methylpyrimidine with benzylamine at 180° gave 4-benzylamino-2-chloro- (49%) and 2-benzylamino-4-chloro-6-methylpyrimidine (23%),⁴⁸⁴⁹ treatment of 2,4-dichloro-5- α -

chlorovinylpyrimidine with ethanolic ammonia at 0° gave 4-amino-2-chloro- (28%) and 2-amino-4-chloro-5- α -chlorovinylpyrimidine (11%);⁵²⁸⁷ treatment of 2,4-dichloro-6-methylpyrimidine with aziridine in benzene gave only 2-aziridino-4-chloro-6-methylpyrimidine (108), but since the yield was only 42%, the isomer may have been lost during workup;⁵⁸⁸⁰ and other examples have been reported.⁵¹⁰⁶ The utility of such "first-stage aminolysis products" is that their remaining chloro substituent may be replaced by a second different amino group (or indeed by an alkoxy and so on) as required. This extended process is illustrated by the conversion of 2,4-dichloropyrimidine, by aqueous anthranilic acid at 50°, into 4-*o*-carboxyanilino-2-chloropyrimidine which, with ethanolic ammonia at 120°, gave 2-amino-4-*o*-carboxyanilinopyrimidine;⁴⁸²³ as well as in the sequential conversion of 2,4-dichloro- into 2-chloro-4-piperidino- and thence into 2-amino-4-piperidinopyrimidine.⁴⁶⁶³ Examples of the replacement of both chloro substituents by the same amine include the formation of 2,4-bis-*p*-carboxyanilino-6-methylpyrimidine (109),⁵⁸⁸⁴ 2,4-bis-*p*-chloroanilino-5-methylpyrimidine (amine hydrochloride in water at reflux for 1 h; 92%),⁶⁰⁵⁹ 2,4-diamino-6-propylpyrimidine (methanolic ammonia; 150°; 7 h),⁵⁸⁰⁷ and 2,2',4'-trisdimethylamino-6-phenyl-4,5'-bipyrimidine (ethanolic dimethylamine under reflux for 6 h; 60%).⁶²⁵⁵ The second stage of such diaminolysis has sometimes to be considered in isolation because the substrate, which could be made (theoretically) by a first-stage aminolysis, has been made more easily by other means, for example, primary synthesis. Such second-stage aminolyses are illustrated in the conversion of 2-amino-4-chloro- into 2,4-diamino-6-isopropylpyrimidine (methanolic ammonia at 160°),⁵⁸⁰⁷ 2-anilino-4-chloro-6-methyl- into 2-anilino-4-methyl-6-piperidinopyrimidine (no solvent; reflux for 2 h),⁵⁹⁸⁶ 4-chloro- into 4-amino-2-morpholinopyrimidine (ammonia gas into a refluxing phenol solution with Cu²⁺ catalyst; 76%),⁵⁸⁶⁶ 5-adamant-1'-yl-2-amino-4-chloro- into 5-adamant-1'-yl-2,4-diamino-6-ethylpyrimidine (ethanolic ammonia; 150°),⁵⁴⁵³ the 6-methyl homologue of the above,⁵²⁹⁷ 4-chloro- into 4-amino-2-methylamino-pyrimidine (110) (in phenol; 69%),⁴⁶⁷⁰ and others.^{5298, 6304}

The aminolysis of a 4,6-*dihalogenopyrimidine* is less complicated at the first stage because only one aminohalogenopyrimidine can be formed on account of symmetry. Thus, 4,6-dichloropyrimidine and ethanolic benzylamine or cyclohexylamine at 100° gave 4-benzylamino-6-chloro- (111, R = CH₂Ph) or 4-chloro-6-cyclohexylaminopyrimidine (111, R = C₆H₁₁), each in *c.* 70% yield;⁵³⁵⁷ 4,6-difluoro- gave 4-amino- or 4-dimethylamino-6-fluoropyrimidine (ethanolic amine at 25°; 50%



or 97%, respectively);⁴⁷⁵² and 4,6-dichloro- gave 4-chloro-6- β,β -diethoxyethylaminopyrimidine (94%).⁵¹⁰⁶ Replacement of both halogeno substituents is represented in the formation of 2-phenyl-4,6-dipiperidino-pyrimidine (refluxing piperidine plus a drop of hydrochloric acid; 2.5 h; 68%);⁴⁹⁷² 2-methyl-4,6-bis(trimethylammonio)pyrimidine dichloride (111, R = Me) (trimethylamine in benzene at 25°; not characterized);⁵⁰⁹⁰ and 4,6-bis(trimethylammonio)pyrimidine dichloride (111, R = H), which lost methyl chloride prior to isolation as 4-dimethylamino-6-trimethylammonio-pyrimidine chloride (112) (not characterized),⁵³⁹³ and 4,6-diamino-5-3',4'-dimethoxybenzylpyrimidine (ethanolic ammonia at 160°).⁶¹¹³ Examples of second-stage aminolysis of existing 4-amino-6-chloropyrimidines are provided in the transformation of 4-amino-6-chloro-2-methyl- into 4-amino-2-methyl-6-pyrrolidinopyrimidine (no solvent; 140°; 90%)^{4959, 5859} and of 4-amino-6-chloro- into 4-amino-6-dimethylamino-2-methyl(or phenyl)pyrimidine in *c.* 65% yield by heating in dimethylformamide at 185°.⁴⁹⁷⁰

The aminolysis of simple 2,4,6-*trihalogenopyrimidines* gets progressively more difficult as amino substituents are inserted. For simplicity, the following examples are classified as stage 1, stage 2, stage 3, or combinations thereof. Stage 1 is illustrated in the conversion of 2,4,6-trichloro- into 2,4-dichloro-6-isopropylaminopyrimidine (113) by ethanolic isopropylamine at more than 30°,⁵⁷⁵⁶ and of the same substrate into a separable mixture of 4,6-dichloro-2- and 2,4-dichloro-6-guanidinopyrimidine by guanidine in acetone at 20°.⁶³⁸⁴ Stage 2 is illustrated in the conversion of the above product (113) into 2-amino-4-chloro-6-isopropylaminopyrimidine (114) by aqueous ammonia at 140°,⁵⁷⁵⁶ of 2-amino-4,6-dichloro- into 2,4-diamino-6-chloro-5-3',4',5'-

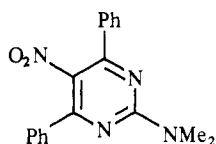
trimethoxybenzylpyrimidine by ethanolic ammonia at 120° ,⁵⁸⁰⁷ of 4-amino-2,6-dichloro- into 4-amino-6-chloro-2-piperidinopyrimidine by methanolic piperidine at 60° ,⁵⁷⁷⁵ and of 2-amino-4,6-dichloro- into 2-amino-4-chloro-6-methylaminopyrimidine (70%) by aqueous methanolic methylamine at 25° for 12 h.⁴⁶⁵⁵ Stages 1 + 2 are illustrated in the conversion of 2,4,6-trichloro- into 4-chloro-2,6-dipiperidinopyrimidine (ethanolic piperidine at 50°)⁵⁹⁹⁸ or into 4,6-diaziridino-2-chloropyrimidine (aziridine and triethylamine in benzene at 25° ; 73%),⁶⁰⁶⁰ although the inconsistency of the two structures should be noted. Stage 3 is illustrated in the conversion of 2-amino-4-chloro- into 2-amino-4-dimethylamino-6-methylaminopyrimidine (23%) by methanolic dimethylamine at 170° ,⁴⁶²³ of 2,4-diamino-6-chloro- into 2,4-diamino-6-dimethylamino-5-3',4',5'-trimethoxybenzylpyrimidine by ethanolic dimethylamine at 130° ,⁵⁸⁰⁷ and 2,4-diamino-6-chloro- into 2,4-diamino-6-dimethylaminopyrimidine by refluxing dimethylformamide.⁴⁹⁷⁰ Stages 2 + 3 are illustrated in the conversion of 4-amino-2,6-dichloro- into 4-amino-2,6-bisdimethylaminopyrimidine by refluxing dimethylformamide,⁴⁹⁷⁰ of 2-amino-4,6-dichloro- into 2-amino-4,6-dipiperidinopyrimidine (88%) by refluxing piperidine,⁵¹⁸⁸ or into 2-amino-4,6-di-*o*-toluidinopyrimidine by *o*-toluidine in refluxing acetic acid containing a little hydrochloric acid.⁵³⁷⁴ Stages 1 + 2 + 3 are illustrated in the conversion of 2,4,6-trichloro- into 2,4,6-trisdimethylamino- (95%) by ethereal dimethylamine at 0° then at 190° for 2 h,⁶¹⁰⁶ or into 2,4,6-triaziridinopyrimidine (115) in poor yield by aziridinyllithium [a better yield was obtained by using 2,4-diaziridino-6-chloropyrimidine (116) as substrate].⁶⁰⁶⁰

(2) *Aminolysis of Halogenonitropyrimidines (H 193, E 134)*

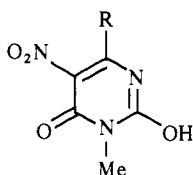
Halogeno-5-nitropyrimidines undergo aminolysis more easily than the corresponding simple halogenopyrimidines and, in addition, the preference for 4/6- rather than 2-aminolysis is more marked. Halogeno-nitroso- and arylazohalogenopyrimidines are also included in this heading, as are substrates that have functional groups as well as a nitro, arylazo, or nitroso group.

(a) *Aminolysis of Monochloronitropyrimidines.* The facility of this reaction in simple cases is indicated in the conversion of 2-chloro- into 2-dimethylamino-5-nitro-4,6-diphenylpyrimidine (117) by ethanolic dimethylamine at 25° ⁶¹⁴⁷ and of 2-chloro-5-nitropyrimidine into 5-nitro-2-trimethylammonio-4,6-diphenylpyrimidine chloride (> 90%) by brief(?) treatment with trimethylamine in benzene.⁵³⁴² The presence of additional

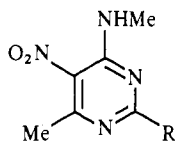
functional groups (usually of an electron-donating nature) decreases the reactivity somewhat, as indicated in the transformation of 4-chloro-2,6-dihydroxy- into 2,4-dihydroxy-6-isopropylamino- (methanolic amine under reflux; 78%),⁴⁶²⁷ 2,4-dihydroxy-6- β -hydroxyethylamino- (aqueous amine under reflux; 75%),⁶⁰²⁰ 4-*N*-ethylanilino-2,6-dihydroxy- (neat amine at 90°; 92%),⁵⁰¹⁶ and 4-carboxymethylamino-2,6-dihydroxy-5-nitropyrimidine (aqueous glycine at 90°; 79%),⁴⁵¹¹ as well as of 6-chloro (118, R = Cl) into 6-isopropylamino- (118, R = NHP*r*)⁴⁶²⁷ or 6- β -hydroxyethylamino-3-methyl-5-nitrouracil (118, R = NHCH₂CH₂OH)⁶⁰²⁰ by refluxing alcoholic amine.



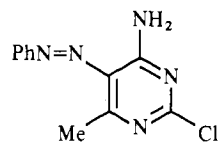
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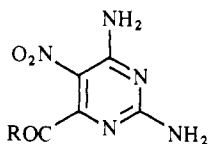
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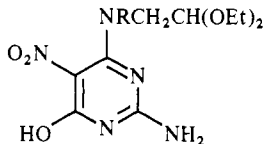
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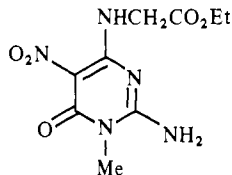
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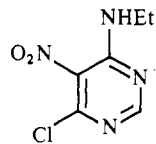
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(122)



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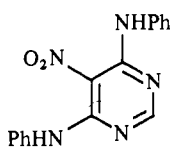
(b) *Aminolysis of 2,4-Dichloronitropyrimidines.* In simple cases, the first stage of such aminolyses occurs very easily and exclusively at the 4-position; the second stage is less facile. These facts are illustrated in the conversion of 2,4-dichloro-5-nitropyrimidine, by a slight excess of aniline in dichloromethane at -5° , into 4-anilino-2-chloro-5-nitropyrimidine, whereas an excess of aniline at 20° gave 2,4-dianilino-5-nitropyrimidine (94%);⁵⁸⁸⁹ of 2,4-dichloro-6-ethyl-5-nitropyrimidine, by buffered methylamine at 0° , into 2-chloro-4-ethyl-6-methylamino-5-nitropyrimidine (45%) or, by ethanolic methylamine at 25° , into 4-ethyl-2,6-bismethylamino-5-nitropyrimidine;⁵⁶⁷⁴ of 2,4-dichloro-6-methyl-5-nitropyrimidine, by buffered methylamine in aqueous dioxane at 10° , into 2-chloro-4-methyl-6-methylamino-5-nitropyrimidine (119, R = Cl) with a little 4-methyl-2,6-bismethylamino-5-nitropyrimidine (119, R = NHMe);⁵⁶⁸⁵ of the former product (119, R = Cl), by ethanolic dimethylamine at 25° , into 2-dimethylamino-4-methyl-6-methylamino-5-nitropyrimidine (119, R = NMe₂); of 2,4-dichloro-, by aziridine/

triethylamine at 25°, into 2,4-diaziridino-6-methyl-5-nitropyrimidine;⁵⁸⁸⁰ of the same substrate, by refluxing ethanolic ethanolamine, into 2,4-bis-β-hydroxyethylamino-6-methyl-5-nitropyrimidine;⁵⁴³⁷ and of 2,4-dichloro-, by ethereal ammonia at less than 5°, into 4-amino-2-chloro-6-phenyl-5-phenylazopyrimidine (120) in 72% yield.⁶⁰⁶⁷ Less simple examples in the presence of other functional groups include the first-stage conversions of 2,4-dichloro- into 4-amino-2-chloro-5-nitro-6-trifluoromethylpyrimidine (75%) by ammonia in ethanolic chloroform at 20°;⁵⁴⁴⁰ the first- plus second-stage conversion of 2,4-dichloro-6-methoxycarbonyl-5-nitropyrimidine by cold aqueous ammonia into 2,4-diamino-6-methoxycarbonyl-5-nitropyrimidine (121, R = OMe) or by ethanolic ammonia at 100° into 2,4-diamino-6-carbamoyl-5-nitropyrimidine (121, R = NH₂);⁵⁷⁶⁷ and the second-stage conversion of 4-chloro-2-dimethylamino-6-methoxy- into 2-methylamino-4-methoxy-6-methylamino-5-nitropyrimidine (aqueous methylamine "unter Erwärmen"; 94%);⁴⁶³¹ 2-amino-4-chloro- into 2-amino-4-cyclohexylamino-6-hydroxy-5-nitropyrimidine (ethanolic amine under reflux; 81%);⁵³⁵⁶ the same substrate into 2-amino-4-γ-aminopropylamino-6-hydroxy-5-nitropyrimidine (neat amine at 25° for 15 h; 65%);⁵⁶⁴⁶ 4-amino-2-chloro- into 4-amino-2-dimethylamino-5-nitro-6-trifluoromethylpyrimidine (aqueous ethanolic dimethylamine at 25°; c. 50%);⁵⁸²³ 2-amino-4-chloro- into 2-amino-4-N-(β,β-diethoxyethyl)methylamino-6-hydroxy-5-nitropyrimidine (122) (ethanolic 2-methylaminoacetaldehyde acetal under reflux; 60%);⁵⁸⁴² or into the 4-γ,γ-diethoxypropylamino analogue (60%);⁴⁶⁵⁹ 2-amino-4-chloro- into 2-amino-4-ethoxycarbonylmethylamino-1,6-dihydro-1-methyl-5-nitro-6-oxopyrimidine (123) (glycine ethyl ester in dimethylformamide at 95°; 63%);⁴⁶¹⁸ 4-β-acetylhydrazino-2-chloro- into 4-β-acetylhydrazino-2-amino-5-nitro-6-trifluoromethylpyrimidine (ethanolic ammonia under reflux; c. 60%);⁵⁷⁹⁰ and others.^{4641, 4648, 4864}

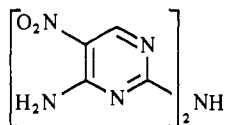
(c) *Aminolysis of 4,6-Dichloronitropyrimidines.* These dichloronitropyrimidines undergo complete aminolysis slightly more easily than their 2,4-dichloro analogues but, because of symmetry, there is no ambiguity of structure after monoaminolysis. Such essentially first-stage aminolysis is illustrated in the conversion of the appropriate dichloronitropyrimidines into 4-chloro-6-ethylamino-5-nitropyrimidine (124) (ethylamine in aqueous dioxane at pH 8 and 0°; c. 80%);⁵⁴⁴² 4-t-butylamino-6-chloro-5-nitropyrimidine (t-butylamine as above at 20°; byproduct of the 4,6-bis-t-butylamino analogue);⁵⁴⁴² 4-chloro-6-β-chloroethylamino-2-methyl-5-nitropyrimidine (amine in methanol containing sodium acetate at 20°; c. 50%);⁵⁴³⁸ 4-amino-6-chloro-5-nitro-2-

phenylpyrimidine (ammonia in tetrahydrofuran at 20° or in methanolic ether at 0°; byproduct of the 4,6-diamino analogue),^{5439, 5792} 4-chloro-6-cyclohexylamino-5-nitropyrimidine (amine in ether at 20°; 68%),⁴³⁹⁶ 4-amino-6-chloro-2-methylthio-5-nitropyrimidine (methanolic ammonia in ether at 20°; c. 60%),⁵⁷⁸⁷ and others.^{4570, 5433, 5791} Complete aminolysis occurred on treatment of 4,6-dichloro-5-nitropyrimidine with aniline in dibutyl ether at 20° to give greater than 90% of 4,6-dianilino-5-nitropyrimidine (125)⁵⁸⁸⁹ and on treatment of 4,4',6,6'-tetrachloro- with butanolic ammonia to give 4,4',6,6'-tetra-amino-5,5'-dinitro-di-(pyrimidin-2-yl)amine (126).⁵³⁹⁴ Isolated second-stage aminolyses include the conversion of 4-amino-6-chloro-2-methyl- into 4-amino-2-methyl-6-methylamino-5-nitropyrimidine (methanolic methylamine under reflux; 90%),⁵⁰⁴³ 4-amino-6-chloro- into 4-amino-6-ethylamino-5-nitropyrimidine (ethylamine in aqueous β -ethoxyethanol under reflux; 89%)⁵⁰⁷⁸ or 4-amino-5-nitro-6-piperidinopyrimidine (ethanolic piperidine under reflux; 95%),⁴⁷⁸⁹ and similar reactions.^{4475, 4795, 5230}

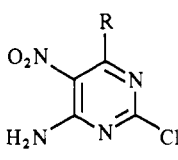
(d) *Aminolysis of 2,4,6-Trichloro-5-nitropyrimidine.* Although there are few recent examples in this category, it is evident that the presence of a 5-nitro group is insufficiently activating to make third-stage aminolysis easy. Thus, although 4-amino-2,6-dichloro-5-nitropyrimidine (127, R = Cl) reacted with benzylamine at 25° to give 4-amino-6-benzylamino-2-chloro-5-nitropyrimidine (127, R = PhCH₂NH), only at 140° did further aminolysis occur to afford 4-amino-2,6-bis-benzylamino-5-nitropyrimidine (128);⁵⁷⁴⁶ 2,4-diamino-6-chloro-5-nitropyrimidine required refluxing neat piperidine to give 2,4-diamino-5-nitro-6-piperidinopyrimidine (71%)⁵¹⁸⁸ or prolonged refluxing in methanolic amine to give 2,4-diamino-6- δ -diethylamino- α -methylbutylamino-5-nitropyrimidine (68%).⁵²³⁰ Other examples are comparable.⁴⁶⁴⁶



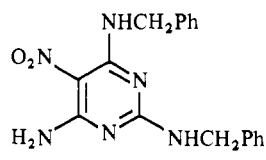
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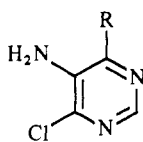
(126)



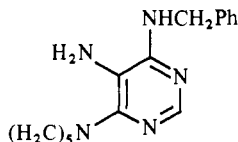
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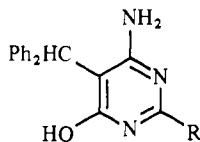
(128)



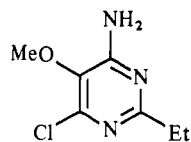
(129)



(130)



(131)



(132)

(3) *Aminolysis of 5-Aminochloropyrimidines (H 196, E 137)*

In contrast to the activating effect of a 5-nitro substituent, a 5-amino group significantly deactivates chloro substituents. This is seen even in the first-stage conversions of 5-amino-4,6-dichloro- (129, R = Cl) into 5-amino-4-chloro-6-isopropylamino- (129, R = NHPrⁱ) (ethanolic isopropylamine at 125° for 6–10 h, 70%)^{5578, 5753} into 5-amino-4-*t*-butylamino-6-chloro- (129, R = NHBu^t) (ethanolic *t*-butylamine at 160° for 24 h; 70%),⁵⁷⁵³ into 4-allylamino-5-amino-6-chloro- (129, R = NHCH₂CH:CH₂) (ethanolic allylamine at 130°; 79%),⁵⁶⁰⁹ into 5-amino-4-benzylamino-6-chloro- (129, R = NHCH₂Ph) (neat benzylamine at 150°, then 120°; 93%),^{5611, 5747} or into 5-amino-4-chloro-6- α -(hydroxymethyl)heptylamino-*pyrimidine* [129, R = NHCH(CH₂OH)C₆H₁₃];⁵⁶⁰⁷ of 4,6-dichloro- into 4-amino-6-chloro-5-methylamino-*pyrimidine* (ethanolic ammonia at 175°; 85%);⁵³³⁸ of 5-amino-2,4-dichloro- into 4,5-diamino-2-chloro-*pyrimidine* (aqueous ammonia at 125°; >90%);⁴⁶⁸⁰ and in other cases.^{4750, 4785} As might be expected, the second-stage aminolysis of 5-amino-4-benzylamino-6-chloro-*pyrimidine* (129, R = NHCH₂Ph) to 5-amino-4-benzylamino-6-piperidino-*pyrimidine* (130) required vigorous conditions, that is, ethanolic piperidine at 180° for 7 h.⁵⁷⁴⁷

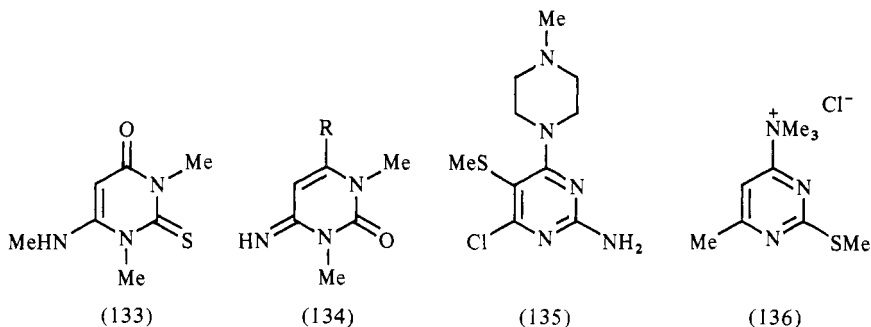
(4) *Aminolysis of Halogeno-(hydroxy, alkoxy, or oxo)pyrimidines (H 197, E 138)*

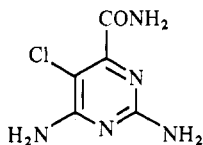
Hydroxy, alkoxy, and oxo substituents have a mild deactivating effect on chloro substituents. In the case of *halogenohydroxypyrimidines*, some anion formation will occur by virtue of the amine present during aminolysis, and this will further deactivate the chloro substituent. Thus, 4-fluoro- gave 4-amino- (60%) or 4-benzylamino-2,6-dihydroxy-5-methyl-*pyrimidine* (81%) only on heating with aqueous ammonia at 130° or heating with neat benzylamine under reflux, respectively;⁴⁵²⁶ 4-chloro- gave 4-amino-5-fluoro-2-hydroxy-*pyrimidine* (80%) in refluxing methanolic ammonia (the extra 5-fluoro substituent activated the chloro substituent);⁴⁸⁹⁵ 4-chloro- gave 4-benzylamino-2,6-dihydroxy-*pyrimidine* (32%) in refluxing aqueous benzylamine;⁵⁸⁷⁷ 4-chloro- gave 4-amino-5-diphenylmethyl-2,6-dihydroxy-*pyrimidine* (131, R = OH) (30%) and (unexpectedly) 2,4-diamino-5-diphenylmethyl-6-hydroxy-*pyrimidine* (131, R = NH₂) (70%) by heating in ethanolic ammonia at 150°;⁵⁵⁰² 4-chloro- gave 4-*N*-butylanilino-2,6-dihydroxy-*pyrimidine* (85%) by heating in neat *N*-butylaniline at 175°;⁴⁹⁸³ and 2-amino-4-

chloro- underwent second-stage aminolysis by aniline in refluxing acetic acid containing a little hydrochloric acid to give 2-amino-4-anilino-6-hydroxypyrimidine.⁴⁶³⁵

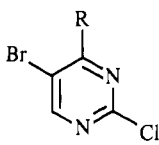
The aminolysis of *alkoxyhalogenopyrimidines* usually involves only displacement of the chloro substituent but, under excessively vigorous conditions, a 2/4-alkoxy group can also undergo displacement or an $O \rightarrow N$ -rearrangement of the alkyl group. Regular halogen displacements are typified in the conversion of 4-chloro- into 4-dimethyl-amino-2,6-dimethoxypyrimidine (methanolic dimethylamine at 25° for 2 days; 94%),⁶¹⁰⁶ 4-chloro- into 4-amino-5-methoxy-2-phenylpyrimidine (ethanolic ammonia at 150°; 80%),⁴⁶⁷⁴ 2-amino-4-chloro- into 2,4-diamino-5-cyano-6-ethoxypyrimidine (ethanolic ammonia at 120°; 46%),⁴⁴⁸⁶ 5-bromo-2-chloro-4-methoxy- into 5-bromo-4-methoxy-2-piperidinopyrimidine (refluxing etherial piperidine; 78%; 5-bromo substituent activated the chloro substituent),⁴⁷⁰⁶ and 4-chloro- into 4-amino-5-methoxy-6-methoxymethyl-2-methylthiopyrimidine (liquid ammonia at 25°; 93%).⁴³⁹⁷ An effective first-stage aminolysis occurred on treatment of 4,6-dichloro-2-ethyl-5-methoxypyrimidine with liquid ammonia at 25° to give 4-amino-6-chloro-2-ethyl-5-methoxypyrimidine (132) in 90% yield.³⁵⁰³

Aminolysis of *halogeno-oxopyrimidines* occurs fairly readily. It is illustrated in the formation (from the chloro analogues) of 1,3-dicyclohexyl-1,2,3,4-tetrahydro-6-methylamino-2,4-dioxypyrimidine (aqueous ethanolic methylamine under reflux for 15 min; 81%),⁴⁶⁵⁷ 4-dimethyl-amino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenylpyrimidine (methanolic dimethylamine under reflux for 30 min; 93%),⁵⁵⁸⁷ 4-anilino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (neat aniline at 180°; 87%),^{5009, 5657} 1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-4-oxo-2-thiopyrimidine (133) (aqueous methylamine at 25°; 67%),⁴⁶⁶¹ 4-dimethylamino-5-formyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-pyrimidine (ethanolic dimethylamine at *c.* 90°; 43%),⁴⁹²³ and others.⁴⁹³⁵

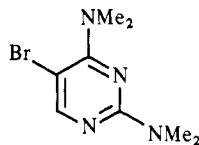




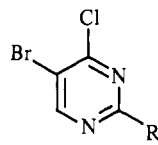
(137)



(138)



(139)



(140)

It is also illustrated in the conversion of 4-chloro-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxopyrimidine (134, R = Cl) into its 4-amino analogue (134, R = NH₂) by methanolic ammonia at 95°,⁴⁹⁶⁹ in related reactions,^{4994, 5657} and in the conversion of 4-bromo-1,3-diethyl-1,2,3,6-tetrahydro-6-imino-2-oxopyrimidine into its 4-anilino analogue by aniline containing a little hydrochloride at 170°.⁴⁹⁷¹

(5) Aminolysis of Chloro-alkylthiopyrimidines (H 198, E 140)

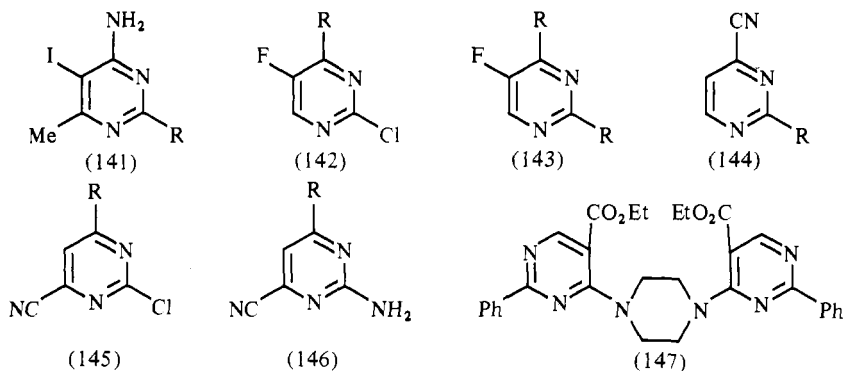
There are relatively few examples of the aminolysis of a chloropyrimidine bearing also an alkylthio group; conditions must be gentle enough to avoid displacement of a 2/4 thioether group as well as chlorine. Thus, 2-amino-4,6-dichloro-5-methylthiopyrimidine and *N*-methylpiperazine were boiled under reflux for 3 h to give 2-amino-4-chloro-6-*N*-methylpiperazino-5-methylthiopyrimidine (135);⁶⁰⁶¹ 4,6-dichloro-5-formyl-2-methylthiopyrimidine and ammonia were heated at 95° in a sealed tube to give 4,6-diamino-5-formyl-2-methylthiopyrimidine (*c.* 70%; the formyl group probably activated the chloro substituents);⁵⁴⁶⁶ 5-bromo-2-chloro-4-methylthiopyrimidine and ethanolic dimethylamine at 25° gave 5-bromo-2-dimethylamino-4-methylthiopyrimidine;⁴⁷⁰⁶ 4-chloro-6-methyl-2-methylthiopyrimidine and trimethylamine in cool benzene gave *c.* 50% of 4-methyl-2-methylthio-6-trimethylammonio-2,4-dihydropyrimidin-5-yl chloride (136) after 3 days.⁵²⁸⁴ More complicated examples have been reported.^{4424, 5476, 5638}

(6) Aminolysis of Chloropyrimidines Substituted by Other Groups (H 199, E 141)

All 5-halogeno substituents have a mild activating effect on 2/4-chloro substituents,⁵⁶⁶⁴ but there are no kinetic data to determine the relative efficiency of the different 5-halogens. The preparative aminolysis of such 5-chlorinated substrates is illustrated in the formation of 4-amino-6-*t*-butyl-5-chloropyrimidine or its 2,6-di-*t*-butyl homologue (ethanolic ammonia at 130°; 54 and 85%, respectively),⁴⁶⁶⁴ in the

second-stage conversion of 2-amino-4,5-dichloro- into 2,4-diamino-5-chloro-6-methylpyrimidine (ethanolic ammonia at 115° ; 73%),⁵¹⁸⁸ and in the conversion of 2,4,5-trichloro-6-cyano- into 2,4-diamino-6-carbamoyl-5-chloropyrimidine (137) (ethanolic ammonia at 120° ; note hydrolysis of nitrile).⁵⁹⁷¹ Aminolytic displacement of 2/4-chloro substituents from 5-brominated substrates is seen in the preparation of 5-bromo-2-isoamylaminopyrimidine (neat amine at 30° for 10 min),⁵⁶⁶⁴ 5-bromo-4-piperidinopyrimidine (ethanolic piperidine at 0° for 3 days, 54%),⁴⁶⁶³ 4-anilino-5-bromopyrimidine (as above; 94%),⁴⁶⁶³ 5-bromo-4-methylaminopyrimidine (as above; 80%),⁴⁶⁸² as well as in the stepwise conversion of 5-bromo-2,4-dichloropyrimidine (138, R = Cl) into 5-bromo-2-chloro-4-dimethylaminopyrimidine (138, R = NMe₂) (etherial amine at $<5^{\circ}$; 88%) and thence into 5-bromo-2,4-bisdimethylaminopyrimidine (139) (ethanolic amine under reflux; 94%),⁴⁷⁰³ as well as the first-stage aminolysis of the same substrate to afford 5-bromo-2-chloro-4-diethylamino- (138, R = NEt₂) and the isomeric 5-bromo-4-chloro-2-diethylaminopyrimidine (140, R = NEt₂) in 10:1 ratio,⁴⁷⁰³ 5-bromo-2-chloro-4-N-isopropyl-N-methylamino- (138, R = NMePrⁱ) and 5-bromo-4-chloro-2-N-isopropyl-N-methylaminopyrimidine (140, R = NMePrⁱ) in 16:1 ratio,⁶¹⁷² and other analogues.⁴⁷⁸⁰ Aminolysis in the presence of a 5-iodo substituent gave 4-amino-5-iodo-6-methylpyrimidine (141, R = H) and its 2-alkyl derivative (141, R = Me, Prⁱ, or Ph) (all by ethanolic ammonia at 120° ; >80%),⁶³⁵¹ while treatment of 2,4-dichloro-5-iodopyrimidine with the sodium salt of leucine in boiling water gave 4- α -carboxy- δ -methylbutylamino-2-chloro-5-iodopyrimidine.⁴⁷⁸⁰ Aminolysis in the presence of a 5-fluoro substituent has been used to convert 2,4-dichloro-5-fluoropyrimidine (142, R = Cl) into 4-amino-2-chloro-5-fluoropyrimidine (142, R = NH₂) by aqueous ethanolic ammonia at more than 30° ;⁵⁶³⁶ into 2-chloro-4-cyclohexylamino-5-fluoropyrimidine (142, R = NHC₆H₁₁),⁵⁸³⁷ 2,4-dianilino-5-fluoropyrimidine (149, R = NHPh),⁵⁹⁵⁶ or 5-fluoro-2,4-dipiperidinopyrimidine [143, R = N(CH₂)₅]⁵⁹⁵⁶ by heating with the amine; and into 4-carboxymethylamino-2-chloro-5-fluoropyrimidine (142, R = NHCHCO₂H) by aqueous sodium glycinate at 95° .⁴⁷⁸³ Other such reactions are also known.⁵⁹⁹⁷

The *cyano group* and all *carbonyl-containing groups* are electron-withdrawing and hence activate 2/4-halogeno substituents towards aminolysis. Apart from the remote possibilities of hydrolysis or aminolysis of a nitrile or ester under sufficiently vigorous conditions, the above ancillary substituents are stable to the aminolytic conditions required to convert 2/4-halogeno- into aminopyrimidines. Thus, 2-

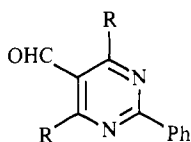


chloro-4-cyanopyrimidine (144, R = Cl) was heated with neat or ethanolic amine on the water bath to give 4-cyano-2-diethylamino- (79%) or 2-*p*-chloroanilino-4-cyanopyrimidine (91%);⁶⁰⁷⁵ the same substrate (144, R = Cl) with ethanolic dimethylamine at 25° gave 4-cyano-2-dimethylaminopyrimidine (144, R = NMe₂) in 66% yield;⁶¹⁸¹ 2-chloro-4-cyano-6-methylpyrimidine (145, R = Me) with ammonia in tetrahydrofuran at 20° gave the 2-amino analogue (146, R = NH₂);⁴⁸²⁰ 2-chloro-4,6-dicyanopyrimidine (145, R = CN), under similar conditions, gave 2-amino-4,6-dicyanopyrimidine (146, R = CN) in 80% yield but, when benzene was used as solvent, the expected product (146, R = CN) was accompanied by an equal yield (37%) of 4-amino-2-chloro-6-cyanopyrimidine (145, R = NH₂), formed by aminolytic displacement of one cyano group instead of the halogen;⁴⁸²⁰ 4-chloro-5-cyano- was heated with ethanolic ammonia at 120° to give 4-amino-5-cyano-6-phenylpyrimidine (>95%);⁵⁸¹⁶ 4,6-dichloro-5-cyano- was treated with buffered piperidine in dioxane at 15° to give 4-chloro-5-cyano-6-piperidinopyrimidine (c. 80%);⁵⁷⁶⁸ and 5-cyano-2,4,6-trifluoropyrimidine with ammonia in aqueous tetrahydrofuran at 30° gave 2,4-diamino-5-cyano-6-fluoropyrimidine in 84% yield.⁵⁷⁷⁰

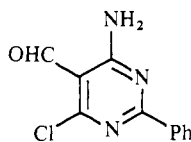
Aminolyses in the presence of ester groups are exemplified in the treatment of 4-chloro-5-ethoxycarbonylpyrimidine with *o*-phenylenediamine and triethylamine in ethyl acetate under reflux to give 4-*o*-aminoanilino-5-ethoxycarbonylpyrimidine in 54% yield;⁵²⁵² of 4-chloro-5-ethoxycarbonyl-2-phenylpyrimidine with ethanolamine in refluxing acetone to give 5-ethoxycarbonyl-4-β-hydroxyethylamino-2-phenylpyrimidine (95%);⁴⁹⁷⁶ of the same substrate with piperazine and sodium carbonate in dimethylformamide under reflux to give 1,4-bis(5'-ethoxycarbonyl-2'-phenylpyrimidin-4'-yl)piperazine (147); of 4-chloro-2-methoxycarbonylmethylpyrimidine with trimethylamine in benzene to give 2-methoxycarbonylmethyl-4-trimethylammonio-4'-pyrimi-

dine chloride;⁵⁶⁹³ and in other reactions.^{4422, 4423, 5766, 6538} Aminolysis in the presence of an amide occurred when 2,4-dichloro-5-*N*-(3',4',5'-trimethoxyphenyl)carbamoylpyrimidine was treated with liquid ammonia plus aqueous ammonia at 180° to give its 2,4-diamino analogue in *c.* 65% yield.⁵⁴⁶²

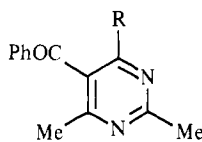
Aminolyses in the presence of aldehydo and keto groups are illustrated in the conversion of 4,6-dichloro- (148, R = Cl) into 4-amino-6-chloro-5-formyl-2-phenylpyrimidine (149) by treatment with ammonia in benzene at 20°;⁴⁴⁷¹ or into the 4,6-diamino analogue (148, R = NH₂) by treatment with aqueous ethanolic ammonia in a sealed vessel at 100°;⁵⁴⁶⁶ of 4-chloro- into 4-dimethylamino-6-*N*-ethyl-anilino-5-formylpyrimidine (70%) by dimethylamine in ethanolic toluene at 60°;⁵⁷³⁰ of 5-acetyl-4,6-dichloro- into 5-acetyl-4-chloro-6-morpholinopyrimidine (*c.* 60%) by morpholine in dioxane at 20°;⁵⁷⁶⁸ of 5-benzoyl-4-chloro- (150, R = Cl) into 4-amino-5-benzoyl-2,6-dimethylpyrimidine (150, R = NH₂) by aqueous ethanolic ammonia at 180° for 24 h;⁴⁴⁵⁶ of 5-acetonyl-4,6-dichloro- into 5-acetonyl-4-chloro-6-dimethylaminopyrimidine (85%) by refluxing aqueous dimethylamine;⁵⁷⁰³ and in other reactions.⁵⁰⁷³ Aminolyses in the presence of other ancillary groups are exemplified in the conversion of 4-chloro-6-methyl- (151, R = Cl) into 4-methyl-6-trimethylammonio-pyrimidine 1-oxide chloride (151, R = NMe₃Cl⁻);⁴⁶⁸⁵ of 2,4-dichloro- (152, R = Cl) into 4-amino-2-chloro-5-trifluoromethylpyrimidine (152, R = NH₂) in 98% yield by liquid ammonia at 20°, or into a mixture (95%) of 4-benzylamino-2-chloro- (152, R = NHCH₂Ph) and the isomeric 2-benzylamino-4-chloro-5-trifluoromethylpyrimidine (153) (using ethanolic benzylamine at 40°) from which pure samples of both were isolated;⁵⁷⁸⁹ and of 2,4-dichloro- into 2,4-diamino-6-cyanomethylpyrimidine (154) by treatment with ethanolic ammonia at 130°.⁶⁰⁶³



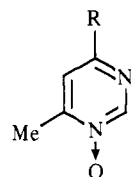
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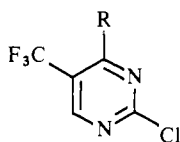
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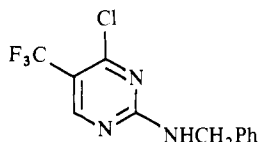
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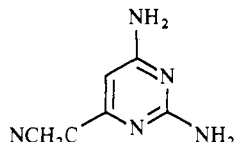
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(152)



(153)



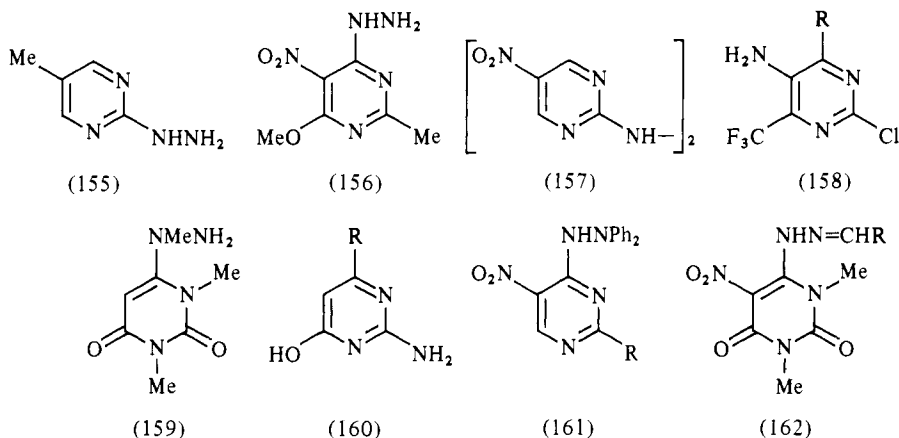
(154)

C. Replacement of 2-, 4-, and 6-Chloro by Hydrazino, Hydroxyamino, Azido, and Related Groups (*H* 199, *E* 143)

Hydrazine reacts readily with most 2/4-chloropyrimidines to give the corresponding hydrazinopyrimidines, which are often required as intermediates for triazolopyrimidines and such like bicyclic systems or simply as a means of indirectly removing an unwanted chloro substituent oxidatively when direct or indirect reductive removal is contraindicated.

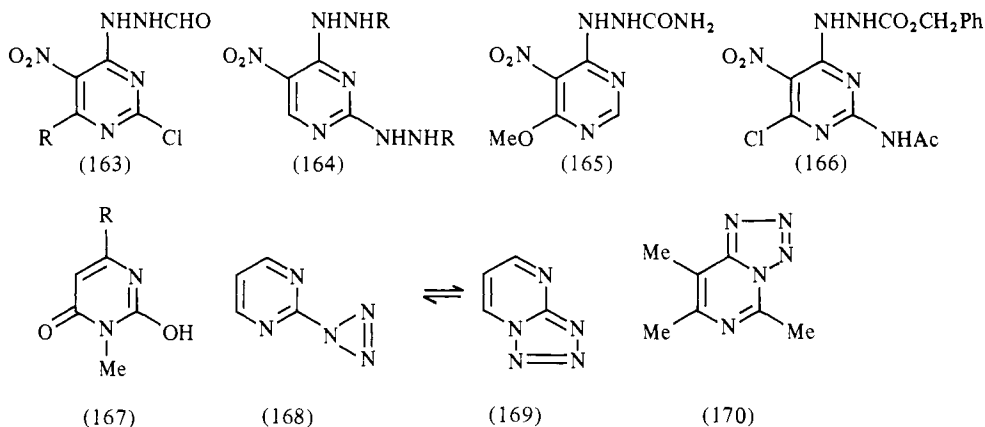
Hydrazinolysis is illustrated in the formation, from the corresponding chloropyrimidines, of 2-hydrazino-5-methylpyrimidine (155) (ethanolic hydrazine under reflux; 70%),⁵⁶⁹¹ 4,6-diethyl-2-hydrazinopyrimidine (as above; 82%),⁵⁶⁹¹ 4-hydrazino-2-methyl-6-phenylpyrimidine (as above; 90%) for subsequent removal of the hydrazino group by copper sulfate to afford 2-methyl-6-phenylpyrimidine,⁶⁰³⁹ 4-hydrazino-2-methyl-6-pyrid-2'-ylpyrimidine (similarly),⁶⁰³⁹ 4-hydrazino-6-methyl-2-pyrid-4'-ylpyrimidine (similarly; *c.* 80%),⁶²⁹⁸ 2-hydrazino-5-3',4'-dimethoxyphenylpyrimidine (as above; 93%),⁶⁰⁸⁰ 4-*t*-butyl-5-chloro-6-hydrazinopyrimidine (76%) for oxidative (Ag^+) conversion into 4-*t*-butyl-5-chloropyrimidine,⁴⁶⁶⁴ 5-bromo-2,4-di-*t*-butyl-6-hydrazinopyrimidine (96%),⁴⁶⁶⁴ 5-bromo-4-hydrazino-2,6-dimethylpyrimidine (as above; > 95%),⁵⁰⁹⁴ 5-amino-4-hydrazino-2-phenylpyrimidine (75%) for oxidative removal,⁵⁷⁹² 4-hydrazino-6-methoxy-2-methyl-5-nitropyrimidine (156) (ethanolic hydrazine at -10° ; 85%) for oxidative conversion (Ag_2O) into 4-methoxy-2-methyl-5-nitropyrimidine,⁵⁶³⁴ 2-amino-4-hydrazino-6-hydroxy-5-nitropyrimidine (methanolic hydrazine at 20° ; 93%),⁵²³⁴ 5-acetamido-4-hydrazino-2,6-dihydroxypyrimidine (ethanolic hydrazine containing triethylamine probably to avoid deacylation of the acetamido group by excess hydrazine),⁵³⁸⁷ 2-amino-4-hydrazino-6-hydroxypyrimidine (butanolic hydrazine under reflux; 86%),⁵⁰⁰¹ 2-anilino (or benzylamino)-4-hydrazino-6-methylpyrimidine (boiling ethanolic hydrazine hydrate; > 70%),⁵⁰⁵⁴ 4-hydrazino-2,6-dihydroxypyrimidine (aqueous hydrazine under reflux; 99%),⁵⁹⁶⁸ 4-hydrazino-2,6-dimethyl-5-nitropyrimidine (methanolic hydrazine at 20° ; 75%),⁵⁹⁹⁴ 4-hydrazino-6-hydroxypyrimidine (ethanolic hydrazine under reflux; 90%),⁵⁴⁹¹ and 5-benzyloxy-2-hydrazino-4-methoxy-6-methylpyrimidine (as above; 63%).⁵⁷²⁹ If the chloropyrimidine is in appropriate excess, hydrazinolysis often gives an hydrazo compound. For example, 2-chloro-5-nitropyrimidine (2 mol) and hydrazine (1 mol) in butanolic triethylamine (to pick up the hydrogen chloride) gave the hydrazo compound *N,N'*-(bis-5-nitropyrimidin-2-yl)hydrazine (157) in moderate yield; *N,N'*-(bis-4-methoxypyrimidin-2-yl)hydrazine and several

analogues were made similarly.⁴⁵⁸² Dichloropyrimidines can undergo preferential monohydrazinolysis under appropriate conditions. Thus, 5-amino-2,4-dichloro- (158, R = Cl) gave 5-amino-2-chloro-4-hydrazino-6-trifluoromethylpyrimidine (158, R = NHNH₂) in *c.* 75% yield,⁵⁷⁹⁰ 5-amino-2,4-dichloro-6-ethoxycarbonyl- gave 5-amino-2-chloro-4-ethoxycarbonyl-6-hydrazinopyrimidine (*c.* 60%; note survival of the ester group),⁵²⁶⁰ 4,6-dichloro- gave 4-chloro-6-hydrazino-2-morpholino-pyrimidine (hot ethanolic hydrazine for 15 min; 80%),⁵⁸⁶⁶ and 2-acetamido-5-amino-4,6-dichloro- gave 2,5-diamino-4-chloro-6-hydrazinopyrimidine (ethanolic hydrazine at 20° for 3 days; note deacylation).⁵²²⁹ Other hydrazinolyses have been reported.⁶¹⁹⁷



Substituted hydrazines react similarly with chloropyrimidines. Thus, monoalkylhydrazines react at the (more basic?) N-atom bearing the substituent to give, for example, 1,2,3,4-tetrahydro-1,3-dimethyl-6-1'-methylhydrazino-2,4-dioxypyrimidine (159),⁴⁹⁹¹ 3-methyl-6-1'-methylhydrazino-5-nitrouracil (ethanolic methylhydrazine at 20° for 10 min),⁴⁹⁹² and 2-amino-4-1'-methylhydrazinopyrimidine (methanolic methylhydrazine under reflux; 50%).⁵⁴⁰² In contrast, monoarylhydrazines appear to react predominantly at the unsubstituted N-atom, which is less reduced in basicity by the aromatic ring and hence is the more basic center in such hydrazines. Thus, 2-amino-4-chloro-6-hydroxypyrimidine (160, R = Cl) and aqueous phenylhydrazine under reflux gave 2-amino-4-hydroxy-6-2'-phenylhydrazinopyrimidine (160, R = NHNHPH) and its 6-1'-phenylhydrazino isomer (160, R = NPhNH₂) in 5:4 ratio,⁶²⁵³ while 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine appears to have given only 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-2'-phenylhydrazinopyrimidine on comparable treatment.⁴⁹²⁴ With *N,N*-disubstituted hydrazines no such ambiguity

is possible, so that the reaction of *N,N*-diphenylhydrazine with 2,4-dichloro-5-nitropyrimidine at 20° in chloroform gave 2-chloro-4-2',2'-diphenylhydrazino- (161, R = Cl), and under reflux gave 2,4-bis-2',2'-diphenylhydrazino-5-nitropyrimidine (161, R = NHNPh₂) both in good yield.⁶¹⁶⁴ Likewise, ethylidenehydrazine (acetaldehyde hydrazone) or benzylidene hydrazine reacted with 4-chloro- to give 4-ethylidenehydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine (162, R = Me) or the 4-benzylidenehydrazino analogue (162, R = Ph), both of which underwent cyclization (with loss of nitrous acid) to give appropriate pyrazolo[3,4-*d*]pyrimidines.⁴⁹²¹ Unlike alkyldiazines, acylhydrazines retain only one basic center, their β-amino group. Accordingly, chloropyrimidines undergo (unambiguous) aminolysis by acylhydrazines, as illustrated in the conversion of 2,4-dichloro-6-methyl-5-nitropyrimidine by ethanolic formylhydrazine at 0° into 2-chloro-4-β-formylhydrazino-6-methyl-5-nitropyrimidine (163, R = Me);⁵⁶⁶⁸ in the analogous preparation of 4-β-acetylhydrazino-2-chloro-5-nitro-6-propylpyrimidine;⁵⁶⁶⁸ and in the conversion of 2,4-dichloro-5-nitropyrimidine into a separable mixture of 2-chloro-4-β-formylhydrazino- (163, R = H) and 2,4-bis-β-formylhydrazino-5-nitropyrimidine (164, R = CHO), or into a similar mixture of 4-β-acetylhydrazino-2-chloro- and 2,4-bis-β-acetylhydrazino-5-nitropyrimidine (164, R = Ac).⁵⁶⁶⁶ The same sort of reactions are those of 2-amino-4-chloro- with benzenesulfonhydrazide to give 2-amino-4-benzenesulfonylhydrazino-5-methylthiopyrimidine, which underwent alkaline treatment to yield 2-amino-5-methylthiopyrimidine (56%);⁴³³² of 4-chloro-6-methoxy-5-nitropyrimidine with semicarbazide to give 4-methoxy-5-nitro-6-semicarbazidopyrimidine (165);⁵⁶⁷⁴ and of 2-acetamido-4,6-dichloro-5-nitropyrimidine with benzyl carbazate to give 2-acetamido-4-β-benzyl-oxy-carbonylhydrazino-6-chloro-5-nitropyrimidine (166).⁵²²⁹

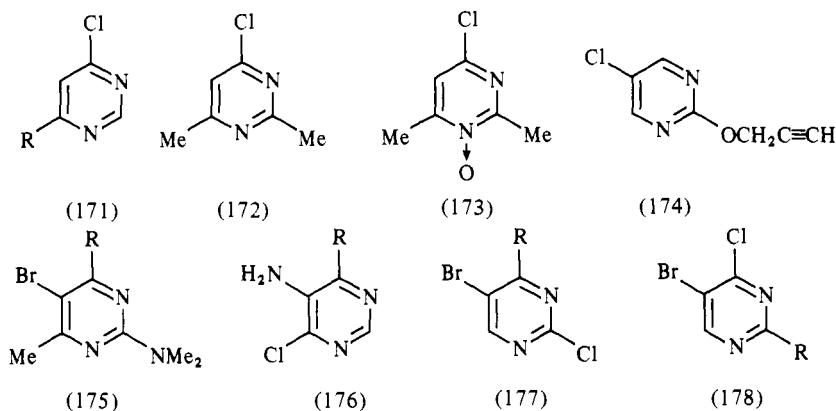


Aminolysis by hydroxylamine is exemplified in the conversion of 6-chloro-3-methyluracil (167, R = Cl), by hydroxylamino in methoxyethanol at 150°, into 6-hydroxyamino-3-methyluracil (167, R = NHOH),^{4952, 5042} as well as in the formation of 2-hydroxyaminopyrimidine and other simple analogues.⁶⁴²³

Sodium azide reacts with halogenopyrimidines to give the corresponding azidopyrimidines, usually in tautomeric equilibrium with tetrazolopyrimidines. In this way, 2-chloropyrimidine gave "2-azidopyrimidine" (168), which existed predominantly by tetrazolo[1,5-*a*]-pyrimidine (169), in 60% yield;⁵³⁵⁵ 4-chloro-2,5,6-trimethylpyrimidine gave the 4-azido analogue, which existed as 5,7,8-trimethyltetrazolo[1,5-*c*]pyrimidine (170);⁵³⁵⁵ 4-chloro- gave 4-azido-2,6-dimethoxypyrimidine which, in contrast to the above, existed as such;⁵³⁵⁵ 4-chloro- (by stirring with sodium azide in dimethylformamide containing lithium chloride) gave 4-azido-5-phenylpyrimidine (96%) (8-phenyl-tetrazolo[1,5-*c*]pyrimidine)⁵⁵⁸⁴ as well as the *p*-methoxy and *p*-chloro derivatives;⁵⁴⁸⁷ 4-chloro- gave 4-azido-2,6-dimethyl-5-nitropyrimidine (ethanolic sodium azide under reflux);⁶³⁵² 4-chloro- gave 4-azido-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine (80%; by stirring with sodium azide in tetrahydrofuran at 20°);^{4952, 4993} and other cases.^{5737, 6025} A particularly interesting example was the treatment of 2,4,5,6-tetrafluoropyrimidine with sodium azide in acetonitrile, which gave a separable mixture of 4-azido-2,5,6-trifluoro- and 4,6-diazido-2,5-difluoropyrimidine in a ratio depending on the conditions employed.⁶⁰⁷⁸

D. Replacement of 2-, 4-, and 6-Halogens by Alkoxy Groups (*H* 201, *E* 145)

Nucleophilic displacement of 2- and 4/6-halogen substituents by alkoxide ion occurs very easily, except in cases of extreme deactivation, occasioned for example by the presence of two or three amino groups. Second-order rate constants have been measured for the methoxylation of several 4-chloropyrimidines. Thus, 4,6-dichloropyrimidine (171, R = Cl) underwent monomethoxylation 16 times faster than the parent 4-chloropyrimidine (171, R = H), by virtue of electron-withdrawal by the second chloro substituent, whereas 4-chloro-6-methyl- (171, R = Me) and 4-chloro-6-methoxypyrimidine (171, R = OMe) underwent the same reaction, respectively at 0.6 and 0.03 times the rate for the parent (171, R = H) because of electron-release by the substituents.⁴⁶⁰³ The competitive reaction of ethoxide ion with 4-chloro-2,6-dimethylpyrimidine (172) and its 1-oxide (173) has been carried



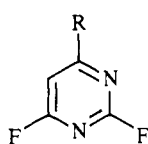
out quantitatively, but the results are not easy to analyze beyond the fact that *N*-oxidation increased the rate 5–10-fold.⁶⁰⁸²

*Simple preparative alkoxylation*s are represented in the formation (usually by the action of alcoholic alkoxide on the corresponding chloropyrimidines) of 2-methoxy-5-phenylpyrimidine (methanolic methoxide under reflux; 95%),⁵⁶³⁵ 4-methoxy-2-phenylpyrimidine (90%),⁴⁴⁴⁹ 4-ethoxy-6-phenylpyrimidine (72%),⁴⁶⁹² 4-ethoxy-2-phenylpyrimidine (65%),⁴⁶⁹² 2-methoxy-4,6-diphenylpyrimidine (80%),⁶¹⁰⁵ 5-bromo-4-methoxypyrimidine (methanolic methoxide at 20°; 79%),⁴⁷⁰⁵ 2-butoxy-5-chloropyrimidine (butanolic butoxide at 20°),⁶⁰²⁸ 5-chloro-2-prop-2'-ynyloxy-pyrimidine (174) (20°),⁶⁰²⁸ 5-bromo-4-ethoxy-6-methylpyrimidine (20°; 55%),⁵⁸⁰⁵ 5-bromo-2-methoxy-4-methylthiopyrimidine (ethereal methanolic methoxide at 30°; 76%),⁴⁷⁰⁶ 4-ethoxy-2-methylthiopyrimidine (88%),⁶¹³² 4-methoxy-6-methyl-2-methylthiopyrimidine (ethereal methanolic methoxide under reflux; >95%),⁵³⁵⁵ 4-methoxy-5,6-dimethyl-2-methylthiopyrimidine (methanolic methoxide under reflux; 95%),⁴³⁹⁴ 2-anilino-4-ethoxy-6-methylpyrimidine (ethanolic ethoxide under reflux; 88%),⁵⁹⁸⁶ 4-amino-6-methoxypyrimidine (methanolic sodium hydroxide under reflux; 91%),⁵⁸⁵³ 2-dimethylamino-4-methoxy-6-methylpyrimidine (under reflux; 93%),⁵³⁹⁰ 4,6-diethoxypyrimidine (under reflux; 71%),⁴⁶⁷² 4,5-dibenzoyloxy-2-methylpyrimidine (sodium benzyloxide in refluxing benzene; 85%),⁵³⁴⁵ 4-carboxy-6-methoxypyrimidine (under reflux; *c.* 40%),⁴⁷⁷⁰ 4-*o*-carboxyanilino-2-methoxypyrimidine (under reflux),⁴⁸²³ and others.^{5580, 5599, 5785, 5786, 5826, 6111} Of especial interest was the conversion of 4-anilino-6-chloro-5-formylpyrimidine by ethanolic hydrogen chloride into 4-anilino-6-ethoxypyrimidine (ethoxylation and deformylation),⁵⁷³⁰ of 4-chloro-5-fluoro-2-hydroxy- into 5-fluoro-2-hydroxy-4-methoxypyrimidine by methanolic hydrogen chloride at 20°,⁴⁸⁹⁵ of

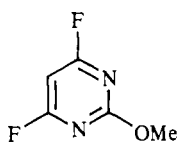
4-chloro- into 4-ethoxy-6-methoxy-5-nitropyrimidine by refluxing in ethanol containing silver oxide; of 4-amino-2-chloro- into 4-amino-2-ethoxy-5-nitro-6-trifluoromethylpyrimidine (75%) by boiling in ethanolic pyridine;⁵⁸²³ of 4-chloro-5-ethoxycarbonyl- into 4-methoxy-5-methoxycarbonyl-2-phenylpyrimidine by boiling methanolic sodium methoxide (transesterification);⁴⁹⁷⁶ and of 2-benzyl-4-chloro- into 2-benzyl-4- β -dimethylaminoethoxy-6-methylpyrimidine by sodium dimethylaminoethoxide in refluxing toluene.⁶⁰¹⁸ For logical enough reasons in the main, some simple alkoxylation proved quite difficult, as indicated in the severe conditions apparently required for the conversion of 4-amino-6-chloro-2-dimethylamino- into 4-amino-2-dimethylamino-6-methoxypyrimidine (methanolic sodium methoxide at 130° in an autoclave for 12 h; *c.* 65%);⁴⁶³³ in the similar formation of 2-dimethylamino-4-methoxy-6-methylaminopyrimidine (150°, 12 h; 67%);⁴⁶⁵⁶ in the conversion of 5-butyl-4-chloro- (175, R = Cl) into 5-butyl-4- β -diethylaminoethoxy-2-dimethylamino-6-methylpyrimidine (175, R = OCH₂CH₂NEt₂) (sodium β -diethylaminoethoxide in the parent alcohol at 140°; 53%);⁵³⁹² in the formation of 2,4-bisdimethylamino-6-methoxypyrimidine (saturated methanolic sodium methoxide under reflux for 24 h);⁶¹⁰⁶ in the formation of 2-methylamino-4-4'-methylpiperazino-5-methylthio-6-propoxypyrimidine (propanolic potassium hydroxide under reflux);⁶⁰⁶¹ and others.^{3503, 4634, 5789}

Selective alkoxylation of di- or tri-halogenopyrimidines is usually possible. Thus, 5-amino-4,6-dichloro- (176, R = Cl) gave 5-amino-4-chloro-6-methoxypyrimidine (176, R = OMe) by heating under reflux in methanol containing 1 mol of sodium hydroxide;⁵⁷⁸⁴ 4,6-dichloro- gave 4-chloro-6-ethoxypyrimidine (ethanolic sodium ethoxide at 20°; 77%);⁴⁶⁷² 4,6-dichloro- gave 4-chloro-6-methoxy-2-methoxycarbonylmethylpyrimidine (methanolic sodium methoxide at 25°; 75%);⁵⁶⁸⁸ 4,6-dichloro- gave 4-chloro-6- β -dimethylaminoethoxy-2-phenylpyrimidine (90%) by warming with an excess of neat β -dimethylaminoethanol, which took up the hydrogen chloride formed;⁵⁹⁹³ and 4,6-difluoro- gave 4-fluoro-6-methoxypyrimidine (6°; 20%).⁴⁷⁵² The (unsymmetrical) 2,4-dihalogenopyrimidines usually showed a strong preference for initial 4-alkoxylation. Thus, 5-bromo-2,4-dichloro- (177, R = Cl), at 5–20° with methanol containing sodium methoxide (1 mol), gave a separable mixture of 5-bromo-2-chloro-4-methoxy- (177, R = OMe) (82%) and the isomeric 5-bromo-4-chloro-2-methoxypyrimidine (178, R = OMe) (3%), both of which gave 5-bromo-2,4-dimethoxypyrimidine on further treatment with an excess of the same reagent at 20°;⁴⁷⁰³ the same dichloro substrate (177, R = Cl) behaved similarly with potassium t-

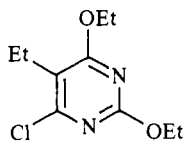
butoxide to give 5-bromo-4-t-butoxy-2-chloro- (177, $R = \text{OBu}^t$) (78%) and 5-bromo-2-t-butoxy-4-chloropyrimidine (178, $R = \text{OBu}^t$) (17%);⁴⁷⁰³ 2,4-dichloro-5-fluoropyrimidine with sodium ethoxide (1 mol) in ethanol at 20° apparently gave only 2-chloro-4-ethoxy-5-fluoropyrimidine (83%);⁵⁹⁵⁶ the same substrate with potassium t-butoxide similarly gave only 4-t-butoxy-2-chloro-5-fluoropyrimidine;⁵⁹⁷⁸ and 5-acetoxy-2,4-dichloro-6-methylpyrimidine in refluxing methanolic sodium methoxide gave 2-chloro-5-hydroxy-4-methoxy-6-methylpyrimidine in which deacylation of the 5-substituent as well as selective 4-methoxylation had occurred.⁵⁷²⁹ Selective alkoxylation of 2,4,6-trihalogenopyrimidines is illustrated, albeit incompletely, in the reaction of 2,4,6-trifluoropyrimidine (179, $R = \text{F}$) with methanol containing sodium carbonate at 20° to give an unseparated mixture (77%) of 2,4-difluoro-6-methoxy- (179, $R = \text{OMe}$) and 4,6-difluoro-2-methoxypyrimidine (180) in 2:1 ratio (¹H nmr);⁵⁷⁷⁰ of 2,4,6-trichloro-5-ethylpyrimidine with ethanolic sodium ethoxide (2 mol) at 5° to give 4-chloro-2,6-diethoxy-5-ethylpyrimidine (181) in 60% yield;⁵⁷⁹⁷ of 2,4,6-trifluoro-5-methylpyrimidine with sodium benzyloxide (2 mol) in toluene at 25°



(179)



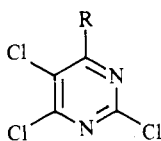
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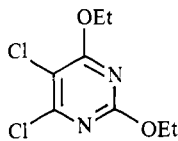
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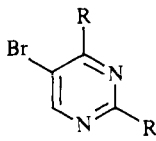
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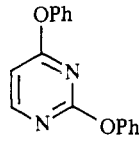
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(184)



(185)



(186)

to give 2,4-dibenzyloxy-6-fluoro-5-methylpyrimidine (63%),⁴⁵²⁶ of 2,4,6-trichloro-5-di(β-chloroethyl)aminopyrimidine with methanolic sodium methoxide at 30° to give 4-chloro-5-di(β-chloroethyl)amino-2,6-dimethoxypyrimidine (93%) without affecting the (quite active) extracyclic chloro substituents;⁴⁷⁷⁴ of 2,4,5-trifluoro-6-iodopyrimidine (182, $R = \text{F}$) with methanolic sodium methoxide (1 mol) at 0° to give 2,5-difluoro-4-iodo-6-methoxypyrimidine (182, $R = \text{OMe}$) (74%), indicating the preference for methoxylation of a fluoro rather than a

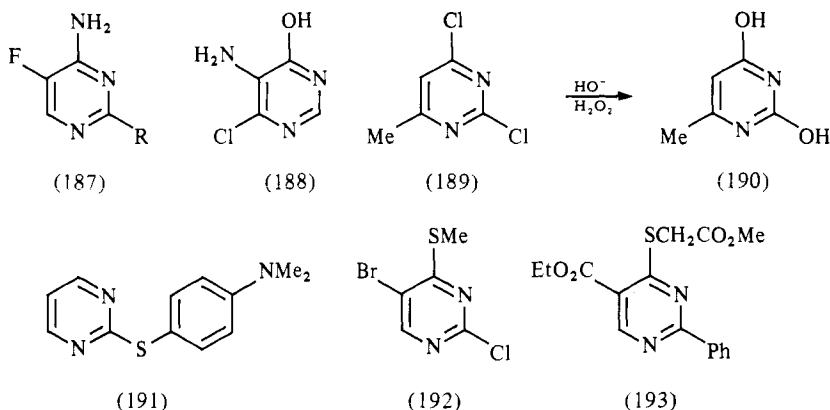
comparably placed iodo substituent;⁵⁷⁷⁹ and the ethoxylation of 2,4,5-trichloro-6-cyanopyrimidine (183, R = CN) to give, initially 2,4,5-trichloro-6-ethoxypyrimidine (183, R = OEt) by preferential displacement of the nitrile group and, subsequently, 4,5-dichloro-2,6-diethoxypyrimidine (184).⁵⁹⁷¹

Complete alkoxylation of di- and tri-halogenopyrimidines is well represented, although in many cases the conditions used are probably much more vigorous than necessary. The process is exemplified in the formation of 4,6-dimethoxy-5-nitropyrimidine (methanolic methoxide under reflux; 76%),⁵⁷⁸⁴ 2,4-dibenzyloxy-5-bromopyrimidine (185, R = OCH₂Ph) (sodium benzyloxide in benzyl alcohol at 10°; 86%),⁵⁵⁹² 5-bromo-2,4-di-*t*-butoxypyrimidine (185, R = OBu^t),⁵⁹³⁵ 4,6-dimethoxypyrimidine (methanolic methoxide at c. 60°),⁵³²³ 4,6-dibenzyloxy-2-methyl(or phenyl)pyrimidine (sodium benzyloxide in toluene under reflux; 87; 97%),⁶⁰⁵⁸ 5-ethyl-4,6-dimethoxypyrimidine (methanolic methoxide under reflux; 81%),⁴⁵⁷⁷ 4-amino-2,6-dimethoxy-5-methylpyrimidine (methanolic methoxide under reflux for 15 h; 82%),⁵¹⁵⁴ 2,4-diethoxypyrimidine (ethanolic ethoxide under reflux for 10 min; 93%),⁵⁶³² 5-nitro-2,4-dipropoxypyrimidine (propanolic propoxide briefly under reflux),⁵⁶⁷⁴ 4,6-diethoxy-5-nitropyrimidine (30°; 73%),⁵⁴⁹¹ 2,2',4,4'-tetramethoxy-5,5'-bipyrimidine (reflux; 70%),⁴³⁷⁵ 5-ethyl-4,6-dimethoxy-2,2'-bipyrimidine (reflux; 85%),⁴⁵⁸⁰ 5-chloro-2,2',4',6-tetramethoxy-4,5'-bipyrimidine (80°; 78%),⁴⁷⁰⁴ 2,4,6-trimethoxy-5-nitropyrimidine (25°; 66%),⁶³⁸¹ 2,4,6-trimethoxypyrimidine (boiling; c. 20%),⁵³²³ and 5-di(β-chloroethyl)amino-2,4,6-trimethoxypyrimidine.⁵⁹⁰⁵

Aryloxylation of halogenopyrimidines is relatively uncommon, but the formation of the following aryloxypyrimidines will indicate the procedure and conditions: 2-methyl-4-phenoxy pyrimidine (sodium phenoxide in phenol containing a little copper powder at 160° for 8 h; 30%),⁶⁰³⁹ 4-amino-2-methyl-6-phenoxy pyrimidine (phenol and potassium carbonate in dimethylformamide under reflux; 57%; with 4-amino-6-dimethylamino-2-methylpyrimidine as an 18% by-product),^{4959, 5859} 2-amino-4-(2',4'-dichlorophenoxy)-6-phenylpyrimidine (potassium hydroxide in neat 2,4-dichlorophenol at 85° for 36 h; 77%),⁶¹⁹⁵ 2,4-diamino-6-(2',4'-dichlorophenoxy)pyrimidine (as above at 150° for 3 h; c. 80%),³⁵⁰⁸ 2,4-diamino-6-phenoxy pyrimidine (equimolar phenol in aqueous sodium hydroxide in an autoclave at 150° for 20 h; c. 5%),⁵⁴⁰⁰ 2,4-diphenoxypyrimidine (186) (phenol and potassium carbonate at 120°; 95%),⁵³⁶² and 2-amino-4,6-diphenoxypyrimidine (as above at 160°; 62%).⁵³⁷⁵

E. Replacement of 2-, 4- and 6-Halogens by Hydroxy Groups (*H* 203, *E* 148)

Although the replacement of a chloro by an hydroxy substituent was often done in the past indirectly through an alkoxy or acetoxy group, there is seldom any good reason for such a procedure since direct hydrolysis in acid or alkali is usually quite satisfactory. Thus, *acidic hydrolysis* of 4-amino-2-chloro-5-fluoro- (187, $R = Cl$) gave 4-amino-5-fluoro-2-hydroxypyrimidine (187, $R = OH$) in 96% yield by heating in 10 M hydrochloric acid at 95° for 2 h;⁵⁶³⁶ 4-*o*-carboxyanilino-2-chloro- gave 4-*o*-carboxyanilino-2-hydroxypyrimidine (50%) in hot 1 M hydrochloric acid;⁴⁸²³ 4-amino-2-chloro- gave 4-amino-2-hydroxy-5-trifluoromethylpyrimidine (0.1 M hydrochloric acid under reflux; 61%);⁵⁷⁸⁹ and 2-chloro-4-ethylthio-5-fluoro- gave 5-fluoro-2,4-dihydroxypyrimidine (6 M hydrochloric acid under reflux; 74%; note hydrolysis of thioether also).⁴⁸⁹⁵ When there are more than one active halogen present, selective acid hydrolysis is often possible, as in the formation of 4-chloro-6-hydroxy-2-methylpyrimidine (3 M hydrochloric acid under reflux; or refluxing aqueous butanolic hydrochloric acid; 60%),^{3505, 5015} 5-amino-4-chloro-6-hydroxypyrimidine (188) (6–10 M hydrochloric acid at $95-100^\circ$; 40–50%),^{4816, 5435} and 2-chloro-4-hydroxy-6-methyl-5-nitropyrimidine (aqueous ethanolic acetic acid buffered by sodium acetate at 15° ; c. 50%).⁵⁴³⁸



Alkaline hydrolyses are represented in the conversion of appropriate chloro- or dichloropyrimidines into 2-hydroxy-4-methyl-6-methylamino-5-nitropyrimidine (1 M sodium hydroxide at 95° ; 38%),⁵⁴³² 2-amino-4-chloro-5-formyl-6-hydroxypyrimidine (86%),⁶⁵⁰³ 5-acetyl-4-chloro-6-hydroxypyrimidine (0.4 M potassium hydroxide under reflux;

51%),⁵⁷⁰³ 4-chloro-6-hydroxy-2-phenylpyrimidine (3 M sodium hydroxide under reflux for 8 h; 92%),⁵⁴⁹¹ and 2-chloro-5-fluoro-4-hydroxypyrimidine (1 mol of 2 M sodium hydroxide at 45° for 0.75 h; 80%).⁵⁶²⁶ The conversion of chloro- into hydroxypyrimidines in alkali is apparently catalyzed by the presence of hydrogen peroxide. Thus, the hydrolysis of 2,4-dichloro-6-methylpyrimidine (189) to 2,4-dihydroxy-6-methylpyrimidine (190), by aqueous sodium hydroxide containing a little hydrogen peroxide, took 5 min at 20°, whereas, under similar conditions without hydrogen peroxide, completion of the reaction took 27 h,⁴⁸⁵⁵ the accelerating effect of peroxide, presumably by participation of the highly nucleophilic hydroperoxy ion, has been used in the conversion of 2-amino-4,6-dichloro- into 2-amino-4-chloro-6-hydroxypyrimidine (20°; 40%),⁴⁸⁵⁵ of 2,4,6-trichloro- into 4-chloro-2,6-dihydroxypyrimidine (20°; 70%),⁴⁸⁵⁵ and in other (acidic) hydrolyses.⁴⁸⁸⁵

F. Replacement of 2-, 4- and 6-Chloro by Alkylthio and Arylthio Groups (*H* 205, *E* 149)

Apart from a few primary syntheses, there is no practical route to arylthiopyrimidines apart from the treatment of chloropyrimidines with thiophenoxide ion. Alkylthiopyrimidines may be made similarly but the process is less important since they are usually made more easily by *S*-alkylation. *Arylthioxylation* is illustrated in treatment of 2-chloropyrimidine with the sodium salt of *p*-dimethylaminobenzenthioi in ethanol under reflux to give 2-*p*-dimethylaminophenylthiopyrimidine (191) in *c.* 60% yield.⁵⁶³³ Other *p*-substituted analogues were made similarly.^{5633, 6045} Similar procedures gave 2,4-dimethyl-6-phenylthiopyrimidine (98%),⁶⁰⁸² 2,4-dihydroxy-6-phenylthiopyrimidine (thiophenol and sodium hydroxide in aqueous ethanol or methoxyethanol under reflux; 90%),^{5877, 6122} 5-ethoxycarbonyl-2-methyl-4-*o*-nitrophenylthiopyrimidine (*o*-nitrobenzenethioxide in ethanol under nitrogen; 73%);⁵²⁵² and 4-phenyl-2-phenylthiopyrimidine (60%).⁶⁰⁴⁰ *Alkylthioxylation* has been used, usually for specific reasons, to afford 2,4-bismethylthio-5-nitropyrimidine (methanethiol in methanolic sodium methoxide at 0°; *c.* 80%),⁵⁶⁶¹ 5-bromo-2-chloro-4-methylthiopyrimidine (192) (from the 2,4-dichloro analogue by treatment with 1 mol of methanethioxide in ether at -5° to achieve preferential reaction of the 4-chloro substituent),⁴⁷⁰⁶ 2-chloro-4-ethylthio-5-fluoropyrimidine (1 mol of ethanethioxide in dioxane under reflux; 79%),⁴⁸⁹⁵ 2-methylthio-4-phenylpyrimidine (sodium methanethioxide and anhydrous toluene in a sealed tube at 160°!),⁶⁰⁴⁰ 5-ethoxycarbonyl-4-methoxycarbonylmethylthio-2-phenylpyrimidine (193) (methyl 2-

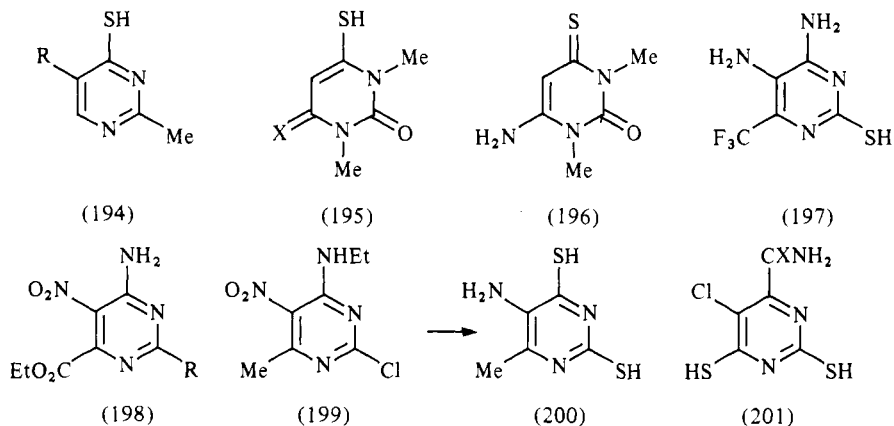
mercaptoacetate and ethanolic sodium carbonate under reflux; 57%),⁵⁵⁸¹ 2- β -dimethylaminoethylthio-4-thien-2'-ylpyrimidine (β -dimethylamino-ethanethioide in ethanol under reflux; *c.* 50%),⁶²⁸⁷ and related compounds.⁶²⁸⁸

G. Replacement of 2-, 4- and 6-Halogens by Mercapto Groups (*H* 205, *E* 150)

Although 2-mercapto groups can be introduced easily by the Principal Synthesis and 4/6-mercapto groups can usually be obtained by direct thiation of hydroxy groups with phosphorus pentasulfide, it is often more convenient to obtain such mercaptopyrimidines from the corresponding chloropyrimidines. This can be done directly by treatment with sodium hydrogen sulfide or indirectly by treatment with thiourea to give the thiuronium chloride, which undergoes ready decomposition (usually in alkali) to furnish the mercaptopyrimidine.

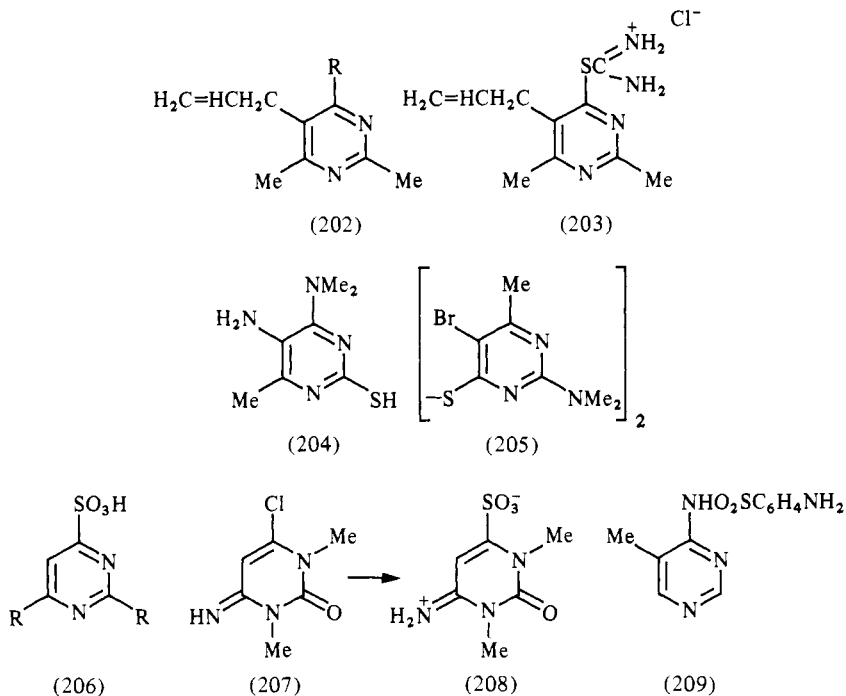
The simple *use of sodium hydrogen sulfide* is illustrated in the formation of 4-hydroxy-6-mercapto-2-methylpyrimidine (sodium hydrogen sulfide in ethoxyethanol under reflux; 91%),⁵⁶⁶⁷ 5-bromo(or ethoxy)-4-mercapto-2-methylpyrimidine (194, R = Br or OEt) (ethanolic potassium hydrogen sulfide under reflux for 10 h; 84; 30%),⁵⁹⁵⁸ 1,2,3,4-tetrahydro-6-mercapto-1,3-dimethyl-2,4-dioxypyrimidine (195, X = O) (ethanolic sodium hydrogen sulfide at room temperature; 64%),⁵¹³⁸ 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-thiopyrimidine (196) [aqueous sodium hydrogen sulfide under reflux; 89%; the reaction is more easily visualized as giving the minor tautomer (195, X = NH) initially],⁴⁹⁶⁹ 5-benzamidomethyl-4-mercapto-2-methylpyrimidine (ethanolic sodium hydrogen sulfide at 70°; 93%),⁵⁷⁹³ and 5-formamido-4-mercapto-6-methylthiopyrimidine (methanolic sodium hydrogen sulfide under reflux; 88%).⁴³⁵⁸ Although it is difficult to see any logic in the process, treatment of 5-amino-4-chloro-6-methylthiopyrimidine with phosphorus pentasulfide in hot pyridine gave 5-amino-4-mercapto-6-methylthiopyrimidine (76%), and a similar process gave the homologous 5-amino-4-benzylthio-6-mercaptopyrimidine (63%).⁴⁷⁶⁶

While it is replacing a chloro by a mercapto substituent, sodium hydrogen sulfide may bring about other reactions, desirable or otherwise. For example, its reducing properties may be utilized as in the conversion of 2-amino-4-chloro-6-hydroxy-5-nitro- into 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (60%),⁴⁷⁶⁶ of 4,6-dichloro-2-methyl-5-nitro- into 5-amino-4,6-dimercapto-2-methylpyrimidine (sodium hydrogen sulfide in hot aqueous dioxane; 95%),⁵⁶⁸⁹ of 4-amino-2-chloro-5-nitro- into 4,5-diamino-2-mercapto-6-trifluoromethylpyrimi-



dine (197) (aqueous sodium hydrogen sulfide; *c.* 55%);⁵⁴⁴⁰ of 4-butylamino-6-chloro-5-nitro- into 5-amino-4-butylamino-6-mercaptopyrimidine (64%);⁴³⁹⁶ of 4-amino-6-chloro-5-nitro- into 4,5-diamino-6-mercapto-2-phenylpyrimidine (*c.* 70%);⁵⁴³⁹ and of 6-chloro-3-methyl-5-nitro- into 5-amino-6-mercapto-3-methyluracil.⁵⁴³⁵ Reduction of the nitro group can be avoided by using sodium sulfide under gentle conditions. Treatment of 4-amino-2-chloro-6-ethoxycarbonyl-5-nitropyrimidine (198, R = Cl) with aqueous sodium sulphide plus sodium hydrogen carbonate at 15° gave crude 4-amino-6-ethoxycarbonyl-2-mercapto-5-nitropyrimidine (198, R = SH), which was isolated and characterized as the 2-methylthio analogue (198, R = SMe);⁵⁴⁴³ however, when a nitro group is to be retained, it is easier to use thiourea (see below). Treatment of 2-chloro-4-ethylamino-6-methyl-5-nitropyrimidine (199) with aqueous sodium hydrogen sulfide at 95° not only replaced the chloro substituent and reduced the nitro group but also replaced the secondary amino group by mercapto, to give 5-amino-2,4-dimercapto-6-methylpyrimidine (200) in greater than 80% yield!⁵⁶⁷⁷ A further side reaction in the use of sodium hydrogen sulfide is seen in the conversion of 2,4,5-trichloro-6-cyanopyrimidine into 4-carbamoyl-5-chloro-2,4-dimercapto-6-methylpyrimidine (201, X = O),⁵⁹⁷¹ although the corresponding thioamide (201, X = S) might reasonably have been expected had a sufficient excess of reagent been employed.

The use of a *thiouronio intermediate* between chloro- and mercapto-pyrimidines is exemplified in the conversion of 5-allyl-4-chloro-2,6-dimethylpyrimidine (202, R = Cl) into 5-allyl-2,4-dimethyl-6-thiouroniopyrimidine chloride (203), by refluxing with thiourea in acetone, and thence into 5-allyl-4-mercapto-2,6-dimethylpyrimidine



(203, R = SH), by heating with ethanolic sodium ethoxide; the overall yield was 86%.⁶³⁴⁶ Likewise, 5-bromo-2,4-dichloropyrimidine with ethanolic thiourea gave 5-bromo-2,4-bisthiouronipyrimidine dichloride (78%), which on treatment with hot aqueous sodium hydroxide gave 5-bromo-2,4-dimercaptopyrimidine (88%).⁴⁷⁰⁷ Often, the thiouronio intermediate remains unisolated and/or uncharacterized because its degradation occurs spontaneously during the initial reaction period or sodium hydroxide is added after a time to the reaction mixture to achieve a convenient "one pot" reaction sequence. In this way were made 4-benzylamino-2-mercapto-6-methylpyrimidine (no alkali used; 17%),⁴⁸⁴⁹ 5-dimethylamino-2,4-dimercaptopyrimidine (no alkali; 82%),⁶⁰⁶² 4-mercapto-6-methyl-2-pyrid-2'-ylpyrimidine (ethanolic thiourea under reflux for 20 h; 74%),⁶⁰⁸⁷ 5-bromo-4-mercaptopyrimidine (ethanolic thiourea under reflux; intermediate crystallized from hot mixture but soon redissolved; 32%),⁴⁷⁰⁵ 5-benzoyl-4-mercapto-6-methyl-2-phenylpyrimidine (prolonged refluxing in ethanolic thiourea followed by treatment of the crude product with alkali; 83%),⁴⁴⁵⁶ and 2-mercapto-4-phenylpyrimidine (ethanolic thiourea followed by refluxing with alkali for 1 h; 68%).⁶⁰⁴⁰ Although 4,6-dichloro-5-nitropyrimidine reacted very easily with ethanolic thiourea to give 4,6-

dimercapto-5-nitropyrimidine after mere reprecipitation of the product from cold alkali, 4,6-dichloro-2-methylpyrimidine first gave the (characterized) 4-mercapto-2-methyl-6-thiouroniopyrimidine chloride, which on dissolution in alkali and reprecipitation gave 4,6-dimercapto-2-methylpyrimidine (>95%).⁶³⁷⁴ Abnormal procedures or results in such reactions are illustrated in the ready formation of 5-nitro-2-thiouroniopyrimidine chloride, which was then dissolved in warm alkali with the addition of methyl iodide to give 2-methylthio-5-nitropyrimidine (46%);^{6372, 6423} in the formation of 5-hydroxy-4,6-dimethyl-2-thiouroniopyrimidine chloride and thence 5-hydroxy-4,6-dimethyl-2-methylthiopyrimidine (87%);⁶³⁷³ in the formation of 4-dimethylamino-2-mercapto-6-methyl-5-nitropyrimidine in the usual way followed, without characterization, by the addition of dithionite to afford 5-amino-4-dimethylamino-2-mercapto-6-methylpyrimidine (204) as prime product in poor yield;⁵³⁴⁶ and in the treatment of 5-bromo-4-chloro-2-dimethylamino-6-methylpyrimidine with ethanolic thiourea under reflux for 6 h to give, on concentration, only bis(5-bromo-2-dimethylamino-6-methylpyrimidin-4-yl) disulfide (205) in 35% yield.⁵²⁸⁴

H. Replacement of 2-, 4-, or 6-Halogens by Other Sulfur-Containing Groups (*H* 207, *E* 152)

The direct displacement of a chloro substituent by sodium sulfite to give the corresponding sulfo derivative as sodium salt has been used with limited success in the past. It has now been shown that freshly made potassium sulfite dihydrate⁵⁶⁶⁷ is a better reagent, especially for preparing the salts of simple sulfopyrimidines, which are difficult to separate from extraneous inorganic salts. Thus, 4-chloro-2,6-dimethylpyrimidine was boiled for 20 min in an equimolar aqueous solution of potassium sulfite and the thoroughly dried residue from evaporation was extracted with methanol to yield 2,4-dimethyl-6-sulfopyrimidine (206, R = Me) as pure potassium salt in greater than 70% yield.⁵⁶⁶⁷ A similar procedure gave pure potassium salts of 4,6-dimethyl-2-sulfo- (51%), 4,5-dimethyl-6-sulfo-, 4,5-dimethyl-2-sulfo-, and 4-methyl-2-sulfopyrimidine, as well as several others, for example, 2-methyl-4-sulfopyrimidine, as potassium salts contaminated with potassium chloride (only) from which they could not be purified.⁵⁶⁶⁷ In fact, most were prepared subsequently in a pure state (and more conveniently) by the oxidation⁵⁶⁶⁹ of mercaptopyrimidines with potassium permanganate [see Ch. VIII, Sect. 1.D(7)]. Less active chloropyrimidines required more drastic treatment with sulfite. For example, 2,4-diamino-6-chloropyrimidine and aqueous sodium sulfite required heating at

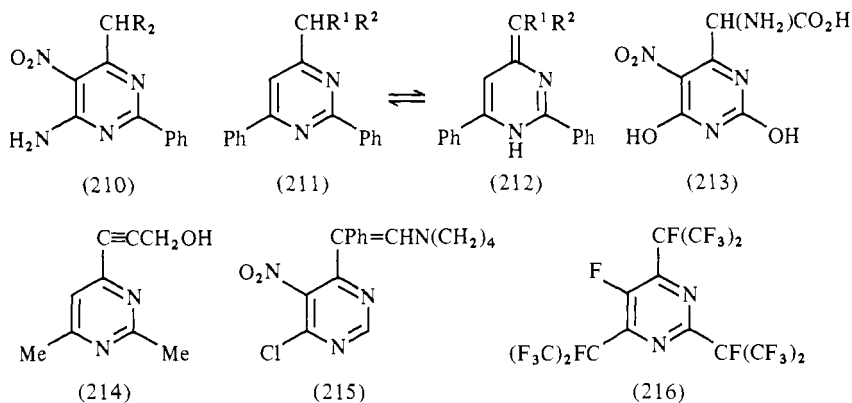
145° for 25 h in an autoclave to give 2,4-diamino-6-sulfopyrimidine (206, R = NH₂) as sodium salt in reasonable yield.⁵⁴⁰⁰ A particularly interesting reaction was that of 4-chloro-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxopyrimidine (207) with aqueous sodium hydrogen sulfite at room temperature to give the "free" sulfonic acid (1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxo-6-sulfopyrimidine), which could be isolated on account of the relative insolubility of its zwitterion (208), in which form it naturally existed.⁴⁹⁶⁹

One useful route to potential sulfonamide drugs involves treatment with a chloropyrimidine with sodio sulfanilamide or a related compound. For example, 4-chloro-5-methylpyrimidine and sodio sulfanilamide in dimethyl sulfoxide at 90° for 1 h gave 5-methyl-4-sulfanilamidopyrimidine (209) in greater than 60% yield.⁵⁷⁸⁶ Many other such displacements are described.^{5812, 5934, 5999, 6000}

I. Other Reactions of 2-, 4-, and 6-Chloropyrimidines (*H* 208, *E* 153)

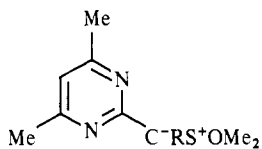
One of the important reactions of halogenopyrimidines, that is, replacement of the halogen by an (unsubstituted) alkyl, alkenyl, or alkynyl residue to generate a C,C-bond, has been discussed already in the more logical environment of Ch. IV, Sect. 2.A(2). However, any such reaction which leads to substituted alkyl, alkenyl, or alkynyl substituents, rightly belongs here. Thus, 4-amino-6-chloro-5-nitro-2-phenylpyrimidine reacted with diethyl sodiomalonate in tetrahydrofuran to give 4-amino-6-di(ethoxycarbonylmethyl)-5-nitro-2-phenylpyrimidine (210, R = CO₂Et), which in hot concentrated hydrochloric acid underwent hydrolysis and decarboxylation to give 4-amino-6-methyl-5-nitro-2-phenylpyrimidine (210, R = H) in good overall yield.⁵⁴³⁹ The less activated fluoro substituent in 5-bromo-2-fluoropyrimidine reacted quite sluggishly with diethyl potassiomalonate in acetonitrile, but on the addition of 18-crown-6 ether and heating under reflux for 10 h, a 22% yield of 5-bromo-2-di(ethoxycarbonylmethyl)pyrimidine resulted.⁵⁶⁹³ 4-Chloro-2,6-diphenylpyrimidine reacted in refluxing dimethyl sulfoxide with diethyl or dimethyl sodiomalonate, with ethyl sodiocyanoacetate, or with sodiomalononitrile to give good yields of 4-di(ethoxycarbonylmethyl)- (211, R¹ = R² = CO₂Et), 4-di(methoxycarbonylmethyl)- (211, R¹ = R² = CO₂Me), 4-(C-cyano-C-ethoxycarbonylmethyl)- (211, R¹ = CN, R² = CO₂Et), or 4-dicyclomethyl-2,6-diphenylpyrimidine (211, R¹ = R² = CN) respectively, which were all examined spectroscopically for evidence of a substantial contribution by the methylene tautomers (212).⁴⁸¹⁵ 4-Dicyanomethyl- and 4-(C-

cyano-*C*-ethoxycarbonyl)methyl-2,6-dimethylpyrimidine 1-oxide were made similarly,⁶⁰⁸² and 4-chloro-2,6-dihydroxy-5-nitropyrimidine reacted with dimethyl α -acetamido- α -sodiummalonate to give (after boiling in 6 M hydrochloric acid) 4-(*C*-amino-*C*-carboxymethyl)-2,6-dihydroxy-5-nitropyrimidine (213).⁴⁵¹¹

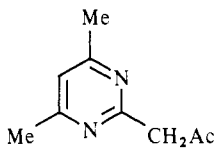


The reaction of substituted alkynyl and alkenyl residues with halogenopyrimidines is illustrated in the condensation of prop-2-ynol with 2-iodo-4,6- or 4-iodo-2,6-dimethylpyrimidine (in the presence of bistrisphenylphosphinepalladium dichloride, cuprous iodide, and triethylamine) to give 2-3'-hydroxyprop-1'-ynyl-4,6- and 4-3'-hydroxyprop-1'-ynyl-2,6-dimethylpyrimidine (214),⁵⁰⁹³ of 4,6-dichloro-5-nitropyrimidine with β -pyrrolidinostyrene in dichloromethane containing triethylamine to give 4-chloro-5-nitro-6-1'-phenyl-2'-pyrrolidinovinylpyrimidine (215) in 40% yield;⁵²³² and of 1,4,5,6-tetrafluoropyrimidine with hexafluoropropene in a dipolar aprotic solvent in the presence of caesium fluoride to give successively 2,4,5-trifluoro-6-heptafluoroisopropyl-, 2,5-difluoro-4,6-bisheptafluoroisopropyl-, and 5-fluoro-2,4,6-trisheptafluoroisopropylpyrimidine (216).⁵²⁴²

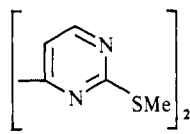
2-Chloro-4,6-dimethylpyrimidine condensed in a fascinating way with dimethyloxosulfonium methylide ($\text{Me}_2\text{O}^+\text{S}^-\text{CH}_2$) to yield dimethyloxosulfonium 4,6-dimethylpyrimidin-2-ylmethylide (217, $\text{R} = \text{H}$), which underwent *C*-acylation to (217, $\text{R} = \text{Ac}$) and subsequent desulfurization with Raney nickel to give 2-acetyl-4,6-dimethylpyrimidine (218).⁵⁶⁵³ 4-Chloropyrimidines behaved similarly and a variety of products has been reported.⁶²⁴⁹ It is clear that the potential utility of the reaction has to be explored further.



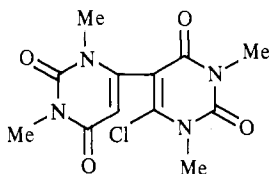
(217)



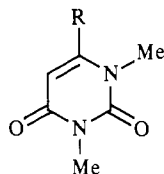
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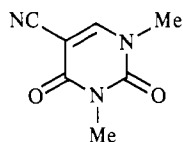
(219)



(220)



(221)



(222)

When 4-iodo-2-methylthiopyrimidine was heated in dimethylformamide with copper bronze, a small yield of 2,2'-bismethylthio-4,4'-bipyrimidine (219) was obtained. An unexpected reaction occurred on treatment of 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine with diazomethane or with tertiary amines to give as the sole product, 4'-chloro-1,1',2,2',3,3',6,6'-octahydro-1,1',3,3'-tetramethyl-2,2',6,6'-tetraoxo-4,5'-bipyrimidine (220).⁵⁹⁴⁸ Secondary amines gave mainly the expected products, for example, 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-piperidinopyrimidine.⁵⁹⁴⁸

The replacement of a chloro by a cyano substituent is usually done indirectly *via* a derived trimethylammonio, sulfo, or methylsulfonyl substituent (*q.v.*), but sometimes direct replacement is possible, as exemplified in the transformation of 4-chloro-5-cyano- into 4,5-dicyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (43%) by stirring with sodium cyanide in anhydrous dimethyl sulfoxide.⁴⁹⁹⁷ However, care is warranted because similar treatment (at 90°) of 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (221, R = Cl) gave, not the expected 4-cyano analogue (221, R = CN), but 5-cyano-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (222) in 73% yield, probably *via* an initial dehydrochlorination of the ring.⁴⁴⁷⁹ A "one pot" indirect conversion is seen in the treatment of 4-chloro-6-methylpyrimidine with aqueous sodium sulfite to give crude 4-methyl-6-sulfopyrimidine (sodium salt), which was promptly dry distilled with potassium cyanide to give a low yield of 4-cyano-6-methylpyrimidine.⁵⁰⁷⁴

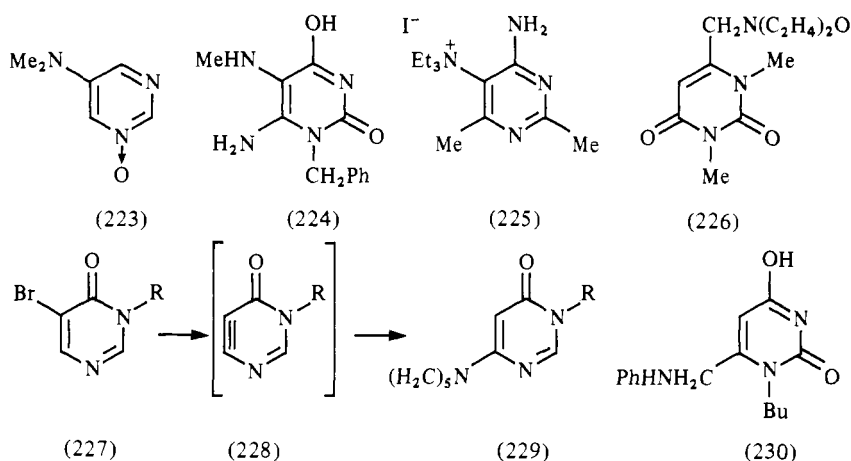
2-Chloro-4-methyl- and 2,4-dichloro-6-methylpyrimidine reacted with *t*-butylhydroperoxide as barium salt in light petroleum to give 2-*t*-butylperoxy-4-methyl- (67%) and 4-*t*-butylperoxy-2-chloro-6-methylpyrimidine (58%), respectively.⁴⁴⁶⁶

6. Reactions of 5-Halogenopyrimidines (*H* 210, *E* 156)

In fact, 5-halogenopyrimidine can be forced to undergo many of the reactions that activated 2- or 4/6-halogenopyrimidines undergo so much more readily. However, be warned that apparent nucleophilic replacement of a 5-halogeno substituent can sometimes yield a 4/6- or even an extranuclear- instead of a 5-substituted product, evidently by a different mechanism. Examples are found in several categories below.

A. The Action of Amines on 5-Halogenopyrimidines (*H* 210, *E* 156)

Regular aminolysis of 5-halogenopyrimidines is illustrated in the conversion of 5-bromo- into 5-dimethylamino-pyrimidine 1-oxide (223) (aqueous amine sealed at 100° for 4 h; 20%);⁵⁵⁰⁰ of 5-bromo- into 5-benzylamino-2,4-dihydroxypyrimidine (neat amine at 120° for 5 h; 90%);⁵⁰⁶⁰ of 5-bromo- into 5-allylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (neat amine under reflux for 5 h; 70%);⁵⁴¹⁵ of 5-bromo- into 5-adamant-1'-ylamino-2,4-dihydroxypyrimidine (amine in pyridine under reflux for 48 h; *c.* 30%);⁵²⁹⁶ of 6-amino-1-benzyl-5-bromo- into 6-amino-1-benzyl-5-methylaminouracil (224) (aqueous methylamine at 20°; 95%; note remarkably gentle conditions);⁴⁹¹⁴ of 1-allyl-5-bromo- into 1-allyl-5-dimethylamino-6-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-3-phenylpyrimidine (amine in aqueous dimethylformamide sealed at 100° for 8 h; 83%);⁴⁹³¹ of 4-amino-5-iodo- into 4-amino-5-dimethylamino-2,6-dimethylpyrimidine or its 5-methylamino homologue (aqueous alcoholic amine under reflux for 4 h or at

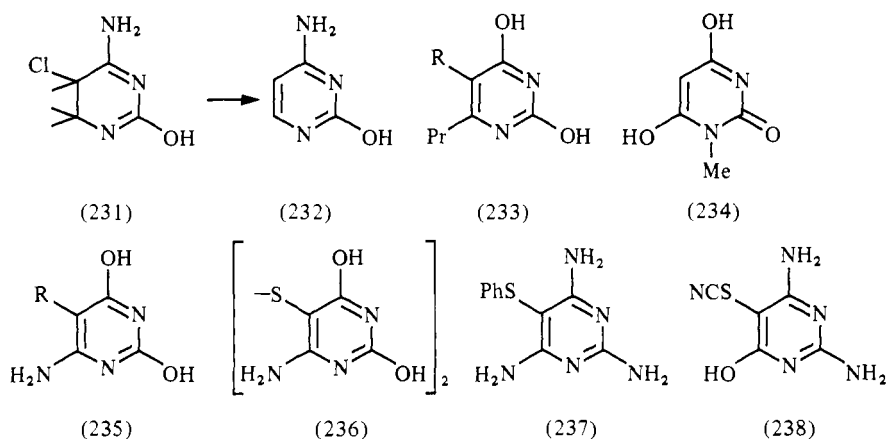


20° for 2 weeks; 30–40%);⁴⁵⁰⁶ of 5-bromo- into 5-amino-4-carbamoyl-6-hydroxy-2-methylthiopyrimidine (aqueous ammonia and copper powder sealed at 100° for 3 h; 77%),⁵¹⁵¹ of 4-amino-5-iodo-2,6-dimethyl- into 4-amino-2,6-dimethyl-5-trimethyl(or triethyl)ammonio-pyrimidine iodide [methanolic trimethylamine at 20° for 10 days, 71%; aqueous ethanolic triethylamine under reflux for 3 h, 67%; note unusual formation of triethylammonio homologue (225) and its remarkable stability];⁴⁵⁰⁶ and of 4,5-dichloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo- into 1,2,3,4-tetrahydro-5,6-bis- β -hydroxyethylamino-1,3-dimethyl-2,4-dioxypyrimidine (aqueous amine at 95°; 39%).⁴⁶⁶² Less straightforward results are seen in the conversion of 5-bromo-2-dimethylamino-4-methoxy- into 2-dimethylamino-5- β -dimethylaminoethylamino-4-hydroxypyrimidine (neat amine at 140° for 4 h; 51%);⁶¹⁸⁰ of 5-bromo-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxypyrimidine into 1,2,3,4-tetrahydro-1,3,6-trimethyl-5-morpholino-2,4-dioxypyrimidine (morpholine in dimethylformamide at 100°; 66%) or into the same product plus 27% of 1,2,3,4-tetrahydro-1,3-dimethyl-6-morpholinomethyl-2,4-dioxypyrimidine (226) (same reactants at 150°);^{6274, 4938} of 5-bromo- or 5-chloropyrimidine into 4-piperidino- and 4-diethylaminopyrimidine as well as other products (neat or alcoholic amine at 100–180°);⁴⁴⁸³ of 5-bromo-4-hydroxy- (227, R = H) or 5-bromo-1,6-dihydro-1-methyl-6-oxopyrimidine (227, R = Me) into 4-hydroxy-6-piperidinopyrimidine (229, R = H) or 1,6-dihydro-1-methyl-6-oxo-4-piperidinopyrimidine (229, R = Me), respectively [neat piperidine under reflux; 28, 62%; note failure of reaction with 5-bromo-4-hydroxy-6-methylpyrimidine suggesting the dehydro pyrimidines (228) as intermediates in the above reactions];⁶⁰⁹⁴ and of 5-bromo-1-butyl-6-methyluracil (and analogues) into 6-anilinomethyl-1-butyluracil (230) (and analogues) (treatment with aniline).⁴⁹²⁶ Although 5-halogenopyrimidines have failed in the past to react with sodium azide, 5-bromo-4-phenylpyrimidine 1-oxide did so to afford 5-azido-4-phenylpyrimidine 1-oxide (50%) and thence on treatment with phosphorus trichloride, 5-azido-4-phenylpyrimidine.⁶²⁵⁶ The conversion of 5-bromo-4-t-butyl- into 4-amino-6-t-butylpyrimidine by sodium amide has been found useful despite a rather poor yield.⁶⁶⁶⁷

B. Other Reactions of 5-Halogenopyrimidines (*H* 211, *E* 153)

5-Dehalogenation has proven successful when applied to 5-chloro-2,4-dihydroxypyrimidine (hydriodic acid at 105°; 60% yield),⁵⁶⁷³ 5-bromo-2-dimethylamino-4-hydroxypyrimidine (hydrogenolysis over

palladium; 40%),⁴⁷⁰³ 5-bromo-2,4-bismethylthiopyrimidine (butyllithium followed by water; 92%),⁴⁷⁰⁷ 5-bromo-2,4-dihydroxypyrimidine (boiling ethylene glycol for 24 h; 64%),⁴⁸⁵⁷ 2,4-dihydroxy-5-iodo-6-methylpyrimidine (boiling ethylene glycol for 8 h; 17%),⁴⁸⁵⁷ and 1,2,3,4-tetrahydro-5-iodo-1,3-dimethyl-2,4-dioxo-6-phenoxy-pyrimidine (photolysis in acetonitrile; 14%).⁴⁵⁷⁸ Dehydrochlorination of 4-amino-5-chloro-5,6-dihydro-2-hydroxypyrimidine (231) by ethanolic triethylamine under reflux gave 4-amino-2-hydroxypyrimidine (232) in 68% yield;⁵⁷⁹⁸ dehydrobromination of 4-amino-5-bromo-1-ethyl-1,2,5,6-tetrahydro-2-oxypyrimidine by methanolic potassium hydroxide at 35° gave 4-amino-1-ethyl-1,2-dihydro-2-oxypyrimidine (88%).⁵⁷⁹⁸

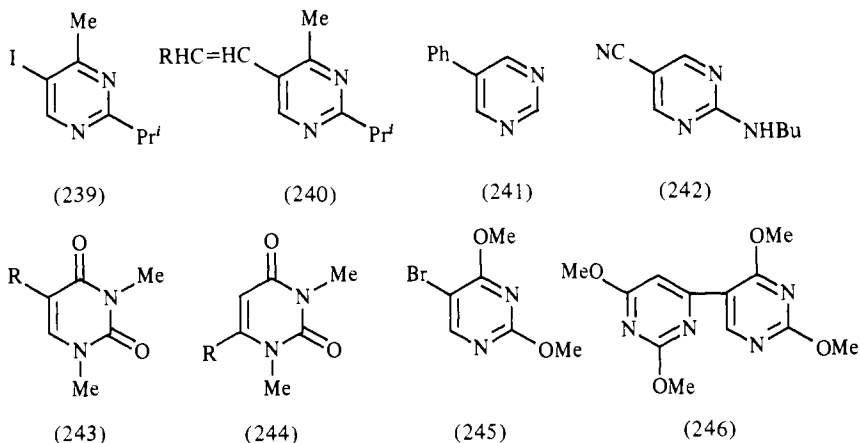


Hydrolysis and alcoholysis of 5-halogenopyrimidines were used to convert 5-bromo-2,4-dihydroxy- (233, R = Br) into 2,4,5-trihydroxy-6-propylpyrimidine (233, R = OH) in 86% yield by boiling aqueous sodium hydrogen carbonate;⁵⁵³² 1-benzyl-5-bromo-1,2,3,6-tetrahydro- into 1-benzyl-1,2,3,6-tetrahydro-5-hydroxy-3-methyl-2,6-dioxypyrimidine in 80% yield by a rather similar procedure; and 4-amino-5-iodo- into 4-amino-5-methoxy-2,6-dimethylpyrimidine in 88% yield by standing in methanolic sodium methoxide for 10 days(?).⁴⁵⁰⁶ In contrast, heating 5-bromo-1-methyluracil in aqueous sodium hydroxide at 60° gave, not 5-hydroxy-, but 6-hydroxy-1-methyluracil (234) in 54% yield.⁵⁴⁰⁷

The *thiolysis, thioalcoholysis, and thiophenolysis* of 5-halogenopyrimidines are represented recently only in the first and third of these processes. Thus, 4-amino-5-bromo-2,6-dihydroxypyrimidine (235, R = Br) reacted with aqueous thiourea to give mainly 4-amino-2,6-dihydroxy-5-thiouroniopyrimidine [235, R = S(NH₂)N⁺H₂] isolated as

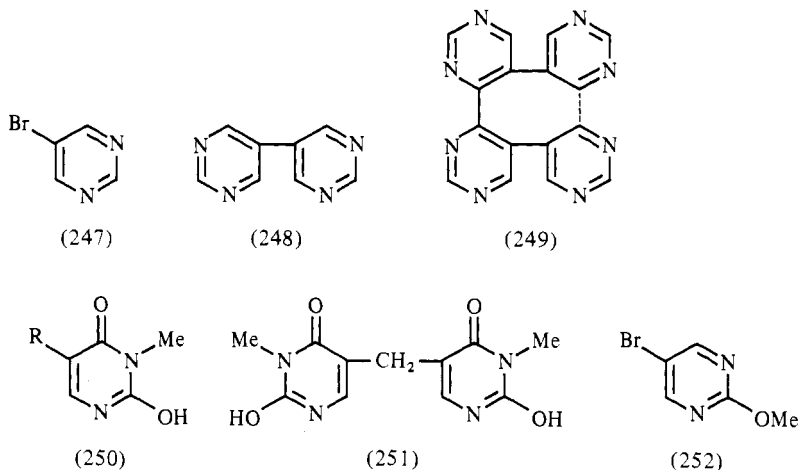
its chloride, which underwent alkaline degradation within 5 min in hot aqueous sodium hydroxide *free of oxygen* to give 4-amino-2,6-dihydroxy-5-mercaptopyrimidine (235, R = SH); being a true thiophenol (unlike 2- or 4/6-mercaptopyrimidines which are really cyclic thioamides), the above 5-mercaptopyrimidine proved quite unstable towards aerial oxidation, which gave bis-(4-amino-2,6-dihydroxypyrimidin-5-yl) disulfide (236). The same product resulted from degradation of the thiouronio intermediate in aerated alkali.⁵²⁴⁴ 2,4-Diamino-5-bromo-6-hydroxypyrimidine behaved similarly in affording 2,4-diamino-6-hydroxy-5-thiouronopyrimidine bromide, but the degradation of the latter under a variety of conditions gave either bis-(2,4-diamino-6-hydroxypyrimidin-5-yl) sulfide or disulfide, as indeed did the reaction of the original bromopyrimidine with sodium hydrogen sulfide.⁵²⁵¹ Treatment of 5-bromo-1-methyluracil with sodium hydrogen sulfide in dimethyl sulfoxide gave mainly bis(1-methyluracil-5-yl) disulfide (54%) along with a little 1-methyluracil.⁵²⁹² The replacement of 5-halogeno by 5-arylthio substituents is seen in the conversion of 2,4,6-triamino-5-bromo- into 2,4,6-triamino-5-phenylthiopyrimidine (237) by refluxing with thiophenol in butanol containing triethylamine for 48 h;⁵¹⁸⁸ of 4-carboxy-5-chloro-2-methylthio- into 4-carboxy-2-methylthio-5-phenylthiopyrimidine (sodium thiophenoxide in refluxing dimethylformamide 82%);⁴⁴⁰⁰ of 5-bromo- into 5-*p*-chlorophenylthio-2-dimethylamino-4-hydroxy-6-methylpyrimidine (*p*-chlorothiophenoxide in ethylene glycol at 150°; 54%);⁵³⁹¹ and in related examples.^{4330, 4400} The replacement of a 5-bromo by a 5-thiocyanato substituent afforded 2,4-diamino-6-hydroxy-5-thiocyanatopyrimidine (238) (aqueous potassium thiocyanate under reflux; *c.* 75%),⁵²⁵¹ 4,6-diamino-5-thiocyanatopyrimidine (methanolic potassium thiocyanate; 42%);⁵²⁴⁴ and 2,4,6-triamino-5-thiocyanatopyrimidine (similarly; 72%).⁵²⁴⁴

The replacement of 5-halogeno by *carbon-linked substituents* is illustrated in the reaction of 5-iodo-2-isopropyl-4-methylpyrimidine (239) with ethyl acrylate, acrylonitrile, or styrene (in the presence of triphenylphosphine, triethylamine, and palladium acetate) to give 5- β -ethoxycarbonylvinyl-2-isopropyl-4-methyl- (240, R = CO₂Et), 5- β -cyanovinyl-2-isopropyl-4-methyl- (240, R = CN), or 2-isopropyl-4-methyl-5-styrylpyrimidine (240, R = Ph), respectively;^{5654, 5655} of 5-iodopyrimidine with benzene, furan, thiophene, and so on, in acetonitrile under irradiation to give 5-phenyl- (241), 5-fur-2'-yl-, and 5-thien-2'-ylpyrimidine, and so forth, in reasonable yield;⁵²⁶² and of 2-chloro- or 2,4-dichloro-5-iodopyrimidine with furan (similarly) to give 2-chloro- or 2,4-dichloro-5-fur-2'-ylpyrimidine in which the active



chloro substituents remained unaffected.⁵²⁶² The introduction of a 5-cyano group is achieved in the conversion of 5-bromo- into 5-cyano-4-hydroxy-6-phenylpyrimidine (84%) by heating with cuprous cyanide in refluxing quinoline,⁵⁸¹⁶ as well as in the conversion of 5-bromo-2-butylamino- into 2-butylamino-5-cyanopyrimidine (242) by irradiation in alcoholic potassium cyanide.⁵⁹⁵⁵ When 5-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (243, R = Br) was stirred with sodium cyanide (1 mol) in dimethylformamide at room temperature, 4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (244, R = CN) resulted in 95% yield; however, heating this product or the original 5-bromopyrimidine with an excess of sodium cyanide in dimethylformamide at 80° gave the isomeric 5-cyano-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (243, R = CN), whereas replacement of dimethylformamide by refluxing aqueous ethanol in the original reaction gave 4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (244, R = CONH₂) in 86% yield.⁴⁹³⁷ Other examples of these reactions have been reported.^{4927, 4937, 4940}

The *lithiation* of 5-halogenopyrimidines leads to useful reactions. Thus, contrary to earlier reports, 5-bromo-2,4-dimethoxypyrimidine (245) and butyllithium in tetrahydrofuran at -65°, followed by treatment with carbon dioxide, gave 2,2',4',6-tetramethoxy-4,5'-bipyrimidine (246), proven in structure beyond doubt.⁴⁷⁰⁰ In a similar way, 5-bromo-4-methylthiopyrimidine gave 4',6-bismethylthio-4,5'-bipyrimidine (56%),⁴⁷⁰⁵ 5-bromo-4-methoxypyrimidine gave 4',6-dimethoxy-4,5'-bipyrimidine (43%),⁴⁷⁰⁵ 5-bromo-2-dimethylaminopyrimidine gave 2,2'-bisdimethylamino-4,5'-bipyrimidine (45%),⁶¹⁸⁰ and other examples have been reported.^{4702, 6180} In contrast, treatment of 5-bromopyrimidine (247) with butyllithium and cuprous chloride gave a product con-

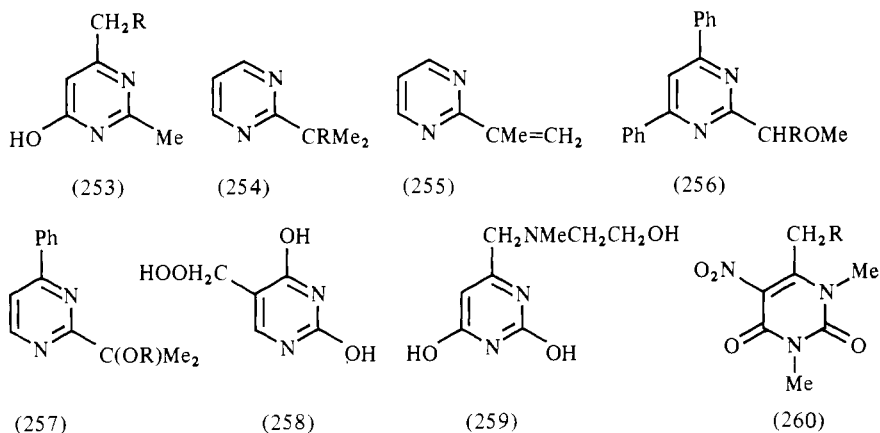


fidently formulated on nmr evidence as 5,5'-bipyrimidine (248) (57%); subsequent treatment with lithium diisopropylamide gave mainly 5,5':4,4'':5'',5'''-quarterpyrimidine (249) with some of the dehydro material, cyclized as shown by the dotted bond in formula (249).⁴⁴⁹⁴ Thermolysis of 5-bromo-3-methyl-6-phenoxyuracil (250, R = Br) in *N,N'*-dimethylacetamide at 160° gave bis(3-methyl-6-phenoxyuracil-5-yl)methane (251) along with the debrominated byproduct (250, R = H); the ratio of products in this and related reactions depended on the substitution pattern.⁶²⁷³ Irradiation of 5-bromo-2-methoxypyrimidine (252) in methanol gave several products including 2-methoxy-, 5-bromo-2-methoxy-4-methyl-, 2-methoxy-4-methyl-, 5-bromo-4-hydroxymethyl-2-methoxy- and 4-hydroxymethyl-2-methoxypyrimidine. 5-Bromo-2-phenyl- and 5-bromo-2-dimethylaminopyrimidine behaved similarly.⁴³⁵⁹

7. Reactions of Extranuclear Halogenopyrimidines (*H* 214, *E* 160)

The processes of *dehalogenation* and *dehydrohalogenation* of extranuclear halogenopyrimidines to give alkyl-, alkenyl-, or alkynylpyrimidines has been discussed in Ch. IV, Sect. 2.A (2). Typical examples of each are the hydrogenolysis of 2-chloromethyl-4-hydroxy-6-methylpyrimidine (253, R = Cl) over palladium in methanol containing magnesium oxide to give 4-hydroxy-2,6-dimethylpyrimidine (253, R = H) in 52% yield;⁵⁰⁷⁹ the treatment of 2- α -bromo- α -methylethylpyrimidine (254, R = Br) with hot methanolic sodium methoxide to give 2-isopropenylpyrimidine (255) in 70% yield;⁴⁶⁹⁰ and the treatment

of 2,4-dichloro-5- α -chlorovinylpyrimidine with sodium methoxide in methanol to give 5-ethynyl-2,4-dimethoxypyrimidine (87%).⁶³⁴⁹ Electrolytic reduction of 2-phenyl-4-trichloromethylpyrimidine gave the dichloromethyl analogue in 92% yield.⁶⁷³⁴

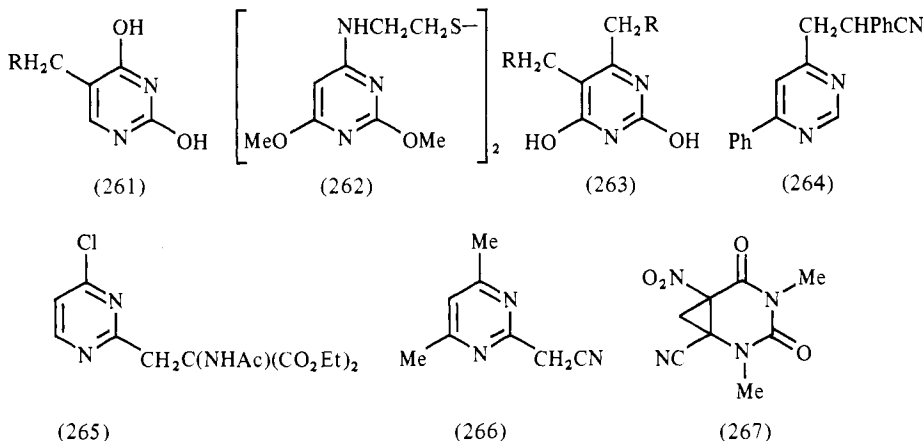


Alcoholysis and related processes, as applied to extranuclear halogenopyrimidines, are illustrated in the conversion of 2-bromo-methyl- and 2-dibromomethyl-4,6-diphenylpyrimidine by boiling methanolic sodium methoxide into 2-methoxymethyl- (256, $\text{R} = \text{H}$) and 2-dimethoxymethyl-4,6-diphenylpyrimidine (256, $\text{R} = \text{OMe}$), respectively;⁴⁸⁷⁵ of 5-chloromethyl-1,2,3,4-tetrahydro-1,3-dimethyl- into 1,2,3,4-tetrahydro-1,3-dimethyl-5-*p*-nitrophenoxymethyl-2,4-dioxo-pyrimidine (76%) by stirring with sodium *p*-nitrophenoxide in dimethyl-formamide at 25° ;⁶²³⁹ of 5-chloromethyl-2,4-dihydroxy-6-methoxy-carbonylpyrimidine (made *in situ*) into 2,4-dihydroxy-6-methoxy-carbonyl-5-methoxymethylpyrimidine (78%) by methanolic hydrogen chloride;⁶¹⁹³ of 2- α -bromo- α -methylethylpyrimidine (254, $\text{R} = \text{Br}$) into 2- α -methoxy- α -methylethylpyrimidine (254, $\text{R} = \text{OMe}$) (60%) by boiling with anhydrous methanol (for reaction with methanolic methoxide, see preceding paragraph);⁵⁶⁹⁰ of 2- α -bromo- α -methylethyl-4-phenylpyrimidine into 2- α -acetoxy- α -methylethyl-4-phenylpyrimidine (257, $\text{R} = \text{Ac}$) by silver acetate in hot acetic acid, and thence into 2- α -hydroxy- α -methylethyl-4-phenylpyrimidine (257, $\text{R} = \text{H}$) by hot aqueous sodium hydroxide;⁵⁶⁹⁰ of 5-bromomethylpyrimidine into 5-hydroxymethylpyrimidine (52%) by aqueous sodium hydroxide at 40° ;⁵⁶⁸² and of 5-chloromethyl- into 5-hydroperoxymethyl-2,4-dihydroxypyrimidine (258) (92%) by 50% hydrogen peroxide at 20° .⁵²¹¹

The *aminolysis* of such halogenopyrimidines is well documented in the transformation of 2-bromomethyl- and 4-chloromethyl-pyrimidine into 2- and 4-piperidinomethylpyrimidine (ethanolic piperidine under reflux: 60%, 70%);⁵⁶⁸² of 2-chloromethylpyrimidine into 2-trimethylammoniomethylpyrimidine chloride (trimethylamine in benzene; 78%);⁵⁶⁸² of 4-chloro-2-chloromethyl-6-hydroxy- into 4-hydroxy-6-morpholino-2-morpholinomethylpyrimidine (neat morpholine at 25°: 77%);⁵²⁵³ of the same substrate into 4-chloro-2-hydrazonomethyl-6-hydroxypyrimidine (ethanolic phenylhydrazine under reflux; note apparent oxidation of expected phenylhydrazinomethyl analogue);⁵²⁵³ of 5-chloromethyl- into 5-dimethylaminomethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenylpyrimidine (dimethylamine in dimethylformamide sealed at 100°: 30%);⁴⁹³² of 4-bromomethyl- into 4-allylaminomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxopyrimidine (ethanolic allylamine under reflux: 91%);⁴⁹⁴⁵ of 4-chloromethyl-2,6-dihydroxy- into 2,4-dihydroxy-6-*N*- β -hydroxyethyl-*N*-methylaminomethylpyrimidine (259) (β -methylaminoethanol in propan-2-ol at 25°: >90%);⁵⁸⁵⁴ and of 5-bromoacetyl-2,4-dihydroxypyrimidine into 2,4-dihydroxy-5-trimethylammonioacetylpyrimidine bromide (methanolic amine at 20°).⁵⁴⁷³ Similar use of aromatic amines gave 4-anilinomethyl- from 4-chloromethyl-2,6-dihydroxypyrimidine (aniline in dimethylformamide at 95°: 35%);⁶²⁷⁴ 2,4-dihydroxy-5-*p*-nitroanilino-methylpyrimidine from its chloromethyl analogue (*p*-nitroaniline in acetone under reflux: 62%);⁵⁴⁷⁵ and 2,4-diamino-6-*p*-ethoxycarbonyl-anilinomethylpyrimidine from its 6-bromomethyl analogue (ethyl *p*-aminobenzoate in dimethylformamide at 25°: 53%).⁵³⁸⁴ 4-Bromomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxopyrimidine (260, R = Br) reacted normally with methylhydrazine (2 mol) in ethyl acetate at 0° to give the expected 1,2,3,4-tetrahydro-1,3-dimethyl-6-(α -methylhydrazino)methyl-5-nitro-2,4-dioxopyrimidine (260, R = NMeNH₂), but when this product (or the original substrate) was treated with an excess of methylhydrazine under the same conditions a complicated reaction ensued, with elimination of nitrous acid, to afford 1,2,3,4-tetrahydro-1,3-dimethyl-6-methylhydrazonomethyl-2,4-dioxopyrimidine (83%); a plausible mechanism has been offered.⁴⁹⁴³ Treatment of 1- γ -bromopropyl- with sodium azide in refluxing acetonitrile gave 1- γ -azidopropyl-5-methyluracil (76%).⁵⁵¹⁰

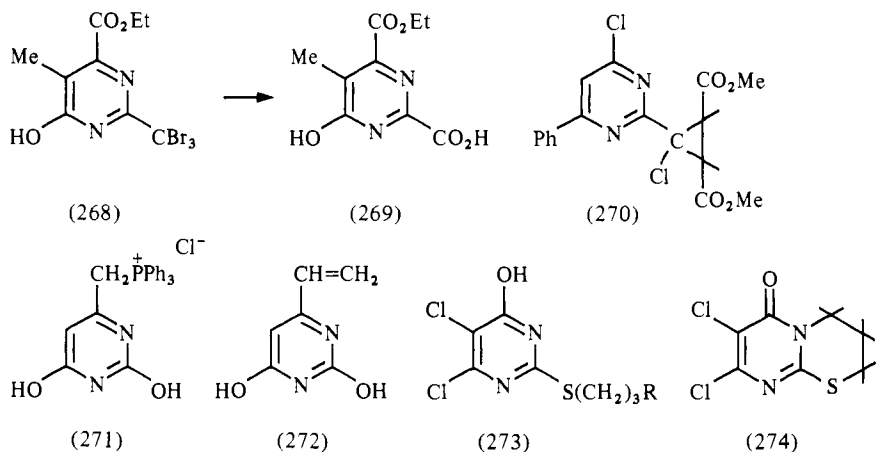
The *thiolysis* and related reactions of extranuclear halogenopyrimidines are represented (rather poorly) in the conversion of 5-chloromethyl-2,4-dihydroxypyrimidine (261, R = Cl) by thioacetamide in dimethylformamide at 40° into 5-acetiminothiomehyl-2,4-dihydroxy-

pyrimidine (261, R = SCMe·NH) and thence by boiling methanol into 2,4-dihydroxy-5-mercaptomethylpyrimidine (261, R = SH) in 50% overall yield;⁵⁶⁴¹ of 4-β-chloroethylamino-2,6-dimethoxypyrimidine by aqueous ethanolic sodium sulfide into bis[β-(2,6-dimethoxypyrimidin-4-ylamino)ethyl] disulfide (262);⁴⁷¹⁴ of 4,5-bischloromethyl-2,6-dihydroxypyrimidine (263, R = Cl) by ethanolic sodium methanethiolate into 2,4-dihydroxy-5,6-bismethylthiomethylpyrimidine (263, R = SMe) (65%) or by ethanolic sodium methanesulfinate into 2,4-dihydroxy-5,6-bismethylsulfonylmethylpyrimidine (263, R = SO₂Me);⁵⁶⁰³ and of 4-bromomethyl-6-phenylpyrimidine by aqueous ethanolic sodium benzenesulfinate into 4-phenyl-6-phenylsulfonylmethylpyrimidine (63%).⁵²⁵⁵



The replacement of extranuclear halogens by *carbon-linked* substituents is exemplified in transformation of 4-bromomethyl-6-phenylpyrimidine into 4-β-cyanophenethyl-6-phenylpyrimidine (264) in 32% yield by sodiophenylacetonitrile in liquid ammonia,^{5239, 5246} of 5-benzyloxy-4-chloro-2-chloromethylpyrimidine into 2-β-acetamido-β,β-diethoxycarbonyl-ethyl-5-benzyloxy-4-chloropyrimidine (265) by treatment with diethyl α-acetamido-α-sodiummalonate in hot dimethylformamide (note preferential reaction with the extranuclear chloro substituent);⁵³⁴⁵ of 2-chloromethyl- into 2-cyanomethyl-4,6-dimethylpyrimidine (266) in 84% yield by hot aqueous ethanolic sodium cyanide;⁶⁰⁰⁸ and of 4-bromomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine into "6-cyano-1,3-dimethyl-5-nitro-5,6-dihydrocyclothymines" (267) by potassium cyanide in aqueous dimethylformamide.⁶¹³⁸ In addition, 4-ethoxycarbonyl-6-hydroxy-5-methyl-2-tribromomethylpyrimidine (268) underwent a classical

reaction with silver nitrate in hot aqueous acetic acid to afford 2-carboxy-4-ethoxycarbonyl-6-hydroxy-5-methylpyrimidine (269), albeit in poor yield.⁶¹⁴⁰ 4-Chloro-2-phenyl-6-trichloromethylpyrimidine reacted with dimethyl fumarate in benzene containing *t*-butyl isocyanide and copper powder to give 4-chloro-2-1'-chloro-2',3'-dimethoxycarbonylcyclopropyl-2-phenylpyrimidine (270).⁶¹³⁹ The conversion of 4-bromomethyl- into 4-cyanomethyl-2,6-dimethoxy-5-nitropyrimidine (55%) occurred in ethanolic cyanide.⁶⁵¹⁷



Miscellaneous reactions of extranuclear halogenopyrimidines include the conversion of 4-chloromethyl-2,6-dihydroxypyrimidine by boiling ethanolic triphenylphosphine into 2,4-dihydroxy-6-triphenylphosphoniomethylpyrimidine chloride (271), which underwent a normal Wittig reaction with paraformaldehyde in ethanolic sodium ethoxide to give 2,4-dihydroxy-6-vinylpyrimidine (272).⁵⁴⁰³ Although 2- γ -bromopropylthio-4,5-dichloro-6-hydroxypyrimidine (273, R = Br) reacted at 0° with diethylamine to give 4,5-dichloro-2- γ -diethylamino-propylthio-6-hydroxypyrimidine (273, R = NEt₂), at 50° instantaneous cyclization occurred to give 7,8-dichloro-2,3-dihydro-6-oxo-4H,6H-pyrimido[2,3-*b*][1,3]thiazine (274).⁴⁸⁹²

CHAPTER VII

Hydroxy- and Alkoxypyrimidines (*H* 227, *E* 166)

In the last decade, little attention has been paid to the tautomeric form of hydroxypyrimidines while work on the photodimerization of hydroxypyrimidines has continued vigorously, albeit mainly on the non-natural analogues of uracil and thymine. The formation and existence of hydroxypyrimidines in space has continued to fascinate scientists.^{5542, 5565, 6532}

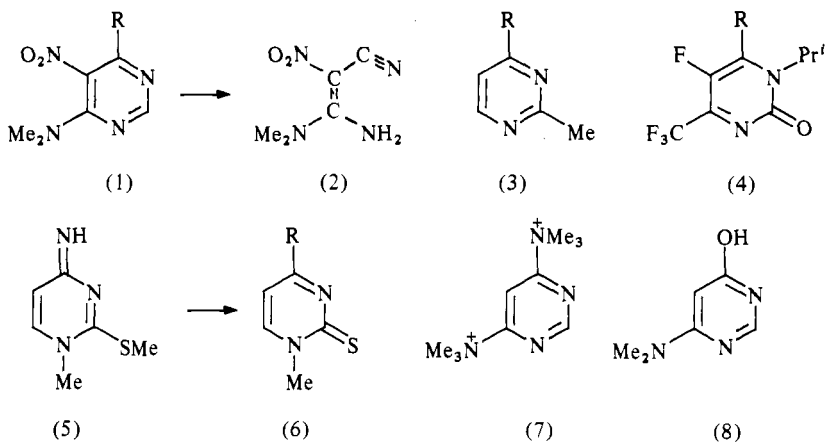
1. Preparation of 2-, 4-, and 6-Hydroxypyrimidines (*H* 227, *E* 166)

A and B. By Primary Syntheses (*H* 227, 228; *E* 166)

Innumerable examples of the formation of mono- to tetrahydroxypyrimidines by the Principal Synthesis or other primary syntheses have been discussed in Ch. II and III, respectively. One recent random example can be mentioned as illustration: *N,N'*-dimethylurea underwent condensation with two molecules of acetic anhydride in pyridine containing 4-dimethylaminopyridine (base?) to afford 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxypyrimidine (83%) by a mechanism that is still doubtful; analogues were made similarly.⁶⁴⁰¹

C. By Hydrolysis of Halogenopyrimidines (*H* 228, *E* 167)

The direct hydrolysis of halogenopyrimidines has been treated in Ch. VI, Sect. 5.E. The indirect route by conversion into alkoxypyrimidines (Ch. VI, Sect. 5.D) and subsequent hydrolysis (Sect. 1.E, below) has not been used frequently of late. The direct hydrolytic route can



sometimes lead to unexpected results. Thus, while 4-chloro-6-dimethylamino-5-nitropyrimidine (1, R = Cl) in refluxing aqueous acetic acid/sodium acetate gave 4-dimethylamino-6-hydroxy-5-nitropyrimidine (1, R = OH) as expected, the same substrate in refluxing aqueous hydrochloric acid gave the acyclic product, 4-amino-3-dimethylamino-2-nitroacrylonitrile (2).⁵⁴⁴²

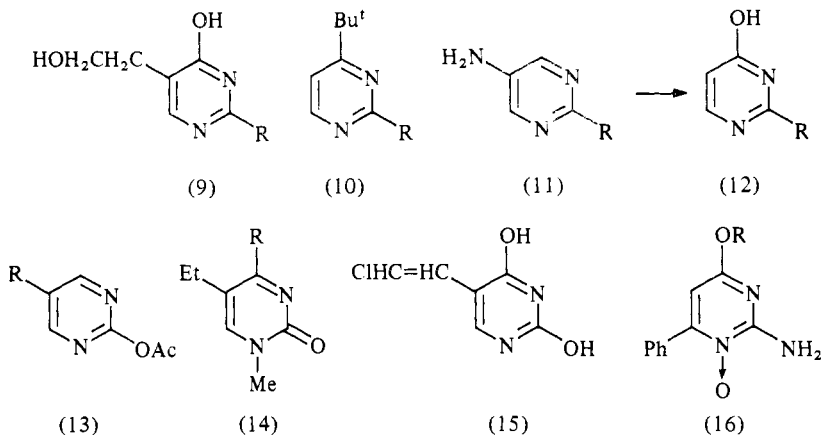
D. From Aminopyrimidines (*H* 229, *E* 167)

The *acid hydrolysis* of aminopyrimidines is seen in the transformation of 4-amino- into 4-hydroxy-6-methylpyrimidine (10 M hydrochloric acid sealed at 150°, 50%);⁴⁶⁸⁴ of 4-amino- (3, R = NH₂) into 4-hydroxy-2-methylpyrimidine (3, R = OH) (6 M hydrochloric acid under reflux, 65%);⁵⁸²⁹ of 2-amino-4,6-dimethyl-5-phenyl- into 2-hydroxy-4,6-dimethyl-5-*p*-nitrophenylpyrimidine (during nitration in nitric acid/polyphosphoric acid at 60°);⁵⁶⁶² of 4-amino- into 4-hydroxy-5-*p*-methoxyphenylpyrimidine (10 M hydrochloric acid plus hydrogen chloride at 90°, 83%);⁵⁴⁸⁷ and of 4-amino-5-fluoro-2,3-dihydro-3-isopropyl-2-oxo-6-trifluoromethylpyrimidine (4, R = NH₂) into 5-fluoro-3-isopropyl-6-trifluoromethyluracil (4, R = OH) (refluxing 3 M hydrochloric acid, 75%).⁵⁵⁸⁹ Some less usual examples include the conversion of 4-amino-5-ethylamino- into 4,5-dihydroxypyrimidine (10 M hydrochloric acid sealed at 100°, 83%);⁵⁸⁷³ of 2-cyanoamino- into 2-hydroxy-4-*o*-hydroxyphenyl-5-methylpyrimidine (boiling aqueous hydrochloric acid/sulfuric acid, 57%);⁴⁴¹³ and of 6-methylcytidine into 6-methyluridine (aqueous sodium hydrogen sulfite and acetic acid at pH 5 and 95°, 53%).⁵⁴⁰³

The *alkaline hydrolysis* is especially applicable to trimethylammoniopyrimidine but is used sometimes with regular aminopyrimidines. Thus, 2-amino- gave 2-hydroxypyrimidine by heating in 10 M sodium hydroxide* at *c.* 120°, ^{4600, 5349} and treatment of 1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine (5) with aqueous sodium hydrogen sulfide at 135° (sealed) gave not only 4-amino-1,2-dihydro-1-methyl-2-thiopyrimidine (6, R = NH₂) but also 1-methyl-2-thiouracil (6, R = OH) on account of the rather vigorous alkaline conditions. ⁴⁴⁹⁰ However, much more gentle conditions sufficed to convert 2- or 4-trimethylammoniopyrimidine chloride into 2- or 4-hydroxypyrimidine, respectively (0.1 M sodium hydroxide at 20° for 5 min); ⁵³⁴² 5-nitro-2-trimethylammoniopyrimidine chloride into 2-hydroxy-5-nitropyrimidine (similar conditions, *c.* 75%); ⁵³⁴² 4,6-bistrimethylammoniopyrimidine dichloride (7) into 4-dimethylamino-6-hydroxypyrimidine (8) (dilute sodium hydroxide at 18°); ⁵³⁹³ and 5-bromo-4-pyrimidinopyrimidine chloride in hot 3 M sodium hydroxide gave some 5-bromo-4-hydroxypyrimidine. ⁵⁵⁹⁴

Deamination (of primary amines only) by *nitrous acid* can be surprisingly effective as illustrated by the conversion of 2-amino-4-hydroxy- (9, R = NH₂) into 2,4-dihydroxy-5-β-hydroxyethylpyrimidine (9, R = OH) in 60% yield by treatment with aqueous acetic acid/sodium nitrite initially at 0° and subsequently at 15° for several hours; ⁵³⁶¹ of 2-amino-5-ethoxy- into 5-ethoxy-2-hydroxypyrimidine (42%) similarly, but without heating; ⁴³⁸⁴ of 2-amino-4-*t*-butyl- (10, R = NH₂) into 4-*t*-butyl-2-hydroxy- (10, R = OH) and 4-*t*-butyl-2-chloropyrimidine (10, R = Cl) in *c.* 1:1 ratio by treatment with 10 M hydrochloric acid/sodium nitrite at less than 0°; ⁵⁴⁸⁴ of 4,6-diamino-5-cyano- into 4-amino-5-cyano-6-hydroxy-2-phenylpyrimidine (17%) similarly but at 20°; ⁵⁷⁶⁷ of 2-amino- into 2-hydroxy-4,6-diphenylpyrimidine (70%) by 50% sulfuric acid/sodium nitrite initially at -10° and then at 25°; ⁵⁶⁷³ of 4-amino- into 4-hydroxy-6-methoxy-2-methylthiopyrimidine (55%); ⁴⁶⁵⁶ and of 2,2'-diamino- into 2,2'-dihydroxy-5,5'-bipyrimidine (80%). ⁵⁵⁸⁰ Interestingly, treatment of 2,5-diaminopyrimidine (11, R = NH₂) with nitrosyl sulfuric acid at 0° gave 2-amino-4-hydroxypyrimidine (12, R = NH₂) (40%). Likewise, 5-amino- (11, R = SMe) gave 4-hydroxy-2-methylthiopyrimidine (12, R = SMe), and 5-amino-2-methylsulfonyl- (11, R = SO₂Me) gave 2,4-dihydroxypyrimidine. ⁴³⁸² Also, treatment

*This well-known procedure (*E* 168) again gave the low melting modification (m.p. 160°) when made for the first time in Chile. ⁴⁶⁰⁰ In contrast, repetition in Canberra, even after a lapse of 10 years, gave immediately the high melting modification (m.p. 178°), ⁵³⁴⁹ presumably because of seeds in the laboratories.



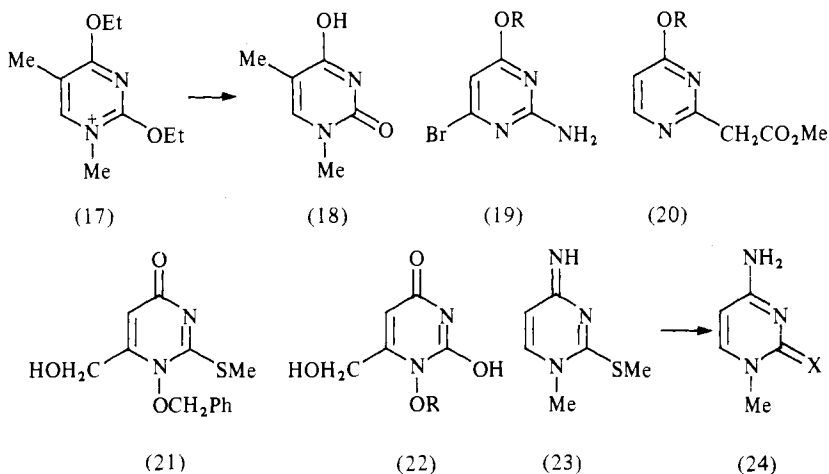
of 2-aminopyrimidine or 2-amino-5-dimethylaminomethyleneamino-pyrimidine with glacial acetic acid/sodium nitrite gave, respectively, 2-acetoxypyrimidine (13, R = H) or its 5-dimethylaminomethylene-amino derivative (13, R = N:CHNMe₂) in good yield.⁴³⁸²

E. From Alkoxy-pyrimidines (H 232, E 169)

Providing other substituents can stand the conditions, *hydrolysis in hot aqueous mineral acid* is usually satisfactory for converting alkoxy- into hydroxypyrimidines. Thus, 4-chloro-2,6-dimethoxy- gave 4-chloro-2,6-dihydroxypyrimidine (75%) by refluxing in aqueous acetic acid containing some hydrochloric acid;⁵⁹⁷⁹ 5-amino-4-methoxy- gave 5-amino-4-hydroxy-2-methylpyrimidine (35%) by heating in 10 M hydrochloric acid;⁵⁰⁹⁹ 4-ethylamino-2,6-dimethoxy- gave 4-ethylamino-2,6-dihydroxypyrimidine (27%) by refluxing in glacial acetic acid containing 10% of 2 M hydrochloric acid;⁵⁵⁴¹ 4-benzylamino-6-methoxy- gave 4-benzylamino-6-hydroxypyrimidine (35%) by refluxing in 10 M hydrochloric acid;⁵³⁵⁷ 4-benzylamino-2-methoxy- gave 4-benzylamino-2-hydroxy-5-trifluoromethylpyrimidine (48%) by similar treatment;⁵⁷⁸⁹ 4-ethoxy-5-ethyl-1,2-dihydro-1-methyl-2-oxopyrimidine (14, R = OEt) gave 5-ethyl-1-methyluracil (14, R = OH) in 82% yield by similar treatment;⁵⁷⁹⁷ both 2-ethoxy-5-ethynyl-4-hydroxy- and 4-ethoxy-5-ethynyl-2-hydroxypyrimidine underwent hydrolysis (and addition of hydrogen chloride to the triple bond), simply by evaporating with 2 M hydrochloric acid, to give 5- α -chlorovinyl-2,4-dihydroxypyrimidine (15) in greater than 70% yield;⁵³²⁹ 2,2'-diethoxy- gave 2,2'-dihydroxy-5,5'-bipyrimidine (84%) on heating in 10 M hydrochloric acid;⁵⁵⁸⁰

2,2',4',6-tetramethoxy- gave 2,2',4',6-tetrahydroxy-4,5'-bipyrimidine (90%) on heating in 5 M hydrobromic acid at 110° ; ⁴⁷⁰⁰ 4,6-di-*t*-butyl-2-ethoxy- gave 4,6-di-*t*-butyl-2-hydroxypyrimidine (38%) in refluxing 6 M hydrochloric acid; ⁶¹⁰⁵ 2-amino-4-2',4'-dichlorophenoxy-6-phenylpyrimidine 1-oxide (16, R = C₆H₄Cl₂) gave 2-amino-4-hydroxy-6-phenylpyrimidine 1-oxide (16, R = H) (90%) in aqueous butanolic hydrochloric acid at 75° ; ⁶¹⁹⁵ and other such reactions are known. ^{4716, 5023, 5935}

Alkoxy-pyrimidines do undergo slow *alkaline hydrolysis* as indicated in the transformation of 2,4-dimethoxy- into 4-hydroxy-2-methoxy-5-methylpyrimidine (69%) by aqueous methanolic sodium hydroxide under reflux for 2 days; ⁵⁴⁹⁰ of 2,4-diethoxy- into 2-ethoxy-4-hydroxy-5-methylpyrimidine (68%) by aqueous ethanolic sodium hydroxide under reflux for 1 week; ⁶¹³¹ and of 2,4-diethoxy- to a separable mixture of 4-ethoxy-2-hydroxy- and 2-ethoxy-4-hydroxypyrimidine by aqueous ethanolic sodium hydroxide under reflux for 3 days. ⁵⁶¹² In contrast, 2,4-diethoxy-1,5-dimethylpyrimidinium iodide (17) had such activated leaving groups that mere standing at 25° in aqueous sodium hydroxide gave 1,5-dimethyluracil (18). ⁵⁰⁶¹



In the presence of hydrolysis-sensitive groups, or for other reasons, it may be desirable to convert alkoxy into hydroxy groups by *splitting under virtually anhydrous conditions*. The process is illustrated in the conversion of 4,6-dibenzyloxy-pyrimidine and its 2- or 5-methyl derivatives into 4-benzyloxy-6-hydroxypyrimidine (82%) and its 2- or 5-methyl derivative, respectively, by standing in acetonitrile containing hydrogen chloride; ⁴³⁹³ of 2,4-dimethoxy-6-sulfo- and 4-chloro(or fluoro)-2,6-dimethoxypyrimidine into 2,4-dihydroxy-6-sulfo- and 4-

chloro(or fluoro)-2,6-dihydroxypyrimidine, respectively, in greater than 70% yield by iodotrimethylsilane in sulfolane at 40°;⁵⁷³⁴ of 2-methoxy- into 2-hydroxy-4,6-dimethylpyrimidine by standing in ether containing (undried) hydrogen chloride;⁴⁴⁶⁷ of 4-ethoxy-6-ethylamino- into 4-ethylamino-6-hydroxypyrimidine (c. 60%) by glacial acetic acid containing potassium iodide under reflux;³⁴⁷⁵ of 2-isopropyl-4-methoxy- into 4-hydroxy-2-isopropylpyrimidine (80%) by stirring in benzene containing hydrogen bromide at 50°;⁵⁶⁹⁴ of 2-amino-4-bromo-6-methoxy (or isopropoxy)- (19, R = Me or Prⁱ) into 2-amino-4-bromo-6-hydroxypyrimidine (19, R = H) (82%) by standing in glacial acetic acid containing 30% of hydrogen bromide;⁵¹⁵⁴ and of 4-methoxy- (20, R = Me) into 4-hydroxy-2-methoxycarbonylmethylpyrimidine (20, R = H) (80%) by stirring in benzene containing hydrogen bromide at 50°.⁵⁶⁹³

F. From Mercaptopyrimidines and Related Derivatives (*H* 233, *E* 170)

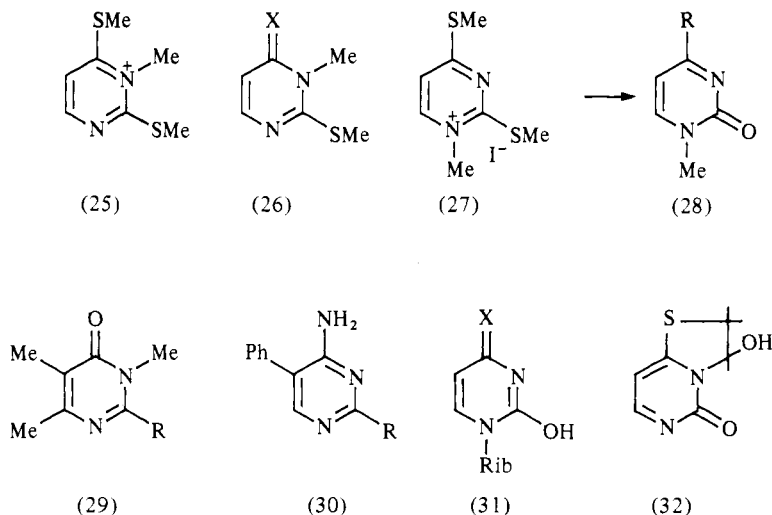
Mercaptopyrimidines seldom undergo direct hydrolysis into hydroxypyrimidines. However, the same result may be achieved in three ways: by *S*-alkylation to give alkylthiopyrimidine followed by acidic or alkaline hydrolysis, by oxidation to sulfinic or sulfonic acid followed by hydrolysis, or by *S*-alkylation followed by oxidation to a sulfoxide or sulfone followed by hydrolysis. The intermediates may, of course, be made by routes not involving the mercaptopyrimidine.

(1) Via *Hydrolysis of Alkylthiopyrimidines* (*H* 233, *E* 171)

The corresponding 2-, 4-, or 6-methylthiopyrimidines have been used to provide 4-amino-2-hydroxy-5-hydroxymethylpyrimidine (M hydrochloric acid under reflux, 78%),⁵⁶¹⁵ 4-carboxy-2,6-dihydroxypyrimidine (from the 2-methylthio analogue; 2 M hydrochloric acid under reflux, 79%),⁵⁶¹⁸ 5-bromo-2-dimethylamino-4-hydroxypyrimidine (hydrochloric acid sealed at 130°),⁴⁷⁰⁶ 5-ethoxycarbonyl-1,6-dimethyluracil (from the 4-methylthio analogue; 2 M hydrochloric acid under reflux for 10 min, 61%; note survival of the ester),⁵⁶⁰¹ 5-fluoro-3-methyluracil (from the 2-methylthio analogue; methanolic hydrochloric acid at 60°, 87%),⁴⁸⁸⁹ 2,4-dihydroxy-5-methoxy-6-methylpyrimidine (from the 2-methylthio analogue; refluxing 2 M hydrochloric acid, 44%),⁴³⁹⁷ 1- γ -carboxypropyluracil (from 1- γ -ethoxycarbonylpropyl-1,2-dihydro-4-methylthio-2-oxypyrimidine; M hydrochloric acid under

reflux, 90%),⁵²⁴⁰ 6-amino-3-methyluracil (from the 2-methylthio analogue; 2 M sodium hydroxide under reflux, 79%),⁴⁶⁵⁸ 6-amino-3-methyl-5-nitrouracil (from the 2-methylthio analogue; 6 M hydrochloric acid under reflux, 93%),⁴⁶²⁰ 3- β -cyanoethyluracil (from the 2-methylthio analogue; M hydrochloric acid under reflux, 69%),⁵⁹²⁴ and 2,4-dihydroxy-6-hydroxymethylpyrimidine (from the 2-methylthio analogue; 2 M hydrochloric acid at 95°, 99%).⁵¹⁷⁵ When 1-benzyloxy-1,4-dihydro-6-hydroxymethyl-2-methylthio-4-oxopyrimidine (21) was treated with boiling 10 M hydrochloric acid, 1-hydroxy-6-hydroxymethyluracil (22, R = H), that is, 2,4-dihydroxy-6-hydroxymethylpyrimidine 1-oxide, resulted, but when the acidity was decreased somewhat by using aqueous chloroacetic acid, the benzyloxy group remained intact and the product was 1-benzyloxy-6-hydroxymethyluracil (22, R = CH₂Ph) in 60% yield. The hydrolysis of methylthiopyrimidines has also been used successfully in several bipyrimidine series thus leading, for example, to 2,2'-dihydroxy-5,5'-bipyrimidine (3 M hydrochloric acid under reflux, 80%),^{4386, 5580} 4',6-dihydroxy-4,5'-bipyrimidine (10 M hydrochloric acid sealed at 130°, 73%),⁴⁷⁰⁵ and others.^{4707, 6180} A strange reaction occurred when 1,4-dihydro-4-imino-1-methyl-3-methylthiopyrimidine (23) was treated in mildly alkaline solution with β -mercaptoethanol or ethane-1,2-dithiol. The respective products were 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (24, X = O) or the thio analogue (24, X = S) in 90% yield; the mechanism is not obvious.⁴⁴⁶⁸ Other interesting reactions are seen in the conversion of 1-methyl-2,6-bis-methylthiopyrimidinium iodide (25) into 1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine (26, X = O) by stirring in M sodium hydroxide at 25°;⁵⁶⁶⁵ of 1,6-dihydro-1-methyl-2-methylthio-6-thiopyrimidine (26, X = S) or 3-methyl-2,4-dithiouracil into the same product (26, X = O) by treatment with methyl iodide/aqueous sodium hydroxide;⁵⁶⁶⁵ of 4-methyl-2-methylthio-1,6-diphenylpyrimidinium iodide into 1,2-dihydro-4-methyl-2-oxo-1,6-diphenylpyrimidine by hydrolysis in (wet?) methanolic sodium methoxide;⁶⁰⁸⁵ of 1-methyl-2,4-bismethylthiopyrimidinium iodide (27) into 1,2-dihydro-1-methyl-4-methylthio-2-oxopyrimidine (28, R = SMe) and its 4-methoxy analogue (28, R = OMe) as byproduct, by treatment with silver carbonate in methanol;⁵⁰⁵⁸ and of 1-methyl-2-methylthiopyrimidinium iodide into 1,2-dihydro-1-methyl-2-oxopyrimidine by aqueous sodium hydroxide at 25° (when followed spectrally, the reaction was seen to take place in two distinct phases).⁵³⁴³

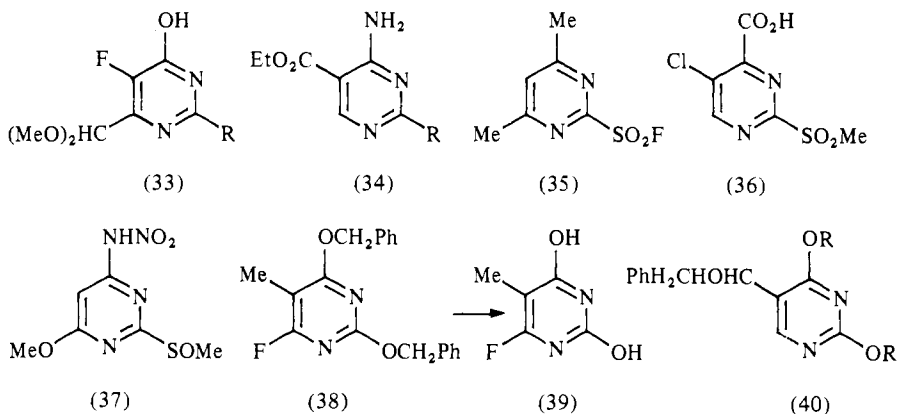
The traditional route from a mercapto- to an hydroxypyrimidine *via* a (usually unisolated) carboxymethylthiopyrimidine, by simply



boiling with aqueous chloroacetic acid, is illustrated in the formation of 4-amino-2-hydroxypyrimidine (95%),²⁹¹⁵ 4-cyclohexyl-2,6-dihydroxypyrimidine (from the 2-mercapto analogue, 75%),⁶⁰⁵² 3,5,6-trimethyluracil (29, R = OH) from the 2-thiouracil (29, R = SH) in 61% yield,⁴⁷²⁶ 2,4-dihydroxy-5,6-dimethylpyrimidine from the 2-mercapto analogue,⁴⁷²⁵ 4-acetyl-5-carboxy-2-hydroxypyrimidine (50%),⁴⁴³⁸ 4-cyclopropyl-2,6-dihydroxypyrimidine (from the 2-mercapto analogue, 36%),⁴³⁷⁶ 2,4-dihydroxy-5-methylpyrimidine (and twelve homologues, from appropriate 2-mercapto analogues),⁵⁷⁵⁴ 3-amino-6-methyluracil (from the 2-thiouracil, 51%),⁵¹⁶⁶ and other instances.^{5753, 5875, 5963, 6210} Examples in which the intermediate was isolated and characterized include the sequence 4-amino-2-mercapto- (30, R = SH) to 4-amino-2-carboxymethylthio- (30, R = SCH₂CO₂H) to 4-amino-2-hydroxy-5-phenylpyrimidine (30, R = OH) in *c.* 75% yield,⁵⁸⁶¹ the sequence 2-mercapto- to 2-carboxymethylthio- to 2-hydroxy-5-methylpyrimidine (*c.* 65%),⁴³⁸⁴ and the sequence 4-adamant-1'-yl-6-amino-2-mercapto- to 4-adamant-1'-yl-6-amino-2-carboxymethylthio- to 4-adamant-1'-yl-6-amino-2-hydroxypyrimidine.⁴³⁸⁹ To avoid the acidity of chloroacetic acid while maintaining electron-withdrawal to facilitate S,C-bond cleavage, aqueous chloroacetaldehyde at pH 6 was used to convert 4-thiouridine (31, X = S) into uridine (31, X = O) at 37° in good yield; unfortunately, 2-hydroxy-4-mercaptopyrimidine formed an embarrassingly stable intermediate (32), which made the conversion into 2,4-dihydroxypyrimidine exceedingly slow under similar conditions.⁴⁷⁴³

(2) Via *Hydrolysis of Sulfo- or Sulfino-pyrimidines* (H 234, E 172)

The oxidative conversion of mercapto- into hydroxypyrimidines without isolation of the intermediate sulfonic or sulfinic acid is usually done by treatment with hydrogen peroxide in alkaline solution. For example, 4-benzyl-6-hydroxy-2-mercapto- so gave 4-benzyl-2,6-dihydroxy-5-phenylazopyrimidine (58%), 4-dimethoxymethyl-5-fluoro-6-hydroxy-2-mercapto- (33, R = SH) gave 4-dimethoxymethyl-5-fluoro-2,6-dihydroxypyrimidine (33, R = H),⁵⁵²⁵ 4-amino-6-carboxy-5-ethyl-2-mercapto- gave 4-amino-6-carboxy-5-ethyl-2-hydroxypyrimidine (78%),⁵⁷⁴⁵ and several 5-alkyl homologues of the last product were made similarly.⁵⁷⁴⁵ However, other oxidants may be used, although it remains very doubtful whether an intermediate acid is involved at all. Thus, treatment of 4-hydroxy-2-mercapto-, 2-hydroxy-4-mercapto-, or 2,4-dimercaptopyrimidine with dimethyl sulfoxide containing sulfuric acid at 80° gave 2,4-dihydroxypyrimidine in 75–80% yield with the evolution of dimethyl sulfide and the isolation of elemental sulfur.⁴⁷¹⁸ The method is applicable in the presence of a hydrolysis-sensitive group, as indicated by the conversion of 4-amino-5-ethoxycarbonyl-2-mercaptopyrimidine (34, R = SH) into the corresponding 2-hydroxy compound (34, R = OH) in 80% yield, or by the similar formation of uridine and cytidine from thio analogues.⁴⁷¹⁸ A somewhat analogous reaction is that of 4-hydroxy-2-mercapto-6-methylpyrimidine in *t*-butanolic potassium *t*-butoxide containing a little iodine, chlorine, or bromine which eventually afforded 2,4-dihydroxy-6-methylpyrimidine in *c.* 80% yield.⁶¹⁵⁷ 1-Methyl-4-thiouracil was converted into 1-methyluracil (70%) by passing air through an aqueous solution containing sulfite ion. The mechanism has been investigated in some detail.⁵¹⁶⁰



The oxidation of a mercapto- to an isolated sulfopyrimidine followed by hydrolysis is illustrated in the permanganate oxidation at 5° of 4-mercapto- to 4-sulfopyrimidine (>90%) and its subsequent alkaline hydrolysis (kinetics measured) to 4-hydroxypyrimidine.⁵⁶⁶⁹ The isolation of other 2- and 4-sulfopyrimidines, formed by oxidation⁵⁶⁶⁹ or other means,⁵⁶⁶⁷ has been described, and details for the hydrolysis of 2,4-dimethyl-6-sulfo- to 4-hydroxy-2,6-dimethylpyrimidine have been given.⁵⁶⁶⁷ An analogous sequence is exemplified in the treatment of an aqueous solution of 2-mercapto-4,6-dimethylpyrimidine containing potassium hydrogen difluoride with chlorine to give 2-fluorosulfonyl-4,6-dimethylpyrimidine (35) in 90% yield followed by hydrolysis in boiling water to give 2-hydroxy-4,6-dimethylpyrimidine in 47% yield.⁵⁶⁶⁹

(3) Via *Hydrolysis of Alkylsulfonyl- or Alkylsulfinylpyrimidines*
(H 236, E 172)

Although the whole sequence, mercapto- to methylthio- to methylsulfonyl (or methylsulfinyl)- to hydroxypyrimidine, has not been illustrated recently, individual steps are well represented. Thus, the S-methylation step is covered in Ch. VIII, Sect. 1.D(2); the oxidation step in Ch. VIII, Sect. 5.B; and the hydrolytic step in the following examples: 4-carboxy-5-chloro-2-methylsulfonyl- (36) gave 4-carboxy-5-chloro-2-hydroxypyrimidine (91%) on stirring in 5 M sodium hydroxide;⁴⁸⁹⁰ 4-methoxy-6-methyl-2-methylthiopyrimidine or its 5,6-dimethyl homologue gave 2-hydroxy-4-methoxy-6-methylpyrimidine (37%) or its 5,6-dimethyl homologue (48%), respectively, by treatment in methanolic sodium methoxide with 25% aqueous hydrogen peroxide followed by warming, the intermediate sulfones were not isolated;^{4387, 4394} 4-amino-6-methoxy-2-methylthiopyrimidine was converted by cold fuming nitric acid into 4-methoxy-2-methylsulfinyl-6-nitroaminopyrimidine (37) accompanied by the hydrolysis product, 2,4-dihydroxy-6-nitroaminopyrimidine, derived therefrom;⁴⁶⁵⁶ and 4-carboxy-6-hydroxy-2-methylthiopyrimidine gave 4-carboxy-2,6-dihydroxypyrimidine (87%) by treatment in concentrated sulfuric acid with fuming nitric acid, without isolation of a sulfone.⁵⁶¹⁸

G. By Reductive Cleavage of Benzyloxypyrimidines (H 237, E 173)

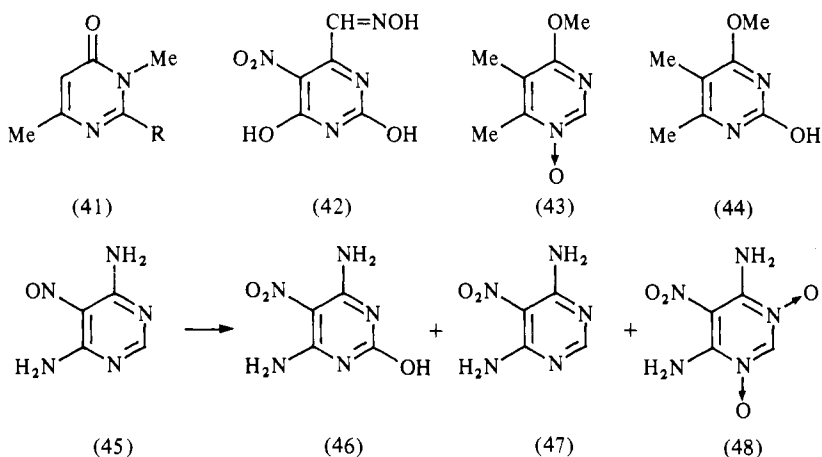
This occasionally useful route to hydroxypyrimidines has been employed recently to convert 2,4-dibenzyloxy-6-fluoro- (38) into 4-

fluoro-2,6-dihydroxy-5-methylpyrimidine (39) (95%) by using hydrogenation over palladium in methanol to avoid affecting the active halogen,⁴⁵²⁶ as well as to convert 2,4-dibenzyloxy- (40, R = CH₂Ph) into 2,4-dihydroxy-6- α -hydroxy- β -phenylethylpyrimidine (40, R = H) in 40% yield.⁵⁵⁹²

H. By Other Methods (E 173)

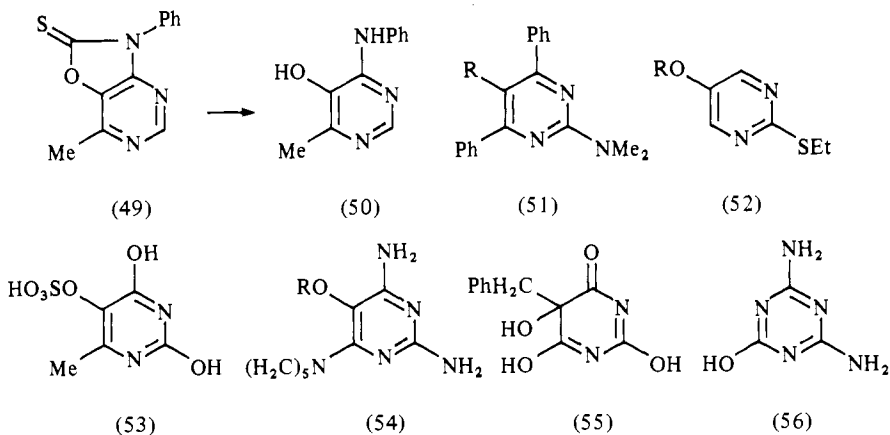
The quite rare replacement of a cyano by an hydroxy group is seen in the conversion of 2-cyano-1,6-dihydro-1,4-dimethyl-6-oxo-pyrimidine (41, R = CN) into 3,6-dimethyluracil (41, R = OH) by refluxing in 50% sulfuric acid,⁵⁰⁹⁰ and of 2,4,5-trichloro-6-cyano- into 2,4,5-trichloro-6-hydroxypyrimidine (*c.* 75%) by stirring with 2 M sodium hydroxide at 0°. ⁵⁹⁷¹ A somewhat analogous reaction is the hydrolytic removal of the whole hydroxyiminomethyl (or nitroso-methyl) group from 2,4-dihydroxy-6-hydroxyiminomethyl-5-nitropyrimidine (42) by boiling in M potassium hydroxide to give 2,4,6-trihydroxy-5-nitropyrimidine (*c.* 50%).⁵⁵⁷⁶

Treatment of 4-methoxy-5,6-dimethylpyrimidine in glacial acetic acid with hydrogen peroxide gave 78% of its 1-oxide (43) which, on treatment with *p*-toluenesulfonyl chloride followed by base, afforded 2-hydroxy-4-methoxy-5,6-dimethylpyrimidine (44) in *c.* 30% yield.⁴³⁸⁷ When 4,6-diamino-5-nitrosopyrimidine (45) was oxidized by hydrogen peroxide in acetic acid, trifluoroacetic acid, or water, 4,6-diamino-2-hydroxy-5-nitropyrimidine (46) was formed in 40–50% yield, along with 4,6-diamino-5-nitropyrimidine (47) and its 1,3-dioxide (48) which varied in proportion according to the conditions used.⁵⁶⁴⁷



2. Preparation of 5-Hydroxypyrimidines (*H* 237, *E* 173)

Many examples of the *primary synthesis* of 5-hydroxypyrimidines (as such, or protected as an *O*-acyl derivative etc.) have been given in Ch. II and III. One interesting case, not there included, involved the easy formation of 2,3-dihydro-7-methyl-3-phenyl-2-thio-1,3-oxazolo-[4,5-*d*]pyrimidine (49) and its subsequent treatment with either Raney nickel or potassium hydroxide to give 4-anilino-5-hydroxy-6-methylpyrimidine (50) in 44 or 84% yield, respectively; conversion of 4-anilino-5-bromo-6-methylpyrimidine into the same product (50), by aqueous barium hydroxide and copper at 190°, gave only a 12% yield.⁵⁹⁸⁶



5-Amino-2-dimethylamino-4,6-diphenylpyrimidine (51, R = NH₂) was converted into 2-dimethylamino-5-hydroxy-4,6-diphenylpyrimidine (51, R = OH) *via its diazonium salt* in boiling 60% sulfuric acid; the yield was 55%.⁶¹⁴⁷ 5-Hydroxypyrimidines have also been derived effectively *from 5-alkoxypyrimidines* as exemplified in the conversion of 2-benzylthio-5-methoxy- into 2-benzylthio-5-hydroxypyrimidine (refluxing glycol containing sodium hydroxide; 18%; note survival of the alkylthio group);⁴³⁹⁵ of 2-ethylthio-5-methoxy- (52, R = Me) into 2-ethylthio-5-hydroxypyrimidine (52, R = H) (concentrated ammonia sealed at 190°, 33%; note survival of alkylthio group and hydrolysis rather than aminolysis of the methoxy group);⁴³⁹⁵ of 5-methoxy- into 5-hydroxy-2,4,6-triphenylpyrimidine (boiling acetic acid containing some 63% hydrobromic acid, 84%);⁴⁴⁷⁷ and 5-benzyloxy-2-hydroxy-

into 2,5-dihydroxypyrimidine (boiling 33% hydrobromic acid for 2 min, 25%).⁴³⁸⁴

The oxidative introduction of a 5-hydroxy group is best done indirectly by the *Elbs persulfate synthesis*. This involves treatment of a cold alkaline solution of the substrate with ammonium persulfate, isolation (and sometimes characterization) of the intermediate sulfo-oxy-pyrimidine, and its subsequent acid hydrolysis to the 5-hydroxypyrimidine. The process has been used to make 2,4,5-trihydroxy-6-methylpyrimidine (50%) *via* the sulfo-oxy intermediate (53);^{5729, 6373} 2,4-diamino-5-hydroxy-6-methylpyrimidine (72%), from 2,4-diamino-6-methylpyrimidine, using a mild acidic hydrolysis of the intermediate;⁵⁰⁴⁵ 2-amino-4,5-dihydroxy-6-methylpyrimidine (58%), from the same substrate but using a vigorous acidic hydrolysis of the intermediate so that the 4-amino group was hydrolyzed also;⁵⁰⁴⁵ 2,4-diamino-5,6-dihydroxypyrimidine (divicine, 50% overall) *via* the characterized intermediate;⁴⁸⁶⁰ 2,4,5-trihydroxypyrimidine (64% on second step);⁵⁵⁰⁷ 4-amino-2,5-dihydroxypyrimidine (77% on second step);⁵⁵⁰⁷ 2,5-dihydroxy-4,6-dimethylpyrimidine (78% on second step);⁶³⁷³ 2,4-bisdimethylamino-5-hydroxypyrimidine;⁶³⁷³ and several analogues.⁶³⁷³ It appears that a 2,4-diamino, a 4,6-diamino, a 2-amino-4-hydroxy, a 4-amino-2-hydroxy, a 2,4-dihydroxy (4,6-dihydroxy is inadequate), or a similarly trisubstituted substrate is required for the successful formation of a sulfo-oxy intermediate.⁶³⁷³ *Other indirect oxidative routes* to 5-hydroxypyrimidines are illustrated in the treatment of 2,4-diamino-6-piperidinopyrimidine with benzoyl peroxide to give 2,4-diamino-5-benzoyloxy-6-piperidinopyrimidine (54, R = Bz), which was converted by dimethylamine at 0° into 2,4-diamino-5-hydroxy-6-piperidinopyrimidine (54, R = H) in 30% overall yield (several intermediate 5-benzoyloxy derivatives were made similarly but without debenzoylation being described);⁵⁵⁵³ in the treatment of 2,4,6-trimethylpyrimidine 1,3-dioxide with acetic anhydride in refluxing chloroform to give 5-acetoxy-2,4,6-trimethylpyrimidine 1-oxide in low yield;⁶¹⁶⁰ in the similar treatment of 4-phenylpyrimidine 1,3-dioxide to give, after standing in water to hydrolyze the acetoxy intermediate(?), 5-hydroxy-6-phenylpyrimidine 1-oxide in 40% yield.⁶²⁵⁴

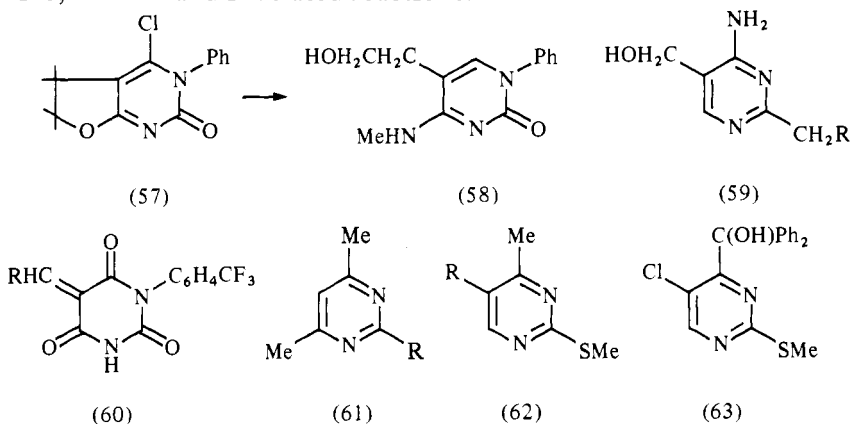
The direct *oxidation by hydrogen peroxide* of several 5-alkyl-barbituric acids gave, for example, 5-benzyl-5-hydroxybarbituric acid (55).⁵⁹⁰² However, extension of the reaction to 2,4-diamino-6-hydroxypyrimidine as substrate led to the formation of 2-amino-4,6-dihydroxy-1,3,5-triazine (56) in 80% yield and to analogous triazines; a Dimroth-like rearrangement has been postulated.⁴⁸⁶²

3. Preparation of Extranuclear Hydroxypyrimidines (*H* 241, *E* 174)

Extranuclear hydroxypyrimidines have been made by a number of methods, exemplified and discussed briefly below.

A. By Primary Synthesis (*H* 242, *E* 175)

Some examples of the formation of extranuclear hydroxypyrimidines or their precursors by primary synthesis are found in Ch. II and III. Of special interest is the ring fission of furopyrimidines and related heterobicyclic systems, as exemplified in the conversion of 4-chloro-2,3,5,6-tetrahydro-2-oxo-3-phenylfuro[2,3-*d*]pyrimidine (57) into 4-chloro-2,3-dihydro-5- β -hydroxyethyl-6-methylamino-2-oxo-3-phenylpyrimidine (58) in 75% yield by treatment with ethanolic methylamine,^{4452, 6333} and in related reactions.^{2884, 6072}



B. From Amino Derivatives (*H* 242, *E* 175)

This transformation is usually achieved by treatment with nitrous acid. Thus, 4-amino-5-aminomethyl-2-cyclopropylmethylpyrimidine dihydrochloride and sodium nitrite in aqueous solution at 50° gave 4-amino-2-cyclopropylmethyl-5-hydroxymethylpyrimidine (59, R = C₃H₅) (c. 79%);⁵⁴⁶⁹ 4-amino-5-aminomethyl-2-methylpyrimidine hydrochloride similarly gave 4-amino-5-hydroxymethyl-2-methylpyrimidine (59, R = H) (95%);⁵⁸²⁹ and 4-aminomethyl-2,6-dihydroxy- gave 2,4-dihydroxy-6-hydroxymethylpyrimidine (67%).⁵⁸⁶⁸ Another amine, formulated as 5-aminomethylenehexahydro-2,4,6-trioxo-1-*m*-trifluoromethylphenylpyrimidine (60, R = NH₂), was converted into its hexahydro-5-hydroxymethylene analogue (60, R = OH) on alkaline treatment.⁴⁵⁹⁹

C. From Halogeno Derivatives (*H* 243, *E* 175)

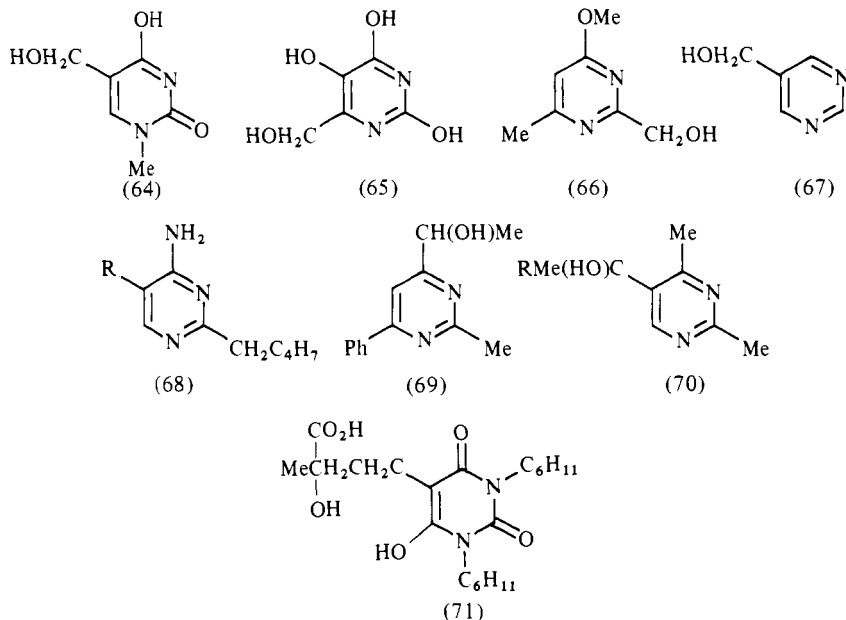
Examples of this route have been given in Ch. VI, Sect. 7.A.

D. From Esters (*H* 243, *E* 175)

The conversion of esters into the corresponding hydroxymethyl derivatives is done by reduction. Thus, 2-methoxycarbonyl- (61, $R = CO_2Me$) gave 2-hydroxymethyl-4,6-dimethylpyrimidine (61, $R = CH_2OH$) (45%) by treatment in ether with lithium aluminum hydride;⁵⁶⁸² 5-ethoxycarbonyl-4-hydrazino- similarly gave 4-hydrazino-5-hydroxymethyl-2-methylthiopyrimidine (67%);³⁴⁷⁴ 4-amino-5-ethoxycarbonyl- gave 4-amino-5-hydroxymethyl-2-methylthiopyrimidine (82%);⁵⁶²⁴ 4-amino-5-ethoxycarbonyl- gave 4-amino-5-hydroxymethyl-2-methoxypyrimidine (69%);⁵⁶²³ and 4-butoxycarbonyl-2,6-dihydroxy- gave 2,4-dihydroxy-6-hydroxymethylpyrimidine (52%).⁵³⁶⁶ Such reductions can sometimes go too far; 5-ethoxycarbonyl-4-methyl-2-methylthiopyrimidine (62, $R = CO_2Et$) so gave a separable mixture of 5-hydroxymethyl-4-methyl- (62, $R = CH_2OH$) and 4,5-dimethyl-2-methylthiopyrimidine (62, $R = Me$).³⁴⁷⁴ A second route from an ester to an alcohol is by treatment with a Grignard reagent; 5-chloro-4-ethoxycarbonyl-2-methylthiopyrimidine with phenylmagnesium bromide in ether followed by acidification gave 5-chloro-4- α -hydroxydiphenylmethyl-2-methylthiopyrimidine (63) in 55% yield.⁵⁸⁵⁵

E. By the Action of Formaldehyde (*H* 243, *E* 176)

Although formaldehyde usually attacks the 5-position of appropriate pyrimidines to give an hydroxymethyl derivative, in suitable cases, attack may occur at the 2-, 4-, or 6-position or on an activated methyl group. Some examples include the conversion of 4-diethoxymethyl-2,6-dihydroxypyrimidine into its 5-hydroxymethyl derivative (46%) by warming with alkaline formalin;⁴⁵²⁸ of 1-methyluracil into 5-hydroxymethyl-1-methyluracil (64) (56%) by warming with formalin saturated with hydrogen chloride;⁵⁵⁷⁵ of 2,4,5-trihydroxypyrimidine into its 6-hydroxymethyl derivative (65) (73%) by warming in alkaline formalin;⁶²⁴⁸ of 5-hydroxy-1-methyluracil into its 6-hydroxymethyl derivative (61%) likewise;⁵⁴¹⁵ of 2,4- or 4,6-dimethylpyrimidine into the 6- (54%) or 2-hydroxymethyl derivative (93%), respectively, by an oxidative (homolytic) reaction with ammonium persulfate in methanolic



sulfuric acid,^{5086, 6008} and of 4-methoxy-6-methylpyrimidine into its 2-hydroxymethyl derivative (66).⁵⁰⁸⁶

F. From Pyrimidine Aldehydes and Ketones (*H* 244, *E* 176)

Like the esters (above), *C*-formyl- and *C*-acylpyrimidines may be reduced to alcohols. Thus, 5-formylpyrimidine reacted with lithium aluminum hydride in tetrahydrofuran to give 5-hydroxymethylpyrimidine (67) in 78% yield;⁵⁷⁹⁴ 4-formyl- gave 4-hydroxymethyl-2-methyl-6-phenylpyrimidine (93%) by reduction with sodium borohydride in methanol;⁶¹³⁶ 5-bromo-4-formyl-2,6-dihydroxy- gave 5-bromo-2,4-dihydroxy-6-hydroxymethylpyrimidine (sodium borohydride/water, 85%);⁴⁵⁰⁷ 4-amino-5-formyl-2-β-hydroxyethyl- gave 4-amino-2-β-hydroxyethyl-5-hydroxymethylpyrimidine (sodium borohydride/water, 84%);⁴⁴³³ and 4-amino-5-cyano-2-cyclobutylmethylpyrimidine (68, R = CN) underwent hydrogenation over palladium in dilute acid to give the 5-iminomethyl (68, R = CH:NH), and thence the 5-formyl analogue (68, R = CHO) (both unisolated), followed by reduction to 4-amino-2-cyclobutylmethyl-5-hydroxymethylpyrimidine (68, R = CH₂OH) in 76% overall yield.⁵⁴⁶⁹ Likewise, 4-acetyl- gave the secondary alcohol 4-α-hydroxyethyl-2-methyl-6-phenylpyrimidine (69) in 66% yield by reduction with sodium borohydride in ethanol,⁶²⁹⁹ and 5-

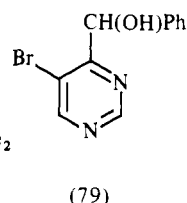
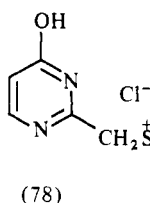
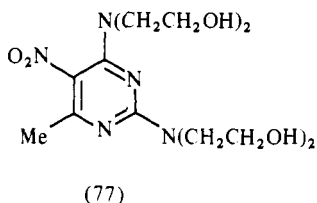
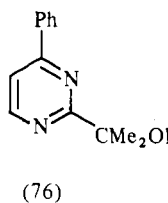
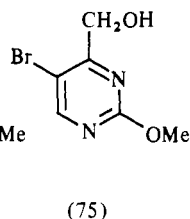
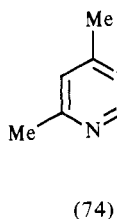
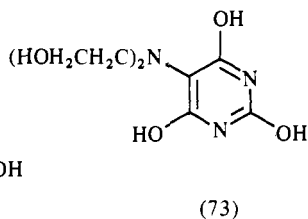
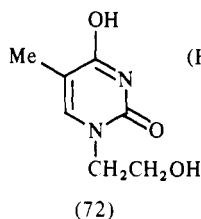
hydroxyacetyl- gave 5- α , β -dihydroxyethyl-1-methyluracil (60%) by reduction with sodium borohydride in dilute alkali.⁵²³⁸

Treatment of pyrimidine aldehydes or ketones with Grignard reagents also gives (secondary or tertiary) alcohols. Thus, 4,6-dichloro-5-formylpyrimidine and methylmagnesium iodide gave 4,6-dichloro-5- α -hydroxyethylpyrimidine (85%);⁵⁷⁶⁸ 5-acetyl-2,4-dimethylpyrimidine and ethylmagnesium bromide gave 5- α -hydroxy- α -methylpropyl-2,4-dimethylpyrimidine (70%);⁵⁰⁸⁹ and the same substrate with phenylmagnesium bromide gave up to 68% of 5- α -hydroxy- α -methylbenzyl-2,4-dimethylpyrimidine (70, R = Ph).^{5089, 5855}

When the ketone 5- β -acetyethyl-1,3-dicyclohexyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxypyrimidine was submitted to the Strecker reaction (hydrogen cyanide/ammonia), the 5- γ -carboxy- γ -hydroxybutyl analogue (71, R = OH) was obtained in place of the expected amine (71, R = NH₂).⁴⁹¹⁹ Condensation of 2-formyl-4,6-dimethylpyrimidine with nitromethane gave 2- α -hydroxy- β -nitroethyl-4,6-dimethylpyrimidine (50%) initially, and only on treatment with acetic anhydride did the expected dehydration occur to give 4,6-dimethyl-2- β -nitrovinylpyrimidine.⁴⁸³⁶

G. By Hydroxyalkylation (*H* 244, *E* 177)

Without attempting a complete coverage, *N*-hydroxyalkylation has produced 1- β -hydroxyethyl-5-methyluracil (72) (from thymine and ethylene carbonate in dimethylformide under reflux; 70%);⁵⁸¹⁸ 1,2,3,4-tetrahydro-1,3-bis- β -hydroxyethyl-2,4-dioxypyrimidine (from uracil and ethylene carbonate *via* both 1- and 3- β -hydroxyethyluracil);⁴⁸⁷¹ 1,2-dihydro-1- β -hydroxyethyl-2-oxypyrimidine (from 2-hydroxypyrimidine and β -chloroethanol in aqueous base, 28%);⁶⁰⁶⁸ 1,2-dihydro-1- β -hydroxyethyl-2-iminopyrimidine hydrobromide (from 2-aminopyrimidine and β -bromoethanol in butanol);⁶²⁵⁹ 1- β , γ -dihydroxypropyl-4-ethoxy-1,2-dihydro-2-oxypyrimidine (using glycidol, i.e., 2,3-epoxypropanol);⁵⁰²³ and 5-bis(β -hydroxyethyl)amino-2,4,6-trihydroxypyrimidine (73) (from 5-amino-2,4,6-trihydroxypyrimidine and an excess of ethylene oxide, 68%).⁴⁷⁷⁴ An easier process, *S*-hydroxyalkylation, is represented in the treatment of 2-mercapto-4,6-dimethylpyrimidine with β -chloroethanol or β -chloropropanol to give, respectively, 2- β -hydroxyethylthio- or 2- β -hydroxypropylthio-4,6-dimethylpyrimidine (74).⁵⁸¹⁵ Although rare, *C*-hydroxyalkylation does occur sometimes, as in the irradiation of 5-bromo-2-methoxypyrimidine in methanol to give *inter alia* 4-hydroxymethyl-2-methoxypyrimidine and its 5-bromo



derivative (75).⁴³⁵⁹ It must be remembered also that the introduction of C-hydroxymethyl groups using formaldehyde or methanol/ammonium persulfate (see Sect. E, above) could reasonably be classified as *de facto* C-hydroxyalkylations.

H. By Other Means (*H* 274, *E* 177)

Miscellaneous ways of making extranuclear hydroxypyrimidines are illustrated in the conversion of 2- α -acetoxy- α -methylethyl- (76, R = Ac) into 75% of 2- α -hydroxy- α -methylethyl-4-phenylpyrimidine (76, R = H) by warming in aqueous alkali;⁵⁶⁹⁰ of 4-amino-5-ethoxymethyl- into 4-hydroxy-5-hydroxymethyl-2-methylpyrimidine (>90%) by refluxing in 6 M hydrochloric acid;⁶²⁰¹ of 2,4-diamino-5-3',4',5'-trimethoxybenzylpyrimidine (trimethoprim) into its 4'-hydroxy analogue by heating with 48% hydrobromic acid;^{5468, 6537} of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-trityloxymethyl- into 1,2,3,4-tetrahydro-5-hydroxymethyl-1,3-dimethyl-2,4-dioxo-pyrimidine (71%) by warming in 80% acetic acid;⁶³⁹¹ of 2,4-dichloro- into 2,4-bis-(β -hydroxyethyl)amino-6-methyl-5-nitropyrimidine (77) by aminolysis with β -aminoethanol;⁵⁴³⁷ of related substrates to similar products;^{5106, 5438, 6020} of the chloride of 2-dimethyloxosulfoniomethyl-4-hydroxy- (78) into 4-hydroxy-2-hydroxymethylpyrimidine by irradiation of an aqueous solution;⁶¹¹⁹ of 5- β -methylallyl-2-phthalimido- into 2-amino-5- β -hydroxy- β -methylpropylpyrimidine by hydrolysis and hydration of the double bond during treatment with hot aqueous acid;⁵⁷⁶² of 5-benzylidenearbituric acid into 2,4,6-trihydroxy-5- α -hydroxybenzylpyrimidine (80%) by hydration during mild alkaline

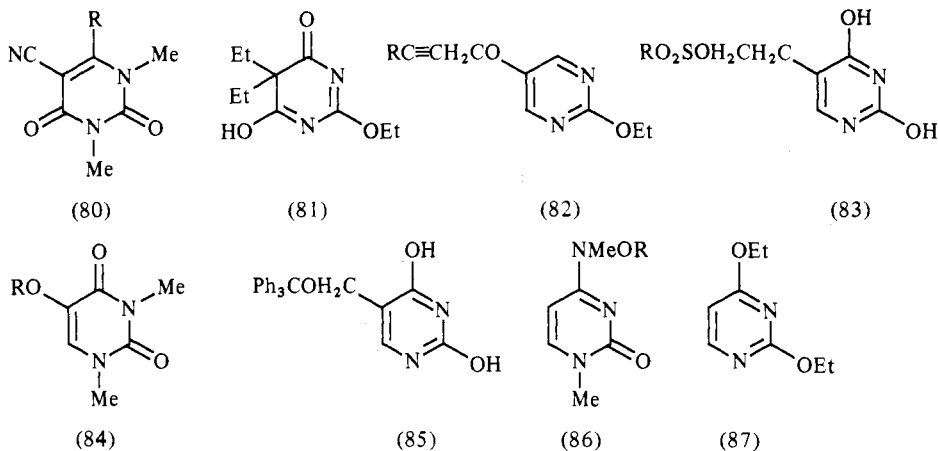
4. Preparation of Alkoxy- and Aryloxy-pyrimidines (*H* 245, *E* 178)

A. By Primary Synthesis (*H* 245, *E* 178)

B. From Halogenopyrimidines (*H* 246, *E* 178)

C. By Other Displacement Reactions (*H* 247, *E* 179)

Although a halogen substituent is usually the leaving-group of choice, several other types of leaving-groups have been used in making alkoxy pyrimidines, as illustrated below. *From trimethylammonio-pyrimidines*: 2- or 4-trimethylammonio-pyrimidine was allowed to stand at 20° for 5 min with methanolic sodium methoxide to give 2- or 4-methoxypyrimidine in 90 and 74% yield, respectively; 2-methoxy-5-nitropyrimidine (70%) was made similarly.⁵³⁴⁰ *From cyanopyrimidines*: 4-cyano- gave 4-methoxy-2-methyl-6-phenylpyrimidine (methanolic sodium methoxide under reflux, 53%),⁵⁰⁹⁰ 4-cyano-6-ethoxy- gave 4,6-diethoxy-2-methylpyrimidine (ethanolic sodium ethoxide under reflux, 33%),⁵⁰⁹⁰ 4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo- gave 1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxopyrimidine



(methanolic sodium methoxide under reflux, 75%),⁴⁹³⁹ and 4,5-dicyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo- (80, R = CN) gave 5-cyano-1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxypyrimidine (80, R = OMe) (methanolic sodium methoxide at 20°, 41%; note activation by relatively inert 5-cyano group was reflected in gentle conditions required).⁴⁹⁴⁷ *From a mercaptopyrimidine:* 5,5-diethyl-2-thiobarbituric acid was refluxed in a suspension of silver oxide in ethanol to give 2-ethoxy-5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine (81).⁴³⁶³ *From alkylthiopyrimidines:* 5-fluoro-1,2-dihydro-1-methyl-4-methylthio- gave 5-fluoro-1,2-dihydro-4-methoxy-1-methyl-2-oxopyrimidine (methanolic sodium methoxide at 20°, 58%),⁶¹¹¹ 1-benzyl-5-fluoro-1,2-dihydro-4-methylthio- similarly gave 1-benzyl-5-fluoro-1,2-dihydro-4-methoxy-2-oxopyrimidine (51%),⁶¹¹¹ 4-hydroxy-6-methyl-2-methylthio- gave 2-butoxy-4-hydroxy-6-methylpyrimidine (37%) on boiling in butanol containing pyridine and mercuric chloride,⁴⁸⁴⁵ 4-hydroxy-2-methylthio- similarly gave 2-butoxy-4-hydroxypyrimidine (12%),⁴⁸⁴⁵ and irradiation of 1,2-dihydro-1-methyl-4-methylthio-2-oxopyrimidine in the appropriate alcohol gave 1,2-dihydro-4-methoxy-, 4-ethoxy-1,2-dihydro-, 1,2-dihydro-4-isopropoxy-, and 4-t-butoxy-1,2-dihydro-1-methyl-2-oxopyrimidine in 30–40% yield.⁴⁴³⁷ *From methylsulfinylpyrimidines:* 2-methylsulfinyl-5-prop-2'-ynyloxy-pyrimidine in aqueous ethanolic sodium hydroxide under reflux gave the 2-ethoxy analogue (82, R = H), which was isolated and characterized after iodination to 2-ethoxy-5-3'-iodoprop-2'-ynyloxy-pyrimidine (82, R = I) (24%);⁴³⁹⁵ 2-alkoxy homologues were made similarly, including even 2,5-bis(3'-iodoprop-2'-ynyloxy)pyrimidine,⁴³⁹⁵ and 4-methoxy-2-methylsulfinyl- gave 2,4-dimethoxy-6-nitroamino-

pyrimidine (22%) by treatment with methanolic sodium methoxide at 25°. ⁴⁶⁵⁶ *From alkylsulfonylpyrimidines*: 4-amino-5-ethoxycarbonyl-2-ethylsulfonyl- gave 4-amino-5-ethoxycarbonyl-2-methoxypyrimidine (76%) by stirring in methanolic sodium methoxide at 10°; ⁵⁶²³ 5-methyl-2-methylsulfonyl- gave 2-methoxy-5-methylpyrimidine (79%) similarly but under reflux; ⁴³⁹⁹ and 5-fluoro-2-methylsulfonyl- gave 2,5-dimethoxypyrimidine (39%) similarly. ⁴³⁹⁹ *From a fluorosulfonylpyrimidine*: 2-fluorosulfonyl-4,6-dimethylpyrimidine reacted with methanolic sodium methoxide under reflux to give 2-methoxy-4,6-dimethylpyrimidine (60%), probably *via* a methoxysulfonyl intermediate. ⁵⁶⁶⁹ The kinetics of this reaction and similar ones of 2-fluorosulfonylpyrimidine and its 4- and 5-methyl derivatives were followed and compared. ⁵⁶⁶⁹ *From a tosyloxypyrimidine*: 2,4-dihydroxy-5- β -tosyloxyethylpyrimidine (83) in refluxing ethanol gave 5- β -ethoxyethyl-2,4-dihydroxypyrimidine. ⁵⁴²⁷ *From a dimethyloxosulfoniopyrimidine*: irradiation of 2-dimethyloxosulfoniomethyl-4-hydroxypyrimidine chloride (78) in methanol gave 4-hydroxy-2-methoxymethylpyrimidine. ⁶¹¹⁹ The *indirect conversion* of 5-fluoro-2-hydroxy-4-mercapto- into 4-butoxy-5-fluoro-2-hydroxypyrimidine by initial treatment with thionyl chloride followed by butanol at 25°, has been reported without comment. ⁶⁵¹⁵

D. By *O*-Alkylation of Hydroxypyrimidines (*H* 247, *E* 179)

Being phenolic and alcoholic respectively, 5- and extra-nuclear-hydroxypyrimidines can usually be *O*-alkylated to afford the corresponding alkoxy pyrimidines; however, 2- and 4/6-hydroxypyrimidines are akin to cyclic amides, so that alkylation is prone to give more *N*-than *O*-alkylated product. The bulk of such cases are therefore discussed in Ch. X, Sect. 1.A(3), and only those cases in which *O*-alkylation predominates are mentioned below.

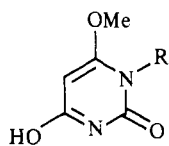
The process of 5-*O*-alkylation is illustrated in the conversion of 1,2,3,4-tetrahydro-5-hydroxy-1,3-dimethyl-2,4-dioxo- (84, R = H) into 72% of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-prop-2'-ynyloxypyrimidine (84, R = CH₂C:CH) by refluxing with prop-2'-ynyl bromide in acetone containing potassium carbonate; ⁵⁴⁰⁵ of the same substrate into 5-allyloxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine (84, R = CH₂CH:CH₂) (82%) by refluxing with allyl bromide in methanolic sodium methoxide; ⁵⁴¹⁵ of 4,5-dihydroxy-2-mercapto- into 4-hydroxy-5-methoxy-2-methylthio-6-propylpyrimidine (70%) by dimethyl sulfate/alkali at 25°; ⁵⁵³² of 5-hydroxy- into 5-prop-

2'-ynyloxypyrimidine (propynyl bromide, potassium carbonate, acetone), which was isolated in low yield as the derived 5-3'-iodoprop-2'-ynyloxypyrimidine,⁴³⁹⁵ of 5-hydroxy- into 5-methoxy-6-phenylpyrimidine 1-oxide by diazomethane;⁶²⁵⁴ of 4-anilino-5-hydroxy- into 4-anilino-5-methoxy-6-methylpyrimidine by diazomethane;⁵⁹⁸⁶ of 5-hydroxy-2-methylthio- into 2-methylthio-5-prop-2'-ynyloxypyrimidine (propynyl chloride/potassium carbonate/dimethyl sulfoxide at 50°, 80%);⁶¹⁴² and of 1-benzyl-1,2,3,6-tetrahydro-5-hydroxy- into 1-benzyl-1,2,3,6-tetrahydro-5-methoxy-3-methyl-2,6-dioxypyrimidine (diazomethane).⁵⁴¹⁰

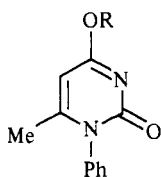
Extranuclear-O-alkylation is represented in the transformation of 2,4-dihydroxy-5-hydroxymethyl- to 5-allyloxymethyl-2,4-dihydroxypyrimidine (54%), by heating in allyl alcohol containing a little hydrochloric acid,⁴⁴⁹³ to 5-benzylloxymethyl-2,4-dihydroxypyrimidine, by refluxing with benzyl alcohol containing a little hydrochloric acid,^{6104, 6229} or to 2,4-dihydroxy-5-trityloxymethylpyrimidine (85) (60%), by refluxing with trityl chloride in pyridine;⁶³⁹¹ of 1,2,3,4-tetrahydro-5-hydroxymethyl- to 1,2,3,4-tetrahydro-5-methoxymethyl-1,3-dimethyl-2,4-dioxypyrimidine (74%) by boiling in methanol containing a little hydrochloric acid;⁶²³⁹ and (to stretch a point) of 1,2-dihydro-4-*N*-hydroxy-*N*-methylamino- (86, R = H) to 1,2-dihydro-4-*N*-methoxy-*N*-methylamino-1-methyl-2-oxypyrimidine (86, R = Me) by treatment with diazomethane.⁵³¹³

As explained above 2- or 4/6-*O*-alkylation is seldom a really useful way to make alkoxy pyrimidines. However, the process has been used quite effectively with rather specialized substrates and/or reagents. The use of a *Meerwein reagent* is illustrated in the conversion for 2,4-dihydroxy- into 2,4-diethoxypyrimidine (87) (43%) by treatment with triethyloxonium tetrafluoroborate without solvent at 75°;⁵⁵⁵⁵ of 4-hydroxy- into 4-ethoxy-2-methyl-6-phenylpyrimidine (same reagent in refluxing dichloromethane, 46%);⁵⁵⁵⁵ of 4-hydroxy- into 4-ethoxy-2,6-dimethylpyrimidine (similarly, 76%);⁵⁵⁵⁵ and of 2-amino-4-hydroxy- into 2-amino-4-ethoxy-6-methylpyrimidine (same reagent in liquid sulfur dioxide; 56% net after recovery of some substrate).⁵⁵⁵⁵ *Diazomethane* in ether tends to give both *O*- and *N*-methylated products. Thus, 2,4,6-trihydroxypyrimidine gave 2,4-dihydroxy-6-methoxypyrimidine (c. 10%), 6-methoxy-1-methyluracil, 1,6-dihydro-2,4-dimethoxy-1-methyl-6-oxypyrimidine, and other products;^{5321, 5322} 5-ethyl-2,4,6-trihydroxypyrimidine gave 5-ethyl-2-hydroxy-4,6-dimethoxypyrimidine and several unidentified *N*-methylated products;⁵³²¹ 2,4,6-trihydroxy-5-phenylpyrimidine gave 2,4,6-trimethoxy-5-phenyl-

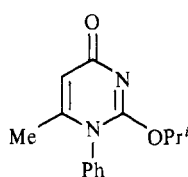
pyrimidine (c. 5%), 1,6-dihydro-2,4-dimethoxy-1-methyl-6-oxo-5-phenylpyrimidine, and other products;^{5321, 5322} 1,5-diethyl-6-hydroxyuracil gave *inter alia* 1,5-diethyl-1,6-dihydro-2,4-dimethoxy-6-oxo-pyrimidine;⁵³²³ other barbiturates gave broadly similar results;^{5321, 5323} and 4,5-dihydroxy- gave 4,5-dimethoxy-6-methoxycarbonyl-2-phenylpyrimidine and an unidentified *N*-methyl isomer.⁵⁰⁰⁰ More successful were the methylations of 2,4,6-trihydroxypyrimidine and 6-hydroxy-1-phenyluracil (*N*-phenylbarbituric acid) with *methanolic hydrogen chloride*, which gave 2,4-dihydroxy-6-methoxypyrimidine (88, R = H) in 7% yield and 6-methoxy-1-phenyluracil (88, R = Ph) in 85% yield, respectively.⁴⁷⁴² Considerable work has been done on the reactions of various *salts of hydroxypyrimidines* with several types of *alkyl halide* with a view to increasing *O*-alkylation at the expense of *N*-alkylation, but the emerging picture is quite confused. Accordingly, some examples are given of reactions and conditions that have given appreciable amounts of alkoxy products in practice without attempting any rationalization of the situation. Thus, of several salts of 6-methyl-1-phenyluracil (89, R = H) allowed to react with alkyl halides, only a combination of the magnesium bromide half-salt with isopropyl iodide in toluene gave an appreciable amount of an *O*-alkylated product, that is, 1,2-dihydro-4-isopropoxy-6-methyl-2-oxo-1-phenylpyrimidine (89, R = Prⁱ) (30%).^{4848, 5910} Other "successful" transformations included 4-hydroxy- into 4-isopropoxy-2,6-dimethylpyrimidine (sodium salt/isopropyl iodide/dimethylformamide, 32%),⁵⁹¹⁰ 4-hydroxy- into 4-isopropoxy-6-methyl-2-methylthiopyrimidine (similarly; 50%),⁵⁹¹⁰ 6-methyl-1-phenyluracil (89, R = H) into 1,4-dihydro-2-isopropoxy-6-methyl-4-oxo-1-phenylpyrimidine (90) (silver salt/isopropyl iodide/



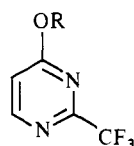
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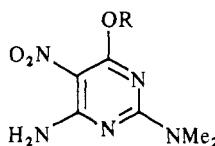
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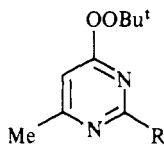
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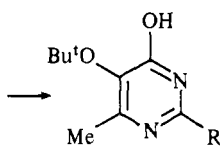
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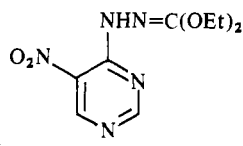
(92)



(93)



(94)



(95)

t-butyl alcohol; 43%; see the use of toluene above),^{4773, 4859} and 1-ethyl-(or butyl)-6-methyluracil into 1-ethyl(or butyl)-1,2-dihydro-4-isopropoxy-6-methyl-2-oxopyrimidine (silver salt/isopropyl iodide/toluene, c. 55%).⁴⁸⁴⁷ In most of the above cases, use of methyl iodide under similar conditions appears to have given mainly *N*-methylated products at the expense of methoxypyrimidines.⁵²⁹⁴ *O*-Alkylation of 4-hydroxy-2-trifluoromethylpyrimidine was particularly successful. Treatment of the sodium salt with ethyl bromide in dimethylformamide gave an almost quantitative yield of 4-ethoxy-2-trifluoromethylpyrimidine (91, R = Et).⁵²⁹⁴ So too was the treatment of 4-amino-2-dimethylamino-6-hydroxy-5-nitropyrimidine (92, R = H) with methyl iodide or benzyl chloride (in dimethylformamide containing anhydrous potassium carbonate), which gave 4-amino-2-dimethylamino-6-methoxy- (92, R = Me) or 4-amino-6-benzyloxy-2-dimethylamino-5-nitropyrimidine (92, R = CH₂Ph), respectively, in greater than 80% yield.^{4632, 4649} Other examples are known.^{6036, 6355, 6356}

E. Other Routes (*New*)

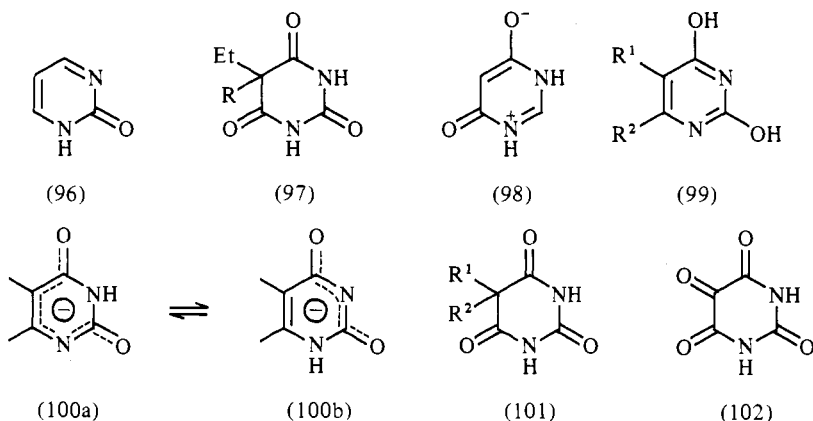
An interesting preparation of several 5-*t*-butoxypyrimidines involves the rearrangement of 4-*t*-butylperoxypyrimidines, easily available from the corresponding chloropyrimidine with barium *t*-butylperoxide.⁴⁴⁶⁶ Thus, 4-*t*-butylperoxy-6-methylpyrimidine (98, R = H) or its 2-chloro derivative (93, R = Cl) underwent rearrangement on standing as light petroleum solutions for 3 weeks to yield 5-*t*-butoxy-4-hydroxy-6-methylpyrimidine (94, R = H) or its 2-chloro derivative (94, R = Cl), respectively, in greater than 80% yield.⁴⁴⁶⁶ The formation of extranuclear methoxypyrimidines, seldom thought of as such, is exemplified in the conversion of 4-dibromomethyl- into the acetal, 4-dimethoxymethyl-6-phenylpyrimidine 3-oxide, by sodium methoxide;⁴⁸¹¹ of 4-hydrazino- into 4-diethoxymethylenehydrazino-5-nitropyrimidine (95) by treatment with tetraethoxymethane in ethanol;⁵⁶⁷⁴ and of 4-hydrazino- into 4-dipropoxymethylenehydrazino-6-methoxy-5-nitropyrimidine using tetrapropoxymethane.⁵⁶⁸¹

5. Fine Structure of Hydroxypyrimidines (*H* 249, *E* 180)

Although the broad formulation of 2- and 4/6-hydroxypyrimidines as oxopyrimidines is no longer in question, considerable work, mainly aimed at the rational interpretation of the spectra of particular hydroxy-

pyrimidines, has continued. The tautomerism and electronic structures of "biological pyrimidines" (uracil, thymine, cytosine, and the rare bases of nucleic acids) were reviewed expertly in 1975,⁴⁷¹⁷ while modern methods for determining tautomerism in general (and including the case of pyrimidines) were nicely summarized in 1973.⁴⁴⁵⁸

The X-ray structure of *2-hydroxypyrimidine* confirmed that it existed in the solid state as 1,2-dihydro-2-oxypyrimidine (96) which differed markedly from pyrimidine, for example in a bond angle at C2 of 118° (a reduction of 10°) and in N1, C2- and C2, N3-bonds lengthened by 0.05 Å.⁴⁸⁹³ Similarly, crystal structures for 5-ethyl-2,4,6-trihydroxypyrimidine (*5-ethylbarbituric acid*) and *5-ethyl-5-hydroxybarbituric acid* confirmed their fine structure as 5-ethylhexahydro-2,4,6-trioxopyrimidine (97, R = H) and 5-ethylhexahydro-5-hydroxy-2,4,6-trioxopyrimidine (97, R = OH), respectively, although the latter has been confused previously with a monohydrate of the former.⁵⁹¹⁶



Despite an apparently definitive paper in 1966 indicating the principal tautomer of 4,6-dihydroxypyrimidine as the betaine (98),³⁰⁵² continuing work on the electronic spectra^{4761, 4727} and calculations⁴⁷²⁷ for the parent dihydroxypyrimidine, some of its 5-alkyl derivatives, and its 4-thio analogue do suggest that other forms may yet prove to be equally or better represented in the equilibria. Spectral studies on the monoanions of 2,4-dihydroxypyrimidines (uracil, its 5- and/or 6-alkylated, and their *N*-alkylated derivatives) have indicated that the equilibria depended largely on the substituents. For example, in 5-butyluracil (99, R¹ = Bu, R² = H) the equilibrium strongly favored the anionic form (100a), whereas in 5-ethyl-6-propyluracil (99, R¹ = Et, R² = Pr) the reverse pertained [(100a):(100b) = 39:61].^{4724, 6196}

Studies of line width and chemical shift *versus* temperature for OH and NH signals from *barbituric acid* (101, $R^1 = R^2 = H$), *dialuric acid* (101, $R^1 = H$, $R^2 = OH$), *alloxan hydrate* (101, $R^1 = R^2 = OH$), and *alloxan* (102) have proven consistent with the structures given and have ruled out any appreciable contribution from enolic forms in all cases.⁵⁵⁷⁰ In contrast, infrared and molecular orbital calculations have suggested that *dilituric acid* (2,4,6-trihydroxy-5-nitropyrimidine) exists to a large extent as 1,2,3,4-tetrahydro-6-hydroxy-5-nitro-2,4-dioxypyrimidine.^{4746, 4747, 5906} *Thiobarbituric acid* (4,6-dihydroxy-2-mercaptopyrimidine) has been studied similarly, but results for some 5,5-dialkyl derivatives were complicated by an alkali induced reversible ring-fission reaction.⁴⁷²⁹

Recent infrared studies on the *tautomerism of hydroxypyrimidines in the gas phase* and in low-temperature matrices have revealed that 2-hydroxypyrimidine exists as such under these conditions, whereas 4-hydroxypyrimidine contains comparable contributions from the hydroxy- and oxo-forms. However, uracil shows absolutely no contribution from any hydroxy form and presumably exists (as in solution) as 1,2,3,4-tetrahydro-2,4-dioxypyrimidine entirely.⁶¹⁶²

6. Reactions of Hydroxypyrimidines (*H* 250, *E* 183)

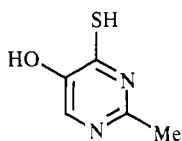
A. Conversion into Halogenopyrimidines (*H* 250, *E* 183)

This important reaction for 2-, 4/6-, and extranuclear-hydroxypyrimidines has been discussed in Ch. VI, Sects. 1 and 3; 5-hydroxypyrimidines do not yield 5-halogenopyrimidines.

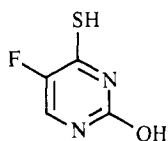
B. Conversion into Mercaptopyrimidines (*H* 251, *E* 183)

Most 2- or 4/6-hydroxypyrimidines are converted into the corresponding mercaptopyrimidines by heating with (pure) phosphorus pentasulfide in pyridine, but 2-hydroxypyrimidines usually need more severe conditions; 2- and 4/6-oxypyrimidines also undergo the reaction as does the occasional 5-hydroxypyrimidine. The old procedure, using tetrahydronaphthalene or xylene as solvent, has all but fallen into disuse, while several new solvents such as picoline, quinoline, dioxane, or tetramethylene sulfone, have given encouraging results. Thiations in the presence of amino groups, once considered difficult, are now commonplace.

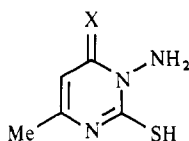
These general points are illustrated in the 4-thiation with phosphorus pentasulfide of 4-hydroxy- to 4-mercaptopyrimidine (pyridine, 74%);⁵⁶²⁵ 2-amino-4-hydroxy- to 2-amino-4-mercapto-5-phenylpyrimidine (pyridine, 78%);³⁵³² 5-amino-4-hydroxy- to 5-amino-4-mercaptopyrimidine (pyridine, "high yield");⁴³⁵⁷ 4-hydroxy- to 4-mercapto-2-methylpyrimidine (pyridine, 60%);^{4449, 4832} 4,5-dihydroxy- to 5-hydroxy-4-mercapto-2-methylpyrimidine (103) (pyridine, 86%);⁵⁹⁵⁸ 4-hydroxy- to 4-mercapto-5-methoxy-2-methylpyrimidine (pyridine, 88%);⁶³⁴⁸ 5-fluoro-4-hydroxy-2-methoxy- to 5-fluoro-2-hydroxy-4-mercaptopyrimidine (104) (pyridine plus a little water; note hydrolysis of 2-methoxy group and its failure to thiate);⁴⁸⁹⁵ 4,5-diamino-6-hydroxy-2-mercapto- to 4,5-diamino-2,6-dimercaptopyrimidine (pyridine, 55%);⁴⁶¹⁶ 3-amino-6-methyl-2-thiouracil (105, X = O) to 3-amino-6-methyl(dithiouracil) (105, X = S) (2-picoline, 44%);⁵¹⁶⁶ 4-hydroxy-2-mercapto- to 2,4-dimercaptopyrimidine (2-picoline, 56%);²⁹¹⁵ 4-hydroxy-2-mercapto- to 2,4-dimercapto-6-methylpyrimidine (3-picoline, 63%);⁵⁶⁹⁷ 2,4,5-triamino-6-hydroxy- to 2,4,5-triamino-6-mercaptopyrimidine (quinoline, 70%);⁶²²³ 5-fluoro-2,4-dihydroxy- to 5-fluoro-2-hydroxy-4-mercaptopyrimidine (dioxane, 86%);⁴³⁸⁵ 5-fluoro-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo- (106, X = O) to 5-fluoro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thiopyrimidine (106, X = S) (dioxane, 60%; note transformation of fixed oxo substituent);⁶⁰²⁶ 4-adamant-1'-yl-6-hydroxy-2-mercapto- to 4-adamant-1'-yl-2,6-dimercaptopyrimidine (tetralin; 48%);⁴³⁸⁹ 4-acetoxymethyl-2,6-dihydroxy- to 4-acetoxymethyl-2-hydroxy-6-mercaptopyrimidine (pyridine, 41%);⁵³⁶⁶ 2,4-dihydroxy- to 2-hydroxy-4-mercapto-6-methylpyrimidine (pyridine, 76%);^{5712, 6202} 6-amino-1-benzyluracil (107, R = OH) to 6-amino-1-



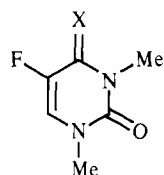
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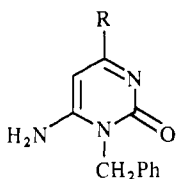
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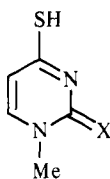
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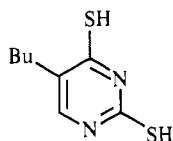
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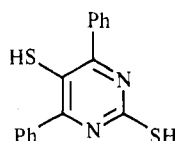
(107)



(108)



(109)



(110)

benzyl-4-thiouracil (107, R = SH) (wet pyridine, 52%);⁵⁰³⁶ 1-cyclohexyluracil to 1-cyclohexyl-4-thiouracil (pyridine, 52%);⁴⁹²⁰ 6-methoxycarbonyl-3-methyluracil to 6-methoxycarbonyl-3-methyl-4-thiouracil (dioxane, c. 75%);⁵⁴¹⁴ and other examples.^{4719, 5727, 6554}

The relatively few recorded 2-thiations are typified in the conversion of 1-methyl-4-thiouracil (108, X = O) into 1-methyl(dithiouracil) (108, X = S) (tetralin at 180°, 23%);⁵⁰⁵⁸ of 2,4-dihydroxy- into 2,4-dimercaptopyrimidine (tetramethylene sulphone at 185°, 97%);⁴⁸⁴² of 1-cyclohexyluracil into 1-cyclohexyl(dithiouracil) (pyridine, 75%);⁶¹¹⁴ of 5-butyl-2,4-dihydroxy- into 5-butyl-2,4-dimercaptopyrimidine (109) (dioxane, 72%);⁵⁹⁶³ and of 2,5-dihydroxy- into 2,5-dimercapto-4,6-diphenylpyrimidine (110), by treatment in acetonitrile with phosphorus pentasulfide followed by triethylamine at room temperature, to give a 46% yield.^{6387, 6542} Lawesson's reagent,⁶⁵²² 2,4-bis-*p*-methoxyphenyl-1,3-dithia-2,4-diphosphetane-2,4-disulfide, has been used as a thiating agent to make 2-mercapto-4-methyl-6-phenylpyrimidine (69%), 1-benzyl-1,2-dihydro-4,6-diphenyl-2-thiopyrimidine (86%), and other 2-mercapto- or 2-thiopyrimidines.⁶⁴⁵⁹

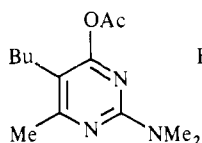
C. *O*-Acylation and Related Reactions (*H* 252, *E* 185)

All hydroxypyrimidines will undergo acylation to give derivatives such as acetoxy- or benzenesulfonyloxypyrimidines, but the process is more commonly used with 5- or extranuclear-hydroxypyrimidines than with 2- or 4/6-hydroxypyrimidines; the reagent is usually an acid chloride or anhydride.

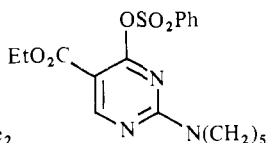
Acylation of 2- or 4/6-hydroxypyrimidines is illustrated in the formation of 4-acetoxy-5-butyl-2-dimethylamino-6-methylpyrimidine (111) (acetic anhydride under reflux, 86%);⁵³⁹² 4-benzenesulfonyloxy-5-ethoxycarbonyl-2-piperidinopyrimidine (112) (benzenesulfonyl chloride/aqueous alkali, 38%);⁴⁹⁷⁶ 2-amino-4-*p*-bromobenzenesulfonyloxy-6-methylpyrimidine (73%);⁵³⁹² 2-*t*-butyl-4-methanesulfonyloxypyrimidine (methanesulfonyl chloride in benzene containing triethylamine);⁴³⁶⁰ 4-methyl-6-*p*-toluenesulfonyloxypyrimidine (*p*-toluenesulfonyl chloride in pyridine);⁴³⁶⁰ 4-methyl-2-methylthio-6-*p*-toluenesulfonyloxypyrimidine (30%);⁵²⁶⁷ and 4-methanesulfonyloxy-6-methyl-2-methylthiopyrimidine (c. 50%).⁵²⁶⁷

Acylation of 5-hydroxypyrimidines is seen in the preparation of 5-acetoxy-2,4-dihydroxy-6-methylpyrimidine (113) (acetic anhydride under reflux, 86%; note survival of 2- and 4-hydroxy groups);⁵⁷²⁹ 5-acetoxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (from

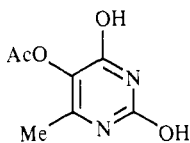
the hexahydro-5-hydroxy analogue with acetic anhydride in dimethyl sulfoxide to provide the oxidant; also by treatment of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine directly by treatment with acetic anhydride in pyridine at 50°, *c.* 65%),⁵⁷³² 4-acetamido-5-acetoxy-2,6-dihydroxypyrimidine (from 6-amino-5-hydroxyuridine and acetic anhydride/pyridine, 61%; note loss of sugar and *N*-acylation),⁵⁰⁶⁰ 2,4-diamino-5-benzoyloxy-6-methylpyrimidine (benzoyl chloride/pyridine at 60°, 77%; note survival of amino groups),⁵⁰⁴⁵ 2,4-diacetamido-5-acetoxy-6-methylpyrimidine (114, R = Ac) [from the 2,4-diamino-5-hydroxy analogue with acetic anhydride alone under reflux; 78%; note the formation of 2,4-diacetamido-5-hydroxy analogue (114, R = H) when acetic anhydride was diluted with xylene],⁵⁰⁴⁵ 2,4-diamino-5-ethoxycarbonyloxy-6-methylpyrimidine (115) (ethyl chlorocarbonate, 67%)⁵⁰⁴⁵ 2,4-diamino-5-carboxyacetoxy-6-methylpyrimidine (from the 5-hydroxy analogue with malonyl chloride/sodium hydroxide, 45%),⁵⁰⁵¹ and in the direct conversion of 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine into its 5-benzoyloxy derivative by treatment with benzoyl peroxide in acetic acid/chloroform.⁵⁷¹¹ 5-Hydroxy-2-methylthiopyrimidine and thiophosgene gave *O,O*-bis(2-methylthiopyrimidin-5-yl) thiocarbonate in good yield.⁴⁴⁰¹



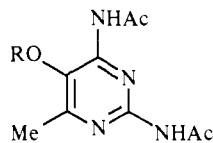
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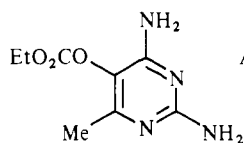
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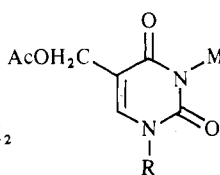
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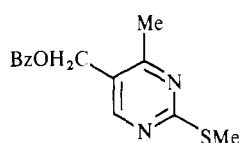
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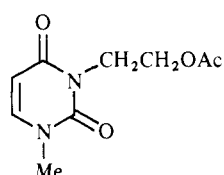
(115)



(116)



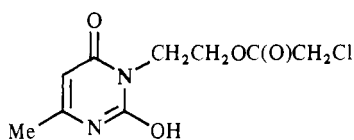
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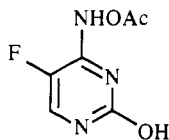
(118)

Acylation of extranuclear hydroxypyrimidines have given 5-acetoxymethyl-3-methyluracil (116, R = H) (acetic anhydride/acetic acid at 75°, 90%),⁶²³⁹ 5-acetoxymethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (116, R = Me) (acetic acid, 49%; acetic acid/acetic anhydride, 76%),^{6239, 6391} 4-acetoxymethyl-6-methyl-2-phenylpyrimidine 3-oxide (acetic anhydride in chloroform at 20°,

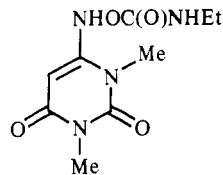
79%),⁶¹³⁶ 5-benzoyloxymethyl-4-methyl-2-methylthiopyrimidine (117) (benzoyl chloride/pyridine, 55%),³⁴⁷⁴ 5-acetoxy-4-acetoxymethyl-2,6-dihydroxypyrimidine (from 2,4,5-trihydroxy-6-hydroxymethylpyrimidine with acetic anhydride/pyridine at 25°, 83%),⁶²⁴⁸ 1- β -acetoxylethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxypyrimidine (118),⁵⁵⁰⁹ 5-hexyl-2-*p*-propionyloxyphenylpyrimidine (propionyl chloride/pyridine, 53%; also 33 homologues!),⁴⁵⁴² 3- β -(chloroacetoxy)ethyl-6-methyluracil (119) (chloroacetyl chloride/pyridines in chloroform, 66%),⁶²¹⁸ 4-acetoxymethyl-2,6-dihydroxypyrimidine (acetic anhydride/pyridine, 78%),⁵³⁶⁶ and other compounds.⁴⁵⁶⁹ In this list must be included the conversion of 5-fluoro-2-hydroxy-4-hydroxyamino- into 4-acetoxamino-5-fluoro-2-hydroxypyrimidine (120) (acetic anhydride/acetic acid),³⁴⁶⁴ and of 1,2,3,4-tetrahydro-6-hydroxyamino-1,3-dimethyl-2,4-dioxo- into 4-(*N*-ethylcarbamoyl)oxyamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (121) by boiling with ethyl isocyanate in pyridine.⁵⁰⁴² Acylations with sulfonyl chlorides have led to 5-bromo-4-carboxy-2-*p*-toluenesulfonyloxymethylpyrimidine (*p*-toluenesulfonyl chloride/ether/aqueous alkali, 30%),⁵⁹³² 2,4-dihydroxy-5- β -(methanesulfonyloxy)ethylpyrimidine (methanesulfonyl chloride/*N*-methylmorpholine in dimethylformamide, 83%;⁶⁰⁴³ or in pyridine alone, 87%),⁵⁴²⁷ and 2,4-dihydroxy-5- β -(*p*-toluenesulfonyloxy)ethylpyrimidine.⁵⁴²⁷



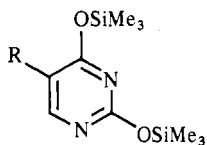
(119)



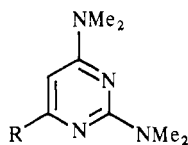
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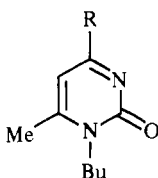
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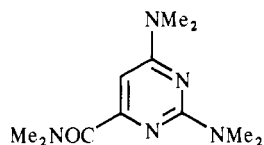
(122)



(123)



(124)



(125)

D. *O*-Trimethylsilylation (*New*)

Treatment of all types of hydroxypyrimidine with hexamethyldisilazane and/or chlorotrimethylsilane affords the corresponding trimethylsilyloxypyrimidines but seldom, if ever, an *N*-trimethylsilyl derivative. The process is useful to characterize an otherwise too high-

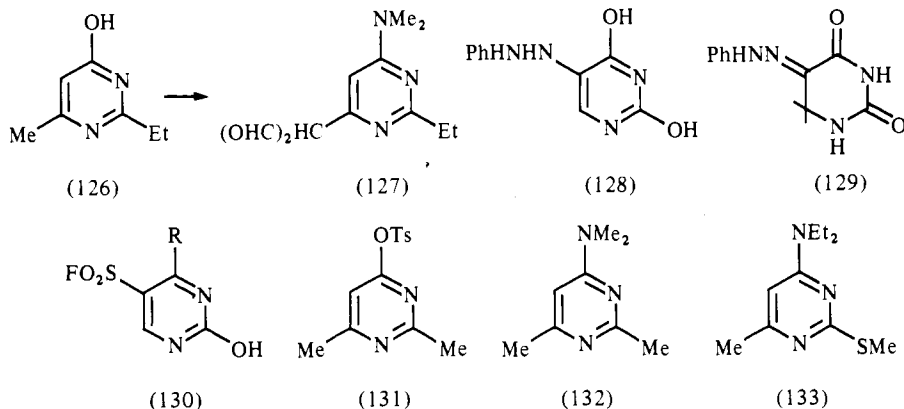
melting pyrimidine, to supply a volatile derivative for glc and so on, or to protect a hydroxy group during other molecular modifications. It should be remembered that mercaptopyrimidines will undergo *S*-trimethylsilylation as readily as hydroxypyrimidines.⁵⁹⁶³ Typical preparations include those of 2,4-bistrimethylsilyloxypyrimidine (122, R = H) (hexamethyldisilazane without solvent at 150°, 96%),⁶¹³² 5-bromo-2,4-bistrimethylsilyloxypyrimidine (122, R = Br) (chlorotrimethylsilane in benzene containing triethylamine under reflux, 92%),⁵⁹³⁵ 5-butyl-2,4-bistrimethylsilyloxypyrimidine (122, R = Bu) hexamethyldisilazane and ammonium sulfate under reflux: 94%; note similar formation of 4-trimethylsilyloxy-2-trimethylsilylthiopyrimidine from 4-hydroxy-2-mercaptopyrimidine),^{5963, 5418} 5-ethoxymethyl-2,4-bistrimethylsilyloxypyrimidine (122, R = CH₂OEt) (chlorotrimethylsilane in benzene containing triethylamine at 25°, 88%),⁶¹⁰⁴ 5-methoxy-2,4-bistrimethylsilyloxypyrimidine (122, R = OMe) (hexamethyldisilazane and ammonium sulfate under reflux, 96%),⁶²¹⁵ 4-fluoro-5-methyl-2,6-bistrimethylsilyloxypyrimidine (hexamethyldisilazane in refluxing dimethylformamide, 62%),⁶¹⁹¹ and others.⁵⁵⁷⁵

E. Semidirect Aminolysis (New)

The conversion of 2- or 4/6-hydroxypyrimidines into aminopyrimidines has always been done indirectly *via* chloro-, alkylthio-, alkoxy-, or other such derivatives. Extranuclear hydroxy pyrimidines have usually been so converted only *via* chloropyrimidines. This has been necessary because the Bucherer reaction has invariably failed in the pyrimidine series. However, recently workers in Moscow have introduced a semidirect method for the aminolysis of hydroxypyrimidines by heating with amides of phosphoric or phosphorous acid;⁴⁸⁵² unfortunately, the reaction requires quite severe conditions, and its applicability is therefore limited. Thus, phosphoric trisdimethylamide [O=P(NMe₂)₃] and uracil at 235° for 1 h gave 2,4-bisdimethylaminopyrimidine (123, R = H) in 78% yield;⁴⁸⁴⁴ phosphoric trisphenylamide and uracil at 240° gave 2,4-dianilinopyrimidine (46%);⁴⁸⁴⁴ phosphoric trisdiethylamide and 2,4-dihydroxy-6-methylpyrimidine at 200–225° gave 2,4-bisdiethylamino-6-methylpyrimidine (53%);⁴⁸⁴⁴ phosphoric trisdimethylamide and barbituric acid at 230–260° gave trisdimethylaminopyrimidine (123, R = NMe₂) in 33% yield;⁴⁸⁴⁴ and several amino or alkylthio derivatives behaved similarly.⁴⁸⁴⁴ It appears to be important to use unpurified phosphoric amides; when purified materials were used, yields were much lower!⁴⁸⁵¹ Selective aminolysis of 1-alkyluracils

in the 4-position can be achieved by using appropriate amides and conditions. Thus, while 1-butyl-6-methyluracil (124, R = OH) and phosphoric trisdimethylamide gave only 2,4-bisdimethylamino-6-methylpyrimidine (123, R = Me) (note loss of *N*-butyl group),⁴⁸⁴⁴ the same substrate with phosphoric trisphenylamide gave 4-anilino-1-butyl-1,2-dihydro-6-methyl-2-oxopyrimidine (124, R = NHPh) in good yield,⁴⁸⁵⁰ 6-methyl-1-phenyluracil and phosphorous trisdimethylamide [$P(NMe_2)_3$] gave 4-dimethylamino-1,2-dihydro-6-methyl-2-oxo-1-phenylpyrimidine (82%),⁴⁸⁵⁰ and other such reactions are described.⁴⁸⁵⁰ Besides the above mentioned loss of an *N*-alkyl group during aminolysis, 5-halogen or 5-hydroxymethyl substituents may be lost too. For example, 5-bromo-2,4-dihydroxy-6-methylpyrimidine and phosphoric trisdimethylamide gave 2,4-bisdimethylamino-6-methylpyrimidine (41%) as the sole isolable product.⁴⁸⁴⁴ It was later found that the addition of a little of the amine hydrochloride (corresponding to the phosphoric amide being used) improved the rate of reaction considerably. For example, uracil to 2,4-bisdimethylaminopyrimidine reached a 75% yield in 15 min instead of 1 h at the same temperature without catalyst.⁴⁸⁴⁶ Not surprisingly, many substituents do not survive such a reaction. Thus, treatment of 2,4-dichloro-6-methylpyrimidine with phosphorous trisdimethylamide at 160° gave the same product as that expected from 6-methyluracil, that is, 2,4-bisdimethylamino-6-methylpyrimidine;⁴⁸⁴⁶ treatment of 4-amino-2-hydroxypyrimidine with phosphoric trisphenylamide at 230° gave mainly 2,4-dianilinopyrimidine;⁴⁸⁴⁶ and 4-carboxy-2,6-dihydroxypyrimidine with phosphoric trisdimethylamide gave mainly 2,4-bisdimethylamino-6-*N,N*-dimethylcarbamoylpyrimidine (125).⁴⁸⁴⁶

Other isolated conversions of hydroxy- into aminopyrimidines include that of 2-ethyl-4-hydroxy-6-methyl- (126) into 2-ethyl-4-diformylmethyl-6-dimethylaminopyrimidines (127) by warming with phosphoryl chloride in dimethylformamide;⁵⁰⁷³ of 2,4,5-trihydroxy- into 2,4-dihydroxy-5-phenylhydrazinopyrimidine (128) [existing, almost certainly, in the tautomeric form (129)] by heating with phenylhydrazine in acetate buffer;⁶¹⁰³ of 5-fluorosulfonyl-2,4-dihydroxy- (130, R = OH) into 4-amino-5-fluorosulfonyl-2-hydroxypyrimidine (130, R = NH₂) in 55% by gentle treatment with ammonium hydroxide;⁴⁷⁹⁸ of 4-chloro-5-diphenylmethyl-2,6-dihydroxy- into 2,4-diamino-5-diphenylmethyl-6-hydroxypyrimidine (70%) by heating in ethanolic ammonia at 150°;⁵⁵⁰² and of 4-hydroxy-2,6-dimethyl- into 2,4-dimethyl-6-*p*-tosyloxypyrimidine (131) by treatment with tosyl chloride in pyridine, followed by aminolysis with dimethylamine in aqueous

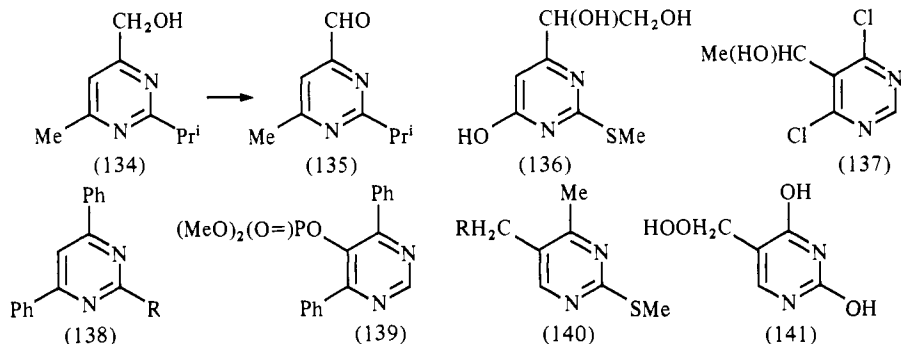


dioxane at 15° to give 4-dimethylamino-2,6-dimethylpyrimidine (132) in 80% yield.⁵²⁶⁷ 4-Diethylamino-6-methyl-2-methylthiopyrimidine (133) and other analogues of the last product were made similarly.⁵²⁶⁷

F. Oxidative and Reductive Reactions (New)

Although 2- and 4/6-hydroxypyrimidines cannot undergo oxidation, 5-hydroxy derivatives can be converted into oxypyrimidines under very specialized circumstances (see Sect. 9 for alloxan and related compounds) and extracyclic hydroxypyrimidines can be readily oxidized to the corresponding aldehyde, ketone, or even carboxylic acid. Thus, 4-hydroxymethyl- (134) with selenium dioxide in dioxane at 25° gave 4-formyl-2-isopropyl-6-methylpyrimidine (135) in 55% yield,⁶⁰⁰⁸ 2,4-dihydroxy-5-hydroxymethyl- with persulfate in water gave 5-formyl-2,4-dihydroxy-6-methylpyrimidine (63%);⁴⁴⁸² 2,4-dihydroxy-5-hydroxymethyl- with aqueous ceric ammonium nitrate gave 5-formyl-2,4-dihydroxypyrimidine (44%);⁵⁴⁷³ 5-hydroxymethyl- with manganese dioxide in dioxane gave 5-formyl-1-methyluracil (48%);⁵⁵⁷⁵ 4- α,β -dihydroxyethyl- (136) with aqueous periodate gave 4-formyl-6-hydroxy-2-methylthiopyrimidine (77%);⁴⁶⁰⁴ 4,6-dichloro-5- α -hydroxyethyl- (137) with manganese dioxide in methylene chloride gave 5-acetyl-4,6-dichloropyrimidine (>80%);⁵⁷⁶⁸ and 5- α -hydroxyethyl- similarly gave 5-acetylpyrimidine (73%).⁶³⁴³

Direct reductive removal of hydroxy groups is not easy. However, reduction of 2-hydroxy-4,6-diphenylpyrimidine (138, R = OH) with lithium aluminum hydride gave 4,6-diphenylpyrimidine (138, R = H) or 1,2(?)-dihydro-4,6-diphenylpyrimidine, according to conditions. In any case, the latter was easily converted into the parent pyrimidine



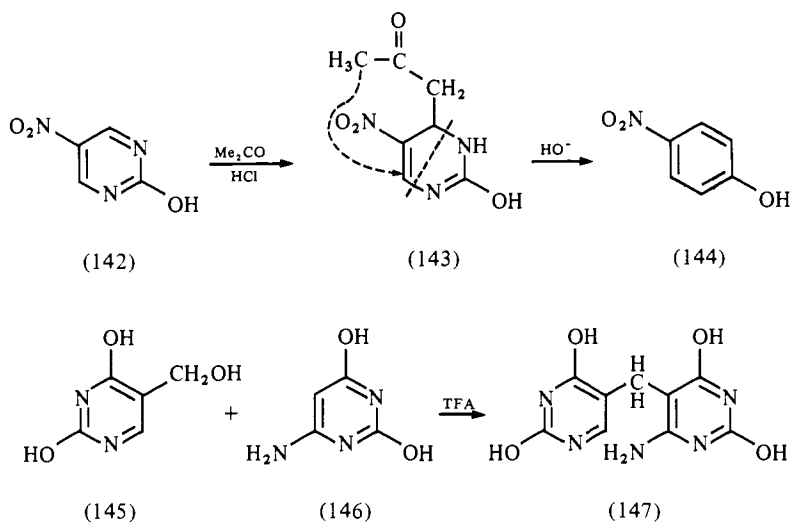
(138, R = H) by gentle oxidation with permanganate.⁴⁸⁸⁴ A 5-hydroxy group has been removed indirectly by treatment of 5-hydroxy-4,6-diphenylpyrimidine with phosphoryl chloride followed by methanol to afford 5-dimethoxyphosphinyloxy-4,6-diphenylpyrimidine (139), which underwent reduction by sodium/liquid ammonia to give 4,6-diphenylpyrimidine (138, R = H) in 57% yield.⁵⁴⁹⁹ Extranuclear-hydroxy groups have also been removed. Thus, 5-ethoxycarbonyl-4-methyl-2-methylthiopyrimidine and lithium hydride gave the 5-hydroxymethyl analogue (140, R = OH) as primary product and 4,5-dimethyl-2-methylthiopyrimidine (140, R = H) as the product of further reduction; 5-methyl-2,4-bismethylthiopyrimidine was made similarly from the 5-ethoxycarbonyl analogue with lithium aluminum hydride.³⁴⁷⁴ Other interesting examples include treatment of 2,4-dihydroxy-5-hydroxymethylpyrimidine with vinyl fluoride and hydrogen fluoride to give 5- γ,γ -difluoropropyl-2,4-dihydroxypyrimidine;⁴⁸⁰⁰ of 2,4-dihydroxy-5- α -hydroxybenzylpyrimidine with benzene or toluene in anhydrous hydrogen fluoride to give 5-benzyl-2,4-dihydroxy- or 2,4-dihydroxy-5-*p*-methylbenzylpyrimidine, respectively, both in greater than 50% yield;⁴⁸⁰¹ and of 5-hydroperoxymethyl-2,4-dihydroxypyrimidine (141) with hydrogen over palladium to give 2,4-dihydroxy-5-methylpyrimidine (93%).

G. Other Reactions (New)

The removal of a 5-hydroxy group in favor of a carbon-linked substituent can be done with a Wittig reagent. Thus, 5-hydroxy-1-methyluracil with $\text{Ph}_3\text{P}=\text{CHCONH}_2$ gave 5-carbamoylmethyl-1-methyluracil (55%); analogues were made similarly, including 5-carbamoyl-methyluridine.⁶¹⁵⁸

The fascinating conversion of 2-hydroxy-5-nitropyrimidine (142) into *p*-nitrophenol (144) *via* the acetone adduct (143) involves loss of the original hydroxy group along with both ring nitrogen atoms as shown. By using other appropriate ketones the reaction becomes, in fact, of some potential synthetic use and yields are quite good.⁶¹²⁴

An unrelated but equally bizarre reaction is that of 2,4-dihydroxy-5-hydroxymethylpyrimidine (145) with 4-amino-2,6-dihydroxypyrimidine (146) in trifluoroacetic acid at room temperature to afford 4-amino-5-(2',4'-dihydroxypyrimidin-5'-ylmethyl)-2,6-dihydroxypyrimidine (147) in 70% yield; the reaction was extended somewhat.⁵³¹¹ Not unrelated is the reaction of 2,4-diamino-5-hydroxymethylpyrimidine with phenol in acidic media (under a variety of conditions) to give 2,4-diamino-5-*p*-hydroxybenzylpyrimidine (55%), or with 1,2,3-trimethoxybenzene to give 2,4-diamino-5-(2',3',4'-trimethoxybenzyl)-pyrimidine (19%), a trimethoprim isomer.⁶⁵²⁰



7. Reactions of Alkoxy- and Aryloxy-pyrimidines (*H* 254, *E* 189)

A. Conversion into Hydroxypyrimidines (*H* 254, *E* 189)

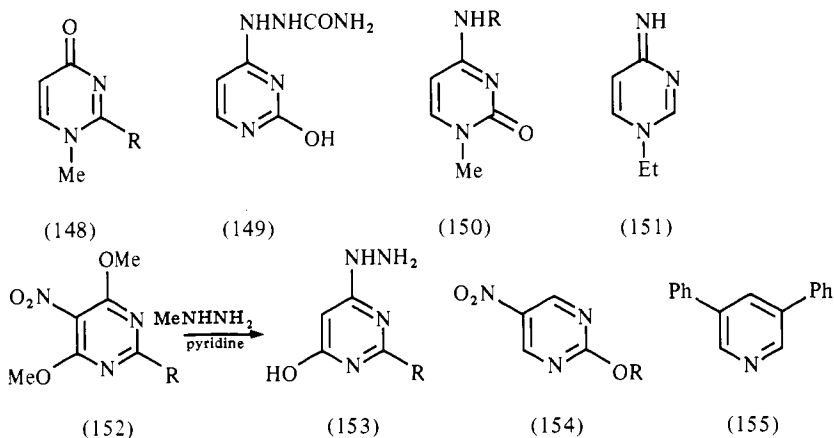
The formation of hydroxypyrimidines from 2- or 4/6-alkoxy- (Sects. 1.E and 1.G), 5-alkoxy- (Sect. 2), and extranuclear-alkoxy-pyrimidines (Sect. 3.H) were discussed previously.

B. Conversion into Halogenopyrimidines (*H* 254, *E* 190)

This seldom-used process is exemplified in Ch. VI, Sect. 3.C.

C. Aminolysis of Alkoxyprymidines (*H* 255, *E* 190)

This very useful process is illustrated in the conversion of 2-ethoxy- (148, $R = OEt$) into 2-amino-1,4-dihydro-1-methyl-4-oxopyrimidine (148, $R = NH_2$) (ethanolic ammonia sealed at 100° , 54%);⁶¹³⁰ of 4-ethoxy- into 4-amino-1,2-dihydro-1,5-dimethyl-2-oxopyrimidine (ethanolic ammonia sealed at 125° , 65%);⁵⁸¹¹ of 4-ethoxy-5-fluoro-1,2-dihydro-1-methyl-2-oxo- into 5-fluoro-1,2-dihydro-1-methyl-4-methyl-amino-2-oxopyrimidine (methanolic methylamine at 115° , >90%);⁶⁰²⁶ of 5-bromo-4,6-dimethoxy- into 4-amino-5-bromo-6-methoxypyrimidine (potassium amide in liquid ammonia; by a complicated mechanism);⁴⁶⁹⁶ of 4-ethoxy-5-ethyl- into 5-ethyl-4-ethylamino-1,2-dihydro-1-methyl-2-oxopyrimidine (methanolic ethylamine at 120° , 72%);⁵⁷⁹⁷ of 4-ethoxy- into 4-dimethylamino-2-hydroxypyrimidine (methanolic dimethylamine at 100° , 72%);⁵⁶¹² of 4-ethoxy- into 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (methanolic ammonia at 100° , 84%);⁵⁶¹³ of 2-amino-4-methoxy- into 2-amino-4-anilino-6-methylpyrimidine [aniline at 180° ; plus a separable byproduct, *N,N*-bis-(2-amino-6-methylpyrimidin-4-yl)aniline];⁵⁰⁵⁰ of 4-ethoxy-2-hydroxy- into 2-hydroxy-4-semicarbazidopyrimidine (149) (aqueous semicarbazide at pH 4, 82%);⁴⁷³⁵ of 1,2-dihydro-4-methoxy- into 1,2-dihydro-4-methoxyamino-1-methyl-2-oxopyrimidine (150, $R = OMe$) (ethanolic methoxyamine under reflux, *c.* 65%);⁵³¹³ of the same substrate into 4-hydrazino-1,2-dihydro-1-methyl-2-oxopyrimidine (150,



R = NH₂) (ethanolic hydrazine hydrate under reflux; "low yield");⁵³¹³ of 2,4-dimethoxy- into 4-hydrazino-2-methoxy-5-nitropyrimidine (ethanolic hydrazine hydrate under reflux, >80%);⁵⁶⁶⁰ of 4,6-dimethoxy- into 4-hydrazino-6-methoxy-2-methyl-5-nitropyrimidine (ethanolic hydrazine at <0°, 85%);⁵⁶³⁴ 5-nitro-2,4-dipropoxy- into 4-hydrazino-5-nitro-2-propoxypyrimidine (ethanolic hydrazine at 25°, c. 80%);⁵⁶⁷⁴ of 4-ethoxy-1-ethylpyrimidinium tetrafluoroborate into 1-ethyl-1,4-dihydro-4-iminopyrimidine (151) (dissolution in liquid ammonia, 68%; several analogues were made similarly);⁴⁶⁹⁷ and of 4-methoxy- into 4-hydrazino-6-methyl-2-methylthiopyrimidine and a little 2,4-dihydrazino-6-methylpyrimidine as byproduct (ethanolic hydrazine hydrate under reflux).⁵³⁵⁵ Unlike the normal reactions above, 4,6-dimethoxy- (152, R = H) and 4,6-diethoxy-5-nitropyrimidine both reacted with methylhydrazine in pyridine to give 4-hydrazino-6-hydroxypyrimidine (153, R = H) as the only product; 4,6-dimethoxy-2-methyl-5-nitropyrimidine (152, R = Me) or its 2-phenyl analogue (152, R = Ph) likewise gave 4-hydrazino-6-hydroxy-2-methyl(or phenyl)-pyrimidine (153, R = Me or Ph), respectively.⁵⁴⁹¹ The proposed complex mechanism has some experimental support but requires confirmation.⁵⁴⁹¹

D. Rearrangement of Alkoxy-pyrimidines (*H* 256, *E* 192)

Such $O \rightarrow N$, $O \rightarrow S$, or $O \rightarrow C$ rearrangements are all discussed in Ch. X, Sect. 1.A(4) for convenience.

E. Other Reactions of Alkoxy-pyrimidines (*New*)

Activated alkoxy-pyrimidines and related systems undergo *trans-alkoxylation*.⁵⁶⁸⁶ Thus, 2-methoxy-5-nitro- (154, R = Me) gave 5-nitro-2-propoxypyrimidine (154, R = Pr) in c. 60% yield by refluxing in propanol containing silver oxide;⁵⁶⁶⁰ 5-nitro-4-propoxy- and 5-nitro-2,4-dipropoxypyrimidine were made similarly, but analogous treatment of 2,4-dimethoxy-6-methyl-5-nitropyrimidine gave only 4-methoxy-6-methyl-5-nitro-2-propoxypyrimidine (81%).⁵⁶⁶⁰ Unactivated alkoxy-pyrimidines, such as 2-methoxy-, 2,4-dimethoxy-6-methyl-, or 4-methoxy-2,6-dimethyl-5-nitropyrimidine, withstood transalkoxylation under the above conditions.⁵⁶⁶⁰ 2-Methoxy- has been converted into 2-ethoxypyrimidine by heating under reflux in ethanol containing triethylamine.⁶¹²³

The activated diaryloxypyrimidine, 1-methyl-2,4-diphenoxypyrimidinium iodide, reacted with methanolic sodium hydrogen sulfide at 25° to give 1-methyl-2,4-dithiouracil (85%).⁵⁰⁶¹

When ammonolysis of 2-methoxy-5-phenylpyrimidine was attempted at 200°, the expected 2-amino-5-phenylpyrimidine was obtained in lower yield than a separable byproduct, 3,5-diphenylpyridine (155). Several analogues such as 3,5-bis(*p*-dimethylamino-phenyl)- and 3,5-di-*p*-tolylpyridine were made similarly, but the mechanism remains obscure.⁵⁶⁵⁸

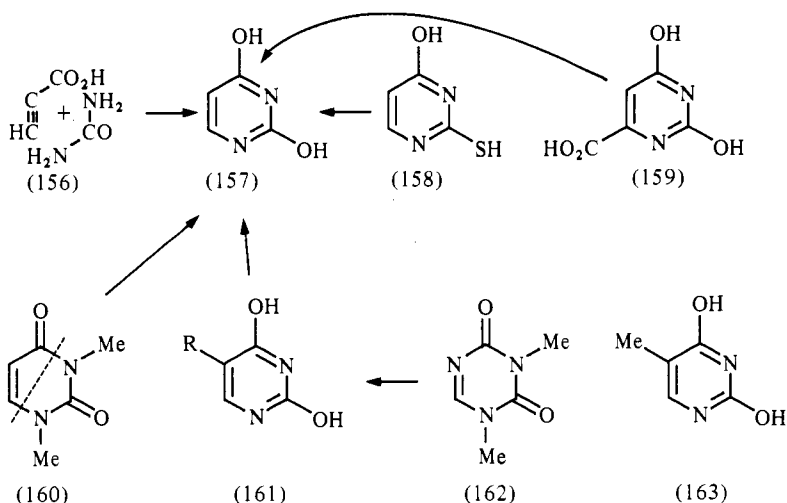
4,6-Dimethoxy-5-nitropyrimidine reacted with acetone or acetophenone in the presence of potassium hydroxide to give Meisenheimer complexes, which underwent oxidation by ferric chloride to give 2-acetonyl-4,6-dimethoxy-5-nitro- and 4,6-dimethoxy-5-nitro-2-phenacylpyrimidine, respectively, in good yield.⁴⁸⁰⁹

8. Some Naturally Occurring Hydroxypyrimidines (*H* 256, 258; *E* 193)

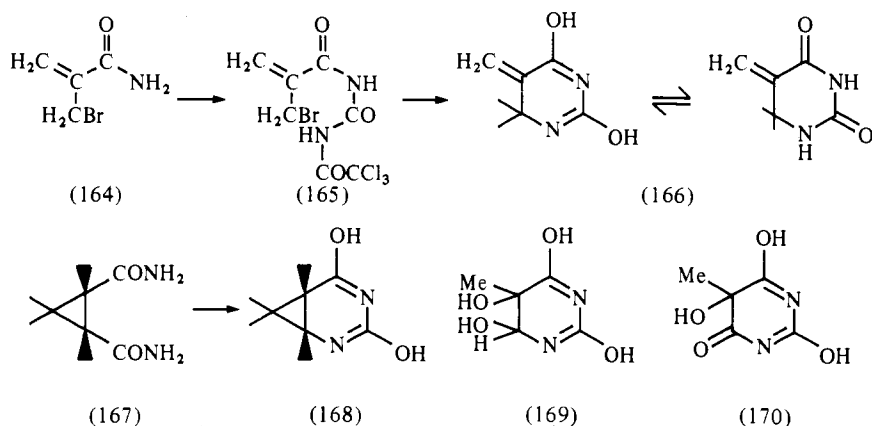
For pragmatic reasons, cytosine and related compounds are discussed in Ch. IX and orotic acid in Ch. XI.

A and B. Uracil and Thymine (*H* 256, *E* 193)

The classical primary synthetic route to uracil (157) from malic acid and urea in sulfuric acid (*H* 257) is probably still superior to synthesis from propiolic acid (156) and urea in benzene containing a little sulfuric acid,⁵⁵¹³ or from maleic acid and urea in polyphosphoric acid.⁵⁰³⁰ Moreover, the old metathetical route to uracil from 2-thiouracil (158) by boiling with aqueous chloroacetic acid (*H* 257) remains marginally superior to the same conversion using an oxidative route with dimethyl sulfoxide in strong sulfuric acid.⁴⁷¹⁸ Uracil (157) has also been made in poor yield by an Fe³⁺- or Cu²⁺-catalyzed photochemical decarboxylation of its 6-carboxy derivative (orotic acid; 159), a reaction of some significance in "chemical evolution";⁵⁵²⁰ also by treatment of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (160) with urea in ethanolic sodium ethoxide under reflux (yield 64%),^{5416, 5417} or by the similar treatment of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-1,3,5-triazine (162) with malondiamide or cyanoacetamide to give 5-carbamoyl- (161, R = CONH₂) or 5-cyano-2,4-dihydroxypyrimidine (161, R = CN), respectively, followed by hydrolysis and decarboxylation.⁵⁴²¹ A new synthesis *via* 5,6-dihydrouracil will prove very useful.⁶⁵⁹⁰



The best primary synthesis of thymine (163) remains that from 3-methylmalic acid and urea in sulfuric acid (*H* 258), although a more direct version, giving a 50% yield from ethyl α -formylpropionate and urea in oleum, has been reported.⁴⁸⁵⁶ Two stable structural isomers (tautomers?) of thymine have been made. Thus, α -(bromomethyl)-acrylamide (164) reacted with trichloroacetyl isocyanate to give *N*- α -(bromomethyl)acryloyl-*N'*-trichloroacetylurea (165), which underwent deacylation and loss of hydrogen bromide in warm sodium hydrogen carbonate solution to afford 4,5-dihydro-2,6-dihydroxy-5-methylene-pyrimidine (166); on melting (*c.* 215°), this partly rearranged into thymine (163).⁴³³⁸ The second isomer, "cyclothymine" (168), was made by treatment of *cis*-cyclopropane-1,2-dicarboxamide (167) with sodium hypochlorite.⁴³³⁸

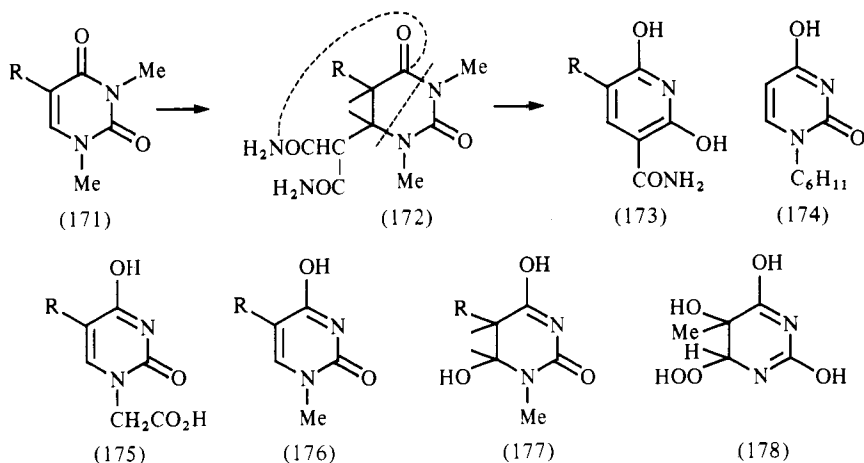


Few novel reactions of uracil or thymine have been reported recently. It has long been known that permanganate oxidation of thymine under uncontrolled conditions gives a variety of degradation fragments. However, treatment of thymine in pH 7 phosphate buffer at 15° with permanganate for 2 min gave only two products, *cis*-“thymine glycol” (4,5-dihydro-2,4,5,6-tetrahydroxypyrimidine, 169) and 5-hydroxy-5-methylbarbituric acid (4,5-dihydro-2,4,5-trihydroxy-5-methyl-4-oxopyrimidine, 170), but the former proved not to be an intermediate in the formation of the latter.^{5896, 6576} The epimerization of *cis*-thymine glycol in warm aqueous solution was studied subsequently because of its likely role in mutagenesis.⁴⁴⁰⁷ Although the parents, uracil and thymine, did not so react, treatment of 1,2,3,4-tetrahydro-1,3-dimethyl- (171, R = H) and 1,2,3,4-tetrahydro-1,3,5-trimethyl-2,4-dioxypyrimidine (171, R = Me) with malondiamide in ethanolic sodium ethoxide gave 2,6-dihydroxy- (173, R = H) and 2,6-dihydroxy-5-methylnicotinamide (173, R = Me), respectively, by way of the adduct (172) as shown.⁵⁴²⁰ The kinetics for association/dissociation of the hydrogen-bond stabilized dimer of 1-cyclohexyluracil (174) have been followed by ultrasonic attenuation measurements in chloroform.⁵⁴⁵⁵ The pattern of OH radical additions to uracils has been studied in detail.⁶⁵⁷⁷

In contrast to the recent paucity of data on the regular chemistry of uracils and thymines, the flow of results on the photochemistry and photobiology of those and related pyrimidines has continued unabated. Fortunately, much such work was expertly and systematically reviewed* in 1976,⁵²²⁸ so that what follows is simply meant to flag some interesting chemical, rather than biochemical, aspects. Standard abbreviations for pyrimidine photoproducts have been suggested⁵²⁰⁸ by three leading workers in this area, although they are not used below.

Photohydration and photodecarboxylation both occurred when 1-carboxymethyluracil (175, R = H) underwent irradiation in aqueous solution to give a mixture of 1-methyluracil (176, R = H) and its hydrate, 5,6-dihydro-6-hydroxy-1-methyluracil (177, R = H), which varied in proportion according to conditions.^{5200, 5204} In contrast, 1-carboxymethyl-5-methyluracil (175, R = Me) gave only 1,5-dimethyluracil (176, R = Me) with no indication of any hydrate (177, R = Me), 1- β -carboxyethyluracil gave only a hydrate with no decarboxylation,

*The editor, Professor Shih Yi (Sydney) Wang, was born in mainland China but lived for many years in the United States. His contributions to research in this area were legion, and his death in 1983 was a sad loss to bio-organic chemistry, to his dear wife Julie and their family, and to his friends and colleagues throughout the world, among whom the present author was proud to include himself.

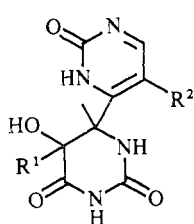


1- β -carboxyethyl-5-methyluracil proved stable to irradiation, 1-carbamoylmethyluracil gave its hydrate, and 1-ethoxycarbonylmethyluracil gave its hydrate.⁵²⁰⁴ Although 5-ethyl-2,4-dihydroxypyrimidine proved stable, irradiation of 5-ethyl-1-methyluracil (176, R = Et) led to loss of the ethyl group by initial addition of water to give the hydrate (177, R = Et) followed by loss of ethanol to give 1-methyluracil (176, R = H) and its hydrate (177, R = H).⁴⁷³³ The photohydration and other reactions of deoxyuridine have been examined in some detail,⁵²²⁶ and the quite complicated mechanism(s) for photohydration of simple uracils and thymine have been discussed in depth.^{5201, 5213}

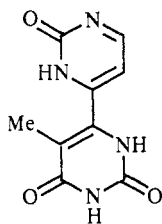
The *photoperoxidation* of thymine by γ -irradiation in aerated aqueous solution is now known to give mainly 4,5-dihydro-4-hydroperoxy-2,5,6-trihydroxy-5-methylpyrimidine (178), instead of its 5-hydroperoxy-2,4,6-trihydroxy isomer, as believed for many years.^{4429, 5209} The same hydroperoxide (178) was made in good yield from either geometric isomer of thymineglycol (169) by treatment with peroxide.⁵²⁰⁹ This substance (178) has been shown to be highly mutagenic in a bacterial system.^{5212, 5224} The initial step in the dye-sensitized oxidation of thymine to thymineglycol (169) and other products might well be thymine-5,6-epoxide, which would account satisfactorily for such products.⁵²¹⁷

In addition to the well-known cyclobutane-dimers, (see below), irradiation of thymine in frozen aqueous solution gave a second type of dimer in which the two thymine residues were joined by a single bond on spectral evidence.⁵¹⁹⁷ Such a "nose-to-tail dimer" was considered to be of more biological importance than the cyclobutane type,⁵¹⁹⁹ and subsequently it was shown by an X-ray diffraction analysis

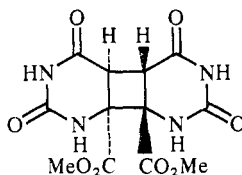
to be 1,2,2',3,3',4,5,6-octahydro-5-hydroxy-5,5'-dimethyl-2,2',6-trioxo-4,4'-bipyrimidine (179, $R^1 = R^2 = \text{Me}$).⁵¹⁹⁰ Uracil formed an exactly similar product (179, $R^1 = R^2 = \text{H}$),⁵¹⁹⁸ and a mixture of uracil and thymine gave mainly the monomethyl analogue (179, $R^1 = \text{Me}$, $R^2 = \text{H}$) which underwent facile dehydration to 1,2,2',3,3',6-hexahydro-5-methyl-2,2',6-trioxo-4,4'-bipyrimidine (180), identical with a product isolated from acid-hydrolyzates of ultraviolet-irradiated DNA.⁵¹⁹⁴ Further irradiation of the last-mentioned "mixed dimer" (180) gave a "cyclic tetramer" consisting of 4 pyrimidine and 2 methyl residues which have formed themselves into a 12-membered ring with an excruciating systematic name.⁵¹⁹² A mixture of cytosine and thymine behaved similarly on irradiation to afford an analogous dimer⁵¹⁹⁶ and cyclic tetramer.⁵¹⁹³ 5-Bromouridine and related compounds also form such dimers, but they are 5,5'-bipyrimidine derivatives.⁵²¹⁴



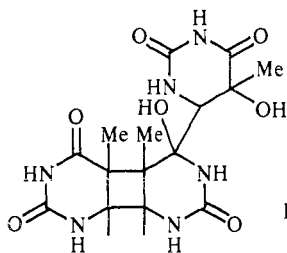
(179)



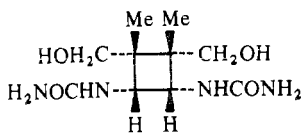
(180)



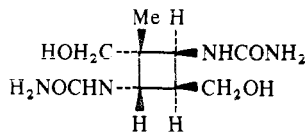
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(182)



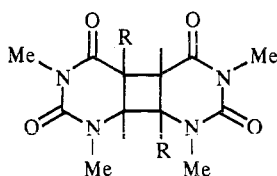
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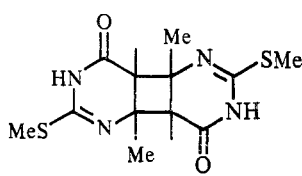
(184)

The *cyclobutane dimers* of uracil derivatives are still being investigated, but the center of chemical interest has shifted quite naturally to related areas. Thus, crystal structures have been reported for the *cis-syn* photodimer of 2,4-dihydroxy-6-methylpyrimidine,⁵²⁰³ the *cis-anti* hydrated photodimer of uracil,⁵²⁰³ the *trans-syn* photodimer (181) of 2,4-dihydroxy-6-methoxycarbonylpyrimidine (methyl orotate),⁵³¹⁹ one *dl* photodimer of 1,2,3,4-tetrahydro-1,3,5-trimethyl-2,4-dioxypyrimidine,⁵³¹⁸ and a thymine phototrimer (182) which is a mixed cyclobutane and nose-to-tail type.^{5202, 5205} The *cis-syn*- and *trans-anti*-photodimer

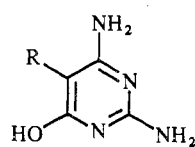
of thymine behave rather differently on reduction in aqueous solution with an excess of sodium borohydride; the former gave three products, of which a single stereoisomer of 1,2-bishydroxymethyl-1,2-dimethyl-3,4-diureidocyclobutane (183) predominated; the second photodimer gave only one product, 1,3-bishydroxymethyl-1,3-dimethyl-2,4-diureidocyclobutane in the configuration shown (184).⁶¹²⁰ When photodimers of uracil were treated with methyl iodide in dimethylformamide or dimethyl sulfoxide containing silver oxide at 25°, complete *N*-methylation occurred to give the corresponding dimer (185, R = H) of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine.^{4584, 6392} It was later found that remethylation under similar conditions slowly gave the corresponding *C,C*-dimethyl derivatives without loss of configuration; the *trans-anti* isomer of (185, R = Me) formed least slowly and in excellent yield.⁵²¹⁵ Field ionization mass spectral measurements have been found to be very useful in structural elucidation of photopolymers of thymine.⁵²⁰⁷ When water was replaced by deuterium oxide as solvent during irradiation of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine at 10 mM concentration, the ratio of hydrate:dimer was altered dramatically from 65:35 in water to 25:75 in deuterium oxide.⁵¹⁹¹ The photodimer (186) from 4-hydroxy-6-methyl-2-methylthiopyrimidine has been shown to have an *anti*-configuration by hydrolysis to a known dimer from 6-methyluracil.⁴⁹¹³ Dimers of both nose-to-tail and cycloalkane types have been described from the photolysis of 2-hydroxy-4,6-dimethylpyrimidine.^{4738, 6393} In addition, there are many cases of photocycloaddition to uracil and related pyrimidines that afford products akin to the cyclobutane dimers or polymers.^{4454, 5457, 5748, 5801, 6121}



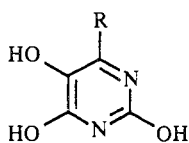
(185)



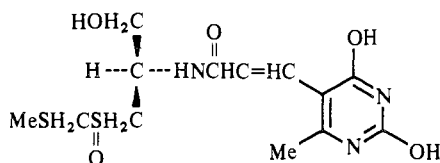
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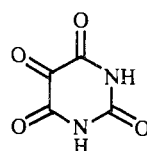
(187)



(188)



(189)



(190)

C. Divicine: 2,4-Diamino-5,6-dihydroxypyrimidine (*H* 259, *E* 198)

An excellent synthesis of divicine (187, $R = OH$) by an Elbs persulfate oxidation of the commercially available 2,4-diamino-6-hydroxypyrimidine (187, $R = H$) has been reported.⁵⁸⁶⁰ Divicine and some related compounds have shown marked antimalarial activity against *Plasmodium vinckei* in mice.⁶³⁹⁴

E. Isouramil: 4-Amino-2,5,6-trihydroxypyrimidine (*H* 260)

The aglycone, isouramil (188, $R = NH_2$), from the glycoside, convicine, has now been shown by direct comparison to be identical with synthetic 4-amino-2,5,6-trihydroxypyrimidine, prepared by reduction of 2,4,5-trihydroxy-6-nitrosopyrimidine (188, $R = NO$); convicine was shown to be its 5- β -D-glucopyranoside.⁵⁷⁰⁸ The aglycone (188, $R = NH_2$) is one of the substances which induce an acute haemolytic crisis (called favism) in certain individuals who eat fava beans.

F. Sparsomycin (*New*)

The antibiotic, sparsomycin, was isolated from the fermentation liquors of *Streptomyces sparsogenes* in 1962.⁶³⁹⁶ It proved to have antibacterial, antifungal, and antineoplastic activity, although this potential was never realized because of toxicity *in vivo*.⁶³⁹⁷ The structure (189) was eventually elucidated^{4687, 5643, 6084} and subsequent work has been devoted to preparing potential antitumor analogues, without conspicuous success.^{5471, 5644, 6601}

9. The Alloxan Group of Pyrimidines (*H* 260, *E* 199)

There has been little recent chemical work on alloxan (190). However, a rapid synthesis by oxidation of uracil at pH 3.5 with permanganate has been described.⁴⁴²⁹ In addition, extensive work on the electrochemical oxidation and reduction of uracil, thymine, barbituric acid, alloxan, and related hydroxypyrimidines has appeared from Oklahoma.⁵⁵⁵⁷⁻⁵⁵⁶⁴ A dramatic reduction in parasitemia by damage to intraerythrocytic malarial parasites in mice infected with *Plasmodium vinckei* has been observed after a single injection of alloxan; the mechanism appears to involve a reactive oxygen species, possibly hydroxy radicals, produced *in situ* within the red cells.⁶³⁹⁵

CHAPTER VIII

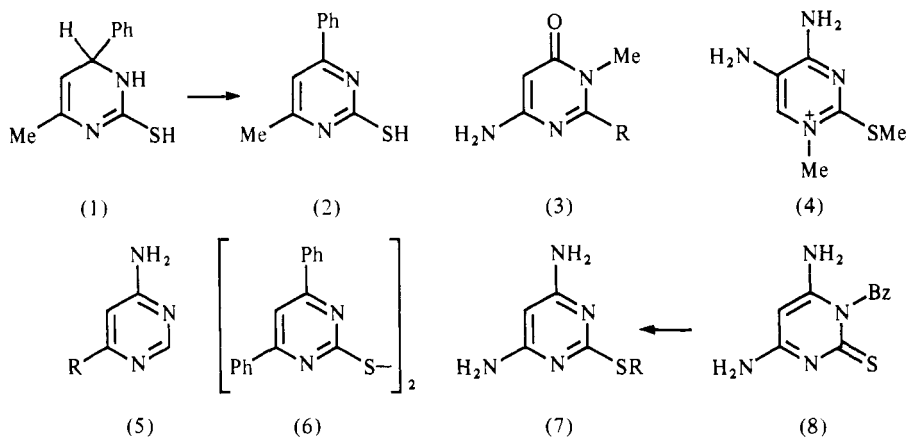
Sulfur-Containing Pyrimidines (*H* 272, *E* 202)

1. The Mercaptopyrimidines (*H* 272, *E* 202)

A. Preparation of 2- and 4/6-Mercaptopyrimidines (*H* 272, *E* 202)

The primary synthesis of such mercaptopyrimidines is covered in Ch. II and III. The main indirect routes from halogenopyrimidines (Ch. VI, Sect. 5.G) and from hydroxypyrimidines (Ch. VII, Sect. 6.B) have also been discussed in detail.

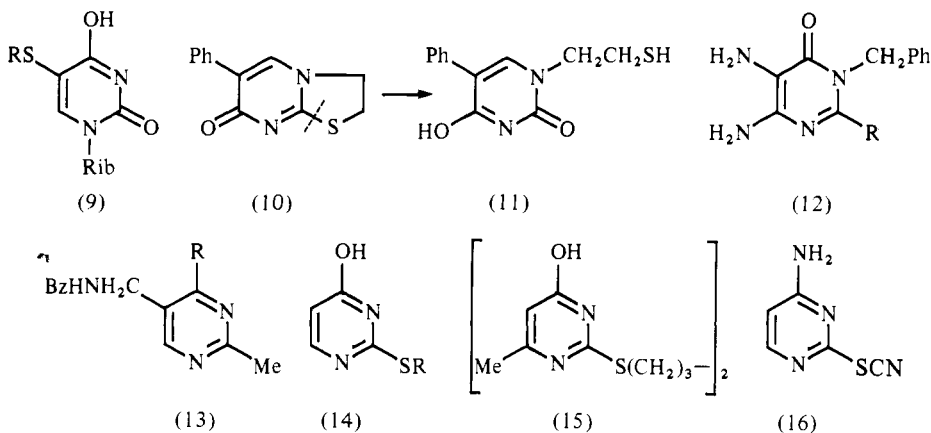
In addition, mercaptopyrimidines may be derived from the corresponding dihydropyrimidines, alkylthiopyrimidines, acylthiopyrimidines, sulfonyloxypyrimidines, or disulfides. Thus, 1,6-dihydro-2-mercapto- (1) was boiled with sulfur in xylene to give 2-mercapto-4-methyl-6-phenylpyrimidine (2) in 75% yield without oxidation of the mercapto group.⁶²¹² Treatment of 4-amino-1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine (3, R = SMe) with aqueous sodium hydrogen sulfide at 110–115° gave 6-amino-3-methyl-2-thiouracil (3, R = SH) in 83% yield;⁴⁶⁵⁸ similarly, 4-amino- or 4,5-diamino-1-methyl-2-methylthiopyrimidinium iodide (4) and ethanolic sodium hydrogen sulfide gave 4-amino-⁴⁴⁹⁰ or 4,5-diamino-1,2-dihydro-1-methyl-2-thiopyrimidine,⁵³⁴⁴ respectively, while 4-amino-6-methoxy-2-methylsulfonylpyrimidine and sodium hydrogen sulfide gave 4-amino-2-mercapto-6-methoxypyrimidine (by displacement) accompanied by some of its 2-methylthio analogue (by reduction of the sulfone).⁴⁶⁵⁶ In contrast to the above displacements, 4-amino-6-chloro-2-methylthiopyrimidine underwent reductive splitting of its thioether group (and concomitant removal of the chloro substituent) in sodium/liquid ammonia to afford 4-amino-2-mercapto-6-methoxypyrimidine (66%),⁴³⁵⁶



and under similar conditions 4-amino-6-methylthio- (5, R = SMe) gave 4-amino-6-mercaptopyrimidine (5, R = SH) in 70% yield.⁴³⁵⁶ The reduction of disulfides to mercaptopurines has been illustrated by the treatment of bis-4,6-diphenylpyrimidin-2-yl disulfide (6) in hot concentrated hydrochloric acid with tin to give 2-mercapto-4,6-diphenylpyrimidine (70%),⁶²¹⁰ and of bis(2-methyl-6-methylthio-pyrimidin-4-yl) disulfide with ethanolic mercaptoethanol to give 4-mercapto-2-methyl-6-methylthiopyrimidine (90%).⁶³⁷⁴ The use of deacylation reactions to make mercaptopurines is seen in the formation (>95%) of 4,6-diamino-2-mercaptopyrimidine (7, R = H) from 4,6-diamino-2-benzoylthiopyrimidine (7, R = Bz) by boiling in water or from 4,6-diamino-1-benzoyl-1,2-dihydro-2-thiopyrimidine (8) by boiling in methanol;⁶¹²⁶ also in the formation of 2-mercapto-4,6-dimethylpyrimidine (97%) by treatment of 2-benzoylthio-4,6-dimethylpyrimidine with diethylamine in benzene at 25°. ⁶¹²⁶ The conversion of 2,4-dimethyl-6-*p*-toluenesulfonyloxypyrimidine into 4-mercapto-2,6-dimethylpyrimidine (68%) by stirring with ethanolic thiourea is a procedure with significant potential.⁵²⁶⁷ The replacement of the whole N-C-N portion of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine by thiourea to give 4-hydroxy-2-mercaptopyrimidine (91%) is also a reaction with potential.^{5416, 5417}

B and C. Preparation of 5- or Extranuclear-Mercaptopurines (*H* 276, *E* 202)

Routes to such mercaptopurines are still very poorly represented. Treatment of uridine with thiocyanogen chloride gave its 5-thiocyanato derivative (9, R = CN) (48%), which underwent reduction



by dithionite/mercaptoethanol to afford 5-mercaptouridine (9, R = H).⁵⁵⁴³ Ring fission of 2,3-dihydro-7-oxo-6-phenyl-7H-thiazolo[3,2-a]pyrimidine (10) by hot aqueous alkali gave 1-β-mercaptoethyl-5-phenyluracil (11) in greater than 95% yield;⁶²⁴¹ analogues were made similarly.⁶²⁴¹

D. Reactions of 2- and 4/6-Mercaptopyrimidines (H 277, E 203)

(1) Removal of Mercapto Groups (H 277, E 203)

The reductive removal of 2- or 4/6-mercapto groups, by treatment in aqueous or alcoholic solution (often containing ammonia to improve solubility) with Raney nickel catalyst in quantity, has been used extensively. In this way have been made 4,5-diamino-6-trifluoromethylpyrimidine (c. 60%),⁵⁴⁴⁰ 4-benzylamino-6-methylpyrimidine,⁴⁸⁴⁹ 4-hydroxy-2-methylpyrimidine (93%),⁵⁶⁶⁷ 4-cyclopropyl-6-hydroxy-5-methylpyrimidine,⁵⁹⁹⁹ 4-cyclopropyl-6-hydroxypyrimidine,⁵⁸¹² 4,5-diamino-2-phenylpyrimidine (c. 65%),^{5439, 5792} 4-amino-6-hydroxypyrimidine,⁵⁸⁵³ 2-hydroxy-5-methylpyrimidine (66%),⁵⁶⁹¹ 4-amino-5-3',4',5'-trimethoxybenzylpyrimidine (from its 2-mercapto derivative, 40%),⁶¹¹³ 4,5-diamino-2-butyl(or propyl)pyrimidine (>85%),⁴⁵⁷⁰ 4,5-diamino-6-phenylpyrimidine (c. 80%),⁵⁴⁴¹ 1,6-dihydro-4-methyl-6-oxo-1-phenylpyrimidine (79%),⁴⁹³⁰ 4-cyclopropyl-6-hydroxy-5-methoxypyrimidine,⁶⁰⁵³ 4-isopropyl-5-methylpyrimidine (from its 2-mercapto derivative, 64%),⁶³¹⁹ 4,5-diamino-3-benzyl-3,6-dihydro-6-oxopyrimidine (12, R = SH) [from 5,6-diamino-3-benzyl-2-thiouracil (12, R = SH)],⁴⁵⁷⁵ 4-hydroxy-5-methoxy-6-methoxymethylpyrimidine (c.

55%),⁴³⁹⁷ 1,4-dihydro-4-imino-1-methylpyrimidine (hydrochloride) (from 4-amino-1,2-dihydro-1-methyl-2-thiopyrimidine; 30%),⁵⁶⁶⁵ 4-hydroxy-5,6-dimethylpyrimidine (>90%),⁴³⁸⁷ and others.^{5156, 5414, 6069} In addition, 5-benzamidomethyl-4-mercapto-2-methylpyrimidine (13, R = SH) was desulfurized to 5-benzamidomethyl-2-methylpyrimidine (13, R = H) by Raney nickel (82%) for comparison with dechlorination of 5-benzamidomethyl-4-chloro-2-methylpyrimidine (13, R = Cl) by hydrogenation (palladium/magnesium oxide) which gave the same product (13, R = H) in 78% yield.⁵⁷⁹³ Oxidative removal of mercapto groups seems to have been neglected recently.

(2) *S*-Alkylation of Mercaptopyrimidines (*H* 282, *E* 206)

The 2- and 4/6-mercaptopyrimidines are usually *S*-alkylated by treatment of a solution of their anionic species in aqueous or alcoholic alkali with an alkyl halide at room temperature. Sometimes other solvents, such as acetone or dimethylformamide, may be used; dimethyl or diethyl sulfate may replace the halide; warming may be required; and alkali may be deleted altogether or replaced by potassium carbonate (in nonaqueous solvents) or by aqueous sodium hydrogen carbonate. Typical examples of the use of such mundane procedures are given in Table XIIIa and elsewhere.^{4656, 5774} The *S*-alkylation of 4-hydroxy-2-mercaptopyrimidine and its simple *C*-alkyl derivatives has long been possible only with poor yield. However, by stirring the parent 2-thiouracil (14, R = H) at 25° in anhydrous dimethylformamide containing methyl iodide in the dark, 4-hydroxy-2-methylthiopyrimidine (14, R = Me) was obtained in 82% yield and even 2-*t*-butylthio-4-hydroxypyrimidine (14, R = Bu^t) was obtained in 32% yield.⁵⁴¹⁸ The use of phase transfer catalysis principles has also led to reasonable yields in this reaction.⁶³⁸⁵ Other noteworthy examples are the conversion of 4-hydroxy-2-mercapto-6-methylpyrimidine (as sodium salt) into 1,6-bis(4'-hydroxy-6'-methylpyrimidin-2'-ylthio)hexane (15) by heating with 1,6-dibromohexane in dimethylformamide;⁴⁸⁸⁰ of the same substrate into 4-hydroxy-2-hydroxyboromethylthio-6-methylpyrimidine (87%) by treatment with dibutyl iodomethaneboronate in acetonitrile;⁵⁵²³ of 4-amino-2-mercaptopyrimidine into 6-amino-2-thiocyanatopyrimidine (16) by treatment with cyanogen bromide in aqueous alcoholic sodium hydroxide;⁴⁴⁹⁰ of 2-hydroxy-4-mercapto- into 2-hydroxy-4-thiocyanatopyrimidine by cyanogen bromide in pH 9 buffer;⁶²⁰⁶ of 1-methyl-4-thiouracil into 1,2-dihydro-1-methyl-2-oxo-4-thiocyanatopyrimidine (66%) similarly;⁵⁵⁰⁶ of 4-amino-1,2-

TABLE XIIIa. Examples of *S*-Alkylation of Mercaptopyrimidines (*E* 206)

Pyrimidine Produced	Reagents	Yield %	Reference
5-Acetamido-4-methyl-2,6-bismethylthio-	MeI/NaHCO ₃	79	5689
4-Acetylthio-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	AcCH ₂ Br/base(?)	93	5138
4-Adamant-1'-yl-6-hydroxy-2-methylthio-	MeI/NaOH	80	4389
4-Amino-3-benzyl-2,3-dihydro-4-methylthio-	MeI/NaOH	60	5036
5-Amino-4-benzylthio-6-hydrazino-	PhCH ₂ Cl/NaOH	78	5235
5-Amino-2-carbamoylmethylthio-4-methyl-6-methylthio-	H ₂ NOCCH ₂ Cl/NaHCO ₃	85	5687
2-Amino-5-cyano-4-methylthio-	MeI/NaOMe	73	6527
4-Amino-3,6-dihydro-3-methyl-2-methylthio-6-oxo-	MeI/K ₂ CO ₃ in Me ₂ CO	42	4616
	MeI/NaOH	88	4711
4-Amino-5-ethoxycarbonyl-2-methylthio-	Me ₂ SO ₄ /KOH	77	5624
4-Amino-5-ethoxycarbonylmethylthio-6-hydroxy- ^a	BrCH ₂ CO ₂ Et/NaOEt	>95	6252
4-Amino-6-ethoxycarbonyl-2-methylthio-5-nitro-	MeI/NaHCO ₃	60	5443
2-β-Aminoethylthio- ^a	H ₂ NCH ₂ CH ₂ Br/Pr ⁱ OH	40	6056
5-Amino-4-ethylthio-6-methylamino-	EtI/NaOH	>90	5678
4-Amino-6-hydroxy-2-methylthio-	MeI/NaOH	>90	5853
5-Amino-4-methoxy-6-methylthio- ^a	Me ₂ SO ₄ /K ₂ CO ₃ in Me ₂ CO	78	4816
5-Amino-4-methylamino-2-methylthio-	MeI/NaOH	—	5354
4-Amino-6-phenylacetamido-2-propylthio-	PrI/NaOEt in Me ₂ CO	56	6126
2-Benzylthio-1,4-dihydro-1,6-dimethyl-4-oxo-	PhCH ₂ Cl/NaOEt	67	4568
4,6-Bis- <i>p</i> -methoxyphenyl-2-thien-2'-ylthio- ^a	2-I-thiophene/NaH in DMF	43	6399
4,6-Bismethylthio-5-nitro-	MeI/NaOH	40	6374
5-Bromo-2,4-bismethylthio-	Me ₂ SO ₄ /NaOH	74	4707
5-Bromo-4-β-dimethylaminoethylthio-	Me ₂ NCH ₂ CH ₂ Cl/NaOH	53	6181
2- <i>p</i> -Bromophenacylthio-4,5-dichloro-6-hydroxy-	BrC ₆ H ₄ COCH ₂ Br/Me ₂ CO	60	4892

TABLE XIIIa (Continued)

Pyrimidine Produced	Reagents	Yield %	Reference
2-Butylthio-4-hydroxy-6-propyl- ^a	BuI/KOH in DMF	70	5121
4- α -Carbamoylthio- ^a	H ₂ NOCCHMeBr/ NaHCO ₃	80	5698
2-Carbamoylmethylthio- ^a	H ₂ NOCCH ₂ Cl/NaHCO ₃	60	5698
2-Carbamoylmethylthio-4-hydroxy-6-methyl- ^a	H ₂ NOCCH ₂ Cl/NaHCO ₃	20	5476
4-Carbamoylmethylthio-6-methyl-2-pyridin-2'-yl- ^a	H ₂ NOCCH ₂ Cl/NaOH	62	6087
2-Chloromethylthio-	ClCH ₂ Br/Na ⁺ in DMF	58	4873, 5519
5-Cyano-2,4-dimethyl-6-phenacylthio-	PhCOCH ₂ Br/Pr ⁱ OH	85	5364
4-Cyclopropyl-6-hydroxy-5-methoxy-2-methylthio-	MeI/NaOH	—	6000
2,5-Diamino-4,6-bisbenzylthio-	PhCH ₂ Cl/DMF	68	5234
4,5-Diamino-2-methylthio-6-trifluoromethyl-	MeI/NaOH	>90	5823
1,2-Dihydro-1-methyl-6-methylthio-2-oxo-	MeI/NaOH or MeI/MeOH	62, 89	5665, 6554
1,4-Dihydro-6-methyl-2-methylthio-4-oxo-1-phenyl- ^b	MeI/NaOH	—	4930
1,6-Dihydro-4-methyl-2-methylthio-6-oxo-1-phenyl-	MeI/NaOH	95	4930
1,6-Dihydro-1-methyl-2-methylthio-6-thio-	MeI/NaOH	93	5665
2,4-Dihydroxy-6-methylthio-	MeI/NaOH	74	5445
4,6-Dimethyl-2-methylthio-5-phenyl-	MeI/NaOH	93	5662
4,6-Dimethyl-2-5'-nitrothiazol-2'-ylthio- ^a	2-Cl-5-NO ₂ -thiazole/ NaOEt	82	4537
5-Ethoxycarbonyl-1,2-dihydro-1,6-dimethyl-4-methylthio-2-oxo-	MeI/NaOH	74	5601
5-Ethoxycarbonylmethyl-4-hydroxy-2-methylthio-	MeI/NaOH	90	5973
5-Ethoxy-4- β -hydroxyethylthio-2-methyl-	HOCH ₂ CH ₂ Cl/NaOH	50	5958
4-Ethylamino-6-methyl-2-methylthio-5-nitro- ^a	MeI/NaOH	63	5677
2-Ethylthio-4-hydroxy- ^a	Et ₂ SO ₄ /KOH in DMF	23	5121
2-Ethylthio-4-hydroxy-5-methoxy-	Me ₂ SO ₄ /NaOH	79	4395

TABLE XIIIa (Continued)

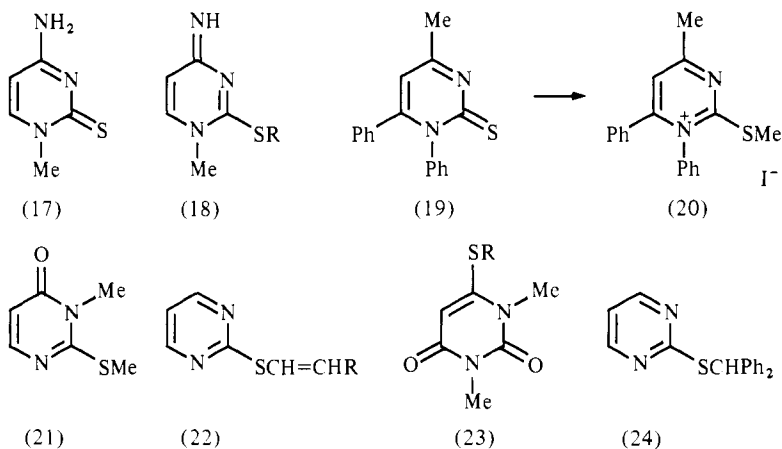
Pyrimidine Produced	Reagents	Yield %	Reference
4-Ethylthio-5-methoxy-2-methyl- ^a	EtI/KOH	80	6348
2-β-Fluoroethylthio-4,6-dimethyl- ^a	FCH ₂ CH ₂ Br/Na ⁺ in DMF	77	4873
5-Fluoro-2-hydroxy-4-methylthio- ^a	MeI/NaOMe	79	4385
5-Hexyl-4-hydroxy-6-methyl-2-methylthio- ^a	MeI/Pr ⁱ OH	—	5124
4-Hydrazino-6-methyl-2-methylthio-	MeI/NaOH	88	5697
4-Hydroxy-6-hydroxymethyl-2-methylthio- ^a	Me ₂ SO ₄ /NaOH	74	5175
2-Hydroxy-4-methyl-6-methylthio-	MeI/NaOH	71	6202
4-Mercapto-2-methyl-6-methylthio-	MeI (1 mol)/NaOH	46	6374
2-Methoxycarbonylmethylthio-4,6-dimethyl- ^a	MeO ₂ CCH ₂ Cl/NaOMe	75	4535
4-Methylamino-2-methylthio	MeI/NaOH	94	5665
2-Methyl-4,6-bismethylthio-	MeI/NaOH	80	6374
2-Methyl-4-methylthio- ^a	MeI/NaOH	95	4449
4-Methyl-6-methylthio-2-pyridin-2'-yl-	MeI/NaOH	67	6087
2-Methylthio-4,6-diphenyl-	Me ₂ SO ₄ /K ₂ CO ₃	75	6210
2-Methylthio-5-nitro-	MeI/NaOH	46	6372

^a And analogues.^b Plus 3,6-dimethyl-1-phenyl-2-thiouracil (9%).

dihydro-1-methyl-2-thiopyrimidine (17), presumably as its tautomer (18, R = H), into 2-ethylthio-1,4-dihydro-4-imino-1-methylpyrimidine (18, R = Et) by boiling with methanolic ethyl iodide and isolating the product as hydriodide (81%);⁴⁴⁹⁰ and of 1,2-dihydro-4-methyl-1,6-diphenyl-2-thiopyrimidine (19) into 4-methyl-2-methylthio-1,6-diphenylpyrimidinium iodide (20) by heating with methyl iodide in a sealed tube at 120°.⁶⁰⁸⁵

The process of *S*-methylation may be done in aprotic media by boiling with the dimethyl acetal of dimethylformamide, Me₂NCH(OMe)₂, in benzene or toluene; in this way, 2,4-dimercapto- gave 2,4-bismethylthiopyrimidine (73%);⁶¹⁷⁶ 5-dimethylaminomethyleneamino-2-mercapto- gave 5-dimethylaminomethyleneamino-2-methylthiopyrimidine (96%).⁴³⁸³ Note, however, that 4-hydroxy-2-mercapto-2-pyrimidine

underwent both *S*- and *N*-methylation to afford 1,6-dihydro-1-methyl-2-methylthio-6-oxypyrimidine (21).⁶¹⁷⁶ *S*-Alkenylation of mercaptopyrimidines can be done by their addition reaction to acetylene derivatives. Thus, 2-mercaptopyrimidine, in aqueous dioxane containing potassium hydroxide, reacted with acetylene under pressure to afford 2-vinylthiopyrimidine (22, R = H) in 80% yield;⁶³⁸³ likewise, phenylacetylene gave 2-styrylthiopyrimidine (22, R = Ph),⁶³⁸³ and 1,3-dimethyl-4-thiobarbituric acid (23, R = H) with methyl propiolate gave 1,2,3,4-tetrahydro-6- β -methoxycarbonylvinylthio-1,3-dimethyl-2,4-dioxypyrimidine (23, R = CH:CHCO₂Me) in 85% yield.⁵¹⁵⁰ 2-Mercaptopyrimidine also reacted with diphenylmethanol (cation) in glacial acetic acid to afford 2-diphenylmethylthiopyrimidine (24).⁵⁵⁰³

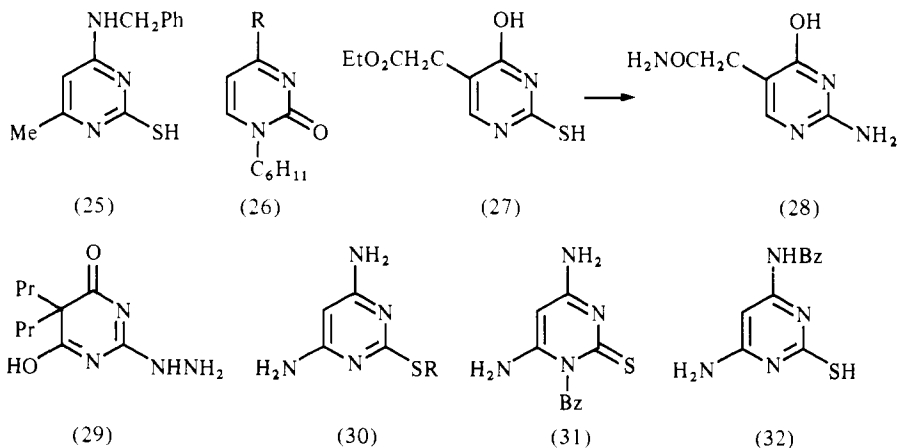


(3) *Mercapto- to Hydroxypyrimidines* (H 284, E 212)

This process is discussed in Ch. VII, Sect. 1.F.

(5) *Mercapto- to Aminopyrimidines* (H 284, E 212)

The preferential aminolysis of a 2,4-dimercaptopyrimidine at the 4-position continues to be used. Thus, further details of the conversion of 2,4-dimercapto- into 4-amino-2-mercaptopyrimidine (66%), by hot aqueous ammonia, have been reported.²⁹¹⁵ Rather similarly, 2,4-dimercapto- gave 4-benzylamino-2-mercapto-6-methylpyrimidine (25) by heating with neat benzylamine at 100°;⁴⁸⁴⁹ 4-adamant-1'-yl-2,6-dimercapto- gave 4-adamant-1'-yl-6-amino-2-mercaptopyrimidine (61%)



by heating in aqueous ammonia;⁴³⁸⁹ 2,4-dimercapto- gave 4-hydrazino-2-mercaptopyrimidine (94%) by boiling in hydrazine hydrate;⁴³⁶⁸ and 2,4-dimercapto- gave 4-hydrazino-2-mercapto-6-methylpyrimidine satisfactorily.⁵⁶⁹⁷

Other (nonpreferential) aminolyses of 4-mercaptopyrimidines are illustrated in the conversion of 1-cyclohexyl-4-thiouracil (26, R = SH) into 4-amino-1-cyclohexyl-1,2-dihydro-2-oxypyrimidine (26, R = NH₂) (ethanolic ammonia at 100°, 47%; or at 120°, 76%),^{4720, 6114} of 4-acetoxymethyl-6-mercapto-2-hydroxy- into 4-amino-2-hydroxy-6-hydroxymethylpyrimidine (methanolic ammonia at 100°, 53%; note incidental *O*-deacetylation),⁵³⁶⁶ and in other such reactions,⁴⁷¹⁹ also in the transformation of 2-hydroxy-4-mercapto- into 4-hydrazino-2-hydroxypyrimidine (ethanolic hydrazine under reflux, 67%),⁵⁷¹² 4-acetoxymethyl-2-hydroxy-6-mercapto- into 4-hydrazino-2-hydroxy-6-hydroxymethylpyrimidine (ethanolic hydrazine hydrate under reflux, 58%),⁵³⁶⁶ and other such reactions.⁶²⁷⁶

The aminolysis of a 2-mercaptopyrimidine was previously considered extremely rare and difficult. However, of late it has been used with some success in the conversion of 5-ethoxycarbonylmethyl-4-hydroxy-2-mercapto- (27) into 2-amino-5-carbamoylmethyl-4-hydroxypyrimidine (28) (ethanolic ammonia at 120°, 54%; note concomitant aminolysis of ester group),⁵⁹⁷³ of 4-hydroxy-2-mercapto- into 2-dimethylamino-4-hydroxy-6-methyl-5-phenylazopyrimidine (t-butoxy-bisdimethylaminomethane in dimethylformamide at 60°, 52%),⁵⁴¹⁹ and of 5,5-dipropyl-2-thiobarbituric acid into 2-hydrazino-4,5-dihydro-6-hydroxy-4-oxo-5,5-dipropylpyrimidine (29) (hydrazine in ethanolic acetic acid at 3°, 51%; also other 5,5-dialkyl analogues similarly).⁴³⁶⁵

However, the action of hydrazine on some 2-mercaptopyrimidines and 1-alkyl-1,2-dihydro-2-thiopyrimidines can be much more complicated (see Ch. X, Sect. 3).

(6) *S-Acylation of Mercaptopyrimidines (H 286)*

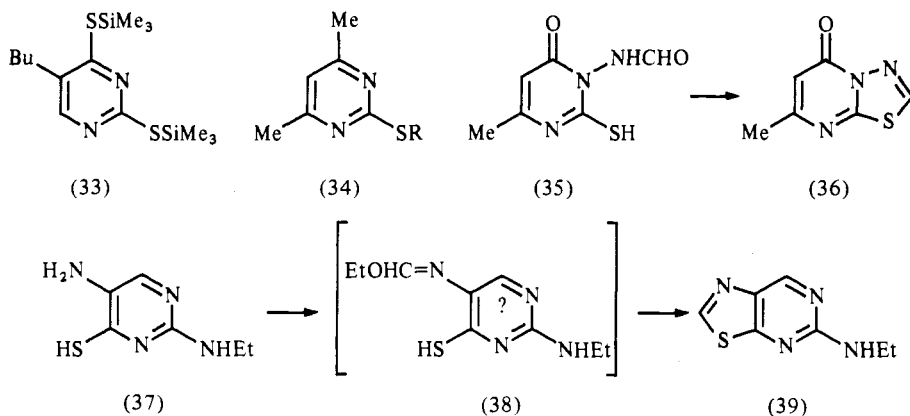
Acylation of mercaptopyrimidines can give either *S*-acyl or *N*-acyl derivatives according to conditions; it seems possible that the *N*-acyl may be formed by rearrangement of the *S*-acyl derivatives, which are formed more easily. For example, 4,6-diamino-2-mercaptopyrimidine (30, R = H) and benzoyl chloride in dimethylformamide or acetonitrile containing triethylamine at 20° gave 4,6-diamino-2-benzoylthiopyrimidine (30, R = Bz) in 80% yield and the nicotinoylthio or substituted-benzoylthio analogues were made similarly;⁶¹²⁵ the same reactions at 80°, however, gave 4,6-diamino-1-benzoyl-1,2-dihydro-2-thiopyrimidine (31) (93%) and its analogues, while at 120° 4-amino-6-benzamido-2-mercaptopyrimidine (32) was obtained in 61% yield.⁶¹²⁵ 2-Benzoylthio- was obtained likewise from acylation of 2-mercapto-4,6-dimethylpyrimidine under gentle conditions.⁶¹²⁵ 2-Mercapto-4-methyl- and 2-mercapto-4,6-dimethylpyrimidine have been converted into the corresponding pyrimidin-2-yl esters of several thioacids of arsenic and antimony.⁶²¹³

(7) *Oxidation of Mercaptopyrimidines (H 286, E 213)*

Such oxidations to disulfides or sulfonic acids are discussed below in Sects. 3 and 4.A, respectively.

(8) *Other Reactions of Mercaptopyrimidines (E 214)*

The conversion of mercapto- into thiocyanatopyrimidines by cyanogen bromide is covered in Sect. D(2) above. Trimethylsilylation of mercaptopyrimidines has been illustrated in the treatment of 5-butyl-2,4-dimercaptopyrimidine with hexamethyldisilazane to give 5-butyl-2,4-bistrimethylsilylthiopyrimidine (33) in 94% yield.⁵⁹⁶³ The formation of a sulfenamide from a mercaptopyrimidine has been done by allowing the latter to react with chloroamine. In this way, 2-mercapto- (34, R = H) gave the sulfenamide, 2-aminothio-4,6-dimethylpyrimidine (34, R = NH₂), albeit in only 11% yield because of concomitant oxidation of the substrate to bis(4,6-dimethylpyrimidin-2-yl) disulfide (59%).⁵⁶⁶⁹

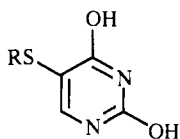


The complexes formed between 4-hydroxy-2-mercaptopyrimidine and the metal ions Cu^{2+} , Ni^{2+} , Co^{2+} , Fe^{3+} , Rh^{3+} , Pd^{2+} , Pd^{4+} , Pt^{2+} , and Pt^{4+} have been prepared, and their structures have been determined to a large extent.^{5370, 5383}

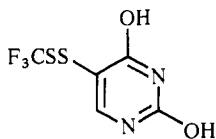
Mercapto groups can become involved in ring-formation. For example, 3-formamido-6-methyl-2-thiouracil (35) in refluxing phosphoryl chloride underwent dehydrative cyclization to 7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (36),⁵¹⁴⁰ and 5-amino-2-ethylamino-4-mercaptopyrimidine (37) reacted with triethyl orthoformate to afford 5-ethylaminothiazolo[5,4-*d*]pyrimidine (39), probably *via* the ethoxymethyleneamino intermediate (38).⁵⁷⁴²

E. Reactions of 5- and Extranuclear-Mercaptopyrimidines (*H* 286, *E* 215)

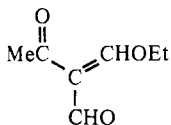
The oxidation of such mercaptopyrimidines is covered in Sects. 3 and 4.A below; few other reactions have been recorded recently. *S*-**Acylation** is seen in the conversion of 2,4-dihydroxy-5-mercapto- (40, $\text{R} = \text{H}$) into 5-acetylthio-2,4-dihydroxypyrimidine (40, $\text{R} = \text{Ac}$) (acetic anhydride in pyridine, 72%),⁵⁷²⁸ as well as in that of 4-amino-2,6-dihydroxy-5-mercapto- into 5-acetylthio-4-amino-2,6-dihydroxypyrimidine (boiling acetic anhydride, 20%).⁵²⁴⁴ *S*-**Alkylation** is illustrated by the transformation of the same substrate (40, $\text{R} = \text{H}$) into 2,4-dihydroxy-5-methylthiopyrimidine (40, $\text{R} = \text{Me}$) (methyl iodide/aqueous alkali, 69%),⁵⁷²⁸ into 5-butylthio-2,4-dihydroxypyrimidine (40, $\text{R} = \text{Bu}$) (butyl bromide/aqueous alcoholic alkali, 73%),⁵⁷²⁸ 5-allylthio-2,4-dihydroxypyrimidine (40, $\text{R} = \text{CH}_2\text{CH}=\text{CH}_2$) (allyl bromide/methanolic sodium methoxide, 81%),⁵⁸⁹³ and 5-carbamoylmethylthio-2,4-dihydroxypyrimidine (40, $\text{R} = \text{CH}_2\text{CONH}_2$) (2-iodoacetamide/



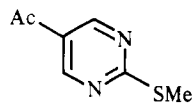
(40)



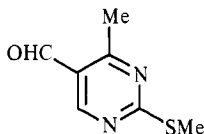
(41)



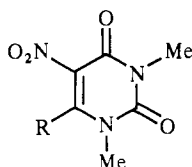
(42)



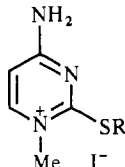
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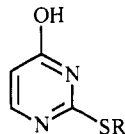
(44)



(45)



(46)



(47)

alkali under nitrogen, 89%);⁵⁸⁹³ a similar type of reaction is that of the same substrate (40, R = H) with trifluoromethanesulfonyl chloride (F_3CSSCl) in tetrahydrofuran to afford the disulfide, 2,4-dihydroxy-5-trifluoromethyldithiopyrimidine (41) in 54% yield.⁴⁴⁶⁹

2. The Thioethers: Alkyl- and Arylthiopyrimidines (*H* 286, *E* 217)

Although dipyrimidinyl sulfides fall into this class, they are treated with the disulfides in Sect. 3.

A. Preparation of 2- and 4/6-Alkylthiopyrimidines (*H* 286, *E* 217)

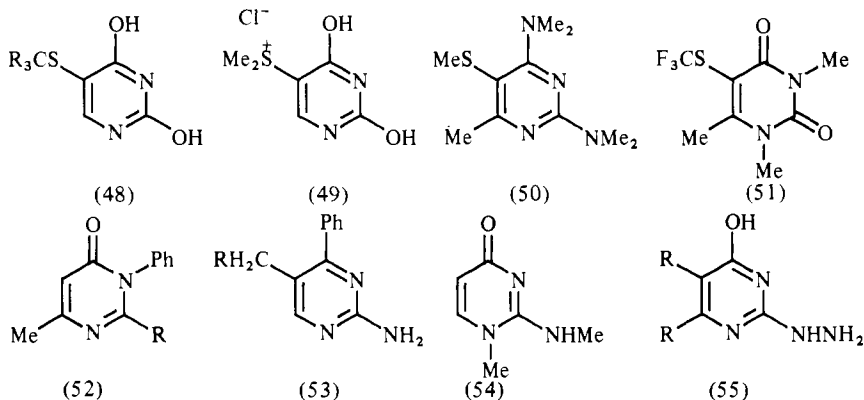
The three chief ways of making these alkylthiopyrimidines have been discussed: primary synthesis in Ch. II and III, the *S*-alkylation of mercaptopyrimidines in Sect. 1.D(2) above, and directly from halogenopyrimidines in Ch. VI, Sect. 5.F. For example, 4-ethoxy-3-formylbut-3-en-2-one (42) reacted with *S*-methylthiourea in dimethylformamide containing potassium *t*-butoxide to give a separable mixture of 5-acetyl-2-methylthio- (43) and 5-formyl-4-methyl-2-methylthiopyrimidine (44) in about equal amounts, because the substrate reacted in part as a dialdehyde and in part as an aldehydo ketone.⁶³⁹⁸ Another example is the conversion of 4-chloro- (45, R = Cl) into 4-ethoxycarbonylmethylthio-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxypyrimidine (45, R = $\text{SCH}_2\text{CO}_2\text{Et}$) by treatment with ethyl 2-mercaptoacetate in the presence of triethylamine.⁶²⁹⁷ The interchange of alkylthio groups is also a useful displacement reaction. Thus, 4-amino-1-methyl-2-methylthiopyrimidinium iodide (46, R = Me) gave 4-amino-2-ethylthio-1-

methylpyrimidinium iodide (46, R = Et) in 82% yield by simply stirring with an excess of neat ethanethiol;⁴⁴⁹⁰ 4-hydroxy-6-methyl-2-methylthiopyrimidine (as sodium salt) gave 4-acetonyloxy-2-acetylthio-6-methylpyrimidine as a product (10%) on treatment with chloroacetone, although the mechanism remains obscure;⁶³⁵⁵ 4-hydroxy-2-methylthiopyrimidine (47, R = Me) gave 88% of 4-hydroxy-2-octylthiopyrimidine (47, R = C₈H₁₇), and other such derivatives, by boiling with the appropriate mercaptan in ethanol containing triethylamine;⁶¹⁸⁵ and 2-ethylthio-4-hydroxy-6-methylpyrimidine gave 2- β -diethylaminoethylthio-4-hydroxy-6-methylpyrimidine (50%) on warming at 100° with chloroethyl-diethylamine hydrochloride in dimethylformamide.⁶¹⁸⁵

An interesting reaction with potential generality was that of bis(4,6-di-*p*-methoxyphenylpyrimidin-2-yl) disulfide with *p*-fluorophenyl magnesium bromide to give 2-*p*-fluorophenylthio-4,6-di-*p*-methoxyphenylpyrimidine (47%).⁶³⁹⁹

B. Preparation of 5-Alkylthiopyrimidines (H 288, E 217)

Direct electrophilic attack at the 5-position of uracil and related compounds by sulfenyl chlorides appears to have been discovered fortuitously in 1966 when chloromethylation of uracil was attempted with chloromethyl methyl ether in dimethyl sulfoxide.⁵¹⁴² In fact, 2,4-dihydroxy-5-methylthiopyrimidine (48, R = H) resulted in 70% yield, and it was found that the same product was obtained when the chloroether was replaced by acetyl chloride or chloroacetyl chloride, but when hydrogen chloride was used, the main product was 5-dimethylsulfonio-2,4-dihydroxypyrimidine chloride (49). It was suggested that a mechanism for the formation of the 5-methylthiopyrimidine could involve methanesulfenyl chloride (MeSCl) formed *in situ*.⁵¹⁴² It was



shown subsequently that uracil and other pyrimidines with at least two electron-releasing groups were attacked by *n*-alkanesulfonyl chlorides to give, for example, 2-dimethylamino-4-hydroxy-6-methyl-5-methylthiopyrimidine (40 or 74% according to conditions and initial reagents),⁵³⁹⁰ 2,4-bisdimethylamino-6-methyl-5-methylthiopyrimidine (50) in 93% yield,⁵³⁹⁰ 5-*p*-chlorophenylthio-2-dimethylamino-4-hydroxy-6-methylpyrimidine (58%),⁵³⁹⁰ 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-trifluoromethylthiopyrimidine (51) in 47% yield,⁴⁴⁸⁷ 4-amino-2-hydroxy-5-trifluoromethylthiopyrimidine (36%),⁴⁴⁶⁹ 4-carboxy-2,6-dihydroxy-5-trifluoromethylthiopyrimidine (51%),⁴⁴⁶⁹ 2,4-dihydroxy-5-methylthiopyrimidine (improved methods, *c.* 90%),^{5167, 5168} 5-ethylthio-2,4-dihydroxypyrimidine (72%),⁵¹⁶⁸ 2,4-dihydroxy-5-phenylselenopyrimidine (76%),⁵¹⁶⁸ and many analogues.⁵¹⁶⁸

C. Reactions of Alkylthiopyrimidines (*H* 288, *E* 217)

(1) *Reductive Removal of Alkylthio Groups* (*H* 288, *E* 203)

Because mercapto groups, from which most alkylthio groups are derived, can be readily desulfurized by Raney nickel, there is now little call to so remove alkylthio groups themselves. However, the process has been used recently to convert 1,6-dihydro-4-methyl-2-methylthio-6-oxo-1-phenylpyrimidine (52, R = SMe) into its de(methylthio) derivative (52, R = H) (Raney nickel in boiling methanol, 66%),⁴⁹³⁰ 4-amino-6-methoxy-2-methylthiopyrimidine into 4-amino-6-methoxypyrimidine (nickel in 95% ethanol, 80%),⁵⁸⁵³ the extranuclear thioethers, 2-amino-5-methylthiomethyl-4-phenylpyrimidine (53, R = SMe), its 5-ethylthiomethyl homologue, (53, R = SEt) and its 5-benzylthiomethyl homologue (53, R = SCH₂Ph) into 2-amino-5-methyl-4-phenylpyrimidine (53, R = H), all in greater than 80% yield,⁵³⁸² and others.⁵³⁸²

(2) *Alkylthio- to Hydroxypyrimidines* (*H* 289, *E* 217)

The direct and indirect routes for this transformation have been covered in Ch. VII, Sects. 1.F(1) and (3).

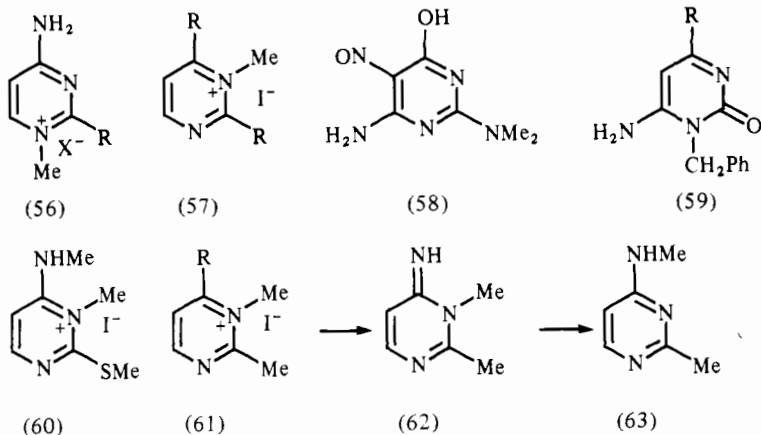
(3) *Aminolysis of Alkylthiopyrimidines* (*H* 289, *E* 217)

Like the aminolysis of chloropyrimidines, 4-alkylthio- are converted more easily into aminopyrimidines than are 2-alkylthiopyrimi-

dines. Moreover, activation of the leaving group by a nitro, nitroso, or ethoxycarbonyl group, or by a quaternary nitrogen improves the ease of reaction considerably. In two different cases, prior oxidation to a sulfoxide or sulfone facilitates aminolysis enormously.

Aminolysis of the corresponding 2-methylthiopyrimidine (except where indicated otherwise) has been used to prepare 4-hydroxy-2-morpholinopyrimidine (neat morpholine at 140° , 89%),⁵⁸⁶⁶ 1,4-dihydro-1-methyl-2-methylamino-4-oxopyrimidine (54) (neat methylamine sealed at 65° for 7 days, 82%),⁵⁶⁰⁰ 1,6-dihydro-1-methyl-2-methylamino-6-oxopyrimidine (from 2-benzylthio analogue in ethanolic methylamine at 150° , 98%),⁴⁵⁶⁹ 1,6-dihydro-2- β -hydroxyethylamino-1,4-dimethyl-6-oxopyrimidine (from 2-benzylthio analogue in ethanolic β -aminoethanol at 145° , 60%),⁴⁵⁶⁸ 4-hydroxy-2-isopropylamino-5-methylpyrimidine (neat isopropylamine at 180° , 63%; also >40 analogues),⁴⁵⁷² 2-anilino-4-hydroxypyrimidine (from 2-ethylthio analogue with neat aniline at 100° , 66%),⁴⁶⁷⁰ 2-dimethylamino-4-hydroxypyrimidine (neat dimethylammonium acetate at 160° , 78%),⁴⁶⁷⁰ 2-(3',5'-dibromo-4'-ethoxyanilino)-4-hydroxy-6-methylpyrimidine (3,5-dibromophenetidine at 130° , 62%),⁶³⁰⁴ 1,6-dihydro-1,4-dimethyl-2-methylamino-6-oxopyrimidine (neat methylammonium acetate at 140° , 85%),⁴⁵⁷³ 2-anilino-4-hydroxy-5-methyl-6-phenylpyrimidine (from 2-ethylthio analogue with aniline in refluxing β -methoxyethanol),⁵⁷³⁷ 2-carboxymethylamino-4-hydroxy-5-methylpyrimidine (from 2-ethylthio analogue with glycine in aqueous sodium carbonate under reflux, 23%),⁴⁴⁷⁶ and others.^{4520, 6578} Hydrazinolysis proceeded marginally more easily to give 2-hydrazino-4-hydroxypyrimidine (55, R = H) (hydrazine hydrate in glacial acetic acid under reflux, 56%),⁴³⁶⁸ 2-hydrazino-4-hydroxy-6-methyl-5-octylpyrimidine,⁵¹²⁴ and 2-hydrazino-4-hydroxy-5,6-dimethylpyrimidine (55, R = Me) (from 2-ethylthio analogue in ethanolic hydrazine hydrate under reflux, c. 30%).⁵⁰⁵³

The above conditions may be compared with those used for aminolysis of activated 2-alkylthiopyrimidines, as exemplified in the conversion of 4-amino-1-methyl-2-methylthiopyrimidinium chloride (56, R = SMe, X = Cl) into 4-amino-2- β -hydroxyethylamino-1-methylpyrimidinium chloride (56, R = NHCH₂CH₂OH) (ethanolic β -aminoethanol at 35° , 65%),⁴⁴⁶⁸ of the same substrate (56, R = SMe, X = I) into 2,4-diamino-1-methylpyrimidinium iodide (56, R = NH₂, X = I) (methanolic ammonia at 25° , 87%),⁴⁴⁹⁰ of 1-methyl-2,6-bismethylthiopyrimidinium iodide (57, R = SMe) into 1-methyl-2,6-bismethylamino-pyrimidinium iodide (57, R = NHMe) (ethanolic methylamine at 60° ,



91%),⁵⁶⁶⁵ of 4-amino-6-hydroxy-2-methylthio-5-nitrosopyrimidine into 4-amino-2-5'-carboxypentylamino-6-hydroxy-5-nitrosopyrimidine (aqueous 6-aminoheptanoic acid under reflux; *c.* 65%),⁵⁰⁵² of the same substrate into 4-amino-2-dimethylamino-6-hydroxy-5-nitrosopyrimidine (58) (aqueous dimethylamine under reflux for 20 min, 60%),⁵⁸²⁰ of 5-acetyl-4-methyl-2-methylthiopyrimidine into 5-acetyl-4-methyl-2-piperidinopyrimidine (neat piperidine at 100°, 54%; also analogues),⁵³⁷⁸ and others.^{4389, 4907, 5885}

Aminolysis of 4-methylthiopyrimidines is typified in the formation of 4,6-diamino-1-benzyl-1,2-dihydro-2-oxopyrimidine (59, R = NH₂) [from 4-amino-3-benzyl-2,3-dihydro-6-methylthio-2-oxopyrimidine (59, R = SMe) with methanolic ammonia at 170°, 62%],⁵⁰³⁶ 4-amino-1,2-dihydro-1-β-hydroxyethoxymethyl-2-oxopyrimidine (methanolic ammonia at 110°, 85%),⁶¹⁴³ 2,2'-bisdimethylamino-4'-β-dimethylaminoethylamino-6-methylthio-4,5'-bipyrimidine (neat β-dimethylaminoethylamine at 170°, 89%),⁶¹⁸⁰ 4-hydrazino-2-hydroxypyrimidine and its 5-fluoro derivative (aqueous hydrazine hydrate under reflux, *c.* 70%),⁴³⁸⁵ 4-carboxymethylamino-2-hydroxy-5-methylpyrimidine (glycine in refluxing aqueous sodium carbonate, 77%),⁴⁸⁷² 4-heptylamino-2-hydroxypyrimidine (ethanolic heptylamine under reflux, 76%),⁴⁵³⁸ 2,3-bis(2'-hydroxypyrimidin-4'-ylamino)propionic acid (2,3-diaminopropionic acid in boiling aqueous sodium carbonate, 15%),⁴⁵⁴⁰ 1-methyl-6-methylamino-2-methylthiopyrimidin-1-ium iodide (60) [from 1-methyl-2,6-bismethylthiopyrimidin-1-ium iodide (57, R = SMe, X = I) by treatment with ethanolic methylamine at 0° for 2 min, 99%],⁵⁶⁶⁵ 2,4-diamino-6-anilino-5-nitrosopyrimidine (aniline plus aniline hydrochloride in refluxing butanol, 94%),⁵⁷⁴⁴ and 2-methyl-4-methylaminopyrimidine (63) [from 1,2-dimethyl-6-methylthiopyrimidin-1-ium iodide

(61, $R = SMe$) *via* Dimroth rearrangement of the anhydro-base (62) of the initial product (61, $R = NH_2$) during treatment with ammonia in chloroform at 25° ; 50%];⁴⁴⁴⁹ also in other cases.⁶⁵⁵⁴

(4) *Alkylthio- to Mercaptopyrimidines* (H 291, E 217)

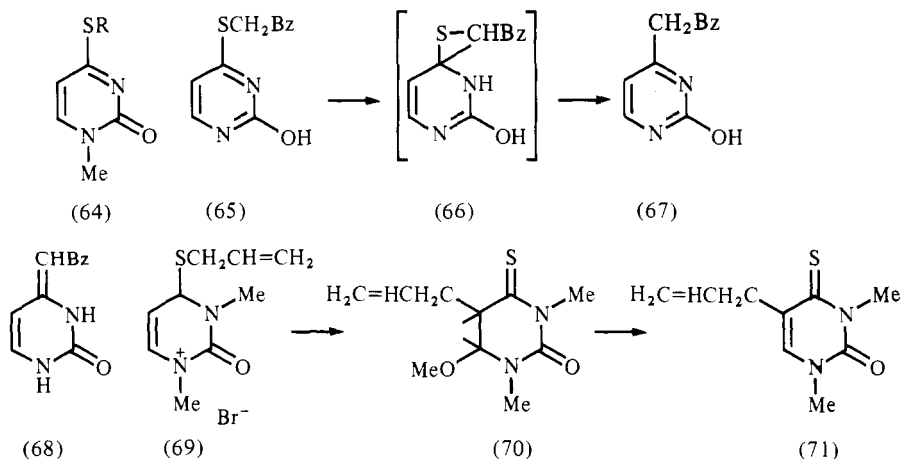
The ways for doing this have been mentioned in Sect. 1.A above.

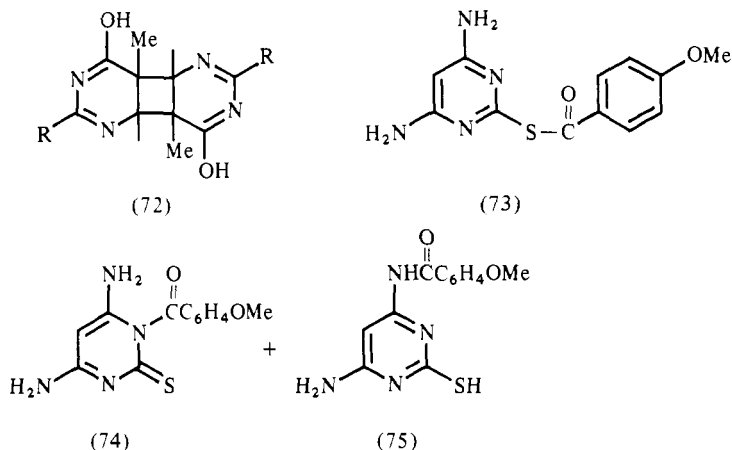
(5) *Oxidation of Alkylthiopyrimidines* (H 291, E 217)

Such oxidation to sulfoxides and sulfones is covered in Sect. 5.A.

(6) *Miscellaneous Reactions (New)*

1,2-Dihydro-1-methyl-4-methylthio-2-oxopyrimidine (64, $R = Me$) underwent a nucleophilic reaction with potassium thiocyanate in refluxing acetonitrile to give 1,2-dihydro-1-methyl-2-oxo-4-thiocyanatopyrimidine (64, $R = CN$) in *c.* 50% yield.⁶²⁰⁶ 2-Hydroxy-4-phenacylthiopyrimidine (65) has been shown to undergo an interesting sulfur-extrusion on boiling in methoxyethanol to give, *via* the episulfide (66), 2-hydroxy-4-phenacylpyrimidine (67), which is said to exist largely in the tautomeric form (68); 2-phenacylthiopyrimidines behaved similarly, as did substituted-phenacylthio derivatives; but a 2/4-hydroxy/oxo substituent was essential.⁶⁰⁰¹ A "thio-Claisen" rearrangement occurred when 4-allylthio-2,3-dihydro-1,3-dimethyl-2-oxopyrimidinium iodide (69) was treated with acetone-methanol containing sodium carbonate

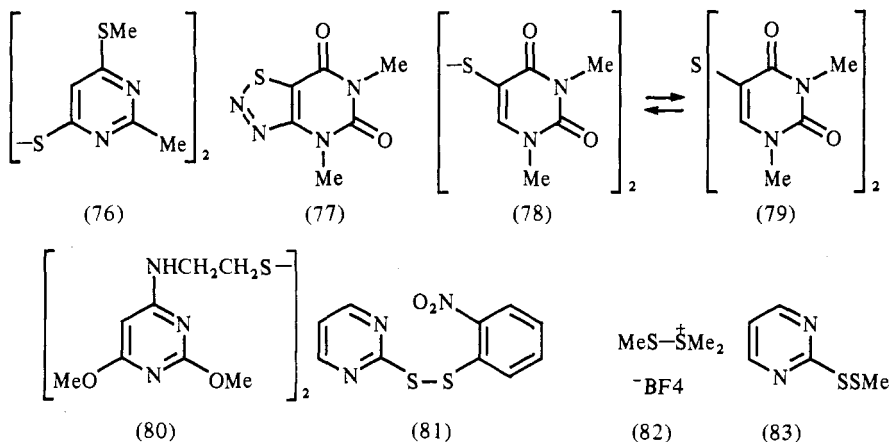




to give initially 5-allylhexahydro-4-methoxy-1,3-dimethyl-2-oxo-6-thiopyrimidine (70), which in refluxing chloroform lost methanol to give 5-allyl-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thiopyrimidine (71) in 75% overall yield.⁴⁴²¹ Photolysis of 4-hydroxy-5-methyl-2-methylthiopyrimidine in acetone gave the "cyclobutane type" of dimer (72, R = SMe) which, on treatment with dilute hydrochloric acid, gave a known dimer of thymine (72, R = OH).⁶⁰⁸⁶ 4,6-Diamino-2-*m*-methoxybenzoylthiopyrimidine (73) underwent isomerization on brief heating in dimethylformamide to give a separable mixture of 4,6-diamino-1,2-dihydro-1-*m*-methoxybenzoyl-2-thiopyrimidine (74) and 4-amino-2-mercapto-6-*m*-methoxybenzamidopyrimidine (75); analogues behaved similarly.⁶¹²⁶ 2- ω -Bromoalkylthio-4,6-dimethylpyrimidines took part in several rather complicated reactions on heating.⁶³⁷¹ 5-Chloro-2-prop-2'-ynylthiopyrimidine rearranged into 2-allenylthio-5-chloropyrimidine on treatment with potassium *t*-butoxide in *t*-butyl alcohol.⁶⁵³⁵

3. Dipyrimidinyl Disulfides and Sulfides (*H* 291, *E* 219)

Little work has been reported recently in this area. 4-Amino-2,6-dihydroxy-5-mercaptopyrimidine was oxidized in dimethyl sulfoxide at 100° to give bis(4-amino-2,6-dihydroxypyrimidin-5-yl) disulfide (30%);⁵²⁴⁴ 2-mercapto-4,6-dimethylpyrimidine and iodine in alkali gave bis(4,6-dimethylpyrimidin-2-yl) disulfide (96%);⁵⁶⁶⁹ 2-mercaptopyrimidine similarly gave dipyrimidin-2-yl disulfide (85%);⁵⁶⁶⁹ 4-mercapto-2-methyl-6-methylthiopyrimidine and aqueous nitrous acid gave bis(2-methyl-6-methylthiopyrimidin-4-yl) disulfide (76) in greater than 95% yield;⁶³⁷⁴ 2-mercapto-4,6-diphenylpyrimidine with glacial



acetic acid containing nitrous acid gave bis(4,6-diphenylpyrimidin-2-yl) disulfide (>95%);⁶²¹⁰ 5-dimethylaminomethyleneamino-2-mercaptopyrimidine in acidified dimethyl sulfoxide at 25° gave bis(5-dimethylaminomethyleneaminopyrimidin-2-yl) disulfide (69%);⁴³⁸³ and 1-methyl-4-thiouracil with cyanogen bromide in ethanol containing triethylamine gave, not the expected 4-thiocyanato analogue, but bis(1,2-dihydro-1-methyl-2-oxypyrimidin-4-yl) disulfide in 71% yield,⁵⁵⁰⁶ which was identical with the product from iodine oxidation of the same substrate.⁵⁴⁵⁴

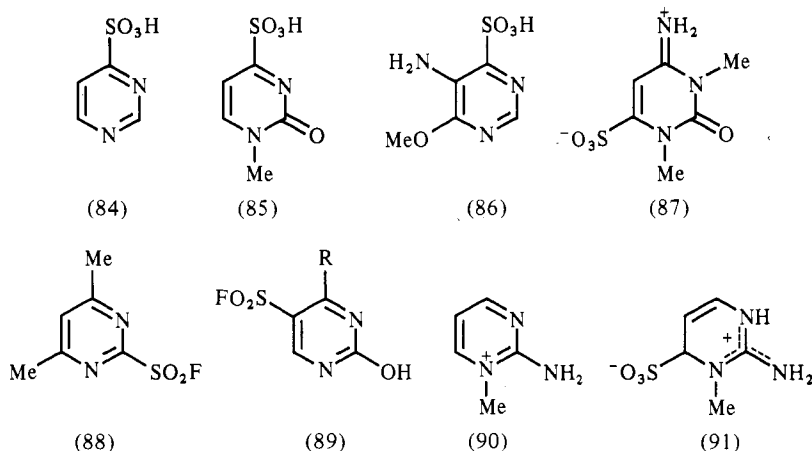
Other routes to disulfides included irradiation of 4,5,6,7-tetrahydro-4,6-dimethyl-5,7-dioxo-1,2,3-thiadiazolo[4,5-*d*] pyrimidine (77) to give 50% of bis(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidin-5-yl) disulfide (78), which was converted into the corresponding sulfide (79) by heating at *c.* 275°, a reaction claimed to be also thermally reversible;⁶⁰¹⁴ treatment of 2,4-diamino-6-hydroxy-5-thiocyanatopyrimidine in boiling pH 8 phosphate buffer to give some bis(2,4-diamino-6-hydroxypyrimidin-5-yl) disulfide;⁵²⁵¹ treatment of 2,4-dihydroxypyrimidine in boiling formic acid with either sulfur monochloride or sulfur dichloride to give bis(2,4-dihydroxypyrimidin-5-yl) sulfide (70 or 35%, respectively),⁵⁶⁷² similar treatment of appropriate uracil derivatives to give bis(2,4-dihydroxy-6-propylpyrimidin-5-yl), bis(1-methyluracil-5-yl), bis(3-methyluracil-5-yl), bis(tetrahydro-1,3-dimethyl-2,4-dioxypyrimidin-5-yl) (79), and bis(2,4,6-trihydroxypyrimidin-5-yl) sulfide;⁵⁶⁷² and treatment of 1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxypyrimidine with thionyl chloride to give *inter alia* bis(1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxypyrimidin-5-yl) sulfide (70%).⁶⁰³⁷

Two more logical approaches to disulfides/sulfides are seen in the treatment of 4- β -chloroethylamino-2,6-dimethoxypyrimidine with aqueous ethanolic sodium sulfide to give bis[β -(2,6-dimethoxypyrimidin-4-ylamino)ethyl] disulfide (80);⁴⁷¹⁴ and in the condensation of 5-chloromethyl-2,4-dihydroxypyrimidine with 2,4-dihydroxy-5-mercaptomethylpyrimidine to give bis(2,4-dihydroxypyrimidin-5-ylmethyl) sulfide (>95%).⁵⁶⁴¹ As indicated previously (Sect. 1.E), unsymmetrical disulfides can be obtained from mercaptopyrimidines with sulfenyl chlorides. For example, 2-mercaptopyrimidine reacted with *o*-nitrophenylsulfenyl chloride in methanolic sodium methoxide to afford 2-*o*-nitrophenyldithiopyrimidine (81) in 37% yield.⁴⁷¹⁴ A second route to such disulfides is the condensation of dialkyl-*S*-alkylthiosulfonium salts with mercaptopyrimidines, as illustrated in the reaction of 2-mercaptopyrimidine with dimethyl-*S*-methylthiosulfonium tetrafluoroborate (82) to give 2-methyldithiopyrimidine (83) in 71% yield.⁴⁸⁹⁷

4. Pyrimidine Sulfonic Acids and Related Compounds (*H* 295, *E* 221)

A. Preparation (*H* 295, *E* 221)

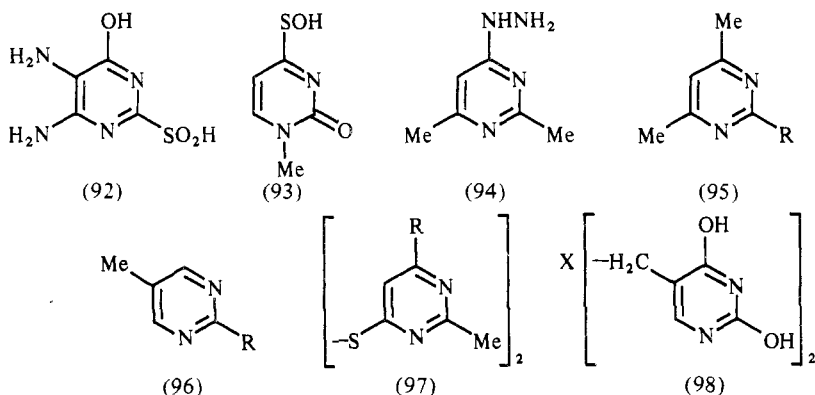
The replacement of a chloro by a sulfo substituent has been covered in Ch. VI, Sect. 5.H.⁵⁶⁶⁷ In addition, a few examples of the oxidative formation of sulfo- from mercaptopyrimidines, in the context of converting mercapto- into hydroxypyrimidines, have been given in Ch. VII, Sect. 1.F(2). The best reagent for oxidation of mercapto- into sulfopyrimidines is permanganate, as exemplified in the formation (usually as potassium salts) of 4,6-dimethyl-2-sulfo- (65%), 5-methyl-2-sulfo- (76%), 4-methyl-6-sulfo- (>90%), 2-sulfo- (74%), and 4-sulfopyrimidine (84) (>90%);⁵⁶⁶⁹ as well as in the conversion of 1-methyl-4-thiouracil into 1,2-dihydro-1-methyl-2-oxo-4-sulfopyrimidine (85) (82%),^{6098, 6099} and 4-hydroxy-2-mercapto- into 4-hydroxy-2-sulfopyrimidine (60%).⁵¹⁵⁹ The use of hydrogen peroxide is illustrated in the formation of 5-amino-4-methoxy-6-sulfopyrimidine (86) (41%)⁴⁸²⁵ and 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxo-6-sulfopyrimidine (85%), almost certainly existing as a zwitterion such as (87).⁴⁹⁶⁹ Oxidation of 2-mercapto-4,6-dimethylpyrimidine, in aqueous methanol containing potassium hydrogen difluoride, by a stream of chlorine gas at less than -10° gave 2-fluorosulfonyl-4,6-dimethylpyrimidine (88) in 78% yield; 2-fluorosulfonylpyrimidine and its 4- and 5-methyl derivatives were made similarly in comparable yield.⁵⁶⁶⁹ A different approach to a 5-fluorosulfonylpyrimidine is seen in the direct fluorosulfonation



of 2,4-dihydroxypyrimidine by treatment with fluorosulfonic acid at 160° to give 92% of 5-fluorosulfonyl-2,4-dihydroxypyrimidine (89, $R = OH$), which in dilute ammonia gave, not the expected sulfonamide, but 4-amino-5-fluorosulfonyl-2-hydroxypyrimidine (89, $R = NH_2$).⁴⁷⁹⁸ The related 5-chlorosulfonyl-2,4-dihydroxypyrimidine was made similarly with chlorosulfonic acid. Subsequent treatment with phosphoryl chloride gave 2,4-dichloro-5-chlorosulfonylpyrimidine, which reacted with acetone-water to give 2,4-dichloro-5-sulfonypyrimidine.⁶⁰⁷⁴

Sodium hydrogen sulfite adds to some pyrimidines to afford initially a dihydrosulfonypyrimidine. Thus, the 2-amino-1-methylpyrimidinium ion (90) formed two isomeric 1:1-adducts with bisulfite ion: one was shown by X-ray data to be the zwitterionic dihydro-1-methyl-6-sulfonypyrimidine (91) and the other was believed to be the corresponding dihydro-1-methyl-4-sulfo isomer;⁵⁴⁵⁶ the thermodynamics and kinetics of these and related additions have been studied in depth.^{5456, 5530} The analogous addition and elimination of bisulfite ion to 2,4-dihydroxypyrimidine, 1-methyluracil, 3-methyluracil, 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine, and its 5-nitro derivative, have been studied too.^{5451, 5452} It is interesting that when air was drawn through a solution of 4-hydroxy-2-mercaptopyrimidine in the presence of bisulfite ion, 4-hydroxy-2-sulfonypyrimidine was formed quantitatively and was converted into 2,4-dihydroxypyrimidine by treatment with acid; without bisulfite, no reaction occurred.⁵¹⁹⁹

Controlled oxidation of 4,5-diamino-6-hydroxy-2-mercaptopyrimidine by alkaline hydrogen peroxide at less than 0° gave 4,5-diamino-6-hydroxy-2-sulfinopyrimidine (92) in 87% yield, which was converted into 6-hydroxypurine by boiling in anhydrous formic acid, with loss of the sulfinio group.⁵⁰⁵⁹



The alkaline cleavage of a disulfide has been used to make a pyrimidinesulfenic acid. Thus, bis(1,2-dihydro-1-methyl-2-oxopyrimidin-4-yl) disulfide was stirred in 0.1 M sodium hydroxide at 25° to give 1-methyl-4-thiouracil and 1,2-dihydro-1-methyl-2-oxo-4-sulfenopyrimidine (93), isolated as its silver salt in 30% yield, from which the free acid was prepared.⁵⁴⁵⁴

B. Reactions (*H* 297, *E* 222)

Besides the reactions mentioned incidentally above, sulfopyrimidines and their acid fluorides undergo several useful transformations, illustrated in the conversion of 2,4-dimethyl-6-sulfo- into 4-hydroxy-2,6-dimethylpyrimidine by acidic (80% yield) or alkaline (66% yield) hydrolysis;⁵⁶⁶⁷ of 1,2-dihydro-1-methyl-2-oxo-4-sulfopyrimidine into 1-methyluracil (72%) by acidic hydrolysis [for other hydrolyses see Ch. VII, Sect. 1.F(2)];⁶⁰⁹⁹ of the same substrate into 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (93%) or its 4-dimethylamino analogue (84%) by treatment with aqueous ammonia or dimethylamine, respectively, at 25°;^{6098, 6099} of 2,4-dimethyl-6-sulpho- into 4-hydrazino-2,6-dimethylpyrimidine (94) (methanolic hydrazine under reflux, 56%);⁵⁶⁶⁹ of 4,6-dimethyl-2-sulfo- (95, R = SO₃H), 4,6-dimethyl-2-sulfamoyl- (95, R = SO₂NH₂), 2-fluorosulfonyl-4,6-dimethyl- (95, R = SO₂F), or even 2-*N*-aminosulfamoyl-4,6-dimethylpyrimidine (95, R = SO₂NHNH₂) into 2-hydrazino-4,6-dimethylpyrimidine (95, R = NHNH₂) by treatment with hot methanolic hydrazine;⁵⁶⁶⁹ of 1,2-dihydro-1-methyl-2-oxo-4-sulfopyrimidine into 1-methyl-4-thiouracil (91%) by bubbling hydrogen sulfide through an aqueous solution of the sodium salt;⁶⁰⁹⁹ of 2-fluorosulfonyl-4,6-dimethyl- (95, R = SO₂F) or 4,6-dimethyl-2-sulfo- (95, R = SO₃H) into 4,6-dimethyl-2-sulfamoyl-

pyrimidine (95, $R = SO_2NH_2$) (80%) by dissolution in liquid ammonia for 5 min;⁵⁶⁶⁹ of 2-fluorosulfonyl- (95, $R = SO_2F$) into 2-*N,N*-diethylsulfamoyl-4,6-dimethylpyrimidine (95, $R = SO_2NEt_2$);⁵⁶⁶⁹ of 2-fluorosulfonyl- (96, $R = SO_2F$) into 2-hydrazino-5-methylpyrimidine (96, $R = NHNH_2$) in greater than 90% yield;⁵⁶⁶⁹ of the same substrate into 2-azido-5-methylpyrimidine (96, $R = N_3$) (55%) by treatment with aqueous methanolic sodium azide at 25°;⁵⁶⁶⁹ and others.⁵⁶⁶⁹

5. Alkylsulfonyl- and Alkylsulfinylpyrimidines (*H* 298, *E* 224)

The pyrimidine sulfones and sulfoxides have continued to draw attention, mainly because they are invaluable intermediates in which the 2- and 4/6-alkylsulfonyl or alkylsulfinyl groups undergo nucleophilic displacement with the greatest ease.

A. Preparation (*H* 298, *E* 225)

Because most sulfones and sulfoxides are made by oxidation of the corresponding thioethers, it is understandably easier to make the sulfone in a pure state (by employing a slight excess of oxidant) than it is to make pure sulfoxide, which initially contains both thioether and sulfone, no matter how carefully controlled is the oxidative reaction. Accordingly, the sulfone is usually preferred to the sulfoxide as an intermediate and this is reflected in the relative numbers of substances reported in each class.

Recent examples of *sulfones* made by regular oxidations of the thioethers are presented in Table XIIIb. In addition, bis(2-methyl-6-methylthiopyrimidin-4-yl) disulfide (97, $R = SMe$) gave the corresponding sulfone (97, $R = SO_2Me$) on treatment with *m*-chloroperoxybenzoic acid,⁶³⁷⁴ and bis(2,4-dihydroxypyrimidin-5-methyl) sulfide (98, $X = S$) gave the corresponding sulfone (98, $X = SO_2$) on treatment with trifluoroperoxyacetic acid.⁵⁶⁴¹ Another approach to sulfones is seen in the reaction of 2-bromopyrimidine with sodium *p*-acetamidobenzenesulfinate to give 2-*p*-acetamidophenylsulfonylpyrimidine (99) in 37% yield;⁵⁵⁷⁴ and such a displacement probably accounts for the reaction of 5-bromo-2-methylsulfonylpyrimidine (100) with sodium cyanide in dimethyl sulfoxide at 100° to give 2-cyano-5-methylsulfonylpyrimidine (101) because the initially displaced sodium methanesulfonate subsequently reacted with the 5-bromo substituent.⁴³⁹⁹ Irradiation of 2-dimethylamino-4-methanesulfonyloxy-6-methylpyrimi-

TABLE XIIIb. Pyrimidine Sulfones Made by Oxidation of Alkyl- or Aryl-thiopyrimidines (E 225)

Pyrimidine Produced	Reagents	Yield %	Reference
2- <i>p</i> -Acetamidobenzenesulfonamido-2-methylsulfonyl-	AcO ₂ H	83	4332
2-Allylsulfonyl-5-chloro-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	70	6535
4-Amino-6-benzyloxy-2-methylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	53	6252
5-Amino-4,6-bismethylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	> 95	6374
2-Amino-4-ethylsulfonyl-6-phenyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	—	5038
4-Amino-2-ethylsulfonyl-6-phenyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	—	5038
4-Amino-6-methoxy-2-methylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	74	4656
2-Amino-5-methylsulfonylmethyl-4-phenyl-	AcO ₂ H	65	5382
4-Benzyloxy-2-methylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	98	5925
5-Bromo-4-carboxy-2-methylsulfonyl-	AcO ₂ H	75 or 50	4399 5380
5- <i>p</i> -Butoxyphenyl-2-methylsulfonyl- ^a	AcO ₂ H	79	4545
4-Carboxy-5-chloro-2-methylsulfonyl-	AcO ₂ H	65	4399
4-Carboxy-5- <i>o</i> -chloro-phenylsulfonyl-2-methylthio- ^{a, b}	AcO ₂ H	31	5380
5-Chloro-2-chloromethylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	63	6378
	MoO ₅ complex	53	6378
5-Chloro-2-iodomethylsulfonyl-	MoO ₅ complex	52	6378
4-Chloro-5-methoxy-2-methylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	73	5662
2- <i>p</i> -Chlorophenylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	—	5633
5-Chloro-2-prop-2'-ynylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	73	6535
5-Cyano-2-methylsulfonyl-	Cl ₂	90	4399
2,4-Diamino-5- <i>p</i> -β-naphthylsulfonylphenyl- ^{a, c}	AcO ₂ H or <i>m</i> -ClC ₆ H ₄ CO ₃ H	40	5479
2,4-Diamino-6-phenylsulfonyl-[3-oxide]	F ₃ CCO ₃ H	60 or 48 ^d	5188
2,4-Dihydroxy-5-methylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	<i>c.</i> 90	5167
2,4-Dihydroxy-6-phenylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	66	6082
2,4-Dihydroxy-5-trifluoromethylsulfonyl-	CrO ₃	58	4469
2-Dimethylamino-4-hydroxy-6-methyl-5-methylsulfonyl-	KMnO ₄	58	5390

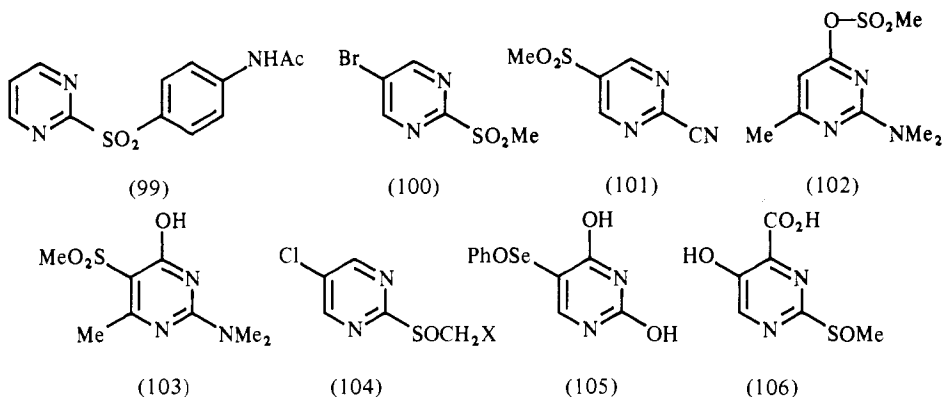
TABLE XIIIb (Continued)

Pyrimidine Produced	Reagents	Yield %	Reference
5-Dimethylaminomethylene-amino-2-methylsulfonyl-	NaOCl	91	4383
4,6-Dimethyl-2-methylsulfonyl-5-phenyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	89	5662
4-Ethoxy-2-ethylsulfonyl-	NaOCl	65	6132
4-Ethoxy-2-methylsulfonyl-	NaOCl	80	6132
4-Ethylsulfonyl-2-methoxycarbonylmethyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	40	5693
4-Hydroxy-2-methyl-6-methylsulfonyl-	AcO ₂ H	<i>c.</i> 90	3505
5-Methoxycarbonyl-2-methylsulfonyl-	Cl ₂	64	4399
5-β-Methoxyethoxy-2-methylsulfonyl-	NaOCl	92	4399
5-Methoxy-4-methoxymethyl-2-methylsulfonyl-	NaOCl	60	4397
2- <i>p</i> -Methoxyphenylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	—	5633
2-Methyl-4,6-bismethylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	60	6374
5-Methyl-2-methylsulfonyl-	Cl ₂	90	4399
	AcO ₂ H	59	4399
2-Methylsulfonyl-	NaOCl	86	4399
2-Methylsulfonyl-5-nitro-	Cl ₂	48	5285
2-Methylsulfonyl-4-phenyl-	Cl ₂	59	6040
2- <i>p</i> -Nitrophenylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	84	5574
			5633
4-Phenyl-2-phenylsulfonyl-	Cl ₂	80	6040
2- <i>p</i> -Tolylsulfonyl-	<i>m</i> -ClC ₆ H ₄ CO ₃ H	<i>c.</i> 85	5633

^a And analogues.^b Note preferential oxidation at 5-position.^c Misnamed in original experiment.^d From the thioether or thioether *N*-oxide, respectively.

dine (102) induced rearrangement to 2-dimethylamino-4-hydroxy-6-methyl-5-methylsulfonylpyrimidine (103) in 60% yield.⁵³⁹¹

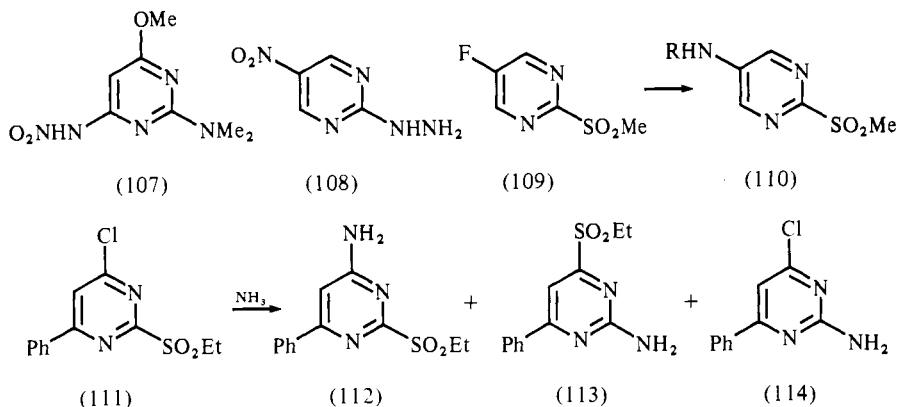
The oxidative preparation of *sulfoxides* is illustrated in the formation of 4-amino-6-chloro(or methoxy)-2-methylsulfinylpyrimidine (*m*-chloroperoxybenzoic acid, 1 equivalent, 42 or 44%),⁴⁶⁵⁶ 5-chloro-2-chloro(or iodo)methylsulfinylpyrimidine (104, X = Cl or I) (*m*-chloroperoxybenzoic acid, 73 or 41%),⁶³⁷⁸ 2,4-dihydroxy-5-*p*-tolylsulfinyl-



pyrimidine (*m*-chloroperoxybenzoic acid, 74%),⁵¹⁶⁸ 2,4-dihydroxy-5-phenylseleninylpyrimidine (105) (*m*-chloroperoxybenzoic acid, 66%),⁵¹⁶⁸ 2,4-dihydroxy-5-methylsulfinylpyrimidine (*m*-chloroperoxybenzoic acid, *c.* 70%),⁵¹⁶⁷ 2-dimethylamino-4-hydroxy-6-methyl-5-methylsulfinylpyrimidine (sodium periodate, 28%),⁵³⁹⁰ 2,4-dihydroxy-5-trifluoromethylsulfinylpyrimidine (fuming nitric acid at 25°, 57%),⁴⁴⁶⁹ 5-dimethylaminomethyleneamino-2-methylsulfinylpyrimidine (sodium hypochlorite, 76%),⁴³⁸³ 2-methyl-4,6-bismethylsulfinylpyrimidine (*m*-chloroperoxybenzoic acid, 60%; note that less oxidant gave 2-methyl-4-methylsulfinyl-6-methylthiopyrimidine while more gave 2-methyl-4-methylsulfinyl-6-methylsulfonylpyrimidine or 2-methyl-4,6-bismethylsulfonylpyrimidine according to the amount),⁶³⁷⁴ 2-*p*-chlorophenylsulfinylpyrimidine (*m*-chloroperoxybenzoic acid; also analogues similarly),⁵⁶³³ 4-carboxy-5-hydroxy-2-methylsulfinylpyrimidine (106) (from the 5-chloro thioether in dimethyl sulfoxide/alkali),⁵⁸⁵⁵ and others.⁶⁵³⁵

B. Reactions (*H* 300, *E* 226)

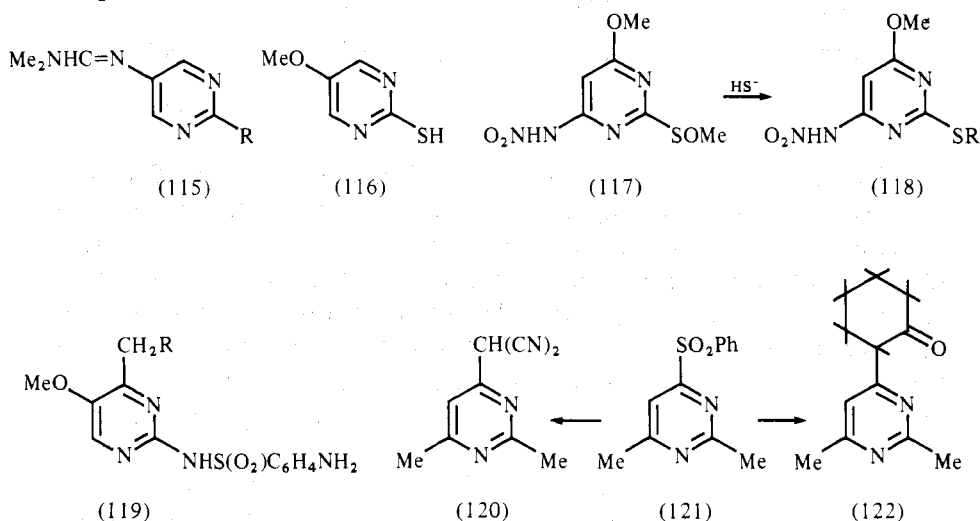
The conversion of alkylsulfonyl- and alkylsulfinylpyrimidines into hydroxypyrimidines has been studied kinetically;⁵⁶³³ it is typified by the reaction of 4-amino-6-benzyloxy-2-methylsulfonylpyrimidine with aqueous alcoholic alkali to give 4-amino-6-benzyloxy-2-hydroxypyrimidine (38%),⁶²⁵² and full treatment is accorded in Ch. VII, Sect. 1.F(3). The similar conversion of sulfones/sulfoxides into alkoxy-pyrimidines, for example, 2-dimethylaminomethyleneamino-2-methylsulfonyl- into 2-dimethylaminomethyleneamino-2-methoxypyrimidine (95%) by methanolic sodium methoxide,⁴³⁸³ has been covered in Ch. VII, Sect. 4.C.



The useful *aminolysis* of sulfones/sulfoxides is illustrated in the conversion of 4,6-dimethyl-2-methylsulfonyl- into 4,6-dimethyl-2-methylamino-5-phenylpyrimidine (ethanolic methylamine at 100°; 90%),⁵⁶⁶² of 5-methoxy-2-methylsulfonyl- into 5-methoxy-2-methylaminopyrimidine (similarly, 90%),⁵⁶⁶² of 4-methoxy-2-methylsulfonyl-6-nitroaminopyrimidine (or its methylsulfonyl analogue) into 2-dimethylamino-4-methoxy-6-nitroaminopyrimidine (107) (ethanolic dimethylamine at 25°, 47 or 72%),⁴⁶⁵⁶ of 2,4-diamino-6-phenylsulfonyl- into 2,4-diamino-6-ethylaminopyrimidine 3-oxide (ethanolic ethylamine at 130°, 53%),⁵¹⁸⁸ of 2-methylsulfonyl- into 2-hydrazino-5-nitropyrimidine (108) (ethanolic hydrazine, >95%),⁵²⁸⁵ and of 5-methoxy-2-methylsulfonyl- into 2-hydrazino-5-methoxypyrimidine (hydrazine hydrate in dimethyl sulfoxide at 100°, 71%; also analogues).⁴³⁹⁹ The aminolyses of pyrimidines bearing both chloro and alkylsulfonyl substituents have given unexpected products. Thus, 5-fluoro-2-methylsulfonylpyrimidine (109) reacted with benzylamine or hydrazine to give 5-benzylamino- (110, R = CH₂Ph) or 5-hydrazino-2-methylsulfonylpyrimidine (110, R = NHNH₂), respectively, perhaps because the 5-fluoro substituent is so activated by the powerfully electron-withdrawing alkylsulfonyl group;⁴³⁹⁹ 4-chloro-2-ethylsulfonyl-6-phenylpyrimidine (111) in ethanolic ammonia at 25° gave a mixture of 4-amino-2-ethylsulfonyl- (112), 2-amino-4-ethylsulfonyl- (113), and 2-amino-4-chloropyrimidine (114). The explanation given for these and other such data leaves much to be desired, although the facts cannot be in dispute.⁵⁰³⁸

The conversion of a *sulfone into a nitrile* is represented by the reaction of 5-dimethylaminomethyleneamino-2-methylsulfonyl- (115, R = SO₂Me) with potassium cyanide in dimethylformamide at 100° to give 2-cyano-5-dimethylaminomethyleneaminopyrimidine (115, R = CN) in 85% yield;⁴³⁸³ of 5-*p*-heptyloxyphenyl-2-methylsulfonyl-

with sodium cyanide in dimethyl sulfoxide at 40–60° to give 2-cyano-5-*p*-heptyloxyphenylpyrimidine (79%);⁴⁵⁴⁵ of 5-chloro(or bromo)-2-methylsulfonylpyrimidine with sodium cyanide in dimethyl sulfoxide at 10° to give 5-chloro(or bromo)-2-cyanopyrimidine (75%); and of 5-fluoro-2-methylsulfonylpyrimidine with sodium cyanide to give, according to conditions, 2-cyano-5-fluoro- or 2-cyano-5-methylsulfonylpyrimidine (an explanation of the latter is given towards the end of the preceding Sect. A).⁴³⁹⁹



Other reactions are illustrated in the conversion of 5-methoxy-2-methylsulfonyl- into 2-mercapto-5-methoxypyrimidine (116) by heating in aqueous sodium hydrogen sulfide;⁴³⁹⁹ of 4-methoxy-2-methylsulfinyl- (117) into 2-mercapto-4-methoxy- (118, $\text{R} = \text{H}$) (sodium hydrogen sulfide), and thence into 4-methoxy-2-methylthio-6-nitroaminopyrimidine (118, $\text{R} = \text{Me}$) (34% overall) by methyl iodide/alkali;⁴⁶⁵⁶ of 4-amino-6-methoxy-2-methylsulfonyl- into 4-amino-2-mercapto-6-methoxypyrimidine, plus a little of its *S*-methyl derivative, using aqueous sodium hydrogen sulfide (probably two independent reactions, displacement and reduction);⁴⁶⁵⁶ of 5-methoxy-4-methoxy-methyl-2-methylsulfonyl- into 5-methoxy-4-methoxymethyl-2-sulfanilamidopyrimidine (119, $\text{R} = \text{OMe}$) (27%) by heating with potassium carbonate and sulfanilamide without solvent at 120°;⁴³⁹⁷ of 5-methoxy-4-methyl-2-methylsulfonyl- into 5-methoxy-4-methyl-2-sulfanilamidopyrimidine (119, $\text{R} = \text{H}$) (29%) by a similar process at 150°;⁴³⁹⁷ of 4-benzyloxy-2-methylsulfonyl- into 4-benzyloxy-2-diethoxycarbonylmethylpyrimidine (38%) by treatment with diethyl sodiomalonate;⁵⁹²⁵

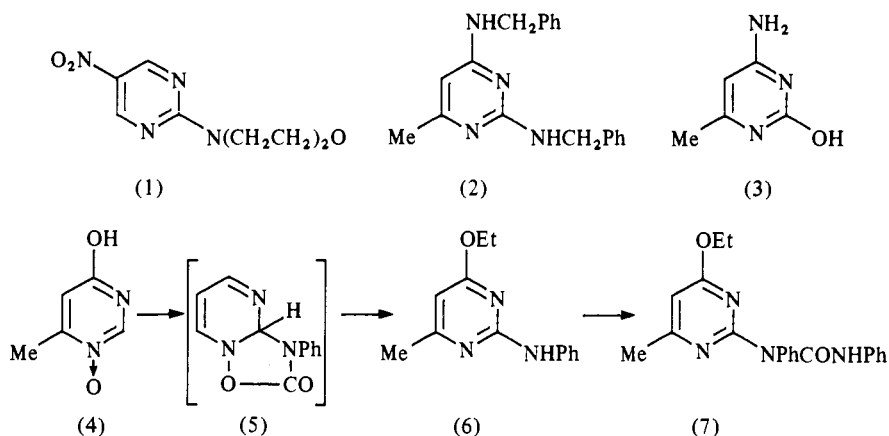
of 2,4-dimethyl-6-phenylsulfonyl- (121) into 4-dicyanomethyl-2,4-dimethyl- (120) or 2,4-dimethyl-6-2'-oxocyclohexylpyrimidine (122) by warming in tetrahydrofuran containing sodium hydride and malononitrile or cyclohexanone, respectively;⁶⁰⁸² and of 4,6-dimethyl-2-methylsulfinylmethyl- into 2-dimethoxymethyl-4,6-dimethylpyrimidine (81%) by refluxing in methanol containing 2 mol of iodine.⁶⁰⁰⁸

CHAPTER IX

The Aminopyrimidines (*H* 306, *E* 230)

1. Preparation of 2- and 4/6-Aminopyrimidines (*H* 306, *E* 230)

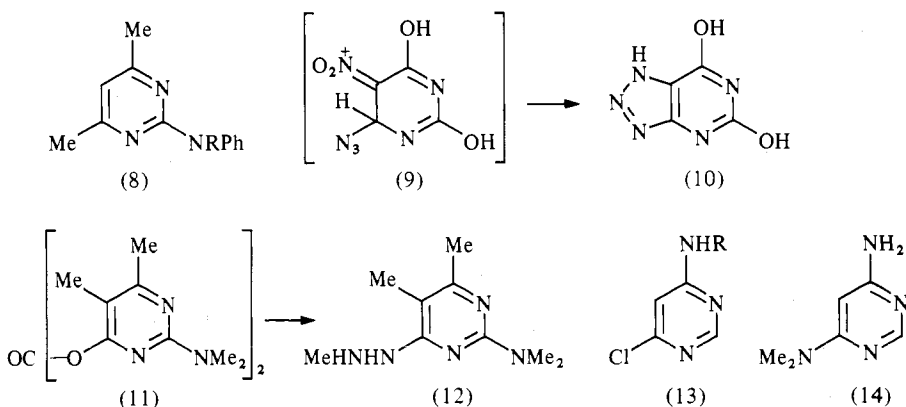
All the usual ways for making such aminopyrimidines are discussed elsewhere: *by primary synthesis* in Ch. II and III;⁶⁵³³ *from hydroxypyrimidines* in Ch. VII, Sect. 6.E; *from alkoxyprymidines* in Ch. VII, Sect. 7.C; *from halogenopyrimidines* in Ch. VI, Sect. 5.B and 5.C; *from mercaptopyrimidines* in Ch. VIII, Sect. 1.D(5); *from alkylthiopyrimidines* in Ch. VIII, Sect. 2.C(3); *from sulfopyrimidines* in Ch. VIII, Sect. 4.B; *from alkylsulfonyl- or alkylsulfinylpyrimidines* in Ch. VIII, Sect. 5.B; and *by Dimroth rearrangement* in Ch. X, Sect. 2.B. A few random examples (not given elsewhere) from the above processes include the condensation of α -nitromalondialdehyde with *S*-methylthiourea in aqueous morpholine to give directly 2-morpholino-5-nitropyrimidine (1),⁵²⁸⁵ the conversion of 2,4-dihydroxy- into 2,4-bisbenzylamino-6-methylpyrimidine (2) by heating with phosphoric



tribenzylamide [$\text{O} = \text{P}(\text{NHCH}_2\text{Ph})_3$] at 230° ;⁴⁸⁴⁹ the aminolysis of 2-hydroxy-4-methyl-6-methylthiopyrimidine by methanolic ammonia at 130° to give 4-amino-2-hydroxy-6-methylpyrimidine (3);⁶²⁰² a practical method for converting the awkwardly insoluble sulfate of 2,4,5-triamino-6-hydroxypyrimidine into its amenable dihydrochloride, using barium chloride;^{6247, 6405} and semi-quantitative data on the formation of 2-amino-4-phenylpyrimidine by the action of sodium amide in liquid ammonia on 4-phenylpyrimidine bearing the following 2-substituents: methylthio (72%), methylsulfonyl (68%), phenylthio (84%), phenylsulfonyl (87%), thiocyanato (32%), cyano (56%), and trimethylammonio (chloride, 62%).⁶⁰⁴⁰

C. By Direct or Indirect Amination (H 308)

Phenyl isocyanate reacted at 100° with 4-ethoxy-6-methylpyrimidine 1-oxide (4) to give initially the 1,3-dipolar cycloaddition intermediate (5), which then lost carbon dioxide to afford 2-anilino-4-ethoxy-6-methylpyrimidine (6) and thence, by reaction with more phenyl isocyanate, the final product 2-*N,N'*-diphenylureido-4-ethoxy-6-methylpyrimidine (7).⁵⁰⁸⁷ *N*-Phenylbenzimidoyl chloride ($\text{PhN}=\text{CPhCl}$) reacted with 4,6-dimethylpyrimidine 1-oxide to give benzanilide plus two products, 2-*N*-benzoylanilino- (8, $\text{R} = \text{Bz}$) and 2-anilino-4,6-dimethylpyrimidine (8, $\text{R} = \text{H}$). 4-Methylpyrimidine 3-oxide behaved similarly to give 2-*N*-benzoylanilino- and 2-anilino-4-methylpyrimidine.⁵⁸⁸⁷ When 2,4-dihydroxy-5-nitropyrimidine was heated with sodium azide in dimethylformamide, an initial nucleophilic attack by azide ion occurred at the 6-position (*de facto* amination) to give the complex (9), which underwent loss of nitrous acid to give 5,7-di-

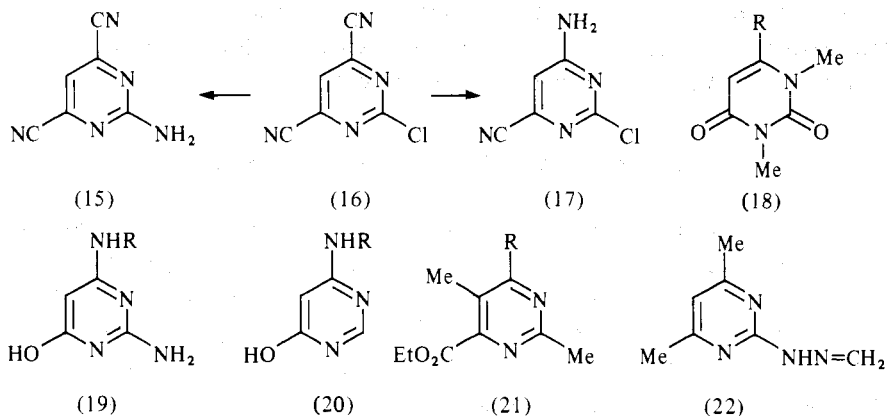


hydroxy-*v*-triazolo[4,5-*d*]pyrimidine (10). Related nitropyrimidines behaved similarly, thereby affording an excellent route to such triazolo-pyrimidines.^{5406, 5408} Methylhydrazine reacted with bis(2-dimethylamino-5,6-dimethylpyrimidin-4-yl) carbonate (11) with loss of carbon dioxide to give 2-dimethylamino-4,5-dimethyl-6- β -methylhydrazino-pyrimidine (12) in good yield.⁴⁶⁷⁸ On treating 1-methyl-4-phenylpyrimidinium iodide with cyanamide or *O*-methylurea and so on in basic media, ring-fission followed by transamination and reclosure occurred in give 2-amino-4-phenylpyrimidine. 2-Amino-5-phenylpyrimidine was made similarly, and the mechanism has been verified.⁴⁶⁹⁰

H. By Other Methods Including Transamination (*H* 310, *E* 230)

Aminopyrimidines may naturally be made *from their acyl derivatives* or Schiff bases. For example, 4-chloro-6-formamido- (13, *R* = CHO) in warm aqueous ammonia gave 4-amino-6-chloropyrimidine (13, *R* = H),⁵⁸⁵² and 4-chloro-6-dimethylaminomethyleneaminopyrimidine in strong alkali gave 4-amino-6-dimethylaminopyrimidine (14) by initial splitting of the Schiff base to 4-amino-6-chloropyrimidine (13, *R* = H) and subsequent reaction with dimethylamine produced from the other part (dimethylformamide) of the Schiff base.⁵⁸⁵²

The *aminolysis of cyanopyrimidines* can sometimes give aminopyrimidines quite effectively. Thus, 2-chloro-4,6-dicyanopyrimidine (16) reacted with ammonia in tetrahydrofuran to give only the expected 2-amino-4,6-dicyanopyrimidine (15), but a similar reaction in benzene gave a separable mixture of equal parts of the same product (15) and 4-amino-2-chloro-6-cyanopyrimidine (17),⁴⁸²⁰ 4-cyano- (18, *R* = CN) in boiling butylamine or hydrazine hydrate gave 4-butylamino (or



hydrazino)-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (18, R = NHBu or NHNH₂) in 76 or 51% yield, respectively;⁴⁹³⁹ and 4,5-dicyano- similarly gave 4-butylamino-5-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (99%).⁴⁹⁴⁷ Hydroxyiminomethyl groups can also be displaced; 2,4-dihydroxy-6-hydroxyiminomethyl-5-nitropyrimidine in boiling aqueous ethylamine or butylamine gave 4-ethyl- (or butyl)amino-2,6-dihydroxy-5-nitropyrimidine in unstated yield.⁵⁵⁷⁶

The process of *transamination* can be most useful. Thus, 4-amino-6-hydroxy- gave 4-hydroxy-6-morpholino-2-phenylpyrimidine (50%) by simply boiling in morpholine containing a little hydrochloric acid to provide some cation;⁴⁹⁷² 4-amino- gave 4-hydrazino-2,6-dihydroxypyrimidine (82%) on refluxing in aqueous hydrazine;⁵⁹⁶⁸ 2-amino-4-chloro- gave 2,4-dianilino-6-hydroxypyrimidine (43%) on treatment with aniline at 185°;⁴⁶³⁵ 2,4-diamino-6-hydroxy- (19, R = H) gave 2-amino-4-benzylamino-6-hydroxy- (19, R = CH₂Ph) or 2-amino-4-hydroxy-6-β-hydroxyethylaminopyrimidine (19, R = CH₂CH₂OH) on boiling in ethylene glycol containing benzylamine or ethanolamine, respectively;⁴⁸⁶³ 2(or 4)-trimethylammonio-pyrimidine chloride gave 2(or 4)-propylamino(or hydrazino)pyrimidine on warming with neat amine;⁵³⁴⁰ 2-trimethylammonio-5-nitropyrimidine chloride gave 5-nitro-2-propylaminopyrimidine (72%) by standing in propylamine at 20° for 5 min;⁵³⁴⁰ 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo- gave 1,2,3,4-tetrahydro-6-γ-hydroxypropylamino-1,3-dimethyl-2,4-dioxypyrimidine by heating at 190° with γ-aminopropanol and, without isolation, the product was converted by thionyl chloride into 4-γ-chloropropylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine in 67% overall yield;⁴⁵⁵⁰ and other examples have been reported.^{4987, 6252}

An interesting *hydrazinolysis reaction* is that of 5-cyano-4-phenyl-2,6-bistrichloromethylpyrimidine with neat hydrazine at 100° to give successively 5-amino-2-hydrazino-4-phenyl-6-trichloromethyl- and 5-cyano-2,4-dihydrazino-6-phenylpyrimidine.⁵⁹⁵³

I. Modification of Existing Amino Groups (H 311)

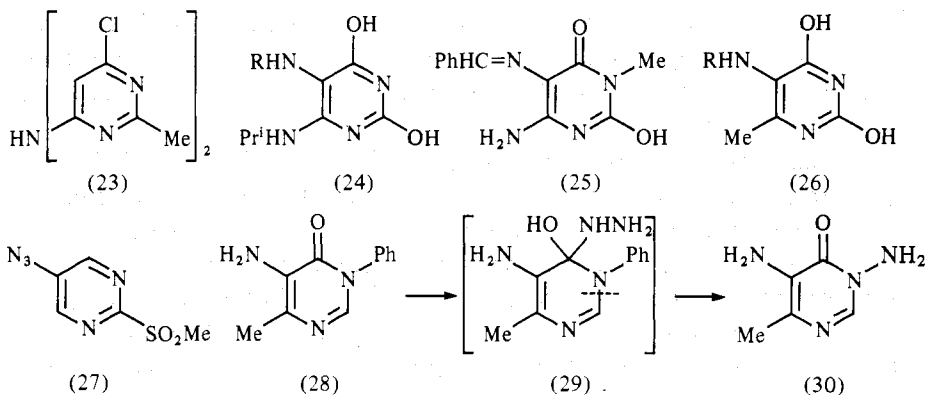
Modification of an amino group (in the generic sense) can be very useful. Several such procedures are exemplified in the reduction of 4-hydrazino- to 4-amino-6-methyl-2-pyridin-4'-ylpyrimidine (*c.* 75%) by hydrogenation over Raney nickel;⁶²⁹⁸ in the reduction of 4-hydrazino- (20, R = NH₂) to 4-amino-6-hydroxypyrimidine (20, R = H) (79%) by boiling with Raney nickel in aqueous ammonia;⁵⁴⁹¹ in the conversion of

4- β,β -diphenylhydrazino-2-hydrazino- into 2-amino-4- β,β -diphenylhydrazino-5-nitropyrimidine by stirring with silver acetate in water (this is an unique reaction; complete removal of the hydrazino group was expected);⁶¹⁴⁶ in the reduction of 4-azido- (21, R = N₃) to 4-amino-6-ethoxycarbonyl-2,5-dimethylpyrimidine (21, R = NH₂) in 97% yield by hydrogenation over palladium;⁶¹⁴⁰ in the alkylation of 4-amino-2-dimethylamino(or methoxy)pyrimidine to 4- β,β -diethoxycarbonylvinylamino-2-dimethylamino(or methoxy)pyrimidine by heating with diethyl ethoxymethylenemalonate at 130°;^{4980, 5018} in the similar preparation of 4- β,β -diethoxycarbonylvinylamino-2-pyrid-3' (or 4')-ylpyrimidine (160–170°; 5 h; 82%);⁶⁵⁰⁹ in the indirect alkylation of 2-hydrazino-4,6-dimethylpyrimidine by treatment with ethanolic paraformaldehyde to give 4,6-dimethyl-2-methylenehydrazinopyrimidine (22) and subsequent hydrogenation over palladium to give 4,6-dimethyl-2- β -methylhydrazinopyrimidine (70%);⁶¹¹⁵ in the rather rare dealkylation of 4-*t*-butylamino-2-chloro-5-fluoropyrimidine (with hydrolysis of the chloro substituent) to 4-amino-5-fluoro-2-hydroxypyrimidine by boiling in concentrated hydrochloric acid;⁵⁹⁶² in the loss of methyl chloride from 4-phenyl-6-trimethylammoniopyrimidine chloride on warming in dimethyl sulfoxide to give 4-dimethylamino-6-phenylpyrimidine;⁶¹¹⁷ in the similar loss of ethyl chloride from 2-chloro-4-methyl-6-triethylammoniopyrimidine chloride, during attempted isolation, to give 2-chloro-4-diethylamino-6-methylpyrimidine;⁴⁴⁶⁶ in the apparent oxidation of 4-amino- to 4-hydroxyamino-2,5,6-triphenylpyrimidine by hydrogen peroxide in acetic acid;⁴⁶¹⁴ in the peculiar reaction of 4-amino-6-chloro(or hydroxy)-2-methylpyrimidine in phosphoryl chloride at 230° (“under reflux”; no mention of a sealed tube) to give bis(6-chloro-2-methylpyrimidin-4-yl)amine (23) in 65% yield.^{4859, 4967}

2. Preparation of 5- and *N*-Aminopyrimidines (*H* 313, *E* 234)

Most 5-aminopyrimidines have been made by reduction of the corresponding nitro- (Ch. V, Sect. 1.B), nitroso- [Ch. V, Sect. 2.B(1)], or arylazopyrimidines (Ch. V, Sect. 3.B); some have been prepared by the aminolysis of 5-halogenopyrimidines (Ch. VI, Sect. 6.A).

The remaining miscellaneous methods are exemplified in the *deacylation* of 5-formamido- (24, R = CHO) to 5-amino-2,4-dihydroxy-6-isopropylaminopyrimidine (24, R = H) by boiling with methanolic hydrogen chloride;⁴⁶²⁷ in the *hydrolysis of the Schiff base*, 2-butoxy-5-dimethylaminomethyleneaminopyrimidine, by hot aqueous potassium carbonate to give 5-amino-2-butoxypyrimidine (55%),⁶⁵¹⁰ and of 2-



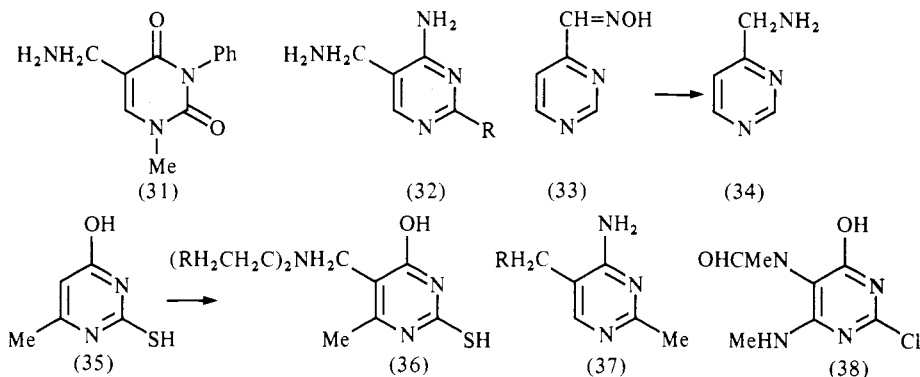
amino-5-dimethylaminomethyleneaminopyrimidine, by aqueous sodium carbonate to give 2,5-diaminopyrimidine (85%);⁴³⁸⁰ in the hydrolysis of 5-dimethylaminomethyleneamino-2-mercaptopyrimidine by dilute sulfuric acid to give 5-amino-2-mercaptopyrimidine (87%);⁴³⁸⁰ in the *indirect benzoylation* of the 5-amino group in 5,6-diamino-3-methyluracil by treatment with benzaldehyde to give the Schiff base, 6-amino-5-benzylideneamino-3-methyluracil (25), and subsequent hydrogenation over Raney nickel to afford 6-amino-5-benzylamino-3-methyluracil (*c.* 50% overall);⁵⁸⁵⁰ in the similar transformation of 2,4,5-triamino- into 2,4-diamino-5-benzylideneamino- and thence into 2,4-diamino-5-benzylamino-6-hydroxypyrimidine (71%);⁴⁶⁴⁷ in the *direct alkylation* of the 5-amino group in 5-amino-2,4-dihydroxy-6-methylpyrimidine (26, R = H), by treatment in dimethylformamide with 1-bromo-2-fluoroethane and triethylamine, to give 5- β -fluoroethylamino-2,4-dihydroxy-6-methylpyrimidine (26, R = CH₂CH₂F) in 70% yield;⁴⁷⁶⁹ in the conversion by *nitrous acid* of 5-hydrazino- into 5-azido-2-methylsulfonylpyrimidine (27);⁶²⁵⁶ in the *thermal rearrangement* of 5-allylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo- into 4-allyl-5-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (24%);⁵⁴¹⁵ in the *photochemical reaction* of 4-azido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine with dimethylamine to give 5-amino-4-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (59%) (several other amines gave similar products);⁴⁹⁴² in the equally complicated *addition of hydroxylamine-O-sulfonic acid* to 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine with subsequent loss of sulfate and so on to afford 5-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine;⁵¹⁴³ and in the *hydrazinolysis* of the 5-hydroxy group in 2,4,5,6-tetrahydroxy-pyrimidine to give 5-hydrazino-2,4,6-trihydroxypyrimidine (33%) (also related compounds).⁴⁷⁹³

(29). 5049, 6076

A. By Reduction of Nitriles (*H* 316, *E* 237)

aqueous acid over palladium.⁵⁷⁹³

above).



C. By the Mannich Reaction (*H* 318, *E* 237)

The attachment of an aminoalkyl group to an activated methyl group on pyrimidine or to the 5-position of pyrimidine has been covered in Ch. IV, Sect. 2.C(7). A Mannich reaction was also used to convert 4-hydroxy-2-mercapto-6-methylpyrimidine (35) into its 5-diethylaminomethyl (36, $R = H$) or its 5-(bis- β -chloroethyl)amino-methyl derivative (36, $R = Cl$) and for like purposes, employing the appropriate secondary amine and formalin.⁴⁵⁹³

D. By Primary Syntheses (*H* 318, *E* 238)

Several examples of this rather rare route have been given in Ch. II and III. An indirect example is the condensation of acetamide with the aldehydonitrile, 2-dimethoxymethyl-3-ethoxypropionitrile to give, *via* 4-amino-5-ethoxymethyl-2-methylpyrimidine (37, $R = OEt$), 5-acetamidomethyl-4-amino-2-methylpyrimidine (37, $R = NHAc$) and thence 4-amino-5-aminomethyl-2-methylpyrimidine (37, $R = NH_2$) in good yield.⁵⁸²⁹

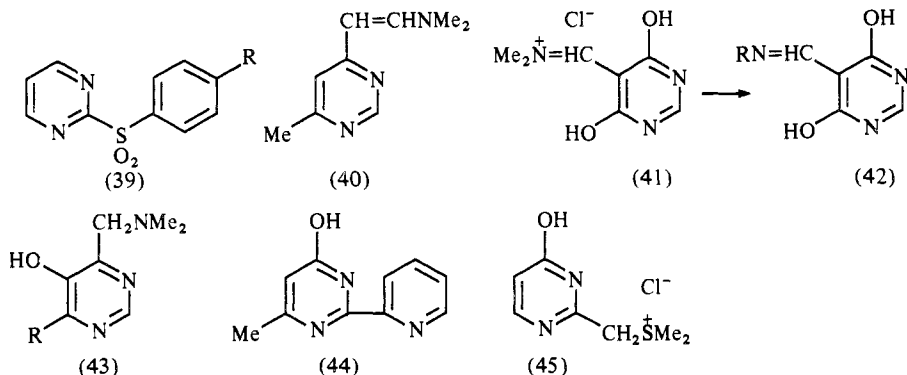
E. By Other Routes (*H* 319, *E* 238)

Several other minor routes to extranuclear aminopyrimidines are exemplified briefly below.

From acylaminopyrimidines. 2-Chloro-4-hydroxy-6-methylamino-5-*N*-methylformamido- (38, $R = CHO$) gave 2,4-dihydroxy-5,6-bis-methylaminopyrimidine (82%) on boiling in ethanolic hydrogen chloride;⁶⁰⁹⁶ 1- δ -phthalimidobutyluracil gave 1- δ -aminobutyluracil (76%) on boiling in 6 M hydrochloric acid;⁵³⁰³ and 4-*p*-acetamido- gave 4-*p*-amino-benzylamino-2,6-dihydroxypyrimidine (54%) on heating in dilute sodium hydroxide.⁵⁴⁸¹

By reduction of azidopyrimidines. Hydrogenation of 4- α -azido-ethylpyrimidine over platinum gave 4- α -aminoethylpyrimidine in low yield; 5- α -aminoethylpyrimidine was made similarly.⁴³⁷⁹

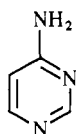
By reduction of nitropyrimidines. Examples of extranuclear aminopyrimidines being made from their nitro analogues are given in Ch. V, Sect. 1.3. Another is the very gentle reduction of 2-*p*-nitrophenylsulfonylpyrimidine (39, $R = NC_2$) by iron powder in dilute acetic acid to give 2-*p*-aminophenylsulfonylpyrimidine (39, $R = NH_2$) (72%) without affecting the sulfone linkage.⁵⁵⁷⁴



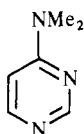
By attachment of an amino-bearing portion. 4,6-Dimethylpyrimidine reacted at one of its methyl groups with the dimethyl acetal of dimethylformamide on the water bath to give 4-β-dimethylaminovinyl-6-methylpyrimidine (40) in only 6% yield. In contrast, similar treatment of 2,4-dimethoxy-6-methyl-5-nitropyrimidine (with a more activated methyl group) afforded 4-β-dimethylaminovinyl-2,6-dimethoxy-5-nitropyrimidine in 98% yield.⁶⁴⁰² The reaction of 4,6-dihydroxypyrimidine with dimethylformamide/phosgene gave 5-dimethyliminomethyl-4,6-dihydroxypyrimidine chloride (41) (93%), which reacted with methylamine or phenylhydrazine to give 4,6-dihydroxy-5-methyliminomethylpyrimidine (42, R = Me) or the 5-phenylhydrazonomethyl analogue (42, R = NHPH), respectively, in *c.* 70% yield.⁵⁷⁹⁴ 5-Hydroxypyrimidine reacted with neat bisdimethylaminomethane ($\text{Me}_2\text{N}-\text{CH}_2-\text{NMe}_2$) under reflux to give 4-dimethylaminomethyl-5-hydroxypyrimidine (43, R = H) in 26% yield; when heating was continued for much longer, 4,6-bis(dimethylaminomethyl)-5-hydroxypyrimidine (43, R = CH_2NMe_2) was obtained as the main product in 53% yield.⁶³⁴⁷ 4-Hydroxy-6-methylpyrimidine reacted at the 2-position with pyridine *N*-oxide in a little pyridine containing a platinum/palladium catalyst to give 4-hydroxy-6-methyl-2-pyrid-2'-ylpyrimidine (44) (*c.* 40%); 4,6-dimethyl-2-pyrid-2'-ylpyrimidine was made similarly.⁵¹¹⁶ 2,4-Diamino-6-chloropyrimidine underwent a quite normal nucleophilic reaction with sodium β-dimethylaminoethoxide in xylene to give 2,4-diamino-6-β-dimethylaminoethoxypyrimidine (74%).⁵⁷⁴⁴ The aminolysis of extranuclear chloropyrimidines is discussed in Ch. VI, Sect. 7. An example of the similar aminolysis of an extranuclear dimethylsulfonio group is seen in the conversion of 2-dimethylsulfoniomethyl-4-hydroxypyrimidine chloride (45) into 2-dimethylaminomethyl-4-hydroxypyrimidine (73%) by standing in methanolic dimethylamine at 25°.⁶¹¹⁹

4. Properties of Aminopyrimidines (*H* 320, *E* 241)

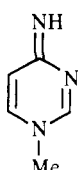
Apart from some pre-1950 suggestions, there has never been any real doubt that amino- and alkylaminopyrimidines existed as such rather than as dihydroimino *tautomers*. As early as 1955, ultraviolet comparisons of 2-aminopyrimidine with 2-dimethylaminopyrimidine and 1,2-dihydro-2-imino-1-methylpyrimidine under carefully controlled conditions of pH showed that 2-aminopyrimidine existed in aqueous solution as such.¹¹⁷⁷ However, a similar comparison of 4-aminopyrimidine (46) with 4-dimethylaminopyrimidine (47), 1,4-dihydro-4-imino-1-methylpyrimidine (48), and 1,6-dihydro-6-imino-1-methylpyrimidine (49) could not be completed until 1971 when the imine (49) was at last made and it was shown that 4-aminopyrimidine, too, existed as such.⁵⁶⁶⁵ Meanwhile, two authoritative reviews of the tautomerism of amino and other tautomeric pyrimidines appeared and should be consulted for details of other phenomena used in such studies.^{6406, 6407}



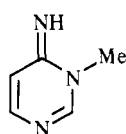
(46)



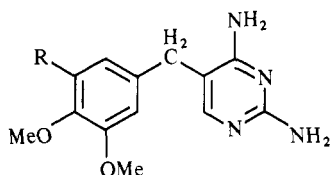
(47)



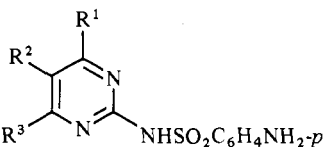
(48)



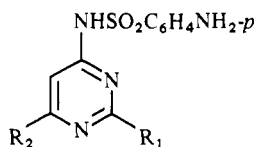
(49)



(50)



(51)



(52)

Several interesting aspects of the *spectra* of aminopyrimidines have been reported. In 1973 a most useful spectral correlation was noticed between the cation of an aminoheterocycle and the neutral species of the corresponding hydroxyheterocycle.⁵³³⁴ In the context of pyrimidines, the Albert–Taguchi rule might read: “the cation of a 2-aminopyrimidine has an ultraviolet spectrum similar to that of the corresponding 2-hydroxypyrimidine as neutral species; it does not apply to 4- or 5-aminopyrimidines.” This is complementary to the older Jones rule^{6408, 6409} which might be paraphrased in the present context²⁷⁶⁰ as “the neutral species of a 2-, 4-, or 5-aminopyrimidine has an ultraviolet spectrum similar to that of the corresponding 2-, 4-, or 5-hydroxy-

pyrimidine as anion." Data and commentary on the ultraviolet spectra of amino and other pyrimidines have been published.^{6412, 6413}

Other spectral areas of interest include reports on the mass spectra of 4-aminopyrimidines,^{4805, 6410} barriers to rotation in 4-dialkylaminopyrimidines and fused pyrimidines as revealed in ¹H nmr spectra,^{4581, 6315} correlation of the chemical shifts for amino-group protons with the *sigma* constants of substituents in the substituted aminopyrimidines,⁵⁸²⁵ ¹⁵N nmr studies of aminopyrimidines,^{6092, 6113, 6366} and a general review of ¹H nmr spectra of pyrimidines.⁶³⁶⁸ For recent non-proton nmr information, see Ch. XIII, Sect. 3.

The ionization constants of aminopyrimidines and related systems have been discussed^{5327, 6411} and, more specifically, those of 2,4-diaminopyrimidines have been studied in some detail.^{5397, 5400} Practical aspects of the measurement of pK_a values,⁶⁴¹³ a manual for the prediction of ionization constants,⁶⁴¹⁴ and massive updating compilations of pK_a values from the literature^{6415, 6416} have appeared.

The enormous success⁶⁴²⁵ of *trimethoprim* (50, R = OMe) and *diaveridine* (50, R = H) in combination with sulfonamides against human bacterial infections and avian coccidial infections, respectively, and their disappointing performances as antimalarial drugs,⁵⁵³⁵ have led to considerable work on improved preparative procedures and the synthesis of analogues for testing in all three areas. The field has been reviewed.^{4544, 4565, 4896, 4905, 5459, 5460, 5467, 5474, 5806, 5892, 5939, 6379, 6502, 6504}

The "sulfapyrimidine" type of drug is still used quite extensively in general antibacterial therapy, although the actual agents in use have changed quite markedly. Thus, at present, *sulfadiazine* (51, R¹ = R² = R³ = H) is still widely used, *sulfamerazine* (51, R¹ = Me, R² = R³ = H) is not used, the homologous *sulfadimidine* (51, R¹ = R³ = Me, R² = H) is little used although it still appears in pharmacopoeias, the isomeric *sulfasomidine* (52, R¹ = R² = Me) is used clinically, the 5-methoxy compound *sulfametoxydiazine* (51, R¹ = R³ = H, R² = OMe) is used, the dimethoxy compound *sulfadimethoxine* (52, R¹ = R² = OMe) is used, and the analogous *sulfametomidine* (52, R¹ = Me, R² = OMe) is also used. The practical pharmacology of sulfapyrimidines and related agents has been summarized.⁶⁴¹⁷

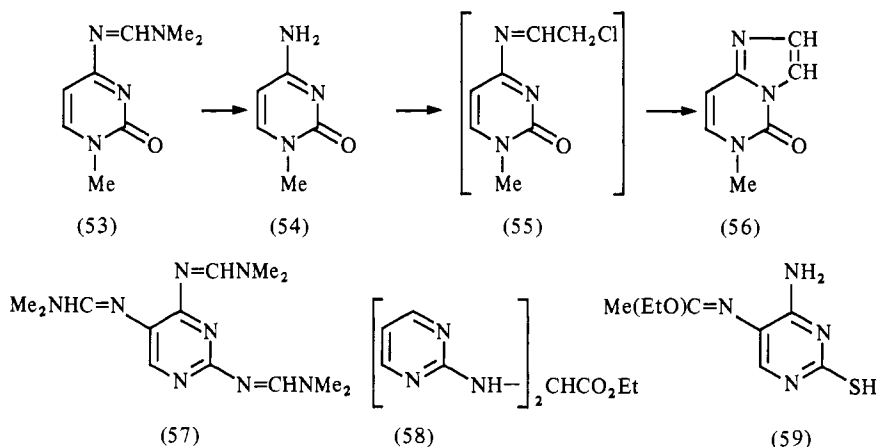
5. Reactions of Aminopyrimidines (H 321, E 243)

The conversion of *amino- into hydroxypyrimidines* is discussed in Ch. VII, Sect. 1.D (2- and 4/6-aminopyrimidines), Sect. 2 (5-amino-

pyrimidines), and Sect. 3.B (extranuclear aminopyrimidines). The conversion of *amino- into halogenopyrimidines* is covered in Ch. VI, Sect. 1.C–F (2- and 4/6-aminopyrimidines), Sect. 2.C (5-aminopyrimidines), and Sect. 3.E (extranuclear aminopyrimidines).

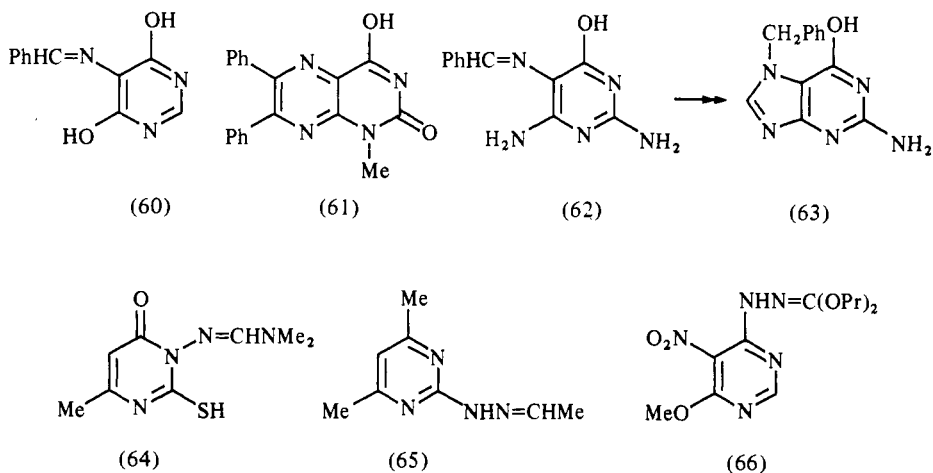
C. Formation of Schiff Bases (*H* 321, *E* 243)

All types of amino- and hydrazinopyrimidines will form Schiff bases with aldehydes or acetals. The formation and use of such derivatives *from 2- and 4/6-aminopyrimidines* can be seen in the treatment of 4-amino-2-hydroxypyrimidine (cytosine) with dimethylformamide dimethyl acetal in the presence of a little trifluoroacetic acid to give 4-dimethylaminomethyleneamino-1,2-dihydro-1-methyl-2-oxopyrimidine (53) (97%); the concomitant methylation evident in the product (53) afforded an excellent route to 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (54) (1-methylcytosine, 97%) by simply stirring the initial product (53) in aqueous ammonia.⁶¹⁷¹ The second product (54) was treated with chloroacetaldehyde to give a second (unisolated) Schiff base (55), which underwent spontaneous cyclization to 5,6-dihydro-6-methyl-5-oxoimidazo[1,2-*c*]pyrimidine (56).⁴⁷⁷² Likewise, 2,4,5-triaminopyrimidine and dimethylformamide dimethyl acetal under a variety of conditions gave the triple Schiff base, 2,4,5-tris-(dimethylaminomethyleneamino)pyrimidine (57),⁶²⁸⁹ 4-amino- gave 4-dimethylaminomethyleneamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-phenylazopyrimidine (85%),⁴⁹⁹⁵ and 4-amino-6-methoxypyrimidine gave several unisolated Schiff bases;⁴⁸⁶⁸ 2-aminopyrimidine reacted abnormally with ethyl glyoxylate to give ethyl bis(pyrimidin-2-



ylamino)acetate (58) in 70% yield.⁵⁵³⁸ 2-Phosphoranylideneamino-pyrimidine and *p*-nitrobenzaldehyde reacted slowly in boiling benzene to give 2-*p*-nitrobenzylideneaminopyrimidine (63%).⁶⁵³⁰

Schiff bases form even more easily from 5-aminopyrimidines; indeed, preferential reaction of the 5-amino group in 4,5-diaminopyrimidines can be achieved with ease. The general process is exemplified in the formation of 4-amino-5-1'-ethoxyethylideneamino-2-mercaptopyrimidine (59) (triethyl orthoacetate/acetic anhydride, 40%),⁵⁶⁷⁰ 4-amino-5-ethoxycarbonylmethyleneamino-6-hydroxy-2-mercaptopyrimidine (ethyl glyoxylate hemiacetal, 85%),⁴⁶⁶¹ 5-diethoxymethyleneamino-2-ethylthio-4-methyl-6-methylaminopyrimidine (tetraethoxymethane, 81%),⁵⁶⁷⁸ 5-ethoxymethyleneamino-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxypyrimidine (triethyl orthoformate, 75%),⁴⁹³⁶ 5-benzylideneamino-2,4-dihydroxypyrimidine (60) (benzaldehyde in boiling aqueous ethanol, 98%; also six substituted-benzylidene analogues),⁵³⁶⁷ 5,6-bisbenzylideneamino-1-methyluracil which cyclized at 180° to give 1-methyl-6,7-diphenylumazine (61),⁴⁶²⁹ 4-amino-5-benzylideneamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (ethanolic benzaldehyde under reflux, 83%; also many analogues),^{4986, 5006, 5164, 6030} and 2,4-diamino-5-benzylideneamino-6-hydroxypyrimidine (62) (82%), which was reduced by sodium borohydride to the 5-benzylamino analogue for conversion by diethoxymethyl acetate into 2-amino-7-benzyl-6-hydroxypurine (63).⁵⁶⁰⁸ The cyclization reactions of dimethylaminomethyleneaminopyrimidines (i.e., pyrimidinyl amidines) have been reviewed, along with those of similar derivatives in other series.⁵⁶⁰¹



A Schiff base *from an N-aminopyrimidine* has been made by using dimethylformamide/phosphoryl chloride to convert 3-amino- into 3-dimethylaminomethyleneamino-6-methyl-2-thiouracil (64), among other products.⁵¹⁵²

Schiff bases *from hydrazinopyrimidines* are very common, especially as intermediates, and they may equally well be designated as pyrimidinylhydrazones of aliphatic or aromatic aldehydes or ketones! They are exemplified in 2-ethylidenehydrazino-4,6-dimethylpyrimidine (65) (ethanolic acetaldehyde at 25°, 82%),⁶²⁶² 2,4-dimethyl-4-(1'-methylpropylidene)hydrazinopyrimidine (butan-2-one, 43%),⁵²⁶⁵ 4-dimethylaminomethylenehydrazinopyrimidine (dimethylformamide dimethyl acetal, 48%),⁴⁹¹⁰ 4-benzylidenehydrazino-6-chloropyrimidine (benzaldehyde in hot ethanolic acetic acid, 70%),⁴⁸⁰⁷ 6-(2'-ethylidene-1'-methylhydrazino)-3-methyluracil (92%),⁴⁹⁹⁷ 4-dipropoxymethylenehydrazino-6-methoxy-5-nitropyrimidine (66) (tetrapropoxymethane at 160°, *c.* 75%),⁵⁶⁸¹ 5-amino-4-chloro-6-diethoxymethylenehydrazinopyrimidine (tetraethoxymethane, *c.* 80%),⁵⁶⁷⁴ 4- α -ethoxyethylidenehydrazino-2(or 6)-methoxy-5-nitropyrimidine (triethyl orthoacetate, *c.* 70%),^{5634, 5660} 2-benzylidenehydrazinopyrimidine (benzaldehyde, 74%),⁵⁶⁹¹ and many others.^{4374, 4626, 4928, 4929, 4950, 4954, 4989, 4996, 4999, 5054, 5139, 5659, 5671, 6529}

D. Acyl Derivatives of Aminopyrimidines (*H* 324, *E* 245)

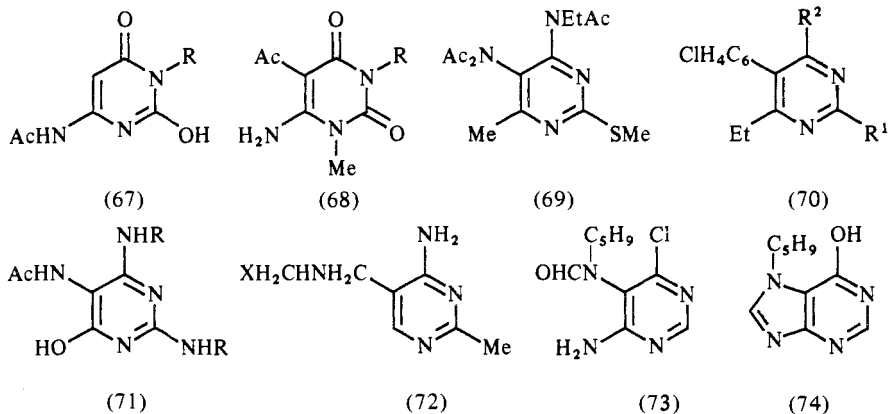
All primary and secondary aminopyrimidines will undergo acylation, usually by treatment with an acyl halide, acid anhydride, or the like, and often in pyridine. Selected examples are given briefly below under several categories.

(1) *Acetylation and Haloacetylation* (*H* 324, *E* 245)

The following acetamido- and halogenoacetamidopyrimidines were prepared from the corresponding aminopyrimidines by using the given reagents: 5-acetamido-4,6-diamino-2-phenylpyrimidine (glacial acetic acid under reflux),⁵³⁹⁹ 2,4,6-triamino-5-chloroacetamidopyrimidine (chloroacetic acid, 51%),⁵³⁸⁶ 4-acetamido-2-hydroxypyrimidine (acetic anhydride in pyridine at 100°),⁵³⁸⁹ 2-*p*-acetamidophenylsulfonylpyrimidine (acetic anhydride in pyridine, 89%),⁵⁵⁷⁴ 2-acetamido-4-chloro-6-hydroxy-5-nitropyrimidine (acetic anhydride and a little sulfuric acid, *c.* 80%),⁵⁶³⁷ 5-acetamido-2,4-dimercapto-6-methyl-

pyrimidine (boiling acetic anhydride, 61%),⁵⁶⁸⁹ 2-acetamido-4-dimethoxymethyl-6-hydroxypyrimidine (acetic anhydride at 100°, 97%),⁵³⁰⁰ 2-acetamido-4-methoxy-6-methoxycarbonylmethylpyrimidine,⁵²⁴³ 2,4-diacetamido-6-piperidinopyrimidine 3-oxide (acetic anhydride at 25°, 70%),^{3508, 5606} 4-acetamido-2-dimethylamino-6-hydroxy-(or methoxy)pyrimidine (acetic anhydride),⁴⁶³³ 4-acetamido-5-3',5'-dimethoxyphenylpyrimidine (acetic anhydride and a little sulfuric acid, 49%),⁵¹⁰⁸ 4-amino-6-benzylamino-5-trifluoroacetamidopyrimidine (trifluoroacetic anhydride in benzene, 53%),⁴⁷⁹⁴ 4-acetamido-2,6-dihydroxy-5-methoxypyrimidine (acetic anhydride/sodium acetate under reflux),⁵⁷⁰⁸ 2- β -acetylhydrazino-4,6-dihydroxypyrimidine (acetic anhydride, 76%),⁴⁷²¹ 4-methylamino-5-trifluoroacetamidopyrimidine (trifluoroacetic acid/trifluoroacetic anhydride; main product was 9-methyl-8-trifluoromethylpurine),⁶²⁶⁹ 2-acetamido-4-hydroxy-6-methoxycarbonylpyrimidine (acetic anhydride at 110°, 61%),⁵⁵¹¹ 2-chloroacetamido-4-hydroxy-6-methylpyrimidine (chloroacetyl chloride in dioxane under reflux; 50%),⁴⁵⁷³ 5-butyl-2-chloroacetamido-4-hydroxy-6-methylpyrimidine (chloroacetyl chloride in dimethylformamide at 25°, 70%),⁵³⁹² 4-cyanoacetamido-2-dimethylamino-5-nitropyrimidine (cyanoacetyl chloride at 25°),⁶²⁹⁵ 4-acetamido-6-methoxycarbonyl-2,5-dimethylpyrimidine (acetyl chloride/pyridine/chloroform, 57%),⁶¹⁴⁰ and others.⁵⁷⁰⁴

The acetylation of 4-amino-2,6-dihydroxypyrimidine and its (nuclear)*N*-methylated derivatives by boiling acetic anhydride/acetic acid is of interest. Thus, 4-amino-2,6-dihydroxypyrimidine and 6-amino-3-methyluracil gave their respective acetamido derivatives (67, R = H or Me), whereas 6-amino-1-methyluracil and 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine gave their respective 5-acetyl derivatives (68, R = H or Me).⁵⁴⁴⁶ When 5-amino-4-ethylamino-6-methyl-2-methylthiopyrimidine was treated with acetic anhydride in ethanol at 25°, only monoacetylation occurred to give the 5-acetamido analogue but, when neat acetic anhydride under reflux was used, the triacetyl derivative, 5-diacetyl-amino-4-*N*-ethylacetamido-6-methyl-2-methylthiopyrimidine (69), resulted.⁵³⁴⁸ Similarly, acetylation of pyrimethamine (2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine) gave the mono- to tetraacetyl derivatives (70, R¹ = NHAc, R² = NH₂), (70, R¹ = R² = NHAc), (70, R¹ = NHAc, R² = NAc₂), or (70, R¹ = R² = NAc₂) according to conditions.⁵⁹⁵² Likewise, 2,4,5-triamino-6-hydroxypyrimidine in refluxing acetic acid gave only 5-acetamido-2,4-diamino-6-hydroxypyrimidine (71, R = H), whereas in refluxing acetic anhydride it gave 2,4,5-triacetamido-6-hydroxypyrimi-



dine (71, R = Ac).⁴⁶⁴² Not unexpectedly, 2,4-diamino-5-hydroxy-6-methylpyrimidine gave either 2,4-diacetamido-5-hydroxy- or 2,4-diacetamido-5-acetoxymethylpyrimidine, according to the severity of conditions.⁵⁰⁴⁵ 4-Amino-5-*p*-chlorophenyl- gave 5-*p*-chlorophenyl-4-diacetylaminopyrimidine (acetic anhydride/boiling pyridine, 75%).⁵⁴⁷⁷

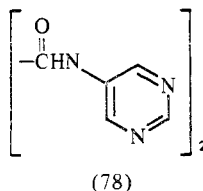
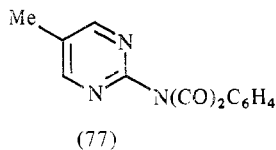
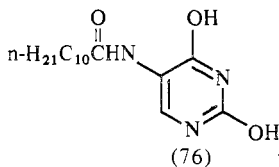
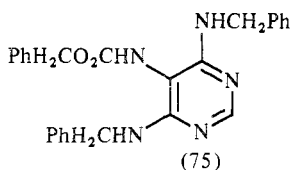
(2) Formylation (*H* 325, *E* 246)

The usual formylating agent is boiling 90–98% formic acid. Its use is illustrated in the conversion of appropriate aminopyrimidines into 5-formamido-2,4-dimercapto-6-methylpyrimidine (62%),⁵⁶⁸⁹ 4-chloro-5-formamido-6-methylthiopyrimidine (93%),⁴³⁵⁸ 4-dimethylamino-5-formamido-6-methyl-2-methylthiopyrimidine (c. 55%),⁵³⁴⁶ 4- β -formylhydrazino-6-hydroxy-5-nitropyrimidine (78%),⁵²³¹ 6-amino-5-*N*-methylformamido-1-methyluracil,⁶²³¹ 4-amino-5-formamido-1,2-dihydro-1-methyl-2-thiopyrimidine (c. 80%),⁵³⁴⁴ 4- β -formylhydrazino-6-methyl-2-methylthiopyrimidine (54%),⁵⁶⁹⁷ 2-dimethylamino-5-formamido-4-methyl-6-methylaminopyrimidine (>90%),⁵⁶⁷⁰ 5-formamido-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxypyrimidine (89%),⁴⁹³⁶ and others.⁴⁷²¹ In addition, 4-amino-5-aminomethyl-2-methylpyrimidine underwent formylation on heating with alcoholic formamidine hydrochloride to give 4-amino-5-formamidomethyl-2-methylpyrimidine (72, X = O); the corresponding thioformamidomethyl compound (72, X = S) was made also.⁵¹⁷⁴ The alkylation of a primary amino group can be facilitated by initial formylation, and the product may be of use to make, for example, a 7-alkylpurine. Thus, 4-amino-6-chloro-5-formamidopyrimidine underwent alkylation by bromocyclopentane in dimethylformamide containing potassium

carbonate to give 4-amino-6-chloro-5-*N*-cyclopentylformamidopyrimidine (73), which underwent cyclization (and hydrolysis) in boiling formic acid to give 7-cyclopentyl-6-hydroxypurine (74);⁵²³³ there are other examples.^{5346, 6231}

(3) Other Acylations (*H* 327, *E* 247)

Some examples from the many other acylations described include the formation of 4-hydroxy-5,6-di-isobutyramidopyrimidine (isobutyryl chloride/pyridine, 71%),⁵⁴⁴⁷ 4,6-bisbenzylamino-5-benzyloxycarbonylaminopyrimidine (75) (benzyloxycarbonyl chloride/ethyl acetate/potassium acetate, 51%),⁵⁷⁴⁷ 5-glycolamido-2,4-dimercapto-6-methylpyrimidine (acetoxyacetyl chloride/pyridine followed by acid hydrolysis of the protecting acetoxy group, 44%),⁵⁶⁸⁹ 5-acetoacetamido-4-aminopyrimidine (neat ethyl acetoacetate at 185°, 84%),⁵⁵⁷⁸ 2,4-dihydroxy-5-undecanamidopyrimidine (76) (undecanoyl chloride/pyridine, >72%),⁴⁵⁹⁷ 2-hydroxy-4-octanamidopyrimidine (78%; and homologues),⁴⁵⁹⁶ 5-methyl-2-phthalimidopyrimidine (77) (phthalic anhydride at 200°, 56%),⁵⁷⁶² 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5,6-diphthalimidopyrimidine (phthaloyl chloride at 160°, 55%),⁴⁷¹² 2-3'-chloropropionamidopyrimidine (3-chloropropionyl chloride/pyridine at 5°, 28%),⁵⁴⁹² 5-3'-bromopropionamido-4-mercapto-6-methoxypyrimidine (3-bromopropionyl chloride/potassium carbonate in acetone, 70%),⁴⁸²⁵ and *N,N'*-dipyrimidin-5-yloxamide (78) (oxalyl chloride in chloroform, 84%).⁶²⁶¹



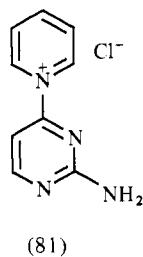
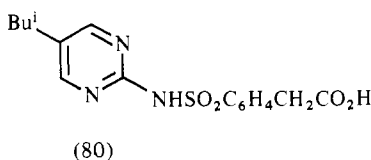
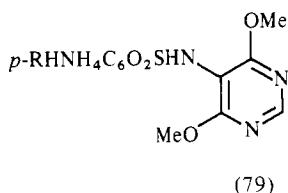
(4) Other Ways of Preparing Acylaminopyrimidines (*H* 328, *E* 249)

Apart from acylation, acylaminopyrimidines may be made by primary syntheses (Ch. II and III)^{5399, 6013, 6231} or by reduction of a

nitro-, nitroso-, or arylazopyrimidine by zinc/formic acid or the like [Ch. V, Sects. 1.B, 2.B(1), and 3.B].⁴⁶²⁰

(5) *Deacylation of Acylaminopyrimidines* (H 329, E 249)

The deformylation of formamidopyrimidines by hydrogen chloride has been exemplified already (Ch. V, Sect. 1.B). Other examples include the deformylation of 6-amino-3-methyl-5-*N*-methylformamido-uracil (by methanolic hydrogen chloride),⁴⁶¹⁵ and the deacetylation of 5-*p*-acetamidobenzenesulfonamido-4,6-dimethoxypyrimidine (79, R = Ac) to 4,6-dimethoxy-5-sulfanilamidopyrimidine (79, R = H) in 90% yield by aqueous sodium hydroxide under reflux;⁵⁷⁸⁴ 5-methylthio-2-sulfanilamidopyrimidine was made similarly from its acetyl derivative.⁴³³²



(6) *Arylsulfonamidopyrimidines and the Like* (H 329, E 250)

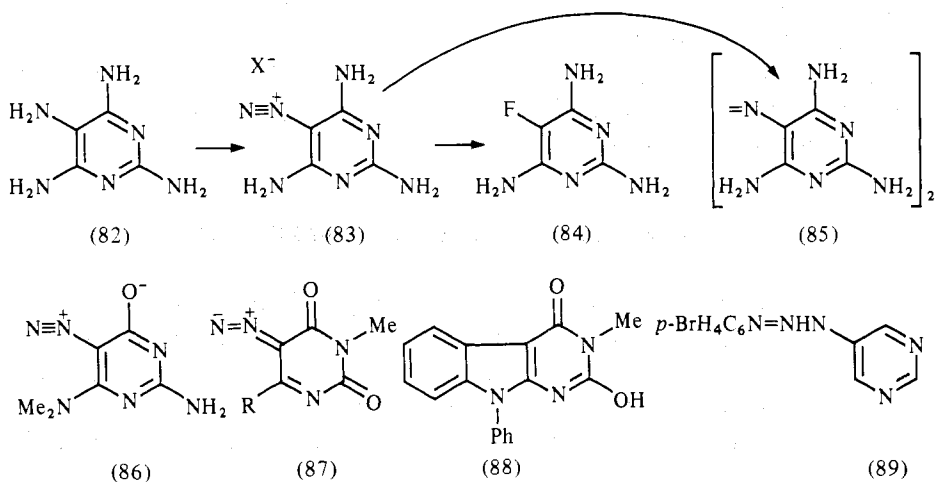
The regular formation of sulfonamidopyrimidines is illustrated in the conversion of 5-amino- into 5-*p*-acetamidobenzenesulfonamido- or 5-bis(*p*-acetamidobenzenesulfonyl)amino-4-chloro-6-methoxypyrimidine by treatment with acetylsulfanilyl chloride;⁵⁷⁸⁴ of 2-amino- into 2-*p*-acetamidobenzenesulfonamido-5-methylthiopyrimidine (81%), similarly;⁴³³² of 2-amino- into 2-*p*-carboxymethylbenzenesulfonamido-5-isobutylpyrimidine (80) by treatment with *p*-methoxycarbonylmethylbenzenesulfonyl chloride in pyridine followed by alkaline treatment at 90° (to complete the saponification?);⁴⁵³² and in related conversions.^{5161, 6934} Less usual results are seen in the reaction of 2-amino-4-hydroxypyrimidine with butanesulfonyl chloride in pyridine, which gave a small yield of the expected 2-butanefulfonamido-4-hydroxypyrimidine, accompanied by twice the yield of 2-amino-4-pyridinio-pyrimidine chloride (81), probably formed *via* 2-amino-4-butanefulfonyl-oxy-pyrimidine;⁵⁵⁸⁶ in the reaction of 4-amino-6-chloro-2-methoxy-

pyrimidine with *p*-nitrobenzenesulfonyl chloride in pyridine, which gave some 4-chloro-2-methoxy-6-*p*-nitrobenzenesulfonamidopyrimidine but also 2-methoxy-4-*p*-nitrobenzenesulfonamido-6-pyridiniopyrimidine chloride, isolated as its betaine;⁵⁰⁹⁵ and in other such examples.⁵⁰⁶⁹

A related case is seen in the reaction of 2-amino-4-hydroxy-5-methylthiopyrimidine with phosphoryl chloride to afford 4-chloro-2-dichlorophosphorylamino-5-methylthiopyrimidine (71%).⁴³³²

E. Diazotization and Related Reactions (*H* 331, *E* 252)

The diazotization and subsequent reaction(s) of 5-aminopyrimidines can be seen in the conversion of 2,4,5,6-tetraaminopyrimidine (82), by treatment in aqueous tetrafluoroboric acid with sodium nitrite at 0°, into (solid) 2,4,6-triamino-5-diazoniopyrimidine tetrafluoroborate (83, X = BF₄), which underwent thermolysis in paraffin at 225° to give 2,4,6-triamino-5-fluoropyrimidine (84) in 65% yield;⁴⁷⁴⁴ in the analogous formation of chloride (83, X = Cl) and its subsequent coupling with 2,4,6-triaminopyrimidine at the 5-position to give 2,2',4,4',6,6'-hexa-amino-5,5'-azopyrimidine (85) (63%);⁴⁷⁴⁴ in the conversion of 2,5-diamino-4-dimethylamino-6-hydroxypyrimidine, by treatment in methanolic hydrogen chloride with isoamyl nitrite, into (solid) 2-amino-5-diazonio-4-dimethylamino-6-hydroxypyrimidine chloride, which was converted in an appropriate ion-exchange medium to the betaine (86);⁴⁶²⁸ in the treatment of 5-amino-3-methyluracil with aqueous sodium nitrite/hydrochloric acid followed by alkali to give



5-diazo-3-methyluracil, formulated as (87, R = H) and which underwent covalent addition of methanol to afford the 1,6-adduct;⁵⁴⁴⁸ in the treatment of 5-amino-4-carboxypyrimidine in strong sulfuric acid with sodium nitrite to give the diazonio derivative (?), which on dilution with water lost carbon dioxide and nitrogen to give, not 5- but 4-hydroxypyrimidine by a postulated addition-elimination mechanism;⁴³⁶⁴ in the treatment of 5-amino-6-diphenylamino-3-methyluracil with sodium nitrite/acetic acid to give 5-diazo-6-diphenylamino-3-methyluracil (87, R = NPh₂), which underwent cyclization on irradiation to 3,4-dihydro-2-hydroxy-3-methyl-4-oxo-9-phenylpyrimido[4,5-*b*]indole (88) with loss of nitrogen;⁵⁰¹⁰ in the diazotization of 5-amino-2,4-dihydroxypyrimidine and subsequent treatment with cuprous cyanide to give 5-cyano-2,4-dihydroxypyrimidine (64%);^{5777, 6007} in the diazotization of 5-amino-2-methoxy-4,6-diphenylpyrimidine and subsequent treatment with potassium azide to give the 5-azido analogue;⁶¹⁴⁷ in the conversion of 5-diazonio-2,4-dihydroxypyrimidine chloride (?) into 2,2',4,4'-tetrahydroxy-5,5'-bipyrimidine (48%) by treatment with copper powder;⁴³⁷⁵ in the conversion of the covalent hydrate, 5-diazo-hexahydro-4-hydroxy-1,3-dimethyl-2,6-dioxypyrimidine,⁵⁴⁴⁸ by liquid hydrogen cyanide, into the 4-cyano analogue and thence by treatment with sodium hydrogen carbonate into 4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (52%);⁶¹⁸⁹ and some related reactions.^{4342, 5994}

In this context should be noticed the coupling of 5-aminopyrimidine with *p*-bromobenzenediazonium chloride to give 5-3'-*p*-bromophenyltriazenopyrimidine (89) and other products,⁶²⁸³ as well as the conversion of 5-diazoacetyl- into 5-bromacetyl-pyrimidine by ice-cold hydrobromic acid.⁴⁴⁷³

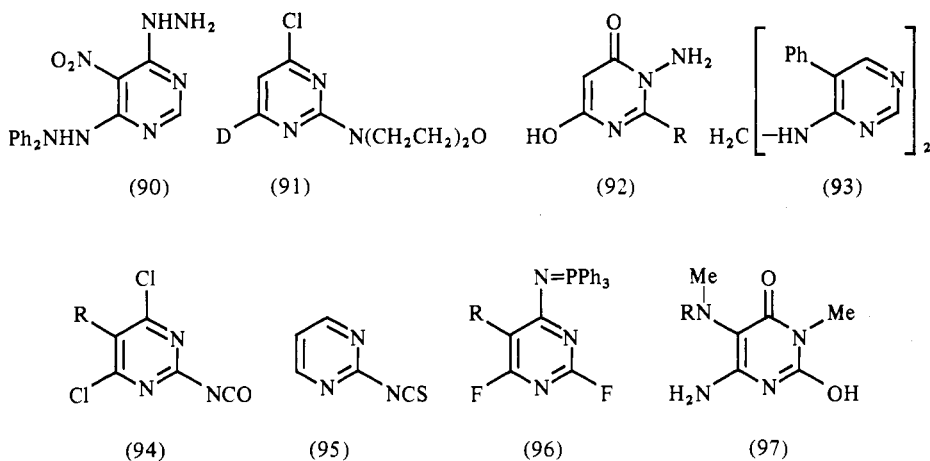
The conversion of amino- into hydroxypyrimidines, *via* (unisolated) diazo intermediates, is covered in Ch. VII, Sects. 1.D, 2, and 3.B. The similar conversion of amino- into halogenopyrimidines has been discussed in Ch. VI, Sects. 1.C, 1.D, and 1.F.

F. Heterocycles from Aminopyrimidines (*H* 333, *E* 252)

The illustration of routes from aminopyrimidines to fused pyrimidines, for example, purines, pteridines, and other heterobicyclic systems, seems no longer necessary because of reviews or monographs on the formation of such systems being now available.^{4839, 6335, etc.} In addition, the annelation of a pyrimidine ring to another ring has been well reviewed.^{6338, 6418}

G. Other Reactions (*H* 335, *E* 254)

Hydrazino groups can be removed readily from pyrimidines by oxidation. This offers a good route to remove chloro, alkylthio, alkylsulfonyl, mercapto, alkoxy, or other substituents when reductive conditions are contraindicated simply by preliminary hydrazinolysis, which is usually quite easy. The oxidative process is illustrated in the *dehydrazinolysis* of 4- β,β -diphenylhydrazino-6-hydrazino-5-nitropyrimidine (90) (aqueous silver acetate, 65%; the diphenylhydrazino group survived),⁶¹⁴⁶ 4-hydrazino-2-methyl-6-phenylpyrimidine (aqueous cupric sulfate, 80%),⁶⁰³⁹ 4-hydrazino-5-iodo-2-isopropyl-6-methylpyrimidine (silver acetate, 73%),⁵⁰⁹⁴ 4-hydrazino-6-methoxy-5-nitropyrimidine (silver acetate, 65%),⁶¹⁴⁴ 4-chloro-6-hydrazino-2-morpholino-pyrimidine [silver acetate/D₂O, 30% yield of the 6-deuteropyrimidine (91)],⁵⁸⁶⁶ 4,6-dihydrazino-5-nitropyrimidine (silver acetate, 70%),⁵⁹³⁸ 5-bromo-4-hydrazino-2-*N*-methylanilinopyrimidine (silver acetate, 40%),⁴⁶⁷⁰ 4-hydrazino-2-hydroxypyrimidine (silver oxide/water, 79%),⁴³⁸⁵ 5-fluoro-4-hydrazino-2-hydroxypyrimidine (silver oxide, 34%),⁴³⁸⁵ 4-hydrazino-6-methoxy-2-methyl-5-nitropyrimidine (silver oxide/methanol, *c.* 45%),⁵⁶³⁴ 4-hydrazino-2-methyl-5-nitropyrimidine (silver oxide),⁵⁶³⁴ and 4-hydrazino-5-nitropyrimidine and its 6-methoxy derivative (silver oxide in deuteromethanol, 4-deuterated products).⁵¹⁷⁰ *Deamination* occurred when 1-aminobarbituric acid (92, R = OH) was treated with nitrous acid; the product was 2,4,6-trihydroxy-5-nitrosopyrimidine (*c.* 40%). 1-Amino-2-thiobarbituric acid (92, R = SH) behaved similarly to give 4,6-dihydroxy-2-mercapto-5-nitrosopyrimidine (17%).⁵¹⁸⁶



The *alkylation* of amino groups is discussed in Sect. 1.I above. It is further exemplified in the conversion of 4-aminopyrimidines into their *N*-(protected) ribosyl derivatives,⁴⁶³⁹ of 4-amino- into 4- β -cyano- β -ethoxycarbonylvinylamino-2-methylpyrimidine (ethyl 2-cyano-3-ethoxyacrylate at 115° without solvent; *cis* and *trans* products, equal parts),⁴⁹⁶⁵ of 4,5-diamino- into 4-amino-5- β , β -diethoxycarbonylvinylamino-2,6-dihydroxypyrimidine (diethoxy ethoxymethylenemalonate/ethanolic sodium ethoxide, 61%),⁴⁵⁰⁹ and of 4-amino-5-phenylpyrimidine into di(5-phenylpyrimidin-4-ylamino)methane (93) (dimethyl sulfoxide at 160°, 15%).⁵¹¹⁷

The transformation of *amino-into isocyanato- and isothiocyano-*pyrimidines is illustrated in the formation of 4,6-dichloro-2-isocyanatopyrimidine (94, R = H) and its 5-phenyl derivative (94, R = Ph) in greater than 90% yield by treatment of the corresponding 2-aminopyrimidines with oxalyl chloride in refluxing benzene,⁴⁸²² 2,4-dihydroxy-5-isothiocyantopyrimidine (aqueous thiophosgene, 77%);⁶⁰⁹⁷ and 2-isothiocyantopyrimidine (95) (thiophosgene and 2-trimethylsilylamino-2-pyrimidine in ether at -65°, 48%).⁶²⁰⁸

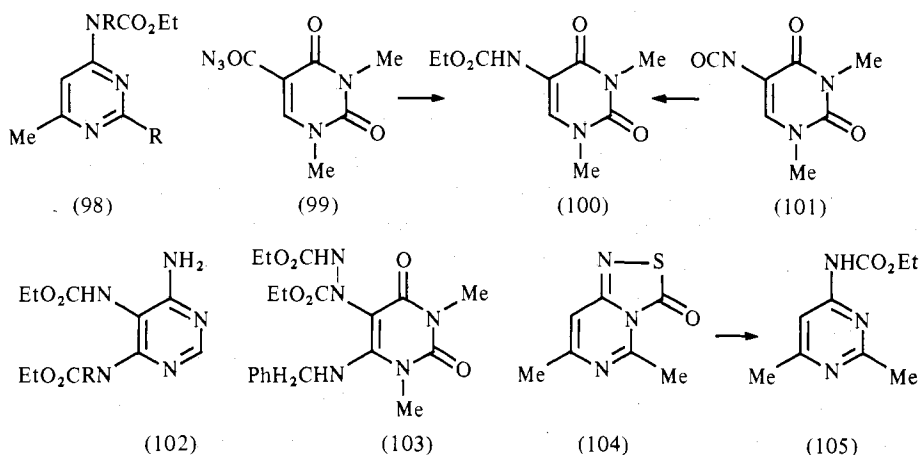
Some *miscellaneous reactions* include the condensation of 4-azido-2,5,6-trifluoropyrimidine with triphenylphosphine to give 2,4,5-trifluoro-6-triphenylphosphoranylideneaminopyrimidine (96, R = F) (81%) with loss of nitrogen;⁶⁰⁷⁸ the 5-chloro analogue (96, R = Cl) was made similarly,⁶⁰⁸⁷ as were other reactions of probably little importance.^{5186, 6078} 1-Amino-4,6-dimethylpyrimidinium salts undergo ring contraction to 3,5-dimethylpyrazole in hydrazine.⁶⁵²⁴

6. Urethanes: Alkoxycarbonylamino-2-pyrimidines (*H* 336, *E* 257)

Little work has appeared in this area. However, the preparation of urethanes from aminopyrimidines and alkyl chloroformates or the like is illustrated in the reaction of 5,6-diamino-1(or 3)-methyluracil with ethyl chloroformate in aqueous alkali to give 6-amino-5-ethoxycarbonylamino-1(or 3)-methyluracil (> 60%),⁴⁶¹⁵ of 6-amino-3-methyl-5-methylaminouracil (97, R = H) with ethyl chloroformate in alkali to give 6-amino-5-*N*-ethoxycarbonyl-*N*-methylamino-3-methyluracil (97, R = CO₂Et) (60%),⁴⁶¹⁵ of 4,5-diamino-6-propylaminopyrimidine with ethyl chloroformate in pyridine to give 4-amino-5-ethoxycarbonylamino-6-propylaminopyrimidine (44%);⁵⁸⁷¹ of 4-amino-2-hydroxypyrimidine with hexyl chloroformate in pyridine to give 4-hexyloxycarbonylamino-2-hydroxypyrimidine;⁵³⁸⁹ of 4,5,6-triaminopyrimidine with ethyl chloroformate in pyridine to give 4,6-diamino-5-ethoxycarbonyl-

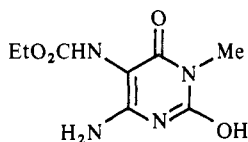
aminopyrimidine (58%);⁵⁸⁷¹ and of 4-amino-2,6-dimethylpyrimidine with 1-ethoxycarbonylpyridinium chloride in pyridine to give 4-ethoxycarbonylamino-2,6-dimethylpyrimidine (98, R = H) (80%) or with diethyl pyrocarbonate $[O(CO_2Et)_2]$ in refluxing ethanol to give 4-di(ethoxycarbonyl)amino-2,6-dimethylpyrimidine (98, R = CO_2Et) (38%).⁶¹⁵²

Other methods of preparation are exemplified in the conversion of 5-azidocarbonyl-1,2,3,4-tetrahydro- (99) or 1,2,3,4-tetrahydro-5-isocyanato- (101) into 5-ethoxycarbonylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (100) by prolonged treatment with ethanol (note that some of the names used in the original paper are misleading);⁵⁸⁹⁵ of 6-hydroxypurine into 4-amino-6-ethoxycarbonylamino-5-*N*-ethoxycarbonylformamidopyrimidine (102, R = CHO), by treatment with ethyl chloroformate in a two-phase system of ethyl acetate and aqueous potassium acetate, followed by deformylation in boiling water to give 4-amino-5,6-bisethoxycarbonylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (102, R = H);⁵⁵⁹⁶ of 6-amino-9-propylpurine into a separable mixture of 4-amino-5-ethoxycarbonylamino-6-*N*-propylformamidopyrimidine and related pyrimidines by treatment with diethyl pyrocarbonate;⁵⁸⁷¹ of 4-benzylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine into its 5- α,β -diethoxycarbonylhydrazino derivative (103) (85%) by heating with diethyl azodicarboxylate at 165° ;^{4990, 5012} and of analogous substrates into similar products.⁵⁰¹² In addition, 5,7-dimethyl-3-oxo-3*H*-[1,2,4]thiadiazolo[4,3-*c*]pyrimidine (104), which was easily made from 4-amino-2,6-dimethylpyrimidine and chloroformylsulfur chloride (ClCOSCl) in chloroform containing triethylamine, gave 63% of 4-ethoxycarbonylamino-2,6-dimethylpyrimidine (105) on dissolution in

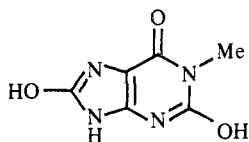


ethanolic hydrochloric acid.⁵⁷⁶⁹ A compound akin to a dithiourethane is represented by 2- β -dithiocarboxyhydrazinopyrimidine (from 2-hydrazinopyrimidine and carbon disulfide in aqueous ethanolic sodium hydroxide; 72%).⁵⁶⁹²

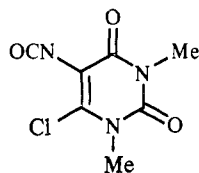
The main use of urethanes is as intermediates for bicyclic systems, as illustrated in the conversion of 6-amino-5-ethoxycarbonylamino-3-methyluracil (106) into 1-methyluric acid (107) by heating in aqueous alkali.⁴⁶¹⁵ They may also be converted into ureidopyrimidines (see Sect. 7 below) or into isocyanates, as exemplified in the treatment of 5-ethoxycarbonylamino-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxypyrimidine with "wet" phosphoryl chloride to give 4-chloro-1,2,3,6-tetrahydro-5-isocyanato-1,3-dimethyl-2,6-dioxypyrimidine (108) (65%).⁵³⁹⁶



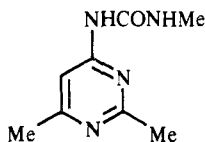
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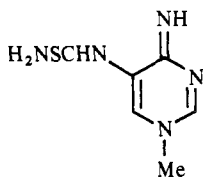
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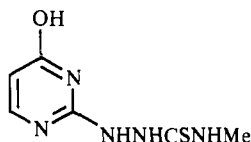
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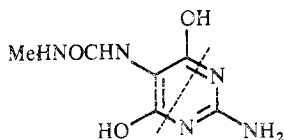
7. Ureidopyrimidines (*H* 339, *E* 259)

The common route to ureidopyrimidines is by treatment of the corresponding primary or secondary amines with cyanic acid, an alkyl isocyanate, their thio analogues, or a related reagent, as seen in the formation of 2,4-dimethyl-6-*N'*-methylureidopyrimidine (109) (methyl isocyanate in dioxane),⁶¹⁵⁶ 2-hydroxy-4-*N'*-phenylureidopyrimidine (phenyl isocyanate at 150°, *c.* 81%),⁵²⁷³ 4-phenyl-2-*N'*-phenylureidopyrimidine 1-oxide (phenyl isocyanate in refluxing xylene, 48%),⁶³⁴² 2,4-dihydroxy-6-ureidomethylpyrimidine (from 4-amino-2,6-dihydroxypyrimidine and nitrourea in aqueous base, 56%),⁵⁸⁶⁸ 2-*N,N'*-diphenylureido-4-methoxy-6-methylpyrimidine (from the 2-anilino analogue and phenyl isocyanate in chloroform; 60%),⁵⁹⁸⁶ 4-*N'*-*t*-butyl-*N*-methyl-

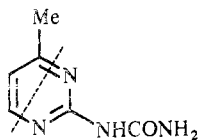
ureido-2-pyrid-4'-ylpyrimidine (t-butyl isocyanate in dimethylformamide containing sodium hydride, 57%; also analogues),⁶²⁹⁸ 4-amino-5-*N*-ethyl-*N'*-phenyl(thioureido)pyrimidine (from the 5-ethylamino analogue and phenyl isothiocyanate in dioxane; 69%),⁵⁸⁷³ 1,4-dihydro-4-imino-1-methyl-5-thioureidopyrimidine (110) (by fusion of the 5-amino analogue with thiourea, low yield),⁵³⁴⁴ 5-methoxy-2-*N'*-phenyl(thioureido)pyrimidine (phenyl isothiocyanate in benzene, >90%),⁵⁸³⁸ 4-hydroxy-2-4'-methyl(thiosemicarbazido)pyrimidine (111) (from the 2-hydrazino analogue and methyl isothiocyanate, >95%),⁶¹³³ 2,4-bis-4'-ethyl(thiosemicarbazido)pyrimidine (>95%),⁶¹³³ and 2-*N'*-pyrid-2'-yl(thioureido)pyrimidine (from 2-aminopyrimidine with methyl *N*-pyrid-2'-yldithiocarbamate in refluxing toluene, 49%).⁶⁵⁴⁰ Some thioureidopyrimidines are less thermostable than might be anticipated.⁶²¹⁶

Other approaches are illustrated by the reaction of 4-ethoxy-2-hydroxypyrimidine with semicarbazide at pH 4 to give 2-hydroxy-4-semicarbazidopyrimidine (82%);⁴⁷³⁵ in the primary synthesis (see also Ch. II and III) of 2-amino-4,6-dihydroxy-5-*N'*-methylureidopyrimidine (112) in 73% yield from diethyl *N'*-methylureidomalonate and guanidine carbonate in ethanol under reflux,⁵²⁹⁵ in the condensation of carbamoylguanidine with 4,4-dimethoxybutan-2-one to give 4-methyl-2-ureidopyrimidine (113),⁶⁰¹⁵ and in the ring-fission of 2,3-dihydro-8-hydroxy-1,3,9-trimethylpurinium iodide (114) by alkaline hydrolysis to afford 1,2,3,4-tetrahydro-1,3-dimethyl-5-*N'*-methylureido-2,4-dioxypyrimidine.⁵³³⁶

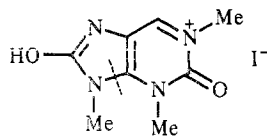
The closely related thiouronipyrimidine halides, for example, 5-nitro-2-thiouronipyrimidine chloride (115),⁶³⁷² are made by the action of thiourea on the corresponding chloropyrimidine. Their decomposition in alkali leads to the corresponding mercaptopyrimidine (see Ch. VI, Sect. 5.G).



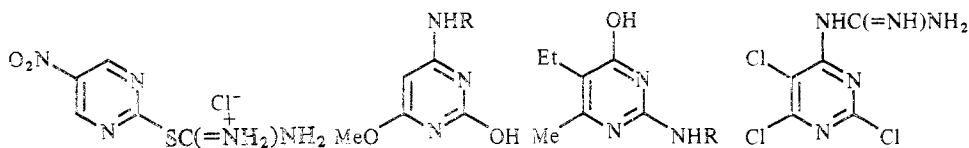
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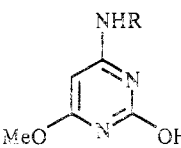
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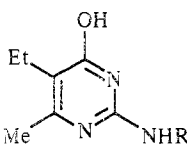
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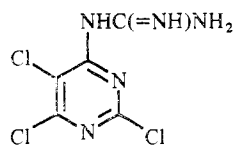
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(117)



(118)

8. Other (Substituted-amino)pyrimidines (*H* 341, *E* 260)

The formation of (*nitroamino*)pyrimidines by nitration of amino-pyrimidines has been mentioned in Ch. V, Sect. 1.A(2). A few such compounds have also been made by using nitroguanidine in the Principal Synthesis (Ch. II).

Although a nitroamino group may be expected to furnish a hydrazino group on reduction, this does not always happen. Hydrogenation of 2-hydroxy-4-methoxy-6-nitroaminopyrimidine (116, $R = NO_2$) over palladium gave 4-amino-2-hydroxy-6-methoxypyrimidine (116, $R = H$), presumably by reductive cleavage of the N,N-bond of the intermediate hydrazinopyrimidine (116, $R = NH_2$).⁴⁶⁵⁶ In view of this complication, the best way to convert a nitroamino into an hydrazino group appears to be indicated by the transamination (or reduction?) of 4-hydroxy-6-methyl-2-nitroaminopyrimidine or its 5-ethyl derivative (117, $R = NO_2$) to 2-hydrazino-4-hydroxy-6-methylpyrimidine (79%) or its 5-ethyl derivative (117, $R = NH_2$) (71%), respectively, by simply boiling with aqueous hydrazine.⁶¹⁴⁸

A few (*cyanoamino*)pyrimidines have been made by the Principal Synthesis, using cyanoguanidine as the N—C—N fragment (Ch. II); also by displacement of an halogeno substituent by sodium cyanamide (Ch. VI, Sect. 5.B). Cyanoaminopyrimidines can give guanidinopyrimidines: 2-cyanoamino- with *p*-aminobenzophenone gave 2-*N'*-*p*-benzoyl-phenylguanidino-4-hydroxy-6-trifluoromethylpyrimidine (70%).⁶⁵⁰⁶ In addition the cyanoaminopyrimidines are potentially good intermediates for bicyclic systems. For example, 2-cyanoamino-4,6-dimethylpyrimidine reacted with formalin and methanolic hydrazine to give 4,6-dimethyl-2-(1',2',4'-triazol-5'-ylamino)pyrimidine (40%) at 20°. ⁶⁵¹³

The *guanidinopyrimidines* are usually made by the Principal Synthesis using biguanide as the N—C—N fragment (Ch. II) or by displacement of an halogeno substituent with free guanidine, as in the conversion of 2,4,5,6-tetrachloropyrimidine by aqueous acetic guanidine into a separable mixture of 4,5,6-trichloro-2-guanidino- and 2,4,5-trichloro-6-guanidinopyrimidine (118).⁶³⁸⁴

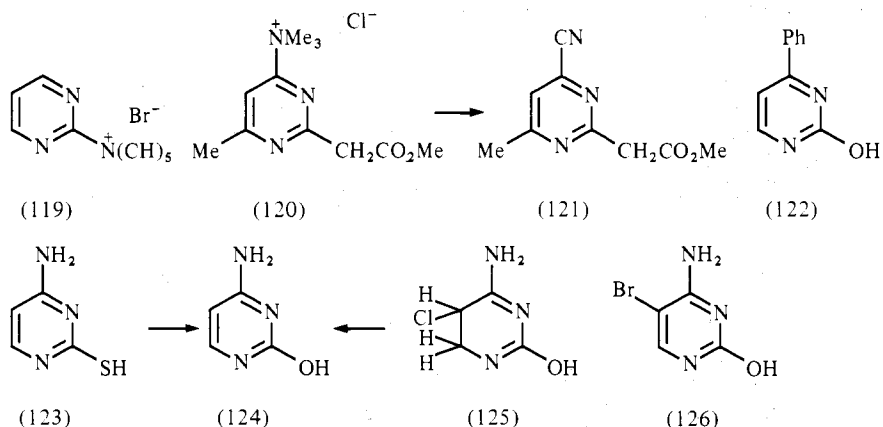
Most (*hydroxyamino*)pyrimidines have been made by nucleophilic displacement of a chloro or other leaving group from a pyrimidine with free hydroxylamine; see, for example, Ch. VI, Sect. 5.B.

Nearly all *trimethylammoniopyrimidine halides* are made by treatment of an active chloropyrimidine with trimethylamine in benzene at room temperature (see Ch. VI, Sect. 5.B). *Pyridiniopyrimidine halides* have been made similarly, as exemplified in the reaction of 2-bromo-

methylpyrimidine with pyridine to give 2-pyridiniomethylpyrimidine bromide (119) in 81% yield,⁵⁶⁸² and in the reaction of 4-carboxy-5-chloro-2,6-dihydroxypyrimidine with anhydrous pyridine to give 4-carboxy-2,6-dihydroxy-5-pyridiniopyrimidine chloride (96%).⁵¹³⁷

Trimethylammonio substituents are excellent leaving groups for all manner of nucleophiles, for example, hydroxide ion,⁵³⁴² as long as mild temperature conditions are maintained, otherwise, loss of methyl halide occurs to give the corresponding dimethylaminopyrimidine.⁵³⁹³ Such quaternary salts are especially useful for displacement by cyanide ion, with which chloro, alkylsulfonyl, and other leaving groups are notoriously temperamental. Thus, 2-methoxycarbonylmethyl-4-methyl-6-trimethylammonioypyrimidine chloride (120) with potassium cyanide in acetamide at 70° gave 4-cyano-2-methoxycarbonylmethyl-6-methylpyrimidine (121) along with the 4-dimethylamino analogue as a by-product,⁵⁶⁹³ 4-methyl-2-methylthio-6-trimethylammonioypyrimidine chloride similarly gave 4-cyano-6-methyl-2-methylthiopyrimidine (17%),⁵²⁸⁴ and 4-phenyl-2-trimethylammonioypyrimidine chloride with potassium cyanide in dimethyl sulfoxide at room temperature gave 2-cyano-4-phenylpyrimidine (122) in 58% yield.⁶⁰⁴⁰

Reports of (*nitrosoamino*)pyrimidines are rare. An example⁵⁵³⁸ is given in Ch. V, Sect. 2.A(1)

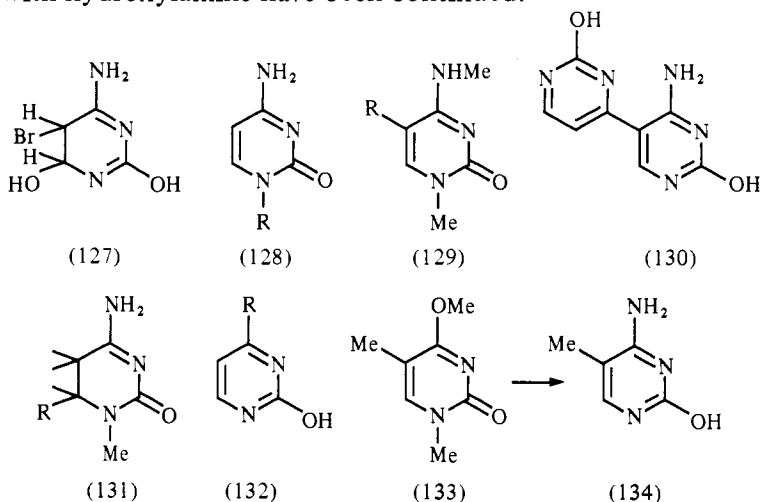


9. Some Naturally Occurring Aminopyrimidines (*H* 346, *E* 264)

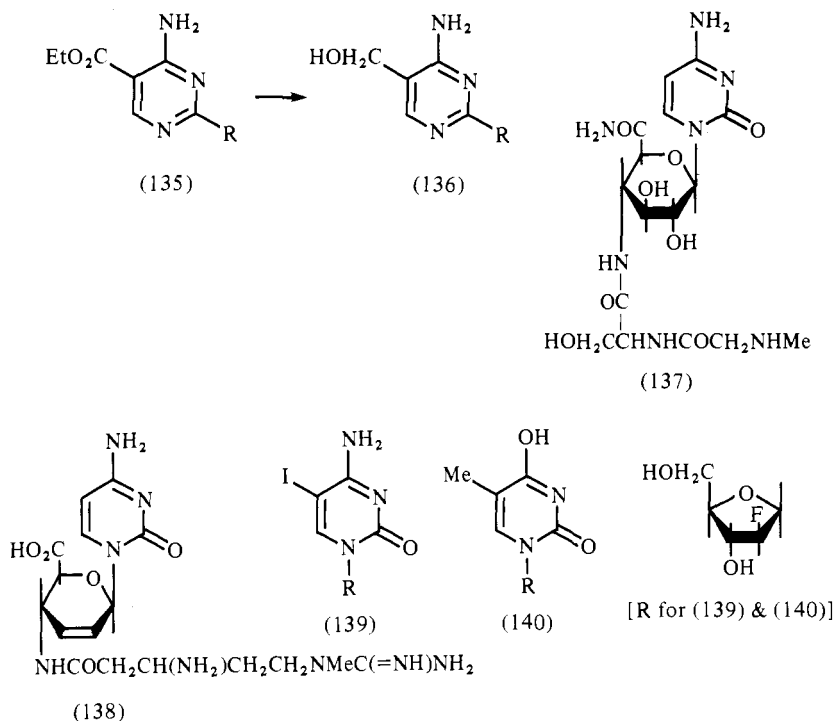
Relatively little has been added recently to the chemistry (as distinct from the biochemistry) of *cytosine* (4-amino-2-hydroxypyrimidine) or its biologically important derivatives. Two new routes to cytosine (124) have been reported: one involving warming thiocytosine

(123) in dimethyl sulfoxide containing a little sulfuric acid,⁴⁷¹⁸ the other was a primary synthesis of 5-chloro-5,6-dihydrocytosine (125) followed by dehydrochlorination.⁵⁷⁹⁸

The addition of bromine to an aqueous suspension of cytosine at room temperature gave 5-bromocytosine (126) in 79% yield.⁵²²⁷ However, like the bromination of uracil, this reaction is by no means simple and passes through the bromohydrin (127) and/or other intermediates formed by initial addition of hypobromous acid to the substrate. The bromination of 5-bromocytosine (126), cytidine (128, R = ribose), 5-bromocytidine, 1-methylcytosine (128, R = Me), 5-bromo-1-methylcytosine, 1,2-dihydro-1-methyl-4-methylamino-2-oxypyrimidine (129, R = H), its 5-bromo derivative (129, R = Br), and several other methylated cytosines have been investigated and discussed.⁵²²⁷ Under irradiation, cytosine reacts with 4-thiouracil to give 4'-amino-2,2'-dihydroxy-4,5'-bipyrimidine (130) with loss of sulfur,⁶⁴¹⁹ and the structure (130) was proven subsequently by an unambiguous synthesis.⁵⁴⁹⁸ The irradiation of 1-methylcytosine (128, R = Me) in propan-2-ol gave both 5,6-dihydro-1-methylcytosine (131, R = H) and the adduct, 4-amino-1,2,5,6-tetrahydro-6- α -hydroxy- α -methylethyl-1-methyl-2-oxypyrimidine (131, R = CMe₂OH); analogues behaved similarly.⁵⁸⁹¹ Investigations of the reactions of cytosine and its derivatives with hydroxylamine have been continued.^{5313, 5314, 6562}



Following the isolation of *N*-methylcytosine (2-hydroxy-4-methylaminopyrimidine) (132, R = NHMe) as a minor component from ribosomal ribonucleic acid,⁶⁴²⁰ a new synthesis was reported, the essential step in which was the methylaminolysis of 4-ethoxy-2-hydroxy-



pyrimidine (132, R = OEt) in methanolic methylamine at 100°. ⁵⁶¹² A new synthesis has also been described for the isomeric *5-methylcytosine* (134), involving treatment of 2,4-dimethoxy-5-methylpyrimidine with acetyl chloride to give 1-acetyl-1,2-dihydro-4-methoxy-5-methyl-2-oxypyrimidine (133), which underwent deacylation and aminolysis in aqueous ammonia to afford the required methylcytosine (134). ³⁴⁶⁵ The classical synthetic route to *5-hydroxymethylcytosine* (136, R = OH) has also been improved by a new procedure for the reduction of 4-amino-5-ethoxycarbonyl-2-methylthiopyrimidine (135, R = SMe) by lithium aluminum hydride to give 4-amino-5-hydroxymethyl-2-methylthiopyrimidine (136, R = SMe), which gave 5-hydroxymethylcytosine (136, R = OH) on hydrolysis. ⁵⁶²⁴ The closely related antibiotic, *bacimethrin* or 4-amino-5-hydroxymethyl-2-methoxypyrimidine (136, R = OMe), has been made by a modified synthesis (*E* 268) involving methoxylation of 4-amino-5-ethoxycarbonyl-2-ethylsulfonylpyrimidine (135, R = SO₂Et) to its 2-methoxy analogue (135, R = OMe) and subsequent lithium aluminum hydride reduction. ⁵⁶²³

A total synthesis of *gougerotin*, a complicated nucleoside (137) of cytosine, has been achieved, but most of the work went into the

sugar portion.^{5404, 5409} Work has continued on the structurally related *blasticidin S* (138).^{e.g. 5802} Meanwhile, simple modifications of the natural structures have led to the synthesis of FIAC (139) and FMAU (140), which are potent and selective against *Herpes simplex* types 1 and 2 at very low levels.^{6164, 6421}

CHAPTER X

The *N*-Alkylated Pyrimidines and the Pyrimidine *N*-Oxides (*H* 356, *E* 269)

In view of the considerable volume of work on pyrimidine *N*-oxides, the last section of this chapter has been expanded into a more general essay, in which Dr William B. Cowden presents the new information within the context of previous work.

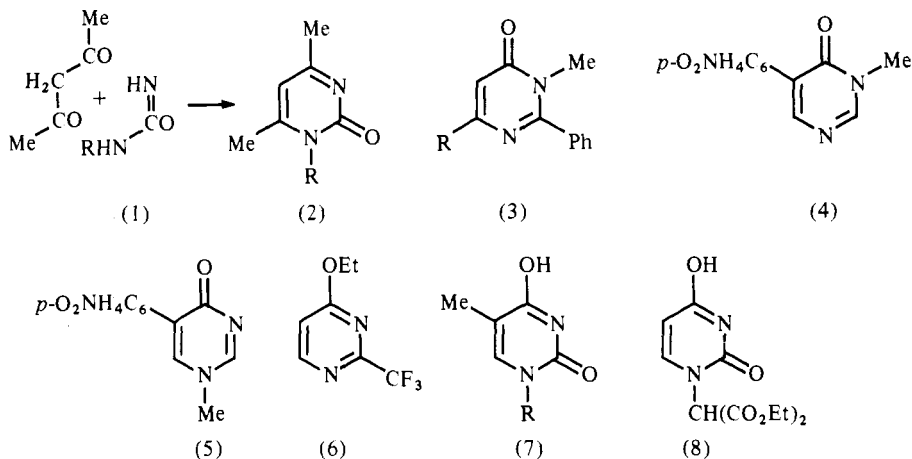
1. The Oxypyrimidines (*H* 357, *E* 269)

As before, all nontautomeric oxypyrimidines are included below, whether they are associated with *N*-alkylation, *N*-acylation, or some other factor which maintains them in that form.

A. Preparation of Oxypyrimidines (*H* 357, *E* 269)

(1) and (2) *By Primary Syntheses* (*H* 357, *E* 269)

Many examples of the formation of oxypyrimidines by primary syntheses may be found in Ch. II and III. A typical illustration is the condensation of acetylacetone with *N*-benzoyl- (1, R = Bz), *N*-phenyl- (1, R = Ph), or *N*-cyclohexyl-urea (1, R = C₆H₁₁) by heating under reflux without solvent to give 1-benzoyl-1,2-dihydro-4,6-dimethyl-2-oxypyrimidine (2, R = Bz), its 1-phenyl analogue (2, R = Ph), or its 1-cyclohexyl analogue (2, R = C₆H₁₁), respectively, all in *c.* 70% yield.⁴³⁹²



(3) By Alkylation of Hydroxypyrimidines (H 359, E 270)

The *O*-alkylation and *O*-acylation of hydroxypyrimidines has been covered in Ch. VII, Sects. 4.D and 6.C, but *N*-alkylation is much more widely used and important.

(a) *Cases with One Hydroxy Group* (H 359, E 270). The *N*-alkylation of 2- or 4-monohydroxypyrimidines is illustrated in the formation of 1,6-dihydro-1-methyl-6-oxo-2-phenylpyrimidine (3, R = H) (dimethyl sulfate/alkali, 90%),⁴⁴⁴⁹ 1,6-dihydro-1,4-dimethyl-6-oxo-2-phenylpyrimidine (3, R = Me) (54%),⁴⁹³⁰ 1-diphenylmethyl-1,2-dihydro-2-oxypyrimidine (diphenylmethanol/glacial acetic acid, 13%),⁵⁵⁰³ 1-diphenylmethyl-1,6-dihydro-6-oxopyrimidine (similarly, 51%),⁵⁵⁰³ 1-benzyl-1,2-dihydro-2-oxypyrimidine (benzyl chloride/methanolic sodium methoxide, 43%),⁴³⁹⁸ analogues,⁶⁹³³ 1,2-dihydro-4,6-dimethyl-1,4'-(*N*-methyl-*N*-phenylsulfamoyl)butyl-2-oxopyrimidine (4-chloro-*N*-methyl-*N*-phenylbutanesulfonamide/sodium salt of substrate in butanol; 28%; also a trace of the *O*-alkylated isomer),⁴⁸²⁹ 1-allyl-1,2-dihydro-2-oxopyrimidine (allyl bromide/ethanolic ethoxide, 73%),⁵⁷²¹ and 1,2-dihydro-1-β-hydroxyethyl-2-oxopyrimidine (2-chloroethanol, 28%).⁶⁰⁶⁸ In addition, two interesting studies of such alkylations have been made. Methylation of 5-aryl-4-hydroxypyrimidines with dimethyl sulfate/alkali occurred mainly on the ring-nitrogen adjacent to the hydroxy group. For example, 4-hydroxy-5-*p*-nitrophenylpyrimidine gave 1,6-dihydro-1-methyl-5-*p*-nitrophenyl-6-oxopyrimidine (4) (62%), the isomeric 1,4-dihydro-1-methyl-5-*p*-nitrophenyl-4-oxopyrimidine (5) (35%), and a trace of 4-methoxy-5-*p*-nitrophenylpyrimidine; in methanol,

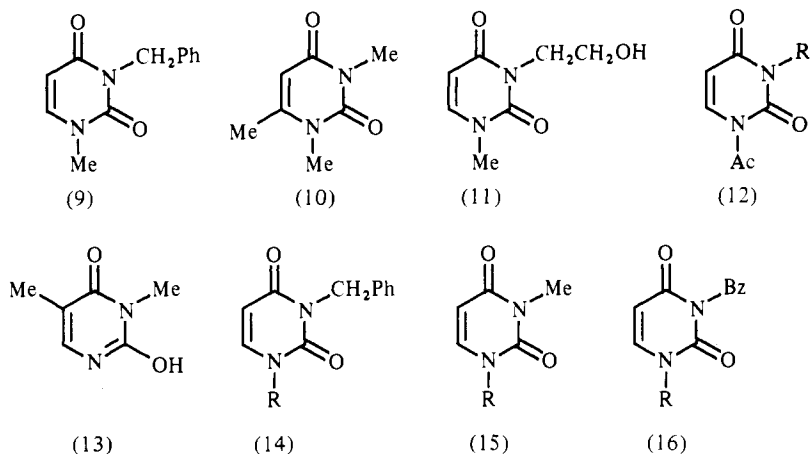
the ratio (4):(5) was 62:38; in dimethylformamide, 100:0; in ethyl acetate, 34:66; and in tetrahydrofuran, 27:73. The use of diazomethane in chloroform-ether gave 25% of (4), 53% of (5), and 22% of 4-methoxy-5-*p*-nitrophenylpyrimidine; variations of the aryl substituent caused only minor changes in the overall picture.⁶⁰³⁶ The other study involved the alkylation of salts of 4-hydroxypyrimidine and some 2-substituted 4-hydroxypyrimidines with alkyl halides in various solvents. It emerged that cation-solvating media favored the formation of 3-alkyl derivatives, but the proportion of 1-alkyl derivatives increased in hydrogen-bonding and low dielectric-constant solvents. In dimethylformamide, variation of the alkyl halide from methyl through ethyl to isopropyl, or variation of the 2-substituent from hydrogen through methyl to ethyl, both caused a marked increase in *O*- at the expense of 3-alkylation, without greatly affecting the 1-alkylation. With 4-hydroxy-2-trifluoromethylpyrimidine, ethylation gave 100% of 4-ethoxy-2-trifluoromethylpyrimidine (6). The original paper should be consulted for details.⁵²⁹⁴

(b) *Cases with Two Hydroxy Groups* (*H* 360, *E* 271). Most of the alkylations described recently in this category are, in fact, of 2,4-dihydroxypyrimidines (i.e., uracils). By using a variety of conditions, selective monoalkylation without much dialkylation may usually be achieved. Examples are divided roughly into first-stage, second-stage, and dialkylations for convenience.

First-stage monoalkylations are illustrated in the formation of 5-methyl-1-propyluracil (7, *R* = Pr) (propyl bromide/dimethyl sulfoxide/potassium carbonate at 25°, 44%),^{5629, 5646} 1-acetonyl-5-methyluracil (7, *R* = CH₂Ac) (bromoacetone/dimethyl sulfoxide/potassium carbonate at 25°, 65%),⁵⁴⁸³ 1-carboxymethyl-5-methyluracil (7, *R* = CH₂CO₂H) (aqueous sodium chloroacetate under reflux, 71%),⁵²⁶⁹ 1-di(ethoxycarbonyl)methyluracil (8) (potassium salt of uracil/diethyl bromomalonate/dimethylformamide at 100°, 70%; omission of solvent led to 1,3-bis(diethoxycarbonyl)methyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine in 20% yield),⁵¹⁹⁵ 5-ethyl-1,2'-hydroxy-3'-methylbenzyluracil (2-dimethylaminomethyl-6-methylphenol/dimethylformamide/potassium carbonate under reflux, 17%; also analogous reactions in which the leaving group is again dimethylamino),^{4709, 4710} 1-allyl-5-propyluracil (allyl bromide/aqueous ethanolic sodium hydroxide, *c.* 50%),⁶²³³ 1-benzyluracil or 1,3-dibenzyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (benzyl chloride/aqueous sodium hydroxide under reflux, > 75%, product depends on the excess of reagents),⁴³⁹⁰ 1-(tetrahydro-2'-oxofur-3'-yl)uracil (α-bromobutyrolactone/dimethylformamide/sodium hydride at 80°, *c.* 45%),⁴⁸⁷⁴ 1-acetonyluracil (bromoacetone with potassium salt

of uracil in dioxane under reflux; 44%; also made by treatment of 1-carboxymethyluracil with acetyl chloride in pyridine under reflux, 25%),^{4854, 5483} 1- β , β -diethoxyethyl-5-methyluracil [7, R = CH₂CH(OEt)₂] (1-bromo-2,2-diethoxyethane/sodium hydride/dimethylformamide at 150°, 35%),⁴⁷⁴⁹ 1- β -carboxyethyl-5-methyluracil (7, R = CH₂CH₂CO₂H) (β -propiolactone/sodium hydroxide/dimethylformamide, 36%),⁵⁰³⁵ 1,5-dimethyluracil (7, R = Me) (trimethyl phosphate/naphthalene under reflux, 80%; an excess of ester gave 1,2,3,4-tetrahydro-1,3,5-trimethyl-2,4-dioxypyrimidine, 87%),⁵⁰¹⁹ 1- β -hydroxyethyluracil (ethylene carbonate/sodium salt of uracil/dimethylformamide, separable mixture with 1,2,3,4-tetrahydro-1,3-bis- β -hydroxyethyl-2,4-dioxypyrimidine),^{5495, 4871} 1- β -cyanoethyluracil (acrylonitrile/sodium salt of uracil/aqueous triethylamine at 60°, 72%; more vigorous conditions gave 1,3-bis- β -cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine, 76%),⁵⁹²⁴ 1- β -hydroxyethyl-5-methyluracil (7, R = CH₂CH₂OH) ethylene carbonate/dimethylformamide/trace of sodium hydroxide under reflux, 36%),⁵⁸¹⁸ 1- γ -acetylthiopropyluracil (*S*- γ -bromopropyl thioacetate/potassium carbonate/potassium iodide/dimethyl sulfoxide; or sodium hydride/dimethylformamide),⁵²⁴⁰ 3- γ -acetylthiopropyluracil (same reagent/sodium hydride/dimethyl sulfoxide!),⁵²⁴⁰ and other such uracil derivatives.^{4858, 4879, 5288, 6070, 6127, 6245} Although 5-ethyl-2,4-dihydroxypyrimidine has been described as giving 1-acetyl-5-ethyluracil with acetic anhydride,⁴⁷³⁴ undecanoyl chloride and uracil appear to have given 3-undecanoyluracil.⁴⁵⁹⁷ Two general methods have been devised to distinguish between simple 1- and 3-alkyluracils: one was based on nmr data,⁴⁶⁶⁶ the other on mass spectrometric fragmentation.⁵⁶⁴⁸

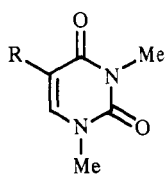
Isolated second-stage monoalkylations are exemplified in the conversion of 1-methyluracil into 3-benzyl-1-methyluracil (1-benzyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxypyrimidine) (9) (benzyl bromide/ethanolic alkali under reflux, 73%),⁵⁴¹⁰ of 1,6-dimethyluracil to 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxypyrimidine (10) (dimethyl sulfate/alkali, 54%),⁴⁹²⁵ of 6-methyl-3-phenyluracil into 1-ethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenylpyrimidine (ethyl bromide/ethanolic ethoxide, 95%),⁴⁹²⁵ of 1-methyluracil into 1,2,3,4-tetrahydro-3- β -hydroxyethyl-1-methyl-2,4-dioxypyrimidine (11) (ethylene carbonate/potassium carbonate/dimethylformamide under reflux, 95%),⁵⁵⁰⁹ of 6-methyl-1-phenyluracil into 1,2,3,4-tetrahydro-3-isopropyl-6-methyl-2,4-dioxo-1-phenylpyrimidine (isopropyl iodide/sodium salt of substrate/dimethylformamide at 25°, 72%),⁴⁸⁴⁷ and others.⁶¹²² Such second-stage alkylations may be used to obtain a uracil, monoalkylated in the 3- rather than the usual 1-position. Thus, initial first-stage 1-



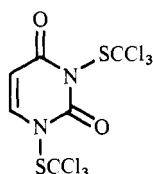
substitution is carried out with an acyl or removable alkyl group (e.g., benzyl) followed successively by a second-stage 3-alkylation with the required group and subsequent removal of the 1-substituent by appropriate means. This general process is illustrated in the conversion of 2,4-dihydroxy-5-methylpyrimidine into 1-acetyl-5-methyluracil (12, R = H) followed by methylation with diazomethane to 1-acetyl-1,2,3,4-tetrahydro-3,5-dimethyl-2,4-dioxypyrimidine (12, R = Me) and deacylation in aqueous ammonia to 3,5-dimethyluracil (13) in 71% yield,⁶²⁹² in the sequence 2,4-dihydroxypyrimidine → 1-tetrahydropyran-2'-yluracil → 1,2,3,4-tetrahydro-2,4-dioxo-3-propyl-1-tetrahydropyran-2'-ylpyrimidine (propyl bromide/potassium carbonate/dimethylformamide, 93%) → 3-propyluracil (aqueous methanolic hydrogen chloride, 68%),⁵⁵⁹¹ in the sequence 2,4-dihydroxypyrimidine → 1-β-cyanoethyluracil → 1-benzyl-3-β-cyanoethyl-1,2,3,6-tetrahydro-2,6-dioxypyrimidine (14, R = CH₂CH₂CN) (67%) → 3-benzyluracil (14, R = H) (ethanolic sodium ethoxide under reflux, 67%);⁴³⁹⁰ and in the sequence 2,4-dihydroxypyrimidine → 1-acetyluracil (acetic anhydride) → 1-acetyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxypyrimidine (15, R = Ac) (diazomethane) → 3-methyluracil (15, R = H) (ethanolic hydrochloric acid; 75% overall).⁵⁴⁹⁵ Deacylation is also useful in a slightly different context, for example, in the conversion of 1,3-dibenzoyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (16, R = Bz) into 3-benzoyluracil (16, R = H) by careful preferential hydrolysis. Subsequent identification was carried out by diazomethane methylation to 1-benzoyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxypyrimidine (16, R = Me).⁵⁴⁹⁵

Several 1,3-dialkylations of uracils are mentioned in the preceding paragraphs. Others, in which the intermediate 1- and/or 3-alkyluracils

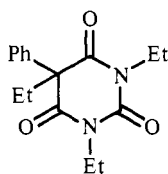
have not been isolated, include the formation of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (17, R = H) (dimethyl sulfate/alkali, 88%;⁵⁵²² or trimethyloxosulfonium hydroxide/dimethylformamide at 80°, 81%⁵⁰³⁹), its 1,3,5-trimethyl analogue (17, R = Me) (both methods; 61 or 71%),^{5039, 5522} 1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine and its 5-methyl derivative (diethyl sulfate/alkali, 87 and 78%, respectively),⁶⁰⁷¹ 1,3-dibenzyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine and its 5-methyl derivative (benzyl bromide/potassium carbonate/acetone under reflux, *c.* 80%),⁶¹²¹ 1,2,3,4-tetrahydro-1,3-bis-4'-(*N*-methyl-*N*-phenylsulfamoyl)butyl-2,4-dioxypyrimidine [4-chloro-*N*-methyl-*N*-phenylbutanesulfonamide/sodium salt of uracil/dimethylformamide, 20%; also 1-4'-(*N*-methyl-*N*-phenylsulfamoyl)butyluracil, 47%],⁴⁸²⁹ 1,2,3,4-tetrahydro-2,4-dioxo-1,3-bistrichloromethylthiopyrimidine (18) (perchloromethanethiol/pyridine at <0°, 50%),⁴⁴⁸⁷ and others.^{5493, 6068} In addition, it has been observed that tetrabutylammonium fluoride catalyzes alkylations by alkyl halides, sulfates, or phosphates. Thus, 2,4-dihydroxypyrimidine with dimethyl or diethyl sulfate in tetrahydrofuran containing the catalyst at 25° gave 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (99%) or 1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (91% plus 4% of 1-ethyluracil);⁵³³¹ likewise, 2,4-dihydroxypyrimidine with other alkylating agents under similar conditions gave 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (methyl bromide, 99%; trimethyl phosphate, 97%), 1,3-dibenzyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (benzyl chloride, 96%), 1,3-dibutyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (butyl bromide at 25°, 90%; tributyl phosphate at 75°, 60%), and 1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (triethyl phosphate at 75°, 60%).^{5328, 5330}



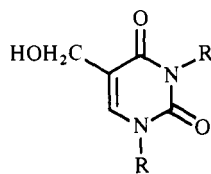
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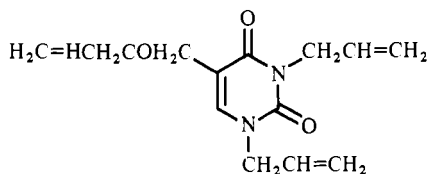
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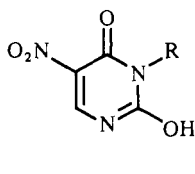
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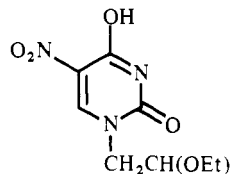
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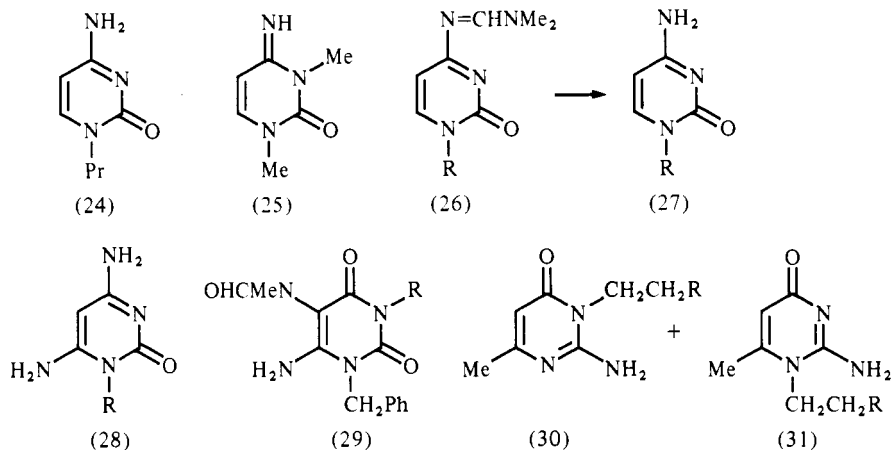


(23)

(c) *Cases with Three Hydroxy Groups* (*H* 362, *E* 273). There has been little recent work on the alkylation of barbituric acid or its derivatives, except with diazomethane, which gave difficultly separable mixtures of *O*- and *N*-methyl derivatives.⁵³²¹⁻⁵³²³ Treatment of the dilithium salt of 5-ethyl-5-phenylbarbituric acid with ethyl chloroformate gave 1,3,5-triethylhexahydro-2,4,6-trioxo-5-phenylpyrimidine (19) in 80% yield;⁵⁵⁴⁶ methyl chloroformate gave the lower homologue, 5-ethylhexahydro-1,3-dimethyl-2,4,6-trioxo-5-phenylpyrimidine (85%);⁵⁵⁴⁶ and benzyl chloroformate gave 1,3-dibenzyl-5-ethylhexahydro-2,4,6-trioxo-5-phenylpyrimidine (92%).⁵⁵⁴⁶ Thiobarbiturates behaved similarly.⁵⁵⁴⁹ The different type of trihydroxypyrimidine, 2,4-dihydroxy-5-hydroxymethylpyrimidine (20, *R* = *H*) reacted with allyl bromide/barium oxide in dimethylformamide at 25° to give 1,3-diallyl-5-allyloxymethyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (21) in 68% yield.⁴⁴⁹³ In contrast, treatment of the same substrate (20, *R* = *H*) in an unnamed solvent with methyl iodide/potassium carbonate gave 1,2,3,4-tetrahydro-5-hydroxymethyl-1,3-dimethyl-2,4-dioxypyrimidine (20, *R* = *Me*) in 88% yield.⁶²³⁹

(d) *In the Presence of a Nitro Group* (*H* 363, *E* 273). Although 2,4-dihydroxy-5-nitropyrimidine and its 6-methyl derivative usually undergo initial alkylation at the 1-position, it has been found possible to change the point of first attack to the 3-position by alkylation of the di- rather than the mono-anion. Thus, 2,4-dihydroxy-5-nitropyrimidine with methyl iodide or benzyl chloride in dimethylformamide containing tetrabutylammonium hydroxide gave 3-methyl- (22, *R* = *Me*) or 3-benzyl-5-nitrouracil (22, *R* = *CH*₂*Ph*), respectively, in 40–50% yield; 2,4-dihydroxy-6-methyl-5-nitropyrimidine likewise gave 3,6-dimethyl-5-nitrouracil (53%) or 3-benzyl-6-methyl-5-nitrouracil (65%), and the former was also obtained in strong aqueous sodium hydroxide in comparable yield.⁵⁴¹² Alkylation of 2,4-dihydroxy-5-nitropyrimidine with 1-bromo-2,2-diethoxyethane gave 1-β,β-diethoxyethyl-5-nitrouracil (23) and thence, by hydrolysis, the 1-formylmethyl analogue (91%).⁶²³⁶

(e) *In the Presence of Amino Groups* (*H* 364, *E* 273). The alkylation/acylation of cytosine (4-amino-2-hydroxypyrimidine) on a ring-nitrogen is illustrated in the formation of 4-amino-1,2-dihydro-2-oxo-1-propylpyrimidine (24) (propyl iodide/potassium hydroxide/dimethyl sulfoxide at 60°, 44%;⁶²⁵² or better by treatment of 4-acetamido-2-hydroxypyrimidine similarly at 25° followed by deacylation in alcoholic ammonia, overall yield 55%⁵⁶²⁹), 4-amino-1,2-dihydro-1-β-hydroxyethyl-2-oxopyrimidine (ethylene carbonate/dimethylformamide under reflux, 70%),⁵⁸¹⁸ 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine [tri-



methyl phosphate containing tetrabutylammonium fluoride, 70% plus 30% of 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine (25);⁵³²⁸ similar use of dimethyl sulfate and catalyst gave the same separable mixture of products but in 88% and 12% yield, respectively;⁵³³¹ hexamethylenedisilazane plus chlorotrimethylsilane with methyl iodide gave the monomethyl product (76%) in a very clean reaction;^{6562, 6821} and trimethyloxosulfonium hydroxide/dimethylformamide at 80°, 87% of the monomethylated product only⁵⁰³⁹], and 4-amino-1-ethoxycarbonyl-1,2-dihydro-2-oxopyrimidine (aqueous triethyl carbonate, *c.* 40%; note that ethyl chloroformate gave 4-ethoxycarbonylamino-2-hydroxypyrimidine).⁴⁵⁷⁹ Perhaps the best way to make 1-alkylcytosines is by the action of dimethylformamide dialkyl acetals on cytosine with a trace trifluoroacetic acid as catalyst. Thus, cytosine and the dimethyl acetal gave 4-dimethylaminomethyleneamino-1,2-dihydro-1-methyl-2-oxopyrimidine (26, R = Me) and thence, by stirring with 0.1 M hydrochloric acid, 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (27, R = Me) in 95% overall yield.⁶¹⁷¹ The diallyl acetal similarly gave 1-allyl-4-dimethylaminomethyleneamino-1,2-dihydro-2-oxopyrimidine (26, R = CH₂CH:CH₂) and thence 1-allyl-4-amino-1,2-dihydro-2-oxopyrimidine (27, R = CH₂CH:CH₂) in greater than 95% yield.⁶²⁵¹ Several other acetals gave similar results.⁶²⁵¹

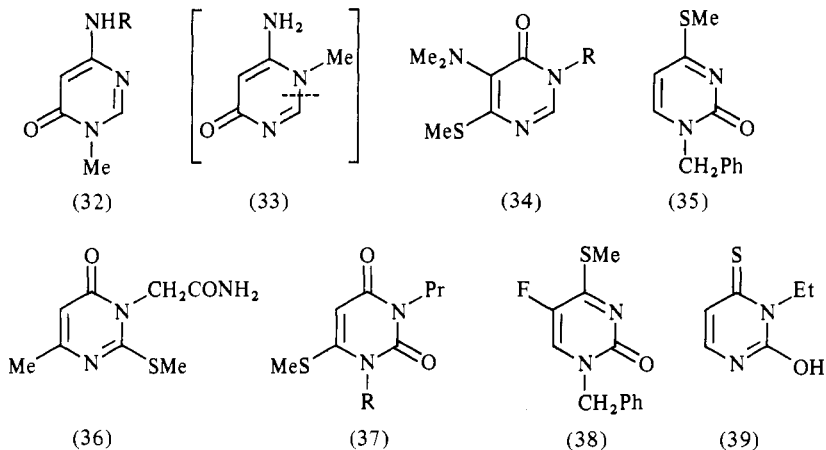
Substituted cytosines behaved rather similarly. For example, 4,6-diamino-2-hydroxypyrimidine (28, R = H) gave 4,6-diamino-1,2-dihydro-1-methyl-2-oxopyrimidine (28, R = Me) (dimethyl sulfate/aqueous buffer of pH 11.6, 62%),⁵²⁴⁵ 4-amino-2-hydroxy-5-phenylpyrimidine gave 4-amino-1,2-dihydro-2-oxo-1- γ -phenoxypentyl-5-phenylpyrimidine (1-bromo-3-phenoxypentane/sodium hydride/di-

methyl sulfoxide, 78%; the original experimental section suggests that the 2-mercaptopyrimidine was used as substrate, but the discussion suggests otherwise!),⁵⁸⁶¹ 6-amino-1-benzyl-5-*N*-methylformamido-uracil (29, R = H) gave 4-amino-3-benzyl-1,2,3,6-tetrahydro-1-methyl-5-*N*-methylformamido-2,6-dioxypyrimidine (29, R = Me) (dimethyl sulfate/alkali, 90%; subsequent hydrogenolysis gave 6-amino-3-methyl-5-*N*-methylformamidouracil, 94%),⁴⁹¹⁴ and 6-amino-1-benzyloxyuracil gave 4-amino-1-benzyl-3-benzyloxy-1,2,3,6-tetrahydro-2,6-dioxypyrimidine (benzyl chloride/aqueous alcoholic sodium carbonate, 73%),⁵⁴²⁵

Isocytosine (2-amino-4-hydroxypyrimidine) derivatives also underwent such alkylations. Thus, 2-amino-4-hydroxy-6-methylpyrimidine was treated with 2-chloroethanol in boiling aqueous methanolic alkali to afford a separable mixture of 2-amino-1,6-dihydro-1- β -hydroxyethyl-4-methyl-6-oxopyrimidine (30, R = OH) and 2-amino-1,4-dihydro-1- β -hydroxyethyl-6-methyl-4-oxopyrimidine (31, R = OH) in about equal amounts.⁵⁸¹⁵ However, the same substrate with 3-chloropropanol gave only 2-amino-1,6-dihydro-1- γ -hydroxypropyl-4-methyl-6-oxopyrimidine (30, R = CH₂OH) without mention of the isomer (31, R = CH₂OH).⁵⁸²⁴ Likewise, the same substrate with acrylonitrile in aqueous sodium hydroxide apparently gave only 2-amino-1- β -cyanoethyl-1,6-dihydro-4-methyl-6-oxopyrimidine (31, R = CN) in 50% yield,⁵⁷⁷³ although with bromoacetic acid/aqueous alkali it gave a separable mixture of 2-amino-1-carboxymethyl-1,6-dihydro-4-methyl-6-oxopyrimidine (70%) and 2-amino-1-carboxymethyl-1,4-dihydro-6-methyl-4-oxopyrimidine (18%).⁴⁷⁶⁴

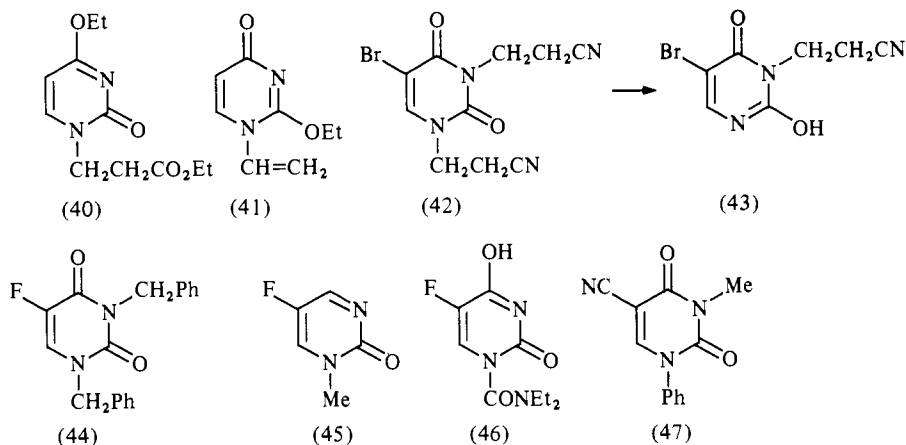
4-Amino-6-hydroxypyrimidine has been converted into 4-amino-1,6-dihydro-1-methyl-6-oxopyrimidine (32, R = H) (30%) by dimethyl sulfate/alkali, and it is now known that a substantial by-product is 1,6-dihydro-1-methyl-4-methylamino-6-oxopyrimidine (32, R = Me), probably formed from the isomeric product (33) by Dimroth rearrangement and subsequent 1-methylation.⁵³⁴⁴

(f) *In the Presence of Mercapto or Alkylthio Groups (H 368, E 275).* Alkylation of hydroxymercaptopyrimidines usually occurs first at sulfur and only subsequently and more slowly at nitrogen if an excess of reagents is present; the final result is the same as if an alkylthio-hydroxypyrimidine had been used as substrate. The whole process is illustrated by random examples in the conversion of 5-dimethylamino-4-hydroxy-6-methylthiopyrimidine (34, R = H) into 5-dimethylamino-1,6-dihydro-1-methyl-4-methylthio-6-oxopyrimidine (34, R = Me) in 65% yield by either methyl iodide/methanolic potassium hydroxide or dimethyl sulfate/acetic potassium carbonate;⁴⁸¹⁶ or 2-hydroxy-4-



methylthiopyrimidine into 1-benzyl-1,2-dihydro-4-methylthio-2-oxopyrimidine (35) (benzyl bromide/methanolic sodium methoxide, 91%),⁵⁷²⁷ of 4-hydroxy-6-methyl-2-methylthiopyrimidine into 1-carbamoylmethyl-1,6-dihydro-4-methyl-2-methylthio-6-oxopyrimidine (36) (2-chloroacetamide/methanolic sodium methoxide, 65%; when 2-bromoacetamide was used, 47% of the same product plus 22% of 4-carbamoylmethoxy-6-methyl-2-methylthiopyrimidine resulted),⁴⁵⁶⁹ of 2-ethylthio-5-fluoro-4-hydroxypyrimidine into a separable mixture of 2-ethylthio-5-fluoro-1,6-dihydro-1-methyl-6-oxopyrimidine (c. 70%) and 2-ethylthio-5-fluoro-1,4-dihydro-1-methyl-4-oxopyrimidine (c. 10%),⁶¹⁸⁵ and of 6-methylthio-3-propyluracil (37, R = H) into 1,2,3,4-tetrahydro-1-methyl-6-methylthio-2,4-dioxo-3-propylpyrimidine (37, R = Me) (methyl iodide/aqueous alcoholic alkali, 75%).⁴⁸⁰⁶ The use of other alkylating agents is illustrated in the conversion of 4-hydroxy-2-mercaptopyrimidine into 1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine (dimethylformamide dimethyl acetal in refluxing toluene);⁶¹⁷⁶ of 5-fluoro-2-hydroxy-4-methylthiopyrimidine into 1-benzyl-5-fluoro-1,2-dihydro-4-methylthio-2-oxopyrimidine (38) (dimethylformamide dibenzyl acetal in dimethylformamide at 80°, 48%; or *O*-benzyl-*N,N'*-dicyclohexylurea in 1,2-dimethoxyethane under reflux, 68%);⁶¹¹¹ of 2-hydroxy-4-mercaptopyrimidine into a separable mixture of 4-ethylthio-2-hydroxypyrimidine (c. 30%) and 3-ethyl-4-thiouracil (39) (c. 20%) (triethyl orthopropionate/propionic anhydride under reflux).⁵⁶⁷⁵

(g) *In the Presence of Other Groups* (H 369, E 276). Regular *N*-alkylations or acylations in the presence of an *alkoxy group* are seen in the formation of 4-ethoxy-1- β -ethoxycarbonyl-ethyl-1,2-dihydro-2-



oxypyrimidine (40) (ethyl acrylate/ethanol with a trace of sodium ethoxide, 80%),⁴⁶⁷¹ 5-ethoxy-1,6-dihydro-1,2-dimethyl-6-oxopyrimidine (methyl iodide/ethanolic potassium hydroxide),⁵⁹⁵⁸ 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-trityloxymethylpyrimidine (from the 2,4-dihydroxy substrate with methyl iodide/barium oxide/dimethylformamide, 87%),⁶³⁹¹ 4-ethoxy-1,2-dihydro-1-methyl- (18%) and 4-ethoxy-2,3-dihydro-3-methyl-2-oxypyrimidine (24%) (dimethyl sulfate/alkali),⁶¹³⁰ 2-ethoxy-1,4-dihydro-4-oxo-1-vinylpyrimidine (41) (vinyl acetate/ethyl acetate containing Hg^{2+} and H^+ , 10%),⁵⁴⁹⁶ the isomeric 4-ethoxy-1,2-dihydro-2-oxo-1-vinylpyrimidine (similarly, 55%),⁵⁴⁹⁵ 1-acetyl-5-methoxymethyluracil (acetic anhydride, 85%),^{6229, 6230} and others.⁴⁷⁷⁵

A *halogeno substituent* can sometimes affect *N*-alkylations as is illustrated in the preparation of 6-chloro-3-methyluracil (dimethyl sulfate/alkali, 51%),⁴⁷³⁹ 6-chloro-1-methyluracil (diazomethane, 52%),⁴⁷³⁹ 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (dimethyl sulfate/alkali, 68%),⁴⁷³⁹ 5-bromo-1- β -cyanoethyluracil (acrylonitrile/aqueous base, 73%),⁴³⁹¹ 5-bromo-1,2,3,4-tetrahydro-1,3-bis- β -cyanoethyl-2,4-dioxypyrimidine (42) [similarly, using an excess of reagents, 75%; subsequent decyanoethylation by methanolic methoxide gave 5-bromo-3- β -cyanoethyluracil (43) (70%) or, if prolonged, 5-bromo-2,4-dihydroxypyrimidine (64%)],⁴³⁹¹ 1-carboxymethyl-5-fluorouracil (chloroacetic acid/alkali, 66%),⁵⁰⁸¹ 1-ethoxycarbonylmethyl-5-fluorouracil (ethyl 2-bromoacetate/potassium carbonate/dimethylformamide, 57%; plus 1,3-bisethoxycarbonylmethyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxypyrimidine, 22%),⁵⁰⁸¹ 1-allyl-6-chloro-1,2,3,4-tetrahydro-3-methyl-2,4-dioxypyrimidine (from 6-chloro-3-

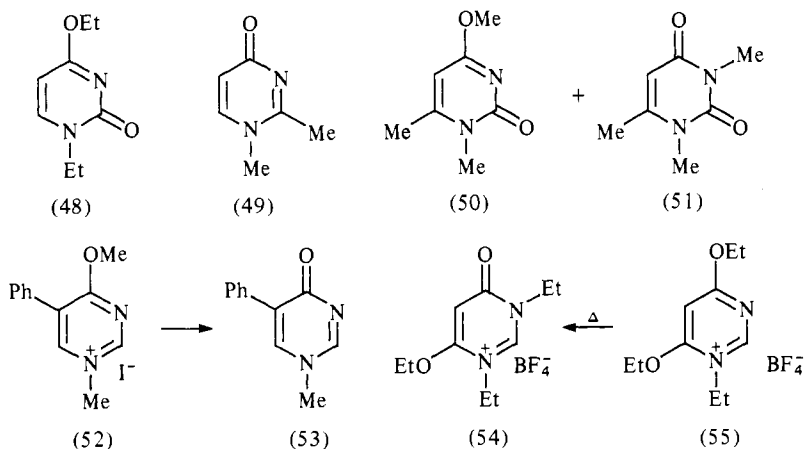
methyluracil with allyl bromide/potassium carbonate/dimethylformamide, 52%),⁴⁶⁵⁷ 1,3-dibenzyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (44) (benzyl bromide/potassium carbonate/dimethylformamide, 84%; plus 1-benzyl-5-fluorouracil, 6%),^{6350, 6511} 1,3-diacetonyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (chloroacetone/potassium carbonate/dimethyl sulfoxide, 15%),⁴⁸⁸⁹ 5-fluoro-1,2-dihydro-1-methyl-2-oxypyrimidine (45) (methyl iodide/methanolic sodium methoxide; 67%),⁴³⁹⁸ 1-*N,N*-diethylcarbamoyl-5-fluorouracil (46) (*N,N*-diethylcarbamoyl chloride/sodium hydride/dimethylacetamide, 76%),⁵¹¹² and others.^{4452, 5082, 5085, 5589, 6145, 6233, 6400}

The *N*-alkylation of hydroxypyrimidines bearing *other groups* is seen in the conversion of 5-cyano-1-phenyluracil into 5-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenylpyrimidine (47) (dimethyl sulfate/alkali, 95%),⁴⁹⁴¹ of 5-bromo-4-carboxy-2,6-dihydroxypyrimidine into 1,3-dibenzyl-5-bromo-4-carboxy-1,2,3,6-tetrahydro-2,6-dioxypyrimidine (benzyl chloride/alkali, 67%),⁴³⁹⁰ of 5-acetyl-1-cyclohexyluracil into 5-acetyl-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxypyrimidine (dimethyl sulfate/alkali, 80%),⁴⁹⁴¹ and of 4-hydroxy-2-methyl-6-methylsulfonylpyrimidine into 1,6-dihydro-1,2-dimethyl-4-methylsulfonyl-6-oxypyrimidine (methyl iodide/ethanolic sodium ethoxide; *c.* 70%).³⁵⁰⁵

(4) *From Alkoxy- and Alkylpyrimidines (H 371, E 276)*

The transformation of alkoxy- into *N*-alkyldihydrooxypyrimidines may be done by the classical Hilbert–Johnson reaction (treatment with an alkyl halide, *via* a quaternary intermediate) or by thermal rearrangement usually in the presence of a tertiary base or a trace of strong organic acid. More recently, trimethylsilyloxy- and trimethylsilyl-alkoxy- substituted pyrimidines have become widely used as substrates, instead of alkoxy- and alkyloxy- substituted pyrimidines, for treatment with alkyl halides in the so-called “Silyl Hilbert–Johnson” reaction⁵⁸⁹⁴ to afford *N*-alkyl (or acyl)dihydrooxypyrimidines.

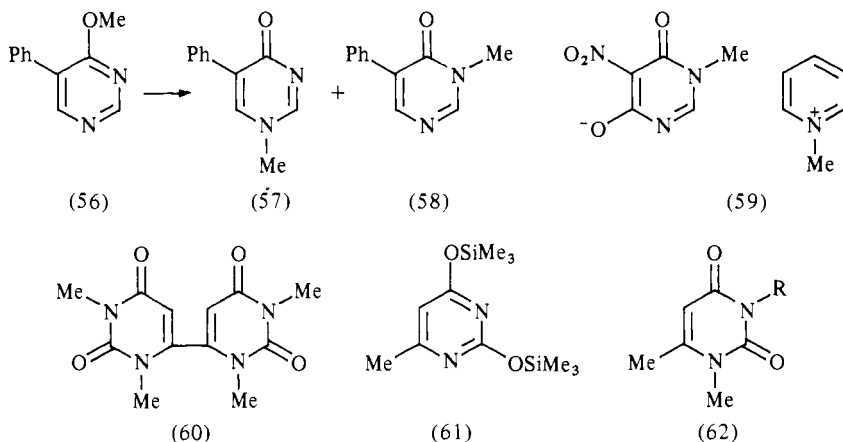
(a) *By the Classical Hilbert–Johnson Reaction (H 371, E 277).* Although this reaction still finds its greatest use in preparing nucleosides,^{e.g., 4387, 4388, 5062} it has been used to convert 2,4-diethoxypyrimidine into 4-ethoxy-1-ethyl-1,2-dihydro-2-oxypyrimidine (48) (ethyl iodide at 20° for 4 weeks, 50%),⁵⁵²⁸ 4-methoxy-2-methylpyrimidine into 1,4-dihydro-1,2-dimethyl-4-oxypyrimidine (49) (methyl iodide at 20° for 4 days, 93%),⁵⁰⁹⁹ 2,4-dimethoxypyrimidine into 1-ethyl-1,2-dihydro-4-methoxy-2-oxypyrimidine (ethyl iodide at 20° for 7 days, 27%),⁵⁴⁹⁰ 2,4-dimethoxy-6-methylpyrimidine into a separable mixture



of 1,2-dihydro-4-methoxy-1,6-dimethyl-2-oxopyrimidine (50) and 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine (51) (methyl iodide at 25° for 60 h, 63% and 4%, respectively),⁴³⁸⁷ 4-methoxy-5-phenylpyrimidine into 1,4-dihydro-1-methyl-4-oxo-5-phenylpyrimidine (53) [methanolic methyl iodide for 12 h gave 4-methoxy-1-methyl-5-phenylpyrimidinium iodide (52) (75%), which on treatment with Ag⁺ and so on gave the product (53) in 44% yield],⁴⁵⁹⁴ 2,4,6-trimethoxy-pyrimidine into 1,6-dihydro-2,4-dimethoxy-1-methyl-6-oxopyrimidine (methyl iodide under reflux; the original paper used a confused name),⁵³²¹ 2,4-diethoxypyrimidine into 4-ethoxy-1,2-dihydro-1-β-hydroxyethyl-2-oxopyrimidine (2-bromoethanol at 55° for 5 days, 20%),⁵⁸¹⁸ and 2,4-dimethoxy- or 2,4-dimethoxy-5-methylpyrimidine into 1-acetyl-1,2-dihydro-4-methoxy-2-oxopyrimidine or its 5-methyl derivative, respectively (acetyl chloride at 20°, 62% and 82%).⁴³⁹⁴ In addition, 4,6-diethoxypyrimidine was converted by triethyloxonium tetrafluoroborate (> 2 mol) into 4-ethoxy-1,3-diethyl-1,6-dihydro-6-oxopyrimidinium tetrafluoroborate (54) (Hilbert–Johnson mechanism, 80%) and the same product was obtained by simply heating 4,6-diethoxy-1-ethylpyrimidinium tetrafluoroborate (55) (thermal rearrangement, 60%);⁴⁶⁹² several other such products have been described^{4692, 4695} as well as more conventional examples.^{5797, 6242} The “Silyl Hilbert–Johnson” reaction is described in Sect. (c) below.

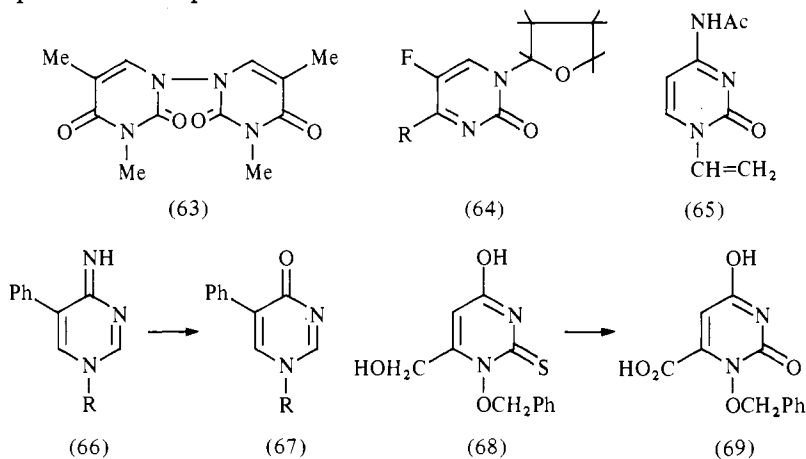
(b) *By Thermal Rearrangement* (H 371, E 280). Thermal rearrangement of alkoxy-pyrimidines can be done, as a rule, only on a small scale. However, it has been used to convert 4-methoxy-5-phenylpyrimidine (56), by heating at 200°, into a 1:3 mixture (90%) of 1,4-dihydro-1-methyl-4-oxo- (57) and 1,6-dihydro-1-methyl-6-oxo-5-phenyl-

pyrimidine (58),⁶⁰³⁶ the same reaction at 170° in the presence of triethylamine gave a separable 1:1 mixture of the same products, and its kinetics, as well as those for *p*-substituted-phenyl analogues, were measured.⁵⁶³⁵ Other examples include the transformation of 2,4-dimethoxy-6-methylpyrimidine into 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxypyrimidine (180° with a trace of *p*-toluenesulfonic acid for 3 min, 80%);⁵⁰⁵⁰ of 4,6-dimethoxy-5-nitropyrimidine into 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxypyrimidine, initially as its methylpyridinium salt (59) (pyridine under reflux, 26%; note the demethylation of the pyrimidine by the pyridine);⁵⁴⁹¹ of 2,2',4,4'-tetramethoxy-5,5'-bipyrimidine into 1,1',2,2',3,3',4,4'-octahydro-1,1',3,3'-tetramethyl-2,2',4,4'-tetraoxo-5,5'-bipyrimidine (60) (neat at 230°, 80%);⁴³⁷⁵ and related examples.^{4922, 5258, 6019}



(c) *By the Silyl Hilbert–Johnson Reaction (New).* The use of trimethylsilyloxypyrimidines as substrates for the Hilbert–Johnson reaction has proven very useful, mainly because hydroxypyrimidines can be converted directly into the corresponding trimethylsilyloxy derivatives so easily, and partly because the subsequent alkylation is often quite facile. Thus, 4-methyl-2,6-bistrimethylsilyloxypyrimidine (61, R = H) gave 1,6-dimethyluracil (62) (76%) by refluxing in methyl iodide, along with a little 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxypyrimidine (62, R = Me) and other by-products;⁵⁹⁵⁷ 5-methyl-2,4-bistrimethylsilyloxypyrimidine and a 15-fold excess of 1,3-dibromopropane at 110° (or at 25° for a long period) gave 1- γ -bromopropyl-5-methyluracil (*c.* 80%),^{4474, 5628} but with only 0.5 mol of dibromopropane, the product was 1,3-bis(1',2',3',4'-tetrahydro-5'-methyl-2',4'-dioxypyrimidin-1'-yl)propane (63) (85%);^{4713, 4728} 5-methyl-2,4-

bistrimethylsilyloxypyrimidine and propyl bromide at 25° for 10 days gave 5-methyl-1-propyluracil (48%);⁵⁶⁴⁶ 2,4-bistrimethylsilyloxypyrimidine with acetyl chloride in benzene gave 1-acetyluracil (43%),⁶¹³² or with tosyl chloride gave 1-tosyluracil (46%);⁴⁸⁵³ 5-fluoro-2,4-bistrimethylsilyloxypyrimidine with 2-acetoxytetrahydrofuran in acetonitrile containing a little sodium iodide (or in methylene chloride containing stannic chloride) gave 5-fluoro-1-tetrahydrofur-2'-yluracil (64, R = OH) (80–90%), which was subsequently resolved into optical isomers;^{4824, 5113} 4-trimethylsilylamino-2-trimethylsilyloxypyrimidine likewise gave 4-amino-5-fluoro-1,2-dihydro-2-oxo-1-tetrahydrofur-2'-ylpyrimidine (64, R = NH₂) in 33% yield;⁴⁸²⁴ the same substrate with vinyl acetate plus a little mercuric acetate and sulfuric acid gave 4-acetamido-1,2-dihydro-2-oxo-1-vinylpyrimidine (65);⁵⁵⁶⁷ 4-*N*-trimethylsilylacetamido-2-trimethylsilyloxypyrimidine with an excess of 1,3-dibromopropane for 20 days gave 4-acetamido-1- γ -bromopropyl-1,2-dihydro-2-oxopyrimidine (43%);⁵⁶²⁸ and there are several other more complicated examples.^{5418, 5894, 6006, 6252}



(5) By Hydrolysis of Iminopyrimidines (*H* 373, *E* 282)

This process has been seldom reported in recent years. However, 4-amino-5-phenylpyrimidine underwent alkylation to 1,4-dihydro-4-imino-1-methyl- (66, R = Me) and 1-ethyl-1,4-dihydro-4-imino-5-phenylpyrimidine (66, R = Et), which in hot or even cold alkali afforded 1,4-dihydro-1-methyl- (67, R = Me) and 1-ethyl-1,4-dihydro-4-oxo-5-phenylpyrimidine (67, R = Et), respectively.⁵⁹¹⁴ The 5-*p*-nitrophenyl (65%) and 5- α -naphthyl (85%) analogues were made similarly,⁶⁰⁴⁴ as

was 1-ethyl-1,4-dihydro-4-oxo-2-phenylpyrimidine (55%),⁴⁶⁹⁷ and others.⁵¹⁸⁴

(6) *From Thiopyrimidines (E 282)*

No examples of the conversion of a *fixed* thiopyrimidine into a fixed oxypyrimidine seem to have been reported recently. However, 1-benzyloxy-6-hydroxymethyl-2-thiouracil (68) has been converted by oxidation with nickel peroxide in aqueous alkali, into 1-benzyloxy-6-carboxyuracil (69) in 24% yield.⁵¹⁷⁵

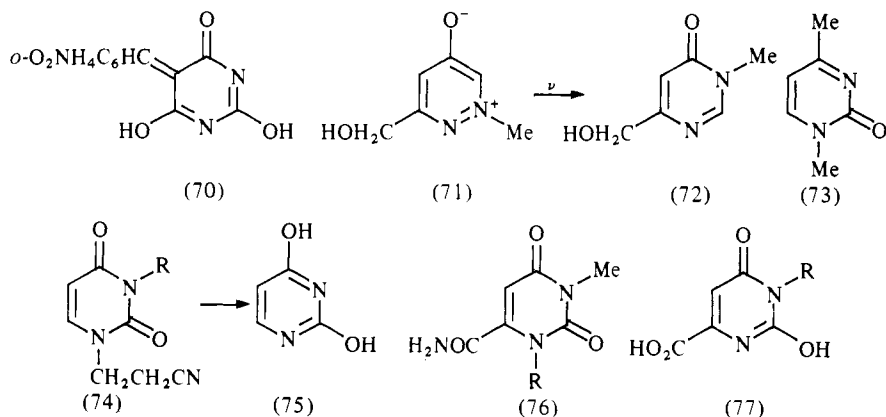
(7) *Minor Routes (New)*

Some minor routes of little importance which lead to oxopyrimidines are exemplified in the conversion of 2,4,6-trihydroxypyrimidine into 5-*o*-nitrobenzylidene-barbituric acid (70), which *must* have at least one oxo substituent either at the 2- or 4/6-position, by refluxing with *o*-nitrobenzaldehyde in water;⁵³⁸⁵ of 4,6-dihydroxy-2-mercaptopyrimidine into 5-*p*-methylbenzylidene-2-thiobarbituric acid by warming with *p*-methylbenzaldehyde in acetic acid/acetic anhydride;⁴⁸⁶⁶ of the anhydro-base (71) of 5-hydroxy-3-hydroxymethyl-1-methylpyridazinium hydroxide into 1,6-dihydro-4-hydroxymethyl-1-methyl-6-oxopyrimidine (72) (75%) by irradiation in ethanol;⁴⁹³³ and of 4,6-dimethylpyrimidine *N*-oxide into 1,6-dihydro-1,4-dimethyl-6-oxopyrimidine (73) (13%) as well as other products, by irradiation in methanol.⁶¹⁷⁵

B. Reactions of Oxopyrimidines (*H* 375, *E* 283)

Oxopyrimidines undergo thiation as do hydroxypyrimidines (Ch. VII, Sect. 6.B). For example, 1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine with phosphorus pentasulfide in α -picoline gave the corresponding 6-thiopyrimidine (87%); both 1,2-dihydro-1-methyl-6-methylthio-2-thiopyrimidine (15%) and 1,4-dihydro-1-methyl-2-methylthio-4-thiopyrimidine (91%) were made similarly;⁵⁶⁶⁵ and 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine gave the dithio analogue (63%) under vigorous conditions.⁶⁵⁵⁴

Other reactions are few, although conversion of an oxo- into an hydroxypyrimidine can be achieved by *N*-*dealkylation*. This quite rare process is illustrated in the treatment of 1- β -cyanoethyluracil (74, R = H) or 1,3-bis- β -cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine



(74, R = CH₂CH₂CN) with refluxing ethanolic sodium ethoxide to give 2,4-dihydroxypyrimidine (75) in greater than 80% yield;⁶⁰⁴⁸ in the *N*-de-s-alkylation of 4-carbamoyl-3-cyclohexyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxypyrimidine (76, R = C₆H₁₁) to 6-carbamoyl-3-methyluracil (76, R = H) (89%) or the corresponding 6-carboxy compound (98%) by heating with sulfuric acid or hydrobromic acid, respectively;⁴⁹⁴⁶ in the similar dealkylation (and hydrolysis) of 1-benzyl-6-carbamoyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxypyrimidine by hydrobromic acid to 6-carboxy-3-methyluracil (95%);⁴⁹⁴⁶ and the conversion of 6-carboxy-3-cyclohexyluracil (77, R = C₆H₁₁) into orotic acid (77, R = H) (82%) by heating in sulfuric acid.⁴⁹⁴⁶ A totally different type of *N*-dealkylation has been achieved by simply replacing the N—C—N section of the pyrimidine along with its substituents. 1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine reacted with urea in hot ethanolic sodium ethoxide to give 2,4-dihydroxypyrimidine (65%);^{5416, 5417} likewise, the same substrate and *N*-methylguanidine gave 4-hydroxy-2-methylaminopyrimidine (59%).⁵⁴¹⁷ The conversion of 4-oxopyrimidines into their Dewar forms (with a 2,5-bond), by irradiation at a low temperature, has been described in detail for a series of 1,6-dihydro-1-methyl-6-oxopyrimidines bearing other *C*-alkyl groups. The spectral and other properties of the Dewar products have been reported.⁶⁵²¹

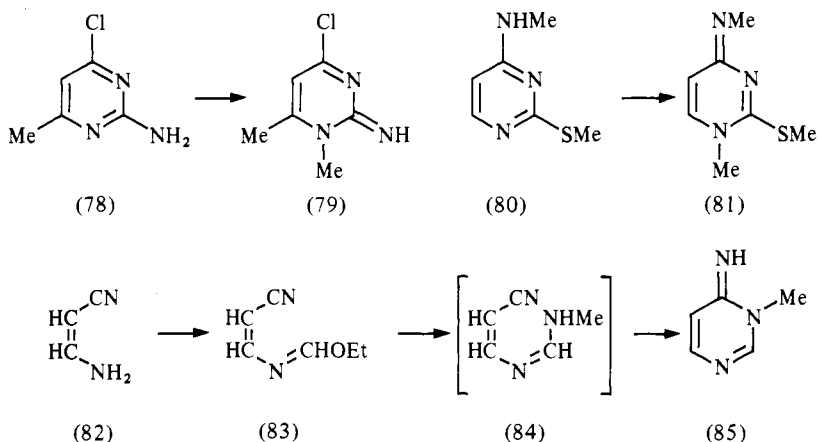
2. The Iminopyrimidines (*H* 377, *E* 284)

A. Preparation of Iminopyrimidines (*H* 377, *E* 284)

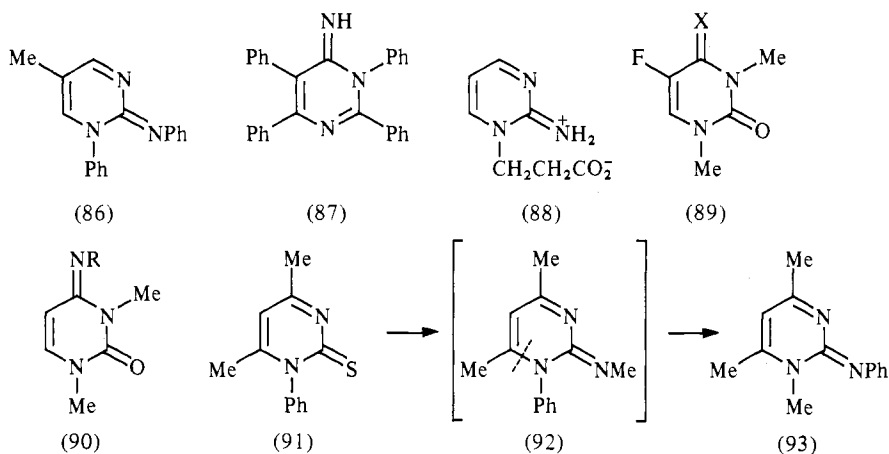
The usual route to iminopyrimidines is by *alkylation* of aminopyrimidines on one or other ring-nitrogen. Thus, 2-amino-4-chloro-6-

methylpyrimidine (78) with methyl iodide at 125° (sealed) gave 4-chloro-1,2-dihydro-2-imino-1,6-dimethylpyrimidine (79) as hydriodide (72%);⁵⁶⁶² 2-amino-5-methoxypyrimidine with methanolic methyl iodide at 25° gave 1,2-dihydro-2-imino-5-methoxy-1-methylpyrimidine hydriodide (>80%);⁵⁶⁶² 4-amino-2-phenylpyrimidine with triethyl-oxonium tetrafluoroborate in refluxing methylene chloride gave 1-ethyl-1,4-dihydro-4-imino-2-phenylpyrimidine as tetrafluoroborate salt (31%);⁴⁶⁹⁷ 2-amino-5-*p*-tolylpyrimidine with methyl iodide at 130° (sealed) gave 1,2-dihydro-2-imino-1-methyl-5-*p*-tolylpyrimidine hydriodide (65%);⁵⁶⁶³ 2-aminopyrimidine with 2-bromoethanol in butanolic dimethylformamide under reflux gave 1,2-dihydro-1- β -hydroxyethyl-2-iminopyrimidine hydrobromide (80%);⁶²⁵⁹ 2-aminopyrimidine with ethyl bromoacetate in refluxing ethanol gave 1-ethoxycarbonylmethyl-1,2-dihydro-2-iminopyrimidine hydrobromide (57%);^{4764, 5996} 4-amino-5-phenylpyrimidine with dimethyl sulfate gave 1,4-dihydro-4-imino-1-methyl-5-phenylpyrimidine sulfate;⁵⁹¹⁴ 4-amino-5-*p*-nitrophenylpyrimidine with methanolic methyl iodide gave 1,4-dihydro-4-imino-1-methyl-5-*p*-nitrophenylpyrimidine hydriodide (70%) and thence the free imine (85%);⁶⁰⁴⁴ 4-methylamino-2-methylthiopyrimidine (80) and methyl iodide at 25° gave 1,4-dihydro-1-methyl-4-methylimino-2-methylthiopyrimidine (81) as hydriodide (>90%);⁵⁶⁶⁵ 2-aminopyrimidine with picryl fluoride (2 mol) gave *free* 1,2-dihydro-1-picryl-2-picryliminopyrimidine, suggesting that the profusion of nitro groups had reduced the basic strength drastically;⁵⁵⁹³ and other examples are known.^{4904, 5289, 5328, 5331, 5600}

A few iminopyrimidines have been made by *primary syntheses*. Reduction of malononitrile with lithium aluminum hydride gave 3-aminoacrylonitrile (82), which reacted successively with triethyl ortho-



formate/acetic anhydride to give 3-(ethoxymethyleneamino)acrylonitrile (83) and with methylamine to give the uncharacterized intermediate (84) which underwent cyclization on refluxing in ethanol to give 1,6-dihydro-6-imino-1-methylpyrimidine (85), isolated in 70% yield as its hydriodide.⁵⁶⁷⁹ The use of appropriately substituted intermediates gave several analogues, for example, 1,6-dihydro-6-imino-4,5-di-isopropyl-1-methylpyrimidine,⁵⁶⁷⁹ and related imines.⁵⁶⁸³ Other syntheses of less scope are exemplified in the condensation of 3-amino-2-methylacrolein with diphenylcarbodiimide at 120° to give 1,2-dihydro-5-methyl-1-phenyl-2-phenyliminopyrimidine (86) (47%);⁴⁴⁶⁴ in the condensation of 3-(α -chlorobenzylidene)amino-2,3-diphenylacrylonitrile with aniline to give 1,6-dihydro-6-imino-1,2,4,5-tetraphenylpyrimidine (87);⁴⁵⁸⁹ in the degradation of 3,4-dihydro-2-oxo-2*H*-pyrimido[1,2-*a*]pyrimidine by aqueous potassium carbonate to give 1- β -carboxyethyl-1,2-dihydro-2-iminopyrimidine, which exists as the betaine (88) or related structure;⁵⁴⁹² and in the condensation of 1-acetyl-2-aminopropene with diphenylcarbodiimide in dimethylformamide containing sodium hydride to give 1,2-dihydro-4,6-dimethyl-1-phenyl-2-phenyliminopyrimidine (59%).⁶⁵²⁸

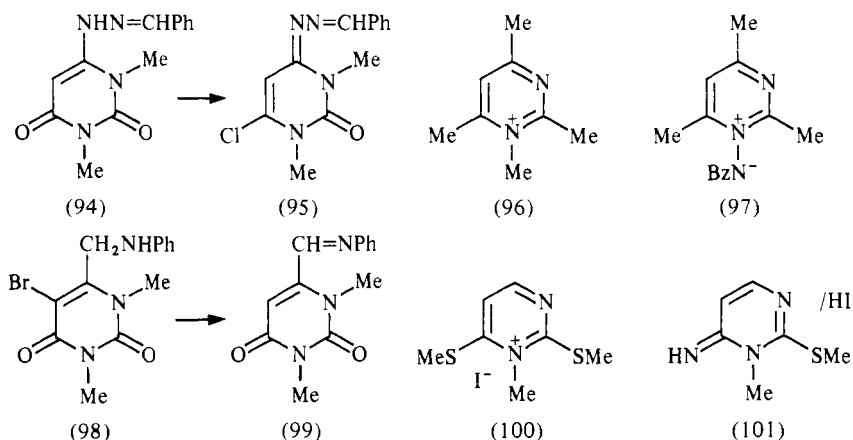


The synthesis of imino- *from* thiopyrimidines is seen in the conversion of 5-fluoro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thiopyrimidine (89, X = S) into 5-fluoro-1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine (89, X = NH) (60%) by ethanolic ammonia at 115°;⁶⁰²⁶ of the similar substrate, 1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thiopyrimidine, into 4-hydrazono-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxopyrimidine (90, R = NH₂) (c. 60%) by refluxing ethanolic hydrazine, or into 1,2,3,4-tetrahydro-4-hydroxyimino-1,3-dimethyl-2-oxopyrimi-

dine (90, R = OH) (c. 70%) by refluxing ethanolic hydroxylamine,⁵³¹³ of 1,2-dihydro-4,6-dimethyl-1-phenyl-2-thiopyrimidine (91) into 1,2-dihydro-1,4,6-trimethyl-2-phenyliminopyrimidine (93) by Dimroth rearrangement of the (unisolated) methylamino isomer (92), using methanolic methylamine in the presence of silver perchlorate at 25° and isolating the final product (48%) as its perchlorate salt,⁶³⁸⁸ and of 1,2-dihydro-1,4,6-trimethyl-2-thiopyrimidine into 1-amino-2-hydrazono-1,2-dihydro-4,6-dimethylpyrimidine (10%) *via* a complicated but rational mechanism, simply by brief treatment with hydrazine.⁵¹⁸⁰

Some *miscellaneous routes* to iminopyrimidines include the conversion of 4-benzylidenehydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (94) by phosphoryl chloride into the substituted imino derivative, 4-benzylidenehydrazono-6-chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxypyrimidine (95) (97%),⁵¹⁶² of 5-nitroso- or 5,5-dibromo-barbituric acid into products that probably exist as 5-(substituted-imino)pyrimidines but which are not fixed as such,^{5044, 5055} of 1-amino-2,4,6-trimethylpyrimidinium (96) (as mesitylenesulfonate), by treatment with benzoyl chloride, into the "iso-electronic *N*-iminopyrimidine" (97), a stable entity obtained in 47% yield;⁶¹⁷⁴ and of 4-anilinomethyl-5-bromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (98) into the extranuclear-iminopyrimidine 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenyliminomethylpyrimidine (99) by treatment with triethylamine [note that other such Schiff bases, hydrazones, and so on from pyrimidine aldehydes or ketones (see Ch. XI) are also truly extranuclear-iminopyrimidines].⁶²⁷⁴

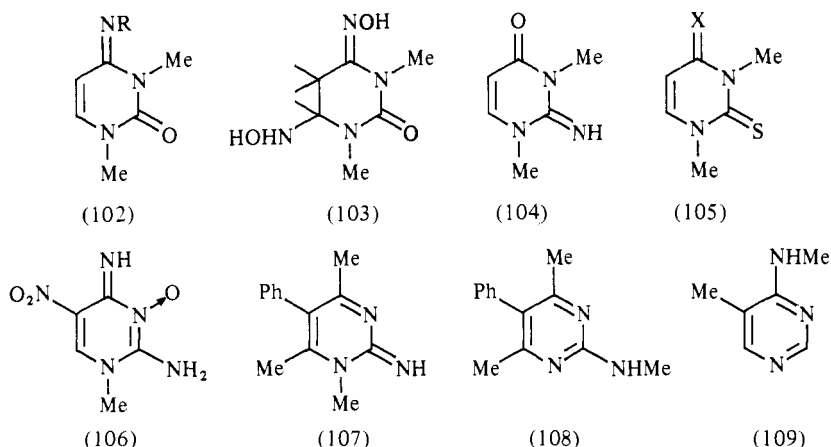
Aminolysis of an *N*-alkyl-2(or 4/6)-methylthiopyrimidinium salt can give an iminopyrimidine, as illustrated in the treatment of 1-methyl-2,6-bismethylthiopyrimidinium iodide (100) with ethanolic ammonia



at 25° to give 1,6-dihydro-6-imino-1-methyl-2-methylthiopyrimidine hydriodide (101) in 92% yield (note that the iminopyrimidine was a stronger base than ammonia and hence retained the iodide ion).⁵⁶⁶⁵

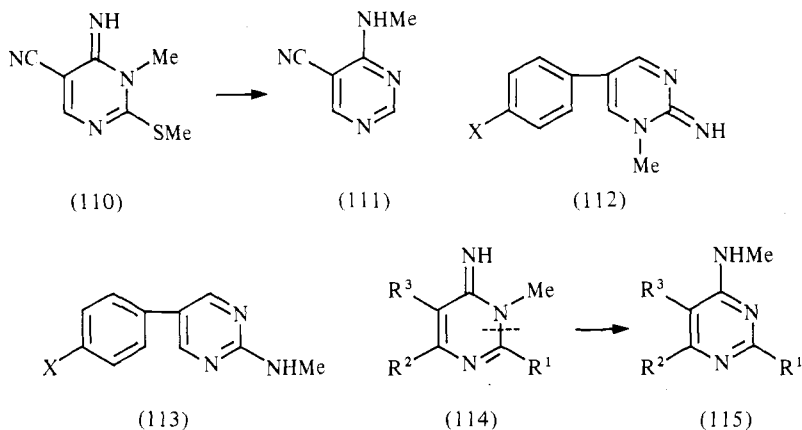
B. Reactions of Iminopyrimidines: Dimroth Rearrangement (*H* 379, *E* 287)

The *hydrolysis* of imino- to oxypyrimidines is discussed above in Sect. 1.A(5). Other reactions of minor importance include *transamination*, as exemplified in the treatment of 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxypyrimidine (102, R = H) with anhydrous hydroxylamine at 37° followed by hot hydrochloric acid to give 1,2,3,4-tetrahydro-4-hydroxyimino-1,3-dimethyl-2-oxypyrimidine (102, R = OH), probably *via* the adduct (103);⁵³¹³ conversion into thiopyrimidines, as exemplified in the *thiation* of 1,2,3,4-tetrahydro-2-imino-1,3-dimethyl-4-oxypyrimidine (104) with phosphorus pentasulfide in boiling pyridine to give a separable mixture of 1,2,3,4-tetrahydro-1,3-dimethyl-4-oxo-2-thiopyrimidine (105, X = O) and the 2,4-dithio analogue (105, X = S);⁵⁶⁰⁰ and the conversion of an iminopyrimidine into its *N*-oxide, for example, 2-amino-1,4-dihydro-4-imino-1-methyl-5-nitropyrimidine 3-oxide (106) by hydrogen peroxide.⁵¹⁸⁸



Compared with the extensive work in the period from 1960 to 1970, more recent reports of *Dimroth rearrangement* in the pyrimidine series have been relatively few. An excellent second review of the Dimroth rearrangement appeared in early 1970 from Leipzig,⁴⁴⁹⁶ followed by one from Louvain⁴³⁶² entitled "The Dimroth Reaction," which covered a method of synthesis in the triazole series, with but passing reference to the rearrangement in that series alone.

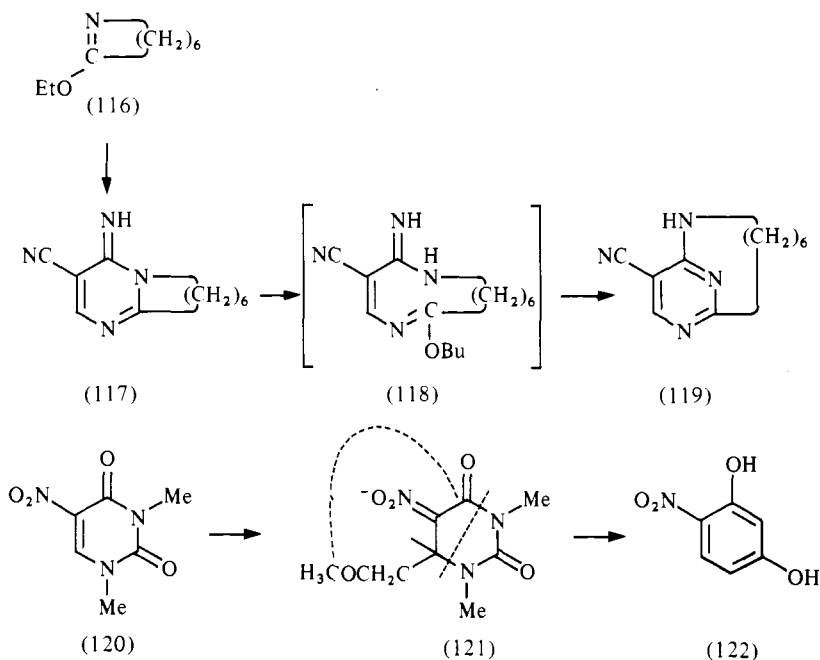
Recent original work on the rearrangement in pyrimidines is illustrated in the isomerization of 1,2-dihydro-2-imino-1,4,6-trimethyl-5-phenylpyrimidine (107) to 4,6-dimethyl-2-methylamino-5-phenylpyrimidine (108) (warm sodium hydroxide, 84%);⁵⁶⁶² 1,2-dihydro-2-imino-1,6-dimethylpyrimidine to 4-methyl-2-methylaminopyrimidine (aqueous sodium hydroxide at 40°, 82%);⁵⁶⁶² 1,6-dihydro-6-imino-1-methylpyrimidine to 4-methylaminopyrimidine (warm sodium hydroxide, 90%);⁵⁶⁶⁵ 1-ethyl-1,6-dihydro-6-imino-4-phenylpyrimidine to 4-ethylamino-6-phenylpyrimidine (hot aqueous potassium hydroxide; 65%);⁴⁶⁹⁷ 1,2-dihydro-2-imino-1-methyl-5-*p*-tolylpyrimidine to 2-methylamino-5-*p*-tolylpyrimidine (aqueous sodium hydroxide at 25°, 81%; other *p*-substituted analogues rearranged similarly);⁵⁶⁶³ 1,6-dihydro-6-imino-1,5-dimethylpyrimidine to 5-methyl-4-methylaminopyrimidine (109) (aqueous sodium hydroxide at 80°, 92%; also 14 analogues similarly);⁵⁶⁷⁹ 5-cyano-1,6-dihydro-6-imino-1-methyl-2-methylthiopyrimidine (110) to 5-cyano-4-methylaminopyrimidine (111) (rearrangement during desulfurization with Raney nickel in ethanol, 62%);⁵⁶⁸³ and others.^{4366, 5943} It seems likely that Dimroth rearrangement can occur on electron bombardment. Thus, those 1,6-dihydro-6-imino-1-methylpyrimidines which undergo rearrangement in solution have mass spectra indistinguishable from those of their methylamino isomers, whereas those imines which do not rearrange easily in solution have their own fragmentation patterns, quite unlike those of their methylamino isomers.⁵⁶⁸⁴



Rates have been measured for Dimroth rearrangement of a series of 1,2-dihydro-2-imino-1-methyl-5-(*p*-substituted-phenyl)pyrimidines (112) into the corresponding 2-methylamino-5-(*p*-substituted-phenyl)pyrimidines (113). Although the mesomeric effects of the *p*-substituents

were severely attenuated by a considerable interplanar angle between the benzene and pyrimidine rings (independently confirmed⁵⁶⁶³ by pK_a and spectral measurements), rearrangement rates decreased in the order $\text{NO}_2 > \text{F} > \text{Cl} > \text{Br} > \text{Me} > \text{OMe} > \text{NH}_2 > \text{NMe}_2$, thus following qualitatively the σ_p values for the substituents.⁵⁶⁶² Rates of rearrangement of a series of 1,6-dihydro-6-imino-1-methylpyrimidines (114), *C*-alkylated in the 2-, 4-, and/or 5-position(s), into the corresponding 4-methylaminopyrimidines (115), have also been measured.⁵⁶⁷⁹ It emerged that the rate varied widely with the nature, number, and position(s) of the alkyl groups. Thus, a 5-alkyl group slowed rearrangement 25- to 190-fold, a 2- or 4-alkyl group caused only a fivefold slowing, and in the 5- but not in the 2- or 4-position, the relative effects of different alkyl groups lay in the order $\text{Pr}^i > \text{Et} > \text{Me}$; rational explanations have been offered.⁵⁶⁷⁹

The preparation and rearrangement of some (bicyclic) polymethyleneiminopyrimidines have also been studied.^{5679, 5683, 5684} For example, 2-ethoxy-3,4,5,6,7,8-hexahydroazocine (116) condensed with aminomethylenemalononitrile to give 3-cyano-6,7,8,9,10,11-hexahydro-4-imino-4*H*-pyrimido[1,2-*a*]azocine (117), which underwent Dimroth rearrangement in boiling butanol to give 12-cyano-2,10,13-triazabicyclo[7,3,1]trideca-1(13),9,11-triene (119), probably *via* the intermediate (118).⁵⁶⁸³



an argon atmosphere gave a small yield of 1-methyl-2-thiouracil (127) and its 3-methyl isomer (128), although neither is *fixed* in the thio-pyrimidine tautomeric form.⁵⁴¹⁸

Thiopyrimidines undergo few reactions not already discussed. Hydrazinolysis of 1,2-dihydro-1,4,6-trimethyl-2-thiopyrimidine was found to be a complicated reaction, yielding at least three products: 1-amino-2-hydrazono-1,2-dihydro-4,6-dimethylpyrimidine (129), 3,5-dimethylpyrazole, and 4-amino-5-hydrazino-3-mercapto-1,2,4-triazole (130);⁵¹⁸⁰ the formation of the last mentioned compound (130) proved a reliable test for any heterocyclic entity which included a "thioureido moiety,"⁵¹⁷³ and the analogous reactions of related mercapto- or thio-pyrimidines have been explored in some depth.^{5180, 5181}

4. The Pyrimidine *N*-Oxides* (*H* 382, *E* 294)

Pioneering work on the pyrimidine *N*-oxides was conducted by a Japanese school under the direction of E. Ochiai: 4-methylpyrimidine *N*-oxide, prepared by the action of peroxyacetic acid on 4-methylpyrimidine, was reported in 1945,⁴⁷⁰ but it was found subsequently to be a separable mixture of the 1- and 3-oxide.⁶⁴⁵⁴ While much of such early work based on oxidative preparations was hampered by structural ambiguity in asymmetrical products, it nonetheless set a framework for the principal approach to such compounds for the future; reviews have appeared.^{6454, 6455}

A. Preparation of Pyrimidine *N*-Oxides (*H* 382, *E* 294)

(1) *By Direct Oxidation (New)*

The *N*-oxidation of pyrimidines by *peroxycarboxylic acids* remains the most facile method of obtaining pyrimidine *N*-oxides. The earliest reported methods generally employed peroxyacetic acid, most often prepared *in situ* by the addition of various concentrations of aqueous hydrogen peroxide to glacial acetic acid. Yields with this reagent vary from poor to excellent (Table XVk). Discussions of the advantages and disadvantages of this reagent vis-a-vis other peroxycarboxylic acids, have been published.⁶⁴⁵⁵

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TABLE XVk. The *N*-Oxidation of Pyrimidines by Peroxyacetic Acid (*New*)

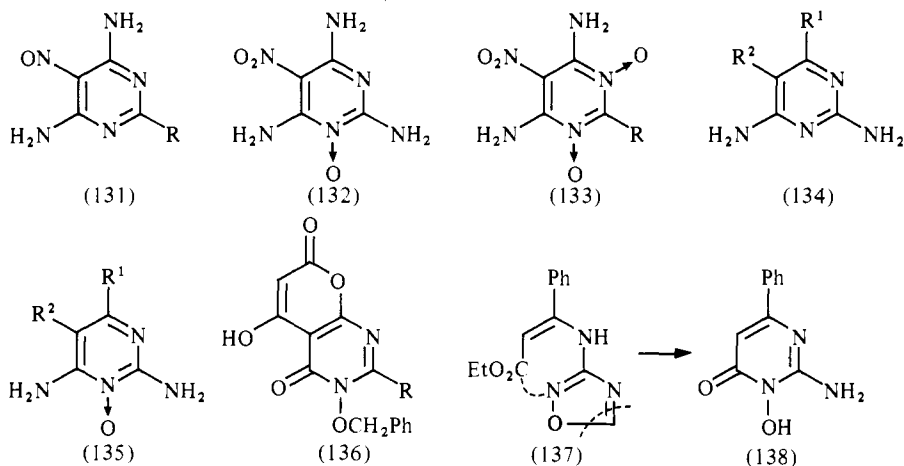
Substituents				Yield(s) of Oxide(s)		Reference
2-	4-	5-	6-	N1	N3	
Me	Et	—	Me	30	25	6445
Pr ⁱ	Et	—	Me	28	18	6445
Ph	Me	—	Me	45	—	6445
Me	CH ₂ Ph	—	Me	18	15	6445
Me	Ph	—	Me	40	0.6	6445
—	OMe	Me	Me	78	0	4387
Me	Me	—	Pr ⁱ	18	28	5088
Ph	Et	—	Me	22	12	6445

Peroxymaleic acid is a useful reagent for preparing pyrimidine *N*-oxides when anhydrous conditions are required. This is specially so when used in the presence of hydrolytically labile substituents such as the halogens.⁵⁰⁷¹ Table XVI gives examples of the use of this reagent.

Trifluoroperoxyacetic acid is a powerful oxidizing agent and its use has increased considerably in recent years. An indication of the great potential of this reagent can be seen in the multiple oxidations which may take place with its use. For example, when 2,4,6-triamino-5-nitrosopyrimidine (131, R = NH₂) is treated with trifluoroperoxyacetic acid, the mono- (132) and di-*N*-oxide (133, R = NH₂) of the corresponding 5-nitropyrimidine are formed.⁶³³⁵ The ratio of mono- to dioxide can be controlled by the amount of reagent used. A similar reaction with 4,6-diamino-5-nitrosopyrimidine (131, R = H) gave the corresponding nitro di-*N*-oxide (133, R = H), albeit in low yield.⁵⁶⁴⁷ 2,4-Diamino-5-chloro-6-methylpyrimidine gave the corresponding di-*N*-

TABLE XVI. The *N*-Oxidation of Pyrimidines by Peroxymaleic Acid (*New*)

Substituents				Yield(s) of Oxide(s)		Reference
2-	4-	5-	6-	N1	N3	
Me	Cl	—	Me	34	0	5071
Et	Cl	—	Me	57	0	5071
Pr ⁱ	Cl	—	Me	74	0	5071
Cl	Me	—	Me	34	—	6456
—	OPh	—	Me	50	0	4684
—	Cl	—	Me	30	0	6457
—	Cl	—	Ph	26	0	6457
—	Br	—	Ph	22	0	4685
—	OPh	—	Ph	52	0	4685
—	Cl	Ph	Ph	42	0	4685
—	Ph	—	Ph	37	—	6105
—	Bu ^t	—	Bu ^t	42	—	6105



oxide upon similar treatment.⁵¹⁸⁸ Another example of multiple oxidation occurring with this reagent is seen with 2,4-diamino-6-phenylthiopyrimidine (134, $R^1 = \text{SPh}$, $R^2 = \text{H}$), which gives 2,4-diamino-6-phenylsulfonylpyrimidine 3-oxide (135, $R^1 = \text{SO}_2\text{Ph}$, $R^2 = \text{H}$) in 60% yield.⁵¹⁸⁸ This reagent has also been used to prepare *N'*-oxides of *N*-methylated pyrimidines⁵¹⁸⁸ and *N*-oxides of 5,5-disubstituted barbituric acids.⁵²¹⁸

Peroxyacetic acid oxidation of 2,4-diamino-6-chloropyrimidine (134, $R^1 = \text{Cl}$, $R^2 = \text{H}$) gives the corresponding 5,6-dichloro 3-oxide (135, $R^1 = R^2 = \text{Cl}$), a phenomenon which has been described elsewhere.⁵⁰⁷¹ However, when trifluoroperoxyacetic acid from 90% hydrogen peroxide is used at 0° , only the chloro 3-oxide (135, $R^1 = \text{Cl}$, $R^2 = \text{H}$) is formed.⁵⁵⁸⁵

TABLE XVm. The *N*-Oxidation of Pyrimidines by *m*-Chloroperoxybenzoic Acid (*New*)

Substituents				Yield(s) of Oxide(s)		
2-	4-	5-	6-	<i>N</i> 1	<i>N</i> 3	Reference
OH	NH ₂	F	—	0	34	3464
Cl	NH ₂	F	—	0	20	3464
NH ₂	NH ₂	TMB ^a	—	38.5	22.8	6460
NH ₂	NH ₂	—	Cl	0	44.7	6461
NH ₂	Me	—	Cl	0	8	6461
NH ₂	Me	—	DCP ^b	0	64	5724
NH ₂	OTs	—	MCA ^c	73	0	6536

^aTMB = 3',4',5'-trimethoxybenzyl-.

^bDCP = 2',4'-dichlorophenoxy-.

^cMCA = methoxycarbonylamino-.

TABLE XVn. The *N*-Oxidation of Pyrimidines with Hydrogen Peroxide and Sodium Tungstate (New)

Substituents				Yield of Oxide		Reference
2-	4-	5-	6-	N1	N3	
—	—	—	—	17	—	6462
—	—	Br	—	19	—	5500
—	—	OMe	—	61	—	5500
—	Ph	—	—	70	0	4810
Me	Ph	—	—	60	0	4810

The use of *m*-chloroperoxybenzoic acid has gained in popularity recently, no doubt due to its convenience and commercial availability. It is frequently used in acetic acid with good results (Table XVm). Cytosine arabinoside 3-oxide was prepared in 54% yield by this method.⁶⁴⁵⁸

Some *other methods of oxidation* have been used to prepare a number of pyrimidine *N*-oxides. For example, hydrogen peroxide solution in the presence of sodium tungstate appears to have produced reasonably good results (Table XVn). In addition, 4,6-dimethylpyrimidine *N*-oxide and 4-methyl-6-phenylpyrimidine 3-oxide were isolated in 27% and 18% yield, respectively, when the parent pyrimidines were treated with hydroxylamine-*O*-sulfonic acid.⁶⁴⁶³

(2) By Primary Synthesis (New)

The earliest examples of pyrimidine *N*-oxide formation by the *Principal Synthesis* involved the N—O portion being incorporated into the ring as part of the one-carbon fragment.^{3464, 6464} Syntheses of this type are still to be found in the recent literature. For example, contrary to an earlier claim,³⁹³⁶ it is seen that hydroxyurea condenses with ethyl acetoacetate in ethanolic sodium ethoxide solution to give 1-hydroxy-6-methyluracil.⁵³⁵⁰ The synthesis was extended to a 5,6-disubstituted-1-hydroxyuracil and other 6-substituted uracils. Other examples of this type are to be found,⁵²¹⁸ including the reaction of *N,N'*-dibenzoyloxyurea with 5,5-diethyl- and 5-ethyl-5-phenylmalonyl dichloride to give the *N,N'*-dibenzoyloxy derivatives of the clinically significant drugs barbital and phenobarbital, respectively.⁶²⁶⁸ The benzyl protecting groups were cloven catalytically or with hydrogen bromide in acetic acid to give the *N,N'*-dihydroxy derivatives. Various *O*-benzyl amidoximes condense with carbon suboxide and substituted malonyl dichlorides to

give various 2- and 5-substituted-*N*-benzyloxy-4-hydroxy-6-oxopyrimidines.^{4337, 4353} The same oxime-ether condenses with malonyl dichloride or malonic acid to give *N*-benzyloxypyranopyrimidines (136, R = Me, Et, or Ph).^{4337, 4353} Similarly, benzamidoxime condenses with substituted-malonyl dichlorides in the presence of triethylamine to give 5-substituted-3,4-dihydro-3,6-dihydroxy-4-oxo-2-phenyl pyrimidines.⁴⁹¹⁶

Several *other primary syntheses* have been used also. The alkoxide-catalyzed reaction between various *N*-aralkoxyurethanes and α,β -unsaturated amides gives various 1-aralkoxy-5,6-dihydrouracils. The same uracils can be formed in like manner from *N*-aralkoxyureas and α,β -unsaturated esters and by similar methods.⁵⁹¹² Ethyl *N*-(γ -halogenopropyl)carbamate reacts with hydroxylamine in aqueous solution to give hexahydro-1-hydroxy-2-oxopyrimidine. The 3-methyl and 3-ethyl derivatives are made in the same manner.⁶⁴⁶⁵ 3-Anilinopropamidoximes condense with aliphatic and aromatic aldehydes to give 4-amino-1,2,5,6-tetrahydro-1-phenyl-2-substituted-pyrimidine 3-oxides.⁶⁴⁶⁶ Various substituted β -ketothiocyanates react with hydroxylamine in aqueous acidic solution to give tetrahydro-1-hydroxy-2-thio-4,5,6-trisubstituted-pyrimidines in yields ranging from 31 to 96%.⁶⁴⁶⁷ 1,3-Hydroxyamino oximes cyclize with aldehydes or ketones to give 1,2,5,6-tetrahydro-1-hydroxypyrimidine 3-oxides.⁶⁴⁶⁸ Those compounds, derived from aldehydes, can be oxidized with manganese dioxide to give the corresponding pyrimidine di-*N*-oxides.^{4757, 4814, 4861} Triaminopyrimidine *N*-oxides can be prepared in good yield by the action of hydroxylamine on 3-amino-3-cyanoiminopropanenitriles.^{5508, 5566}

Yet other primary syntheses involving *ring transformations* to yield *N*-oxides have been described. 1,3-Oxazines react with hydroxylamine to give *N*-hydroxypyrimidines. Thus, when 6-methyl-1,3-oxazine-2,4-dione is treated with hydroxylamine, 1-hydroxy-6-methyluracil is produced.^{6469, 6470} Similarly, 6-hydroxymethyl-2-thio-1,3-thiazin-4-one reacted with benzyloxyamine to give 1-benzyloxy-6-hydroxymethyl-2-thiouracil. This reacted with dimethyl sulfate to give the *S*-methyl derivative, which hydrolyzed to give 1-benzyloxy-6-hydroxymethyluracil and 1-hydroxy-6-hydroxymethyluracil. Alternatively, the *S*-methyl compound reacted with an excess of nickel peroxide to give 1-benzyloxyorotic acid.⁵¹⁷⁵

1-Aminopyrimidinium mesitylenesulfonates react with an excess of hydroxylamine to give pyrimidine *N*-oxides in good yield. Thus, 1-amino-4,6-dimethyl- and 1-amino-4,6-diphenylpyrimidinium salts gave 85% and 35% of the corresponding *N*-oxides, while 1-amino-2,4,6-trimethylpyrimidinium salts gave 90% of the 1-oxide.⁴⁶⁹¹ The

1,2,4-oxadiazole (137), when heated under anhydrous conditions with *p*-toluenesulfonic acid, gives 2-amino-1,6-dihydro-1-hydroxy-6-oxo-4-phenylpyrimidine (138); this pyrimidine is formed by the base-catalyzed hydrolysis of 2,7-diphenyl-[1,3,4]-oxadiazolo[2,3-*a*]pyrimidine 4-oxide as well.⁴⁵⁹¹ 4,5-Diamino-1,6-dihydro-1-hydroxy-6-oxopyrimidine and its 2-methyl derivative are formed by the action of an excess of hydroxylamine on 3,4-dihydro-3-hydroxy-4-oxopteridine and its 2-methyl derivative, respectively.⁵⁶⁵⁰ 7,9-Dimethylxanthine 3-oxide bisulfate in alkali gives 1-hydroxy-6-methylamino-5-*N*-methylformamido-uracil.⁵⁴²⁴

B. Properties and Reactions of Pyrimidine *N*-Oxides (*H* 383, *E* 295)

(1) *E.S.R.*, *Dipole Moment*, and *M.O. Studies* (New)

In the 1960s, T. Kubota studied the electronic spectra and determined the electronic structure²⁴¹⁶ and dipole moment of 4-methylpyrimidine *N*-oxide.²⁴¹⁷ Dipole moments of other pyrimidine *N*-oxides have been determined.^{2418, 3424} E.s.r. and polarographic studies of anion radicals of heterocyclic amine *N*-oxides, including pyrimidine *N*-oxide, have been published.⁶⁴⁷¹ Similarly, the half-wave oxidation and reduction potentials of pyrimidine *N*-oxide have been determined.^{6472, 6473} Ionization energies and photoelectronic spectra of several diazine *N*-oxides, including pyrimidine *N*-oxide, have been published.⁶⁴⁷⁴ A discussion of several molecular orbital calculations and their relationships with nmr chemical shifts has appeared.⁶⁴⁷⁵

(2) *NMR Studies* (New)

Proton coupling constants for pyrimidine *N*-oxides have been determined along with their relative signs in ¹⁴N decoupled experiments.^{5179, 6476} The effects of *N*-oxidation upon benzene shielding of ring protons has been determined for 2-methyl-, 4-methyl-, 5-methyl-, 2,4-dimethyl-, and 4,6-dimethylpyrimidine *N*-oxide.⁶⁴⁷⁷

An outstanding nmr technique for determining the site of *N*-oxidation in alkylpyrimidine *N*-oxides has been devised.⁵⁰⁸⁸ The method is based on changes in chemical shift for protons adjacent to the pyrimidine ring upon addition of a lanthanide shift reagent. Such α -protons, which are in a position adjacent to an *N*-oxide substituent, undergo the greatest change in chemical shift. The method is effective in distinguishing

the 1- and 3-oxides of 4-ethyl-2,6-dimethylpyrimidine. The structures of these *N*-oxides have been confirmed by chemical means. The ^{14}N chemical shift of N1 relative to N3 in pyrimidine *N*-oxide is known.⁶⁴⁴⁴ The ^{15}N nmr of pyrimidine *N*-oxides has been used for structural determinations,⁶¹¹³ but the efficacy of this method for such determinations within the 2,4-diaminopyrimidine *N*-oxides has been questioned.⁶⁰⁹² Pyrimidine *N*-oxide and various alkylpyrimidine *N*-oxides are included in a ^{15}N nmr study of heteroaromatic *N*-oxides. This work indicates that a relationship exists between the ^{15}N chemical shifts and N—O infrared absorption frequencies.⁶⁴⁷⁸

(3) *Infrared and Ultraviolet Spectra; X-Ray Crystallography (New)*

The infrared spectra of pyrimidine *N*-oxides were examined in some detail in the 1950s and 1960s.^{438, 2415, 2869} A combination of infrared and ultraviolet spectra with dissociation constants have been used to determine the tautomeric structures of 1,2-dihydro-1-methoxy-, 1-benzyloxy-1,2-dihydro-, and 1,2-dihydro-1-hydroxy-4,6-dimethyl-2-oxypyrimidine.²⁸⁶⁹ The infrared spectrum of the iodine complex of pyrimidine *N*-oxide provides evidence, under the conditions employed, that the oxygen atom of the N—O portion is the basic center of the molecule.^{6479, 6480} A detailed account of ultraviolet spectra for pyrimidine *N*-oxides appeared in 1961; solvent and substituent effects were determined and discussed.⁶⁴⁸¹

The crystal structure of the dihydrate of 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine 1-oxide has been determined.⁶⁴⁸² This substance is a major metabolite of the antibacterial drug, trimethoprim. The potassium and rubidium salts of 5-bromo-3-hydroxy-3-methyluracil have been prepared and their crystal structures were determined: these acid salts are nonisomorphous.⁶²³⁷

(4) *Ionization Constants (New)*

Only a few ionization constants of pyrimidine *N*-oxides have been determined. The earliest example, that of 1,2-dihydro-1-hydroxy-4,6-dimethyl-2-oxypyrimidine, indicates a base-weakening effect ($\text{p}K_{\text{a}}$ 2.85; *cf.* 3.75 for the parent pyrimidine) and an acid-strengthening effect ($\text{p}K_{\text{a}}$ 6.1; *cf.* 9.9 for parent) upon *N*-oxidation.²⁸⁶⁹ Similarly, oxidation at N3 of cytosine causes an increase in acid strength of *c.* 2 units; this oxidation, however, causes a slight increase in basic strength.³²¹⁵ The

ionization constants for a number of aminopyrimidine *N*-oxides have been determined and in each case oxidation causes a decrease in basic strength. The 1-oxides of 2,4-diaminopyrimidine and its 5-(3',4',5'-trimethoxybenzyl) derivative are weaker bases than the isomeric 3-oxides.⁶⁴⁸³

Ionization constants of several *N*-hydroxy- and *N,N'*-dihydroxy-barbituric acid derivatives show these compounds to be stronger acids than the parent substances. This is especially true for the *N,N'*-dihydroxy derivatives of the barbiturate drugs, barbital and phenobarbital.⁶⁴⁸⁴ The equilibrium constants and ΔH^0 values for the interaction of phenol with pyrimidine *N*-oxide in dichloromethane have been determined.⁶⁴⁸⁵

(5) *Miscellaneous Physical Properties (New)*

Pyrimidine *N*-oxide is included in a large study of the kinetics of deuterium exchange of heteroaromatic substances in base.⁶⁴⁸⁶ A more detailed examination of the base-catalyzed deuterium exchange rates and kinetics of exchange of ring protons in 5-substituted-pyrimidine 1-oxides indicates that the exchange rate for H6 is strongly influenced by the inductive effect of the 5-substituent.⁵⁵⁰⁰ A linear free energy relationship exists between $\log k_{H6}$ and σ_I substituent constants; this is not true for H2. The hydrogen atoms adjacent to the *N*-oxide function exchange more readily than hydrogen atoms adjacent to ring-nitrogen in the parent pyrimidines.⁵⁵⁰⁰

Partition coefficients for a range of 2,4-diamino-6-(disubstituted-amino)pyrimidine 3-oxides have been determined by an high-pressure liquid chromatographic method.⁶⁴⁸⁷ The copper complexes of the 1- and 3-oxides of 2,4-diamino-5(3',4',5'-trimethoxybenzyl)pyrimidine have been described.⁶⁴⁶⁰

(6) *Reductions (New)*

The pyrimidine *N*-oxides are generally susceptible to the common chemical and catalytic means of reduction. Thus, *catalytic reduction* is usually effective in reducing pyrimidine *N*-oxides to the parent pyrimidines,^{5424, 5426, 5647, 6460, 6488} although some of the *N*-hydroxypyrimidines resist such treatment.⁵²¹⁸ It is often possible by choice of catalyst and conditions, to reduce other functional groups in the presence of an *N*-oxide function.⁶³³⁵ For example, 2,4-diamino-6-chloropyrimidine

3-oxide,⁶⁰⁹² as well as 4-chloro-6-methyl-⁶⁴⁵⁷ and 4-chloro-6-phenylpyrimidine 1-oxide⁶⁴⁵⁷ are all dehalogenated by one equivalent of hydrogen in the presence of a palladium catalyst without reducing the *N*-oxide function.

A number of chemical reducing agents can be effective in reducing the N—O bond of pyrimidine *N*-oxides; typically such compounds as dithionite^{6445, 6460} and phosphorus trichloride⁶⁴⁵⁹ are employed successfully. Titanium trichloride appears to be an excellent reducing agent for pyrimidine *N*-oxides.⁶⁴⁸⁹ Neat triethyl phosphite reduces both *N*-oxide functions in 4-phenyl- and 5-ethyl-4-phenylpyrimidine, 1,3-dioxide. The same reagent in tetrahydrofuran or dioxane gives from each the isomeric mono-*N*-oxide.⁴⁷⁵⁷ Although no recent examples have appeared, zinc in hydrochloric acid is also effective in reducing *N*-oxides²²⁶² as is iron in acetic acid.⁴⁶⁸⁴ Chemical methods may also be used to reduce selectively other groups in the molecule bearing the *N*-oxide function.⁵⁴²⁶

(7) Halogenation (New)

Electrophilic halogenation at C5 is well represented in the *N*-oxides.^{4810, 6459, 6483} Halogenations in positions adjacent to ring-nitrogens by the standard reagents, phosphorus halides, of necessity require the *N*-oxide to be masked by a protecting group. Several examples are given in the early literature.²²⁶²

(8) Nitrosation and Nitration (New)

Both nitrosation and nitration of *N*-oxides are represented in recent literature. Nitrosation of pyrimidine *N*-oxides with three electron-donating groups present in the ring, appears to be a facile reaction.^{3397, 5425, 6490} Nitrations are less well represented.⁵⁴²⁶

(9) Acylation (New)

Early interest in acylations was a result of the molecular rearrangements^{791, 3215} that occurred with acetic anhydride. Normal reactions are probably more common. For example, 2,4-diamino-6-piperidinopyrimidine 3-oxide reacts with a molar equivalent of acetic anhydride to give 79% of the 4-acetamido and 3% of the 2-acetamido *N*-oxide. Similar results are obtained with one equivalent of benzoic anhydride and glutaric anhydride which react preferentially with the 4-amino group.

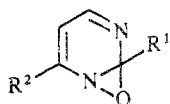
With an excess of acetic anhydride, the corresponding 2,4-diacetamido *N*-oxide is isolated.⁵⁶⁰⁶ 2,4-Diamino-6-piperidinopyrimidine 3-oxide and sulfur trioxide with an organic base gave the corresponding 3-sulfoxy derivative as the pyrimidinium hydroxide inner salt.⁶⁷⁰²

(10) Alkylations (New)

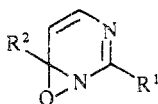
There do not appear to be any examples of the alkylation of pyrimidine *N*-oxides except for those catalyzed by base. In many such cases, the N—O group is masked by a protecting group.^{3397, 5425} Base catalyzed methylation of 5,5-diethyl-*N*-hydroxybarbituric acid gave mostly the corresponding *N*-methoxy derivative, along with a trace of the *N*-methoxy-*N'*-methyl derivative. Benzylation gave a 3 : 2 mixture of the *O*-benzylated and *O,N*-dibenzylated compounds.⁵²¹⁸

(11) Photochemical Reactions (New)

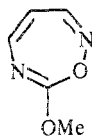
The photochemistry of simple pyrimidine *N*-oxides has been well investigated.^{6488, 6491} The initial reaction appears to involve the formation of oxaziridinopyrimidine intermediates (139) and (140). The proposed mechanism for the photolysis of 2-methoxypyrimidine *N*-oxide involves the oxaziridine intermediate (139, $R^1 = \text{OMe}$, $R^2 = \text{H}$) undergoing ring-expansion to the methoxy-1,2,6-oxadiazepine (141), while the isomeric oxaziridine (140, $R^1 = \text{OMe}$, $R^2 = \text{H}$) forms the 1,2,4-oxadiazepine (142).⁶⁴⁹² These intermediates undergo rearrangements to β -methoxycarbonylaminoacrylonitrile (143, $R = \text{H}$) and 4-formyl-2-methoxyimidazole (144), respectively. 5-Methoxypyrimidine *N*-oxide gives, in a similar manner, from initial reaction at C2, the methoxy nitrile (143, $R = \text{OMe}$) and 4-methoxycarbonyl-



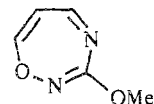
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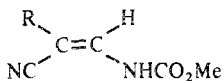
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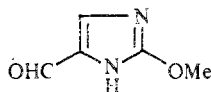
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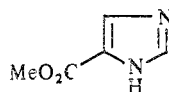
(142)



(143)



(144)



(145)

imidazole (145).⁶⁴⁹² 4,6-Disubstituted pyrimidine *N*-oxides can undergo a similar rearrangement to imidazoles, but another major product is an *N*-substituted oxopyrimidine.⁶¹⁷⁵ For example, 4,6-dimethylpyrimidine *N*-oxide gives a mixture of 4-acetyl-5-methylimidazole and 1,6-dihydro-1,4-dimethyl-6-oxopyrimidine.⁶¹⁷⁵ Similarly, from the photolysis of 4-methyl-6-phenylpyrimidine 3-oxide is isolated 4-acetyl-5-phenylimidazole and 1,6-dihydro-1-methyl-6-oxo-4-phenylpyrimidine.⁶¹⁷⁵ When the substituents in the 4- and 6-positions are both bulky, entirely different products are formed.⁶¹⁰⁵ For example, photolysis of 4,6-diphenylpyrimidine *N*-oxide in methanol gives 3,5-diphenylpyrazole and 2-methoxy-4,6-diphenylpyrimidine. When the reaction is carried out in benzene, only the diphenylpyrazole is formed. 4,6-Di-*t*-butylpyrimidine *N*-oxide undergoes photolysis in methanol to give 3,5-di-*t*-butylpyrazole and 4,6-di-*t*-butyl-2-hydroxypyrimidine.⁶¹⁰⁵

The photolysis of 2,4,6-trisubstituted pyrimidine *N*-oxides has been studied.⁶⁴⁹³ When 2,4,6-trimethyl-, 4-chloro-2,6-dimethyl- and 4-methoxy-2,6-dimethylpyrimidine 1-oxide are photolyzed, 4-acetyl-2,5-dimethyl-, 4-chloro-2-methyl-, and 5-methoxy-2-methylimidazole are isolated, respectively. The other principal products in these cases are the corresponding 1,6-dihydro-1,2,4-trimethyl-, 4-chloro-1,6-dihydro-1,2-dimethyl-, and 1,6-dihydro-4-methoxy-1,2-dimethyl-6-oxopyrimidine, respectively.⁶⁴⁹³

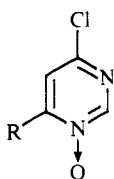
(12) *Molecular Rearrangements (New)*

The action of aqueous acid on 4-phenylpyrimidine 1-oxide gives 5-phenylisoxazole.⁶⁴⁹⁴ This observation has been employed for structural determination in unsymmetrical pyrimidine *N*-oxides.⁵⁰⁸⁸ Thus, 4-ethyl-2,6-dimethylpyrimidine 1-oxide treated with aqueous acid gives 5-ethyl-3-methylisoxazole, while the 3-oxide gives 3-ethyl-5-methylisoxazole. Similar results were obtained with the 1- and 3-oxides of 4-ethyl-2-isopropyl-6-methylpyrimidine.

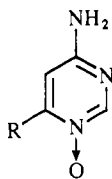
When 4-chloro-6-methylpyrimidine 1-oxide (146, R = Me) is treated with potassium amide in liquid ammonia at -75° , 4-amino-6-methylpyrimidine 1-oxide (147, R = Me) is isolated in 12% yield. However, the major product from this reaction is the isoxazole (148, R = Me), which is isolated in 62% yield. 4-Chloro-6-phenylpyrimidine 1-oxide (146, R = Ph) gives the 4-amino-1-oxide (147, R = Ph) in 30% yield.⁶⁴⁵⁷ When the chloropyrimidine *N*-oxides are kept in boiling liquid ammonia for 2 h, the same aminopyrimidine *N*-oxides and

aminoisoxazoles result, although in different yields. Several other pyrimidine *N*-oxide substrates have been investigated in this regard.⁴⁶⁸⁵ There are two competing mechanisms involved in these transformations.⁴⁶⁸⁴

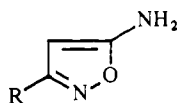
4-Phenylpyrimidine 1-oxide reacts with ethyl cyanoacetate in the presence of acetic anhydride to give ring-open products.⁶⁴⁹⁵ Similarly, 4,6-dimethylpyrimidine 1-oxide reacts with active methylene compounds to give ring-open products, but with 5-amino-3-methylisoxazole to give 2-(5'-amino-3'-methylisoxazol-4'-yl)-4,6-dimethylpyrimidine.⁵⁰⁹⁷ 4-Phenylpyrimidine 1,3-dioxide reacts with ethyl cyanoacetate in the presence of acetic anhydride to give ethyl (5-acetoxy-1,6-dihydro-4-phenylpyrimidin-6-ylidene) cyanoacetate.⁶²⁵⁴ 5-Methylpyrimidine 1-oxide, when heated with perfluoropropene, gives a 3:1 mixture of 5-methyl-4- and 5-methyl-2-(1',2',2',2'-tetrafluoroethyl)pyrimidine.⁶²¹¹



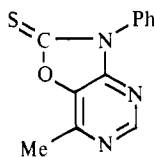
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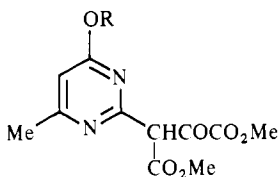
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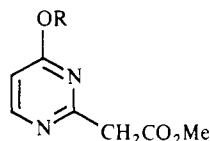
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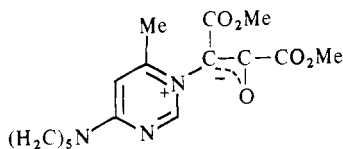


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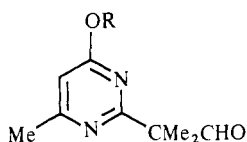


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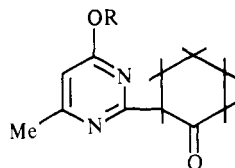
4-Ethoxy-6-methylpyrimidine 1-oxide undergoes a 1,3-dipolar cycloaddition with phenyl isocyanate to give 2-anilino-4-ethoxy-6-methylpyrimidine. With phenyl isothiocyanate, however, the same *N*-oxide reacts to give 2,3-dihydro-7-methyl-3-phenyl-2-thiooxazo-[4,5-*d*]pyrimidine (149).^{5087, 5986} 4-Benzyloxy-6-methylpyrimidine 1-oxide reacts with dimethyl acetylenedicarboxylate to give the diester (150, R = CH₂Ph). When this substance is subjected to alumina chromatography, only the methyl pyrimidinylacetate (151, R = CH₂Ph) is isolated. Similarly, the methoxy (151, R = Me) and ethoxy (151, R = Et) analogues are obtained from 4-methoxy- and 4-ethoxy-6-methylpyrimidine 1-oxide, respectively.^{5087, 5805} 4-Methyl-6-piperidino-pyrimidine 3-oxide reacts with dimethyl acetylenedicarboxylate to give the betaine (152).⁵⁸⁰⁵



(152)



(153)



(154)

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 (153, R = Me, Et, Prⁱ, or CH₂Ph) in 60–70% yield. When the alkoxy group is replaced by methyl or phenyl, yields of the corresponding aldehydes are only 15% in each case.⁵⁰⁸³ When 1-morpholinocyclohexene replaces the previous enamine in this reaction, 4-alkoxy-6-methyl-2- α -oxocyclohexylpyrimidines (154, R = Me, Et, Prⁱ, or CH₂Ph) are isolated in from 70 to 90% yield. Again, when a methyl or phenyl replaces the alkoxy group of the pyrimidine *N*-oxide, yields of the corresponding products are lower.⁵⁰⁸³

4-Methylpyrimidine 3-oxide reacts with *N*-phenylbenzimidoyl chloride to give 2-*N*-benzoylanilino- and 2-anilino-4-methylpyrimidine in low yield. 4,6-Dimethylpyrimidine *N*-oxide reacts similarly to give low yields of 2-*N*-benzoylanilino- and 2-anilino-4,6-dimethylpyrimidine.⁵⁸⁸⁷ However, in the presence of triethylamine, 4-methylpyrimidine 3-oxide reacts with *N*-phenylbenzimidoyl chloride on the methyl group rather than on C2; the products of this reaction are 4-benzoylanilinomethylpyrimidine and 4-*p*-benzamidobenzylpyrimidine, which are isolated in 52 and 19% yield, respectively.⁶⁴⁹⁶

Pyrimidine *N*-oxide reacts with hydroxylamine to give isoxazole. 4,6-Dimethyl- and 4-methyl-6-phenylpyrimidine 3-oxide give 3,5-dimethyl- and 3-methyl-5-phenylisoxazole, respectively. With ¹⁵N labeling, it was shown that the N–O portion of the resulting isoxazole is derived from the hydroxylamine and not from the *N*-oxide function of the pyrimidine.⁶⁴⁹⁷ 5,5-Diethyl-1-hydroxybarbituric acid reacts with hydrazine to give 4,4-diethylpyrazolidine-3,5-dione.⁵²¹⁸

(13) *Biological Properties of Pyrimidine N-Oxides (New)*

The 2,4,6-triaminopyrimidine *N*-oxides are potent antihypertensive drugs. 2,4-Diamino-6-piperidinopyrimidine 3-oxide is a clinically useful drug, Minoxidil. It appears to be effective in cases that are resistant to other therapy.^{6498, 6499} Some arylsulfonylhydrazones of

4-formylpyrimidine 3-oxide have marginal activity against sarcoma 180 in mice.⁶⁵⁰⁰ Hexahydro-1-hydroxy-2-oxopyrimidine has *in vitro* activity against rat hepatoma 35 and Wilm's tumor, as well as *in vivo* activity against L-1210 in mice.⁶⁴⁶⁵ Several *N*-aralkoxydihydrouracils possess anti-inflammatory activity.⁵⁹¹²

CHAPTER XI

The Pyrimidine Carboxylic Acids and Related Derivatives (*H* 389, *E* 296)

This chapter covers, not only the carboxylic acids and their derivatives, but also the nitriles, aldehydes, ketones, isocyanates, and all their thio analogues where possible. A recent excellent review on pyrimidines with a carbon functional group has covered some of this territory in brief.⁵⁹⁹²

1. The Carboxypyrimidines (*H* 389, *E* 296)

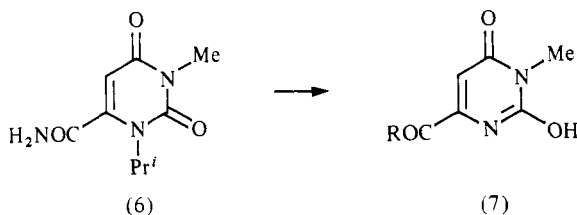
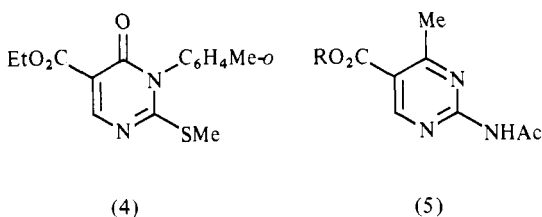
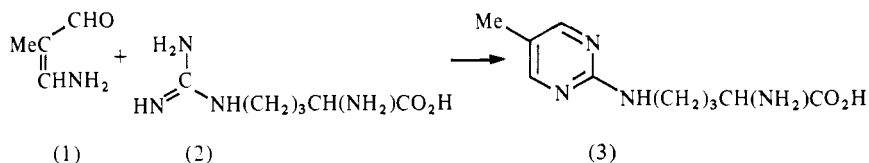
A. Preparation of Carboxypyrimidines (*H* 389, *E* 296)

(1) *By Primary Synthesis* (*H* 389, *E* 296)

A great many carboxypyrimidines have been made directly or indirectly by the Principle Synthesis (Ch. II) or other primary syntheses (Ch. III). Two unusual random examples are the condensation of 3-amino-2-methylacrolein (1) with arginine (2) in ethanolic sodium ethoxide to give 2-(4'-amino-4'-carboxybutyl)amino-5-methylpyrimidine (3),⁴⁴⁷⁶ and the condensation of *N*-hydroxybenzamidine with dimethyl acetylenedicarboxylate to give 4,5-dihydroxy-6-methoxycarbonyl-2-phenylpyrimidine and thence, by gentle alkaline hydrolysis, 4-carboxy-5,6-dihydroxy-2-phenylpyrimidine in good yield.⁵⁸⁰⁰

(2) *By Hydrolysis of Esters, Amides, or Nitriles* (*H* 390, *E* 296)

The corresponding carboxypyrimidines have been obtained from the *esters*: 5-ethoxycarbonyl-2-ethylpyrimidine (aqueous alkali, 42%),⁵⁷¹⁵ 5-ethoxycarbonyl-1,6-dihydro-2-methylthio-6-oxo-1-*o*-tolyl-



pyrimidine (4) (0.1 M sodium hydroxide, 60°, 48 h, 70%),⁶³⁵⁸ 2-ethoxycarbonylmethylpyrimidine (boiling aqueous alkali, 60% as sodium salt),⁵⁶⁸⁸ 2-ethoxycarbonylmethoxy-5-phenylpyrimidine (aqueous ethanolic alkali at 25°, 92%),⁶⁰⁸⁰ 5-β-ethoxycarbonyl-4-hydroxy-2-methylpyrimidine (1 M potassium hydroxide under reflux, 54%),⁵⁷⁶⁶ 2,4-dihydroxy-5-methoxycarbonylpyrimidine (1 M hydrochloric acid under reflux, 96%),⁶²⁷⁷ 2-ethoxycarbonylmethyl-4,6-diphenylpyrimidine (2.5 M alkali under reflux),⁵⁸³⁶ 4-ethylsulfonyl-2-methoxycarbonylmethylpyrimidine (1% alkali at < 5°, 6% as sodium salt; note survival of the sulfone function),⁵⁶⁹³ 5-amino-4-ethoxycarbonylpyrimidine (aqueous alkali, "high yield"),⁴³⁶⁴ 2,4-diamino-5-ethoxycarbonylpyrimidine (aqueous ethanolic alkali at 100°, c. 50%),⁵⁴⁰⁰ 4-acetyl-5-chloro-2-hydroxy-6-methoxycarbonylpyrimidine (1 M alkali at 25°, 67%),⁴⁸⁹⁰ 2-amino-4-dimethylamino-5-ethoxycarbonylpyrimidine (2.5 M alkali under reflux, 92%),⁴³⁸⁴ 4,5-dichloro-2-β-ethoxycarbonyl-6-hydroxypyrimidine (1 M alkali under reflux, 70%; note survival of the 4-chloro substituent),⁴⁸⁹² 4,5-diethoxycarbonyl-2-phenylpyrimidine (aqueous alkali under reflux, 98%),⁵⁶⁰⁴ 4-anilino-5-ethoxycarbonylpyrimidine (aqueous alkali; also a dozen analogues),⁵⁸⁷⁸ 1-ethoxycarbonylmethoxy-1,2-dihydro-2-oxypyrimidine (boiling acetic acid containing hydrogen bromide, 99% as hydrobromide),⁴⁵⁸³ 2-benzamidomethyl-5-ethoxycarbonylpyrimidine (0.5 M sodium hydroxide, 25°, 15 min, 77%),⁶⁰⁹¹

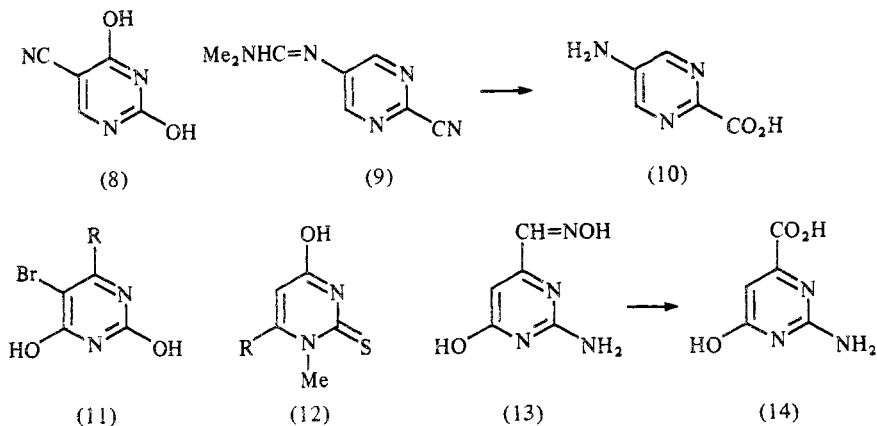
and others.^{5345, 5981} Benzyl esters are useful as substrates when there is another hydrolysis-prone substituent present, because such esters may be converted into the carboxylic acids by hydrogenation. For example, 2-acetamido-5-benzoyloxycarbonyl-4-methylpyrimidine (5, R = CH₂Ph) gave 2-acetamido-5-carboxy-4-methylpyrimidine (5, R = H) by hydrogenation over palladium, albeit in rather poor yield.⁵²⁴⁸

Carboxypyrimidines have been obtained by the hydrolysis of the *amides*: 4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (48% hydrobromic acid under reflux, 75%),⁴⁹⁴⁶ 5-carbamoyl-2,4-dihydroxy-6-methylpyrimidine (butyl nitrite/glacial acetic acid/hydrogen chloride, 47%),⁶⁰⁸³ and others.⁴⁹⁶⁰ It is interesting that 4-carbamoyl-1,2,3,6-tetrahydro-3-isopropyl-1-methyl-2,6-dioxypyrimidine (6) in 98% sulfuric acid underwent only loss of the secondary alkyl group to give 6-carbamoyl-3-methyluracil (7, R = NH₂), whereas in hydrobromic acid, both dealkylation and hydrolysis of the amide occurred to give 6-carboxy-3-methyluracil (7, R = OH); primary alkyl groups were not so removed.⁴⁹³⁴

Carboxypyrimidines have often been prepared from the corresponding *nitriles*, presumably *via* the unisolated intermediate amides. Such hydrolyses have been carried out on 5-cyano-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (6 M hydrochloric acid under reflux, 35%),⁴⁴⁷⁹ 5-cyano-2,4-dihydroxypyrimidine (8) (50% sulfuric acid under reflux, 65%),⁵⁷⁷⁷ 4-amino-5-cyano-2- β -hydroxyethylpyrimidine (aqueous sodium hydroxide at 50° for 15 h, 98%),⁴⁴³³ 5-cyano-1-cyclohexyluracil (2.5 M sodium hydroxide under reflux, 21%),⁴⁷²⁰ 5-chloro-2-cyanopyrimidine (2 M alkali under reflux, 61%),⁴³⁹⁹ 5-cyano-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-phenylpyrimidine (hydrochloric acid in glacial acetic acid under reflux, 17%),⁴⁹²⁰ and others.^{5773, 6008} Treatment of 2-cyano-5-dimethylaminomethyleneaminopyrimidine (9) in refluxing 2 M sodium hydroxide gave 5-amino-2-carboxypyrimidine (10) in 79% yield.⁴³⁸⁰

(3) By Oxidative Procedures (H 391, E 298)

The direct oxidation of alkyl- or alkenylpyrimidines to carboxypyrimidines is covered in Ch. IV, Sect. 2.C. The oxidation of substituted-alkyl groups is exemplified in the conversion of 5-bromo-4-carboxymethyl- (11, R = CH₂CO₂H) into 5-bromo-4-carboxy-2,6-dihydroxypyrimidine (11, R = CO₂H) (sodium dichromate/aqueous sulfuric acid, 80°, *c.* 70%),⁵⁹³⁰ of 2,4-dihydroxy-6-hydroxymethyl- into 4-carboxy-2,6-dihydroxypyrimidine (nickel peroxide in aqueous alkali suspension,



33%);⁵¹⁷⁵ of 6-hydroxymethyl-1-methyl- (12, R = CH₂OH) into 6-carboxy-1-methyl-2-thiouracil (12, R = CO₂H) (similarly, 71%);⁵¹⁷⁵ and of 4-amino-5-hydroxymethyl- into 4-amino-5-carboxy-2-methylpyrimidine (permanganate/aqueous sodium carbonate at 20°, 50%).⁵⁸²⁹

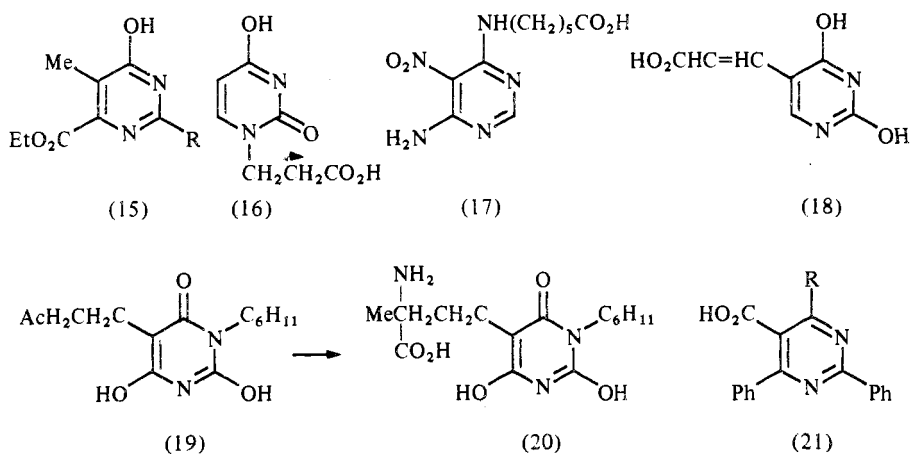
The oxidation of formyl- to carboxypyrimidines is exemplified in the formation of 4-carboxy-2,6-dihydroxypyrimidine (hydrogen peroxide/aqueous alkali, 30%);⁵⁸⁷⁶ and 5-carboxypyrimidine (permanganate/aqueous alkali, 72%);⁵⁷⁹⁴ also in the conversion of 4-formyl-6-hydroxy-2-methylthio- into 4-carboxy-2,6-dihydroxypyrimidine (silver oxide suspended in aqueous ethanol, > 50%);⁴⁶⁰⁶ in the direct conversion of the oxime, 2-amino-4-hydroxy-6-hydroxyiminomethylpyrimidine (13) into 2-amino-4-carboxy-6-hydroxypyrimidine (14) (potassium nitrate/sulfuric acid, 100°, c. 25%);⁵⁷⁶³ and in the permanganate oxidation of 4-formyl- to 4-carboxy-6-phenylpyrimidine (> 95%).⁵⁰⁷³

(4) By Other Means (H 392, E 298)

The convenient method of making carboxypyrimidines by treatment of trihalogenomethylpyrimidines with silver nitrate, has been employed to convert 4-ethoxycarbonyl-6-hydroxy-5-methyl-2-tribromomethylpyrimidine (15, R = CBr₃) into 2-carboxy-4-ethoxycarbonyl-6-hydroxy-5-methylpyrimidine (15, R = CO₂H) in low yield. When the reaction was done in a methanolic instead of an aqueous medium, 4-ethoxycarbonyl-6-hydroxy-2-methoxycarbonyl-5-methylpyrimidine (15, R = CO₂Me) resulted in 90% yield.⁶¹⁴⁰

The formation of extranuclear carboxypyrimidines by the addition of a side chain bearing a carboxy group, can be done by *S*- or *N*-

alkylation, by aminolysis, or by other nucleophilic displacements. Such processes are illustrated by the conversion of 2,4-dihydroxypyrimidine into 1- β -carboxyethyluracil (16) (β -propiolactone/aqueous alkali under reflux, 28%);⁵⁰³⁵ of 5-fluoro-2,4-dihydroxypyrimidine into 1-carboxymethyl-5-fluorouracil (chloroacetic acid/aqueous alkali at 25°, 66%);⁵⁰⁸¹ of 4-amino-6-chloro-5-nitropyrimidine into 4-amino-6-5'-carboxypentylamino-5-nitropyrimidine (17) (6-aminohexanoic acid, 90%);⁴⁴⁷⁵ of 2,4-dichloro- into 4-*o*-carboxyanilino-2-chloropyrimidine (anthranilic acid in aqueous hydrochloric acid, 78%);⁴⁸²³ of 2-ethylthio- into 2-carboxymethylamino-4-hydroxy-6-methylpyrimidine (glycine in aqueous sodium carbonate, 31%);⁴⁴⁷⁶ and in other such transformations.^{4474, 4750, 4780, 5204, 5267} Less simple but relevant reactions include that of 5-formyl-2,4-dihydroxypyrimidine with malonic acid in pyridine containing piperidine to give (with concomitant decarboxylation) 5- β -carboxyvinyl-2,4-dihydroxypyrimidine (18) in 84% yield,⁵⁴⁷³ as well as the classical Strecker reaction on 5-acetonilmethyl-1-cyclohexylbarbituric acid (19), which gave mainly 5-3'-amino-3'-carboxybutyl-1-phenylbarbituric acid (20).⁴⁹¹⁹



B. Reactions of Carboxypyrimidines (*H* 393, *E* 299)

The effect of substituents on the acidic strength of carboxypyrimidines has been studied.^{4770, 4771} The infrared spectra of carboxypyrimidines, with and without additional tautomeric groups, have been measured and discussed.⁴⁷⁶⁷

(1) *Decarboxylation* (*H* 393, *E* 299)

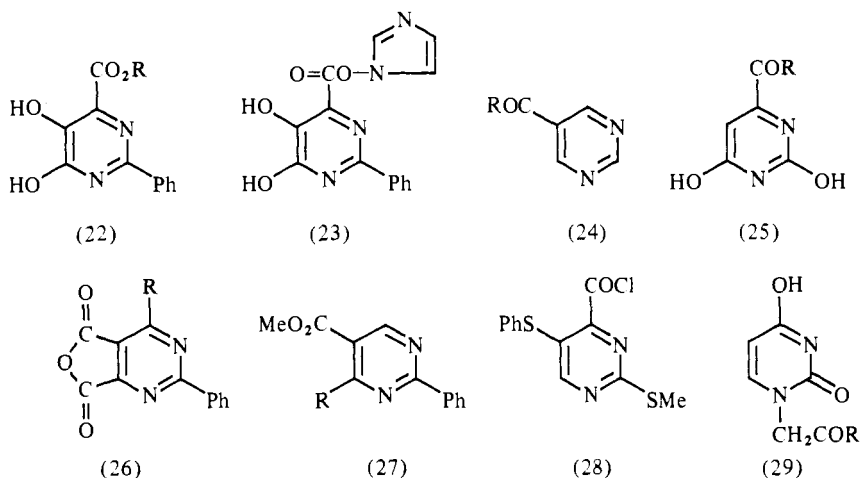
This most useful process is illustrated in the removal of the carboxy group from 5- β -carboxyvinyl-2,4-dihydroxypyrimidine (quinoline at 180°, low yield),⁵⁴²⁷ 4-carboxy-2-methylthio-5-phenylthiopyrimidine (neat at 200°, 90%),⁴⁴⁰⁰ 4-carboxy-5,6-dihydroxy-2-phenylpyrimidine (6 M hydrochloric acid under reflux, *c.* 50%),⁵⁸⁰⁰ 5-carboxy-1,6-dihydro-2-methylthio-6-oxo-1-*o*-tolylpyrimidine (quinoline containing copper powder under reflux; 24%),⁶³⁵⁸ and 5-carboxy-2,4-dihydroxypyrimidine (in refluxing cyclohexanol or ethylene glycol).⁴⁷²⁰

Less simple examples include the conversion of 4,5-dicarboxy-2,6-diphenylpyrimidine (21, R = CO₂H) into 5-carboxy-2,4-diphenylpyrimidine (21, R = H) and subsequently into 2,4-diphenylpyrimidine at a higher temperature;⁵⁹⁷² of 5-cyano-1-cyclohexyluracil into 1-cyclohexyluracil (orthophosphoric acid at 170°, 66%; the intermediate carboxylic acid was not isolated);⁴⁷²⁰ of 2-cyanomethyl-4,6-dimethylpyrimidine into 2,4,6-trimethylpyrimidine (aqueous ethanolic hydrochloric acid under reflux, 59%; intermediate carboxylic acid unisolated);⁶⁰⁰⁸ of 1-carboxymethyl-5-methyluracil into 1,5-dimethyluracil (irradiation in aqueous solution or thermally at 290°);⁵²⁰⁰ and of 4-carboxypyrimidine into 4,4'-bipyrimidine (5%) by pyrolysis of the dry copper salt.⁵⁹⁵⁹

(2) *Esterification* (*H* 393, *E* 300)

The esterification of carboxypyrimidines is illustrated in the formation of 2,4-dihydroxy-5-methoxycarbonylmethylpyrimidine (methanol containing a trace of sulfuric acid under reflux, 73%),⁵⁹⁷³ 4-methoxycarbonyl-2,6-dimethylpyrimidine (methanol containing a trace of hydrochloric acid under reflux, 60%),⁵⁶⁸² 5- β -bromoethyl-4-ethoxycarbonyl-2,6-dihydroxypyrimidine (ethanol containing hydrogen bromide under reflux),⁴⁷⁷⁸ 5-methoxycarbonyl-4-*m*-trifluoromethyl-anilinopyrimidine (etherial diazomethane, 67%),⁵⁸⁷⁸ 2-amino-4-dimethylamino-5-methoxycarbonylpyrimidine (etherial diazomethane/aqueous methanol, 61%),⁴³⁸⁴ 5-chloro-2-hydroxy-4-methoxycarbonylpyrimidine (methanol containing hydrogen chloride at 25°, 82%),⁴⁸⁹⁰ 2,4-diamino-6-methoxycarbonylpyrimidine (methanolic hydrogen chloride under reflux, isolated as the hydrochloride),⁵⁴⁰⁰ 2-amino-1,6-dihydro-4-methyl-6-oxo-1- β -propoxycarbonyl-ethylpyrimidine (propanolic hydrogen chloride),⁵⁷⁷³ 2-amino-4-hydroxy-6-methoxycarbonylpyrimidine (methanol/sulfuric acid, *c.* 30%),⁵⁷⁶³ 4-ethoxycarbonyl-6-

hydroxy-2,5-dimethylpyrimidine (ethanol/sulfuric acid/thionyl chloride under reflux; 98%; note peculiar conditions),⁶¹⁴⁰ 4,5-dihydroxy-6-methoxycarbonyl-2-phenylpyrimidine (22, R = Me) [from the acid (22, R = H) by treatment with carbonyldiimidazole to give the uncharacterized intermediate (23), which reacted with boiling methanol to give the product (22, R = Me) in good yield],⁵⁸⁰⁰ 5-β-methoxycarbonylvinyl-2,4-dihydroxypyrimidine (methanol/sulfuric acid under reflux, >90%),⁵⁴²⁷ 5-chloro-4-ethoxycarbonyl-2-methylpyrimidine (ethanolic hydrogen chloride at 70°, 69%),⁵⁸⁵⁵ and 2,4-bis(*p*-ethoxycarbonylanilino)pyrimidine (ethanolic sulfuric acid under reflux, 75%).⁴⁹⁰⁹



Esterification may be done indirectly, *via* the corresponding acyl chloride or anhydride. For example, 5-carboxypyrimidine (24, R = OH) was converted by thionyl chloride into 5-chlorocarbonylpyrimidine (24, R = Cl) (80%), which reacted with etherial ethanol under reflux to give 5-ethoxycarbonylpyrimidine (24, R = OEt) (56%);⁵⁷⁹⁴ 4-carboxy-2-methylpyrimidine with methanolic thionyl chloride gave 4-methoxycarbonyl-2-methylpyrimidine, presumably *via* the unisolated acyl chloride;⁵⁶⁵² 2-amino-5-carboxymethyl- gave 2-amino-5-butoxy (or ethoxy) carbonylmethyl-4-hydroxypyrimidine similarly (butanolic or ethanolic thionyl chloride);⁶⁵¹⁹ 2-amino-5-*p*-carboxybenzyl- gave 2-amino-5-*p*-ethoxycarbonylbenzyl-4,6-dihydroxypyrimidine, similarly;⁶⁵³⁴ 4-carboxy-2,6-dihydroxypyrimidine was converted into 4-chlorocarbonyl-2,6-dihydroxypyrimidine (25, R = Cl), which reacted with butanethiol (or homologues) to afford 4-(butylthio)carbonyl-2,6-dihydroxypyrimidine and homologues in *c.* 30% yield (note that the structural formula

in the original paper is incorrect);⁵⁴⁶⁴ and 4,5-dicarboxy-2-phenylpyrimidine with thionyl chloride gave not the acyl chloride but the anhydride (26, R = H) (75%), which with methanol gave 4-carboxy-5-methoxycarbonyl-2-phenylpyrimidine (27, R = CO₂H) (76%) and thence by heating with copper powder at greater than 250°, 5-methoxycarbonyl-2-phenylpyrimidine (27, R = H) (38%).⁵⁶⁰⁴ 4-Ethoxy- and 4-*t*-butoxycarbonyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine were made similarly.⁶⁸⁵³

(3) *Formation of Acid Chlorides (H 294, E 301)*

Besides the acid chlorides mentioned in the preceding paragraph, thionyl chloride (or other such agent) has been used to convert appropriate carboxypyrimidines into 4-chlorocarbonyl-2-methylthio-5-phenylthiopyrimidine (28) (75%),⁴⁴⁰⁰ 5-chlorocarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (trace of dimethylformamide as catalyst, 82%),⁴⁴⁷⁹ 4-chlorocarbonyl-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxypyrimidine (similarly),⁶⁸⁵³ 2,4-dichloro-5-chlorocarbonylpyrimidine (from 5-carboxy-2,4-dihydroxypyrimidine with phosphorus pentachloride in phosphoryl chloride, 50%),^{5462, 5919} and 4-chlorocarbonyl-5-ethoxycarbonyl-2-hydroxy-6-phenylpyrimidine.⁶⁵⁹⁸

(4) *Other Reactions (H 395, E 302)*

One anhydride (26) is mentioned in Sect. (2) immediately above; another is that (26, R = Ph) of 4,5-dicarboxy-2,6-diphenylpyrimidine.⁵⁹⁷² The formation of mixed anhydrides and their conversion into amides offers practical advantages in some cases.⁶⁶⁰¹

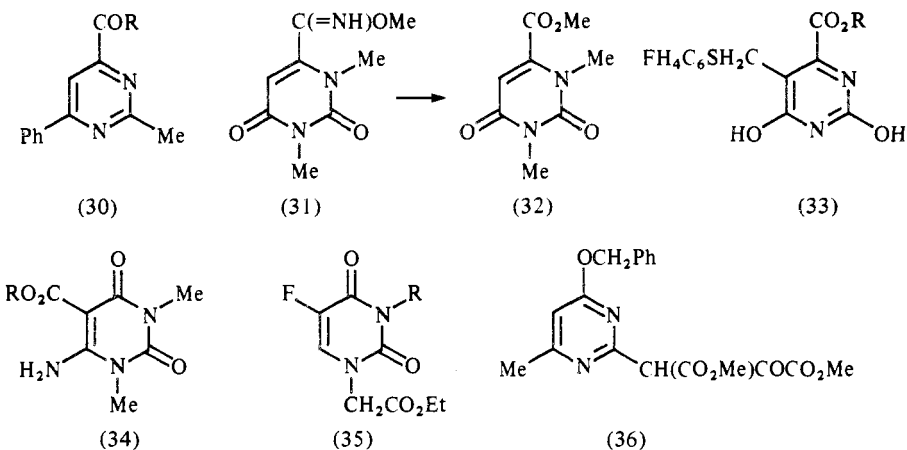
The conversion of 1-carboxymethyl- (29, R = OH) into the ketone, 1-acetonyluracil (29, R = Me) has been done by heating with acetyl chloride in pyridine.⁴⁸⁵⁴

2. Alkoxycarbonylpyrimidines (Esters) (H 395, E 302)

A. Preparation of Esters (H 395, E 302)

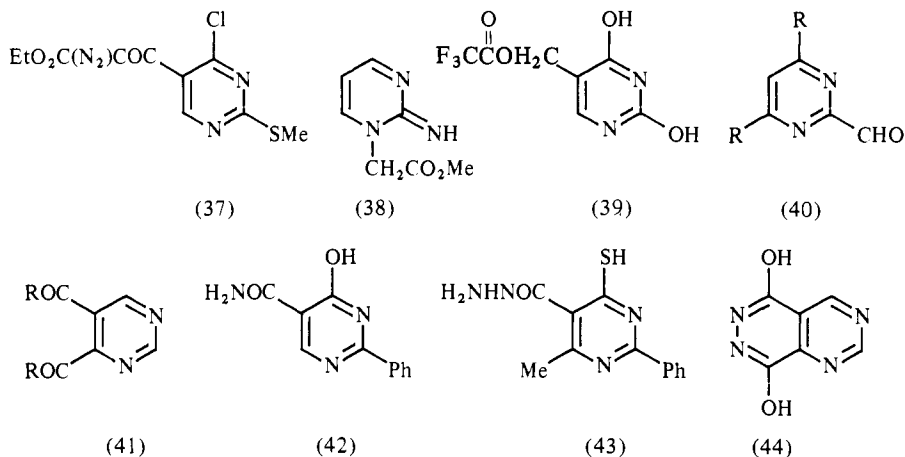
The formation of pyrimidine esters by primary synthesis has been covered in Ch. II and III, the esterification of carboxypyrimidines in Sect. 1.B (2) above, and the formation of esters *via* acid chlorides in the same section.

The conversion of amides into esters is exemplified in the treatment of 4-carbamoyl-2-methyl-6-phenylpyrimidine (30, R = NH₂) with hot methanolic boron trifluoride etherate to give 4-methoxycarbonyl-2-methyl-6-phenylpyrimidine (30, R = OMe) in 95% yield.⁵⁶⁵² The conversion of iminoethers into esters is illustrated in the treatment of 1,2,3,4-tetrahydro-6-methoxyformimidoyl-1,3-dimethyl-2,4-dioxypyrimidine (31) with warm dilute hydrochloric acid to give 1,2,3,4-tetrahydro-6-methoxycarbonyl-1,3-dimethyl-2,4-dioxypyrimidine (32) in 61% yield,⁴⁹³⁹ as well as in the treatment of 4,6-dichloro-2-(*C*-methoxyformimidoyl)methylpyrimidine with warm water to give 4,6-dichloro-2-methoxycarbonylmethylpyrimidine (>50%).⁵⁶⁸⁸ Transesterification is seen in the treatment of 4-ethoxycarbonyl-5-*p*-fluorophenylthiomethyl-2,6-dihydroxypyrimidine (33, R = Et) with methanolic sodium methoxide or propanolic sodium cyanide to give, respectively, 5-*p*-fluorophenylthiomethyl-2,4-dihydroxy-6-methoxy(or propoxy)carboxylpyrimidine (33, R = Me or Pr).⁶³⁵⁴



The direct introduction of a 5-alkoxycarbonyl grouping is exemplified in the formation of 4-amino-5-ethoxycarbonyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (34, R = Et) or its 5-phenoxy-carbonyl analogue (34, R = Ph) (refluxing pyridine containing ethyl or phenyl chloroformate, respectively; c. 80%),^{4410, 4953, 4974} The similar introduction of a 5-ethoxycarbonylmethyl group occurred on treatment of the same substrate with ethyl bromoacetate in dimethylformamide to give 4-amino-5-ethoxycarbonylmethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (25%).⁵¹³⁸ The reaction of 5-formyl-2,4-dihydroxypyrimidine with ethoxycarbonylmethylenetriphenylphosphorane gave 5-β-ethoxycarbonylvinyl-2,4-dihydroxypyrimidine (28%).⁵⁴⁷³

Other examples of the introduction of extranuclear ester groups by alkylation or other processes include the conversion of 2-chloro- into 2-ethoxycarbonylmethyl-4,6-dimethylpyrimidine (diethyl malonate/sodium/toluene under reflux, 20%; must include partial hydrolysis and decarboxylation during work-up);⁵⁶⁸² of 5-fluoro-2,4-dihydroxypyrimidine into 1-ethoxycarbonylmethyl-5-fluorouracil (35, R = H) (57%) plus 1,3-bisethoxycarbonylmethyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (35, R = CH₂CO₂Et) (22%) (ethyl bromoacetate/dimethylformamide/potassium carbonate at 100°);⁵⁰⁸¹ of 4-iodo- into 4-β-ethoxycarbonylvinyl-2,6-dimethylpyrimidine (ethyl acrylate/triethylamine/palladium on charcoal at 80° 73%);⁶³⁰¹ of 2-amino-4-mercapto-6-*N*-methylhydrazino- into 2-amino-4-mercapto-6-*N'*-α-methoxycarbonylethylidene-*N*-methylhydrazinopyrimidine (ethyl pyruvate in methanol, 77%);⁵⁴⁰² of 4-benzyloxy-6-methylpyrimidine 1-oxide into 4-benzyloxy-2-*C*-methoxalyl-*C*-methoxycarbonylmethyl-6-methylpyrimidine (36) (dimethyl acetylenedicarboxylate/dioxane, 66%; a rational mechanism was suggested);^{5087, 5805} of 3-methyl-6-*N*-methylanilinouracil into 5-*N,N'*-diethoxycarbonylhydrazino-3-methyl-6-*N*-methylanilino-uracil (diethyl azodiformate/methoxyethanol under reflux, 65%);⁵⁰⁰⁵ of 4-chloro-5-chlorocarbonyl- into 4-chloro-5-α-diazo-α-ethoxycarbonyl-acetyl-2-methylthiopyrimidine (37) (ethyl diazoacetate at 50°, 62%);⁵⁰⁴⁰ of 4-phenylpyrimidine 1,3-dioxide into 5-acetoxy-4-*C*-cyano-*C*-ethoxycarbonylmethyl-6-phenylpyrimidine (ethyl cyanoacetate/acetic anhydride, 23%);⁶²⁵⁴ of 2-mercaptopyrimidine and its 4,6-dimethyl derivative into 2-ethoxycarbonylmethylthiopyrimidine and its 4,6-dimethyl derivative, respectively (ethyl chloroacetate/sodium hydrogen carbonate);^{4535, 5698} of 4-amino-6-chloro- into 4-amino-6-diethoxycarbonylmethyl-5-nitro-2-phenylpyrimidine (diethyl malonate/tetrahydro-



furan/aqueous alkali, *c.* 80%; subsequent treatment with hot hydrochloric acid gave the 6-methyl analogue),⁵⁴³⁹ of 2-amino- into 1,2-dihydro-2-imino-1-methoxycarbonylmethylpyrimidine (38) (methyl bromoacetate/methanol, 50% as hydrobromide),⁴⁷⁶⁴ of 5-hydroxy- into 5-ethoxycarbonylmethyl-1-methyluracil (ethoxycarbonylmethylenetriphenylphosphorane in acetonitrile under reflux, 81%),⁶¹⁵⁸ and in other such reactions.^{4579, 4671, 4980, 5654}

It should be recalled that "back-to-front" pyrimidine esters, derived from hydroxypyrimidines and an organic acid, are covered in Ch. VII, Sect. 6.C. A typical example is 2,4-dihydroxy-5-trifluoroacetoxymethylpyrimidine (39).⁵³¹¹

B. Reactions of Esters (*H* 396, *E* 304)

The hydrolysis of pyrimidine esters to carboxylic acids is discussed in Sect. 1.A (2) above. The reduction of esters to extranuclear hydroxypyrimidines is covered in Ch. VII, Sect. 3.D. The partial reduction of esters is illustrated in the treatment of 2-methoxycarbonyl-4,6-dimethyl (or diphenyl)pyrimidine with lithium aluminum hydride in tetrahydrofuran at -70° to give 2-formyl-4,6-dimethyl- (40, *R* = Me) (52%) or 2-formyl-4,6-diphenylpyrimidine (40, *R* = Ph) (58%).⁵⁹⁷⁷

The only other common reaction of esters is aminolysis to afford amides or hydrazides, as in the conversion of 4,5-diethoxycarbonyl- (41, *R* = OEt) into 4,5-dicarbamoylpyrimidine (41, *R* = NH₂) (concentrated aqueous ammonia at 25° , 78%),⁴⁴⁵³ of 4,5-diamino-6-ethoxycarbonyl- into 4,5-diamino-6-carbamoyl (or *N*-ethylcarbamoyl)pyrimidine (aqueous ammonia at 25° or ethanolic ethylamine at 155° , respectively, *c.* 50%),⁵⁴³⁶ of 2,4-dihydroxy-6-methoxycarbonyl- into 4-carbamoyl-2,6-dihydroxy-5-nitropyrimidine (methanolic ammonia at 100° , 60%),⁵⁷⁶⁷ of 5-ethoxycarbonyl- into 5-carbamoyl-4-hydroxy-2-phenylpyrimidine (42) (aqueous ammonia at 100° , *c.* 70%),⁵⁵⁸² of 4-ethoxycarbonylmethyl- into 4-carbamoylmethyl-2,6-dihydroxypyrimidine (methanolic ammonia at 25° containing sodium methoxide, 89% as sodium salt),⁶⁰⁶³ of 4-ethoxycarbonyl- into 4-carbamoyl-5-ethoxymethyl-2,6-dihydroxypyrimidine (aqueous ammonia at 25° , 96%),⁶¹⁹³ of 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-phenoxy-carbonyl- into 4-amino-5-*N*-ethylcarbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (ethylamine in pyridine under reflux, 82%),⁴⁴⁴² of 5-ethoxycarbonyl- into 5-hydrazinocarbonyl-4-mercapto-6-methyl-2-phenylpyrimidine (43) (propanolic hydrazine, 70%),⁴⁷²³ of 2-acetamido-5- β -ethoxycarbonylethyl- into the 2-amino-5- β -hydrazinocar-

bonylethyl-4-hydroxy-6-methylpyrimidine (ethanolic hydrazine hydrate under reflux, 73%; note deacetylation of amino group by hydrazine);⁵⁷⁰⁷ and other such reactions.^{4792, 6354} A closely related (cyclization) reaction is that of 4,5-diethoxycarbonylpyrimidine (41, R = OEt) with methanolic hydrazine to give 5,8-dihydroxypyrimido[4,5-*d*]pyridazine (44) (63%).⁶³²⁹

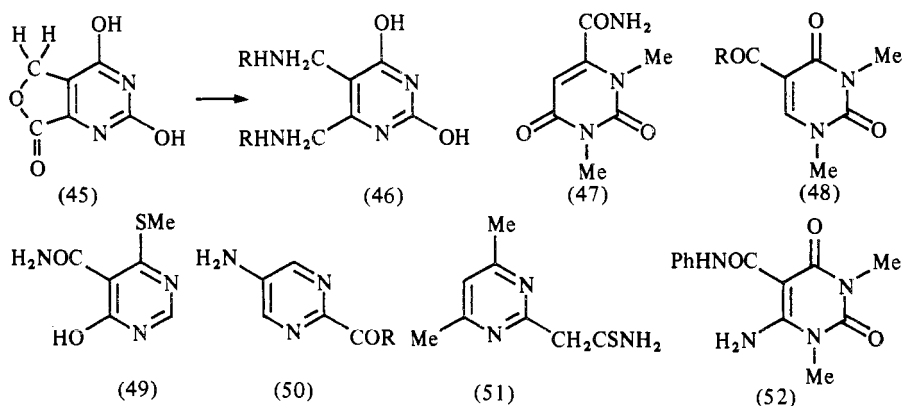
The conversion of esters into ketones by a Claisen reaction is treated in Sect. 6 below.

3. Pyrimidine Amides, Hydrazides, and Azides (*H* 397, *E* 305)

A. Preparation of Amides (*H* 397, *E* 305)

(1) *From Esters and Acid Chlorides* (*H* 397, *E* 305)

The conversion of esters into amides is covered in Sect. 2.B immediately above, but two closely related reactions leading to amides are represented in the aminolytic ring-fission of the lactone (45) of 4-carboxy-2,6-dihydroxy-5-hydroxymethylpyrimidine by ammonia or aniline to give 5-aminomethyl-4-carbamoyl-2,6-dihydroxy- (46, R = H) or 5-anilinomethyl-2,4-dihydroxy-6-*N*-phenylcarbamoylpyrimidine (46, R = Ph), respectively, in good yield;⁴⁹⁴⁸ as well as in the conversion of the iminoether, 1,2,3,4-tetrahydro-6-methoxyformimidoyl-1,3-dimethyl-2,4-dioxypyrimidine (31) into 4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (47) by refluxing in dimethylformamide containing ammonium chloride or methylamine hydrochloride (60–65%), by heating with aniline hydrochloride at 150° (76%), by stirring with thionyl or phosphoryl chloride at 25° (52–55%), or by warming with phosphorus pentachloride at 100° (60%).⁴⁹³⁹



The transformation of acid chlorides into amides has been used quite extensively of late. The process is illustrated in the aminolysis of 2,4-dichloro-5-chlorocarbonylpyrimidine to 2,4-dichloro-5-*N*-3',4',5'-trimethoxyphenylcarbamoylpyrimidine (3,4,5-trimethoxyaniline/triethylamine/tetrahydrofuran);⁵⁴⁶² of 5-chlorocarbonyl- (48, R = Cl) to 5-carbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (48, R = NH₂) (benzene saturated with ammonia, under reflux, 71%);⁴⁴⁷⁹ of 5-chlorocarbonyl- to 5-carbamoylpyrimidine (dry ammonia/benzene under reflux, 62%);⁵⁷⁹⁴ and of 2,4-dichloro-6-chlorocarbonyl- to 2,4-diamino-6-carbamoylpyrimidine (ethanolic ammonia at 160°).⁵⁴⁰⁰ Anhydrides are also useful intermediates between carboxy- and carbamoylpyrimidines.⁶⁶⁰¹

(2) *By Primary Syntheses (H 398, E 305)*

Although rather uncommon, several examples of the formation of carbamoylpyrimidines by primary syntheses are given in Ch II and III.

(3) *By Controlled Hydrolysis of Nitriles (H 398, E 305)*

The controlled hydrolysis of cyano- to carbamoylpyrimidines is usually done in rather strong sulfuric acid, which naturally has limited hydrolytic capacity. In this way, the corresponding cyanopyrimidines gave 2-amino-5-carbamoyl-4-dimethylaminopyrimidine (90% sulfuric acid at 100°, 88%);⁴³⁸⁴ 5-carbamoyl-1-phenyluracil (97% sulfuric acid at 50°, 99%);⁴⁹²⁰ 4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (98% sulfuric acid at 90°, 68%; note that similar treatment of 1-*s*-alkyl analogues resulted in 1-dealkylation as well as hydrolysis of the nitrile group);^{4934, 4946} 5-carbamoyl-2,4-dihydroxy-6-methylpyrimidine (*c.* 90% sulfuric acid at 110°, 62%);⁶⁰⁸³ 5-carbamoyl-4-hydroxy-6-methylthiopyrimidine (49) (90% sulfuric acid at 100°, >95%; note the survival of the thioether group because of lack of hydrolytic capacity);⁵⁹⁶⁹ 4-amino-5-carbamoyl-2-hydrazinopyrimidine (98% sulfuric acid at 25°, 76%);⁵⁷⁷² 5-carbamoyl-1-pyridin-2'-yluracil (60% sulfuric acid at 60°, 65%);⁶²⁷⁰ and 2,4-diamino-5-carbamoyl-6-phenylpyrimidine (98% sulfuric acid at 30°, 96%).⁵⁷⁶⁷

Alkaline hydrolysis is sometimes used but is more effectively controlled in the presence of hydrogen peroxide (the Radziszewski reaction). Thus, 2-cyano-5-dimethylaminomethyleneaminopyrimidine in very dilute aqueous sodium hydroxide at 100° gave 5-amino-2-carba-

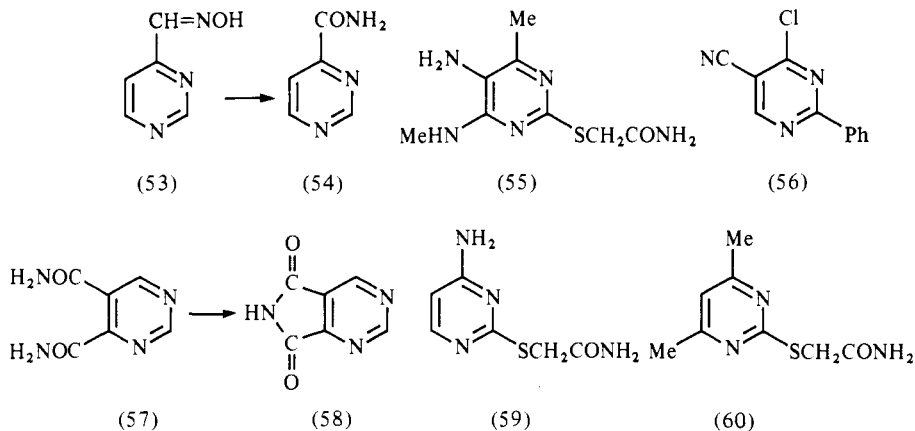
moylpyrimidine (50, R = NH₂), but in stronger alkali only 5-amino-2-carboxypyrimidine (50, R = OH) was isolated.⁴³⁸⁰ However, 5-chloro-2-cyanopyrimidine in aqueous ethanolic alkali containing hydrogen peroxide gave only 2-carbamoyl-5-chloropyrimidine (82%) whereas, without hydrogen peroxide, 2-carboxy-5-chloropyrimidine was formed in 61% yield.⁴³⁹⁹

The thiolysis of a cyanopyrimidine is exemplified in the conversion of 2-cyanomethyl-4,6-dimethylpyrimidine into 4,6-dimethyl-2-thiocarbamoylmethylpyrimidine (51) by heating at 100° in a sealed tube with pyridine/triethylamine presaturated with hydrogen sulfide. Analogues were made similarly.⁵⁹⁷⁴

(4) *By Other Means (H 399, E 306)*

The direct attachment of a carbamoyl or thiocarbamoyl group to a vacant position on the pyrimidine nucleus can be done with an isocyanate or isothiocyanate, as illustrated in the preparation of 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-*N*-phenylcarbamoylpyrimidine (52) (phenyl isocyanate in pyridine under reflux, 63%),⁴⁴¹⁰ 4-dimethylamino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl-5-*N*-phenylcarbamoyl[or phenyl(thiocarbamoyl)]pyrimidine (neat phenyl isocyanate or phenyl isothiocyanate, respectively, at 150°, 80, 90%),⁵⁵⁸⁷ 5-fluoro-1-*N*-phenylcarbamoyluracil (phenyl isocyanate in dimethyl sulfoxide at 25°, 81%),⁵¹¹² 4-amino-1,2,3,6-tetrahydro-2,6-dioxo-5-*N*-phenyl(thiocarbamoyl)-1,3-dipropylpyrimidine (neat phenyl isothiocyanate at 100°, 55%; also many analogues),⁴⁴⁷² and 4-amino-5-*N*-*p*-chlorophenyl(thiocarbamoyl)-3-ethyl-3,6-dihydro-6-oxopyrimidine (*p*-chlorophenyl isothiocyanate in refluxing pyridine, 75%).⁵⁰³⁷ Such "amidation" can also be done with formamide or dimethylformamide in the presence of a suitable oxidizing agent. Thus, 4,6-dimethylpyrimidine reacted with formamide in dilute acid containing equimolar amounts of ferrous sulfate and *t*-butyl hydroperoxide at 15° to give 2-carbamoyl-4,6-dimethylpyrimidine (*c.* 40%), 4-*N,N*-dimethylcarbamoyl-6-methyl-2-phenylpyrimidine (*c.* 30%), 4-carbamoyl-2-methyl-6-phenylpyrimidine (*c.* 90%). Other analogues were made similarly.⁵⁹⁸⁷

A rarely used route to a carbamoylpyrimidine involves Beckmann rearrangement of the oxime, 4-hydroxyiminomethylpyrimidine (53), in formic acid/sodium formate under reflux to give 4-carbamoylpyrimidine (54) (70%).⁵⁸⁶² Other minor routes to carbamoylpyrimidines include the conversion of 1,2,3,4-tetrahydro-5-hydroxy- into 5-carbamoyl-methyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (55) (car-



bamoylmethylenetriphenylphosphorane; 55%);⁶¹⁵⁸ the reaction of 1,2,3,4-tetrahydro-1,3-dimethyl-5-nitro-2,4-dioxypyrimidine with malondiamide to give 5-carbamoyl-1-methyluracil (84%; see Ch. V, Sect. 1.B);⁶⁰³⁴ the alkylation of 5-amino-2-mercapto- to 5-amino-2-carbamoylmethylthio-4-methyl-6-methylaminopyrimidine (55) (chloroacetamide/aqueous sodium hydrogen carbonate; 85%),⁵⁶⁸⁷ and other sequences.^{6087, 6128}

B. Reactions of Amides (*H* 400, *E* 306)

The hydrolysis of amides to carboxylic acids is covered in Sect. 1.A(2) above. The Hofmann and related degradations of amides have been neglected recently in the pyrimidine series.

The dehydration of amides to afford nitriles is usually done by treatment with phosphoryl chloride or the like, which at the same time convert any 2- or 4/6-hydroxy groups into chloro substituents. Thus, 5-carbamoyl-4-hydroxy-2-phenylpyrimidine in refluxing phosphoryl chloride gave 4-chloro-5-cyano-2-phenylpyrimidine (56) (>90%);⁵⁵⁸² 4-carbamoylmethyl-2,6-dihydroxypyrimidine likewise gave 2,4-dichloro-6-cyanomethylpyrimidine (39%);⁶⁰⁶³ and 4-carbamoyl-2,6-dihydroxy-5-nitropyrimidine in a refluxing mixture of phosphoryl chloride and phosphorus pentachloride gave 2,4,5-trichloro-6-cyanopyrimidine (note replacement of the 5-nitro by a 5-chloro substituent).⁵⁹⁷¹ Heating 5-β-carbamoylethyl-4-chloro-6-methyl-2-phenylpyrimidine in a vacuum at 230° has been reported to afford 5-β-cyanoethyl-4-hydroxy-6-methyl-2-phenylpyrimidine as a sublimate in "quantitative yield."⁵⁷⁶⁶

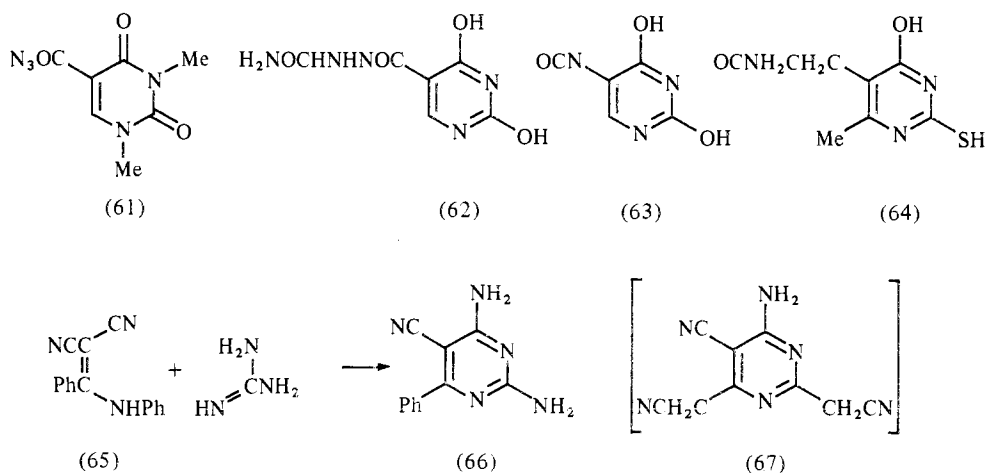
Prolonged heating of 4,6-diamino-5-carbamoyl-2-phenylpyrimidine with thiourea at 180°, followed by treatment with aqueous alkali,

resulted in the complete removal of the carbamoyl group to afford 4,6-diamino-2-phenylpyrimidine in low yield.⁵⁷⁶⁷ Heating 4,5-dicarbamoylpyrimidine (57) at 200° gave a low yield of the cyclic imide (58).⁴⁴⁵³ The unusually rapid hydrolysis of 4-amino-2-carbamoylmethylthiopyrimidine (59) in acidic media has been ascribed to "catalysis by pyrimidine nitrogen".⁵²⁸⁶ Several pyrimidine amides, for example, 2-carbamoylmethylthio-4,6-dimethylpyrimidine (60), have proved to be fairly active amplifiers of the antibiotic, phleomycin, against bacteria.⁶²⁷⁸

C. Preparation and Reactions of Hydrazides and Azides (*H* 400, *E* 307)

The usual route to hydrazides is by hydrazinolysis of esters, as indicated in Sect. 2.B above. Additional examples include the conversion of 5-ethoxycarbonyl- into 5-hydrazinocarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (85% hydrazine hydrate in butanol under reflux, *c.* 84%),⁵⁸⁹⁵ of 5- β -ethoxycarbonyl-ethyl- into 5- β -hydrazinocarbonyl-ethyl-2,4-dihydroxy-6-methylpyrimidine (ethanolic hydrazine hydrate at 100°, 59%),⁵⁷⁰⁷ and of 4-ethoxycarbonylmethyl- into 4-hydrazinocarbonylmethyl-2,6-dihydroxypyrimidine (>90%).⁶¹⁰¹

Azidocarbonylpyrimidines are made by treatment of the hydrazinocarbonyl analogues with nitrous acid, as exemplified in the formation of 5-azidocarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (61) (aqueous nitrous acid at 0°, 80%),⁵⁸⁹⁵ 5-azidocarbonyl-2,4-dihydroxypyrimidine (similarly, 78%),⁵⁸⁹⁵ and 5- β -azidocarbonyl-ethyl-4-hydroxy-2-mercapto-6-methylpyrimidine (aqueous nitrous acid at 5°, 76%).⁵⁷⁰⁷



Apart from conversion into azidocarbonylpyrimidines, as outlined immediately above, hydrazides do undergo a few reactions as illustrated in the conversion of 4-hydrazinocarbonyl-2,6-dihydroxypyrimidine into 2,4-dihydroxy-6-semicarbazidocarbonylpyrimidine (62) (cyanic acid; c. 90%);⁶¹⁰¹ of 5-bromo-4-hydrazinocarbonyl-2-methylthiopyrimidine into 5-bromo-2-methylthio-4-[4'-phenyl(thiosemicarbazido)carbonyl]-pyrimidine (phenyl isothiocyanate in ethanol under reflux, 58%);⁵³⁷⁷ and other such reactions.^{5377, 6101}

The main reaction of azidocarbonylpyrimidines is the formation of isocyanatopyrimidines such as 2,4-dihydroxy-5-isocyanatopyrimidine (63) (refluxing in xylene, 98%),⁵⁸⁹⁵ 1,2,3,4-tetrahydro-5-isocyanato-1,3-dimethyl-2,4-dioxypyrimidine (refluxing in benzene, 95%),⁵⁸⁹⁵ and 4-hydroxy-5- β -isocyanatoethyl-2-mercapto-6-methylpyrimidine (64) (refluxing in toluene, 76%).⁵⁷⁰⁷

4. Pyrimidine Nitriles (*H* 401, *E* 308)

A. Preparation of Cyanopyrimidines (*H* 401, *E* 308)

(1) *By Primary Syntheses* (*H* 401, *E* 308)

The formation of cyanopyrimidines by primary syntheses is discussed in Ch. II and III. A typical example involved the condensation of α -(α' -anilinobenzylidene)malononitrile (65) with guanidine to give 2,4-diamino-5-cyano-6-phenylpyrimidine (66) in 55% yield.⁴⁹¹² A "trimer," obtained from malononitrile under basic conditions and previously formulated as 4-amino-5-cyano-2,6-biscyanomethylpyrimidine (67), is no longer believed to be a pyrimidine at all.⁵¹⁸⁹

(2) *By Dehydration of Amides* (*H* 404, *E* 308)

This route to nitriles is covered in Sect. 3.B above.

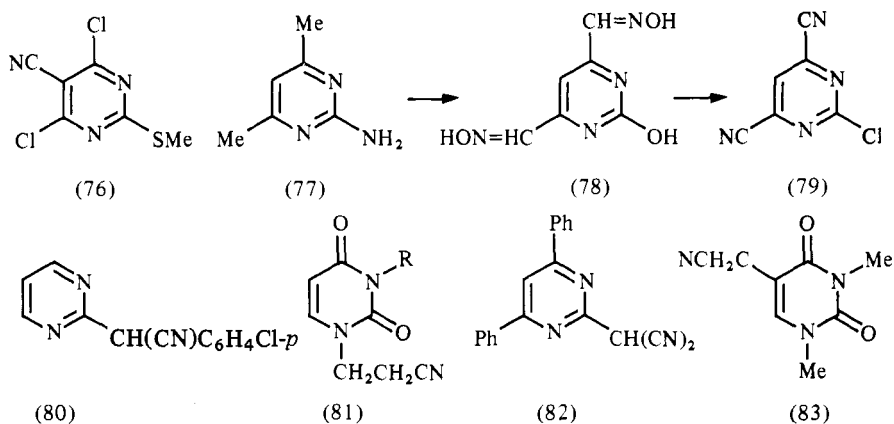
(3) *By Other Means* (*H* 404, *E* 308)

Cyanopyrimidines may be made by *displacement* of other leaving groups with cyanide ion. Such displacement of an halogen (Ch. VI, Sects. 5.I, 6.B, and 7) is not always simple. Thus, treatment of 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (68) or 5-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (70) with

5-Cyanopyrimidines may be made *from* the corresponding 5-*diazoniopyrimidine halides* (derived from the 5-amino precursors). Thus, treatment of 5-diazonio-2,4-dihydroxypyrimidine chloride with aqueous potassium cyanide containing suspended cuprous cyanide under reflux gave 5-cyano-2,4-dihydroxypyrimidine (73) in 64% yield;^{577, 6007} and 2-amino-5-cyano-4,6-dihydroxypyrimidine (65%), 5-cyano-4-hydroxy-2-mercaptopyrimidine, and 2-amino-5-cyano-4-hydroxy-6-methylpyrimidine (62%) were made similarly.⁵⁷⁷ In contrast, treat-

ment of the methanol adduct of 5-diazouracil (74, R = H) or 5-diazo-1,3-dimethyluracil (74, R = Me) with aqueous potassium cyanide gave 4-cyano-2,6-dihydroxypyrimidine (75, R = H) or 4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (75, R = Me), respectively, in 50–60% yield, *via* the HCN adducts akin to (74).⁶¹⁸⁹

The *dehydration of hydroxyiminomethylpyrimidines* (aldehyde oximes) has been used to make nitriles such as 4,6-dichloro-5-cyano-2-methylthiopyrimidine (76) (thionyl chloride under reflux, 43%),⁵⁵⁸¹ and 5-cyanopyrimidine (thionyl chloride, 79%; acetic anhydride, *c.* 15%).⁵⁷⁹⁴ Treatment of 2-amino-4,6-dimethylpyrimidine (77) with nitrous acid gave initially 2-hydroxy-4,6-bishydroxyiminomethylpyrimidine (78), which with phosphoryl chloride/diethylaniline gave 2-chloro-4,6-dicyanopyrimidine (79) in 28% overall yield.⁴⁸²⁰ An analogous reaction is the removal of methanol from 1,2,3,4-tetrahydro-6-*C*-methoxyformimidoyl-1,3-dimethyl-2,4-dioxypyrimidine with phosphoryl chloride to give 4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (83%),⁴⁹³⁹ although such a reaction can be of little utility since iminoethers are invariably made from the nitriles! Other dehydrations are known.⁶⁵⁰³



Miscellaneous routes to extranuclear pyrimidine nitriles are seen in the reaction of 2-chloropyrimidine with *p*-chlorophenylacetonitrile (sodium hydride/tetrahydrofuran) to give 64% of 2-*p*-chloro- α -cyano-benzylpyrimidine (80),⁴³⁴¹ in the cyanoethylation of 6-amino-1-propyluracil by acrylonitrile in pyridine hydrate to give 6-amino-5- β -cyanoethyl-1-propyluracil,⁴²³⁴ in the *N*-cyanoethylations of 5-bromo-2,4-dihydroxypyrimidine by acrylonitrile to give (according to conditions) 5-bromo-1- β -cyanoethyluracil (81, R = H) or 5-bromo-1,3-bis- β -cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxypyrimidine (81, R =

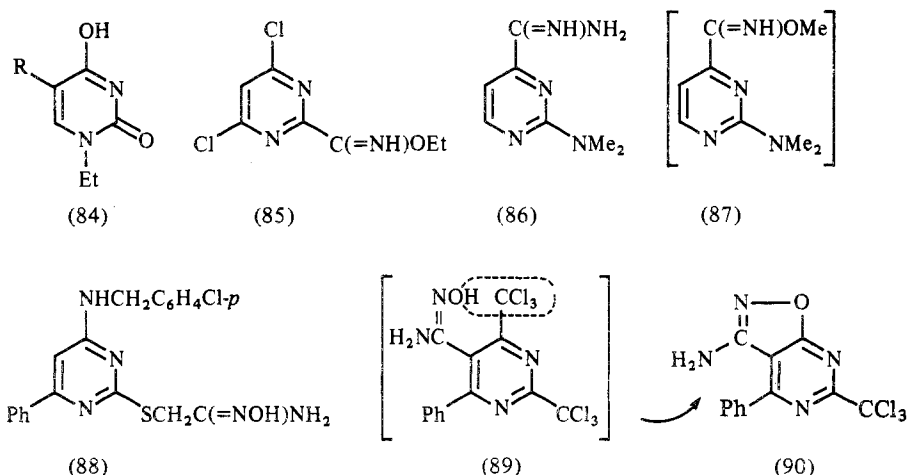
$\text{CH}_2\text{CH}_2\text{CN}$) in *c.* 70% yield;⁴³⁹¹ in the similar cyanoethylation of 5-bromo-4-carboxy-2,6-dihydroxypyrimidine to give 5-bromo-4-carboxy-1,3-bis- β -cyanoethyl-1,2,3,6-tetrahydro-2,6-dioxypyrimidine (76%);⁴³⁹⁰ in the cyanoacetylation of 4-amino-2-dimethylamino-5-nitropyrimidine to give 4-2'-cyanoacetamido-2-dimethylamino-5-nitropyrimidine (>60%);⁶²⁹⁵ in the cyanoethylation of 4-hydroxy-2-mercaptopyrimidine (acrylonitrile triethylamine/water under reflux) to give 1,3-bis- β -cyanoethyl-1,2,3,4-tetrahydro-4-oxo-2-thiopyrimidine (79%);⁵⁹²⁴ in the *S*-cyanomethylation of 5-amino-4-mercapto-6-methoxypyrimidine (chloroacetonitrile/methanolic alkali) to give 5-amino-4-cyanomethylthio-6-methoxypyrimidine (78%);⁴⁷⁶⁶ in the condensation of 2-chloro-4,6-diphenylpyrimidine with malononitrile in dimethylformamide containing sodium hydride to give 2-dicyanomethyl-4,6-diphenylpyrimidine (82) (*c.* 80%);⁵⁸³⁶ and in the reaction of 1,2,3,4-tetrahydro-5-hydroxy-1,3-dimethyl-2,4-dioxypyrimidine with cyanomethylenetriphenylphosphorane to give 5-cyanomethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (83).⁶¹⁵⁸

B. Reactions of Cyanopyrimidines (*H* 405, *E* 309)

Cyano groups may be *removed* by hydrolysis and subsequent decarboxylation, often without isolation of the carboxylic acid. For example, 5-cyano-1-ethyluracil (84, $\text{R} = \text{CN}$) in refluxing 48% hydrobromic acid gave the (unisolated) 5-carboxy analogue (84, $\text{R} = \text{CO}_2\text{H}$), which decarboxylated concomitantly to give 1-ethyluracil (84, $\text{R} = \text{H}$), and this was brominated (bromine/chloroform) without purification to afford 5-bromo-1-ethyluracil (84, $\text{R} = \text{Br}$) in 58% yield. Six homologues were made likewise.⁴⁹⁴⁰ Rather similarly, 4-benzylamino-5-cyano-2,6-diphenylpyrimidine in phosphoric acid at 160° underwent hydrolysis of both the cyano and amine group followed by decarboxylation to give 4-hydroxy-2,6-diphenylpyrimidine in unstated yield.⁵⁹⁴¹

The *hydration* and *addition of hydrogen sulfide* to nitriles to give amides and thioamides, respectively, have been covered in Sect. 3.A(3) above; their *hydrolysis* to carboxylic acids in Sect. 1.A(2); their complete *reduction* to aminomethylpyrimidines in Ch. IX, Sect. 3.A; and their partial reduction to iminomethylpyrimidines followed by hydrolysis to aldehydes in Sect. 5.A(3) below. The *displacement* of a cyano group by amines and so forth is mentioned in several places (see Index) and is exemplified in the aminolytic and alcoholytic reactions of 4,5-dicyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine to give 4-butylamino-5-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypy-

rimidine (butylamine at 25°, 99%) and 5-cyano-1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxypyrimidine (methanolic sodium methoxide under reflux, 41%), respectively.⁴⁹⁴⁷



The *addition of alcohols* to nitriles to give "iminoethers" may be done with alcoholic hydrogen chloride or alcoholic sodium alkoxide. For example, 4,6-dichloro-2-cyanomethylpyrimidine with ethanolic hydrogen chloride in ether-benzene gave 4,6-dichloro-2-(C-ethoxyformimidoyl)methylpyrimidine (85) as hydrochloride (90%),⁵⁶⁸⁸ while 4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine with methanol containing sodium methoxide or potassium hydroxide gave 1,2,3,4-tetrahydro-6-C-methoxyformimidoyl-1,3-dimethyl-2,4-dioxypyrimidine as base (66–80%).⁴⁹³⁹

In the past, *addition of amines* to nitriles to give amidines has usually been done indirectly *via* iminoethers, but nowadays it is done directly. Thus, fusion of 4-cyano-2-dimethylaminopyrimidine with ammonium benzenesulfonate at 265° gave 4-amidino-2-dimethylaminopyrimidine (86) as its benzenesulfonate salt (56%).⁶¹⁸¹ Alternatively, the same cyano substrate with methanolic sodium methoxide at 25° gave 2-dimethylamino-4-C-methoxyformimidoylpyrimidine (87) which, on treatment with ammonium chloride, gave the amidine (86) as its hydrochloride (81%).⁶³⁷⁷ Another example is the conversion of 4-*p*-chlorobenzylamino-2-cyanomethylthio-6-phenylpyrimidine into 4-*p*-chlorobenzylamino-2-*N*-hydroxyamidinomethylthio-6-phenylpyrimidine (88) (58%) by heating with hydroxylamine in dimethylformamide.⁵⁴⁷⁶ A similar reaction between 5-cyano-4-phenyl-2,6-bistrichloromethylpyrimidine and ethanolic hydroxylamine resulted in loss of chloroform

from the unisolated intermediate *N*-hydroxyamidine (89) to give 3-amino-4-phenyl-6-trichloromethylisoxazolo[5,4-*d*]pyrimidine (90), correctly formulated but incorrectly named in the original paper.⁵⁹⁵³

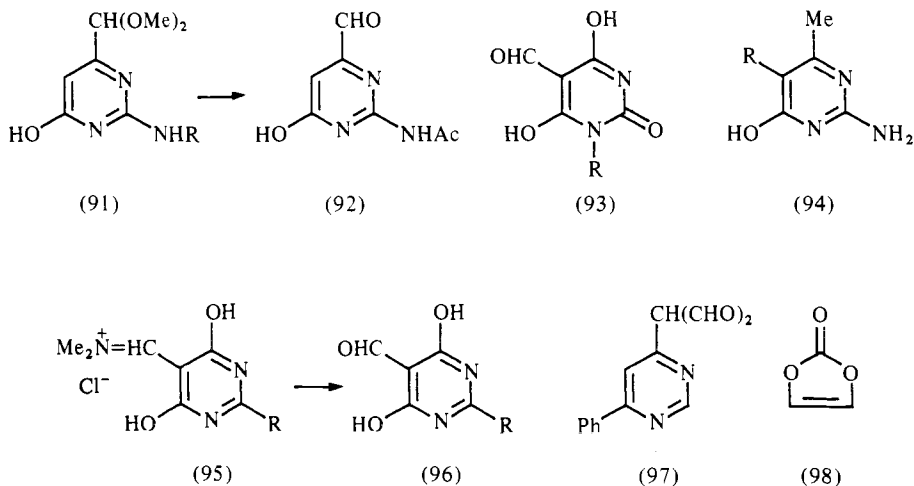
The conversion of a cyano- into an hydroxymethylpyrimidine is possible without isolation of the intermediates. For example, pressure hydrogenation of 4-amino-5-cyano-2-cyclopentylpyrimidine in hydrochloric acid over palladium gave 4-amino-2-cyclopentyl-5-hydroxymethylpyrimidine, presumably *via* the 5-iminomethyl and 5-formyl intermediates.⁵⁴⁶⁹

5. Pyrimidine Aldehydes and Their Acetals (*H* 406, *E* 311)

A. Preparation of Formylpyrimidines (*H* 406, *E* 311)

(1) *By Primary Syntheses* (*H* 406, *E* 311)

Although free formylpyrimidines are not made by primary syntheses, many of their acetals have been so made (Ch. II and III) and have been converted into the free aldehydes subsequently. For example, condensation of ethyl dimethoxyacetoacetate with guanidine carbonate in ethanol gave 2-amino-4-dimethoxymethyl-6-hydroxypyrimidine (91, *R* = *H*), which was acetylated to the 2-acetamido analogue (91, *R* = *Ac*) and then hydrolyzed in formic acid to give 2-acetamido-4-formyl-6-hydroxypyrimidine (92) in 94% yield.⁵³⁰⁰ Other examples of the hydrolysis of acetals to aldehydes are noted below in Sect. 5.A(5).



(2) *By Semi-Direct C-Formylation (H 408, E 311)*

Boiling 2,4,6-trihydroxypyrimidine or 1-methylbarbituric acid in triethyl orthoformate gave 5-formyl-2,4,6-trihydroxypyrimidine (93, R = H) or 5-formyl-1-methylbarbituric acid (93, R = Me), respectively, in good yield.⁵⁹⁰⁰

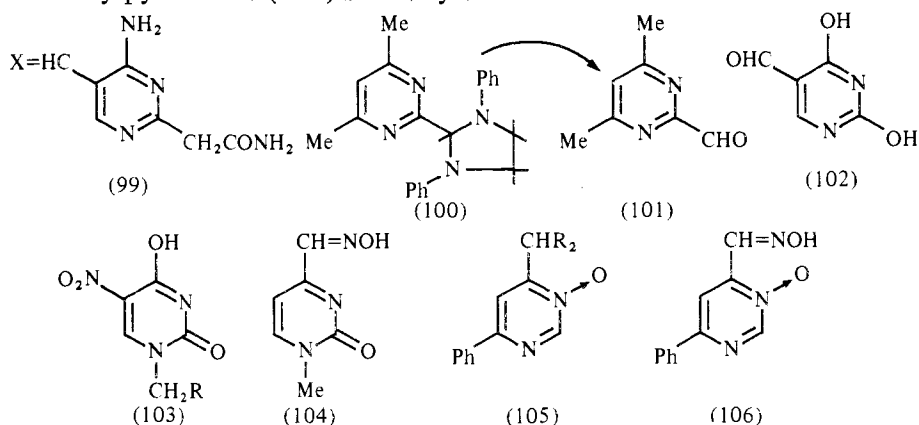
The Reimer–Tiemann synthesis (chloroform/concentrated potassium hydroxide) has been used to convert 2-amino-4-hydroxy-6-methylpyrimidine (94, R = H) into its 5-formyl derivative (94, R = CHO) in 63% yield,⁴⁵¹¹ and for analogous preparations.⁵⁸¹⁹ The Vilsmeier reaction (dimethylformamide/phosphoryl, thionyl, or other such chlorides) has been used more extensively to introduce a 5-formyl group or to attach a formyl group to an activated methyl group. Thus, treatment of 4,6-dihydroxypyrimidine with a mixture of dimethylformamide and phosphoryl chloride in chloroform at 60° gave the intermediate 5-dimethylimmoniomethyl-4,6-dihydroxypyrimidine chloride (95, R = H), which underwent hydrolysis in aqueous solution to afford 5-formyl-4,6-dihydroxypyrimidine (96, R = H).⁵⁸¹⁹ Likewise, 4,6-dihydroxy-2-phenylpyrimidine gave the intermediate (95, R = Ph) and thence 5-formyl-4,6-dihydroxy-2-phenylpyrimidine (96, R = Ph) (71%);⁵⁷⁹⁴ 2-amino-4,6-dihydroxy- gave 2-amino-4,6-dichloro-5-formylpyrimidine;⁶⁵⁰³ 2,4-dihydroxy-6-phenylthiopyrimidine gave its 5-formyl derivative (96%);⁶¹¹² 1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxypyrimidine gave its 5-formyl derivative (60%);⁴⁹²³ 4-ethoxycarbonylmethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine gave its 5-formyl derivative (63%);⁴⁹³⁵ and 6-amino-1-ethyluracil gave its 5-formyl derivative (dimethylformamide/thionyl chloride; 75%).⁵⁰³⁶ The Vilsmeier formylation of methyl groups is covered in Ch. IV, Sect. 2.C(8); typical examples are the conversion of 4-methyl-6-phenylpyrimidine into 4-diformylmethyl-6-phenylpyrimidine (97) (48%),⁵⁰⁷³ and of 2-methyl- into 2-diformylmethylpyrimidine (dimethylformamide/phosgene, 47%).⁵⁸⁶³

The conversion of 2,4-dihydroxy-5-methylpyrimidine into 5-methyl-2,4-bistrimethylsilyloxypyrimidine, followed by treatment with propynal and then hydrolysis, gave 1- β -formylvinyl-5-methyluracil, which proved to be highly cytotoxic to a variety of tumor cell lines.⁷¹²⁰

Irradiation of a mixture of 2,4-dihydroxypyrimidine and vinylene carbonate (98) gave an adduct which was degraded by triethylamine in dimethylformamide to afford 5-formylmethyl-2,4-dihydroxypyrimidine.⁵⁵⁴⁸

(3) *From Cyanopyrimidines (H 410)*

Cyanopyrimidines have been converted into formylpyrimidines by partial reduction to iminomethylpyrimidines, which usually underwent hydrolysis (without isolation) to the aldehydes. Thus, 4-amino-2-carbamoylmethyl-5-cyanopyrimidine underwent hydrogenation (and hydrolysis) in aqueous hydrochloric acid over palladium to give 4-amino-2-carbamoylmethyl-5-formylpyrimidine (99, X = O) *via* the intermediate (99, X = NH) (46%; note that both substrate and product are incorrectly named in the original paper).⁴⁴³³ An ingenious way to trap the intermediate prior to hydrolysis has been devised. Thus, 2-cyano-4,6-dimethylpyrimidine was hydrogenated in the presence of an equivalent of dianilinoethane (acetic acid/Raney nickel) to give 2-(1',3'-diphenylimidazolidin-2'-yl)-4,6-dimethylpyrimidine (100) (45%), which underwent hydrolysis in 6 M hydrochloric acid to afford 2-formyl-4,6-dimethylpyrimidine (101) in 66% yield.⁴⁷⁵³

(4) *By Other Reductive or Oxidative Processes (H 411, E 312)*

The formation of aldehydes by partial reduction of esters is illustrated⁵⁹⁷⁷ in Sect. 2.B above. The oxidation of methyl- or alkenyl- to formylpyrimidines (selenium dioxide^{6136, 6299} or ozone⁶⁰⁶⁴) is covered in Ch. IV, Sect. 2.C(4). The oxidation of an hydroxymethyl- to a formylpyrimidine is seen in the treatment of 2,4-dihydroxy-5-hydroxymethylpyrimidine with warm aqueous ammonium ceric nitrate [$\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$] to give 5-formyl-2,4-dihydroxypyrimidine (102) in *c.* 45% yield,⁵⁶⁴² and in the oxidation of 2-hydroxymethyl- to 2-formyl-4,6-dimethylpyrimidine (49%) using selenium dioxide.⁶⁰⁰⁸

(5) *By Other Means* (H 412, E 313)

Free pyrimidine aldehydes have been made from 5-fluoro-4-dimethoxymethyl-6-hydroxy-2-methylthiopyrimidine (50% acetic acid at 100°, 89% yield),⁵⁵²⁵ 5-benzyl-4-diethoxymethyl-6-hydroxy-2-mercaptopyrimidine (c. 4% sulfuric acid in aqueous dioxane under reflux, 95%),⁵⁷⁴³ 4-amino-5-dimethoxymethyl-2-phenylpyrimidine (50% acetic acid, c. 70%),⁵¹⁰⁴ 2-amino-4-dimethoxymethyl-6-hydroxy-5-phenethylpyrimidine (hydrogen chloride in aqueous dioxane under reflux, 95%),⁵⁵²⁶ and other acetals.^{5525, 5526, 5743} Alkylation of 2,4-dihydroxy-5-nitropyrimidine with 1-bromo-2,2-diethoxyethane gave 1- β,β -diethoxyethyl-5-nitrouracil [103, R = CH(OEt)₂] which, on stirring with an appropriate resin, gave 1-formylmethyl-5-nitrouracil (103, R = CHO) in 45% overall yield.⁶²³⁶ Similar sequences have been described.^{4749, 5288}

The nitrosation of an activated methyl group on a pyrimidine can result in the formation of the oxime of the corresponding aldehyde [Ch. IV, Sect. 2.C(6)], for example, 1,2-dihydro-4-hydroxyimino-methyl-1-methyl-2-oxopyrimidine (104),⁵⁴¹⁴ thus providing a potential route from methyl- to formylpyrimidines. The same sort of potential route is evident in the conversion of 4-dibromomethyl-6-phenylpyrimidine 3-oxide (105, R = Br) by sodium methoxide into the acetal, 4-dimethoxymethyl-6-phenylpyrimidine 3-oxide (105, R = OMe),⁴⁸¹¹ as well as in the conversion of 4-bromomethyl-6-phenylpyrimidine 3-oxide by an excess of hydroxylamine into the oxime, 4-hydroxyiminomethyl-6-phenylpyrimidine 3-oxide (106), which was obtained only in minute yield by the obvious route from the dibromomethyl substrate (105, R = Br).⁴⁸¹¹ The Schiff base of an aldehyde gives the free aldehyde on mildly acidic treatment, for example, 4-*p*-dimethylaminophenylimino-methyl- gave 4-formyl-5-hydroxymethyl-2-methylthiopyrimidine (87%) on shaking in ethyl acetate/aqueous hydrochloric acid.³⁴⁴³

B. Reactions of Formylpyrimidines (H 413, E 315)(1) *Oxidation and Reduction* (H 413, E 315)

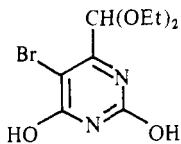
The oxidation of aldehydes to carboxylic acids and their reduction to hydroxymethylpyrimidines is covered in Sect. 1.A(3) and in Ch. VII, Sect. 3.F respectively; typical examples of reduction are the use of borohydride to transform 5-bromo-4-formyl-2,6-dihydroxy- to 5-bromo-2,4-dihydroxy-6-hydroxymethylpyrimidine (85%),⁴⁵⁰⁷ and of

4-amino-5-formyl- to 4-amino-5-hydroxymethyl-2-phenylpyrimidine (c. 60%).⁵¹⁰⁴

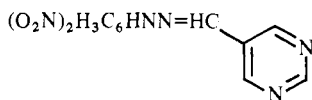
(2) *Formation of the Usual Aldehyde Derivatives (H 413, E 315)*

The conversion of pyrimidine aldehydes into their *acetals* is illustrated in the formation of 5-bromo-4-diethoxymethyl-2,6-dihydroxypyrimidine (107) (ethanolic hydrogen bromide, 87%), 5-dimethoxymethyl-2,4-dihydroxypyrimidine (methanolic *p*-toluenesulfonic acid, 67%),^{5472, 5642} 4-amino-5-dimethoxymethylpyrimidine (*p*-toluenesulfonic acid and trimethyl orthoformate in methanol, 87%),⁴⁴⁷¹ 5-diethoxymethylpyrimidine (triethyl orthoformate/*o*-toluenesulfonic acid, 58%),⁵⁷⁹⁴ and 4,6-dichloro-5- β,β -diethoxyethylpyrimidine (ammonium chloride in ethanol, 90%).⁶⁰⁶⁴ Some kinetic measurements for the first stage of acetal formation, that is, hemiacetal formation, from formylpyrimidines, have been reported.⁴⁷⁵³

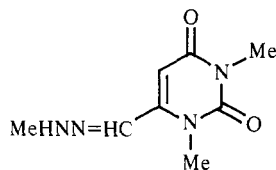
The transformation of aldehydes into their *hydrazones* is seen in the preparation of 5-2',4'-dinitrophenylhydrazonomethylpyrimidine (108) (dinitrophenylhydrazine in methanolic sulfuric acid, >80%),⁵⁷⁹⁴ 4-2',4'-dinitrophenylhydrazonomethyl-2,6-dihydroxypyrimidine,⁵⁸⁷⁶ 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-5-methylhydrazonomethyl-2,6-



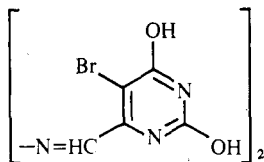
(107)



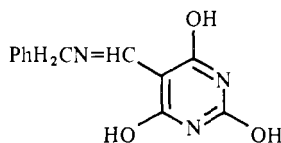
(108)



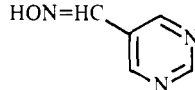
(109)



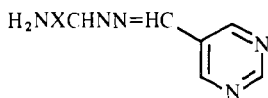
(110)



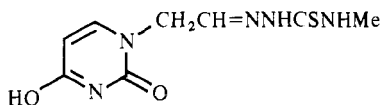
(111)



(112)



(113)



(114)

dioxypyrimidine (109) (*c.* 60%),⁴⁹²⁴ 5-hydrazonomethyl-2,4-dihydroxypyrimidine (30% hydrazine at 25°, 68%),⁴⁴⁸² 4-hydrazonomethylpyrimidine (from the acetal, *c.* 40%),⁴⁴⁴⁸ and 5-2',4'-dinitrophenylhydrazonomethyl-4,6-dihydroxypyrimidine.⁵⁸¹⁹ 5-Bromo-4-formyl-2,6-dihydroxypyrimidine and hydrazine gave the 4-hydrazonomethyl analogue (79%) or the azine *N,N'*-bis(5-bromo-2,6-dihydroxypyrimidin-4-ylmethylene) hydrazine (110) (69%) according to conditions employed.⁴⁵⁰⁷

The formation of *Schiff bases* from pyrimidine aldehydes has produced 5-benzyliminomethyl-2,4,6-trihydroxypyrimidine (111) (warm ethanolic benzylamine, 84%),⁵⁹⁰⁰ 5-*p*-chlorophenyl-4- β -dimethyliminoethyliminomethyl-4-hydroxy-2-mercaptopyrimidine (refluxing ethanolic β -dimethylaminoethylamine, 81%),⁵⁵²⁶ 2,4,6-trimethoxy-5-phenyliminomethylpyrimidine (aniline in boiling ethanol, 80%),⁵⁹⁸⁸ 4,6-dichloro-5-*p*-chlorophenyliminomethyl-2-methylthiopyrimidine (*p*-chloroaniline in acetic acid, 30%),⁵⁵³¹ 4-amino-5-benzyliminomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (benzylamine in refluxing benzene, *c.* 40%),⁵⁴³⁴ and others.⁶⁰²⁴

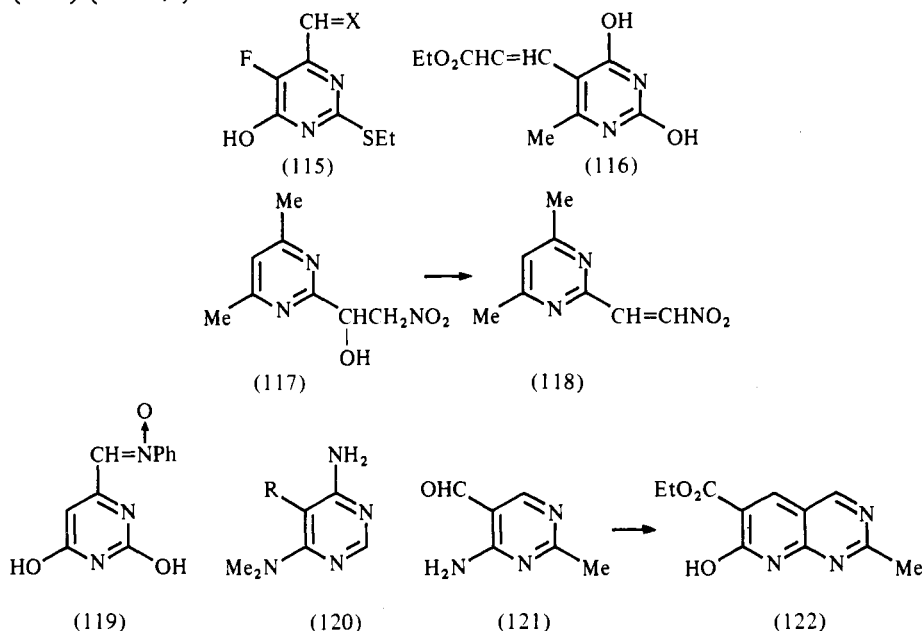
Pyrimidine aldehydes have also been converted into *aldoximes*, such as the 5-hydroxyiminomethylpyrimidine (112) (hydroxylamine hydrochloride/sodium acetate/water at 50–60°, >90%),⁵⁷⁹⁴ 4,6-dichloro-5-hydroxyiminomethyl-2-methylthiopyrimidine (hydroxylamine hydrochloride in 90% acetic acid, 55%),⁵⁵⁸¹ and 2-hydroxyiminomethylpyrimidine (aqueous hydroxylamine at pH 7–8, 70%).⁴⁷⁵¹

Pyrimidine aldehyde *semicarbazones* and *thiosemicarbazones* are represented in 5-semicarbazonomethyl- (113, X = O) and 5-thiosemicarbazonomethylpyrimidine (113, X = S) (reagent hydrochloride in aqueous sodium acetate, >80%),⁵⁷⁹⁴ 5-benzyl-4-hydroxy-2-mercapto-6-thiosemicarbazonomethylpyrimidine (63%),⁵⁵²⁶ 5-bromo-2,4-dihydroxy-6-thiosemicarbazonomethylpyrimidine (aqueous thiosemicarbazide, 75%),⁴⁵⁰⁷ 4,6-dihydroxy-5-thiosemicarbazonomethylpyrimidine,⁵⁸¹⁹ and 1- β -[4'-methyl(thiosemicarbazono)] ethyluracil (114).⁵⁹²⁶

(3) Other Reactions (*H* 414, *E* 317)

Other reactions of aldehydes are seen in the treatment of 2-ethylthio-5-fluoro-4-formyl-6-hydroxypyrimidine (115, X = O) with acetone in aqueous alkali to give 4-acetonylidenemethyl-2-ethylthio-5-fluoro-6-hydroxypyrimidine (115, X = CHAc) (75%),⁵⁵²⁵ in the reaction of 5-formyl-2,4-dihydroxy-6-methylpyrimidine with the Wittig reagent, ethoxycarbonylmethylenetriphenylphosphorane ($\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$), to give 5- β -ethoxycarbonylviny-2,4-dihydroxy-6-

methylpyrimidine (116);⁴⁶⁸⁷ in the condensation of 2-formyl-4,6-dimethylpyrimidine with nitromethane initially to give 2- α -hydroxy- β -nitroethyl-4,6-dimethylpyrimidine (117) and, after dehydration in acetic anhydride, 4,6-dimethyl-2- β -nitrovinylpyrimidine (118).⁴⁸³⁶ in the reaction of 4-formyl-2,6-dihydroxypyrimidine with *N*-phenylhydroxylamine in refluxing ethanol to give the nitrone 2,4-dihydroxy-2-phenyliminomethylpyrimidine *N*2'-oxide (119);⁵⁰⁴⁷ in the deformylation of 4-amino-6-dimethylamino-5-formylpyrimidine (120, R = CHO) by refluxing in dilute hydrochloric acid, to give 4-amino-6-dimethylaminopyrimidine (120, R = H) in *c.* 70% yield;^{5444, 5730} and in the further cyclization of 4-amino-5-formyl-2-methylpyrimidine (121) with diethyl malonate (in benzene containing benzoic acid and piperidine!) to give 6-ethoxycarbonyl-7-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine (122) (*c.* 80%).⁵¹⁰¹



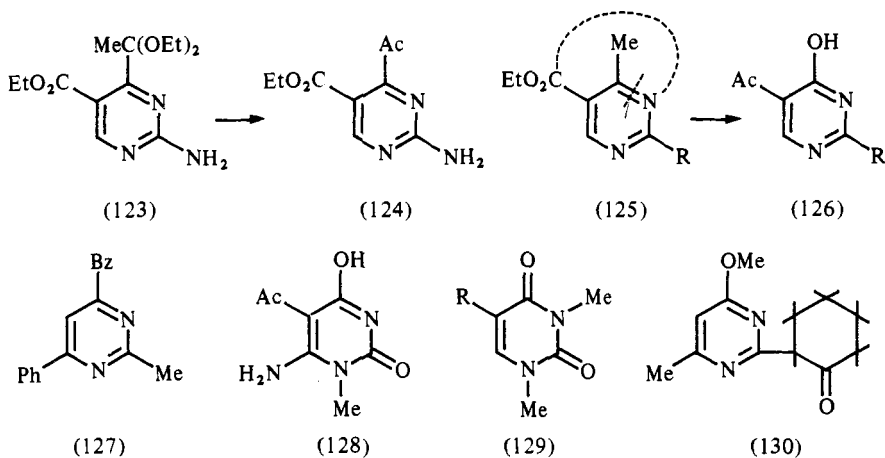
6. Pyrimidine Ketones and Derivatives (*H* 415, *E* 317)

A. Preparation of *C*-Acylpyrimidines (*H* 415, *E* 317)

Pyrimidine ketones have been made by a great variety of processes, although the number of such ketones is not overly great. *Primary syntheses* have been covered in Ch. II and III. A random example is

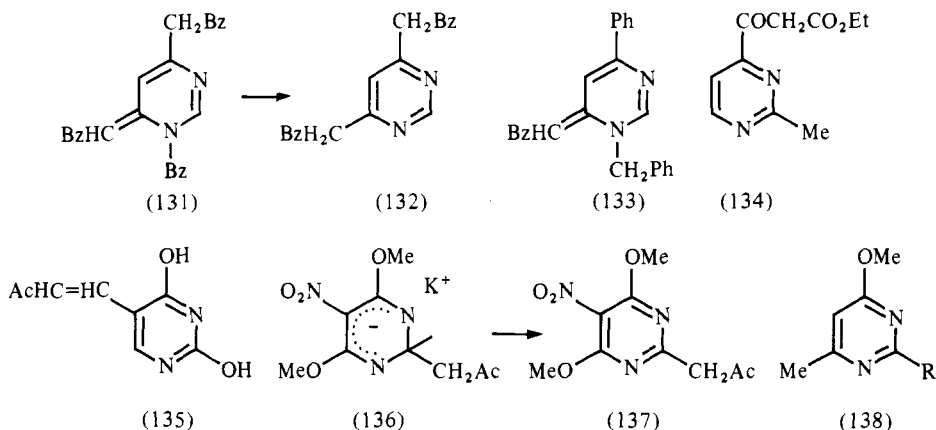
the hydrogenation of 4,5,6,7-tetrahydro-3,5,7-trimethyl-4,6-dioxo-isoxazolo[3,4-*d*]pyrimidine to give 5-acetyl-4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (61%).⁵⁰⁴² Examples also include some *acetals* of pyrimidine ketones which were so prepared and then converted into the free ketones; the latter process is illustrated in the conversion of 2-amino-4- α,α -diethoxyethyl- (123) into 4-acetyl-2-amino-5-ethoxycarbonylpyrimidine (124) (hydrochloric acid at 25°, 90%),⁴⁴³⁸ and of 2,4-diamino-5-*p*-chlorophenyl-6- α,α -dimethoxyethyl- into 4-acetyl-2,6-diamino-5-*p*-chlorophenylpyrimidine (aqueous methanolic hydrochloric acid under reflux, 95%).⁵⁴⁷⁴ Another reaction akin to primary synthesis is the sodium ethoxide catalyzed "rearrangement" of 2-amino-5-ethoxycarbonyl-4-methylpyrimidine (125, R = NH₂) into 5-acetyl-2-amino-4-hydroxypyrimidine (126, R = NH₂) with loss of ethanol; 5-ethoxycarbonyl-2-mercapto-4-methyl- (125, R = SH) similarly gave 5-acetyl-4-hydroxy-2-mercapto-pyrimidine (126, R = SH).⁶²⁸⁴

Many pyrimidine ketones have been made by *C-acylation* of the pyrimidine ring or of a methyl group attached thereto. Thus, homolytic acylation of simple pyrimidines with (i) pyruvic acid/ammonium persulfate/silver nitrate/sulfuric acid, or (ii) acetaldehyde/*t*-butyl hydroperoxide/ferrous sulfate/sulfuric acid, introduced an acetyl group into the 4/6-position but never the 2-position. In this way were made 4-acetyl-6-phenyl- (25, 45%),⁵⁰⁹¹ 4-acetyl-6-methyl- (25, 34%),⁵⁰⁹¹ 4-acetyl-2,6-dimethyl- [(i), 29%],⁵⁹⁸⁷ and 4-acetyl-2-methyl-6-phenylpyrimidine (52, 75%);⁵⁹⁸⁷ also others.⁵⁹⁸⁷ Appropriate variations in the aldehyde component in method (ii), gave 2-methyl-4-phenyl-6-propionylpyrimidine (78%), 4-benzoyl-2-methyl-6-phenylpyrimidine (127) (12%), and 4-isobutyryl-2-methyl-6-phenylpyrimidine (53%).⁵⁹⁸⁷



Providing they are 1-alkylated, 6-aminouracil and related compounds undergo acylation in the 5-position. Thus were made 5-acetyl-6-amino-1-methyluracil (128) (acetic anhydride/acetic acid under reflux, >95%),⁵⁴⁴⁶ 5-acetyl-4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (similarly, 83%,⁵⁴⁴⁶ acetyl chloride/pyridine, 68%⁴⁴¹⁰), 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-phenylacetylpyrimidine (phenylacetyl chloride/pyridine, 51%),⁴⁴¹⁰ 4-amino-5-benzoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine (benzoyl chloride/pyridine, 65%),⁴⁴¹⁰ and others.⁴⁴¹⁰ Related reactions are seen in the irradiation of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidine (129, R = H) with 2,5-diphenyl-1,3,4-oxadiazole to give, *inter alia*, the 5-benzoylated pyrimidine (129, R = Bz),⁵⁸⁵¹ as well as in the treatment of 4-methoxy-6-methylpyrimidine 1-oxide with *N*-(cyclohex-1-enyl)morpholine in the presence of benzoyl chloride, followed by treatment with hydrochloric acid, to give 4-methoxy-6-methyl-2'-oxocyclohexylpyrimidine (130) in 80% yield.⁵⁰⁸³

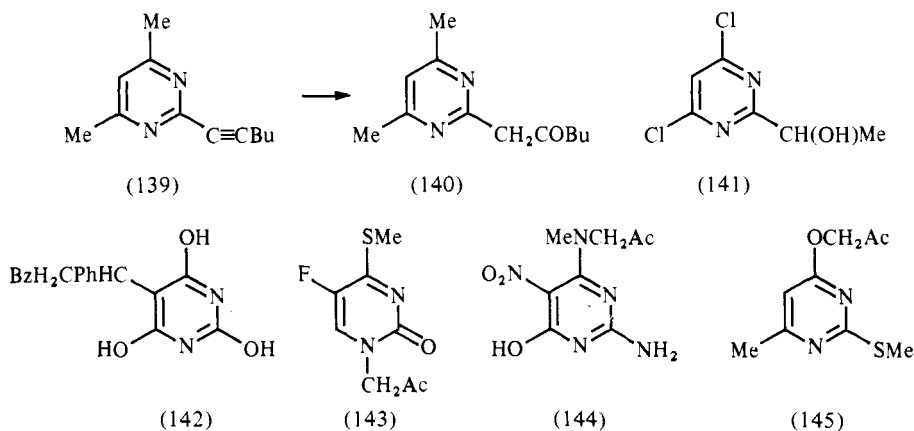
The acylation of alkyl groups attached to pyrimidine has been mentioned in Ch. IV, Sect. 2.C(6). Further examples include the conversion of 4,6-dimethylpyrimidine into 1-benzoyl-1,6-dihydro-4-phenacyl-6-phenacylidene-pyrimidine (131) by benzoyl chloride/triethylamine and subsequently into 4,6-diphenacylpyrimidine (132) by boiling in butanol;^{4768, 4803} of 1-benzyl-6-methyl-4-phenylpyrimidinium bromide into 1-benzyl-1,6-dihydro-6-phenacylidene-4-phenylpyrimidine (133) by benzoyl chloride/alkali;⁵²⁵⁵ and others.^{5090, 6023}



Further routes to ketones by the formation of a *C,C-bond to an existing substituent* are illustrated in the conversion of 4-methoxycarbonyl-2-methylpyrimidine into 4-ethoxymalonyl-2-methylpyrimidine (134) (ethyl acetate/sodium ethoxide/toluene, 73%; a classical Claisen

reaction),⁶³⁰⁰ of 2-methoxycarbonyl-4,6-diphenylpyrimidine into 2-cyanoacetyl-4,6-diphenylpyrimidine (acetonitrile/sodium hydride/dimethylformamide; 67%; another Claisen reaction),⁴⁷⁵⁹ of 5-formyl-2,4-dihydroxypyrimidine into 5- β -acetylvinyl-2,4-dihydroxypyrimidine (135) (acetone/piperidine/glacial acetic acid; 65%),⁵⁴⁷³ and of 4,6-dimethoxy-5-nitropyrimidine into the sigma complex (136) by addition of acetone, followed by oxidation with dichlorodicyanobenzoquinone to give 2-acetyl-4,6-dimethoxy-5-nitropyrimidine (137).⁶³⁴⁴

The *modification of existing groups* in other ways can lead to ketones. Thus, oxidation of 2-benzyl-4-methoxy-6-methylpyrimidine (138, R = CH₂Ph) with selenium dioxide gave the 2-benzoyl analogue (138, R = Bz) in 83% yield,⁵⁰⁷⁴ hydration of the triple bond in 2-hex-1'-ynyl-4,6-dimethylpyrimidine (139) gave 2-butyrylmethyl-4,6-dimethylpyrimidine (140) (mercuric sulfate/sulfuric acid in aqueous acetone, 68%; piperidine/toluene then hydrated oxalic acid/ether, 73%),⁶³⁵³ oxidation of 4,6-dichloro-5- α -hydroxyethylpyrimidine (141) by manganese dioxide in methylene chloride gave 5-acetyl-4,6-dichloropyrimidine (>90%);⁵⁷⁶⁸ and treatment of 2-*p*-chloro- α -cyanobenzylpyrimidine with sodium hydride in dimethylformamide followed by prolonged aeration, gave 2-*p*-chlorobenzoylpyrimidine (87%).⁴³⁴¹ Oxidation of trimethoprim with neat manganese dioxide gave 2,4-diamino-5-3',4',5'-trimethoxybenzoylpyrimidine.⁶⁵³⁷



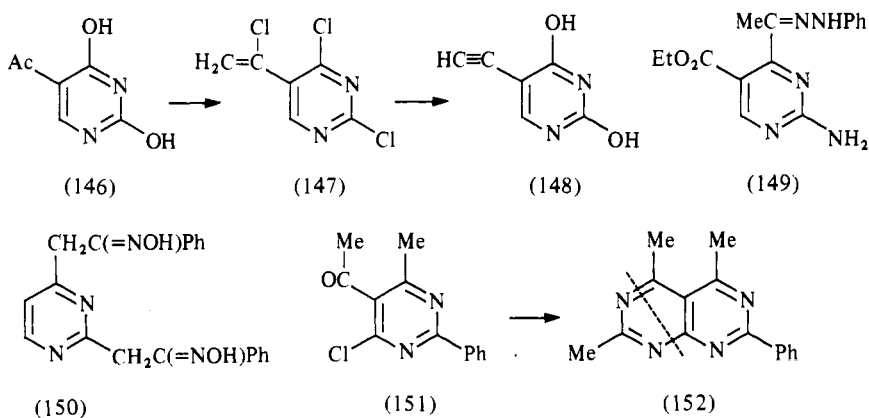
The *attachment of an existing ketone* to the pyrimidine nucleus by alkylation and so forth has been used to convert 5-cyano-4-mercapto-2,6-dimethylpyrimidine into 5-cyano-2,4-dimethyl-6-phenacylthiopyrimidine (phenacyl bromide/isopropyl alcohol, *c.* 90%);⁵³⁶⁴ 2,4,6-trihydroxypyrimidine into 5- β -benzoyl- α -phenylethylbarbituric acid (142)

(methanolic chalcone under reflux, 90%);^{477b} 2,4-diamino-6-mercapto-pyrimidine into 2,4-diamino-6-*p*-bromophenacylthiopyrimidine (*p*-bromophenacyl bromide/sodium methoxide/ethylene glycol, 90%);⁵⁴⁰¹ of 5-fluoro-2-hydroxy-4-methylthiopyrimidine into 1-acetonil-5-fluoro-1,2-dihydro-4-methylthio-2-oxopyrimidine (143) (chloroacetone in dimethyl sulfoxide, 85%);⁴⁸⁸⁹ of 2-amino-4-chloro-6-hydroxy-5-nitropyrimidine into 4-*N*-acetonil-*N*-methylamino-2-amino-6-hydroxy-5-nitropyrimidine (144) (methylaminoacetone/dimethylformamide containing triethylamine, 38%);⁴⁶⁴⁸ of 4-hydroxy- into 4-acetoxymethoxy-6-methyl-2-methylthiopyrimidine (145) (chloroacetone on sodium salt of substrate; also a second product);⁶³⁵⁵ and others.^{5949, 6628}

The *rearrangement* of pyrimidines has been used to make pyrimidine ketones. For example, treatment of 2-amino-5-ethoxycarbonyl-4-methylpyrimidine with sodium ethoxide caused ring-fission at the 3,4-bond with recyclization to 5-acetyl-2-amino-4-hydroxypyrimidine (79%).⁶⁵²³

B. Reactions of *C*-Acylpyrimidines (H 417, E 318)

Remarkably few reactions of pyrimidine ketones have been reported recently, although they are, of course, just as reactive and potentially useful as any other type of ketone. However, the meager information includes, for example, the reaction of 5-acetyl-2,4-dihydroxypyrimidine (146) with phosphoryl chloride/dimethylaniline to give 2,4-dichloro-5- α -chlorovinylpyrimidine (147) which, on boiling in dioxane containing aqueous alkali, gave 5-ethynyl-2,4-dihydroxypyrimidine (148) in 32% overall yield;⁵³²⁹ the conversion (by the usual means) of 4-acetyl-2-amino-5-ethoxycarbonyl- into 2-amino-5-ethoxycarbonyl-



4- α -(phenylhydrazono)ethylpyrimidine (149);⁴⁴³⁹ the conversion of 5-acetyl-2,4-dimethyl- into 2,4-dimethyl-5- α -(semicarbazono)ethylpyrimidine;⁵⁰⁷⁷ and the conversion of 4,6-diphenacylpyrimidine into its dioxime, 4,6-bis(β -hydroxyimino- β -phenylethyl)pyrimidine (150) (hydroxylamine/pyridine).⁴⁷⁶⁸ Simple oximes have been described.⁶⁶²⁸

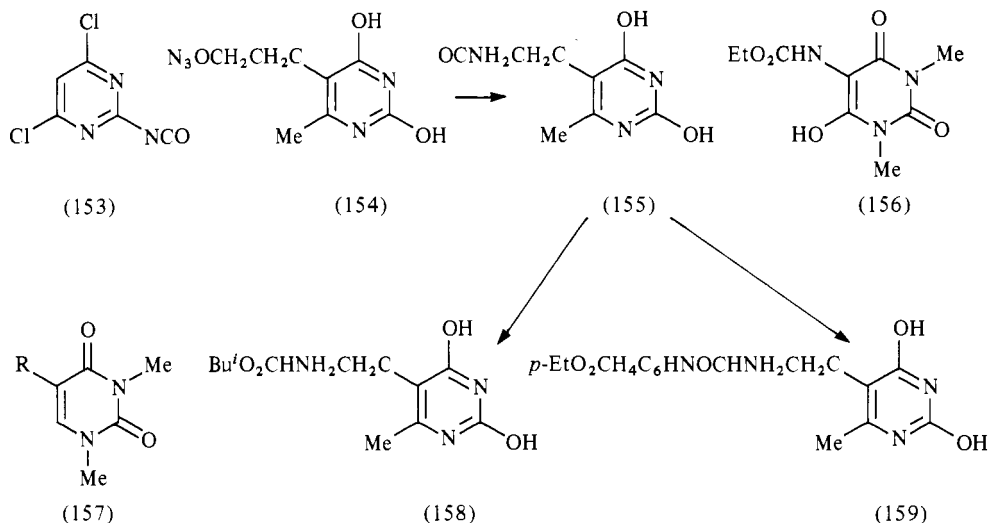
An indication of the potential use of pyrimidine ketones is gleaned from the condensation of 5-acetyl-4-chloro-6-methyl-2-phenylpyrimidine (151) with acetamidine to give 2,4,5-trimethyl-7-phenylpyrimido[4,5-*d*]-pyrimidine (152) in 63% yield. The same and similar pyrimidine ketones also condensed with all manner of amino compounds to give derivatives in several heterotricyclic and heterobicyclic systems.⁴⁴⁵⁶

7. The Isocyanato-, Thiocyanato-, and Isothiocyanatopyrimidine Family (H 418, E 319)

Relatively little has been reported recently in this area.

A. Isocyanatopyrimidines (H 418, E 319)

The preparation of *isocyanato- from aminopyrimidines* has been done by treatment with oxalyl chloride, as illustrated in the conversion of 2-amino-4,6-dichloro- into 4,6-dichloro-2-isocyanato-5-phenylpyrimidine (153, R = Ph) (oxalyl chloride in benzene under reflux, 98%; no intermediate isolated);⁴⁸²² of 2-amino-4,5,6-trichloropyrimidine into 4,5,6-trichloro-2-isocyanatopyrimidine (153, R = Cl) (similarly, 90%);⁴⁵¹⁷ and of 4-amino-5,6-dichloro- into 4,5-dichloro-6-isocyanato-2-phenyl(or trichloromethyl)pyrimidine (similarly, 95, 75%).⁴⁵¹⁷ The formation of *isocyanates from azides or urethanes* is illustrated in the conversion of 5- β -azidocarbonyl-2,4-dihydroxy- (154) into 2,4-dihydroxy-5- β -isocyanatoethyl-6-methylpyrimidine (155) (prolonged refluxing in toluene, 70%);⁵⁷⁰⁷ of 5-azidocarbonyl-2,4-dihydroxy- into 2,4-dihydroxy-5-isocyanatopyrimidine (refluxing xylene, c. 80%);⁵⁸⁹⁵ of 4-azidocarbonyl- (made *in situ* from the 4-chlorocarbonyl analogue) into 4-isocyanato-2-methylthio-5-phenylthiopyrimidine (refluxing toluene, 72% on the chloride substrate);⁴⁴⁰⁰ and of 5-ethoxycarbonyl-amino-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxypyrimidine (156) into 4-chloro-1,2,3,6-tetrahydro-5-isocyanato-1,3-dimethyl-2,6-dioxypyrimidine (by heating with "wet" phosphoryl chloride, 65%).⁵³⁹⁶ The formation of *isocyanato- from chloropyrimidines* is illustrated in the treatment of 5-chloro-1,2,3,4-tetrahydro- (157, R = Cl) with silver

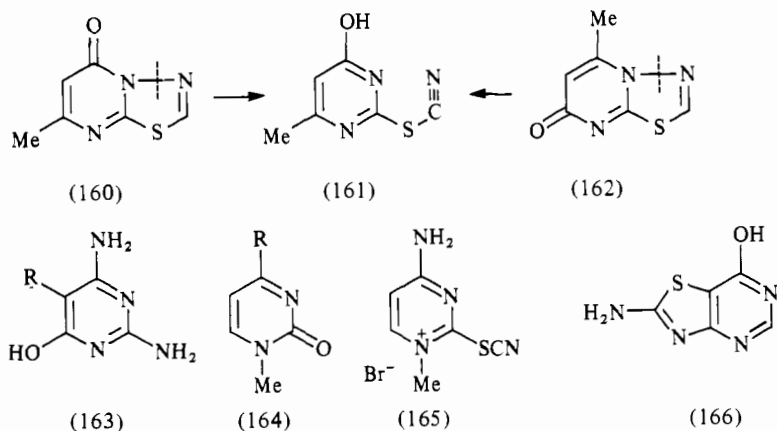


cyanate in refluxing benzene to give 1,2,3,4-tetrahydro-5-isocyanato-1,3-dimethyl-2,4-dioxypyrimidine (157, R = NCO) in *c.* 50% yield.⁵⁸⁹⁵

A few reactions of isocyanatopyrimidines are represented in the treatment of 2,4-dihydroxy-5-β-isocyanatoethyl-6-methylpyrimidine (155) with boiling isobutyl alcohol or ethyl *p*-aminobenzoate to afford the urethane 2,4-dihydroxy-5-β-(isobutoxycarbonylamino)ethyl-6-methylpyrimidine (158) or the urea 5-β-(*N'*-*p*-ethoxycarbonylphenylureido)ethyl-2,4-dihydroxy-6-methylpyrimidine (159), respectively;⁵⁷⁰⁷ in the hydrolysis (including decarboxylation) of 4,6-dichloro-2-isocyanato- to 2-amino-4,6-dichloropyrimidine (aqueous acetone at 25°, 99%), the alcoholysis of the same substrate to 4,6-dichloro-2-methoxycarbonylamino-2-methylpyrimidine (benzene containing methanol at 25°, >95%), and the aminolysis of the same substrate to 4,6-dichloro-2-*N'*-phenylureidopyrimidine (aniline in benzene at 20°, 97%);⁴⁸²² and in related reactions.⁵⁸⁹⁵

B. Thiocyanatopyrimidines (*H* 419, *E* 319)

In general, thiocyanatopyrimidines must be made under reasonably mild conditions to avoid isomerization. Their preparation by the several available routes is illustrated in the conversion of 5-methyl-7-oxo-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine (160) or 7-methyl-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine (162) into 4-hydroxy-6-methyl-2-thiocyanatopyrimidine (161) by ring-fission (liquid ammonia at -50°, 86 and 70%, respectively; a primary synthesis);^{6334, 5146} of



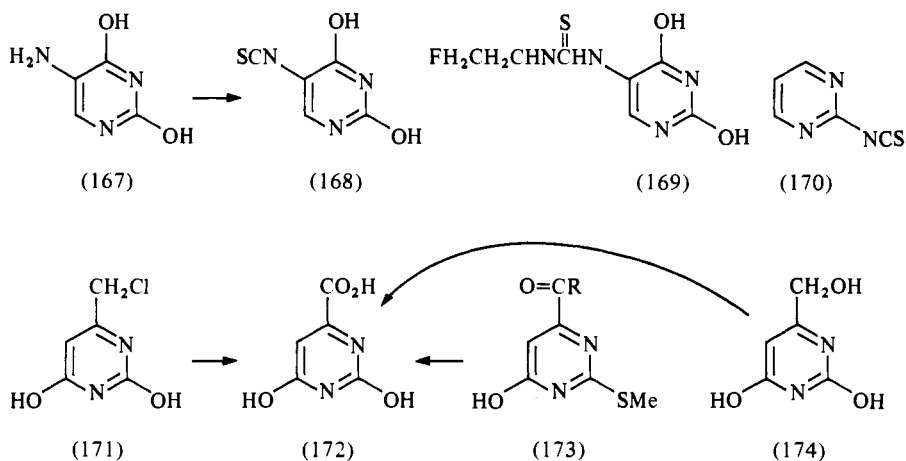
2,4-diamino-6-hydroxypyrimidine (163, R = H) into its 5-thiocyanato derivative (163, R = SCN) (addition of bromine to substrate plus potassium thiocyanate in acetic acid, >90%);⁵²⁵¹ of 4-amino-2,6-dihydroxypyrimidine into its 5-thiocyanato derivative (rather similarly or in pyridine/dimethylformamide/bromine, 75%);⁵²⁴⁴ of 2,4-diamino-5-bromo-6-hydroxypyrimidine (163, R = Br) into 2,4-diamino-6-hydroxy-5-thiocyanatopyrimidine (163, R = SCN) (potassium thiocyanate in water or dimethylformamide at 80–100°, c. 90%);⁵²⁵¹ of 2,4,6-triamino-5-bromo- into 2,4,6-triamino-5-thiocyanatopyrimidine (ethanolic potassium thiocyanate plus acetic acid under reflux, 72%);⁵²⁴⁴ of 1,2-dihydro-1-methyl-4-methylthio-2-oxo- (164, R = SMe) into 1,2-dihydro-1-methyl-2-oxo-4-thiocyanatopyrimidine (164, R = SCN) (potassium thiocyanate in acetonitrile under reflux, c. 50%);⁶²⁰⁶ of 1-methyl-4-thiouracil (164, R = SH) into the same product (164, R = SCN) (cyanogen bromide/alkali or aqueous alcoholic buffer of pH 9, c. 60%);^{5506, 6206} of 4-amino-2-mercapto- into 4-amino-2-thiocyanatopyrimidine (cyanogen bromide/aqueous alcoholic alkali, 13%);⁴⁴⁹⁰ and of 4-amino-1,2-dihydro-1-methyl-2-thiopyrimidine into 4-amino-1-methyl-2-thiocyanatopyrimidinium bromide (165) (ethanolic cyanogen bromide at 0°, 73%).⁴⁴⁹⁰

Although thiocyanatopyrimidines could undergo a variety of reactions, few such have been reported recently. Among these were the acidic or alkaline hydrolysis of 1,2-dihydro-1-methyl-2-oxo-4-thiocyanatopyrimidine (164, R = SCN) to 1-methyluracil (164, R = OH) (c. 50%);⁶²⁰⁶ the conversion of 2,4-diamino-6-hydroxy-5-thiocyanatopyrimidine by aqueous phosphate buffer (pH 8) into bis(2,4-diamino-6-hydroxypyrimidine-5-yl) disulfide;⁵²⁵¹ the reduction of 5-thiocyanato- to 5-mercaptouridine by sodium dithionite/mercaptoethanol;⁵⁵⁴³ and

the further cyclization of 4-amino-6-hydroxy-5-thiocyanatopyrimidine in boiling water to afford 2-amino-7-hydroxythiazolo[5,4-*d*]pyrimidine (166).⁵²⁴⁴

C. Isothiocyanatopyrimidines (*H* 421, *E* 319)

This area has been neglected recently. Treatment of 5-amino-2,4-dihydroxypyrimidine (167) with aqueous thiophosgene at 20° gave 2,4-dihydroxy-5-isothiocyanatopyrimidine (168) in 77% yield; it was converted by 2-fluoroethylamine into 5-*N'*-β-fluoroethyl(thioureido)-2,4-dihydroxypyrimidine (169) in 71% yield.⁶⁰⁹⁷ 2-Trimethylsilylamino-pyrimidine with thiophosgene in ether at -50° gave 2-isothiocyanatopyrimidine (170) in 48% yield.⁶²⁰⁸



8. Orotic Acid (*H* 427, *E* 320)

Chemical, as distinct from biochemical, aspects of orotic acid have received relatively little attention recently.

Several new or improved syntheses of orotic acid (4-carboxy-2,6-dihydroxypyrimidine, 172) include the primary synthesis of 4-chloromethyl-2,6-dihydroxypyrimidine (171) in good yield, followed by treatment with hydrogen peroxide/sodium hydroxide to give orotic acid (172) in 75% yield;⁴⁵¹² the primary synthesis of 4-carboxy-6-hydroxy-2-methylthiopyrimidine (173, R = OH) in 60% yield, followed by acidic hydrolysis (2 M hydrochloric acid under reflux) or oxidative hydrolysis (sulfuric acid/fuming nitric acid at 15°) to give orotic acid

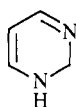
(172) in 79 and 87% yield, respectively;⁵⁶¹⁸ the oxidation of 2,4-dihydroxy-6-hydroxymethylpyrimidine (174) by nickel peroxide in alkali to give orotic acid (172) in 33% yield;⁵¹⁷⁵ and the oxidative hydrolysis of 4-formyl-6-hydroxy-2-methylthiopyrimidine (173, R = H) by silver oxide in water to give orotic acid (172) in *c.* 60% yield.⁴⁶⁰⁴

The thioesterification of orotic acid by treatment of the derived acid chloride ("orotyl chloride") with alkanethiols has been used to afford 4-(butylthio)carbonyl-, 4-(decylthio)carbonyl-, and 4-(cyclohexylthio)carbonyl-2,6-dihydroxypyrimidine as well as other homologues in up to 30% yield.⁵⁴⁶⁴ Numerous orotic acid analogues have been prepared and tested as antimetabolites of orotic acid in antiviral, general antimicrobial, and antimalarial screens.⁵⁷⁴⁵ The formation and structure of photodimers of orotic acid and its methyl ester have been reported.⁵³¹⁹ The photo-decarboxylation of orotic acid has been studied in depth.⁵⁵²⁰ Some mixed-ligand platinum complexes of 1,2-diaminocyclohexane and orotic acid have been described.⁵⁷¹⁶ Quantitative relationships, between structure and biological activity of orotic acid analogues as antimetabolites, have been claimed.⁴³⁶⁷

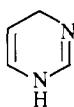
CHAPTER XII

The Reduced Pyrimidines* (*H* 430, *E* 322)

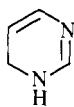
An earlier review (*E* 322) pointed out that although formally there was a total of nine hydrogenated derivatives (1–9) of pyrimidine (five dihydro, three tetrahydro, and one hexahydro), no allowance had been made hitherto for the complications due either to tautomerism, which arose from the mobile nature of hydrogen atoms attached to ring nitrogen atoms, or to the possible existence of ring conformational isomers. The theoretical chemists have now added their contributory modification to the above statement in pointing out that their calculations suggest 1,3-dihydro-1,3-diazine (10) in its C_s structure will have lower energy and singlet stability compared with the C_{2v} structure.⁶⁵⁴⁴



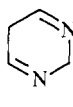
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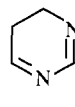
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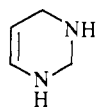
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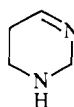
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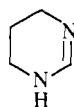
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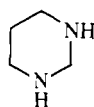
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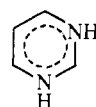
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(10)

The period under present review coincided with the first widespread availability of ^1H (especially high resolution) and ^{13}C nuclear magnetic resonance spectrometers, with the first ready access to X-ray spectrometers, and with the introduction of catalysts based on the less plentiful metals of the periodic table; all of these factors have affected the dihydropyrimidine field. The dihydropyrimidine section of this review is naturally swamped by reactions involving the 5,6-double bond

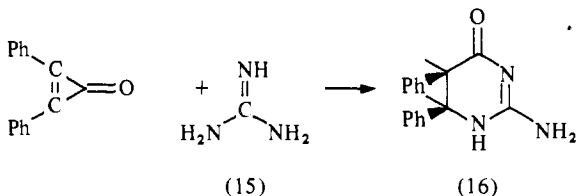
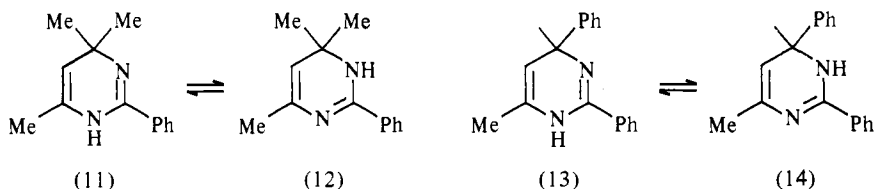
*By R.F. Evans, Department of Chemistry, University of Queensland, St. Lucia, Australia 4067.

of uracil, thymine, and cytosine either free or when combined in the biologically important nucleoside and nucleotide molecules. This intense interest has carried over into the 5-fluoro derivatives, especially 5-fluorouracil because of its important anti-tumor effect. Another structural pattern that becomes evident, especially in the Russian and technical literature, is one that can be traced back to the ready availability of acetone, or more correctly its dimeric condensation product mesityl oxide, as a cheap starting material for synthetic purposes.

1. Preparation of Dihydropyrimidines (*H* 431, *E* 323)

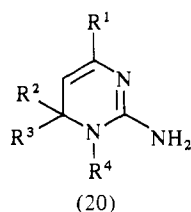
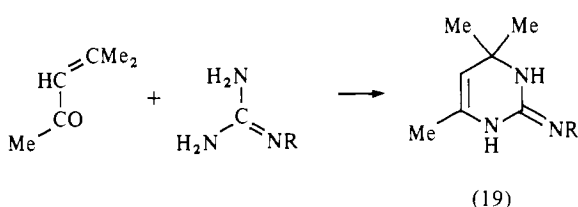
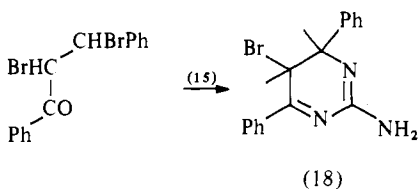
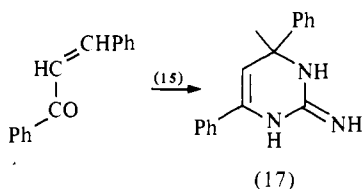
A. By a Modified Principal Synthesis (*H* 431, *E* 323)

The condensation of a three-carbon entity with an N—C—N compound continued to attract attention, particularly when the latter feature was contained in the urea, thiourea, or guanidine molecule or in their *N*-, *S*-, or *O*-substituted derivatives. A popular provider of the three-carbon entity was the α,β -unsaturated ketone system of mesityl oxide or phorone, either used directly or produced *in situ* from the self-condensation of acetone in the reaction medium. The earlier statement,³⁵³⁴ that the reaction of benzamidine with mesityl oxide affords a tautomeric mixture of the 1,4- and 1,6-dihydro compounds (11) and (12), explains the ^1H nmr spectrum of a carefully purified DMSO- d_6 solution. However, X-ray analysis 20 years after the initial observation confirms that the solid product is wholly the 1,6(or 3,4)-tautomer (12),⁶⁵⁴⁸ in which the double bonds of the reduced pyrimidine ring are conjugated with those of the phenyl substituent. By contrast, the solid product from an analogous condensation of benzylideneacetone with benzamidine has been shown to have the structure (13)



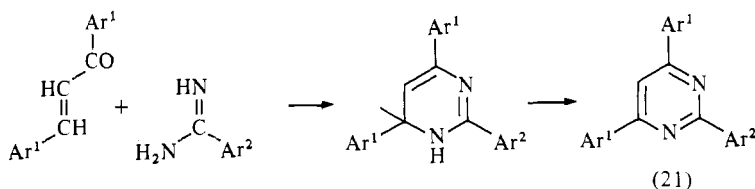
with the alternative 1,4-arrangement⁶⁵⁴⁹ and only one double bond of the reduced pyrimidine system conjugated with one of the phenyl groups. The tautomer (14) appears in equilibrium with (13) in solution.

Amidines and guanidine itself (15) also react with diphenylcyclopropenones by a process of cycloaddition,^{4549, 6543} the three-membered ring providing the three-carbon fragment required to complete the ring of a 5,6-dihydropyrimidin-4-one (16) with a *cis* arrangement of the two phenyl substituents. Heating this product (16) causes a *cis-trans* isomerization in which the 6-phenyl group has inverted its position.



More straightforward cyclocondensations arise between guanidine itself (15) and a chalcone or its dibromide,⁶⁵⁴² to give for example (17) or (18), as well as between *N*-methyl-, *N*-benzyl-, or *N*-phenylguanidine and the ubiquitous mesityl oxide,⁶⁵⁵² in which the substituent ends up on the exocyclic nitrogen atom in the products (19, $R = \text{Me}, \text{PhCH}_2$, or Ph). By contrast, recent work⁶⁵⁵⁵ has shown how important it is to carry out the cyclization reaction with guanidine or *N*-monoalkylguanidine at a low temperature (25°) and to avoid protic solvents for crystallization of the products. In this way, thermal isomerization and dimerization to give a mixture of products may be avoided⁶⁶⁶¹ and pure solids comprising solely the 2-amino-1,6-dihydro compounds, (e.g., 20, $R^1 = R^2 = R^3 = \text{Me}, R^4 = \text{H}, \text{Me}$, or Et ; or $R^1 = R^2 = \text{Ph}, R^3 = R^4 = \text{H}$), are obtained. An added complication is that the alkaline conditions of the reaction mixture will facilitate aromatization of the dihydropyrimidine ring. Aerial oxygen is sometimes an unrecognized agent, although transfer of hydrogen to other hydrogen-acceptors like ketones³⁸⁴ (*H* 102) has already been noted. Under such alkaline conditions, guanidine was found to react with chalcones derived from the condensation of various heterocyclic aldehydes with alkyl aryl ketones, to give

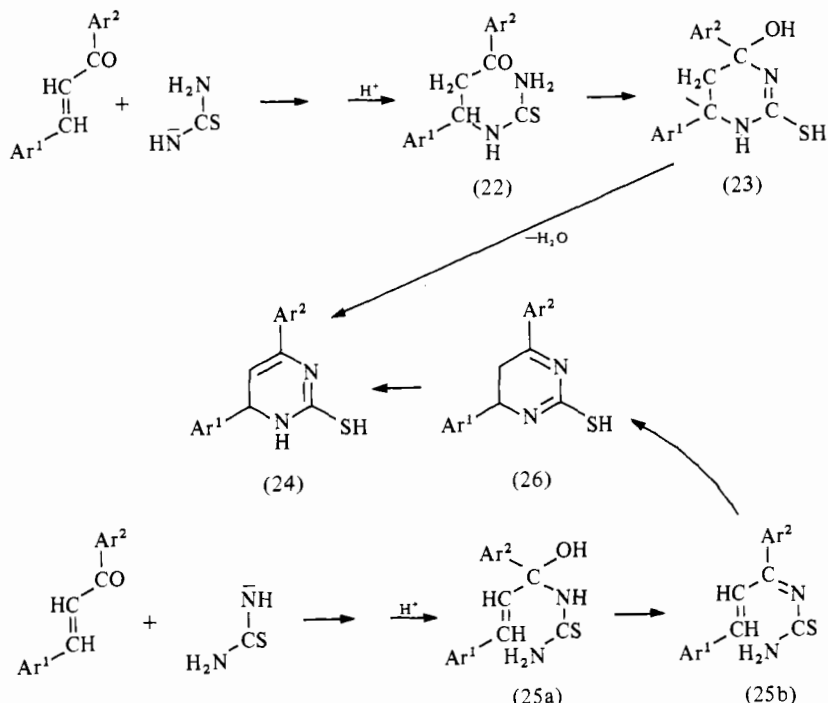
the 2-amino-4,6-diarylpyrimidines (20, R^1 = aryl, R^2 = heteroaryl, $R^3 + R^4$ = bond).⁶⁵⁵⁶ Similarly, *o*-hydroxybenzamidines condensed with chalcone in hot dimethyl sulfoxide (DMSO) in a stream of air, which caused dehydrogenation of the intermediate dihydro compound, to give the heteroaromatic compound (21, Ar^1 = Ph, Ar^2 = *o*-hydroxyphenyl).⁶⁶²¹



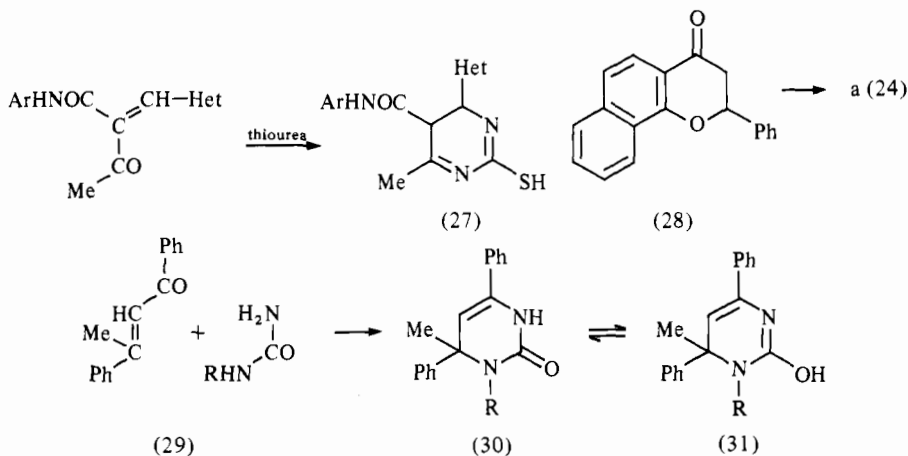
The chalcones, 1,3-diarylprop-2-en-1-ones, also condense with thiourea under strongly alkaline conditions (sodium ethoxide) to give 4,6-diaryl-1,6 (3,4)-dihydro-2-mercaptopyrimidines (24)⁶⁵⁵⁷ and not the earlier reported 5,6-dihydro counterparts.⁶⁶¹¹ The 1,6-dihydro derivative probably results from an initial 1,4-addition of the thiourea anion to the activated olefinic double bond⁶⁶⁵⁵ and the Michael addition product (22) may then cyclize to a tetrahydropyrimidine derivative (23), which readily loses a molecule of water to give the 1,6-dihydro compound (24) directly. An alternative mechanism could start with a 1,2-addition product (25a) which must undergo dehydration to give an intermediate (25b) with a $C=C$ bond sufficiently activated, compared with the same feature in (25a), to undergo internal nucleophilic attack and thus form the six-membered ring of the 5,6-dihydro derivative (26). This must finally tautomerize to the 1,6-isomer (24). The 1,6-dihydro compound can undergo aerial oxidation, or if the reaction is carried out under nitrogen will transfer hydrogen to the chalcone, so that again the fully aromatic pyrimidine compound is either the sole product or accompanies its dihydro derivative.⁶⁵³¹

When the thiourea molecule has a choice of reacting with a substrate that is both a chalcone and a 1,3-dicarbonyl compound, the former wins out to give, for example, the product (27, Ar = *o*-alkylphenyl, Het = thien-2-yl).⁶⁵⁹⁷ Any *o*-hydroxy group(s) in the aromatic ring of the aroyl part of the chalcone seems to prevent complications due to concomitant aromatization, whether free or concealed in prior ring formation as a flavenone, for example (28), which gave the product (24, Ar^1 = Ph, Ar^2 = 1-hydroxynaphth-2-yl).⁶⁶¹²

By contrast, the condensations with urea seem to be free from the complications arising from aromatized products so that dypnone (29),

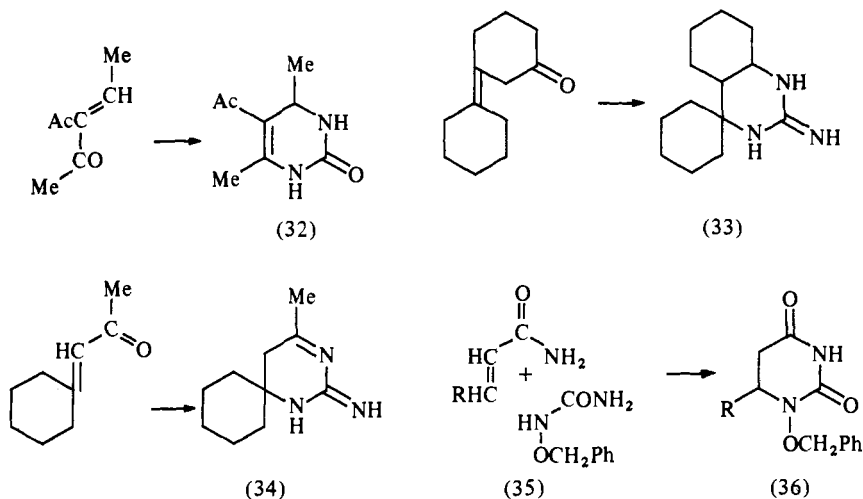


produced *in situ* by acid-catalyzed self-condensation of acetophenone, reacts with both urea and its *N*-methyl derivative to form the appropriate tetrahydro-2-oxypyrimidine (30, R = H or Me).⁶⁶¹³ Assuming that the NHMe group is the more nucleophilic end of the *N*-methylurea molecule, structure (30) fits in with a reaction scheme involving Michael addition to the ethylenic double bond; ¹H nmr evidence suggests that (30, R = H) tautomerizes in solution with (31, R = H).



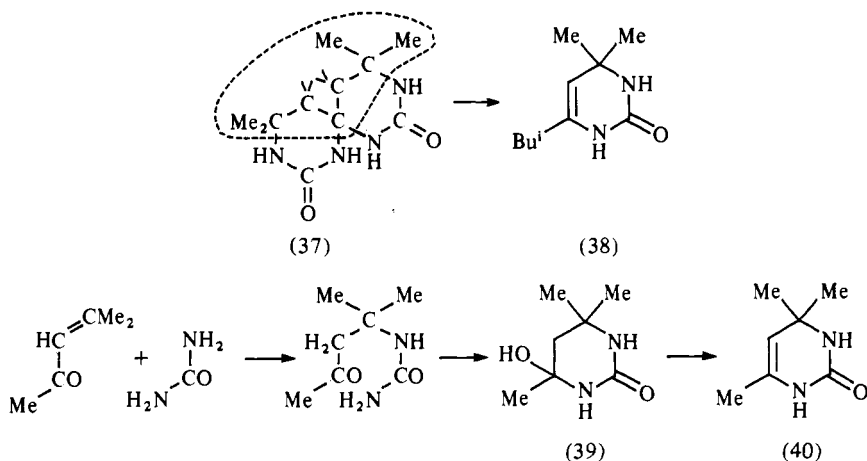
Similar results were obtained from the reaction of 1-phenylbut-2-en-1-one with urea (30, R = H, bottom Ph = H)⁶⁶¹⁴ or with thiourea, but the completely aliphatic but-3-en-2-one afforded only a fused bicyclic molecule with both urea and its *N*-methyl derivative.⁶⁶¹⁵ The ethylidene derivative of acetylacetone behaves as an ethylenic ketone in this condensation (and not as a β -diketone) to give the product (32).⁶⁶¹⁶

Various completely aliphatic α,β -unsaturated ketones incorporating one or more cyclohexane moieties also react with urea, guanidine, or ammonium thiocyanate, the last acting as a precursor to thiourea.^{6655, 6690} In most cases, these reactions lead to di- or tricyclic compounds in which a cycloalkane or cycloalkene ring is fused on to a pyrimidine ring in a reduced state that is sometimes below the dihydro stage. Thus, 2-cyclohexylidenecyclohexanone affords such a compound (33) with guanidine whereas the cyclohexylideneacetone molecule gives the spiro compound (34) at the correct level of reduction.



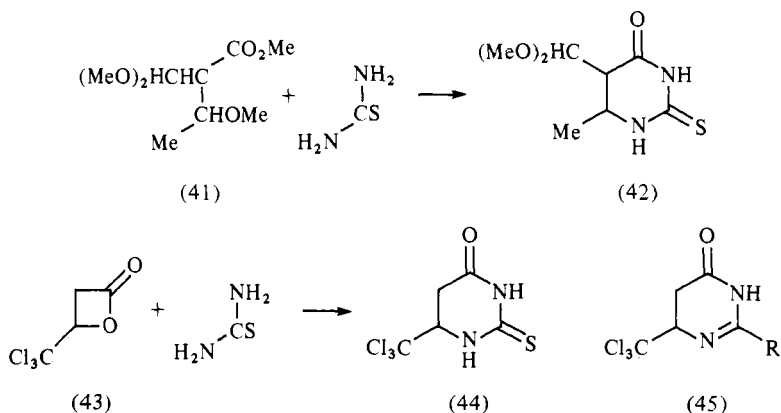
An interesting substituted-urea in these reactions with α,β -unsaturated carbonyl compounds is *N*-benzyloxyurea (35). With α,β -unsaturated carboxamides under alkaline conditions it forms 1-benzyloxy-5,6-dihydrouracils (36, R = H, Me, Ph). The aralkoxy substituent renders the NH proton in the urea molecule (35) more acidic than the NH_2 protons. Therefore the anion is formed preferentially by loss of the proton at this point and subsequently adds to the β -carbon atom of the α,β -unsaturated system.⁵⁹¹²

The fascinating series of reactions between urea and acetone (or its condensation products, mesityl oxide and phorone), causes an overlap between di- and tetrahydropyrimidine chemistry. The spiran (37) is produced from acetone and urea mixtures, catalyzed either by hydrogen chloride at 40° or sulfuric acid at slightly higher temperatures (50°). An initial self-condensation between three molecules of acetone seems to be involved since phorone and urea at higher temperatures (132°) give one and the same spiro compound in which the phorone carbon skeleton is outlined by the dotted area in formula (37).⁵¹⁷² The spiro compound suffers a rhodium-catalyzed hydrogenolysis under acidic conditions (phosphoric acid) with hydrogen at high temperatures and pressures to give the monocyclic dihydropyrimidine derivative (38). 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 (39) and dehydration to the final product (40).⁵¹⁷²



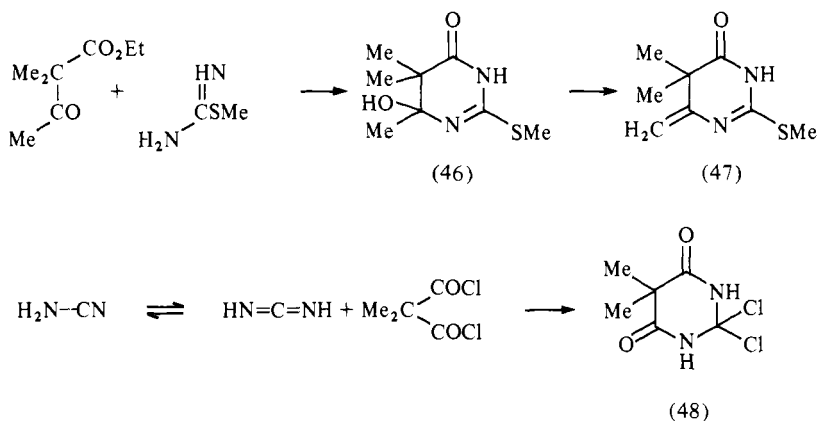
The reaction between thiourea and the methoxy acetal ester (41) can give up to four products containing a pyrimidine ring. The dihydropyrimidine (42) is one of the four produced by a reaction in which the ester has functioned as a concealed β -keto ester (*H* 48) rather than as a masked β -aldehyde ester (*H* 38).⁵⁴²⁸

The three carbon atoms in the strained ring of the oxetanone or β -propiolactone derivative (43) form the C—C—C backbone of the dihydropyrimidine compound (44), which is formed by ring expansion upon fusion with thiourea.^{6668, 6669} Analogous products (45, R = aryl) arise from similar condensations with benzamides and also with the complex *p*-aminobenzenesulfonylguanidine to give the product (45, R = *p*-H₂NC₆H₄SO₂NH).⁶⁶⁷⁰



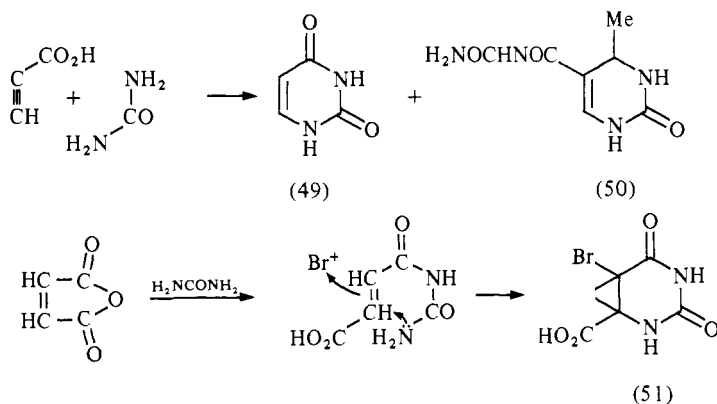
The reaction between *S*-methylthiourea and the non-enolizable dimethyl derivative of ethyl acetoacetate leads to an unusual hydroxylated dihydropyrimidine (46), the subsequent dehydration of which involves the *C*-methyl substituent and not the ring NH group to afford (47). The 2-*S*-ethyl and 2-*O*-methyl analogues of (46) were also prepared using the appropriate substituted thiourea or urea.⁵²⁸⁰

An unusual molecule to furnish the N—C—N region of a pyrimidine ring is the tautomer of cyanamide, which gives a chlorinated 2,5-dihydropyrimidine derivative (48) upon reaction with dimethylmalonyl chloride.⁶⁶⁷¹

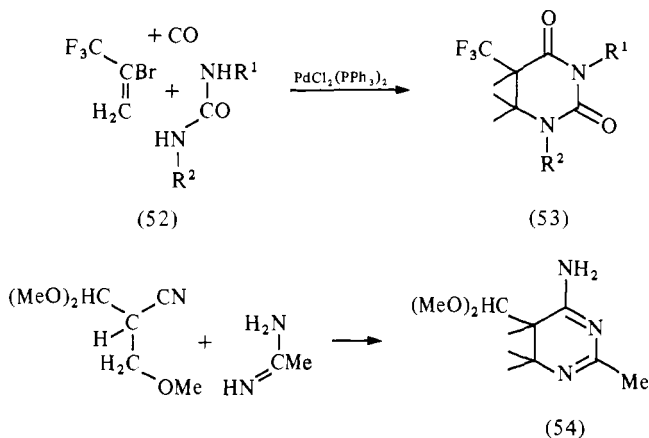


Other reactions that may be classified loosely as modified Principal Syntheses are so designated because one of the reagents furnishes either the C—C—C backbone of the pyrimidine molecule or the N—C—N fragment to make up the rest of the ring. Thus, the acid-catalyzed reaction of urea and propiolic acid, using benzene to remove the water liberated as an azeotrope, provides uracil (49) in *c.* 30% yield by a normal Principal

Synthesis. However, in this case the uracil is accompanied by a ureido dihydropyrimidine derivative (50), probably resulting from an initial dimerization of the acid prior to its condensation with urea.⁶⁶¹⁷ Maleic anhydride reacts with urea, probably to form a ureide, which upon bromination also undergoes simultaneous cyclization with the formation of 5-bromo-5,6-dihydro-orotic acid (51). Perhaps electronic assistance is rendered to the π -electron cloud of the ethylenic double bond in capturing the electrophilic bromine cation by nucleophilic attack by the end amino group of the ureide; this process will involve formation of the six-membered ring.^{6676, 6677}

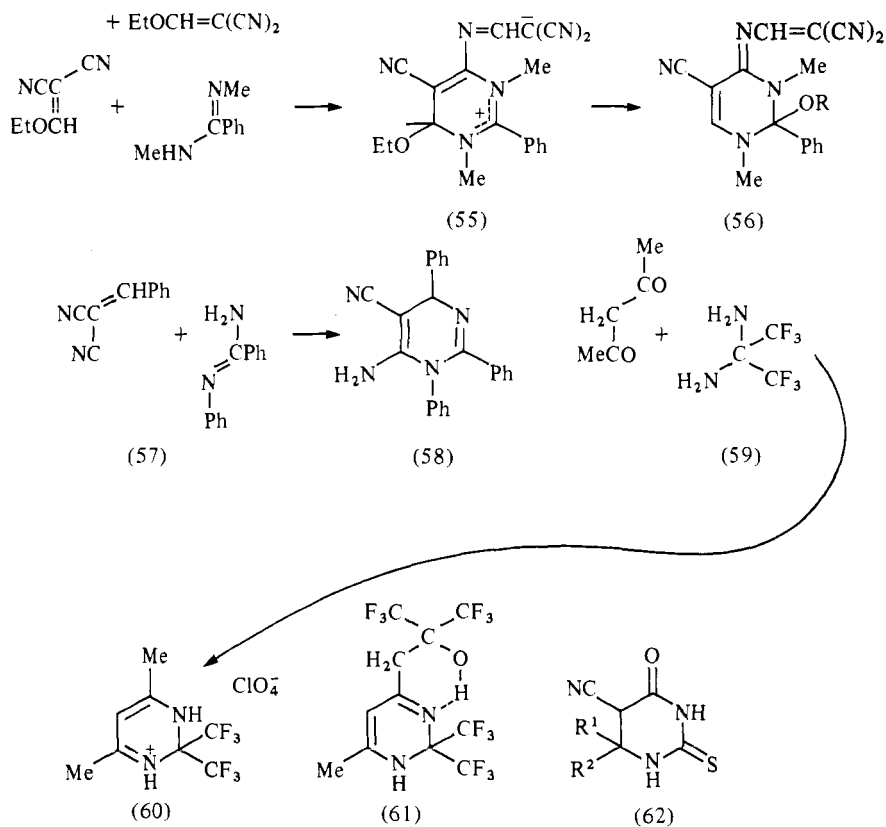


A novel reaction of urea (and its *N*-methyl and *N,N'*-dimethyl derivatives) is its use together with carbon monoxide under pressure in the ureidocarbonylation of the fluorinated alkene (52) which is catalyzed by a palladium complex. This one-pot reaction affords 5,6-dihydro-5-trifluoromethyluracils (53, $\text{R}^1 = \text{H}$ or Me , $\text{R}^2 = \text{H}$ or Me) in good yields.⁶⁵¹⁶



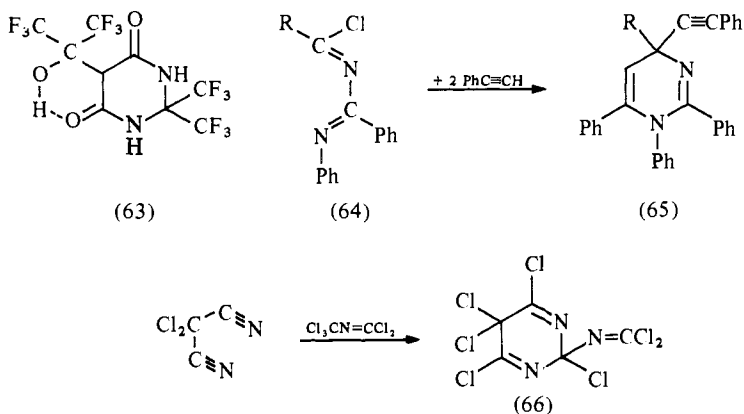
The reaction of acetamidine with 3,3-dimethoxy-2-(methoxymethyl)propionitrile, acting as a β -cyanoether and not as a concealed β -aldehydonitrile (*H* 59), gave the 5,6(4,5)-dihydropyrimidine (54), which is a key intermediate in the production of the vitamin, thiamine.⁶⁶¹⁸ In another amidine example, one mole of *N,N'*-dimethylbenzamidine formed a zwitterionic adduct (55) which could be rearranged in boiling methanol or ethanol to give the corresponding 2-alkoxy-1,2-dihydropyrimidines (56, R = Me or Et).⁶⁶¹⁹

Another type of molecule which can partner an amidine in a dihydropyrimidine cyclization reaction is the benzyldenemalononitrile (57). This reacts with *N*-phenylbenzamidine in tetrahydrofuran held at low temperatures to give the product (58).⁴³⁶⁶ An unusual N—C—N component used to complete the pyrimidine ring with acetylacetone is the geminal diamine molecule (59) in which the perfluoroalkyl groups must help to stabilize the molecule. These condense under acidic conditions (perchloric acid in tetrahydrofuran) to give the salt of the dihydro compound (60) which as a vinylogous amidinium system



possesses resonance stability.⁶⁶⁷² The demethylated compound arises from the replacement of acetylacetone by a protected malondialdehyde derivative.⁶⁶⁷² Accompanying (60) in the above reaction is a covalent uncharged product (61), in which one of the methyl groups has been sufficiently activated to condense with hexafluoroacetone produced *in situ* by simultaneous hydrolysis of the geminal diamine.⁶⁶⁷²

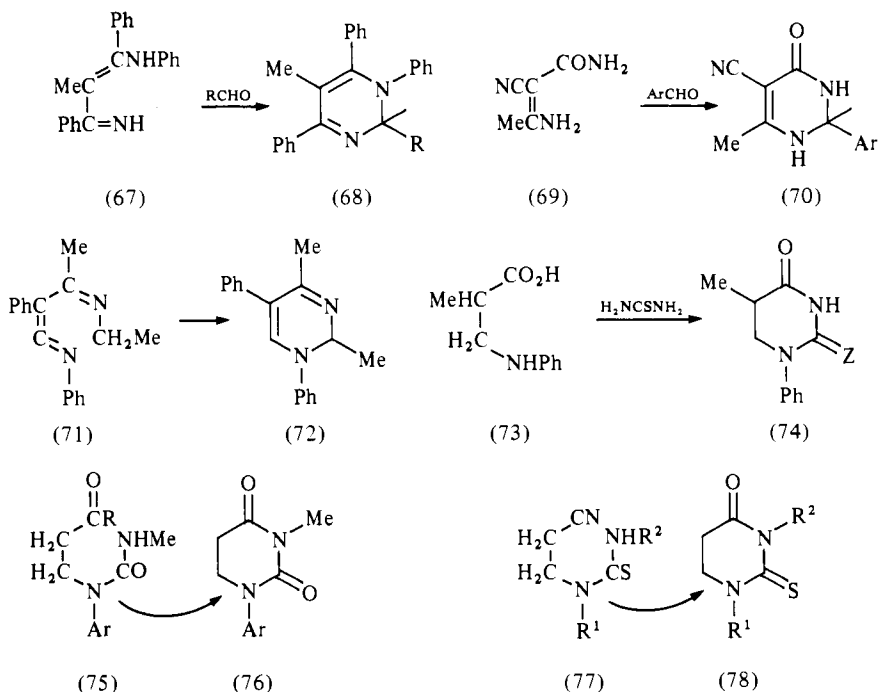
A mixture of ethyl cyanoacetate, acetone, and thiourea condenses readily under alkaline conditions to afford the hydropyrimidine (62, $R^1 = R^2 = \text{Me}$). The use of 3,4-dimethoxybenzaldehyde in place of acetone also gives a dihydro derivative (62, $R^1 = 3,4\text{-dimethoxyphenyl}$, $R^2 = \text{H}$), whereas a selection of other aromatic aldehydes and some aliphatic aldehydes gave aromatized products resulting from dehydrogenation of (62) *in situ*, as mentioned earlier in connexion with the reaction of thiourea with α,β -unsaturated carbonyl derivatives. This lends credence to a mechanism that involves an initial condensation between the carbonyl compound and the activated methylene group situated between the two electron-withdrawing groups of the ester to form an intermediate with an olefinic double bond, in turn activated twice over by the two electron-withdrawing groups.⁶⁶⁷³ Russian workers found⁶⁵⁸⁸ that hexafluoroacetone reacted with cyanoacetamide in the absence of thiourea to give a dihydropyrimidine derivative (63), in the stabilization of which, hydrogen bonding may play a part.



A curious reaction in which the pyrimidine ring, at the correct level of oxidation (reduction), is completed by an acetylenic compound is illustrated by the condensation of an *N,N'*-disubstituted benzamidine (63, $R = \text{morpholino}$) in quick succession with two molecules of phenylacetylene (as its lithium salt) to give the 1,4-dihydro compound (65).⁶⁶⁷⁴ Another equally curious reaction involves dichloromalon-

nitrile, which already possesses all but the C2-atom of a pyrimidine ring; the missing carbon can be provided by reaction with trichloromethyl isocyanide dichloride to give the highly chlorinated 2,5-dihydropyrimidine (66).⁶⁶⁷⁵

Another example illustrating the completion of a dihydropyrimidine ring by insertion of the missing C2 atom is given by the aluminum chloride catalyzed reaction of the amino-imine (67) (which can be regarded as a derivative of a β -dicarbonyl compound) with aldehydes to give the dihydropyrimidines (68); the aldehyde molecule can be replaced by derivatives like its Schiff base or acetal, while ketones react only in the form of their ketals.^{6564, 6678} Aromatic aldehydes can also be used to complete the six-membered ring starting with enaminoamides such as (69) to give (70).⁶⁶²²

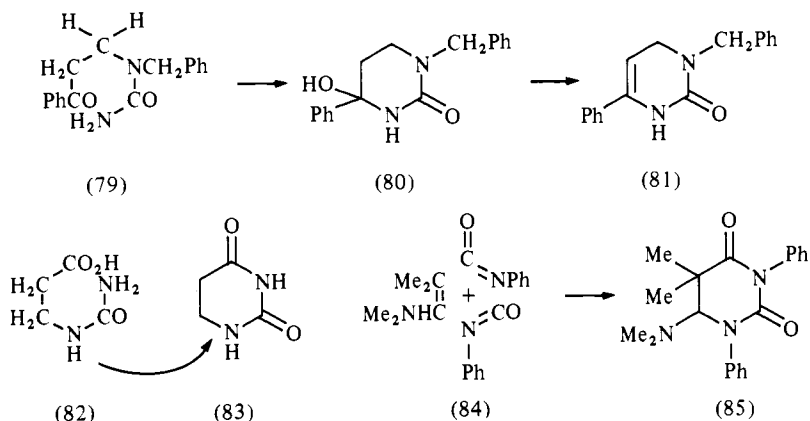


A logical extrapolation is the use of an aliphatic precursor that contains all the requisite atoms to form the six-membered dihydropyrimidine ring. Thus, the imidoalkyl ketene (71), amongst other members of this class of compounds, rearranges readily at ambient temperature through a 1,5-H shift to give (72).⁶⁵⁸⁰

B. From an Aminopropane Derivative and an Isocyanate (*H* 434, *E* 324)

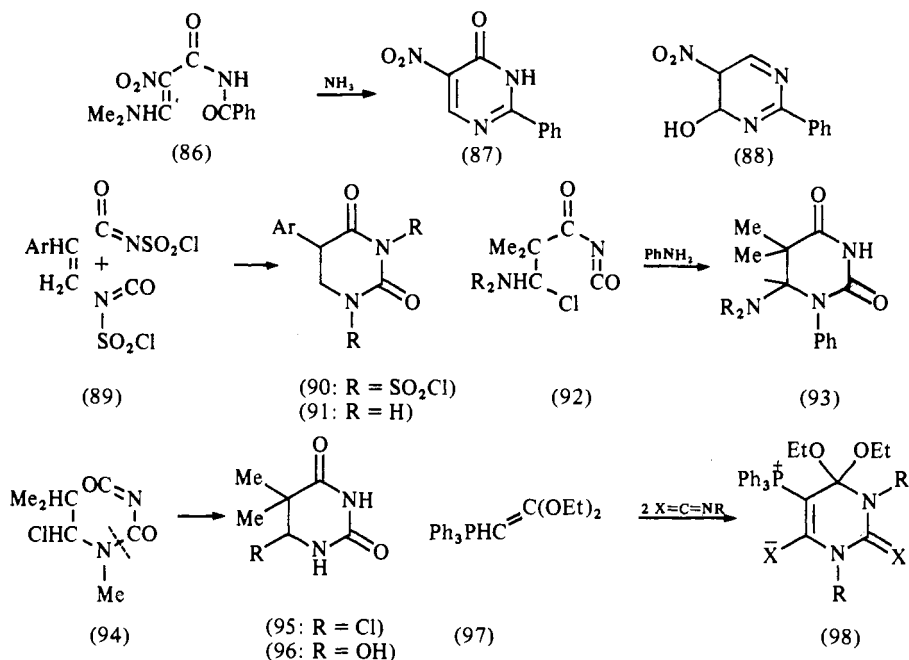
Aniline adds to the activated olefinic double bond of acrylic acids to form a β -arylaminoacrylic acid (73), which can be cyclized with urea or various metal isocyanates to form the dihydrouracil derivatives (74, $Z = O$ or S).^{6563, 6679} Presumably an intermediate ureidopropionic acid is formed since cyclodehydration of these preformed substances (75, $R = OH$) in acidic media to afford the corresponding dihydrouracils (76) is the subject of a recent Japanese patent.⁶⁶⁸⁰ Likewise, the thio-analogue of (75, $R = NH_2$) is the cyclizable precursor during the conversion of the cyanoethylated thiourea (77) into a 5,6-dihydro-2-thiouracil (78).⁴⁵⁴³

The Mannich product from acetophenone, formaldehyde, and benzylamine (or other primary amines) reacts with potassium cyanate to give the β -ureidopropiophenone (79). This readily cyclizes at room temperature to a cyclic *O,N*-acetal, the tetrahydropyrimidine (80), which can be easily dehydrated thermally or by a trace of acid, to give the dihydropyrimidine (81).⁶⁶⁸¹ β -Ureidopropionic acid (82), formed from β -alanine and urea, was observed to cyclize under mild conditions,⁶⁶⁸² especially in the presence of a clay mineral montmorillonite,^{6683, 6684} to give 5,6-dihydrouracil (83). It is under current investigation as a plausible prebiotic synthetic pathway to biologically occurring pyrimidines.



Organic isocyanates are also capable of closing the dihydropyrimidine ring with starting molecules other than those containing a $C-C-CO$ or $C-C-C-N$ unit. In particular, two moles of phenyl isocyanate (84) react with one mole of an enamine in a process of cycloaddition to give the dihydrouracil (85).⁶⁶⁸⁵ In addition, benzoyl isocyanate was used in

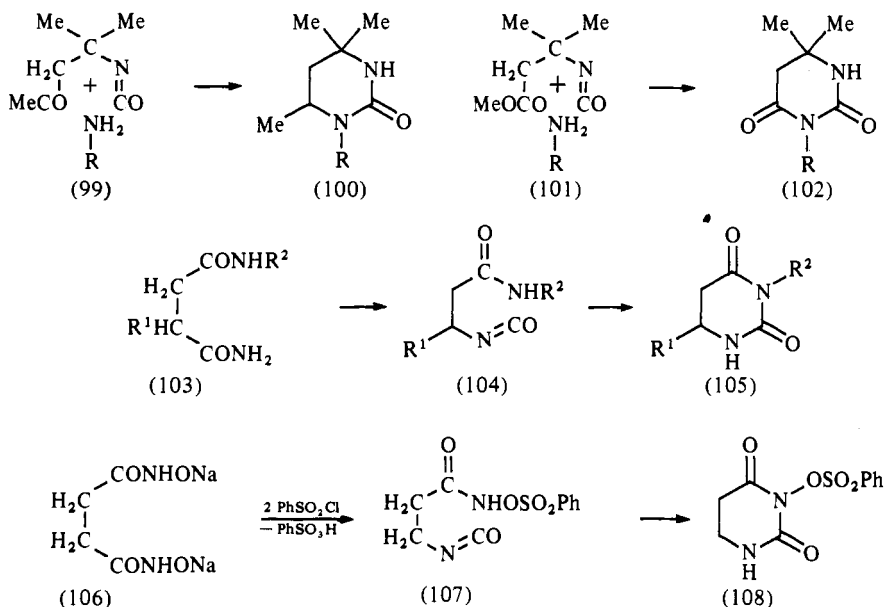
place of phenyl isocyanate.³⁵⁴⁶ If a substituent on the β -carbon atom of the enamine is electron-withdrawing, it is possible to isolate an intermediate. Thus, 1-dimethylamino-2-nitroethylene undergoes conjugate addition with benzoyl isocyanate to give the open-chain compound (86),²³²² subsequently cyclized by ammonia to the aromatized compound (87) perhaps through the dihydro species (88). Other cycloaddition reactions involve chlorosulfonyl isocyanate (89), two moles of which react with the side-chain double bond of one molecule of an *ortho*-dialkylaminostyrene to give an *N,N'*-disubstituted dihydrouracil (90), which loses its chlorosulfonyl substituents upon mild hydrolysis to give the final product (91).⁶⁶⁸⁷ One of the activated olefinic double bonds of phorone also reacts with two moles of chlorosulfonyl isocyanate to afford a dihydrouracil.⁶⁶⁸⁹ Chloroformyl isocyanate reacted with an enamine at low temperatures to give the acyclic intermediate (92) which could be isolated and treated with aniline to give the dihydrouracil (93, NR_2 = morpholino or piperidino).⁶⁶⁸⁸ Chloroformyl isocyanate also adds to the double bond of Schiff bases. The first isolable product, for example (94), rapidly cyclizes upon gentle heating to form the dihydropyrimidine (95) in which the chlorine atom undergoes ready replacement by nucleophiles to give, for example, the product (96).^{6691, 6692} Another substrate containing an activated double bond which can take part in a mixed cyclotrimerization with two moles of



an isocyanate (or isothiocyanate) is 2,2-diethoxyvinylidene triphenylphosphorane (97). With the methyl or phenyl reagents, the zwitterionic dihydropyrimidine derivatives (98: X = O or S; R = Me or Ph) are produced.⁶⁵⁶⁵

C. From an Isocyanatopropane Derivative and an Amine (*H* 436, *E* 325)

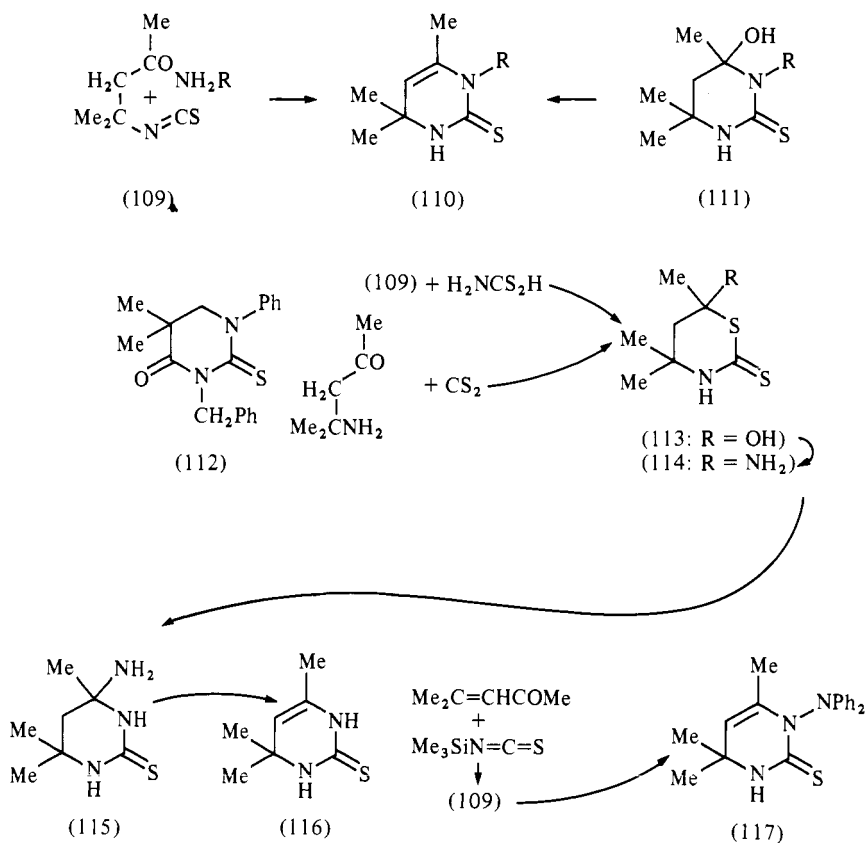
Unlike its well-known sulfur counterpart, it is only recently that 4-isocyanato-4-methylpentan-2-one (99) has been obtained and shown to react with simple primary amines like methylamine or aniline to give the dihydropyrimidine (100, R = Me or Ph).⁶⁶⁰⁶ With an ester analogue (101), a complex heterocyclic primary amine has been used to give the serotonin antagonist [102, R = (CH₂)₃N(CH₂CH₂)₂NPh].⁶⁶⁵⁹ Although it contained a primary amino group, methylhydrazine did not give a 1-methylamino derivative of the dihydropyrimidine but instead caused ring expansion with the formation of a triazepine.⁶⁶⁰⁶



The intramolecular equivalent to the attack of an isocyanatopropane derivative by a separate primary amine probably occurs during the lead tetra-acetate oxidation of succinamides to dihydrouracil.^{5254, 6590} One primary amide group in (103), in preference to any secondary amide group that may be present,⁵²⁵⁴ is transformed into an isocyanato group in (104),⁶⁶⁹³ which then undergoes intramolecular attack from

the other end of the molecule to give (105: $R^1 = H$ or Me; $R^2 = H$ or Me). Another example of intramolecular cyclization probably occurs in the Lossen rearrangement^{6694, 6695} of the disodium salt of succinic acid bishydroxamate (106). Thus, treatment of (106) with benzenesulfonyl chloride probably afforded a monoisocyanato intermediate (107), which cyclized to the 3-benzenesulfonyloxy derivative of 5,6-dihydro-uracil (108).

As mentioned indirectly earlier, the reaction of 4-isothiocyanato-4-methylpentan-2-one (109)^{1509, 1510} and other β -isothiocyanato ketones^{6596, 6663} with ammonia⁶⁶⁴³ or primary amines⁶⁶⁴³ has gradually become the basis of a general method for the synthesis of dihydropyrimidine-2(1*H*)-thiones (110). Sometimes an intermediate carbinol-amine of the type (111) was also isolated and had to be dehydrated thermally to give the dihydropyrimidine.^{6596, 6663} Examples of (110) are now known on spectroscopic evidence to exist predominantly as the thione tautomer (110).^{6581, 6627, 6643} The amine group of ethyl β -amino-



crotonate, or the anilino group of the corresponding β -anilino ester, reacts with (109) to give a complex which on hydrolysis affords (110, R = H or Ph), so that in effect the ester provides only the second nitrogen atom of the hydroxypyrimidine ring along with the atom or group attached to it.⁶⁶⁹⁹ The isothiocyanato compounds result from the reaction of ammonium thiocyanate with α,β -unsaturated ketones,⁶⁶⁹⁶ and the cyclization reaction with primary amines proceeds through N,N' -disubstituted thioureas which are sometimes isolated and independently cyclized.⁶⁶⁹⁶ A related synthesis employs the reaction of N,N' -disubstituted thioureas with β -haloacyl halides in alkaline biphasic solution to give reduced 4-oxo-2-thiopyrimidines such as (112).⁶⁷⁰⁰

4-Isothiocyanato-4-methylpentan-2-one (109) reacts with dithiocarbamic acid to give the 1,3-thiazine (113).⁶⁶⁴⁹ The same compound is formed during the reaction of acetone with carbon disulfide in the presence of ammonia, *via* diacetoneamine. The hydroxy group of the thiazine (113) is replaced by the amino group on further reaction with ammonia, and the product (114) rearranges to (115), which loses ammonia to afford the dihydropyrimidine (116), identical with that from thiourea and mesityl oxide.

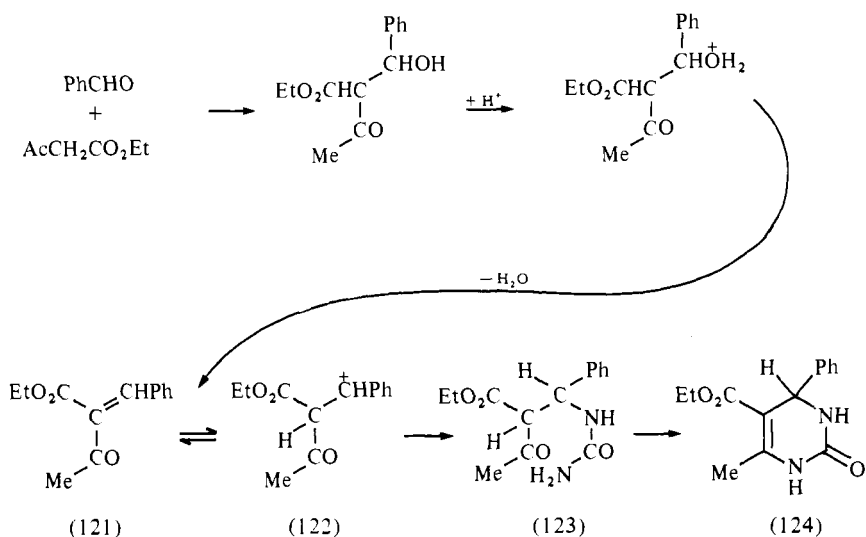
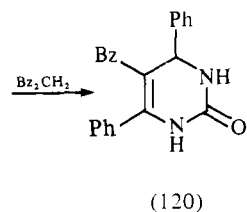
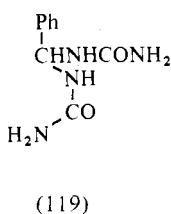
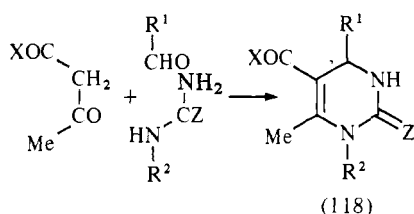
An unusual organometallic isothiocyanate, the trimethylsilyl congener, has attracted attention for use in a so-called many-component reaction. Thus, it reacts with N,N -diphenylhydrazine in an excess of acetone to give hexamethyldisiloxane and the dihydropyrimidine (117) in which the outlines of mesityl oxide can be detected.⁶⁶⁹⁷ The same product results if mesityl oxide is used instead of acetone,⁶⁶⁹⁸ and mesityl oxide has been shown independently to react with trimethylsilyl isocyanate in the presence of a little water to give the β -isothiocyanato ketone (109).⁶⁵⁶⁷ The same isothiocyanate has also been first allowed to react with primary amines to form alkylammonium thiocyanates. These salts convert ketones into ketiminium thiocyanates, $(R^1NH=CR^2R^3)^+SCN^-$, which can react with the same or another ketone to yield the 3,4-dihydropyrimidine-2-thione; thus, aniline, acetone, and the isothiocyanate gave the final product (110, R = Ph).⁶⁵⁶⁷

E. Syntheses Involving Amide Intermediates (H 438)

Intramolecular cyclizations of β -isocyanatopropionamides, suspected of being formed as intermediates from lead tetra-acetate oxidations of succinamides, were incorporated under Sect. C above because this reaction seemed to be a logical extension of the intermolecular reaction between the two functional groups discussed there.

F. The Biginelli Reaction (*H* 440, *E* 326)

The original condensation of ethyl acetoacetate with urea and an aldehyde to give dihydro compounds (118, $X = \text{OEt}$, $Z = \text{O}$) has been extended widely to include variations in all three components. Thus, the aldehyde component now includes both aliphatic and aromatic aldehydes,^{6574, 6701} α,β -unsaturated aldehydes,^{6569, 6574} a protected carbohydrate like the cyclic 3,4-di-*O*-benzoyl-2,5-anhydroaldehyd-ribose,⁶⁶²⁴ and acyclic derivatives like 1,2:3,4-di-*O*-isopropylidene-D-arabinotetrahydroxybutyl.⁶⁶⁰⁴ Primary, secondary, and tertiary amide derivatives^{6559, 6573, 6595, 6598} have been used in place of the ester to produce (118: $R^2 = \text{H}$; $X = \text{NH}_2$, NHR , or NR_2 ; $Z = \text{O}$), while substituted ureas and thioureas can replace the urea component.^{6559, 6595}

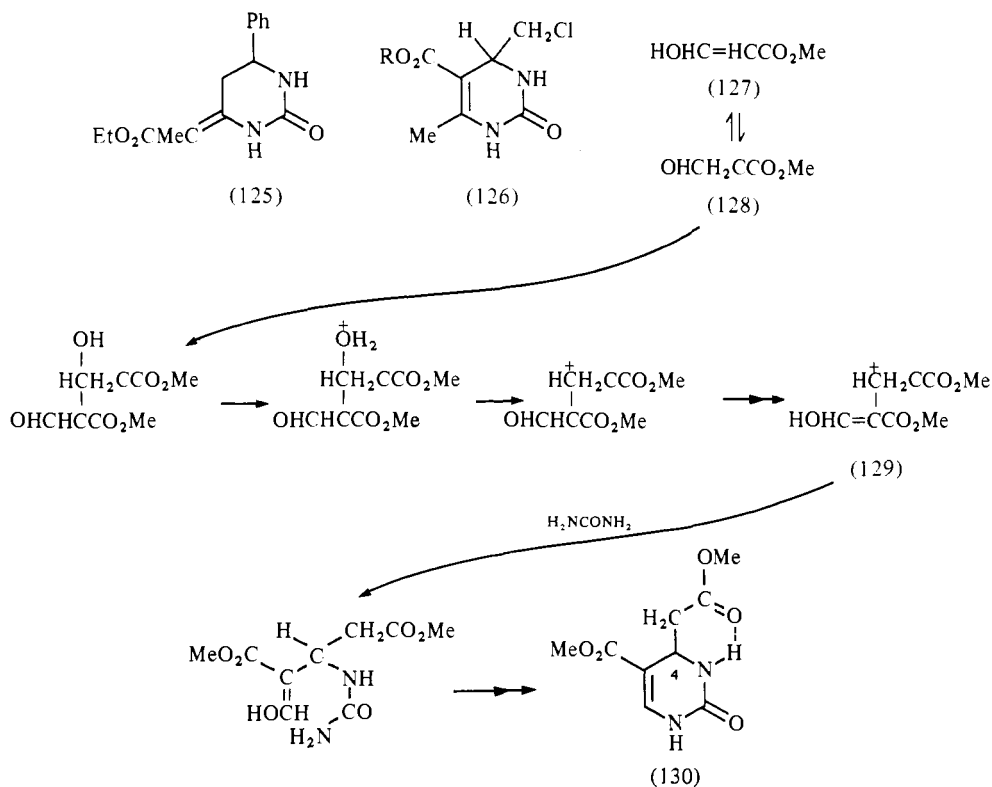


Although doubt has been cast upon whether α,α -bisureidotoluene (119) is a key intermediate in the Biginelli reaction,⁵⁴³⁰ it can be used to form Biginelli-type products (120) with β -diketones like dibenzoylmethane⁶⁵⁸⁹ as well as with phenylacetone and the unsaturated ketone 1,4-diphenylbut-3-en-2-one.⁵⁹⁸⁴ Recent work suggests that an aldol

condensation precedes the reactions with urea. Thus, the *cis-trans* mixture of ethyl benzylideneacetoacetate (121), obtained independently from a piperidine-catalyzed condensation of benzaldehyde and ethyl acetoacetate, reacted with *N*-methylurea in an acid-catalyzed reaction to give the same product (118, $R^1 = \text{Ph}$, $R^2 = \text{H}$, $X = \text{OEt}$) as was obtained from the three-component Biginelli reaction.⁵⁴³⁰ Interception of the carbocation (122) by the urea molecule affords an intermediate (123) ready for cyclization to a dihydropyrimidinone (124).

Such a mechanism explains why an alkyl group on C2 of the β -ketoester not only hinders aldol condensation at that site but deflects it in another direction, that is, to the unhindered unsubstituted terminal methyl group of the molecule. Thus, ethyl 2-methylacetoacetate gives (125) with benzaldehyde and urea. However, it should be noted that in this mechanism *N*-methylurea reacts exclusively *via* the NH_2 end of the molecule, that is, at the less nucleophilic site.

An unusual substitute for an aldehyde in the orthodox Biginelli reaction with urea and ethyl acetoacetate has been α,β -dichloroethyl ether, which affords the 4-chloromethyl derivative (126).⁶⁵⁶⁰ The

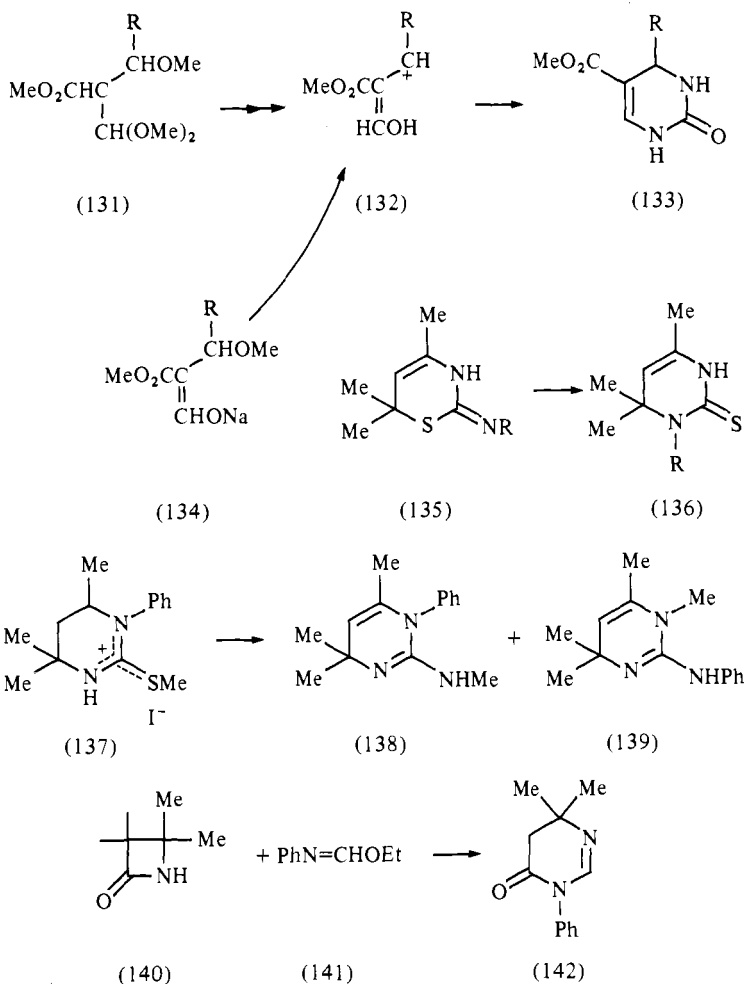


same compound results from the condensation of the same ether with 2-ureidocrotonic esters,⁶⁵⁶⁶ in the Folkers/Johnson modification of this reaction.¹⁵³⁴

G. Other Syntheses (*H* 442, *E* 326)

A synthesis which overlaps with the Principal Synthetic method and also has cross-links with the Biginelli reaction on mechanistic grounds, consists of the reaction of urea or its *N*-monoalkyl derivatives with certain polyfunctional substrates. These molecules, although free or protected β -dialdehydes (*H* 32, *E* 20) or β -aldehyde esters (*H* 38, *E* 25), do not behave as such in a Principal Synthesis. Thus, methyl 3-methoxyacrylate does not react in a direct way with urea in acidic media. It first hydrolyzes to give the corresponding hydroxyacrylate (127), which is the tautomer of the β -aldehyde ester (128). Two molecules of the latter undergo an aldol condensation: the protonated product in turn loses water to produce a secondary carbocation which in its enolic form (129) has allylic type stability. This is now intercepted by the urea molecule to form a ureide which cyclizes with dehydration to afford a 3,4-dihydropyrimidin-2-one (130).⁵⁴³⁰ This product (130) is accompanied by the monocarboxylic acid (130, $\text{CH}_2\text{CO}_2\text{H}$ at the 4-position) as well as the decarboxylated material (130, Me at the 4-position). It is believed that the above hydrolysis at C4 is facilitated under the acidic conditions of the preparation by participation of an NH group as indicated in formula (130). Interception of similar allylic carbocations has been used to explain the reaction of urea with the acetal derivatives of the β -aldehyde esters or β,β' -dialdehyde ester to form similar dihydropyrimidine compounds, according to the sequence $(131 \rightarrow 132 \rightarrow 133, \text{R} = \text{H or Me})$.⁵⁴²⁸ A similar reaction route is easily envisaged for the conversion of the sodio enolate of methyl 2-formyl-3-methoxypropionate (134, $\text{R} = \text{H}$) by urea into the intermediate (132, $\text{R} = \text{H}$) and the product (133, $\text{R} = \text{H}$).

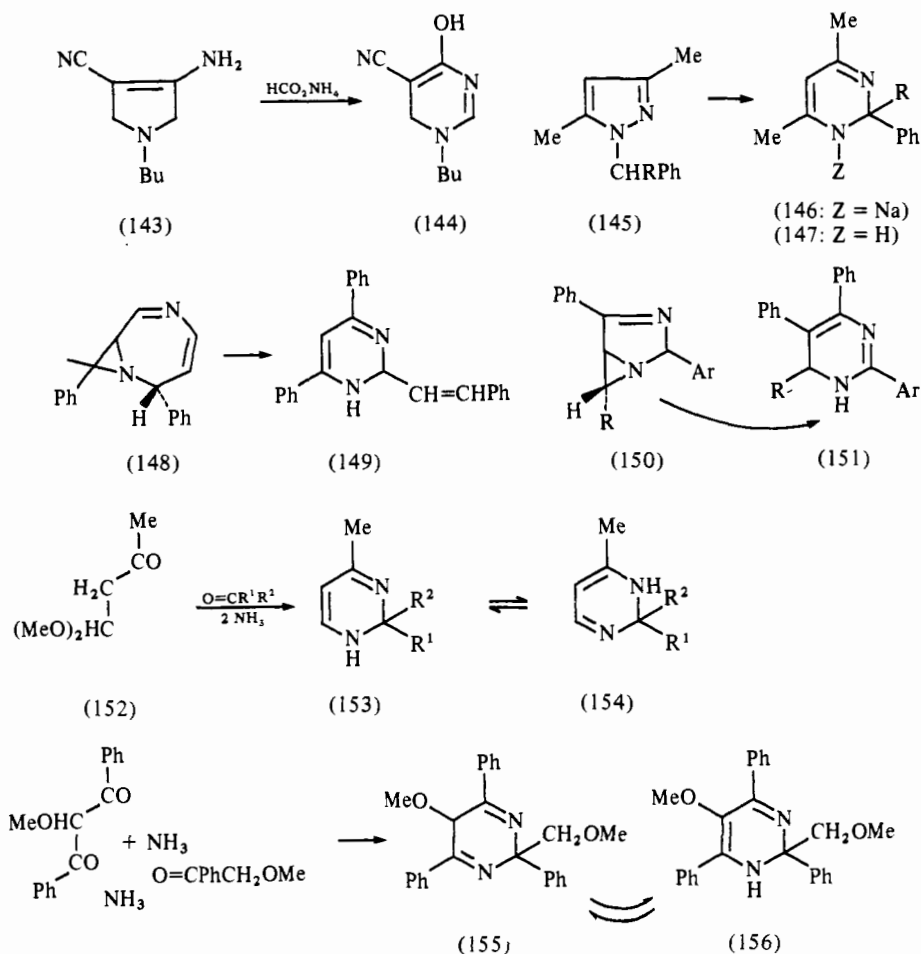
There are several recent examples of the conversion of other heterocyclic systems into dihydropyrimidines. The rearrangement of 1,3-thiazines into dihydropyrimidines in refluxing formic acid has already been noted (*E* 327). Other examples of how the chemistry of reduced pyrimidines and 1,3-thiazines intertwine are furnished by the conversion of (114) into (115), mentioned previously,⁶⁶⁴⁹ and the Dimroth-like rearrangement of the 2-imino-1,3-thiazine system (135, $\text{R} = \text{H, Me, or Ph}$) to the isomeric dihydropyrimidines (136, $\text{R} = \text{H, Me, or Ph}$). Again, the carbon skeletal outline of mesityl oxide can be



detected in these molecules.⁶⁶⁶⁵ Dimroth rearrangement also plays its part in the interconversion of substituents on the dihydropyrimidine ring; methylamine with the dihydropyrimidinium salt (137) gives both the 2-methylamino analogue (138) and the rearranged molecule (139).⁶²⁶⁰

In the period under review, heteromonocyclic compounds with ring sizes below six-membered have also served as starting materials for the synthesis of reduced pyrimidines. Typical examples have ranged from the conversion of the four-membered azetidin-2-ones, for example (140), by heating with an imidic ester (141) to give the product (142),⁶⁷⁰³ to the ring expansion of five-membered rings like the amino-pyrroline (143) to (144), which occurs in a Leukart reaction brought about by ammonium formate,⁶⁶²⁵ or the rearrangement of certain

N-substituted pyrazoles (145) to give (146) and thence (147, R = H), which is brought about by sodium amide at high temperatures.^{6654, 6704} It should also be mentioned here that the ring sulfur atom in iminothiazolines can be extruded with trialkylphosphines to give momentarily the imidoylketenes (71), which have already been recorded as rearranging to dihydropyrimidines (72).⁶⁵⁸⁰ Similarly, certain *N*-thiocarbamoyl-lactams are involved with the previously described formation of dihydropyrimidine (112) from thioureas and β -haloacyl halides.⁶⁷⁰⁵



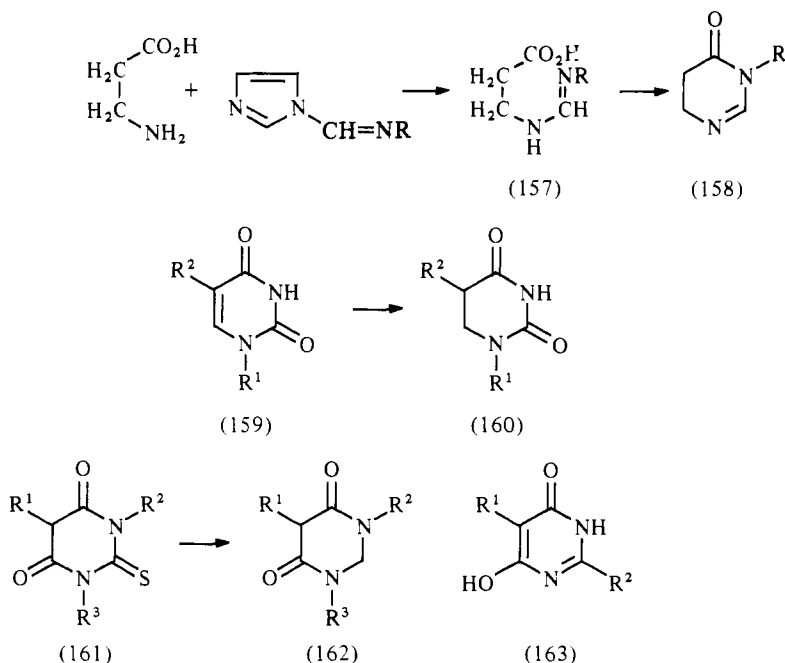
In other work, certain diazabicyclic systems have been observed to rearrange into dihydropyrimidines under basic conditions, as illustrated in the transformations (148 $\rightarrow$ 149)⁶⁷⁰⁶ and (150 $\rightarrow$ 151, Ar = *p*-NO₂C₆H₄, R = H or Ph).⁶⁶²⁶

The condensation involving reaction of a ketone, an oxoacetal, and ammonia in the presence of ammonium nitrate (*E* 326) has potential as a general method for making 1,2-dihydropyrimidines. Thus, the products from such a reaction of 4,4-dimethoxybutan-2-one with a series of aliphatic ketones (but only one aldehyde) were revealed by ^1H nmr spectroscopy as tautomeric mixtures typified by ($153 \rightleftharpoons 154$, $\text{R}^1 = \text{R}^2 = \text{Et}$).⁶⁵⁸⁷ The monoacetal of acetylacetone with diethyl ketone gave the symmetrical 2,2-diethyl-4,6-dimethyl analogue of ($153/154$).⁶⁶⁰⁰ However, extrapolation of this synthesis to aromatic entities was only partially successful because of the tendency of the dihydropyrimidines to undergo aromatization. Thus, α -methoxydibenzoylmethane, ω -methoxyacetophenone, and ammonium acetate in acetic acid afforded the tautomeric dihydropyrimidine ($155/156$),⁴⁴⁷⁷ which was stable in the protonated form; however, as free base it underwent elimination of the methoxymethyl substituent as dimethyl ether with concomitant aromatization to 5-methoxy-2,4,6-triphenylpyrimidine. Only the aromatized 2,4,6-triphenylpyrimidine could be isolated from the reaction mixture if an aromatic aldehyde like benzaldehyde was used in place of the acetophenone.⁴⁴⁷⁷

An interesting observation worthy of further exploration involves the initial use of 1-(*N*-alkyliminoformyl)imidazoles to replace one of the active hydrogen atoms in amino acids like β -alanine by an *N*-alkyliminoformyl group. Thus, the product (157) contains all the atoms required to constitute the pyrimidine ring, and heating with acetic anhydride completes cyclization to form the dihydropyrimidine (158 , $\text{R} = \text{Bu}^t$ or C_6H_{11}).⁶⁷⁰⁸

H. By Reduction of Pyrimidines (*H* 442, *E* 327)

Catalytic reduction, one of the 12 methods of reduction enumerated³⁵⁴⁹ previously (*E* 327), continued to be a convenient means of obtaining reduced pyrimidines. This applied especially to the 5,6-dihydro derivatives of the three biologically important pyrimidine bases (uracil, cytosine, and thymine), particularly when they were combined as the related nucleosides or nucleotides or in other naturally occurring molecules. Thus, 5,6-dihydrouracil has attracted attention recently because of its occurrence in some streptoviridins,⁶⁷¹⁰ 5,6-dihydro-uridine was the first natural reduced pyrimidine nucleoside to be discovered as an unusual component in transfer-RNA,⁶⁷¹¹ and its 5-methyl analogue is a minor constituent in the chromosomal RNA of a rat ascites tumor.⁶⁷¹²

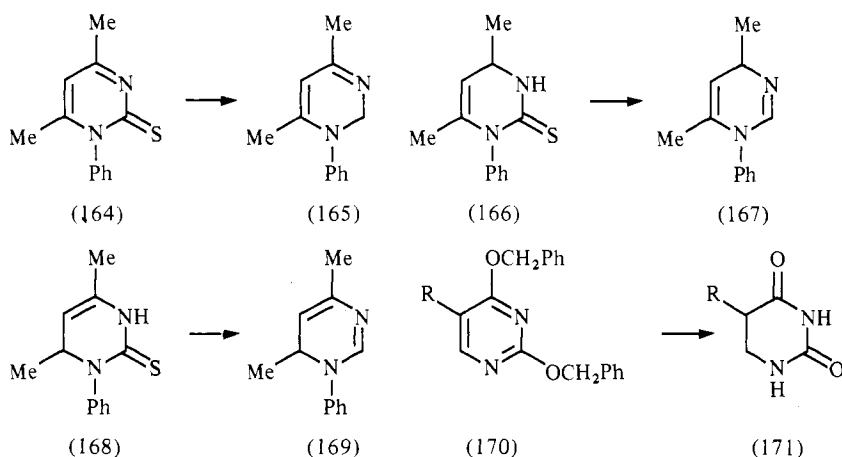


Rhodium-on-alumina was the catalyst of choice for hydrogenation of the 5,6-double bond of the uracil part in α - and β -uridine 3',5'-cyclic monophosphate, as indicated in the reaction (159 $\rightarrow$ 160, R^1 = sugar phosphate, R^2 = H)^{6713, 6714} and in the simpler 5-aminouracils (159 $\rightarrow$ 160; R^1 = H, R^2 = NH_2 or NMeCH_2Ph).⁶⁵⁷² With 1- β -D-ribofuranosyl-thymine, rhodium-on-alumina catalyzed hydrogenation generated diastereoisomers of the corresponding dihydropyrimidine derivative, as indicated by (159 $\rightarrow$ 160, R^1 = β -ribofuranosyl, R^2 = Me).⁶⁶⁴⁵ When the investigators switched to the 2',3'-*O,O*-isopropylidene derivative, nmr evidence indicated a 3:2 ratio in the mixture of diastereoisomers produced upon reduction in water. By contrast, hydrogenation in methanol with rhodium-on-charcoal catalyst afforded a 1:1 mixture of diastereoisomers which could be separated *via* their 5'-*O*-benzoyl derivatives.⁶⁶⁴⁶ Rhodium-on-charcoal was also a satisfactory catalyst for hydrogenation of the 5,6-double bond of the pyrimidine ring in the 2,3'-*O,O*-isopropylidene derivatives of both uridine⁶⁷¹⁵ and 2-*N*-methylated isocytidine,⁶⁶⁴⁴ as well as with 1- β -D-arabinofuranosyl-uracil.⁶⁷¹⁶

Raney nickel has been used widely for the removal of sulfur when it is part of the heterocyclic ring or of a substituent.⁶⁷¹⁷ In view of the pharmaceutical importance of barbiturates, it is not surprising to find

that Raney nickel has been used to smoothly dethiate and reduce the C2 thiocarbonyl part of various 2-thiobarbiturates to CH_2 thus giving the corresponding 1,2-dihydropyrimidine derivatives; for example, (161 $\rightarrow$ 162, $\text{R}^1 = \text{Bu}$, $\text{R}^2 = \text{R}^3 = \text{Ph}$; $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{R}^3 = \text{H}$; $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$; or $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{Me}$).^{3553, 6718} The same type of compound was obtained by catalytic hydrogenation under pressure of the 1,2-double bond in 5-substituted 4,6-dihydroxypyrimidines (163, $\text{R}^1 = \text{Et}$ or Ph , $\text{R}^2 = \text{H}$; or $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Et}$).⁶⁷¹⁹

Raney nickel has recently been used successfully with much simpler pyrimidine-2-thiones to obtain specific specimens of 1,2-, 1,4-, and 1,6-dihydropyrimidines of unequivocal structure. The first example involved reductive desulfurization, for example of (164), with Raney nickel and hydrogen to give (165), while the latter two involved dethiation (166 $\rightarrow$ 167, 168 $\rightarrow$ 169) with Raney nickel under methanol in the absence of hydrogen gas.^{6545, 6594}

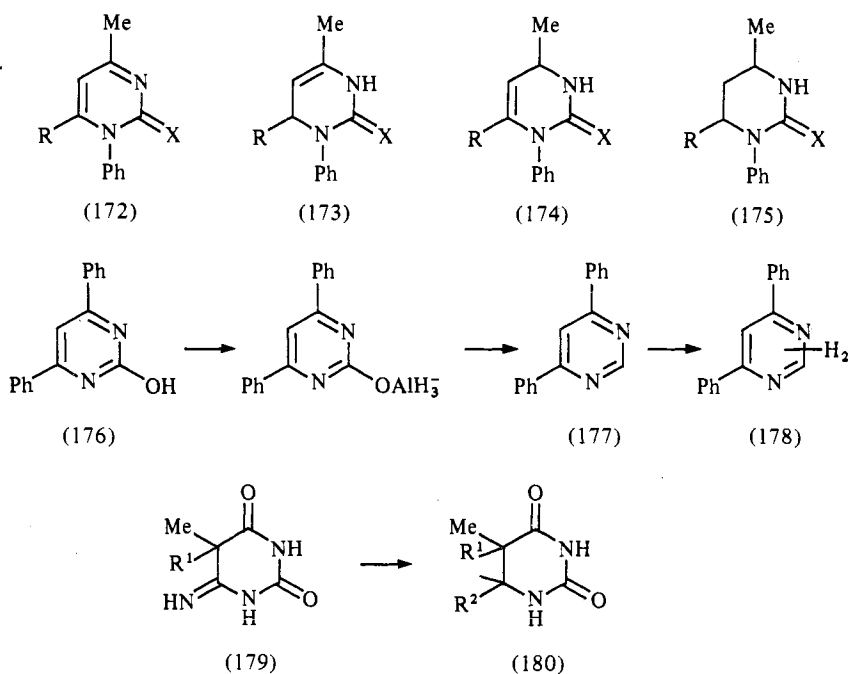


An example of the use of a different Group VIII metal catalyst is the palladium-on-charcoal catalyzed hydrogenolysis of the *O,O*-dibenzylated ether (170, $\text{R} = \text{Me}_3\text{Si}$). This probably involves initial hydrogenolytic deprotection by removal of the benzyl groups, followed by addition of hydrogen to the 5,6-bond to give the reduced 5-trimethylsilyluracil (171, $\text{R} = \text{Me}_3\text{Si}$).⁶⁷²⁰

Complex metal hydrides, which act as a source of hydride ions, comprise another large group of reducing agents. Their use in pyrimidine chemistry seems unduly concentrated on the hydroxy/oxo derivatives and their sulfur analogues, particularly those of biological or medical importance. When the 4,6-dimethyl-1-phenylpyrimidinone (172, $\text{R} = \text{Me}$, $\text{X} = \text{O}$) was treated with sodium borohydride in methanol,

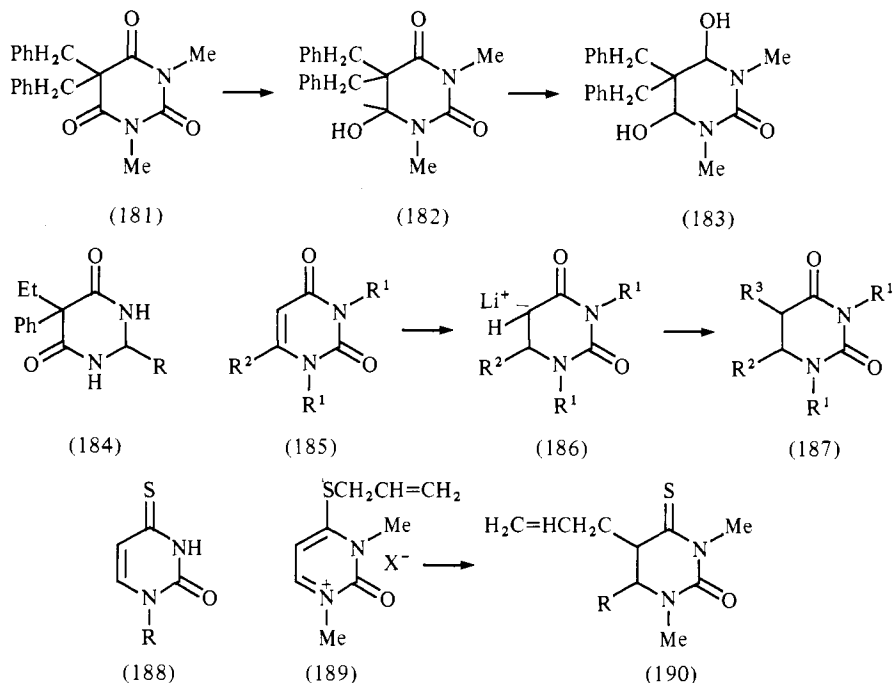
three products were obtained: the 3,6-dihydro (173, R = Me, X = O), the 3,4-dihydro (174, R = Me, X = O), and the tetrahydro derivative (175, R = Me, X = O), in the ratio 37:13:50.⁶¹³⁵ This ratio was sensitive to the reaction conditions. Thus, switching the solvent to ethanol, in which the reducing agent was more stable, led to exclusive formation of the dihydro compound (173, R = Me, X = O), a result which was duplicated in reducing the thione analogue (172, R = Me, X = S) to (173, R = Me, X = S). Formation of both dihydro derivatives (172) and (173) at the expense of the tetrahydro compound (175) was also considerably enhanced by the deliberate addition of trimethyl borate (a methanolysis product of sodium borohydride) to the reduction medium. Sodium acetoxyborohydride, a more powerful reducing agent, is present when sodium borohydride is dissolved in acetic acid.⁶⁷⁰⁷ This reagent reduces various pyrimidinones and pyrimidinethiones of the type (172) to the tetrahydro stage in the majority of cases; in a minority of cases, the tetrahydro product was accompanied by significant amounts of the 3,4-dihydro derivative with no trace of the 3,6-isomer. The 3,4-dihydro product predominated heavily (10:1) over the tetrahydro product in the reduction of the substrate (172, R = Ph, X = O).

Ethereal lithium aluminum hydride with the same group of compounds based on (172, X = S or O) frequently gave mixtures of either



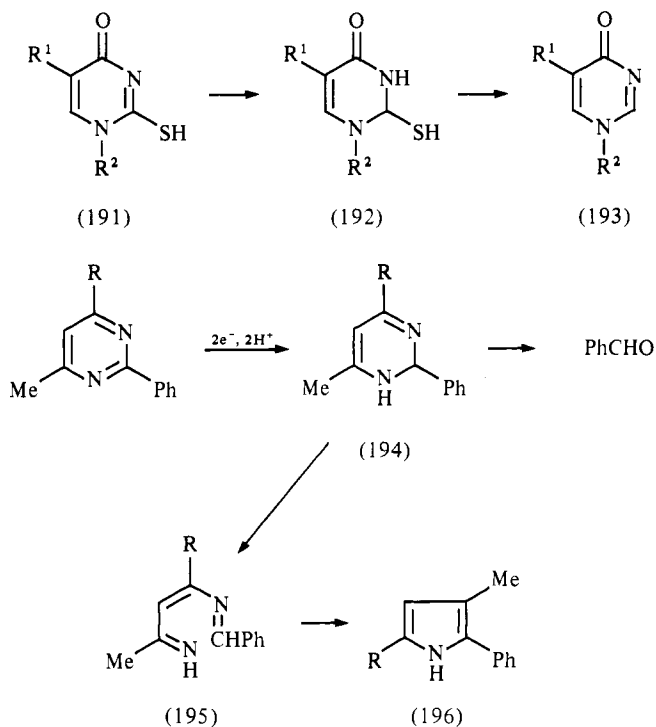
the 3,6- and 3,4-dihydro compounds or of the tetrahydro derivative with some of the 3,4-dihydro compound. The last mentioned product was the only one from (172, R = Ph, X = O or S). By contrast, Russian work on such reduction of the unprotected hydroxypyrimidine (176) reveals that deoxygenation to the pyrimidine base (177) probably occurs initially *via* complex anion formation by displacement of the acidic proton from OH or NH, and this is followed by reduction to a dihydropyrimidine (178) of unknown configuration.⁴⁸⁸⁴ Among the more spectacular demonstrations of the utility of active metal hydrides in this field was the sodium cyanoborohydride reductive deamination of 5,6-dihydro-6-imino-5-(α -thyminyl)thymine (179, R¹ = α -thyminyl) to (180, R¹ = α -thyminyl, R² = H), which proved to be identical with the principal photoproduct obtained from ultraviolet irradiation of calf thymus DNA.⁵³¹¹ Sodium cyanodeuteride gave the 6-deutero analogue (180, R¹ = α -thyminyl, R² = D). Shorter reaction times enabled the isolation of a methanol adduct (180, R¹ = α -thyminyl, R² = OMe) in which the methanol was replaced by water in aqueous solution to give (180, R¹ = α -thyminyl, R² = OH).

An early model compound for the investigation of metal hydride reduction of barbiturates was 5,5-dibenzyl-1,3-dimethylbarbituric acid (181). Methanolic sodium borohydride easily reduced the 4- and 6- but not the 2-oxo substituent to give CHOH entities; two principle products were the 6-hydroxydihydrouracil (182) and the *trans*-4,6-dihydroxy derivative (183).⁶⁷²² The product (182) could be reduced separately to (183), which isomerized subsequently to the more stable *cis* form in the presence of either strong base or dilute mineral acid. 5,5-Diallyl-1-methylbarbituric acid was reduced much more easily⁶⁷²³ than the unmethylated compound. This unsymmetrical molecule underwent reduction with sodium borohydride at both C4 and C6 to give a mixture of the 4- and 6-hydroxy compounds, together with a *cis-trans* mixture of the 4,6-diols; other barbiturates also underwent reduction of the carbonyl entities at C4 and C6 of the molecule.^{6632, 6723-6727} The important anticonvulsant primidone (184, R = H) can be manufactured by reducing the alkoxy derivatives (184, R = methoxy to hexyloxy) with sodium borohydride.⁶⁷²⁸ An interesting development is the recent discovery that the 5,6-double bond of the *N,N'*-disubstituted uracils (185, R¹ = Me, CH₂Ph, CH₂OCH₂Ph; R² = H) and of methyl orotates (185, R¹ = Me etc.; R² = CO₂Me) is specifically reduced by lithium tri-*s*-butyl borohydride, "L-Selectride," to give the corresponding derivatives of (186 and 187, R³ = H),⁶⁵⁸³ substituents like F or C $\equiv$ CSiMe₃ in the 5-position, which might not survive alternative hydrogenation



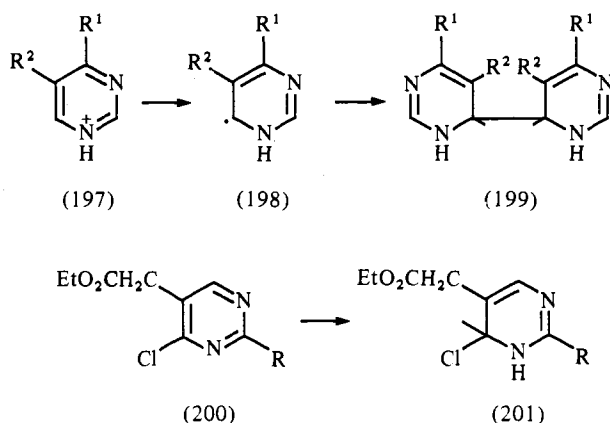
methods like catalytic reduction, remained unaffected. An additional advantage is that the intermediate anion (186) can be trapped by an alkylating agent, for example ethyl or benzyl bromide, with the formation of the 5-substituted uracil (187, R² = H, R³ = Et or CH₂Ph). Uracil itself was not reduced by this reagent under a variety of conditions; by contrast, aqueous sodium borohydride slowly reduced the 5,6-double bond of the thiouracils (188, R = H or ribos-1'-yl), and simultaneous irradiation with ultraviolet light accelerated the reduction.⁶⁶³⁹ Sodium borohydride reduction of the electron-deficient ring in (189, X = Br or I) was accompanied by one of the rare "thio-Claisen" rearrangements in pyrimidine chemistry to give (190, R = H).⁴⁴²¹

Strong evidence was adduced in the decade following 1960 to show that di-imide (HN=NH) was the active reducing species in certain reductions involving hydrazine and its derivatives. In the pyrimidine field, di-imide was implicated recently in the dethiation (191 → 193, R¹ = CH₂CO₂Me, R² = β-D-ribofuranosyl) of 5-methoxycarbonylmethyl-2-thiouridine by various hydrazine derivatives now recognized as precursors of di-imide.⁶⁷³¹ An unstable 1,2-dihydropyrimidine (192) was postulated as a fugitive intermediate which readily lost hydrogen sulfide to give a pyrimidinone (193).



It has been known for some time that the polarographic reduction of pyrimidine is dependent upon the pH of the aqueous solution. In acidic solution, two one-electron waves are observed; in a neutral medium, two two-electron waves are observed; and in alkaline solution, a four-electron reduction is effected, *via* 1,6-dihydropyrimidine, to a tetrahydropyrimidine of unknown structure.^{3560, 6732, 6733, 6784, 6785} However, the invention, development, and application of new instrumentation to the electrochemistry of pyrimidine derivatives has permitted their precise reduction under controlled conditions of potential, coulombs of current passed, and so forth, especially on a preparative scale. This has enabled chemical information to be gathered about the nature of the sometimes unstable reduction-products to supplement that obtained from their ultraviolet spectra. 4,6-Dimethyl-2-phenylpyrimidine can be reduced electrolytically in an acetate buffer.⁶⁷³⁴ After the consumption of two electrons, a product is obtained which is the unstable 1,2-dihydro compound (194, R = Me) since it is readily hydrolyzed to benzaldehyde. If the reduction is allowed to proceed until four electrons are consumed, the dihydro derivative is believed to ring-open to a tautomer (195, R = Me), which undergoes further reduc-

tion and cyclization to a pyrrole (196, $R = \text{Me}$). In the absence of the 2-phenyl substituent, the initial reduction is directed towards the 1,6- rather than the 1,2-bond. In dilute acid, one electron is added to C6 of the protonated molecule and the free radical gives a dimer, as indicated in the sequence ($197 \rightarrow 198 \rightarrow 199$, $R^1 = \text{Me}$ or Ph , $R^2 = \text{H}$; $R^1 = \text{H}$, $R^2 = \text{Me}$). In borate buffer at pH 9, these three pyrimidines were reduced to the tetrahydro stage. The tetrahydro derivatives were easily hydrolyzed to formaldehyde so that they were definitely not the 1,4,5,6-tetrahydro species (8). This contrasted with 4-methoxy-6-methyl-2-phenylpyrimidine, which could be reduced in dimethylformamide solution to the 1,4,5,6-tetrahydro-6-methoxy derivative, a structure supported by ^1H nmr evidence. Other investigations revealed that pyrimidines with nonreducible groups like amino or methyl were reduced in a single one-electron diffusion-controlled step very similar to that for pyrimidine itself.⁶⁷³⁵ The one-electron reduction of uracil was complicated by proton-transfer from the parent compound to the radical anion initially formed.⁶⁷³⁶ A useful summary of the experimental data incorporates some generalizations regarding the ease of electrochemical reduction of substituted pyrimidines, especially tautomerizable compounds.⁶⁷³⁷



The dissolving-metal class of reduction is represented by the zinc and acetic acid reduction of certain 4-chloropyrimidines.⁶⁶⁰² As with electrochemical reduction, ring contraction to pyrroles occurred, but some 1,6-dihydropyrimidines were produced as by-products as in the reduction ($200 \rightarrow 201$, $R = p\text{-ClC}_6\text{H}_4$). Indeed, 5-*p*-chlorophenyl-2-methylpyrimidine gave only its 1,6-dihydro derivative with zinc and acetic acid.⁶⁶⁰²

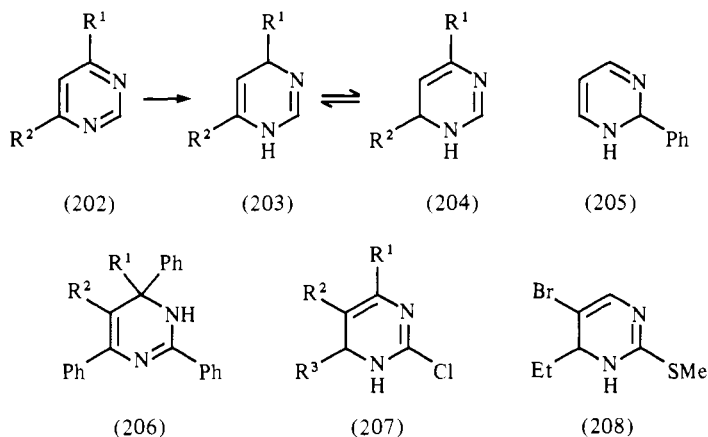
Examples of other types of reductive method are best seen with the biologically important molecules uracil, thymine, cytosine, and orotic acid; these have proven fertile substrates for many reducing agents. It is now well recognized that 5,6-dihydro derivatives are the major metabolites of these substances as well as of others like the anti-tumor derivative, 5-fluorouracil.⁶⁷³⁸ Much work has been expended in elucidating the details of this biological reduction. Thus, in a variety of organisms,^{6739, 6740} uracil is first metabolized to 5,6-dihydrouracil in a reduction process which is catalyzed by dihydrouracil dehydrogenase (E.C. 1.3.1.2), and which involves *trans*-addition of hydrogen at the si-faces of both C6 and C5.⁶⁷⁴¹ Thus, [carboxy-¹⁴C]orotic acid was incubated in the presence of an excess of NADH to drive the reaction catalyzed by L-dihydro-orotate dehydrogenase. However, this enzyme was contaminated by another L-dihydro-orotase which caused the isotopically labeled dihydro-orotic acid to be accompanied by its ring-opened hydrolysis product, *N*-carbamoyl L-[¹⁴C]aspartate.⁶⁷⁴² 1-Benzyl-1,4-dihydronicotinamide, used as a simple model for NADPH, reductively debrominates rather than reduces the 5,6-double bond in some 5-bromouracils. A one-electron transfer process is probably involved.⁶⁷⁴³

Photochemical reduction is represented by the conversion of uracil and thymine, again to their 5,6-dihydro derivatives, when their aqueous solutions are irradiated in the presence of tryptophan and other indole derivatives as sensitizers.⁶⁷⁴⁴ It was suggested that a metastable charge transfer complex, originating from the first excited state of the sensitizer, initially transferred an electron to the pyrimidine base.⁶⁷⁴⁴ By contrast with the parent uracil, its 5-bromo derivative reductively dehalogenated first upon photoreduction in isopropyl alcoholic solution.^{6607, 6648, 6745}

I. Addition of Reagents Other than Hydrogen to a Double Bond (*E* 330)

The electron-deficient nucleus in pyrimidine and some of its derivatives remains an attractive target for attack by a variety of nucleophiles. *Carbon nucleophiles* are mainly represented by organometallic compounds based on lithium and magnesium. Thus, ethereal phenyllithium reacts with pyrimidine itself (202, $R^1 = R^2 = H$) to afford a tautomeric mixture of 1,4- and 1,6-dihydro derivatives of 4-phenylpyrimidine (203, $R^1 = Ph$, $R^2 = H$) and (204, $R^1 = H$, $R^2 = Ph$), which probably also contained at least 4% of the 1,2-isomer (205). 4-Phenylpyrimidine (202, $R^1 = Ph$, $R^2 = H$) behaved similarly in giving (203 + 204, $R^1 =$

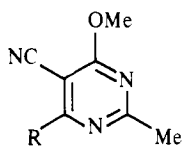
$R^2 = \text{Ph}$), but attack at C2 could be enhanced to nearly 40% by pre-complexing the phenyllithium with N,N,N',N' -tetramethylethylenediamine.⁶⁵⁴⁶ The tautomeric mixture (203 + 204, $R^1 = R^2 = \text{Ph}$) or its lithio derivative reacted with electrophilic reagents like methyl iodide or methyl chloroformate to form largely N -substituted derivatives of the 1,6-dihydro tautomer (204, $R^1 = R^2 = \text{Ph}$ with NMe or NCO_2Me in place of NH).⁶¹⁷⁸ Addition of alkyllithium occurs even when all reactive positions are occupied by phenyl groups to give (206, $R^1 = \text{Me}$ or Bu , $R^2 = \text{H}$).^{6746, 7119} A variety of heteroaryl lithium compounds also reacted with pyrimidine to form the analogous 6-heteroaryl-1,6-dihydropyrimidines (204, $R^1 = \text{H}$, $R^2 = \text{thien-2' or 3'-yl, fur-2'-yl, 1'-methylpyrrol-2'-yl, or pyrid-3'-yl}$),⁶⁶³¹ which on acetone-sensitized photolysis isomerized to the corresponding 5-substituted 1,2-dihydropyrimidines.⁴⁶⁹⁹



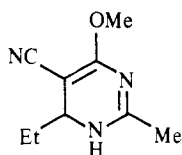
In halogenated pyrimidines, the halogen atom(s) reduce the electron-deficiency of the ring still further so that addition frequently competes successfully with halogen-metal exchange, not only with alkyl and aryllithium reagents, but also with Grignard reagents. So 2-chloropyrimidine and its 5-(3',4'-dimethoxyphenyl) derivative afforded the 1,6-dihydro derivatives (207, $R^1 = R^2 = \text{H}$, $R^3 = \text{Bu}$; $R^1 = \text{H}$, $R^2 = \text{dimethoxyphenyl}$, $R^3 = \text{Ph}$) with the appropriate lithium reagent.^{6080, 6747} With two 2,4,5-trihalogenated pyrimidines, phenyl magnesium bromide and a nickel chloride/phosphine complex as catalyst brought about addition to the unsubstituted position giving (207, $R^1 = R^2 = \text{Cl}$, $R^3 = \text{Ph}$; or $R^1 = \text{Cl}$, $R^2 = \text{F}$, $R^3 = \text{Ph}$).⁶⁵⁷⁵ 5-Chloropyrimidine added butyllithium to give the 4-butyl-5-chloro-3,4-dihydropyrimidine.⁶⁵⁹³ By contrast, 5-bromopyrimidine and butyllithium formed 5-lithiopy-

rimidine, because on quenching with deuterium oxide, 5-deuteriopyrimidine was formed.⁶⁷⁴⁸ Direct metalation of 5-bromopyrimidine with the strongly basic lithium di-isopropylamide afforded 5-bromo-4-lithiopyrimidine which then added to the 1,6-double bond of unreacted bromo compound.⁵⁵¹⁵

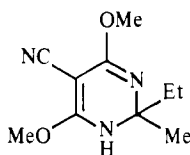
The bromine atom in 5-bromo-2-methylthiopyrimidine was not reactive enough to form a Grignard compound with magnesium. However, ethyl magnesium bromide found the ring sufficiently denuded of electrons to form the 6-ethyl-1,6-dihydro derivative (208).⁵⁸⁵⁵ While 2- and 4-cyanopyrimidines gave the expected acyl compounds with Grignard reagents, the 5-cyanopyrimidine (209, R = H) reacted at its vacant 6-position with ethyl magnesium bromide to give (210); the dimethoxy compound (209, R = OMe), on the other hand, reacted at its substituted 2-position to give (211).⁵⁰⁸⁹ The reactions of *N*-phenylpyrimidin-2-ones and thiones with lithium and magnesium organometallics have been thoroughly investigated.⁶⁴²² Thus, 1,2-dihydro-4,6-dimethyl-2-oxo-1-phenylpyrimidine (172, R = Me, X = O) reacted with methyl magnesium iodide to afford a mixture of the isomers (212) and (213) in which the former predominates (95:5). Methyl lithium behaves analogously, except that now the 3,6-isomer predominates (15:85). This reversal in behavior was noted also with the 2-thio analogue. It was concluded that while methyl and other alkyl Grignard reagents attacked the 6-position in preference to the 4-position, the corresponding alkyl-lithium reagents attacked the 4-position preferentially. In the case of 1,2-dihydro-2-oxo-1-phenylpyrimidine itself, the expected predominant



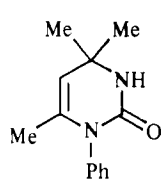
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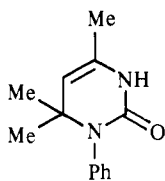
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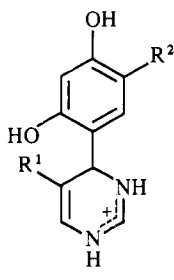
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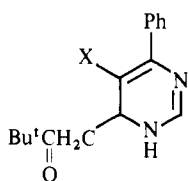
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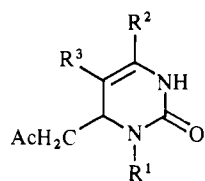
(213)



(214)



(215)



(216)

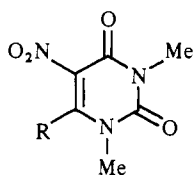
product became the exclusive product. This regioselectivity was enhanced by the use of bulky alkyl groups in the organometallic reagent. For example, both types of isopropyl reagent afforded only the 3,4-dihydro derivative with the above pyrimidin-2-one.⁶⁴²² A regioselective effect was observed with the two *N*-phenyl derivatives of 4-methyl-6-phenylpyrimidin-2-one, both giving exclusively a product bearing *C,C*-gem dimethyl groups. Phenyllithium added to the vacant 4-position of 1-ethyl-6-phenylpyrimidin-2-one.⁶⁷⁴⁹

The electron density of the ring in pyrimidine and 5-methylpyrimidine is reduced still further on protonation in trifluoroacetic acid. The protonated molecules are effective electrophiles for bringing about monosubstitution in the electron-rich rings of phenols like resorcinol to form salts containing the cations of dihydropyrimidines like (214, $R^1 = R^2 = H$; or $R^1 = Me$, $R^2 = H$). Some disubstitution was also observed.⁴⁴⁹⁵

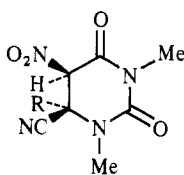
A few examples of carbanionic attack (apart from those from organometallics) on pyrimidines are known. 5-Halogeno-4-phenylpyrimidines react with the enolate anion of pinacolone in liquid ammonia so that, besides $S_{RN}1$ substitution of the halogen atom, some addition to the 1,6-azomethine bond in the pyrimidine ring occurred with formation of appreciable amounts of an isolable adduct (215, $X = Cl$ or Br).⁶⁶²⁸ Crystalline adducts like (216, $R^1 = R^2 = H$, $R^3 = NO_2$) and (216, $R^1 = Me$, $R^2 = CO_2Me$, $R^3 = Cl$) were also isolated from the addition of acetone and other carbonyl compounds to the 1,6-bond of the electron-deficient rings of nitropyrimidinones⁶¹²⁴ and chloropyrimidinecarboxylates.⁴⁸⁹⁰ The adducts from certain 5-nitrouracils have attracted attention because they readily underwent a ring transformation reaction to afford nitroresorcinols.⁶³⁵⁷

The conversion of 5-cyano-1,3-dimethyluracil into bicyclic products also depends on nucleophilic attack at C6 by a variety of carbanions.⁶⁷⁵⁰ Cyanide ion has also been added to C6 of the activated 5,6-double bond in 5-nitrouracils (217, $R = Me$ or Et), that is, even when a substituent is present already, to give isolable stable products of one diastereoisomeric configuration (218, $R = Me$ or Et).⁶¹³⁸ 5-Bromouracils react with sodium cyanide to afford 6-cyanouracils *via* similar 5,6-dihydro intermediates which are detectable by deuterium-labeling experiments.⁴⁹³⁷ The 6-bromomethyl compound (217, $R = CH_2Br$) underwent intramolecular cyclization with potassium cyanide to give the cyclothymine derivative (219), a class of compound hitherto obtained from the intermolecular cyclization of uracils and other hydroxypyrimidines with dimethyloxosulfonium methyllide,^{6121, 6751}

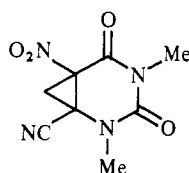
metal carbenes,^{6752, 6753} or dichlorocarbene.⁶⁷⁵² The latter reagent, produced by decomposition of (bromodichloromethyl)phenylmercury in preference to the base-catalyzed α -dehydrochlorination of chloroform, cyclopropanates the 5,6-double bond of uracils. However, trichlorogermane does not produce the germanium analogue of the carbene, instead, it affords the Michael-addition product (220, R = H or F) with the *N*-acetylated derivatives of uracil and 5-fluorouracil.⁶⁷⁵⁴



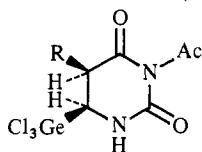
(217)



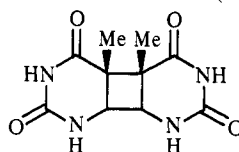
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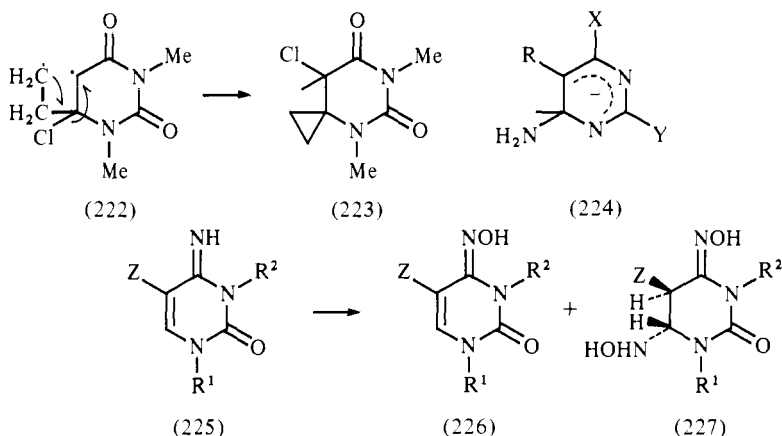
(220)



(221)

Formation of cyclobutane dimeric products, in which the pyrimidine ring has attained the dihydro stage of reduction, is a noteworthy reaction of uracil and thymine nuclei under ultraviolet irradiation, which has repercussions in the biomedical area. Such photodimers, especially the *cis-syn* variety (221) derived from thymine, have been introduced randomly into nucleosomal DNA on ultraviolet irradiation⁶⁷⁵⁵ as well as being formed as the major type of cyclobutane dimer upon γ -radiolysis of aqueous solutions of thymine itself at 77° K.⁶⁷⁵⁶ Other photodimerization reactions occur with 5-fluorouracil,⁶⁷⁵⁷ methylcytosines,⁵²¹⁶ a 4-hydroxypyrimidine derivative,⁶⁷⁵⁸ and as a highly stereospecific process with 1,3-dimethylthymine in cholesteric and smectic solvents.⁶⁷⁵⁹ Cyclobutane rings fused on to the 5,6-double bond of uracil, and its congeners are also found in products formed by photocycloaddition of alkynes and alkenes.^{5748, 6591, 6605, 6635, 6636, 6786-6788} The cyclobutane derivative is sometimes accompanied by other variants on 5,6-addition. Thus, one of the products obtained from acetone-sensitized irradiation of 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxypyrimidine with ethylene is (223), formed by a rearrangement in the biradical intermediate (222) and from which the chlorine can be removed subsequently by zinc and acetic acid.⁶⁵⁹¹ Finally

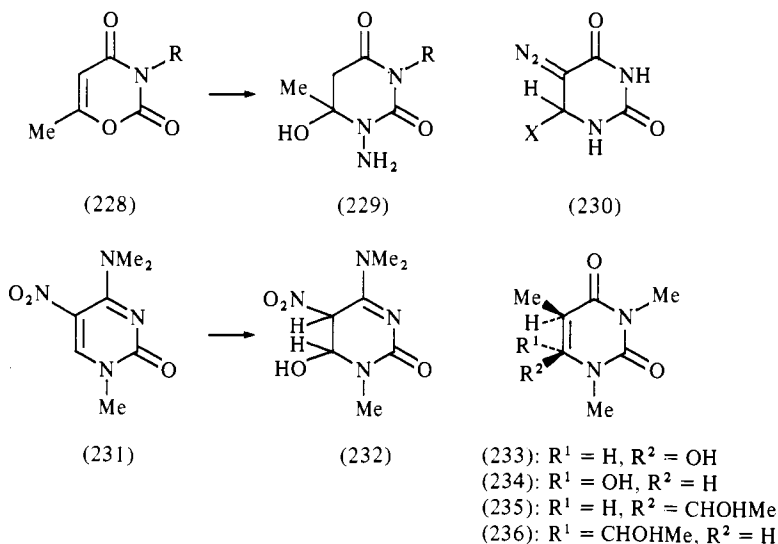
in this subsection, mention must be made of the importance of cyclobutane ring formation which stems from photocycloaddition of thymidine residues to the activated olefinic double bonds of the photosensitizing drugs known as psoralens,^{6592, 6761, 6762} other coumarins,⁵⁸⁰¹ and deaminated metabolites of histidine.⁶⁷⁶³



Attack by *nitrogen nucleophiles* is 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 (224, $R = X = Y = H$) of 4-amino-1,4 (or 1,6)-dihydropyrimidine.⁶⁶⁶⁶ Similar anions (224, $R = H$, $X = Cl$, $Y = NMe_2$; or $R = Br$, $X = Bu^t$, $Y = H$) and related types of σ -adducts⁶⁷⁶⁴ play a part in the indirect substitution of the halogen atoms as well as in ring transformation of pyrimidines.⁶⁷⁶⁵ The ring of quaternized pyrimidine derivatives is sufficiently denuded of electrons so that ammonia itself, a much weaker base than the amide ion, will add to the 6-position or, if the latter is blocked, to the 2-position.^{4688, 6766} Similar intermediates are implicated in the ring-contraction of various *N*-substituted pyrimidinium salts into pyrazoles^{6524, 6767} or pyrimidine 1-oxides,⁴⁶⁹¹ brought about by hydrazine or hydroxylamine respectively, as well as in the rearrangement of 2-alkylpyrimidines into 2-aminopyridines, brought about by methylamine.⁴⁸⁴¹

Benzamidine completely replaces the N—C—N portion of the pyrimidine ring of *N*-methylpyrimidinium salts by first adding at C6.⁴⁶⁹⁰ Similar 1,2- or 1,6-dihydro derivatives or their anions are involved in ring-transformation reactions of 5-nitropyrimidine with amidines.^{6123, 6525} Other Group V nucleophiles, known to add to the 6-position of the electron-denuded ring of 5-nitropyrimidine, are azide ion⁵⁴⁰⁶ and dialkyl phosphites.⁶⁷⁷⁰

The reactions of hydroxylamine at the 5,6-bond of pyrimidine nucleosides have attracted recent attention. With cytosine and its derivatives (225) not only is there replacement of the 4-amino or imino group to give (226), but also a predominantly *trans*-addition of hydroxylamine across the 5,6-double bond to give two products (227, Z = H or F), the ratio of which is dependent upon the pH of the reaction medium.⁶⁵⁶² Reaction of the methylcytosines in heavy water is accompanied by partial deuteration at C5.⁶⁷⁷¹ The hydroxylamine can be eliminated from (227) by subjection to strongly acidic conditions.^{6561, 6772} The addition of hydroxylamine to uracil and 5-halogenated uracils proved reversible⁶⁷⁷³ and was an intermediate stage in the dehalogenation of the 5-bromo and 5-iodo compounds.⁶⁷⁷⁴ Other examples of probable initial attack of a nitrogen nucleophile at C6 include the hydrazinolysis of 5-formyluracils,⁶⁷⁷⁵ aminolysis and hydrazinolysis of 1,3,6-trimethyl-5-nitrouracil,⁶⁵⁸⁶ amination of 1,3,6-trimethyluracil with hydroxylamine-*O*-sulfonic acid,⁵¹⁴³ and the reaction of the ϵ -amino group of lysine with the photo-excited cytosine molecule.⁶⁶³⁷ Reaction of the oxazine derivative (228, R = H or Me) with hydrazine involved nucleophilic attack at the C2 carbonyl group which led to formation of the dihydrouracils (229, R = H or Me).⁶⁶⁵⁷



There are some examples of the attack of *oxygen nucleophiles* on pyrimidines. Thus, derivatives such as thymine, cytosine, and 5-nitrouracil crystallize from water as hydrates⁶⁷⁷⁶ or exist as hydrates in solution. It has been shown, by ¹⁷O nmr measurements⁶⁷⁷⁷ on solutions of uridine derivatives, that such hydration involves hydrogen bonding

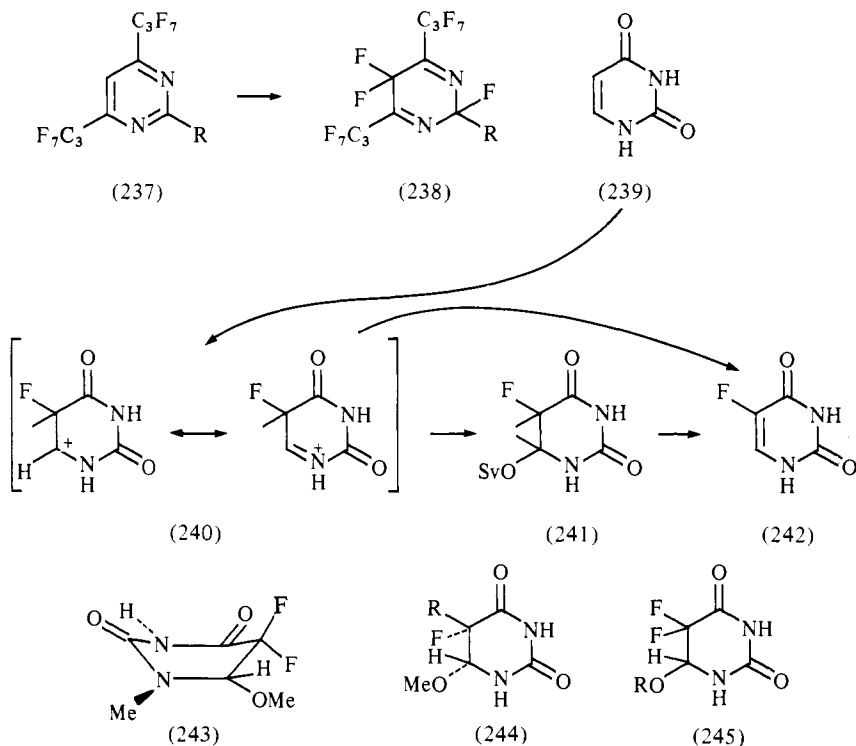
through the 4-carbonyl group. In the phosphate salts of individual DNA base constituents, the ionic phosphate groups remain the primary hydration sites.⁶⁷⁷⁸ Hydration of pyrimidine bases, free or combined in nucleosides, continues to be a subject for theoretical calculations,⁶⁷⁷⁹ thermochemical investigations,⁶⁷⁸⁰ ultrasonic studies,⁶⁷⁸¹ and it plays a part in the field ionization mass spectra of alkylated uracils.^{6647, 6783} However, the isolated pyrimidine ring is not sufficiently denuded of electrons to form an isolable covalent hydrate,^{6558, 6768} and even the 5,6-double bond of uracil and its derivatives requires activation by another electron-withdrawing substituent. Thus, 5-diazouracil readily forms a 1,6-hydrate (230, X = OH) in water and a similar adduct with methanol (230, X = OMe),⁶⁷⁶⁹ which is converted by aqueous hydrogen cyanide into the analogous cyanide adduct (230, X = CN).⁶¹⁸⁹ Although there is no apparent ionizable proton in the nitro compound (231), it does have an acidic pK_a of 9.04, which has been ascribed to covalent hydrate formation involving the 5,6-bond to give (232).⁵⁴⁰⁶ A 5-nitro group also renders the ring in pyrimidine or 2-methoxypyrimidine susceptible to attack by methoxide ion at C2 and C4, respectively.^{5170, 6782} Introduction of a 5-nitro group into 1,3-dimethyluracil renders C6 vulnerable to attack by a whole series of nucleophiles which includes the hydroxyl ion⁵⁴⁵¹ and the ethoxide ion, long known to form a stable crystalline sodium salt of the Meisenheimer type.⁴⁸⁷ The electron-deficiency of the pyrimidine ring is enhanced when it is part of a quaternary system. Such a nucleus in the thiouracil derivative (188), not only adds methanol under weakly alkaline conditions, but simultaneously undergoes a "thio-Claisen" rearrangement to give (189, R = OMe).⁴⁴²¹

The formation of dihydropyrimidines by *photohydration* has a large literature. As late as 1977,⁴⁴³⁷ it was claimed that uracil and 5-fluorouracil were the only hydroxypyrimidines that reacted efficiently with water or methanol under the influence of ultraviolet light.⁶⁷⁸⁹⁻⁶⁷⁹¹ Since then, more examples have gradually accumulated (especially with *N*-alkyl derivatives) in which the photo-excited molecule undergoes addition to its 5,6-double bond. Thus, 1,3-dimethylthymine, upon radiation with long-wavelength light, gave both stereoisomeric forms (233) and (234) of the photohydrate.⁶⁷⁹² The photohydration of aqueous 1,3-dimethyluracil⁶⁷⁹³ also involved covalent addition of water to the 5,6-bond, and the reaction has been suggested as the basis of a chemical actinometer, both for photoreactions with low efficiency and for irradiation between 240 and 280 nm.⁶⁷⁹³⁻⁶⁷⁹⁵ An interesting difference between the use of water and heavy water in these photohydrations has been uncovered.⁵¹⁹¹ Other photohydrates are known with cyti-

dine,⁶⁷⁹⁶ cytidylic acid,⁶⁷⁹⁶ and 1,N⁴-dimethylcytosine⁵³¹⁰ (in which photohydration competes successfully with dimerization only at low concentrations). Photohydration plays a part in the successful 5-trifluoromethylation of uracil with bistrifluoromercury.⁶⁷⁹⁷ With alcohols, α -hydroxyalkyl radicals are involved so that 1,3-dimethylthymine in ethanol gives *cis*- and *trans*-5,6-dihydro-6- α -hydroxyethyl-1,3-dimethylthymine (235/236) as major products.⁶⁶⁴¹ Similar adducts were noted as a result of photochemical experiments in propan-2-ol solution with the 1,3-dimethyl derivatives of uracil and thymine,^{6607, 6798} with 1,N⁴-dimethylcytosine, and with 1,3-dimethyluracil in both ethanol and propanol.⁵³⁰¹ Similar adducts arose from treatment of alcoholic solutions of pyrimidine bases with free-radical initiators like di-*t*-butyl peroxide,^{6798, 6799} supporting the intervention of α -hydroxyalkyl radicals in the photochemical work. Sometimes the adduct was accompanied by products in which the 5,6-double bond of the original substrate had been reduced.^{4426, 5310} Such photochemical hydrogenation predominated with uracil and 1,3-dimethyluracil in propan-2-ol or in aqueous solutions of ethylenediaminetetraacetic acid or ($\pm$)-methionine.³⁷⁷³ In other organic solvents, especially in the presence of ketonic sensitizers, dimerization of 1,3-dimethyluracil became very evident.⁴⁵⁸⁴

Adduct formation involving photolysis of various pyrimidinones in the presence of primary amines,⁴⁴¹² tetrahydrofuran,⁶⁶²⁰ and diethyl ether⁶⁸⁰⁰ has been observed, as well as reductive dimerization in the presence of a tertiary amine.⁴⁴⁰⁴ In all cases, a new C—C bond is formed at the 6-position of the ring(s).

Dihydropyrimidines can also be formed by *halogenation*. Thus, direct fluorination by cobalt trifluoride of perfluoroisopropylated pyrimidines, for example (237), leads not only to replacement of nuclear hydrogen atoms but also to addition forming perfluorinated 2,5-dihydropyrimidines (238, R = F or C₃F₇).⁶⁸⁰¹ In other cases of direct fluorination, either with elemental fluorine diluted with an inert gas like nitrogen⁶⁸⁰² or argon,⁶¹⁶³ with trifluoromethyl hypofluorite,⁵⁴⁸⁹ or with caesium fluoroxysulfate,⁶⁸⁰³ there is frequently an overlap with covalent solvation. The fluorination of uracil (239) is well represented in the patent literature because of the anti-tumor importance of 5-fluorouracil. Thus, fluorination of uracil in acetic acid probably proceeds through an intermediate resonance-stabilized carbocation (240) in which extra electron-deficiency results in the capture of a nucleophilic solvent molecule (SvOH) to give again a 5,6-adduct (241, Sv = Ac)^{6163, 6802, 6804} or (241, Sv = Ac, F = ¹⁸F).⁶⁸⁰⁵ This loses acetic acid upon sublimation in a vacuum to give 5-fluorouracil (242), while it

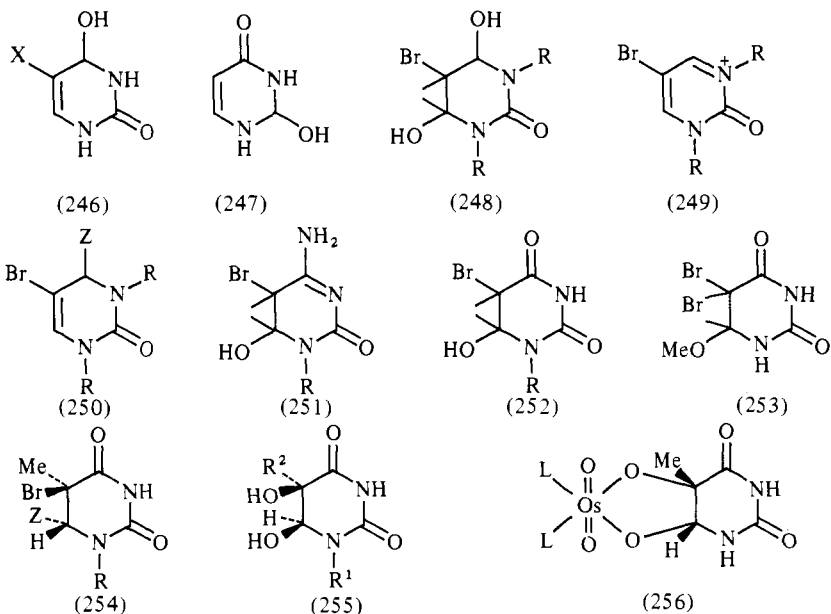


also solvolyzes with a series of alcohols to give the corresponding alkoxy compounds (241, Sv = Me, Et, or Bu).⁶¹⁶³ The trifluoroacetyl analogue (241, Sv = CF₃CO) also solvolyzes with a variety of alcohols, fluorinated alcohols, and thiols.⁶⁸⁰⁶ Aqueous trifluoroacetic acid⁵⁴⁸⁹ or water alone^{6807, 6808} as reaction medium led to the isolation of the covalent hydrate (241, Sv = H), which in turn could be dehydrated to 5-fluorouracil (242) upon heating in a stream of acidic gas⁶⁸⁰⁹ and under other conditions.⁶⁸¹⁰ The reaction of methanolic trifluoromethyl hypofluorite with 1-methyluracil is stereoselective in affording ($\pm$)-*cis*-5,5-difluoro-5,6-dihydro-6-methoxyuracil, which has the boat form (243) in the solid state and in solution.⁶⁸¹¹

Bromination of 5-fluorouracil in methanol gave the *trans* form of the methanol adduct (244, R = Br). It was possible to hydrogenolyze catalytically (Pd/C) the bromine atom in the presence of sodium acetate to give (244, R = H), in which the original *cis* arrangement of F and OMe groups was retained and which was identical with the product obtained by direct fluorination of uracil.⁶⁸¹¹ Chlorination of 5-fluorouracil in water, in acetic acid, or in a series of alcohols gave solvates analogous to (244, R = Cl; OH or OR for OMe). Catalytic removal of

the chlorine atom gave results identical with those obtained with (244, R = Br) except that a small percentage of the *trans* isomers could be isolated with adducts derived from long-chain alcohols.⁶⁶²³ Gem difluorination at C5 occurs with further fluorination of 5-fluorouracil in aqueous hydrofluoric acid to give the hydrate (245, R = H)⁶⁸¹² or with trifluoromethyl hypofluorite to give the analogous methanolate (245, R = Me).⁶⁸¹¹ Direct fluorination of 6-*O*-cyclocouracil nucleosides also led to isolation of a product in which 5,5-difluorination of the uracil ring had occurred with the primary alcoholic group of the sugar moiety simultaneously acting as the oxygen nucleophile bonding to C6 of the uracil part.⁶⁸¹³ Other workers, however, have claimed the intermediacy of unstable 5,6-difluoro-5,6-dihydro derivatives in the fluorination of pyrimidinones.^{4398, 6814, 6815} A sequence of events similar to that found for uracil can be related about the fluorination of 5-substituted uracils^{6277, 6816-6819} and orotic acid derivatives.⁶⁸²⁰ Fluorination of cytosine in trifluoroacetic acid gave the trifluoroacetate salt of a 5,6-adduct.⁶⁸⁰⁶

Quantitative aspects of the fast bromination of various pyrimidinones were investigated extensively during the period under review. The kinetics of 5-bromination of 2- and 4-hydroxypyrimidine in various aqueous solutions were explained in terms of electrophilic attack upon the activated enamine systems of the covalent hydrates, like (246, X = H) and (247), present in equilibrium with the anhydrous molecules.^{6652, 6653} Although these species were estimated to be present in quite minute amounts (0.05% and 0.003%, respectively) they obviously had to be extremely reactive entities in order to explain their dramatic effect upon the reactivity of the parent pyrimidine systems. Unlike fluorination, therefore, solvent participation had occurred before and not after electrophilic halogen attack. Although the majority of the hydrated species were too labile to be isolated, they could be detected in solution especially by ultraviolet and ¹H nmr spectroscopy.^{5326, 6650} In the case of bromination of 2-hydroxypyrimidine, such species were the dihydro compound (246, X = Br) and the tetrahydro species (248, R = H), which subsequently underwent slow acid-catalyzed conversion into 5-bromo-2-hydroxypyrimidine. However, reaction of the quaternary cation (249, R = Me) with an excess of bromine led to isolation of the 5,5-dibrominated solid akin to (248, R = Me) from an aqueous medium and the 4,6-dimethoxy analogue from a methanolic medium.⁵³³⁶ The substrate (249, R = Me) also added a variety of nucleophiles to give products which were stable in solution for lengthy periods and again could be detected spectroscopically.⁵²⁶⁶



Bromination of cytosine and its derivatives also involves an addition-elimination sequence. Careful work enabled the isolation of the 5-bromo-6-hydroxy adducts (251, R = H, Me or ribose) and their methanol equivalents without too many complications arising from the ready replacement of the exocyclic amino group by hydroxy.^{5227, 6821} 1-Substituted uracils produced the relevant adduct or bromohydrin (252) following bromination in an aqueous medium at pH 7,⁶¹⁵⁴ or the analogous crystalline methanol adduct following the reaction with methanolic bromine.⁵²⁹² *N*-Iodosuccinimide in ethanol produced the 6-ethoxy-5-iodo analogue.⁶¹⁵⁴ The dibrominated adduct (253) resulted from a brominative replacement of the methylsulfinyl group in 5-methylsulfinyluracil by bromine in a methanolic dimethylformamide medium.⁵¹⁶⁷

The hypobromite adduct of thymine (254, Z = OH, R = H) has been known since 1925,¹⁰³⁷ but only recently has a series of *trans*-alkoxy and *trans*-acyloxy adducts of thymidine (254, Z = OMe, OEt, OBu, OC₅H₁₁, OAc, OBz; R = deoxyribose) been described.⁶⁸²² Mild reduction with zinc and acetic acid of the two enantiomers of *trans*-5-bromo-5,6-dihydro-6-hydroxythymidine led to fixing of the absolute configuration of the *cis*-5,6-dihydro-6-hydroxythymidine obtained.⁶⁸²³ Halogenation of certain 6-*O*-cyclonucleosides led to a novel type of 5,6-dihalogenonucleoside possessing two oxygen bridges between the pyrimidine base and the sugar.⁶⁸²⁴

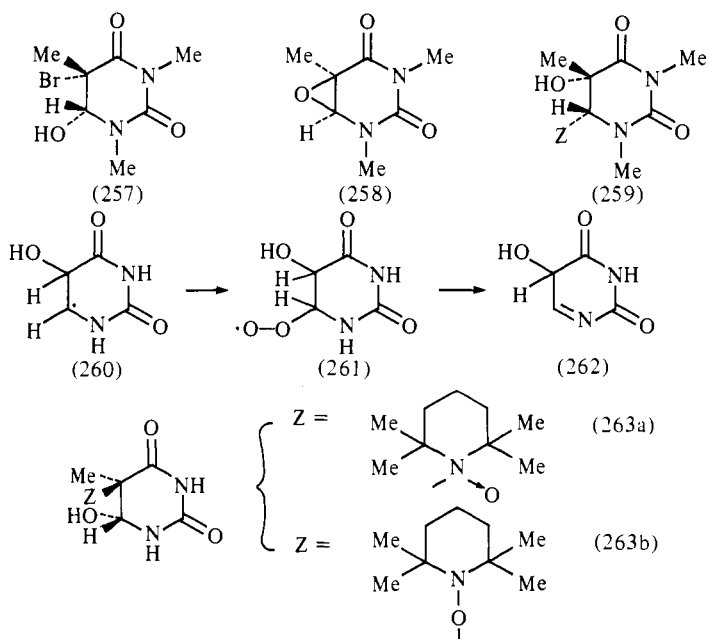
Dihydropyrimidines are also formed by the (theoretical) addition of hydrogen peroxide to give *5,6-dihydroxy adducts or glycols*. Indeed, this is a major factor in the wealth of literature on dihydropyrimidines. Thus, the 5,6-double bond of uracil and various 5- and 6-substituted derivatives, including ^{14}C -labeled thymine and thymidine,⁶⁸²⁵ have been subjected to the action of potassium permanganate, one of the classical reagents for detection of olefinic double bonds in an organic molecule. Various yields of *cis*-diols, for example (255, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$)^{5896, 6826} or (255, $\text{R}^1 = \text{deoxyribose}$, $\text{R}^2 = \text{Me}$),⁶⁸²⁷⁻⁶⁸²⁹ resulted. The reaction involves a concerted (3 + 2) cycloaddition across the 5,6-double bond to form a cyclic ester which subsequently hydrolyzes to the *cis*-glycol and a soluble Mn(IV) species.^{6576, 6830} The isomeric *trans*-glycols (such as those of the thymine, thymidine, and 1,3-dimethylthymine series) were obtained by chromatographic separation from the mixtures resulting from isomerization of the *cis*-glycols.⁶⁸³¹

Another olefinic double bond reagent, osmium tetroxide, added across the 5,6-bond of cytosine,⁶⁸³² 5-methylcytosine,⁶⁸³² and 1-methylthymine⁶⁵⁹⁹ to give cyclic osmic esters. Both *cis*- and *trans*-glycols in the thymine series reacted with the monomer of the Os(VI) species, $\text{Os}_2\text{O}_6(\text{pyridine})_4$, to give the corresponding bis(pyridine) *cis*-osmate (VI) esters (256, $\text{L} = \text{pyridino}$).⁶⁸³¹

An interesting experimental observation bearing on glycol formation is the finding that tertiary-amine-induced hydrolysis of the *trans*-1,3-dimethylthymine bromohydrin (257) gives a mixture of *cis*- and *trans*-5,6-glycols through an intermediate thymine 5,6-epoxide (258).⁵²²⁵ By contrast, the 5,6-epoxide produced by the α -diketone-sensitized photo-oxidation of 1,3-dimethylthymine can be intercepted by water, acetic acid, or thiophenol molecules to give only *cis*-adducts (259, $\text{Z} = \text{OH}$, OAc , or SPh).⁵²¹⁷ However, phenol did not give the analogue (259, $\text{Z} = \text{OPh}$); unexpected carbon-carbon coupling products (259, $\text{Z} = o$ - and p - HOC_6H_4) were obtained.⁶⁵⁶⁸ The near-ultraviolet irradiation of various uracils and thymines in the presence of hydrogen peroxide afforded a 20% yield of both *cis*- and *trans*-glycols.⁶⁸³³

Some dihydropyrimidines are produced by *radiolysis and sonolytic reactions involving the addition of hydroxyl radicals*. Thus, the radiolysis of uracil and thymine in aqueous solutions serves as a model for the effect of ionizing radiations upon nucleic acids.⁶⁸³⁴ Under the influence of γ -radiation, water produces solvated electrons which react with the gases in aqueous uracil solution saturated with a nitrous oxide-oxygen mixture to produce hydroxyl radicals.⁶⁸³⁵ Such radicals then add to the 5,6-bond of uracil, 18% at C6 and 82% at C5,⁶⁶⁴⁰ the latter

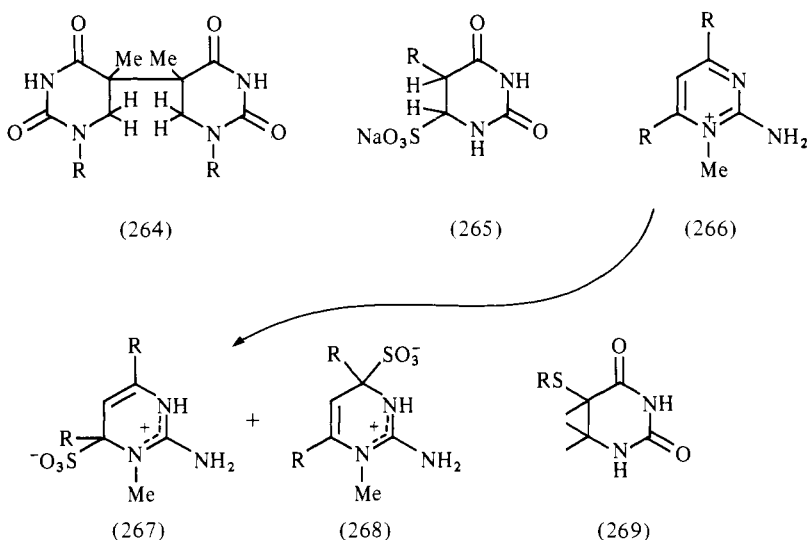
figure dropping to 65% when nitrous oxide alone was used.⁶⁵⁷⁷ The major new radical (260) is converted by oxygen into a peroxy radical (261) which undergoes spontaneous as well as base-induced elimination of HO_2/O_2^- to give 5-hydroxyuracil (262) as an intermediate. One of the reactions undergone by (262) is water addition leading to a mixture of the *cis*-(255, R = H) and *trans*-(255, R = H and interchanged with 5-OH) glycols described above. A similar mixture of *cis*- and *trans*-glycols results from the γ -irradiation of an aerated aqueous solution of uridine.⁶⁸³⁶



The primary reactions in the sonolysis of aqueous solutions of uracil parallel those of radiolysis, providing that the acoustic intensity is sufficient to produce cavitation.⁶⁶⁵⁸ The gases dissolved in the water play a part in producing sonoreactions.⁵²²²

There are some similarities between the radiolytic behavior of aqueous solutions of uracil and of thymine. The latter reacts with hydroxyl radicals to give ultimately the *cis*- and *trans*-thymine glycols,⁶⁸³⁷ 5,6-dihydro-5 (and 6)-hydroxythymine, and 5-hydroxymethyluracil following γ -ray irradiation of the nitrous oxide-saturated aqueous solution.⁶⁸³⁸ In the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl derivatives, glycol formation was promoted.^{6839, 6840} In separate experiments, some of the radicals were trapped with formation of the dihydro adducts (263a) and (263b).⁶⁸⁴¹

2-Methyl-2-nitrosopropane was used as a spin-trapping agent in earlier work with the 5'-monophosphates of thymidine and uridine⁶⁸⁴² both alone and in conjunction with the esr technique.⁶⁸⁴³ Pulse radiolysis with optical detection followed by electron-transfer reactions,⁶⁸⁴⁴ as well as steady state esr, were two more techniques applied to working out the pattern of hydroxyl radical addition to the 5,6-bonds in the molecules of cytosine and its derivatives,⁶⁸⁴⁴ or of thymine both in the free state⁶⁸⁴⁴ and as combined in the DNA chain.⁶⁸⁴⁵ Recently, a novel dimeric product (264, R = 1- β -2'-deoxy-D-ribofuranosido), which did not contain the usual cyclobutane ring, was isolated from the mixture of products obtained by γ -irradiation of aqueous solutions of thymidine containing sodium formate.⁶⁸⁴⁶



Some *sulfur nucleophiles* have been used to produce dihydropyrimidines. Such work has played a significant role in the current understanding of the chemical modification of nucleic acids which may cause mutation. In particular, the addition of hydrogen sulfite anion to pyrimidine nucleosides has been widely used in the chemical modification of nucleic acids⁶⁸⁴⁷ and this has raised the question of potential genetic hazard from atmospheric sulfur dioxide and bisulfite towards living organisms.⁶⁸⁴⁸ Thus, the 5,6-bond of uracil suffers nucleophilic attack from sodium sulfite or bisulfite to give the 5,6-dihydrouracil (265, R = H), which is isolable as a solid product.⁶⁸⁴⁹ A similar fate befalls the pyrimidine ring in 5-fluorouracil,⁶⁸⁵⁰ *N*-alkyluracils,⁶⁸⁵¹ thiouracils,^{6851, 6852} 1,3-dimethylorotolaldehyde,⁶⁸⁵³ uracil nucleo-

sides,^{6848, 6854, 6855} cytidine,⁶⁸⁴⁹ and other cytosine derivatives,^{6848, 6854-6857} where replacement of the 4-amino group by a co-operative effect with other nucleophiles like water,⁶⁸⁵⁴ hydroxylamine,^{6847, 6857, 6858} hydrazine,⁶⁸⁵⁵ or analogous nitrogenous bases^{6858, 6859} is likely to be an extra complication. Sodium hydrogen sulfite adds reversibly in a *trans* fashion across the 5,6-bond of thymine to give (265, R = Me).⁶⁸⁶⁰ The isomeric *cis*-adduct can be prepared by hydrogen sulfite-mediated deamination of 5-methylcytosine.⁵¹⁴⁹ Bisulfite ion, as well as the anion derived from β -mercaptoethanol, can also be added to the 5,6-bond of the electron-deficient nucleus of 1,3-dimethyl-5-nitrouracil.⁵⁴⁵¹ Addition to the even more electron-deficient ring of the unsymmetrical pyrimidinium cation (266, R = H) occurs at both the 4- and the 6-position with the formation of two zwitterionic products (267, R = H) and (268, R = H),⁵⁴⁵⁶ the additions are prevented if methyl groups are already present at those positions, for example in (266, R = Me).⁵⁵³⁰

Addition of sulfite ion to the 5,6-bond is also implicated in the bisulfite-mediated dehalogenation of 5-chloro-, 5-bromo-, and 5-iodouracils⁶⁸⁶¹⁻⁶⁸⁶⁴ as well as in the replacement of the 4-amino group of cytidine by hydrazine.⁶⁸⁵⁵ The first stage in the addition of bisulfite consists of nucleophilic attack by the sulfite ion through its sulfur atom at C6 of the molecules concerned, where calculations have shown that the lowest unoccupied molecular orbital has its highest density.⁶⁸⁶⁵ Photoaddition of bisulfite ion to the 5,6-bond of 5-deuterouracil takes place at a much lower concentration than that required for thermal addition and it is stereochemically random.⁶⁸⁶⁶

The cross-linking of proteins to DNA under the influence of ultraviolet light might be responsible for another biological lesion. This is the reason behind model experiments which demonstrate that cysteine cross-links to uracil or thymine through its sulfur atom with formation of adducts like $[269, R = CH_2CH(\dot{N}H_3)CO_2^-]$.^{6867, 6868} The same uracil adduct is one of the three products formed in the acetone-sensitized photochemical reaction between cytosine and cysteine in water.⁵⁵⁵¹ As with bisulfite, cysteine addition across the 5,6-bond seems to be involved in the dehalogenation of 5-chloro- and 5-bromo-2'-deoxyuridine in the presence of the α -amino acid.⁶⁸⁶⁹

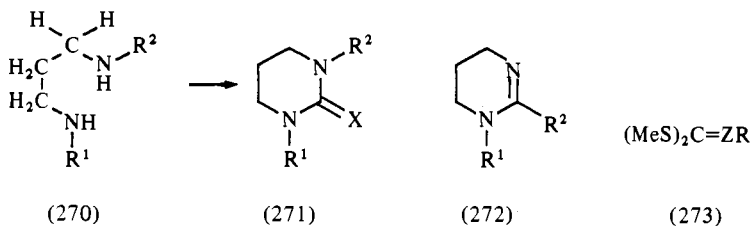
2. Preparation of Tetrahydropyrimidines (*H* 445, *E* 331)

Of the three isomeric possibilities, the 1,4,5,6-system (8) remains the most investigated because of its ease of preparation and the great stability associated with the cyclic amidinium resonance of the proto-

nated molecule. The resonance possibilities in the protonated 2-amino-1,4,5,6-tetrahydropyrimidine molecule are even greater, which may have a bearing on the occurrence of this system in various natural products such as the antibiotics belonging to the viomycin, capreomycin, and tuberactinomycin families.^{6870, 6871}

A. From 1,3-Diaminopropane or a Derivative (*H* 445, *E* 331)

Only one extra carbon atom is required to connect both nitrogen atoms of these readily available precursor molecules and so form the desired tetrahydropyrimidine ring. The missing carbon atom can be supplied by single-carbon molecules such as carbon disulfide which converts the precursors (270) into the products (271, $R^1 = \text{Me}$, $R^2 = \text{H}$, $X = \text{S}$;⁶⁸⁷² $R^1 = \text{Ph}_2\text{CH}$, $R^2 = \text{H}$, $X = \text{S}$;⁶⁸⁷³ or $R^1 = \text{H}$, alkyl, or Ph, $R^2 = \text{Me}$, $X = \text{S}$)⁶⁸⁷⁴ or even carbon monoxide in the presence of nickel carbonyl, which can bring about the reaction ($270 \rightarrow 271$, $R^1 = R^2 = \text{H}$, $X = \text{O}$) and which can also give the parent (8).⁶⁸⁷⁵ Other compounds containing a thiocarbonyl grouping and which have been used to complete a tetrahydropyrimidine ring, include aryl isothiocyanates [$(270) \rightarrow (271$, $R^1 = R^2 = \text{H}$, $X = p\text{-BuC}_6\text{H}_4\text{N:})$]⁶⁸⁷⁶ and aromatic *N*-ethoxycarbonylthioamides,⁶⁸⁷⁷ which give 2-aryl-1,4,5,6-tetrahydropyrimidines (272, $R^1 = \text{H}$, $R^2 = \text{Ar}$). The 2-phenyl compound (272, $R^1 = \text{H}$, $R^2 = \text{Ph}$) results when 1,3-diaminopropane reacts with benzo-trichloride.⁶⁸⁷⁸



Phosgene *O*-tetrahydropyran-2-yloxime or phosgene *O*-(*N*-methylcarbamoyl)oxime functions as a synthon for a single-carbon entity, carbonyl oxime, which has thus been used to complete the tetrahydropyrimidine ring of the cyclic hydroxyguanidine in the reaction [$(270) \rightarrow (271$, $R^1 = \text{Me}$, $R^2 = \text{PhCH}_2$, $X = \text{:NOH})$].⁶⁸⁷⁹ Thiophosgene, produced from carbon tetrachloride and sulfide ion under phase-transfer conditions,⁶⁸⁸⁰ reacts with 1,3-diaminopropane to give the cyclic thiourea (271, $R^1 = R^2 = \text{H}$, $X = \text{S}$).⁶⁷⁶⁰ The carbon atom of dichlorodiazomethane, this time complexed with a ligated tungsten atom, can

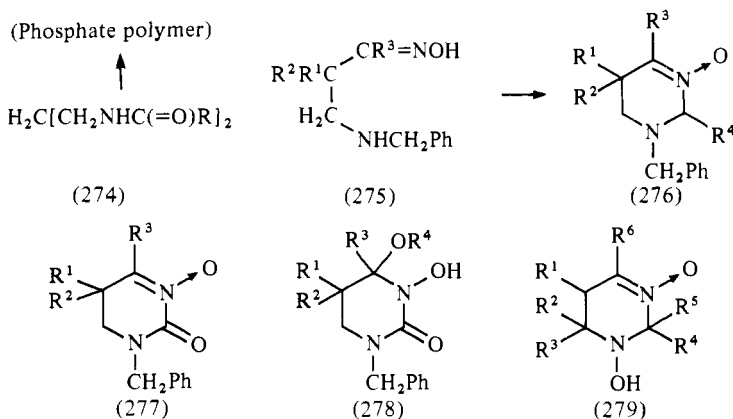
also be incorporated into a tetrahydropyrimidine ring by reaction with 1,3-bis(methylaminopropyl) [270] $\rightarrow$ (271, $R^1 = R^2 = \text{Me}$, $X = :N_2:WL_2Br$).⁶⁸⁸¹ 1,3-Diaminopropane also condenses with *S,S*-dimethyl *N*-tosyliminodithiocarbonimidate (273, $ZR = N$ -tosyl) to give the cyclic *N*-tosylguanidine derivative (272, $R^1 = H$, $R^2 = NH$ tosyl).⁶⁸⁸² Related reactions involve a cyanoimidodithiocarbonate (273, $ZR = NCN$)⁶⁸⁸³ and nitroketene mercaptals (273, $ZR = CHNO_2$).⁶⁸⁸⁴

An interesting reaction is the condensation of 1,3-diaminopropane with 2,2,4,4-tetramethyl-1,3-cyclobutanedione. The net result is incorporation of the carbon atom of one carbonyl group into an hydro-pyrimidine ring and cleavage of the cyclobutane ring, thus giving (272, $R^1 = H$, $R^2 = CMe_2COPr^i$).⁶⁸⁸⁵ Buta-1,3-diyne behaves as a latent 1,3-dicarbonyl compound in its reaction with 1,3-diaminopropane to give the mixture [272, $R^1 = H$, $R^2 = H$ and Me].⁶⁸⁸⁶

Following early precedents,³⁵⁶⁷⁻³⁵⁷⁶ nitriles continue to be used frequently as sources of C2 for tetrahydropyrimidines. Thus, 1,3-diaminopropane monotosylate reacts with both nitrile groups of succinonitrile affording 1,2-bis(1',4',5',6'-tetrahydropyrimidine-2'-yl) ethane.⁶⁵⁵³ It also reacts with trichloroacetonitrile to form the tosylate salt of (272, $R^1 = H$, $R^2 = CCl_3$) without harm to the trichloromethyl group;⁶⁸⁸⁷ aromatic nitriles were also so used.⁶⁸⁸⁸ A novel variation was the use of the isomeric isocyanide group which, linked to a *t*-butyl group, reacted with 1,3-diaminopropane in a silver cyanide-catalyzed reaction to give the parent compound (8).⁶⁸⁸⁹ The nitrile group of both aliphatic and aromatic nitriles was activated for the purpose of such cyclizations by prior conversion into an *N*-methylnitrilium salt with methyl trifluoromethanesulfonate.⁶⁵⁴¹ The alternative method of first converting the nitrile into the imide^{3591, 3592} was also followed,^{6890, 6891} especially with the cyanohydrins of aromatic aldehydes and ketones, so leading to the isolation of optical isomers of the protonated molecules [272, $R^1 = H$, $R^2 = CH(OH)Ar$].⁶⁸⁹²

Although carboxylic acids themselves have been used to convert 1,3-diaminopropanes into the corresponding 1,4,5,6-tetrahydropyrimidines, this reaction suffers from the disadvantage that both amino groups of the propanediamine are acylated equally easily and the diamide (274) cyclizes only after a long period at a high temperature. However, the introduction of phenyl phosphorodiamidate⁶⁸⁹³ as a rapid-cyclization reagent affords, *via* a phosphate polymer, good yields of the hydro-pyrimidine in short reaction times by the sequence [(270, $R^1 = R^2 = H$) $\rightarrow$ (274) $\rightarrow$ (272, $R^1 = H$, $R^2 = C_9, 11, 13, 15, \text{ or } 17 \text{ alkyl}$)]. Both polyphosphoric acid and its ethyl ester were successful in aiding

the cyclization of 1-arylamino-3-arylamino propanes to the otherwise difficultly obtainable 1,2-diaryl compounds (272, $R^1 = R^2 = \text{Ar}$).⁶⁸⁹⁴ The single-carbon part of formamide has also been turned into the C2 of a cyclic formamide molecule (272, $R^1 = \text{alkyl}$ or aralkyl, $R^2 = \text{H}$)⁶⁸⁹⁵ as has the PhC fragment of methyl benzoate, into a 2-phenylated cyclic amidine molecule.⁶⁸⁹⁶ Ethyl 4,4,4-trifluoro-3-oxobutanoate condenses with 1,3-diaminopropane at the ketonic group to form (272, $R^1 = \text{H}$, $R^2 = \text{CF}_3$).⁶⁸⁹⁷ This observation lends some support to the thesis that the hydrogen analogue, ethyl acetoacetate, is not deacylated³⁵⁸⁸ when it forms 1,4,5,6-tetrahydro-2-methylpyrimidine rings with various 1,3-diaminopropanes in the reaction $[(270, R^1 = \text{Pr}^i, \text{etc}, R^2 = \text{H}) \rightarrow (272, R^1 = \text{alkyl}, R^2 = \text{Me})]$.^{6553, 6898}



When one or both of the 1,3-substituents on a propane chain is nitrogenous and derived from hydroxylamine, a similar situation pertains in which only one carbon atom is required to complete the hydropyrimidine ring. Thus, the 3-benzylamino oxime (275) with aldehydes gives the corresponding 1,2,5,6-tetrahydro derivative (276).⁶⁸⁹⁹ With phosgene, ring closure gives an unstable intermediate (277) which, when both R^1 and R^2 in (275) are not hydrogen, adds either one molecule of water or of methanol to give the tetrahydro adduct (278, $R^4 = \text{H}$ or Me).⁶⁵⁷⁹ A similar condensation occurs between the amidoxime (275, $R^1 = R^2 = \text{H}$, $R^3 = \text{NH}_2$) and aldehydes to give (276, $R^1 = R^2 = \text{H}$, $R^3 = \text{NH}_2$).⁶⁹⁰⁰ β -Hydroxylamino oximes can be cyclized by formaldehyde to give the tetrahydropyrimidine N,N' -dioxide derivatives (279, $R^6 = \text{Ph}$, $R^1 = \text{H}$ or Me ; or $R^6 = R^1 = R^2 = R^3 = \text{H}$),⁴⁷⁵⁷ while a gem dimethyl analogue (279, $R^6 = R^2 = R^3 = R^4 = R^5 = \text{Me}$, $R^1 = \text{H}$) results from the aerial oxidation of the product from a Grignard reaction with a β -hydroxylaminonitrone.⁶⁹⁰¹

1,3-Diaminopropane has been used as a source of hydrogen in palladium-catalyzed hydrogen-transfer investigations. The diamine is converted into 2-ethyl-1,4,5,6-tetrahydropyrimidine (272, $R^1 = H$, $R^2 = Et$) after a series of dehydrogenation, addition, and cyclization reactions.⁶⁹⁰²⁻⁶⁹⁰⁴ A hot mixture of the 1,3-diamine with *N*-methylbenzylamine and palladium affords the 2-phenyl analogue (272, $R^1 = H$, $R^2 = Ph$).⁶⁹⁰²

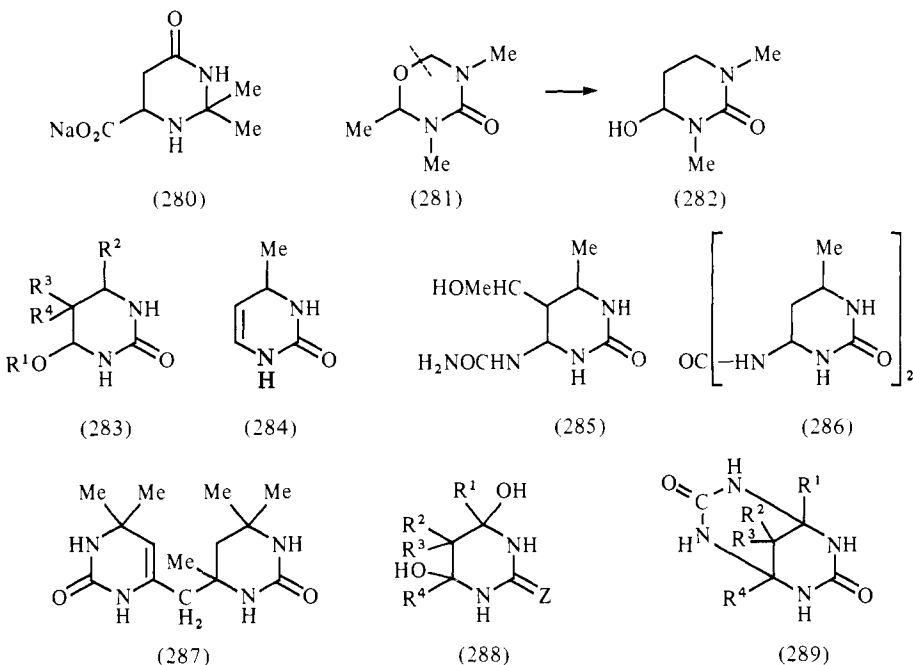
Cyanogen bromide has been used to cyclize 1,3-bisarylaminopropanes.⁶⁹⁰⁵ The latter readily condense with the activated carbonyl group of aromatic tertiary amides after prior reaction with dimethyl sulfate.⁶⁹⁰⁶ Several dehydrogenative cyclizations involving a 1,3-diamino compound and sulfur are also on record.⁶⁹⁰⁷⁻⁶⁹⁰⁹

The 1,3-arrangement of amino groups in the α -amino acid asparagine leads to its inclusion here. The long-known cyclization reaction with formaldehyde has been reinvestigated recently,^{6910, 6911} acetone was found to give a tetrahydropyrimidine (280).⁶⁹¹² Certain ω -guanidino- α -amino acids have also been cyclized to tetrahydropyrimidinecarboxylic acids.⁶⁹¹³

B. From Carbonyl Compounds with Ammonia, Amines, or Ureas (*H* 448, *E* 336)

Urea was one of the earliest components used in reactions designed to form the pyrimidine ring.^{50, 51} Besides its cyclization role with 1,3-diaminopropanes, where an intermediate 3-aminopropyl isocyanate is now believed to be implicated,⁶⁹¹⁴ the ureidoalkylation⁶⁹¹⁵ of aldehydes and ketones has been thoroughly exploited. Urea and *N*-alkylureas react with aldehydes or a mixture of aldehydes to give initially an oxadiazine. Thus, *N,N'*-dimethylurea with formaldehyde and acetaldehyde gives the oxadiazine (281); in acid solution the ring opens at the ring-oxygen and subsequent recyclization occurs so that the formerly activated α -methyl group of the acetaldehyde molecule forms the 5-methylene part of the hydropyrimidine (282). From urea and higher aldehydes, for example, isobutyraldehyde or its hemiacetal chloride,⁶⁹¹⁶ the hydropyrimidine derivative (283, $R^1 = H$, $R^2 = Pr^i$, $R^3 = R^4 = Me$) is isolated directly under acidic conditions. With alcohols, the corresponding alcoholates are obtained. Both hydroxy and alkoxy derivatives of (283) can be converted into 6-alkylthio or 6-arylthio compounds by reaction with the appropriate thiols and into 6-ureido derivatives after reaction with more urea. With phenol, however, the product (283) undergoes C—C coupling to give (283, C_6H_4OH for OR^1). Such coupling also occurs between aldehydes containing activated α -CH groupings and

the product based on *N,N'*-dimethylurea to give, for example, (283, NMe for both NH, $R^2 = H$, $R^3 = R^4 = Me$, CMe_2CHO for OR^1).⁶⁹¹⁷ The hydroxy or alkoxy groups in (283) can also be replaced by hydrogen, either under catalytic conditions or with formate. Acetaldehyde and urea mixtures cause the formation of a hydrate (283, $R^1 = H$, $R^2 = Me$, $R^3 = R^4 = H$).⁶⁹¹⁸ This readily loses water under the acidic conditions of the reaction to give (284), which in turn can add urea (reversibly)⁶⁹¹⁹ and acetaldehyde in sequence to give compounds like (283, $R^2 = Me$, $R^3 = R^4 = H$, H_2NCONH for OR^1) and (285); under some acidic conditions, a bispyrimidinone (286) was obtained.⁶⁹²⁰



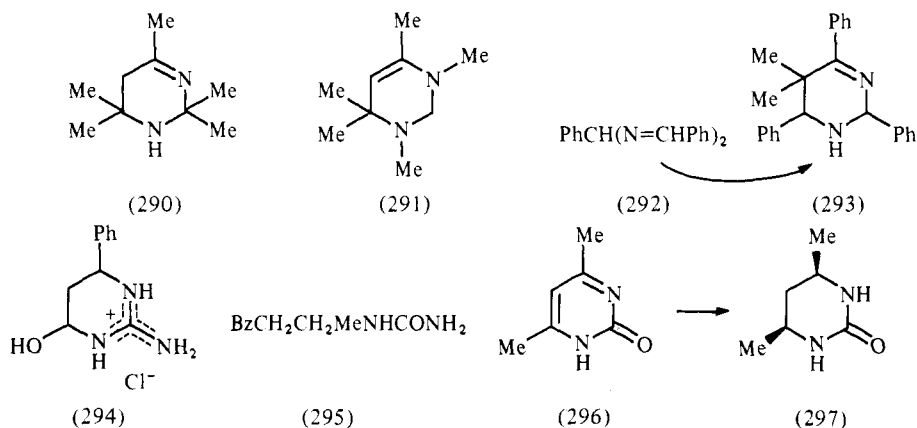
Like acetone, other saturated and unsaturated ketones form spirocyclic structures. The spiro compound obtained from the reaction of urea with the unsaturated ketone derived from the condensation of mesityl oxide and benzaldehyde has been resolved (33, PhCH for one CMe_2 group).⁵¹⁷¹ Mesityl oxide itself does not form a spiro compound with urea; the product is (287).⁶⁹²¹ *N*-Methylurea but not *N,N'*-dimethylurea reacts similarly.

The condensation of 1,3-dialdehydes, β -diketones, and β -ketoaldehydes with ureas and thioureas has been a significant component of the Principal Synthesis (see Ch. II, Sects. 2–4). If this reaction is contemplated as proceeding *via* addition of NH groups to the carbonyl

groups to give the dihydroxy intermediates (288), it is not surprising that such material loses two molecules of water under acidic conditions to give the heteroaromatic pyrimidin-2-one or its thio analogue. Although these are usually the main products, varying amounts of the bicyclic ureas (e.g. 289, $R^1 = R^4 = \text{Me}$, $R^2 = R^3 = \text{H}$), are formed and even become the major products when R^2 and R^3 are not hydrogen.⁶⁷²¹

The α -ureidoalkylation of olefines is possible only with strongly polarized alkenes unless a metal catalyst is used. Thus, urea reacts with a mixture of ethylene and oxygen in the presence of a complex palladium catalyst to give (283, $R^2 = \text{Me}$, $R^3 = R^4 = \text{H}$, H_2NCONH for OR^1).⁶⁹²²

The reaction between acetone and ammonia leading to the tetrahydro pyrimidine acetonin (290) continued to attract attention especially in the field of promoters which could be added to the usual ammonium or amine salt catalyst. Thus, one patent mentions 18 promoters, including a selection of alkali metal and ammonium salts, which brought about major increases in yields.⁶⁹²³ The interest was associated with the conversion of acetonin into 2,2,6,6-tetramethyl-4-oxopiperidine (triacetoneamine).⁶⁹²⁴ Other carbonyl compounds can be used in this reaction with ammonia,⁶⁹²⁵ eventually yielding 4-oxopiperidines.⁶⁹²⁶ A 1,2,3,4-tetrahydropyrimidine analogue (291) results from the cyclocondensation of mesityl oxide, methylamine, and formaldehyde in the presence of alkali;⁶⁹²⁹ ammonia can replace the amine.⁶⁹²⁸



Certain ketones, like isopropyl phenyl ketone, react with benzaldehyde N,N' -dibenzylidene amins (292), in which there is a 1,3-arrangement of nitrogen atoms, by Michael addition. Hydrolytic removal of an aldehyde molecule from the intermediate affords another 1,2,5,6-tetrahydropyrimidine (293).⁶⁹²⁹

Occasionally, α,β -unsaturated aldehydes react with guanine hydrochloride so that an intermediate hydrate like (294) can be isolated.⁶⁶⁶² The hydroxy group can be replaced by the 4-hydroxy-2,6-dimethylphenyl group upon treatment with 2,6-dimethylphenol. Similar hydrates are known from the intramolecular cyclization of β -ureidopropiophenones (295).⁶⁶⁸¹

C. From 1,3-Dihalogenopropane Derivatives (*H* 449, *E* 337)

There appear to be no recent examples of this condensation, but alkaline cyclization of a γ -chloroalkylurea, a likely intermediate from 1,3-dihalogenopropanes and urea, may be noted.⁶⁹³⁰

D. By Reduction of Pyrimidines or Dihydropyrimidines (*H* 450, *E* 337)

Catalytic reduction of 2-hydroxy-4,6-dimethylpyrimidine (296) over palladium at ambient conditions led to saturation of the ring and formation of the *cis*-stereoisomer (297).^{6931, 6932} A series of 1-benzyl-1,2-dihydro-2-oxypyrimidines was also catalytically reduced to the tetrahydropyrimidine stage,⁶⁹³³ as were *N*-methyl derivatives of 5-methoxycarbonyl-2-*p*-toluenesulfonamidopyrimidine,⁶⁹³⁴ and various *N*-alkyldihydropyrimidine-2-thiones.⁶⁵⁹⁶ Hydrogenation of 2-amino-4- α -hydroxyimino- α -methoxycarbonylmethylpyrimidine over palladium in aqueous methanol gave the tetrahydro compound, capreomycin, and its epimer.⁵²⁴³

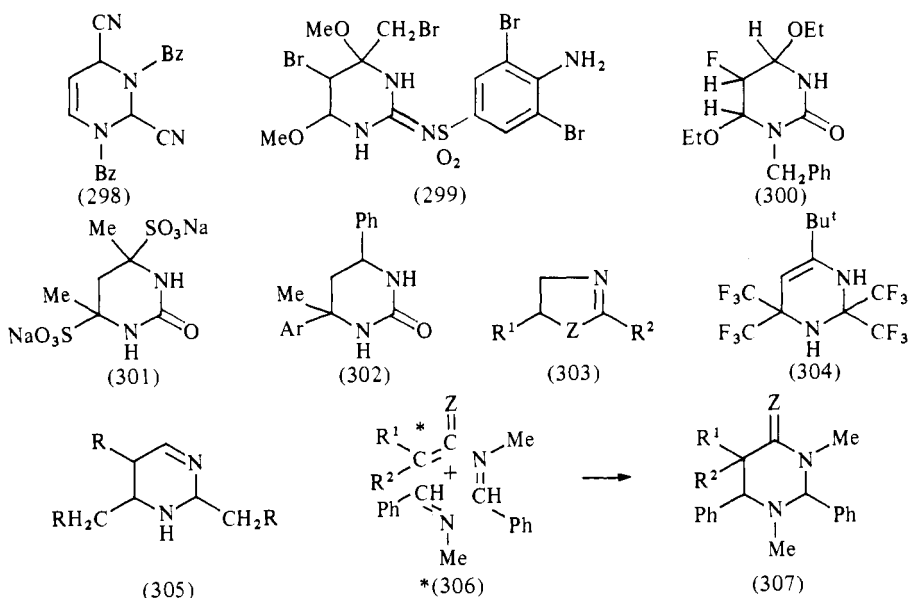
Of the other types of reducing agent used, lithium aluminum hydride has been pre-eminent in reducing the C4/C6 carbonyl group to CH_2 before a C2 carbonyl or a C6 carbonyl grouping in 5,6-dihydro-1-methyl-5,6-diphenyluracil,⁶⁹³⁶ and in other 4,6-dioxo⁶⁹³⁷ or 4-oxo-2-thio compounds.⁶⁹³⁸ The substituent, as well as the 2-oxo part, in 5-ethoxycarbonyl-1,6-dihydro-2-hydroxypyrimidine undergoes reduction.³⁶²⁹ The sodium borohydride reduction of the 4- and 6-carbonyl groups of various barbituric acids to a mixture of *cis*- and *trans*-diols has already been mentioned.⁶⁷²²

E. By Addition of Reagents Other than Hydrogen to the Pyrimidine Nucleus (*E* 341)

The first example of Reissert compound formation in a monocyclic azabenzene was discovered when pyrimidine reacted at room temperature with trimethylsilyl cyanide, benzoyl chloride, and a little

aluminum chloride as catalyst; the 1,2,3,4-tetrahydropyrimidine derivative (298) was obtained.⁶¹⁵¹

Bromination of methanolic 4-methyl-2-sulfanilamidopyrimidine occurs in the methyl substituent, the benzene ring, and the pyrimidine ring. The product is rendered sufficiently electron-deficient to attract two molecules of methanol in the final product (299).⁶⁹³⁹ Similarly, fluorination of certain *N*-alkylated 2-oxypyrimidine substrates is accompanied by addition of two solvent molecules with the formation of adducts like (300).⁴³⁹⁸ Likewise, the pyrimidine ring in (296) is susceptible to attack by nucleophiles so that it adds two molecules of sodium hydrogen sulfite to give (301).⁶⁷²¹



Carbon nucleophiles, in the shape of alkyl lithiums, also add to *N*-alkyldihydropyrimidines so that 1,6-dihydro-1-methyl-4,6-diphenylpyrimidine reacts with methyl lithium to afford the 1,2,5,6-tetrahydro-1,2-dimethyl derivative.⁶¹⁷⁸ Formation of a C—C bond between dihydropyrimidin-2-ones and hindered phenols like 2,6-xenol to give tetrahydropyrimidin-2-ones can be regarded as involving protonation at a β -carbon atom of the α,β -enamine system of the heterocycle followed by electrophilic attack of this species upon the vacant position of the phenol. Molecules like (302, Ar = 4-OH-3,5-Me₂C₆H₂) result.^{4349, 4351, 6664}

Electron-deficient olefines undergo photoaddition to the thiocarbonyl bond of a 5,6-dihydro-4-thiouracil to afford a spirocyclic thietane derivative with a formal tetrahydropyrimidine ring.⁶⁹⁴⁰

F. From Other Heterocyclic Substances (*E* 341)

The ring-expansion of 4,5-dihydroimidazoles (303, Z = NH or NR)⁶⁸⁹³ and oxazoles (303, Z = O)⁴⁵¹⁶ with 1,3-diaminopropanes leads to the incorporation of C2 plus its attached alkyl group as the corresponding feature of the hydroypyrimidine molecule [(303) + (270) → (272)]. Metal salts catalyze the condensation with the dihydroimidazole.⁶⁹⁴¹ Ring-expansion of fluorinated pyrazolines on treatment with bases afford 1,2,3,4-tetrahydropyrimidines like the hindered molecule (304).⁶⁹⁴³ Other ring-expansions to hydroypyrimidines take place during the thermolysis of oxazolin-5-one derived from *N*-acylated dipeptides.⁶⁹⁴⁴ A perhydro-1,3-oxazine undergoes thermal rearrangement to a reduced 1-benzoyl-3-phenylpyrimidin-2-one.⁶⁹⁴⁶

The facile deammoniation of 2,4,6-trialkylhexahydro-1,3,5-triazines, either by heat or traces of acid, leads to a mixture containing significant amounts of tetrahydropyrimidines (e.g. 305, R = Me, Et, or Pr).⁶⁹⁴⁷

G. Miscellaneous Preparations (*New*)

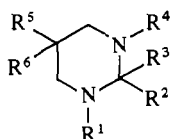
This residual repository of methods includes the cycloaddition of two molecules of azomethines like benzylidene methylamine with one molecule of ketenes. Thus, *t*-butylcyanoketene (306, R¹ = Bu^t, R² = CN, Z = O) gives *cis*- and *trans*-forms of the hydroypyrimidine (307)⁶⁹⁴⁸ and a whole series of thioketenes and various azomethines give the sulfur analogues thereof.⁶⁹⁴⁹

A Knoevenagel type condensation between one mole of nitroacetaldehyde dimethyl acetal and two moles of benzylidene methylamine gives a product similar to (307), that is, a 5-nitro-1,3-disubstituted 1,2,3,4-tetrahydropyrimidine.⁶⁹⁵⁰ Other complex cyclocondensations include those from a diarylacetylamide with methylamine and formaldehyde⁶⁹⁵¹ and bis(methoxycarbonyl)malononitrile dimer with *o*-substituted benzaldehydes.⁶⁹⁵²

3. Preparation of Hexahydropyrimidines (*H* 452, *E* 341)

The reaction between 1,3-diaminopropanes and aldehydes or ketones³⁶¹⁰ continued to be selected as a reliable, convenient, and highly yielding method for the synthesis of hexahydropyrimidines (308). However, a bias in favour of aldehydes instead of ketones is apparent.⁶⁹²⁷

The use of formaldehyde is pre-eminent among aldehydes. It can close the ring with 1,3-diaminopropane,^{3610, 6935} as well as with its *N*- and *N,N'*-substituted derivatives where the substituent(s) can vary from a series of alkyl groups, aryl groups, benzyl,^{3640, 6953} or acyl groups containing up to 18 carbon atoms.⁶⁹⁵⁴ An indication of the range of complexity of substituents is given by the synthesis of a series of nitrogen-mustard hexahydropyrimidines [e.g. 308, $R^1 = R^4 = p\text{-(ClCH}_2\text{CH}_2)_2\text{NC}_6\text{H}_4\text{CH}_2$].^{3640, 6955} The carbon atoms of the trimethylene chain, separating the two nitrogen atoms in the diamine, may in turn have alkyl groups attached to them in addition to any substituents already present on the nitrogen atoms.⁶⁹⁵⁶⁻⁶⁹⁵⁸



(308)

Formaldehyde has also been used in conjunction with hydrogen cyanide⁶⁹⁵⁹ or glycollonitrile⁶⁹⁶⁰ to give biscyanomethyl derivatives (like 308, $R^1 = R^4 = \text{CH}_2\text{CN}$, $R^2 = R^3 = R^5 = \text{H}$, $R^6 = \text{H}$ or OH).⁶⁹⁵⁹ In a gas-phase reactor packed with an alumina catalyst, formaldehyde and 1,3-diaminopropane yielded a mixture of 1-methyl- and 1,3-dimethylhexahydropyrimidine.⁵⁰⁶⁶ 1,3-Diaminopropane alone undergoes a high-temperature reaction over tungsten oxide to produce a mixture of hexahydropyrimidine and its 2-methyl and 2-ethyl derivatives.⁶⁹⁶¹ The yield of the 2-methyl compound could be improved by mixing the diamine with ethylene glycol and changing the catalyst to alumina-silicate.⁵⁰⁶⁵ Under the influence of palladium, 1,3-diaminopropane and allylamine undergo a complex cyclo-dehydrogenative condensation to form 2-ethylhexahydropyrimidine.⁶⁹⁰² An adventitious formation of hexahydropyrimidines occurred when some 1,3-diamines were recrystallized from alcoholic solvents containing traces of formaldehyde as impurity. This led to the appearance of anomalous ion peaks in the mass spectrum above the molecular ion peak expected for the diamine.⁶⁹⁶³

Both formaldehyde^{6964, 6965} and acetaldehyde⁶⁹⁶⁶ condense with the polyamine, spermidine, so that a six and not a seven-membered ring [308, $R^1 = R^2 = R^5 = R^6 = \text{H}$, $R^3 = \text{H}$ or Me , $R^4 = (\text{CH}_2)_4\text{NH}_2$] is formed. Use of the appropriately labeled formaldehyde has led to hexahydropyrimidines with either a $^{14}\text{CH}_2$ ⁶⁹³⁵ or a CD_2 ⁶⁹⁶⁷ group at C2 of the ring.

Another aliphatic aldehyde of note is pivalaldehyde, which gives the hindered molecule (308, $R^1 = R^4 = R^5 = R^6 = \text{Me}$, $R^2 = \text{H}$, $R^3 = \text{Bu}^t$). Higher aliphatic aldehydes,^{6947, 6968} aromatic aldehydes,^{6947, 6969} and heterocyclic aldehydes⁶⁹⁷⁰ cause no problem in the condensation reaction even though some quite crowded cyclic molecules are obtained.⁶⁹⁵⁶⁻⁶⁹⁵⁸ Buta-1,3-diyne behaves as a latent 1,3-dicarbonyl compound in its reactions with 1,3-diamines forming hexahydropyrimidines as well as tetrahydropyrimidines.^{6886, 6971}

Another direction in which formaldehyde reveals itself as a special case is in its ability to condense with primary nitroalkanes.⁶⁹⁷² In the presence of primary amines and an excess of formaldehyde, the 1,3-diol, for example $\text{O}_2\text{NCHR}(\text{CH}_2\text{OH})_2$, is formed and then undergoes cyclocondensation to give hexahydropyrimidines with a nitro group in the 5-position (e.g. 308, $R^1 = R^4 = \text{Ph}$, $R^2 = R^3 = R^5 = \text{H}$, $R^6 = \text{NO}_2$).⁶⁹⁷³ Some 5,5-dinitro derivatives were prepared by making use of 1,1-dinitroalkanes⁶⁹⁷⁴ or the bis(hydroxymethyl) compound⁶⁹⁷⁵ derived therefrom. 1,4-Dinitrobutane has also been examined in this type of reaction.⁶⁹⁷⁶ By contrast, nitroacetaldehyde oxime, although containing a primary nitro group, furnishes derivatives of a 5-nitrotetrahydropyrimidine upon reaction with formaldehyde and primary amines.⁶⁹⁷²

Amino acids⁶⁹⁷⁷ can provide the nitrogen atoms of the hydro-pyrimidine ring in these cyclocondensations with formaldehyde and primary nitroalkanes; so can ammonia, but the NH groups are then further alkylated with one or more molecules of the nitroalkane.^{6978, 6979} Formaldehyde and free primary amines can undergo cyclocondensation with other aldehydes like isobutyraldehyde to yield hexahydropyrimidines.⁶⁹⁸⁰

Surprisingly few hexahydropyrimidines are reported as arising by the reduction of a pyrimidine or of a di- or tetrahydropyrimidine. The solitary $\text{C}=\text{N}$ bond in various 1,2,5,6-tetrahydropyrimidines can be reduced by sodium borohydride,^{6928, 6947} but the more powerful lithium aluminum hydride is required to cope with the reduction of ring $\text{C}=\text{O}$ groups to CH_2 in tetrahydropyrimidin-4-ones,⁶⁹⁸¹ dihydouracils,⁶⁹⁸² and barbituric acids.⁶⁹⁸³ The electron-withdrawing nitro group in *N,N'*-disubstituted 1,2,3,4-tetrahydro-5-nitropyrimidine activated the 5,6-double bond to the point where it is reducible by (nucleophilic) sodium borohydride.⁶⁹⁸⁴ In the case of certain *N,N'*-substituents, catalytic reduction over platinum affects the 5,6-bond before the nitro substituent and a hexahydro-5-nitropyrimidine results.^{6984, 6985} Catalytic reduction over palladium of some chlorinated methylaminopyrimidines is claimed to reduce the ring to the hexa-

hydro stage while leaving chlorine atoms elsewhere in the molecule untouched.⁵⁸⁸¹

Although somewhat incongruous, it is possible to obtain a completely reduced pyrimidine ring from an oxidative process. Thus, alkaline ferricyanide oxidation of 3-dimethylaminopropylamine gives a little hexahydro-1-methylpyrimidine⁶⁹⁸⁶ and the copper-catalyzed aerial oxidation of spermine, 1,4-bis(γ -aminopropylamino)butane, gives a bicyclic compound which is formally a hexahydropyrimidine.⁶⁹⁸⁷

To end this section, mention is made of the Michael addition of various active methylene compounds CH_2XY to N,N' -dibenzylidene phenylmethane diamine (292) to give 2,4,6-triarylhexahydropyrimidines with the activating electron-withdrawing groups like CN, CONH_2 , CO_2Me , and NO_2 appearing at C5 of the ring.⁶⁹⁸⁸

4. Reactions of Reduced Pyrimidines (*H* 454, *E* 345)

A. Reductions (*H* 454, *E* 345)

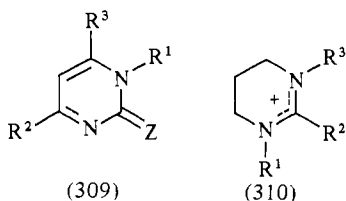
Since many reductions of di- and tetrahydropyrimidines have been discussed already in the relevant parts of Sects. 2 and 3 above, this section concentrates upon a few cases of over-reduction which leads to fission of the hydropyrimidine ring. Thus, prolonged sodium borohydride reduction (over 3 days) of some barbiturate drugs leads to reductive cleavage of the malonyl portion of the ring to give 2,2-disubstituted-1,3-diols.^{3555, 3557, 6991} However, 5,5-dibenzyl-1,3-dimethylbarbituric acid (181) proved exceptional in yielding the monohydric 2-benzyl-3-phenylpropanol.⁶⁷²² 2-Thiouracil (191, $\text{R}^1 = \text{R}^2 = \text{H}$) undergoes sodium borohydride reduction under the influence of ultraviolet light to afford 2-ureidopropanol.⁶⁶³⁸ At the 1,4,5,6-tetrahydro stage, di-isobutyl aluminum hydride reduces the ring to the hexahydro stage, which is followed by ring fission to a 1,3-diamine.⁶⁵⁵³ Thus, the 1-isopropyl-2-methyl derivative (272, $\text{R}^1 = \text{Pr}^i$, $\text{R}^2 = \text{Me}$) gives the open chain diamine (270, $\text{R}^1 = \text{Pr}^i$, $\text{R}^2 = \text{Et}$) while the analogous reduction of 1,2-bis(1',4',5',6'-tetrahydropyrimidin-2'-yl)ethane constitutes a convenient synthesis of spermine, 1,4-bis(γ -aminopropylamino)butane.⁶⁵⁵³

Lithium aluminum hydride caused reductive ring opening of 1-aryl-3,4,5,6-tetrahydro-4,6-dimethylpyrimidin-2-ones to the corresponding 2-arylamino-4-aminopentanes,⁶⁹⁹² the 2-carbonyl group of 1-aryl-3-methyl substrates was reduced by this reagent to CH_2 but the ring remained intact.

Catalytic hydrogenolysis of a 1,3-dibenzylhexahydropyrimidine over palladium caused ring opening to a 1,3-diamino compound containing only one of the benzyl groups.⁵¹⁴⁴

B. Oxidation (*H* 455, *E* 347)

The removal of hydrogen atoms from a dihydropyrimidine ring is aided by the gain in stability associated with aromatization. This could be one of the driving forces for the transfer of hydrogen under mild conditions from specimens of 1,2-, 1,4-, and 1,6-dihydropyrimidines to malachite green.⁶⁵⁹⁴ Dihydro-*o*-rotic acid (187, $R^1 = R^3 = H$, $R^2 = CO_2H$) and some of its derivatives undergo both dehydrogenation and decarboxylation at the graphite anode of an electrochemical cell to give the corresponding uracil.⁶⁹⁹³ Manganese dioxide was chosen for the dehydrogenation of certain 1,4-dihydropyrimidin-2-ones to the parent molecules [309, $R^1 = Me$, $R^2 = 3,4-(OMe)_2C_6H_3$, $R^3 = Ph$, $Z = O$] while dichlorodicyanobenzoquinone served for aromatization of the sulfur analogues.⁶⁹⁹⁴ For the facile dehydrogenation of several *N*-aryl derivatives of 1,4-dihydropyrimidin-2-ones to products such as (309, $R^1 = Ar$, $R^2 = R^3 = Me$), the tetrachloro-*p*-benzoquinone, chloranil, proved to be much more effective than manganese dioxide, potassium ferricyanide, or potassium permanganate.⁵⁹⁵¹ Dichlorodicyanoquinoline, mentioned as a dehydrogenating agent for various reduced 1-methylpyrimidin-2-ones, may well be a misprint for dichlorodicyanoquinone.⁴²⁴⁸ Manganese dioxide was also selected for the aromatization of reduced pyrimidine *N*-oxides of the type (279, $R^1 = R^2 = R^3 = H$, alkyl, or Ph; $R^4 = R^5 = R^6 = H$) to the fully heteroaromatic pyrimidine *N,N'*-dioxides.^{4861, 6995} Lead dioxide, on the other hand, oxidized the *N*-OH group of (279, $R^1 = R^3 = R^4 = R^5 = R^6 = Me$, $R^2 = H$) to the corresponding nitroxyl radical.⁶⁹⁰¹



Hexahydropyrimidines can be dehydrogenated by mercuric acetate,⁶⁹⁹⁶ *N*-bromosuccinimide,⁶⁹⁶⁹ or a palladium catalyst⁵¹⁴⁵ to salts containing the resonance-stabilized 1,4,5,6-tetrahydropyrimidinium cation, (for example 310, $R^1 = R^3 = CH_2Ph$, $R^2 = H$)⁶⁹⁹⁶ or (310,

$R^1 = R^3 = \text{Me}$, $R^2 = \text{Ar}$).⁶⁹⁶⁹ In the absence of catalysts, air disrupts the hexahydropyrimidine ring in some instances.⁵¹⁴⁵ Dehydrogenation to the free 1,4,5,6-tetrahydropyrimidine base is brought about by a nickel/kieselguhr catalyst.⁶⁹²⁸

On passage at high temperature over a palladium, platinum, or rhodium catalyst, a mixture of 1,3-diaminopropane and an aldehyde cyclizes to 2-alkylhexahydropyrimidine, which then dehydrogenates to the aromatic 2-alkylpyrimidine.⁵⁰⁶³ The dehydrogenative tendencies of hexahydropyrimidines are exploited in the use of 2-ethylhexahydropyrimidine as a source of hydrogen for the selective reduction of cyclic dienes.⁶⁹⁰³

C. Nitration and Nitrosation (*H* 455, *E* 348)

The synthesis of hexahydro-1,3-dinitroso(2-¹⁴C)pyrimidine has been reported to involve direct nitrosation of the parent compound.⁶⁹³⁵ The unlabeled compound, known for some time,³⁶¹⁰ was listed in a collection of *N*-nitroso compounds undergoing computer-assisted studies of structure/activity relationships with respect to carcinogenicity.⁶⁹⁹⁷ *N*-Mononitrosation has been observed with trimethylene-urea, the stable tautomeric form of 1,4,5,6-tetrahydro-2-hydroxypyrimidine (271, $R^1 = R^2 = \text{H}$, $X = \text{O}$).⁶⁹⁹⁸ The ring of the *N*-nitroso compound withstood subsequent reduction with zinc and water to give the corresponding *N*-amino compound. 5,6-Dihydro-1-nitrosopyrimidine⁷⁰⁰³ is a potent carcinogen.^{7004, 7005}

Hexahydro-1,3-dinitropyrimidine is known.⁶⁹⁹⁹ Hexahydro-1,3,5,5-tetranitropyrimidine has been prepared by an unusual displacement of isopropyl groups in hexahydro-1,3-di-isopropyl-5,5-dinitropyrimidine by nitric acid⁷⁰⁰⁰ and by a cyclocondensation of a polynitroguanidine derivative with formaldehyde.⁷⁰⁰¹ Nitration of 7-nitro-1,3,5-triazaadamantane in the presence of ammonium nitrate caused ring fission with the formation of a hexahydrotrinitropyrimidine.⁷⁰⁰²

D. Acylation (*H* 456, *E* 349)

Acetylation seems to have been the acylation studied in most detail. Acetyl chloride in benzene was recommended for acetylation of ring NH groups in the molecules of 1,4,5,6-tetrahydro-2-methylpyrimidine (272, $R^1 = \text{H}$, $R^2 = \text{Me}$) and its hexahydro 2- and 3-methyl counterparts.⁶⁹⁸⁹ Such *N*-acetylation is hazardous since the ring opens

readily to give 1,3-diacetamidopropane (270, $R^1 = R^2 = \text{Ac}$); this helps to explain the modest yields obtained on acetylation, benzylation, benzenesulfonation, or methanesulfonation.⁶⁹⁹⁰ It has been claimed that acetic anhydride is preferable for the synthesis of 1,3-diacetylhexahydro-2-methylenepyrimidine, akin to trapping an unstable tautomer of (272, $R^1 = \text{H}$, $R^2 = \text{Me}$).⁶⁹⁸⁹ Acetic anhydride acetylates one NH group of 1,4,5,6-tetrahydropyrimidine-2-thione (271, $R^1 = R^2 = \text{H}$, $X = \text{S}$) faster than the other, enabling both products to be isolated; the sulfur atom is unaffected.³⁶⁹⁰ Treatment of *S*-alkyl derivatives of the same thione with various acyl chlorides is a key step in the synthesis of exocyclic thio analogues of azacepham.⁶⁹⁶² Regioselective monoacetylation of the polyamine, spermidine, depends upon prior conversion with formaldehyde to "protected" spermidine, the hexahydropyrimidine [308, $R^1 = R^2 = R^3 = R^5 = R^6 = \text{H}$, $R^4 = (\text{CH}_2)_4\text{NH}_2$].⁶⁹⁶⁵ Protonation of the side-chain primary amino group and complexing this end of the molecule with 18-crown-6 ether opens the way to acetylation of the ring NH group with acetic anhydride in the presence of triethylamine. With the dihydropyrimidinone (36, $R = \text{Me}$) and its thio analogue, acetylating agents cause reaction, not at nitrogen, but at the methyl group with the formation of the corresponding 6-acetonyl compound.⁴³³⁶

E. Halogenation (*H* 457, *E* 350)

t-Butyl hypochlorite converts both NH groups of the cyclic urea, 1,4,5,6-tetrahydropyrimidin-2-one (271, $R^1 = R^2 = \text{H}$, $X = \text{O}$) into NCl groups in the unstable 1,3-dichloro compound (271, $R^1 = R^2 = \text{Cl}$, $X = \text{O}$). Its 4,4,6,6-tetramethyl derivative, however, yields more stable mono- and dichloro compounds on similar treatment.⁷⁰⁰⁶

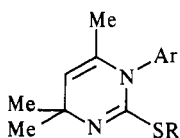
F. Metatheses of Mercapto and Hydroxy Compounds (*H* 457, *E* 350)

Although nmr results indicate that dihydromercaptopyrimidines possess the more stable tautomeric thione structure, for example (110, $R = \text{Ar}$), methyl iodide under phase-transfer conditions methylates at sulfur rather than nitrogen to give the methylthio derivative (311, $R = \text{Me}$) of the unstable tautomer.⁶⁶²⁷ However, 1,2-dibromoethane and α -halogenoketones cause alkylation at both sulfur and a nitrogen, thereby leading to fused bicyclic compounds.⁷⁰⁰⁷

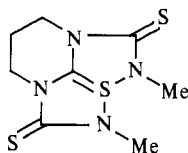
The methylthio group is displaced by nucleophiles; 1,4,5,6-

tetrahydro-2-methylthiopyrimidine (272, $R^1 = H$, $R^2 = SMe$) and hydroxylamine afford the unstable cyclic guanidine (271, $R^1 = R^2 = H$, $X = NOH$).^{7008, 7009} Hydrazine behaves similarly to give the analogue (271, $R^1 = R^2 = H$, $X = NNH_2$).⁷⁰¹⁰ With diketene, a bicyclic compound is formed which undergoes hydrolysis to (271, $R^1 = H$, $R^2 = COCH_2Ac$, $X = O$).⁶⁸⁷² The tetrahydro-2-phenacylthiopyrimidine (272, $R^1 = H$, $R^2 = SCH_2Bz$)⁷⁰¹² extruded sulfur on treatment with triphenylphosphine to form (271, $R^1 = R^2 = H$, $X = CHBz$),⁷⁰¹¹ and reacts with methyl thiocyanate to give a symmetrical tricyclic compound in which one sulfur atom seems to have a covalency of four (312).⁷⁰¹³

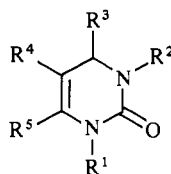
The methoxy group may also be displaced. Thus, 1,4,5,6-tetrahydro-2-methoxypyrimidine and hydrazine give the above mentioned product (271, $R^1 = R^2 = H$, $X = NNH_2$).⁷⁰¹⁰ It also cyclizes with 2-amino-3-ethoxycarbonylquinoline to give a tetracyclic compound.⁷⁰¹⁴



(311)



(312)



(313)

Like its dihydro counterpart, 1,4,5,6-tetrahydropyrimidine-2-thione reacts with halogeno ketones under dehydrating conditions to yield fused bicyclic products like thiazolo[3,2-*a*]pyrimidines.⁷⁰¹⁵

Phosphorus pentasulfide (sometimes in the presence of a tertiary base) remains the reagent of choice for the conversion of an oxo into a thio substituent at the pyrimidine or hydropyrimidine level.^{6387, 7016}

G. *N*-Alkylation (*H* 458, *E* 350)

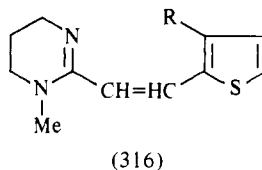
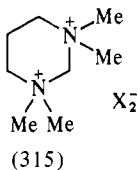
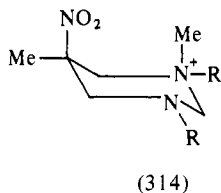
N-Alkylation can be carried out by a variety of reagents although a $C=S/C-SH$ group will compete for the reagent. Thus, a cyclic thiourea undergoes stepwise alkylation with alkyl halides in alkali containing a quaternary ammonium salt as a phase-transfer agent: first at sulfur, then at N1, and finally at N3 to give a thiouronium salt. This was hydrolyzed to the 2-oxo compound so that the net result was (271, $R^1 = R^2 = H$, $X = S$) $\rightarrow$ (271, $R^1 = R^2 = Me$ or Et , $X = O$).⁷⁰¹⁷ In contrast, oxygen analogues do not compete with nitrogen as sites for alkylation; the disodio salt of the cyclic urea (271, $R^1 = R^2 = H$, $X =$

O) reacts with β -dimethylaminoethyl chloride to give alkyl groups on each nitrogen in (271, $R^1 = R^2 = \text{CH}_2\text{CH}_2\text{NMe}_2$, $X = \text{O}$). The exocyclic dimethylamino groups can be quaternized subsequently with methyl iodide and treated with silver oxide (Hofmann reaction) to give the divinyl compound (271, $R^1 = R^2 = \text{CH}:\text{CH}_2$, $X = \text{O}$), suitable for polymerizations.⁷⁰¹⁸ By contrast, in another (dihydro) case (313, $R^1 = \text{Na}$, $R^2 = R^3 = \text{Me}$, $R^4 = \text{H}$, $R^5 = \text{Ph}$) the negative charge in the (anionic) sodio derivative is delocalized to the unblocked C5 position of the enamine system so that addition occurs across the activated double bond of acrylonitrile to give (313, $R^1 = \text{H}$, $R^2 = R^3 = \text{Me}$, $R^4 = \text{CH}_2\text{CH}_2\text{CN}$, $R^5 = \text{Ph}$), a C-alkylation product.⁶⁶¹⁴ If the 5-position is blocked and deactivated, for example by an electron-withdrawing ethoxycarbonyl group, *N,N'*-dialkylation occurs to give a compound such as (313, $R^1 = R^2 = \text{CH}_2\text{CH}_2\text{CN}$, $R^3 = R^5 = \text{H}$, $R^4 = \text{CO}_2\text{Et}$).³⁶⁷² The nitrile groups in such compounds can be hydrogenated over nickel under vigorous conditions to yield aminomethyl groups without affecting the hydropyrimidine ring.⁷⁰¹⁹ Other examples are known in which aldehyde groups on side chains are reductively converted into hydroxymethyl groups.⁷⁰²⁰ Such aldehyde groups resulted from sequential reactions with formaldehyde and isobutyraldehyde.^{7021, 7022}

Formaldehyde is a special case again, ranging from being a vital component of both the Mannich aminomethylation reaction, through enabling aldehydes to undergo a mixed ureidoalkylation reaction upon nitrogen, to taking part in the Leuckart reductive methylation involving formic acid. The last has been used to convert ring NH groupings into NMe groupings.⁶⁹⁷⁸ The Mannich reaction causes progressive transformation of one and then two ring-NH groupings of the trimethyleneurea or its sulfur analogue (271, $R^1 = R^2 = \text{H}$, $X = \text{O}$ or S) into $\text{N-CH}_2\text{NR}_2$ groupings when a secondary amine like morpholine is used in conjunction with formaldehyde.⁷⁰²³ At the dihydropyrimidine level, complications arise in the presence of an activated allylic C-Me region in the molecule because reaction occurs first at this point³⁶⁸¹ as with, for example (313, $R^5 = \text{Me}$),⁴³⁴⁷ which subsequently aminoalkylates at the 5-position of the pyrimidine ring.⁴³⁵² With hexahydropyrimidines, reductive alkylation can take place between a 1- β -hydroxyethyl compound and a ketone like octan-2-one using hydrogen under pressure and a platinum catalyst to give (271, $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{CHMe}(\text{CH}_2)_5\text{Me}$, $X = \text{O}$).⁷⁰²⁴

The stereochemistry of quaternization of *N,N'*-dialkylhexahydropyrimidines by alkyl halides has been investigated with those compounds possessing an axial 5-nitro group. The conclusion was that there

was a preference for axial methylation to afford compounds like (314, $R = \text{Et}$ or Pr^i). Large equatorial alkyl groups on the ring nitrogen atoms (314, $R = \text{Bu}^t$ or C_6H_{11}) totally prevented quaternization.⁷⁰²⁵ However, it is possible to force two molecules of alkylating agent to quaternize both nitrogen atoms in hexahydro-1,3-dimethylpyrimidine by using the very active agent, trimethyloxonium borofluoride; despite the electrostatic repulsion between the two close positive charges, various solid salts of the dication (315, $X = \text{Br}, \text{Cl}, \text{or } \text{BF}_4$) can be isolated.⁷⁰²⁶ β -Anilinoethyl bromide has been used recently as an alkylating agent with 1-alkylhexahydropyrimidines to give (308, $R^2 = R^3 = R^5 = R^6 = \text{H}$, $R^1 = \text{alkyl}$ or CH_2Ph , $R^4 = \text{CH}_2\text{CH}_2\text{NHPh}$).⁷⁰²⁷



H. Other Reactions (*H* 459, *E* 351)

(1) *Non-Hydrogenolytic Ring Opening* (*E* 351)

The hydrolysis of some reduced pyrimidines has turned out to be a convenient way of preparing certain amino-substituted acyclic compounds. Thus, hydrolysis of the stereoisomeric cyclic urea (297) by aqueous acid, followed by liberation of the free amine with alkali, gives the meso form of 2,4-diaminopentane.⁶⁹³² Similarly, alkaline or acidic hydrolysis of dihydrouracils is recommended as a means of obtaining β -amino acids without elimination to unsaturated products.^{6572, 7028} Such hydrolyses involve splitting the ring along the 1,2- and 3,4-bonds. The catabolism of dihydrouracil involves ring-opening in the 3,4-region to give β -ureidopropionic acid.⁷⁰²⁹

Derivatization of 1,4,5,6-tetrahydropyrimidines unsubstituted at C2 is a chancy operation because it is frequently accompanied by hydrolytic ring fission. The parent compound (8) together with 1-fluoro-2,4-dinitrobenzene gave the ring-opened formamido compound [270, $R^1 = \text{CHO}$, $R^2 = \text{C}_6\text{H}_2(\text{NO}_2)_2$].⁷⁰³⁰ The 1,2-diphenyl compound (272, $R^1 = R^2 = \text{Ph}$) lasts significantly longer even in aqueous alkali but it eventually gives the acyclic diacylated diamine (270, $R^1 = R^2 = \text{Bz}$); in comparison with its 5-membered imidazolinium counterpart, no isolable intermediate was involved in this hydrolysis.⁷⁰³¹ Hydrolytic

ring cleavage of derivatives of the cyclic thiourea (271, $R^1 = R^2 = H$, $X = S$) has also been used to prepare unsymmetrical sulfur derivatives of 1,3-diaminopropane.⁷⁰³² Aqueous acid also brings about hydrolytic fission of the hexahydropyrimidine ring to give the 1,3-diamino compound and carbonyl-containing compound,⁶⁹⁴⁷ from which the hexahydropyrimidine was originally obtained in many cases (Sect. 3).

(2) *Reactions with Aldehydes (E 353)*

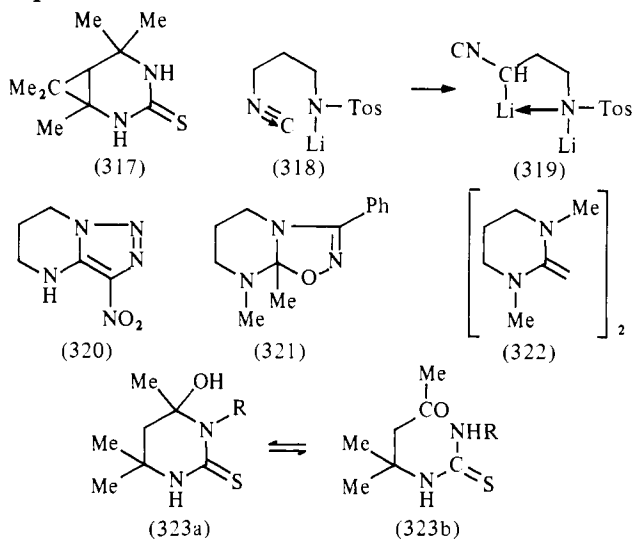
The 2-methyl group of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine (272, $R^1 = R^2 = Me$) is activated by the electron-withdrawing $C=N$ grouping in the ring. It was pointed out previously (E 353) that this molecule would react with a series of aldehydes, especially under dehydrating conditions, to give a conjugated system (316). This series of aldehydes has been extended to include 2-formylthiophene and its 3-methyl derivative.⁷⁰³³⁻⁷⁰³⁵ Since the products, in the form of their tartrates, proved to be potent anthelmintic agents [pyrantel: (316, $R = H$); morantel: (316, $R = Me$)],^{7036, 7037} interest has been fueled in the preparation of analogues and isotopically labeled molecules.^{5461, 7038-7040} A variant on such reactions is condensation with an aromatic aldehyde in the presence of sulfur to give a thioacylketene aminal (271: $R^1 = Me$, Et , or C_6H_{11} ; $R^2 = H$; $X = ArC(:S)CH :$).⁷⁰⁴¹

(3) *Miscellaneous Reactions (E 355)*

The 5,6-double bond in certain 1,4(1,6)-dihydro-6-methylpyrimidin-2-ones (19, $:O$ for $:NR$) activates the methyl group so that it undergoes allylic bromination⁷⁰⁴² and the bromine does not add to the double bond. In the sulfur analogue, the 5,6-double bond does behave as such, and dichlorocarbene gives the diazobicycloheptanethione (317).⁷⁰⁴³ The tosyl derivative of 1,4,5,6-tetrahydropyrimidine (272, $R^1 = tosyl$, $R^2 = H$) exchanges the hydrogen atom on C2 for lithium by treatment with butyllithium; the lithio derivative ring-opens to (318), which reacts with a second molecule of butyllithium to give a dilithio compound, postulated as (319).⁷⁰⁴⁴

The nitromethylene compounds (271, $R^1 = R^2 = H$, $X = O_2NCH :$) react with 4-chlorobenzenesulphonyl azide to form fused bicyclic compounds like (320).⁷⁰⁴⁵ 1,4,5,6-Tetrahydro-1,2-dimethylpyrimidine has another reactive site besides its 2-methyl group; cycloaddition with benzonitrile oxide involves the ring $C=N$ bond to give another bicyclic

molecule (321).⁷⁰⁴⁶ 1,4,5,6-Tetrahydropyrimidine-2-thione (271, $R^1 = R^2 = H$, $X = S$) is a cyclic thiourea in which the relatively acidic NH protons react with ethyl magnesium bromide to give ethane and the magnesium complex (271, $R^1 = R^2 = MgBr$). This complex has attracted attention recently as an excellent transcarboxylating agent for ketones and so forth.⁷⁰⁴⁷ The molecules of the oxygen analogue (271, $R^1 = R^2 = H$, $X = O$), when incorporated into the macrocyclic rings of hemispherands, become the main hydrogen bond accepting sites when complexes are formed with the cations of guest molecules like *t*-butyl ammonium picrate.⁷⁰⁴⁸



Bis(1,4,5,6-tetrahydro-1,3-dimethylpyrimidine-2-ylidene) (322) is an electron-rich olefin which forms carbene complexes with molybdenum and tungsten hexacarbonyls.^{7049, 7050} Methoxide ion at a high temperature reductively removes the nitro group from hexahydro-1,3,5-trimethyl-5-nitropyrimidine.⁷⁰⁵¹

Organo lithiums introduce substituents into the 2-, 4-, and 6-positions of the pyrimidine ring but not into the 5-position which is inert to nucleophilic attack. However, photolysis of 4-aryl-1,4(3,4)-dihydropyrimidines leads to rearrangement, *via* an intermediate diazabicyclohexane,⁷⁰⁵² to the isomeric 5-substituted dihydro species.⁴⁶⁹⁹ These can be aromatized oxidatively by aerial oxygen or permanganate.⁴⁶⁹⁹ Some 4-heteroaryl analogues like the thien-2-yl or thien-3-yl compounds also isomerize under these photolytic conditions.⁶⁶³¹ Others, like the pyridin-2 (or 4)-yl species, undergo ring contraction to give 4-heteroarylimidazole derivatives.⁶⁶⁵⁶

5. Properties of Reduced Pyrimidines (*E* 355)

A. Ionization (*E* 355)

One of the few systematic investigations into pK_a values during the present period is that of 1,2-diaryl-1,4,5,6-tetrahydropyrimidines.⁷⁰⁵³ Both aryl substituents markedly reduce the pK_a value from that for tetrahydropyrimidine itself (13.0) to a lower limit of 9.16 when both aryl groups are *p*-nitrophenyl. The ionization constants of the bases were related by an expression to the rate constants for their alkaline hydrolysis. These six-membered cyclic amidines were also found to have pK_a values above those of their seven-, eight-, and five-membered cyclic counterparts.⁷⁰⁵⁴ Isolated pK_a determinations recorded include those of 11.42 and 11.57 for 5,6-dihydrouracil and 5,6-dihydrothymine, respectively,⁷⁰⁵⁵ and some work on dihydrouracil in dimethyl sulfoxide solution.⁷⁰⁵⁶

It is interesting to note that although hexahydropyrimidine and its 1,3-dimethyl derivative do not last long enough in aqueous acids for both their pK_a values to be determined, it is still possible to isolate both a mono- and a dihydrochloride of the 1,3-dimethyl compound by working in anhydrous organic media.⁷⁰²⁶

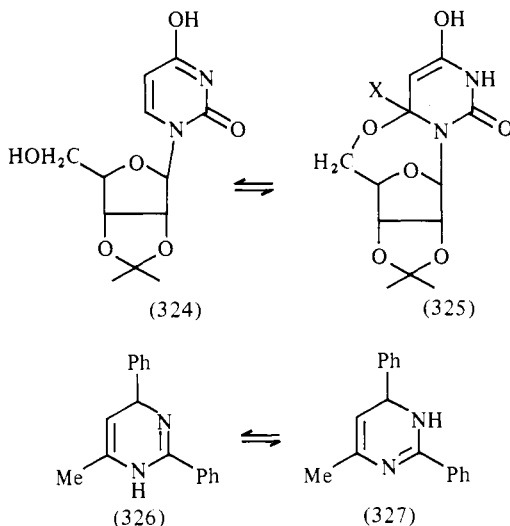
B. Tautomerism (*E* 357)

Examples of *ring-chain tautomerism* continue to appear in the hydropyrimidine series. They include the hydroxy compound (323, R = Ar), in which infrared and ultraviolet spectra indicate the presence of a tautomeric equilibrium [(323a) $\rightleftharpoons$ (323b)].⁷⁰⁵⁷ Tautomers have also been detected when the substituent on N3 in (323) is a complex protected-glycosyl substituent,⁷⁰⁵⁸ and in other systems.⁷⁰⁵⁹ In the case of the tetrahydropyrimidine *N,N'*-dioxide (279, R⁴ = H, R⁵ = Me), a mixture of cyclic and open-chain tautomers was obtained.⁶⁴⁶⁸

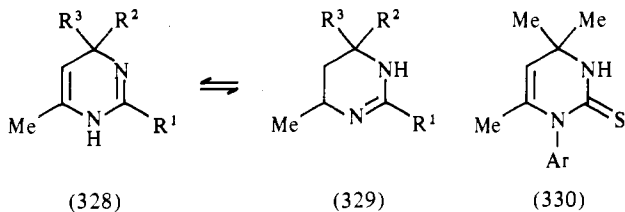
The isopropylidene derivative of 3-(β -D-ribofuranosyl)uracil (isouridine) (324) exists in solution as a mixture with the corresponding O⁶,5'-cyclonucleoside (325, X = H) in which the pyrimidine ring has been reduced by an internal addition.^{6630, 7060} Chloranil, otherwise a good dehydrogenating agent for dihydropyrimidin-2-ones,⁵⁹⁵¹ caused introduction of a chlorine atom to give (325, X = Cl), which in turn could be exchanged for a cyano group on treatment with potassium cyanide in anhydrous dimethyl sulfoxide. Likewise, treatment of the chloro compound with aqueous alkali caused replacement of the chloro

by a hydroxy substituent, which was followed by ring opening to afford (324); this underwent clean deprotection by strong cation exchange resin to give isouridine itself.

Ring-chain equilibria have also been observed in trifluoroacetic acid solutions of hexahydro-1,3-dimethylpyrimidine⁶⁹⁶⁷ and various 2-alkyl- or 2-aryl-1,2,3,4-tetrahydro-5-nitropyrimidines.⁷⁰⁶¹



Only recently has the question of the structure and relative stabilities of the tautomeric 1,4- and 1,6-dihydropyrimidines, that is, *annular tautomerism*, been investigated with the battery of modern spectroscopic techniques now available. Thus, it has been mentioned that 1,4-dihydro-6-methyl-2,4-diphenylpyrimidine exists as such in the solid state.⁶⁵⁴⁹ As revealed by the 270 MHz proton nmr spectrum, it is also the major component in the tautomeric equilibrium [(326) $\rightleftharpoons$ (327)] which exists in very dilute solutions in aprotic dipolar solvents like deuterated dimethyl sulfoxide. In such a medium, the rate of proton transfer between the two nitrogen atoms is slowed down because of strong intermolecular hydrogen bonding with the solvent. Care was taken to free the solvent from water, hydrogen ions, and paramagnetic impurities, all of which speeded up hydrogen transfer and resulted in averaged spectra. Dilute deuteriochloroform solutions exhibited an averaged spectrum except at low temperature (-50°C) under argon after the solution had been filtered through alumina to remove traces of acidic impurities. Under these circumstances, and despite the lack of hydrogen bond stabilization, peaks due to both tautomers were observed and it was concluded that now the 1,6-

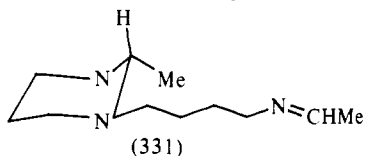


dihydro compound was in slight excess. Tautomeric equilibria could also be detected in deuterated dimethyl sulfoxide solutions of other 2-substituted-4(6)-methyl compounds (328/329, $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{Ph}$ or furan-2-yl; or $R^1 = \text{NH}_2$, $R^2 = R^3 = \text{Me}$).^{4351, 6548, 6551} Fewer substituents around the pyrimidine ring seem to render it impossible to observe the equilibrium even at lower temperatures.^{4495, 6178, 6546, 6656}

The advent of ^{13}C nmr spectrometers has aided the detection of other types of tautomerizations involving migration of hydrogen between two heteroatoms. In particular, the thione–thiol equilibrium in the case of the dihydro compound (330) has been settled in favor of the structure shown because of the presence of a peak at 176.5 ppm representing C2.⁶⁶²⁷

C. Nuclear Magnetic Resonance (E 358)

Instruments for *proton nmr spectra* have been widely available for at least a quarter of a century so that it is commonplace for data on 60–100 MHz instruments to be buried as a matter of course in the experimental sections in many of the papers on hydropyrimidines quoted in Sects. 1–3 above. However, over the last 10 years access to 270–500 MHz instruments has increased markedly. A spectacular demonstration of the power of such instruments involved the condensation of spermidine with acetaldehyde to give a chair (331) with equatorial substituents: at 400 MHz this compound exhibited a spectrum which on first-order analysis yielded chemical shifts and coupling constants for all but three protons in the molecule!⁶⁹⁶⁶ Likewise, 270 MHz ^1H nmr spectra proved invaluable in studying the photohydrates of cytidine, uridine, and cytidylic acids.⁶⁷⁹⁶



Some useful ^{13}C *nmr spectra* for hydropyrimidines have also been reported. Thus, data for the nuclear carbon atoms and for the 4-methyl group in a series of arylidihydro-4-methylpyrimidines have appeared,⁶⁵⁸⁰ the shielding effects in hexahydro-*N*-nitrosopyrimidines have been studied effectively,⁶⁹⁹⁹ and the tautomeric equilibria in *N*-monoalkylated and *N,N'*-dialkylated 1,4,5,6-tetrahydropyrimidine-2-thiones have been elucidated.⁷¹¹⁸

Although ^{15}N *nmr data* have been largely neglected because of experimental difficulty, some examples have begun to appear in the hydropyrimidine field. For example, an examination of the natural product, viomycin, by ^{15}N -spectra (natural abundance) at *c.* 36 MHz, helped to confirm the nature of a suspected tetrahydrohydroxypyrimidine as one part of the molecule.⁷⁰⁶² Likewise, such data for *N*-amino- and *N,N'*-diaminodihydrouracils proved critical for distinguishing the structures from those of the isomeric oxazines.⁶⁶⁵⁷ Other useful cases have been recorded.⁶⁹⁰⁰

Some uses for *sundry nmr data* are exemplified in the following cases. The stereochemical arrangements 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 ($J_{\text{H6},\text{F}}$) in the proton *nmr spectra* and were confirmed subsequently by a single crystal X-ray analysis of one of the compounds, *cis*-6-ethoxy-5-fluoro-5,6-dihydrouracil.⁶⁶²³ *Nmr* and other spectroscopic evidence elicited the existence of restricted rotation about aryl-nitrogen bonds in 1-aryl-1,4-dihydropyrimidine-2-thiones and enabled parameters like energy of activation to be abstracted.⁶⁶²⁷

D. Conformation (*E* 360)

There is clearly overlap between this and the previous section in view of the utility of coupling constants in elucidating conformation(s). Thus, certain 1,4-dihydropyrimidin-2-ones appear to undergo conformational transitions of the boat-boat type,⁷⁰⁶³ and a half-chair conformation was considered likely for the photohydrate of 1-ethyl-dihydrouracil.⁶⁸⁶⁶

A significant number of hydropyrimidines, especially with nucleic acid connections, has been examined by X-ray crystallography. Thus for one enantiomer of 5,6-dihydro-5-hydroxythymidine and for 5,6-dihydrouracil, a twisted half-chair conformation for the reduced pyrimidine ring with C5 and C6 on opposite sides of the plane of the other four ring atoms, was found.^{7065, 7068} Ring puckering was also

observed in the 5,6-dihydro derivatives of 2-thiouracil and 2,4-dithiouracil, 5,6-dihydrouridine, the bisulfite adduct of 2-thiouracil, the combined bisulfite and hydroxylamine adduct of cytosine, and 5,6-dihydro-6-methyluracil.^{6852, 6857, 7064, 7066, 7067, 7069, 7070}

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. The complexity of the situation is illustrated by the fact that in discussions of variable temperature ¹H and ¹³C nmr of 1,3-diethylhexahydro-2-methylpyrimidine, equilibria involving no less than eight conformers (all with chair-shaped rings) were postulated.⁷⁰⁷¹ In considering the various inversion barriers it was important to define clearly the ground state.⁷⁰⁷³ Such energy barriers to ring inversion are about 11 kcal mol⁻¹ while the barrier to nitrogen inversion is considerably smaller.⁷⁰⁷² Hexahydro-1-methylpyrimidine has an N-H in axial setting. In the 1,3-dimethyl homologue, diequatorial and axial-equatorial conformations are present in about equal amounts. Interpolation of a 2-methyl substituent into the latter molecule causes a predominance of conformers with the 2-methyl group equatorial but in 1,3-diethylhexahydro-2-methylpyrimidine, the position is reversed because of the substantial buttressing effect of the ethyl groups.⁷⁰⁷¹ Other conformations have been investigated.^{6900, 7117}

E. Mass Spectra (E 362)

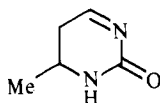
Little new information on the mass spectra of hydropyrimidines has appeared. However, mass spectra have been used to identify the products obtained from the radiolysis of thymine⁷⁰⁷⁴ and to differentiate between some unsymmetrical dihydrobarbiturate isomers.⁷⁰⁷⁵

F. Applications of Hydropyrimidines (E 366)

Reference to the indices of *Chemical Abstracts* under, for example, 1,4,5,6-tetrahydropyrimidin-2-one and its derivatives, reveals the impossibility of making more than a small subjective selection from the multitude of uses, both biological and otherwise, to which hydropyrimidines are put.

At the dihydro level, the dihydromethylpyrimidinone (332) has been claimed both as an hypnotic and as a fertilizer, surely a prime example of broad spectrum activity.⁶⁹¹⁹ 1-Acetyl- and 1,3-diacetyl-5,6-dihydrouracil appear to be good activators for sodium perborate

bleaching agent in cleaning solutions.⁷⁰⁷⁶ 5,5-Dichloro-5,6-dihydro-3-isopropyl-6-methoxy-6-trifluoromethyluracil, first used as an experimental herbicide, was found to have stimulated the growth of nitrogen-fixing bacteria in the soil.⁷⁰⁸⁰ A dihydrohydroxynitrothymine inhibited the growth of some tumor cells and bacteria,⁷⁰⁸¹ and various 5-alkoxy-carbonyl-5-fluoro-5,6-dihydrouracils have attracted attention as anti-tumor agents akin to 5-fluorouracil.^{6623, 7082}



(332)

Some derivatives of dihydropyrimidine-2-one act as insect chemosterilants⁷⁰⁸³ and nematocidal agents.⁷⁰⁸⁴ Some analogous dihydropyrimidine-2-thiones, especially those with substitution patterns resulting from mesityl oxide as a starting material, exhibit spasmolytic, anti-histaminic, and anti-inflammatory activities;⁷⁰⁸⁵ they also inhibit dopamine β -hydroxylation *in vivo*⁷⁰⁸⁶ and have a moderate radioprotectant action.⁷⁰⁸⁷ Various 1-amino and 1-substituted-amino derivatives form useful complexes with a series of heavy metals,⁷⁰⁸⁸ especially in the area of photometric determination of ruthenium, rhenium, and iridium.^{7078, 7079}

At the tetrahydro level, 1,4,5,6-tetrahydropyrimidines have been pre-eminent in the variety of uses to which they have been put. On the inanimate scene, such derivatives have been used in polymeric materials used as quenchers for fluorescent whitening agents,⁷⁰⁸⁹ as antioxidants, vulcanization accelerators, and other additives used to improve rubber and tire technology,⁷⁰⁹⁰⁻⁷⁰⁹⁴ and (when they contain long alkyl substituents at the 1- or 2-position) as anti-icing additives⁷⁰⁹⁵ and corrosion inhibitors in fuels and lubricants.⁷⁰⁹⁶ The cationic derivatives of 2-stearyl derivatives of such tetrahydropyrimidines can be used as a dyeing aid for polyamide fibres,⁷⁰⁹⁷ while the undecyl analogues solubilize anionic dyes.⁷⁰⁹⁸

Besides accelerating the formation of urethane foams, tetrahydropyrimidines are also used for curing epoxy resins for use as coatings, castings, sealants and adhesives.⁷¹⁰⁰ The 1-methyl derivative is useful as a cycloamidine desensitizer for pressure-sensitive copying papers,⁷⁰⁷⁷ while the 1-ethyl-2-undecyl compound is included as an antistatic formulation in polypropene.⁷¹⁰²

In the living world, 2-arylamino-1,4,5,6-tetrahydropyrimidines uncouple phosphorylation in isolated spinach chloroplasts⁷¹⁰³ and various long-chain (8–20 carbon atoms) 2-alkylthio derivatives accelerate the maturation of sugar cane and increase its sugar content.⁷¹⁰⁴ In contrast, 1-dodecyl-1,4,5,6-tetrahydro-2-methylpyrimidine is used for defoliation purposes in agriculture.⁷¹⁰⁵ Insecticidal activity is shown by unsaturated ketonic derivatives of 2-hydrazino-1,4,5,6-tetrahydropyrimidine.⁷¹⁰⁶ The important anthelmintics, morantel and pyrantel, have been mentioned above; 2-nitromethylene derivatives function as bactericides, protozoacides, and insecticides,^{7101, 7107} and 2-heptadecyl-1,4,5,6-tetrahydro-4,4,6-trimethylpyrimidine proved very effective in controlling biodeterioration in stored wood chips.⁷¹⁰⁸ On the human plane, the tetrahydropyrimidine ring appears in compounds that are hypertensives,⁷¹⁰⁹ vasoconstrictors,⁷¹¹⁰ nasal decongestants,⁷¹¹⁰ and gastric acid secretion inhibitors.⁷¹¹¹

Among other types of tetrahydropyrimidine, mention must be made of tetrahydro-4-hydroxy-1- β -D-ribofuranosylpyrimidin-2-one, tetrahydrouridine, which is a potent inhibitor of cytidine deaminase. Used in conjunction with 1- β -D-arabinofuranosylcytosine (ara-C), an important antileukaemic, immunosuppressive, and anti-DNA viral active compound,⁷¹¹² it hinders deamination of ara-C thereby assisting in the effective conversion of the latter to its active 5'-phosphate within the cell.^{7113, 7114}

At the hexahydropyrimidine level, *N,N'*-bis- β -chloropropionyl derivatives have been shown to be effective against Ehrlich's carcinoma, LK lymphoma, as well as *Staphylococcus aureus*.⁷¹¹⁵ 5-Ethylhexahydro-4,6-dihydroxy-5-phenylpyrimidine, "Mizodin," has been known for some time for its neurotropic properties.⁷¹¹⁶

CHAPTER XIII

The Ionization and Spectra of Pyrimidines (*H* 464, *E* 368)

Many ionization constants and spectral data, both electronic and ^1H nmr, have been reported since 1970 but little new in principle has emerged. In contrast, ^{15}N , ^{14}N , and ^{13}C nmr spectra have become widely available for the first time. Accordingly, this supplementary chapter consists mainly of two parts: Table XVI, comprising new $\text{p}K_a$ values reported since 1970, and an essay by Dr. M. David Fenn on the non-proton nmr spectra of pyrimidines with tables of chemical shifts and other data. The mass spectra of heterocycles, including the available data on pyrimidines, has been reviewed elsewhere.⁶⁴¹⁰

1. The Ionization Constants of Pyrimidines (*H* 464, *E* 368)

Modern procedures for the determination of ionization constants have been described in detail,⁶⁴¹³ and a general discussion of the ionization of pyrimidines and related systems has appeared.⁶⁴¹¹ The prediction of ionization constants has reached a high level of reliability.⁶⁴¹⁴

2. Absorption Spectra of Pyrimidines (*H* 477)

Since the original section on the ultraviolet spectra of pyrimidines (*H* 477 *et seq.*) was written about 1960, a full theoretical introduction to the ultraviolet spectra of heterocycles⁶⁴⁵³ and an invaluable collection of data to illustrate it⁶⁴²⁴ have appeared; these, along with a more specialized review of such pyrimidine spectra,⁶⁴¹² make it unnecessary here to supplement S. F. Mason's original treatment.

It must be mentioned that little notable infrared or Raman work in the pyrimidine area has appeared since 1960, that is, since the advent of nuclear magnetic resonance spectroscopy as a general tool in the laboratory. However, a small amount of excellent work is noted elsewhere in this supplement.

3. The Nuclear Magnetic Resonance Spectra of Pyrimidines (*E* 386)*

Since the reviews⁶³⁶⁸ (*E* 386) by the late T. J. Batterham, there have been considerable advances in the technique of nuclear magnetic resonance spectroscopy. The advent of Fourier transform pulse techniques and the remarkable improvement in low-noise electronics have led to nuclei other than ^1H becoming readily accessible for study. Of obvious interest to pyrimidine chemists are carbon and nitrogen nmr data. Accordingly, this section concentrates on spectra of these two elements. While carbon has only one naturally occurring isotope possessing a magnetic moment (^{13}C , with a spin number $I = 0.5$) and a sensitivity relative to protons of 1.76×10^{-4} , nitrogen possesses two isotopes with magnetic moments. These are ^{14}N (with a relative sensitivity of 1×10^{-3} , some 20 times better than carbon; a spin $I = 1$; and a moderate quadrupole moment) and ^{15}N (with a very low relative sensitivity of 3.85×10^{-6} , only 1% of that for ^{13}C , but with the advantage of possessing a spin number $I = 0.5$). In addition, ^{15}N has a negative magnetogyric ratio and may show very long relaxation times.⁶⁴²⁶ Both these properties present problems for data acquisition. Nevertheless, a considerable number of ^{14}N and ^{15}N spectra (Table XIXf) and ^{13}C spectra (Table XIXg) have been obtained for pyrimidines.

A. Assignment of Resonances (*New*)

(1) Resonances for ^{15}N and ^{14}N (*New*)

Chemical shifts for the isotopes ^{15}N and ^{14}N are similar, and the chemical shifts of one may be used to assign chemical shifts for the other (see Table XIXf). The chemical shifts of both nuclei are influenced strongly by temperature, solvent, concentration, and pH value.⁶⁴²⁷⁻⁶⁴³⁰ These factors must be taken into account when spectra are compared.

Chemical shifts for the ring-nitrogen atoms occur over a wide

* This section is by M. David Fenn, Medical Chemistry Group, John Curtin School of Medical Research, G.P.O. Box 334, Canberra, Australia 2601.

TABLE XVI. The pK_a Values^a for Some Pyrimidines in Water (*H* 472, *E* 368)

Pyrimidine	Acidic pK_a	Basic pK_a	Ref.
Unsubstituted		—6.92 (second)	6359
4-Acetylrimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-	3.71		6554
4-Acetylrimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-thio-	3.20		6554
1-Allyl-1,2-dihydro-4-methoxy-6-nitroamino-2-oxo-	3.52		4656
4-Amino-		5.70	4837
2-Amino-5- <i>p</i> -aminophenyl-		4.21, 2.63	5663
2-Amino-5- <i>p</i> -aminophenyl-4,6-dimethyl-		5.12, 3.71	5662
2-Amino-4-anilino-5-formamido-6-hydroxy-	10.48	1.53	4648
2-Amino-4-benzylamino-5-formamido-6-hydroxy-	10.65	1.25	4648
2-Amino-4-benzylmethylamino-5-diazo-6-hydroxy- (internal salt)		4.79 (?)	4628
2-Amino-4,6-bisdimethylamino-		7.18, 0.80	5397
2-Amino-5- <i>p</i> -bromophenyl-		3.06	5663
2-Amino-5-carboxy-	4.47		4771
4-Amino-5-carboxy-	5.62		4771
4-Amino-6-carboxy-	6.25		4770
4-Amino-2,5'-carboxyamylamino-6-hydroxy-5-nitroso-	2.49	8.10	5052
4-Amino-2- α -carboxyethylamino-6-hydroxy-5-nitroso-	2.31	7.86	5052
4-Amino-2- β -carboxyethylamino-6-hydroxy-5-nitroso-	2.41	7.91	5052
4-Amino-2-carboxymethylamino-6-hydroxy-5-nitroso-	2.31	7.98	5052
2-Amino-5- <i>N</i> -carboxymethylformamido-4-hydroxy-6-methylamino	10.97	3.74, 1.69	4625
4-Amino-2- γ -carboxypropylamino-6-hydroxy-5-nitroso-	2.46	7.87	5052
2-Amino-4- <i>p</i> -chloroanilino-5-formamido-6-hydroxy-	1.11	10.62	4648
2-Amino-5-chloro-4,6-dimethoxy-		0.60	5769
2-Amino-5- <i>p</i> -chlorophenyl-		3.14	5663
2-Amino-5- <i>N</i> -cyanomethylformamido-4-hydroxy-6-methylamino-	10.30	1.39	4625
2-Amino-5-diazo-4-dibenzylamino-6-hydroxy- (internal salt)		4.66 (?)	4628
2-Amino-5-diazo-4-di-isopropylamino-6-hydroxy- (internal salt)		5.42 (?)	4628
2-Amino-5-diazo-4-dimethylamino-6-hydroxy- (internal salt)		5.06 (?)	4628
2-Amino-5-diazo-4-hydroxy-6-morpholino- (internal salt)		4.73 (?)	4628
2-Amino-5-diazo-4-hydroxy-6-piperidino- (internal salt)		4.97 (?)	4628

TABLE XVI. Continued

Pyrimidine	Acidic pK_a	Basic pK_a	Ref.
4-Amino-2,3-dihydro-3-methyl-2-oxo-		7.38 (?)	6554
4-Amino-2,6-dihydroxy-	8.69, 15.32	0.00	5341
5-Amino-2,4-dihydroxy-	9.52	3.20	5341
2-Amino-4,6-dimethoxy-		3.36	5769
4-Amino-2,6-dimethyl-		6.30 ^b	5769
2-Amino-4-dimethylamino-6-hydroxy-5-nitro-	8.53	-0.62	4628
2-Amino-5- <i>p</i> -dimethylaminophenyl-		4.67, 2.48	5663
2-Amino-5- <i>p</i> -dimethylaminophenyl-4,6-dimethyl-		5.31, 3.86	5662
4-Amino-5-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-		3.82	4662
2-Amino-4,6-dimethyl-5- <i>p</i> -nitrophenyl-		4.47	5662
2-Amino-4,6-dimethyl-5- <i>p</i> -nitrophenyl-		4.54	5662
2-Amino-4,6-dimethyl-5-phenyl-		4.91	5662
2-Amino-4,6-dipiperidino-		7.56, 1.67	5397
4-Amino-5-ethyl-1,2-dihydro-1-methyl-2-oxo		4.95	5797
4-Amino-5-fluoro-1,2-dihydro-1-methyl-2-oxo		2.75	6026
2-Amino-5- <i>p</i> -fluorophenyl-		3.25	5663
2-Amino-5-formamido-4-hydroxy-6-methylamino-	10.82	1.90	4648
2-Amino-5-formamido-4-hydroxy-6- <i>p</i> -toluidino-	10.50	1.50	4648
4-Amino-2-hydroxy-6-methoxy-	10.88	4.55	4656
2-Amino-4-hydroxy-6-methoxy-5-nitro-	7.41		2718
5-Amino-4-hydroxy-2-methyl-	10.01	3.88, -1.12	5099
2-Amino-4-hydroxy-6-methylamino-5-trifluoroacetamido-	10.30	1.53	4642
4-Amino-2-mercaptop-6-methoxy-	8.85	3.20	4656
2-Amino-5- <i>p</i> -methoxyphenyl-		3.32	5663
2-Amino-5- <i>p</i> -nitrophenyl-		2.70	5663
2-Amino-5-phenyl-		3.34	5663
5- <i>p</i> -Aminophenyl-1,2-dihydro-2-imino-1-methyl-		10.97, 3.41	5663
5- <i>p</i> -Aminophenyl-1,2-dihydro-2-imino-1,4,6-trimethyl-		11.71, 3.64	5662
5- <i>p</i> -Aminophenyl-1,2-dihydro-1-methyl-2-oxo-		3.91, 1.82	5635
5- <i>p</i> -Aminophenyl-4,6-dimethyl-2-methylamino-		5.29, 3.77	5662

5- <i>p</i> -Aminophenyl-2-methoxy-			5635
5- <i>p</i> -Aminophenyl-2-methylamino-			5663
2-Amino-5- <i>p</i> -tolyl-			5663
1-Benzyl-1,2-dihydro-2-oxo-			4583
4,6-Bisethylthio-2-methoxycarbonylmethyl-			5693
2-Bromo-			5664
5-Bromo-2-carboxy-	2.80		4771
4-Bromo-2-carboxymethyl-	3.67		5693
4-Bromo-5-chloro-2,6-dihydroxy-	4.83		4650
5-Bromo-4-chloro-2,6-dihydroxy-	4.86		4650
4-Bromo-2,6-dihydroxy-	5.86		4650
5-Bromo-2,4-dihydroxy-	8.60		4736
4-Bromo-2,6-dihydroxy-5-iodo-	5.27		4650
5-Bromo-2,4-dihydroxy-6-iodo-	5.86		4650
5-Bromo-2-(1',4'-dimethylpentyl)amino-		2.20	5664
5-Bromo-2-isopentylamino-		2.31	5664
5- <i>p</i> -Bromophenyl-1,2-dihydro-2-imino-1-methyl	10.45		5663
5- <i>p</i> -Bromophenyl-1,2-dihydro-1-methyl-2-oxo-		1.89	5635
5- <i>p</i> -Bromophenyl-2-hydroxy-	8.56	1.63	5635
5- <i>p</i> -Bromophenyl-2-methoxy-		0.61	5635
5- <i>p</i> -Bromophenyl-2-methylamino-		3.17	5663
4- <i>t</i> -Butyl-2-carboxymethyl-	3.95	1.75	5693
4- <i>t</i> -Butyl-2-methoxycarbonylmethyl-		1.74	5693
5-Carbamoyl-4-hydroxy-2-methyl-	7.59	1.32	5099
5-Carbamoyl-4-methoxy-2-methyl-		2.49	5099
2-Carboxy-	2.99		4771
4-Carboxy-	2.98		4770
5-Carboxy-	3.16		4771
4-Carboxy-6-chloro-	2.80		4770
4-Carboxy-2,6-dichloro-	2.81		4770
5-Carboxy-2,4-dichloro-	3.10		4771
5-Carboxy-2,4-dihydroxy-	4.32		4771
4-Carboxy-6-hydroxy-	2.83		4770
5-Carboxy-2-hydroxy-	3.49		4771

TABLE XVI. Continued

Pyrimidine	Acidic pK_a	Basic pK_a	Ref.
4-Carboxy-6-hydroxy-2-mercapto-	2.72		4770
5-Carboxy-4-hydroxy-2-mercapto-	3.87		4771
5-Carboxy-4-hydroxy-2-methyl-	4.40, 9.85	0.81	5099
4-Carboxy-6-mercapto-	3.02		4770
4-Carboxy-6-methoxy-	3.68		4770
1-Carboxymethoxy-1,2-dihydro-2-oxo-	2.40	0.60	4583
2-Carboxymethyl-	3.65	0.58	5693
4-Carboxy-6-methyl-	3.07		4770
2-Carboxymethyl-4,6-bisethylthio-	4.04	1.23	5693
2-Carboxymethyl-4-chloro-	3.60		5693
2-Carboxymethyl-4-chloro-6-methoxy-	3.66		5693
2-Carboxymethyl-4-chloro-6-methyl-	3.75		5693
2-Carboxymethyl-4,6-dichloro-	3.34		5693
2-Carboxymethyl-4,6-dimethoxy-	3.89	1.23	5693
2-Carboxymethyl-4-ethylsulfonyl-	3.47		5693
2-Carboxymethyl-4-ethylthio-	4.15	1.96	5693
2-Carboxymethyl-4-fluoro-	3.63		5693
2-Carboxymethyl-4-iodo-	3.68	-0.37	5693
2-Carboxymethyl-4-isopropyl-	3.90	1.56	5693
2-Carboxymethyl-4-methoxy-	4.22	1.81	5693
2-Carboxymethyl-4-methyl-	3.86	1.35	5693
2-Carboxymethyl-4-phenyl-	3.73	1.45	5693
5-Carboxy-2-methylthio-	3.39		4771
2-Chloro-		-1.90	5664
4-Chloro-6- <i>N'</i> , <i>N'</i> -di(β -chloroethyl)-hydrazino-2-hydroxy-	8.54	2.80	4791
4-Chloro-2,6-dihydroxy-	5.75		4650
5-Chloro-2,4-dihydroxy-	7.90		4736
4-Chloro-6- <i>N'</i> , <i>N'</i> -di(β -hydroxyethyl)-hydrazino-2-hydroxy-	9.02		4791
4-Chloro-2,6-dihydroxy-5-iodo-	5.04		4650
4-Chloro-2,6-dihydroxy-5-methyl-	6.50		4526

4- β -Chloroethylhydrazino-2-ethylthio-	3.80	4882
4- β -Chloroethylhydrazino-2-ethylthio-5-fluoro-	3.10	4882
4-Chloro-2-methoxycarbonylmethyl-	-0.77 ^b	5693
4-Chloro-6-methoxy-2-methoxycarbonylmethyl-	c. -1.44 ^b	5693
5- <i>p</i> -Chlorophenyl-1,2-dihydro-2-imino-1-methyl-	10.45	5663
5- <i>p</i> -Chlorophenyl-1,2-dihydro-1-methyl-2-oxo-	1.78	5635
5- <i>p</i> -Chlorophenyl-2-hydroxy-	1.62	5635
5- <i>p</i> -Chlorophenyl-2-methoxy-	0.62	5635
5- <i>p</i> -Chlorophenyl-2-methylamino-	3.26	5635
5-Cyano-1,4-dihydro-1,2-dimethyl-4-oxo-	-0.01	5099
5-Cyano-1,6-dihydro-1,2-dimethyl-6-oxo-	-0.06	5099
5-Cyano-4-hydroxy-2-methyl-	-0.18	5099
5-Cyano-4-methoxy-2-methyl-	0.80	5099
4-Cyano methylimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-	5.96	6554
4-Cyano methylimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-thio-	5.12	6554
2,4-Diamino-	7.40 or 7.50	5400, 6439
4,5-Diamino-	6.04, -0.97	5341
2,4-Diamino-5-anilino-	6.79	5400
2,5-Diamino-4-anilino-6-hydroxy-	5.17	4648
2,4-Diamino-5-benzoyl-	4.63	5400
2,4-Diamino-5-benzyl-	7.27	5400
2,4-Diamino-5-benzylamino-6-hydroxy-	5.14, 1.21	4647
2,5-Diamino-4-benzylamino-6-hydroxy-	5.27	4648
2,4-Diamino-5-benzyl-6-methyl-	7.62	5400
2,4-Diamino-5-bromo-	5.60	5400
2,4-Diamino-5-3'-bromo-4',5'-dimethoxybenzoyl-	4.48	5400
2,4-Diamino-6- <i>p</i> -bromophenacylthio-	4.98	5400
2,4-Diamino-5- <i>o</i> -bromophenyl-	6.70	5400
2,4-Diamino-6-carbamoyl-	4.90	5400
2,4-Diamino-5-carboxy-	2.94 ^d	5400
2,4-Diamino-6-carboxy-	1.35 ^d	5400
2,4-Diamino-5-chloro-	5.52	5400
2,4-Diamino-6-chloro-	3.60	5400
2,5-Diamino-4- <i>p</i> -chloroanilino-6-hydroxy-	4.75	4648
	8.57	
	6.22	
	10.89	
	6.79 ^d	
	7.79 ^d	

TABLE XVI. Continued

Pyrimidine	Acidic pK_a	Basic pK_a	Ref.
2,4-Diamino-5- <i>p</i> -chlorobenzoyl-		4.58	5400
2,4-Diamino-5- <i>p</i> -chlorobenzyl-		7.17	5400
2,4-Diamino-5- <i>p</i> -chlorobenzyl-6-ethyl-		7.71	5400
2,4-Diamino-5- <i>p</i> -chlorobenzyl-6-propyl-		7.71	5400
2,4-Diamino-5- <i>p</i> -chlorobenzyl-6-methyl-		7.58	5400
2,4-Diamino-5- <i>p</i> -chlorophenoxy-		6.16	5400
2,4-Diamino-5- <i>m</i> -chlorophenyl-		6.70	5400
2,4-Diamino-5- <i>p</i> -chlorophenyl-		6.79	5400
2,4-Diamino-5- <i>p</i> -chlorophenylazo-		4.93 ^e	5400
2,4-Diamino-5- <i>p</i> -chlorophenyl-6-ethyl-		7.34	5400
2,4-Diamino-5- <i>p</i> -chlorophenyl-6-hydroxy-		3.06	5400
2,4-Diamino-5- <i>p</i> -chlorophenyl-6-isobutyl-		7.39	5400
2,4-Diamino-5- <i>p</i> -chlorophenyl-6-methyl-		7.26	5400
2,4-Diamino-5- <i>p</i> -chlorophenyl-6-propyl-		7.35	5400
2,4-Diamino-5- <i>p</i> -chlorophenylthio-		5.70	5400
2,4-Diamino-5- <i>p</i> -chlorophenylthio-		5.02	5400
2,4-Diamino-5- <i>p</i> -chlorophenylthio-6-ethyl-		6.27	5400
2,4-Diamino-5-cyano-		3.75	5400
2,4-Diamino-5-3',4'-dichlorophenyl-6-ethyl-		7.20	5400
2,4-Diamino-5-3',4'-dichlorophenyl-6-methyl-		7.15	5400
2,4-Diamino-1,6-dihydro-1-methyl-6-oxo-5-trifluoroacetamido-4,5-Diamino-2,6-dihydroxy-	10.70 (?)	2.25	4642
		4.56	5341
2,5-Diamino-4-di-isopropylamino-6-hydroxy-		5.36	4628
2,4-Diamino-5,6-dimethyl-		8.07	5400
2,4-Diamino-6-dimethylamino-		7.21, 0.68	5397
2,4-Diamino-5-ethoxycarbonyl-		5.07	5400
2,4-Diamino-5-formamido-		6.03	5400
2,5-Diamino-4-hydroxy-6-methylamino-	10.89	5.28, 1.15	4647
2,4-Diamino-6-hydroxy-5- <i>N</i> -methyltrifluoroacetamido-	9.90	2.19	4642
2,5-Diamino-4-hydroxy-6-piperidino-		4.91	4628

2,4-Diamino-6-hydroxy-5-propionamido-	10.18	2.62	4642
2,5-Diamino-4-hydroxy-6- <i>p</i> -toluidino-		5.13	4648
2,4-Diamino-6-hydroxy-5-trifluoroacetamido-	9.80	1.95	4642
2,4-Diamino-5-iso butyl-6-methyl-		8.06	5400
2,4-Diamino-6-mercapto-	10.19	1.73	5400
2,4-Diamino-5-methoxy-		7.23	5400
2,4-Diamino-6-methoxy-		5.48	5400
2,4-Diamino-6-methoxycarbonyl-		5.32	5400
2,4-Diamino-5- <i>p</i> -methoxyphenylthio-		5.94	5400
2,4-Diamino-5-methyl-		7.69	5400
2,4-Diamino-6-methyl-		7.63	5400
2,4-Diamino-6-methylamino-		7.21, 1.05	5397
2,4-Diamino-6-methyl-5-phenoxy-		6.47	5400
2,4-Diamino-6-methyl-5-phenyl-		7.40	5400
4,5-Diamino-2-methyl-6-phenyl-		6.57	5441
4,5-Diamino-6-methyl-2-phenyl-		5.84	5439
2,4-Diamino-6-morpholino-		6.73, -0.35	5397
2,4-Diamino-5-nitro-		2.58	5400
2,4-Diamino-5-phenoxy-		6.26	5400
2,4-Diamino-6-phenoxy-		4.80	5400
2,4-Diamino-5-phenyl-		6.90	5400
2,4-Diamino-6-phenyl-		6.70	5400
4,5-Diamino-2-phenyl-		5.78	5439
4,5-Diamino-6-phenyl-		5.66	5441
2,4-Diamino-5-phenyl-6-trifluoromethyl-		3.25	5400
2,4-Diamino-6-piperidino-		7.20, 0.58	5397
4,6-Diamino-2-piperidino-		6.78, 0.86	5397
2,4-Diamino-6-sulfo-	4.69 ^d		5400
4,5-Diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-		4.44	5341
2,4-Diamino-5-3',4',5'-trimethoxybenzyl-		7.12	5400
2,4-Diamino-5-3',4',5'-trimethoxyphenyl-		6.70	5400
4,5-Diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	12.58		4662
4,5-Dibromo-2,6-dihydroxy-	5.03		4650
4,5-Dichloro-2,6-dihydroxy-	4.74		4650

TABLE XVI. Continued

Pyrimidine	Acidic pK_a	Basic pK_a	Ref.
4,6-Dichloro-2-methoxycarbonylmethyl- 4,5-Diethyl-2,6-dihydroxy- 1,4-Dihydro-1,2-dimethyl-4-oxo- 1,6-Dihydro-1,2-dimethyl-6-oxo- 1,2-Dihydro-4,6-dimethyl-2-oxo-1-phenyl- 1,6-Dihydro-6-imino-4,5-di-isopropyl-1-methyl- 1,2-Dihydro-2-imino-1,6-dimethyl- 1,6-Dihydro-6-imino-1,2-dimethyl- 1,6-Dihydro-6-imino-1,4-dimethyl- 1,6-Dihydro-6-imino-1,5-dimethyl- 1,6-Dihydro-6-imino-2-isopropyl-1-methyl- 1,6-Dihydro-6-imino-4-isopropyl-1-methyl- 1,6-Dihydro-6-imino-5-isopropyl-1-methyl- 1,2-Dihydro-2-imino-5-methoxy-1-methyl- 1,2-Dihydro-2-imino-5- <i>p</i> -methoxyphenyl-1-methyl- 1,6-Dihydro-6-imino-1-methyl-2-methylthio- 1,6-Dihydro-6-imino-1-methyl-5- <i>p</i> -nitrophenyl- 1,2-Dihydro-2-imino-1-methyl-5-phenyl- 1,2-Dihydro-2-imino-1-methyl-5- <i>p</i> -tolyl- 1,6-Dihydro-6-imino-1,2,4,5-tetramethyl- 1,6-Dihydro-6-imino-1,2,4-trimethyl- 1,6-Dihydro-6-imino-1,2,5-trimethyl- 1,6-Dihydro-6-imino-1,4,5-trimethyl- 1,2-Dihydro-2-imino-1,4,6-trimethyl-5- <i>p</i> -nitrophenyl- 1,2-Dihydro-2-imino-1,4,6-trimethyl-5-phenyl- 1,4-Dihydro-5-methoxy-1,2-dimethyl-4-oxo- 1,6-Dihydro-5-methoxy-1,2-dimethyl-6-oxo- 1,2-Dihydro-4-methoxy-1-methyl-6-nitroamino-2-oxo- 1,2-Dihydro-1-methoxy-2-oxo-	10.45	c. -2.60 2.69 2.74 3.30 10.35 10.86 10.35 10.08 9.82 10.32 10.56 9.86 11.44 10.88 10.04 9.87 10.05 10.75 10.82 10.88 11.01 10.14 10.76 11.03 11.48 2.79 2.72 0.50	5693 4716 5099 5099 5125 5679 5662 5679 5679 5679 5679 5679 5662, 5663 5663 5665 5663 5663 5679 5679 5679 5662 5662 5099 5099 4656 4583

1,2-Dihydro-5- <i>p</i> -methoxyphenyl-1-methyl-2-oxo			2.08	5635
1,2-Dihydro-1-methyl-6-methylamino-2-methylimino- (or tautomer)			11.58	5665
1,2-Dihydro-1-methyl-6-methylamino-2-oxo-	14.3 (?)		7.35	6554
1,6-Dihydro-1-methyl-6-methylimino-2-methylthio-			10.30	5665
1,2-Dihydro-1-methyl-6-methylthio-2-oxo-			4.07 (?)	6554
1,6-Dihydro-1-methyl-2-methylthio-6-oxo-			1.05	6554
1,6-Dihydro-1-methyl-2-methylthio-6-thio-			-0.3	6554
1,2-Dihydro-1-methyl-5- <i>p</i> -nitrophenyl-2-oxo-			1.53	5635
1,4-Dihydro-1-methyl-5- <i>p</i> -nitrophenyl-4-oxo-			1.40	5635
1,6-Dihydro-1-methyl-5- <i>p</i> -nitrophenyl-6-oxo-			1.25	5635
1,2-Dihydro-1-methyl-2-oxo-5-phenyl-			2.01	5635
1,4-Dihydro-1-methyl-4-oxo-5-phenyl-			1.99	5635
1,6-Dihydro-1-methyl-6-oxo-5-phenyl-			1.50	5635
1,2-Dihydro-1-methyl-2-oxo-5- <i>p</i> -tolyl-			2.07	5635
1,4-Dihydro-1,2,5-trimethyl-4-oxo-			3.46	5099
1,6-Dihydro-1,2,5-trimethyl-6-oxo-			3.42	5099
2,4-Dihydroxy-5,6-di-iodo	6.13			4650
2,4-Dihydroxy-5,6-dimethyl-	10.34			4716
2,4-Dihydroxy-5-iodo-	8.40			4736
2,4-Dihydroxy-6-iodo-	6.63			4650
4,5-Dihydroxy-2-methyl-	7.57, 12.74	2.93		5099
2,4-Dihydroxy-6-methyl-5-nitro-	6.38			5412
2,4-Dihydroxy-6-nitroamino-	5.52, 12.91			4656
2,4-Dihydroxy-5,6-pentamethylene-	10.30			4716
2,4-Dihydroxy-5,6-tetramethylene-	10.40			4716
2,4-Dihydroxy-5,6-trimethylene-	9.62			4716
2,5-Diisopropyl-6-methylamino-			7.05	5679
4,6-Dimethoxy-2-methoxycarbonylmethyl-			1.07	5693
4,5-Dimethoxy-2-methyl-			4.11	5099
2,4-Dimethoxy-6-nitroamino-				4656
2-Dimethylamino-	3.82			4837
4-Dimethylamino-			4.00	4837
4-Dimethylamino-5-fluoro-1,2-dihydro-1-methyl-2-oxo-			6.30	6026
4-Dimethylamino-6-methoxy-			2.20	6026
			4.23	4791

TABLE XVI. Continued

Pyrimidine	Acidic pK_a	Basic pK_a	Ref.
2-Dimethylamino-4-methoxy-6-methylnitroamino-		1.54	4656
2-Dimethylamino-4-methoxy-6-nitroamino-		0.01	4656
5- <i>p</i> -Dimethylaminophenyl-1,2-dihydro-2-imino-1-methyl-	5.66	11.26, 3.19	5663
5- <i>p</i> -Dimethylaminophenyl-2-methoxy-		4.31, 0.22	5635
5- <i>p</i> -Dimethylaminophenyl-2-methylamino-		4.72, 2.82	5663
2,5-Dimethyl-4-methylamino-		7.61	5679
4,5-Dimethyl-6-methylamino-		6.97	5679
4,6-Dimethyl-2-methylamino-5- <i>p</i> -nitrophenyl-		4.41	5662
4,6-Dimethyl-2-methylamino-5-phenyl-		5.12	5662
2-(1',4'-Dimethylpentyl)amino-		4.06	5664
2-(1',4'-Dimethylpentyl)amino-4,6-dimethyl-		5.40	5664
4-(1',4'-Dimethylpentyl)amino-2,6-dimethyl-		7.80	5664
2,4-Dimethyl-6-piperidino-		8.02	5676
4,6-Dimethyl-2-piperidino-		5.21	5676
2,4-Dimethyl-6-sulfo-	1.62		5667
4,5-Dimethyl-2-sulfo-	-0.33		5667
4,5-Dimethyl-6-sulfo-	1.20		5667
4,6-Dimethyl-2-sulfo-	-0.09		5667
5-Ethoxycarbonylamino-4-hydroxy-2-methyl-	8.05	2.72	5099
5-Ethoxycarbonyl-1,4-dihydro-1,2-dimethyl-4-oxo-		1.50	5099
5-Ethoxycarbonyl-1,6-dihydro-1,2-dimethyl-6-oxo-		1.38	5099
5-Ethoxycarbonyl-4-hydroxy-2-methyl-		1.27	5099
1-Ethoxycarbonylmethoxy-1,2-dihydro-2-oxo-	7.77	0.60	4583
5-Ethoxycarbonyl-4-methoxy-2-methyl-		2.36	5099
2-Ethoxycarbonylmethyl-4-methyl-		1.42	5693
2-Ethyl-1,6-dihydro-6-imino-1-methyl-		10.05	5679
5-Ethyl-1,6-dihydro-6-imino-1-methyl-		9.86	5679
5-Ethyl-1,2-dihydro-1-methyl-4-methylamino-2-oxo-		4.66	5797
4-Ethyl-2,6-dihydroxy-5-methyl-	10.37		4716
5-Ethyl-2,4-dihydroxy-6-methyl-	10.40		4716

5-Ethyl-2,4-dihydroxy-6-propyl-	10.26		4716
5-Ethyl-4-ethylamino-1,2-dihydro-1-methyl-2-oxo-		4.70	5797
4-Ethylhydrazino-2-ethylthio-5-fluoro-		3.40	4882
2-Ethyl-4-methylamino-		7.28	5679
5-Ethyl-4-methylamino-		6.68	5679
2-Ethylthio-5-fluoro-4-hydrazino-		4.82	4882
2-Ethylthio-4-hydrazino-		4.76	4882
4-Ethylthio-2-methoxycarbonylmethyl-		1.97	5693
5-Fluoro-1,2-dihydro-1-methyl-4-methylamino-2-oxo-		2.40	6026
4-Fluoro-2,6-dihydroxy-5-methyl-	4.80		4526
5- <i>p</i> -Fluorophenyl-1,2-dihydro-2-imino-1-methyl-		10.62	5663
5- <i>p</i> -Fluorophenyl-2-methylamino-		3.39	5663
5-Fluoro-1,2,3,4-tetrahydro-1,3-dimethyl-4-methylimino-2-oxo-		7.15	6026
2-Hydroxy-/ <i>N</i> -oxide	5.10	0.50	4583
2-Hydroxy-4,5-dimethyl-		3.37	5667
4-Hydroxy-2,5-dimethyl-		3.23	5099
4-Hydroxy-5-hydroxymethyl-2-methyl-	9.64	2.71	5099
4-Hydroxy-5-methoxy-2-methyl-	9.19		5099
2-Hydroxy-4-methoxy-6-nitroamino-	9.05	2.58	4656
2-Hydroxy-5- <i>p</i> -methoxyphenyl-	3.56, 10.99		5635
4-Hydroxy-2-methyl-	8.86	1.91	5099, 5667
2-Hydroxy-5- <i>p</i> -nitrophenyl-	9.06	2.73 or 2.51	5635
2-Hydroxy-5- <i>p</i> -tolyl-	8.17	1.42	5635
4-Iodo-2-methoxycarbonylmethyl-	8.74	1.96	5693
2-Isopentylamino-		−0.57 ^b	5664
2-Isopentylamino-4,6-dimethyl-		4.14	5664
4-Isopentylamino-2,6-dimethyl-		5.37	5664
4-Isopropyl-2-methoxycarbonylmethyl-		7.73	5693
2-Isopropyl-4-methylamino-		1.58	5679
4-Isopropyl-6-methylamino-		7.41	5679
5-Isopropyl-4-methylamino-		6.48	5679
2-Methoxycarbonylmethyl-		6.76	5693
2-Methoxycarbonylmethyl-4-phenyl-		0.53	5693
4-Methoxy-2,5-dimethyl-		1.45	5099
		4.79	

TABLE XVI. Continued

Pyrimidine	Acidic pK_a	Basic pK_a	Ref.
4-Methoxy-2-methoxycarbonylmethyl- 2-methoxy-5- <i>p</i> -methoxyphenyl-		2.05 0.78	5693 5635
4-Methoxy-2-methyl- 5-Methoxy-2-methylamino-		3.99 3.44	5099 5662
4-Methoxy-2-methylthio-6-nitroamino- 4-Methoxy-5- <i>p</i> -nitrophenyl-	3.73	2.40	4656
2-Methoxy-5-phenyl- 4-Methoxy-5-phenyl-		0.79 2.94	5635 5635
5- <i>p</i> -Methoxyphenyl-2-methylamino- 2-Methoxy-5- <i>p</i> -tolyl-		3.54 0.77	5663 5635
2-Methyl- 4-Methyl-		2.30 2.00	4837 4837
2-Methylamino-5- <i>p</i> -nitrophenyl- 2-Methylamino-5-phenyl-		2.81 3.42	5663 5663
2-Methylamino-5- <i>p</i> -tolyl- 2-Methyl-4-methylamino-		3.59 7.19	5663 5679
4-Methyl-6-methylamino- 5-Methyl-4-methylamino-		6.65 6.56	5679 5679
2-Methyl-4-sulfo- 4-Methyl-2-sulfo-	0.78 -0.76		5667 5667
4-Methyl-6-sulfo- 5-Methyl-2-sulfo-	0.23 -1.21		5667 5667
2-Sulfo- 4-Sulfo-	-1.70 -0.53		5667 5669
2,4,5,6-Tetra-amino- 1,2,3,4-Tetrahydro-5,6-bis- β -hydroxyethylamino-1,3-dimethyl-2,4-dioxo-		6.82	5669
1,2,3,4-Tetrahydro-1,3-dimethyl-5,6-bismethylamino-2,4-dioxo-		3.95	4643
1,2,3,4-Tetrahydro-1,3-dimethyl-4-methylimino-2-oxo-		4.89	4662
1,2,3,4-Tetrahydro-1,3-dimethyl-2-oxo-4-phenylimino-		9.78	6554
1,2,3,4-Tetrahydro-1,3-dimethyl-2-oxo-4-phenylimino-		6.00	6554
1,2,3,4-Tetrahydro-1,3-dimethyl-2-oxo-4-semicarbazono-	14.1 (?)	4.03	6554
1,2,3,4-Tetrahydro-1,3-dimethyl-4-semicarbazono-2-thio-	13.7 (?)	3.30	6554
1,2,3,4-Tetrahydro-6-hydroxy-1,3-dimethyl-4-oxo-2-thio-	2.60		4729

1,2,3,4-Tetrahydro-4-hydroxyimino-1,3-dimethyl-2-oxo-					
1,2,3,4-Tetrahydro-4-imino-1,3-dimethyl-2-oxo-					
1,2,3,4-Tetrahydro-4-imino-1,3-dimethyl-2-thio-					
2-Thiobarbituric acid/ <i>N</i> -methyl-	2.50, 11.40				6554
4-Thiouracil/3-methyl-	8.20				6554
2,4,6-Triamino-5- <i>o</i> -aminophenylthio-		5.95, 2.59,			5397
		-0.53			
2,4,6-Triamino-5-benzyl-		6.55			5397
2,4,6-Triamino-5-bromo-		5.17, -0.30			5397
2,4,6-Triamino-5-chloro-		5.15, 0.35			5397
2,4,6-Triamino-5- <i>p</i> -chlorophenyl-		6.19			5397
2,4,6-Triamino-5- <i>p</i> -chlorophenylazo-		4.91			5397
2,4,6-Triamino-5-ethyl-		6.84, 1.55			5397
2,4,6-Triamino-5-formamido-		5.73 or 5.57			4643, 5397
2,4,6-Triamino-5-nitro-		3.22			5397
2,4,6-Triamino-5-phenylazo-		4.97			5397
2,4,6-Triamino-5-phenylthio-		5.66, 0.08			5397
2,4,5-Trimethyl-6-methylamino-		8.14			5679
2,4,5-Trimethyl-6-sulfo-					5667
2,4,5-Trisacetamido-6-hydroxy-	2.33				
Uracil/3-Benzyl-6-methyl-5-nitro-	7.65				4642
Uracil/5-Bromo-6-chloro-3-methyl-	6.47				5412
Uracil/5-Bromo-1-methyl-	4.85				4650
Uracil/6-Bromo-3-methyl-	8.40				4736
Uracil/6-Chloro-5-iodo-3-methyl-	6.12				4650
Uracil/6-Chloro-3-methyl-	5.15				4650
Uracil/5,6-Dichloro-3-methyl-	5.95				4650
Uracil/5,6-Di-iodo-3-methyl-	4.84				4650
Uracil/1,6-Dimethyl-5-nitro-	6.17				4650
Uracil/3,6-Dimethyl-5-nitro-	7.40				5412
Uracil/6-Iodo-3-methyl-	6.78				5412
Uracil/3-Methyl-5-nitro-	6.93				4650
	5.65				5412

^d Zwitterion.

^e In ethanol-water, 1:4.

^a The second decimal place is seldom of significance.

^b In 50% aqueous acetone.

^c In 5% aqueous methanol.

TABLE XIXf. Nitrogen Chemical Shifts for Pyrimidines (*New*)

Pyrimidine	Shift ^a	Strength and Solvent	Ref.
Unsubstituted	-84.8 (N1,N3) -134.8 (N1,N3) -84.8 (N1,N3) -84 ± 1* -92 ± 2* -86 ± 4* -90.0 (N3) -80.3 (N1) -89.9 (N3) -79.5 (N1) -99 ± 10* (N3) -90 ± 1* (N1) -73 ± 4* -129.9 (N1,N3) -297.9 (NH ₂) -178.8 (N1,N3) -294.3 (NH ₂) -126.35 (N1,N3) -293.0 (NH ₂) -135 ± 4* (N1,N3)	0.5 M in DMSO ^b 0.5 M in TFA ^b 0.5 M in DMSO ^b 0.15 M in AcMe 0.5 M in H ₂ O c. 5% in AcMe in DMSO ^b in CHCl ₃ ^b in AcMe 5% in AcMe 0.5 M in DMSO ^b 0.5 M in TFA ^b 4.5 M in DMSO c. 5% in AcMe in DMSO ^b in H ₂ O ^b 0.5 M in DMSO ^b	6113 6113 6451 6452 6452 6365 6113 6113 6444 6365 6113 6113 6092 6365 6113 6113 6451
/1-oxide			
2-Acetoxy- 2-Amino-			
/1-oxide			
4-Amino-5-cyano-2-ethyl-			

4-Amino-5-cyano-2-methyl-	-288.3 (NH ₂) -134.7 (CN)	0.5 M in DMSO ^b	6451
2-Amino-4,6-dichloro-	-108.9 (N1) -120.2 (N3) -288.3 (NH ₂) -134.2 (CN)	0.5 M in DMSO ^b	6451
2-Amino-4,6-dimethoxy-	-141.5 (N1,N3) -292.0 (NH ₂)	0.5 M in DMSO ^b	6451
2-Amino-4,6-dimethyl-	-180.2 (N1,N3) -296.4 (NH ₂)	0.5 M in DMSO ^b	6451
4-Amino-2,5-dimethyl-	-138.0 (N1,N3) -300.4 (NH ₂)	0.5 M in DMSO ^b	6451
4-Amino-2,6-dimethyl-	-121.3 (N1) -134.0 (N3) -299.6 (NH ₂)	0.5 M in DMSO ^b	6451
4-Amino-5-ethoxycarbonyl-2-methylthio-	-121.0 (N1) -139.2 (N3) -299.0 (NH ₂)	0.5 M in DMSO ^b	6451
2-Amino-4-methyl-	-128.8 (N1) -142.0 (N3) -289.4 (NH ₂)	0.5 M in DMSO ^b	6451
4-Amino-2-phenyl-5-(3',4',5'-trimethoxybenzyl)-	-138.2 (N1) -130.3 (N3) -299.5 (NH ₂)	0.5 M in DMSO ^b	6113
	-127.8 (N1) -141.3 (N3) -297.8 (NH ₂) -227.6 (N1,N3) -281.2 (NH ₂)	0.5 M in TFA ^b	6113

TABLE XIXf. Continued

Pyrimidine	Shift ^a	Strength and Solvent	Ref.
4-Amino-5-(3',4',5', trimethoxybenzyl)-	-120.9 (N1)	0.5 M in DMSO ^b	6113
	-132.7 (N3)		
	-298.4 (NH ₂)	0.5 M in TFA ^b	6113
	-217.9 (N1)		
	-218.6 (N3)		
2-Bromo-	-278.3 (NH ₂)	c. 5% in AcMe	6365
	-86 ± 4*		
	-88.2 (N1,N3)		
2-Chloro-	-92 ± 4*	0.5 M in DMSO ^b	6113
		c. 5% in AcMe	6365
4-Chloro-2-methylthio-	-100.5 (N1)	0.5 M in DMSO ^b	6451
	-102.4 (N3)		
2-Chloro-5-nitro-	-91.3 (N1,N3)	0.5 M in DMSO ^d	6451
	-17.6 (NO ₂)		
2-Cyano-	-67 ± 4* (N1,N3)	c. 5% in AcMe	6365
	-* (CN)		
2,4-Diamino-	-160.1 (N1)	4.5 M in DMSO	6092
	-169.2 (N3)		
	-295.4 (2-NH ₂)		
	-294.1 (4-NH ₂)		
	-164.5 (N1)	0.5 M in DMSO ^b	6113
	-173.4 (N3)		
	-301.6 (2-NH ₂)		
	-299.6 (4-NH ₂)		
	-168.2 (N1)	4.5 M in H ₂ O (pH 11)	6092
	-175.4 (N3)		
	-300.5 (2-NH ₂)		
	-296.1 (4-NH ₂)		

/3-oxide	-253.5 (N1)	0.5 M in TFA ^b	6113
	-231.6 (N3)		
	-296.4 (2-NH ₂)		
	-276.2 (4-NH ₂)		
4,5-Diamino-	-166.8 (N1)	in DMSO ^b	6113
	-167.8 (N3)		
	-306.2 (2-NH ₂)		
	-307.4 (4-NH ₂)	4.5 M in DMSO	6092
	-162.4 (N1)		
	-163.4 (N3)		
	-301.4 (2-NH ₂)		
4,6-Diamino-	-300.1 (4-NH ₂)	0.5 M in DMSO ^b	6113
	-132.6 (N1)		
	-133.5 (N3)		
	-305.9 (4-NH ₂)	0.5 M in TFA ^b	6113
	-338.0 (5-NH ₂)		
	-215.1 (N1,N3)		
	-282.3 (4-NH ₂)		
4,6-Diamino-	-335.8 (5-NH ₂)	0.5 M in DMSO ^b	6113
	-149.4 (N1,N3)		
	-309.1 [4,6-(NH ₂) ₂]		
	-210.3 (N1,N3)	0.5 M in TFA ^b	6113
	-289.0 [4,6-(NH ₂) ₂]		
2,4-Diamino-6-chloro-	-166.1 (N1)	0.5 M in DMSO ^b	6113
	-178.7 (N3)		
	-297.7 (2-NH ₂)		
	-296.6 (4-NH ₂)	0.5 M in TFA ^b	6113
	-227.4 (N1)		
	-229.1 (N3)		
	-297.9 (2-NH ₂)		
	-283.5 (4-NH ₂)	0.5 M in TFA ^b	6113

TABLE XIXf. Continued

Pyrimidine	Shift ^a	Strength and Solvent	Ref.
4,6-Diamino-5- <i>p</i> -chlorophenyl-	-151.8 (N1,N3)	0.5 M in DMSO ^b	6113
	-304.5 [4,6-(NH ₂) ₂]		
	-209.9 (N1,N3)	0.5 M in TFA ^b	6113
	-297.2 [4,6-(NH ₂) ₂]		
2,4-Diamino-5- <i>p</i> -chlorophenyl-6-ethyl-	-176.3 (N1,N3)	0.5 M in DMSO ^b	6113
	-300.9 (2-NH ₂)		
	-299.4 (4-NH ₂)	0.5 M in TFA ^b	6113
	-247.5 (N1,N3)		
	-294.5 (2-NH ₂)		
	-274.9 (4-NH ₂)		
2,4-Diamino-5-methoxymethyl-/β-oxide	-164.8 (N1)	in DMSO ^b	6113
	-169.2 (N3)		
	-308.1 (2-NH ₂)		
	-311.1 (4-NH ₂)		
4,6-Diamino-2-piperidino-	-190.2 (N1,N3)	0.5 M in DMSO ^b	6113
	-308.2 [2-N(CH ₂) ₅]		
	-306.2 [4,6-(NH ₂) ₂]	0.5 M in TFA ^b	6113
	-266.1 (N1,N3)		
	-295.8 [2-N(CH ₂) ₅]		
	-293.3 [4,6-(NH ₂) ₂]		
2,4-Diamino-5,6-tetramethylene-	-174.1 (N1,N3)	0.5 M in DMSO ^b	6113
	-305.1 (2-NH ₂)		
	-302.6 (4-NH ₂)	0.5 M in TFA ^b	6113
	-247.1 (N1)		
	-245.1 (N3)		
	-296.4 (2-NH ₂)		
2,4-Diamino-5-(3',4',5'-trimethoxybenzyl)-	-278.7 (4-NH ₂)	0.5 M in DMSO ^b	6113
	-163.0 (N1)		

		-174.4 (N3) -304.6 (2-NH₂) -302.3 (4-NH₂) -156.1 (N1) -168.4 (N3) -299.2 (2-NH₂) - (4-NH₂)	0.4 M in DMSO	6042
	/3-oxide	-164.9 (N1) -168.8 (N3) -308.6 (2-NH₂) -309.5 (4-NH₂) -160.5 (N1) -164.2 (N3) -304.6 (2-NH₂) -303.9 (4-NH₂)	in DMSO ^b	6113
		-92.6 (N1) -94.5 (N3) -93.7 (N1,N3) -246.9 (N1) -98.6 (N3) -194.4 (=NH)	4.5 M in DMSO	6092
499	2,4-Dichloro-	-229.2 (N1) -115.7 (N3) -283.3 (NH₂) -150.0 (N1) -160.9 (N3)	0.5 M in DMSO ^b	6451
	4,6-Dichloro-	-132.0 (N1,N3) -311.9 (NMe₂) -94.5 (N1) -85.4 (N3)	0.5 M in DMSO ^b	6451
	1,2-Dihydro-2-imino-1-methyl-		0.5 M in DMSO ^b	6113
	/HCl		0.5 M in DMSO ^b	6113
	2,4-Dimethoxy-		0.5 M in DMSO ^b	6451
	2-Dimethylamino-		0.5 M in DMSO ^b	6113
	5-Ethoxycarbonyl-2,4-dimethyl-		0.5 M in DMSO ^b	6451

TABLE XIX: Continued

Pyrimidine	Shift ^a	Strength and Solvent	Ref.
2-Fluoro-	-133 ± 4*	c. 5% in AcMe	6365
2-Iodo-	-69 ± 4*	c. 5% in AcMe	6365
2-Methoxy-	-127 ± 4*	c. 5% in AcMe	6365
2-Methoxysulfinyl-	-101 ± 4*	c. 5% in AcMe	6365
4-Methyl-	-93.1 (N1) -84.7 (N3)	0.5 M in DMSO ^b	6451
5-Methyl-	-85.9 (N1,N3)	0.5 M in DMSO ^b	6451
2-Methyl-5-phenyl-	-87.5 (N1,N3)	0.5 M in DMSO ^b	6451
2-Methylthio-	-101 ± 4*	c. 5% in AcMe	6365
4-Phenyl-	-89.2 (N1) -94.5 (N3)	0.5 M in DMSO ^b	6451
2,4,5-Triamino-	- (N1,N3) -311.2 (2-NH ₂) -316.3 (4-NH ₂) -357.3 (5-NH ₂)	0.5 M in DMSO ^b	6113
/HCl	-218.8 (N1,N3) -310.1 (2-NH ₂) -309.0 (4-NH ₂) -357.3 (5-NH ₂)	0.5 M in DMSO ^b	6113
2,4,6-Triamino-	-189.5 (N1,N3) -304.0 (2-NH ₂) -306.0 [4,6-(NH ₂) ₂] -261.7 (N1,N3) -291.3 [(NH ₂) ₃]	0.5 M in DMSO ^b 0.5 M in TFA ^b	6113 6113

4,5,6-Triamino-			
	-152.7 (N1,N3)		
	-309.8 [4,6-(NH ₂) ₂]		
	-346.9 (5-NH ₂)	0.5 M in DMSO ^b	6113
/HCl			
	-181.7 (N1,N3)		
	-301.5 [4,6-(NH ₂) ₂]	0.5 M in DMSO ^b	6113
	-343.2 (5-NH ₂)		
2,4,5-Triamino-6-styryl-			
	-173.0 (N1)	0.5 M in DMSO ^b	6113
	-180.2 (N3)		
	-303.4 (2-NH ₂)		
	-311.5 (4-NH ₂)		
	-345.9 (5-NH ₂)		
/HCl			
	-260.8 (N1,N3)	0.5 M in DMSO ^b	6113
	-303.1 (2-NH ₂)		
	-279.4 (4-NH ₂)		
	-336.1 (5-NH ₂)		
	-253.3 (N1)	0.5 M in TFA ^b	6113
	-226.3 (N3)		
	-299.0 (2-NH ₂)		
	-279.0 (4-NH ₂)		
2,4,6-Triamino-5-(3',4',5'-trimethoxybenzyl)-			
	-191.6 (N1,N3)	0.5 M in DMSO ^b	6113
	-305.5 (2-NH ₂)		
	-306.4 [4,6-(NH ₂) ₂]		
	-261.5 (N1,N3)	0.5 M in TFA ^b	6113
	-297.5 (2-NH ₂)		
	-295.9 [4,6-(NH ₂) ₂]		

^aIn ppm from neat nitromethane as external standard, ¹⁴N shifts marked by * and represent N1 + N3 except as indicated; ¹⁵N shifts unmarked.

^bWith 0.1 M Cr(acac)₃ added.

range, from -67 ppm for 2-cyanopyrimidine to -231.5 ppm for 2-aminopyrimidine-*N*-oxide, and although no rules have been reported which enable assignment of the ring-nitrogen resonances by inspection, they are easily distinguished from those of substituent amino groups (*c.* -300 ppm) and nitro groups (*c.* -25 ppm). Cyano groups at *c.* -130 ppm may cause some confusion but they usually exhibit little or no long-range proton coupling in the fully coupled ^{15}N spectra. Assignment of the resonances for individual ring-nitrogen atoms may be very difficult; where a direct comparison with published spectra is impossible or inappropriate, assignment may be simplified by ^{15}N – ^1H coupling constants and selective decoupling of the proton spectra. Particularly difficult assignments have been made with the aid of $\text{Yb}(\text{fod})_3$ -induced shifts.⁶¹¹³ Finally, one method that has proved useful in this laboratory is isotopic enrichment: a specific site in the molecule is enriched by chemical synthesis and assignment is then based on the enriched site, giving rise to greatly increased peak heights.

(2) Resonances for ^{13}C (New)

Assignments in the fully decoupled ^{13}C spectra of pyrimidine derivatives are not straightforward. However, several observations may be made which enable the majority of resonances to be assigned. Fully substituted carbon nuclei relax much more slowly than those with no substituent. Thus, the peak height for a pyrimidine ring-carbon bearing a substituent is much smaller than for a carbon bearing no substituent, enabling the two types of carbon to be distinguished (see Table XIXg). Carbon-5 always appears at a higher field than any of the other ring-carbons. For the great majority of pyrimidine derivatives, this shift to high field for C5 occurs regardless of solvent, of the type, number and position of substituents, and of the state of protonation or otherwise of the ring-nitrogen atoms. There is one condition in which C5 is *not* the resonance at the highest field, namely in the presence of a strongly electron-donating group at the 5-position. Thus, for 5-amino-, 5-dimethylamino-, 5-methoxy- and 5-hydroxypyrimidine, C5 occurs at a lower field than C4 or C6. Even so, the presence of a second substituent, such as an amino or chloro in the 4- or 6-position, is sufficient to re-establish C5 as the highest field resonance.

If one or more of the ring-carbons is unsubstituted, then carbon–proton coupling constants may be used to assign unambiguously all resonances in the spectrum. It has been shown, for a wide range of

pyrimidine derivatives,⁶³¹⁷ that the magnitudes of the C–H coupling constants depend on the positions of the carbon atoms relative to the ring-nitrogen atoms. Hence, for one-bond coupling,

$$^1J(\text{C2}, \text{H2}) > ^1J(\text{C6}, \text{H6}) \simeq ^1J(\text{C4}, \text{H4}) > ^1J(\text{C5}, \text{H5})$$

and are usually of the order of 200, 180, 180, and 170 Hz, respectively. Two- and three-bond couplings show a similar dependence:

$$^2J(\text{C5}, \text{H6}) > ^2J(\text{C6}, \text{H5}) \geq ^2J(\text{C4}, \text{H5}) \quad \text{and}$$

$$^3J(\text{C2}, \text{H6}) > ^3J(\text{C4}, \text{H2}) \simeq ^3J(\text{C6}, \text{H2}) > ^3J(\text{C4}, \text{H6}).$$

Similar rules may be expressed for protonated pyrimidine derivatives.⁶³¹⁸ In general, all one-bond coupling constants increase on protonation of the ring, the increase being larger for carbon atoms closer to the site of protonation. The relative values for one-bond coupling constants are the same as for the unprotonated species. Hence,

$$^1J(\text{C2}, \text{H2}) > ^1J(\text{C6}, \text{H6}) \simeq ^1J(\text{C4}, \text{C4}) > ^1J(\text{C5}, \text{H5})$$

In general, three-bond coupling constants decrease across the protonated nitrogen. The decrease depends on the position (α , β , or γ) of the carbon and hydrogen atom considered, with respect to the site of protonation. Conceivably, these changes in magnitude of coupling constants could be used to elucidate sites of protonation.

B. Differentiation of *O*- and *N*-Methylated Pyrimidines (*New*)

The differentiation of methoxy and *N*-methyl derivatives is not always a simple task. Methoxy resonances in proton-spectra occur in the range of 4.0–4.5 ppm, whereas for *N*-methyl derivatives the range is 3.5–4.2 ppm; hence, there is some overlap between methoxy and *N*-methyl resonances. As many *N*-methyl derivatives of heterocycles have such signals which occur towards the low-field end of the range, this overlap may make it quite difficult to distinguish between methoxy and *N*-methyl resonances.⁶⁴³¹ No such overlap exists in the ¹³C spectra. The range for methoxy carbons is 55–65 ppm while that for *N*-methyl carbons is 35–45 ppm.⁶⁴³² Hence ¹³C is better than ¹H nmr for this purpose. Similar *S*-methyl derivatives are easily distinguished by either ¹H nmr (range: 2.6–2.9 ppm) or by ¹³C nmr (range: 11–15 ppm) spectroscopy.

TABLE XIXg. The ^{13}C Spectra of Pyrimidines^d

Pyrimidine	C2	C4	C5	C6	Other	Solvent	Ref.
Unsubstituted	158.39	156.90	121.86	156.90		DMSO	6312
	159.85	158.35	123.30	158.35		DMSO	6314
	158.60	158.40	123.65	158.40		H ₂ O	6314
	159.06	156.78	121.42	156.78		CDCl ₃	6445
	159.10	157.00	121.70	157.00		CDCl ₃	6450
	153.50	159.85	126.10	159.85		TFA	6314
	152.30	157.90	—	157.90		TFA	6447
	160.00	157.60	—	157.60		neat	6447
	159.20	157.60	122.60	157.60		neat	6448
	159.69	157.66	122.28	157.66		neat	6362
/HCl	157.65	158.55	124.00	158.55		DMSO	6314
/H ₂ SO ₄	153.50	158.90	125.00	158.90		H ₂ O	6314
	152.41	158.99	125.32	158.99		D ₂ O	6362
2-Acetoxy-	156.50	158.00	123.50	158.00	Me: 53.00 CO: 163.80	AcMe	5282
4-Acetoxy-	159.90	155.90	121.80	160.20	Me: 53.30 CO: 165.40	AcMe	5696
5-Acetoxy-2,4-dichloro-	163.86	162.54	122.74	162.06	—	CDCl ₃	6445
2-Amino-	164.90	159.30	111.50	159.30		DMSO	6314
	163.42	157.85	110.04	157.85		DMSO	6312
/HCl	157.45	159.40	112.85	159.40		TFA	6314
	157.65	158.40	111.35	158.40		DMSO	6314
4-Amino-	158.27	163.19	105.06	154.62		DMSO	6312
	153.65	166.70	108.90	144.60		TFA	6314
5-Amino-	147.90	142.35	142.15	142.35		DMSO	6445
	148.90	143.70	144.90	143.70		DMSO	5696
5-Amino-2,4-dichloro-	147.91	146.24	137.13	144.50		CDCl ₃	6445

2-Amino-4,5-dimethyl-	161.93	165.40	116.29	156.96	4-Me:21.58 5-Me:14.33	DMSO	6312
	155.80	177.55	123.10	153.45	4-Me:21.40 5-Me:14.60	TFA	6314
2-Amino-4,6-dimethyl-	163.17	166.61	108.59	166.61	4,6-Me ₂ :23.33	DMSO	6312
	156.80	172.05	133.55	172.05	4,6-Me ₂ :22.10	TFA	6314
4-Amino-2,6-dimethyl-	165.90	163.61	99.93	163.61	2-Me:23.59 6-Me:23.36	DMSO	6312
	165.80	165.70	105.70	158.35	2-Me:21.10 6-Me:19.40	TFA	6314
2-Amino-4,5-dimethyl-	154.54	160.69	109.50	161.89	4-Me:21.55 5-Me:11.62	DMSO	6312
	150.85	154.25	116.25	165.65	5-Me:11.55	TFA	6314
2-Amino-4-methyl-	163.24	166.90	109.35	157.48	Me:23.51	DMSO	6312
	157.00	177.40	113.40	154.05	Me:23.40	TFA	6314
2-Amino-5-methyl-	161.92	157.59	117.87	157.59	Me:14.18	DMSO	6312
	156.00	158.95	124.15	158.95	Me:14.40	TFA	6314
4-Amino-2-methyl-	166.41	163.21	102.00	154.75	Me:25.57	DMSO	6312
	166.35	165.90	107.15	144.80	Me:21.45	TFA	6314
4-Amino-5-methyl-	156.06	153.50	112.82	162.13	Me:15.88	DMSO	6312
	151.75	142.20	119.50	166.55	Me:14.00	TFA	6314
4-Amino-6-methyl-	157.76	163.53	102.90	163.90	Me:23.39	DMSO	6312
	153.55	166.40	107.50	158.00	Me:19.50	TFA	6314
2-Amino-4,5,6-trimethyl-	160.74	164.31	114.27	164.31	4,6-Me ₂ :21.94 5-Me:12.71	DMSO	6312
	154.45	170.10	121.80	170.10	4,6-Me ₂ :20.85 5-Me:12.75	TFA	6314
2-Anilino-	160.70	158.10	112.50	103.00	—	CDCl ₃	4688
2-Anilino-4-chloro-	160.30	159.10	112.20	161.60	—	CDCl ₃	4688

TABLE XIXg (continued)

Pyrimidine	C2	C4	C5	C6	Other	Solvent	Ref.
2-Bromo-	153.40	160.50	121.50	160.50		AcMe	5282
	153.60	159.40	120.20	159.40		CDCl ₃	5282
5-Bromo-	157.30	158.40	121.30	158.40		AcMe	5696
	156.54	157.68	120.76	157.68		CDCl ₃	6445
5-Bromo-2,4-dichloro-	158.82	161.40	118.78	161.52		CDCl ₃	6445
5-Bromo-4,6-dichloro-	155.40	162.00	120.50	162.00		CDCl ₃	6450
5-Bromo-2-piperidino-	160.20	158.00	105.00	158.00	—	CDCl ₃	4688
5-Bromo-2,4,6-trichloro-	160.90	163.10	119.00	163.10		CDCl ₃	6450
4-Carboxy-	166.40	157.20	122.50	161.10	CO : 166.90	DMSO	5696
2-Chloro-	162.00	161.00	121.40	161.00		AcMe	5282
	160.30	160.50	120.80	160.50		DMSO	5282
4-Chloro-	159.10	158.30	122.30	161.40		CDCl ₃	4688
4-Chloro-2-dimethylamino-	162.30	158.70	108.30	161.10	—	CDCl ₃	4688
4-Chloro-2-methylamino-	163.00	159.30	109.70	161.10	—	CDCl ₃	4688
4-Chloro-2- <i>N</i> -methylamino-	161.90	158.80	110.20	161.00	—	CDCl ₃	4688
4-Chloro-2-morpholino-	161.70	158.90	109.60	161.40	—	CDCl ₃	4688
4-Chloro-2-phenyl-	165.60	158.30	119.30	161.60	—	CDCl ₃	4688
4-Chloro-2-piperidino-	161.60	158.80	108.30	161.20	—	CDCl ₃	4688
2-Cyano-	145.50	159.60	125.20	159.60	CN : 116.60	AcMe	5282
2,4-Diamino-	163.05	163.85	95.00	155.50		DMSO	6313
4,6-Diamino-	157.70	163.35	82.60	163.35		DMSO	6313

4,5-Diamino-	149.50	139.10	126.60	155.30	D ₂ O	6446
	144.00	124.80	127.60	157.60	1 M DCl	6446
2,4-Diamino-6-methyl-	163.10	164.45	93.30	164.45	DMSO	6313
				Me : 23.30		
2,4-Dichloro-	162.66	161.04	120.28	159.96	CDCl ₃	6445
4,6-Dichloro-	158.80	162.10	122.00	162.10	CDCl ₃	6450
2,4-Dichloro-5-dimethylamino-	154.27	150.97	143.36	148.93	CDCl ₃	6445
2,4-Dichloro-5-methyl-	157.92	162.30	128.85	159.84	CDCl ₃	6445
2,4-Dichloro-5-nitro-	162.53	155.58	140.83	156.36	CDCl ₃	6445
4,6-Dichloro-5-phenyl-	156.50	161.20	129.10	161.20	CDCl ₃	6450
				Cl' : 132.70		
				C2'-6' : c. 128.75		
1,2-Dihydro-1-methyl-2-oxo-	156.89	165.99	103.96	148.55	CDCl ₃	6432
1,4-Dihydro-1-methyl-4-oxo-	142.04	169.76	112.82	152.45	CDCl ₃	6432
1,6-Dihydro-1-methyl-6-oxo-	151.53	153.58	115.66	161.44	CDCl ₃	6432
1,2-Dihydro-1-methyl-2-thio-	183.38	159.22	109.00	148.65	CDCl ₃	6432
1,4-Dihydro-1-methyl-4-thio-	148.38	197.78	125.15	137.83	DMSO	6432
1,6-Dihydro-1-methyl-6-thio-	152.69	147.49	128.50	183.29	DMSO	6432
2,4-Dimethyl-	166.64	166.29	117.73	156.47	DMSO	6312
				2-Me : 25.54		
				4-Me : 23.54		
				2-Me : 22.60		
				4-Me : 23.85	TFA	6314
4,5-Dimethyl-	155.68	165.06	129.23	155.83	DMSO	6312
				4-Me : 21.59		
				5-Me : 15.17		
				4-Me : 21.90	TFA	6314
				5-Me : 16.20		
4,6-Dimethyl-	157.56	165.89	120.02	165.89	DMSO	6312
	152.40	172.60	126.10	172.60	TFA	6314
				4,6-Me ₂ : 23.39		
				4,6-Me ₂ : 22.85		

TABLE XIXg (continued)

Pyrimidine	C2	C4	C5	C6	Other	Solvent	Ref.
/HCl	153.60	168.90	123.80	168.90	4,6-Me ₂ :23.65	DMSO	6314
2-Dimethylamino-	162.60	157.60	109.00	157.60	—	CDCl ₃	4688
4-Dimethylamino-	157.20	161.70	102.60	153.50	NMe ₂ :37.10	CDCl ₃	6449
5-Dimethylamino-	147.50	140.20	143.60	140.20	NMe ₂ :39.40	CDCl ₃	6449
	147.31	140.07	143.36	140.07	—	CDCl ₃	6445
4-Dimethylamino-1,2-dihydro- 1,5-dimethyl-2-oxo-	156.60	166.50	102.30	146.00	NMe ₂ :40.30 5-Me:18.30 1-Me: —	CDCl ₃	6449
4-Dimethylamino-1,2-dihydro- 1-methyl-2-oxo-	156.90	164.10	91.10	145.50	NMe ₂ :37.60 1-Me: —	CDCl ₃	6449
5-Dimethylamino-4-methyl-	152.00	159.80	148.80	145.70	NMe ₂ :43.20 4-Me:21.50	CDCl ₃	6449
4-Ethoxy-	159.10	169.70	109.10	157.90	Me:14.50 CH ₂ :62.70	AcMe	5696
5-Ethoxycarbonyl-	161.60	158.10	124.60	158.10	Me:14.20 CH ₂ :62.00 CO:163.70	AcMe	5696
4-Ethylthio-	158.80	170.50	119.80	155.20	Me:14.60 CH ₂ :24.00	AcMe	5696
2-Fluoro-	163.90	162.40	120.90	162.40		AcMe	5282
	163.20	161.60	120.10	161.60		CDCl ₃	5282
2-Hydroxy-	159.25	156.78	105.07	156.78		CDCl ₃	6432
/anion	160.70	160.50	108.90	160.50		D ₂ O	5282
/cation	168.50	161.90	110.50	161.90		NaOD/D ₂ O	5282
	150.20	161.90	107.60	161.90		DCl/D ₂ O	5282

4-Hydroxy- /anion /cation	148.98	163.88	116.42	155.72	CDCl ₃	6432
	153.30	169.40	117.20	153.30	D ₂ O	5696
	150.40	161.20	115.90	153.80	DMSO	5696
	156.70	172.70	116.10	154.70	NaOD/D ₂ O	5696
	152.90	161.80	119.70	143.90	DCI/D ₂ O	5696
5-Hydroxy- /anion /cation	151.80	147.60	154.80	147.60	D ₂ O	5696
	129.70	132.90	146.70	132.90	NaOD/D ₂ O	5696
	144.80	147.30	155.00	147.30	DCI/D ₂ O	5696
	130.00	159.60	121.80	159.60	AcMe	5282
2-Iodo-	129.50	158.40	120.80	158.40	CDCl ₃	5282
	181.20	154.00	109.20	154.00	DMSO	5282
2-Mercapto- /anion /cation	184.20	159.20	116.60	159.20	NaOD/D ₂ O	5282
	173.80	159.10	111.70	159.10	DCI/D ₂ O	5282
	149.86	182.82	128.32	149.73	DMSO	6432
4-Mercapto- /anion	156.10	183.80	126.50	151.00	NaOD/D ₂ O	5696
	166.40	160.00	115.80	160.00	AcMe	5282
2-Methoxy-	165.70	159.30	115.00	159.30	CDCl ₃	5282
	158.51	169.35	108.70	156.89	CDCl ₃	6432
5-Methoxy-	152.00	143.80	154.40	143.80	DMSO	5696
	151.57	143.12	153.49	143.12	CDCl ₃	6445
2-Methoxysulfinyl-	166.90	159.60	125.20	159.60	AcMe	5282
	159.80	166.50	117.70	161.80	AcMe	5696
4-Methoxysulfinyl-	167.10	156.81	118.49	156.81	CDCl ₃	6312
	166.30	160.00	123.10	160.00	TFA	6314
2-Methyl-	157.96	166.48	121.07	156.38	DMSO	6312
	159.40	167.95	122.55	157.85	DMSO	6314
4-Methyl- /HCl	152.90	177.30	126.20	155.40	TFA	6314
	155.00	170.90	124.10	156.45	DMSO	6314

TABLE XIX_g (continued)

Pyrimidine	C2	C4	C5	C6	Other	Solvent	Ref.
5-Methyl-	156.42 155.75 150.70	156.96 156.74 159.40	130.83 131.01 138.95	156.96 156.74 159.40	Me: — Me: 15.12 Me: 16.30	CDCl ₃ DMSO TFA	6445 6312 6314
2-Methylamino-	163.40	158.10	110.30	158.10	Me: —	CDCl ₃	4688
2- <i>N</i> -Methylamino-	162.30	157.70	110.80	157.70	Me: —	CDCl ₃	4688
2-Methylthio-	172.90 172.80 173.03	157.60 157.10 157.11	116.90 116.10 116.20	157.60 157.10 157.11	SMe: 13.90 SMe: 13.90 SMe: 14.03	AcMe CDCl ₃ CDCl ₃	5282 5282 6432
4-Methylthio-	158.70 158.24 157.78	170.80 170.70 170.13	119.20 118.86 118.53	154.80 154.02 154.80	SMe: 12.30 SMe: 12.35 SMe: 12.00	AcMe CDCl ₃ DMSO	5696 6432 6432
2-Morpholino-	162.10	157.80	110.30	157.80	—	CDCl ₃	4688
5-Nitro-	163.00 162.50	153.00 152.50	144.00 142.70	153.00 152.50	—	AcMe CDCl ₃	5696 5696
2-Phenyl-	165.00	157.30	119.10	157.30	—	CDCl ₃	4688
2-Piperidino-	162.00	157.70	109.20	157.70	—	CDCl ₃	4688
2,4,5,6-Tetrachloro-	156.40	160.90	127.90	160.90	—	CDCl ₃	6450
2,4,6-Triamino-	162.80	164.30	74.80	164.30	—	DMSO	6313
2,4,6-Trichloro-	160.20	163.10	120.60	163.10	—	neat	6450
2,4,6-Trichloro-5- α -ethoxyethyl-	157.80	160.70	169.20	160.70	—	CDCl ₃	6450
4,5,6-Trichloro-2- α -ethoxyethyl-	171.60	160.00	127.10	160.00	—	CDCl ₃	6450
2,4,6-Trimethyl-	166.23	165.88	116.73	165.88	2-Me: 25.39 4,6-Me ₂ : 23.30	DMSO	6312

4,5,6-Trimethyl- /HCl	167.70	167.35	118.20	167.35	2-Me: 26.95	DMSO	6314
	164.85	172.35	122.90	172.35	4,6-Me ₂ : 24.75	TFA	6314
	167.35	169.00	121.35	169.00	2-Me: 22.20	DMSO	6314
	154.49	163.75	127.14	163.75	4,6-Me ₂ : 22.70	DMSO	6312
					2,4,6-Me ₃ : 23.15	DMSO	6314
					4,6-Me ₂ : 22.08	DMSO	6312
	149.20	170.15	135.85	170.15	5-Me: 13.58	TFA	6314
					4,6-Me ₂ : 21.65		
					5-Me: 14.45		

^a Chemical shifts in ppm from tetramethylsilane.

C. Hydroxy-Oxo and Mercapto-Thioxo Tautomerism (*New*)

Studies of tautomerism in pyrimidines require that a reliable criterion be established for distinguishing between quinonoidal and aromatic structures, such as those illustrated in Fig. 9. It would be reasonable to believe *a priori* that nmr spectroscopy would be a useful technique to employ in the characterization of such structures. Any investigation of tautomerism in this way would require the synthesis of suitable derivatives in order to "fix" each of the tautomeric forms, followed by a comparison of spectra of the parent compound with those of the derivatives to determine which tautomer is present. For instance, to investigate 2-hydroxypyrimidine, two derivatives (2-methoxypyrimidine and 1,2-dihydro-1-methyl-2-oxypyrimidine) are required for comparison, as indicated in Fig. 9(a). 4-Hydroxypyrimidine presents a more complex situation [Fig. 9(b)] because there are three possible tautomers: the aromatic form, the quinonoidal form with the proton residing at N1, and the quinonoidal form with the proton at N3. Thus, three derivatives need to be synthesized. A similar discussion would apply to 2- and 4-mercaptopyrimidine [Fig. 9(a), 9(b)]. Both ^1H and ^{13}C nmr spectroscopy could be used, but for the above simple pyrimidines only ^{13}C studies have been reported recently.^{6432, 6433}

Several criticisms may be leveled against the simplistic view outlined above. Spectra are obtained at relatively high concentrations, and consequently erroneous conclusions may be drawn if the tautomeric equilibrium is concentration-dependent. A far more serious objection is that the presence of a methoxy or an *N*-methyl group would perturb

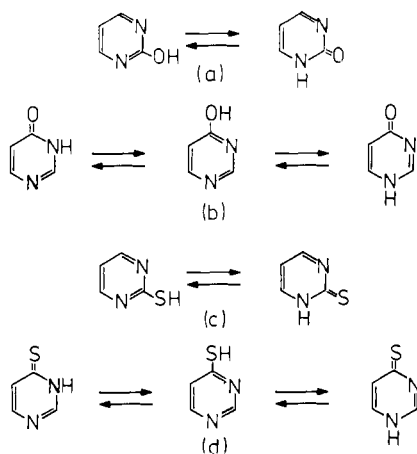


Fig. 9. Tautomeric forms of 2-hydroxy-, 4-hydroxy-, 2-mercapto-, and 4-mercaptopyrimidine (*New*).

the electronic configuration of the pyrimidine ring sufficiently to disturb the chemical shifts of carbon and proton nuclei, thus making a direct spectral comparison of the parent with its derivatives invalid.

The ^{13}C chemical shifts for two tautomeric pyrimidines, together with those for their fixed tautomeric derivatives, are listed in Table XIXh. It has been shown unambiguously that for hydroxy- and mercaptopyrimidines (at least for concentrated solutions in DMSO) the labile proton is resident on the ring-nitrogen adjacent to the carbon bearing sulfur or oxygen.⁶⁴³⁴ Hence, it could be expected that the spectra of 2-hydroxypyrimidine and 1,2-dihydro-1-methyl-2-oxopyrimidine would be similar, and likewise those of 4-mercaptopyrimidine and 1,6-dihydro-1-methyl-6-thiopyrimidine. Table XIXh indicates that for 2-hydroxypyrimidine, only C5 has a shift similar to that of the corresponding carbon atom in 1,2-dihydro-1-methyl-2-oxopyrimidine. In fact, the shifts for C4 and C6 are so dissimilar in the two compounds that the chemical shifts for the corresponding carbon atoms in 2-methoxypyrimidine are closer to those of the parent compound! A comparable situation occurs with 4-mercaptopyrimidine. The chemical shifts for C4 and C5 compare favorably with the corresponding shifts in 1,6-dihydro-1-methyl-6-thiopyrimidine but shifts for C2 and C6 do not. It must be concluded that comparison of ^{13}C chemical shifts of derivatives with those of the parent compound (with the possible exception of C5) may be unreliable for determining tautomeric forms.

A recent publication⁶⁴³³ has raised the possibility of examining tautomeric equilibria by the use of carbon-proton coupling constants. Single-bond coupling constants for quinonoidal structures appear to be smaller than those for aromatic structures but, unfortunately, the

TABLE XIXh. The ^{13}C Chemical Shifts for Some Tautomeric Pyrimidines (*New*)

Pyrimidine	Shifts ^a					Solvent
	C2	C4	C5	C6	Me	
2-Hydroxy-	159.25	156.78	105.07	156.78		CDCl_3
2-Methoxy-	165.70	159.30	115.00	159.30	54.70	CDCl_3
1,2-dihydro-1-methyl-2-oxo-	156.89	165.99	103.96	148.55	39.33	CDCl_3
4-Mercapto-	149.86	182.82	128.32	149.73		DMSO
4-Methylthio-	157.78	170.13	118.53	154.80	12.00	DMSO
1,4-Dihydro-1-methyl-4-thio-	148.38	197.78	125.15	137.83	39.74	DMSO
3,4-Dihydro-3-methyl-4-thio- ^b	152.69	183.29	128.50	147.49	40.97	DMSO

^a Shifts in ppm from trimethylsilane. See reference 6432.

^b Named thus instead of 1,6-dihydro-1-methyl-6-thiopyrimidine to facilitate comparisons.

difference appears to be too small to be of practical use. Two- and three-bond coupling constants show a considerable variation with structure. The long-range coupling constants that appear to be most useful are $^3J(C\alpha, H\alpha')$ and $^2J(C\beta, H\alpha)$ where α or α' and β refer to the position of the carbon of interest with respect to the nitrogen atom bearing a labile proton. The coupling constant $^3J(C\alpha, H\alpha')$ lies in the range of 9.7–12.4 Hz for the aromatic structures and in the range of 4.4–7.1 Hz for quinonoidal structures. The corresponding ranges for $^2J(C\beta, H\alpha)$ are 7.8–8.2 and 2.4–3.7 Hz, respectively. The facts that the ranges of values do not overlap and that they appear to be only slightly dependent on solvent and substituent effects⁶³¹⁷ give distinct advantages for this method of examining tautomeric equilibria compared with the one described previously.

D. Measurement of pK_a ; Protonation Sites (*New*)

Either ^1H or ^{13}C nmr spectroscopy may be used to determine the ionization constant(s) of a pyrimidine. In the case of ^1H nmr, the signals for those protons adjacent to the site where protonation occurs move downfield. This movement may be substantial on the proton scale (up to 1.0 ppm).^{6435, 6436} By obtaining spectra at a series of pH values, a titration curve of pH against chemical shift may be drawn; the pK_a value may be obtained from the inflection point in this curve.

The situation for ^{13}C spectra is quite different. Here, resonances for carbon atoms adjacent to the site of protonation move upfield to the extent of 5–15 ppm.^{6437, 6438} Resonances for carbon atoms further removed from the site of ionization are generally shifted to a lower field, with the observed shifts being much smaller. As with the use of proton nmr, ^{13}C spectra are obtained at several pH values and a titration curve of pH against chemical shift is drawn; the pK_a is represented by the inflection thereon. Such titration curves for 2,4-diaminopyrimidine are illustrated in Fig. 10.⁶⁴³⁹ Note that both C2 and C4 show an upfield shift on protonation, clearly indicating the site as N1 rather than N3 or either of the amino groups.

Some difficulties may arise when measuring pK_a by means of nmr spectroscopy. A problem encountered in proton nmr arises from the necessity to use deuterated solvents, and some ambiguity exists in the precise measurement of pD values. Although the working rule, pD = pH meter reading + 0.40, may be used to determine pD, it is applicable only to ionic strengths of less than 0.1. Ionic strengths commonly encountered in nmr spectroscopy are much greater than 0.1, so that

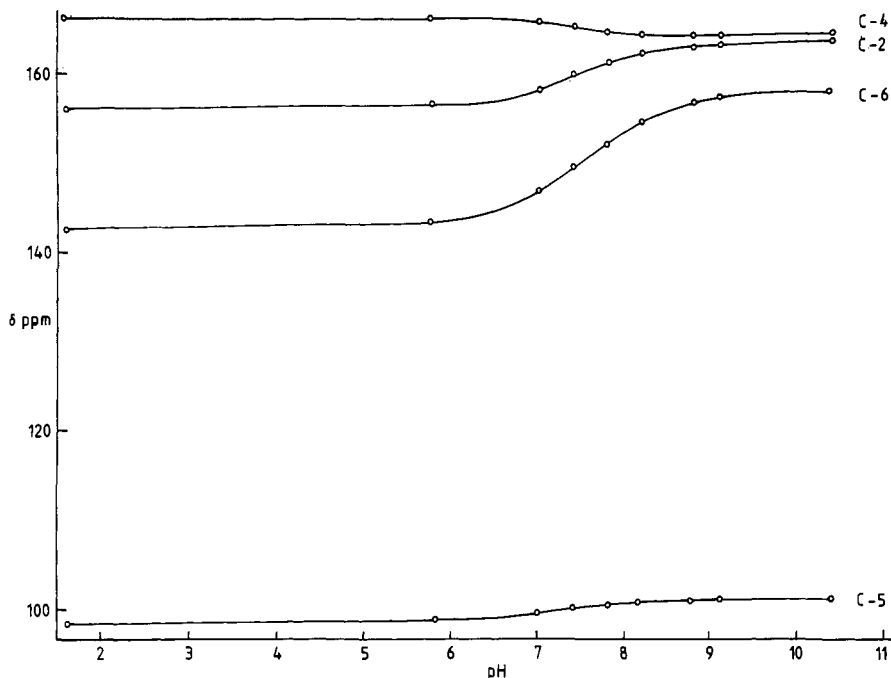


Fig. 10. Titration curves for 2,4-diaminopyrimidine (δ values from sodium trimethylsilylpropanesulfonate).

some discrepancy will exist between the true and measured pD. This applies even more particularly to ^{13}C spectroscopy, in which the lower nuclear sensitivity necessarily requires high concentrations of solute. Furthermore, it must be remembered that, where deuterated solvents are used, the method measures $\text{p}K_a(\text{D}_2\text{O})$ rather than $\text{p}K_a(\text{H}_2\text{O})$, and that the two values may differ by as much as 0.6 units.⁶⁴⁴⁰ This difficulty may be overcome by the use of ^{13}C spectroscopy in nondeuterated solvents.

Concentration effects must also be taken into account. As pointed out above, such effects introduce some ambiguity into the measurement of pD, and it is well known that $\text{p}K_a$ values are also concentration dependent. Ideally, $\text{p}K_a$ measurements should be made at several concentrations and the results extrapolated to zero concentration.

A practical difficulty arises in determining the exact position of the inflection point on the titration curve: visual estimation is inaccurate and a far better technique would be to make use of the Henderson-Hasselbalch equation:⁶⁴⁴¹

$$\text{pH} = \text{p}K_a + \log \frac{\delta_{\max} - \delta}{\delta - \delta_{\min}}.$$

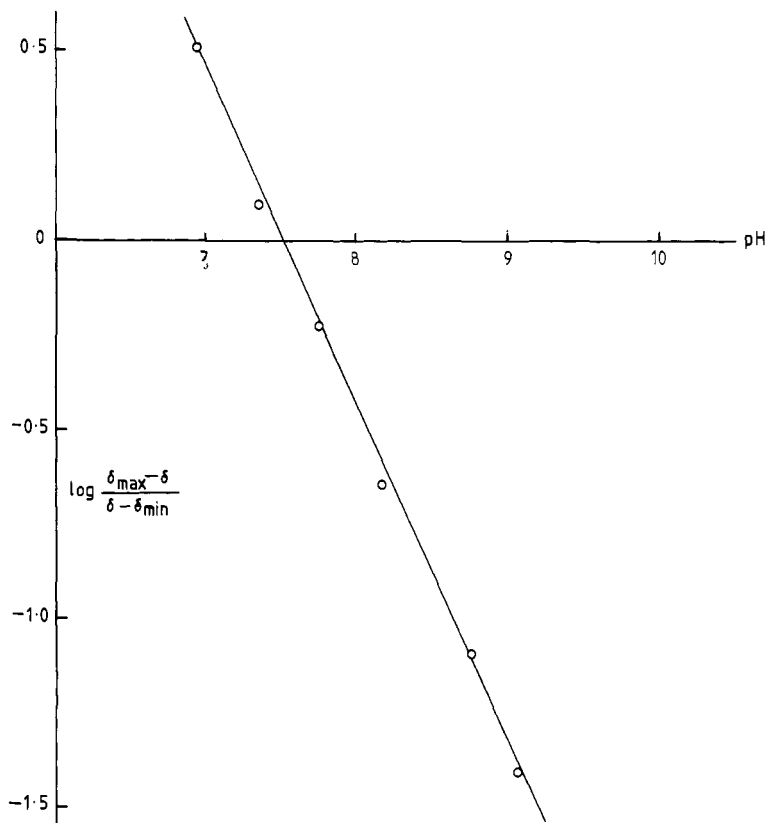


Fig. 11. Titration data for C6 of 2,4-diaminopyrimidine, plotted according to the Henderson-Hasselbalch equation: pK_a 7.50.

The equation is linear in the region of the inflection point, with pK_a indicated at the intersection of the plot with the x -axis. Figure 11 illustrates such data for 2,4-diaminopyrimidine,⁶⁴³⁹ indicating a pK_a value of 7.50 ± 0.05 , which is in reasonable agreement with a published value of 7.40.⁵⁴⁰⁰ Using a similar procedure,⁶⁴³⁸ a pK_a value of 1.55 was obtained for unsubstituted pyrimidine (*cf.* 1.31 by traditional means; *H* 472).

By making use of the above-mentioned observation that carbon atoms adjacent to a site of protonation exhibit an upfield shift, whereas carbon atoms further away move downfield, sites of protonation may be elucidated.^{6433, 6442, 6443} For example, in 2,4-diaminopyrimidine both C2 and C4 move upfield on protonation, indicating that the site of positive charge is N1. It is worth remembering that proton nmr spectroscopy cannot be used with any great success in determining sites of

ionization. The reason is that protons adjacent to the site of ionization in heterocycles do not necessarily show the largest downfield shift on protonation; in fact, protons β to the site of ionization often show a shift as large as, or larger than, those of protons α to the site of ionization.⁶⁴³⁶ Thus, confusion may exist as to which is the α -proton and an incorrect interpretation could be made.

E. Site of *N*-Oxidation (*New*)

The presence of two nitrogen atoms in the pyrimidine molecule presents an obvious problem in the structural elucidation of unsymmetrical-pyrimidine mono-*N*-oxides. An approach that immediately springs to mind is the use of nitrogen nmr spectroscopy. Several authors^{6113, 6444} have reported substantial upfield shifts on mono-*N*-oxidation of pyrimidines. Others⁶⁰⁹² report that for mono-*N*-oxidation of 2,4-diaminopyrimidine and its 5-(3',4',5'-trimethoxybenzyl) derivative the shifts were small, downfield, and of no diagnostic value. All authors agree that a serious problem exists in assignment of nitrogen resonances, which severely limits the utility of nitrogen nmr spectroscopy. It appears therefore that the situation is confused and that nitrogen spectroscopy may prove of little use in elucidating the sites of mono-*N*-oxidation.

A method that appears to be more reliable is to make use of the lanthanide shift reagent, $\text{Eu}(\text{fod})_3$, with proton nmr spectroscopy.^{5088, 6445} It has been shown that $\text{Eu}(\text{fod})_3$ coordinates preferentially to the *N*-oxide function and substantial shifts for protons adjacent to the *N*-oxide can be expected, whereas for those remote from the *N*-oxide function, little or no shift can be anticipated. Thus, the 1- and 3-oxides have been readily so distinguished in 4-ethyl-2,6-dimethyl-, 2,4-dimethyl-6-phenyl-, 4-benzyl-2,6-dimethyl-, 4-ethyl-2-isopropyl-6-methyl-, 4-ethyl-6-methyl-2-phenyl-, and 4-ethoxy-6-methylpyrimidine. Although the method easily distinguishes between the 1- and 3-oxides of the above pyrimidines, the situation may be more complex when there is an alternative site available for coordination with the lanthanide shift reagent. Such a situation could conceivably arise in the case of amino- or hydroxypyrimidines. Clearly, more work is required before this method can be considered as a general technique for distinguishing 1- from 3-oxides.

Appendix

TABLE LVIII. Alphabetical List of Simple Pyrimidines Described in the Approximate Period 1968–1983 Inclusive

Pyrimidine	Melting Point, etc.	References
2-Acetamido	146–147	H, 4760
4-Acetamido-5-acetonyl-6-hydroxy-2-mercaptop	> 300	5982
4-Acetamido-5-acetoxy-2,6-dihydroxy	> 260 or > 300	5060, 5708
2-Acetamido-5-acetoxy-4-hydroxy	269–270	E, 6372
4-Acetamido-1- β -acetylthioethyl-1,2-dihydro-2-oxo	gel	5240
4-Acetamido-1- γ -acetylthiopropyl-1,2-dihydro-2-oxo	148–150	5240
4-Acetamido-2-amino-6-benzoyloxy-5-nitroso	182–183	4633
2-Acetamido-5-amino-4,6-dichloro	135–138	5229, 5637
5-Acetamido-4-amino-2,6-dihydroxy	> 320 (?)	H, E, 5841
5-Acetamido-4-amino-6-hydroxy	> 300	E, 5447
4-Acetamido-2-amino-6-isopropyl-5-nitroso	177–180	4633
5-Acetamido-4-amino-2-mercaptop	> 260	5670
4-Acetamido-6-amino-2-methoxy-5-nitro	185–190	4633
4-Acetamido-2-amino-6-methoxy-5-nitroso	220	4633
5-Acetamido-4-amino-2-methyl	208–210	2562, 5174
5-Acetamido-4-amino-6-methyl-2-methylthio	239–240	5348
4-Acetamido-6-amino-2-methylthio-5-nitroso	184–185	4633
2-Acetamido-4-amino-6-piperidino	3-N-ox: 153	5606
4-Acetamido-2-amino-6-piperidino	3-N-ox: 204	5606
4-Acetamido-1- γ -azidopropyl-1,2-dihydro-2-oxo	133–134	5646
5-Acetamido-4-benzylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	174–175	5850
5-Acetamido-2-benzyl-4,6-dihydroxy	317–321	4715
2-Acetamido-5-benzoyloxy-carbonyl-4-methyl	147–149	5248
4-Acetamido-1-6'-bromohexyl-1,2-dihydro-2-oxo	131–133	5646
2-Acetamido-5-bromo-4-hydroxy-6-methoxycarbonylmethyl	198–200	5704
4-Acetamido-1- γ -bromopropyl-1,2-dihydro-2-oxo	139–142	5628, 5646
2-Acetamido-5-butyl-4-hydroxy-6-methyl	151–153	5392, 5722
4-Acetamido-1- β -s-butylideneamino-oxethyl-1,2-dihydro-2-oxo	205–206	5289
2-Acetamido-4-t-butyl-5-phenyl	105–108	5484
5-Acetamido-4-carbamoyl-2,6-dihydroxy	—	4792

2-Acetamido-5-carboxy-4-methyl	247–249	5248
5-Acetamido-4-carboxy-2-phenyl	179–180	5699
5-Acetamido-4-chloro-2,6-dihydroxy	241–242	5387
2-Acetamido-4-chloro-6-hydroxy-5-nitro	260	5229, 5637
2-Acetamido-4-chloro-5-isoamyl-6-methyl	95–97	2816
4-Acetamido-5-diacetylamino-6-methyl-2-methylthio	147–148	5348
5-Acetamido-2,4-diamino-6-hydroxy	>320	E, 4642
4-Acetamido-2,5-diamino-6-methoxy	122	4633
4-Acetamido-5,6-diamino-2-methylthio	210 then 285–290	4633
5-Acetamido-4,6-diamino-2-phenyl	285–286	5399
2-Acetamido-4,6-dichloro-5-nitro	224	5229, 5637
4-Acetamido-1,2-dihydro-1- γ -isothiuronio-6-oxo	bromide: 228–230	5240
4-Acetamido-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo	168	4644
4-Acetamido-1,2-dihydro-2-oxo-1-vinyl	240–242	5567
4-Acetamido-2,6-dihydroxy	>350	5446
4-Acetamido-2,6-dihydroxy-5-methoxy	>300	5708
5-Acetamido-2,4-dihydroxy-6- <i>N</i> -phenylcarbonyl	—	4792
5-Acetamido-2,4-dimercapto-6-methyl	344–347	5689
2-Acetamido-4-dimethoxymethyl-6-hydroxy	163–166	5300
2-Acetamido-4,6-dimethyl	123; 1- <i>N</i> -Ox: 148	H, 4592, 6342
4-Acetamido-2,6-dimethyl	182–183	H, E, 5098
4-Acetamido-2-dimethylamino-6-hydroxy	293–295	4633
4-Acetamido-2-dimethylamino-6-hydroxy-5-nitro	273–275	4633
4-Acetamido-2-dimethylamino-6-methoxy	c. 170	4644
4-Acetamido-2-dimethylamino-6-methoxy-5-nitro	189	E, 4633
4-Acetamido-2-dimethylamino-5-nitro	160	4633
2-Acetamido-4,6-diphenyl	168	4633
5-Acetamido-4-ethoxycarbonyl-2,6-dihydroxy	226–227	4760, 6210
4-Acetamido-1- β -ethoxycarbonyl-1,2-dihydro-2-oxo	277	4792
2-Acetamido-5- β -ethoxycarbonyl-4-hydroxy-6-methyl	131–132	5240
4-Acetamido-5-ethoxycarbonyl-2-hydroxy	135–137	5707
2-Acetamido-5-ethoxycarbonyl-4-methyl	217	3474
5-Acetamido-4-ethoxycarbonyl-2-phenyl	177–179	5248
	147–149	5699

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Acetamido-1- γ -ethoxycarbonylpropyl-1,2-dihydro-2-oxo	112-113	5240
5-Acetamido-4- <i>N</i> -ethylacetamido-6-methyl-2-methylthio	148-149	5348
5-Acetamido-4-ethylamino-6-methyl-2-methylthio	218-219	5348
2-Acetamido-4-formyl-6-hydroxy	>300	5300
5-Acetamido-4-hydrazinocarbonyl-2,6-dihydroxy	>330	4792
5-Acetamido-4-hydrazinocarbonyl-2-phenyl	—	5700
5-Acetamido-4-hydrazino-2,6-dihydroxy	324-325	5387
4-Acetamido-2-hydroxy	304-306 or 325	H, E, 5389, 6252
5-Acetamido-2-hydroxy-4,6-diphenyl	302-304	4756
2-Acetamido-4-hydroxyimino methyl	228-229	5243
2-Acetamido-4-hydroxy-5-isoamyl-6-methyl	199-201	2816
2-Acetamido-4-hydroxy-6-methoxycarbonyl	196-201 or 206-207	5511, 5512
2-Acetamido-4-hydroxy-6-methoxycarbonylmethyl	185-186	5704
2-Acetamido-4-hydroxy-6-methyl	222	H, E, 4592
4-Acetamido-2-hydroxy-6-methyl	>300	4387
2-Acetamido-4-hydroxy-6-methyl	307	5722
2-Acetamido-4-hydroxy-5-phenyl	254	E, 4592
2-Acetamido-4-hydroxy-6-phenyl	Cl: 187-189	2816
2-Acetamido-5-isoamyl-4-isothiuronio-6-methyl	162-164	4781
5-Acetamido-4-methoxy	crude; nmr	6140
4-Acetamido-6-methoxycarbonyl-2,5-dimethyl	118-120	5243
2-Acetamido-4-methoxycarbonylmethyl	222-223	6147
5-Acetamido-2-methoxy-4,6-diphenyl	89-91	5243
2-Acetamido-4-methoxy-6-methoxycarbonylmethyl	98-99	5392
2-Acetamido-4-methoxy-6-methyl	153-154	E, 4760
2-Acetamido-4-methyl	140	E, 4449
4-Acetamido-2-methyl	206-207	5103
5-Acetamidomethyl-4-amino-2-ethyl	205 or 209	5103, 5829
5-Acetamidomethyl-4-amino-2-methyl	171-173	5689
5-Acetamido-4-methyl-2,6-bismethylthio	—	5868
4-Acetamidomethyl-2,6-dihydroxy	—	—

2-Acetamidomethyl-4-hydroxy-6-methyl	196-197	6275
5-Acetamido-4-methyl-6-methylamino-2-piperidino	169-170	5685
2-Acetamido-4-methyl-6-phenyl	145-146 or 148	H, 4592, 4760
2-Acetamido-4-phenyl	220-221; 1-N-Ox: 178	4760, 6342
4-Acetamido-5-phenyl	139-143	5477
5-Acetamido-2-phenyl	208-209	H, 3463
5-Acetamido-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	221-222	3278
5-Acetamido-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo	230-231	H, 6013
4-Acetamido-2,5,6-trihydroxy	> 300	5708
5-Acetimidoylamino-4-carboxy-2,6-dihydroxy	360	5705
4-Acetimidoylamino-2,6-dimethyl	148	5135
5-Acetimidoylaminoethyl-4-amino-2-methyl	HCl: 246-250	5103
5-Acetimidoylaminoethyl-4-hydroxy-2-methyl	HCl: 197-202	5103
5-Acetonyl-2-amino-4,6-dihydroxy	> 280	5702
5-Acetonyl-2-amino-4-hydroxy-6-methyl	234	5701
4-Acetonyl-2-amino-6-methyl	136	4417
5-Acetonyl-2-benzyl-4-hydroxy-6-methyl	211	4459
5-Acetonyl-4-t-butyl	oil; anal	6628
4-Acetonyl-6-carboxy-5-chloro-2-hydroxy	192	4890
5-Acetonyl-4-chloro-2,6-dimethyl	80-81	5701
5-Acetonyl-4-chloro-6-dimethylamino	78	5703
5-Acetonyl-4-chloro-6-dimethylamino-2-methyl	52	5703
5-Acetonyl-4-chloro-6-ethyl-2-phenyl	93	4462
4-Acetonyl-5-chloro-2-hydroxy	197	4890
5-Acetonyl-4-chloro-6-hydroxy	170-171	5703
4-Acetonyl-5-chloro-2-hydroxy-6-methoxycarbonyl	225-226	4890
5-Acetonyl-4-chloro-6-hydroxy-2-methyl	188-189	5703
5-Acetonyl-4-chloro-6-methyl-2-methylthio	94-95	5701
5-Acetonyl-4-chloro-6-piperidino	95	5703
4-Acetonyl-2-cyanoamino-6-methyl	207-209	4414
5-Acetonyl-4,6-dichloro	76-77	5703
4-Acetonyl-2,6-dihydroxy	218; oxime: 283	4440
5-Acetonyl-4,6-dihydroxy	265-266	5703
5-Acetonyl-4,6-dihydroxy-2-mercapto	220	5702

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Acetonyl-2,4-dihydroxy-6-methyl	258-259	5701
5-Acetonyl-4,6-dihydroxy-2-methyl	321	5703
5-Acetonyl-4,6-dihydroxy-2-phenyl	299-300	5702
2-Acetonyl-4,6-dimethoxy-5-nitro	86 or 99-100	4809, 6344
4-Acetonyl-2,6-dimethoxy-5-nitro	122-124	6344
2-Acetonyl-4,6-dimethyl	95/4	5653, 6249
4-Acetonyl-2,6-dimethyl	72-74/1	6082, 6249
5-Acetonyl-4-ethyl-1,6-dihydro-1-methyl-6-oxo-2-phenyl	99	4462
5-Acetonyl-4-ethyl-6-methoxy-2-phenyl	122	4462
5-Acetonyl-2-ethylthio-4-hydroxy-6-methyl	172-173	5701
1-Acetonyl-5-fluoro-1,2-dihydro-4-methylthio-2-oxo	195-196	4889
5-Acetonyl-4-hydroxy-2,6-dimethyl	199-200 or 202	4459
4-Acetonyl-6-hydroxy-2-mercaptop	190	4440, 5701
5-Acetonyl-4-hydroxy-2-mercaptop-6-methyl	257-260	5701
4-Acetonyl-2-hydroxy-6-methyl	250	4414
5-Acetonyl-4-hydroxy-6-methyl-2-methylthio	206-208	4459, 5701
5-Acetonyl-4-hydroxy-6-methyl-2-phenyl	227	H, 4459
4-Acetonyl-2-mercaptop-6-methyl	249	4417
4-Acetonyl-2-methoxy-5-nitro	118-120	6344
4-Acetonyl-6-methyl-2-nitroamino	232-233	4414
4-Acetonyl-6-methyl-2-phenyl	138/3	6249
4-Acetonyl-6-methyl-2-phenylguanidino	204-206	4414
5-Acetonyl-4-phenyl	oil; nmr; anal	6628
2-Acetoxy	75-78/0.4	4382
5-Acetoxy-4-acetoxymethyl-2,6-dihydroxy	255-258	6248
5-Acetoxy-4-acetoxymethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	114-115	6248
5-Acetoxy-4-amino-2,6-dihydroxy	>195	5708
4-Acetoxy-5-benzyl-1-benzylloxy-1,6-dihydro-2-methyl-6-oxo	103	4337
4-Acetoxy-5-benzyl-1-benzylloxy-1,6-dihydro-6-oxo-2-phenyl	113-114	4337
4-Acetoxy-6-benzyl-2-dichloromethyl-5-phenyl	81-82	4740

4-Acetoxy-5-benzyl-1-ethoxy-1,6-dihydro-6-oxo-2-phenyl	100-101	4337
4-Acetoxy-1-benzyl-1,6-dihydro-2,5-dimethyl-6-oxo	97-98	4337
4-Acetoxy-1-benzyl-1,6-dihydro-5-methyl-6-oxo-2-phenyl	136-137	4337
4-Acetoxy-5-benzyl-2-dimethylamino-6-methyl	128-130/0.25	5392
2-Acetoxy-5-benzyl-4,6-diphenyl	189-192	5911
5-Acetoxy-2,4-dichloro-6-methyl	78-80	5729
1-Acetoxy-1,2-dihydro-2-imino-4-phenyl	HClO ₄ : 155	6342
5-Acetoxy-4,6-dihydroxy-2-hydroxyamino	168	4793
5-Acetoxy-2,4-dihydroxy-6-methyl	295	5729
5-Acetoxy-4,6-dihydroxy-2-phenylhydrazino	175	4793
5-Acetoxy-4,6-dihydroxy-2-semicarbazido	200	4793
5-Acetoxy-4,6-dihydroxy-2-thiosemicarbazido	300	4793
2-Acetoxy-5-dimethylamino-methylenamino	102-103	4382
4-Acetoxy-2-dimethylamino-6-methyl-5-propyl	69	5723
5-Acetoxy-2-ethoxycarbonyl-4,6-diphenyl	113-115	5499
4-Acetoxy-1-ethoxy-1,6-dihydro-5-methyl-6-oxo-2-phenyl	93-94	4337
5-β-Acetoxyethyl-4-β-carboxyethyl-6-hydroxy-2-methylthio	140	4569
1-β-Acetoxyethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	160/0.1	5495
1-β-Acetoxyethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	— (anal)	5509
2-Acetoxy-methyl-5-benzyl-4-chloro-6-hydroxy	175-180	5731
5-Acetoxy-methyl-4-carbamoyl-2-methylthio	138-139	3443
5-Acetoxy-methyl-4-cyano-2-methylthio	37-38	3443
2-Acetoxy-methyl-4,5-dichloro-6-hydroxy	203-208	5731
4-Acetoxy-methyl-2,6-dihydroxy	240-242	5366
2-Acetoxy-methyl-4,6-dimethyl	N-Ox: 100	6160
4-Acetoxy-methyl-2,6-dimethyl	H ₂ O: 56	6160
2-α-Acetoxy-α-methyl-ethyl-4-phenyl	75-76	5690
4-Acetoxy-methyl-2-hydroxy-4-mercaptop	206-208	5366
4-Acetoxy-methyl-6-methyl-2-phenyl	3-N-Ox: 97	6136
4-Acetoxy-methyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	128	6274
5-Acetoxy-methyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	99-101	6239, 6391
5-Acetoxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	151-152	5732
5-Acetoxy-2,4,6-trimethyl	N-Ox: 106	6160
2-Acetyl	52	6343

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Acetyl	65-67	E, 6343
5-Acetyl	87-88	6343
4-Acetyl-2-amino-5-ethoxycarbonyl	160	4438, 4439
5-Acetyl-2-amino-4-hydroxy	301-302	6284, 6523
5-Acetyl-2-amino-4-methyl	227; pic: 195	1209
5-Acetyl-4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	202 to 214	E, 4410, 5042, 5446
5-Acetyl-2-benzyl-4-hydroxy-6-methyl	188	5092
5-Acetyl-4-benzyl-6-hydroxy-2-phenyl	215	5092
5-Acetyl-1,3-bis- δ -bromobutyl-1,2,3,4-tetrahydro-2,4-dioxo	²⁰ 1.5670	4828
1-Acetyl-5-bromo-1,2,3,4-tetrahydro-3-isopropyl-6-methyl-2,4-dioxo	69-70	5733
2- δ -Acetylbutyl-4-benzyl-oxo	oil; SC: 123-126	5925
4-Acetyl-5-carboxy-2-hydroxy	236	4438, 4439
4-Acetyl-5-carboxy-2-mercaptop	246	4438, 4439
5-Acetyl-4-chloro-2,6-dihydroxy	> 300	6017
5-Acetyl-4-chloro-2,6-dimethyl	104/8	5077
5-Acetyl-4-chloro-6-methyl-2-phenyl	81	4456
5-Acetyl-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	116 or 132	4941, 5238
5-Acetyl-4,6-dichloro	90-91	5768
1-Acetyl-1,2-dihydro-4-methoxy-5-methyl-2-oxo	107	3465, 5490
1-Acetyl-1,2-dihydro-4-methoxy-2-oxo	93-94	3465
5-Acetyl-1,6-dihydro-1,2,4-trimethyl-6-oxo	89-90	5077
5-Acetyl-2,4-dihydroxy	sp; 294	H, E, 5849, 6017, 6349
5-Acetyl-2,4-dihydroxy-6-methyl	226-227	5601
2-Acetyl-4,6-dimethyl	39-41; 70-72/3	5987, 6343
4-Acetyl-2,6-dimethyl	96-98/20	5987
5-Acetyl-2,4-dimethyl	62-64/3; 96/15	1209, 5077
5-Acetyl-2-dimethylamino-4-methyl	56-57	458
2-Acetyl-4,6-diphenyl	147-150	6343
4-Acetyl-5-ethoxycarbonyl	85/0.05	4438

4-Acetyl-5-ethoxycarbonyl-2-methyl	98/0.03; phenylhydrazone: 176	4438, 4439
4-Acetyl-5-ethoxycarbonyl-2-phenyl	73	4438
4-β-Acetylmethyl-6-amino-2-mercapto-5-phenyl	167	5982
5-Acetyl-4-ethyl-6-hydroxy-2-phenyl	215	5092
5-Acetyl-2-ethyl-4-mercapto-6-methyl	137	E, 6291
4-β-Acetylmethyl-6-phenyl	165–166/0.5	5255
4-β-Acetylhydrazino-2-amino-5-nitro-6-trifluoromethyl	214	5790
4-β-Acetylhydrazino-2-chloro-5-nitro	135 or 137	3214, 5666
4-β-Acetylhydrazino-2-chloro-5-nitro-6-propyl	156–157	5668
4-β-Acetylhydrazino-2-chloro-5-nitro-6-trifluoromethyl	140	5790
4-β-Acetylhydrazino-2,6-dihydroxy	274–275	4721
4-β-Acetylhydrazino-2-dimethylamino-5-nitro-6-trifluoromethyl	208–210	5790
4-β-Acetylhydrazino-2-ethoxy-5-nitro-6-trifluoromethyl	164	5790
4-β-Acetylhydrazino-6-hydroxy-5-nitro	223	5661
4-β-Acetylhydrazino-2-methoxy-5-nitro-6-trifluoromethyl	176	5790
5-Acetyl-4-hydroxy-2,6-dimethyl	207	5077
5-Acetyl-4-hydroxy-2,6-diphenyl	278–280 or 297	4485, 5092
5-Acetyl-4-hydroxy-2-mercapto	310–311	6284, 6523
4-Acetylrimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo	156	H, 6554
4-Acetylrimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-thio	180	6554
5-Acetyl-4-mercapto-6-methyl-2-phenyl	125	E, 6291
4-Acetyl-2-methoxy-6-methyl	61–62	5987
4-Acetyl-6-methyl	74–76	5091
4-Acetyl-4-methyl-2,6-diphenyl	90–92	4485
4-Acetylmethyl-2-hydroxy-6-methyl	202	6001
2-Acetyl-4-methyl-6-phenyl	tosylhydrazone: 152	5987
4-Acetyl-2-methyl-6-phenyl	94–95	5987
4-Acetyl-6-methyl-2-phenyl	82–83	5987
5-Acetyl-4-methyl-2-phenyl	103–104	H, 6258
5-Acetyl-2-methylthio	133–134	6398
2-Acetyl-4-phenyl	116–117	6300
4-Acetyl-6-phenyl	53–54	5091
5-Acetyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	170 or 175	4941, 5238

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Acetyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	160	4941
5-Acetylthio-4-amino-2,6-dihydroxy	> 300	5244
5-Acetylthio-2,4-bis(trimethylsilyloxy)	110–111/0.35	E, 5728
5-Acetylthio-2,4-dihydroxy	253–255	E, 5728
1- γ -Acetylthiopropyl-1,2-dihydro-4-methylthio-2-oxo	60	5240
5- β -Acetylvinyl-2,4-dihydroxy	276–277	5473
5-Allenyl-2-amino-4,6-dimethyl	142	2700
5-Allenyl-4,6-dimethyl-2-methylamino	101	2700
2-Allenylsulfonyl-5-chloro	130	6535
2-Allenylthio-5-chloro	32–34	6535
Alloxan	—	H, E, 4429, 5557
Alloxan/1,3-dimethyl	—	H, E, 5561
Alloxan/1-methyl	—	H, E, 5561
4-Allylamino-5-amino-6-chloro	113	5609
4-Allylamino-6-methyl	<i>N</i> -1-Ox: 255	5724
5-Allyl-2-amino-4-azido-6-phenyl	180–181	5725
1-Allyl-6-amino-3,5-bis- β -cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxo	151	4234
2-Allylamino-5-butyl-4-hydroxy-6-methyl	165–167	5722
2-Allylamino-5- δ -carboxybutyl-4,6-dihydroxy	255–261	6518
4-Allylamino-6-chloro-5-formyl	50–51	5730
4-Allylamino-5-cyano-6-phenyl	93	6129
5-Allyl-2-amino-1- β -diethylaminoethyl-1,6-dihydro-6-oxo-4-phenyl	—	5717
1-Allyl-4-amino-1,2-dihydro-2-oxo	236 or 250–252	5727
2-Allylamino-4,6-dimethyl	73	2700
5-Allyl-2-amino-4,6-dimethyl	133	H, 2700
5-Allyl-4-amino-2,6-dimethyl	190–191	6508
2-Allylamino-5- δ -ethoxycarbonylbutyl-4,6-dihydroxy	238–239	6518
4-Allylamino-5-formyl-6-hydroxy	194–195	5730
2-Allylamino-4-hydroxy-5-methyl	182–183	4572
5-Allyl-2-amino-4-hydroxy-6-methyl	266–267	H, 5722

4-Allylamino-methyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	82–83	4945
5-Allylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	107–109	5415
4-Allyl-5-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	pic: 159–161	5415
4-Allylamino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl	234–236	4660
4-Allylamino-1,2,3,6-tetrahydro-5-nitroso-2,6-dioxo-1,3-diphenyl	310	4660
5-Allyl-4-benzylamino-2,6-dimethyl	104–105	6508
1-Allyl-5-bromo-6-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-3-phenyl	114	4931
1-Allyl-5-bromo-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	136	4925
1-Allyl-5-bromo-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	175	4925
5-N-Allylcarbamoyl-4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	156	4410
1-Allyl-6-chloro-3,5-diethyl-1,2,3,4-tetrahydro-2,4-dioxo	120/0.1	4527
1-Allyl-5-chloro-1,2-dihydro-2-oxo	130–131	6028
5-Allyl-2-chloro-4,6-dimethyl	115/4	2700
5-Allyl-4-chloro-2,6-dimethyl	95/vac	6346
1-Allyl-6-chloro-3-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-5-propyl	162–163/14	5719
1-Allyl-6-chloro-5-ethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	140–141/0.3	5726
1-Allyl-6-chloro-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	50	4657
1-Allyl-5-chloro-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	136	4925
1-Allyl-5-chloro-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	157	4925
1-Allyl-6-chloro-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-5-propyl	190/16	5719
1-Allyl-5-cyano-1,2-dihydro-2-oxo	147–148	E, 5720
1-Allyl-5,6-diamino-3-ethyl-1,2,3,4-tetrahydro-2,4-dioxo	143–145	E, 5718
5-Allyl-4,6-dichloro	96–98/8; 74–76/0.8	4883, 6064
5-Allyl-2-diethylamino-4-hydroxy-6-methyl	110–111	5722
1-Allyl-3,5-diethyl-1,2,3,4-tetrahydro-2,4-dioxo	138/0.3	5726
1-Allyl-1,2-dihydro-2-imino	sp	E, 2633
1-Allyl-1,2-dihydro-2-imino-4,6-dimethyl	HI: 184–186	2700
5-Allyl-1,2-dihydro-2-imino-1,4,6-trimethyl	HI: 203; pic: 146	2700
1-Allyl-1,2-dihydro-4-methoxy-6-nitroamino-2-oxo	163–164	4656
1-Allyl-1,6-dihydro-4-methylthio-6-oxo	69–71	4806
1-Allyl-1,2-dihydro-2-oxo	62–64	5721
5-Allyl-4,6-dihydroxy	240–272	4883, 5882, 6064
1-Allyl-5-dimethylamino-6-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-3-phenyl	132	4931
5-Allyl-2-dimethylamino-4-hydroxy	94	5722

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Allyl-2-dimethylamino-4-hydroxy-6-methyl	96 or 174	5392, 5722
5-Allyl-2-dimethylamino-4-hydroxy-6-phenyl	196	5722
1-Allyl-4-dimethylaminomethyleneamino-1,2-dihydro-2-oxo	133-134	6251
1-Allyl-5-dimethylamino-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	139	4925
1-Allyl-5-dimethylamino-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	180-183/0.4	4925
5-Allyl-2,4-dimethyl-6-methylamino	90-91	6508
5-Allyl-4,6-dimethyl-2-methylamino	92	2700
1-Allyl-5-ethoxycarbonyl-1,2-dihydro-2-oxo	119-122	E, 5720
1-Allyl-5-fluoro-1,2-dihydro-4-methylthio-2-oxo	117	4889
5-Allyl-2-hydroxy-4,6-dimethyl	176	2700
5-Allyl-4-mercapto-2,6-dimethyl	140-141	6346
5-Allylmethylamino-4-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	—	5735
2-Allyloxy	50-52/0.5	5721
2-Allyloxy-5-chloro	25	6028
4-Allyloxy-2-dimethylamino	63-65/01	5392, 5722
5-Allyloxymethyl-4-carbamoyl-2,6-dihydroxy	173-175	6193
5-Allyloxymethyl-2,4-dihydroxy	204	4493
5-Allyloxymethyl-4-ethoxycarbonyl-2,6-dihydroxy	166-169	6193
5-Allyloxymethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	37-39	4993
5-Allyloxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	103-104	5415
2-Allylsulfinyl-5-chloro	82	6535
2-Allylsulfonyl-5-chloro	84	6535
5-Allyl-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thio	oil (anal)	4421
4-Allyl-1,2,3,6-tetrahydro-5-hydroxy-1,3-dimethyl-2,6-dioxo	104-106	5415
1-Allyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-5-propyl	265/760 mm (?)	5739
1-Allyl-1,2,3,4-tetrahydro-3-methyl-6-methylamino-2,4-dioxo	179-180	4657
2-Allylthio-4-amino-6-hydroxy	201-203	5121
2-Allylthio-4-amino-6-hydroxy-5-nitroso	191	6168
2-Allylthio-5-chloro	62-63/0.1	6535

2-Allylthio-4-chloro-5-methoxy	30	4395
2-Allylthio-4,5-dichloro-6-hydroxy	172-174	4894
4-Allylthio-1,2-dihydro-1-methyl-2-oxo	121-123	4421
4-Allylthio-2,3-dihydro-3-methyl-2-oxo	88-89	4421
5-Allylthio-2,4-dihydroxy	231-234	5893
2-Allylthio-4-hydroxy	135 or 140	5121, 6185
2-Allylthio-5-hydroxy	100	4395
2-Allylthio-4-hydroxy-5-methoxy	132-133	4395
2-Allylthio-4-hydroxy-6-methyl	131	H, 5121
2-Allylthio-4-hydroxy-6-phenyl	205-208	5121
2-Allylthio-4-hydroxy-6-propyl	101	5121
2-Allylthio-5-methoxy	140/20	4395
2-Amidino	PhSO ₃ H: 190	E, 2603
2-Amidino-4,6-dimethyl	PhSO ₃ H: 226	H, 2603
4-Amidino-2-dimethylamino	PhSO ₃ H: 228-230; HCl: 286	6181, 6377
4-Amidino-2-methoxy	HCl: 210	6377
2-Amidino-4-methyl-6-phenyl	PhSO ₃ H: 222	2603
4-Amidino-6-methyl-2-phenyl	PhSO ₃ H: 240	2603
2-Amino	pic: 235-237	H, E, 2603, 4356, 5340
4-Amino	149-151; HI: 180	H, E, 4356, 5034, 5340, 5673
5-Amino	164-170 or 171-172	H, E, 4380, 6374
2-Amino-5- α -aminoethylideneamino-4-methyl	165-167	4781
4-Amino-5-aminomethyl	HCl: 270	H, E, 5793
4-Amino-5-aminomethyl-6-carboxy-2-chloro	237	2884
4-Amino-5-aminomethyl-2- β -chlorocyclopropylmethyl	—	5740
4-Amino-5-aminomethyl-2-cyclobutylmethyl	2HCl: 259-262	5469, 5740, 5783
4-Amino-5-aminomethyl-2-cyclopropyl	170-171	5469
4-Amino-5-aminomethyl-2-cyclopropylmethyl	2HCl: 229 or 234	5469, 5783
4-Amino-5-aminomethyl-2-methyl	HCl: 250 or 262	H, E, 4900
4-Amino-5-aminomethyl-2-phenyl	2HI: 268-272	H, E, 5104
4-Amino-1- β -amino-oxyethyl-1,2-dihydro-2-oxo	2HCl: 209 or 210	5240, 5289
4-Amino-1- γ -amino-oxypropyl-1,2-dihydro-2-oxo	2HCl: 106-108	5240

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-4- γ -aminopropylamino-6-hydroxy-5-nitro	268–270	5646
4-Amino-1- γ -aminopropyl-1,2-dihydro-2-oxo	138–140 or 159–162	5240, 5510, 5646
2-Amino-5- γ -aminopropyl-4-hydroxy-6-phenyl	—	5736
2-Amino-5-amyl-4-chloro-6-methyl	HCl: 140	H, 5453
2-Amino-4-amyl-6-hydroxy-5- β -hydroxyethyl	180–181	5361
2-Amino-5-amyl-4-hydroxy-6-methyl	234	5722
4-Amino-2-amyl-oxyl	49–51	6252
2-Amino-4-amyl-oxyl-6-methylamino	97	4655
2-Amino-4-amyl-oxyl-6-methylamino-5-nitro	120	4655
4-Amino-6-amyl-oxyl-2-methylamino-5-nitro	163	4655
2-Amino-4-amyl-oxyl-6-methylamino-5-nitroso	143	4655
4-Amino-6-amyl-oxyl-2-methylamino-5-nitroso	220	4655
4-Amino-2-amylthio	65–66	6252
4-Amino-2-anilino	pic: 270–275	H, 4670
4-Amino-5-anilino	215–216	E, 5128
5-Amino-2-anilino	137	5738
5-Amino-4-anilino	164–165	5128
2-Amino-4-anilino-5- β -chloroethyl	HCl: 186–187	5741
2-Amino-4-anilino-5-cyano-6-phenyl	284–286	4557
2-Amino-4-anilino-1,6-dihydro-1-methyl-5-nitro-6-oxo	292	E, 4635
1-Amino-2-anilino-1,6-dihydro-4-methyl-6-oxo	190–192	4514
4-Amino-5-anilino-2,6-dimethyl	153–154	4506
2-Amino-4-anilino-5-formamido-1,6-dihydro-1-methyl-6-oxo	250	4635
2-Amino-4-anilino-5-formamido-6-hydroxy	252	4635
4-Amino-6-anilino-5-formyl-2-methyl	177–178	4964, 4970
2-Amino-4-anilino-6-hydroxy	259	E, 4635
4-Amino-6-anilino-2-hydroxy	337–339 or 340	E, 5358, 6252
2-Amino-4-anilino-6-hydroxy-5-nitro	328	E, 4635
2-Amino-4-anilino-6-hydroxy-5-nitroso	294	4635
4-Amino-6-anilino-2-methyl	193–195	H, E, 5859

4-Amino-2-anilino-5-methyl-6-phenyl	—	5737
4-Amino-6-anilino-5-nitro	218–219	H, 5078
2-Amino-4-azido-5-butyl-6-phenyl	130–131	5725
2-Amino-4-azido-5-but-2'-ynyl-6-phenyl	172–173	5725
2-Amino-4-azido-5- β -ethoxyethyl-6-phenyl	162–164	5725
2-Amino-4-azido-5- γ -ethoxypropyl-6-phenyl	H ₂ O: 179–180	5725
2-Amino-4-azido-5-ethyl-6-phenyl	180–181	5725
2-Amino-4-azido-5- β -hydroxy- α -methyl-6-phenyl	171–172	5725
2-Amino-4-azido-5- β -methoxyethyl-6-phenyl	197–198	5725
2-Amino-4-azido-5-methoxymethyl-6-phenyl	—	5725
2-Amino-4-azido-5- β -methyl-6-phenyl	185–187	5725
2-Amino-4-azido-5-methyl-6-phenyl	212; HCl: 190	5725
2-Amino-4-azido-6-phenyl	221–222	5725
2-Amino-4-azido-6-phenyl-5-propyl	125–128	5725
2-Amino-4-azido-6-phenyl-5-prop-2'-ynyl	190–191	E, 5725
4-Amino-6-benzamido-2-benzoylthio	185–186	6126
4-Amino-6-benzamido-2-mercapto	220	6125
2-Amino-4-benzamido-6-methoxy-5-nitroso	211–213	4633
4-Amino-6-benzamido-2-methylthio	201–202	6126
2-Amino-4-benzamido-6-piperidino	3-N-Ox: 219	5606
4-Amino-2-benzamido-6-piperidino	3-N-Ox: 162	5606
4-Amino-5-benzoyl-2,6-dimethyl	175	4456
2-Amino-5-benzoyl-4-methoxycarbonyl	208	4438
4-Amino-5-benzoyl-6-methyl-2-phenyl	130	4456
2-Amino-4-benzoyloxy-6-phenyl	122–123	5723
4-Amino-5-benzoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	258	4410
4-Amino-2-benzyl	138–139	4670
4-Amino-5-benzylamino	203–204	3475
5-Amino-4-benzylamino	136	E, 2675
5-Amino-4-benzylamino-6-chloro	202 or 204	E, 5611, 5747
4-Amino-6-benzylamino-2-chloro-5-nitro	217–218	5746
4-Amino-5-benzylamino-2,6-dihydroxy	nmr	5850
4-Amino-5-benzylamino-6-hydroxy	214–216	3475
4-Amino-6-benzylamino-2-hydroxy	304–306	6252

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Amino-4-benzylamino-6-hydroxy	184-185	5357
2-Amino-4-benzylamino-6-hydroxy-5-nitroso	289	E, 4635
5-Amino-2-benzylamino-4-mercapto	157-158	5742
2-Amino-4-benzylamino-6-methyl	<i>N</i> -1-Ox: 229	5724
4-Amino-6-benzylamino-2-methylthio	117-119	6252
4-Amino-6-benzylamino-5-nitro	205-206	H, E, 5078
5-Amino-4-benzylamino-6-piperidino	151	5747
4-Amino-5-benzylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	nmr	5850
4-Amino-1-benzyl-3-benzoyloxy-1,2,3,6-tetrahydro-2,6-dioxo	174-175	5425
4-Amino-1-benzyl-3-benzoyloxy-1,2,3,6-tetrahydro-5-nitroso-2,6-dioxo	190	5425
5-Amino-4- <i>N</i> -benzylcarbamoyl-2,6-dihydroxy	275	4792
2-Amino-5-benzyl-4-carboxy-6-hydroxy	272-273	3183
4-Amino-5-benzyl-6-carboxy-2-hydroxy	258-260	5745
4-Amino-5-benzyl-6-carboxy-2-mercapto	277-279	5745
4-Amino-2-benzyl-6-chloro	166-170	3504
4-Amino-5-benzyl-6-chloro-2-methoxymethyl	171	E, 5751
2-Amino-4-benzyl-5-cyano-6-hydroxy	315-316	6527
4-Amino-6-benzyl-5-cyano-2-phenyl	187	4508
2-Amino-1-benzyl-1,6-dihydro-5-isoamyl-4-methyl-6-oxo	161-163	2816
4-Amino-3-benzyl-2,3-dihydro-6-methylthio-2-oxo	232-233	5036
4-Amino-1-benzyl-1,2-dihydro-2-oxo	300-303	E, 6251, 6252
5-Amino-2-benzyl-4,6-dihydroxy	270-273	4715
2-Amino-5-benzyl-4-dimethylamino-6-hydroxy	233-235	5743
4-Amino-3-benzyl-6-ethoxy-2,3-dihydro-2-thio	229-230	5985
2-Amino-5-benzyl-4-formyl-6-hydroxy	> 300	5743
2-Amino-4- α -benzylhydrazino-6-hydroxy	> 270	5402
4-Amino-2-benzyl-6-hydroxy	253-255	3504
2-Amino-5-benzyl-4-hydroxy-6-methyl	277-278	H, 5722
4-Amino-5-benzylideneamino-2,6-dihydroxy	> 340	H, 5006
4-Amino-5-benzylideneamino-6-hydroxy-2-mercapto	350	5006

4-Amino-5-benzylideneamino-2-methyl	187-189	2562
4-Amino-5-benzylideneamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	225 or 233-235	5006, 5164
2-Amino-4-benzylidenehydrazino-6-hydroxy	285	5001
2-Amino-5-benzylloxy	86-87	4384
4-Amino-2-benzylloxy	80-81	6252
4-Amino-6-benzylloxy	176-178	6252
2-Amino-5-benzylloxy-2-carbonyl-4-methyl	195-197	5248
4-Amino-6-benzylloxy-2-dimethylamino	162-164	4632
4-Amino-6-benzylloxy-2-dimethylamino-5-nitro	132-134	4632, 4649
4-Amino-6-benzylloxy-2-dimethylamino-5-nitroso	164-165	4632
2-Amino-4-benzylloxy-6-formamido-5-nitroso	190	4633
4-Amino-3-benzylloxy-5-formamido-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	230	3397
4-Amino-3-benzylloxy-5-formyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	190	3397
4-Amino-6-benzylloxy-2-hydroxy	235 then 285	6252
2-Amino-4-benzylloxy-5-isoamyl-6-methyl	96-97	2816
4-Amino-6-benzylloxy-2-methylsulfonyl	210-211	6252
4-Amino-6-benzylloxy-2-methylthio	123-124	6252
4-Amino-3-benzylloxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	233-234	5711
4-Amino-3-benzylloxy-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	233	3397
4-Amino-3-benzylloxy-1,2,3,6-tetrahydro-1-methyl-5-nitroso-2,6-dioxo	189	3397
4-Amino-3-benzyl-1,2,3,6-tetrahydro-1-methyl-5-N-methylformamido-2,6-dioxo	204-206	4914
4-Amino-2-benzylthio	118-119	6252
5-Amino-4-benzylthio-6-chloro	75-77	4766
4-Amino-2-benzylthio-3,6-dihydro-5-nitroso-6-oxo-3-phenyl	187-188	6168
5-Amino-4-benzylthio-6-hydrazino	131	5235
4-Amino-2-benzylthio-6-hydroxy	242-244	H, 5121
4-Amino-2-benzylthio-6-hydroxy-5-nitroso	205-206	6168
5-Amino-4-benzylthio-6-mercaptop	178-179	4766
5-Amino-4-benzylthio-6-methoxy	60-62	4816
4-Amino-2,6-bisbenzylamino-5-nitro	183-185	5746
4-Amino-1,5-bis- β -cyanoethyl-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxo	170-171	4234
4-Amino-1,5-bis- β -cyanoethyl-1,2,3,6-tetrahydro-2,6-dioxo-3-propyl	145	4234

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-2,6-bisdimethylamino	105 or 114–116	E, 4643, 4970
4-Amino-2,6-bisdimethylamino-5-nitroso	225–228	4643
2-Amino-4,6-bisdimethylamino-5-nitroso	264–266	E, 5744
5-Amino-4,6-bisdimethylsulfonyl	182–187	6374
5-Amino-4,6-bisdimethylthio	90–92	E, 6374
2-Amino-5-bromo	235–237; <i>N</i> -1-Ox: 236	H, E, 5161, 6729
4-Amino-5-bromo	209–211	H, 5594
5-Amino-2-bromo	182–183	4380
4-Amino-5-bromo-4-bromomethyl-6-hydroxy	200–210	5763
2-Amino-5-bromo-4- <i>t</i> -butyl	120	2602
2-Amino-5-bromo-4-dibromomethyl-6-hydroxy	240–247	5763
2-Amino-5-bromo-4-carboxymethyl-6-hydroxy	HBr: 232	H, 5763
2-Amino-5-bromo-1,6-dihydro-1,4-dimethyl-6-oxo	262	4569
2-Amino-5-bromo-1,6-dihydro-1- β -hydroxyethyl-4-methyl-6-oxo	HBr: 173	4784
2-Amino-5-bromo-1,6-dihydro-1- β -hydroxypropyl-4-methyl-6-oxo	HBr: 193	4784
4-Amino-5-bromo-2,6-dihydroxy	> 320	H, E, 5244
2-Amino-5-bromo-1- β , γ -dihydroxypropyl-1,6-dihydro-4-methyl-6-oxo	214–215	4784
2-Amino-5-bromo-4,6-dimethyl	174–177	H, E, 5161
4-Amino-5-bromo-2,6-diphenyl	160–161	5760
2-Amino-4-bromo-6-hydroxy	233–234	5154, 5158
4-Amino-2-bromo-6-hydroxy	> 280	5153, 5156
4-Amino-5-bromo-2-hydroxy	170–171; HBr: 256	H, E, 5227
4-Amino-5-bromo-6-hydroxy	281–283	E, 5244
2-Amino-5-bromo-4-hydroxy-6-methyl	250	H, E, 5417
2-Amino-4-bromo-6-methoxy	161–163	5154, 5158
4-Amino-5-bromo-4-methoxy	125–126	E, 5156
2-Amino-2-bromo-6-methoxy	186–188	5154, 5158
4-Amino-5-bromo-6-methoxy	158–160	4663
2-Amino-5-bromo-4-methoxy-6-methyl	245–248	E, 5161
2-Amino-5-bromo-4-methyl	192–195	H, E, 5161

4-Amino-5-bromo-2-methyl	138–140	H, 5101
4-Amino-5-bromomethyl-2-methyl	2HB: 207	H, E, 4427
2-Amino-5-bromo-4-methyl-6-methylthio	138–140	E, 5161
4-Amino-5-bromo-2-phenyl	139–141	5755
4-Amino-5-bromo-6-phenyl	178–180	4663
2-Amino-4-bromo-6-propoxy	81–82	5154
5-Amino-2-butoxy	71–73	H, 6510
2-Amino-5-butoxycarbonylmethyl-4-hydroxy	217–218	6519
4-Amino-6-butoxy-2-chloro	91–92	5154
2-Amino-4-butyl	97–99	5757, 6050
2-Amino-4-t-butyl	102–104	H, 5484
4-Amino-5-butyl	103–105	5034, 5752
4-Amino-6-t-butyl	166–170	E, 6667
5-Amino-2-t-butyl	138–139	4364
5-Amino-4-t-butyl	163–165	5753
2-Amino-4-s-butylamino-6-chloro	—	5756
2-Amino-4-t-butylamino-6-chloro	—	5756
5-Amino-4-t-butylamino-6-chloro	174–175	5753
2-Amino-4-t-butylamino-1,6-dihydro-1-methyl-5-nitro-6-oxo	234–237	E, 4635
4-Amino-5-butylamino-2,6-dimethyl	189–190	4506
4-Amino-5-butylamino-6-hydroxy	153–154	3475
4-Amino-6-butylamino-2-hydroxy	303–304	6252
2-Amino-4-t-butylamino-6-hydroxy-5-nitro	>350	E, 4635
5-Amino-4-butylamino-6-mercapto	172–173	4396
4-Amino-5-N-butylcarbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo		
5-Amino-2-t-butyl-4-carboxy	130	4410
2-Amino-5-butyl-4-carboxy-6-hydroxy	105–107	4364
4-Amino-5-butyl-6-carboxy-2-hydroxy	171–172	3183
4-Amino-5-butyl-6-carboxy-2-mercapto	217–218	5745
4-Amino-6-t-butyl-5-chloro	216–217	5745
4-Amino-6-butyl-2-chloro-5-cyano	148–150	4664
4-Amino-2-butyl-6-chloro-5-nitro	185	4901
4-Amino-2-t-butyl-6-chloro-5-nitro	125–126	H, 4570
	116–122	5753

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-6-t-butyl-2-chloro-5-nitro	187-188	5753
2-Amino-1-butyl-4-diethylamino-1,6-dihydro-6-oxo	120	5521
4-Amino-1-butyl-1,2-dihydro-2-oxo	229-231 or 231-233	5727, 6251
4-Amino-1-s-butyl-1,2-dihydro-2-oxo	217-220	5727
2-Amino-1-butyl-1,6-dihydro-6-oxo-4-piperidino	197-198	5521
2-Amino-1-butyl-4-ethoxy-1,6-dihydro-6-oxo	109-111	5521
2-Amino-4- α -butylhydrazino-6-hydroxy	208-215	5402
2-Amino-5-butyl-4-hydroxy	188-189	5754
2-Amino-5-butyl-4-hydroxy-6-methyl	237-239 or 257	E, 5722, 5754
4-Amino-1- β -s-butylideneamino-oxethyl-1,2-dihydro-2-oxo	203-205	5289
2-Amino-4-butyl-5-methyl	127-128	5762
2-Amino-4-t-butyl-5-phenyl	124-125	5484
4-Amino-2-butylthio-6-hydroxy	179-182	E, 5121
4-Amino-2-butylthio-6-hydroxy-5-nitroso	233-234	6168
2-Amino-5- <i>N'</i> -butylureido-4,6-dichloro	228-229	5295
2-Amino-5- <i>N'</i> -butylureido-4,6-dihydroxy	350	5295
2-Amino-5-but-2'-ynyl-4-chloro-6-phenyl	150-151	5725
2-Amino-5-but-2'-ynyl-4-hydroxy-6-phenyl	308-310	5725
5-Amino-2-carbamoyl	233-235	4380
4-Amino-6-carbamoyl-2-chloro-5-hydroxymethyl	237	2884
2-Amino-5-carbamoyl-4,6-dimethyl	281-282	2633
4-Amino-5-carbamoyl-2,6-dimethyl	212-214	5767
2-Amino-5-carbamoyl-4-dimethylamino	246-248	4384
4-Amino-5-carbamoyl-2-hydrazino	280-282	5772
5-Amino-4-carbamoyl-6-hydroxy-2-methylthio	278-279 or 280	5151, 5776
2-Amino-5-carbamoyl-4-methyl	287	2602
4-Amino-2-carbamoylmethyl-5-formyl	249-250	4433
2-Amino-5-carbamoylmethyl-4-hydroxy	295	H, 5973
4-Amino-2-carbamoylmethyl-5-hydroxymethyl	230-231	4433
4-Amino-5-carbamoylmethyl-2-methyl	250	H, 4427

4-Amino-5-carbamoyl-6-phenyl	256-257	5767
4-Amino-5-carbamoyl-2-propyl	204-205	4570
4-Amino-5-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	257-259	5514
2-Amino-4-carboxy	275	H, E, 5621
5-Amino-2-carboxy	270-274	4380
5-Amino-4-carboxy	256-258	4364
4-Amino-5- δ -carboxybutyl-2,6-dihydroxy	293-295	6519
4-Amino-5- δ -carboxybutyl-6-hydroxy-2-mercapto	288-290	6519
4-Amino-5-carboxy-2-carboxymethyl	258	4433
5-Amino-4-carboxy-2-chloro	155	4364
4-Amino-5-carboxy-2,3-dihydro-3-methyl-2-thio	306	5665
4-Amino-5-carboxy-2,3-dihydro-2-oxo-3-phenyl	284-286	4920
2-Amino-5-carboxy-4,6-dihydroxy	270-275	5777
5-Amino-4-carboxy-2,6-dihydroxy	HCl: > 220	H, E, 5137
2-Amino-5-carboxy-4-dimethylamino	> 250	4384
4-Amino-6-carboxy-5-ethoxymethyl-2-hydroxy	> 200	5745
4-Amino-6-carboxy-5-ethoxymethyl-2-mercapto	> 200	5745
2-Amino-1- β -carboxyethyl-1,6-dihydro-4-methyl	244-245	5773
4-Amino-1- β -carboxyethyl-1,2-dihydro-2-oxo	266-268	5240
2-Amino-4-carboxy-5-ethyl-6-hydroxy	275-276	3183
4-Amino-6-carboxy-5-ethyl-2-hydroxy	247-248	5745
4-Amino-6-carboxy-5-ethyl-2-mercapto	238-239	5745
4-Amino-5- β -carboxyethyl-2-methyl	HCl: > 300	E, 5766
4-Amino-5- β -carboxyethyl-6-methyl-2-phenyl	HCl: 187-189	5766
2-Amino-4-carboxy-6-hydroxy	> 300	H, E, 5763
4-Amino-5-carboxy-2-hydroxy	256	H, E, 5778
4-Amino-5-carboxy-2- β -hydroxyethyl	270-272	4433
4-Amino-6-carboxy-2-hydroxy-5-isobutyl	249-250	5745
4-Amino-6-carboxy-2-hydroxy-5-isopropoxymethyl	> 200	5745
2-Amino-4-carboxy-6-hydroxy-5-isopropyl	241-242	3183
2-Amino-4-carboxy-6-hydroxy-5-methyl	300-301	E, 3183
2-Amino-5-carboxy-4-hydroxy-6-methyl	263-265	E, 5777
4-Amino-6-carboxy-2-hydroxy-5-methyl	258-260	5745
5-Amino-4-carboxy-6-hydroxy-2-methylthio	247-249	5776

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-6-carboxy-2-hydroxy-5-phenyl	356–359	5745
2-Amino-4-carboxy-6-hydroxy-5-propyl	278–279	3183
4-Amino-6-carboxy-2-hydroxy-5-propyl	219–221	5745
4-Amino-6-carboxy-5-isobutyl-2-mercapto	231–232	5745
4-Amino-6-carboxy-5-isopropoxymethyl-2-mercapto	> 220	5745
4-Amino-6-carboxy-2-mercapto-5-methyl	241–243	5745
4-Amino-6-carboxy-2-mercapto-5-phenyl	279–281	5745
4-Amino-6-carboxy-2-mercapto-5-propyl	233–234	5745
4-Amino-5-carboxy-2-methyl	270 to 280	H, E, 4433, 4908, 5829
2-Amino-1-carboxymethyl-1,4-dihydro-6-methyl-4-oxo	228–230	4764
2-Amino-1-carboxymethyl-1,6-dihydro-4-methyl-6-oxo	240–241	H, 4764
4-Amino-1-carboxymethyl-1,2-dihydro-2-oxo	280	5269
4-Amino-3-carboxymethyl-2,3-dihydro-2-oxo	HCl: > 300	5771
4-Amino-5-carboxymethyl-2,6-dihydroxy	—	H, 5422
2-Amino-4-carboxymethyl-6-hydroxy	185–190	H, 5763
2-Amino-5-carboxymethyl-4-hydroxy	317–319	6519
4-Amino-2-carboxymethyl-5-hydroxymethyl	167	4433
2-Amino-4-carboxymethylthio-5-phenyl	271–272	3532
4-Amino-2-carboxymethylthio-5-phenyl	138–140	5861
2-Amino-1- γ -carboxypropyl-1,2-dihydro-2-oxo	235	5240
2-Amino-5-chloro	232 to 238; N-Ox: 219	H, E, 4488, 5662, 5673, 6729
4-Amino-2-chloro	200	H, E, 5327
4-Amino-6-chloro	218–220	H, E, 5153, 5852, 5853
5-Amino-2-chloro	196–198	H, 4380
2-Amino-4-chloro-5- β -chloroethyl	170–171	5741
2-Amino-4-chloro-5- α -chlorovinyl	178–179	5287
4-Amino-2-chloro-5- α -chlorovinyl	159–160	5287

4-Amino-2-chloro-6-cyano	232–234	4820
4-Amino-6-chloro-5-cyano	200	5768
2-Amino-4-chloro-5-cyano-6-dimethylamino	219–221	4486
2-Amino-4-chloro-5-cyano-6-ethoxy	191	2286
4-Amino-2-chloro-5-cyano-6-ethyl	232	4901
2-Amino-4-chloro-5-cyano-6-hydroxy	> 350	6503
4-Amino-2-chloro-5-cyano-6-isopropyl	199	4901
2-Amino-2-chloro-5-cyano-6-methyl	253 or 254	4901, 6286
2-Amino-4-chloro-5-cyano-6-methylamino	279	4486
2-Amino-4-chloro-5-cyano-6-methylthio	crude	4901
4-Amino-2-chloro-5-cyano-6-methylthio	crude	4901
4-Amino-6-chloro-5-cyano-2-methylthio	223–226	5581
4-Amino-5-chloro-2-cyclohexyl	124	5755
2-Amino-4-chloro-6-cyclohexylamino	—	5756
2-Amino-4-chloro-5-cyclohexyl-6-methyl	HCl: 230	5453
4-Amino-6-chloro-5- <i>N</i> -cyclopentylformamido	184	5233
2-Amino-4-chloro-6-cyclopropyl	—	5774
4-Amino-2-(2-chlorocyclopropyl)methyl-5-hydroxymethyl	—	5740
4-Amino-2-chloro-6-diallylamino	119–120	5566
2-Amino-5-chloro-4,6-difluoro	crude	5770
4-Amino-5-chloro-2,6-difluoro	crude	5770
2-Amino-5-chloro-1,4-dihydro-4-imino-1-methyl	HI: 268; TFA: 268; TFA/3- <i>N</i> -Ox: 185	5188
4-Amino-5-chloro-2,3-dihydro-3-isopropyl-2-oxo-6-trifluoromethyl	218–220	5589
5-Amino-4-chloro-1,6-dihydro-1-methyl-6-oxo	139	4816
2-Amino-5-chloro-4,6-dimethoxy	176	5769
4-Amino-5-chloro-2,6-dimethyl	164–166	H, E, 5765
5-Amino-4-chloro-2,6-dimethyl	73	H, 5634
4-Amino-6-chloro-2-dimethylamino	154–156	H, E, 5775
5-Amino-2-chloro-4,6-diphenyl	141–143	6147
4-Amino-2-chloro-6-ethoxy	132–133	E, 5154, 5158
5-Amino-6-chloro-2-ethoxy	54–55	4816, 4825
5-Amino-2-chloro-4-ethoxycarbonyl-6-hydrazino	274–276	5260
5-Amino-2-chloro-4-ethoxycarbonyl-6-isopropylidenehydrazino	197–198	5260

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-4-chloro-5-ethoxycarbonyl-6-methyl	crude	4470
2-Amino-4-chloro-6-ethoxycarbonylmethyl	83–84	5759
4-Amino-2-chloro-5-ethoxycarbonyl-6-methyl	crude	4470
4-Amino-2-chloro-6-ethoxycarbonyl-5-nitro	173–174	E, 3199
2-Amino-4-chloro-5- β -ethoxyethyl-6-phenyl	102–105	5725
2-Amino-5-chloro-4-ethoxy-6-methyl	123–125	5161
2-Amino-4-chloro-5-ethyl	178–179	5797
4-Amino-2-chloro-5-ethyl	146–147	5797
4-Amino-5-chloro-1-ethyl-1,2-dihydro-2-oxo	194–196	5798
2-Amino-4-chloro-6-ethyl-5-hexyl	HCl: –	5453
4-Amino-6-chloro-2-ethyl-5-methoxy	193–194	3503
2-Amino-5-chloro-4-ethylthio-6-methyl	125–127	5161
4-Amino-2-chloro-5-fluoro	191 or 197; 3-N-Ox: 200	E, 3464, 5636, 5962
2-Amino-4-chloro-6-fluoromethyl	162	5785
4-Amino-2-chloro-6-fluoromethyl	201–203	5785
4-Amino-6-chloro-2-fluoromethyl	180–181	5785
4-Amino-6-chloro-5-formyl	163–165	E, 5794
5-Amino-4-chloro-6- β -formylhydrazino	–	5231
2-Amino-4-chloro-5-formyl-6-hydroxy	> 190	6503
4-Amino-6-chloro-5-formyl-2-methyl	192–193	4471
4-Amino-6-chloro-5-formyl-2-phenyl	172–174	4471
2-Amino-4-chloro-6-guanidino	220	6384
4-Amino-6-chloro-2-guanidino	2HCl: 245	6384
4-Amino-4-chloro-6-guanidino	HCl: 230	6384
2-Amino-4-chloro-6-hexylamino	–	5756
2-Amino-4-chloro-5-hexyl-6-methyl	HCl: –	5453
5-Amino-2-chloro-4-hydrazino	172	5666
5-Amino-2-chloro-4-hydrazino-6-methyl	crude	5666
5-Amino-4-chloro-6-hydrazino-2-phenyl	176–178	5792
5-Amino-2-chloro-4-hydrazino-6-trifluoromethyl	175	5790

2-Amino-4-chloro-6-hydroxy	257–259 or 261	H, E, 4855, 5722
4-Amino-2-chloro-6-hydroxy	>300	5153, 5156
5-Amino-4-chloro-6-hydroxy	236 or 241	E, 4816, 5435
2-Amino-4-chloro-5- β -hydroxyethyl-6-phenyl	—	5725
4-Amino-2-chloro-6-hydroxy-5-methyl	220	5153, 5156
4-Amino-6-chloro-5-hydroxy-2-methyl	212–220	6373, 6423
2-Amino-4-chloro-6-hydroxy-5-nitro	278	E, 5627, 5646
4-Amino-2-chloro-6-hydroxy-5-phenyl	260–261	5153, 5156
4-Amino-5-chloro-6-hydroxy-2-phenyl	289	4963
2-Amino-4-chloro-6-isobutylamino	—	5756
4-Amino-2-chloro-6-isopropoxy	119–120	5154, 5158
2-Amino-4-chloro-6-isopropyl	99–102	5807
2-Amino-4-chloro-6-isopropylamino	—	5756
5-Amino-4-chloro-6-isopropylamino	182 or 183	5578, 5753
5-Amino-2-chloro-4-isopropylidenehydrazino-6-trifluoromethyl	119–120	5790
5-Amino-2-chloro-4-mercapto	—	E, 2590
2-Amino-4-chloro-6-methoxy	168–169	H, E, 5154
4-Amino-2-chloro-6-methoxy	184–185 or 238	E, 5154, 5158, 5826, 5828
4-Amino-6-chloro-5-methoxy	171	E, 5782
5-Amino-4-chloro-6-methoxy	62–64	E, 5784
2-Amino-4-chloro-6-methoxycarbonylmethyl	104 or 106	5243, 5759
2-Amino-4-chloro-3- β -methoxyethyl-6-phenyl	—	5725
2-Amino-4-chloro-5-methoxy-6-methyl	124–125	E, 5786
2-Amino-4-chloro-6-methoxy-5-methyl	187–189	5154
2-Amino-5-chloro-4-methoxy-6-methyl	142–144	E, 5161
4-Amino-2-chloro-6-methoxy-5-methyl	168–169	5154, 5158
5-Amino-2-chloro-4-methoxy-6-methyl	71–75	E, 5786
2-Amino-4-chloro-5-methoxymethyl-6-phenyl	—	5725
2-Amino-4-chloro-6-methoxy-5-phenyl	211–213	5154
4-Amino-2-chloro-6-methoxy-5-phenyl	174–175	5154, 5158
2-Amino-4-chloro-5-methyl	—	H, 5780
2-Amino-4-chloro-6-methyl	—	H, E, 5780
4-Amino-2-chloro-5-methyl	—	5796

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-2-chloro-6-methyl	—	H, 5780
4-Amino-6-chloro-2-methyl	189	H, E, 5780, 5859
4-Amino-6-chloro-5-methyl	237–238	H, 3520
5-Amino-2-chloro-4-methyl	—	H, 5780
5-Amino-4-chloro-2-methyl	—	5780
2-Amino-4-chloro-5- β -methylallyl-6-phenyl	134–136	5725
2-Amino-4-chloro-6-methylamino	161	H, E, 4655
4-Amino-6-chloro-2-methylamino	208–210	E, 5775
4-Amino-6-chloro-5-methylamino	138–140	5338
5-Amino-2-chloro-4-methylamino	145–146	3783
4-Amino-5-chloromethyl-2-cyclopropyl	HCl: 180–181	5469
4-Amino-5-chloromethyl-2-cyclopropylmethyl	—	5783
2-Amino-4-chloro-6- α -methylhydrazino	196–198	5402
2-Amino-5-chloro-4-methyl-6-methylthio	137–139	5161
2-Amino-4-chloro-6-methyl-5-propyl	HCl: —	E, 5453
4-Amino-6-chloro-2-methylsulfanyl	242–243	4656
2-Amino-4-chloro-5-methylthio	199–200	E, 4332
4-Amino-6-chloro-2-methylthio	132–135	H, E, 5853
5-Amino-4-chloro-6-methylthio	93–95	E, 4766
4-Amino-6-chloro-2-methylthio-5-nitro	179–180	5787
4-Amino-2-chloro-5-nitro	217–218	H, E, 5327
4-Amino-6-chloro-5-nitro-6-phenyl	152–154	H, E, 5791
4-Amino-6-chloro-5-nitro-2-phenyl	213–214	5441
4-Amino-6-chloro-5-nitro-2-propyl	184 or 188	5439, 5792
4-Amino-6-chloro-5-nitro-2-styryl	143	4570
4-Amino-2-chloro-5-nitro-6-trifluoromethyl	196–198	2562
2-Amino-4-chloro-5-phenoxy	125	5440
2-Amino-4-chloro-6-phenyl	—	H, 5780
4-Amino-5-chloro-2-phenyl	—	H, 5725
	139	5755

5-Amino-4-chloro-2-phenyl	144–145	5792
4-Amino-2-chloro-6-phenyl-5-phenylazo	239–241	6067
2-Amino-4-chloro-6-phenyl-5-prop-2'-ynyl	175–177	E, 5725
4-Amino-2-chloro-6-piperidino	223–225	5566
4-Amino-6-chloro-2-piperidino	155–157	5775
4-Amino-2-chloro-6-propoxy	104–105	5154, 5158
2-Amino-4-chloro-6-trifluoromethyl	93	5785
4-Amino-2-chloro-5-trifluoromethyl	146	5789
2-Amino-5-cyano	250	H, E, 4384
4-Amino-5-cyano	250 to 258	H, E, 3752, 3764, 5793
5-Amino-2-cyano	230–231	4380
4-Amino-5-cyano-2,6-biscyanomethyl	—	cf. 5170
4-Amino-5-cyano-2,6-bistrifluoromethyl	168–169	E, 6341
4-Amino-5-cyano-2-cyclobutylmethyl	179–181	5469, 5740, 5783
4-Amino-5-cyano-3-cyclohexyl-2,3-dihydro-2-oxo	249	4941
4-Amino-5-cyano-2-cyclopentyl	161–162	5469, 5783
4-Amino-5-cyano-2-cyclopropyl	185–188	5469
4-Amino-5-cyano-2-cyclopropylmethyl	182–183	5469, 5740, 5783
4-Amino-5-cyano-2,3-dihydro-3-methyl-2-thio	255	5683
4-Amino-5-cyano-2,3-dihydro-2-oxo-3-phenyl	290	H, 4941
2-Amino-5-cyano-4,6-dihydroxy	268–270	5777
2-Amino-5-cyano-4,6-dimethyl	250	2633
4-Amino-5-cyano-2,6-dimethyl	pic: 195	H, E, 4978
2-Amino-5-cyano-4-dimethylamino	161–162	4384
2-Amino-5-cyano-4-dimethylamino-6-ethoxy	113	4486
4-Amino-5-cyano-2,6-diphenyl	211 or 214	H, 4485, 4508
2-Amino-4-cyano-5-ethoxycarbonyl	230–231	2599
4-Amino-2-cyano-5-ethoxycarbonyl	136–138	2599
2-Amino-5-cyano-4-ethoxy-6-methylamino	176	4486
2-Amino-5-cyano-4-ethoxy-6-phenyl	151 or 152–154	4557, 6286
4-Amino-5-cyano-6-ethyl	—	5795
4-Amino-5-β-cyanoethyl-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxo	147	4234
4-Amino-1-β-cyanoethyl-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxo	243–244	4234

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-5-cyano-4-ethyl-6-hydroxy	316-317	6527
4-Amino-5-cyano-2-ethyl-6-isopropyl	—	5795
4-Amino-5-cyano-2-ethyl-6-methyl	—	5809
4-Amino-5-cyano-6-ethyl-2-methyl	—	5809
4-Amino-5- β -cyanoethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	232-235	4234
4-Amino-1- β -cyanoethyl-1,2,3,6-tetrahydro-2,6-dioxo-3-propyl	202-203	4234
4-Amino-5- β -cyanoethyl-1-ethyl-1,2,3,6-tetrahydro-3- β -hydroxyethyl-2,6-dioxo	171-173	4234
4-Amino-5-cyano-2-ethylthio	141	H, E, 3752
4-Amino-5-cyano-2-ethylthio-6-methyl	—	H, 4901
4-Amino-5-cyano-2-hydrazino	234-236	5053
2-Amino-5-cyano-4-hydroxy	>300	4960, 4961
4-Amino-5-cyano-2-hydroxy	—	H, E, 3752, 5781
2-Amino-5-cyano-4-hydroxy-6-methyl	200-265 (?) or >300	5777, 5788, 6527
2-Amino-5-cyano-4-hydroxy-6-phenyl	340-342	6286, 6527
4-Amino-5-cyano-6-hydroxy-2-phenyl	>300	5767
2-Amino-5-cyano-4-isopropoxy-6-phenyl	131-132	6286
4-Amino-5-cyano-6-isopropyl	—	5810
2-Amino-5-cyano-4-mercapto	>260	6527
4-Amino-5-cyano-2-mercapto	>270	H, E, 3752
2-Amino-5-cyano-4-mercapto-6-methyl	>260	6527
2-Amino-5-cyano-4-mercapto-6-phenyl	286-287	6527
2-Amino-5-cyano-4-methoxy	207-208	6286
4-Amino-5-cyano-2-methoxy	221-222	H, E, 6286
2-Amino-5-cyano-4-methoxy-6-methyl	254-255	6286
2-Amino-5-cyano-4-methoxy-6-phenyl	183	6286
4-Amino-5-cyano-2-methoxy-6-phenyl	217	6286
2-Amino-4-cyano-6-methyl	199-200	H, E, 4820
2-Amino-5-cyano-4-methyl	270	H, 2602
4-Amino-5-cyano-2-methyl	249 to 258	H, E, 3752, 4900, 4908

2-Amino-5-cyano-6-methyl-2-phenyl	186–187	4508
2-Amino-5-cyano-4-methylthio	263–264	6527
2-Amino-5-cyano-4-methylthio-6-phenyl	203–205	4557
4-Amino-5-cyano-6-methylthio-2-phenyl	180–182	E, 5767
4-Amino-5-cyano-6-phenyl	194–195	5816, 6129
4-Amino-5-cyano-2-trichloromethyl-6-trifluoromethyl	183–185	6341
4-Amino-2-cyclobutylmethyl-5-hydroxymethyl	133–137	5469, 5740, 5783
4-Amino-5-cyclohex-1'-enyl	162	E, 4489
5-Amino-4-cyclohexylamino-6-hydroxy	210–212	5357
2-Amino-4-cyclohexylamino-6-hydroxy-5-nitro	—	5356
5-Amino-4-cyclohexylamino-6-mercapto	200–202	4396
4-Amino-6-cyclohexylamino-5-nitro	203–204	E, 5078
4-Amino-1-cyclohexyl-1,2-dihydro-2-oxo	271–274	4720, 6114
4-Amino-1-cyclohexyl-5-ethoxycarbonyl-1,2-dihydro-2-oxo	245	4941
2-Amino-5-cyclohexyl-4-hydroxy-6-methyl	315–317	5453
4-Amino-2-cyclohexyl-5-isopropoxymethyl	118–120	5469
2-Amino-5-cyclohexyloxy	—	E, 5813
4-Amino-5-cyclopent-1'-enyl	160	4489
5-Amino-4-cyclopentylamino-6-mercapto	195–197	4396
4-Amino-2-cyclopentyl-5-hydroxymethyl	101–104; HCl: 111 or 133	5469, 5783
2-Amino-4-cyclopropyl	135–137	5774
2-Amino-5-cyclopropyl	—	5774
4-Amino-6-cyclopropyl	—	E, 5812
2-Amino-5-cyclopropyl-4,6-dihydroxy	260	5774
2-Amino-5-cyclopropyl-4,6-dimethoxy	86–88	5774
2-Amino-4-cyclopropyl-6-hydroxy	202–203	5774
2-Amino-4-cyclopropyl-6-hydroxy-5-methyl	72–74	5774
4-Amino-2-cyclopropyl-5-hydroxymethyl	158–162	5469
4-Amino-2-cyclopropyl-5-isopropoxymethyl	118–120	5469
2-Amino-4-cyclopropyl-6-methoxy	—	5774
4-Amino-2-cyclopropylmethyl-5-hydroxymethyl	H ₂ O: 140–141	5469, 5740, 5783
4-Amino-2-cyclopropylmethyl-5-isopropoxymethyl	107–108	5740
5-Amino-2,4-dianilino-6-hydroxy	HCl: 260	4635
2-Amino-5-diazonio-4-di-isopropylamino-6-hydroxy	Cl: 182; zwitterion: 144	4628

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-5-diazonio-4-dimethylamino-6-hydroxy	Cl: 159; zwitterion: 178	4628
2-Amino-5-diazonio-4-hydroxy-6-piperidino	Cl: 176; zwitterion: 165	4628
2-Amino-4,6-dibenzamido-5-nitroso	232-234	4633
4-Amino-2,6-dibenzyl-5-phenyl	105-106	5814
5-Amino-1,3-dibenzyl-1,2,3,4-tetrahydro-2,4-dioxo	181-183	5817
2-Amino-4,6-di- <i>t</i> -butyl	127	6137
4-Amino-2,6-di- <i>t</i> -butyl	88-90	4664
4-Amino-2,6-di- <i>t</i> -butyl-5-chloro	70-72	4664
4-Amino-1,3-dibutyl-1,2,3,6-tetrahydro-2,6-dioxo-5- <i>N</i> -phenyl(thiocarbamoyl)	98-100	4472
2-Amino-4,6-dichloro	218-221	H, E, 4822
4-Amino-2,6-dichloro	270	H, E, 3520
5-Amino-4,6-dichloro	144 or 146	H, E, 5619, 5784
2-Amino-4,6-dichloro-5-cyclopropyl	166-167	5774
5-Amino-2,4-dichloro-6-ethoxycarbonyl	114	5260
2-Amino-4,6-dichloro-5-formyl	> 130; oxime: 150	E, 6503
4-Amino-5,6-dichloro-2-guanidino	HCl: 319	6384
2-Amino-4,5-dichloro-6-isopropylamino	-	5756
4-Amino-5,6-dichloro-2-methyl	145	4963
4-Amino-2,6-dichloro-5-nitro	-	H, 5746
2-Amino-4,6-dichloro-5-phenyl	217-219	H, 4822
4-Amino-5,6-dichloro-2-phenyl	185-187	4963
5-Amino-2,4-dichloro-6-phenyl	133-134	4686
5-Amino-4,6-dichloro-2-phenyl	138-140	5792
2-Amino-4,6-dicyano	195-196	4820
4-Amino-2-di(ethoxycarbonyl)methyl-5-nitro-6-phenyl	94-95	5441
4-Amino-6-di(ethoxycarbonyl)methyl-5-nitro-2-phenyl	122-124	5439
4-Amino-1- β -diethoxyethyl-1,2-dihydro-2-oxo	234 or 243	4749, 5288
2-Amino-4- α -diethoxyethyl-5-ethoxycarbonyl	197	4438
2-Amino-4-diethoxymethyl-5-ethoxycarbonyl	117	4438

5-Amino-2-diethylamino-4,6-diphenyl	128–130	6147
4-Amino-5-diethylamino-2-hydroxy	>300	3475
4-Amino-5-diethylamino-6-hydroxy	207–209	3475
4-Amino-6- δ -diethylamino- α -methylbutylamino-5-nitro	HCl: 131–133	5230
5-Amino-4-diethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	pic: 164–165	4942
4-Amino-2,6-diethyl-5-methyl	–	H, E, 5135
4-Amino-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxo	198–200	H, 5036
4-amino-1,3-diethyl-1,2,3,6-tetrahydro-5-methyl-2,6-dioxo	155–157	E, 5036
4-Amino-1,3-diethyl-1,2,3,6-tetrahydro-5- <i>N</i> -methyl(thiocarbamoyl)-2,6-dioxo	185–190	5037
4-Amino-1,3-diethyl-1,2,3,6-tetrahydro-5- <i>N</i> -methyl(thiocarbamoyl)-6-oxo-2-thio	190–193	5037
4-Amino-1,3-diethyl-1,2,3,6-tetrahydro-2-oxo-6-thio	174–175	4971
2-Amino-4,6-difluoro	230	E, 3520, 5770
4-Amino-2,6-difluoro	206 or 213	5779
4-Amino-2,6-difluoro-6-iodo	195–197	3520
2-Amino-4,6-difluoro-5-methyl	220–223	3520
4-Amino-2,6-difluoro-5-methyl	183–184	5184
1-Amino-1,2-dihydro-4,6-dimethyl-2-oxo	HCl: 250–252	H, 5050
2-Amino-1,6-dihydro-1,4-dimethyl-6-oxo	172–174 (?)	H, E, 5811
4-Amino-1,2-dihydro-1,5-dimethyl-2-oxo	308–310	5815
2-Amino-1,4-dihydro-1- β -hydroxyethyl-6-methyl-4-oxo	194–195	5815
2-Amino-1,6-dihydro-1- β -hydroxyethyl-4-methyl-6-oxo	182	6077
2-Amino-1,4-dihydro-1- β -hydroxyethyl-4-oxo	211–212	5818
4-Amino-1,2-dihydro-1- β -hydroxyethyl-2-oxo	228–229	5824
2-Amino-1,6-dihydro-1- β -hydroxypropyl-4-methyl-6-oxo	198–199	5240
4-Amino-1,2-dihydro-1- γ -hydroxypropyl-2-oxo	HCl: 165–167	E, 4490
2-Amino-1,4-dihydro-4-imino-1-methyl	HI: 280	4506
2-Amino-1,6-dihydro-5-iodo-1,4-dimethyl-6-oxo	223–224	6252
4-Amino-1,2-dihydro-1-isoamyl-2-oxo	240–242	5727
4-Amino-1,2-dihydro-1-iso-butyl-2-oxo	256–257	5773
2-Amino-1,6-dihydro-1- β -isopropoxycarbonyl-4-methyl-6-oxo	HCl: 146–147	4635
2-Amino-1,6-dihydro-4-isopropylamino-1-methyl-5-nitro-6-oxo	H ₂ O: 189–194	5727
4-Amino-1,2-dihydro-1-isopropyl-2-oxo	201–203	

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-2,3-dihydro-3-isopropyl-2-oxo-6-trifluoromethyl	233-235	5589
2-Amino-1,6-dihydro-1- β -methoxycarbonyl-4-methyl-6-oxo	HCl: 142-143	5773
4-Amino-1,6-dihydro-1-methyl-2-methylthio-5-nitro-6-oxo	208	4632
4-Amino-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo	234	4616
4-Amino-3,6-dihydro-3-methyl-2-methylthio-5-nitroso-6-oxo	225 or > 300	4616, 6168
4-Amino-3,6-dihydro-3-methyl-2-methylthio-6-oxo	286	E, 4711
4-Amino-1,6-dihydro-1-methyl-5-nitroso-6-oxo-2-piperidino	182-183	5820
2-Amino-1,4-dihydro-1-methyl-4-oxo	279 or 283-285	E, 5417, 6130
2-Amino-1,6-dihydro-1-methyl-6-oxo	257-260	E, 5665, 6130
4-Amino-1,2-dihydro-1-methyl-2-oxo	268 to 303	H, E, 4468, 5039, 5328, 5613, 6098, 6099, 6171, 6251, 6562, 6821
4-Amino-1,6-dihydro-1-methyl-6-oxo	—	E, 5344
4-Amino-2,3-dihydro-3-methyl-2-oxo	HI: 277	E, 6554
5-Amino-1,6-dihydro-4-methyl-6-oxo-1-phenyl	188-189	5049, 6076
2-Amino-1,6-dihydro-4-methyl-6-oxo-1- β -propoxycarbonyl-ethyl	HCl: 158-159	5773
4-Amino-1,2-dihydro-5-methyl-2-oxo-1-vinyl	220-221	4548
2-Amino-1,6-dihydro-1-methyl-6-thio	232	E, 5665
4-Amino-1,2-dihydro-1-methyl-2-thio	> 240 to 271	E, 4468, 5058, 5665
4-Amino-1,2-dihydro-2-oxo-1-phenyl	337-339	5798
4-Amino-3,6-dihydro-6-oxo-3-phenyl	259-261	5037
4-Amino-1,2-dihydro-2-oxo-1-propyl	256-259	5629, 5646, 5727, 6251, 6252
1-Amino-1,6-dihydro-6-oxo-2,4,5-triphenyl	190	5827
4-Amino-1,2-dihydro-2-oxo-1-vinyl	217-218	4548, 5567
4-Amino-2,5-dihydroxy	> 300	H, E, 5507, 6373
4-Amino-2,6-dihydroxy	278 or > 350	H, E, 4431, 5341
5-Amino-2,4-dihydroxy	—	H, E, 5341
4-Amino-5-2',3'-dihydroxycyclopentyl-2-hydroxy	270	3762

2-Amino-4- α , β -dihydroxyethyl-6-hydroxy			
2-Amino-4,6-dihydroxy-5- β -hydroxyethyl			
5-Amino-2,4-dihydroxy-6-isopropylamino			
4-Amino-2,6-dihydroxy-5-isothiuronio			
4-Amino-2,6-dihydroxy-5-mercapto			
5-Amino-2,4-dihydroxy-6-methoxycarbonyl			
2-Amino-4,5-dihydroxy-6-methyl			
4-Amino-2,5-dihydroxy-6-methyl			
4-Amino-2,6-dihydroxy-5-methyl			
4-Amino-5,6-dihydroxy-2-methyl			
4-Amino-2,6-dihydroxy-5- <i>N</i> -methylformamido			
2-Amino-4,6-dihydroxy-5- <i>N'</i> -methylureido			
2-Amino-4,6-dihydroxy-5-nitro			
4-Amino-2,6-dihydroxy-5-nitroso			
2-Amino-4,6-dihydroxy-5-phenylazo			
5-Amino-2,4-dihydroxy-6-phenylazo			
2-Amino-1- β -dihydroxypropyl-1,6-dihydro-4-methyl-6-oxo			
2-Amino-1- β -dihydroxypropyl-1,2-dihydro-2-oxo			
5-Amino-2,4-dihydroxy-6-sulfo			
4-Amino-2,6-dihydroxy-5-thiocyanato			
2-Amino-4,6-dihydroxy-5-ureido			
2-Amino-4,6-di-isopropyl			
2-Amino-4-di-isopropylamino-6-hydroxy-5-nitro			
5-Amino-2,4-dimercapto			
5-Amino-2,4-dimercapto-6-methyl			
5-Amino-4,6-dimercapto-2-methyl			
4-Amino-2,6-dimethoxy			
4-Amino-5,6-dimethoxy			
5-Amino-4,6-dimethoxy			
2-Amino-4,5-dimethoxy-6-methyl			
2-Amino-4,6-dimethoxy-5-methyl			
4-Amino-2,6-dimethoxy-5-methyl			
4-Amino-5-dimethoxymethyl			
	HCl: 255		4604
	280–281		2638
	HCl: > 300		4627
	Cl: –		5244
	> 320		5244
	255 or 270		4792, 5767
	> 300		H, 5045
	> 300		6373
	310 or 312		H, E, 4526, 5840
	> 203		6373
	314–326		E, 4914
	240–242		5295
	> 320		H, E, 4972
	> 300		H, E, 4574, 4586, 5423
	> 360		H, 5465
	–		5060
	166–167		5824
	178–179		5023
	–		H, E, 5344
	> 300		5244, 5867
	> 400		H, 5295
	80		6137
	266		4628
	–		H, E, 2590
	> 300		H, 5677
	> 360		5689
	188–191 (?)		H, E, 5826
	–		E, 5828
	95–96		E, 5784, 5786
	117–118		E, 5786
	116		H, 3520
	125–126		5154
	78–79		4471

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-4-dimethoxymethyl-6-hydroxy	202–206	5300
2-Amino-4-dimethoxymethyl-6-hydroxy-5-phenylazo	200–202	5300
4-Amino-5-dimethoxymethyl-2-methyl	105 or 108	E, 4471, 5103
4-Amino-5-dimethoxymethyl-2-phenyl	117–118	4471, 5100, 5104
4-Amino-2,6-dimethoxy-5-nitro	180–182	H, 5710
4-Amino-2,6-dimethoxy-5-nitroso	178–181	5710
2-Amino-4,5-dimethyl	159 (?)	H, E, 5821
2-Amino-4,6-dimethyl	152 to 155	H, E, 4476, 4488, 4592, 5821
4-Amino-2,5-dimethyl	—	H, E, 5822
4-Amino-2,6-dimethyl	185 or 190	H, E, 4831, 4978, 5135, 5809
4-Amino-2-dimethylamino	148	E, 4670, 4980
4-Amino-5-dimethylamino	121–124	6107
4-Amino-6-dimethylamino	178 (?) or 212–213	E, 5730, 5852
4-Amino-2-dimethylamino-1,6-dihydro-1-methyl-5-nitro-6-oxo	259–260	4632
4-Amino-2-dimethylamino-1,6-dihydro-1-methyl-5-nitroso-6-oxo	206 or 258–259	4632, 5820
4-Amino-5-dimethylamino-2,6-dimethyl	161–162	4506
5-Amino-2-dimethylamino-4,6-diphenyl	130–132	6147
2-Amino-4-dimethylamino-5-ethoxycarbonyl	106–107	4384
5-Amino-2-dimethylamino-4-ethylamino-6-methyl	94–96	5677
2-Amino-1- β -dimethylaminoethyl-1,6-dihydro-5-methyl-6-oxo-4-phenyl	197	E, 5717
5-Amino-2-dimethylamino-4-ethyl-6-methylamino	69–71	5677
4-Amino-2-dimethylamino-6-ethyl-5-nitro	132–133	5677
4-Amino-6-dimethylamino-5-formyl	201–202	5730
2-Amino-4-dimethylamino-5-hydroxy	pic: 203	6373
2-Amino-4-dimethylamino-6-hydroxy	351	E, 4628
4-Amino-5-dimethylamino-6-hydroxy	219–224	3475
4-Amino-2-dimethylamino-6-hydroxy-5-nitro	292–293	E, 4632, 4633
2-Amino-4-dimethylamino-6-hydroxy-5-nitroso	205	4628

4-Amino-2-dimethylamino-6-hydroxy-5-nitroso	259	H, E, 5820
4-Amino-2-dimethylamino-6-hydroxy-5-sulfo-oxy	208–212	6373
5-Amino-4-dimethylamino-2-mercapto-6-methyl	250	5346
4-Amino-2-dimethylamino-6-methoxy	89	E, 4633
2-Amino-4-dimethylamino-5-methoxycarbonyl	136–137	4384
4-Amino-2-dimethylamino-6-methoxy-5-nitro	188 or 192–193	4632, 4633
4-Amino-2-dimethylamino-6-methoxy-5-nitroso	214	4632
2-Amino-4-dimethylamino-6-methyl	166–167	H, E, 4844
4-Amino-2-dimethylamino-6-methyl	132	3520
4-Amino-6-dimethylamino-2-methyl	190–191	E, 4955, 4964, 4970, 5859
2-Amino-4-dimethylamino-6-methylamino	175–185	4623
2-Amino-4-dimethylamino-6-methylamino-5-nitroso	206	4623
2-Amino-5-dimethylaminomethyleneamino	187–188	4383
4-Amino-6-dimethylaminomethyleneamino-2-thiocyanato	198–199	2859
5-Amino-2-dimethylamino-4-methyl-6-methylamino	109–110	5670
5-Amino-4-dimethylamino-6-methyl-2-methylthio	71–72	H, 5346
4-Amino-2-dimethylamino-6-methyl-5-nitro	148–149	5677
4-Amino-6-dimethylamino-2-methyl-5-nitroso	187	6294
2-Amino-4-dimethylamino-5-methylthio	102–105	4332
4-Amino-2-dimethylamino-5-nitro-6-trifluoromethyl	110	5823
2-Amino-5-dimethylamino-4-phenyl	87–90	6107
4-Amino-6-dimethylamino-2-phenyl	89–91	E, 4970
2-Amino-4-dimethylamino-5-sulfo-oxy	254–258	6373
5-Amino-4-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	142–143	4942
4-Amino-5-dimethylcarbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	182–184	6128
4-Amino-2,6-dimethyl-5-methylamino	261–262	4506
5-Amino-2,4-dimethyl-6-methylamino	185–186	5670
4-Amino-5,6-dimethyl-2-methylthio	157–159	H, 6141
4-Amino-2,6-dimethyl-5-nitro	160	E, 5670
2-Amino-4,6-dimethyl-5-phenyl	179	H, 5662
2-Amino-4,6-dimethyl-5-phenylazo	230	H, 5363
2-Amino-4,5-dimethyl-6-piperidino	3-N-Ox: 173	5724
4-Amino-2,6-dimethyl-5-piperidino	180–181	4506

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-4,6-dimethyl-5-propyl	165-167	2700
2-Amino-4,6-dimethyl-5-prop-1'-ynyl	214	2700
2-Amino-4,6-dimethyl-5-prop-2'-ynyl	153	2700
4-Amino-5- <i>N,N'</i> -dimethylthioureido	191-192	5873
4-Amino-2,6-dimethyl-5-triethylammonio	I: 179-180	4506
4-Amino-2,6-dimethyl-5-trimethylammonio	I: 217-218	4506
2-Amino-4,6-diphenoxy	158	5375
2-Amino-4,6-diphenyl	135-137 or 139	H, E, 4760, 5821, 6210, 6542
4-Amino-2,6-diphenyl	123-124	H, 5760
4-Amino-5,6-diphenyl	224; 1- <i>N</i> -Ox: 252	4685
2-Amino-4,6-dipiperidino	188-189	5188
2-Amino-5-ethoxy	107-109	E, 4384, 4532
5-Amino-4-ethoxy	—	5832
5-Amino-4-ethoxycarbonyl	148	4364
4-Amino-1-ethoxycarbonyl-1,2-dihydro-5-hydroxymethyl-2-oxo	crude	4579
4-Amino-1-ethoxycarbonyl-1,2-dihydro-2-oxo	>280	4579
4-Amino-5-ethoxycarbonyl-2,3-dihydro-2-oxo-3-phenyl	200	4941
5-Amino-4-ethoxycarbonyl-2,6-dihydroxy	284	H, 4792
2-Amino-1- β -ethoxycarbonylmethyl-1,6-dihydro-4-methyl-6-oxo	HCl: 123-124	5773
4-Amino-6-ethoxycarbonyl-2,5-dimethyl	148	6140
2-Amino-5-ethoxycarbonyl-4-hydroxy	—	H, 2599
4-Amino-5-ethoxycarbonyl-2-hydroxy	260-270	H, 2599, 4718, 5389
4-Amino-5-ethoxycarbonyl-2-methoxy	151-153	E, 5623
2-Amino-5-ethoxycarbonyl-4-methyl	212-213	H, E, 6523
4-Amino-1-ethoxycarbonylmethyl-1,2-dihydro-2-oxo	237-239	6245
2-Amino-4-ethoxycarbonylmethyl-6-hydroxy	178	5763
2-Amino-5-ethoxycarbonylmethyl-4-hydroxy	217-218	6519
4-Amino-2-ethoxycarbonylmethyl-6-hydroxy	209	H, 5098
4-Amino-5-ethoxycarbonylmethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	181-182	5138

2-Amino-5-ethoxycarbonyl-4-methylthio	153-154	2599
4-Amino-5-ethoxycarbonyl-2-methylthio	128-130	H, E, 5624
4-Amino-6-ethoxycarbonyl-2-methylthio-5-nitro	130	5443
2-Amino-5-ethoxycarbonyl-4-phenyl	153-154	E, 6166
4-Amino-5-ethoxycarbonyl-2-phenyl	115	4960
5-Amino-4-ethoxycarbonyl-2-phenyl	78-80	5494
4-Amino-5-ethoxycarbonyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	207-208	4410, 4953, 4974
4-Amino-5- β -ethoxycarbonylvinyl-2,6-dimethyl	152	6351
4-Amino-5- β -ethoxycarbonylvinyl-2-isopropyl-6-methyl	93	6351
4-Amino-5- β -ethoxycarbonylvinyl-6-methyl	161-162	6351
4-Amino-5- β -ethoxycarbonylvinyl-6-methyl-2-phenyl	122	6351
4-Amino-6-ethoxy-2,3-dihydro-2-oxo-3-phenyl	265	5985
4-amino-6-ethoxy-2,3-dihydro-3-phenyl-2-thio	260	5985
2-Amino-5- β -ethoxyethoxy	47-49	5813
2-Amino-5- β -ethoxyethoxyethoxy	-	5813
2-Amino-4-ethoxy-5-ethyl	57-58	5797
4-Amino-2-ethoxy-5-ethyl	51-52	5797
2-Amino-5- β -ethoxyethyl-4-hydroxy-6-phenyl	278-280	5725
4-Amino-2-ethoxy-5-fluoro	-	5833
2-Amino-4-ethoxy-6-hydroxy	> 300	E, 4361
4-Amino-2-ethoxy-6-hydroxy	245-246	H, 5153, 5156
5-Amino-4-ethoxy-6-mercapto	193-195	5435
2-Amino-4-ethoxy-6-methyl	86-88	H, E, 5555
2-Amino-5-ethoxymethyl	130-132	5813
4-Amino-6-ethoxy-2-methyl	123	E, 5859
4-Amino-5-ethoxymethyl-2-methyl	85 or 90	H, E, 4427, 5829, 6201
2-Amino-4-ethoxy-6-methyl-5-phenyl	125	5381
4-Amino-2-ethoxy-5-nitro-6-trifluoromethyl	160	5823
2-Amino-4-ethoxy-6-phenyl	143	5371
4-Amino-5-ethoxy-2-phenyl	110-111	4674
4-Amino-5- β -ethoxyvinyl-2-methyl	110-112	5830
2-Amino-4-ethyl	139-141	H, E, 5757, 6050
2-Amino-5-ethyl	142	H, E, 4532

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4- α -Aminoethyl	92–93/12	4379
4-Amino-5-ethyl	160–162	H, 5034, 5752
5- α -Aminoethyl	90–95/15	4379
4-Amino-5- <i>N</i> -ethylacetamido-6-methyl-2-methylthio	174–175	5348
2- β -Aminoethylamino-1,4-dihydro-4-imino-1-methyl	2HCl: 280	4468
4-Amino-2-ethylamino-6-hydroxy	—	5835
4-Amino-5-ethylamino-2-hydroxy	254–256	3475
4-Amino-5-ethylamino-6-hydroxy	207–210	3475
5-Amino-4-ethylamino-6-hydroxy	194–196	3475
4-Amino-2-ethylamino-6-hydroxy-5-nitroso	—	5835
5-Amino-2-ethylamino-4-mercapto	156	5742
5-Amino-4-ethylamino-2-mercapto-6-methyl	>300	5677
5-Amino-4-ethylamino-6-methyl-2-methylthio	143–144	5677
4-Amino-6-ethylamino-5-nitro	185–186	5078
5-Amino-4-ethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	pic: 246	4942
5-Amino-4-ethyl-2,6-bismethylamino	133–134	5677
4-Amino-5- <i>N</i> -ethylcarbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	172	4410, 4442
2-Amino-5-ethyl-1,4-dihydro-4-imino-1-methyl	HI: 288; TFA: 217	5188
4-Amino-5-ethyl-1,2-dihydro-1-methyl-2-oxo	246	5797
4-Amino-1-ethyl-1,2-dihydro-2-oxo	245–247; HBr: 207	5727, 5798, 6251
4-Amino-1-ethyl-1,6-dihydro-6-oxo	pic: 176–177	4697
4-Amino-3-ethyl-3,6-dihydro-6-oxo	215–217	5037
2-Amino-1-ethyl-1,6-dihydro-6-oxo-4-piperidino	276–277	5521
1- β -Aminoethyl-1,6-dihydro-6-oxo-2,4,5-triphenyl	186	5827
2-Amino-5-ethyl-4,6-dihydroxy	340	H, 5296
4- β -Aminoethyl-2,6-dihydroxy	258	E, 4511
4-Amino-5-ethyl-2,6-dihydroxy	321–323	H, 5797
4-Amino-2-ethyl-5,6-dimethoxy	98–100	3503
4-Amino-6-ethyl-2,5-dimethyl	—	5831
4-Amino-5-ethylformamido-6-methyl-2-methylthio	137–138	5348

2-Amino-4-ethyl-5-hexyl-6-hydroxy	184–188	5453
2-Amino-4- α -ethylhydrazino-6-hydroxy	249–250	5402
2-Amino-5-ethyl-4-hydroxy	228 or 232	5754, 5797
4-Amino-5-ethyl-2-hydroxy	277; HCl: 237	H, 5797
2-Amino-4-ethyl-6-hydroxy-5- β -hydroxyethyl	239–240	5361
4-Amino-5-ethyl-6-hydroxy-2-methoxy	226	5153, 5156
2-Amino-5-ethyl-4-hydroxy-6-methyl	283 or 288–289	H, E, 5722, 5754
5- α -Aminoethylidenamino-4-methoxy	140–142	4781
5-Amino-4-ethyl-2-mercapto-6-methylamino	310	5677
4-Amino-6-ethyl-2-mercapto-5-nitro	225	5677
2-Amino-4-ethyl-5-methyl	—	H, 6322
4-Amino-2-ethyl-5-methyl	—	E, 5831
4-Amino-2-ethyl-6-methyl	166–167	5098
5- β -Aminoethyl-4-methyl	132/16; pic: 185	E, 5834
5-Amino-4-ethyl-6-methylamino-2-methylthio	154–155	5677
4-Amino-6-ethyl-5-methyl-2-methylthio	122–123	6141
4-Amino-6-ethyl-2-methylthio-5-nitro	122	5677
4-Amino-5- <i>N</i> -ethyl- <i>N'</i> -methyl- <i>N'</i> -methylthioureido	182–183	5873
2-Amino-5-ethyl-4-phenyl	148–149	5382
2-Amino-4-ethylsulfonyl-6-phenyl	177–178	5038
4-Amino-2-ethylsulfonyl-6-phenyl	195–196	5038
2-Amino-5-ethylthio	116	4532
4-Amino-5- <i>N</i> -ethyl(thiocarbamoyl)-2,6-dihydroxy	> 300	5037
4-Amino-2-ethylthio-3,6-dihydro-5-nitroso-6-oxo-3-phenyl	228–229	6168
4-Amino-2-ethylthio-6-hydroxy	213–215	E, 5121
4-Amino-2-ethylthio-6-hydroxy-5-nitroso	222	H, 6168
5-Amino-4-ethylthio-6-methylamino	91	5678
2-Amino-5-ethylthiomethyl-4-phenyl	86	5382
2-Amino-5- <i>N'</i> -ethylureido-4,6-dihydroxy	> 300	5295
4-Amino-5-ethynyl-2-hydroxy	> 225	5287
2-Amino-5-fluoro	196–198	E, 5857, 5858
4-Amino-6-fluoro	154–155	4752
5-Amino-2-fluoro	178–179	4380
4-Amino-6-fluoro-2,5-bisheptafluoroisopropyl	118–119	5291

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-5-fluoro-2,3-dihydro-3-isopropyl-2-oxo-6-trifluoromethyl	207–209	5589
4-Amino-5-fluoro-1,2-dihydro-1-methyl-2-oxo	> 300	E, 6562
4-Amino-5-fluoro-2,6-dihydroxy	> 300	5840
4-Amino-2-fluoro-5,6-dimethyl	226–228	3520
4-Amino-6-fluoro-2,5-dimethyl	195–196	3520
2-Amino-5-fluoro-4-hydroxy	274–276	E, 5417
4-Amino-5-fluoro-2-hydroxy	295–300; 3-N-Ox: 255	E, 3464, 4895, 5636, 5833, 5962
2-Amino-4-fluoro-6-methyl	198	3520
4-Amino-2-fluoromethyl	151–153	5785
4-Amino-2-fluoro-6-methyl	209–210	3520
4-Amino-6-fluoro-2-methyl	175–176	3520
4-Amino-6-fluoro-5-methyl	232–233	3520
2-Amino-4-fluoromethyl-6-methoxy	121–122	5785
4-Amino-2-fluoromethyl-6-methoxy	156–158	5785
4-Amino-6-fluoromethyl-2-methoxy	141–143	5785
4-Amino-2-fluoromethyl-6-methyl	161–163	5785
4-Amino-6-fluoromethyl-2-methylthio	103–104	5785
4-Amino-6-fluoro-2-phenyl	114	5860
4-Amino-6-fluoro-5-phenyl	152	5860
4-Amino-5-fluorosulfonyl-2-hydroxy	H ₂ O: 209–210	4798
2-Amino-5-formamido	221–222	4380
4-Amino-5-formamido	sp	H, E, 2675
2-Amino-5-formamido-1,6-dihydro-4-isopropylamino-1-methyl-6-oxo	238–240	4635
2-Amino-5-formamido-1,6-dihydro-1-methyl-4-methylamino-6-oxo	> 300	3253
4-Amino-5-formamido-1,6-dihydro-1-methyl-2-methylamino-6-oxo	300–302	3253
4-Amino-5-formamido-1,2-dihydro-1-methyl-2-thio	270–275	5344
4-Amino-5-formamido-2,6-dihydroxy	> 320	H, E, 5841
2-Amino-5-formamido-4-hydroxy-6-isopropylamino	265–267	4635
2-Amino-5-formamido-4-hydroxy-6-methyl	> 300	E, 3253

4-Amino-5-formamido-6-hydroxy-2-methylamino	> 300	3253
2-Amino-4-formamido-6-isopropoxy-5-nitroso	190	4633
2-Amino-4-formamido-6-methoxy-5-nitroso	190	4633
4-Amino-5-formamidomethyl-2-methyl	222–225; pic: 193	H, 5174
4-Amino-5-formamido-6-methyl-2-methylthio	235	2675
4-Amino-5-formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	250	H, E, 4626
4-Amino-5-formyl	181 or 192–193	3764, 4471
4-Amino-5-formyl-2,6-dihydroxy	> 300	6382
5-Amino-4-formyl-2,6-dihydroxy	oxime: > 300	5576
5-Amino-4-formylhydrazino-6-hydroxy	225	5661
2-Amino-4-formyl-6-hydroxy	oxime: sp	5763
4-Amino-5-formyl-2-hydroxy	thiosemicarbazone: –	E, 5846
4-Amino-5-formyl-2-β-hydroxyethyl	162–163	4433
2-Amino-5-formyl-4-hydroxy-6-methyl	340	H, E, 4511
4-Amino-5-formyl-2-methyl	197–198	H, E, 4471, 5830
4-Amino-1-formylmethyl-1,2-dihydro-2-oxo	HCl: sp	4749
4-Amino-5-formyl-2-phenyl	180–181	4471, 5100, 5104
4-Amino-5-formyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	oxime: 248–249	E, 5434
2-Amino-4-guanidino	HCl: 290	6384
2-Amino-4-guanidinoamino-6-methyl	250	5848
2-Amino-5-α-guanidinoiminoethyl-4-methyl	295	5378
4-Amino-2-guanidino-5-nitro	HCl: 303	6384
4-Amino-5-hexyl	119	5034, 5752
5-Amino-4-hexylamino-6-mercapto	151–152	4396
2-Amino-5-hexyl-4-hydroxy	207–208	5754
2-Amino-4-hexyl-6-hydroxy-5-β-hydroxyethyl	210–211	5361
2-Amino-5-hexyl-4-hydroxy-6-methyl	217 to 253	E, 5453, 5722, 5754
2-Amino-5-β-hydrazinocarbonylethyl-4-hydroxy-6-methyl	> 270	5707
2-Amino-4-hydrazino-5,6-dimethyl	220	5848
5-Amino-4-hydrazino-2,6-dimethyl	2HCl: 218–220	5634
2-Amino-4-hydrazino-6-hydroxy	297	E, 5001
4-Amino-2-hydrazino-6-hydroxy	264 or 310	E, 4827, 5053
2-Amino-4-hydrazino-6-hydroxy-5-nitro	> 264	5234
5-Amino-4-hydrazino-6-mercapto	–	E, 5235

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-4-hydrazino-5-methyl	230–234	5848
4-Amino-6-hydrazino-2-methyl	240–242	5859
2-Amino-4-hydrazino-6-methyl-5-nitro	184–185	5848
4-Amino-6-hydrazino-2-methyl-5-nitro	252	2562
4-Amino-6-hydrazino-5-nitro	199; HCl: > 300	E, 2562
4-Amino-6-hydrazino-5-nitro-2-styryl	212–214	2562
1-Amino-2-hydrazono-1,2-dihydro-4,6-dimethyl	122–123	5180
2-Amino-4-hydroxy	247 or 274; 1-N-Ox: 292	H, E, 4591, 4718, 5417
4-Amino-2-hydroxy	310 or 320–325	H, E, 4718, 5798
4-Amino-6-hydroxy	264–265 or 274	H, E, 5491, 5853
5-Amino-4-hydroxy	206–208	H, E, 4357
2-Amino-4-hydroxyamino-6-methyl	> 200	6423
2-Amino-4-hydroxy-5,6-dimethyl	303–306	H, E, 5722, 5754
4-Amino-2-hydroxy-5,6-dimethyl	—	H, E, 4387
4-Amino-2- β -hydroxyethyl-5-hydroxymethyl	167–168	4433
2-Amino-4-hydroxy-5-4'-hydroxybut-1'-enyl	221–224	5429
4-Amino-6-hydroxy-5- β -hydroxyethyl-2-methyl	265–268	4465
4-Amino-6-hydroxy-5- β -hydroxyethyl-2-phenyl	216–220	4465
2-Amino-4-hydroxy-5- β -hydroxyethyl-6-propyl	245–246	5361
4-Amino-2-hydroxy-5-hydroxymethyl	—	H, E, 5615
4-Amino-2-hydroxy-6-hydroxymethyl	> 210	5366
4-Amino-2-hydroxy-5-hydroxysulfonyloxy	—	5507
2-Amino-4-hydroxy-6-iodo	243–244	H, 5154
4-Amino-2-hydroxy-5-iodo	248	H, E, 5847, 6421
2-Amino-4-hydroxy-5-iodo-6-methyl	225–226	4506
4-Amino-6-hydroxy-2-isoamylthio	123–126	5121
4-Amino-6-hydroxy-2-isoamylthio-5-nitroso	224	6168
4-Amino-6-hydroxy-5-isobutyramido	266–268	5447
2-Amino-4-hydroxy-6-isopropyl	246–248	5807

2-Amino-4-hydroxy-6-isopropylamino-5-nitro	300	4635
4-Amino-6-hydroxy-2-isopropylthio-5-nitroso	219–221	6168
2-Amino-4-hydroxy-6-mercapto	250	E, 4361
4-Amino-6-hydroxy-2-mercapto	300	H, E, 5059, 5853
5-Amino-4-hydroxy-2-mercapto	—	5418
2-Amino-4-hydroxy-6-mercapto-5-nitro	crude	6134
4-Amino-6-hydroxy-2-mercapto-5-nitroso	—	H, E, 5127
4-Amino-2-hydroxy-6-methoxy	—	5864
4-Amino-6-hydroxy-2-methoxy	220 or 227–233	4656, 5826
4-Amino-6-hydroxy-5-methoxy	221	H, 5153, 5156
2-Amino-4-hydroxy-6-methoxycarbonyl	219–220	E, 5782
2-Amino-4-hydroxy-5- β -methoxyethyl-6-phenyl	270 to 288–291	E, 5511, 5512, 5763
2-Amino-4-hydroxy-5-methoxy-6-methyl	193 or 194–197	1995, 5243
4-Amino-6-hydroxy-2-methoxy-5-methyl	292–293	5725
2-Amino-4-hydroxy-5-methoxymethyl-6-phenyl	223–224	E, 5786
4-Amino-6-hydroxy-2-methoxy-5-phenyl	243	E, 5153, 5156
2-Amino-4-hydroxy-2-methoxy-5-methyl	—	5725
2-Amino-4-hydroxy-6-methyl	241	5153, 5156
4-Amino-2-hydroxy-5-methyl	274 or 281–283	H, 5417, 5754
4-Amino-2-hydroxy-6-methyl	272 or 290–292	H, E, 4511, 5417
4-Amino-5-hydroxy-2-methyl	—	H, E, 3465
4-Amino-6-hydroxy-2-methyl	361–363	H, E, 4978, 6202
5-Amino-4-hydroxy-2-methyl	HCl: 270–273	6373, 6423
2-Amino-4-hydroxy-6-methylamino-5-nitro	296 or 301	H, E, 5098, 5859
2-Amino-4-hydroxy-6- α -methylhydrazino	237; HCl: 258	5099
4-Amino-5-hydroxymethyl-2-methoxy	218–219	E, 5634
4-Amino-5-hydroxymethyl-6-methyl	>300	E, 5842
5-Amino-4-hydroxy-2-methyl-6-methylamino	274–280	5402
4-Amino-5-hydroxymethyl-2-methylthio	173–174	E, 5623
4-Amino-4-hydroxy-2-methyl-6-methylthio	—	H, 5829
2-Amino-4-hydroxy-6-methyl-5-nitro	221	5680
4-Amino-5-hydroxymethyl-2-phenyl	126–128	E, 5624
	H ₂ O: >300	H, E, 5763
	134–135	H, E, 5104

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amino-4-hydroxy-6-methyl-5-propyl	268-270	E, 5754
2-Amino-5- β -hydroxy- β -methylpropyl	131	5762
4-Amino-2-hydroxy-6-methyl-5-sulfo-oxy	265-267	6373
4-Amino-6-hydroxy-2-methyl-5-sulfo-oxy	265-267	6373
2-Amino-4-hydroxy-5-methylthio	248-252	E, 4332
4-Amino-6-hydroxy-2-methylthio	265 to 278	H, E, 5121, 5853, 6252
4-Amino-6-hydroxy-2-methylthio-5-nitroso	245 or 249	H, 4616, 6168
4-Amino-6-hydroxy-2-methylthio-5-phenylazo	—	H, 5864
4-Amino-2-hydroxy-5-nitro	3- <i>N</i> -Ox: 220	H, E, 5426
4-Amino-6-hydroxy-5-nitro	> 300	H, 5442
4-Amino-6-hydroxy-2-nitroamino	270	4827
4-Amino-6-hydroxy-5-nitro-2-phenyl	280 or > 300	4972, 5439
2-Amino-4-hydroxy-5-nitro-6-piperidino	275	4628
2-Amino-4-hydroxy-5-nitro-6-propylamino	325	5646
2-Amino-4-hydroxy-5-nitroso-6-piperidino	234	4628
4-Amino-6-hydroxy-5-nitroso-2-propylthio	221	6168
2-Amino-4-hydroxy-5-phenyl	264-266	H, 3532, 5722
2-Amino-4-hydroxy-6-phenyl	1- <i>N</i> -Ox: 131	H, E, 6195
4-Amino-2-hydroxy-5-phenyl	335 or > 340	H, E, 5861, 6081
2-Amino-4-hydroxy-6-phenyl-5-prop-2'-ynyl	261-263	5717, 5725
2-Amino-4-hydroxy-6-piperidino	336	E, 4628
4-Amino-6-hydroxy-5-pivalamido	242-243	5447
2-Amino-4-hydroxy-5-propyl	238-239	5754
2-Amino-4-hydroxy-6-propyl	209	5392
4-Amino-6-hydroxy-2-propylthio	207-209	E, 5121
5-Amino-4-hydroxy-6-sulfo	250-251	4825
4-Amino-6-hydroxy-5-thiocyanato	260-262	5244
4-Amino-2-hydroxy-5-trifluoromethyl	250-255	5789
4-Amino-6-iodo	207-210	5153

4-Amino-5-iodo-2,6-dimethyl	142 or 154–155	H, E, 4506, 6351
4-Amino-5-iodo-2-isopropyl-6-methyl	145–147	6351
2-Amino-5-iodo-4-methoxy-6-methyl	155–156	4506
2-Amino-5-iodo-4-methyl	154–155	4506
4-Amino-5-iodo-6-methyl	164–165	6351
4-Amino-5-iodo-6-methyl-2-phenyl	166–167	6351
2-Amino-5-isoamyl-4-mercapto-6-methyl	220–225	2816
2-Amino-5-isoamyl-4-methyl	161–163	2816
4-Amino-5-isoamyl-6-methyl	131–133	2816
2-Amino-5-isobutyl	134	4532
4-Amino-5-isobutyramido	197–198	5753
4-Amino-5-isobutyramido-2-mercapto	266	6125
2-Amino-5-isopropoxy	67	E, 4532
2-Amino-5- β -isopropoxymethoxy	–	5813
5-Amino-4-isopropylamino	186 or 188–189	5578, 5753
2-Amino-4-isopropyl-5-methyl	–	6322
4-Amino-2-mercapto	275 or 277–279	H, E, 2915, 4356
4-Amino-6-mercapto	304–305	E, 4356
5-Amino-4-mercapto	207	E, 4357
4-Amino-2-mercapto-6-methoxy	219	4656
5-Amino-4-mercapto-6-methoxy-2-methyl	crude: 193	5689
5-Amino-4-mercapto-6-methylamino	–	H, 4396
2-Amino-4-mercapto-6- α -methylhydrazino	244–247	5402
5-Amino-2-mercapto-4-methyl-6-methylamino	280–285	E, 2675
5-Amino-4-mercapto-2-methyl-6-methylamino	272	2675
2-Amino-4-mercapto-6-methylthio	241–243	4766
4-Amino-2-mercapto-5-phenyl	267–269	3532
2-Amino-4-methoxy	290 or 296–299	H, E, 5861, 6081
2-Amino-5-methoxy	1-Mel: crude	H, E, 5061
4-Amino-6-methoxy	70–73 or 80–81	E, 4384, 5813
5-Amino-2-methoxy	168	H, E, 5069
5-Amino-4-methoxy	157–160	E, 5853
	119–120	4380
	71–73	E, 2562

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-6-methoxycarbonyl-2,5-dimethyl	crude; nmr	6140
2-Amino-4-methoxycarbonylmethyl	120–142	5243
4-Amino-5-methoxycarbonyl-2-methyl	184; HCl: 181	1394, 4908
5-Amino-4-methoxycarbonyl-2-phenyl	119–122	5494
4-Amino-2-methoxy-5,6-dimethyl	178	E, 3520
4-Amino-5-methoxy-2,6-dimethyl	148–150	4506
4-Amino-6-methoxy-2,5-dimethyl	110	E, 5786
5-Amino-2-methoxy-4,6-diphenyl	crude; nmr	6147
2-Amino-5- β -methoxyethoxy	—	E, 5813
4-Amino-2- β -methoxyethoxy	87–89	6252
2-Amino-4-methoxy-6-methoxycarbonylmethyl	107–109	5243
4-Amino-5-methoxy-6-methoxymethyl-2-methylthio	94–95	4397
2-Amino-4-methoxy-6-methyl	—	H, E, 5392
2-Amino-5-methoxymethyl	—	E, 5813
2-Amino-5-methoxy-4-methyl	121–122	5786
4-Amino-2-methoxy-6-methyl	144–146	H, 5050
4-Amino-5-methoxy-6-methyl	122–123	E, 5786
4-Amino-6-methoxy-2-methyl	165	H, 5859
5-Amino-4-methoxy-6-methyl	69–72	E, 5786
2-Amino-4-methoxy-6- α -methylhydrazino	150–152	5402
4-Amino-5-methoxymethyl-2-methyl	118–120	H, 5103
5-Amino-2-methoxy-4-methyl-6-methylamino	134–135	5670
2-Amino-4-methoxy-6-methyl-5-nitro	185	H, 4763
2-Amino-4-methoxy-6-methyl-5-phenyl	154	5381
4-Amino-5-methoxymethyl-2-phenyl	125–127 or 130	5100, 5104
4-Amino-6-methoxy-2-methylsulfenyl	187–189	4656
4-Amino-6-methoxy-2-methylsulfonyl	217–218	4656
4-Amino-6-methoxy-2-methylthio	138–142; sulf: 192	E, 4656, 5853
5-Amino-4-methoxy-6-methylthio	70–71	4816
4-Amino-2-methoxy-5-nitro-6-trifluoromethyl	164	5823

2-Amino-4-methoxy-6-phenyl	152	5371
4-Amino-5-methoxy-2-phenyl	102-103	4674
5-Amino-4-methoxy-6-semicarbazido	236	5674
5-Amino-4-methoxy-6-sulfo	212-214	4825
2-Amino-4-methoxy-6-trifluoromethyl	114	5785
4-Amino-6-methoxy-2-trifluoromethyl	171	5785
2-Amino-4-methyl	159-160; pic: 232	H, E, 5243, 5757, 6050
2-Amino-5-methyl	196	E, 4476
4-Aminomethyl	pic: 156-157	5862
4-Amino-2-methyl	202 to 205	H, E, 5605, 5829, 5859
4-Amino-5-methyl	173 or 178-179	H, 4601, 5034, 5752
5-Amino-2-methyl	158-161	H, 6510
4-Amino-5- <i>N</i> -methylacetamido-2-methylthio	250-251	5685
4-Amino-2-methylamino	132	E, 4670
4-Amino-5-methylamino	193-195	H, E, 5338
5-Amino-4-methylamino-2-methylthio	108-111	5344, 5354
4-Amino-6-methylamino-5-nitro	243-245	H, E, 5078
4-Amino-2-methylamino-5-sulfo-oxy	254-258	6373
5-Aminomethyl-4-anilino-6-carboxy-2-chloro	160	2884
4-Aminomethyl-5-bromo-2,6-dihydroxy	HCl: -	5868
2-Aminomethyl-5-carboxy	241-243	6091
5-Aminomethyl-2-carboxy	280-281	6091
5-Aminomethyl-1-cyclohexyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	270	4932
5-Aminomethyl-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	285	4932
5-Aminomethyl-1-cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	226	4932
4-Aminomethyl-2,6-dihydroxy	296-298; HCl: 328	5854, 5868
4-Aminomethyleneamino-5-dimethoxymethyl-2-methyl	crude: 106	4471
4-Aminomethyleneamino-5-formyl-2-methyl	150-154	4471
2-Amino-4- α -methylhydrazino	141-143	5402
5-Aminomethyl-4-hydroxy-2-methyl	HCl: 167 (?)	H, E, 5829
4-Amino-6-methyl-5-methylamino	133-135	2675

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Amino-2-methyl-4-methylamino	103–105	2675
5-Amino-4-methyl-6-methylamino	165–167	2675, 5432
4-Amino-6-methyl-5-methylamino-2-methylthio	120–121	2675
5-Amino-2-methyl-4-methylamino-6-methylthio	108	2675
5-Amino-4-methyl-6-methylamino-2-methylthio	160	5670
4-Amino-2-methyl-6-methylamino-5-nitro	242–243	5043
5-Amino-4-methyl-6-methylamino-2-piperidino	121–124	5685
4-Amino-6-methyl-5-methylformamido	178–179	2675
4-Amino-6-methyl-5-methylformamido-2-methylthio	166–167	2675
4-Amino-6-methyl-2-methylthio	135–137	H, 5872
4-Amino-2-methyl-5-nitro	277–278	2562
4-Amino-2-methyl-5-nitro-6-phenyl	195	5441
4-Amino-6-methyl-5-nitro-2-phenyl	158–159	5439
2-Amino-4-methyl-5-nitro-6-piperidino	3-N-Ox: 199	E, 5724
4-Amino-2-methyl-5-nitro-6-piperidino	3-N-Ox: –	5724
2-Amino-4-methyl-6-phenoxy	192–194; 3-N-Ox: 190–193	H, 5724
4-Amino-2-methyl-6-phenoxy	177–179	4959, 5859
2-Amino-4-methyl-6-phenyl	170 to 175	H, E, 4760, 5382, 5821, 5869
2-Amino-5-methyl-4-phenyl	154 or 181–182	E, 5382, 5484
4-Amino-2-methyl-5-phenyl	193–194	5309
4-Amino-5-methyl-2-phenyl	105–107	5792
2-Amino-4-methyl-6-phenylhydrazino	243–245	5054
2-Amino-4-methyl-6-phenyl-5-phenylazo	156–157	H, 5869
2-Amino-4-methyl-5-phenyl-6-propoxy	108	5381
2-Amino-4-methyl-6-piperidino	3-N-Ox: –	H, E, 5724
4-Amino-2-methyl-6-piperidino	210–211; 3-N-Ox: 200	5724, 5859
2-Amino-4-methyl-6-pivaloyloxy	105	5392
2-Amino-5-2'-methylprop-1-enyl	110	5762
4-Amino-2-methyl-5-propionamidomethyl	181	5103

5-Amino-2-methylsulfonyl	140–141	4380
2-Amino-5-methylsulfonylmethyl-4-phenyl	185–186	5382
5-Aminomethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	269	4932
5-Aminomethyl-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-phenyl	275	4932
5-Aminomethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	297	4932
2-Amino-5-methylthio	160–161	E, 4332
4-Amino-6-methylthio	168–169	E, 4356
5-Amino-2-methylthio	110–111	E, 4380
2-Amino-5- α -methylthioethyl-4-phenyl	121	5382
4-Amino-2-methyl-5-thioformamidomethyl	174–180; pic: 166	H, E, 5174
2-Amino-5-methylthiomethyl-4-phenyl	124	5382
2-Amino-4-methylthio-6-phenyl	121–122	5371
4-Amino-2-methylthio-6-phenyl	177–178	6141
4-Amino-5-methylthio-2-phenyl	73–74	4674
4-Amino-6-methylthio-2-trifluoromethyl	131	5785
2-Amino-4-methyl-6-trifluoromethyl	129	E, 5785, 5865
4-Amino-2-methyl-6-trimethylammonio	Cl ⁻ : 210	3520
4-Amino-6-methyl-2-trimethylammonio	Cl ⁻ : 190	3520
2-Amino-5-neopentyl	189	4532
2-Amino-5-nitro	233 to 238	H, E, 4488, 5340, 6123
4-Amino-5-nitro	212–214	2562
2-Amino-5-nitro-4,6-dipiperidino	231–232	5188
4-Amino-5-nitro-2-phenyl-6-piperidino	240	4972
4-Amino-5-nitro-6-piperidino	142	4789
4-Amino-5-nitro-6-propylamino	163–164	5871
4-Amino-5-nitro-2-styryl	227	2562
1-(β -Amino-oxyethyl)-1,2-dihydro-4-methylamino-2-oxo	200	5289
1-(β -Amino-oxyethyl)-1,2,3,4-tetrahydro-4-imino-3-methyl-2-oxo	2HCl: 214	H, E, 4488, 4690, 4760, 6042, 6342
2-Amino-4-phenyl	164 or 165; 1-N-Ox: 193	H, E, 4488, 4690, 5658, 5663
2-Amino-5-phenyl	158 to 162–163	H, 4697, 5605, 6038
4-Amino-2-phenyl	138–140	

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Amino-5-phenyl	148 to 157	H, E, 4501, 4594, 5117, 5477, 6081
4-Amino-6-phenyl	226–228	E, 4675
5-Amino-2-phenyl	94–96	H, 3463, 6510
4-Amino-2-phenyl-6-piperidino	HCl: 310	4972
2-Amino-4-phenyl-5-prop-2'-enyl	202	5382
2-Amino-4-phenyl-6-propoxy	103	5371
2-Amino-4-phenyl-5-propyl	95–97	5382
2-Amino-4-phenyl-6-trifluoromethyl	133–134	5865
2-Amino-4-phenyl-5-vinyl	144	5382
2-Amino-4-piperidino	133–134	H, 4663
4-Amino-2-piperidino	147	5866
4-Amino-5-pivalamido	197–198	5753
4-Amino-2-propoxy	76–78	E, 6252
2-Amino-4-propyl	121–123	H, E, 5757, 6050
4-Amino-5-propyl	162	5034, 5752
1-Amino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	151–152	5070
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	285 or > 300	H, E, 4431, 4927, 4939, 6014
5-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	136–138; HCl: 290	H, 5143, 5448
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-phenoxycarbonyl	280	4410
5-Amino-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	260	4925
5-Amino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	251	4925
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5- <i>N</i> -phenylcarbamoyl	250	4410
5-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-piperidino	128–130	4941
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-thiocyanato	> 200	5867
5-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxo	pic: 189–190	E, 4941
5-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-4-oxo-2-thio	120–124	4661
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-5- <i>N</i> -methylcarbamoyl-2,6-dioxo	230	4410, 4442

4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-5- <i>N</i> -methylformamido-2,6-dioxo	222	6231
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxo	252 or 252–260	H, E, 4431, 4608, 5127, 5895
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-thio-1,3-dipropyl	260	E, 4969, 4971
4-Amino-1,2,3,6-tetrahydro-5-ethyl-1-methyl-2,6-dioxo-3-piperidino	106–109	4472
4-Amino-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxo	209–211	2870
4-Amino-1,2,3,6-tetrahydro-3-isobutyl-1-methyl-5-nitroso-2,6-dioxo	HCl: 310	4969
5-Amino-1,2,3,4-tetrahydro-6-isopropylamino-1,3-dimethyl-2,4-dioxo	223–224	5281
5-Amino-1,2,3,4-tetrahydro-4-oxo-1,3-diphenyl-2-thio	121–122	4942
4-Amino-2-thiocyanato	190–192	5870
4-Amino-2,5,6-trichloro	169	4490
4-Amino-2,5,6-trifluoro	161–163	H, E, 4963
2-Amino-4-trifluoromethyl	156–157	E, 3521
4-Amino-2-trifluoromethyl	175	5785
4-Amino-2,5,6-trihydroxy	182–185	E, 5785
5-Amino-2,4,6-trimethoxy	>300	H, 5708, 6373
2-Amino-4,5,6-trimethyl	105–106	5786
4-Amino-2,5,6-triphenyl	208	H, 5821, 6320
2-Amyl	183–185	H, 4614
5-Amyl	135/100	5063
2-Amylamino-4,6-dimethyl	94–95/11	4515
4-Amylamino-2,6-dimethyl	142/11	E, 5883
4-Amylamino-2-hydroxy	155–160/12	E, 5883
2-Amylamino-5-hydrazinocarbonyl-4-hydroxy	163–166	E, 6252
5-Amyl-4-benzoyloxy-2-dimethylamino-6-methyl	218–220	5885
5- <i>s</i> -Amyl-4-benzoyloxy-2-dimethylamino-6-methyl	57	5392, 5723
1-Amyl-3-benzyl-5-fluoro-1,2,3,6-tetrahydro-2,6-dioxo	63	5723
2-Amyl-5-butyl-4-chloro-6-hydroxy	liq.	6511
4-Amyl-5-butyl-2,6-dihydroxy	109–111	5029
4-Amyl-5-butyl-6-mercaptop	166–168	5875, 5964
5-Amyl-2-carboxy	171–173	5875, 5964
	86–87	5715

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Amyl-4,5-diethoxycarbonyl	nmr	6329
5-Amyl-4,6-dihydroxy	270-272	5882
5-Amyl-4,6-dihydroxy-2-mercapto	146-148	5882
4-Amyl-2,6-dihydroxy-5-phenylazo	148-149	5874
5-Amyl-2,4-dihydroxy-6-trifluoromethyl	157-158	5874
2-Amyl-4,6-dimethyl	85/4	5096
5-Amyl-2-dimethylamino-4-hydroxy-6-methyl	84	5392, 5722
5-Amyl-2-dimethylamino-4-methyl-6-methylsulfonyloxy	69	5392
1-Amyl-4-ethoxy-1,2-dihydro-2-oxo	crude: nmr	5888
5-Amyl-2-hydroxy	97	4463
4-Amyl-6-hydroxy-5- β -hydroxyethyl-2-mercapto	194-195	5361
4-Amyl-6-hydroxy-5- β -hydroxyethyl-2-methylthio	126-127	5361
4-Amyl-6-hydroxy-2-mercapto-5-phenylazo	169-170	5874
5-Amyl-4-hydroxy-2-mercapto-6-trifluoromethyl	168-169	5874
2-Amyloxy-4-ethoxy	crude: nmr	5888
2-Amyloxy-5-fluoro-4-hydroxy	117	6515
4-Anilino	139-142	H, 5034
2-Anilino-4-azido-5-methyl-6-phenyl	-	5737
2-Anilino-1-benzamido-1,6-dihydro-4-methyl-6-oxo	255-257	2514
4-Anilino-5-benzylideneamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	183-185	6030
4-Anilino-6-benzylidenehydrazono-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo	230-232	5162
4-Anilino-2-benzyl-6-methyl	115-117	6018
5-Anilino-1,3-bis- δ -bromobutyl-1,2,3,4-tetrahydro-2,4-dioxo	n_D^{20} 1.6120	4828
5-Anilino-1,3-bis- δ -bromobutyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	n_D^{20} 1.5920	4828
4-Anilino-5-bromo	68-70	4663
4-Anilino-5-bromo-6-methyl	92-93	5986
2-Anilino-4- <i>t</i> -butyl	110-112	5484
4-Anilino-1-butyl-1,2-dihydro-6-methyl-2-oxo	197-199; pic: 178	4850
4-Anilino-6-carbamoyl-2-chloro-5-hydroxymethyl	160	2884
4-Anilino-5-carboxy	272-275	5878

5-Anilino-4-carboxy-2,6-dihydroxy	320	4839
2-Anilino-4-chloro	127-128	H, 4670
4-Anilino-6-chloro	158-159	H, 6088
4-Anilino-2-chloro-5-ethoxycarbonyl-6-methyl	125-126	4470
4-Anilino-5- β -chloroethyl	75-77; HCl: 171	5881
4-Anilino-5- β -chloroethyl-2-methyl	HCl: 198-200	5741
4-Anilino-2-chloro-6-methyl	—	5884
2-Anilino-4-chloro-5-methyl-6-phenyl	171-172	5737
4-Anilino-2-chloro-5-nitro	106	5889
4-Anilino-5-chloro-2-phenyl	167-169	5755
4-Anilino-6-chloro-5-phenyl	174-175	6088
4-Anilino-5-cyano	150-152	E, 3764
4-Anilino-6-cyano	268 or 272-273	6088
4-Anilino-5-cyano-2,6-diphenyl	204-207	4366, 4372, 4557
4-Anilino-5-cyano-2-methyl-6-phenyl	224-225	4557
4-Anilino-5-cyano-2-methylthio-6-phenyl	218-219	5942
4-Anilino-5-cyano-2-phenyl	237	6129
4-Anilino-5-cyano-6-phenyl	218-220	6088
4-Anilino-6-cyano-5-phenyl	280-281	4947
4-Anilino-5-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	203-204	4971
4-Anilino-1,3-diethyl-1,2,3,6-tetrahydro-6-imino-2-oxo	195-200	4888
2-Anilino-1,6-dihydro-1,4-dimethyl-6-oxo	299-300	H, 4888
4-Anilino-1,2-dihydro-1,6-dimethyl-2-oxo	92	6259
2-Anilino-1,6-dihydro-1- β -hydroxyethyl-4-methyl-6-oxo	155	5879
2-Anilino-1,4-dihydro-6-methoxycarbonyl-4-oxo-1-phenyl	256-258 or 259	4847, 4850, 4859
4-Anilino-1,2-dihydro-1-methyl-2-oxo	263-265 or 266	4847, 4850
4-Anilino-1,2-dihydro-6-methyl-2-oxo-1-phenyl	147-148	5049, 6076
5-Anilino-1,6-dihydro-4-methyl-6-oxo-1-phenyl	180-182	4548
4-Anilino-1,2-dihydro-5-methyl-2-oxo-1-vinyl	325-327	E, 5877
4-Anilino-2,6-dihydroxy	310	H, E, 4839
5-Anilino-2,4-dihydroxy	307-308	5358
4-Anilino-2,6-dihydroxy-5-phenylazo	92; N-Ox: 156	H, 5887, 6276
2-Anilino-4,6-dimethyl	148	6294
4-Anilino-6-dimethylamino-2-methyl-5-nitroso		

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Anilino-2,6-diphenyl	124-125	6730
4-Anilino-6-ethoxy	121-123; HCl: 161	E, 5730
4-Anilino-5-ethoxycarbonyl	103-104	E, 5878
4-Anilino-5-ethoxycarbonyl-2-mercapto-6-methyl	218-220	4470
2-Anilino-4-ethoxy-6-methyl	70-71 or 72-73	5087, 5986
4-Anilino-5-ethylamino	185-186	5873
4-Anilino-5-formyl-6-hydroxy	257	5730
2-Anilino-4-hydrazino-6-methyl	178-180	5054
2-Anilino-4-hydroxy	234	H, 4670
4-Anilino-2-hydroxy	276-278 or 280	H, E, 4538, 6252
4-Anilino-6-hydroxy	248-250	E, 5730
4-Anilino-5-hydroxy-6-methyl	239 or 242-247	5087, 5986
2-Anilino-4-hydroxy-5-methyl-6-phenyl	-	H, 5737
4-Anilino-6-hydroxy-2-phenyl	206	H, 4966
4-Anilino-6-hydroxy-2-phenyl-5-phenylazo	302	4966
4-Anilino-5-iodo-2,6-dimethyl	sulf: 288-289	4506
4-Anilino-6-methoxy	149-151	6088
4-Anilino-5-methoxy-6-methyl	140-141	5986
2-Anilino-4-methyl	92-94	H, E, 5887
4-Anilino-5-methylamino	197-198	5873
4-Anilinomethyl-5-bromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	171-172	6274
5-Anilinomethyl-2,4-dihydroxy	240	5475
2-Anilino-4-methyl-6-phenyl	112-113; 1-N-Ox: 176	6276, 6388
2-Anilino-4-methyl-6-piperidino	135-137	5986
4-Anilinomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	192	6274
4-Anilinomethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-1-phenyl	228	6274
2-Anilino-5-nitro	202-203	5738
4-Anilino-5-phenyl	113-114	E, 6088
2-Anilino-5-propionamido	188	5738
4-Anilino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	187 or 190-192	E, 4987, 4988, 5009

4-Anilino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-phenylazo	212–214	6030
4-Anilino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-phenylimino	179–180	4969, 5657
4-Anilino-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxo	204	4969
2-Anilino-2,5,6-trifluoro	96–97	3521
2-Azido	120	5335
4-Azido-2- β -carbamoyl ethyl-6-ethoxycarbonyl-5-methyl	149	6025
5-Azidocarbonyl-2,4-dihydroxy	176	5895
5- β -Azidocarbonyl ethyl-2,4-dihydroxy-6-methyl	100–110	5707
5- β -Azidocarbonyl ethyl-4-hydroxy-2-mercapto-6-methyl	100–110	5707
4-Azidocarbonyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	58–59	5895
5-Azidocarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	105	5895
4-Azido-2- β -carboxyethyl-6-ethoxycarbonyl-5-methyl	144	6025
4-Azido-5-chloro-2,6-difluoro	34–36	6078
2-Azido-4-chloro-6-methyl	58–60	5355
2-Azido-1,4-dihydro-4-imino-1-methyl	HI: sp only	4490
2-Azido-4,6-dihydroxy	250	5886
4-Azido-2,6-dihydroxy-5-methyl	268–270	5840
4-Azido-2,6-dimethoxy	41–42	E, 5355
2-Azido-4,6-dimethyl	–	E, 4503, 5355
4-Azido-2,6-dimethyl	84–85	5355
4-Azido-2-dimethylamino-5-methyl-6-phenyl	74–75	5725
4-Azido-6-ethoxycarbonyl-2,5-dimethyl	104–105	6140
4-Azido-6-ethoxycarbonyl-2- β -ethoxycarbonyl ethyl-5-methyl	60–61	6025, 6140
4- α -Azidoethyl	95–98/15	4379
5- α -Azidoethyl	75–83/15; nmr	4379
4-Azido-2-ethylamino-5-methyl-6-phenyl	–	5725
5-Azido-2-methoxy	42–43	6256
5-Azido-2-methoxy-4,6-diphenyl	73–75	6147
2-Azido-4-methoxy-6-methyl	163–164	5355
2-Azido-5-methyl	123	5669
4-Azido-5-methyl-2-methylamino-6-phenyl	142–143	5725
2-Azido-4-methyl-6-methylthio	151–152	5355
4-Azido-6-methyl-2-methylthio	66–67	5355
2-Azido-5-methyl-4-phenyl	76–77	5931

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Azido-2-methylsulfonyl	142-145	6256
4-Azido-5-phenyl	164-165	5584
5-Azido-4-phenyl	79-80; 1-N-Ox: 157	6256
4-Azido-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	148-149	4952, 4993
4-Azido-2,5,6-trifluoro	55/18	6078
4-Azido-2,5,6-trimethyl	96-97	5355
4-Azido,2,5,6-triphenyl	137-140	4602
2-Aziridino-4-chloro-6-methyl	51-52	E, 5880
Barbituric acid/1-amino	135-138	5186
Barbituric acid/1-amino-5-ethyl	149-153	5185
Barbituric acid/1-amino-5-methyl	153-155	5186
Barbituric acid/5-benzylidene	252	E, 4887
Barbituric acid/5-benzylidene-1-methyl	237	6002
Barbituric acid/1-benzylloxy-5-ethyl	156-157	5218
Barbituric acid/5-bromo-5-ethyl	-	H, E, 5903
Barbituric acid/5-bromo-5-ethyl-1-methyl	-	5903
Barbituric acid/5,5-dichloro	m/s	H, E, 5563
Barbituric acid/5,5-dichloro-1-methyl	-	H, E, 5561
Barbituric acid/1,5-diethyl	90-91	E, 5323
Barbituric acid/5,5-difluoro	210-213	5552
Barbituric acid/5,5-dimethoxy	147-149	5901
Barbituric acid/1,5-dimethyl	169-170 or 173	H, 5898, 5899
Barbituric acid/1-dimethylamino-5-methyl	145-146	2870
Barbituric acid/1-ethyl-5,5-dimethyl	142-145	5898
Barbituric acid/5-ethyl-5-hydroxy	crystal structure	H, E, 5916
Barbituric acid/5-ethylidene	223	5897
Barbituric acid/1-ethyl-5-methyl	147	5898
Barbituric acid/5-ethyl-5-nitro	-	H, 5906
Barbituric acid/5-ethyl-1-piperidino	145-146	2870
Barbituric acid/5-formyl-1-methyl	197-199	5900

Barbituric acid/5-hydroxy-5-methyl	226–227	E, 5896
Barbituric acid/1-methyl	131–132	H, E, 5321, 5322, 5407
Barbituric acid/5-methylaminomethylene	> 330	4599
Barbituric acid/1-methyl-5-nitro	142–143	H, 4748
Barbituric acid/5-methyl-1-piperidino	192–193	2870
Barbituric acid/1,5,5-trimethyl	160–161	5898
4-Benzamido-5-benzoyl-2,6-diphenyl	200	5133
1-Benzamido-2-butylamino-1,6-dihydro-4-methyl-6-oxo	167–168	2514
4-Benzamido-5-cyano-2,6-diphenyl	240	5133
2-Benzamido-5-ethoxycarbonyl-4-methyl	88–91	5248
4-Benzamido-2-hydroxy	335–339	H, 6252
2-Benzamido-4-hydroxy-6-phenyl	198	4591, 4592
4-Benzamido-5-methoxycarbonyl-2,6-diphenyl	186	5133
2-Benzamidomethyl-5-carboxy	187–189	6091
5-Benzamidomethyl-4-chloro-2-methyl	205–206	5793
2-Benzamidomethyl-4,6-dimethyl	115–117	H, 6091
2-Benzamidomethyl-5-ethoxycarbonyl	110–111	6091
2-Benzamidomethyl-4-hydroxy-6-methyl	230–232	6275
5-Benzamidomethyl-4-hydroxy-2-methyl	242	5793
5-Benzamidomethyl-4-mercapto-2-methyl	203–205	5793
5-Benzamidomethyl-2-methyl	136	5793
2-Benzamido-4-phenyl	1-N-Ox: 177	6342
5-Benzenesulphonamido-2-benzyl-4,6-dihydroxy	252–254	4715
4-Benzenesulphonamido-6-chloro-2-methoxy	138	5095
4-Benzenesulphonyloxy-5-ethoxycarbonyl-2-piperidino	98–99	4976
5-Benzoyl-4-chloro-2,6-dimethyl	129	4456
5-Benzoyl-4-chloro-6-methyl-2-phenyl	132	4456
1-Benzoyl-1,2-dihydro-4,6-dimethyl-2-oxo	123–125	4392
4-Benzoyl-2,6-dihydroxy	250–252	H, 5877
5-Benzoyl-4-ethoxy-2-hydroxy-6-mercapto	265–273	5536
5-Benzoyl-4-ethoxy-6-methyl-2-phenyl	132	4456
5-Benzoyl-4-ethylthio-2,6-dihydroxy	278–280	5536
4-Benzoylhydrazino-2,6-dihydroxy	294–295	4721

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Benzoyl-4-hydroxy-2,6-diphenyl	296	5134
5-Benzoyl-2-hydroxy-4-methoxycarbonyl	239–240	4438
1-Benzoylimino-4,6-dimethyl (zwitterion)	155	6174
1-Benzoylimino-4,6-diphenyl (zwitterion)	187	6174
1-Benzoylimino-2,4,6-trimethyl (zwitterion)	pic: 192	6174
5-Benzoyl-4-mercapto-6-methyl-2-phenyl	219	E, 4456
2-Benzoyl-4-methoxy-6-methyl	64 or 66; 160/2; oxime: 164	5074, 5089
4-Benzoyl-6-methoxy-2-methyl	75–76; 135/1	5089
4-Benzoyl-2-methyl-6-phenyl	64–65	5987
4-Benzoyloxy-6-benzyl-2-dichloromethyl-5-phenyl	137–138	4740
4-Benzoyloxy-5-benzyl-2-dimethylamino-6-methyl	92	5723
4-Benzoyloxy-5-bromo-2-dimethylamino-6-methyl	128–129	5723
4-Benzoyloxy-5-butyl-2-dimethylamino-6-methyl	59	5392, 5723
4-Benzoyloxy-5-butyl-2-ethylamino-6-methyl	69–70	5392, 5723
4-Benzoyloxy-5-butyl-2-ethylmethylamino-6-methyl	45	5723
4-Benzoyloxy-2-dimethylamino-5-ethyl-6-methyl	89	5723
4-Benzoyloxy-2-dimethylamino-5-ethyl-6-propyl	62	5723
4-Benzoyloxy-2-dimethylamino-6-methyl-5-propyl	52 or 58	5392, 5723
4-Benzoyloxy-2-dimethylamino-5-nitro	125–126	5723
4-Benzoyloxy-5-ethoxycarbonyl-2,6-diphenyl	157–158	5134
2-Benzoyloxymethyl-5-benzyl-4-chloro-6-hydroxy	191–198	5731
2-Benzoyloxymethyl-4-chloro-5-ethyl-6-hydroxy	163–168	5731
2-Benzoyloxymethyl-4-chloro-6-hydroxy	170–175	5731
2-Benzoyloxymethyl-4-chloro-6-hydroxy-5-methyl	200–205	5731
2-Benzoyloxymethyl-4,5-dichloro-6-hydroxy	208–213	5731
4-Benzoyloxy-6-methyl-2-piperidino	120	5392, 5723
4-Benzoyl-6-phenyl	78–79	5091
5-Benzoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	159–161	5851
4-Benzoylthio-5-butyl-2-dimethylamino-6-methyl	174–177/0.12	5723
2-Benzoylthio-4,6-dimethyl	72–73	6125

5-Benzoyl-2,4,6-triphenyl	181 or 184–187	4485, 5134
2-Benzylamino	81–82	H, E, 4399
4-Benzylamino-5-N-benzylcarbamoyl-2-phenyl	148–149	4976
4-Benzylamino-6-benzylidenehydrazono-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo (?)	184–186	5162
4-Benzylamino-6-benzylimino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo	110–112	4971
4-Benzylamino-6-benzylloxy-2-dimethylamino-5-nitro	125–126	4649
2-Benzylamino-5-bromo	136–138	H, 4399
2-Benzylamino-4-t-butyl	105–107	5484
2-Benzylamino-5-butyl-4-hydroxy-6-methyl	76	5722
2-Benzylamino-5- δ -carboxybutyl-4,6-dihydroxy	234–236	6518
2-Benzylamino-5-chloro	130–132	H, 4399
4-Benzylamino-6-chloro	122–123	E, 5357
4-Benzylamino-6-chloro-5-cyano-2-methylthio	164–166	5581
4-Benzylamino-5- β -chloroethyl	96–97	5741
4-Benzylamino-5- β -chloroethyl-2-methyl	92–94	5741
4-Benzylamino-6-chloro-5-formyl	69–70	5730
4-Benzylamino-6-chloro-2-guanidino	HCl: 250	6384
2-Benzylamino-4-chloro-6-methyl	133–134	H, 4849
4-Benzylamino-2-chloro-6-methyl	93–95	4849, 5884
2-Benzylamino-4-chloro-5-trifluoromethyl	82	5438
4-Benzylamino-2-chloro-5-trifluoromethyl	110	5789
4-Benzylamino-5-cyano	106	5789
4-Benzylamino-5-cyano-2,6-diphenyl	136–139	3764
4-Benzylamino-5-cyano-6-phenyl	199–200	5941
4-Benzylamino-1,2-dihydro-6-methyl-2-oxo-1-phenyl	137	6129
1-Benzylamino-1,6-dihydro-6-oxo-2,4,5-triphenyl	234–235	4859
4-Benzylamino-2,6-dihydroxy	245–247	5827
5-Benzylamino-2,4-dihydroxy	316–317	E, 5877
2-Benzylamino-4,6-dihydroxy-5- δ -methoxycarbonylbutyl	280	5060
4-Benzylamino-2,6-dihydroxy-5-methyl	256–257	6518
5-Benzylamino-2,4-dihydroxy-6-phenylazo	274	4526
2-Benzylamino-4,6-dihydroxy-5- δ -propoxycarbonylbutyl	–	5060
	241–242	6518

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Benzylamino-2,6-dimethyl	81-82	5883
2-Benzylamino-4-formylhydrazino-6-methyl	158	5054
4-Benzylamino-5-formyl-6-hydroxy	238-239	5730
2-Benzylamino-2-guanidino	2HCl: 223	6384
2-Benzylamino-5-hydrazinocarbonyl-4-hydroxy	229-230	5885
2-Benzylamino-4-hydrazino-6-methyl	143-144	5054
4-Benzylamino-2-hydroxy	225-227	H, E, 6252
4-Benzylamino-6-hydroxy	241-242	E, 5357
2-Benzylamino-4-hydroxy-5-N-isopropylcarbamoyl	247-248	5885
2-Benzylamino-4-hydroxy-5-methyl	231-233	4572
4-Benzylamino-2-hydroxy-6-methyl	—	5884
4-Benzylamino-6-hydroxy-2-methyl	243	E, 5015
4-Benzylamino-6-hydroxy-2-phenyl	231	5015
4-Benzylamino-6-hydroxy-5-phenylazo	204-205	5357
4-Benzylamino-2-hydroxy-5-trifluoromethyl	HCl: 175-187	5789
4-Benzylamino-2-mercapto-6-methyl	253-255	4849
2-Benzylamino-5-methoxy	101-102	4399
4-Benzylamino-6-methoxy	137-138	5357
2-Benzylamino-4-methoxy-5-trifluoromethyl	120-121	5789
2-Benzylamino-4-methyl	85	5789
2-Benzylamino-5-methyl	73	H, 4849
4-Benzylamino-6-methyl	107-108	4339
5-Benzylamino-2-methylsulfonyl	99-100	4849
2-Benzylamino-5-nitro-4-thiocyanato	114-115	4399
2-Benzylamino-4-phenyl	165	5742
4-Benzylamino-5-phenyl	126-128	6342
4-Benzylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-phenylimino	—	5914
4-Benzylamino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl	260	4994
4-Benzylamino-1,2,3,6-tetrahydro-5-nitroso-2,6-dioxo-1,3-diphenyl	224	E, 4657
	350	4657

5-Benzyl-2-benzylamino-4,6-dihydroxy	318–320	6279
2-Benzyl-4-benzylamino-6-methyl	HCl: 140–142	6018
1-Benzyl-2-benzylidenedihydrazino-5-ethoxycarbonyl-1,6-dihydro-6-oxo	204–206	E, 5903
5-Benzyl-1-benzyl-1,6-dihydro-4-hydroxy-2-methyl-6-oxo	260	4353
5-Benzyl-1-benzyl-1,6-dihydro-4-hydroxy-6-oxo-2-phenyl	160–161	4353
5-Benzyl-2-benzylthio-4-chloro-6-hydroxy	205–206	4894
5-Benzyl-4,6-bisethylamino-2-phenyl	105–106	5131
2-Benzyl-4,6-bisisopropylidenedihydrazino	165–167	4917
5-Benzyl-4,6-bismethylamino-2-phenyl	142	5131
4-Benzyl-5-bromo-2,6-dihydroxy	244–245	H, 2655
1-Benzyl-5-bromo-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	135	4925
1-Benzyl-5-bromo-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	158–160	H, 4940
1-Benzyl-5-bromo-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	124–125	5410
1-Benzyl-5-but-2'-enyl-1,6-dihydro-3-methyl-2,6-dioxo	81–83	5415
1-Benzyl-4-butyl-1,6-dihydro-6-oxo-2-phenyl	pic: 99–100	4484
5-Benzyl-2-butylthio-4-chloro-6-hydroxy	128–129	4894
1-Benzyl-6-carbamoyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	203–205	4940
5-Benzyl-4-carboxy-2,6-dihydroxy	308–309	3183
5-Benzyl-4-carboxy-6-hydroxy-2-methylthio	227–228	3183
2-Benzyl-4-chloro	32–33; 138/4	4670
5-Benzyl-4-chloro-2-chloromethyl-6-hydroxy	213–218	5731
1-Benzyl-5-chloro-1,2-dihydro-2-oxo	197	6028
2-Benzyl-5-chloro-4,6-dihydroxy	308	4917
5-Benzyl-4-chloro-2,6-dihydroxy	235–236	5915
5-Benzyl-4-chloro-2-ethylamino-6-methyl	–	5908
5-Benzyl-4-chloro-2-ethylthio-6-hydroxy	167–169	4894
2-Benzyl-4-chloro-6-hydrazino-5-phenyl	152–154	4917
5-Benzyl-4-chloro-6-hydroxy-2-methoxymethyl	159	E, 5751
5-Benzyl-4-chloro-6-hydroxy-2-methyl	200–204	5731
2-Benzyl-4-chloro-6-hydroxy-5-phenyl	235–236	5026
5-Benzyl-4-chloro-6-isopropylidenedihydrazino-5-phenyl	150–151	4894
2-Benzyl-4-chloro-2-methoxymethyl-6-methylamino	158–160	4917
5-Benzyl-4-chloro-2-methoxymethyl-6-methylamino	130–131	E, 5751
5-Benzyl-4-chloro-2-methoxymethyl-6-piperidino	174–176/0.3	E, 5751

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Benzyl-4-chloro-6-methyl	80-81	H, 6018
5-Benzyl-4-chloro-6-methyl-2-phenyl	80-81	5076
1-Benzyl-6-chloro-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	79-81	4657
1-Benzyl-3- β -cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxo	98-100	4390
1-Benzyl-3- β -cyanoethyl-1,2,3,6-tetrahydro-2,6-dioxo	93-95	4390
1-Benzyl-6-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	110-112	4920
2-Benzyl-4,6-dichloro	62-64	E, 4917
2-Benzyl-4,5-dichloro-6-hydroxy	203-206	5731
4-Benzyl-2-dichloromethyl-6-ethoxy-5-phenyl	92-93	4740
4-Benzyl-2-dichloromethyl-6-hydroxy-5-phenyl	153-154	4740
2-Benzyl-4,6-dichloro-5-phenyl	136-138 or 138-139	4917, 5021, 5026
2-Benzyl-4,6-dihydrazino	222-224	4917
2-Benzyl-4,6-dihydrazino-5-phenyl	188-190	4917
1-Benzyl-1,2-dihydro-4,6-dimethyl-2-oxo	170-171	4392
1-Benzyl-1,2-dihydro-4,6-diphenyl-2-thio	231-232	6459
1-Benzyl-1,4-dihydro-2,5-diphenyl-4-thio	225-227	5572
1-Benzyl-1,2-dihydro-2-imino	HBr: 158-159	E, 2633
1-Benzyl-1,6-dihydro-6-imino-2,4,5-triphenyl	196	4589
1-Benzyl-1,6-dihydro-4-isopropyl-6-oxo-2-phenyl	118-119; pic: 111	4510
1-Benzyl-1,6-dihydro-4-methyl-6-oxo-2-phenyl	128; pic: 161-162	4484, 4510
1-Benzyl-1,2-dihydro-4-methylthio-2-oxo	151-152	H, 5727
1-Benzyl-1,4-dihydro-2-methylthio-4-oxo	176-177	6111
1-Benzyl-1,6-dihydro-2-methylthio-6-oxo	97	6111
1-Benzyl-1,2-dihydro-2-oxo	134-135	E, 4398, 5324
1-Benzyl-1,2-dihydro-2-oxo-4,6-diphenyl	164-165	6290
1-Benzyl-1,6-dihydro-6-oxo-2,4-diphenyl	161-162; pic: 100	4484, 4510
1-Benzyl-1,6-dihydro-6-oxo-2-phenyl-4-propyl	78-80; pic: 103	4484, 4510
1-Benzyl-1,6-dihydro-6-oxo-2,4,5-triphenyl	257	4589
2-Benzyl-4,6-dihydroxy	303-305	E, 4917
5-Benzyl-2,4-dihydroxy	278 to 293	H, 4801, 5861, 5915

4-Benzyl-2,6-dihydroxy-5-iodo	240–241	2655
2-Benzyl-4,6-dihydroxy-5-phenyl	320–322	4917
5-Benzyl-4,6-dihydroxy-2-phenyl	<i>N</i> -Ox: 232	H, E, 4353, 4916
4-Benzyl-2,6-dihydroxy-5-phenylazo	221–223	5874
5-Benzyl-2,4-dihydroxy-6-trifluoromethyl	207–208	5874
2-Benzyl-4,6-dimercapto	204–206	4917
2-Benzyl-4,6-dimercapto-5-phenyl	191	4917
5-Benzyl-4-dimethoxymethyl-2-ethylthio-6-hydroxy	97–98	5743
5-Benzyl-4-dimethoxymethyl-6-hydroxy-2-mercaptop	161–162	5743
2-Benzyl-4,6-dimethyl	125/4	H, 4812, 5096, 5249
4-Benzyl-2,6-dimethyl	48–49; 130/15	5096
5-Benzyl-2-dimethylamino-4-hydroxy-6-methyl	188–190	5722
1-Benzyl-4-dimethylamino-methylenamino-1,2-dihydro-2-oxo	192–193	6251
1-Benzyl-5-dimethylamino-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	185–195/0.2	4925
5-Benzylthio-2,4-dihydroxy	> 210	5168
1-Benzyl-5-ethoxycarbonyl-1,2-dihydro-2-oxo	131–132	E, 5720
5-Benzyl-1-ethoxy-1,6-dihydro-4-hydroxy-6-oxo-2-phenyl	174–175	4353
1-Benzyl-4-ethoxy-1,2-dihydro-2-oxo	crude; nmr	5888
5-Benzyl-4-ethoxy-2-ethylamino-6-methyl	–	5908
5-Benzyl-2-ethylamino-4,6-dimethyl	pic: 135	4551
1-Benzyl-4-ethyl-1,6-dihydro-6-oxo-2-phenyl	89–91; pic: 123	4484, 4510
4-Benzyl-2-ethyl-6-hydroxy-5-phenyl	205–206	5909
1-Benzyl-2-ethylthio-5-fluoro-1,4-dihydro-4-oxo	118–119	6111
1-Benzyl-2-ethylthio-5-fluoro-1,6-dihydro-6-oxo	46	6111
5-Benzyl-2-ethylthio-4-formyl-6-hydroxy	151–154	5743
1-Benzyl-5-fluoro-1,2-dihydro-4-methoxy-2-oxo	132–134	6111
1-Benzyl-5-fluoro-1,2-dihydro-4-methylthio-2-oxo	177–180 (?)	6111
1-Benzyl-5-fluoro-1,2-dihydro-2-oxo	127–129	4398
5-Benzyl-4-formyl-6-hydroxy-2-mercaptop	180–181; thiosemicarbazone: 201	5526, 5743
2- <i>N'</i> -Benzylguanidino-4,6-dimethyl	204	4975
2- <i>N'</i> -Benzylguanidino-4-methyl-6-phenyl	182	4975
2-Benzyl-4-hydroxy	178–180	4670
4-Benzyl-6-hydroxy	180	E, 5918

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Benzyl-2-hydroxy-4,6-dimethoxy	205–207	5122
2-Benzyl-6-hydroxy-2,5-diphenyl	237–238	E, 5909
5-Benzyl-2-hydroxy-4,6-diphenyl	285–288	5911
4-Benzyl-6-hydroxy-5- β -hydroxyethyl-2-mercapto	191–192	5917
4-Benzyl-6-hydroxy-2-isopropyl-5-phenyl	180–181	5909
5-Benzyl-4-hydroxy-6-isopropyl-2-phenyl	249–250	5909
4-Benzyl-6-hydroxy-2-mercapto-5-phenylazo	189–190	5874
5-Benzyl-4-hydroxy-2-mercapto-6-trifluoromethyl	205–206	5874
2-Benzyl-4-hydroxy-5-methoxycarbonyl-6-trichloromethyl	199–200	5913
2-Benzyl-4-hydroxy-6-methyl	173–175	H, 5075, 6169
4-Benzyl-6-hydroxy-2-methyl-5-phenyl	228 or 229–230	E, 4740, 5909
5-Benzyl-4-hydroxy-6-methyl-2-phenyl	242–243	H, 5076
4-Benzyl-6-hydroxy-5-phenyl-2-propyl	140–141	5909
1-Benzylideneamino-1,6-dihydro-6-oxo-2,4,5-triphenyl	175	5827
5-Benzylideneamino-2,4-dihydroxy	319–320	5367
5-Benzylideneamino-4-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	170	5006
5-Benzylideneamino-4-ethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	114–115	6030
5-Benzylideneamino-2-methoxy-4,6-diphenyl	147–149	6147
5-Benzylideneamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	133–134	3278
5-Benzylideneamino-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxo	159–161	6030
5-Benzylidenehexahydro-1,3-dimethyl-2,4,6-trioxo	158 or 164	4887, 4991, 5122
2-Benzylidenehydrazino	178–180	E, 5691
4-Benzylidenehydrazino-6-chloro	213–214	4807
4-Benzylidenehydrazino-2,6-dihydroxy	344	5968
4-Benzylidenehydrazino-6-ethoxy	177–178	4807
2-Benzylidenehydrazino-4-hydroxy	228–229	4368
2-Benzylidenehydrazino-4-hydroxy-6-methyl-5-propyl	199	5722

2-Benzylidenedihydrazino-4-methoxy-6-methyl	150	4840
4-Benzylidenedihydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	253 or 261	4621, 4626, 4954, 4991
4-Benzylidenedihydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	201–202	4921
4-Benzylidenedihydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxo	130 (?) or 270	4621, 4626
4-Benzylidenedihydrazono-6-chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo	146–147	5162
4-Benzylidenedihydrazono-6-ethoxy-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo	115–116	5162
4-Benzylidenedihydrazono-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo	145–147	5162
4-Benzylidenedihydrazono-1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2-oxo	178–180	5162
4-Benzylimino-6-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo	90–92	4971
4-Benzylimino-6-chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo	81	4969, 4994
4-Benzyl-6-isopropoxy-2-methylthio	112–115/2	5910
2-Benzyl-4-methoxy-6-methyl	pic: 137–138	6018
2-Benzyl-4-methyl-6-piperidino	HCl: 151–153	6018
2-Benzyl-5-chloro	98	6028
5-Benzyl-4-chloro-2-chloromethyl	109–111	5345
4-Benzyl-2-chloro-5-fluoro	109	6111
5-Benzyl-2-chloro-4-methoxy-6-methyl	175–177/6	5729
5-Benzyl-4-chloro-2-methyl	96–99	5345
4-Benzyl-2-diethoxycarbonylmethyl	–	5925
4-Benzyl-1,6-dihydro-1,5-dimethyl-6-oxo	88 and 94–95	E, 3768
1-Benzyl-1,4-dihydro-6-hydroxymethyl-2-methylthio-4-oxo	174–175	5175
4-Benzyl-1,6-dihydro-1-methyl-6-oxo	107 and 116–117	E, 3768
1-Benzyl-1,2-dihydro-2-oxo	93; HCl: 144	4583
4-Benzyl-2-dimethylamino	118–120/0.1	5392, 5722
2-Benzyl-4-ethoxy	crude; mmr	5888
4-Benzyl-2-ethoxycarbonylmethyl	–	5925
4-Benzyl-2-ethylthio-5-fluoro	128–130/0.01	6111
4-Benzyl-6-fluoro-2,5-dimethyl	148–149/6	3520
2-Benzyl-5-fluoro-4-hydroxy	146–147	6515
4-Benzyl-6-fluoro-2-methyl	141/7	3520

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Benzylloxy-6-fluoro-5-methyl	148–149/9.5	3520
4-Benzylloxy-2- α -formyl- α -methylethyl-6-methyl	130–135/1	5083
5-Benzylloxy-2-hydrazino-4-methoxy-6-methyl	96–97	5729
2-Benzylloxy-4-hydrazino-6-methyl-5-nitro	131–133	5661
4-Benzylloxy-6-hydroxy	196–197	E, 4393, 6058
5-Benzylloxy-2-hydroxy	196–197	E, 4384
5-Benzylloxy-4-hydroxy-2-hydroxymethyl	148–149	5345
4-Benzylloxy-6-hydroxy-2-methyl	177–179	E, 4393, 6058
4-Benzylloxy-6-hydroxy-5-methyl	222	E, 4393
5-Benzylloxy-4-hydroxy-2-methyl	186–189	E, 5345
4-Benzylloxy-6-hydroxy-2-phenyl	233–234	E, 4393, 6058
4-Benzylloxy-6-hydroxy-5-phenyl	192–193	E, 4393
5-Benzylloxy-2-mercapto	180–192 (<i>sic</i>)	4384
4-Benzylloxy-2-methoxycarbonylmethyl-6-methyl	150–160/2	5087, 5805
4-Benzylloxy-6-methyl	1-N-Ox: 141–143	E, 5927
2-Benzylloxy-2'-methylcyclopent-1'-enyl	nmr	5925
4-Benzylloxy-2-methylsulfonyl	76–77	5925
5-Benzylloxy-2-methylsulfonyl	93–95	3000
4-Benzylloxy-2-methylthio	118/0.01 or 141/0.3	5925, 6111
5-Benzylloxy-2-methylthio	69–71	E, 3000
5-Benzylloxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	95–97	5415
1-Benzylloxy-1,2,3,4-tetrahydro-6-hydroxymethyl-3-methyl-4-oxo-2-thio	166–167	5175
1-Benzyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	165	H, 4925
5-Benzyl-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thio	109–110	4442
4-Benzyl-1,2,3,6-tetrahydro-5-hydroxy-1,3-dimethyl-2,6-dioxo	180–181	5415
1-Benzyl-1,2,3,6-tetrahydro-5-hydroxy-4- α -methylallyl-2,6-dioxo	118–120	5415
1-Benzyl-1,2,3,6-tetrahydro-5-hydroxy-3-methyl-2,6-dioxo	163–164	5410
1-Benzyl-1,2,3,6-tetrahydro-5-methoxy-3-methyl-2,6-dioxo	146–147	5410
1-Benzyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	105–106	5410
1-Benzyl-1,2,3,4-tetrahydro-3-methyl-6-methylamino-2,4-dioxo	180–181	4657

1-Benzyl-1,2,3,4-tetrahydro-3-methyl-6-methylamino-5-nitroso-2,4-dioxo	137	4657
1-Benzyl-1,2,3,4-tetrahydro-3-methyl-2-oxo-4-thio	89–90	4441
1-Benzyl-1,2,3,6-tetrahydro-3-methyl-2-oxo-6-thio	110–111	4442
2-Benzylthio-4,6-bis(trifluoromethyl)	82(0.05; n _D ²⁰ 1.5064	5947
5-Benzylthio-2,4-bis(trimethylsiloxy)	147–149/0.15	5728
4-Benzylthio-5-butyl-2-dimethylamino-6-methyl	52–53	5722
2-Benzylthio-4-t-butyl-6-heptafluoropropyl	122/0.2	5947
2-Benzylthio-4-t-butyl-6-trifluoromethyl	138/0.5	5947
4-(Benzylthio)carbonyl-2,6-dihydroxy	228–230	5464
2-Benzylthio-4-carboxy-6-hydroxy-5-methyl	227–228	3183
2-Benzylthio-4-chloro-6-hydroxy-5-phenyl	211–218	4894
2-Benzylthio-4-chloro-5-methoxy	62–64	4395
2-Benzylthio-4,5-dichloro-6-hydroxy	222–223	4894
2-Benzylthio-4,6-diethyl	129/0.1	6271
2-Benzylthio-1,4-dihydro-1,6-dimethyl-4-oxo	146–147	4568
2-Benzylthio-1,6-dihydro-1,4-dimethyl-6-oxo	74–75	4568
4-Benzylthio-1,2-dihydro-1-methyl-2-oxo	150–151	4441
4-Benzylthio-2,3-dihydro-3-methyl-2-oxo	130–131	4441
2-Benzylthio-1,6-dihydro-4-methyl-6-oxo-1-phenyl	113–114	5923
5-Benzylthio-2,4-dihydroxy	296–297	H, 5728
2-Benzylthio-4,6-diisopropyl	120/1	6271
2-Benzylthio-4-dimethoxymethyl-5-fluoro-6-hydroxy	132–134	5525
2-Benzylthio-4,6-dimethyl	63	H, E, 6271
5-Benzylthio-2-dimethylamino-4-hydroxy-6-methyl	174 or 175–176	5390, 5722
2-Benzylthio-5-fluoro-4-formyl-6-hydroxy	165–167	5525
2-Benzylthio-5-fluoro-4-hydroxy	222	E, 5921
2-Benzylthio-4-hydroxy	188–189 or 186–192	H, E, 5121, 5418, 6185
2-Benzylthio-5-hydroxy	170	4395
2-Benzylthio-4-hydroxy-5-methoxy	186–188	4395
2-Benzylthio-4-hydroxy-6-methyl	176	H, E, 5121
2-Benzylthio-4-hydroxy-6-phenyl	247	5121
2-Benzylthio-4-isoamyl-6-trifluoromethyl	137/0.2	5947
2-Benzylthio-4-isobutyl-6-trifluoromethyl	101/0.01; HClO ₄ : 121	5947

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Benzylthio-4-isopropyl-6-trifluoromethyl	98/0.15; HClO ₄ : 163	5947
2-Benzylthio-5-methoxy	47-48	4395
4-Benzylthio-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	132-133	6297
2-Benzyl-4,5,6-trichloro	95-96	4917
5-Benzyl-2,4,6-trimethoxy	100	H, 5322
2,4-Bisacetamido-6-piperidino	3-N-Ox: 205	3508
1,3-Bis-β-acetoxyethyl-1,2,3,4-tetrahydro-2,4-dioxo	50-52	5495
4,6-Bisacetoxyethyl-2-methyl	di-N-Ox: 86	6160
2,4-Bis-β-acetylhydrazino-5-nitro	266-267	5666
2,4-Bisallylamino-5-ethoxycarbonyl-6-methyl	94-95	4470
2,4-Bisbenzylamino-6-methyl	114-115; pic: 153	4849
4,6-Bisbenzylamino-2-methyl-5-nitroso	123	6294
4,6-Bisbenzylthio-2-phenyl	119-120	4949
1,3-Bis-ε-bromoamyl-1,2,3,4-tetrahydro-2,4-dioxo	nd ²⁰ 1.5500	6127
1,3-Bis-ε-bromoamyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	nd ²⁰ 1.5512	4828
1,3-Bis-δ-bromobutyl-1,2,3,4-tetrahydro-2,4-dioxo	nd ²⁰ 1.5600	4828, 6127
1,3-Bis-δ-bromobutyl-1,2,3,4-tetrahydro-2,4-dioxo-6-phenyl	liq (anal)	1627
1,3-Bis-δ-bromobutyl-1,2,3,4-tetrahydro-5-methyl-2,4-dioxo	nd ²⁰ 1.5542	4828
1,3-Bis-δ-bromobutyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	64-65	4828
1,3-Bis-δ-bromobutyl-1,2,3,4-tetrahydro-6-methyl-5-nitro-2,4-dioxo	61-62	4828
1,3-Bis-δ-bromohexyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	nd ²⁰ 1.5380	4828
4,6-Bisbromomethyl-2-ethyl	di-N-Ox: 154	6160
2,4-Bisbromomethyl-6-methyl	di-N-Ox: 157	6160
4,6-Bisbromomethyl-2-methyl	di-N-Ox: 146	6160
1,3-Bis-γ-bromopropyl-1,2,3,4-tetrahydro-2,4-dioxo	nd ²⁰ 1.5657	4828
1,3-Bis-γ-bromopropyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	nd ²⁰ 1.5720	4828
2,4-Bisbutylamino-6-methyl	pic: 145	4844
4,6-Bis- <i>t</i> -butylamino-5-nitro	106-107	5442
2,4-Bisbutylthio-5-ethoxycarbonyl-6-methyl	179-182/0.3	4470
1,3-Bis-β-carboxypropyl-1,2,3,4-tetrahydro-2,4-dioxo	215-217	5920

1,3-Bis-β-chloroethyl-1,2,3,4-tetrahydro-2,4-dioxo	160/0.1	5495
1,3-Bis-β-chloroethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	71–72	6218
4,5-Bischloromethyl-2,6-dihydroxy	190–194	5603
1,3-Bis-β-cyanoethyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	105–108	6515
1,3-Bis-β-cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxo	108–110	E, 5924
1,3-Bis-β-cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxo	96–98	5924
1,3-Bis-β-cyanoethyl-1,2,3,4-tetrahydro-5-methoxy-2,4-dioxo	143–145	5924
1,3-Bis-β-cyanoethyl-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-thio	107–109	5924
1,3-Bis-β-cyanoethyl-1,2,3,4-tetrahydro-5-methyl-2,4-dioxo	113–115	5924
1,3-Bis-β-cyanoethyl-1,2,3,4-tetrahydro-4-oxo-2-thio	175/19	5072
4,6-Bischloromethyl		
1,3-Bis(C, C-diethoxycarbonyl-C-methoxycarbonyl)methyl-1,2,3,4-tetrahydro-2,4-dioxo	77–78	5195
1,3-Bisdiethoxycarbonylmethyl-1,2,3,4-tetrahydro-2,4-dioxo	95	5195
2,4-Bisdiethylamino-5-ethoxycarbonyl-6-methyl	140–142/0.3	4470
2,4-Bisdiethylamino-6-methyl	92–95/2; pic: 140	4844, 4846
2,4-Bisdimethylamino	41 to 55	E, 2676, 4844, 6093
4,6-Bisdimethylamino	105–107	E, 4844, 5284
4,6-Bisdimethylamino-2,5-difluoro	93–94	3521
2,4-Bisdimethylamino-5-ethoxycarbonyl-6-methyl	121–123/0.1	4470
2,4-Bisdimethylamino-6-fluoro	23–25; 103/5	4752
2,4-Bisdimethylamino-5-hydroxy	Na: anal, m/s	6373
2,4-Bisdimethylamino-6-methoxy	42–43	6106
4,6-Bisdimethylamino-2-methoxy	53–55	6106
2,4-Bisdimethylamino-5-methyl	46; pic: 177	4846
2,4-Bisdimethylamino-6-methyl	85/2; pic: 182	E, 4844, 4846
4,6-Bisdimethylamino-methyleneamino-2-thiocyanato	130–131	2859
4,6-Bisdimethylaminomethyl-5-hydroxy	105–107	6347
2,4-Bisdimethylamino-5-methylthio	100–102/0.06	5390
4,6-Bisdimethylamino-2-methyl-5-nitroso	125	6294
2,4-Bisdimethylamino-5-sulfo-oxy	214–220	6373
2,4-Bisdimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	–	5735
2,4-Bisdimethylcarbamoyl-6-hydroxy-5-methyl	crude: nmr	6140
1,3-Bis-β-ethoxycarbonyllallyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	liq; anal	6400
1,3-Bisethoxycarbonylmethyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	92	6400

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,3-Bisethoxymethyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	54	6515
4,5-Bisethylamino-6-hydroxy	152-154	3475
4,6-Bisethylthio-2-methoxycarbonylmethyl	204-206/2	5693
2,4-Bis-4-ethyl(thiosemicarbazido)	180-181	6133
4,6-Bisformamido-2-thiocyanato	249	2859
4,6-Bis- β -formylhydrazino	285-287	5697
2,4-Bis- β -formylhydrazino-6-methyl	225-227	5697
2,4-Bis- β -formylhydrazino-5-nitro	209-210	5666
1,3-Bisformylmethyl-1,2,3,4-tetrahydro-2,4-dioxo	semicarbazone: 230; thiosemicarbazone: 227	5926
1,3-Bisformylmethyl-1,2,3,4-tetrahydro-5-nitro-2,4-dioxo	methylthiosemicarbazone: 127	5926
2,4-Bisguanidininoamino	192	5848
2,4-Bisguanidininoamino-5-methyl	220	5848
2,4-Bisguanidininoamino-6-methyl	235	5848
2,4-Bisheptafluoroisopropyl-5,6-bis-pentafluoroethyl	nmr, m/s; g. c.	5922
2,4-Bishexylamino-6-methyl	176/1; pic: 145	4846
4,6-Bishydroxyiminomethyl	220	5862
4,5-Bishydroxymethyl-2-methylthio	72-73	3443
2,4-Bis(isopropylidenehydrazino-6-methyl	170-171	5848
4,5-Bismethylamino	140-141	E, 5873
4,6-Bis- α -methylhydrazino-5-nitro	175-177	5491
2,4-Bismethylthio	110/1; 1-Mel: 145; 3-Mel: 157	E, 2599, 4707, 5058, 5665, 6176
4,6-Bismethylthio	52-53	E, 4949
2,4-Bismethylthio-5-nitro	129-130	5661
4,6-Bismethylthio-5-nitro	148-152	6374
4,6-Bismethylthio-2-phenyl	81-82	4949
2,4-Bis-4-methyl(thiosemicarbazido)	222-223	6133
4,6-Bistriacetylhydrazino	158	5697
4,6-Bistrichloromethyl	49-50	5072

4,6-Bis(trimethylammonio) 2,4-Bis(trimethylsiloxy) 2-Bromo 5-Bromo	Cl ₂ : nmr 31–33; 120/18 53 or 56–57 73–74; 1- <i>N</i> -Ox: 167	5393 E, 5632, 6132 E, 2603, 4382 H, E, 4483, 4677, 5500, 5594
5-Bromoacetyl	HBr: 134–135	4473
5-Bromo-1,3-bis-β-cyanoethyl-4-carboxy-1,2,3,6-tetrahydro-2,6-dioxo	167–168	4390
5-Bromo-1,3-bis-β-cyanoethyl-1,2,3,4-tetrahydro-2,4-dioxo	167–168	4391
5-Bromo-2,4-bisdimethylamino	25–26	4703
5-Bromo-4,6-bisdimethylaminomethyleneamino-2-thiocyanato	180–182	2859
5-Bromo-2,4-bisdimethylsiloxy	–	5935
5-Bromo-2,4-bismethylthio	65–66	4707
4-Bromo-2,6-bis(trimethylsiloxy)	c. 60/high vac.	5935
5-Bromo-2,4-bis(trimethylsiloxy)	c. 80/high vac.	5935
5-Bromo-2-bromomethyl-4-chloro-6-hydroxy	260–261	5253
5-Bromo-4-bromomethyl-1,2-dihydro-1-methyl-2-oxo	3-MeBr: 205	5266
5-Bromo-4-bromomethyl-6-phenyl	3- <i>N</i> -Ox: 158	4810
5-Bromo-4-but-3'-enyl-6-hydroxy-2-piperidino	150–151	4569
5-Bromo-2-t-butoxy-4-chloro	anal; nmr	4703
5-Bromo-4-t-butoxy-2-chloro	32–34	4703
4-Bromo-6-t-butyl	97–98/12	4667, 5929
5-Bromo-4-t-butyl	–	E, 4667
5-Bromo-2-t-butyl-4-carboxy	140	4364
5-Bromo-4-t-butyl-1,2-dihydro-2-imino-1-methyl	HJ: 220	2602
1-δ-Bromobutyl-1,6-dihydro-4-methyl-2-methylthio-6-oxo	n ^D ₂₀ 1.5746	4828
5-Bromo-1-butyl-1,6-dihydro-4-methylthio-6-oxo	90–92	4806
5-Bromo-1-s-butyl-1,6-dihydro-4-methylthio-6-oxo	140–142	4806
4-γ-Bromobutyl-6-hydroxy-2-piperidino	145; HBr: 181	4569
5-Bromo-4-t-butyl-6-methyl	–	4676
5-Bromo-2- <i>N</i> -butyl- <i>N</i> -methylamino-4-chloro	nmr	6172
5-Bromo-4- <i>N</i> -butyl- <i>N</i> -methylamino-2-chloro	anal	6172
5-Bromo-4- <i>N</i> -butyl- <i>N</i> -methylamino-2-methoxy	m/s; nmr	6172
1-δ-Bromobutyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	70–72	4828
1-δ-Bromobutyl-1,2,3,6-tetrahydro-1,4-dimethyl-2,6-dioxo	88–90	4828

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Bromo-1-butyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	60-61	4940
5-Bromo-1-s-butyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	73-75	4940
5-Bromo-2-carbamoyl	208-210	E, 4399
5-Bromo-4-carbamoyl	244-245	5151
5-Bromo-4-carbamoyl-6-hydroxy-2-methylthio	—	5937
5-Bromo-4-carbamoylmethyl-2,6-dihydroxy	299	4939
5-Bromo-4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	197-198	H, E, 4399
5-Bromo-2-carboxy	286-288 or 316	H, E, 2880, 4390, 5930
5-Bromo-4-carboxy-2,6-dihydroxy	—	—
5-Bromo-4-carboxy-2-hydroxymethyl	152-153; K: 252	5932
5-Bromo-4-carboxy-2-methoxy	171-173	4399
4-Bromo-2-carboxymethyl	Na: > 300	5693
5-Bromo-4-carboxymethyl-2,6-dihydroxy	278-280	2880, 5930
5-Bromo-4-carboxy-2-methylsulfonyl	192-193	4399, 5380
5-Bromo-1-carboxymethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	192	4925
5-Bromo-1-carboxymethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	252	4925
5-Bromo-4-carboxy-2-methylthio	K salt	H, E, 4330
5-Bromo-4-carboxy-2-phenyl	156-158	H, 2603
5-Bromo-2-chloro	—	E, 5664
5-Bromo-4-chloro	100/10	H, 4705
5-Bromo-4-chloro-6-cyclopropyl	86-87	5934
5-Bromo-4-chloro-6-dibromomethyl-6-hydroxy	> 300	5253
5-Bromo-2-chloro-4-diethylamino	anal; nmr	4703
5-Bromo-4-chloro-2-diethylamino	anal; nmr	4703
4-Bromo-5-chloro-2,6-dihydroxy	305-306	4650
5-Bromo-4-chloro-2,6-dihydroxy	303-305	4650
5-Bromo-4-chloro-2,6-dimethyl	45	H, 5161
5-Bromo-2-chloro-4-dimethylamino	62-64	4703

5-Bromo-4-chloro-2-dimethylamino-6-methyl	79–80	5284
5-Bromo-4-chloro-2,6-diphenyl	156–157	5760, 5761
5-Bromo-2-chloro-4- <i>N</i> -ethyl- <i>N</i> -methylamino	22–26	6172
5-Bromo-4-chloro-2-fluoromethyl-6-hydroxy	220	5253
5-Bromo-2-chloro-4- <i>N</i> -isopropyl- <i>N</i> -methylamino	34–35	6172
5-Bromo-4-chloro-2- <i>N</i> -isopropyl- <i>N</i> -methylamino	39–40	6172
5-Bromo-2-chloro-4-methoxy	73–75	4703
5-Bromo-4-chloro-2-methoxy	anal; nmr	4703
5-Bromo-4-chloro-2-methyl	—	H, 5958
5-Bromo-4-chloro-6-methyl	53–56	E, 5161
5-Bromo-4-chloro-6-methyl-2-methylthio	72–73	H, E, 5161
5-Bromo-2-chloro-4-methylthio	56–58	4706
4-Bromo-5-chloro-2-phenyl	138	5755
5-Bromo-4-chloro-2-phenyl	134–136	H, 5755
5-Bromo-2-chloro-4-piperidino	65–67	4703
5-Bromo-4-chloro-2-piperidino	76–78	4703
5-Bromo-4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	162–163	4650, 6110
5-Bromo-2-cyano	120–121	4399
5-Bromo-1-β-cyanoethyl-1,6-dihydro-2-methylthio-6-oxo	127–129	4391
5-Bromo-4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	125	4927, 4939
5-Bromo-1-cyclohex-2'-enyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	247	4925
5-Bromo-1-cyclohexyl-1,6-dihydro-4-methylthio-6-oxo	163–165	4806
4-Bromo-6-cyclohexylimino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo	128–129	4971
5-Bromo-1-cyclohexyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	240	4925
5-Bromo-1-cyclohexyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	175	E, 4925
5-Bromo-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	128–129	4931
5-Bromo-1-cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	153–154	4931
5-Bromo-1-cyclopentyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	158	4925
5-Bromo-1-cyclopentyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	174	4925
5-Bromo-4-cyclopropyl-6-hydroxy	—	5934
5-Bromo-2,4-di- <i>t</i> -butoxy	—	5935
5-Bromo-4,6-di- <i>t</i> -butoxy	60–62 or 63–64	4700, 4701
5-Bromo-2,4-di- <i>t</i> -butyl	anal; nmr	4664

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Bromo-2,4-di- <i>t</i> -butyl-6-chloro	anal; nmr 94–96	4664
5-Bromo-2,4-di- <i>t</i> -butyl-6-hydrazino	187–188	4664
5-Bromo-2,4-di- <i>t</i> -butyl-6-hydroxy	104/6 or 93/5	H, 5161, 5592, 5935
5-Bromo-2,4-dichloro	42–43	H, E, 5161
5-Bromo-2,4-dichloro-6-methyl	150–152/2	5693
5-Bromo-2-di(ethoxycarbonyl)methyl	75–76	5517
4-Bromo-2,6-diethoxy-5-methyl	195 or 210–212	4507, 5046
5-Bromo-4-diethoxymethyl-2,6-dihydroxy	anal; u.v.	5936
4-Bromo-6-diethylamino-2- <i>N,N</i> -diethylcarbamoylmethyl	m/s; nmr	6172
5-Bromo-4-diethylamino-2-methoxy	97–98	4971
5-Bromo-1,3-diethyl-1,2,3,6-tetrahydro-6-imino-2-oxo	113	4930
5-Bromo-1,6-dihydro-1,4-dimethyl-6-oxo-2-phenyl	HI: 220; pic: 203	2602
5-Bromo-1,2-dihydro-2-imino-1,4-dimethyl	nmr	E, 2602
5-Bromo-1,2-dihydro-1-methyl-4-methylamino-2-oxo	175–176; HBr: > 256	5227
5-Bromo-1,6-dihydro-1-methyl-2-methylthio-6-oxo	130	6111
5-Bromo-1,6-dihydro-1-methyl-4-methylthio-6-oxo	120–122	4806
5-Bromo-1,2-dihydro-1-methyl-2-oxo	237–239; 3-MeBr: 268 or 275	5266, 5326
5-Bromo-1,6-dihydro-1-methyl-6-oxo	154 or 158	E, 2630, 6094
5-Bromo-1,4-dihydro-6-methyl-4-oxo-1-phenyl	235	4930
5-Bromo-1,6-dihydro-4-methyl-6-oxo-1-phenyl	182–183	4930, 5049, 6076
5-Bromo-1,6-dihydro-4-methylthio-6-oxo-1-phenyl	170	4806
5-Bromo-1,6-dihydro-4-methylthio-6-oxo-1-propyl	120–121	4806
4-Bromo-2,6-dihydroxy	> 260	E, 4650
5-Bromo-2,4-dihydroxy	295 to 318; 1- <i>N</i> -Ox: 240	H, E, 3464, 4391, 5046, 5121, 6277
5-Bromo-4,6-dihydroxy	261–263	H, E, 5316
5-Bromo-2,4-dihydroxy-6-hydroxymethyl	173–174	4507
4-Bromo-2,6-dihydroxy-5-iodo	260–261	4650
5-Bromo-2,4-dihydroxy-6-iodo	284–286	4650

5-Bromo-2,4-dihydroxy-6-methoxycarbonylmethyl	5937	
5-Bromo-2,4-dihydroxy-6-methyl	247 to 278; 1-N-Ox: X-ray	H, E, 2880, 4568, 5046, 5121, 5957, 6237
5-Bromo-2,4-dihydroxy-6-phenyl	276–278	2655
5-Bromo-2,4-dihydroxy-6-phenylthio	310–317	6273
5-Bromo-2,4-dihydroxy-6-propyl	221–222	2655
5-Bromo-2,4-dihydroxy-6-trifluoromethyl	236–240	5933
5-Bromo-2,4-dihydroxy-6-vinyl	>250	5403
5-Bromo-2,4-dimercapto	253–255	4707
5-Bromo-2,4-dimethoxy	65–66	H, E, 4700
2-Bromo-4,6-dimethyl	71–72	E, 2603, 5664
4-Bromo-2,6-dimethyl	54–55	5664
5-Bromo-2,4-dimethyl	41–42; 80/18	H,
5-Bromo-2-dimethylamino	81–82	4359
5-Bromo-2-dimethylamino-4-β-dimethylaminoethylamino	HB: 143	6180
4-Bromo-6-dimethylamino-2-N,N-dimethylcarbamoylmethyl	anal; u.v.	5936
5-Bromo-2-dimethylamino-4-hydroxy	246–247	4703, 4706
5-Bromo-2-dimethylamino-4-hydroxy-6-methyl	229 or 232–233	E, 5284, 5722
5-Bromo-2-dimethylamino-4-methoxy	65–67	4703
5-Bromo-4-dimethylamino-2-methoxy	29–31	4703
2-Bromo-5-dimethylaminomethylencamino	96–97	4382
5-Bromo-2-dimethylamino-4-methylthio	58–60	4706
2-Bromo-4,6-diphenyl	128–129	4681
4-Bromo-2,6-diphenyl	113–114	5760
5-Bromo-2-ethoxy	56–57	2630
5-Bromo-4-ethoxycarbonyl-2,6-dihydroxy	264–265	5046
5-Bromo-1-β-ethoxycarbonyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	174	4925
5-Bromo-4-ethoxycarbonylmethyl-2,6-dihydroxy	228–230	5046, 5937
5-Bromo-1-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	247	4925
5-Bromo-1-ethoxycarbonylmethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	184	4925

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Bromo-5-ethoxycarbonyl-2-methylthio	63	2599
5-Bromo-4-ethoxycarbonyl-2-methylthio	33–34; 123/0.3	5855
5-Bromo-4-ethoxycarbonyl-2-phenyl	73	2603
5-Bromo-4-ethoxy-6-methyl	113/15; <i>N</i> -1-Ox: 97	5805
4- α -Bromoethyl	crude; nmr	4379
5- α -Bromoethyl	crude; nmr	4379
2- α -Bromoethyl-4-chloro-6-hydroxy	178–180	5253
5- α -Bromoethyl-4,6-dichloro	102/0.25	4575
5-Bromo-1-ethyl-1,6-dihydro-4-methylthio-6-oxo	130–132	4806
5-Bromo-1-ethyl-1,2-dihydro-2-oxo	149–150	2630
5- α -Bromoethyl-4,6-dimethoxy	crude	4575
5-Bromo-4- <i>N</i> -ethyl- <i>N</i> -methylamino-2-methoxy	m/s; nmr	6172
5-Bromo-4-ethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	139–141	2880
5-Bromo-1-ethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	148–149	4940
5-Bromo-1-ethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	165	4925
5-Bromo-1-ethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	209	4925
5-Bromo-4-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-1-phenyl	174	4931
5-Bromo-2-ethylthio-4-formyl-6-hydroxy	183–185	5743
5-Bromo-2-fluoro	92–93	5693
2-Bromo-5-formamido	130–131	4380
5-Bromo-4-formamidomethyl-2,6-dihydroxy	—	5868
5-Bromo-4-formyl-2,6-dihydroxy	268–270 or 275; thiosemicarbazone: > 280	4507, 5403, 5526, 5743
5-Bromo-4-formyl-6-hydroxy-2-methylthio	231–232	5743
5-Bromo hexahydro-1,3,5-trimethyl-2,4,6-trioxo	114	5928
5-Bromo-4-hydrazino-2,6-dimethyl	145–146	5094
5-Bromo-4-hydrazino-2-phenyl	200	5755
5-Bromo-4-hydroxy	198–199	H, E, 4677
5-Bromo-4- α -hydroxybenzyl	88–89	5515
5-Bromo-4-hydroxy-2,6-diphenyl	300–305	H, 5760

5-Bromo-4-hydroxy-2-mercapto-6-phenyl	226–227	5532
5-Bromo-4-hydroxy-6-methoxycarbonyl-2-methylthio	207–208	5151
5-Bromo-2-hydroxymethyl	93–94	5932
5-Bromo-4-hydroxy-2-methyl	226	H, 5958
5-Bromo-4-hydroxymethyl-2-methoxy	crude: 124	4359
5-Bromo-4-hydroxy-6-methyl-2-methylthio	250–252	H, E, 4568
5-Bromo-4-hydroxy-2-methylthio	245	H, E, 6111
5-Bromo-4-hydroxy-2-phenyl	258–260	H, 5755
5-Bromo-4-hydroxy-6-phenyl	—	E, 5816
5-Bromo-4-iodo-2-isopropyl-6-methyl	78	5655
5-Bromo-4-iodo-2-methylthio	130–131	5284
5-Bromo-2-isoamylamino	84–85	5664
5-Bromo-4- <i>N</i> -isopropyl- <i>N</i> -methylamino-2-methoxy	m/s; nmr	6172
5-Bromo-2-isopropyl-4-piperidino	105–106/1	5694
5-Bromo-2-mercapto	214–215	E, 4384
5-Bromo-4-mercapto-2-methyl	200–204	5958
5-Bromo-2-methoxy	57	4399
5-Bromo-4-methoxy	66–68	E, 4705
4-Bromo-2-methoxycarbonylmethyl	50–53	5693
5-Bromo-2-methoxy-4-methyl	crude; nmr	4359
5-Bromo-4-methoxy-6-methyl-2-phenyl	67	4930
5-Bromo-2-methoxy-4-methylthio	68–70	4706
5-Bromo-4-methoxy-2-methylthio	86	6111
5-Bromo-4-methoxy-2-piperidino	81–85	4706
2-Bromomethyl	anal	5682
4-Bromomethyl	anal	5682
5-Bromo-2-methylamino	121	E, 4359
5-Bromo-4-methylamino	128–129	4682
5-Bromo-4-methyl-2,6-bis(trimethylsiloxy)	121–124/2.5	5957
2-Bromomethyl-4-chloro-6-hydroxy	194–195	5253
5-Bromomethyl-2,4-dihydroxy-6-methoxycarbonyl	206–210	6193
4-Bromomethyl-2,6-dimethoxy-5-nitro	liq	6517
4-Bromomethyl-2,6-dimethyl	di- <i>N</i> -Ox: 150	6160
2-Bromomethyl-4,6-diphenyl	153–158	4875

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2- α -Bromo- α -methyleneethyl	85–86	5690
2- α -Bromo- α -methyleneethyl-4-chloro	80–82/1.5	5694
2- α -Bromo- α -methyleneethyl-4-fluoro	65–68/22	5694
2- α -Bromo- α -methyleneethyl-4-methoxy	72–74/0.3	5690
4-Bromoethyl-2-ethyl-6-methyl	di- <i>N</i> -Ox: 124	6160
2- α -Bromo- α -methyleneethyl-4-phenyl	86–87	5690
5-Bromomethyl-2-methoxycarbonyl	121–123	6091
5-Bromo-4-methyl-2-methylamino	87–88	E, 2602
2-Bromomethyl-4-phenyl	1- <i>N</i> -Ox: 146	4810
4-Bromomethyl-6-phenyl	67–68; 3- <i>N</i> -Ox: 188–191	4810, 5255
5-Bromo-4-methyl-6-phenyl	3- <i>N</i> -Ox: 121	4810
5-Bromo-2-methylsulfonyl	132–133	4399
4-Bromomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	143–144	4943, 6138
5-Bromo-4-methylthio	71–73	E, 4705
2-Bromo-4-phenyl	85 or 89–90	5959, 6042
4-Bromo-6-phenyl	85–86; 1- <i>N</i> -Ox: 98	4675, 4685, 5816
5-Bromo-2-phenyl	104–105	H, 4359
5-Bromo-4-phenyl	95 or 97; 1- <i>N</i> -Ox: 213	E, 4810, 5595
5-Bromo-2-piperidino	57–58	4688
5-Bromo-4-piperidino	164/18; pic: 149	4663
1- γ -Bromopropyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	102–103	4828
1- γ -Bromopropyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	73–74	4828
5-Bromo-1,2,3,4-tetrahydro-1,3-bis- β -hydroxyethyl-6-methyl-2,4-dioxo	174–175	4784
4-Bromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	132–133	4650
5-Bromo-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	198	4925
5-Bromo-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	238	4925
5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenylthio	138–139	6273
5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylhydrazonomethyl-2,4-dioxo	104–106	6274
4-Bromo-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-propylimino	68	4971

5-Bromo-1,2,3,4-tetrahydro-1- β -hydroxyethyl-6-methyl-2,4-dioxo-3-phenyl	164	4925
5-Bromo-1,2,3,4-tetrahydro-3- β -hydroxyethyl-6-methyl-2,4-dioxo-1-phenyl	188	4925
4-Bromo-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxo	190	4971
4-Bromo-1,2,3,6-tetrahydro-5-iodo-1,3-dimethyl-2,6-dioxo	170-171	4650
5-Bromo-1,2,3,4-tetrahydro-1-isobutyl-3-methyl-2,4-dioxo	128	4940
5-Bromo-1,2,3,4-tetrahydro-1-isopropyl-3-methyl-2,4-dioxo	115-120	4940
5-Bromo-1,2,3,4-tetrahydro-3-isopropyl-6-methyl-2,4-dioxo-1-phenyl	230	4925
5-Bromo-1,2,3,4-tetrahydro-6-C-methoxyformimidoyl-1,3-dimethyl-2,4-dioxo	137	4939
5-Bromo-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-phenyl	244	4931
5-Bromo-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	204	4931
5-Bromo-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-propyl	97-99	4940
5-Bromo-1,2,3,4-tetrahydro-1-methyl-6-methylthio-2,4-dioxo-3-propyl	28-30	4806
5-Bromo-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo	138 or 141-142	H, 2880, 4925
5-Bromo-2,4,6-trihydroxy	—	H, E. 5961
5- β -Bromovinyl-2,4-dihydroxy	220	5849
5- α -Bromovinyl-2,4-dimethoxy	107-108	4575
2-Butanesulfonamido-4-hydroxy	246-248	5586
1-But-2'-enyl-6-chloro-5-ethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	145-147/0.4	5726
1-But-2'-enyl-3,5-diethyl-1,2,3,4-tetrahydro-2,4-dioxo	150-152/0.2	5726
4-But-3'-enyl-6-hydroxy-2-mercapto	202	4569
4-But-3'-enyl-6-hydroxy-2-methylthio	144	4569
4- β -But-2'-enylidene- α -methylthydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	151	4950, 4991
4-Butoxycarbonyl-2,6-bis(trimethyl)siloxy	159-161/3	5957
5-Butoxycarbonyl-2,4-dichloro-6-methyl	138/1; n _D ²⁰ 1.5105	4470
4-Butoxycarbonyloxy-5-butyl-2-dimethylamino-6-methyl	122-123	5723
4-Butoxycarbonyloxy-2-dimethylamino-5,6-dimethyl	105/0.03	5723
4-t-Butoxycarbonyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	95-96	6853
2-Butoxy-5-chloro	112-114/14	6028
4-Butoxy-2-chloro-5-fluoro	128-130/25	5956
5-t-Butoxy-2-chloro-4-hydroxy-6-methyl	150	4466

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Butoxy-1,6-dihydro-1- δ -hydroxybutyl-4-methyl-6-oxo	liq; anal	6266
4-t-Butoxy-1,2-dihydro-1-methyl-2-oxo	—	4437
2-Butoxy-5-dimethylamino methyleneamino	69–70	6510
2- β -Butoxyethyl-4-hydroxy-6-methyl	108–109	4513
2- β -s-Butoxyethyl-4-hydroxy-6-methyl	108–110	4513
2-Butoxy-5-fluoro-4-hydroxy	127–129	6515
4-Butoxy-5-fluoro-2-hydroxy	151	6515
4-Butoxy-5-fluoro-2-piperidino	167/11; HCl: 105	5956
2-Butoxy-4-hydroxy	85–86	4845
2-Butoxy-4-hydroxy-6-methyl	87–88	4845
5-t-Butoxy-4-hydroxy-6-methyl	150	4466
5-Butoxymethyl-2,4-dihydroxy	215–217	E, 6104
2-Butyl	122/100	5063
2-t-Butyl	anal; nmr; chloroaurate: 147	4690
4-Butyl	87/12; pic: 92	5758, 6220
5-Butyl	79–80/11	4515
4-t-Butylamino	143	2630
4-Butylamino-5-butylaminomethyl-6-carboxy-2-chloro	99	2884
4-Butylamino-6-N-butylcarbamoyl-2-chloro-5-hydroxymethyl	99	2884
2-Butylamino-5- δ -carboxybutyl-4,6-dihydroxy	257–260	6518
2-Butylamino-4- β -carboxyethyl-6-hydroxy	244–246	4569
4-Butylamino-6-chloro	74–76	5960
4-Butylamino-2-chloro-5- β -chloroethyl	HCl (?): 164–165	5881
4-t-Butylamino-2-chloro-5-ethoxycarbonyl-6-methyl	66–68; 112/0.2	4470
4-Butylamino-5- β -chloroethyl	HCl: 151–153	5881
4-Butylamino-5- β -chloroethyl-2-methyl	HCl: 138–139	5741
4-t-Butylamino-2-chloro-5-fluoro	98–99	5962
4-Butylamino-6-chloro-5-nitro	—	4396
4-t-Butylamino-6-chloro-5-nitro	64	5442
2-Butylamino-5-cyano	122–124	5955

4-Butylamino-5-cyano-6-phenyl	103	6129
4-Butylamino-5-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	199–201	4946
4-Butylamino-1,2-dihydro-6-methyl-2-oxo-1-phenyl	191–192	4859
4-Butylamino-2,6-dihydroxy-5-nitro	260–262	5576
4-Butylamino-2,6-dimethyl	anal	E, 5135
2-Butylamino-5-ethoxycarbonylbutyl-4,6-dihydroxy	255–257	6518
4-Butylamino-6-hydroxy-2-methyl	179	5015
4-Butylamino-6-hydroxy-5-nitro	171–173	4396
4-t-Butylamino-6-hydroxy-5-nitro	216–218	5442
4-Butylamino-5-iodo-2,6-dimethyl	sulf: 145–146	4506
5-Butylaminomethyl-4-N-butylcarbamoyle-2,6-dihydroxy	167; HCl: 225	4948
5-Butylaminomethyl-2,4-dihydroxy	HCl: 276	5475
4-t-Butylamino-5-nitro	34; pic: 132–134	2562
2-Butylamino-5-nitro-4-thiocyanato	103–104	5742
4-Butylamino-5-phenyl	–	5914
5-Butylamino-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	110	4925
5-s-Butylamino-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	151	4925
5-Butyl-2,4-bis(trimethylsiloxy)	97–99/0.03	5963
5-Butyl-2,4-bis(trimethylsilyl)thio	–	5963
4-t-Butyl-2-t-butylamino	70–73	5484
5-Butyl-2-butylamino-4-hydroxy-6-methyl	143	5722
4-t-Butyl-2-carbamoylmethyl-6-hydroxy	200–202	5640, 5688
5-t-Butylcarbamoylemethyl-4-hydroxy-2,6-dimethyl	206–207	E, 5965
1-Butyl-6-carbamoyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	160–162	4940
1-s-Butyl-6-carbamoyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	193–194	4940
2-Butyl-5-carboxy	99–100	5715
4-t-Butyl-2-carboxy	Na: > 300	5688
5-Butyl-2-carboxy	129–130	5715
5-Butyl-4-carboxy-2,6-dihydroxy	297–298	E, 3183
5-Butyl-4-carboxy-6-hydroxy-2-methylthio	181–182	3183
4-t-Butyl-2-carboxymethyl	94–96	5693
1-Butyl-6-carboxy-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	172–174	4934, 4946
2-t-Butyl-4-chloro	80–81/15	3754
4-t-Butyl-2-chloro	70–75/01 or 75/1	2602, 5484

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-t-Butyl-5-chloro	84–85/15	4664
4-t-Butyl-6-chloro	38–39	E, 3754
4-t-Butyl-6-chloro-2-cyanomethyl	41–42	5688
5-s-Butyl-4-chloro-1,6-dihydro-1-methyl-6-oxo-2-phenyl	68–69	5351
1-Butyl-5-chloro-1,6-dihydro-4-methylthio-6-oxo	101–102	4806
1-Butyl-5-chloro-1,2-dihydro-2-oxo	125	6028
5-Butyl-4-chloro-2,6-dihydroxy	197–198	4527, 5915
5-Butyl-4-chloro-2-dimethylamino-6-methyl	96–97/0.1	5392
4-t-Butyl-5-chloro-6-hydroxy	108–109	4664
4-t-Butyl-5-chloro-6-hydroxy	152–154	4664
5-Butyl-4-chloro-6-hydroxy-2-phenyl	194–196	5025
2-Butyl-4-chloro-6-hydroxy-5-phenyl	136–137	5028
4-t-Butyl-6-chloro-2-methoxycarbonylmethyl	94–96/0.5	5688
4-t-Butyl-6-chloro-2-methoxyformimidoylmethyl	HCl: 110–112	5688
5-Butyl-4-chloro-6-methyl-2-phenyl	49–50	4348
1-Butyl-4-chloro-1,2,3,6-tetrahydro-2,6-dioxo-3,5-dipropyl	140/0.4	4527
1-Butyl-6-chloro-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	34–37	4657
5-Butyl-2-cyanoamino-4-hydroxy-6-methyl	295–298	5722
4-t-Butyl-2-cyanoamino-5-phenyl	152–153	5484
4-Butyl-5-cyano-2,6-dihydroxy	281	4901
1-Butyl-6-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	78–79	4940
1-s-Butyl-6-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	99	4940
4-t-Butyl-2-diacetylamino-5-phenyl	121–122	5484
4-t-Butyl-5,6-dichloro	45–47; 110/15	4664
2-Butyl-4,5-dichloro-6-hydroxy	158–167	5731
2-Butyl-4,6-dichloro-5-nitro	125–130/3	H, 4570
2-t-Butyl-4,6-dichloro-5-nitro	83–84	5753
4-t-Butyl-2,6-dichloro-5-nitro	52–54	5753
5-Butyl-4,6-dichloro-2-phenyl	62–63	5025
5-s-Butyl-4,6-dichloro-2-phenyl	48–49	5351

4-t-Butyl-2-diethylamino-6-heptafluoropropyl	67/0.01; n _D ²⁰	1.4308	4559
4-t-Butyl-2-diethylamino-6-trifluoromethyl	74/0.01; n _D ²⁰	1.4610	4559
4-t-Butyl-1,2-dihydro-2-imino-1-methyl	HI: 227; pic:	175	2602
1-Butyl-1,6-dihydro-6-imino-2,4,5-triphenyl	134		4589
1-Butyl-1,2-dihydro-4-isopropoxy-6-methyl-2-oxo	87–88		4847
4-t-Butyl-1,2-dihydro-1-methyl-2-oxo	125		2602
1-Butyl-1,6-dihydro-4-methylthio-6-oxo	84–85		4806
1-s-Butyl-1,6-dihydro-4-methylthio-6-oxo	47–48		4806
1-t-Butyl-1,2-dihydro-2-oxo	MeHSO ₄ : 147		E, 5324
1-Butyl-1,6-dihydro-6-oxo-2,4,5-triphenyl	173		4589
2-Butyl-4,6-dihydroxy	299–300		H, 4570
2-t-Butyl-4,6-dihydroxy	242–246		5753
4-t-Butyl-2,6-dihydroxy	227–229		5753
5-Butyl-2,4-dihydroxy	286–288 or 291		H, E, 5754, 5915, 5963
5-t-Butyl-2,4-dihydroxy	375–380		5875, 5964
5-Butyl-2,4-dihydroxy-6-methyl	–		H, E, 5967
2-Butyl-4,6-dihydroxy-5-nitro	295		H, 4570
2-t-Butyl-4,6-dihydroxy-5-nitro	>300		5753
4-t-Butyl-2,6-dihydroxy-5-nitro	303–305		5753
4-Butyl-2,6-dihydroxy-5-propyl	203–205 or 207		5875, 5964
5-Butyl-2,4-dimercapto	232–234		5963
2-Butyl-4,6-dimethyl	95/16		5096
4-t-Butyl-2-dimethylamino	50–55/0.1		5458
5-Butyl-2-dimethylamino-4-ethoxycarbonyloxy-5-methyl	109–110/0.01		5723
5-Butyl-2-dimethylamino-4-ethyl-6-hydroxy	100		5722
5-Butyl-2-dimethylamino-4-hydroxy	84		5722
5-Butyl-2-dimethylamino-4-β-hydroxyethoxy-6-methyl	126–128/0.4		5722
5-Butyl-2-dimethylamino-4-hydroxy-6-methyl	102		E, 5392, 5722
5-Butyl-2-dimethylamino-4-hydroxy-6-phenyl	182		5722
5-Butyl-2-dimethylamino-4-mercaptop-6-methyl	105–106		5722
1-Butyl-4-dimethylaminomethyleneamino-1,2-dihydro-2-oxo	122–123		6251
5-Butyl-2-dimethylamino-4-methyl-6-3'-methylisocrotonyloxy	²⁴ 1.5261		5392
5-Butyl-2-dimethylamino-4-methyl-6-methylsulfonyloxy	67 or 162		5392, 5723

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Butyl-2-dimethylamino-4-methyl-6-propoxycarbonyloxy	118–119/0.04	5723?
5-Butyl-4-dimethylamino-6-methyl-2-phenyl	45–47	4348
5-Butyl-2-dimethylamino-4-methyl-6-pivaloyloxy	134–136/0.25; n_D^{25}	5392
1-Butyl-5-dimethylaminomethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	HCl: 180–182	4932
1-Butyl-5-dimethylamino-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	64	4925
4-t-Butyl-2,5-diphenyl	96–97	5484
4-t-Butyl-2-ethoxycarbonylamino-5-phenyl	179–180	5484
4-t-Butyl-2-ethylamino-6-heptafluoropropyl	62/0.01; n_D^{20}	4558
5-Butyl-2-ethylamino-4-hydroxy-6-methyl	159	5392, 5722
5-Butyl-2-ethylamino-4-methyl-6-methylsulfonyloxy	81–82	5392
4-t-Butyl-2-ethylamino-6-trifluoromethyl	78/0.02	4558
5-Butyl-2-ethylmethethylamino-4-hydroxy-6-methyl	101	5722
5-Butyl-2-hydrazino-4-hydroxy-6-methyl	201–202	E, 5722
4-t-Butyl-2-hydrazino-5-phenyl	250–251	5484
2-t-Butyl-4-hydroxy	147–148	3754, 4364
4-t-Butyl-2-hydroxy	194–195 or 197–198	2602, 5484
5-Butyl-4-hydroxy-2-isopropylamino-6-methyl	135–137	5722
4-t-Butyl-6-hydroxy-2-mercapto	178–179	H, 5753
5-Butyl-4-hydroxy-2-mercapto	151–152	H, E, 5963, 5964
5-t-Butyl-4-hydroxy-2-mercapto	280–300 or 321–325	5875, 5890, 5964
4-Butyl-6-hydroxy-2-mercapto-5-propyl	200–202	5875, 5964
5-Butyl-4-hydroxy-6-methyl-2-methylamino	—	5966
5-Butyl-4-hydroxy-6-methyl-2-phenyl	248–250	4348
5-s-Butyl-4-hydroxy-6-methyl-2-phenyl	189–190	4348
5-Butyl-4-hydroxy-6-methyl-2- β -phenylhydrazino	185	5722
5-Butyl-4-hydroxy-6-methyl-2-piperidino	126	5722
5-Butyl-4-hydroxy-6-methyl-2-propylamino	154	5392, 5722
5-Butyl-4-hydroxy-6-methyl-2-ureido	207	5722

4-Butylidenedihydrazino-2,6-dihydroxy	232	5968
4-s-Butylidenedihydrazino-2,6-dimethyl	crude: 190–193	5265
4-Butylidenedihydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	179	4929
4-s-Butylidenedihydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	130–132 or 132–134	4928, 4929, 5265
4-Butylidenedihydrazino-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-phenyl	107–108	4929
4(<i>N</i> -s-Butylidene- <i>N</i> -methylhydrazino)-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	78–79	4929
4-Butyl-2-mercapto	HCl: 230	4777
4-t-Butyl-2-mercapto	170–171	5484
5-Butyl-2-mercapto	210	E, 4463
4-t-Butyl-2-methoxy-carbonylmethyl	anal; sp	5688
4-t-Butyl-2-methoxy-6-trifluoromethyl	53/0.05	4546
4-t-Butyl-2-methyl	pic: 148–152	5693
5-Butyl-2-methyl	107–110/2.5	4463
4-t-Butyl-2-methylamino	48–51/0.2; pic: 194	2602, 5484
4- <i>N</i> -Butyl- <i>N</i> -methylamino	m/s; nmr	6172
4- <i>N</i> -Butyl- <i>N</i> -methylamino-2-chloro	m/s; nmr	6172
4-t-Butyl-2-methylamino-5-phenyl	120–124	5484
4-t-Butyl-2-methyl-5-phenyl	89–90/0.1	5484
2-t-Butyl-4-methylsulfonyloxy	u.v.	4360
4-t-Butyl-2-methylthio	70–80/0.5	5484
4-t-Butyl-2-methylthio-6-trifluoromethyl	60/1; nD ₂₀ 1.4760	4546
2-t-Butyl-5-nitro	55–56	6123
4-t-Butylperoxy-2-chloro-6-methyl	anal; nmr	4466
4-t-Butylperoxy-6-methyl	anal; nmr	4466
4-t-Butyl-5-phenyl	115–120/0.5	5484
4-t-Butyl-5-phenyl-2-ureido	244–245	5484
4-t-Butyl-5-pivaloylmethyl	oil; anal; oxime: 184	6628
4-t-Butyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dithio	199	4432
1-Butyl-1,2,3,6-tetrahydro-2,6-dioxo-3-trimethylsilyl	99–101/0.1	5488
1-Butyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	99	4925
1-Butyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	186	4925
1-Butyl-1,2,3,4-tetrahydro-3-methyl-6-methylamino-2,4-dioxo	81–86	4657
1-Butyl-1,2,3,4-tetrahydro-3-methyl-6-methylamino-5-nitroso-2,4-dioxo	64	4657

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1-s-Butyl-1,2,3,6-tetrahydro-3-methyl-4-methylthio-2,6-dioxo	58	4806
5-Butylthio-2,4-bis(trimethylsiloxy)	109–111/0.2	5728
4-(Butylthio)carbonyl-2,6-dihydroxy	187–188	5464
2-Butylthio-4-chloro-6-hydroxy-5-phenyl	187–189	4894
2-Butylthio-4-chloro-5-methoxy	150/4	4395
2-Butylthio-4,5-dichloro-6-hydroxy	149–151	4894
5-Butylthio-2,4-dihydroxy	260–262	5728
5-Butylthio-2,4-dihydroxy-6-methyl	199–200	5168
5-Butylthio-2-dimethylamino-4-hydroxy-6-methyl	110	5390
2-Butylthio-4-hydroxy	92–95	5121
2-t-Butylthio-4-hydroxy	143–145	5418
2-Butylthio-5-hydroxy	114	4395
2-Butylthio-4-hydroxy-5-methoxy	121–122	4395
2-Butylthio-4-hydroxy-6-methyl	79–81	E, 5121
2-Butylthio-4-hydroxy-6-phenyl	169–170	5121
2-Butylthio-4-hydroxy-6-propyl	85	5121
2-Butylthio-5-methoxy	130/4	4395
5-Butylthiomethyl-4-carbamoyl-2,6-dihydroxy	232–235	6193
5-Butylthiomethyl-4-ethoxycarbonyl-2,6-dihydroxy	212–214	6193
5-Butyl-4-trimethylsiloxy-2-trimethylsilylthio	108/0.1	5963
4-N'-Butylureido-2,6-dimethyl	126	6156
2-Butylamidomethyl-4-hydroxy-6-methyl	199–201	6275
4-β-Butylrylhydrazino-2,6-dihydroxy	270–272	4721
4-Carbamoyl	194	E, 5862
5-Carbamoyl	212–214	H, E, 5794
5-Carbamoyl-4-carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	164–166	4947
2-Carbamoyl-5-chloro	207–208	4399
4-Carbamoyl-2-chloro	151–153	5621
4-Carbamoyl-6-chloro	162–163	4770
4-Carbamoyl-2-chloro-6-cyano	185–186	4820

4-Carbamoyl-5-chloro-2,6-dimercapto	190	5971
4-Carbamoyl-6-chloro-2,5-dimethyl	nmr	6140
4-Carbamoyl-2-chloro-6-methyl	181–182	E, 4820
4-Carbamoyl-3-cyclohexyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	179–180	4937
5-Carbamoyl-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	242	4920
5-Carbamoyl-1-cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	306	4920
4-Carbamoyl-2,6-dichloro-5-nitro	190	5971
4-Carbamoyl-5-diethylaminomethyl-2,6-dihydroxy	228–234	6193
5-Carbamoyl-1,2-dihydro-1,4-dimethyl-2-oxo	223	2602
5-Carbamoyl-1,4-dihydro-1,2-dimethyl-4-oxo	248–249	5099
5-Carbamoyl-1,6-dihydro-1,2-dimethyl-6-oxo	251	5099
5-Carbamoyl-1,2-dihydro-2-imino-1,4-dimethyl	HI: 247; pic: 200	2602
5-Carbamoyl-1,2-dihydro-2-imino-1-methyl	–	E, 2633
5-Carbamoyl-1,2-dihydro-2-imino-1,4,6-trimethyl	HI: 255; pic: 215	2633
5-Carbamoyl-2,4-dihydroxy	>300	H, 5421, 6277
4-Carbamoyl-2,6-dihydroxy-5-isopropoxymethyl	194–197	6193
4-Carbamoyl-2,6-dihydroxy-5-(β -methoxyethoxy)methyl	186	6193
4-Carbamoyl-2,6-dihydroxy-5-methoxymethyl	220	6193
5-Carbamoyl-2,4-dihydroxy-6-methyl	>300	6083
4-Carbamoyl-2,6-dihydroxy-5-nitro	285 or >300	5767, 5971
4-Carbamoyl-2,6-dihydroxy-5-piperidinomethyl	213–218	6193
4-Carbamoyl-2,6-dihydroxy-5-propoxymethyl	193–195	6193
4-Carbamoyl-2,6-dihydroxy-5-propylthiomethyl	283	6193
2-Carbamoyl-4,6-dimethyl	183–184	H, 5987
4-Carbamoyl-5-dimethylaminomethyl-2,6-dihydroxy	214–217	6193
5-Carbamoyl-4,6-dimethyl-2-methylamino	222; pic: 241	2633
2-Carbamoyl-4-ethoxycarbonyl-6-hydroxy-5-methyl	180–181	6140
4-Carbamoyl-5-ethoxymethyl-2,6-dihydroxy	223–228	6193
5- β -Carbamoyl-4-chloro-2-methyl	134 then 180–196	5766
5- β -Carbamoyl-4-chloro-6-methyl-2-phenyl	164–165	5766
4-Carbamoyl-3-ethyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	225	4940
5-Carbamoyl-4-hydroxy-2-methyl	275	5969
5-Carbamoyl-4-hydroxy-6-methyl	253–254	5099
4-Carbamoyl-5-hydroxymethyl-2-methylthio	177–179	3443

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Carbamoyl-4-hydroxy-2-methyl-6-methylthio	333	5969
4-Carbamoyl-6-hydroxy-2-methylthio	275–276	5151
5-Carbamoyl-4-hydroxy-6-methylthio	340	5969
5-Carbamoyl-4-hydroxy-6-methylthio-2-phenyl	336	5969
5-Carbamoyl-4-hydroxy-2-phenyl	292–295	5582
4-Carbamoyl-6-methoxy	181–182	5074
5-Carbamoyl-4-methoxy-2-methyl	175	5099
2-Carbamoylmethyl-4-carboxy-6-hydroxy	248–250	5693
1-Carbamoylmethyl-1,6-dihydro-4-methyl-2-methylthio-6-oxo	241	4569
4-Carbamoylmethyl-2,6-dihydroxy	284–285	E, 5937, 6063
2-Carbamoylmethyl-4-ethyl-6-hydroxy	196–197	5693
2-Carbamoylmethyl-4-hydroxy-6-isopropyl	164–165	5688
5-Carbamoylmethyl-4-hydroxy-2-mercaptop	269–270	E, 5973
2-Carbamoylmethyl-4-hydroxy-6-methyl	245–247	H, 5640, 5688
2-Carbamoylmethyl-4-hydroxy-6-phenyl	251–253	H, 5640, 5688
5-Carbamoyl-4-methyl-2-methylamino	238; pic: 225	2602
4-Carbamoyl-5-methyl-2-methylthio	151–152	3443
2-Carbamoyl-4-methyl-6-phenyl	165–167	5987
4-Carbamoyl-2-methyl-6-phenyl	149–152	5987
4-Carbamoyl-6-methyl-2-phenyl	144–146 or 149–150	2603, 5987
5-Carbamoylmethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	255–256	6158
1-Carbamoylmethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	254	4925
4-Carbamoyl-6-phenyl	172–173	5074
4-Carbamoyl-2-piperidino	147–148	4790
4-Carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	238–240	E, 4937, 4939
5-Carbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	216–218 or 220	4479, 4947
4-Carbamoyl-1,2,3,6-tetrahydro-3-isobutyl-1-methyl-2,6-dioxo	173–175	4940
4-Carbamoyl-1,2,3,6-tetrahydro-3-isopropyl-1-methyl-2,6-dioxo	171–172	4940
4-Carbamoyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-phenyl	274–275	4937
5-Carbamoyl-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-phenyl	> 315	4920

5-Carbamoyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	256	4920
4-Carbamoyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-propyl	165-168	4940
4-Carboxy	226-230	H, E, 5480
5-Carboxy	266-269	H, E, 5794
4-Carboxy-2,6-bismethylamino-5-aminomethyl	163	2884
5-Carboxy-2,4-bismethylthio	206-209	E, 4707
4-δ-Carboxybutyl	140-142	5970
5-δ-Carboxybutyl-2-cyanoamino-4,6-dihydroxy	209-214	6518
5-δ-Carboxybutyl-4,6-dihydroxy-2-methylamino	262-264	6518
5-δ-Carboxybutyl-4,6-dihydroxy-2-propylamino	256-258	6518
5-δ-Carboxybutyl-2-ethylamino-4,6-dihydroxy	275-278	6518
2-δ-Carboxybutyl-4-hydroxy-6-methyl	207-209	6526
4-Carboxy-2-β-carboxyvinyl-6-hydroxy-5-methyl	257-258	6140
2-Carboxy-5-chloro	206-207	4399
4-Carboxy-6-chloro	132-133	4770
4-Carboxy-5-chloro-2,6-dihydroxy	251-252	H, E, 5137
4-Carboxy-5-chloro-2-hydroxy	145-147	4890
4-Carboxy-5-chloro-2-methoxy	170-172	4399
4-Carboxy-5-chloro-2-methylsulfonyl	178-180	4399
5-Carboxy-1-cyclohexyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	192-193	4920
4-Carboxy-1-cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	195-197	4946
5-Carboxy-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,6-dioxo	208	4920
5-Carboxy-1-cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	233	4920
4-Carboxy-2,6-dichloro-5-nitro	--	2590
5-Carboxy-4-α,α-diethoxyethyl-2-mercapto	265	4438
4-Carboxy-2-diethylamino	129-130	6075
4-Carboxy-1,2-dihydro-1-methyl-2-oxo	209-210	5414
4-Carboxy-2,6-dihydroxy	245 (?); 330 to 341; 3-N-Ox: 261	H, E, 4512, 4606, 4856, 5175, 5618, 5876
5-Carboxy-2,4-dihydroxy	283-286	H, E, 5777, 6277
4-Carboxy-2,6-dihydroxy-5-isopropyl	282-283	3183
4-Carboxy-2,6-dihydroxy-5-methyl	325-327	H, E, 3183
5-Carboxy-2,4-dihydroxy-6-methyl	242	6083

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Carboxy-2,6-dihydroxy-5-piperidino	HCl: 152–153	5137
4-Carboxy-2,6-dihydroxy-5-propyl	302–303	3183
4-Carboxy-2,6-dimercapto-5-nitro	—	2590
5-Carboxy-4-dimethylamino-2-mercaptop	—	4384
5-Carboxy-2,4-diphenyl	184–186	5972
4-Carboxy-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-oxo-6-phenyl	172–174	6598
2-Carboxy-4-ethoxycarbonyl-6-hydroxy-5-methyl	223–225	6140
4-Carboxy-5-ethoxycarbonyl-2-hydroxy-6-phenyl	121–123	6598
5-Carboxy-2-ethyl	182–183	5715
1- β -Carboxyethyl-1,2-dihydro-2-imino	171–172	5492
4-Carboxy-5-ethyl-2,6-dihydroxy	311–313	E, 3183
5- β -Carboxyethyl-2,4-dihydroxy-6-methyl	302–304	5643
5- β -Carboxyethyl-4-dimethylamino-2-methyl	HCl: 190–192	5766
5- β -Carboxyethyl-4-dimethylamino-6-methyl-2-phenyl	HCl: 222–224	5766
4-Carboxy-5-ethyl-2-ethylthio-6-hydroxy	208–209	3183
5- β -Carboxyethyl-4-hydroxy-2,6-dimethyl	K: > 300	5766
4- β -Carboxyethyl-6-hydroxy-5- β -hydroxyethyl-2-mercaptop	245	4569
4- β -Carboxyethyl-6-hydroxy-5- β -hydroxyethyl-2-methylthio	174–175	4569
4- β -Carboxyethyl-6-hydroxy-2-mercaptop	272–274 or 282–284	4569, 5532
2- β -Carboxyethyl-4-hydroxy-6-methyl	193–194	6526
5- β -Carboxyethyl-4-hydroxy-2-methyl	210–211	5766
5- β -Carboxyethyl-4-hydroxy-6-methyl-2-phenyl	219–220	H, 5766
4- β -Carboxyethyl-6-hydroxy-2-methylthio	174–175	4569
4-Carboxy-5-ethyl-6-hydroxy-2-methylthio	232–233	3183
5- β -Carboxyethyl-4-hydroxy-2-phenyl	233–234	5766
4- β -Carboxyethyl-6-hydroxy-2-piperidino	275	4569
4-Carboxy-2-ethylthio-6-hydroxy-5-isopropyl	206–207	3183
4-Carboxy-5-ethynyl-2,6-dihydroxy	NH ₄ : nmr	6153
4-Carboxy-5-fluoro-2,6-dihydroxy	256–259	E, 5552
4-Carboxy-5-guanidino-2,6-dihydroxy	HCl: 162–163	5137

2-Carboxy-5-hexyl	89-91	5715
4-Carboxy-5-hydrazino-2,6-dihydroxy	NH ₂ NH ₂ : 213-214	H, 5137
4-Carboxy-2-hydroxy	225	E, 5621
4-Carboxy-6-hydroxy-2,5-dimethyl	260-261	6140
5-Carboxy-4-hydroxy-2,6-diphenyl	258	H, 3522
5-Carboxy-4-hydroxy-2-mercapto	284-287	H, 5777
5-Carboxy-4-hydroxy-2-methyl	201	5099
4-Carboxy-6-hydroxy-5-methylamino-2-methylthio	209-210	5776
4-Carboxy-6-hydroxy-5-methyl-2-methylthio	234-235	H, 3183
5-Carboxy-4-hydroxy-6-methyl-2-phenyl	238-240	4723
4-Carboxy-5-hydroxy-2-methylsulfinyl	182-184	5855
4-Carboxy-6-hydroxy-2-methylthio	253-254	H, E, 5618
4-Carboxy-6-hydroxy-2-methylthio-5-phenyl	219-220	3183
4-Carboxy-6-hydroxy-5-methyl-2-3',3',3'-trichloroprop-1'-enyl	205-206	6140
5-Carboxy-2-hydroxy-4-styryl	276-278	5983
4-Carboxy-2-mercapto	201-202	E, 5621
5-Carboxy-4-mercapto-6-methyl-2-phenyl	215-217	4723
4-Carboxy-2-methoxy	235-237	6075
4-Carboxy-6-methoxy	198	4770
4-Carboxy-5-methoxycarbonyl-2-phenyl	226-229	5604
5-Carboxy-4-methoxy-6-methylamino-2-phenyl	203-205	5544
2-Carboxymethyl	Na: 220	5688
5-Carboxy-2-methyl	197-198	E, 5715
2-Carboxymethyl-4,6-bisethylthio	Na: 165-166	5693
2-Carboxymethyl-4-chloro	Na: > 300	5693
2-Carboxymethyl-4-chloro-6-methoxy	Na: > 305	5693
2-Carboxymethyl-4-chloro-6-methyl	Na: > 310	5693
5-Carboxymethyl-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	145	4920
2-Carboxymethyl-4,6-dichloro	Na: > 320	5688
4-Carboxymethyl-2,6-dihydroxy	-	H, E, 5981
5-Carboxymethyl-2,4-dihydroxy	311-312 or 315-318	H, 5973, 5981
5-Carboxymethyl-2,4-dihydroxy-6-methyl	crystal structure	H, 5976
2-Carboxymethyl-4,6-dimethoxy	Na: 241-243	5693
2-Carboxymethyl-4,6-diphenyl	123-124	5836

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Carboxymethyl-4-ethoxy-2-methylthio	144–146	4400
2-Carboxymethyl-4-ethylsulfonyl	Na: > 295	5693
2-Carboxymethyl-4-ethylthio	Na: > 290	5693
2-Carboxymethyl-4-fluoro	Na: > 310	5693
2-Carboxymethyl-4-hydroxy	Na: > 300	5693
5-Carboxymethyl-4-hydroxy-2,6-dimethyl	240–241	E, 5965
5-Carboxymethyl-4-hydroxy-2-mercapto	275–279	H, 5973
5-Carboxymethyl-4-hydroxy-2-propyl	180	5975
2-Carboxymethyl-4-iodo	Na: > 300	5693
2-Carboxymethyl-4-isopropyl	Na: 220–222	5688
4-Carboxymethyl-2-mercapto-6-methyl	Na: > 300	4417
2-Carboxymethyl-4-methoxy	Na: > 300	5688
5-Carboxymethyl-4-methoxy-2-phenyl	118–120	5980
2-Carboxymethyl-4-methyl	Na: 257–261	5688
5-Carboxymethyl-4-methyl	189–190	5982
4-Carboxymethyl-6-methyl-2-phenyl	Na: 208–210	5980
2-Carboxymethyl-4-phenyl	Na: 255	5688
2-Carboxymethylthio-5-methyl	153–154	4384
4-Carboxy-2-methylthio-5-phenylthio	169–170	4400
4-Carboxy-2-phenyl	185–187 or 188	2603, 5073
4-Carboxy-6-phenyl	178–179	5073
5-Carboxy-2-phenyl-4-styryl	229–231	5983
2-Carboxy-5-propyl	103	5715
5-Carboxy-2-propyl	108–109	5715
2- γ -Carboxypropyl-4-hydroxy-6-methyl	191–192	6526
4-Carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	145–148 or 153	H, E, 4934, 4946, 6853
5-Carboxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	180–182	H, 4479
5-Carboxy-1,2,3,4-tetrahydro-4-imino-1-methyl-2-oxo-3-phenyl	275–280	4920
5-Carboxy-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-phenyl	199	4920

5-Carboxy-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	208	4920
4-Carboxy-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-propyl	164–168	4934, 4946
4-Carboxy-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxo	203–205	E, 6853
5- β -Carboxyvinyl	crude	5794
5- β -Carboxyvinyl-2,4-dihydroxy	(trans) 283–284	H, 5427, 5473
5- β -Carboxyvinyl-2,4-dihydroxy-6-methyl	265 or 270	4687, 5643
2- β -Carboxyvinyl-4,6-dimethyl	194–197	4836
2- β -Carboxyvinyl-4,6-diphenyl	230–232	5977
2-Chloro	65–66	H, E, 4382
5-Chloro	37	H, 4483, 6003
2- α -Chloro benzyl-4,6-dimethyl	112	5241
5-Chloro-4,6-bisdimethylamino	61	5393
2-Chloro-4,6-bis(trichloromethyl)	101–102	H, 5072
4-Chloro-2,6-bis(trimethylsiloxy)	crude	5979
2-Chloro-4- <i>t</i> -butoxy-5-fluoro	–	5978
4-Chlorocarbonyl	crude: 105	E, 5794
4-Chlorocarbonyl-5-ethoxycarbonyl-2-hydroxy-6-phenyl	198–200	6598
4-Chlorocarbonyl-2-methylthio-5-phenylthio	72–74	4400
5-Chlorocarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	155	4479
4-Chlorocarbonyl-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxo	54–56	6853
4-Chloro-5- β -chloroethyl	92–94/2; HCl: 140	5881
4-Chloro-5- β -chloroethyl-2- γ -chloropropyl-6-hydroxy	122–123	5028
4-Chloro-5- β -chloroethyl-2-methyl	93–94/2.5; HCl: 125	5741
2-Chloro-5- β -chloroethyl-4-methylamino	132–133	5881
4-Chloro-2-chloromethyl-6-hydroxy	173	5253
4-Chloro-2-chloromethyl-6-hydroxy-5-methyl	209–212	5731
4-Chloro-2-chloromethyl-6-hydroxy-5-phenyl	176–182	5731
4-Chloro-2- γ -chloropropyl-6-hydroxy-5-methyl	180–230	5731
4-Chloro-5- β -chloropropyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-phenyl	112–115	4452
4-Chloro-3-crotyl-1-ethyl-1,2,3,6-tetrahydro-5-methyl-2,6-dioxo	146/0.4	4527
2-Chloro-4-cyano	50–51	E, 5621
4-Chloro-5-cyano	45–47	3764
5-Chloro-2-cyano	78 or 85–86	4399, 5284

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Chloro-4-cyano-2,6-bisdimethylamino	80-82	5971
4-Chloro-5-cyano-2,6-difluoro	108-110/40	5770
4-Chloro-5-cyano-2-dimethylamino	147-149	E, 5581
4-Chloro-5-cyano-6-dimethylamino	107-108	5768
4-Chloro-5-cyano-2-dimethylamino-6-methoxy	-CN→O: 154-155	2815
2-Chloro-4-cyano-6-β-dimethylaminovinyl	161-163	6402
4-Chloro-2-cyano-6-ethoxycarbonyl-5-methyl	crude: nmr	6140
2-Chloro-4-cyano-6-methyl	45-47	2592, 4820
4-Chloro-2-cyanomethyl-6-isopropyl	oil; anal	5688
4-Chloro-2-cyanomethyl-6-methyl	78-79	5688
4-Chloro-2-cyanomethyl-6-phenyl	134-135	5688
4-Chloro-5-cyano-2-methylthio	61-63	E, 5581
2-Chloro-4-cyano-6-phenyl	126	2592
4-Chloro-5-cyano-2-phenyl	190 or 193-195	5581, 5582
4-Chloro-5-cyano-6-phenyl	137-138	5816
4-Chloro-5-cyano-6-piperidino	54-55	5768
4-Chloro-5-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	171-172	4947
4-Chloro-6-cyclohexylamino	120-121	5357
2-Chloro-4-cyclohexylamino-5-fluoro	78	5837
4-Chloro-6-cyclohexylamino-5-nitro	60	4396
5-Chloro-1-cyclohexyl-1,6-dihydro-4-methylthio-6-oxo	150-152	4806
4-Chloro-1-cyclohexyl-1,6-dihydro-6-oxo-5-propyl	102-103	5351
5-Chloro-2-cyclohexyl-4-hydroxy	198	5755
4-Chloro-6-cyclohexylimino-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo	108	4969
4-Chloro-6-cyclopentylamino-5-nitro	77-78	4396
4-Chloro-6-cyclopropyl	-	E, 5812
4-Chloro-6-cyclopropyl-2,5-dimethyl	oil	5999
5-Chloro-4-cyclopropyl-6-hydroxy	218-220	5999
4-Chloro-6-cyclopropyl-5-methoxy	-	5999
4-Chloro-6-cyclopropyl-2-methoxy-5-methyl	61-62	5999

4-Chloro-6-cyclopropyl-5-methoxy-2-methylthio	—	6000
4-Chloro-6-cyclopropyl-5-methyl	80–82	5999
4-Chloro-6-cyclopropyl-5-methyl-2-methylsulfonyl	110–113	5774
4-Chloro-2-cyclopropyl-5-methyl-6-methylthio	49–51	5999
4-Chloro-6-cyclopropyl-5-methyl-2-methylthio	—	5774
4-Chloro-6-cyclopropyl-2-methylsulfonyl	102–104	5774
4-Chloro-6-cyclopropyl-2-methylthio	—	5774
4-Chloro-2- α , α -dichloro benzyl-6-trichloromethyl	110–115/4	5072
4-Chloro-2- β , β -dichloro- α , α -difluoroethyl-6-methyl	33–35	5995
4-Chloro-6-dichloromethyl-2-phenyl	80	6734
2-Chloro-4,6-dicyano	93–95 or 116	4820, 5284
4-Chloro-1,3-dichlohexyl-5-formyl-1,2,3,6-tetrahydro-2,6-dioxo	180–181	4920
4-Chloro-1,3-dicyclohexyl-1,2,3,6-tetrahydro-2,6-dioxo	95–96	4657
4-Chloro-2,6-diethoxy-5-ethyl	159/26	5797
2-Chloro-4,6-diethyl	66/0.3	5691
2-Chloro-4-diethylamino	m/s; nmr	6172
4-Chloro-6-diethylamino	105–109/2	4356
2-Chloro-4-diethylamino-5-ethoxycarbonyl-6-methyl	130–132/0.1	4470
2-Chloro-4-diethylamino-5-fluoro	102–103/3	5997
2-Chloro-4-diethylamino-6-methyl	anal; nmr	H, 4466
5-Chloro-4-diethylaminomethyleneamino-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxo	crude	5036
4-Chloro-1,3-diethyl-1,2,3,6-tetrahydro-2,4-dioxo	>67–68	E, 6110
4-Chloro-1,3-diethyl-1,2,3,6-tetrahydro-6-imino-2-oxo	105–106	4971
5-Chloro-2,4-difluoro	72–73/90	4752
5-Chloro-2,4-difluoro-6-methoxy	crude	5770
5-Chloro-4,6-difluoro-2-methoxy	crude	5770
4-Chloro-1,6-dihydro-1,5-dimethyl-6-oxo-2-phenyl	143–144	5351
4-Chloro-2,3-dihydro-5- β -hydroxyethyl-6-methylamino-2-oxo-3-phenyl	207–209	4452
4-Chloro-1,2-dihydro-2-imino-1,6-dimethyl	HI: 257	5662
4-Chloro-1,6-dihydro-6-imino-1-methoxycarbonylmethyl	HBr: —	5996
5-Chloro-1,2-dihydro-2-imino-1-methyl	HCl: 277	E, 2633
5-Chloro-1,2-dihydro-1-isopropyl-6- <i>N'</i> -isopropylureido-2-oxo-4-trifluoromethyl	139–141	5589

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Chloro-1,2-dihydro-4-methoxycarbonyl-1-methyl-2-oxo	135	4890
5-Chloro-1,2-dihydro-1-methyl-2-oxo	3-MeCl: 244	5266
5-Chloro-1,6-dihydro-4-methyl-6-oxo-1-phenyl	165-166	6076
5-Chloro-1,6-dihydro-4-methylthio-6-oxo-1-phenyl	167	4806
5-Chloro-1,6-dihydro-4-methylthio-6-oxo-1-propyl	126-127	4806
5-Chloro-1,2-dihydro-2-oxo-1-prop-2'-ynyl	130	6028
4-Chloro-2,6-dihydroxy	295 or 300-302	H, E, 4511, 4527, 4855, 5734, 5979
5-Chloro-2,4-dihydroxy	300 or 321	H, E, 4736, 5137, 6277
4-Chloro-2,6-dihydroxy-5-iodo	266-267	4650
2-Chloro-4,5-dihydroxy-6-methyl	> 300	4466
4-Chloro-2,6-dihydroxy-5-methyl	266-267	E, 4527, 5915
5-Chloro-2,4-dihydroxy-6-methyl	325	H, E, 4885
4-Chloro-2,6-dihydroxy-5-nitro	218 or 244-246	E, 4511, 5387
4-Chloro-2,6-dimethoxy	74	H, E, 4511
4-Chloro-6-dimethoxymethyl-2-ethylthio-5-fluoro	102-103/0.2	5525
4-Chloro-2,6-dimethoxy-5-nitro	67-69	5994
2-Chloro-4,6-dimethyl	sp	H, E, 2700
4-Chloro-2,5-dimethyl	nmr	H, 6003
4-Chloro-2,6-dimethyl	82/15; N-1-Ox: 102	H, E, 2603, 5071, 5135, 6003, 6082
4-Chloro-5,6-dimethyl	51-52	H, E, 4387, 6003
5-Chloro-2,4-dimethyl	nmr; M ⁺	6003
5-Chloro-4,6-dimethyl	nmr; M ⁺	6003
2-Chloro-4-dimethylamino	81	H, 4581
4-Chloro-2-dimethylamino	38	H, 4670
4-Chloro-2-dimethylamino-5,6-dimethyl	40-41	5284
4-Chloro-6-dimethylamino-2-formamido-5-formyl	190-193	6503
4-Chloro-6-dimethylamino-5-formyl	139-141	E, 5730

4-Chloro-5-dimethylamino-6-formylamino-3,6-dihydro-3-methyl	125	5335
4-Chloro-2-dimethylamino-5-formyl-6-methoxy	128; oxime: 225	2815
5-Chloro-4-dimethylamino-6-hydroxy	215	5393
5-Chloro-2-dimethylamino-4-hydroxy-6-methyl	246	5390
4-Chloro-2-dimethylamino-6-methoxy	56	2815
2-Chloro-4-dimethylamino-5-methyl	68–70	E, 5797
4-Chloro-2-dimethylamino-6-methylamino	71	H, E, 4656
2-Chloro-5-dimethylaminomethyleneamino	102–103	4382
4-Chloro-6-dimethylaminomethyleneamino	93–94	5852
5-Chloro-4-dimethylaminomethyleneamino-1,3-diethyl- 1,2,3,6-tetrahydro-2,6-dioxo	149	5036
4-Chloro-2-dimethylamino-5-methyl-6-phenyl	88–90	5725
2-Chloro-4-dimethylamino-6-phenyl	122	6575
4-Chloro-2-dimethylamino-5-phenyl	c. 135/0.4	6578
4-Chloro-2,6-dimethyl-5-nitro	35	E, 5634, 5670
2-Chloro-4,6-dimethyl-5-prop-1'-ynyl	56–58	2700
2-Chloro-4,6-dimethyl-5-prop-2'-ynyl	127	2700
2-Chloro-4,5-diphenyl	114	2700
2-Chloro-4,6-diphenyl	135–139	6080
4-Chloro-2,5-diphenyl	112–113	E, 5673, 5836
4-Chloro-2,6-diphenyl	123	4674
4-Chloro-5,6-diphenyl	104–105 or 109	H, 5352, 5577, 6377
2-Chloro-4,5-diphenyl-6-styryl	122; N-1-Ox: 112	4685
4-Chloro-2,6-dipiperidino	147–150	5984
4-Chloro-6-ethoxy	117–118	H, E, 5998
4-Chloro-5-ethoxycarbonyl	anal	4672
4-Chloro-6-ethoxycarbonyl-2,5-dimethyl	—	E, 5252
4-Chloro-6-ethoxycarbonyl-2- β -ethoxycarbonylethyl-5-methyl	oil; nmr	6140
4-Chloro-6-ethoxycarbonyl-2- β -ethoxycarbonylvinyl-5-methyl	oil; nmr	6140
2-Chloro-5-ethoxycarbonyl-4-ethylamino-6-methyl	66–67	4470
4-Chloro-5- β -ethoxycarbonylethyl-2,6-dimethyl	142/0.7	5766
4-Chloro-5- β -ethoxycarbonylethyl-2-methyl	29–31	H, 5766
4-Chloro-5- β -ethoxycarbonylethyl-6-methyl-2-phenyl	69–70	5766

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Chloro-5- β -ethoxycarbonyl-2-phenyl	56–57	5766
4-Chloro-6-ethoxycarbonyl-2-formyl-5-methyl	63	6024
4-Chloro-5-ethoxycarbonyl-2-methyl	88–91/0.4	H, E, 4976, 5252
5-Chloro-4-ethoxycarbonyl-2-methyl	88/1; n_D^{20} 1.5062	5855
4-Chloro-2-ethoxycarbonylmethyl-6-methyl	59–60	5688
2-Chloro-5-ethoxycarbonyl-4-methyl-6-methylamino	78–80	4470
4-Chloro-6-ethoxycarbonylmethyl-2-phenyl	41	5980
2-Chloro-5-ethoxycarbonyl-4-methyl-6-propylamino	126–127/0.1	4470
4-Chloro-5-ethoxycarbonyl-2-methylthio	—	H, E, 2599, 4976
5-Chloro-4-ethoxycarbonyl-2-methylthio	120/0.5; n_D^{25} 1.5630	5855
4-Chloro-5-ethoxycarbonyl-2-phenyl	126 or 130–131	4976, 5649
4-Chloro-5-ethoxycarbonyl-2-piperidino	48–49	4976
4-Chloro-5- β -ethoxycarbonylmethyl-2,6-dimethyl	122–125/2	6351
4-Chloro-5- β -ethoxyethyl-2- γ -ethoxypropyl-6-hydroxy	93–94	5028
4-Chloro-2- β -ethoxyethyl-6-methyl	129–135/22	5096
2-Chloro-4-ethoxy-5-fluoro	82/3	E, 5956
4-Chloro-2-ethoxy-5-fluoro	—	5833
4-Chloro-5-ethoxy-2-methyl	46–47	5958
4-Chloro-2-ethoxy-6-phenyl	58–59	5038
4-Chloro-5-ethoxy-2-phenyl	93–95	4674
4-Chloro-6-ethoxy-2-phenyl	62–64	5993
4-Chloro-6-ethylamino	124–126	3475
4-Chloro-6-ethylamino-5-formyl	76–77	5730
4-Chloro-2-ethylamino-6-methyl	nmr	E, 4466
2-Chloro-4-ethylamino-6-methyl-5-nitro	66 or 71–72	5438, 5677
4-Chloro-6-ethylamino-5-methyl-6-phenyl	—	5725
4-Chloro-6-ethylamino-5-nitro	114	5442
5-Chloro-1-ethyl-1,6-dihydro-4-methylthio-6-oxo	126–128	4806
4-Chloro-5-ethyl-2,6-dihydroxy	213–215	5797
4-Chloro-1-ethyl-3-hexyl-1,2,3,6-tetrahydro-2,6-dioxo	172/0.2	4527

4-Chloro-2-ethyl-6-hydroxy	162	E, 5253
5-β-Chloroethyl-4-hydroxy-2-mercapto-6-methyl	205–206	2638
4-Chloro-2-ethyl-6-hydroxy-5-methyl	203–204	5027, 5028, 5731
4-Chloro-5-ethyl-6-hydroxy-2-methyl	198–205	H, 5731
5-Chloro-2-ethyl-4-hydroxy-6-methyl	168	5071
4-Chloro-5-ethyl-6-hydroxy-2-phenyl	219–220	5025
4-Chloro-5-ethyl-6-hydroxy-2-propyl	156–157	5028
4-Chloro-2-ethyl-6-methyl	1-N-Ox: 76	E, 5071
5-β-Chloroethyl-4-methyl	32; 112/8	5834
2-Chloro-4-N-ethyl-N-methylamino	m/s; nmr	6172
5-β-Chloroethyl-4-methylamino	115–116	5881
2-Chloro-4-ethyl-6-methylamino-5-nitro	75–76	5677
5-β-Chloroethyl-2-methyl-4-methylamino	97–98	5741
4-α-Chloroethyl-2-methyl-6-phenyl	145–147/3	6299
4-α-Chloroethyl-6-methyl-2-phenyl	140–145/3	6299
2-Chloro-4-ethyl-6-phenyl	liq; nmr	6575
1-β-Chloroethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	88–89	5495
1-β-Chloroethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	93–94	5509
4-Chloro-3-ethyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	80–85	4657
4-Chloro-1-ethyl-1,2,3,6-tetrahydro-5-methyl-2,6-dioxo-3-propyl	138/0.3	4527
4-Chloro-2-ethylthio	131/18; n _D ²⁰ 1.5808	H, 6132
2-Chloro-4-ethylthio-5-fluoro	90/0.5 (solid)	4895
4-Chloro-2-ethylthio-6-hydroxy-5-phenyl	160–162	4894
4-Chloro-2-ethylthio-5-methoxy	71	4395
4-Chloro-6-ethylthio-2-methoxycarbonylmethyl	142–144/2	5693
4-Chloro-2-ethylthio-6-methyl	87/3	H, E, 4885
4-Chloro-2-ethyl-6-trichloromethyl	133/9	5072
4-Chloro-5-ethynyl-2,6-dihydroxy	> 300	6017
2-Chloro-5-fluoro-4-hydroxy	176 and 243	E, 5626
4-Chloro-5-fluoro-2-hydroxy	173–176	4895
2-Chloro-5-fluoro-4-hydroxyamino	165	3464
2-Chloro-5-fluoro-4-isopropylamino	60–61	5837
2-Chloro-5-fluoro-4-methoxy	67/5	5956
4-Chloro-2-fluoromethyl-6-hydroxy	192–193	5253

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Chloro-2-fluoromethyl-6-methyl	114/22	5785
4-Chloro-6-fluoromethyl-2-methylthio	67-70	5785
2-Chloro-5-fluoro-4-phenoxy	71-72	5956
2-Chloro-5-fluoro-4-piperidino	52-55	5956
2-Chloro-5-fluoro-4-propoxy	85-86/5	5956
2-Chloro-5-formamido	120-122	4380
4-Chloro-6-formamido	143-145	5852
4-Chloro-5-formamido-6-methyl	90	5634
4-Chloro-5-formamido-6-methylthio	163-164	4358
2-Chloro-4- β -formylhydrazino-6-methyl-5-nitro	crude	5668
2-Chloro-4- β -formylhydrazino-5-nitro	130-131	5666
4-Chloro-5-formyl-6-piperidino	78-79	5730
4-Chloro-5-formyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	150; oxime: 135	4923, 4947
4-Chloro-5-formyl-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl	232-234	4923
4-Chloro-2-guanidino-6-methylamino	HCl: 264	6384
4-Chloro-6-hexylamino-5-nitro	25-27	4396
4-Chloro-3-hexyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	48	4527
4-Chloro-2-hexylthio-5-methoxy	140/0.2	4395
2-Chloro-4-hydrazino-6-methyl	> 320	5697
5-Chloro-4-hydrazino-2-phenyl	199	5755
4-Chloro-6-hydroxyamino	165	6423
2-Chloro-5-hydroxy-4,6-dimethyl	H ₃ PO ₄ : 169	6373, 6423
4-Chloro-6-hydroxy-2,5-dimethyl	225-229	H, 5731
5-Chloro-2-hydroxy-4,6-dimethyl	241-245	6033
5-Chloro-4-hydroxy-2,6-dimethyl	191-193 or 199	H, 5071, 6033
5-Chloro-2-hydroxy-4,6-diphenyl	235-236	4756
4-Chloro-6-hydroxy-2-iodomethyl	205-207	5253
4-Chloro-6-hydroxy-2-iso butyl-5-isopropyl	113-115	5028
5-Chloro-4-hydroxy-2-isopropyl-6-methyl	160	5071
5-Chloro-4-hydroxy-2-mercapto-6-methyl	262-263	H, 5137

5-Chloro-2-hydroxy-4-methoxycarbonyl	160–161	4890
2-Chloro-5-hydroxy-4-methoxy-6-methyl	149–150	5729
4-Chloro-6-hydroxy-2-methoxymethyl-5-phenyl	185–186	E, 5751
2-Chloro-4-hydroxy-6-methyl	123–125	H, 4466
4-Chloro-6-hydroxy-2-methyl	235–236; HCl: > 240	H, E, 3505, 5015, 5027, 5028, 5029
4-Chloro-6-hydroxy-5-methyl	198–199	E, 3520
5-Chloro-4-hydroxy-2-methyl	228	E, 5755
2-Chloro-4-hydroxy-6-methylamino-5-methylformamido	271–272	6096
2-Chloro-4-hydroxy-6-methyl-5-nitro	HCl: > 200	5438
4-Chloro-6-hydroxy-5-methyl-2-phenyl	272–274	5025
5-Chloro-4-hydroxy-6-methyl-2-phenyl	235	5071
2-Chloro-4-hydroxy-6-phenyl	185	6575
4-Chloro-6-hydroxy-2-phenyl	226–231	H, 5002, 5025, 5491
5-Chloro-4-hydroxy-2-phenyl	247–249	5755
5-Chloro-4-hydroxy-6-phenyl	237	5071
4-Chloro-6-hydroxy-2-phenyl-5-propyl	195–197	5025
4-Chloro-6-hydroxy-2-propyl	171	H, 5253
2-Chloro-5-iodo	129–130	5644
4-Chloro-5-iodo	61–62	5262
4-Chloro-5-iodo-2,6-dimethyl	92–94	6351
4-Chloro-5-iodo-2-isopropyl-6-methyl	118/3	5094
5-Chloro-4-iodo-2-isopropyl-6-methyl	83–85	5655
4-Chloro-5-iodo-6-methyl	117–118	6351
2-Chloroiodomethyl-4,6-dimethyl	73–75	5449
4-Chloro-5-iodo-6-methyl-2-phenyl	101–102	6351
5-Chloro-4-isobutylamino-2-phenyl	44; 140/0.2	5755
4-Chloro-2-isobutylthio-5-methoxy	120/0.6	4395
4-Chloro-2-isopropyl	39–41/1	5694
4-Chloro-6-isopropylamino-5-nitro	73–75	5442
4-Chloro-2-isopropyl-6-methoxy	59–61/0.6	5690
4-Chloro-6-isopropyl-2-methoxycarbonylmethyl	110–112/1	5688
4-Chloro-6-isopropyl-2-methoxyformimidoylmethyl	HCl: 106–108	5685
4-Chloro-2-isopropyl-6-methyl	1-N-Ox: 95	E, 5071

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Chloro-2-isopropyl-6-phenyl	164-166/9	5690
4-Chloro-2-iso propyl-6-piperidino	61-63	5694
4-Chloro-2-iso propyl-6-trichloromethyl	140-142/20	5072
5-Chloro-2-mercaptop	221-222	H, 4384, 4399, 4488
2-Chloro-5-methoxy	—	H, 6032
5-Chloro-2-methoxy	51-52	H, 4399
4-Chloro-2-methoxycarbonylmethyl	86-88/0.4	5693
4-Chloro-2-methoxycarbonylmethyl-6-methyl	crude: 102/1.5	5693
4-Chloro-2-methoxycarbonylmethyl-6-phenyl	anal	5688
4-Chloro-5-methoxycarbonyl-2-methylthio	76-78	4399
4-Chloro-2-methoxyformimidoylmethyl-6-methyl	HCl: 105-106	5688
4-Chloro-2-methoxyformimidoylmethyl-6-phenyl	HCl: 110-112	5688
4-Chloro-6-methoxy-2-methoxycarbonylmethyl	116-118/1.5	5688
4-Chloro-5-methoxy-6-methoxymethyl	115/11	E, 4397
4-Chloro-5-methoxy-6-methoxymethyl-2-methylthio	44-45	4397
4-Chloro-5-methoxy-6-methyl	55-56/7	E, 5786
4-Chloro-5-methoxy-6-methyl-2-methylthio	58-59	4397
2-Chloro-4-methoxy-6-methyl-5-nitro	62-63	E, 5786
4-Chloro-5-methoxy-2-methylsulfonyl	148	5662
2-Chloro-4-methoxy-6-phenyl	105	6575
4-Chloro-5-methoxy-2-phenyl	156-157	4674
4-Chloro-5-methoxy-2-propylthio	119/0.4	4395
2-Chloromethyl	101-103/26	5682, 6608
2-Chloro-4-methyl	—	H, E, 5278
2-Chloro-5-methyl	91-92	H, 2630, 5673, 5691
4-Chloromethyl	50-51/6	5682, 6608
4-Chloro-2-methyl	54 to 60	H, E, 3754, 5667, 5829, 6003
4-Chloro-6-methyl	35-36	H, E, 3754, 4603, 6003

5-Chloro-2-methyl	54–55	H, 5682, 6003
5-Chloro-4-methyl	49–50	5682, 6003
4-Chloro-2-methylamino	123	E, 4670
5-Chloro-2-methylamino	122; pic: 175	H, 2633
4-Chloro-5-methylamino-6-methylthio	48–50	4816
2-Chloro-4-methylamino-5-nitro	90–91	H, E, 3783
4-Chloro-2-methylamino-5-nitro	172–173	E, 3783
4-Chloro-6-methylamino-5-nitro	150–151	H, 4396
2-Chloromethyl-3,6-diethoxy	81–85/0.1	4949
4-Chloromethyl-2,6-dihydroxy	240 or 249–251	H, 4512, 5403, 5868
5-Chloromethyl-2,4-dihydroxy	350 to 355	H, E, 2071, 4511, 5641
5-Chloromethyl-2,4-dihydroxy-6-methyl	338	H, E, 4387
2-Chloromethyl-4,6-dimethyl	65–66; <i>N</i> -Ox: 118	E, 6008, 6160
2-Chloro-5-methyl-4,6-diphenyl	136–138	4756
5-Chloromethyl-4-ethoxycarbonyl-2,6-dihydroxy	210–211	6193
2-Chloromethyl-4-hydroxy-6-methyl	164–165	5079
4-Chloromethyl-2-isopropyl-6-methoxy	101–102/23	6608
4-Chloromethyl-2-isopropyl-6-methyl	118–120/20	6008
2-Chloromethyl-4-methoxy	69–70/2	6608
4-Chloromethyl-4-methoxy	60–61/2	E, 6608
2-Chloro-4-methyl-6-methylamino-5-nitro	–	E, 5685
4-Chloro-2-methyl-6-methylamino-5-nitro	138–139	2675
4-Chloro-5-methyl-2-methylamino-6-phenyl	144–145	5725
4-Chloromethyl-6-methyl-2-phenyl	127/3	6608
2-Chloro-4-methyl-5-nitro-6-phenoxy	–	6035
2-Chloro-4-methyl-5-nitro-6-piperidino	96–97	5651
2-Chloro-4-methyl-6-phenoxy	–	E, 6035
2-Chloromethyl-4-phenyl	144–146/2	6608
2-Chloro-4-methyl-6-phenyl	50–51 or 53; 3- <i>N</i> -Ox: 177	H, 6345, 6377, 6575
2-Chloro-5-methyl-4-phenyl	89–90; 1- <i>N</i> -Ox: 155; 3- <i>N</i> -Ox: 134	5931, 6345
4-Chloromethyl-6-phenyl	130/2	6608
4-Chloro-2-methyl-6-phenyl	58–59	E, 6039, 6377

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Chloro-5-methyl-2-phenyl	90-91 or 92-93	4478, 5792
4-Chloro-6-methyl-2-phenyl	70 or 73-74	H, 5577, 6377
5-Chloro-2-methylsulfonyl	123-125	4399
5-Chloromethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	147-149	5895, 6239
4-Chloro-2-methylthio	112/12	H, 6132
5-Chloro-2-methylthio	55-57	4399
4-Chloro-5-methylthio-2-phenyl	110-111	4674
4-Chloro-2-methylthio-6-trifluoromethyl	105/25	5785
4-Chloro-2-methyl-6-trichloromethyl	127-129/19	5072
4-Chloro-2-methyl-6-trifluoromethyl	144/at	E, 5785
4-Chloro-6-methyl-2-vinyl	67/5	5096
2-Chloro-5-nitro	108 or 109	H, E, 3463, 6372, 6423
4-Chloro-5-nitro-6-piperidino	68	5442
2-Chloro-4-phenoxy	—	6035
2-Chloro-4-phenyl	87-88; 3- <i>N</i> -Ox: 128	H, 6042, 6345
2-Chloro-5-phenyl	122-124 or 124-128	5262, 5635, 6080
4-Chloro-2-phenyl	73-74	H, 6038
4-Chloro-6-phenyl	103	E, 5816, 5927
5-Chloro-2-phenyl	96	H, 4488
5-Chloro-2-phenyl-4-piperidino	88	5755
4-Chloro-2-phenyl-6-trichloromethyl	122 or 124	5072, 6734
2-Chloro-4-piperidino	79-80	4663
4-Chloro-2-piperidino	52-53	5866
5-Chloro-2-piperidino	48-49	4790
4-Chloro-2-propyl-6-trichloromethyl	140-142/14	5072
5-Chloro-2-prop-2'-ynyloxy	66	6028
5-Chloro-2-prop-2'-ynylsulfonyl	92	6535
5-Chloro-2-prop-2'-ynylsulfonyl	70	6535
5-Chloro-2-prop-2'-ynylthio	66	6535

4-Chloro-1,2,3,6-tetrahydro-1,3-diisopropyl-2,6-dioxo	75–78	4657
4-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	110–112	H, E, 4739
5-Chloro-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	158	4925
5-Chloro-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	232	4925
5-Chloro-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxo	190–192	E, 6037
4-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-5-methylhydrazonomethyl-2,6-dioxo	crude: 170–180	4924
4-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	69 or 85–87	E, 4511, 5435
4-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-phenylimino	103	4969
4-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6-propylimino	63	4969
4-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-6-oxo-2-thio	122–123 or 189–190	4661, 6014
4-Chloro-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl	138	E, 4657
4-Chloro-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxo	150	4969
4-Chloro-1,2,3,6-tetrahydro-5-iodo-1,3-dimethyl-2,6-dioxo	170–171	4650
4-Chloro-1,2,3,6-tetrahydro-5-isocyanato-1,3-dimethyl-2,6-dioxo	145–146	5396
4-Chloro-1,2,3,6-tetrahydro-6-isopropylimino-1,3-dimethyl-2-oxo	52	4969
4-Chloro-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-phenyl	273–275	4931
4-Chloro-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-propyl	44–47	4657
5-Chloro-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo	151	H, 4925
4-Chloro-6-trichloromethyl	125–126/19	5072
5-Chloro-2,4,6-triethoxy	57	E, 5971
5-Chloro-2,4,6-trifluoro	115/at	E, 3521, 5770
5-Chloro-2,4,6-trihydroxy	–	H, E, 5961
2-Chloro-4,5,6-trimethyl	91	5247
4-Chloro-2,5,6-trimethyl	nmr	H, 6003
5-Chloro-2,4,6-trimethyl	84/17	5247, 6003
4-Chloro-2,5,6-triphenyl	140–142	4602
5- α -Chlorovinyl-2,4-dihydroxy	275–278	5329
2-Cyano	–	H, E, 4383
4-Cyano	31–32	E, 6343
5-Cyano	86–88	E, 5794
2-Cyanoamino-4,6-dimethyl	224–225	H, 6513
2-Cyanoamino-4-hydroxy	295–300	5417
2-Cyanoamino-4-hydroxy-6-phenyl	crude	H, 6507

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Cyanoamino-4-hydroxy-6-trifluoromethyl	Na: crude	6507
2-Cyanoamino-4-methyl	200	6050
2-Cyanoamino-4-propyl	200	6050
5-Cyano-2,4-bismethylthio-6-phenyl	149-151	4557
5-Cyano-4-cyclohexylamino-6-phenyl	164	6129
5-Cyano-1-cyclohexyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	217	4941
5-Cyano-1-cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	180	4941
4-Cyano-3-cyclohexyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	209-211	4937
5-Cyano-1-cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	204	H, 4941
4-Cyano-2-diethylamino	159-169/13	6075
5-Cyano-2,4-dihydrazino-6-phenyl	180	5953
2-Cyano-1,6-dihydro-1,4-dimethyl-6-oxo	70-72	5090
5-Cyano-1,4-dihydro-1,2-dimethyl-4-oxo	201-202	5099
5-Cyano-1,6-dihydro-1,2-dimethyl-6-oxo	83	5099
5-Cyano-1,2-dihydro-2-imino-1,4-dimethyl	crude	2602
5-Cyano-1,6-dihydro-6-imino-1,2-diphenyl	198-200	5942
5-Cyano-1,6-dihydro-6-imino-1,2-diphenyl-4-trifluoromethyl	235-236	6341
5-Cyano-1,2-dihydro-2-imino-1-methyl	—	E, 2633
5-Cyano-1,6-dihydro-6-imino-1-methyl-2-phenyl-6-trifluoromethyl	219	6341
5-Cyano-1,2-dihydro-2-imino-1,4,6-trimethyl	HI: 239; pic: 183	2633
5-Cyano-1,6-dihydro-6-imino-1,2,4-triphenyl	210-212	4372, 4373
5-Cyano-1,6-dihydro-4-mercapto-6-oxo-1,2-diphenyl	220	4533
5-Cyano-1,2-dihydro-1-methyl-2-methylamino	—	E, 2633
5-Cyano-1,2-dihydro-1-methyl-2-oxo	233-234	E, 5720
5-Cyano-1,2-dihydro-1,4,6-trimethyl-2-methylimino	HI: 203; pic: 162	2633
4-Cyano-2,6-dihydroxy	> 260	6189
5-Cyano-2,4-dihydroxy	280 to 296	H, E, 4530, 4902, 5421, 5777, 6007
5-Cyano-2,4-dihydroxy-6-methyl	> 280 or 350	E, 4901, 4902, 6083
5-Cyano-2,4-dihydroxy-3- γ -methylaminopropyl	256	4902

5-Cyano-2,4-dihydroxy-6-methylthio	299	4901
5-Cyano-2,4-dihydroxy-6-phenyl	> 250 or 298	4902, 6296
2-Cyano-4,6-dimethyl	—	H, E, 5839
4-Cyano-2-dimethylamino	112–113 (or 118?)	5284 (?), 6181
4-Cyano-6-dimethylamino	88–90	5284
5-Cyano-2-dimethylamino	133–134	5955
5-Cyano-4-dimethylamino	109–111	E, 3764
5-Cyano-2-dimethylamino-4,6-dimethyl	—CN+O: 180	2815
5-Cyano-4-dimethylamino-2-mercaptop	230–231	4384
4-Cyano-6-dimethylamino-2-methyl	140–141	5090
2-Cyano-5-dimethylamino methylencamino	136–137	4383
5-Cyano-4-β-(dimethylcarbamoyl)ethyl-2,6-dihydroxy	281	4902
5-Cyano-4,6-dimethyl-2-methylamino	198; pic: 152	2633
2-Cyano-4,6-diphenyl	193	E, 5839
4-Cyano-5-ethoxycarbonyl-2-methylthio	46–47	2599, 3474
4-Cyano-6-ethoxy-2-methyl	52–53	5090
5-Cyano-4-ethoxy-2-methyl-6-phenyl	90–92	4557
1-β-Cyanoethyl-1,6-dihydro-2-methylthio-6-oxo	100–102	E, 5924
5-Cyano-4-ethyl-2,6-dihydroxy	281	E, 6083
5-Cyano-4-ethyl-6-hydroxy-2-methyl	acetamidinium salt: 200	5089
5-β-Cyanoethyl-4-hydroxy-6-methyl-2-phenyl	238–239	5766
5-Cyano-4-ethyl-6-methoxy-2-methyl	31–32	5089
1-β-Cyanoethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	137–139	6048
4-Cyano-3-ethyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo	114–115	4940
5-Cyano-4-ethylthio	61–63	3764
5-Cyano-2-ethylthio-4-hydroxy	220	H, 4960
2-Cyano-5-fluoro	44–45	4399
5-Cyano-2-fluoro-4,6-dimethoxy	crude	5770
5-Cyano-4-fluoro-2,6-dimethoxy	crude	5770
2-Cyano-5-formamido	192–193	4380
5-Cyano-4-hexylamino-6-phenyl	92	6129
5-Cyano-2-hydrazino	163–164	4399
5-Cyano-4-hydrazino	260	3764
4-Cyano-2-hydrazino-6-methyl	195	2592

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Cyano-2-hydrazino-4-phenyl-6-trichloromethyl	260	5953
5-Cyano-4-hydroxy	247	E, 5683
5-Cyano-4-hydroxy-2,6-diphenyl	343-345	E, 4485, 5134
5-Cyano-4-hydroxy-2-mercapto	280-282	H, E, 5777
5-Cyano-4-hydroxy-2-methyl	243-245	H, 4960
5-Cyano-4-hydroxy-2-methyl-6-methylthio	304	5969
5-Cyano-4-hydroxy-2-methyl-6-phenyl	240-242	6302
5-Cyano-4-hydroxy-6-methylthio	239	5969
5-Cyano-4-hydroxy-6-methylthio-2-phenyl	331	5969
5-Cyano-4-hydroxy-2-methyl-6-trichloromethyl	190-192	5913
5-Cyano-4-hydroxy-2-phenyl	>300	H, 4960
5-Cyano-4-hydroxy-6-phenyl	233-236	5816
5-Cyano-2-mercapto	175-176	4384
5-Cyano-4-mercapto	202-205	E, 3764
5-Cyano-4-mercapto-2,6-dimethyl	210-211	E, 6302
5-Cyano-4-mercapto-2-methyl-6-phenyl	273-274	E, 6302
5-Cyano-4-mercapto-6-methyl-2-phenyl	224	E, 6291
5-Cyano-2-methoxy	81	4399
5-Cyano-4-methoxy	93-96	3764
4-Cyano-2-methoxycarbonylmethyl-6-methyl	55-56	5693
4-Cyano-6-methoxy-2-methyl	65-66; 120/15	5089
5-Cyano-4-methoxy-2-methyl	79-80	E, 5099
2-Cyano-5-methyl	66-67	4399
4-Cyano-6-methyl	92-94/10	5074
5-Cyano-4-methylamino	222-223	3764, 5683
4-Cyanomethyl-2,6-dimethoxy-5-nitro	75-77	6517
2-Cyanomethyl-4,6-dimethyl	78-79	6008
4-Cyanomethyl-2-isopropyl-6-methyl	120-123/20	6008
5-Cyano-2-methyl-4-methylamino	153-154	H, 5683
5-Cyano-4-methyl-2-methylamino	171	2602

4-Cyano-5-methyl-2-methylthio	56-57	3443
4-Cyano-6-methyl-2-methylthio	65-66	5284
5-Cyano-2-methyl-4-methylthio-6-phenyl	142-143	4557, 6302
2-Cyano-4-methyl-6-phenyl	110	2603
4-Cyano-2-methyl-6-phenyl	96-98	5090
4-Cyano-6-methyl-2-phenyl	108-109	2603
2-Cyano-5-methylsulfonyl	191-192	4399
5-Cyano-2-methylsulfonyl	172-173	4399
5-Cyanomethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	116-118	6158
4-Cyano-2-methylthio	76-77	E, 5284
5-Cyano-2-methylthio	81	4399
5-Cyano-4-methylthio-2,6-diphenyl	169-171	4557
2-Cyano-4-phenyl	158 or 161-162	5839, 6040
5-Cyano-4-phenyl-2,6-bis(trichloromethyl)	150	5953
5-Cyano-4-β-phenylhydrazino	192-196	3764
5-Cyano-4-phenyl-6-propylamino	114	6129
4-(2'-Cyanoprop-1'-enyl)-6-phenyl	102-104	5246
2-α-Cyanopropyl-4,6-dichloro-5-ethyl	39-40	5347
5-γ-Cyanopropyl-4,6-dihydroxy-2-methyl	>300	5290
4-γ-Cyanopropyl-2,6-dimethyl	149-150/20	5098
4-β-Cyanopropyl-6-phenyl	pic: 148-149	5246
4-Cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	168-170	4927, 4937, 4939, 6189
5-Cyano-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	155 to 165	4479, 4927, 4937, 4939, 4941
5-Cyano-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	237	4941
4-Cyano-1,2,3,6-tetrahydro-3-isobutyl-1-methyl-2,6-dioxo	98	4940
4-Cyano-1,2,3,6-tetrahydro-3-isopropyl-1-methyl-2,6-dioxo	128-130	4940
5-Cyano-1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxo	165-167	4947
5-Cyano-1,2,3,4-tetrahydro-6-methoxy-2,4-dioxo-1,3-diphenyl	240	6049
4-Cyano-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-phenyl	205	4937
5-Cyano-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-phenyl	253	4941
5-Cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	243	H, 4941
4-Cyano-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-propyl	70-71	4940

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Cyano-2,4,6-trifluoro	33-34	5770
5-Cyano-2,4,6-trimethoxy	-CN→O: 142 or 147	2815, 3518
5-Cyano-2,4,6-triphenyl	260-261	5134
5-Cyano-2,4,6-trisheptafluoroisopropyl	99-100	5242
2-β-Cyanovinyl-4,6-dimethyl	75 (<i>trans</i>), 83 (<i>cis</i>)	6301, 6390
4-β-Cyanovinyl-2,6-dimethyl	70-72	6301, 6390
5-β-Cyanovinyl-2,4-dimethyl	92 (<i>trans</i>)	6301, 6390
5-β-Cyanovinyl-2-isopropyl-4-methyl	85 or 89	5654, 6390
5-Cyclobutyl-2,4-dihydroxy	325	5890
5-Cyclobutyl-4-hydroxy-2-mercapto	206-208	5890
1-Cyclohex-1'-en-1'-ylamino-4,6-dimethyl	45-47	4502
4-Cyclohexylamino-6-hydroxy	266-269	5357
2-Cyclohexylamino-4-hydroxy-6-methyl-5-propyl	220	5722
4-Cyclohexylamino-6-hydroxy-5-nitro	196-198	4396
4-Cyclohexylamino-6-hydroxy-5-phenylazo	225-226	5357
4-Cyclohexylamino-6-methoxy	96-97	5357
4-Cyclohexylamino-5-phenyl	-	5914
4-Cyclohexylamino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl	228	4657
4-Cyclohexylamino-1,2,3,6-tetrahydro-5-nitroso-2,6-dioxo-1,3-diphenyl	186	4657
1-Cyclohexyl-1,2-dihydro-4,6-dimethyl-2-oxo	233-235	4392
1-Cyclohexyl-1,4-dihydro-2,5-diphenyl-4-thio	215-217	5572
1-Cyclohexyl-1,2-dihydro-5-methyl-4,6-diphenyl-2-thio	221-223	5764
4-Cyclohexyl-1,2-dihydro-5-methyl-1,6-diphenyl-2-thio	241-243	5764
1-Cyclohexyl-1,2-dihydro-5-methyl-2-oxo-4,6-diphenyl	194-196	5764
4-Cyclohexyl-1,2-dihydro-5-methyl-2-oxo-1,6-diphenyl	242-244	5764
1-Cyclohexyl-1,6-dihydro-4-methylthio-6-oxo	96-98	4806
1-Cyclohexyl-1,2-dihydro-2-oxo	3-Mel: 208	5324
4-Cyclohexyl-2,6-dihydroxy	286-287	6052
1-Cyclohexyl-5-dimethylaminomethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	HCl: 201	4932

1-Cyclohexyl-5-dimethylaminomethyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	HCl: 234	4932
1-Cyclohexyl-5-dimethylaminomethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	HCl: 233	4932
1-Cyclohexyl-5-dimethylaminomethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	HCl: 214	4932
1-Cyclohexyl-5-dimethylamino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	122	4925
1-Cyclohexyl-5-dimethylamino-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	154	4931
1-Cyclohexyl-4- β -dimethylaminovinyl-1,2,3,6-tetrahydro-3-methyl-5-nitro-2,6-dioxo	209–210	4936
1-Cyclohexyl-3-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	132	4925
1-Cyclohexyl-5-ethoxycarbonyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	120	4941
1-Cyclohexyl-5-formyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	172	4923
1-Cyclohexyl-5-formyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	96–97	4923
1-Cyclohexyl-5-formyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	172	4923
2- <i>N'</i> -Cyclohexylguanidino-4,6-dimethyl	237	4975
4-Cyclohexyl-6-hydroxy-2-mercapto	282–283	H, 6052
4-Cyclohexylidenehydrazino-2,6-dimethyl	129–130	5265
4-Cyclohexylidenehydrazino-2,6-diphenyl	158–159	5265
4-Cyclohexylidenehydrazino-2-methyl	115–116	5265
4-Cyclohexylidenehydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	134–135	5265
4-Cyclohexylidenehydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	128–130	4921
1-Cyclohexyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	214	4925
1-Cyclohexyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	137	4925
1-Cyclohexyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-5-piperidino	145	4925
1-Cyclohexyl-1,2,3,4-tetrahydro-3,6-dimethyl-5-nitro-2,4-dioxo	156	4925
1-Cyclohexyl-1,2,3,4-tetrahydro-6-hydroxyamino-3-methyl-2,4-dioxo	125–129	5042
1-Cyclohexyl-1,2,3,6-tetrahydro-4-hydroxyamino-3-methyl-2,6-dioxo	153–155	5042
1-Cyclohexyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	103	4920
1-Cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	127	4920

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-(Cyclohexylthio)carbonyl-2,6-dihydroxy	248–249	5464
5-Cyclopentylcarbonylmethyl-4-hydroxy-2,6-dimethyl	300–304	E, 5965
5-Cyclopentyl-2,4-dihydroxy	294–295 or 327	3762, 5890
1-Cyclopentyl-5-dimethylamino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	104	4925
1-Cyclopentyl-5-dimethylamino-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	142	4925
1-Cyclopentyl-3-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	98	4925
1-Cyclopentyl-4-ethoxy-1,2-dihydro-2-oxo	crude; nmr	5888
5-Cyclopentyl-4-hydroxy-2-mercapto	233–234	5890
2-Cyclopentyl-4-ethoxy	crude; nmr	5888
1-Cyclopentyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo	146	4925
1-Cyclopentyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo	120	4925
4-Cyclopropyl	35; 70/12	6051
5-Cyclopropylcarbonylmethyl-4-hydroxy-2,6-dimethyl	272–274	5965
5-Cyclopropyl-4-cyclopropylmethyl-2,6-dihydroxy	241–242	5890
5-Cyclopropyl-4-cyclopropylmethyl-6-hydroxy-2-mercapto	197–198	5890
4-Cyclopropyl-2,6-dihydroxy	211–217 or 215–224	4376, 5774
5-Cyclopropyl-2,4-dihydroxy	sp; anal	4376
5-Cyclopropyl-4,6-dihydroxy	246	3816
2-Cyclopropyl-4,6-dihydroxy-5-methyl	> 300	5999
4-Cyclopropyl-2,6-dihydroxy-5-methyl	264–269	5890
5-Cyclopropyl-2,4-dihydroxy-6-methyl	253	5890
5-Cyclopropyl-4,6-dihydroxy-2-methylthio	—	5774
4-Cyclopropyl-6-hydroxy	163–165	E, 5812
4-Cyclopropyl-6-hydroxy-2,5-dimethyl	218–220	5999
4-Cyclopropyl-6-hydroxy-2-mercapto	234 or 239–240	H, 4376, 4377, 5774, 5812
5-Cyclopropyl-4-hydroxy-2-mercapto	210–212	4376, 5896

4-Cyclopropyl-6-hydroxy-2-mercapto-5-methoxy	211–213 or 215	5999, 6000, 6053
4-Cyclopropyl-6-hydroxy-2-mercapto-5-methyl	220–230 or 234	5890, 5999
5-Cyclopropyl-4-hydroxy-2-mercapto-6-methyl	208–209	5890
4-Cyclopropyl-6-hydroxy-5-methoxy	120–122	5999, 6053
4-Cyclopropyl-6-hydroxy-2-methoxy-5-methyl	205–207	5999
4-Cyclopropyl-6-hydroxy-5-methoxy-2-methylthio	165–167	6000
4-Cyclopropyl-6-hydroxy-5-methyl	180–182	5999
4-Cyclopropyl-6-hydroxy-5-methyl-2-methylthio	201–211	5774
4-Cyclopropyl-6-hydroxy-2-methylthio	196–198	E, 5774
2,5-Diacetamido	294–295	4380
2,4-Diacetamido-5-acetoxy-6-methyl	228–229	5045
4,6-Diacetamido-2-amino-5-nitroso	200	E, 4633
2,4-Diacetamido-6-benzoyloxy-5-nitroso	194–195	4633
2,4-Diacetamido-6-chloro-5-isoamyl	206–208	2816
4,6-Diacetamido-2-dimethylamino	205–206	4633
2,4-Diacetamido-4-hydroxy-5-isoamyl	281–284	2816
2,4-Diacetamido-5-hydroxy-6-methyl	215–216	5045
2,4-Diacetamido-6-isopropoxy-5-nitroso	211–212	4633
2,4-Diacetamido-6-methyl	231	5045
4,5-Diacetamido-6-methyl-2-methylthio	204–205	5348
4,6-Diacetamido-2-methylthio-5-nitro	161–162	4633
2,4-Diacetamido-6-piperidino	3-N-Ox: 217	5606
1,3-Diacetonyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	130 or 132	4889, 6400
5-2',3'-Diacetoxycyclopentyl-2,4-dihydroxy	256–257	3762
5-2',3'-Diacetoxycyclopentyl-2-hydroxy-4-mercapto	238–239	3762
5-Diacetyl-amino-4-N-ethylacetamido-6-methyl-2-methylthio	102–103	5348
5-Diacetyl-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	175–176	3278
2,5-Diacetyl-4,6-dimethyl	110–112/3	5987
2,5-Diacetyl-4-methyl-6-phenyl	123–125	5987
1,3-Diallyl-5-allyloxymethyl-1,2,3,4-tetrahydro-2,4-dioxo	126–130/0.001	4493
5-Diallylamino-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	87	4925
5-Diallylamino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	93	4925
1,3-Diallyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	38	6350
1,3-Diallyl-1,2,3,4-tetrahydro-5-hydroxymethyl-2,4-dioxo	35–38	4493

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,4-Diamino	3- <i>N</i> -Ox: 193; 1- <i>N</i> -Ox: 289	H, E, 4356, 6092, 6113
2,5-Diamino	212–213	H, E, 4380, 4381
4,6-Diamino	pic: 300	H, E, 5153
2,4-Diamino-5-amyl-6-methyl	143–144	E, 5453
2,4-Diamino-6-amyl-6-methyl	crude	4624
2,4-Diamino-6-amyl-6-methyl-5-nitro	172	4655
2,4-Diamino-6-amyl-6-methyl-5-nitroso	220	4624
2,5-Diamino-4-anilino-1,6-dihydro-1-methyl-6-oxo	2HCl: 249	4635
2,5-Diamino-4-anilino-1,6-dihydro-1-methyl-6-oxo	> 320; 2HCl: 238	E, 4635
2,5-Diamino-4-anilino-6-hydroxy	3- <i>N</i> -Ox: 212–214	5188
2,4-Diamino-6-anilino-5-nitro	245–246	E, 5744
2,4-Diamino-6-anilino-5-nitroso	223–225	5744
4,6-Diamino-2-anilino-5-nitroso	170	4633
2,5-Diamino-4-benzamido-6-methoxy	254–256	6125
4,6-Diamino-1-benzoyl-1,2-dihydro-2-thio	155–156	5553
2,4-Diamino-5-benzoyloxy-6-ethylamino	180–183; HCl: 248	5045
2,4-Diamino-5-benzoyloxy-6-methyl	122; 3- <i>N</i> -Ox: 152	5553
2,4-Diamino-5-benzoyloxy-6-piperidino	260	6125
4,6-Diamino-2-benzoylthio	194–196	H, E, 4544, 6514
2,4-Diamino-5-benzyl	2HCl: 160–162	3475
4,6-Diamino-5-benzylamino	2HCl: 199–200	3475
2,4-Diamino-5-benzylamino-1,6-dihydro-1-methyl-6-oxo	2HCl: 244–245	3475
2,4-Diamino-5-benzylamino-3,6-dihydro-3-methyl-6-oxo	248 or 254; 2HCl: 176	3475, 4647, 5608
2,4-Diamino-5-benzylamino-6-hydroxy	215; 2HCl: 245	4635
2,5-Diamino-4-benzylamino-6-hydroxy	230–235	E, 5744
4,6-Diamino-2-benzylamino-5-nitroso	248–249	5745
2,4-Diamino-5-benzyl-6-carboxy	260–265	5036
4,6-Diamino-1-benzyl-1,2-dihydro-2-oxo	278 or > 350	H, 4647, 5608
2,4-Diamino-5-benzylideneamino-6-hydroxy	244–246	E, 6055
4,6-Diamino-2-benzyl-5-nitroso		

2,4-Diamino-6-benzyl-5-phenyl	204–207	E, 4834
4,6-Diamino-5-benzyl-2-phenyl	180–182	5131
4,5-Diamino-2-benzylthio	151–153	5344
2,5-Diamino-4-benzylthio-6-hydrazino	144	5234
2,5-Diamino-4-benzylthio-6-mercaptop	247	5234
2,5-Diamino-4,6-bisbenzylthio	75	5234
4,5-Diamino-2,6-bisdimethylamino	sulf: 203–205	H, 4643
4,6-Diamino-2-bromo	255	5153, 5157
4,6-Diamino-2-bromo-5-ethyl	241–244	5153, 5157
2,4-Diamino-5-bromo-6-hydroxy	264–265	H, E, 5251
2,4-Diamino-5-bromomethyl	crude; HBr: > 280	5384, 6054
4,6-Diamino-2-bromo-5-methyl	208–210	5153, 5157
2,4-Diamino-5-bromomethyl-6-hydroxy	> 300 (HBr ?)	6054
4,6-Diamino-2-bromo-5-phenyl	250–252	5153, 5157
4,5-Diamino-2-butyl	122–123	H, 4570
4,5-Diamino-2-t-butyl	162–164	5753
4,5-Diamino-6-t-butyl	163–165	5753
2,4-Diamino-6-butylamino	3-N-Ox: 221	5508
2,4-Diamino-5-butylamino-6-hydroxy	2HCl: 166–169	3475
2,4-Diamino-5-butyl-6-carboxy	245–246	5745
4,5-Diamino-2-t-butyl-6-chloro	142–143	5753
4,5-Diamino-6-t-butyl-2-chloro	153–154	5753
2,4-Diamino-6-butyl-5-ethylthio	152–153	6012
4,5-Diamino-2-butyl-6-mercaptop	187	H, 4570
2,4-Diamino-6-butyl-5-phenyl	176–177	4833
2,4-Diamino-6-carbamoyl	> 300	5400
4,5-Diamino-6-carbamoyl	300	5436
2,4-Diamino-6-carbamoyl-5-chloro	253	5971
2,4-Diamino-6-carbamoyl-5-nitro	> 285	5767
2,4-Diamino-5-carbamoyl-6-phenyl	211–213	5767
4,6-Diamino-5-carbamoyl-2-phenyl	240–241	5767
2,4-Diamino-5-carboxy	295–305	4960, 5400
4,5-Diamino-6-carboxy	> 250	3199
2,4-Diamino-5- δ -carboxybutyl-6-hydroxy	267–268	6519

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,4-Diamino-6-carboxy-5-ethyl	252–253	5745
2,4-Diamino-6-carboxy-5-isobutyl	238–239	5745
4,5-Diamino-6-carboxy-2-mercaptop	234	3199
2,4-Diamino-6-carboxy-5-methyl	260–261	5745
2,4-Diamino-5-carboxymethyl-6-hydroxy	> 350	6519
2,4-Diamino-6-carboxy-5-phenyl	238–240	5745
2,4-Diamino-5- β -carboxypropionyloxy-6-methyl	HCl: 220–222	5051
2,4-Diamino-6-carboxy-5-propyl	243–244	5745
2,4-Diamino-5-chloro	215–216	5400
2,4-Diamino-6-chloro	3- <i>N</i> -Ox: 190	H, E, 5585
2,4-Diamino-6-chloro	> 260	2590
2,5-Diamino-4-chloro	220	H, 2590, 4686
4,5-Diamino-2-chloro	248 or 249–250	H, E, 4722, 5791
4,5-Diamino-6-chloro	273–274	5153, 5157
4,6-Diamino-2-chloro	> 360	4486
4,6-Diamino-2-chloro-5-cyano	238–240	5153, 5157
4,6-Diamino-2-chloro-5-ethyl	240	3461
2,4-Diamino-6-chloro-5-formyl	> 260	5229
2,5-Diamino-4-chloro-6-hydrazino	155–157	2816
2,4-Diamino-6-chloro-5-isoamyl	175–176; 1,3-Diox: 237	5188
2,4-Diamino-5-chloro-6-methyl	244–245	5153, 5157
4,6-Diamino-2-chloro-5-methyl	220–222	E, 5620
2,4-Diamino-6-chloro-5-nitro	205–206	4686, 6067
4,5-Diamino-2-chloro-6-phenyl	249–251	5153, 5157
4,6-Diamino-2-chloro-5-phenyl	232–234; HCl: 279	2562
4,5-Diamino-6-chloro-2-styryl	226–227	5823
4,5-Diamino-2-chloro-6-trifluoromethyl	> 270	H, E, 3752
2,4-Diamino-5-cyano	220 or 222	E, 4486, 5381
2,4-Diamino-5-cyano-6-ethoxy	262	4486
2,4-Diamino-5-cyano-6-fluoro	> 300	5770

2,4-Diamino-5-cyano-6-methyl	287 or 292; HCl: > 300	4508, 4978, 5767
2,4-Diamino-6-cyanomethyl	crude: 295	6063
4,6-Diamino-2-cyanomethyl-5-nitroso	> 300	5744
2,4-Diamino-5-cyano-6-phenyl	253–254	E, 4912
2,4-Diamino-6-cyclohexylamino	3- <i>N</i> -Ox: 218–220	E, 5508
2,5-Diamino-4-cyclohexylamino-6-hydroxy	HCl: crude	5356
2,4-Diamino-5-cyclohexyl-6-ethyl	146–148	5453
2,4-Diamino-5-cyclohexyl-6-methyl	258–262	5453
2,5-Diamino-4,6-dibenzamido	123–125	4633
2,4-Diamino-5,6-dichloro	3- <i>N</i> -Ox: 185	H, E, 5585
2,5-Diamino-4,6-dichloro	188–191; HCl: > 264	H, 5229, 5637
4,6-Diamino-2,5-dichloro	300–301	H, 2859
2,4-Diamino-5- β , β -diethoxyethyl-6-hydroxy	187–189	E, 4492
2,4-Diamino-6-diethylamino	3- <i>N</i> -Ox: 255	5566
2,4-Diamino-6- β -diethylaminoethoxyethylamino-5-nitroso	165 or 200	4907, 5744
4,6-Diamino-2,5-difluoro	232–233	3521
2,4-Diamino-3,6-dihydro-6-imino-3-methyl-5-nitro	1- <i>N</i> -Ox: 202	5188
2,4-Diamino-3,6-dihydro-6-imino-3-methyl-5-nitroso	TFA: 238	5188
2,5-Diamino-1,6-dihydro-4-isopropylamino-1-methyl-6-oxo	230–234	4635
2,4-Diamino-1,6-dihydro-1-methyl-5-methylamino-6-oxo	2HCl: > 300	3475
2,4-Diamino-3,6-dihydro-3-methyl-5-methylamino-6-oxo	2HCl: 303–304	3475
4,5-Diamino-3,6-dihydro-3-methyl-2-methylthio-6-oxo	crude	4616
2,4-Diamino-1,6-dihydro-1-methyl-5-nitroso-6-oxo	> 320	E, 4632
1,2-Diamino-1,6-dihydro-4-methyl-6-oxo	283	5140
1,5-Diamino-1,6-dihydro-4-methyl-6-oxo	145–146	5049, 6076
2,4-Diamino-1,6-dihydro-1-methyl-6-oxo	sulf: 237; H ₂ O: 245	E, 4632
4,6-Diamino-1,2-dihydro-1-methyl-2-oxo	sulf: 325	E, 5245
4,5-Diamino-1,2-dihydro-1-methyl-2-thio	266–267	5344
4,6-Diamino-1,2-dihydro-1-methyl-2-thio	249–251	5181
1,2-Diamino-1,6-dihydro-6-oxo	178–180	5140
1,2-Diamino-1,6-dihydro-6-oxo-4-phenyl	233–235	5140
2,4-Diamino-5,6-dihydroxy	> 300	H, E, 4860
4,5-Diamino-2,6-dihydroxy	sulf: anal	H, E, 5341
4,6-Diamino-2,5-dihydroxy	> 300	6373

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,5-Diamino-4-di-isopropylamino-6-hydroxy	219	4628
4,5-Diamino-2,6-dimercapto	310	H, E, 4616
2,4-Diamino-6-dimethoxymethyl-5-phenyl	247-248	5526
2,4-Diamino-5-dimethylamino	159-160	E, 6107
2,4-Diamino-6-dimethylamino	180-181	H, 4970
4,5-Diamino-2-dimethylamino	crude	H, E, 4623
4,5-Diamino-2-dimethylamino-6-ethyl	116-117	5677
4,6-Diamino-2- β -dimethylaminoethylamino-5-nitroso	—	5744
4,5-Diamino-2-dimethylamino-6-formamido	285-287	5399
2,4-Diamino-5-dimethylamino-6-hydroxy	2HCl: 210-213	3475
2,5-Diamino-4-dimethylamino-6-hydroxy	230	4628
4,5-Diamino-2-dimethylamino-6-methyl	153	5677
2,5-Diamino-4-dimethylamino-6-methylamino	crude	4623
4,5-Diamino-6-dimethylamino-2-methylthio	crude	H, 4617
2,4-Diamino-6-dimethylamino-5-nitro	234	4655
2,4-Diamino-6-dimethylamino-5-nitroso	252-254	H, 4643, 5744
4,6-Diamino-2-dimethylamino-5-nitroso	—	H, E, 5744
4,6-Diamino-2- γ -dimethylaminopropylamino-5-nitroso	—	5744
4,5-Diamino-2-dimethylamino-6-trifluoromethyl	118-120	5823
2,4-Diamino-5-ethoxycarbonyl	215-217	H, E, 2599, 4960, 4961
4,5-Diamino-6-ethoxycarbonyl	243	3199
4,5-Diamino-6-ethoxycarbonyl-2-mercaptop	206-208	E, 3199
2,4-Diamino-5-ethoxycarbonyl-6-methyl	165-166	4470
4,5-Diamino-6-ethoxycarbonyl-2-methylthio	227	5443
2,4-Diamino-5-ethoxycarbonyloxy-6-methyl	135-136	5045
2,4-Diamino-5- β -(ethoxycarbonyl)propionyloxy-6-methyl	155	5051
2,4-Diamino-6- β -ethoxyethoxy	129-130	5744
2,4-Diamino-6- β -ethoxyethoxy-5-nitroso	202	5744
2,4-Diamino-5-ethoxymethyl	165-166	E, 6054

2,4-Diamino-6-ethoxy-5-phenyl	108–109	5381
4,5-Diamino-2-ethoxy-6-trifluoromethyl	120	5823
2,4-Diamino-6-ethylamino	3- <i>N</i> -Ox: 273–275	5188, 5508
2,4-Diamino-5-ethylamino-6-hydroxy	2HCl: 190–195	3475
2,4-Diamino-6-ethylamino-5-nitro	crude: 220; 3- <i>N</i> -Ox: 259	5188
2,4-Diamino-6-ethylamino-5-nitroso	3- <i>N</i> -Ox: 264	5188
4,5-Diamino-6- <i>N</i> -ethylcarbamoyl	168	5436
2,4-Diamino-6-ethyl-5-ethylthio	156	6012
4,5-Diamino-6-ethyl-2-methylthio	193–194	5677
2,4-Diamino-6-ethyl-5-phenyl	238–240	H, E, 4833
4,5-Diamino-2-ethylthio	155–157	5675
4,6-Diamino-2-ethylthio	HBr: 169–173	H, 6056
2,4-Diamino-5-ethylthio-6-isopropyl	118–119	6012
2,4-Diamino-5-ethylthio-6-methyl	138	6012
2,4-Diamino-5-ethylthio-6-phenyl	193–194	6012
2,4-Diamino-5-fluoro-6-hydroxy	anal; sp	4744
4,6-Diamino-2-fluoro-5-nitro	> 250	5770
2,4-Diamino-5-formamido-1,6-dihydro-1-methyl-6-oxo	294–295	H, E, 3253
2,4-Diamino-5-formamido-6-hydroxy	> 350	H, 4635
2,4-Diamino-5-formyl	265–268; oxime: 291	E, 5384
2,4-Diamino-5-formyl-6-hydroxy	> 300	6382
4,6-Diamino-5-formyl-2-methylthio	228–230	5466
2,4-Diamino-6-formyl-5-phenyl	> 300	5526
4,6-Diamino-5-formyl-2-phenyl	217–218	5466
4,5-Diamino-2-guanidino	2HCl: 225	6384
4,5-Diamino-6-guanidino	sul: 305	6384
4,6-Diamino-2-guanidino	HCl: 274	6384
2,4-Diamino-6-guanidino-5-nitro	HCl: 324	6384
4,6-Diamino-2-hexylamino-5-nitroso	168–172	5744
2,4-Diamino-5-hexyl-6-methyl	123–125	5453
2,4-Diamino-6-hydroxy	260–265	H, E, 5365
4,5-Diamino-2-hydroxy	3- <i>N</i> -Ox/HCl: –	H, E, 5426
4,5-Diamino-6-hydroxy	1- <i>N</i> -Ox: 203–204	H, E, 5650
4,6-Diamino-5-hydroxy	265–268	6373

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,4-Diamino-6-hydroxy-5- β -hydroxyethyl	295–300	H, 4465
2,5-Diamino-4-hydroxy-6-isopropylamino	2HCl: > 320	4635
2,4-Diamino-6-hydroxy-5-isothiuronio	Br: 273–274	5251
2,5-Diamino-4-hydroxy-6-mercaptop	> 300	4766, 6134
4,5-Diamino-6-hydroxy-2-mercaptop	—	H, E, 5059
2,4-Diamino-5-hydroxy-6-methyl	154–155; sulf: 280	5045
2,4-Diamino-6-hydroxy-5-methyl	320–324	E, 5296
2,5-Diamino-6-hydroxy-2-methyl	1-N-Ox: 245–246	H, E, 5650
2,4-Diamino-6-hydroxy-5-methylamino	2HCl: 252	E, 3475
2,5-Diamino-4-hydroxy-6-methylamino	HCl: 236	E, 5048, 5842
4,5-Diamino-6-hydroxy-2-methylamino	—	H, E, 5048
4,6-Diamino-2-hydroxy-5-nitro	> 360	E, 5647
2,4-Diamino-6-hydroxy-5-phenylazo	> 300 or > 320	H, E, 5365, 5465
2,4-Diamino-5-hydroxy-6-piperidino	149	5553
2,5-Diamino-4-hydroxy-6-piperidino	275	4628
2,4-Diamino-6-hydroxy-5-propionamido	HCl: 280	H, 4642
2,4-Diamino-6-hydroxy-5-propylamino	2HCl: 176–182	3475
4,5-Diamino-6-hydroxy-2-sulfino	188–190	E, 5059
2,4-Diamino-6-hydroxy-5-sulfo-oxy	> 300	4860, 6373
4,6-Diamino-2-hydroxy-5-sulfo-oxy	> 300	6373
2,4-Diamino-6-hydroxy-5-thiocyanato	258	5251
2,4-Diamino-6-isobutyl-5-phenyl	141–143	4834
4,6-Diamino-5-isobutylamido	288	5447
2,4-Diamino-6-isopropyl	HCl: 181–184	5807
2,4-Diamino-6-isopropylamino-5-nitroso	193–194	5744
4,6-Diamino-2-isopropylamino-5-nitroso	204–208	5744
2,4-Diamino-6-isopropyl-5-methylthio	145	6012
2,4-Diamino-6-isopropyl-5-phenyl	184–186	4834
2,5-Diamino-4-mercaptop	217 or 235	E, 2590, 5742
4,5-Diamino-2-mercaptop	—	H, 2590

4,6-Diamino-2-mercapto	> 300	H, E, 2859, 5444, 5730
4,5-Diamino-6-mercapto-2-methylthio	239	4616
4,6-Diamino-2-mercapto-5-nitroso	—	H, E, 2859
4,5-Diamino-2-mercapto-6-phenyl	275	5441
4,5-Diamino-6-mercapto-2-phenyl	238–239	E, 5439
4,5-Diamino-6-mercapto-2-propyl	184–185	4570
4,5-Diamino-2-mercapto-6-trifluoromethyl	225–226	5440
2,4-Diamino-6-methoxycarbonyl	HCl: anal	5400
2,4-Diamino-6-methoxycarbonyl-5-nitro	> 300	5767
2,4-Diamino-5-β-(methoxycarbonyl)-propionyloxy-6-methyl	169–170	5051
2,4-Diamino-5-methoxymethyl	3- <i>N</i> -Ox: 240; 1- <i>N</i> -Ox: 236	6113
2,4-Diamino-6-methoxy-5-nitro	240	4634
4,5-Diamino-2-methoxy-6-trifluoromethyl	140	5823
2,4-Diamino-6-methyl	179 or 186; pic: 287	H, E, 4844, 4846, 5309, 5788
4,6-Diamino-2-methyl	295–297	H, 5859
2,4-Diamino-6-methylamino	3- <i>N</i> -Ox: 188	H, 5508
2,4-Diamino-6-methylamino-5-nitro	240–241	H, 5744
4,6-Diamino-2-methylamino-5-nitroso	288–290	5744
2,4-Diamino-6-α-methylhydrazino	214–217	5402
2,4-Diamino-6-methyl-5-phenyl	240–250	H, E, 4833
4,5-Diamino-2-methyl-6-phenyl	150–151	5441
4,5-Diamino-6-methyl-2-phenyl	184–185	5439
2,4-Diamino-6-methyl-5-phenylazo	216	E, 5465
2,5-Diamino-4-methyl-6-piperidino	3- <i>N</i> -Ox: 193	5724
2,4-Diamino-6-methyl-5-propyl	195–197	5453
2,4-Diamino-6-methylthio-5-nitroso	crude	E, 5744
4,6-Diamino-2-methylthio-5-thiocyanato	211–214	5244
4,5-Diamino-2-methylthio-6-trifluoromethyl	150–152	5823
2,4-Diamino-5-nitro	245–250	H, E, 5620
4,6-Diamino-5-nitro	> 300; 1,3-Diox: > 240	H, E, 5647, 5791
4,6-Diamino-5-nitro-2-phenyl	262	E, 5439
2,4-Diamino-5-nitro-6-piperidino	3- <i>N</i> -Ox: 250	3508

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4,6-Diamino-5-nitro-2-propyl	198	4570
2,4-Diamino-5-nitroso-6-piperidino	212–214; 3- <i>N</i> -Ox: 191	H, 3508, 5744
4,6-Diamino-5-nitroso-2-piperidino	193–195	E, 5744
4,6-Diamino-5-nitroso-2-trifluoromethyl	> 360	E, 2949
2,4-Diamino-6-phenoxy	176–177	5400
2,4-Diamino-5-phenyl	162–164	H, 4833
2,4-Diamino-6-phenyl	162–163	H, E, 2944
4,5-Diamino-2-phenyl	137 or 144–145	E, 5439, 5792
4,5-Diamino-6-phenyl	200–201	5441
4,6-Diamino-2-phenyl	194–196	H, E, 5767
2,4-Diamino-5-phenylazo	275	5465
2,4-Diamino-5-phenylazo-6-piperidino	178–179	5358
2,4-Diamino-6-phenyl-5-phenylazo	238–239	2944
2,4-Diamino-6-phenyl-5-phenylthio	207–209	6012
2,4-Diamino-5-phenyl-6-propyl	171–173	4833
2,4-Diamino-5-phenylsulfonyl	304–306	5583
2,4-Diamino-6-phenylsulfonyl	3- <i>N</i> -Ox: 258	5188
2,4-Diamino-6-phenylthio	156–157; 3- <i>N</i> -Ox: 254–256	5188
2,4-Diamino-5-phenyl-6-trifluoromethyl	277–278	5400
2,4-Diamino-6-piperidino	3- <i>N</i> -Ox: 262	H, 3508, 5508
4,5-Diamino-6-piperidino	161–163	4789
4,6-Diamino-5-pivalamido	> 300	5447
2,4-Diamino-6-propyl	HCl: 190–194	5807
4,5-Diamino-2-propyl	148–150	4570
4,5-Diamino-6-propylamino	HCl: 198–199	5871
4,5-Diamino-2-styryl	191–193	2562
2,4-Diamino-6-sulfo	Na: anal	5400
4,6-Diamino-5-sulfo-oxy	> 300	6373
4,5-Diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	210; HCl: > 350	H, E, 4431, 4620
4,6-Diamino-5-thiocyanato	184–185	5244

4,5-Diamino-6-trifluoromethyl	209	5440
1,3-Diamyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	liq; anal	6400, 6511
2,4-Dianilino	134–136; pic: 234	H, 4844, 4846
2,4-Dianilino-5-β-chloroethyl	136; HCl: 189	5881
4,6-Dianilino-2,5-difluoro	192–193	3521
2,4-Dianilino-5-ethoxycarbonyl-6-methyl	155–156	4470
2,4-Dianilino-5-fluoro	166–167; HCl: 228	5956
2,4-Dianilino-5-formamido-6-hydroxy	280	4635
2,4-Dianilino-6-hydroxy	217–218	E, 4635
2,4-Dianilino-6-hydroxy-5-nitroso	285–287	4635
2,4-Dianilino-5-methyl	175–177	6059
2,4-Dianilino-6-methyl	109–110; pic: 207	4844
2,4-Dianilino-5-nitro	209	H, E, 5889
4,6-Dianilino-5-nitro	168	E, 5889
4,5-Dianilino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	192–193	4662
2,4-Diazido-5-bromo-6-phenyl	95–96	5931
2,4-Diazido-5-buty-2'-ynyl-6-phenyl	101–102	5931
4,6-Diazido-5-chloro-2-fluoro	121–122	6078
4,6-Diazido-2,5-difluoro	106	6078
2,4-Diazido-5-β-ethoxyethyl-6-phenyl	52–53	5931
2,4-Diazido-5-methyl	—	5355
2,4-Diazido-6-methyl	—	H, E, 5355
2,4-Diazido-5-methyl-6-phenyl	111–112	5931
2,4-Diazido-6-phenyl-5-prop-2'-ynyl	97	5931
4,6-Diaziridino-2-chloro	118–119	6060
2,4-Diaziridino-6-methyl-5-nitro	H ₂ O: 101–102; MeOH: 37–38	E, 5880
5-Diazo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	3-N-Ox: 200–201	5448
2,4-Dibenzamido-6-piperidino	—	5606
1,3-Dibenzoyl-4-benzoyloxy carbonyl-5-bromo-1,2,3,6-tetrahydro-2,6-dioxo	98–100	4390
1,3-Dibenzyl-5-bromo-1,2,3,4-tetrahydro-2,4-dioxo	124–127	4391
1,3-Dibenzyl-4-ethyl-1,2,3,6-tetrahydro-5-methyl-2,6-dioxo	102–103	6401
1,3-Dibenzyl-5-fluoro-1,2,3,4-tetrahydro-2,4-dioxo	liq; sp	6350, 6511

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4,6-Dibenzylloxy	44–46; 210/0.5	3768
2,4-Dibenzylloxy-5-bromo	86–88	E, 5592
2,4-Dibenzylloxy-6-fluoro-5-methyl	66–67	4526
2,4-Dibenzylloxy-5- α -hydroxy- α -methylethyl	81–82	5592
2,4-Dibenzylloxy-5- α -hydroxy- δ -methylpentyl	74–76	5592
2,4-Dibenzylloxy-5- α -hydroxy- β -methylpropyl	92–93	5592
4,5-Dibenzylloxy-2-methyl	53–54	5345
4,6-Dibenzylloxy-2-methyl	27–29	E, 6058
4,6-Dibenzylloxy-5-methyl	65–66	E, 3768
2,4-Dibenzylloxy-6-methyl-5-nitro	85	5661
4,6-Dibenzylloxy-2-phenyl	91–92	E, 6058
4,6-Dibenzylloxy-5-phenyl	86–87	E, 3768
1,3-Dibenzyl-1,2,3,4-tetrahydro-2,4-dioxo	61–63 or 76	4390, 5328, 6121
1,3-Dibenzyl-1,2,3,4-tetrahydro-5-methoxy-2,4-dioxo	116–118	4391
1,3-Dibenzyl-1,2,3,4-tetrahydro-5-methyl-2,4-dioxo	90–91	6121
1,3-Dibenzyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	72	6401
1,3-Dibenzyl-1,2,3,4-tetrahydro-5-nitro-2,4-dioxo	147–148	5817
2,5-Dibromo	83–84; <i>N</i> -Ox: 107	5664, 6729
4,6-Dibromo	48–50	4677
4,3',4'-Dibromobutyl-6-hydroxy-2-methylthio	152	4569
4,5-Dibromo-2,6-dihydroxy	313–315	4650
4,5-Dibromo-2,6-diphenyl	161–162	5760
5,5-Dibromohexahydro-1,3-dimethyl-2,4,6-trioxo	148–149	H, E, 6110
4,6-Dibromo-2-isopropylamino	—	6327
2-Dibromomethyl	liq; anal	5682
4-Dibromomethyl	liq; anal	5682
4-Dibromomethyl-2,6-dimethoxy-5-nitro	90–91	6517
2-Dibromomethyl-4,6-dimethyl	82–84	5449
2-Dibromomethyl-4,6-diphenyl	164–167	4875
2-Dibromomethyl-4-ethoxycarbonyl-6-hydroxy-5-methyl	nmr	6140

2-Dibromomethyl-4-phenyl	1-N-Ox: 147–149	4810
4-Dibromomethyl-6-phenyl	1-N-Ox: 139–141	4810
1- β , γ -Dibromopropyl-1,6-dihydro-4-methylthio-6-oxo	105–106	4806
4,5-Dibromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	166–167	6110
2,4-Dibut-2'-enyloxy-6-methyl	85–87/0.3	5050
1,3-Dibut-2'-enyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	82–85/0.01	5050
1,3-Dibut-3-en-2'-yl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	39–41	5050
4,6-Di-t-butoxy	84	3768
2,4-Dibutoxy-5-fluoro	141/9; n _D ²⁰ 1.4730	5956, 6515
2,4-Dibutoxy-5-fluoro	89/2	6515
2,4-Di-s-butoxy-5-fluoro	72/2	6515
4,6-Di-t-butyl	101/13; N-Ox: 116	6105
2,4-Di-t-butyl-5-chloro	liq; anal; nmr	4664
2,4-Di-t-butyl-6-chloro	liq; anal; nmr	4664
2,4-Di-t-butyl-5-chloro-6-hydrazino	70–72	4664
2,4-Di-t-butyl-5-chloro-6-hydroxy	181–182	4664
2,4-Di-t-butyl-5,6-dichloro	140/15	4664
4,6-Di-t-butyl-2-ethoxy	crude	6105
2,4-Di-t-butyl-6-hydroxy	164–165	4664
4,6-Di-t-butyl-2-hydroxy	223–224	6105
1,3-Dibutyl-1,2,3,4-tetrahydro-2,4-dioxo	—	5328
5-N,N-Dibutyl(thiocarbamoyloxy)-2-methylthio	183–196/1	4401
4,5-Dicarbamoyl	224–225	4453
4,6-Dicarbamoyl-2-chloro	288–289	4820
4,5-Dicarboxy-2,6-diphenyl	175–176; anhydride: 203	5972
4,5-Dicarboxy-2-phenyl	282–284	H, 5604
2,4-Dichloro	61–62	H, E, 5622
2,5-Dichloro	N-Ox: 102	H, 6729
4,6-Dichloro	—	H, E, 4663
2,4-Dichloro-5-chlorocarbonyl	90–91/0.3; 130/12	5462, 5919
2,4-Dichloro-5-chlorocarbonyl-6-trichloromethyl	101–103/0.1; 166/12	4470
2,4-Dichloro-5- β -chloroethyl	112–115/2	5881
4,6-Dichloro-2- β -chloroethyl-5-chloromethyl	47–48; 116/3	5021
4,5-Dichloro-2- β -chloroethyl-6-hydroxy	211–215	5731

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4,6-Dichloro-5- β -chloroethyl-2-methylthio	92-93	2638
4,6-Dichloro-2-chloromethyl	40	E, 5253
4,5-Dichloro-2-chloromethyl-6-hydroxy	211 or 217-220	5028, 5253
4,5-Dichloro-2- γ -chloropropyl-6-hydroxy	147-155	5731
2,4-Dichloro-5-chlorosulfonyl	97-99; 142/12	E, 6074
2,4-Dichloro-5- α -chlorovinyl	liq; anal	5329
2,4-Dichloro-6-cyano	—	6065
4,5-Dichloro-6-cyano-2-dimethylamino	147-150	5971
4,6-Dichloro-5-cyano-2-dimethylamino	CN $\rightarrow$ O; 159-162	3518
4,6-Dichloro-2- α -cyanoethyl-5-methyl	83-84	5347
2,4-Dichloro-5-cyano-6-fluoro	crude	5770
4,6-Dichloro-5-cyano-2-fluoro	crude	5770
2,4-Dichloro-6-cyanomethyl	113-115	6063
4,6-Dichloro-2- α -cyano- β -methylpropyl-5-isopropyl	43-45	5347
4,6-Dichloro-5-cyano-2-methylthio	103-104	5581
4,6-Dichloro-2- α -cyanopropyl-5-ethyl	39-40	5347
4,5-Dichloro-2-cyclohexyl	110/0.3	5755
2,4-Dichloro-6-cyclopropyl	—	5774
4,5-Dichloro-6-cyclopropyl	—	5999
4,6-Dichloro-2-cyclopropyl-5-methyl	—	5999
4,6-Dichloro-5-cyclopropyl-2-methylsulfonyl	134-136	5774
4,6-Dichloro-5-cyclopropyl-2-methylthio	78-80	5774
2,4-Dichloro-6-dichloromethyl-5-ethoxycarbonyl	114-116/0.25	4470
4,5-Dichloro-2,6-diethoxy	98	5971
4,6-Dichloro-5- β , β -diethoxyethyl	120/8	6064
2,4-Dichloro-6-diethylamino-5-methylthio	—	6061
4,6-Dichloro-2-diethylamino-5-methylthio	—	6061
4,6-Dichloro-2-diethylamino-5-phenyl	115/0.1	6610
5,5-Dichloro-1,3-diethylhexahydro-2,4,6-trioxo	80 or 89-90	H, 5163, 6110
4,5-Dichloro-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxo	110-111	6110

2,β-Dichloro-α, α-difluoroethyl-4-hydroxy-6-methyl	66-68	5995
4,5-Dichloro-1,6-dihydro-1-methyl-6-oxo	108	4933
4,5-Dichloro-2,6-dihydroxy	200 or 299-301	4650, 5971
2,5-Dichloro-4,6-dimethyl	63-64	6033
2,4-Dichloro-5-dimethylamino	91	E, 6062
4,6-Dichloro-2-dimethylamino	53	H, E, 6610
4,6-Dichloro-2-dimethylamino-5-formyl	142; oxime: 165	3518
2,4-Dichloro-5-dimethylamino-6-methyl	-	5796
4,6-Dichloro-2-dimethylamino-5-methyl	60-61	6610
2,4-Dichloro-6-dimethylamino-5-methylthio	-	6061
4,6-Dichloro-2-dimethylamino-5-methylthio	81 or 82-83	6061
4,6-Dichloro-2-dimethylamino-5-phenyl	143-146	6578, 6610
2,5-Dichloro-4,6-diphenyl	133-134	4756
4,6-Dichloro-2,5-diphenyl	-	4497, 5352
2,4-Dichloro-6-dipropylamino-5-methylthio	-	6061
4,6-Dichloro-2-dipropylamino-5-methylthio	118-120/0.5	6061
2,4-Dichloro-5-ethoxycarbonyl-6-methyl	50-51	4470
4,6-Dichloro-2-ethoxycarbonylmethyl	140-142/0.15	5688
2,4-Dichloro-5-ethoxycarbonyl-6-phenyl	HCl: 141-143	4470
4,6-Dichloro-2-ethoxyformimidoylmethyl	51	5688
2,4-Dichloro-5-ethyl	106-110/20	5797
4,6-Dichloro-5-ethyl	135-136	4575
2,4-Dichloro-6-ethylamino-5-phenylazo	217-223	5541
4,5-Dichloro-2-ethyl-6-hydroxy	-	5731
4,6-Dichloro-2-ethyl-5-methoxy	111/21	3503
4,6-Dichloro-2-ethyl-5-methyl	74-75	5021
4,6-Dichloro-5-ethyl-2-phenyl	84-85/3	5025, 5351
4,6-Dichloro-5-ethyl-2-propyl	204-205	H, 5021
4,5-Dichloro-2-ethylthio-6-hydroxy	35-36 or 38	4894
2,4-Dichloro-5-fluoro	61-64	E, 4783, 5626
2,4-Dichloro-6-fluoromethyl	-	5785
4,6-Dichloro-2-fluoromethyl	56 or 58-59	5253, 5785
4,5-Dichloro-2-fluoromethyl-6-hydroxy	195-196	5253
4,6-Dichloro-5-formyl	59-61	5794

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4,6-Dichloro-5-formylmethyl	84-86	6064
4,6-Dichloro-5-formyl-2-methyl	103-105	E, 5794
4,6-Dichloro-5-formyl-2-methylthio	82-84; oxime: 112	5581
4,6-Dichloro-5-formyl-2-phenyl	152-154	E, 5794
2,4-Dichloro-6-guanidino	225 then 360	6384
4,6-Dichloro-2-guanidino	>360	6384
5,5-Dichlorohexahydro-1,3-dimethyl-2,4,6-trioxo	156-157	H, 5163, 6110
4,6-Dichloro-5- α -hydroxyethyl	111-112	5768
4,5-Dichloro-6-hydroxy-2-isopropyl	227-230	5731
4,5-Dichloro-6-hydroxy-2-isopropylthio	192-194	4894
4,5-Dichloro-6-hydroxy-2-mercaptop	236-238	4892
4,5-Dichloro-6-hydroxy-2-methoxymethyl	196-201	5731
4,5-Dichloro-6-hydroxy-2-methyl	245-251	5731
4,5-Dichloro-6-hydroxy-2-methylthio	271	4894
4,5-Dichloro-6-hydroxy-2-phenyl	280-287	5731
4,5-Dichloro-6-hydroxy-2-phenylthio	216-217	4894
4,5-Dichloro-6-hydroxy-2-propyl	185-192	5731
4,5-Dichloro-6-hydroxy-2-propylthio	165-166	4894
4,6-Dichloro-2-isobutyl-5-isopropyl	liq; sp	5020
4,6-Dichloro-2-isocyanato	37-38; 48-50/0.03	4822
4,5-Dichloro-6-isocyanato-2-pentachloroethyl	143-144/0.1	4517
4,5-Dichloro-6-isocyanato-2-phenyl	147-148/0.1	4517
4,6-Dichloro-2-isocyanato-5-phenyl	144-147	4822
4,5-Dichloro-6-isocyanato-2-trichloromethyl	115-117/0.1	4517
2,4-Dichloro-5-isopropoxycarbonyl-6-methyl	120-122/0.5	4470
4,6-Dichloro-2-isopropyl	50-53/1	E, 5690
2,4-Dichloro-6-isopropylamino	-	5756
4,5-Dichloro-2-mercaptop-6-thiocarbamoyl	>80	5971
4,6-Dichloro-5-methoxy	57-58	E, 5828
2,4-Dichloro-5-methoxycarbonyl-6-methyl	79-81; 150/14	4470

4,6-Dichloro-2-methoxycarbonylmethyl	62–63	5688
4,6-Dichloro-5- β -methoxyformimidoylmethyl	HCl: 136–137	5688
2-Dichloromethyl	liq; anal	5682
2,4-Dichloro-5-methyl	26 or 27–29	E, 5622, 5797
2,4-Dichloro-6-methyl	46–47	H, E, 5072, 5884
4-Dichloromethyl	liq; anal	E, 5682
4,5-Dichloro-2-methyl	185/0.3	5755
4,6-Dichloro-2-methyl	45–46	H, 5021, 5027, 5028
2,4-Dichloro-5-methylamino	139	E, 6062
4,6-Dichloro-2-methylamino-5-methylthio	158	6061
2-Dichloromethyl-4,6-dimethyl	77–78	E, 5449
4-Dichloromethyl-6-ethoxy-2-phenyl	79	6734
2-Dichloromethyl-4-hydroxy-6-methyl	184–186	5079
4-Dichloromethyl-2-phenyl	45	6734
2,4-Dichloro-5-methyl-6-phenyl	92–93	5931, 6345
4,6-Dichloro-5-methyl-2-phenyl	110 or 111–113	E, 5025, 5351
4,6-Dichloro-2-methyl-5-propyl	–	H, 5351
4-Dichloromethyl-6-trichloromethyl	190/19	5072
4,6-Dichloro-5-nitro	101	H, E, 4722, 5619
2,4-Dichloro-5-nitro-6-phenyl	90	5441
2,4-Dichloro-5-nitro-6-propyl	43–44	5668
4,5-Dichloro-5-nitro-2-propyl	39; 107/4	4570
4,6-Dichloro-5-nitro-2-styryl	169–170	2562
2,4-Dichloro-6-phenyl	83 to 88	H, 4500, 6345, 6575
4,5-Dichloro-2-phenyl	127	5755
4,5-Dichloro-6-phenyl	72–74	5071
4,6-Dichloro-2-phenyl	97–98	H, E, 5025
2,4-Dichloro-6-phenyl-5-phenylazo	114–115	E, 6067
4,6-Dichloro-5-phenyl-2-phenylureido	218–220	4822
4,6-Dichloro-2-phenyl-5-propyl	69–71	5025, 5351
2,4-Dichloro-6-phenyl-5-prop-2'-ynyl	–	5931
4,6-Dichloro-2-phenylureido	195–197	4822
4,6-Dichloro-5-propyl	–	5351
2,4-Dichloro-5-sulfo	Na: –	E, 6074

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4,5-Dichloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	155–157	4650
2,4-Dichloro-6-trichloromethyl	83 or 85–86	4500, 5072, 5954
4,6-Dichloro-2-trichloromethyl	130/10	E, 5785
2,4-Dichloro-6-trifluoromethyl	92/65	5785
2,5-Dicyano	127–128	4399
2,5-Dicyano-4,6-bisheptafluoroisopropyl	169–170	5242
2-Dicyanomethyl-4,6-dimethoxy-5-nitro	K: anal, sp	6381
4-Dicyanomethyl-2,6-dimethoxy-5-nitro	K: anal, sp	6381
4-Dicyanomethyl-2,6-dimethyl	310; 1-N-Ox: 182	6082
2-Dicyanomethyl-4,6-diphenyl	267–270	5836
2-Dicyanomethyl-4-methoxy-5-nitro	K: anal, sp	6381
4-Dicyanomethyl-2-methoxy-5-nitro	K: anal, sp	6381
4-Dicyanomethyl-6-methoxy-5-nitro	dec, anal, sp	6381
2-Dicyanomethyl-5-nitro	dec, anal, sp	6381
4-Dicyanomethyl-5-nitro	K: anal, sp	6381
4,5-Dicyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	182–185	4947
1,3-Dicyclohexyl-1,2,3,4-tetrahydro-6-methylamino-2,4-dioxo	216–218	4657
1,3-Dicyclohexyl-1,2,3,4-tetrahydro-6-methylamino-5-nitroso-2,4-dioxo	98	4657
2,4-Diethoxy	19–20; 1-Mel: 58	H, 5061, 5490, 5555, 5622
4,6-Diethoxy	25; 109/15; EtBF ₄ : 98	4672
4,5-Diethoxycarbonyl	sp	H, 4453, 6329
4,5-Diethoxycarbonyl-2-ethyl	128–129/0.1	6329
2,4-Diethoxycarbonyl-6-hydroxy-5-methyl	120–122	6140
4,5-Diethoxycarbonyl-2-hydroxymethyl	153–160/0.1	6329
4-Di(ethoxycarbonyl)methyl-6-methyl-2-phenyl	50–51	5980
4,5-Diethoxycarbonyl-2-phenyl	175–179/0.3	6329
4,6-Diethoxy-2-ethoxycarbonyl	116–120/0.1	4949
2,4-Diethoxy-5-ethoxycarbonyl-6-methyl	118–120/0.5	4470
2,4-Diethoxy-5-ethyl	110/5	5797

1- β , β -Diethoxyethyl-1,2-dihydro-4-methylthio-2-oxo	98–99	4749
4- α , α -Diethoxyethyl-5-ethoxycarbonyl	100/0.1	4438
4- α , α -Diethoxyethyl-5-ethoxycarbonyl-2-methyl	98/0.05	4438
4- α , α -Diethoxyethyl-5-ethoxycarbonyl-2-phenyl	150/0.02	4438
2,4-Diethoxy-5-fluoro	148–150/88	E, 5956
2,4-Diethoxy-6-formyl	oxime: 125–126	5074
4,6-Diethoxy-2-hydroxy	196–198	4949
2,4-Diethoxy-5-methyl	35–36; 1-Mel: 77–78	H, E, 5061, 5517, 5622
5-Diethoxymethyl	113/12	5794
4,6-Diethoxy-2-methyl	107/20 or 105/31	4672, 5090
4,6-Diethoxy-5-methyl	41	4672
4-Diethoxymethyl-1,6-dihydro-1-methyl-6-oxo	135–140	6069
4-Diethoxymethyl-2,6-dihydroxy	177	H, 6066
4-Diethoxymethyl-2,6-dihydroxy-5-hydroxymethyl	162–163	4528
2-Diethoxymethyl-4,6-dimethyl	78–80/0.1	5449
4-Diethoxymethyl-5-ethoxycarbonyl	111/0.1	4438
4-Diethoxymethyl-5-ethoxycarbonyl-2-methyl	95–96/0.1	4438
4-Diethoxymethyl-6-hydroxy	119–120	H, E, 6069
4-Diethoxymethyl-6-hydroxy-2-mercapto	158–160	H, E, 6066, 6069
4-Diethoxymethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	73–74	E, 6853
4,6-Diethoxy-5-nitro	62–63	E, 5491
4,6-Diethoxy-2-phenyl	41: 179/13	4672
4,6-Diethoxy-2-styryl	68–70	4949
2-Diethylamino	86–87/11; pic: 128	6073, 6172
4-Diethylamino	liq; pic: 149–150	4483, 6172
5-Diethylamino-2- <i>N,N</i> -diethylcarbamoylmethyl	liq; pic: 135–136	4483
4-Diethylamino-1,2-dihydro-1,6-dimethyl-2-oxo	liq; anal; nmr	5936
4-Diethylamino-2,6-dihydroxy	142–143	4888
5-Diethylamino-2,4-dihydroxy-6-methyl	239–241	5946
2-Diethylamino-4,6-diisopropyl	193–195	4769
2-Diethylamino-4,6-dimethyl	70/0.1; n _D ²⁰ : 1.4952	4562
4-Diethylamino-2,5-dimethyl	41; pic: 126	4562, 4669, 5883
	127/18; pic: 157	4478

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Diethylamino-2,6-dimethyl	110/4; pic: 147	H, E, 5267, 5883
2-Diethylamino-4,6-diphenyl	132	4562
2-Diethylamino-4,6-dipropyl	78/0.02	4562
4-Diethylamino-5-ethoxycarbonyl-6-methyl-2-propylamino	140-142/0.2	4470
4-Diethylamino-2-ethoxy-5-ethoxycarbonyl-6-methyl	132-135/0.2	4470
4- β -Diethylaminoethylamino-5-ethoxycarbonyl-2-methylthio	178	5885
5-Diethylamino-4-ethylamino-6-hydroxy	149-152	3475
1- β -Diethylaminoethyl-1,6-dihydro-6-oxo-2,4,5-triphenyl	146	5827
2-Diethylamino-5-ethyl-4-hydroxy-6-methyl	121-122	5722
4-Diethylamino-5-ethyl-6-hydroxy-2-phenyl	141	6072
2-Diethylamino-4-ethyl-6-methyl	55/0.02	4562
1- β -Diethylaminoethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	anal	5509
5-Diethylamino-1-ethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	110	4925
5-Diethylamino-1-ethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-1-phenyl	173-175/0.3	4925
2-Diethylamino-4-ethyl-6-trifluoromethyl	64/0.02; HClO ₄ : 178	4559
4-Diethylamino-5-fluoro-2-methylthio	42-43	5997
2-Diethylamino-4-hydroxy-6-methyl-5-methylsulfonyl	218	5391
2-Diethylamino-4-hydroxy-6-methyl-5-methylthio	137	5390
2-Diethylamino-4-hydroxy-6-methyl-5-propyl	114-115	5722
2-Diethylamino-4-isoamyl-6-trifluoromethyl	84/0.02	4559
2-Diethylamino-4-iso-butyl-6-methyl	65/0.2	4562
2-Diethylamino-4-iso-butyl-6-trifluoromethyl	75/0.01	4559
2-Diethylamino-4-iso-propyl-6-trifluoromethyl	52/0.2	4559
4-Diethylamino-5-methyl	pic: 110-112	4478
4-Diethylamino-5-methyl-2,6-bistrifluoromethyl	43/0.01	6285
4-Diethylamino-methyl-2,6-dihydroxy	310-312	5854
5-Diethylamino-methyl-2,4-dihydroxy-6-methyl	270	4593
5-Diethylamino-methyl-4-ethoxycarbonyl-2,6-dihydroxy	153-156	6193
5-Diethylamino-methyl-4-hydroxy-2-mercapto	196	4593
5-Diethylamino-methyl-4-hydroxy-2-mercapto-6-methyl	170-171	H, 4593

2-Diethylaminomethyl-4-hydroxy-5-phenyl	125–126	4344
2-Diethylamino-4-methyl-6-methylsulfonyloxy	47	5391
4-Diethylamino-6-methyl-2-methylthio	135/4	5267
2-Diethylamino-4-methyl-6-phenyl	pic: 222; HClO ₄ : 234	4562
4-Diethylamino-5-methyl-2-phenyl	45; pic: 235–236	4478
5-Diethylaminomethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	135	4932
2-Diethylamino-4-methyl-6-trifluoromethyl	41/0.02	4559
2-Diethylamino-5-nitro-4,6-diphenyl	175–177	6147
5-Diethylamino-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	121	4925
5-Diethylamino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	89	4925
1,5-Diethyl-1,6-dihydro-2,4-dimethoxy-6-oxo	86–87	5323
1,2-Diethyl-1,4-dihydro-4-oxo	108–111	5294
1,2-Diethyl-1,6-dihydro-6-oxo	anal	5294
4,5-Diethyl-2,6-dihydroxy	245	4716
1,3-Diethyl-4-ethylimino-1,2-dihydro-2-oxo	pic: 168–170	6071
1,3-Diethyl-5-formyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo	—	5904
1,3-Diethyl-5-formyl-1,2,3,4-tetrahydro-6-hydroxy-4-oxo-2-thio	—	5904
4,6-Diethyl-2-hydrazino	77–79	5691
4-β,β-Diethylhydrazino-2-ethylthio-5-fluoro	HCl: 118	4882
4-Diethylhydrazonomethyl-2,6-dihydroxy	228	6066
5-Diethylhydrazonomethyl-2,4-dihydroxy-6-methyl	229	6066
4-Diethylhydrazonomethyl-6-hydroxy-2-mercaptop	193	6066
4,6-Diethyl-2-hydroxy	HCl: 205–207	5691
4,6-Diethyl-2-methoxy	60/0.1	4467
2,4-Diethyl-6-methyl	125/100	5096
4,6-Diethyl-2-methyl	132–135/15	5096
4,6-Diethyl-2-methylthio	68/0.05	4467
2,4-Diethyl-6-phenyl	liq; nmr	6375
2- <i>N,N</i> -Diethylsulphamoyl-4,6-dimethyl	60	5669
1,3-Diethyl-1,2,3,4-tetrahydro-2,4-dioxo	—	H, 5328, 5331, 6071
1,3-Diethyl-1,2,3,4-tetrahydro-6-hydroxyamino-2,4-dioxo	112–113	5042
1,3-Diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo	52–53	H, 5321
1,3-Diethyl-1,2,3,4-tetrahydro-6-methoxy-2,4-dioxo	68–69	5321

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,3-Diethyl-1,2,3,4-tetrahydro-5-methyl-2,4-dioxo	56-57	H, 6070, 6071
1,3-Diethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo	50-53	H, E, 6401
1,3-Diethyl-1,2,3,4-tetrahydro-6- α -methylhydrazino-2,4-dioxo	102-104	6014
1,3-Diethyl-1,2,3,4-tetrahydro-6-phenyl-2,4-dithio	80	6188
4,6-Diethyl-2-ureido	190	6015
2,4-Difluoro	68-70/135	E, 4755
2,5-Difluoro	100-112/760 mm	5779
4,6-Difluoro	112-114/760 mm	E, 4752
2,4-Difluoro-5,6-bisheptafluoroisopropyl	148-150/760 mm	5645, 5922
2,5-Difluoro-4,6-bisheptafluoroisopropyl	147/760 mm	5242, 6066
4,6-Difluoro-2,5-bisheptafluoroisopropyl	148-149/760 mm	5250, 5291
2,5-Difluoro-4,6-bismethylamino	180-182	3521
2,4-Difluoro-5,6-bisnonafluoro-s-butyl	-	5645
2,4-Difluoro-5,6-bisnonafluoroethyl	129-130/760 mm	5268, 5922
2,5-Difluoro-4,6-di-iodo	185	5779
2,5-Difluoro-4,6-dimethoxy	106-108	3521
2,4-Difluoro-5,6-dimethyl	167/760 mm	3520
4,6-Difluoro-2,5-dimethyl	148-150/760 mm	3520
2,5-Difluoro-4-iodo-6-methoxy	109-110	5779
2,4-Difluoro-6-methoxy	crude	5770
4,6-Difluoro-2-methoxy	crude	5770
2,4-Difluoro-6-methoxy-5-trifluoromethyl	crude	5770
2,5-Difluoro-4-methoxy-6-trifluoromethyl	crude	5770
4,6-Difluoro-2-methoxy-5-trifluoromethyl	crude	5770
2,4-Difluoro-6-methyl	145/760 mm	E, 3520
4,6-Difluoro-2-methyl	120-122/760 mm	3520
4,6-Difluoro-5-methyl	132-134/760 mm	3520
5-Difluoromethyl-2,4-dihydroxy	285-300	E, 5631
4,6-Difluoro-2-phenyl	118-119	5866
4,6-Difluoro-5-phenyl	88-90	5860

2,4-Difluoro-6-propenyl-5-trifluoromethyl	crude	5770
2,5-Difluoro-4-propenyl-6-trifluoromethyl	crude	5770
4,5-Difluoro-6-propenyl-2-trifluoromethyl	crude	5770
4,6-Difluoro-2-propenyl-5-trifluoromethyl	crude	5770
5-γ,γ-Difluoropropyl-2,4-dihydroxy	256–258	4800
4,6-Diformyl	dioxime: 220	E, 5862
4,6-Diformyl-2-hydroxy	–	5278
4-Diformylmethyl	225–228 or 229	E, 5073, 5863
4-Diformylmethyl-6-dimethylamino-2-ethyl	181	5073
2-Diformylmethyl-4-dimethylamino-6-methyl	200–202	5073
4-Diformylmethyl-6-dimethylamino-2-methyl	215	5073
4-Diformylmethyl-2-hydroxy	253–255	5498
2-Diformylmethyl-4-phenyl	220	5073
4-Diformylmethyl-2-phenyl	158–160	5073
4-Diformylmethyl-6-phenyl	220	5073
4,6-Diformyl-2-phenyl	133–135	6136
2,4-Dihex-1'-ynyl-6-methyl	173/3	5093, 5094
4,6-Dihex-1'-ynyl-2-methyl	160/2	5093, 5094
2,4-Dihydrazino	216	H, 5848
2,4-Dihydrazino-5-methyl	200–201	5848
2,4-Dihydrazino-6-methyl	208–210 or 212	H, E, 5355, 5848
2,4-Dihydrazino-6-methyl-5-nitro	198	5660
4,6-Dihydrazino-2-methyl-5-nitro	sp	E, 2562
1,6-Dihydro-2,4-dimethoxy-1-methyl-6-oxo	85–94	5321
1,4-Dihydro-1,6-dimethyl-2-N-methylacetamido-4-oxo	196	4573
1,6-Dihydro-1,4-dimethyl-2-N-methylacetamido-6-oxo	129–130	4573
1,2-Dihydro-1,5-dimethyl-4-methylamino-2-oxo	177–179	5811
1,4-Dihydro-1,6-dimethyl-2-methylamino-4-oxo	241–242	4569
1,6-Dihydro-1,4-dimethyl-2-methylamino-6-oxo	213–214	4573
1,6-Dihydro-1,4-dimethyl-6-methylene-2-phenyl	48–53; 140/0.1	5706
1,6-Dihydro-1,2-dimethyl-4-methylsulfonyl-6-oxo	151–152	3505
1,2-Dihydro-1,5-dimethyl-4-methylthio-2-oxo	104–106	H, 4385
1,2-Dihydro-1,6-dimethyl-4-methylthio-2-oxo	173	H, 4569
1,4-Dihydro-1,6-dimethyl-2-methylthio-4-oxo	221–225; HI: 212	E, 4567

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,6-Dihydro-1,4-dimethyl-2-methylthio-6-oxo	89-90	H, E, 5910
1,2-Dihydro-1,4-dimethyl-2-oxo	157; 3-MeHSO ₄ ; 159	E, 2602, 5266, 5324, 6404
1,2-Dihydro-1,5-dimethyl-2-oxo	132-134; HCl: > 230	2630, 4385
1,2-Dihydro-1,6-dimethyl-2-oxo	HCl: 229	E, 2602
1,4-Dihydro-1,2-dimethyl-4-oxo	182 or 190; HI: 118	H, 4449 (?), 5099, 5294
1,4-Dihydro-1,5-dimethyl-4-oxo	140-141	2630
1,6-Dihydro-1,2-dimethyl-6-oxo	63-65	H, E, 4449 (?), 5294
1,6-Dihydro-1,4-dimethyl-6-oxo	82	H, 2630
1,6-dihydro-1,5-dimethyl-6-oxo	59	2630
1,2-Dihydro-1,4-dimethyl-2-oxo-6-phenyl	181-182 or 185	5152, 5951, 6388
1,2-Dihydro-1,6-dimethyl-2-oxo-4-phenyl	180-182	5152
1,2-Dihydro-4,6-dimethyl-2-oxo-1-phenyl	245-246	4392, 5951
1,6-Dihydro-1,4-dimethyl-6-oxo-2-phenyl	85 to 92	H, 4484, 4510, 4930
1,2-Dihydro-1,5-dimethyl-2-oxo-4-semicarbazido	< 360	4735
1,2-Dihydro-1,4-dimethyl-6-phenyl-2-phenylimino	HClO ₄ : 255	6388
1,2-Dihydro-4,6-dimethyl-1-phenyl-2-phenylimino	148-149	6528
1,2-Dihydro-4,6-dimethyl-1-phenyl-2-thio	209	6459
1,2-Dihydro-1,4-dimethyl-2-thio	3-MeHSO ₄ : 156	5266
1,4-Dihydro-1,2-dimethyl-4-thio	244-246 (?)	4449
1,6-Dihydro-1,2-dimethyl-6-thio	108-109	4449
1,4-Dihydro-1,5-diphenyl-4-phenylimino	163-164; HClO ₄ : 278	4556
1,4-Dihydro-2,5-diphenyl-1-propyl-4-thio	206-208	5572
1,4-Dihydro-2-hydroxyamino-4-imino-1-methyl	HI: 258	4490
4,5-Dihydro-6-hydroxy-5,5-dimethyl-4-methylene-2-methylthio	108-109	5280
1,2-Dihydro-1-β-hydroxyethyl-4,6-dimethyl-2-oxo	122-123	5815
1,4-Dihydro-1-β-hydroxyethyl-2,5-diphenyl-4-thio	221-223	5572
1,4-Dihydro-1-β-hydroxyethyl-2-imino	HBr: 186; pic: 164	2633, 6259
1,6-Dihydro-1-β-hydroxyethyl-6-imino-4-methoxy	HBr: 122-124	6259

1,4-Dihydro-1- β -hydroxyethyl-2-methoxy-5-methyl-4-oxo	128–130	6077
1,2-Dihydro-1- β -hydroxyethyl-2-oxo	138–139	6068
1,6-Dihydro-1- β -hydroxyethyl-6-oxo-2,4,5-triphenyl	235–237	5827
1,2-Dihydro-4- <i>N</i> -hydroxy- <i>N</i> -methyldamino-1-methyl-2-oxo	173–175	5313
1,4-Dihydro-6-hydroxymethyl-1-methyl-2-methylthio-4-oxo	237–238	5175
1,6-Dihydro-4-hydroxymethyl-1-methyl-6-oxo	118	4933
1,6-Dihydro-4-hydroxymethyl-6-oxo-1-phenyl	201	4933
1,2-Dihydro-1- β -hydroxypropyl-4,6-dimethyl-2-oxo	122–123	5815
1,6-Dihydro-6-imino-4,5-di-isopropyl-1-methyl	HI: 252	5679
1,6-Dihydro-6-imino-2,4-dimethoxy-1-methoxycarbonylmethyl	HBr: —	5996
1,2-Dihydro-2-imino-1,4-dimethyl	pic: 204	E, 2602
1,2-Dihydro-2-imino-1,6-dimethyl	HI: 220	5662
1,4-Dihydro-4-imino-1,2-dimethyl	HI: 248	4449
1,6-Dihydro-6-imino-1,2-dimethyl	HI: 246	5679
1,6-Dihydro-6-imino-1,4-dimethyl	HI: 216	5679
1,6-Dihydro-6-imino-1,5-dimethyl	HI: 224	5679
1,2-Dihydro-2-imino-4,6-dimethyl-1-prop-2'-ynyl	HBr: 203	2700
1,2-Dihydro-2-imino-5-iodo-1-methyl	pic: 204–205	E, 2633
1,2-Dihydro-2-imino-1-isopropyl	pic: 182–183	2633
1,6-Dihydro-6-imino-2-isopropyl-1-methyl	HI: 204	5679
1,6-Dihydro-6-imino-4-isopropyl-1-methyl	HI: 216	5679
1,6-Dihydro-6-imino-5-isopropyl-1-methyl	HI: 222	5679
1,2-Dihydro-2-imino-1-isopropyl-4-phenyl	146–148/0.7	4679
1,2-Dihydro-2-imino-1-methoxycarbonylmethyl	HBr: > 280	4764
1,6-Dihydro-6-imino-4-methoxy-1-methoxycarbonylmethyl	HBr: —	5996
1,2-Dihydro-2-imino-5-methoxy-1-methyl	HI: 190	5662
1,2-Dihydro-2-imino-1-methoxy-4-phenyl	HClO ₄ : 183	6342
1,2-Dihydro-2-imino-1-methyl	HCl: 278	H, E, 4904
1,4-Dihydro-4-imino-1-methyl	HCl: 207	H, E, 5665
1,6-Dihydro-6-imino-1-methyl	HI: 218–220	5665, 5679
1,4-Dihydro-4-imino-1-methyl-2-methylamino	HI: 231	4490
1,4-Dihydro-4-imino-1-methyl-2-methylthio	HI: 225	E, 5061
1,6-Dihydro-6-imino-1-methyl-2-methylthio	57; HI: 231	5665
1,2-Dihydro-2-imino-1-methyl-5-phenyl	HI: 262	5663

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,4-Dihydro-4-imino-1-methyl-2-phenyl	HI: 234	4449
1,4-Dihydro-4-imino-1-methyl-5-phenyl	148–149; MeHSO ₄ : 148	4590, 4594, 5914
1,4-Dihydro-4-imino-1-methyl-2-thiocyanato	HBr: 185	4490
1,2-Dihydro-2-imino-1-propyl	HI: 163; HBr: 147	E, 2633
1,2-Dihydro-2-imino-1-prop-2'-ynyl	HBr: 195	E, 2700
1,6-Dihydro-6-imino-1,2,4,5-tetramethyl	HI: 249	5679
1,6-Dihydro-6-imino-1,2,4,5-tetraphenyl	256	4589
1,2-Dihydro-2-imino-1,4,6-trimethyl	—	E, 5662
1,6-Dihydro-6-imino-1,2,4-trimethyl	HI: 246	5679
1,6-Dihydro-6-imino-1,2,5-trimethyl	HI: 244	5679
1,6-Dihydro-6-imino-1,4,5-trimethyl	HI: 244	5679
1,2-Dihydro-2-imino-1,4,6-trimethyl-5-phenyl	HI: 225	5662
1,2-Dihydro-2-imino-1,4,6-trimethyl-5-propyl	HI: 191; pic: 197	2700
1,2-Dihydro-2-imino-1,4,6-trimethyl-5-prop-1'-ynyl	HCl: 257; HI: 224	2700
1,2-Dihydro-2-imino-1,4,6-trimethyl-5-prop-2'-ynyl	HI: 195–196	2700
1,6-Dihydro-6-imino-2,4,5-triphenyl-1-propyl	167	4589
1,2-Dihydro-1-isobutyl-2-oxo	84–85	2630
1,2-Dihydro-4-isopropoxy-1-isopropyl-2-oxo-6-trifluoromethyl	sp.	5589
1,6-Dihydro-2-isopropoxy-1-isopropyl-6-oxo-4-trifluoromethyl	<i>n</i> _D ²⁰ 1.4450	5589
1,2-Dihydro-4-isopropoxy-1-methyl-2-oxo	83–85	4437, 4847
1,2-Dihydro-4-isopropoxy-6-methyl-2-oxo-1-phenyl	90 to 95	4773, 4847, 4859, 5910
1,4-Dihydro-2-isopropoxy-6-methyl-4-oxo-1-phenyl	127–129	4773, 4859
1,2-Dihydro-1-isopropyl-2-oxo	MeHSO ₄ : 137	5324
1,2-Dihydro-1-isopropyl-2-oxo-4,5-diphenyl	138–140	6079
1,2-Dihydro-1-isopropyl-2-oxo-5-phenyl	120–122	6079
1,2-Dihydro-5-isopropyl-1-phenyl-2-phenylimino	82–83	4464
1,2-Dihydro-4-methoxyamino-1-methyl-2-oxo	127	5313
1,2-Dihydro-4-methoxycarbonyl-1-methyl-2-oxo	241–245	5414
1,2-Dihydro-5-methoxycarbonyl-1-methyl-2-oxo	204; HBr: 186	5430

1,2-Dihydro-5-methoxycarbonyl-2-oxo-1-phenyl	HB α : 176–177	5430
1,2-Dihydro-4-methoxy-1,5-dimethyl-2-oxo	144	H, 5490
1,2-Dihydro-4-methoxy-1,6-dimethyl-2-oxo	139–140	H, 4387
1,4-Dihydro-5-methoxy-1,2-dimethyl-4-oxo	214; HI: 211	5099
1,6-Dihydro-2-methoxy-1,5-dimethyl-6-oxo	106–108	5493
1,6-Dihydro-4-methoxy-1,2-dimethyl-6-oxo	84–85; HCl: 175	E, 3768
1,6-Dihydro-4-methoxy-1,5-dimethyl-6-oxo	89–90	E, 3768
1,6-Dihydro-5-methoxy-1,2-dimethyl-6-oxo	113	5099
1,2-Dihydro-4- <i>N</i> -methoxy- <i>N</i> -methylamino-1-methyl-2-oxo	96	5313
1,2-Dihydro-4-methoxy-1-methyl-6-nitroamino-2-oxo	178–179	4656
1,2-Dihydro-4-methoxy-1-methyl-5-nitro-6-oxo	149	4922
1,6-Dihydro-4-methoxy-1-methyl-5-nitro-6-oxo-2-phenyl	200	4922
1,2-Dihydro-4-methoxy-1-methyl-2-oxo	140 or 149–150	H, E, 4437, 5058, 5490
1,4-Dihydro-6-methoxy-1-methyl-4-oxo	—	E, 3001, 3055
1,6-Dihydro-2-methoxy-1-methyl-6-oxo	93–95	5493
1,6-Dihydro-4-methoxy-1-methyl-6-oxo	145; 3-Mel: 135	E, 3768
1,6-Dihydro-4-methoxy-1-methyl-6-oxo-5-phenyl	104–105	E, 3768
1,2-Dihydro-4-methoxy-1-methylsulfonyl-2-oxo	172–175	3465
1,2-Dihydro-1-methoxy-2-oxo	HCl: 145	4583
1,6-Dihydro-1- γ -methoxypropyl-4-methylthio-6-oxo	57–59	4806
1,2-Dihydro-4-methyl-1,6-diphenyl-2-phenylimino	179–180	6528
1,2-Dihydro-6-methyl-1,4-diphenyl-2-phenylimino	150–152	6528
1,2-Dihydro-1-methyl-4,6-diphenyl-2-thio	205–207	6459
1,2-Dihydro-4-methyl-1,6-diphenyl-2-thio	217	6085
1,2-Dihydro-6-methyl-1,4-diphenyl-2-thio	210–211 or 215	6403, 6459
1,4-Dihydro-1-methyl-2,5-diphenyl-4-thio	214–216	5572
1,6-Dihydro-1-methyl-2-methylamino-6-methylimino	HI: 255	5665
1,2-Dihydro-1-methyl-4-methylamino-2-oxo	183; HI: 233; 3- <i>N</i> -Ox: > 300	H, E, 5313, 5613, 6026, 6098, 6099
1,2-Dihydro-1-methyl-6-methylamino-2-oxo	HI: 274	E, 6554
1,4-Dihydro-1-methyl-2-methylamino-4-oxo	200–201	5600
1,6-Dihydro-1-methyl-2-methylamino-6-oxo	101–102	5600
1,6-Dihydro-1-methyl-4-methylamino-6-oxo	—	E, 5344

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,2-Dihydro-1-methyl-4- α -methylhydrazino-2-oxo	189	5313
1,4-Dihydro-1-methyl-4-methylimino-2-methylthio	HI: 184	5665
1,6-Dihydro-1-methyl-6-methylimino-2-methylthio	HI: 198	5665
1,2-Dihydro-1-methyl-6-methylthio-2-oxo	142; HI: 191; Mel: 219	5665, 6554
1,4-Dihydro-1-methyl-2-methylthio-4-oxo	181-183	H, 5418
1,6-Dihydro-1-methyl-2-methylthio-6-oxo	123 to 127	H, 5665, 6111, 6176, 6554
1,6-Dihydro-1-methyl-4-methylthio-6-oxo	169-171	E, 4806
1,4-Dihydro-6-methyl-2-methylthio-4-oxo-1-phenyl	222	4930
1,6-Dihydro-4-methyl-2-methylthio-6-oxo-1-phenyl	145 or 150	H, 4930, 5923, 6246
1,4-Dihydro-1-methyl-2-methylthio-4-oxo-6-propyl	40-42	5532
1,2-Dihydro-5-methyl-4-methylthio-2-oxo-1-vinyl	154-156	4534
1,2-Dihydro-1-methyl-4-methylthio-2-thio	150	5058
1,2-Dihydro-1-methyl-6-methylthio-2-thio	125; Mel: 146	5665, 6554
1,4-Dihydro-1-methyl-2-methylthio-4-thio	148	5665
1,6-Dihydro-1-methyl-2-methylthio-6-thio	128 or 138	5665, 6554
1,2-Dihydro-1-methyl-5-nitro-2-oxo	169-170	E, 6124
1,6-Dihydro-1-methyl-5-nitro-6-oxo	101-102	2630
1,2-Dihydro-1-methyl-2-oxo	130-132; 3-Mel: 234	H, E, 4385, 5266, 5324, 5326, 5343
1,4-Dihydro-1-methyl-4-oxo	155-156	H, E, 5294
1,6-Dihydro-1-methyl-6-oxo	122 or 125; 3-EtBF ₄ : 102	H, E, 4692, 5294, 5665
1,2-Dihydro-1-methyl-2-oxo-4,5-diphenyl	133-136	6079
1,2-Dihydro-1-methyl-2-oxo-4,6-diphenyl	170-175	6095
1,2-Dihydro-4-methyl-2-oxo-1,6-diphenyl	151	5951, 6085
1,2-Dihydro-6-methyl-2-oxo-1,4-diphenyl	222	5951, 6085
1,6-Dihydro-4-methyl-6-oxo-1,2-diphenyl	240	6246
1,2-Dihydro-1-methyl-2-oxo-5-phenyl	188-189	H, 5266, 5635, 6079
1,4-Dihydro-1-methyl-4-oxo-5-phenyl	172 or 175	H, 4594, 5635, 5914

1,4-Dihydro-6-methyl-4-oxo-1-phenyl	176-179	4930
1,6-Dihydro-1-methyl-6-oxo-2-phenyl	154-155	4449
1,6-Dihydro-1-methyl-6-oxo-4-phenyl	201 or 204-206	E, 5918, 6175
1,6-Dihydro-1-methyl-6-oxo-5-phenyl	110	H, 5635
1,6-Dihydro-2-methyl-6-oxo-1-phenyl	210-211	6246
1,6-Dihydro-4-methyl-6-oxo-1-phenyl	139-140	4930
1,2-Dihydro-4-methyl-2-oxo-1-phenyl-6-propyl	126-127	5152
1,2-Dihydro-6-methyl-2-oxo-1-phenyl-4-propyl	165-166	5152
1,6-Dihydro-4-methyl-6-oxo-2-phenyl-1-propyl	56-59; pic: 182	4484, 4510
1,6-Dihydro-1-methyl-6-oxo-4-piperidino	166-168	6094
1,2-Dihydro-1-methyl-2-oxo-4-semicarbazido	172-173	4735
1,2-Dihydro-1-methyl-2-oxo-4-sulfeno	sp; Ag; anal	5454
1,2-Dihydro-1-methyl-2-oxo-4-sulfo	K: 248-252	5160, 6098, 6099
1,2-Dihydro-1-methyl-2-oxo-4-thiocyanato	145-146 or 149	5506, 6206
1,6-Dihydro-1-methyl-6-oxo-2-trifluoromethyl	anal	5294
1,2-Dihydro-5-methyl-2-oxo-1,4,6-triphenyl	213-215	5764
1,6-Dihydro-1-methyl-6-oxo-2,4,5-triphenyl	230	5827
1,2-Dihydro-5-methyl-1-phenyl-2-phenylimino	165	4464
1,2-Dihydro-4-methyl-1-phenyl-2-phenylimino-6-propyl	88-89	6528
1,2-Dihydro-1-methyl-5-phenyl-2-thio	3-MeClO ₄ : 288	5266
1,6-Dihydro-1-methyl-2-phenyl-6-thio	112	4449
1,2-Dihydro-1-methyl-2-thio	3-MeBr: 201	E, 5266
1,4-Dihydro-1-methyl-4-thio	235-236	E, 4838
1,6-Dihydro-1-methyl-6-thio	98-99	E, 4838
1,6-Dihydro-4-methylthio-6-oxo-1-phenyl	118-120	4806
1,6-Dihydro-4-methylthio-6-oxo-1-propyl	79	4806
1,2-Dihydro-4-methylthio-2-oxo-1-vinyl	145-146	4534
1,2-Dihydro-5-methyl-1,4,6-triphenyl-2-thio	298-299	5764, 6403
1,2-Dihydro-2-oxo-1-phenyl	155-156; Mel: 132	2630, 5324, 6170
1,6-Dihydro-6-oxo-1,2,4,5-tetraphenyl	295-296	4589, 5259
1,2-Dihydro-2-oxo-1,4,6-triphenyl	246-247	5764
1,6-Dihydro-6-oxo-2,4,5-triphenyl-1-propyl	168	4589
1,2-Dihydro-1-phenyl-2-phenylimino-5-propyl	106-108	4464
1,2-Dihydro-1,4,5,6-tetramethyl-2-oxo	88-89	6325

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,2-Dihydro-1,4,6-trimethyl-2-oxo	MeHSO ₄ : 147	H, E, 5266, 6404
1,4-Dihydro-1,2,5-trimethyl-4-oxo	175–176; HI: 114	5099
1,6-Dihydro-1,2,4-trimethyl-6-oxo	53–54	H, E, 5910
1,6-Dihydro-1,2,5-trimethyl-6-oxo	150–157/32	E, 5099
1,2-Dihydro-1,4,6-trimethyl-2-oxo-5-sulfo	221–223	6100
1,2-Dihydro-1,4,6-trimethyl-2-phenylimino	HClO ₄ : 195	6388
1,2-Dihydro-1,4,5-trimethyl-2-thio	3-MeHSO ₄ : 198	5266
1,2-Dihydro-1,4,6-trimethyl-2-thio	157	H, 6459
1,2-Dihydro-1,4,6-triphenyl-2-thio	202–203	6459
2,5-Dihydroxy	> 300	E, 3000, 4384
4,5-Dihydroxy	300: HCl: > 270	H, E, 5873
4,6-Dihydroxy	HCl: > 225	H, E, 3768, 4693, 4722
2,4-Dihydroxy-5,6-bismethylamino	247; HCl: 259	H, 6096
2,4-Dihydroxy-5,6-bismethylsulfonylmethyl	288–289	5603
2,4-Dihydroxy-5,6-bismethylthiomethyl	193–195	5603
5-2',3'-Dihydroxycyclopentyl-2,4-dihydroxy	296–298	3762
5-2',3'-Dihydroxycyclopentyl-2,4-dihydroxy-6-methyl	232–237	3762
5-2',3'-Dihydroxycyclopentyl-2-hydroxy-4-methylthio	256–257	3762
2,4-Dihydroxy-5,6-diiodo	269–270	4650
2,4-Dihydroxy-5,6-dimethyl	299 to 306	H, E, 4387, 4716, 4718, 4725
2,5-Dihydroxy-4,6-dimethyl	> 300	H, E, 6373
4,6-Dihydroxy-2,5-diphenyl	> 300	4497
4- α , β -Dihydroxyethyl-2,6-dihydroxy	215–217	4604
4- α , β -Dihydroxyethyl-6-hydroxy-2-mercaptop	220–221	4604
4- α , β -Dihydroxyethyl-6-hydroxy-2-methylthio	149–150	4604
2,4-Dihydroxy-5- β -hydroxyamyl	271–272	5478
2,4-Dihydroxy-5,4'-hydroxybut-1'-enyl	<i>cis</i> : 245–246; <i>trans</i> : 239–241	5429
2,4-Dihydroxy-5- β -hydroxybutyl	266–267	5478

2,4-Dihydroxy-5- β -hydroxyethyl	264–265	5427, 5849
4,6-Dihydroxy-5- β -hydroxyethyl	239–240	H, 2638
4,6-Dihydroxy-5- β -hydroxyethyl-2-mercaptop	196–197	H, 2638
2,4-Dihydroxy-5- β -hydroxyethyl-6-methyl	263–265	E, 5361
4,6-Dihydroxy-5- β -hydroxyethyl-2-methylthio	218–220	2638
2,4-Dihydroxy-6-hydroxyiminomethyl	—	5868
2,4-Dihydroxy-6-hydroxymethyl	254 or 260–261	H, 5175, 5366, 5868
2,4-Dihydroxy-5- α -hydroxy- δ -methylamyl	> 250	5592
2,4-Dihydroxy-5-3'-hydroxymethylcyclopentyl	<i>cis</i> : 274–275	5431
2,4-Dihydroxy-5- α -hydroxy- β -methylpropyl	> 200	5592
2,4-Dihydroxy-5- β -hydroxypropyl	258–260	5478
2,4-Dihydroxy-5-hydroxysulfonyloxy	K: anal.	5507
2,4-Dihydroxy-5-iodo	1- <i>N</i> -Ox: 210; 3- <i>N</i> -Ox: 235	H, E, 3464
2,4-Dihydroxy-6-iodo	280	E, 5673
2,4-Dihydroxy-5- β -iodoethyl	265	5427
2,4-Dihydroxy-5-iodo-6-methyl	263–265	E, 5957
2,4-Dihydroxy-5-isobutyl	296–298	5592
2,4-Dihydroxy-6-isobutyl-5-isopropyl	241–242	5890
2,4-Dihydroxy-5-isobutylthio	267–268	5168
2,4-Dihydroxy-5-isobutylthio-6-methyl	226–227	5168
2,4-Dihydroxy-5-isocyanato	318	5895
2,4-Dihydroxy-5- β -isocyanatoethyl-6-methyl	240–244	5707
2,4-Dihydroxy-5-isohexyl	271–273	5592
2,4-Dihydroxy-5-isopropyl	284 to 290	H, 5592, 5875, 5964
4,6-Dihydroxy-2-isopropyl	313–315	E, 5690
4,6-Dihydroxy-2-isopropylamino	—	6327
2,4-Dihydroxy-6-isopropylamino-5-nitro	291–293	4627
2,4-Dihydroxy-5-isopropyl-6-methyl	289–292	5890, 5894
2,4-Dihydroxy-6-isopropyl-5-methyl	250–251	5890
2,4-Dihydroxy-5-isothiocyanato	> 300	6097
2,4-Dihydroxy-5-mercaptopmethyl	270	E, 5641
4,5-Dihydroxy-2-mercaptop-6-propyl	249–252	5532
2,4-Dihydroxy-6-methoxy	259 or 264–269	4742, 5321
4,6-Dihydroxy-5-methoxy	—	E, 5828

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,4-Dihydroxy-5-methoxycarbonyl	253–256	H, 6277
2,4-Dihydroxy-6-methoxycarbonyl-5-methoxymethyl	174	6193
2,4-Dihydroxy-5-methoxycarbonylmethyl	236–237	5973
2,4-Dihydroxy-6-methoxycarbonyl-5-propylthiomethyl	215–217	6193
2,4-Dihydroxy-6-methoxycarbonyl-5-trimethylsilylethynyl	170–173	6153
2,4-Dihydroxy-6-methoxycarbonyl-5-methyl	242	6193
2,4-Dihydroxy-6-methoxycarbonylmethyl	—	H, 6101
2,4-Dihydroxy-5- β -methoxycarbonylvinyl	288–289	5427, 5473
2,4-Dihydroxy-5- β -methoxycarbonylvinyl-6-methyl	305–307	5643
4,6-Dihydroxy-5-methoxy-2-methoxymethyl	213–214	3911
2,4-Dihydroxy-5-methoxymethyl	203–204	E, 6104
2,4-Dihydroxy-5-methoxy-6-methyl	240–241	3497
2,4-Dihydroxy-5-methyl	314 to 326	H, E, 4338, 4856, 5569, 5754, 5915
2,4-Dihydroxy-6-methyl	300 to 325	H, E, 4470, 4569, 4718, 4787, 4849, 4855, 4857, 5070, 5121, 5513, 5734, 6157, 6194, 6590
4,5-Dihydroxy-2-methyl	280	H, E, 5099, 5958
4,5-Dihydroxy-6-methyl	230–231	5049
4,6-Dihydroxy-5-methyl	> 330	H, E, 3768, 4393
2,4-Dihydroxy-5-methylamino	—	H, E, 6062
2,4-Dihydroxy-5-methylaminomethyl	HCl: 230–232	6102
2,4-Dihydroxy-6-methylamino-5-methylformamido	1-N-Ox: 242–249	H, 5424
4,6-Dihydroxy-2-methylamino-5-methylthio	> 250	6061
2,4-Dihydroxy-5-methylamino-6-phenylazo	—	5060
2,4-Dihydroxy-6-methyl-5-methylamino	298–305	5168
2,4-Dihydroxy-6-methyl-5-nitro	290	H, E, 5660, 5685, 5894

4,6-Dihydroxy-2-methyl-5-pent-4'-enyl	> 200	5290
2,4-Dihydroxy-5-methyl-6-phenyl	241–243	5022
4,6-Dihydroxy-5-methyl-2-phenyl	<i>N</i> -Ox: 260	E, 4916
2,4-Dihydroxy-6-methyl-5-phenylazo	256–257	H, 5874
2,4-Dihydroxy-6-β-methyl-β-phenylhydrazino	> 300	5458
2,4-Dihydroxy-6-methyl-5-piperidino	245–248	2880
2,4-Dihydroxy-6-methyl-5-propylthio	229–231	5168
2,4-Dihydroxy-5-methylsulfinyl	237	E, 3765, 5167
2,4-Dihydroxy-5-methylsulfonyl	> 300 or 309	3765, 5167
2,4-Dihydroxy-5-β-methylsulfonyloxethyl	180–182	5427
2,4-Dihydroxy-5-methylthio	> 300 or 308	E, 3765, 5142, 5167, 5168, 5728
2,4-Dihydroxy-6-methylthio	328–330	5445, 5536
4,6-Dihydroxy-2-methylthio	> 300	H, E, 5866
2,4-Dihydroxy-5-nitro	> 300	H, E, 5516
4,6-Dihydroxy-5-nitro	> 300	H, E, 5619
2,4-Dihydroxy-5-nitroamino	> 330	4656
2,4-Dihydroxy-5-nitro-6-phenyl	280	5441
2,4-Dihydroxy-5-nitro-6-propyl	226–227	2655
4,6-Dihydroxy-5-nitro-2-propyl	301–302	4570
2,4-Dihydroxy-5-nitro-6-propylamino	274–275	5576
2,4-Dihydroxy-5-β, γ, γ, γ-pentafluoropropyl	260–262	4800
5-δ, ε-Dihydroxypentyl-2,4-dihydroxy	217–220	5548
2,4-Dihydroxy-6-pentylidenehydrazino	210–212	5968
2,4-Dihydroxy-6-phenoxy	302–304	5877
2,4-Dihydroxy-5-phenyl	> 350	H, 5861
4,5-Dihydroxy-2-phenyl	216–218	E, 5800
4,6-Dihydroxy-5-phenyl	> 300 or 375	H, E, 3768, 5882
2,4-Dihydroxy-5-phenylhydrazino	<i>anti</i> : 252; <i>syn</i> : 243	H, 6103
2,4-Dihydroxy-6-β-phenylhydrazino	> 330	E, 5458
2,4-Dihydroxy-5-phenyliodonio	Cl: 273; Br: 267	4843
2,4-Dihydroxy-6-phenyl-5-phenylazo	230–233 or 234	E, 5874, 6067
2,4-Dihydroxy-5-phenylseleno	256–258	5168
2,4-Dihydroxy-5-phenylseleninyl	170 then 205	5168

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,4-Dihydroxy-6-phenylsulfonyl	277–279	E, 5877
2,4-Dihydroxy-5-phenylthio	271–272	5168
2,4-Dihydroxy-6-phenylthio	270–272 or 275	5877, 6112
2,4-Dihydroxy-6-piperidino	> 280	E, 5946
2,4-Dihydroxy-6-piperidinomethyl	294–300	5854
2,4-Dihydroxy-6-prop-1'-enylidenehydrazino	249–250	5968
2,4-Dihydroxy-6- β -propionylhydrazino	257–258	4721
2,4-Dihydroxy-5-propoxymethyl	221–222	6104
2,4-Dihydroxy-5-propyl	292 or 294	4718, 5754
2,4-Dihydroxy-6-propyl	219–221; 3-N-Ox: 179	H, E, 5350, 5532
4,6-Dihydroxy-2-propyl	309–310	H, E, 4570
4,6-Dihydroxy-5-propyl	> 300	5882
1- β - γ -Dihydroxypropyl-1,2-dihydro-2-oxo	pic: 130–132	6068
5- β , γ -Dihydroxypropyl-2,4-dihydroxy	251–253	5478
1- β , γ -Dihydroxypropyl-4-ethoxy-1,2-dihydro-2-oxo	112–113	5023
2,4-Dihydroxy-5-propylthio	261	E, 5168
2,4-Dihydroxy-6-(propylthio)carbonyl	208–209	5464
2,4-Dihydroxy-5-prop-2'-ynylthio	215–217	5893
2,4-Dihydroxy-6-sulfamoyl	—	5734
2,4-Dihydroxy-6- β -sulfoethyl	Na: 318–321	5403
2,4-Dihydroxy- β , γ , γ -tetrafluoropropyl	261–263	4800
4,6-Dihydroxy-2-trichloromethyl	220	5785
2,4-Dihydroxy-5-trifluoromethyl	247–249	E, 4552, 5631
2,4-Dihydroxy-5- γ , γ -trifluoropropyl	266–269	4800
2,4-Dihydroxy-5-trimethylsilylethynyl	275–276	6349
2,4-Dihydroxy-6-ureidomethyl	—	5868
2,4-Dihydroxy-5-vinyl	> 230	5427, 5428, 6043
2,4-Dihydroxy-6-vinyl	> 350	5403
4,5-Di-iodo-2-isopropyl-6-methyl	78–79	5655
4,6-Di-iodo-2-methyl	195–197	5094

4-Di-isobutylamino-5-methyl	—	5796
2,4-Di-isobutyl-6-methyl	—	6108
4,5-Di-isobutyramido-6-hydroxy	239–240	5447
2,4-Di-isopropoxy-5-methyl	76/0.3; 1-MeI: 81	5061
2,4-Di-isopropoxy-6-methyl	132–134/25	H, 4387
2,4-Di-isopropoxy-6-trifluoromethyl	nd ²⁵ 1.4328	5589
2,4-Di-isopropyl-6-methyl	—	6108
4,5-Di-isopropyl-6-methylamino	130	5679
2- <i>N,N</i> -Di-isopropylsulfamoyl-4,6-dimethyl	235	5669
2,4-Dimercapto	> 265 or 300	H, E, 2590, 2915, 4842, 6062
2,4-Dimercapto-5,6-dimethyl	—	H, 2590
2,5-Dimercapto-4,6-diphenyl	95	6387
2,4-Dimercapto-5-methyl	—	H, E, 2590
2,4-Dimercapto-6-methyl	> 290	H, E, 5697
4,6-Dimercapto-2-methyl	> 300	6374
2,4-Dimercapto-5-nitro	—	H, E, 2590
4,6-Dimercapto-5-nitro	> 300	6374
2,4-Dimethoxy	18; 202/at	H, E, 5490, 5622
2,5-Dimethoxy	70–71	3000, 4399
4,6-Dimethoxy	36–40/0.2	E, 5323
4,6-Dimethoxycarbonyl	81–82	5652
4,5-Dimethoxycarbonyl-2,6-diphenyl	126–127	5972
4,6-Dimethoxycarbonyl-2-methyl	150–152	5652
4,6-Dimethoxycarbonyl-2-phenyl	163–164	5652
2,4-Dimethoxy-5-methoxycarbonyl	96–97	2599
4,6-Dimethoxy-2-methoxycarbonylmethyl	100–104/0.5	5693
4,5-Dimethoxy-6-methoxycarbonyl-2-phenyl	64–65	5800
2,4-Dimethoxy-6-methoxycarbonyl-5-trimethylsilylethynyl	57–58	6153
4-Dimethoxymethyl	45–50/0.2	4448
2,4-Dimethoxy-5-methyl	60–61	H, 5490, 5622
2,4-Dimethoxy-6-methyl	—	H, E, 5050
4,5-Dimethoxy-2-methyl	54	E, 5099
4,6-Dimethoxy-2-methyl	53; EtBF ₄ : 174	E, 3768, 4692

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4,6-Dimethoxy-5-methyl	87	E, 3768
4-Dimethoxymethyl-2,6-dihydroxy	182-183	5743
5-Dimethoxymethyl-2,4-dihydroxy	194-195 or 200	5472, 5642
2-Dimethoxymethyl-4,6-dimethyl	118-120/7	6008
2-Dimethoxymethyl-4,6-diphenyl	85-88	4875
4-Dimethoxymethyl-2-ethylthio-5-fluoro-6-hydroxy	105-106	5525
4-Dimethoxymethyl-2-ethylthio-6-hydroxy	121-122	5743
4-Dimethoxymethyl-5-fluoro-2,6-dihydroxy	215-216	5525
4-Dimethoxymethyl-5-fluoro-6-hydroxy-2-mercapto	201-202	5525
4-Dimethoxymethyl-5-fluoro-6-hydroxy-2-methylthio	135-137	5525
4-Dimethoxymethyl-5-fluoro-6-hydroxy-2-propylthio	77-79	5525
4-Dimethoxymethyl-5-hexyl-6-hydroxy-2-mercapto	99-100	5526
4-Dimethoxymethyl-6-hydroxy-2-methylthio	154-155	5743
2,4-Dimethoxy-6-methyl-5-nitro	sp	H, E, 5660
4,6-Dimethoxy-2-methyl-5-nitro	123-124	H, E, 5491
4-Dimethoxymethyl-6-phenyl	3-N-Ox: nmr	4811
2,4-Dimethoxy-5-nitro	—	H, E, 5660
4,6-Dimethoxy-5-nitro	170-171	H, E, 5784
2,4-Dimethoxy-6-nitroamino	118	4656
4,6-Dimethoxy-5-nitro-2-phenyl	122-123	5491
4,6-Dimethoxy-2-phenyl	61; EtBF ₄ : 131	E, 3768, 4692
4,6-Dimethoxy-5-phenyl	111-113	3768
2,4-Dimethoxy-6-pivaloyl	59-60	6153
2,4-Dimethoxy-5-trimethylsilyl ethynyl	73-74	6349
4,6-Dimethoxy-5-vinyl	54-56/0.3	4575
2,4-Dimethyl	1-N-Ox/pic: 112	H, E, 5927
2,5-Dimethyl	75-77/25	H, E, 4463
4,5-Dimethyl	71/21 or 102/9; pic: 161	E, 5118, 5982
4,6-Dimethyl	159/at; Mel: 250; N-Ox: 115	H, E, 4668, 4918, 5673, 5927

4-Dimethylamino	40; 60/0.1	H, E, 5034, 6093
5-Dimethylamino	79–80; 1-N-Ox: 154; pic: 172	5500, 6062
2-Dimethylamino-1,4-dihydro-1,6-dimethyl-4-oxo	77–78	4569
4-Dimethylamino-1,2-dihydro-1,5-dimethyl-2-oxo	194–197	5797
5-Dimethylamino-1,6-dihydro-1-methyl-4-methylthio-6-oxo	78–79	4816
2-Dimethylamino-1,6-dihydro-1-methyl-6-oxo	95	E, 5600
4-Dimethylamino-1,2-dihydro-1-methyl-2-oxo	178 to 183	H, E, 4850, 5613, 6098, 6099
4-Dimethylamino-1,2-dihydro-6-methyl-2-oxo-1-phenyl	228–229; pic: 159	4850
5-Dimethylamino-1,6-dihydro-4-methyl-6-oxo-1-phenyl	2HBr: 208	4930
4-Dimethylamino-2,6-dihydroxy	312–314	H, E, 6109
5-Dimethylamino-2,4-dihydroxy	300 or 305–307	H, E, 4769, 6062
2-Dimethylamino-4,6-dihydroxy-5-β-hydroxyethyl	–	2638
2-Dimethylamino-4,6-dihydroxy-5-phenyl	crude	6578
5-Dimethylamino-2,4-dihydroxy-6-phenylazo	–	5060
5-Dimethylamino-2,4-dimercapto	256	6062
2-Dimethylamino-4,6-dimethoxy	68	6106
4-Dimethylamino-2,6-dimethoxy	42	6106
2-Dimethylamino-4,6-dimethyl	91/15; pic: 158	H, 2815
4-Dimethylamino-2,6-dimethyl	107/13; pic: 171	H, E, 4846, 5073, 5267
2-Dimethylamino-5-β-dimethylaminoethylamino-4-hydroxy	221–224	6180
2-Dimethylamino-4-dimethylcarbamoxyloxy-5,6-dimethyl	91	5275
2-Dimethylamino-4,5-dimethyl-6-β-methylhydrazino	141	4678
2-Dimethylamino-4,6-diphenyl	104–108 or 131–132	4681, 5836, 6290
4-Dimethylamino-2,6-diphenyl	182–183	5761
5-Dimethylamino-2,4-diphenyl	83	6107
4-Dimethylamino-5-ethoxycarbonyl-2-mercapto	186–188	4384
4-Dimethylamino-5-ethoxycarbonyl-2-methylthio	50	2599
2-Dimethylamino-4-ethoxycarbonyloxy-5,6-dimethyl	106–109/0.01	5723
2-Dimethylamino-5-β-ethoxyethyl-4-hydroxy-6-methyl	104–105	5722
4-Dimethylamino-2-ethoxy-5-methyl	20–21	5797
2-Dimethylamino-4-ethylacetamido-6-methoxy-5-nitro	110–112	4633
4-β-Dimethylaminoethylamino-2,6-diphenyl	2HBr: 247	6377

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Dimethylamino-4-ethylamino-6-methyl-5-nitro	117-118	5677
4-Dimethylamino-6-ethylamino-2-methyl-5-nitroso	68	6294
2- β -Dimethylaminoethylamino-4-methyl-6-phenyl	2HBr: 275	6377
4- β -Dimethylaminoethylamino-2-methyl-6-phenyl	2HBr: 167	6377
4- β -Dimethylaminoethylamino-6-methyl-2-phenyl	2HBr: 265	6377
4-Dimethylamino-5-ethylformamido-6-methyl-2-methylthio	109-110	5346
2-Dimethylamino-4-ethyl-6-hydroxy	140	5722
2-Dimethylamino-5-ethyl-4-hydroxy	124-125	5722
2-Dimethylamino-5-ethyl-4-hydroxy-6-methyl	141 or 143	5392, 5722
2-Dimethylamino-5-ethyl-4-hydroxy-6-phenyl	175	5722
2-Dimethylamino-5-ethyl-4-hydroxy-6-propyl	103-104	5392, 5722
2-Dimethylamino-5-ethyl-4-mercapto-6-methyl	140-141	5722
2-Dimethylamino-4-ethyl-6-methylamino-5-nitro	145-146	5677
4-Dimethylamino-5-ethylmethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	-	5735
5-Dimethylamino-1-ethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	190	4925
5-Dimethylamino-1-ethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	91	4925
5-Dimethylamino-4-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-1-phenyl	127-128	4931
2-Dimethylamino-5-ethylthio-4-hydroxy-6-methyl	117	5390
2-Dimethylamino-4-ethylthiomethyl-6-hydroxy	118	5392, 5722
2-Dimethylamino-4-fluoro	25-27; 69/70	4752
4-Dimethylamino-2-fluoro	63-64	4755
4-Dimethylamino-6-fluoro	105-107	4752
4-Dimethylamino-5-fluoro-1,2-dihydro-1-methyl-2-oxo	152-153	6026
2-Dimethylamino-5-formamido-4-methyl-6-methylamino	229	5670
4-Dimethylamino-5-formamido-6-methyl-2-methylthio	179-181	5346
2-Dimethylamino-5-formyl-4,6-dimethyl	151; oxime: 145	2815
4-Dimethylamino-5-formyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	184	4923
2-Dimethylamino-4-hexyl-6-hydroxy	80-81	5392, 5722
2-Dimethylamino-5-hexyl-4-hydroxy-6-methyl	80	5722

2-Dimethylamino-4-hydrazino-5-methyl-6-phenyl	176–177	5725
2-Dimethylamino-4-hydroxy	170 to 176	H, E, 4670, 4703, 5722
4-Dimethylamino-2-hydroxy	254–255	E, 5612
4-Dimethylamino-6-hydroxy	284	E, 5393
2-Dimethylamino-4-hydroxy-5,6-dimethyl	174–175	4678
2-Dimethylamino-4-hydroxy-5,6-dinitro	190	6293
2-Dimethylamino-5-hydroxy-4,6-diphenyl	123–125	6147
2-Dimethylamino-4- β -hydroxyethoxy-5,6-dimethyl	79–80	5722
2-Dimethylamino-4-hydroxy-5- β -hydroxyethyl-6-methyl	165–167	2638
4-Dimethylamino-6-hydroxyiminomethyl-2-methyl	227–228	5090
2-Dimethylamino-4-hydroxy-5-isoamyl-6-methyl	151	5722
2-Dimethylamino-4-hydroxy-5-isobutyl-6-methyl	150	5722
2-Dimethylamino-4-hydroxy-5-isopropyl-6-methyl	181–183	5722
5-Dimethylamino-4-hydroxy-2-mercapto	228–230	6107
2-Dimethylamino-4-hydroxymethyl	crude: nmr	4359
2-Dimethylamino-4-hydroxy-5-methyl	186–187	5392
2-Dimethylamino-4-hydroxy-6-methyl	175–176	H, E, 5722
4-Dimethylamino-2-hydroxy-5-methyl	156–159	5797
5-Dimethylamino-4-hydroxy-6-methylamino	194–200	3475
2-Dimethylamino-4-hydroxy-6-methyl-5-methylsulfinyl	175	5390
2-Dimethylamino-4-hydroxy-6-methyl-5-methylsulfonyl	229 to 235	5390, 5391, 5722
2-Dimethylamino-4-hydroxy-6-methyl-5-methylthio	181–182	5390
2-Dimethylamino-4-hydroxy-5-methyl-6-phenyl	–	5725
2-Dimethylamino-4-hydroxy-6-methyl-5-phenylazo	147–150	H, 5722
2-Dimethylamino-4-hydroxy-6-methyl-5-propyl	120	5392, 5722
2-Dimethylamino-4-hydroxy-5-methylsulfonyl	259–261	5391
5-Dimethylamino-4-hydroxy-6-methylthio	203–205	4816
2-Dimethylamino-4-hydroxy-5-nitro	301	H, 5722
4-Dimethylamino-6-hydroxy-5-nitro	207–208	E, 5442
2-Dimethylamino-4-hydroxy-5-nitro-6-nitroamino	219	4633
2-Dimethylamino-4-hydroxy-5-nitro-6-propylamino	257–259	6116
2-Dimethylamino-4-hydroxy-6-phenyl	243	5722
2-Dimethylamino-4-hydroxy-6-propyl	127	5722

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Dimethylamino-4-iodo-5,6-dimethyl	45	5284
2-Dimethylamino-4-mercapto	149	E, 5722
4-Dimethylamino-2-mercapto	> 250	H, E, 4384
2-Dimethylamino-4-mercapto-5,6-dimethyl	162-163	5722
2-Dimethylamino-4-mercapto-6-methyl	154-155	5722
2-Dimethylamino-4-methoxy	14	E, 6106
4-Dimethylamino-2-methoxy	HBr: 135-140	E, 4703
2-Dimethylamino-4-methoxy-6-methyl	112/13; n_D^{23} 1.5223	5390
2-Dimethylamino-4-methoxy-6- <i>N</i> -methylacetamido-5-nitro	136-137	4633
2-Dimethylamino-4-methoxy-6-methylamino	45	4656
2-Dimethylamino-4-methoxy-6-methylamino-5-nitro	180	4631
2-Dimethylamino-4-methoxy-6-methyl-5-methylthio	140/14; n_D^{23} 1.5583	5390
2-Dimethylamino-4-methoxy-6- <i>N</i> -methylnitroamino	95-96	4656
2-Dimethylamino-4-methoxy-6-nitroamino	147-148	4656
4-Dimethylamino-5-methyl	-	5796
4-Dimethylamino-6- <i>N</i> -methylacetamido-5-nitro	100-101	4633
4-Dimethylaminomethyl-2,6-dihydroxy	322-334	5854
5-Dimethylaminomethyl-2,4-dihydroxy	HBr: 270-273	E, 5475, 5806
5-Dimethylaminomethyleneamino	128-130/0.3; HClO ₄ : 215-220	4383
4-Dimethylaminomethyleneamino-1,3-diethyl-5-formyl- 1,2,3,6-tetrahydro-2,6-dioxo	128-130	5036
4-Dimethylaminomethyleneamino-1,3-diethyl-1,2,3,6-tetrahydro- 2,6-dioxo	137-138	5036
4-Dimethylaminomethyleneamino-1,2-dihydro-2-oxo-1-methyl	203-204	6171, 6251
4-Dimethylaminomethyleneamino-1,2-dihydro-2-oxo-1-propyl	142-143	6251
5-Dimethylaminomethyleneamino-2,4-dihydroxy-6-methyl	285	5419
5-Dimethylaminomethyleneamino-4- β -dimethylaminovinyl-2,6-dihydroxy	242	5419
4-Dimethylaminomethyleneamino-1-ethyl-1,2-dihydro-2-oxo	147-148	6251
5-Dimethylaminomethyleneamino-2-fluoro	96-97	4382

5-Dimethylaminomethylenearmino-2-hydroxy	206–208	4380
5-Dimethylaminomethylenearmino-2-mercaptop	192–196	4383
5-Dimethylaminomethylenearmino-2-methoxy	87–88	4383
5-Dimethylaminomethylenearmino-2-methyl	68–70	6510
5-Dimethylaminomethylenearmino-2-methylsulfanyl	103–104	4383
5-Dimethylaminomethylenearmino-2-methylsulfonyl	132–133	4383
5-Dimethylaminomethylenearmino-2-methylthio	102–103	4383
5-Dimethylaminomethylenearmino-2-phenyl	103–104	6510
4-Dimethylaminomethylenearmino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-phenylazo	203	4995
5-Dimethylaminomethylenhexahydro-1,3-dimethyl-2,4,6-trioxo	109	4923
4-Dimethylaminomethylenhydrazino	119–121	4910
5-Dimethylaminomethyl-4-ethoxycarbonyl-2,6-dihydroxy	190–198	6193
2-Dimethylaminomethyl-4-hydroxy	152–155	6119
4-Dimethylaminomethyl-5-hydroxy	199–201	6347
2-Dimethylamino-4-methyl-6-methylamino-5-nitro	147	5670
2-Dimethylamino-4-methyl-6-methylsulfonyloxy	87	5391, 5392, 5723
2-Dimethylamino-4-methyl-6-methylsulfonyloxy-5-propyl	71	5392, 5723
4-Dimethylamino-6-methyl-2-methylthio	39 to 44; 138/4; pic: 188 or 190	4844, 5267, 5872
4-Dimethylamino-2-methyl-5-nitroso-6-piperidino	100	6294
5-Dimethylamino-2-methyl-4-phenyl	65–67	6107
2-Dimethylamino-4-methyl-6-phenylsulfonyloxy-5-propyl	72	5392, 5723
2-Dimethylamino-4-methylsulfonyloxy	76	5391, 5392, 5723
5-Dimethylaminomethyl-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	HCl: 263	4932
5-Dimethylaminomethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	HBr: 240	4932
5-Dimethylaminomethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	HCl: 236	4932
2-Dimethylamino-5-nitro	222	H, 3519
2-Dimethylamino-5-nitro-4,6-diphenyl	164–166	6147
4-Dimethylamino-2-phenyl	70 or 72	4449, 6093
4-Dimethylamino-6-phenyl	70–71	6117
5-Dimethylamino-4-phenyl	65–66	6107

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1- γ -Dimethylamino-4-formyl-1,6-dihydro-6-oxo	oxime: 173–176	6069
4-Dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	nmr	E, 4786
5-Dimethylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	nmr	4786
5-Dimethylamino-1,2,3,4-tetrahydro-1,6-dimethyl-3-phenyl	135	4925
5-Dimethylamino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	118	4925
5-Dimethylamino-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxo	nmr	4786
4-Dimethylamino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl	204–205	5587
4-Dimethylamino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl-5-phenylcarbamoyl	320–323	5587
4-Dimethylamino-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl-5- <i>N</i> -phenyl(thiocarbamoyl)	330–331	5587
5-Dimethylamino-1,2,3,4-tetrahydro-1- β -hydroxyethyl-6-methyl-2,4-dioxo-3-phenyl	197	4925
5-Dimethylamino-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-phenyl	197	4931
5-Dimethylamino-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl	125	4931
5-Dimethylamino-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo	94	4925
4-Dimethylamino-2,5,6-trifluoro	45–47	3521
4- β -Dimethylaminovinyl	46–48; HCl: 210	E, 5863
2- β -Dimethylaminovinyl-4,6-dimethoxy-5-nitro	132–136	6402
4- β -Dimethylaminovinyl-2,6-dimethoxy-5-nitro	157–159	6402
4- β -Dimethylaminovinyl-6-methyl	92–95	6402
4- β -Dimethylaminovinyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	185–186	4936
4,5-Dimethyl-2,6-bis(trimethylsiloxy)	83–85	5957
5- <i>N,N</i> -Dimethylcarbamoyl-1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo	113–130 (!)	5037
4-Dimethylcarbamoyl-2-methyl-6-phenyl	81–83	5987
4-Dimethylcarbamoyl-6-methyl-2-phenyl	90–92	5987
5- β -(<i>N,N</i> -Dimethylcarbamoyl)vinyl-2,4-dihydroxy	312–314 (<i>trans</i>)	5473

2,4-Dimethyl-5,6-diphenyl	105–106	6118
5-Dimethylmoniomethyl-4,6-dihydroxy	Cl: 231–232	5819
2,5-Dimethyl-4-methylamino	114	5679
4,5-Dimethyl-6-methylamino	127	5679
4,6-Dimethyl-2-methylamino	99; <i>N</i> -Ox: 144	H, E, 5486, 6276
2,4-Dimethyl-6-methylamino-5-nitro	107–108	5670
4,6-Dimethyl-2-methylamino-5-phenyl	133	5662
4,6-Dimethyl-2-methylamino-5-propyl	114	2700
4,6-Dimethyl-2-methylamino-5-prop-1'-ynyl	161	2700
4,6-Dimethyl-2-methylamino-5-prop-2'-ynyl	132	2700
4,6-Dimethyl-2- α -methylhydrazino	59–60	6115
4,6-Dimethyl-2- β -methylhydrazino	86–89	6115
4,6-Dimethyl-2-methylsulfinylmethyl	73–75	6008
4,6-Dimethyl-2-methylsulfonyl-5-phenyl	146	5662
4,5-Dimethyl-2-methylthio	80/0.2	E, 3474
4,6-Dimethyl-2-methylthio	27; 47/0.05	H, E, 4467
4,6-Dimethyl-2-methylthiomethyl	111/4	6008
4,6-Dimethyl-2-methylthio-5-phenyl	69	5662
2,4-Dimethyl-6- <i>N'</i> -methylureido	173	6156
4,6-Dimethyl-2- β -nitrovinyl	123–124	4836
2,4-Dimethyl-6-2'-oxocyclohexyl	45–47	6082
2,6-Dimethyl-2- <i>N'</i> , <i>N'</i> -pentamethyleneguanidino	185	4975
4,6-Dimethyl-2-pent-1-enyl	90–95/3; 118–120/20 (<i>cis</i>)	6008
4,6-Dimethyl-2-pent-1'-ynyl	108–110/3	6008
2,4-Dimethyl-6-phenyl	124/4	5096
2,5-Dimethyl-4-phenyl	205–209/at (?)	E, 5484
4,6-Dimethyl-2-phenyl	83–84	H, E, 4918, 5096, 5706
4,6-Dimethyl-2- <i>N'</i> -phenylguanidino	203 or 207–209	4975, 6205
2,4-Dimethyl-6-phenylsulfonyl	93–95	6082
2,4-Dimethyl-6-phenylsulfonyloxy	55–56	4360
2,4-Dimethyl-6-phenylthio	78–80	6082
2,4-Dimethyl-6- <i>N'</i> -phenylureido	226	6156
4,6-Dimethyl-2-phenylureido	198–200	6205

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,4-Dimethyl-6-piperidino	33–35; 154/18	H, 5556, 5676, 5883
4,6-Dimethyl-2-piperidino	62–63	H, E, 5676, 5883
2,4-Dimethyl-6-prop-1'-ynyl	58–60; 110/3	5093, 5094
4,6-Dimethyl-2-prop-1'-ynyl	105–106; 140/18	5093, 5094
4,6-Dimethyl-2-prop-2'-ynylamino	119	2700
2,4-Dimethyl-5-styryl	80–81	5654
2,4-Dimethyl-6-styryl	57–58 (<i>E</i>)	6390
4,6-Dimethyl-2-styryl	47–48 (<i>E</i>)	6390
4,6-Dimethyl-2-sulfamoyl	198–199	H, E, 5669
4,6-Dimethyl-2-sulfenamoyl	99–100	5669
2- <i>S</i> , <i>S</i> -Dimethylsulfimido	c. 40	5261, 6375
4- <i>S</i> , <i>S</i> -Dimethylsulfimido	100–105	6375
2- <i>S</i> , <i>S</i> -Dimethylsulfimido-4,6-dimethyl	120; pic: 180	5261, 6375
4- <i>S</i> , <i>S</i> -Dimethylsulfimido-2,6-dimethyl	101–106	6375
4- <i>S</i> , <i>S</i> -Dimethylsulfimido-2-methoxy	71–75	6375
4- <i>S</i> , <i>S</i> -Dimethylsulfimido-6-methoxy	115–118	6375
2- <i>S</i> , <i>S</i> -Dimethylsulfimido-4-methyl	95	5261, 6375
4- <i>S</i> , <i>S</i> -Dimethylsulfimido-2-methylthio	67; pic: 175	6375
2,4-Dimethyl-6-sulfo	K: 326	H, 5667
4,5-Dimethyl-6-sulfo	K: 314	5667
4,6-Dimethyl-2-sulfo	K: 293 or 295	5667, 5669
5-Dimethylsulfonio-2,4-dihydroxy	Cl: 190	5142
5-Dimethylsulfonio-2,4,6-triphenyl	145–151 (?)	5068
4,6-Dimethyl-2-thiocarbamoylmethyl	149–150	5974
5- <i>N</i> , <i>N</i> -Dimethyl(thiocarbamoyloxy)-2-methylthio	100–101	4401
4,6-Dimethyl-2-ureido	209	H, 6015
2,4-Dimethyl-6-valeryl-methyl	120–125/3	6353
4,6-Dimethyl-2-valeryl-methyl	140–145/3	6353
4- α , δ -Dioxopentyl-6-ethoxy-2-methyl	75/0.01	6139
4- α , δ -Dioxopentyl-6-ethoxy-2-phenyl	52–54	6139

2,4-Diphenoxy	110–112; 1-Mel: 186	H, E, 5061, 5362
2,4-Diphenyl	71; 190–196/3	H, E, 4488, 4817, 5972
2,5-Diphenyl	181 or 185	4488, 4497
4,5-Diphenyl	3- <i>N</i> -Ox: 164–166	4979
4,6-Diphenyl	87 to 101; <i>N</i> -Ox: 108	H, E, 4884, 5499, 5673, 6105
2,4-Diphenyl-5,6-bistrifluoromethyl	113–114	4813
4,6-Diphenyl-2-piperidino	161–162	4790
4,6-Diphenyl-2-propylamino	96–99	6290
2,4-Diphenyl-6-trimethylammonio	Cl: 185	5761
4,6-Diphenyl-2-trimethylammonio	Cl: –	5839
4,6-Dipropyl-2-ureido	134	6015
Dithiouracil/3-amino-6-methyl	174–177	5166
Dithiouracil/1-cyclohexyl	224–226	6114
Dithiouracil/1-methyl	258	E, 5058, 5061
2- α , β -Epoxy- α -methyl-ethyl-4-phenyl	158–160/0.5	5690
2-Ethoxalylmethyl-1,6-dihydro-1,4-dimethyl-6-oxo	164–165	5090
4-Ethoxy	63/15; EtBF ₄ : oil	4692, 4694, 5294
5-Ethoxycarbonyl	106–108/13	E, 5794
4-Ethoxycarbonylamino-2-hydroxy	> 290	4579
5-Ethoxycarbonyl-2,4-bismethylthio	82–83	E, 2599
5- δ -Ethoxycarbonylbutyl-4,6-dihydroxy-2-methylamino	122–124	6518
5- δ -Ethoxycarbonylbutyl-4,6-dihydroxy-2-propylamino	252–254	6518
5- δ -Ethoxycarbonylbutyl-2-ethylamino-4,6-dihydroxy	244–246	6518
5-Ethoxycarbonyl-1,2-dihydro-1,6-dimethyl-4-methylthio-2-oxo	76–78	5601
5-Ethoxycarbonyl-1,4-dihydro-1,2-dimethyl-4-oxo	187–188; HI: 163	5099
5-Ethoxycarbonyl-1,6-dihydro-1,2-dimethyl-6-oxo	61–62	5099
5-Ethoxycarbonyl-1,6-dihydro-4-mercapto-6-oxo-1,2-diphenyl	195	4533
5-Ethoxycarbonyl-1,4-dihydro-6-methyl-1,2-diphenyl-4-thio	215	E, 4533
5-Ethoxycarbonyl-1,2-dihydro-1-methyl-2-oxo	HBr: 187–189 (?)	E, 5720
5-Ethoxycarbonyl-1,6-dihydro-2-methylthio-6-oxo-1-phenyl	138	H, 6358
5-Ethoxycarbonyl-1,6-dihydro-6-oxo-1,2-diphenyl	148	6358
5-Ethoxycarbonyl-1,2-dihydro-2-oxo-1-phenyl	103–104	E, 5720

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
5-Ethoxycarbonyl-2,4-dihydroxy	234 or 242	H, E, 4902, 6277
4-Ethoxycarbonyl-2,6-dihydroxy-5-isopropoxymethyl	179-181	6193
4-Ethoxycarbonyl-2,6-dihydroxy-5-(β -methoxyethoxy)methyl	171-172	6193
4-Ethoxycarbonyl-2,6-dihydroxy-5-methoxymethyl	166-167	6193
5-Ethoxycarbonyl-2,4-dihydroxy-6-methyl	226 or 233-234	4470, 5601
5-Ethoxycarbonyl-2,4-dihydroxy-6- γ -methyllaminopropyl	202	4902
4-Ethoxycarbonyl-2,6-dihydroxy-5-propoxymethyl	180	6193
5-Ethoxycarbonyl-2,4-dimercapto-6-methyl	270	4470
5-Ethoxycarbonyl-2,4-diphenyl	58-59	6166
4-Ethoxycarbonyl-2- β -ethoxycarbonyl-6-hydroxy-5-methyl	124-125	6025, 6140
4-Ethoxycarbonyl-2- β -ethoxycarbonylvinyl-6-hydroxy-5-methyl	139-141	6140
4-Ethoxycarbonyl-5-ethoxymethyl-2,6-dihydroxy	199-201	6193
5-Ethoxycarbonyl-1-ethyl-1,6-dihydro-4-mercaptop-6-oxo-2-phenyl	157	4533
5-Ethoxycarbonyl-1-ethyl-1,4-dihydro-6-methyl-2-phenyl-4-thio	181	4533
5- β -Ethoxycarbonyl-2,4-dihydroxy-6-methyl	204-205	5707
5- β -Ethoxycarbonyl-2,4-dihydroxy-2,6-dimethyl	112-114	5766
5- β -Ethoxycarbonyl-4-hydroxy-2-mercaptop-6-methyl	195-196	5707
5- β -Ethoxycarbonyl-4-hydroxy-2-methyl	110-112; HBr: 210	H, 5766
5- β -Ethoxycarbonyl-4-hydroxy-6-methyl-2-phenyl	145-146	5766
5- β -Ethoxycarbonyl-4-hydroxy-2-phenyl	145-146	5766
5-Ethoxycarbonyl-2-ethyl-4-mercaptop-6-methyl	155	6291
5-Ethoxycarbonyl-4-ethylthio-2,6-dihydroxy	203-204	5536
5-Ethoxycarbonyl-4-fluoro-2-methylthio	48-49	2599
5-Ethoxycarbonyl-4-formyl	76/0.02 (unstable)	4438
5-Ethoxycarbonyl-4-formyl-2-methyl	88-89/0.1 (unstable)	4438
5-Ethoxycarbonyl-4-formyl-2-methylthio	oxime: 191	2599
5-Ethoxycarbonyl-4-formyl-2-phenyl	136	5379
4-Ethoxycarbonyl-5-hydrazino-2,6-dihydroxy	237-239	6101
5-Ethoxycarbonyl-2-hydrazino-4-methyl	185	E, 5378
4-Ethoxycarbonyl-6-hydroxy-2,5-dimethyl	171-172	6140

2-Ethoxycarbonyl-5-hydroxy-4,6-diphenyl	227–228; 1- <i>N</i> -Ox: 219	5499
5-Ethoxycarbonyl-2-hydroxy-4,6-diphenyl	215–216	5499
5-Ethoxycarbonyl-4-hydroxy-2,6-diphenyl	174–176	4485
4-Ethoxycarbonyl-6-hydroxy-2-methoxycarbonyl-5-methyl	154–155	6140
5-Ethoxycarbonyl-2-hydroxy-4-methyl	248–249	H, E, 6523
4-Ethoxycarbonyl-6-hydroxy-2-(methylthio)carbonyl-5-methyl	nmr	6140
4-Ethoxycarbonyl-6-hydroxy-5-methyl-2-tribromomethyl	155	6140
4-Ethoxycarbonyl-6-hydroxy-5-methyl	160–162	6140
5-Ethoxycarbonyl-4-hydroxy-2-piperidino	142–143	5885
5-Ethoxycarbonyl-4-iodo-2-methylthio	74	E, 2599
5-Ethoxycarbonyl-4-isopropylamino-2-methylthio	50	5885
5-Ethoxycarbonyl-2-mercapto-4-methyl	188–189	H, 6523
5-Ethoxycarbonyl-2-mercapto-4-methyl-6-methylamino	215	4470
5-Ethoxycarbonyl-4-mercapto-6-methyl-2-phenyl	130 or 150–151	E, 4723, 6291
5-Ethoxycarbonyl-4-methoxycarbonylmethylthio-2-phenyl	111–112	5581
2-Ethoxycarbonyl-5-methoxy-4,6-diphenyl	117–119; 1- <i>N</i> -Ox: 171	5499
5-Ethoxycarbonyl-4-methoxy-2-methyl	48–49	E, 5099
2-Ethoxycarbonylmethyl	96–98/3	5688
5-Ethoxycarbonyl-4-methyl-2,6-bismethylamino	124–125	4470
5-Ethoxycarbonyl-4-methyl-2,6-bistrichloromethyl	165–170/0.3	4470
5-Ethoxycarbonylmethyl-2,4-bis(trimethylsiloxy)	85–87/0.02	5973
1-Ethoxycarbonylmethyl-1,2-dihydro-2-imino	HBr: > 280	4764
4-Ethoxycarbonylmethyl-2,6-dihydroxy	1- <i>N</i> -Ox: 172–173	H, E, 5350
5-Ethoxycarbonylmethyl-2,4-dihydroxy	205–207	H, 5973
2-Ethoxycarbonylmethyl-4,6-dimethyl	62 to 67	4812, 5653, 5682, 5836, 6008, 6249
2-Ethoxycarbonylmethyl-4,6-diphenyl	68–70	5836
4-Ethoxycarbonylmethyl-5-hydrazino-2,6-dihydroxy	274–276	6101
5-Ethoxycarbonylmethyl-4-hydroxy-2-mercapto	185–187	H, E, 5418, 5973
5-Ethoxycarbonylmethyl-4-hydroxy-2-methylthio	181 or 191–192	E, 5418, 5973
5-Ethoxycarbonylmethyl-4-hydroxy-2-phenyl	169–175	E, 5965
5-Ethoxycarbonylmethyl-4-hydroxy-2-propyl	144	E, 5975
4-Ethoxycarbonylmethyl-6-methoxy-2-phenyl	43–47; 152/0.5	5980
2-Ethoxycarbonylmethyl-4-methyl	liq; anal.	5688

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Ethoxycarbonylmethyl-2-methyl	liq; M ⁺	5682
5-Ethoxycarbonylmethyl-4-methyl	120/5; pic: 194	E, 5982
4-Ethoxycarbonylmethyl-6-methyl-2-phenyl	132/2	6249
5-Ethoxycarbonyl-4-methyl-2-methylthio	59-60	E, 2599, 5378
5-Ethoxycarbonylmethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	78-80	6158
1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	123	4925
1-Ethoxycarbonylmethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	176	4925
5-Ethoxycarbonyl-2-methylthio-4-phenoxy	78-79	2599
5-Ethoxycarbonyl-2-methylthio-4-phenyl	57-58	6166
4-Ethoxycarbonyl-2-methylthio-5-phenylthio	47-48	4400
5-Ethoxycarbonyl-2-methylthio-4-phenylthio	83-84	2599
5-Ethoxycarbonyl-2-methylthio-4-trimethylammonio	Cl: 109-111	2599
2-β-Ethoxycarbonyl-α-methylvinyl-4,6-dimethyl	130-135/2	6299
4-β-Ethoxycarbonyl-α-methylvinyl-2-methyl-6-phenyl	65-66	6299
4-β-Ethoxycarbonyl-α-methylvinyl-6-methyl-2-phenyl	75-77	6299
5-Ethoxycarbonyl-2-phenyl-4-piperidino	95-96	4976
1-γ-Ethoxycarbonylpropyl-1,2-dihydro-4-methylthio-2-oxo	53-54	5240
4-Ethoxycarbonyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	60	6853
5-Ethoxycarbonyl-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo	138	4480
5-Ethoxycarbonyl-1,2,3,4-tetrahydro-4-imino-1-methyl-2-oxo-3-phenyl	150-152	4920
1-Ethoxycarbonyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo	70-72	4579
5-Ethoxycarbonyl-2,4,6-triphenyl	109 or 110-111	H, 4477, 5134
4-β-Ethoxycarbonylvinyl-2,6-dihydroxy	255-257	5403
5-β-Ethoxycarbonylvinyl-2,4-dihydroxy	215-219 (<i>trans</i>)	5473
2-β-Ethoxycarbonylvinyl-4,6-dimethyl	55-56 (<i>E</i>)	6299, 6301, 6390
4-β-Ethoxycarbonylvinyl-2,6-dimethyl	67-69 (<i>E</i>)	6301, 6390
5-β-Ethoxycarbonylvinyl-2,4-dimethyl	66 or 68-69	5654, 6301, 6390
5-β-Ethoxycarbonylvinyl-4-hydroxy-2,6-dimethyl	222-223	6351
4-β-Ethoxycarbonylvinyl-2-isopropyl-6-methyl	56 (<i>E</i>)	6390
5-β-Ethoxycarbonylvinyl-2-isopropyl-4-methyl	135/2	5654, 6390

4- β -Ethoxycarbonylvinyl-2-methyl-6-phenyl	74-75	6299
4- β -Ethoxycarbonylvinyl-2-phenyl	78-80	6299
2-Ethoxy-4,6-diethyl	57-58/0.01	6271
5-Ethoxy-1,6-dihydro-1,2-dimethyl-6-oxo	100	5958
2-Ethoxy-1,4-dihydro-1- β -hydroxyethyl-5-methyl-4-oxo	133-135	6077
4-Ethoxy-1,2-dihydro-1- β -hydroxyethyl-2-oxo	82-83	5818
1-Ethoxy-1,6-dihydro-4-hydroxy-5-methyl-6-oxo-2-phenyl	161-162	4353
1-Ethoxy-1,6-dihydro-4-hydroxy-6-oxo-2-phenyl	149-150	4337
2-Ethoxy-1,4-dihydro-1-methyl-4-oxo	112-115	6130
2-Ethoxy-1,6-dihydro-1-methyl-6-oxo	59-60	5496, 6130
4-Ethoxy-1,2-dihydro-1-methyl-2-oxo	136	H, 4437, 5490, 5613
5-Ethoxy-1,6-dihydro-2-methyl-6-oxo-1- β -sulfoethyl	193-194	5958
4-Ethoxy-1,2-dihydro-1-methyl-2-thio	134-135	5061
2-Ethoxy-1,4-dihydro-4-oxo-1-vinyl	97-99	3770
4-Ethoxy-1,2-dihydro-2-oxo-1-vinyl	77-78	5495
4-Ethoxy-2,6-dimethyl	68/2.7; 1- <i>N</i> -Ox: 104	E, 5555, 5986, 6082
4-Ethoxy-2,6-dipiperidino	63-65	5998
4-Ethoxy-1- β -ethoxycarbonylethyl-1,2-dihydro-2-oxo	—	4671
4-Ethoxy-5-ethoxycarbonyl-2-hydroxy-6-mercapto	195-203	E, 5536
4-Ethoxy-5-ethoxycarbonyl-2-methyl	53-55	E, 5097, 5555
4-Ethoxy-2-ethyl	anal.	5294
4-Ethoxy-6-ethylamino	88-89	4697
4-Ethoxy-3-ethyl-3,6-dihydro-6-imino	HBF ₄ : 198	4697
4-Ethoxy-1-ethyl-1,6-dihydro-2-methyl-6-oxo	3-EtBF ₄ : 228	4692
4-Ethoxy-5-ethyl-1,2-dihydro-1-methyl-2-oxo	91	5797
2-Ethoxy-1-ethyl-1,4-dihydro-4-oxo	crude: 94-97	5496
4-Ethoxy-1-ethyl-1,2-dihydro-2-oxo	88	H, E, 5490, 5528
4-Ethoxy-1-ethyl-1,6-dihydro-6-oxo	3-EtBF ₄ : 182	4692
4-Ethoxy-1-ethyl-1,6-dihydro-6-oxo	3-EtBF ₄ : 170	4692
4-Ethoxy-1-ethyl-1,6-dihydro-6-oxo-2-phenyl	242-244	5427
5- β -Ethoxyethyl-2,4-dihydroxy	120-122/20	5096
2- β -Ethoxyethyl-4,6-dimethyl	109-110	5797
2-Ethoxy-5-ethyl-4-hydroxy	158-160	5797
4-Ethoxy-5-ethyl-2-hydroxy	124-127	4513, 5080, 5096
2- β -Ethoxyethyl-4-hydroxy-6-methyl		

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Ethoxy-2-ethylsulfonyl	194/4.5	H, 6132
1- β -Ethoxyethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	50-51	5524
4-Ethoxy-2-ethylthio	124/11	H, 6132
2-Ethoxy-5-ethynyl-4-hydroxy	178-180	5329
4-Ethoxy-5-ethynyl-2-hydroxy	198-201	5287, 5329
2-Ethoxy-5-fluoro-4-hydroxy	182-183	6515
4-Ethoxy-5-fluoro-2-hydroxy	165-167	4895
4-Ethoxy-5-fluoro-2-methoxy	45-47	5956
4-Ethoxy-5-fluoro-2-phenoxy	69-70	5956
4-Ethoxy-5-fluoro-2-piperidino	145/8; HCl: 125	5956
4-C-Ethoxyformimidoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	98-100	4937, 4939
4-Ethoxy-2- α -formyl- α -methyl-6-methyl	73/1	5083
4-Ethoxy-6-hydrazino	118-119	4672
2-Ethoxy-4-hydroxy	127-129	H, 5490, 5612
4-Ethoxy-2-hydroxy	167-168	H, E, 5490, 5612, 6132
5-Ethoxy-2-hydroxy	108-109	4384
4-Ethoxy-6-hydroxyiminomethyl-2-methyl	216-217	5090
2-Ethoxy-4-hydroxy-6-methoxy	150-152	5153, 5156
4-Ethoxy-6-hydroxy-2-methoxy	184-185	5153, 5156
2-Ethoxy-4-hydroxy-5-methyl	147-148	6131
2-Ethoxy-4-hydroxy-6-methyl	210	H, E, 4408
4-Ethoxy-6-hydroxy-2-methyl	191	H, 4361
5-Ethoxy-4-hydroxy-2-methyl	164 and 171	5958
4-Ethoxy-6-hydroxy-2-phenyl	177-179	4361
5-Ethoxy-4-hydroxy-2-phenyl	217-219	4674
5-Ethoxy-4-iodo-2-isopropyl	145/20	5655
4-Ethoxy-6-mercapto	196-199	5536
5-Ethoxy-2-mercapto	203-205	H, 4384
5-Ethoxy-4-mercapto-2-methyl	177-181	5958

4-Ethoxy-2-mercapto-6-methyl-5-phenyl	194–196	5381
4-Ethoxy-2-mercapto-6-phenyl	158	5371
2-Ethoxy-4-methoxy	80/10	5496
4-Ethoxy-2-methoxycarbonylmethyl-6-methyl	92–95/3	5805
5-Ethoxy-4-methoxy-2-methyl	110/14	5958
4-Ethoxy-6-methoxy-5-nitro	69–71	5660
2-Ethoxy-4-methyl	nmr	H, 2630
2-Ethoxy-5-methyl	78–79/2; pic: 166	2630
4-Ethoxy-2-methyl	anal.; sp	5294
5-Ethoxymethyl-2,4-dihydroxy	212–213	E, 6104
2-Ethoxymethyl-4-hydroxy-6-methyl	69–72	5079
4-Ethoxy-2-methyl-6-phenyl	90–100/0.2; pic: 152	5555
4-Ethoxy-2-methylsulfonyl	182/4	6132
2-Ethoxy-4-methylthio	1-Mel: sp	E, 5061
2-Ethoxy-2-methylthio	117/10; 1-Mel: –	5061, 6132
2-Ethoxy-5-nitro	51–53	E, 6123
4-Ethoxy-2-phenyl	163–164/20; pic: 197–198	H, 4692
4-Ethoxy-6-phenyl	172–173/23; 1-N-Ox: 164; pic: 146	4692
5-Ethoxy-2-phenyl	105–107	5858
5-Ethoxy-2-N'-phenyl(thioureido)	181–182	5838
4-Ethoxy-1,2,3,6-tetrahydro-2,6-dioxo-1,3-diphenyl	186–187	5587
4-Ethoxy-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxo	141–142	4971
1-Ethoxy-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	154–156	5524
4-Ethoxy-2-trimethylsiloxy	115–117/17	E, 6132
2-Ethyl	107/200	5063
4-Ethyl	85/70	E, 5758, 6220
5-Ethyl	176/at: 86/60	E, 4515, 4575
4-Ethylamino-1,2-dihydro-1,5-dimethyl-2-oxo	144	5811
4-Ethylamino-2,6-dihydroxy	288–289	E, 5541
4-Ethylamino-2,6-dihydroxy-5-nitro	299–301	5576
4-Ethylamino-2,6-dihydroxy-5-phenylazo	262–263	5541
2-Ethylamino-4,6-di-isopropyl	78/0.2; n _D ²⁰ 1.5076	4551
4-Ethylamino-2,6-dimethoxy	96–97	5541

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Ethylamino-2,6-dimethoxy-5-phenylazo	109–110	5541
2-Ethylamino-4,6-dimethyl	66–68	E, 4551
2-Ethylamino-4,6-diphenyl	68 or 72; HCl: 146	4551, 6290
2-Ethylamino-4,6-dipropyl	78/0.01; n _D ²⁰ 1.5142	4551
4-Ethylamino-5-ethylformamido-6-methyl-2-methylthio	122–123	5346
4-Ethylamino-5-formamido-2,6-dimethoxy	145–146	5541
4-Ethylamino-5-formyl-6-hydroxy	244–245	5730
4-Ethylamino-6-hydroxy	217–220	3475
2-Ethylamino-4-hydroxy-5-methyl-6-phenyl	–	5725
4-Ethylamino-6-hydroxy-5-nitro	217 or 226–229	3475, 5442
2-Ethylamino-4-isoamyl-6-trifluoromethyl	99/0.6; n _D ²⁰ 1.4687	4558
2-Ethylamino-4-isobutyl-6-methyl	69/0.01; n _D ²⁰ 1.5147	4551
2-Ethylamino-4-isobutyl-6-trifluoromethyl	68/0.01; HClO ₄ : 132	4558
2-Ethylamino-4-isopropyl-6-trifluoromethyl	69/0.01; n _D ²⁰ 1.4662	4558
4-Ethylamino-2-mercapto-6-methyl-5-nitro	198	5677
4-Ethylamino-6-methoxy-2-methyl	oil; anal; nmr	4697
4-Ethylamino-6-methoxy-2-phenyl	50–52	4697
5-Ethylamino-4-methylamino	154–155	5873
4-Ethylamino-6-methyl-2-methylthio-5-nitro	107–108	5677
2-Ethylamino-4-methyl-6-phenyl	pic: 257	4551
2-Ethylamino-4-methyl-6-trifluoromethyl	44; pic: 109	4558
2-Ethylamino-5-nitro-4-thiocyanato	166–167	5742
4-Ethylamino-5-phenyl	–	5914
4-Ethylamino-6-phenyl	oil; anal; nmr	4697
5-Ethylamino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	110	4925
2-Ethylamino-4,5,6-trimethyl	82; pic: 177	4551
4-Ethylamino-2,5,6-triphenyl	152–153	6730
4-Ethyl-2,6-bis(methylamino)-5-nitro	147	5677
5-Ethyl-2,4-bis(trimethylsiloxy)	19	4713
2-Ethyl-4,6-dichloro-5-methyl	111/21	5021

1-Ethyl-1,6-dihydro-2,4-dimethoxy-5-methyl-6-oxo	81–82	5323
5-Ethyl-1,2-dihydro-4,6-dimethoxy-1-methyl-2-oxo	77	5322
1-Ethyl-1,2-dihydro-4,6-dimethyl-2-phenylimino	HClO ₄ : 202	6388
1-Ethyl-1,4-dihydro-4-imino	HBf ₄ : 127–128	4697
1-Ethyl-1,4-dihydro-4-imino-6-methoxy-2-methyl	HBf ₄ : 208–209	4697
2-Ethyl-1,6-dihydro-6-imino-1-methyl	HI: 215	5679
5-Ethyl-1,2-dihydro-2-imino-1-methyl	nmr	E, 5663
5-Ethyl-1,6-dihydro-6-imino-1-methyl	HI: 240	5679
1-Ethyl-1,4-dihydro-4-imino-2-phenyl	HBf ₄ : 182–183	4697
1-Ethyl-1,6-dihydro-6-imino-4-phenyl	HBf ₄ : 158–159	4697
1-Ethyl-1,4-dihydro-4-imino-5-phenyl	HCl: 201	4594, 5914
1-Ethyl-1,6-dihydro-6-imino-2,4,5-triphenyl	183	4589
1-Ethyl-1,2-dihydro-4-isopropoxy-6-methyl-2-oxo	70–71	4847
1-Ethyl-1,2-dihydro-4-methoxy-2-oxo	91–92	5490
5-Ethyl-1,2-dihydro-1-methyl-4-methylamino-2-oxo	128–130	5797
1-Ethyl-1,2-dihydro-4-methyl-2-oxo	hygros; anal.	2630
1-Ethyl-1,2-dihydro-5-methyl-2-oxo	85	2630
1-Ethyl-1,2-dihydro-6-methyl-2-oxo	98–99; HCl: 203	2630
1-Ethyl-1,4-dihydro-2-methyl-4-oxo	129–130	5294
1-Ethyl-1,6-dihydro-2-methyl-6-oxo	44–45	5294
1-Ethyl-1,6-dihydro-4-methyl-6-oxo	3-EtBF ₄ : 126	4695
1-Ethyl-1,2-dihydro-4-methyl-2-oxo-6-phenyl	147	6388
1-Ethyl-1,2-dihydro-4-methyl-6-phenyl-2-phenylimino	HClO ₄ : 227	6388
1-Ethyl-1,2-dihydro-4-methylthio-2-oxo	66–67	E, 5727
1-Ethyl-1,6-dihydro-4-methylthio-6-oxo	86–88	4806
1-Ethyl-1,2-dihydro-5-nitro-2-oxo	nmr	E, 2630
1-Ethyl-1,2-dihydro-2-oxo	3-Mel: 213	5324
1-Ethyl-1,4-dihydro-4-oxo	64–66	E, 5294
1-Ethyl-1,6-dihydro-6-oxo	70–71; 3-EtBF ₄ : 117	E, 4692, 5294
1-Ethyl-1,2-dihydro-2-oxo-4,5-diphenyl	120–123	6079
1-Ethyl-1,2-dihydro-2-oxo-5-phenyl	166–169	6079
1-Ethyl-1,4-dihydro-4-oxo-2-phenyl	3-EtBF ₄ : 190	4697
1-Ethyl-1,6-dihydro-6-oxo-2,4,5-triphenyl	172 or 173	4589, 5827
5-Ethyl-1,2-dihydro-1-phenyl-2-phenylimino	146	4464

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Ethyl-2,6-dihydroxy	202 or 204–207	H, E, 4511, 5403
5-Ethyl-2,4-dihydroxy	300–302	H, E, 4734, 4856, 5754, 5797, 5849
5-Ethyl-4,6-dihydroxy	—	H, E, 4577
4-Ethyl-2,6-dihydroxy-5-methyl	258 or 263	4716, 5022
5-Ethyl-2,4-dihydroxy-6-methyl	246–248	H, E, 4716
5-Ethyl-2,4-dihydroxy-6-propyl	223 to 232	3766, 4716, 5022, 5875, 5964
5-Ethyl-4,6-dimethoxy	34–35	4575
2-Ethyl-4,6-dimethyl	85/27; di-N-Ox. 135	5096, 6160
4-Ethyl-2,6-dimethyl	85/28; 1-N-Ox: 96/2; 3-N-Ox: 79–81	H, 5088, 5096
5-Ethyl-4,6-dimethyl-2-methylthio	95/0.05	4554
5-Ethyl-2,4-diphenyl	45; 130/0.001	4499
5-Ethyl-4-ethylamino-1,2-dihydro-1-methyl-2-oxo	99–101	5797
4-Ethyl-2-ethylamino-6-methyl	69/0.01; pic: 112	4551
4-Ethyl-2-ethylamino-6-trifluoromethyl	54/0.02	4558
1-Ethyl-4-fluoro-1,6-dihydro-6-oxo	86–88	4697
4-Ethyl-5-formamido-2,6-bismethylamino	151	5677
4-β-Ethylhydrazino-2-ethylthio-5-fluoro	HCl: 118	4882
5-Ethyl-2-hydrazino-4-hydroxy-6-methyl	320	E, 6148
2-Ethyl-4-hydroxy	116 to 120	E, 5294, 5550
5-Ethyl-2-hydroxy	167	E, 4463
5-Ethyl-4-hydroxy	83–85	4741
5-Ethyl-2-hydroxy-4,6-dimethoxy	213 or 215	5321, 5322
5-Ethyl-4-hydroxy-2,6-dimethoxy	221	5153, 5156
2-Ethyl-4-hydroxyiminomethyl	116–118	5074
2-Ethyl-4-hydroxy-6-isopropyl	62–63; 130/2	5909
5-Ethyl-2-hydroxy-4-mercapto	> 250	5573

5-Ethyl-4-hydroxy-2-mercapto-6-methyl	208–210	H, 4716
5-Ethyl-4-hydroxy-2-mercapto-6-phenyl	—	H, 5931
5-Ethyl-4-hydroxy-2-mercapto-6-propyl	209 or 215–216	3766, 4716, 5875, 5964
2-Ethyl-4-hydroxy-6-methyl	156 to 159	H, E, 5071, 5075, 5550, 6169
4-Ethyl-2-hydroxy-6-methyl	HCl: 220	4467
2-Ethyl-4-hydroxy-5-methylsulfonyl	192–195	3506
2-Ethyl-4-hydroxy-6-phenyl	227–229	H, 5550
4-Ethyl-6-hydroxy-2-phenyl	221–222	6339
2-Ethylidenehydrazino-4,6-dimethyl	122–123	6262
4-Ethylidenehydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	210–212	4929
4-Ethylidenehydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	135–136	4921
4-Ethylidenehydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxo	150 or 152	4621, 4626
4- β -Ethylidene- α -methylhydrazino-1,2,3,4-tetrahydro-1,3-dimethyl-2,6-dioxo	131	4950, 4991
5-Ethyl-4-iodo-2-isopropyl-6-methyl	45–47	5655
2-Ethyl-4-isopropoxy-6-methyl	1- <i>N</i> -Ox: 95	5927
4-Ethyl-2-isopropyl-6-methyl	1- <i>N</i> -Ox: 94/3; 3- <i>N</i> -Ox: 90/3	5088
4-Ethyl-2-mercapto	218; HCl: 244	4777
5-Ethyl-2-mercapto	202 or 228	E, 4384, 4463
4-Ethyl-2-mercapto-6-methylamino-5-nitro	210–211	5677
5-Ethyl-4-methoxy	116/65	4575
5-Ethyl-2-methoxy-4,6-dimethyl	74/0.05	4554
2-Ethyl-4-methoxy-6-methyl	1- <i>N</i> -Ox: 62–63	5071, 5927
4-Ethyl-2-methoxy-6-methyl	48/0.05; HCl: 150	4467
4-Ethyl-2-methoxy-6-trifluoromethyl	34/0.05	4546
4-Ethyl-5-methyl	75–78/13	E, 5118
5-Ethyl-2-methyl	80–82/25	E, 4463
2-Ethyl-4-methylamino	HCl: 247	5679
4- <i>N</i> -Ethyl- <i>N</i> -methylamino	MS; nmr	6172
5-Ethyl-4-methylamino	148	5679
2- <i>N</i> -Ethyl- <i>N</i> -methylamino-4-hydroxy-6-methyl-5-propyl	116–117	5722

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Ethyl-6-methylamino-2-methylthio-5-nitro	84-85	5677
5- <i>N</i> -Ethyl- <i>N</i> -methylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	—	5735
4-Ethyl-6-methyl-2-methylthio	67/0.05	4467
4-Ethyl-2-methylthio-6-trifluoromethyl	51/0.1	4546
4-Ethyl-6-methyl-2-ureido	168	6015
2-Ethyl-5-nitro	MS; nmr	6123
5-Ethyl-2-phenyl-4-propyl	90/0.001	4499
2- α -Ethylpropyl	125/100	5063
2- <i>N</i> -Ethylsulfamoyl-4,6-dimethyl	130-131	5669
4-Ethylsulfonyl-2-methoxycarbonylmethyl	165-166/0.7	5693
5-Ethyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-propyl	77-78	3766
4-Ethyl-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	119-120	6512
1-Ethyl-1,2,3,4-tetrahydro-6-hydroxy-3,5-dimethyl-2,4-dioxo	78-79	6250
1-Ethyl-1,2,3,4-tetrahydro-6-hydroxy-3-methyl-2,4-dioxo	108-109	6250
5-Ethyl-1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxo	84	6184
1-Ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo	73-75	H, 5518
1-Ethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-phenyl	177	4925
1-Ethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl	211	4925
4-Ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-1-phenyl	148	4931
1-Ethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl-5-piperidino	104	4925
1-Ethyl-1,2,3,4-tetrahydro-3-methyl-6-methylamino-2,4-dioxo	208-211	4657
1-Ethyl-1,2,3,4-tetrahydro-3-methyl-6-methylamino-5-nitroso-2,4-dioxo	270-275	4657
4-Ethyl-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxo	116-118	6401
2-Ethylthio	77/2.5	H, E, 6383
5-Ethylthio-2,4-bis(trimethylsiloxy)	96-97/0.2	5728
2-Ethylthio-1,4-dihydro-1,5-dimethyl-4-oxo	159-160	H, E, 4571
2-Ethylthio-1,6-dihydro-1,5-dimethyl-6-oxo	60-61	H, E, 4571
2-Ethylthio-1,4-dihydro-4-imino-1-methyl	HI: 184-185	4490
4-Ethylthio-1,2-dihydro-5-methyl-2-oxo-1-vinyl	115-117	4534
4-Ethylthio-2,6-dihydroxy	230-233	5536

5-Ethylthio-2,4-dihydroxy	255-257	E, 5168, 5728
5-Ethylthio-2,4-dihydroxy-6-methyl	253-256	5168
2-Ethylthio-5-fluoro-1,4-dihydro-1-methyl-4-oxo	152-153	6185
2-Ethylthio-5-fluoro-1,6-dihydro-1-methyl-6-oxo	95-96	6185
2-Ethylthio-5-fluoro-4-formyl-6-hydroxy	182; oxime: 240	5525
2-Ethylthio-5-fluoro-4- β -formylvinyl-6-hydroxy	136-138	5525
2-Ethylthio-5-fluoro-4-hydrazino	55	4882
2-Ethylthio-5-fluoro-4-hydroxy	193-194	E, 6111
2-Ethylthio-5-fluoro-4-hydroxy-6-hydroxymethyl	136-138	5525
2-Ethylthio-4-hydrazino	75	4882
2-Ethylthio-4-hydroxy	151 to 156	H, E, 5121, 5675
2-Ethylthio-5-hydroxy	120	4395
4-Ethylthio-2-hydroxy	176-178	5675
2-Ethylthio-4-hydroxy-5-methoxy	140	4395
2-Ethylthio-4-hydroxy-6-methyl	154-156	H, E, 5121
2-Ethylthio-4-hydroxy-5-methylcarbamoylmethyl	203-206	5965
2-Ethylthio-4-hydroxy-6-methyl-5-methylcarbamoylmethyl	243-245	5965
2-Ethylthio-4-hydroxy-6-phenyl	215	H, 5121
2-Ethylthio-4-hydroxy-6-propyl	91	5121
2-Ethylthio-5-methoxy	86/0.4	4395
4-Ethylthio-2-methoxycarbonylmethyl	114-116/0.5	5693
4-Ethylthio-5-methoxy-2-methyl	53-54	6348
2,4'-Ethyl[(thiosemicarbazido)-4-hydroxy	183-184	6133
2,4'-Ethyl[(thiosemicarbazido)-4-hydroxy-5-methyl	202-203	6133
4-Ethylthio-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	127-128	4971
4-Ethylthio-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo	110-111	6297
4-Ethylthio-1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-2-oxo	66	4971
5-Ethyl-2,4,6-trihydroxy	194; <i>N</i> -Ox: 191	H, E, 5218, 5321, 5322, 5797, 5916
1-Ethyl-3,5,5-trimethyl-2,4,6-trioxo	39-41	5898
4- <i>N'</i> -Ethylureido-2,6-dimethyl	161	6156
2-Ethynyl	95-96	6265
5-Ethynyl-2,4-dihydroxy	>300 or 320	5329, 6017, 6349
5-Ethynyl-2,4-dimethoxy	83-84	6349
5-Ethynyl-2,4-dimethoxy-6-methoxycarbonyl	135-137	6153

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Fluoro	17 to 25; 86/135	4382, 4755, 5676
5-Fluoro	102/at; n_D^{20} 1.4693	5857, 5858
5-Fluoro-1,3-bisethoxycarbonylmethyl-1,2,3,4-tetrahydro-2,4-dioxo	84–85	5081
5-Fluoro-1,3-bis- β -formylethyl-1,2,3,4-tetrahydro-2,4-dioxo	liq; anal.	6400
5-Floro-2,4-bismethylthio	39	4889
5-Fluoro-1,3-dihexyl-1,2,3,4-tetrahydro-2,4-dioxo	42	6400
5-Fluoro-1,2-dihydro-1- β -hydroxyethyl-4-methylthio-2-oxo	161–162	4889
5-Fluoro-1,2-dihydro-4-methoxy-1-methyl-2-oxo	nmr	E, 6111
5-Fluoro-1,2-dihydro-1-methyl-4-methylamino-2-oxo	129–130	6026
5-Fluoro-1,2-dihydro-1-methyl-4-methylthio-2-oxo	154	4889, 6111
5-Fluoro-1,6-dihydro-1-methyl-2-methylthio-6-oxo	126–128	4889
5-Fluoro-1,2-dihydro-1-methyl-2-oxo	MS; anal.	4398
5-Fluoro-1,2-dihydro-4-methylthio-2-oxo-1-prop-2'-ynyl	141–142	4889
4-Fluoro-2,6-dihydroxy	—	E, 5734
5-Fluoro-2,4-dihydroxy	278 to 287; 1-N-Ox: 240	E, 3464, 4870, 4895, 5489, 5552, 5856, 5921, 6163, 6277, 6386, 6505
4-Fluoro-2,6-dihydroxy-5-methyl	210	4526
5-Fluoro-2,4-dimethoxy	48–50	E, 5956
2-Fluoro-4,6-dimethyl	12–14, 75/18	4755, 5676
4-Fluoro-2,6-dimethyl	72/21; n_D^{20} 1.4618	4755, 5676
5-Fluoro-2,4-diphenoxy	91–93	5956
2-Fluoro-4,6-diphenyl	94–96 or 95–98	4681, 4755
4-Fluoro-2,6-diphenyl	94–95	5761
5-Fluoro-2,4-dipiperidino	167/4; HCl: 100	5956
5-Fluoro-2,4-dipropoxy	117/8; n_D^{20} 1.4750	5956
2-Fluoro-5-formamido	116–118	4380
5-Fluoro-4-formyl-2,6-dihydroxy	262–263	5525
5-Fluoro-4-formyl-6-hydroxy-2-mercapto	> 300	5525

5-Fluoro-4-formyl-6-hydroxy-2-methylthio	220–222; oxime: 262	5525
5-Fluoro-4-formyl-6-hydroxy-2-propylthio	129–131	5525
5-Fluoro-2-hexyloxy-4-hydroxy	115	6515
5-Fluoro-4-hydrazino-2-hydroxy	> 250	4385
5-Fluoro-2-hydroxy	169 to 172	E, 4385, 4398, 4895, 5858
4-Fluoro-6-hydroxy-2, 5-dimethyl	222–223	3520
5-Fluoro-2-hydroxy-4-hydroxyamino	260	3464
5-Fluoro-2-hydroxy-4-mercapto	275 or 277–278	2581, 4385, 4895
5-Fluoro-2-hydroxy-4-methoxy	189–190	4895
5-Fluoro-4-hydroxy-2-methoxy	195–197	E, 4895, 6515
4-Fluoro-6-hydroxy-2-methyl	229–230	3520
4-Fluoro-6-hydroxy-5-methyl	199–200	3520
5-Fluoro-2-hydroxy-4-methylthio	221–223	E, 4385
5-Fluoro-4-hydroxy-2-methylthio	240	E, 4889
5-Fluoro-4-hydroxy-2-phenoxy	224–225	6515
5-Fluoro-4-hydroxy-2-propoxy	154	6515
4-Fluoro-2-isopropyl	141–142/720	5694
5-Fluoro-2-mercapto	160–161	5857, 5858
2-Fluoro-4-methoxy	76–79/135	4755
4-Fluoro-2-methoxy	65–66/135	4752
4-Fluoro-6-methoxy	6–7; 74/135	4752
5-Fluoro-2-methoxy	52/12; n_D^{20} 1.4785	4399
4-Fluoro-2-methoxycarbonylmethyl	anal.	5693
5-Fluoro-4-methoxy-2-piperidino	121/3; HCl: 92–93	5956
2-Fluoro-4-methyl	56/17; 68/120	4755, 5676
4-Fluoro-2-methyl	32/20; 66/140	4752, 5676
4-Fluoro-6-methyl	19–20; 60/187	4752, 5676
5-Fluoro-2-methyl	118–119/at	5857, 5858
4-Fluoro-5-methyl-2, 6-bis(trimethylsiloxy)	125/15	6191
4-Fluoromethyl-6-hydroxy-2-methylthio	226–227	E, 5785
2-Fluoro-4-methyl-6-phenyl	95–96	4755
4-Fluoro-6-methyl-2-phenyl	46–47; 144/12	4752
2-Fluoro-4-phenyl	57 or 61; 126/3	4755, 6041

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Fluoro-2-phenyl	47-48; 135/17	4752
4-Fluoro-6-phenyl	70 or 72; 120/5	4752, 6117
5-Fluoro-2-phenyl	66-68	5857, 5858
5-Fluoro-2-piperidino-4-propoxy	145/5; HCl: 106	5956
2-Fluorosulfonyl	57	5669
5-Fluorosulfonyl-2,4-dihydroxy	255-256	4798
2-Fluorosulfonyl-4,6-dimethyl	58	5669
2-Fluorosulfonyl-4-methyl	101-102/0.3	5669
2-Fluorosulfonyl-5-methyl	76-77	5669
5-Fluoro-1,2,3,4-tetrahydro-1,3-bis- β -hydroxyethyl-2,4-dioxo	liq; anal.	6400
5-Fluoro-1,2,3,4-tetrahydro-1,3-bis- γ -hydroxypropyl-2,4-dioxo	liq; anal.	6400
5-Fluoro-1,2,3,4-tetrahydro-1,3-bismethoxymethyl-2,4-dioxo	liq; anal.	6400
5-Fluoro-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	131 or 141	E, 6026, 6350
5-Fluoro-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thio	171-172	6026
5-Fluoro-1,2,3,4-tetrahydro-2,4-dioxo-1,3-bis- β -propionylethyl	75	6400
5-Fluoro-1,2,3,4-tetrahydro-2,4-dioxo-1,3-bispropoxymethyl	liq; anal.	6400
5-Fluoro-1,2,3,4-tetrahydro-2,4-dioxo-1,3-diprop-2'-ynyl	98	6350
5-Fluoro-1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxo	114-115	6026
4-Fluoro-2-trifluoromethyl	71-72/135	4752
5-Fluoro-2,4,6-trimethoxy	98-99	3521
5-Fluoro-2,4,6-trisheptafluoroisopropyl	163/at	5242
5-Fluoro-2,4,6-trisperfluoro-s-butyl	-	6192
5-Formamido	186-187	4380
5-Formamido-2,4-bis- <i>N</i> -methylformamido	>300	6289
5-Formamido-1,6-dihydro-1-methyl-2,4-bismethylamino-6-oxo	291-292	3253, 5048
4-Formamido-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo	169-170	4644
5-Formamido-2,4-dihydroxy-6-isopropylamino	264	4627
5-Formamido-2,4-dimercapto-6-methyl	285-287	5689
5-Formamido-2-hydroxy	>360	4380
5-Formamido-4-hydroxy-2,6-bismethylamino	282-283	3253, 5048

5-Formamido-4-hydroxy-6-methyl	190–191	5634
5-Formamido-2-mercapto	295–298	4380
5-Formamido-4-mercapto-6-methyl-2-methylthio	248–250	5689
5-Formamido-4-mercapto-6-methylthio	213–214	4358
5-Formamido-2-methoxy	181–182	4380
5-Formamido-4-methyl-2,6-bismethylthio	180–181	5689
4-Formamidomethyl-2,6-dihydroxy	–	5868
5-Formamido-2-methyl-4-methylamino-6-methylthio	222–223	2675
5-Formamido-2-methylsulphonyl	161–162	4380
4-Formamidomethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	–	5868
4-Formamidomethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-1-phenyl	238	6274
5-Formamido-2-methylthio	122–123	4380
5-Formamido-2-phenyl	170–171	6510
5-Formamido-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	160	4936
5-Formamido-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxo	250 then 285	6231
5-Formamido-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo	152	4936
2-Formyl	78–80; oxime (<i>syn</i>): 240; DNP: 273	4751, 5977
5-Formyl	39–41	E, 5794
2-Formyl-1,6-dihydro-1,4-dimethyl-6-oxo	oxime: 194	5090
5-Formyl-1,6-dihydro-1-methyl-4-methylamino-6-oxo-2-phenyl	211–212	6190
4-Formyl-1,2-dihydro-1-methyl-2-oxo	oxime: 240	5414
4-Formyl-1,6-dihydro-1-methyl-6-oxo	oxime: 257	6069
4-Formyl-2,6-dihydroxy	273–275	H, E, 4604, 5617, 5876, 6066
5-Formyl-2,4-dihydroxy	304–306	E, 4482, 5211, 5473, 5642, 5846
5-Formyl-4,6-dihydroxy	250–252	E, 5794, 5819
4-Formyl-2,6-dihydroxy-5-hydroxymethyl	212–213	4528
5-Formyl-2,4-dihydroxy-6-methyl	220–223	E, 4482, 5643
5-Formyl-4,6-dihydroxy-2-methyl	230–240	E, 5794
5-Formyl-2,4-dihydroxy-5-nitro	oxime: 218–220	5576
5-Formyl-4,6-dihydroxy-2-phenyl	340–345	E, 5794
5-Formyl-2,4-dihydroxy-6-phenylthio	> 300	6112

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Formyl-2,6-dimethoxy	107	5597
5-Formyl-2,4-dimethoxy	123	5597
2-Formyl-4,6-dimethyl	89–90; oximes (<i>syn</i>): 198; (<i>anti</i>): 78	H, 4751, 4753, 5977, 6008
2-Formyl-4,6-diphenyl	126–128; DNP: 260	4875, 5977
5-Formylethynyl-2,4-dimethoxy-6-methoxycarbonyl	156–158	6153
4-Formyl-5-hexyl-6-hydroxy-2-mercapto	123–125	5526
4-Formylhydrazino-2,6-dihydroxy	> 230	4721
4- β -Formylhydrazino-2,6-dimethyl-5-nitro	157–158	5634
4- β -Formylhydrazino-6-hydroxy-5-nitro	242 or 265	5231, 5661
4- β -Formylhydrazino-6-methyl-2-methylthio	191 or 200	5054, 5697
4-Formyl-2-hydroxy	226	5621
5-Formyl-4-hydroxy	245–247	3764
4-Formyl-6-hydroxy-2-mercapto	249	H, E, 6066
4-Formyl-2-hydroxy-6-methyl	oxime: 274	2592
4-Formyl-5-hydroxymethyl-2-methylthio	135–136	3443
5-Formyl-4-hydroxy-6-methyl-2-piperidino	235	H, E, 5722
4-Formyl-2-hydroxy-6-phenyl	oxime: 236	2592
4-Formyl-2-isopropyl-6-methyl	100–102/20	6008
2-Formyl-4-methyl	oxime: ?	5074
4-Formyl-2-methyl	oxime; ?	E, 5074
4-Formyl-5-methyl	oxime: 155	5862
4-Formyl-6-methyl	oxime: 150	E, 5074
5-Formylmethyl-2,4-dihydroxy	sp; DNP 257	5548
2- α -Formyl- α -methylethyl-4,6-dimethyl	65/1	5083
2- α -Formyl- α -methylethyl-4-isopropoxy-6-methyl	75–80/1	5083
2- α -Formyl- α -methylethyl-4-methoxy-6-methyl	70/1	5083
2- α -Formyl- α -methylethyl-4-methyl-6-phenyl	85; 125/1	5083
4-Formyl-5-methyl-2-methylthio	oxime: 178	3443
5-Formyl-4-methyl-2-methylthio	63–64	6398

4-Formyl-2-methyl-6-phenyl	63–64; 3- <i>N</i> -Ox: 206	6136
4-Formyl-6-methyl-2-phenyl	80–81; 3- <i>N</i> -Ox: 216	E, 6136
2-Formyl-4-phenyl	1- <i>N</i> -Ox/oxime: 249	4811
4-Formyl-2-phenyl	116–117	E, 6299
4-Formyl-6-phenyl	3- <i>N</i> -Ox/oxime: 254	4811
4-Formyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	76–77	6853
5-Formyl-1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl	200	4923
5-Formyl-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo	121–122	4923
5-Formyl-2,4,6-trihydroxy	230 to 340	H, E, 5819, 5900, 6066
5-Formyl-2,4,6-trimethoxy	oxime: 249	E, 2815, 5988
2-Guanidinoamino-4,6-bis(trifluoromethyl)	HNO ₃ : 262	6009
2-Guanidinoamino-4-isoamyl-6-trifluoromethyl	HNO ₃ : 178	6009
2-Guanidinoamino-4-isobutyl-6-trifluoromethyl	HNO ₃ : 201	6009
2-Guanidinoamino-4-methyl-6-trifluoromethyl	HNO ₃ : 191	5713
2-Guanidinoamino-4-phenyl-6-trifluoromethyl	HNO ₃ : 197	6010
2-Guanidino-4-hydroxy-6-methyl-5-propyl	291–292	5722
Hexahydro-5-hydroxy-1,3,5-trimethyl-2,4,6-trioxo	107	E, 5899
Hexahydro-1,3,5,5-tetramethyl-2,4,6-trioxo	109	H, E, 3768
5-Hex-5'-enyl-4,6-dihydroxy-2-methyl	anal.; sp	5290
5-Hex-5'-enyl-4-hydroxy-2,6-dimethyl	89–91	5290
4-Hexylamino-6-hydroxy-5-nitro	169–170	4396
5-Hexylaminomethyl-2,4-dihydroxy	HCl: 270	5475
1-Hexyl-1,2-dihydro-4-isopropyl-6-methyl-2-oxo	74–75	4847
5-Hexyl-2,4-dihydroxy	273–274	H, 5754
2-Hexy-4,6-dimethyl	85/4	5096
4-Hexyl-6-hydroxy-5-β-hydroxyethyl-2-mercapto	145–146	5361
5-Hexyl-4-hydroxy-6-methyl-2-methylthio	146–147	5124
4-Hexylenediazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	158	4929
2-Hexylthio-5-hydroxy	101	4395
2-Hexylthio-4-hydroxy-5-methoxy	98	4395
2-Hexylthio-5-methoxy	120/0.3	4395
2-Hex-1'-ynyl	125/3; pic: 76	5094
4-Hex-1'-ynyl-2,6-dimethoxy	160/3	5094

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Hex-1'-ynyl-4,6-dimethyl	135/3 or 170/3	5093, 5094, 6353
4-Hex-1'-ynyl-2,6-dimethyl	125/3	5093, 5094
4-Hex-1'-ynyl-2-isopropyl-6-methyl	130/3	5094
5-Hex-1'-ynyl-2-isopropyl-4-methyl	140-143/3	5094
2-Hex-1'-ynyl-4-methoxy-6-methyl	135/3	5094
4-Hex-1'-ynyl-6-methyl-2-methylthio	165/3	5094
4-Hex-1'-ynyl-2-methyl-6-phenyl	170-175/3	6353
4-Hex-1'-ynyl-6-methyl-2-phenyl	170-175/3	5094
2-Hex-1'-ynyl-4-methyl-6-piperidino	165/3	5094
2-Hydrazino	108	H, E, 5340
4-Hydrazino	132-134	H, 5340
5- β -Hydrazinocarbonyl-2,4-dihydroxy-6-methyl	268-270	5707
5- β -Hydrazinocarbonyl-4-hydroxy-2-mercapto-6-methyl	276-280	5707
5-Hydrazinocarbonyl-4-hydroxy-2-isoamylamino	214-215	5885
5-Hydrazinocarbonyl-4-mercapto-6-methyl-2-phenyl	284-286	4723
4-Hydrazinocarbonylmethyl-2,6-dihydroxy	> 300	H, E, 6101
5-Hydrazinocarbonylmethyl-4-methyl	141-142	5982
4-Hydrazinocarbonyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo	212-213	5895
5-Hydrazinocarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo	202-203	5895
4-Hydrazino-1,2-dihydro-1,5-dimethyl-2-oxo	169-172	4385
4-Hydrazino-1,2-dihydro-1-methyl-2-oxo	> 150 or 177-179	E, 4385, 5313
4-Hydrazino-1,2-dihydro-6-methyl-2-oxo-1-phenyl	257-258	4859
4-Hydrazino-2,6-dihydroxy	290	E, 5968
2-Hydrazino-4,6-dimethoxy	101-104	E, 6197
4-Hydrazino-2,6-dimethoxy-5-nitro	155-156	5994
2-Hydrazino-4,6-dimethyl	162	H, E, 5669
4-Hydrazino-2,5-dimethyl	198-200	5695
4-Hydrazino-2,6-dimethyl	186-187	E, 5669
4-Hydrazino-2,6-dimethyl-5-nitro	127-128	5634, 5994
2-Hydrazino-5-hydrazinocarbonyl-4-hydroxy	275	5885

2-Hydrazino-4-hydroxy	190–191	E, 4368
4-Hydrazino-2-hydroxy	> 350	E, 4385, 5712
4-Hydrazino-6-hydroxy	> 230 or 255	5491, 5681
2-Hydrazino-4-hydroxy-5- β -hydroxyethyl-6-methyl	227–228	5053
4-Hydrazino-2-hydroxy-6-hydroxymethyl	> 250	5366
2-Hydrazino-4-hydroxy-6-methyl	–	H, E, 6148
4-Hydrazino-2-hydroxy-6-methyl	–	H, E, 5712
4-Hydrazino-6-hydroxy-2-methyl	155–156	5491
4-Hydrazino-5-hydroxymethyl-2-methylthio	145–146	3474
4-Hydrazino-2-hydroxy-6-methyl-5-nitro	228–229	5660
2-Hydrazino-4-hydroxy-6-methyl-5-propyl	216–218	E, 5722
4-Hydrazino-2-hydroxy-5-nitro	208–209	5661
4-Hydrazino-6-hydroxy-2-phenyl	227–228	5491
2-Hydrazino-5-iodo	196–197	5262
4-Hydrazino-5-iodo-2-isopropyl-6-methyl	108–109	5094
4-Hydrazino-2-mercapto-6-methyl	280	E, 5697
2-Hydrazino-5-methoxy	141–142	4399
4-Hydrazino-6-methoxy	148–149	6197
2-Hydrazino-5-methoxycarbonyl	224–226	4399
2-Hydrazino-4-methoxy-6-methyl	113–114	H, E, 6197
4-Hydrazino-2-methoxy-6-methyl	154–156	6197
4-Hydrazino-6-methoxy-2-methyl	148–149	6197
4-Hydrazino-2-methoxy-6-methyl-5-nitro	136–138	5660
4-Hydrazino-6-methoxy-2-methyl-5-nitro	144–145	5634
4-Hydrazino-2-methoxy-5-nitro	135–136	5660
4-Hydrazino-6-methoxy-5-nitro	154–155	2562
2-Hydrazino-4-methyl	–	H, E, 4408
2-Hydrazino-5-methyl	137 to 144	4399, 5669, 5691
4-Hydrazinomethyl-2,6-dihydroxy	288–290	5854
4-Hydrazino-6-methyl-2-methylthio	142–145	E, 5054, 5355, 5697
4-Hydrazino-2-methyl-5-nitro	152	3312, 5634
4-Hydrazino-6-methyl-5-nitro-2-propoxy	107–109	5660
4-Hydrazino-2-methyl-6-phenyl	138–139	6039
5-Hydrazino-2-methylsulfonyl	186–189	4399

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Hydrazino-2-methylthio-5-nitro	198	5661
2-Hydrazino-5-nitro	169 or 173–175	3463, 5285
4-Hydrazino-5-nitro	148 or 151	2857, 2858, 5674
4-Hydrazino-5-nitro-2-propoxy	83–84	5674
4-Hydrazino-5-phenyl	141–143	H, E, 4683
2-Hydrazinosulfonyl-4, 6-dimethyl	124–125	5669
4-Hydrazino-1, 2, 3, 4-tetrahydro-1, 3-dimethyl-2, 6-dioxo	220 or 226–229	E, 4927, 4939
4-Hydrazino-1, 2, 3, 6-tetrahydro-1, 3-dimethyl-6-oxo-2-thio	223–224	6014
4-Hydrazino-1, 2, 3, 6-tetrahydro-1-methyl-2, 6-dioxo-3-phenyl	230–232	4929
4-Hydrazino-2, 5, 6-triphenyl	202; HCl: 303	4602
4-Hydrazonomethyl-1, 2, 3, 6-tetrahydro-1, 3-dimethyl-2, 6-dioxo	232–233	4943
4-Hydrazono-1, 2, 3, 4-tetrahydro-1, 3-dimethyl-2-oxo	129	5313
5-Hydroperoxymethyl-2, 4-dihydroxy	> 230	5211
2-Hydroxy	315–320	6204
4-Hydroxy	161 or 178–180; 1-N-Ox/HBr: 220 162–164	H, E, 4385, 4583, 4600, 5342 H, E, 4364, 5342, 5550
2-Hydroxyamino	180	6423
2-Hydroxyamino-4, 6-dimethyl	207–210	E, 6423
4-Hydroxyamino-2, 6-dimethyl	198–200	6423
2-Hydroxyamino-4-methyl	105	6423
4-Hydroxyamino-2, 5, 6-triphenyl	205–207; O-Ac: 178	4614
4- α -Hydroxybenzyl	95–96	5515
2- α -Hydroxybenzyl-4, 6-dimethyl	80	5241
4-Hydroxy-2, 6-bismethylamino	242–245	E, 3253
2-Hydroxy-4, 6-bismethylthio	208–210	E, 4949
4-Hydroxy-2, 5-bismethylthio	206–208	3765
4-Hydroxy-2, 6-diisopropyl	109–110	5909
4-Hydroxy-2, 6-dimethoxy	195	5153, 5156

4-Hydroxy-2,6-dimethoxy-5-methyl	224–226	5153, 5156
4-Hydroxy-2,6-dimethoxy-5-phenyl	239–240	5153, 5156
2-Hydroxy-4,6-dimethyl	199; HCl: 260 or 281	H, E, 4467, 5349, 5669, 6932
4-Hydroxy-2,5-dimethyl	—	H, E, 6201
4-Hydroxy-2,6-dimethyl	190 to 200	H, E, 5071, 5075, 5079, 5267, 5550, 5667, 6169
4-Hydroxy-5,6-dimethyl	208–209	H, E, 4387
4-Hydroxy-2,6-dimethyl-5-methylcarbamoylmethyl	272–275	E, 5965
4-Hydroxy-5,6-dimethyl-2-methylthio	220–223	H, E, 5124
5-Hydroxy-4,6-dimethyl-2-methylthio	225–229	6373, 6423
4-Hydroxy-2,6-dimethyl-5-pent-4'-enyl	111–112	5290
4-Hydroxy-5,6-dimethyl-2-piperidino	157	5722
2-Hydroxy-4,6-dimethyl-5-propyl	181	2700
2-Hydroxy-4,6-dimethyl-5-prop-1'-ynyl	257	2700
2-Hydroxy-4,6-dimethyl-5-prop-2'-ynyl	231	2700
4-Hydroxy-2,6-dimethyl-5-prop-2'-ynylcarbamoylmethyl	257–258	E, 5965
2-Hydroxy-4,6-diphenyl	232 or 235–238	E, 4681, 4756, 5673, 6210, 6542
4-Hydroxy-2,5-diphenyl	297 or 300	E, 4497, 4674
4-Hydroxy-2,6-diphenyl	287 or 290–291	H, 3522, 5760, 5941, 5943, 6339, 6377
5-Hydroxy-4,6-diphenyl	181–182	5499
2-Hydroxy-4,6-diphenyl-5-phenylthio	275–277	4756
2-Hydroxy-4,5-diphenyl-6-styryl	268–270	5984
4-Hydroxy-2,6-dipiperidino	211–213	5946
4-Hydroxy-5,6-dipivalamido	251–253	5447
5-β-Hydroxyethyl-4-methyl	155–156/8	5834
4-α-Hydroxyethyl-2-methyl-6-phenyl	160–165/3	6299
4-α-Hydroxyethyl-6-methyl-2-phenyl	160–163/3	6299
4-Hydroxy-6-hydroxyamino-2-methyl	338	5969
4-Hydroxy-5,4'-hydroxybut-1'-enyl-2-mercaptop	<i>cis</i> : 206, <i>trans</i> : 226	5429
4-Hydroxy-5,4'-hydroxybut-1'-enyl-2-methylthio	171–172	5429

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Hydroxy-5- β -hydroxyethyl	153–155	5881
4-Hydroxy-5- β -hydroxyethyl-2-mercapto	—	E, 5881
4-Hydroxy-5- β -hydroxyethyl-2-mercapto-6-methyl	251 or 257–258	H, E, 5361, 5917
4-Hydroxy-5- β -hydroxyethyl-2-mercapto-6-phenyl	192–193	5917
4-Hydroxy-5- β -hydroxyethyl-2-mercapto-6-propyl	267–268	5361
4-Hydroxy-2- α -hydroxyethyl-6-methyl	134–135	5075
4-Hydroxy-5- β -hydroxyethyl-6-methyl-2-methylthio	HCl: 194–195	E, 4566
4-Hydroxy-2-hydroxymethyl	194	E, 6119
4-Hydroxy-5-3-hydroxymethylcyclopentyl-2-mercapto	<i>cis</i> : 211–213	5431
2-Hydroxy-4-hydroxymethyl-6-mercapto	226–227	5366
4-Hydroxy-6-hydroxymethyl-2-mercapto	263–264	H, 5175
4-Hydroxy-5-hydroxymethyl-2-methyl	207	H, E, 6201
4-Hydroxy-6- γ -hydroxymethyl-2-methylthio	221–222	E, 5175
4-Hydroxy-6- γ -hydroxypropyl-2-mercapto	247–249	5532
4- α -(Hydroxyimino)ethyl	184–185	5862
4-Hydroxyiminomethyl-2, 6-dimethyl	hyd: 195; di- <i>N</i> -Ox: 220	E, 5284, 6160
4-Hydroxyiminomethyl-2-isopropyl-6-methoxy	146–147	5074
4-Hydroxyiminomethyl-6-methoxy-2-methyl	230–231	5089
4-Hydroxyiminomethyl-6-methoxy-2-phenyl	135–136	5074
4-Hydroxyiminomethyl-5-methyl	155	5862
4-Hydroxyiminomethyl-6-methyl	150 or 180 (?)	E, 5074, 5284
4-Hydroxyiminomethyl-2-methyl-6-phenyl	200–202	5090
2-Hydroxy-5-iodo	>200	5664
4-Hydroxy-5-iodo-2-isopropyl-6-methyl	185–186	5094
2-Hydroxy-5-iodo-4-methoxy	228–229	3399
4-Hydroxy-5-isoamyl-2-mercapto-6-methyl	222–223	H, 2816
4-Hydroxy-5-isoamyl-6-methyl	124–126	2816
4-Hydroxy-2-isoamylthio	105–108	H, 5121
4-Hydroxy-2-isoamylthio-6-methyl	92–94	5121
4-Hydroxy-2-isoamylthio-6-phenyl	164–165	5121

4-Hydroxy-2-isoamylthio-6-propyl	52–53	5121
4-Hydroxy-2- β -isobutoxyethyl-6-methyl	110–112	4513
4-Hydroxy-6-isobutyl-5-isopropyl-2-mercapto	201–203	5890
4-Hydroxy-5-isobutyl-2-isopropyl-6-methyl	154–155	5076
5-Hydroxy-2-isobutylthio	128	4395
4-Hydroxy-2-isobutylthio-5-methoxy	151	4395
4-Hydroxy-5- β -isocyanatoethyl-2-mercapto-6-methyl	207–209	5707
4-Hydroxy-2-isopropenyl-6-methyl	147–148	5080
4-Hydroxy-5-isopropoxycarbonylmethyl-2,6-dimethyl	277–280	5965
4-Hydroxy-2- β -isopropoxyethyl-6-methyl	129–130	4513
2-Hydroxy-4-isopropoxy-6-methyl	142–143	4387
4-Hydroxy-2-isopropoxy-6-trifluoromethyl	131	5589
2-Hydroxy-5-isopropyl	94	4463
4-Hydroxy-2-isopropyl	143–144	5694
4-Hydroxy-2-isopropylamino-5-methyl	170–171	4572
4-Hydroxy-6-isopropylamino-5-nitro	208–209	5442
4-Hydroxy-5-isopropyl-2-mercapto	237 to 245	H, 5875, 5890, 5964
4-Hydroxy-5-isopropyl-2-mercapto-6-methyl	257–258	H, 5890
4-Hydroxy-6-isopropyl-2-mercapto-5-methyl	179–180	5890
4-Hydroxy-2-isopropyl-6-methyl	172 or 172–174	H, E, 5075, 5080, 6169
4-Hydroxy-6-isopropyl-2-methyl	138–139	5909
4-Hydroxy-5-isopropyl-4-methyl-2-phenyl	202–204	4348
4-Hydroxy-2-isopropyl-6-phenyl	233–234	H, 5690
4-Hydroxy-6-isopropyl-2-phenyl	160–161	5909
4-Hydroxy-6-isopropyl-2-propyl	55–56; 181/2	5909
2-Hydroxy-4-mercapto	317–321	H, E, 5712
4-Hydroxy-2-mercapto	–	H, E, 5417
4-Hydroxy-2-mercapto-5,6-dimethyl	286 or 288–290	H, E, 4716, 4725
4-Hydroxy-2-mercapto-5-methoxy	301–303	H, E, 6048
4-Hydroxy-2-mercapto-5-methoxycarbonylmethyl	211	5973
4-Hydroxy-2-mercapto-5- α -methoxyethyl	168–169	5428
4-Hydroxy-2-mercapto-5-methoxy-6-methyl	215 or 291	E, 4397, 5786
2-Hydroxy-4-mercapto-6-methyl	341–342	H, 5712

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Hydroxy-4-mercapto-5-methyl	306-307	H, E, 5573
2-Hydroxy-4-mercapto-6-methyl	339-341	6202
4-Hydroxy-2-mercapto-5-methyl	265-267	H, E, 5417, 5418
4-Hydroxy-6-mercapto-2-methyl	297 or 301	H, 4361, 5667
5-Hydroxy-4-mercapto-2-methyl	226-228	5958
4-Hydroxy-2-mercapto-5-methylcarbamoylmethyl	310-315	E, 5965
4-Hydroxy-2-mercapto-6-methyl-5-methylcarbamoylmethyl	299-303	E, 5965
4-Hydroxy-2-mercapto-5-methylthio	271-273	3765
4-Hydroxy-2-mercapto-5-nitro	243-245	E, 5418
4-Hydroxy-2-mercapto-5-phenyl	308-311	H, 5861
4-Hydroxy-2-mercapto-6-phenyl	-	H, E, 4675
4-Hydroxy-6-mercapto-2-phenyl	357	4361
4-Hydroxy-2-mercapto-5-propyl	159-161	H, 5890, 5964
4-Hydroxy-2-mercapto-6-propyl	-	H, E, 6199
4-Hydroxy-2-mercapto-5- α -thioureidoethyl	202-203	5428
4-Hydroxy-2-mercapto-5-vinyl	>170	5428
2-Hydroxy-4-methoxy	203 to 216	H, E, 3399, 4394, 5490
2-Hydroxy-5-methoxy	187-189	3000
4-Hydroxy-2-methoxy	167-168	5490
2-Hydroxy-5-methoxycarbonyl	192; HBr: 178	5430
4-Hydroxy-5- β -methoxycarbonylethyl-2-methyl	crude	6200
4-Hydroxy-2-methoxycarbonylmethyl	180-181	5693
4-Hydroxy-6-methoxycarbonyl-2-methyl	224-226	E, 4821
4-Hydroxy-5-methoxycarbonyl-2-methylthio	207-209	4399
4-Hydroxy-5-methoxycarbonyl-2-methyl-6-trichloromethyl	235-236	5913
4-Hydroxy-5-methoxycarbonyl-2-phenyl-6-trichloromethyl	281-283	5913
4-Hydroxy-6-methoxycarbonyl-2-pyrrolidino	178	6227
4-Hydroxy-6-methoxycarbonyl-2-trichloromethyl	165-167	4821
2-Hydroxy-4-methoxy-5,6-dimethyl	249-250	E, 4387, 4394

2-Hydroxy-5-methoxy-4,6-diphenyl	238–240	4756
4-Hydroxy-2- β -methoxyethyl-6-methyl	133–135	4513
4-Hydroxy-5-methoxy-6-methoxymethyl	149–150	E, 4397
2-Hydroxy-4-methoxy-5-methyl	220 to 227	E, 4394, 5490
4-Hydroxy-2-methoxymethyl	HCl: 228–231	6119
4-Hydroxy-2-methoxy-5-methyl	198–199	5490
4-Hydroxy-5-methoxy-2-methyl	212–215	E, 6348
4-Hydroxy-5-methoxy-6-methyl	158–159	E, 5786
4-Hydroxy-2- α -methoxy- α -methyl-ethyl	98–100	5690
4-Hydroxy-5- α -methoxy- α -methyl-ethyl-2-phenyl	188–191	6198
4-Hydroxy-5-methoxy-6-methyl-2-methylthio	202–203	4397
4-Hydroxy-5-methoxymethyl-2-phenyl	188–191	5105
4-Hydroxy-6-methoxy-2-methylthio	198–199	E, 4656
4-Hydroxy-5-methoxy-2-methylthio-6-propyl	90–92	5532
4-Hydroxy-6-methoxy-5-nitro	242–243	E, 5491
2-Hydroxy-4-methoxy-6-nitroamino	181	4656
4-Hydroxy-5-methoxy-2-phenyl	213–215	E, 4674
4-Hydroxy-5-methoxy-2-propylthio	143–144	4395
2-Hydroxy-4-methyl	pic: 192	H, E, 2602
2-Hydroxy-5-methyl	209 to 218	E, 4384, 4463, 5691
4-Hydroxymethyl	67–68	5682
4-Hydroxy-2-methyl	213–214; HCl: 260	H, E, 5253, 5550, 5667, 5829, 6119
4-Hydroxy-5-methyl	150 or 154–156	H, E, 4741, 5676
4-Hydroxy-6-methyl	142 to 149	H, E, 4466, 4684, 4819, 5084, 5918
5-Hydroxymethyl	60	5794
2-Hydroxy-4-methylamino	271	H, E, 5612
4-Hydroxy-2-methylamino	215 or 217–218	E, 4670, 5417
4-Hydroxy-6-methylamino-5- <i>N</i> -methylcarbamoyl-2-phenyl	> 300	4953
4-Hydroxy-6-methylamino-5-nitro	> 300	H, 5442
4-Hydroxy-6-methylamino-5-nitroso-2-phenyl	253	5002
4-Hydroxy-6-methylamino-2-phenyl	270	5002
5-Hydroxymethyl-2,4-bis(methylamino)-6-methylcarbamoyl	163	2884

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Hydroxy-4-3'-methylbut-2'-enylamino	sol: 229-230	3471
2-3'-Hydroxy-3'-methylbut-1'-ynyl	78-79	6265
4-Hydroxy-5-methylcarbamoymethyl-2-methylthio	213-216	E, 5965
4-Hydroxy-5-methylcarbamoymethyl-2-phenyl	310-315	E, 5965
2-Hydroxymethyl-4,6-dimethyl	87-89	5086, 5682, 6008
4-Hydroxymethyl-2,6-dimethyl	109-110	5682, 6008
2-Hydroxy-5-methyl-4,6-diphenyl	238-240	4756
2- α -Hydroxy- α -methyl-4-phenyl	liq; MS	5690
4-Hydroxymethyl-2-isopropyl-6-methyl	135-138/20	6008
4-Hydroxymethyl-2-methoxy	crude: 105; nmr	4359
2-Hydroxymethyl-4-methoxy-6-methyl	56-57	5086
4-Hydroxymethyl-2-methoxy-6-methyl	146-147	5086
4-Hydroxymethyl-6-methoxy-2-methyl	116	5086
5-Hydroxymethyl-4-methylamino-2-methylthio	157-158	3474
2-Hydroxy-4-methyl-6-methylamino-5-nitro	246-249	H, E, 5432
4-Hydroxy-5-methyl-2-methylamino-6-phenyl	220	5725
5-Hydroxymethyl-4-methylcarbamoyl-2,6-bismethylamino	163	2884
4-Hydroxy-6-methyl-5-methylcarbamoymethyl-2-methylthio	266-269	E, 5965
5-Hydroxymethyl-4-methyl-2-methylthio	48-49	3474
2-Hydroxymethyl-4-methyl-6-phenyl	149-150/1	5086
4-Hydroxymethyl-2-methyl-6-phenyl	94-96	5086, 6136
4-Hydroxymethyl-6-methyl-2-phenyl	152/1; 3-N-Ox: 138	5086, 6136
4-Hydroxy-2-methyl-5-methylsulfonyl	220-223	3506
4-Hydroxy-2-methyl-6-methylsulfonyl	215-216	3505
4-Hydroxy-6-methyl-5-methylsulfonyl-2-piperidino	252	5391
2-Hydroxy-4-methyl-6-methylthio	178-180	H, 5712, 6202
4-Hydroxy-2-methyl-6-methylthio	222-224	H, 3505
4-Hydroxy-6-methyl-2-methylthio	222	H, E, 5121
5-Hydroxymethyl-2-methylthio	63-64	3443
4-Hydroxymethyl-2-methylthio-5-phenylthio	70-71	4400

4-Hydroxy-6-methyl-2-methylthio-5-propyl	181–182	H, E, 5124
4-Hydroxy-5-methyl-2,4'-methyl(thiosemicarbazido)	222–223	6133
4-Hydroxy-6-methyl-5-nitro	228–229	5634
4-Hydroxy-2-methyl-5-pent-4'-enyl-6-phenyl	91–93	5290
2-Hydroxy-4-methyl-6-phenyl	228–229	H, 2592, 6212
4-Hydroxymethyl-2-phenyl	crude; nmr	4359
4-Hydroxy-2-methyl-6-phenyl	235–237 or 246–248	H, E, 5550, 6377
4-Hydroxy-5-methyl-2-phenyl	185–186 or 201	4478, 5792
4-Hydroxy-6-methyl-2-phenyl	213–215 or 218–221	H, E, 4484, 5075, 6169, 6339, 6377
4-Hydroxy-6-methyl-2-phenylguanidino	256–258	6205
4-Hydroxy-5-methyl-2-phenyl-6-piperidino	240	6072
4-Hydroxy-6-methyl-2-phenylureido	275–276	6205
4-Hydroxy-5-methyl-2-piperidino	160–161	4572
4-Hydroxy-6-methyl-2-piperidinomethyl	212–216	5722
4-Hydroxy-6-methyl-2-prop-1'-enyl	185–187	5080
4-Hydroxy-6-methyl-2- β -propoxyethyl	112–114	4513
4-Hydroxy-6-methyl-2-propyl	143 or 148–149	H, E, 5075, 5080
4-Hydroxy-2-methyl-6-propylamino	198	5015
5- α -Hydroxy- α -methylpropyl-2,4-dimethyl	120/1	5089
4-Hydroxy-6-methyl-2-propylthio	123	5121
5-Hydroxy-2-methylsulfinyl	148–149	4395
5-Hydroxy-2-methylsulfonyl	180–182	3000
4-Hydroxy-2-methylthio	196 to 201	H, E, 4368, 5121, 5418
4-Hydroxy-6-methylthio	229–234	E, 5536
4-Hydroxy-6-methyl-2-thiocyanato	100–101 or 168–169	5146, 6334
4-Hydroxy-5-methylthio-2,6-diphenyl	287–290	5068
4-Hydroxy-5-methylthio-2-phenyl	203–204	4674
4-Hydroxy-2-methylthio-6-propyl	119 or 155–157	H, E, 5121, 5532
4-Hydroxy-2,4'-methyl(thiosemicarbazido)	192–193	6133
4-Hydroxy-2-methylthio-6-trifluoromethyl	181–182	5785
4-Hydroxy-6-methyl-2-thioureido	232	6203
4-Hydroxy-2-methyl-6-trichloromethyl	194–195	5072

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Hydroxy-6-methyl-2-trichloromethyl	175 or 177–179	5079, 6033
2-Hydroxy-4-methyl-6-trifluoromethyl	HCl: 195	4467
2-Hydroxy-5-nitro	199–200 or 203; EtOH: 205–208	H, E, 5342, 5411, 6372
4-Hydroxy-5-nitro	190–192	E, 4357, 5411
4-Hydroxy-5-nitro-2,6-diphenyl	310–312	4485
4-Hydroxy-5-nitro-6-piperidino	160	5442
2-Hydroxy-5-phenoxy-4,6-diphenyl	257–260	4756
2-Hydroxy-4-phenyl	239–241	H, E, 6042
2-Hydroxy-5-phenyl	237	H, 5635
4-Hydroxy-2-phenyl	204–206	H, 4364, 6038
4-Hydroxy-5-phenyl	173 to 178	H, E, 4501, 4601, 5477
4-Hydroxy-6-phenyl	270	H, E, 5816, 5918, 5927
5-Hydroxy-4-phenyl	3-N-Ox: 246	6254
4-Hydroxy-2-phenylguanidino-5,6-bistrifluoromethyl	253–254	6506
4-Hydroxy-6-phenyl-2-propylthio	190–192	5121
4-Hydroxy-2-phenylthio	178–180	6185
2-Hydroxy-4- <i>N'</i> -phenylureido	anal.	5273
4-Hydroxy-2-piperidino	154	E, 5866
4-Hydroxy-6-piperidino	259–263	6094
2-Hydroxy-5-propyl	116	4463
4-Hydroxy-6-propyl	110–112	E, 5918
4-Hydroxy-2-propylthio	66	5121
4-Hydroxy-2-propylthio	102–104	H, 5121
5-Hydroxy-2-propylthio	102	4395
5-3'-Hydroxyprop-1'-ynyl-2,4-dimethoxy-6-methoxycarbonyl	136–137	6153
2-3'-Hydroxyprop-1'-ynyl-4,6-dimethyl	155–157	5093, 5094
4-3'-Hydroxyprop-1'-ynyl-2,6-dimethyl	121–123	5093, 5094

4-3'-Hydroxyprop-1'-ynyl-2-isopropyl-6-methyl	145/2	5094
5-3'-Hydroxyprop-1'-ynyl-2-isopropyl-4-methyl	155/1	5094
2-3'-Hydroxyprop-1'-ynyl-4-methoxy-6-methyl	158-160	5094
4-3'-Hydroxyprop-1'-ynyl-6-methyl-2-methylthio	102-103	5094
2-Hydroxy-4-semicarbazido	sp	4735
4-Hydroxy-2-sulfo	K: anal.	5159
2-Hydroxy-6-thiocyanato	225-227	6206
4-Hydroxy-2-trifluoromethyl	—	E, 5294
2-Hydroxy-4,5,6-trimethyl	243; HCl: 278	H, 5247, 6325
4-Hydroxy-2,5,6-triphenyl	292 to 310	H, E, 4602, 4614, 5827, 5944
5-Hydroxy-2,4,6-triphenyl	203-204	4477
2-Iodo	30-32	E, 5673
5-Iodo	126	5262
5-Iodo-2,4-dimethoxy-6-methoxycarbonyl	112-113	6153
2-Iodo-4,6-dimethyl	127-129	2603
4-Iodo-2,6-dimethyl	111 or 112	2603, 5673
5-Iodo-2,4-dimethyl	81-82	6390
5-Iodo-2,4-dimethyl-6-methylamino	137-138	4506
4-Iodo-2,6-diphenyl	111-112	5761
4-Iodo-2-isopropyl-6-methyl	135/18	5094
5-Iodo-2-isopropyl-4-methyl	125/18	5094
5-Iodo-2-isopropyl-4-methyl-6-styryl	84-85	5655
4-Iodo-2-methoxycarbonylmethyl	59-61	5693
2-Iodo-4-methoxy-6-methyl	74-75; 140/18	5094
2-Iodo-4-methyl	87-89	6390
4-Iodo-6-methyl	1-N-Ox: 89-91	H, 4685
5-Iodo-2-methylamino	136-137; pic: 209	2633
5-Iodo-4-methyl-2,6-bis(trimethyl)siloxy	135-139/3.5	5957
4-Iodo-6-methyl-2-methylthio	100-101	2603
2-Iodo-4-methyl-6-phenyl	78-79	2603
4-Iodo-2-methyl-6-phenyl	73-74	6089
4-Iodo-6-methyl-2-phenyl	49-51	2603
2-Iodo-4-methyl-6-piperidino	112-113	5094

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Iodo-2-methylthio	45-46	E, 5284
2-Iodo-4-phenyl	61-63	6041
4-Iodo-5-phenyl	67-68	2603
4-Iodo-6-phenyl	99-100; 1-N-Ox: 89	4685, 6117
2-Isoamylamino	138/15	5664
2-Isoamylamino-4,6-dimethyl	144/11	E, 5664
4-Isoamylamino-2,6-dimethyl	140-142/2	E, 5664
4-Isoamyl-2-methoxy-6-trifluoromethyl	61/0.05	4546
4-Isoamyl-2-methylthio-6-trifluoromethyl	80/0.4	4546
2-Isobutoxy	104/18	E, 2630
2-Isobutylamino-4,6-diphenyl	58-61	6290
4-Isobutyl-2-methoxy-6-trifluoromethyl	43/0.1	4546
4-Isobutyl-2-methylthio-6-trifluoromethyl	62/0.2	4546
4-Isobutyl-6-methyl-2-ureido	167	6015
2-Isobutylthio-5-methoxy	120/0.6	4395
4-Isobutyryl-2-methyl-6-phenyl	60-62	5987
4-Isobutyryl-6-phenyl	120-121/3	5091
4-Isocyanato-2-methylthio-5-phenylthio	142-144	4400
2-Isopropenyl	35-37/0.05	5690
2-Isopropenyl-4-methoxy	85-87/18	5690
2-Isopropenyl-4-phenyl	128-130/0.5	5690
4-Isopropoxy-2,6-dimethyl	58-61/2; 1-N-Ox: 85	5910, 5927
4-Isopropoxy-2,6-dipiperidino	63-64	5998
4-Isopropoxy-2-isopropyl-6-methyl	1-N-Ox: 164/28	5927
4-Isopropoxy-6-methyl-2-methylthio	100-105/2	5910
4-Isopropoxy-6-methyl-2-propyl	1-N-Ox: 79	5927
2-Isopropyl	46-47/2; 115/200	5063, 5690
5-Isopropyl	96-97/40	E, 4515
2-Isopropylamino	pic: 175	E, 2633, 6327
4-Isopropylamino-6-phenyl	143-144	4679

4-Isopropylamino-2,5,6-triphenyl	129–130	6730
5-Isopropyl-2,4-bis(trimethylsiloxy)	–	6207
2- <i>N'</i> -Isopropylguanidino-4,6-dimethyl	222	4975
5-Isopropyl-2-mercapto	241	E, 4463
4-Isopropyl-2-mercapto-5-methyl	176–177	6319
2-Isopropyl-4-methoxy	42–43/0.3	5690
4-Isopropyl-2-methoxycarbonylmethyl	120–122/6	5688
2-Isopropyl-4-methoxy-6-methyl	1- <i>N</i> -Ox: 51	5927
4-Isopropyl-2-methoxy-6-trifluoromethyl	33/0.05	4546
4-Isopropyl-5-methyl	71–72/20	6319
5-Isopropyl-2-methyl	81–83/20	4463
2-Isopropyl-4-methylamino	HCl: 195	5679
4- <i>N'</i> -Isopropyl- <i>N</i> -methylamino	MS; nmr	6172
4-Isopropyl-6-methylamino	HCl: 257	5679
5-Isopropyl-4-methylamino	121	5679
2-Isopropyl-4-methyl-6-pent-1'-enyl	<i>trans</i> : 90–94/2	6008
2-Isopropyl-4-methyl-6-prop-1'-ynyl	118/18	5094
2-Isopropyl-4-methyl-5-styryl	180/2	5654
4-Isopropyl-2-methylthio-6-trifluoromethyl	46/0.05	4546
2-Isopropyl-4-phenyl	136–140/4	5690
2-Isopropyl-4-trimethylammonio	Cl: 124–125	5694
4- <i>N'</i> -Isopropylureido-2,6-dimethyl	150	6156
2-Isothiocyano	34; 58/0.005	6208
5-Isothiocyano-2-methylthio	–	6216
2-Mercapto	222–223	H, E, 4384
4-Mercapto	190–192	H, E, 5625
4-Mercapto-2,6-dimethoxy	–	H, E, 5536
2-Mercapto-4,6-dimethyl	Na: > 300	H, E, 4535
4-Mercapto-2,6-dimethyl	224 or 226–228	H, 4831, 5267
2-Mercapto-4,6-diphenyl	166–167 or 170	6210, 6531
2-Mercapto-4-methoxy	> 250	5536
2-Mercapto-5-methoxy	176 or 179–181	4399, 4384
4-Mercapto-6-methoxy	crude: 190	E, 5536
4-Mercapto-5-methoxy-2-methyl	206–208	6348

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Mercapto-4-methyl	208 or 220–221; HCl: 250	H, E, 4384, 4777
2-Mercapto-5-methyl	218 or 252	E, 4384, 4463
4-Mercapto-2-methyl	146 or 151	4449, 4832
2-Mercapto-4-methyl-6-methylamino-5-nitro	217–218	5677
4-Mercapto-2-methyl-6-methylsulfonyl	172–174	6374
4-Mercapto-2-methyl-6-methylthio	228–238	6374
4-Mercapto-6-methyl-2-methylthio	248	H, E, 5267
2-Mercapto-4-methyl-6-phenyl	190 or 201	H, 6212, 6377, 6459
2-Mercapto-4-phenyl	187–188	H, 6040
2-Mercapto-5-phenyl	214 or 225–227	E, 4488, 5663
4-Mercapto-2-phenyl	128	4449
2-Mercapto-5-piperidino	185	6281
4-Mercapto-6-propoxy	160–162	5536
2-Mercapto-4-propyl	213–215; HCl: 239	4771
2-Mercapto-5-propyl	219	E, 4463
4-Mercapto-2-styryl	198–199	4832
2-Methoxy	pic: 106–108	H, E, 2603, 5340
4-Methoxy	pic: 126; 1- <i>N</i> -Ox: 132–134	H, E, 4692, 5340, 5927
5-Methoxy	<i>N</i> -Ox: 162	H, E, 5500
2-Methoxy-4,6-bistrifluoromethyl	26/0.01; n_D^{20} 1.3865	4546
5-Methoxy-2,4-bistrimethylsiloxy	104/0.6	6215
2-Methoxycarbonyl	103–104	E, 5977
4-Methoxycarbonyl	63–68	E, 5480
4-Methoxycarbonyl-2,6-bistrimethylsiloxy	138–140/4	5957
2-Methoxycarbonyl-4,6-dimethyl	150–155/16	H, 5652, 5977
4-Methoxycarbonyl-2,6-dimethyl	53–55 or 55–56	E, 5652, 5682
2-Methoxycarbonyl-4,6-diphenyl	135–137	5977
2-Methoxycarbonylmethyl	90–93/4	5693
4-Methoxycarbonyl-2-methyl	54–55	5652

4-Methoxycarbonyl-6-methyl	66–68	5652
2-Methoxycarbonylmethyl-4-methyl-6-trimethylammonio	Cl: 134–137	5693
2-Methoxycarbonylmethyl-4-phenyl	liq; anal.	5688
2-Methoxycarbonyl-4-methyl-6-phenyl	85–89	5652
4-Methoxycarbonyl-2-methyl-6-phenyl	91–93	5652
4-Methoxycarbonyl-6-methyl-2-phenyl	102–103	5652
5-Methoxycarbonyl-2-methylsulfonyl	129–131	4399
5-Methoxycarbonyl-2-methylthio	95–96	4399
2-Methoxycarbonylmethyl-4-trimethylammonio	Cl: 150–152	5693
5-Methoxycarbonyl-2-phenyl	161–163	5604
5- β -Methoxycarbonylvinyl-2,4-bistrimethylsiloxy	117–118/0.001	5427
2-Methoxy-4,6-dimethyl	pic: 137–139; HCl: 224	H, E, 2603, 4467, 5669
4-Methoxy-2,5-dimethyl	89–90/30	E, 5099
4-Methoxy-2,6-dimethyl	78/11; 1- <i>N</i> -Ox: 88	H, E, 4763, 5071, 5927
4-Methoxy-5,6-dimethyl	118/40; 1- <i>N</i> -Ox: 159	4387
4-Methoxy-5,6-dimethyl-2-methylthio	40–41	4387, 4394
2-Methoxy-4,6-diphenyl	81–82	6105
5-Methoxy-4,6-diphenyl	69–70	5499
2-Methoxy-4,5-diphenyl-6-styryl	146–148	5984
4-Methoxy-2,6-dipiperidino	75–76	5998
5- β -Methoxyethoxy-2-methylsulfonyl	87–88	4399
5- β -Methoxyethoxy-2-methylthio	56–58	4399
2-Methoxy-4-methoxycarbonyl	46–50; 180/13	6075
2-Methoxy-5-methoxycarbonyl	128–129	4399
4-Methoxy-2-methoxycarbonylmethyl	100–102/1.5	6075
4-Methoxy-2-methoxycarbonylmethyl-6-methyl	101–102/2	5688
4-Methoxy-5-methoxycarbonylmethyl-2-phenyl	62–63	5087, 5805
4-Methoxy-5-methoxycarbonyl-2-methylthio	66–68	5980
4-Methoxy-5-methoxycarbonyl-2-phenyl	120–122	2599
5-Methoxy-4-methoxymethyl	118–120/10	4976
5-Methoxy-4-methoxymethyl-2-methylsulfonyl	95–97	4397
5-Methoxy-4-methoxymethyl-2-methylthio	168/10; 32–33	4397

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Methoxy-4-methyl	nmr	H, E, 4359
2-Methoxy-5-methyl	79/8; pic: 120	2630, 4399
4-Methoxy-2-methyl	60/17; pic: 164; 1- <i>N</i> -Ox: 114	E, 4763, 5099, 5294, 5927
4-Methoxy-5-methyl	94/35; pic: 175	2630
4-Methoxy-6-methyl	1- <i>N</i> -Ox: 136	H, E, 5927
5-Methoxy-4-methyl	90-92/15	4397
5-Methoxy-2-methylamino	96	5662
4-Methoxy-2-methylamino-5-nitro	206-207	E, 3783
2-Methoxymethyl-4,6-diphenyl	66-68	4875
2- α -Methoxy- α -methylethyl	41-43/0.1	5690
2- α -Methoxy- α -methylethyl-4-phenyl	49-50	5690
4-Methoxy-6- α -methylethyl-4-phenyl	201-202	5491
4-Methoxy-6- α -methylethylhydrazino-5-nitro	185	6214
2-Methoxy-6- α -methylethylhydrazino-5-nitro-2-phenyl	130-131	5670
5-Methoxy-4-methyl-6-methylamino-5-nitro	106-107	4397
4-Methoxy-6-methyl-2-methylthio	—	H, E, 5355
5-Methoxy-2-methyl-4-methylthio	90	6348
5-Methoxy-4-methyl-2-methylthio	53-54	4397
4-Methoxy-2-methyl-5-nitro	48	3312, 5634
4-Methoxy-6-methyl-5-nitro-2-propoxy	104-106/0.3	5660
4-Methoxy-2-methyl-6-phenyl	145-150/22	5090
4-Methoxy-6-methyl-2-phenyl	pic: 172; 1- <i>N</i> -Ox: 104	H, 2603, 5927
4-Methoxy-6-methyl-2- <i>N</i> -phenylcarbamoyl	95-96	5074
4-Methoxy-2-methyl-6-propionyl	47-48; 65/1	5089
4-Methoxy-6-methyl-2-propionyl	47-48	5089
4-Methoxy-6-methyl-2-propyl	1- <i>N</i> -Ox: 75	5927
4-Methoxy-6-methyl-2-prop-1'-ynyl	140/18	5094
4-Methoxy-2-methylsulfinyl-6-nitrosoamino	164-165	4656
2-Methoxy-5-methylsulfonyl	160-161	4399

4-Methoxy-2-methylsulfonyl-6-nitrosoamino	167–168	4656
4-Methoxy-2-methylthio	35	6111
4-Methoxy-2-methylthio-6-nitroamino	112–113	4656
2-Methoxy-4-methyl-6-trifluoromethyl	25/0.1	4546
2-Methoxy-5-nitro	66–68 or 70	H, E, 5340, 5660, 6123
4-Methoxy-5-nitro	39–40	E, 2562, 5170, 6144
2-Methoxy-5-nitro-4,6-diphenyl	134–135	6147
4-Methoxy-5-nitro-6-semicarbazido	211	5674
2-Methoxy-4-phenyl	oil: sp; anal.; 3- <i>N</i> -Ox: 163	6345
2-Methoxy-5-phenyl	73–74	5635
4-Methoxy-2-phenyl	45	4449
4-Methoxy-5-phenyl	49–50	297, 5635
4-Methoxy-6-phenyl	pic: 152; 1- <i>N</i> -Ox: 161	5927
5-Methoxy-4-phenyl	1- <i>N</i> -Ox: 173–176; 3- <i>N</i> -Ox: 215–218	4810, 6254
5-Methoxy-2- <i>N'</i> -phenylthioureido	203	5838
2-Methoxy-4-phenyl-6-trifluoromethyl	48–49	4555
4-Methoxy-2-piperidino	35–36	4790
4-Methoxy-6-piperidino	112–115/1.5	6094
5-Methoxy-2-propylthio	34; 100/0.6	4395
2-Methoxy(thiocarbonyl)-4,6-dimethyl	anal.	6213
4-Methoxy-2-trifluoromethyl	anal.	5294
2-Methoxy-4,5,6-trimethyl	38–40; 62/0.05	4554
5-Methoxy-2,4,6-triphenyl	126–127	4477
2-Methyl	129/at; Mel: 174; <i>N</i> -Ox: 50	H, E, 4689, 5063, 5682, 5927
4-Methyl	1-Mel: 112; 139/at; 1- <i>N</i> -Ox: 78	H, E, 4838, 5673, 5682, 5758, 5927
5-Methyl	153/at; 1- <i>N</i> -Ox: 116	H, E, 4488, 4515, 5673, 5927
4- <i>N</i> -Methylacetamido	125–130/10	4449
4- <i>N</i> -Methylacetamido-2-phenyl	77	4449
2-Methylamino	58–59	H, E, 4600

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Methylamino	69–72	H, E, 5665
5-Methylamino	96	6062
4-Methylamino-5- <i>N</i> -methylformamido-6-methylthio	169–171	6234
4-Methylamino-2-methylthio	76–78	5665
2-Methylamino-5-nitro-4,6-diphenyl	200–202	6147
2-Methylamino-5-nitro-4-thiocyanato	191–192	5742
2-Methylamino-5-phenyl	124	5663
4-Methylamino-2-phenyl	106	4449
4-Methylamino-5-phenyl	104–105	E, 4594, 5914
4-Methylamino-2,5,6-triphenyl	144–145	6730
4-Methylamino-5-vinyl	—	5881
4-Methyl-2,6-bismethylamino-5-nitro	252	E, 5685
2-Methyl-4,6-bismethylamino-5-nitroso	204	6294
2-Methyl-4,6-bismethylsulfanyl	122–126	6374
2-Methyl-4,6-bismethylsulfonyl	192–196	6374
2-Methyl-4,6-bismethylthio	31–32	6374
5-Methyl-2,4-bismethylthio	35–36	3474
4-Methyl-2,6-bismethylthio-5-nitro	88–89	5661
4-Methyl-2,6-bismethylsiloxy	75–78	4387, 5957
5-Methyl-2,4-bis(trimethyl)siloxy	63–65 or 74–75	E, 5632, 5728
5-Methyl-2,4-diphenoxy	85–87	5362
2-Methyl-4,6-diphenyl	89 or 96–97	5096, 5836
5-Methyl-4,6-diphenyl-2-piperidino	172–174	4790
5-Methyl-4,6-diphenyl-2-propyl	91; 135/0.001	4499
4- α -Methylhydrazino-5-nitro	127–128	2858
2-Methyl-4- <i>N</i> -methylacetamido	28–29; 130/10	4449
2-Methyl-4-methylamino	80 or 90	4449, 5679
4-Methyl-2-methylamino	55–56	E, 5662
4-Methyl-6-methylamino	115	5679
5-Methyl-4-methylamino	124	5679

4-Methyl-6-methylamino-5-nitro-6-piperidino	166–168	5685
4-Methyl-2-methylamino-6-phenyl	152–153	6388
2-Methyl-4-methylsulfinyl-6-methylsulfonyl	135–141	6374
2-Methyl-4-methylsulfinyl-6-methylthio	79–81	6374
5-Methyl-2-methylsulfonyl	79–81	4399
4-Methyl-6-methylsulfonyloxy-2-methylthio	74–75	5267
4-Methyl-6-methylsulfonyloxy-2-piperidino	112	5391
2-Methyl-4-methylthio	88–90/15	4449
4-Methyl-2-methylthio-6-prop-1'-ynyl	76–77; 120/3	5094
4-Methyl-2-methylthio-6-trifluoromethyl	42–43; 50/0.01	4546
2-Methyl-5-nitro	57–59	H, E, 6123
2-Methylnitrosoamino	82	3491
4-Methylnitrosoamino	68	3491
4-Methyl-2- <i>N'</i> , <i>N'</i> -pentamethyleneguanidino-6-phenyl	179	4975
2-Methyl-4-phenoxy	pic: 171–172	E, 4669, 6039
4-Methyl-6-phenoxy	1- <i>N</i> -Ox: 122–123	E, 4684
2-Methyl-4-phenyl	54–55; pic: 206;	E, 4669, 4810, 6039,
	1- <i>N</i> -Ox: 154	6089, 6167
	69–70	4488
2-Methyl-5-phenyl	21–22; 140/12	H, E, 4488, 5073
4-Methyl-2-phenyl	76	5118, 5119
4-Methyl-5-phenyl	148/12; pic: 202; 1- <i>N</i> -Ox:	H, E, 2603, 5073,
4-Methyl-6-phenyl	137; di- <i>N</i> -Ox: 164	5927, 6345
	105/0.1; 1- <i>N</i> -Ox: 153;	
	3- <i>N</i> -Ox: 148;	
5-Methyl-4-phenyl	1,3-di- <i>N</i> -Ox: 227	E, 4757, 4814, 5484
	95–97	5987
2-Methyl-6-phenyl-4-propionyl	3- <i>N</i> -Ox: 113–115	E, 4685
4-Methyl-6-phenylthio	150–151/20	H, 5676
2-Methyl-4-piperidino	125–126/13	H, 5676
4-Methyl-2-piperidino	148/17	H, E, 5676
4-Methyl-6-piperidino	148–150/15	5676
5-Methyl-4-piperidino	140/18; pic: 154	5094
4-Methyl-6-piperidino-2-prop-1'-ynyl	82–84/17	4463
2-Methyl-5-propyl		

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4-Methyl-2-sulfamoyl	163	5669
5-Methyl-2-sulfamoyl	151–152	5669
2-Methyl-4-sulfo	K: —	5667
4-Methyl-2-sulfo	K: 295	H, 5667
4-Methyl-6-sulfo	K: 260	5667, 5669
5-Methyl-2-sulfo	K: > 310	5667, 5669
2-Methylsulfonyl	72–74	E, 4399
2-Methylsulfonyl-5-nitro	157–158	5285
2-Methylsulfonyl-4-phenyl	135	6040
2-Methylsulfonyl-5-phenyl	178	5663
5-Methyl-2',2',2'-tetrafluoroethyl	168/at	6211
5-Methyl-4',2',2'-tetrafluoroethyl	34	6211
2-Methylthio	Mel: 156	H, E, 5343
4-Methylthio	1-Mel: 144; 3-Mel: 135	E, 4838, 5343
2-Methylthio-4,6-bistrifluoromethyl	31/0.1	4546
5-Methylthio-2,4-bistrimethylsiloxy	36–37	5728
2-Methylthio-4,6-diphenyl	152–153	6210
2-Methylthio-5-nitro	80–81	H, E, 5285, 6372, 6423
2-Methylthio-4-phenyl	86–87	H, 6040
2-Methylthio-5-phenyl	95–96	4488, 5663
4-Methylthio-2-phenyl	180/1.5	4449
2-Methylthio-5-phenylthio	46–49	4400
2-Methylthio-4-phenyl-6-trifluoromethyl	68–70	E, 4555
2-Methylthio-5-prop-2'-ynyloxy	85–86	6142
5-Methylthio-2,4,6-triphenyl	111–113	5068
2-Methyl-4-trichloromethyl	39–40	5954
2-Methyl-4-trimethylammonio	Cl: 155–157	5676
4-Methyl-6-trimethylammonio	Cl: 169–172	4685, 5676
5-Methyl-4-trimethylammonio	Cl: 186–187	5676

4-Methyl-2,5,6-triphenyl	6209
5-Methyl-2,4,6-triphenyl	H, E, 4499, 5804
4-Methyl-2-ureido	6015
4-Neopentyl	6220
2-Nitro	6267
5-Nitro	E, 5170, 5938
5-Nitro-2,4-dipropoxy	5660, 5674
4-Nitromethyl	6217
5-Nitro-2-phenyl	H, 6123
5-Nitro-2- β -phenylhydrazino-4-thiocyanato	5742
5-Nitro-2-propoxy	5660
5-Nitro-4-propoxy	5660
5-Nitro-2-propylamino	H, 5340
5-Nitro-2-propylamino-4-thiocyanato	5742
5-Nitro-2-trimethylammonio	5342
5-Nitro-4-trimethylsiloxy-2-trimethylsilylthio	5418
4-Phenoxy-2,6-dipiperidino	5998
4-Phenoxy-6-phenyl	4685
2-Phenyl	H, E, 2603, 4488, 4690, 5063
4-Phenyl	H, E, 4488, 4683, 4699, 4757, 4814, 4861, 4884, 5927
5-Phenyl	H, 4488, 4683
5-Phenyl-2,4-bistrifluoromethyl	6285
2-Phenyl-4,6-dipiperidino	4972
4-Phenyl-2-phenylsulfonyl	6040
4-Phenyl-2-phenylthio	6040
4-Phenyl-2-piperidino	4790
5-Phenyl-2-piperidino	4790
4-Phenyl-5-pivaloylmethyl	6628
4-Phenyl-6-propionyl	5091
5-Phenyl-4-propylamino	5914
2-Phenylsulfinyl	E, 5633
—	—
181	—
229	—
95/15; pic: 105	—
57–58	—
56–58 or 59–60	—
32–33; 117/0.25	—
125	—
225–226	—
158	—
37–38; 91/0.4	—
20; 116/5	—
116	—
134–135	—
Cl: 204	—
140/0.1	—
78–80	—
91–92; 1- <i>N</i> -Ox: 164	—
38; 110/6	—
64; 1- <i>N</i> -Ox: 152; 3- <i>N</i> -Ox: 155; di- <i>N</i> -Ox: 218	—
78/1; 40–41; Mel: 196	—
72–73	—
128–130	—
149–150	—
69–70	—
52–53	—
89–90	—
oil: anal; oxime: 186	—
140–141/5	—
—	—
—	—

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Phenylsulfonyl	—	E, 5633
2-Phenylthio	—	E, 5633
4-Phenyl-2-thiocyanato	87–88	6040
2-Phenyl-4-trichloromethyl	86	6734
4-Phenyl-2-trimethylammonio	Cl: 157 or 162	5839, 6041
4-Phenyl-6-trimethylammonio	Cl: 175	6117
2-Piperidino	120/16	H, 5676, 6073
4-Piperidino	48 or 52–53; pic: 132	4483, 4663
2-Piperidinomethyl	liq; anal.	5682
4-Piperidinomethyl	liq; anal.	5682
2-Propyl	126/200	5063
4-Propyl	71/11; pic: 89	E, 5758, 6220
5-Propyl	68–69/11	4515
2-Propylamino	pic: 151	E, 5340
4-Propylamino	pic: 161	5340
2-Prop-2'-ynylamino	—	E, 2700
Pyrimidine (Unsubstituted)	126/at; MeI: 137; <i>N</i> -Ox: 95; di- <i>N</i> -Ox: 228	H, E, 4515, 4757, 4814, 4861, 5594, 5673, 5927
2-Sulfamoyl	181	H, 5669
2-Sulfo	K: 328	H, 5667, 5669
4-Sulfo	K: 330	5669
2,4,5,6-Tetra-amino	sul: > 350; <i>N</i> -Ox: anal.	H, E, 4643, 6335
2,4,5,6-Tetrachloro	68	H, E, 4500
2,4,5,6-Tetrafluoro	82–83/at	E, 3521, 5645
1,2,3,4-Tetrahydro-1,3-bis- β -hydroxyethyl-2,4-dioxo	153–154	E, 4871, 5495, 6068
1,2,3,4-Tetrahydro-1,3-bis- β -hydroxyethyl-6-methyl-2,4-dioxo	111–112	6068
1,2,3,4-Tetrahydro-5,6-di-iodo-1,3-dimethyl-2,4-dioxo	213–215	4650
1,2,3,4-Tetrahydro-1,3-di-isopropyl-2,4-dioxo-6-trifluoromethyl	²⁵ 1.4562	5589
1,2,3,4-Tetrahydro-1,3-di-isopropyl-6-methylamino-2,4-dioxo	181–182	4657

1,2,3,4-Tetrahydro-1,3-dimethyl-5,6-bismethylamino-2,4-dioxo	—	E, 4662
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo	120 to 124	H, E, 5019, 5039, 5123, 5328, 5331, 5490, 5522
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenoxy	107–108	4578
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenoxy-5-phenyl	119–120	4578
1,2,3,4-Tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl	283 or 300	H, 4925, 5910
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-5-phenylhydrazino	121 (<i>syn</i>): 208 (<i>anti</i>)	6103
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenylhydrazino	206–208	4924
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenylhydrazonomethyl	240	6274
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenyliminomethyl	136–137	6274
1,2,3,4-Tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl-5-piperidino	200	4925
1,2,3,4-Tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl-5-piperidino	132	4925
1,2,3,4-Tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl-5-piperidinomethyl	HCl: 263–265	4932
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenylthio	129–130 or 131	4578, 4971
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-propyl	60–61	H, 5415
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-propylenedehydrazino	197 or 203	4928, 4929, 5265
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-5-prop-2'-ynyloxy	140–142	5405
1,2,3,4-Tetrahydro-5,6-dimethyl-1,3-diphenyl-2,4-dithio	260	4432, 6188
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dithio	124	H, E, 5600, 6554
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxo	—	E, 4991
1,2,3,4-Tetrahydro-1,6-dimethyl-5-methylamino-2,4-dioxo-3-phenyl	152	4925
1,2,3,4-Tetrahydro-3,6-dimethyl-5-methylamino-2,4-dioxo-1-phenyl	129	4925
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxo-5-phenylcarbamoyl	191	4410
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylaminomethyl-5-nitro-2,4-dioxo	99–100	4945
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylamino-5-nitroso-2,4-dioxo	147–148	E, 4645
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylamino-5-nitroso-4-oxo-2-thio	120	4661
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylamino-4-oxo-2-thio	238–239	4661
1,2,3,4-Tetrahydro-1,3-dimethyl-6- α -methylhydrazino-2,4-dioxo	135–137	E, 4950, 4991
1,2,3,4-Tetrahydro-1,3-dimethyl-6-(α -methylhydrazino)methyl-5-nitro-2,4-dioxo	126–127	4943
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylhydrazonomethyl-2,4-dioxo	216–217	4943
1,2,3,4-Tetrahydro-1,3-dimethyl-4-methylimino-2-oxo	HI: 180	H, 6554

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,2,3,4-Tetrahydro-1,3-dimethyl-5- <i>N</i> -methylureido-2,4-dioxo	234 and 332 (dimorphic)	5336
1,2,3,4-Tetrahydro-1,3-dimethyl-5-nitro-2,4-dioxo	158–159	H, E, 5516
1,2,3,4-Tetrahydro-1,3-dimethyl-2-oxo-4-phenylimino	HI: 222	6554
1,2,3,4-Tetrahydro-3,6-dimethyl-4-oxo-1-phenyl-2-thio	171	4930
1,2,3,4-Tetrahydro-1,3-dimethyl-2-oxo-4-semicarbazono	268	6554
1,2,3,4-Tetrahydro-1,3-dimethyl-4-oxo-2-thio	108–109	E, 5353, 5417, 5600
1,2,3,4-Tetrahydro-1,3-dimethyl-5-phenyl-2,4-dithio	181	6188
1,2,3,4-Tetrahydro-1,3-dimethyl-6-phenyl-2,4-dithio	146	4432, 6188
1,2,3,4-Tetrahydro-1,3-dimethyl-4-semicarbazono-2-thio	263	6554
1,2,3,4-Tetrahydro-2,4-dioxo-1,3,6-triphenyl	200–201	E, 3761
1,2,3,4-Tetrahydro-6-hydroxyamino-1,3-dimethyl-2,4-dioxo	148–150	E, 5042
1,2,3,4-Tetrahydro-6-hydroxyamino-3-methyl-2,4-dioxo-1-phenyl	195–200	5042
1,2,3,4-Tetrahydro-6-hydroxy-1,3-bis- β -methoxycarbonyl-2,4-dioxo	74	6219
1,2,3,4-Tetrahydro-5-2-hydroxycyclopentyl-1,3-dimethyl-2,4-dioxo	–	E, 3762
1,2,3,4-Tetrahydro-5-hydroxy-1,3-dimethyl-2,4-dioxo	201	H, E, 5732
1,2,3,4-Tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo	118 to 124	H, E, 5322, 5365, 6014, 6250
1,2,3,4-Tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-5-phenylazo	255–256	5365
1,2,3,4-Tetrahydro-5-hydroxy-1,3-dimethyl-2,4-dioxo-6-propyl	95–97	5415
1,2,3,4-Tetrahydro-6-hydroxy-1,3-dimethyl-5-methylcarbamoyl-2,4-dioxo	178	E, 4480
1,2,3,4-Tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenyl-5-phenylcarbamoyl	226–228	5587
1,2,3,4-Tetrahydro-3- β -hydroxyethyl-1,6-dimethyl-2,4-dioxo	112–115	6218
1,2,3,4-Tetrahydro-5- β -hydroxyethyl-1,3-dimethyl-2,4-dioxo	140–142	3762
1,2,3,4-Tetrahydro-3- β -hydroxyethyl-4-iso-propylimino-1-methyl-2-oxo	57–60	5509
1,2,3,4-Tetrahydro-3- β -hydroxyethyl-1-methyl-2,4-dioxo	138–140	E, 5509
1,2,3,4-Tetrahydro-1- β -hydroxyethyl-6-methyl-2,4-dioxo-3-phenyl	140	4925
1,2,3,4-Tetrahydro-3- β -hydroxyethyl-6-methyl-2,4-dioxo-1-phenyl	145	4925
1,2,3,4-Tetrahydro-5-hydroxy-6-hydroxymethyl-1,3-dimethyl-2,4-dioxo	187–188	6248
1,2,3,4-Tetrahydro-4-hydroxyimino-1,3-dimethyl-2-oxo	170 or 180; HCl: 215	5313, 6554

1,2,3,4-Tetrahydro-5-hydroxymethyl-1,3-dimethyl-2,4-dioxo	138–142	3762, 6239, 6391
1,2,3,4-Tetrahydro-5-hydroxymethyl-1,6-dimethyl-2,4-dioxo-3-phenyl	200	4932
1,2,3,4-Tetrahydro-6-hydroxy-5-nitroso-4-oxo-1,3-diphenyl-2-thio	226–228	5870
1,2,3,4-Tetrahydro-6-hydroxy-4-oxo-1,3-diphenyl-2-thio	242–244	5870
1,2,3,4-Tetrahydro-6-hydroxy-1,3,5-trimethyl-2,4-dioxo	–	H, E, 6250
1,2,3,4-Tetrahydro-2-imino-1,3-dimethyl-4-oxo	139–140; HI: 263	5600
1,2,3,4-Tetrahydro-4-imino-1,3-dimethyl-2-oxo	144 or 147; HI: 260	H, E, 4969, 5328, 5331, 6554
1,2,3,4-Tetrahydro-4-imino-1,3-dimethyl-2-oxo-6-phenylthio	96	4971
1,2,3,4-Tetrahydro-4-imino-1,3-dimethyl-2-oxo-6-sulfo	> 360	4969
1,2,3,4-Tetrahydro-4-imino-1,3-dimethyl-2-thio	162; HI: 206	6554
1,2,3,4-Tetrahydro-4-imino-6-methoxy-1,3-dimethyl-2-oxo	156	4969
1,2,3,4-Tetrahydro-6-iodo-1,3-dimethyl-2,4-dioxo	174–175	4650
1,2,3,4-Tetrahydro-5-iodo-1,3-dimethyl-2,4-dioxo-6-phenoxy	128	4578
1,2,3,4-Tetrahydro-5-iodo-1,6-dimethyl-2,4-dioxo-3-phenyl	235	4925
1,2,3,4-Tetrahydro-5-iodo-3,6-dimethyl-2,4-dioxo-1-phenyl	216	4925
1,2,3,4-Tetrahydro-5-iodo-1,3-dimethyl-2,4-dioxo-6-phenylthio	185–186	4578
1,2,3,4-Tetrahydro-1-β-iodoethyl-3,5-dimethyl-2,4-dioxo	114–115	6077
1,2,3,4-Tetrahydro-1-β-iodethyl-3-methyl-2,4-dioxo	94–96	6077
1,2,3,4-Tetrahydro-6-isobutylidenehydrazino-1,3-dimethyl-5-nitroso-2,4-dioxo	104 or 108	4621, 4626
1,2,3,4-Tetrahydro-5-isocyanato-1,3-dimethyl-2,4-dioxo	150–151	5895
1,2,3,4-Tetrahydro-5-isocyanatomethyl-1,3-dimethyl-2,4-dioxo	81–82	5895
1,2,3,4-Tetrahydro-5-isopropylamino-1,6-dimethyl-2,4-dioxo-3-phenyl	183	4925
1,2,3,4-Tetrahydro-5-isopropylamino-3,6-dimethyl-2,4-dioxo-1-phenyl	118	4925
1,2,3,4-Tetrahydro-6-isopropylamino-2,4-dioxo-1,3-diphenyl	185	4657
1,2,3,4-Tetrahydro-6-isopropylaminomethyl-1,3-dimethyl-5-nitroso-2,4-dioxo	88	4945
1,2,3,4-Tetrahydro-6-isopropylidenehydrazino-1,3-dimethyl-2,4-dioxo	146 or 147–148	E, 4928, 4929
1,2,3,4-Tetrahydro-3-isopropyl-6-methyl-2,4-dioxo-1-phenyl	175–176 or 182	4925, 5910
1,2,3,4-Tetrahydro-3-isopropyl-1-methyl-2,4-dioxo-6-trifluoromethyl	liq; anal.	5589
1,2,3,4-Tetrahydro-3-isopropyl-1-methyl-6-methylthio-2,4-dioxo	5758	4806
1,2,3,4-Tetrahydro-3-isopropyl-1-methylthiomethyl-2,4-dioxo-6-trifluoromethyl	sp	5589

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
1,2,3,4-Tetrahydro-6-methoxycarbonyl-1,3-dimethyl-2,4-dioxo	70–74 or 76–77	E, 4939, 5896, 6853
1,2,3,4-Tetrahydro-5-methoxycarbonylmethyl-1,3-dimethyl-2,4-dioxo	99–100	6158
1,2,3,4-Tetrahydro-5-methoxycarbonyl-3-methyl-2,4-dioxo-1-phenyl	221	4920
1,2,3,4-Tetrahydro-6-methoxycarbonyl-4-oxo-1,3-diphenyl-2-phenylimino	225	5879
1,2,3,4-Tetrahydro-6-methoxycarbonyl-1,3,5-trimethyl-2,4-dioxo	125–126	6853
1,2,3,4-Tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxo	156 to 166	H, 4939, 5321, 5322
1,2,3,4-Tetrahydro-6-methoxy-1,3-dimethyl-5-methylcarbonyl-2,4-dioxo	106	4486
1,2,3,4-Tetrahydro-6-methoxy-2,4-dioxo-1,3-diphenyl	214	2535
1,2,3,4-Tetrahydro-3- β -methoxyethyl-1-methyl-2,4-dioxo	97–98	5509, 5524
1,2,3,4-Tetrahydro-6-C-methoxyformimidoyl-1,3-dimethyl-2,4-dioxo	120	4939
1,2,3,4-Tetrahydro-4-methoxymino-1,3-dimethyl-2-oxo	77	5313
1,2,3,4-Tetrahydro-5-methoxymethyl-1,3-dimethyl-2,4-dioxo	130 or 275	3762, 6239
1,2,3,4-Tetrahydro-6-methylamino-2,4-dioxo-1,3-diphenyl	242	4657
1,2,3,4-Tetrahydro-6-methylamino-5-nitroso-2,4-dioxo-1,3-diphenyl	330	4657
1,2,3,4-Tetrahydro-1-methyl-2,4-dioxo-3-phenyl	134	4920
1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-phenyl	133 or 138	4920, 4931
1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-vinyl	95–97	5495
1,2,3,4-Tetrahydro-3-methyl-1,3-diphenyl-2,4-dithio	225	4432, 6188
1,2,3,4-Tetrahydro-3-methyl-6-methylamino-2,4-dioxo-1-propyl	182–185	4657
1,2,3,4-Tetrahydro-3-methyl-6- α -methylhydrazino-2,4-dioxo-1-phenyl	146	4929
1,2,3,4-Tetrahydro-1-methyl-6-methylthio-2,4-dioxo-3-propyl	100–101	4806
1,2,3,4-Tetrahydro-1,3,5,6-tetramethyl-2,4-dithio	199	6188
1,2,3,4-Tetrahydro-1,3,5-trimethyl-2,4-dioxo	138 (?) or 153–155	H, E, 5019, 5039, 5490, 5522, 6070
1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxo	106 to 115	H, E, 4387, 4857, 4879, 4925, 5050, 6401, 6853
1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dithio	127	4432, 6188
1,2,3,4-Tetrahydro-1,3,6-trimethyl-5-phenyl-2,4-dithio	207	4432, 6188
2,4,5,6-Tetrahydroxy	X-ray	H, E, 6222

2,4,5,6-Tetrakisheptafluoroisopropyl	17–18; 191/at	5242
2-Thiobarbituric acid/1-amino	208–209	5186
2-Thiobarbituric acid/5-benzylidene	–	E, 4866
2-Thiobarbituric acid/1-methyl	195–196	H, E, 5181
2-Thiobarbituric acid/5-methylaminomethylene	> 330	4599
4-Thiobarbituric acid/5-amino-1-methyl	> 300	5435
4-Thiobarbituric acid/1,3-dimethyl	126	5138
2-Thiouracil/5-acetamido-6-amino-1-phenyl	266–267	2982
2-Thiouracil/1-acetyl	242–243	6221
2-Thiouracil/1-acetyl-6-propyl	225–227	5532
2-Thiouracil/1-allyl-6-methyl	167	4569
2-Thiouracil/3-allyl-6-methyl	190–191	H, 5373
2-Thiouracil/3-amino	217–218	5140
2-Thiouracil/3-amino-6-methyl	237 or 247–248	5140, 5166
2-Thiouracil/6-amino-1-methyl	271–272	H, 5181
2-Thiouracil/6-amino-3-methyl	> 315	4658
2-Thiouracil/6-amino-1-methyl-5-nitroso	220 to > 300	H, 2159, 4616, 5127, 5182
2-Thiouracil/6-amino-3-methyl-5-nitroso	221–223	4658
2-Thiouracil/6-amino-5-nitroso-1-phenyl	200	2982, 5127
2-Thiouracil/6-amino-1-phenyl	233 or 239–241	H, 2982, 5127
2-Thiouracil/1-benzyl	230–232	H, E, 5353
2-Thiouracil/1-benzyl-6-methoxy	226–227	E, 5175
2-Thiouracil/1-benzyl-6-hydroxymethyl	185	5175
2-Thiouracil/1-butyl	132–133	5417
2-Thiouracil/1- <i>N</i> -butylcarbamoylmethyl-6-methyl	244–245	4573
2-Thiouracil/5-carboxy-3-methyl	298	5665
2-Thiouracil/6-carboxy-1-methyl	231–232	5175
2-Thiouracil/1-carboxymethyl-6-methyl	263–265	4573
2-Thiouracil/1-β-cyanoethyl	215–217	E, 5924
2-Thiouracil/3-β-cyanoethyl	152–154	6048
2-Thiouracil/1-β-cyanoethyl-5-methoxy	240–242	5924
2-Thiouracil/3-β-cyanoethyl-5-methoxy	242–244	6048
2-Thiouracil/1-β-cyanoethyl-5-methyl	192–194	5924

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2-Thiouracil/5-cyano-3-methyl	257	5665
2-Thiouracil/3-cyclohexyl-5-methyl-6-trifluoromethyl	—	5933
2-Thiouracil/5,6-diamino-1-benzyl	242–244	E, 4575
2-Thiouracil/5,6-diamino-1-methyl	265–268	H, E, 5182
2-Thiouracil/5,6-diamino-3-methyl	292–293	4658
2-Thiouracil/5,6-diamino-1-phenyl	246–247	2982
2-Thiouracil/6-diethoxymethyl-3-methyl	122–125	6069
2-Thiouracil/1,6-dimethyl	268–270	H, 4568
2-Thiouracil/3-dimethylaminomethylenamino-6-methyl	244–246	5155
2-Thiouracil/1-ethoxycarbonylmethyl-6-methyl	210	4573
2-Thiouracil/6-ethoxy-1-phenyl	209–212	5536
2-Thiouracil/1-ethyl	239–241	H, E, 5675
2-Thiouracil/1-ethyl-6-hydroxymethyl	193–194	5175
2-Thiouracil/3-formamido	196–198	5140
2-Thiouracil/3-formamido-6-methyl	219–220	5140
2-Thiouracil/6-hydroxymethyl-1-methyl	226–227	5175
2-Thiouracil/3-isopropyl-6-trifluoromethyl	178–179	5933
2-Thiouracil/6-methoxycarbonyl-3-methyl	188	6227
2-Thiouracil/1-methoxymethyl	167–169	5418
2-Thiouracil/1-methyl	227–229	E, 4490, 5353, 5417, 5418
2-Thiouracil/3-methyl-5-phenyl	263	6225
2-Thiouracil/6-methyl-1-phenyl	247–248	H, 4930
2-Thiouracil/6-methyl-3-phenyl	264	H, 4930
2-Thiouracil/1-methyl-6-propyl	170–172	5532
2-Thiouracil/1-phenyl	236	E, 5353
2-Thiouracil/3,5,6-trimethyl	268–269	H, 4726
4-Thiouracil/1-acetyl	122–125	5727
4-Thiouracil/5-allyl-3-methyl	155–157	4421
4-Thiouracil/6-amino-1-benzyl	crude	5036

4-Thiouracil/3-amino-6-methyl	176–178	5166
4-Thiouracil/5-benzyl-1-methyl	168–170	4441
4-Thiouracil/1-butyl	68–70	5727
4-Thiouracil/1-s-butyl	96–97	5727
4-Thiouracil/1-cyclohexyl	192 or 202–203	4720, 6114
4-Thiouracil/1- β -diethylaminoethyl-5-ethyl	124–125	5573
4-Thiouracil/1,5-dimethyl	211–213	5811
4-Thiouracil/1,6-dimethyl	241	4569
4-Thiouracil/1,5-diphenyl	219–220	5573
4-Thiouracil/5-ethoxycarbonyl-1,6-dimethyl	214–215	5601
4-Thiouracil/5-ethoxycarbonyl-1- β -hydroxyethyl-6-methyl	147–148	5573
4-Thiouracil/1-ethyl	156–157	5727
4-Thiouracil/3-ethyl	160–162	5675
4-Thiouracil/5-ethyl-1- β -hydroxyethyl	213–215	5573
4-Thiouracil/5-ethyl-1-methyl	171–172	5573
4-Thiouracil/5-ethyl-1-phenyl	235–236	5573
4-Thiouracil/1-iso butyl	91–93	5727
4-Thiouracil/1-isopropyl	147–149	5727
4-Thiouracil/6-methoxycarbonyl-3-methyl	234–235	5414
4-Thiouracil/1-methyl	193 or 195–197	E, 5058, 6098, 6099
4-Thiouracil/3-methyl	185–187	E, 5665, 6554
4-Thiouracil/1-methyl-5-phenyl	282–283	5573
4-Thiouracil/1-propyl	89–90	5727
4-Thio [pseudo] uracil/1-allyl	135–137	4806
4-Thio [pseudo] uracil/1-butyl	143–145	4806
4-Thio [pseudo] uracil/1-s-butyl	156–158	4806
4-Thio [pseudo] uracil/5-cyano-1,2-diphenyl	220	4533
4-Thio [pseudo] uracil/1-cyclohexyl	242	4806
4-Thio [pseudo] uracil/1-ethyl	148–150	4806
4-Thio [pseudo] uracil/1-isobutyl	185	4806
4-Thio [pseudo] uracil/1- γ -methoxypropyl	142–144	4806
4-Thio [pseudo] uracil/1-methyl	210–212	E, 4806
4-Thio [pseudo] uracil/1-phenyl	153–155	4806
4-Thio [pseudo] uracil/1-propyl	153–156	4806

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
4,5,6-Triacetamido-2-dimethylamino	231–232	5399
2,4,5-Triacetamido-6-hydroxy	244–248	4642
2,4,6-Triacetamido-5-nitroso	217–218	E, 4633
2,4,6-Triamino-5-benzoyloxy	196–200	5553
2,4,5-Triamino-6-benzoyloxy	149–151	H, E, 6226
2,4,6-Triamino-5-bromo	202 or 206–208	5244, 5296
2,4,5-Triamino-6-carbamoyl	286–288	5767
2,4,6-Triamino-5-carbamoyl	211–213	5767
2,4,6-Triamino-5- δ -carboxybutyl	276–278	6519
2,4,6-Triamino-5-chloro	202–203	H, 5188
4,5,6-Triamino-1,2-dihydro-1-methyl-2-oxo	sul: > 300	E, 5245
1,4,6-Triamino-1,2-dihydro-2-thio	265	2859
2,4,5-Triamino-6-dimethylamino	crude	H, 4623
2,4,6-Triamino-5-fluoro	anal.; u.v.	4744
2,4,6-Triamino-5-formyl	> 250	6382
2,4,5-Triamino-6-hydroxy	2HCl: > 300; sul: > 264 or > 320	H, E, 3475, 5234, 5339, 6247
	> 300	6373
2,4,6-Triamino-5-hydroxy	–	6057
2,4,5-Triamino-6-hydroxymethyl	270	H, E, 6223
2,4,5-Triamino-6-mercaptop	217	5767
2,4,5-Triamino-6-methoxycarbonyl	crude	H, E, 4617
4,5,6-Triamino-2-methylthio	<i>N</i> -Ox: anal.; di- <i>N</i> -Ox: anal.	E, 6235
2,4,6-Triamino-5-nitro	> 300	H, E, 4643
2,4,6-Triamino-5-nitroso	197–198	2944
2,4,5-Triamino-6-phenyl	186–190	H, E, 6055
4,5,6-Triamino-2-phenyl	261	H, E, 5293, 5465
2,4,6-Triamino-5-phenylazo	160	5188
2,4,6-Triamino-5-phenylthio	HCl: –	H, 3508
2,4,5-Triamino-6-piperidino	> 300	6373
2,4,6-Triamino-5-sulfo-oxy		

2,4,6-Triamino-5-thiocyanato	219–220	5244
2,4,5-Triamino-6-trifluoromethyl	204	E, 5823
2,4,6-Triaziridino	132–133	E, 6060
2,4,6-Tribromo	112–113	H, 4677
2-Tribromomethyl	crude	5682
4-Tribromomethyl	crude	E, 5682
2,4,6-Tribromo-5-methyl	136–137	5517
2,4,6-Trichloro	93 (?); 102/18	H, E, 4500, 4511
		5988
2,4,5-Trichloro-6-chloromethyl	130–145/0.5	4500
2,4,6-Trichloro-5-chloromethyl	112	4500
4,5,6-Trichloro-2-chloromethyl	28–30	E, 5021
2,4,6-Trichloro-5- α -chlorovinyl	39	6017
2,4,5-Trichloro-6-cyano	80	5971
2,4,6-Trichloro-5-cyano	119	E, 5770
2,4,6-Trichloro-5-cyanomethyl	125	4500
2,4,5-Trichloro-6-ethoxy	66	5971
2,4,6-Trichloro-5-ethyl	74–76	H, 5797
2,4,6-Trichloro-5-formyl	186	5000
2,4,5-Trichloro-6-guanidino	> 300	6384
4,5,6-Trichloro-2-guanidino	> 360	6384
2,4,5-Trichloro-6-hydroxy	197	5971
2,4,5-Trichloro-6-isocyanato	81–82/0.1	4517
4,5,6-Trichloro-2-isocyanato	90–91/0.06	4517
2-Trichloromethyl	crude; nmr	5682
4-Trichloromethyl	24–26	E, 5682, 5954
2,4,6-Trichloro-5-methyl	68	H, E, 4500
2,4,6-Trichloro-5-methylthio	105–107/2	6061
2,4,6-Trichloro-5-nitro	56	H, E, 5770
2,4,5-Trichloro-6-phenyl	90	E, 6575
2,4,6-Trichloro-5-phenyl	159	H, 4500
2,4,5-Trichloro-6-trichloromethyl	100/2	5954
2,4,6-Tricyclopropyl	82	6051
2,4,6-Triethoxy	–	H, E, 4694

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
2,4,6-Triethyl	120/80	5096
1,3,5-Triethylhexahydro-5-hydroxy-2,4,6-trioxo	63-64	5898
1,3,5-Triethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo	n_D^{25} 1.4855	5898
1,3,4-Triethyl-1,2,3,6-tetrahydro-5-methyl-2,6-dioxo	81-82	6401
2,4,5-Trifluoro	89-91/at	5779
2,4,6-Trifluoro	98/at or 102/at	E, 3520, 3521, 4755
4,5,6-Trifluoro	crude	5779
2,4,5-Trifluoro-6-heptafluoroisopropyl	117/at	5242, 5922
2,4,6-Trifluoro-5-heptafluoroisopropyl	nmr	5922
2,4,5-Trifluoro-6-hydroxy	125-126	E, 3521
2,4,5-Trifluoro-6-iodo	25-26; 68/18	5779
2,4,5-Trifluoro-6-methoxy	55-56/20	3521
2,4,6-Trifluoro-5-methyl	132-133/at	3520, 4526
2,4,5-Trifluoro-6-methylamino	122-123	3521
5-Trifluoromethyl-2,4-bis(trimethyl)siloxy	58/1.5	E, 6224
2,4,6-Trifluoro-5-nitro	36-38	5770
2,4,5-Trifluoro-6-pentafluoroethyl	anal.; nmr	5268, 5922
2,4,6-Trifluoro-5-pentafluoroethyl	anal.; nmr	5268, 5922
2,4,5-Trifluoro-6-trifluoromethyl	crude	5770
2,4,6-Trifluoro-5-trifluoromethyl	crude	5770
4,5,6-Trifluoro-2-trifluoromethyl	crude	5770
2,4,6-Trihydrazino	217-218	5848
2,4,5-Trihydroxy	330; 3-N-Ox: sp	H, E, 5426, 5507, 6280, 6373
2,4,6-Trihydroxy	243-245	H, E, 5322
2,4,6-Trihydroxy-5-hydroxyamino	208	4793
2,4,6-Trihydroxy-5- β -hydroxyethyl	193-194	H, 2638
2,4,5-Trihydroxy-6-hydroxymethyl	> 300	H, 6248
2,4,5-Trihydroxy-6-methyl	> 300	H, E, 5729, 6373

2,4,6-Trihydroxy-5-methyl	202–203	H, E, 2872
2,4,6-Trihydroxy-5-nitro	181–183	H, E, 4748
2,4,6-Trihydroxy-5-nitroso	245–246	H, E, 5186
2,4,6-Trihydroxy-5-phenyl	256–258	5882
2,4,5-Trihydroxy-6-phenylazo	—	5060
2,4,6-Trihydroxy-6-piperidino	345–350	5178
2,4,5-Trihydroxy-6-propyl	232–234	5532
2,4,6-Trimercapto	—	H, E, 6228
2,4,6-Trimethoxy	50–52	H, E, 5321, 5323, 5988
2,4,6-Trimethoxy-5-nitro	122–123	6381
2,4,6-Trimethoxy-5-phenyl	crude	5321
2,4,6-Trimethoxy-5-phenyliminomethyl	110–112	5988
2,4,6-Trimethoxy-5-piperidino	106–107	5178
2,4,6-Trimethyl	60/11; di- <i>N</i> -Ox: 209	H, 4689, 4814, 6008, 6108
4,5,6-Trimethyl	76/12	6319
2-Trimethylammonio	Cl: 205; pic: 176	4580, 5342
4-Trimethylammonio	Cl: 138; pic: 160	5342
2-Trimethylammoniomethyl	Cl: 230–233	5682
2,4,5-Trimethyl-6-methylamino	94–96	5679
4,5,6-Trimethyl-2-methylthio	51–52; 74/0.05	4554
4-Trimethylsiloxy-2-trimethylsilylthio	crude	5418
2,4,5-Trimethyl-6-sulfo	K: —	5667
2,4,5-Triphenyl	—	6209
2,4,6-Triphenyl	183 to 190	H, 4477, 4817, 5096, 5804, 6575, 6746
2,4,6-Triphenyl-5-propyl	135–137	5804, 6746
2,4,6-Trisacetoxymethyl	di- <i>N</i> -Ox: 108	6160
2,4,6-Trisbromomethyl	di- <i>N</i> -Ox: 188	6160
2,4,6-Trisdimethylamino	142–145	6106
2,4,5-Trisdimethylaminomethyleneamino	192–196	6289
2,4,6-Tris(trimethylsiloxy)	38–41	5957

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil (unsubstituted)	320 to 335	H, E, 4718, 4720, 4857, 5030, 5123, 5417, 5421, 5513, 5734, 6590
Uracil/5-acetamido-6-amino-1-methyl	305	H, E, 5841
Uracil/5-acetamido-6-amino-1-phenyl	240	2982
Uracil/3-acetamido-5-ethoxycarbonyl	221-227	6232
Uracil/6-acetamido-3-methyl	280-281	5446
Uracil/1-acetonyl	205 or 209-210	4854, 5483
Uracil/1-acetonyl-5-fluoro	220	4889
Uracil/1-acetonyl-5-hydroxymethyl	217	5483
Uracil/1-acetonyl-5-methyl	197	5483
Uracil/5-acetoxy-6-acetoxymethyl-1-methyl	204-205	6248
Uracil/1- β -acetoxyethyl	136-138	5495
Uracil/5-acetoxymethyl-1-acetyl	113-114	6229
Uracil/5-acetoxymethyl-1-methyl	157 or 162-164	5308, 6239
Uracil/5-acetoxymethyl-3-methyl	144-145	5308, 6239
Uracil/1-acetyl	188-190	E, 6132
Uracil/5-acetyl-6-amino-1-methyl	308-310	5446
Uracil/1-acetyl-5-t-butyl	168	4726
Uracil/5-acetyl-1-butyl	182	4941
Uracil/5-acetyl-1-cyclohexyl	265	4941
Uracil/5-acetyl-1,6-dimethyl	211-212	5601
Uracil/1-acetyl-5-ethyl	142-145	4734
Uracil/1- α -acetyloethyl-5-bromo	201-202	5167
Uracil/1-acetyl-5-methoxymethyl	164-166	6229, 6230
Uracil/5-acetyl-1-methyl	243	E, 4941
Uracil/5-acetyl-6-methyl-1-phenyl	196-197	5601
Uracil/5-acetyl-1-phenyl	277	E, 4941
Uracil/1-acetyl-6-propyl	230-232	5532

Uracil/1- γ -acetylthiopropyl	110–112	5240
Uracil/3- γ -acetylthiopropyl	170–171	5240
Uracil/1-allyl	105–108	5727, 6233
Uracil/3-allyl	133–134	5591
Uracil/1-allyl-5-allyloxymethyl	105–107	4493
Uracil/6-allylamino-3-benzyl	234–236	4660
Uracil/6-allylamino-3-benzyl-5-nitroso	162–165	4660
Uracil/1-allyl-6-amino-5- β -cyanoethyl	260–263	4234
Uracil/6-allylamino-3-methyl	252–255	4660
Uracil/6-allylamino-3-methyl-5-nitroso	190	4660
Uracil/1-allyl-5-bromo	170	6233
Uracil/1-allyl-5-butyl	75	6233
Uracil/1- <i>N</i> -allylcarbamoyl-5-fluoro	130–131	5112
Uracil/1-allyl-5-cyano	149–152	5727
Uracil/1-allyl-5-fluoro	125 or 126–127	4889, 6350
Uracil/1-allyl-5-hydroxymethyl	118–120	4493
Uracil/3-allyl-5-methyl	175–177	5591
Uracil/3-allyl-6-methylthio	176–178	4806
Uracil/5-allyloxymethyl-1-methyl	76–78	4493
Uracil/1-allyl-5-propyl	112–114	6233
Uracil/3-allyl-6-trifluoromethyl	158–160	5933
Uracil/3- <i>e</i> -aminoamyl-6-carboxy	322–323	4782
Uracil/6-amino-1-benzyl	285–286	425, 4914
Uracil/6-amino-5-benzylamino-1-methyl	226	5850
Uracil/6-amino-5-benzylamino-3-methyl	206	E, 5850
Uracil/6-amino-5-benzyl-1-benzylloxy	216	5425
Uracil/6-amino-1-benzyl-5-bromo	219	4914
Uracil/6-amino-1-benzyl-5- <i>N</i> -ethyl(thiocarbamoyl)	287	5037
Uracil/6-amino-5-benzylideneamino-1-methyl	> 340	5006, 5850
Uracil/6-amino-5-benzylideneamino-3-methyl	–	5850
Uracil/6-amino-1-benzyl-5-methyl	235–237	5037
Uracil/6-amino-1-benzyl-5-methylamino	220–221	4914
Uracil/6-amino-1-benzyl-5- <i>N</i> -methylformamido	252–253	4914
Uracil/6-amino-1-benzylloxy-5- β , β -diethoxyethyl	152	5422

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/5- γ -aminobutyl	HCl: 230–231	5303
Uracil/3-amino-5-carboxy	215–216	6232
Uracil/6-amino-5- β -cyanoethyl-1-propyl	250–252	4234
Uracil/6-amino-1-dimethylamino-5-ethyl	276–278	2870
Uracil/6-amino-1-dimethylamino-5-methyl	296–299	2870
Uracil/3- β -aminoethyl-6-carboxy	287–288	4782
Uracil/6-amino-1-ethyl-5-formyl	295–300	5036
Uracil/6-amino-5-ethyl-1-piperidino	253–255	2870
Uracil/6-amino-5-formamido-1-methoxy	215	5425
Uracil/6-amino-5-formamido-1-methyl	> 320 or > 340	H, E, 4620, 5841
Uracil/6-amino-5-formyl-3-methyl	1- <i>N</i> -Ox: 250	3397
Uracil/6-amino-1- β -hydroxyethyl	255	H, E, 6020
Uracil/6-amino-1- β -hydroxyethyl-5-nitroso	> 200	H, E, 6020
Uracil/6-amino-5-hydroxy-1-methyl	—	5060
Uracil/6-amino-1-isobutyl-5-nitroso	235–236	5281
Uracil/5-amino-6-isopropylamino-3-methyl	HCl: > 280	4627
Uracil/6-amino-1-methoxy	248–249	5425
Uracil/6-amino-1-methoxy-5-nitroso	194	5425
Uracil/6-amino-1- β -methoxypropyl-5-nitroso	223–226	5281
Uracil/1-amino-6-methyl	242–244	5070
Uracil/3-amino-6-methyl	272 or 275–279	4519, 5166, 5950, 6232
Uracil/5-amino-1-methyl	248–250	H, 5448
Uracil/5-amino-3-methyl	202–204	5448
Uracil/6-amino-3-methyl	330	E, 4658
Uracil/6-amino-1-methyl-5- <i>N</i> -methylformamido	338–340	6231
Uracil/6-amino-3-methyl-5- <i>N</i> -methylformamido	335–341	4914
Uracil/6-amino-3-methyl-5-nitro	354	4620
Uracil/6-amino-1-methyl-5-nitroso	> 300 or > 340	H, E, 4620, 5127
Uracil/6-amino-3-methyl-5-nitroso	—	E, 4574

Uracil/5-amino-1-methyl-6-phenylazo	5060
Uracil/6-amino-5- <i>N</i> -methyl(thiocarbamoyl)-1-phenyl	5037
Uracil/6-amino-5-nitroso-1-phenyl	2982, 5127
Uracil/1-β-(amino-oxy)ethyl	5240
Uracil/1-γ-(amino-oxy)propyl	5240
Uracil/6-amino-1-phenyl	2982, 5127
Uracil/1-γ-aminopropyl	5510
Uracil/3-γ-aminopropyl-6-carboxy	4782
Uracil/1-γ-aminopropyl-5-methyl	5510, 5646
Uracil/1- <i>N</i> -amylcarbonyl-5-fluoro	5112
Uracil/1-amyl-5-fluoro	6511
Uracil/3-amyl-5-fluoro	E, 6511
Uracil/6-anilino-1-methyl	E, 4487, 4988
Uracil/6-anilino-3-methyl	E, 5656
Uracil/6-anilinomethyl-1-butyl	6274
Uracil/6-anilinomethyl-1-phenyl	6274
Uracil/1-γ-azidopropyl	5510
Uracil/1-γ-azidopropyl-5-methyl	5510
Uracil/3-benzamido-5-carboxy	6232
Uracil/3-benzamido-5-ethoxycarbonyl	6232
Uracil/3-benzamido-6-methyl	4519, 6232
Uracil/3-benzoyl	E, 3770
Uracil/1-benzyl	H, E, 4390, 5630
Uracil/3-benzyl	H, 4390, 4847, 5591
Uracil/6-benzylamino-5-formamido-3-methyl	E, 5850
Uracil/1-benzylamino-6-methyl	5070
Uracil/6-benzylamino-3-methyl	E, 5656
Uracil/1-benzyl-5-bromo	H, E, 4940
Uracil/6-benzyl-5-bromo-3-cyanomethyl	2655
Uracil/1- <i>N</i> -benzylcarbonyl-5-fluoro	5112
Uracil/3-benzyl-6-carboxy	H, 4949
Uracil/1-benzyl-5-chloro-6-dimethylaminomethyleneamino	5036
Uracil/1-benzyl-5-cyano	H, 4940
Uracil/1-benzyl-6-cyano	4940

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/1-benzyl-5-fluoro	166–168 or 171	E, 6350, 6511
Uracil/3-benzyl-6-hydrazino	212–213	6014
Uracil/5-benzylideneamino-6-butyldamino-3-methyl	225–227	6030
Uracil/1-benzylideneamino-6-methyl	236	5070
Uracil/3-benzylideneamino-6-methyl	239–240	6232
Uracil/5-benzylideneamino-3-methyl-6-methylamino	284–286	6030
Uracil/5-benzylideneamino-3-methyl-6-propylamino	248–250	6030
Uracil/5-benzylidene-6-benzylidenehydrazino-3-methyl	278–279	4995, 5007
Uracil/6-benzylidenehydrazino-3-methyl	298	4954, 4991
Uracil/6-benzylidenehydrazino-3-methyl-5-nitro	259–261	4989
Uracil/6-benzylidenehydrazino-3-methyl-5-nitroso	205–206	4989
Uracil/1-benzyl-6-methyl	230–231	H, 6194
Uracil/3-benzyl-5-methyl	207 or 208–209	H, 6070, 6292
Uracil/3-benzyl-6-methyl	198–200	H, E, 4387, 4388
Uracil/3-benzyl-6- α -methylhydrazino	166–168	4996
Uracil/3-benzyl-6-methyl-5-nitro	267–268	5412
Uracil/3-benzyl-5-nitro	230–232	E, 5412
Uracil/1-benzylloxy	176 or 185	E, 3464, 5175
Uracil/1-benzylloxy-5-bromo	175–177	3464
Uracil/3-benzylloxy-5-bromo	230–233	3464
Uracil/1-benzylloxy-6-carboxy	sp	5175
Uracil/1-benzylloxy-5-chloro	178	3464
Uracil/1-benzylloxy-5-fluoro	184–186	3464
Uracil/1-benzylloxy-6-hydroxymethyl	179	5175
Uracil/1-benzylloxy-5-iodo	187–188	3464
Uracil/3-benzylloxy-5-iodo	209–211	3464
Uracil/1- ϵ -bromoamyl	57–59	4474
Uracil/3- ϵ -bromoamyl	76–78	6127
Uracil/1- ϵ -bromoamyl-5-methyl	104 or 122	4474, 4713, 6238
Uracil/1- δ -bromobutyl	94–96	4474, 4828

Uracil/5-bromo-1-butyl	180-183	4940
Uracil/5-bromo-1-s-butyl	185-186	4940
Uracil/3- δ -bromobutyl-6-carboxy	181-183	4778
Uracil/5-bromo-3-s-butyl-6-chloromethyl	187-189	5588
Uracil/3- δ -bromobutyl-6-ethoxycarbonyl	137-138	4778
Uracil/1- δ -bromobutyl-5-methyl	124-126	4474
Uracil/3- δ -bromobutyl-6-methyl	174-175	4828
Uracil/5-bromo-1-butyl-6-methyl	164	4925
Uracil/3- δ -bromobutyl-6-methyl-5-nitro	154-156	6127
Uracil/5-bromo-3-butyl-6-methylthio	211	4806
Uracil/5-bromo-3-s-butyl-6-methylthio	222	4806
Uracil/3- δ -bromobutyl-6-phenyl	174-176	6127
Uracil/5-bromo-3-butyl-6-trifluoromethyl	128-130	5933
Uracil/5-bromo-3-s-butyl-5-trifluoromethyl	130-132	5933
Uracil/5-bromo-1- β -carbamoylethyl	281	4877
Uracil/5-bromo-1- β -carboxyethyl	250	4877
Uracil/5-bromo-1-carboxymethyl	> 280	H, 5204
Uracil/5-bromo-6-chloro-3-methyl	232-233	4650
Uracil/5-bromo-1- β -cyanoethyl	232-234	4391
Uracil/5-bromo-3- β -cyanoethyl	176-178	4391
Uracil/5-bromo-1-cyclohexyl	224-225	4720, 6114
Uracil/5-bromo-1-cyclohexyl-6-methyl	261	4925
Uracil/5-bromo-3-cyclohexyl-6-methylthio	234	4806
Uracil/6-bromo-3-cyclohexyl-6-trifluoromethyl	187-189	5933
Uracil/5-bromo-1-cyclopentyl-6-methyl	185	4925
Uracil/5-bromo-3- β , γ -dibromopropyl-6-trifluoromethyl	154-155	5933
Uracil/5-bromo-1-di(ethoxycarbonyl)methyl	108-111	5167
Uracil/5-bromo-1- β , β -diethoxyethyl	121-122	6236
Uracil/5-bromo-1- β , γ -dihydroxypropyl	202-204	5032
Uracil/5-bromo-3- β , γ -dihydroxypropyl-6-methyl	205-206	4784
Uracil/5-bromo-1,6-dimethyl	264	4925
Uracil/5-bromo-3-ethoxycarbonylmethyl-6-trifluoromethyl	185-189	5933
Uracil/3- β -bromoethyl	159-160	6127
Uracil/5-bromo-1-ethyl	250-253	4940

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/3- β -bromoethyl-6-carboxy	220–222	4778
Uracil/3- β -bromoethyl-6-ethoxycarbonyl	196–197	4778
Uracil/1- β -bromoethyl-5-methyl	209–210	6077
Uracil/5-bromo-3-ethyl-6-methylthio	216	4806
Uracil/5-bromo-6-ethyl-3-phenyl	227	4931
Uracil/5-bromo-3-ethyl-6-trifluoromethyl	197–198	5933
Uracil/5-bromo-1-formylmethyl	230–233	6236
Uracil/1-6'-bromohexyl-5-methyl	111–113	5646
Uracil/5-bromo-3- β -hydroxyethyl-6-methyl	213–214	4784
Uracil/5-bromo-1-iso butyl	237–238	4940
Uracil/5-bromo-3-iso butyl-6-methylthio	227	4806
Uracil/5-bromo-1-iso propyl	214–215	E, 4940
Uracil/5-bromo-3-iso propyl-6-methylthio	220	4806
Uracil/5-bromo-3-iso propyl-6-trifluoromethyl	151–154	5933
Uracil/5-bromo-1- β -methoxycarbonylethyl	159–160	4877
Uracil/6-bromo-3-methyl	281–282	4650
Uracil/5-bromo-3-methyl-6-phenoxy	253–255	6273
Uracil/5-bromo-6-methyl-1-phenyl	293	4925
Uracil/5-bromo-6-methyl-3-phenyl	281	H, E, 4925
Uracil/5-bromo-3-methyl-6-phenylthio	214–215	6273
Uracil/5-bromo-6-methylthio-3-phenyl	255	4806
Uracil/5-bromo-6-methylthio-3-propyl	241	4806
Uracil/5-bromo-3-methyl-6-trifluoromethyl	212–213	5933
Uracil/5-bromo-1-phenyl	285	4931
Uracil/5-bromo-3-phenyl-6-trifluoromethyl	207–209	5933
Uracil/1- γ -bromopropyl	87 or 87–96	4474, 5646
Uracil/5-bromo-1-propyl	189–190	4940
Uracil/1- γ -bromopropyl-5-ethyl	106–110	4713, 6238
Uracil/1- γ -bromopropyl-5-methyl	136–138	4474, 5628, 5646
Uracil/3- γ -bromopropyl-6-methyl	204–206	4828

Uracil/5-bromo-3-propyl-6-trifluoromethyl	169–172	5933
Uracil/1-butoxycarbonyl-5-fluoro	144–146	6515
Uracil/1- α -butoxyethyl-5-fluoro	57–59	6145
Uracil/1-butoxymethyl-5-fluoro	67–69	6145
Uracil/1-butyl	100–104	E, 5328, 5630, 5648, 5727
Uracil/1-s-butyl	108–113	5727
Uracil/3-butyl	147–153	E, 5417, 5488, 5648, 5754, 6070
Uracil/6-butylamino-3-methyl-5-nitroso	240	E, 6539
Uracil/1-N-butylcarbamoyl-5-fluoro	137	5112
Uracil/1-N-t-butylcarbamoyl-5-fluoro	108	5112
Uracil/3-butyl-5-chloro	188	E, 4527
Uracil/3-butyl-6-chloro-5-ethyl	122	4527
Uracil/3-butyl-6-chloro-5-formyl	123–125	4923
Uracil/3-s-butyl-5-chloro-6-methylthio	198	4806
Uracil/3-butyl-5-chloro-6-trifluoromethyl	138–139	5933
Uracil/1-butyl-5-cyano	187 or 191–193	H, 4940, 4941
Uracil/1-s-butyl-5-cyano	272–274	H, 4940
Uracil/1-butyl-6-cyano	164–166	4940
Uracil/1-s-butyl-6-cyano	148–150	4940
Uracil/3-t-butyl-6-diethylamino-5-ethyl	133	6072
Uracil/3-butyl-6- β -dimethylaminovinyl-5-nitro	253	4936
Uracil/1-butyl-5-fluoro	124–126	6515
Uracil/1-butyl-5-methyl	138–139	E, 5019
Uracil/1-butyl-6-methyl	132–133	E, 6194
Uracil/3-butyl-5-methyl	73	E, 6070
Uracil/3-butyl-6-methyl	177	E, 5754
Uracil/5-t-butyl-1-methyl	219–221	4726
Uracil/5-t-butyl-3-methyl	213–214	4726
Uracil/3-butyl-6-methylthio	177–179	4806
Uracil/3-s-butyl-6-methylthio	165–167	4806
Uracil/3-butyl-5-nitro-6-trifluoromethyl	148–151	5933
Uracil/3-butyl-6-trichloromethyl	150–152	5588

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/3-butyl-6-trifluoromethyl	174–176	5589, 5933
Uracil/3-s-butyl-6-trifluoromethyl	106–108	5589, 5933
Uracil/3-t-butyl-6-trifluoromethyl	165–167	5933
Uracil/5-carbamoyl-1-cyclohexyl	306	4920, 6034
Uracil/5-carbamoyl-3-cyclohexyl	302	4920
Uracil/1- β -carbamoylethyl-5-iodo	230	4877
Uracil/1-carbamoylmethyl	288–290	E, 5204
Uracil/5-carbamoyl-1-methyl	—	6034
Uracil/6-carbamoyl-1-methyl	> 300	4946
Uracil/6-carbamoyl-3-methyl	> 300	4934, 4946
Uracil/5-carbamoyl-6-methyl-1-phenyl	275–278	6270
Uracil/5-carbamoyl-1-phenyl	> 300 or 327	4920, 6270
Uracil/5-carbamoyl-3-phenyl	308	4920
Uracil/1-e-carboxyamyl	162	5920
Uracil/1- δ -carboxybutyl-5-cyano	165	5920
Uracil/5-carboxy-1-e-carboxyamyl	182–183	5920
Uracil/5-carboxy-1- α -carboxy- β -methylbutyl	183–184	5129
Uracil/5-carboxy-1- α -carboxy- β -methylpropyl	199–200	5129
Uracil/5-carboxy-1-cyclohexyl	310 or 316	4720, 4920
Uracil/5-carboxy-3-cyclohexyl	235	4920
Uracil/5-carboxy-1-cyclohexyl-6-methyl	219	4920
Uracil/5-carboxy-1- α , β -dicarboxyethyl	211–212	5129
Uracil/5-carboxy-1- α , γ -dicarboxypropyl	127	5129
Uracil/5-carboxy-3-dimethylamino	235–243	2870
Uracil/1- β -carboxyethyl	175 or 188–189	E, 5035, 5204
Uracil/6-carboxy-1-ethyl	250–251	H, 5175
Uracil/1- β -carboxyethyl-5-cyano	218–219	5920
Uracil/1- α -carboxyethyl-5-ethoxycarbonyl	159–161	5129
Uracil/1- β -carboxyethyl-5-ethoxycarbonyl	183	5129
Uracil/1- β -carboxyethyl-5-iodo	180–181	4877

Uracil/1- β -carboxyethyl-5-methyl	170–175	E, 5035
Uracil/6-carboxy-3- δ -hydroxybutyl	210–212	4778
Uracil/6-carboxy-3- β -hydroxyethyl	231–232	4778
Uracil/5-carboxy-3- β -mercaptoethyl	220–221	5395
Uracil/1-carboxymethyl	287	H, E, 5269
Uracil/3-carboxymethyl	222–224	5771
Uracil/6-carboxy-1-methyl	257	H, E, 5175
Uracil/6-carboxy-3-methyl	> 300	H, 4934, 4946
Uracil/1- α -carboxy- γ -methylbutyl-5-ethoxycarbonyl	174–175	5129
Uracil/1-carboxymethyl-5-ethoxycarbonyl	181–182	5129
Uracil/1-carboxymethyl-5-fluoro	276–277; NH ₄ : 227	4378, 5081
Uracil-1-carboxymethyl-5-iodo	248–249	4378
Uracil/1-carboxymethyl-5-methyl	270	H, 5269
Uracil/1-carboxymethyl-6-methyl	263–264	4573
Uracil/3-carboxymethyl-6-methyl	254–255	4569
Uracil/6-carboxy-5-methyl-3-phenyl	302	E, 3751
Uracil/5-carboxy-1-phenyl	278	H, 4920
Uracil/5-carboxy-3-phenyl	264	H, 4920
Uracil/5-carboxy-3-piperidino	227–228	2870
Uracil/1- γ -carboxypropyl	188–191	5240
Uracil/1- γ -carboxypropyl-5-cyano	200	5920
Uracil/5- β -carboxyvinyl-1-methyl	284–286	5427
Uracil/5-chloro-1-cyclohexyl	223–224	4720
Uracil/6-chloro-3-cyclohexyl-5-formyl	166–168	4923
Uracil/5-chloro-6-dichloromethyl-3-isopropyl	187–190	5588
Uracil/1- β -chloroethyl	162 to 167	E, 5495, 5818, 6077
Uracil/6-chloro-1-ethyl	165	4527
Uracil/6-chloro-3-ethyl	220	E, 4527
Uracil/1- β -chloroethyl-5-fluoro	199–201	4889
Uracil/1- β -chloroethyl-5-methyl	203–205	5818
Uracil/3- β -chloroethyl-6-methyl	196–197	6218
Uracil/5-chloro-3- α -ethylpropyl-6-trifluoromethyl	103–106	5933
Uracil/6-chloro-5-formyl-3-methyl	crude: 188	4984, 5000
Uracil/6-chloro-5-formyl-3-phenyl	230	4923

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/6-chloro-5-hexyl-3-methyl	127	4527
Uracil/6-chloro-5-iodo-3-methyl	247-248	4650
Uracil/6-chloro-5-isobutyl-1-phenyl	220	4452
Uracil/5-chloro-3-isopropyl-6-trifluoromethyl	141 or 143-144	5589, 5933
Uracil/6-chloro-1-methyl	196-197	4739
Uracil/6-chloro-3-methyl	275-276	E, 4527, 4739
Uracil/6-chloro-5-(2'-methylallyl)-1-phenyl	crude	4452
Uracil/5-chloromethyl-3-methyl	239-241	6239
Uracil/5-chloro-6-methyl-1-phenyl	> 300	4925
Uracil/5-chloro-6-methyl-3-phenyl	257	E, 4925
Uracil/6-chloro-5-(2'-methylprop-1'-enyl)-1-phenyl	crude	4452
Uracil/6-chloro-3-propyl	194	4527
Uracil/5-cyano-1-cyclohexyl	> 300 or 321	H, 4720, 4941
Uracil/5-cyano-3-cyclohexyl	220	H, 4941
Uracil/5-cyano-1-cyclohexyl-6-methyl	296	4941
Uracil/1- β -cyanoethyl	235-237	E, 5924
Uracil/3- β -cyanoethyl	141-142	5924, 6048
Uracil/5-cyano-1-ethyl	212-213	H, 4940
Uracil/6-cyano-1-ethyl	178-180	4940
Uracil/1- β -cyanoethyl-5-methoxy	226-228	5924
Uracil/3- β -cyanoethyl-5-methoxy	220-221	6048
Uracil/1- β -cyanoethyl-5-methyl	204-206	E, 5924
Uracil/5-cyano-1-isobutyl	221-222	H, 4940
Uracil/6-cyano-1-isobutyl	182	4940
Uracil/5-cyano-1-isopropyl	227-228	H, 4940
Uracil/6-cyano-1-isopropyl	178-180	4940
Uracil/5-cyano-1-methyl	267	H, 4941
Uracil/6-cyano-1-methyl	228-229	4937
Uracil/5-cyano-6-methyl-1-phenyl	> 290 or > 300	E, 4941, 6270
Uracil/5-cyano-1-phenyl	266 or 298	H, 4941, 6270

Uracil/5-cyano-3-phenyl	> 300	4941
Uracil/6-cyano-1-phenyl	242–245	4937
Uracil/5-cyano-1-propyl	172–174	H, 4940
Uracil/6-cyano-1-propyl	181–183	4940
Uracil/1-cyclohexyl	215 to 220	E, 4720, 4920, 5630, 6114
Uracil/3-cyclohexyl	270	E, 4920
Uracil/1-cyclohexylcarbamoyl-5-fluoro	156–157	5112
Uracil/1-cyclohexyl-5-dimethylamino-6-methyl	189	4925
Uracil/3-cyclohexyl-5-ethoxycarbonyl	226	4941
Uracil/1-cyclohexyl-5-ethoxycarbonyl-6-methyl	167–169	4941
Uracil/1-cyclohexyl-5-methyl	198	6114
Uracil/1-cyclohexyl-6-methyl	230	E, 4920
Uracil/1-cyclohexyl-6-methyl-5-nitro	235–237	4925
Uracil/3-cyclohexyl-6-methylthio	266–268	4806
Uracil/3-cyclohexyl-6-trifluoromethyl	195–197	5589, 5933
Uracil/1-cyclopentyl-5-dimethylamino-6-methyl	234	4925
Uracil/3-cyclopropyl-6-trifluoromethyl	158–160	5589
Uracil/5,6-diamino-1-hydroxyethyl	255	H, 6020
Uracil/5,6-diamino-1-methyl	HCl: > 300	H, E, 4620
Uracil/5,6-diamino-1-phenyl	232–233	2982
Uracil/5-diazo-1-methyl	H ₂ O: 158; MeOH: 123	5448
Uracil/5-diazo-3-methyl	123–124; MeOH: 97	5448
Uracil/5,6-dichloro-3-methyl	231–233	4650
Uracil/1-diethoxycarbonylmethyl	118–120	5195
Uracil/1-β,β-diethoxyethyl	89	E, 5288
Uracil/1-β,β-diethoxyethyl-5-fluoro	114–115	4749
Uracil/1-β,β-diethoxyethyl-5-methyl	76–78	4749, 5288
Uracil/1-β,β-diethoxyethyl-5-nitro	91	6236
Uracil/1- <i>N,N</i> -diethylcarbamoyl-5-fluoro	157–160	5112
Uracil/5-(2',3'-dihydroxycyclopentyl)-3-methyl	232–237	3762
Uracil/5-α,β-dihydroxyethyl-1-methyl	104	5238
Uracil/1-β,γ-dihydroxypropyl	143–144	5023
Uracil/3-β,γ-dihydroxypropyl	165–166	6068

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/1- β , γ -dihydroxypropyl-5-fluoro	147–149	5032
Uracil/1- β , γ -dihydroxypropyl-5-iodo	196–198	5032
Uracil/1- β , γ -dihydroxypropyl-5-methyl	145–146	5032
Uracil/3- β , γ -dihydroxypropyl-6-methyl	175–176	6068
Uracil/5,6-di-iodo-3-methyl	265	4650
Uracil/1,5-dimethyl	257 or (281 to 297)	H, E, 5019, 5204, 5490, 5575, 5811
Uracil/1,6-dimethyl	220 to 227; 3- <i>N</i> -Ox: 171	H, E, 4387, 4858, 4888, 5957
Uracil/3,5-dimethyl	205 to 218	H, E, 5308, 5490, 6239, 6292
Uracil/3,6-dimethyl	259 to 263	H, E, 4879, 4888, 5070, 5090, 5754
Uracil/3-dimethylamino-5-ethoxycarbonyl	203–205	2870
Uracil/5-dimethylamino-6-methyl-1-phenyl	191	4925
Uracil/1- <i>N,N</i> -dimethylcarbamoyl-5-fluoro	194–196	5112
Uracil/3,6-dimethyl-5-nitro	231–233	H, 5412
Uracil/1,5-dimethyl-6-phenyl	238–240	6244
Uracil/1,6-diphenyl	271	6240
Uracil/1-ethoxycarbonyl	120	E, 4579
Uracil/5-ethoxycarbonyl-1,6-dimethyl	200–201	5601
Uracil/1-ethoxycarbonyl-5-fluoro	128–130	6515
Uracil/1-ethoxycarbonylmethyl	137–138 or 150	E, 5204, 6245
Uracil/1-ethoxycarbonyl-5-methyl	180	4579
Uracil/1-ethoxycarbonylmethyl-5-fluoro	164–165	5081
Uracil/3-ethoxycarbonylmethyl-5-fluoro	131–132	6515
Uracil/1-ethoxycarbonylmethyl-5-methyl	172–173	6245
Uracil/5-ethoxycarbonylmethyl-1-methyl	126–128	6158
Uracil/5-ethoxycarbonyl-6-methyl-1-phenyl	273–274	5601

Uracil/3-ethoxycarbonylmethyl-6-trifluoromethyl	149–151	5589, 5933
Uracil/5-ethoxycarbonyl-3-phenyl	250	H, 4941
Uracil/5-ethoxycarbonyl-3-piperidino	213–215	2870
Uracil/1- α -ethoxyethyl-5-fluoro	116–118	6145
Uracil/1-ethoxymethyl-5-fluoro	129–131	6145, 6515
Uracil/1-ethyl	144 to 148	H, E, 5019, 5328, 5331, 5528, 5648
Uracil/3-ethyl	173 or 174–175	H, 5331, 5648, 5754
Uracil/1- <i>N</i> -ethylcarbamoyl-5-fluoro	165	5112
Uracil/1-ethyl-6-hydroxyamino	205–227 (1)	5042
Uracil/1-ethyl-6-hydroxymethyl	211–212	5172
Uracil/6- β -ethylidene- α -methylhydrazino-3-methyl	183 or 202	4997, 4999
Uracil/1-ethyl-5-methyl	222–223 or 233	H, 5019, 6070
Uracil/1-ethyl-6-methyl	195–196	H, E, 6194
Uracil/3-ethyl-5-methyl	202	6070
Uracil/3-ethyl-6-methyl	196	H, E, 5754
Uracil/5-ethyl-1-methyl	162	5797
Uracil/5-ethyl-1-methyl-6-propyl	197–199	4726
Uracil/3-ethyl-3-methyl-6-propyl	125–127	4726
Uracil/3-ethyl-6-methylthio	236–240	4806
Uracil/5-ethyl-1-phenyl	176–178	4802
Uracil/6-ethyl-3-phenyl	212	4931
Uracil/1-ethylsulfonyl-5-fluoro	214–215	5082
Uracil/6-ethylthio-3-phenyl	237–239	5536
Uracil/3-ethyl-6-trifluoromethyl	199–200	5589, 5933
Uracil/5-fluoro-1-formylmethyl	292	4749
Uracil/5-fluoro-1- <i>N</i> -hexylcarbamoyl	110–111	5112
Uracil/5-fluoro-1- β -hydroxyethyl	159–160	4889
Uracil/5-fluoro-1-isobutoxycarbonyl	130–132	6515
Uracil/5-fluoro-1- <i>N</i> -isopropylcarbamoyl	145	5112
Uracil/5-fluoro-3-isopropyl-6-trifluoromethyl	150–153	5589
Uracil/5-fluoro-1-methoxycarbonylmethyl	185–186	5081
Uracil/5-fluoro-1-methoxymethyl	132–134	6145
Uracil/5-fluoro-1-methyl	236 (?) or 263–264	E, 4889, 5575

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/5-fluoro-3-methyl	190–191	E, 4889
Uracil/5-fluoro-1- <i>N</i> -methylcarbamoyl	170	5112
Uracil/5-fluoro-1-methylsulfonyl	223–224	5082
Uracil/5-fluoro-1-phenoxy carbonyl	177–181	6515
Uracil/5-fluoro-1-phenyl	170–172	5082
Uracil/5-fluoro-1- <i>N</i> -phenylcarbamoyl	280	5112
Uracil/5-fluoro-1-phenylsulfonyl	256–257	5082
Uracil/5-fluoro-1-propionyl	124–125	5082
Uracil/5-fluoro-1- α -propoxyethyl	104–106	6145
Uracil/5-fluoro-1-propoxymethyl	72–74	6145
Uracil/5-fluoro-1- <i>N</i> -propylcarbamoyl	145	5112
Uracil/5-fluoro-1-prop-2'-ynyl	150–151	4889
Uracil/5-fluoro-1-vinyl	197–199	4889
Uracil/5-fluoro-1- <i>N</i> -vinylcarbamoyl	150–160 (!)	5112
Uracil/5-formamido-6-isopropylamino-3-methyl	235	4627
Uracil/1-formylmethyl	semicarbazone: 225	E, 5288, 5926
Uracil/5-formyl-1-methyl	227–229	5575
Uracil/1-formylmethyl-5-methyl	300	4749, 5288
Uracil/1-formylmethyl-5-nitro	236–237	5926, 6236
Uracil/5-formyl-3-methyl-6-phenylthio	207	6112
Uracil/5-formyl-3-phenyl-6-phenylthio	127	6112
Uracil/3-hexyl-6-trifluoromethyl	143–144	5589
Uracil/5-hydrazino-1-methyl	<i>anti</i> : 232; <i>syn</i> : 207	6103
Uracil/6-hydrazino-3-propyl	242–243	6014
Uracil/6-hydroxyamino-1-isobutyl	203–205	5042
Uracil/6-hydroxyamino-1-methyl	248–250	5042
Uracil/6-hydroxyamino-3-methyl	190 or 203–206	4952, 5042
Uracil/1- δ -hydroxybutyl	²⁰ 1,5642	4828
Uracil/3- δ -hydroxybutyl-6-methyl	142–143	6266
Uracil/1- β -hydroxyethyl	136–138	E, 4871, 5495, 5818

Uracil/3-β-hydroxyethyl	179–181	E, 4871
Uracil/1-β-hydroxyethyl-5-methyl	205–207	5818
Uracil/3-β-hydroxyethyl-6-methyl	219–221	6068
Uracil/1-3'-hydroxy-4'-hydroxymethylcyclopentyl-5-methyl	195–196	E, 5236
Uracil/5-hydroxy-6-hydroxymethyl-1-methyl	cis: 147–148	5415
Uracil/5-3-(hydroxymethyl)cyclopentyl-1-methyl	239–242	5431
Uracil/5-hydroxymethyl-1-methyl	170–171	5308, 5575
Uracil/6-hydroxymethyl-3-methyl	225–226	5308, 6239
Uracil/6-hydroxymethyl-1-methyl	–	5175
Uracil/5-hydroxy-1-methyl-6-phenylazo	167–169	5060
Uracil/5-hydroxymethyl-1-prop-1'-enyl	162–163	4493
Uracil/3-β-hydroxypropyl-6-methyl	156–157	6068
Uracil/3-γ-hydroxypropyl-6-methyl	201–203	6266
Uracil/3-β-iodoethyl-6-methyl	185–186	6218
Uracil/5-iodo-1-β-methoxycarbonylethyl	289–291	4877
Uracil/6-iodo-3-methyl	94–95	4650
Uracil/1-isobutyl	230	5727
Uracil/3-isobutyl-6-methylthio	131–134	4806
Uracil/1-isopropyl	126–127	5648, 5727
Uracil/3-isopropyl	260–263	5648
Uracil/6-isopropylamino-3-methyl-5-nitro	134–135	4627
Uracil/3-isopropyl-5-methyl	210	6292
Uracil/3-isopropyl-6-methylthio	125–128	4806
Uracil/3-isopropyl-6-trichloromethyl	115–118	5588
Uracil/1-isopropyl-6-trifluoromethyl	139–142	5589
Uracil/3-isopropyl-6-trifluoromethyl	197–198	5589, 5933
Uracil/3-β-mercaptopethyl	201–203	5395
Uracil/1-β-mercaptopethyl-5-phenyl	167–168	6241
Uracil/3-β-mercaptopethyl-5-phenyl	225	6241
Uracil/3-β-mercaptopethyl-6-phenyl	203–210	6241
Uracil/6-methoxycarbonyl-3-methyl	256–260	H, 5414
Uracil/5-β-methoxycarbonylvinyl-1-methyl	230 (?) or 235–239	5427
Uracil/6-methoxy-1-methyl	225 (?)	5321, 5322
Uracil/6-methoxy-3-methyl		5322

TABLE LVIII (continued)

Pyrimidine	Melting Point, etc.	References
Uracil/5-methoxymethyl-1-methyl	143 or 146–147	5308, 6239
Uracil/5-methoxymethyl-3-methyl	144–146	5308, 6239
Uracil/6-methoxy-1-phenyl	262	4742
Uracil/1-methyl	224 to 237	H, E, 4858, 5019, 5204, 5292, 5490, 5513, 5575, 5630, 5648, 6048, 6132
Uracil/3-methyl	177 to 184	H, E, 3770, 4853, 5490, 5754, 5513, 5648, 6070
Uracil/6- α -methylthydrazino-3-propyl	119–120	6014
Uracil/3-methyl-6-methylamino-5-nitroso	294	E, 6539
Uracil/3-methyl-6- α -methylhydrazino-5-nitro	199–200	E, 4992
Uracil/1-methyl-5-nitro	264–265	H, E, 5516
Uracil/3-methyl-5-nitro	266–267	H, E, 5412
Uracil/3-methyl-5-nitroso-6-propylamino	242	5002, 6539
Uracil/1-methyl-5-phenyl	216–218	5861
Uracil/5-methyl-1-phenyl	199	E, 5236
Uracil/6-methyl-1-phenyl	273 to 283	E, 4925, 4930, 6194
Uracil/6-methyl-3-phenyl	255	H, E, 4930
Uracil/1-methyl-5-phenylthio	<i>syn</i> : 207; <i>anti</i> : 231	6103
Uracil/3-methyl-6-phenylthio	222	6112
Uracil/1-methyl-6-propyl	192–193	5532
Uracil/5-methyl-1-propyl	134–137	E, 5629, 5646
Uracil/6-methyl-1-propyl	170–172	H, E, 5648
Uracil/6-methyl-3-propyl	185 or 190	H, E, 5648, 5754
Uracil/3-methyl-6-propylamino	243	5002, 5656
Uracil/1-methylthiomethyl-6-trifluoromethyl	120–121	5589
Uracil/6-methylthio-3-phenyl	240–242	4806
Uracil/6-methylthio-3-propyl	171	4806

Uracil/1-methyl-5-trifluoromethyl	244-248	4552, 5575
Uracil/3-methyl-6-trifluoromethyl	236-238	5589, 5933
Uracil/5-methyl-1-vinyl	205-207	5818
Uracil/1-phenyl	251	H, E, 4920
Uracil/3-phenyl	242 or 253	H, E, 4920, 5754
Uracil/3-phenyl-6-phenylthio	223	6112
Uracil/3-phenyl-6-trifluoromethyl	235-236	5589, 5933
Uracil/1-propyl	119 to 123	5646, 5648, 5727
Uracil/3-propyl	157-158	5591, 5648
Uracil/3-propyl-6-trifluoromethyl	173-174	5589, 5933
Uracil/1,5,6-trimethyl	258 or 261-262	H, 4726, 5957
Uracil/3,5,6-trimethyl	227-228	H, E, 4726
Uracil/1-vinyl	180 to 189	5495, 5567, 5818
[Pseudo] uracil/2-anilino-1-phenyl	-	6243
[Pseudo] uracil/5-benzyl-1,3-diphenyl (betaine)	241	4354
[Pseudo] uracil/5-benzyl-2-methyl-1,2-diphenyl (betaine)	284	4354
[Pseudo] uracil/1-benzyl-2,5-dimethyl	220	4353
[Pseudo] uracil/1-benzyl-2-methyl	184-186	4337
[Pseudo] uracil/1-benzyl-5-methyl-2-phenyl	174-175	4353
[Pseudo] uracil/1-benzyl-2-phenyl	176	4353
[Pseudo] uracil/5-benzyl-1,2,3-triphenyl (betaine)	268	4354
[Pseudo] uracil/1,5-dimethyl	307-310	E, 3768
[Pseudo] uracil/5-isopropyl-1,2,3-triphenyl (betaine)	287	4354
[Pseudo] uracil/1-methyl	151-152	E, 6242
[Pseudo] uracil/1-methyl-5-nitro	265-269	5491
[Pseudo] uracil/2-methyl-1,3,5-triphenyl (betaine)	276	4354
[Pseudo] uracil/1,2,3,5-tetraphenyl (betaine)	293	4354
5-Vinyl	86/45	4575
2-Vinylthio	62-63/1	6383

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Index

This index covers the text and all included tables except Table XVI (pK_a values), Tables XIXf-h (^{13}C , ^{15}N , and ^{14}N nmr data), and Table LVIII (list of simple pyrimidines), all of which are alphabetical and hence self-indexing.

The page number(s) immediately following each primary entry refer to syntheses or general information. A number in parentheses indicates that, although the subject is treated on that page, the actual name of the primary entry appears there only in part, as a synonym, or even simply by inference. The letter *f* after a page number indicates that the subject is mentioned more than once on that and/or on the following page(s).

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