THE PYRIMIDINES

This is the sixteenth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*

THE PYRIMIDINES

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The Australian National University
Canberra

WITH AN ESSAY BY

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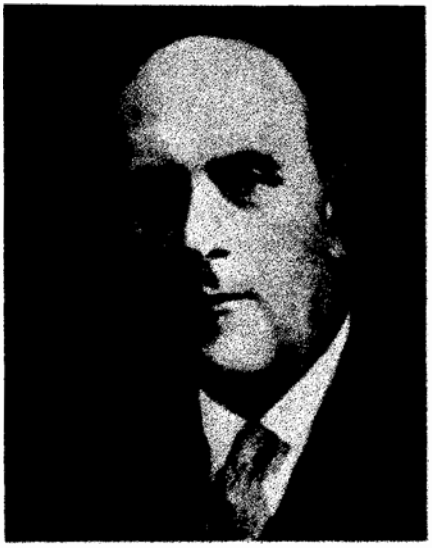
To the Memory of

TREAT BALDWIN JOHNSON



Treat B. Johnson

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.

ARNOLD WEISSBERGER

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Preface

This book is intended as a critical review of pyrimidine chemistry with emphasis on practical rather than theoretical aspects. The literature from the earliest times to 1960 is used to furnish examples illustrating syntheses, physical properties, and reactions, but no attempt is made to include all relevant data. The tables interspersed with the text serve to multiply and diversify these examples, but are likewise not intended as complete catalogues. In general, if a simple example suffices to make a point, examples involving more highly substituted pyrimidines are omitted. The more biological aspects of pyrimidine chemistry, such as the nucleic acids or the structural requirements for activity in barbiturates, are treated quite briefly, in particular as adequate reviews by workers in such fields exist.

The tables grouped in the Appendix give ready access to the literature and melting points of known simple pyrimidines. All such compounds described up to the end of 1957 are included, and they are supplemented by a selection of important or interesting members described thereafter until mid-1960.

The world-wide appeal of pyrimidine chemistry may be judged by the following approximate analysis of the origins of the twenty two hundred references used in the book:

United States of America	36.5%
Germany (East and West)	22.7%
British Commonwealth	19.4%
Japan	8.0%
France and Switzerland	3.0%
Italy and Spain	2.6%
Russia	2.2%
Netherlands and Belgium	1.5%
Eastern Europe	1.3%
China	1.3%
Austria	1.1%
Scandinavia and Others	0.4%

It will be realised that the present-day output of pyrimidine papers is very different to the above, which covers the last 140 years. The United States remains the centre of gravity, but the output of Japan, China, and Eastern Europe has risen considerably and mainly at the expense of Germany.

Many kind people have helped me enormously during the years of writing. My friend and former colleague, Dr. S. F. Mason, wrote a learned essay on pyrimidine spectra for Chapter XIII, a task which would have been quite beyond me. Professor Adrien Albert carefully read the entire text, and made numerous helpful suggestions from his wide knowledge and experience in heterocyclic work. Dr. J. P. English and Dr. J. H. Clark of American Cyanamid Company, loaned me a fine card index covering the earlier pyrimidine literature. Dr. S. Matsuura helped me with Japanese papers. Dr. J. F. W. McOmie sent me much unpublished material, and Dr. H. Mautner, Dr. H. B. Vickery, Dr. J. Staněk, Dr. D. I. Magrath, Dr. R. F. Evans, Dr. E. Spinner, and Dr. N. W. Jacobsen helped in other ways. The National Academy of Sciences (Dr. H. L. Dryden) kindly gave me Johnson's photograph. Mr. J. Harper, Mr. B. T. England, and Mrs. D. McLeod assisted nobly with the references and in other ways. Miss P. L. Baetons typed most of the manuscript and among the others who helped in various ways are Miss M. Bell, Mrs. H. Edmonston, who drew the curves, Mrs. S. M. Schenk, Mr. H. Satrapa, Mr. F. V. Robinson, Mrs. E. M. Lee, and Miss S. Green. Professor F. Bergel, F. R. S., generously provided facilities for me at the Chester Beatty Institute, London, at the proof stage. To these, to the unnamed others, and in particular to my wife for her help and remarkable patience, I offer my gratitude and thanks.

The Australian National University, Canberra D. J. Brown

Contents

Chapter I. Introduction to the Pyrimidines 1
1. History 1
2. Nomenclature 3
3. The Unique Basis of Pyrimidine Chemistry 5
   A. The "Active" 2-, 4-, and 6-Positions 7
   B. The "Aromatic" 5-Position 8
   C. The Effect of Electron-releasing Groups 8
   D. The Effect of Electron-withdrawing Groups 8
   E. Tautomeric Groups 9
4. General Summary of Pyrimidine Chemistry 9
   A. Electrophilic Substitution 10
      (1) Nitration and Nitrosation 10
      (2) Diazo Coupling 11
      (3) Halogenation 11
      (4) Sulphonation 11
      (5) Attack by Chloroform or Chloral 11
      (6) Other Electrophilic Attacks 11
   B. Direct Nucleophilic Substitution 12
   C. Nucleophilic Metatheses 12
      (1) Replacement of Halogens 13
         (a) By Amino and Substituted-amino Groups 13
         (b) By Methoxy and Similar Groups 13
         (c) By Hydroxy Groups 14
         (d) By Methylthio and Related Groups 14
         (e) By Mercapto Groups 14
         (f) By Sulpho and Thiocyanato Groups 15
      (2) Replacement of Methoxy, Methylthio, and Methylsulphonyl Groups 15
   D. Other Metatheses 16
      (1) Hydroxy- to Chloro-pyrimidines 16
      (2) Hydroxy- to Mercapto-pyrimidines 16
      (3) Mercapto- to Hydroxy-pyrimidines 17
      (4) Mercapto- to Amino-pyrimidines 17
      (5) Amino- to Hydroxy-pyrimidines 17
      (6) Amino- to Chloro-pyrimidines 18
      (7) Replacements of Quaternary Amino Groups 18

E. Addition Reactions 18
- (1) Quaternization 18
- (2) Formation of N-Oxides 19
- (3) Addition of Hypobromous Acid 19
- (4) Addition of Water 20
- (5) Addition of Grignard Reagents and Lithium Alkyls 20

F. Oxidative Reactions 20
G. Reductive Reactions 21
- (1) Nuclear Reduction 21
- (2) Reductive Removal of Groups 22
- (3) Reductive Modification of Groups 23

H. The Modification of Substituents 24
- (1) Amino Groups 24
- (2) Hydroxy Groups 25
- (3) Mercapto Groups 25
- (4) Methyl Groups 26

I. A Free Radical Reaction 26

5. Physical Properties of Pyrimidines 26
   - A. Electronic Structures 27
   - B. Ionization Constants 27
   - C. Spectra 28
   - D. Dipole Moments 28
   - E. Polarography 28
   - F. Solubility and Melting Point 29

Chapter II. The Principal Synthetic Method 31
1. General Scope 31
2. Use of β-Dialdehydes 32
3. Use of β-Aldehydo Ketones 34
4. Use of β-Diketones 36
5. Use of β-Aldehydo Esters 38
   - A. Aldehydo Esters with Thioureas 38
   - B. The Davidson—Baudisch Synthesis 38
   - C. The Use of α-Ethoxymethylene Esters 39
6. Use of β-Keto Esters 48
   - A. Keto Esters with Thioureas 48
   - B. Keto Esters with Amidines 49
   - C. Keto Esters with Guanidines 49
   - D. Keto Esters with Urea and Derivatives 50
7. Use of β-Diesters (Malonic Esters) 51
   - A. Malonic Esters and Amidines 52
   - B. Malonic Esters with Urea and its Alkyl Derivatives 52
   - C. Malonic Esters with Thiourea and Derivatives 54
   - D. Malonic Esters with Guanidine and its Alkyl Derivatives 55
8. Use of β-Aldehydo Nitriles 59
   - A. Aldehydo Nitriles with Ureas 59
   - B. Aldehydo Nitriles with Thioureas 60

C. Aldehydo Nitriles with Amidines 61
D. The Whitehead Synthesis of Cytosine Derivatives 62
E. Aldehydo Nitriles with Guanidine 64
9. Use of β-Keto Nitriles 65
10. Use of β-Ester Nitriles 67
A. Ester Nitriles with Amidines 67
B. Ester Nitriles with Urea and Alkyl Ureas 68
C. Ester Nitriles with Thioureas 70
D. Ester Nitriles with Guanidines 71
11. Use of β-Dinitriles (Malononitriles) 72

Chapter III. Other Methods of Primary Synthesis 82
1. General Remarks 82
2. Syntheses Involving Preformed Amino-methylene Groups 82
A. Aminomethylene Derivatives with Isocyanates 82
B. Aminomethylene Derivatives with Imino-ethers or Imidoyl Chlorides 84
C. Aminomethylene Derivatives with Thioamides 85
D. Use of Acylated Aminomethylene Derivatives 85
E. The Shaw Synthesis from Aminomethyleneacylurethanes 87
3. Syntheses Involving an Aminomethylene Group Formed *In Situ* 90
A. β-Dinitriles or β-Ester Nitriles with Amidines 90
B. Formamide with Compounds Containing an Active Methylene Group 91
C. Formamide with β-Dicarbonyl and Related Compounds 92
D. The Frankland and Kolbe Synthesis from Nitriles and Alkali Metal 93
4. Syntheses from Malondiamides and Malondiamidine 97
A. Malondiamides with Esters: The Remfry—Hull Synthesis 97
B. Malondiamides with Amides 98
C. Malondiamides with Oxalyl Chloride and Carbonic Acid Derivatives 99
D. The Use of Malondiamidine 100
5. Other Syntheses of Pyrimidines 101
A. Ethoxymethyleneacetic Acid to Uracil Derivatives 101
B. Maleic Diamide to Uracil 102
C. The Alkylamidine–Acetic Anhydride Synthesis 102
D. Amidines with αβ-Unsaturated Ketones 102
E. Synthesis of Pyrimidines from Other Ring Systems 103
(1) Pyrimidines from Hydantoins 103
(2) Pyrimidines from Iso-oxazoles and Thiazines 104
(3) Pyrimidines from Hydroxyiminopyrroles 105
(4) Pyrimidines from Quinazolines and Purines 105
(5) Pyrimidines from Pteridines 106
6. Formation of Pyrimidine Ring in Fused Heterocycles 107
A. Quinazolines from Benzene Derivatives 107
B. Purines from Glyoxalines 108

C. Thiazolo[5:4-d]pyrimidines from Thiazoles 108
D. Pteridines from Pyrazines 108
E. Pyridopyrimidines from Pyridines 109
F. Pyrazolopyrimidines from Pyrazoles 110

Chapter IV. Pyrimidine and Its C-Alkyl and C-Aryl Derivatives 116
1. Pyrimidine (Unsubstituted) 116
  A. Preparation of Pyrimidine 116
  B. Properties of Pyrimidine 117
  C. Reactions of Pyrimidine 118
2. *C*-Alkyl- and *C*-Aryl-pyrimidines 119
  A. Preparation of Alkylpyrimidines 119
    (1) Direct Syntheses of Alkylpyrimidines 119
    (2) Alkylpyrimidines from Alkylchloropyrimidines 120
    (3) Alkylpyrimidines from their Carboxy, Mercapto and Other Derivatives 120
    (4) Interconversion of Alkyl Groups in Pyrimidines 122
    (5) Direct Introduction of Alkyl Groups 123
    (6) Ethynylpyrimidines 124
  B. Properties of Alkylpyrimidines 124
  C. Reactions of Alkyl- and Aryl-pyrimidines 124
    (1) Methyl- to Styryl-pyrimidines 125
    (2) Chloral with Methylpyrimidines 126
    (3) Permanganate Oxidation of Alkyl- to Carboxy-pyrimidines: Removal of Alkyl Groups 126
    (4) Other Oxidations of Alkylpyrimidines; *N*-Oxides 128
    (5) Halogenation of Alkylpyrimidines 130
    (6) Claisen Reactions of Methylpyrimidines 131
    (7) Mannich Reactions of Methylpyrimidines 132
    (8) Other Reactions of Alkyl- and Aryl-pyrimidines 134

Chapter V. Nitro-, Nitroso-, and Arylazo-pyrimidines 138
1. The Nitropyrimidines 138
  A. Preparation of Nitropyrimidines 138
    (1) Nitropyrimidines by Direct Synthesis 139
    (2) Nitropyrimidines by Nitration 139
    (3) Nitropyrimidines by Indirect Syntheses 142
  B. Reactions of Nitropyrimidines: Reduction 143
2. Nitrosopyrimidines 146
  A. Preparation of Nitrosopyrimidines 147
    (1) Nitrosopyrimidines by Nitrosation 148
    (2) Nitrosopyrimidines by Direct Synthesis 149
  B. Reactions of Nitrosopyrimidines 149
    (1) Reduction of Nitrosopyrimidines 149
    (2) Other Reactions of Nitrosopyrimidines 151
  C. 4-Nitrosopyrimidines 151
3. The Arylazopyrimidines 152

- A. Preparation of Arylazopyrimidines 152
  - (1) Direct Synthesis of 5-Arylazopyrimidines 152
  - (2) Arylazopyrimidines by Coupling 153
  - (3) Other Preparations of Arylazopyrimidines 155
- B. The Reduction of Arylazopyrimidines 156

Chapter VI. Halogenopyrimidines 162

- 1. The Preparation of 2-, 4-, and 6-Halogenopyrimidines 162
  - A. Phosphoryl Chloride on 2-, 4-, and 6-Hydroxypyrimidines 162
    - (1) Simple Cases 162
    - (2) In the Presence of Nitro Groups 163
    - (3) In the Presence of Amino Groups 163
    - (4) In the Presence of Other Groups 164
  - B. The Use of Phosphorus Pentachloride to Produce Chloropyrimidines 165
  - C. Other Ways of Preparing 2-, 4-, and 6-Chloropyrimidines 166
  - D. The Preparation of 2-, 4-, and 6-Bromopyrimidines 167
  - E. The Preparation of 2-, 4-, and 6-Iodopyrimidines 168
- 2. The Preparation of 5-Halogenopyrimidines 168
  - A. 5-Halogenopyrimidines by Direct Halogenation 169
    - (1) 5-Halogenation of Alkylpyrimidines 169
    - (2) 5-Halogenation of Amino- or Hydroxy-pyrimidines 169
    - (3) 5-Halogenation of Aminohydroxypyrimidines 170
    - (4) 5-Halogenation of Mercapto- or Alkylthio-pyrimidines 170
    - (5) 5-Halogenation of Miscellaneous Pyrimidines 171
    - (6) 5,5-Dihalogenation of Pyrimidines 172
      - (a) Barbituric Acid Derivatives 172
      - (b) Uracil, Cytosine, and Derivatives 172
  - B. 5-Halogenopyrimidines by Direct Synthesis 174
  - C. Other Methods of Preparing 5-Halogenopyrimidines 175
- 3. The Preparation of Extranuclear Halogenopyrimidines 176
  - A. By Direct Halogenation 176
  - B. From the Corresponding Hydroxyalkylpyrimidine 178
  - C. From the Corresponding Alkyloxyalkylpyrimidine 179
  - D. By Direct Synthesis 179
  - E. By Other Means 180
- 4. Properties of Halogenopyrimidines 181
- 5. Reactions of 2-, 4-, and 6-Halogenopyrimidines 183
  - A. Removal of 2-, 4-, and 6-Halogens 183
    - (1) In the Presence of Only Alkyl Groups 183
    - (2) In the Presence of Amino Groups 184
    - (3) In the Presence of Other Groups 185
    - (4) Indirect Removal of 2-, 4-, and 6-Chloro Substituents 187
  - B. Replacement of 2-, 4-, and 6-Halogens by Amino Groups 187
    - (1) Amination of Halogeno- and Alkyl-halogenopyrimidines 188
      - (a) With One Active Halogen 188
      - (b) With Two or More Active Halogens 188

- (2) Amination of Halogenonitropyrimidines ... 193
  - (a) Aminations of Monochloronitro Derivatives ... 193
  - (b) Aminations of 2,4-Dichloronitro Derivatives ... 193
  - (c) Aminations of 4,6-Dichloronitro Derivatives ... 195
  - (d) Aminations of Trichloro-5-nitropyrimidine ... 196
- (3) Amination of 5-Aminochloropyrimidines ... 196
- (4) Amination of Chloro-(hydroxy-, alkoxy-, or oxo-)pyrimidines ... 197
- (5) Amination of Chloro-alkylthiopyrimidines ... 198
- (6) Amination of Chloropyrimidines Substituted by Other Groups ... 199

C. Replacement of 2-, 4-, and 6-Chloro by Hydrazino, Hydroxyamino, Azido, and Related Groups ... 199
D. Replacement of 2-, 4-, and 6-Halogens by Alkoxy Groups ... 201
E. Replacement of 2-, 4-, and 6-Halogens by Hydroxy Groups ... 203
F. Replacement of 2-, 4-, and 6-Chloro by Alkylthio Groups ... 205
G. Replacement of 2-, 4-, and 6-Halogens by Mercapto Groups ... 205
H. Replacement of 2-, 4-, and 6-Chloro by Sulpho, Thiocyanato, Isothiocyanato, and Isocyanato Groups ... 207
I. Replacement of 2-, 4-, or 6-Chloro by Other Groups ... 208

6. Reactions of 5-Halogenopyrimidines ... 210
   A. Amination of 5-Bromopyrimidine Derivatives ... 210
   B. Other Reactions of 5-Halogenopyrimidine Derivatives ... 211
   C. Reactions of 5,5-Dihalogeno and Related Pyrimidines ... 213
7. Reactions of Extranuclear Halogenopyrimidines ... 214
   A. Replacement by an Alkoxy, Hydroxy, or Acetoxy Group ... 214
   B. Replacement by Other Groups ... 215

Chapter VII. Hydroxy- and Alkoxy-pyrimidines ... 227

1. Preparation of 2-, 4-, and 6-Hydroxypyrimidines ... 227
   A. By the Principal Synthesis ... 227
   B. By Other Primary Syntheses ... 228
   C. By Hydrolysis of Halogenopyrimidines ... 228
   D. From Aminopyrimidines ... 229
      (1) Simple Examples ... 229
      (2) In the Presence of Other Groups ... 231
   E. From Alkoxypyrimidines ... 232
   F. From Mercaptopyrimidines and Related Derivatives ... 233
      (1) By *S*-Alkylation and Hydrolysis of the Alkylthiopyrimidine ... 233
      (2) By Oxidation to Sulphinic or Sulphonic Acid and Hydrolysis ... 234
      (3) By *S*-Alkylation, Oxidation to Sulphone, and Hydrolysis ... 236
   G. By Reductive Cleavage of Benzyloxypyrimidines ... 237
2. Preparation of 5-Hydroxypyrimidines ... 237
   A. Miscellaneous Useful Methods ... 237

- B. Through Primary Primary Synthesis of a 5-"Protected"-hydroxypyrimidine 238
- C. By Persulphate Oxidation 241

3. Preparation of Extranuclear Hydroxypyrimidines 241
   - A. By Direct Synthesis 242
   - B. From Amino Derivatives 242
   - C. From Halogeno Derivatives 243
   - D. By Reduction of Esters 243
   - E. By the Action of Formaldehyde 243
   - F. From Pyrimidine Aldehydes 244
   - G. By Other Means 244
4. Preparation of Alkoxy- and Aryloxy-pyrimidines 245
   - A. By the Principal Synthesis 245
   - B. From Halogenopyrimidines 246
   - C. By Other Means 247
5. Properties and Structure of Hydroxy- and Alkoxy-pyrimidines .. 249
6. Reactions of Hydroxypyrimidines 250
   - A. Conversion into Halogenopyrimidines 250
   - B. Conversion into Mercaptopyrimidines 251
   - C. Other Reactions of Hydroxypyrimidines 252
7. Reactions of Alkoxy- and Aryloxy-pyrimidines 254
   - A. Hydrolysis to Hydroxypyrimidines 254
   - B. Conversion into Halogeno Derivatives 254
   - C. Amination of Alkoxypyrimidines 255
   - D. Rearrangement of Alkoxypyrimidines 256
8. Some Naturally Occurring Hydroxypyrimidines 256
   - A. Uracil; 2,4-Dihydroxypyrimidine 256
   - B. Thymine; 2,4-Dihydroxy-5-methylpyrimidine 258
   - C. Divicine; 2,4-Diamino-5,6-dihydroxypyrimidine 259
9. The Alloxan Group of Pyrimidines 260
   - A. Alloxan 260
   - B. Alloxantin 262
   - C. Dialuric Acid and Isodialuric Acid 262
   - D. Murexide and Purpuric Acid 263

Chapter VIII. Sulphur-containing Pyrimidines 272

1. The Mercaptopyrimidines 272
   - A. Preparation of 2-, 4-, and 6-Mercaptopyrimidines 272
     - (1) By the Principal Synthesis 272
     - (2) By Other Primary Syntheses 273
     - (3) From Chloropyrimidines 273
     - (4) From Hydroxypyrimidines 274
     - (5) From Alkylthiopyrimidines 274
     - (6) From Thiocyanatopyrimidines 275
     - (7) From Aminopyrimidines 275
     - (8) By Direct Introduction 276
   - B. Preparation of 5-mercaptopyrimidines 276

C. Preparation of Extranuclear Mercaptopyrimidines 277
D. Reactions of 2-, 4-, and 6-Mercaptopyrimidines 277
(1) Removal of Mercapto Groups 277
(2) Alkylation of Mercaptopyrimidines 282
(3) Mercapto- to Hydroxy-pyrimidines 284
(4) Mercapto- to Chloro-pyrimidines 284
(5) Mercapto- to Amino-pyrimidines 284
(6) Acylation of Mercaptopyrimidines 286
(7) Oxidation of Mercaptopyrimidines 286
E. Reactions of 5- and Extranuclear-Mercaptopyrimidines 286
2. The Thioethers: Alkylthio- and Arylthio-pyrimidines 286
A. Preparation of 2-, 4-, and 6-Alkylthiopyrimidines 286
(1) By the Principal Synthesis 287
(2) By Alkylation of Mercaptopyrimidines 287
(3) From Chloropyrimidines 287
B. Preparation of 5-Alkylthiopyrimidines 288
C. Reactions of Alkylthiopyrimidines 288
(1) Reductive Removal of Alkylthio Groups 288
(2) Alkylthio- to Hydroxy-pyrimidines 289
(3) Amination of Alkylthiopyrimidines 289
(4) Alkylthio- to Mercapto-pyrimidines 291
(5) Oxidation of Alkylthiopyrimidines 291
3. Dipyrimidinyl Disulphides and Sulphides 291
A. Preparation 291
B. Reactions 294
4. Pyrimidine Sulphonic Acids and Related Compounds 295
A. Preparation 295
B. Reactions 297
5. Alkylsulphonylpyrimidines 298
A. Preparation 298
B. Reactions 300
6. Thiouracil and Homologues 300

Chapter IX. The Aminopyrimidines 306
1. Preparation of 2-, 4-, and 6-Aminopyrimidines 306
A. By the Principal Synthesis 306
B. By Other Primary Syntheses 307
C. By Direct Amination 308
D. From Chloropyrimidines 308
E. From Mercapto- and Alkylthio-pyrimidines 308
F. From Alkoxypyrimidines 309
G. From Thiocyanatopyrimidines 309
H. By Other Methods 310
I. Secondary and Tertiary Aminopyrimidines by Alkylation 311
2. Preparation of 5-Aminopyrimidines 313
A. By Primary Synthesis 313
B. By Reduction of 5-Nitro-, Nitroso-, or Arylazo-pyrimidines .. 314

- C. From 5-Halogenopyrimidines 314
- D. From 5-Carbamoylpyrimidines 314
- E. Secondary 5-Aminopyrimidines by Alkylation 315

3. Preparation of Extranuclear Aminopyrimidines 316
   - A. By Reduction of a Nitrile 316
   - B. From Amides and Hydrazides by Hofmann and Curtius Reactions 317
   - C. By the Mannich Reaction 318
   - D. By Primary Synthesis 318
   - E. By Other Routes 319
4. Properties of Aminopyrimidines 320
5. Reactions of Aminopyrimidines 321
   - A. Replacement of Amino by Hydroxy Groups 321
   - B. Replacement of Amino by Chloro Substituents 321
   - C. Formation of Anils (Schiff's Bases) 321
   - D. Acyl Derivatives of Aminopyrimidines 324
     - (1) Acetylation 324
     - (2) Formylation 325
     - (3) Benzoylation and Other Acylations 327
     - (4) Other Ways of Preparing Acylaminopyrimidines 328
     - (5) Deacylation of Acylaminopyrimidines 329
     - (6) Arylsulphonamidopyrimidines 329
   - E. Diazotization 331
   - F. Bicyclic Heterocycles from Aminopyrimidines 333
   - G. Other Reactions 335
6. Urethanes (Alkoxycarbonylaminopyrimidines) 336
7. Ureidopyrimidines 339
8. Other Substituted-amino-pyrimidines 341
   - A. Nitroamines 341
   - B. Cyanoamines 343
   - C. Sulphoamines 343
   - D. Chloroamines 343
   - E. Guanidinopyrimidines 344
   - F. Hydroxyamines 344
   - G. Trimethylpyrimidinylammonium Chlorides 345
9. Some Naturally Occurring Aminopyrimidines 345
   - A. Cytosine; 4-Amino-2-hydroxypyrimidine 346
   - B. 5-Methylcytosine 347
   - C. 5-Hydroxymethylcytosine 347

Chapter X. The N-Alkylated Pyrimidines and Pyrimidine-N-Oxides 356

1. The Oxopyrimidines 357
   - A. Preparation of Oxopyrimidines 357
     - (1) By the Principal Synthesis 357
     - (2) By Other Primary Syntheses 358
     - (3) By Alkylation of Hydroxypyrimidines 359
       - (a) Cases with One Hydroxy Group 359

- (b) Cases with Two Hydroxy Groups 360
- (c) Cases with Three Hydroxy Groups 362
- (d) In the Presence of Nitro Groups 363
- (e) In the Presence of Amino Groups 364
- (f) In the Presence of Alkylthio Groups 368
- (g) In the Presence of Other Groups 369
- (4) By Rearrangement of Alkoxypyrimidines 371
- (5) By Hydrolysis of Iminopyrimidines 373
- B. Properties and Reactions of Oxopyrimidines 375
- 2. The Iminopyrimidines 377
  - A. Preparation of Iminopyrimidines 377
  - B. Reactions of Iminopyrimidines 379
- 3. The *N*-Methylated Thiopyrimidines 381
- 4. The Pyrimidine-*N*-Oxides 382
  - A. Preparation of Pyrimidine-N-Oxides 382
  - B. Reactions of Pyrimidine-N-Oxides 383

Chapter XI. The Pyrimidine Carboxylic Acids and Related Derivatives .. 389
- 1. The Carboxypyrimidines 389
  - A. Preparation of Carboxypyrimidines 389
    - (1) By Primary Synthesis 389
    - (2) By Hydrolysis of Esters, Amides, and Nitriles 390
    - (3) By Oxidation of Methyl-, Styryl-, Formyl-, Hydroxymethyl-, and Acetyl-pyrimidines 391
    - (4) By Other Methods 392
  - B. Reactions of Carboxypyrimidines 393
    - (1) Decarboxylation 393
    - (2) Esterification 393
    - (3) Formation of Acid Chlorides 394
    - (4) Other Reactions 395
- 2. Alkoxycarbonylpyrimidines (Pyrimidine Esters) 395
  - A. Preparation of Esters 395
  - B. Reactions of Esters 396
- 3. Carbamoylpyrimidines (Amides) and Related Compounds (Hydrazides and Azides) 397
  - A. Preparation of Amides 397
    - (1) From Esters and Acid Chlorides 397
    - (2) By Primary Synthesis 398
    - (3) By Controlled Hydrolysis of Nitriles 398
    - (4) By Other Means 399
  - B. Reactions of Amides 400
  - C. Preparation and Reactions of Hydrazides and Azides 400
- 4. Pyrimidine Nitriles 401
  - A. Preparation of Cyanopyrimidines 401
    - (1) By Primary Synthesis 401
    - (2) By Dehydration of Amides 404
    - (3) By Other Means 404

B. Reactions of Cyanopyrimidines 405
5. Pyrimidine Aldehydes and Their Acetals 406
A. Preparation of Formylpyrimidines 406
(1) By the Principal Synthesis 406
(2) By Direct and Indirect *C*-Formylation 408
(3) From Cyanopyrimidines 410
(4) By Oxidative Processes 411
(5) By Other Means 412
B. Reactions of Formylpyrimidines 413
(1) Oxidation and Reduction 413
(2) Formation of the Usual Aldehyde Derivatives 413
(3) Other Reactions 414
6. Pyrimidine Ketones and Derivatives 415
A. Preparation of *C*-Acylpyrimidines 415
B. Reactions of *C*-Acylpyrimidines 417
7. The Isocyanato-, Thiocyanato-, and Isothiocyanato-pyrimidine Family 418
A. Isocyanatopyrimidines 418
B. Thiocyanatopyrimidines 419
C. Isothiocyanatopyrimidines 421
8. Orotic Acid: Biosynthesis of Pyrimidines 422

Chapter XII. The Reduced Pyrimidines 430
1. Preparation of Dihydropyrimidines 431
A. By a Modified Principal Synthesis 431
B. From an Aminopropane Derivative and an Isocyanate 434
C. From an Isocyanatopropane Derivative and an Amine 436
D. From an Aminopropane Derivative and *O*-Methylurea 438
E. Syntheses Involving Amide Intermediates 438
F. The Biginelli Reaction 440
G. Other Syntheses 442
H. By Reduction of Pyrimidines 442
2. Preparation of Tetrahydropyrimidines 445
A. From 1,3-Diaminopropane or Derivative 445
B. From Carbonyl Compounds and Ammonia or Amines 448
C. From 1,3-Dihalogenopropane Derivatives 449
D. By Reduction of Pyrimidines or Dihydropyrimidines 450
3. Preparation of Hexahydropyrimidines 452
4. Reactions of Reduced Pyrimidines 454
A. Reductions 454
B. Oxidations 455
C. Nitrosation and Nitration 455
D. *N*-Acylation 456
E. Halogenation 457
F. Metatheses of Mercapto and Hydroxy Derivatives 457
G. *N*-Alkylation 458
H. Other Reactions 459

Chapter XIII. The Ionization and Absorption Spectra of Pyrimidines.... 464
1. Ionization of Pyrimidines.................................. 464
   A. The pK_a of Pyrimidine 465
   B. The Acidic pK_a Values of Pyrimidines 466
   C. The Basic pK_a Values of Pyrimidines 468
   D. The pK_a Values of Amino-Hydroxy and Related Pyrimidines.. 470
2. The Absorption Spectra of the Pyrimidines (By S. F. Mason)...... 472
   A. Ultraviolet Spectra: Experimental Studies 472
   B. Ultraviolet Spectra: Theoretical Studies 485
   C. Infrared Spectra of Substituted Pyrimidines 494
   D. The Vibrations of the Pyrimidine Nucleus 495

Tables Integrated with the Text

TABLE I Trivial Names of Pyrimidines 6
TABLE II Additional Examples of the Use of Aldehydo Esters in the Principal Synthesis 40
TABLE III Additional Examples of the Use of Keto Esters in the Principal Synthesis 44
TABLE IV Additional Examples of the Use of Malonic Esters in the Principal Synthesis 56
TABLE V Typical Examples of the Whitehead Synthesis 64
TABLE VI Additional Examples of the Condensation of Aminomethylene Derivatives with Imino Ethers 86
TABLE VII Examples of Pyrimidine Synthesis from β-Dicarbonyl (or Equivalent) Compounds and Formamide 94
TABLE VIII Some Alkyl- and Aryl-pyrimidines Produced by Dehalogenation 121
TABLE IX Melting Points of Simple Chloropyrimidines 182
TABLE X Rate Constants of the Reaction of Chloropyrimidines with Piperidine and Morpholine 182
TABLE XI Some Dechlorinations of Amino-chloropyrimidines by Hydrogenation 186
TABLE XII Solubility in Water and Melting Point of Simple Hydroxypyrimidines 249
TABLE XIII Some Raney-nickel Desulphurizations 279
TABLE XIV Melting Points of Aminopyrimidines 320
TABLE XV Comparison of Melting Points of Simple 2-, 4-, and 6-Hydroxy, Oxo, and Alkoxy Derivatives 375
TABLE XVI The pK_a Values of Some Pyrimidines in Water 472
TABLE XVII Electronic Absorption Spectra of Neutral, Anionic, and Cationic Forms of Some Non-tautomeric Pyrimidines in Ethanol, Cyclohexane, and Aqueous Solution 491
TABLE XVIII Electronic Absorption Spectra of Neutral, Cationic, Anionic and Zwitterionic Forms of Some Tautomeric Pyrimidines and of their Methyl Derivatives of Fixed Structures in Ethanol, Cyclohexane and in Aqueous Solution 492
TABLE XIX Frequencies of the Bands Observed in the Infrared Absorption and Raman Emission Spectra of Pyrimidine, and their Assignment to the Active Vibrations of the Molecule 498

The Appendix

Systemic Tables of Simple Pyrimidines

Introduction 501
Pyrimidines Excluded from the Tables 501
Terms Used in Tables 502
TABLE XX Alkyl and Aryl Pyrimidines 503
TABLE XXI Aminopyrimidines 505
TABLE XXII Carboxypyrimidines 516
TABLE XXIII Halogenopyrimidines 518
TABLE XXIV Nitropyrimidines 521
TABLE XXV Oxypyrimidines without *C*- or *N*-Alkyl Groups 521
TABLE XXVI Oxypyrimidines with *C*-, but without *N*-, Alkyl Groups.... 522
TABLE XXVII Oxypyrimidines with *N*-Alkyl Groups 530
TABLE XXVIII Sulphonylpyrimidines 535
TABLE XXIX Thiopyrimidines 536
TABLE XXX Amino-Carboxypyrimidines 537
TABLE XXXI Amino-Halogenopyrimidines 539
TABLE XXXII Amino-Nitropyrimidines 545
TABLE XXXIII Amino-Oxypyrimidines without $N_{(1)}$-, or $N_{(3)}$-, Substituents 547
TABLE XXXIV Amino-Oxypyrimidines with $N_{(1)}$-, or $N_{(3)}$-, Alkyl Groups 561
TABLE XXXV Amino-Sulphonylpyrimidines 566
TABLE XXXVI Amino-Thiopyrimidines 567
TABLE XXXVII Amino-Oxypyrimidines with other Functional Groups 573
TABLE XXXVIII Amino-Thiopyrimidines with other Functional Groups 581
TABLE XXXIX Amino-Oxy-Thiopyrimidines 585
TABLE XL Aminopyrimidines with Two Minor Functional Groups.... 588
TABLE XLI Carboxy-Halogenopyrimidines 589
TABLE XLII Carboxy-Oxypyrimidines 590
TABLE XLIII Carboxy-Sulphonylpyrimidines 598
TABLE XLIV Carboxy-Thiopyrimidines 599
TABLE XLV Halogeno-Nitropyrimidines 600
TABLE XLVI Halogeno-Oxypyrimidines 600
TABLE XLVII Halogeno-Sulphonylpyrimidines 604
TABLE XLVIII Halogeno-Thiopyrimidines 605
TABLE XLIX Nitro-Oxypyrimidines 606
TABLE L Nitro-Sulphonylpyrimidines 608
TABLE LI Nitro-Thiopyrimidines 608

TABLE LII Oxy-Sulphonylpyrimidines 608
TABLE LIII Oxy-Thiopyrimidines 609
TABLE LIV Oxy-Thiopyrimidines with other Functional Groups 616
TABLE LV Oxypyrimidines with Two Minor Functional Groups 621
TABLE LVI Thiopyrimidines with Two Minor Functional Groups 623

General List of References 624

Index 677

CHAPTER I

Introduction to the Pyrimidines

1. History

In 1818 Gaspare Brugnatelli[1, 2] isolated the first pyrimidine derivative, alloxan, by oxidation of uric acid with nitric acid. A few years later his experiments were put on a sound basis and extended to other derivatives by Wöhler and Liebig in their outstanding paper: Untersuchungen über die Natur der Harnsäure.[3] In 1848 Frankland and Kolbe[4] carried out the first primary synthesis of a pyrimidine by the action of metallic potassium on propionitrile. It later proved[5] to be 4-amino-2,6-diethyl-5-methylpyrimidine (I). The next landmark in pyrimidine chemistry was the synthesis by Grimaux,[6–8] in 1878 of barbituric acid from malonic acid and urea. This was the first example of what has become the principal pyrimidine synthesis. But it was not until 1884 that Pinner[9] made his first pyrimidine derivative. The following year[10] he recognized pyrimidine as an hexagonal brother of benzene, pyridine, and triazine, and he named the new ring system with the words: "Die neue von der Grundsubstanz, $C_4H_4N_2$, sich herleitende Verbindungsklasse möchte ich als Pyrimidin bezeichnen". Three years later an attempt was made by Widmann[11] to systematize the nomenclature of nitrogen heterocycles, and "miazine" was suggested in place of pyrimidine. Although this name did enjoy a limited vogue, by 1905 von Meyer[12] was able to say, "Die von O. Widmann statt Pyrimidin vorgeschlagene Bezeichnung *Miazin* hat, so viele Vorzüge sie bietet, keinen Eingang gefunden". The parent compound (II) was first isolated by Gabriel and Colman[13] in 1899.

The beginnings of pyrimidine chemistry have been reviewed very appropriately by T. B. Johnson,[14]* who, during forty years of work in the pyrimidine field, nobly and almost alone bridged the gap between two great periods of pyrimidine history. The first of these embraced the classical contributions of Robert Behrend,[15] Siegmund Gabriel,[16, 17] Emil Fischer,[18] Wilhelm Traube[19] and Ernst von Meyer,[20] and was stimulated to some extent by the isolation of thymine, uracil, and cytosine from biological material, and by the advent of the barbiturates. The second period was even more biologically based. It arose from vitamin B_1 in the late thirties, and was amply nourished thereafter by resurgence of interest in the nucleic acid field, by the discovery of sulphadiazine, by the immensely useful anti-thyrotoxicotic activity of the alkyl thiouracils, and by the searches for more effective anti-malarials (*e.g.* "Daraprim"), oral diuretics (*e.g.* "Amisometradine"), and other drugs. Further, the new interest in folic acid and the simple pteridines as well as the renewed interest in purines, greatly stimulated research in the chemistry of their pyrimidine intermediates. To forecast the future trends would indeed be bold.

The recent discovery by Professor M. Calvin[22, 23] that the soluble fraction from a meteorite contained a nitrogeneous heterocycle, which from spectra might well be cytosine, is fascinating. The observation has already been confirmed in other meteorites,[24] and if the presence of cytosine (or other nucleic acid constituents) can be conclusively proven, the finding must rank as one of the most significant in history.

The best review of the older literature of pyrimidines (to 1920) is in the text-book of Meyer and Jacobson.[25] Similar types of review have been written by Johnson and Harn[26] (1933) and by Johnson[27] (1938). More concise reviews have appeared from Lythgoe[28] in 1949, from Kenner[29] in 1950, from Brown[30] and Wiley[31] in 1953, and from Bendich[32] in 1955. The fullest treatment to date has come from Kenner and Todd[33] in 1957, covering the literature to several years before publication. An excellent sixty-page review of pyrimidines has been written by Ramage and Landquist,[34] and the best idea of the place of pyrimidines in heterocyclic chemistry can be gained from Albert.[35]

* Treat Baldwin Johnson was born in Bethany, Connecticut, in 1875. In 1898 he published from Yale his first paper with Henry L. Wheeler from whom he acquired an interest in pyrimidines. He finally contributed about 180 papers on this subject alone, and an equal number on related topics. Despite the occasional error in his voluminous writings, this "kindly, simple-mannered man" exerted a profound influence on the course of pyrimidine chemistry.[21] The dedication of this book is a small tribute to a great chemist and teacher.

Other reviews of more specific aspects of pyrimidines (*e.g.* nucleic acids) are noted in the appropriate sections that follow.

2. Nomenclature

Pyrimidine is now generally written as (II) with the numbering shown, but the misleading (IIa) still persists in occasional publications,* perhaps because it is easier to type and print. Since pyrimidine is symmetrical about the line joining 2 to 5, the positions 4 and 6 are equivalent, as are also 1 and 3. Thus 2,4- and 2,6-dihydroxypyrimidine are one and the same compound (uracil). Even this simple fact has led to confusion as, for example, in the 1956 catalogue of a well-known British firm offering 2,4-dichloro- and 2,6-dichloro-pyrimidine at different prices.

More serious is the confusion which results from *N*-substitution in association with the traditional trivial names of pyrimidines. Thus cytosine, for example, is numbered in *Beilstein* and in most biochemical literature, as 6-amino-2-hydroxypyrimidine (III) (in line with purine numbering) but in *Chemical Abstracts* and some chemical journals as 4-amino-2-hydroxypyrimidine (IV). When cytosine is methylated it gives (V) which is then known as 1- or 3-methylcytosine according to the system being used.**

The obvious answer to this difficulty would be to call (V), 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine. This name, however, suffers from several disadvantages: (a) it is long; (b) it seems (wrongly) to indicate a reduced state of the nucleus; (c) by assigning a precise tautomeric form it excludes the possibility that (V) may ultimately be proved to exist at least partly as the tautomer (VI). The shorter name 1-(or 3-) methylcytosine is therefore in some ways preferable, but the long name is used in this book on the grounds of avoiding trivial names where possible (see below). Whenever trivial names are in fact used, it is clearly important to state, in each publication the system of numbering being used, and in consulting the literature to check the point from a structural formula in each paper. Failure to do this has led several authors to surprising and erroneous conclusions. In

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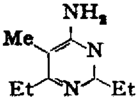
* For example in the *Journal of the American Chemical Society*, 1958, on p. 1665.

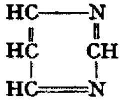
** The *Journal of the Chemical Society*, 1955, used one system on p. 214, the other on p. 855!

the present treatment, uracil, thio- and dithio-uracils are numbered as 2,4-disubstituted pyrimidines, and the numbering of most other trivial names has been avoided (see below).

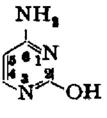


(I)

(II)



(IIa)



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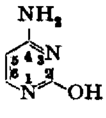

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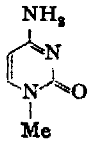
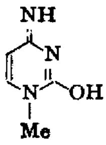


(V)

$\rightleftharpoons$

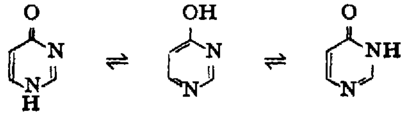


(VI)

A further difficulty arises in the nomenclature of pyrimidines carrying a potentially tautomeric substituent in the 2-, 4-, or 6-positions. Thus (VII) in the English language alone, could be (and is) called 4-hydroxypyrimidine, 4-pyrimidol, 4-pyrimidinol, 4-pyrimidone, 4-pyrimidinone, 4(1)-pyrimidone, 4(3)-pyrimidone, 1,4-dihydro-4-oxopyrimidine, 3,4-dihydro-4-oxopyrimidine, and other less likely names. This makes the use of the formula index a necessity when searching the literature for any such compound, especially if it is further complicated by other tautomeric substituents.

In this review, all such compounds are named as hydroxy, mercapto, or amino derivatives whatever the evidence for the predominant tautomeric form may indicate. Further, the general nomenclature of the International Union of Pure and Applied Chemistry is used,[36] and all substituents are written in alphabetical order as prefixes to the parent name. Thus the unknown compound (VIII) would be written as 2-carboxy-4-ethoxycarbonyl-6-formyl-5-sulphopyrimidine. Trivial names are avoided except where ambiguity of structure makes them necessary. For example since it is not known whether 3-methyluracil is predominantly (IX) or (IXa), it is called neither 1,6-dihydro-2-hydroxy-1-methyl-6-oxopyrimidine (IX) nor 1,2-dihydro-6-hydroxy-1-methyl-2-oxopyrimidine (IXa), but the trivial name 3-methyluracil; the other possibility, 1,2,3,4-tetrahydro-3-methyl-2,4-dioxopyrimidine (IXb), is precluded by the rule adopted above calling for hydroxy, mercapto, and amino groups to be written as such.

Similarly, the 2-thio analogue of (IX) would be called 3-methyl-2-thiouracil where "2-thiouracil" is used as a trivial name. On the other hand no such ambiguity arises (except on paper) in the case of the 2-amino analogue of (IX) because it is known on general experimental evidence (see Chapter XIII) that such a compound will almost surely assume the amino-oxo form (X) rather than the hydroxy-imino form. It would therefore be called 2-amino-1,6-dihydro-1-methyl-6-oxopyrimidine rather than 3-methylisocytosine. Similarly (V) would here be called 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine rather than 1-methylcytosine. In practice, only the trivial names indicated in Table I by a letter *a* have been unavoidably used in the nomenclature of this book.



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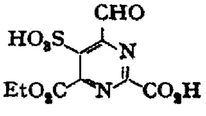

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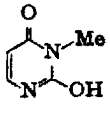

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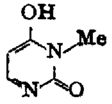
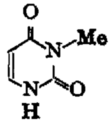
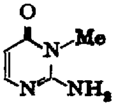


(IXa)



(IXb)



(X)

Regarding trivial names, it must be admitted that several, such as uracil, are so entrenched in the literature as to be necessarily accepted, and indeed as mentioned above they are often convenient. A few others, like deoxyuridine, have an obvious advantage over their full name, but most trivial names have now little point, and lead only to confusion. Thus, why do some authors call the universally understood 2,4-dihydroxy-5-hydroxymethylpyrimidine, "thyminyl alcohol"?

3. The Unique Basis of Pyrimidine Chemistry

In considering the specific reactions and properties of pyrimidine and of its derivatives, it is useful first to consider five simple principles of pyrimidine chemistry which together make it unique. It is surprising how often the most diverse phenomena fit logically into their context, and indeed how often predictions made with their help prove to be correct experimentally.

TABLE I. Trivial Names of Pyrimidines

Trivial Name	Systematic or better name
Acetonin	1,2,5,6-Tetrahydro-2,2,4,6,6-pentamethylpyrimidine
Alloxan[a]	Hexahydrotetraoxopyrimidine
Amicetin	An antibiotic[39]
2-Aminobarbituric acid[a]	2-Amino-4,6-dihydroxypyrimidine
5-(and 6-)Aminocytosine	4,5-(and 4,6)Diamino-2-hydroxypyrimidine
5-(and 6-)Aminouracil	5-(and 6-)Amino-2,4-dihydroxypyrimidine
Aneurin	Vitamin B_1
Barbituric Acid[a]	2,4,6-Trihydroxypyrimidine
Bromouracil	5-Bromo-2,4-dihydroxypyrimidine
Convicine	A glucoside of 4-amino-2,4,6-trihydroxypyrimidine[40]
Cyanmethine	See Kyanmethin
Cytidine	1-β-D-Ribofuranosidocytosine
Cytosine	4-Amino-2-hydroxypyrimidine
Deoxycytidine	1-β-2′-Deoxy-D-ribofuranosidocytosine
Deoxyuridine	1-β-2′-Deoxy-D-ribofuranosidouracil
Dialuric Acid	Tetrahydroxypyrimidine
Diaminocytosine	4,5,6-Triamino-2-hydroxypyrimidine
Diaminouracil	4,5-Diamino-2,6-dihydroxypyrimidine
Dilituric Acid	2,4,6-Trihydroxy-5-nitropyrimidine
Dithiouracil[a]	2,4-Dimercaptopyrimidine
Divicine	2,4-Diamino-5,6-dihydroxypyrimidine
Hydrouracil	4,5-Dihydro-2,6-dihydroxypyrimidine
Isobarbituric Acid	2,4,5-Trihydroxypyrimidine
Isocytosine	2-Amino-4-hydroxypyrimidine
Isodialuric Acid	4,5-Dihydro-2,4,6-trihydroxy-5-oxopyrimidine (?)
Isouracil	2,5-Dihydroxypyrimidine
Isouramil	4-Amino-2,5,6-trihydroxypyrimidine
Isovioluric Acid	2,4,5-Trihydroxy-6-nitrosopyrimidine
5-Ketobarbituric Acid	Hexahydrotetraoxopyrimidine
Kyanmethin	4-Amino-2,6-dimethylpyrimidine[b]
Methylcytosine	4-Amino-2-hydroxy-5-methylpyrimidine
5-Methyldeoxycytidine	1-β-2′-Deoxy-D-ribofuranisido-5-methylcytosine
Miazine	Pyrimidine
Nitrouracil	2,4-Dihydroxy-5-nitropyrimidine
Orotic Acid	4-Carboxy-2,6-dihydroxypyrimidine
Orotidine	A D-riboside of 4-carboxy-2,6-dihydroxypyrimidine[41]
Piperimidine	Hexahydropyrimidine
Pseudouric Acid	2,4,6-Trihydroxy-5-ureidopyrimidine
Spongo Thymidine	1-β-D-Arabofuranosidothymine[37]
Spongo Uridine	1-β-D-Arabofuranosidouracil[38]
Tartronyl Urea	Tetrahydroxypyrimidine
Thiamine	Vitamin B_1
2-Thiobarbituric Acid[a]	4,6-Dihydroxy-2-mercaptopyrimidine
Thiouramil	5-Amino-4,6-dihydroxy-2-mercaptopyrimidine
2-(and 4-)Thiouracil[a]	4-(and 2-)Hydroxy-2-(and 4-)mercaptopyrimidine
Thymidine	1-β-2′-Deoxy-D-ribofuranosidothymine

(Table continued)

TABLE I *(continued)*

Trivial Name	Systematic or better name
Thymine	2,4-Dihydroxy-5-methylpyrimidine
Thyminyl alcohol	2,4-Dihydroxy-5-hydroxymethylpyrimidine
Uracil[a]	2,4-Dihydroxypyrimidine
Uramil	5-Amino-2,4,6-trihydroxypyrimidine
Uridine	1-β-D-Ribofuranosidouracil
Vicine	2,4-Diamino-5-β-D-glucopyranosidoxy-6-hydroxypyrimidine
Violuric Acid	2,4,6-Trihydroxy-5-nitrosopyrimidine

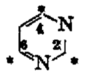
[a] Names used in the nomenclature of this book.

[b] The "Kyanalkine" are 4-amino-2,6-dialkyl-5-(alkyl less CH$_2$)-pyrimidines. Thus "Kyanisobutin" would be 4-amino-2,6-di-isobutyl-5-isopropylpyrimidine.[12]

A. The "Active" 2-, 4-, and 6-Positions

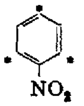
The 2-, 4-, and 6-positions, marked in pyrimidine (XI), are naturally electron-deficient by virtue of the powerful electron-withdrawing effect of the ring nitrogen atoms. In this, they resemble qualitatively the α-, and γ-positions in pyridine (XII) and to some extent the 2-, 4- and 6-positions of nitrobenzene (XIII) and 1,3-dinitrobenzene (XIV), in which the nitro groups are acting as the electron attractors. Because the nitrogen atoms of pyrimidine are *meta* to each other, their separate effects reinforce each other (as in 1,3-dinitrobenzene) and the resultant is greater in pyrimidine than in its isomers pyrazine and pyridazine, in which the nitrogen atoms exert electronic effects that partly antagonize one another.

The electron deficiency at the marked positions is reflected in the reactivity of substituent groups there. Thus for example a halogen atom at these points is easily attacked by nucleophilic reagents;



(XI)

(XII)



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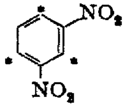


(XIV)

ammonia or amines replace it by an amino group, water (catalysed by acid or alkali) by a hydroxy group, sodium hydrogen sulphide by a mercapto group, sodium alkoxide by an alkoxy group, or sodium alkyl mercaptide by a thio-ether group. Moreover, carboxy groups at such positions are rather labile and methyl groups are reactive towards aromatic aldehydes to give styryl groups, and are easily oxidized.

B. The "Aromatic" 5-Position

The 5-position is not so electron-deficient as the 2-, 4- or 6-position, although it is made slightly so by the general inductive effect. It therefore resembles more the β-position of pyridine and is the nearest to a truly "aromatic" position in pyrimidine. Consequently a 5-halogen atom does not so easily react with ammonia or amines, nor is a 5-carboxy group so labile; ethers are very stable, and methyl groups rather unreactive. On the other hand electrophilic reagents attack (if at all) at this point, and under certain conditions (see below) nitration, nitrosation, halogenation, and coupling with diazonium salts easily take place here.

C. The Effect of Electron-releasing Groups

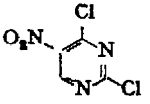
With the progressive introduction into any position of electron-releasing substituents such as hydroxy, amino, or mercapto groups, the π-electrons depleted by the electrophilic ring nitrogen atoms are restored, and the overall picture approximates more nearly to an aromatic ring. Thus the 5-position (if free) can readily be halogenated, nitrated, nitrosated, and coupled with diazonium salts; on the other hand, substituents in the 2-, 4-, and 6-positions become "deactivated" so that for example halogens are no longer so easily hydrolysed or replaced by amino groups.

D. The Effect of Electron-withdrawing Groups

Powerful electron-withdrawing groups have been introduced only in the 5-position of pyrimidine. A 5-nitro group naturally accentuates the electron deficiency of the other positions, and chloro groups for example become even more reactive towards nucleophilic attack. Thus 2,4-dichloro-5-nitropyrimidine (XV) reacts rapidly with ammonia at 0° C to give 4-amino-2-chloro-5-nitropyrimidine (XVI). The new electron-releasing amino group now opposes the electron-withdrawing effect of the nitro group, and replacement of the second chlorine becomes much slower and is best done above 100°, to give 2,4-diamino-5-nitropyrimidine.

E. Tautomeric Groups

When they stand in the 2-, 4-, or 6-position, the hydroxy, mercapto, and amino groups are tautomeric with oxo, thio, and imino respectively, the hydrogen being accommodated on a ring nitrogen. It follows that *N*- as well as *O*-alkylation is possible in such a substance as 2-hydroxypyrimidine (XVII). The tautomerism of such groups can also involve the 5-position as a receptor of a hydrogen atom; such a state is seen as a stable entity in 1,3,5,5-tetramethylbarbituric acid (XVIII). Experimental evidence of predominant structure in such tautomers as (XVII) will be discussed later, but it can be briefly said here that hydroxy groups strongly prefer the oxo form, mercapto groups the thio form, but amino groups normally exist as true —NH_2 groups. Tautomerism seems to involve the 5-position only when there is no ring nitrogen atom available and then probably only in response to an attacking reagent.



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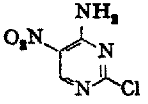

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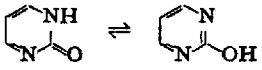

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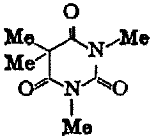

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4. General Summary of Pyrimidine Chemistry

The pyrimidine ring carrying various substituents may be built up from two or three aliphatic fragments by the principal synthesis (Ch. II), or by a variety of other syntheses which are complimentary rather than alternatives to it (Ch. III). A second type of synthesis is the isomerization or breakdown of another heterocycle such as an hydantoin or purine, but such routes are but infrequently used (Ch. III, Sect. 5.E). It seems inappropriate to discuss synthesis further at this stage, but the chief reactions which pyrimidines undergo are outlined below. To help those who may wish to read more deeply, cross references are given to relevant later sections containing more details and literature references.

Pyrimidine is not truly aromatic because of the depletion of the π-electron layer by the electron-withdrawing nitrogen atoms of the ring. This is seen in its instability to prolonged treatment with alkali. However, this imbalance is rectified by substitution with electron-supplying groups (OH, NH_2, SH), and the ring system then becomes extraordinarily stable to hydrolytic cleavage.

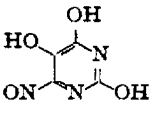
A. Electrophilic Substitution

Electrophilic reagents almost invariably attack pyrimidines at the 5-position, which is the point least depleted of electrons, but, according to the strength of the reagent, one or more electron-supplying groups are needed in the molecule to permit such substitution.

(1) *Nitration and Nitrosation*

(Ch. V, Sect. 1.A(2) and 2.A(1))

Pyrimidines normally require the presence of at least two electron-supplying groups for successful nitration or nitrosation. The positions of these groups are important for while 4,6-dihydroxy- and 4,6-diaminopyrimidine nitrate and nitrosate, 2,4-dihydroxypyrimidine will only nitrate, and 2,4-diaminopyrimidine undergoes neither process. When three electron-supplying groups are present, as in isobarbituric acid (2,4,5-trihydroxypyrimidine), even the 6-position can be attacked by nitrous acid to give the 6-nitroso compound (XIX). The corresponding nitration is not successful.



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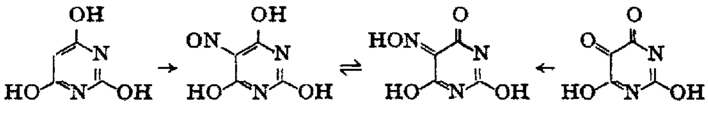


(XX) (XXI) (XXII)

Nitrosopyrimidines are tautomeric with hydroxyimino derivatives (oximes) in which a hydrogen atom has been borrowed from a neighbouring tautomeric group. Thus violuric acid (XXI) can be prepared by nitrosating barbituric acid (XX) or by the action of hydroxylamine on alloxan (XXII).

(2) *Diazo Coupling*

(Ch. V, Sect. 3.A(2))

Pyrimidines with one electron-supplying group couple with diazotized amines to give 5-arylazo derivatives. The reaction is extraordinarily useful for introducing a 5-amino group because it can be done under such gentle conditions. A few 4-(or 6-) arylazo derivatives can also be made this way, provided (as with similar nitrosations) that three facilitating groups are present.

(3) *Halogenation*

(Ch. VI, Sect. 2.A)

Halogenation normally requires one electron-releasing group and the halogen atom invariably enters the 5-position (or occasionally a methyl or other substituent). Unsubstituted pyrimidine can be brominated, but probably only because an intermediate perbromide is formed, as in the authenticated case of pyridine.

(4) *Sulphonation*

(Ch. VIII, Sect. 4.A)

Sulphonation at position-5 will take place in the presence of one amino or hydroxy group, but only under very vigorous conditions. These can be moderated for dihydroxy and similar derivatives, but the process has been little used.

(5) *Attack by Chloroform or Chloral*

(Ch. XI, Sect. 5.A(2))

Initial electrophilic attack is also involved in the Reimer–Tiemann reaction, which introduces an aldehydo group into the 5-position of pyrimidines already having two or three electron-releasing groups. Chloral also attacks such pyrimidines to give their 5-$\beta\beta\beta$-trichloro-α-hydroxyethyl derivatives, *e.g.* (XXIII), which may be subsequently hydrolysed to aldehydes.

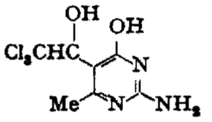
(6) *Other Electrophilic Attacks*

Formaldehyde (Ch. VII, Sect. 3.E) readily attacks uracil to give

2,4-dihydroxy-5-hydroxymethylpyrimidine (XXIV), which is a stable compound, but when an aromatic aldehyde is used in such a reaction, water is eliminated from the initial product to give for example benzalbarbituric acid (XXV). The related Mannich reaction (Ch. IV, Sect. 2.C(7)) is also undergone by pyrimidines with a free 5-position and carrying two or three electron-releasing groups, to give for example 4,6-dihydroxy-2-methyl-5-piperidinomethylpyrimidine. In the absence of facilitating groups, the methyl group itself, which is then more active than is the 5-position, becomes involved in the reaction. The introduction of a 5-carbamoyl group into 4,6-dihydroxy-2-methylpyrimidine by fusion with urea is probably also an electrophilic reaction (Ch. XI, Sect. 3.A(4)).

B. Direct Nucleophilic Substitution

Although the 2-, 4-, and 6-positions of pyrimidine are obviously ripe for direct nucleophilic attack, only a few examples of the process are known. The most definite of these is the amination (Ch. IX, Sect. 1.C) of 4-methylpyrimidine with sodamide to give *inter alia* its 2-amino and 2,4-diamino derivatives. Two other possible cases are the formation of 5-amino-4-methylamino-2,6-dimercaptopyrimidine from 2-chloro-4-methylamino-5-nitropyrimidine during reduction with sodium bisulphide (Ch. VIII, Sect. 1.A(8)), and the direct introduction (Ch. VI, Sect. 5.J) of a diethoxycarbonylmethyl group into the 2-position of 4,6-dichloro-5-nitropyrimidine giving (XXVI). The mechanisms of these reactions are not entirely clear.



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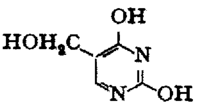

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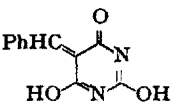

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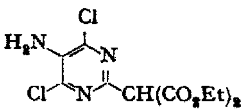


(XXVI)

C. Nucleophilic Metatheses

Compared with the paucity of direct nucleophilic substitutions of hydrogen, there are a vast number of examples in which halogen atoms or other labile groups undergo replacement by a variety of substituents. The initial step in these metatheses is nucleophilic attack by the reagent on the carbon atom to which the halogen is attached.

(1) *Replacement of Halogens*

(Ch. VI, Sects. 5 and 6)

The nucleophilic replacement of 2-, 4-, and 6-halogen substituents is normally very facile. It is made even easier by the presence of an electron-withdrawing group (*e.g.* nitro), but markedly more difficult by successive introduction of electron-supplying groups. Although 5-bromopyrimidine undergoes such reactions fairly readily, the presence of hydroxy or, more particularly, amino groups can make nucleophilic replacements exceedingly difficult or even impossible. Replacements of extra-nuclear halogenopyrimidines differ little from such reactions in the benzene series (Ch. VI, Sect. 7).

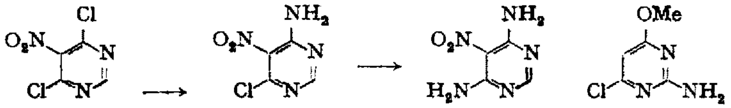
(a) *By Amino and Substituted-amino Groups* (Ch. VI, Sects. 5.B and 5.C). The most active chloro substituents react with alcoholic or aqueous ammonia below room temperature (*e.g.* in the formation of 4-amino-6-chloro-5-nitropyrimidine (XXVIII) from 4,6-dichloro-5-nitropyrimidine (XXVII)), but a less active chlorine, such as the now partly deactivated one in the above example (XXVIII), requires 100°, or sometimes even higher temperatures, for satisfactory replacement, *e.g.* to give (XIX). The lower aliphatic primary and secondary amines, being stronger bases than ammonia, even more avidly replace chlorine. Similar replacements with less strongly basic amines such as aniline, are markedly catalysed by the presence of a little of the cation.

The kinetics of such nucleophilic aminations have been studied in simple chloropyrimidines (Ch. VI, Sect. 4). These indicate that chlorine in position-4 is more activated than in position-2, and that the introduction of a gently electron-releasing *C*-methyl group slightly deactivates both chlorines.

With the exception of 5-bromopyrimidine itself, most of the known 5-halogenopyrimidines either require high temperatures for amination, or indeed cannot be satisfactorily aminated at all (Ch. VI, Sect. 6.A). In several such sluggish reactions the addition of a little copper has been found to improve the yield.

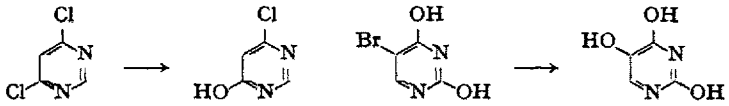
(b) *By Methoxy and Similar Groups* (Ch. VI, Sect. 5.D). Almost all 2-, 4-, and 6-chloropyrimidines are readily replaced by a methoxy group with the help of methanolic sodium methoxide. Only in cases of powerful deactivation (*e.g.* of the 4-chlorine of (XXX)) are temperatures above the boiling point of methanol ever used. Other alkoxides and aryloxides behave similarly.

The need for completely anhydrous alcohols for use in such reactions, is underlined by the formation of 2-ethoxy-4-hydroxy-5-nitropyrimidine (and its isomer) to the extent permitted by the water content of the "absolute alcohol" used in preparing 2,4-diethoxy-5-nitropyrimidine from its dichloro analogue. 5-Bromopyrimidine reacts with sodium methoxide at 100°, but examples using less active 5-bromo or 5-chloro derivatives are unavailable.



(XXVII) (XXVIII) (XXIX) (XXX)

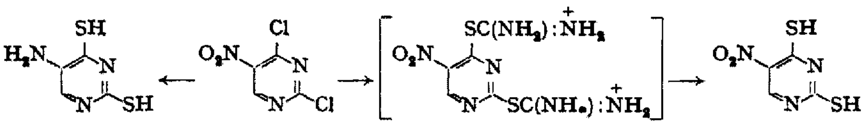
(c) *By Hydroxy Groups* (Ch. VI, Sects. 5.E and 6.B). The direct hydrolysis of an active halogen is not always easy in practice, and sometimes it is best to pass through a methoxy compound. However, the partial hydrolysis of a dichloropyrimidine, *e.g.* (XXXI) to (XXXII), is often practicable, and both acidic and alkaline media have been used for this purpose. In the past it has been customary to treat 5-bromo compounds very vigorously to bring about hydrolysis, but it has been recently reported that 5-bromouracil (XXXIII) yields isobarbituric acid (XXXIV) on mere boiling with sodium bicarbonate solution.



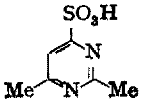
(XXXI) (XXXII) (XXXIII) (XXXIV)

(d) *By Methylthio and Related Groups* (Ch. VI, Sects. 5.F and 6.B). Active chloropyrimidines on boiling with alcoholic sodium methylmercaptide, yield the corresponding methylthio compounds. Aromatic thioethers have been made similarly by using the free thiophenol or its sodium derivative. Isolated examples of such replacement of a 5-bromo substituent are known.

(e) *By Mercapto Groups* (Ch. VI, Sect. 5.G). When a 2-, 4-, or 6-chloropyrimidine is treated with alcoholic or aqueous sodium bisulphide, a mercaptopyrimidine usually results. The method is often used in conjunction with the reduction of a nitro group, as in the formation of 5-amino-2,4-dimercaptopyrimidine (XXXV) from 2,4-dichloro-5-nitropyrimidine (XXXVI). If reduction is to be avoided, it is better to replace the chlorine by a thiouronium salt residue as in (XXXVII), and subsequently to hydrolyse by alkali to the required mercapto compound (XXXVIII).


(XXXV) (XXXVI) (XXXVII) (XXXVIII)

(f) *By Sulpho and Thiocyanato Groups* (Ch. VI, Sect. 5.H). Simple chloropyrimidines react with aqueous sodium sulphite to give the corresponding sulphonic acids, *e.g.*, 2,4-dimethyl-6-sulphopyrimidine (XXXIX). These serve as convenient intermediates for the corresponding nitriles, which cannot be made directly from the chloro compounds. Many chloropyrimidines such as (XL) also react with potassium thiocyanate to give thiocyanato derivatives typified by (XLI). If the reaction time is prolonged, or the thiocyanate is heated in an inert solvent (*e.g.* toluene), isomerization to the corresponding isothiocyanate (XLII) takes place. Strongly deactivated halogenopyrimidines, including 5-bromo derivatives, do not undergo the reaction.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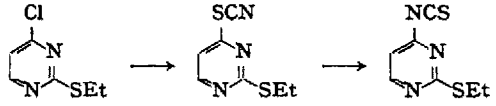

(XL) (XLI) (XLII)

(2) *Replacement of Methoxy, Methylthio, and Methylsulphonyl Groups*

All these groups will undergo most nucleophilic replacements in much the same circumstances as will a halogen, but as a rule not nearly so easily. For comparison, 4-chloro-2-methylpyrimidine is aminated quickly below 100°, but 4-methoxypyrimidine (which moreover lacks the deactivation of a *C*-methyl group) is aminated but slowly at 160°. Phenoxy groups require even more vigorous conditions for amination. The reaction once formed the basis of the standard synthesis of cytosine and isocytosine (Ch. VII, Sect. 7.C). Further direct simple comparison with the amination of methylthio and methylsulphonyl derivatives cannot be made for lack of data, but more complicated examples indicate that the conditions required approximate to those for alkoxy replacement rather than to those for halogens (Ch. VIII, Sects. 2.C and 5.B).

These activated ethers (Ch. VII, Sect. 1.E), thioethers (Ch. VII, Sect. 1.F(1)), and sulphones (Ch. VII, Sect. 1.F(3)) can all be hydrolysed by acid (and the sulphones also by alkali) to give hydroxypyrimidines; indeed this is their greatest use. The carboxymethylthio derivatives, which are made from mercapto compounds with aqueous chloroacetic acid, are especially useful because of their convenient solubility, in the conversion of mercapto- into hydroxy-pyrimidines.

D. Other Metatheses

It is convenient at this stage to outline several other metatheses without reference to their type. Such reactions in the extranuclear positions will again be ignored as being in no way peculiar to the pyrimidine series.

(1) *Hydroxy- to Chloro-pyrimidines*

(Ch. VI, Sect. 1)

Pyrimidines with hydroxy groups in the 2-, 4-, or 6-position often give their chloro analogues on boiling with phosphoryl chloride. In a difficult case, as when a nitro group is present, the addition of some *NN*-diethylaniline (or other tertiary base) is generally beneficial, and as a last resort phosphorus pentachloride may be useful. So powerful a reagent is the last, that if the 5-position is free, *C*-chlorination often takes place there also. Bromo compounds can be formed with phosphoryl bromide. 5-Hydroxy groups do not react with phosphoryl halides.

(2) *Hydroxy- to Mercapto-pyrimidines*

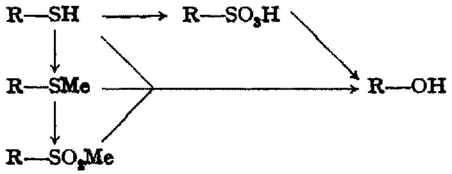
(Ch. VII, Sect. 6.B)

The thiation of 2-, 4-, and 6-hydroxypyrimidines is carried out by heating with phosphorus pentasulphide in xylene, tetralin, or pyridine. The reaction generally fails in the presence of nitro, nitroso, or amino groups, and 5-hydroxy groups cannot be thus replaced. Oxo and alkylthio derivatives also undergo thiation to give respectively thio (=S) and mercapto derivatives.

(3) *Mercapto- to Hydroxy-pyrimidines*

(Ch. VII, Sect. 1.F)

Only rarely can a mercaptopyrimidine be directly hydrolysed to a hydroxypyrimidine. The transformation is best done by *S*-alkylation to a methylthio- or carboxymethylthio-pyrimidine, followed by acid hydrolysis, but it can sometimes be done by oxidation to a sulphinic or sulphonic acid followed by hydrolysis. There is danger in the second process of replacing the mercapto group by hydrogen instead of by a hydroxy group. Should acid hydrolysis be contraindicated by the presence of another acid-labile group, a third route may be used *via* alkylthio to alkylsulphonyl and thence by alkaline hydrolysis to the desired hydroxy derivative. The processes have not been applied to 5-mercaptopyrimidines.



(4) *Mercapto- to Amino-pyrimidines*

(Ch. VIII, Sect. 1.D(5))

Mercapto groups in the 4-position may be aminated to amino or substituted-amino groups by the action of ammonia or amines at about 100°. 2-Mercapto groups cannot be aminated unless a nitro group is present, and the reaction fails in both positions when amino groups are already present. The process is very useful, and is used in the best preparation of cytosine.

(5) *Amino- to Hydroxy-pyrimidines*

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

Aminopyrimidines may be converted into their hydroxy analogues by direct acid or alkaline hydrolysis, or, in the case of primary amino compounds, by the action of nitrous acid. Both processes are applicable to an amino group in any position, but the hydrolytic one is most used for 4-amino derivatives.

(6) *Amino- to Chloro-pyrimidines*

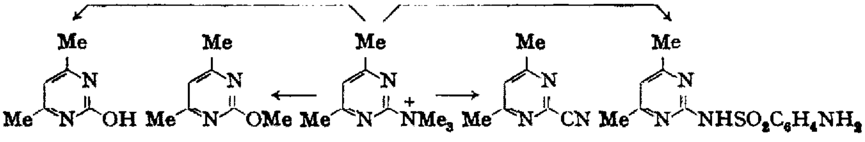
(Ch. VI, Sects. 1.C and 2.C)

Several 2-chloropyrimidines have been made by treating the corresponding aminopyrimidine with nitrous acid and an excess of concentrated hydrochloric acid. A 5-iodopyrimidine has been made by diazotization of the 5-amino analogue followed by a Sandmeyer reaction.

(7) *Replacements of Quaternary Amino Groups*

(Ch. VI, Sect. 8.G)

Trimethylamine slowly converts simple chloropyrimidines into quaternary derivatives. Such a product, 4,6-dimethylpyrimidin-2-yltrimethylammonium chloride (XLV), yields 2-methoxy-4,6-dimethylpyrimidine (XLIV) with sodium methoxide, or 2-hydroxy-4,6-dimethylpyrimidine (XLIII) by treatment with caustic soda. Potassium cyanide similarly gives (XLVI), and sodium sulphanilamide gives (XLVII).



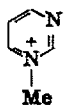
(XLIII) (XLIV) (XLV) (XLVI) (XLVII)

E. Addition Reactions

Although a great many reactions may involve addition as an initial step, the term is here confined to cases in which the primary addition product can be isolated.

(1) *Quaternization*

Simple pyrimidines add methyl iodide in the usual way to give for example pyrimidine methiodide (XLVIII). Pyrimidines with amino or hydroxy groups in the 2-, 4-, or 6-position constitute a special case (see Chapter X), for the quaternary product is in fact the hydriodide of an N_1- or N_3-methyl-imino(or oxo)pyrimidine, *e.g.*, (XLIX). On making alkaline, this yields a free base (LI), which is the anhydrobase derived from the quaternary hydroxide (L). The imine corresponding to (LI) is a cyclic guanidine and a strong base.



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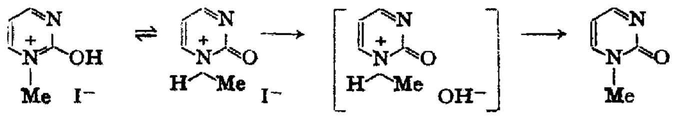


(XLIX) (L) (LI)

(2) *Formation of* N-*Oxides*

(Ch. IV, Sect. 2.C(4) and Ch. X, Sect. 4.A)

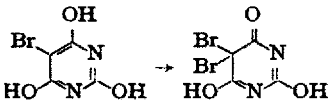
Pyrimidine is largely destroyed during formation of its *N*-oxide, but the alkyl- and alkoxy-pyrimidines give mono-*N*-oxides in good yield by the action of hydrogen peroxide in acetic acid.

The oxides may be reduced to the parent pyrimidine by hydrogenation or with phosphorus trichloride. They undergo the usual reactions of *N*-oxides such as the Reissert reaction, which is illustrated in the conversion of 4-methoxy-6-methylpyrimidine-*N*-oxide into 2-cyano-4-methoxy-6-methylpyrimidine with benzoyl chloride and potassium cyanide.

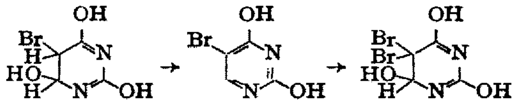
(3) *Addition of Hypobromous Acid*

(Ch. VI, Sect. 2.A(6))

The bromination in water of barbituric acid, uracil, and related compounds is abnormal. Barbituric acid yields 5-bromo- and 5,5-dibromo-barbituric acid (LII) and (LIII). Uracil yields finally a true



(LII) (LIII)



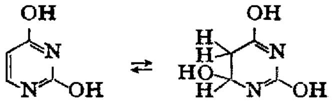
(LIV) (LV) (LVI)

dihydro derivative, 5,5-dibromo-4,5-dihydro-2,4,6-trihydroxypyrimidine (LVI). The mechanism of the formation of (LIII) is unknown, but it could be addition of HOBr to the 4,5-bond of the monobromo derivative (LII), followed by dehydration. On the other hand, the route to (LVI) has been recently worked out, and it does involve addition of HOBr to give (LIV), followed by dehydration to 5-bromouracil (LV), which then again adds HOBr to give the stable entity (LVI).

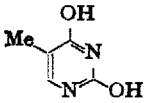
(4) *Addition of Water*

(Ch. VII, Sect. 8.A)

On ultraviolet irradiation in aqueous solution, uracil (LVII) adds H_2O across the 5,6-bond to give 4,5-dihydro-2,4,6-trihydroxypyrimidine (LVIII). Treatment with acid reverses the process. 1,3-Dimethyluracil behaves similarly, but in thymine (LIX) the 5-methyl substituent is sufficient to preclude such hydration.



(LVII) (LVIII)

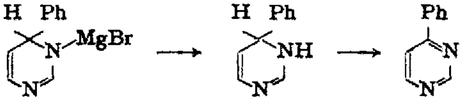


(LIX)

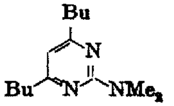
(5) *Addition of Grignard Reagents and Lithium Alkyls*

(Ch. IV, Sects. 1.C and 2.A(5))

Grignard reagents readily add to the 1,6-bond of pyrimidine, giving for example (LX), which on hydrolysis gives the dihydro derivative (LXI), and this on oxidation gives 4-phenylpyrimidine (LXII). Lithium phenyl adds similarly, and eventually also yields (LXII). Not surprisingly, two alkyl groups can thus be introduced, as in 4,6-dibutyl-2-dimethylaminopyrimidine (LXIII).



(LX) (LXI) (LXII)



(LXIII)

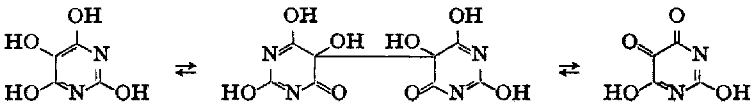
F. Oxidative Reactions

Oxidation of a pyrimidine is seen in the direct introduction of a 5-hydroxy group into 2-hydroxy-4,6-dimethylpyrimidine by the Elbs persulphate reaction (Ch. VII, Sect. 2.C). The intermediate ester, the 5-pyrimidinyl hydrogen sulphate, has been isolated. Such oxidation required the presence of at least one electron-releasing group, and has only been recorded in the 5-position.

Elevation to an oxidation state above that of pyrimidine is seen in the oxidation of dialuric acid (tetrahydroxypyrimidine; LXIV) to alloxan (LXVI). The process is reversible, and in each direction passes through alloxantin (probably LXV), which empirically is a dimer of a dialuric acid molecule which has lost a hydrogen atom (Ch. VII, Sect. 9).

Degradative oxidation of pyrimidines, although it is occasionally informative, has been little used.

Oxidative modification of groups differs little in principle from similar procedures in the benzene series. Thus a *C*-methyl- or styrylpyrimidine yields a carboxylic acid with permanganate, a hydroxymethyl group may be oxidized to an aldehyde or acid according to conditions, a mercapto group may be oxidized to a disulphide with iodine (but not by air, except in the 5-position), and this in turn yields a sulphonic acid with hydrogen peroxide or permanganate. Monosulphides give sulphones with permanganate, and alkylthio derivatives yield sulphones similarly, or with chlorine. A hydrazino group has been removed in favour of hydrogen by treatment of the pyrimidine with copper sulphate.



(LXIV) (LXV) (LXVI)

G. Reductive Reactions

Compared with the paucity of oxidative reactions, there are many important reductive processes used in pyrimidine chemistry. These may be divided into three classes.

(1) *Nuclear Reduction*

(Ch. XII, Sects. 1.H, 2.D, and 3)

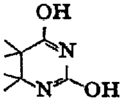
A vast field of reduced pyrimidines awaits adequate exploration. The three groups (di-, tetra-, and hexa-hydropyrimidines) include no fewer than nine distinct series, of which several are virtually untouched. Most of the known hydropyrimidines have been made by primary synthesis, but some by reduction of pyrimidines.

Speaking generally, catalytic hydrogenation over palladium or platinum in acid tends to reduce more easily those double bonds free of an attached group (halogen excepted). Such a reduction in any case normally stops at the tetrahydro stage, and the remaining unsaturation is usually a 1,2- or 2,3-double-bond. Uracil is thus reduced to 4,5-dihydro-2,6-dihydroxypyrimidine (LXVII), but reductive dehalogenation of 2-amino-4,6-dichloropyrimidine gives a 2-amino-tetrahydropyrimidine, and pyrimidine itself yields 1,4,5,6-tetrahydropyrimidine (LXIX).

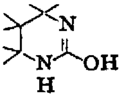
Boiling with Raney nickel has a similar effect, reducing uracil to its dihydro derivative (LXVII), but 2-hydroxypyrimidine to its tetrahydro derivative (LXVIII). 4-Hydroxy- and 4-aminopyrimidine are stable to such treatment, but yield to hydrogenation over palladium or platinum.

Most of the classical chemical reducing agents do not reduce the pyrimidine nucleus, but lithium aluminium hydride gives tetrahydro derivatives from barbiturates. Valuable aspects of this reagent are that it does not necessarily reduce at the same place as does hydrogenation, and that a mercapto group can be present and remain unaffected during a reduction, which might lead for example to (LXX). Electrolytic reductions have been reported to give a variety of products from pyrimidines, but in the present state of knowledge the method is of little use.

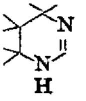
Very few hexahydropyrimidines have been made by reduction, but the well-characterized 2-aminohexahydropyrimidine is one.



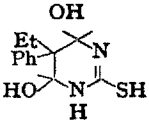
(LXVII)



(LXVIII)



(LXIX)



(LXX)

(2) *Reductive Removal of Groups*

Primary synthesis often gives a pyrimidine bearing unwanted groups. Chloro, mercapto, and carboxy substituents can be removed with ease, and others can often be changed into one of these and then removed.

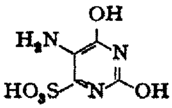
Chlorine, especially in position-4, may be removed by chemical reducing agents (Ch. IV, Sect. 2.A(2) and Ch. VI, Sect. 5.A), the best of which is zinc dust with water or mildly acid solution. Commercial preparations of 2-aminopyrimidine from its 4-chloro derivative have made use of this reagent. A better way to remove chlorine is catalytic hydrogenation over palladium, but in the presence of a base, without which nuclear reduction may also take place. Pyrimidine can thus be made from any of its mono, di, or trichloro derivatives. These hydrogenations do not differentiate at all between chlorine in different positions, and a poly-chloropyrimidine on partial dechlorination invariably gives a mixture of products.

Mercapto and methylthio groups can be most conveniently removed by boiling a solution with an excess of Raney nickel catalyst (Ch. VIII, Sect. 1.D(1)). The method always desulphurizes 2-mercaptopyrimidines efficiently, but when it is applied to 4-mercaptopyrimidines, nuclear reduction sometimes accompanies desulphurization. The same is true of 5,5-dialkyl-2-thiobarbituric acids.

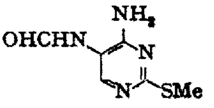
(3) *Reductive Modification of Groups*

The reduction of 5-nitro-, 5-nitroso-, and 5-arylazo-pyrimidines to their amino analogues can be done, as in other series, by a variety of chemical agents, but catalytic hydrogenation and sodium hydrosulphite are particularly favoured. An interesting deviation from normal is the formation of 5-amino-2,4-dihydroxy-6-sulphopyrimidine (LXXI) by hydrosulphite reduction of nitrouracil.

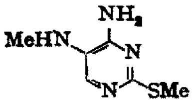
The reduction of other groups is by no means unique to pyrimidines, but the method of making a secondary amine, *e.g.* (LXXIII), from an acylated primary amine (LXXII) with lithium aluminium hydride, is mentioned as being useful in position-5, where such groups are difficult to introduce by other means.



(LXXI)



(LXXII)



(LXXIII)

H. The Modification of Substituents

As distinct from a complete metathesis, modification of a group does not involve rupture of the bond joining it to the parent ring system. Several cases of such modification involving oxidation or reduction have already been discussed, as in the reduction of a nitro group to an amino group, or the oxidation of a mercaptan to a disulphide.

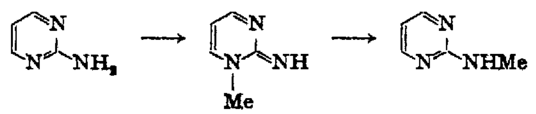
(1) *Amino Groups*

(Ch. IX and Ch. X, Sect. 2.A)

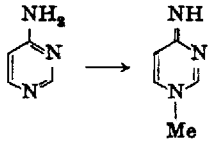
Only 5-aminopyrimidines can be diazotized and subsequently coupled. The amino group in other positions, although no less truly —NH_2 in structure, is involved as a cyclic guanidine, *e.g.* (LXXIV), or a cyclic amidine, *e.g.* (LXXVII), and therefore does not diazotize.

Amino groups in any position may be acylated, but a 2,5- or 4,5-diaminopyrimidine acylates preferentially at position-5, and only much more slowly does it form a 2,5- or 4,5-bisacylamino derivative. There are few examples of an amino group bearing two acyl groups.

Simple 5-aminopyrimidines can sometimes be alkylated or arylated on the amino group. When the amino group occupies another position, initial alkylation on a ring nitrogen atom practically always occurs. Thus 2-aminopyrimidine (LXXIV) and methyl iodide yield the strongly basic 1,2-dihydro-2-imino-1-methylpyrimidine (LXXV) as hydriodide. Such bases can be isolated and characterized, but are unstable in alkali. They either rearrange to the corresponding methylamino derivative, *e.g.* (LXXVI), or, when the imino group is γ to the methyl group as in (LXXVIII), they often simply hydrolyse to the corresponding oxo derivative. The mechanism of the rearrangement of (LXXV) involves rupture of the 1,6-bond, rotation about the 2,3-axis, and ring closure.



(LXXIV) (LXXV) (LXXVI)



(LXXVII) (LXXVIII)

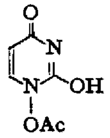
A pyrimidine bearing an amino group in any position can be converted into an anil with aldehydes, a urethane with ethyl chloroformate, and a ureide with isocyanates. In these reactions, a 5-amino group generally reacts preferentially to an amino group elsewhere.

(2) *Hydroxy Groups*

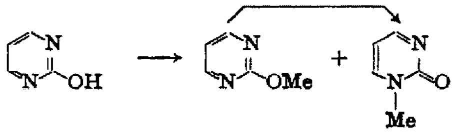
(Ch. X, Sects. I.A(3) and (4))

Only 5-hydroxy groups can be *O*-acylated. Other hydroxy derivatives, such as uracil, sometimes can be acylated on a ring nitrogen to yield an unstable *N*-acyl-oxopyrimidine, *e.g.* (LXXIX).

Alkylation of 5-hydroxypyrimidines gives the 5-alkoxy derivative, but if the hydroxy group is in another position, a mixture of *O*- and *N*-alkyl derivatives results, in which the latter predominates. Thus 2-hydroxypyrimidine and diazomethane give (LXXXI) and (LXXXII) in the ratio of 1:4, and even this is an unusually high proportion of *O*-alkyl isomer. Prolonged heating of such a methoxy derivative as (LXXXI) above its melting point removes the methyl group to the ring nitrogen standing next to it, thus giving the *N*-methyl-oxo compound (LXXXII). The same rearrangement, but probably by a more complicated mechanism, can often be brought about at room temperature by long standing with methyl iodide. It must not be concluded that any appreciable amount of the *N*-methyl derivative (LXXXII) is formed *via* the methoxy derivative (LXXXI) during normal methylation of 2-hydroxypyrimidine.



(LXXIX)



(LXXX) (LXXXI) (LXXXII)

(3) *Mercapto Groups*

(Ch. VIII, Sects. I.D(2) and (6))

Unlike their oxygen analogues, mercaptopyrimidines (whatever the position of the group) acylate and alkylate exclusively on sulphur. The greater polarizability of sulphur compared with oxygen seems to account for this, and the fact that the tautomeric equilibrium of a

2-, 4-, or 6-mercaptopyrimidine is known to overwhelmingly favour the thioamide form is obviously irrelevant.

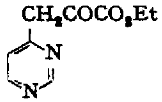
(4) *Methyl Groups*

(Ch. IV, Sect. 2.C)

When it is in the 2-, 4-, or 6-position, a methyl group is active in the sense of that in 2,4-dinitrotoluene. Thus 2,4,6-trimethylpyrimidine gives with benzaldehyde and a zinc chloride catalyst, 2,4,6-tristyrylpyrimidine. A methyl group in position-5 does not so react, so that 2,5-dimethylpyrimidine treated similarly gives only 5-methyl-2-styrylpyrimidine. Other catalysts include acetic anhydride, alcoholic potash, and piperidine or other organic bases. Chloral also condenses with activated methyl groups, but the initial condensation product, $RCH_2CHOHCCl_3$, is stable and does not eliminate water to give the equivalent of a styryl group.

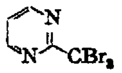
Methyl groups in the active positions undergo both the Claisen and Mannich reactions, giving for example from 4-methylpyrimidine, respectively (LXXXIII) and (LXXXIV). The Mannich reaction may involve the 5-position if electron-releasing groups are present to deactivate the methyl group.

Halogenation of methyl groups proceeds normally, and even tribromomethyl derivatives such as (LXXXV) have been prepared.



(LXXXIII)

(LXXXIV)



(LXXXV)

I. A Free Radical Reaction

Addition of *p*-nitrobenzenediazonium chloride to pyrimidine results, not in coupling at position-5, but in a mixture of 2- and 4-*p*-nitrophenylpyrimidines slowly formed by a Gomberg type of reaction.

5. Physical Properties of Pyrimidines

Apart from spectra and ionization constants, the physical properties of pyrimidines have not been widely investigated, analysed, or even recorded.

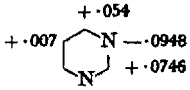
A. Electronic Structures

The distribution of electrical charges (*i.e.* the gain or loss of π-electrons at each atom of the molecule) has been recently calculated[42] for pyrimidine (LXXXVI), pyrazine (LXXXVII), pyridazine (LXXXVIII), and pyridine (LXXXIX), by a refined method.

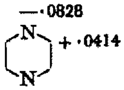
The essential difference between this "VESCF" method and earlier ones is in the calculation of effective nuclear charges in the field of which the π-electrons move. Here the occupation number of the 2p-π atomic orbital on a conjugated atom is taken to be the π-electron density for the atom in the molecule, rather than that for the neutral isolated atom.[42] The method has been outlined.[43]

The diagram for pyrimidine (LXXXVI) shows the considerable depletion of electron density at positions -2 and -4, the slight depletion at position-5, and the greatly enhanced density at the nitrogen atoms. The changes in α- and γ-positions are naturally more marked in pyrimidine (where the nitrogen atoms act in unison) than in pyrazine or pyridazine (where they do not), or in pyridine (which has but one electron-withdrawing centre). On this of course depends the unique character of pyrimidine chemistry. Previous calculations for pyrimidine[44–47], although differing in detail, express the same pattern.

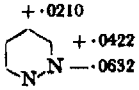
Such calculations have been extended[47] to pyrimidines of biological interest, for example to the various possible tautomeric forms of uracil. The density assigned, for example, in the dioxo form of uracil to position-5 (*viz.* —.219) is particularly interesting compared with a figure of virtually nil in pyrimidine. It is this enhanced electron density, consequent on the insertion of electron-releasing groups, which now permits ready electrophilic substitution and discourages nucleophilic activity at position-5 in uracil.



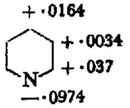
(LXXXVI)



(LXXXVII)



(LXXXVIII)



(LXXXIX)

B. Ionization Constants

Because of their utility in problems of structure, and their essential role in the precise measurement of the ultraviolet spectra of pure species, the ionization constants of pyrimidines have been widely recorded of recent years.

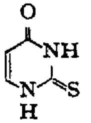
Pyrimidine (pK_a 1.3) is a weak base compared with pyridine (pK_a 5.2). This is understandably due to depletion of the π-electrons caused by the insertion of the strongly electron-withdrawing second nitrogen atom. Pyrimidine is therefore more akin to 3-nitropyridine (pK_a 0.8), which contains the strongly electron-withdrawing nitro group, than to the parent pyridine. The pK_a values of pyrimidines are discussed in Ch. XIII, Sect. 1, and most of the known figures are collected in Table XVI.

C. Spectra

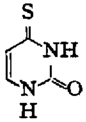
The infrared, ultraviolet, and Raman spectra of pyrimidines are discussed in the essay by S. F. Mason (Ch. XIII, Sect. 2). The nuclear magnetic resonance spectra of some pyrimidines of biological interest have also been reported and discussed.[48]

D. Dipole Moments

The dipole moment of pyrimidine (2.42 D; dioxane at 35°) may be compared[49] with pyridazine (3.94), pyrazine (0.6), pyridine (2.3; benzene). The only extensive use of dipole moments in a pyrimidine problem was the comparison[50] of the moments of 2-thiouracil (4.2) and 4-thiouracil (4.47) with those of their various *S*-, *N*-, and *O*-alkylated derivatives. It was concluded that the two thiouracils existed in dioxane as the oxo–thio forms (XC) and (XCI). Unfortunately, uracil proved insufficiently soluble in dioxane for comparative measurement.[50]



(XC)



(XCI)

E. Polarography

The polarography of pyrimidines forms a very sketchy picture. Apart from a little fundamental work[50a] aimed at elucidation of the tautomeric forms of simple amino- and hydroxy-pyrimidines, most other papers have dealt with naturally occurring materials or with barbiturates. Thus uracil,[51,52] thiouracils,[51] barbituric acid,[53] 5,5-diethylbarbituric acid,[54] and a range of 5,5-dialkyl-2-thiobarbituric acids[55] have been submitted to polarography. The results do not warrant discussion here, but have been summarised elsewhere.[56] The polarography of 5-hydroxypyrimidines has been reported.[57]

F. Solubility and Melting Point

Pyrimidine is completely miscible with water, but as with other heteroaromatic series, hydroxy, mercapto, and amino substituents diminish the aqueous solubility. This effect is due to hydrogen bonding between molecules, because it is brought about by hydroxy but not by methoxy groups, by mercapto but not by methylthio groups, and by amino but not by dimethylamino groups. Rise in melting point follows the insolubilising effect of the groups. Table XII presents the known data for simple hydroxypyrimidines, but a more extensive picture of these interesting phenomena can be seen in the pteridine series.[58, 59] The solubilities of pyrimidines in non-aqueous solvents are not abnormal.

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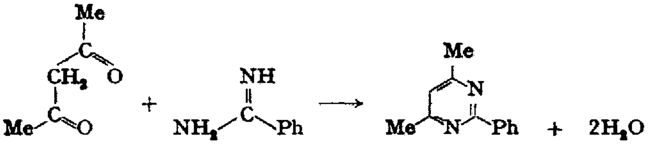
CHAPTER II

The Principal Synthetic Method

1. General Scope

The name "Principal Synthesis" (the "Common Synthesis") is used here to describe a series of related reactions which are the most widely used of all pyrimidine syntheses. Not only is the Principal Synthesis highly versatile, so that a wide variety of pyrimidines can be derived from it, but the products are themselves capable of further diversification by exchange of groups. This synthesis is exemplified by the condensation of acetylacetone (I) with benzamidine (II) to give 4,6-dimethyl-2-phenylpyrimidine (III). The reaction is usually done under alkaline conditions such as in ethanol containing sodium ethoxide, but other solvents and even neutral or strongly acidic conditions have often been used to advantage.

The great versatility of the Common Synthesis lies in the fact that one or both functional groups of the three-carbon fragment (I) may be replaced by almost any other kind of carbonyl group (such as an aldehyde or ester), or by a —C≡N group. These lead respectively to an unsubstituted 4- or 6- position, to hydroxy, or to amino groups. Further, by prior substitution of the methylene group of (I), a 5-substituted pyrimidine results. The amidine (II) may also be replaced by urea, thiourea, guanidine, or formamidine, and these yield a pyrim-



(I) (II) (III)

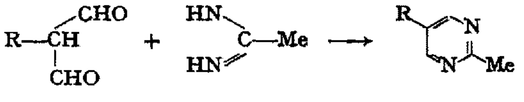
idine substituted in the 2-position by hydroxy, mercapto, amino, or without a group. When these reagents already carry an *N*-, *O*-, or *S*-alkyl group, *N*-substituted pyrimidines or 2-alkoxy or alkylthio derivatives are obtained.

In practice not every combination cyclizes as expected, but by a careful choice of intermediates a wide range of tetra-, tri-, di-, and even mono-substituted pyrimidines can be produced. In the following pages a systematic survey of this Common Synthesis is presented. Examples are given of the condensation of the main classes of three-carbon fragment with amidines, urea, thiourea, guanidine, and where data is available, with their *N*-, *S*-, or *O*-alkyl or aryl derivatives. Where there is sufficient information, tables are used to expand the text.

2. Use of β-Dialdehydes

Condensation of malondialdehyde* with formamidine has not been achieved yet, but acetamidine gives about 2 % of 2-methylpyrimidine[2] (IV; R=H). *N*-Methylthiourea, however, gives a good yield of 1,2-dihydro-1-methyl-2-thiopyrimidine[3] (V) under acid conditions, although *S*-methylthiourea fails to give a pyrimidine;[4] thiourea itself gives a 66 % yield of 2-mercaptopyrimidine under similar conditions,[6] although under others it failed to react.[4,5] Urea gives 2-hydroxypyrimidine,[6] and *N*-methylurea gives 72 % of 1,2-dihydro-1-methyl-2-oxopyrimidine.[8]

Nitromalondialdehyde reacts satisfactorily with a variety of aryl and benzyl amidines to give 2-aryl (or benzyl) -5-nitropyrimidines.[7,9,10] 2-Methyl-5-nitropyrimidine (IV; R=NO_2) can also be made in this way with acetamidine but only in very small yield.[9]



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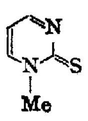

(V)

Nitromalondialdehyde also reacts with urea[7] and with guanidine,[7,11-13] yielding respectively 2-hydroxy- and 2-amino-5-nitro-

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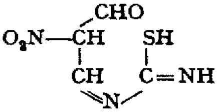
* Malondialdehyde is commercially available as its triethyl monomethyl acetal (1,1,3-triethoxy-3-methoxypropane) and as other acetals; they satisfactorily take its place in the Principal Synthesis.

pyrimidine, but with thiourea no pyrimidine is obtained. Instead, the intermediate thioureide (VI) was said to cyclize to 2-imino-5-nitro-1,3-thiazine[14] (VII). This has been denied,[15] and the product from the condensation with piperidine as basic catalyst, was shown in fact to be 5-nitro-2-piperidinopyrimidine. When *S*-methylthiourea replaces thiourea, ring closure can no longer take place on to S and the expected 2-methylthio-5-nitropyrimidine[15] (VIII) is formed. Unusual catalysts used in these condensations are benzyltrimethylammonium hydroxide[9] and ethylpiperidine.[15]



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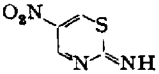

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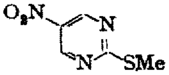
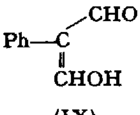


(VIII)

Further condensations of complex *S*-substituted thioureas with nitromalondialdehyde have been reported[16, 17] to yield pyrimidines. Chloromalondialdehyde has been condensed with benzamidine and with *p*-nitrobenzamidine to give 5-chloro-2-phenyl-(and *p*-nitrophenyl-) pyrimidine,[18] and with guanidine to give 2-amino-5-chloropyrimidine.[11] Phenylazomalondialdehyde has been condensed both with guanidine and *S*-methylthiourea under alkaline conditions to give respectively 2-amino- and 2-methylthio-5-phenylazopyrimidine.[19]

An interesting condensation[20] involves hydroxymethylene phenylacetaldehyde[21] (IX), which may be thought of as the stable half enolic form of phenylmalondialdehyde. Gentle treatment with urea gives the compound (X) which no longer shows aldehydic properties. On warming at 120°, however, without catalyst or solvent 2-hydroxy-5-phenylpyrimidine (XI) is produced.



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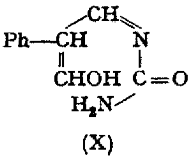
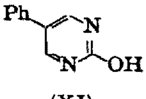


(X)

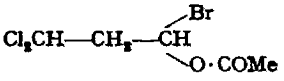


(XI)

The above is an illustration of how a related form of some required intermediate can be used for the Common Synthesis. Even better examples are furnished by the condensation in alcoholic acid of 1,3,3-triethoxypropene[22] (XII) or 1,1-dichloro-3,3-dimethoxypropane[25] (XIII) (both virtually malondialdehyde!) with guanidine to yield 2-aminopyrimidine. Methyl 1-bromo-3,3-dichloropropyl acetate[25] (XIV) and even propynal[26] (XV) have been used similarly to make 2-aminopyrimidine, as has also 1-bromo-1,3-dichloro-2-propene,[24] and 3-phenoxyacrolein (PhOCH:CHCHO).[23]

$\mathrm{Et{-}CH{=}CH{-}CH(OEt)_2}$
(XII)

$\mathrm{Cl_2CH{-}CH_2{-}CH(OMe)_2}$
(XIII)



$\mathrm{Cl_2CH{-}CH_2{-}CH(Br)(O{\cdot}COMe)}$

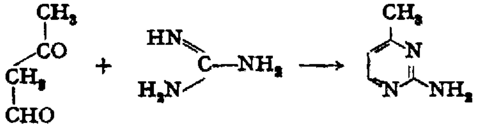
(XIV)

$\mathrm{CH{\equiv}C{-}CHO}$
(XV)

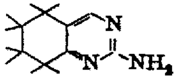
3. Use of β-Aldehydo Ketones

Surprisingly few examples are known of β-aldehydo ketones being used in the Common Synthesis. Although formyl acetone (XVI) fails to condense with benzamidine,[1] with guanidine carbonate in ethanol it gives 2-amino-4-methylpyrimidine[27, 28] (XVII). α-Formylcyclohexanone similarly gives 2-amino-5,6,7,8-tetrahydroquinazoline (XVIII), but when urea is used in place of guanidine the ring will not close.[28]

On the other hand the acetals of formylacetone (*e.g.* $\mathrm{MeCOCH_2CH(OMe)_2}$) condense readily with benzamidine giving 4-methyl-2-phenylpyrimidine,[29] with urea to give 2-hydroxy-4-methylpyrimidine,[30] and with thiourea to give 2-mercapto-4-methylpyrimidine,[30, 31] as well as with guanidine to give 2-amino-4-methylpyrimidine,[29, 31, 32] and with dicyandiamide (cyanoguanidine) to give 2-cyanoamino-4-methylpyrimidine.[29] Other such acetals have also been condensed with guanidine[33] and its derivatives,[34–37] and with urea to give for example 2-hydroxy-4,5-dimethylpyrimidine.[33, 38]



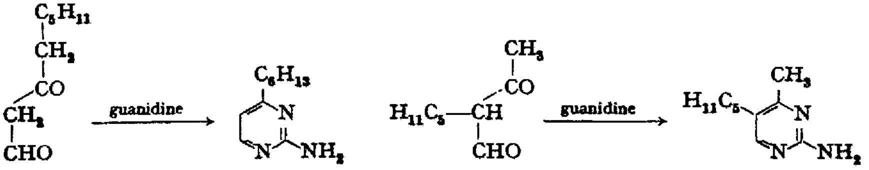
(XVI) (XVII)



(XVIII)

Because of disagreement as to which side of a higher aliphatic ketone is formylated, the pyrimidine from formylated hexyl methyl ketone (XIX) or (XXI) and guanidine has been described as 2-amino-

4-hexylpyrimidine[27] (XX) and as 2-amino-5-amyl-4-methylpyrimidine[39] (XXII). The balance of evidence seems to favour the former structure (XX). By analogy, the structures of 2-amino-4-propylpyrimidine[27, 28] and of 2-amino-4,5-dimethylpyrimidine[28, 33, 39] must be accepted with slight reserve.



(XIX) (XX) (XXI) (XXII)

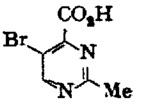
Benzoylacetaldehyde (or hydroxymethyleneacetophenone) condenses with guanidine in pyridine to give 2-amino-4-phenylpyrimidine.[18, 27, 28] The *p*-methyl and *p*-methoxy analogues do likewise, but *p*-nitrobenzoylacetaldehyde fails in this reaction.[34]

Besides the acetals mentioned above, other indirect intermediates used include 4-methoxybutenyne (XXIII), equivalent to formylacetone, and bromomucic acid (XXIV), equivalent to formylbromopyruvic acid (XXIVa). The former gives with guanidine, 2-amino-4-methylpyrimidine or with butyl- or phenylguanidine the corresponding 2-butyl- or phenyl-amino derivative.[40, 41] Thiourea gives 2-mercapto-4-methylpyrimidine.[6] Bromomucic acid (XXIV) has been condensed with acetamidine to give 5-bromo-4-carboxy-2-methylpyrimidine[42]

$MeO\cdot CH{=}CH{-}C{\equiv}CH$ (XXIII)

$HO_2C\cdot CBr{=}CBr{-}CHO$ (XXIV)

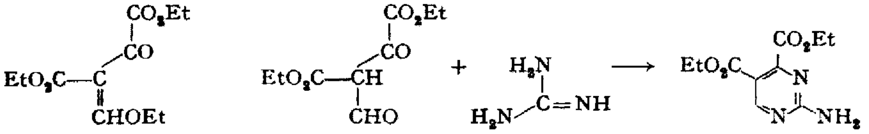
$HO_2C\cdot CO\cdot CHBr\cdot CHO$ (XXIVa)

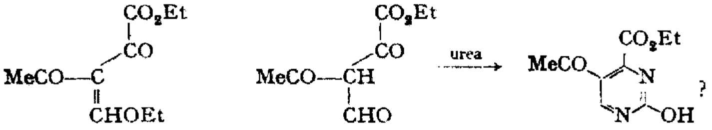


(XXV)

(XXV), and chloro- or bromomucic acid with benzamidine gives the 2-phenyl analogue.[43] Benzoylacetylene with guanidine gives 2-amino-4-phenylpyrimidine.[44] Bromomucic acid (XXIV) has been condensed with *S*-methylthiourea in the presence of triethylamine to give 5-bromo-4-carboxy-2-methylthiopyrimidine.[45]

Two other examples[46] of intermediates which react as aldehydo ketones are furnished by diethyl ethoxymethyleneoxalacetate (XXVI) which is equivalent to (XXVIa), and by ethyl ethoxymethyleneacetylpyruvate (XXVII), equivalent to (XXVIIa). The former with guanidine gives 2-amino-4,5-diethoxycarbonylpryimidine (XXVIII) and with urea, 4,5-diethoxycarbonyl-2-hydroxypyrimidine, while (XXVII) with urea gives probably 5-acetyl-4-ethoxycarbonyl-2-hydroxypyrimidine (XXIX) (of unproven structure).


(XXVI) (XXVIa) (XXVIII)



(XXVII) (XXVIIa) (XXIX)

4. Use of β-Diketones

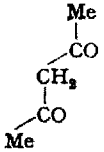
Even the simplest β-diketone, acetylacetone (XXX), has been used extensively in pyrimidine syntheses. With acetamidine in cold aqueous potassium carbonate, 2,4,6-trimethylpyrimidine (XXXI) is produced[47-49] and with benzamidine the product is 4,6-dimethyl-2-phenylpyrimidine.[1] The yields in the latter reaction have been recorded[50] at various pH values and clearly indicate the value of media as alkaline as is consistent with stability of benzamidine *i.e. ca.* pH 10. Similar reactions with propionylacetone and with α-acetyl-α-methylacetone produce the expected pyrimidines.[49] Dibenzoylmethane and benzamidine failed to give 2,4,6-triphenylpyrimidine.[51]

Benzamidine (and the like) condense with 2-acetylcyclohexanone to give 4-methyl-5,6-tetramethylene-2-phenylpyrimidine and derivatives; the best yields are obtained in alcohol with piperidine as catalyst.[52]

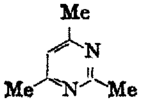
Acetylacetone reacts with urea under acidic conditions to give 2-hydroxy-4,6-dimethylpyrimidine.[53-56] At one time it was believed that two forms of this compound existed,[57] perhaps representing the two tautomeric forms, but crystallographic evidence has disposed of this.[58–60] Valerylacetone failed to give a pyrimidine with urea,[61] but benzoylacetone cyclizes with it under alkaline conditions.[53] Acetylacetone reacts with *N*-methylurea in alcoholic sulphuric acid to give 1,2-dihydro-1,4,6-trimethyl-2-oxopyrimidine[57] (XXXII), and with *N*-methylthiourea to give the corresponding 2-thio-derivative.[57,62] With thiourea itself, 2-mercapto-4,6-dimethylpyrimidine is formed,[6,54,63] and with *S*-methylthiourea, 4,6-dimethyl-2-methylthiopyrimidine.[64]

The condensation of guanidine carbonate with acetylacetone is remarkably ready; indeed on warming in aqueous solution it is exceedingly vigorous.[65,66] At room temperature, the reaction proceeds ten times more quickly in strong light than in the dark.[67] Two stable tautomeric forms of 2-amino-4,6-dimethylpyrimidine have been postulated,[68] but the evidence is unconvincing. Methylguanidine carbonate on refluxing with acetylacetone gives only one product, 4,6-dimethyl-2-methylaminopyrimidine. It was identified by hydrolysis to 2-hydroxy-4,6-dimethylpyrimidine. The other possibility, 1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine, was sought but not found.[69]

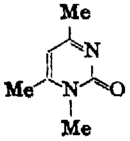
Dicyandiamide (cyanoguanidine) is said to condense with acetylacetone to give a single product previously formulated as 1-cyano-1,2-dihydro-2-imino-4,6-dimethylpyrimidine[69] but more recently as 2-cyanoamino-4,6-dimethylpyrimidine.[71] However, Fabbrini[72] strongly suggests both products are present. Condensation of acetylacetone has also been successful with such substituted guanidines as sulphanilylguanidine,[73] and with *p*-phenoxyphenylguanidine.[74]



(XXX)



(XXXI)



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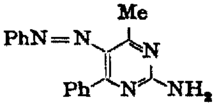


(XXXIII)

As an example of using a *β*-diketone with a substituted methylene group may be mentioned 2-amino-4-methyl-6-phenyl-5-phenylazopyrimidine[70] (XXXIII) from phenylazobenzoylacetone, and many other cases are known.[70,75]

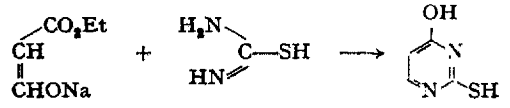
4-Alkyl-2-amino-6-2′-thienyl(and 3′-pyridyl)pyrimidines have been prepared[76a] by fusion of guanidine carbonate with the appropriate diketone. The products, typified by 2-amino-4-methyl-6-2′-thienylpyrimidine were obtained in *ca.* 20 % yield.

5. Use of β-Aldehydo Esters

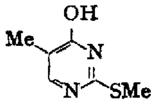
In this group occur the best synthetic routes to the important pyrimidines, uracil, thymine, isocytosine, and thiouracil.

A. Aldehydo Esters with Thioureas

Ethyl formylacetate as its sodio derivative generally written as (XXXIV) reacts in aqueous solution with thiourea, with $[^{14}C]$ or $[^{35}S]$ thiourea, or with selenourea giving respectively thiouracil[76] (XXXV), $[2\text{-}^{14}C]$thiouracil[74], $[^{35}S]$thiouracil, or 2-selenouracil.[79] A similar ready reaction takes place with *S*-methyl- and *S*-ethyl-thiourea giving 4-hydroxy-2-methylthiopyrimidine and its ethyl homologue.[80] When ethyl α-formylpropionate is used similarly, 4-hydroxy-5-methyl-2-methylthiopyrimidine[80] (XXXVI) (or the ethylthio analogue[81]) is obtained. If thiourea is used the product is 2-thiothymine[81] and in the past this was used for an intermediate in thymine synthesis; if selenourea is used the product is 2-selenothymine.[79] Ethyl α-methyl-ββ-diethoxy propionate and $[^{14}C]$thiourea in the same way yield 4-hydroxy-2-mercapto-5-methyl$[2\text{-}^{14}C]$pyrimidine.[77]



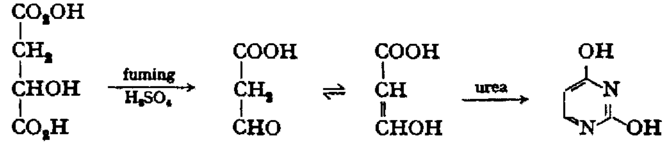
(XXXIV) (XXXV)



(XXXVI)

B. The Davidson-Baudisch Synthesis

Early attempts[76,80] to prepare uracil from the above reaction with urea in place of thiourea, and in aqueous and alkaline solution, failed. Even in hydrochloric acid the wrong product was formed.[82] Davidson and Baudisch noticed that von Pechmann[83] had shown that malic acid (XXXVII) in fuming sulphuric acid first gave formylacetic acid (XXXVIII) which subsequently underwent auto-condensation. They made use of the transient intermediate in its unpromising medium by adding urea, and there resulted a yield of over 50 % of uracil[82] (XXXIX). When thiourea is substituted for urea, 2-amino-6-oxo-1,3-thiazine is formed which slowly rearranges to the isomeric 4-hydroxy-2-mercaptopyrimidine (thiouracil) in dilute ammonia.[84] With *N*-butylurea, a 45 % yield of only 3-butyluracil has been reported.[85]

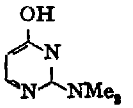


(XXXVII) (XXXVIII) (XXXIX)

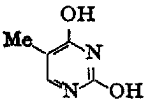
Later, guanidine was substituted for urea and under similar conditions 2-amino-4-hydroxypyrimidine (isocytosine) is formed.[86,87] *NN*-Dimethylguanidine similarly produces 2-dimethylamino-4-hydroxypyrimidine[88] (XL). The reaction was further extended to use β-methylmalic acid (or its ester) with urea, to form 5-methyluracil[89] (thymine; XLI), and with guanidine to form 5-methyl-isocytosine[89] (XLII).

Acetamidine reacts with ethyl formylacetate in aqueous solution to yield 4-hydroxy-2-methylpyrimidine;[90] other examples of the use of amidines are given in Table II.

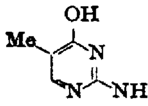
Substituted β-aldehydo esters have been widely used (as in the thymine synthesis above) to introduce substituents directly into the 5-position of uracil, isocytosine, thiouracil and 4-hydroxy-2-methylpyrimidine. Examples such as (XLIII) are shown in Table II, and the formation of 4-hydroxy-5-β-methoxycarbonylethyl-2-methylpyrimidine and similar compounds has been described.[91]



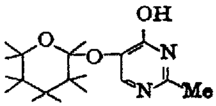
(XL)



(XLI)



(XLII)



(XLIII)

C. The Use of α-Ethoxymethylene Esters

Another interesting case of prior substitution is the use of diethyl ethoxymethylenemalonate (XLIV) which is virtually diethyl formylmalonate (XLIVa). This could then react say with acetamidine as an aldehydo ester, or as a diester and would give respectively 5-ethoxy-

TABLE II. Additional Examples of the Use of Aldehydo Esters in the Principal Synthesis

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Ethyl formylchloroacetate	*S*-methylthiourea	water; pH 11; 20°; 24 hr.	5-chloro-4-hydroxy-2-methylthio- (38%)	103
Ethyl formylfluoroacetate	*S*-ethylthiourea	alcohol; sodium ethoxide; reflux; 2 hr.	5-fluoro-4-hydroxy-2-ethylthio- (24%)	104
Ethyl formylfluoroacetate	*S*-methylthiourea	alcohol; sodium ethoxide; reflux; 2 hr.	5-fluoro-4-hydroxy-2-methylthio	104
Ethyl benzamidoformylacetate	*S*-methylthiourea	water; alkali; 37°; 48 hr.	5-benzamido-4-hydroxy-2-methylthio- (91%)	105
Ethyl formylfluoroacetate	*O*-methylurea	alcohol; sodium ethoxide; reflux; 2 hr.	5-fluoro-4-hydroxy-2-methoxy-	104
Ethyl benzyloxyformylacetate	urea	alcohol; sodium ethoxide; reflux; 4 hr.	5-benzyloxy-2,4-dihydroxy- (70%)	106
Ethyl benzyloxyformylacetate	guanidine	alcohol; sodium ethoxide; 20°	2-amino-5-benzyloxy-4-hydroxy- (78%)	106, 107
Ethyl benzyloxyformylacetate	acetamidine	alcohol; sodium ethoxide; 60°; 4 hr.	5-benzyloxy-4-hydroxy-2-methyl (93%)	106
Methyl methoxyformylacetate	thiourea	alcohol; sodium ethoxide; reflux; 5 hr.	4-hydroxy-2-mercapto-5-methoxy- (52%)	108
Ethyl benzyloxyformylacetate	thiourea	alcohol; sodium ethoxide; 20°	5-benzyloxy-4-hydroxy-2-mercapto- (92%)	106
Ethyl *o*-chlorophenoxyformylacetate	guanidine	alcohol; some sodium ethoxide; reflux; 16 hr.	2-amino-5-*o*-chlorophenoxy-4-hydroxy-[a]	109, 110

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Ethyl methoxyformylacetate	guanidine	alcohol; sodium ethoxide; reflux; 16 hr.	2-amino-4-hydroxy-5-methoxy-[b]	109
Ethyl ethoxyformylacetate	guanidine carbonate	alcohol; reflux; 60 hr.	2-amino-4-hydroxy-5-ethoxy-	111
Ethyl formylpropionate	dicyandiamide	alcohol; sodium ethoxide	2-cyanoamino-4-hydroxy-5-methyl-	112
Ethyl β-phenylformylpropionate	guanidine	alcohol; reflux; 12 hr.	2-amino-5-benzyl-4-hydroxy[c]	113
Ethyl tetrahydropyran-2-yloxyformylacetate	acetamidine	alcohol; sodium ethoxide; reflux; 3 hr.	4-hydroxy-2-methyl-5-tetrahydropyran-2′-yloxy- (42%); (XLIII)[d]	107
Ethyl formylacetoacetate	acetylsulphanilylguanidine	alcohol; sodium ethoxide; reflux; 5 hr.	2-acetylsulphanilylamino-4-hydroxy (40%)	114
Ethyl β-cyanoformylpropionate	acetamidine	alcohol; sodium ethoxide; reflux; 5 hr.	5-cyanomethyl-4-hydroxy-2-methyl-	92
Ethyl β-ethoxymethoxymethylpropionate[e]	acetamidine	alcohol; sodium ethoxide; reflux; 21 hr.	4-hydroxy-2,5-dimethyl	115

[a] And sixteen other examples with substituted phenoxy groups and four examples with substituted naphthoxy groups.

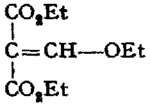
[b] And three other examples with 5-alkoxy groups.

[c] And six other examples with substituted benzyl groups.

[d] And two examples with a 2-amino group.

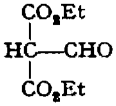
[e] Also from ethyl β-methoxymethylenepropionate in a similar way and yield.

carbonyl-4-hydroxy-2-methylpyrimidine (XLV) or 5-formyl-4,6-dihydroxy-2-methylpyrimidine (XLVI). In fact, only one product (XLV) is formed,[92–94] indicating the aldehyde to be the more reactive group.



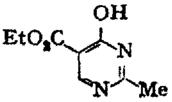
$$\begin{array}{l}\mathrm{CO_2Et}\\ |\\ \mathrm{C{=}CH{-}OEt}\\ |\\ \mathrm{CO_2Et}\end{array}$$

(XLIV)

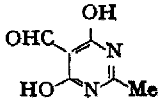


$$\begin{array}{l}\mathrm{CO_2Et}\\ |\\ \mathrm{HC{-}CHO}\\ |\\ \mathrm{CO_2Et}\end{array}$$

(XLIVa)

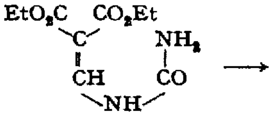


(XLV)

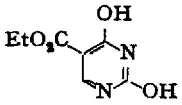


(XLVI)

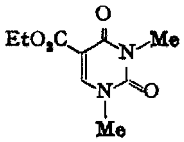
Although it had been early reported[95] that urea did not react with diethyl ethoxymethylenemalonate, Whitehead[96] showed that in ethanolic sodium ethoxide, diethyl ureidomethylenemalonate (XLVII) was formed, and this cyclized on heating in the same medium to 5-ethoxycarbonyl-2,4-dihydroxypyrimidine (5-ethoxycarbonyluracil; XLVIII). *NN′*-Dimethylurea behaved similarly when simply heated with diethyl ethoxymethylenemalonate at *ca.* 120°, and 5-ethoxycarbonyl-1,3-dimethyluracil (5-ethoxycarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine; (XLIX)) was directly isolated.



(XLVII)

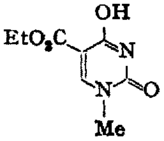


(XLVIII)

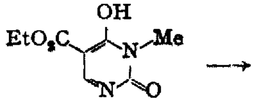


(XLIX)

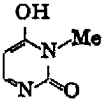
N-Monomethylurea (and its homologues) reacted similarly; the single product could be the 1-methyl or 3-methyl derivative of 5-ethoxycarbonyluracil, (L) or (LI).* The latter would seem more likely and was



(L)



(LI)



(LII)

proven correct[96] by saponification and decarboxylation to 3-methyluracil (LII), which was considered of authentic structure, and in any case was afterwards shown to be so in another connection.[97]

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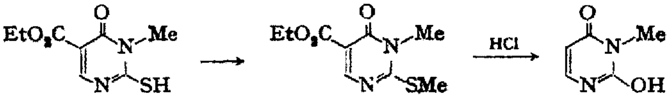
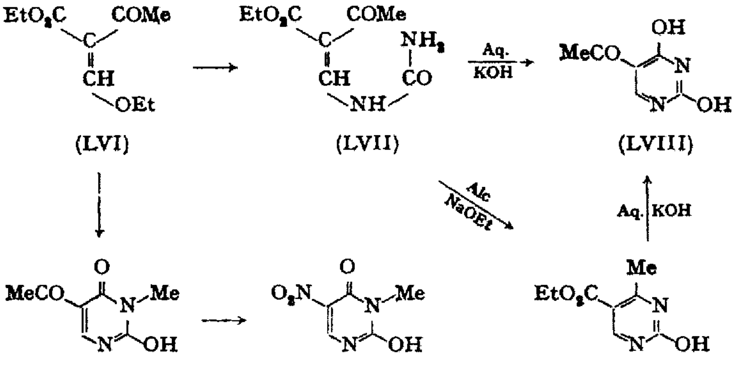
* These and similar formulae could of course be written in alternative tautomeric forms.

Thiourea behaved like urea with diethyl ethoxymethylenemalonate and formed 5-ethoxycarbonyl-4-hydroxy-2-mercaptopyrimidine.[98] *S*-Benzylthiourea similarly formed 2-benzylthio-5-ethoxycarbonyl-4-hydroxypyrimidine,[95,98] while *N*-methylthiourea and its alkyl and aryl homologues gave, for example, 5-ethoxycarbonyl-3-methyl-2-thiouracil[99] (LIII). The position of the methyl group was checked by *S*-methylation to 5-ethoxycarbonyl-3,4-dihydro-3-methyl-2-methylthio-4-oxopyrimidine (LIV) which was saponified, decarboxylated, and hydrolysed by boiling hydrochloric acid to 3-methyluracil (LV).



(LIII) (LIV) (LV)

A similar case is the condensation of ethyl ethoxymethyleneacetoacetate (LVI) with urea[100] to give first the intermediate ethyl ureidomethyleneacetoacetate (LVII). This is said to cyclize through the ester group when dissolved in warm aqueous potassium hydroxide



(LVI) (LVII) (LVIII)

(LX) (LXI) (LIX)

to give 5-acetyl-2,4-dihydroxypyrimidine (LVIII), but through the keto group when dissolved in warm alcoholic sodium ethoxide, giving 5-ethoxycarbonyl-2-hydroxy-4-methylpyrimidine (LIX). Further, the latter gives the 5-acetyl derivative (LVIII) on warming in aqueous potassium hydroxide.[101] Thus, the ethyl ethoxymethyleneacetoacetate has virtually reacted with urea as an aldehydo ester or as an aldehydo ketone according to conditions.

TABLE III. Additional Examples of the Use of Keto Esters in the Principal Synthesis

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Ethyl methylacetoacetate	*S*-ethylthiourea	aq. alkali; 20°; 48 hr.	2-ethylthio-4-hydroxy-5,6-dimethyl-[a]	80, 124
Ethyl ethylacetoacetate	*S*-methylthiourea	aq. alkali (or carbonate) 20°; 48 hr.	5-ethyl-4-hydroxy-6-methyl-2-methylthio-; *ca.* 25% (alk.); 90% (carb.)	80, 124
Ethyl benzoylacetate	*S*-methylthiourea	alkali; 20°; 48 hr.	4-hydroxy-2-methylthio-6-phenyl-	80
2-Ethoxycarbonylcyclohexanone	thiourea	methanol; sodium methoxide; 5½ hr.	5,6-cyclohexeno-4-hydroxy-2-mercapto;[b] *ca.* 65%	151
Ethyl chloroacetoacetate	*S*-methylthiourea	water at pH 10–12; 20°; 24 hr.	5-chloro-4-hydroxy-6-methyl-2-methylthio-; 32%	103
2-Ethoxycarbonylcyclohexanone	*S*-methylthiourea	aq. alkali	5,6-cyclohexeno-4-hydroxy-2-methylthio;[b] *ca.* 15%	151
Diethyl fluoro-oxalacetate	*S*-ethylthiourea	alcohol; sodium ethoxide; reflux; 2 hr.	6-ethoxycarbonyl-2-ethylthio-5-fluoro-4-hydroxy-[c]	104
Diethoxycarbonyl acetone	*S*-ethylthiourea	aq. alkali; 20°; 1 hr.	6-ethoxycarbonylmethyl-2-ethylthio-4-hydroxy- *ca.* 90%	152
Ethyl benzoylacetate	acetamidine	aq. alkali; 20°; 14 days	4-hydroxy-2-methyl-6-phenyl-	126
Ethyl methylacetoacetate	propionamidine	aq. alkali; 20°; 14 days	2-ethyl-4-hydroxy-5,6-dimethyl-[d]	126
Ethyl acetoacetate	phenylacetamidine	aq. alkali; 20°; 14 days	2-benzyl-4-hydroxy-6-methyl-[e]	126
Ethyl benzylacetoacetate	benzamidine	aq. alkali; 20°; "few hours"	5-benzyl-4-hydroxy-6-methyl-2-phenyl-[f]	126
Diethyl oxalacetate	thiourea	alcohol; 20°; 3 hr.	6-ethoxycarbonyl-2-mercapto-4-hydroxy-[g]	153
Ethyl *p*-methoxyphenoxy-acetoacetate	guanidine carbonate	alcohol; reflux; 16 hr.	2-amino-4-hydroxy-5-*p*-methoxyphenoxy-6-methyl-[h]	109
Ethyl benzylacetoacetate	guanidine	alcohol; sodium ethoxide 20°; 12 hr.; reflux; 2 hr.	2-amino-5-benzyl-4-hydroxy-6-methyl-; 65%	154

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Ethyl *m*-methylbenzylacetoacetate	guanidine	alcohol; reflux; 6 hr.	2-amino-4-hydroxy-6-methyl-5-*m*-methylbenzyl-[i]	113
2-Ethoxycarbonylcyclohexanone	guanidine	alcohol; sodium ethoxide; 20°; 12 hr.; reflux; 2 hr.	2-amino-5,6-cyclohexeno-4-hydroxy-;[j] 91%	52, 154
Ethyl propionylacetate	guanidine carbonate	alcohol; reflux; 4 hr.	2-amino-4-ethyl-6-hydroxy-; *ca.* 50%	155
3-Ethoxycarbonyl-1-methyl-4-piperidone	benzamidine	aq. sodium carbonate	4-hydroxy-2-phenyl-5,6-(1,2,3,6-tetrahydro-1-methyl-5:4-pyrido)pyrimidine[k] *ca.* 40%	156
Ethyl ethoxyethylacetoacetate	guanidine carbonate	175°; 2 hr.	2-amino-5-ethoxyethyl-4-hydroxy-6-methyl-;[l] 45%	111
Ethyl acetoacetate	dicyandiamide	alcohol; sodium ethoxide; 100°	2-cyanoamino-4-hydroxy-6-methyl-;[d] 50%	112, 167
Ethyl (α-phenylazo) trifluoroacetoacetate	guanidine	butanol; sodium butoxide; reflux; 15 min.	2-amino-4-hydroxy-5-phenylazo 6-trifluoromethyl-;[c] 80%	158
Ethyl butyrylacetate	thiourea	alcohol; sodium ethoxide; reflux; 6 hr.	4-hydroxy-2-mercapto-6-propyl-[m]	157
Ethyl propionylacetate	thiourea	alcohol; sodium ethoxide; reflux; 6 hr.	6-ethyl-4-hydroxy-2-mercapto-; 78%	157, 159
Ethyl α-ethoxyethylidene cyanoacetate	*N*-butylthiourea	alcohol; sodium ethoxide; 20°; 5 days	1-butyl-5-cyano-1:2-dihydro-6-hydroxy-4-methyl-2-thiopyrimidine-;[n] 46%	99
Ethyl *n*-hexanoylacetate	thiourea	alcohol; sodium ethoxide; reflux; 6 hr.	4-amyl-6-hydroxy-2-mercapto-;[l] 33%	61, 157
Ethyl *n*-heptanoylacetate	thiourea	alcohol; sodium ethoxide; reflux; 6 hr.	6-*n*-hexyl-4-hydroxy-2-mercapto-; 27%	157, 160

(Table continued)

TABLE III *(continued)*

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Ethyl methylacetoacetate	thiourea	alcohol; sodium ethoxide; reflux; 6 hr. (3 hr.)	4-hydroxy-2-mercapto-5:6-dimethyl-;[o] 93%	161, 157 162, 154
Cyclopropyl ethoxycarbonylmethyl ketone	thiourea	alcohol; sodium ethoxide; reflux; 16 hr.	6-cyclopropyl-4-hydroxy-2-mercapto-;[p] 60%	163
Butyl α,γ-dimethoxyacetoacetate	thiourea	methanol; sodium methoxide; reflux; 6 hr.	4-hydroxy-2-mercapto-5-methoxy-6-methoxymethyl-;[q] 68%	164
Ethyl acetoacetate	1,2-ethylene-*bis*-*S*-thiourea	aqueous sodium carbonate; 20°; 4 days	1,2-*bis*-(4-hydroxy-6-methyl-2-pyrimidinylthio) ethane; 34%	124
Ethoxythiocarbonylpropan-2-thione	thiourea	alcohol; sodium ethoxide; reflux; 30 min.	6-methyl-2,4-dimercapto	169
Ethyl acetoacetate	*O*-allylurea	20°; some hours	2-allyloxy-4-hydroxy-6-methyl-[d]; 90%	171
Diethyl ethoxycarbonylacetylphosphonate	urea	acetic acid; HCl (dry); 5°; 12 hr.	2,4-dihydroxypyrimidinyl-6-phosphonic acid-; *ca.* 20%	173
Ethyl trifluoroacetoacetate	urea	butanol; sodium butoxide; reflux; 3 hr.	2,4-dihydroxy-6-trifluoromethyl-;[rs] 3%	158
Ethyl γ,γ-diethoxyacetoacetate	thiourea	ethanol; sodium ethoxide; reflux; 7 hr.	4-diethoxymethyl-6-hydroxy-2-mercapto-;[t] 80%	174, 170
Ethyl α-*p*-chlorophenyl-α-propionylacetate	dichloroacetamidine	ethanol; reflux; 3 hr.	5-*p*-chlorophenyl-2-dichloromethyl-4-ethyl-6-hydroxy-	172
Ethyl acetoacetate	nitroguanidine	ethanol; sodium ethoxide; reflux; 1.5 hr.	4-hydroxy-6-methyl-2-nitroamino-; 53%	176
α-Acetyl-γ-butyrolactone	urea	ethanol; HCl; reflux; 2 hr.; KOH (to cyclise)	2,4-dihydroxy-5-hydroxymethyl-6-methyl-; 45%	178

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Ethyl oxalacetate	*N*-methylurea	crude ester hydrolysed with NaOH	6-carboxy-3-methyluracil;[v,u]	180
2-Ethoxycarbonylcyclopentanone	urea	ethanol; sodium ethoxide; 100°; 8 hr.	5,6-cyclopenteno-2,4-dihydroxy-;[c] *ca.* 25%	181

[a] Corresponding 5-ethyl derivative.[65]

[b] And corresponding cyclopento derivative. Perhaps better named as 5,6-tetra (and tri)methylene derivatives of the pyrimidines.

[c] And another example.

[d] And two similar examples.

[e] And three analogues.

[f] And four other examples.

[g] Unstable: immediately hydrolysed by alkali to carboxy analogue.

[h] Also five phenoxy and three naphthoxy analogues.

[i] And seventeen analogues.

[j] And the cyclopenteno derivative (62%);[184] and other 2-amino and 2-aryl derivatives.[53]

[k] And similar condensations with benzamidine, urea, and others.

[l] And six analogues.

[m] And twenty-six other examples.

[n] See Chapter II. Sect. 8.

[o] Corresponding 5-ethyl derivative.[157,165]

[p] And eleven similar examples.

[q] And six other alkoxy derivatives.

[r] Because of the poor yield is better made indirectly from the 2-thio analogue.[166]

[s] Also the 2-amino analogue in 72% yield.

[t] This acetal is converted with acid into the aldehyde, 4-formyl-6-hydroxy-2-mercaptopyrimidine.[174]

[u] Thiourea gives the corresponding 2-mercapto derivative.

[v] Structure confirmed.[168]

A potentially even more complicated reaction is that of ethyl ethoxymethyleneacetoacetate (LVI) with *N*-methylurea. The former could react as an aldehydo ketone, an aldehydo ester, or a keto ester, and in each case methyl could appear on N_1 or N_3. In practice only one product, 5-acetyl-3-methyluracil (LX), was isolated.[102] It was identified by oxidative nitration to 3-methyl-5-nitrouracil (LXI). Although this result must be slightly suspect until confirmed, it would seem that the intermediate reacts as an aldehydo ester in preference to an aldehydo ketone which might appear to be more likely. *N*-alkyl- and arylthioureas reacted similarly[99] to give for example 5-acetyl-3-ethyl-2-thiouracil, but the structures of the pyrimidines seem to rest only on analogy with the above. The reactions of ethoxymethylenecyanoacetate as an aldehydo ester are treated in Chapter II, Sect. 8.

6. Use of β-Keto Esters

As might be expected, β-keto esters behave very like β-aldehydo esters when they participate in the Common Synthesis.

A. Keto Esters with Thioureas

Ethyl acetoacetate condenses with thiourea under a variety of conditions including mere admixture,[116] solution in alcoholic hydrogen chloride,[117] in alcoholic sodium ethoxide,[118] in methanolic sodium methoxide,[119–121] in aqueous alkali,[122] or in aqueous potassium carbonate.[122] The last mentioned is probably the least troublesome and gives a 95% yield of 4-hydroxy-2-mercapto-6-methylpyrimidine (methylthiouracil).* Because of their anti-thyrotoxic activity many 6-alkyl, 5,6-dialkyl, and related thiouracils have been made. Examples are given in Table III. An interesting variation, although of little practical value, is the use of imino or methylimino derivatives corresponding to acetoacetate. Thus ethyl β-iminobutyrate gives with thiourea, 4-hydroxy-2-mercapto-6-methylpyrimidine, and ammonia is lost.[123] When *S*-methylthiourea replaces thiourea, the condensation with acetoacetic ester takes place at room temperature during 48 hours in aqueous alkali[80] (or better in sodium carbonate[124]) giving 4-hydroxy-6-methyl-2-methylthiopyrimidine. Similar reactions are noted in Table III. Some

---

* When the reaction is carried out in fuming sulphuric acid 2-amino-4-methyl-6-oxo-1,3-thiazine is formed.[84]

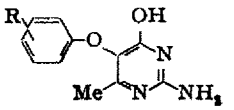
interesting observations on the formation of thiouracils have been reported.[125]

B. Keto Esters with Amidines

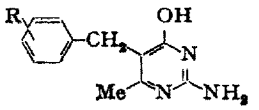
Ethyl acetoacetate reacts with, for example, acetamidine or 2-methylpropionamidine in the presence of aqueous alkali to give respectively 4-hydroxy-2,6-dimethylpyrimidine and 4-hydroxy-2-isopropyl-6-methylpyrimidine.[126, 127] Phenylacetamidine, benzamidine, and other amidines react similarly (see Table III). Formamidine gives an anomalous product,[128] but with ethyl methylacetoacetate it gives the expected 4-hydroxy-5,6-dimethylpyrimidine. Diethyl ethylidenemalonate [$CH_3CH{:}C(CO_2Et)_2$] reacts with acetamidine rather similarly giving 5-ethoxycarbonyl-4,5-dihydro-6-hydroxy-2,4-dimethylpyrimidine.[129] This is a Principal Synthesis at a lower oxidation state (Ch. XII, Sect. 1.A).

C. Keto Esters with Guanidines

Guanidine reacts readily with β-keto esters giving 6-substituted isocytosines. Thus ethyl acetoacetate and guanidine, heated together without solvent,[26, 130] or in ethanol[132, 133] yield 2-amino-4-hydroxy-6-methylpyrimidine. Similarly *NN*-dimethylguanidine (alcohol; sodium ethoxide) leads to 2-dimethylamino-4-hydroxy-6-methylpyrimidine.[134] As with the aldehydo esters, ethyl acetoacetate carrying substituted phenoxy, naphthoxy, and benzyl groups has been condensed with guanidine to obtain 2-amino-4-hydroxy-6-methylpyrimidines with the appropriate group in the 5-position (*e.g.* LXII and LXIII). Several other examples appear in Table III.



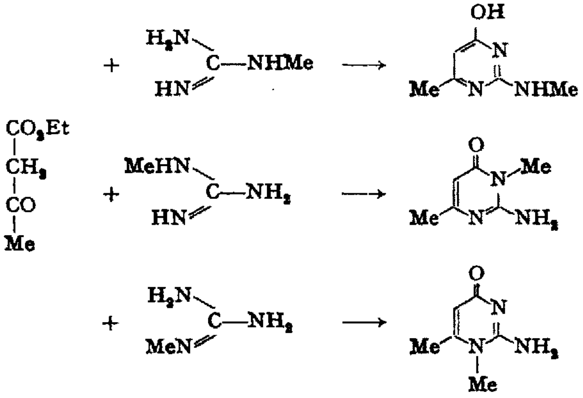
(LXII)



(LXIII)

An interesting problem arises with monomethylguanidine. It could give with ethylacetoacetate three products as shown in (LXIV), (LXV), and (LXVI). In practice only two products, 4-hydroxy-6-methyl-2-methylaminopyrimidine (LXIV) and 2-amino-1,4-dihydro-

1,6-dimethyl-4-oxopyrimidine (LXVI) were isolated.[69] Because yields were not given, it is not impossible that the third product was simply missed. Allylguanidine gives analogous products.[69]

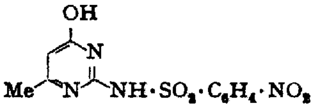


(LXIV)

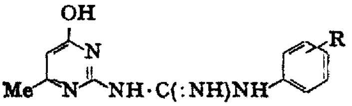
(LXV)

(LXVI)

Occasionally, complicated guanidine derivatives have been used in the Principal Synthesis: thus *p*-nitro-, *p*-amino-, and *p*-acetamidobenzenesulphonylguanidine have been condensed[73] with keto esters giving for example 4-hydroxy-6-methyl-2-*p*-nitrobenzenesulphonamidopyrimidine (LXVII). Many substituted phenyldiguanides have been similarly used[135] to produce in aqueous alkali at room temperature such compounds as 4-hydroxy-6-methyl-2-phenylguanidinopyrimidine (LXVIII; R=H).



(LXVII)

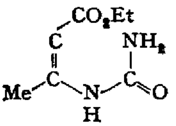


(LXVIII)

D. Keto Esters with Urea and Derivatives

The condensation of urea with ethyl acetoacetate takes place more obviously in two stages than do most Common Syntheses. The best method,[136] following essentially early procedures,[137–139] effects condensation to ethyl *β*-ureidocrotonic acid (LXIX) in ethanol containing hydrochloric acid, and by solution in hot alkali and reprecipitation with acid cyclizes it to 2,4-dihydroxy-6-methylpyrimidine (LXX) in 75%

yield. Dicarboxyacetone (LXXI) (made *in situ* from citric acid) reacts with urea in fuming sulphuric acid[140] giving 4-carboxymethyl-2,6-dihydroxypyrimidine, but ethyl oxalacetate (LXXII), although it gives the expected 4-carboxy-2,6-dihydroxypyrimidine,[141–143] has been shown to proceed there through an isomeric hydantoin[144] (Ch. III, Sect. 5.E(1)), which had been mistaken at times for the pyrimidine. Similar doubts have been cast on the "ethyl ester of 3-phenylorotic acid" and related compounds[145] which are probably hydantoins.[146] The preparations cannot therefore be classified strictly as Common Syntheses. Diketene (LXXIII) (which can easily be hydrolysed to ethyl acetoacetate) reacts with urea directly in inert solvents, giving 2,4-dihydroxy-6-methylpyrimidine[147,148] (LXX). With *sym*-disubstituted ureas it gives *e.g.* 1,3-diallyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine.[148]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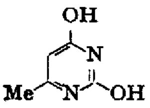
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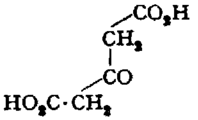
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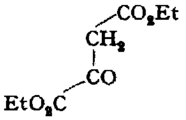
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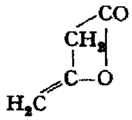

(LXXIII)

O-Methyl- and *O*-ethyl-urea condense with ethyl acetoacetate to yield 4-hydroxy-2-methoxy-6-methylpyrimidine and 2-ethoxy-4-hydroxy-6-methylpyrimidine respectively.[62,149] Ethyl ethylacetoacetate and *O*-methylurea give 5-ethyl-4-hydroxy-2-methoxy-6-methylpyrimidine.[149]

N-Methyl-, and *N*-cyclohexyl-ureas condense with ethyl acetoacetate in two stages as does urea.[150] *N*-Phenylurea, however, reacts abnormally.[150]

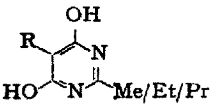
7. Use of β-Diesters (Malonic Esters)

This section contains among others all the barbituric acid derivatives, of which many hundreds of examples are recorded in the literature. The following treatment gives representative examples of a simple nature.

A. Malonic Esters and Amidines

Esters of malonic acid react readily with amidines giving 4,6-dihydroxypyrimidines. Even formamidine, which is often difficult, reacts at room temperature with diethyl malonate to give 80% of 4,6-dihydroxypyrimidine.[128] Acetamidine,[175,177,179,182,183] propionamidine,[175,184] and butyramidine[185] similarly condense with diethyl malonate, and with a variety of its α-alkyl derivatives, to give 2-methyl-(ethyl- or propyl-)-5-alkyl-4,6-dihydroxypyrimidines (LXXIV). Examples appear in Table IV. Carbamoyl acetamidine has also been used to give 2-carbamoylmethyl-4,6-dihydroxypyrimidine[186] (LXXV). Diethyl ethylidenemalonate reacts with acetamidine to give 5-ethoxycarbonyl-4,5-dihydro-6-hydroxy-2,4-dimethylpyrimidine.[129]

Benzamide has been condensed not only with malonic ester[187] and its monoalkyl derivatives,[177] but also with $\alpha\alpha$-dialkyl derivatives.[177] Thus benzamide and diethyl diethylmalonate in alcoholic sodium ethoxide yield 5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxo-2-phenylpyrimidine (LXXVI) which is generally written in the 4,6-dioxo-tautomeric form. In such a compound, however, valency requires but one of the two hydroxy groups to be fixed in the oxo-form. An interesting variant of this compound was prepared from ethyl trimethylenemalonate and benzamidine which gave 4,5-dihydro-6-hydroxy-4-oxo-2-phenyl-5,5-trimethylenepyrimidine[188] (LXXVII) in 60% yield.



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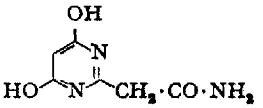

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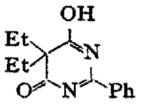

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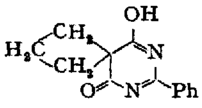

(LXXVII)

B. Malonic Esters with Urea and its Alkyl Derivatives

Malonic acid was first condensed with urea to give barbituric acid (LXXVIII) by Grimaux[189] in 1878. He used phosphoryl chloride as condensing agent as did later Conrad and Guthzeit[190] and acetic anhydride has also been used.[191,192] The best synthesis of barbituric acid, however, is from diethyl malonate and urea in the presence of sodium ethoxide. Several procedures have been recorded[193–198] culminating in a precise method,[199] which uses molecular proportions of the reactants in ethanol under reflux for 7 hours and gives up to 80% yield. *NN'*-

Dimethylurea has been condensed with diethyl malonate in the presence of sodium ethoxide,[202, 204] with malonyl chloride in phosphoryl chloride,[201] and best with malonic acid in the acetic acid–acetic anhydride mixture[192, 200] to give 1,3-dimethylbarbituric acid (LXXIX). An appreciable by-product in the last case has been shown to be almost certainly 5-ethoxycarbonylacetyl-1,3-dimethylbarbituric acid, and the conditions of reaction have been amended in order to largely avoid its formation.[203] *O*-Allylurea readily condenses with dimethyl malonate to yield 2-allyloxy-4,6-dihydroxypyrimidine.[171] Table IV shows other examples of the use of alkylureas.

The condensation of the *C*:*C*-dialkyl malonic esters with urea takes place less readily, but has been extensively used in making the barbiturate drugs. Fischer and Dilthey[206] first reported ten such reactions in 1904 as well as several with alkyl ureas. They found that it was necessary to heat the reactants at 105–108° in alcohol containing sodium ethoxide for about 5 hours, with resulting yields of about 70 %. No real advance on this procedure seems to have been found to the present day, although interesting variants have been sometimes proposed. One such is the use of sodio-urea with diethyl ethylmalonate in acetone at room temperature to give 5-ethylbarbituric acid in 80 % yield.[205]

Much of the huge literature of the barbiturate drugs consists of patents, and no attempt will be made to summarize it here.

Although several items must anticipate reactions to be described later, mention must be made in this section of the historically important 5,5-diethylbarbituric acid[206] (LXXX; barbitone; barbital; Veronal) which is the parent compound of the drug series, and of the following barbituric acid derivatives in current use.

5-Ethyl-5-phenyl- (phenobarbitone; phenobarbital; Luminal).[206]

5-Ethyl-5-1′-methylbutyl- (pentobarbitone; pentobarbital; Nembutal).[207]

5-Ethyl-5-isoamyl- (amylobarbitone; amobarbital; Amytal).[208]

5-Allyl-5-1′-methylbutyl- (quinalbarbitone; secobarbital; Seconal). This barbiturate was first prepared directly but in an impure state[209] due to partial rearrangement of the intermediate to diethyl α-allyl-α-1-ethylpropylmalonate.[210] Later this was avoided by preparing it[211] and related barbiturates[212] by 5-allylation of 5-monoalkylbarbituric acids with allyl bromide and sodium hydroxide.

5-Cyclohex-1′-enyl-1,5-dimethyl- (hexobarbitone; hexobarbital; Evipal; Evipan). This is best made by condensing ethyl α-cyclohex-1-enyl-α-cyanopropionate with *N*-methylurea and submitting the resulting 4-aminopyrimidine derivative[*] to acid hydrolysis.[213]

5-Cyclohex-1′-enyl-5-ethyl- (cyclobarbitone; Phanodorn etc.). Prepared as above.[214]

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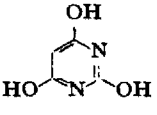
[*] The general route to barbituric acid derivatives by way of hydrolysis of a 4-amino derivative[220,221] has now been widely used.

5-Ethyl-5-1′-methylbut-1′-enyl- (vinbarbital; vinbarbitone; Delvinal). This was best made by condensing ethyl α-ethyl-α-1-methylbut-1-enylcyanoacetate with guanidine and then hydrolysing the 2,4-diaminobarbiturate with acid.[215, 216]

5-Ethyl-5-1′-methylbutyl-2-thio- (thiopentone; Pentothal). Besides the direct synthesis,[217, 218] this was made from the corresponding 4-amino derivative[219] and by thiation of 5-ethyl-5-1′-methylbutylbarbituric acid with phosphorus pentasulphide.[222] The methods have been compared.[223]

5-Allyl-5-cyclohex-2′-enyl-2-thio- (thialbarbitone; Kemithal).[224]

The pharmacology of the barbiturates has been briefly reviewed,[225, 226] and collections of references to their chemistry are given in Meyer and Jacobson's "Lehrbuch"[228] and in "Thorpe's Dictionary".[229] A paper[227] on short-acting thiobarbiturates related to thiopentone includes 5-s-butyl-5-ethyl-1-methyl-2-thiobarbituric acid, a potential addition to the clinically useful members of this class.



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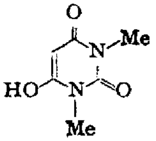

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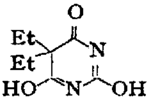

(LXXX)

C. Malonic Esters with Thiourea and Derivatives

Although it is clear that thiourea condenses with diethylmalonate to give 4,6-dihydroxy-2-mercaptopyrimidine (thiobarbituric acid (LXXXI)), the literature of this pyrimidine and its derivatives is rather unsatisfactory. Thiobarbituric acid has been made from diethyl sodiomalonate and thiourea[193, 230] (no yield given), but a later more normal method was developed using the ester, thiourea and sodium ethoxide in ethanol: 80° for 10 hours gives 30 % yield; 105° for 15 hours gives a 45 % yield.[231] A number of 5-mono- and di-alkyl-thiobarbituric acids have been made. The conditions used are 80° for 5–8 hours and the yields indicate that the alkylated malonic esters seem to react rather more readily with thiourea than does the parent ester. Table IV contains further examples. Although Johnson and Hill[232] suspected anomalous open chain products from two such reactions aimed at 5,5-diallyl-, and 5-allyl-5-benzyl- 2-thiobarbituric acids (LXXXII) these products were later shown[233] to be in fact the required barbiturates.*

Substituted thioureas have scarcely been used in these reactions. However, *NN′*-diphenylthiourea reacted with malonicacidinphosphoryl

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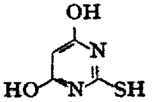
* The two most important thiobarbiturates have been mentioned in Ch. II, Sect. B.

chloride to give 1,3-diphenyl-2-thiobarbituric acid[234] (1,2,3,4-tetrahydro-6-hydroxy-4-oxo-1,3-diphenyl-2-thiopyrimidine) (LXXXIII). It has been reported that *S*-alkylthioureas react normally with malonic esters,[235] but this was later disputed.[236] An authentic example is, however, the condensation under normal conditions of diethyl benzyloxymalonate with *S*-ethylthiourea to give 5-benzyloxy-2-ethylthio-4,6-dihydroxypyrimidine (LXXXIV) in 51 % yield.[237]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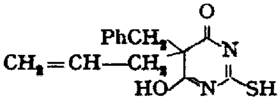
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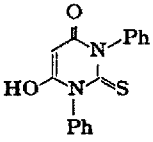
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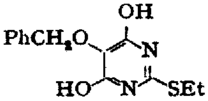

(LXXXIV)

D. Malonic Esters with Guanidine and its Alkyl Derivatives

Guanidine reacts with diethyl malonate under a variety of conditions to give 2-amino-4,6-dihydroxypyrimidine.[230, 238, 239] The best conditions seem to be refluxing for only ½ hour in alcoholic sodium ethoxide (54 %).[240] Similarly 2-amino-5-ethyl-4,6-dihydroxypyrimidine (LXXXV) has been made from diethyl ethylmalonate and guanidine carbonate,[111] and the corresponding 5,5-diethyl derivative from diethyl diethylmalonate,[206] from diethylmalonic acid (in the presence of fuming sulphuric acid etc.),[241] or diethylmalonyl chloride.[242]

Substituted guanidines have been quite widely used with malonic esters. Thus *NN*-dimethylguanidine with diethyl malonate in methanolic sodium methoxide gives 4,6-dihydroxy-2-dimethylaminopyrimidine in good yield.[243] When methylguanidine is used, two products [4,6-dihydroxy-2-methylaminopyrimidine (LXXXVI); 2-amino-1,6 (1,4)-dihydro-4(6)-hydroxy-1-methyl-6(4)-oxopyrimidine, (LXXXVII)] might be expected. In fact, the former (90 %) predominates almost to the exclusion of the latter.[69, 244] *NN'*-Diphenylguanidine and malonyl chloride in ether is said to give 1,2,3,4-tetrahydro-6-hydroxy-2-imino-4-oxo-1,3-diphenylpyrimidine[245] (LXXXVIII) but as no structural evidence was presented, the product could equally well have been 1,6-dihydro-4-hydroxy-6-oxo-1-phenyl-2-phenylaminopyrimidine (LXXXIX). When diguanide is boiled with diethyl malonate in alcohol the product is 2-guanidino-4,6-dihydroxypyrimidine,[246] (XC) and when dicyanodiamide (cyanoguanidine) is used, 2-cyanoamino-4,6-dihydroxy-

TABLE IV. Additional Examples of the Use of Malonic Esters in the Principal Synthesis

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Diethyl malonate	α-furylamidine	alcohol; sodium ethoxide; reflux; 2 hr.	2-α-furyl-4,6-dihydroxy-; 42%	128
Diethyl butylmalonate	acetamidine	alcohol; sodium ethoxide; 20°; 48 hr.	5-butyl-4,6-dihydroxy-2-methyl-;[a] 92%	179
Diethyl propylmalonate	butyramidine	probably alcohol; sodium ethoxide; 20°; 48 hr.	4,6-dihydroxy-2,5-dipropyl-;[b] 72%	185
Diethyl benzyloxymalonate	acetamidine	alcohol; sodium ethoxide; 70°; 6 hr.	5-benzyloxy-4,6-dihydroxy-2-methyl-; 54%	237
Diethyl benzylmalonate	benzamidine	alcohol; sodium ethoxide; 40°; 12 hr.	5-benzyl-4:6-dihydroxy-2-phenyl-;[c] 100%!	177
Malonic acid	*N*-methylurea	acetic acid/anhydride; 90°; 6 hr.	1-methylbarbituric acid;[d] 70%	192
Malonyl chloride	*NN'*-diethylurea	ether; reflux; 1 hr.	1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2:4-dioxo-; 67%	251
Malonic acid	*N*-phenylurea	chloroform; phosphoryl chloride; reflux; 6 hr.	1-phenylbarbituric acid	252
Malonyl chloride[e]	*NN'*-diphenylurea	chloroform; reflux; 4 hr.	1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenyl-; *ca.* 80%	253
Dimethyl malonic acid	urea	phosphoryl chloride; 100°; 2 hr.	5,5-dimethylbarbituric acid	254
Diethyl butylmalonate	sodio urea	acetone; 20°; 12 hr.	5-butyl-2,4,6-trihydroxy-;[f] 79%	205
Diethyl amylethylmalonate	urea	liquid ammonia; KOH; 20°; 2 hr.	5-amyl-5-ethylbarbituric acid[g]	255
Diethyl diethylmalonate	urea	alcohol; sodium ethoxide; 105–108°; 5 hr.	5,5-diethylbarbituric acid[g]; (LXXX) 70%	206, 198
Dimethyl malonate	*O*-cyclohexylurea	20°; some hours	2-cyclohexyloxy-4,6-dihydroxy-; 70%	171

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Diethyl methylmalonate	urea	alcohol; sodium ethoxide; 105–108°; 5 hr.	5-methyl-2,4,6-trihydroxy;[h] 37%	206
Diethyl diethylmalonate	*N*-methylurea	alcohol; sodium ethoxide; 105–108°; 5 hr.	5,5-diethyl-1-methylbarbituric acid[f]	206
Diethyl trimethylenemalonate	urea	alcohol; sodium ethoxide; 105–108°; 5 hr.	5,5-trimethylenebarbituric acid; 71%	188
Diethyl trimethylenemalonate	*N*-methylurea	alcohol; sodium ethoxide; 105–108°; 4 hr.	1-methyl-5,5-trimethylene-barbituric acid;[i] 31%	188
Diethyl methylmalonate	thiourea	alcohol; sodium ethoxide; reflux; 5 hr.	4,6-dihydroxy-2-mercapto-5-methyl;[j] *ca.* 50%	64
Diethyl dimethylmalonate	thiourea	alcohol; sodium ethoxide; reflux; 6 hr.	5,5-dimethyl-2-thiobarbituric acid;[k] 56%	256
Diethyl isopropylmalonate	thiourea	alcohol; sodium ethoxide; reflux; 7 hr.	4,6-dihydroxy-5-isopropyl-2-mercapto	236
Diethyl diethylmalonate	thiourea	alcohol; sodium ethoxide; 105°; 4 hr.	5,5-diethyl-2-thiobarbituric acid; 30%	206
Diethyl ethyl-(1-methylbutyl)-malonate	thiourea	alcohol; sodium ethoxide reflux (or 100–120°); 10 hr.	5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid[l]	233
Diethyl ethylpropylmalonate	thiourea	alcohol; sodium ethoxide; reflux; 7 hr.	5-ethyl-5-propyl-2-thio-barbituric acid	257
Diethyl nitrosomalonate	thiourea	alcohol; sodium ethoxide; reflux; 3 hr.	4,6-dihydroxy-2-mercapto-5-nitroso-; < 10%	258
Diethyl ethoxymalonate	guanidine carbonate	alcohol; reflux; 60 hr.	2-amino-5-ethoxy-4,6-dihydroxy-; 60%	111
Diethyl trimethylenemalonate	guanidine carbonate	alcohol; sodium ethoxide; 105°; 4 hr.	2-amino-4,5-dihydro-6-hydroxy-4-oxo-5,5-trimethylene-; 90%	188

(Table continued)

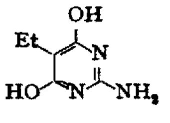
TABLE IV *(continued)*

Three-carbon fragment	One-carbon fragment	Solvent and conditions	Pyrimidine and yield	References
Diethyl malonate	acetylsulphanilylguanidine	alcohol; sodium ethoxide; reflux; 5 hr.	2-acetylsulphanilylamino-4,6-dihydroxy-; 64%	114
Diethyl benzyloxymalonate	guanidine	alcohol; sodium ethoxide; 20°; 6 hr.	2-amino-5-benzyloxy-4,6-dihydroxy-; 83%	237
Dimethyl tetrahydropyranyloxymalonate	guanidine	alcohol; sodium ethoxide; reflux; 4 hr.	2-amino-4,6-dihydroxy-5-tetrahydropyran-2′-yloxy-; 71%	107
Dimethyl dimethylmalonate	phenylguanidine	alcohol; sodium methoxide;	4,5-dihydro-6-hydroxy-5,5-dimethyl-4-oxo-2-phenylamino-; (probably)	259
Diethylmalonyl chloride	phenylguanidine	carbon tetrachloride; 100°; 4 hr.	4,5-dihydro-6-hydroxy-5,5-diethyl-4-oxo-2-phenylamino-; (probably)	260
Diethyl nitrosomalonate	guanidine	alcohol; sodium ethoxide; reflux; 1 hr.	2-amino-4,6-dihydroxy-5-nitrosopyrimidine	261

[a] And eight similar 2-methyl derivatives.
[b] And six similar 2-propyl derivatives.
[c] And twenty similar derivatives with one or two alkyl groups in 5-position.
[d] Also 1-ethyl- and 1,3-diethyl-analogues.
[e] Also used malonic acid and phosphoryl chloride; yield *ca.* 60%.
[f] And two homologues.
[g] And nine analogues.
[h] And two other 5-alkyl derivatives.
[i] And *N*-ethyl-, phenyl-, and benzyl- derivatives.
[j] And 5-ethyl- derivative (40%).
[k] And 5-ethyl- (44%) and 5,5-dipropyl- (30%) derivatives.
[l] And seventeen other homologues. No yields given.

pyrimidine (XCI) results.[167] From diethyl diethylmalonate, the corresponding 2-cyanoamino-5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine is obtained.[247, 249] *N*-Alkyl-*N'*-cyanoguanidine has also been used in such syntheses.[248]

The only example of a 4-mercaptopyrimidine made by the Principal Synthesis is furnished by the condensation of ethyl methoxycarbonyldithioacetate ($MeO_2C \cdot CH_2 \cdot CS_2Et$) with guanidine. 2-Amino-4-hydroxy-6-mercaptopyrimidine is formed in 40% yield.[250]



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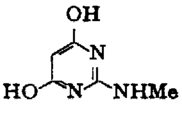

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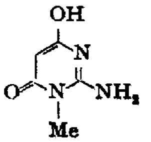

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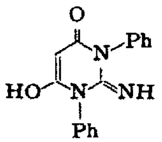

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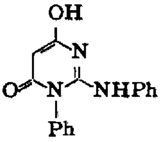

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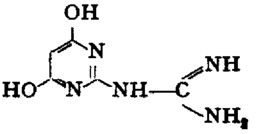

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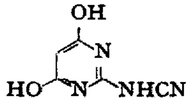


(XCI)

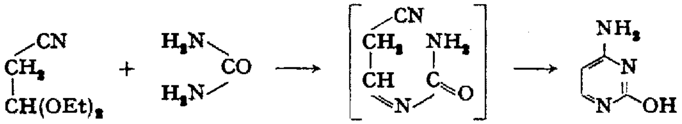
8. Use of β-Aldehydo Nitriles

When one (or both) of the terminal groups in the three-carbon fragment used in a Principal Synthesis is a cyano group, an amino group results at position-4 and/or -6 in the pyrimidine. An aldehydo nitrile is the simplest case of such a fragment.

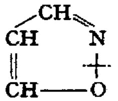
A. Aldehydo Nitriles with Ureas

The use of an aldehydo nitrile is typified by the condensation of cyanoacetaldehyde (as its diethylacetal, "cyanoacetal"; (XCII)) with urea to give 4-amino-2-hydroxypyrimidine (cytosine; (XCIV)).[262] The reaction was not ready and refluxing in butanol containing sodium butoxide was required to form the intermediate (XCIII), which was subsequently ring closed by solution in hot dilute sulphuric acid. This route to cytosine (56%) was used to introduce ^{15}N atoms into the ring.

Use was made of the following sequence of reactions to produce cytosine by a similar elegant route.[263] Malondialdehyde diacetal (now commercially available) with hydroxylamine gave isoxazole (XCV; 70%), and ethylation and fission of this yielded β-ethoxyacrylonitrile (ethoxymethyleneacetonitrile; XCVI) and cyanoacetal (XCII), which for purposes of synthesis both behave as cyanoacetaldehyde. Condensation with urea as above gave cytosine.



(XCII) (XCIII) (XCIV)

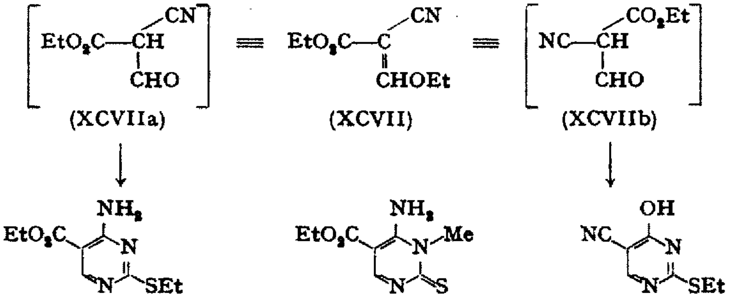


(XCV)

(XCVI)

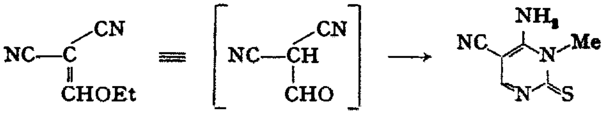
B. Aldehydo Nitriles with Thioureas

Ethyl ethoxymethylenecyanoacetate (XCVII) has been used as an aldehydo nitrile as it is virtually ethyl formylcyanoacetate (XCVIIa). Of course, it can also function as an aldehydo ester (XCVIIb), or perhaps as an ester nitrile. When condensed with *S*-ethylthiourea[264, 265] in cold methanol it gave 14% of 4-amino-5-ethoxycarbonyl-2-ethylthio-



(XCVIIa) (XCVII) (XCVIIb)

(XCVIII) (C) (XCIX)



(CI) (CII)

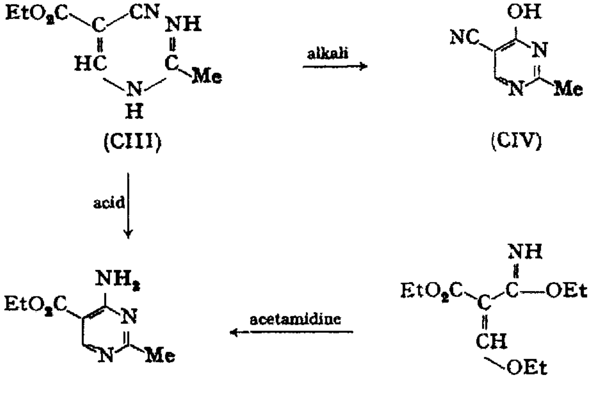
pyrimidine (XCVIII) and mainly 5-cyano-2-ethylthio-4-hydroxypyrimidine (XCIX). When thiourea was used, the ratios were reversed[266, 267, 269] with 4-amino-5-ethoxycarbonyl-2-mercaptopyrimidine (54–80 %) predominating over 5-cyano-4-hydroxy-2-mercaptopyrimidine (14 %).[157] A previous statement[268] that no 5-cyano derivative was formed is in error. A variety of *N*-alkyl- and *N*-aryl-thioureas have been used to give 4-amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-thiopyrimidine (C) and its homologues in good yield.[99] No other isomers seem to have been formed. These same thioureas react with ethoxymethylenemalononitrile (CI) to give 4-amino-5-cyano-2,3-dihydro-3-methyl-2-thiopyrimidine (CII) and homologues.[99] Similarly (CI) with thiourea gives 4-amino-5-cyano-2-mercaptopyrimidine and with *S*-ethylthiourea gives 4-amino-5-cyano-2-ethylthiopyrimidine.[270]

C. Aldehydo Nitriles with Amidines

With acetamidine, ethyl ethoxymethylenecyanoacetate reacted under alkaline conditions only as an aldehydo ester by forming 5-cyano-4-hydroxy-2-methylpyrimidine alone.[93] However, it has been shown[272] that the conditions of ring closure of the intermediate ethyl amidinomethylenecyanoacetate (CIII) is the deciding factor in this case: in acid it gives 4-amino-5-ethoxycarbonyl-2-methylpyrimidine (CV); in alkali the 5-cyano-4-hydroxy-2-methylpyrimidine (CIV); in any case prior conversion of the cyano group to its imino ether (CVI) causes cyclization to the amino pyrimidine. Another interesting acetamidine condensation is that with *α*-acetoxymethylene-*β*-ethoxypropionitrile [$EtOCH_2C(CN):CHO_2CMe$] to give 4-amino-5-ethoxymethyl-2-methylpyrimidine.[273]

Ethoxy methylenemalononitrile [$Et.O.CH{=}C(CN)_2$] reacts as an aldehydo nitrile with acetamidine and benzamidine[129, 175, 270, 271, 275] (or the corresponding imino ethers in the presence of ammonia[276, 277]) and gives respectively 4-amino-5-cyano-2-methylpyrimidine and 4-amino-5-cyano-2-phenylpyrimidine. Aminomethylenemalononitrile [$H_2NCH:C(CN)_2$] also ostensibly behaves as an aldehydo nitrile and with formamidine gives 4-amino-5-cyanopyrimidine (Sect. 10 and Ch. III, Sect. 3.A).

The interesting and rather complicated behaviour of *β*-ethoxy-*α*-methoxymethyleneproprionitrile ($EtOCH_2C(CN):CHOMe$) and *β*-ethoxy-*α*-ethoxymethoxymethylpropionitrile ($EtOCH_2CH(CN)CH(OMe)OEt$) as aldehydo nitriles, (as well as the corresponding esters as aldehydo esters), with acetamidine has been investigated[278-282] by Takamizawa and colleagues and summarized in English,[283] with bibliography and suggested mechanisms. The above nitriles give *inter alia* 4-amino-5-ethoxymethyl-2-methylpyrimidine, and the reactions have been used to synthesize the intermediate for vitamin B_1, 4-amino-5-aminomethyl-2-methylpyrimidine.[286] Similarly, α-ethoxymethoxymethylpropionitrile yields with acetamidine, 4-amino-2,5-dimethylpyrimidine.[284]



(CIII) (CIV) (CV) (CVI)

D. The Whitehead Synthesis of Cytosine Derivatives

The condensation of urea with ethyl ethoxymethylenecyanoacetate and related aldehydo nitriles has been widely explored in particular by C. W. Whitehead. He has carried out these Common Syntheses in such an uncommon and ingenious way that the name "Whitehead Synthesis" is proposed. As pioneered by him[287,288] and extended elsewhere[289,290] the synthesis leads to cytosine bearing 3-alkyl or 3-aryl and 5-cyano, -carboxy, -ethoxycarbonyl, -carbamoyl, or -nitro groups [CXII; R = alkyl or aryl; R′ = —CN, —CO_2H, —CO_2Et, —COX (X = NH_2, NHR, NR_2), or —NO_2]. Most of these compounds are unavailable by other means. The crux of the reaction is the formation of the ureidomethylene compound (CXI) directly from a threefold mixture of nitrile (CVII), ethyl orthoformate (CVIII), and *N*-alkyl or -aryl urea (CX).* The ureido compound is then cyclized generally

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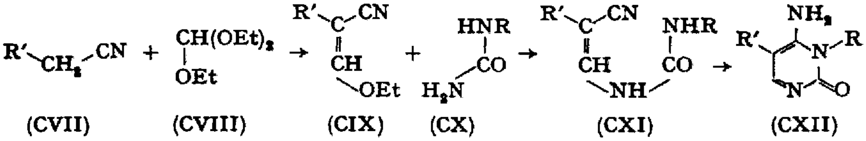
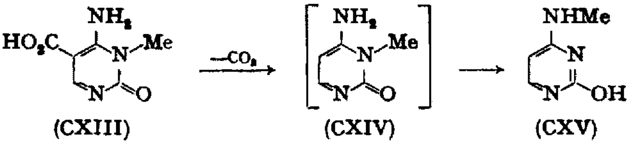
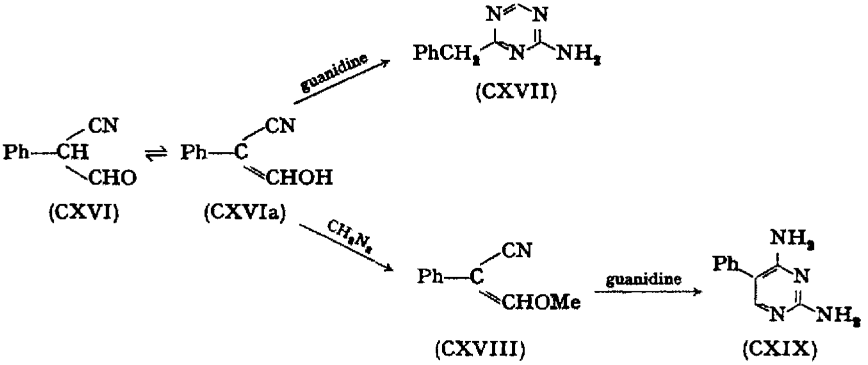
* This seems to proceed through (CIX) and the mechanism shown and also by an alternative route for which there is good evidence.[288] Relevant information has also been published separately.[287,291]

with sodium ethoxide. The ethoxymethylene compound (CIX) may be preformed if desired, or alternatively not even the ureido compound (CXI) need always be isolated. Table V contains some typical examples.





Although the 5-carboxy-3-alkylcytosines apparently offer a ready route to 3-alkylcytosines (not otherwise available), at least in the case of 5-carboxy-3-methylcytosine (4-amino-5-carboxy-2,3-dihydro-3-methyl-2-oxopyrimidine; CXIII) decarboxylation led not to 3-methylcytosine[288] (CXIV) but to 2-hydroxy-4-methylaminopyrimidine (CXV).[99, 289] The rearrangement presumably takes place by ring opening of the 2,3-bond, rotation about $C_{(4)}$ and ring closure in the opposite way. The reaction using nitroacetonitrile (CVII; $R' = NO_2$) and methylurea is normal, leading to 3-methyl-5-nitrocytosine (4-amino-



2,3-dihydro-3-methyl-5-nitro-2-oxopyrimidine). When other alkylureas were used, ring closure of the intermediate ureides was accompanied by rearrangement similar to that mentioned above, and there resulted a mixture of the desired product and 4-alkylamino-2-hydroxy-5-nitropyrimidine.[290]

TABLE V. Typical[a] Examples of the Whitehead Synthesis

Pyrimidine	Method[b]	Yield[c]	Ref.
4-amino-5-ethoxycarbonyl-2-hydroxy-	A	96%	281
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-oxo-	B	32%	288
	A	86%	289
4-amino-5-ethoxycarbonyl-3-ethyl-2,3-dihydro-2-oxo-	B	47%	288
	A	63%	288
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-β-hydroxyethyl-2-oxo-	B	90%	288
4-amino-3-benzyl-5-ethoxycarbonyl-2,3-dihydro-2-oxo-	A	91%	288
4-amino-5-ethoxycarbonyl-3-hexyl-2,3-dihydro-2-oxo-	A	90%	288
4-amino-5-carboxy-2,3-dihydro-3-methyl-2-oxo-	A	62%	289, 288
4-amino-3-butyl-5-carboxy-2,3-dihydro-2-oxo-	A	68%	288
4-amino-5-carbamoyl-2,3-dihydro-2-oxo-3-propyl-	A	56%	288
4-amino-3-ethyl-2,3-dihydro-2-oxo-5-phenylcarbamoyl-	A	45%	288
4-amino-2,3-dihydro-3-methyl-5-morpholinoformyl-2-oxo-	A	64%	288
4-amino-2,3-dihydro-3-methyl-5-nitro-2-oxo-	A	33%	290
4-amino-5-cyano-2,3-dihydro-3-methyl-2-oxo-	A	56%	288
4-amino-5-cyano-3-ethyl-2,3-dihydro-2-oxo-	B	84%	288
4-amino-5-cyano-2,3-dihydro-3-β-methoxyethyl-2-oxo-	A	96%	288
4-amino-3-*p*-chlorophenyl-5-cyano-2,3-dihydro-2-oxo-	C	54%	288
4-amino-5-cyano-2,3-dihydro-2-oxo-3-phenyl-	D	61%	288
4-amino-3-benzyl-5-cyano-2,3-dihydro-2-oxo-	A	75%	288

[a] About 50 examples are known.

[b] Briefly the methods are as follows:

A: Ethyl cyanoacetate, cyanoacetic acid, cyanoacetamide, *N*-alkylcyanoacetamide, or malononitrile, + ethyl orthoformate + the urea; ureido intermediate isolated.

B: Ethyl ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile + the urea in alcoholic sodium ethoxide gives the pyrimidine directly.

C: Malononitrile + ethyl orthoformate + arylurea + acetic anhydride giving the pyrimidine directly.

D: From malononitrile + *NN'*-*bis*phenylcarbamoylformamidine [PhNHCONH·CH=NCONHPh] giving the pyrimidine directly.

[c] Yield was calculated on ureido intermediate if isolated; otherwise on primary starting material.

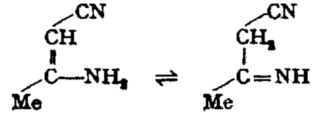
E. Aldehydo Nitriles with Guanidine

A variety of arylformylacetonitriles (*e.g.* phenylformylacetonitrile; CXVI) have been condensed with guanidine. If this is done directly an anomalous reaction ensues to give 2-amino-4-benzyl-1,3,5-triazine (CXVII).[285] The reason for the anomalous reaction of these formyl intermediates may possibly be due to their existence mainly as enols (*e.g.* CXVIa) which might well have too high an acidic strength for normal condensation.[274] When they were first converted with diazomethane to the enol ethers (*e.g.* CXVIII)* they readily condensed with guanidine in boiling ethanol to give the expected pyrimidines[274] (*e.g.* 2,4-diamino-5-phenylpyrimidine; CXIX). Ethylguanidine reacted similarly to guanidine to form only one pyrimidine, but whether the ethyl group was attached to a nuclear or an extra-nuclear *N*-atom is unknown.[274]

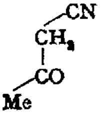
Enol ethers such as (CXVIII) do not react with urea or *S*-ethylthiourea,[274] but do so with formamidine (giving 4-amino-5-phenylpyrimidine) and with acetamidine, benzamidine, etc. to give appropriately 2-substituted derivatives.[274]

9. Use of β-Keto Nitriles

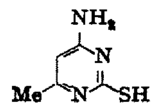
Little use has been made of keto nitriles in the Common Synthesis. Although cyanoacetone (CXXb) does not seem to have been used, the corresponding imine (2-amino-1-cyanopropene, CXX, or β-iminopropionitrile, CXXa) condenses under usual conditions with thiourea to give 60% of 4-amino-2-mercapto-6-methylpyrimidine (CXXI).[123] The *N*-phenyl and *N*-β-naphthyl derivatives of (CXX) react equally well giving the same product; aniline and β-naphthylamine respectively are eliminated. Attempts to replace the thiourea by guanidine, urea, *O*-methylurea, *S*-methylthiourea, or acetamidine failed.[123]



(CXX) (CXXa)



(CXXb)



(CXXI)

As with the aryl formylacetonitriles (Ch. II, Sect. 8.F), the corresponding keto derivatives, *e.g.* phenylacetylacetonitrile (CXXII), yield triazines** on condensation with guanidine, but if they are first *O*-alkylated to the enol ethers (*e.g.* CXXIII), condensation is normal and gives *e.g.* 2,4-diamino-6-methyl-5-phenylpyrimidine (CXXIV). Many examples carrying 5-aryl (or -thienyl) and 4-alkyl (or -aryl) groups have

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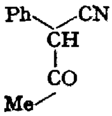
* Chase and Walker[286] have briefly reviewed alkylation of these enols.

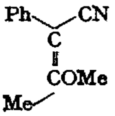
** The so-called "2,4-diamino-5,6-diphenylpyrimidine" prepared from phenylbenzoylacetonitrile[292] has also been shown to be a triazine.[285]

been described[274,286,293,294] as well as one without a 5-substituent.[286] Guanidine may be replaced by amidines which give 2-alkyl or -aryl derivatives such as 4-amino-6-methyl-2,5-diphenylpyrimidine[274] (CXXV).

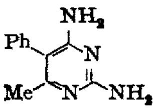
The typical enol ether, α-ethoxyethylidenemalononitrile (CXXVI), reacts as the keto nitrile (CXXVII), and, on condensation with *e.g.* *N*-butylthiourea, gives 4-amino-3-butyl-5-cyano-2,3-dihydro-6-methyl-2-thiopyrimidine[99] (CXXVIII). On the other hand, the analogous ethyl α-ethoxyethylidenecyanoacetate [$MeCOMe{:}C(CN)CO_2Et$] reacts as a keto ester giving not the 5-ethoxycarbonyl derivative corresponding to (CXXVIII) but 3-butyl-5-cyano-2,3-dihydro-4-hydroxy-6-methyl-2-thiopyrimidine[99] (CXXIX).



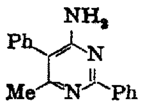
(CXXII)



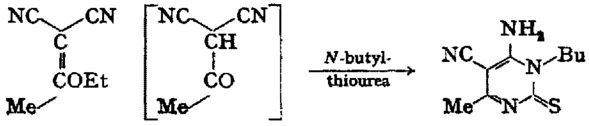
(CXXIII)



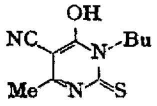
(CXXIV)



(CXXV)

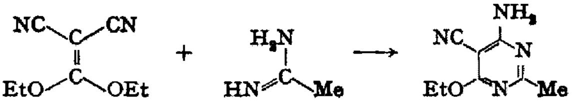


(CXXVI) (CXXVII) (CXXVIII)



(CXXIX)

Reactions which are clearly related to the combination of keto nitriles with amidines, but which do not fit exactly into the category, involve substituted dicyanoketenes. Thus dicyanoketene diethylacetal (diethoxymethylenemalononitrile; CXXX) and acetamidine give 4-amino-5-cyano-6-ethoxy-2-methylpyrimidine (CXXXI). The ketene reacts as a keto nitrile and neither as a dinitrile nor as an aldehydo nitrile. Similarly the dithio analogue of (CXXX), dimethylthiomethylenemalononitrile, gives 4-amino-5-cyano-2-methyl-6-methylthiopyrimidine. Further, amidines can be replaced by guanidine and by *S*-methyl-



(CXXX) (CXXXI)

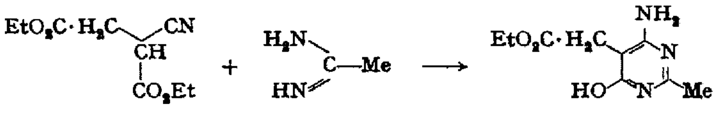
thiourea to give appropriate 2-amino- and 2-methylthio- derivatives, and several related reactions are described.[295]

10. Use of β-Ester Nitriles

The Common Syntheses with ester nitriles lead to 4-amino-6-hydroxypyrimidine derivatives.

A. Ester Nitriles with Amidines

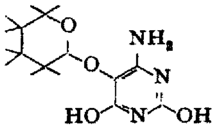
Ethyl cyanoacetate and formamidine do not form a pyrimidine: ammonia is eliminated, ethyl aminomethylenecyanoacetate [$H_2NCH{:}C(CN)CO_2Et$] is formed, and the reaction does not proceed further although this might reasonably be expected.[128] Benzamidine and ethyl cyanoacetate in alcohol give in roughly equal amounts, ethyl aminophenylmethylenecyanoacetate [$H_2NCPh{:}C(CN)CO_2Et$] and 4-amino-6-hydroxy-2-phenylpyrimidine, but if sodium ethoxide is present, the latter predominates markedly.[128, 296] Acetamidine lies between formamidine and benzamidine: with ethylcyanoacetate in ethanol, ethyl aminomethylmethylenecyanoacetate [$H_2NCMe{:}C(CN)CO_2Et$] is alone formed;[128] with one molecular proportion of sodium ethoxide, up to 37 % of the 4-amino-6-hydroxy-2-methylpyrimidine is formed,[154, 297, 298] along with the aliphatic by-product;[299] with four molecular proportions of sodium methoxide in methanol, over 80 % of the pyrimidine is formed with no aliphatic compound.[300] Conversion of ethyl cyanoacetate to its imino ether and subsequent condensation with acetamidine gives the pyrimidine.[299] When ethyl cyanoacetate is α-substituted, the appropriate pyrimidine is invariably alone formed. Thus ethyl cyanosuccinate (CXXXII) and acetamidine or benzamidine condense to 4-amino-5-ethoxycarbonylmethyl-6-hydroxy-2-methylpyrimidine (CXXXIII)[275, 299] or its 2-phenyl analogue.[275] Ethyl nitrosocyanoacetate and acetamidine give 4-amino-6-hydroxy-2-methyl-5-nitrosopyrimidine.[261]

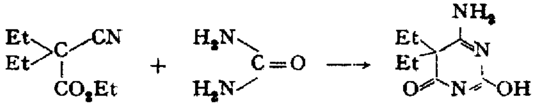


(CXXXII) (CXXXIII)

B. Ester Nitriles with Urea and Alkyl Ureas

Ethyl cyanoacetate reacts readily with urea in the presence of sodium ethoxide to give 4-amino-2,6-dihydroxypyrimidine.[302–305] Acetylurea can replace urea[306] (when ethyl acetate is eliminated) and sodium or sodamide (in xylene) has been used as condensing agent.[307] Cyanoacetic acid on the other hand condenses with urea in the presence of phosphoryl chloride[201,308] or, better, acetic anhydride.[309–311] In each case the intermediate cyanoacetylurea ($NC{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2$) required dissolution in aqueous alkali for cyclization. An example of a substituted intermediate is furnished by ethyl tetrahydropyran-2-yloxycyanoacetate which reacts with urea to give 4-amino-2,6-dihydroxy-5-tetrahydropyran-2′-yloxypyrimidine[107] (CXXXIV). Ethyl diethylcyanoacetate (CXXXV) (or the free acid) has been condensed with urea under conditions similar to the parent ethyl cyanoacetate (or free acid) giving 6-amino-5,5-diethyluracil[220,302,313,314] (CXXXVI).* Ethyl nitrosocyanoacetate and urea give directly 4-amino-2,6-dihydroxy-5-nitrosopyrimidine.[261,315] Similarly, ethyl α-cyano-γγ-diethoxybutyrate ($EtO_2C{\cdot}\ CH(CN)CH_2CH(OEt)_2$) and urea give 4-amino-5-ββ-diethoxyethyl-2,6-dihydroxypyrimidine.[316]


(CXXXIV)



(CXXXV) (CXXXVI)

Although Traube[317] claims (without experimental detail) to have condensed *NN′*-dimethylurea with ethyl cyanoacetate in alcoholic sodium ethoxide this has elsewhere been denied.[302,318] A mixture of pyridine and phosphoryl chloride was, however, found effective,[319] as was also sodamide,[307] in preparing 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (CXXXVIII), and its 1,3-diethyl homologue.[320]** Later, acetic anhydride was found to be more effective with *sym*-dialkylureas,[318,321–324] but cyclization of the intermediate (*e.g.* CXXXVII) required dissolution in aqueous alkali. Ring closure

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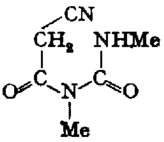
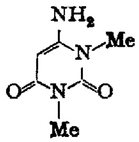
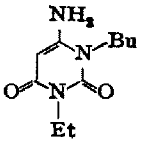
* Similar 4-amino derivatives have been extensively used as intermediates in the preparation of barbiturates with unsaturated 5-substituents such as Epival, Delvinal, and Pentothal (Sect. 7.B).

** The m.p. of this product was 58° below the m.p. of that prepared later.[318]

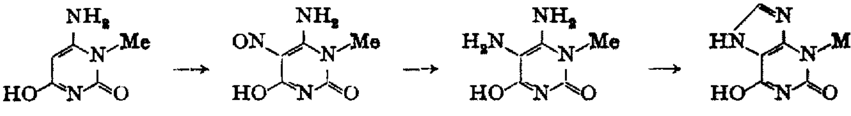
did not take place, however, when ureas carrying an α-branched carbon chain (*e.g.* *NN'*-di-isopropylurea, or *N*-cyclohexylurea) were used.[318, 324] With unsymmetrical dialkyl ureas two isomeric products are formed, but the one carrying the larger group on $N_{(1)}$ predominates. Thus *N*-ethyl-*N'*-propylurea and cyanoacetic acid give approx. 80% of 4-amino-1-ethyl-1,2,3,6-tetrahydro-2,6-dioxo-3-propylpyrimidine (CXXXIX) and 20% of the 3-ethyl-1-propyl isomer which were separated. The configurations in some cases were checked by unambiguous syntheses,* but other compounds have been described with the following warning: "This material may consist of two isomers. It is probable that the predominant constituent has the assigned structure..."[324] *N*-Alkenyl-*N'*-alkylureas similarly give mixtures of isomers, some of which have been separated and identified.[324, 325] Ethyl nitrosocyanoacetate condenses with dimethylurea in benzene containing suspended dry sodium ethoxide to give 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine.[315]


(CXXXVII)


(CXXXVIII)


(CXXXIX)

Unlike the dialkylureas, *N*-methylurea reacts readily with ethyl cyanoacetate in the presence of sodium ethoxide to form 6-amino-1-methyluracil (CXL).[302, 319] It was precluded from being the 3-methyl isomer by conversion into 3-methylxanthine[319] (CXLI) previously synthesized by an unequivocal route.[326] *N*-Ethyl-[327], *N*-phenyl-[323], and


(CXL) (CXLI)

other *N*-alkyl-urea derivatives[324] give similar pyrimidines with cyanoacetic acid in acetic anhydride followed by cyclization in ammonia or, better, hot sodium hydroxide solution. Cyclization fails when ureas with α-branched carbon chains (*e.g.* isopropyl) are used.[324]

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* For example by appropriate alkylation of an authentic *N*-monoalkyl pyrimidine or by the synthesis mentioned in Ch. III, Sect. 2.A.

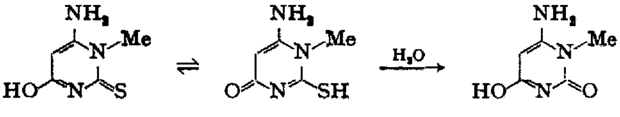
The condensation may also be effected with *N*-acetyl-*N'*-alkylureas in the presence of sodium ethoxide[306, 315] or sodamide,[328] and with dicyanodiamide.[315]

O-Methylurea with ethyl cyanoacetate yields 4-amino-6-hydroxy-2-methoxypyrimidine[329, 330] and *O*-ethylurea, the 2-ethoxy derivative.[330] 4-Amino-6-hydroxy-2-methoxy-5-methylpyrimidine was made similarly.[331]

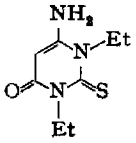
C. Ester Nitriles with Thioureas

Ethyl cyanoacetate gives with thiourea in alcoholic sodium ethoxide the expected 4-amino-6-hydroxy-2-mercaptopyrimidine[332, 333] but *S*-alkylthioureas fail to react.[268]* Ethyl nitrosocyanoacetate with thiourea gives 4-amino-6-hydroxy-2-mercapto-5-nitrosopyrimidine.[261] *N*-Methylthiourea, unlike the *S*-alkylthioureas, gives 6-amino-1-methyl-2-thiouracil (CXLII and CXLIIa).[333, 335] The position of the methyl group was shown[335] by oxidative hydrolysis to the known 6-amino-1-methyluracil (CXLIII). *N*-Allylthiourea,[333] and 3-diethylaminopropylthiourea[336] react similarly although the attachment of the allyl- and diethylaminopropyl-groups to $N_{(1)}$ rather than to $N_{(3)}$ must be considered as likely but unproven.

Symmetrical *NN'*-dialkylthioureas condense with cyanoacetic acid in acetic anhydride to yield for example, 4-amino-1,3-diethyl-1,2,3,6-tetrahydro-6-oxo-2-thiopyrimidine (CXLIV).[337]



(CXLII) (CXLIIa) (CXLIII)



(CXLIV)

Unsymmetrical *NN'*-dialkylthioureas have also been used[337, 338] but whether such a product as 4-amino-1-ethyl-1,2,3,6-tetrahydro-6-oxo-3-propyl-2-thiopyrimidine is in fact as claimed, or is the 3-ethyl-1-propyl isomer, seems to be unproven.

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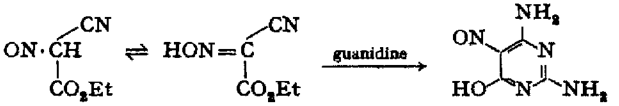
* It has been inferred that *S*-methylthiourea does give the expected 4-amino-6-hydroxy-2-methylthiopyrimidine.[333] This has been kindly checked for the author by Mr. J. Harper who found that the yield was in fact only 1% under the conditions recorded. The compound is better made indirectly.[334]

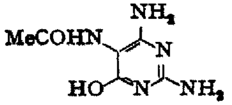
D. Ester Nitriles with Guanidines

Guanidine and ethyl cyanoacetate (as its sodio derivative) readily give 2,4-diamino-6-hydroxypyrimidine. The best method[339] made use of the experience of earlier papers.[304, 340–342] When alcoholic guanidine is used with free ethyl cyanoacetate, a mixture of the pyrimidine with the intermediate cyanoacetylguanidine is obtained.[308] The reaction has also been done with ethyl nitrosocyanoacetate (CXLV) (or ethyl hydroxyiminocyanoacetate; CXLVa) to give directly 2,4-diamino-6-hydroxy-5-nitrosopyrimidine (CXLVI).[261, 315, 343] Ethyl acetamidocyanoacetate similarly with guanidine produces 2,4-diamino-5-acetamido-6-hydroxypyrimidine (CXLVII),[344] and ethyl tetrahydropyran-2-yloxycyanoacetate gives 2,4-diamino-6-hydroxy-5-tetrahydropyran-2′-yloxypyrimidine.[107] Ethyl diethylcyanoacetate and guanidine yield 2,4-diamino-5,5-diethyl-5,6-dihydro-6-oxopyrimidine.[301]

An unusual (if unpractical) condensation[345] is that of ethyl bromocyanoacetate with guanidine to give directly 2,4-diamino-5-bromo-6-hydroxypyrimidine (which is better made indirectly). The survival of the aliphatic bromo group even for the few minutes at 100° required for the reaction is interesting.

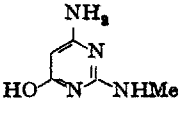


(CXLV) (CXLVa) (CXLVI)

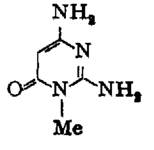


(CXLVII)

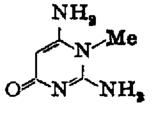
When methylguanidine is condensed with ethyl cyanoacetate, three pyrimidines (CXLVIII, CXLIX, CL) could result. It was first claimed, without experimental detail,[346] that only 2,4-diamino-3,6-dihydro-3-methyl-6-oxopyrimidine (CL) was formed.* Later it was shown[347] that two products were formed, 4-amino-2-methylamino-6-



(CXLVIII)



(CXLIX)



(CL)

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* The very low m.p. given for this product confirms, in the light of later work, that either the ring was still open or that the product was a mixture.

hydroxypyrimidine (CXLVIII) and a second pyrimidine formulated on rather insecure evidence as (CXLIX). This second product has since proved to be not (CXLIX) but (CL).[348, 349]

No such ambiguity can arise with *NN*-dimethylguanidine and ethylcyanoacetate which readily yield 4-amino-2-dimethylamino-6-hydroxypyrimidine.[347] Phenylguanidine and dicyanodiamide have also been condensed with ethyl cyanoacetate and are said to give respectively 4-amino-6-hydroxy-2-phenylaminopyrimidine[260] and 4-amino-2-cyanoamino-6-hydroxypyrimidine,[167] but these structures seem to be unproven.

11. Use of β-Dinitriles (Malononitriles)

The condensation of amidines with malononitrile is abnormal. Thus formamidine yields[350] not 4,6-diaminopyrimidine but 4-amino-5-cyanopyrimidine (CLII). This comes about by initial condensation of formamidine and malononitrile at the methylene group with elimination of ammonia to give aminomethylene-malononitrile (CLI). This then apparently* reacts[128] as a virtual aldehydo nitrile (CLIa) in a Common Synthesis with more formamidine to give (CLII). Benzamidine similarly gives 4-amino-5-cyano-2,6-diphenylpyrimidine,[128] but acetamidine, under conditions of equimolar quantities in alcoholic solution gives not 4-amino-5-cyano-2,6-dimethylpyrimidine as first reported,[128] but an uncyclized isomer, $H_2NC(Me):NC(Me):C(CN)_2$. The pyrimidine is, however, obtained[351] by using excess of amidine in the above reaction or by cyclizing the isomer with alcoholic amidine (or presumably any other strong base).

When the methylene group of malononitriles is blocked by a substituent, the normal Common Synthesis takes place: thus phenylazomalononitrile reacts with formamidine or acetamidine to give 4,6-diamino-5-phenylazopyrimidine,[350] and 4,6-diamino-2-methyl-5-phenylazopyrimidine.[352] *p*-Chloro-, but not *p*-nitrophenylazomalononitrile behaves similarly.[352] Ethoxymethylenemalononitrile, however, reacts with amidines as an aldehydo nitrile (Sect. 8.C).

Nitrosomalononitrile has been also used in the above type of condensation, but in a rather abnormal way.[353] For example, on treatment of the silver salt of nitrosomalononitrile with acetamidine hydro-

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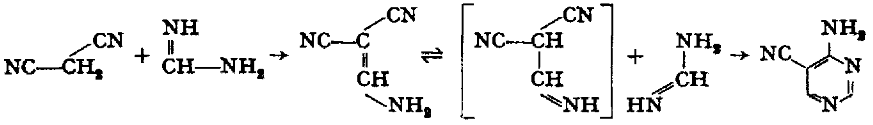
* In fact this stage is almost certainly *not* a Common Synthesis, although for practical purposes it can be thought of as such (Ch. III, Sect. 3.A).

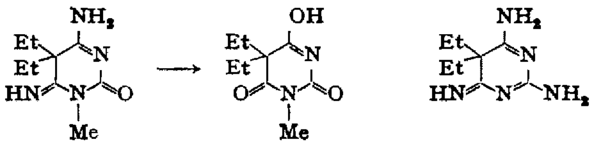
chloride, the acetamidine-nitrosomalononitrile salt is formed. This on heating in a high boiling homologue of pyridine is converted into 4,6-diamino-2-methyl-5-nitrosopyrimidine in good yield. The 2-ethyl, 2-benzyl, 2-*p*-methoxyphenyl-, and other homologues were made similarly,[353] and the amidine was replaced by guanidine and S-methyl thiourea giving respectively 2,4,6-triamino-5-nitrosopyrimidine and 4,6-diamino-2-methylthio-5-nitrosopyrimidine. Yields were better by this procedure than by the normal type of condensation in alcoholic sodium ethoxide.



(CLI) (CLIa) (CLII)

Neither urea nor its alkyl derivatives have been successfully condensed with malononitrile,* and 4,6-diamino-2-hydroxypyrimidine has been made only indirectly.[64, 354] Diethylmalononitrile and urea (or acetyl urea) are claimed in patents[355, 356] to yield 4,6-diamino-5,5-diethyl-2,5-dihydro-2-oxopyrimidine, and *N*-methylurea to give correspondingly 4-amino-5,5-diethyl-1,2,5,6-tetrahydro-6-imino-1-methyl-2-oxopyrimidine (CLIII). On hydrolysis these gave respectively 5,5-diethylbarbituric acid and its *N*-methyl derivative (CLIV).

Thiourea on the other hand readily reacts with malononitrile to give 4,6-diamino-2-mercaptopyrimidine.[332, 354, 357] Ethylmalononitrile similarly gives 4,6-diamino-5-ethyl-2-mercaptopyrimidine, and diethylmalononitrile gives 4,6-diamino-5,5-diethyl-2,5-dihydro-2-thiopyrimidine.[357] Alkyl thioureas seem to have escaped notice in these reactions.



(CLIII) (CLIV) (CLV)

Guanidine reacts with malononitrile in ethanol[358, 359] and in the

* In the case of urea, *O*-methyl- and *N*-methyl-urea, this statement has been kindly checked for the author by Mr. J. Harper. No pyrimidines were obtained.

presence of sodium ethoxide,[360] to give 2,4,6-triaminopyrimidine. By using ethyl-,[359] isopropyl-, benzyl-, or substituted benzyl-malononitrile appropriately 5-substituted triaminopyrimidines have been obtained;[361] phenylmalononitrile fails in this reaction.[361] It has been claimed in the patent literature[359] that diethylmalononitrile and guanidine yield 2,4(4,6)-diamino-5,5-diethyl-5,6(2,5)-dihydro-6(2)-iminopyrimidine (CLV or tautomer). *NN*-Dimethylguanidine and malononitrile conveniently serve to prepare 4,6-diamino-2-dimethylaminopyrimidine.[347]

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CHAPTER III

Other Methods of Primary Synthesis

1. General Remarks

Although the other general syntheses of pyrimidines are not comparable in scope to the Principal Synthesis, they are almost entirely complementary to it. On this account they are, considered collectively, the more useful and important. A logical classification of the methods is very difficult. Reviews written by various members of the Cambridge School[1–3] usually classify syntheses as Type I (Common Synthesis; —C—C—C— + —N—C—N—), Type II (—C—C—C—N— + —C—N—), Type III (—N—C—C—C—N— + —C—), and miscellaneous. In the present review, all but the first item in this classification is abandoned in favour of a more discursive treatment designed to help in the selection of a useful method for a given synthesis. To this end the known scope of each reaction is outlined.

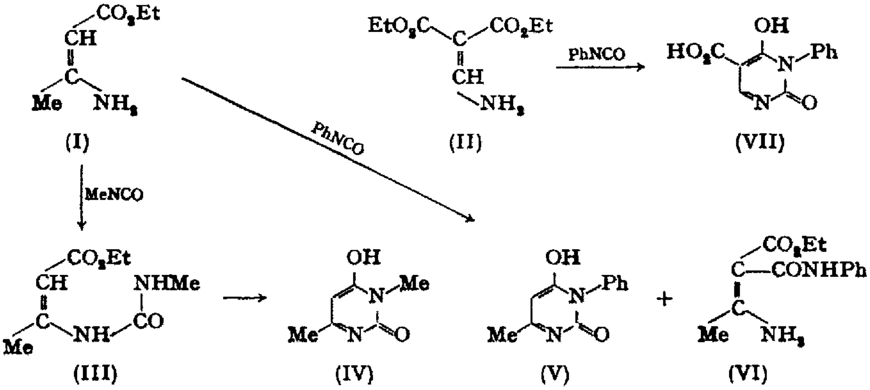
2. Syntheses Involving Preformed Aminomethylene Groups

The intermediates that have been used in these syntheses are typified on the one hand by ethyl β-aminocrotonate (I) and on the other by ethyl aminomethylenemalonate (II). The latter type is normally prepared from the corresponding ethoxymethylene derivative, itself prepared from a compound (*e.g.* diethylmalonate) having a methylene activated by two groups such as cyano, keto, or ester. One of these activating groups will finally appear in the 5-position of the resulting pyrimidine.

A. Aminomethylene Derivatives with Isocyanates

When ethyl β-aminocrotonate (I) reacts with methyl isocyanate, the substituted urea (III) is formed, and this readily cyclises to 3,6-

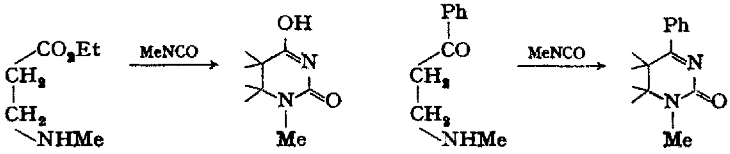
dimethyluracil [2,3(3,4)-dihydro-4(2)-hydroxy-3,6-dimethyl-2(4)-oxopyrimidine] (IV).[4] The analogous reaction with phenyl isocyanate leads to 6-methyl-3-phenyluracil [2,3(3,4)-dihydro-4(2)-hydroxy-6-methyl-2(4)-oxo-3-phenylpyrimidine] (V), but at the same time the unwanted ethyl β-amino-α-phenylcarbamoylcrotonate (VI) is formed.[4] Phenyl isothiocyanate similarly gave a poor yield of 6-methyl-3-phenyl-2-thiouracil[4] and methyl isothiocyanate gave only 10% of 3,6-dimethyl-2-thiouracil at 150° (or at 100° in the presence of water), but only the unwanted ethyl β-amino-α-methylthiocarbamoylcrotonate at 100° without water.[5] Other examples are known,[6] and 1-amino-2-ethoxycarbonylcyclohexene reacts with cyanic acid to give 5,6-cyclopentenouracil, with phenyl isocyanate to give 5,6-cyclopenteno-3-phenyluracil, and with methyl isothiocyanate to give 5,6-cyclopenteno-3-methyl-2-thiouracil.[7]



When the aminomethylenemalonate (II) is treated with phenyl isocyanate and the resulting ureido compound cyclised with alkali, 5-carboxy-3-phenyluracil (VII) is formed.[8] Similarly ethyl aminomethyleneacetoacetate gives 5-acetyl-3-phenyluracil.[8]

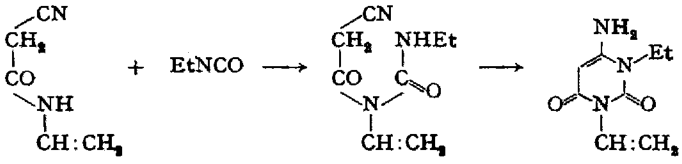
The above reactions may be applied to intermediates lacking the double bond (*e.g.* β-amino esters) when 5,6-dihydropyrimidines result.[9-12] β-Alkylamino esters[10] react similarly so that ethyl β-methylaminopropionate (VIII) and cyanic acid give 5,6-dihydro-1-methyluracil (IX),[14] and the reaction has been extended to yield a number of 1-alkyldihydrouracil[13] and 1-alkyldihydrothymine derivatives.[15] These dihydro derivatives were converted to the pyrimidines by bromination and dehydrobromination. The analogous dihydro derivative (1,2,5,6-

tetrahydro-1-methyl-2-oxo-4-phenylpyrimidine) (XI) from a β-alkylamino ketone (β-methylaminoethyl phenyl ketone) (X) and cyanic acid is interesting in that it disproportionates into 1,2-dihydro-1-methyl-2-oxo-4-phenylpyrimidine and 1,2,3,4,5,6-hexahydro-1-methyl-2-oxo-4-phenylpyrimidine.[16] The synthesis and oxidation of hydropyrimidines is treated more fully in Chapter XII.



(VIII) (IX) (X) (XI)

An unusual reaction which is best classified with the present reaction is that of *N*-allylcyanoacetamide (XII) with ethyl isocyanate to give *N*-allyl-*N*-cyanoacetyl-*N*′-ethylurea (XIII) by refluxing for one day in toluene. On dissolving in aqueous sodium hydroxide cyclisation "occurs with great violence" to 1-allyl-4-amino-3-ethyl-1,2,3,6-tetra-hydro-2,6-dioxopyrimidine (XIV).[17, 19] The thio analogue (1-allyl-4-amino-3-ethyl-1,2,3,6-tetrahydro-6-oxo-2-thiopyrimidine)[18] and 4-amino-1-butyl-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxopyrimidine[19] seem to be the only other examples of this potentially good method.



(XII) (XIII) (XIV)

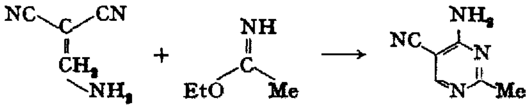
The above general method of synthesis is applicable to pyrimidines and dihydropyrimidines with *O*- or *S*- in the 2-position, carrying if required 4- and 5-substituents, and 1- or 3- alkyl groups. It has been very little explored to date. Attempts to extend it by ring closing *N*-β-cyanoethyl-*N*′-methylthiourea and *N*-β-cyanoethyl-*N*′-ethylurea to 4-amino-2,3,5,6-tetrahydro-3-methyl-2-thiopyrimidine (and analogue) have failed.[20]

B. Aminomethylene Derivatives with Imino-ethers or Imidoyl Chlorides

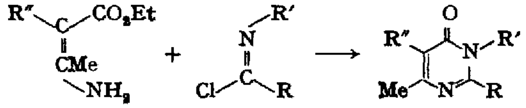
The first of these reactions is typified by that between aminomethylenemalononitrile (XV) and ethyl acetimidate giving 4-amino-

5-cyano-2-methylpyrimidine (XVI).[21, 23] Table VI contains a summary of other examples, and Dornow's paper is perhaps relevant.[194]

The imidoyl chloride reaction is represented by the conversion of 2-alkyl-β-aminocrotonic esters (XVa) with imidoyl chlorides into 3-alkyl-4-oxo-dihydropyrimidines (XVII). A variety of examples have been reported[22] where R = aryl group, R′ = aryl or ethyl group, and R″ = alkyl group.



(XV) (XVI)

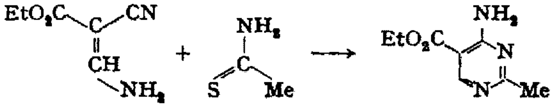


(XVa) (XVII)

The only examples of the imino ether reaction are those quoted above. There seems little reason why it should not be extended to other types of aminomethylene derivative (to avoid 5-substitution), and to dihydropyrimidines. The imidoyl chloride reaction is potentially very useful but no simple examples seem to be known. The imidoyl chlorides were easily obtained[22] by rearranging ketoximes with phosphorus pentachloride[24] and the condensation has been applied to the synthesis of quinazolones.[26]

C. Aminomethylene Derivatives with Thioamides

Aminomethylenemalononitrile and ethyl aminomethylenecyanoacetate (XVIII) react with thioacetamide to give respectively 4-amino-5-cyano-2-methylpyrimidine and 4-amino-5-ethoxycarbonyl-2-methylpyrimidine (XIX).[18, 28, 29] The synthesis is otherwise unexplored.



(XVIII) (XIX)

D. Use of an Acylated Aminomethylene Derivative

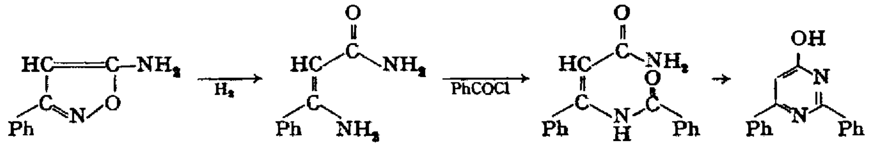
When 5-amino-3-phenylisoxazole (XX) is hydrogenated, aminocinnamamide (XXI) is formed. Acylation of the amino group gives an

TABLE VI. Additional Examples of the Condensation of Aminomethylene Derivatives with Imino Ethers

Aminomethylene compound	Imino ether	Pyrimidine formed	Ref.
Ethoxymethylenemalononitrile + NH_3	ethyl acetimidate	4-amino-5-cyano-2-methyl-	21, 25
Aminomethylenemalononitrile	ethyl phenylacetimidate	4-amino-2-benzyl-5-cyano-	21, 23
Aminomethyleneacetylacetone	ethyl benzoimidate	5-acetyl-4-methyl-2-phenyl-	21, 23
Ethyl aminomethylenecyanoacetate	ethyl acetimidate	4-amino-5-ethoxycarbonyl-2-methyl-	21, 23
Ethyl aminomethylenecyanoacetate	ethyl benzoimidate	5-cyano-4-hydroxy-2-phenyl-	21, 23
Ethyl α-aminomethylene-β-ethoxypropionate	methyl acetimidate	5-ethoxymethyl-4-hydroxy-2-methyl-	27

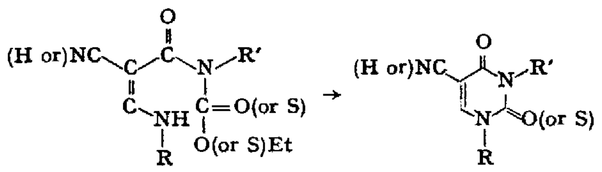
intermediate, *e.g.* (XXII), which cyclizes by warming in aqueous alkali to 4-hydroxy-2,6-diphenylpyrimidine (XXIII). Cyclization to 4-hydroxy-2-methyl-6-phenylpyrimidine requires heating without alkali.[30] When the corresponding 5-acetamidoisoxazole is used, the same pyrimidine is obtained by way of Ph.C(NH_2):CHCONHCOMe and an equally gentle cyclization.[30] Other examples are known.[31]

Although the pyrimidine (XXIII) is much more easily made by a Common Synthesis[32] the method has possibilities where gentle conditions of cyclization might be dictated by the presence of a labile group. Thus a strictly analogous method has been used to make 5-*p*-chlorophenyl-2-dichloromethyl-4-ethyl-6-hydroxypyrimidine from dichloroacetyl chloride and 2-amino-1-carbamoyl-1-*p*-chlorophenyl-1-butene (obtained from an oxazole), the dichloromethyl group surviving the synthesis.[33] The structure was checked by a Common Synthesis (Table III).


(XX) (XXI) (XXII) (XXIII)

E. The Shaw Synthesis from Aminomethyleneacylurethanes

A general synthesis of uracil and thiouracil derivatives applicable to the preparation of nucleosides because of the gentle conditions used, has been developed since 1955 by G. Shaw and his colleagues.[34–43] It is best thought of in simple general terms as the cyclization of an aminomethyleneacylurethane, such as (XXIV), under mildly alkaline conditions to give the pyrimidine (XXV).

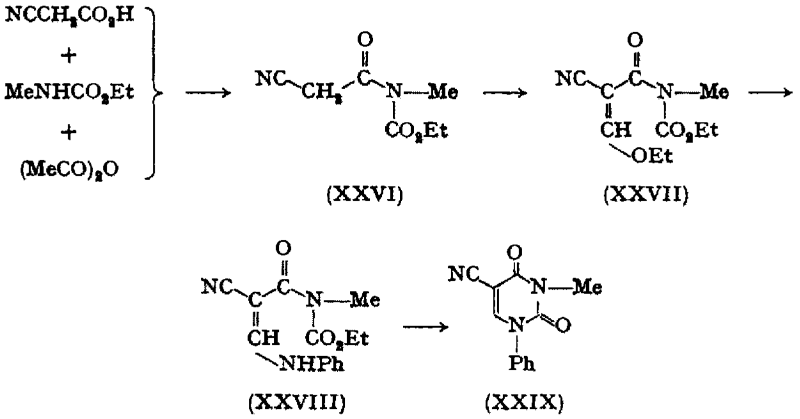

(XXIV) (XXV)

R = H or Me, Ph, etc.
R′ = H or Me, Ph, Sugar, $-CH_2CO_2H$, etc.

The preparation of the intermediate follows two general routes according to whether a CN or other group is to appear in the 5-position of the pyrimidine or whether it is to be free.

For example, the preparation of 5-cyano-1-phenyl-3-methyluracil

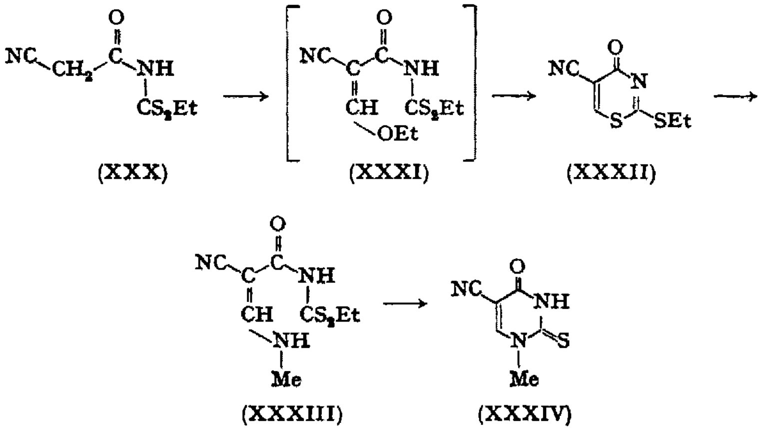
(XXIX) started from cyanoacetic acid, methylurethane and acetic anhydride which gave *N*-cyanoacetyl-*N*-methylurethane (XXVI).[35] This with ethyl orthoformate and acetic anhydride gave the ethoxy methylene derivative (XXVII) which on treatment with aniline gave (XXVIII) and thence the pyrimidine (XXIX).[37] A very similar route led to 5-cyano-1-2′-hydroxyethyluracil and related derivatives.[42]



(XXVI) (XXVII)

(XXVIII) (XXIX)

When dithiourethanes are used in such a synthesis, the reaction takes a slightly different course.[36] Thus on forming the ethoxymethylene derivative (XXXI) from cyanoacetyldithiourethane (XXX), ring



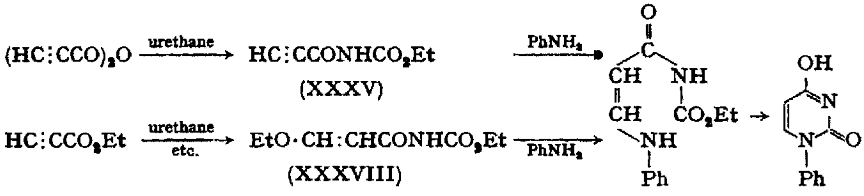
(XXX) (XXXI) (XXXII)

(XXXIII) (XXXIV)

closure occurs to give 5-cyano-2-ethylthio-4-oxo-1,3-thiazine (XXXII) which however reacts with, say, methylamine under mild conditions giving first the intermediate (XXXIII) and thence 5-cyano-1-methyl-2-thiouracil (XXXIV).[36] The cyano group has been replaced by *p*-tolylsulphonyl and similar groups.[39]

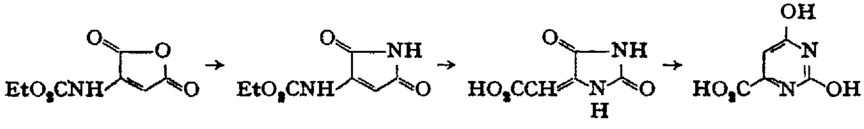
When the 5-position is to be free, or occupied by a methyl group (for thymines), the route is different in detail. Thus propiolic anhydride and urethane give *inter alia* propioloylurethane (XXXV). This reacts vigorously with aniline giving (XXXVI) which cyclizes to 1-phenyluracil (XXXVII). An alternative route from ethyl propiolate and urethane passes through ethoxymethyleneacetylurethane (XXXVIII).[38] The analogous hydroxymethylmethyleneacetylurethane (HO(Me)C:CH·CO·NH·CO_2Et) also reacts with amines and the resulting analogues of (XXXVI) cyclize to give for example 6-methyl-1-phenyluracil (XXXVII) and several other 1-substituted analogues.[40]

A related reaction[42] leading to similar pyrimidines is typified by the reaction of *β*-methoxy-*α*-methylacryloyl isothiocyanate (MeOCH:CMeCONCS) with propylamine to give the thiourea (MeO·CH:CMe·CO·NH·CS·NH·C_3H_7) which on alkaline ring closure gave 1-propyl-2-thiothymine. Similarly the analogous acylurea, *N*-*β*-chlorocrotonoyl-*N'*-phenylurea (MeCCl:CH·CO·NH·CO·NH·Ph) cyclized to 6-methyl-1-phenyluracil.[40]



(XXXVI) (XXXVII)

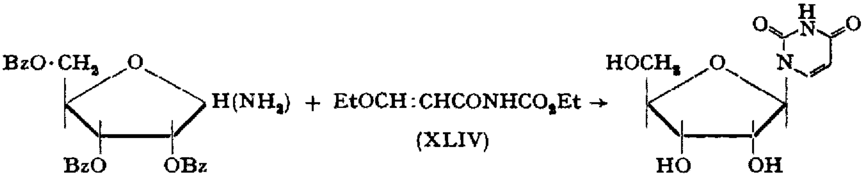
A route to 6-carboxy-2,4-dihydroxypyrimidine (orotic acid) and its 3-alkyl derivatives also follows these general lines. Oxaloacetic acid with urethane gives ethoxycarbonylaminomaleic anhydride (XXXIX)



(XXXIX) (XL) (XLI) (XLII)

which with ammonia gives (XL). This is recyclized to the hydantoin (XLI) and with alkali converted into orotic acid (XLII). When ammonia is replaced with amines, 3-substituted orotic acids result.[38] By a similar route, 3-phenyl-2-thio-orotic acid has been prepared.[40]

The above methods (and those described in Sect. 5.A) have been successfully applied to the preparation of nucleosides (*e.g.* uridine, thiouridine, and related compounds).[41,43] For example the ribosylamine (XLIII) with (XLIV) followed by debenzoylation, gives uridine (XLV).



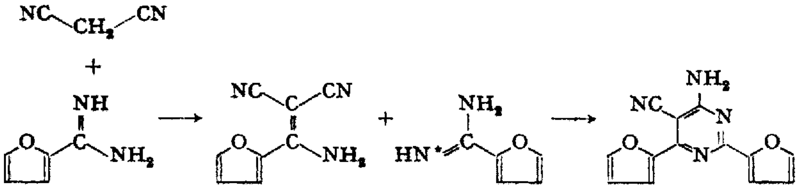
(XLIII) (XLIV) (XLV)

3. Syntheses Involving an Aminomethylene Group Formed *In Situ*

There is fundamentally little difference between the syntheses requiring preformed aminomethylene compounds and those in which the aminomethylene group is formed during the reaction. Indeed in the following section it will be noticed that the intermediate has in fact been isolated in several instances although this is neither necessary nor advantageous.

A. β-Dinitriles or β-Ester Nitriles with Amidines

The fact that unsubstituted malononitrile and amidines first condense to form aminomethylenemalononitriles and these react with more amidine giving 4-amino-5-cyanopyrimidines, has already been noted (Ch. II, Sect. 10). This mechanism is upheld by the fact that aminomethylenemalononitrile readily condenses with formamidine to form 4-amino-5-cyanopyrimidine.[28] In one case the actual intermediate β-(α-furyl)-β-aminomethylenemalononitrile (XLVII) was isolated from the condensation of α-furoamidine (XLVI) and malononitrile. At a higher temperature it reacted with fresh amidine to give the expected 4-amino-5-cyano-2,6-di-α-furylpyrimidine (XLVIII).[28] Further it seems almost certain that the second stage of this reaction proceeds by the elimination of N^* (as NH_3) from the new molecule of amidine rather than from the NH_2 of the aminomethylene intermediate, because the corresponding imino ether can replace the amidine and give the same product.[28] The second stage is not therefore a Common Synthesis since the amidine does not supply both nuclear *N*-atoms in the final pyrimidine.

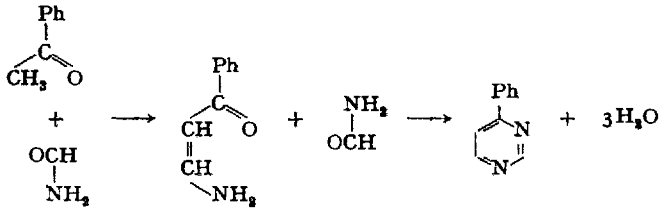


(XLVI) (XLVII) (XLVIII)

Ethyl cyanoacetate and formamidine (or other reactive amidines) give the expected ethyl aminomethylenecyanoacetate [$H_2NCH{:}C(CN)CO_2Et$] but this does not cyclize with more amidine.[28] They can, however, be cyclized by other methods. The less reactive amidines tend to undergo a normal Common Synthesis with ethyl cyanoacetate (Ch. II, Sect. 10.A).

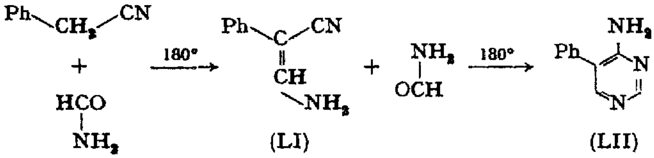
B. Formamide with Compounds Containing an Active Methylene Group

The first example of this reaction was the preparation of 4-phenylpyrimidine (L) from formamide, acetophenone, and zinc chloride at a high temperature[44] *via* (XLIX). 4-Methylpyrimidine results from trisformamidomethane and acetone with toluene sulphonic acid.[192]



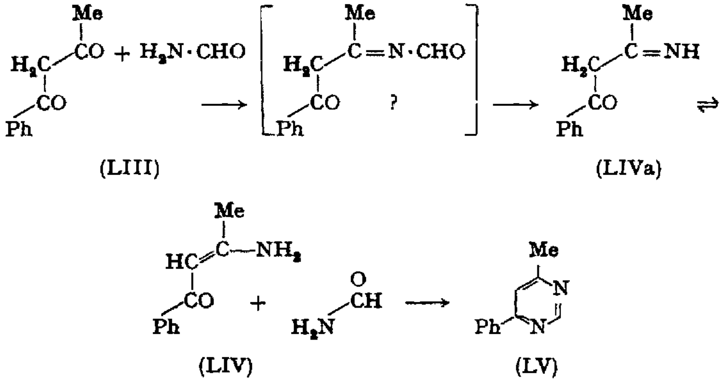
(XLIX) (L)

When phenylacetonitrile and formamide are heated under ammonia for 7 hours at *ca.* 180° and the volatiles allowed to distil, 4-amino-5-phenylpyrimidine (LII) (in 54% yield) and some aminomethylenephenylacetonitrile (LI) remain.[45] The latter (which can be readily made from ammonia and formylphenylacetonitrile) gives the pyrimidine (52%) in only 1 hour on similar treatment. These data suggest that the aminomethylene compound (LI) is indeed the intermediate in the pyrimidine synthesis. The reaction fails with acetamide, thioacetamide, and thioformamide; also with simple aliphatic nitriles which have an insufficiently activated methylene group. The same pyrimidine was, however, obtained when *a*-acetyl- or *α*-phenylaminomethylenephenylacetonitrile was heated with formamide.[45] *o*- and *p*-Methoxy-, *p*-chloro-, and *p*-nitro-phenylacetonitrile underwent reaction to 4-amino-5-*o*-methoxyphenyl-, 4-amino-5-*p*-methoxyphenyl-, 4-amino-5-*p*-chlorophenyl-, and 4-amino-5-*p*-nitrophenyl-pyrimidine.[46] It is said[45] that the similarly prepared product described as 2-benzyl-1,3,5-triazine[47] is in fact 4-amino-5-phenylpyrimidine. This being so, the product called 2-naphthylmethyl-1,3,5-triazine is probably 4-amino-5-*α*-naphthylpyrimidine.



(LI) (LII)

A more recent addition to the reaction has been made in a brief letter,[48] and 1-amino-2-cyanocyclopentene reacts with formamide to give 4-amino-5,6-cyclopentenopyrimidine.[7]



(LIII) (LIVa) (LIV) (LV)

C. Formamide with *β*-Dicarbonyl and Related Compounds

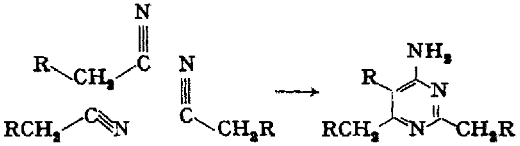
A closely related synthesis has been developed by Bredereck and colleagues[49–53] who used a variety of *β*-dicarbonyl and related compounds with a tenfold excess of formamide at *ca.* 200°. For example, benzoylacetone (LIII) with formimide at 220° gave 4-methyl-6-phenylpyrimidine (LV) (60%). The course of the reaction was indicated by using a lower temperature, 150°, when the intermediate "benzoylacetone-imide" (1-benzoyl-2-iminopropane) (LIV) was isolated; it gave the pyrimidine on refluxing with formamide. The condensation of 1-chloro-2-formylcyclopentene with formamide to give 4,5-trimethylenepyrimidine,[154] of α,β-dimethyl-β-chloroacrolein with formamide to give 4,5-dimethylpyrimidine,[55] and of α-methyl-β-diethylaminoacrolein with formamide to give 5-methylpyrimidine,[53, 55] are all essentially the same reaction. Table VII summarizes examples of these reactions.

The scope of the above reaction is parallel to that of formamidine in Common Synthesis: if formamidine will theoretically give a certain pyrimidine from a certain intermediate, by a Common Synthesis, then formamide can potentially do the same by the synthesis of Bredereck *et al.*

One further pyrimidine synthesis involving formamide is described later (Sect. 4.B) in a more logical context.

D. The Frankland and Kolbe Synthesis from Nitriles and Alkali Metal

Simple nitriles having a CH_2 group adjacent to the cyano group undergo trimerization in the presence of alkali metals giving 4-amino-2,5,6-trialkylpyrimidines, the "kyanalkine" or "cyanalkines" (LVI). The 5-substituent will have one less CH_2 group than the 2- and 6-alkyl groups.



(LVI)

As a practical synthesis the scope is severely limited as indicated above. However, the best way of making 4-amino-2,6-dimethylpyrimidine is from acetonitrile and potassium ethoxide[56] or sodium methoxide.[57] The mechanism of the reaction is not understood, and indeed in some cases a *sym*-triazine intermediate may be implicated. Thus it is reported[57] that propionitrile trimerizes under high pressure without catalyst to 2,4,6-triethyl-1,3,5-triazine (LVII). This can be converted into 4-amino-2,6-diethyl-5-methylpyrimidine (LVIII) by

TABLE VII. Examples of Pyrimidine Synthesis from β-Dicarbonyl (or Equivalent) Compounds and Formamide[49–55]

β-Dicarbonyl Derivative or Equivalent	Pyrimidine formed	Yield
1,3,3-Triethoxy-1-methoxypropane; $(EtO)_2CHCH_2CH(OEt)OMe$	unsubstituted	65%–72%
1,3,3-Triethoxy-1-propene; $(EtO)_2CHCH:CHOEt$	unsubstituted	20%
3,3-Diethoxy-1-propyne; $(EtO)_2CHC:CH$	unsubstituted	25%
1,1-Dimethoxy-3-butanone; $(MeO)_2CHCH_2COCH_3$	4-methyl-	70%
1-Dimethylamino-1-buten-3-one; $Me_2NCH:CHCOCH_3$	4-methyl-	40%
1-Ethoxy-1-buten-3-one; $EtOCH:CHCOCH_3$	4-methyl-	40%
1-Chloro-1-buten-3-one; $ClCH:CHCOCH_3$	4-methyl-	40%
3-Diethylamino-2-methylpropenal; $Et_2NCH:CMeCHO$	5-methyl-	85%
1-Chloro-1-penten-3-one; $ClCH:CH\cdot CO\cdot CH_2CH_3$	4-ethyl-	55%
3-Dimethylamino-2-ethylpropenal; $Me_2NCH:CEtCHO$	5-ethyl-	71%
1-Chloro-1-hexen-3-one; $ClCH:CHCO(CH_2)_2CH_3$	4-propyl-	60%
3-Dimethylamino-2-isopropylpropenal; $Me_2NCH:C(CHMe_2)CHO$	5-isopropyl-	72%
1-Chloro-5-methyl-1-hexen-3-one; $ClCH:CHCOCH_2CH(CH_3)_2$	4-isobutyl-	60%
3-Dimethylamino-2-heptylpropenal; $Me_2NCH:C(C_7H_{15})CHO$	5-heptyl-	93%
Acetylacetone; $CH_3COCH_2COCH_3$	4,6-dimethyl-	35%
2-Imino-4-pentanone; $CH_3COCH_2C(:NH)CH_3$	4,6-dimethyl-	25%
2-Methylimino-4-pentanone; $CH_3COCH_2C(:NMe)CH_3$	4,6-dimethyl-	25%
3-Chloro-2-methyl-2-butenal; $MeCCl:CMeCHO$	4,5-dimethyl-	64%
4-Chloro-3-octen-2-one; $C_4H_9C(Cl):CHCOCH_3$	4-butyl-6-methyl-	60%
Sodiobenzoylacetaldehyde; $PhCOCHNaCHO$	4-phenyl-	38%
Benzoylvinylacetate; $PhCOCH:CHOCOCH_3$	4-phenyl-	45%
1-Benzoyl-2-dimethylaminoethylene; $PhCOCH:CHNMe_2$	4-phenyl-	65%
1-Benzoyl-2-diethylaminoethylene; $PhCOCH:CHNEt_2$	4-phenyl-	60%
1-Benzoyl-2-chloroethylene; $PhCOCH:CHCl$	4-phenyl-	38%
Benzoylacetone: $PhCOCH_2COCH_3$	4-methyl-6-phenyl-	60%
Sodiobenzoylacetone; $PhCOCHNaCOCH_3$	4-methyl-6-phenyl-	35%
1-Benzoyl-2-iminopropane; $PhCOCH_2C(:NH)CH_3$	4-methyl-6-phenyl-	36%
2-Acetylimino-1-benzoylpropane; $PhCOCH_2C(:NCOCH_3)CH_3$	4-methyl-6-phenyl-	25%
1-Methoxy-1-phenyl-1-buten-3-one; $Ph(MeO)C:CHCOCH_3$	4-methyl-6-phenyl-	20%
1-Benzoyl-2-ethoxy-1-propene; $PhCOCH:C(OEt)CH_3$	4-methyl-6-phenyl-	40%
1-Chloro-1-phenyl-1-buten-3-one; $Ph(Cl)C:CHCOCH_3$	4-methyl-6-phenyl-	60%

(Table continued)

TABLE VII *(continued)*

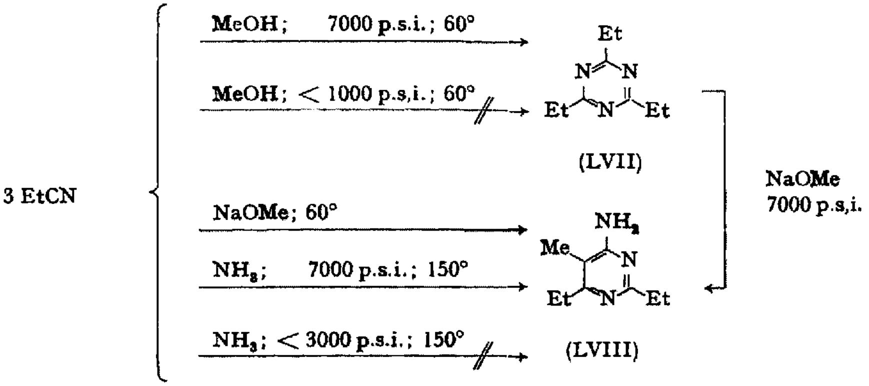
β-Dicarbonyl Derivative or Equivalent	Pyrimidine formed	Yield
3-Chloro-2-methyl-3-phenylpropenal; PhCCl:CMeCHO	5-methyl-4-phenyl-	60%
1-Benzoyl-2-butanone; $\mathrm{PhCOCH_2COC_2H_5}$	4-ethyl-6-phenyl-	22%
1-Phenyl-2-propionylacetylene; PhC:CCOEt	4-ethyl-6-phenyl-	46%
1-Chloro-1-phenyl-1-penten-3-one; $\mathrm{Ph(Cl)C{:}CHCOC_2H_5}$	4-ethyl-6-phenyl-	42%
1-Chloro-1-phenyl-1-hexen-3-one; $\mathrm{Ph(Cl)C{:}CHCOC_3H_7}$	4-phenyl-6-propyl-	50%
Dibenzoylmethane; $\mathrm{PhCOCH_2COPh}$	4,6-diphenyl-	32%
1-Benzoyl-2-phenylacetylene; PhCOC:CPh	4,6-diphenyl-	35%
1-Benzoyl-2-methoxy-2-phenylethylene; PhCOCH:C(OMe)Ph	4,6-diphenyl-	30%
Benzoyl-*p*-nitrobenzoylmethane; $\mathrm{PhCOCH_2COC_6H_4NO_2}$	4-*p*-nitrophenyl-6-phenyl-	20%
2-Acetylcyclohexanone; $\overline{\mathrm{(CH_2)_4COC}}\mathrm{HCOCH_3}$	4-methyl-5,6-tetramethylene-	25%
2-Formylcyclohexanone; $\overline{\mathrm{(CH_2)_4COC}}\mathrm{HCHO}$	5,6-tetramethylene-	30%
β-Imino-β-phenylpropionitrile; $\mathrm{NCCH_2C({:}NH)Ph}$	4-amino-6-phenyl-	55%
Ethyl benzoylacetate; $\mathrm{PhCOCH_2CO_2Et}$	4-hydroxy-6-phenyl-	?
1-chloro-2-formylcyclopentene; $\overline{\mathrm{(CH_2)_3CCl{:}C}}\mathrm{CHO}$	4,5-trimethylene- *(homologues similarly)*	?

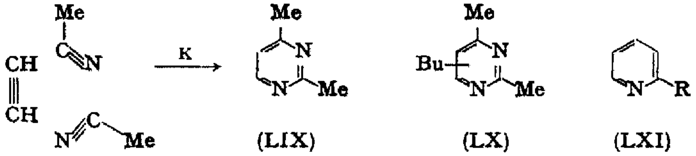
alkali, and the pyrimidine can be made (directly) from the nitrile by use of strongly basic catalysts, or by weak bases when combined with high pressure.

The trimerization of glycolonitrile (cyanomethanol) under alkaline conditions has been reported[58] to give 4-amino-5-hydroxy-2,6-bishydroxymethylpyrimidine, but the extraordinary instability of the compound, even to boiling water, is puzzling.

In an analogous reaction benzonitrile reacted with methyl lithium, giving a triazine which lost ammonia at 300° giving 2,4,6-triphenyl pyrimidine. Ethyl lithium and propyl lithium gave respectively 5-methyl- and 5-ethyl-2,4,6-triphenylpyrimidine.[49]

A rather analogous reaction,[60] between two molecules of a nitrile and one of an acetylene at 20 atmospheres in the presence of potassium, yields pyrimidines. Thus acetonitrile and acetylene give 2,4-dimethylpyrimidine (LIX) while pent-1-yne with acetonitrile gives a product analysing for 4 (and/or 5)-butyl-2,6-dimethylpyrimidine (LX). With excess of acetylene 2-alkylpyridine (LXI) is formed.





Frankland and Kolbe's synthesis[61] in 1848 of "Kyanäthin" from propionitrile and metallic potassium was the first primary synthesis of a pyrimidine. It was performed in Bunsen's laboratory at Marburg and their paper "Über die Zersetsungsprodukte des Cyanäthyls durch Einwirkung von Kalium" makes interesting reading with its spirited and precise description of their experiments and the ultimate analyses of the products.

The topic was kept alive by two papers of Bayer[62,63] on Kyanmethin and in 1880 Ernst von Meyer and his colleagues at Leipzig began a fascinating series of papers on the reaction. They first improved the experimental conditions, extended it to other homologues, converted them to "hydroxy bases" with nitrous acid, and degraded them by bromine oxidation to aliphatic acids, and generally explored related topics.[64–81]

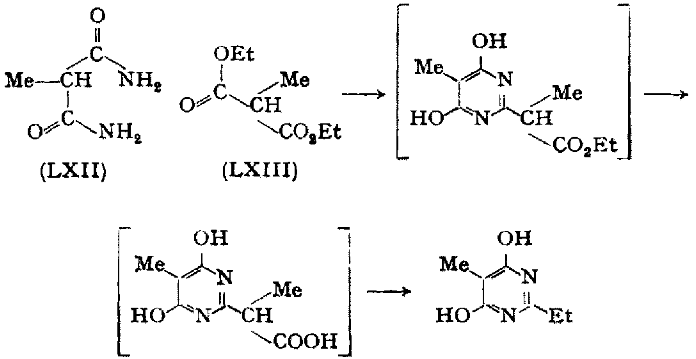
In 1889 a brief note[82] announced the structure of kyanäthin proved as 4-amino-2,6-diethyl-5-methylpyrimidine by synthesis of 2,4-diethyl-6-hydroxy-5-methylpyrimidine, identical with the nitrous acid deamination product of Kyanäthin. A few months later Meyer summarized[83] the relevant papers to that date. Hereafter a little appeared from Leipzig[84–86] and later Dresden,[87,88] and Meyer virtually concluded the work in 1905 by reviewing the reaction at length. The original[89] is not widely available but it provides more detail and interest than the abstract[9] might suggest.

4. Syntheses from Malondiamides and Malondiamidine

In this class of synthesis both N atoms destined for inclusion in the pyrimidine ring are supplied already attached to the three-carbon fragment: it only remains to insert the carbon for position-2. The scope of the reaction is limited by the fact that malondiamides will lead to 4,6-dihydroxypyrimidines and the diamidine to 4,6-diaminopyrimidines. The carbon for ring closure can be supplied in a variety of reagents leading to the resulting 2-position being either unsubstituted or substituted. The 5-position can be substituted by preattachment of the required group to the malonic acid moiety.

A. Malondiamides with Esters: The Remfry–Hull Synthesis

In 1911 Remfry[91] showed that alkylmalondiamides reacted with diethyl malonate (or its alkyl derivatives) in alcoholic sodium ethoxide to give 2,5-dialkyl-4,6-dihydroxypyrimidines. Thus methylmalondiamide (LXII) and diethyl methylmalonate (LXIII) yield 2-ethyl-4,6-dihydroxy-5-methylpyrimidine (LXIV) by the route shown. The simplest possible reaction of this type (malondiamide with diethyl malonate to give 4,6-dihydroxy-2-methylpyrimidine) failed, although several other dialkylpyrimidines were made successfully.

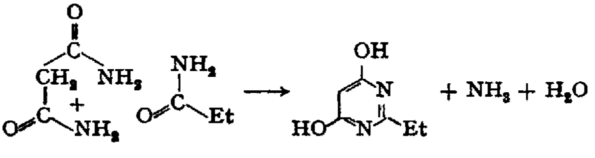

(LXII) (LXIII)

(LXIV)

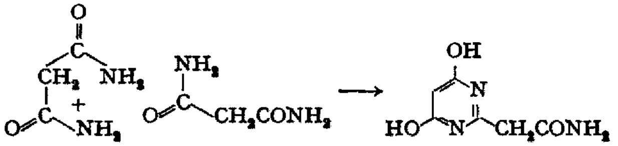
Forty years later, Hull[92,193] simplified this synthesis by condensing malondiamide and ethyl formate to give 4,6-dihydroxypyrimidine (until then made by a Common Synthesis from diethyl malonate and formamidine).[28] By presubstitution of the malondiamide, 5-ethyl and 5-phenyl derivatives of the dihydroxypyrimidine were produced[92] as well as the 5-tetrahydropyran-2′-yloxy derivative.[93] The reaction was later extended[94] to the use of methylaminomalondiamide with ethyl formate giving 4,6-dihydroxy-5-methylaminopyrimidine, and also to the use of other esters. Thus malondiamide with ethyl valerate gave mainly 2-butyl-4,6-dihydroxypyrimidine, along with an easily separated by-product (*v.i.*).

B. Malondiamides with Amides

The ester of the Remfry–Hull synthesis can often be replaced to advantage by the corresponding amide.* Thus malondiamide and its methylamino derivative with formamide gave respectively 4,6-dihydroxypyrimidine in better yield, and 4,6-dihydroxy-5-methylaminopyrimidine in comparable yield to that prepared with ethyl formate. Similarly propionamide and malondiamide in alcoholic sodium ethoxide gave 2-ethyl-4,6-dihydroxypyrimidine (LXV).[94] Further it was shown that the considerable by-product formed from the reaction of higher esters with malondiamide (*v.s.*) was independent of the ester and in fact was formed by self condensation of malondiamide. Thus malondiamide (LXVI) in alcoholic sodium ethoxide quickly yields 2-carbamoylmethyl-4,6-dihydroxypyrimidine[94] (LXVII), which had been synthesized unambiguously in another connection.[96] No evidence was observed of a dipyrimidinylmethane derivative formed from further condensation of the carbamoyl group with more malondiamide.[97]



(LXV)



(LXVI) (LXVII)

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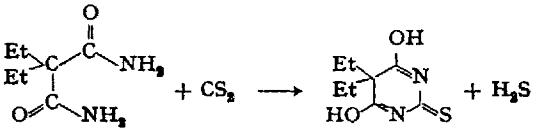
* At least one example exists of the use of an acid chloride in place of an ester, in the preparation of 1,5-diethyltetrahydro-2-methyl-4,6-dioxo-5-phenylpyrimidine.[95]

C. Malondiamides with Oxalyl Chloride and Carbonic Acid Derivatives

This synthesis has been used to make barbituric acid and its 5-alkyl and dialkyl derivatives only.

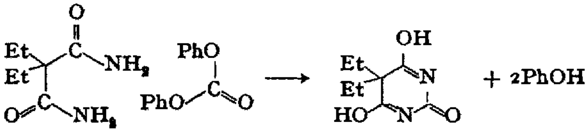
Malondiamide and oxalyl chloride when refluxed in benzene slowly give barbituric acid[98] while monophenyl and diphenyl- or dialkylmalondiamide give respectively 5-phenyl-, 5,5-diphenyl-, and 5,5-diethyl-barbituric acid.[99, 100] The addition of acetic anhydride facilitates such ring closures which then proceed at 20°.[101] The mechanism of the reaction has not been investigated.

Although carbon dioxide does not seem to have been used to supply the 2-carbon atom of barbituric acid, carbon bisulphide and carbon oxysulphide when heated with alcoholic sodium ethoxide and diethylmalondiamide (LXVIII) give respectively 5,5-diethyl-2-thiobarbituric acid (LXIX) and diethylbarbituric acid.[102]



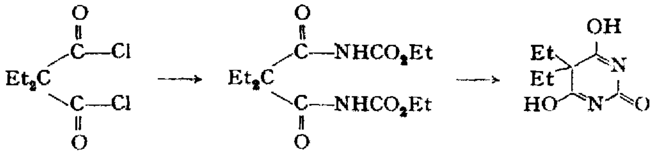
(LXVIII) (LXIX)

Phosgene has been used similarly (at 150° without catalyst)[99, 103] and esters of carbonic acid such as diphenyl carbonate (LXX) or diethyl carbonate react with diethylmalondiamide giving diethylbarbituric acid (LXXI).[104, 105] 5-*m*-Chlorophenyl-5-ethylbarbituric acid has been made by a similar route using diethyl carbonate.[95] Similar condensations on 20° in liquid ammonia containing sodium hydroxide have given barbituric acid and a variety of 5-alkyl and 5,5-dialkyl derivatives in good yield.[106]



(LXX) (LXXI)

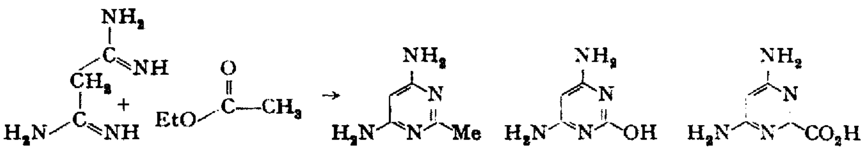
A closely related reaction was described by Traube. Diethylmalonyl chloride (LXXII) reacted with urethane giving *NN'*-diethoxycarbonyldiethylmalondiamide (LXXIII).[107,108] Ring closure of this under a variety of conditions[108–110] including the addition of urea or diphenyl carbonate,[111] gave 5,5-diethylbarbituric acid (LXIV).


(LXXII) (LXXIII) (LXXIV)

D. The Use of Malondiamidine

Although it is less easy to prepare, malondiamidine (LXXV) is naturally a much more reactive intermediate than the diamide. Thus it reacts in the cold with ethyl formate,* ethyl acetate, and ethyl benzoate giving good yields of 4,6-diaminopyrimidine,[112] 4,6-diamino-2-methylpyrimidine[112] (LXXVI), and 4,6-diamino-2-phenylpyrimidine[113]. The first of these can, however, be now made more easily by an indirect method.[114] Both diethyl carbonate and ethyl chloroformate yield 4,6-diamino-2-hydroxypyrimidine (LXXVII) (also better made indirectly),[115] while diethyl oxalate gives 4,6-diamino-2-carboxypyrimidine (LXXVIII) and no trace of the possible tetra-aminodipyrimidinyl. Acetic anhydride gives 4,6-diacetamido-2-methylpyrimidine. Ethyl butyrate, ethyl pyruvate, diethyl malonate, urethane (and derivatives), and methyl dithioacetate gave no pyrimidines.[113]

N-Substituted malondiamidines have been used with success. Thus for example ethyl formate with *NN'*-diallylmalondiamidine or *NN'*-dioctylmalondiamidine gives respectively 4,6-bisallylamino-, or 4,6-bisoctylamino-pyrimidine.[116]


(LXXV) (LXXVI) (LXXVII) (LXXVIII)

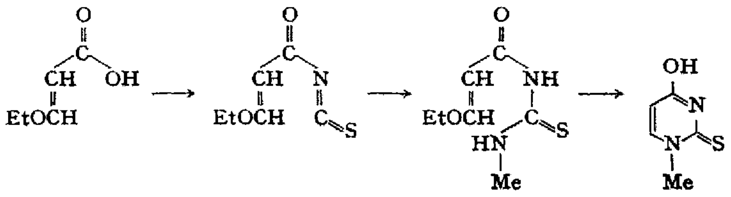
* Hot formamide gives 4-amino-6-formamidopyrimidine, but when phenylazomalondiamidine is used, 4,6-diamino-5-phenylazopyrimidine (not its formyl derivative) is formed.[116]

When the monoamide-monoamidine of malonic acid (α-carbamoylacetamidine) was condensed with ethyl formate it gave 4-amino-6-hydroxypyrimidine (isolated as its 5-nitro derivative).[117] It is easier to make it indirectly.[114] In a rather similar way the monoamide-monoamidine of phenylazomalonic acid gives with formamide, 4-amino-6-hydroxy-5-phenylazopyrimidine.[118]

5. Other Syntheses of Pyrimidines

A. Ethoxymethyleneacetic Acid to Uracil Derivatives

Ethoxymethyleneacetic acid (LXXIX), which is the enol ether of formylacetic acid, is readily converted to the acid chloride and thence with potassium thiocyanate to ethoxymethyleneacetyl isothiocyanate (LXXX). This treated with an amine (*e.g.* methylamine) gives the intermediate *N*-ethoxymethyleneacetyl-*N'*-methylthiourea (LXXXI), which cyclizes on warming in aqueous alkali to 1-methyl-2-thiouracil[43] (LXXXII).



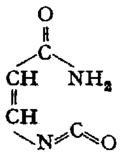
(LXXIX) (LXXX) (LXXXI) (LXXXII)

Several variations can be introduced. Thus by addition of an α-methyl group on (LXXIX), the final product is 1,5-dimethyl-2-thiouracil (1-methyl-2-thiothymine) or the alkyl substituent on $N_{(1)}$ can be varied.[43] Further, thiocyanate can be replaced by cyanate leading to 1-methyluracil by an analogous route, to 1-methylthymine, or to other uracil derivatives.[119] It has been applied to nucleoside formation.[41]

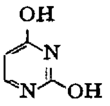
The ease of the above sequences of reaction suggested their use in nucleoside formation. In addition, the method is useful as a direct way to 1-alkylthiouracils and uracils when a Common Synthesis using an aldelydo ester with *N*-alkylthiourea or urea would normally lead to 3-alkylpyrimidines (Ch. II, Sect. 2.C).

B. Maleic Diamide to Uracil

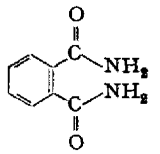
When maleic diamide is treated with sodium hypochlorite, 2,4-dihydroxypyrimidine (LXXXIV) results in a good yield.[120] It would seem that one amide group undergoes a Hofmann reaction to an isocyanate (LXXXIII) which then ring closes on to the other amide group. Although there is no other example in the pyrimidine series, fused pyrimidines have been made this way (Sect. 6.D), and also several dihydropyrimidines. Thus for example phthalic diamide (LXXXV) gives 2,4-dihydroxyquinazoline (LXXXVI),[121] succindiamide gives 5,6-dihydrouracil,[122,123] and phenyl- and α-methyl-β-phenylsuccindiamide give 6-phenyldihydrouracil and (probably) 5-methyl-6-phenyldihydrouracil respectively.[124,125]



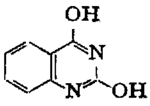
(LXXXIII)



(LXXXIV)



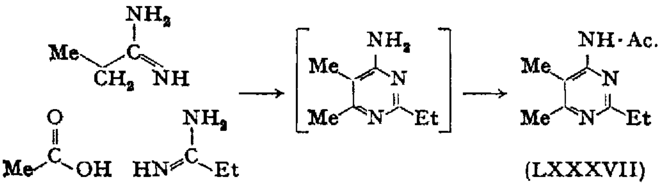
(LXXXV)



(LXXXVI)

C. The Alkylamidine-Acetic Anhydride Synthesis

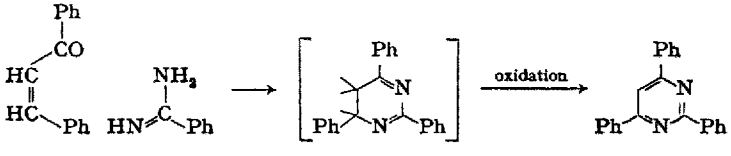
It has been shown[126] that acetamidine reacts with acetic anhydride to give 4-acetamido-2,6-dimethylpyrimidine (the acetyl derivative of kyanmethin). Propionamidine gives 4-acetamido-2-ethyl-5,6-dimethylpyrimidine (LXXXVII) which indicates that the condensation takes place so that the amidine supplies C$_{(2)}$, C$_{(4)}$, and C$_{(5)}$ while the anhydride supplies C$_{(6)}$. (Acetic anhydride is written below as acetic acid for simplicity.)



(LXXXVII)

D. Amidines with αβ– Unsaturated Ketones

An interesting reaction of simple αβ-unsaturated ketones with amidines has been reported.[127] The first product is probably a dihydropyrimidine which is oxidized by the unsaturated ketone to pyrimidine and saturated ketone. Thus benzamidine and β-benzoylstyrene (LXXXVIII) probably give in alcoholic potassium hydroxide, 4,5-dihydro-2,4,6-triphenylpyrimidine (LXXXIX) which is oxidized by the excess of ketone (or less efficiently by an air stream) to 2,4,6-triphenylpyrimidine (XC) in 85 % yield.



(LXXXVIII) (LXXXIX) (XC)

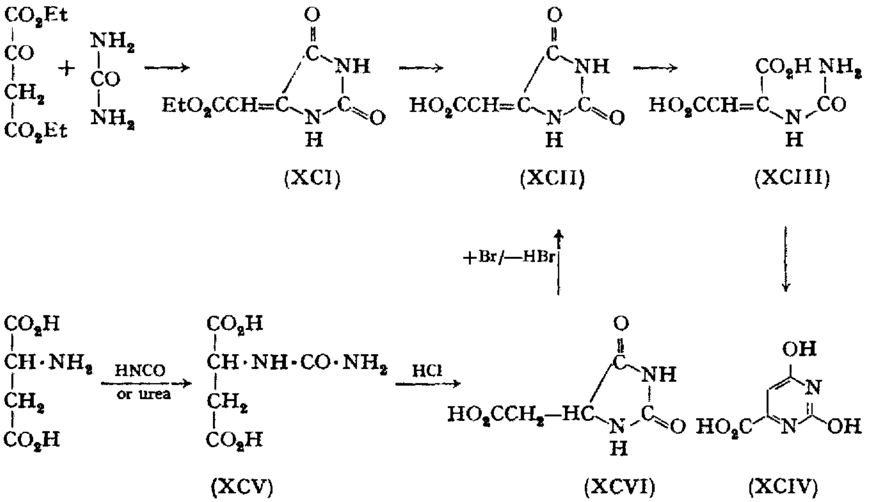
By variation of the ketone and amidine several other analogues were prepared. Substitution of *S*-benzylthiourea for the amidine led to a 5 % yield of 2-benzylthio-4,6-diphenylpyrimidine. The synthesis seems to be confined to aryl or tertiary alkyl derivatives.

E. Synthesis of Pyrimidines from Other Ring Systems

It is occasionally useful to prepare pyrimidines from other heterocyclic systems, either by rearrangement in the case of a mono-cyclic compound or by degradation in the case of di- or poly-cyclic types. Often in the latter case, the larger molecule has itself been made from a pyrimidine, and not infrequently from the self-same pyrimidine to which it reverts on degradation. Such cases will be ignored. Some examples of useful syntheses are given briefly below.

(1) *Pyrimidines from Hydantoins*

Hydantoins sometimes arise from reactions designed to produce pyrimidines. In these cases they readily undergo rearrangement (generally under hydrolytic conditions) to pyrimidines. The hydantoins are seldom if ever desired, or intended as precursors of pyrimidines. For example may be taken the condensation of ethyl oxalacetate with urea, which does not give 4-ethoxycarbonyl-2,6-dihydroxypyrimidine directly as would be expected[128–130] by a Common Synthesis. Instead, the 5-ethoxycarbonylmethylene hydantoin (XCI) is formed. Gentle alkaline treatment gives the corresponding 5-carboxymethylenehydantoin (XCII) and more vigorous treatment isomerizes this to 6-carboxy-2,4-dihydroxypyrimidine (orotic acid) (XCIV) through the open chain compound (XCIII).[131] In a parallel sequence from ureidosuccinic acid (XCV) use has been made of the hydantoin stage to introduce a missing double bond (by bromination and dehydrobromination) into 5-carboxymethylhydantoin (XCVI) giving (XCII).[132,133] The synthesis does not seem very versatile as 5-carboxyethylidene-, 5-benzal-, and 5-cinnamal-hydantoin failed to rearrange to pyrimidines.[134]



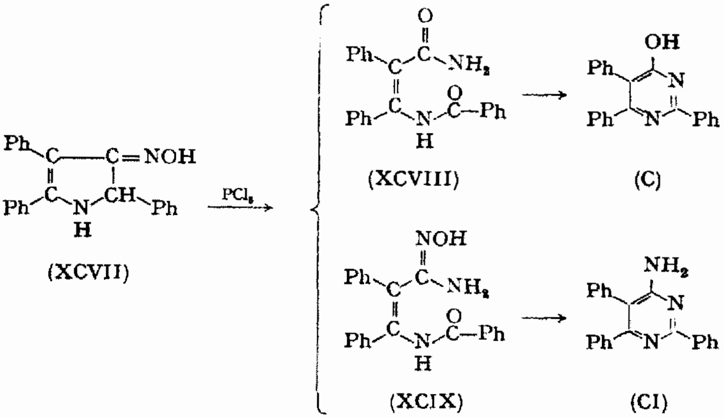
Other examples of hydantoin intermediates in pyrimidine synthesis are known, such as the routes to 4-carboxy-2,6-dihydroxy-5-methylpyrimidine and to 2-amino-4-carboxy-6-hydroxy-5-methylpyrimidine which are similar to the above,[135–137] and so on.[38]

(2) *Pyrimidines from Isoxazoles and Thiazines*

The preparation of pyrimidines from isoxazole derivatives[30] and from thiazines[36,41,138] is indirect in that aliphatic intermediate products have been isolated. Examples have already been discussed (Sects. 2.D and E; Ch. II, Sects. 5.A and 6.A). Diketen reacts with derivatives of urea to give, often *via* 1,3-oxazine derivatives, a wide variety of *N*-alkylated oxopyrimidines.[139–141]

(3) *Pyrimidines from Hydroxyiminopyrroles*

A rearrangement which is interesting, if of little use, involves 4-hydroxyimino-2,3,5-triphenylpyrrole (XCVII). On treatment with phosphorus pentachloride in ether, two intermediate products (XCVIII and XCIX) are isolated. The former on heating gives 4-hydroxy-2,5,6-triphenylpyrimidine (C), and the latter on reduction with zinc and acetic acid gives 4-amino-2,5,6-triphenylpyrimidine (CI).[142] If the 3-position of the pyrrole is unoccupied, the 5-position of the pyrimidine is also free.[143, 144] When phosphorus pentachloride in chloroform is used no intermediates are isolated.[143]* The author's theoretical discussion of the mechanisms[144] is unconvincing.



(XCVII) (XCVIII) (C) (XCIX) (CI)

(4) *Pyrimidines from Quinazolines and Purines*

When quinazoline (CII) is oxidized with permanganate, 4,5-dicarboxypyrimidine (CIII) results[145] and from this, 5-carboxypyrimidine was prepared by removal of the more labile 4-carboxy group. On hydrolytic degradation, quinazolines naturally give benzene rather than pyrimidine derivatives.

2-Hydroxypurine (CIV), 2-mercaptopurine, and 2-methylthiopurine are hydrolysed to give 4,5-diamino-2-hydroxypyrimidine (CV) 4,5-diamino-2-mercaptopyrimidine and 4,5-diamino-2-methylthiopyr-

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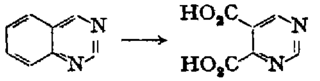
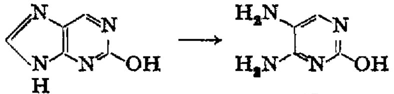
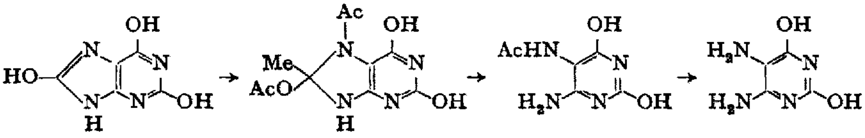
* It is remarkable that both Chemical Abstracts and British Abstracts made complete (and different) errors in naming the major product (C) of this reaction.[143]

imidine.[146] 9-Methylpurine is almost quantitatively degraded by alkali to 5-amino-4-methylaminopyrimidine.[146] These syntheses are of little value because the pyrimidines are normally the precursors of the purines. On the other hand, the readily available natural uric acid (2,6,8-trihydroxypurine; CVI) can be converted by treatment with acetic anhydride and pyridine into the "triacetate" (CVII);* then to "monoacetate" (CVIII), which on alkaline hydrolysis gives 4,5-diamino-2,6-dihydroxypyrimidine (CIX) in good yield. This route[147] is the best available to the intermediate for xanthine, lumazine (2,4-dihydroxypteridine), and a host of derivatives.

Of the variety of possible procedures presented in the paper it is best to purify the "triacetate", convert it to "monoacetate", and then use methanolic hydrogen chloride to give the hydrochloride of diaminodihydroxypyrimidine. Sulphuric acid hydrolysis of crude "triacetate" is less satisfactory.[148] There are other relevant papers.[149, 150]


(CII) (CIII)


(CIV) (CV)


(CVI) (CVII) (CVIII) (CIX)

As other examples of the useful preparation of pyrimidines from purines may be mentioned: alloxan (hexahydrotetraoxopyrimidine) by oxidation of uric acid with nitric acid,[151] chlorate,[152, 153] or chlorine;[154] 6-thiouramil (5-amino-2,4-dihydroxy-6-mercaptopyrimidine) from uric acid with ammonium bisulphide;[155, 156] and 1-methyl-[156] and 1,3-dimethyl-6-thiouramil[155, 156] from the corresponding methylated uric acids in a similar way.

(5) *Pyrimidines from Pteridines*

Most pteridines are made from 4,5-diaminopyrimidine derivatives: some of the less stable ones revert to their precursors under hydrolytic

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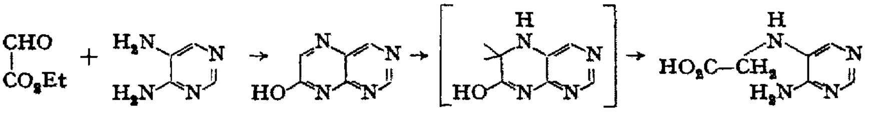
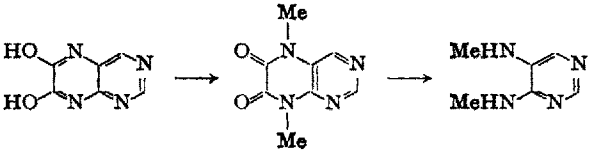
* (CVII) was once thought to be the isomeric triacetyl derivative of (CIX), and so arose the name "triacetate".

conditions.[157] This process could be useful if the pteridine was made by another method or if the pteridine was altered (*e.g.* methylated) after formation. In this way was found[158] a convenient synthesis of 4-amino-5-carboxymethylaminopyrimidine (CXII) by reduction of 7-hydroxypteridine (CXI), which was prepared from 4,5-diaminopyrimidine (CX) and ethyl glyoxylate. Analogously, 5-amino-4-carboxymethylaminopyrimidine was prepared from 7,8-dihydro-6-hydroxypteridine.[159]


(CX) (CXI) (CXII)

Attempts to prepare 4,5-bismethylaminopyrimidine (CXV) failed by ordinary means[20] but it is conveniently made by methylation of 6,7-dihydroxypteridine (CXIII) to 5,6,7,8-tetrahydro-5,8-dimethyl-6,7-dioxopteridine (CXIV) followed by hydrolysis.[160]


(CXIII) (CXIV) (CXV)

6. Formation of Pyrimidine Ring in Fused Heterocycles

Many examples of the completion of the pyrimidine part of a fused heterocyclic system are closely related to ordinary methods of pyrimidine synthesis. Such reactions logically belong not here, but in reviews of the resulting systems. The brief following sections indicate where such information has been reviewed, and a short summary is given in the case of pteridines where no complete review exists.

A. Quinazolines from Benzene Derivatives

The application of many pyrimidine syntheses to the preparation of quinazolines has been well reviewed.[161]

B. Purines from Glyoxalines

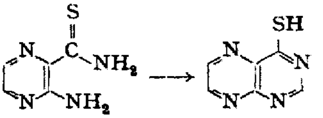
Apart from the implication of 5-amino-4-carbamoylglyoxaline in the biosynthesis of purines,[162,164] several examples of purine syntheses from glyoxalines are known. They have been briefly reviewed.[163] More recent noteworthy contributions have been made.[165,166]

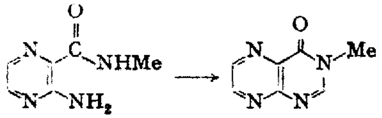
C. Thiazolo[5 4-d]pyrimidines from Thiazoles

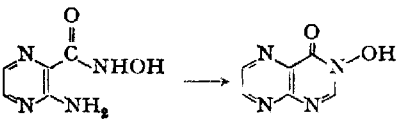
Known examples of the conversion of thiazole derivatives into thiazolo[5,4-d]pyrimidines are analogues to the preparation of purines from glyoxalines. They are contained in two papers.[167,168]

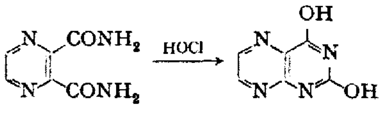
D. Pteridines from Pyrazines

2-Amino-3-carbamoylpyrazine and 2-amino-3-thiocarbamoyl-pyrazine (CXVI) cyclize with ethyl orthoformate (or formic acid) in the presence of acetic anhydride to 4-hydroxypteridine and 4-mercaptopteridine (CXVII) respectively,[169] while 2-amino-3-methylcarbamoylpyrazine similarly gives 3,4-dihydro-3-methyl-4-oxopteridine (CXIX).[157] A particularly interesting example is the similar conversion of 2-amino-3-hydroxycarbamoylpyrazine (CXX) to 3,4-dihydro-3-hydroxy-4-oxopteridine (CXXI).[170] More complicated pteridines have likewise been prepared[171,172] and 2-amino-3-hydrazinocarbonylpyrazine (as its isopropylidene derivative) similarly yields 3-amino-3,4-dihydro-4-oxopteridine.[173] 2,3-Dicarbamoylpyrazine (CXXII) when treated with sodium hypochlorite undergoes a partial Hofmann rearrangement and 2,4-dihydroxypteridine (CXXIII) results in good yield.[174]


(CXVI) (CXVII)

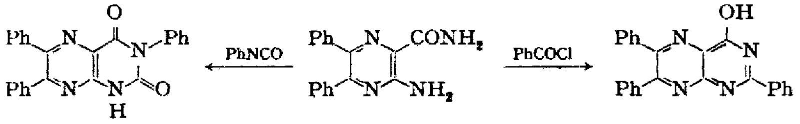

(CXVIII) (CXIX)


(CXX) (CXXI)

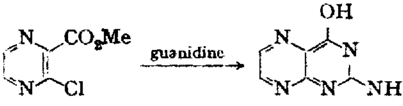


(CXXII) (CXXIII)

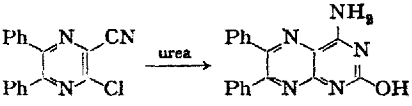
Several other routes to pteridines have been described. Thus for example 2-amino-3-carbamoyl-5,6-diphenylpyrazine (CXXIV) with phenyl isocyanate gives 3,6,7-triphenyl-lumazine (CXXIII) and with benzoyl chloride gives 4-hydroxy-2,6,7-triphenylpteridine (CXXV).[175] 2-Chloro-3-methoxycarbonylpyrazine (CXXVI) and its 5,6-diphenyl derivative with guanidine give respectively 2-amino-4-hydroxy-pteridine and its 6,7-diphenyl derivative (CXXVII).[176] 2-Chloro-3-cyano-5,6-diphenylpyrazine (CXXVIII) with guanidine, urea or thiourea gives the 2,4-diamino-, 4-amino-2-hydroxy- (CXXIX), and 4-amino-2-mercapto-pteridine.[177] Some of the above work has been reviewed,[178] and other such syntheses have been reported.[179]



(CXXIII) (CXXIV) (CXXV)



(CXXVI) (CXXVII)



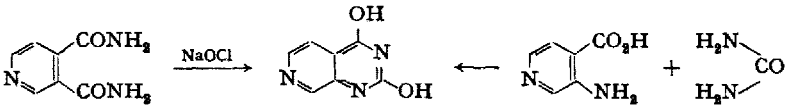
(CXXVIII) (CXXIX)

E. Pyridopyrimidines from Pyridines

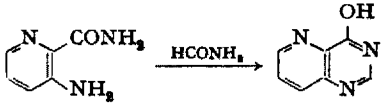
Pyridopyrimidines are easily formed from pyridines by analogous methods to those outlined above. A few random examples follow to illustrate this.

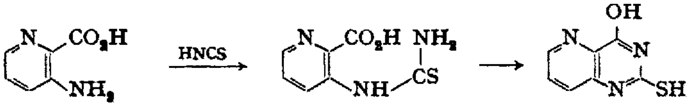
3,4-Dicarbamoylpyridine (CXXX) with sodium hypochlorite gives one compound, 2,4-dihydroxypyrido[3,4-d]pyrimidine (CXXXI).[180, 181] The same compound is obtained from 3-amino-4-carboxypyridine (CXXXII) by fusion with urea,[181] and formamide, acetamide,[181] and thiourea[182] give the expected analogous products. Similarly 2,3-dicarbamoylpyridine (CXXXIII) yields 2,4-dihydroxypyrido[2,3-d]pyrimidine (CXXXIV), but not the other possible [3,2-d]isomer.[183] The substance obtained from 4-carbamoyl-3-cyano-6-methylpyridine with hypochlorite and said to be 2,4-dihydroxy-6-methylpyrido[3,4-d]-pyrimidine[184] has been shown[183] to be an altogether different type of isomeric compound. 3-Amino-2-carbamoylpyridine (CXXXV) and formamide give 4-hydroxypyrido[3,2-d]pyrimidine (CXXXVI),[185] while

3-amino-2-carboxypyridine (CXXXVII) can be converted into the thioureide (CXXXVIII) and thence to 4-hydroxy-2-mercaptopyrido-[3,2-d]pyrimidine (CXXXIX);[186] analogous reactions using guanidine and cyanic acid yield respectively 2-amino-4-hydroxy- and 2,4-dihydroxy-pyrido[3,2-d]pyrimidine.[186]*


(CXXX) (CXXXI) (CXXXII)

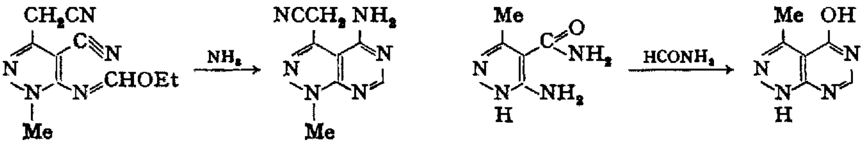

(CXXXIII) (CXXXIV)


(CXXXV) (CXXXVI)


(CXXXVII) (CXXXVIII) (CXXXIX)

F. Pyrazolopyrimidines from Pyrazoles

A number of pyrazolo[3,4-d]pyrimidines have been made[187–189] from pyrazole intermediates. Typical are the condensations of 4-cyano-


(CXL) (CXLI) (CXLII) (CXLIII)

3-cyanomethyl-5-ethoxymethyleneamino-1-methylpyrazole (CXL) with ammonia to give 4-amino-3-cyanomethyl-1-methylpyrazolo[3,4-d]-

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* These compounds are mistakenly named in the experimental section of reference 186.

pyrimidine (CXLI), or the refluxing of 5-amino-4-carbamoyl-3-methylpyrazole (CXLII) with formamide to give 4-hydroxy-3-methylpyrazolo[3,4-d]pyrimidine (CXLIII). Several pyrazolo[2,3-d]pyrimidines have also been made from pyrazoles,[188] and some pyrazolo[4,3-d]pyrimidines similarly.[190, 191]

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CHAPTER IV

Pyrimidine and Its *C*-Alkyl and *C*-Aryl Derivatives

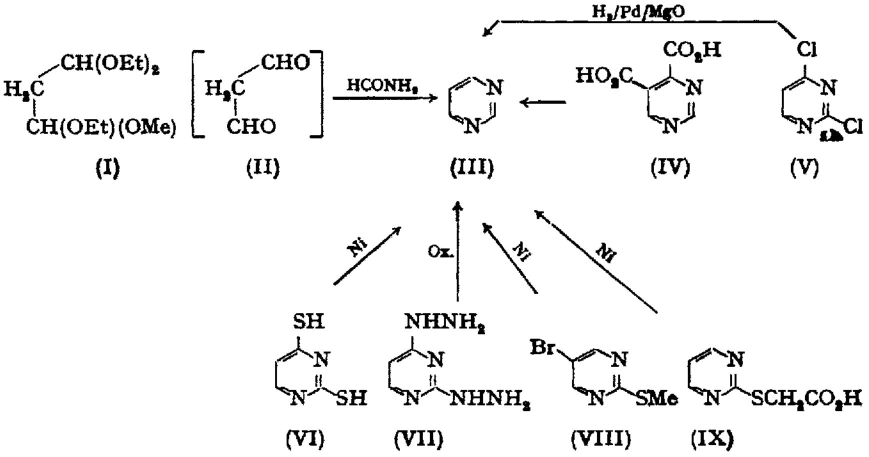
Pyrimidine was first prepared in Berlin by S. Gabriel and James Colman in 1899, some eighty years after the beginning of pyrimidine chemistry. But even then, it and the simple alkyl derivatives remained end-products and chemical curiosities for many years.

1. Pyrimidine (Unsubstituted)

Until recently, pyrimidine was an exceedingly rare substance, but several good methods of preparation have now made it readily available in quantity.

A. Preparation of Pyrimidine

The best way of making pyrimidine (III) in quantity is by the direct synthesis (Ch. III, Sect. 3.C) of Bredereck, Gompper, and Morlock[1-4] from the commercially available 1,3,3-triethoxy-1-methoxypropane (I) or other equivalent to malondialdehyde (II), and formamide. The process has even been made continuous by use of a heterogeneous catalyst.[5,6] The earliest methods of preparation were by decarboxylation of 4-carboxy-, or 4,6-dicarboxy-pyrimidine[7,8] (IV), and the latter has now been described as a useful preparative method on a reasonable scale.[9] Pyrimidine has also been made by dehalogenation of its 2,4,6-trichloro-, or 2,4,5,6-tetrachloro- derivative with zinc[10,11] but catalytic hydrogenations over palladium are much better. Thus 2-chloropyrimidine yields pyrimidine under a variety of conditions,[12] as do also 2,4,5,6-tetrachloro-,[13] 2,4,6-trichloro-,[13,14] 5-bromo-2,4-dichloro-,[15] 2,5-dichloro-,[16] 4,6-dichloro-,[13] and 2,4-dichloro-pyrimidine[13,15] (V). The last of these (in the presence of magnesium oxide) seems to be the most practical hydrogenation route to pyrimidine. Other less satisfactory but interesting methods have made use of 2-mercapto- or 2,4-dimercapto-pyrimidine (VI) with Raney nickel[9,12,17] or hydrogen peroxide,[9] and have started from 2,4-bisbenzenesulphonylhydrazinopyrimidine and 2,4-dihydrazinopyrimidine[12] (VII). 5-Bromo-2-methylthiopyrimidine (VIII) on boiling with Raney nickel gives pyrimidine (as mercurichloride) in 38% yield,[18] and 2-carboxymethylthiopyrimidine (IX) does so in 14% yield.[9]

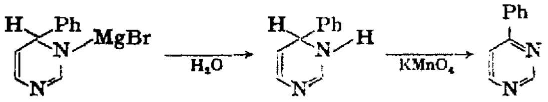


B. Properties of Pyrimidine

Pyrimidine is a water-soluble colourless hygroscopic solid of m.p. 22.5° and b.p. 124° (758 mm).[15] As a supercooled liquid it has n_D^{20}: 1.4960;[2] it has a dipole moment of 2.4 D,[19] and a resonance energy calculated at 26 Kcal[20] or 38 Kcal.[19] Electron density diagrams[19] (Ch. I, Sect. 5.A) and polarographic reduction data[21] have been published. It is a weak base (pK_a 1.3 and *ca.* —6.1) and forms a picrate (m.p. 156°),[2,7] an oxalate (m.p. 160°), a reineckate (m.p. 284–286°),[12] a methiodide (m.p. 136–137°),[15] and other salts and metal salt complexes as well as monoquaternary salts with dialkyl sulphates, *p*-toluenesulphonic esters, and bromoacetophenone.[5,6] Isolation of pyrimidine from aqueous solution is probably best done by continuous chloroform extraction[2] but use has been made of the insoluble mercuric chloride complex[12,16] from which it is best recovered by distillation with sodium sulphide.[16] Other metallic salt complexes are known,[5,7] and a complex with a flavan has been used to isolate and purify pyrimidine.[12]

C. Reactions of Pyrimidine

Unsubstituted pyrimidine resists nitration[16] but despite the widely held belief that pyrimidine would need at least one electron-releasing substituent to permit halogenation, it does in fact brominate in the 5-position.[5,6] This takes place only when pyrimidine hydrochloride is used as starting material, and it is not unreasonable to suppose that the mechanism is analogous to that of pyridine. In that case, a temperature of 500° is needed for the direct bromination of pyridine, but if the hydrochloride is used, a red perbromide can be isolated, and on heating to only 160° it gives 3-bromopyridine.[22] Diazotized *p*-nitroaniline does not couple with pyrimidine, but some 2- and 4-*p*-nitrophenylpyrimidines are formed.[16] The mono-*N*-oxide is formed in small yield by hydrogen peroxide in acetic acid,[6,9,23,24] the bulk of the pyrimidine being degraded by oxidation.[5] Hydrogenation of pyrimidine in the presence of acid yields tetrahydropyrimidine (as hydrochloride), and it has also been characterized as oxalate and benzoyl derivatives.[13] Pyrimidine is stable to cold alkali, but is slowly decomposed by boiling *N*-sodium hydroxide, and yields 60% of its nitrogen as ammonia in 60 hours. It leaves what is probably a polymer of acrolein.[24a] It is advantageous to use alkali during the isolation of pyrimidine made by dehalogenation, in order to decompose any tetrahydropyrimidine present.[13,15]

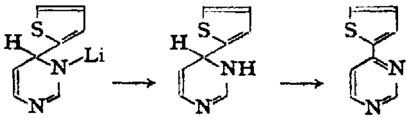


(X) (XI) (XII)

At room temperature, Grignard reagents readily add to the 3,4-bond of pyrimidine. The product (X) from phenylmagnesium bromide, after hydrolysis to (XI) and permanganate oxidation, yields 4-phenylpyrimidine (XII). 4-*p*-Tolyl-, 4-*p*-anisyl-, 4-α-furyl-, and 4-2′-thiazolylpyrimidine have been made similarly.[5,6]

Pyrimidine is even more reactive towards lithium derivatives. Thus 2-thiophen-lithium at 30° gives (XIII) which is hydrolysed to

(XIV) and then oxidized to the fully aromatic 4-2′-thienylpyrimidine[5,6] (XV). 4-Phenylpyrimidine, 4-*p*-tolylpyrimidine and other analogues were made similarly.[6]



(XIII) (XIV) (XV)

2. *C*-Alkyl and *C*-Aryl Pyrimidines

A. Preparation of Alkyl Pyrimidines

Most alkyl or aryl pyrimidines can be made by a direct synthesis with only the required groups already in place. The intermediates are, however, not always easy of access, and it is often easier to make a pyrimidine containing additional functional groups which can be later removed to obtain the required pyrimidine.* In any case, the alkyl groups are almost invariably put in position during the initial ring synthesis.

(1) *Direct Syntheses of Alkylpyrimidines*

Condensation of β-dialdehydes, β-aldehydo ketones, or β-diketones with an amidine could yield a great variety of alkyl and polyalkyl pyrimidines. Thus, for example, acetylacetone and methylacetylacetone with acetamidine yield 2,4,6-trimethylpyrimidine[25-27] and 2,4,5,6-tetramethylpyrimidine[27] respectively; other examples can be found in (Ch. II, Sect. 4). The condensation of amidines with αβ-unsaturated ketones[28] has also been used to produce polyaryl and alkyl aryl pyrimidines, such as 5-methyl-2,4,6-triphenylpyrimidine (Ch. III, Sect. 5.D). When no group is required in the 2-position, the direct synthesis of Bredereck, Gompper, and Morlock[1-3,6,29] is very useful and a variety of simple alkylpyrimidines have been so made (Ch. III, Sect. 3.C). Two other syntheses of alkyl and aryl pyrimidines by rather obscure routes[30,31] from simple nitriles have been already discussed (Ch. III, Sect. 3.D).

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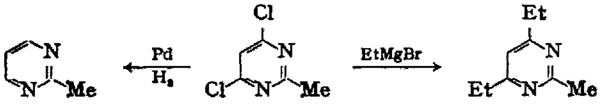
* The dangerous practice of considering alkyl and aryl groups as entirely non-functional has led to the indiscriminate introduction of these groups into pyrimidines simply because the intermediates may be more easily available. While this is clearly very undesirable in principle, it is only in recent years that unwanted and irrevelant alkyl groups are being avoided at all.

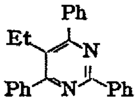
(2) *Alkylpyrimidines from Alkylchloropyrimidines*

Alkylpyrimidines with 2-, 4-, or 6-hydroxy groups are readily made, and are easily converted into alkylchloropyrimidines. Pyrimidines with halogen in the 5-position are also readily available. Dehalogenation of all these compounds yields alkylpyrimidines, and in addition the 2-, 4-, and 6-chloro groups can sometimes be replaced by another alkyl group through the use of a Grignard reagent, or phenyl-lithium, or the reaction described in (Ch. VI, Sect. 5.J).

Thus for example 4,6-dichloro-2-methylpyrimidine (XVII), on hydrogenation over palladized charcoal in the presence of a base, yields 2-methylpyrimidine (XVI) in 96% yield.[13,32] The same compound on treatment with ethyl magnesium bromide gives 4,6-diethyl-2-methylpyrimidine[33] (XVIII). Another Grignard example is the treatment of 4-chloro-5-ethyl-2,6-diphenylpyrimidine with phenyl magnesium bromide to give 5-ethyl-2,4,6-triphenylpyrimidine,[30] (XIX) and similarly phenyl-lithium reacts with 4-chloro-2,6-diphenyl-5-propylpyrimidine to give 2,4,6-triphenyl-5-propylpyrimidine.[30] Other examples of the use of alkyl-lithium derivatives[34] and a replacement of chloro by benzyl under Friedel–Crafts conditions are known.[35] Other examples of alkylpyrimidines produced by dehalogenation are contained in Table VIII. Perhaps it scarcely needs emphasizing that hydrogenation is now normally the best method of reductive dehalogenation.



(XVI) (XVII) (XVIII)



(XIX)

(3) *Alkylpyrimidines from their Carboxy,* Mercapto and Other Derivatives*

Alkylpyrimidines have also been prepared by removal of groups other than halogen. Thus 2-carboxy-4,6-dimethyl-, 5-carboxy-4-methyl-2,6-diphenyl-, and 5-carboxy-2,4,6-triphenyl-pyrimidines yield on distillation, respectively 4,6-dimethyl-,[7] 4-methyl-2,6-diphenyl-,[52] and 2,4,6-triphenyl-pyrimidine.[52] Removal by Raney nickel of a mercapto group from the 2-position of the appropriate pyrimidine gives

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* The reactions described in (Ch. VI, Sect. 5.J) are also relevant.

TABLE VIII. Some Alkyl and Aryl pyrimidines Produced by Dehalogenation

Pyrimidine Produced and Yield	Starting Pyrimidine	Reagent	References
2-methyl-; 47%	4-chloro-2-methyl-	H_2; Pd/$BaCO_3$; NH_3	36
2-methyl-; 38%	4-chloro-2-methyl-	Zn/H_2O	37
2-methyl-; 84%	4-chloro-2-methyl-	H_2; Pd/C; NH_3	38
2-methyl-; 92%	4,6-dichloro-2-methyl-	H_2; Pd/C; NaOH	13
2-methyl-	4,6-dichloro-2-methyl-	H_2; Pd/C; MgO	32
4-methyl-; 65%	4-chloro-6-methyl-[c]	H_2; Pd/$BaCO_3$; NH_3	36
4-methyl-; 35%	2,4-dichloro-6-methyl-	Zn/H_2O	7, 36, 39
4-methyl-	2,4-dichloro-6-methyl-	H_2; Pd; $CaCO_3$	40
4-methyl-; 30 & 68 & 75%	2,4-dichloro-6-methyl-	H_2; Pd/C; MgO	36, 41, 42
4-methyl-; 93%	2,4-dichloro-6-methyl-	H_2; Pd/C; NaOH	13
4-methyl-; 38%	2,4-dichloro-6-methyl-	H_2; Pd/C; NH_3	38
4-methyl-; 43%	5-bromo-2,4-dichloro-6-methyl-	H_2; Pd/C; MgO	43
5-methyl-; 70%	4-chloro-5-methyl-	H_2; Pd/$BaCO_3$; NH_3	36
5-methyl-; 87%	2,4-dichloro-5-methyl-	H_2; Pd/C; NaOH	13
5-methyl-; 55%	2,4,6-trichloro-5-methyl-	H_2; Pd/C; MgO	42
2-phenyl-; 90%	5-chloro-2-phenyl-	H_2; Pd/$BaSO_4$; NaOH	16
2-phenyl-	4-chloro-2-phenyl-	H_2; Pd/$BaSO_4$; NaOH	16
2-phenyl-; 84%	4-chloro-2-phenyl-	H_2; Pd/$BaCO_3$; NH_3	36
Not 2-phenyl-;[a] 46%	5-bromo-4-chloro-2-phenyl-(?)	Zn/H_2O	44
4-phenyl-	4-chloro-6-phenyl-	H_2; Pd/$BaCO_3$; NH_3	36
4-phenyl-	2-chloro-4-phenyl-	H_2; Pd/$BaSO_4$; NaOH	16
4-phenyl-	2,4-dichloro-6-phenyl-	H_2; Pd; $CaCO_3$	40
5-phenyl-	4-chloro-5-phenyl-	H_2; Pd/$BaSO_4$; NaOH	16
4-amyl-[b]	4-amyl-2,6-dichloro-	H_2; Pd; $CaCO_3$	46
2,4-dimethyl-; 65%	4-chloro-2,6-dimethyl-	Zn/H_2O	48
2,5-dimethyl-	4,6-dichloro-2,5-dimethyl-	H_2; Pd/C; MgO	32
2-butyl-4-methyl-	2-butyl-4-chloro-6-methyl-	H_2; Pd; $CaCO_3$	46
4-methyl-2-phenyl-	4-chloro-6-methyl-2-phenyl-	Zn/H_2O	48
4-methyl-6-phenyl-	2-chloro-4-methyl-6-phenyl-	HI/red P[d]	50
2-benzyl-4-methyl-	2-benzyl-4-chloro-6-methyl-	Zn/H_2O	51
4-benzyl-6-methyl-	4-benzyl-2-chloro-6-methyl-	Zn/H_2O	51

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[a] This compound described as 2-phenylpyrimidine[44] melted 90° above that obtained later in three other ways.[16]

[b] A compound previously described as 4-amylpyrimidine[51] was shown to be so described in error.[46]

4-methylpyrimidine,[9] 5-phenylpyrimidine,[53] 4-methyl-6-phenylpyrimidine,[53] and 4,6-dimethylpyrimidine.[9,12] The last compound is better so prepared than by the above decarboxylation. It has also been made by the oxidative removal[12] of the hydrazino group from 2-hydrazino-4,6-dimethylpyrimidine (prepared from the 2-chloro analogue), and in the same way 4-methylpyrimidine has been made from its 2-hydrazino derivative.[54] Although direct removal of a hydroxy group is a most uncommon process in the series, 2-ethyl-4-hydroxy-6-methylpyrimidine when distilled with zinc dust gives 2-ethyl-4-methylpyrimidine.[55]

(4) *Interconversion of Alkyl Groups in Pyrimidines*

There are several examples of the preparation of one alkyl pyrimidine from another. 2,4,6-Trimethylpyrimidine with phenyl-lithium, followed by methyl iodide or dodecyl bromide, gives respectively 4-ethyl-2,6-dimethylpyrimidine[27] or 2,4-dimethyl-6-tridecylpyrimidine.[56] By less direct means, 4-methylpyrimidine (XX) can be converted by formaldehyde into 4-hydroxyethylpyrimidine (XXI) which on treatment with molten potassium hydroxide yields 4-vinylpyrimidine[41] (XXII), and hydrogenation gives 4-ethylpyrimidine[41] (XXIII). Rather analogously 2- and 4-methylpyrimidine condense with benzaldehyde giving respectively 2-styrylpyrimidine[32] and the 4-isomer;[57] the latter has been hydrogenated to 4-phenylethylpyrimidine[51] and other such reductions are known.[26] Conversion of methyl into styryl groups is more fully treated in section 3.C(1). One other method of producing a styrylpyrimidine can be mentioned here: it is the condensation of a pyrimidine aldehyde with the active methylene group of *p*-nitrophenylacetic acid (followed by decarboxylation).

$$\mathrm{RCHO + H_2C(CO_2H)C_6H_4NO_2 \longrightarrow RCH{:}CHC_6H_4NO_2 + CO_2 + H_2O}$$

The compound produced in this way was 4-hydroxy-6-methyl-5-*p*-nitrostyryl-2-piperidinopyrimidine.[58]

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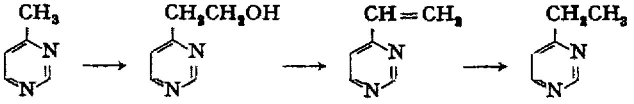
[c] 2-Chloro-4-methylpyrimidine did not give satisfactory results.

[d] Dechlorination with hydriodic acid can have surprising results as in the formation of 4-hydroxy-,[45] 4-hydroxy-5,6-dimethyl-,[75] and 4-hydroxy-6-ethyl-[47] pyrimidine from the corresponding 2,4-dichloro derivatives; as in the formation of 4-hydroxy-6-methyl- or 4-iodo-6-methyl-pyrimidine according to conditions from 2,4-dichloro-6-methylpyrimidine;[7,49] and as in the formation of 4-iodo-6-methylpyrimidine from the 4-chloro analogue.[49]

It was at one time believed[51] by analogy with a pyridine analogue[59,64] that 4-methylpyrimidine when treated with sodamide and butyl bromide gave 4-amylpyrimidine. The same authors showed

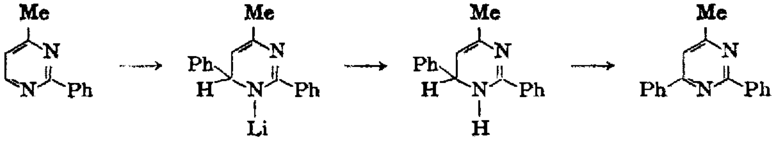


(XX) (XXI) (XXII) (XXIII)

later that it was, however, neither 4-amylpyrimidine nor 2-butyl-4-methylpyrimidine[46] by unequivocal syntheses of these substances.

(5) *Direct Introduction of Alkyl Groups*

Besides the examples mentioned in Sects. 2.C and 3.A(4), and in Ch. VI, Sect. 5.J, there are cases of introduction of alkyl or aryl groups. 4-Methyl-2-phenylpyrimidine (XXIV) adds phenyl-lithium to give (XXV), and hydrolysis yields 1,6-dihydro-4-methyl-2,6-diphenylpyrimidine (XXVI) which has been isolated, and oxidized with permanganate to 4-methyl-2,6-diphenylpyrimidine (XXVII). Similar treatment of 4-methylpyrimidine gave a mixture of the 2- and 6-phenyl derivatives which, however, were not isolated.[56] 2-Aminopyrimidine and phenyl-lithium give only 2-amino-4-phenylpyrimidine.[65] When 2-dimethylaminopyrimidine was treated with one equivalent of butyl-lithium, 4-butyl-2-dimethylaminopyrimidine was formed; with three equivalents, 4,6-dibutyl-2-dimethylaminopyrimidine.[66] The above re-



(XXIV) (XXV) (XXVI) (XXVII)

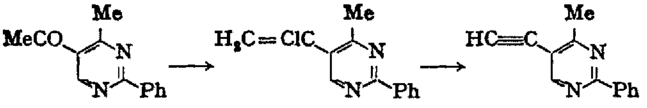
actions are more of theoretical than of synthetic importance at this stage of their development, but the conversion of 5-methylpyrimidine into its 4-phenyl derivative goes with phenyl-lithium in 37 % yield.[29]

Barbituric acid and its derivatives with a free 5-position, condense with benzaldehyde or with αα-dichlorodiphenylmethane giving respectively the 5-phenylmethylene and 5-diphenylmethylene derivatives.[60,61]

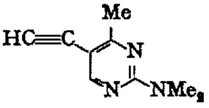
These can be reduced with zinc and acetic acid to the corresponding 5-benzyl or 5-diphenylmethyl derivatives.[61] Hexamethylenetetramine and barbituric acid gives the rather unstable 5-methylenebarbituric acid, as the ammonium salt.[62] Alkylation in the 5-position of barbituric acid has been occasionally reported: for example allyl bromide and sodium acetate is said to yield 5-allyl- or 5,5-diallylbarbituric acid according to the amount of allyl bromide.[63]

(6) *Ethynylpyrimidines*

5-Acetyl-4-methyl-2-phenylpyrimidine (XXVIII) has been converted with phosphorus pentachloride into the 5-α-chlorovinylpyrimidine (XXIX) which with potassium hydroxide gave 5-ethynyl-4-methyl-2-phenylpyrimidine (XXX). The 2-dimethylamino analogue (XXXI) has been similarly made.[67]



(XXVIII) (XXIX) (XXX)



(XXXI)

B. Properties of Alkylpyrimidines

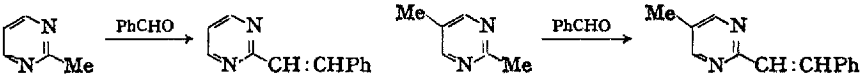
The alkylpyrimidines are liquids or low melting solids similar to pyrimidine (Sect. 2.B) in properties and forming similar salts and complexes. The lower members are highly soluble in all kinds of solvent and being rather more lipophilic than the parent, they are the more readily removed from aqueous solution by continuous extraction with chloroform or even ether. Boiling points and melting points rise as would be expected with molecular weight, for example from 2-methylpyrimidine (b.p. 138°; m.p. —4°) to 4,6-diphenylpyrimidine (b.p. 190°/0.01 mm; m.p. 103°). The methyl pyrimidines are slightly stronger bases than pyrimidine, *e.g.* 4-methylpyrimidine has pK_a 2.0.

C. Reactions of Alkyl and Aryl Pyrimidines

Besides analogous reactions to the parent pyrimidine, the alkyl pyrimidines undergo several reactions directly associated with the alkyl groups. When they occur in the 2-, 4-, or 6-position, methyl groups are active in the sense of that in 2,4-dinitrotoluene, but in the 5-position a methyl group resembles more closely that of toluene itself.

(1) *Methyl- to Styryl-pyrimidines*

Methyl groups in the 2-, 4-, or 6-position of a pyrimidine can generally be converted to styryl derivatives by condensation with benzaldehyde or *p*-dimethylaminobenzaldehyde. Thus 2-methylpyrimidine or 4-methylpyrimidine with benzaldehyde in the presence of zinc chloride gives 2-styrylpyrimidine[32] (XXXIII) or the 4-isomer.[57] 2,4-Dimethylpyrimidine similarly gives 2,4-distyrylpyrimidine[57] and 4,6-dimethyl-2-phenylpyrimidine gives 2-phenyl-4,6-distyrylpyrimidine.[68] 2,5-Dimethylpyrimidine (XXXIV), however, gives only 5-methyl-2-styrylpyrimidine (XXXV) because the 5-methyl group is inactive.[32] 2,4,6-Trimethylpyrimidine on the other hand gives with an excess of benzaldehyde (zinc chloride) 2,4,6-tristyrylpyrimidine,[25,69] and with less benzaldehyde a mixture of dimethylstyrylpyrimidine and methyldistyrylpyrimidine.[69,70] The first of these was said to be 4,6-dimethyl-2-styrylpyrimidine on the evidence of oxidation studies[70] but it seems more likely to be 2,4-dimethyl-6-styrylpyrimidine.[26] It would seem therefore that 4-methyl groups are more reactive towards aldehydes than are 2-methyl groups. Styryl group formation is also successful in the presence of other groups as shown by the formation (with zinc chloride) of 5-bromo-2-styrylpyrimidine from 5-bromo-2-methylpyrimidine.[18]

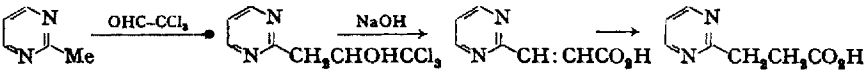


(XXXII) (XXXIII) (XXXIV) (XXXV)

Zinc chloride is not always the catalyst of choice: this is particularly true when the starting methylpyrimidine contains hydroxy groups, which deactivate the methyl group. Thus 2,4-dihydroxy-6-methylpyrimidine does not condense with benzaldehyde in the presence of zinc chloride, acetic anhydride, alcoholic sodium hydroxide, or even piperidine,[71] but when the methyl group is partly reactivated by insertion of a 5-nitro group (2,4-dihydroxy-6-methyl-5-nitropyrimidine), the styryl compound can be formed at least in the presence of piperidine.[71] Likewise *p*-dimethylaminobenzaldehyde condenses neither with 2,4-dihydroxy-6-methylpyrimidine nor its 2-mercapto analogue in the presence of zinc chloride, but does so in aniline; the anil seems to be almost certainly implicated[72] in preparation of the 2,4-dihydroxy- and 4-hydroxy-2-mercapto-6-styrylpyrimidine. Benzaldehyde itself does not condense under these conditions.[72] Again, while *p*-dimethylaminobenzaldehyde is catalysed by zinc chloride to react with 4-methylpyrimidine to give 4-*p*-dimethylaminostyrylpyrimidine,[73] it reacts better with 2-hydroxy-4,6-dimethylpyrimidine in the presence of a piperidine or hydrochloric acid catalyst to give 4-*p*-dimethylaminostyryl-6-methyl- or 4,6-bis-*p*-dimethylaminostyryl-2-hydroxypyrimidine according to the amount of aldehyde.[73,74] 2-Amino-4,6-dimethylpyrimidine condenses similarly in acetic anhydride to yield 2-acetamido-4-*p*-dimethylaminostyryl-6-methylpyrimidine.[73] Among other aldehydes used to form styryl compounds in the series are 3,4-dihydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde,[73] and *p*-nitrobenzaldehyde.[71]

(2) *Chloral with Methylpyrimidines*

When the aliphatic aldehyde, chloral, is condensed with 2-methylpyrimidine (XXXVI) no elimination of water occurs (as would happen with benzaldehyde), and 2-(3,3,3-trichloro-2-hydroxypropyl)pyrimidine (XXXVII) is formed. Treatment of this with sodium hydroxide yields the unsaturated 2-*β*-carboxyvinylpyrimidine (XXXVIII), which on reduction gave 2-*β*-carboxyethylpyrimidine (XXXIX). These reactions have also been done with 4-methylpyrimidine[38] as starting material.



(XXXVI) (XXXVII) (XXXVIII) (XXXIX)

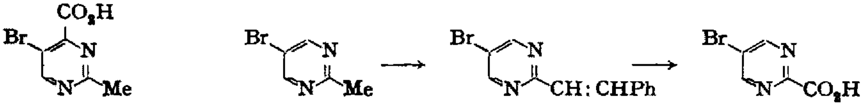
(3) *Permanganate Oxidation of Alkyl- to Carboxy-pyrimidines: Removal of Alkyl Groups*

Oxidation to a carboxy group and decarboxylation constitutes the only effective way to remove an alkyl group from a pyrimidine. The process is therefore of some importance. For example, 4-methylpyrimidine on treatment with permanganate yields 4-carboxypyrimidine,[7] the decarboxylation of which once constituted an important preparation of pyrimidine. Similarly 4,6-dimethylpyrimidine with a limited amount of permanganate[8] (XL) gives 4-carboxy-6-methyl- or, more easily, 4,6-dicarboxy-pyrimidine (XLI),[8,9] but (as with formation of styryl derivatives) 4,5-dimethylpyrimidine (XLII) gives only 4-carboxy-5-methylpyrimidine (XLIII), the 5-methyl group being resistant to attack;[75] decarboxylation gave 5-methylpyrimidine. Phenyl groups are also resistant to oxidative attack in any position. Thus 4,6-dimethyl-2-phenylpyrimidine (XLIV) with permanganate gives (according to the amount of reagent) 4-carboxy-6-methyl- or 4,6-dicarboxy-2-phenylpyrimidine (XLV).[25] When, however, the phenyl group carries a *p*-hydroxy group as in 2-*p*-hydroxyphenyl-4,6-dimethylpyrimidine (XLVI) it is even more easily oxidized than are the methyl groups, and controlled oxidation yields 2-carboxy-4,6-dimethylpyrimidine[7] (XLVII) which was decarboxylated to 4,6-dimethylpyrimidine. Quinazoline is oxidized under vigorous conditions to 4,5-dicarboxypyrimidine.[76]


(XL) (XLI) (XLII) (XLIII)


(XLIV) (XLV) (XLVI) (XLVII)

As in other series it often seems advantageous to convert methyl to styryl groups before oxidation to carboxylic acids. Thus while 5-bromo-4-carboxy-2-methylpyrimidine (XLVIII) resisted both nitric


(XLVIII) (XLIX) (L) (LI)

acid* and permanganate oxidation,[18] the closely related 5-bromo-2-methylpyrimidine (XLIX) after prior conversion into 5-bromo-2-

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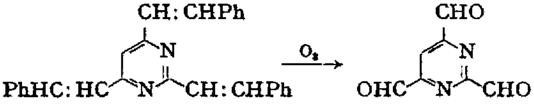
* However, at least with nitric acid, the corresponding 4-carboxy-5-chloro-2-methylpyrimidine gave 2,4-dicarboxy-5-chloropyrimidine.[77]

styrylpyrimidine (L) readily gave with permanganate, 5-bromo-2-carboxypyrimidine[18] (LI). Similarly 2-styrylpyrimidine and its 5-methyl derivative gave respectively 2-carboxy- and 2-carboxy-5-methylpyrimidine.[32] Unfortunately no direct experiments are recorded on the efficacy of forming a styryl group prior to oxidation.

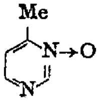
(4) *Other Oxidations of Alkylpyrimidines;* N-*Oxides*

When 2,4,6-tristyrylpyrimidine (LII) was treated with ozone, 2,4,6-triformylpyrimidine (LIII) was formed and isolated as a mono-*p*-nitrophenylhydrazone.[69] Aldehydes are similarly formed from a dimethylstyrylpyrimidine and from a methyldistyrylpyrimidine,[70] but the isomeric configurations are not yet beyond doubt.[26,70]

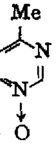
Although pyrimidine is largely destroyed during *N*-oxide formation, the alkylpyrimidines give much better yields. Of the two methods which have been used, hydrogen peroxide in acetic acid solution at 70° is the better. In this way 4-methylpyrimidine-*N*-oxide is formed in 28–43 % yield,[5,6,23,78] but by the use of peracetic acid in ether only 8 % was obtained.[78,79] Other preparations using the former method include 2-methylpyrimidine-1-oxide, 31 %;[23] 5-methylpyrimidine-1-oxide, 36 %;[23] 2,4-dimethylpyrimidine-*N*-oxide, 44 %;[78] 4,6-dimethyl-1-oxide, 75 %;[5,6,9] 4-methyl-6-phenylpyrimidine-*N*-oxide, 74 %;[5,6] 2,4,6-trimethylpyrimidine-1-oxide, 36 %.[23] It is not yet known which ring nitrogen atom is involved in oxide formation in such a case as 4-methylpyrimidine-*N*-oxide, (LIV) or (LV). 2-Phenylpyrimidine and several other derivatives failed to give *N*-oxides.[9] Pyrimidine-*N*-oxides have been reviewed[80] (in Japanese).



(LII) (LIII)

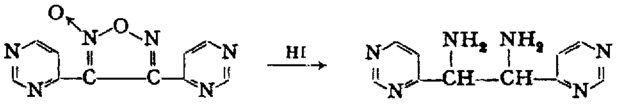


(LIV)



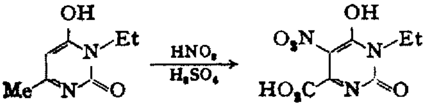
(LV)

When attempts were made to nitrate 4-methylpyrimidine, only oxidation occurred and a base $C_{10}H_6N_6O_2$ was isolated. On reduction with hydrogen iodide, a stronger base $C_{10}H_{12}N_6$ was formed. By comparison with benzene analogues these compounds were formulated[81] respectively as the oxadiazole (LVI) and the diaminoethane derivative (LVII). 2,4-Dimethylpyrimidine forms a similar compound, but it is not known whether the 2- or the 4-methyl groups are involved in the new ring.[81]

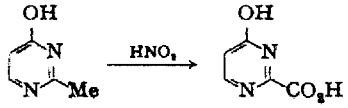


(LVI) (LVII)

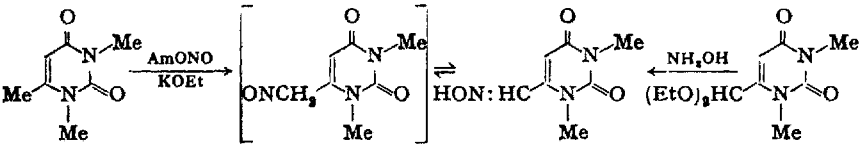
At least one example of simultaneous nitration and methyl group oxidation is known.* 3-Ethyl-6-methyluracil (LVIII) on treatment with nitric and sulphuric acids gives in 43 % yield, 6-carboxy-3-ethyl-5-nitrouracil[83] (LIX). Nitrous acid has also been implicated as an oxidizing agent of 4-hydroxy-2-methylpyrimidine (LX) to 2-carboxy-4-hydroxypyrimidine (LXI) but unfortunately experimental details are lacking.[84,85] An interesting oxidation of the C-methyl group in 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine (LXII) to an aldehyde, occurs on treatment in ether with isoamyl nitrite in the presence of potassium ethoxide. A Claisen type of condensation ensues giving the nitroso compound (LXIII) which is in fact the aldehyde oxime, 1,2,3,4-tetrahydro-6-hydroxyiminomethyl-1,3-dimethyl-2,4-dioxopyrimidine[42] (LXIV). The structure was established[42] by unambiguous



(LVIII) (LIX)



(LX) (LXI)



(LXII) (LXIII) (LXIV) (LXV)

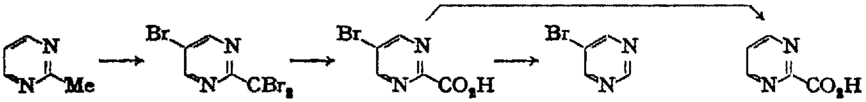
synthesis with hydroxylamine from the corresponding diethylacetal, 4-diethoxymethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (LXV), which was made by methylation of the known 4-diethoxymethyl-2,6-dihydroxypyrimidine.[87]

* An example of nitric acid oxidation after nitration is the conversion of 2,4-dihydroxy-6-methyl-5-nitropyrimidine into 4-carboxy-2,6-dihydroxy-5-nitropyrimidine in 78% yield.[83]

Methylpyrimidines have been directly converted into carbamoyl derivatives by oxidation with potassium ferricyanide and ammonia. Examples are the preparation of 4-carbamoyl-2,6-dihydroxypyrimidine,[86] 6-carbamoyl-1-methyluracil,[88] and 4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine.[88]

(5) *Halogenation of Alkylpyrimidines*

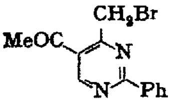
Little use has been made of the ability of methyl or other alkyl pyrimidines to halogenate either on the alkyl group or in the 5-position. Indeed it was for a long time considered that 5-bromination was impossible in a pyrimidine unless an electron-releasing group was present.[89] Pyrimidine itself, however, can be brominated[5] and when 2-methylpyrimidine (LXVI) is brominated "in glacial acetic acid in the presence of fused sodium acetate" not only is the methyl converted into a tribromomethyl group but a 5-bromo group is also introduced, giving 5-bromo-2-tribromomethylpyrimidine[90] (LXVII). Treatment with silver nitrate and acetic acid[91] gave 5-bromo-2-carboxypyrimidine (LXVIII) which on decarboxylation gave 5-bromopyrimidine (LXIX), and on dehalogenation, 2-carboxypyrimidine[90] (LXX). These reactions not only confirmed the structure of (LXVII) but also formally constitute another route whereby a methyl group may be removed. 4,6-Dimethylpyrimidine gives similarly 4,6-bistribromomethypyrimidine,[9] and 4-methyl- gives 4-di(or tri)bromo(or chloro)methyl-pyrimidine.[106]

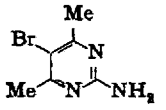


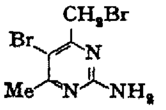
(LXVI) (LXVII) (LXVIII) (LXIX) (LXX)

Other brominations of methyl groups have been recorded. 5-Acetyl-4-methyl-2-phenylpyrimidine on treatment with bromine in chloroform gives 5-acetyl-4-bromomethyl-2-phenylpyrimidine[92] (LXXI). 2-Amino-4,6-dimethylpyrimidine when brominated in boiling acetic acid in ultraviolet light and with peroxide gives mainly 2-amino-5-bromo-4,6-dimethylpyrimidine (LXXII) but a little 2-amino-5-bromo-4-bromomethyl-6-methylpyrimidine (LXXIII). When the reaction is done in water there is formed in addition to (LXXII) and (LXXIII), some 2-amino-5-bromo-4,6-bisbromomethylpyrimidine[93] (LXXIV).

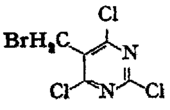
N-Bromosuccinimide is a convenient reagent for bromination of methyl groups, and has been used with pyrimidines. In this way 2,4,6-trichloro-5-methylpyrimidine yields 5-bromomethyl-2,4,6-trichloropyrimidine (LXXV) in 78% yield. Direct bromination in strong light gives a comparable yield (85%). 4,6-Dichloro-2,5-dimethylpyrimidine (LXXVI) likewise with *N*-bromosuccinimide gives 5-bromomethyl-4,6-dichloro-2-methylpyrimidine (LXXVII) (74%) and in this case is more specific than is direct bromination, which also substitutes a bromine for one chlorine atom, giving 4-bromo-5-bromomethyl-6-chloro-2-methylpyrimidine[94] (LXXVIII) in 45% yield.

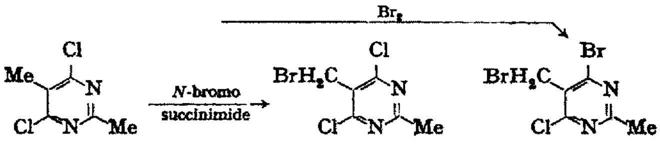

(LXXI)


(LXXII)


(LXXIII)

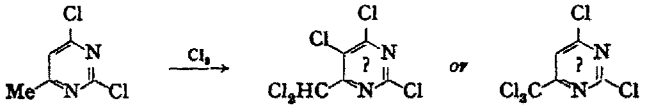

(LXXIV)


(LXXV)



(LXXVI) (LXXVII) (LXXVIII)

The chlorination at 140° of 2,4-dichloro-6-methylpyrimidine (LXXIX) gives a single pentachloro compound which is probably 2,4,5-trichloro-6-dichloromethylpyrimidine (LXXX) or 2,4-dichloro-6-trichloromethylpyrimidine[81] (LXXXI). The formation of 5-chloromethyluracil is discussed in Chapter VI, Sect. 3.A, because its reported direct preparation has proven wrong.



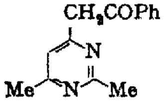
(LXXIX) (LXXX) (LXXXI)

(6) *Claisen Reactions of Methylpyrimidines*

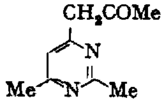
The Claisen condensation of a nitrite ester with a methyl pyrimidine has already been mentioned (Sect. 3.C(4)), and, not surprisingly, carboxylic esters also undergo such condensation. Thus 4-methylpyrimidine (LXXXII) and diethyl oxalate with potassium ethoxide in ether gives 4-ethoxyoxalylmethylpyrimidine (LXXXIII) in 60% yield[42]; sodamide catalysis gives only 12% yield.[26] Further study of some twenty varied methylpyrimidine derivatives, with the same ester and potassium ethoxide, has indicated the scope of the reaction:[42] only "active" 2-, 4-, or 6-methyl groups condense; "inactive" *N*- or 5-methyl groups do not; 4- and 6-methyl groups are rather more active than 2-groups; the presence of methoxy or oxo groups does not preclude condensation of active methyl groups but more than one amino group does so, by deactivation. Nitro groups strongly activate methyl groups but introduce untoward side issues. When two or three active methyl groups are present in the molecule, only one undergoes condensation.

Ethyl benzoate and phenyl acetate have also been used,[26] in these cases with 2,4,6-trimethylpyrimidine in the presence of sodamide, giving respectively 2,6-dimethyl-4-phenacylpyrimidine (LXXXIV) and 4-acetonyl-2,6-dimethylpyrimidine (LXXXV). The fact that condensation had taken place at position-4 was checked by independent synthesis of (LXXXIV).

(LXXXII) (LXXXIII)



(LXXXIV)

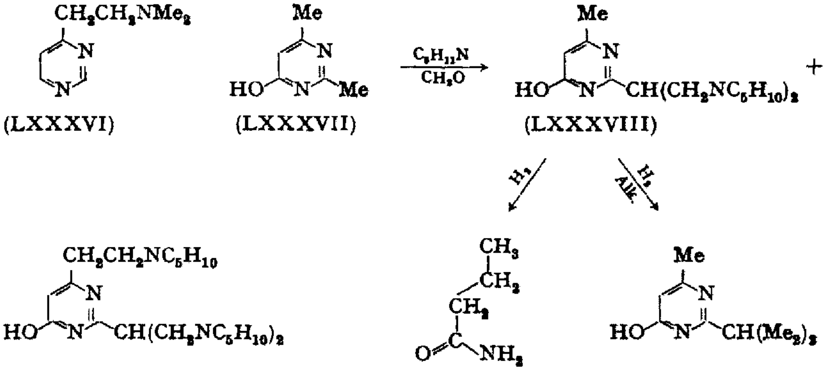


(LXXXV)

(7) *Mannich Reactions of Methylpyrimidines*

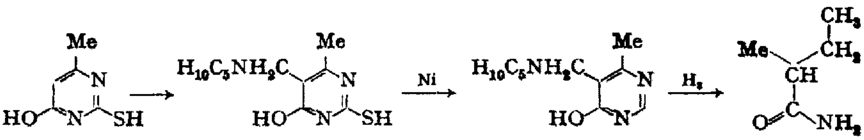
4-Methylpyrimidine reacts with formaldehyde and dimethylamine in acid solution to give a 70% yield of the Mannich base 4-dimethylaminoethylpyrimidine[41] (LXXXVI). 2,6-Dimethyl-4-hydroxypyrimidine (LXXXVII), formaldehyde, and piperidine (or morpholine, but not dimethylamine) react less simply to give 2-bis(piperidinomethyl)-methyl-4-hydroxy-6-methylpyrimidine (LXXXVIII) and probably 2-bis(piperidinomethyl)methyl-4-hydroxy-6-piperidinomethylpyrimidine (LXXXIX) (or the corresponding morpholino derivatives).[95] The structure (LXXXVIII) was based largely on neutral reductive cleavage to butyramide (XC) and alkaline hydrogenation to 4-hydroxy-2-isopropyl-6-methylpyrimidine (XCI). It would seem that the 2- is more reactive than the 4-methyl group in this reaction, whereas on the available evidence the reverse is true in styryl group formation (Sect. 3.C(1)), and in the Claisen Reaction (Sect. 3.C(6)).

When a similar Mannich condensation was tried with 4-hydroxy-2-mercapto-6-methylpyrimidine (XCII) (or its *S*-ether, 4-hydroxy-6-methyl-2-methylthiopyrimidine), the methyl group was not involved. Instead, a piperidinomethyl group was introduced in the 5-position,



(LXXXVI) (LXXXVII) (LXXXVIII) (LXXXIX) (XC) (XCI)

giving 4-hydroxy-2-mercapto-6-methyl-5-piperidinomethylpyrimidine[97] (XCIII). The structure was based mainly on the isolation of 2-methylbutyramide (XCV) after vigorous hydrogenation of the desulphurized product (XCIV). It would not be easy to predict that the reaction would take such a fundamentally different course with (LXXXVII) and with (XCII), but it is clearly associated with the further deactivation of the methyl group by the added electron-supplying group in (XCII). Since the type of Mannich reaction with an active methyl is no longer possible, the alternate "phenol type" of Mannich[99] takes place at the site now ready for electrophilic substitution, the 5-position.



(XCII) (XCIII) (XCIV) (XCV)

Other examples[96,98] are known. They include the preparation of the following from the corresponding 5-unsubstituted pyrimidines: 4,6-dihydroxy-2-methyl-, 4-hydroxy-2-methyl-6-methylamino-, and 4-amino-6-hydroxy-2-methyl-, 5-piperidinomethylpyrimidine (and analogues). The last-named compound gave, with an excess of formaldehyde and piperidine, 4-hydroxy-2-methyl-5-piperidinomethyl-6-piperidinomethylaminopyrimidine.[98, 103]

A compound produced from (XCII) under acid conditions with piperidine and formaldehyde and also formulated as (XCIII) without structural evidence,[100] has been shown[97] to be different to the authentic (XCIII). The structure of the analogous "5-diethylaminomethyl-4-hydroxy-2-mercapto-6-methylpyrimidine"[100] must therefore be treated as doubtful.

The methyl group of thymine (2,4-dihydroxy-5-methylpyrimidine) can be involved in a Mannich reaction[104] to give 2,4-dihydroxy-5-morpholino(*or* piperidino)methylpyrimidine. The structures of these products were proven,[104] and a previous suggestion[105] for the second one, is therefore in error.

(8) *Other Reactions of Alkyl and Aryl Pyrimidines*

Pyrimidines containing only alkyl groups have not been successfully nitrated, but oxidation takes place under nitrating conditions (Sect. 3.C(4)). 2- And 4-phenylpyrimidine on the other hand readily nitrate in the benzene ring giving respectively 2- and 4-*m*-nitrophenylpyrimidine.[16] This behaviour should be contrasted with that of 2- and 4-phenylpyridine which yield a threefold mixture of *o*-, *m*-, and *p*-nitrophenylpyridine in each case.[101] The mononitro derivative obtained from 4,6-dimethyl-2-phenylpyrimidine[68] has been shown by direct synthesis to be 4,6-dimethyl-2-*m*-nitrophenylpyrimidine.[16]

4-Methylpyrimidine can be directly aminated with sodamide in decalin. The product contains 2-amino- and 2,4-diamino-6-methylpyrimidine.[102]

Several other reactions of methylpyrimidines have been dealt with under the heading of "interconversion of alkyl groups" (Sect. 3.A(4)) and with them should now be mentioned the polymerization[41] of 4-vinylpyrimidine (in the presence of 2,2′-azobisisobutyronitrile) to a polymer of molecular weight around 870.

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CHAPTER V

Nitro-, Nitroso-, and Arylazo-pyrimidines

Nitro, nitroso, and arylazo derivatives have several points in common. They are known only in the 5-position of pyrimidine (with a very few exceptions). They can all be introduced by direct synthesis or by an electrophilic substitution. These electrophilic substitutions are permitted only when electron-releasing groups are already attached to the ring: one is sufficient for arylazo introduction; two are normally required for nitrations or nitrosations. On reduction, all these derivatives give a 5-amino pyrimidine, and indeed this is their main use in pyrimidine chemistry.

1. The Nitropyrimidines

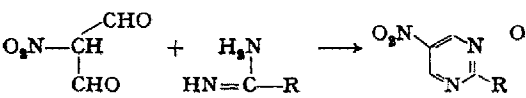
The most interesting aspect of the nitro group is its activating effect on other groups such as halogeno, methylthio, methoxy, mercapto, and even methyl. Being strongly electron-withdrawing, the nitro group activates such substituents towards nucleophilic replacement to a marked degree. Thus, while 2,4-dichloropyrimidine requires ammonia at 100° for 2 hours[1] (or at 20° for 18 hours)[2] to replace one chlorine atom, 2,4-dichloro-5-nitropyrimidine undergoes a similar reaction at 0° in a few minutes.[3] These effects are dealt with under the heading of the activated group: *e.g.* the activation of a methyl by a nitro group in styryl group formation has been covered in Chapter IV.

A. Preparation of Nitropyrimidines

Because nitration is such a widely applicable process in the series, relatively few direct syntheses of nitropyrimidines have been done. They have been necessary, however, to make the simpler nitropyrimidines because the electron-releasing groups required to allow nitration cannot subsequently be removed easily without reduction at some stage in the process, and nitro groups cannot withstand reduction.

(1) *Nitropyrimidines by Direct Synthesis*

In a few cases aliphatic residues carrying nitro groups have been converted by direct syntheses in 5-nitropyrimidines. Thus nitromalondialdehyde reacts readily with arylamidines, giving a variety of 2-aryl-5-nitropyrimidines (I) in good yield,[4] but fails with alkylamidines, although a 1 % yield has been reported with acetamidine.[4,5] It also condenses with *S*-methylthiourea,[6] with guanidine,[7] and with urea[8] to give respectively 2-methylthio-, 2-amino-, and 2-hydroxy-, 5-nitropyrimidine. Further examples are given in Chapter II, Sect. 2. Another direct synthesis of a nitropyrimidine, made useful by the fact that the raw material for nitration is unknown, is the preparation of 4-amino-2,3-dihydro-3-methyl-5-nitro-2-oxopyrimidine (II) from nitroacetonitrile, ethyl orthoformate, and methylurea (Ch. II, Sect. 8.E).[14] At least one direct synthesis leading to a *N*-nitroamine has been described: nitroguanidine and ethyl acetoacetate give 4-hydroxy-6-methyl-2-nitroaminopyrimidine[9] (III). The structure seems well authenticated. A nitro group on the 2-substituent has been introduced by using for example *m*-nitrobenzamidine with chloromalondialdehyde or acetylacetone giving respectively 5-chloro-2-*m*-nitrophenylpyrimidine and 4,6-dimethyl-2-*m*-nitrophenylpyrimidine.[10]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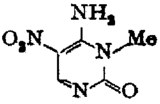
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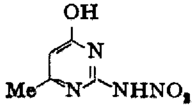

(III)

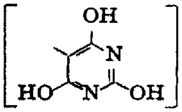
(2) *Nitropyrimidines by Nitration*

Nitration of pyrimidines normally requires the presence in the molecule of at least two electron-releasing groups. Thus 2- or 4-hydroxypyrimidine will not nitrate but 2,4-dihydroxypyrimidine (uracil) does so in boiling fuming nitric acid to give 2,4-dihydroxy-5-nitropyrimidine.[3,11] When alkyl or amino groups are present, less vigorous conditions are called for so that 2-amino-4-hydroxy-,[12] 4-amino-2-hydroxy-,[13] 4-butylamino-2-hydroxy-,[14] 4-hydroxy-6-methylamino-,[15] 4,6-diamino-,[16][*] and 2,4-dihydroxy-6-methyl-pyrimidine[17, 18] are best nitrated in sulphuric acid, by the theoretical amount of nitric acid, generally at 40–50°. Similar conditions are satisfactory for *N*-alkyl derivatives such as 1- and 3-methyluracil[19] and 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine.[19, 20] Even milder conditions are often called for especially when 4,6-dihydroxypyrimidine or a derivative is to be nitrated. This is achieved by nitrating in acetic acid, often about 20° or below. In this way are prepared 4,6-dihydroxy-,[21, 22] 2-butyl-4,6-dihydroxy-,[23] and 4,6-dihydroxy-2-methyl-5-nitropyrimidine.[18, 24]

It is possible that the unusual sensitivity of 4,6-dihydroxypyrimidines to normal treatment with nitric acid may be connected with the fact that one of the hydroxy groups (unlike 2,4-dihydroxy derivatives) is truly phenolic and cannot be in the oxo form save by donating its hydrogen atom to $C_{(5)}$: an unnatural procedure.

Nitrations in the presence of 3 electron-releasing groups are less common because nitrosation is so readily applicable for the usual purpose of introducing a 5-amino group: 2,4,6-Trihydroxy-5-nitropyrimidine is readily formed from barbituric acid,[26–28] and its chief use (for which it cannot be replaced by the corresponding nitroso derivative) is to prepare 2,4,6-trichloro-5-nitropyrimidine. 2,4,6-Triamino-5-nitropyrimidine,[29] 2-amino-4,6-dihydroxy-5-nitropyrimidine,[30] 4-amino-2,6-dihydroxy-5-nitropyrimidine,[31] and other such compounds have all been prepared by nitration.

The process of nitration can sometimes displace other groups from the 5-position to make room for the nitro group. Thus 2,4,6-trihydroxy-5-nitropyrimidine has been formed not only from barbituric acid (see above) but also by nitration of hydurilic acid[32] (2,4,6:2′,4′,6′-hexahydroxy-5,5′-dipyrimidinyl; IV), 2,4,6-trihydroxy-5-mercaptopyrimidine[33] (V), violuric acid[32, 34] (2,4,6-trihydroxy-5-nitrosopyrimidine; VI) [an oxidation?[35]], 2,4,6-trihydroxy-5-isothioureidopyrimidine[36, 37] (VII), and 5-carbamoyl-2,4,6-trihydroxypyrimidine[38] (VIII).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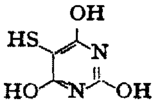
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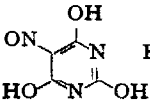
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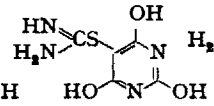
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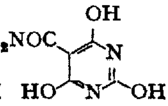
(VIII)

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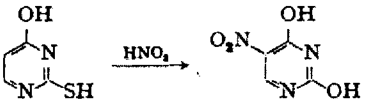
[*] 2,4-Diaminopyrimidine did not nitrate under a variety of conditions; conditions vigorous enough for nitration hydrolysed an amino group;[25] 2,4-diamino-6-methylpyrimidine gives a 5-nitro derivative normally.[17]

Although 4-amino-6-hydroxy-2-methylthiopyrimidine has been nitrated at 0°,[39] mercapto and related groups cannot normally be used in their electron-supplying capacities for making nitration possible, because they are oxidized so readily. Thus 4-hydroxy-2-mercaptopyrimidine (thiouracil; IX), 2-ethylthio-4-hydroxypyrimidine, and 2-ethylthio-4-chloropyrimidine on treatment with nitric acid all give 2,4-dihydroxy-5-nitropyrimidine[40] (X) but the vigour of the reaction and its indifferent yield preclude it as a large-scale method of preparation. Methyl groups may also be oxidized during nitration. In this way 2,4-dihydroxy-6-methylpyrimidine gives, under gentle conditions, 2,4-dihydroxy-6-methyl-5-nitropyrimidine,[17,18] but 4-carboxy-2,6-dihydroxy-5-nitropyrimidine[41–43] under vigorous conditions. A fine preparative route[44] to the last compound (XII) is from 4-hydroxy-2-mercapto-6-methylpyrimidine (XI) with nitric acid which converts mercapto into hydroxy, methyl into carboxy, and nitrates in one operation and in 55 % yield!

The trifluoromethyl group is stable during nitration as shown in the preparation of 2,4-dihydroxy-5-nitro-6-trifluoromethylpyrimidine.[45]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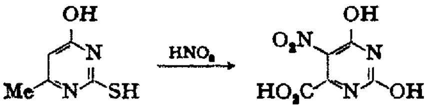
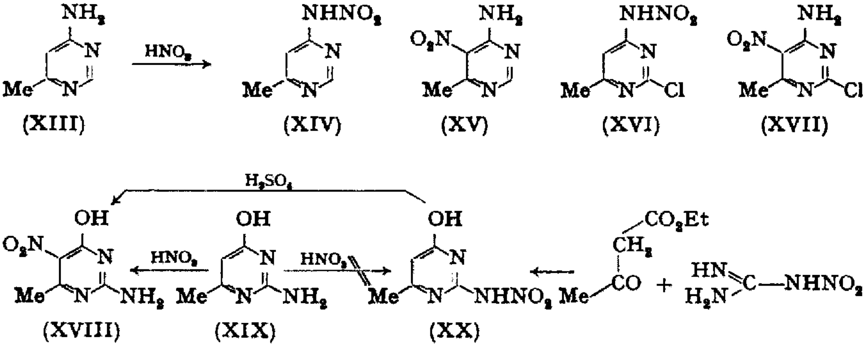

(XI) (XII)

Alkyloxy groups function satisfactorily as electron donors for nitration purposes, and are remarkably stable to nitrating conditions considering their lability to acid hydrolysis. 2,4-Diethoxypyrimidine and its 6-methyl derivative both nitrate readily[46] giving respectively 2,4-diethoxy-5-nitropyrimidine and its 6-methyl derivative.

Examples of nitration of phenylpyrimidines in which the nitro group enters the phenyl group have been mentioned in Chapter II, Sect. 2.C(8). Occasionally a nitro group attaches itself to an amino group: thus nitration of 4-amino-6-methylpyrimidine (XIII) gives 4-methyl-6-nitroaminopyrimidine[17] (XIV) which was shown to be different from 4-amino-6-methyl-5-nitropyrimidine (XV) made by an unequivocal route, and to be reduced to 4-hydrazino-6-methylpyrimidine, not 4,5-diamino-6-methylpyrimidine. 4-Amino-2-chloro-6-methylpyrimidine similarly gives 2-chloro-4-methyl-6-nitroaminopyrimidine[17] (XVI) on nitration, likewise shown not to be 4-amino-

2-chloro-6-methyl-5-nitropyrimidine (XVII). The claim[47] to have nitrated 2-amino-4-hydroxy-6-methylpyrimidine (XIX) to give 4-hydroxy-6-methyl-2-nitroaminopyrimidine (XX) was withdrawn[48] on discovering that the proposed nitroamine was in fact simply 2-amino-4-hydroxy-6-methyl-5-nitropyrimidine (XVIII) and that its reduction product, thought to be 2-hydrazino-4-hydroxy-6-methylpyrimidine, was only 2,5-diamino-4-hydroxy-6-methylpyrimidine. All these structures were meanwhile confirmed[9] by a direct synthesis of the authentic nitroamine (XX) (Sect. 1.A(1)), reduction of it to authentic hydrazino derivative, rearrangement of it in sulphuric acid to the 5-nitro compound (XVIII), and other reactions.



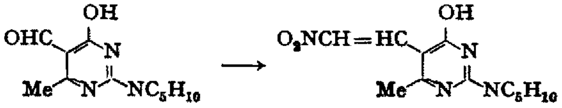
(XIII) (XIV) (XV) (XVI) (XVII)

(XVIII) (XIX) (XX)

(3) *Nitropyrimidines by Indirect Syntheses*

Apart from the possibility that the conversion of 2,4,6-trihydroxy-5-nitrosopyrimidine to the 5-nitro derivative is an oxidation,[32, 34, 35] the only indirect syntheses lead to nitro groups not directly attached to the pyrimidine ring. Thus nitrophenyl compounds have been made by a type of Gomberg reaction[10] (Ch. IV, Sect. 1.C). A nitro group on an aliphatic side-chain has been achieved by treatment of 5-formyl-4-hydroxy-6-methyl-2-piperidinopyrimidine (XXI) or the corresponding 5-phenyliminomethyl derivative, with nitromethane to give 4-hydroxy-6-methyl-5-β-nitrovinyl-2-piperidinopyrimidine[49] (XXII).

Nitrophenylazopyrimidines such as 4,6-diamino-5-*p*-nitrophenylazopyrimidine (XXIII) have been formed by coupling pyrimidines with diazotized nitroanilines,[50, 51] and nitrostyryl derivatives from *p*-nitrobenzaldehyde and methylpyrimidines have been mentioned in Chapter IV, Sect. 2.C(1). Schiff's bases such as 5-*p*-nitrobenzylideneaminopyrimidine[52] (XXIV) have been made, and 2- (*m*- and *p*-aminophenyl)-pyrimidine have been converted by diazotization and treatment with cupric sulphate and sodium sulphite into 2-(*m*- and *p*-nitrophenyl)-pyrimidine.[10]



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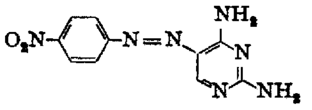

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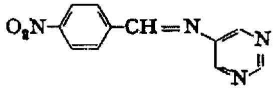


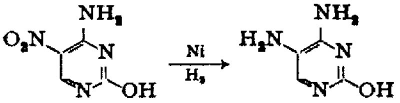
(XXIV)

B. Reactions of Nitropyrimidines: Reduction

Reduction to amino is the only reaction which the nitro group in a pyrimidine undergoes. It can be done in many ways, and the choice often depends on what other groups may be present.

Hydrogenation over Raney nickel or palladium has the widest application and is contraindicated only in the presence of mercapto groups which "poison" the catalyst and sometimes halogeno groups which may be removed by such treatment. Pressures greater than one atmosphere are unnecessary, and insolubility of the nitro compound or product in ethanol or methanol is generally no bar to the use of these solvents as vehicles for hydrogenation. 4-Amino-2-hydroxy-5-nitropyrimidine (nitrocytosine; XXV) although virtually insoluble in methanol is hydrogenated over Raney nickel therein to give 4,5-diamino-2-hydroxypyrimidine (XXVI) (which is also little soluble in methanol) in good yield.[53] These remarks apply equally to the similar preparation of 4,5-diamino-1,2-dihydro-1-methyl-2-oxopyrimidine (XXVII) and of 5-amino-2-hydroxy-4-methylaminopyrimidine[15] (XXVIII). That hydrogenations can be applicable in the presence of chloro- and alkylthio-groups is shown by the reduction to 5-amino-derivatives of 2-chloro-4-methyl-6-methylthio-5-nitropyrimidine (XXIX), 4-benzylaminomethyl-6-methyl-2-methylthio-5-nitropyrimidine and other similar compounds,[54] and also of 4-amino-2,6-dichloro,[31] 4,6-dichloro-, and 2,4,6-trichloro- 5-nitropyrimidine,[55] as well as other compounds.[91] Hydrogenation over palladium (but not nickel) successfully reduced 5-nitro-2-phenylpyrimidine (and analogues) to 5-amino derivatives when a variety of classical reducing agents had failed.[4] The use of massive quantities of Raney nickel (without added hydrogen) reduced the nitro group of 2-methylthio-5-nitropyrimidine at the same time as desulphurising the molecule to give 5-aminopyrimidine.[6]

Hydrogenation over palladium in the presence of alkoxy groups is exemplified in the formation from corresponding 5-nitro derivatives of 5-amino-2,4-diethoxypyrimidine, 5-amino-4-methoxy-2,6-dimethylpyrimidine, and others.[57,76]



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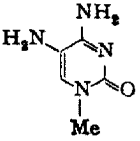

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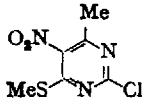
(XXVIII)



(XXIX)

Although 2,4-diamino-5-nitropyrimidine[53,56] and the 4,6-diamino analogue[58] hydrogenate normally, catalytic reduction of 2,4-dihydroxy-5-nitropyrimidine is unsatisfactory.[59,60] Classical methods such as tin and hydrochloric acid,[61] zinc and hydrochloric acid,[42] aluminium amalgam and ammonia,[40,62] zinc dust and ammonia[62] also met with only moderate success and the acidic of these gave large amounts of 2,4,5-trihydroxypyrimidine (isobarbituric acid) which constitutes the best preparation of it.[63]* The best method of reducing nitrouracil seems to be ferrous hydroxide which gives up to 70% yield of 5-amino-2,4-dihydroxypyrimidine.[65,83] This method is also satisfactory in the presence of easily hydrolysed groups, so that it has been used to reduce 2,4-dichloro-5-nitropyrimidine,[52] 4,6-dichloro-5-nitropyrimidine,[66] 2-hydroxy-4-methylamino-5-nitropyrimidine,[15] and 4-amino-2-hydroxy-5-nitropyrimidine.[13] In the case of the last two compounds the method is rather inferior to hydrogenation.[15,53] Zinc dust and water[68,76] is also a gentle reducing agent and has been used successfully on 4-chloro-6-furfurylamino-5-nitropyrimidine without loss of the chlorine (which is the danger),[6,67] probably on account of its partial deactivation by the furfurylamino group.[68] Stannous chloride has also been used in the presence of a partly deactivated chloro group to reduce 4,6-diamino-2-chloro-5-nitropyrimidine[31] to the triamine in 70% yield.

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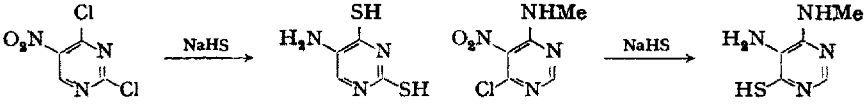
* 1,3-Dimethylisobarbituric acid (1,2,3,4-tetrahydro-5-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine) is made similarly.[64]

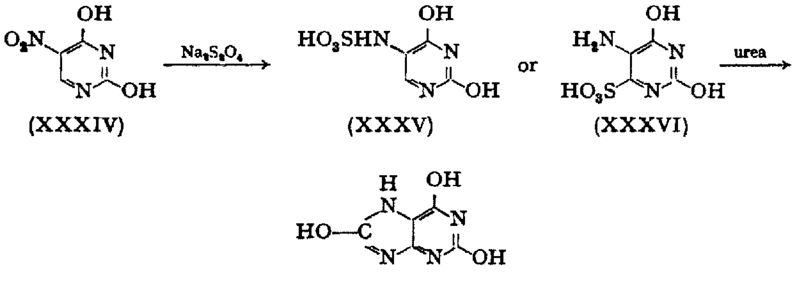
A good reducing agent for nitro pyrimidines is sodium bisulphide: it can be used in the presence of mercapto groups but is generally reserved for those occasions when a nitro group is to be reduced at the same time as active chloro groups are to be converted into mercapto groups. In this way 2,4-dichloro-5-nitropyrimidine (XXX) and its 6-methyl derivative yield respectively 5-amino-2,4-dimercaptopyrimidine[52] (XXXI) and its 6-methyl derivative.[54] Similarly 4-amino-2-(and 6-)chloro-5-nitropyrimidine and 4-chloro-6-methylamino-5-nitropyrimidine (XXXII) give 4,5-diamino-2-mercaptopyrimidine,[3,69] its 6-mercapto analogue,[18] and 5-amino-4-mercapto-6-methylaminopyrimidine.[53] These operations are done in one step but it is probable that the chloro groups are replaced first, followed by the reduction, because the sequence of reactions can be sometimes stopped half way, as in the conversion of 4-benzylmethylamino-2-chloro-6-methyl-5-nitropyrimidine into 4-benzylamino-2-mercapto-6-methyl-5-nitropyrimidine,[54] or 2,4-dichloro-5-nitropyrimidine into 2,4-dimercapto-5-nitropyrimidine[70] at 20°.



(XXX) (XXXI) (XXXII) (XXXIII)

As well as those mentioned above in connection with nitrouracil, most of the other agents commonly used to reduce nitro groups have occasionally been used to advantage in the pyrimidine series. Thus for example nitrobarbituric acid is reduced to uramil (5-amino-2,4,6-trihydroxypyrimidine) in 70% yield with tin and hydrochloric acid,[71] and 4-hydroxy-6-methyl-2-nitroaminopyrimidine to 2-hydrazino-4-hydroxy-6-methylpyrimidine with hydrazine hydrate itself.[9] Although sodium dithionite has been used so extensively to reduce nitrosopyrimidines (see below), it has not been widely used for nitropyrimidines. However, 2,4-dimercapto-5-nitropyrimidine,[66,70] 2,4-diamino-5-nitropyrimidine[73] and related compounds,[72,74] gave the 5-amino derivatives satisfactorily, although the second one is better reduced by hydrogenation.[53] 5-Amino-4-carboxy-2,6-dihydroxypyrimidine is also made with sodium dithionite.[44] The action of dithionite on nitrouracil (XXXIV) is not simple, and gives a product analysing for aminouracil plus a sulphonic acid residue. The compound was first formulated 2,4-dihydroxy-5-sulphoaminopyrimidine[75] (XXXV), but later evidence, as well as analogy with aromatic systems suggested 5-amino-2,4-dihydroxy-6-sulphopyrimidine (XXXVI) as a more reasonable structure.[77]* The compound is of some importance because with urea or formamide it gives respectively uric acid (XXXVII) and xanthine,[75] and its alkylated derivatives also give purines.[90] With suitable after-treatment, dithionite reduction of nitrouracil, however, gives a good yield of 5-amino-2,4-dihydroxypyrimidine[57,79] and its 6-methyl-, 6-ethyl-, and 6-carboxy-derivatives can be made similarly.[79,82]

The gentle agent, iron powder with aqueous or methanolic acetic acid, should not be overlooked. From the corresponding 5-nitro compounds it has been used to prepare 5-amino-2,4-diethoxy(or methoxy)-pyrimidine,[57,74] 2,5-diamino-4-ethoxypyrimidine,[72] 5-amino-2-chloro-4-thiocyanatopyrimidine,[78] 5-amino-2,4(or 4,6)-dichloropyrimidine,[78,80] and 5-amino-2-chloropyrimidine.[7]



(XXXIV) (XXXV) (XXXVI)

(XXXVII)

2. Nitrosopyrimidines

The nitroso group in pyrimidine chemistry is used as a convenient means of introducing a 5-amino group. Very little else has been done with it and its activating effect on other substituents (apart from that on the hydrolysis of 4-amino groups[81]) and potential reactions, are virtually unknown territory. Indeed, it is uncertain whether they exist as —N=O or as =N—OH or as both forms since they always have this possibility of tautomerism because of necessary neighbouring groups. This last tautomeric formulation is upheld by the fact that violuric acid (2,4,6-trihydroxy-5-nitrosopyrimidine; XXXIX) can be made either

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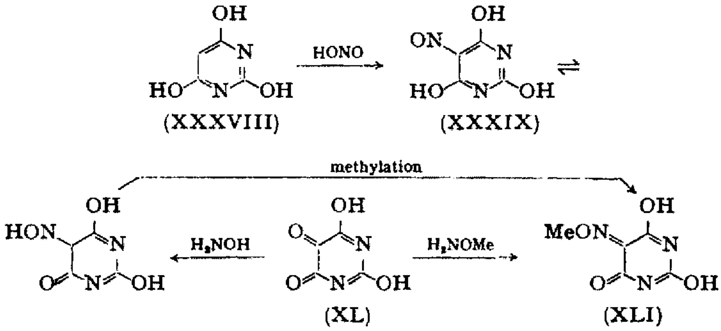
* This inevitably poses the question whether "4-sulphoaminouracil"[90] from chlorosulphonation of 4-amino-2,6-dihydroxypyrimidine might be 4-amino-2,6-dihydroxy-5-sulphopyrimidine.

by nitrosation of 2,4,6-trihydroxypyrimidine (XXXVIII) with nitrous acid[83] or by treating the ketone, alloxan (XL), with hydroxylamine.[84,85] Methylation of (XXXIX) gives the methoxyimino derivative[84,86] (XLI) which has been synthesized from alloxan (XL) with *O*-methylhydroxylamine.[87]



(XXXVIII) (XXXIX) (XL) (XLI)

Nitroso groups are known only in the 5-position (with two exceptions: Sect. 2.C). They are coloured compounds (pink, green, blue, orange-brown, etc.), and although this has fascinated chemists for many years little meaningful scientific work has resulted. A very large number of the salts of 5-nitrosopyrimidines have been made and they vary widely in colour according to the metal or base used, as well as with the structure of the pyrimidine. The latter has been varied through violuric acid (2,4,6-trihydroxy-5-nitrosopyrimidine,)[88,89,92] 4-amino-2,6-dihydroxy-5-nitrosopyrimidine,[93] 5-nitroso-1,3-diphenyl-2-thiobarbituric acid and analogues,[94,95] 5-nitroso-1,3-diphenylbarbituric acid,[96] 4,6-dihydroxy-2-mercapto-5-nitrosopyrimidine,[92] and 2-amino-4,6-dihydroxy-5-nitrosopyrimidine.[97] Explanations of the various colours, along the line of "strained structures" associated with iso-nitroso–keto–nitroso–hydroxy tautomerism in the molecules, are presented in several papers quoted above but the overall picture is not clear. The modern general review of *C*-nitroso compounds[98] is helpful in conjunction with any attempt to clarify the picture.

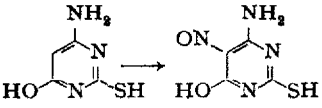
A preliminary study of the co-ordinating properties of violuric acid and its 1,3-dimethyl derivative with iron, copper, and cobalt has been made.[99]

A. Preparation of Nitrosopyrimidines

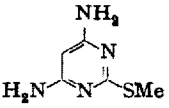
Nitrosopyrimidines are generally made by nitrosation of a pyrimidine, but the presence of at least two and sometimes three electron-releasing groups, is required for success. A few nitroso pyrimidines have been made by direct synthesis.

(1) *Nitrosopyrimidines by Nitrosation*

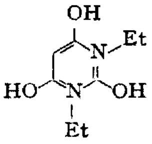
When three electron-releasing groups are present, as for example in 4-amino-6-hydroxy-2-mercaptopyrimidine[100] (XLII), treatment of the pyrimidine in aqueous acetic acid with sodium nitrite at room temperature produces good yields of the 5-nitroso compound, *e.g.* (XLIII). Most threefold combinations of amino, hydroxy, and mercapto groups have been used, as well as a variety of their derivatives alkylated on the substituents (*e.g.* 4,6-diamino-2-methylthiopyrimidine[101]) (XLIV) or on the ring *N*-atom, as in 1,3-diethylbarbituric acid[102] (XLV). A study has been made of optimum conditions of time and pH for nitrosation of barbituric acid.[103] Some pyrimidines containing only two electron-supplying groups will nitrosate, but normally not with acetic acid/sodium nitrite, but with mineral acid/sodium nitrite. Further, 4-(and 6-) groups seem more effective than 2-groups so that 4,6-diaminopyrimidine[50, 104, 105] and its 2-methyl derivative,[101] yield 5-nitroso derivatives in the presence of mineral acid, but 2,4-diaminopyrimidine will not;[25] likewise 4,6-dihydroxy-, but not 2,4-dihydroxy-, pyrimidine nitrosates.[50] Further examples are presented in a table[50] but apparently the observations are based on colour formation rather than on isolation.



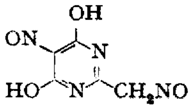
(XLII) (XLIII)



(XLIV)



(XLV)



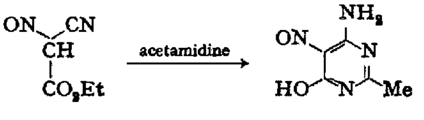
(XLVI)

An interesting nitrosation[106] is that of 4,6-dihydroxy-2-methylpyrimidine which inserts not only a 5-nitroso group, but also one on the methyl group giving 4,6-dihydroxy-5-nitroso-2-nitrosomethylpyrimidine (XLVI) which was reduced to 5-amino-2-aminomethyl-4,6-dihydroxypyrimidine. One nitrosation of a pyrimidine containing only one electron-releasing group has been claimed:[107] 2-hydroxy-4,6-dimethylpyrimidine is said to give a nitrite salt which on warming in water gives 2-hydroxy-4,6-dimethyl-5-nitrosopyrimidine.

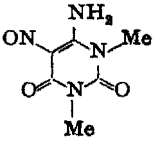
(2) *Nitrosopyrimidines by Direct Synthesis*

By employing ethyl nitrosocyanoacetate (XLVII) several 5-nitrosopyrimidines have been made directly. Thus condensation with acetamidine gives 4-amino-6-hydroxy-2-methyl-5-nitrosopyrimidine[108] (XLVIII), with urea gives 4-amino-2,6-dihydroxy-5-nitrosopyrimidine,[108, 109] with thiourea gives 4-amino-6-hydroxy-2-mercapto-5-nitrosopyrimidine,[108] with dimethylurea gives 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine[109] (XLIX), and with guanidine gives 2,4-diamino-6-hydroxy-5-nitrosopyrimidine.[109–110] Similarly diethyl nitrosomalonate with thiourea or guanidine gives 4,6-dihydroxy-2-mercapto-5-nitrosopyrimidine[111] (L) or 2-amino-4,6-dihydroxy-5-nitrosopyrimidine.[108]

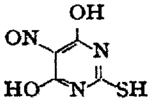
There seems little reason why this type of synthesis of nitroso pyrimidines should not be extended (in particular to simple nitroso pyrimidines where nitrosation is difficult or impossible), provided the aliphatic nitroso compound can be made and is sufficiently stable to withstand the conditions of synthesis.



(XLVII) (XLVIII)



(XLIX)



(L)

B. Reactions of Nitrosopyrimidines

Almost the only used reaction of the nitroso group in pyrimidines, is its reduction to an amino group.

(1) *Reduction of Nitrosopyrimidines*

This has been done in a variety of ways. In the days of Traube* ammonium sulphide was a favoured reagent and it was used to reduce such compounds as 4,6-diamino-2-mercapto-,[100] 4-amino-6-hydroxy-

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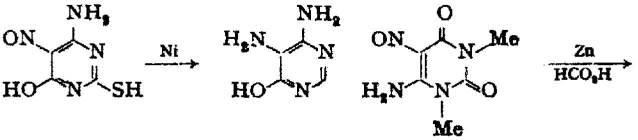
* Not only was Wilhelm Traube a great pyrimidine and purine chemist, but he contributed significantly to other fields both organic and inorganic. An account of the life and work of this beloved man was written by his colleagues[111a] for his 60th birthday in 1926.

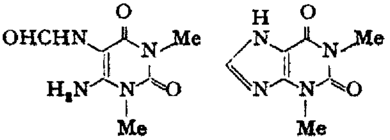
2-mercapto-[100] and 4-amino-2,6-dihydroxy- 5-nitrosopyrimidine,[112] as well as 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine.[112] In regard to the last compound, a survey of 11 methods of reduction showed that ammonium sulphide was in fact the best,[113] so that it still finds occasional use for compounds similar to the last[114] and in the reduction of 4,6-diamino-2-methylthio-, and 4,6-diamino-2-methyl- 5-nitrosopyrimidine.[101] Yields are normally 50–80 %.

Sodium dithionite is now generally used in place of ammonium sulphide to convert the above nitroso compounds into their 5-amino analogues. As examples of its use may be quoted the preparation of 4,5-diamino-2,6-dihydroxy-,[79, 108, 115] 4,5-diamino-6-hydroxy-2-mercapto-,[73] 4,5-diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-,[113, 116] 2,5-diamino-4,6-dihydroxy-,[108] 5-amino-2,4,6-trihydroxy-,[117] 5-amino-2,4-dihydroxy-6-methylamino-,[118] and 4,5-diamino-6-dimethylamino-2-methylthio- pyrimidine.[119] Although generally done in solution (or suspension) in aqueous alkali, such reductions can be carried out in acetone as for example in the preparation of 4,5-diamino-6-diethylamino-2-methylthiopyrimidine and analogues.[120]

Catalytic hydrogenation has been little used with nitroso compounds, but proved useful to reduce 2,4-diamino-6-hydroxy-5-nitrosopyrimidine[113] and 4,6-diamino-5-nitrosopyrimidine.[121] Excess of Raney nickel[108] (without added hydrogen) has also been used to reduce 4-amino-6-hydroxy-2-methyl-5-nitrosopyrimidine, and 4-amino-6-hydroxy-2-mercapto-5-nitrosopyrimidine (LI); from the latter it also naturally removed the mercapto group giving 4,5-diamino-6-hydroxypyrimidine (LII). Zinc and sulphuric acid proved effective for reducing 4-amino-2,6-dihydroxy-5-nitrosopyrimidine,[113] and hydrogen iodide has been used to reduce 1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-5-nitroso-2,4-dioxopyrimidine in 95 % yield.[102] The use of zinc dust and formic acid has found some favour in purine work because it yields directly a 5-formamido group ready for ring closure: in this way 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine (LIII) yields 4-amino-5-formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (LIV)[122] which cyclizes to 1,3-dimethylxanthine (theophylline; LV); a similar reduction gave 6-amino-5-formamido-1-methyluracil[123] in 90 % yield for the preparation of 3-methylxanthine. An electrolytic method for the reduction of 2,4-diamino-6-hydroxy-5-nitrosopyrimidine in 97 % yield, has been published,[124] and iron with hydrochloric acid reduces 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-

5-nitroso-2,6-dioxopyrimidine in 95% yield.[125] Stannous chloride has been used to efficiently reduce 4-amino-2,6-dihydroxy-5-nitrosopyrimidine to diaminouracil in a micro-isotopic synthesis.[126]

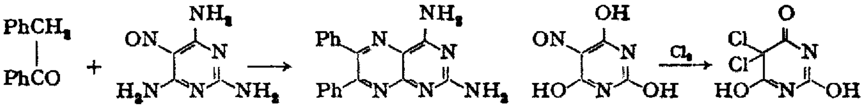

(LI) (LII) (LIII)


(LIV) (LV)

(2) *Other Reactions of Nitrosopyrimidines*

The nitrosopyrimidines react with active methylene groups in the important unambiguous synthesis of pteridines devised by Timmis.[127] For example, 2,4,6-triamino-5-nitrosopyrimidine (LVII) condenses with benzyl phenyl ketone (LVI) giving 2,4-diamino-6,7-diphenylpteridine (LVIII) which corresponds with that prepared in the usual way.[128]

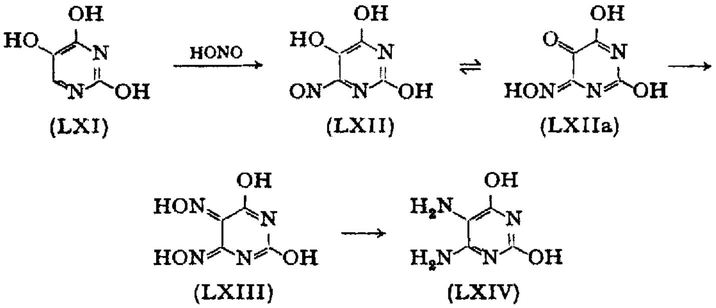
The possible oxidation of violuric acid (LIX) to dilituric acid (5-nitroso- to 5-nitro-barbituric acid) (LIX) has already been mentioned in (Sect. 1.A(2)). Violuric acid also yields 5,5-dichlorobarbituric acid (LX) on treatment with chlorine.[129]


(LVI) (LVII) (LVIII) (LIX) (LX)

C. 4-Nitrosopyrimidines

Just as violuric acid can be made from barbituric acid so isovioluric acid (LXII) comes from isobarbituric acid (LXI) on treatment with nitrous acid.[131] It is tautomeric with the hydroxyimino form (LXIIa) on account of the proximity of the 5-hydroxy group. The position of the nitroso group was shown[131] by reduction to 4-amino-2,5,6-trihydroxypyrimidine and the formation with hydroxylamine of the dioxime (LXIII) which on reduction with ammonium sulphide gave 4,5-diamino-2,6-dihydroxypyrimidine (LXIV).

Similarly 2-amino-4,5-dihydroxypyrimidine with nitrous acid yielded a 4-nitroso derivative which on catalytic reduction gave 2,4-diamino-5,6-dihydroxypyrimidine (divicine).[130, 132]



(LXI) (LXII) (LXIIa)

(LXIII) (LXIV)

3. The Arylazopyrimidines

Like the nitro- and nitroso-pyrimidines, 5-arylazopyrimidines have generally been made simply as a means of introducing a 5-amino group into the molecule by subsequent reduction. Because they can be formed and reduced under very mild conditions, the process has been used especially where sugar residues or other labile groups are already present.

A. Preparation of Arylazopyrimidines

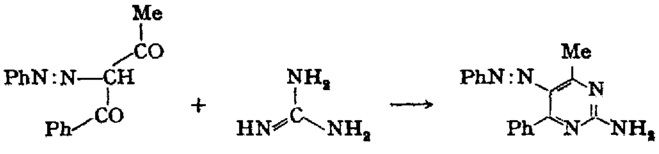
Most arylazopyrimidines have been made by direct synthesis or by coupling of a pyrimidine in the 5-position with a diazo compound. A few less direct ways have been used occasionally.

(1) *Direct Synthesis of 5-Arylazopyrimidines*

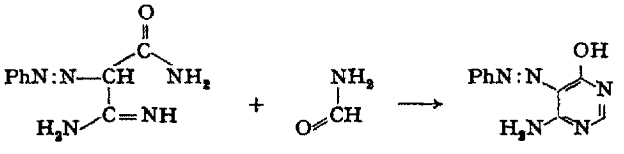
The direct synthesis of an arylazopyrimidine is typified by the condensation of the β-diketone phenylazoacetylacetone or phenylazobenzoylacetone (LXV) with guanidine to give respectively 2-amino-4,6-dimethyl-5-phenylazopyrimidine or 2-amino-4-methyl-6-phenyl-5-

phenylazopyrimidine (LXVI).[133] Other examples are the formation of 4,6-diamino-5-phenylazopyrimidine[134] (LXVII) or its 2-methyl derivative[50] from phenylazomalononitrile and respectively formamidine or acetamidine. *p*-Chloro- but not *p*-nitro-phenylazomalononitrile behaves similarly,[50] and several other substituted-phenylazo derivatives are known.[135]

A direct synthesis which is not a Common Synthesis has also been used to make 4-amino-6-hydroxy-5-phenylazopyrimidine (LXVIII) from phenylazomalonamide-amidine (LXVII) and formamide.[136]



(LXV) (LXVI)



(LXVII) (LXVIII)

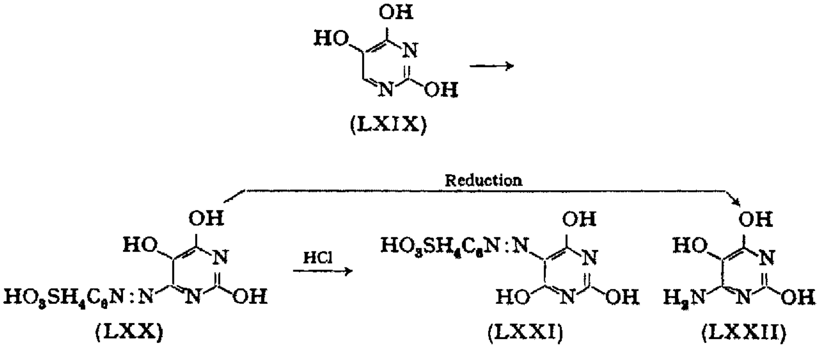
(2) *Arylazopyrimidines by Coupling*

The conditions under which pyrimidines can be coupled in the 5-position with diazo compounds have been surveyed.[50,137] When at least two electron-releasing groups are present, coupling takes place readily and generally in good yield; thus under alkaline conditions 4,6-dihydroxy-2-methyl-5-phenylazopyrimidine is formed in 87% yield,[137] 4-amino-2,6-dihydroxy-5-phenylazopyrimidine in *ca.* 90% yield,[138] and 2,6-diamino-5-*p*-chlorophenylazopyrimidine in 35% yield.[16] 4,6-Diamino-2-methylpyrimidine couples with diazotized *p*-chloro- or *p*-nitro-aniline, but not aniline.[50] Many other examples are known.[*] Coupling is much less ready when only one electron-releasing group is present; indeed a 4-hydroxy or a 4-amino group does not seem to permit coupling at all, although a 2-hydroxy group does so in that 2-hydroxy-4-methyl- and 2-hydroxy-4,6-dimethyl-5-phenylazopyrimidine can be so prepared in appreciable yield.[137] The presence of mercapto groups

[*] See refs. 105, 106, 133, 135, 139–147.

can cause abnormalities such as the production of 2-*p*-chlorophenylthio-4-hydroxypyrimidine from diazotized *p*-chloroaniline and 2-thiouracil,[148] so that the reported positive coupling between diazotized *p*-nitroaniline and 4-hydroxy-2-mercapto-6-methylpyrimidine and related compounds[50] must be accepted with reserve. 4,6-Diamino-2-mercaptopyrimidine gives both normal and abnormal products.[144]

Despite the occupied 5-position in isobarbituric acid (2,4,5-trihydroxypyrimidine; LXIX), it was early noticed[149] that coupling appeared to take place with diazotized sulphanilic acid. This was later confirmed[150] and the product shown to be almost certainly 2,4,5-trihydroxy-6-*p*-sulphophenylazopyrimidine (LXX) which was reduced to 4-amino-2,5,6-trihydroxypyrimidine (LXXII) and which was reported to give in acid 2,4,6-trihydroxy-5-*p*-sulphophenylazopyrimidine (LXXI). Diazotized aniline similarly gave 2,4,5-trihydroxy-6-phenylazopyrimidine.[150] 4,5-Dihydroxypyrimidine and its 2-amino derivative have been coupled with diazotized amines, giving respectively 4-*p*-chlorophenylazo-5,6-dihydroxypyrimidine and 2-amino-4,5-dihydroxy-6-*p*-sulphophenylazopyrimidine. Dithionite reduction gives 4-amino- and 2,4-diamino- 5,6-dihydroxypyrimidine, of which the latter is divicine.[130, 132]

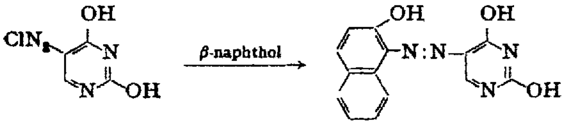


(LXIX)

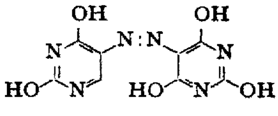
(LXX) (LXXI) (LXXII)

In the case of thymine (2,4-dihydroxy-5-methylpyrimidine), coupling apparently takes place with diazotized sulphanilic acid, but the red product is too unstable for analysis;[151] this observation was confirmed later, but variation of the 5-alkylpyrimidine and coupling agent failed to give a product any more stable.[50] As a result of work during development of a colorimetric method for estimating thymine,[152] a theory of coupling on the ring-*N* (position 1) has been advanced.[153]

A 5-amino group in pyrimidine can often be diazotized, so that the reverse of the usual type of coupling is possible. Although these diazo compounds were once reported not to couple with phenols or amines,[154] this was shown to be in error first qualitatively[155] and later by isolation of azo compounds such as 2,4-dihydroxy-5-(2′-hydroxy-1′-naphthylazo)pyrimidine (LXXIV) from diazotized 5-amino-2,4-dihydroxypyrimidine (LXIII) and β-naphthol.[150] Coupling of these diazopyrimidines with other pyrimidines (such as barbituric acid) gives for example uracilazobarbituric acid [2,4,6-trihydroxy-5-(2′,4′-dihydroxy-5′-pyrimidinylazo)pyrimidine][150] (LXXV).



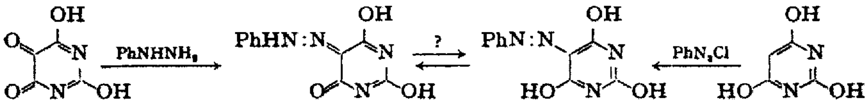
(LXXIII) (LXXIV)



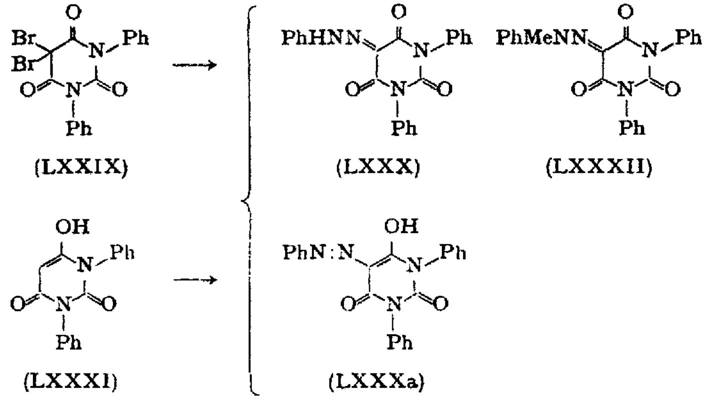
(LXXV)

(3) *Other Preparations of Arylazopyrimidines*

When alloxan (LXXVI) is treated with phenylhydrazine hydrochloride, the phenylhydrazone (LXXVII) is formed;[156] the same compound was made by coupling barbituric acid (LXXVIII) with



(LXXVI) (LXXVII) (LXXVIIa) (LXXVIII)

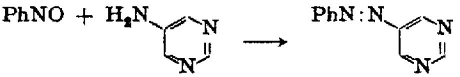


(LXXIX) (LXXX) (LXXXII)

(LXXXI) (LXXXa)

diazotized aniline indicating the existence of a tautomeric system (LXXVII–LXXVIIa) or at least the capacity of one to rearrange to the other. The latter explanation in favour of the hydrazone (LXXVII) was proposed by Whiteley:[157] she made 1,3-diphenylalloxan-5-phenylhydrazone (LXXX) from 5,5-dibromo-1,3-diphenylalloxan (LXXIX) and the same compound (LXXXa) by coupling diazotized aniline with 1,3-diphenylbarbituric acid (LXXXI). This product in its general properties closely resembled 1,3-diphenylalloxan-5-methylphenylhydrazone (LXXXII), in which no tautomerism is possible. The inference was drawn that the hydrazone form (LXXX) is probably a better representation of such a compound than is (LXXXa). A similar product has been made from 2-naphthylhydrazine and 5,5-dibromo- or 5,5-dichloro-barbituric acid.[156]

The simple 5-phenylazopyrimidine (LXXXIII) has been prepared by the action of nitrosobenzene on 5-aminopyrimidine.[52] There seems little reason to preclude the extension of this reaction to substituted pyrimidines and/or phenyl groups; perhaps even the reverse condensation of a nitroso pyrimidine with aniline (or derivatives) might be possible.

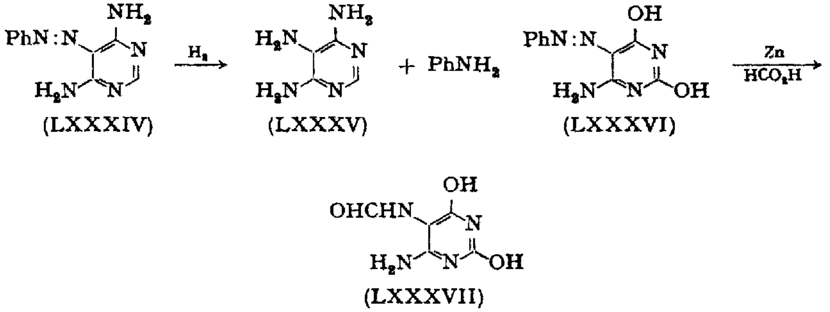


(LXXXIII)

B. The Reduction of Arylazopyrimidines

The only general reaction of the arylazo group in pyrimidines is its reductive clearage to a 5-aminopyrimidine and an aromatic amine. Many reducing agents can bring this about although catalytic reduction is now generally used. Thus for example 4,6-diamino-5-phenylazopyrimidine[134] (LXXXIV) has been hydrogenated to 4,5,6-triaminopyrimidine (LXXXV) over Raney nickel at 100° and 60 atm; 2-guanidino-4,6-dimethyl-5-phenylazopyrimidine[133] to 5-amino-2-guanidino-4,6-dimethylpyrimidine over Raney nickel at n.t.p.; 4-amino-2,6-dihydroxy-5-phenylazopyrimidine[138] to 4,5-diamino-2,6-dihydroxypyrimidine over palladized charcoal at n.t.p.; and 2,4-diamino-5-*p*-chlorophenylazo-6-methylaminopyrimidine[139] to 2,4,5-triamino-6-methylaminopyrimidine over Raney nickel at 95° and 50 atm. Many other examples are known; cf. refs. 21, 50, 105, 133, 139, 159. The use of pressures above 50 atm and temperature above 90° is rare in these reductions; indeed the use of conditions above n.t.p. seems to be more a convenience than a necessity.

Among the more common chemical reducing agents for arylazopyrimidines are zinc dust with acid, and sodium dithionite. Zinc dust (or iron) with sulphuric acid has been used to reduce 4-amino-2,6-dihydroxy-5-phenylazopyrimidine (LXXXVI)[138] to 4,5-diamino-2,6-dihydroxypyrimidine. The same reduction of (LXXXVI) with zinc and formic acid[138] yields directly 4-amino-5-formamido-2,6-dihydroxypyrimidine (LXXXVII), which is useful in purine syntheses. There are many examples of the use of zinc with acetic acid.[105, 143, 160] Sodium dithionite has been used to reduce 2,4-diamino-6-hydroxy-5-phenylazopyrimidine[142] to 2,4,5,-triamino-6-hydroxypyrimidine, for reducing several related 2-aryl derivatives,[161] for 2-hydroxy-4,6-dimethyl-5-phenylazopyrimidine,[162] for 4-amino-6-hydroxy-2-methyl-5-phenylazopyrimidine,[146] and related compounds.[163]


(LXXXIV) (LXXXV) (LXXXVI) (LXXXVII)

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CHAPTER VI

Halogenopyrimidines

It has already been pointed out (Ch. I) that halogen atoms in the 2-, 4-, or 6-position of pyrimidine have activity akin to those in aliphatic halogeno compounds, or perhaps more nearly to that of the chlorine atom in chloro-2,4-dinitrobenzene. Most 5-halogenopyrimidines on the other hand are unreactive almost in the sense of chlorobenzene. Because of their reactivity, halogens in the 2-, 4-, or 6-position are the most useful substituents in synthetic pyrimidine chemistry. Most such halogenopyrimidines are in fact chloro compounds because not only is chlorine the most easily introduced halogen, but it is at least as reactive as is bromine or iodine in the same position.

1. The Preparation of 2-, 4-, and 6- Halogenopyrimidines

Halogens in the active positions cannot be introduced in the course of a direct synthesis nor can they be introduced by halogenation of a preformed pyrimidine. The chloro compounds are almost invariably made by the action of phosphoryl chloride or phosphorus pentachloride on hydroxy (or occasionally mercapto) derivatives. Bromo and iodo compounds are often made from the corresponding chloro compounds. The latter give fluoro derivatives with sulphur tetrafluoride.[1a]

A. Phosphoryl Chloride on 2-, 4-, and 6- Hydroxypyrimidines

(1) *Simple Cases*

In simple cases such as 2-chloro-,[1] 4-chloro-,[2] and 2,4-dichloro-[3] pyrimidines, mere boiling of the corresponding hydroxy compounds with phosphoryl chloride is sufficient. This applies equally to *C*-alkyl derivatives such as 2-chloro-4-methyl,[4,5] 2-chloro-4,6-dimethyl-,[6] 4-chloro-6-methyl-,[4,7] 4-chloro-5-methyl-,[8] 4-chloro-2-methyl-,[9] 2,4-dichloro-6-methyl-,[4,10] and 4-amyl-2,6-dichloro- pyrimidine.[11] *C*-Arylhydroxypyrimidines react similarly to give, for example, 4-chloro-6-phenyl-[8] and 2,4-dichloro-6-phenyl- pyrimidine.[12]

(2) *In the Presence of Nitro Groups*

When other substituents (particularly a nitro group) are present, and in the case of barbituric acid and its derivatives, treatment of the hydroxy compound with phosphoryl chloride alone is often unsuccessful. The addition of a molecular proportion of *NN*-dimethyl- or better diethyl- aniline almost invariably rectifies this, and indeed greater yields with dimethylaniline in even such a simple case as 2,4-dichloropyrimidine have been reported.[2,13] Barbituric acid reacts with phosphoryl chloride alone[14,15] under pressure and with agitation only at 140°, but on addition of dimethylaniline, 2,4,6-trichloropyrimidine is easily produced on refluxing and in 59% yield.[16,17] 2,4,6-Trihydroxy-5-nitropyrimidine (nitrobarbituric acid; (I)) failed to yield 2,4,6-trichloro-5-nitropyrimidine (II) with phosphoryl chloride and dimethylaniline,[13] but did so in 20% yield when diethylaniline was used.[18] Other examples of the use of dimethyl- or diethyl-aniline are the preparation of 4,6-dichloro-,[19,20] 4,6-dichloro-2-methyl-,[21] 2,4-dichloro-5-nitro-,[13,22]* 4,6-dichloro-5-nitro-,[23] 2,4-dichloro-6-methyl-5-nitro-,[24] 4,6-dichloro-2-methyl-5-nitro- (38% yield with dimethylaniline;[17] 78% with diethylaniline[24]), and 4,6-dichloro-5-nitro-2-phenyl-pyrimidine.[25] Pyridine also serves as base in the preparation of 4,6-dichloropyrimidine.[26]

Phosphoryl chloride with the sodium salt of a hydroxy pyrimidine has occasionally been used; such a case is the formation of 2-chloro-5-nitropyrimidine from 2-hydroxy-5-nitropyrimidine sodium salt.[27]

(3) *In the Presence of Amino Groups*

Conversion of hydroxy into chloro groups in the presence of amino groups is not always easy. On the whole, 2-amino groups are less

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* The older method[28] of heating nitrouracil under pressure with phosphoryl chloride gives poor and inconsistent yields; moreover, opening of the reaction vessel is fraught with danger.[29]

troublesome than are 4- or 5-amino groups. A practical difficulty can also arise when the basic pK_a of the product is close to that of the dialkylaniline catalyst (which is often necessary). In such cases it is very troublesome to separate the two, and if possible it is better to avoid dialkylaniline by using phosphorus pentachloride or a strong and volatile base such as triethylamine. As examples of the successful preparation of 2-amino-chloro- from 2-amino-hydroxy- pyrimidines may be quoted: 2-amino-4-chloropyrimidine (phosphoryl chloride alone,[30] with sulphuric acid,[31] or with chlorosulphonic acid[32]), 2-amino-4,6-dichloropyrimidine (phosphoryl chloride alone[33] or with dimethylaniline; > 80 %* yield[34]), 4-chloro-2-dimethylamino-5-nitropyrimidine (phosphoryl chloride alone; 55 % yield),[35] 4-chloro-5-cyano-2-dimethylaminopyrimidine (phosphoryl chloride; 90% yield),[36] 2-anilino-4-chloropyrimidine (phosphoryl chloride);[37] examples of 4-amino-chloro derivatives similarly prepared are, 4-amino-6-chloropyrimidine (phosphoryl chloride and diethylaniline; 60 % yield),[38] 4-amino-6-chloro-2-methylpyrimidine (phosphoryl chloride[39] or with diethylaniline[40]), its homologues similarly,[41] 2,4-diamino-6-chloropyrimidine (phosphoryl chloride and dimethylaniline; poor yield),[34] 4-amino-6-chloro-2-methylthiopyrimidine (phosphoryl chloride alone gives *ca.* 25 % yield;[42] with dimethylaniline, yield 62 %[43]); 5-amino-4-chloro-6-hydroxy-2-methylpyrimidine similarly gives 5-amino-4,6-dichloro-2-methylpyrimidine.[44]

(4) *In the Presence of Other Groups*

Conversion of hydroxy into chloro groups with phosphoryl chloride (sometimes with diethylaniline) is also successful in the presence of some other groups (including alkoxy, styryl, 5-halogeno, 5-cyano, alkylthio, ethoxycarbonyl and carboxy, but not including mercapto).** Thus for example, were prepared, 2-chloro-4-methoxy-6-methylpyrimidine,[45] 4-chloro-6-*p*-dimethylaminostyrylpyrimidine,[46] 5-bromo-2,4-dichloropyrimidine,[47] 5-bromo-4,6-dichloropyrimidine,[48] 5-bromo-2,4-dichloro-6-methylpyrimidine,[49] 2,5-dichloropyrimidine[50] (from 5-chloro-2-hydroxypyrimidine), 2,4,5- and 4,5,6-trichloropyrimidine[48] (from 5-chloro-2,4- or -4,6-dihydroxypyrimidine), 4,6-dichloro-5-cyano-2-

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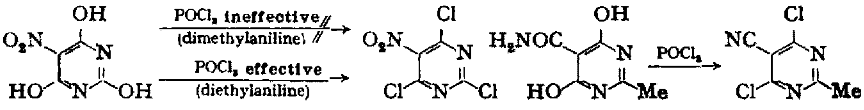
* This yield would seem to refer to very crude material. The better process is with phosphoryl chloride alone and even that gives but 25% of pure material.[29]

** Phosphoryl chloride is unsatisfactory in the presence of mercapto groups: for example, 4-hydroxy-2-mercaptopyrimidine gives mainly what appears to be di(4-chloropyrimidin-2-yl) disulphide.[29]

methylpyrimidine (IV) (from 5-carbamoyl-4,6-dihydroxy-2-methylpyrimidine (III) with phosphoryl chloride alone (40%) or with added dimethylaniline, 76%; the amide group is dehydrated to a nitrile during the reaction,)[51] 4-chloro-2-methylthiopyrimidine,[6] 2-benzylthio-4-chloropyrimidine,[52] 5-bromo-4-chloro-2-methylthiopyrimidine,[53] 5-carboxy-2,4-dichloropyrimidine,[54] and 2,4-dichloro-5-ethoxycarbonylpyrimidine.[54] In the last two examples repeated efforts without dialkylaniline present produced no product.[55,56] The conversion of 1,3-dimethylbarbituric acid (1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine) into 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine[57] was readily carried out in good yield with partly hydrolysed phosphoryl chloride (4% water). The 5-methyl derivative was made similarly.[58]



(I) (II) (III) (IV)

B. The Use of Phosphorus Pentachloride to Produce Chloropyrimidines

Phosphorus pentachloride is less convenient to use than phosphoryl chloride but, especially in the older literature, it has been widely used to convert hydroxy- into chloro-pyrimidines. It is rather more powerful than is phosphoryl chloride and the two are sometimes used together when the phosphoryl chloride functions as a solvent for both hydroxy compound and the phosphorus pentachloride. As examples of products from the use of phosphorus pentachloride may be quoted, 4-chloro-2-phenylpyrimidine[59] and 4,6-dichloro-2-methylthiopyrimidine[60] (both phosphorus pentachloride alone); 2-chloropyrimidine,[6][*] 5-bromo-2,4-dichloropyrimidine,[61] and 2-butylthio-4-chloro-5-methylpyrimidine[62] (all with a mixture of phosphoryl chloride and phosphorus pentachloride).

The use of phosphorus pentachloride involves the peculiar danger of C-chlorination of the pyrimidine in the 5-position. Thus 2-amino-4,6-dihydroxypyrimidine and 4,6-diamino-2-hydroxypyrimidine give respectively 2-amino-4,5,6-trichloropyrimidine[63] (V) and 4,6-diamino-2,5-dichloropyrimidine[64] (VI), and barbituric acid (VIII) gives 2,4,5,6-

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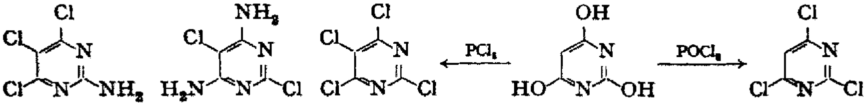
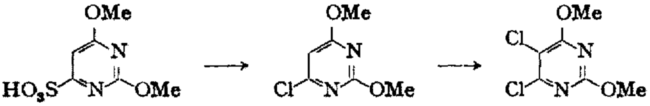
[*] Addition of phosphorus pentachloride to phosphoryl chloride decreases reaction time from 12 hours to 1 hour.

tetrachloropyrimidine[63] (VII) although by using phosphoryl chloride and dialkylaniline only 2,4,6-trichloropyrimidine (IX) is formed.[16,17] 4-Chloro-2,6-dimethoxypyrimidine with phosphorus pentachloride gives 4,5-dichloro-2,6-dimethoxypyrimidine.[65]



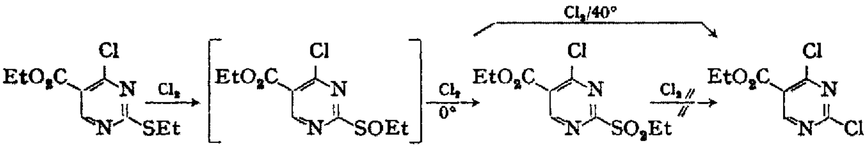
(V) (VI) (VII) (VIII) (IX)

Phosphorus pentachloride is sometimes successful in converting mercapto groups into chloro groups: in this way 4-hydroxy-2-mercaptopyrimidine gives 2,4-dichloropyrimidine.[66] An analogous reaction is the conversion of 2,4-dimethoxy-6-sulphopyrimidine (X) under gentle conditions into 4-chloro-2,6-dimethoxypyrimidine (XI) and under vigorous conditions one step further into 4,5-dichloro-2,6-dimethoxypyrimidine.[65]


(X) (XI) (XII)

C. Other Ways of Preparing 2-, 4-, and 6- Chloropyrimidines

When 4-chloro-5-ethoxycarbonyl-2-ethylthiopyrimidine (XIII) is treated with chlorine at 0°, the expected sulphone (XV) (4-chloro-5-ethoxycarbonyl-2-ethylsulphonylpyrimidine) is the chief product. At 40°, however, 2,4-dichloro-5-ethoxycarbonylpyrimidine (XVI) predominates. The mechanism of its formation is not from the sulphone (XV) which is stable to chlorine and it has been suggested that the sulphoxide (XIV) is the common precursor of both products.[67] Similarly, 2-chloro-5-ethoxycarbonylpyrimidine is formed from 5-ethoxycarbonyl-2-ethylthiopyrimidine.[55]



(XIII) (XIV) (XV) (XVI)

2-Chlorosulphonyl-4,6-dimethylpyrimidine, prepared by chlorine oxidation of 2-mercapto-4,6-dimethylpyrimidine, spontaneously looses sulphur dioxide to give 2-chloro-4,6-dimethylpyrimidine.[68]

Although aminopyrimidines are often prepared from chloro derivatives, it is sometimes useful to do the reverse, and in particular in the 2-position where an amino group can be so easily inserted by a direct synthesis. The treatment of such an amino group with nitrous acid (under diazotizing conditions, in the presence of an excess of hydrochloric acid) achieves this. The best preparation of 2-chloropyrimidine (from the commercially available 2-aminopyrimidine) can be so done,[69,70] and likewise a variety of derivatives such as 2-chloro-4-methyl-, 2,5-dichloro-, 2-chloro-4-methoxy-, and 2-chloro-4-phenyl- pyrimidine,[69] as well as 2-chloro-4-methoxy-6-methylpyrimidine.[71]

D. The Preparation of 2-, 4-, and 6- Bromopyrimidines

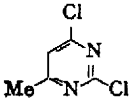
Phosphoryl bromide has been used to change several hydroxypyrimidines to the corresponding bromo derivatives. Barbituric acid (or its 5-benzyl derivative) gives a 61 % yield 2,4,6-tribromopyrimidine[72,73] (or its 5-benzyl derivative),[74] and other products from the appropriate hydroxy derivatives include 2-amino-4-bromo-,[72] 2-amino-4,6-dibromo-,[72] 2-amino-4-bromo-6-methyl-,[72] 4,6-dibromo-2-ethyl-,[75] and 4-bromo-2-ethyl-6-hydroxy- pyrimidines,[75] as well as a sulphonamide.[72] Phosphorus pentabromide (diluted with phosphoryl *chloride*) converts tetrahydroxypyrimidine into 2,4,5,6-tetrabromopyrimidine.[76] It has been reported[77] that 3-bromo-1,3-dichloroprop-1-ene and guanidine in fuming sulphuric acid give not only the expected 2-aminopyrimidine (by a Common Synthesis) but also in comparable amount, a 2-aminobromopyrimidine. The authors report analyses and the fact that dehalogenation gives 2-aminopyrimidine, but do not give a structure. *Chemical Abstracts*[77] has recorded it as 2-amino-4-bromopyrimidine, which is undoubtedly wrong since the m.p. is not that of the 4-bromo-[72] but that of the 5-bromo derivative.[78,79] Further, Japanese workers have recorded[80] the production of 2-amino-5-bromopyrimidine in a very similar reaction.

Chlorine may sometimes be replaced by bromine, as for example during the bromination of 4,6-dichloro-2,5-dimethylpyrimidine, which gives 4-bromo-5-bromomethyl-6-chloro-2-methylpyrimidine.[81]

E. The Preparation of 2-, 4-, and 6- Iodopyrimidines

Pyrimidines substituted with 2-, 4-, or 6-iodo atoms are made from the corresponding chloro compounds with hydrogen iodide. There are not many known, and most of these seem to have arisen by mistake during attempted removal of a chlorine atom by reduction with hydriodic acid. They appear to be in no way more useful than the chloro compounds.

2,4-Dichloro-6-methylpyrimidine (XVII) gives with hydriodic acid under different conditions, 2,4-di-iodo-, 4-iodo-, and 2-chloro-4-iodo- or 4-chloro-2-iodo- 6-methylpyrimidine[7, 11] (XVIII–XXI). 2-Amino-4,6-dichloro- gives 2-amino-4,6-di-iodo-pyrimidine,[82] and 2,4-diamino-6-iodopyrimidine,[33] 2,4-diamino-5-benzyl-6-iodopyrimidine[83] and 2-benzyl-4-iodo-6-methylpyrimidine[11] are likewise made from the corresponding chloro compounds. 4-Amino-2,6-dichloro-5-ethylpyrimidine gives 4-amino-5-ethyl-6-iodopyrimidine;[84] the available evidence suggests that when a 2,4-dichloropyrimidine is treated with hydriodic acid, the 2-chloro tends to be replaced by hydrogen, and the 4-chloro by an iodo substituent.



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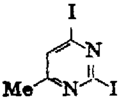

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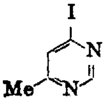

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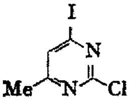

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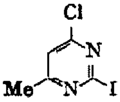
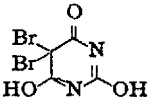


(XXI)

2. The Preparation of 5-Halogenopyrimidines

Direct halogenation leads always to 5-halogenopyrimidines. This operation goes easily if one or more electron-releasing groups are present, but even pyrimidine hydrochloride will brominate under abnormal conditions[85] (Ch. IV, Sect. 1.C) to give 5-bromopyrimidine. Direct halogenation is therefore the most used method of preparation, although direct synthesis and other minor methods have been used necessarily for fluoro, often for iodo, and sometimes for chloro and bromo derivatives. From compounds such as barbituric acid it is possible to produce for example a stable 5,5-dibromo derivative (XXII) which is strictly comparable with alloxan (XXIII) or with a 5,5-dialkylbarbituric acid (XXIV) in configuration; from such a compound, one bromine can be removed by reduction, leading to normal 5-bromobarbituric acid (XV). The action of halogens on uracil and cytosine derivatives also sometimes gives dibromo compounds but the picture is far less simple (Sect. 2.A(6)(b)).



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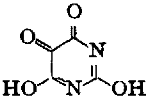

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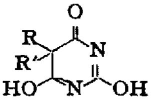

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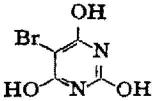


(XXV)

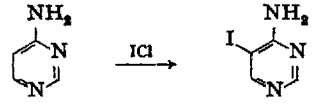
A. 5-Halogenopyrimidines by Direct Halogenation

(1) *5-Halogenation of Alkylpyrimidines*

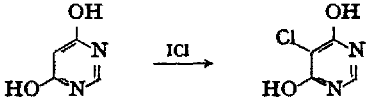
The halogenation of pyrimidine and alkylpyrimidines has already been discussed (Ch. IV, Sects. 1.C and 2.C(5)).

(2) *5-Halogenation of Amino- or Hydroxy- pyrimidines*

2-Aminopyrimidine and its *C*-methyl derivatives have been both chlorinated and brominated in warm aqueous solution,[78] most satisfactorily in the presence of calcium carbonate, or other solid base, to neutralize the acid formed.[79] When one of these, 2-amino-4,6-dimethylpyrimidine, was brominated in aqueous alcohol at 0°, a perbromide was formed which on reduction with sulphur dioxide gave the 5-bromo derivative.[86] 2,4- and 4,6- Diaminopyrimidine brominate readily in water.[29,78] 2-Aminopyrimidine has been iodinated in the presence of mercuric acetate,[50] and 4-aminopyrimidine (XXVI) has been iodinated directly with iodine monochloride giving 4-amino-5-iodopyrimidine (XXVII),[87] although this same reagent with 4,6-dihydroxypyrimidine (XXVIII) gave 5-chloro-4,6-dihydroxypyrimidine (XXIX) instead of the expected iodo derivative.[48] 5-Bromo-4,6-dihydroxypyrimidine has been made by bromination in acetic acid[48] or better, in water.[29] 5-Bromo- and 5-chloro- 4-hydroxypyrimidine have been formed by halogenation in acetic acid[48] and 5-bromo-4-hydroxy-2,6-dimethylpyrimidine in water.[88] 2-Hydroxypyrimidine has been 5-halogenated[87a] and 2-hydroxy-4,6-dimethylpyrimidine gives a 5-bromo derivative either with bromine in dilute acetic acid or with sodium hypobromite;[89] under other conditions these last brominations lead to several distinct "perbromides".[89] 2,4-Dihydroxypyrimidine (uracil) has been normally brominated in warm water[90,91] and iodinated by iodine and aqueous sodium hydroxide;[92] the best yield of 5-chlorouracil is obtained from uracil with *N*-chlorosuccinimide in acetic acid;[93] 1,3-diethyluracil (1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidine) has been brominated in ethanol[94] and 4-benzyl-2,6-dihydroxypyrimidine in acetic acid.[95] The introduction of 2 bromine atoms into the 5-position is dealt with in Sect. 2.A(6), and other procedures for brominating uracil and orotic acid, such as the use of dioxane dibromide in dioxane, or treatment with a mixture of aqueous sulphuric acid, sodium bromide, and hydrogen peroxide, are recorded.[97,98]



(XXVI) (XXVII)



(XXVIII) (XXIX)

(3) *5-Halogenation of Aminohydroxypyrimidines**

Halogenations of aminohydroxypyrimidines are typified by the preparation of bromoisocytosine[96] (2-amino-5-bromo-4-hydroxypyrimidine) in an aqueous medium, bromocytosine[90] (4-amino-5-bromo-2-hydroxypyrimidine) in acetic acid, and iodocytosine[92] (4-amino-2-hydroxy-5-iodopyrimidine) or 2,4-diamino-6-hydroxy-5-iodopyrimidine[99] with iodine and aqueous potassium hydroxide.

(4) *Halogenation of Mercapto- or Alkylthio- pyrimidines*

Mercaptopyrimidines cannot normally be halogenated although 4-amino-5-bromo-6-hydroxy-2-mercaptopyrimidine (XXX) has exceptionally been produced by bromine in acetic acid.[42] Alkylthio groups, however, are unaffected by halogenation and among alkylthiopyrimidines with a directly introduced 5-halogen may be quoted, 5-chloro-2-methylthio-4-hydroxypyrimidine[93,100,101] and 5-chloro-2-ethylthio-4-hydroxy-6-methylpyrimidine and its isopropylthio analogue[100,101] (chlorine and ferric chloride catalyst in acetic acid), 5-bromo-2-methylthiopyrimidine (XXXI) and its ethylthio analogue[102] (bromine in

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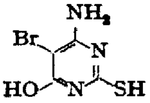
* As an example of 5-halogenation of a nucleoside may be quoted the photocatalysed bromination and chlorination of cytidine in acetic acid and pyridine mixture,[105] and of deoxycytidine under similar conditions.[106]

carbon tetrachloride at 125°), 5-bromo-2-ethylthio-4-hydroxypyrimidine[103] and its methylthio analogue[100] (bromine and acetic acid), 2-benzylthio-4-hydroxy-5-iodopyrimidine[100] and its ethylthio analogue,[92] 2-allylthio-4-hydroxy-5-iodo-6-methylpyrimidine (XXXII)[104] (iodine in methanol) and its 3-methyl derivative (XXXIII)[104] (iodine and alkali).



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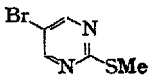

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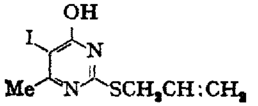

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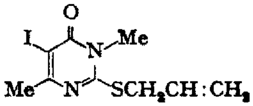
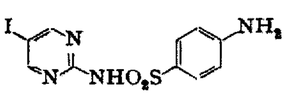


(XXXIII)

(5) *5-Halogenation of Miscellaneous Pyrimidines*

A variety of other pyrimidines have been directly halogenated in the 5-position. Included in these may be quoted for example the chlorination of orotic acid (4-carboxy-2,6-dihydroxypyrimidine) by hydrochloric acid and hydrogen peroxide,[107] the iodination in the presence of mercuric acetate of 2-sulphanilamido-[102] to give (XXXIV) and phenylsulphonamido-pyrimidine,[50] as well as the chlorination and bromination of the latter without mercury[50] and the iodination of several phenyl-substituted derivatives.[50, 102] Alkoxypyrimidines have been brominated as in the preparation of 5-bromo-2-ethoxy-4,6-dimethylpyrimidine[108] and 2-amino-5-bromo-4-methoxypyrimidine.[50] 5-Bromo-4-carboxy-6-hydroxypyrimidine has been made with sodium hypobromite.[110] 4-Chloro-2,6-dimethoxypyrimidine and 2,4-dimethoxy-6-methylaminopyrimidine, 5-brominate readily with *N*-bromosuccinimide in a mixture of acetic anhydride and acetic acid.[109]



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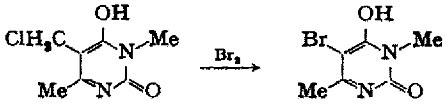
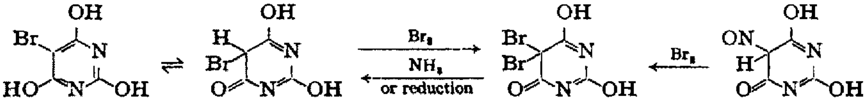


(XXXV) (XXXVI)

There are some examples where one halogen displaces another, as in the formation of 5-chloro-1,3-dimethylbarbituric acid from the 5-bromo analogue with hydrochloric acid;[111] in the case of 5-chloromethyl-3,6-dimethyluracil (XXXV), bromination displaces the whole 5-substituent in favour of bromine, giving 5-bromo-3,6-dimethyluracil[112] (XXXVI).

(6) *5,5-Dihalogenation of Pyrimidines*

(a) ***Barbituric Acid Derivatives.*** When barbituric acid is brominated, 5-bromobarbituric acid (XXXVII) is first formed,[113] and this then possibly reacts in the tautomeric form (XXXVIIa) with more bromine,* to give 5,5-dibromobarbituric acid[113-115] (XXXVIII). The dibromo derivative can, however, best be made by bromination of 2,4,6-trihydroxy-5-nitrosopyrimidine[111] (violuric acid; XXXIX), and also from 2,4,6-trihydroxy-5-nitropyrimidine,[114] 5-acetyl-2,4,6-trihydroxypyrimidine,[116] or 5-benzylidene-2,4,6-trihydroxypyrimidine;[113] in these cases the original 5-substituents are displaced. The dibromo gives the monobromo derivative (XXXVII) conveniently on treatment with ammonia,[111, 118] but also by reduction with sodium amalgam,[117] zinc,[117] hydrazine,[118] hydrogen iodide,[119] and cyclohexene.[120]



(XXXVII) (XXXVIIa) (XXXVIII) (XXXIX)

The *N*-alkyl derivatives of barbituric acid behave similarly to the parent in the above bromination reactions.[111, 116] Chlorinations are very similar to brominations. Thus 5-chlorobarbituric is obtained by chlorination of barbituric acid[121] or better, by treatment of 5-bromobarbituric acid with hydrochloric acid.[111, 121] Further chlorination gives 5,5-dichlorobarbituric acid,[118, 121] and the 1- and 3-alkyl derivatives behave again like the parent.[111, 122] It is possible to convert 5,5-dichloro- into 5-chloro-barbituric acid with *e.g.* hydrazine[118] but not with stannous chloride, which gives barbituric acid.[111] Excessive chlorination of barbituric acid in aqueous alkali gives dichloroacetylurea.[123]

(b) *Uracil, Cytosine, and Derivatives.* Halogenation of the uracil family is normal as far as mono-5-halogenation is concerned. The introduction of a second halogeno atom at position 5 is, however, fundamentally different to the case of barbituric acid above. No true 5,5-dihalogeno-uracil is formed but (in the presence of water) only 5,5-dibromo-4,5-dihydro-2,4,6-trihydroxypyrimidine** (XL; R=H), or the

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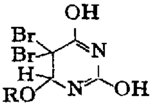
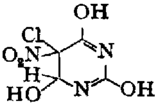
* It is emphasized that the mechanism is unknown. It could well be an addition of HOBr across the 4,5-bond followed by dehydration.

** The configuration of the homologous 5,5-dibromo-4,5-dihydro-2,4,6-trihydroxy-4-methylpyrimidine (or its dichloro analogue) has been shown by oxidative removal of the methyl group (and oxidation) with nitric acid to give 5,5-dibromo-(or dichloro-) barbituric acid.[128]

dichloro analogue, is obtained.[107, 124, 125] Although it is relatively stable, the dibromo compound is reconverted into 5-bromouracil by prolonged boiling with 2N-hydrochloric acid.[126] The dichloro-4-methyl compound strangely gives 5-chloro-4-chloromethyl-2,6-dihydroxypyrimidine.[127] When the halogenation is done in an alcohol, the appropriate alkoxy group replaces the 4-hydroxy group, giving a compound of the type of (XL; R = alkyl) *e.g.* 4-benzyl-5,5-dichloro-4,5-dihydro-2,4,6-trihydroxy-4-methoxypyrimidine;[95] in other solvents no dihalogenation takes place. If a 5-group is present an additional halogen may enter or the group may be displaced and two halogen atoms enter. Thus 5-nitrouracil and 5-methyluracil (thymine) give, with the appropriate halogen, respectively 5-chloro-4,5-dihydro-2,4,6-trihydroxy-5-nitropyrimidine[107] (XLI) and 5-bromo (or chloro)-4,5-dihydro-2,4,6-trihydroxy-5-methylpyrimidine.[107, 129, 130] On the other hand, 5-carboxy-2,4-dihydroxypyrimidine[107] gives 5,5-dichloro-4,5-dihydro-2,4,6-trihydroxypyrimidine (XLIII) and 5-iodouracil[107] (XLII) gives the same product (XLIII). In contrast to the last example, 5-bromo-5-chloro-4,5-dihydro-2,4,6-trihydroxypyrimidine (XLV) is formed[125] either by chlorine water and 5-bromouracil (XLIV) or bromine water and 5-chlorouracil


(XL)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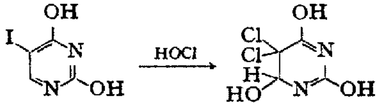
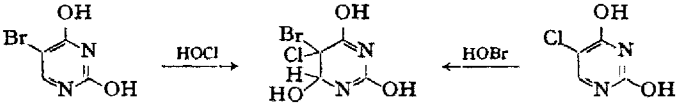
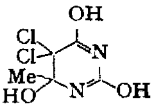
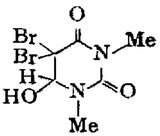


(XLII) (XLIII)



(XLIV) (XLV) (XLVI)


(XLVII)

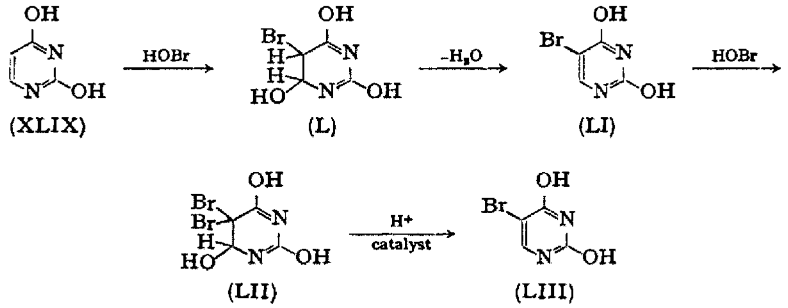

(XLVIII)

(XLVI). The halogen sometimes affects groups in other positions. For example, 4-hydroxy-2-mercapto-6-methylpyrimidine,[131] as well as 2,4-dihydroxy-6-methylpyrimidine,[128] with chlorine gives 5,5-dichloro-4,5-dihydro-2,4,6-trihydroxy-4-methylpyrimidine (XLVII), 2-ethylthio-4-

hydroxypyrimidine gives 5,5-dichloro-4,5-dihydro-2,4,6-trihydroxypyrimidine[107] (XLIII), and 4-amino-2-hydroxypyrimidine (cytosine) gives also the same product[107] (XLIII) or the dibromo analogue.[124] Under less vigorous conditions, however, cytosine gives some 4-amino-5,5-dibromo-5,6-dihydro-2,6-hydroxypyrimidine.[90]

1,3-Dimethyluracil and isocytosine (2-amino-4-hydroxypyrimidine) behave similarly to uracil in giving respectively 5,5-dibromohexahydro-4-hydroxy-1,3-dimethyl-2,6-dioxopyrimidine[132] (XLVIII), and 2-amino-5,5-dichloro-4,5-dihydro-4,6-dihydroxypyrimidine.[107] Prolonged heating of the reaction mixture from the first of these gives the monobromo derivative.[133]

Renewed interest has recently been shown in the mechanism of halogenation of the uracil group of pyrimidines.[134, 135] Wang,[91, 126] has advanced a sequence of reaction based on careful experiments with uracil and 1,3-dimethyluracil, and his scheme for the bromination of uracil is briefly outlined in formulae (XLIX) to (LIII). The evidence is convincing, and has been independently confirmed and extended.[136]



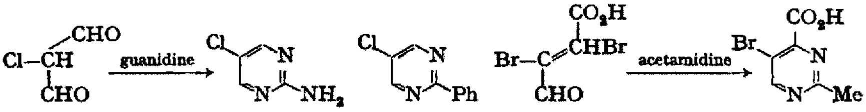
(XLIX) (L) (LI) (LII) (LIII)

B. 5-Halogenopyrimidines by Direct Synthesis

Aliphatic compounds already containing a halogen atom have sometimes been used to make a 5-halogenopyrimidine by a direct synthesis. This approach has been particularly useful in the case of very simple pyrimidines which do not halogenate readily, for pyrimidines with oxidizable substituents or groups which would be sensitive to halogens, and in the case of the important 5-fluoro derivatives, which have been made only in this way.

Chloromalondialdehyde (LIV) has been condensed with guanidine in fuming sulphuric acid or chlorosulphonic acid to give 2-amino-5-

chloropyrimidine[137,138] (LV), and with benzamidine (or its *m*- or *p*-nitro derivative) in alcoholic alkali, to give 5-chloro-2-phenylpyrimidine (LVI) and its *m*- or *p*-nitro derivatives.[139] Mucobromic acid (LVII) and mucochloric acid give with acetamidine, respectively 5-bromo-4-carboxy-2-methylpyrimidine (LVIII) and the chloro analogue.[141] Similarly, condensation with benzamidine gives 5-bromo-4-carboxy-2-phenylpyrimidine or the chloro analogue,[142] and the use of *S*-methylthiourea gives 5-bromo-4-carboxy-2-methylthiopyrimidine.[387] Chloromucic acid with guanidine in methanolic sodium methoxide yields crude 2-amino-4-carboxy-5-chloropyrimidine (?), which on dry distillation gives 60% overall yield of 2-amino-5-chloropyrimidine.[140] (The preparation, which includes details for making chloromucic acid, is described in English, and is more convenient than the synthesis *via* chloromalondialdehyde above.) Ethyl bromocyanoacetate and guanidine give 2,4-diamnio-5-bromo-6-hydroxypyrimidine.[99]



(LIV) (LV) (LVI) (LVII) (LVIII)

5-Fluoro-2,4-dihydroxypyrimidine (LXI) and 4-carboxy-5-fluoro-2,6-dihydroxypyrimidine (LXIII) have been shown[143,144] to have antitumour activity.[*] The first of these (LXI) was made by condensation of ethyl formylfluoroacetate (LIX) with *S*-ethylthiourea to give 2-ethylthio-5-fluoro-4-hydroxypyrimidine (LX) followed by acid hydrolysis.[145] An analogous condensation of diethyl fluoro- oxalacetate and *S*-ethylthiourea gave 4-ethoxycarbonyl-2-ethylthio-5-fluoro-6-hydroxypyrimidine (LXII) which was acid hydrolysed to 4-carboxy-5-fluoro-2,6-dihydroxypyrimidine[145] (LXIII). Other examples of 5-fluoropyrimidines are given in Table II.

C. Other Methods of Preparing 5-Halogenopyrimidines

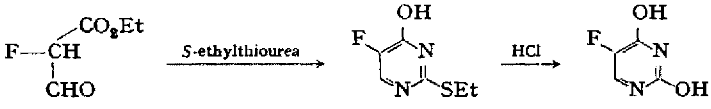
There is at least one example of the formation of a 5-halogeno derivative from the corresponding 5-amino derivative. 2,5-Diamino-4,6-dimethylpyrimidine, on diazotization and treatment with potassium

---

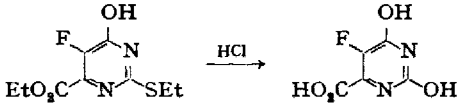
[*] The fluoro derivatives and related compounds have been reviewed from the metabolic antagonist point of view.[147]

iodide gave a good yield of 2-amino-5-iodo-4,6-dimethylpyrimidine[146] (Ch. IX, Sect. 5.E).

The 5-bromo group in several cases has been exchanged for chlorine or iodine. Thus treatment of the ammonium salt of 5-bromo-1-ethylbarbituric acid with hydrochloric acid gave 5-chloro-1-ethylbarbituric acid,[116] and 2,4-diamino-5-bromo-6-hydroxypyrimidine with potassium iodide in boiling dilute acetic acid gave 87% of the 5-iodo analogue.[99] 5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine when heated with ammonium chloride in alcohol gives the 5-chloro analogue.[109]



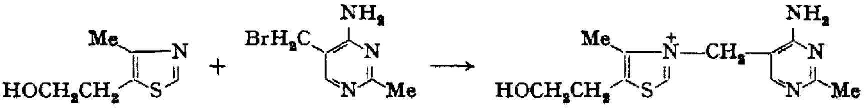
(LIX) (LX) (LXI)



(LXII) (LXIII)

3. The Preparation of Extranuclear Halogenopyrimidines

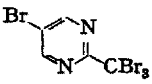
Compared with the large number of other halogenopyrimidines, those with a halogen atom on a side chain are very few. They have been made by a variety of methods. The best-known compound of this type is 4-amino-5-bromo-methyl-2-methylpyrimidine (LXV) which, condensed with 5-hydroxyethyl-4-methylthiazole (LXIV), yields[145] vitamin B_1 (LXVI); the necessity of the commercial synthesis of this pyrimidine in the years 1935–1940 stimulated interest in this type of halogeno derivative.



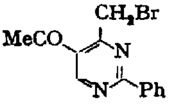
(LXIV) (LXV) (LXVI)

A. By Direct Halogenation

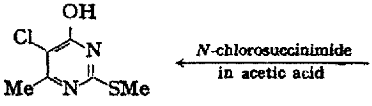
The direct bromination or chlorination of alkylpyrimidines is rather uncertain in the extent of substitution, and moreover is almost sure to introduce a 5-halogen atom if that position is unoccupied. Thus 2-methylpyrimidine on vigorous bromination gives 5-bromo-2-tribromomethylpyrimidine[149] (LXVII) and 4,6-dimethylpyrimidine similarly gives 4,6-bistribromomethylpyrimidine.[150] Bromination of 2-amino-4,6-dimethylpyrimidine gives first the 5-bromo derivative and then a mixture of 2-amino-5-bromo-4-bromomethyl-6-methylpyrimidine and 2-amino-5-bromo-4,6-bisbromomethylpyrimidine.[151] Less well-authenticated structures resulting from direct halogenation have also appeared in the literature.[152,153] One of the few definite monobrominations is that producing 5-acetyl-4-bromomethyl-2-phenylpyrimidine.[154]



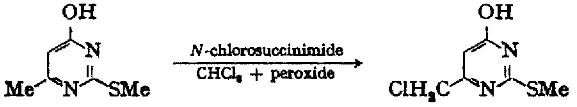
(LXVII)



(LXVIII)



(LXIX)

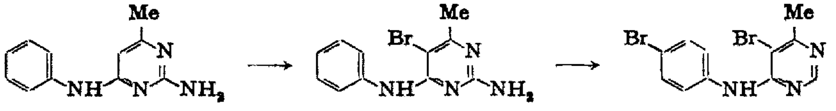


(LXX) (LXXI)

The disadvantages of direct halogenation are largely overcome by the use of *N*-bromo- or *N*-chloro-succinimide. In this way 2,4,6-trichloro-5-methylpyrimidine gives the 5-bromomethyl derivative (LXIX), but direct bromination also gives the same product in this case.[81] 4,6-Dichloro-2,5-dimethylpyrimidine is selectively brominated on the 5-group by *N*-bromosuccinimide to give 5-bromomethyl-4,6-dichloro-2-methylpyrimidine, but direct bromination also replaces one of the chlorines to give 4-bromo-5-bromomethyl-6-chloro-2-methylpyrimidine.[81] In glacial acetic acid, *N*-chlorosuccinimide causes nuclear substitution of uracil and related compounds converting, for example, 4-hydroxy-6-methyl-2-methylthiopyrimidine (LXX) into the 5-chloro derivatives (LXIX). The claim that in chloroform (and with benzoyl peroxide present) the same reagent causes only side chain chlorination and gives, from (LXX), 4-chloromethyl-6-hydroxy-2-methylthiopyrimidine[93] (LXXI) defies repetition[154a]. With thymine, the same reagent is said to give 5-chloromethyl-2,4-dihydroxypyrimidine,[93] but it seems[154a,155] that the product depends on the use of chloroform containing ethanol, and that it probably is 5-chloro-4-

ethoxy-4,5-dihydro-2,6-dihydroxy-5-methylpyrimidine. Authentic 5-chloromethyluracil has, however, been made by treatment of uracil with formaldehyde and hydrochloric acid,[155, 157] and its structure has been confirmed.

The direct halogenation of an aryl moiety attached to pyrimidine is rare, but a brief study[156] of the bromination of three anilino pyrimidines has indicated that both 5-substitution in the pyrimidine ring and *p*-substitution in the benzene ring occur. 2-Amino-4-anilino-6-methylpyrimidine (LXXII) gives first the 5-bromo derivative (LXXIII), and then (with more bromine) the 5,*p*-dibromo derivative (LXXIV). The behaviour of 4-anilino-2,6-dimethylpyrimidine is similar, but 2-anilino-4,6-dimethylpyrimidine even with one equivalent of bromine gives a mixture of 5-bromo, *p*-bromo, and 5,*p*-dibromo derivatives.



(LXXII) (LXXIII) (LXXIV)

B. From the Corresponding Hydroxyalkylpyrimidine

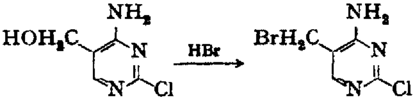
Several hydroxymethylpyrimidines have been converted into halogenomethyl derivatives with thionyl chloride or hydrogen bromide in acetic acid. 4-Amino-2-chloro-5-hydroxymethylpyrimidine (LXXV) yields 4-amino-5-bromomethyl-2-chloropyrimidine (LXXVI) (or the 5-chloromethyl analogue) by these reagents,[158] and 4-amino-5-bromomethyl-2-methylpyrimidine has been made similarly.[159–163] They have also been used to make 4-amino-5-chloro(or bromo)methyl-2-ethylthiopyrimidine,[158] 4-β-chloropropyl-2,6-diethoxypyrimidine[73], 5-(2-bromoisobutyl)-4-chloro-2-methylpyrimidine[164] and halogeno methyluracils[154a] from their hydroxy analogues.* Phosphorus halides have also been used, in particular when hydroxy groups directly attached to the pyrimidine ring (as well as that indirectly attached) need converting into chloro groups. Thus phosphoryl chloride converted 4-hydroxy-5-hydroxymethyl-2-methyl-pyrimidine into 4-chloro-5-chloromethyl-2-methylpyrimidine,[165] and phosphorus pentachloride, 2,4-dihydroxy-5-

* It is reported[175] that the promising anti-tumour agent, 5-bis(β-chloroethyl)-amino-2,4-dihydroxypyrimidine, was made with thionyl chloride from the corresponding hydroxy derivative.[176]

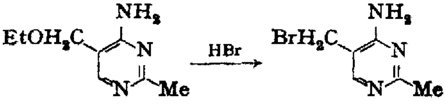
hydroxymethyl- into 2,4-dichloro-5-chloromethyl- 6-methylpyrimidine.[163] Other cases are the formation of 4-amino-5-chloromethyl-2-methylpyrimidine,[162] and 4-amino-5-chloromethyl-2,6-dihydroxypyrimidine.[166]

C. From the Corresponding Alkyloxyalkylpyrimidine

Extranuclear ethers such as 4-amino-5-ethoxymethyl-2-methylpyrimidine (LXXVII) are split by hot hydrogen bromide in acetic acid to give for example 4-amino-5-bromomethyl-2-methylpyrimidine[167–170] (LXXVIII). The method has been used for the 2-ethyl[171] and 2-butyl[172] analogues of (LXXVIII), and to convert 2-amino-5-ethoxyethyl-4-methylpyrimidine into 2-amino-5-bromoethyl-4-methylpyrimidine.[173] Hydrochloric acid at 150° likewise splits such ethers to give for example 5-chloroethyl-4-hydroxy-6-methylpyrimidine,[174] and another good example is the fission (at 140° with hydrochloric acid) of the extranuclear ether group of 2,4-dihydroxy-5-phenoxy-6-phenoxymethylpyrimidine (without affecting the similar 5-ether group) to give 4-chloromethyl-2,6-dihydroxy-5-phenoxypyrimidine.[177]



(LXXV) (LXXVI)

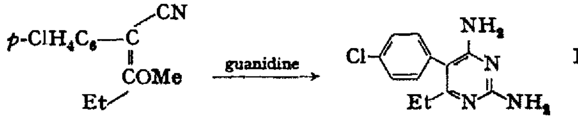


(LXXVII) (LXXVIII)

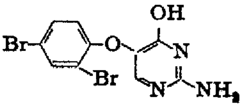
D. By Direct Synthesis

Pyrimidines bearing a trifluoromethyl group have been made by direct synthesis. For example guanidine and ethyl α-phenylazotrifluoroacetoacetate give 2-amino-4-hydroxy-5-phenylazo-6- trifluoromethylpyrimidine.[178] The corresponding 2-mercapto derivative was made similarly.[178] Ethyl trifluoroacetoacetate has been condensed directly with urea in the presence of sodium ethoxide to give 2,4-dihydroxy-6-trifluoromethylpyrimidine,[179] and with thiourea to give 4-hydroxy-2-mercapto-6-trifluoromethylpyrimidine.[180] In order to put a trifluoromethyl group in the 2-position, trifluoroacetamidine has been condensed with diethyl ethoxymethylenemalonate and with ethoxymethylenemalononitrile to give respectively 5-ethoxycarbonyl-4-hydroxy- and 4-amino-5-cyano- 2-trifluoromethylpyrimidine.[181] The compounds mentioned above have been used to make other trifluoromethyl derivatives by metathesis. Fluoroacetamidine gives 2-fluoromethyl-4,6-dihydroxypyrimidine.[181a]

The development of the anti-malarial "Daraprim"[182, 183] led to the preparation of a large number of pyrimidines with fluoro-, chloro-, or bromo-phenyl groups attached directly[184], or through an ether[185] or methylene[186] linkage, to the 5-position of a pyrimidine. These were made by direct synthesis, typified by the condensation of guanidine with the enol ether of α-(*p*-chlorophenyl)propionylacetonitrile (LXXIX) to give 2,4-diamino-5-chlorophenyl-6-ethylpyrimidine[184] ("Daraprim"; LXXX), or by the condensation of guanidine with ethyl (2,4-dibromophenoxy)formylacetate to give 2-amino-5-(2,4-dibromophenoxy)-4-hydroxypyrimidine[185] (LXXXI).



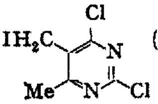
(LXXIX) (LXXX)



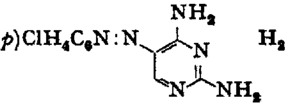
(LXXXI)

E. By Other Means

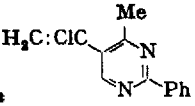
When 6-methyluracil was heated at 100° with chloromethyl methyl ether ($ClCH_2OMe$) a chloromethyl group entered the 5-position to give 5-chloromethyl-2,4-dihydroxy-6-methylpyrimidine.[187]



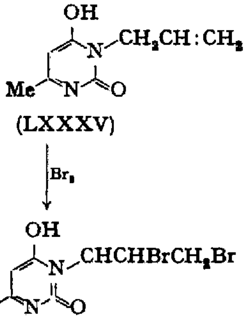
(LXXXII)



(LXXXIII)



(LXXXIV)



(LXXXV)

(LXXXVI)

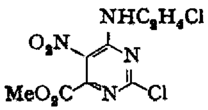
2,4-Dichloro-5-chloromethyl-6-methylpyrimidine has been converted into its 5-iodomethyl analogue (LXXXII) with sodium iodide in acetone.[163, 188]

Many 5-*p*-chlorophenylazo derivatives such as 2,4-diamino-5-*p*-chlorophenylazopyrimidine[87] (LXXXIII) have been made by coupling diazotized *p*-chloroaniline with the appropriate pyrimidines, and the reaction has been covered in Chapter V, Sect. 3.A(2); *p*-chlorophenylhydrazones of pyrimidines have been described.[213]

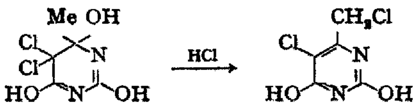
5-Acetyl-4-methyl-2-phenylpyrimidine has been converted into 5-α-chlorovinyl-4-methyl-2-phenylpyrimidine (LXXXIV) by phosphorus pentachloride.[189] 3-Allyl-6-methyluracil (LXXXV) adds bromine across its double bond to give 3-(2,3-dibromopropyl)-6-methyluracil (LXXXVI), and the 5,6-dimethyl analogue was made similarly.[190] Hydrogen chloride has been added across 5-allyl-2,4-dihydroxy-6-methylpyrimidine to give 5-β-chloropropyl-2,4-dihydroxy-6-methylpyrimidine[191], and another example has been described.[192]

Chloroalkylamino derivatives of pyrimidines have been made by condensation of a chloropyrimidine with a chloroalkylamine, as in the preparation of 2-chloro-4-β-chloroethylamino-6-methoxycarbonyl-5-nitropyrimidine (LXXXVII) from the 4-chloro analogue.[193]

An interesting, but isolated, preparation of a chloromethyl derivative is that of 5-chloro-4-chloromethyl-2,6-dihydroxypyrimidine[187] (LXXXIX) by the action of hydrochloric acid on 5,5-dichloro-4,5-dihydro-2,4,6-trihydroxy-4-methylpyrimidine (LXXXVIII). The product (LXXXIX) was previously wrongly described as a derivative of a "bicyclouracil".[194, 195]



(LXXXVII)



(LXXXVIII) (LXXXIX)

4. Properties of Halogenopyrimidines

Pyrimidines containing only halogeno substituents are oils or low melting colourless solids, with characteristic odour. The melting points of the chloro compounds are given in Table IX. Most of them are at least mildly irritating to the skin and eyes. Alkyl derivatives are similar, but 5-nitro derivatives are more active (Ch. I), rather less stable on keeping, and more irritating.

The kinetics of the nucleophilic displacement reactions of several 2- and 4- chloropyrimidines with organic bases, as well as the effect of

TABLE IX. Melting Points of Simple Chloropyrimidines

2-chloro-, 64.5°	2,4-dichloro-, 62°	2,4,5-trichloro-, oil[d]
4-chloro-, oil[a]	2,5-dichloro-, 57.5° [b]	2,4,6-trichloro-, 21°
5-chloro-, 36.5°	4,5-dichloro-, oil[c]	4,5,6-trichloro-, 49–51°
	4,6-dichloro-, 67.5°	2,4,5,6-tetrachloro-, 66–68°

[a] unstable; hydrochloride, m.p. 193–194° (decomp.)
[b] non-irritating
[c] b.p. 82° (34 mm)
[d] b.p. 73–74° (3 mm)

nuclear methyl groups on the reactivity of chloropyrimidines, has been studied.[196] In such work, aromatic amines were unsatisfactory because the formation of the cation of the chloro compound has a catalytic effect on the reaction[197] and aromatic amines were too weak to prevent this. The rate of reaction with pyridine was too low to make the rather slow self-quaternization of the chloro compounds negligible. Work with piperidine and morpholine in ethanol, however, indicated a series of regular second-order reactions. The constants[196] are summarized in Table X and indicate that the 4-chloro substituent is more active than the 2-chloro, and that *m*-methyl groups decrease the activity in both cases. This is parallel to preparative experience.

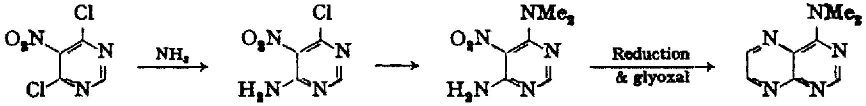
TABLE X. Rate Constants of the Reaction of Chloropyrimidines with Piperidine and Morpholine

	Average of extreme values of 10^4 *K* in l. mole^{-1} sec^{-1}:					
		Piperidine			Morpholine	
Pyrimidine	20°	30°	40°	20°	30°	40°
2-chloro	33.3	68.6	129	7.7	15.1	28.5
2-chloro-4-methyl-	13.7	28.6	54.1	3.3	6.7	14.0
2-chloro-4,6-dimethyl-	5.7	11.3	21.4	1.37	2.8	5.45
4-chloro-2-methyl-	165	300	522	43.2	77.3	135
4-chloro-6-methyl-	115	215	369	28.8	55.6	98.2

Other significant contributions to the study of rate of reaction of chloropyrimidines have been made,[197–199] and an interesting comparison of the rates of reaction of active chloro derivatives in several π-deficient *N*-heterocyclic series (including pyrimidine) has been given by Albert.[200]

5. Reactions of 2-, 4-, and 6-Halogenopyrimidines

Pyrimidines with halogen substituents in the active positions undergo a great variety of reactions. Most of these have naturally been done with the chloro compounds which are easier to make, and much of what follows will therefore describe the reactions of chloropyrimidines. In the course of a synthetic route it is often essential to react each chloro group of a di- or tri-chloro-pyrimidine derivative singly, and with different reagents. Thus for example, 4,6-dichloro-5-nitropyrimidine (XC) can with care be monoaminated to 4-amino-6-chloro-5-nitropyrimidine[23] (XCI). Treatment with dimethylamine then gives 4-amino-6-dimethylamino-5-nitropyrimidine[201] (XCII) which, after reduction of the nitro group, can be condensed with glyoxal to yield 4-dimethylaminopteridine[201] (XCIII). Such differential reactions are very important in synthetic pyrimidine chemistry.

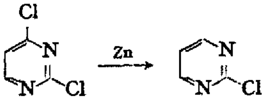


(XC) (XCI) (XCII) (XCIII)

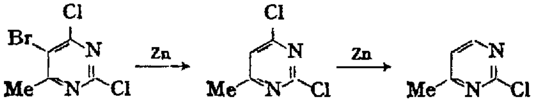
A. Removal of 2-, 4-, and 6-Halogens

(1) *In the Presence of Only Alkyl Groups*

The complete removal of the halogen from pyrimidine derivatives initially carrying only halogeno or halogeno plus alkyl or aryl groups, has been fully treated respectively in Chapter IV, Sects. 1.A and 2.A(2). The partial removal of halogen from such compounds is also possible under controlled conditions. Thus 2,4-dichloropyrimidine (XCIV), on boiling with zinc dust in aqueous ammonium chloride or aqueous alcoholic ammonia, yields 2-chloropyrimidine[2,12] (XCV), and 2,4-dichloro-6-methylpyrimidine (XCVII) and its 6-phenyl analogue yield respectively 2-chloro-4-methylpyrimidine (XCVIII) and 2-chloro-4-phenylpyrimidine in good yield.[12] In contrast, 5-bromo-2,4-dichloro-6-methylpyrimidine (XCVI), under almost the same conditions except for a shorter boiling period, loses only the 5-bromo group, giving 2,4-dichloro-6-methylpyrimidine[12] (XCVII): an extraordinary reaction. Attempts, for example,[47,49] selectively to remove by hydrogenation one halogen and leave others, have generally failed even when the halogeno substituents involved have widely differing activities; exceptional to this is the preparation[139] of 5-chloropyrimidine by partial hydrogenation of 2,5-dichloropyrimidine, under conditions not precisely stated.



(XCIV) (XCV)



(XCVI) (XCVII) (XCVIII)

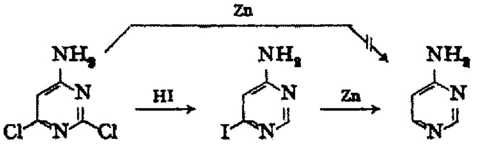
(2) *In the Presence of Amino Groups*

There are many examples of the removal of active halogen in the presence of amino groups. A simple illustration is the preparation of 2-aminopyrimidine[202–205] by the action of zinc dust and aqueous ammonia on 2-amino-4-chloropyrimidine (itself prepared from isocytosine[206]). Yields are said to be improved by the addition of a little stannous or bismuth salt.[207] 2-Amino-4-ethyl-[208] and 2-amino-4-methylpyrimidines were also prepared with zinc dust and water[7] or ammonia,[209] from 2-amino-4-chloro-6-ethyl (or methyl)pyrimidine, but the process is quicker and more reliable if some ammonium chloride and a catalytic amount of Raney nickel is added.[210] Again, heavy metal salts improve the yield[211] of the above, and also of 2-aminopyrimidine from 2-amino-4,6-dichloropyrimidine, when compared with the older method.[33] Zinc and boiling water reduce 4-chloro-1,6-dihydro-6-imino-1,2-dimethylpyrimidine hydriodide to 1,6-dihydro-6-imino-1,2-dimethylpyrimidine hydriodide.[212] The removal of a 2-chloro group with zinc is not usually possible; for example failure has been reported in dechlorinating 4-amino-2-chloropyrimidine[213] and 4-amino-2,6-dichloropyrimidine[33] (XCIX). Hydriodic acid and red phosphorus, however, converted the first of these directly into 4-aminopyrimidine,[124, 213] and the second dichloro-compound (XCIX) with the same reagents gave 4-amino-6-iodopyrimidine (C) which gave 4-aminopyrimidine (CI) by boiling in water with zinc.[33] 4-Methylaminopyrimidine was first prepared[214] by an exactly analogous route. Similarly 2,4-diamino-6-chloropyrimidine with hydriodic acid gave 2,4-diamino-6-iodopyrimidine which with zinc yielded 2,4-diaminopyrimidine.[33]

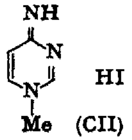
2-Chloro-1,4-dihydro-4-imino-1-methylpyrimidine hydriodide and its 6-methyl derivative on warming with hydriodic acid give respectively 1,4-dihydro-4-imino-1-methylpyrimidine hydriodide[215] (CII), and its 6-methyl derivative.[212] An electrolytic dechlorination of 2-amino-4-chloropyrimidine to 2-aminopyrimidine has been recorded.[216]

Hydrazine hydrate in alcoholic alkali and in the presence of palladium on strontium carbonate, has been used to dehalogenate 4,5-diamino-6-ethyl-2-chloropyrimidine.[218] 2-Aminopyrimidine results similarly in 87 % yield from its 4-chloro derivative.[217]

Hydrogenation over palladium also affords a good means of dehalogenation in the presence of amino groups. A proton acceptor such as barium oxide, magnesium oxide, or alkali, is generally needed if nuclear reduction is to be avoided,[54] but neither pressure nor high temperature is required. Examples of this method are recorded in Table XI.



(XCIX) (C) (CI)



(CII)

(3) *In the Presence of Other Groups*

Relatively few examples of dechlorination are known when the pyrimidine carries groups other than amino or alkyl. 2-Methylthio-,[52] 2-ethylthio-,[229] and 2-hydroxy-[230] pyrimidine have been prepared from their 4-chloro derivatives, as well as 4-ethyl-2-ethylthiopyrimidine[208] and 2-ethylthio-4-methylpyrimidine[229] from their 6-chloro derivatives, all by the action of zinc dust in aqueous ethanol, in an approximately 70 % yield. The same reagent has also been used to convert 4-chloro-5-ethoxy-2-ethylthiopyrimidine into 5-ethoxy-2-ethylthiopyrimidine,[229] and to remove only one chloro group of 2,4-dichloro-5-ethoxypyrimidine to give 2-chloro-5-ethoxypyrimidine.[229] 5-Ethoxycarbonyl-2-ethylthiopyrimidine[55] has been made from its 4-chloro derivatives with zinc and ethanol, and 2,4-diethoxy-[214] and 2,4-dimethoxypyrimidine[30] have been prepared from their 6-chloro derivatives with zinc dust in alcohol and hydrochloric acid.

Especially in the presence of more easily hydrolysed groups, hydrogenation has been useful for dehalogenation. Thus 4-chloro-2,6-dimethoxy- and 2,4-dichloro-6-methoxy-pyrimidine give respectively 2,4-dimethoxy- and 4-methoxy-pyrimidine when hydrogenated in

TABLE XI. Some Dechlorinations of Amino Chloro Pyrimidines by Hydrogenation

Pyrimidine Produced and Yield	Starting Pyrimidine	Conditions	References
2-amino-; —	2-amino-4-chloro-	Pd/$CaCO_3$; ethanol; BaO	206
2-amino-; 88%	2-amino-4,6-dichloro-	Pd/C; methanol; KOH	220
2-amino-;[a] 70%	2-amino-4,6-dichloro-	Pd/$CaCO_3$; methanol; KOH	221
2-amino-; 85%	2-amino-4,6-dichloro-	Pd/$CaCO_3$; water; KOH	221
2-amino-; 88%	2-amino-4,6-dichloro-	Pd/C; water–ether; KOH	54
2-amino-4-methyl-; 71%	2-amino-4-chloro-6-methyl-	Pd/$CaCO_3$; ethanol; BaO	206, 222
2-amino-4-methyl-; 68%	2-amino-4-chloro-6-methyl-	Pd/$SrCO_3$; acetone–water; KOH	4
2-amino-4-methylamino-; 97%	2-amino-4-chloro-6-methylamino-	Pd/C; water, MgO	219
4-amino-; —	4-amino-2,6-dichloro-	Pd/C; methanol; KOH	220
4-amino-; 73%	4-amino-2,6-dichloro-	Pd/C; water–ether; KOH	54
4-amino-2-methyl-; 98%	4-amino-6-chloro-2-methyl-	Pd/C; aq. HCl	39, 141
4-amino-2-methyl-; 37%	4-amino-5-chloro-2-methyl-	Pd/$BaSO_4$; water	141
4-amino-6-methyl-; 65%	4-amino-2-chloro-6-methyl-	Pd/C; methanol	4, 222
4,5-diamino-; —	4,5-diamino-2-chloro-	Pd/C; BaO	223
5-amino-; 77%	5-amino-2,4-dichloro-	Pd/C; water;[b] MgO	13
5-amino-; 91%	5-amino-2,4-dichloro-	Pd/C; water–ether; KOH	54
5-amino-4-methyl-; 43%	5-amino-2-chloro-4-methyl-	Pd/$CaCO_3$; methanol; BaO	222
5-amino-4-methyl-; 40%	5-amino-2-chloro-4-methyl-	Pd/$SrCO_3$; water	4
5-amino-2-methyl-; 85%	5-amino-4,6-dichloro-2-methyl-	Pd/C; MgO	224
5-amino-4-methyl-; —	5-amino-2-chloro-4-methyl-	Pd/C; ethanol; MgO	49
5-amino-4-methyl-; 31%	5-amino-2,4-dichloro-6-methyl-	Pd/C; ethanol?; MgO	49
5-amino-4-methylamino-; 71%	5-amino-4-chloro-6-methylamino-	Pd/C; water; MgO	225
5-amino-4-ethylamino-; 65%	5-amino-4-chloro-6-ethylamino-	Pd/C; water; MgO	226
5-amino-2-dimethylamino-;[c] —	4-chloro-2-dimethylamino-5-nitro-	Raney Ni; ethanol; triethylamine	35
2-dimethylamino-; 68%	4-chloro-2-dimethylamino-	Pd/C; aq. ethanol; MgO	70
2-dimethylamino-4-methyl-; 82%	4-chloro-2-dimethylamino-6-methyl-	Pd/C; aq. ethanol; MgO	227
4,5-diamino-6-methyl-; —	4-amino-2-chloro-6-methyl-5-nitro-	Pd/C; aq. ethanol; NH_3	228

[a] When the hydrogenation was made very slow by insufficient catalyst, 2-amino-4-chloro-6-methoxypyrimidine and 2-amino-4-methoxypyrimidine were isolated; without potassium hydroxide, 2-amino-hexahydropyrimidine was formed.

[b] Rate became progressively slower as water was replaced by ethanol.

[c] No analysis given.

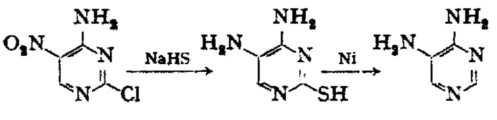
ether over palladium/charcoal in the presence of sodium hydroxide,[54] and rather similarly 2-amino-4-methoxypyrimidine and 5-amino-4-methoxy-2-methylpyrimidine are formed from the 6-chloro derivatives.[221, 224] 2,4-Dichloro-5-ethoxycarbonylpyrimidine gave 5-carboxypyrimidine[54] under the same conditions, in contrast with the action of hydriodic acid, which gave 5-carboxy-4-hydroxypyrimidine[55] (Ch. VII, Sect. 4.C).

(4) *Indirect Removal of 2-, 4-, and 6- Chloro Substituents*

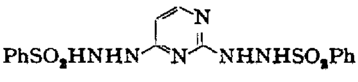
It is occasionally convenient to remove chlorines by conversion into mercapto groups (Sect. 5.G) which can then be oxidized or reduced respectively with hydrogen peroxide (Ch. VIII, Sect. 1.D(1)) or Raney nickel (see Table XIII). An illustration of this method is the conversion of 4-amino-2-chloro-5-nitropyrimidine (CIII) with sodium bisulphide into 4,5-diamino-2-mercaptopyrimidine[22, 231] (CIV) and treatment of this with Raney nickel to give 4,5-diaminopyrimidine[22] (CV). The reactions can equally well be applied to a 4-chloro atom as in the sequence from 4-amino-2-butyl-6-chloro-5-nitropyrimidine to 4,5-diamino-2-butyl-6-mercaptopyrimidine to 4,5-diamino-2-butylpyrimidine.[232]

Another potentially useful way[233] of removing an active chlorine has been applied at least once in the pyrimidine series. 2,4-Dichloropyrimidine was condensed with benzene sulphonhydrazide to give 2,4-bisbenzenesulphonylhydrazinopyrimidine (CVI), which on alkaline hydrolysis gave pyrimidine in 66 % yield.[234]

Another potentially useful removal of chlorine is conversion into the corresponding sulphonic acid[235] followed either by direct hydrolysis, as in the oxidative removal of mercapto groups, or by conversion into the nitrile,[235] hydrolysis to carboxylic acid and decarboxylation.



(CIII) (CIV) (CV)



(CVI)

B. Replacement of 2-, 4-, and 6-Halogens by Amino Groups

There are almost as many examples of a chloro's being replaced by an amino or substituted amino group as there are amino pyrimidines known. This very important topic is treated below in some detail, especially in regard to selective amination when more than one active halogen atom is present.

(1) *Amination of Halogeno- and Alkylhalogenopyrimidines*

(a) *With One Active Halogen.* The kinetics of the amination of chloropyrimidines have already been briefly treated in Sect. 4, but the examples that follow will indicate the general conditions for such reactions in preparative chemistry.

2-Chloropyrimidine with alcoholic ammonia at 130° gives 2-aminopyrimidine[236] (which is, however, better made in practice by other means); methylamine and dimethylamine similarly give at 80–120° 2-methylaminopyrimidine[70, 236, 237] and 2-dimethylaminopyrimidine.[70, 237] 2-Chloropyrimidine and aniline when warmed at 100° give 2-anilinopyrimidine.[2, 238]

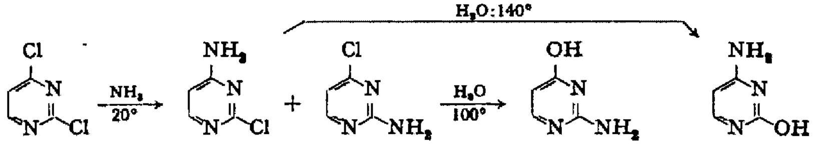
C-Alkyl-2-chloropyrimidines behave similarly with amines, giving for example 2-amino-5-methyl-,[239] 2-amino-4-ethyl-[208] 2-amino-4,6-dimethyl-,[108] and 2-anilino-4,6-dimethylpyrimidine as well as others.

4-Chloropyrimidine, being unstable, is normally avoided, and its amination products have been made by other routes. 4-Chloro-2-methyl-[9] and 4-chloro-6-methyl-pyrimidine,[7] however, give with alcoholic ammonia at 100° respectively 4-amino-2- and 4-amino-6-methylpyrimidine. 4-Chloro-2,6-dimethylpyrimidine and piperidine give 2,4-dimethyl-6-piperidinopyrimidine,[198, 240] and 4-chloro-6-methylpyrimidine with dimethylamine at 50° gives 4-dimethylamino-6-methylpyrimidine,[241] or with aniline on a water bath gives 4-anilino-6-methylpyrimidine.[7] Many other such reactions lead, for example, to 4-amino-6-ethyl-,[242] 4-amino-2,6-dimethyl-,[243] 4-amino-5,6-dimethyl-,[244] and 4-amino-2-phenyl- pyrimidine[59] and the like.[240] Reactions with tertiary bases are discussed in Chapter IX, Sect. 8.G.

There is at least one case of a simple active monoiodopyrimidine's undergoing amination. When treated with alcoholic ammonia at 100° (as for the corresponding chloro analogue), 4-iodo- gave 4-amino-6-methylpyrimidine.[245]

(b) *With Two or More Active Halogens.* On treating 2,4-dichloropyrimidine (CVII) with alcoholic ammonia at room temperature a mixture of 2-chloro-4-aminopyrimidine (CVIII) (40 %) and 4-chloro-2-aminopyrimidine (CIX) (60 %) results.[3] Early attempts at separation[246] met with little success, and even the best separation by steam distillation[3] was attended by considerable loss. The structures were shown by hydrolysis respectively to cytosine (CXI) (water at 140°, with some uracil also formed) and isocytosine (CX) (water at 100°). Better routes to these compounds have been found.

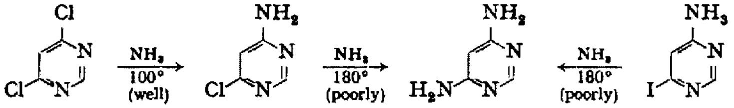
After one chloro has been replaced by an amino group, the second chlorine in (CVIII) or (CIX) becomes rather deactivated and more vigorous conditions are required for this replacement. Thus 2-amino-4-chloropyrimidine requires methanolic ammonia at 180° to produce 2,4-diaminopyrimidine from it.[247] The diamine is best made directly from 2,4-dichloropyrimidine in phenol at 190° with a stream of ammonia,[87] and the reaction is catalysed by copper, which improved the yield in comparable experiments from 65 % to 80 %.



(CVII) (CVIII) (CIX) (CX) (CXI)

In the case of the analogous 2,4-dichloro-6-methylpyrimidine, treatment with ethanolic ammonia at 90° gives[4] 4-amino-2-chloro-6-methylpyrimidine (47 % yield) and 2-amino-4-chloro-6-methylpyrimidine (40 % yield). The solubility of the latter in hot benzene served to separate them cleanly.[4,7] Amination under more vigorous conditions (6 hours at 105° with methanolic ammonia) gives mainly 2,4-diamino-6-methylpyrimidine.[4] Similarly 2,4-dichloro-5,6-dimethylpyrimidine gives[244] a separable mixture of 2-amino-4-chloro- and 4-amino-2-chloro-5,6-dimethylpyrimidine (alcoholic ammonia at 100°), and either of these can be diaminated to 2,4-diamino-5,6-dimethylpyrimidine only at 150°. 2,4-Dichloro-6-α-furylpyrimidine on amination gives only 2-amino-4-chloro-6-α-furylpyrimidine without any of the 4-amino-2-chloro isomer; the structure was checked by a direct synthesis.[248] 2,4-Diamino-6-ethylpyrimidine is formed[86,249] from 2-amino-4-chloro-6-ethylpyrimidine with ethanolic ammonia at 180°. An interesting series of replacements[250] which make use of the catalytic effect of amine cation in these nucleophilic reactions is typified by the preparation of 2-amino-4-anilino- from 2-amino-4-chloro-pyrimidine by boiling with an aqueous suspension of aniline containing a little aniline hydrochloride, which gives a 92 % yield in 30 minutes.

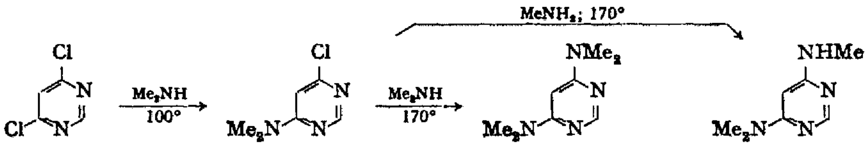
Being symmetrical, 4,6-dichloropyrimidine (CXIII) can yield with ammonia only one mono-aminated isomer, 4-amino-6-chloropyrimidine (CXIV), and this it does at 100° in ethanol.[251] Heating to 180° is required to replace the second chlorine, and in this particular case the 4,6-diaminopyrimidine (CXV) formed is largely destroyed.[19] Similar treatment of 4-amino-6-iodopyrimidine (CXVI) gives also a very small yield.[33] 4,6-Dichloro-2-methylpyrimidine, however, behaves normally, giving 4-amino-6-chloro-2-methylpyrimidine at 130° and 4,6-diamino-2-methylpyrimidine at 200° with methanolic ammonia.[252] The corresponding bromo derivatives seem to be comparably reactive if judged by the formation[75] from 4,6-dibromo-2-ethylpyrimidine of 4-amino-6-bromo-2-ethylpyrimidine in 95 % yield (aqueous ammonia, 70°) and of 4,6-diamino-2-ethylpyrimidine in 81 % yield (150°).



(CXIII) (CXIV) (CXV) (CXVI)

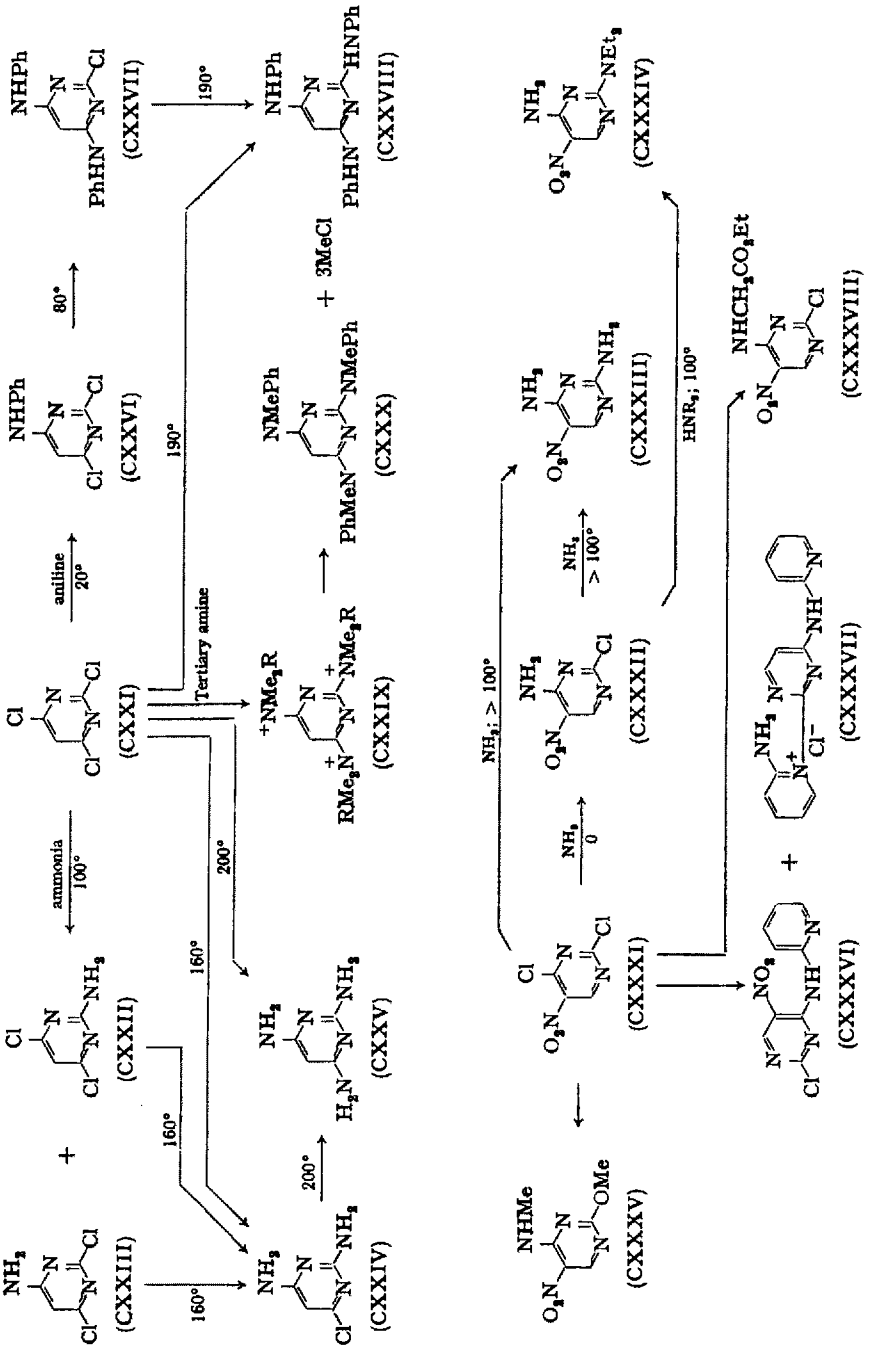
The reactions of 2,4-dihalogenopyrimidines with primary or secondary alkylamines have not been worked out well. The patent literature[253] describes, however, the selective preparation of 2-bromo-4-dimethylamino-6-methylpyrimidine from 2,4-dibromo-6-methylpyrimidine with alcoholic dimethylamine, and analogous preparations of 2-chloro-4-dimethylaminopyrimidine and several other such compounds. Diamination of 2,4-dihalogeno compounds proceeds readily to give for example 2,4-bisdimethylamino-6-methylpyrimidine[241] (at 40°) and 2,4-dianilino-5,6-dimethylpyrimidine[244], but other simple examples seem to be missing. 2-Amino-4-chloro-6-methylpyrimidine and dimethylamine at 110° give 2-amino-4-dimethyl-amino-6-methylpyrimidine,[254] and 4-chloro-6-methyl-2-piperidinopyrimidine with ammonia at 150° gives 4-amino-6-methyl-2-piperidinopyrimidine.[255] The amination of 5-benzyl-2,4-dichloropyrimidine has been investigated.[256, 257] Thus methylamine or dimethylamine at room temperature gives exclusively 5-benzyl-2-chloro-4-methylamino- or 5-benzyl-2-chloro-4-dimethylaminopyrimidine, and at 100° 5-benzyl-2,4-bismethylamino- or 5-benzyl-2,4-bisdimethylaminopyrimidine.

The simple alkylaminations of 4,6-dichloropyrimidine (CXVII) are rather better understood. Thus alcoholic methylamine and dimethylamine at 100° give respectively 4-chloro-6-methylaminopyrimidine[258] and 4-chloro-6-dimethylaminopyrimidine (CXVIII)[251] in good yield, aqueous piperidine at 100° gives 4-chloro-6-piperidinopyrimidine,[38] and aniline (containing a little hydrochloride) readily gives 4-anilino-6-chloropyrimidine.[259] Diamination is typified by the conversion[258] of 4,6-dichloropyrimidine into 4,6-bismethylaminopyrimidine with aqueous methylamine at 170°, or by the preparation of 4,6-bisdimethylamino-2-methylpyrimidine,[241] but it has often been done in two steps: in this way the two substituted amino groups may be the same or different as required. Thus a great variety of 4-amino-6-alkyl(or aryl)-aminopyrimidines[38] and their 2-methyl derivatives[260] has been made by treating 4-amino-6-chloropyrimidine with the appropriate amine at 120° or by long reflux at *ca.* 100°. Further, 4-chloro-6-dimethylaminopyrimidine (CXVIII) (see above) gives[251] with dimethylamine 4,6-bisdimethylaminopyrimidine (CXIX), or with methylamine, 4-dimethylamino-6-methylaminopyrimidine (CXX). Similarly, 4-chloro-6-anilinopyrimidine (with methylamine) at 150° gives 4-anilino-6-methylaminopyrimidine, and its 2-alkyl and 2-aryl derivatives behave similarly.[259]



(CXVII) (CXVIII) (CXIX) (CXX)

Amination of 2,4,6-trichloropyrimidine (CXXI) proceeds in a surprisingly orderly way.[33, 261] Alcoholic ammonia at 20–100° gives a separable mixture of 2-amino-4,6-dichloropyrimidine (CXXXII) and 4-amino-2,6-dichloropyrimidine (CXXIII). At 160°, each of these or the trichloro compound gives only 2,4-diamino-6-chloropyrimidine (CXXIV), and at 200° any of the foregoing gives 2,4,6-triaminopyrimidine (CXXV). Exactly similar behaviour was observed[214] with ethylamine at slightly lower temperatures: 20°, 70°, and 170°. Aniline, on the other hand, gives[214] only one product (4-anilino-2,6-dichloropyrimidine (CXXVI)) at 20°, one product (a dianilinochloropyrimidine (CXXVII)) at 80°, and finally 2,4,6-trianilinopyrimidine (CXXVIII) at 190°. It would be interesting to confirm the aniline series of reactions with aids such as paper chromatography and electrophoresis, which were unavailable at the time of the original work. With


(CXXIII)
(CXXII)
ammonia
100°
(CXXI)
aniline
20°
(CXXVI)
80°
(CXXVII)
160°
160°
160°
200°
Tertiary amine
190°
190°
(CXXIV)
200°
(CXXV)
(CXXIX)
(CXXX)
+ 3MeCl
(CXXVIII)
(CXXXV)
(CXXXI)
NH₃
0
(CXXXII)
NH₃
> 100°
(CXXXIII)
NH₃; > 100°
HNR₂; 100°
(CXXXIV)
(CXXXVI)
+
(CXXXVII)
(CXXXVIII)

the secondary amine, dimethylamine, the first stage, at least, resembles ammonia in giving at room temperature 2,4-dichloro-6-dimethylaminopyrimidine and 4,6-dichloro-2-dimethylaminopyrimidine.[262, 263] Hereafter, the series is incomplete although the second of these was aminated with ammonia, methylamine, and dimethylamine (at 120°) to give respectively 4-amino-6-chloro-2-dimethylaminopyrimidine, 4-chloro-2-dimethylamino-6-methylaminopyrimidine, and 4-chloro-2,6-bis-dimethylaminopyrimidine.[263] Treatment of 2,4,6-trichloropyrimidine with the tertiary amine, trimethylamine, is said to give at room temperature 2,4,6-tris(trimethylammonium)pyrimidine trichloride (CXXIX; R = Me).[264] Similarly, boiling *NN*-dimethylaniline with 2,4,6-trichloropyrimidine gives 2,4,6-trismethylanilinopyrimidine[265] (CXXX), presumably by loss of three molecules of methyl chloride from the tris quaternary intermediate (CXXIX: R = Ph). This type of reaction has also been encountered[266] in the formation of a little dichloromethylanilinopyrimidine during the preparation of 2,4,6-trichloropyrimidine by the action of phosphoryl chloride and dimethylaniline on barbituric acid, and in a similar case.[4, 267] Incomplete data have been reported on the products from 2,4,6-trichloro-5-ethylpyrimidine[84] and 5-benzyl-2,4,6-trichloropyrimidine[83] with ammonia.

(2) *Amination of Halogenonitropyrimidines*

The electron-withdrawing 5-nitro group further activates halogeno groups in the 2-, 4-, and 6-positions (Ch. I).

(a) *Aminations of Monochloronitro Derivatives.* In the simple cases of the monochloronitropyrimidines, there is little to uphold the above statement because most of the known 2-(substituted) amino-5-nitropyrimidines (and corresponding 5-phenylazo derivatives) have been made by direct synthesis. However, although 2-chloropyrimidine requires alcoholic dimethylamine at 120° for 1 hour[237] or 80° for 5 hours[70] to give 2-dimethylaminopyrimidine, 2-chloro-5-nitropyrimidine requires only 80° for 30 minutes to give a comparable yield of 2-dimethylamino-5-nitropyrimidine.[268] 2-Methylamino-5-nitropyrimidine and other secondary and tertiary amino derivatives have been similarly obtained.[268]

(b) *Aminations of 2,4-Dichloronitro Derivatives.* In the case of 2,4-dichloro-5-nitropyrimidine (CXXXI), monoamination takes place at 0° in a few minutes with alcoholic[28] or aqueous[22, 269] ammonia, in contrast to the long standing at 20° required for 2,4-dichloropyrimidine. Moreover only one product, 4-amino-2-chloro-5-nitropyrimidine (CXXXII), is formed, instead of the two, 2-amino-4-chloro- and 4-amino-2-chloro-pyrimidine, when no nitro group is present. The nitro group has clearly activated the 4-chloro more than the 2-chloro group, although this could scarcely be anticipated. The phenomenon is also seen with 6-alkyl-2,4-dichloro-5-nitropyrimidines in the exclusive formation of 4-amino-2-chloro-6-methyl(or ethyl)-5-nitropyrimidine.[24, 218, 245, 270, 271]

When monoamination of 2,4-dichloro-5-nitropyrimidine was attempted under similar conditions with methylamine, only diamination to 2,4-bismethylamino-5-nitropyrimidine resulted,[225] probably because of the higher basic strength of methylamine compared with ammonia. When conditions were made exceptionally mild, 2-methoxy-4-methylamino-5-nitropyrimidine (CXXXV) (an intermediate of the above) was isolated.[225, 272] 2,4-Bisdimethylamino-6-methyl-5-nitropyrimidine was the only product when dimethylamine was used similarly[273] on the appropriate dichloro derivative, but F.L. Rose was able to achieve monoamination to 4-dimethylamino-2-chloro-5-nitropyrimidine[273] (and to its 6-methyl derivative[146, 273]) by using dimethylamine acetate (salt)* in aqueous dioxane at room temperature. The technique was applied also to make 2-chloro-4-methylamino-5-nitropyrimidine,[272] and 4-benzylmethylamino-2-chloro-5-nitropyrimidine.[273] Further monoaminations are known in less simple systems, such as the formation of 2-chloro-4-β-chloroethylamino-6-methoxycarbonyl-5-nitro-pyrimidine[193] from the 2,4-dichloro analogue with 2-chloroethylamine, or the formation of 2-chloro-4-2′-pyridylamino-5-nitropyrimidine[274] (CXXXVI) from 2,4-dichloro-5-nitropyrimidine (CXXXI) and 2-aminopyridine in methanol at 0°; in the latter case, a considerable by-product, the quaternary derivative (CXXXVII), is formed. Further examples are provided by the preparation from 2,4-dichloro-5-nitropyrimidine of 2-chloro-4-ethoxycarbonylmethylamino-5-nitropyrimidine[23, 275] (CXXXVIII) (with glycine ester), of 4-acetonylamino-2-chloro-5-nitropyrimidine[276] (with aminoacetone), and of their 6-methyl and other derivatives.[277] These and derived compounds are important as intermediates in an unambiguous synthesis of 7,8-dihydropteridine derivatives, which has been briefly reviewed.[196]

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* Aqueous dimethylamine neutralized to pH 8 (brilliant-yellow) i.e. 100% cation.

2,4-Dichloro-5-nitropyrimidine (CXXXI) and 4-amino-2-chloro-5-nitropyrimidine (CXXXII) are both readily converted into 2,4-diamino-5-nitropyrimidine (CXXXIII) by passing ammonia into a solution in phenol[269] at 140° (*cf.* 190° for the similar reaction without a nitro group present), or by heating at 100° with alcoholic ammonia.[28, 279] Methylamine and dimethylamine readily replace both chlorine atoms even at room temperature, giving 2,4-bismethylamino-5-nitropyrimidine[225] and 2,4-bisdimethylamino-6-methyl-5-nitropyrimidine[273] from the appropriate dichloro compounds. Similar replacements led to diamines such as 2,4-dianilino-,[219, 280] 2,4-bispropylamino-,[280] 2,4-diaziridino-,[25] and 2,4-bisethoxycarbonylmethylamino-,[93] and other[281, 282] 5-nitropyrimidines. Moreover, by monoamination in the 4-position, followed by treatment with a different amine, there have resulted such mixed diamines as, 4-amino-2-diethylamino- (CXXXIV),[276] 4-amino-2-dimethylamino-,[269] 4-amino-2-methylamino-,[201] 4-amino-2-diethylamino-6-methyl-,[301] and 2-amino-4-dimethylamino-6-methyl-,[146]* and 2-amino-4-β-hydroxyethylamino- 5-nitropyrimidine.[280, 284]

(c) *Aminations of 4,6-Dichloronitro Derivatives.* The behaviour of 4,6-dichloro-5-nitropyrimidine with ammonia and amines is closely parallel to that of the 2,4-isomer, except that there is even greater tendency to diamination. This is because both chlorines are in the most favoured positions for activation by the nitro group. Thus treatment with alcoholic ammonia (2 mol.), diluted with a large volume of ether at 20°, gave 4-amino-6-chloro-5-nitropyrimidine (50 %) but also some dichloro and diamino derivatives.[23, 291] The 4,6-diamino-5-nitropyrimidine is conveniently prepared[285] in 95 % yield by warming with alcoholic ammonia at 60° for 5 minutes (*cf.* 2,4-analogue: 100° for several hours). 4,6-Dichloro-2-methyl- and 2-butyl-4,6-dichloro-5-nitropyrimidine behave similarly to the above in forming 4-amino-6-chloro-2-methyl-,[23] 4-amino-2-butyl-6-chloro-,[232] and 4,6-diamino-2-methyl- 5-nitropyrimidine.[17, 86]

Monoamination of 4,6-dichloro-5-nitropyrimidine with amines is represented by the formation of 4-chloro-6-dimethylamino (or methylamino)-5-nitropyrimidine with the amine acetate salt at room temperature.[17, 272] If the amine is not neutralized, diamination occurs** at

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* Made by dimethylamination of 2-amino-4-chloro-6-methyl-5-nitropyrimidine which was not made by an amination.

** The relatively weakly basic amine, morpholine, is exceptional and at 4° in methanol gives 4-chloro-6-morpholino-5-nitropyrimidine.[267]

room temperature to give for example 4,6-bismethylamino-,[225] 4,6-biscyclohexylamino-,[286] 4,6-bisfurfurylamino-,[267, 286] 4,6-diaziridino-,[25] and 4,6-bisethoxycarbonylmethylamino-,[267, 286] 5-nitropyrimidine.[23] Diamination has also been performed in two steps to give different amino substituents in 4- and 6-positions. Thus 4,6-dichloro-5-nitropyrimidine was taken to 4-amino-6-chloro-5-nitropyrimidine, and this with the appropriate amine under fairly mild conditions gave diamines such as 4-amino-6-methylamino-,[287] 4-amino-6-anilino-,[287] 4-amino-6-diethylamino-,[276] 4-amino-6-dimethylamino-,[201, 288] and 4-amino-6-cyclohexylamino-5-nitropyrimidine.[288] Similarly 4-acetonylamino-6-chloro-5-nitropyrimidine (itself a monoamination product) with morpholine gave 4-acetonylamino-6-morpholino-5-nitropyrimidine,[276] and similar processes produced 4-furfurylamino-6-morpholino- and 4-dimethylamino-6-furfurylamino- 5-nitropyrimidine,[267] and other analogues.[290]

(d) *Aminations of Trichloro-5-nitropyrimidine.* Trichloro-5-nitropyrimidine on treatment with etherial ammonia at 0° gives 4-amino-2,6-dichloro-5-nitropyrimidine.[18] This, or the trichloro compound, in alcoholic ammonia at 20°, gives 4,6-diamino-2-chloro-5-nitropyrimidine.[18, 271] (This behaviour is in contrast with that found when the 5-nitro group is missing: monoamination to mixed 4- and 2- amino derivatives at 20° and diamination at 160°.) 4,6-Dichloro-2-dimethylamino-5-nitropyrimidine (itself not made by amination) gives with aziridine, 4,6-diaziridino-2-dimethylamino-5-nitropyrimidine.[292]

(3) *Amination of 5-Aminochloropyrimidines*

It will be realized that the amination of chloro substituents in the presence of 2-, 4-, and 6-, amino groups is being dealt with throughout this section (Sect. 5.B) in the replacement of the second (or third) chloro group of a di- or trichloro derivative. The presence of a 5-amino group has much the same deactivating effect as such groups in other positions. Thus while 4,6-dichloropyrimidine and its 5-nitro derivative are monomethylaminated under mild conditions 5-amino-4,6-dichloropyrimidine "did not react with 15 % aq. ammonia",[18] and yields 5-amino-4-chloro-6-methylaminopyrimidine[225] with methylamine only at 130°. This has been useful in achieving monoamination without the diamination so often troublesome in the presence of a nitro group (assuming the latter is to be reduced later in any case).[225, 226, 289] Being less powerful in aminations than methylamine, ammonia requires 200° in order to aminate for example 5-amino-2-chloro- to 2,5-diamino-4-methylpyrimidine.[245] Such reactions have not been extensively used, but boiling aqueous alcoholic aniline containing some hydrochloride converts 5-amino-4,6-dichloropyrimidine into 5-amino-4-anilino-6-chloropyrimidine in good yield.[291]

(4) *Amination of Chloro-(hydroxy-, alkoxy-, or oxo-)pyrimidines*

Hydroxy, alkoxy, and oxo groups deactivate chloro substituents but to a far less extent than do amino groups. There are, however, relatively few examples of such aminations because the known starting materials are themselves limited in number. Examples in the presence of hydroxy groups are the conversion of 4-chloro-2,6-dihydroxypyrimidine with methylamine at 130° into 2,4-dihydroxy-6-methylaminopyrimidine,[16] or with D-ribamine at 120° to give the 6-ribitylaminopyrimidine,[293] of 4-bromo- into 4-amino- 2-ethyl-6-hydroxypyrimidine with aq. ammonia at 100°, of 4-chloro- into 4-amino- 6-hydroxy-2-methylpyrimidine[294] with aq. ammonia at 170°, of 5-alkyl-4-chloro- into 5-alkyl-4-amino- 6-hydroxy-2-methylpyrimidine under the same conditions,[294] and of 4-chloro-5-ethyl-6-hydroxy-2-methylpyrimidine with *p*-chloroaniline (containing a little hydrochloride) at 165° into 4-*p*-chloroanilino-5-ethyl-6-hydroxy-2-methylpyrimidine.[296]

Amination of chloropyrimidines which have alkoxy groups (which themselves can be replaced by amino groups if they occupy an "active" position; Ch. VII, Sect. 7.C) are exemplified in the transformation of 2,4-dichloro-6-methoxypyrimidine to 2-amino-4-chloro-6-methoxypyrimidine[30] with ammonia at 100°, of 5-benzyl-2,4-dichloro-6-methoxypyrimidine to 2-amino-5-benzyl-4-chloro-6-methoxypyrimidine[83] under the same conditions, of 2-anilino-4-chloro-5-ethoxypyrimidine to 4-amino-2-anilino-5-ethoxypyrimidine[37] with ammonia at 180°,* of 2,4-dichloro-6-ethoxypyrimidine to 4-chloro-6-ethoxy-2-methylaminopyrimidine[214] with methylamine at < 60°, and of 4-chloro-2,6-diethoxypyrimidine to 2,4-diethoxy-6-methylaminopyrimidine[214] with methylamine at 100°. It will be noticed above that with the 4-alkoxy-2,6-dichloropyrimidines amination at the 2-position occurred. The evidence of structure in each case seems convincing, but there are

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* Additional deactivation by the anilino group accounts for the high temperature required.

too few examples to determine whether this is a general phenomenon.

Amination of chloro substituents in the presence of oxo groups are seen in the preparation (from the corresponding chloro derivatives) of the following: 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine[297] by methanolic ammonia at 150°; 1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine[57] by alcoholic methylamine at room temperature, and the 6-ethylamino-, 6-β-hydroxyethylamino-, 6-dimethylamino, and 6-butylamino analogues[57] by warming with the appropriate amine for a few minutes; 4-anilino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine[58] by boiling in aniline for 6 hours; 1,2,3,4-tetrahydro-1,3,5-trimethyl-6-methylamino-2,4-dioxopyrimidine and its 6-butylamino analogue,[58] by warming with the amine for a few minutes.

(5) *Amination of Chloro-alkylthiopyrimidines*

Like its oxygen analogue, the methylthio group seems to be very mildly deactivating to chloro substituents. A great many examples of amination of 4-chloro in the presence of 2-alkylthio groups are known, but other combinations are rare. Although alkylthio groups can be replaced also by amino groups, in the usual relationship above, the 4-chloro is far more reactive than is the 2-alkylthio group. Thus 4-chloro-2-ethylthiopyrimidine heated with alcoholic methylamine at 50° gives 2-ethylthio-4-methylaminopyrimidine[298, 299] but at 150° gives 2,4-bismethylaminopyrimidine;[298] at 105° a mixture is obtained with alcoholic methylamine,[298] but only the monoamine with aqueous methylamine.[300] The same compound reacts with aqueous ethylamine, at 100° or alcoholic ammonia at *ca.* 120° to give respectively 4-ethylamino-[301] or 4-amino-, 2-ethylthiopyrimidine;[42, 96] with ammonia at 190° 2,4-diamonopyrimidine is formed.[42] Besides examples closely related to the above,[61, 66, 103, 302–310] some interesting transformations are: 4-chloro- to 4-amino- 5-methyl-2-octylthiopyrimidine[62] (alcoholic ammonia at 145°); 4,6-dichloro-2-methylthiopyrimidine to 4-amino-6-chloro-2-methylthiopyrimidine[60] (alcoholic ammonia at 125°), to 4,6-diamino-2-methylthiopyrimidine[42] (aqueous ammonia at 185°), to 2,4,6-triaminopyrimidine[60] (alcoholic ammonia at 220°); 4-chloro-1,2-dimethyl-6-methylthiopyrimidinium iodide to 1,4-dihydro-4-imino-1,2-dimethyl-6-methylthiopyrimidine hydriodide[259] (by stirring with aqueous ammonia*) or to the corresponding phenylimino derivative[259] (by warming with aniline). Further examples appear below.

(6) *Amination of Chloropyrimidines Substituted by Other Groups*

Aminations of chloropyrimidines with other groups present are scattered through the literature. Examples are furnished by conversions such as 4,6-dichloro-5-cyano-2-methylpyrimidine into 4-amino-6-chloro-5-cyano-2-methylpyrimidine[51] with alcoholic ammonia at 50°, 5-bromo-4-chloro-2-ethylthiopyrimidine into 4-amino-5-bromo-2-ethylthiopyrimidine[42,103] with ammonia at 150°, the corresponding 5-iodo compounds,[92] 4-chloro-5-ethoxycarbonyl-2-ethylthiopyrimidine into 4-amino-5-ethoxycarbonyl-2-ethylthiopyrimidine,[311] 5-carboxymethyl-4-chloro-2-ethylthio-6-methylpyrimidine into the 4-amino compound,[312] 4-chloro-2-ethylsulphonyl-5-methylpyrimidine into 4-amino-2-ethylsulphonyl-5-methylpyrimidine[313] with ammonia at 100°, and 4-chloro- into 4-amino- 5-ethoxycarbonyl-2,6-dimethylpyrimidine[314] at 100°. Finally, the aldehyde 4-chloro-2-ethylthio-6-formylpyrimidine is said to give with ammonia at 120° 4-amino-2-ethylthio-6-iminomethylpyrimidine,[315] and other products.

Amination of 2,4-diamino-6-chloro-5-*p*-chlorophenylazopyrimidine with dimethylamine (or morpholine etc.) takes place at 100°, indicating the activating effect of the arylazo group.[316] The product, 2,4-diamino-6-dimethylamino-5-*p*-chlorophenylazopyrimidine, is equally well made by heating the chloro derivative with dimethylformamide and guanidine in ethanol at 80°. Several examples of this peculiar reaction have been described.[316] On the other hand, 2-amino-4-chloro-6-hydroxy-5-phenylazopyrimidine heated at 90° with ethylamine in aqueous dimethylformamide gives only 2-amino-4-ethylamino-6-hydroxy-5-phenylazopyrimidine,[317] and other analogues are described.[317]

C. Replacement of 2-, 4-, and 6-Chloro by Hydrazino, Hydroxyamino, Azido, and Related Groups

2-Chloropyrimidine reacts with hydrazine in boiling ethanol to give 2-hydrazinopyrimidine (CXXXIX). The melting point of the product was first recorded[71] as 86–88°, but later[318] as 110–111°. The latter

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* Being a strong base the iminopyrimidine was recovered as hydriodide even from aqueous ammonia.

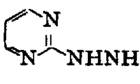
range was confirmed by a preparation from 2-methoxypyrimidine.[48] 2-Chloro-4-methylpyrimidine similarly gives 2-hydrazino-4-methylpyrimidine[318–320] and again an earlier recorded melting point is quite wrong.[321] 4-Chloro-6-methylpyrimidine gives 4-hydrazino-6-methylpyrimidine[318, 322] and other simple compounds known include 2-hydrazino-4,6-dimethylpyrimidine,[234] 2-hydrazine-4 (and 5)-phenylpyrimidine,[48] 5-bromo (and chloro)-4-hydrazinopyrimidine.[48] Less simple compounds, also prepared with hydrazine from the corresponding chloro derivatives, include 2-hydrazino-4-methoxy-6-methylpyrimidine,[71,318] 2-hydrazino-4- (and 5)-methoxypyrimidine,[318, 323] 4-ethoxy-2-hydrazino-6-methylpyrimidine,[318] 4-hydrazino-6-methyl-2-methylthiopyrimidine[318] (with a by-product of 2,4-dihydrazino-6-methylpyrimidine), 4-hydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine[57] (and its 5-methyl derivative[58]), 4-hydrazino-5-methoxypyrimidine[323, 323a] and its 2-methylthio derivatives.[323]

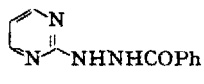
The successive replacement of halogeno by hydrazino groups is possible. Thus 4,6-dichloropyrimidine gives at room temperature 4-chloro-6-hydrazinopyrimidine,[48] 2,4,5-trichloropyrimidine gives 2,5-dichloro-4-hydrazinopyrimidine[48] but 2,4-dichloropyrimidine (apparently even under similar conditions but with more hydrazine) gives 2,4-dihydrazinopyrimidine.[234, 324] 2,4-Dihydrazino-6-methylpyrimidine,[325] 4-α-furyl-2,6-dihydrazinopyrimidine[248] and 2-chloro-4-hydrazino-5-methoxypyrimidine[323] were made by warming the dichloro compounds with hydrazine, and the related 2-amino-4-hydrazino-6-methylpyrimidine from the 4-chloro compound similarly.[71, 322]

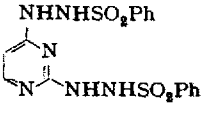
Being derived from a difunctional base, the acid hydrazides can still react (albeit less readily) with chloro pyrimidines. Thus 2-chloropyrimidine and its 4-methyl derivative yield with benzoylhydrazine, respectively 2-benzoylhydrazinopyrimidine (CXL) and the 4-methyl derivative.[71] The second compound was also obtained by benzoylating 2-hydrazino-4-methylpyrimidine.[71] Similarly 2,4-dichloropyrimidine yields with benzenesulphonhydrazide, 2,4-bisbenzenesulphonylhydrazinopyrimidine[234] (CXLI).

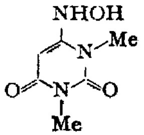
The formation of hydroxyamino from chloro derivatives is typified by the conversion of 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine by boiling with alcoholic hydroxylamine into 1,2,3,4-tetrahydro-6-hydroxyamino-1,3-dimethyl-2,4-dioxopyrimidine[58] (CXLII).

Several azidopyrimidines have also been made. Thus 2,4-dichloropyrimidine boiled with sodium azide in ethanol, or hydrazoic acid in benzene, gave 2,4-diazidopyrimidine (CXLIII). The same compound resulted from 2,4-dihydrazinopyrimidine and nitrous acid.[324] The 6-furyl, 6-methyl, and 6-phenyl derivatives were made similarly by the first method,[324] and 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine on boiling with aqueous sodium azide gives the corresponding azidopyrimidine.[57]


(CXXXIX)


(CXL)


(CXLI)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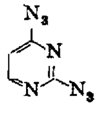
(CXLIII)

D. Replacement of 2-, 4-, and 6-Halogens by Alkoxy Groups

Simple kinetic studies indicate a range of reactivities of chloropyrimidines towards sodium alkoxides. From a preparative point of view, however, the state of activation (*e.g.* in a nitrochloropyrimidine) or deactivation (*e.g.* in an aminochloropyrimidine) is of little consequence, and replacement with an alkoxy group is easily done in good yield. By careful control of conditions, alkoxy groups can be successively substituted for chloro groups in a di- or tri-chloropyrimidine. In the examples that follow it may be assumed, unless otherwise indicated, that the corresponding chloro compound was warmed or refluxed with the appropriate anhydrous alcohol (or phenol) which had previously reacted with at least one atom of sodium per chlorine to be replaced.

In this way were prepared for example 2- and 4-methoxypyrimidine,[21,237] 2-methoxy-4-methylpyrimidine,[4] 4-methoxy-6-methylpyrimidine,[4] 2-methoxy (and ethoxy)-4,6-dimethylpyrimidine,[108] and 2 (and 4)-benzyloxy-4,6 (and 2,6)-dimethylpyrimidine.[150,326] 2-Phenoxypyrimidine was prepared normally,[108] but better by treating 2-chloropyrimidine with phenol and potassium carbonate at 150° without solvent,[327] or by refluxing the same mixture in toluene.[328] Analogues were made similarly.[330,331]

When 2,4-dichloropyrimidine is treated with one mole of sodium methoxide in methanol at room temperature, only 2-chloro-4-methoxypyrimidine is formed.[297,329] Similarly, 4,6-dichloropyrimidine gives 4-chloro-6-methoxypyrimidine in 77 % yield.[333] The use of two or more moles readily (even at room temperature) gives for example 2,4-dimethoxy-6-methylpyrimidine*[4,7,325] and 2,4-diethoxy (and dimethoxy)-6-methyl-5-propylpyrimidine[332] from the corresponding dichloro compounds. An interesting comparison of the reactivity of bromo and chloro groups has been given:[81] 5-bromomethyl-4,6-dichloro-2-methylpyrimidine (CXLIV) and 4-bromo-5-bromomethyl-6-chloro-2-methylpyrimidine (CXLVI) were both treated with sodium methoxide in methanol under the same conditions. The first gave 4-chloro-6-methoxy-5-methoxymethyl-2-methylpyrimidine (CXLV), but the second gave 4,6-dimethoxy-5-methoxymethyl-2-methylpyrimidine (CXLVII). The explanation is not obvious.

The chlorines of 2,4,6-trichloropyrimidine and its 5-alkyl derivatives can be replaced stepwise by alkoxy groups. Treatment at 0° with one mole of sodium alkoxide gives 4-alkoxy derivatives such as 2,4-dichloro-6-methoxypyrimidine,[23,30] 2,4-dichloro-6-ethoxypyrimidine,[214] and 2,4-dichloro-5-ethyl-6-methoxypyrimidine.[84] At room temperature or lower, two moles of sodium alkoxide give 2,4-dialkoxy derivatives exemplified by 4-chloro-2,6-dimethoxypyrimidine,[16,30,33,334,335] 4-chloro-2,6-diethoxypyrimidine,[214] 4-chloro-5-ethyl-2,6-dimethoxypyrimidine,[84] and 4-chloro-2,6-dimethoxy-5-methylpyrimidine.[239] Complete replacement of chlorine occurs at 70–100° with an excess of sodium alkoxide to give for example 2,4,6-trimethoxypyrimidine,[33,334] its 5-ethyl derivative,[84] and its 5-s-butyl derivative[336] 2,4,6-triethoxypyrimidine,[214,337] and its 5-s-butyl derivative,[336] as well as 5-s-butyl derivative of 2,4,6-tripropoxy- and -tributoxy-pyrimidine.[336] 2,4,6-Tribromopyrimidine has been converted into 4-bromo-2,6-diethoxypyrimidine.[73]

As would be expected, chloronitropyrimidines react extremely readily with alkoxides. 2-Chloro-5-nitropyrimidine gives for example 2-butoxy-5-nitropyrimidine, and 2,4 (and 4,6)-dichloro-5-nitropyrimidine give 2,4 (and 4,6)-dimethoxy-5-nitropyrimidine at room temperature.[44,272,335] At least in the cases of 4,6-dichloro-5-nitropyrimidine and its 2-methyl derivative, reaction in the cold with sodium ethoxide limited to 1 mole[276] gives 4-chloro-6-ethoxy-5-nitropyrimidine (and its 2-methyl derivative); more sodium ethoxide gives for example 4,6-diethoxy-2-methyl-5-nitropyrimidine, and 2,4-diethoxy-5-nitropyrimidine has been reported by a similar route.[224,339]

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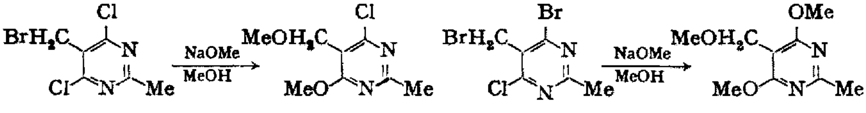
[*] The ease of formation is indicated by the unintentional preparation of it during an attempt to dechlorinate catalytically 2,4-dichloro-6-methylpyrimidine in methanol in the presence of magnesium oxide and palladium.[227]

An interesting facet of the last reaction is the necessity for completely anhydrous ethanol: when it contains one or more moles of water per mole of 4,6-dichloro-5-nitropyrimidine (as do the many samples of "absolute alcohol" which are not better than 99.5% ethanol), a mixture of 2-ethoxy-4-hydroxy- and 4-ethoxy-2-hydroxy- 5-nitropyrimidine is formed. 2,4-Diethoxy-5-nitropyrimidine under the same conditions gives a similar mixture.[340] Rather analogous behaviour has been reported[341] with 2,4-dichloro- and 2,4-diethoxypyrimidine.

Other representative examples of the conversion of a chloro into an alkoxy pyrimidine are provided by the following: 4-amino-2,6-dimethoxy-5-nitropyrimidine,[343] 5-chloro-2,4-dimethoxypyrimidine,[48] 4-methoxy-6-methyl-2-methylthiopyrimidine,[238,318]* 2-dimethylamino-4-methoxy-5-nitropyrimidine,[35] 4-ethoxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine,[57] 1,2,3,4-tetrahydro-6-methoxy-1,3,5-trimethyl-2,4-dioxopyrimidine,[58] 2-amino-4-methoxy-6-methylpyrimidine[71] (methanolic potassium hydroxide), 2-methoxy-4-methylamino-5-nitropyrimidine,[372] 4-amino-2 (and 6)-methoxy-5-nitropyrimidine,[201] an ethoxy analogue,[228] 4-chloro-5-cyano-6-ethoxy (and methoxy)-2-methyl-pyrimidine[51] (from the dichloro compound by warming in the appropriate alcohol containing 10 % water and zinc dust), and 5-cyano-4,6-diethoxy-2-methylpyrimidine.[51] Even such a compound as 5-amino-2,4-dichloropyrimidine reacts readily with sodium methoxide in boiling methanol to give the dimethoxy compound.[224] On the other hand 2-amino-4,6-dichloropyrimidine seems to require sodium methoxide at 140° to give 2-amino-4,6-dimethoxypyrimidine, although at 20° 2-amino-4-chloro-6-methoxypyrimidine is formed.[345] 2-Amino-4-chloropyrimidine gives 2-amino-4-ethoxypyrimidine at reflux temperature.[137]

Sodium phenoxide readily reacts with 2,4-dichloro-5-nitropyrimidine to give 5-nitro-2,4-diphenoxypyrimidine.[335]



(CXLIV) (CXLV) (CXLVI) (CXLVII)

E. Replacement of 2-, 4-, and 6- Halogens by Hydroxy Groups

The conversion of an active halogeno into an hydroxy group is rather uncommon, and not always easy. In fact it is often advantageous

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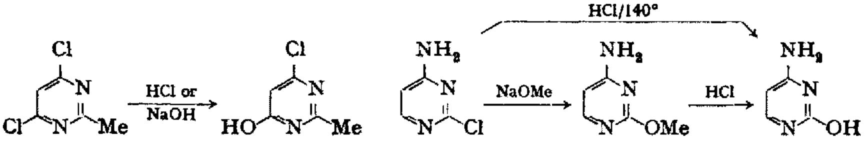
* The apparently anomalous melting point (137°) given in *Chemical Abstracts*[238] is that of the picrate.[344]

to pass through a methoxy[3,250] group rather than to take the direct hydrolytic route.

The partial hydrolysis of dihalogeno compounds has, however, been found useful. Thus 4,6-dichloropyrimidine,[346] its 2-methyl derivative (CXLVIII),[294,347] its 2-phenyl derivative,[259] and its 5-ethyl-2-methyl derivative,[296] on boiling with hydrochloric acid give 4-chloro-6-hydroxy-, 4-chloro-6-hydroxy-2-methyl (or phenyl) (CXLIX), and 4-chloro-5-ethyl-6-hydroxy-2-methyl- pyrimidine in good yield. 5-Amino-4,6-dichloro-2-methylpyrimidine yields 5-amino-4-chloro-6-hydroxy-2-methylpyrimidine satisfactorily with boiling 6N-hydrochloric acid.[44] Hydrolysis by alkali is also effective, although yields seem rather lower. In this way, 4-chloro-6-hydroxy-2-methylpyrimidine (CXLIX) and its 5-methyl and 5-ethyl derivatives and analogues were prepared by boiling the appropriate dichloro compound with *N*-sodium hydroxide.[294,348] 4,6-Dibromo-2-ethylpyrimidine likewise gave 4-bromo-2-ethyl-6-hydroxypyrimidine.[76] The acid hydrolysis of 2,4-dichloro-6-methylpyrimidine to 2-chloro-4-hydroxy-6-methylpyrimidine has been reported,[349] but the preparation is unsatisfactory. Vigorous hydrolysis (with hydrochloric acid at 160°) has been used to convert 2,4-dichloro-6-phenylpyrimidine into 6-phenyluracil,[350] but the same compound was obtained less vigorously from 4-chloro-2-ethylthio-6-phenylpyrimidine.[304]

The hydrolysis of 2-amino-4-chloro- and 4-amino-2-chloro-pyrimidine is interesting. The first isomer on boiling for a day with water gives 2-amino-4-hydroxypyrimidine (isocytosine), but the second isomer (CL) is unchanged by such treatment, and only at 140° does it give 4-amino-2-hydroxypyrimidine (cytosine) (CLII).[3] Hydrochloric acid at 100° is better,[133] but it must be added that the indirect hydrolytic route to the last compound *via* 4-amino-2-methoxypyrimidine (CLI) is preferred.[3]



(CXLVIII) (CXLIX) (CL) (CLI) (CLII)

The action of hydriodic acid on dichloropyrimidines often leads to hydrolysis of the 4-chloro group and reductive removal of the 2-

group. For example, 2,4-dichloropyrimidine gives 4-hydroxypyrimidine,[213] and its *C*-alkyl derivatives behave similarly.[7,10,242,244]

F. Replacement of 2-, 4-, and 6- Chloro by Alkylthio Groups

Most pyrimidine thio-ethers have been made by alkylation of the corresponding mercapto compound, but occasionally a chloro has been directly converted into an alkylthio group. Thus 4-chloro-6-methylpyrimidine refluxed for 5 hours with alcoholic sodium methyl mercaptide gives 4-methyl-6-methylthiopyrimidine;[4] 2,4-dichloropyrimidine and sodium ethyl mercaptide in toluene gives 2,4-bisethylthiopyrimidine;[67] and 4-chloro-2-ethylthio-5-methylpyrimidine gives 2,4-bisethylthio-5-methylpyrimidine,[67] under similar conditions. 4-Amino-2-chloro-5-nitropyrimidine with boiling methanolic sodium methyl mercaptide for 15 minutes yields 4-amino-2-methylthio-5-nitropyrimidine,[351] and similarly 5-amino-2,4-dichloropyrimidine with sodium ethyl mercaptide yields 5-amino-2-chloro-4-ethylthiopyrimidine.[352] 4-Chloro-3,6-dihydro-6-imino-2,3-dimethylpyrimidine hydriodide and sodium methyl mercaptide with added methyl mercaptan gives 1,4-dihydro-4-imino-1,2-dimethyl-6-methylthiopyrimidine hydriodide.[259]

Aryl thiophenols have been used for the same purposes, either as sodium derivatives or free. An example is the conversion of 2-chloro-4-β-diethylaminoethylamino-6-methylpyrimidine with *p*-chlorothiophenol at 130° into the corresponding 2-*p*-chlorophenylthio derivative.[330] Sodium *p*-chlorothiophenate in ethanol was used for an isomeric compound, and many other analogues were made by both methods.[330]

G. Replacement of 2-, 4-, and 6- Halogens by Mercapto Groups

A mercapto group in the 2-position can be readily introduced during initial synthesis of a pyrimidine, but this cannot often be done in the 4- or 6-position. Most such groups have therefore been made from hydroxy derivatives through a chloro intermediate, and even 2-mercapto derivatives are sometimes made in this way. Chlorines may be replaced by mercapto groups by the action of sodium hydrogen sulphide or by treatment with thiourea to give a thiouronium salt (*e.g.* CLIV) which undergoes alkaline hydrolysis to a mercapto derivative. The examples which follow illustrate the use of the methods.

2-Chloropyrimidine has been converted into 2-mercaptopyrimidine by both the above methods: methanolic sodium hydrogen sulphide gives 30 % yield,[68] but alcoholic thiourea gives 50 % without isolation of a thiouronium intermediate.[2] 4-Chloro- similarly gives 4-mercaptopyrimidine by both methods,[2,354] and 4-chloro- gives 4-mercapto-6-methylpyrimidine in better yield by thiourea[4] than by alcoholic potassium hydrogen sulphide.[7] Although the conversion of 2-chloro-4,6-dimethylpyrimidine (CLIII) into 2-mercapto-4,6-dimethylpyrimidine (CLV) is similarly less satisfactory with potassium hydrogen sulphide[108] than with thiourea,[2] the latter method in this case does require isolation of the thiouronium chloride (CLIV) followed by alkaline hydrolysis. The same is true in the preparation of the isomeric 4-mercapto-2,6-dimethylpyrimidine.[270, 355]

2,4-Dichloropyrimidine readily gives 2,4-dimercaptopyrimidine by warming with aqueous (or alcoholic) potassium hydrogen sulphide,[356, 357] but more easily (and directly) in 90 % yield with thiourea.[2] The same applies to the 6-methyl derivative,[17, 270] but in the formation of 4,6-dimercaptopyrimidine, the intermediate is isolated.[358] 2,4,6-Trimercaptopyrimidine has been made in 50 % yield from the trichloro compound with alcoholic potassium hydrogen sulphide and the heat of reaction seems to have been sufficient to complete it.[33]

When a chloronitropyrimidine is treated with aqueous (or alcoholic) sodium hydrogen sulphide, the chloro groups are replaced first and then the nitro group is reduced. The second step can be sometimes avoided by using a limited amount of reagent and gentle conditions. Thus 2,4-dichloro-5-nitropyrimidine gives a good yield of 5-amino-2,4-dimercaptopyrimidine,[13] 4-amino-2(and 6)-chloro-5-nitropyrimidine give 4,5-diamino-2(and 6)-mercaptopyrimidine,[22, 24, 231] and 2-chloro-4-methylamino-5-nitropyrimidine gives 5-amino-2-mercapto-4-methylaminopyrimidine;[272][*] isomers[272] and *C*-alkyl analogues[24, 232] have also been made in this way. Reduction of the nitro group has been avoided in making 4-benzylmethylamino-2-mercapto-6-methyl-5-nitropyrimidine,[273] and also in 2-chloro-4-mercapto-6-methyl-5-nitropyrimidine (CLVI) (isolated as *S*-methyl derivative) which is in addition a rare example of the preferential reaction of a 4-chloro group (in a 2,4-dichloro compound) with sodium hydrogen sulphide.[272] Another way to avoid reduction of the nitro group is to use the thiourea method. With its help have been made 2,4-dimercapto-5-nitropyrimidine (thiouro-

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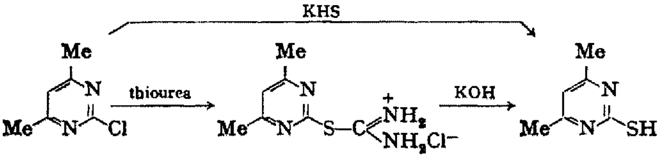
[*] A considerable amount of 5-amino-2,6-dimercapto-4-methylaminopyrimidine was also formed by an unproven mechanism.[272]

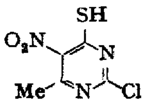
nium salt isolated),[225] its 6-methyl derivative,[270] 4-amino-2-mercapto-6-methyl-5-nitropyrimidine,[228, 270] and others.

The metathesis of chloro- to mercapto-pyrimidines has been done in the presence of a variety of other groups to give, for example, 5-amino-4-mercaptopyrimidine (KHS),[359] 5-amino-4-chloro-6-mercaptopyrimidine (with KHS from the 4,6-dichloro compound),[359] 5-amino-2-chloro-4-mercaptopyrimidine (with KHS from the 2,4-dichloro compound),[352] 4-hydroxy-6-mercapto-2-methylpyrimidine (NaHS),[259] 5-chloro-2(and 4)-mercaptopyrimidine (thiourea),[358] 2,4-dimethoxy-6-mercaptopyrimidine (NaHS);[335] 2-ethylthio-4-mercaptopyrimidine* (KHS)[356, 360] and its 6-methyl derivative (thiourea);[355] 5-ethoxy-4-mercapto-2-methylthiopyrimidine* (KHS);[302] 2-amino-4-mercapto-6-methylpyrimidine (KHS),[7] its 4-amino-2-mercapto isomer[7] and *C*-alkyl analogues.[244, 361] The use of NaHS in glycol at 140° has been reported in the difficult case of 4-hydroxy-6-mercaptopyrimidine.[333]

Finally must be mentioned the formation of 2,4-diselenylpyrimidine from 2,4-dichloropyrimidine and alcoholic sodium hydrogen selenide.[357]



(CLIII) (CLIV) (CLV)



(CLVI)

H. Replacement of 2-, 4-, and 6- Chloro by Sulpho, Thiocyanato, Isothiocyanato, and Isocyanato Groups

Ochiai and Yamanaka[235] have described the conversion of 4-chloro-2,6-dimethylpyrimidine with aqueous sodium sulphite into 2,4-dimethyl-6-sulphopyrimidine which was analysed as the dihydrate of its sodium salt. 2-Sulphopyrimidine and 4-methyl-2-sulphopyrimidine were also prepared but used in the crude state to prepare the corresponding cyano derivatives by the action of potassium cyanide.

There is a large number of thiocyanatopyrimidines known and the majority have been made by the action of potassium thiocyanate on

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* The possibility of replacing an alkylthio group by a mercapto group while using sodium hydrogen sulphide[212] should not be overlooked in exploring reactions of this type.

a chloro derivative. Most of them contain in addition an alkylthio group, although there is no apparent reason for this except conservatism. A typical example of the reaction[362] is the conversion of 4-chloro-2-ethylthiopyrimidine (CLVII) with potassium thiocyanate in boiling acetone, into 2-ethylthio-4-thiocyanatopyrimidine (CLVIII); heating at 90° for several hours rearranges this (and others at slightly varying temperatures) to the corresponding isothiocyanato derivative (CLIX). The following derivatives of 2-ethylthio-4-thiocyanatopyrimidine have been rather similarly prepared: 5-methyl,[362] 6-methyl,[363] 5-ethyl,[364] 5,6-dimethyl,[365] 5-phenyl,[366, 367] 6-phenyl,[368] 5-carboxymethyl,[369] 5-ethoxycarbonyl,[370] 5-ethoxy,[371] and 5-bromo.[362] 2-Amino-4-chloro-6-methylpyrimidine fails to undergo this reaction.[373]

When 2,4-dichloropyrimidine is treated with potassium thiocyanate in boiling ethanol, 2-chloro-4-thiocyanatopyrimidine is formed,[147] and 2,4-dichloro-5-nitropyrimidine similarly treated (at 10° in acetic acid) yields 2-chloro-5-nitro-4-thiocyanatopyrimidine.[339]

It has been mentioned that thiocyanato rearrange to isothiocyanato derivatives by heating in an inert solvent. This process can be combined with the initial thiocyanate formation so that an isothiocyanate is formed directly. Thus for example 4-chloro-2-ethylthiopyrimidine (CLVII) and potassium thiocyanate in boiling toluene (*cf.* acetone for thiocyanate formation) yields directly 2-ethylthio-4-isothiocyanatopyrimidine (CLIX) and the 5-bromo derivative is made similarly.[372]

The formation of 5-ethoxycarbonyl-2-ethylthio-4-isocyanatopyrimidine (from the corresponding chloro derivative with potassium cyanate) has been inferred by amination to the corresponding ureide.[374]

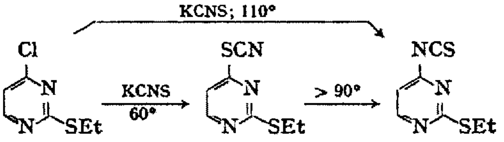
I. Replacement of 2-, 4-, or 6- Chloro by Other Groups

Sodio diethyl malonate condenses readily with the chlorine of 2-amino-4-chloro-6-methyl-5-nitropyrimidine (CLX; R = Cl) to give 2-amino-4-diethoxycarbonylmethyl-6-methyl-5-nitropyrimidine (CLX; R = $CH(CO_2Et)_2$), which on acid hydrolysis is decarboxylated to 2-amino-4,6-dimethyl-5-nitropyrimidine (CLX; R = Me), the original chloro group being now replaced by a methyl group.[273] The process has been applied to the transformation of 4-amino-2-chloro-6-methyl-5-nitropyrimidine to 4-amino-2,6-dimethyl-5-nitropyrimidine,[228] of 2,4-

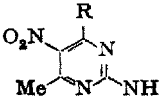
dichloro-6-methyl-5-nitropyrimidine to 2-chloro-4-diethoxycarbonylmethyl-6-methyl-5-nitropyrimidine[273] (but no further), of 4,6-dichloro-2-methyl-5-nitropyrimidine to 4-chloro-6-diethoxycarbonylmethyl-2-methyl-5-nitropyrimidine and thence to 4-hydroxy-2,6-dimethyl-5-nitropyrimidine.[273] Application of the process to 4,6-dichloro-5-nitropyrimidine, however, does not yield normal products (as first described[273]) but involves the free 2-position in the nucleophilic introduction of a diethoxycarbonylmethyl group, at the same time reducing the 5-nitro group: the product is therefore 5-amino-4,6-dichloro-2-diethoxycarbonylmethylpyrimidine (CLXI; R = $CH(CO_2Et)_2$), which on acid hydrolysis (with decarboxylation) gave 5-amino-4-chloro-6-hydroxy-2-methylpyrimidine[44]. A similar reaction to that with diethyl malonate occurs when ethyl acetoacetate or acetylacetone is condensed with 4,6-dichloro-5-nitropyrimidine,[44] to give (CLXI; R = $MeCOCH(CO_2Et)$- or $(MeCO)_2CH$-).

If the original ester (CLX; R = $CH(CO_2Et)_2$) is hydrolysed by alkali instead of acid, partial decarboxylation only takes place, giving 4-carboxymethyl-2-hydroxy-6-methyl-5-nitropyrimidine in which, in addition, the 2-amino group has hydrolysed to hydroxy.[273]

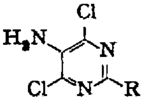
Other more direct replacements of chloro by alkyl groups by using Grignard or lithium derivatives have been mentioned in Ch. IV, Sect. 2.A(2). Similar replacement by a carboxy group is known.[73]



(CLVII) (CLVIII) (CLIX)



(CLX)



(CLXI)

The reaction of chloropyrimidines with other substances containing an active methylene group has been reported.[375][*] Thus 2-chloro-4,6-dimethylpyrimidine condensed with sodio benzyl methyl ketone to give 4,6-dimethyl-2-1′-phenylacetonylpyrimidine. Ethyl phenylacetate and benzyl cyanide reacted similarly with the pyrimidine to give respectively 2-α-ethoxycarbonylbenzyl- and 2-α-cyanobenzyl- 4,6-dimethylpyrimidine.[375]

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[*] This work is not easily accessible, but the conditions used are closely analogous to those for similar reactions with a chlorothiazole.[376]

6. Reactions of 5-Halogenopyrimidines

Until Bredereck *et al.*[377] produced 5-bromopyrimidine in quantity, examples of 5-halogenopyrimidines had been confined to those carrying in addition electron-releasing groups (to facilitate halogenation) or such groups as 2- or 4-chloro. The first of these deactivated the 5-halogen and the second type reacted preferentially with any nucleophilic reagent to become new electron-releasing groups. The 5-halogeno group therefore acquired a reputation for unreactivity, which is undeserved when it stands in isolation. Thus 5-bromopyrimidine reacts with sodium methoxide in methanol at 100° to give 70 % of 5-methoxypyrimidine,[377] and with sodium ethylmercaptide in refluxing ethanol to give 60 % of 5-ethylthiopyrimidine.[377] Although 5-chloropyrimidine is known,[139] no reactions have been reported.

A. Amination of 5-Bromopyrimidine Derivatives

Despite early failures to react 4-amino-5-bromo-6-methylpyrimidine[245] and 5-bromo-2-ethylthio-4-hydroxypyrimidine[103] with ammonia*, 5-bromouracil (CLXII) and its *C*- and *N*-methyl derivatives were shown to react at about 180° with methylamine and dimethylamine, to give such compounds as 2,4-dihydroxy-5-methylaminopyrimidine,[378] its 6-methyl derivative,[60] 1(and 3)-methyl-5-methylaminouracil[378], and 5-dimethylamino-2,4-dihydroxypyrimidine.[60] The bromo group of 5-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine is peculiarly reactive. With the appropriate amine in boiling alcohol it quickly gives the 5-methylamino, 5-hydroxyethylamino, and other analogues.[109] Similarly, 4-benzylamino-5-bromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine with dimethylamine at 70° yields[379] its 5-dimethylamino analogue, and other amines have also successfully reacted[380] with 5-bromouracil (CLXII) to give among others the following 5-derivatives in good yield: ethylamino, cyclohexylamino, *N*-benzylethylamino, piperidino (CLXIII), and anilino. Hydrazine reacts with 5-bromo-2,4-dihydroxy-6-methylpyrimidine at 120° to give the 5-hydrazino analogue.[381] 5-Bromo-4,6-

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* In a supreme example of scientific optimism, Gabriel and Colman[245] heated their bromo compound with alcoholic ammonia for many hours at 300°, and rather sadly report a product consisting of a black water-insoluble powder(!) and a smelly tar. Wheeler and Johnson[103] simply record that their aminations "did not lead to a smooth result".

dihydroxypyrimidine (CLXIV), however, with piperidine under rather similar conditions gave, not the 5-piperidino derivative but α-piperidinomalondiamide (CLXV), because the ring of 4,6-dihydroxypyrimidine derivatives opens easily in the presence of alkali or even strong organic bases.[232]

As would be expected, the bromine of 2-amino-5-bromo-4-hydroxypyrimidine (5-bromoisocytosine) is less active than that in 5-bromouracil, and only limited success has been reported in its replacement. Thus piperidine and morpholine give 2-amino-4-hydroxy-5-piperidino (or morpholino)pyrimidine,[382] but butylamine, ethylamine, or benzylmethylamine failed to react. Amination of 4-amino-5-bromo-6-hydroxypyrimidine with methylamine under a variety of conditions was unsuccessful in producing a pyrimidine, although the bromine became quantitatively ionic during the reaction.[29] However, 2,4-diamino-5-bromo-6-hydroxypyrimidine aminates in morpholine.[383] 5-Bromocytidine and 5-bromouridine when treated with liquid ammonia at 40–50° for 5 days give respectively 12 % and 63 % of 5-aminocytidine[105] and 5-aminouridine.[384] 5-Bromo (or chloro)-4-carboxy-2-phenylpyrimidine with ammonia at 180° gives 5-amino-4-carboxy-2-phenylpyrimidine,[142] but the related 5-bromo-4-carboxy-2-methylpyrimidine has been shown[141] to give the 5-amino-4-carboxy-2-methylpyrimidine satisfactorily at 100° for 2 hours with aqueous ammonia *provided* that copper is present. The anilino analogue is made rather similarly.[338] Treatment of 2-amino-5-bromo-4,6-dimethylpyrimidine with alcoholic ammonia and copper powder at 240°, on the other hand, resulted not in amination, but in loss of the bromo group to give 2-amino-4,6-dimethylpyrimidine.[86]

B. Other Reactions of 5-Halogenopyrimidine Derivatives

5-Halogeno groups are readily removed by hydrogenation, as in the cases of 4-amino-5-chloro-2-methylpyrimidine,[141] 5-bromo-2,4-dichloropyrimidine[47] and its 5-methyl derivative,[12] 2,5-dichloropyrimidine,[139] 5-chloro-2-phenylpyrimidine,[139] 5-bromo-2-carbamoylpyrimidine,[385] and 5-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine.[386]

In addition, 5-chloro-2(*N*-*m*-aminobenzenesulphonyl-*N*-methylamino)pyrimidine can be reduced with Raney nickel alloy in aqueous-methanolic potassium hydroxide solution to give the dechlorinated product.[50] Raney nickel (catalyst) has been used to convert 5-bromo-4-carboxy-2-methylthiopyrimidine into 4-carboxy-2-methylthiopyrimidine (or under more vigorous conditions to 4-carboxypyrimidine), and 5-bromo-2-methylthiopyrimidine into pyrimidine.[387] Hydrazine readily debrominates 5-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine.[109]

5-Bromo-4-hydroxypyrimidine is dehalogenated by boiling in water with zinc dust.[110] 5-Halogen has several times been replaced by cyano. Thus 2-amino-5-bromopyrimidine when heated with cuprous cyanide in quinoline for 40 minutes gave a 40% yield of 2-amino-5-cyanopyrimidine,[50] and its 4-methyl derivative[388] was made similarly. 2-Benzenesulphonamido-5-cyanopyrimidine resulted in an analogous way from the 5-iodo analogue.[50]

Replacement of a 5-bromo by a hydroxy group can sometimes be readily done. Thus 5-bromo-2,4-dihydroxypyrimidine and 5-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine are converted into their 5-hydroxy analogues by simple boiling with sodium bicarbonate solution.[389] In the past, much more drastic conditions have been used when these[386] and similar transformations required to be done. Examples are the conversion of 2-amino-5-bromo-4,6-dimethylpyrimidine into 2-amino-5-hydroxy-4,6-dimethylpyrimidine[390] by aqueous barium hydroxide and copper powder at 180° and of 5-bromouridine into 5-hydroxyuridine[384, 391] by the addition of lead oxide to the hot aqueous solution.

Although simple replacement by a mercapto group has not been reported, treatment of 5-bromo-2,4,6-trihydroxypyrimidine with thiourea[392, 393] gives the intermediate 5-amidinothio-2,4,6-trihydroxypyrimidine, whence alkali gives di-(2,4,6-trihydroxypyrimidin-5-yl)-disulphide.[392]* Di-(4-amino-2,6-dihydroxypyrimidin-5-yl) sulphide (*not* disulphide) was made by a similar process, or in one step with aqueous alkaline thiourea.[392] The disulphide was later obtained by using sodium disulphide (Na_2S_2) with the bromo compound, and *N*-alkylated derivatives were made similarly.[396] A mixed sulphide with 6-mercaptopurine has also been described.[396] Thiourea has also been successfully condensed with 5-bromo-2-(5-carboxyamylamino)pyrimidine to give the corresponding 5-amidinothio derivative, but no hydrolysis was attempted.[398] Thiosalicylic acid and 2,4-diamino-5-bromo-6-hydroxy-

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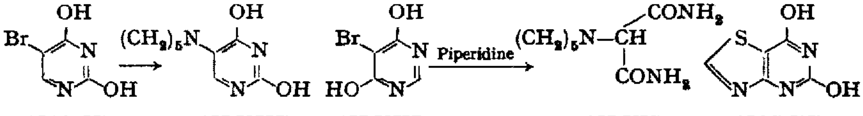
* Early reports of 2,4,6-trihydroxy-5-mercaptopyrimidine made similarly[394] or *via* the thiocyanato intermediate[395] require substantiation.

pyrimidine give the 5-thioether,[383] and 5-iodo-2-*p*-nitrobenzenesulphonamidopyrimidine on heating at 190° with cupric thiophenolate in quinoline gives 58 % of the 5-phenylthio analogue.[397]

5-Bromo-2,4-dimethoxypyrimidine reacts in one minute at —80° with butyl-lithium, and immediate treatment with carbon dioxide gives 5-carboxy-2,4-dimethoxypyrimidine in 75 % yield.[73] The bromine may also be replaced by an alkyl group.[399]

Although the 5-bromo group in 5-bromo-2,4,6-trihydroxypyrimidine (and its *N*-alkyl derivatives) has been described as sufficiently active to participate in the formation of thiazolo [4,5-d] pyrimidines (*e.g.* CLXVI) when treated with thioformamide or thioacetamide,[400,401] this work has been retracted[402] and shown to be unrepeatable,[373,403,404] but a more recent paper[383] should be read.



(CLXII) (CLXIII) (CLXIV) (CLXV) (CLXVI)

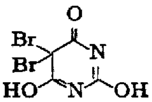
C. Reactions of 5,5-Dihalogeno and Related Pyrimidines

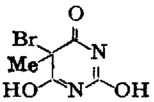
As can be gathered from Sect. 2.A(6a), one of the halogen atoms in 5,5-dihalogenobarbituric and derivatives is very reactive, and normal monohalogenobarbituric acids can be produced from them by removal of the reactive halogen with ammonia, hydrazine, hydrogen iodide, and other reducing agents. By the same mechanism, the dibromo compounds can act as brominating agents and in this way dibromo barbituric acid (CLXVII) loses half its bromine in converting aniline into *p*-bromoaniline;[405] a similar reaction with dimethylaniline in ethanol was said to be vigorous and gave 75 % yield of *p*-bromodimethylaniline.[406]

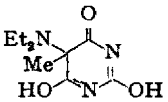
The analogous 5-alkyl-5-halogenobarbituric acid derivatives (*e.g.* CLXVIII) also have an active halogen. Thus it is easily removed by reduction[407] and the kinetics of the catalytic hydrogenation over colloidal platinum and tungsten have been studied.[408,409] It can also be replaced by prolonged treatment with an amine at 50–60° to give for example 5-diethylamino-5-methylbarbituric acid (CLXIX) and its homologues,[410,411] and 5-β-hydroxyethylamino-5-methylbarbituric acid and its homologues.[412] More vigorous treatment with an organic base produces a hydantoin.[413]

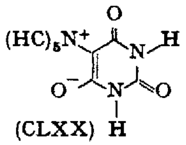
The action of pyridine on 5,5-dibromobarbituric acid is of interest. It gives a nicely crystalline compound, shown[414] to be "1-[5-(2,4,6-trioxohexahydropyrimidyl)] pyridinium betaine" (CLXX); 5,5-dichloro- or 5-bromo-5-nitro-barbituric acid gives the same product, but monohalogenobarbituric acids do not react; 5,5-dibromo-1,3-dimethylbarbituric acid gives a similar product [1,3-dimethyl-(CLXX)], and γ-picoline, but not α-picoline, forms analogous products.

The reactions of dihalogenated uracil (*e.g.* 5,5-dibromo-4,5-dihydro-2,4,6-trihydroxypyrimidine) and related compounds have been outlined in Sect. 2.A(6b).


(CLXVII)


(CLXVIII)


(CLXIX)


(CLXX)

7. Reactions of Extranuclear Halogenopyrimidines

Halogen atoms attached only indirectly to the pyrimidine nucleus (at any position) react generally as an independent aliphatic entity might be expected to behave. For that reason, such reactions are treated but briefly below.

A. Replacement by an Alkoxy, Hydroxy, or Acetoxy Group

Both 5-bromomethyl-4,6-dichloro-2-methylpyrimidine and 4-bromo-5-bromomethyl-6-chloro-2-methylpyrimidine react readily with sodium methoxide in methanol at 20° in 12 hours after the initial reaction. The first compound gives 4-chloro-6-methoxy-5-methoxymethyl-2-methylpyrimidine, but the second gives 4,6-dimethoxy-5-methoxymethyl-2-methylpyrimidine.[81] Sodium ethoxide reacts similarly.

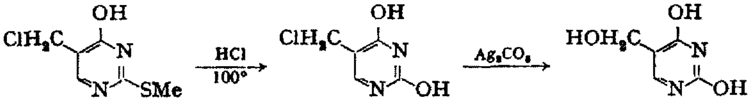
Hydrolysis of halogenoalkyl pyrimidines seems to be best done under alkaline conditions or with silver carbonate. Thus 5-chloro methyl-4-hydroxy-2-methylthiopyrimidine (CLXXI) with hydrochloric acid at 100° for 4 hours gives only 5-chloromethyl-2,4-dihydroxypyrimidine (CLXXII) but treatment of the latter with silver carbonate in water gives hydrolysis to 2,4-dihydroxy-5-hydroxymethylpyrimidine[155] (CLXXIII). Similarly 4-chloromethyl-2,6-dihydroxypyrimidine on treatment with silver sulphate followed by barium hydroxide gives 2,4-dihydroxy-6-hydroxymethylpyrimidine,[415] 2-amino-5-β-bromoethyl-4-methylpyrimidine by heating with aqueous potassium carbonate gives 2-amino-5-β-hydroxyethyl-4-methylpyrimidine,[173] and 5-β-chloroethyl-4-hydroxy-6-methylpyrimidine by heating with water at 150° gives 4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine.[174]

Silver acetate in acetic acid is said (without detail) to convert 5-bromomethyl-4,6-dichloro-2-methylpyrimidine into 5-acetoxymethyl-4,6-dichloro-2-methylpyrimidine and 5-acetoxymethyl-4-chloro-6-hydroxy-2-methylpyrimidine.[81] 4-Acetoxymethyl-2,6-dihydroxy-5-methylpyrimidine is formed similarly and hydrolysis yields the hydroxymethyl analogue.[416, 417] This furnishes one of the few examples in this series of the conversion of an active halogen group to hydroxy *via* acetoxy, a process elsewhere found to be quite useful.

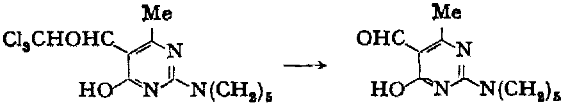
B. Replacement by Other Groups

Aminoalkyl pyrimidines are commonly made by reduction of nitriles or by Mannich reactions, so that the replacement of extranuclear halogeno by amino groups is unexplored, although several examples are known.[154, 154a, 155, 418]

Such halogens have, however, been replaced by mercapto and related groups although sometimes rather indirectly. Thus 4-amino-5-bromomethyl-2-methylpyrimidine with thioacetic acid in pyridine yields a mixture of 4-amino-5-mercaptomethyl-2-methylpyrimidine and the corresponding disulphide, with sodium methyl mercaptide it yields 4-amino-2-methyl-5-methylthiomethylpyrimidine mixed with some di(4-amino-2-methylpyrimidin-5-ylmethyl) sulphide, with potassium thiocyanate it yields 4-amino-2-methyl-5-thiocyanatomethylpyrimidine, and with thiourea it yields a mixture of the above sulphide and disulphide.[420] Similar reactions of 4-amino-5-bromomethyl-2-methylthiopyrimidine are recorded.[420] 4-Chloromethyl-2,6-dihydroxy-5-phenoxypyrimidine on boiling in ethanol with potassium thiocyanate yields the 4-mercaptomethyl derivative,[177] and 4-amino-5-chloromethyl-2-methylpyrimidine with thiourea or *N*-substituted derivatives gives thiouronium salts. These all give the one dipyrimidinyl sulphide (not the mercapto derivative) on warming with sodium bicarbonate. Alkaline peroxide oxidation of the thiouronium compounds furnishes one disulphide.[419] Finally, the disulphide with peroxide in acetic acid gives 4-amino-2-methyl-5-sulphomethylpyrimidine.[421] The analogously formed thiouronium salt from 4-amino-5-chloromethyl-2,6-dimethyl-pyrimidine undergoes similar reactions.[166] Both 4-amino-2-methyl- and 4-amino-2,6-dimethyl- 5-sulphomethylpyrimidine have also been made directly from the chloromethyl compounds by treatment with aqueous sodium hydrogen sulphite at 100°,[421] and the first of these from the bromomethyl compound similarly;[314] it is the same sulphonic acid obtained from vitamin B_1 with sodium bisulphite.[422, 423]



(CLXXI) (CLXXII) (CLXXIII)



(CLXXIV) (CLXXV)

The trihalogenomethyl group on treatment with silver nitrate yields a carboxypyrimidine. Thus 4,6-bistribromomethylpyrimidine gives 4,6-dicarboxypyrimidine[150] and 5-bromo-2-tribromomethylpyrimidine gives 5-bromo-2-carboxypyrimidine.[149] A rather similar reaction is that, for example, of 4-hydroxy-6-methyl-2-piperidino-5-(2,2,2-trichloro-1-hydroxyethyl)pyrimidine (CLXXIV) (the product from condensing chloral with 4-hydroxy-6-methyl-2-piperidinopyrimidine) with alkali to give 5-formyl-4-hydroxy-6-methyl-2-piperidinopyrimidine[255] (CLXXV).

The replacement of an extranuclear halogen atom by hydrogen is represented in the reduction of 5-chloromethyluracil to thymine,[155, 157] and 4-trichloromethyl- to 4-methyl-pyrimidine.[424]

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CHAPTER VII

Hydroxy- and Alkoxy-pyrimidines

The hydroxypyrimidines fall naturally into three divisions according to whether the hydroxy group occupies the 2-, 4-, or 6-position, the 5-position, or is separated from the nucleus as in a hydroxymethyl derivative. They are of peculiar interest, for in the class occur several important natural products (uracil, thymine, vicine), and the barbituric acid derivatives which are so important as sedatives in medicine.

1. Preparation of 2-, 4-, and 6-Hydroxypyrimidines

At least half of all known pyrimidines contain a hydroxy, alkoxy, or oxo grouping in the 2- or 4-position. Alkoxy and oxo derivatives are nearly always obtained from the hydroxy in some way, so that the preparation of hydroxypyrimidines is of great importance.

A. By the Principal Synthesis

A great many examples of the preparation of hydroxy pyrimidines by the Principal Synthesis have been discussed in Chapter II. It will be recalled that the use of urea as the one-carbon fragment in this synthesis yields a 2-hydroxy derivative, and that the use of an ester or 1,3-diester as three-carbon fragment yields respectively a 4-hydroxy- or 4,6-dihydroxypyrimidine. Thus urea condenses with malondialdehyde to give 2-hydroxypyrimidine,[1, 1a] acetamidine with ethyl formylacetate gives 4-hydroxy-2-methylpyrimidine,[2] and formamidine with diethyl malonate yields 4,6-dihydroxypyrimidine.[3] Combinations are exemplified by the reaction of urea with formylacetic acid to give 2,4-dihydroxypyrimidine,[4] or with diethyl malonate (I) to give 2,4,6-trihydroxypyrimidine[5] (II).

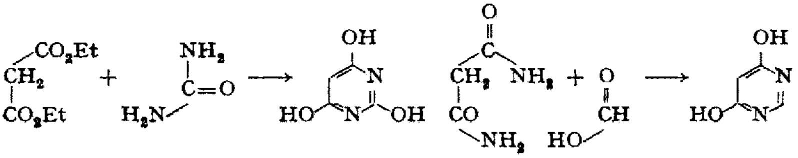
B. By Other Primary Syntheses

Several other ways of making hydroxypyrimidines by primary synthesis have been treated in Chapter III. To avoid repetition, only the more useful methods are briefly mentioned below.

A variety of uracil derivatives with or without 5-substituents can be made by the Shaw synthesis in its various forms (Ch. III, Sect. 2.E), and it can be applied to simple nucleoside synthesis.

Related to this synthesis is the condensation of, for example, ethyl β-aminocrotonate with phenyl isocyanate to give after cyclization, 6-methyl-3-phenyluracil,[6] and other examples are given in Chapter III, Sect. 2.A. Malondiamide (III) condenses with ethyl formate in the Remfry–Hull synthesis[7,8] or with formamide[9] to give 4,6-dihydroxypyrimidine (IV), and the synthesis is applicable to 2- and 5-substituted derivatives by using appropriate starting materials (Ch. III, Sects. 4.A and B). Some more complicated ring systems yield hydroxypyrimidines on degradation; one of the more useful of these is the preparation[9] of 4,5-diamino-2,6-dihydroxypyrimidine from the readily available uric acid by acetic anhydride in pyridine followed by hydrolysis of the intermediate "triacetate" (Ch. III, Sect. 5.E(4)).

A small yield of 4-hydroxypyrimidine has been obtained by the action of hydrogen peroxide on pyrimidine.[10]



(I) (II) (III) (IV)

C. By Hydrolysis of Halogenopyrimidines

The conversion of halogeno into hydroxypyrimidines has been treated in Chapter VI, Sect. 5.E. Since most 2-, 4-, or 6- halogenopyrimidines are derived from the corresponding hydroxy derivatives themselves, the synthesis is of utility only in a small number of cases. Most of these involve a partial hydrolysis of a dihalogeno compound. Thus the best route to 4-chloro-6-hydroxy-2-methylpyrimidine is by acid or alkaline hydrolysis,[11,12] of 4,6-dichloro-2-methylpyrimidine which is readily available. Sometimes it is better to convert a halogeno into an alkoxy and thence into a hydroxypyrimidine; a example of the process is in the conversion of 4-chloro-6-methylaminopyrimidine into 4-methoxy- and then 4-hydroxy-6-methylaminopyrimidine,[13] because when direct hydrolysis was attempted the methylamino group was also hydrolysed at a comparable rate.

D. From Aminopyrimidines

Conversion of amino- into hydroxypyrimidine can be done most easily by acid hydrolysis, less easily by the action of nitrous acid, and sometimes by alkaline hydrolysis. Acid hydrolysis is easier with 4-amino groups than with those in the 2-position. There seems to be little difference in reactivity between analogous primary and secondary amines.

(1) *Simple Examples*

The following pyrimidines have been prepared from their 4-amino analogues: 4-hydroxy-2,6-dimethylpyrimidine (VI) by heating (V) at 180° with hydrochloric acid[14] or with nitrous acid,[15] 4-hydroxy-2,6-diphenylpyrimidine by hydrochloric acid[16] and its 5-methyl derivative by hydrochloric acid or nitrous acid,[16, 17] 2,4,5,6-tetrahydroxypyrimidine by warm hydrochloric acid,[18] uracil with nitrous acid,[19] 1,6-dimethyluracil with alkali,[20] 2,4-dibenzyl-6-hydroxy-5-phenylpyrimidine by strong acids or nitrous acid,[21, 22] and analogous compounds.[21, 23]

From their 2-amino analogues were prepared: 2-hydroxypyrimidine (VIII) from (VII) with nitrous acid or better at 120° with sodium hydroxide,[24] 5-chloro-2-hydroxypyrimidine with nitrous acid,[25] 2,4-dihydroxy-6-phenylpyrimidine with nitrous acid or at 200° with hydrochloric acid,[26] 2-hydroxy-4,6-dimethylpyrimidine with nitrous acid[27] or better alkali,[28] and 2,4-dihydroxy-5-methylpyrimidine at 160° with diluted sulphuric acid.[29] Hydrochloric acid at 160°, but naturally not nitrous acid, converted 2-methylaminopyrimidine and its 4,6-dimethyl derivative into the 2-hydroxy analogues.[27, 27a]

Other simple examples are furnished by the conversion of 4,5-diamino-2-hydroxypyrimidine into 2,4,5-trihydroxypyrimidine,[30] of 4-hydroxy-2-hydroxyamino-6-methyl- (IX) into 2,4-dihydroxy-6-methyl- pyrimidine with tin and hydrochloric acid,[31]* of 4-hydroxy-

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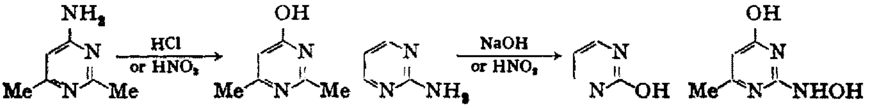
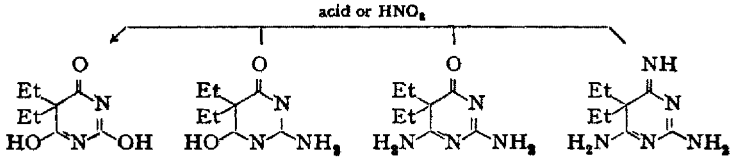
* It seems possible that the acid would have been equally effective without the tin!

6-methyl-2-phenylhydrazino- and 2-benzylidenehydrazino-4-hydroxy-6-methyl- into 2,4-dihydroxy-6-methyl- pyrimidine by acid hydrolysis,[32,33] and of 2,4,6-triamino-5-ethyl- into 5-ethyl-2,4,6-trihydroxypyrimidine at 120° with acid.[34]

The last example indicates a method of preparing barbiturates which has found considerable use, because of the relative ease of introducing an amino group into the 2- or 4-position during a Common Synthesis. Thus 5,5-diethylbarbituric acid (X) has been made by acid hydrolysis of 2-amino(or anilino)-5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine[35] (XI), of 2,4-diamino-5,5-diethyl-5,6-dihydro-6-oxopyrimidine[36,37] (XII), or of 5,5-diethyl-"triaminobarbituric acid"[34] (XIII). 4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine with hot hydrochloric acid gives in a few minutes 1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine (1,3-dimethylbarbituric acid).[38,39] Some of the same conversions have also been done with nitrous acid.[41] Other examples of the technique have been given in Chapter II, Sect. 7.B.



(V) (VI) (VII) (VIII) (IX)



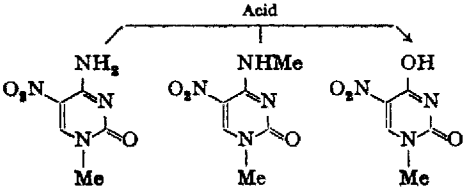
(X) (XI) (XII) (XIII)

Preferential acid hydrolysis of the 4-amino group in 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine to give 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine[40] points to a potentially useful procedure. When a nitroso group occupies the 5-position, the picture is parallel in that 2,4,6-triamino- and 2,4-diamino-6-hydroxy- 5-nitrosopyrimidine both give 2-amino-4,6-dihydroxy-5-nitrosopyrimidine,[42] but when the nitroso is changed to a 5-amino group, the resulting analogues are stable at least under the gentle conditions of hydrolysis used.[43]

(2) *In the Presence of Other Groups*

The conversion of amino- into hydroxy-pyrimidines in the presence of other groups falls naturally into two divisions. The first is where the other group is neither easily hydrolysed nor attacked by nitrous acid, and the second is where the other group reacts as well as the amino group.

The first division is typified by the brief hydrolysis of 2-amino-5-nitropyrimidine with dilute alkali or even aqueous ammonia at 100° to give 2-hydroxy-5-nitropyrimidine.[43] The ease of this reaction should be contrasted with the 12 hours at 120° with 10N-sodium hydroxide required for hydrolysis when no nitro group is present.[24] Several methylated derivatives of 5-nitrocytosine have been hydrolysed with 25 % sulphuric acid at *ca.* 150° to the corresponding known uracil derivatives in order to check the position of methylation. Thus 4-amino-1,2-dihydro-1-methyl-5-nitro-2-oxopyrimidine[44] (XIV) and 1,2-dihydro-1-methyl-4-methylamino-5-nitro-2-oxopyrimidine[45] (XV) both give 1-methyl-5-nitrouracil (XVI), and 4-amino-1,2-dihydro-1,6-dimethyl-5-nitro-2-oxopyrimidine[46] gives 1,6-dimethyl-5-nitrouracil. A similar derivative, 3-methyl-5-nitrocytosine, did not hydrolyse satisfactorily.[47] Other examples are the alkaline hydrolysis of 4-amino-5-carboxy-2,3-dihydro-3-methyl-2-oxopyrimidine (XVII) to 5-carboxy-3-methyluracil,[13] the acid hydrolysis of 4-amino-5-cyano-3-cyclohexyl-2,3-dihydro-2-oxopyrimidine to 5-cyano-3-cyclohexyluracil,[48] the nitrous acid conversion of 4-amino-5-bromo-2,6-dimethylpyrimidine into



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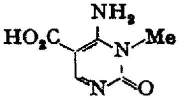
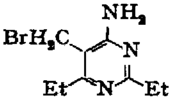


(XVII)



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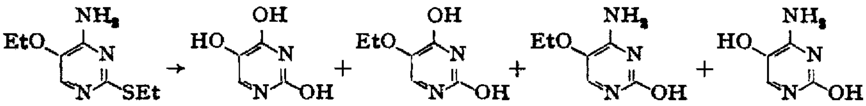

(XIX) (XX) (XXI) (XXII) (XXIII)

5-bromo-4-hydroxy-2,6-dimethylpyrimidine,[15, 49] and the similar conversion of 4-amino-5-bromomethyl (or chloromethyl)-2,6-diethylpyrimidine (XVIII) and similar halogenated derivatives into their 4-hydroxy analogues.[50, 51]

The second division (where another group is also hydrolysed or reacts with nitrous acid) may be briefly exemplified by the preparation of 5,5-diethyl- and dimethyl- barbituric acid respectively from 6-amino-5,5-diethyl- and 6-amino-5,5-dimethyl- 2-thiouracil by hydrolysis at 150° with acid,[52] and also by the acid hydrolysis of 4-amino-5-ethoxy-2-ethylthiopyrimidine (XIX) which gave,[53] under slightly different conditions, four isolated products: 2,4,5-trihydroxypyrimidine (XX), 5-ethoxy-2,4-dihydroxypyrimidine (XXI), 4-amino-5-ethoxy-2-hydroxypyrimidine (XXII), and 4-amino-2,5-dihydroxypyrimidine (XXIII). Other examples can be found but they are of little utility.

E. From Alkoxypyrimidines

2-, 4-, and 6-Alkoxypyrimidines are readily hydrolysed to hydroxy derivatives, but this process is not often of use except to show the structure of the alkoxypyrimidine or in the rare conversion of a chloro into a hydroxypyrimidine *via* an alkoxy derivative.

An illustration of the first use is furnished by the isolation[54] of a methoxy methylamino-5-nitropyrimidine in methylamination of 2,4-dichloro-5-nitropyrimidine. It was shown to be the 2-methoxy-4-methylamino isomer by hydrolysis at 100° with hydrochloric acid[55] to 2-hydroxy-4-methylamino-5-nitropyrimidine.

The second use mentioned above is illustrated by the preparation of 4-hydroxy-6-methylaminopyrimidine from 4-chloro-6-methylaminopyrimidine. Direct hydrolysis is unsatisfactory but the chloro compound easily gives 4-methoxy-6-methylaminopyrimidine which at 100° with hydrochloric acid gives the hydroxy compound.[13] The 4-dimethylamino-6-methoxy analogue has been similarly used for preparing 4-dimethylamino-6-hydroxypyrimidine.[56]

Other instances of the hydrolysis of alkoxypyrimidines are 2-benzyloxy- to 2-hydroxy- 4,6-dimethylpyrimidine by boiling with 6 N-hydrochloric acid,[1] 1,2-dihydro-4-methoxy-1,6-dimethyl-2-oxopyrimidine to 1,6-dimethyluracil with boiling acid,[57] and 4-amino-1,6-dihydro-2-methoxy-1-methyl-6-oxopyrimidine to 6-amino-3-methyluracil with hydrochloric acid at room temperature.[58]

F. From Mercaptopyrimidines and Related Derivatives

A 2-, 4-, or 6-mercapto group can seldom be conveniently changed into a hydroxy group by direct hydrolysis. Exceptionally, 2-ethylthio-4-mercaptopyrimidine gives uracil on prolonged hydrolysis,[59] and 4-hydroxy-2-mercapto-6-methylpyrimidine gives 6-methyluracil at 150° with hydrochloric acid.[60] The conversion of mercapto to hydroxy is very often done by *S*-alkylation followed by acid hydrolysis, by oxidation (to sulphonic or sulphinic acid; *e.g.* XXIX) followed by hydrolysis, or even less directly by alkylation followed by mild oxidation to a sulphone and subsequent hydrolysis.

(1) *By S-Alkylation and Hydrolysis of the Alkylthiopyrimidine*

Most mercaptopyrimidines are readily *S*-methylated by dissolution in alkali and shaking with methyl iodide or dimethyl sulphate. The resulting alkylthio derivative is then boiled with 6 N-hydrochloric acid to give the hydroxy derivative with the evolution of methylmercaptan. The alkylation part of this process is treated in Chapter VIII, Sect. 1.D(2) and the following examples of the acid hydrolysis of alkylthio groups are typical: 2-hydroxy-* from 2-ethylthiopyrimidine;[61] 2,4-dihydroxypyrimidine from 4-hydroxy-2-methylthio-,[62] 2-benzylthio-4-hydroxy-,[63] or 4-ethoxy-2-ethylthio- pyrimidine;[29] 4,6-diamino-2-hydroxypyrimidine by brief hydrolysis, and 2,4,6-trihydroxypyrimidine by long hydrolysis of 4,6-diamino-2-methylthiopyrimidine;[64] 1- and 3-methyluracil from 1,4(and 1,6)-dihydro-1-methyl-2-methylthio-4-(and 6-)oxopyrimidine;[65] 4-amino-2-hydroxy- from 4-amino-2-ethylthio- pyrimidine by boiling with hydrobromic[66] or hydrochloric acid.[29]

A widely used version of this process for converting mercapto- into hydroxy-pyrimidines involves alkylation of the former with aqueous chloroacetic acid to give a carboxymethylthio derivative in solution. This may often be isolated if desired, but generally hydrochloric acid is simply added to the solution and on further refluxing hydrolysis to thioglycollic acid and the hydroxypyrimidine ensues. In this way, for example, is best made 4,6-diamino-2-hydroxypyrimidine. It will be recalled that malononitrile does not condense satisfactorily with urea to

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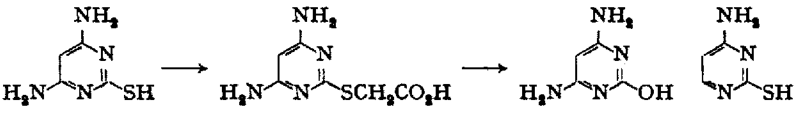
* Isolated and analysed as hydrochloride. The (unanalysed) base supposedly made from it did not correspond in any way to authentic material prepared later,[24] but the hydrochlorides had the same m.p.

give this compound. Thiourea, however, does so readily, to give 4,6-diamino-2-mercaptopyrimidine (XXIV) which on treatment with chloroacetic acid followed by 2 N-sulphuric acid gives the required hydroxypyrimidine (XXVI) in good yield;[67] the intermediate (XXV) may be isolated if an excess of chloroacetic acid is avoided, or if it is neutralized before starting the reaction. The process is also a step in convenient preparations of uracil[63,68,69] from 2-thiouracil (which is available in quantity), and in preparing cytosine[69,70] from 2-thiocytosine (XXVII) which is readily made. In these cases, the intermediates are not normally isolated. Other hydroxypyrimidines made from their 2-mercapto analogues in this way include 2,4-dihydroxy-5-methylpyrimidine,[71] 2-hydroxy-4-methylaminopyrimidine,[13] 4-amino-5-ethoxycarbonyl-2-hydroxypyrimidine,[72]* 2,4-dihydroxy-5-methoxy-6-methoxymethylpyrimidine (and homologues),[73,74] 4-amino-2-hydroxy-5-methylpyrimidine,[70] 2,4-dihydroxy-6-methylpyrimidine,[75] and related compounds.[76,77]

Since 4- or 6-mercapto groups are invariably introduced either directly or indirectly from hydroxy groups, there is little call for the reverse process. A good example, however, is the conversion of 2-hydroxy-4-mercaptopyrimidine into uracil with chloroacetic acid in 70 % yield.[63]

Any analogous grouping may be substituted for the carboxymethylthio group, and hydrolysis still gives a hydroxypyrimidine. Thus 2-α-carboxy-α-methylethylthio-4-hydroxy-6-methylpyrimidine with boiling dilute hydrochloric acid gave 2,4-dihydroxy-6-methylpyrimidine in 95 % yield.[78]



(XXIV) (XXV) (XXVI) (XXVII)

(2) *By Oxidation to Sulphinic or Sulphonic Acid and Hydrolysis*

Oxidative hydrolysis of mercaptopyrimidines can lead to removal of the mercapto group either in favour of hydrogen (desulphurization) or in favour of hydroxyl. Sometimes both products[79] are formed. The

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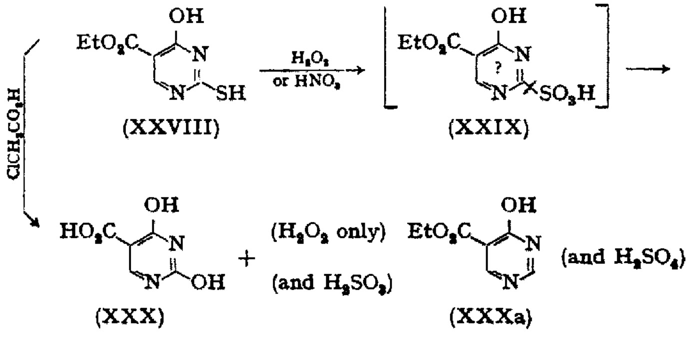
* Experimental details are lacking. The ester might have been expected to hydrolyse during the acid treatment.

picture is rather confused and would benefit from a systematic study; at present it is not easy to forecast which course the reaction will take in a given case. For preparative purposes, and in the present state of knowledge, it is better to avoid the process.

Dilute nitric acid, at least, seems to give only hydroxy from mercapto derivatives. Thus 4-ethyl-6-hydroxy-2-mercaptopyrimidine on warming with 2·5 N-nitric acid gives 4-ethyl-2,6-dihydroxypyrimidine,[80] and 4,5-diamino-6-hydroxy-2-mercaptopyrimidine with "25 % nitric acid" gives (presumably) 4,5-diamino-2,6-dihydroxypyrimidine, which was isolated as a triazolopyrimidine because it reacted with the nitrous acid produced during the oxidation by nitric acid.[81] 5-Ethoxycarbonyl-4-hydroxy-2-mercaptopyrimidine (XXVIII) with dilute nitric acid gives 5-carboxy-2,4-dihydroxypyrimidine (XXX) in good yield,[32,83] with chloroacetic acid it gives the same product (XXX),[32] but with hydrogen peroxide in dilute acid it gives the same product mixed with the desulphurization product, 5-ethoxycarbonyl-4-hydroxypyrimidine[32] (XXXa). The rather analogous 4-hydroxy-5-β-hydroxyethyl-2-mercapto-6-methylpyrimidine with alkaline hydrogen peroxide gives a good yield of only the 2,4-dihydroxy derivative,[84] and other examples[85,86] are known. The normal reaction, however, with hydrogen peroxide is replacement of mercapto by hydrogen (Sect. 1.D(1)). Concentrated nitric acid in glacial acetic acid has been used to convert 5-ethoxycarbonyl-3-octyl-2-thiouracil into the corresponding uracil, and 7·5N-nitric acid for the analogous preparation of 5-carboxy-3-phenyluracil from 5-ethoxycarbonyl-3-phenyl-2-thiouracil,[87] both in good yield.

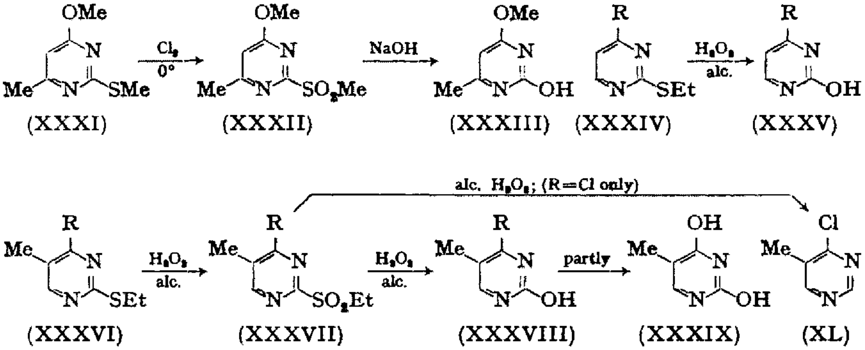


(3) *By S-Alkylation, Oxidation to Sulphone, and Hydrolysis*

The *S*-alkylation of mercaptopyrimidines and the subsequent oxidation to (isolated) sulphones are dealt with in Chapter VIII, Sects. 1.D(2) and 5.A respectively. The present section gives some examples of the hydrolysis of sulphones to hydroxy derivatives, and of the sulphone formation as well when this intermediate is not isolated.

Sulphones can be hydrolysed conveniently by boiling with 6 N-hydrochloric acid or more gently with aqueous alkali. Thus 4-methoxy-6-methyl-2-methylsulphonylpyrimidine (XXXII) (from the corresponding thioether (XXXI) by chlorine oxidation) with aqueous sodium hydroxide gave 2-hydroxy-4-methoxy-6-methylpyrimidine[88] (XXXIII), and 4-ethoxy-2-ethylsulphonyl-5-methylpyrimidine or its 5-bromo analogue gave with alkali respectively 4-ethoxy-2-hydroxy-5-methyl- and 5-bromo-4-ethoxy-2-hydroxy- pyrimidine.[89] Similarly 2-ethylsulphonyl-4-ethoxy(and methoxy)-6-methyl-5-propylpyrimidine give the corresponding 2-hydroxy derivatives,[90,91] and the 5-ethyl and 5-methyl analogues did likewise.[92,93] On the other hand, hydrolysis with 6 N-hydrochloric acid converted 4-amino-2-ethylsulphonyl- into 4-amino-2-hydroxy- 5-methylpyrimidine[89] and similar hydrolysis of nine more 2-ethylsulphonylpyrimidines (all containing in addition a hydrolysable 4-group) have been reported[94] without experimental detail, to give the corresponding dihydroxy derivatives. This list includes hydrolysis of 2,4-bisethylsulphonylpyrimidine, 4-chloro-2-ethylsulphonylpyrimidine, and 4-ethoxy-2-ethylsulphonylpyrimidine, to uracil, and of the similar formation of some 5-substituted uracils.

The action of hydrogen peroxide on ethanolic solutions of alkylthiopyrimidines has been studied by Yuoh-fong Chi and his colleagues. With ethylthiopyrimidines represented by (XXXIV; R = Cl, OMe, OEt, NH_2, NHMe, or NEt_2) alcoholic hydrogen peroxide gives the corresponding 2-hydroxy derivatives (XXXV; R as before). A sulphone intermediate was postulated but could not be isolated; in one case (4-chloro-2-ethylsulphonylpyrimidine) it was made by the cold chlorine oxidation of (XXXIV; R = Cl) and hydrogen peroxide on this sulphone gave the appropriate 2-hydroxy derivative.[95,96] When a 5-methyl group was present in the ethylthiopyrimidine (XXXVI; R as before), the intermediate sulphone (XXXVII) was easily isolated after peroxide treatment in each case, and further oxidation gave the appropriate hydroxy compound (XXXVIII). In one case (R = Cl) partial loss of the 2-group occurred giving some 4-chloro-5-methylpyrimidine (XL), and in other cases the 2-hydroxy products in part underwent further reaction to thymine (XXXIX).[97,98] The best conditions for obtaining maximum yields of products from (XXXIV) and (XXXVI) have been explored and tabulated.[98,100]



(XXXI) (XXXII) (XXXIII) (XXXIV) (XXXV)

(XXXVI) (XXXVII) (XXXVIII) (XXXIX) (XL)

G. By Reductive Cleavage of Benzyloxypyrimidines

The formation of hydroxypyrimidines by reductive fission of benzyloxy derivatives could be of great use when hydrolysis is contraindicated because of other labile groups in the molecule. The process has been little used in the series, but is represented by the conversion of 4-benzyloxy-2-carbamoyl-6-methylpyrimidine (by hydrogenation over palladium) into 85 % of 2-carbamoyl-4-hydroxy-6-methylpyrimidine,[101] and less simply by the conversion of 4-benzyloxy-6-methylpyrimidine-*N*-oxide into 4-hydroxy-6-methylpyrimidine.[101]

2. Preparation of 5-Hydroxypyrimidines

Although not a great many 5-hydroxypyrimidines have been made, there are now two good general methods of producing them as well as the older and more limited ways. These less generally useful procedures will be treated first.

A. Miscellaneous Useful Methods

5-Hydroxypyrimidines have been made from 5-bromo derivatives. Thus aqueous barium hydroxide and copper powder at 180° converted

2-amino-5-bromo-4,6-dimethylpyrimidine into the 5-hydroxy analogue,[102] and 5-bromouridine and deoxyuridine, when treated in hot aqueous solution with lead oxide gave respectively 5-hydroxy-uridine[103, 104] and -deoxyuridine.[105] 5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine similarly gives the 5-hydroxy analogue,[106] but it (and 2,4,5-trihydroxypyrimidine) are best made by simple boiling with aqueous sodium bicarbonate.[107]

The direct hydrolysis of a 5-amino- to a 5-hydroxy-pyrimidine has been used in the preparation of 2,4,5-trihydroxypyrimidine (from 5-nitrouracil by tin and hydrochloric acid reduction with subsequent hydrolysis),[108–110] 2-amino-4,5-dihydroxypyrimidine (from 2,5-diamino-4-hydroxypyrimidine with 20 % sulphuric acid at 140°),[111] 2-methyl-4,5-dihydroxypyrimidine (from the 5-ethoxycarbonylamino derivative with hydrochloric acid at 120°),[112] and 4,5-dihydroxypyrimidine (from 4,5-diamino-,[113] 5-amino-4-hydroxy-,[113] or 5-benzamido-4-hydroxy-,[114] pyrimidine[114] with 6 N-hydrochloric acid). Alloxan (hexahydrotetraoxopyrimidine), on stannous chloride or other reduction, yields dialuric acid (tetrahydroxypyrimidine).[115–117]

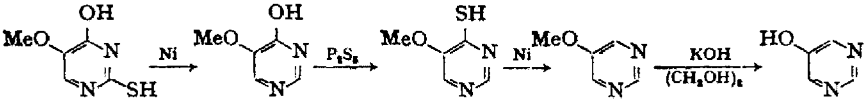
The first serious attempt to make 5-hydroxypyrimidine itself was the treatment of 5-aminopyrimidine with nitrous acid. Nitrogen was evolved but no product was isolated.[118] However, successful preparation of 2-carboxyamylamino-5-hydroxypyrimidine by diazotization of the corresponding 5-amino derivative has been described.[119]

The assignment of a 2,4-diaryl-5-hydroxypyrimidine structure to several compounds[120, 121] was later shown to be wrong.[113, 122]

B. Through Primary Synthesis of a 5-"Protected"-hydroxypyrimidine

The most versatile method of making 5-hydroxypyrimidines is by primary synthesis of a pyrimidine-5-ether of a type which can be easily hydrogenated or hydrolysed to a 5-hydroxy derivative. The most satisfactory "protected"-hydroxy groups (ethers) have been methoxy, benzyloxy, and tetrahydropyran-2-yloxy groups.

The use of the methoxy group is typified in the preparation of 5-hydroxypyrimidine itself. Methyl-α-formyl-α-methoxyacetate ($MeOCH(CHO)CO_2Me$) was condensed with thiourea to give 4-hydroxy-2-mercapto-5-methoxypyrimidine (XLI) which was desulphurized with nickel to 4-hydroxy-5-methoxypyrimidine (XLII). Treatment with phosphorus pentasulphide (or with phosphoryl chloride followed by thiourea) gave 4-mercapto-5-methoxypyrimidine (XLIII) which was desulphurized to 5-methoxypyrimidine* (XLIV). Hydrolysis with potassium hydroxide in glycol gave 5-hydroxypyrimidine[123, 123a] (XLV).



(XLI) (XLII) (XLIII) (XLIV) (XLV)

Benzamidine was then used in place of thiourea in the initial Common Synthesis above and an analogous sequence gave 5-hydroxy-2-phenylpyrimidine.[123, 123a] By employing benzyl formylbenzyloxyacetate in the initial synthesis the penultimate 5-benzyloxypyrimidine was made similarly, but the last step to 5-hydroxypyrimidine was unsatisfactory.[113]

4,5-Dihydroxypyrimidine was prepared by aqueous hydrobromic acid hydrolysis of 4-amino-, 4-methylthio-, and 4-hydroxy- 5-methoxypyrimidine.[113] There are also a few examples of 5-ethoxypyrimidines (produced initially by primary synthesis) being converted into 5-hydroxy derivatives: 4-amino-5-ethoxy-2-ethylthiopyrimidine gives a mixture of 4-amino-2,5-hydroxy- and 2,4,5-trihydroxy- pyrimidine,[53] and rather similar routes lead to 1 (and 3)-benzyl-5-hydroxyuracil,[125] 5-hydroxy-1-methyluracil,[126] and 5-hydroxy-1 (and 3)-methyl-2-thiouracil.[126] An interesting ether hydrolysis is that of 4-hydroxy-5-isobutoxy-6-isobutoxymethyl-2-mercaptopyrimidine with hydriodic acid.[73] The extranuclear ether is first split and reduced to give 4-hydroxy-5-isobutoxy-2-mercapto-6-methylpyrimidine which on prolonged boiling is again split at the 5-ether to give 4,5-dihydroxy-2-mercapto-6-methylpyrimidine. The homologue with isopropoxy groups gives the same final product,[73] and the analogous 2,4-dihydroxy-5-isobutoxy-6-isobutoxymethylpyrimidine likewise gives finally 2,4,5-trihydroxy-6-methylpyrimidine.[73]

The use of a benzyloxy group on the way to a 5-hydroxypyrimidine is particularly useful because the protective part can be finally removed either by hydrolysis or by hydrogenation. A typical synthesis started with ethyl α-benzyloxy-α-formylacetate and guanidine to give 2-amino-5-benzyloxy-4-hydroxypyrimidine (XLVIII) which was hy-

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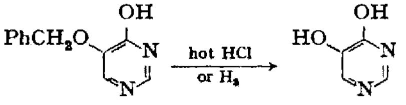
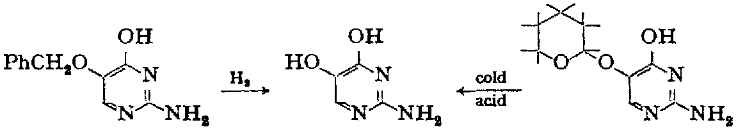
* This could be more easily made now from 5-bromopyrimidine, itself obtained directly from pyrimidine.[124]

drogenated over palladium to yield 2-amino-4,5-dihydroxypyrimidine[127,128] (XLIX). The 2-hydroxy and 2-methyl analogues were prepared by using urea and acetamidine in the initial synthesis, and the benzyloxy group was removed by hydrogenation[127] or hydrolysis.[113] Use of thiourea resulted in 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine which was desulphurized, and the 5-benzyloxy-4-hydroxypyrimidine (XLVI) was either hydrogenated,[127] or acid hydrolysed[113] in slightly poorer yield, to 4,5-dihydroxypyrimidine (XLVII). Similar syntheses starting with diethyl benzyloxymalonate gave finally after hydrogenation 2-amino-4,5,6-trihydroxypyrimidine, its 2-methyl analogue, its 2-hydroxy analogue (dialuric acid), and 4,5,6-trihydroxypyrimidine.[129] 4-Amino-5-hydroxypyrimidine has been made[113] by hydrogenation or hydrolysis of the corresponding benzyloxy derivative.

Another "protected" hydroxy group is tetrahydropyran-2-yloxy; it is much more easily hydrolysed to hydroxy than is a benzyloxy group. Its utility is exemplified by condensation of ethyl α-formyl-α-tetrahydropyran-2-yloxyacetate* and guanidine to give 2-amino-4-hydroxy-5-tetrahydropyran-2′-yloxypyrimidine (L) which on shaking with dilute sulphuric acid for an hour gave 92 % of 2-amino-4,5-dihydroxypyrimidine[128] (XLIX). Other pyrimidines made by appropriate modifications of this synthesis include 4,5-dihydroxy-2-methylpyrimidine, 2-amino-4,5-dihydroxy-6-hydroxymethylpyrimidine, 2,4-diamino-5,6-dihydroxypyrimidine (divicine), 4(and 2)-amino-2(and 4),5,6-trihydroxypyrimidines, tetrahydroxypyrimidine, 4,5,6-trihydroxypyrimidine and its 2-mercapto, 2-phenyl, and 2-methyl derivatives.[128]



(XLVI) (XLVII)



(XLVIII) (XLIX) (L)

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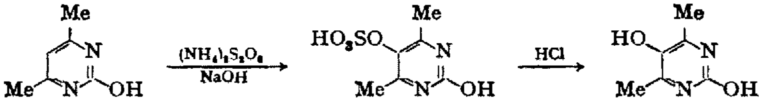
* Made by addition of ethyl glycollate to 2,3-dihydropyran, and treatment of the resulting ethyl tetrahydropyran-2-yloxyacetate with sodium and ethyl formate.

Finally, 5-hydroxy derivatives have been made with the hydroxy group protected only as an ester instead of an ether: 3-acetoxypentane-2,4-dione [MeCOCH(OAc)COMe] on condensation with urea and thiourea gave respectively 2,5-dihydroxy-4,6-dimethylpyrimidine and 5-hydroxy-2-mercapto-4,6-dimethylpyrimidine directly. The latter on desulphurization with Raney nickel gave 5-hydroxy-4,6-dimethylpyrimidine.[113]

C. By Persulphate Oxidation

A very valuable extension of the Elbs persulphate oxidation of mono- to di-hydroxybenzenes was introduced to the pyrimidine series by R. Hull.[130] Treatment, for example, of 2-hydroxy-4,6-dimethylpyrimidine (LI) with cold alkaline persulphate gave 2-hydroxy-4,6-dimethylpyrimidin-5-yl hydrogen sulphate (LII) and this ester was hydrolysed by boiling 5 N-hydrochloric acid to 2,5-dihydroxy-4,6-dimethylpyrimidine (LIII). Other 5-hydroxy derivatives similarly produced[130] include 2-amino-4,5-dihydroxypyrimidine, its 6-methyl derivative, 4,5-dihydroxy-6-methyl-2-piperidinopyrimidine, 2,4-diamino-5-hydroxypyrimidine, and its 6-methyl derivative. 4-Amino-5,6-dihydroxypyrimidine has been made by the same route.[113] The reaction was further explored, without isolating products, by treating several pyrimidines with persulphate, hydrolysing, and taking the production of a blue colour with ferric chloride as a criterion of the insertion of a 5-hydroxy group. Positive reactions to this procedure were given by 2-dimethylamino-4-hydroxy-, 2,4-dihydroxy-6-methyl-, 4,6-dihydroxy-2-methyl-, and other pyrimidines.[130] Persulphate oxidation of pyrimidines requires the presence of at least one electron-releasing group.



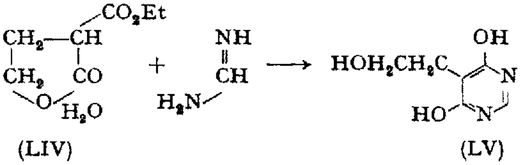
(LI) (LII) (LIII)

3. Preparation of Extranuclear Hydroxypyrimidines

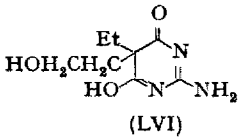
There are not a great many known pyrimidines with hydroxy groups attached indirectly to the nucleus, but they have been made by a variety of methods.

A. By Direct Synthesis

This rarely used route is exemplified in the following cases: hydroxyacetamidine and ethyl acetoacetate condense in aqueous alkali to give 4-hydroxy-2-hydroxymethyl-6-methylpyrimidine.[131] The same amidine with ethyl α-ethoxy-α-methylacetoacetate [$EtOCH_2COCH(Me)CO_2Et$] gave 4-ethoxymethyl-6-hydroxy-2-hydroxymethyl-5-methylpyrimidine whence, by refluxing with aqueous hydrobromic acid, 4-hydroxy-2,6-bishydroxymethyl-5-methylpyrimidine was obtained.[131] α-Ethoxycarbonyl-α-butyrolactone (LIV) has been condensed with formamidine, acetamidine, benzamidine, and other amidines to give 4,6-dihydroxy-5-β-hydroxyethylpyrimidine (LV) and its 2-alkyl derivatives.[132] Similarly α-acetyl-γ-butyrolactone and thiourea give 4-hydroxy-5-hydroxymethyl-2-mercapto-6-methylpyrimidine,[133] and α-ethoxycarbonyl-α-ethyl-γ-butyrolactone and guanidine gave 2-amino-5-ethyl-4,5-dihydro-6-hydroxy-5-hydroxyethyl-4-oxopyrimidine (LVI). Several other 5-alkyl derivatives have been made and the mechanism of the reactions discussed.[132] Direct syntheses have also been used to make pyrimidines typified by 2-amino-4-hydroxy-5-hydroxyethyl-6-methylpyrimidine,[134] and by 2,4-diamino-5-(2,3-dihydroxypropyl)-6-hydroxypyrimidine.[135]



(LIV) (LV)



(LVI)

B. From Amino Derivatives

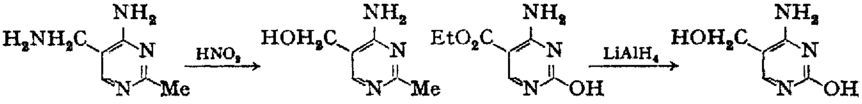
Several hydroxymethyl intermediates of vitamin B_1 or analogues have been made by the action of nitrous acid on the corresponding aminomethyl derivative (*e.g.* LVII). In this way was prepared 4-amino-5-hydroxymethyl-2-methylpyrimidine[136,137] (LVIII), its 6-methyl derivative,[138] and 4-hydroxy-5-hydroxymethyl-2-methylpyrimidine.[139–141] The general conditions used were to add sodium nitrite to an aqueous solution of the amine hydrochloride, and warm at 60–70°. The method has also been used to make 5-hydroxymethyluracil.[142]

C. From Halogeno Derivatives

The conversion of extranuclear halogenopyrimidines into the corresponding hydroxy derivatives has been discussed in Chapter VI, Sect. 7.A.

D. By Reduction of Esters

Pyrimidines with an ester grouping in the 5-position (*e.g.* LIX) have been reduced with lithium aluminium hydride to the corresponding 5-hydroxymethyl derivatives. There seems to be no reason why this reaction should not be extended to other positions. As examples may be quoted the preparation of 4-amino-2-ethylthio-5-hydroxymethylpyrimidine,[143,144,146] 4-amino-5-hydroxymethyl-2-methylthiopyrimidine,[145] 4-amino-2-hydroxy-5-hydroxymethylpyrimidine[146,147] (hydroxymethylcytosine; also made from the above ethylthio derivative by acid hydrolysis[144,146]), 4-amino-2-chloro-5-hydroxymethylpyrimidine,[144] and 4-amino-5-hydroxymethyl-2-trifluoromethylpyrimidine.[148] 5-Hydroxymethylcytosine and 5-hydroxymethyluracil occur in some virus nucleic acids.[149]



(LVII) (LVIII) (LIX) (LX)

E. By the Action of Formaldehyde

2,4-Dihydroxy-6-methylpyrimidine, on boiling with an excess of aqueous formaldehyde, gave 2,4-dihydroxy-5-hydroxymethyl-6-methylpyrimidine,[150] and the hydroxymethyl derivative corresponded in properties and melting point to material made by another route.[151] Although failure to make the lower homologue, 2,4-dihydroxy-5-hydroxymethylpyrimidine, by similar means was reported[142] in 1936, more recently Cline, Fink, and Fink[152] have shown that paraformaldehyde and uracil do in fact give the desired product in 80 % yield. The condensation is best done in aqueous alkali but even acidic media permit a small yield. Material obtained from the original 5-hydroxymethyluracil synthesis from 5-aminomethyl-2,4-dihydroxypyrimidine and nitrous acid[142] is identical[152] with the directly made material. Furthermore, its supposed instability[142] is largely illusory; and despite loss of a little formaldehyde on prolonged boiling in water, only a trace of uracil is reformed.[152]

Other 5-hydroxymethyl derivatives made with formaldehyde include those of uridine (20 %), deoxyuridine (20 %), and orotic acid (8 %), the last being isolated as its lactone.[152]

Active methyl groups on pyrimidines have been converted into β-hydroxyethyl groups with formaldehyde. Thus 4-methylpyrimidine and paraformaldehyde at 165° gave 87 % of 4-β-hydroxyethylpyrimidine.[153] 2-Dimethylamino-4-β-hydroxyethylpyrimidine was made similarly, but in this case some dehydration took place to give a considerable amount of a by-product, 2-dimethylamino-4-vinylpyrimidine.[153]

An interesting case of hydroxymethylation with formaldehyde is the conversion of the dihydropyrimidine, 5-ethylhexahydro-2-methoxy-4,6-dioxo-5-phenylpyrimidine with aqueous alkaline formaldehyde into 5-ethylhexahydro-1,3-bishydroxymethyl-2-methoxy-4,6-dioxo-5-phenylpyrimidine[154] (LXI).

F. From Pyrimidine Aldehydes

The Cannizzaro reaction has been used to make hydroxymethylpyrimidines, but since the number of pyrimidine aldehydes known is limited, the method is not of wide application. The simplest example is the conversion of 4-formyl-6-hydroxypyrimidine (LXII) (as its diethyl acetal) with alkali at 100°, into 4-hydroxy-6-hydroxymethylpyrimidine (LXIV) and the corresponding carboxylic acid (LXIII), in reasonable yield.[155] Other aldehydes gave 4-hydroxy-6-hydroxymethyl-2-mercaptopyrimidine,[156] 4-hydroxy-6-hydroxymethyl-2-methylthiopyrimidine,[155] and 2,4-dihydroxy-6-hydroxymethylpyrimidine.[156]

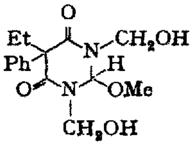
Pyrimidine aldehydes have also been reduced[155] with sodium borohydride to give for example 4-hydroxy-6-hydroxymethylpyrimidine (LXIV) and its 2-methylthio derivative. The yields are better than by using a Cannizzaro reaction. Catalytic reduction of aldehydes has also been used: for example, 4-amino-5-formyl-2-methylpyrimidine hydrogenated over platinum oxide gives 70 % of 4-amino-5-hydroxymethyl-2-methylpyrimidine,[157] and the reduction can also be done over nickel or palladium catalysts.[159]

G. By Other Means

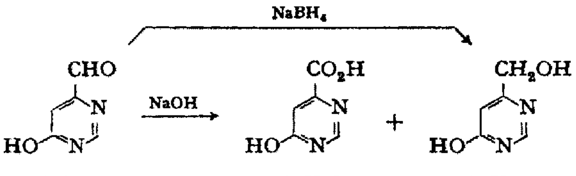
2,4-Dichloro-6-methyl-5-nitropyrimidine reacts with ethanolamine at — 10° in methanol to give 2-chloro-4-β-hydroxyethylamino-6-

methyl-5-nitropyrimidine.[158] Examples of this type of hydroxy derivative (such as the condensation products of hydroxybenzaldehydes with hydrazinopyrimidines[160]) could be multiplied but their preparation is generally obvious (although not by any means always easy).

Extranuclear hydroxy derivatives may be prepared from the corresponding ethers, provided the rest of the molecule will withstand vigorous hydrolysis. The chloro or bromo analogue is generally formed by treatment with hydrochloric or hydrobromic acid (Ch. VI, Sect. 3.C), and then hydrolysed by alkali, Ch. VI, Sect. 7.A.



(LXI)



(LXII) (LXIII) (LXIV)

4. Preparation of Alkoxy- and Aryloxy-pyrimidines

In the 2-, 4-, and 6- positions alkoxy groups are normally prepared from hydroxy *via* chloro derivatives, but in the 5-position or as extranuclear substituents, they are usually made by the Principal Synthesis. There are, however, sufficient exceptions to this statement to justify care in choosing a convenient route to a given alkoxypyrimidine.

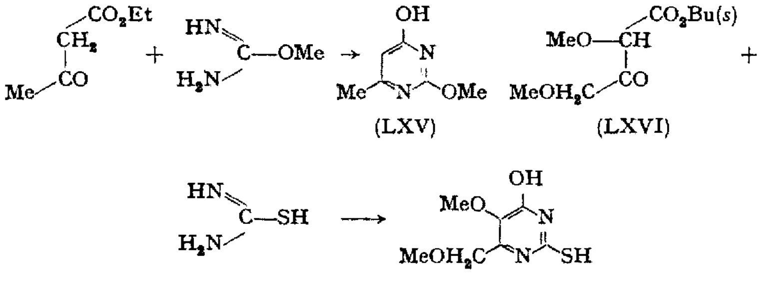
A. By the Principal Synthesis

A few 2-alkoxypyrimidines have been made by using an *O*-alkylurea in a Common Synthesis. Thus *O*-methyl- and *O*-ethyl-urea condense with ethyl acetoacetate to give 4-hydroxy-2-methoxy-6-methylpyrimidine (LXV) and the 2-ethoxy homologue,[161, 162] and *O*-methylurea with ethyl ethylacetoacetate gives 5-ethyl-4-hydroxy-2-methoxy-6-methylpyrimidine.[161] Similar condensation with ethyl formylfluoroacetate gives 5-fluoro-4-hydroxy-2-methoxypyrimidine.[163] *O*-Allylurea with ethyl acetoacetate and diethyl malonate yields respectively 2-allyloxy-4-hydroxy-6-methylpyrimidine and 2-allyloxy-4,6-dihydroxypyrimidine.[164] Now that *O*-methylurea is readily available in quantity,[165, 166] its use in direct syntheses may increase.

The exceptional production[167] of 6-ethoxypyrimidines by a Common Synthesis involving diethoxymethylenemalononitrile has been described at the end of Chapter II, Sect. 9.

Many 5-alkoxy- and 5-aryloxy-pyrimidines have been made by Common Synthesis and examples can be found in Chapter II. Typical are the preparation of 2-amino-5-benzyloxy-4-hydroxypyrimidine[127, 128] (from ethyl benzyloxyformylacetate and guanidine), 2,4-diamino-5-ethoxy-6-hydroxypyrimidine[168] (from guanidine and ethyl ethoxycyanoacetate), the variety of 5-aryloxypyrimidines described[169] in connection with antimalarial studies, and 4-hydroxy-2-mercapto-5-methoxy-6-methoxymethylpyrimidine[73] (LXVII) (from s-butyl *αγ*-dimethoxyacetoacetate (LXVI) and thiourea).

The last example above includes an extranuclear ether (in 6-position) prepared by the Principal Synthesis. Other such compounds (4- and 5-positions) are 2-amino-5-ethoxyethyl-4-ethyl-6-hydroxypyrimidine[170] (from guanidine and ethyl ethoxyethylacetoacetate), 5-ethoxymethyl-2-ethyl-4-hydroxypyrimidine[171] (from ethyl *β*-ethoxyformylpropionate and propionamidine), 4-amino-5-methoxymethyl-2-methylpyrimidine[172] (from *β*-methoxy-*α*-methoxymethylenepropionitrile and acetamidine), 2-amino (and hydroxy)-4-methoxymethyl-6-methylpyrimidine,[173] and a variety of similar compounds.[174, 175] Extranuclear ethers attached to the 2-position are represented by the condensation of anisamidine with ethyl acetoacetate to give 4-hydroxy-2-*p*-methoxyphenyl-6-methylpyrimidine.[176]


(LXV) (LXVI) (LXVII)

B. From Halogenopyrimidines

The replacement of 2-, 4-, and 6- halogeno by alkoxy groups has been discussed in some detail in Chapter VI, Sect. 5.D. Most such alkoxy or aryloxy groups are made in this way. Examples of extranuclear ethers made similarly have also been given in Chapter VI, Sect. 7.A.

5-Halogeno groups cannot normally be replaced by alkoxy, but 5-bromopyrimidine gives 5-methoxypyrimidine by treatment at 120° with methanolic sodium methoxide.[124]

C. By Other Means

Although a number of 2-alkylsulphonylpyrimidines have been made, and although such groups have been converted into alkoxy groups in related systems (*e.g.* in making 8-methoxypurine[177]), there seem to be only a few examples of its use in pyrimidines. 4-Ethoxy-2-ethylsulphonyl-5-methylpyrimidine on boiling with alcoholic sodium hydroxide gave 2,4-diethoxy-5-methylpyrimidine in about 40 % yield,[94] and other alkoxypyrimidines made in this way, but with sodium alkoxide in an alcohol,[89] include 2,4-dimethoxy-5-methylpyrimidine, 5-bromo-2,4-diethoxypyrimidine, and 4-amino-2-ethoxy-5-ethoxycarbonylpyrimidine, as well as 5-ethyl-2,4-dimethoxy-6-methylpyrimidine and its diethoxy analogue.[92] Since sulphones are easily made from thio-ethers, this transformation appears a facile route from mercapto- or methylthio- to methoxy-pyrimidines:

$$\text{R—SH} \xrightarrow[\text{NaOH}]{\text{MeI}} \text{R—SMe} \xrightarrow[\text{or } \text{H}_2\text{O}_2]{\text{Cl}_2} \text{R—SO}_2\text{Me} \xrightarrow[\text{or NaOH}]{\text{NaOMe}} \text{R—OMe } \textit{or } \text{R—OH}$$

Alkylation of hydroxypyrimidines is not satisfactory for preparing alkoxy derivatives because the process (even with diazomethane) almost invariably gives an *N*-alkylated oxopyrimidine (Ch. X), sometimes with a little of the alkoxy derivative. Thus 2-hydroxypyrimidine with diazomethane gave 52 % of 1,2-dihydro-1-methyl-2-oxopyrimidine and only 17 % of 2-methoxypyrimidine.[65] 4-Hydroxypyrimidine similarly treated gave 51 % of 1,6-dihydro-1-methyl-6-oxopyrimidine and only 9 % of 4-methoxypyrimidine,[65] and 4-chloro-6-hydroxypyrimidine gave ten times as much 4-chloro-1,6-dihydro-1-methyl-6-oxopyrimidine as 4-chloro-6-methoxypyrimidine.[56] The literature contains several claims of at least predominant *O*-alkylation, for example in the formation of 2-benzoylmethylthio-4-ethoxy(and methoxy)-6-methylpyrimidine,[178] 4-amino-6-methoxy-2-methylthiopyrimidine[179] (which was later shown to be an *N*-methyl derivative[180]), 4-ethoxy-2-phenylpyrimidine,[181] and its 6-methyl derivative.[182] These structures must be accepted with some reserve at present although the last compound seems also to have been made from 4-chloro-6-methyl-2-phenylpyrimidine with sodium ethoxide.[183] Even 5-hydroxypyrimidine, which is a phenolic substance, does not methylate satisfactorily with methyl iodide,[113] but 2,4,5-trihydroxypyrimidine with diazomethane[184] or dimethyl sulphate[198] fully methylates to give 1,2,3,4-tetrahydro-5-methoxy-1,3-dimethyl-2,4-dioxopyrimidine. Extranuclear hydroxy groups should methylate normally, but as most known examples of such pyrimidines also carry nuclear tautomeric groups, the additional complication of *N*-methylation would exist. This has been obviated in the case of 2,4-dihydroxy-5-hydroxymethylpyrimidine by forming the extranuclear ethers by boiling with excess of an alcohol containing a little hydrochloric acid. In this way were made[152] 5-butoxymethyl-, and 5-ethoxymethyl-2,4-dihydroxypyrimidine as well as the methoxymethyl analogue, all in good yield.

Several simple alkoxypyrimidines have been satisfactorily made by removal of other groups, notably chloro and mercapto. Thus 4-methoxypyrimidine was obtained by hydrogenation (Pd/$BaSO_4$) of its 2-chloro derivative in the presence of magnesium oxide,[186, 199] and 5-methoxypyrimidine by Raney-nickel desulphurization of 4-mercapto-5-methoxypyrimidine.[113, 123] There are many less simple examples such as the preparation of the extranuclear ether, 4-ethoxymethyl-6-hydroxy-5-methylpyrimidine, from its 2-mercapto derivative with hydrogen peroxide,[171] and these processes (and decarboxylation) should not be overlooked in planning the synthesis of an alkoxypyrimidine.

Under vigorous conditions, one alkoxy group may replace another. Thus 2-amino-4-chloro-6-methoxypyrimidine with an excess of sodium ethoxide at 170° gives 2-amino-4,6-diethoxypyrimidine, and similarly 2-amino-4-chloro-6-ethoxypyrimidine with sodium methoxide gives 2-amino-4,6-dimethoxypyrimidine. When less than 1 mole of alkoxide is used some 2-amino-4-ethoxy-6-methoxypyrimidine is formed in each case.[187] Other examples are known[189, 191] under much gentler conditions.

Cyano groups in the 2-, 4-, or 6- position have been replaced by alkoxy groups. Thus 4-cyano-2,6-dimethylpyrimidine on boiling with methanolic sodium methoxide gives 4-methoxy-2,6-dimethylpyrimidine in good yield,[188, 191] 2-cyano-4-methoxy-6-methylpyrimidine gives 2,4-dimethoxy-6-methylpyrimidine,[190] 2-cyano-4-methoxypyrimidine gives 2,4-dimethoxypyrimidine,[199] and other butoxy and methoxy examples are known.[191]

5. Properties and Structure of Hydroxy- and Alkoxy-pyrimidines

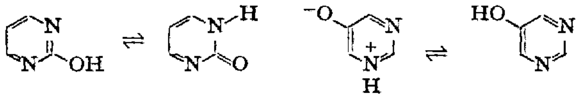
The monohydroxypyrimidines are more soluble in water (and lower melting) than are the di- and tri-hydroxy derivatives. In this they resemble the hydroxy derivatives in other *N*-heterocyclic series having a deficiency of π-electrons, and these phenomena have been discussed and explained.[192] Table XII contains the relevant figures.

TABLE XII. Solubility in Water and Melting Point of Simple Hydroxypyrimidines

	Solubility, parts water (20°)	Melting point
Unsubstituted	< 1	22.5°
2-Hydroxy-	2	180°
4-Hydroxy-	3	165°
5-Hydroxy-	"very sol."	211° (dec.)
2,4-Dihydroxy-	300	*ca.* 340° (dec.)
4,6-Dihydroxy-	400	300° (dec.)
4,5-Dihydroxy-		*ca.* 300° (dec.)
2,5-Dihydroxy-		
2,4,6-Trihydroxy-	150	*ca.* 246° (dec.)
2,4,5-Trihydroxy-		*ca.* 355° (dec.)
4,5,6-Trihydroxy-		
2,4,5,6-Tetrahydroxy-	"slightly sol."	*ca.* 215° (dec.)

The alkoxypyrimidines on the other hand are liquids or low melting solids, and have the expected solubilities according to the size of the alkoxy or aryloxy group. Thus the methoxy derivatives are highly soluble in water, and all the alkoxy derivatives soluble in organic solvents.

As has been mentioned in Chapter I, the 2-, 4-, and 6- "hydroxy" group (*e.g.* in LXVIII) is in tautomeric equilibrium with the oxo form (LXVIIIa) where the hydrogen has removed to a ring nitrogen atom. The position of this equilibrium in aqueous solution has been studied by ultraviolet spectra and ionization constants (as explained in Ch. XIII, Sect. 2.A), and so far all such "hydroxy" derivatives have been found to be almost entirely in the oxo form. To save confusion and to simplify nomenclature, it seems best to retain the name "hydroxy" whenever this form *could* be present, even if the experimental evidence points to the compound's being predominantly oxo in form. Infrared spectra give some idea of the equilibrium in the solid state or in solution in lipophilic solvents (Ch. XIII, Sect. 2.C). 5-Hydroxy groups are truly hydroxyl (or phenolic) in character. They are β- to the ring nitrogen atoms and therefore no tautomerism of the hydroxy–oxo type can take place. Moreover, even in water the ratio of zwitterionic form (LXVIIIb) to enol form (LXVIIIc) is very low.[193] They give colour reactions with ferric chloride.[130,168] Extranuclear hydroxy groups differ from 5-hydroxy groups only in that they are insulated from the aromatic ring and therefore have the hydroxyl character of an alcohol rather than that of a phenol. Excepted from this are those hydroxylphenyl derivatives of pyrimidines which naturally have phenolic properties by virtue of the phenyl entity. Ionization of the various hydroxy derivatives is treated in Chapter XIII, Sect. 1.B.


(LXVIII) (LXVIIIa) (LXVIIIb) (LXVIIIc)

6. Reactions of Hydroxypyrimidines

A. Conversion into Halogenopyrimidines

By far the most important reaction of a 2-, 4-, or 6-hydroxypyrimidine is its conversion into a halogenopyrimidine. This is normally done by heating with a phosphorus halide, often in the presence of dimethylaniline, and the processes have been already discussed in detail in Chapter VI, Sect. 1. Iodo groups cannot be thus introduced directly, but only *via* chloro or bromo derivatives. Hydroxy groups have not yet been successfully replaced by fluoro groups.

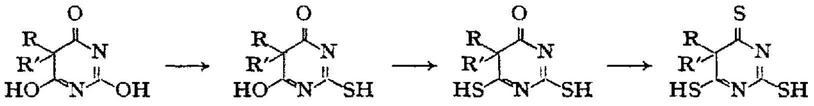
5-Hydroxy groups do not respond to treatment with phosphorus halides, and there is no general way of converting them into halogeno groups. Dialuric acid, however, gives tetrabromo- or tetrachloro-pyrimidine by heating with phosphorus pentahalide at 120°.[194]

Extranuclear hydroxy groups behave as alcohols and can be transformed to halogeno groups with phosphorus halides, thionyl chloride, or hydrogen bromide in acetic acid. Details and examples have been given in Chapter VI, Sect. 3.B.

B. Conversion into Mercaptopyrimidines

2-, 4-, and 6-(but not 5- or extranuclear) hydroxy groups can often be directly transformed into mercapto groups with phosphorus pentasulphide. Alternatively the change can be achieved indirectly *via* a chloro derivative.

The direct change of amide to thioamide with phosphorus pentasulphide is well known.[195] It was first applied to the cyclic amides of the pyrimidine series by Henze and Smith[196] who converted 5,5-diethyl- and 5-ethyl-5-phenyl- barbituric acid (LXIX) to their trithio analogues (LXXII) by refluxing with phosphorus trisulphide in tetralin. Carrington[197] expanded this study by thiating twelve similar barbituric acid derivatives with a mixture of phosphorus pentasulphide and alkali polysulphides. In boiling toluene 2-thio- and 2,4-dithio-barbiturates (LXX and LXXI) were formed, and in xylene the same dithio and 2,4,6-trithio derivatives (LXXI and LXXII) resulted. The presence of even one branched alkyl group in position 5 virtually halted thiation at the mono stage.



(LXIX) (LXX) (LXXI) (LXXII)

Elion and Hitchings[198] first applied the technique to simple pyrimidines, and as examples of its use may be quoted the conversion of 2,4-dihydroxy- or 4-hydroxy-2-mercapto-pyrimidine into 2,4-dimercaptopyrimidine[69,198*] in tetralin or xylene at 140–180°, of 4-hydroxy-2-mercapto-5 (or 6)-methylpyrimidine (LXXIII) into 2,4-dimercapto-5-(or 6)-methylpyrimidine (LXXIV) in tetralin[198,200,201] or xylene,[47] of 4-hydroxy-2-mercapto-6-phenylpyrimidine into 2,4-dimercapto-6-phenylpyrimidine,[198] and of 5-benzyluracil into 5-benzyl-2,4-dimercaptopyrimidine.[202] Thiation of barbituric acid and of 2,4-dihydroxy-5-nitropyrimidine was unsatisfactory,[198] and experience indicates that the presence of nitro or of amino groups often inhibits thiation. Exceptions[203,203a] include 5-amino-4-hydroxypyrimidine being converted into

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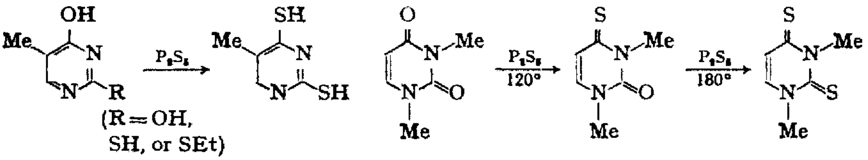
[*] The crude "dimercapto" compound made from uracil contains considerable amounts of 2-hydroxy-4-mercaptopyrimidine identified by amination to cytosine.[206]

5-amino-4-mercaptopyrimidine in reasonable yield.[203] Some non-tautomeric hydroxy groups have been shown, in the quinoline series for example, to resist thiation,[204] and 5-hydroxypyrimidines are likewise resistant. Further, 4,6-dihydroxypyrimidine in which only one hydroxy group can be tautomeric does not satisfactorily thiate under a variety of conditions.[205] Alkylthio groups which are present during thiation are converted into mercapto groups as in the preparation of 2,4-dimercapto-5-methylpyrimidine (LXXIV) from 2-ethylthio-4-hydroxy-5-methylpyrimidine[198] (LXXIII; R = SEt) and of 3-methyldithiouracil from 1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine.[47]

The last example indicates that oxo-groups can be thiated and several other cases are known: 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine (LXXV) at 120° gives 1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thiopyrimidine[198] (LXXVI), but at 180° is completely thiated to 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dithiopyrimidine[56] (LXXVII). 1 (and 3)-Methyluracil thiate at 180° in tetralin to give 1 (and 3)-methyldithiouracil,[47, 56] and 1,6(and 1,4)-dihydro-1-methyl-6 (and 4)-oxopyrimidine give their thio analogues by refluxing with phosphorus pentasulphide in pyridine.[206]

The use of pyridine as a solvent for thiation is further exemplified by the preparation from the corresponding hydroxy compounds of 4-mercapto-5-methoxypyrimidine,[123, 123a] 5-benzyloxy-4-mercaptopyrimidine,[123a] and 4-mercapto-5-methoxy-2-phenylpyrimidine,[123a] and by the formation of 2-hydroxy-4-mercaptopyrimidine by thiation in damp pyridine of 2-ethoxy-4-hydroxypyrimidine.[207] 1-Methyluracil is likewise thiated in pyridine to 1-methyl-4-thiouracil.[209]



(LXXIII) (LXXIV) (LXXV) (LXXVI) (LXXVII)

C. Other Reactions of Hydroxypyrimidines

Acylation of 2-, 4-, and 6-hydroxypyrimidines is normally unsuccessful, but uracil and thymine do in fact acetylate on the ring nitrogen atom at position 1.[210] The products, 1-acetyluracil (LXXVIII) and 1-acetylthymine, are very labile, function as powerful acetylating agents, and are rapidly hydrolysed in aqueous solution. Two acetylated derivatives of 4-hydroxypyrimidine, described in the nineteenth century as 4-acetoxy-6-methyl-2-phenylpyrimidine[210a] and 4-acetoxy-2,6-dibenzyl-5-phenylpyrimidine,[21] are likely in fact to have been *N*-acetyl derivatives. Acetylation of 4-hydroxypyrimidine gives an *N*-acetyldihydro-4-oxopyrimidine[124] distinct from authentic 4-acetoxypyrimidine prepared from the *N*-oxide.

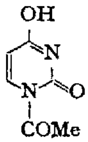
5-Hydroxypyrimidines form *O*-acetyl derivatives. 2,4,5-Trihydroxypyrimidine and its 6-methyl derivative, with acetic anhydride yield 5-acetoxy-2,4-dihydroxypyrimidine[109] (LXXIX) and its 6-methyl derivative.[211] Tetrahydroxypyrimidine yields 5-acetoxy-2,4,6-trihydroxypyrimidine,[212] 2,5-dihydroxy-4,6-dimethylpyrimidine gives 5-acetoxy-2-hydroxy-4,6-dimethylpyrimidine,[130] and 2-amino-4,5-dihydroxy-6-methylpyrimidine gives 2-acetamido-5-acetoxy-4-hydroxy-6-methylpyrimidine[130] with acetic anhydride, although benzoylation yields 2-amino-5-benzoyloxy-4-hydroxy-6-methylpyrimidine.[130] 5-Acetoxy derivatives have also been produced by abnormal reactions.[185, 213] Being alcohols, extranuclear hydroxypyrimidines should acylate, but most such acetoxy derivatives have been made from the halogenated analogues with silver acetate. Thus 4-chloromethyl- gives 4-acetoxymethyl- 2,6-dihydroxy-5-methylpyrimidine,[214, 215] 5-chloromethyl- gives 5-acetoxymethyl- 2,4-dihydroxy-6-methylpyrimidine,[151] and 5-bromomethyl- gives 5-acetoxymethyl- 4,6-dichloro-2-methylpyrimidine.[216] However, 2,4-dihydroxy-5-hydroxymethylpyrimidine has been converted directly into 5-acetoxymethyl- and 5-propionyloxymethyluracil by treatment with acetic or propionic acids containing a little hydrochloric acid.[152]

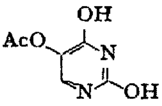
The conversion of hydroxypyrimidines into alkoxy derivatives has been discussed (Sect. 4.C), and into oxopyrimidines (by *N*-alkylation etc.) is treated in Chapter X, Sect. 1.A(3).

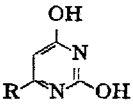
The direct removal of a hydroxy group is uncommon in pyrimidines, but 2-ethyl-4-hydroxy-6-methylpyrimidine when heated with zinc dust under distillation conditions gave 2-ethyl-4-methylpyrimidine.[217] Further, 2,4-dihydroxy-6-hydroxymethylpyrimidine (LXXX; $R{=}CH_2OH$) and its 5-methyl derivative, on treatment with hydriodic acid and red phosphorus gave respectively 2,4-dihydroxy-6-methylpyrimidine[218] (LXXX; R=Me) and the 5,6-dimethyl analogue.[214, 215] Reduction of 2,4-dihydroxy-5-hydroxymethyl-6-methylpyrimidine with tin and hydrochloric acid, like the 6-hydroxymethyl analogues, yields 2,4-dihydroxy-5,6-dimethylpyrimidine,[150] and hydrogenation of 2,4-dihydroxy-5-hydroxymethylpyrimidine over platinum yields 2,4-dihydroxy-5-methylpyrimidine in 95 % yield.[152] Although it is agreed that 6-hydroxymethyl groups are stable to hydrolysis, it has been reported[142,150] that 5-hydroxymethyl groups are removed hydrolytically. This has been shown to be incorrect.[152] Hydroxy groups are normally removed *via* chloro or mercapto derivatives.

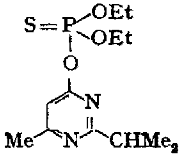
The condensation of *OO*-diethyl chlorothiophosphate [$Cl_3(S{:})P(OEt)_2$] with the alkali salt of 4-hydroxy-2-isopropyl-6-methylpyrimidine gives the powerful insecticide "Diazinon", or *OO*-diethyl *O*-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphorothioate (LXXXI). Related phosphoric esters were also made.[219,220]

The oxidation of (extranuclear) hydroxymethylpyrimidines to formyl- or carboxypyrimidines is treated in Chapter XI, Sects. 1.A(3) and 5.A(4).


(LXXVIII)


(LXXIX)


(LXXX)


(LXXXI)

7. Reactions of Alkoxy- and Aryloxy-pyrimidines

A. Hydrolysis to Hydroxypyrimidines

The ready hydrolysis of 2-, 4-, and 6-pyrimidine ethers has already been discussed in Section 1.E, the difficult hydrolysis of those in the 5-position in Section 2.B, and the indirect hydrolysis of extranuclear ethers *via* halogeno derivatives in Section 3.G.

B. Conversion into Halogeno Derivatives

Only extranuclear ethers may be converted in the corresponding halogeno compounds by fission with hydrochloric or hydrobromic acid (Ch. VI, Sect. 3.C).

C. Amination of Alkoxypyrimidines

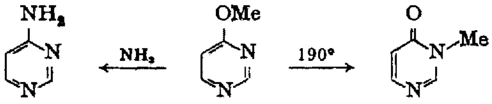
The 2-, 4-, or 6-pyrimidine ethers can be aminated to give aminopyrimidines, and they normally undergo this reaction rather less readily than the corresponding chloro compounds. It is possible that alkoxypyrimidines are sometimes transitory intermediates in the conversion of halogeno into aminopyrimidines when alcoholic amines are used. Indeed 2,4-(and 4,6)-dichloro-5-nitropyrimidine on very mild treatment at 0° with methanolic methylamine give respectively 2-methoxy-4-methylamino- and 4-methoxy-6-methylamino- 5-nitropyrimidine, and at 10° give entirely 2,4-(and 4,6)-bismethylamino-5-nitropyrimidine.[54] However, the methoxy "intermediates" do not in fact yield any bismethylamino derivatives even on attempted amination at 30°, so that two competing reactions must be postulated in this case.[54, 55]

4-Methoxypyrimidine (LXXXIII) has been aminated[186] to 4-aminopyrimidine (LXXXII) (isolated as 4-acetamidopyrimidine), and 1,2-dihydro-4-methoxy-1-methyl-2-oxopyrimidine with ammonia, methylamine, and dimethylamine gave respectively 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (1-methylcystosine)[186, 221] and the 4-methylamino and dimethylamino analogues.[186] Phenoxy groups can be replaced with difficulty as in the conversion of 2-*p*-chlorophenyl-4-methyl-6-phenoxypyrimidine into 2-*p*-chlorophenyl-4-diethylaminoethylamino-6-methylpyrimidine[222] in 30 % yield, or 4-methyl-2-phenoxy- into 2-hydrazino-4-methyl- pyrimidine.[223] In contrast to the last example, 2- and 4-methoxypyrimidine readily yield 2- and 4-hydrazinopyrimidine by refluxing with methanolic hydrazine hydrate,[224] and 4-ethoxy- similarly gives 4-hydrazino- 2-hydroxypyrimidine.[209]

Alkoxy groups, like chloro groups, are deactivated by the presence of hydroxy and amino groups. Despite this, successful preparations of cytosine and isocytosine have been based on the amination (120° for 8 hours) of 4-ethoxy-2-hydroxypyrimidine and 2-ethoxy-4-hydroxypyrimidine,[225] and although 2-amino-4-methoxypyrimidine will not aminate at 110°, at 200° it yields 2,4-diaminopyrimidine.[175] This temperature should be contrasted with the 110° required for aminations when the existing amino group is acylated, as in the conversion of 4-methoxy-2-sulphanilylaminopyrimidine into its 4-amino or 4-3′-diethylaminopropylamino analogues.[175] Similar conditions are adequate for the amination[226] of 2 (and 4)-ethoxy-4(and 2)-hydroxy-5-nitropyrimidine to 5-nitrocytosine and 5-nitroisocytosine; in these cases the deactivating effect of the hydroxy is counterbalanced by the activation caused by the nitro group.

D. Rearrangement of Alkoxypyrimidines

When some 2-, 4-, or 6-methoxypyrimidines are heated (particularly easily in the presence of methyl iodide), they rearrange to the oxopyrimidines, methylated on the ring nitrogen atom adjacent to the oxo group. Thus 4-methoxypyrimidine (LXXXIII) at 190° gave 1,6-dihydro-1-methyl-6-oxopyrimidine[65] (LXXXIV). Such rearrangements are dealt with fully in Chapter X, Sect. 1.A(4).



(LXXXII) (LXXXIII) (LXXXIV)

8. Some Naturally Occurring Hydroxypyrimidines

No attempt will be made to discuss the pyrimidine nucleosides and nucleotides, because this has been done in detail by experts in that field.

Thus the book of Levene and Bass[227] in 1931 forms the first great review of the subject, and the two volumes of Chargaff and Davidson[228] in 1955 the reference work. More recent reviews, which are more restricted in scope, have appeared.[229,230] and the Nobel Prize Lecture of Todd[231] is a fitting contribution from such a prominent name in the field. Less detailed introductions to the subject have appeared.[232,233]

The isolation from natural sources, synthesis and reactions of uracil, thymine, and vicine are, however, summarized below; similar treatment will be given later to cytosine, 5-methylcytosine, and 5-hydroxymethylcytosine (Ch. IX, Sects. 9.A,B, and C). The electronic structure of the natural pyrimidines has been discussed.[234,237a]

A. Uracil; 2,4-Dihydroxypyrimidine

Uracil was first isolated[235,236] by hydrolysis of herring sperm in 1900, and its structure proven by synthesis[237] in the following year. It has also been obtained from bovine thymus or spleen[236,238] and from wheat germ.[239]

Controlled hydrolysis of material containing the polymeric ribonucleic acid first gives the several nucleotides, phosphoric acid esters of uridine (1-β-*D*-ribofuranosido-uracil), known under various names such as uridylic acids a and b, and uridine monophosphate* etc. The next stage in hydrolysis is removal of the phosphate giving uridine itself, and finally this glycoside undergoes fission to uracil.

The best synthetic routes to uracil at present are the Principal Synthesis from formylacetic acid (made *in situ* from malic acid) and urea in fuming sulphuric acid,[4] or the treatment of the easily obtainable 2-thiouracil with chloroacetic acid followed by acid hydrolysis.[63,68]

Uracil is readily nitrated to 2,4-dihydroxy-5-nitropyrimidine,[68] converted into 2,4-dichloropyrimidine with phosphoryl chloride and dimethylaniline,[118,240] and methylated with dimethyl sulphate to 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine.[4] It gives with potassium chloroacetate 1-carboxymethyluracil,[241] and acetylation gives the labile 1-acetyluracil.[210] Oxidation by air or hydrogen peroxide in the presence of Fe^{++} yields urea,[242] as does also iodine in aqueous bicarbonate solution.[243] Iodine in sodium hydroxide, however, gives 2,4-dihydroxy-5-iodopyrimidine,[244] and other 5-halogenation and "dihalogenation" has been discussed in Chapter VI, Sect. 2.A. As early as 1923 hydrogenation in the presence of platinum was shown[245] to give a 5,6-dihydrouracil. The rather complicated Wheeler–Johnson colour test for uracil[246] although rather non-specific is sometimes useful. A good way of detecting uracil, thymine, and cytosine on paper chromatograms by spraying with phenol and sodium hypochlorite to give a bright blue spot has been described.[247]

Although it has been long known that the ultraviolet spectra of natural pyrimidines suffer profound changes on exposure to ultraviolet light,[248,249] it is only more recently that the precise nature of the changes has been investigated. It has been shown[250] that uracil (LXXXV) on irradiation in solution yields 4,5-dihydro-2,4,6-trihydroxypyrimidine (LXXXVI) in which H_2O has added across the 5,6 double bond of uracil. The product was also made by an independent synthesis, and treatment with acid reversed the process of hydration to yield

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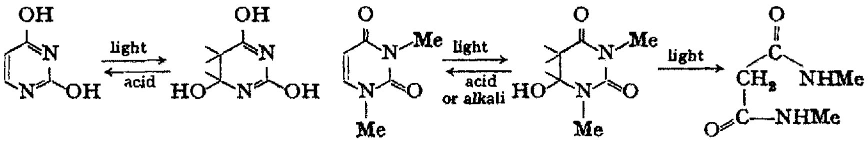
* Because of the confusion in meaning of these names to various types of chemist, it is best to indicate the position of attachment of the phosphate moiety by names such as uridine-5′-monophosphate.

uracil. This work with uracil was based on a similar and more detailed initial study[251,252] of 1,3-dimethyluracil (1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine) (LXXXVII) which is likewise hydrated on irradiation to hexahydro-4-hydroxy-1,3-dimethyl-2,6-dioxopyrimidine (LXXXVIII). The constitution of the latter was proven beyond doubt,[106,254] and its reconversion into 1,3-dimethyluracil by acid or alkaline treatment studied,[106] and it was shown[256] to ring-open irreversibly on further irradiation to give the bismethylamide of malonic acid (LXXXIX).

The whole subject of the photochemistry of nucleic acids and of simple pyrimidines has been carefully reviewed in English (with nearly 200 references) by Shugar and Wierzchowski,[257] and the subject is being actively pursued.[253,255,257a]



(LXXXV) (LXXXVI) (LXXXVII) (LXXXVIII) (LXXXIX)

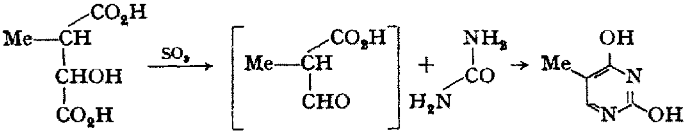
B. Thymine: 2,4-Dihydroxy-5-methylpyrimidine

Thymine was isolated in 1893, several years before uracil. Kossel and Neumann[258,259] obtained it from bovine thymus and spleen, and by the time it was first synthesized[237] in 1901 its structure was already virtually beyond doubt.[260–262] With exceptions,[263,265] thymine does not arise from ribonucleic acids, but from the deoxyribonucleic acids derived from a variety of sources. The hydrolysis of these is not as easily controlled as is that of ribonucleic acids, but the same general stages can be isolated. The nucleoside thymidine is 3-D-2′-deoxyribofuranosido-thymine, but whether α- or β-configuration at the glycosidic link is yet unknown.

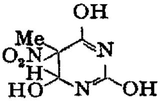
The best laboratory synthesis of thymine (XCI) is probably from β-methylmalic acid (XC) (or ester) with urea in sulphuric acid giving a 50 % yield.[264]

Having an occupied 5-position, thymine does not nitrate or halogenate normally. Fuming nitric acid, however, adds across the 5,6-double bond to give 4,5-dihydro-2,4,6-trihydroxy-5-methyl-5-nitropyrimidine[266,267] (XCII), and aqueous bromine in a similar way gives

5-bromo-4,5-dihydro-2,4,6-trihydroxy-5-methylpyrimidine.[268, 269] Phosphoryl chloride gives 2,4-dichloro-5-methylpyrimidine,[270] and methylation gives 1,3-dimethylthymine (1,2,3,4-tetrahydro-1,3,5-trimethyl-2,4-dioxypyrimidine).[271] Thymine undergoes oxidative ring-fission[248, 272] similarly to uracil, and a fairly specific colour test for thymine (or 5-methylcytosine) has been described.[273] Thymine is relatively unaffected by ultraviolet irradiation of its solution.[249]



(XC) (XCI)



(XCII)

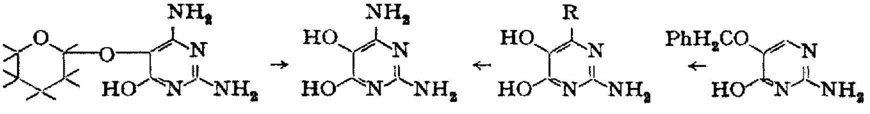
C. Divicine: 2,4-Diamino-5,6-dihydroxypyrimidine

Vicine was first isolated from the seeds of a vetch (*vicia sativa*) in 1870 by Ritthausen[274, 275] but only in 1896 did he realize[276] that it was the glycoside of a base, "divicine". Vicine was first considered[277] in 1911 as a pyrimidine glycoside, and in 1914 Johnson[278] suggested 4,5-diamino-2,6-dihydroxypyrimidine as the structure of divicine. In the same year Levene claimed[279, 280] that the structure was really 2,5-diamino-4,6-dihydroxypyrimidine, and there the matter rested, apparently solved,[281] for forty years. In 1953 Bendich and Clements published a monumental paper[168] which traces first a fully documented history of vicine and divicine, and then goes on to consider both the old structural evidence and new experimental findings. The conclusion is inescapable that divicine is in fact 2,4-diamino-5,6-dihydroxypyrimidine (XCIV) and that vicine is represented as its 5-β-D-glucopyranoside.

Two syntheses of divicine were achieved in 1956 by Bowman, Davoll and Laney,[128, 282] and by McOmie and Chesterfield.[123] The first of these[128] made use of a Common Synthesis from ethyl tetrahydropyran-2-yloxycyanocetate and guanidine, to give 2,4-diamino-6-hydroxy-5-tetrahydropyran-2′-yloxypyrimidine (XCIII), which on gentle acid hydrolysis gave divicine (XCIV). The second route[113, 123] made use of a Common Synthesis to get 2-amino-5-benzyloxy-4-hydroxypyrimidine (XCVI), which was converted into 2-amino-4,5-dihydroxypyrimidine (XCV; R = H); this nitrosated in position 6 to (XCV; R = NO) and the nitroso compound reduced to divicine (XCIV).

The divicine work has, among other things, led to a mass of data on colour reactions as applied to reducing pyrimidines. These[128,168] and related papers[127,283] should be consulted for details.

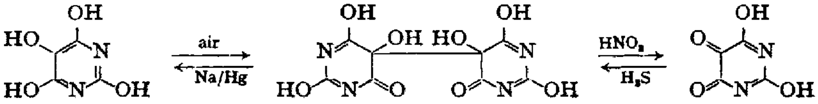
Another pyrimidine glycoside, "convicine", was also isolated at an early stage.[275,284] Its aglycone is probably 4-amino-2,5,6-trihydroxypyrimidine[284] and this has now been synthesized,[18,128] although no careful comparisons seem to have been made.


(XCIII) Divicine (XCIV) (XCV) (XCVI)

9. The Alloxan Group of Pyrimidines

The relationship of alloxan, alloxantin and dialuric acid, is best shown by their oxidative and reductive interconversion.

Gentle oxidation[285] of the true pyrimidine, dialuric acid (tetrahydroxypyrimidine; XCVII), yields alloxantin, generally formulated as (XCVIII), and more vigorous oxidation,[286] alloxan (5-oxobarbituric acid, mesoxalylurea, or hexahydrotetraoxopyrimidine; XCIX). The process can be reversed by reducing alloxan with hydrogen sulphide to alloxantin,[287] and thence with sodium amalgam[288] or directly with more hydrogen sulphide[117] or stannous chloride,[116,289] to dialuric acid. Alloxantin can also be made by mixing equal parts of alloxan and dialuric acid in water.[117] The redox potentials of the system have been studied.[290]

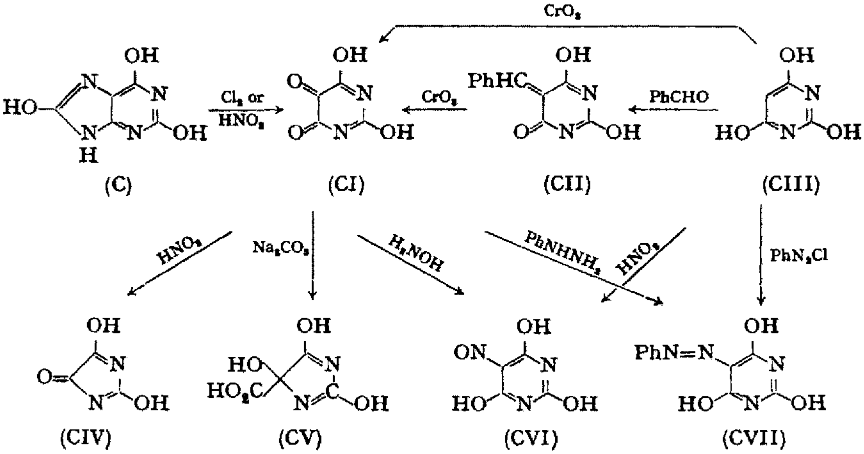

(XCVII) Dialuric acid (XCVIII) Alloxantin (XCIX) Alloxan

A. Alloxan

The preparation of alloxan by Brugnatelli[291,292] in 1818 was the first pyrimidine synthesis. He oxidized uric acid with nitric acid, chlorine, or iodine, and the preparation was modified later by Wöhler and Liebig[115] to give good yields. In 1845 Schlieper[293] performed the oxidation with chlorine, generated *in situ* from potassium chlorate and hydrochloric acid; the solution of alloxan was reduced to the less soluble alloxantin, which was isolated and oxidized back to alloxan. This forms the basis of one modern process of preparation,[286, 287] but in others the alloxan is isolated directly after the initial oxidation.[116, 294] Alloxan (CI) can be conveniently made by the direct oxidation of uric acid (C) with chlorine,[295, 296] of barbituric acid (CIII) with chromium trioxide,[297] or of 5-benzylidenebarbituric acid[298] (CII).

Alloxan crystallizes as a tetrahydrate from water, but also forms other hydrates and alcoholates. Spontaneous explosive decomposition of old specimens was recorded in the mid-nineteenth century[299–302] and the phenomenon was rediscovered* in 1910 by Wheeler[303] and by others.[304–306] Oxidation with nitric acid gives parabanic acid[307] (CIV) with loss of carbon dioxide, and hydrolysis gives alloxanic acid[293, 307] (probably[308] CV) which hydrolyses further to aliphatic products.[309]

Being ketonic in the 5-position, alloxan forms a sodium bisulphite complex,[310] an oxime[311–313] which is the same substance as the violuric acid (CVI) obtained by nitrosating barbituric acid,[314] a phenylhydrazone[315, 316] (CVII) which can also be prepared from barbituric acid (CIII) by coupling with diazotized aniline,[317] and a derivative with semicarbazide.[318]



Alloxan reacts with two molecules of benzene in concentrated sulphuric acid to give 5,5-diphenylbarbituric acid[296] (CIX), which cannot be made by the obvious Principal Synthesis[319] owing to the

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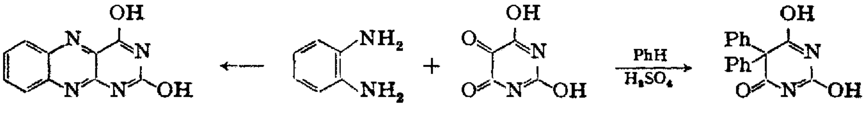
* The four delightful notes begotten of this rediscovery should not be missed by any student of humanism in chemistry.

lability of the required intermediate, diethyl diphenylmalonate.[320] With *o*-diaminobenzene, alloxan yields alloxazine[321, 322] (CVIII), and its reactions with mono-amines, phenols, ketones, and other reagents, are dealt with in the review by Whiteley and Thorpe.[323] The diabetic condition produced by administration of alloxan is of great interest,[324, 325] and the removal of zinc may be implicated in the destruction of the beta cells of Langerhan's islets which is the mechanism of diabetogenesis.[326, 327]

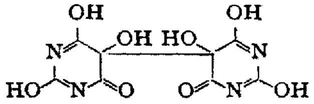


(CVIII) (CIX)

B. Alloxantin

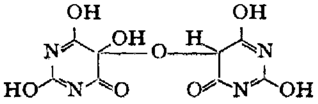
Despite a great deal of work, the structure of alloxantin is still uncertain. Early work[184, 328–333] seems to have finally narrowed the field to two possibilities, the pinacol form (CX) and the hemiacetal form (CXI). Although the opinion of more recent workers is still divided,[294, 334–336] the rather authoritative statement of Moubasher and Othman[336] that "the pinacol formula (CX) has to be accepted" seems probably correct.

Alloxantin is made by the partial reductions of alloxan with hydrogen sulphide.[287] Alternatively, equimolar quantities of dialuric acid and alloxan in water[116, 117] give alloxantin which crystallizes out, being only 0.3 % soluble in water at 25°. An aqueous solution of alloxantin is about 80 % dissociated into alloxan and dialuric acid.[332] It forms an acetyl[212] and a benzoyl[212] derivative, and many alkylated homologues are known.[337] Redox measurements have been recorded.[338, 339] Treatment with methylamine gives 2,4,6-trihydroxy-5-methylaminopyrimidine.[340]



(CX)

or

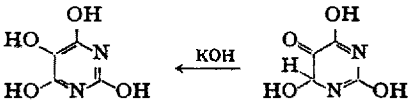


(CXI)

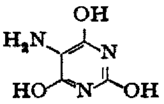
C. Dialuric Acid and Isodialuric Acid

Dialuric acid (CXII) (tetrahydroxypyrimidine) has normally been made by reduction of alloxan with stannous chloride[116] or hydrogen sulphide.[117] More recently it has been made by a Common Synthesis from dimethyl tetrahydropyran-2-yloxymalonate and urea with hydrolysis of the resulting 5-ether.[128] It is a strong acid ($\mathrm{p}K_a$ 3.15) and is easily oxidized to alloxantin or alloxan. Amino analogues of dialuric acid include uramil (5-amino-2,4,6-trihydroxypyrimidine; CXIV) made by reduction of 5-nitrobarbituric acid with tin and hydrochloric acid,[341] and also isouramil (4-amino-2,5,6-trihydroxypyrimidine; CXV). The latter is probably the aglycone of convicine, and was synthesized from ethyl tetrahydropyran-2-yloxycyanoacetate and urea with subsequent hydrolysis,[128] and also by less direct means.[18]

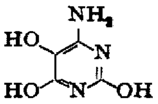
Isodialuric acid (from 2,4,5-trihydroxypyrimidine and bromine water[109]) has been formulated as (CXIII) on the grounds that it is isomeric with dialuric acid, is converted into it by treatment with alkali,[285] and gives an oxime, a methyl ether, and a phenylhydrazone.[185, 342] If (CXIII) really represents isodialuric acid, it must be considered simply as an extraordinarily stable tautomer of dialuric acid (CXII). Isodialuric acid is said to be one step in the Wheeler–Johnson colour test for uracil and cytosine.[247]



(CXII) (CXIII)



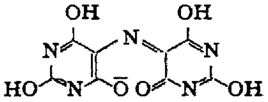
(CXIV)
Uramil



(CXV)
Isouramil

D. Murexide and Purpuric Acid

Murexide is the ammonium salt of purpuric acid.[343] It was first made in 1819 by the oxidation of uric acid followed by treatment with ammonia[115, 344] and virtually by the same process when alloxantin is treated with ammonium acetate in acetic acid.[345] Murexide is currently formulated[335] as (CXVI), based on older work.[328, 343, 346] The well-known murexide reaction[347] for detecting uric acid and other purines is simply a crudely executed preparation of murexide.



(CXVI)

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CHAPTER VIII

Sulphur-containing Pyrimidines

The sulphur-containing pyrimidines are a closely knit family. Thus the parent mercapto derivative (RSH) may be alkylated to a thio ether (alkylthio derivative; RSR′) which may be oxidized to a sulphone (alkylsulphonyl derivative; RSO_2R'). The parent may also be oxidized directly through sulphide (RSR) or disulphide (RSSR) to a sulphinic acid (sulphino derivative; RSO_2H), and finally to a sulphonic acid (sulpho derivative; RSO_3H). Consideration of the thiocyanato (RSC:N), isothiocyanato (RN:C:S), and derived thioureido ($RNHC(:S)NH_2$) compounds is deferred to Chapter XI, and the ring-*N* alkylated dihydrothiopyrimidines are treated with *O*- and *N*- analogues in Chapter X.

1. The Mercaptopyrimidines

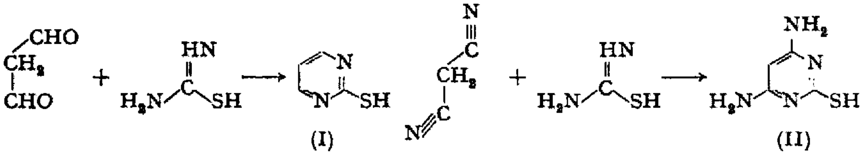
A. Preparation of 2-, 4-, and 6-Mercaptopyrimidines

Many examples of all the chief methods of preparing 2-, 4-, and 6-mercaptopyrimidines have already been given. Here follows a brief summary of each method with cross references.

(1) *By the Principal Synthesis*

Many 2-mercaptopyrimidines may be directly made by the Principal Synthesis using thiourea as the one-carbon fragment, but the use of dithio esters (or possibly monothio esters) as par tof the three-carbon fragment in order to introduce 4- or 6-mercapto groups, is almost entirely unexplored.

The simplest example of a 2-mercapto derivative is furnished by the condensation of thiourea with malondialdehyde (as diacetal) to give 2-mercaptopyrimidine[1] (I), and many other examples will be found with all types of three-carbon fragments in Chapter II. Indeed thiourea is probably the most successful one-carbon fragment used in the Common Synthesis. It reacts readily even when urea is unreactive. Thus with malononitrile no product is obtained with urea, but with thiourea 4,6-diamino-2-mercaptopyrimidine (II) is formed in good yield and can be converted into the missing hydroxy analogue.[2]



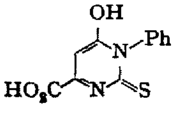
(I) (II)

(2) *By Other Primary Syntheses*

The Shaw synthesis (Ch. III, Sect. 2.E) can give certain 2-mercaptopyrimidines among which are 5-cyano-1-methyl-2-thiouracil,[3] 5-methyl-1-propyl-2-thiouracil,[4] 3-phenyl-2-thio-orotic acid[5] (III), 2-thiouridine,[6] and 1-methyl-2-thiouracil[7] (IV). This gentle synthesis is particularly useful when labile groups are required as in a molecule such as thiouridine.

Other primary syntheses lead to 6-methyl-3-phenyl-2-thiouracil[6a] and 3,6-dimethyl-2-thiouracil[8] (Ch. III, Sect. 2.A), to 5,5-diethyl-2-thiobarbituric acid[9] (from diethylmalondiamide and carbon bisulphide), and to 5-amino-2,4-dihydroxy-6-mercaptopyrimidine (VI) by fission of uric acid (V) at 100° with ammonium sulphide.[10,11]

Attempts to use malondithioamide in a Remfry–Hull synthesis with ethyl formate to give 4,6-dimercaptopyrimidine have failed,[12] but the compound has been obtained indirectly.[13]



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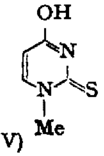

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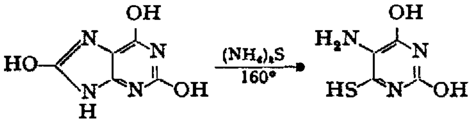


(V) (VI)

(3) *From Chloropyrimidines*

2-, 4-, and 6-Mercaptopyrimidines may be prepared from the corresponding chloropyrimidines by treatment with sodium hydrogen sulphide, or with thiourea followed if necessary by alkaline hydrolysis of the thiouronium salt formed. 2-Chloropyrimidine has been converted into 2-mercaptopyrimidine by both methods giving 30% yield by the first[14] and 50% by the second,[15] but these figures cannot be taken as a general comparison of the methods which are quite comparable in utility. They are discussed fully in Chapter VI, Sect. 5.G.

(4) *From Hydroxypyrimidines*

The direct thiation of 2-, 4-, or 6-hydroxypyrimidines with phosphorus pentasulphide is generally successful when nitro and amino groups are absent but occasionally[16,39a] with an amino group present. A good example is the preparation of 2,4-dimercaptopyrimidine (IX) from 4-hydroxy-2-mercaptopyrimidine[17,18] (VIII) or from 2,4-dihydroxypyrimidine.[17,19] The thiation reaction is fully treated in Chapter VII, Sect. 6.B.

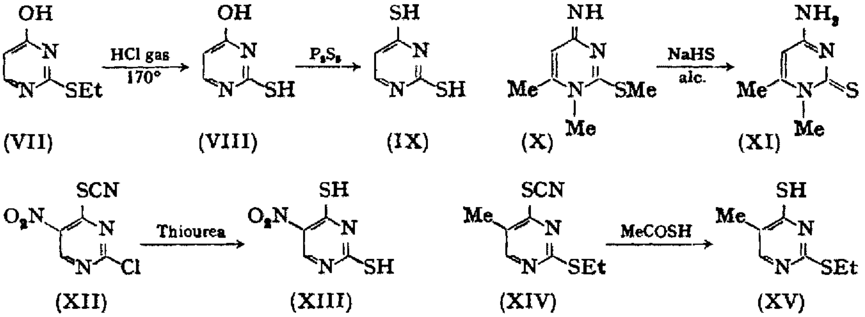
(5) *From Alkylthiopyrimidines*

An alkylthio can be changed to a mercapto group by phosphorus pentasulphide as in the preparation of 2,4-dimercapto-5-methylpyrimidine from 2-ethylthio-4-hydroxy-5-methylpyrimidine,[17] and of 3-methyldithiouracil from 1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine.[20] Another way is to split such thio ethers by treatment of the molten compound with hydrogen chloride. At 170° in this way 2-ethylthio-4-hydroxypyrimidine (VII) and its 4-mercapto analogue gave respectively 4-hydroxy-2-mercaptopyrimidine (VIII) and 2,4-dimercaptopyrimidine.[21] The method proved unsatisfactory when applied to 5-halogenated thiouracils in which the mercapto group had been protected by alkyl groups during halogenation. Anhydrous hydrogen iodide in glacial acetic acid, however, proved effective, and by such means[22] 5-chloro-4-hydroxy-2-methylthiopyrimidine and its ethylthio homologue and their 6-methyl derivatives were split in good yield to 5-chloro-4-hydroxy-2-mercaptopyrimidine and its 6-methyl derivative. Similarly were prepared 5-bromo-4-hydroxy-2-mercaptopyrimidine, 4-hydroxy-5-iodo-2-mercaptopyrimidine, and their 6-methyl derivatives.[22] The above iodo compounds were in fact prepared from their benzylthio ethers, and although the method was satisfactory on a small scale, the use of aluminium bromide in toluene was later reported[23, 24] superior for large-scale preparations of 5-iodo-2-thiouracil. 4-Amino-6-benzylthio-5-formamidopyrimidine is elegantly debenzylated by sodium in liquid ammonia.[25]

The peculiar transformation of 1,4-dihydro-4-imino-1,6-dimethyl-2-methylthiopyrimidine (X) into 4-amino-1,2-dihydro-1,6-dimethyl-2-thiopyrimidine (XI) has been reported[26] to proceed in alcoholic sodium hydrogen sulphide on the water bath.

(6) *From Thiocyanatopyrimidines*

A thiocyanatopyrimidine has been shown to react with aqueous thiourea to yield the corresponding mercapto derivative, as in the case of 2-chloro-5-nitro-4-thiocyanatopyrimidine (XII) passing to 2,4-dimercapto-5-nitropyrimidine[27] (XIII). When the analogous 2-amino (and anilino)-5-nitro-4-thiocyanatopyrimidine were treated with sodium ethoxide in ethanol, two products were obtained in each case: these were the expected 2-amino(and anilino)-4-ethoxy-5-nitropyrimidine and also 2-amino(and anilino)-4-mercapto-5-nitropyrimidine. Other conversions from thiocyanato into mercapto pyrimidines have been done with thioacetic or thiobenzoic acids generally at 100°. In this way, from their 4-thiocyanato analogues, *e.g.* (XIV), were made 2-ethylthio-4-mercapto-5-methylpyrimidine[28] (XV), its 6-methyl derivative,[29] its 5-phenyl analogue,[30] its 6-phenyl analogue,[31] and its 5-bromo analogue.[28]



(7) *From Aminopyrimidines*

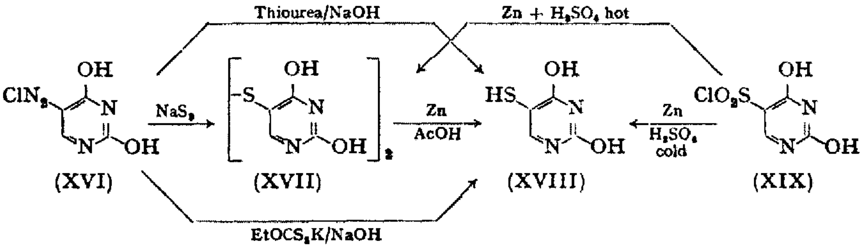
The preparation of 5-*p*-chlorophenyl-4-ethyl-2,6-dimercaptopyrimidine by the action of phosphorus pentasulphide in tetralin at 190° on either 2-amino-5-*p*-chlorophenyl-4-ethyl-4,5-dihydro-6-hydroxypyrimidine or 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine has been reported.[32] This points to a possible new general use of the thiation technique. Alcoholic hydrogen sulphide at 150° converts 6-amino-5,5-diethyluracil into 5,5-diethyl-4-thiobarbituric acid.[33]

(8) *By Direct Introduction*

When 2-chloro-4-methylamino-5-nitropyrimidine is treated with hot aqueous sodium hydrogen sulphide, not only the expected 5-amino-2-mercapto-4-methylaminopyrimidine was isolated, but also the less soluble 5-amino-2,4-dimercapto-6-methylaminopyrimidine, in which a mercapto group had been introduced into the 4-position directly.[34] It is possible that such introductions are not unusual in these commonly used conditions of reaction, but the dimercapto derivatives being rather insoluble may be thrown away in the sulphur debris from the reaction.

B. Preparation of 5-Mercaptopyrimidines

There are only a few 5-mercaptopyrimidines known. Diazotization of 5-amino-2,4-dihydroxypyrimidine to (XVI) and treatment with thiourea gave a thiouronium salt which by alkaline hydrolysis in nitrogen gave 13 % of 2,4-dihydroxy-5-mercaptopyrimidine[35] (XVIII). Alternatively, treatment of the diazo solution with sodium disulphide gave the dipyrimidinyl disulphide (XVII) which was reduced with zinc dust in glacial acetic acid to give 25 % of the mercapto compound[36]



(XVIII). In a third method, the diazotized aminouracil (XVI) was treated with potassium ethyl xanthate and the product hydrolysed in alkali to yield 22 % of 5-mercaptouracil.[35]

Difficulties were experienced at first with the zinc reduction of 4-amino-5-chlorosulphonyl-2,6-dihydroxypyrimidine to 4-amino-2,6-

dihydroxy-5-mercaptopyrimidine and of 5-chlorosulphonyl-2,4-dihydroxypyrimidine (XIX) to 5-mercaptouracil[36] (XVIII). They were overcome, however, at least in the latter case, and the mercapto compound was finally obtained in good yield by reducing with an excess of zinc in cool dilute sulphuric acid.[37] When less zinc was used in warm solution, the disulphide (XVII) was formed.[37] Overall processes of chlorosulphonation followed by reduction have been described to give 25% of mercapto compound or 41% of disulphide as required.[37] 5-Mercaptouracil has anti-tumour activity.[38]

C. Preparation of Extranuclear Mercaptopyrimidines

This type of pyrimidine is represented by two examples. An attempt to prepare 4-amino-5-mercaptomethyl-2-methylpyrimidine from 4-amino-5-chloromethyl-2-methylpyrimidine with thiourea gave the corresponding sulphide, but the thiol was obtained[39] by alkaline degradation of the pyrimido-*m*-thiazine derivative (XX). 4-Chloromethyl-2,6-dihydroxy-5-phenoxypyrimidine on boiling with potassium thiocyanate in alcohol yields the 4-mercaptomethyl analogue.[40]

(XX)

D. Reactions of 2-, 4-, and 6-Mercaptopyrimidines

Despite the fact that the investigated cases of mercaptopyrimidines have proved to be almost entirely thione in structure when in aqueous solution,[41,42] they naturally undergo reactions to be expected of mercaptans, as well as of thioamides.

(1) *Removal of Mercapto Groups*

Mercapto groups may be replaced by hydrogen ("desulphurized") either by boiling a solution with Raney-nickel catalyst or by oxidation (generally with hydrogen peroxide) to a sulphonic or sulphinic acid followed by hydrolysis.

The nickel process is of comparatively recent origin and the first example in the pyrimidine series[43] seems to be the desulphurization in

1945 of 4,5-diamino-6-hydroxy-2-mercaptopyrimidine (XXI; R=SH) to give 4,5-diamino-6-hydroxypyrimidine (XXI; R=H). Since that time the process has become of immense importance. The normal technique is to dissolve completely one part of the mercaptopyrimidine in hot dilute ammonia, add about four parts of wet Raney nickel catalyst and boil for one hour. Water, alcohol, and other solvents, have been used especially with thio ethers, but generally they are less satisfactory with mercaptans. Although the quality of Raney nickel is important in this reaction,[44, 45, 46] it is generally convenient because of the large quantities involved, to use a quickly prepared grade[18] rather than the laboriously prepared types sometimes used for catalytic hydrogenations. Table XIII indicates some of the desulphurizations carried out with Raney nickel; naturally most of them involve removal of a mercapto group from the 2-position where it was placed by any primary synthesis. In order to keep all such reactions together, the table also includes examples of desulphurization of thio ethers. In this regard, better yields are almost invariably obtained by desulphurizing a mercapto compound than from the corresponding alkylthio derivative. Further, 2-mercaptopyrimidines are generally desulphurized in better yield than are 4-mercapto derivatives, and since it has been reported[47] that 2-hydroxy-4-mercaptopyrimidine and 1-methyl-4-thiouracil with Raney nickel give respectively "trimethylene urea" (XXII) and its *N*-methyl derivative, in this nuclear reduction may lie the reason for poor yields.

2-Hydroxypyrimidine and 1,2-dihydro-1-methyl-2-oxopyrimidine are easily reduced under similar conditions by Raney nickel to (XXII) and *N*-methyl-(XXII), but 4-hydroxypyrimidines are stable. It has therefore been inferred[47] that the 4-desulphurizations proceed normally, and when 2-hydroxypyrimidines are formed they are then reduced further. This is upheld by u.v.-spectral changes during such reactions. Whether this explanation can be applied to cases where 2-hydroxypyrimidines are not formed awaits experimental evidence. Several authors[1,48] have previously raised the question of whether nuclear reduction occurs during desulphurizations.

5,5-Dialkyl (or aryl)-2-thiobarbituric acids, *e.g.* (XXIII), desulphurize abnormally to give dihydropyrimidines such as 5-ethyl-2,5-dihydro-4,6-dihydroxy-5-phenylpyrimidine,[49] (XXIV) and indeed thiobarbituric acid itself has been reported to give a dihydro-4,6-dihydroxypyrimidine.[50] 5-Phenyl-2-thiobarbituric acid, however, behaves normally to give 4,6-dihydroxy-5-phenylpyrimidine,[49] while 1,3-diphenyl-2-thiobarbituric acid gives hexahydro-4,6-dioxo-1,3-diphenylpyrimidine.[50]

TABLE XIII. Some Raney nickel Desulphurizations

Pyrimidine produced	Derivative desulphurized	Yield (%)	References
Unsubstituted	2-SH	25[a]	1, 48
	2,4-diSH	17	48
	2-SCH$_2$CO$_2$H	14	1
	5-Br-2-SMe	38	51
4-Acetamido-1,6-dihydro-1-methyl-6-oxo-	2-SMe	*ca.* 70	52
4-Acetamido-6-methoxy-	2-SMe	*ca.* 35	52
4-Amino-	2-SH	61	18
5-Amino-	2-SMe-5-NO$_2$	75	15
4-Amino-5-carboxy-	2-SH[b]	47	53
5-Amino-4-chloro-	6-SH	*ca.* 30	16
2-Amino-5-*p*-chlorophenyl-4-ethyl-	6-SMe	—	32
4-Amino-5-*p*-chlorophenyl-6-ethyl-	2-SMe	—	32
4-Amino-5-*ββ*-diethoxyethyl-6-hydroxy-[k]	2-SH	75	54
4-Amino-6-diethylamino-5-formamido-	2-SMe	86	56
4-Amino-1,6-dihydro-1,5-dimethyl-6-oxo-	2-SMe	*ca.* 30	52
4-Amino-3,6-dihydro-3,5-dimethyl-6-oxo-	2-SH	*ca.* 70	52
4-Amino-1,6-dihydro-1-methyl-6-oxo-	2-SMe	*ca.* 50	52
4-Amino-3,6-dihydro-3-methyl-6-oxo-[c]	2-SH	*ca.* 50	52
5-Amino-4,6-dihydroxy-	2-SH-5-NO	56	55
2-Amino-4-hydroxy-	6-SH	80	57
4-Amino-6-hydroxy-	2-SH	16	58
		87	18
		60	52
5-Amino-4-hydroxy-	2-SEt	*ca.* 50	59
4-Amino-6-methoxy-	2-SMe	*ca.* 40	52
4-Amino-5-methylamino-	2-SMe	*ca.* 40	60
5-Amino-4-methylamino-	6-SMe	25	34
2-Amino-4,5-trimethylene-	6-SH	55	61
4-Amylamino-	2-SH	67	62
4-*p*-Anisidino-	2-SCH$_2$CO$_2$H	good	62
5-Benzamido-4-hydroxy-	2-SMe	—	59
5-Benzyl-4,6-dihydroxy-	2-SH	69	63
5-Benzyloxy-	4-SH	42	64
5-Benzyloxy-4-hydroxy-	2-SH	62	64
4-t-Butyl-6-hydroxy-	2-SH	97	65
4-Carboxy-[d]	5-Br-2-SMe	47	51
5-Carboxy-4-hydroxy-	5-CO$_2$Et-2-SH	14	66
4-Diacetylamino-1,6-dihydro-1,5-dimethyl-6-oxo-	2-SMe	*ca.* 40	52
4,5-Diamino-	2-SH	65	67
4,6-Diamino-	2-SH	24	58
		87	18
4,5-Diamino-2-butyl-	2-SH	87	68
4,6-Diamino-5-*β*,*β*-diethoxyethyl-[k]	2-SH	70	54

(Table continued)

TABLE XIII *(continued)*

Pyrimidine produced	Derivative desulphurized	Yield (%)	References
4,5-Diamino-1,6-dihydro-1-methyl-6-oxo	2-SMe	*ca.* 45	68a
4,5-Diamino-6-hydroxy-	2-SH	76	69
		ca. 90	43
4,5-Diamino-2-methyl-	6-SH	80	70
4,5-Diamino-6-methyl-	2-SH	82	70
4-Diethoxymethyl-6-hydroxy-	2-SH	77; 90	71, 73
1,4-Dihydro-4-imino-1,6-dimethyl-[h]	2-SH	—	26
1,4-Dihydro-1-methyl-4-oxo-	2-SMe	57	72
1,6-Dihydro-1-methyl-6-oxo-	2-SMe	34	26, 72
4,6-Dihydroxy-5-isoamyl-	2-SH	58	63
4,6-Dimethyl-	2-SH	55[e]	1, 48
	2-SMe	—	1
4-Dimethylamino-	2-SH	50	74
5-Ethyl-4,6-dihydroxy-	2-SH	37	63
4-Hydroxy-	2-SH	30	75
		82	18
5-Hydroxy-4,6-dimethyl-	2-SH	25	64
4-Hydroxy-5-β-hydroxyethyl-6-methyl-	2-SH	82	76
	2-SMe	68	76
	2-SEt	70	76
4-Hydroxy-5-methoxy-	2-SH	70	64, 78
4-Hydroxy-5-methyl-	2-SH	*ca.* 80	52, 77
4-Hydroxy-6-methyl-	2-SH	93	45, 80, 77
	2-SMe	25	45, 81, 77
	di-SCH_2Ph[i]	48	79
4-Hydroxy-6-methyl-5-piperidinomethyl-	2-SMe	10–61[f]	45
	2-SH	83	45
4-Hydroxy-6-phenyl-	2-SH	*ca.* 40	77
5-Methoxy-	4-SH	42	78, 64
5-Methoxy-2-phenyl-	4-SH	47	64
4-Methyl-	2-SH	20	1
4-Methyl-6-phenyl-	2-SH	—	82
4-Methyl-6-piperidino-	2-SH	65	62
4-Methylamino-	2-SH	54	74
5-Phenyl-	2-SH	—	82
4,5,6-Triamino-	2-SH	78	83
4,5-Trimethylene-	6-SH	58[g]	61

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[a] Hydrogen peroxide gave a better yield.[1]

[b] 5-Ethoxycarbonyl- analogue as starting material.

[c] Rearranged during reaction to 4-hydroxy-6-methylamino-pyrimidine.[1a]

[d] Isolated as nickel salt.

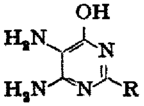
[e] Best desulphurized in aqueous alcoholic hydrochloric acid.

[f] Ordinary Raney nickel gave 10%, an active grade[46] gave 61%.

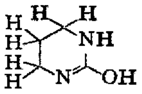
[g] Isolated as picrate.

[h] Product isolated as hydriodide. Starting material 4-amino-1,2-dihydro-1,6-dimethyl-2-thiopyrimidine.

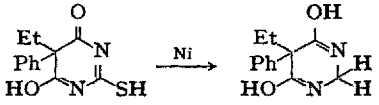
Oxidative removal of sulphur-containing groups is an old process which gives very variable results. Except where the scale of an operation demands a cheap reagent, it is now preferable to remove mercapto groups with Raney nickel. Desulphurization *via* isolated sulpho- and sulphino-pyrimidines is treated in Section 4.B.



(XXI)



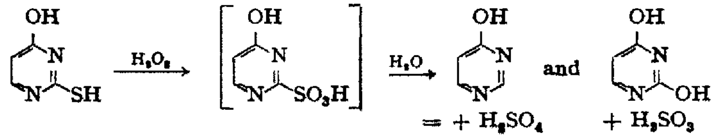
(XXII)



(XXIII) (XXIV)

The action of alkaline hydrogen peroxide on a mercaptopyrimidine may remove the sulphur in favour of hydrogen or in favour of a hydroxy group. The reactions may occur simultaneously and in this way 4-hydroxy-2-mercaptopyrimidine (XXV) gives 40% yield of 4-hydroxypyrimidine (XXVI) plus 44% yield of 2,4-dihydroxypyrimidine[84] (XXVII). Desulphurization alone has been recorded in the preparation of unsubstituted pyrimidine,[1] of 4-hydroxy-5(and 6)-methylpyrimidine,[85] of 4-hydroxy-5,6-dimethylpyrimidine,[85] of 4-ethoxymethyl-6-hydroxy-5-methylpyrimidine,[86] and of 5-β-ethoxyethyl-4-ethyl-6-hydroxypyrimidine,[87] all from their 2-mercapto derivatives. On the other hand, replacement by a hydroxy group alone has been recorded in the cases of 4-amyl-6-hydroxy-2-mercaptopyrimidine to 4-amyl-2,6-dihydroxypyrimidine,[88] and 4-diethoxymethyl-6-hydroxy-2-mercaptopyrimidine to 4-diethoxymethyl-2,6-dihydroxypyrimidine,[89] and the other cases in Chapter VII, Sect. 1.F(2).

Although nitric acid oxidation has resulted in desulphurization in the purine series,[90] the normal reaction with mercaptopyrimidines is replacement by a hydroxy group (Ch. VII, Sect. 1.F(2)) as, for example, in the conversion of 4-ethyl-6-hydroxy-2-mercaptopyrimidine into 4-ethyl-2,6-dihydroxypyrimidine.[91]



(XXV) (XXVI) (XXVII)

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[j] Starting material 2-benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine.

[k] And two analogous compounds.[54]

(2) *Alkylation of Mercaptopyrimidines*

Alkylation of mercaptopyrimidines invariably proceeds quickly and easily to give an S-alkyl derivative. Any possible *O*- or *N*-alkylation of the molecule is always less ready and hence easily avoided.[39a]

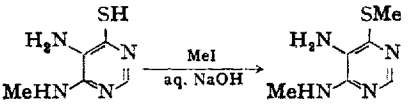
Many mercaptopyrimidines, *e.g.* (XXVIII), can be methylated by dissolving in N-sodium hydroxide (1.1 mol.), adding methyl iodide (1.1 mol.) and shaking at room temperature when the *S*-alkylthio-derivative precipitates if insoluble in water. In this way for example were prepared 4,5-diamino-2(and 6)-methylthiopyrimidine,[70,92] and 5-amino-4-methylamino-6-methylthiopyrimidine.[34] Dimethyl sulphate can be used rather similarly as in the preparation of 2-methylthiopyrimidine,[93] its 4,6-dimethyl derivative,[1] 4,6-dihydroxy-5-isopropyl-2-methylthiopyrimidine,[94] and 5-carboxy-4-hydroxy-2-methylthiopyrimidine.[66] Methylation with methyl iodide in methanolic sodium methoxide is represented by the formation of 4-hydroxy-2-methyl-6-methylthiopyrimidine,[95] and 4-hydroxy-5-methyl-2-methylthiopyrimidine,[96] as well as in the older literature.[21,97–99]

The usual procedures for methylation give poor results with 4-hydroxy-2-mercaptopyrimidine and its 6-methyl derivative. Use of molecular proportions of methylating agents gives a very poor yield;[100] two moles give about 25 %, and three moles give largely *SN*-dimethylated derivatives.[100] However, by using methyl iodide in aqueous alcoholic sodium hydroxide first at 30° and then at 60°, a 63 % yield of 4-hydroxy-2-methylthiopyrimidine[22] was attained, and 90 % of its 6-methyl derivative.[22]

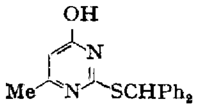
Although no simple cases are recorded, there is an indication that 2,4-dimercaptopyrimidines may preferentially methylate in the 4-position. Thus 5,5-diethyl-2,4,6-trithiobarbituric acid on treatment in aqueous alkali with dimethyl sulphate gave only 5,5-diethyl-6-methylthio-2,4-dithiouracil, the structure of which was shown by acid hydrolysis (with loss of methanthiol) to 5,5-diethyl-2,4-dithiobarbituric acid.[101]

S-Alkylations other than methylations are not quite so ready, and are generally done in alcoholic sodium alkoxide with alkyl halide. They are typified by ethylations leading to 4-amino-2-ethylthiopyrimidine,[102] to 2-ethylthio-4-hydroxypyrimidine,[21,22,103] to its 6-methyl[22,100,104] and other alkyl derivatives,[29,104–107] to 2-ethylthio-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine,[76] to 5-ethoxy-2-ethylthiopyrimidine[108] (XXIX), to 4-diethoxymethyl-2-ethylthio-6-hydroxypyrimidine,[109] and to 5-amino-2-chloro-4-ethylthiopyrimidine.[110] Other similar alkylations include as products 2-allylthio-4-hydroxy-6-methylpyrimidine,[111] 2-benzylthio-4-formyl-6-hydroxypyrimidine,[112] 2-benzylthio-4-hydroxypyrimidine,[21] 4-amino-2-benzylthio-6-hydroxypyrimidine,[56] other benzylthio derivatives,[100,105,113] 4-(2,4-dinitrophenylthio)-2,6-dimethoxypyrimidine,[114] and 2-diphenylmethylthio-4-hydroxy-6-methylpyrimidine[105] (XXX). The anomalous *N*-benzylation and *N*-methylation of 4-carboxy-6-hydroxy-2-mercaptopyrimidine, reported by Bachstez,[165] was later shown[112] to be imaginary, the products being in fact 2-benzylthio-4-carboxy-6-hydroxypyrimidine and its methylthio analogue. 5-Amino-4,6-dimercaptopyrimidine can easily be mono-*S*-benzylated.[116]

S-Alkylation by using chloroacetic acid is common because the resulting carboxymethylthio derivative is easily hydrolysed to hydroxy (Ch. VII, Sect. 1.F(1)) or replaced by an amino group.[62] For the latter process, isolation is necessary and this can be assured by boiling the mercapto compound in 1 equivalent of aqueous sodium hydroxide or carbonate, with chloroacetic acid: the sodium hydroxide can often be omitted, especially in the presence of amino groups which stabilize the derivative towards hydrolysis. The preparation of such derivatives is exemplified in the following 2-carboxymethylthiopyrimidines: unsubstituted,[1] 4-amino,[117] 4,6-diamino,[2] 4-amino-5(and6-)-methyl,[62,117] 4-benzylamino,[62] 4-anilino and analogues,[62] all made without alkali present, and also the following made in the presence of alkali: 4-methyl,[1] 4,6-dimethyl,[48] 4,6-dihydroxy,[45] 4-hydroxy (as ethyl ester by using ethyl chloroacetate),[21] 4-hydroxy-6-methyl-5-propyl (as ethyl ester),[118] 5-phenylazo (as methyl ester)[119] and 4-hydroxy-6-propyl.*[120] The condensation of diethyl bromomalonate with 4-amino-6-hydroxy-2-mercaptopyrimidine in aqueous alkali gives 4-amino-2-diethoxycarbonylmethylthio-6-hydroxypyrimidine.[121] Exceptionally, 2-carboxy-



(XXVIII) (XXIX)



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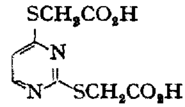

(XXXI)

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* This 2-carboxymethylthiopyrimidine was also made by an interesting Principal Synthesis from *S*-carboxymethylthiourea and ethyl butyrylacetate in aqueous alkali.[123,124]

methylthio - 5 - ethoxypyrimidine[108] and 2,4 - biscarboxymethylthiopyrimidine[21] (XXXI) are stable enough to be made without alkali present.

Although selenylpyrimidines have not been methylated, 6-selenylpurine on treatment in aqueous sodium hydroxide with methyl iodide gives 6-methylselenopurine.[122]

(3) *Mercapto- to Hydroxy-pyrimidines*

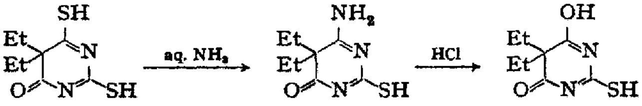
This important transformation has been discussed in detail in Chapter VII. Sect 1.F.

(4) *Mercapto- to Chloro-pyrimidines*

The direct conversion of mercaptopyrimidines into their corresponding chloro analogues is almost unknown, but 2,4-dichloropyrimidine has been reported as prepared in *ca.* 50% yield by the action of phosphorus pentachloride on 4-hydroxy-2-mercaptopyrimidine.[125] Repetition of this work has revealed[75] that under normal conditions (bath at 120° for one hour) the only product is almost certainly di(4-chloropyrimidin-2-yl) disulphide, but at 110° for 20 minutes about 30% of 2,4-dichloropyrimidine is indeed formed. It is much better made from 2,4-dihydroxypyrimidine,[18, 126] and this indicates the most general route from mercapto- to chloro-pyrimidine *via* a hydroxypyrimidine.

(5) *Mercapto- to Amino-pyrimidines*

The preparation of amidines from thioamides is a well-known reaction, but it was applied to the mercaptopyrimidines only in 1944. In that year, Carrington recorded[101] the amination of 5,5-diethyl-2,4-dithiobarbituric acid (XXXII) to 6-amino-5,5-diethyl-2-thiouracil



(XXXII) (XXXIII) (XXXIV)

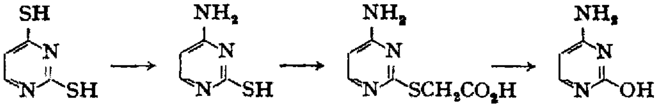
(XXXIII) which was identified by acid hydrolysis to 5,5-diethyl-2-thiobarbituric acid (XXXIV). Similarly 5,5-diethyl-2,4,6-trithiobarbituric acid gave 6-amino-5,5-diethyl-2,4-dithiouracil.[101]

The logical development of the above reaction by Hitchings, Elion, Falco, and Russell, followed. They showed[102] that a 2,4-dimercaptopyrimidine could be aminated subject to certain steric factors. Furthermore, with ammonia or amines it gave only a 4-amino-2-mercaptopyrimidine, no isomer, and scarcely ever any diamine. Thus with a free 5-position, 2,4-dimercaptopyrimidine reacted with ammonia, primary aliphatic or aromatic amines, secondary cyclic amines, and those secondary aliphatic or aromatic amines in which one alkyl group was methyl. 6-Substituents did not interfere, but 5-substituents precluded reaction with all secondary amines and with a few bulky primary amines.

Examples are furnished by the preparation (in good yield) from 2,4-dimercaptopyrimidine (XXXV) with aqueous amine generally at *ca.* 100°, of the following derivatives of 2-mercaptopyrimidine: 4-amino[117] (XXXVI), 4-methylamino,[74,102] 4-benzylamino,[102] 4-piperidino,[102] 4-dimethylamino,[74,102] 4-anilino,[102] 4-*N*-methylanilino,[102] but not[102] 4-diethylamino or diphenylamino even at 180°. Similarly from 2,4-dimercapto-6-methylpyrimidine were prepared 4-amino, 4-piperidino, and 4-anilino derivatives of 2-mercapto-6-methylpyrimidine.[102] 2,4-Dimercapto-5-methylpyrimidine aminated similarly to give 4-amino(and anilino)-2-mercapto-5-methylpyrimidine[102] but did not react with piperidine or dimethylamine. Some 20 more positive and negative cases are recorded.[102] 1-Methyl-4-thiouracil is aminated easily at 120° to give 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (1-methylcytosine).[127]

In 5-amino-2,4-dimercaptopyrimidine, the 4-mercapto group is so deactivated by the amino group that no amination occurs even under vigorous conditions;[128] conversely, 2,4-dimercapto-5-nitropyrimidine with methylamine under very mild conditions produced 2,4-bismethylamino-5-nitropyrimidine[128] but no monoaminated product. Exceptionally, 5-*p*-chlorophenyl-4-ethyl-2,6-dimercaptopyrimidine on amination gives a separable mixture of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine and the expected 4-amino isomer.[32] These last cases and the production of 2,4-diamino-6-methylpyrimidine (25% yield) from 2,4-dimercapto-6-methylpyrimidine under forcing conditions,[102] are the only examples of the direct amination of 2-mercapto groups known. They can normally be aminated only after *S*-alkylation (Sect. 2.C(3)).

The utility of the above preferential 4-amination is shown in the useful synthesis of cytosine (XXXVIII) from 2,4-dimercaptopyrimidine (XXXV), *via* 4-amino-2-mercaptopyrimidine (XXXVI) and 4-amino-2-carboxymethylthiopyrimidine[18,117] (XXXVII).



(XXXV) (XXXVI) (XXXVII) (XXXVIII)

(6) *Acylation of Mercaptopyrimidines*

S-Acylation of mercaptopyrimidines has been rather neglected. It is represented by the benzoylation, under Schotten–Baumann conditions, of 2-amino-4-mercapto-6-methylpyrimidine to 2-amino-4-benzoylthio-6-methylpyrimidine (the *S*-acylation of which was confirmed by its insolubility in alkali[129]), and by the acetylation of 5-amino-2,4-dimercapto- to 5-acetamido-2,4-diacetylthiopyrimidine.[130]

(7) *Oxidation of Mercaptopyrimidines*

The 2-, 4-, and 6-mercaptopyrimidines, unlike the 5-isomers, are stable in air. Their oxidation to disulphides and sulphonic acids is treated in Sections 3.A and 3.B.

E. Reactions of 5- and Extranuclear Mercaptopyrimidines

Apart from ready oxidation, no reactions seem to be recorded for 5-mercaptopyrimidines. 4-Amino-5-mercaptomethyl-2-methylpyrimidine diacetylates to 4-acetamido-5-acetylthiomethyl-2-methylpyrimidine.[39] The oxidation of both types of mercaptan is treated in Sections 3.A and 3.B

2. The Thioethers: Alkylthio- and Arylthio-pyrimidines

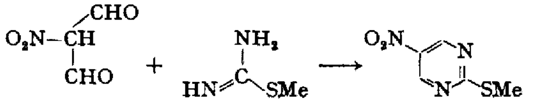
Although the dipyrimidinyl sulphides belong in this class, they are treated with the disulphides in Section 3.

A. Preparation of 2-, 4-, and 6- Alkylthiopyrimidines

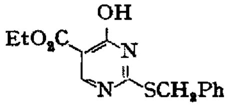
The three ways of making these alkylthiopyrimidines have already been discussed, but here follows a summary of the methods.

(1) *By the Principal Synthesis*

Syntheses of the common type may be used to make a variety of 2-alkylthiopyrimidine. Thus, for example, *S*-methylthiourea with nitromalondialdehyde (XXXIX) gives 2-methylthio-5-nitropyrimidine[15] (XL), with acetylacetone it gives 4,6-dimethyl-2-methylthiopyrimidine,[99] and with ethyl α-formylpropionate it gives 4-hydroxy-5-methyl-2-methylthiopyrimidine.[131] Other *S*-alkyl-thioureas are equally effective as exemplified in the preparation of 2-benzylthio-5-ethoxycarbonyl-4-hydroxypyrimidine[132, 133] (XLI), 2-ethylthio-4-hydroxy-5,6-dimethylpyrimidine,[81, 131] 5-benzyloxy-2-ethylthio-4,6-dihydroxypyrimidine,[134] and 4-amino-5-cyano-2-ethylthiopyrimidine.[135] Further Common Syntheses with an *S*-alkylthiourea and almost all the possible types of three-carbon fragment will be found in Chapter II.



(XXXIX) (XL)



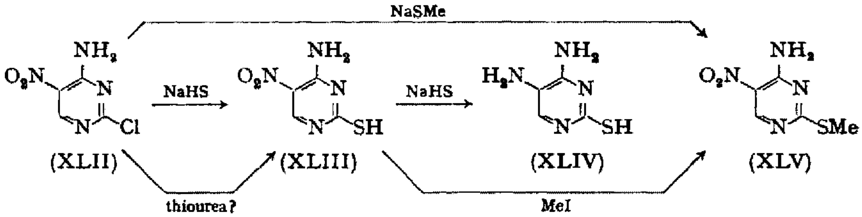
(XLI)

(2) *By Alkylation of Mercaptopyrimidines*

This is the most used way of making the thioethers and it has been discussed fully in Section 1.D(2).

(3) *From Chloropyrimidines*

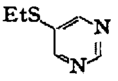
It is occasionally useful to prepare an alkylthiopyrimidine directly from a chloropyrimidine with sodium alkylmercaptide, without passing through a mercaptopyrimidine. Thus in the conversion of 4-amino-2-



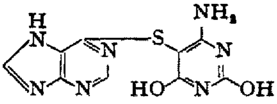
chloro-5-nitropyrimidine (XLII) into 4-amino-2-methylthio-5-nitropyrimidine (XLV), the usual route through treatment with sodium hydrogen sulphide to give the mercapto compound (XLIII), followed by methylation, is precluded by the unwanted reduction[67,136] of the nitro group to give (XLIV). Thiourea could possibly be used to make the mercapto compound in two stages, but in any case the complete conversion can be safely done with methanolic sodium methyl mercaptide in a few minutes.[92] Other examples of the metathesis are quoted in Chapter VI, Sect. 5.F.

B. Preparation of 5-Alkylthiopyrimidines

The simple 5-ethylthiopyrimidine (XLVI) has been made in 60% yield by the action of ethanolic sodium ethyl mercaptide on 5-bromopyrimidine.[137] The only other example is at the opposite extreme of complexity: 4-amino-5-bromo-2,6-dihydroxypyrimidine on treatment with 6-mercaptopurine gives a small amount of 4-amino-2,6-dihydroxy-5-purin-6′-ylthiopyrimidine[138] (XLVII).



(XLVI)



(XLVII)

C. Reactions of Alkylthiopyrimidines

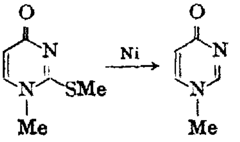
The 2-, 4-, and 6- thioethers have a lability towards hydrolysis, amination, and reductive removal, intermediate between that of the corresponding chloro and mercapto analogues. Very little is recorded about 5-thioethers, but they would be expected to be more stable in these respects.

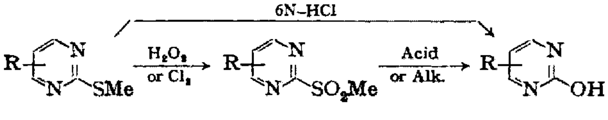
(1) *Reductive Removal of Alkylthio Groups*

Alkylthio groups can be removed from pyrimidines by boiling in water or alcohol with Raney-nickel catalyst. Unlike mercapto-group removal, no ammonia or base is used, rather more nickel is usually required (6 parts perhaps), and yields are generally rather lower. Typical examples are the conversion of 1,4-dihydro-1-methyl-2-methylthio-4-oxopyrimidine (XLVIII) into 1,4-dihydro-1-methyl-4-oxopyrimidine (XLIX) in 57% yield,[72] the desulphurization of 4-hydroxy-6-methyl-2-methylthiopyrimidine in 25% yield[45,81] (*cf.* 93% from 2-mercapto analogue[45,80]) and the preparation of pyrimidine (14 %) from 2-carboxymethylthiopyrimidine.[1] Other examples will be found in Table XIII.

(2) *Alkylthio- to Hydroxy-pyrimidines*

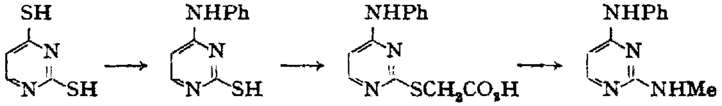
This metathesis of (L) to (LII) can be done by direct acid hydrolysis or indirectly by oxidation to a sulphone (LI) followed by acid or alkaline hydrolysis. The methods are discussed respectively in Chapter VII, Sects. I.F(1) and (3).


(XLVIII) (XLIX)


(L) (LI) (LII)

(3) *Amination of Alkylthiopyrimidines*

Mercapto groups can be replaced by amino groups only when they occupy the 4- or 6-position, but alkylthio groups even in position 2 undergo amination fairly readily. This was utilized, for example, in converting 2,4-dimercaptopyrimidine into a series of 2,4-bis (substituted amino) pyrimidines.[62] 2,4-Dimercaptopyrimidine (LIII), for instance, was aminated to 4-anilino-2-mercaptopyrimidine[102] (LIV), this converted with aqueous chloroacetic acid to 4-anilino-2-carboxymethylthiopyrimidine[102] (LV) and this aminated at 150° with aqueous methylamine to give 4-anilino-2-methylaminopyrimidine[62] (LVI). Other amines similarly prepared through 2-carboxymethylthio intermediates are exemplified in 2-amino-4-anilino-, 2-amino-4-piperidino-


(LIII) (LIV) (LV) (LVI)

and 4-anilino-2-benzylamino- pyrimidine.[62] The preparation of 2-hydrazino-5-phenylazopyrimidine from 2-methoxycarbonylmethylthio-5-phenylazopyrimidine and aqueous-alcoholic hydrazine is analogous.[119]

The amination of methylthio- and ethylthio-pyrimidines has a large literature which is full of apparent anomalies. Any analysis of the situation from the literature can but be subjective, and the reaction needs a new, simple, systematic, and extensive experimental study. Meanwhile, the following treatment will give an idea of the scope of the reaction as a preparative procedure. 4-Chloro-2-ethylthiopyrimidine (LVIII) reacts with ammonia at 115° to give 85% of 4-amino-2-ethylthiopyrimidine[139] (LVII), but at 190° the ethylthio group is also replaced yielding 2,4-diaminopyrimidine[140] (LIX). With aqueous methylamine,[141] the first stage goes at 50°, and 2,4-bismethylaminopyrimidine is formed at 150°. Similarly 4-amino-6-chloro-2-methylthiopyrimidine with aniline at 100° gives only the 6-anilino analogue, but at 150° 4-amino-2,6-dianilinopyrimidine is formed;[140] in the same case ammonia seems to require 220° to form 2,4,6-triaminopyrimidine.[99] 2-Ethylthio-4-hydroxypyrimidine reacts with *N*-methylaniline at 100° to give 75% of 4-hydroxy-2-*N*-methylanilinopyrimidine,[142] and 5-bromo-2-ethylthio-4-hydroxypyrimidine gives at 100° with aniline the 2-anilino-5-bromo-4-hydroxypyrimidine.[143] The presence of a 4-hydroxy group *seems* rather strangely to activate a 2-methylthio group towards amination. Thus 4-hydroxy-6-methyl-2-methylthiopyrimidine and aniline at 130° give *ca.* 60% of 2-anilino-4-hydroxy-6-methylpyrimidine, but 4,6-dimethyl-2-methylthiopyrimidine and aniline require 180° to yield 10% of 2-anilino-4,6-dimethylpyrimidine.[144] 4-Hydroxy-5,6-dimethyl-2-methylthiopyrimidine and β-diethylaminoethylamine at 160° gave 98% of 2-β-diethylaminoethylamino-4-hydroxy-5,6-dimethylpyrimidine, but 4-amino-5,6-dimethyl-2-methylthiopyrimidine and the same amine give 4-amino-2-β-diethylaminoethylamino-5,6-dimethylpyrimidine in only 10% yield even at 200°.[145] Deletion of the 5-methyl group makes little difference.[146] Comparison of the results of amination of 2-hydroxy-4-methyl-6-methylthio-[146] and 4-hydroxy-6-methyl-2-methylthio- pyrimidine[147] with aromatic amines indicates that the methylthio group shows comparable activity in these positions. 5-Ethoxycarbonyl-4-methyl-2-methylthiopyrimidine has been readily aminated at 115° with several alcoholic primary amines to give for example 2-amino-, 2-ethylamino-, and 2-benzylamino-,* 5-ethoxycarbonyl-4-methylpyrimidine.[148] On the other hand secondary amines such as dimethylamine and piperidine, and hindered (?) primary

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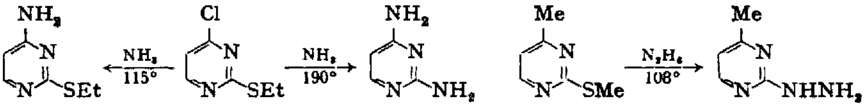
* The benzylamino derivative has also been made[152] by an interesting Common Synthesis from ethyl ethoxymethyleneacetoacetate, *S*-methylthiourea and benzylamine in aqueous alkali.

amines such as isopropylamine and aniline, "did not react even at a higher temperature".[148] The related derivative, 4-chloro-5-ethoxycarbonyl-2-ethylthiopyrimidine with alcoholic ammonia at 170° gives 2,4-diamino-5-ethoxycarbonylpyrimidine,[149] and 4-carboxy-2-ethylthio-6-hydroxy-5-methylpyrimidine gives with aqueous methylamine at 140°, 4-carboxy-6-hydroxy-5-methyl-2-methylaminopyrimidine.[150] Simple cases are exemplified in the formation of 2-benzylaminopyrimidine.[151] Hydrazines and alkyl hydrazines readily replace alkylthio groups, as in (LX), to give for example 2-hydrazino-4-methyl (LXI)-, 2-hydrazino-4-hydroxy-6-methyl-, 4-hydroxy-6-methyl-2-methylhydrazino-, 4-hydroxy-6-methyl-2-phenylhydrazino-, and 1,6-dihydro-2-hydrazino-1,4-dimethyl-6-oxo- pyrimidine,[96] as well as 2-hydrazino-4-hydroxypyrimidine.[149] Gentle treatment of 4-chloro- (or methoxy)-6-methyl-2-methylthiopyrimidine, gave 4-hydrazino-6-methyl-2-methylthiopyrimidine, and more vigorous conditions the 2,4-dihydrazino-6-methylpyrimidine.[96] 5-Ethoxycarbonyl-4-methyl-2-methylthiopyrimidine reacted with hydrazine to give the 2-hydrazino analogue, but with phenylhydrazine no reaction took place.[148]



(LVII) (LVIII) (LIX) (LX) (LXI)

(4) *Alkylthio- to Mercapto-pyrimidines*

The change, which can be done with phosphorus pentasulphide or by acidic ether cleavage, has been discussed in Section 1.A(5).

(5) *Oxidation of Alkylthiopyrimidines*

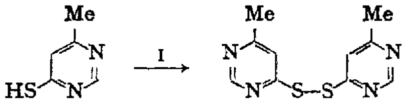
The oxidation of thio ethers to sulphones is found in Section 5.A.

3. Dipyrimidinyl Disulphides and Sulphides

A. Preparation

2-, 4-, and 6- Mercaptopyrimidines do not normally oxidize in air, but 5- and extranuclear types do so.

When 4-mercapto-6-methylpyrimidine (LXII) in aqueous alkali is treated with iodine in potassium iodide solution, di(4-methylpyrimidin-6-yl) disulphide (LXIII) is formed.[129] Similarly 4-hydroxy-2-mercaptopyrimidine and 2-hydroxy-4-mercaptopyrimidine give respectively di(4-hydroxypyrimidin-2-yl) and di(2-hydroxypyrimidin-4-yl) disulphides. The reactions also proceeded in pH 6.8 buffer.[153] "4-Thiouridine disulphide" and "4-thiothymidine disulphide" were made similarly.[127] Hydrogen peroxide has also been used to effect such oxidations as in the formation of di(2,4-dimethoxypyrimidin-6-yl) disulphide in 73% yield.[114] When poor quality dioxane was used as a solvent in the above reaction there was sufficient organic peroxide present for the oxidation without addition of hydrogen peroxide.[114] Di(4-chloropyrimidin-2-yl) disulphide has been made from thiouracil and phosphorus pentachloride[75] (Sect.1.D(4)).

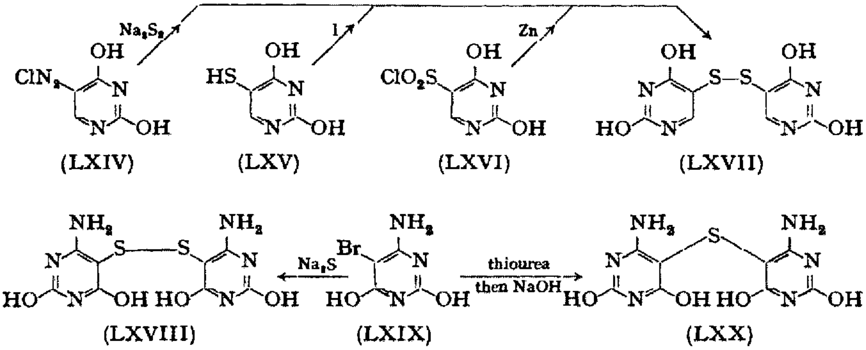


(LXII) (LXIII)

When 2-amino-4-hydroxy-6-phenyl-5-thiocyanatopyrimidine is allowed to stand in aqueous sodium hydroxide at room temperature, a quantitative yield of di(2-amino-4-hydroxy-6-phenylpyrimidin-5-yl) disulphide results,[154] and other cases are known.[155]

Diazotized 5-amino-2,4-dihydroxypyrimidine (LXIV) and alkaline sodium disulphide give 40% of di(2,4-dihydroxypyrimidin-5-yl) disulphide[35] (LXVII), and the same compound can be obtained by iodine oxidation of 2,4-dihydroxy-5-mercaptopyrimidine[35] (LXV), or in 82% yield by controlled zinc/sulphuric acid reduction of 5-chlorosulphonyl-2,4-dihydroxypyrimidine[36, 37] (LXVI). Di(4-amino-2,6-dihydroxypyrimidin-5-yl) disulphide (LXVIII) has also been made, albeit unsatisfactorily, by reduction of a 5-chlorosulphonyl derivative,[36] but it is more easily made in good yield by refluxing 4-amino-5-bromo-2,4-dihydroxypyrimidine (LXIX) with aqueous sodium disulphide.[138] This last method has also been used to prepare di(6-amino-1-methyluracil-5-yl) disulphide. Treatment of 5-bromo-2,4,6-trihydroxypyrimidine (or even 5,5-dibromobarbituric acid) with thiourea gave 5-amidinothio-2,4,6-trihydroxypyrimidine which on alkaline hydrolysis yielded di(2,4,6-trihydroxypyrimidin-5-yl) disulphide,[36] but attempted application of the reaction to 4-amino-5-bromo-2,6-dihydroxypyrimidine

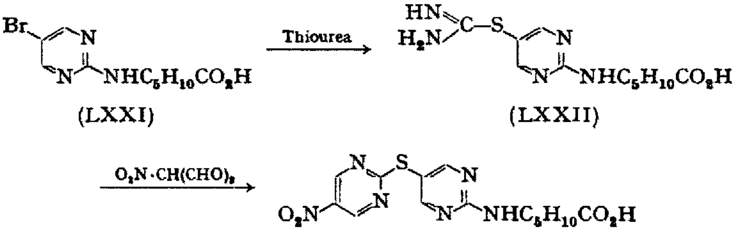
(LXIX) gave not the disulphide (LXVIII) but di(4-amino-2,6-dihydroxypyrimidin-5-yl) sulphide[36] (LXX). Similar formation of monosulphides has been reported in thecase of di(2-amino-4-methylpyrimidin-6-yl) sulphide,[156] and in other heterocyclic series.[157–160]



(LXIV) (LXV) (LXVI) (LXVII)

(LXVIII) (LXIX) (LXX)

An interesting Common Synthesis of an unsymmetrical sulphide is furnished by the condensation of 5-bromo-2-carboxyamylaminopyrimidine (LXXI) with thiourea to give the 5-amidinothio analogue (LXXII) which was then condensed with nitromalondialdehyde to give 2-carboxyamylamino-5-(5-nitropyrimidin-2-yl)thiopyrimidine[161] (LXXIII). Another example is given in Chapter XI, Sect. 5.A(2).

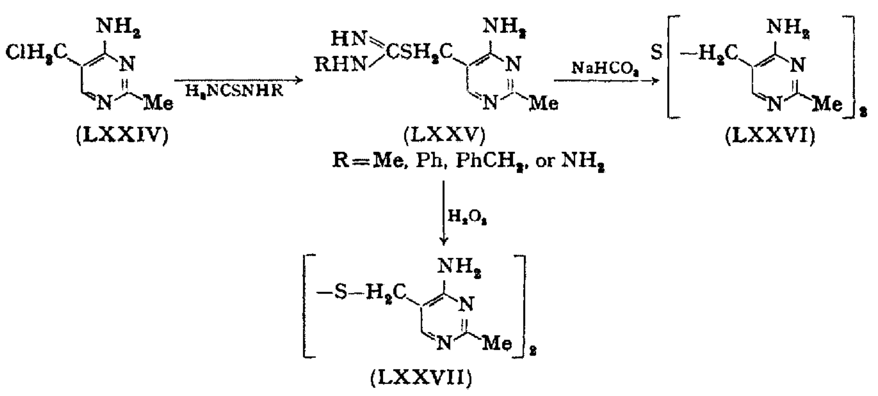


(LXXI) (LXXII)

(LXXIII)

Extranuclear sulphides and disulphides are represented[162,163] by di(4-amino-2-methylpyrimidin-5-ylmethyl) sulphide (LXXVI) and disulphide (LXXVII). 4-Amino-5-chloromethyl-2-methylpyrimidine (LXXIV) was condensed with *N*-methyl-, phenyl-, or benzyl-thiourea to give *e.g.* 4-amino-2-methyl-5-methylamidinothiomethylpyrimidine salt (LXXV; R=Me) (or homologue). All of these on neutralizing with sodium bicarbonate and boiling, deposited the same sulphide (LXXVI).

On the other hand, treatment of an alkaline solution of (LXXV) with hydrogen peroxide gave the disulphide (LXXVII). The use of thiosemicarbazide in place of a thiourea was equally effective in producing (*via* LXXV; $R{=}NH_2$) the sulphide and disulphide.[162] Di(4-amino-2,6-dimethylpyrimidin-5-ylmethyl) sulphide and disulphide have also been made by similar routes using thiourea itself in the initial condensation.[164] Di(4-amino-2-methylthiopyrimidin-5-ylmethyl) disulphide was made similarly.[163]



(LXXIV) (LXXV) (LXXVI)

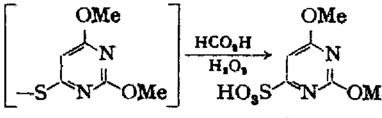
$R{=}Me$, Ph, $PhCH_2$, or NH_2

(LXXVII)

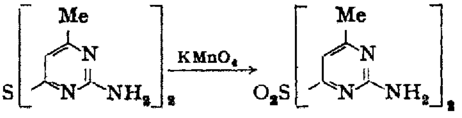
B. Reactions

Disulphides are oxidized to sulphonic acids, and sulphides to dipyrimidinyl sulphones. Thus di(2,4-dimethoxypyrimidin-6-yl) disulphide (LXXVIII) on treatment in formic acid with hydrogen peroxide gives 78 % of 2,4-dimethoxy-6-sulphopyrimidine[114] (LXXIX), and similarly, di(4-amino-2,6-dimethylpyrimidin-5-ylmethyl) disulphide gives 4-amino-2,6-dimethyl-5-sulphomethylpyrimidine.[39] Oxidation of sulphides is exemplified in the treatment of di(2-amino-4-methylpyrimidin-6-yl) sulphide (LXXX) with acid permanganate to give the corresponding sulphone[156] (LXXXI), and by the peroxide treatment of 2-carboxyamylamino-5-(5-nitropyrimidin-2-yl)thiopyrimidine to give the corresponding pyrimidinylsulphonylpyrimidine.[161]

Reduction of a disulphide gives the parent mercaptopyrimidine as shown in the reactions of di(2,4-dimethoxypyrimidin-6-yl) disulphide with lithium aluminium hydride to give 75 % of 4-mercapto-2,6-dimethoxypyrimidine,[114] of di(4-hydroxypyrimidin-2-yl) disulphide with sodium hydrogen sulphite (at pH 9) to give 4-hydroxy-2-mercaptopyrimidine,[153] and of di(2,4-dihydroxypyrimidin-5-yl) disulphide with zinc and acetic acid to give 63% of 2,4-dihydroxy-5-mercaptopyrimidine.[35]



(LXXVIII) (LXXIX)



(LXXX) (LXXXI)

4. Pyrimidine Sulphonic Acids and Related Compounds

A. Preparation

Although many pyrimidine sulphonic acids must have been made and immediately hydrolysed during the oxidative removal of mercapto groups with hydrogen peroxide (Sect.1.D(1)), only a relative few have been isolated. Moreover most of these have been made by non-oxidative methods, although several oxidations of disulphide to sulphonic acid have been given above (Sect. 3.B).

Several sulphonyl chlorides have been prepared by the direct oxidation[165] of mercaptopyrimidines by chlorine at 0–5°. In this way were obtained 2-chlorosulphonylpyrimidine, its 4,6-dimethyl derivative, and its 5-chloro derivative.[14] They were converted into the corresponding sulphonamides with liquid ammonia.[14]

Some halogenopyrimidines have been converted directly into sulphonic acids with sodium sulphite. Thus 2-chloropyrimidine (LXXXII) and boiling aqueous sodium sulphite gave 2-sulphopyrimidine as the sodium salt (LXXXIII), and 2,4-dimethyl-6-sulphopyrimidine and 4-methyl-2-sulphopyrimidine were made in the same way.[166] Sodium hydrogen sulphite was used rather similarly to convert 4-amino-5-bromomethyl-2-methylpyrimidine or 4-amino-5-chloromethyl-2-methyl(and 2,6-dimethyl)pyrimidine into 4-amino-2-methyl (and 2,6-dimethyl)-5-sulphomethylpyrimidine.[39, 167]

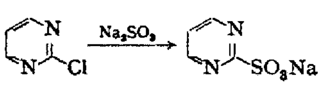
The monomethyl compound was first isolated from the fission of vitamin B_1 with sodium hydrogen sulphite.[168–170] Acid hydrolysis gave 4-hydroxy-2-methyl-5-sulphomethylpyrimidine[169] which was synthesized by heating 5-ethoxymethyl-4-hydroxy-2-methylpyrimidine with aqueous sodium sulphite.[171]

Chlorosulphonation of uracil at 110° gives reasonable yields of

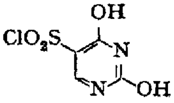
5-chlorosulphonyl-2,4-dihydroxypyrimidine[36,37,172] (LXXXIV) which with sodium carbonate or acetate gives 2,4-dihydroxy-5-sulphopyrimidine.[172] Similar treatment of cytosine and 6-methylcytosine, however, gave not the sulphonyl chlorides, but the sulphonic acids, 4-amino-2-hydroxy-5-sulphopyrimidine (LXXXV) and its 6-methyl derivative, directly in good yield.[172,173]

2,4-Diamino-6-methylpyrimidine on chlorosulphonation gives 2,4-diamino-5-chlorosulphonyl-6-methylpyrimidine, but if the quenched reaction mixture is allowed to stand at room temperature for a day or warmed for a short time, 2,4-diamino-6-methyl-5-sulphopyrimidine is isolated. 2-Amino-4-methylpyrimidine even immediately after chlorosulphonation gives only the 5-sulpho derivative.[173]

The sulphopyrimidine obtained by reduction of nitrouracil with sodium dithionite has been described as 2,4-dihydroxy-5-sulphoaminopyrimidine and also as 5-amino-2,4-dihydroxy-6-sulphopyrimidine. It, and analogous compounds, have already been discussed in Chapter V, Sect. 1.B; the related 2,4,6-triamino-5-sulphoaminopyrimidine has been made in three ways:[174] by reduction of 2,4,6-triamino-5-nitropyrimidine with sodium hydrogen sulphite, by treating tetra-aminopyrimidine with sulphuryl chloride, and from the tetramine by fusion with sulphamide ($H_2N.SO_3H$).

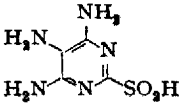


(LXXXII) (LXXXIII)



(LXXXIV)

(LXXXV)



(LXXXVI)

Several sulphophenylazopyrimidines have been made. Typical is the coupling of diazotized sulphanilic acid with 2,4-diamino-6-methylpyrimidine to give 2,4-diamino-6-methyl-5-*p*-sulphophenylazopyrimidine.[175]

At least two sulphinic acids have been described. 4,5,6-Triamino-2-mercaptopyrimidine on treatment with cold alkaline hydrogen peroxide gave 4,5,6-triamino-2-sulphinopyrimidine[176,177] (LXXXVI). 4,6-Diamino-2-sulphinopyrimidine was similarly made.[177]

The direct sulphonation of 2-aminopyrimidine with fuming sulphuric acid at 180°, yields 23 % of 2-hydroxy-5-sulphopyrimidine, but not any of the 2-amino analogue.[178] 2-Chloro-5-chlorosulphonylpyrimidine results from the hydroxy compound and phosphorus pentachloride.[178]

B. Reactions

Sulphonic and sulphinic acids are readily hydrolysed by acid and sometimes by alkali, and this property has been extensively used during the oxidative removal of mercapto groups (Sect. 1.D(1)). Examples of the acid hydrolysis of isolated acids are furnished by the conversion of 2,4-dimethoxy-6-sulphopyrimidine into 2,4,6-trihydroxypyrimidine[114] in which the sulpho group has been replaced by a hydroxy group, and of 5-chlorosulphonyl-2,4-dihydroxypyrimidine into 2,4-dihydroxypyrimidine,[172] in which the chlorosulphonyl group has been replaced by hydrogen. 4,5,6-Triamino-2-sulphinopyrimidine is stable to alkali but in N-acid it quickly gives 4,5,6-triaminopyrimidine.[176, 177] 4,6-Diamino-2-sulphinopyrimidine, on the other hand, with N-acid gave a mixture of 4,6-diaminopyrimidine and its 2-hydroxy derivative. However, the use of concentrated hydrochloric acid, or, better, 20 N- sulphuric acid gave excellent yields of 4,6-diaminopyrimidine. A theoretical explanation of this behaviour has been offered.[177]

The sulpho group of 2,4-dimethoxy-6-sulphopyrimidine can be replaced by chlorine by treatment with phosphorus pentachloride; according to conditions, either 4-chloro-, or 4,5-dichloro- 2,6-dimethoxypyrimidine[179] is formed.

The sodium salts of 2-sulphopyrimidine, its 4-methyl derivative, and 2,4-dimethyl-6-sulphopyrimidine, on distilling with potassium cyanide gave the corresponding nitriles, 2-cyano-, 2-cyano-4-methyl-, and 4-cyano-2,6-dimethyl- pyrimidine.[166]

Reduction of sulphonyl chlorides to mercaptopyrimidines or dipyrimidinyl disulphides and sulphides, has already been discussed (Sect. 1.B).

The formation of sulphonic esters is exemplified in the preparation of 2,4-dihydroxy-5-phenoxysulphonylpyrimidine (LXXXVII) from the corresponding sulphonyl chloride[37] (LXXXVIII). Sulphonamides are readily produced from the sulphonyl chlorides, with liquid or alcoholic ammonia or amines.* In this way were made 5-(*NN*-dimethylsulphamoyl)-2,4-dihydroxypyrimidine[37] (XC), 2,4-dihydroxy-5-(*N*-phenylsulphamoyl)pyrimidine,[37] 2,4-dihydroxy-5-sulphamoylpyrimidine,[36, 172] 2-sulphamoylpyrimidine,[14] its 5-chloro derivative,[14] 4,6-

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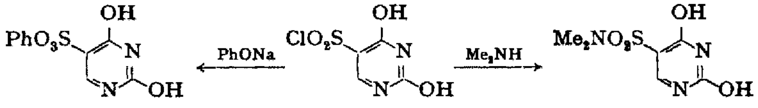
* These sulphamoylpyrimidine derivatives must be distinguished from the useful "pyrimidine sulphonamide" drugs which are sulphanilyl derivatives of aminopyrimidines (Ch. IX, Sect. 5.D(6) (e.g. LXXXIX).

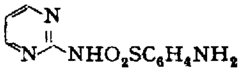
dimethyl-2-sulphamoylpyrimidine,[14] 2-(*N*-benzylsulphamoyl)-4,6-dimethylpyrimidine,[180] and other such derivatives.[178,180]

An interesting route[179] to a sulphamoylpyrimidine started with 4-mercapto-2,6-dimethoxypyrimidine. Treatment of an alkaline solution with chloramine gave 4-aminothio-2,6-dimethoxypyrimidine (XCI) which on permanganate oxidation gave 64% of 2,4-dimethoxy-6-sulphamoylpyrimidine (XCII) the structure of which was confirmed by acid hydrolysis to the known 5-sulphamoyluracil.[179]

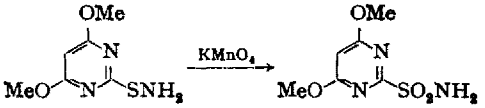
The pyrimidin-5-yl hydrogen sulphates ($ROSO_3H$) prepared by the action of ammonium persulphate on appropriate pyrimidines,[181] have been treated in Ch. VII, Sect. 2.C.



(LXXXVII) (LXXXVIII) (XC)



(LXXXIX)



(XCI) (XCII)

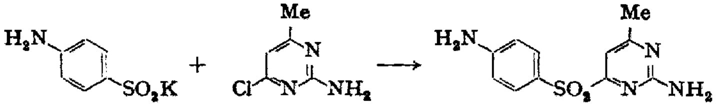
5. Alkylsulphonylpyrimidines

The alkylsulphonylpyrimidines are useful intermediates in metathesis, but in this role they have been rather neglected. However, a number of 2-alkylsulphonyl derivatives are known.

A. Preparation

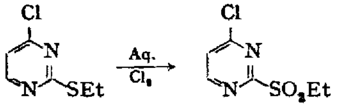
Most alkylsulphonylpyrimidines have been made by oxidation of the corresponding alkylthiopyrimidines with chlorine or hydrogen peroxide. Another method is represented only by the condensation of 2-amino-4-chloro-6-methylpyrimidine (XCIV) with the potassium salt of *p*-sulphinoaniline (XCIII) or *p*-sulphinoacetanilide to give respectively 2-amino-4-aminophenylsulphonyl-6-methylpyrimidine (XCV) and 4-*p*-acetamidophenylsulphonyl-2-amino-6-methylpyrimidine.[182] If these products are indeed sulphones, a rearrangement of the intermediate ester must have taken place.

The oxidation process using chlorine in aqueous solution is exemplified in the change from 2-alkylthio derivatives such as (XCVI) to 4-chloro-2-ethylsulphonylpyrimidine (XCVII), its 5-bromo and 5-methyl derivatives, 4-ethoxy-2-ethylsulphonylpyrimidine, its 5-bromo and 5-methyl derivatives, and 4-chloro-5-ethoxycarbonyl-2-ethylsulphonylpyrimidine.[183] Other examples so prepared include 5-ethyl-2-ethylsulphonyl-4-methoxy-6-methylpyrimidine,[184] its 4-ethoxy and 4-chloro analogues,[184] 2-ethylsulphonyl-4-methoxy-5,6-dimethylpyrimidine,[185] its 4-chloro analogue,[185] 4,6-diamino-2-methylsulphonylpyrimidine,[121] 5-ethoxycarbonyl-2-ethylsulphonylpyrimidine[132] in small yield, 2,4-bisethylsulphonylpyrimidine,[183] and 4-methoxy-6-methyl-2-methylsulphonylpyrimidine.[186] The formation for example of (XCVIII), with 4-chloroamino- in place of 4-amino-, 2-ethylsulphonyl-5-methylpyrimidine[187] is a warning against careless use of the method in the presence of amino groups. The presence of hydroxy groups also interferes with the normal oxidation.[187]

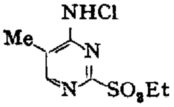


(XCIII) (XCIV) (XCV)

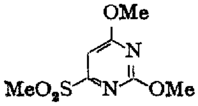
The oxidation of alkylthiopyrimidines using hydrogen peroxide is exemplified in the preparation (80%) of 2,4-dimethoxy-6-methylsulphonylpyrimidine (XCIX) by treatment of the corresponding methylthio derivative in formic acid with 30% hydrogen peroxide at room temperature,[179] and also in the preparation of 2-benzylsulphonyl-4,6-diphenylpyrimidine.[188] The action of hydrogen peroxide *in ethanol* on alkylthiopyrimidines,[189, 190] which sometimes leads to isolated sulphones, has already been discussed in Chapter VII, Sect. 1.F(3). Di(2-amino-4-methylpyrimidin-6-yl) sulphone was prepared from the corresponding sulphide by permanganate oxidation.[166]



(XCVI) (XCVII)



(XCVIII)



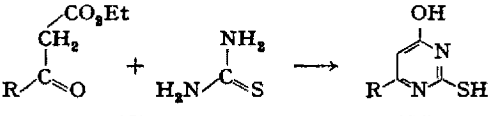
(XCIX)

B. Reactions

The ready conversion of alkylsulphonylpyrimidines into alkoxy- and hydroxy-pyrimidines has been discussed in Section 4.C and 1.F(3) respectively. Alkylsulphonyl derivatives may also be aminated, but since the alkylthio derivatives from which they are made also aminate readily, there is little point in the procedure, and examples are in fact few. 4-Amino-5-ethoxycarbonyl-2-ethylsulphonylpyrimidine on heating at 100° with alcoholic ammonia gives about 90% of 2,4-diamino-5-ethoxycarbonylpyrimidine, but 4-chloro-2-ethylsulphonyl-5-methylpyrimidine under similar conditions gives only 4-amino-2-ethylsulphonyl-5-methylpyrimidine.[191] Finally, 4-ethoxy-2-ethylsulphonyl-5-methylpyrimidine with aniline at 100–130° gives rather surprisingly 2-anilino-4-ethoxy-5-methylpyrimidine.[191]

6. Thiouracil and Homologues

Because of their use in the treatment of thyrotoxicosis, 2-thiouracil and its 6-alkyl homologues have become important, well known, and readily available substances. Thiouracil (CI; R=H) is made commercially by the Principal Synthesis from the aldehydo-ester, ethyl α-formylacetate (C; R=H) and thiourea in alcoholic sodium ethoxide, by a modification of Wheeler and Liddle's method.[21] Its homologues result from the appropriate keto-ester such as ethyl acetoacetate (C; R=Me) used rather similarly (Ch. II, Sect. 6.A) to give for example 6-methyl-2-thiouracil[80,192] (CI; R=Me) or 6-propyl-2-thiouracil[193,194] (CI; R=C_3H_7).



(C) (CI)

The pyrimidines so formed are not only useful as drugs, but are some of the best starting materials available for the synthesis of a large variety of pyrimidines, purines, and pteridines such as uracil,[21,67] cytosine,[18,117] 4-hydroxypyrimidine,[18] 4,5-diaminopyrimidine,[67] pteridine,[69] purine,[92] alkyl derivatives of these,[70,80] and a host of other related compounds. The thiouracils may be conveniently estimated by a bromide–bromate titrimetric method.[196]

The first observation of goitrogenic activity seems to have been that of Chesney, Clawson, and Webster,[197] in 1928, who showed that rabbits fed on cabbage developed thyroid hyperplasia. The sulphur compounds contained therein, and later thiourea-like compounds in general, were slowly implicated[198–201] in this activity. In 1943, Astwood[202] showed that thiouracil was the most active of a large group of the structural derivatives of thiourea, and reported its clinical use in human hyperthyroidism.[203, 204] By preparation of a series of 5- and 6-substituted derivatives a maximum activity at 6-propyl- or 6-butyl-2-thiouracil was indicated,[205] and other types of substituent removed activity. Thiouracil was incorporated into the British Pharmacopoeia in 1948, but was deleted in favour of its more effective 6-methyl and 6-propyl derivatives in 1953. The U.S.P. currently lists the last two pyrimidines as well as Methiminazole (2-mercapto-1-methylglyoxaline). In addition the N.N.R. lists Iothiouracil or 5-iodo-2-thiouracil (for preparation see Sect. 1.A(5)) which is said to combine the antithyrotoxicotic actions of thiouracil and of iodine. Pharmacological aspects of the thiouracil group of drugs have been reviewed[206] in the context of the other antithyroid drugs.

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CHAPTER IX

The Aminopyrimidines

The number of aminopyrimidines known is second only to that of hydroxypyrimidines. Not only is the amino group found in natural pyrimidines such as cytosine and divicine, but it occurs in the pyrimidine breakdown products from purines, pteridines, and other fused systems, and in the many pyrimidine intermediates used for synthetic work in those series. The term "aminopyrimidine" in this chapter will often be used in a generic sense to include primary, secondary, and tertiary amines.

1. Preparation of 2-, 4-, and 6-Aminopyrimidines

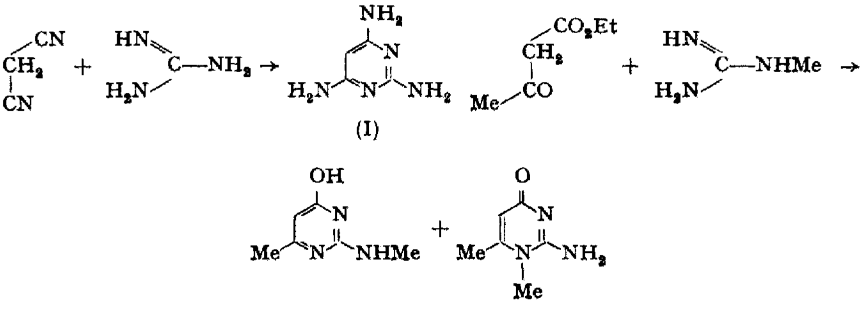
Although all the important methods of preparation have already been discussed elsewhere in this book, the sub-sections following indicate the scope of each method and where the detailed discussion can be found.

A. By the Principal Synthesis

A primary amino group results in position 2 when guanidine is used as the one-carbon fragment in a Principal Synthesis. The same group in position 4 and/or 6 arises by using a nitrile or dinitrile as a three-carbon fragment. These possibilities are briefly exemplified in the condensation of guanidine with acetylacetone to give 2-amino-4,6-dimethylpyrimidine,[1,2] of thiourea with ethyl cyanoacetate to give 4-amino-6-hydroxy-2-mercaptopyrimidine,[3,4] and of guanidine with malononitrile to give 2,4,6-triaminopyrimidine[5-7] (I).

Secondary and tertiary amino groups cannot be placed in position 4 or 6 by the Principal Synthesis, but tertiary and sometimes secondary groups can be put in position 2, by using respectively an *NN*-dialkylguanidine or an alkylguanidine. Using the latter reagent, one or (theoretically) even two isomeric pyrimidines may be formed in place of (or as well as) the expected 2-alkylaminopyrimidine. These isomers carry the alkyl group on one or other ring nitrogen. Thus ethyl acetoacetate with *NN*-dimethylguanidine unequivocally gives 2-dimethylamino-4-hydroxy-6-methylpyrimidine,[8] but with methylguanidine gives[9] both 4-hydroxy-6-methyl-2-methylaminopyrimidine (II) and 2-amino-1,4-dihydro-1,6-dimethyl-4-oxopyrimidine (III); the third isomer was not isolated in this case.

Further examples of aminopyrimidines made by the Common Synthesis will be found in each section of Chapter II.



(I)

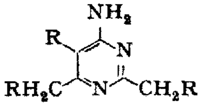
(II) (III)

B. By Other Primary Syntheses

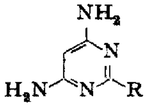
Aminopyrimidines may be made by many of the syntheses described in Chapter III, but on the whole they are rather restricted in scope. The Frankland and Kolbe Synthesis (Ch. III, Sect. 3.D) is typical: the trimerization of simple nitriles, in the presence of alkali metals, gives 4-amino-2,5,6-trialkylpyrimidines such as (IV) in which the 2- and 6-alkyl groups have one more carbon atom than has the 5-alkyl group. It is, for example, the best method of preparing 4-amino-2,6-dimethylpyrimidine (IV; R=H).[10, 11]

Another useful synthesis (Ch. III, Sect. 4.D) is that of 4,6-diamino-2-alkylpyrimidines (V) from malondiamidine and simple esters. 4,6-Diaminopyrimidine (V; R=H) and its 2-methyl derivative (V; R=Me) can be conveniently made in this way.[12] The synthesis may be modified by using, for example, the monoamide–monoamidine of malonic acid with ethyl formate, when 4-amino-6-hydroxypyrimidine (VI) results.[13]

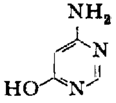
The degradation of the cheaply available uric acid with acetic anhydride and pyridine (Ch. III, Sect. 5.E(4)) is the best way to make the important intermediate 4,5-diamino-2,6-dihydroxypyrimidine[14] (VII), and degradation of 5,6,7,8-tetrahydro-5,8-dimethyl-6,7-dioxopteridine (itself easily derived by methylation of 6,7-dihydroxypteridine) is a good (and the only known) way of preparing 4,5-bismethylaminopyrimidine[15] (VIII).



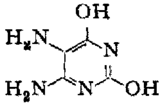
(IV)



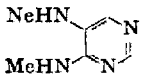
(V)



(VI)



(VII)



(VIII)

C. By Direct Amination

Very little has been reported about the direct amination of pyrimidines, but when 4-methylpyrimidine is treated with sodium amide in decalin, 2-amino- and 2,4-diamino-6-methylpyrimidine have been isolated, as well as other unidentified products.[16]

D. From Chloropyrimidines

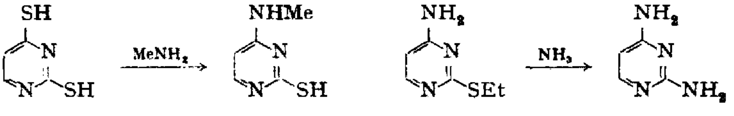
The treatment of a chloropyrimidine with ammonia or amine is the most usual way to make aminopyrimidines. The huge literature of the process has been discussed in detail in Chapter VI, Sects. 5.B and C, and the kinetics of such nucleophilic displacements in Chapter VI, Sect. 4.

The veterinary drug "Antrycide" was first made by this general method. 4,6-Diamino-2-methylquinoline was condensed in aqueous acid with 2-amino-4-chloro-6-methylpyrimidine to give 4-amino-6-(2-amino-4-methylpyrimidin-6-ylamino)-2-methylquinoline.[17] "Antrycide", the bismethochloride,[18] is one of the best prophylactics for trypanosome infection in cattle reared in tropical Africa.

E. From Mercapto- and Alkylthio-pyrimidines

4-Mercaptopyrimidines can usually be converted into 4-amino- or substituted-amino-pyrimidines by treatment with ammonia or an amine. 2-Mercapto groups, however, resist such treatment except when activated, for example, by a nitro group. Thus 2,4-dimercaptopyrimidine (IX) with methylamine at 120° gives 2-mercapto-4-methylaminopyrimidine (X) and not any of the isomer.[19] On the other hand, 2,4-dimercapto-5-nitropyrimidine even under gentle conditions gives 2,4-bismethylamino-5-nitropyrimidine.[20] The reaction has been discussed in Chapter VIII, Sect. 1.D(5).

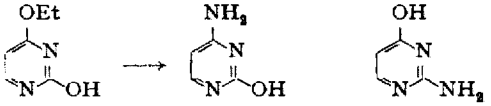
Even 2-alkylmercaptopyrimidines generally react with ammonia or amines as exemplified in the amination at 190° of 4-amino-2-ethylthiopyrimidine (XI) to 2,4-diaminopyrimidine[21] (XII). As they can be so readily made from the parent 2-mercaptopyrimidines, 2-carboxymethylthio derivatives have often been used as starting materials for such aminations.[22] These reactions have been treated in Chapter VIII, Sect. 2.C(3).



(IX) (X) (XI) (XII)

F. From Alkoxypyrimidines

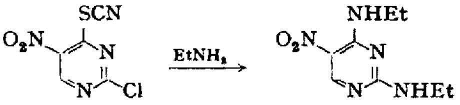
There is generally little point in using alkoxypyrimidines to prepare aminopyrimidines since the former are normally made from chloro derivatives and these can be equally well aminated directly. However, the method is occasionally useful and is typified in the conversion of 4-methoxy- into 4-amino-pyrimidine,[23] and in the old preparations of cytosine (XIV) and isocytosine (XV) by amination respectively of 4-ethoxy-2-hydroxypyrimidine (XIII) and 2-ethoxy-4-hydroxypyrimidine.[24] A further discussion is given in Chapter VII, Sect. 7.C.



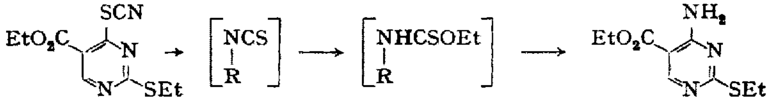
(XIII) (XIV) (XV)

G. From Thiocyanatopyrimidines

Under *strongly* basic conditions the thiocyanato group has been replaced directly by amino groups. Thus 2-chloro-5-nitro-4-thiocyanatopyrimidine (XVI) with ammonia in benzene and alcohol solution, or aniline, gives 2-amino(or anilino)-5-nitro-4-thiocyanatopyrimidine, but with aqueous ammonia or ethylamine under similar gentle conditions gives 2,4-diamino- or 2,4-bisethylamino- 5-nitropyrimidine[25] (XVII). Earlier, a similar conversion was done by a completely different route: 5-ethoxycarbonyl-2-ethylthio-4-thiocyanatopyrimidine (XVIII) heated with alcohol at 150° gave a good yield of 4-amino-5-ethoxycarbonyl-2-ethylthiopyrimidine[26] (XXI)*. It is likely that the route involved an initial rearrangement to the isothiocyanato derivative (XIX), alcoholysis of this to a thiourethane (XX), and final degradation to the amine (XXI).



(XVI) (XVII)



(XVIII) (XIX) (XX) (XXI)

H. By Other Methods

Although 4-nitrosopyrimidines are very rare, the few known such as (XXII) have been reduced to the corresponding amino derivatives, 4-amino-2,5,6-trihydroxypyrimidine,[27] 4,5-diamino-2,6-dihydroxypyrimidine,[27] and 2,4-diamino-5,6-dihydroxypyrimidine[28,29] (XXIII).

Parallel to these reactions is the reduction of the uncommon 4-arylazopyrimidines (as XXIV) to give 4-amino-2,5,6-trihydroxypyrimidine,[30] 4-amino-5,6-dihydroxypyrimidine,[29] and 2,4-diamino-5,6-dihydroxypyrimidine[28,29] (XXIII).

The Hofmann reaction has been used to convert 5-bromo-4-carbamoyl-2-methylpyrimidine (XXV) into 4-amino-5-bromo-2-methylpyrimidine (XXVI) in good yield.[31] The 5-chloro analogue has been made similarly.[31]

Many simple aminopyrimidines have been made by dechlorination of amino-chloropyrimidines. Such a reaction is the production of

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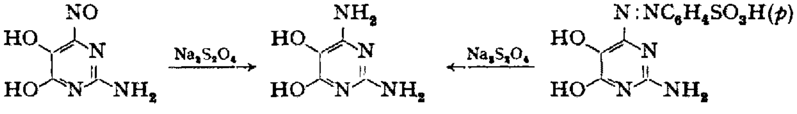
*The authors' assurance[26] that "this compound gave no test for sulphur", need not perhaps be taken too seriously since their analytical figures indicate the presence of 14.4%!

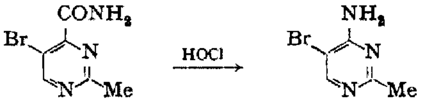
2-aminopyrimidine by hydrogenation of its chloro derivative[32] or its 4,6-dichloro derivative,[33–35], or by chemical means from the 2-amino-4-chloropyrimidine.[36–39] The reaction is treated in Chapter VI, Sect. 5.A(2) and Table XI. Simple aminopyrimidines have also been made by desulphurization of their mercapto derivatives as in the formation of 4-aminopyrimidine from its 2-mercapto derivative with Raney nickel.[40] Other examples will be found in Table XIII.

Aminopyrimidines can be produced from their benzyloxy derivatives by reduction. Thus 2-amino-4-benzyloxyamino-6-methyl-5-nitropyrimidine (from the 4-chloro compound with benzyloxyamine) is reduced to 2,4,5-triamino-6-methylpyrimidine by hydrogenation, ferrous hydroxide, or hydrazine.[41] An interesting partial reduction to 2,4-diamino-6-methyl-5-nitropyrimidine (73 %) resulted when aqueous ethanolic ammonium sulphide was used.[41]

Some substituted-amino- and hydrazino-pyrimidines have been made from the corresponding nitroamino-pyrimidines (Sect. 8.A).



(XXII) (XXIII) (XXIV)

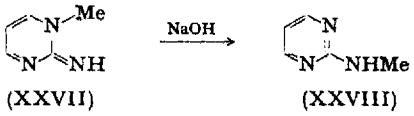


(XXV) (XXVI)

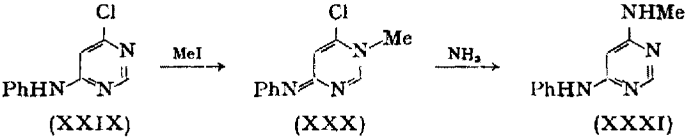
I. Secondary and Tertiary Aminopyrimidines Mainly by Alkylation

As will be seen (Chapter X, Sect. 2.A) 2-, 4-, or 6- aminopyrimidines normally alkylate on a ring nitrogen atom with the formation of an iminopyrimidine. A typical example is the conversion of 2-aminopyrimidine with methyl iodide into 1,2-dihydro-2-imino-1-methylpyrimidine[42] (XXVII). However, if this product is treated with hot alkali, rearrangement occurs in good yield to 2-methylaminopyrimidine[42] (XXVIII), and this is the isolated product if the methylation is carried out in the presence of potassium carbonate.[43] The indirect conversion of 2-amino- into 2-methylamino-pyrimidine could not be extended to the 4-position because initial methylation occurs at $N_{(1)}$ instead of

$N_{(3)}$ and is followed by ready hydrolysis of the intermediate 1,4-dihydro-4-imino-1-methylpyrimidine to 1,4-dihydro-1-methyl-4-oxopyrimidine,[42,44] but the rearrangement did lead in several less simple cases to ultimate alkylation of a 4-amino group. Thus 4-anilino-6-chloropyrimidine (XXIX) with methyl iodide gave 4-chloro-3,6-dihydro-3-methyl-6-phenyliminopyrimidine (XXX) (as the hydriodide), which on treatment with alcoholic ammonia gave 4-anilino-6-methylaminopyrimidine[45] (XXXI). Its 2-methyl and 2-phenyl derivatives were obtained by rather similar means.[45] The rearrangement is more fully treated in Chapter X, Sect. 2.B.



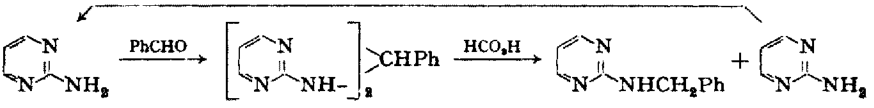
(XXVII) (XXVIII)



(XXIX) (XXX) (XXXI)

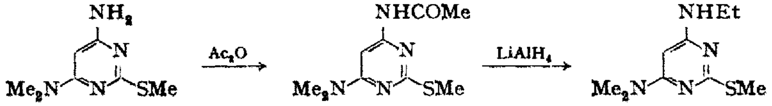
When 2-methylaminopyrimidine is treated with lithium amide followed by methyl iodide, the product is 2-dimethylaminopyrimidine.[43] 2-Aminopyrimidine has also been converted to its stable sodium salt by sodium amide in boiling benzene, and subsequent treatment with β-dimethylaminoethyl chloride (and such like) gave 2-β-dimethylaminoethylaminopyrimidine and analogues.[46] 2-Amino-4-methoxypyrimidine behaved similarly to give for example 2-β-diethylaminoethylamino-4-methoxypyrimidine. No structural confirmation of the compounds was presented. Some alkyl chlorides such as ethylene chlorohydrin, 1-chloro-3-cyanopropane, and 1-bromo-3-chloropropane, failed to react satisfactorily.[46]

Another method of alkylating primary aminopyrimidines is the so-called reductive alkylation, typified in the treatment of 2-aminopyrimidine (XXXII) with benzaldehyde in refluxing formic acid. There is reasonable evidence that the alkylation proceeds not through the obvious Schiff's base ($C_4H_3N_2N$:CHPh), but through di(2-pyrimidinylamino)methylbenzene (XXXIII) which is reduced by formic acid to 2-aminopyrimidine (which is used again) and to the product, 2-benzylaminopyrimidine[47,48] (XXXIV). The yield was 50%. Substituted benzaldehydes were also effective,[47,48] and more complicated examples are known.[49] The reductive benzylation of 2-amino-4-methylpyrimidine might reasonably be expected to follow that of 2-aminopyrimidine above. Indeed the product was reported as 2-benzylamino-4-methylpyrimidine.[48,50] It has been claimed,[51,52] however, that the product is really a mixture of 2-amino-4-styrylpyrimidine and 2-benzylamino-4-styrylpyrimidine. 4-Benzylamino-2-hydroxypyrimidine and analogues may be made by heating cytosine with benzylamine *etc.*[306]



(XXXII) (XXXIII) (XXXIV)

A good, but little used, indirect way of alkylating amino groups is represented in the 4-position by acetylation of 4-amino- to 4-acetamido-6-dimethylamino-2-methylthiopyrimidine (XXXV and XXXVI) followed by reduction with lithium aluminium hydride to 4-dimethylamino-6-ethylamino-2-methylthiopyrimidine (XXXVII) in 65 % overall yield.[53] The method has also been used for alkylating 5-aminopyrimidines (Sect. 2.E).

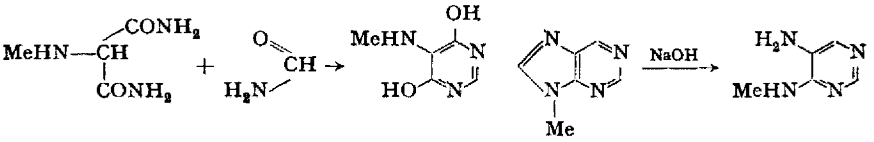


(XXXV) (XXXVI) (XXXVII)

2. Preparation of 5-Aminopyrimidines

A. By Primary Synthesis

5-Aminopyrimidines can rarely be made by any primary synthesis. However, methylaminomalondiamide condenses with ethyl formate or formamide to give 4,6-dihydroxy-5-methylaminopyrimidine[54] (XXXVIII), and the degradation of several fused pyrimidine systems often gives 4,5-diaminopyrimidines. Examples of these are 4,5-diamino-2,6-dihydroxypyrimidine from uric acid,[14] 5-amino-4-methylaminopyrimidine (XL) from 9-methylpurine[55] (XXXIX), 4,5-diamino-2-hydroxy (or mercapto, or methylthio)pyrimidine from 2-hydroxy,- mercapto-, or methylthio-purine,[55] 5-amino-2,4-dihydroxy-6-mercaptopyrimidine from uric acid with ammonium bisulphide,[56,57] 4-(and 5)-amino-5(and 4)-carboxymethylaminopyrimidine from 7- and 6-hydroxypteridine by reduction and hydrolysis,[58,59] and 4,5-bismethylaminopyrimidine by hydrolysis of 5,6,7,8-tetrahydro-5,8-dimethyl-6,7-dioxopteridine.[15]



(XXXVIII) (XXXIX) (XL)

B. By Reduction of 5-Nitro-, Nitroso-, or Arylazo-pyrimidines

This is the usual way of producing 5-amino derivatives. The methods of reduction have been discussed in detail in Chapter V, Sects. 1.B, 2.B(1), and 3.B.

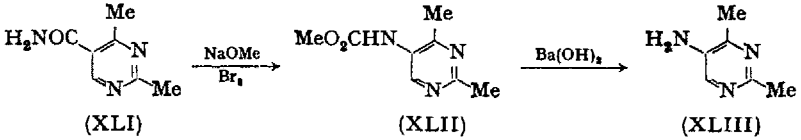
C. From 5-Halogenopyrimidines

The amination of the rather unreactive 5-halogenopyrimidines is seldom easy. Typical of the few which are of preparative value is the conversion[60] of 5-bromo-2,4-dihydroxypyrimidine into 2,4-dihydroxy-5-methylaminopyrimidine by heating with methylamine at 180°. It has been shown[61,62] that the above reaction takes place with a variety of amines, but its scope is very restricted when the starting material is 2-amino-5-bromo-4-hydroxypyrimidine. Other positive and negative examples are given in Chapter VI, Sect. 6.A.

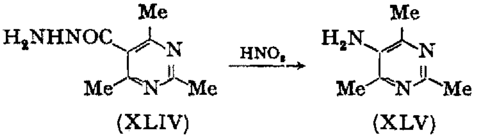
D. From 5-Carbamoylpyrimidines

There are examples of 5-carbamoylpyrimidines being changed into 5-aminopyrimidines. Thus 5-carbamoyl-2,4-dimethylpyrimidine (XLI) in methanol containing sodium methoxide, when treated with bromine, gives 94% of the urethane, 5-methoxycarbonylamino-2,4-dimethylpyrimidine (XLII). Hydrolysis of this compound in boiling aqueous barium hydroxide gave 5-amino-2,4-dimethylpyrimidine (XLIII) in 85% yield.[63] In the same way, 5-amino-2-ethyl-4-methylpyrimidine was made.[63] A rather analogous reaction involved a hydrazide. 5-

Hydrazinocarbonyl-2,4,6-trimethylpyrimidine (XLIV) on treatment with alcoholic nitrous acid gave 5-amino-2,4,6-trimethylpyrimidine[63] (XLV).



(XLI) (XLII) (XLIII)



(XLIV) (XLV)

E. Secondary 5-Aminopyrimidines by Alkylation

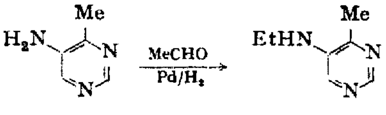
Reductive alkylation of a 5-aminopyrimidine has been successful in at least one case: 5-amino-4-methylpyrimidine (XLVI) and acetaldehyde were hydrogenated in ethanol over palladium. 5-Ethylamino-4-methylpyrimidine (XLVII) resulted in 78% yield.[64]

5-Methylamino derivatives have been prepared *via* the formamido derivatives. Thus formylation of a 5-amino derivative as (XLVIII) gives 4-amino-5-formamido-2-methylthiopyrimidine[65] (XLIX) and its 6-dimethylamino derivative,[53] which on reduction with lithium aluminium hydride gave 4-amino-5-methylamino-2-methylthiopyrimidine (L) and its 6-dimethylamino derivative. Attempts to reduce 4-amino-5-formamidopyrimidine failed due to insolubility of the starting material.[65]

When the possibility of ring-nitrogen alkylation is absent, 5-aminopyrimidines may be alkylated normally. Thus 5-amino-1-butyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxopyrimidine and related compounds, with dimethyl sulphate and calcium oxide in methanol, give their 5-dimethylamino analogues.[66] The chief product from a similar ethylation is 1-cyclohexyl-5-ethylamino-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxopyrimidine, which can be further alkylated to give for example its 5-ethylmethylamino analogue.[66] The alkylation of 5-aminopyrimidines with ethyl chloroformate to give the corresponding urethane is treated later (Sect. 6).

The direct arylation of a 5-aminopyrimidine is known. Thus 5-amino-2-methoxypyrimidine on heating in amyl alcohol with 2,4-

dichlorobenzoic acid (in the presence of copper and potassium carbonate) gives 5-(2-carboxy-5-chloroanilino)-2-methoxypyrimidine.[67] 5-Aminouracil is similarly arylated in an aqueous medium.[67]



(XLVI) (XLVII)

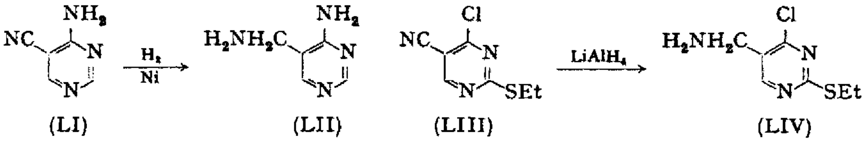
(XLVIII) (XLIX) (L)

3. Preparation of Extranuclear Aminopyrimidines

Most of the known extranuclear aminopyrimidines have been derived by reduction of a nitrile, by the Hofmann reaction from an amide, or by a Mannich reaction.

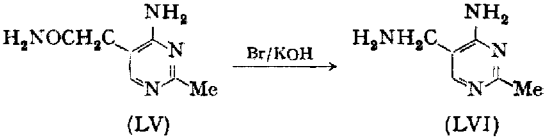
A. By Reduction of a Nitrile

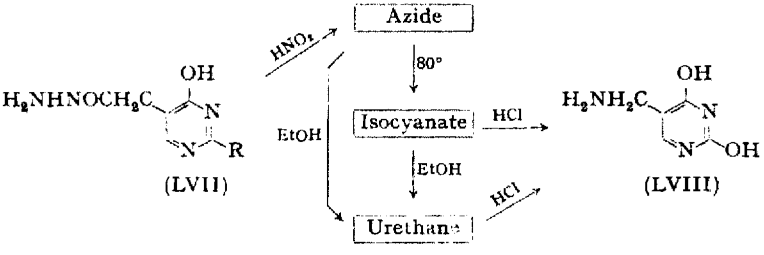
The reduction of a cyano group to an aminomethyl group has been used extensively. The best method seems to be hydrogenation in alcoholic ammonia over Raney nickel (rather than palladium or platinum[68]) at 20–100° under pressure, but other conditions and reducing agents have been used successfully. Catalytic reduction is exemplified by the preparation, from the corresponding nitrile, of 4-amino-5-aminomethylpyrimidine[69] (LII from LI), its 2-methyl derivative,[68,70,71] its 2-benzyl derivative,[72] its 2,6-dimethyl derivative,[73] its 2-ethyl (and phenyl) derivatives both in acid media with palladium,[74] and 2,4-diamino-5-aminomethylpyrimidine.[68,75] Reduction of a nitrile and reductive removal of chlorine have been done together in the preparation of 4-amino-5-aminomethyl-2-methylpyrimidine from 4-amino-6-chloro-5-cyano-2-methylpyrimidine.[76] Other methods of nitrile reduction include electrolytic reduction with a palladium black cathode, in the preparation of 4-amino-5-aminomethyl-2-butylpyrimidine,[77] and the use of lithium aluminium hydride in making 5-aminomethyl-4-chloro-2-ethylthiopyrimidine[78] (LIV) from (LIII), and 4-amino-5-aminomethyl-2-ethylthiopyrimidine.[78] This last method should be of great use in the presence of groups which preclude catalytic hydrogenation, and yields were excellent.



B. From Amides and Hydrazides by Hofmann and Curtius Reactions

There are several examples of an extranuclear amide serving as starting material to make the corresponding amine. Thus 4-amino-5-carbamoylmethyl-2-methylpyrimidine (LV) on treatment in alkaline solution with bromine gives 4-amino-5-aminomethyl-2-methylpyrimidine[79–81] (LVI), isolated conveniently as a benzaldehyde Schiff's base, which was hydrolysed by acid to give the product. The isomeric 4-amino-5-aminomethyl-6-methylpyrimidine was made similarly,[80] as was also 4-amino-5-aminomethyl-2-benzylpyrimidine,[81] and 4-amino-5-aminomethyl-2-ethylpyrimidine.[81] A Hofmann reaction was used on 2-β-carbamoylethylpyrimidine to give in good yield 2-β-aminoethylpyrimidine, and also for the 4-isomer.[82]



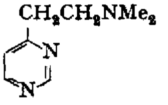


The related Curtius reaction has been used to convert 5-hydrazinocarbonylmethyl-4-hydroxy-2-methylpyrimidine into 5-aminomethyl-4-hydroxy-2-methylpyrimidine.[81] The reaction (in the broadest sense) has also been used[83] to convert 2-ethylthio-5-hydrazinocarbonylmethyl-4-hydroxypyrimidine (LVII; R=SEt), *via* the azide and the isocyanate or urethane, into 5-aminomethyl-2,4-dihydroxypyrimidine (LVIII), the ethylthio group being hydrolysed in the process. The same compound has also been made[84] by similar routes from 5-hydrazinocarbonylmethyl-2,4-dihydroxypyrimidine (LVII; R=OH). The 6-methyl derivative of (LVIII) has been made directly from the corresponding azide by treatment with 50% acetic acid.[85]

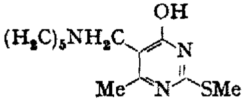
C. By the Mannich Reaction

The preparation of extranuclear amino derivatives by the Mannich reaction is typified by the condensation of 4-methylpyrimidine with formaldehyde and dimethylamine to give 70% of 4-dimethylaminoethylpyrimidine[8] (LIX). When methyl groups are deactivated as in 4-hydroxy-6-methyl-2-methylthiopyrimidine, treatment for example with piperidine and formaldehyde involves the 5-position, giving 4-hydroxy-6-methyl-2-methylthio-5-piperidinomethylpyrimidine[86] (LX). The reaction is fully discussed in Chapter IV, Sect. 3.C(7).

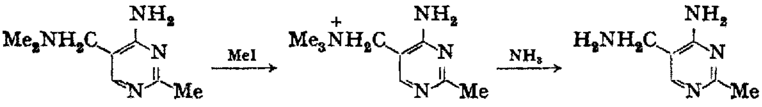
Ancillary to the Mannich preparation of the tertiary base, 4-amino-5-dimethylaminomethyl-2-methylpyrimidine (LXI), is its quaternization to (LXII) and conversion therefrom with aqueous ammonia into the primary base, 4-amino-5-aminomethyl-2-methylpyrimidine[87] (LXIII).



(LIX)



(LX)



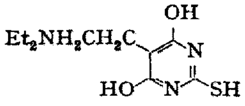
(LXI) (LXII) (LXIII)

D. By Primary Synthesis

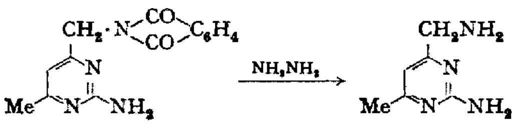
There is at least one direct Principal Synthesis of an extranuclear amino compound, and several are known using "protected" amino groups.

The direct synthesis is the condensation of diethyl β-diethylaminoethylmalonate with thiourea, which is reported as giving 5-β-diethylaminoethyl-4,6-dihydroxy-2-mercaptopyrimidine[88] (LXIV).

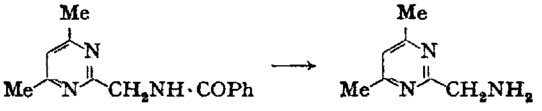
For example, in the second category 1-phthalimidopentan-2,4-dione when refluxed with guanidine carbonate in ethanol gives 2-amino-4-methyl-6-phthalimidomethylpyrimidine (LXV). On treatment of this with hydrazine, 2-amino-4-aminomethyl-6-methylpyrimidine (LXVI) resulted.[89] Again, α-benzamidoacetamidine, acetylacetone, and potassium carbonate in ethanol gave 2-benzamidomethyl-4,6-dimethylpyrimidine (LXVII), which on treatment with hot aqueous hydrochloric acid gave 2-aminomethyl-4,6-dimethylpyrimidine[90] (LXVIII). Similar condensations with malononitrile and with ethyl cyanoacetate failed to give pyrimidines.[90] 5-Acetamidomethyl-4-amino-2-methylpyrimidine has been made by a primary synthesis *via* an intermediate pyrimidopyrimidine.[91, 93]



(LXIV)



(LXV) (LXVI)



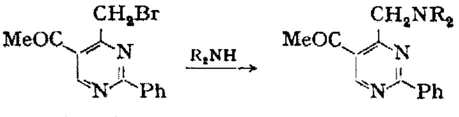
(LXVII) (LXVIII)

E. By Other Routes

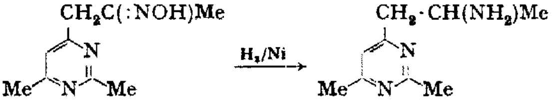
Extranuclear bromopyrimidines such as (LXIX) have been aminated as in the preparation of 5-acetyl-4-diethylamino(or dimethylamino, or morpholino)methyl-2-phenylpyrimidine[92] (LXX). 4-Amino-2-methyl-5-piperidinomethylpyrimidine and 4-amino-5-dimethylamino (or diethylamino)methyl-2-methylpyrimidine have been similarly made.[87] Such aminations are very easily done in a few minutes in warm benzene. 5-Aminomethyluracil can be nicely made from the chloro analogue with hexamethylenetetramine.[94]

Reduction of 4,6-dihydroxy-5-nitroso-2-nitrosomethylpyrimidine with ammonium sulphide gives 5-amino-2-aminomethyl-4,6-dihydroxypyrimidine.[95] Similarly, 4-acetonyl-2,6-dimethylpyrimidine forms an oxime (LXXI) which on hydrogenation over Raney nickel gives 4-β-aminopropyl-2,6-dimethylpyrimidine[96] (LXXII). The oxime of 2,4-dimethyl-6-phenacylpyrimidine likewise gives 4-β-aminophenylethyl-2,6-dimethylpyrimidine.[96]

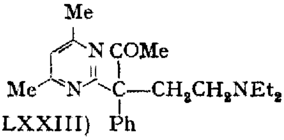
Some rather complicated examples of the direct attachment of a diethylaminoethyl residue on to an activated methylene group attached to pyrimidine are known.[97] The products are typified by (LXXIII).



(LXIX) (LXX)



(LXXI) (LXXII)



(LXXIII)

4. Properties of Aminopyrimidines

All the simple aminopyrimidines are readily soluble in water. The primary amines are higher melting than are the corresponding methylamino derivatives, which are in turn higher than the dimethylamino derivatives. There is a general increase in melting point with the number of amino groups. Table XIV gives the available melting points for the simple compounds. The ionization constants of aminopyrimidines are discussed in Chapter XIII, Sect. 1, and spectra in Chapter XIII, Sect. 2.

TABLE XIV. Melting Points of Aminopyrimidines

Positions of substitution	Amino	Methylamino	Dimethylamino
2-	128°	61°	liq.
4-	151°		40°
5-	172°		
2,4-di	150°	130°	
2,5-di	208°		
4,5-di	202°	142°	
4,6-di	270°	209°	107°
2,4,6-tri	252°		
2,4,5-tri	179°		
4,5,6-tri	257°		
2,4,5,6-tetra	205°		

There is every indication that the aminopyrimidines are truly amino in form (LXXIV) and that the amount of the tautomeric imino form (LXXIVa) present at equilibrium in aqueous solution, or in the solid state, is very small.[42] This is in marked contrast to the state of affairs in hydroxy- and mercapto-pyrimidines. For discussion see Chapter XIII, Sect. 2.A.

(LXXIV) (LXXIVa)

5. Reactions of Aminopyrimidines

A. Replacement of Amino by Hydroxy Groups

2-, 4-, and 6-Aminopyrimidines can often be converted into hydroxy derivatives by acid hydrolysis or by treatment with nitrous acid; less frequently, alkaline hydrolysis is effective. The reaction is discussed in Chapter VII, Sect. 1.D. 5-Amino groups undergo the transformation less readily although 2,4,5-trihydroxypyrimidine is best made by acid hydrolysis of 5-amino-2,4-dihydroxypyrimidine.[98] Other examples are given in Chapter VII, Sect. 2.A. Not surprisingly, the aliphatic type of amino group in extranuclear aminopyrimidines has been converted into hydroxy with nitrous acid. The formation of 4-hydroxy-5-hydroxymethyl-2-methylpyrimidine is a good example of the reaction.[80,99] Other examples are given in Chapter VII, Sect. 3.B.

B. Replacement of Amino by Chloro Substituents

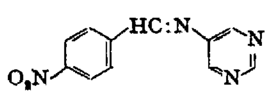
2-Aminopyrimidine[43,100] and several derivatives have been converted into their chloro analogues by treatment with nitrous acid in the presence of an excess of hydrochloric acid (Ch. VI, Sect. 1.C). 2,5-Diamino-4,6-dimethylpyrimidine, on diazotization and treatment with potassium iodide gives 2-amino-5-iodo-4,6-dimethylpyrimidine[101] and this is probably the only example of the metathesis in the 5-position.

C. Formation of Anils (Schiff's Bases)

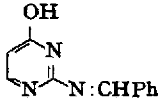
There is remarkably little straightforward literature on pyrimidine anils. It is likely, however, that primary aminopyrimidines in all nuclear positions do form such derivatives,[*] although the 5-position is most favourable. Thus 5-aminopyrimidine on heating with *p*-nitrobenzaldehyde in acetic acid at 160° gives a good yield of 5-*p*-nitrobenzylideneaminopyrimidine[102] (LXXV). 2-Amino-4-hydroxypyrimidine has been reported[103] to give with benzaldehyde, 2-benzylidenamino-4-hydroxypyrimidine (LXXVI), but its extraordinary stability to acid makes some confirmation of structure desirable.

It is the anil cation which is unstable towards acid hydrolysis. Thus if an amine is substituted so that its basic strength is progressively weakened, its anil will resist more and more concentrated acid. It is known,[104] for example, that benzylidene-*p*-nitroaniline is far more stable than is benzylideneaniline itself. As the base-weakening effect of the nuclear nitrogen atoms in pyrimidine approximates to that exerted on aniline by two nitro groups, it would perhaps not be too surprising to find that pyrimidine anils are rather stable. This stability should, however, be decreased by the presence of electron-releasing groups.

Preferential anil formation at position 5 in a 4,5-diaminopyrimidine has been recorded[105] in the reaction of benzaldehyde or *o*-hydroxybenzaldehyde with 4,5-diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine or 5,6-diamino-1-methyluracil to give respectively 4-amino-5-benzylideneamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (LXXVII) and its three analogues. When 2-amino-4-methylpyrimidine is heated at 200° with benzaldehyde, not an anil, but 2-amino-4-styrylpyrimidine (LXXVIII) is said to be the product;[51] on the other hand, 2,5-diamino-4-hydroxy-6-methylpyrimidine and benzaldehyde in aqueous ethanol do give an anil, 2-amino-5-benzylideneamino-4-hydroxy-6-methylpyrimidine.[106] The 2-acetamido analogue was made similarly.[106] In the preparation of 4-amino-5-aminoethyl-2(and 6)-methylpyrimidine from the corresponding amide, the product was isolated[80] as a "Kondensationsprodukt mit Benzaldehyd" or "Benzylidenverbindung" (unanalysed) which was



(LXXV)



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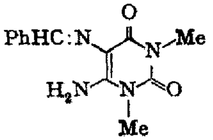
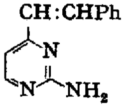


(LXXVII)



(LXXVIII)

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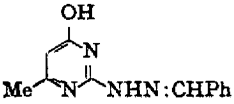
[*] The anils from pyrimidine aldehydes and aromatic amines are mentioned in Chapter XI, Sect. 5.B(4).

then split by acid. It is tempting to think of these compounds as 5-benzylideneaminoethyl derivatives (*i.e.* extranuclear), but in fact there is little clue to their structure.

Several patents exist[107–109] which relate to resinous materials prepared from polyaminopyrimidines (*e.g.* 2,4,5,6-tetra-aminopyrimidine) and aliphatic aldehydes. Phenols were sometimes included.

Compounds very closely related to Schiff's bases are the "hydrazones" or condensation products of hydrazines with aldehydes. On account of their interest for tuberculostatic testing, these are well represented in this series by the condensation in dilute acetic acid of 2-hydrazino-4-hydroxy-6-methylpyrimidine with a great variety of aromatic and heterocyclic aldehydes and ketones. A selection of the carbonyl compounds was also condensed with other hydrazines including 4-hydroxy-6-methyl-2-α-methylhydrazinopyrimidine, 2-hydrazino-4-hydroxy-6-hydroxymethylpyrimidine, 2-hydrazino-4-hydroxy-5-methylpyrimidine, 2-hydrazino-4-methoxypyrimidine and others. In all, over 100 benzylidenehydrazino compounds are described.[110] They are typified by 2-benzylidenehydrazino-4-hydroxy-6-methylpyrimidine[110, 111]* (LXXIX), 2-(2-hydroxy-α-methylbenzylidene)hydrazino-4-hydroxy-6-methylpyrimidine[110] (LXXX), 4-hydroxy-6-methyl-2-γ-pyridylmethylenehydrazinopyrimidine,[110] and 4-methyl-2,6-bis-*o*-hydroxybenzylidenehydrazinopyrimidine.[110] Other types of related hydrazone had been made and tested by Japanese workers.[111–114]



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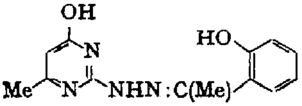
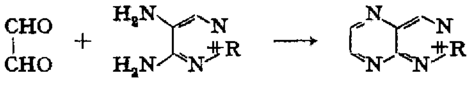


(LXXX)



(LXXXI) (LXXXII)

The condensation of 4,5-diaminopyrimidine or a derivative (LXXXI) with glyoxal to give pteridine or a derivative, (LXXXII), is at least on paper, simply the formation of a double Schiff's base. The

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* This compound was first made[115] in 1898 by a delightful Principal Synthesis from benzylideneaminoguanidine and ethyl acetoacetate in alcohol containing nitric acid!

product is, however, so conjugated that there is in fact little resemblance to the classical Schiff's base. Thus pteridine gives derivatives of pyrazine with acid.

D. Acyl Derivatives of Aminopyrimidines

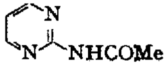
Most acylamidopyrimidines are made by acylation of the amines. The 5- and extranuclear-amino derivatives acylate very easily, but 2-, 4-, and 6-amino derivatives rather less readily. Thus a 2,5(or 4,5)-diaminopyrimidine always acylates first at position 5, and there the reaction normally stops, unless conditions are sufficiently vigorous to acylate the other amino group.

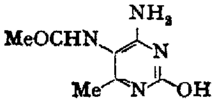
(1) *Acetylation*

Simple 2- and 4-aminopyrimidines have been acetylated by boiling with acetic anhydride to give for example 2-acetamidopyrimidine[116,117] (LXXXIII), its 4,6-dimethyl derivative,[118] 4-acetamidopyrimidine,[23,116,119] 2-acetamido-4-hydroxypyrimidine,[117,120] 4-acetamido-2-hydroxypyrimidine,[120,121] 4-acetamido-6-hydroxypyrimidine,[122] 2-acetamido-5-piperidinopyrimidine,[117] 2-acetamido-5-nitropyrimidine[123,124] (and with boiling acetic acid[125]), 4,6-bisacetamidopyrimidine,[126] its 2-methyl derivative,[127] 2,4-bisacetamido-6-hydroxypyrimidine,[117] 2,4,6-trisacetamidopyrimidine,[117] and others.[121,128] Treatment with acetic anhydride in pyridine is a good method, used for example in making 4-acetamido-6-dimethylamino-2-methylthiopyrimidine,[53] 2-acetamido-4-mercapto-5-methyl-6-phenylpyrimidine,[129] and 4-acetamido-6-amino-2-methylthiopyrimidine.[130] The last compound was also made with acetyl chloride in ethyl acetate.[130]

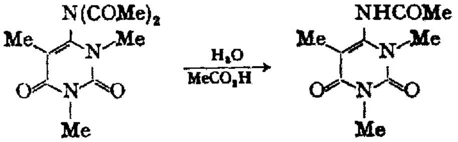
5-Aminopyrimidine is acetylated to 5-acetamidopyrimidine by warming with acetic anhydride in benzene;[102] 5-acetamido-2-phenylpyrimidine and 5-acetamido-2,4-dimethylpyrimidine[63] are also easily formed;[131] 2,4,5-triamino-6-hydroxypyrimidine gives its 5-acetamido analogue (LXXXIV) by treatment at 5° in aqueous sodium hydroxide with acetic anhydride;[132] and other preferential 5-acetylations are the formation of 5-acetamido-4-amino-6-hydroxypyrimidine[133] and of 5-acetamido-2-amino-4,6-dimethylpyrimidine.[101] Thioacetylation is represented by 2,4-dihydroxy-6-methyl-5-thioacetamidopyrimidine[134] (LXXXV), and extranuclear acetamido derivatives by 5-acetamidomethyl-2-methyl-4-methylaminopyrimidine,[135] made from the 5-aminomethyl analogue with acetic anhydride and triethylamine or by the reduction of the 5-cyano analogue in the presence of acetic anhydride.

Despite the seeming unlikelihood,[117] aminopyrimidines with two acetyl groups attached to the one amino group, have been made by Pfleiderer and colleagues. Thus 4-amino-1,6-dihydro-1,5-dimethyl-6-oxopyrimidine on boiling with acetic anhydride for 20 minutes yields the 4-acetamido analogue, but on treatment with boiling acetic anhydride in pyridine for one hour it yields the 4-diacetylamino analogue.[122] 4-Amino-1,2,3,6-tetrahydro-1,3,5,-trimethyl-2,6-dioxopyrimidine on boiling for 6 hours with acetic anhydride gives the 4-diacetylamino analogue (LXXXVI), and this on refluxing with dilute acetic acid for 8 hours is partly hydrolysed to the 4-acetamido (*i.e.* the monoacetylamino) analogue[136] (LXXXVII). Several similar 4-diacetylamino derivatives are described.[136] Diacetylation of an amino group in position 5 can also be done: 5-amino-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine can give[137] with acetic anhydride either the acetamido (gentle warming) or diacetylamino analogue (reflux).


(LXXXIII)


(LXXXIV)


(LXXXV)


(LXXXVI) (LXXXVII)

Simple hydrazinopyrimidines are readily acetylated or formylated to give for example 2-acetylhydrazinopyrimidine,[138] 2-formylhydrazinopyrimidine,[138] their 4,6-dimethyl derivatives,[138] and 2-acetylhydrazino-4-hydroxy-6-methylpyrimidine.[139]

(2) *Formylations*

The monoformylation of 4,5-diaminopyrimidines is very much used as an essential step in the usual synthesis of purines. These, and other formylations, are generally done by boiling with formic acid (90–98 %). In this way were made 4-amino-5-formamidopyrimidine[65,140] (LXXXVIII) which cyclizes to purine (XC) on melting, 5-formamido-4-methylaminopyrimidine[126] which cyclizes to 9-methylpurine on sublimation at its melting point, 4-amino-2-butyl-5-formamidopyrimidine[141] which cyclizes to 2-butylpurine at 195°, 5-formamido-4-methylamino-6-methylthiopyrimidine[141] which cyclizes at 210°, 4-amino-5-formamido-2-methylthiopyrimidine[55]* which cyclizes at 185°, 4-amino-2-dimethylamino-5-formamidopyrimidine,[395] its 2-diethylamino homologue,[142] 4-amino-5-formamido-6-mercaptopyrimidine,[143] and many others.[143–147] Where formic acid failed to yield a satisfactory formyl derivative, acetic formic anhydride at 50° has been used as in the preparation of 4,5-bisformamido-2-methoxypyrimidine and (unisolated) monoformylated derivative.[55] 4-Amino-2,6-dihydroxypyrimidine has been formylated with formic acid–formamide mixture at the boil.[148]

Thioformylation is likewise selective to 5-amino groups and was introduced[134] in 1936 and developed by A.R. Todd, F. Bergel, and their colleagues. Such thioformamido compounds are made with sodium dithioformate in aqueous solution or in pyridine at room temperature, and the products are cyclized to purines under conditions gentle enough to permit the presence of labile sugar groups for purine nucleoside synthesis.

Typical examples of 5-thioformamidopyrimidines include 4-amino-6-ethyl(and methyl)- (XCI),[134] 2,4-diamino-6-methyl-,[134] 4,6-diamino-2-methyl-,[149] 4,6-diamino-2-methylthio- and analogues,[149] 4,6-diamino,[150] 4-amino-2-methyl-6-methylamino,[151] 4-amino-2-methyl-6-d-xylosidoamino-,[151] and such like compounds.[152,153]

Extranuclear formamido and thioformamido pyrimidines have generally been made in connexion with the synthesis of vitamin B_1 or its analogues. Again, extranuclear amino groups are formylated in preference to 2- or 4-amino groups, but there seems to be no example to test the preference between extranuclear- and 5-amino groups. A typical 5-formamidomethylpyrimidine is the 4-amino-2-methyl derivative (XCII) made by formylation with formic acid,[154] or with formamide,[155] by reduction of the nitrile in the presence of formamide,[156]

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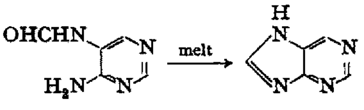
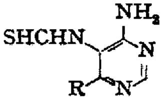
* This is the first case of a 4,5-diaminopyrimidine in which monoformylation was rigorously proven[65] to occur on the 5-amino group. Wilson[132] had already shown this was the case for acetylation.

or by heating the corresponding thioformamido derivative with water at 120° for 2 hours.[135] Other examples are 5-formamidomethyl-2-methyl-4-methylaminopyrimidine,[136] and 4-amino-2-benzyl(and ethyl)-5-formamidomethylpyrimidine.[157]

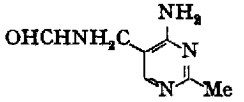
Extranuclear thioformamidopyrimidines are exemplified in 2-amino-4-methyl-[158] 2-methyl-4-methylamino-,[135] 2,4-diamino-[75] (XCIII), and 4-amino-[69] 5-thioformamidomethylpyrimidine. They were all made by thioformylation with sodium dithioformate in aqueous solution at room temperature.



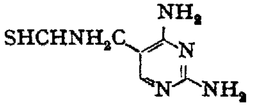
(LXXXVIII) (XC)



(XCI)



(XCII)



(XCIII)

Enol-ethers of formamido (and other acylamido derivatives) can also be readily made[158a] and appropriate ones are useful in purine syntheses. 4,5-Diaminopyrimidine, for example, on brief boiling with ethyl orthoformate yields 4-amino-5-ethoxymethylene-aminopyrimidine, which is easily cyclized to purine.

(3) *Benzoylation and Other Acylations*

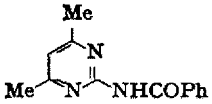
Most benzoylations have been done with benzoyl chloride either in pyridine or under Schotten–Baumann conditions. No dibenzoylation of the same amino group has been recorded. Typical examples of the products include 2-benzamido-4,6-dimethylpyrimidine[118] (XCIV), 2-benzamidopyrimidine[159] (by heating at 180° with phenyl benzoate), 5-benzamidopyrimidine,[102] 2-acetamido-5-benzamidopyrimidine,[160] 4-benzamido-1,2-dihydro-1-methyl-2-oxopyrimidine,[23,161] 2,4-diamino-5-benzamido-6-hydroxypyrimidine,[132] 2-amino-5-benzamido-4-hydroxy-6-methylpyrimidine,[106] 4-amino-5-benzamidopyrimidine,[55] and 4,5-bisbenzamidopyrimidine.[55] A variety of substituted-benzamido pyrimidines has been described.[162]

The complete benzoylation of 4-amino-2-hydroxypyrimidine in pyridine is particularly interesting in yielding 1,3-dibenzoyl-4-benzoylimino-1,2,3,4-tetrahydro-2-oxopyrimidine, which on gentle acid or alkaline hydrolysis is converted into 4-benzamido-2-hydroxypyrimidine.[121] 4-Amino-1,2-dihydro-1-methyl-2-oxopyrimidine, on similar treatment with an excess of benzoyl chloride in pyridine, gives a dibenzoyl derivative which on gentle hydrolysis yields[121] the monobenzoyl derivative previously reported[23,161] (*v.s.*).

Examples of other acylations (apart from sulphonylations *q.v.*) are not numerous but are equally facile. As examples, might be quoted 4,6-diamino-5-cyanacetamido-2-mercaptopyrimidine[13] (XCV) (from the 5-amino analogue with aqueous cyanocetic acid), 4-amino-5-β-carboxypropionamido-6-hydroxypyrimidine[13] (succinic acid at 200°), 2,4-diamino-5-α-hydroxypropionamido-6-hydroxypyrimidine[132] (lactic acid at 125°), 4-amino-5-αα-dichloropropionamidopyrimidine[163] (XCVI), 4,5-bis-αα-dichloropropionamidopyrimidine[163] (αα-dichloropropionyl chloride in boiling pyridine gives mainly monoacyl derivative), and 4-amino-5-cyanoacetamido-6-hydroxypyrimidine[13] from heating the 5-amino derivative with cyanoacetamide at 200°.

(4) *Other Ways of Preparing Acylaminopyrimidines*

Acylamino derivatives have occasionally been prepared by primary synthesis. Thus, 2-benzamidomethyl-4,6-dimethylpyrimidine was made by condensing benzamidoacetamidine with acetylacetone,[90] 5-benzamido-4-hydroxy-2-methylthiopyrimidine from sodio ethyl benzamido formylacetate and S-methylthiourea in aqueous alkali,[164] 5-acetamido-2,4-diamino-6-hydroxypyrimidine from ethyl acetamidocyanoacetate and guanidine,[132] 5-acetamidomethyl-4-amino-2-methylpyrimidine by a



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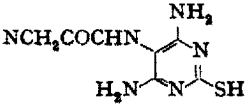

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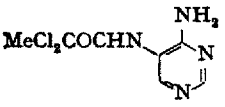

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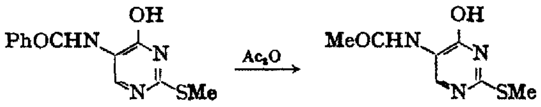


(XCVII) (XCVIII)

complicated route,[165] and many sulphonamido derivatives exemplified in the condensation of *p*-acetamidobenzenesulphonylguanidine and ethyl acetoacetate to give 2-*p*-acetamidobenzenesulphonamido-4-hydroxy-6-methylpyrimidine.[166]

Formylation can accompany reduction by using, for example, zinc and formic acid to reduce 4-amino-2,6-dihydroxy-5-phenylazopyrimidine to 4-amino-5-formamido-2,6-dihydroxypyrimidine.[167]

Interconversion of acylamino groups has been recorded. Thus, 5-benzamido-4-hydroxy-2-methylthiopyrimidine (XCVII) on refluxing with acetic anhydride for 1 hour gave 5-acetamido-4-hydroxy-2-methylthiopyrimidine[164] (XCVIII). The rearrangement of 2-amino-4-benzoylthio-6-methylpyrimidine to 2-benzamido-4-mercapto-6-methylpyrimidine takes place by heating at 180° for 30 minutes.[168]

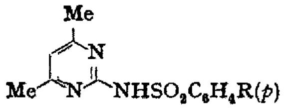
(5) *Deacylation of Acylaminopyrimidines*

Acylaminopyrimidines need fairly vigorous hydrolysis to give the parent amine, and if other labile groups are present, the process may well be impractical. Examples of these hydrolytic conditions are furnished by 2-acetamido- to 2-aminopyrimidine by refluxing with methanolic hydrogen chloride,[117] 4-amino-5-cyanoacetamido- to 4,5-diamino- 6-hydroxypyrimidine "by heating with concentrated sodium-hydroxy solution",[13] 6-amino-5-formamido- to 5,6-diamino- 3-methyluracil by refluxing in 10% methanolic hydrogen chloride for 5 hours,[147] 4-acetylimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxopyrimidine to the 4-imino derivative by refluxing with sodium methoxide in methanol,[23] 2-benzamidomethyl- to 2-aminomethyl- 4,6-dimethylpyrimidine by boiling with 6N- hydrochloric acid,[90] and 2-acetamido-5-amino- to 2,5-diamino- pyrimidine with N-sodium hydroxide.[125] Aqueous alcoholic hydrochloric acid at 50° has been used.[165] A kinetic study of the acidic and alkaline hydrolysis of 2- and 5-formamido-, acetamido-, and benzamido-pyrimidines has been reported.[169]

(6) *Arylsulphonamidopyrimidines*

A great many aryl sulphonamidopyrimidines have been made. The two methods used have been direct acylation of aminopyrimidines with arylsulphonyl chlorides, and to a less extent the Principal Synthesis. The first is exemplified by the treatment of 2-amino-4,6-dimethylpyrimidine with *p*-toluenesulphonyl chloride in pyridine at 100° to give 4,6-dimethyl-2-*p*-toluenesulphonamidopyrimidine[118] (XCIX; R=Me), by the similar preparations of 2-*p*-toluenesulphonamidopyrimidine,[170] 2-benzenesulphonamidopyrimidine,[170,171] its 4-methyl derivative,[171] and its 4,6-dimethyl derivative.[172] Many similar sulphonamides, substituted both in the benzene part and in the pyrimidine ring, have been made with the appropriate sulphonyl chloride and aminopyrimidine.[172,173] A little-used variation of the method involves the condensation of a benzene sulphonamide with an active chloropyrimidine. Thus, orthanilamide and 2,5-dichloropyrimidine on heating at 170° in nitrobenzene with potassium carbonate gave 2-*o*-aminobenzenesulphonamido-5-chloropyrimidine.[173]

The preparation of arylsulphonamidopyrimidines by the Common Synthesis is illustrated by the condensation of 2-*p*-nitrobenzenesulphonylguanidine with acetylacetone to give 4,6-dimethyl-2-*p*-nitrobenzenesulphonamidopyrimidine (XCIX; R=NO_2). Reduction with ferrous hydroxide gave 2-*p*-aminobenzenesulphonamido-4,6-dimethylpyrimidine[166] (XCIX; R=NH_2). The same compound was made directly from *p*-aminobenzenesulphonylguanidine and acetylacetone[166] and earlier by the acylation of 2-amino-4,6-dimethylpyrimidine with *p*-acetamidobenzenesulphonyl chloride to give 2-*p*-acetamidobenzenesulphonamido-4,6-dimethylpyrimidine (CXIX; R=NHCOMe), followed by deacetylation.[124,174,175,] Some confusion about low and high melting forms was shown by Rose and Swain[166] to be caused by the existence of a metastable hemihydrate, as well as the anhydrous material. Sulphaguanidine condensations also yield *e.g.* 4-methyl-6-octyl-2-sulphanilamidopyrimidine.[175a]



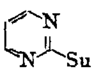
(XCIX)

An example of acylation of a hydrazino derivative is furnished by the formation from benzenesulphonyl chloride of 2-benzenesulphonylhydrazino-5-ethoxycarbonyl-4-methylpyrimidine.[176]

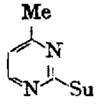
Of the relatively few sulphonamide drugs which are now prescribed, three are derivatives of pyrimidine. Their chief advantage over earlier heterocyclic sulphonamides was not any particular activity but much greater water solubility of their acetyl derivatives, which mitigated (especially in the dimethyl derivative) the bogey of kidney blockage associated with sulphapyridine and sulphathiazole. The greatly increased water intake previously required could now be safely lessened, and even patients with impaired renal function could receive sulphonamide therapy. The position was further improved by mixing several sulphonamides, since their therapeutic action is additive but their tendency to precipitate in the kidneys as acetyl derivatives is not.[177]

Sulphadiazine B.P., U.S.P. (2-*p*-aminobenzenesulphonamidopyrimidine) (C) and Sulphamerazine B.P., U.S.P. (its 4-methyl derivative) (CI) were first described by Roblin, Williams, Winnik, and English[82] in 1940. They were made by acylation of 2-aminopyrimidine or its 4-methyl derivative with *p*-acetamidobenzenesulphonyl chloride in pyridine, followed by deacetylation. Alternatively, *p*-nitrobenzenesulphonyl chloride was used, and the resulting *p*-nitrobenzenesulphonamidopyrimidine reduced to the amino derivative. The preparation of sulphadiazine by the Common Synthesis has also been described[178] using *p*-acetamidobenzenesulphonylguanidine and 1,1-dichloro-3,3-diethoxypropane (virtually malondialdehyde) to give acetylated sulphadiazine, followed by deacetylation.

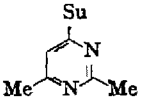
The preparation of the third homologue, Sulphadimidine B.P., Sulphamethazine U.S.P. or "Sulphamezathine" (2-*p*-aminobenzenesulphonamido-4,6-dimethylpyrimidine) (XCIX; R $=$ NH$_2$) was first described by Caldwell, Kornfeld, and Donnell[174] in 1941 and subsequently by others[124,166,175] (see above). Fulfilling the promise of early pharmacological studies,[178a,179] Suphadimidine is still held in high regard, and renal complications are normally absent.[177]



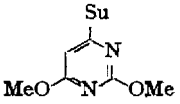
(C)



(CI)



(CII)



(CIII)

(Su $=$ *p*-aminobenzenesulphonamido)

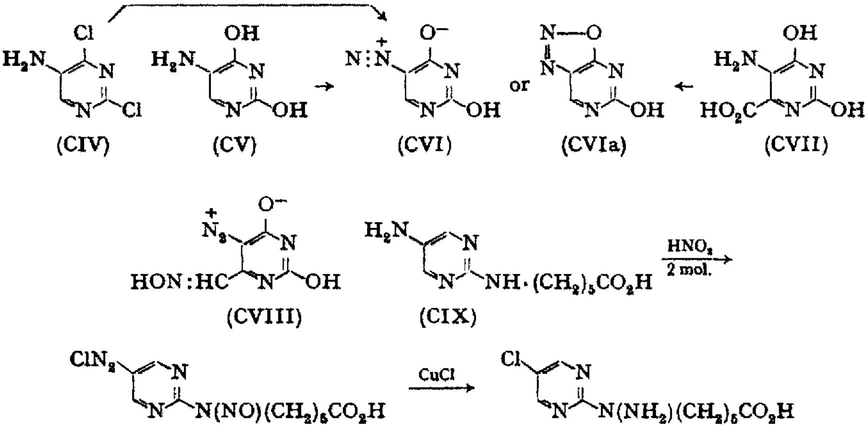
Other pyrimidines include Sulphasomidine B.P.C. (4-*p*-aminobenzenesulphonamido-2,6-dimethylpyrimidine)[180] (CII) which is an isomer of Sulphadimidine, and being but slightly acetylated in the body has not caused renal damage, and the more recent "Madribon" (4-*p*-aminobenzenesulphonamido-2,6-dimethoxypyrimidine) (CIII) which is claimed to be long-acting and excreted in the urine as a soluble glucuronide.[181] Both of these compounds have been prepared by an interesting method[182,183] involving fusion of sodio sulphanilamide, acetamide (as solvent) and 2,4-dimethyl(or dimethoxy)-pyrimidin-6-yltrimethylammonium chloride. The dimethyl compound at least has also been made by more usual means.[184,185]

E. Diazotization

Some 5-aminopyrimidines can be diazotized, and a few 2- and 4-amino derivatives undergo some reactions which could be the outcome of diazotization.

5-Aminopyrimidine itself, when treated at 0° with nitrous acid, evolves spontaneously about 80% of a mole of nitrogen, but no 5-

hydroxy pyrimidine could be isolated.[102] 5-Amino-2,4-dichloropyrimidine (CIV), however, has been diazotized and coupled with β-napthylamine to give 5-(2-aminonaphth-1-ylazo)-2,4-dihydroxypyrimidine, the chlorine atoms having hydrolysed during the diazotization. When the same diazotized solution was neutralized, the heat-stable "diazouracil" (CVI) crystallized out.[102] Diazouracil was more normally obtained by diazotization of 5-amino-2,4-dihydroxypyrimidine (CV) followed by neutralization;[30,186,187] the product dried at room temperature analysed for a diazonium hydroxide, but after drying at 100° for an anhydride which is generally assumed to be similar to those derived, for example, from sulphanilic acid, and therefore to be represented by (CVI) or perhaps (CVIa). Diazouracil was also made by the spontaneous decarboxylation of the diazonium hydroxide from 5-amino-4-carboxy-2,6-dihydroxypyrimidine[188] (CVII). Diazouracil has been coupled with α- and β-naphthol and with "R-salt", as well as with 2,4,6- and 2,4,5-trihydroxypyrimidines, respectively in the 5 and 6 position.[30,187] The action of nitrous acid on 5-amino-2,4-dihydroxy-6-methylpyrimidine yields[101,188] the homologue of diazouracil, additionally complicated by nitrosation of the 6-methyl group to give what is probably (CVIII).



(CIV) (CV) (CVI) (CVIa) (CVII)

(CVIII) (CIX)

(CX) (CXI)

The reaction of diazotized 5-amino-2,4-dihydroxypyrimidine with sodium disulphide gives di(2,4-dihydroxypyrimidin-5-yl) disulphide, with thiourea gives (*via* the thiouronium salt) 2,4-dihydroxy-5-mercaptopyrimidine, and with potassium ethyl xanthate gives the same mercapto derivative.[189]

2,5-Diamino-4,6-dimethylpyrimidine, upon diazotization and treatment with potassium iodide, gives 2-amino-5-iodo-4,6-dimethylpyrimidine[101] and it may also be coupled readily with dimethylaniline to give 2-amino-5-*p*-dimethylaminophenylazo-4,6-dimethylpyrimidine.[101] 5-Amino-2-carboxyamylaminopyrimidine (CIX) has been diazotized, and warming the solution gives the 5-hydroxy analogue.[190] The same amine, if diazotized with excess of nitrous acid, gives the *N*-nitroso derivative (CX), which undergoes the Sandmeyer reaction with cuprous chloride, and at the same time has the nitroso group reduced, to give 2-α-(carboxyamylamino)hydrazino-5-chloropyrimidine (CXI). The 5-bromo analogue was prepared similarly.[190] 2,5-Diamino-4-methyl-6-methylthiopyrimidine can be diazotised and then converted into 2-amino-5-cyano(or formyl)-4-methyl-6-methylthiopyrimidine by the appropriate reagent.[192]

Pyrimidines with 2-, 4-, or 6-amino groups have been converted into the corresponding hydroxy derivatives by the action of nitrous acid, possibly *via* an unstable diazo derivative. Typical examples are the preparations of 4-hydroxy-2,6-dimethylpyrimidine,[191] 2,4-dihydroxypyrimidine from 4-amino-2-hydroxypyrimidine,[193] and 5-chloro-2-hydroxypyrimidine.[173] Other examples are given in Chapter VII, Sect. 1.D. Extranuclear aminopyrimidines have also been converted into their hydroxy analogues, *e.g.* 4-amino-5-hydroxymethyl-2-methylpyrimidine[80,99] and other related compounds.[84,194–197]

Some 2-aminopyrimidines have been used to prepare 2-chloro analogues by the action of nitrous acid under diazotization conditions in the presence of concentrated hydrochloric acid. The best preparation of 2-chloropyrimidine (from the readily available 2-aminopyrimidine) is by these means,[43,100] and other derivatives have been so made.[100,114]

The action of nitrous acid on 4,5-diaminopyrimidines is discussed immediately below.

F. Bicyclic Heterocycles from Aminopyrimidines

Below are given a few brief examples of the use of aminopyrimidines in the formation of some representative bicyclic systems which incorporate the amino nitrogen atom as part of the second ring. The list of systems is not intended to be complete.

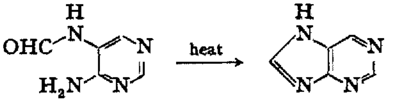
Purine (CXIII) is formed by thermal cyclization of 4-amino-5-

formamidopyrimidine[5b,65] (CXII). Preliminary reaction with bistrimethylsilylamine facilitates some cyclizations.[309]

8-Azapurine (CXV) is formed by the action of nitrous acid on 4,5-diaminopyrimidine[198–200] (CXIV), and a great many derivatives have been made similarly,[200–203] especially following the discovery that guanine in the living cell is powerfully inhibited by 8-azaguanine.[202–205]

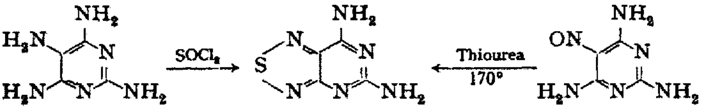
8-Thiapurines have been made[206,207] from aminopyrimidines. For example, 2,6-diamino-8-thiapurine (CXVII) was made either by the action of thionyl chloride on tetra-aminopyrimidine (CXVI) or by melting together 2,4,6-triamino-5-nitrosopyrimidine (CXVIII) and thiourea.[207] 8-Selenapurines have been similarly made,[208] for example by the action of selenous acid on 4,5,6-triaminopyrimidine to give 6-amino-8-selenapurine.[209]

Pteridines have been made from 4,5-diaminopyrimidines since 1901, when 4,5-diamino-6-methylpyrimidine was condensed with benzyl to give 4-methyl-6,7-diphenylpteridine[201] (CXIX). Pteridine itself was later made from 4,5-diaminopteridine and glyoxal.[210,211] Other pteridine syntheses from monoaminopyrimidines are known.[212–214] The subject has been reviewed.[215]

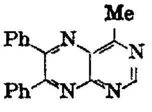


(CXII) (CXIII)

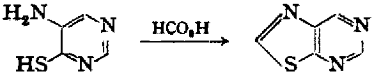
(CXIV) (CXV)



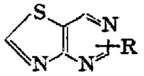
(CXVI) (CXVII) (CXVIII)



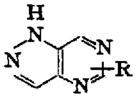
(CXIX)



(CXX) (CXXI)



(CXXII)



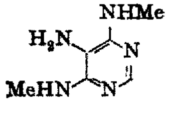
(CXXIII)

Thiazolo[5,4-d]pyrimidine (CXXI) has been made by treating 5-amino-4-mercaptopyrimidine (CXX) with formic acid,[216] and many derivatives in the series by similar means.[56,141,143,217,218] Thiazolo [4,5-d]pyrimidines (CXXII),[219] 1,2,4,6-tetra-azanidenes (CXXIII)[101] and other ring systems[101] have also been made from amino pyrimidines.

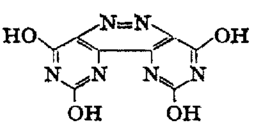
G. Other Reactions

Aminopyrimidines have occasionally been converted into the corresponding mercapto derivatives with phosphorus pentasulphide or hydrogen sulphide, as described in Chapter VIII, Sect. 1.A(7).

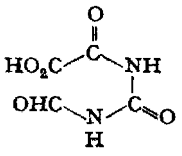
Anyone who has handled 4,5-diaminopyrimidines will be familiar with the way many of these compounds darken on keeping as free bases. The triamines and alkoxy-diamines are particularly troublesome, and 4,5-diamino-2-dimethylaminopyrimidine obtained by dithionite reduction of its nitro analogue, appears to be almost black.[211] Even the rapid filtration of the colourless alcoholic solution of 2,4,5-triaminopyrimidine produced by catalytic hydrogenation of its 5-nitro-analogue, will result in a red solution, and finally a red solid.[126] It must be added that the decomposition is slight, and these dark solids are quite suitable as intermediates for pteridines, which are produced in good yield from such material. That the coloration is indeed due to aerial oxidation is shown by the production of 5-amino-4,6-bismethylaminopyrimidine (CXXIV) as a white solid, by working in a nitrogen box throughout the isolation and recrystallizations.[220] The salts of these amines are relatively stable, and they are often isolated and kept as such for this reason. No work has been done on the constitution of the coloured oxidation products, although observations on the fluorescence of some of them have been reported.[221]



(CXXIV)



(CXXV)



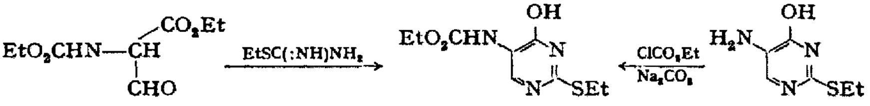
(CXXVI)

The oxidation of 5-amino-2,4-dihydroxypyrimidine with ferricyanide[222] is interesting in giving what is probably a symmetrical dipyrimidinopyridazine (1,3,6,8-tetrahydroxy-2,4,5,7,9,10-hexaazaphenanthrene) (CXXV). Oxidation with bromine-water[223] gives "isodialuric acid", and permanganate oxidation[224] opens the ring to give (CXXVI).

5-Aminopyrimidine condenses with nitrosobenzene in boiling acetic acid to give 5-phenylazopyrimidine.[102]

6. Urethanes (Alkoxycarbonylaminopyrimidines)

Urethanes of the pyrimidine series have been made by several methods. The Principal Synthesis has been used to make, for example, 5-ethoxycarbonylamino-4-hydroxy-2-methylpyrimidine from ethyl α-ethoxycarbonylamino-α-formylacetate (CXXVII) and acetamidine in aqueous alkali.[74] The same aliphatic starting material (CXXVII) was used with *S*-ethylthiourea to give 5-ethoxycarbonylamino-2-ethylthio-4-hydroxypyrimidine[225] (CXXVIII). The "open chain intermediate" isolated at the same time has been shown[164] to be really 2-ethylthio-5-formamido-4-hydroxypyrimidine, which arose from the use of crude starting material. Both pyrimidines were made[164] by unambiguous routes by treatment of 5-amino-2-ethylthio-4-hydroxypyrimidine (CXXIX) respectively with ethyl chloroformate and amyl formate.



(CXXVII) (CXXVIII) (CXXIX)

Ethyl chloroformate has also been used to make other urethanes, generally by treatment of the corresponding amino derivative in dilute aqueous alkali. Secondary amines, as well as 4- and 5-primary amino derivatives, respond to such treatment, giving, for example, 4-ethoxycarbonylamino-2,6-diethyl-5-methylpyrimidine,[226][*] 6-amino-5-ethoxycarbonylamino-1-ethyluracil,[227] 4-amino-5-ethoxycarbonylamino-2,6-dihydroxypyrimidine,[228] 5-ethoxycarbonylamino-1,2,3,4,-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine,[229] the same compound without the 6-hydroxy group,[228] 5-(*N*-ethoxycarbonyl-*N*-methylamino)-2,4-dihydroxy-6-methylaminopyrimidine,[230] and the corresponding 5-(*N*-ethyl-*N*-methoxycarbonylamino) analogue.[231]

Hofmann or Curtius reactions can also give urethanes. The first is represented by the treatment of 5-carbamoyl-2,4-dimethylpyrimidine (CXXX) in methanol with bromine to give 94% of 5-methoxycarbonylamino-2,4-dimethylpyrimidine[63] (CXXXI). A 2-ethyl homologue was made similarly.[63] The Curtius reaction has been used in the conversion of 5-hydrazinocarbonylmethyl-2,4-dihydroxy-6-methylpyrimidine, by

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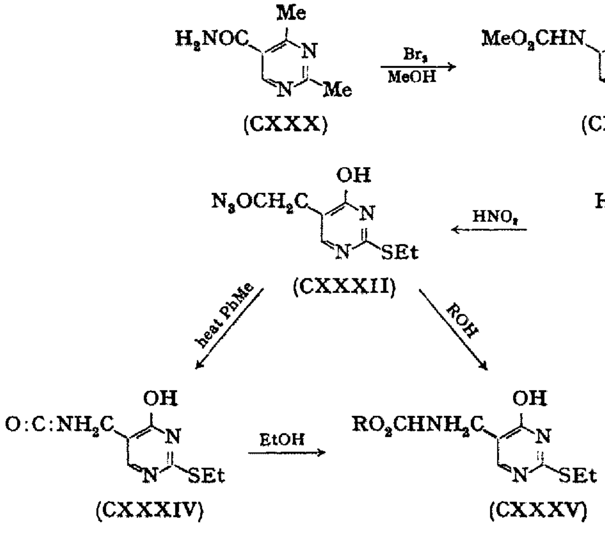
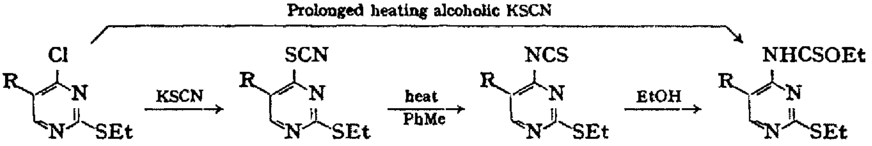
[*] These structures must be treated with some reserve. Alkylation may well occur in some cases on $N_{(1)}$ or $N_{(3)}$.

treatment with nitrous acid, into the 5-azidocarbonylmethyl analogue, which loses nitrogen on heating with alcohol to give 5-ethoxycarbonylaminomethyl-2,4-dihydroxy-6-methylpyrimidine.[85] Similar procedures were used to make the last compound lacking its 6-methyl group,[83] and to make 5-ethoxycarbonylaminomethyl-2-ethylthio-4-hydroxypyrimidine[83] (CXXXV; R=Et) from (CXXXIII). The intermediate azide (CXXXII) for this, on treatment with benzyl alcohol in place of ethanol gave the corresponding benzylurethane, 5-benzyloxycarbonylaminomethyl-2-ethylthio-4-hydroxypyrimidine (CXXXV; R=CH_2Ph), and the same azide (CXXXII) was also converted into the isocyanate (CXXXIV) by heating in toluene and this alcoholized, to provide[83] a second route to the urethane (CXXXV; R=Et). Another example of the Curtius reaction is the treatment of 5-hydrazinocarbonyl-2,4,6-trimethylpyrimidine with alcoholic nitrous acid to give (unanalysed) 5-ethoxycarbonylamino-2,4,6-trimethylpyrimidine.[63]



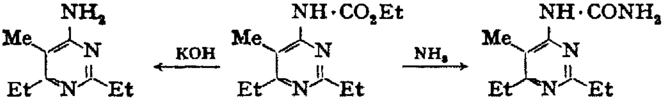
Many thiourethanes have been made from isothiocyanates. The route generally involves treatment of a chloropyrimidine, *e.g.* (CXXXVI), with potassium thiocyanate, to give the thiocyanato derivative (CXXXVII), which is isomerized by heating in toluene or xylene to the isothiocyanato derivative (CXXXVIII). Warming this in an alcohol gives the thiourethane (CXXXIX). In this way have been made 4 - ethoxythiocarbonylamino - 2 - ethylthio - 5 - phenylpyrimidine[232]

(CXXXIX; R=Ph), its 6-phenyl analogue,[233] alkoxy homologues of these,[232,233] 5-ethoxycarbonyl-4-ethoxythiocarbonylamino-2-ethylthiopyrimidine,[86] and other analogues.[234] An abbreviated form of the above route, whereby prolonged boiling of the chloro compound with alcoholic potassium thiocyanate serves rather poorly to perform all three steps in one operation, is exemplified in the conversion of 4-chloro-2-ethylthiopyrimidine (CXXXVI; R=H), or its 5-ethoxy derivative, respectively into 4-ethoxythiocarbonylamino-2-ethylthiopyrimidine[235] (CXXXIX; R=H) and its 5-ethoxy derivative.[236]

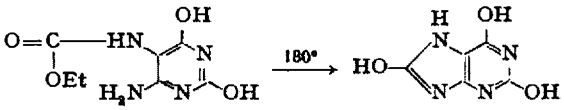


(CXXXVI) (CXXXVII) (CXXXVIII) (CXXXIX)

The most important reaction of a urethane is its alkaline hydrolysis and decarboxylation to the corresponding amine (as in the Curtius reaction). Thus 5-ethoxycarbonylamino-2-ethylthio-4-hydroxypyrimidine on heating with aqueous sodium hydroxide gives 5-amino-2-ethylthio-4-hydroxypyrimidine,[225] and 4-ethoxycarbonylamino-2,6-diethyl-5-methylpyrimidine (CXLI) with alkali, or more slowly by boiling water, gives its 4-amino analogue[226] (CXL). 5-Ethoxycarbonylamino-2,4-dimethylpyrimidine is conveniently converted (86%) into 5-amino-2,4-dimethylpyrimidine by boiling with aqueous barium hydroxide,[63] and 5-amino-2,4,6-trimethylpyrimidine is formed from its urethane by dry distillation with calcium hydroxide.[63] Acid hydrolysis of urethanes seems to be unsatisfactory.[83,85]



(CXL) (CXLI) (CXLII)

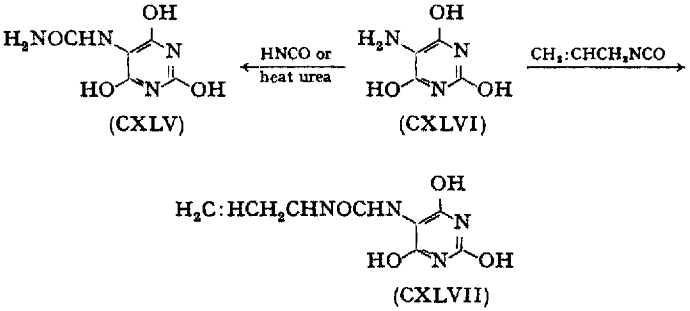


(CXLIII) (CXLIV)

Urethanes, on treatment with ammonia or amines, give ureido or substituted ureido pyrimidines, as in the preparation of 2,4-diethyl-5-methyl-6-ureidopyrimidine (CXLII) or its 6-phenylureido analogue by warming the urethane (CXLI) with ammonia or aniline.[226] Cyclic ureido compounds can be formed when there is an amino group next to the urethane group. Thus 4-amino-5-ethoxycarbonylamino-2,6-dihydroxypyrimidine (CXLIII) on heating at 180° gives uric acid[228] (CXLIV), and other examples are known.[227,230]

7. Ureidopyrimidines

Ureidopyrimidines have been used as intermediates in purine synthesis, but apart from this they are of no great interest. Several have been made[226] by treatment of urethanes with ammonia or amines (see above), but the usual method of preparation is by the action of aqueous potassium cyanate on the hydrochloride of an aminopyrimidine. 5-Amino-2,4-dihydroxypyrimidine in this way gives 2,6-dihydroxy-5-ureidopyrimidine;[237-240] its 6-methyl derivative was made

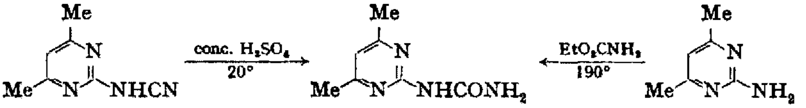


(CXLV) (CXLVI)

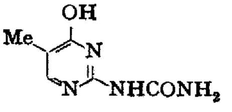
(CXLVII)

similarly[241,242] and also 2,4,6-trihydroxy-5-ureidopyrimidine or "pseudouric acid"[243] (CXLV). The last compound may also be made by heating 5-amino-2,4,6-trihydroxypyrimidine with urea.[244] The use of substituted isocyanates is exemplified in the treatment of 5-amino-2,4,6-trihydroxypyrimidine (CXLVI) with allyl isocyanate to give 5-allylureido-2,4,6-trihydroxypyrimidine[245] (CXLVII). The 5-amino group is preferentially attacked in this way, so that 4,5-diamino-2,6-dihydroxypyrimidine gives 4-amino-2,6-dihydroxy-5-ureidopyrimidine,[246] which cyclizes to uric acid, or using phenyl isocyanate gives the corresponding phenylureido derivative,[246] which cyclizes to 9-phenyluric acid. 6-Amino-1-phenyl-5-ureidouracil and analogues were made similarly.[247]

2-Ureidopyrimidines have been made by acid hydrolysis of the corresponding cyanoaminopyrimidines, which were generally made by primary synthesis. This route is illustrated by the condensation of dicyanodiamide (cyanoguanidine) with acetylacetone to give 2-cyanoamino-4,6-dimethylpyrimidine* (CXLVIII), which on treatment with sulphuric acid gives 4,6-dimethyl-2-ureidopyrimidine[248] (CXLIX). The same compound was made by heating at 190° 2-amino-4,6-dimethylpyrimidine (CL) and urethane.[248] Cyanoaminopyrimidines were also hydrolysed by boiling with 10% hydrochloric acid to give 4-hydroxy 5-methyl-2-ureidopyrimidine (CLI) and several related compounds.[249]



(CXLVIII) (CXLIX) (CL)



(CLI)

Thioureidopyrimidines may be made by treating aminopyrimidines with potassium thiocyanate or with thiourea. Thus 5-amino-2,4-dihydroxy-6-methylpyrimidine (CLII) with thiocyanate gives[252] 2,4-dihydroxy-6-methyl-5-thioureidopyrimidine** (CLIII), and 5,6-diamino-1-methyluracil with phenyl isothiocyanate gives 6-amino-1-methyl-5-phenylthioureido-uracil[246] Fusion of 4-amino-5-bromo-2,6-dimethylpyrimidine with thiourea in a sealed tube at 180° gave 5-bromo-2,6-dimethyl-4-thioureidopyrimidine.[253]

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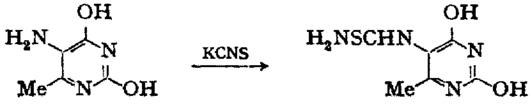
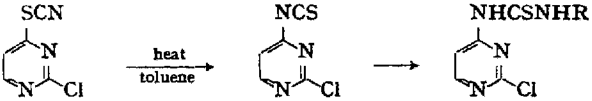
* This compound was first made by Hale and Vilbrans[250] who formulated it as 1-cyano-1,2-dihydro-2-imino-4,6-dimethylpyrimidine. This has been declared incorrect, and the structure written as a 2-cyanoamino derivative on the grounds of an unambiguous synthesis from 2-chloro-4,6-dimethylpyrimidine and sodium cyanamide.[248] Despite this, Fabbrini[251] has advanced evidence that the initial product is a mixture of the two isomers.

** The Western-language *Supplement*,[252] *Chemisches Zentralblatt*, and *Chemical Abstracts* all err in giving "nitrouracil" instead of "the nitrouracil" (*i.e.* methyl nitrouracil), as the starting point of this synthesis. The lack of the definite article in Japanese probably explains this error.

The other general method of preparing thioureidopyrimidines is treatment of isothiocyanatopyrimidines with ammonia or amines. An illustration is provided by the rearrangement of 2-chloro-4-thiocyanatopyrimidine (CLIV) (by heating in toluene) to 2-chloro-4-isothiocyanatopyrimidine (CLV) followed by gentle treatment with ammonia



(CLII) (CLIII)



(CLIV) (CLV) (CLVI)

or aniline to give[254] respectively 2-chloro-4-thioureidopyrimidine (CLVI; R=H) or 2-chloro-4-phenylthioureidopyrimidine (CLVI; R=Ph). Similarly prepared were 2-ethylthio-4-thioureidopyrimidine[235] and its 6-methyl,[219,255] 5-methyl,[235] 5,6-dimethyl,[256] 5-ethyl, and other such derivatives.[232,233] The corresponding phenylthioureido derivatives are also described in the same papers.

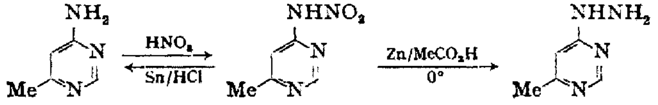
A few semicarbazido- and thiosemicarbazidopyrimidines are known. Thus 2-hydrazino-4-methylpyrimidine hydrochloride with potassium thiocyanate gives 4-methyl-2-thiosemicarbazidopyrimidine[113] (*cf.* an earlier attempt[258]). The same compound was also made from 2-chloro-4-methylpyrimidine with thiosemicarbazide.[113] The isomeric 4-methyl-6-thiosemicabazidopyrimidine was made by the thiocyanate method,[110] and 4-methyl-6-semicarbazidopyrimidine from 4-hydrazino-6-methylpyrimidine hydrochloride with potassium cyanate.[110] 4-Hydroxy-6-methyl-2-semicarbazidopyrimidine was made similarly.[110]

8. Other Substituted-amino-pyrimidines

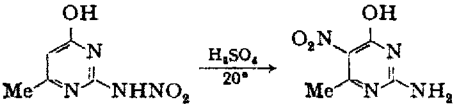
Some examples of aminopyrimidines which carry groups (other than alkyl) attached to the amino substituent, are given below.

A. Nitroamines

The nitroamino group is represented in pyrimidines by 4-methyl-6-nitroaminopyrimidine (CLVIII) and its 2-chloro derivative, made by nitration of the corresponding aminopyrimidines.[201] Reduction of the first nitroamine (CLVIII) with tin and hydrochloric acid produced 4-amino-6-methylpyrimidine (CLVII), but gentle reduction with zinc and acetic acid at 0° gave 4-hydrazino-6-methylpyrimidine (CLIX). These facts, along with the solubility of the nitroamine in ammonia, constitute good evidence for the nitroamino structure of (CLVIII). On the other hand, the so-called "nitroamine" produced by nitration of 2-amino-4-hydroxy-6-methylpyrimidine, and the "hydrazine" produced from it by reduction,[258] have been shown to be respectively 2-amino-4-hydroxy-6-methyl-5-nitropyrimidine (CLXI) and 2,5-diamino-4-hydroxy-6-methylpyrimidine.[111, 259] Authentic 4-hydroxy-6-methyl-2-nitroaminopyrimidine (CLX) was, however, made[111] by condensing ethyl acetoacetate and nitroguanidine. It was converted into 2-hydrazino-4-hydroxy-6-methylpyrimidine by treatment with hydrazine hydrate, and the hydrazino group could be removed with cuprous hydroxide to give 4-hydroxy-6-methylpyrimidine.[111] The nitroamine (CLX) rearranges to the 5-nitro derivative (CLXI) at 20° in concentrated sulphuric acid.[111]



(CLVII) (CLVIII) (CLIX)

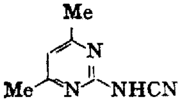


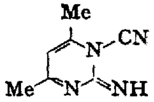
(CLX) (CLXI)

This work has been greatly extended[257a, 257b] by the preparation of more 2-nitroaminopyrimidines with nitroguanidine in a Principal Synthesis. Moreover, the nitroamino group in these compounds may be replaced not only by hydrazine and substituted hydrazines, but by primary and secondary amines. Thus, for example, 4-hydroxy-6-methyl-2-nitroaminopyrimidine on warming with aniline or hydroxylamine for a few minutes on the steam bath, gives respectively 2-anilino-4-hydroxy-6-methylpyrimidine and 4-hydroxy-2-hydroxyamino-6-methylpyrimidine.

B. Cyanoamines

Cyanoaminopyrimidines have been made by using dicyanodiamide as the "one-carbon fragment" in Common Syntheses. Despite some contrary statements[250, 251, 260] the cyanoamino isomer does seem at least to predominate in the product of such condensations, and the isomer with a cyano group attached to the ring nitrogen is a minor constituent, if indeed it occurs at all.[248, 261] Thus dicyanodiamide and acetylacetone give mainly 2-cyanoamino-4,6-dimethylpyrimidine[248] (CLXII) and not* 1-cyano-1,2-dihydro-2-imino-4,6-dimethylpyrimidine[250] (CLXIII).


(CLXII)


(CLXIII)

Other 2-cyanoaminopyrimidines made in this way are typified by the 4-hydroxy-6-methyl, 4-hydroxy-6-phenyl, and 4-hydroxy-5-methyl derivatives.[249] The acid hydrolysis of cyanoamino compounds produces ureido derivatives (Sect. 7).

C. Sulphoamines

The constitution of the product produced from nitrouracil[148, 262, 263] by dithionite reduction has been discussed in Chapter V, Sect. 1.B. Whether it is 5-amino-2,4-dihydroxy-6-sulphopyrimidine or 2,4-dihydroxy-5-sulphoaminopyrimidine, is at present uncertain. This uncertainty does not apply to 2,4,6-triamino-5-sulphoaminopyrimidine made by the reduction of the corresponding nitroso derivative with sodium hydrogen sulphite or from tetra-aminopyrimidine with sulphuryl chloride,[206] or to 2,4,6-trihydroxy-5-sulphoaminopyrimidine made from alloxan or violuric acid with ammonium sulphide.[264, 265]

D. Chloroamines

The action of chlorine in aqueous alcoholic hydrochloric acid on 4-amino-2-ethylthio-5-methylpyrimidine is said[266] to give 4-chloroamino-2-ethylsulphonyl-5-methylpyrimidine. The only evidence advanced for this formulation could equally well fit the simple hydrochloride of 4-amino-2-ethylsulphonyl-5-methylpyrimidine!

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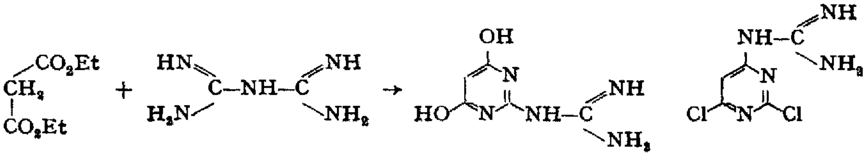
* See, however, the footnote in Section 7.

E. Guanidinopyrimidines

2-Guanidinopyrimidines may be made by the Principal Synthesis using diguanide (CLXIV). Thus, with diethyl malonate, 2-guanidino-4,6-dihydroxypyrimidine (CLXV) is formed,[267] or with phenylazoacetylacetone, 2-guanidino-4,6-dimethyl-5-phenylazopyrimidine is formed.[101]

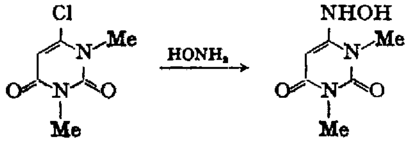


(CLXIV) (CLXV) (CLXVI)

Replacement of a chlorine by a guanidino group is naturally possible, and in this way from 2,4,6-trichloropyrimidine and guanidine in aqueous acetone was made 2,4-dichloro-6-guanidinopyrimidine[268] (CLXVI).

F. Hydroxyamines

Hydroxyaminopyrimidines have been made by replacing chlorine by hydroxylamine. Thus 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (CLXVII) on refluxing with alcoholic hydroxylamine gives mainly 1,2,3,4-tetrahydro-6-hydroxyamino-1,3-dimethyl-2,4-dioxopyrimidine (CLXVIII). Acetylation gave the corresponding acetoxyamino analogue, catalytic reduction gave the corresponding amino



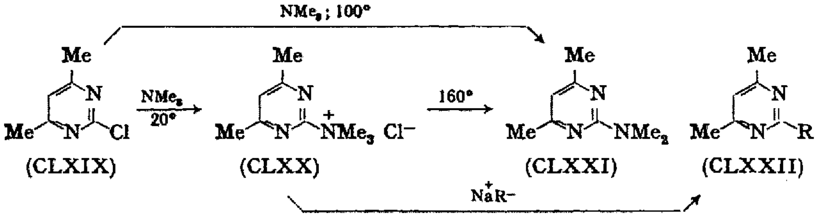
(CLXVII) (CLXVIII)

derivative, and diazomethane the corresponding methoxyamino compound.[269]

The nitroamino group has also been replaced by hydroxylamine. For example may be quoted the formation of 2-hydroxyamino-4,6-dimethylpyrimidine from the corresponding 2-nitroamino compound by warming with aqueous hydroxylamine.[257a]

G. Trimethylpyrimidinylammonium Chlorides

Simple chloropyrimidines react slowly with trimethylamine in benzene to give quaternary derivatives. Thus 2-chloro-4,6-dimethylpyrimidine (CLXIX) gives 4,6-dimethylpyrimidin-2-yltrimethylammonium chloride[270] (CLXX), and 4-chloro-2,6-dimethyl- and 4-chloro-2,6-dimethoxy-pyrimidine give similar quaternary compounds.[270] 2,4,6-Trichloropyrimidine gives a tris quaternary compound[271] (Ch. VI, Sect. 5.B(1)(b)). When the preparation of (CLXX) was attempted at 100°, methyl chloride was lost, and the product (62 %) was 2-dimethylamino-4,6-dimethylpyrimidine[270] (CLXXI). The same product was obtained[272] by heating (CLXX) at 160°, and the 4-isomer behaved similarly. Treatment of (CLXX) with sodium methoxide, sodium phenoxide, and sodium *p*-nitrophenoxide led to replacement of the entire quaternary grouping in favour of the alkoxy group, thus producing respectively 2-methoxy-4,6-dimethylpyrimidine (CLXXII; R=OMe) and its phenoxy and *p*-nitrophenoxy analogues.[272] Similarly, sodium hydroxide gave mainly 2-hydroxy-4,6-dimethylpyrimidine (CLXXII; R=H), and potassium cyanide 2-cyano-4,6-dimethylpyrimidine[272, 273] (CLXXII; R=CN). The 4-cyano-isomer and 4-cyano-2,6-dimethoxypyrimidine were produced similarly.[272, 273] The same reaction with, for example, sodium sulphanilamide has produced useful sulphonamides[182,183] (Sect. 5.D(6)).



9. Some Naturally Occurring Aminopyrimidines

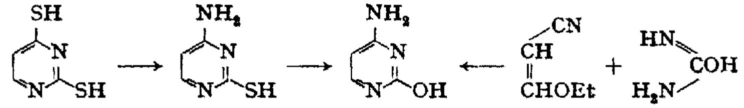
References to the major reviews of nucleosides and nucleotides have already been given in Chapter VII, Sect. 8. Below are summarized the isolation, synthesis and reactions of cytosine, 5-methylcytosine, and 5-hydroxymethylcytosine.

A. Cytosine: 4-Amino-2-hydroxypyrimidine

Cytosine (CLXXV) was first isolated in 1894 from the nucleic acid of calf thymus.[274] By 1903 its structure was known,[193,275–277] and Wheeler and Johnson[120,278] synthesized it from 2-ethylthio-4-hydroxypyrimidine *via* the 4-chloro analogue. The acid hydrolysis of ribonucleic acid gives the nucleotides among which are the cytidylic acids, a and b. These are the 2′- and 3′-phosphates of cytidine, and further hydrolysis removes the phosphate ester to give cytidine (the 1-β-D-ribofuranoside of cytosine), and thence cytosine itself. The deoxyribonucleic acids also yield deoxynucleotides including cytosine deoxyriboside-5′-phosphate, from which the phosphate can be removed to give cytosine deoxyriboside and on glycoside-fission cytosine again results.

There are two good ways to make cytosine in quantity: thiouracil is thiated to 2,4-dimercaptopyrimidine (CLXXIII), amination with ammonia gives 4-amino-2-mercaptopyrimidine (CLXXIV) which with chloroacetic acid gives cytosine[40,279,280] (CLXXV). The second method is a Common Synthesis from β-ethoxyacrylonitrile (CLXXVI) (virtually cyanoacetaldehyde) and urea.[281]

Cytosine is oxidized by permanganate to oxalic acid, biuret, and other products,[193] and with nitrous acid it yields uracil[193] although it has been observed that much more than the theoretical volume of nitrogen is evolved.[282] Nitration readily gives 5-nitrocytosine,[283] but bromination can give 5-bromocytosine,[284] 4-amino-5,5-dibromo-5,6-dihydro-2,6-dihydroxypyrimidine,[284] or 5,5-dibromo-4,5-dihydro-2,4,6-trihydroxypyrimidine[285] according to conditions. The dichloro analogue of the last compound is also known.[286] Acetylation of cytosine gives 4-acetamido-2-hydroxypyrimidine,[120] and this formulation is upheld by the analogous behaviour of 1-methylcytosine.[23] Methylation of cytosine gives little 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine[287] which is, clearly impure,[288] and it is better made by less direct means.[23,161,288] For main products see Chap. x, Sect. 1. A (3) (e).



(CLXXIII) (CLXXIV) (CLXXV) (CLXXVI)

Ultraviolet irradiation of cytosine and some of its derivatives leads to unstable products, which, however, revert to the starting materials in acid or alkali, or even on standing in a neutral medium. While these changes have been likened[289,290] to the reversible photochemical hydration of uracil, it has also been suggested that a tautomer with two hydrogen atoms attached to C_5 (*i.e.* 4-amino-2,5-dihydro-2-oxopyrimidine) might be involved.[291]

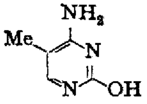
B. 5-Methylcytosine

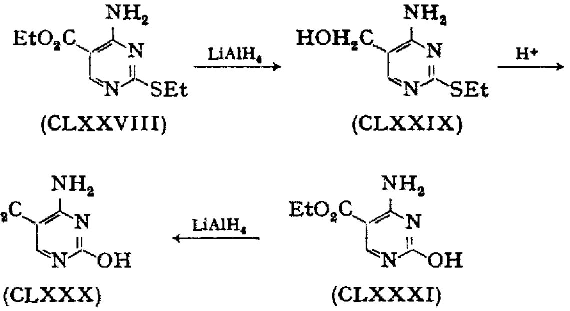
In 1904 Wheeler and Johnson[292] synthesized 5-methylcytosine (CLXXVII) and suggested it as a likely constituent of nucleic acids. In 1925 Johnson and Coghill[293] reported its isolation as a picrate from tubercle bacilli hydrolysates, but in 1949 this "discovery" was shown[294] to be mere wishful thinking by examination of the original specimen of the picrate which was in fact only impure cytosine picrate. 5-Methylcytosine was, however, found in[295–299] and isolated from, the deoxyribonucleotide fractions from thymus, wheat germ, and other sources.[300] Both deoxy-5-methylcytidylic acid (nucleotide)[301,302] and the corresponding nucleoside[303] have been prepared.

The best route to 5-methylcytosine is that from 4-amino-2-mercapto-5-methylpyrimidine by treatment with chloroacetic acid.[280]

C. 5-Hydroxymethylcytosine

In 1952 Wyatt and Cohen[304,305] isolated 5-hydroxymethylcytosine (CLXXX) from the T-even bacteriophages of *E. coli*, where it occurs in place of cytosine. Two good syntheses have been reported. Ethyl ethoxymethylenecyanoacetate and *S*-ethylthiourea gave 4-amino-5-ethoxycarbonyl-2-ethylthiopyrimidine (CLXXVIII) which with lithium


(CLXXVII)



aluminium hydride was reduced to 4-amino-2-ethylthio-5-hydroxymethylpyrimidine (CLXXIX). Hydrolysis thence gave 5-hydroxymethylcytosine[78,306] (CLXXX). The other synthesis is the direct lithium aluminium hydride reduction of 5-ethoxycarbonylcytosine[306,307] (CLXXXI).

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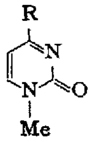
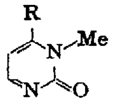
CHAPTER X

The *N*-Alkylated Pyrimidines and Pyrimidine-*N*-Oxides

Normal substitution of the ring nitrogen of pyrimidine is impossible as it lacks a hydrogen atom. However, the presence of a tautomerizable group (such as –OH, –SH, or –NH_2) in the α- or γ-position to a nitrogen atom permits at least a portion of the substance to be in a form having hydrogen attached to the ring nitrogen. In these circumstances, substitution becomes possible and leads to the formation of *N*-alkyl-dihydro-oxo-, imino-, or thio- pyrimidines such as (I), (II), (III), (IV), and their analogues. The accepted nomenclature of such compounds, involving the pedantic term dihydro (or tetrahydro for an *NN'*-dialkyl derivative), is both misleading, in suggesting a reduced ring system, and quite unnecessary in that "1-methyl-4-oxopyrimidine" would be as precise a name for (III) as is 1,4-dihydro-1-methyl-4-oxopyrimidine; furthermore, from the shorter name it is much easier to visualize the structure of (III). The lengthier nomenclature is, however, followed in the present work, because it accords with the rulings of I.U.P.A.C.



(I)



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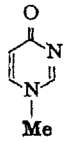
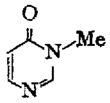


(III)



(IV)

It is also possible for addition to occur at a ring nitrogen atom. Thus pyrimidine can be transformed into pyrimidine-*N*-oxide or into pyrimidine methohalides. It will be appreciated, however, that an α- or γ-hydroxypyrimidine can give the same methohalide either by substitution or addition; the hydriodide of 1,2-dihydro-1-methyl-2-oxopyrimidine is, for example, the same as 2-hydroxypyrimidine methiodide.

1. The Oxopyrimidines

A. Preparation of Oxopyrimidines

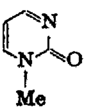
In the methods of preparation given below, there is more often than not ambiguity of structure in the final product. This is simply illustrated by the methylation of 4-hydroxypyrimidine: will it give a 1-methyl-, 3-methyl-, or *O*-methyl derivative? There are all too many cases in the literature where this has been ignored or not been realised by authors, and structures have been boldly written down without adequate confirmatory evidence. In other cases, structures have been based on analogy to rather similar compounds, and this practice is almost as dangerous as the first. A good example in these matters is the history of the condensation of methylguanidine with ethyl cyanoacetate, outlined briefly in Chapter II, Sect. 10.D.

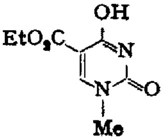
It should be recalled here that oxopyrimidines arising from acylation of hydroxypyrimidines on a ring nitrogen atom, are also known. Thus *N*-acetyldihydro-4-oxopyrimidine[1] and 1-acetyluracil[2] were made by vigorous acetylation of 4-hydroxypyrimidine and of uracil. They are readily hydrolysed.

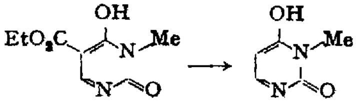
(1) *By the Principal Synthesis*

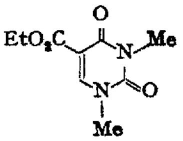
When an *N*-alkylurea is used as a one-carbon fragment in a Principal Synthesis, a 2-oxopyrimidine results. Thus *N*-methylurea and malondialdehyde give 1,2-dihydro-1-methyl-2-oxopyrimidine[3] (V) and there is no ambiguity of structure because the molecule (apart from the methyl group) is symmetrical about a 2–5 line. For the same reason, the formation of 1,2-dihydro-1,4,6-trimethyl-2-oxopyrimidine from *N*-methylurea and acetylacetone,[4,5] is also unambiguous. On the other hand, diethyl α-formylmalonate (in the form of diethyl ethoxymethylenemalonate) reacts as an aldehydo ester with *N*-methylurea to give what could be either 5-ethoxycarbonyl-1-(or 3-)methyluracil[6] (VI or VII). In fact only one isomer was formed, and it proved to be the 3-methyl derivative because, after saponification, decarboxylation gave

3-methyluracil[6] (VIII), and the structure of this was considered known; in any case it was later rigorously confirmed.[7] When *NN'*-dimethylurea is used in the same reaction, 5-ethoxycarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine (IX) is formed,[6] and there is now again no ambiguity of structure. Many such examples of 2-oxopyrimidines will be found in all sections of Chapter II, particularly in Section 8.E where the Whitehead Synthesis is discussed, and other examples are briefly noted in the sections following this.


(V)

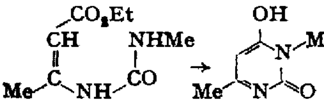

(VI)

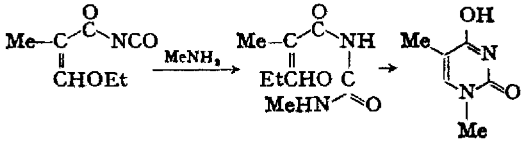

(VII) (VIII)


(IX)

(2) *By Other Primary Syntheses*

The use of other primary syntheses more often leads to an unambiguous result than does the use of the Principal Synthesis. Thus ethyl *β*-aminocrotonate and methyl isocyanate (after cyclization of the intermediate; X) give 3,6-dimethyluracil[8] (XI), and ethyl aminomethyleneacetoacetate and phenyl isocyanate give 5-acetyl-3-phenyluracil.[9] These reactions (and analogous ones which start with an aliphatic lacking a double bond and hence yield first a dihydropyrimidine)[7,10–12] have been particularly useful in checking the configuration of the 1- and 3-alkyluracils made (more easily) by ambiguous routes.


(X) (XI)

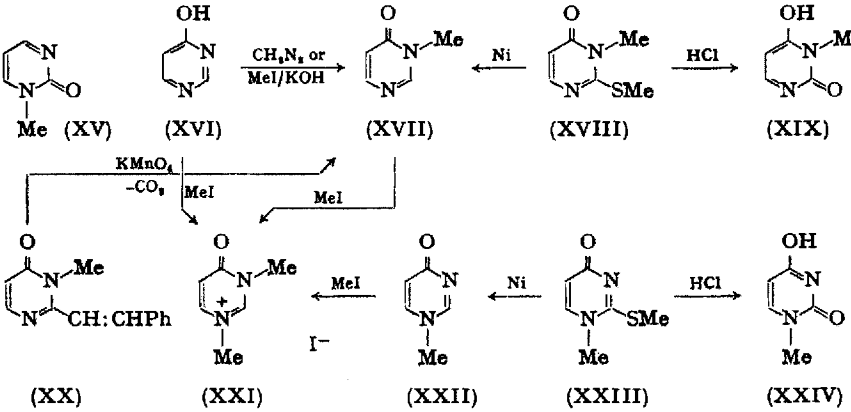

(XII) (XIII) (XIV)

The Shaw synthesis in its various aspects is most valuable in making *N*-alkylated pyrimidines (including nucleosides) and has been discussed in detail in Chapter III, Sect. 1.E. A rather analogous synthesis[13] of 1,5-dimethyluracil (XIV) (and related compounds) *via* the amination of *α*-ethoxymethylene-*α*-methylacetyl isocyanate (XII) with methylamine, and cyclization of the resulting urea (XIII), has also been applied to nucleoside synthesis.[14] Details of the above and several other less important syntheses will be found in Chapter III.

(3) *By Alkylation of Hydroxypyrimidines*

Although 2- and 4-hydroxy derivatives of pyrimidine normally yield *N*-alkylated oxo derivatives, a little alkoxy derivative is sometimes formed, and occasionally appreciable amounts. Some examples have been given in Chapter VII, Sect. 4.C, and alkoxy compounds are easy to detect, for hydrolysis gives the corresponding hydroxy derivative.

(a) *Cases with One Hydroxy Group.* 2-Hydroxypyrimidine with etherial diazomethane gives 52% of 1,2-dihydro-1-methyl-2-oxopyrimidine (XV) along with 17% of 2-methoxypyrimidine.[7] 4-Hydroxy-



pyrimidine similarly gives 51% of 1,6-dihydro-1-methyl-6-oxopyrimidine (XVII) and some 9% of 4-methoxypyrimidine.[7] The same oxopyrimidine is obtained by the action of methyl iodide in alcoholic potash on 4-hydroxypyrimidine,[15] and its structure was shown by making it by desulphurization of 1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine[7,15] (XVIII), whose structure was in turn known because acid hydrolysis gives 3-methyluracil[7] (XIX). It was also made by oxidation and subsequent decarboxylation of 1,6-dihydro-1-methyl-6-oxo-2-styrylpyrimidine[15] (XX). When 4-hydroxypyrimidine was treated with methanolic methyl iodide, a small yield of the quaternary salt, 1,4-(3,4)-dihydro-1,3-dimethyl-4-oxopyrimidinium iodide (XXI) was isolated.[7] The same iodide was also obtained by treating either 1,6-dihydro-1-methyl-6-oxopyrimidine (XVII) or 1,4-dihydro-1-methyl-4-oxopyrimidine (XXII) with methyl iodide.[15] The 1,4-dihydro-1-methyl-4-oxopyrimidine (XXII) does not occur in the products of methylation of 4-hydroxypyrimidine, but has been made indirectly by desulphurizing 1,4-dihydro-1-methyl-2-methylthio-4-oxopyrimidine[7] (XXIII), the structure of which was checked by hydrolysis to 1-methyluracil (XXIV).

Many *C*-alkyl and aryl derivatives of 2- and 4-hydroxypyrimidine have been alkylated. Thus the silver salt of 2-hydroxy-5-phenylpyrimidine on boiling with methyl iodide is said to give 1,2-dihydro-1-methyl-2-oxo-5-phenylpyrimidine,[16] and this is probably true, although no evidence to exclude its being (the unknown) 2-methoxy-5-phenylpyrimidine was presented.

4-Hydroxy-6-methylpyrimidine treated with diazomethane gives, besides a little 4-methoxy-6-methylpyrimidine, a single *N*-methyl derivative[5] which by analogy with 4-hydroxypyrimidine and on independent spectral evidence is probably 1,6-dihydro-1,4-dimethyl-6-oxopyrimidine. Both this compound and its isomer have been prepared from the corresponding imino derivatives,[15] but, being isolated only as picrates, no comparison of m.p. is possible. 4-Hydroxy-2 methylpyrimidine in alcoholic potash gives with methyl iodide[15] or diazomethane,[16a] 1,6-dihydro-1,2-dimethyl-6-oxopyrimidine. This structure was proven by styrylation of the 2-methyl group and its oxidative removal to give the known 1,6-dihydro-1-methyl-6-oxopyrimidine.[15] The isomeric 1,4-dihydro-1,2-dimethyl-4-oxopyrimidine was made from the corresponding imino derivative.[15] 4-Hydroxy-5-phenylpyrimidine on methylation with dimethyl sulphate and alkali gives two isomeric *N*-methyl derivatives[17] distinct from the methoxy compound, but which isomer represents the 1-methyl and which the 3-methyl derivative is unknown.

(b) *Cases with Two Hydroxy Groups.* Efforts to monomethylate 2,4-dihydroxypyrimidine (and its 5- and 6-methyl derivatives), with diazomethane failed,[18] although 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine, is readily formed (from uracil) with diazomethane,[18] methyl iodide in alcoholic potash,[19] or best (94 %) with dimethyl sulphate in alkali.[20,21] The *N*-monomethyluracils have therefore been made by less direct methods: 1-methyluracil has been made by an unambiguous primary synthesis* *via* 5,6-dihydro-1-methyluracil,[7] 3-methyluracil *via* its 5-ethoxycarbonyl derivative,[6] and both isomers can be made as follows: 2-ethylthio-4-hydroxypyrimidine can only monomethylate and gives a separable mixture of 2-ethylthio-1,4-(and 1,6)-dihydro-1-methyl-4(and 6)-oxopyrimidine (XXVI) and (XXVII). The first of these isomers on acid hydrolysis gives 1-methyluracil (XXV), and the other isomer gives 3-methyluracil[22,23] (XXVIII). A more streamlined, but essentially similar process, starting with thiouracil is probably the best at present available[7] for both isomers. 3-Ethyluracil has been made by a rather similar route,[22] but 1-ethyluracil has only been isolated as a by-product in nucleoside synthesis.[24] 1,3-Diethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidine has been made by alkylation of uracil with diethyl sulphate and alkali,[25,26] and its 5-methyl derivative similarly.[26]

The methylation of 2,4-dihydro-6-methylpyrimidine has been extensively investigated. The use of methyl iodide and alcoholic alkali gives a separable mixture of 1,6- and 3,6-dimethyluracil, and 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine,[8,27–32] and a similar mixture is obtained with dimethyl sulphate and alkali.[33] An excess of methylating agent[5] or remethylation of the dimethyluracils, gives good yields of the trimethyluracil, and if, for example, 3,6-dimethyluracil is ethylated, 1-ethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxopyrimidine (1-ethyl-3,6-dimethyluracil) is formed.[26] The 1-butyl[34] and 1-benzyl[35] analogues were made similarly and the latter also by initial benzylation of 6-methyluracil followed by methylation.[35] 3-Cyclohexyl-6-methyluracil has similarly been ethylated and methylated to the appropriate *NN′*-dialkyl derivative.[36] 3,6-Dimethyluracil has also been made by the methylation of 4-hydroxy-2-mercapto-6-methylpyrimidine and 2-ethylthio-4-hydroxy-6-methylpyrimidine respectively to 1,6-dihydro-1,4-dimethyl-2-methylthio-6-oxopyrimidine[35,37] and its ethylthio homologue[38] (which has also been made by a Common Synthesis),[22] and subsequent acid hydrolysis. In the case of the methylthio compound, a small amount of 1,4-dihydro-1,6-dimethyl-2-methylthio-4-oxopyrimidine can be separated and hydrolysed[37] to 1,6-dimethyluracil, which is, however, best made by an unrelated route[39] (Sect. 1.A(4)). The isomeric 1,5- and 3,5-dimethyluracils (the *N*-methylthymines) have been made by way of methylation of related thio ethers[19,40] and other examples

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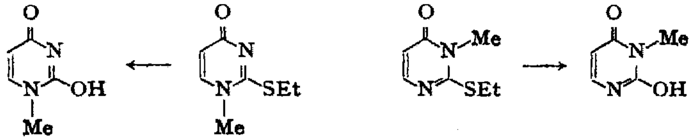
* Despite their importance, the structures of 1- and 3-methyluracils provisionally based on work of Johnson and Heyl[22] were not firmly established until 1955.[7]

of such methylation, ethylation, propylation, and butylation are known.[37,41] 1,2,3,4-Tetrahydro-1,3,5-trimethyl-2,4-dioxopyrimidine was made by methylation of thymine,[18,19] but from the methylation of 2,4-dihydroxy-6-methyl-5-propylpyrimidine only 3,6-dimethyl-5-propyluracil (40 %) was isolated,[42] whereas similar treatment of the 5-butyl analogue gave the 1,3-dimethylated product, 5-butyl-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine[43] in unstated yield. It is not unlikely that this apparent anomaly is simply due to the solubilities of the products in the reaction media. The 1- and 3-benzyluracils have been made by benzylation of 2-ethylthio-4-hydroxypyrimidine, separation of the resulting isomers, and hydrolysis. When 2-hydroxy-4-methylthiopyrimidine was treated similarly only one benzylated isomer was formed which gave finally 1-benzyluracil.[23] 2,4-Dihydroxy-6-propylpyrimidine gives one *N*-monoethyl derivative with diethyl sulphate,[44] but assignment of the ethyl group to the 1-position "based on the work of Hilbert and Johnson[25] who determined that the $N_{(1)}$ position was alkylated (preferentially) over the $N_{(3)}$ position in the case of 2,4-dimethoxypyrimidine", cannot be taken seriously. 2,4-Dihydroxy-6-phenylpyrimidine on alkylation with ethyl chloroacetate gives 1-ethoxycarbonylmethyl-6-phenyluracil (and some dialkylated material) which can be further methylated to 1-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-6-phenylpyrimidine. The isomer with alkyl substituents reversed was made similarly and structures have been authenticated.[45] A good general method of 1,3-dimethylating *C*-alkyluracils has been given.[44]

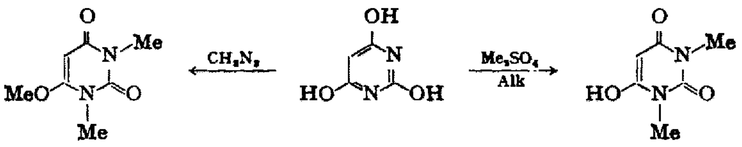


(XXV) (XXVI) (XXVII) (XXVIII)

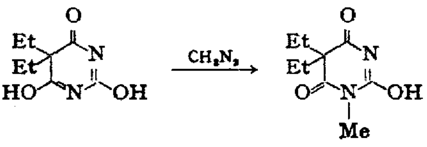
(c) *Cases with Three Hydroxy Groups.* Barbituric acid (XXX) and diazomethane give (as do also the 1-methyl and 1,3-dimethyl derivatives) 1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxopyrimidine[46,47] (XXIX), but dimethyl sulphate and alkali with barbituric acid gives only 1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine[46] (XXXI). Methanolic methyl iodide and silver barbiturate give a different type of product; 5,5-dimethylbarbituric acid and the

5,5-diethyl homologue (XXXII)* is formed similarly.[48,49] When such 5,5-dialkylbarbituric acids are treated with diazomethane, 5,5-diethyl-1-methylbarbituric acid[50] (XXXIII) (identical with that made by the Common Synthesis[51]) and its 5,5-dialkyl homologues[46] result. In each case, it is accompanied by a separable monomethoxy derivative of unknown configuration. On the whole, a Principal Synthesis is generally more satisfactory to make 1-alkyl (or 1,3-dialkyl)-5-alkyl(or 5,5-dialkyl) barbituric acids.[47,51–53]

2,4,5-Trihydroxypyrimidine (isobarbituric acid) gives with diazomethane, a trimethylated compound, *viz.* 1,2,3,4-tetrahydro-5-methoxy-1,3-dimethyl-2,4-dioxopyrimidine.[54] The same compound is also obtained with dimethyl sulphate and alkali.[55] The *N*-monomethyl derivatives have been made indirectly by tin and hydrochloric acid reduction (and subsequent hydrolysis) of 1- and 3-methyl-5-nitrouracils.[56–58]



(XXIX) (XXX) (XXXI)



(XXXII) (XXXIII)

An interesting alkylation with diazoethane has been recorded.[59] 6-Hydroxy-1-methyl-5-ureidouracil on brief treatment gives the 6-ethoxy analogue, but on repeated treatment *N*-ethylates as well, to give 4-ethoxy-1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-5-ureidopyrimidine.

(d) *In the Presence of Nitro Groups.* 2-Hydroxy-5-nitropyrimidine (as sodium salt) heated with methyl iodide is said to give 2-methoxy-5-nitropyrimidine,[60] but the structure needs confirming. 2,4-Dihydroxy-5-nitropyrimidine (XXXIV) (nitrouracil) with methyl iodide at 140°

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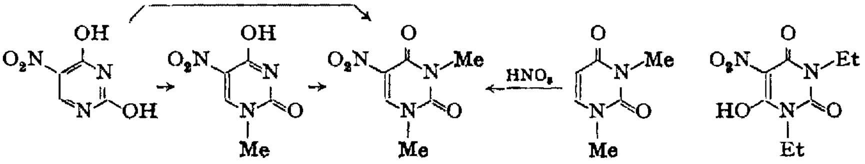
* It will be realised that this, and all 5,5-disubstituted derivatives of barbituric acid and such pyrimidines, are oxo compounds by necessity.

gives 1-methyl-5-nitrouracil[28,61] (XXXV), but it is more conveniently made with dimethyl sulphate[57,62] or can even be obtained by nitrating 1-methyluracil.[7] In turn, 1-methyl-5-nitrouracil can be further methylated to give 1,2,3,4-tetrahydro-1,3-dimethyl-5-nitro-2,4-dioxopyrimidine[58,61] (XXXVI), or this may be made directly from nitrouracil.[62] The dimethyl compound can also be made by nitration of dimethyluracil (XXXVII).[7] Nitrouracil has been ethylated to 1-ethyl-5-nitrouracil[28,61] which has then been methylated to 1-ethyl-1,2,3,4-tetrahydro-3-methyl-5-nitro-2,4-dioxopyrimidine,[28,61] and this compound can also be made by ethylation[28] of 3-methyl-5-nitrouracil (itself obtainable not by methylation, but best by nitration of 3-methyluracil).[7]* 1-Ethyl-1,2,3,6-tetrahydro-3-methyl-5-nitro-2,6-dioxopyrimidine can similarly be made by two distinct alkylations.[6,28] 2,4-Dihydroxy-6-methyl-5-nitropyrimidine on methylation gives 1,2,3,4-tetrahydro-1,3,6-trimethyl-5-nitro-2,4-dioxopyrimidine,[63] but whether its monomethylation has been achieved[61] seems doubtful in the light of later work.[64,65]



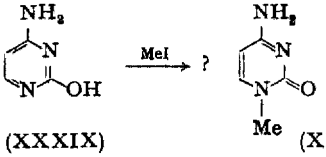
(XXXIV) (XXXV) (XXXVI) (XXXVII) (XXXVIII)

N-Alkylated nitro (or nitroso) barbituric acids have been generally made by nitration or nitrosation *e.g.* of 1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxopyrimidine to its 5-nitro derivative[66] (XXXVIII), or 5-nitroso derivative.[67]

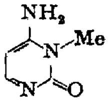
(e) *In the Presence of Amino Groups.* The monomethylation of amino hydroxypyrimidines is logically treated here because the hydroxy group rather than the amino group is the one affected (changed to an oxo group) by such *N*-methylation. 4-Amino-2-hydroxypyrimidine (cytosine; XXXIX) has been methylated.[19,157] The product melts 25° lower than 1-methylcytosine (XL) made by another route. It is a mixture of a dimethyl derivative and 3-methylcytosine (4-amino-2,3-dihydro-3-methyl-2-oxopyrimidine; XLI). A substance reported as the latter was in fact rearranged to 2-hydroxy-4-methylaminopyrimidine[71,72] (XLII). It may be significant that a

* The directions of Johnson and Heyl[22] for this nitration at 100° lead to complete destruction of the product.[7]

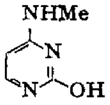
picrate described as that of 3-methylcytosine[73] and made by the methylation and subsequent vigorous hydrolysis of cytidine, has almost the same m.p. as that of 2-hydroxy-4-methylaminopyrimidine picrate.[71] 6-Methylcytosine (4-amino-2-hydroxy-6-methylpyrimidine) has not been methylated, but its 1-methyl derivative has been made by other means.[74] 5-Methylcytosine, however, is said[19] to yield 4-amino-1,2-dihydro-1,5-dimethyl-2-oxopyrimidine, and its structure seems to rest on reasonable evidence.



(XXXIX) (XL)

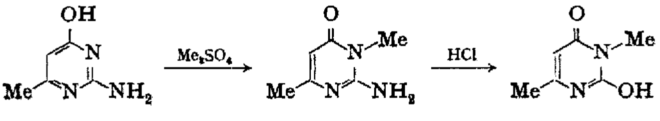


(XLI)

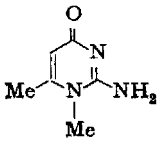


(XLII)

Isocytosine (2-amino-4-hydroxypyrimidine) has now been methylated,[100,158] giving both *N*-methyl derivatives not made by other means. The related 2-anilino-4-hydroxypyrimidine on methylation gives, as well as some 2-anilino-4-methoxypyrimidine, 2-anilino-1,6-dihydro-1-methyl-6-oxopyrimidine, the structure of which has been proven by unambiguous synthesis.[75] 6-Methylisocytosine (2-amino-4-hydroxy-6-methylpyrimidine; XLIII) on methylation gives 2-amino-1,6-dihydro-1,4-dimethyl-6-oxopyrimidine[76–79] (XLIV). It has also been made by primary syntheses,[77,80,81] and the structure indicated by



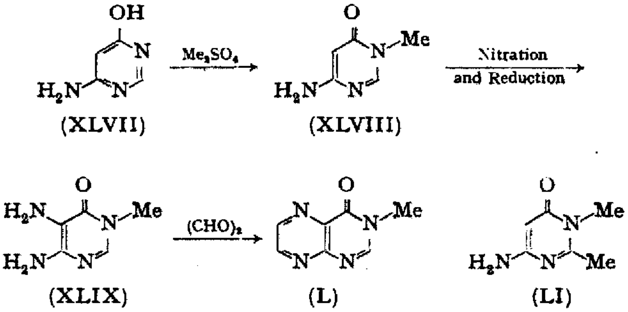
(XLIII) (XLIV) (XLV)



(XLVI)

hydrolysis to 3,6-dimethyluracil[79] (XLV), and other means.[82] The isomeric 2-amino-1,4-dihydro-1,6-dimethyl-6-oxopyrimidine (XLVI) has been made indirectly.[82]

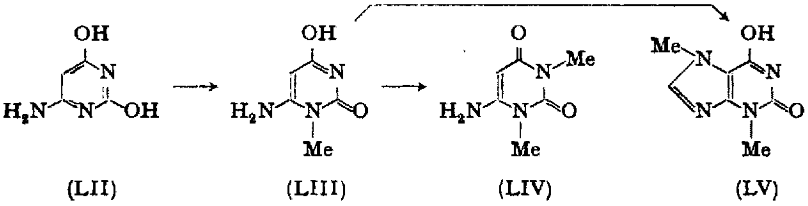
4-Amino-6-hydroxypyrimidine (XLVII) on treatment with dimethyl sulphate gives a single *N*-methyl derivative[83,84] (XLVIII), which on nitration, reduction to (XLIX) and condensation with glyoxal gave the known 3,4-dihydro-3-methyl-4-oxopteridine (L). The initial *N*-methyl derivative was therefore 4-amino-1,6-dihydro-1-methyl-6-oxopyrimidine[84] (XLVIII). The same compound was also made by desulphurization[83] of its 2-methylthio derivative, 4-amino-1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine, which had been made by methylation of 4-amino-6-hydroxy-2-mercaptopyrimidine[83,85] but whose structure had not been rigorously proven.[85] The isomeric 4-amino-3,6-dihydro-3-methyl-6-oxopyrimidine was attempted by desulphurizing 6-amino-1-methyl-2-thiouracil,[83] but it rearranged during the



(XLVII) (XLVIII) (XLIX) (L) (LI)

desulphurization.[84] 4-Amino-6-hydroxy-2-methylpyrimidine on methylation gives 4-amino-1,6-dihydro-1,2-dimethyl-6-oxopyrimidine[86] (LI). The structure, resting on ultraviolet evidence and analogy to the above, is beyond reasonable doubt. Other methylations of amino- and acetamido-hydroxypyrimidines have been described.[83]

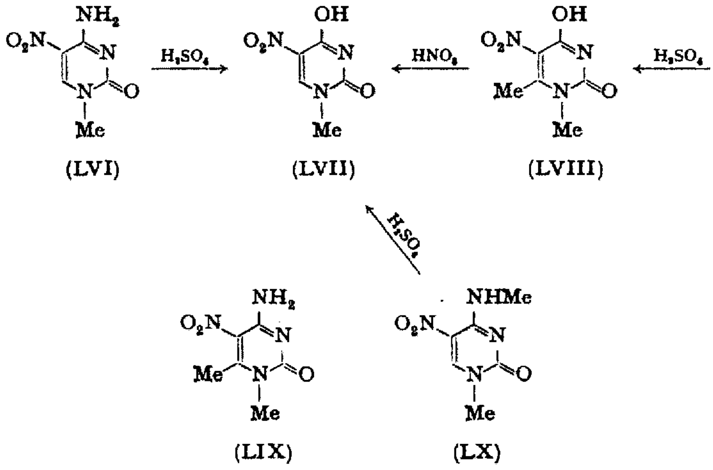
The major product of the methylation of 4-amino-2,6-dihydroxypyrimidine (LII) with one mole of dimethyl sulphate is 6-amino-1-methyluracil[87] (LIII). Its structure was proven by conversion consecutively into its 5-nitroso and 5-amino derivatives, ring closure to


(LII) (LIII) (LIV) (LV)

3-methylxanthine and methylation to theobromine[87] (LV), and it has also been made by primary synthesis.[88] The use of more dimethyl sulphate gives 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (LIV) either from the unmethylated[89,90] or monomethylated compound.[91,92] Primary syntheses, as for example by Blicke and Godt,[93] have also been used. Combinations of the above methods have produced many di-alkylated homologues such as 4-amino-1-ethyl-1,2,3,6- tetrahydro-3-methyl-2,6-dioxopyrimidine,[87,88,91] 1-allyl-6-amino-1,2,3,4-tetrahydro-3-methyl-2,4-dioxopyrimidine,[94] and the like.[95]

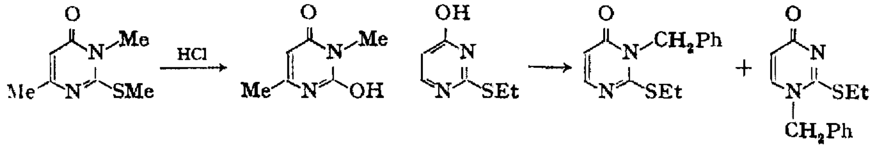
Analogues of the above are among the most potent diuretics known. "Amisometradine" for example, is indeed comparable with "Meralluride" in potency. Unlike the mercurial, which must be given by the intramuscular route, the pyrimidine may be given by mouth. An interesting pharmacological report on "Aminometradine" (1-allyl-6-amino-3-ethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidine) and related compounds should be consulted for references to earlier literature.[95a].

Methylation of 5-nitrocytosine (4-amino-2-hydroxy-5-nitropyrimidine) with methyl iodide[96] or, better, dimethyl sulphate[97] gives only 4-amino-1,2-dihydro-1-methyl-5-nitro-2-oxopyrimidine (LVI), an important intermediate for purine and pteridine syntheses. The position of methylation was found by acid hydrolysis to 1-methyl-5-nitrouracil[7,96] (LVII). The isomeric, 4-amino-2,3-dihydro-3-methyl-5-nitro-2-oxopyrimidine was made by primary synthesis.[98] 4-Amino-2-hydroxy-6-methyl-5-nitropyrimidine with dimethyl sulphate similarly gives 4-amino-1,2-dihydro-1,6-dimethyl-5-nitro-2-oxopyrimidine[65] (LIX), which was confirmed by hydrolysis to 1,6-dimethyl-5-nitrouracil (LVIII), and this in turn oxidized with fuming nitric acid, and decarboxylated to the known 1-methyl-5-nitrouracil[65] (LVII). The closely related 2-hydroxy-4-methylamino-5-nitropyrimidine also methy-

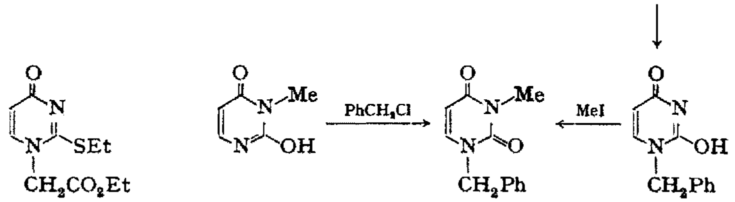


lated in the 1-position to give 1,2-dihydro-1-methyl-4-methylamino-5-nitro-2-oxopyrimidine[97,99] (LX). It was also hydrolysed to 1-methyl-5-nitrouracil (LVII). The methylation of 4-amino-6-hydroxy-5-nitropyrimidine was unsatisfactory,[100] but 4-amino-1,6-dihydro-1-methyl-5-nitro-6-oxopyrimidine was obtained by nitration.[84]

(f) *In the Presence of Alkylthio Groups.* Several references to alkylation of hydroxypyrimidines containing thioether groups have already been made in Section 1.A(3(b)). The utility of such a group is



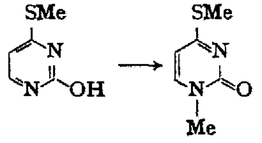
(LXI) (LXII) (LXIII) (LXIV) (LXV)



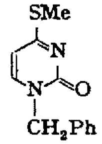
(LXVI) (LXVII) (LXVIII) (LXIX)

exemplified by the following: although 2,4-dihydroxypyrimidine can be dimethylated, it cannot be satisfactorily monomethylated, but if 2-ethylthio-4-hydroxypyrimidine is methylated a mixture of 1- and 3-methyl derivatives is formed and acid hydrolysis gives respectively 1- and 3-methyluracil.[22,23] A useful preparative method uses the methylthio analogue.[7] Furthermore, such alkylthio groups can be removed by Raney nickel and in this way were made 1,4-dihydro-1-methyl-4-oxopyrimidine and 1,6-dihydro-1-methyl-6-oxopyrimidine from their 2-methylthio derivatives. Since the same derivatives were hydrolysed respectively to the known 1- and 3-methyluracil, the configurations of the desulphurized products were proven.[7] When the homologous 4-hydroxy-6-methyl-2-methylthiopyrimidine is methylated only one *N*-methyl derivative has been isolated. By hydrolysis to 3,6-dimethyluracil (LXII), it was shown to be 1,6-dihydro-1,4-dimethyl-2-methylthio-6-oxopyrimidine[35,81,101] (LXI), and it has also been made by primary synthesis.[80] This formation of only one isomer is exceptional, and 2-ethylthio-4-hydroxy-5-methylpyrimidine and 5-ethoxy-2-ethylthio-4-hydroxypyrimidine both give two *N*-methyl isomers[19,102] and 2-ethylthio-4-hydroxypyrimidine (LXIII) gives 3- and 1-benzyl derivatives[103] (LXIV) and (LXV). Their structures were shown rather ingeniously by hydrolysing one (LXV) to the *N*-monobenzyluracil (LXIX) and methylating this to *N*-benzyl-*N*′-methyluracil (LXVIII). The known 3-methyluracil (LXVII) was then benzylated to 1-benzyl-3-methyluracil (LXVIII), which was identical with the above isomer. The structures of the *N*-benzyluracils were thus found and this also fixes those of the original monobenzyl derivatives[103] (LXIII) and (LXIV). This general process was used by the Yale School on several other occasions, as for example in finding the structure of the single *N*-ethoxycarbonylmethyl derivative produced by alkylating 2-ethylthio-4-hydroxypyrimidine with ethyl chloroacetate.[104] It proved to be 1-ethoxycarbonylmethyl-2-ethylthio-1,4-dihydro-4-oxopyrimidine (LXVI).

A 4-thioether is sometimes even more useful than one in the 2-position. Thus 2-hydroxy-4-methylthiopyrimidine (LXX) and its *C*-alkyl derivatives on alkylation give in each case only one isomer, which is a 1-alkyl derivative, such as 1,2-dihydro-1-methyl-4-methylthio-2-oxopyrimidine[23] (LXXI) (which is hydrolysed to 1-methyluracil), 1-benzyl-1,2-dihydro-4-methylthio-2-oxopyrimidine[23] (LXXII) (which is hydrolysed to 1-benzyluracil), and 1,2-dihydro-1,5-(and 1,6)-dimethyl-4-methylthio-2-oxopyrimidines[40,105] (which are hydrolysed respectively to 1,5(and 1,6)-dimethyluracil). Combined with a new method of preparing 2-hydroxy-4-mercaptopyrimidine by thiation of uracil,[106] these should be useful routes to 1-alkyluracil derivatives.



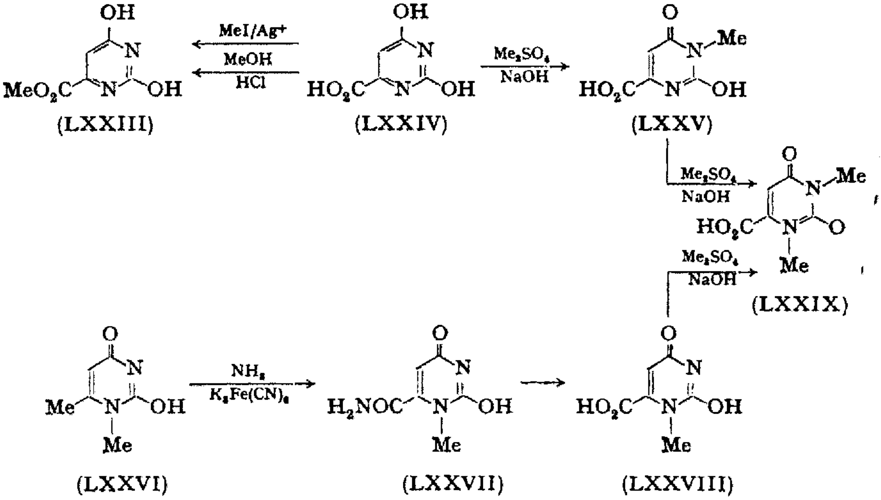
(LXX) (LXXI)



(LXXII)

(g) *In the Presence of Other Groups.* Hydroxypyrimidines substituted by several other types of group have been *N*-methylated. Thus, 4-chloro-6-hydroxypyrimidine with diazomethane gives a little 4-chloro-6-methoxypyrimidine and mainly 4-chloro-1,6-dihydro-1-methyl-6-oxopyrimidine.[84] The position of methylation was found by amination to the known 4-amino-1,6-dihydro-1-methyl-6-oxopyrimidine. The analogous compound, 4-chloro-1,2-dihydro-1-methyl-2-oxopyrimidine, was made by the action of phosphoryl chloride on 1-methyluracil, and its structure determined similarly by amination.[107] 5-Bromo-2-ethylthio-4-hydroxypyrimidine has been benzylated and the resulting 1-benzyl-5-bromo-2-ethylthio-1,4-dihydro-4-oxopyrimidine hydrolysed to 1-benzyl-5-bromouracil, which was made unambiguously by bromination of 1-benzyluracil.[103]

The alkylation of 4-carboxy-2,6-dihydroxypyrimidine (orotic acid; XXIV) has been a vexed question for many years. Its history has been nicely summarized by Fox, Yung, and Wempen,[108] and should be read



(LXXIII) (LXXIV) (LXXV) (LXXIX) (LXXVI) (LXXVII) (LXXVIII)

before reference is made to the highly confused earlier literature[109–115] and later papers.[116,117] In fact[108] orotic acid (LXXIV) is alkylated as follows: methanolic and ethanolic hydrogen chloride give respectively 2,4-dihydroxy-6-methoxycarbonylpyrimidine (LXXIII) and its ethoxy homologue, and the action of methyl iodide and ethyl iodide on the silver salt of orotic acid gives the same products. The condensation of ethyl oxalacetate and *N*-methylurea followed by alkaline saponification gives 6-caboxy-3-methyluracil (LXXV) shown by decarboxylation to 3-methyluracil. The same product (LXXV) is obtained by methylation of orotic acid with dimethyl sulphate and alkali, and further methylation gives with difficulty some 4-carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (LXXIX). 6-Carboxy-1-methyluracil (LXXVIII) may be obtained by ammoniacal ferricyanide oxidation of

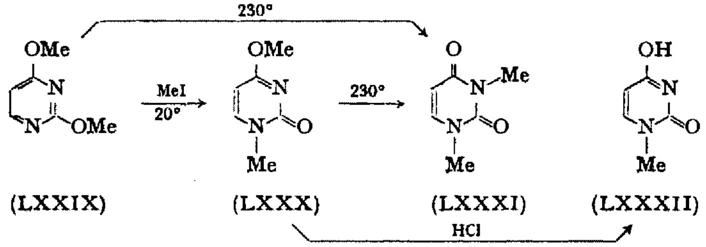
1,6-dimethyluracil (LXXVI) followed by saponification of the amide (LXXVII), and (unlike its isomer) it is readily methylated to 4-carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (LXXIX), which can also be obtained directly by oxidation of 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine.

(4) *By Rearrangement of Alkoxypyrimidines*

2-, 4-, or 6-Alkoxypyrimidines can often be rearranged to the isomeric *N*-alkyloxopyrimidines by heating. The alkyl group migrates only to the α- and never to the γ-nitrogen atom. A similar result is often attained by dissolution of the alkoxy compound in an alkyl iodide, best containing a little pyridine. In such a case transalkylation can occur, as, for example, when an ethoxypyrimidine is dissolved in methyl iodide and gives an *N*-methyloxopyrimidine. This process has been widely used to make nucleosides (see below), and is undoubtedly not a simple rearrangement, but a rather complex reaction proceeding *via* a quaternary salt between the pyrimidine and alkyl halide.

The rearrangement of alkoxypyrimidines was first described by Johnson and Hilbert[118] in 1929, and has been used quite extensively since then. 2- and 4-Methoxypyrimidine on heating at 200° for 2–3 hours give respectively 1,2-dihydro-1-methyl-2- and 1,6-dihydro-1-methyl-6- oxopyrimidine.[7] Of more preparative interest is the conversion of 2,4-dimethoxypyrimidine (LXXIX) into 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine (LXXXI) by heating at 230°, or into 1,2-dihydro-4-methoxy-1-methyl-2-oxopyrimidine (LXXX) by dissolution in methyl iodide for 12 hours.[25] The structure of the last compound (which is also transformed into the 1,3-dimethyl derivative by heat) is known by its hydrolysis to 1-methyluracil (LXXXII) and it constitutes a useful route to this compound.[25] The rearrangement of 2,4-diethoxypyrimidine is not so ready, and heating at 260° for 24 hours, or refluxing in ethyl iodide for a week, is needed to convert it into 1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidine.[25] On refluxing for 24 hours with ethyl iodide and a little pyridine it is converted into 4-ethoxy-1-ethyl-1,2-dihydro-2-oxopyrimidine;[26] with methyl iodide, however, 4-ethoxy-1,2-dihydro-1-methyl-2-oxopyrimidine is formed in 12 hours at room temperature, and the rearrangement may be thermally completed at 250° to give 1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxopyrimidine.[25] 2,4-Dimethoxy-5-methyl-,[119] 2,4-diethoxy-5-methyl-,[26,119] 2,4-dimethoxy-6-methyl-,[26,120]* 2,4-dimethoxy-6-methyl-5-propyl-,[43] and 5-butyl-2,4-dimethoxy-6-methyl-[43] pyrimidine have all been rearranged to the *N*-monoalkyl and *NN'*-dialkyl isomers under similar conditions to the above. 4-Cyano-2,6-dimethoxypyrimidine with methyl iodide at 120° gives 4-cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine.[121]

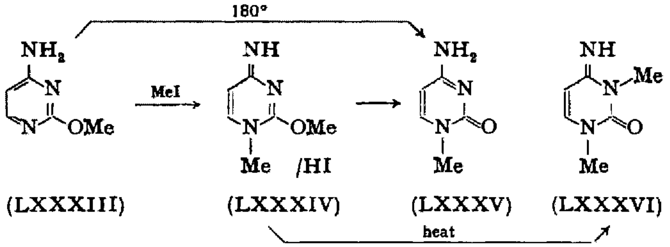
The phenomenon of transalkylation already mentioned has been used to make nucleosides by rearrangements analogous to the above. Thus 2,4-diethoxypyrimidine and 1-bromo-tetra-acetyl-D-glucose in



(LXXIX) (LXXX) (LXXXI) (LXXXII)

the presence of one equivalent of pyridine give 50% of 4-ethoxy-1,2-dihydro-2-oxo-1-tetra-acetyl-β-D-glucosidopyrimidine.[26,122] Other such compounds have been made,[24,26,118,122–128]

Other reports of such rearrangements are not numerous. 4-Hydroxy-2-methoxy-6-methylpyrimidine was thermally isomerized[5] and the product shown[39] to be 3,6-dimethyluracil. On the other hand, 2-hydroxy-4-methoxy-6-methylpyrimidine on heating, gave mainly



(LXXXIII) (LXXXIV) (LXXXV) (LXXXVI)

2,4-dihydroxy-6-methylpyrimidine, and exceptionally a little 1,6-dimethyluracil, but no 3,6-dimethyluracil which would be expected.[39] 2,4,6-Trimethoxypyrimidine on prolonged treatment with methyl

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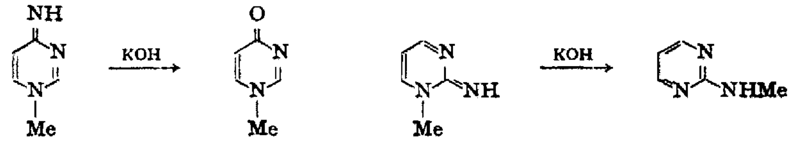
* The melting points for 1,2-dihydro-4-methoxy-1,6-dimethyl-2-oxopyrimidine given by the American and Chinese authors differ by 23°. Both, however, gave 1,6-dimethyluracil on hydrolysis and it has been described[39] as a good preparative method for this compound.

iodide gives probably 1,2-dihydro-4,6-dimethoxy-1-methyl-2-oxopyrimidine (or an isomer) which in any case on hydrolysis gives 1-methylbarbituric acid.[129] 4-Chloro-2,6-dimethoxypyrimidine with methyl iodide at 100° gives 4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine.[129,130] 4-Amino-2-methoxypyrimidine (LXXXIII) on heating at 180° gives some 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (1-methylcytosine; LXXXV; also made otherwise[69,107]), but treatment with methyl iodide to give a methiodide (LXXXIV) followed by boiling alcohol, silver sulphate, or aqueous hydrochloric acid gives a better yield.[68] The methiodide is thermally converted into 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine[68] (LXXXVI), which suggests that it is 1,4-dihydro-4-imino-2-methoxy-1-methylpyrimidine (LXXXIV).

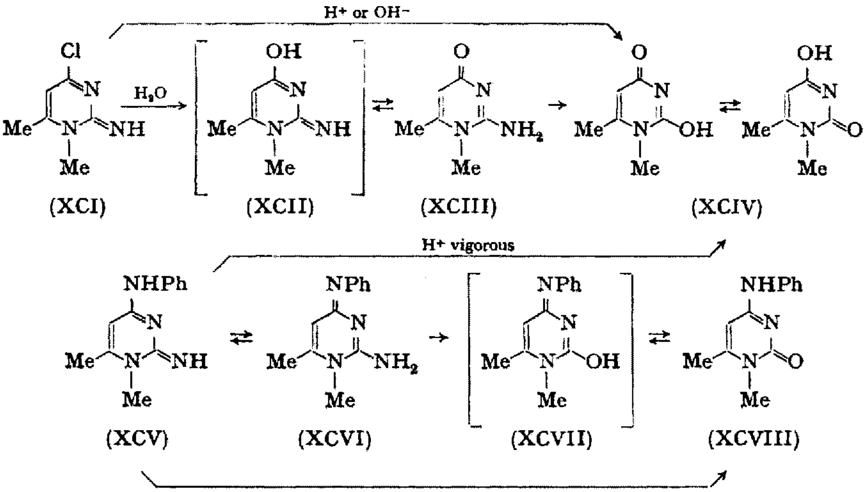
(5) *By Hydrolysis of Iminopyrimidines*

Imino-*N*-methylpyrimidines normally undergo one of two reactions on treatment with alkali. If the methyl group occupies a ring nitrogen adjacent to the imino group, rearrangement to a methylaminopyrimidine may occur and possibly be followed by hydrolysis to a hydroxypyrimidine (Sect. 2.B). If the methyl group is γ to the imino group, hydrolysis to an *N*-methyloxopyrimidine will probably ensue. The



(LXXXVII) (LXXXVIII) (LXXXIX) (XC)

hydrolytic second reaction is exemplified by the formation of 1,4-dihydro-1-methyl-4-oxopyrimidine (LXXXVIII) by treatment of 1,4-dihydro-4-imino-1-methylpyrimidine (LXXXVII) with dilute alkali at room temperature[131] or in the water bath.[15] In contrast, 1,2-dihydro-2-imino-1-methylpyrimidine (LXXXIX) rearranges in alkali to 2-methylaminopyrimidine[131] (XC). Other examples of the hydrolysis of iminopyrimidines are the formation of 1,4-dihydro-1,2(and 1,6)-dimethyl-4-oxopyrimidine[15] with dilute alkali at 100° on the corresponding imine, of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine from 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine during a rather involved process,[68] and of (probably) 1,4-dihydro-1-methyl-4-oxo-5-phenylpyrimidine from the corresponding imine with alkali.[17] There is no evidence for the position of the methyl group in the last compound apart from the fact that rearrangement, rather than hydrolysis, might have been expected had it occupied position 3.



Related hydrolyses are known, which appear to be imino-oxo transformations at first sight, but which are not necessarily so because of tautomeric possibilities. Thus 4-chloro-1,2-dihydro-2-imino-1,6-dimethylpyrimidine (XCI) with acid or alkali gives 1,6-dimethyluracil[82] (XCIV), but gentle treatment with water hydrolyses only the chlorine,[82] giving "1,2-dihydro-4-hydroxy-2-imino-1,6-dimethylpyrimidine" (XCII), which would immediately enter the preferred tautomeric form of 2-amino-1,4-dihydro-1,6-dimethyl-4-oxopyrimidine (XCIII). Further hydrolysis to 1,6-dimethyluracil (XCIV) would then consist only in the conversion of an amino into a hydroxy group. Again, 4-anilino-1,2-dihydro-2-imino-1,6-dimethylpyrimidine (XCV), which could equally well be 2-amino-1,4-dihydro-1,6-dimethyl-4-phenyliminopyrimidine (XCVI), on vigorous acid hydrolysis gives 1,6-dimethyluracil[82] (XCIV), but gentler conditions give 4-anilino-1,2-dihydro-1,6-dimethyl-2-oxopyrimidine (XCVIII), which could be formed directly from (XCV) by hydrolysis of the imino group or from (XCVI) *via* "1,4-dihydro-2-hydroxy-1,6-dimethyl-4-phenyliminopyrimidine" (XCVII), by hydrolysis of an amino group.

B. Properties and Reactions of Oxopyrimidines

The oxo-*N*-methylpyrimidines are more soluble in water and in organic solvents than are the parent hydroxy compounds or their corresponding *C*-methyl derivatives, but rather less so than are the corresponding methoxy derivatives. Their melting points also occupy an intermediate range between the other types, and this is clearly connected with the decreased intermolecular hydrogen bonding in the oxo compound compared with the hydroxy derivatives. Table XV indicates melting points of representative members as nearly comparable in molecular weight as possible. The ultraviolet spectra are discussed in Chapter XIII, Sect. 2. In brief, those of the hydroxy and oxo derivatives are similar, and differ markedly from the methoxy derivatives.

TABLE XV. Comparison of Melting Points of Simple 2-,4-, and 6-Hydroxy, Oxo, and Alkoxy Derivatives

Hydroxypyrimidine		Oxopyrimidine		Methoxypyrimidine	
2-OH	180°				
		1-Me-2-O	128°	2-OMe	71°/15 mm[b]
2-OH-4-Me	150°				
4-OH	165°				
4-OH-2-Me	212°	1-Me-4-O	156°	4-OMe	70°/40 mm[b]
4-OH-6-Me	150°	3-Me-4-O	126°		
4-OH-5-Me	154°				
2,4-*di*OH	340° (dec.)				
2,4-*di*OH-6-Me	320° (dec.)				
2,4-*di*OH-5-Me	340° (dec.)	1,3-*di*Me-2,4-*di*O	124°	2,4-*di*OMe	204°/760 mm[b]
2,4-*di*OH-5,6-*di*Me	294° (dec.)				
4,6-*di*OH	300° (dec.)				
4,6-*di*OH-2-Me	> 300°	—[a]		4,6-*di*OMe	85°/16 mm[b]
4,6-*di*OH-2,5-*di*Me	< 360° (dec.)				
2,4,6-*tri*OH	355° (dec.)	1,3,5,5-*tetra*Me-2,4,6-*tri*O	110°	2,4,6-*tri*OMe	53°
2,4,6-*tri*OH-5-Bu	215°			5-Et-2,4,6-*tri*OMe	68°

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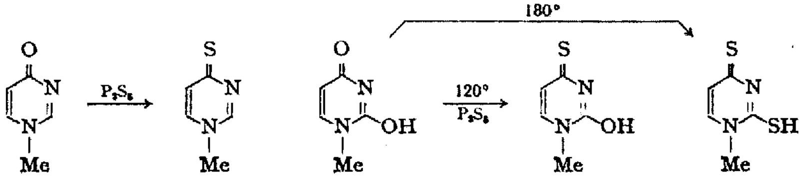
[a] Simple *NN'*-dialkyl-4,6-dioxopyrimidines cannot exist for reasons of valency.

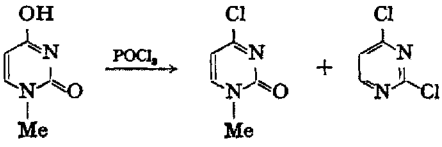
[b] Boiling Point.

Singularly little can be done with the oxo group or with the *N*-alkyl group associated with it. Direct thiation is possible, and in this way 1,4(and 1,6)-dihydro-1-methyl-4(and 6)-oxopyrimidines *e.g.* (XCIX) have been converted in pyridine with phosphorus pentasulphide into the 4- and 6-thio analogues[132] (C). 1,2-Dihydro-1-methyl-2-oxopyrimidine resisted such treatment.[132] 3-Methyluracil with phosphorus pentasulphide in tetralin at 180° gave 3-methyldithiouracil[98] and 1-methyluracil (CI) similarly gave 1-methyldithiouracil[84] (CIII). However, by using pyridine at 115° the thiation of 1-methyluracil has been stopped at 1-methyl-4-thiouracil[133] (CII). Likewise, if thiated at 120°, 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine yields the 2-oxo-4-thio analogue,[134] but at 180° the 2,4-dithio analogue is formed.[84]



(XCIX) (C) (CI) (CII) (CIII)

Oxo groups are quite stable during nitration, nitrosation, and halogenation of the molecule, and the associated *N*-methyl groups resist oxidation and styrylation even under conditions where *C*-methyl groups in the same molecule react. Direct amination of oxo groups is unexplored and little is known of the action of phosphorus halides' except that 1-methyluracil (CIV) and phosphoryl chloride give mainly 4-chloro-1,2-dihydro-1-methyl-2-oxopyrimidine (CV) accompanied by a little 2,4-dichloropyrimidine[107] (CVI).



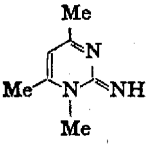
(CIV) (CV) (CVI)

2. The Iminopyrimidines

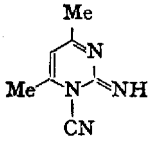
Although the imino form of a potentially tautomeric aminopyrimidine is normally present in minute amount, alkylation usually occurs on a ring nitrogen and thus fixes the less usual form. Such iminopyrimidines are more strongly basic than the parent amino derivative, and the pK_a is often confirmatory or even diagnostic of this condition.

A. Preparation of Iminopyrimidines

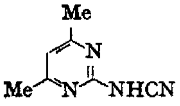
It is theoretically possible to produce 2-iminopyrimidines by condensation of *N*-methylguanidine or *N*:*N*′-dimethylguanidine with, for example, acetylacetone. The first of these has been tried[77] and gave 4,6-dimethyl-2-methylaminopyrimidine but not any 1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine (CVII). The position is not as clear when cyanoguanidine (dicyanodiamide) is used. The product has been formulated as 1-cyano-1,2-dihydro-2-imino-4,6-dimethylpyrimidine[135] (CVIII), as 2-cyanoamino-4,6-dimethylpyrimidine[136] (CIX), and even as a mixture of the two.[137] Iminopyrimidines can also arise by virtue of 5,5-dialkylation. Thus diethylmalononitrile and guanidine are said[138] to give 2,4(4,6)-diamino-5,5-diethyl-5,6(2,5)-dihydro-6(2)-iminopyrimidine (CX).



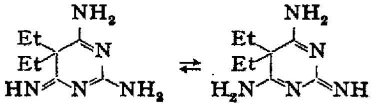
(CVII)



(CVIII)

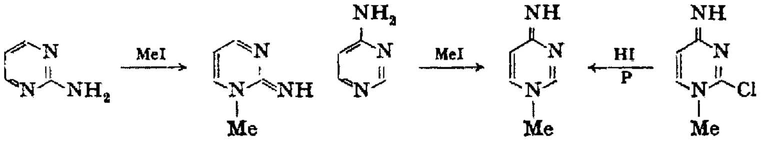


(CIX)

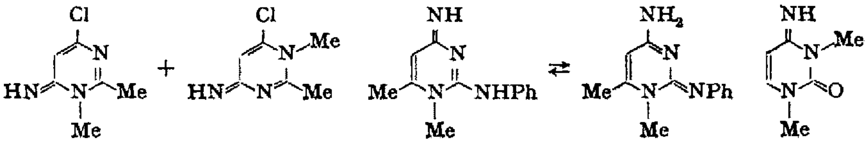


(CX)

Most iminopyrimidines have been made by alkylation of the parent amino compound. Thus 2-aminopyrimidine (CX) and methyl iodide in methanol give 1,2-dihydro-2-imino-1-methylpyrimidine hydriodide, which can be converted into the free base (CXII) with ice-cold sodium hydroxide.[131] If warm sodium hydroxide is used at this stage or a base added in the methylation, 2-methylaminopyrimidine is isolated (Sect. 2.B).[136,139] 4-Aminopyrimidine (CXIII) treated with methyl iodide could give two isomers, but only one is formed,[15,131] and it was shown to be 1,4-dihydro-4-imino-1-methylpyrimidine (CXIV) by alkaline hydrolysis to 1,4-dihydro-1-methyl-4-oxopyrimidine.[15,131] The same imine has also been made indirectly by dehalogenation of its 2-chloro derivative (CXV) with hydriodic acid and phosphorus.[74] 4-Amino-6-methylpyrimidine similarly gives 1,4-dihydro-4-imino-1,6-dimethylpyrimidine, which has been also made by dehalogenation of the 2-chloro derivative, and by desulphurization of the 2-thio derivative (4-amino-1,2-dihydro-1,6-dimethyl-2-thiopyrimidine) with Raney nickel.[15] The isomeric 1,4-dihydro-4-imino-1,2-dimethylpyrimidine was made by similar routes,[15] and what is probably 1,4-dihydro-4-imino-1-methyl-5-phenylpyrimidine by methyl iodide and 4-amino-5-phenylpyrimidine.[17] Other less simple derivatives of 4-aminopyrimidine, also made by the direct action of methyl iodide, include 2-chloro-1,4-dihydro-4-imino-1-methylpyrimidine[14] (CXV), its 1,6-dimethyl analogue,[74] a separable mixture of 4-chloro-1,6(and 3,6-)dihydro-6-imino-1,2(and 2,3)-dimethylpyrimidine[15] (CXVI), 1,4-dihydro-4-imino-1,6-dimethyl-2-methylthiopyrimidine,[74] 2-anilino-1,4-dihydro-4-imino-1,6-dimethylpyrimidine[74] (CXVIa)*, a separable mixture of 4-anilino-1,6(and 3,6)-dihydro-6-imino-1,2(and 2,3)-dimethylpyrimidine,[15] 4-amino-1,6(3,6)-dihydro-6-imino-1(3)-methylpyrimidine,[140] 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine (CXVII) (which was the first true imine, made by Hilbert in 1934 from methyl iodide and 1-methylcytosine[68] and later[107] made more conveniently with diazomethane), and its 4-methylimino, 4-acetylimino, and 4-benzoylimino analogues.[107]



(CXI) (CXII) (CXIII) (CXIV) (CXV)



(CXVI) (CXVIa) (CXVII)

Other miscellaneous imines which have been made directly, and the structures of which have been adequately confirmed, are exemplified

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* These could equally well be written in their tautomeric amino-phenylimino forms.

in 4-anilino-1,2-dihydro-2-imino-1,6-dimethylpyrimidine,[82*] its 4-chloro analogue,[82] 1,4-dihydro-1,6-dimethyl-2-methylthio-4-phenyliminopyrimidine,[82] 4-chloro-3,6-dihydro-3-methyl-6-phenyliminopyrimidine[141] (made with dimethyl sulphate), its 2,3-dimethyl analogue,[141] and 4-butylamino-6-butylimino-1,6(3,6)-dihydro-1(3)-methylpyrimidine.[142]

It will be noticed that in most of the above cases only one isomer is formed on quaternizing an aminopyrimidine, and that the methyl group (where possible) appears in the γ-position to the resulting imino group. There is yet no case of both nuclear nitrogen atoms being methylated to give a di-imine. Thus 2,4-diaminopyrimidine gave only 2 (4)-amino-1,4 (1,2)-dyhydro-4 (2)-imino-1-methylpyrimidine.[100,131]

B. Reactions of Iminopyrimidines

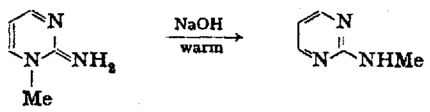
The chief reaction of iminopyrimidines is hydrolysis to oxo derivatives, and in cases where the imino group is adjacent to the *N*-methyl group, rearrangement to methylamino derivatives. Hydrolysis has already been discussed (Sect. 1.A(5)).

In 1954 the first example[139] of the rearrangement of an iminopyrimidine was unrecognized as such. Treatment of 2-aminopyrimidine with methyl iodide gave a methiodide, later shown[131] to be 1,2-dihydro-2-imino-1-methylpyrimidine (CXVIII) hydriodide, which on warming with aqueous or alcoholic sodium hydroxide produced 2-methylaminopyrimidine (CXIX). In the following year, Carrington, Curd, and Richardson[141] described several such rearrangements typified by that of 4-anilino-1,6-dihydro-6-imino-1,2-dimethylpyrimidine (CXX) to 4-anilino-2-methyl-6-methylaminopyrimidine (CXXI) by heating with alcoholic piperidine or ammonia or with aqueous sodium carbonate, and the formation of the same compound during amination with ammonia of 4-chloro-3,6-dihydro-2,3-dimethyl-6-phenyliminopyrimidine (CXXII), presumably *via* (CXX). Replacement of ammonia in the last reaction by methylamine might be expected to lead first to 4-anilino-1,6-dihydro-1,2-dimethyl-6-methyliminopyrimidine and then by rearrangement to a dimethylamino derivative. The reaction sequence in fact stops short of the rearrangement,[141] and no case is yet known where an alkylimino group is involved. Another simple example

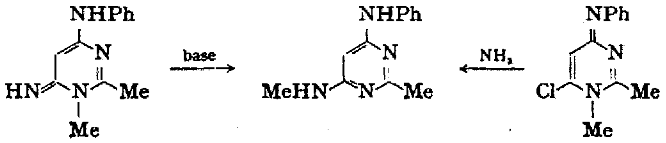
[*] These could equally well be written in their tautomeric amino-phenylimino forms.

is the transformation of 4-amino-1,6-dihydro-6-imino-1-methylpyrimidine (CXXIII) into 4-amino-6-methylaminopyrimidine (CXXIV) simply by dissolution in *N*-alkali at 20° for a few hours,[140] and other cases are known.[106]

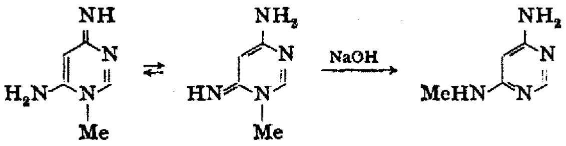
Such rearrangements have also been observed under other conditions. Thus thermal decarboxylation of an indubitable specimen of 4-amino-5-carboxy-2,3-dihydro-3-methyl-2-oxopyrimidine (CXXV) gave not 3-methylcytosine, but 2-hydroxy-4-methylaminopyrimidine[70,71,143] (CXXVI). Again, ring closure of 1-cyano-1-nitro-2-(3-ethylureido)ethylene (CXXVII) gave not 4-amino-3-ethyl-2,3-dihydro-5-nitro-2-oxopyrimidine, but mainly 4-ethylamino-2-hydroxy-5-nitropyrimidine[98] (CXXVIII), identified by unambiguous synthesis. The



(CXVIII) (CXIX)



(CXX) (CXXI) (CXXII)



(CXXIII) (CXXIV)

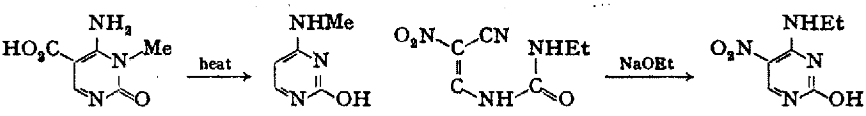
corresponding methyl analogue did not rearrange under similar conditions. The rearrangement has also been reported under acid conditions: 4-amino-1,6-dihydro-6-imino-1-methylpyrimidine (CXXIX) on nitration under a variety of gentle conditions gave only 4-amino-6-methylamino-5-nitropyrimidine[140] (CXXX).

Perusal of a bibliography[141] of such alkaline rearrangements in pteridine[144] and other heterocyclic series, and of pyridine precedents under nitrating conditions,[145,146] gives no real indication of mechanism, but it is tempting to postulate a ring cleavage and recyclization as indicated in (CXXXI), (CXXXII), and (CXXXIII). In accord with this theory is the failure (mentioned above) of 4-anilino-1,6-dihydro-1,2-dimethyl-6-methyliminopyrimidine to rearrange to a dimethylamino derivative, and indeed the mechanism has recently been confirmed[156] by use of ^{15}N-labelled 2-aminopyrimidine.

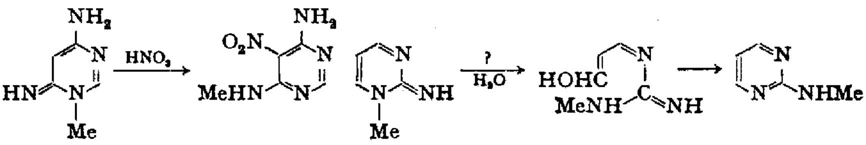
3. The *N*-Methylated Thiopyrimidines

Alkylation of a mercaptopyrimidine invariably leads to an *S*-alkyl derivative, and for this reason the *N*-alkyl isomers are a little-known family.

N-Alkyl-2-thiopyrimidines have been made by the Principal Synthesis using *N*-alkylthiourea as one-carbon fragment. Thus malondialdehyde (as a diacetal) and *N*-methylthiourea in alcoholic hydrogen chloride give 1,2-dihydro-1-methyl-2-thiopyrimidine,[132] and acetylacetone and *N*-methylthiourea give 1,2-dihydro-1,4,6-trimethyl-2-thiopyrimidine[4,5] (CXXXIV). More complicated examples are the condensation of *NN'*-diphenylthiourea with malonic acid in phosphoryl chloride to give 1,2,3,4-tetrahydro-6-hydroxy-4-oxo-1,3-diphenyl-2-thiopyrimidine[147] (CXXXV), and the formation of 4-amino-5-ethoxycarbonyl(or cyano)-2,3-dihydro-3-methyl-2-thiopyrimidine (CXXXVI)



(CXXV) (CXXVI) (CXXVII) (CXXVIII)

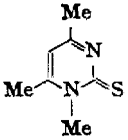


(CXXIX) (CXXX) (CXXXI) (CXXXII) (CXXXIII)

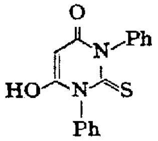
and homologues by condensing *N*-alkyl- or aryl-thioureas, respectively, with ethyl ethoxymethylenecyanoacetate, or with ethoxymethylenemalononitrile.[143]

The only other used method for forming such thiopyrimidines is by direct thiation of *N*-alkyl-oxopyrimidines. It is typified in the formation of 3-methyldithiouracil (CXXXVII) by boiling 3-methyluracil in xylene with phosphorus pentasulphide,[98] and has been discussed in more detail in Section 1.B.

Although 1,2-dihydro-1,4,6-trimethyl-2-thiopyrimidine is stable to prolonged boiling in hydrochloric acid, it is reported[148] to yield the 2-oxo analogue on treatment with aqueous chloroacetic acid. It is not easy to postulate a reasonable mechanism for this reaction.

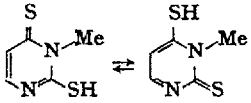


(CXXXIV)



(CXXXV)

(CXXXVI)



(CXXXVII)

4. The Pyrimidine-*N*-Oxides

The literature of pyrimidine-*N*-oxides although as yet very limited in scope, is full of interest.

A. Preparation of Pyrimidine-*N*-Oxides

The preparation of pyrimidine-*N*-oxide and of its *C*-alkyl derivatives has already been discussed in Chapter IV, Sect. 2.C(4). Almost all other examples are *N*-oxides of alkoxypyrimidines, a study started by E. Ochiai and continued by H. Yamanaka. Thus 4-methoxy-,[149] 2-methoxy-4-methyl-,[150] 4-methoxy-6-methyl-,[150,151] 2,4-dimethoxy-6-methyl-,[150] 4-ethoxy-6-methyl-,[151] 4-butoxy-6-methyl-,[151] 4-benzyloxy-6-methyl-[151] (CXXXIX), 4-methyl-6-phenoxy-,[151] and 4-benzyloxy-2,6-dimethyl-[152] pyrimidine-*N*-oxide were made, generally by the action of hydrogen peroxide in acetic acid solution at *ca.* 60° for several hours. Some, however, were made by treatment with perphthalic acid in ether at room temperature for several days. Oxidation is sometimes said to occur specifically in the γ-position to the alkoxy group, but no structural confirmation is presented. A few *N*-oxides have been made by metathesis of the above alkoxy derivatives (see below).

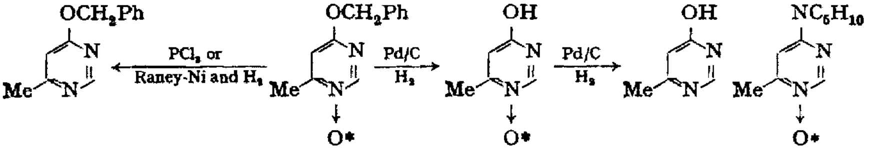
B. Reactions of Pyrimidine-*N*-Oxides

N-Oxides may be reduced to the parent pyrimidine by two methods. Phosphorus trichloride in chloroform may be used for example to remove the *N*-oxide to give 4-methylpyrimidine,[150] 4-methoxy-6-methylpyrimidine,[150] and 4-benzyloxy-6-methylpyrimidine (CXXXVIII).[151]

A better method is catalytic reduction. Thus 4-ethoxy(and methoxy)-6-methylpyrimidines are formed in good yield by hydrogenation of their respective *N*-oxides in methanol over Raney nickel.[151, 152] 4-Benzyloxy-6-methylpyrimidine (CXXXVIII) can also be similarly formed from its oxide (CXXXIX) in 94% yield, but by using a palladium–charcoal catalyst reduction takes another course, giving[152] first 4-hydroxy-6-methylpyrimidine-1-oxide (CXL) with one mole of hydrogen, and then 4-hydroxy-6-methylpyrimidine itself (CXLI) with 2 moles of hydrogen. 4-Benzyloxy-2,6-dimethylpyrimidine-*N*-oxide is similarly reduced over palladium–charcoal in two steps,[152] to yield 4-hydroxy-2,6-dimethylpyrimidine.

4-Methyl-6-phenoxypyrimidine-*N*-oxide may be aminated with, for example, piperidine to give 4-methyl-6-piperidinopyrimidine-*N*-oxide (CXLII), which on catalytic reduction with Raney nickel yields 4-methyl-6-piperidinopyrimidine.[153]

A third method of reduction, involving sulphur dioxide, has proven ineffective.[150]



(CXXXVIII) (CXXXIX) (CXL) (CXLI) (CXLII)

A type of Reissert reaction[154] has been applied to pyrimidine-*N*-oxides: 4-ethoxy-6-methylpyrimidine-*N*-oxide (CXLIII) dissolved in aqueous potassium cyanide and treated with benzoyl chloride gives a product, which if dissolved in ether and treated with sodium hydroxide gives 2-cyano-4-ethoxy-6-methylpyrimidine (CXLIV) in 85% yield.[151] The same method has been used to make 4-benzyloxy-2-cyano-6-methyl-,[151] 2-cyano-4-methyl-6-phenoxy-,[151] 4-butoxy-2-cyano-6-

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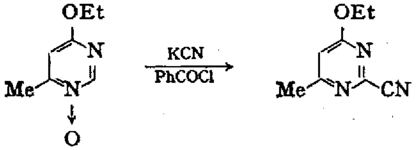
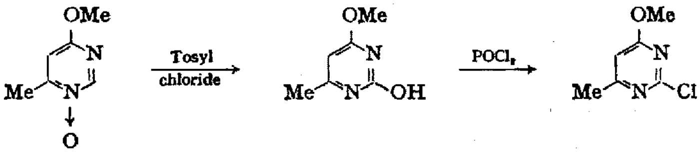
* The oxide may in fact be on $N_{(3)}$ in these and succeeding formulae.

methyl-,[151] 2-cyano-4-methoxy-6-methyl-,[150] 4-cyano-2,6-dimethyl-,[150] 2-cyano-4-methyl-[150] and 2-cyano-4-methoxy-[149] pyrimidine. The structures of some of the above have been checked by conversion into amides and comparison with authentic materials, and by other means.

If potassium carbonate replaces potassium cyanide, treatment with an acid chloride (*e.g.* toluene-*p*-sulphonyl chloride) gives a *C*-hydroxy derivative. In this way 4-methoxy-6-methylpyrimidine-*N*-oxide



(CXLIII) (CXLIV)



(CXLV) (CXLVI) (CXLVII)

(CXLV) gave 2-hydroxy-4-methoxy-6-methylpyrimidine (CXLVI); which was identified by conversion with phosphoryl chloride into the 2-chloro analogue (CXLVII) and treatment with sodium methoxide to give 2,4-dimethoxy-6-methylpyrimidine.[150]

Pyrimidine-*N*-oxide on refluxing in acetic anhydride yields 4-acetoxypyrimidine,[1] and 4,6-dimethylpyrimidine-*N*-oxide yields 4-acetoxymethyl-6-methylpyrimidine.[155] The same *N*-oxide with toluene-*p*-sulphonyl chloride probably gives 4-chloromethyl-6-methylpyrimidine.[155]

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CHAPTER XI

The Pyrimidine Carboxylic Acids and Related Derivatives

This chapter includes the following derivatives of Pyrimidine: Carboxylic acids, Esters, Amides, Nitriles, Aldehydes, Ketones, Cyanates, thio analogues of all of these, and some related derivatives at present of minor importance. With one exception, they form a group of compounds, more important as intermediates in synthetic processes, than directly in the chemistry of naturally occurring or biologically active pyrimidines. The exception of course is orotic acid (4-carboxy-2,6-dihydroxypyrimidine), which, as orotidine, is probably an essential step in the biosynthesis of all pyrimidines.

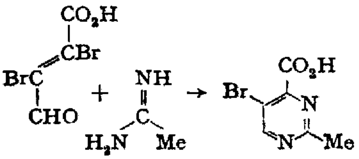
1. The Carboxypyrimidines

A. Preparation of Carboxypyrimidines

Carboxypyrimidines have been made by three chief methods: by primary synthesis, by hydrolysis of the corresponding esters, amides, or nitriles, and by oxidation of alkyl or formyl derivatives. Moreover, the compounds used in the two latter methods are nearly always themselves made directly by primary synthesis.

(1) *By Primary Synthesis*

The Principal Synthesis cannot be widely used to produce carboxypyrimidines directly. There is no convenient one-carbon fragment with which to make 2-carboxy derivatives. Three-carbon fragments bearing a carboxy group (which could appear in 4-, 5-, or an extranuclear position) react at that group instead of leaving it intact for attachment to the resulting pyrimidine. This can be obviated only by supplying two other groups more reactive in the synthesis. Thus bromomucic acid (I) reacts as an aldehydo-ketone with acetamidine, benzamidine, or *S*-methylthiourea to give respectively 5-bromo-4-carboxy-2-methylpyrimidine[1] (II), its 2-phenyl analogue,[2] and its 2-methylthio analogue.[3] Dicarboxyacetone (made *in situ* from citric acid) reacts with urea in fuming sulphuric acid to give 4-carboxymethyl-2,6-dihydroxypyrimidine[4] (III). Cyanoacetic acid has been used with ethyl orthoformate and methylurea in the Whitehead synthesis to give directly 4-amino-5-carboxy-2,3-dihydro-3-methyl-2-oxopyrimidine[5] (IV).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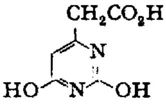
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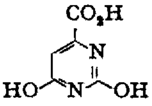
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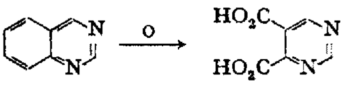
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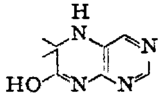
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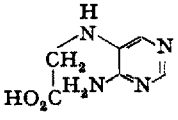

(IX)

Other syntheses leading to carboxy derivatives are typified by the Shaw synthesis of 4-carboxy-2,6-dihydroxypyrimidine (V) and its 1-alkyl derivatives[6] already described in Ch. III, Sect. 2.E, by related syntheses *via* hydantoins[7–9] described in Ch. III, Sect. 5.E(1), and by the violent reaction of malondiamidine with ethyl oxalate to give (presumably *via* the ester) 4,6-diamino-2-carboxypyrimidine.[10] Further, quinazoline (VI) is oxidized by permanganate to 4,5-dicarboxypyrimidine[11] (VII), and 7-hydroxypteridine on reduction to the 5,6-dihydro derivative (VIII) ring opens conveniently to give 4-amino-5-carboxymethylaminopyrimidine[12] (IX).

(2) *By Hydrolysis of Esters, Amides, and Nitriles*

Because they can be made much more readily by primary synthesis than can the free acids, the hydrolysis of esters and nitriles is an important way of preparing carboxypyrimidines.

Some typical examples of the hydrolysis of esters are the preparation of 5-carboxy-4-hydroxy-2-mercaptopyrimidine by boiling 20 % sulphuric acid,[13] 4-carboxy-2,6-dihydroxypyrimidine by boiling N-sodium hydroxide,[14] 4-amino-5-carboxy-3-ethyl-2,3-dihydro-2-oxopyrimidine by 12N-hydrochloric acid on the steam bath,[15] 5-carboxy-1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine by boiling 3N-hydrochloric acid,[16] 5-carboxy-2,4,6-triphenylpyrimidine by alcoholic alkali,[17] 5-carboxy-2-ethylthiopyrimidine by alcoholic alkali,[18] 4-carboxymethyl-2-ethoxy-6-hydroxypyrimidine by alkali,[19] and others.[20–22]

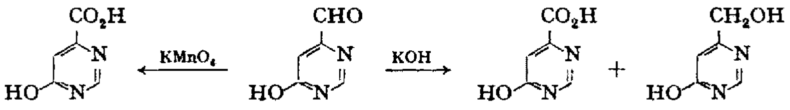
Pyrimidine nitriles have been hydrolysed (*via* amides) to carboxypyrimidines, generally with aqueous alkali. Thus 2-cyano-4,6-dimethylpyrimidine in N-alkali at 60° gives 75 % of 2-carboxy-4,6-dimethylpyrimidine[23], and 4-carboxy-2,6-dimethyl-,[23] 4-carboxy-2,6-dimethoxy-,[23] 4-amino-5-carboxy-,[24] and 4-amino-5-carboxy-2-methyl-[25] pyrimidine were made rather similarly. The conversion of amides into carboxypyrimidines is typified in the formation of 4-amino-5-carboxypyrimidine in 90 % yield with hot 10 % alkali,[24] of 4-carboxy-2,6-dihydroxypyrimidine under similar conditions,[26] and of 5-carboxymethyl-2,4,6-trihydroxypyrimidine with hot 20 % hydrochloric acid.[27] 4-Amino-6-carbamoylpyrimidine treated with warm dilute sulphuric acid and sodium nitrite yields 4-carboxy-6-hydroxypyrimidine.[28]

(3) *By Oxidation of Methyl-, Styryl-, Formyl-, Hydroxymethyl-, and Acetyl-pyrimidines*

Many examples of the permanganate or nitric acid oxidation of simple methyl- and styryl- pyrimidines to carboxy derivatives have been given in Ch. IV, Sect. 2.C(3) and (4). The process is of use in removing an unwanted alkyl group by means of decarboxylation.

Pyrimidine aldehydes and their acetals have also been oxidized to the corresponding acids, but as the aldehydes are generally more difficult to make than are the acids by other means, the process is of infrequent use, except as a confirmation of structure. An example is the conversion of 4-formyl-6-hydroxypyrimidine (XI) into 4-carboxy-6-hydroxypyrimidine (X) by treatment with alkaline permanganate at room temperature,[29] and the same reagent has been used to form 2-amino-5-carboxy-4-hydroxy-6-methylpyrimidine[30] and 2,4,6-tricarboxypyrimidine[31] from the corresponding aldehydes. One of the few useful examples of this oxidation is the preparation of orotic acid (4-carboxy-2,6-dihydroxypyrimidine) by treatment of 4-formyl-6-hydroxy-2-mercaptopyrimidine, its acetal, its ethylthio analogue, or 4-formyl-2,6-dihydroxypyrimidine, with dichromate in acid.[32] The method had been adapted to a micro scale for making isotopically labelled orotic acid.[33]

The Cannizzaro reaction has been used to disproportionate 4-formyl-6-hydroxypyrimidine (XI) (and its 2-methylthio derivative)



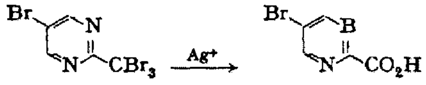
(X) (XI) (XII) (XIII)

into 4-carboxy-6-hydroxypyrimidine (XII) and 4-hydroxy-6-hydroxymethylpyrimidine (XIII) (and their 2-methylthio derivatives) in the usual way.[29] 4-Carboxy-2,6-dihydroxypyrimidine and 4-carboxy-6-hydroxy-2-mercaptopyrimidine have also been made by this reaction.[34]

2,4-Dihydroxy-5-hydroxymethylpyrimidine has been oxidized in 63 % yield by chromic acid mixture,[35] and in smaller yield by oxygen in the presence of platinum oxide to give 5-carboxy-2,4-dihydroxypyrimidine,[36] and 5-acetyl-4-methyl-2-phenylpyrimidine on treatment with permanganate gives the 5-carboxy analogue without any 4,5-dicarboxy-2-phenylpyrimidine.[37]

(4) *By Other Methods*

The device of treating tribromomethylpyrimidines with silver nitrate to give acids has been applied in the series. Thus 2-methylpyrimidine on vigorous bromination gave 5-bromo-2-tribromomethyl-



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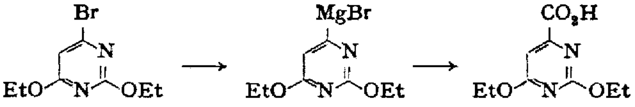

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pyrimidine (XIV), which then gave 5-bromo-2-carboxypyrimidine[38] (XV) on hydrolysis with aqueous silver nitrate. 4,6-Bistribromomethylpyrimidine likewise gave 4,6-dicarboxypyrimidine.[39]

Carboxypyrimidines have also been made from halogeno derivatives through Grignard and lithium derivatives. Thus a Grignard compound (XVII) was made from 4-bromo-2,6-diethoxypyrimidine (XVI) and treated with solid carbon dioxide at —80° to give 35 % of 4-carboxy-2,6-diethoxypyrimidine (XVIII). The same transformation was done in 50 % yield *via* 2,4-diethoxypyrimidin-6-yl-lithium. 5-Carboxy-2,4-dimethoxypyrimidine has been made similarly *via* 2,4-dimethoxypyrimidin-5-yl-lithium in 75 % yield.[40]

B. Reactions of Carboxypyrimidines

(1) *Decarboxylation*

The most useful reaction of carboxypyrimidines is their decarboxylation on heating. In this way, unwanted alkyl groups, which are often convenient during primary synthesis, may be oxidized to carboxy groups and then removed. Many simple examples of such cases are given in Chapter IV, Sect. 2.C(3), and the decarboxylation of the following acids are less simple examples: 4-amino-5-carboxypyrimidine (XIX) at 280° in benzophenone,[24] 5-bromo-2-carboxypyrimidine at 250° without solvent,[3,38] 6-carboxy-3-methyluracil at 310° dry[14] or in poor yield in quinoline,[6] 5-carboxy-3-methyluracil (and homologues) at 255° dry,[41] and 6-carboxy-3-phenyluracil catalysed by copper in boiling quinoline.[6] Yields are often better when such decarboxylations are done in small quantities.

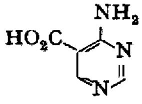
(2) *Esterification*

Carboxypyrimidines are seldom esterified: the opposite is more used. However, the preparation of the following esters from the corresponding acids exemplify the processes: 4-Ethoxycarbonylpyrimidine by hydrogen chloride in ethanol[42,43] or sulphuric acid in ethanol,[44] 5-methoxycarbonylpyrimidine by hydrogen chloride in methanol,[45] 2,4-dihydroxy-6-methoxycarbonylpyrimidine by hydrogen chloride in methanol or methyl iodide on the silver salt of the acid,[14,46–48] the ethoxycarbonyl analogue by similar methods,[14,48] 4-hydroxy-2-

mercapto-6-methoxycarbonylpyrimidine by hydrogen chloride in methanol,[48] 2,4-dihydroxy-6-methoxycarbonyl-5-nitropyrimidine by sulphuric acid in methanol,[49] 5-bromo-2-methoxycarbonylpyrimidine by diazomethane,[50] 5-bromo (and chloro)-4-ethoxycarbonyl-2-methylpyrimidine,[1] 2-methoxycarbonyl-5-methylpyrimidine,[51] and 2- and 4- β-methoxycarbonylethylpyrimidine (unanalysed) by diazomethane or methanolic hydrogen chloride.[52] Unable to be made by normal methods, 4-amino-5-methoxycarbonyl-2-methylpyrimidine resulted in 76 % yield from dissolution of the carboxylic acid in concentrated sulphuric acid and slow addition of methanol.[25] 4-Ethoxycarbonylpyrimidine has been conveniently made from the acid *via* the acid chloride.[53]

(3) *Formation of Acid Chlorides*

Pyrimidine acid chlorides have but rarely been mentioned. Typical are 4-chloro-6-chlorocarbonyl-5-methyl-2-phenylpyrimidine (XXI) which was formed on treatment of 4-carboxy-6-hydroxy-5-methyl-2-phenylpyrimidine (XX) at 130° with phosphorus pentachloride[54] and 4-chloro-5-chlorocarbonyl-2-ethylthiopyrimidine prepared with phosphoryl chloride.[55] Although esters have normally been used for this purpose in the pyrimidine series, acid chlorides are good intermediates in the formation of amides. Thus the reaction of 5-bromo(or chloro)-4-carboxy-2-methylpyrimidine with thionyl chloride and treatment of the resulting (crude) acid chloride with ammonia, gives the amides in 86 % yield.[1] Similarly, the 2-methylthio analogue has been used to yield amides[56] and the (unanalysed) acid chloride from 5-carboxypyrimidine gives a low yield of amide[45] (which, however, is better made from the ester).



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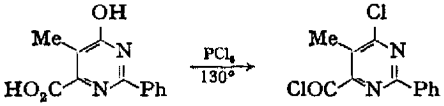

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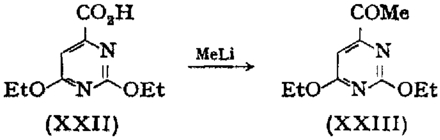


(XXII) (XXIII)

(4) *Other Reactions*

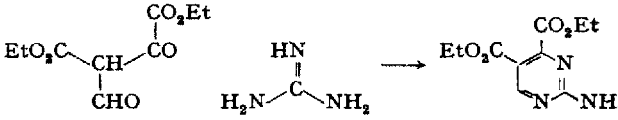
4-Carboxy-2,6-diethoxypyrimidine (XXII) when treated with methyl-lithium gives 4-acetyl-2,6-diethoxypyrimidine (XXIII) in 60 % yield. The structure was confirmed by hydrolysis to 4-acetyl-2,6-dihydroxypyrimidine.[40]

2. Alkoxycarbonylpyrimidines (Pyrimidine Esters)

A. Preparation of Esters

The esterification of carboxypyrimidines has already been discussed above. In addition, many esters can be made conveniently by primary synthesis, and a few by other means such as alcoholysis of nitriles.

In the Principal Synthesis, the three-carbon fragment may carry an ester grouping besides two other more reactive functional groups, and the intact ester finally occupies the 5, or less frequently, the 4 or an extranuclear position. Thus diethyl ethoxymethyleneoxalacetate, which is equivalent to the keto-aldehyde (XXIV), reacts with guanidine to give 2-amino-4,5-diethoxycarbonylpyrimidine[57] (XXV). Similarly, diethyl ethoxymethylenemalonate reacts as an aldehydo-ester with acetamidine to give 5-ethoxycarbonyl-4-hydroxy-2-methylpyrimidine[58–60] (XXVI), with urea to give 5-ethoxycarbonyl-2,4-dihydroxypyrimidine,[41] with *NN'*-dimethylurea to give 5-ethoxycarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine,[41] or with thiourea and its derivatives to give 2-thio-analogues.[16,61–62] Diethoxycarbonylacetone and *S*-ethylthiourea give 90 % of the extranuclear



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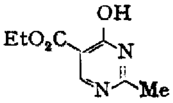

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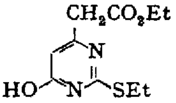

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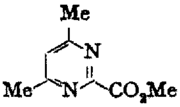


(XXVIII)

ester, 4-ethoxycarbonylmethyl-2-ethylthio-6-hydroxypyrimidine[63] (XXVII). There are many more examples[15,16,64–68] in Chapter II differing little in principle from the above, and a rather different type of synthesis is emplified in the condensations of ethyl aminomethylenecyanoacetate with thioacetamide to give 4-amino-5-ethoxycarbonyl-2-methylpyrimidine.[69]

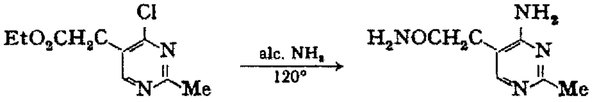
Alcoholysis of a nitrile in the presence of hydrogen choride has been used to convert 2-cyano-4,6-dimethylpyrimidine into 2-methoxycarbonyl-4,6-dimethylpyrimidine,[23] but in poor yield because the major product was 4,6-dimethylpyrimidine.

B. Reactions of Esters

The hydrolysis of pyrimidine esters to the corresponding carboxy derivatives has been discussed above (Sect. 1.A(2)), and the reduction of esters to hydroxymethylpyrimidines in Chapter VII, Sect. 3.D. The only other important reaction is their conversion into amides, hydrazides, and related compounds.

Amides are generally made from esters by treating them with alcoholic ammonia often at room temperature for several days. In this way, 5-methoxycarbonylpyrimidine gives a 64 % yield of 5-carbamoylpyrimidine,[45] but the use of aqueous ammonia reduces this yield to 34 %. Aqueous ammonia has also been used to make 4-amino-5-carbamoyl-2-hydroxypyrimidine[70] and 4-amino-5-carbamoyl-2-methylpyrimidine.[59] Methanolic ammonia at 100° gives 82 % of 5-carbamoyl-2,4-dimethylpyrimidine,[64] and 5-bromo-2-carbamoylpyrimidine.[50] Aqueous ammonia, however, gives a good yield of 4-carbamoylpyrimidine,[43] and of 5-carbamoylmethyl-2,4-dihydroxypyrimidine.[71] Other extranuclear amides made from esters include 2- and 4-β-carbamoylethylpyrimidine by alcoholic ammonia for several days,[52] 4-amino-5-carbamoylmethyl-2-methylpyrimidine (XXX) from 4-chloro-5-ethoxycarbonylmethyl-2-methylpyrimidine (XXIX) at 120° with alcoholic ammonia,[72–74] 4-amino-2-benzyl-5-carbamoylmethylpyrimidine similarly,[73] and 2-carbamoylmethyl-4,6-diethoxypyrimidine with aqueous ammonia.[75] It should be noted that esters sometimes have remarkable powers of withstanding ammonia. Thus 4-amino-2-chloro-5-ethoxycarbonylpyrimidine (XXXI) and an excess of alcoholic ammonia at 80–135° gives 94 % of 2,4-diamino-5-ethoxycarbonylpyrimidine[68] (XXXII), 5-ethoxycarbonyl-4-methyl-2-methylthiopyrimidine and alcoholic ammonia at 120° gives only 2-amino-5-ethoxycarbonyl-4-methylpyrimidine,[20] and, more understandably, 4-chloro-5-ethoxycarbonyl-2-trifluoromethylpyrimidine and alcoholic ammonia at 5° gives only the 4-amino analogue.[76]

Nearly all pyrimidine hydrazides have been made by the action of hydrazine hydrate (generally in alcohol) on an ester. Examples of the process are the conversion of 4-ethoxycarbonyl- to 4-hydrazinocarbonylpyrimidine (XXXIII) by warming with hydrazine hydrate for 5–10 minutes,[42–44,77] and the rather similar preparation of its 2,6-dimethyl derivative[78] (also made by treating the corresponding amide with hydrazine), 5-hydrazinocarbonylpyrimidine,[43] its 2,4,6-trimethyl-derivative,[64] its 4-methyl-2-phenyl derivative,[20] 2,4-diamino-5-hydrazinocarbonylpyrimidine,[79] 5-hydrazinocarbonylmethyl-2,4-dihydroxypyrimidine,[80] its 6-methyl derivative,[81] 4-amino-5-hydrazinocarbonyl-2-hydroxypyrimidine,[79] and its 2-methyl analogue.[25,82].



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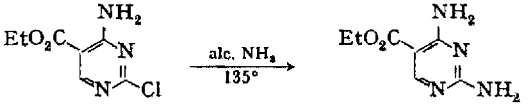

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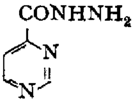


(XXXIII)

3. Carbamoylpyrimidines (Amides) and Related Compounds (Hydrazides and Azides)

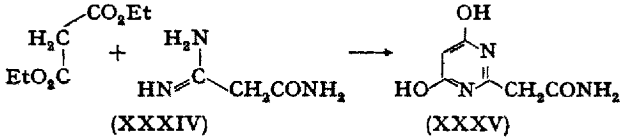
A. Preparation of Amides

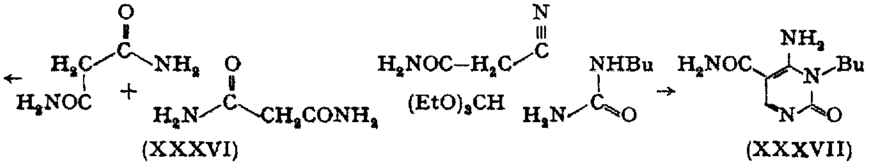
(1) *From Esters and Acid Chlorides*

The amination of esters is an important way of making amides. It has been discussed immediately above. The little used route *via* acid chlorides is exemplified by the conversion of 5-chlorocarbonyl- into 5-carbamoyl-pyrimidine[45] (see Sect. 1.B(3)).

(2) *By Primary Synthesis*

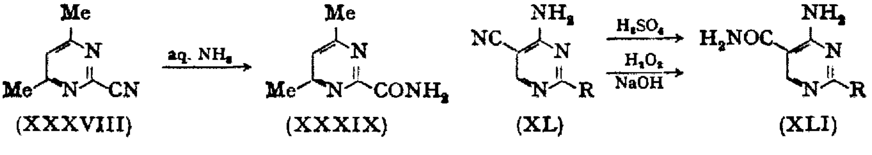
Primary Synthesis of amides is represented rather poorly: diethyl malonate condenses with carbamoylacetamidine (XXXIV) to give 2-carbamoylmethyl-4,6-dihydroxypyrimidine[76] (XXXV) and the same compound is better obtained by the self condensation of malondiamide (XXXVI) in sodium ethoxide.[83] The Whitehead Synthesis gives 4-amino-3-butyl-5-carbamoyl-2,3-dihydro-2-oxopyrimidine (XXXVII) by condensation of *N*-butylurea with ethyl orthoformate and cyanoacetamide, followed by cyclization of the ureide so formed, and in the same synthesis an 5-*N*-alkylcarbamoyl group and different 3-substituent can be introduced by starting with the appropriate cyano-*N*-alkylacetamide and *N*-alkylurea.[15]





(3) *By Controlled Hydrolysis of Nitriles*

Some pyrimidine nitriles can be converted into the corresponding amides by warming with dilute aqueous ammonia. Klötzer[23] has illustrated this process in making 2-carbamoyl-4,6-dimethylpyrimidine (XXXIX) (75 %) from (XXXVIII), 4-carbamoyl-2,6-dimethylpyrimidine, 4-carbamoyl-2,6-dimethoxypyrimidine, and 4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine. Acid hydrolysis of ni-



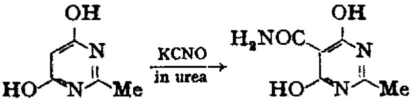
triles has also been used in the series: good examples are the conversion of 4-amino-5-cyano-2-methyl (and ethylthio) pyrimidine (XL) into the 5-carbamoyl analogues (XLI) by dissolution in concentrated sulphuric acid,[70,79] and the similar preparation of 2,4-diamino-, 4-amino-2-hydroxy-, and 4-amino-2-mercapto- 5-carbamoylpyrimidine.[70] The preparation of 5-carbamoyl-4-hydroxy-6-methyl-2-piperidinopyrimidine from its 5-cyano analogue was done at 100° with sulphuric acid.[30]

The Radziszewski reaction[84–86] involving treatment of a nitrile with aqueous hydrogen peroxide under basic conditions, to give an amide, has been found very useful in the pyrimidine series. Thus were made 4-amino-5-carbamoylpyrimidine[24] (XLI; R=H), its 2-methyl derivative[70] (XLI; R=Me), its 2-ethylthio derivative[70] (XLI; R=SEt), 2-carbamoyl-4-methoxy-6-methylpyrimidine,[87] 4-carbamoyl-2,6-dimethylpyrimidine,[78] 2-carbamoyl-4-ethoxy-6-methylpyrimidine,[88] and several 4-alkoxy homologues.[88]

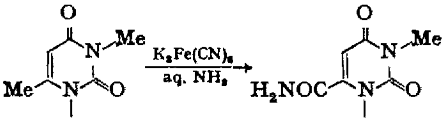
Pyrimidine thioamides have occasionally been made from nitriles. For example when 2-cyano-4,6-dimethylpyrimidine in ether containing a little diethylamine is saturated with hydrogen sulphide and allowed to remain at room temperature for 2 days, 4,6-dimethyl-2-thiocarbamoylpyrimidine results in 95 % yield.[23] 2,4-Dimethyl(and dimethoxy)-6-thiocarbamoylpyrimidine were made similarly.[23]

(4) *By Other Means*

When 4,6-dihydroxy-2-methylpyrimidine (XLII) is heated with potassium cyanate in molten urea, a 54 % yield of the 5-carbamoyl derivative (XLIII) is obtained.[89] (Omission of the cyanate leads to a rather lower yield.[89]) This potentially useful reaction is almost unexplored, although another example and a few early references have been reported.[89a]



(XLII) (XLIII)

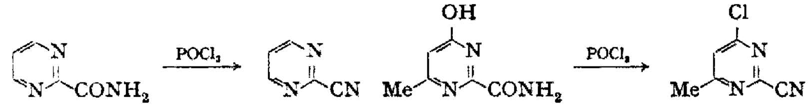


(XLIV) (XLV)

So too, is the oxidation of a *C*-methylpyrimidine by ferricyanide in the presence of ammonia, to give an amide. In this way, for example, 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine (XLIV) yields 4-carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine[14] (XLV), and 6-carbamoyl-1-methyluracil is made similarly.[14] The reaction seems to have been first used in the series by Behrend and Struve[26] to convert 2,4-dihydroxy-6-methyl- into 4-carbamoyl-2,6-dihydroxy-pyrimidine.

B. Reactions of Amides

The hydrolysis of amides to carboxypyrimidines has been treated already in Sect. 1.A(2). The dehydration of an amide on the other hand gives a nitrile, and although the reaction has been but little used it is exemplified in the formation of 2-cyano- (XLVII) from 2-carbamoyl-pyrimidine (XLVI) by boiling with phosphoryl chloride,[50] and



(XLVI) (XLVII) (XLVIII) (XLIX)

the same reagent has been used to change 2-carbamoyl-4-hydroxy-6-methyl- (XLVIII) into 4-chloro-2-cyano-6-methyl-pyrimidine[90] (XLIX), 5-carbamoyl-4,6-dihydroxy-2-methyl- into 4,6-dichloro-5-cyano-2-methyl-pyrimidine,[89] 2-carbamoylmethyl-4,6-dihydroxy- into 4,6-dichloro-2-cyanomethyl-pyrimidine,[75] and 5-bromo (and chloro)-4-carbamoyl-2-methyl- into 5-bromo(and chloro)-4-cyano-2-methyl-pyrimidine.[1] There does not seem to be an example of the thiation of a carbamoyl- to a thiocarbamoyl-pyrimidine.

The Hofmann Reaction has been used to convert carbamoyl- into amino-pyrimidines in the 4-position (Ch. IX, Sect. 1.H), the 5-position (Ch. IX, Sect. 2.D), and the extranuclear positions (Ch. IX, Sect. 3.B).

C. Preparation and Reactions of Hydrazides and Azides

The formation of hydrazides from esters (or amides) has been discussed in Section 2.B. Azides are made by nitrous acid treatment of the corresponding hydrazides. This is illustrated by the formation from 2-ethylthio-5-hydrazinocarbonylmethyl-4-hydroxypyrimidine (L) in aqueous nitrous and at 0°, of 5-azidocarbonylmethyl-2-ethylthio-4-hydroxypyrimidine (LI) in 60 % yield,[80] and also by the similar preparation of 5-azidocarbonylmethyl-2,4-dihydroxypyrimidine,[80] its (uncharacterized) 6-methyl derivative,[81] 4-amino-5-azidocarbonyl-2-methyl(and hydroxy)-pyrimidine,[79] and 2,4-diamino-5-azidocarbonylpyrimidine.[79] Other instances of the use of azides in the Curtius reaction without isolation[64,73,91] have been discussed in Chapter IX, Sects. 2.D and 3.B.

The chief reaction of hydrazides is their conversion into azides with nitrous acid (see above). Apart from this, 4-hydrazinocarbonyl-2,6-dimethylpyrimidine (LII) condenses with piperonal to give a type of Schiff's base, 2,4-dimethyl-6-piperonylidenehydrazinocarbonylpyrimidine (LIII), and with benzaldehyde and glucuronolactone to give probably similar compounds.[78]

Hydrazides can be acylated. Thus 4-amino-5-hydrazinocarbonyl-2-methylpyrimidine with benzenesulphonyl chloride yields (indubitably) 4-amino-5-benzenesulphonylhydrazinocarbonyl-2-methylpyrimidine.[25]

Azides readily react with alcohols to give urethanes. Thus 5-azidocarbonylmethyl-2-ethylthio-4-hydroxypyrimidine (LI) on heating with ethanol, looses nitrogen to give finally the urethane, 5-ethoxycarbonylaminomethyl-2-ethylthio-4-hydroxypyrimidine[80] (LV). The same azide (LI) on heating in toluene gives 2-ethylthio-4-hydroxy-5-isocyanatomethylpyrimidine[80] (LIV). Other simple examples of these reactions are given in Chapter IX, Sect. 6, and an interesting purine synthesis[79] is based on the second (isocyanate) reaction. When 4-amino-5-azido-carbonyl-2-methylpyrimidine (LVI) is heated in xylene, the resulting isocyanate (LVII) cyclizes immediately to give 8-hydroxy-2-methylpurine (LVIII); 2-amino-8-hydroxy- and 2,8-dihydroxy- purine have been made similarly.[79]

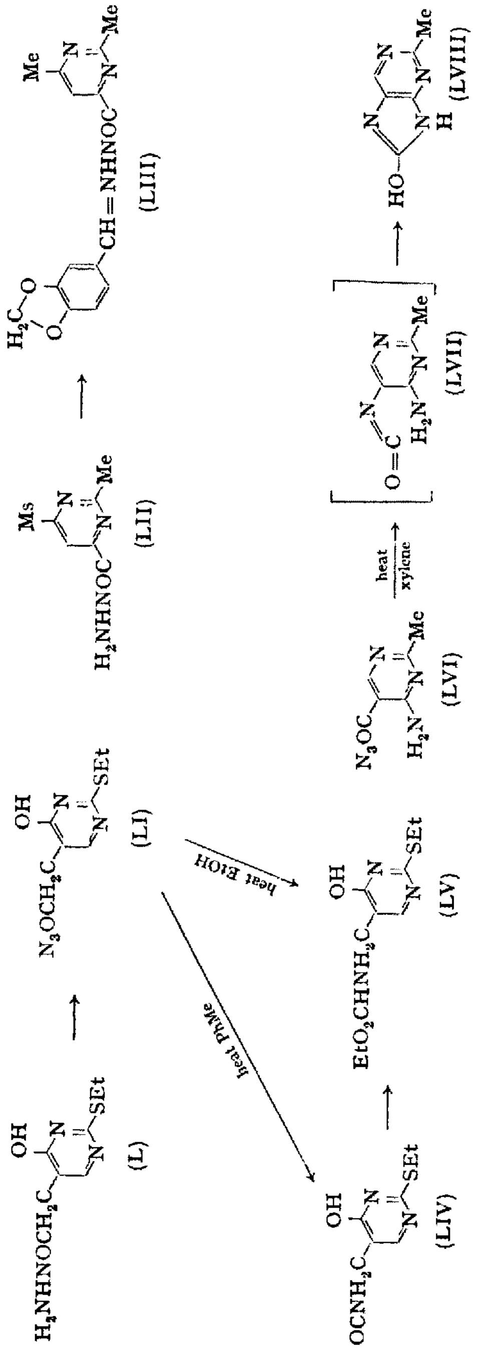
4. Pyrimidine Nitriles

Although cyanopyrimidines are important intermediates in making all types of carboxylic acid derivative and aminomethylpyrimidines, and can be made in several ways, they form a relatively little explored family.

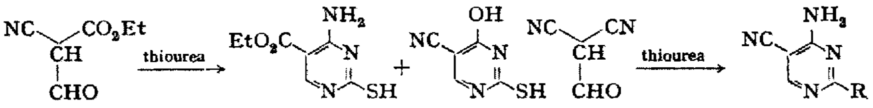
A. Preparation of Cyanopyrimidines

(1) *By Primary Synthesis*

Pyrimidines with a cyano group in the 5-position can sometimes be made by a Principal Synthesis. However, the route is restricted by


(L)
(LI)
(LII)
(LIII)
(LIV)
(LV)
(LVI)
(LVII)
(LVIII)
heat EtOH
heat PhMe
heat
xylene

the reactivity of the cyano group attached to the aliphatic starting material. This limitation is illustrated by the condensation of ethyl ethoxymethylenecyanoacetate (virtually ethyl formylcyanoacetate; LIX) with thiourea[92] to give a mixture of 54 % 4-amino-5-ethoxycarbonyl-2-mercaptopyrimidine (LX), with only 14 % of 5-cyano-4-hydroxy-2-mercaptopyrimidine (LXI). The first product predominates because thiourea reacts with the cyano group at the expense of the ester group in the aliphatic compound. On the other hand, when ethoxymethylenemalononitrile (virtually LXII) is used, the choice is only between two cyano groups, so that 4-amino-5-cyano-2-mercaptopyrimidine (LXIII; R=SH), is formed in good yield with thiourea,[70] 4-amino-5-cyano-2-ethylthiopyrimidine with *S*-ethylthiourea,[70] and 4-amino-5-cyano-2,3-dihydro-3-methyl-2-thiopyrimidine and its 3-alkyl homologues with *N*-methylthiourea and its homologues.[16] Similar reactions occur[67,70,93–95] with amidines, (Ch. II, Sect. 8.C) and with urea and its *N*-alkyl derivatives[15] (Ch. II, Sect. 8.E), leading to 4-amino-5-cyanopyrimidine substituted by a 2-alkyl (LXIII; R=alkyl) or 2-hydroxy group (LXIII; R=OH). The interesting reaction of unsubstituted malononitrile with formamidine to give 4-amino-5-cyanopyrimidine[69,96] (LXIII; R=H) has been discussed in Chapter II, Sect. 11 and Chapter III, Sect. 3.A. The reaction of ethyl ethoxymethylenecyanoacetate with acetamidine to give either 5-cyano-4-hydroxy-2-methylpyrimidine by alkaline ring closure or 4-amino-5-ethoxycarbonyl-2-methylpyrimidine by acidic cyclization, has been treated in Chapter II, Sect. 8.C.



(LIX) (LX) (LXI) (LXII) (LXIII)

When ethyl β-cyano-α-formylpropionate is condensed with acetamidine, 5-cyanomethyl-4-hydroxy-2-methylpyrimidine is formed;[58] there are also other minor methods of primary synthesis, used to make cyano derivatives,[97–99] and the Shaw synthesis (Ch. III, Sect. 1.E) offers[100–102] a variety of 5-cyanopyrimidines as products. The use of dicyanodiamide in preparing 2-cyanoaminopyrimidines has been outlined in Chapter IX, Sect. 8.B.

(2) *By Dehydration of Amides*

This useful but neglected method of making nitriles has been discussed above (Sect. 3.B).

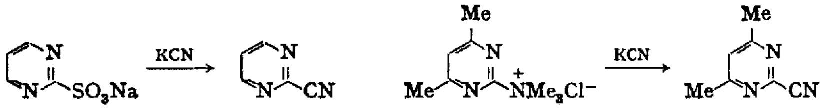
(3) *By Other Means*

The sodium salts of 2-sulphopyrimidine (LXIV) and related *C*-alkyl derivatives, on distillation with potassium cyanide give 2-cyanopyrimidine (LXV) and derivatives.[50,103] Since the sulphopyrimidines are readily made from the corresponding chloro derivatives, the process allows the transformation of a 2- or 4-chloro into a cyano group, which has not been done directly in the series.

A quaternary amino group such as that in 4,6-dimethylpyrimidin-2-yltrimethylammonium chloride (LXVI) can be replaced by a cyano group[23,104] to give 2-cyano-4,6-dimethylpyrimidine (LXVII) and related compounds (Ch. IX, Sect. 8.G).

The aldoxime, 4-hydroxy-5-hydroxyiminomethyl-6-methyl-2-piperidinopyrimidine (LXVIII), on heating with acetic anhydride is dehydrated to 5-cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine[30] (LXIX). The dehydration is also successful with phosphoryl chloride, to give 4-chloro-5-cyano-6-methyl-2-piperidinopyrimidine (LXX), which can alternatively be made[30] with the same reagent on (LXIX). Other cases of dehydration are recorded.[30]

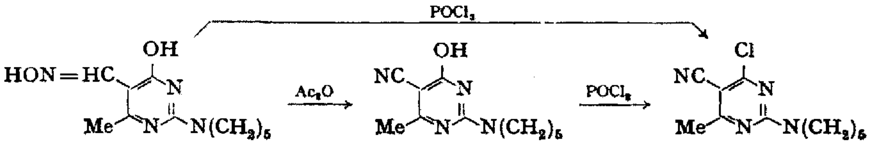
There are several examples of 5-cyanopyrimidines made directly from 5-halogeno derivatives. The reaction is sluggish, and it requires heating in quinoline with cuprous cyanide to prepare 2- (and 4-) amino-5-cyanopyrimidine from their bromo analogues,[105,106] or 2-benzenesulphonamido-5-cyanopyrimidine from its 5-iodo analogue.[105]



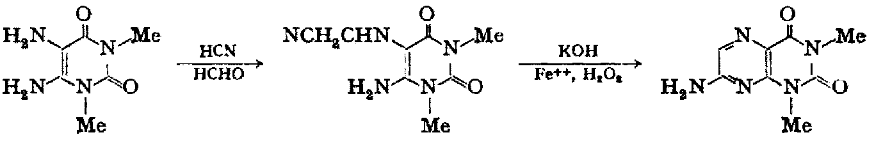
(LXIV) (LXV) (LXVI) (LXVII)

2,5-Diamino-4-methyl-6-methylthiopyrimidine has been diazotized and then treated with sodium cyanide to yield 2-amino-5-cyano-4-methyl-6-methylthiopyrimidine.[107]

Direct introduction of a cyano group into the 5-position of barbituric acid has been reported[108] by treatment with mercury fulminate plus potassium cyanide in aqueous solution. The cyano group is supplied by the fulminate because the same product is formed when the potassium cyanide is replaced by potassium iodide. A little-known



(LXVIII) (LXIX) (LXX)



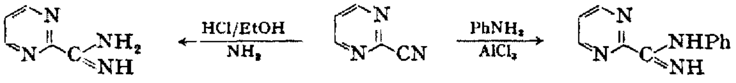
(LXXI) (LXXII) (LXXIII)

cyanomethylation reaction should here be mentioned. 4,5-Diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (LXXI) treated successively with methanolic hydrogen cyanide and formaldehyde gives 72 % of the 4-amino-5-cyanomethylamino analogue (LXXII). The structure was indicated by cyclization and oxidation to 7-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopteridine[109] (LXXIII). When 4,5-diaminopyrimidine was treated in water as above, 50 % of the simple analogue, 4-amino-5-cyanomethylaminopyrimidine, was isolated as an unstable solid.[110]

B. Reactions of Cyanopyrimidines

The hydrolysis of nitriles to carboxylic acids and to amides has been discussed respectively in Sections 1.A(2) and 3.A(3), and the action of hydrogen sulphide to give thioamides also in Section 1.A(2). Reduction of nitriles by lithium aluminium hydride or by catalytic hydrogenation to give aminomethyl derivatives has been outlined in Chapter IX, Sect. 3.A. A cyano group in the 2-, 4-, or 6-position may be replaced by an alkoxy group (Ch. VII, Sect. 4.C), and indirectly by an aldehyde group (Sect. 5.A(3)).

Amidines are normally made by treatment of a nitrile with hydrogen chloride and ethanol to give the imino ether, followed by ammonia. This method of Pinner has been used to make 2-amidinopyrimidine (LXXIV) from 2-cyanopyrimidine[50] (LXXV) and several



(LXXIV) (LXXV) (LXXVI)

arylamidinopyrimidines (*e.g.* 2-phenylamidinopyrimidine; LXXVI) have been made by treatment at 70° of 2-cyanopyrimidine (LXXV) and a primary amine with aluminium chloride.[50]

5. Pyrimidine Aldehydes and Their Acetals

There are now a reasonable number and variety of pyrimidine aldehydes and their acetals known. They are being made by a variety of routes, and undergo numerous reactions.

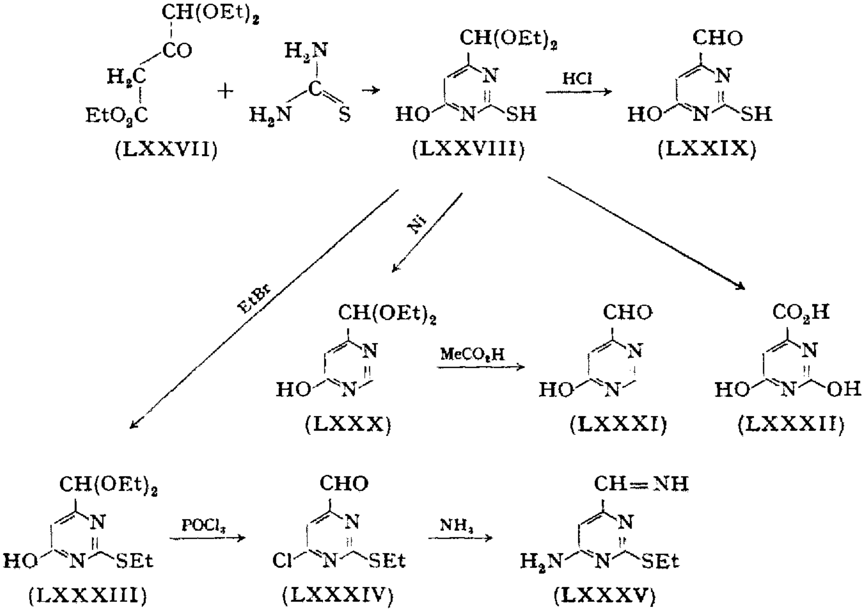
A. Preparation of Formylpyrimidines

(1) *By the Principal Synthesis*

Although free aldehydes cannot be made by the Principal Synthesis, several of their acetals are best prepared in this way. They nearly all have the dialkoxymethyl group in position 4. The condensation of ethyl γγ-diethoxyacetoacetate (LXXVII) with thiourea leads to 4-diethoxymethyl-6-hydroxy-2-mercaptopyrimidine (LXXVIII) in 80 % yield,[32,33,111] and its 5-methyl derivative can be made similarly.[112] These acetals are converted into the free aldehydes, 4-formyl-6-hydroxy-2-mercaptopyrimidine (LXXIX), and its 5-methyl derivative, by treatment with dilute hydrochloric acid. Related acetals, such as 4-diethoxymethyl-6-hydroxypyrimidine[29,113] (LXXX) and its derivative[32] (LXXXIII) which were made from (LXXXVIII) respectively with Raney nickel and by ethylation, although not so satisfactorily converted into free aldehydes with hydrochloric acid[29,32] readily gave 4-formyl-6-hydroxy-[113] (LXXXI) and 2-ethylthio-4-formyl-6-hydroxy-[32,113] pyrimidine by digestion with aqueous acetic acid. Treatment of the mercapto acetal (LXXVIII) with sulphuric acid and sodium dichromate furnishes orotic acid[32,33] (LXXXII), and treatment of the ethylthio derivative (LXXXIII) with phosphoryl chloride gives

4-chloro-2-ethylthio-6-formylpyrimidine (LXXXIV), which with ammonia gives *inter alia* 4-amino-2-ethylthio-6-iminomethylpyrimidine[114] (LXXXV) (the imino analogue of an aldehyde).

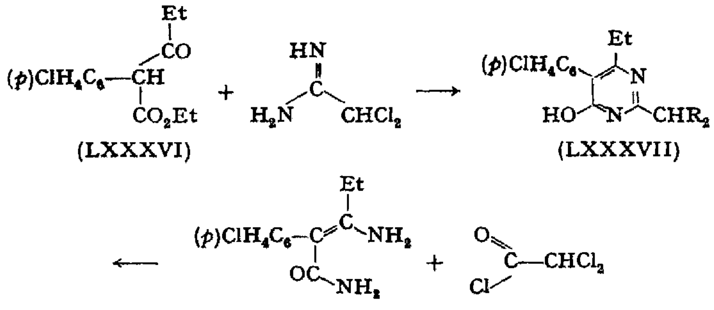
Ethyl γγ-diethoxyacetoacetate has also been condensed with benzamidine to give 4-diethoxymethyl-6-hydroxy-2-phenylpyrimidine[115] (converted into the 4-formyl analogue with acid) and with guanidine to give 2-amino-4-diethoxymethyl-6-hydroxypyrimidine.[116]



The latter product with phosphoryl chloride gave 2-amino-4-chloro-6-diethoxymethylpyrimidine and after dechlorination, 2-amino-4-diethoxymethylpyrimidine.[116] The Principal Synthesis has also been used to make 2-amino-4-diethoxymethyl (or dimethoxymethyl)-6-methoxymethyl (or methyl) pyrimidine.[116]

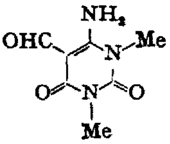
One pyrimidine with a 2-diethoxymethyl grouping has been made,[117] albeit rather indirectly, by the Principal Synthesis. Dichloro acetamidine was condensed with ethyl α-*p*-chlorophenyl-α-propionylacetate (LXXXVI) in ethanol to give 5-*p*-chlorophenyl-2-dichloromethyl-4-ethyl-6-hydroxypyrimidine (LXXXVII; R=Cl), which was also made by another primary synthesis from 2-amino-1-carbamoyl-1-*p*-chlorophenylbut-1-ene (LXXXVIII) and dichloroacetyl chloride.[117]

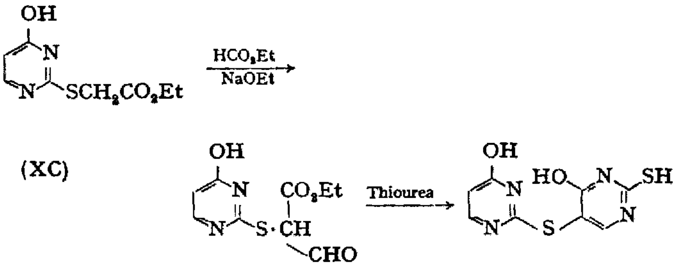
Subsequent treatment with ethanolic sodium ethoxide at 160° gave 5-*p*-chlorophenyl-2-diethoxymethyl-4-ethyl-6-hydroxypyrimidine (LXXXVII; R=OEt).


(LXXXVI) (LXXXVII) (LXXXVIII)

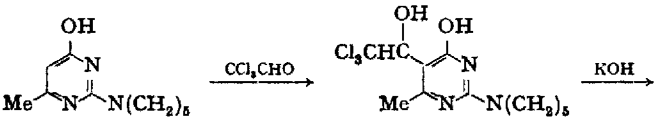
(2) *By Direct and Indirect* C-*Formylation*

When 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine is treated with the vigorous formylating agent, acetic formic anhydride, the 5-formyl derivative (LXXXIX) is formed, although the amino group remains unattacked.[118] The spectral evidence for this peculiar reaction is reasonable, and the aldehyde easily gives a phenylhydrazone.[118] Direct *C*-formylation of a side chain is known in the conversion of 2-ethoxycarbonylmethylthio-4-hydroxypyrimidine (XC) with ethyl formate and sodium ethoxide, into 2-ethoxycarbonylformylmethylthio-4-hydroxypyrimidine[119] (XCI). The position of formylation was ingeniously shown by using (XCI) as an aldehydo ester with thiourea in a Principal Synthesis yielding 4-hydroxy-5-(4-hydroxypyrimidin-2-yl)thio-2-mercaptopyrimidine (XCII).

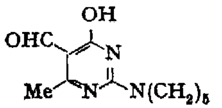

(LXXXIX)


(XC) (XCI) (XCII)

There are several less direct ways of introducing a 5-formyl group into position 5. Some 4-hydroxypyrimidines react with chloral to give 4-hydroxy-5-(2,2,2-trichloro-1-hydroxyethyl)pyrimidines which can be hydrolysed to 5-formyl-4-hydroxypyrimidines.[30] Thus 4-hydroxy-6-methyl-2-piperidinopyrimidine (XCIII) heated with chloral in pyridine gives the 5-(2,2,2-trichloro-1-hydroxyethyl) derivative (XCIV), which is hydrolysed by hot aqueous-alcoholic alkali to 5-formyl-4-hydroxy-6-methyl-2-piperidinopyrimidine (XCV) in good yield. Its 2-dimethylamino, 2-methylamino, and 2-amino analogues were made similarly.[30] In the absence of the 4-hydroxy group, the reaction fails, however. Thus, applied to 4-amino-6-methyl-2-piperidinopyrimidine, the chloral attacks not the 5-position but the amino group to give 4-methyl-2-piperidino-6-(2,2,2-trichloro-1-hydroxyethylamino)pyrimidine (XCVI), from which alkaline hydrolysis gives back the starting material. The same thing happens with 2-amino-4-chloro-6-methyl-, 2-amino-4-methyl-6-methylthio-, and 2-amino-4-chloro-6-methyl-5-nitro-pyrimidine. As well as attacking the 5-position and primary amino groups, chloral also reacts with some methyl groups: 4,6-dihydroxy-2-methyl-5-nitropyrimidine yields 4,6-dihydroxy-5-nitro-2-(3,3,3-trichloro-2-hydroxypropyl)pyrimidine, and with 4-hydroxy-2,6-dimethylpyrimidine 4-hydroxy-6-methyl-5-(2,2,2-trichloro-1-hydroxyethyl)-2-(3,3,3-trichloro-2-hydroxypropyl)pyrimidine is formed.[30]



(XCIII) (XCIV)

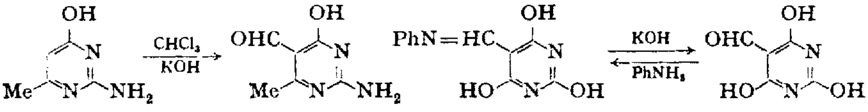


(XCV)

(XCVI)

The Reimer–Tiemann aldehyde synthesis has also been applied[30] to some 4-hydroxypyrimidines: 2-amino-4-hydroxy-6-methylpyrimidine (XCVII), treated with chloroform and concentrated aqueous potassium hydroxide, gives 2-amino-5-formyl-4-hydroxy-6-methylpyrimidine (XCVIII) in about 40 % yield. The 2-dimethylamino, and 2-piperidino analogues as well as 5-formyl-2,4-dihydroxy-6-methyl-, 5-formyl-4,6-dihydroxy-2-piperidino-, and 5-formyl-4,6-dihydroxy-2-phenyl- pyrimidine (and other derivatives) were made similarly.[30, 186]

Barbituric acid when fused with diphenylformamidine (Ph.N:CH.NHPh) yields 2,4,6-trihydroxy-5-phenyliminomethylpyrimidine (XCIX).

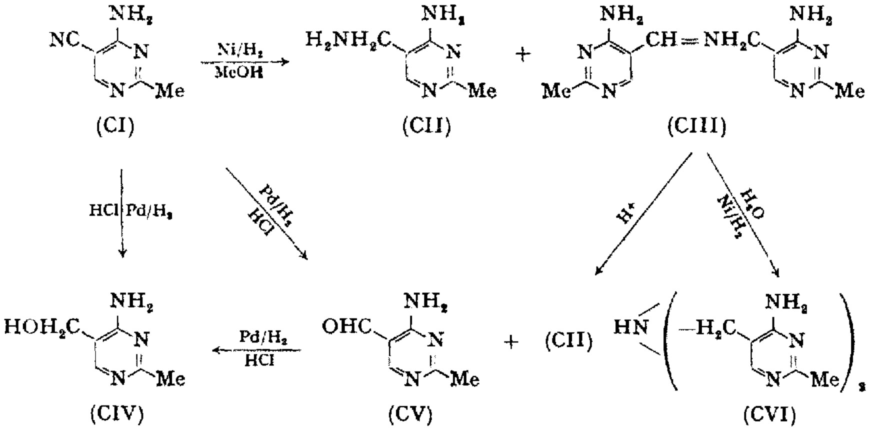


(XCVII) (XCVIII) (XCIX) (C)

On treating this anil with alkali, 5-formyl-2,4,6-trihydroxypyrimidine (C) is formed, and it is reconverted into the Schiff's base (XCIX) by warming with aniline.[120] The aldehyde (C) is similarly formed from 2,4,6-trihydroxy-5-iminomethylpyrimidine.[121]

(3) *From Cyanopyrimidines*

Although the conversion of 4-amino-5-cyano-2-methylpyrimidine (CI) into 4-amino-5-formyl-2-methylpyrimidine (CV) has been well



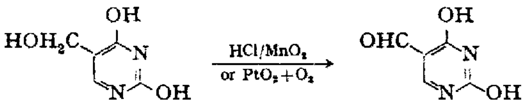
(CI) (CII) (CIII) (CIV) (CV) (CVI)

worked out, the reaction has not been applied to other pyrimidines. In 1938, Delépine[122] showed that catalytic hydrogenation of (CI) with a nickel catalyst gave not only 4-amino-5-aminomethyl-2-methylpyrimidine (CII) (the intermediate for vitamin B_1) but also a complex compound which on treatment with acetic acid gave 4-amino-5-formyl-2-methylpyrimidine (CV). The complex compound was later made in better yield and it was shown[123–128] on acid hydrolysis to give *both* (CII) and (CV), and to be reduced under vigorous conditions to the secondary amine (CVI), thus indicating it as the Schiff's base (CIII). Reduction of the nitrile (CI) over palladium gives the aldehyde (CV) directly in 77 % yield;[129] under more vigorous conditions 4-amino-5-hydroxymethyl-2-methylpyrimidine (CIV) is formed from either the nitrile[124] (CI) or the aldehyde[25,123] (CV). The aldehyde (CV) is best purified through its nickel complex[129] (*cf.* refs. 122, 130).

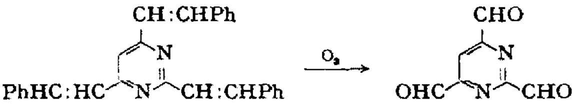
(4) *By Oxidative Processes*

2,4-Dihydroxy-5-hydroxymethylpyrimidine (CVII) can be oxidized[36] to 5-formyl-2,4-dihydroxypyrimidine (CVIII) with manganese dioxide in hydrochloric acid, but after separation from unchanged material and the 5-carboxy-2,4-dihydroxypyrimidine formed simultaneously the yield is only 5 %. Oxygenation in the presence of platinum oxide is a more promising process for (CVIII) and analogues, but it has not been adapted to a preparative scale.[36]

2,4,6-Trimethylpyrimidine can be converted with benzaldehyde into 4,6-dimethyl-2-styryl-, 4-methyl-2,6-distyryl-, and (CIX) 2,4,6-tristyryl-pyrimidine. Ozonization of these (followed by catalytic reduction) yields 2-formyl-4,6-dimethyl-, 2,4-diformyl-6-methyl-, and 2,4,6-triformyl-pyrimidine (CX), isolated as *p*-nitrophenylhydrozones.[31,131]



(CVII) (CVIII)



(CIX) (CX)

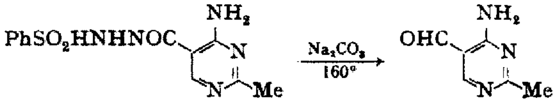
The processes are of little preparative importance.

On the other hand, 4-amino-5-hydroxymethyl-2-methylthiopyrimidine in acetic acid is oxidized by dichromate to give some 70 % of 4-amino-5-formyl-2-methylthiopyrimidine, which was further characterized as its oxime.[132]

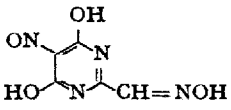
(5) *By Other Means*

Treatment of diazotized 2,5-diamino-4-methyl-6-methylthiopyrimidine with a reagent made from hydroxylamine, formaldehyde, and copper sulphate gives 2-amino-5-formyl-4-methyl-6-methylthiopyrimidine,[107] but no other examples of such reactions seem to be described.

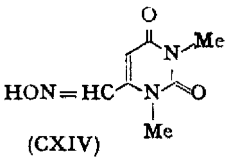
Use has been made[25] of the McFadyen and Stevens aldehyde synthesis in the following interesting sequence: 4-amino-5-cyano-2-methylpyrimidine was converted, *via* the acid and ester, into 4-amino-5-hydrazinocarbonyl-2-methylpyrimidine and thence to 4-amino-5-benzenesulphonylhydrazinocarbonyl-2-methylpyrimidine (CXI). Sodium carbonate in glycol at 160° gave 4-amino-5-formyl-2-methylpyrimidine (CXII) in 44 % yield. A similar sequence failed when applied to the preparation of 5-formylmethyl-4-hydroxy-2-methylpyrimidine.[25]



(CXI) (CXII)



(CXIII)



(CXIV)

Oximes of aldehydes have been made by direct nitrosation of a methyl group in pyrimidines. Thus 4,6-dihydroxy-2-methylpyrimidine gives 4,6-dihydroxy-5-nitroso-2-nitrosomethylpyrimidine[133] (tautomeric with the oxime, 4,6-dihydroxy-2-hydroxyiminomethyl-5-nitrosopyrimidine; CXIII). Reduction gave 5-amino-2-aminomethyl-4,6-dihydroxypyrimidine.[133] Likewise, 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine yields the oxime, 1,2,3,4-tetrahydro-6-hydroxyiminomethyl-1,3-dimethyl-2,4-dioxopyrimidine (CXIV), identical with material formed by an unambiguous route.[134]

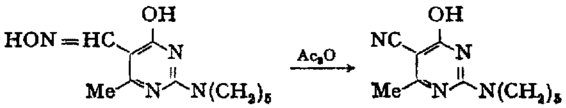
B. Reactions of Formylpyrimidines

(1) *Oxidation and Reduction*

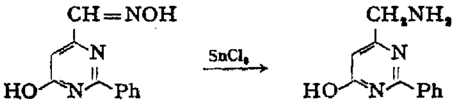
The oxidation of formylpyrimidines to carboxylic acids is discussed in Sect. 1.A(3), and examples of the Cannizzaro disproportionation are also included therein. The reduction of aldehydes to hydroxymethylpyrimidines has been outlined in Chapter VII, Sect. 3.F.

(2) *Formation of the Usual Aldehyde Derivatives*

The pyrimidine aldehydes are not exceptional in their formation of the classical derivatives. A few examples of each follow, and included are any reactions peculiar to each derivative.



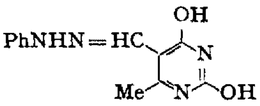
(CXV) (CXVI)



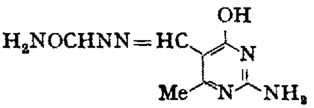
(CXVII) (CXVIII)

Typical oximes are 4-hydroxy-6-hydroxyiminomethyl-2-phenylpyrimidine,[115] 4-hydroxy-6-hydroxyiminomethyl-2-mercapto-5-methylpyrimidine,[112] 2,4-dihydroxy-6-hydroxyiminomethyl-5- methylpyrimidine,[112] and 4-hydroxy-5-hydroxyiminomethyl-6-methyl-2-piperidinopyrimidine[30] (CXV). The last oxime has been dehydrated with acetic anhydride to give 5-cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine[30] (CXVI), and reduction of an oxime is typified in the formation[115] of 4-aminomethyl-6-hydroxy-2-phenylpyrimidine (CXVIII), from (CXVII) with stannous chloride, and by 5-amino-2-aminomethyl-4,6-dihydroxypyrimidine (ammonium hydrogen sulphide[113]).

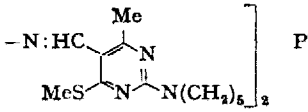
The phenylhydrazone family of derivatives is exemplified by 2,4-dihydroxy-6-methyl-5-phenylhydrazonomethylpyrimidine[30] (CXIX), 4-chloro-2-ethylthio-6-phenylhydrazonomethylpyrimidine,[114] 4-hydroxy-6-*p*-nitrophenylhydrazonomethylpyrimidine,[113] 5-(2,4-dinitrophenyl)-hydrazonomethyl-4,6-dihydroxy-2-piperidinopyrimidine,[30] and related derivatives.[30, 31, 112, 131]



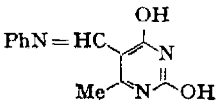
(CXIX)



(CXX)



(CXXI)



(CXXII)

Semicarbazones and thiosemicarbazones are represented by 2-amino-4-hydroxy-6-methyl-5-semicarbazono(and thiosemicarbazono)-methylpyrimidine[30] (CXX), and by 4-hydroxy-6-methyl-2-piperidino-5-thiosemicarbazonomethylpyrimidine.[30] There are several aldazines[30] typified by "5-azinomethyl-4-methyl-6-methylthio-2-piperidinopyrimidine" (CXXI), and other less usual derivatives are reported by Hull.

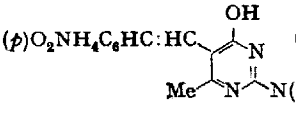
Brief warming of a pyrimidine aldehyde with an aromatic amine produces a Schiff's base* such as 2,4-dihydroxy-5-methyl-6-phenyliminomethylpyrimidine[112] (CXXII) or 4-amino-2-methyl-5-*p*-tolyliminomethylpyrimidine.[91] This type of anil is readily hydrolysed back to the aldehyde by acid treatment.

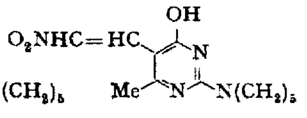
(3) *Other Reactions*

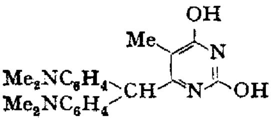
Formylpyrimidines have been condensed with compounds containing an activated methylene or methyl group[30]. Thus 5-formyl-4-hydroxy-6-methyl-2-piperidinopyrimidine, with *p*-nitrophenylacetic

* These should be distinguished from the Schiff's bases formed from aminopyrimidines and aromatic aldehydes (Ch. IX, Sect. 5.C).

acid at 160° gives 4-hydroxy-6-methyl-5-*p*-nitrostyryl-2-piperidinopyrimidine (CXXIII), with acetophenone gives 5-benzoylvinyl-4-hydroxy-6-methyl-2-piperidinopyrimidine, with malonic acid gives 5-β-carboxyvinyl-4-hydroxy-6-methyl-2-piperidinopyrimidine, and with nitromethane gives 4-hydroxy-6-methyl-5-β-nitrovinyl-2-piperidinopyrimidine (CXXIV).


(CXXIII)


(CXXIV)


(CXXV)

4-Formyl-2,6-dihydroxy-5-methylpyrimidine on heating with *NN*-dimethylaniline and zinc chloride gives an analogue of (leuco) malachite green, 4-bis(*p*-dimethylaminophenyl)methyl-2,6-dihydroxy-5-methylpyrimidine (CXXV) and two analogues were made similarly.[135] The formation of members of several other heterocyclic systems from pyrimidine aldehydes has been recorded.[30]

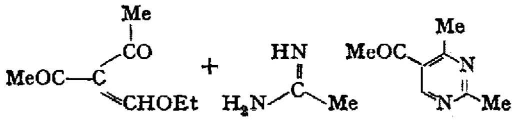
6. Pyrimidine Ketones and Derivatives

There are relatively few pyrimidine ketones described, and they are not representative of the potential family.

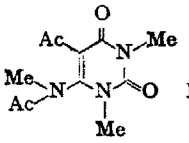
A. Preparation of *C*-Acylpyrimidines

The Principal Synthesis has been used to make 5-acylpyrimidines. Thus ethoxymethyleneacetylacetone (virtually formylacetylacetone CXXVI) with acetamidine gives 5-acetyl-2,4-dimethylpyrimidine[136] (CXXVII) with guanidine (and *NN*-dimethylguanidine) it gives 5-acetyl-2-amino(and dimethylamino)-4-methylpyrimidine,[136, 137] and with benzamidine it gives 5-acetyl-4-methyl-2-phenylpyrimidine.[37] Ethyl ethoxymethyleneacetoacetate reacts with urea, *N*-alkylureas and *N*-alkylthioureas to give under some conditions, respectively 5-acetyl-2,4-dihydroxypyrimidine,[138,139] 5-acetyl-3-alkyluracil,[140] and 5-acetyl-3-alkyl-2-thiouracil.[16] A discussion of these reactions has been given in Chapter II, Sect. 5.C. The Whitehead type of synthesis has also been employed to make 5-acetyl-4-ethoxycarbonyl-2-hydroxypyrimidine.[57]

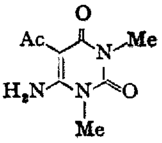
Barbituric acid and its *N*-alkyl derivatives can be acetylated in the 5-position by boiling with acetic anhydride[118, 141] to give, for example, 5-acetyl-2,4,6-trihydroxypyrimidine, 5-acetyl-1-ethylbarbituric acid, and 5-acetyl-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine. These compounds can also be made[141] by carrying out a Common Synthesis in acetic anhydride with a few drops of sulphuric acid; in this way, for example, 5-acetyl-1-ethylbarbituric acid was made from *N*-ethylurea and diethyl malonate. Direct acetylation has also been used to prepare 5-acetyl-4-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine.[118] As might be expected, similar treatment of the corresponding secondary base, 1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine yields 5-acetyl-1,2,3,4-tetrahydro-1,3-dimethyl-6-*N*-methylacetamido-2,4-dioxopyrimidine[118] (CXXVIII). However, similar treatment of the corresponding primary base, 4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine is reported[118] to yield only the 5-acetyl derivative (CXXIX), the amino group remaining unacetylated. Furthermore, the acetyl group is removed by methanolic hydrogen chloride.[118] 5-Ethoxycarbonylacetyl-2,4,6-trihydroxypyrimidine can be made by treatment of barbituric acid with acetic anhydride and malonic acid followed by ethanol.[142]



(CXXVI) (CXXVII)



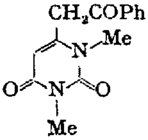
(CXXVIII)



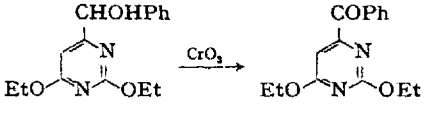
(CXXIX)

Extranuclear *C*-acylation is exemplified by the formation of 4-benzoylmethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine (CXXX) by the action of methyl benzoate in potassium t-butoxide on the unacylated compound,[134] and other examples[134, 143] of such Claisen reactions are given in Chapter IV, Sect. 3.C(6).

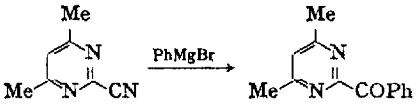
Other preparative methods of ketones are represented in the series. Several secondary alcohols have been oxidized to ketones: 2,4-diethoxy-6-α-hydroxybenzylpyrimidine (CXXXI) and the chromium trioxide–pyridine complex yields 90 % of 4-benzoyl-2,6-diethoxypyrimidine[40] (CXXXII). The related 2,4-diethoxy-6-α-hydroxyethylpyrimidine when similarly oxidized gave only a small yield of ketone, but with activated manganese dioxide in benzene, it gave 85 % of the 4-acetyl-2,6-diethoxypyrimidine.[40] Chromium trioxide in acetic acid proved successful in oxidizing 2,4-dihydroxy-6-α-hydroxybenzylpyrimidine to 4-benzoyl-2,6-dihydroxypyrimidine.[40]



(CXXX)



(CXXXI) (CXXXII)

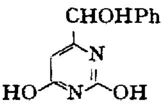


(CXXXIII) (CXXXIV)

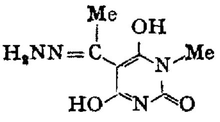
2-Cyano-4,6-dimethylpyrimidine (CXXXIII) treated with phenylmagnesium bromide in the usual way, yields 2-benzoyl-4,6-dimethylpyrimidine[23] (CXXXIV), and 4-carboxy-2,6-diethoxypyrimidine with methyl-lithium yields 60 % of 4-acetyl-2,6-diethoxypyrimidine as a 2,4-dinitrophenylhydrazone.[40]

B. Reactions of C-Acylpyrimidines

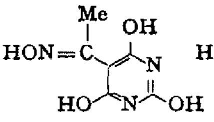
There are few reactions recorded for pyrimidine ketones. 4-Benzoyl-2,6-dihydroxypyrimidine is reduced by sodium borohydride to 2,4-dihydroxy-6-α-hydroxybenzylpyrimidine[40] (CXXXV). Oxidation of 5-acetyl-4-methyl-2-phenylpyrimidine with permanganate gives 5-carboxy-4-methyl-2-phenylpyrimidine,[37] and 5-acetyl-3-methyluracil with nitric acid undergoes oxidation, decarboxylation, and nitration to 3-methyl-5-nitrouracil.[140] 2-Benzoyl-4,6-dimethylpyrimidine was oxidized by permanganate, but only benzoic acid was isolated.[23]



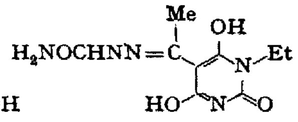
(CXXXV)



(CXXXVI)



(CXXXVII)



(CXXXVIII)

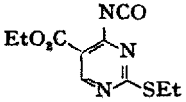
Most of the usual ketone derivatives have been used in the series. Typical preparations are described for 5-α-hydrazonoethyl-1-methylbarbituric acid[141] (CXXXVI), 2,4-diethoxy-6-phenylhydrazonoethylpyrimidine,[40] 2,4,6-trihydroxy-5-phenylhydrazonoethylpyrimidine,[141] 5-α-(2,4-dinitrophenylhydrazono)ethyl-2,4-dihydroxypyrimidine,[40] 2,-4,6-trihydroxy-5-α-hydroxyiminoethylpyrimidine[141] (CXXXVII), 2,4-dihydroxy-5-α-hydroxyiminoethylpyrimidine,[40] and 1-ethyl-5-α-semicarbazonoethylbarbituric acid[141] (CXXXVIII).

7. The Isocyanato-, Thiocyanato-, and Isothiocyanato-pyrimidine Family

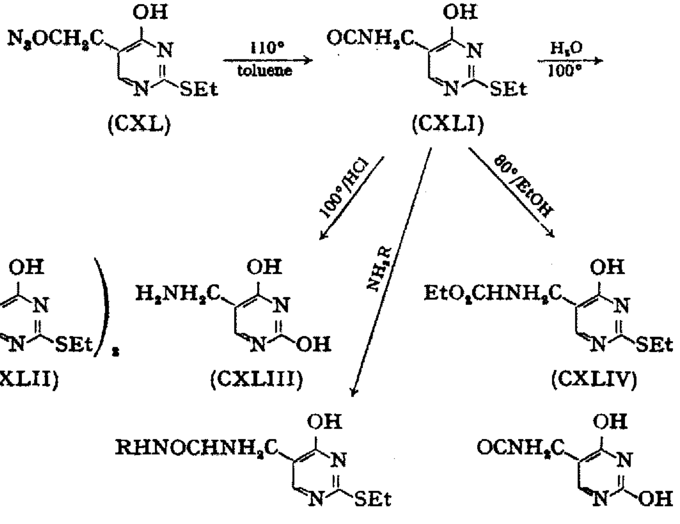
The cyanato derivatives of pyrimidine are unknown and isocyanato ones have been very little investigated. On the other hand, thiocyanato- and isothiocyanato-pyrimidines are well known.

A. Isocyanatopyrimidines

The reaction of 4-chloro-5-ethoxycarbonyl-2-ethylthiopyrimidine in benzene with potassium cyanate seems to give 5-ethoxycarbonyl-2-ethylthio-4-isocyanatopyrimidine (CXXXIX) in solution, because



(CXXXIX)

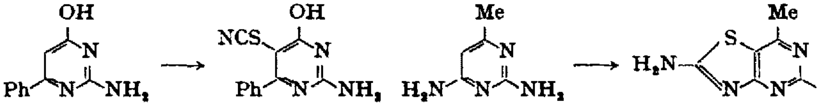


(CXL) (CXLI) (CXLII) (CXLIII) (CXLIV) (CXLV) (CXLVI) subsequent treatment with ammonia or aniline gives 5-ethoxycarbonyl-2-ethylthio-4-ureido(or phenylureido)pyrimidine[144]. The only characterized isocyanates are extranuclear types, 2-ethylthio-4-hydroxy-5-isocyanatomethylpyrimidine (CXLI) which is made by heating 5-azidocarbonylmethyl-2-ethylthio-4-hydroxypyrimidine (CXL) in toluene, and 2:4-dihydroxy-5-isocyanatomethylpyrimidine[80] (CXLVI) (and its unisolated 6-methyl derivative[81]) are made similarly.

The isocyanate (CXLI) on heating with water gives *NN'*-di(2-ethylthio-4-hydroxypyrimidin-5-ylmethyl)urea (CXLII) and a little 5-aminomethyl-2-ethylthio-4-hydroxypyrimidine. With hot mineral acid it gives 5-aminomethyl-2,4-dihydroxypyrimidine (CXLIII), and with hot ethanol the urethane, 5-ethoxycarbonylaminomethyl-2-ethylthio-4-hydroxypyrimidine (CXLIV). With ammonia and aniline it gives respectively 2-ethylthio-4-hydroxy-5-ureido(or phenylureido)-methylpyrimidine[80] (CXLV). The other isocyanate (CXLVI) undergoes similar reactions.[80]

B. Thiocyanatopyrimidines

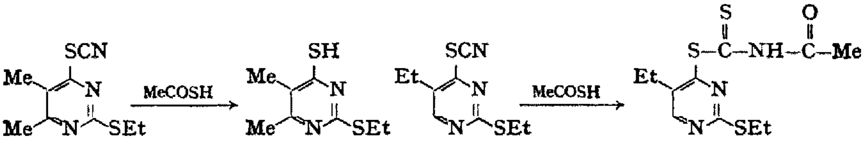
Thiocyanatopyrimidines are generally made from the corresponding chloropyrimidines by the action of potassium thiocyanate, and this method has been reviewed in Chapter VI, Sect. 5.H. Direct introduction of a thiocyanato group into the 5-position is also recorded:[145] 2-amino-4-hydroxy-6-phenylpyrimidine (CXLVII) and sodium thiocyanate in methanolic acetic acid are treated with bromine to give the 5-thiocyanato derivative (CXLVIII). This reaction seems to require the presence of two electron-releasing groups, for failure is recorded with 2-amino-4-chloro-6-methyl-, 2-amino-4,6-dimethyl-, and 4-amino-2-ethylthio-6-methyl- pyrimidine,[146] while success attended the reaction with (CXLVII), and with 2-amino-4-hydroxy- and 2,4-dihydroxy-6-methylpyrimidine.[146] In the last two cases the products could not be isolated as the thiocyanates but only as disulphides. When a primary



(CXLVII) (CXLVIII) (CXLIX) (CL)

amino group occupies the 4-position (and another electron-releasing group the 2- or 6-position) the thiocyanate formed in the reaction immediately cyclizes to a thiazolo[4,5-d] pyrimidine. Thus 2,4-diamino-6-methylpyrimidine (CXLIX) treated with thiocyanogen as above, gives 2,5-diamino-7-methylthiazolo[4,5-d]pyrimidine (CL), and seven other examples are recorded.[145] A similar cyclization occurs on reduction of the nitro group of 2-ethylthio-5-nitro-4-thiocyanatopyrimidine, to give 2-amino-5-ethylthiothiazolo[5,4-d] pyrimidine.[147]

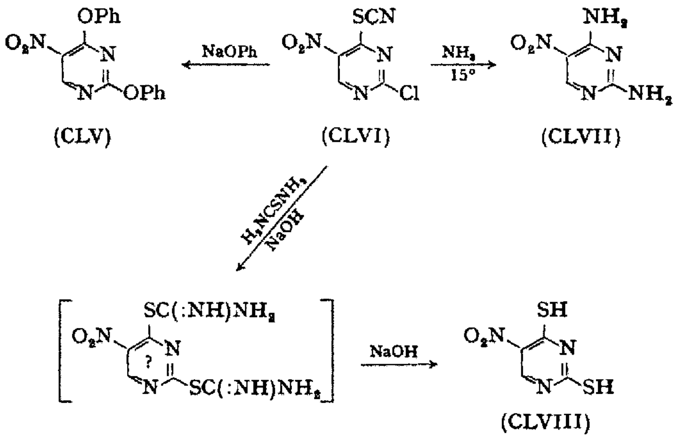
The structure of thiocyanatopyrimidines has generally been checked by their reactivity towards thioacetic acid (with which isothiocyanates do not react). In some cases the corresponding mercapto derivative is formed by heating for 2–3 hours. 2-Ethylthio-4,5-dimethyl-6-thiocyanatopyrimidine (CLI) is a case in point, yielding 2-ethylthio-4-mercapto-5,6-dimethylpyrimidine[148] (CLII), and other examples[149–151] are given in Chapter VIII, Sect. 1.A(6). In some other apparently similar cases, thiocyanates (under the same conditions) yield the corresponding *N*-acetylthiocarbamoylthiopyrimidine, which is presumably an intermediate in the formation of such a mercaptopyrimidine as above. Thus 5-ethyl-2-ethylthio-4-thiocyanatopyrimidine (CLIII) gives 4-*N*-acetylthiocarbamoylthio-5-ethyl-2-ethylthiopyrimidine[152] (CLIV) and 4-*N*-acetylthiocarbamoylthio-2-chloropyrimidine[153] is similarly made. A relevant general discussion on the action of thioacetic acid on thiocyanates was published at the beginning of the century.[154]



(CLI) (CLII) (CLIII) (CLIV)

Thiocyanato groups, at least when activated by a 5-nitro group, can be replaced (possibly indirectly) as can an alkylthio group. For example, 2-chloro-5-nitro-4-thiocyanatopyrimidine (CLVI) with sodium phenoxide gives 5-nitro-2,4-diphenoxypyrimidine (CLV), with aqueous ammonia gives 2,4-diamino-5-nitropyrimidine (CLVII), with ethylamine gives 2,4-bisethylamino-5-nitropyrimidine, and with thiourea followed by alkali gives 2,4-dimercapto-5-nitropyrimidine[155]

(CLVIII). The reaction of a thiocyanate with the lower alkoxides is exemplified in the formation from 2-amino-5-nitro-4-thiocyanatopyrimidine and sodium ethoxide in ethanol at 0°, of a mixture of



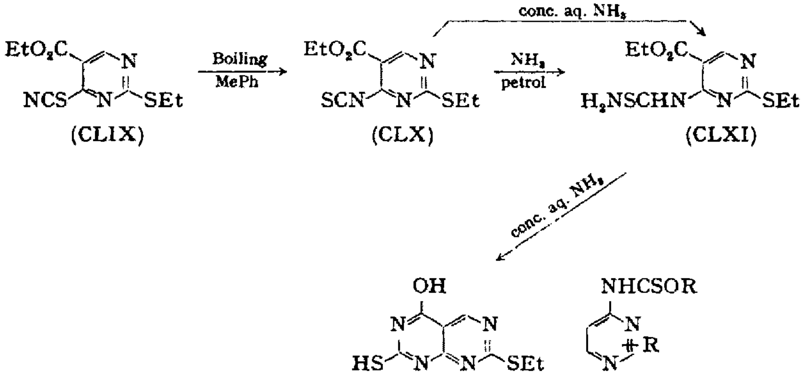
2-amino-4-ethoxy- and 2-amino-4-mercapto- 5-nitropyrimidine.[155] There is little information on the action of aqueous alkali on thiocyanates, but 2,4,6-trihydroxy-5-thiocyanato- with alkali gives 2,4,6-trihydroxy-5-mercapto-pyrimidine.[156] Some interesting but inconclusive observations on the action of chlorine on 2-chloro-4-thiocyanatopyrimidine have been reported.[157]

C. Isothiocyanatopyrimidines

When a thiocyanatopyrimidine, such as (CLIX), is heated in benzene, toluene, or xylene for a long period an isothiocyanate (CLX) is formed. For good yields, temperatures of 110° to 190°, according to the pyrimidine, are generally needed. Examples of this rearrangement are provided in the formation of the following derivatives of 4-isothiocyanatopyrimidine: 2-chloro, at 170° in benzene;[153] 5-ethoxycarbonyl-2-ethylthio (CLX), at 190° in benzene,[158] 5-ethoxycarbonylmethyl-2-ethylthio, in boiling toluene;[159,160] 2-ethylthio-5,6-dimethyl, in boiling xylene;[148] 5-ethyl-2-ethylthio, in boiling toluene;[152] and similar compounds.[149-151,161,162] Some chloropyrimidines have been rather inefficiently converted into isothiocyanatopyrimidines without isolation of the thiocyanato intermediates. Thus 4-chloro-2-ethylthiopyrimidine on prolonged heating in toluene with potassium thiocyanate yields 2-ethylthio-4-isothiocyanatopyrimidine.[163] This and other examples indicate that the short-cut is better avoided.

Isothiocyanatopyrimidines react with ammonia to give thioureidopyrimidines, and with aniline and other amines to give appropriately substituted derivatives. The reaction is of great utility in distinguishing isothiocyanato from the unreactive isomeric thiocyanato derivatives, and examples are given in Chapter IX, Sect. 7.

The reaction has in addition been used to prepare pyrimidopyrimidines. Thus 5-ethoxycarbonyl-2-ethylthio-4-isothiocyanatopyrimidine



(CLIX) (CLX) (CLXI)

(CLXII) (CLXIII)

(CLX) treated with gaseous ammonia in light petroleum gives 5-ethoxycarbonyl-2-ethylthio-4-thioureidopyrimidine (CLXI), but with concentrated aqueous ammonia gives the cyclized 2-ethylthio-5-hydroxy-7-mercaptopyrimido[4,5-d]pyrimidine[164] (CLXII).

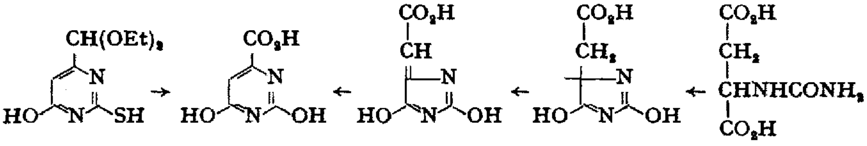
Isothiocyanates react with alcohols to give thiourethanes (alkoxythiocarbonylaminopyrimidines; CLXIII). The reaction is discussed in Chapter IX, Sect. 6.

8. Orotic Acid: Biosynthesis of Pyrimidines

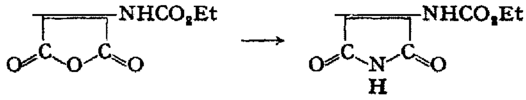
Orotic acid (4-carboxy-2,6-dihydroxypyrimidine) was isolated by Biscaro and Belloni[46] in 1905 from the whey of cow's milk. They showed that oxidation with permanganate gave urea, and proposed a seven-membered ring structure. Wheeler and his colleagues, convinced that orotic acid was a pyrimidine, synthesized both 5-carboxy-[62] and 4-carboxy-2,6-dihydroxypyrimidine.[165] They were discouraged by a large difference in melting point between their products and that reported by the Italians,[46] failed to make direct comparisons with natural material, and remained ignorant that they had in fact synthesized orotic acid. Johnson and Caldwell[166] later prepared 4-carboxy-2,5-dihydroxypyrimidine, and again failing to make a direct comparison, announced it as a synthesis of orotic acid. However, comparisons were at last made by Bachstez,[47] and orotic acid shown to be 4-carboxy-2,6-dihydroxypyrimidine.

Wheeler's unfortunate synthesis of orotic acid[165] had still to bear criticism, for it was shown[7,167] to be not a simple Principal Synthesis as described, but to proceed to orotic acid through ring expansion of a hydantoin (Ch. III, Sect. 5.E(1)). The matter was all the more poignant as Wheeler began his paper by criticizing an earlier worker for omitting to consider that the condensation of ethyl oxaloacetate and urea might give a hydantoin!

Orotic acid (CLXV) can be made by the Müller–Wheeler method[165, 168] or in poor yield by oxidation of 2,4-dihydroxy-6-methylpyrimidine[28] or 4-carboxymethyl-2,6-dihydroxypyrimidine[4] with alkaline ferricyanide (*via* the amide if ammonia is present). A better method[32, 33, 169] makes use of ethyl γ-diethoxyacetoacetate and thiourea



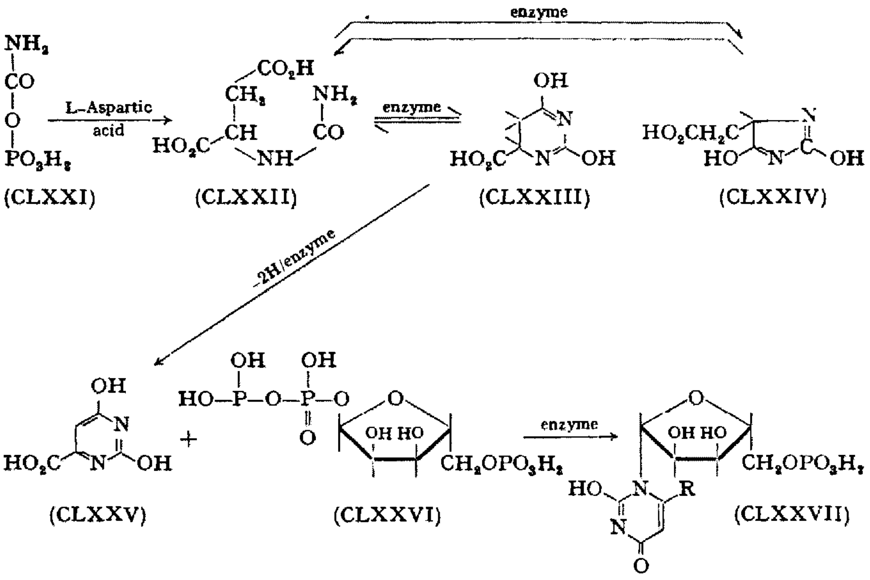
(CLXIV) (CLXV) (CLXVI) (CLXVII) (CLXVIII)



(CLXIX) (CLXX)

to give 4-diethoxymethyl-6-hydroxy-2-mercaptopyrimidine (CLXIV), and oxidation of this aldehyde accompanied by hydrolysis of the mercapto to a hydroxy group, gives orotic acid (CLXV). Another useful method[9, 167] starts with aspartic acid which is converted into the ureide (CLXVIII), this cyclized to 5-carboxymethylhydantoin (CLXVII), a double bond inserted by the familiar bromination/dehydrobromination method giving (CLXVI), and finally the ring expanded in akali to yield orotic acid (CLXV). The intermediate 5-carboxymethylenehydantoin can also be made[6] by the action of oxaloacetic acid with urethane to give N-ethoxycarbonylaminomaleic anhydride (CLXIX), conversion into the imide (CLXX), and final alkaline treatment.

The methylation and esterification of orotic acid has been discussed in Chapter X, Sect. 1.A(3) (g) and the chequered history of the methyl derivatives of orotic acid has been summarized.[14] Bromine water and orotic acid give 5,5-dibromobarbituric acid,[47,165] cold hydrobromic acid and hydrogen peroxide give 5-bromo-orotic acid,[170] and potassium orotate in phosphorus pentachloride and oxychloride give a dichloro derivative without removal of the carboxy group.[47] Nitration gives 4-carboxy-2,6-dihydroxy-5-nitropyrimidine.[47]



Orotic acid is a key-substance in the biosynthesis of pyrimidines for it seems almost certain that all biologically occurring pyrimidines have been formed through it. The subject has been reviewed.[171, 187]

According to Baddiley and Buchanan[171] (who should be consulted for a full bibliography), the biosynthesis begins with the union of ammonia and carbon dioxide in the presence of adenosine triphosphate to give carbamoyl dihydrogen phosphate[172,173] (CLXXI), which has been made synthetically[174]. This substance is enzymically combined with l-aspartic acid, with loss of phosphoric acid to give ureidosuccinic acid (CLXXII),[175,176] This is in enzymic equilibrium with 5-carboxymethylhydantoin (CLXXIV) and with dihydro-orotic acid[177] (CLXXIII), which was identified by synthesis.[178] The next step is dehydrogenation by the enzyme, dihydro-orotate dehydrogenase,[179,180] to give the first pyrimidine, orotic acid (CLXXV). Ribose-5-phosphate-l-pyrophosphate[181,182] (CLXXVI) is combined with orotic acid in the presence of orotidylic pyrophosphorylase to give the nucleotide, orotidylic acid (CLXXVII; R = COOH), which is irreversibly decarboxylated[183,184] by orotidylic decarboxylase to uridine-5′-phosphate (CLXXVII; R = H), and so on, for example, to cytidine triphosphate.[185]

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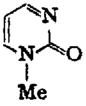
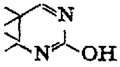
CHAPTER XII

The Reduced Pyrimidines

It is necessary to define "reduced pyrimidines" because of the confusion caused by current nomenclature which would refer to (I) as 1,2-dihydro-1-methyl-2-oxopyrimidine. Reduced pyrimidines are those which have less than 3 double bonds as part of, or directly attached to, the nucleus. Thus (I) is not a reduced pyrimidine, but (II), (III), and (IV) are, being respectively a dihydro, tetrahydro, and hexahydro derivative. In such a compound as (V), a heightened state of confusion is reached, for although by common sense and definition it is a dihydropyrimidine, it is named as 1,2,5,6-tetrahydro-1-methyl-2-oxopyrimidine, where two hydrogens are real and two imaginary. The obvious way out of such folly is to delete imaginary


(I)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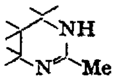
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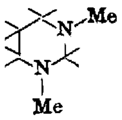
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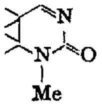
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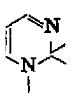
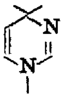

(VI)
1,2-dihydro-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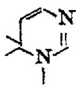
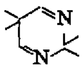
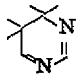
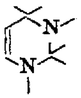
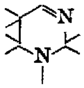
1,4-dihydro-

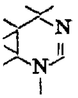

(VIII)
1,6-dihydro-


(IX)
2,5-dihydro-


(X)
4,5-dihydro-


(XI)
1,2,3,4-tetrahydro-


(XII)
1,2,5,6-tetrahydro-


(XIII)
1,4,5,6-tetrahydro-

hydrogens from nomenclature, thereby ensuring clarity without loss in precision.

It has been pointed out by Johnson[1] that "there are eight theoretically possible pyrimidine derivatives, (VI)–(XIII), existing between pyrimidine, $C_4H_4N_2$, and its completely reduced form hexahydropyrimidine, $C_4H_{10}N_2$". Further, it is by no means certain that simple members of some of these series will be stable enough for isolation. Hence it is not surprising that, despite the number of known reduced pyrimidines, the field today remains largely unexplored, and this chapter inevitably has enormous gaps both in methods for preparing simple hydropyrimidines and in their reactions.

1. Preparation of Dihydropyrimidines

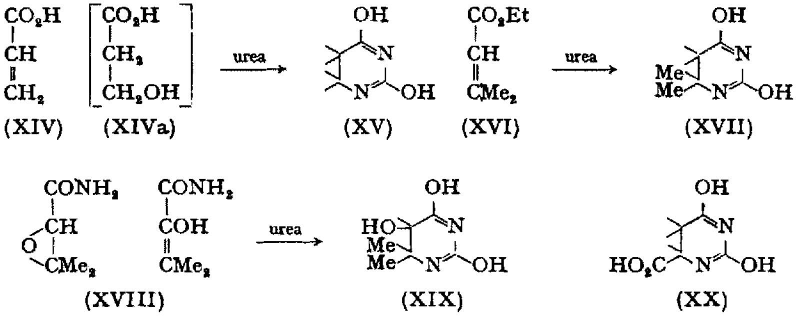
The diverse methods of making dihydropyrimidines fall into three groups: the first is closely related to the Principal Synthesis, the second consists of other primary syntheses, and the third is the chemical reduction or hydrogenation of pyrimidines.

A. By a Modified Principal Synthesis

Compared with its extensive use in making pyrimidines (see Chapter II), the Principal Synthesis has been little used to prepare dihydropyrimidines. Since the one-carbon fragment (urea, etc.) cannot be supplied at a lower oxidation state, one of the remaining double bonds in any resulting dihydropyrimidine must be associated with $C_{(2)}$, thereby excluding the preparation of the series represented by (VI). The three-carbon fragment can, however, be supplied at a lower oxidation state than in a normal synthesis. Thus for example urea condenses with the β-carboxy-aldehyde, formylacetic acid, to give uracil, but by fusion with acrylic acid (XIV)[2] or ester[3] (virtually a β-carboxy-alcohol; XIVa) it gives dihydrouracil (XV; "hydrouracil"; 4,5-dihydro-2,6-dihydroxypyrimidine), which is a substance of the series represented by (X). In the same way, urea with crotonic acid[2] or ester[3] yields 4,5-dihydro-2,6-dihydroxy-4-methylpyrimidine, with α-methylacrylic acid it gives the 5-methyl isomer[2] ("hydrothymine"), with cinnamic acid it gives 4,5-dihydro-2,6-dihydroxy-4-phenylpyrimidine,[2,4] and so on.[5] The reaction has been extended to ethyl β-methylcrotonate (XVI), which on heating with alcoholic urea at 150° gives 4,5-dihydro-2,6-

dihydroxy-4,4-dimethylpyrimidine[6] (XVII) in reasonable yield. Similarly, α-hydroxy-β-methylcrotonamide (XVIII) (made from chloroacetamide, acetone and sodium) with urea gives 4,5-dihydro-2,5,6-trihydroxy-4,4-dimethylpyrimidine (XIX) in 75 % yield.[7] An example of the use of a substituted urea is the condensation of acryloyl chloride with *N*-phenylurea to give 5,6-dihydro-1-phenyluracil:[8] but the reaction is not always straightforward. Bachstez and Cavallini[9] condensed maleic acid with urea to give what analysed as, and appeared to be, 4-carboxy-4,5-dihydro-2,6-dihydroxypyrimidine (dihydro-orotic acid; XX). However, it could not be oxidized to orotic acid[9], it behaved differently in microbiological systems to natural material,[10, 11] and the structure was finally proven wrong by unambiguous synthesis of dihydro-orotic acid.[12] A dihydro-orotic acid made later[13] by catalytic hydrogenation of orotic acid differs by 6–9° from the m.p. of genuine material, and may therefore be an isomer. The compound of Bachstez and Cavallini seems to be "fumarylurea", *i.e.* *N*-(β-carboxyacryloyl)-urea.[13]

An interesting case is the condensation of acetamidine with diethyl ethylidenemalonate. The latter reacts, not as a β-diester to give a pyrimidine, but as a derivative of ethyl crotonate to yield 5-ethoxycarbonyl-4,5-dihydro-6-hydroxy-2,4-dimethylpyrimidine.[14]



(XIV) (XIVa) (XV) (XVI) (XVII)

(XVIII) (XIX) (XX)

When attempts were made to react acrolein (virtually β-hydroxypropionaldehyde) with urea to give 4,5-dihydro-2-hydroxypyrimidine, only failure is recorded.[15–18] On the other hand, β-unsaturated ketones have been used successfully. Thus mesityl oxide (XXI) with guanidine gives 2-amino-4,5-dihydro-4,4,6-trimethylpyrimidine[19] (XXII), and with ammonium thiocyanate (which may be thought of as thiourea)*

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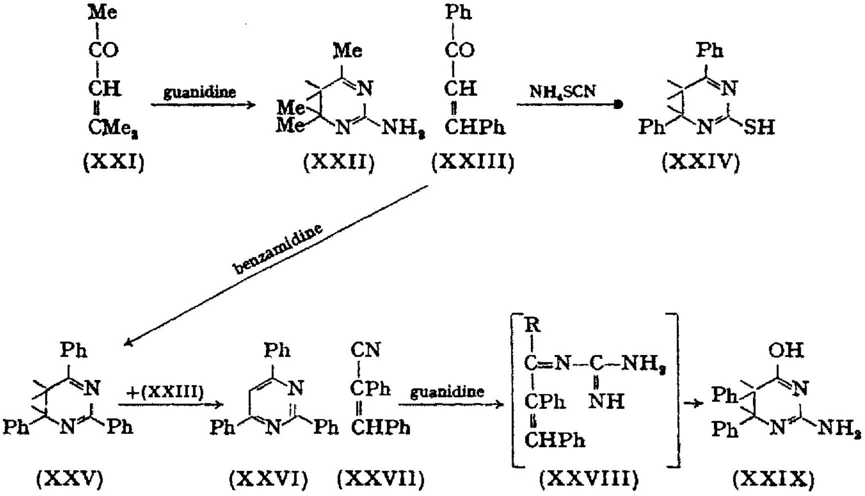
* In fact, thiourea itself yields a tetrahydropyrimidine (Sect. 2.B).

it gives in refluxing cyclohexanol, the 2-mercapto analogue of (XXII), 4,5-dihydro-2-mercapto-4,4,6-trimethylpyrimidine.[20] A similar condensation is that of β-benzoylstyrene (benzylideneacetophenone; XXIII) with ammonium thiocyanate to yield 4,5-dihydro-2-mercapto-4,6-diphenylpyrimidine[21] (XXIV). Mesityl oxide also reacts with benzamidine to give 4,5-dihydro-4,4,6-trimethyl-2-phenylpyrimidine,[19] although the related unsaturated carbonyl compounds, benzylideneacetone, acrolein, and cinnamaldehyde, failed to react in this way.[19]

When β-benzoylstyrene (XXIII) reacts with benzamidine the reaction does not stop at 4,5-dihydro-2,4,6-triphenylpyrimidine (XXV) but this is oxidized by more (XXIII) (which becomes β-phenylpropiophenone) to give 2,4,6-triphenylpyrimidine (XXVI) in 85 % yield under optimum conditions. Several analogues have been similarly made using benzamidine,[22] and 2-benzylthio-4,6-diphenylpyrimidine results by using (XXIII), as its dibromide, with S-benzylthiourea.[22]

Judging on the slender available evidence[23] the use of a β-unsaturated nitrile in such a synthesis is not straightforward. α,β-Diphenylacrylonitrile (XXVII) indeed reacts readily with alcoholic guanidine, but ammonia is evolved, and the product is not 2,4-diamino-5,6-dihydro-5,6-diphenylpyrimidine, but 2-amino-4,5-dihydro-6-hydroxy-4,5-diphenylpyrimidine (XXIX); analogues behave similarly, and it is suggested[23] that hydrolysis precedes ring closure through the intermediate stages (XXVIII; $R{=}NH_2$) and (XXVIII; $R{=}OH$). In this

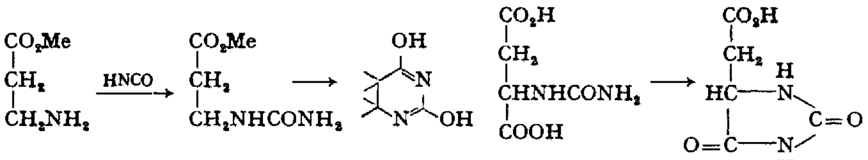


reaction the substituted acrylonitrile can be satisfactorily replaced by a mixture of phenylacetonitrile and benzaldehyde. The 2,4-diamino type of pyrimidine has in fact been attained[23] by this synthesis in some rather complicated examples where a cycloalkylidene grouping appears at position-6.

B. From an Aminopropane Derivative and an Isocyanate

The most used synthesis of dihydropyrimidines involves the reaction of a three-carbon fragment already carrying an amino group with cyanic acid, an alkyl isocyanate, or their thio analogues. The resulting ureido or thioureido compound is easily cyclized as a rule.

The reaction was first used* by Lengfeld and Stieglitz[24] in 1893, who combined methyl β-aminopropionate (XXX) with cyanic acid to give methyl β-ureidopropionate (XXXI), which was thermally cyclized to 4,5-dihydro-2,6-dihydroxypyrimidine (XXXII). The reaction was later improved in detail,[25] and cyclization by boiling in dilute acid introduced, and it has been adapted to make a variety of analogues. Thus cyanic acid with β-aminobutyric acid gives 4,5-dihydro-2,6-dihydroxy-4-methylpyrimidine,[2] with β-amino-β-phenylpropionic acid gives 4,5-dihydro-2,6-dihydroxy-4-phenylpyrimidine,[4,26–29]** with β-amino-β-styrylpropionic acid gives 4,5-dihydro-2,6-dihydroxy-4-styrylpyrimidine,[30] and with β-amino-β-ethylpentanoic acid gives 4,4-diethyl-4,5-dihydro-2,6-dihydroxypyrimidine.[6] Other examples are known.[31–33]



(XXX) (XXXI) (XXXII) (XXXIII) (XXXIV)

Thiocyanic acid behaves similarly with such amines to give for example (although in poor yield), 4,5-dihydro-6-hydroxy-2-mercapto-4-phenyl (and p-methoxyphenyl)pyrimidine.[28] An interesting reaction is that between aminosuccinic acid and cyanic acid which gives ureido

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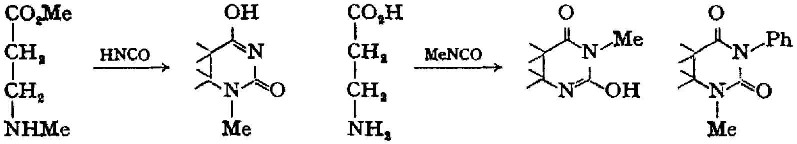
* Hoogewerf and van Dorp three years earlier[36] had heated phenylurea with β-aminopropionic acid and cyclized the resulting ureido compound with acetyl chloride to 5,6-dihydro-3-phenyluracil.

** Chemical Abstracts[29] omits the hydroxy groups in this and its analogues.

succinic acid (XXXIII) normally, but cyclization then preferentially gives the 5-membered ring, 5-carboxymethylhydantoin (XXXIV), in place of the dihydropyrimidine.[34,35]

The use of β-alkylamino-acids leads to $N_{(1)}$-alkylated dihydrouracils. In this way methyl β-methylaminopropionate (XXXV) and aqueous cyanic acid give (without isolation of a ureido intermediate) 5,6-dihydro-1-methyluracil[37] (XXXVI). The reaction was again described later[38] and the 1-benzyl and 1-isopropyl analogues made.[38] The method was unsuitable to 1-aryl analogues[39] but it was further extended[40] by using methyl α-methyl-β-methylaminopropionate, which gave 5,6-dihydro-1,5-dimethyluracil, and alkyl[40] analogues were prepared similarly. The reaction has also been used to make 5,6-dihydro-1-methyl-6-phenyluracil,[4] its analogues[32,41] and rather indirectly 5-benzyl-5,6-dihydro-1-methyluracil.[42]

$N_{(3)}$-Alkylated dihydrouracils may be made by using an alkyl or aryl isocyanate in place of cyanic acid. Thus β-aminopropionic acid (XXXVII) and methyl (or phenyl) isocyanate yield after cyclization, 5,6-dihydro-3-methyl(or phenyl)uracil[43,44] (XXXVIII). Ethyl β-aminobutyrate similarly gives 5,6-dihydro-6-methyl-3-phenyluracil,[45] and β-amino-β-phenylpropionic acid and its p-methoxy derivative have been condensed[28,29] with several isocyanates to give for example 5,6-dihydro-3-β-naphthyl-6-phenyluracil and some 20 analogues. These include several, resulting from the use of phenyl isothiocyanate, with a mercapto group in the 2-position such as 5,6-dihydro-6-p-methoxyphenyl-3-phenyl-2-thiouracil[28]. Other examples are known.[32,46,47] Acetic anhydride was found useful in ring closing some of the rather hindered intermediate ureido derivatives,[28] for which hydrochloric acid had proved fruitless.[45] Other less effective agents include acetyl chloride,[36,44] methanolic hydrochloric acid,[32] sodium ethoxide,[47] and simple heating.[30] Naturally, the combination of a secondary β-amino-acid and an alkyl or aryl isocyanate leads to a 1,3-disubstituted dihydrouracil, as in the reaction of β-methylaminopropionate and phenyl isocyanate to

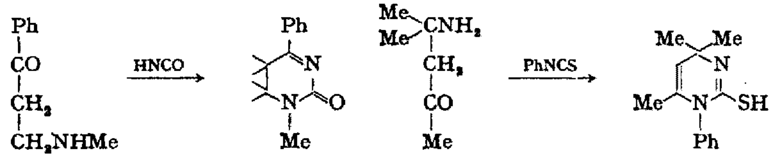


(XXXV) (XXXVI) (XXXVII) (XXXVIII) (XXXIX) give[45] hexahydro-1-methyl-3-phenyl-2,4-dioxopyrimidine (or 5,6-dihydro-1-methyl-3-phenyluracil; XXXIX).

By using the appropriate optically active β-amino-acids, substituted 5,6-dihydrouracils have been made which retain this activity at $C_{(6)}$. This report[47] also contains a brief review of the reaction.

β-Amino-ketones have been used in this reaction, resulting in dihydro-2-hydroxy(or mercapto)-4-alkylpyrimidines. For example, cyanic acid with β-methylaminopropiophenone (XL) yields a ureido intermediate, which on brief treatment with acid cyclizes to 1,2,5,6-tetrahydro-1-methyl-4-phenyl-2-oxopyrimidine[48] (XLI). This dihydropyrimidine on prolonged boiling with hydrochloric acid disproportionates[48] into the corresponding pyrimidine (1,2-dihydro-1-methyl-2-oxo-4-phenylpyrimidine) and tetrahydropyrimidine (hexahydro-1-methyl-2-oxo-4-phenylpyrimidine). Diacetonamine (XLII) reacts with cyanic and thiocyanic acid to give respectively 4,5-dihydro-2-hydroxy-(and mercapto)-4,4,6-trimethylpyrimidine,[49] and with phenyl isothiocyanate to give 1,4-dihydro-2-mercapto-4,4,6-trimethyl-1-phenylpyrimidine[49, 50] (XLIII), the first compound so far encountered that is necessarily a member of the 1,4-dihydro-series represented by (VII). The *p*-tolyl analogue has also been made.[51]

The use of β-amino nitriles in this reaction has failed because intermediates such as *N*-β-cyanoethyl-*N*′-ethylurea, although they are easily formed, have so far resisted cyclization.[52]

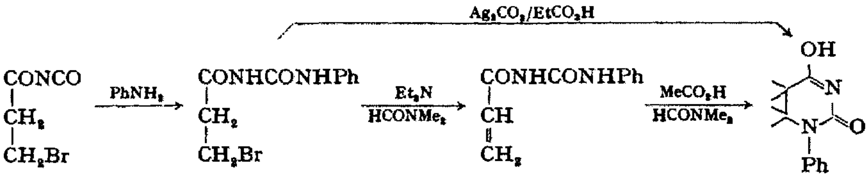


(XL) (XLI) (XLII) (XLIII)

C. From an Isocyanatopropane Derivative and an Amine

This synthesis, which is a reversal of the last, has been but little used to make dihydropyrimidines. The readily available β-bromopropionyl isocyanate (XLIV) reacts with aromatic amines to give, for example, *N*-β-bromopropionyl-*N*′-phenylurea (XLV), which on treatment with silver carbonate in propionic acid cyclizes to 5,6-dihydro-1-phenyluracil[8] (XLVII). Alternatively, (XLV) treated with triethylamine in refluxing dimethylformamide gives *N*-acryloyl-*N*′-phenylurea[8] (XLVI), which can be cyclized to (XLVII) by refluxing in dimethylformamide with acetic acid for 3 days.[39] The intermediate, typified by (XLVI), can be made in other ways.[39, 53]

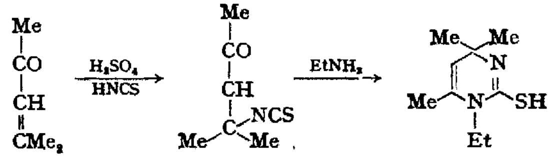
A variation of the above has been described[47, 54] and is exemplified in the following sequence: Ethyl *β*-amino-*β*-phenylpropionate is treated with phosgene to give ethyl *β*-isocyanato-*β*-phenylpropionate ($PhCH(NCO)CH_2CO_2Et$), which is converted with benzylamine into ethyl *β*-benzylureido-*β*-phenylpropionate, and this cyclized in boiling hydrochloric acid to 3-benzyl-5,6-dihydro-6-phenyluracil. If benzylamine is replaced by phenylhydrazine, the 3-anilino analogue results.[54]



(XLIV) (XLV) (XLVI) (XLVII)

The synthesis has also been used to make one type of dihydromercaptopyrimidine.

It will be recalled that mesityl oxide (XLVIII) and ammonium thiocyanate in cyclohexane give 4,5-dihydro-2-mercapto-4,4,6-trimethylpyrimidine.[20] If, however, the same reactants are brought together in 50 % sulphuric acid, 2-isothiocyanato-2-methylpentan-4-one[56]* (XLIX) is formed, and when this is treated with an alkylamine in hydrochloric acid, a thioureido intermediate, and then a 1-alkyl derivative (L) of the above pyrimidine is produced. Compounds so formed



(XLVIII) (XLIX) (L)

are 1-ethyl-1,4-dihydro-2-mercapto-4,4,6-trimethylpyrimidine from ethylamine,[56] the 1-phenyl analogue (previously made by another route[49]) from aniline,[55] the 1-amino analogue from hydrazine,[56] the 1-carboxymethyl analogue from glycine,[57] and many others.[56]

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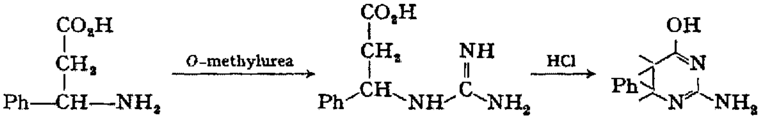
* This compound was first described as a thiocyanato derivative[55, 57] but later corrected.[56]

D. From an Aminopropane Derivative and *O*-Methylurea

This little used but potentially useful synthesis is strictly analogous to that using an isocyanate (Sect. 1.B). It is exemplified[58] by the condensation of *β*-amino-*β*-phenylpropionic acid (LII) with *O*-methylurea to give *β*-guanidino-*β*-phenylpropionic acid (LIII), which can be conveniently cyclized by boiling in hydrochloric acid to give 2-amino-4,5-dihydro-6-hydroxy-4-phenylpyrimidine (LIV). The 4-methyl and other analogues were similarly made,[58] but unexpectedly, *β*-guanidinopropionic acid could not be cyclized.



(LII) (LIII) (LIV)

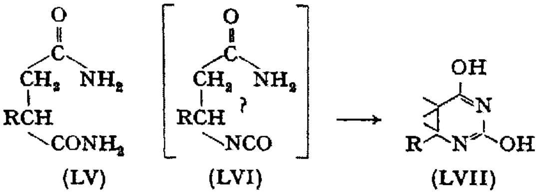
E. Syntheses Involving Amide Intermediates

One of the early syntheses[59] of a dihydropyrimidine made use of succindiamide (LV; R=H), which can be partly degraded by the Hofmann reaction, presumably to *β*-isocyanatopropionamide (LVI; R=H). This then cyclizes to 4,5-dihydro-2,6-dihydroxypyrimidine (LVII; R=H).

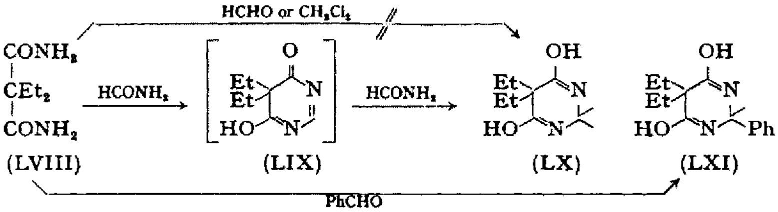
This synthesis of Weidel and Roithner[59] appeared in Austria while similar work of van Dam was in the press in the Netherlands. The latter's paper[60] was curtailed with an explanatory editorial footnote "...Cependant M. van Dam avait fait quelques observations qui ne se trouvent pas mentionnées dans le travail de M.M. Weidel et Roithner; je croyais utile pour cette raison de ne pas supprimer la publication de son travail...". This graciousness of the editor was distinctly revised when he wrote[61] the very next paper as a chemist: "Quelques observations sur l'action des hypobromites alcalins sur les amides, à l'occasion d'un mémoire de M.M. Weidel et Roithner". In particular, he dismissed bluntly the theory contained in the Austrian memoire: "Cette discussion est assez superficielle", and again, "Le mémoire fait voir que ces savants ne connaissent qu'en partie la littérature du sujet qu'ils traitent".

The synthesis was greatly improved[25] to give a 60 % yield, and it has been applied to *α*-methylsuccindiamide[59] (LV; R=Me), from which it gives 4,5-dihydro-2,6-dihydroxy-4-methylpyrimidine (LVII; R=Me). Since no 5-methyl isomer is formed,[59] the intermediate must be *β*-isocyanatobutyramide (LVI; R=Me) rather than the possible isomer.

Although attempts to condense *CC*-diethylmalondiamide[62,63] (LVIII) or *C*-ethyl-*C*-phenylmalondiamide[64] with formaldehyde failed to give the expected dihydropyrimidines (*e.g.* LX), both amides readily condense with benzaldehyde or benzal chloride to give respectively 5,5-diethyl-2,5-dihydro-4,6-dihydroxy-2-phenylpyrimidine[65] (LXI) and 5-ethyl-2,5-dihydro-4,6-dihydroxy-2,5-diphenylpyrimidine.[66]



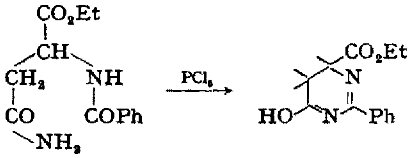
When formamide (or sometimes formic acid) was condensed with the above, and other such amides, the expected (fully oxidized) pyrimidines (*e.g.* 5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine; LIX) were not isolated,[64,66] but instead, the dihydro derivatives (*e.g.* 5,5-diethyl-2,5-dihydro-4,6-dihydroxypyrimidine; LX). Regarding the mechanism[64] of this anomaly, "there is little doubt that the cyclization reaction proceeds *via* the *N*-formyl malondiamide which then cyclizes with loss of water to the pyrimidine, which is in turn reduced by the excess of formic acid or formamide". The intermediate compounds have never been isolated (although they have been made[64] otherwise).



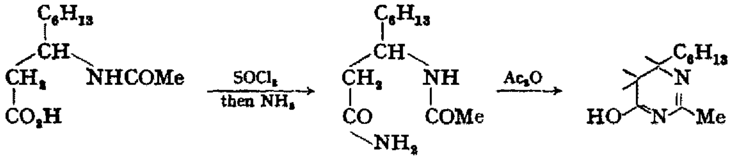
The cyclization of an acylated β-aminoamide is a useful way of preparing dihydropyrimidines with a 4-hydroxy group. Thus β-benzamido-β-ethoxycarbonylpropionamide (LXII) when treated with phosphorus pentachloride in chloroform gives 4-ethoxycarbonyl-4,5-dihydro-6-hydroxy-2-phenylpyrimidine[67] (LXIII). By *N*-substitution of the carbamoyl group of the starting material, an *N*-substituted dihydropyrimidine results. For example, β-benzamido-*N*-ethylpropionamide with phosphorus pentachloride in chloroform gives 4-chloro-

3-ethyl-3,6-dihydro-2-phenylpyrimidine. The additional chlorination, which occurs after cyclization in this example, can be avoided by using phosphorus pentoxide in chloroform, when 1-ethyl-1,4-dihydro-6-hydroxy-2-phenylpyrimidine is isolated.[68] The complete sequence of such a synthesis is illustrated by the conversion of β-aminononanoic acid into its acetyl derivative (LXIV) followed by treatment in turn with thionyl chloride and with ammonia to give 2-acetamido-1-carbamoyloctane (LXV). Cyclization on boiling in acetic anhydride gives 4-hexyl-4,5-dihydro-6-hydroxy-2-methylpyrimidine[69] (LXVI). The 2-phenyl analogue may be made similarly, by using an initially benzoylated intermediate,[69,70] but benzoyl chloride must also be used in place of acetic anhydride for the cyclization, for otherwise transacylation occurs and the methyl derivative (LXVI) results in place of the phenyl one. Several other analogues have been made by related routes.[69,71]

The isolated preparation of 5-ethoxycarbonyl-1,6-dihydro-2-methylpyrimidine from acetamidine and α-cyano-β-ethoxypropionaldehyde probably involves an amino–imino ether as intermediate.[72]



(LXII) (LXIII)

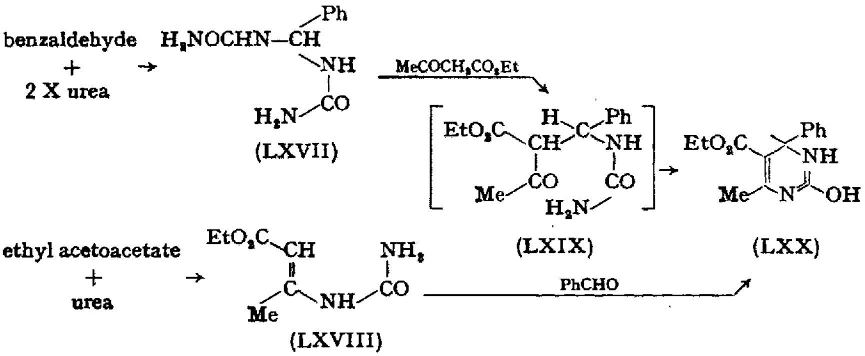


(LXIV) (LXV) (LXVI)

F. The Biginelli Reaction

Following earlier studies[73,74] of the action of aldehydes on urea, Biginelli in 1893 published[75] the first examples of his synthesis. A mixture of benzaldehyde, urea, and ethyl acetoacetate in alcohol gave 5-ethoxycarbonyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine (LXX). A variety of aromatic aldehydes was used and gave analogous pyrimidines.[75] After being neglected for many years, the synthesis was again studied[76] and up to 60 % yield of (LXX) was obtained under the conditions of Hantzsch's pyridine synthesis. In addition, a small quantity of 3,5-dicarboxydihydro-4-phenylpyridine was isolated. Thiourea was also successfully used in the synthesis to give the thio analogue of (LXX) and it was directly converted into (LXX) by the usual means (chloroacetic acid).[76] Soon afterwards, the reaction was shown to be strongly catalysed by acid,[77] and the yield of (LXX) was thereby raised to 89 %. It has also been extended to the use of aliphatic aldehydes, and many analogues of (LXX) with alkyl and substituted aryl groups in place of phenyl are known.[77,78] Several analogues typified by 5-ethoxycarbonyl-1,6-dihydro-2-hydroxy(and mercapto)-6-phenyl-4-trifluoromethylpyrimidine have been made[79] by using ethyl trifluoroacetoacetate, and replacement of this reactant by acetylacetone results in such derivatives as 5-acetyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine and its 6-alkyl and aryl analogues.[80] When benzoylacetone is used, the structure of the dihydropyrimidine is ambiguous, and does not seem to have been yet determined.[81]

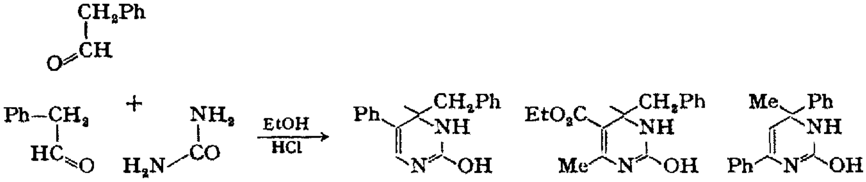
The mechanism has been summarized by Folkers and Johnson:[82] Urea reacts with benzaldehyde to give αα-bisureidotoluene (LXVII) and with ethyl acetoacetate to give ethyl β-ureidocrotonate (LXVIII). Each of these then further reacts with the third component (ethyl acetoacetate or benzaldehyde respectively) giving the dihydropyrimidine (LXX), in one case *via* (LXIX). In this connection it is probably significant that ethyl α-ethylacetoacetate fails to undergo this reaction, presumably because it lacks one of the α-hydrogen atoms.



G. Other Syntheses

Attempts to use phenylacetaldehyde, urea, and ethyl acetoacetate in a Biginelli synthesis indicated that the ethyl acetoacetate was not entering into the reaction, but that a pyrimidine was being formed.[83] In fact, phenylacetaldehyde and urea in ethanolic hydrochloric acid give 60 % of 4-benzyl-3,4-dihydro-2-hydroxy-5-phenylpyrimidine (LXXI). If, however, ethyl acetoacetate is first condensed with urea to give ethyl β-ureidocrotonate ($EtO_2CCH{:}C(Me)NHCONH_2$) and this then treated with phenylacetaldehyde a mixture of (LXXI) and the Biginelli compound, 4-benzyl-5-ethoxycarbonyl-3,4-dihydro-2-hydroxy-6-methylpyrimidine (LXXII), is obtained.[83]

Acetophenone with urea also yields a dihydropyrimidine, 1,6-dihydro-2-hydroxy-6-methyl-4,6-diphenylpyrimidine[83] (LXXIII), which was previously described[84] as an isomeric uncyclized compound. Thiourea gives[85] the 2-mercapto analogue of (LXXIII). This potentially useful reaction is neglected.



(LXXI) (LXXII) (LXXIII)

The formation of such dihydro compounds as 5,5-dibromo-4,5-dihydro-2,4,6-trihydroxypyrimidine, by bromination and addition of HOBr across a double bond of uracil, has already been discussed in Chapter VI, Sect. 2.A(6b). Thymine similarly adds HOBr (without bromination being possible) and the resulting 5-bromo-4,5-dihydro-2,4,6-trihydroxy-5-methylpyrimidine, on treatment with silver oxide,[86,87] or better silver carbonate,[88] yields 4,5-dihydro-2,4,5,6-tetrahydroxy-5-methylpyrimidine. The analogous 5-ethoxycarbonyl-4,5-dihydro-2,4,5,6-tetrahydroxypyrimidine was made similarly.[89] The light-catalysed addition of H_2O across the 5,6-double bond of uracil and related compounds to give dihydro derivatives, has been discussed in Chapter VII, Sect. 8.A.

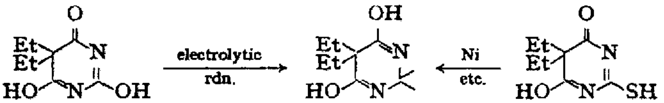
H. By Reduction of Pyrimidines

The classical chemical reduction methods seldom affect the pyrimidine nucleus, but in the cases where they do so, they reduce it beyond the dihydro stage. Lithium aluminium hydride, however, reduces 4-hydroxy-2-mercapto-6-phenylpyrimidine and its 5-ethyl derivative to dihydro derivatives of unproven configuration,[90] although in other cases tetrahydro derivatives were formed easily (Sect. 2.D). The electrolytic reduction in sulphuric acid of barbituric acid, dialuric acid, uramil, or alloxan yields in each case appreciable amounts of 4,5-dihydro-2,6-dihydroxypyrimidine (as well as 1,4,5,6-tetrahydro-2-hydroxypyrimidine)[91,92] and 5-ethylbarbituric acid similarly gives the 5-ethyl derivatives of these products.[93] Barbitone (5,5-diethylbarbituric acid) is also similarly reduced[93] to 5,5-diethyl-2,5-dihydro-4,6-dihydroxypyrimidine.

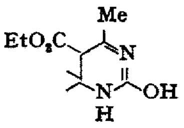
Dihydropyrimidines may be produced during reductive desulphurization of mercapto- or thio- pyrimidines. Thus 5,5-diethyl-2-thiobarbituric acid with sodium amalgam gives among other products 5,5-diethyl-2,5-dihydro-4,6-dihydroxypyrimidine.[94] Raney-nickel desulphurizations have been implicated in the reduction of pyrimidines to the tetrahydro state[95] (Sect. 2.D), but also occasionally dihydro derivatives are produced. Thus 4,6-dihydroxy-2-mercaptopyrimidine and the derived 1,3-diphenyl-2-thiobarbituric acid with Raney nickel in ethanol give respectively 2,5(?)-dihydro-4,6-dihydroxypyrimidine and hexahydro-4,6-dioxo-1,3-diphenylpyrimidine,[96] and 5-ethyl-5-phenyl-2-thiobarbituric acid yields 5-ethyl-2,5-dihydro-4,6-dihydroxy-5-phenylpyrimidine with Raney nickel, sodium amalgam, zinc and formic acid, or by electrolytic reduction.[64] Such Raney-nickel reductions of 2-thiobarbituric acids *e.g.* (LXXVI) to (LXXV) seem to be generally successful[64] even with *N*-substituents, but exceptional are 4,6-dihydroxy-2-mercapto-5-phenylpyrimidine (which gives only 4,6-dihydroxy-5-phenylpyrimidine), and other cases where groups such as cyclohexenyl or chlorophenyl are unstable to hydrogenation, and are also reduced during the desulphurization.[64]

Catalytic hydrogenation of a pyrimidine sometimes yields a dihydro derivative. The first example was the reduction by Levene and La Forge[97] in 1912 of uridine to dihydrouridine with hydrogen and colloidal palladium. This was extraordinarily important because there followed the observation that the sugar could be removed from the reduced nucleoside, to give dihydrouracil, under hydrolytic conditions much gentler than normally possible. 4,5-Dihydro-2,6-dihydroxypyrimidine can naturally be better made directly from uracil (or cytosine) by hydrogenation at 70° over colloidal platinium or palladium,[99–100] and the best results are obtained under a few atmospheres of hydrogen with Adams catalyst in glacial acetic acid,[101] the product being identical[13] in melting point with unambiguously synthesized material.[2] 5,6-Dihydro-1-methyluracil is similarly made.[103] Orotic acid has also been reduced[13] over Adams catalyst in ethanol at 80°, to a dihydro derivative which may be 4-carboxy-4,5-dihydro-2,6-dihydroxypyrimidine although it melts rather lower than does unambiguously produced material.[12] 5-Ethoxycarbonyl-2-hydroxy-4-methylpyrimidine is reduced over platinum-black at 60° to give the 1,6-dihydro derivative[102] (LXXVII), identical with authentic material, and 1,2-dihydro-1-methyl-2-oxo-4-phenylpyrimidine on treatment with 1 mole of hydrogen over palladium on charcoal gives a small yield of the dihydro derivative, 1,2,5,6-tetrahydro-1-methyl-2-oxo-4-phenylpyrimidine[48] (LXXVIII). 4-Ethoxycarbonylmethyl-2,6-dihydroxypyrimidine in 4 atmospheres of hydrogen over platinum yields the 4,5-dihydro derivative[103, 104] as does also 5-acetyluracil.[102] 2-Amino-, 2-amino-4-methyl-, 4-amino-, and 5-amino-pyrimidine when hydrogenated in dilute hydrochloric acid over palladium on charcoal yield dihydro derivatives of unknown configuration.[105] Some observations on the reduction of naturally occurring pyrimidines have been reported.[106]

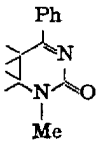
Boiling with an excess of Raney-nickel catalyst, or hydrogenation over rhodium on alumina, are good ways to reduce uracil and its 1-methyl derivative to their 5,6-dihydro derivatives.[95, 107]



(LXXIV) (LXXV) (LXXVI)



(LXXVII)



(LXXVIII)

An interesting reduction of pyrimidines, which inserts at the same time an alkyl group in position 2 or 4, is typified in the reaction of pyrimidine with phenyl magnesium bromide. Addition of the Grignard reagent occurs at the 1,6-bond, and subsequent hydrolysis yields 1,6-dihydro-4-phenylpyrimidine (Ch. IV, Sect. 1.C). Phenyl-lithium and its homologues behave similarly (Ch. IV, Sect. 2.A(5).).

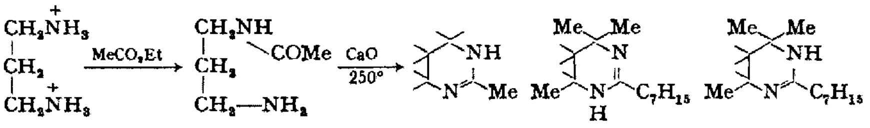
2. Preparation of Tetrahydropyrimidines

In the synthesis of tetrahydropyrimidines, any resemblance to the better known routes to pyrimidines is so attenuated as to be useless. In the following section therefore a purely descriptive classification of the methods is adopted.

A. From 1,3-Diaminopropane or Derivative

When a 1,3-diamine is acylated (or diacylated) and then ring closed, a 2-substituted tetrahydropyrimidine results. In 1888 Hofmann[108] heated 1,3-diacetamidopropane in a stream of hydrogen-chloride and isolated 1,4,5,6-tetrahydro-2-methylpyrimidine (LXXX) as a brown oil. The 2-phenyl analogue was described as being similarly formed from 1,3-dibenzamidopropane,[108] but the results could not be repeated elsewhere.[109] The process was improved by simply treating the diamine dihydrochloride with fused sodium acetate. In this way from 1,3-diaminopropane, the 2-methyl compound (LXXX) was made[110] at 240° in 50 % yield, and from 2,4-diaminopentane resulted 1,4,5,6-tetrahydro-2,4,6-trimethylpyrimidine in 62 % yield.[111] The last compound is described in *cis* and *trans* forms (?) with distinctly different melting points.[111] The best variation of the method had to await a workable process for making monoacyl derivatives of 1,3-diaminopropane by Aspinall.[112] He showed that when 1,3-diaminopropane and ethyl acetate or ethyl benzoate were refluxed for 12 hours, respectively 3-acetamido- (LXXIX) and 3- benzamido-propylamine were formed in good yield. When they were mixed with quicklime and heated at 250°, 90 % of 1,4,5,6-tetrahydro-2-methylpyrimidine (LXXX) and its phenyl analogue resulted. The latter compound has been made similarly but without lime dehydration, and the modified process applied to make several analogues such as 1,4,5,6-tetrahydro-5,5-dimethyl-2-phenylpyrimidine.[113] Rather similar processes have been used to make 2-heptadecyl-1,4,5,6-tetrahydropyrimidine,[114] 1,4,5,6-tetrahydro-2-heptyl-4,4,6-(or 4,6,6)-trimethylpyrimidine, (LXXXI) or

(LXXXII)*, from 2,4-diamino-2-methylpentane and octanoic acid,[114] and such compounds.[114–116] Other variations of the reaction are exemplified in the formation of 1,4,5,6-tetrahydro-4,4,6(or 4,6,6)-trimethyl-2-*p*-tolylpyrimidine by refluxing *p*-toluic acid, 2,4-diamino-2-methylpentane, *p*-toluenesulphonic acid, and xylene for a week,[117] and in the formation of 1,4,5,6-tetrahydro-2-nonylpyrimidine by fusion of nonyl cyanide with the monobenzenesulphonate of 1,3-diaminopropane.[118]



(LXXIX) (LXXX) (LXXXI) (LXXXII)

1,3-Diaminopropane derivatives can also be condensed with carbonic and thiocarbonic acid derivatives, and with guanidine and such like compounds, to give tetrahydropyrimidines, generally with functional groups in position-2. The preparation of the parent 1,4,5,6-tetrahydropyrimidine (LXXXIII; R=H) has been described in three ways by the reaction of 1,3-diaminopropane with ethyl formate followed by cyclization[113,175] with *sym*-triazine[119,175] (virtually a source of formamidine), and with formamidine.[175] The last of these is rapid and gives excellent yields. It is of general application in that other amidine acetates give 2-substituted derivatives.

With 1,3-diaminopropane at 180°, diethyl carbonate,[120] diphenyl carbonate,[95] and dimethyl carbonate[121] yield 1,4,5,6-tetrahydro-2-hydroxypyrimidine (LXXXIII; R=OH), and similarly 2-amino-4-methyl-4-methylaminopentane with diethyl carbonate at 200° gives 1,4,5,6-tetrahydro-2-hydroxy-1,4,6,6-tetramethylpyrimidine[122] (LXXXIV). Phosgene has also been used in such a reaction to give hexahydro-2-oxo-1,3-diphenylpyrimidine[123] from 1,3-dianilinopropane. Although bold heating with urea has been used to convert 2,4-diamino-2-methylpentane into 1,4,5,6-tetrahydro-2-hydroxy-4,6,6-trimethylpyrimidine,[124] it has otherwise been neglected in this reaction; the more gradual approach by reaction with cyanic acid has, however, been used. Thus 3-anilinopropylamine hydrochloride with 1 mole of po-

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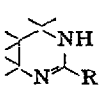
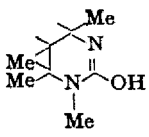
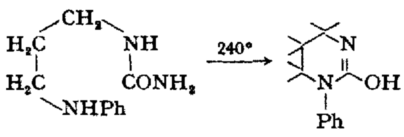
[*] Owing to the unsymmetrical molecule and lack of complication by tautomeric groups, there is a clear case for the existence of two isomers depending on the position of the double bond.

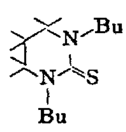
tassium cyanate yields *N*-(3-anilinopropyl)urea (LXXXV) which at 240° cyclizes with loss of ammonia to 1,4,5,6-tetrahydro-2-hydroxy-1-phenylpyrimidine[125] (LXXXVI). The 1-*p*-tolyl homologue was made similarly.[126]

Thio analogues have been made with carbon disulphide. Thus 1,3-diaminopropane with it yields (after boiling in water) 1,4,5,6-tetrahydro-2-mercaptopyrimidine[127] (LXXXIII; R=SH), and its 4,4,6-trimethyl,[114] 1-phenyl,[125] and 1-*p*-tolyl[126] derivatives were made rather similarly. 1,3-Bisbutylaminopropane with methanolic carbon disulphide at 20° followed by heating at 150° yields 30 % of 1,3-dibutylhexahydro-2-thiopyrimidine.[128] Heating the dithiocyanate (salt) of 1,3-diaminopropane at 140° has also been used[128a] to make (LXXXIII; R=SH). The approach *via* an intermediate thiourea has also been used, for example in converting 3-*p*-toluidinopropylamine with thiocyanic acid into *N*-(3-*p*-toluidinopropyl)thiourea which cyclizes spontaneously (unlike the oxygen analogue) to 1,4,5,6-tetrahydro-2-mercapto-1-*p*-tolylpyrimidine.[126] A rather peculiar reaction is fusion of 1-butylamino-3-(*N*-butylformamido)propane ($BuHNCH_2CH_2CH_2N(CHO)Bu$) with sulphur to yield 25 % of 1,3-dibutylhexahydro-2-thiopyrimidine[128] (LXXXVII).


(LXXXIII)

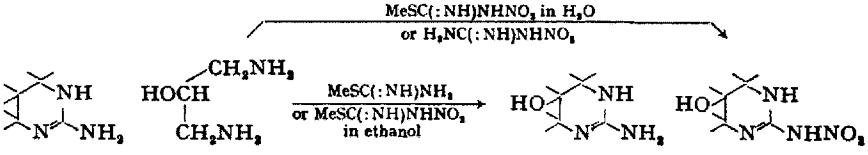

(LXXXIV)


(LXXXV) (LXXXVI)


(LXXXVII)

Condensation of guanidine-like compounds with 1,3-diamines is ill explored. The best synthesis of 2-amino-1,4,5,6-tetrahydropyrimidine (LXXXVIII) is by heating *S*-methylthiourea with 1,3-diaminopropane in aqueous solution,[129] but it can also be made[130] by condensation at 140° of cyanoguanidine (dicyanodiamide) with 1,3-diaminopropane *p*-toluenesulphonate (salt). 2-Amino-1,4,5,6-tetrahydro-5-hydroxypyrimidine (LXXXIX) is made from 1,3-diaminopropan-2-ol with *S*-methylthiourea,[129] or with *S*-methyl-*N*-nitrothiourea in ethanol.[129] If the latter reagent is used in aqueous solution, the main product is 1,4,5,6-tetrahydro-5-hydroxy-2-nitroaminopyrimidine[129] (XC), and it can also be made in 60 % yield with nitroguanidine.[131] The simpler 1,4,5,6-tetrahydro-2-nitroaminopyrimidine and its 4(or

6)-methyl derivative have been also made with nitroguanidine,[131] and in lower yield with *S*-methyl-*N*-nitrothiourea.[129] Other less simple examples have been recorded.[132]



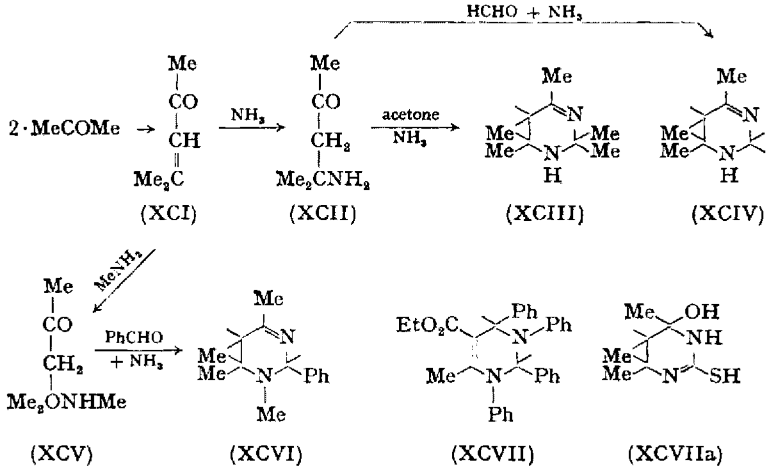
(LXXXVIII) (LXXXIX) (XC)

B. From Carbonyl Compounds and Ammonia or Amines

The fascinating compounds obtained from acetone and ammonia have been investigated for more than a century.[133–137] In 1947, Bradbury, Hancox, and Hatt[124] and elsewhere Matter,[138] (*cf.* ref. [139]), showed beyond doubt that the "acetonin" of Stadeler[133] is 1,2,5,6-tetrahydro-2,2,4,6,6-pentamethylpyrimidine (XCIII). It is obtained in excellent yield when acetone and liquid ammonia, with the catalysts calcium and ammonium chloride, are kept at 20° for 24 hours. When cyclohexanone replaces acetone, 1,2,5,6-tetrahydro-2,6-dipentamethylene-4,5-tetramethylenepyrimidine is formed in 95 % yield.[140, 141] The mechanism of the first example is seen as involving the initial formation of mesityl oxide (XCI) followed by addition of ammonia to give diacetonamine (XCII), and further reaction with ammonia and acetone to give (XCIII). This basic reaction is capable of considerable variation. In the last stage, other ketones or aldehydes may be used.[142, 143] Thus diacetonamine with formaldehyde yields 1,2,5,6-tetrahydro-4,6,6-trimethylpyrimidine (XCIV), with propionaldehyde it gives the 2-ethyl-4,6,6-trimethyl analogue, and with diethyl ketone it gives the 2,2-diethyl-4,6,6-trimethyl analogue.[142] The reaction may also be carried out (without catalysts) by saturating mesityl oxide (or other unsaturated ketone) with ammonia and adding an aldehyde or ketone at once. As well as the above examples which were also made in this way, compounds such as 1,2,5,6-tetrahydro-4,6,6-trimethyl-2-pentamethylenepyrimidine (from cyclohexanone) resulted in good yield.[142] Another variation, which introduces *N*-substitution, is exemplified in the following sequence: mesityl oxide (XCI) is first treated with methylamine to give 2-methyl-2-methylaminopentan-4-one(XCV), which with benzaldehyde and ammonia yields 1,2,5,6-tetrahydro-1,4,6,6-tetramethyl-2-phenylpyrimidine[142] (XCVI).

A fundamentally different reaction of related type is exemplified in the condensation of ethyl acetoacetate, aniline, and benzaldehyde to give 5-ethoxycarbonyl-1,2,3,4-tetrahydro-6-methyl-1,2,3,4-tetraphenylpyrimidine[144] (XCVII). The reaction is based on earlier work[145–147] and has been extended with observations on the possible mechanism.[148]

While the condensation of thiourea with a β-unsaturated ketone, such as mesityl oxide, or with the corresponding β-hydroxy ketone, might reasonably be expected (Sect. 1.A) to give a dihydropyrimidine, in fact a tetrahydro derivative is formed.[148a] Thus mesityl oxide and thiourea in sodium methoxide yield 1,4,5,6-tetrahydro-6-hydroxy-2-mercapto-4,4,6-trimethylpyrimidine (XCVIIa), in which the elements of water have failed to be eliminated from positions 1 and 6 to give the expected dihydro derivative. Several analogues have also been made.[148a]



(XCI) (XCII) (XCIII) (XCIV)

(XCV) (XCVI) (XCVII) (XCVIIa)

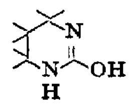
C. From 1,3-Dihalogenopropane Derivatives

This reaction has been but little used. Pinner[149] condensed benzamidine with 1,3-dibromopropane to give some 1,4,5,6-tetrahydro-2-phenylpyrimidine, and the reaction was later improved to be of some practical value.[109] 1,3-Dichloro-2-hydroxypropane and urea (on boiling in pyridine) similarly gave 1,4,5,6-tetrahydro-2,5-dihydroxypyrimidine.[150] However, the product from thiourea with 1,3-dichloroacetone which was first enigmatically described[151] as "2-thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine", is in fact a thiazole.[152]

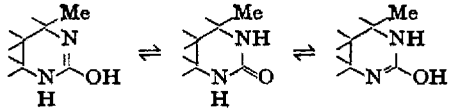
D. By Reduction of Pyrimidines or Dihydropyrimidines

A few tetrahydropyrimidines have been made by electrolytic reduction. Thus, for example, barbituric acid[91] and related compounds[92] yield among other products, "trimethyleneurea" or 1,4,5,6-tetrahydro-2-hydroxypyrimidine (XCVIII), and 2,4-dihydroxy-6-methylpyrimidine yields 1,4,5,6-tetrahydro-2-hydroxy-4(or 6)-methylpyrimidine[153] (XCIX).* The method is of little value.

Several 5,5-dialkylbarbituric acids have been reduced with lithium aluminium hydride.[90] In this way, for example, 5-ethyl-5-phenylbarbituric acid gives 44 % of 5-ethyl-1,4,5,6-tetrahydro-2-hydroxy-5-phenylpyrimidine. This type of reduction is useful because it is possible to retain a 2-mercapto group during the process, and so 5-ethyl-5-phenyl-2-thiobarbituric acid yields 5-ethyl-1,4,5,6-tetrahydro-2-mercapto-5-phenylpyrimidine.[90]



(XCVIII)



(XCIX)

Speaking generally, catalytic hydrogenation of a pyrimidine is much more likely to give a tetrahydro than either a di- or hexa-hydro derivative. Further, the tetrahydro derivative seems likely to have its double bond in the 1,2(2,3)-position. As early as 1922, Mannich and Heilner reported[48] that hydrogenation of 1,2-dihydro-1-methyl-2-oxo-4-phenylpyrimidine over palladium gave mainly 1,4,5,6-tetrahydro-2-hydroxy-1-methyl-4-phenylpyrimidine. Several papers followed from Johnson and colleagues.[83,99,154,155] These indicated little apart from the fact that with Raney nickel or platinum (Adams catalyst), any aromatic group attached to the pyrimidine nucleus was likely to be fully reduced before reduction of the pyrimidine to the tetrahydro state. Compounds prepared were seldom simpler than 4-cyclohexyl-5-ethoxycarbonyl-1,4,5,6-tetrahydro-2-hydroxy-6-methylpyrimidine,[155] and there is little reward for perusal.

More recent examples include the reduction (and reductive dehalogenation) of 4-chloro- and 2,4-dichloro- 5-phenylpyrimidine over palla-

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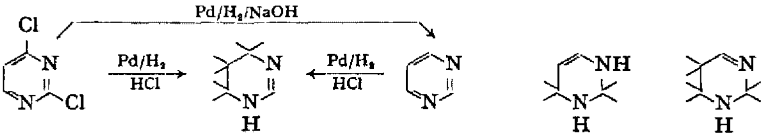
* Since these apparent isomers share the same tautomeric form, hexahydro-4-methyl-2-oxopyrimidine, only one substance in fact exists.

dium to give probably 1,4,5,6-tetrahydro-5-phenylpyrimidine,[156] and treatment of either 4-chloro-5-ethoxycarbonyl-2-methylpyrimidine or 5-ethoxycarbonyl-1,6-dihydro-2-methylpyrimidine with hydrogen over palladized charcoal to give 5-ethoxycarbonyl-1,4,5,6-tetrahydro-2-methylpyrimidine.[72] Other examples are contained in the valuable paper of Smith and Christensen:[105] Pyrimidine (CII) and its methyl derivatives are readily reduced in aqueous hydrochloric acid over palladium on charcoal, to yield almost quantitatively (as hydrochlorides) 1,4,5,6-tetrahydropyrimidine (CI) and its 2-, 4-, and 5-methyl derivatives.[105] These same compounds were also prepared in comparable yield by reductive dehalogenation of chloropyrimidines, *e.g.* (C), in ether over palladium on charcoal when no alkali was present (*i.e.* when the solution was allowed to become acidic during hydrogenation). In this way, tetrahydropyrimidine (CI) was prepared from 2-chloro-, 2,4-dichloro- (C), 4,6-dichloro-, 2,4,6-trichloro-, and 2,4,5,6-tetrachloro-pyrimidine. The homologues were made similarly.[105] When an equivalent amount of alkali (calcium carbonate is often ineffective, but sodium hydroxide, calcium hydroxide, magnesium oxide, and sometimes ammonia give good results) is added during dehalogenation, unreduced pyrimidine (CI) and its homologues are formed in good yield,[105] and this technique has been widely used (Ch. IV, Sect. 2.A(2), Table VIII). It mu stbe realized that while it seemed likely that the above hydropyrimidines were in fact 1,4,5,6-tetrahydro derivatives (*i.e.* 2,3-unsaturated), the only experimental evidence was the fact that each forms only a monobenzoyl derivative.[105] This may be reasonable negative evidence to exclude 5,6-unsaturation as in (CIII), but does not distinguish between 2,3- and 3,4-unsaturation as in (CI) and (CIV). However, the assumption is now proved,[175] and the tetrahydro-2-phenylpyrimidine formed from 5-chloro-2-phenylpyrimidine by reductive dehalogenation over palladium is identical[157] with 1,4,5,6-tetrahydro-2-phenylpyrimidine made by an apparently unambiguous synthesis.[112] A tetrahydro-2-propylpyrimidine is formed by hydrogenating 4,6-dichloro-2-propylpyrimidine over nickel.[157a]

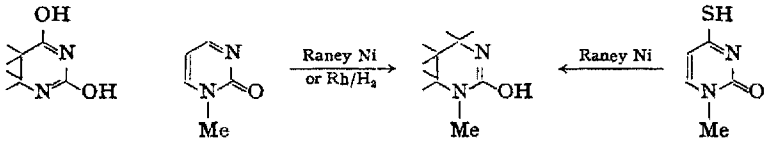
The hydrogenation of simple 2-, 4-, and 5- aminopyrimidines and of 2-amino-4-methylpyrimidine over palladium ceases in each case at a dihydro derivative of unknown configuration,[105] but acid reductive dehalogenation of 2(and 5)-amino-4,6-dichloropyrimidine and of 4-amino-2,6-dichloropyrimidine gives respectively 2-, 5-, and 4- amino-(?)1,4,5,6-tetrahydropyrimidines.[105] Similar treatment of 4-amino-6-

chloro-2-methylpyrimidine, however, is reported to give only 4-amino-2-methylpyrimidine.[158]



(C) (CI) (CII) (CIII) (CIV)

Besides the formation of dihydro derivatives during the desulphurization of thiobarbituric acids (Sect. 1.H), it was suspected[159,160] that massive quantities of Raney nickel might sometimes reduce the nucleus of simple pyrimidines. This was confirmed in a report[107] that reduction of 1-methyluracil to 5,6-dihydro-1-methyluracil with Raney nickel in boiling aqueous ethanol was "essentially complete in five hours". Fox and Van Praag[95] further showed that this 34 % yield could be increased to 86 % by using rhodium on alumina catalyst and hydrogen for the reduction. With Raney nickel they also reduced uracil to 4,5-dihydro-2,6-dihydroxypyrimidine (CV) in 53 % yield, 2-hydroxypyrimidine to "trimethyleneurea" (1,4,5,6-tetrahydro-2-hydroxypyrimidine) in 90 % yield, and 1,2-dihydro-1-methyl-2-oxopyrimidine (CVI) to 1,4,5,6-tetrahydro-2-hydroxy-1-methylpyrimidine (CVII) in 72 % yield. Rhodium on alumina and hydrogen was similarly effective. Tetrahydropyrimidines are also formed[95] during desulphurization of simple 4-mercapto (but not 2-mercapto)-pyrimidines. Thus 2-hydroxy-4-mercaptopyrimidine yields 60 % of 1,4,5,6-tetrahydro-2-hydroxypyrimidine, 1-methyl-4-thiouracil (CVIII) yields 70 % of 1,4,5,6-tetrahydro-2-hydroxy-1-methylpyrimidine (CVII), and two thioribosides have been similarly reduced.



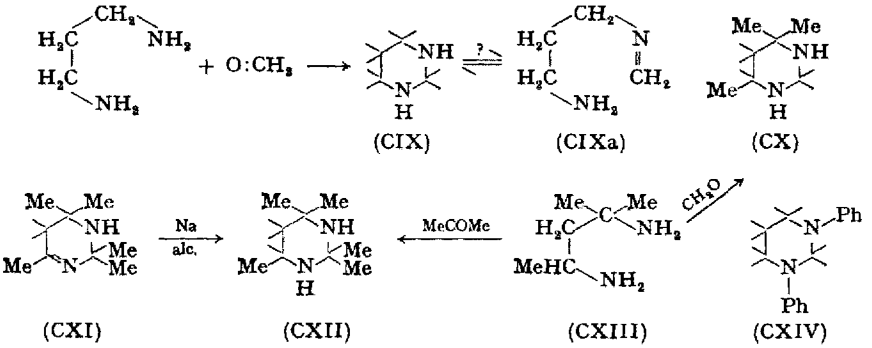
(CV) (CVI) (CVII) (CVIII)

3. Preparation of Hexahydropyrimidines

Most of the known hexahydropyrimidines have been made from 1,3-diaminopropane derivatives and an aldehyde or ketone to supply

$C_{(2)}$. Thus 1,3-diaminopropane and aqueous formaldehyde yield hexahydropyrimidine ("piperimidine"; CIX) which is a liquid that appears to be in tautomeric equilibrium with 1-amino-3-methyleneaminopropane[161, 162] (CIXa). Similarly 2,4-diamino-2-methylpentane (CXIII) and formaldehyde yield hexahydro-4,4,6-trimethylpyrimidine (CX), which on benzoylation gives a dibenzoyl derivative and 2,4-dibenzamido-2-methylpropane, suggesting a ready cleavage of the ring and hydrolytic loss of formaldehyde.[124] The same pentane derivative (CXIII) and acetone yield hexahydro-2,2,4,4,6-pentamethylpyrimidine (CXII), which may also be obtained by careful treatment of acetonin (CXI) in alcohol with sodium.[124, 138]

When *N*-substituted diaminopropanes are used, the resulting pyrimidines are *N*-substituted. Thus 1,3-dianilinopropane with formaldehyde gives hexahydro-1,3-diphenylpyrimidine[163, 164] (CXIV), with benzaldehyde gives hexahydro-1,2,3-triphenylpyrimidine,[164] but does not react satisfactorily with acetaldehyde, other aliphatic aldehydes, or salicylaldehyde.[164] Under different conditions, however, acetaldehyde is said to yield hexahydro-2-methyl-1,3-diphenylpyrimidine and



(CIX) (CIXa) (CX)

(CXI) (CXII) (CXIII) (CXIV)

(with 1,3-dianilino-2-methylpropane) the tetrahgydro homologue.[165] 1,3-Di-*o*-toluidinopropane seems to be too sterically hindered to undergo cyclization with aldehydes,[163] but 1,3-bisbenzylaminopropane does so with aromatic aldehydes giving with benzaldehyde, for example, 1,3-dibenzylhexahydro-2-phenylpyrimidine.[166]

A variety of hexahydro-5-nitropyrimidines has been made by having the nitro group present in the diamine before cyclization.[167–169] Thus 1,3-bisisopropylamino-2-methyl-2-nitropropane and formaldehyde give hexahydro-1,3-di-isopropyl-5-methyl-5-nitropyrimidine, and the same compound can be made either from 2-methyl-2-nitropropan-1,3-diol, formaldehyde, and isopropylamine, or from nitroethane, formaldehyde, and the amine.[167] Many other examples are known.

Reduction of a pyrimidine to a hexahydro derivative is uncommon. However, 2-amino-4,6-dichloropyrimidine was reduced in acidic solution over palladium to give 2-aminohexahydropyrimidine, characterized as picrate and as a carbonate.[170] The reduction of acetonin to hexahydro-2,2,4,4,6-pentamethylpyrimidine[124, 138] has been mentioned above.

4. Reactions of Reduced Pyrimidines

The most noticeable aspect of hydropyrimidines is the very small number of their reactions recorded. In this respect they lag behind the pyrimidines by perhaps eighty years. Indeed there are so few metatheses that for some common transformations no example can be found at all. The sketchiness of what follows will therefore be understandable. Reduced pyrimidines, unlike the pyridine analogues, are prone neither to self condensation nor rapid aerial oxidation.

A. Reductions

Nuclear reductions of dihydro- and tetrahydro-pyrimidines have been treated in the first three sections of this chapter. The fact that a dihydropyrimidine can retain its state of oxidation while an attached phenyl group is hydrogenated to cyclohexyl[154] may sometimes be of use.

Hydrogenation of 5-ethyl-4,5-dihydro-2,6-dihydroxy-5-*m*-nitrophenylpyrimidine (CXV; $R{=}NO_2$) over Adams' catalyst gave a separable mixture of the 5-*m*-aminophenyl analogue (CXV; $R{=}NH_2$) and the corresponding azoxy compound.[64] Several nitro compounds such as hexahydro-1,3,5-trimethyl- and 1,3-dibenzyl-hexahydro-5-methyl-5-nitropyrimidine, have been hydrogenated to the corresponding amino derivatives.[167] Even the severe conditions used (Raney nickel/75 atm./75°) caused no debenzylation of the second example.

The reduction[124,138] of tetrahydro- or of hexahydro-2,2,4,4,6-pentamethylpyrimidine (acetonin or CXVI) with sodium amalgam in moist ether is a good example of reductive ring cleavage. The product is 2-(or 4)-amino-4(or 2)-isopropylamino-2-methylpentane (CXVII).

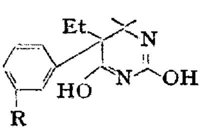
B. Oxidations

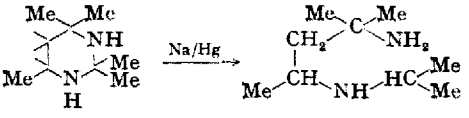
At least one catalytic dehydrogenation is recorded.[157] 1,4,5,6-Tetrahydro-2-phenylpyrimidine (CXVIII) on heating with platinized carbon at 270° in a current of carbon dioxide yields 70 % of 2-phenylpyrimidine. Sulphur has been used at 170° to dehydrogenate 2-amino-4,5-dihydro-6-hydroxy-4,5-diphenylpyrimidine to 2-amino-4-hydroxy-5,6-diphenylpyrimidine in 70 % yield, and analogues were prepared similarly.[23] In the same series dehydrogenations with chloranil were less satisfactory. Oxidation of tetrahydropyrimidines has been done with permanganate. In this way, 5-ethoxycarbonyl-1,4,5,6-tetrahydro-6-methyl-2,4-diphenylpyrimidine[146] was converted[147] into 5-ethoxycarbonyl-4-methyl-2,6-diphenylpyrimidine, and the 2,4,6-triphenyl analogue was similarly made.

The usual way to make pyrimidines from their 4,5-dihydro derivatives has been to brominate in position 5 (giving *e.g.* CXX) and then dehydrobrominate to produce a 4,5-double bond. This technique seems to have been first applied by Fischer and Roeder[2] to make uracil (CXXI) from dihydrouracil[25] (CXIX) and the products from other such oxidations include 2,4-dihydroxy-5(and 6)-methylpyrimidine,[2] 2,4-dihydroxy-6-phenylpyrimidine,[2] 1-methyluracil,[37] 1-phenyl (and other aryl) uracils[39], and similar compounds.[4,38] The actual process of dehydrobromination has been done by simply heating[2,4,25,37] the bromo dihydro derivative, or by boiling it in aqueous sodium hydroxide,[2] in pyridine,[2] in dimethylformamide,[38] or in dimethylformamide containing lithium chloride.[39] In the case of 5,6-dihydro-1,5-dimethyluracil and other such derivatives of thymine, bromination in boiling acetic acid is followed immediately by dehydrobromination to give directly 1,5-dimethyluracil and homologues.[40]

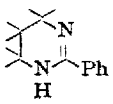
C. Nitrosation and Nitration

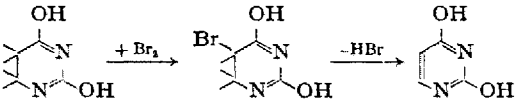
These processes are meagrely represented. 1,2,5,6-Tetrahydro-2,2,4,6,6-pentamethylpyrimidine on treatment with nitrous acid gives a 5-nitroso derivative (CXXII; CXXIIa) in 30 % yield.[171] It forms a benzoyl derivative, and treatment of (CXXII) with warm hydrochloric acid opens the ring to give 2-amino-3-hydroxyimino-2-methylpentan-4-one.[171] The extranuclear nitro compound, 5-ethyl-4,5-dihydro-2,6-dihydroxy-5-*m*-nitrophenylpyrimidine (CXV; $R{=}NO_2$), is conveniently made by nitration of the corresponding phenyl derivative.[64] A few nuclear 5-nitro-hydropyrimidines have been made by using in the synthesis an aliphatic fragment already carrying a nitro group,[167] and the formation of 2-nitroamino compounds by using nitroguanidine[31] or such like[129] in synthesis, has already been discussed at the end of Sect. 2.A.


(CXV)

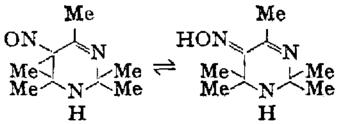


(CXVI) (CXVII)


(CXVIII)



CXIX) (CXX) (CXXI)


(CXXII) (CXXIIa)

D. *N*-Acylation

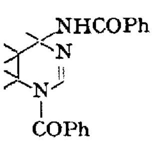
The acylation of amino derivatives is exemplified in the benzoylation of 2-, 4-, and 5- aminodihydropyrimidines to the corresponding benzamido derivatives.[105] When, however, the corresponding 1,4,5,6-tetrahydropyrimidines, are submitted to the Schotten–Baumann reaction, nuclear benzoylation (except in the case of the 2-amino compound) also occurs, to give 4-(or 5-)benzamido-1-benzoyl-1,4,5,6-tetrahydropyrimidine[105] (CXXIII). Another acyl derivative is the 1,3-dibenzoyl derivative of hexahydro-4,4,6-trimethylpyrimidine[124] which is accompanied by a ring opened dibenzamido derivative. Such ring cleavage is not uncommon in attempted benzoylations and this is shown in the benzoylation of 1,4,5,6-tetrahydro-2-phenylpyrimidine which gives the tribenzoyl derivative of 1,3-diaminopropane.[109]

Folkers and Johnson[172] have described several acetylations of reduced pyrimidines with a 5,6-double bond. From dihydropyrimidines such as 5-ethoxycarbonyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine, they obtained *N*-monoacetyl derivatives, and from tetrahydro analogues came *NN'*-diacetyl derivatives which could be deacetylated with alcoholic alkali. The actual configurations of some of the acetyl compounds do not seem to be beyond doubt. An example of ring cleavage during acetylation is the formation of 2,4-diacetamido-2-methylpentane (CXXV) from hexahydro-2,2,4,4,6-pentamethylpyrimidine[138] (CXXIV).

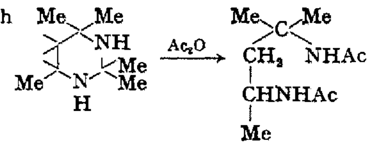
E. Halogenation

The ready monobromination of 5,6-dihydrouracil[2] and its derivatives[4, 37–40] has already been discussed in connection with oxidation of such compounds to pyrimidines (Sect. 4.B). 5-Bromo-5,6-dihydrouracil on boiling with alcoholic potassium thiocyanate gives (probably) 5,6-dihydro-5-thiocyanatouracil[25] and on warming with aniline gives 5-anilino-5,6-dihydrouracil (CXXVI), which on vigorous acid hydrolysis is ring opened to β-anilinoethylamine.[25] Less simple brominations also occur. 1,2,5,6-Tetrahydro-1-methyl-2-oxo-4-phenylpyrimidine treated with bromine in acetic acid gives a tribromo derivative which with cold alkali gives the reasonably stable 5,6(?)-dibromo derivative.[48] Similarly, 5-ethoxycarbonyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine on bromination yields[76] a dibromo compound, which has been formulated[173] seemingly without evidence as an addition of bromine across the 4,5-double bond to give (CXXVII).

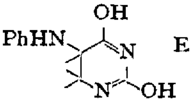
Bromination of 5,6-dihydrouracil with sodium hypobromite at a constant pH value of 6.5–8.5, gives a dibromo derivative formulated as 1,3-dibromohexahydro-2,4-dioxopyrimidine. The analogous dichloro derivative (prepared at pH 1–3) is also described.[174]



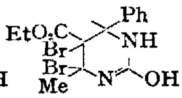
(CXXIII)



(CXXIV) (CXXV)



(CXXVI)

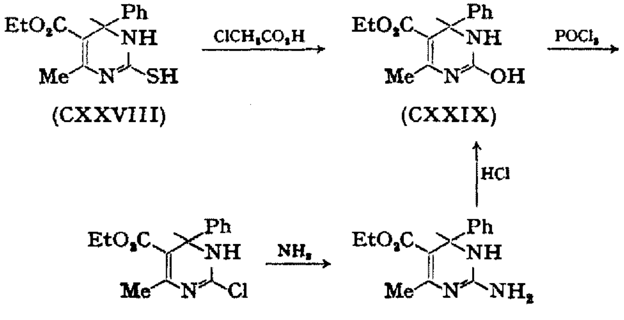


(CXXVII)

F. Metatheses of Mercapto and Hydroxy Derivatives

Conversion of a mercapto into a methylthio group is exemplified in the formation by means of methyl iodide of 1,6-dihydro-6-methyl-2-methylthio-4,6-diphenylpyrimidine.[85] This compound can be changed to the 2-hydroxy analogue by heating with mercuric oxide.[85] Mercapto groups may also be converted into hydroxy by treatment with chloroacetic acid and acid hydrolysis of the carboxymethylthio intermediate. 5-Ethoxycarbonyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine (CXXIX) was made[76] in this way from (CXXVIII). Direct acylation of a mercapto derivative was used to make 2-benzoylthio-1,6-dihydro-6-methyl-4,6-di-*p*-tolylpyrimidine.[85]

Although other examples are lacking, the following sequence[173] demonstrates the possibilities of reduced hydroxypyrimidines in metathesis: 5-ethoxycarbonyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine (CXXIX) with phosphoryl chloride gives a very easily hydrolysed 2-chloro analogue (CXXX). This with ammonia gives the 2-amino analogue (CXXXI), which is also unusually sensitive to hydrolysis so that dilute hydrochloric acid at 25° gives back the hydroxy compound (CXXIX). Sodium methoxide on the chloro compound gives what appears to be an *N*-methyl derivative, presumably by rearrangement of the initially formed methoxy compound.



(CXXVIII) (CXXIX) (CXXX) (CXXXI)

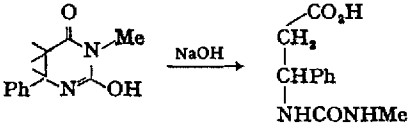
G. *N*-Alkylation

Several *N*-alkyl derivatives of 4,5-dihydro-2,6-dihydroxy-4-phenylpyrimidine have been made.[4] Thus refluxing its sodium salt with methyl iodide gives 5,6-dihydro-3-methyl-6-phenyluracil (CXXXII), which is opened under vigorous alkaline conditions to give *β*-methylureido-*β*-phenylpropionic acid (CXXXIII). Similar alkylation with ethyl chloroacetate gives 3-ethoxycarbonylmethyl-5,6-dihydro-6-phenyluracil, which with acid or alkali gives the corresponding 3-carboxymethyl analogue. Finally, 5,6-dihydro-1-methyl-6-phenyluracil (made by synthesis) can be alkylated by ethyl chloroacetate to yield 1-ethoxycarbonylmethylhexahydro-3-methyl-2,6-dioxo-4-phenylpyrimidine.

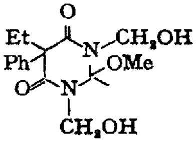
A quite different type of alkylation was carried out[64] by warming 5-ethyl-2,5-dihydro-4,6-dihydroxy-2-methoxy-5-phenylpyrimidine with aqueous formaldehyde and potassium carbonate to give the rather unstable 5-ethylhexahydro-1,3-bishydroxymethyl-2-methoxy-4,6-dioxo-5-phenylpyrimidine (CXXXIV).

H. Other Reactions

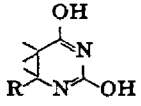
Among the ring cleavages not already mentioned above are those of the 5,6-dihydrouracils. Vigorous acid hydrolysis converts 4,5-dihydro-2,6-dihydroxy-4-isopropylpyrimidine (CXXXV; R=–$CHMe_2$) into β-amino-γ-methylvaleric acid in good yield,[5] and analogues behave similarly. On the other hand, alkaline hydrolysis of the isobutyl analogue (CXXXV; R=–CH_2CHMe_2) stops at the intact δ-methyl-β-ureidohexanoic acid,[47] which can be recyclized by gentle acid treatment.



(CXXXII) (CXXXIII)



(CXXXIV)



(CXXXV)

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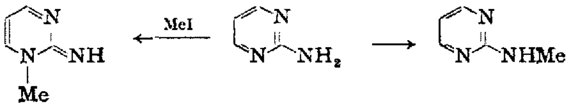
CHAPTER XIII

The Ionization and Absorption Spectra of Pyrimidines

1. Ionization of Pyrimidines

It is beyond doubt that ionization constants which are now so easily measured[1] potentiometrically or spectrophotometrically, are of immense use in heterocyclic chemistry. They are, for example, not only useful criteria of identity but also of homogeneity, which is strongly indicated by self consistency throughout the central 80 % of the titration range. But more important is their use in structural studies: thus isomers can often be distinguished, as when 2-aminopyrimidine (II) is methylated without alkali[2] to give a strong base of pK_a 10.75, or in the presence of alkali[3] to give a rather weak base of pK_a 3.82. The strong base is clearly the imino derivative (I), and the weak one, the methylamino derivative (III). Another important use of ionization constants in structural studies is for deciding which form of a tautomeric substance (such as 4-hydroxypyridine) predominates at equilibrium. Although this is perhaps more easily done qualitatively by the ultraviolet spectra (Sect. 2.A), the ionization constants can be used, at least in simple cases, to determine the ratio of the forms, with a fair degree of accuracy. Finally, knowledge of the pK_a values of a compound is a prerequisite for precise recording of ultraviolet spectra in aqueous buffer of such pH that only one ionic species of the compound is present (Sect. 2.A).



(I) (II) (III)

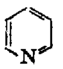
A most useful simple treatment of ionization constants, particularly as applied to heterocyclic chemistry, has been given by A. Albert,[4] and there are more general works[5,6] for background.

A. The pK_a of Pyrimidine

The weakly basic nature of pyrimidine[7,8,8a] (V; pK_a 1.31 and *ca.* — 6.3) is striking in relation to pyridine (IV; pK_a 5.2). It is understandable as an inductive effect (depletion of π-electrons), caused by insertion of the avidly electron-attracting second nuclear nitrogen atom. Pyrimidine may therefore be likened more to β-nitropyridine[37,73] (VI; pK_a 0.8), which contains the equally strongly electron-attracting nitro group, than to the parent pyridine.

Addition of the slightly electron-donating methyl group partly redresses the deficiency in the π layer, so that 4-methylpyrimidine has[10] pK_a 2.0 and 4,6-dimethylpyrimidine,[11] pK_a 2.8. The same factor is seen in 4-methoxypyrimidine[12] (pK_a 2.5), and in 5-hydroxypyrimidine[14] (pK_a 1.87).

The basic strengths of 2-hydroxypyrimidine[15] (pK_a 2.24) and 4-hydroxypyrimidine[13] (pK_a 1.85) are also greater than that of pyrimidine, but for a less simple reason: It is known that these substances exist in aqueous solution almost entirely as cyclic amide tautomers, and from a study of hydroxypyridines, it is also known that the basic strength of a ring nitrogen atom is considerably weakened when it becomes part of such a cyclic amide. The hydroxypyrimidines therefore owe their enhanced basic strength to the nitrogen atom not involved as amide. In uracil (pK_a *ca.* 0.5) and thymine (pK_a *ca.* 0) where both nitrogen atoms are so involved, little basic strength remains. 2-Hydroxypyrimidine probably has a slight exaltation of basic properties[1] through resonance stabilization of the symmetrical cation (VII). The N-methylated derivatives, 1,2-dihydro-1-methyl-2-oxopyrimidine[12] (pK_a 2.5) and 1,6-dihydro-1-methyl-6-oxopyrimidine[12] (pK_a 1.84) differ little from those of the parent hydroxy compounds. The 2- and 4-mercapto-



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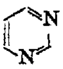

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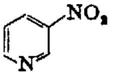

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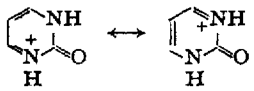


(VII)

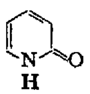
pyrimidines[16, 17] (pK_a values respectively 0.68 and 1.35) have even lower basic strength, as would be expected from the base-weakening character of the –C(:S)– compared with the –C(:O)– grouping. Most other groups also weaken pyrimidine as a base as far as can be judged from the inadequate data available (see Table XVI).

B. The Acidic pK_a Values of Pyrimidines

The carboxy-, hydroxy-, and mercapto-pyrimidines ionize as acids, and therefore the possibility of zwitterion or internal salt formation exists. At least in the first category this is more apparent than real, because even in the most favourable known example[18] of 2-carboxypyrimidine, the pK_a values (2.85 and — 1.13) are almost 4 units apart, and this precludes all but minute amounts of zwitterion even at the isoelectric point. The position is not at present similarly clear with mercapto- and hydroxy-pyrimidines.

2-, 3-, and 4-Hydroxypyridine (pK_a 11.62, 8.72, and 11.09) might reasonably be expected to be stronger acids than phenol (pK_a 9.9) and comparable with nitrophenols (pK_a 7–8), but because of being involved as cyclic amides (VIII) and (IX), the 2- and 4-isomers are in fact weaker than phenol. However, the 3-isomer, which is not so involved, does approach the expected figure. The presence of a second ring nitrogen atom in 2- and 4-hydroxypyrimidine (pK_a 9.17 and 8.59) makes these substances about 1.5 pK_a units stronger than the pyridine analogues, and 5-hydroxypyrimidine[14] (pK_a 6.78) reaches a figure between the mono- and 2,4-di-nitrophenols. 2-Hydroxy-sym-triazine, whose acidity would extend the series, is unknown. The insertion of methyl groups into 2- and 4-hydroxypyrimidine is (as usual) rather acid-weakening, so that 2-hydroxy-4-methyl- and 4-hydroxy-6-methylpyrimidine have pK_a 9.8 and 9.0 respectively.[10] The addition of a second hydroxy group to give uracil[1, 19, 20] (X; pK_a 9.38 and 12) reduces the acidity a little, because both hydroxy groups are involved in cyclic amide formation, and the same mild acid-weakening effect of cyclic amide grouping is seen in 4,5-dihydroxypyrimidine[1] (pK_a 7.48) when compared with 5-hydroxypyrimidine (pK_a 6.78). In 4,6-dihydroxypyrimidines,[1] where valency precludes diamide formation, the second hydroxy group ionizes as a strengthened phenol, (pK_a 5.4), because the anion can form a resonance hybrid from the symmetrical structures (XI). 2,4,5-Trihydroxypyrimidine[1] (pK_a 8.11) is comparable with 4,5-dihydroxypyrimidine, but in 2,4,6,-trihydroxypyrimidine[19] (pK_a 3.9) and 2,4,5,6-tetrahydroxypyrimidine[21] (pK_a 2.83), the acid strength has increased markedly. There is evidence[19] suggesting that it is the (5-) methylene group of the former which deprotonates so easily to give the anion (XII), but this interpretation has been questioned.[1] Nitration of 2,4-dihydroxypyrimidine increases[22] the acidic strength by 4 units to give nitrouracil (pK_a 5.55), and the insertion of the strongly electron-attracting trifluoromethyl group into uracil similarly strengthens[23] the acidity in 2,4-dihydroxy-6-trifluoromethylpyrimidine (pK_a 5.7). Acidic strength is less affected by the insertion of an alkoxy group. Compare for example[24] 2 (and 4) -hydroxypyrimidine (pK_a values 9.17 and 8.59) with 4 (and 2) -ethoxy-2 (and 4) -hydroxypyrimidine (10.7 and 8.2). The 5-nitro derivatives of these are much stronger acids of pK_a 6.6 and 4.88 respectively.[22] The acidic strength of derivatives of barbituric acid has been studied.[19, 25–29]

As acids, 2- and 4-mercaptopyrimidine (pK_a 7.2 and 6.7) are stronger[16] by two units than their hydroxy analogues, and *C*-methyl groups have their usual acid-weakening effect[10] in 2-mercapto-4-methyl- and 4-mercapto-6-methyl-pyrimidine (pK_a 8.0 and 7.3). 2,4-Dimercaptopyrimidine (pK_a 6.46) is three units stronger[30] than is uracil, and 4-hydroxy-2-mercaptopyrimidine (pK_a 7.95) is[31] of an intermediate order. In line with 4,6-dihydroxypyrimidine, and for a similar reason, 4-hydroxy-6-mercaptopyrimidine[37] (pK_a 4.33) is an exceptionally strong acid.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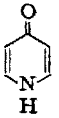
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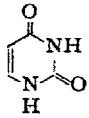
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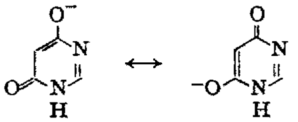
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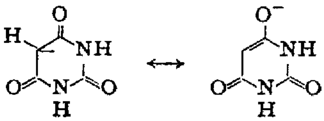

(XII)

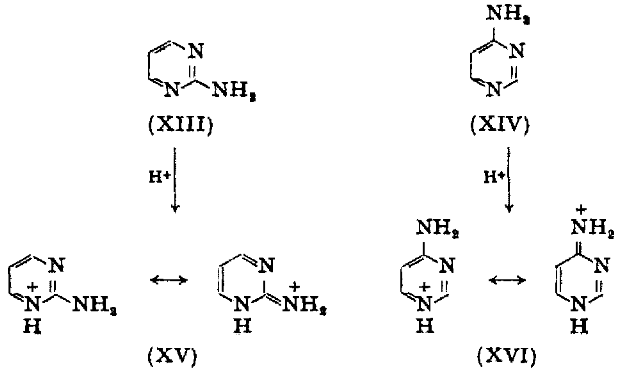
Discussion of the ionization of carboxy pyrimidines is impossible for lack of data. 2-Carboxypyrimidine[18] has pK_a 2.85, 4-carboxy-2,6-dihydroxypyrimidine has pK_a 2.4 (and 9.45), and the figures for

4-carboxy-6-hydroxypyrimidine[32] are 2.8 (and 8.4). The *N*-methylorotic acids (pK_a values < 1) are stronger acids than the parent.[33]

C. The Basic pK_a Values of Pyrimidines

The simple aminopyrimidines, *e.g.* (XIII), are bases of moderate strength with pK_a 4–6. When these are methylated on a ring nitrogen atom, the resulting imines, *e.g.* (XIX), form a class of far stronger bases in the region of pK_a 10–12. Extranuclear aminopyrimidines[34] have pK_a *ca.* 9.

For 2- and 4-aminopyrimidine, the figures[7] (3.54 and 5.71) are above unsubstituted pyrimidine (pK_a 1.31) by an amount out of all proportion to the unit rise expected in passing, *e.g.*, from aniline to the diaminobenzenes. On the other hand, 5-aminopyrimidine (pK_a 2.8) is of the expected order. The large increase in the strength of the 2- and 4-isomers arises from the fact that insertion of an amino group in these positions allows more resonance in the cations (XV) and (XVI) than in the neutral molecule, (XIII) and (XIV), and the molecule will therefore protonate at a lower concentration of hydrogen ions, *i.e.* at a higher pH value. The 4-isomer (XIV) shows this effect more strongly than does the 2-isomer (XIII), because the preferred *p*-quinonoid form contributes to its cationic hybrid (XVI) in place of the *o*-quinonoid form in the case of the 2-isomer (XV). The addition of *C*-methyl groups has the usual base-strengthening effect, so that 2-amino-4-methyl- and 2-amino-4,6-dimethyl-pyrimidine have[7] pK_a 4.15 and 4.85, and the alkylation of aminopyrimidines on the extranuclear nitrogen atom has



a similar strengthening effect, seen in 2-methylaminopyrimidine (pK_a 3.82) and 2-dimethylaminopyrimidine (pK_a 3.96) and the 4-isomers (pK_a 6.12 and 6.35). Understandably, 4,5-diaminopyrimidine[36] (pK_a 6.03), 4,6-diaminopyrimidine[9] (pK_a 6.01) and its alkyl derivatives[37–39*] are a little stronger than 4-aminopyrimidine (pK_a 5.71), because of the electron-releasing effect of an amino group. In these cases, considerations of valency prevent the second amino group contributing to the resonance hybrid, but in 2,4-diaminopyrimidine (pK_a 7.3) this can, and does, take place to give a stronger base. The same thing is seen in 2,4,5-triaminopyrimidine[35] (pK_a 7.63), but the slight lowering evident in 2,4,6-triaminopyrimidine (pK_a 6.8) and 4,5-diamino-6-methylaminopyrimidine[38] (pK_a 5.93) has not been explained.

Apart altogether from the effect of acidic groups on aminopyrimidines, which is treated below, other substituents can have effects on basic strength. For example, the insertion of a *C*-chloro group into 4-aminopyrimidine reduces the basic strength by over three units in 4-amino-6-chloropyrimidine[9,37] (pK_a 2.1), and the corresponding 4-chloro-6-methylamino- and 4-chloro-6-dimethylamino-pyrimidine (pK_a 2.24 and 2.42) are parallel.[37] Likewise, 4-amino-2-methylaminopyrimidine (whose pK_a must be above that of 2,4-diaminopyrimidine, 7.3) is weakened by a chloro group in 4-amino-6-chloro-2-methylaminopyrimidine to 3.73.[9] Alkoxy groups have a mild weakening effect on the strengths of aminopyrimidines. This is seen in passing from 4-amino- (pK_a 5.7) to 4-amino-6(and 2)-methoxy-pyrimidine[24,37] (pK_a 4.02 and 5.3), and other examples[37] are parallel. The considerable base-weakening effect of a nitro group is seen in comparing[38] 4-amino-6-methylaminopyrimidine (pK_a 6.32) and its 5-nitro derivative (pK_a 2.75) or 2-aminopyrimidine (pK_a 3.54) and its 5-nitro derivative[9] (pK_a 0.35).

Substitution of an aminopyrimidine wihch redistributes the double bonds removes the basis of base-strengthening resonance. Indeed, new resonance possibilities can be written in the cation of 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (XVII), but they are neither para-quinonoid nor benzenoid so that the basic strength[40] (pK_a 4.57) is well below that of 4-aminopyrimidine. In 4-amino-1,6-dihydro-1-methyl-6-oxopyrimidine (XVIII) the greatly diminished basic strength[37] (pK_a 0.98) seems inexplicable. It should be noted that in all these discussions no account has been taken of resonances which might stabilize the

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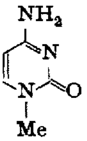
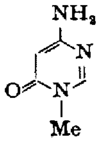
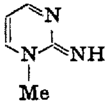
[*] The figures in ref.[39] are not comparable because they were determined in 66% dimethylformamide.

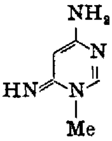
neutral molecule at the expense of the cation. Although the necessary separation of charge in these would make them second-order effects, they may not be trivial.

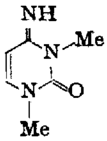
The iminopyrimidines are bases comparable in strength with their pyridine analogues. Thus 1,2-dihydro-2-imino-1-methyl-pyridine (pK_a 12.2) and -pyrimidine (XIX) (pK_a 10.7), and 1,4-dihydro-4-imino-1-methyl-pyridine (pK_a 12.5) and -pyrimidine (pK_a 12.2), are all bases of uncommon strength for heteroaromatic systems.


(XVII)


(XVIII)


(XIX)


(XX)


(XXI)

Similarly 4-amino-1,6-dihydro-6-imino-1-methylpyrimidine[41] (XX) (pK_a 11.98) and 4-butylamino-6-butylimino-1,6-dihydro-1-methylpyrimidine[39] (pK_a *ca.* 12.8) are strong bases, but in the presence of an oxo group, as in 1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine[40] (XXI) (pK_a 9.29), such a high value is not reached.

D. The pK_a Values of Amino-hydroxy and Related Pyrimidines

The acid and basic pK_a values of amino-hydroxypyrimidines indicate that the presence of the amino group has weakened the acidity, and that the hydroxy group has generally weakened the basic strengths.*

The origins of the loss of basic strength have already been discussed above, where the *N*-methylated hydroxypyrimidines offer convenient parallels. Thus in 2-amino-4-hydroxypyrimidine (isocytosine; pK_a 4.01) the basic strength[20] is comparable with that of 2-aminopyrimidine, but in 4-amino-2-hydroxypyrimidine[20] (cytosine; pK_a 4.60) and in 4-amino-6-hydroxypyrimidine[53] (pK_a 1.36), it has been impaired to the extent of one and four units respectively when compared with 4-aminopyrimidine. The alkylamino analogues of cytosine[30] have virtually the same basic strength. When these compounds are methylated (thus

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* There seems no justification for reversing the values by assuming that, as in glycine, these compounds are zwitterions. This would lead for example to the untenable concept of 4-amino-6-hydroxypyrimidine as a strong acid of pK_a 1.36.

losing their acidity) a curious phenomenon appears:[40] the basic strength of 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (XXII; R=R′=H) (pK_a 4.57) is progressively decreased in its 4-methylamino analogue (XXII; R=H; R′=Me) (pK_a 4.47) and its dimethylamino analogue (XXII; R=R′=Me) (pK_a 4.2). Such behaviour is also encountered[37] in comparing 4-amino-6-hydroxypyrimidine (basic pK_a 1.36) with its 4-dimethylamino analogue (pK_a 1.22).

The amino group is normally only slightly acid-weakening, as seen in a comparison of phenol (pK_a 9.9) with *p*-aminophenol (pK_a 10.3) and of benzoic acid (pK_a 4.2) with *p*-aminobenzoic acid (pK_a 4.9). Thus 2-amino-4-hydroxypyrimidine[20] (pK_a 9.42), and 4-amino-6-hydroxypyrimidine[53] (pK_a 10.05) have become weaker acids than 4-hydroxypyrimidine by 1–1½ units. On the other hand, in 4-amino-2-hydroxypyrimidine[20] (cytosine; pK_a 12.16) a very marked decrease of three units compared with 2-hydroxypyrimidine has taken place, and it is unexplained. Similarly, the alkylamino analogues of cytosine[30] have even less acidity (pK_a *ca.* 13).

The addition of nitro groups to amino-hydroxypyrimidines causes the usual marked decrease in basic function and strengthening of acidity, *e.g.*, in 4-amino-2-hydroxy-5-nitropyrimidine[30] (pK_a < 3 and 7.39) or more obviously in 2-hydroxy-4-methylamino-5-nitropyrimidine[30] ($pK_a < 1$ and 7.76). The addition of further amino groups to cytosine and its isomers does not affect the constants greatly (except to introduce a second basic figure). Compare for example[35] 4-amino-2-hydroxypyrimidine (pK_a 4.60 and 12.16) with 4,6-diamino-2-hydroxypyrimidine[9] (pK_a 6.5 and 11.5) or 4,5-diamino-2-hydroxypyrimidine (4.37 and 11.45), and 4-amino-6-hydroxypyrimidine (1.36 and 10.05) with 4,5-diamino-6-hydroxypyrimidine (1.34, 3.57, and 9.86) or 2,4-diamino-6-hydroxypyrimidine[52] (pK_a 3.33 and 10.78).

From the few data available, amino-mercaptopyrimidines are rather stronger acids and weaker bases than the corresponding amino-hydroxy compounds. Thus thiocytosine[30] (4-amino-2-mercaptopyrimidine) has pK_a 3.32 and 10.63, and its 4,5-diamino analogue [35](XXIII), pK_a 2.96 and 10.39.

An indication[42] of the depression (by the hydroxy group) of basic strength in 2-hydrazino-4-hydroxy-6-methylpyrimidine (pK_a 3.8) can be obtained by comparison with 2-hydrazino-4-methoxy-6-methylpyrimidine (pK_a 6.2) and 2-hydrazino-1,6-dihydro-1,4-dimethyl-6-oxopyrimidine (XXIV) (pK_a 5.5).

TABLE XVI. The pK_a Values^{a} of Some Pyrimidines^{b} in Water

Pyrimidine	Acidic pK_a	Basic pK_a	References
(unsubstituted), (20°)		1.31 *ca.* —63	7, 8, 8a
2-amino-, (20°)		3.54	7
4-amino-, (20°)		5.71	7
5-amino-, (25°)		2.60	43
4-amino-6-butylamino-^{c}		5.7	39
4-amino-5-carboxymethylamino-, (20°)	3.02	6.67	36
4-amino-6-chloro-, (20°)		2.10	37
4-amino-6-chloro-2-methylamino-, (20°)		3.73	9
2-amino-4-diethylaminoethylamino-^{h} (25°)		9.55 7.5	34
4-amino-1,6-dihydro-6-imino-1-methyl-, (20°)		11.98	38
4-amino-1,2-dihydro-1-methyl-5-nitro-2-oxo-, (20°)	10.57	< 1	30
4-amino-1,2-dihydro-1-methyl-2-oxo-		4.57	40
4-amino-1,6-dihydro-1-methyl-6-oxo-, (20°)		0.98	37
2-amino-4,5-dihydroxy-	9.60^{d}	4.06^{d}	44
2-amino-4,6-dihydroxy-	7.40^{d} or 7.3		44, 51
2-amino-4,5-dihydroxy-6-hydroxymethyl-	9.78^{d}	4.0^{d}	44
2-amino-4,6-dimethyl-, (20°)		4.85	7, 34
2-amino-4-hydroxy-, (25°)	9.42	4.01	20
4-amino-2-hydroxy-	12.2 or 12.16	4.45 or 4.60	24, 20
4-amino-6-hydroxy-, (20°)	10.05	1.36	53
4-amino-2-hydroxy-5-methyl-	12.4	4.6	24
4-amino-6-hydroxy-2-methylamino-, (20°)	11.03	3.22	52
2-amino-4-hydroxy-5-nitro-, (20°)	6.70		22
4-amino-2-hydroxy-5-nitro-, (20°)	7.34 or 7.39	< 3	22, 30
4-amino-2-mercapto-, (20°)	10.63	3.32	30
4-amino-2-methoxy-		5.3	24
4-amino-6-methoxy-, (20°)		4.02	37
2-amino-4-methyl-, (20°)		4.15	7
4-amino-6-methyl-		6.25	10
5-amino-4-methyl-		3.15	10
4-amino-6-methylamino-, (20°)		6.32	38
4-amino-6-methylamino-5-nitro-, (20°)		2.75	38
2-amino-5-nitro-, (20°)		0.35	9
2-amino-4,5,6-trihydroxy-	2.93^{d}		44
4-amino-2,5,6-trihydroxy-	9.0^{d}		44
5-amyl-4,6-dihydroxy-2-mercapto-, (28°)	2.47; 11.41		54a
Barbituric acid/5,5-diethyl-^{e}	7.89 or 7.80; 12.7		25, 19, 26
Barbituric acid/*N*-methyl-	4.2; 12.8		19
Barbituric acid/5,5-diethyl-*N*-methyl-	8.45 or 8.2		19, 26
4,6-bisdimethylamino-, (20°)		6,36; < 1	37

(Table continued)

TABLE XVI *(continued)*

Pyrimidine	Acidic pK_a	Basic pK_a	References
4,5-bismethylamino-, (20°)		6.03	53
4,6-bismethylamino-, (20°)		6.39	37
5-bromo-4-carboxy-2,6-dihydroxy-	2.21; 7.59		45
4-butylamino-6-butylamino-1,6-dihydro-1-methyl-[a]		12.8	39
4-butylamino-2-hydroxy-, (20°)	> 13	4.69	30
4-butylamino-2-hydroxy-5-nitro-, (20°)	7.80		30
4-butylamino-2-mercapto-, (20°)	11.13	~ 3.2	30
2-carboxy	2.85	−1.13	56
4-carboxy-2,6-dihydroxy-	~ 2.8 or 2.4; 9.45; > 13		24, 32
4-carboxy-6-hydroxy-	2.8	8.4	32
4-carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,4-dioxo-	0.8		33
2-chloro-		< 1	16
4-chloro-6-dimethylamino-, (20°)		2.42	37
4-chloro-6-hydroxy-, (20°)	7.43		37
4-chloro-6-methylamino-, (20°)		2.24	37
2,4-diamino-, (20°)		7.26	7
4,5-diamino-, (20°)		6.03; < 0	36
4,6-diamino-, (20°)		6.01	9
4,6-diamino-5-bromo-, (20°)		4.22	9
2,4-diamino-1,6-dihydro-1-methyl-6-oxo-, (20°)	11.07	3.61	52
2,4-diamino-5,6-dihydroxy-	*ca.* 9.2[d]	*ca.* 3.8[d]	44
2,5-diamino-4,6-dihydroxy-	*ca.* 8.9	*ca.* 3.6	51
2,4-diamino-6-hydroxy-, (20°)	10.78	3.33	51, 52
4,5-diamino-2-hydroxy-	11.45	4.37	35
4,5-diamino-6-hydroxy-	9.86	3.57; 1.34	35
4,6-diamino-2-hydroxy-, (20°)	11.98	6.49	52
4,5-diamino-6-hydroxy-2-methylamino-, (20°)	10.63	5.43	52
4,5-diamino-2-mercapto-	10.39	2.96	35
2,4-diamino-6-methyl-, (25°)		7.7	34
4,5-diamino-6-methylamino-, (20°)		5.93	38
4-diethoxymethyl-6-hydroxy-	7.8	1.5	32
4,5-dihydro-2,6-dihydroxy-, (25°)	~ 11.5		20
1,6-dihydro-1,4-dimethyl-2-methylthio-6-oxo-		0.9	54
1,2-dihydro-2-imino-1-methyl-, (20°)		10.75	2
1,4-dihydro-4-imino-1-methyl-, (20°)		12.22	2
1,2-dihydro-1-methyl-4-methylamino-2-oxo-		4.47	40
1,2-dihydro-1-methyl-2-oxo-, (20°)		2.50	12
1,4-dihydro-1-methyl-4-oxo-		2.02	14
1,6-dihydro-1-methyl-6-oxo-, (20°)		1.84	12

(Table continued)

TABLE XVI *(continued)*

Pyrimidine	Acidic pK_a	Basic pK_a	References
1,2-dihydro-1-methyl-2-thio-, (20°)		1.66	17
1,4-dihydro-1-methyl-4-thio-, (20°)		1.16	17
1,6-dihydro-1-methyl-6-thio-, (20°)		0.56	17
1,2-dihydro-1,4,6-trimethyl-2-oxo-		4.0	10
1,2-dihydro-1,4,6-trimethyl-2-thio-		3.15	10
2,4-dihydroxy-,[f] (20°)	9.38; 12		1
4,5-dihydroxy-, (20°)	7.48; 11.61	1.99	1
4,6-dihydroxy-, (20°)	5.4 or 5.35[d]		1, 44
4,6-dihydroxy-2-mercapto-, (28°)	2.8; 10.72		54a
2,4-dihydroxy-5-methyl-	9.9 or 9.94; > 13		20, 24
2,4-dihydroxy-6-methyl-	9.7 or 9.64	~ 1.2	10, 20
4,5-dihydroxy-2-methyl-	8.93[d]		44
4,6-dihydroxy-2-methyl-	6.55[d]		44
2,4-dihydroxy-6-methylsulphonyl-, (25°)	4.73		46
2,4-dihydroxy-5-nitro-, (20°)	5.3 or 5.55; 11.7 or 11.3		22, 24
4,6-dihydroxy-2-phenyl-	6.54[d]		44
Di(4-hydroxypyrimidin-6-yl) sulphide, (20°)	7.20; 8.48		37
4,6-dihydroxy-2-selenyl-[e]	3.74		25a
2,4-dihydroxy-6-sulphamoyl-, (25°)	5.43		46
2,4-dihydroxy-6-sulpho-, (25°)	7.26[g]		46
2,4-dihydroxy-6-trifluoromethyl-	5.7; *ca.* 13		23
2,4-dimercapto-, (20°)	6.46 or 6.4; 11.19		30, 47
2,4-dimercapto-6-methyl-, (20°)	6.87; 12.02		30
4,6-dimethyl-		2.7	11
2-dimethylamino-, (20°)		3.96	13
4-dimethylamino-, (20°)		6.35	13
4-dimethylamino-1,2-dihydro-1-methyl-2-oxo-		4.2	40
4-dimethylamino-6-hydroxy-, (20°)	10.42	1.22	37
4-dimethylamino-6-methoxy-, (20°)		4.29	37
4-dimethylamino-6-methylamino-, (20°)		6.39	37
2,4-diselenyl-	5.5		47
Dithiouracil/3-methyl-, (20°)	6.96		30
2-ethoxy-4-hydroxy-	8.2		24
4-ethoxy-2-hydroxy-	10.7		24
2-ethoxy-4-hydroxy-5-nitro-, (20°)	4.88		22
4-ethoxy-2-hydroxy-5-nitro-, (20°)	6.6		22
4-ethylamino-2-hydroxy-, (20°)	> 13	4.58	30
4-ethylamino-2-hydroxy-5-nitro-, (20°)	7.74		30
4-ethylamino-2-mercapto-, (20°)	11.13	3.10	30
2-ethylthio-1,6-dihydro-1-methyl-6-oxo-		0.9	54

(Table continued)

TABLE XVI *(continued)*

Pyrimidine	Acidic pK_a	Basic pK_a	References
2-hydrazino-1,6-dihydro-1,4-dimethyl-6-oxo-		5.5	42
2-hydrazino-4-methoxy-6-methyl-		6.2	42
2-hydrazino-4-hydroxy-6-methyl-		3.8	42
2-hydroxy-	9.17	2.24	15
4-hydroxy-, (20°)	8.59	1.85 or 1.69	12, 48
5-hydroxy-	6.78	1.87	14
4-hydroxy-2-mercapto-, (25°)	7.74; 12.7		49, 54
4-hydroxy-6-mercapto-, (20°)	4.33; 10.52		9
4-hydroxy-2-mercapto-6-methyl-	8.1		54
4-hydroxy-5-methoxy-, (20°)	8.60	1.75	1
4-hydroxy-2-methoxy-6-methyl-	8.4	~ 1.6	10
2-hydroxy-4-methyl-	9.8	3.15	10
4-hydroxy-6-methyl-	9.0	2.15	10
2-hydroxy-4-methylamino-, (20°)	> 13	4.55	30
4-hydroxy-6-methylamino-, (20°)	10.47	< 1.7	37
2-hydroxy-4-methylamino-5-nitro-, (20°)	7.76	< 1	30
4-hydroxy-6-methyl-2-methylthio-	7.9		54
4-hydroxy-6-methylthio-, (20°)	8.52		9
4-hydroxy-2-selenyl-	7.18		47
2-mercapto-, (20°)	7.14	1.35	16, 17
4-mercapto-, (20°)	6.9	< 0.68	16, 17
2-mercapto-4,6-dimethyl-	8.5	2.8	11
2-mercapto-4-methyl-	8.0	2.2	10
4-mercapto-6-methyl-	7.3	1.8	10
2-mercapto-4-methylamino-, (20°)	11.10	3.09	30
2-methoxy-		< 1	1
4-methoxy-, (20°)		2.5	12, 13
2-methoxycarbonyl-		—0.68	56
2-methoxy-4-hydroxy-6-methyl-	8.4		10
2-methoxy-4-methyl-		2.1	10
4-methoxy-6-methyl-		3.65	10
4-methoxy-6-methylamino-, (20°)		4.23	37
4-methyl-, (20°)		1.98	7
4-methyl-2-methylthio-		1.95	10
4-methyl-6-methylthio-		3.25	10
2-methylamino-, (22°)		3.82	13
4-methylamino-, (23°)		6.12	13
2-methylthio-, (20°)		0.88	17
4-methylthio-, (20°)		2.48	17
1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	4.6		19
1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxo		9.29	40
2,4,5,6-tetrahydroxy-	2.83 or 3.15;[d] 11		1, 21, 44
2-thiobarbituric acid-5-butyl-5-ethyl-, (28°)	7.37; 12.07[f]		54a

(Table continued)

TABLE XVI *(continued)*

Pyrimidine	Acidic pK_a	Basic pK_a	References
2-thiouracil/6-amino-1-methyl-, (20°)	9.84	0.0	37
2-thiouracil/1-ethyl-	8.7		54
2-thiouracil/3-ethyl-	8.65		54
2,4,5-triamino-		7.63; 2.56	35
2,4,6-triamino-, (20°)		6.84	7
4,5,6-triamino-		5.78; 1.47	35
2,4,5-trihydroxy-	8.11; 11.48		1
2,4,6-trihydroxy-	3.9; 12.5		1, 19
4,5,6-trihydroxy-2-mercapto-	2.56[d]		44
4,5,6-trihydroxy-2-methyl-	6.41[d]		44
4,5,6-trihydroxy-2-phenyl-	6.57[d]		44
Uracil/6-carbamoyl-1-methyl-	9.10		33
Uracil/6-carboxy-1-methyl-(*i.e.* 1-methylorotic acid)	0.7; 9.82		33
Uracil/6-carboxy-3-methyl-(*i.e.* 3-methylorotic acid)	< 1; 10.52		33
Uracil/1-methyl-	9.75 or 9.71		20, 24
Uracil/3-methyl-	9.95 or 9.99		20, 24
Uracil/1-methyl-5-nitro- (20°)	7.20		12

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[a] The second place of decimal is seldom significant.

[b] The list contains most of the pyrimidine pK_a values published before 1960.

[c] And analogues. The values being determined in 66% dimethylformamide are not strictly comparable with other figures.

[d] This pK_a and that of the corresponding 5-tetrahydropyran-2′-yloxy compound were determined[44] in 50% ethanol and are therefore not strictly comparable with other figures. In several cases[44] it is not evident whether a figure refers to proton loss or gain.

[e] The pK_a values for several other barbiturates are reported[25–29].

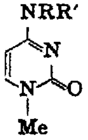
[f] Cf. 9.3 and > 13,[34] and 9.45.[20]

[g] Second acid pK_a only recorded.

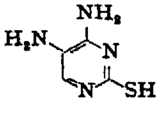
[h] Analogues and derivatives have similar values.[34]

[i] Five analogues have similar values.

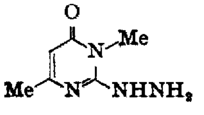
When 4-amino-1,2-dihydro-1-methyl-5-nitro-2-oxopyrimidine



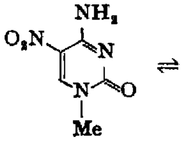
(XXII)



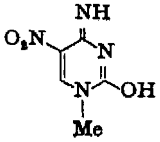
(XXIII)



(XXIV)



(XXV)



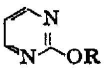
(XXVI)

(XXV) (basic pK_a < 1) is potentiometrically titrated with alkali an apparent acid pK_a value (10.57 ± 0.03) is obtained.[30] Whether this represents simply the pK_a of the hydroxy group in the tautomeric 1,4-dihydro-2-hydroxy-4-imino-1-methyl-5-nitropyrimidine (XXVI) (which is the minority constituent and quite possibly a zwitterion), or whether it is some function of the equilibrium of (XXV) and (XXVI), is unknown.

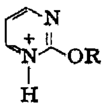
2. The Absorption Spectra of the Pyrimidines*

A. Ultraviolet Spectra: Experimental Studies

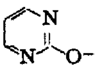
The ultraviolet absorption spectra of the pyrimidines have been extensively investigated, but prior to about 1950 most pyrimidine spectra were recorded without reference to the ionization constants of the compound studied. A useful bibliography of such early work has been given by Marshall and Walker.[10] All pyrimidines are basic, and thus they have both neutral (*e.g.* XXVII) and cationic (*e.g.* XXVIII) forms. Pyrimidines with a substituent bearing an ionizable hydrogen atom, namely, the carboxylic acids, amines, hydroxy-, and mercapto-compounds, can exist in these two forms and also in the anionic form (*e.g.* XXIX), a tautomeric neutral (*e.g.* XXX; R = H) or zwitterion (*e.g.* XXXa; R=H) form, and an isomeric cationic form (*e.g.* XXXI). Early pyrimidine spectra, measured in unbuffered aqueous solution or in solutions of arbitrary pH value, often refer to mixtures of two ionic species. Such spectra are misleading and incompletely characterize the compounds. Since about 1950 it has become customary to measure the ionization constants of the pyrimidines studied, and to determine the spectrum of each ionic form separately by adjusting the pH of the solution to be examined spectroscopically to a value at least two pH units above or below the pK_a value or values of the substance. The spectra obtained serve to characterize the pyrimidine examined, to



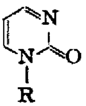
(XXVII)



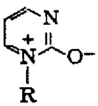
(XXVIII)



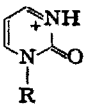
(XXIX)



(XXX)



(XXXa)



(XXXI)

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* By S.F. Mason, Chemistry Department, The University, Exeter, England.

correlate spectra with structure and permit unknown concentrations of the compound to be estimated from the maximum molar extinction coefficients of the absorption bands. The ultraviolet absorption spectra of the various ionic species of a number of pyrimidines, mainly monosubstituted, are given in Tables XVII and XVIII and in the Figures.

The absorption spectrum of pyrimidine in the near ultraviolet consists of two bands (Table XVII, Fig. 1), one at a slightly shorter wavelength than the 250 mμ band of benzene, although more intense, and the other, a weaker band, at longer wavelength. The weaker band is ascribed[55] to an electronic transition from a nitrogen lone-pair non-bonding orbital to an empty π-orbital of the ring (*i.e.* an $n \rightarrow \pi$ transition), because this band shifts to shorter wavelengths on changing from cyclohexane to aqueous solution. The lone-pair electrons of the pyrimidine nitrogen atoms are engaged in hydrogen-bonding in aqueous solution, and the radiation absorbed must be of higher energy (shorter wavelength) in order to provide not only the electronic transition energy but also the energy required to break the hydrogen bonds. The more intense shorter wavelength band in the spectrum of pyrimidine is ascribed[56] to an electronic transition from the occupied π-electron orbital of the ring with highest energy to the empty π-orbital with the lowest energy (*i.e.* a $\pi \rightarrow \pi$ transition), analogous to the transition giving rise to the 250 mμ absorption band of benzene. The band due to the $\pi \rightarrow \pi$ transition in both pyrimidine and benzene is not sensitive to a change of solvent.

On substitution, the $\pi \rightarrow \pi$ absorption band of pyrimidine is shifted to longer wavelengths and, in general, it increases in intensity, although a carboxy group in the 2- or the 5-position reduces the intensity[16] (Tables XVII and XVIII; Figs. 2 and 3). In the monosubstituted pyrimidines the bathochromic shift and the change in the molecular extinction coefficient of the $\pi \rightarrow \pi$ absorption band are characteristic of both the nature of the substituent and its position of substitution.[16] The spectra of the polysubstituted pyrimidines show[11] that the wavelength shifts and the intensity changes due to each substituent separately are approximately additive, provided that not more than one potentially tautomeric substituent is present in the compound. Thus the 4-methyl and the 2-chloro group give rise to bathochromic shifts of 1 and 9.5 mμ respectively and molecular extinction increases of 990 and 290 litre mole^{-1} cm.$^{-1}$ respectively,[11] whilst in 2-chloro-4,6-dimethylpyrimidine the observed wavelength shift is 11.5

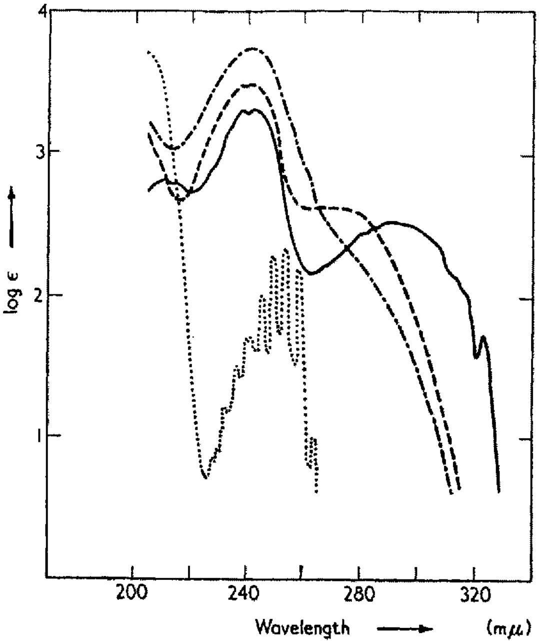


Fig. 1. The ultraviolet absorption spectra of benzene.......... in cyclohexane, and of pyrimidine ——— in cyclohexane, — — — — in water, pH 7, and —·—·—· in 4 N-sulphuric acid.

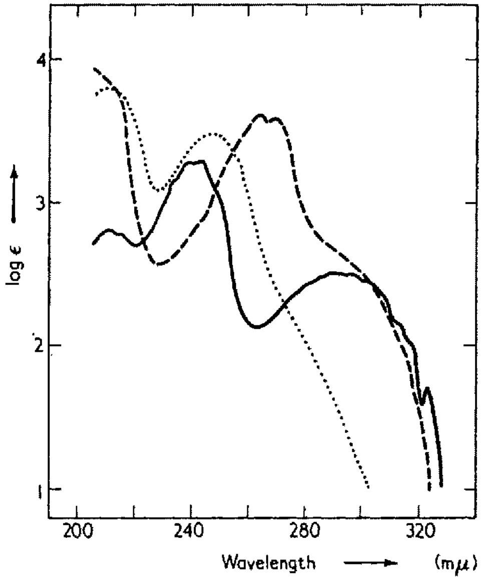


Fig. 2. The ultraviolet absorption spectra in cyclohexane of ——— pyrimidine,— — — — 2-methoxy-, and .... 4-methoxy-pyrimidine.

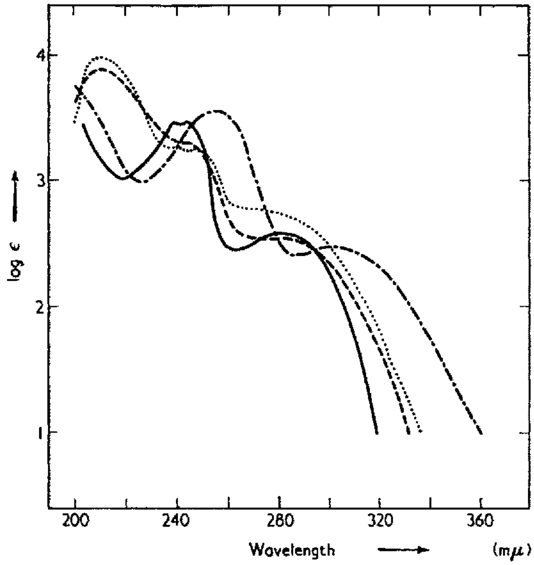
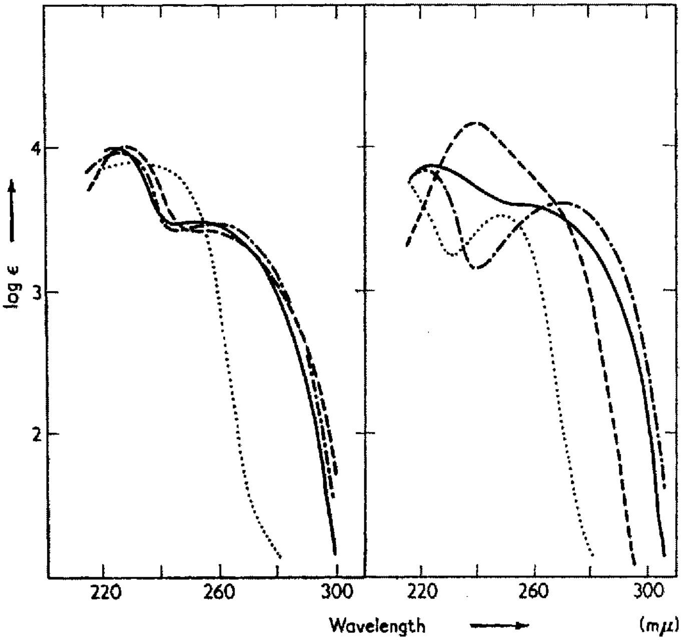


Fig. 3. The ultraviolet absorption spectra in ethanol of ——— pyrimidine, — — — — 2-carboxy-, —·—·— 4-carboxy-, and .... 5-carboxypyrimidine.



Figs. 4 and 5. The ultraviolet absorption spectra in water of ——— 4-hydroxypyrimidine, ... 4-methoxypyrimidine, — — — — 1,4-dihydro-1-methyl-4-oxopyrimidine, and —·—·— 1,6-dihydro-1-methyl-6-oxopyrimidine. Fig. 4 as cations; Fig. 5 as neutral molecules.

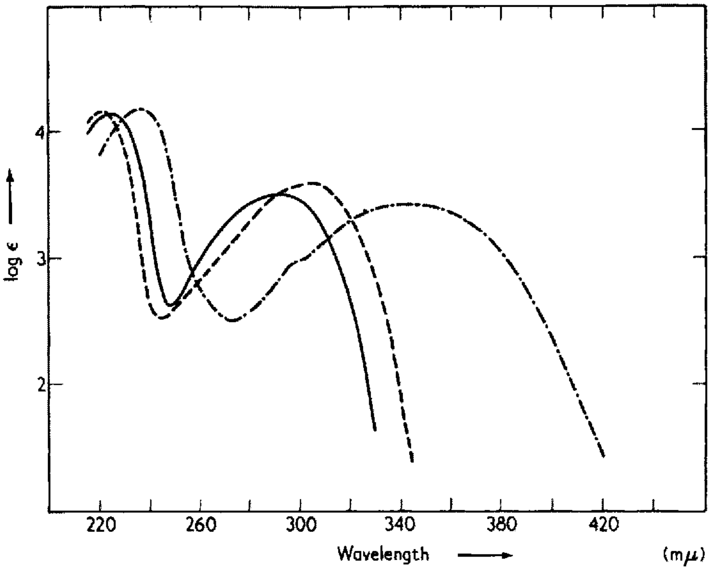


Fig. 6. The ultraviolet absorption spectra in aqueous solution of 2-aminopyrimidine ——— neutral molecule, and — — — — cation, and of .—.—.—. 1,2-dihydro-1-methyl-2-iminopyrimidine (neutral molecule).

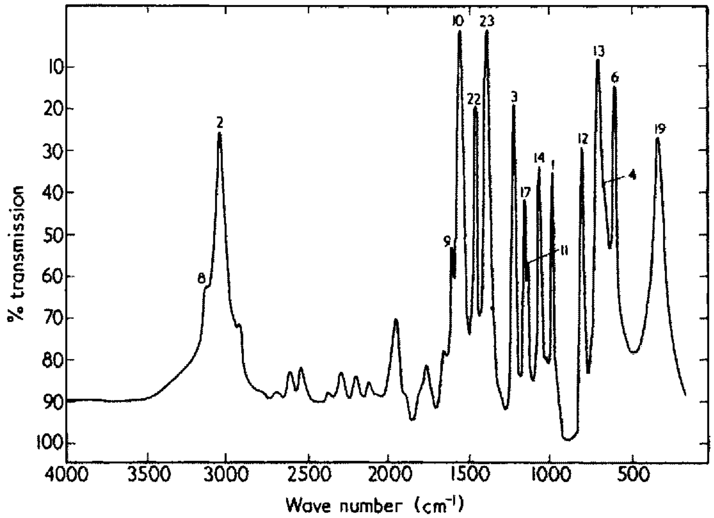
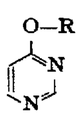
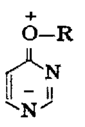


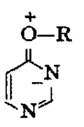
Fig. 7. The infrared spectrum of pyrimidine. The numbers of the bands refer to the vibration modes of Fig. 8, and the assignments of Table XIX.

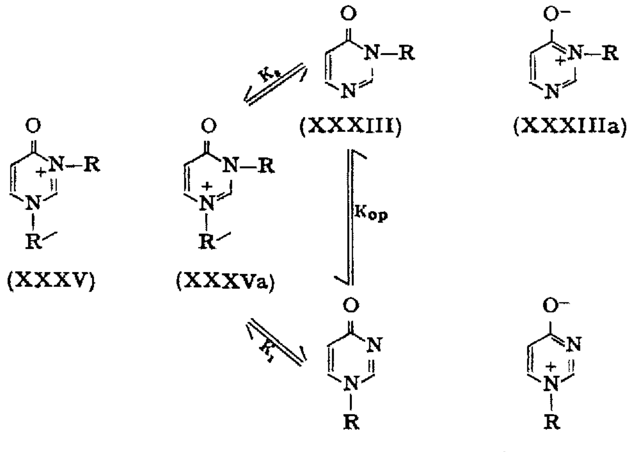
mμ and the intensity increase 2300 litre mole^{-1} cm.$^{-1}$, in excellent agreement with the values obtained by addition of the changes due to each substituent singly.[11] The additivity rule, in general, is only approximate, particularly for substituents which conjugate strongly with the pyrimidine nucleus, such as the amino, hydroxy, or mercapto group,[11] but the rule may aid the determination of the structures of isomeric pyrimidines, since the wavelength and the intensity of the pyrimidine $\pi \rightarrow \pi$ band varies markedly with the position of a given substituent in the ring.[16]

The ultraviolet absorption spectra of the amino-, hydroxy-, and mercapto-pyrimidines have been used extensively to determine the


(XXXII)


(XXXIIa)


(XXXIIb)



(XXXIII) (XXXIIIa)
(XXXV) (XXXVa)
(XXXIV) (XXXIVa)

tautomeric form of these compounds predominant in aqueous solution.[2,10,12,13,57] 4-Hydroxypyrimidine, for example, can exist in the enol form (XXXII; R=H) and in two different pyrimidone forms (XXXIII and XXXIV; R=H).* These forms have similar conjugated

---

* The forms (XXXIIa) and (XXXIIb) are part of the resonance hybrid of (XXXII), and (XXXIIIa) and (XXXIVa) contribute respectively to those of (XXXIII) and (XXXIV).

structures, but the charges upon the oxygen and nitrogen atoms vary from one form to another, so that the energies of the π-electron orbitals are different in the various forms. The transition of an electron from a filled to a vacant π-orbital, due to the absorption of radiation, requires an energy and occurs with a probability, which governs the intensity of absorption, that differs from one tautomeric species to another, resulting in different absorption spectra. For each tautomeric form an *O*- or *N*-methyl derivative (XXXII, XXXIII, XXXIV; R=Me) with a fixed structure can be prepared, and these derivatives are found to have different absorption spectra[12] in neutral aqueous solution (Fig. 5). The methyl group substituted on an exocyclic group or in the pyrimidine nucleus produces only small spectral changes,[16] and so the structure or structures of 4-hydroxypyrimidine in neutral aqueous solution may be inferred from a comparison of the spectra of 4-hydroxypyrimidine and the three methyl derivatives. The results (Fig. 5) show that the spectrum of 4-hydroxypyrimidine in neutral aqueous solution has the closest resemblance to that of 1,6-dihydro-1-methyl-6-oxopyrimidine,[12] and more detailed considerations, based upon the intensity of absorption at 240 mμ where (XXXIII; R=Me) shows a minimum, and (XXXIV; R=Me) a maximum in the spectral curve, suggest[14] that 4-hydroxypyrimidine in neutral solution exists as (XXXIII; R=H) and (XXXIV; R=H) in 5:2 ratio. The relative amount of the enol form (XXXII; R=H) cannot be estimated, but it is probably very small. The ionization constants of the *O*- and *N*-methyl derivatives of the mono-aza *N*-heteroaromatic compounds with a hydroxy group α or γ to the ring nitrogen atom indicate[1, 14] that the amide predominates over the enol tautomer in neutral aqueous solution by a factor in the range 10^3–10^7. In the cases of 2- and 4-hydroxypyrimidine where both of the nitrogen atoms are α or γ to the hydroxy group, the corresponding factor is probably very large, but it cannot be estimated from ionization-constant data since the method requires that the *O*- and *N*-methyl derivatives of a given *N*-heteroaromatic hydroxy compound should form cations with similar structures.[1, 14] The ultraviolet absorption spectra (Fig. 4) show that the cation of 4-hydroxypyrimidine and those of its two *N*-methyl derivatives have similar structures (XXXV; R, R'=H or Me) which differ from that of the cation of 4-methoxypyrimidine. Similar spectral evidence (Table XVIII) indicates that the cations of 2-hydroxypyrimidine and 1,2-dihydro-1-methyl-2-oxopyrimidine have the structure (XXXI; R=H and Me respectively) and that the cation of 2-methoxypyrimidine has the structure (XXVIII; R=Me). However, the ionization constants of 1,4-dihydro-1-methyl-4-oxo- and 1,6-dihydro-1-methyl-6-oxo-pyrimidine afford an estimate of the constant of equilibrium (K_{op}) between the two oxo forms (XXXIII; R=H) and (XXXIV; R=H), of 4-hydroxypyrimidine in neutral aqueous solution, independent of spectroscopic data.[14] If the equilibrium constant, K_{op}, is defined as

$$K_{\text{op}} = \frac{[\textit{ortho}\text{-quinonoid N–H form (XXXIII; R = H)}]}{[\textit{para}\text{-quinonoid N–H form (XXXIV; R = H)}]}$$

then

$$K_{\text{op}} = K_{(\text{XXXIII; R = H})}/K_{(\text{XXXIV; R = H})}$$

$$K_{\text{op}} = K_{(\text{XXXIII; R = Me})}/K_{(\text{XXXIV; R = Me})} \qquad (1)$$

where each K refers to the ionization constant of the structure designated in the subscripts. The ratio of the ionization constants of 1,4-dihydro-1-methyl-4-oxo-, and 1,6-dihydro-1-methyl-6-oxo-pyrimidine indicates that 4-hydroxypyrimidine in neutral solution exists as (XXXIII; R=H) and (XXXIV; R=H) in the ratio of 3:2, a value in satisfactory agreement with that derived from the spectral data.

Similar spectroscopic studies have shown[10, 16] that 2-hydroxypyrimidine assumes largely the amide (XXX; R=H) or zwitterion (XXXa; R=H) form in neutral aqueous solution, and that 5-hydroxypyrimidine tautomerizes[14] to the zwitterion form (XXXVI) to the extent of about 1 part in 50. The spectra[2] of 2- and 4-aminopyrimidine, compared with those of the corresponding exocyclic and nuclear *N*-methyl derivatives, indicate that the amino forms predominate in aqueous solution, and that the cations of these amines and their methyl derivatives have similar structures (*e.g.* XXXVII; R=H or Me). Thus the ionization-constant method may be employed to determine the tautomeric equilibrium constant, K_{t}, where

$$K_{\text{t}} = [\text{amine form}]/[\text{imine form}]$$

so that

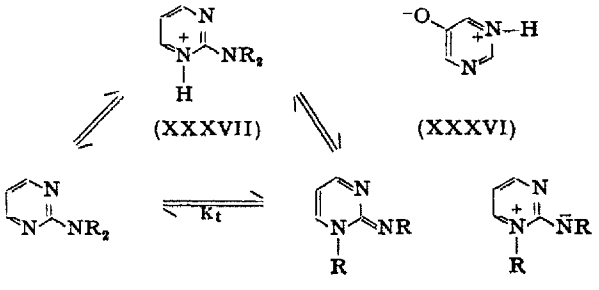
$$K_{\text{t}} = K_{\text{a}}(\text{amine form})/K_{\text{a}}(\text{imine form}) \qquad (2)$$

The ratio of the ionization constants (K_{a}) of the exocyclic and nuclear *N*-methyl derivatives of 2- and 4-aminopyrimidine (Table XVIII) indicates, from equation (2), that the amino predominates over the imino form in aqueous solution by a factor of about 10^6 in both cases.[2]

The spectra of 2- and 4-mercaptopyrimidine, and those of the available *S*- and *N*-methyl derivatives, indicate[10,16] that these compounds exist largely in the thio (=S) form in neutral aqueous solution.*

4-Mercaptopyrimidine and its 6-methyl derivative in neutral solution may exist as an equilibrium mixture of the two thio-forms, analogous to the pyrimidones (XXXIII) and (XXXIV), as their spectra show two high-intensity absorption bands[10,16] (Table XVIII), which may be due to the two thio-pyrimidone forms respectively, whilst the anionic and cationic species show a single high-intensity absorption band. The ionization constants of 2- and 4-mercaptopyrimidine and their *S*- and *N*-methyl derivatives do not give an estimate of the thiol–thione tautomeric equilibrium constant in aqueous solution, since the spectra show that the cations of these mercaptopyrimidines and their *S*-methyl derivatives have different structures, which are probably analogous to those of the cations of the corresponding oxygen analogues, *e.g.* (XXXI) and (XXVIII) respectively.

The pyrimidine carboxylic acids, like the pyridine acids,[58] probably exist in the zwitterionic form to some degree in aqueous solution, since the ionization constants of 2-carboxypyrimidine are separated by only 4 pK_a units, so that a fraction of the molecules at the isoelectric pH will possess simultaneously an ionized carboxy group and a protonated ring nitrogen atom.



(XXXVII) (XXXVI)

(XXXVIII) (XXXIXa) (XXXIXb)

B. Ultraviolet Spectra: Theoretical Studies

The ultraviolet spectra of the pyrimidines and other monocyclic azines have been interpreted theoretically by several workers.[55,56,58]

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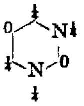
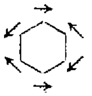
* A forthcoming paper of Albert and Barlin,[17] amply supports this thesis with data on previously unknown *N*-methylated reference compounds.

The weaker band at longer wavelengths in the spectrum of pyrimidine has been assigned to an $n \rightarrow \pi$ electronic transition not only on account of the observed solvent shifts (*v.s.*), but also because of the low intensity, the line-like character of the vibrational components of the band in the vapour-phase spectrum, and the effects of substituents upon the position of the band.[55, 56] The effect of substituents upon the wavelength and intensity of the stronger band at shorter wavelengths may be similarly understood if the band is ascribed to a $\pi \rightarrow \pi$ electronic transition, akin to that responsible for the weak 250 mμ band of benzene.[56]

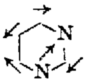
The effect of substituents upon the two absorption bands in the spectrum of pyrimidine differs markedly. Electron-donating substituents shift the $n \rightarrow \pi$ band to shorter wavelengths (a hypsochromic shift), and electron-attracting groups move the band to longer wavelengths (a bathochromic shift), neither type of substituent greatly changing the intensity of the band (Figs. 2 and 3).[56] Both electron-attracting and electron-donating substituents have a bathochromic effect upon the $\pi \rightarrow \pi$ band, and they give rise to increases and decreases in the intensity of the band depending upon the nature of the group and its position.[16]



(XL)



(XLI)



(XLII)

In the $n \rightarrow \pi$ transition an electron from a nitrogen lone-pair orbital is promoted to an empty π-orbital of the ring, so that the π-electron system in the excited state contains seven electrons, as opposed to six in the ground state. The charge distribution of the promoted electron in the excited state is given approximately in (XL). Thus some ring atoms become negatively charged in the excited state, notably the carbon atoms at the 4- and 6-positions, whilst only a small amount of charge (a zero amount in the approximation given by XL) finds its way to the 2- and the 5-positions. The excited state of the $n \rightarrow \pi$ transition is, therefore, considerably stabilized by electron-attracting and correspondingly destabilized by electron-donating substituents in the 4- or 6-position, resulting in large bathochromic and hypsochromic shifts of the $n \rightarrow \pi$ band respectively, whilst the same substituents in the

2- and the 5-position produce only small wavelengths shifts in the same directions. The observed shifts are in accord with the present interpretation, a 4-methoxy producing a large and a 2-methoxy group a small hypsochromic shift of the pyrimidine $n \rightarrow \pi$ band (Fig. 2), and a carboxyl group in the 4-position giving rise to a large and in the 2- or 5-position to a small bathochromic shift (Fig. 3).

The $\pi \rightarrow \pi$ band of pyrimidine and benzene in the near ultraviolet may be ascribed to an electronic transition from the highest occupied to the lowest unoccupied π-orbital of the ring, the probability of the transition being low in the case of benzene as the intensity of absorption is particularly weak (Fig. 1). The promoted electron may be regarded as proceeding round the benzene ring in a clockwise direction in the ground state and in an anti-clockwise direction in the excited state, the large change in the angular momentum of the electron required during the promotion rendering the transition improbable. The electronic motion gives rise to transition dipole moments, designated by the arrows in (XLI), but by vector addition these moments cancel out. In substituted benzenes, however, the moments at the position of substitution are enhanced, and the intensity of the absorption of radiation, which is proportional to the square of the resultant transition moment, is increased. The increase, ΔI, in the intensity of the 250 mμ band of benzene on mono-substitution may be related to a "spectroscopic moment", M, typical of the substituent,[59]

$$\Delta\, \mathrm{I} = \mathrm{M}^2 \tag{3}$$

In di-substituted benzenes the "spectroscopic moments" of each substituent may be added as vectors according to the directions of the arrows in (XLI), giving the intensity increases,

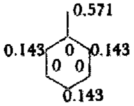
$$\Delta\, \mathrm{I} = \mathrm{M}^2_a + \mathrm{M}^2_b + 2\mathrm{M}_a\mathrm{M}_b \ (\textit{para}) \tag{4}$$

$$\Delta\, \mathrm{I} = \mathrm{M}^2_a + \mathrm{M}^2_b - \mathrm{M}_a\mathrm{M}_b \ (\textit{ortho, meta}) \tag{5}$$

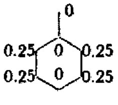
The "spectroscopic moments" of electron-attracting and electron-donating substituents are opposite in sign, some values relevant to the pyrimidine series being,[59] HO + 34, MeO + 31, Me + 7, Cl + 6, COOH — 28, aza-*N* — 38, in units of $\sqrt{(\text{litre mole}^{-1}\ \text{cm.}^{-1})}$. In general, both kinds of substituent shift the 250 mμ band of benzene to longer wavelengths, the bathochromic shift being proportional to the intensity increase and an additive constant.[60]

The pyrimidines may be regarded as "substituted" benzenes, and the intensity changes of the pyrimidine $\pi \rightarrow \pi$ band, due to substitution, should follow the vector addition rules, and the bathochromic shift produced by a given substituent should be proportional to the intensity change that it induces. In pyrimidine itself, the two ring nitrogen atoms *meta* to one another should produce the same intensity increase relative to benzene (eqn. 5) as the single ring nitrogen atom of pyridine. Experimentally, the observed maximum molar extinction coefficients of the $\pi \rightarrow \pi$ band are 2000 for pyridine and 2030 for pyrimidine, both in cyclohexane solution.[56] The resultant transition dipole moment for the $\pi \rightarrow \pi$ transition in pyrimidine has the direction given by the dashed arrow in (XLII), the full arrows giving the directions of the moments induced by electron-attracting groups at the various positions of substitution. For electron-donating substituents the full arrows in (XLII) should be turned through 180°. Thus electron-attracting substituents in the 2- or the 5-position should reduce the intensity of the pyrimidine $\pi \rightarrow \pi$ band, and produce only a small bathochromic shift, whilst in the 4-position such substituents should increase the intensity of the band and give rise to a larger bathochromic shift. These effects are observed experimentally in the case of the pyrimidinecarboxylic acids (Fig. 3). Conversely, electron-donating substituents should produce an intensity increase and a larger bathochromic shift of the pyrimidine $\pi \rightarrow \pi$ band in the 2- or 5-position than in the 4-position, where such substituents should bring about an intensity decrease. Experimentally[16] no 4-substituent reduces the intensity of the pyrimidine $\pi \rightarrow \pi$ band, but the observed intensity increases and bathochromic shifts induced by an electron-donating group are generally smaller when the substituent is in the 4- than when it is in the 2- or 5-position (Fig. 2, Table XVII).

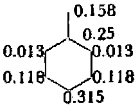
The success of the vector addition treatment of intensity and wavelength changes due to electron-donating substituents in the pyrimidine nucleus is only partial, as such compounds are not simple analogues of benzene. In the pyrimidines with a powerful electron-donating substituent, such as the amino, hydroxy, or mercapto group, the lone-pair electrons of the exocyclic atom are strongly conjugated with the nucleus, and these compounds are more closely hetero-analogues of the benzyl anion than of benzene. The ultraviolet absorption spectra of the amino, hydroxy, and mercapto derivatives differ from those of the pyrimidines with electron-attracting or weakly electron-donating substituents. In general, the $n \rightarrow \pi$ band is submerged, and two $\pi \rightarrow \pi$ bands are observed, the band at longer wavelengths being usually weaker in intensity than that at shorter wavelengths (Table XVIII, Figs. 4–6). For a given amino-, hydroxy-, or mercapto-pyrimidine the wavelength positions of the two $\pi \rightarrow \pi$ bands change on passing from one ionic or tautomeric species to another, and the wavelength shifts may be interpreted by assuming a benzyl anion model for these compounds.[61]



(XLIII)



(XLIV)



(XLV)

In the benzyl anion, an electron in the highest energy filled π-orbital, ψ_N, has its charge distributed according to (XLIII), and the first two $\pi \rightarrow \pi$ absorption bands of the anion should be due to the transition of such an electron from ψ_N to the two lowest energy unfilled π-orbitals, ψ_I and ψ_{II}, which have the one-electron charge distributions (XLIV) and (XLV) respectively. In terms of an empirical energy measure, β, the carbon–carbon resonance integral, the energy required for the transition $\psi_N \rightarrow \psi_I$ is β and for the transition $\psi_N \rightarrow \psi_{II}$ is 1.26β, the former thus giving rise to the absorption of radiation at longer wavelengths than the latter. The intensity of the shorter wavelength band should be the larger, although the absorption in both bands should be strong. On the replacement of carbon by hetero-atoms the general features of the benzyl anion spectrum should be preserved, but detailed changes in the wavelength positions of the absorption bands take place owing to differences of electronegativity between carbon and the hetero-atoms. Each of the π-orbitals, ψ_N, ψ_I, and ψ_{II}, on the replacement of carbon by hetero-atoms is stabilized by an amount of energy equal to the product of the electronic charge density at the position of substitution, given in (XLIII), (XLIV), and (XLV) respectively, and a constant specified by the nature and charge of the hetero-atom, $\Delta\alpha$, the Coulomb integral increment of the hetero-atom relative to carbon. The Coulomb integral increment is a measure of the electronegativity difference between a carbon and the hetero-atom. Values determined experimentally[14] are, for the neutral nitrogen atom, $\Delta\alpha_N = 0.6\beta$, and, for the positively charged nitrogen atom, $\Delta\alpha_{N^+} = 2.5\beta$. Only the inequalities in the values of the Coulomb integral increments are important for the present purpose, and, from the electronegativities of the elements, these are, — $\Delta\alpha_{N^+} > \Delta\alpha_O > \Delta\alpha_N > \Delta\alpha_S \simeq 0 \simeq \Delta\alpha_{O^-} > \Delta\alpha_{N^-} > \Delta\alpha_{S^-}$.

The wavelengths of the band maxima in the spectra of the amino-, hydroxy-, and mercapto-pyrimidines depend upon the energies, E_{I} and E_{II}, required for the electronic transitions, $\psi_{\mathrm{N}} \rightarrow \psi_{\mathrm{I}}$ and $\psi_{\mathrm{N}} \rightarrow \psi_{\mathrm{II}}$. For the 5-substituted pyrimidines these energies are,

$$E_{\mathrm{I}} = \beta + 0.571\Delta\alpha_{\mathrm{X}} - 0.25\Delta\alpha_{\mathrm{N}} - 0.25\Delta\alpha_{\mathrm{N}} \qquad (6)$$

$$E_{\mathrm{II}} = 1.26\beta + 0.134\Delta\alpha_{\mathrm{X}} - 0.118\Delta\alpha_{\mathrm{N}} - 0.118\Delta\alpha_{\mathrm{N}} \qquad (7)$$

where $\Delta\alpha_{\mathrm{x}}$ refers to the Coulomb integral increment of the exocyclic hetero-atom—oxygen in the hydroxy compound, nitrogen in the amine and $\Delta\alpha_{\mathrm{n}}$ refers to that of a nuclear nitrogen atom—neutral in the amine- and in the enol and anionic species of the hydroxy compound, and positively charged in the cationic forms and in the zwitterionic species of the hydroxy compound. Equations (6) and (7) indicate that each absorption band in the spectra of the various charged species of 5-hydroxypyrimidine should lie at wavelengths in the order: zwitterion > anion > cation > enol: and that each absorption band in the spectra of the neutral and cationic forms of 5-aminopyrimidine should lie at a longer wavelength than the corresponding band in the spectrum of the analogous ionic species of the hydroxy compound. The zwitterionic species of 5-hydroxypyrimidine is formed only incompletely at the isoelectric pH of the compound, so that the position of the shorter wavelength band cannot be determined for this species, the region being overlapped by absorption due to the predominant enol form. Apart from this omission, the predicted order of band positions in the spectra of the various ionic forms of 5-amino- and 5-hydroxypyrimidine are observed experimentally (Table XVII).

Equations analogous to (6) and (7) may be written for the transition energies of the absorption bands predicted for 2- and 4-amino-, hydroxy-, and mercapto-pyrimidine, and their various tautomeric and ionic forms. For a particular ionic species and a given position of substitution the predicted wavelength order for each of the two band positions: mercapto > amine > hydroxy: is supported by the experimental data (Table XVIII), although in some of the species of the 4-substituted derivatives the higher-intensity shorter-wavelength band overlaps and obscures the position of the longer-wavelength band

(Fig. 5). For a given group and position of substitution in the pyrimidine nucleus, the predicted shift of band wavelength position with change of ionic species is found experimentally without exception in the case of the longer-wavelength band and is generally observed in the case of the shorter-wavelength band.[61]

TABLE XVII. Electronic Absorption Spectra of the Neutral (N), Anionic (A), and Cationic (C) Forms of some Non-tautomeric Pyrimidines in Ethanol (EtOH), Cyclohexane (C_6H_{12}) and Aqueous Solution.[a]

Compound	pK_a	Solvent	Species	λmax (mμ)[b]	Emax[b]
Pyrimidine[56]	1.30	C_6H_{12}	N	298; 243	326; 2030
		EtOH	N	280; 243	373; 2930
		pH 7	N	271; 243	422; 3210
		H_0-0.8	C	242	5540
2-Methyl-[16]		pH 7	N	248	2900
		pH 0	C	251-252	7400
4-Methyl-[16]	2.0	pH 7	N	244	3400
		pH 0	C	244	5000
2-Chloro-[16]	1.0	pH 7	N	251; 209	2700; 5600
		EtOH	N	282-283; 252	170; 1500
Hydrochloride of 4-chloro-[16]		EtOH	C	248	3200
5-Chloro-[16]		pH 7	N	258; 211	2400; 7100
		EtOH	N	293; 258	330; 2200
5-Bromo-[16]		pH 7	N	261; 216.5	2900; 10,000
		EtOH	N	294; 261; 217.5	340; 2100; 7400
2-Phenyl-[16]		pH 7	N	251	15,000
		pH 0	C	287; 256-258	8300; 11,000
4-Phenyl-6-methyl-[62]		EtOH	N	273	18,000
5-Phenyl-[62]		EtOH	N	256	12,100
2-Methoxycarbonyl-[56]	0.68	C_6H_{12}	N	290; 247	370; 1840
		pH 7	N	*270*; 245	*382*; 2300
		H_0—1.5	C	247	4900
2-Carboxy-[56]	2.85	EtOH		277; 246	374; 2120
	—1.13	pH 7	A	*275*; 246	*410*; 2620
		pH 0.8	N	270; 240	*441*; 2690
4-Carboxy-[16, 56]		EtOH		303; 256	295; 3820
				253	3300
5-Carboxy-[16, 56]		EtOH		*280*; 247	*561*; 1870
		pH 13	A	245	2000

[a] Where pH or acidity function (H_0) values are given, aqueous solution is implied.

[b] Values in italics refer to shoulders or inflexions.

TABLE XVIII. Electronic Absorption Spectra of the Neutral (N), Cationic (C), Anionic (A), and Zwitterionic (Z) Forms of some Potentially Tautomeric Pyrimidines and of their Methyl Derivatives with Fixed Structures in Ethanol (EtOH), Cyclohexane (C_6H_{12}), and in Aqueous Solution.[a]

Compound	pK_a	Solvent	Species[b]	λmax(mμ)[c]	εmax[c]
2-Methoxypyrimidine[16,56,61]	*ca.* 1	C_6H_{12}	N	*295*; 264	*400*; 4180
		pH 7	N	267	4530
		H_0—1.2	C	273	5020
2-Hydroxypyrimidine[12]	2.24	pH 0	C	309	5700
	9.17	pH 13	A	292; 220	4600; 11,700
		pH 6	Z	298; 212	4750; 10,820
1,2-Dihydro-1-methyl-2-oxopyrimidine[12]	2.50	pH 0.3	C	313	7100
		pH 6	Z	302; 215	5400; 10,000
4-Methoxypyrimidine[13,56,61]	2.5	C_6H_{12}	N	*270*; 248	*274*; 3100
		pH 6.9	N	248	3370
		pH 0	C	*240*; 227	*6700*; 7750
4-Hydroxypyrimidine[13]	1.69	H_0—1.2	C	251; 224	2970; 9840
	8.60	pH 13	A	263; 227	3280; 11,100
		pH 6.2	Z	*260*; 223	*3740*; 7320
1,4-Dihydro-1-methyl-4-oxopyrimidine[12,56,61]	2.02	pH 0	C	*250*; 229	*2650*; 10,200
		pH 6	Z	240	14,600
1,6-Dihydro-1-methyl-6-oxopyrimidine[12]	1.84	H_0—0.5	C	258; 226	2940; 9080
		pH 5	Z	269; 221	3900; 6810
5-Hydroxypyrimidine[56,61]	1.87	EtOH	N	276; 218	5330; 9970
	6.78	pH 4.32	N + Z	*325*; 271; 214	*107*; 4750; 9720
		pH 9.5	A	304; 238	4450; 11,240
		H_0—0.25	C	285; 223	4700; 6950
2-Aminopyrimidine[13]	3.54	pH 7	N	292; 224	3200; 13,000
		pH 1	C	302; 221	4000; 14,800
1,2-Dihydro-2-imino-1-methylpyrimidine[2]	10.75	pH 7	C	301; 222	4300; 13,000
		pH 13	Z	345; 236	2900; 15,500
2-Dimethylaminopyrimidine[13]	3.96	pH 7	N	318; 243	2200; 18,000
		pH 1	C	324; 235	2950; 17,000
4-Aminopyrimidine[16]	5.71	pH 13	N	*268*; 233	*5200*; 18,200
		pH 0	C	246	18,600

(Table continued)

TABLE XVIII *(continued)*

Compound	pK_a	Solvent	Species[b]	λmax(mμ)[c]	Emax[c]
1,4-Dihydro-4-imino-1-methylpyrimidine[2]	12.22	pH 7	C	250	16,000
		pH 13	Z	*315*; 253	*620*; 16,200
4-Dimethylaminopyrimidine[13]	6.35	pH 9.3	N	286; 250	3600; 16,600
		pH 3.1	C	262	16,200
5-Aminopyrimidine[43]	2.60	pH 7	N	298; 236	3100; 11,000
		pH 1	C	332; 253	3700; 14,400
4-Methyl-2-methylthiopyrimidine[10]	1.95	pH 7	N	*280*; 250; 210	*2500*; 14,000; 4000
		pH 0	C	304; 253; 215	4600; 14,000; 6000
2-Mercapto-4-methylpyrimidine[10]	2.2	pH 0	C	366; 285; 221	1400; 25,000; 8000
	8.0	pH 11	A	*300*; 269	*2500*; 17,000
		pH 4.7	Z	338; 277; 215	3300; 19,000; 10,000
1,2-Dihydro-1,4,6-trimethyl-2-thiopyrimidine[10]	3.15	pH 0	C	355; 283; 225	2600; 23,000; 8900
		pH 7	Z	332; 277; 220	4500; 17,000; 11,000
4-Methyl-6-methylthiopyrimidine[10]	3.25	pH 7	N	277; 213	10,000; 7000
		pH 1	C	300; 223	20,000; 6600
4-Mercapto-6-methylpyrimidine[10]	1.8	pH 0	C	312	18,000
	7.3	pH 11	A	292	16,000
		pH 4.7	Z	322; 288	11,000; 10,000

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[a] Aqueous solution is implied by inclusion of a pK_a or H_0 value.

[b] The term, "neutral species" (N) is used generically for enol, thiol, and amine forms (*e.g.* XXVII, XXXVIII, R = H or Me), and "zwitterionic species" (Z) is used similarly in a wide sense for amide, thioamide, and imine forms (e.g. XXX, XXXIX, R = H or Me) which are related (*e.g.* XXXa, XXXIXb) to completely zwitterionic species (*e.g.* XXXVI).

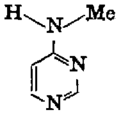
[c] Values in italics refer to shoulders and inflexions.

C. Infrared Spectra of Substituted Pyrimidines

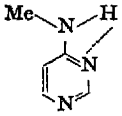
The infrared absorption spectra of the pyrimidines, like the ultraviolet, afford reference data for the identification and the quantitative estimation of the compounds, and they aid the elucidation of isomeric and tautomeric structures. In the latter application the two spectroscopic methods are to some degree complementary, for the ultraviolet spectra refer to electronic transitions within or into the conjugated π-electron system of the compound, whilst the infrared spectra are due to vibrational transitions. Many groups containing single bonds or isolated multiple bonds give rise to a characteristic absorption band in the infrared, falling within a limited frequency range, but the infrared absorption of strongly conjugated multiple bonds cannot, in general, be ascribed to a particular conjugated group of the molecule.

The infrared spectra of many substituted pyrimidines have been measured,[63] and a number of detailed infrared studies have been made of the potentially tautomeric pyrimidines.[2, 12, 13, 64, 65] 2-Hydroxypyrimidine and the 4-isomer in the solid state and in chloroform solution give infrared absorption bands due to the C=O and N–H bond stretching vibrations,[13, 66] and so these compounds in the state examined exist predominantly in the amide form (*e.g.*, IV; R=H). *N*-Heteroaromatic hydroxy compounds with the hydroxyl group α to a ring nitrogen atom have been found[66] in chloroform solution, to give a N–H stretching vibration absorption band in the range 3360–3420 cm.$^{-1}$, whilst the corresponding band in the case of the γ-isomers lies in the range 3415–3445 cm^{-1}. By means of this correlation it has been established[66] that 4-hydroxypyrimidine in chloroform solution assumes mainly the ortho-quinonoid amide form (XXXIII; R=H), the amount of the para-quinonoid isomer (XXXIV; R=H) and the enol form (XXXII; R=H) being undetectable. The vibration spectra (infrared and Raman) of the hydrochlorides[67] and the sodium salts[68] of 2- and 4-hydroxypyrimidines have been determined. In the cations the proton is attached to the double bonded N atom, and it has been suggested that in the anions the negative charge resides essentially on the nitrogen atom adjacent to the C=O group.[68]

The aminopyrimidines in chloroform or carbon tetrachloride solution give two absorption bands in the N–H stretching vibration region of the infrared.[2, 18, 69] These bands have positions (3400 and 3500 cm.$^{-1}$ respectively) and intensities ($\varepsilon_{\max}$ 40–120 litre mole^{-1} cm.$^{-1}$) corresponding to those of the symmetric and antisymmetric stretching vibrations, respectively, of the primary amino group in aromatic amines, the N–H group of *N*-heteroaromatic imines absorbing at a lower frequency (~ 3300 cm.$^{-1}$) and with a lower intensity (ε_{max} ~ 10 litre mole^{-1} cm.$^{-1}$).[18,69] The HNH bond angle, calculated from the absorption frequencies, suggests that the lone-pair electrons of the amino group are more completely conjugated with the nucleus in 2- and 4-aminopyrimidine than in the 5-isomer. The HNH bond angle of 119.3° for 2- and 4-aminopyrimidine indicates nearly trigonal hybridization in the σ bonds of the amino group, leaving the lone-pair electrons in a nitrogen $2p$ orbital, which can conjugate completely with the π-electron system of the nucleus, whilst the corresponding angle in the 5-isomer is 111.8°, as in aniline, suggesting nearly tetrahedral hybridization in the σ bonds of the amino group, with the lone-pair electrons in a s–p hybrid orbital of which only the p-component can conjugate with the nucleus.[18,69] The HNH bond angle in 2- and 4-aminopyrimidine may be opened up by hydrogen-bonding between the hydrogen atoms of the amino group and the ortho-nuclear nitrogen atoms, since the calculated overlap of the 1s orbital of the former and the sp^2 lone-pair orbital of the latter is 0.077, representing a not inconsiderable bonding.[18,69] Experimentally it is found[2] that 4-methylaminopyrimidine in carbon tetrachloride solution gives two closely adjacent bands (3443 and 3466 cm.$^{-1}$) which are probably due to the N–H stretching vibrations of the hydrogen-bonded (XLVII) and the free (XLVI) forms of the amine respectively. The two forms appear to co-exist in comparable proportions, judging from the similar intensities of the two absorption bands, and it is likely that the stabilization conferred by hydrogen-bonding in (XLVII) is offset by the destabilization due to steric hindrance between the methyl- and the *ortho*-CH-group.



(XLVI)



(XLVII)

D. The Vibrations of the Pyrimidine Nucleus

The infrared absorption and Raman emission spectra of pyrimidine have been measured, and the observed bands have been assigned to the vibrations of the nucleus.[70] The more recently determined vibration spectrum of pyrimidine hydrochloride is similar to that of the neutral molecule.[67] A non-linear polyatomic molecule of *N*-atoms has (3N—6) vibrations, so that pyrimidine has 24 independent vibrations (Fig. 8). Not all of these vibrations give rise to an infrared absorption band, which requires a change of dipole moment with the vibration, but all give a Raman emission band, which depends upon a change of polarizability with the vibration. Pyrimidine has two elements of symmetry, namely, the plane of the molecule, and a two-fold axis of rotation through the 2- and the 5-position, these properties placing it in the symmetry class, C_{2v}. The vibrations of pyrimidine fall into four symmetry classes, A_1, B_1, A_2 and B_2. They either occur in the molecular plane or are out-of-plane (subscripts 1 and 2 respectively), and they are either symmetric or antisymmetric with respect to rotation about the two-fold axis (A and B respectively). Symmetry rules show[71] that there are 9 totally symmetric vibrations (A_1), 8 of the B_1 form, 2 of A_2 symmetry, and 5 of B_2. The two A_2 vibrations do not give rise to absorption in the infrared, since a transient dipole generated by such a vibration in one half of the molecule is cancelled by an equal and opposite dipole in the other half (*e.g.* No. 20, Fig. 8). The A_2 vibrations are the only ones which appear in the Raman but not the infrared spectrum of pyrimidine, so they may be readily identified. The A_1 vibrations are similarly ascertained, since only these vibrations give polarized Raman emission bands. The identification of the B_1 and B_2 classes, and the assignment (Table XIX) of the particular Raman and infrared bands (Fig. 7) to the individual vibration modes (Fig. 8), have been made[70] from a knowledge of the characteristic group frequencies and previous assignments for pyridine and benzene.

A knowledge of the frequencies of the pyrimidine vibration modes allows the Raman and infrared spectra of substituted pyrimidines to be interpreted with more certainty. For example, the carbon and hydrogen atoms at the 2- and the 5-position of pyrimidine do not move in the vibration modes, Nos. 7, 8, 9, 11, 18, and 20, (Fig. 8). Accordingly, these modes remain unchanged in the 2- and 5-mono- and 2,5-disubstituted pyrimidines and give Raman and infrared bands at frequencies close to those observed for the unsubstituted nucleus.

The molal thermodynamic properties of a molecule, such as the entropy and heat capacity, may be calculated from its vibration frequencies and moments of inertia, and may then be compared with the values measured calorimetrically. The only azine for which such a study has been reported to date is pyridine.[72]

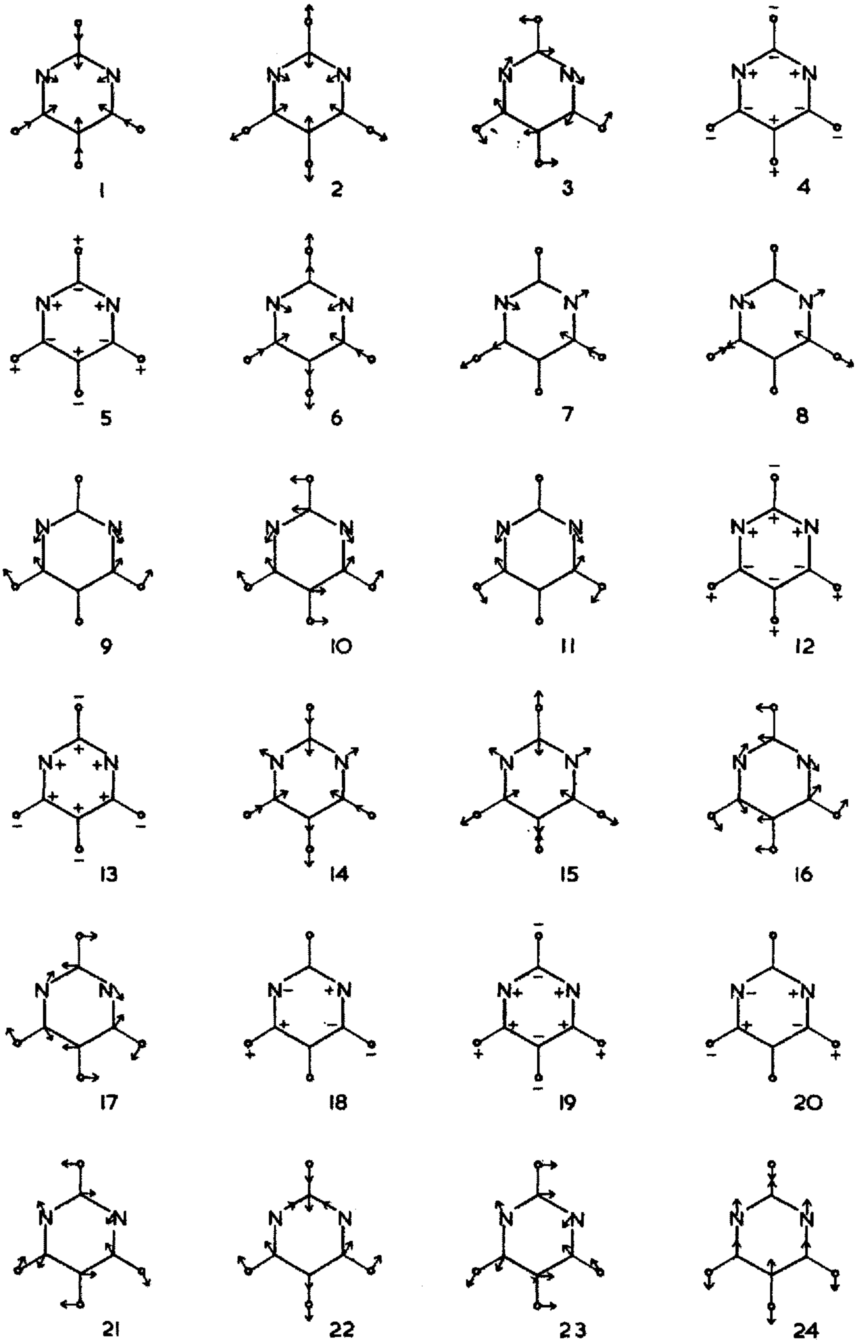


Fig. 8. The vibration modes of pyrimidine. The frequencies and the symmetries of the modes are given in Table XIX.

TABLE XIX.[a] Frequencies of the Bands Observed in the Infrared Absorption and Raman Emission Spectra of Pyrimidine and their Assignment to the Active Vibrations of the Molecule

Raman (liquid)		Infrared (liq. or soln.)				
ν (cm.⁻¹)	Rel. Intensity	ν (cm.⁻¹)	Rel. Intensity[b]	Assignment[c]	Symmetry[d] in C_{2v}	Schematic description
		344	vs	19	B_2	Ring
394	2			18	A_2	Ring
567	0			7	B_1	Ring
623	2p	624	vs	6	A_1	Ring
679	6	679	vs	4	B_2	Ring
		710	m, sh			
724	1	722	vvs	13	B_2	H bend
		795	w			
814	0	806	vs	12	B_2	H bend
870	0			20	A_2	H bend
		980	w, sh	5	B_2	H bend
991	10p	991	vs	1	A_1	Ring
1021	0	1021	vw	21	B_1	H bend
1053	8p	1055	m	14 in resonance	A_1	Ring
1074	8p	1071	vs	with (13 + 19)	A_1	
1137	4p	1141	m	11	A_1	H bend
1160	1	1161	s	17	B_1	H bend
1227	3	1227	vs	3	B_1	H bend
1371	0			16	B_1	Ring
1398	0	1402	vvs	23	B_1	Ring
1466	1	1467	vs	22	A_1	Ring
1566	5	1570	vvs	9, 10	A_1, B_1	Ring
		1612	s	(12 + 12)	A_1	
		1672–2622[e]	vw–m			
2917	1	2925	m	(22 + 22)	A_1	
3001	1			15	A_1	H stretch
		3027	m	(22 + 9 or 10)	A_1 or B_1	
3038	1			24	A_1	H stretch
3048	10p	3047	s	2	A_1	H stretch
		3095	m	8	B_1	H stretch
3129	2	3135	m	9,10 + 9,10	A_1, B_1	

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[a] Data and assignments quoted from ref. 70.

[b] w = weak, m = medium, s = strong, v = very, sh = shoulder, p = polarized.

[c] The numbers in this column refer to the vibration modes of Fig. 8.

[d] The A_1 and B_1 vibrations take place in the plane of the molecule, the former being symmetric and the latter antisymmetric with respect to the two-fold axis of rotation through the 2- and the 5-positions. The A_2 and B_2 modes are out of plane vibrations, the former being symmetric and the latter antisymmetric with respect to the two-fold axis.

[e] Fifteen weak to medium unassigned bands due to combinations and overtones of frequencies due to fundamental vibrations.

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APPENDIX

Systematic Tables of Simple Pyrimidines

Introduction

These Tables (XX to LVI) constitute as complete a list as possible of the simple pyrimidines described up to 1957, with the addition of important compounds described up to 1960. The tables were prepared from *Beilstein** to 1929, from the indices of *Chemical Abstracts* from 1930 to 1957, and (incompletely) from original papers thereafter. Melting (or boiling) points and a selection of the best references are given for each pyrimidine.

Pyrimidines Excluded from the Tables

To keep the tables within manageable proportions, the following categories of pyrimidine have been generally excluded on the grounds that they are not simple.

Those reduced in the nucleus (hydropyrimidines).
Those with heterocyclic substituents (except piperidino).
Those fused with other ring systems.
Those with more than 6 carbon atoms in a substituent (except benzyl).
Those with substituted phenyl groups.
Those with difunctional groups (except the carboxymethylthio).
Those with substituted ureido or thioureido groups.
Barbituric acid derivatives with more than 2 carbon atoms in a substituent attached at position 1, 3, or 5. (This exclusion also applies to

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* Information from *Beilstein* was obtained through a full card-index prepared and very kindly loaned to the author by Dr. J. English and Dr. J. H. Clark of American Cyanamid Company.

such derivatives of 2- or 4-thiobarbituric acid, and 2- or 4- aminobarbituric acid.)
Those with two alkyl (or aryl) substituents at position 5 (except 5,5-dimethylpyrimidines).

Terms Used in Tables

For the sake of brevity the title of each table makes use of inclusive terms for the type of substituent.

ALKYL includes alkyl, aryl, and cycloalkyl groups.

AMINO includes amino, imino, alkylamino, dialkylamino, anilino, hydrazino, acylamino (*e.g.* acetamido), ureido, thioureido, and amidino groups.

CARBOXY includes carboxy (carboxylic acids). alkoxycarbonyl (esters), carbamoyl (amides), hydrazinocarbonyl (hydrazides), chlorocarbonyl (acid chlorides), cyano (nitriles), *C*-formyl (aldehydes), dialkoxymethyl (acetals of aldehydes), *C*-acyl (ketones), cyanato, isocyanato, thiocyanato, isothiocyanato, and carboxymethylthio groups.

HALOGENO includes only the four halogens.

NITRO includes nitro, nitroso (or isonitroso), azo, and nitroamino groups.

OXY includes hydroxy (and hydroxyalkyl), alkoxy (and alkoxyalkyl), aryloxy, acyloxy (e.g. acetoxy), and oxo groups.

SULPHONYL includes alkylsulphonyl (sulphones), sulpho (sulphonic acids), sulphino (sulphinic acids), sulphamoyl (sulphonamides), and alkoxysulphonyl (sulphonic esters) groups.

THIO includes mercapto, alkylthio (thio ethers), and acylthio groups as well as their selenium analogues.

In the melting point column, boiling points are indicated by a pressure in mm. or *at.* (atmospheric) *e.g.* 130°/*at.* or 40°/30 mm. Abbreviations for derivatives (such as *pic.* for picrate, or *hy.* for hydrate) are self-explanatory. A m.p. given *e.g.* as 98–101° indicates the range of melting, one given *e.g.* as 40° *or* 108° indicates a divergence of figure in the literature, and one given *e.g.* as 91° *to* 108° indicates the limits of divergence in a literature of three or more papers.

The term melting point includes all variations such as "melting with decomposition at", "decomposition at" and the like, because these phrases are inexact, and are used so differently by different authors as to be often confusing. The use of "greater than" (*e.g.* > 300°) in the melting-point column indicates that the substance either melted above, or did not melt below, this temperature.

The Use of the Tables. With one exception, all tables include *C*-alkyl derivatives of the type of pyrimidine listed. Thus for example Table XXI (Aminopyrimidines) contains not only those with amino-type substituents but also their *C*-alkyl derivatives; similarly Table XLIV (Carboxy-Thiopyrimidines) contains such a compound as 5-ethoxycarbonyl-2-mercapto-4-methylpyrimidine.

There is a table for each category of pyrimidine with one type of substituent, a table for each possible combination of two types of substituent, but where three types of substituent are present, the tables are triple combinations of only Amino, Oxy, Thio, and Others ("Minor Functional Groups"). Thus 2-acetamido-4-chloro-5-phenoxypyrimidine occurs in Table XXXVII (Amino-Oxypyrimidines with Other Functional Groups), 4-amino-2-chloro-5-ethoxycarbonylpyrimidine occurs in Table XL (Aminopyrimidines with Two Minor Functional Groups), and 2-ethylthio-4-hydroxy-5-iodopyrimidine occurs in Table LIV (Oxy-Thiopyrimidines with Other Functional Groups). Use of the tables is greatly facilitated at first by reference to the Contents at the front of this volume. The principles of the nomenclature used have been outlined in Chapter I, Sect. 2. In the tables (only) when a compound is necessarily named as a derivative of uracil, 2-thiouracil, barbituric acid, etc., the trivial name precedes the substituents thus: 2-thiouracil/1-ethyl-, or barbituric acid/5,5-dimethyl-, the entries being under respectively "t" and "b" in alphabetical sequence.

TABLE XX. Alkyl and Aryl Pyrimidines

Pyrimidine	M.p.	Reference
4-amyl-	130–135°/0.05 mm.	105
5-amyl-4,6-diethyl-2-methyl-	*pic.* 171–172°	129
2-benzyl-4,6-dimethyl-	80°; 274°/*at.*	10
2-benzyl-4-methyl-	36–37°; 135–140°/5 mm.	475
4-benzyl-6-methyl-	*pic.* 148°	475, 105
5-benzyl-2-methyl-4-phenyl-	197°	449
5-butyl-4,6-diethyl-2-methyl-	*pic.* 98–99°	129

(*Table continued*)

TABLE XX *(continued)*

Pyrimidine	M.p.	Reference
5-s-butyl-4,6-diethyl-2-methyl-	*pic.* 162–163°	129
4-t-butyl-2,6-diphenyl-	90–92°	384
2-butyl-4-methyl-	130–135°/5 mm.	105
2,4-diethyl-	68–72°/15 mm.	1637
4,6-diethyl-2,5-dimethyl-	*pic.* 106–107°	129
4,6-diethyl-5-isobutyl-2-methyl-	*pic.* 165–166°	129
2,4-diethyl-5-methyl-	204–205°/*at.*	306, 307, 322
4,6-diethyl-2-methyl-5-propyl-	*pic.* 124–125°	129
2,4-diisopropyl-	77–84°/15 mm.	335, 1637
2,4-dimethyl-	—4°; 150°/*at.*; 37–41°/ 13 mm.; *pic.* 137–140°	712, 335, 1637, 472
2,5-dimethyl-	19°; 59–60°/13 mm.	453
4,5-dimethyl-	170° *or* 159°/*at.*; *pic.* 111°	468, 2163, 2108
4,6-dimethyl-	0°; 159°/*at.*; *pic.* 143°	431, 430, 429, 831, 434, 1638, 1281, 1639, 301
4,6-dimethyl-2-phenyl-	83–84°; 163°/17 mm.	138,1639,457,831,10
4,6-dimethyl-5-phenyl-	61–63.5°; 157–159°/ 215 mm.	1638
2,4-dimethyl-6-propyl-	75°/10mm.; *pic.* 85–86°	1640
2,4-diphenyl-	58–59°; 190–194°/3 mm.	335, 1637
4,6-diphenyl-	102–103°	301
4-ethyl-	158–159°/*at.*; *pic.* 85–87°	301
4-ethyl-2,6-dimethyl-	72–76°/11 mm.; *pic.* 86–87°	139
2-ethyl-4-methyl-	160°/*at.*	452
5-ethyl-4-methyl-	193°/*at.*	836
4-ethyl-6-phenyl-	162–165°/12 mm.; *pic.* 185–187°	301
5-ethyl-2,4,6-triphenyl-	127°	49
5-ethynyl-4-methyl-2-phenyl-	64–65°	458
2-methyl-	—5°; *ca.* 135°/*at.*; *pic.* 105–106°	126, 1641, 474, 644, 453, 440, 438
4-methyl-	141°/*at.*; *pic.* 132°	429, 476, 614, 474, 644, 526, 98, 440, 1642, 431, 438, 606, 487
5-methyl-	28–30°; 152–154°/*at.*	438, 440, 487
4-methyl-2,6-diphenyl-	94°	450, 455
4-methyl-2-phenyl-	22.5°; 279°/*at.*	455, 472, 831
4-methyl-6-phenyl-	45–48°; 146–148°/12 mm.; *pic.* 203–204°	448, 301, 455, 457
5-methyl-2,4,6-triphenyl-	182°	49, 384
2-phenyl-	39°	34, 644, 1643, 1644, 606

(Table continued)

TABLE XX *(continued)*

Pyrimidine	M.p.	Reference
4-phenyl-	61–62° *or* 65–66° 140–145°/15 mm.	34, 476, 301, 606, 428
5-phenyl-	*pic.* 120°	34, 457
2-phenyl-4,6-distyryl-	158–159°	490
pyrimidine	22.5; 124–126°/*at.*; *pic.* 156°	301, 792, 791, 429, 430, 431, 432, 433, 434, 435, 436, 440, 34, 437, 462, 438, 1646
2,4,5,6-tetramethyl-	*pic.* 129–130°	139
4,5,6-triethyl-2-methyl-	*pic.* 101–102°	129
2,4,6-trimethyl-	47°; 168/*at.*; *pic.* 145–146°	1640, 1639, 831, 438, 46,
4,5-trimethylene-	133–135°	1273
2,4,6-triphenyl-	*ca.* 184°	49, 384, 1647, 1648, 450
2,4,6-triphenyl-5-propyl-	135°	49
2,4,6-tristyryl-	199–200°	46, 460
4-vinyl-	56–58°/10 mm.; *pic.* 125–130°	98

TABLE XXI. Aminopyrimidines

Pyrimidine	M.p.	Reference
2-acetamido-	145–146°	726, 1206
4-acetamido-	198–200°	726, 790, 713
5-acetamido-	148–149°	435
2-acetamido-5-amino-	—	773
5-acetamido-2-amino-4,6-dimethyl-	246–247°	63
2-acetamido-5-benzamido-	281–284°	1212
4-acetamido-2,6-diethyl-5-methyl	59°	334
2-acetamido-4,6-dimethyl-	124°	1207
4-acetamido-2,6-dimethyl-	188–189°	304
2-acetamido-4-methyl-6-phenyl-	146°	51
2-acetamido-4-methyl-6-piperidino-	131–132°	1206
4-acetamido-2-phenyl-	174–175°	630
5-acetamido-2-phenyl-	208–209°	26
2-acetylhydrazino-	164–165°	1311
5-allyl-2-amino-4,6-dimethyl-	131–134°	639

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
2-amidino-	125–126°	889
2-amino-	125–126°	624, 440, 1177, 726, 621, 475, 73, 1649, 1650, 290, 91, 408, 305, 1362
4-amino-	151°	624, 356, 440, 1177, 1384, 726, 475
5-amino-	171–172°	28, 30, 435, 644, 440
4-amino-5-aminoethyl-2-methyl-	101°	1595
4-amino-5-aminomethyl-	134°	1183
4-amino-5-aminomethyl-2-benzyl-	*pic.* 214°	1651, 684
4-amino-5-aminomethyl-2-butyl-	*pic.* 148°	1187
4-amino-5-aminomethyl-2,6-dimethyl-	*HCl* 292°	1185
4-amino-5-aminomethyl-2-ethyl-	*pic.* 228–229°	134, 684, 1651
2-amino-4-aminomethyl-6-methyl-	*HCl* 265°	1189
4-amino-5-aminomethyl-2-methyl-	132°	1182, 684, 1404, 1405
4-amino-5-aminomethyl-6-methyl-	*pic.* 238°?	601
4-amino-5-aminomethyl-2-phenyl-	*pic.* 226°	134
2-amino-4-amyl	90°	1652
5-amino-2-amylamino-4,6-dimethyl-	*sul.* 143–144°	63
2-amino-4-amylamino-6-methyl-	99°	1117, 731
2-amino-5-amyl-4-methyl-(?)	92–93°	36, 1652
4-amino-5-amyl-2-methyl-	129–130°	129
2-amino-4-amilino-	156–157°	737, 1117
4-amino-2-amilino-	*HCl* 149–150°	737
2-amino-4-anilino-5,6-dimethyl-	202–203°	468
4-amino-2-anilino-5,6-dimethyl-	166°	468
2-amino-4-anilino-5-ethyl-6-methyl-	158–159°	836
4-amino-6-anilino-4-formamido-	235–238°	511
2-amino-4-anilino-6-methyl-	170–172°	737, 731, 612
4-amino-2-anilino-6-methyl-	118°	612
4-amino-6-anilino-2-methyl-	190–191°	719
2-amino-4-anilino-6-phenyl-	305–306°	1653
2-amino-4-anilino-6-phenyl-5-propyl-	171°	1653
2-amino-5-benzamido-	214–217°	1212
4-amino-5-benzamido-	225°	395
2-amino-5-benzamido-4,6-dimenthyl-	289–290°	63
2-amino-5-benzyl-	133°	642
4-amino-5-benzyl-	156°	642

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
2-amino-5-benzyl-4-cyclohexylamino-	132°	735
4-amino-5-benzyl-2-cyclohexylamino-	128°	735, 1654
2-amino-5-benzyl-4-dimethylamino-	185°	1655
4-amino-2-benzyl-5-formamidomethyl-	*HCl* 176°	1222
2-amino-4-benzyl-6-methyl-	108°	51
2-amino-5-benzyl-4-methylamino-	185°	735
2-amino-5-benzyl-4-methylamino-6-phenyl-	177°	1653
4-amino-2-benzyl-5-thioformamidomethyl-	155°	1651
2-amino-4,6-bisdiethylamino-	73–74°	172
5-amino-2,4-bisdimethylamino-	92–96°	1656
5-amino-2,4-bisdimethylamino-6-methyl	75°	536
2-amino-4,6-bisethylamino-	136°	1657
2-amino-4,6-bismethylamino-	*HCl* 326°	1658
5-amino-4,6-bismethylamino-	150° *or* 178–180°	1656, 753
5-amino-2,4-bispropylamino-	—	779
2-amino-5-butyl-	127–128°	35
2-amino-t-butyl-	103–105°	964
5-amino-2-butylamino-4,6-dimethyl-	*sul.* 150°	63
4-amino-2-butyl-5-formamido-	143°	965
4-amino-2-butyl-6-methyl-	*HCl* 97°	105
4-amino-5-butyl-2-methyl-	102–103°; *pic.* 185°	129
2-amino-4-chloro-6-diethylamino-	104–105°	172
4-amino-2,6-dianilino-	65–70°	426
5-amino-2,4-dianilino-	165–168°	779
5-amino-4,6-diaziridino-2-phenyl-	147–148°	787
4-amino-2,6-dibenzyl-5-phenyl-	107–108°	1660, 1661,325, 1663, 893
4-amino-2,6-diethyl-	166°	322, 318, 316
2-amino-4-diethylamino-	59°	1664
2-amino-4-diethylamino-5,6-dimethyl-	66–68°; 100°/15mm.	141
4-amino-6-diethylamino-5-formamido-	155–157°	1665
2-amino-4-diethylamino-6-methyl-	112–113°	172
4-amino-5-diethylaminomethyl-2-methyl-	*HCl* 293°	869
4-amino-2,6-diethyl-5-methyl-	188–189°	1660, 1661, 11, 331, 327, 328

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2,6-diisoamyl-5-isobutyl-	53°	324
4-amino-2,6-diisobutyl-5-isopropyl-	—	324
2-amino-4,5-dimethyl-	215–216°	41, 468, 40
2-amino-4,6-dimethyl-	152°	138, 62, 1666, 60, 61, 59, 430
4-amino-2,5-dimethyl-	205–206; *pic.* 222°	129, 1667
4-amino-2,6-dimethyl-	184°	654, 303, 1451, 831, 472, 332, 304
4-amino-5,6-dimethyl-	229–231°	1113, 468
5-amino-2-dimenthylamino-	—	507
5-amino-2-dimethylamino-4,6-dimethyl-	122°	63
4-amino-2-dimethylamino-5-formamido-	235°	395
4-amino-5-dimethylamino-5-formamido-	185–187°	554
2-amino-4-dimethylamino-6-methyl-	172°	172, 174
4-amino-5-dimethylaminomethyl-2-methyl-	74–75°	869
5-amino-4,6-dimethyl-2-methylamino-	113°	63
2-amino-4,6-dimethyl-5-phenyl-	180–181°	1638
5-amino-4,6-dimethyl-2-piperidino-	160–162°	63
5-amino-4,6-dimethyl-2-propylamino-	101°	63
2-amino-4,6-diphenyl-	135–137°	964
4-amino-2,6-diphenyl-	102–121°	319
4-amino-2,6-dipropyl-	186–189°	1668
2-β-aminoethyl-	*HCl* 167–168°	474
4-β-aminoethyl-	*HCl* 180–182°	474
2-amino-4-ethyl-	140–141°	722
2-amino-5-ethyl-	142–143°	448
4-amino-5-ethyl-	163°	448
4-amino-6-ethyl-	*hy.* 48°; *pic.* 204–205°	720
5-amino-4-ethylamino-	195–198°	717
5-amino-2-ethylamino-4,6-dimethyl-	72°; *sul.* 145°	63, 1659
4-amino-2-ethyl-5,6-dimethyl-	204°	452, 383
4-amino-5-ethyl-2,6-dipropyl-	115°	323, 333
4-amino-2-ethyl-5-formamidomethyl-	185°	1651, 1222
2-amino-4-ethyl-5-methyl-	200°	1652
2-amino-5-ethyl-4-methyl-	166–167°	35

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
4-amino-5-ethyl-2-methyl-	158–160°	129
4-amino-6-ethyl-5-thioformamido-	178°	99
4-amino-2-ethyl-5-thioformamidomethyl-	145° *or* 160°	1183, 1651
4-amino-5-formamido-	185° *or* 198°	280, 619, 1662, 1665
4-amino-6-formamido-	285°	579
4-amino-5-formamido-6-methyl-	205–209°	504
4-amino-5-formamidomethyl-2-methyl-	224–225°	1219, 1220, 1651, 1221
2-amino-4-hexyl-	93–94°	35, 1652
4-amino-5-hexyl-2-methyl-	119–120°	129
4-amino-5-hexyl-2-propyl-	84–85°	132
2-amino-4-hydrazino-6-methyl-	237–238°	812, 815
2-amino-4-isobutyl	119°	1652
5-amino-2-isobutylamino-4,6-dimethyl-	*sul.* 150°	63
5-amino-2-isopropylamino-4,6-dimethyl-	101°	63, 1659
2-amino-4-methyl-	157–159°	40, 612, 1669, 1366, 1670, 1649, 1671, 1672, 712, 711, 831
4-amino-2-methyl-	205–206°	126, 202, 44, 129, 1673, 831
4-amino-5-methyl-	175–176°	729, 1113
4-amino-6-methyl-	197°	113, 64, 612, 504
5-amino-2-methyl-	155–158°	887
5-amino-4-methyl-	151–152°	1669, 1674, 64, 454, 504
4-amino-5-methylamino-	191–193°	280
5-amino-4-methylamino-	207–210°	534
2-amino-4-methylamino-6-phenyl-	195–196°	1653
2-amino-4-methylamino-6-phenyl-5-propyl-	198°	1653
5-aminomethyl-4-diethylamino-2-methyl-	137°/3mm.	684
2-aminomethyl-4,6-dimethyl-	168°	1190
5-aminomethyl-4-dimethylamino-2-methyl-	132°/3 mm.	684
4-amino-5-methyl-2,6-diphenyl-	168°	317, 319
4-amino-6-methyl-2,5-diphenyl-	—	1675
5-aminomethyl-4-ethylamino-2-methyl-	135°/3 mm.	684
4-amino-2-methyl-5-methylamino-	*pic.* 225°	260
4-amino-2-methyl-6-methylamino-	239–240°	529, 1646

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
5-aminomethyl-2-methyl-4-methylamino-	130°/3 mm.; *HCl* 273°	684, 1651, 1218
2-amino-4-(4-methyl-3-pentenyl)-	155–159°	40
2-amino-4-methyl-6-phenyl-	172–173°	51, 1675
4-amino-2-methyl-6-phenyl-	165°	1675
4-amino-6-methyl-2-phenyl-	130°	1676
4-amino-6-methyl-5-phenyl-	—	1677
2-amino-4-methyl-6-piperidino-	152–153°	731
4-amino-2-methyl-6-piperidino-	206–207°	203
4-amino-5-methyl-2-propyl-	129–130°	132
4-amino-2-methyl-5-thioacetamidomethyl-	228–229°	695
4-amino-6-methyl-5-thioformamido-	168°	99
2-amino-4-methyl-5-thioformamidomethyl-	212–213°	852
4-amino-2-methyl-5-thioformamidomethyl-	190–193°	695, 627, 1651, 1680, 1679, 949
2-amino-4-morpholino-	157–160°	737
2-amino-4-phenyl-	165°	40, 1644, 1670, 456, 45
2-amino-5-phenyl-	162°	1675, 37
4-amino-2-phenyl-	138–139°	630
4-amino-5-phenyl-	152–153°	297, 188, 1681
5-amino-2-phenyl-	90–91°	34, 26
2-amino-4-piperidino-	146–147°	1205, 1117
2-amino-4-propyl-	124–125°	1671, 35, 1670
4-amino-2-propyl-	78–79°	132
4-β-aminopropyl-2,6-dimethyl-	130–131°	47
4-amino-5-thioformamidomethyl-	174°	1183
4-amino-2,5,6-triethyl-	183–184°	323
2-amino-4,5,6-trimethyl-	206–207°	964
4-amino-2,5,6-triphenyl-	161° *to* 184°	323, 392, 188, 1682, 1683
4-amylamino-	61–62°	1117
5-amyl-4,6-dianilino-2-methyl-	113–114°	129
2-anilino-	114–115°	1471, 1684, 1685, 625
4-anilino-	142–143°	718
4-anilino-2-benzylamino-	112–113°	1117
4-anilino-2,6-diethyl-5-methyl-	99°	322
2-anilino-4,6-dimethyl-	96–97° (89°?)	1125, 430
4-anilino-2,6-dimethyl-	104°	472
4-anilino-5,6-dimethyl-	152°	468
2-anilino-4-methyl-	92–93°	1471, 818, 1686
4-anilino-6-methyl-	146°	612, 429

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
4-anilino-2-methylamino-	*HCl* 246°	1117
4-anilino-6-methylamino-	206–207°	786
4-anilino-6-methylamino-2-phenyl-	126–128°	786
4-anilino-2-methyl-6-methylamino-	150°	786
4-anilino-6-methyl-2-phenyl-	160–162°	968, 1687, 1688
2-benzamido-	142°	1211
5-benzamido-	146–147°	435
2-benzamido-4,6-dimethyl-	139–140°	1207
2-benzamidomethyl-4,6-dimethyl-	200°	1190
2-benzylamino-	83–84°	1689, 1690, 818, 1692, 1693, 1694
2-benzylamino-4,6-dimethyl-	110–112°	1689, 1201
2-benzylamino-4-methyl-	72° *to* 86°	1201, 818, 1691
5-benzyl-2,4-bisbenzylamino-	207°	735
5-benzyl-2,4-biscyclohexylamino-	149°	735
5-benzyl-2,4,-bisdimethylamino-	64°; 160°/1 mm.	735
5-benzyl-2,4-bismethylamino-	124°	735
5-benzyl-2,4-dipiperidino-	78°	735
5-benzyl-2,4,6-tripiperidino-	129–131°	643, 1730
2,4-bismethylamino-	130–132°	718, 793
4,5-bismethylamino-	140–142°	402
4,6-bismethylamino-	207–209°	280
2-butylamino-	124/20° mm.; *pic.* 129°	1685, 2152, 171
2-butylamino-4-methyl-	109–110°/6 mm.; *pic.* 133–134°	1686
4-butyl-2-dimethylamino-	102–105°/4.5 mm.; *pic.* 80–81°	1695
2-cyanoamino-4,6-dimethyl-	233°	181
4-cyclolexylamino-2,6-dimethyl-	130°/10^{-3} mm.	141
4,5-diacetamido-	162–164°	292
4,6-diacetamido-2-methyl-	*hy.* 232°	355
2,4-diamino-	149–150°	964, 733, 356, 437, 624, 426
2,5-diamino-	200°	1652, 1696
4,5-diamino-	201–203°	498, 619, 1633
4,6-diamino-	268–270°	356, 354, 1184, 437, 1451
2,4-diamino-5-aminomethyl-	*HCl* 278–280°	1186, 1182, 1651
2,4-diamino-5-aminomethyl-6-methyl-	*HCl* 255°	1698
4,6-diamino-5-amyl-2-methyl-	161–163°	129
2,4-diamino-6-anilino-	174–175°	622
2,5-diamino-4-anilino-	*pic.* 249–250°	980

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
4,5-diamino-6-anilino-	*sul.* >300°	1699, 511
2,5-diamino-4-anilino-6-methyl-	*pic.* 252–253°	980
2,4-diamino-5-benzamido-	213–214°	1700
2,4-diamino-5-benzyl-	195° *or* 145°	735, 642
4,5-diamino-6-benzylamino-	*sul.* >300°	511
2,4-diamino-5-benzyl-6-methyl-	181–182°	83, 1701, 1675
2,4-diamino-5-benzyl-6-phenyl-	222–223°	82, 1702
4,5-diamino-2,6-bisdimethylamino-	182°	174
2,5-diamino-4,6-bismethylamino-	—	1658
4,5-diamino-2,6-bismethylamino-	259°	174
4,5-diamino-2-butyl-	121–122°	352
4,5-diamino-6-butylamino-2-dimethylamino-	*sul.* 238°	1703
4,6-diamino-5-butyl-2-methyl-	151–152°	129
2,5-diamino-4,6-diethyl-	98°	63
2,5-diamino-4-diethylamino-6-dimethylamino-	*oxal.* 221°	174
4,5-diamino-6-diethylamino-2-dimethylamino-	*acet.* 161°	1703
4,5-diamino-2-diethylamino-6-methyl	97°	785
4,5-diamino-6-diethylamino-2-methyl-	117–118°	971
4,5-diamino-2-diethylamino-6-methylamino-	*sul.* 250°	1703
2,4-diamino-5,6-dimethyl-	192°	468, 134
2,5-diamino-4,6-dimethyl-	183–184°	775, 1043
4,5-diamino-2,6-dimethyl-	248° *or* 250–254°	601, 874
4,6-diamino-2,5-dimethyl-	234–235° *or* 225–226°	129, 134
2,4-diamino-6-dimethylamino-	193–194°	1704, 1705
4,5-diamino-2-dimethylamino-	*ca.* 121°; *HCl* 260°	360, 507
4,5-diamino-6-dimethylamino-	157–159°	1699, 783
4,6-diamino-2-dimethylamino-	261–263°	257, 1152
4,5-diamino-2-dimethylamino-6-ethylamino-	*sul.* 239°	1703
4,5-diamino-2-dimethylamino-6-isopropylamino-	*sul.* 235°	1703
2,5-diamino-4-dimethylamino-6-methyl-	117–119°	63
4,5-diamino-2-dimethylamino-6-methylamino-	*sul.* 273°	174
4,5-diamino-6-dimethylamino-2-methylamino-	*sul.* 193°	174
4,5-diamino-2-dimethylamino-6-piperidino-	*sul.* 208°	1703

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
4,5-diamino-2-dimethylamino-6-propylamino-	*sul.* 240°	1703
4,6-diamino-2-dimethylamino-5-thioformamido-	180°	1152
2,4-diamino-5,6-diphenyl-	241–242°	188
2,4-diamino-5-ethyl-	149–151°	448, 134
2,4-diamino-6-ethyl-	160–161°	134, 99
4,5-diamino-6-ethyl-	159–161°	104
4,6-diamino-2-ethyl-	223°	131
4,6-diamino-5-ethyl-	245°	134, 1706, 448
4,5-diamino-2-ethylamino-6-methylamino-	*sul.* 293°	1703
2,4-diamino-5-ethyl-6-methyl-	161–162°	836
2,5-diamino-4-ethyl-6-methyl-	132°	63
4,6-diamino-5-ethyl-2-methyl-	232–233°	129
2,4-diamino-6-ethyl-5-phenyl-	237–240°	188, 1675, 1707
2,4-diamino-5-formamido-	224°	619
4,6-diamino-5-formamido-	—	1110, 1708, 138, 437
2,4-diamino-5-formamido-6-methyl-	*ca.* 300°	63, 504
4,6-diamino-5-hexyl-2-methyl-	149°	129
4,6-diamino-5-hexyl-2-propyl-	139–140°	132
2,4-diamino-5-methyl-	188–189°	729
2,4-diamino-6-methyl-	185–186°	64, 612, 504, 1675, 492
2,5-diamino-4-methyl-	182–183°	63, 504
4,5-diamino-2-methyl-	246–248°	505
4,5-diamino-6-methyl-	208–209°	505, 1710, 504, 874
4,6-diamino-2-methyl-	295–303°	354, 550, 129
4,6-diamino-5-methyl-	243°	729
2,4-diamino-6-methylamino-	192–194°	1704, 1658
4,5-diamino-6-methylamino-	*sul.*>300°	511, 1699
4,5-diamino-6-methylamino-2-piperidono-	—	1703
2,4-diamino-5-methyl-6-phenyl-	196–197°	1702
2,4-diamino-6-methyl-5-phenyl-	249–250°	188, 1677, 1675
2,5-diamino-4-methyl-6-phenyl-	146°	63
2,5-diamino-4-methyl-6-propyl-	114–116°	63
4,6-diamino-5-methyl-2-propyl-	181–182°	129
2,4-diamino-6-methyl-5-thioformamido-	255°	99
4,6-diamino-2-methyl-5-thioformamido-	—	550
2,4-diamino-5-phenyl-	162–163°	1709, 1677, 1675
2,4-diamino-6-phenyl-	162°	1711, 1675
4,6-diamino-2-phenyl-	195–196°	355

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
2,4-diamino-6-phenyl-5-propyl-	165–166°	1711, 1702
2,4-diamino-6-piperidino-	135–136°	1704, 1705
4,6-diamino-2-propyl-	202–203°	132
4,6-diamino-5-thioformamido-	>200°	250
2,4-diamino-5-thioformamidomethyl-	181–182°	1186
4,6-diamino-2-thiosemicarbazido-	—	1712
2,4-diamino-6-thioureido-	—	1712
2,4-diamino-6-ureido-	—	1712
2,4-dianilino-	136–138°	737, 522
2,4-dianilino-5-benzyl-	207°	735, 736
4,6-dianilino-5-butyl-2-methyl-	128–129°	129
4,6-dianilino-5-s-butyl-2-methyl-	91–92°	129
2,4-dianilino-5,6-dimethyl-	133–134°	468
4,6-dianilino-2,5-dimethyl-	194–195°	129
4,6-dianilino-2-dimethylamino-	168–170°	622
4,6-dianilino-5-ethyl-2-methyl-	148–149°	129
2,4-dianilino-5-ethyl-6-methyl-	*HCl* 297°	836
2,4-dianilino-5-formamido-	193–195°	779
4,6-dianilino-5-isobutyl-2-methyl-	96–97°	129
4,6-dianilino-2-methyl-	242–243°	826
4,6-dianilino-2-methyl-5-propyl-	146°	129
2,4-dianilino-5-nitro-	203–204°	779
2,4-diazido-	92°	816
2,4-diazido-6-methyl-	126°	816
2,4-diazido-6-phenyl-	92–93°	816
4,6-diaziridino-2-phenyl-	111–112°	617, 787
4,5-dibenzamido-	179°	395
2,4-dibenzyl-6-methylamino-5-phenyl-	—	325
2,4-diethyl-6-ethylamino-5-methyl-	45°; 260/*at.*	306, 307
2,4-diethyl-5-methyl-6-methylamino-	74°; 258°/*at.*	307
4-diethylamino-2,6-dimethyl-	85°/10^{-3} mm.	141
2,4-dihydrazino-	211–212°	434, 816
2,4-dihydrazino-6-methyl-	213°	817
1,2-dihydro-2-imino-1-methyl-	102–104°; *HI* 247–248°	1177
1,4-dihydro-4-imino-1-methyl-	*HI* 205–206°	1177
1,4-dihydro-1,2,6-trimethyl-4-methylamino-(?)	*pic.* 166°	1713
2-dimethylamino-	78–81°/17 mm.; *pic.* 170–171°	726, 72, 1731
4-dimethylamino-	*ca.* 40°; 131–132°/50 mm.	726
2-dimethylamino-4,6-dimethyl-	*pic.* 160–163°	1279, 1280
4-dimethylamino-2,6-dimethyl-	226°/*at.*; *pic.* 168°	1280

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
2-dimethylamino-4-dimethylaminoethyl-	135–136°/6 mm.; *pic.* 152–153°	98
2-dimethylamino-4-ethyl-	91–92°/15 mm.; *pic.* 110–111°	98
4-dimethylaminoethyl-	120–122°/30 mm.	98
2-dimethylamino-4-methyl-	103–106°/40 mm.	98
2-dimethylamino-4-vinyl-	95–98°/14 mm.; *pic.* 130–133°	98
4,6-dimethyl-2-methylamino-	98°	100
2,4-dimethyl-6-piperidino-	110/10^{-3} mm.	141
4,6-dimethyl-2-piperidino-	60–61°	466
4,6-dimethyl-2-ureido-	211°	181
2-ethylamino-	50–51°; *HI* 119°	2152, 171
5-ethylamino-4-methyl-	55–56°; 123–125°/7 mm.	454
5-formamido-, and 2-isomer	—	1467
5-formamido-2,4-bispropylamino-	159–160°	779
5-formamido-4-methylamino-	142°	292
5-formamidomethyl-2-methyl-4-methylamino-	152–153°	1218
2-formylhydrazino-	166–168°	1311
2-formylhydrazino-4-methyl-	158–159°	2150
2-hydrazino-	108–100° (*or* 86–88°?)	626, 813, (812)
4-hydrazino-	132–134°	626
2-hydrazino-4,6-dimethyl-	165°	434
2-hydrazino-4-methyl-	89–91° (*or* 141°?)	813, 814, 526, (527)
4-hydrazino-6-methyl-	140–142°	815, 1714, 504
2-hydrazino-4-phenyl-	115°	626
4-hydrazino-5-phenyl-	140–141°	626
2-methylamino-	59–61°; 91–92°/14 mm.	726, 725, 72, 1177
4-methylamino-	72°; 142–144°/16 mm.	726, 718
4-methyl-2,6-dipiperidino-	118°	466
4-methyl-2-methylamino-	*pic.* 150–155°	1129
5-methyl-2-methylamino-	102°	1129
2-methyl-4-methylamino-5-thioformamidomethyl-	132°	1218
4-methyl-2-phenyl-6-phenylhydrazino-	115°	704
4-methyl-2-phenyl-6-piperidino-	91°	704
2-methyl-4-piperidino-	*pic.* 169°	702
4-methyl-2-piperidino-	*pic.* 135°	702
4-methyl-6-piperidino-	*pic.* 172°	702, 1117
2-piperidino-	129/14 mm.; *pic.* 121°	702
2,4,5,6-tetra-amino-	*ca.* 205°; *sul.* 255°	266, 1142, 1658, 1716, 74, 264, 512
2,4,6-triacetamido-	304–305°	1206

(Table continued)

TABLE XXI *(continued)*

Pyrimidine	M.p.	Reference
2,4,5-triamino-	*ca.* 179°	778, 292, 1633, 360, 619
2,4,6-triamino-	246 *to* 252°	264, 1716, 1658, 65, 512, 624
4,5,6-triamino-	257°	250, 1181, 531, 1717, 1141, 1633
2,4,6-triamino-5-benzamido-	274–275°	1700, 1215
2,4,6-triamino-5-benzyl-	191–192°	267
4,5,6-triamino-2-benzyl-	223–224°	1181
2,4,6-triamino-5-butyl-	199°	267
4,5,6-triamino-2-butyl-	151–152°	1181
2,4,5-triamino-6-dimethlamino-	209°	1704, 1705, 174
4,5,6-triamino-2-dimethylamino-	*sul.* 314°	174
2,4,5-triamino-6-ethyl-	224–228°	1181
2,4,6-triamino-5-ethyl-	190°	267, 265, 448
4,5,6-triamino-2-ethyl-	272°	1181
2,4,6-triamino-5-formamido-	152–155°	264, 437
4,5,6-triamino-2-isobutyl-	176°	1181
2,4,5-triamino-6-isopropyl-	158–160°	1181
2,4,5-triamino-6-methyl-	242–243°	778, 504, 1674, 513
2,4,6-triamino-5-methyl-	227–228°	729
4,5,6-triamino-2-methyl-	250°	615, 531, 1719
2,4,5-triamino-6-methylamino-	*sul.* 250°	174, 1704, 1658
4,5,6-triamino-2-methylamino-	*sul.* 255°	174
2,4,6-tramino-5-phenyl-	241°	1720
4,5,6-triamino-2-phenyl-	189–190°	1181
2,4,5-triamino-6-piperidino-	—	1704, 1705
2,4,5-triamino-6-propyl-	183–186°	1181
4,5,6-triamino-2-propyl-	171–172°	1181
2,4,6-trianilino-	205°	718
2-triphenylmethylamino-	174–175°	1721
2,4,6-trisdimethylamino-(*triMeCl*)	—	741
2,4,6-trisemicarbazido-	—	1712
2,4,6-trismethylamino-	*pic.* 232–235°	718
2,4,6-triureido-	—	1712

TABLE XXII. Carboxypyrimidines

Pyrimidine	M.p.	Reference
5-acetyl-4-methyl-2-phenyl-	107°	1378
2-amidino-4,6-dimethyl-	155–156°	32
2,4-biscarboxymethylthio-	>200°	48

(Table continued)

TABLE XXII *(continued)*

Pyrimidine	M.p.	Reference
5-carbamoyl-	211–213°	30
2-carbamoyl-4,6-dimethyl-	190–191°	1281
4-carbamoyl-2,6-dimethyl-	185°	1281
2-carbamoylethyl-	135–136°	474
4-carbamoylethyl-	117–118°	474
2-carboxy-	199°	453
4-carboxy-	238–240°	462, 644, 1642, 429
5-carboxy-	—	394, 644
2-carboxy-4,6-dimethyl-	145–146°	1281, 461, 429
4-carboxy-2,6-dimethyl-	198–200°	1281
2-carboxyethyl-	179–180°	474
4-carboxyethyl-	198–199°	474
2-carboxy-5-methyl-	146–147°	453
4-carboxy-5-methyl-	190°	468
4-carboxy-6-methyl-	165–166°	430
5-carboxy-4-methyl-2,6-diphenyl-	207–209°	450
4-carboxy-6-methyl-2-phenyl-	112°	46
5-carboxy-4-methyl-2-phenyl-	243°	1378
2-carboxymethylthio-	199–200°	431
2-carboxymethylthio-5-ethoxycarbonyl-	175–176°	1374
2-carboxymethylthio-4-methyl-6-phenyl-	85°	448
5-caboxy-2,4,6-triphenyl-	229°	450
2-β-carboxyvinyl-	235–237°	474
4-β-carboxyvinyl-	265–267°	474
2-cyano-	42–44°	724
2-cyano-4,6-dimethyl-	85°	1281, 1231, 1715
4-cyano-2,6-dimethyl-	55–57°	1281, 1715, 724,469
2-cyano-4-methyl-	52–57°	724, 469
4,5-dicarboxy-	225°	150
4,6-dicarboxy-	222°	430, 431
4,5-dicarboxy-2-phenyl-	279–281°	482
4,6-dicarboxy-2-phenyl-	165°	46
4,6-dimethoxycarbonyl-	77–79°	431
4-ethoxycarbonyl-	38–40°; 115–116°/6 mm.	1381, 1642
4-ethoxycarbonyl-2-methyl-5-phenyl-	115°/0.04 mm.	1722
5-ethoxycarbonyl-4-methyl-2-phenyl-	99–100°	1378
5-ethoxycarbonyl-4-methyl-2,6-diphenyl-	76°	450
5-ethoxycarbonyl-2,4,6-triphenyl-	99–100°	450
2-formyl-4,6-dimethyl-(?)	—	461
4-hydrazinocarbonyl-	114–145° *or* 147°	1385, 1642
5-methoxycarbonyl-	84°	30

(Table continued)

TABLE XXII *(continued)*

Pyrimidine	M.p.	Reference
2-methoxycarbonyl-4,6-dimethyl-	142°/11 mm.	1281
2-methoxycarbonylethyl-	*liq.*	474
4-methoxycarbonylethyl-	*liq.*	474
2-methoxycarbonyl-5-methyl-	99–101°	453
2,4,6-tricarboxy-	>320°	139, 460
2,4,6-triformyl-	—	460

TABLE XXIII. Halogenopyrimidines

Pyrimidine	M.p.	Reference
4-amyl-2,6-dichloro-	130–135°/3 mm.	105
5-amyl-4,6-dichloro-2-methyl-	109–110°/3 mm.	129
5-amyl-4,6-dichloro-2-propyl-	153–154°/9 mm.	132
2-benzyl-4-chloro-6-methyl-	81–83°; 130–133°/5 mm.	475
4-benzyl-2-chloro-6-methyl-	27–28°	475
5-benzyl-2,4-dichloro-	160°/10 mm.	735, 1718
2-benzyl-4-iodo-6-methyl-	127°	105
5-benzyl-2,4,6-tribromo-	105°	643, 1730
5-benzyl-2,4,6-trichloro-	66–67°	642
4,6-bistribromomethyl-	125–126°	431
5-bromo-	75–76°	462, 644
4-bromo-5-bromomethyl-6-chloro-2-methyl-	135–137°	484
5-bromo-4-chloro-	87°/16 mm.	626, 447
5-bromo-4-chloro-2,6-dimethyl-	45°	645
5-bromo-4-chloro-2-methyl-	107°/27 mm.	447
5-bromo-4-chloro-2-phenyl-	130–131°	447
5-bromo-2,4-dichloro-	112–113°/12 mm.	436
5-bromo-4,6-dichloro-	75–76°	626
5-bromo-2,4-dichloro-6-methyl-	42–43°	614, 454
5-bromo-2,4-dimethyl-	136–137°	645
5-bromo-2-methyl-	83–84°	44, 831, 462
5-bromomethyl-4,6-dichloro-2-methyl-	109–110°	484
5-bromomethyl-2,4,6-trichloro-	134–135°	484
5-bromo-2-phenyl-	104°	270
5-bromo-2-tribromomethyl-	131–132°	480
2-butyl-4-chloro-6-methyl-	110–115°/3 mm.	105
5-butyl-2,4-dichloro-6-methyl-	171°/23 mm.	1327
5-butyl-4,6-dichloro-2-methyl-	113–114°/4 mm.	129
5-s-butyl-4,6-dichloro-2-methyl-	88–89°/2 mm.	129
5-butyl-4,6-dichloro-2-propyl-	130–131°/5 mm.	132

(Table continued)

TABLE XXIII *(continued)*

Pyrimidine	M.p.	Reference
5-s-butyl-2,4,6-trichloro-	40°	1723
2-chloro-	65–66°; 91°/26 mm.	610, 636, 1724, 72, 644, 1725, 611, 614, 1726, 30
4-chloro-	*HCl* 193–194°	1726, 644, 30
5-chloro-	35.5°	34, 644
4-chloro-2,6-bis-α-chloroethyl-5-chloromethyl-(?)	—	314
2-chloro-4,6-bistrichloromethyl-	100–101°	1727
4-chloro-5-chloromethyl-2-methyl-	54°	683
4-chloro-2,6-diethyl-5-methyl-	—	306, 322
2-chloro-4,5-dimethyl-	23–26°	41
2-chloro-4,6-dimethyl-	38°; 223°/*at.*	611, 1639, 1728, 430
4-chloro-2,5-dimethyl-	—	1729
4-chloro-2,6-dimethyl-	39–40°; 182°/*at.*	645, 472
4-chloro-5,6-dimethyl-	48°; 206°/*at.*	1113, 468
2-chloro-4,6-dimethyl-5-phenyl-	122–124°	1638
4-chloro-2,6-diphenyl-	108°	49
4-chloro-2,6-diphenyl-5-propyl-	133°	49
2-chloro-4-ethyl-	89–91°/7 mm.	722
4-chloro-6-ethyl-	193°/*at.*	720
4-chloro-5-ethyl-2,6-diphenyl-	122°	49
2-chloro-4-iodo-6-methyl-(?)	161°	105
4-chloro-2-iodo-6-methyl-(?)	161°	105
2-chloro-4-methyl-	48°; 101°/23 mm.	636, 110, 614, 64
2-chloro-5-methyl-	92.5°	729
4-chloro-2-methyl-	56–57°	1732, 702, 126
4-chloro-6-methyl-	35–36°; 66°/12 mm.	612, 64
5-chloro-2-methyl-	56–57°	44
4-chloro-5-methyl-2,6-diphenyl-	118°	49
2-chloro-4-methyl-6-phenyl-	50–51°	448
4-chloro-6-methyl-2-phenyl-	71°	472, 3, 4
2-chloro-4-phenyl-	87–89°	614
4-chloro-2-phenyl-	74°	630
4-chloro-5-phenyl-	71–72°; 156–158°/19 mm.	297, 457
5-chloro-2-phenyl-	96°	34, 270
4-chloro-2,5,6-trimethyl-	215°/*at.*; *pic.* 132°	141
4,6-dibromo-2-ethyl-	53°	131
2,4-dichloro-	61°; 100°/19 mm.	435, 497, 614, 831
2,5-dichloro-	57°; 190°/*at.*	647, 1733, 636, 831
4,5-dichloro-	82°/34 mm.	626
4,6-dichloro-	67°	354, 351, 831, 1258
2,4-dichloro-5-bromo-	112–113°/12 mm.	436, 522, 648
2,4-dichloro-5-(β-chloroethyl)-6-methyl-	85°; 136°/4 mm.	1734

(Table continued)

TABLE XXIII *(continued)*

Pyrimidine	M.p.	Reference
2,4-dichloro-5-chloromethyl-6-methyl-	39°	601, 46
2,4-dichloro-5,6-dimethyl-	70–71°; 250°/*at.*	468
4,6-dichloro-2,5-dimethyl-	39°	134, 129
4,6-dichloro-2,5-dipropyl-	24–26°; 100–101°/5 mm.	132
2,4-dichloro-6-ethyl-	90–95°/4 mm.	720
4,6-dichloro-2-ethyl-	86–87°/14 mm.	134, 131
2,4-dichloro-5-ethyl-6-methyl-	25–27° *or* 39°	1735, 836
4,6-dichloro-5-ethyl-2-methyl-	100–101°/10 mm.	788, 129
4,6-dichloro-5-ethyl-2-propyl-	115–116°/7 mm.	132
4,6-dichloro-5-hexyl-2-methyl-	134–135°/5 mm.	129
4,6-dichloro-5-hexyl-2-propyl-	160–161°/7 mm.	132
2,4-dichloro-5-iodomethyl-6-methyl-	93–94°	695, 601
4,6-dichloro-5-isobutyl-2-methyl-	91–92°/6 mm.	129
2,4-dichloro-5-methyl-	25–26°; 108–109°/11 mm.	1355, 729, 1736
2,4-dichloro-6-methyl-	47°; 99°/10 mm.	908, 614, 831, 429
4,6-dichloro-2-methyl-	48–49°	550, 129, 831
4,6-dichloro-5-methyl-	56–57°	1737
4,6-dichloro-2-methyl-5-phenyl-	160°	1737, 788, 831
2,4-dichloro-6-methyl-5-propyl-	31–33°; 145–146°/20 mm.	820
4,6-dichloro-2-methyl-5-propyl-	114–115°/11 mm.	129
4,6-dichloro-5-methyl-2-propyl-	24–26°; 100–101°/5 mm.	132
2,4-dichloro-5-phenyl-	78–80°; 181–182°/16 mm.	297
2,4-dichloro-6-phenyl-	84–87°	614, 829
4,6-dichloro-2-phenyl-	96°	617
4,6-dichloro-2-propyl-	98–99°/12 mm.	132
2,4-di-iodo-6-methyl-	90°	105
4-iodo-6-methyl-	*ca.* 20°; *pic.* 120–121°	429, 612
2,4,5,6-tetrabromo-	165°	433
2,4,5,6-tetrachloro-	66–68°	632, 433, 831, 1738
2,4,6-tribromo-	113–115°; 124°/5 mm.	638
2,4,5-trichloro-	73–74°/3 mm.	626, 831
2,4,6-trichloro-	23–25°; 102°/18 mm.	622, 615, 585, 1341, 831
4,5,6-trichloro-	49–51°	626
2,4,6-trichloro-5-ethyl-	75–77°	448
2,4,5-trichloro-6-methyl-	245–247°/*at.*	114
2,4,6-trichloro-5-methyl-	67–68°	729
2,4,6-trichloro-5-phenyl-	159–160°	1709, 617

TABLE XXIV. Nitropyrimidines

Pyrimidine	M.p.	Reference
2-benzyl-5-nitro-	170°	26
2-methyl-5-nitro-	186–187°	26, 499
5-nitro-2-phenyl-	222–224°	25, 26, 499
5-phenylazo-	97–98°	435

TABLE XXV. Oxypyrimidines without *C*- or *N*- Alkyl Groups

Pyrimidine	M.p.	Reference
5-acetoxy-2,4-dihydroxy-	—	115
5-acetoxy-2,4,6-trihydroxy-	210–212°	987, 1739
alloxan	>295°	1054, 1067, 1050, 111, 1, 2
2-allyloxy-4,6-dihydroxy-	171°	179
4-amyl-2,6-dihydroxy-	171–173°	105
barbituric acid/5,5-dihydroxy-; ("alloxan hydrate")		1746
barbituric acid/5-ethoxy 5-hydroxy-	252–254°	1740
barbituric acid/5-hydroxy- 5-methoxy-	235°	1740
5-benzyloxy-	*pic.* 125–127°	913
2-butoxy-4,6-dihydroxy-	—	1741
2-cyclohexyloxy-4,6-dihydroxy-	240°	179
2,4-diethoxy-	19–20°; 224–225°/*at.*	718, 656, 1634, 1451
2,5-diethoxy-	19°; 124°/24 mm.	721
2,4-diethoxy-6-α-hydroxyethyl-	72°	682
2,4-diethoxy-6-α-hydroxypropyl-	49°	682
2,4-dihydroxy-: *see* Uracil		
4,5-dihydroxy-	260–300°	933, 913, 79
4,6-dihydroxy-	*ca.* 230°	127, 351, 352
4,6-dihydroxy-5-β-hydroxyethyl-	247–248°	948
2,4-dihydroxy-5-hydroxymethyl-	260–300°	1168, 76(?), 2071
2,4-dihydroxy-6-hydroxymethyl-	254°	868
4,6-dihydroxy-2-isopropoxy-	—	1741
4,6-dihydroxy-2-methoxy-	—	1741
2,4-dihydroxy-5-methoxymethyl	203°	1168
2,4-dihydroxy-5-phenoxy-	290°	797
4,6-dihydroxy-2-propoxy-	—	1741
2,4-dimethoxy-	202–204°/*at.*	463, 440
2,4-diphenoxy-	—	1451
2-ethoxy-4,6-dihydroxy-	—	1742

(Table continued)

TABLE XXV *(continued)*

Pyrimidine	M.p.	Reference
5-ethoxy-2,4-dihydroxy-	275°	721, 845, 907, 797, 1743
5-ethoxy-4-ethoxymethyl-2,6-dihydroxy-	168°	918
2-ethoxy-4-hydroxy-	127–129°	992, 1634
4-ethoxy-2-hydroxy-	168–170°	807, 992, 804, 1319, 1634, 1358
2-hydroxy-	179–180°	894, 431, 611, 726, 804
4-hydroxy-	163–165°	356, 1726, 1745, 726, 713, 447
5-hydroxy-	211–212°	245, 913
2-hydroxy-4-methoxy-	132–134°	804
4-hydroxy-5-methoxy-	210–211°	245, 913
2-methoxy-	70–71°/15 mm; *pic.* 105–106°	726, 273, 1643
4-methoxy-	69–70°/30 mm.; *pic.* 123–124°	726, 440, 790, 273
5-methoxy-	47°	245
2-phenoxy-	89–91°	818, 819
tetrahydroxy-	>350°	83, 1746, 564, 1056, 1747, 1051, and *Beilstein*
2,4,6-triethoxy-	10°; 255–256/*at.*	718
2,4,5-trihydroxy-	>300°	537, 1749, 502, 1748
2,4,6-trihydroxy-	245°	152, 145, 102, 144, 1001, 1004, 1243, and *Beilstein*
4,5,6-trihydroxy-	—	83, 1747
2,4,6-trihydroxy-5-hydroxyethyl-	>300°	1750
2,4,6-trimethoxy-	53°; 232°/*at.*	624, 1627
2,4,6-triphenoxy-	156°	1751
2,4,6-trisbenzyloxy-	62–64°	583
uracil	*ca.* 318°	67, 498, 48, 66, 804, and *Beilstein*

TABLE XXVI. Oxypyrimidines with *C*-, but without *N*-, Alkyl Groups

Pyrimidine	M.p.	Reference
4-acetoxy-2,6-dibenzyl-5-phenyl-	84–85°	323
5-acetoxy-2,4-dihydroxy-6-methyl-	>230°	986

(Table continued)

TABLE XXVI *(continued)*

Pyrimidine	M.p.	Reference
4-acetoxymethyl-2,6-dihydroxy-5-methyl-	260–261°	989, 990
4-acetoxy-6-methyl-2-phenyl-(?)	40–41°	4
5-allyl-2,4-dihydroxy-6-methyl-	130–132°	1752
5-allyl-4-hydroxy-2,6-dimethyl-	151–152°	1744
2-allyloxy-4-hydroxy-6-methyl-	164°	179
5-allyl-2,4,6-trihydroxy-	167°	1753
5-amyl-4,6-dihydroxy-2-methyl-	>360°	128, 129
5-amyl-4,6-dihydroxy-2-propyl-	*ca.* 300°	132
barbituric acid/5,5-dimethyl-	278–279°	157, 159, 1332
barbituric acid/5,5-dimethylene-(?)	—	1754
barbituric acid/5-ethyl-5-hydroxy-	224–225°	1755, 1756
barbituric acid/ 5-methylene-	—	604
4-benzyl-2,6-dihydroxy-	261–262°	657, 1757
5-benzyl-2,4-dihydroxy-	294–295°	657, 735, 1718, 1328, 642
5-benzyl-4,6-dihydroxy-	354°	1758
5-benzyl-2,4-dihydroxy-6-methyl-	249–250°	86
5-benzyl-4,6-dihydroxy-2-methyl-	>300°	130
5-benzyl-4,6-dihydroxy-2-phenyl-	>300°	130
5-benzyl-2-ethoxy-4,6-dihydroxy-	202°	1759
2-benzyl-5-ethyl-4-hydroxy-6-methyl-	199°	452
2-benzyl-4-hydroxy-5,6-dimethyl-	181°	452
5-benzyl-4-hydroxy-2-isopropyl-6-methyl-	184°	1760
2-benzyl-4-hydroxy-5-methyl-	175°	452
4-benzyl-2-hydroxy-6-methyl-	61–63°	475
5-benzyl-4-hydroxy-6-methyl-	157–158°	1761
5-benzyl-4-hydroxy-6-methyl-2-phenyl-	243°	452
5-benzyl-4-hydroxy-6-methyl-2-propyl-	167°	1760
2-benzyl-4-hydroxy-6-phenyl-	233°	452
2-benzyloxy-4-hydroxy-6-methyl	160°	179
5-benzyloxy-4-hydroxy-6-phenyl-(?)	198–200°	1762
4-benzyloxy-6-methyl-2-phenyl-	150°	1760
5-benzyl-2,4,6-trimethoxy-	99.5°	642
2,4-bisbenzyloxy-6-methyl-	71–72°; *pic.* 134°	817
5-butoxymethyl-4-hydroxy-2-methyl-	139–140°	1049
5-butyl-2,4-diethoxy-6-methyl-	174°/27 mm.	1327

(Table continued)

TABLE XXVI *(continud)*

Pyrimidine	M.p.	Reference
2-butyl-4,6-dihydroxy-	300° *to* 309°	352, 1763
5-butyl-2,4-dihydroxy-	291–293°	1328
5-butyl-2,4-dihydroxy-6-methyl-	245°	1115
5-butyl-4,6-dihydroxy-2-methyl-	>360°	128, 129
5-s-butyl-4,6-dihydroxy-2-methyl-	>360°	129
5-butyl-4,6-dihydroxy-2-phenyl-	296–297°	130
2-butyl-4,6-dihydroxy-5-propyl-	>300°	350
5-butyl-4,6-dihydroxy-2-propyl-	>360°	132
5-butyl-2,4-dimethoxy-6-methyl-	159°/29 mm.	1327
2-butyl-5-ethoxymethyl-4-hydroxy-	116–118°	689
4-t-butyl-6-hydroxy-	217–218°	1764
2-butyl-4-hydroxy-6-methyl-	120°	105
4-butyl-6-hydroxy-2-methyl-5-propyl-	118°	867
5-butyl-4-methyl-2,6-dipropoxy-	193–194°/23 mm.	1327
5-s-butyl-2,4,6-triethoxy-	260–264°/*at.*	823
5-s-butyl-2,4,6-trimethoxy-	245–250°/*at.*	823
5-s-butyl-2,4,6-tripropoxy-	285–290°/*at.*	823
2-cyclohexyloxy-4-hydroxy-6-methyl-	110°	179
2,4-diallyloxy-5-butyl-6-methyl-	192–193°/31 mm.	1327
2,4-diisoamyloxy-6-methyl-	—	908
2,5-dibenzyl-4-hydroxy-6-methyl-	192°	452
2,4-dibenzyl-6-hydroxy-5-phenyl-	180° *to* 187°	323, 893
2,4-dibutoxy-5-butyl-6-methyl-	219°/29 mm.	1327
2,4-dibutoxy-6-methyl-	—	908
2,4-diethoxy-5-ethyl-6-methyl-	138–139°/17 mm.	1735
2,4-diethoxy-5-methyl-	36–37°	807, 1355
2,4-diethoxy-6-methyl-	—	908
2,4-diethoxy-6-methyl-5-propyl-	145–148°/18 mm.	820
2,4-diethyl-6-hydroxy-5-hydroxyethyl-	151°	314
2,4-diethyl-6-hydroxy-5-methyl-	156–157°	306, 12, 322
2,5-diethyl-4-hydroxy-6-methyl-	135°	452
2,4-diethyl-6-methoxy-5-methyl-	225°/*at.*	307
4,5-dihydro-6-hydroxy-5,5-dimethyl-4-oxo-2-phenyl-	184°	130
2,4-dihydroxy-5,6-dimethyl-	294–297°	141, 955, 989, 990, 96, 468, 1765
2,5-dihydroxy-4,6-dimethyl-	>300°	938
4,6-dihydroxy-2,5-dimethyl-	—	128, 129, 484
2,4-dihydroxy-5,6-diphenyl-(?)	268°	1766
4,6-dihydroxy-2,5-dipropyl-	—	132
2,4-dihydroxy-5-ethyl-	*ca.* 303°	634, 448, 1542, 1767
2,4-dihydroxy-6-ethyl-	*ca.* 204°	522, 1181, 1767

(Table continued)

TABLE XXVI *(continued)*

Pyrimidine	M.p.	Reference
4,6-dihydroxy-5-β-hydroxyethyl-2-isoamyl-	244°	948
2,4-dihydroxy-5-hydroxyethyl-6-methyl-	264–265°	587
2,4-dihydroxy-6-α-hydroxyethyl-5-methyl-	219–220°	1768
4,6-dihydroxy-5-β-hydroxyethyl-2-methyl-	275–276°	948
4,6-dihydroxy-5-β-hydroxyethyl-2-phenyl-	248–249°	948
2,4-dihydroxy-6-hydroxyethyl-	—	958
2,4-dihydroxy-5-hydroxymethyl-6-methyl-	314–315°	955, 1168, 694, 828
2,4-dihydroxy-6-hydroxymethyl-5-methyl-	224–225°	989, 990
4,6-dihydroxy-2-isoamyl-	—	1741
4,6-dihydroxy-5-isoamyl-	289°	1758
4,6-dihydroxy-5-isoamyl-2-phenyl-	>300°	130
4,6-dihydroxy-2-isobutoxy-	—	1741
4,6-dihydroxy-5-isobutyl-2-methyl-	—	129
2,4-dihydroxy-6-isopropoxy-5-isopropyl-	—	1769
2,4-dihydroxy-5-isopropyl-	288–289°	1770
2,4-dihydroxy-6-isopropyl-	199–200°	1181
2,4-dihydroxy-6-α-methoxyethyl-5-methyl-	217°	1768
2,4-dihydroxy-5-methoxymethyl-6-methyl-	>330°	694
2,4-dihydroxy-5-methyl-	326° *to* 340°	71, 74, 286, 1030, 1031, 66, 1355, 1771
2,4-dihydroxy-6-methyl-	313–315°	113,114,115,116,505
4,5 dihydroxy-2-methyl-	*ca.* 310°	83, 134
4,6-dihydroxy-2-methyl-	–	128, 129, 1747
4,6-dihydroxy-5-methyl-	320°	775
4,6-dihydroxy-2-methyl-5-phenyl-	>300°	130, 457
4,6-dihydroxy-5-methyl-2-phenyl-	>300°	130
2,4-dihydroxy-6-methyl-5-propyl-	247–248°	1118
4,6-dihydroxy-2-methyl-5-propyl-	>300°	129, 128, 350
4,6-dihydroxy-5-methyl-2-propyl-	—	132
2,4-dihydroxy-5-phenyl-	>350°	1328, 522
2,4-dihydroxy-6-phenyl-	272–274°	1328, 1773, 1639, 1774, 614, 799, 286, 829

(Table continued)

TABLE XXVI *(continued)*

Pyrimidine	M.p.	Reference
2,5-dihydroxy-4-phenyl-	—	1775, 1762
4,6-dihydroxy-2-phenyl-	326°	617, 130, 136
4,6-dihydroxy-5-phenyl-	>300°	351, 954
2,4-dihydroxy-6-propyl-	217–219°	1181
4,6-dihydroxy-2-propyl-	296°	352, 132
2,4-di-isobutoxy-6-methyl-	—	908
2,4-di-isopropoxy-6-methyl-	*pic.* 137°	817, 908
2,4-dimethoxy-5,6-dimethyl-	39–40°; 229°/*at.*	468
4,6-dimethoxy-5-methoxymethyl-2-methyl-	83–84°	484
2,4-dimethoxy-5-methyl-	61°; 322°/*at.*	729, 1355
2,4-dimethoxy-6-methyl-	69–70°; *pic.* 149°	817, 98, 612
2,4-dimethoxy-6-methyl-5-propyl-	135–140°/19 mm.	820
4,6-dimethoxy-2-propyl-	93–94°/8.5 mm.	132
2,4-dimethyl-6-phenoxy-	63°	704
4,6-dimethyl-2-phenoxy-	80–81°	1280, 819, 430
4-ethoxy-2,6-diethyl-5-methyl-	229–231°/*at.*	306
2-ethoxy-4,6-dihydroxy-5-phenyl-	218°	1759
2-ethoxy-4,6-dimethyl-	162°(?)	1375
4-ethoxy-6-ethoxymethyl-2-methyl-	*pic.* 91–93°	1776
2-ethoxy-5-ethyl-4,6-dihydroxy-	211°	1777
5-β-ethoxyethyl-4-hydroxy-6-methyl-	134–137°	690
2-ethoxy-4-hydroxy-6-methyl-	206°; *HCl* 312–314°	828, 1375, 117
4-ethoxy-2-hydroxy-5-methyl-	212–213°	807
4-ethoxy-6-hydroxy-2-methyl-	—	1748
4-ethoxy-2-hydroxy-6-methyl-5-propyl-	178–179°	929
2-ethoxy-4-methyl-	203–205°/*at.*; *pic.* 104–106°	818
5-ethoxymethyl-2,4-diethyl-6-hydroxy-	—	314
4-ethoxymethyl-2,6-dihydroxy-	175°	868
4-ethoxymethyl-2,6-dihydroxy-5-methyl-	220°	990
5-ethoxymethyl-2,4-dihydroxy-6-methyl-	312–315°	694
5-ethoxymethyl-2-ethyl-4-hydroxy-	146°	688
5-ethoxymethyl-2-ethyl-4-hydroxy-6-methyl-	51°	314
4-ethoxymethyl-6-hydroxy-2,5-dimethyl-	157–158°	867

(Table continued)

TABLE XXVI *(continued)*

Pyrimidine	M.p.	Reference
4-ethoxymethyl-6-hydroxy-2-hydroxymethyl-5-methyl-	124–126°	947
4-ethoxymethyl-6-hydroxy-2-methyl-	155–157°	1776
4-ethoxymethyl-6-hydroxy-5-methyl-	118°	688
5-ethoxymethyl-4-hydroxy-2-methyl-	178° *to* 182°	1781, 685, 484, 1049, 1782
4-ethoxy-6-methyl-2-phenyl-	30–31°; 300–301°/*at.*	968
4-ethoxy-2-phenyl-	180°/24 mm.	630
2-ethyl-4,6-dihydroxy-	294° *or* 299°	352, 131, 134
4-ethyl-2,6-dihydroxy-	201–203°	1181, 104, 720, 522
5-ethyl-2,4-dihydroxy-	300–303°	1328, 448, 1542, 634, 1465
5-ethyl-4,6-dihydroxy-	330°	351, 1758
2-ethyl-4,6-dihydroxy-5-β-hydroxyethyl-	267–268°	948
2-ethyl-4,6-dihydroxy-5-methyl-	>300°	350
5-ethyl-2,4-dihydroxy-6-methyl-	237–238°	107, 66, 836
5-ethyl-4,6-dihydroxy-2-methyl-	—	129, 128
5-ethyl-4,6-dihydroxy-2-phenyl-	>300°	130
5-ethyl-4,6-dihydroxy-2-propyl-	>300°	132, 350
5-ethyl-2,4-dimethoxy-	234–236°/*at.*	448
5-ethyl-2,4-dimethoxy-6-methyl-	118°/7 mm.	1735
5-ethyl-4,6-dimethoxy-2-propyl-	106–107°/7 mm.	132
5-ethyl-2-hexyl-4-hydroxy-6-methyl-	89°	1783
4-ethyl-2-hydroxy-	*HCl* 211–213°	722
4-ethyl-6-hydroxy-	170–171°	720
2-ethyl-4-hydroxy-5,6-dimethyl-	165°	452
4-ethyl-6-hydroxy-2,5-dimethyl-	168–169°	867, 319, 318
5-ethyl-4-hydroxy-2,6-dimethyl-	140–141°	867, 452
5-ethyl-4-hydroxy-2,6-diphenyl-	266°	49
5-ethyl-4-hydroxy-2,6-dipropyl-	97–98°	333
5-ethyl-4-hydroxy-2-isoamyl-6-methyl-	97°	1760
5-ethyl-4-hydroxy-2-isopropyl-6-methyl-	153°	1760
5-ethyl-4-hydroxy-2-methoxy-6-methyl-	210°	117
2-ethyl-4-hydroxy-5-methoxymethyl-6-methyl-	—	314
2-ethyl-4-hydroxy-6-methyl-	160°	968
4-ethyl-6-hydroxy-5-methyl-	161–162°	867
5-ethyl-4-hydroxy-6-methyl-2-phenyl-	167°	452, 1760

(Table continued)

TABLE XXVI *(continued)*

Pyrimidine	M.p.	Reference
5-ethyl-4-hydroxy-6-methyl-2-propyl-	121°	1760
2-ethyl-4-hydroxy-6-phenyl-	238°	452, 1760
5-ethyl-2,4,6-trihydroxy-	194°	757, 157, 144, 1784, 1785
5-ethyl-2,4,6-trimethoxy-	67–68°	448
2-hexyl-4,6-dihydroxy-	281°	1763
4-hexyl-2,6-dihydroxy-	186–187° *or* 170°	1521, 106
5-hexyl-2,4-dihydroxy-	272–273°	1328
5-hexyl-4,6-dihydroxy-2-methyl-	—	129
5-hexyl-4,6-dihydroxy-2-propyl-	>300°	132
4-hexyl-2-hydroxy-	—	1786
2-hexyl-4-hydroxy-5,6-dimethyl-	102°	1783
2-hexyl-4-hydroxy-6-methyl-	82°	1783
2-hexyl-4-hydroxy-6-phenyl-	167°	1783
5-hexyl-4-hydroxy-2-propyl-	65–67°	132
4-hydroxy-2,6-bis hydroxymethyl-5-methyl-	*HCl* 167–169°	947
4-hydroxy-2,6-di-isoamyl-5-isobutyl-	—	324
2-hydroxy-4,5-dimethyl-	196° *HCl* 250°	41, 1028
2-hydroxy-4,6-dimethyl-	194–196°	1280, 833, 611, 59, 56, 53, 100
4-hydroxy-2,5-dimethyl-	174°	1113, 1729
4-hydroxy-2,6-dimethyl-	194° *to* 201°	1787,867,1316,1788, 1772,452,308,315
4-hydroxy-5,6-dimethyl-	205-206°	141, 1113, 867, 468
2-hydroxy-4,6-dimethyl-5-phenyl-	241–242°	1638
4-hydroxy-2,5-dimethyl-6-phenyl-	180–181°	867
4-hydroxy-5,6-dimethyl-2-phenyl-	203°	452
4-hydroxy-5,6-dimethyl-2-propyl-	127°	1760
4-hydroxy-2,6-diphenyl-	289–290°	365, 1682, 1789, 452
5-hydroxy-2,6-diphenyl-(?)	—	931
4-hydroxy-2,6-diphenyl-5-propyl-	235°	49
4-hydroxy-2-β-hydroxyethyl-6-methyl-	163–165°	1790
4-hydroxy-5-β-hydroxyethyl-6-methyl-	154–155°	690
4-hydroxy-2-(1-hydroxy-1-methylethyl)-6-methyl-	98°	1760
4-hydroxy-2-(1-hydroxy-1-methylethyl)-6-phenyl-	198°	1760
4-hydroxy-5-hydroxymethyl-2-methyl-	215–216°	683, 950, 951
4-hydroxy-6-hydroxymethyl-2-methyl-	*HCl* 248–250°	1776

(Table continued)

TABLE XXVI *(continued)*

Pyrimidine	M.p.	Reference
4-hydroxy-2-isoamyl-5,6-dimethyl-	109°	1760
4-hydroxy-2-isoamyl-6-methyl-	100°	1760
4-hydroxy-2-isoamyl-6-phenyl-	164°	1760
4-hydroxy-2,6-di-isobutyl-5-isopropyl-	88–89°	324
4-hydroxy-2-isopropyl-5,6-dimethyl-	145°	1760
4-hydroxy-2-isopropyl-6-methyl-	170–172°	92, 1760
4-hydroxy-2-isopropyl-6-phenyl-	227°	1760
2-hydroxy-4-methoxy-6-methyl-	209–211°	469, 925
4-hydroxy-2-methoxy-6-methyl-	207°	117, 925, 831, 64
4-hydroxy-6-methoxymethyl-2,5-dimethyl-	159–160°	867
2-hydroxy-4-methoxymethyl-6-methyl-	*HCl* 162–172°; *pic.* 154–155°	962
4-hydroxy-5-methoxymethyl-2-methyl-	202–203°	1049
2-hydroxy-4-methoxy-6-methyl-5-propyl-	178–179°	929
2-hydroxy-4-methyl-	150°; *HCl* 246°	64, 580, 110, 1788, 570, 1366
4-hydroxy-2-methyl-	213–214°	126, 1792, 1793, 447
4-hydroxy-5-methyl-	153–154°	1113
4-hydroxy-6-methyl-	148–150°	997, 108, 64, 469, 867, 451, 1794, 429, 612, 399
4-hydroxy-5-methyl-2,6-diphenyl-	253°	49, 317, 319
2-hydroxy-4-methyl-6-phenyl-	228–229°	448, 50, 51
4-hydroxy-2-methyl-6-phenyl-	242°	365, 1789, 452,
4-hydroxy-6-methyl-2-phenyl-	215°	1783, 1315, 1789, 1795
4-hydroxy-2-methyl-5-propoxymethyl-	158–159°	1049
4-hydroxy-5-methyl-2-propyl-	145–146°	132
4-hydroxy-6-methyl-2-propyl-	143°	1760
4-hydroxy-6-methyl-5-propyl-	115–116°	1761
2-hydroxy-4-phenyl-	240–241°	34, 365 (?)
2-hydroxy-5-phenyl-	237°	33
4-hydroxy-2-phenyl-	207–208°	1797, 1791, 1760, 447
4-hydroxy-5-phenyl-	173–174°	297
4-hydroxy-6-phenyl-	267°	1796, 365(?)
4-hydroxy-6-phenyl-2-propyl-	183°	1760
4-hydroxy-2-propyl-	106–107°	132
2-hydroxy-4,5,6-trimethyl-	*hy.* 243°	53

(Table continued)

TABLE XXVI *(continued)*

Pyrimidine	M.p.	Reference
4-hydroxy-2,5,6-trimethyl-	176°	452, 1760, 867, 141
4-hydroxy-2,5,6-triphenyl-	>340°	323, 392
2-methoxy-4,6-dimethyl-	35–36°; 208–209°/*at.*	430, 1280
4-methoxy-2,6-dimethyl-	72°/15 mm.; *pic.* 124°	704
2-methoxy-4-methyl-	89°/21 mm.	64
4-methoxy-6-methyl-	69°/2 mm.; *pic.* 117°	64
4-methoxy-6-methyl-2-phenyl-	160°/22 mm.; *pic.* 175°	704
4-methyl-2,6-diphenoxy-	91°	817
4-methyl-2,6-dipropoxy-	*pic.* 101°	817, 908
4-methyl-2-phenoxy-	81–82°	819, 818
4-methyl-6-phenoxy-2-phenyl-	105°	704
2,4,6-tributoxy-5-s-butyl-	310–315°/*at.*	823
2,4,5-triethyl-6-hydroxy-	144°	323
2,4,5-trihydroxy-6-hydroxymethyl-	>320°	918
2,4,5-trihydroxy-6-methyl-	>220°	114, 1320, 986, 1798, 112
2,4,6-trihydroxy-5-methyl-	202–203°	157, 729, 147, 1799, 1800
4,5,6-trihydroxy-2-methyl-	—	83
4,5,6-trihydroxy-2-phenyl-	>230°	83

TABLE XXVII. Oxypyrimidines with *N*-Alkyl Groups

Pyrimidine	M.p.	Reference
alloxan/1,3-diethyl-	—	551
alloxan/1,3-dimethyl-	270–272°	1262, 1740, 1803, 1804, 1805
alloxan/1-ethyl-	*hy.* 103°	1806
alloxan/1-ethyl-3-methyl-	*ca.* 124°; *hy. ca.* 82°	1807
alloxan/1-methyl-	154–156°	1740, 1808, 1809, 1810
1-allyl-3-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-	—	1344
1-allyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-	45–47°	1811
1-allyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo-	59–61°	1811
barbituric acid/1,5-dimethyl-	169–170°	1812
barbituric acid/5-ethoxy-5-hydroxy-1-methyl-	*ca.* 150°	1740
barbituric acid/1-ethyl-	—	145

(Table continued)

TABLE XXVII *(continued)*

Pyrimidine	M.p.	Reference
barbituric acid/5-ethyl-1-methyl-	104°	1334
barbituric acid/5-hydroxy-1-methyl-	184–185°; *hy.* 167–168°	405
barbituric acid/1-methyl-	130–131°	154, 207, 145, 1333, 1813, 1627
barbituric acid/1,3,5-trimethyl-	89–90°	995
1-benzyloxy-1,2-dihydro-4,6-dimethyl-2-oxo-	130–131°	1814
1-benzyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-	84–85°	86, 1314, 1815
1-benzyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo-	166–167°	1314, 1815, 86
1-benzyl-1,2,3,6-tetrahydro-3,5-dimethyl-2,6-dioxo-	101°	1348
1-benzyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-	75°	1348
1-benzyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-phenyl-	226–227°	1314
5-butyl-1,2-dihydro-4-methoxy-1,6-dimethyl-4-oxo-	184°/1 mm.	1327
5-butyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	34–36°; 116°/0.06 mm.	1328
1,5-diethyl-1,6-dihydro-4-methyl-6-oxo-2-phenyl-	82°	941
1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxo-	14–15°; 135°/4 mm.	656
1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-	52–53°; 167°/19 mm.	154, 145, 551
1,3-diethyl-1,2,3,4-tetrahydro-5-methyl-2,4-dioxo-	65–67°; 140–143°/7 mm.	523
1,3-diethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-	52–53°	523, 1314, 1815, 1323, 1811
1,2-dihydro-4,6-dimethoxy-1-methyl-2-oxo-	96–97°	821
1,4-dihydro-1,2-dimethyl-4-oxo-	*pic.* 178–180°	719
1,4-dihydro-1,6-dimethyl-4-oxo-	*pic.* 174–176°	719
1,6-dihydro-1,2-dimethyl-6-oxo-	*pic.* 172°	719
1,6-dihydro-1,4-dimethyl-6-oxo-	80–82°; *pic.* 188–190°	719, 64
1,6-dihydro-4,5-dimethyl-4-oxo-1,2-diphenyl-	157°	941
1,6-dihydro-1,4-dimethyl-6-oxo-2-phenyl-	87–89°	1316
1,6-dihydro-4,5-dimethyl-6-oxo-1-phenyl-2-propyl-	73° (?)	941
1,2-dihydro-4-methoxy-1,5-dimethyl-2-oxo-	144°	1355, 442

(Table continued)

TABLE XXVII *(continued)*

Pyrimidine	M.p.	Reference
1,2-dihydro-4-methoxy-1,6-dimethyl-2-oxo-	134–135° *or* 112.5°	523, 908
1,2-dihydro-4-methoxy 1,6-dimethyl-2-oxo-5-propyl-	180–182°/4.5 mm.	820
1,2-dihydro-4-methoxy-1-methyl-2-oxo-	149–150°	1354, 656
1,2-dihydro-1-methyl-2-oxo-	127–128°; *pic.* 162–164°	273, 1108
1,4-dihydro-1-methyl-4-oxo-	155–156°; *pic.* 164–166°	273, 719, 1177
1,6-dihydro-1-methyl-6-oxo-	125–126°; *pic.* 175–176°	273, 719
1,4-dihydro-1-methyl-4-oxo-5-phenyl-	171–172° *or* 111–112°	297
1,6-dihydro-1-methyl-6-oxo-5-phenyl-	111–112° *or* 171–172°	297
1,2-dihydro-1-methyl-2-oxo-4-phenyl-	217°	291
1,2-dihydro-1-methyl-2-oxo-5-phenyl-	170°	33
1,2-dihydro-1,4,6-trimethyl-2-oxo-	63°	56, 58, 64
1,6-dihydro-1,2,4-trimethyl-6-oxo-(?)	*HI* 215°	1816
4-ethoxy-1,2-dihydro-1,5-dimethyl-2-oxo-	111°	523, 1355
4-ethoxy-1,2-dihydro-1-methyl-2-oxo-	—	1354
4-ethoxy-1-ethyl-1,2-dihydro-5-methyl-2-oxo-	78°	1355
4-ethoxy-1-ethyl-1,2-dihydro-2-oxo-	88°	1319, 523
5-ethoxyhexahydro-5-hydroxy-1,3-dimethyl-2,4,6-trioxo-	*ca.* 95°	1740
1-ethyl-1,6-dihydro-4,5-dimethyl-6-oxo-2-phenyl-	118°	941
5-ethyl-1,6-dihydro-2,4-dimethyl-6-oxo-1-phenyl-	126°(?)	941
5-ethyl-1,6-dihydro-4-methyl-6-oxo-1,2-diphenyl-	159°	941
5-ethyl-1,6-dihydro-4-methyl-6-oxo-1-phenyl-2-propyl-	106°(?)	941
1-ethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-	110–112°	1321, 1817
1-ethyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxo-	112–114°	1321, 1817
5-ethyl-1,2,3,4-tretahydro-1,3-dimethyl-2,4-dioxo-	*ca.* 82°	1328
1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	60–61°; 140–141°/4 mm.	656

(Table continued)

TABLE XXVII *(continued)*

Pyrimidine	M.p.	Reference
1-ethyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-3-propyl-	63–65°	1811
1-ethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxo-3-propyl-	38–40°	1811
hexahydro-5-hydroxy-5-methoxy-1,3-dimethyl-2,4,6-trioxo-	*ca.* 90°	1740
hexahydro-1,3,5,5-tetramethyl-2,4,6-trioxo-	110°	1818
1,2,3,4-tetrahydro-5,6-dihydroxy-1,3-dimethyl-2,4-dioxo-	170°, 218°, *or* 227–229°	849, 1805, 405
1,2,3,4-tetrahydro-5,6-dimethoxy-1,3-dimethyl-2,4-dioxo-	—	969
1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	121–122°	67, 656, 1328, 1317, 1634, 669
1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-phenyl-	147–148°	1328
1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-phenyl-	121–122°	1328, 287
1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-phenyl-	211°	1314, 1315, 1815
1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-phenyl-	300–302°	1314
1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-6-propyl-	60–61°; 173–176°/4.5 mm.	1328
1,2,3,4-tetrahydro-1,6-dimethyl-2,4-dioxo-3-propyl-	85–87°	1811
1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-1-propyl-	52–54°	1811
1,2,3,4-tetrahydro-5-hydroxy-1,3-dimethyl-2,4-dioxo-	198–199°	673, 849, 970, 890
1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	123°	145, 153, 1627, 1819, 996
1,2,3,4-tetrahydro-6-hydroxy-1,3,5-trimethyl-2,4-dioxo-	165°	145
1,2,3,4-tetrahydro-5-methoxy-1,3-dimethyl-2,4-dioxo-	191°	969, 970
1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxo-	164–166°	821, 1627
1,2,3,4-tetrahydro-1,3,5,6-tetramethyl-2,4-dioxo-	123–125°	955
1,2,3,4-tetrahydro-1,3,5-trimethyl-2,4-dioxo-	155°	1355, 669, 1034, 1317
1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-	111–112°	1320, 1321, 114, 1322, 284, 1323, 1324, 659, 1815, 908, 1314

(Table continued)

TABLE XXVII *(continued)*

Pyrimidine	M.p.	Reference
1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-propyl-	74–75°	820
uracil/5-acetoxy-3,6-dimethyl-	209–210°	1821
uracil/5-acetoxy-3-ethyl-6-methyl-	189°	1817
uracil/1-acetyl-	190–191°	985
uracil/1-allyl-6-methyl-	168–169°	1811
uracil/3-allyl-6-methyl-	184°	1811, 696, 1752
uracil/1-benzyl-	173–174°	835, 1348, 628
uracil/3-benzyl-	175°	1348
uracil/3-benzyl-5,6-dihydroxy-	139°	588
uracil/1-benzyl-5-ethoxy-	163–164°	588
uracil/3-benzyl-5-ethoxy-	150°	588
uracil/1-benzyl-5-hydroxy-	200–210°	588
uracil/3-benzyl-5-hydroxy-	230°	588
uracil/3-benzyl-5-hydroxy-6-methyl-	220°	1817
uracil/1-benzyl-5-methyl-	160°	1348
uracil/1-benzyl-6-methyl-	232–235°	1817, 86, 1822
uracil/3-benzyl-5-methyl-	204–205°	1348, 1823
uracil/3-benzyl-6-methyl-	198°	1817, 86, 1314, 1815
uracil/5-butyl-1,6-dimethyl-	151–152°	1327
uracil/1,5-dimethyl-	280° *to* 291°	1355, 88, 669
uracil/1,6-dimethyl-	221–222°	1321, 1824, 1304, 1315, 732, 925
uracil/3,5-dimethyl-	202–205°	669, 2146
uracil/3,6-dimethyl-	263–265° (274°?)	659, 1321, 1318, 1304, 1314, 925, 1326, 2148
uracil/5,6-dimethyl-3-phenyl-	235°	1825
uracil/1,6-dimethyl-5-propyl-	148–150°	820
uracil/3,6-dimethyl-5-propyl-	193–194°	820
uracil/5-ethoxy-3-methyl-	*ca.* 240°	934
uracil/1-ethyl-	147.5°	1319
uracil/3-ethyl-	173–174°	1318
uracil/1-ethyl-5-hydroxy-	250°	1266, 1321
uracil/3-ethyl-5-hydroxy-6-methyl-	230°	1817
uracil/1-ethyl-5-methyl-	223°	1355
uracil/1-ethyl-6-methyl-	194–196°	1817, 1323, 1822, 1811
uracil/3-ethyl-6-methyl-	206° (or 195°)	1314, 1815, (1817, 1811, 1276)
uracil/1-ethyl-6-propyl-	162–163°	1328
uracil/5-hydroxy-3,6-dimethyl-	335°	1829, 1827
uracil/5-hydroxy-1-methyl-	—	1266, 1321, 116
uracil/5-hydroxy-3-methyl-	247°	849, 934

(Table continued)

TABLE XXVII *(continued)*

Pyrimidine	M.p.	Reference
uracil/1-methyl-	233°	273, 656, 835, 1634, 370
uracil/3-methyl-	175° *to* 179°	273, 272, 274, 1634, 790, 1318
uracil/1-methyl-6-phenyl-	194–195°	287, 1828
uracil/3-methyl-6-phenyl-	228–230°	287, 1828
uracil/6-methyl-1-phenyl-	276°	888
uracil/6-methyl-3-phenyl-	244–245° *or* 258–259°	1324, 284, 1315, 1314
uracil/6-methyl-1-propyl-	170–172°	1811, 888
uracil/6-methyl-3-propyl-	184°	1811
uracil/1-phenyl-	246°	370, 1498
uracil/3-phenyl-	244–246°	370, 272, 101
uracil/1,5,6-trimethyl-	172–174°	955
uracil/3,5,6-trimethyl-	217–218°	659

TABLE XXVIII. Sulphonylpyrimidines

Pyrimidine	M.p.	Reference
2-benzenesulphonamido-	231–232°	1226, 647, 1225
2-benzenesulphonamido-4,6-dimethyl-	150–152°	962
2-benzenesulphonamido-4-methyl-	193–194°	1226, 647
2-benzylsulphamoyl-4,6-dimethyl-	130–131°	1143
2-benzylsulphonyl-4,6-diphenyl-	199–200°	384
2,4-bisbenzenesulphonylhydrazino-	219°	434
2,4-bisethylsulphonyl-	87–88°	635
2-chlorosulphonyl-	—	833
2-chlorosulphonyl-4,6-dimethyl-	—	833, 1143
4,6-dimethyl-2-propylsulphamoyl-	111–112°	1143
4,6-dimethyl-2-sulphamoyl-	200°	1143, 833
2,6-dimethyl-4-sulpho-	*Na* 285°	724
4-methyl-2-sulpho-	—	724
2-sulphamoyl-	180–181°	833, 1143
2-sulpho-	—	724

TABLE XXIX. Thiopyrimidines

Pyrimidine	M.p.	Reference
1-benzyl-1,2-dihydro-4-phenyl-2-thio-	160–161°	1802
5-benzyl-2,4-dimercapto-	262°	1123
2-benzylthio-4,6-dimethyl-	65–67°	1820
2-benzylthio-4,6-diphenyl-	147–148°	384
2,4-bisethylthio-	135–140°/6 mm.	635, 910, 804
1,2-dihydro-1-methyl-2-thio-	189–191°	984
1,2-dihydro-1,4,6-trimethyl-2-thio-	156°	58
2,4-dimercapto-	*ca.* 230° *or ca.* 270–280°	974, 356, 1826, 48, 982, 30, 75
2,4-dimercapto-5,6-dimethyl-	>300°	468
2,4-dimercapto-5-methyl-	281°	974, 983
2,4-dimercapto-6-methyl-	240° *to* >280°	281, 776, 832, 982, 612, 1347, 385
2,4-dimercapto-5-phenyl-	—	1829
2,4-dimercapto-6-phenyl-	264–268°	974, 982, 983
4,6-dimethyl-2-methylthio-	24°; 120–122°/17 mm.	1639, 32, 58, 65
2,4-diselenyl-	208–209°	75
dithiouracil/1-methyl-	254–255°	171
dithiouracil/3-methyl-	213°	281
4-ethyl-2,6-dimercapto-5-methyl-	—	982, 983
5-ethyl-2,4-dimercapto-6-methyl-	250–280°	836
4-ethyl-2-ethylthio-	105–107°/4 mm.	722
2-ethylthio-	115°/20 mm. *HCl* 98–99°	628, 721
2-ethylthio-4-mercapto-	149°	835, 48
2-ethylthio-4-mercapto-5,6-dimethyl-	187–188°	96
2-ethylthio-4-mercapto-5-methyl-	181°	88, 837
2-ethylthio-4-mercapto-6-methyl-	205°	776, 832
2-ethylthio-4-mercapto-5-phenyl-	171°	841
2-ethylthio-4-mercapto-6-phenyl-	206–207°	842
2-ethylthio-4-methyl-	123–124°/18 mm.; *HCl* 141–142°	721
2-mercapto-	230°	431, 833, 30, 644, 1644
4-mercapto-	*HCl* 220°	30, 644
2-mercapto-4,6-dimethyl-	210°	431, 30, 1639, 1830
4-mercapto-2,6-dimethyl-	*ca.* 230°	776, 1830
4-mercapto-5,6-dimethyl-	200–265°	468
2-mercapto-4,6-dimethyl-5-phenyl-	225–226°	1638
2-mercapto-4-methyl-	*ca.* 208°	64, 1831, 831, 570, 1366
4-mercapto-6-methyl-	255–260°	64, 612

(Table continued)

TABLE XXIX *(continued)*

Pyrimidine	M.p.	Reference
4-mercapto-6-methyl-2-methylthio-	214°	776, 1347
2-mercapto-4-methyl-6-phenyl-	199–200°	448
4-mercapto-2-methylthio-	—	1767
2-mercapto-4-phenyl-	>180°	1802
4-methyl-2-methylthio-	111°/15 mm.; *pic.* 106–108°	64, 712, 110
4-methyl-6-methylthio-	25–28°; 104°/17 mm.	64
4-methyl-2-methylthio-6-phenyl-	154–160°/1 mm.	631
2-methylthio-	99°/14 mm.; *pic.* 89–90°	628, 629, 611, 712, 1641, 644
2-methylthio-4-phenyl-	86–87°	712
1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dithio-	121°	827, *not* 1832
2,4,6-trimercapto-	—	624

TABLE XXX. Amino-Carboxypyrimidines

Pyrimidine	M.p.	Reference
2-acetamido-5-acetyl-4-methyl-	152–153°	1209
4-amino-5-aminomethyl-2-carbamoylmethyl-	*pic.* 197°	1651
2-amino-5-amyl-4-caboxy-	191–192°	36
2-amino-5-azidocarbonyl-	133–135°	1696
4-amino-2-benzyl-5-carbamoylmethyl-	239°	684
4-amino-2-benzyl-5-cyano-	180°	302, 293, 1651, 1833
4-amino-2-butyl-5-cyano-	148°	1187
4-amino-5-carbamoyl-	254–256°	726
4-amino-6-carbamoyl-	*pic.* 273°	1384
4-amino-5-β-carbamoylethyl-2-methyl-	195–200°	684
2-amino-4-carbamoyl-6-methyl-	—	1451
4-amino-5-carbamoyl-2-methyl-	264–265°	204, 205, 1386
4-amino-2-carbamoylmethyl-5-cyano-	258°	1651
4-amino-5-carbomoylmethyl-2-ethyl-	236°	684
4-amino-carbamoylmethyl-2-methyl-	250°	684, 601, 679, 1834
4-amino-5-carbamoylmethyl-6-methyl-	223°	601

(Table continued)

TABLE XXX *(continued)*

Pyrimidine	M.p.	Reference
2-amino-4-carboxy-	285°	1195
2-amino-5-carboxy-	>300°	89
4-amino-5-carboxy-	278–281°	726, 274
2-amino-4-carboxy-6-methyl-	300–302°	1672
2-amino-5-carboxy-4-methyl-	314–316° (*or* 256–258°)	1672, 1376
4-amino-5-carboxy-2-methyl-	275°	1394, 205, 1673
5-amino-4-carboxy-2-methyl-	191–192°	44
4-amino-2-carboxymethylthio-5-ethoxycarbonyl-	174–177°	194
4-amino-2-carboxymethylthio-6-methylamino-	—	1835
5-amino-4-carboxy-2-phenyl-	196°	270
2-amino-5-cyano-	300–310°	647
4-amino-5-cyano-	250°	250, 127, 1833, 726
4-amino-5-cyano-2,6-dimethyl-	220–225°	134, 127, 1185
4-amino-5-cyano-2,6-diphenyl-	211°	127
4-amino-5-cyano-2-ethyl-	198° *or* 202°	134, 1651
2-amino-4-cyano-6-methyl-(?)	—	1451
2-amino-5-cyano-4-methyl-	269–270°	852
4-amino-5-cyano-2-methyl-	249°	260, 1836, 1651, 1833, 627, 1403, 1182, 459, 1274
2-amino-5-cyano-4-phenyl-	—	1837, 1675
4-amino-5-cyano-2-phenyl-	226°	134
4-amino-5-cyano-2-vinyl-	219–220°	1838
2-amino-4,5-dicarboxy-	>300°	275
2-amino-4,5-diethoxycarbonyl-	151–152°	275
2-amino-4-diethoxymethyl-	134–135°	172
2-amino-4-diethoxymethyl-6-methyl-	87–88°	172
2-amino-4-dimethoxymethyl-6-methyl-	74–75°	172
2-amino-5-ethoxycarbonyl-	147–149°	89
4-amino-5-ethoxycarbonyl-2,6-dimethyl-	129°	260
2-amino-4-ethoxycarbonyl-6-methyl-	151°	1672
2-amino-5-ethoxycarbonyl-4-methyl-	220°	1672, 1376
4-amino-5-ethoxycarbonyl-2-methyl-	120°	204, 302, 127, 1839
4-amino-2-ethyl-5-formyl-	*d.n.p.* 290°	1411
4-amino-5-formimidoyl-2-methyl-(?)	—	1406
4-amino-5-formyl-2-methyl-	195–196°	1394, 1403, 1404, 1840, 1410

(Table continued)

TABLE XXX *(continued)*

Pyrimidine	M.p.	Reference
4-amino-5-hydrazinocarbonyl-2-methyl-	220–221°	1841
4-amino-5-hydrazinocarbonylmethyl-2-methyl-	235°	1218
5-carbamoylmethyl-2-methyl-4-methylamino-	156°	684
5-caboxymethyl-2-methyl-4-methylamino-	217°	684, 1218
5-cyano-2-methyl-4-methylamino-	151–152°	1218
2,4-diacetamido-5-cyano-	197–198°	1186
2,4-diamino-5-carbamoyl-	>320°	459
4,6-diamino-2-carboxy-	>360°	355
2,4-diamino-5-carboxymethyl-6-methyl-	279–280°	809
2,4-diamino-6-carboxymethylthio-	—	1835
4,6-diamino-2-carboxymethylthio-	—	1835
2,4-diamino-5-cyano-	318°	1186, 134
4,6-diamino-2-cyanomethyl-	241–243°	133
4,6-diamino-5-cyano-2-methyl-	—	627
2,4-diamino-5-ethoxycarbonyl-	207°	187, 807, 806
2,5-diamino-4-formyl-6-methyl-	—	536

TABLE XXXI. Amino-Halogenopyrimidines

Pyrimidine	M.p.	Reference
5-acetamido-4-amino-2-chloro-	214–215°	2144
2-acetamido-5-chloro-	188°	1842
5-acetamido-4-chloro-2,6-dimethyl-	141–142°	775
4-amino-5-aminomethyl-2-trifluoromethyl-	147–148°	1000
2-amino-5-amyl-4-chloro-6-methyl-	151–153°	35
4-amino-5-amyl-6-chloro-2-methyl-	144–145°	129
2-amino-4-anilino-5-bromo-6-methyl-	152–153°	677
2-amino-5-benzyl-4-chloro-	183°	82, 1655, 735
4-amino-5-benzyl-2-chloro-	162°	735, 1718
2-amino-5-benzyl-4-chloro-6-methyl-	184–185°	141

(Table continued)

TABLE XXXI *(continued)*

Pyrimidine	M.p.	Reference
2-amino-5-benzyl-4-chloro-6-phenyl-	—	1653
2-amino-5-benzyl-4,6-dichloro-	204–205°	642
4-amino-5-benzyl-2,6-dichloro-	164°	642
4-amino-2,4-bis-α-chloroethyl-5-chloromethyl-	110°	322, 314
4-amino-2,4-bis-β-bromoethyl-5-bromomethyl-	126°	314, 322
2-amino-4-bromo-	>130°	638
2-amino-5-bromo-	235–237°	639, 640, 831
4-amino-5-bromo-	208–210°	626
2-amino-5-bromo-4,6-bis-bromomethyl-	182–184°	483
2-amino-5-bromo-4-chloro-6-methyl-	207–208°	775, 852
4-amino-5-bromo-2,6-diethyl-	155°	316
2-amino-5-bromo-4,6-dimethyl-	187–188°	639, 134, 483, 831
4-amino-5-bromo-2,6-dimethyl-	141–142°	310, 308, 311
4-amino-6-bromo-2-ethyl-	142°	131
2-amino-5-β-bromoethyl-4-methyl-	159–160°	172
4-amino-5-(2-bromoisobutyl)-2-methyl-	*HBr* 187–188°	681
2-amino-4-bromo-6-methyl-	153°	638
4-amino-5-bromo-2-methyl-	137–138°; *hy.* 103–104°	44
4-amino-5-bromomethyl-	—	1843
4-amino-5-bromomethyl-2-butyl-	*HBr* 167–169°	689
4-amino-5-bromomethyl-2-chloro-	*ca.* 210°	187
4-amino-5-bromomethyl-2-ethyl-	*HBr* 175–178°	688, 1843
2-amino-5-bromo-4-methyl-	192–194°	640, 40
4-amino-5-bromo-6-methyl-	197°	504
4-amino-5-bromomethyl-2,6-diethyl-	153°	314, 322
4-amino-5-bromomethyl-2-methyl-	*HBr* 192° *to* 213°	684, 678, 601, 685, 679, 206, 680
4-amino-5-bromomethyl-6-methyl-	—	601
4-amino-5-bromomethyl-2-phenyl-	*HBr* 165°	684
4-amino-5-butyl-6-chloro-2-methyl-	168°	129
2-amino-5-butyl-4,6-dichloro-	170–171°	35
2-amino-4-chloro-	*ca.* 168°	463, 496, 497, 1844, 620
2-amino-5-chloro-	234–236°	28, 639, 1845, 1842, 1846, 640

(Table continued)

TABLE XXXI *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2-chloro-	206–207°	496, 497, 667, 713
4-amino-5-chloro-	192–194°	626
4-amino-6-chloro-	215° *or* 205°	623, 827
5-amino-2-chloro-	198–199°	28
2-amino-4-chloro-5-β-chloroethyl-6-methyl-	165–190°	1847
4-amino-2-chloro-5-chloromethyl-	*HCl* 215°	187
4-amino-6-chloro-5-diethylaminomethyl-2-methyl-	76°	869
2-amino-4-chloro-5,6-dimethyl-	215–216°	172, 468
2-amino-5-chloro-4,6-dimethyl-	182–184°	1848
4-amino-2-chloro-5,6-dimethyl-	182–183°	468
4-amino-5-chloro-2,6-dimethyl-	165°	311, 310
4-amino-6-chloro-2,5-dimethyl-	199°	134, 129
5-amino-4-chloro-2,6-dimethyl-	80°; *pic.* 169°	601, 775, 1657
2-amino-4-chloro-6-dimethylamino-	162–165°	622, 174
4-amino-6-chloro-2-dimethylamino-	142–143° *or* 151°	622, 173
5-amino-2-chloro-4-dimethylamino-6-methyl-	63°	536
4-amino-6-chloro-5-dimethylaminomethyl-2-methyl-	115–116°	869
2-amino-4-chloro-6-ethyl-	120–121° *or* 129–130°	99, 134, 722
2-amino-4-chloro-6-ethylamino-	152–153°	1657
4-amino-6-chloro-2-ethylamino-	113–114°	1849
2-amino-4-chloro-5-ethyl-6-methyl-	156–157°	35, 836
4-amino-2-chloro-5-ethyl-6-methyl-	222°	836
4-amino-6-chloro-5-ethyl-2-methyl-	229–231°	129
2-amino-4-chloro-6-hexyl-	61–62°	35
4-amino-6-chloro-5-hexyl-2-methyl-	152–153°	129
4-amino-6-chloro-5-hexyl-2-propyl-	101–102°	132
2-amino-4-chloro-5-methyl-	184–185°	775
2-amino-4-chloro-6-methyl-	182–183°	64, 1153, 612, 504
2-amino-5-chloro-4-methyl-	189–191°	640
4-amino-2-chloro-6-methyl-	215–216°	64, 612, 504
4-amino-5-chloro-2-methyl-	145–146°	44
4-amino-5-chloro-6-methyl-	197–198°	504
4-amino-6-chloro-2-methyl-	190–191°	550, 202, 129, 870, 916, 914
4-amino-6-chloro-5-methyl-	237–238°	775, 1737

(Table continued)

TABLE XXXI *(continued)*

Pyrimidine	M.p.	Reference
5-amino-2-chloro-4-methyl-	93–94°	1674, 64, 504
2-amino-4-chloro-6-methylamino-	162–163°	1849
5-amino-4-chloro-6-methylamino-	162° *to* 167°	534, 1850
4-amino-5-chloromethyl-2-methyl-	163°; *HCl* 214–215°	684, 1782, 1839
5-amino-4-chloro-2-methyl-6-methylamino-	127–128°	534
2-amino-4-chloro-5-methyl-6-phenyl-	127–128°	1711, 1702
4-amino-6-chloro-5-methyl-2-propyl-	171–172°	132
4-amino-5-chloromethyl-2-trifluoromethyl-	191–192°	353
2-amino-4-chloro-6-phenyl-	148°	1711
2-amino-4-chloro-6-phenyl-5-propyl-	—	1711, 1653
4-amino-6-chloro-2-propyl-	127–129°	132
2-amino-4,6-dibromo-	190–192°	638
2-amino-4,6-dichloro-	221°	622, 714, 624, 632
4-amino-2,6-dichloro-	270°	1231, 512, 624
5-amino-2,4-dichloro-	121–122°	435
5-amino-4,6-dichloro-	147–148°	534, 616
2-amino-4,6-dichloro-5-ethyl-	191–192°	448
4-amino-2,6-dichloro-5-ethyl-	214–216°	448
4-amino-2,6-dichloro-5-formamido-	216–217°	616
2-amino-4.6-dichloro-5-methyl-	249°	729, 775
4-amino-2,6-dichloro-5-methyl-	201°	729
5-amino-2,4-dichloro-6-methyl-	115–116°	1674, 454
5-amino-4,6-dichloro-2-methyl-	70–72°	505, 789
2-amino-4,6-dichloro-5-phenyl-	221–222°	788
4-amino-2,6-diethyl-5-iodomethyl-	152°	314
2-amino-4,6-di-iodo-	—	1851
4-amino-5-ethyl-6-iodo-	191–193°	448
2-amino-5-iodo-	224–225°	655
4-amino-5-iodo-	230–231°	356, 171
2-amino-5-iodo-4,6-dimethyl-	185°	63
4-amino-5-iodo-2,6-dimethyl-	—	327, 328
4-amino-6-iodo-5-methyl-	238°	729
2-amino-4,5,6-trichloro-	236–237°	632
4-amino-2,5,6-trichloro-	170–171°	881
5-amino-2,4,6-trichloro-	116–117°	616
4-amino-6-trifluoromethyl-	165–170°	443
2-anilino-5-bromo-4-chloro-	106°	522
2-anilino-5-bromo-4,6-dimethyl-	179–180°	677
4-anilino-5-bromo-2,6-dimethyl-	98–99°	677

(Table continued)

TABLE XXXI *(continued)*

Pyrimidine	M.p.	Reference
2-anilino-4-chloro-	134°	625
4-anilino-6-chloro-	154–156°	786
2-anilino-4-chloro-6-methyl-	92–93°	1125, 1471
4-anilino-6-chloro-2-methyl-	134–135°	826
4-anilino-6-chloro-2-phenyl-	132–134°	786
4-anilino-2,6-dichloro-	137–138°	718
4-anilino-2(or 4)-iodo-	166°	718
4-aziridino-6-chloro-2-phenyl-	66–67°	617
2-aziridino-4,6-dichloro-	105°	617
4-aziridino-2,6-dichloro-	111°	617
2-benzylamino-5-bromo-	134-136°	1852
2-benzylamino-4-chloro-	255–257° *or* 272°	1201, 1202
2-benzylamino-5-chloro-	130–132°	1852
2-benzylamino-4-chloro-6-methyl-	133–134°	1852, 1691
2-benzylamino-4,6-dichloro-	130–132°	1152, 1852
5-benzyl-4-benzylamino-2-chloro-	118°	735, 1853
5-benzyl-2-chloro-4-cyclohexylamino-	94°	735, 1853
5-benzyl-2-chloro-4-methylamino-	166°	1853, 753
5-benzyl-2-chloro-4-piperidino-	68°	735, 1853
2-bromo-4-dimethylamino-6-methyl-	93°	734
5-bromo-2,6-dimethyl-4-thioureido-	205°	645
5-bromo-4-hydrazino-	185–187°	626
4-bromo-2-isopropylamino-6-methyl-	200–201°	1849
2-butylamino-4-chloro-6-methyl-	154–156°	1849
4-chloro-2,6-bismethylamino-	134°	1849, 718
4-chloro-2,6-bisdimethylamino-	52°	622, 173
2-chloro-4-dibutylamino-6-methyl-	162°/3 mm.	734
2-chloro-4-diethylamino-6-methyl-	150°; *HCl* 162°	734, 1854
4-chloro-2-diethylamino-6-methylamino-	39–40°; *sul.* 148–149°	174, 1855
2-chloro-4-dimethylamino-	81°	734
4-chloro-2-dimenthylamino-	41–42°; *pic.* 144–145°	72
2-chloro-4-dimethylamino-5,6-dimethyl-	92–93°	734
2-chloro-4-dimethylamino-6-ethyl-	128°/2 mm.	734
2-chloro-4-dimethylamino-6-methyl-	87°	734, 1854
4-chloro-2-dimethylamino-6-methyl-	35–36°; *pic.* 128–129°	98

(Table continued)

TABLE XXXI *(continued)*

Pyrimidine	M.p.	Reference
4-chloro-2-dimethylamino-6-methylamino-	78°; 122–125°/1 mm.	173, 174
4-chloro-2,6-dipiperidino-	95–96°	1856
4-chloro-2-ethylamino-6-methylamino-	*sul.* 148°	174
4-chloro-6-ethyl-2-methylamino-	74–75°	1849
2-chloro-4-ethylmethylamino-6-methyl-	119°/1.5 mm.	734
4-chloro-5-formamido-2,6-dimethyl-	158–159°	775
4-chloro-6-hydrazino-	177°	626
5-chloro-4-hydrazino-	190–192°	626
4-chloro-6-methylamino-	137–138°	280, 1849
5-chloro-2-methylamino-	122–124°	647
4-chloro-6-methylamino-2-piperidino-	118°	147
4-chloro-5-methyl-2-methylamino-	131°	1129
4-chloro-6-methyl-2-methylamino-	135°	1129
4-chloro-5-methyl-2-phenylguanidino-	—	1857
2-chloro-4-methyl-6-piperidino-	—	734
4-chloro-6-methyl-2-piperidino-	292–293°/*at.*; *pic.* 98–99°	141
2-chloro-4-thioureido-	316–318°	846
2,4-diamino-5-benzyl-6-chloro-	163°	642
2,4-diamino-5-benzyl-6-iodo-	191–192°	642
2,4-diamino-5-bromo-	217°	639
4,6-diamino-5-bromo-	213°	1858, 171
2,4-diamino-5-β-bromoethyl-6-methyl-	—	1734
2,4-diamino-5-bromo-6-methyl-	188–189°	471
2,4-diamino-6-chloro-	198°	775, 1658, 624, 512
4,5-diamino-2-chloro-	232°	360, 716, 616, 1859
4,5-diamino-6-chloro-	252°	361, 531, 1697, 1859
2,4-diamino-6-chloro-5-ethyl-	183°	448
4,5-diamino-2-chloro-6-ethyl-	203°	104
2,4-diamino-6-chloro-5-methyl-	199–200°	729
2,5-diamino-4-chloro-6-methyl-	198°	63
4,5-diamino-2-chloro-6-methyl-	*ca.* 250°	513, 504
2,4-diamino-6-chloro-5-phenyl-	244–245°	1709
2,4-diamino-5,6-dichloro-	218–220°	632
2,5-diamino-4,6-dichloro-	260–261°	616
4,5-diamino-2,6-dichloro-	268°	513
4,6-diamino-2,5-dichloro-	302–304°	633, 632, 881
2,4-dianilino-5-bromo-	191°	522
4,6- (or 2,4)-dianilino 2 (or 4)-chloro-	HCl 220°	718

(Table continued)

TABLE XXXI *(continued)*

Pyrimidine	M.p.	Reference
2,4-diaziridino-6-chloro-	94–95°	617, 787
2,4-diaziridino-6-chloro-5-phenyl-	116–118°	617, 787
2,4-dichloro-6-dimethylamino-	113°	583
4,6-dichloro-2-dimethylamino-	54°	173, 1855
2,5-dichloro-4-hydrazino-	*ca.* 220°	626
2,4-dichloro-6-methylamino-	186°	718
4,6-dichloro-2-methylamino-	164°	174, 718
2,4,5-triamino-6-chloro-	—	1043
2,4,6-triamino-5-chloro-	201–203°	632, 881
4,5,6-triamino-2-chloro-	250–260°	513

TABLE XXXII. Amino-Nitropyrimidines

Pyrimidine	M.p.	Reference
2-acetamido-5-nitro	187–188°	28, 773, 25
2-amino-4-anilino-6-methyl-5-nitro-	192–193°	930
2-amino-4-anilino-5-nitro-	206–207°	980
4-amino-6-anilino-5-nitro-	212–214°	511
4-amino-6-benzylamino-5-nitro-	191–194°	511
4-amino-2-diethylamino-6-methyl-5-nitro	73–74°	785
4-amino-2-diethylamino-5-nitro-	109–110°	780
4-amino-6-diethylamino-5-nitro-	119°	780
2-amino-4,6-diethyl-5-phenylazo-	156°	63
2-amino-4-dimethylamino-6-methyl-5-nitro-	192–193°	63
4-amino-2-dimethylamino-5-nitro-	210–211°	360, 507
4-amino-6-dimethylamino-5-nitro-	159–161°	361
2-amino-4,6-dimethyl-5-nitro-	225°	536
2-amino-4,6-dimethyl-5-phenylazo-	228–230°	775, 63
2-amino-4-ethyl-6-methyl-5-phenylazo-	171°	63
4-amino-2-methylamino-5-nitro-	226–228°	361
4-amino-6-methylamino-5-nitro-	241–245°	511
2-amino-4-methyl-5-phenylazo-6-propyl-	108°	63
2-amino-4-methyl-6-phenyl-5-phenylazo-	158°	63
2-amino-5-nitro-	236°	28, 773, 499, 25
2-amino-5-phenylazo-	—	774

(Table continued)

TABLE XXXII *(continued)*

Pyrimidine	M.p.	Reference
2-amylamino-4,6-dimethyl-5-phenylazo-	92–93°	63
2-benzylamino-5-nitro-	182–184°	1202
2,4-bisdimethylamino-6-methyl-5-nitro-	122–123°	536
2,4-bisdimethylamino-5-nitro-	88–92°	1656
2,4-bismethylamino-5-nitro-	253–255°	534, 1656
4,6-bismethylamino-5-nitro-	192–195°	534
2-butylamino-4,6-dimethyl-5-phenylazo	89°	63
2-butylamino-5-nitro-	122°	772
4,6-diamino-2-benzyl-5-phenylazo-	275°	1181
4,6-diamino-2-butyl-5-phenylazo-	262°	1181
4,6-diamino-2-dibutylamino-5-nitro-	*ca.* 88–90°	1181
4,6-diamino-2-dimethylamino-5-nitro-	249–250°	174
2,4-diamino-6-dimethylamino-5-nitroso-	258–259°	1704, 1705
4,6-diamino-2-dimethylamino-5-nitroso-	283°	1152, 257, 1705
2,4-diamino-6-ethyl-5-nitro-	179° *and* 191°	1181
4,6-diamino-2-ethyl-5-phenylazo-	263–264°	1181
4.6-diamino-2-isobutyl-5-phenylazo-	260–261°	1181
2,4-diamino-6-isopropyl-5-nitro-	152–154°	1181
2,4-diamino-6-methylamino-5-nitroso-	245–247°	1704, 1705
2,4-diamino-6-methyl-5-nitro-	235°	531, 778, 504, 1275
4,6-diamino-2-methyl-5-nitro-	—	615
4,6-diamino-2-methyl-5-nitroso-	>300°	550, 1860, 1646
2,4-diamino-6-methyl-5-phenylazo-	224–226°	979
2,4-diamino-5-nitro-	345–350°	360, 777, 778
4,6-diamino-5-nitro-	>360°	531, 356, 506, 1181
2,4-diamino-5-nitro-6-propyl-	162–164°	1181
4,6-diamino-5-nitroso-	—	1181, 552
4,6-diamino-5-nitroso-2-phenyl-	—	1860
2,4-diamino-5-nitroso-6-piperidino-	211–213°	1704, 1705
4,6-diamino-5-phenylazo-	282–286° *or* 302°	250, 1110, 1717, 579
4,6-diamino-5-phenylazo-2-propyl-	255–256°	1181
4,6-diamino-2-phenyl-5-phenylazo-	294–295°	1181
2,4-dianilino-5-nitro	203-204°	779, 1372

(Table continued)

TABLE XXXII *(continued)*

Pyrimidine	M.p.	Reference
4,6-diaziridino-2-dimethylamino-5-nitro-	—	787
4,6-diaziridino-2-methyl-5-nitro-	130°	617
2,4-diaziridino-5-nitro-	160°	617, 787
4,6-diaziridino-5-nitro-	130°	617, 787
4,6-diaziridino-5-nitro-2-phenyl-	160°	617, 787
2-diethylamino-5-nitro-	104–105°	772
2-dimethylamino-4,6-dimethyl-5-phenylazo-	99°	63
2-dimethylamino-5-nitro-	222°	772
4,6-dimethyl-2-methylamino-5-phenylazo-	161°	63
4,6-dimethyl-5-phenylazo-2-piperidino-	107°	63
4,6-dimethyl-5-phenylazo-2-propylamino-	136°	63
2-dipropylamino-5-nitro-	45–46°	772
2-ethylamino-4,6-dimethyl-5-phenylazo-	122°	63
2-ethylamino-5-nitro-	175°	772
2-isobutylamino-4,6-dimethyl-5-phenylazo-	104°	63
2-isopropylamino-4,6-dimethyl-5-phenylazo-	75–76°	63
2-methylamino-5-nitro-	227–229°	772
4-methyl-6-nitroamino-	190–200°	504
5-nitro-2,4-bispropylamino-	121–122°	779
5-nitro-2-piperidino-	147–148°	30
5-nitro-2-propylamino-	119°	772
2,4,6-triamino-5-nitro-	>270°	512
2,4,6-triamino-5-nitroso-	—	264, 1716, 1860
2,4,6-triamino-5-phenylazo-	*ca.* 262–263°	980

TABLE XXXIII. Amino-Oxypyrimidines Without $N_{(1)}$- or $N_{(3)}$- Substituents

Pyrimidine	M.p.	Reference
2-acetamido-5-acetoxy-4-hydroxy-6-methyl-	232–233°	938
5-acetamido-4-amino-2,6-dihydroxy-	205–207°	1862, 396, 1863
2-acetamido-5-amino-4-hydroxy-6-methyl-	246°	1196

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
2-acetamido-5-benzamido-4-hydroxy-6-methyl-	278–279°	1196
2-acetamido-5-benzylideneamino-4-hydroxy-6-methyl-	266–268°	1196
4-acetamido-2,6-bisacetoxymethyl-5-hydroxy	115–117°	1392
4-acetamido-5-diacetylamino-2,6-dihydroxy-	—	1865
5-acetamido-2,4-diamino-6-hydroxy-	343–344°	254
2-acetamido-4,6-dihydroxy- (?)	>325°	1206
5-acetamido-2,4-dihydroxy-	—	532
5-acetamido-2,4-dihydroxy-6-methyl-	*ca.* 220°	1265
5-acetamido-2-dimethylamino-4-hydroxy-6-methyl-	225–227°	1866
2-acetamido-4-hydroxy-	249–250°	1206, 650
4-acetamido-2-hydroxy-	>300°	650, 1468
5-acetamido-4-hydroxy-2,6-dimethyl-	275°	775, 1867, 1646
2-acetamido-4-hydroxy-6-methyl-	218–219°	1203
2-acetamido-4-hydroxy-5-methyl-6-phenyl-	289–290°	1208
5-acetamidomethyl-4-hydroxy 2-methyl-	219–220°	683
5-acetamido-2,4,6-trihydroxy-	—	1864, 1868, 1869
2-acetylhydrazino-4-hydroxy-6-methyl	258°	1312
alloxan/5-phenylhydrazino-	—	594, 595, 1955, 859
2-allylamino-4-hydroxy-6-methyl-	149°	100
5-allyl-2-amino-4-hydroxy-6-methyl-	266–267°	1744
5-allyl-2-amino-4-hydroxy-6-phenyl-	302–304°	1870
2-aminoalloxan	—	1871
5-amino-2-aminomethyl-4,6-dihydroxy-	*HCl* 200°	584
4-amino-5-aminoethyl-2-hydroxy-	264–267°	1698
4-amino-5-aminomethyl-2-α-hydroxyethyl-	*HCl* 255°	1651
4-amino-5-aminomethyl-2-β-hydroxyethyl-	*ca.* 270°; *pic.* 216–217°	1838
4-amino-5-aminoethyl-2-hydroxymethyl-	*HCl* 246°	1651
2-amino-4-amoxy-6-methyl-	51–52°	172

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-5-amoxymethyl-2-methyl-	69°	1872
2-amino-5-amyl-4-hydroxy-6-methyl-	249–250°	35
4-amino-5-amyl-6-hydroxy-2-methyl-	250–251°	129
4-amino-2-anilino-5-ethoxy-	133–134°	625
4-amino-2-anilino-6-hydroxy-	244°	226
2-amino-5-benzamido-4-hydroxy-	316° or *ca.* 275°	1873, 503
2-amino-5-benzamido-4-hydroxy-6-methyl-	267–268°	1196
4-amino-5-benzylamino-2,6-dihydroxy-	265°	1267
4-amino-5-benzyl-2-ethoxy-	127°	735, 1718
2-amino-5-benzyl-4-hydroxy-	240°	1655, 82
4-amino-5-benzyl-2-hydroxy-	315°	735, 1718
2-amino-5-benzyl-4-hydroxy-6-methyl-	277–278°	141, 1874
2-amino-5-benzyl-4-hydroxy-6-phenyl-	340° *or* 334°	1711, 82, 1653
4-amino-5-benzylideneamino-2,6-dihydroxy-	—	1267
2-amino-5-benzylideneamino-4-hydroxy-6-methyl-	250–251°	1196
2-amino-5-benzyloxy-4-hydroxy-	247–248°	80, 83, 245
2-amino-4,6-bismethoxymethyl-	133–134°	172
4-amino-2-benzylamino-4-hydroxy-	202–204°	1152
2-amino-4-butoxy-(or 4,2-isomer?)	57–58°; 123–125°/3.5 mm.	1875
5-amino-2-butoxy-	72–73°	1875, 1876
2-amino-4-butoxy-6-dimethylamino-	90–92°	622
2-amino-5-butoxy-4-hydroxy-	236–239°	80
4-amino-5-butoxymethyl-2-methyl-	84°; *pic.* 147–148°	1877, 1878, 961, 1879
2-amino-5-butyl-4,6-dihydroxy-	330°	35
4-amino-2-butyl-5-ethoxymethyl-	48–51°	689
4-amino-5-butyl-2-hydroxy-6-methyl-	299–300°	1115
4-amino-5-butyl-4-hydroxy-2-methyl-	261–262°	129
2-amino-5-butyl-4-hydroxy-6-phenyl-	300–302°	1208
4-amino-2-cyanoamino-6-hydroxy-	—	177
2-amino-4,6-dibutoxy-	58°; 197°/17 mm.	993

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
2-amino-4,5-diethoxy-	94–95°	172
2-amino-4,6-diethoxy-	101°; 265–266°/*at.*	993, 172
2-amino-4-diethylamino-6-methoxy-	84–85°	172
4-amino-5-diethylaminomethyl-4-hydroxy-2-methyl-	*HCl* 291°	869
4-amino-2,6-diethyl-5-methoxymethyl-	130°	314
2-amino-4,5-dihydro-6-hydroxy-5,5-dimethyl-4-oxo-	—	222
2-amino-4,5-dihydroxy-	>300°	938, 83, 1881, 245, 503
2-amino-4,6-dihydroxy-	>330°	172, 207, 170, 160, 169
4-amino-2,5-dihydroxy-	>280°	907
4-amino-2,6-dihydroxy-	>325°	207, 212, 228, 1206, 146, 208, 209, 217, 234
5-amino-2,4-dihydroxy-	—	530, 501, 654, 540, 522, 521
5-amino-4,6-dihydroxy-	*ca.* 208°	1249
2-amino-4,5-dihydroxy-6-hydroxymethyl-	—	83
2-amino-4,5-dihydroxy-6-methyl-	>310°	938, 1881
2-amino-4,6-dihydroxy-5-methyl-	>300°	729
4-amino-2,6-dihydroxy-5-methyl-	355°	1882
5-amino-2,4-dihydroxy-6-methyl-	—	263, 1257, 1798, 1265
2-amino-4,6-dihydroxy-5-phenyl-	—	788
5-amino-2,4-dihydroxy-6-phenyl-	—	1043
4-amino-2,6-dihydroxy-5-propionamido-	—	1883
4-amino-2,6-dihydroxy-5-propyl-	>300°	207
2-amino-4,6-dihydroxy-5-ureido-	—	170
4-amino-2,6-dihydroxy-5-ureido-	—	1267, 1047
2-amino-4,6-di-isopropoxy-	90°; 160°/30 mm.	993
2-amino-4,6-dimethoxy-	97–98°; 252°/*at.*	993, 1884, 821
4-amino-2,6-dimethoxy-	110–140°	1231
2-amino-4,5-dimethoxy 6-methoxymethyl-	132–133°	172
2-amino-4,6-dimethoxy-5-methyl-	112–114°	993
5-amino-2,4-dimethoxy-6-methyl-	73°	1674
5-amino-4,6-dimethoxy-2-methyl-	—	1451
2-amino-4-dimethylamino-6-ethoxy-	145–147°	622

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2-dimethylamino-6-hydroxy-	289–293°	1152, 257, 1705
5-amino-2-dimethylamino-4-hydroxy-	*HCl* >310°	507
5-amino-2-dimethylamino-4-hydroxy-6-methyl-	202–204°	1886
5-amino-2-dimethylamino-4-methoxy-	*HCl* >300°	507
4-amino-5-dimethylaminomethyl-6-hydroxy-2-methyl-	>300°	869
2-amino-5-dimethylaminomethyl-4-hydroxy-6-phenyl-	310–311°	1887
2-amino-5,5-dimethylene-4,5-dihydro-6-hydroxy-4-oxo-	—	1754
2-amino-4,6-dipropoxy-	72°; 184°/42 mm.	993
2-amino-4-ethoxy-	154–156°	28
4-amino-2-ethoxy-	151–152°	35
2-amino-5-ethoxy-4,6-dihydroxy-	>320°	172
2-amino-5-ethoxy-4-ethoxymethyl-	106–107°	172
2-amino-5-ethoxy-4-ethoxymethyl-6-hydroxy-	221°	172
2-amino-5-β-ethoxyethyl-4-hydroxy-6-methyl-	238–239°	172
2-amino-5-β-ethoxyethyl-4-methoxy-6-methyl-	94–95°	172
2-amino-5-β-ethoxyethyl-4-methyl-	159–160°	172
2-amino-5-ethoxy-4-hydroxy-	245–246°	172, 907
4-amino-2-ethoxy-6-hydroxy-	247°	236
4-amino-5-ethoxy-2-hydroxy-	*ca.* 300°	907
2-amino-4-ethoxy-6-methoxy-	98°; 226–228°/*at.*	993
2-amino-4-ethoxy-4-methoxy-6-methoxymethyl-	113–114°	172
2-amino-4-ethoxy-6-methoxymethyl-	90–91°	172
2-amino-4-ethoxy-6-methyl-	91–92°	35, 1888, 1889
4-amino-2-ethoxy-6-methyl-	109–110°	35
4-amino-5-ethoxymethyl-2,6-diethyl-	115°	314
4-amino-5-ethoxymethyl-2-ethyl-	64–65°	688
2-amino-4-ethoxymethyl-6-methyl-	106–108°	964, 1890
4-amino-5-ethoxymethyl-2-methyl-	91°; *pic.* 190°	685, 206, 1891, 1892, 484, 961

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-6-ethoxymethyl-2-methyl-	95–96°	688
4-amino-6-ethoxymethyl-5-methyl-	137–138°	688
4-amino-5-ethylamino-2,6-dihydroxy-	—	1893
2-amino-4-ethylamino-6-hydroxy-	229–230°	1657
5-amino-4-ethylamino-2-hydroxy-	240°	795
5-amino-4-ethylamino-2-hydroxy-6-methyl-	—	801, 1894
2-amino-4-ethylamino-6-methoxy-	137–138°	1657
2-amino-5-ethyl-4,6-dihydroxy-	320°	172, 1895, 869
4-amino-5-ethyl-2,6-dihydroxy-	*ca.* 339°	649, 1896
2-amino-5-ethyl-4,6-dimethoxy-	92–94°	993
4-amino-5-*N*-ethylformamido-2,6-dihydroxy-	—	1893
2-amino-4-ethyl-6-hydroxy-	247–248°	99, 722, 134
4-amino-2-ethyl-6-hydroxy-	245°	131
4-amino-5-ethyl-2-hydroxy-	282–283°	634
2-amino-5-ethyl-4-hydroxy-6-methyl-	288–289°	35, 836, 107
4-amino-5-ethyl-2-hydroxy-6-methyl-	295°	107
4-amino-5-ethyl-6-hydroxy-2-methyl-	272–273°	129
4-amino-5-ethylideneamino-2,6-dihydroxy-	275–300°	1893
4-amino-5-formamido-2,6-dihydroxy-	—	212, 228
4-amino-5-formamido-2,6-dihydroxy-	—	1897, 437, 581
4-amino-5-formamido-6-hydroxy-	—	437
4-amino-5-formamido-2-hydroxy-6-methyl-	>345°	1898
5-amino-2-hexoxy-	81–82°	1875, 1876
2-amino-4-hexyl-6-hydroxy-	199°	35
4-amino-5-hexyl-6-hydroxy-2-methyl-	240–241°	129
4-amino-5-hexyl-6-hydroxy-2-propyl-	199–200°	132
2-amino-4-hydroxy-	274–276°	70, 1899, 1900, 1748, 1901, 463 668, 650, 992
4-amino-2-hydroxy-	305° *to* 323°	917, 356, 804, 185, 497, 668, 650, 654
4-amino-6-hydroxy-	263–264°	356, 437, 1902, 1106

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
5-amino-4-hydroxy-	211–212°	78
4-amino-5-hydroxy-2,6-bishydroxymethyl-	90–95°	1392
2-amino-4-hydroxy-5,6-dimethyl-	330°	172, 95, 1903
4-amino-2-hydroxy-5,6-dimethyl-	*HBr* 291°	803
4-amino-6-hydroxy-2,5-dimethyl-	283°	129
5-amino-4-hydroxy-2,6-dimethyl-	194° or 200°	601, 536, 1657
2-amino-4-hydroxy-5,6-diphenyl-	319°	1175
2-amino-5-β-hydroxyethyl-4-methyl-	159–160°	172
4-amino-5-β-hydroxyethyl-2-methyl-	193–194°	1904
2-amino-4-hydroxy-5-β-hydroxyethyl-6-methyl-	265–270°	1847
2-amino-4-hydroxy-5-β-hydroxyethyl-6-phenyl-	305–310°	1847
4-amino-2-hydroxy-5-hydroxymethyl-	*ca.* 295°	187, 952, 1300, 1608
2-amino-4-hydroxy-5-isobutyl-6-phenyl-	—	1905
2-amino-4-hydroxy-5-methoxy-	266–267°	80
4-amino-6-hydroxy-2-methoxy-	228–229° or 214–216°	235, 236, 909
2-amino-4-hydroxy-5-β-methoxyethyl-6-methyl-	230–232°	172
2-amino-4-hydroxy-5-methoxy-6-methoxymethyl-	196°	172
2-amino-4-hydroxy-6-methoxymethyl-	266–267°	172
2-amino-4-hydroxy-5-methyl-	277–279°	71, 775
2-amino-4-hydroxy-6-methyl-	*ca.* 298°	612, 95, 94, 93, 160, 1315, 1906, 1907, 1339, 1899
4-amino-2-hydroxy-5-methyl-	*ca.* 270°; *pic.* 290–291°	917, 1634, 654, 807, 1306
4-amino-2-hydroxy-6-methyl-	>300°	1908, 800
4-amino-6-hydroxy-2-methyl-	301°	129, 202, 203, 201, 1267
2-amino-4-hydroxy-5-(2-methylallyl)-6-phenyl-	287–288°	1870
4-amino-6-hydroxy-2-methylamino-	227–229°	257
5-amino-2-hydroxy-4-methylamino-	217°	280, 794
5-amino-4-hydroxy-6-methylamino-	210–215°	280

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-5-hydroxymethyl-2,6-dimethyl-	185°	886
4-amino-5-hydroxymethyl-2-methyl-	194–196° (198–200°)	601, 1394, 679, 680, 1404, 1909, 1405, 1839
4-amino-5-hydroxymethyl-6-methyl-	166°	601
5-amino-2-hydroxy-4-methyl-6-methylamino-	>270°	802
5-amino-4-hydroxy-6-methyl-2-methylamino-	208–210°	1886
4-amino-6-hydroxy-2-methyl-5-methylaminomethyl-	*HCl* 281°	869
2-amino-4-hydroxy-6-methyl-5-phenoxy-	*ca.* 300°	80
2-amino-4-hydroxy-5-methyl-6-phenyl-	287°	1711, 1702 ,1208
2-amino-4-hydroxy-6-methyl-5-phenyl-	—	1905
4-amino-5-hydroxymethyl-2-phenyl-	*pic.* 177°	684
4-amino-2-hydroxy-6-methyl-5-propyl-	317–318°	1118, 929
4-amino-6-hydroxy-5-methyl-2-propyl-	209–210°	132
4-amino-5-(2-hydroxy-2-methylpropyl)-2-methyl-	160–102°	681
4-amino-6-hydroxy-2-methyl-5-thioformamido-	>260°	550, 529
4-amino-2-hydroxymethyl-5-thioformamidomethyl-	157°	1651
2-amino-4-hydroxy-5-phenoxy-	255–256°	775
2-amino-4-hydroxy-5-phenyl-	244–245°	188, 1829
2-amino-4-hydroxy-6-phenyl-	294–295° (279–280°)	1910, 829
4-amino-2-hydroxy-5-phenyl-	>310°	798
4-amino-2-hydroxy-6-phenyl-	>300°	799
4-amino-6-hydroxy-2-phenyl-	252°	1911, 127, 195
2-amino-4-hydroxy-6-phenyl-5-propyl-	311–313°	1711, 1653
2-amino-4-hydroxy-6-phenyl-5-vinyl-	>300°	1870
2-amino-4-hydroxy-5-piperidino-	278–280°	851
4-amino-6-hydroxy-2-propyl-	293–295°	132
2-amino-4-methoxy-	119–120°	1205, 1888, 714, 497, 463
4-amino-2-methoxy-	174°	497, 668, 1634

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-6-methoxy-	156–157°	1106
2-amino-4-methoxy-5,6-dimethyl-	154–155°	172, 1885
2-amino-4-methoxy-5-β-methoxyethyl-6-methyl-	82–83°	172
2-amino-4-methoxy-6-methoxymethyl-	116–117°	172
2-amino-5-methoxy-4-methoxymethyl-	137–138°	172
2-amino-4-methoxymethyl-	123–124°	172
2-amino-4-methoxy-6-methyl-	158°	172, 715, 1888, 1912, 812
4-amino-2-methoxy-6-methyl-	145°	715
4-amino-6-methoxy-2-methyl-	164–165°	870
5-amino-2-methoxy-4-methyl-	88–89°	504
2-amino-4-methoxymethyl-6-methyl-	114–116°	962, 1890
4-amino-5-methoxymethyl-2-methyl-	116°	961, 1879
5-aminomethyl-2,4-dihydroxy-	*sul.* 245–246°	956, 1192
5-aminomethyl-2,4-dihydroxy-6-methyl-	>335°	1193
5-aminomethyl-4-hydroxy-2-methyl-	*pic.* 157–158°; *HCl* 280°	950, 951, 683, 1651
4-aminomethyl-6-hydroxy-2-phenyl-	*HCl* 263–265	1398
5-aminomethyl-4-methoxy-2-methyl-	*pic.* 188°; *HCl* 150–151°	601
2-amino-4-methyl-6-phenoxy-	195–196°	172, 1913, 1678
2-amino-4-methyl-6-propoxy-	59–60°	172
4-amino-2-methyl-5-propoxymethyl-	87°; *pic.* 147–148°	961
2-amino-4,5,6-triethoxy-	76–78°	172
2-amino-4,5,6-trihydroxy-	>300°	83
4-amino-2,5,6-trihydroxy-	—	83, 568
5-amino-2,4,6-trihydroxy-	*ca.* 320°	609, 405, 1914, 2, 514, 1915, and *Beilstein*
2-anilino-4,5-dihydro-6-hydroxy-5,5-dimethyl-4-oxo-	249–251°	225, 1917
5-anilino-2,4-dihydroxy-	250–255°	850
2-anilino-5-ethoxy-	130–131°	625
2-anilino-5-ethoxy-4-hydroxy-	231–232°	625
2-anilino-4-ethoxy-5-methyl-	121°	807
2-anilino-5-ethyl-4-hydroxy-6-methyl-	195°	107
2-anilino-4-hydroxy-	230–231°	625, 649

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4-anilino-2-hydroxy-	272–274°	1123, 522
2-anilino-4-hydroxy-5-methyl-	254–255°	807
2-anilino-4-hydroxy-6-methyl-	244–246°	1125, 1471
4-anilino-6-hydroxy-2-methyl-	276°	826
2-anilino-4-hydroxy-5-methyl-6-phenyl-	—	1208
4-anilino-6-hydroxy-2-phenyl-	209°	786
2-anilino-4-methoxy-	119°	625
5-anilino-2,4,6-trihydroxy-	>300°	860, 1750
barbituric acid/5-amino-5-ethyl-	214–216°	1919, 157
barbituric acid/5-amino-5-methyl-	237°	157
barbituric acid/5-hydroxy-5-ureido-	210°	116
barbituric acid/5-methoxy-5-ureido-	202°	1920, 1921
barbituric acid/5-methylamino-5-ureido-	191–192°	1920
5-benzamido-2,4-dihydroxy-	283–287°	532
5-benzamido-4,6-dihydroxy-	310°	1873
4-benzamido-2-hydroxy-	>350°	1468
5-benzamido-4-hydroxy-	249–250°	1866, 78
5-benzamido-4-hydroxy-2,6-dimethyl-	282°	1866
5-benzamido-4-hydroxy-2-methyl-	294–295°	1866, 1873
5-benzamidomethyl-2,4-dihydroxy-	209–211°	1922
2-benzylamino-4,6-dihydroxy-	270–272°	1152, 1852
2-benzylamino-4-ethoxy-6-methyl-	72–73°	1691
2-benzylamino-4-hydroxy-	223–224°	1594, 1852
4-benzylamino-2-hydroxy-	224°	1117
2-benzylamino-4-hydroxy-6-methyl-	(α) 131°; (β) 145–147°	1594, 1831
2-benzylamino-4-methoxy-	85–87°	1923, 1691, 1852
2-benzylamino-4-methoxy-6-methyl-	71–73°	1691, 812
5-benzylamino-2,4,6-trihydroxy-	*ca.* 280°	1081
4-benzyl-2-hydrazino-6-hydroxy-	190°	1924
5-benzyl-2-hydrazino-4-hydroxy-6-methyl-	216–217°	1924
2-benzylideneamino-4-hydroxy-	238–242°	503
4,5-bisacetamido-2,6-dihydroxy-	>300°	1925, 1926, 396, 1863, 1865
2,4-bisacetamido-6-hydroxy-	>340°	1206, 1608
2,4-bisbenzyloxy-6-dimethylamino-	79°	583

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4,6-bisbenzyloxy-2-dimethylamino-	*pic.* 176°	583
2,4-bisbenzyloxy-6-methylamino-	118°	583
4,6-bisbenzyloxy-2-methylamino-	101°	583
4,5-bisformamido-2-methoxy-	180–181°	395
5-butylamino-2,4-dihydroxy-	—	850
2-butylamino-4-hydroxy-6-methyl-	204°	1849
5-butyl-4-hydroxy-6-phenyl-2-propionamido-	—	1208
2-cyanoamino-4,6-dihydroxy-	—	177
2-cyanoamino-5-ethyl-4-hydroxy-6-methyl-	*ca.* 257°	1903
2-cyanoamino-4-hydroxy-5,6-dimethyl-	*ca.* 280°	1903
2-cyanoamino-4-hydroxy-5-methyl-	*ca.* 293°	1903
2-cyanoamino-4-hydroxy-6-methyl-	*ca.* 285°	1903
2-cyanoamino-4-hydroxy-6-phenyl-	—	1903
5-cyanoamino-2,4,6-trihydroxy-	—	1916, 1918
5-cyclohexylamino-2,4-dihydroxy-	>305°	850
4,5-diacetamido-2,6-dihydroxy- (see bis...)		
2,4-diacetamido-6-hydroxy (see bis...)		
2,4-diamino-5-acetamido-6-hydroxy-	—	1267
2,4-diamino-5-benzamido-6-hydroxy-	318–319°	254
2,4-diamino-5-benzylideneamino-6-hydroxy-	276°	1194
2,4-diamino-5-benzyloxy-	142–145°	80
2,4-diamino-6-benzyloxy-	—	1927
2,4-diamino-5-butoxy-	*sul.* 234–236°	80
2,4-diamino-6-butoxy-	73–74°	1927
4,5-diamino-2-cyanoamino-6-hydroxy-	—	1928
2,4-diamino-5,6-dihydro-5,5-dimethyl-6-oxo-	*ca.* 278°	1929, 336
2,4-diamino-5,6-dihydroxy-	>280°	884, 83, 245
2,5-diamino-4,6-dihydroxy-	—	252, 170
4,5-diamino-2,6-dihydroxy-	—	210, 1251, 1893, 1930, 1897, 252, 581, 212, 568

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4,5-diamino-2,6-dimethoxy-	177–178°	825
4,5-diamino-2-dimethylamino-6-hydroxy-	—	1705, 257
2,4-diamino-5-ethoxy-	148–149°	80
2,4-diamino-6-ethoxy-	167–169°	1927, 1931
2,4-diamino-5-ethoxy-6-hydroxy-	260–261°	884
4,5-diamino-2-ethoxy-6-methyl-	136–137°	1932
2,5-diamino-4-ethylamino-6-hydroxy-	236–237°	1657
2,4-diamino-5-formamido-6-hydroxy-	—	249, 437
4,6-diamino-5-formamido-2-hydroxy-	—	437
2,4-diamino-5-hydroxy-	>300°; *pic.* 250°	1881
2,4-diamino-6-hydroxy-	280–283°	246, 1933, 1934, 212, 249
2,5-diamino-5-hydroxy-	*ca.* 245°	503
4,5-diamino-2-hydroxy-	>230°	292, 395, 1633, 502, 1935
4,5-diamino-6-hydroxy-	*HCl* 251–252°	919, 360, 1936, 252
4,6-diamino-2-hydroxy-	—	355, 261, 437, 1181,
2,4-diamino-6-hydroxy-5-hydroxyethyl-	298–300°	1847
2,5-diamino-4-hydroxy-6-methyl-	281–282°	1886, 1866, 451, 528, 95
4,5-diamino-2-hydroxy-6-methyl-	280°	531, 903, 1898
4,5-diamino-6-hydroxy-2-methyl-	*sul.* 265°	1251, 531, 252, 1267
2,4-diamino-5-β-hydroxymethyl-	235°	2169
4,5-diamino-6-hydroxy-2-methylamino-	—	257
4,5-diamino-6-hydroxy-2-phenyl-	228°	195, 1911
2,4-diamino-6-hydroxy-5-propionamido-	—	1267
4,6-diamino-2-hydroxy-5-propyl-	*ca.* 300°	283
2,4-diamino-5-methoxy-	138–140°	80
2,4-diamino-6-methoxy-	161–162° *or* 140–145°	1927, 1931
2,5-diamino-4-methoxy-6-methyl-	*sul.* 167–169°	63
2,4-diamino-6-methyl-5-phenoxy-	180°	80
2,4-diamino-5-phenoxy-	162–165°	80
2,4-diaziridino-6-ethoxy-	107°/0.1 mm.	617, 787
2,4-diaziridino-6-isopropoxy-	114°/0.1 mm.	617, 787
2,4-diaziridino-6-methoxy-	86°	617, 787
2,4-diethoxy-6-methylamino-	—	718
4-diethylamino-2-hydroxy-	280–281°	804
4-diethylaminomethyl-5-α-hydroxyethyl-2-phenyl-	*HCl* 236–237°	482

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
5-diethylamino-2,4,6-trihydroxy-		860
2,4-dihydroxy-5,6-bismethylamino-	*HCl* 261°	1263
2,4-dihydroxy-5,6-bisphenylhydrazino-	—	1937
2,4-dihydroxy-5-methylamino-	242–243°	850
2,4-dihydroxy-6-methylamino-	302°	583
4,6-dihydroxy-2-methylamino-	>310°	583, 174
4,6-dihydroxy-5-methylamino-	240°	352
2,4-dihydroxy-6-methylamino-5-*N*-methylformamido-	—	1263
2,4-dihydroxy-6-methyl-5-methylamino-	—	65
4,5-dihydroxy-6-methyl-2-piperidino-	292°	938
2,4-dihydroxy-6-methyl-5-thioacetamido-	265–267°	99
2,4-dihydroxy-6-methyl-5-thioformamido-	260–262°	99
2,4-dihydroxy-6-methyl-5-thioureido-	278–279°	1271
2,4-dihydroxy-6-methyl-5-ureido-	—	1265, 1266
2,4-dihydroxy-5-phenylhydrazino-	252°	1937, 589
2,4-dihydroxy-5-piperidino-	*HCl* 285–290°	850
4,6-dihydroxy-2-piperidino-	—	1938
2,4-dihydroxy-5-propylamino-	*HCl* 264–265°	850
2,4-dihydroxy-5-ureido-	*ca.* 310° (*or* 210°)	540, 114, 520, 533, 665
2-dimethylamino-4,6-dihydroxy-	> 350° (*or* 320°)	583, 173, 787, 1855
4-dimethylamino-2,6-dihydroxy-	320°	583
5-dimethylamino-2,4-dihydroxy-	297°	65
2-dimethylamino-4-hydroxy-	175-176°	72, 507
4-dimethylamino-6-hydroxy-	271–275°	827
2-dimethylamino-4-hydroxyethyl-	123–125°/1.5 mm. (*dimer*: 109–110°)	98
2-dimethlamino-4-hydroxy-6-methyl	178°(*or* 106)°	580, 1886, 98
2-dimethylamino-4-hydroxy-5-methyl-6-phenyl-	258–259°	1208
5-dimethylamino-2,4,6-trihydroxy-	283–285°	1920
5-ethoxydiazo-2,4-dihydroxy- (?)	80–100°	1240
5-ethylamino-2,4-dihydroxy-	243–245°	850
5-ethylamino-2,4-dihydroxy-6-methylamino-	235°	1264

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
4-ethylamino-5-ethylformamido-2,6-dihydroxy-	262°	1940
4-ethylamino-2-hydroxy-6-methyl-	245–250°	801
5-ethylamino-2,4,6-trihydroxy-	297°	1920, 1083
5-ethylformamido-2,4-dihydroxy-6-methylamino-	262°	1264
4-ethyl-6-hydroxy-2-methylamino-	162–163°	1849
5-ethyl-4-hydroxy-6-methyl-2-phenylhydrazino-	235°	896, 1941
5-ethyl-4-hydroxy-6-methyl-2-ureido-	235°	1903
4-formamido-2,6-dihydroxy-	—	875
5-formamido-2,4-dihydroxy-	*ca.* 310°	87, 540
5-formamido-4,6-dihydroxy-	>240°	1249
5-formamido-4-hydroxy-2,6-dimethyl-	245–248°	1866, 775
5-formamidomethyl-4-hydroxy-2-methyl-	213°	1219
4-formylhydrazino-6-methoxy-2,5-dimethyl-	181°	1942
2-guanidino-4,6-dihydroxy-	—	176
4-guanidino-2,6-dihydroxy-	300°	583
5-hydrazino-2,4-dihydroxy-	—	1240
5-hydrazino-2,4-dihydroxy-6-methyl-	267°	885
2-hydrazino-4-hydroxy-5-methyl-	225°	1924
2-hydrazino-4-hydroxy-6-methyl-	242–244°	451, 1943, 1924, 1714
4-hydrazino-2-hydroxy-6-methyl-	235°	814
2-hydrazino-4-hydroxy-6-phenyl-	224–225°	1924
2-hydrazino-4-hydroxy-6-propyl-	185–186°	1924
4-hydrazino-6-methoxy-2,5-dimethyl-	142°	1942
2-hydrazino-4-methoxy-6-methyl-	112–114°	1944 (?), 812
4-hydroxy-5,6-dimethyl-2-ureido-	269°	1903
4-hydroxy-2-hydroxyamino-6-methyl-	225–228°	895
2-hydroxy-4-methylamino-	275–278°	280, 804, 794, 1317
4-hydroxy-6-methylamino-	250–256°	280
4-hydroxy-2-methyl-6-methylamino-	282°	870
4-hydroxy-5-methyl-2-methylamino-	213°	1129
4-hydroxy-6-methyl-2-methylamino-	201–202°	1129, 100

(Table continued)

TABLE XXXIII *(continued)*

Pyrimidine	M.p.	Reference
2-hydroxy-4-methyl-6-methylamino-5-thioformamido-	>300°	550
4-hydroxy-6-methyl-2-nitroamino-	224°	451
4-hydroxy-2-methyl-6-piperidino-	228°	870
4-hydroxy-6-methyl-2-piperidino-	185°	141
4-hydroxy-2-methyl-5-thioformamidomethyl-	200°	683, 1945
4-hydroxy-5-methyl-2-ureido-	245°	1903
4-hydroxy-6-methyl-2-ureido-	229°	1903
4-hydroxy-6-phenyl-2-ureido-	234°	1903
4-methoxy-6-methylamino-	84–86°	280
2,4,5-triamino-6-benzyloxy-	—	1927
2,4,5-triamino-6-ethoxy-	130–133°	1927, 1931
2,4,5-triamino-6-hydroxy-	—	210, 598, 1947, 1946, 1948, 556, 1608, 1949, 1950, 212, 249, 253, 559
4,5,6-triamino-2-hydroxy-	—	1951, 261
2,4,5-triamino-6-methoxy-	—	1927
2,4,6-trihydroxy-5-iminomethyl-	—	1953
2,4,6-trihydroxy-5-methylamino-	250°	1920, 405, 1083, 147, 1954, 1277
2,4,6-trihydroxy-5-phenylhydrazino-	260°	970
2,4,6-trihydroxy-5-semicarbazido-	>290°	970
2,4,6-trihydroxy-5-thioureido-	—	1916, 1956
2,4,6-trihydroxy-5-ureido-	—	1869, 1920, 1052, 1270

TABLE XXXIV. Amino-Oxypyrimidines with $N_{(1)}$- or $N_{(3)}$-Alkyl Groups

Pyrimidine	M.p.	Reference
5-acetamido-4-acetoxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo- (?)	180°	988
5-acetamido-4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	280°	227, 1883, 1863, 1862 (?)
2-acetamido-1,6-dihydro-1,4-dimethyl-6-oxo-	130–132°	1340
4-acetamido-1,2-dihydro-1-methyl-2-oxo-	268°	790

(Table continued)

TABLE XXXIV *(continued)*

Pyrimidine	M.p.	Reference
5-acetamido-1,2,3,4-tetrahydro-1,3-dimethyl-6-N-methylacetamido-2,4-dioxo-	192–193°	1863, 1939
5-acetamido-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	—	—
5-acetamido-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	208°	1262
4-acetylimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo	156°	790, 1468
4-amino-1,3-diethyl-5-formamido-1,2,3,6-tetrahydro-2,6-dioxo-	235° *to* 261°	227, 1893, 229, 1662
4-amino-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxo-	198–199°	227, 425, 229, 243
5-amino-1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-	*ca.* 200°	551
2-amino-1,4-dihydro-1,6-dimethyl-4-oxo-	284–285°	1304, 1889
2-amino-1,6-dihydro-1,4-dimethyl-6-oxo-	*ca.* 312°	100, 95, 1339, 1304, 1316, 1315, 1340
4-amino-1,2-dihydro-1,5-dimethyl-2-oxo-	300–310°	669
4-amino-1,2-dihydro-1,6-dimethyl-2-oxo-	340–342°	732
4-amino-1,6-dihydro-1,2-dimethyl-6-oxo-	242°	870
2-amino-1,6-dihydro-4-hydroxy-1-methyl-6-oxo-	>360°	174
4-amino-1,6-dihydro-2-methoxy-1-methyl-6-oxo-	216°	235, 243, 1967
5-amino-1,2-dihydro-1-methyl-4-methylamino-2-oxo-	*ca.* 180°; *pic.* 210°	280, 903
4-amino-1,2-dihydro-1-methyl-2-oxo-	300–302	5, 688
4-amino-2,3-dihydro-3-methyl-2-oxo-	*HCl* 241–245°; *pic.* 244–246°	274a, 2168
2-amino-1-ethyl-1,4-dihydro-6-methyl-4-oxo-	289–290°	1889
2-amino-3-ethyl-3,4-dihydro-6-methyl-4-oxo-	—	1451
4-amino-1-ethyl-1,2,3,6-tetrahydro-3-hydroxyethyl-2,6-dioxo-	180–181°	425, 1345
4-amino-3-ethyl-1,2,3,6-tetrahydro-1-hydroxyethyl-2,6-dioxo-	—	1345

(Table continued)

TABLE XXXIV *(continued)*

Pyrimidine	M.p.	Reference
4-amino-1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	208–209°	425, 1341, 1343
4-amino-3-ethyl-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-	232–233°	425
4-amino-5-formamido-1,2-dihydro-6-hydroxy-3-methyl-2-oxo-	—	557
4-amino-5-formamido-1,2-dihydro-1-methyl-2-oxo-	—	902
4-amino-5-formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	252–253°	875, 608, 1960, 1897, 228, 1957, 1662, 1958, 1959
5-amino-4-formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	—	1960
5-aminomethyl-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	228–229°	2120
4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	305–307° *or* 294°	425, 905, 230
5-amino-1,2,3,4,-tetrahydro-1,3-dimethyl-2,4-dioxo-	234° *or* 136–138° *HCl* 298–290°	875, 501, 1210
4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-5-propionamido-	257–258°	227
5-amino-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	*ca.* 200°	401, 1962, 1262, 405, 1805, 1864
4-amino-1,2,3,6-tetrahydro-1-hydroxyethyl-3-methyl-2,6-dioxo-	213–215° *or* 270–272°	1345, 1963
4-amino-1,2,3,6-tetrahydro-3-hydroxyethyl-1-methyl-2,6-dioxo-	216° *to* 221°	425, 1345
4-amino-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-vinyl-	—	1344
5-amino-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-	166°–167°	1336, 1822, 2121
4-amino-1,3,5-triethyl-1,2,3,6-tetrahydro-2,6-dioxo-	170°	1964
4-anilino-1,2-dihydro-1,6-dimethyl-2-oxo-	298–299°	1304
2-anilino-1,6-dihydro-1-methyl-6-oxo-	—	625
2-anilino-1,6-dihydro-4-methyl-6-oxo-1-phenyl-	113-114°	1315
4-anilino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	181–182°	740

(Table continued)

TABLE XXXIV *(continued)*

Pyrimidine	M.p.	Reference
barbituric acid/5-amino-1-ethyl-	225°	1813, 145
barbituric acid/5-amino-1-methyl-	253–256°	401, 1813, 1739, 405, 1965
barbituric acid/1-ethyl-5-ureido-	218°	145
barbituric acid/5-methoxy-1-methyl-5-ureido-	192°	1966
barbituric acid/1-methyl-5-methylamino-	276°	405
barbituric acid/1-methyl-5-ureido-	220°	1965, 1966
4-benzamido-1,2-dihydro-1-methyl-2-oxo-	222°	5, 790
1-benzoyl-4-benzoylimino-1,2,3,4-tetrahydro-3-methyl-2-oxo-	213–215°	1468
4-benzoylimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-	155–156°	1468, 790
4,5-bisacetamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	235°	1883, 1863, (?)
5-diacetylamino-1,2,3,4-tetrahydro-1,3-dimethyl-6-*N*-methylacetamido-2,4-dioxo-	179–181°	1939
4,5-diamino-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxo-	103–104°	1893, 227, 229
4,5-diamino-1,2-dihydro-1,6-dimethyl-2-oxo-	230°	904
4,5-diamino-1,6-dihydro-2-methoxy-1-methyl-6-oxo-	160°	235
2,4-diamino-3,6-dihydro-3-methyl-6-oxo-	265–272°	258, 494
2,4-diamino-1,6-dihydro-1-methyl-6-oxo-	—	unknown; see 258, 494
4,5-diamino-1,2-dihydro-1-methyl-2-oxo-	>220°	280, 902
2,4-diamino-5-formamido-1,6-dihydro-1-methyl-6-oxo-	—	249
4,5-diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	209°; *HCl* 310°	228, 875, 1968, 230, 231
4,5-diamino-1,2,3,6-tetrahydro-1-methyl-2,6-dioxo-3-vinyl-	—	1344
1,3-dibenzoyl-4-benzoylimino-1,2,3,4-tetrahydro-2-oxo-	155–156°	1468
1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-5-ureido-	196°	551
1,2-dihydro-1-methyl-4-N-methyacetamido-2-oxo-	268°	790

(Table continued)

TABLE XXXIV *(continued)*

Pyrimidine	M.p.	Reference
1,2-dihydro-1-methyl-4-methylamino-2-oxo-	179°	790
4-dimethylamino-1,2-dihydro-1-methyl-2-oxo-	179°	790
5-dimethylamino-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	225°	1969
4-ethoxy-1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-5-ureido-	230–234°	1363
4-formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	—	875
5-formamido-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	204°	875
hexahydro-5-methoxy-1,3-dimethyl-2,4,6-trioxo-5-ureido-	186°	1966
1,2,3,4-tetrahydro-1,3-dimethyl-5,6-bis (*N*-methylacetamido)-2,4-dioxo-	222–224°	1863
1,2,3,4-tetrahydro-1,3-dimethyl-5,6-bismethylamino-2,4-dioxo-	193° or 290° or 144°	1974, 1264, 1005
1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-ureido-	>290°	533
1,2,3,4-tetrahydro-1,3-dimethyl-5-*N*-methylacetamido-6-methylamino-2,4-dioxo-	225°	1883
1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-5-*N*-methylformamido-2,4-dioxo-	259–260°	1264
1,2,3,4-tetrahydro-1,3-dimethyl-4-methylimino-2-oxo-	79°	790
1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-5-ureido-	210°	1966, 1805
1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-5-methylamino-2,4-dioxo-	*ca.* 220°	405, 1954
1,2,3,4-tetrahydro-2-imino-1,3,6-trimethyl-4-oxo-	*ca.* 300°; *HI* 219–220°	93
1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxo-	145°	790, 668
1,2,3,4-tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxo-5-ureido-	*ca.* 210°	1363
1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-ureido-	*ca.* 300°	1822
2,4,5-triamino-1,6-dihydro-1-methyl-6-oxo-	—	494

(Table continued)

TABLE XXXIV *(continued)*

Pyrimidine	M.p.	Reference
uracil/5-acetamido-6-amino-1-methyl-	303° *or* 285°	1883, 1863
uracil/5-acetamido-6-amino-3-methyl-?	215–217°	1862
uracil/6-amino-1,5-diethyl-	—	1964
uracil/5-amino-1,6-dimethyl-	281–282°	1337
uracil/5-amino-3,6-dimethyl-	256–257°	1337
uracil/6-amino-1-ethyl	288–290°	425, 1341 (?)
uracil/5-amino-3-ethyl-	171–172°	1811
uracil/5-amino-1-ethyl-6-methyl-	234–236°	1811
uracil/5-amino-3-ethyl-6-methyl-	203–205°	1811
uracil/6-amino-5-formamido-1-methyl-	—	239, 1662
uracil/6-amino-5-formamido-3-methyl-	>300°	235
uracil/6-amino-1-hydroxyethyl-	216–262°	425
uracil/5-amino-1-methyl-	—	1266
uracil/6-amino-1-methyl-	305°	207, 239, 228, 208 217, 234
uracil/5,6-diamino-1-ethyl-	270°	244
uracil/5,6-diamino-1-hydroxyethyl-	253–254°	1971
uracil/5,6-diamino-1-methyl-	—	1251, 1341, 1883, 1968, 1972, 228
uracil/5,6-diamino-3-methyl-	246–248°	1862, 235
uracil/6-ethoxy-1-methyl-5-ureido-	205°	1363
uracil/3-ethyl-5-ureido-	>300°	1811
uracil/1-methyl-5-methylamino-	206°	501
uracil/3-methyl-5-methylamino-	209°	501
uracil/3-methyl-6-methylamino-5-methylformamido-	267°	1973

TABLE XXXV. Amino-Sulphonylpyrimidines

Pyrimidine	M.p.	Reference
4-amino-2-ethylsulphonyl-5-methyl-	136–137°	1153, 807
4-amino-2-ethylsulphonyl-6-methyl-5-propyl-	101–102°	929
4-amino-5-methoxysulphonyl-2-methyl-	*ca.* 350°	1975
2-amino-4-methyl-5-sulpho-	230°	1137

(Table continued)

TABLE XXXV *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2-methyl-5-sulphomethyl-	>440°	1138, 1139, 260, 873
2-amino-5-sulpho-	305–307°	1474
4-chloroamino-2-ethylsulphonyl-5-methyl- (?)	125–126°	1153
4-chloroamino-2-ethylsulphonyl-6-methyl- (?)	133–134°	1153
2,4-diamino-5-chlorosulphonyl-6-methyl-	228–230°	1137
2,4-diamino-6-methyl-5-sulpho-	270–272°	1137
4,6-diamino-2-methylsulphonyl-	197–198°	1152
4,6-diamino-5-sulphino-	168–170°	1181
2,4,6-triamino-5-sulphamoyl-amino-	—	1142
4,5,6-triamino-2-sulpino-	>300°	1141, 1181

TABLE XXXVI. Amino-Thiopyrimidines

Pyrimidine	M.p.	Reference
4-acetamido-6-amino-2-methylthio-	225–226°	1216, 1976, 1646
4-acetamido-6-dimethylamino-2-methylthio-	219–220°	1180
2-acetamido-4-mercapto-5-methyl-6-phenyl-	241–242°	1208
4-amino-5-aminomethyl-2-benzylthio-	116–117°	1698
4-amino-5-aminomethyl-2-benzylthio-6-methyl-	123°	1698
4-amino-5-aminomethyl-2-ethylthio-	148°	187
4-amino-5-aminomethyl-2-mercapto-	220°	1698
4-amino-6-anilino-2-methylthio-	124°	426
4-amino-5-benzyl-2-mercapto-	—	1977
2-amino-4-benzoylthio-6-methyl-	130–133°	612
4-amino-5-benzylthio-2-ethylthio-	68–69°	797
4-amino-6-benzylthio-5-formamido-	202–203° (214–215°?)	1214, 1978
4-amino-2-benzylthio-5-formamido-6-piperidino-	153–154°	555
4-amino-2-benzylthio-6-methyl-	113°	193
4-amino-2-benzylthio-6-piperidino-	*pic.* 194–195°	555
2-amino-4,6-bisethylthio-	52–53°	172

(Table continued

TABLE XXXVI *(continued)*

Pyrimidine	M.p.	Reference
5-amino-2,4-bisethylthio-6-methyl-	75°	536
4-amino-5-butyl-2-ethylthio-6-methyl-	104–105°	1115
4-amino-2-butylthio-5-methyl-	85–86°	631
4-amino-6-diethylamino-5-formamido-2-methylthio-	154–155°	555
4-amino-6-diethylamino-2-methylthio-	*pic.* 210–212°	555
4-amino-1,2-dihydro-1,6-dimethyl-2-thio-	322°	719
2-amino-4,6-dimercapto-	*ca.* 250°	776, 832
5-amino-2,4-dimercapto-	250–270°	435, 534
5-amino-4,6-dimercapto-	>330° *or* >180°	1214, 1249
5-amino-2,4-dimercapto-6-methyl-	—	536
5-amino-2,4-dimercapto-6-methylamino-	>300°	292
5-amino-4-dimethylamino-6-ethylamino-2-methylthio-	—	1180, 1979
4-amino-6-dimethylamino-5-formamido-2-methylthio-	225–226°	554
4-amino-6-dimethylamino-5-methylamino-2-methylthio-	166–167°	1180
5-amino-4-dimethylamino-6-methyl-2-methylthio-	70°	63
4-amino-6-dimethylamino-2-methylthio-	162–164°	554
4-amino-5,6-dimethyl-2-methylthio-	158–159°	775, 1980
4-amino-5-ethyl-2-ethylthio-	74–76°	634
4-amino-5-ethyl-2-ethylthio-6-methyl-	89–91°	107
4-amino-5-ethyl-2-mercapto-	273–274°	1977, 1981
2-amino-5-ethyl-4-mercapto-6-methyl-	230–245°	836
2-amino-4-ethylthio-	156–157°	172
4-amino-2-ethylthio-	85–86°	650, 804, 426
4-amino-2-ethylthio-5,6-dimethyl-	92–93°	803
4-amino-2-ethylthio-6-iminomethyl-	182°	808
4-amino-2-ethylthio-5-methyl-	96–97°	654, 1153
4-amino-2-ethylthio-6-methyl-	104°	193, 800, 1153

(Table continued

TABLE XXXVI *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2-ethylthio-6-methyl--5-propyl-	86–87°	1327
4-amino-2-ethylthio-5-phenyl-	87–88°	798
4-amino-2-ethylthio-6-phenyl-	120°	799
4-amino-5-formamido-2,6-dimercapto-	—	825
4-amino-5-formamido-6-mercapto-	255°	1978
4-amino-5-formamido-2-methylthio-	180–190°	395
4-amino-5-formamido-2-methylthio-6-piperidino-	185–187°	555
4-amino-2-mercapto-	*ca.* 270–280°	917, 356, 1123
2-amino-4-mercapto-5,6-dimethyl-	270°	468
4-amino-2-mercapto-5,6-dimethyl-	>300°	468
2-amino-4-mercapto-6-methyl-	—	612
4-amino-2-mercapto-5-methyl-	273–274°	917, 1123
4-amino-2-mercapto-6-methyl-	>280°	193, 1123, 429, 612
5-amino-2-mercapto-4-methylamino-	255°	292
5-amino-4-mercapto-6-methylamino-	265–270°	292, 1850
4-amino-5-mercaptomethyl-2-methyl-	*pic.* 203°	1982
2-amino-4-mercapto-5-methyl-6-phenyl-	270–274°	1208
4-amino-2-mercapto-5-phenyl-	—	1829
4-amino-5-methylamino-2-methylthio-	202–204°	280
4-amino-6-methylamino-2-methylthio-	143–144°	550
5-amino-4-methylamino-6-methylthio-	116°	292
5-amino-4-methyl-2,6-bismethylthio-	75°	536
2-amino-4-methyl-6-methylthio-	154°	715
4-amino-5-methyl-2-methylthio-	130–131°	631
4-amino-6-methyl-2-methylthio-	136–137°	1885, 775, 193, 831
5-amino-4-methyl-2-methylthio-	141–142°	1885
2-amino-4-methyl-6-phenylthio-	190°	1885
4-amino-2-methylthio-	125–126°	522, 831
4-amino-2-methylthio-6-piperidino-	151–153°	555
2-amino-5-phenylthio-	154–155°	1983

(Table continued)

TABLE XXXVI *(continued)*

Pyrimidine	M.p.	Reference
4-amylamino-2-mercapto-	218°	1123
4-amylamino-2-mercapto-5-methyl-	198°	1123
4-amylamino-2-mercapto-6-methyl-	221°	1123
4-amylamino-2-mercapto-5-methyl-6-propyl-	—	1984
4-amylamino-2-mercapto-6-phenyl-	227–228°	1123
4-amyl-6-anilino-2-mercapto-	227–228°	1984
4-amyl-2-mercapto-5-methyl-6-methylamino-	—	1984
5-amyl-2-mercapto-4-methyl-6-methylamino-	—	1984
5-amyl-2-mercapto-4-methylamino-	198°	1984
4-anilino-2-ethylthio-	68°; *HCl* 196–197°	1123, 847
4-anilino-2-mercapto-	285°	1123
4-anilino-2-mercapto-5-methyl-	232–234°	1123
4-anilino-2-mercapto-6-methyl-	230°	1123
4-anilino-2-mercapto-6-methyl-5-propyl-	—	1984
4-anilino-2-mercapto-6-phenyl-	—	1984
4-anilino-6-methyl-2-methylthio-	114°	1985
2-benzamido-4-mercapto-6-methyl-	189°	612
4-benzylamino-5-ethyl-2-mercapto-6-phenyl-	—	1984
4-benzylamino-2-mercapto-	248–249°	1984
4-benzylamino-2-mercapto-5-methyl-	—	1984
4-benzylamino-6-methyl-2-methylthio-	89–91°	1594
5-benzyl-2-mercapto-4-methylamino-	247–249°	1123
4-benzylthio-2-butylamino-6-methyl-	59–60°	1849
4,6-bismethylamino-2-methylthio-	152–153°	1849
2,4-diamino-6-benzylthio-	—	1927
4,5-diamino-6-benzylthio-	*hy.* 104–106°	1214
2,5-diamino-4-benzylthio-6-methyl-	—	63
4,5-diamino-2,6-bismethylthio-	192–193°	825
4,5-diamino-2-butyl-6-mercapto-	186–187°	352
4,5-diamino-6-diethylamino-2-methylthio-	—	555

(Table continued)

TABLE XXXVI *(continued)*

Pyrimidine	M.p.	Reference
4,5-diamino-2,6-dimercapto-	—	825
4,5-diamino-6-dimethylamino-2-methylthio-	154–155°	554
4,6-diamino-5-ethyl-2-mercapto-	292°	262
4,6-diamino-2-ethylthio-	146–147°	1986
2,4-diamino-5-formamido-6-mercapto-	*ca.* 275°	1214
4,6-diamino-5-formamido-2-mercapto-	—	261, 237
4,6-diamino-5-formamido-2-2-methylthio-	*ca.* 254°	1976
2,4-diamino-6-mercapto-	309–311°	1214
4,5-diamino-2-mercapto-	250°	538, 498, 1633
4,5-diamino-6-mercapto-	257°	1987, 505, 1988
2,5-diamino-4-mercapto-6-methyl-	210°	63
4,5-diamino-2-mercapto-6-methyl-	—	505
4,5-diamino-6-mercapto-2-methyl-	—	505
4,6-diamino-2-mercapto-5-methyl-	318–320°	1989
4,5-diamino-6-methylamino-2-methylthio-	—	1699
2,5-diamino-4-methyl-6-methylthio-	141–142°	63
4,5-diamino-2-methylthio-	157–159°	395
4,5-diamino-6-methylthio-	155–157°	505
4,6-diamino-2-methylthio-	188–189°; *pic.* 212°	1990, 1216, 65
4,6-diamino-2-methylthio-5-thioformamido-	235°	550
4-diethylaminoethyl-2-mercapto-	114–115°	1991
4-diethylamino-2-ethylthio-	—	804
4,6-diamino-2-mercapto-	>280°	1141, 261, 237
4,6-dimercapto-5-thioformamido-	*ca.* 250°	1249
4-dimethylamino-6-ethylamino-5-formamido-2-methylthio-	137–138°	1979
4-dimethylamino-6-ethylamino-2-methylthio-	126–127°	1180
4-dimethylamino-2-mercapto-	280–283°	1123, 1991, 726
4-dimethylamino-2-mercapto-6-methyl-	—	1992
4-ethylamino-2-ethylthio-	200°/11 mm.	795
4-ethylamino-2-ethylthio-6-methyl-	70°	801
2-ethylamino-4-methyl-6-methylthio-	62°	1849
5-ethyl-2-ethylthio-4-thioureido-	143–144°	839
5-ethyl-2-mercapto-4-methylamino-6-phenyl-	—	1984

(Table continued)

TABLE XXXVI *(continued)*

Pyrimidine	M.p.	Reference
5-ethyl-2-mercapto-4-methylamino-6-propyl-	—	1984
4-ethyl-2-mercapto-6-propylamino-	—	1984
2-ethylthio-4,5-dimethyl-6-thioureido-	209–210°	96
2-ethylthio-4-hydrazino-6-methyl-	91–92°	1944
2-ethylthio-4-methylamino-	58°; *HCl* 216°	794, 793, 804
2-ethylthio-4-methyl-6-methylamino-	87°	802
2-ethylthio-4-methyl-6-thioureido-	235–236°	880, 838
2-ethylthio-5-methyl-4-thioureido-	192°	847
2-ethylthio-4-phenyl-6-thioureido-	212–213°	842
2-ethylthio-5-phenyl-4-thioureido-	204°	841
2-ethylthio-4-thioureido-	214°	847
5-formamido-4-methylamino-6-methylthio-	204–205°	965
4-hexylamino-2-mercapto-6-phenyl-	—	1984
4-hydrazino-2-mercapto-	—	1924
2-mercapto-4-methylamino-	236–237°	1123, 1984
2-mercapto-5-methyl-4-methylamino-	—	1984
2-mercapto-4-methyl-6-piperidino-	203–205°	1123
2-mercapto-4-methylpropylamino-	194–195°	1992
2-mercapto-4-piperidino-	227–228°	1123, 1992
2-methylamino-4-methylthio-	80°	1849
4-methyl-6-methylamino-2-methylthio-	112–113°	580
4-methyl-2-methylthio-6-piperidino-	—	1985
4,5,6-triamino-2-ethylthio-	129°	1986
2,4,5-triamino-6-mercapto-	—	1214
4,5,6-triamino-2-mercapto-	—	1141, 261, 237
4,5,6-triamino-2-methylthio-	182°	550, 1142, 1990

TABLE XXXVII. Amino-Oxypyrimidines with Other Functional Groups

Pyrimidine	M.p.	Reference
2-acetamido-4-chloro-5-phenoxy-	163°	775
5-acetamido-2,4-dihydroxy-6-sulpho-	—	541
2-acetamido-4-hydroxy-6-methyl-5-nitro-	254–255°	1196
1-allyl-6-amino-5-cyano-1,2-dihydro-2-oxo-	210°	278
1-allyl-6-amino-5-ethoxycarbonyl-1,2-dihydro-2-oxo-	202°	278
4-amino-5-amylcarbamoyl-2,3-dihydro-3-isoamyl-2-oxo-	218°	278
4-amino-5-amylcarbamoyl-2,3-dihydro-2-oxo-3-propyl-	178°	278
4-amino-3-amyl-5-cyano-2,3-dihydro-2-oxo-	210°	278, 279
2-amino-4-anilino-6-hydroxy-5-phenylazo-	>300°	1272
2-aminobarbituric acid/1-carbamoyl-	—	1993
2-aminobarbituric acid/1-carboxymethyl-5-ethyl-	213°	1994
2-aminobarbituric acid/1-cyano-(?)	—	1993
2-aminobarbituric acid/5,5-dibromo-	—	170
4-amino-3-benzyl-5-carbamoyl-2,3-dihydro-2-oxo-	274°	278
2-amino-5-benzyl-4-chloro-6-methoxy-	162°	642
4-amino-3-benzyl-5-cyano-2,3-dihydro-2-oxo-	249°	278
4-amino-3-benzyl-5-ethoxycarbonyl-2,3-dihydro-2-oxo-	182°	278
4-amino-5-carbamoyl-2-ethylthio-	218–219°	1395
2-amino-5-bromo-4-carboxymethyl-6-hydroxy-	—	1995
4-amino-5-bromo-4-chloro-2-hydroxy-	*ca.* 230°	426
4-amino-5-bromo-1,2-dihydro-1-methyl-2-oxo-	—	669
4-amino-5-bromo-2,6-dihydroxy-	>350°	876, 1996
2-amino-5-bromo-4-hydroxy-	273°	650
4-amino-5-bromo-2-hydroxy-	>235°	847, 654, 1935
2-amino-5-bromo-4-hydroxy-6-methyl-	249–250°	95, 852, 775
4-amino-5-bromo-2-methoxy-	134–136°	648

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-5-bromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	214–216°	1996
4-amino-3-butyl-5-carbamoyl-2,3-dihydro-2-oxo-	271°	278
4-amino-3-butyl-5-carboxy-2,3-dihydro-2-oxo-	210°	278
4-amino-3-butyl-5-cyano-2,3-dihydro-2-oxo-	208°	278
4-amino-3-t-butyl-5-cyano-2,3-dihydro-2-oxo-	215°	278
4-amino-3-butyl-5-ethoxycarbonyl-2,3-dihydro-2-oxo-	192°	278
4-amino-5-carbamoyl-3-cyclohexyl-2,3-dihydro-2-oxo-	245°	278
4-amino-5-carbamoyl-2,3-dihydro-2-oxo-3-propyl-	265°	278
4-amino-5-carbamoyl-2-hydroxy-	>310°	806, 1395
2-amino-4-carbamoylmethyl-6-hydroxy-	>285°	1995
2-amino-5-carbamoylmethyl-4-hydroxy-	*ca.* 280°	1997
5-amino-4-carboxy-2,6-dihydroxy-	—	521, 87, 520
4-amino-5-carboxy-2,3-dihydro-3-isoamyl-2-oxo-	*HCl* 232°	278
4-amino-5-carboxy-2,3-dihydro-3-methyl-2-oxo-	240° or 251°	278, 280
2-amino-1-α-carboxyethyl-1,6-dihydro-4-methyl-6-oxo-	227°	1998
2-amino-1-α-carboxyethyl-5-ethyl-1,6-dihydro-4-methyl-6-oxo-	215°	1994
4-amino-5-carboxy-3-ethyl-2,3-dihydro-2-oxo-	240°	278
2-amino-5-β-carboxyethyl-4-hydroxy-6-methyl-	237–239°	1191
2-amino-4-carboxy-6-hydroxy-	320°	1999
4-amino-5-carboxy-2-hydroxy-	256–257°	1608, 806, 1395
2-amino-4-carboxy-6-hydroxy-5-methyl-	302°	390
2-amino-1-carboxymethyl-1,6-dihydro-4,5-dimethyl-6-oxo-	233°	1994
2-amino-1-carboxymethyl-1,6-dihydro-4-methyl-6-oxo-	240–241°	1998
4-amino-5-carboxymethyl-2,6-dihydroxy-	>338°	1377

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
2-amino-1-carboxymethyl-5-ethyl-1,6-dihydro-4-methyl-6-oxo-	245°	1994
2-amino-4-carboxymethyl-6-hydroxy-	189–190° (*or* 289–290°)	1995, 2000, 2001
4-amino-5-carboxymethyl-2-hydroxy-	>290°; *pic.* 217–218°	2002
2-amino-5-carboxymethyl-4-hydroxy-6-methyl-	315–320°	1847, 809
4-amino-5-carboxymethyl-6-hydroxy-2-methyl-	—	202
2-amino-4-carboxymethyl-6-hydroxy-5-nitro-	309–310°	2001
2-amino-1-(1-carboxy-2-methylpropyl)-1,6-dihydro-4-methyl-6-oxo-	185°	1998
5-amino-4-carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	*ca.* 225°	2003
2-amino-5-chloro-4,6-dihydroxy-	—	2004
2-amino-4-chloro-5-ethoxy-	166–167°	172
2-amino-4-chloro-6-ethoxy-	87°	993
2-amino-4-chloro-5-ethoxy-6-ethoxymethyl-	79–80°	172
2-amino-4-chloro-5-β-ethoxyethyl-6-methyl-	147–148°	172
2-amino-4-chloro-6-hydroxy-	261°	660, 1657, 2005
4-amino-6-chloro-2-hydroxy-	>300	65
2-amino-4-chloro-5-hydroxyethyl-6-methyl-	189–192°	1847
4-amino-2-chloro-5-hydroxymethyl-	206°	187
5-amino-4-chloro-6-hydroxy-2-methyl-	231–233°	789
2-amino-4-chloro-5-hydroxymethyl-6-methyl-	*pic.* 283°	601
4-amino-2-chloro-5-hydroxymethyl-6-methyl-	179°	601
2-amino-4-chloro-6-hydroxy-5-phenylazo-	—	660
2-amino-4-chloro-6-methoxy-	164–166° *to* 170–171°	993, 714, 463
2-amino-4-chloro-5-β-methoxyethyl-6-methyl-	134–135°	172
2-amino-4-chloro-5-methoxy-6-methoxymethyl-	99–100°	172
2-amino-4-chloro-6-methoxymethyl-	131–132°	172

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
2-amino-4-chloro-5-phenoxy-	157°	775
4-amino-5-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	239–240°	1996
4-amino-2-cyanoamino-6-hydroxy-5-nitroso-	—	251, 1928
4-amino-5-cyano-2,3-dihydro-3-isoamyl-2-oxo-	234°	278
4-amino-5-cyano-2,3-dihydro-3-isopropyl-2-oxo-	252°	278
4-amino-5-cyano-2,3-dihydro-3-β-methoxyethyl-2-oxo-	228°	278
4-amino-5-cyano-2,3-dihydro-3-methyl-2-oxo-	>270°	278
4-amino-5-cyano-2,3-dihydro-2-oxo-3-phenyl-	275°	278
4-amino-5-cyano-2,3-dihydro-2-oxo-3-propyl-	225°	278
4-amino-5-cyano-6-ethoxy-2-methyl-	232°	627
4-amino-5-cyano-3-ethyl-2,3-dihydro-2-oxo-	252°	278
4-amino-5-cyano-3-hexyl-2,3-dihydro-2-oxo-	199°	278
4-amino-5-cyano-2-hydroxy-	270°	1698, 278
4-amino-5-cyano-2-α-hydroxyethyl-	197°	1651
4-amino-5-cyano-2-β-hydroxyethyl-	189–190°	1838
4-amino-5-cyano-2-hydroxymethyl-	222°	1651
4-amino-5-cyano-2-methoxy-	218–219°	1698
1-amino-5-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-	128°	369
2-amino-5,5-dichloro-4,5-dihydro-6-hydroxy-4-oxo-	—	2004
2-amino-4,6-dichloro-5-ethoxy-	181–182°	172
2-amino-4-diethoxymethyl-6-hydroxy-	195°	172
2-amino-4-diethoxymethyl-6-methoxy-	84–85°	172
2-amino-4-diethoxymethyl-6-methoxymethyl-	65–66°	172
2-amino-4-diethylamino-6-hydroxy-5-phenylazo-	206°	660

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-1,3-diethyl-1,2,3,6-tetrahydro-5-nitroso-2,6-dioxo-	204–206°	227, 229, 243, 2006
2-amino-1,6-dihydro-4-carboxymethyl-1-methyl-6-oxo-	256–258°	1995
4-amino-1,2-dihydro-1,6-dimethyl-5-nitro-2-oxo-	190–195°	904
4-amino-2,3-dihydro-3-hydroxyethyl-5-methoxycarbonyl-2-oxo-	195°	2007
4-amino-1,6-dihydro-2-methoxy-1-methyl-5-nitroso-6-oxo-	145°	235, 243
4-amino-1,2-dihydro-1-methyl-5-nitro-2-oxo-	274°	273, 902, 1346
4-amino-2,3-dihydro-3-methyl-5-nitro-2-oxo-	>235°	281
2-amino-4,6-dihydroxy-5-iodo-	—	2004
2-amino-4,6-dihydroxy-5-nitro-	—	170
4-amino-2,6-dihydroxy-5-nitro-	>420°	513
2-amino-4,6-dihydroxy-5-nitroso-	—	564, 2008, 170
4-amino-2,6-dihydroxy-5-nitroso-	—	212, 228, 251
2-amino-4,6-dihydroxy-5-phenylazo-	>300°	660
4-amino-2,6-dihydroxy-5-phenylazo-	—	581
4-amino-2,6-dihydroxy-5-sulphoamino-	—	2009
4-amino-2,6-dihydroxy-5-sulphamoyl-	268°	876
5-amino-2,4-dihydroxy-6-sulpho-	—	541, 2010
4-amino-2,6-dimethoxy-5-nitro-	180–181°	825
4-amino-2-dimethylamino-6-hydroxy-5-nitroso-	*ca.* 259°	257
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-hydroxyethyl-2-oxo-	212°	278
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-isoamyl-2-oxo-	199°	278
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-methoxyethyl-2-oxo-	178°	278
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-oxo-	230°	278
4-amino-5-ethoxycarbonyl-2,3-dihydro-2-oxo-3-propyl-	215°	278
5-amino-4-ethoxycarbonyl-2,6-dihydroxy-	260°	521
2-amino-5-ethoxycarbonylethyl-4-hydroxy-6-methyl-	237–239°	1191

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-5-ethoxycarbonyl-3-hexyl-2,3-dihydro-2-oxo-	160°	278
2-amino-4-ethoxycarbonyl-6-hydroxy-	220°	1999
2-amino-5-ethoxycarbonyl-4-hydroxy-	303–304°	921, 1376
4-amino-5-ethoxycarbonyl-2-hydroxy-	260° *to* 286°	279, 187, 1608, 1300, 806, 807
2-amino-4-ethoxycarbonyl-6-hydroxy-5-methyl-	—	1823
4-amino-2-ethoxycarbonylmethyl-6-hydroxy-	206–207°	133
4-amino-2-ethoxycarbonylmethylthio-4-hydroxy-	180°	1152
4-amino-2-ethoxy-5-ethoxycarbonyl-	105–106°	807
4-amino-2-ethoxy-6-methyl-5-nitro-	165–166°	1932
2-amino-4-ethylamino-6-hydroxy-5-nitroso-	265–266°	1657
4-amino-1-ethyl-1,2,3,6-tetrahydro-3-hydroxyethyl-5-nitroso-2,6-dioxo-	172–173°	2012
4-amino-6-formyl-2-hydroxy-	*ca.* 255°	808
2-amino-5-formyl-4-hydroxy-6-methyl-	>300°	1938
5-aminohexahydro-1,3-dimethyl-2,4,6-trioxo-5-sulpho-	—	1805
2-amino-4-hydroxy-6-iodo-	241°	624
4-amino-2-hydroxy-5-iodo-	*ca.* 225–245°	649
4-amino-6-hydroxy-2-methoxy-5-nitroso-	—	243
2-amino-4-hydroxy-6-methyl-5-nitro-	>300°	451, 528
4-amino-2-hydroxy-6-methyl-5-nitro-	280–285°	531, 1898
4-amino-6-hydroxy-2-methyl-5-nitroso-	—	1267
2-amino-4-hydroxy-6-methyl-5-phenylazo-	276–277°	580, 1886
2-amino-4-hydroxy-6-methyl-5-sulpho-	>300°	1137
2-amino-4-hydroxy-5-nitro-	280°	503
4-amino-2-hydroxy-5-nitro-	*ca.* 300°	502, 1935, 654
4-amino-6-hydroxy-5-nitro-	—	1902, 357

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-6-hydroxy-5-nitroso-	—	1902
4-amino-6-hydroxy-5-nitroso-2-phenyl-	—	195
4-amino-6-hydroxy-5-phenylazo-	244–246°	1902, 579
4-amino-6-hydroxy-2-phenyl-5-phenylazo-	306°	1911
2-amino-4-hydroxy-6-phenyl-5-piperidinomethyl-	*HCl* 256–258°	1887
2-amino-4-hydroxy-6-phenyl-5-thiocyanato-	287–289°	880
2-amino-4-hydroxy-5-sulpho-	*Na* 288–290°	1137
4-amino-2-hydroxy-5-sulpho-	—	1136
2-amino-4-methoxy-6-methyl-5-nitro-	199°	63
4-amino-2-methoxy-5-nitro-	203–204°	361
4-amino-6-methoxy-5-nitro-	238–240°	361
4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxo-	*hy.* 223°	230, 2103, 228, 251
4-amino-1,2,3,6-tetrahydro-1-hydroxyethyl-3-methyl-5-nitroso-2,6-dioxo-	—	2012
4-amino-1,2,3,6-tetrahydro-3-hydroxyethyl-1-methyl-5-nitroso-2,6-dioxo-	—	2012
2-anilino-4-chloro-5-ethoxy-	111–112°	625
1-anilino-5-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-	210°	369
barbituric acid/1-amidino-3-nitro-	—	1993
barbituric acid/5-amino-5-bromo (?)	—	2014, 2015
barbituric acid/5-bromo-5-ethylamino-	185°	596
barbituric acid/5-chloro-1-methyl-5-ureido-	—	1966
barbituric acid/5-chloro-5-ureido	—	1920, 1921
4-benzyloxy-6-chloro-2-dimethylamino-	84°	583
4-benzyloxy-6-chloro-2-methylamino-	120°	583
4-carboxy-5-hydrazino-2,6-dihydroxy-	120°	1240
4-carboxy-6-hydroxy-5-methyl-2-methylamino-	260–280°	1129
4-chloro-2-dimethylamino-6-hydroxy-	217°	174

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
4-chloro-2-dimethylamino-6-methoxy-	62°	174
2(4)-chloro-4(2)-ethoxy-6-methylamino-	134°	718
4-chloro-6-ethoxy-2-methylamino-	95°	718
5-chlorohexahydro-1,3-dimethyl-2,4,6-trioxo-5-ureido-	140°	2020
4-chloro-6-hydroxy-2-methylamino-	265°	174
4-chloro-6-methoxy-2-methylamino-	153°	174
2,4-diamino-6-benzyloxy-5-nitroso-	—	1927
2,4-diamino-5-bromo-6-hydroxy-	243° *or* 255°	1608,884,2016,1858
2,4-diamino-6-butoxy-5-nitroso-	216–217°	1927
2,5-diamino-4-carboxymethyl-6-hydroxy-	—	1995
2,4-diamino-5-chloro-6-hydroxy-	305°	632
4,6-diamino-5-chloro-2-hydroxy-	>360°; *pic. ca.* 325°	632
2,4-diamino-5-β,β-diethoxyethyl-6-hydroxy-	156–158°	2011
2,4-diamino-1,6-dihydro-1-methyl-5-nitroso-6-oxo-	—	*unknown;* 257, 258
2,4-diamino-3,6-dihydro-3-methyl-5-nitroso-6-oxo	—	257, 258
2,4-diamino-6-ethoxy-5-nitroso	—	1927
2,4-diamino-6-hydroxy-5-iodo-	233–236°	884
2,4-diamino-6-hydroxy-5-nitroso-	—	252, 1948, 556, 253, 212, 249, 2017
4,6-diamino-2-hydroxy-5-nitroso-	—	1860, 1951
2,4-diamino-6-hydroxy-5-phenylazo-	>300°	598
4,6-diamino-2-methoxy-5-nitro-	—	1811
2,4-diamino-6-methoxy-5-nitroso-	—	1927, 1952
1,2-dihydro-1-methyl-4-methylamino-5-nitro-2-oxo-	203°	1346, 903
4,6-dihydroxy-2-methylthio-5-nitroso-	180–200°	65
2-dimethylamino-4,6-dihydroxy-5-nitro-	—	174
2-dimethylamino-5-formyl-4-hydroxy-6-methyl-	>300°	1938, 524
2-dimethylamino-4-hydroxy, 6-methyl-5-phenylazo-	—	580
2-dimethylamino-4-hydroxy-5-nitro-	304–311°	507

(Table continued)

TABLE XXXVII *(continued)*

Pyrimidine	M.p.	Reference
2-dimethylamino-4-methoxy-5-nitro-	178–179°	507
5-ethoxycarbonyl-1,2,3,4-tetrahydro-4-imino-1,3-dimethyl-2-oxo-	178°	278
4-ethylamino-2-hydroxy 6-methyl-5-nitro-	260–265°	801
4-ethylamino-2-hydroxy-5-nitro-	275°	795
5-formyl-4,6-dihydroxy-2-piperidino-	>300°	1938
5-formyl-4-hydroxy-6-methyl-2-methylamino-	290°	1938, 524
5-formyl-4-hydroxy-6-methyl-2-piperidino-	235°	1938, 524
hexahydro-1,3-dimethyl-5-methylamino-2,4,6-trioxo-5-sulpho-	—	1954
4-hydroxy-6-iodo-2-methylamino-	230°	718
2-hydroxy-4-methylamino-5-nitro-	310–315°	280, 794
4-hydroxy-6-methylamino-5-nitro-	298°	280
2-hydroxy-4-methyl-6-methylamino-5-nitro-	250°	802
2-methoxy-4-methylamino-5-nitro-	135–137°	292, 534
4-methoxy-6-methylamino-5-nitro-	148–150°	292
uracil/6-amino-5-bromo-1-methyl-	278–280°	877
uracil/6-amino-1-carboxymethyl-	—	2021
uracil/1-amino-5-cyano-	228°	369
uracil/6-amino-1-ethyl-5-nitroso-	249°	244
uracil/6-amino-5-formamido-1-methyl-	—	2018, 557, 228
uracil/6-amino-1-hydroxyethyl-5-nitroso-	256°	1971
uracil/6-amino-1-methyl-5-nitroso-		1341 228, 2019, 251
uracil/1-anilino-5-cyano-	334°	366, 369

TABLE XXXVIII. Amino-Thiopyrimidines with other Functional Groups

Pyrimidine	M.p.	Reference
4-amino-3-amyl-5-ethoxycarbonyl-2,3-dihydro-2-thio-	228°	274
4-amino-3-benzyl-5-ethoxy-carbonyl-2,3-dihydro-2-thio-	241°	274

(Table continued)

TABLE XXXVIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2-benzylthio-6-chloro-	103–104°	555
4-amino-2-benzylthio-5-cyano-	171°	1698
4-amino-2-benzylthio-5-cyano-6-methyl-	193–196°	1698
2-amino-4-benzylthio-6-methyl-5-nitro-	155°	63
4-amino-2-benzylthio-5-nitroso-6-piperidino-	152–153°	555
4-amino-2,6-bismethylthio-5-nitro-	220–221°	825
4-amino-5-bromo-6-chloro-2-methylthio-	165°	426
4-amino-5-bromo-2-ethylthio-	124–125°	426, 654, 522
4-amino-5-bromomethyl-2-ethylthio-	*HBr* 283–285°	187
4-amino-5-bromomethyl-2-methylthio-	—	1608
4-amino-3-butyl-5-cyano-2,3-dihydro-6-methyl-2-thio-	256°	274
4-amino-3-butyl-5-cyano-2,3-dihydro-2-thio-	228°	274
4-amino-3-butyl-5-ethoxycarbonyl-2,3-dihydro-2-thio-	249°	274
4-amino-5-carbamoyl-2-ethylthio-	218–219°	1395
4-amino-5-carbamoyl 2-methylthio-	262–263°	2022
4-amino-5-carboxy-2-ethylthio-	230°	806
4-amino-5-carboxy-3-hexyl-2,3-dihydro-2-thio-	>200°	2007
4-amino-5-carboxy-2-mercapto-	276–279°	103, 194
4-amino-5-carboxymethyl-2-ethylthio-6-methyl-	221°	809
4-amino-5-carboxy-2-methylthio-	251–252°	1608, 196
5-amino-4-carboxy-2-methylthio-	190–191°	2023
4-amino-6-chloro-5-carbamoylmethyl-2-ethylthio-	167°	809
4-amino-5-chloromethyl-2-ethylthio-	*HCl* 202–204°	187
4-amino-6-chloro-5-methyl-2-methylthio-	157°	65
5-amino-2-chloro-4-methyl-6-methylthio-	110°	536
4-amino-6-chloro-2-methylthio-	131°	615, 554, 65, 426
4-amino-5-cyano-3-cyclohexyl-2,3-dihydro-6-methyl-2-thio-	>270°	274
4-amino-5-cyano-2,3-dihydro-3-isopropyl-2-thio-	178°	274

(Table continued)

TABLE XXXVIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-5-cyano-2,3-dihydro-3-β-methoxyethyl-6-methyl-2-thio-	233°	274
4-amino-5-cyano-2,3-dihydro-3-β-methoxyethyl-2-thio-	198°	274
4-amino-5-cyano-2,3-dihydro-3-phenyl-2-thio-	242°	274
4-amino-5-cyano-6-ethyl-2,3-dihydro-3-isopropyl-2-thio-	254°	274
4-amino-5-cyano-6-ethyl-2,3-dihydro-3-β-methoxyethyl-2-thio-	202° 202°	274 274
4-amino-5-cyano-2-ethylthio-	146°	187, 134, 1698
4-amino-5-cyano-2-ethylthio-6-methyl-	214–215°	2024
4-amino-5-cyano-2-ethylthio-6-phenyl-	170–171°	2024
4-amino-5-cyano-2-mercapto-	320°	1698
2-amino-5-cyano-4-methyl-6-methylthio-	241–243°	1393
4-amino-3-cyclohexyl-5-ethoxycarbonyl-2,3-dihydro-2-thio-	>250°	274
4-amino-6-diethylamino-2-methylthio-5-nitroso-	133–134°	155
4-amino-6-dimethylamino-2-methylthio-5-nitroso-	219–220°	554
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-isoamyl-2-thio-	252°	274
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-isobutyl-2-thio-	235°	274
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-β-methoxyethyl-2-thio-	206°	274
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-thio-	238°	274
4-amino-5-ethoxycarbonyl-2,3-dihydro-3-phenyl-2-thio-	251°	274
4-amino-5-ethoxycarbonyl-3-ethyl-2,3-dihydro-2-thio-	252°	274
4-amino-5-ethoxycarbonyl-2-ethylthio-	102°	187, 806, 186
4-amino-5-ethoxycarbonyl-3-hexyl-2,3-dihydro-2-thio-	240°	274
4-amino-5-ethoxycarbonyl-2-mercapto-	260–262°; *HCl* 209–211°	1608, 194
4-amino-5-ethoxycarbonyl-2-methylthio-	130–131°	1608, 196

(Table continued)

TABLE XXXVIII *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2-ethylthio-5-iodo-	127°	649
2-amino-5-formyl-4-methyl-6-methylthio-	—	2025
4-amino-2-mercapto-6-methyl-5-nitro	240–245°	776
4-amino-6-methylamino-2-methylthio-5-nitroso-	—	1699, 1646
5-aminomethyl-4-chloro-2-ethylthio-	112°	187
2-amino-4-methyl-6-methylthio-5-nitro-	219°	63
4-amino-2-methylthio-5-nitro-	181–183°	395
4-amino-2-methylthio-5-nitroso-6-piperidino-	169–170°	555
4-anilino-2-ethylthio-5-iodo-	—	649
5-bromo-4-cyanoamino-2-2-ethylthio (?)	*ca.* 310°	847
5-bromo-2-ethylthio-4-thioureido-	219–220°	837, 847
5-bromo-2-ethylthio-4-ureido-	—	847
5-carbamoylmethyl-2-ethylthio-4-thioureido-	230°	843
5-carboxymethyl-2-ethylthio-4-thioureido-	220–221°	843
4-chloro-6-methylamino-2-methylthio-	130–131°	1849
2,4-diamino-6-benzylthio-5-nitroso-	—	1927
4,6-diamino-5-chloro-2-methylthio-	192°	426
4,6-diamino-2-ethylthio-5-nitroso-	—	1986
4,6-diamino-2-mercapto-5-nitroso-	—	261, 237
1,6-dihydro-5-iodo-1,4-dimethyl-2-methylthio-6-oxo-	219°	653
4-dimethylamino-6-ethylamino-2-methylthio-5-nitroso-	119–120°	1180
4-dimethylamino-2-mercapto-6-methyl-5-nitro-	224°	63
4-dimethylamino-6-methyl-2-methylthio-5-nitro-	78°	63
5-ethoxycarbonyl-2-ethylthio-4-thioureido-	165–168°	844
5-ethoxycarbonyl-2-ethylthio-4-ureido-	140–141°	848
5-ethoxycarbonylmethyl-2-ethylthio-4-thioureido-	135–136°	843

(Table continued)

TABLE XXXIX. Amino-Oxy-Thiopyrimidines

Pyrimidine	M.p.	Reference
5-acetamido-4-hydroxy-2-methylthio-	220–221°	78
1-allyl-4-amino-3-ethyl-1,2,3,6-tetrahydro-6-oxo-2-thio-	—	295
1-allyl-6-amino-3-ethyl-1,2,3,4-tetrahydro-4-oxo-2-thio-	—	295
1-allyl-4-amino-1,2,3,6-tetrahydro-6-oxo-3-phenyl-2-thio-	—	295
1-allyl-6-amino-1,2,3,4-tetrahydro-4-oxo-3-phenyl-2-thio-	—	295
4-amino-3-benzyl-1-ethyl-1,2,3,6-tetrahydro-6-oxo-2-thio-	—	241, 2026
4-amino-1-benzyl-1,2,3,6-tetrahydro-3-(2-methylallyl)-6-oxo-2-thio-	—	295
4-amino-3-benzyl-1,2,3,6-tetrahydro-1-(2-methylallyl)-6-oxo-2-thio-	—	295
4-amino-2-benzylthio-6-hydroxy-	243°	555
4-amino-5-benzylthio-2-hydroxy-	240–241°	797
4-amino-5-bromo-6-hydroxy-2-mercapto-	>300°	426
4-amino-5-bromo-6-hydroxy-2-methylthio-	>200°	426
4-amino-5-bromo-6-methoxy-2-methylthio-	135–136°	1608
4-amino-1-(2-butenyl)-3-hexyl-1,2,3,6-tetrahydro-6-oxo-2-thio-	—	295
4-amino-3-(2-butenyl)-1-hexyl-1,2,3,6-tetrahydro-6-oxo-2-thio-	—	295
4-amino-1,3-dibenzyl-1,2,3,6-tetrahydro-6-oxo-2-thio-	—	241
4-amino-1,3-diethyl-1,2,3,6-tetrahydro-6-oxo-2-thio-	178–182°	241
4-amino-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-	235°	1150
4-amino-1,6-dihydro-1-methyl-2-methylthio-6-oxo-	255°	1150
4-amino-1,6-dihydro-1-methyl-2-methylthio-6-oxo-5-phenylazo-	249–250°	580
5-amino-2,4-dihydroxy-6-mercapto-	*ca.* 250°	401, 406
5-amino-4,6-dihydroxy-2-mercapto-	>300°	1249, 2027, 255 1750

(Table continued)

TABLE XXXIX *(continued)*

Pyrimidine	M.p.	Reference
5-amino-2,4-dihydroxy-6-methylthio-	252–253°	406
5-amino-4,6-dihydroxy-2-methylthio-	>300°	65
4-amino-5-ethoxy-2-ethylthio-	105°	907
4-amino-5-ethoxymethyl-2-methylthio-	101–105°	1608
5-β-aminoethyl-4,6-dihydroxy-2-mercapto-	298–300°	1750
4-amino-1-ethyl-1,2,3,6-tetrahydro-6-oxo-3-propyl-2-thio-	—	2026, 241
4-amino-2-ethylthio-1,6-dihydro-1-methyl-5-nitroso-6-oxo-	—	1986
4-amino-2-ethylthio-1,6-dihydro-1-methyl-6-oxo-	203–204°	1986
5-amino-2-ethylthio-4-hydroxy-	159°	78, 1261
4-amino-2-ethylthio-6-hydroxy-	216–217°	426
4-amino-2-ethylthio-5-hydroxymethyl-	151–152° *to* 170°	187, 952, 2028
4-amino-2-ethylthio-6-hydroxy-5-phenylazo-	284–285°	580
4-amino-2-ethylthio-6-hydroxy-	218–219°	426, 2029
4-amino-2-ethylthio-6-hydroxy-5-nitroso-	222°	2030
4-amino-5-formamido-6-hydroxy-2-mercapto-	—	237
4-amino-6-hydroxy-2-mercapto-	>295°	2031, 2032, 237, 207
4-amino-6-hydroxy-2-mercapto-5-methyl-	—	2033
5-amino-4-hydroxy-2-mercapto-6-methyl-	—	1043
4-amino-6-hydroxy-2-mercapto-5-nitro-	—	1902
4-amino-6-hydroxy-2-mercapto-5-nitroso-	—	237, 1902
4-amino-6-hydroxy-2-methylthio-	261–162°	554
4-amino-6-hydroxy-2-methylthio-5-nitro-	299°	1152
4-amino-6-hydroxy-2-methylthio-5-nitroso-	*ca.* 255°	2034
2-amino-4-hydroxy-6-methylthio-5-phenylazo-	260°	1861
4-amino-6-hydroxy-2-methylthio-5-phenylazo-	289–290°	580
4-amino-2-mercapto-5-phenoxy-	270°	1123, 1977

(Table continued)

TABLE XXXIX *(continued)*

Pyrimidine	M.p.	Reference
4-amino-6-methoxy-2-methylthio-	144°	1150, not 426
5-aminomethyl-2-ethylthio-4-hydroxy-	221–222°	1192
4-amino-1,2,3,6-tetrahydro-1,3-bis(β-methylallyl)-6-oxo-2-thio-	—	295
4-amino-1,2,3,6-tetrahydro-1,3-di-isobutyl-6-oxo-2-thio	—	241, 2026
5-amino-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2-oxo-4-thio-	280–282°	401
4-amino-1,2,3,6-tetrahydro-6-oxo-1,3-dipropyl-2-thio-	—	2026
4-anilino-5-ethoxy-2-ethylthio-	60°	845
5-benzamido-2-ethylthio-4-hydroxy-	238–239°	2036
5-benzamido-4-hydroxy-2-mercapto-	300–310°	1261
5-benzamido-4-hydroxy-2-methylthio-	268°	78
4-cyanoamino-5-ethoxy-2-ethylthio-	—	845
4,5-diamino-1,6-dihydro-1-methyl-2-methylthio-6-oxo-	212°	1150, 2130
4,5-diamino-2-ethylthio-1,6-dihydro-1-methyl-6-oxo-	*hy.* 97–98°	1986
4,5-diamino-2-ethylthio-6-hydroxy-	194–195° *or* 202–203°	2029, 2030
4,5-diamino-6-hydroxy-2-mercapto-	—	237, 360, 1936, 1902, 2037
4,5-diamino-6-hydroxy-2-methylthio-	215–216°	1935, 2034
5-diethylaminomethyl-4-hydroxy-2-mercapto-6-methyl-	299–300°	489
1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-4-oxo-2-thio-	103–105°	2038
2,4-dihydroxy-6-mercapto-5-ureido-	—	406
4,6-dihydroxy-2-mercapto-5-ureido-	*ca.* 300°	255
2,4-dihydroxy-6-methylthio-5-thioureido-	*ca.* 350°	406
5-ethoxy-2-ethylthio-4-ureido-	166–167°	845
2-ethylthio-5-formamido-4-hydroxy-	269–270°	78

(Table continued)

TABLE XXXIX *(continued)*

Pyrimidine	M.p.	Reference
4-thiobarbituric acid/5-amino-1,3-dimethyl-	>200°	406
2-thiobarbituric acid/5-amino-1-methyl-	266°	411
2-thiobarbituric acid/5-aminomethylene-	320°	2040
2-thiouracil/1-allyl-6-amino-	230–231°	295, 238
2-thiouracil/1-1-allyl-6-amino-5-isopropyl-	217–220°	2041
2-thiouracil/1-allyl-6-amino-5-methyl-	223–224°	2041
2-thiouracil/6-amino-5,5-dimethyl-	215°	2042
2-thiouracil/6-amino-1-methyl-	—	239, 238
2-thiouracil/6-amino-1-methyl-5-nitroso-	—	239
2-thiouracil/6-amino-1-phenyl-	242–243°	2032
2-thiouracil/5,6-diamino-1-methyl-	—	239

TABLE XL. Aminopyrimidines with Two Minor Functional Groups

Pyrimidine	M.p.	Reference
4-amino-2-butyl-6-chloro-5-nitro-	132°	352
2-amino-4-chloro-6-diethoxymethyl-	100–101°	172
4-amino-6-chloro-2-dimethylamino-5-nitro-	132°	174
4-amino-2-chloro-5-ethoxycarbonyl-	156°	187
4-amino-2-chloroethyl-5-cyano-	>230°	1838
4-amino-2-chloro-6-ethyl-5-nitro-	140–141°	104
4-amino-2-chloro-5-methoxycarbonyl-	159–161°	89
2-amino-4-chloro-6-methyl-5-nitro-	225°	506, 536
4-amino-2-chloro-6-methyl-5-nitro-	172–173°	776, 513, 504
4-amino-6-chloro-2-methyl-5-nitro-	183°	506
4-amino-2-chloro-5-nitro-	215–217°	498, 777, 619
4-amino-6-chloro-5-nitro-	155–156°	506, 1469
4-amino-5-cyano-6-chloro-2-methyl-	245–246°	627

(Table continued)

TABLE XL *(continued)*

Pyrimidine	M.p.	Reference
4-amino-2,6-dichloro-5-nitro-	162–164°	616, 513
4-amino-5-ethoxycarbonyl-2-ethylsulphonyl-	67–68°	635, 807
2-amino-4-formyl-6-methyl-5-nitro- (*deriv.*)	—	536
2-chloro-4-dimethylamino-6-methyl-5-nitro-	97–98°	536, 63
4-chloro-2-dimethylamino-5-nitro-	143°	507
4-chloro-6-dimethylamino-5-nitro-	104°	536
2-chloro-4-methylamino-5-nitro-	80–82°	292
4-chloro-6-methylamino-5-nitro-	147–148° *or* 150–151°	292, 1850
4,6-diamino-2-chloro-5-nitro-	>300°	616, 513
4,6-dichloro-2-dimethylamino-5-nitro-	117–120°	174, 787

TABLE XLI. Carboxy-Halogenopyrimidines

Pyrimidine	M.p.	Reference
2-benzyl-5-ethoxycarbonylmethyl-4-chloro-	188°/3 mm.	684
5-bromo-4-carbamoyl-2-methyl-	157–158°	44
5-bromo-2-carboxy-	192–193°	462, 480
5-bromo-4-carboxy-2-methyl-	172–173°	44
5-bromo-4-carboxy-2-phenyl-	159°	270
5-bromo-4-cyano-2-methyl-	40°; 115–117°/13 mm.	44
4-bromomethyl-5-carboxy-2-phenyl-	—	482
4-carbamoyl-5-chloro-2-methyl-	165–166°	44
4-carboxy-5-chloro-2-methyl-	160°	44
4-carboxy-5-chloro-2-phenyl-	164°	270
5-carboxy-2,4-dichloro-	96–97°	440
5-carboxymethyl-2,4-dichloro-6-methyl-	156–157°	1193
4-chloro-6-chlorocarbonyl-5-methyl-2-phenyl-	99–101°	1380
4-chloro-5-cyano-2-methyl-	64–65°	204, 1218
5-chloro-4-cyano-2-methyl-	100–102°/13 mm.	44
2-chloro-5-ethoxycarbonyl-	61°	89
4-chloro-5-ethoxycarbonyl-2,6-dimethyl-	—	260
4-chloro-5-β-ethoxycarbonylethyl-2-methyl-	130°–131°/4 mm.	684

(Table continued)

TABLE XLI *(continued)*

Pyrimidine	M.p.	Reference
4-chloro-5-ethoxycarbonyl-2-methyl- (?)	102–106°/? mm.	2035
4-chloro-5-ethoxycarbonylmethyl-2-methyl-	40–41°; 110°/4 mm.	601, 684, 679, 681
4-chloro-5-ethoxycarbonylmethyl-6-methyl-	117°/1.5 mm.	601
2-chloro-4-isothiocyanato-	—	846
2-chloro-4-thiocyanato-	125–126°	846, 1415
2,4-dicarboxy-5-chloro-	168–169°	44
4,6-dichloro-2-cyanomethyl-	97–99°	133
4,6-dichloro-5-cyano-2-methyl-	114–115°	627
2,4-dichloro-5-ethoxycarbonyl-	145°/11 mm.	187, 635, 807

TABLE XLII. Carboxy-Oxypyrimidines

Pyrimidine	M.p.	Reference
5-acetonyl-4-hydroxy-6-methyl-2-phenyl-	—	1791
4-acetyl-2,6-diethoxy-	37°	682
5-acetyl-1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-	61–62°; 168–170°/18 mm.	145
4-acetyl-2,6-dihydroxy-	255–260°	682
5-acetyl-2,4-dihydroxy-	295°	2007, 276
5-acetyl-4-ethoxycarbonyl-2-hydroxy-	206–208°	275
5-acetyl-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	95–97°	145, 883
5-acetyl-2,4,6-trihydroxy-	—	145, 144, 1270, 14
1-allyl-5-carboxy-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	161–162°	272
5-amylcarbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	115°	272
1-amyl-5-carboxy-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	152°	272
5-azidocarbonylmethyl-2,4-dihydroxy	75–80°	1192
5-azidocarbonylmethyl-2,4-dihydroxy-6-methyl-	—	1193
barbituric acid/5-acetyl-1-ethyl-	—	145

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
barbituric acid/5-acetyl-1-methyl-	205–208°	1813, 145
4-benzoyl-2,6-diethoxy-	53°	682
4-benzoyl-2,6-dihydroxy-	252–253°	682
5-benzoyl-2,4-dihydroxy-6-methoxy-	105°	151
1-benzoyl-1,2,3,4-tetrahydro-5,6-dihydroxy-3-methyl-2,4-dioxo-	—	1092
2-benzyl-5-ethoxycarbonylmethyl-4-hydroxy-	175°	684
2-benzyl-4-carboxy-6-hydroxy-	230°	452
1-benzyl-5-ethoxycarbonyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	79°	272
5-butylcarbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	125°	272
1-butyl-5-carboxy-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxo-	107°	272
5-butyl-2-carboxymethylthio-4-hydroxy-6-methyl-	117–118°	1115
1-butyl-5-carboxy-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	148°	272
1-butyl-5-ethoxycarbonyl-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxo-	41–43°	272
1-butyl-1,2,3,6-tetrahydro-5-methoxycarbonyl-3-methyl-2,6-dioxo-	60°	272
4-carbamoyl-2,6-dihydroxy-	—	1367
5-carbamoyl-2,4-dihydroxy-	>300°	186
5-carbamoyl-4,6-dihydroxy-2-methyl-	280–285°	627
4-carbamoyl-2,6-dimethoxy-	186°	1281
4-carbamoyl-6-hydroxy-2-phenyl-	—	1791
2-carbamoyl-4-methoxy-6-methyl-	170–171°	469
2-carbamoylmethyl-4,6-diethoxy-	139–140°	133
2-carbamoylmethyl-4,6-dihydroxy-	—	133, 352
5-carbamoylmethyl-2,4-dihydroxy-	—	194
2-carbamoylmethyl-4-hydroxy-6-methyl-	235–237°	1787, 1783
5-carbamoylmethyl-4-hydroxy-2-methyl-	242°	950, 951
2-carbamoylmethyl-4-hydroxy-6-phenyl-	—	1783
5-carbamoylmethyl-4-methoxy-2-methyl	201°	601

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
5-carbamoylmethyl-2,4,6-trihydroxy-	258–261°	1377
5-carbamoyl-2,4,6-trihydroxy-	—	2039, 519, 2043
4-carboxy-2,6-diethoxy-	115–117°	682
5-carboxy-2,4-diethyl-6-hydroxy-	*ca.* 249°	322
5-carboxy-1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxo-	162–163°	90
4-carboxy-2,6-dihydroxy-	325° *to* 345°	1350, 121, 120, 386, 1418, 1349, 387, 488, 1419
5-carboxy-2,4-dihydroxy-	288–290°	921, 89, 366, 682
4-carboxy-2,6-dihydroxy-5-methyl-	326–327°	390, 389
4-carboxy-2,6-dimethoxy-	*hy.* 165°	1281
5-carboxy-2,4-dimethoxy-	167–168°	682
4-carboxy-5-ethoxy-2,4-dihydroxy-	260° *or* 272°	918, 1743
4-carboxy-2-ethyl-6-hydroxy-	216°	2044
5-carboxyethyl-4-hydroxy-6-methyl-2-phenyl-	215°	1791
5-carboxy-1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	172°	272
4-carboxy-2-hexyl-6-hydroxy	219°	1783
5-carboxy-1-hexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	151°	272
4-carboxy-6-hydroxy-	268–270°	1384, 447
5-carboxy-2-hydroxy-	220°	1374
5-carboxy-4-hydroxy-	238°	921, 89
5-carboxy-4-hydroxy-2,6-diphenyl-	236°	318
4-carboxy-2-hydroxy-6-isopropyl-	193–195°	2045
4-carboxy-6-hydroxy-2-methyl-	261° *or* >300°	447, 2044
4-carboxy-6-hydroxy-5-methyl-2-phenyl-	274°	1380 4-c2
4-carboxy-5-hydroxy-2-phenyl- (?)	—	2046
4-carboxy-6-hydroxy-2-phenyl-	247°	452, 1791, 447
5-carboxy-4-hydroxy-2-phenyl-	265°	1797, 2047, 2048, 1376
1-carboxymethyl-5-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-	110°	369
4-carboxymethyl-2,6-dihydroxy-	322°	2049, 1017, 118
5-carboxymethyl-2,4-dihydroxy-	315–320°	194, 1997
5-carboxymethyl-2,4-dihydroxy-6-methyl-	*ca.* 340°	809
4-carboxymethyl-2-ethoxy-6-hydroxy-	—	1375
5-carboxymethyl-4-hydroxy-2-methyl-	245–246°	950

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
5-carboxymethyl-4-hydroxy-6-methyl-	147–149°	1193
5-carboxymethyl-4-hydroxy-6-methyl-2-phenyl-	259°	1791
4-carboxymethyl-4-hydroxy-2-phenyl-	—	1783
1-carboxymethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxo-	200–201°	1340
1-carboxymethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-	239–240°	1017
1-carboxymethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-4-phenyl-	261–263°	287
2-carboxymethylthio-4,6-dihydroxy-	205°	434
2-carboxymethylthio-1,4-dihydro-5-hydroxy-1-methyl-4-oxo-	217°	934
2-carboxymethylthio-5-ethoxy-	137–138°	721
2-carboxymethylthio-4-hydroxy-	178°	48
2-carboxymethylthio-4-hydroxy-6-methyl-	203–204°	1400, 85
2-carboxymethylthio-4-hydroxy-6-methyl-5-propyl-	105–106°	1327
2-carboxymethylthio-4-hydroxy-6-propyl-	152°	1119
5-carboxymethyl-2,4,6-trihydroxy-	*ca.* 250°	1377
4-carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	149–151°	1349
5-carboxy-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	183°	272, 90 (?)
5-carboxyvinyl-2,4-dihydroxy-	285°	67
5-cyano-1-cyclohexyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	175°	278
5-cyano-4,6-diethoxy-2-methyl-	111°	627
5-cyano-2,4-dihydroxy-	295°	186, 366, 187
4-cyano-2,6-dimethoxy-	109°	1281, 1280, 1715
5-cyano-4-ethoxy-2-methyl-	35°	627
5-cyano-1-ethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-	133°	369
5-cyano-4-hydroxy-2-methyl-	235°	204, 1218, 1651, 1836, 205, 366
5-cyano-4-hydroxy-2-phenyl-	303°	302, 293, 1376

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
2-cyano-4-methoxy-6-methyl-	97–99°	469
5-cyano-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	156°	369
5-cyano-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-1-phenyl-	235°	369
5-cyano-2,4,6-trihydroxy-	—	1402
4,5-diethoxycarbonyl-2-hydroxy-	161–162°	275
4,6-diethoxy-2-ethoxycarbonylmethyl-	147–148°/10 mm.	133
4-diethoxymethyl-2,6-dihydroxy-	179°	488
4-diethoxymethyl-6-hydroxy-	123–124°	1396
4-diethoxymethyl-6-hydroxy-2-phenyl-	175°	1398
1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-5-α-hydroxyiminoethyl-2,4-dioxo-	159°	145
2,4-dihydroxy-6-hydroxyiminomethyl-5-methyl-	257°	1397
2,4-dihydroxy-5-isocyanatomethyl-	273–275°	1192
2,4-dihydroxy-5-methoxycarbonyl-	233°	90
2,4-dihydroxy-6-methoxycarbonyl-	243–245°	1349, 121, 1350, 122
2,4-dihydroxy-6-methoxycarbonylmethyl-	216–218°	119
2,4-dihydroxy-5-methoxycarbonylmethyl-6-methyl-	280–282°	809
4-ethoxycarbonyl-2,6-dihydroxy-	210–211°	1349
5-ethoxycarbonyl-2,4-dihydroxy-	236–237°	90
4-ethoxycarbonyl-2,6-dihydroxy-5-methyl-	255°	389, 388
4-ethoxycarbonyl-2,6-dihydroxy-5-phenoxy-	258°	2050
5-β-ethoxycarbonylethyl-4-hydroxy-2-methyl-	111°	684
5-ethoxycarbonyl-1-ethyl-1,2,3,4-tetrahydro-3-isobutyl-2,4-dioxo-	90°	272
5-ethoxycarbonyl-1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-	116°	272
5-ethoxycarbonyl-2-hydroxy-	163–164°	1374
5-ethoxycarbonyl-4-hydroxy-	185°	89
5-ethoxycarbonyl-4-hydroxy-2,6-dimethyl-	160–162°	260
5-ethoxycarbonyl-2-hydroxy-4-methyl-	248–250°	276

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
5-ethoxycarbonyl-4-hydroxy-2-phenyl-	212°	1378
5-ethoxycarbonyl-4-hydroxy-2-methyl-	191°	204, 271, 1836
4-ethoxycarbonylmethyl-2,6-dihydroxy-	187–189°	119
5-ethoxycarbonylmethyl-2,4-dihydroxy-	209–210°	1192, 1997
5-ethoxycarbonylmethyl-2,4-dihydroxy-6-methyl-	221–222°	809
5-ethoxycarbonylmethyl-2-ethyl-4-hydroxy-	164°	684
5-ethoxycarbonylmethyl-4-hydroxy-2-hydroxymethyl-6-methyl-	143–144°	2051
5-ethoxycarbonylmethyl-4-hydroxy-2-methyl-	179°	601, 679, 951
5-ethoxycarbonylmethyl-4-hydroxy-6-methyl-	153°	601
5-ethoxycarbonylmethyl-4-hydroxy-6-methyl-2-phenyl-	178°	1791
4-ethoxycarbonylmethyl-6-hydroxy-2-phenyl-	—	1783
1-ethoxycarbonylmethyl-1,2,3,6-tetrahydro-2,6-dioxo-4-phenyl-	205–206°	287
1-ethoxycarbonylmethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-phenyl-	109–110°	287
2-ethoxycarbonylmethylthio-4-hydroxy-6-methyl-5-popyl-	100–101°	1327
5-ethoxycarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	112°	272
5-ethoxycarbonyl-1,2,3,4-tetrahydro-3-isobutyl-1-methyl-2,4-dioxo-	119°	272
5-ethoxycarbonyl-1,2,3,4-tetrahydro-3-isopropyl-1-methyl-2,4-dioxo-	98°	272
4-ethoxycarbonyl-2,5,6-trihydroxy-	*ca.* 260°	521
5-ethoxycarbonylvinyl-2,4,6-trihydroxy-	335°	2052
5-ethylcarbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	158°	272

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
5-ethoxy-4-ethoxycarbonyl-2,6-dihydroxy-	203–212° *or* 230°	1743, 918
2-ethoxy-4-ethoxycarbonylmethyl-6-hydroxy-	112°	1375
2-ethoxy-5-ethoxycarbonyl-4-hydroxy-	185–186°	807
4-ethoxy-5-ethoxycarbonyl-2-phenyl-	58–59°	1797
5-formamidoyl-2,4,6-trihydroxy-	—	2053
4-formyl-2,6-dihydroxy-	273–275°	488, 473, 2054
4-formyl-2,6-dihydroxy-5-methyl-	212–213°	1397
4-formyl-6-hydroxy-	>330° (?); *HCl* 243–245°	1396, 957
4-formyl-6-hydroxy-2-phenyl-	*hy.* 205°	1398
5-formyl-2,4,6-trihydroxy-	>300°	1401
5-hexylcarbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	121°	272
5-hydrazinocarbonyl-4-hydroxy-2-methyl-	242–243° *or* 248°	271, 814
4-hydrazinocarbonylmethyl-2,6-dihydroxy-	*ca.* 326°	2055, 1192
5-hydrazinocarbonylmethyl-2,4-dihydroxy-6-methyl-	>375°	1193
4-hydroxy-6-hydroxyiminomethyl-2-phenyl-	*ca.* 268°	1398
5-isobutylcarbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	150–151°	272
5-methylcarbamoyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	196°	272
1,2,3,4-tetrahydro-3-methoxycarbonylmethyl-1-methyl-2,4-dioxo-6-phenyl-	157°	287
2,4,6-trihydroxy-5-thiocyanato-	*unstable*	515
uracil/1-acetyl-6-ethoxycarbonyl-	139°	123
uracil/5-acetyl-3-methyl-	197°	101
uracil/5-acetyl-3-phenyl-	228°	101
uracil/3-allyl-5-ethoxycarbonyl-	174°	272
uracil/1-amyl-5-cyano-	176°	369
uracil/3-amyl-5-ethoxycarbonyl-	152°	272
uracil/1-benzyl-6-carboxy- (?)	208–209°	1325
uracil/3-benzyl-6-carboxy-	247°	1325
uracil/3-benzyl-6-carboxy-5-methyl-	277–279°	1823
uracil/1-benzyl-5-cyano-	234°	369

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
uracil/3-benzyl-5-ethoxycarbonyl-	215°	272
uracil/1-butyl-5-cyano-	190°	369
uracil/1-s-butyl-5-cyano-	265°	369
uracil/3-butyl-5-ethoxycarbonyl-	152°	272
uracil/5-carbamoyl-1-carboxymethyl-	275°	369
uracil/1-α-carboxylamyl-5-cyano-	196°	369
uracil/1-α-carboxybutyl-5-cyano-	176°	369
uracil/5-carboxy-1-carboxymethyl-	275°	369
uracil/5-carboxy-3-ethyl-	179°	272
uracil/6-carboxy-1-ethyl-		unknown; 1349, 122, 1325, 1350
uracil/6-carboxy-3-ethyl-	235	1325
uracil/1-α-carboxyethyl-5-cyano-	202°	369
uracil/3-α-carboxyethyl-5-ethyl-6-methyl-	231–232°	2056
uracil/5-carboxy-3-(1-hydroxymethyl-propyl)-	166°	272
uracil/5-carboxy-3-isobutyl-	211°	272
uracil/5-carboxy-3-isopropyl-	192°	272
uracil/5-carboxy-1-methyl-	266°	370
uracil/5-carboxy-3-methyl-	242°	272, 280
uracil/6-carboxy-1-methyl-	273–275°	1349 (earlier refs. incorrect)
uracil/6-carboxy-3-methyl-	300°	370, 1325, 1349
uracil/1-carboxymethyl-	285°	119
uracil/1-α-carboxy-β-methylbutyl-5-cyano-	199°	369
uracil/1-α-carboxy-γ-methylbutyl-5-cyano-	206°	369
uracil/1-carboxymethyl-5-cyano-	232°	369
uracil/1-carboxymethyl-5-methyl-	260–261°	523
uracil/3-carboxymethyl-6-phenyl-	304–305°	287
uracil/1-α-carboxy-β-methylpropyl-5-cyano-	254°	369
uracil/5-carboxy-1-phenyl-	274°	370
uracil/5-carboxy-3-phenyl-	243°	272, 274, 101
uracil/6-carboxy-3-phenyl-	280°	370
uracil/5-carboxy-3-propyl-	172–173°	272
uracil/6-carboxy-1-propyl- (?)	206–207°	1325, 1349
uracil/6-carboxy-3-propyl-	204–205°	1325
uracil/1-β-carboxypropyl-5-cyano-	275°	369
uracil/5-cyano-1-cyclohexyl-	324°	369

(Table continued)

TABLE XLII *(continued)*

Pyrimidine	M.p.	Reference
uracil/5-cyano-3-cyclohexyl-	231°	278
uracil/5-cyano-1-α-ethoxycarbonylethyl-	112°	369
uracil/5-cyano-1-ethyl-	208–209°	369
uracil/5-cyano-1-isoamyl-	215°	369
uracil/5-cyano-1-isobutyl-	221°	369
uracil/5-cyano-1-isopropyl-	274°	369
uracil/5-cyano-1-methyl-	256°	366
uracil/5-cyano-3-methyl-	223°	367
uracil/5-cyano-1-phenyl-	290°	366, 369
uracil/5-cyano-1-propyl-	165°	369
uracil/3-cyclohexyl-5-methoxycarbonyl-	282°	2007, 272
uracil/5-ethoxycarbonyl-3-ethyl-	219°	272
uracil/6-ethoxycarbonyl-3-ethyl-	86°	1325
uracil/5-ethoxycarbonyl-3-hexyl-	140°	272
uracil/5-ethoxycarbonyl-3-hydroxyethyl-	175–176°	272
uracil/5-ethoxycarbonyl-3-(1-hydroxymethyl-propyl)-	161°	272
uracil/5-ethoxycarbonyl-3-isobutyl-	167°	272
uracil/5-ethoxycarbonyl-3-methyl-	221°	272
uracil/6-ethoxycarbonyl-1-methyl- (?)	139°	1325, 123
uracil/6-ethoxycarbonyl-3-methyl- (?)	—	1325
uracil/5-ethoxycarbonyl-3-phenyl-	230–231°	272
uracil/6-ethoxycarbonyl-3-phenyl-	185°	375, 1325, 123
uracil/6-ethoxycarbonyl-3-propyl-	97°	1325
uracil/5-ethylcarbamoyl-3-hydroxyethyl-	222°	272
uracil/1-methoxycarbonylmethyl-	>177°	1017
uracil/6-methoxycarbonyl-3-methyl- (?)	140–141°	1325
uracil/5-methoxycarbonyl-3-propyl-	205°	272

TABLE XLIII. Carboxy-Sulphonylpyrimidines

Pyrimidine	M.p.	Reference
2-benzenesulphonamido-5-cyano-	226–227°	647
5-ethoxycarbonyl-2-ethylsulphonyl-	87–89°	89

TABLE XLIV. Carboxy-Thiopyrimidines

Pyrimidine	M.p.	Reference
5-carboxy-2-ethylthio-	182–183°	1374
5-carboxy-4-mercapto-2-methyl- (?)	184–185°	2035
4-carboxy-2-methylthio-	214–215°	462
5-ethoxycarbonyl-2-ethylthio-	49–51°; 172°/14 mm.	89, 1374
5-ethoxycarbonyl-2-ethylthio-4-isothiocyanato-	32–33°	1417, 844
5-ethoxycarbonyl-2-ethylthio-4-thiocyanato-	104–105°; 204–205/4 mm.	844, 1417, 1416
5-ethoxycarbonyl-4-mercapto-2-methyl- (?)	154°	2035
5-ethoxycarbonylmethyl-2-ethylthio-4-isothiocyanato-	190–200°/4 mm.	843
5-ethoxycarbonyl-2-mercapto-	214–216°	1374
5-ethoxycarbonyl-2-mercapto-4-methyl-	160°	2057
5-ethoxycarbonylmethyl-2-ethylthio-4-mercapto-	130–131°	843
5-ethoxycarbonylmethyl-2-ethylthio-4-thiocyanato-	*impure*	843
2-ethylthio-4,5-dimethyl-6-thiocyanato-	65–66°; 160°/1.5 mm.	96
5-ethyl-2-ethylthio-4-isothiocyanato-	146–149°/8 mm.	839
5-ethyl-2-ethylthio-4-thiocyanato-	46–47°; 158–160°/5 mm.	839
2-ethylthio-4-isothiocyanato-	200–205°/45–50 mm.	847
2-ethylthio-4-isothiocyanato-5,6-dimethyl-	29–30°; 150–152°/1.5mm.	96
2-ethylthio-4-isothiocyanato-6-methyl-	146–148°/1 mm.	838
2-ethylthio-4-isothiocyanato-5-phenyl-	84°	841
2-ethylthio-4-isothiocyanato-6-phenyl-	215–218°/2 mm.	842
2-ethylthio-4-methyl-6-thiocyanato-	69–70°; 155–158°/5 mm.	838
2-ethylthio-5-methyl-4-4-thiocyanato-	95°	837
2-ethylthio-4-phenyl-6-thiocyanato-	88–89°	842
2-ethylthio-5-phenyl-4-thiocyanato-	90°; 215°/2 mm.	841, 840
2-ethylthio-4-thiocyanato-	82°	837

TABLE XLV. Halogeno-Nitropyrimidines

Pyrimid ne	M.p.	Reference
2-butyl-4,6-dichloro-5-nitro-	142–143°/17 mm.	352
2-chloro-5-nitro-	110–111°	28, 499
2-chloro-4-nitroamino-6-methyl-	—	504
2,4-dichloro-6-ethyl-5-nitro-	31°	104
2,4-dichloro-6-methyl-5-nitro-	53–54°; 125°/10 mm.	1710, 513, 64, 776, 778, 505, 504
4,6-dichloro-2-methyl-5-nitro-	54–55°; 106–107°/12 mm.	615, 505, 134
2,4-dichloro-5-nitro-	135°/17 mm.	435, 360, 498, 619
4,6-dichloro-5-nitro-	*ca.* 100°	506, 796
4,5-dichloro-5-nitro-2-phenyl-	168–169°	617
2,4,6-trichloro-5-nitro-	57–58°	616

TABLE XLVI. Halogeno-Oxypyrimidines

Pyrimidine	M.p.	Reference
5-acetoxy-4-chloro-2,6-dihydroxy-	260°	970
5-acetoxy-2,4-dichloro-6-methyl-	55°	601
5-amyl-4-chloro-6-hydroxy-2-methyl-	168–169°	129
barbituric acid/5-bromo-1-ethyl-	103–104°	145
barbituric acid/5-bromo-5-ethyl-	202°	144, 1919, 1755
barbituric acid/5-bromo-1-methyl-	*hy.* 105–106°	154
barbituric acid/5-bromo-5-methyl-	190°	2062
barbituric acid/5-chloro-1-ethyl-	*ca.* 146–151°	145
barbituric acid/5-chloro-5-ethyl-	191–192°	858
barbituric acid/5-chloro-1-methyl-	137°	154
barbituric acid/5,5-dibromo-	234°	121, 561, 514, 102, 661
barbituric acid/5.5-dibromo-1-ethyl-	124°	145
barbituric acid/5,5-dibromo-1-methyl-	145–146°	145, 154
barbituric acid/5,5-dichloro-	219–220°	154, 663, 664
barbituric acid/5,5-dichloro-1-ethyl-	138–143°	145
barbituric acid/5,5-dichloro-1-methyl-	133°	154
4-benzyl-5-bromo-2,6-dihydroxy-	230–232°	657
1-benzyl-5-bromo-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-	123°	1348
4-benzyl-5-chloro-2,6-dihydroxy-	266–267°	657
5-benzyl-4-chloro-2,6-dimethoxy-	48°	642
5-benzyl-2,4-dichloro-6-methoxy-	74°	642

(Table continued)

TABLE XLVI *(continued)*

Pyrimidine	M.p.	Reference
2,4-bis-α-bromoethyl-5-bromomethyl-6-hydroxy-	149°	314
2,4-bis-α-chloroethyl-5-chloromethyl-6-hydroxy-	132°	314
4-bromo-2,6-diethoxy-	179°; 132–133°/10 mm.	682
5-bromo-2,4-diethoxy-	72–74°	648, 807
5-bromo-1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxo-	80–81°	656
5-bromo-1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxo-	81–82°	154
5-bromo-1,2-dihydro-1-methyl-2-oxo-4-phenyl-	177°	291
5-bromo-2,4-dihydroxy-	312°	648, 2058, 2059, 2060, 1858, 1112
5-bromo-4,6-dihydroxy-	263–264°	626, 352
5-bromo-2,4-dihydroxy-6-methyl-	241–242° *or* 251°	454, 2061, 664, 1265, 114, 2147
5-bromo-4,6-dihydroxy-2-phenyl-	*ca.* 320°	136
5-bromo-2,4-dimethoxy-	63–64°	648
5-bromo-2-ethoxy-4,6-dimethyl-	40–41°; 254°/*at.*	430, 1375
5-bromo-4-α-ethoxyethyl-2,6-dihydroxy-	206°	2063
5-bromo-2-ethoxy-4-hydroxy-	163°	648
5-bromo-4-ethoxy-2-hydroxy-	—	648
5-bromo-4-ethoxymethyl-6-hydroxy-2-methyl-	136–138°	1776
5-bromo-4-ethyl-2,6-dihydroxy-	230–231°	522
4-bromo-2-ethyl-6-hydroxy-	157–158°	131
5-bromo-2-ethyl-4-hydroxy-6-methyl-	194–196°	1676
5-bromo-2-hydroxy-	241–243°	626, 831
5-bromo-4-hydroxy-	199–200°	626, 447
5-bromo-2-hydroxy-4,6-dimethyl-	228–231°	646
5-bromo-4-hydroxy-2,6-dimethyl-	195°	645, 311, 308, 1676
5-bromo-4-hydroxy-2,6-diphenyl-	297–298°	2065
5-bromo-4-hydroxy-2-methoxy-	190°	648
5-bromo-4-hydroxy-2-methyl-	231–232°	447
5-bromo-4-hydroxy-6-methyl-2-phenyl-	260°	1676, 968
5-bromo-4-hydroxy-2-phenyl-	252°	447
5-bromomethyl-2,4-diethyl-6-hydroxy-	172°	307, 314
5-bromo-4-methyl-2,6-dihydroxy-	—	2060, 700
5-bromomethyl-4-hydroxy-2-methyl-	199–200°	951

(Table continued)

TABLE XLVI *(continued)*

Pyrimidine	M.p.	Reference
5-bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	184–185°	673, 668, 998
5-bromo-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	97–99°	154
5-bromo-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-	136–137° (*or* 126°)	2061, 1822, 659
5-bromo-2,4,6-trihydroxy-	212–215°	661, 154, 155
2-butyl-4-chloro-5-ethoxymethyl-	—	689
5-butyl-4-chloro-6-hydroxy-2-methyl-	173–174°	129
5-s-butyl-4-chloro-6-hydroxy-2-methyl-	124–125°	129
5-chloro-4-chloromethyl-2,6-dihydroxy-	270–275°	698
4-chloro-2,6-diethoxy-	248°/*at.*	718
4-chloro-1,2-dihydro-1-methyl-2-oxo-	207–208°	790
4-chloro-2,6-dihydroxy-	300°	599
5-chloro-2,4-dihydroxy-	300° *to* 325°	76, 665, 626, 1153, 2064
5-chloro-4,6-dihydroxy-	>230°	626
5-chloro-2,4-dihydroxy-6-methyl-	330–332°	698, 1153, 700, 664
5-chloro-2,4-dihydroxy-6-phenyl-	260–261°	699
5-chloro-4,6-dihydroxy-2-phenyl-	>320°	1589
4-chloro-2,6-dimethoxy-	73–74°	822, 637, 463, 624
5-chloro-2,4-dimethoxy-	72–73°	626
4-chloro-2,6-dimethoxy-5-methyl-	76–77°	729
2-chloro-5-ethoxy-	70°	721
4-chloro-5-ethoxymethyl-2-methyl-	72–3°/0.5 mm.	685
5-chloroethyl-2,4-dihydroxy-6-methyl-	265–270°	1847
4-chloro-5-ethyl-2,6-dimethoxy-	33–34°	448
4-chloro-5-ethyl-6-hydroxy-2-methyl-	209°	788, 129
5-β-chloroethyl-4-hydroxy-6-methyl-	*HCl* 168–169°	690
4-chloro-5-hexyl-6-hydroxy-2-methyl-	144–145°	129
4-chloro-2-hydroxy-	152–154°	804
4-chloro-6-hydroxy-	192–193°	827, 1379
5-chloro-2-hydroxy-	237–238°	647, 831
5-chloro-4-hydroxy-	177–179°	626
4-chloro-6-hydroxy-2,5-dimethyl-	225°	788, 129
5-chloro-4-hydroxy-2,6-dimethyl-	191°	311, 327, 328

(Table continued)

TABLE XLVI *(continued)*

Pyrimidine	M.p.	Reference
4-chloro-6-hydroxy-5-isobutyl-2-methyl-	167–168°	129
2-chloro-4-hydroxy-6-methyl-	*HCl* >275°	828
4-chloro-6-hydroxy-2-methyl-	233°	826, 129
4-chloro-6-hydroxy-2-methyl-5-propyl-	220–221°	129
4-chloro-6-hydroxy-5-methyl-2-propyl-	170–171°	132
4-chloro-5-(2-hydroxy-2-methylpropyl)-2-methyl-	*HCl* 267–268°	681
4-chloro-6-hydroxy-2-phenyl-	—	786
4-chloro-6-hydroxy-2-propyl-	168–169°	132
2-chloro-4-methoxy-	55°	790, 1223
2-chloro-5-methoxy-	51°	34
4-chloro-6-methoxy-	31–32°	1379
5-chloro-2-methoxy-	—	2066
4-chloro-6-methoxy-2,5-dimethyl-	70°/4 mm.	1942
4-chloro-6-methoxy-5-methoxymethyl-2-methyl-	51–53°	484
2-chloro-4-methoxy-6-methyl-	112°/26 mm.	812
2-chloro-4-methoxymethyl-6-methyl-	19–20°; 125°/15 mm.	962
4-chloromethyl-2,6-dihydroxy-	207–209°	76, 868
5-chloromethyl-2,4-dihydroxy-	355°	2071, not 76
4-chloromethyl-2,4-dihydroxy-5-methyl-	244–245°	989, 990
5-chloromethyl-2,4-dihydroxy-6-methyl-	*ca.* 330–335°	694
4-chloromethyl-2,6-dihydroxy-5-phenoxy-	248°	872
4-α-chloropropyl-2,6-diethoxy-	146°/8 mm.	682
5-β-chloropropyl-2,4-dihydroxy-6-methyl-	233°	701
4-chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-	111°	821, 1364
5-chloro-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-	130–132°	1996, 154
5-chloro-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-	—	1822
4-chloro-2,5,6-trihydroxy-	*ca.* 300°	970
5-chloro-2,4,6-trihydroxy-	280° *to* 300°	154, 663, 155
5,5-dibromo-1,3-diethylhexahydro-2,4,6-trioxo-	*ca.* 87°	154, 551, 145
5,5-dibromo-2,5-dihydro-4,6-dimethyl-2-oxo-	160–170°	646

(Table continued)

TABLE XLVI *(continued)*

Pyrimidine	M.p.	Reference
5,5-dibromohexahydro-1,3-dimethyl-2,4,6-trioxo-	172–173°	145, 153, 154
5,5-dichloro-1,3-diethylhexahydro-2,4,6-trioxo-	87°	551
4,5-dichloro-2,6-dimethoxy-	103–104°	637
5,5-dichlorohexahydro-1,3-dimethyl-2,4,6-trioxo-	157°	154, 1262
2,4-dichloro-5-ethoxy-	41–42°	797
2,4-dichloro-6-ethoxy-	*ca.* 25°; 235°/*at.*	718
4,5-dichloro-2-hydroxy-	206°	187
2,4-dichloro-6-methoxy-	51°	463, 624
2,4-diethyl-4-hydroxy-5-iodomethyl-	157°	314
2,4-dihydroxy-5-iodo-	272°	649, 2067
2,4,5-tribromo-6-ethoxy-	—	2068
4-trifluoromethyl-2,6-dihydroxy-	230–232°	999
uracil/1-benzyl-5-bromo-	204°	1348
uracil/3-benzyl-5-bromo-6-methyl-	*ca.* 238°	1817
uracil/3-(2-bromoallyl)-6-methyl-	191°	696
uracil/5-bromo-3,6-dimethyl-	231 *or* 241°	659, 1970
uracil/5-bromo-1-ethyl-6-methyl-	234–235°	1811
uracil/5-bromo-3-ethyl-6-methyl-	203–206°	1811
uracil/5-bromo-1-methyl-	266°	273, 501, 669, 668
uracil/5-bromo-3-methyl-	228–229°	273, 5, 1318
uracil/5-bromo-6-methyl-3-phenyl-	241–242°	284
uracil/5-chloromethyl-3,6-dimethyl-	238–240°	659
uracil/3-β-chloropropyl-6-methyl-	208–209°	100
uracil/3-(2,3-dibromopropyl)-5,6-dimethyl-	140°	696
uracil/3-(2,3-dibromopropyl)-6-methyl-	180°	696

TABLE XLVII. Halogeno-Sulphonylpyrimidines

Pyrimidine	M.p.	Reference
2-benzenesulphonamido-5-bromo-	240–241°	647
2-benzenesulphonamido-5-iodo-	255–256°	647
2-benzenesulphonamido-5-bromo-4-methyl-	205–207°	647
5-bromo-4-chloro-2-ethylsulphonyl-	81–82°	635

(Table continued)

TABLE XLVII *(continued)*

Pyrimidine	M.p.	Reference
5-chloro-2-chlorosulphonyl-	—	833
4-chloro-2-ethylsulphonyl-	57–58°	635, 804, 910
4-chloro-2-ethylsulphonyl-5-methyl-	67–68°	635, 926, 928, 805
4-chloro-2-ethylsulphonyl-6-methyl-	189–191°/3.5 mm.	1153
4-chloro-2-ethylsulphonyl-6-methyl-5-propyl-	99–100°	927, 929
5-chloro-2-sulphamoyl-	135–140°	1143

TABLE XLVIII. Halogeno-Thiopyrimidines

Pyrimidine	M.p.	Reference
2-benzylthio-4-chloro-	48–49°; 210°/18 mm.	628
5-benzylthio-4-chloro-2-ethylthio-	47–48°	797
5-bromo-4-chloro-2-ethylthio-	*ca.* 27°; 168°/25 mm.	654, 847
5-bromo-4-chloro-6-methyl-2-methylthio-	72–73°	826
5-bromo-4-chloro-2-methylthio-	44°	629
5-bromo-1,2-dihydro-4-methyl-1-phenyl-2-thio-	140°	2069
5-bromo-2-ethylthio-	43–45°	629
5-bromo-2-ethylthio-4-mercapto-	198°	837, 847
5-bromo-2-methylthio-	67–68°	462, 831, 629
5-butyl-4-chloro-2-ethylthio-6-methyl-	160°/2 mm.	1115
2-butylthio-4-chloro-5-methyl-	124–126°/1 mm.	631
4-chloro-5,6-dimethyl-2-methylthio-	35–36°	775, 1980
4-chloro-5-ethyl-2-ethylthio-	160–163°/24 mm.	839
4-chloro-6-ethyl-2-ethylthio-	110–112°/4–5 mm.	722
4-chloro-5-ethyl-2-ethylthio-6-methyl-	177–180°/21–23 mm.	107
4-chloro-2-ethylthio-	135°/24 mm.	650, 654, 804
4-chloro-2-ethylthio-5,6-dimethyl-	142–144°/10 mm.	96
4-chloro-2-ethylthio-5-methyl-	146–147°/17 mm.	654
4-chloro-2-ethylthio-6-methyl-	142°/15 mm.	800, 1153
4-chloro-2-ethylthio-6-methyl-5-propyl-	165–166°/11 mm.	1118
4-chloro-2-ethylthio-5-phenyl-	38–39°; 231–232°/20 mm.	841, 840
4-chloro-2-ethylthio-6-phenyl-	232°/26 mm.	799

(Table continued)

TABLE XLVIII *(continued)*

Pyrimidine	M.p.	Reference
4-chloro-5-iodo-2-ethylthio-	69°	649
5-chloro-2-mercapto-	221–222°	2070, 831
5-chloro-4-mercapto-	212°	626
2-chloro-4-methyl-6-methylthio-	166–168°/70 mm.	1849
4-chloro-2-methyl-6-methylthio-	126–128°/19 mm.	786
4-chloro-6-methyl-2-methylthio-	38°; 132°/15 mm.	925, 110, 631, 1347
2-chloro-4-methylthio-	125–126°/15 mm.	1849
4-chloro-2-methylthio-	−2°–0°; 122°/18 mm.	522, 611
4,5-dichloro-2-ethylthio-	199°	187
4,6-dichloro-5-methyl-2-methylthio-	64°	65
4,6-dichloro-2-methylthio-	41–42°; 135–136°/14 mm.	65

TABLE XLIX. Nitro-Oxypyrimidines

Pyrimidine	M.p.	Reference
barbituric acid/1-ethyl-3-methyl-5-nitroso-	95–96°	1807
barbituric acid/1-ethyl-5-nitro-	*hy.* 132–133°	516
barbituric acid/5-ethyl-5-nitro-	183°	2072
barbituric acid/1-ethyl-5-nitroso-	*hy.* 183°	1806, 145
barbituric acid/1-methyl-5-nitro-	143°	516, 2076
barbituric acid/1-methyl-5-nitroso-	202–203°	154, 2076
2-butoxy-5-nitro-	49–50°	1875
2-butyl-4,6-dihydroxy-5-nitro-	265°	352
2,4-diethoxy-6-methyl-5-nitro-	38°	523
4,6-diethoxy-2-methyl-5-nitro-	74°	780
2,4-diethoxy-5-nitro-	45°	523, 824
1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-5-nitro-2,4-dioxo-	116–117°	516
1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-5-nitroso-2,4-dioxo-	*ca.* 107°	551
2,4-dihydroxy-5-(2,4-dihydroxypyrimidin-5-yl)-azopyrimidine	280°	2073
2,4-dihydroxy-6-methyl-5-nitro-	290°	1257, 505, 504, 1898
4,6-dihydroxy-2-methyl-5-nitro-	270–280°	505, 134
2,4-dihydroxy-6-methyl-5-phenylazo-	253–255°	580
4,6-dihydroxy-2-methyl-5-phenylazo-	300°	580

(Table continued)

TABLE XLIX *(continued)*

Pyrimidine	M.p.	Reference
2,4-dihydroxy-5-nitro-	—	498, 435, 501, 665, 522
4,6-dihydroxy-5-nitro-	>300°	506,511
4,6-dihydroxy-5-nitro-2-phenyl-	—	617
2,4-dimethoxy-6-methyl-5-nitro-	81°	1885
4,6-dimethoxy-2-methyl-5-nitro-	—	1451
2,4-dimethoxy-5-nitro-	92–93°	292
4,6-dimethoxy-5-nitro-	173–174°	789
4-ethyl-2,6-didydroxy-5-nitro-	230°	104
1-ethyl-1,2,3,4-tetrahydro-3-methyl-5-nitro-2,4-dioxo-	106°	1266, 1321
1-ethyl-1,2,3,6-tetrahydro-3-methyl-5-nitro-2,6-dioxo-	124°	1266, 1321
4-hydroxy-2,6-dimethyl-5-nitro-	222°	536
2-hydroxy-4,6-dimethyl-5-nitroso- (??)	—	100
2-hydroxy-4,6-dimethyl-5-phenylazo-	>300°	580
4-hydroxy-2,6-dimethyl-5-phenylazo-	186°	601
4-hydroxy-6-methyl-5-nitro-	—	unknown, 536, 789
4-hydroxy-6-methyl-2-nitroamino-	224°	451; *cf.* 527, 528
2-hydroxy-4-methyl-5-phenylazo-	>300°	580
2-hydroxy-5-nitro-	205°	25, 499
2-methoxy-5-nitro-(?)	—	25
1,2,3,4-tetrahydro-1,3-dimethyl-5-nitro-2,4-dioxo-	155–156°	273, 1266, 2003, 849
1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-5-nitro-2,4-dioxo-	146–147° *or* 152°	2003, 1805, 516
1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-5-nitroso-2,4-dioxo-	141° *to* 147°	1962, 978, 2075
1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxo-5-phenylazo-	—	1968
1,2,3,4-tetrahydro-1,3,6-trimethyl-5-nitro-2,4-dioxo-	149–150°	1336
2,4,6-trihydroxy-5-nitro-	*hy.* 180–181°	510, 509, 102, 525 561, 516
2,4,5-trihydroxy-6-nitroso-	*ca.* 250°	568, 2076
2,4,6-trihydroxy-5-nitroso-	—	2076, 561, 564, 562, 563
uracil/1,6-dimethyl-5-nitro-	191° (*or* 249–250°)	904, 1337
uracil/3,6-dimethyl-5-nitro-	149° (*or* 229–230°)	1266, 1337
uracil/1-ethyl-5-nitro-	194–195°	1811, 1321, 1266
uracil/3-ethyl-5-nitro-	159–161°	1811
uracil/1-methyl-5-nitro-	256–264°	273, 904, 902, 903, 116, 1320, 875
uracil/3-methyl-5-nitro-	263–265°	273, 849, 1321

TABLE L. Nitro-Sulphonylpyrimidines

Pyrimidine	M.p.	Reference
5-nitro-2-sulphamoyl-	—	2074

TABLE LI. Nitro-Thiopyrimidines

Pyrimidine	M.p.	Reference
2,4-dimercapto-6-methyl-5-nitro-	240°	776, 832
2,4-dimercapto-5-nitro-	*ca.* 200° *or* 213–215°	534, 747, 748
2-mercapto-4-methyl-5-phenylazo-	—	580
2-methylthio-5-nitro-	82–83°	30
2-methylthio-5-phenylazo-	—	774

TABLE LII. Oxy-Sulphonylpyrimidines

Pyrimidine	M.p.	Reference
barbituric acid/5-hydroxy-1-methyl-5-sulpho-	—	1810
barbituric acid/5-hydroxy-5-sulpho-	—	1071, 2078
5-chlorosulphonyl-2,4-dihydroxy-	—	1104
2,4-dihydroxy-5-dimethylsulphamoyl-	340–342°	1104
2,4-dihydroxy-6-methylsulphonyl-	307–308°	637
2,4-dihydroxy-5-phenoxysulphonyl-	250–253°	1104
2,4-dihydroxy-5-phenylsulphonyl-	*ca.* 350°	371
2,4-dihydroxy-5-sulphamoyl-	305°	876
2,4-dihydroxy-6-sulphamoyl-	>235°	637
2,4-dihydroxy-6-sulpho-	248–250°	637, 822
2,4-dihydroxy-5-sulphoamino-(?)	—	540, 541
2,4-dihydroxy-6-sulphoamino-	280°	875
2,4-dimethoxy-6-methylsulphonyl–	122–123°	637
2,4-dimethoxy-6-sulphamoyl-	189–190°	637
2,4-dimethoxy-6-sulpho-	208–209°	822
4-ethoxy-2-ethylsulphonyl-	—	635
4-ethoxy-2-ethylsulphonyl-5-methyl-	67–68°	635
4-ethoxy-2-ethylsulphonyl-6-methyl-5-propyl-	*impure*	929, 927
5-ethylsulphonyl-2,4-dihydroxy-	282°	371

(Table continued)

TABLE LII *(continued)*

Pyrimidine	M.p.	Reference
2-ethylsulphonyl-4-methoxy-6-methyl-5-propyl-	—	929, 927
hexahydro-5-hydroxy-1,3-dimethyl-5-sulpho-2,4,6-trioxo-	—	1810
4-hydroxy-2-methyl-5-sulphomethyl-	—	1706, 1138
2-hydroxy-2-sulpho-	>300°	1474
4-methoxy-6-methyl-2-methylsulphonyl-	80°	925
1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-sulphoamino-	—	875
uracil/1-ethyl-5-phenylsulphonyl-	222°	371
uracil/5-ethylsulphonyl-3-methyl-	223°	371
uracil/1-methyl-5-sulphoamino-	264°	875

TABLE LIII. Oxy-Thiopyrimidines

Pyrimidine	M.p.	Reference
1-allyl-1,6-dihydro-4,5-dimethyl-2-methylthio-6-oxo-	83°	696
1-allyl-1,6-dihydro-4-methyl-2-methylthio-6-oxo-	48–50°	1752
5-allyl-4-hydroxy-2-mercapto-	185–186°	2077
5-allyl-4-hydroxy-2-mercapto-6-methyl-	188°	701, 1752
5-allyl-4-hydroxy-6-methyl-2-methylthio-	84° (*or* 189–191°?)	1752, (701)
4-allyloxy-6-methyl-2-methylthio-	160–164°/17 mm.	1116
2-allylthio-4,6-dihydroxy-5-isopropyl-	224–225°	164
2-allylthio-1,6-dihydro-1,4-dimethyl-6-oxo-	43°	1116
2-allylthio-4-hydroxy-6-methyl-	132–133° *or* 140°	1752, 653, 1116
4-amyl-6-hydroxy-2-mercapto-	153–154°	103, 105
5-amyl-4-hydroxy-2-mercapto-6-methyl-	216° (*or* 183°?)	2079, *cf.* 2080
2-amylthio-5-ethyl-4,6-dihydroxy-	268–270°	2081
1-benzyl-2-benzylthio-1,4-dihydro-4-oxo-	144–145°	628, 48
5-benzyl-2-benzylthio-4-hydroxy-6-methyl-	194°	86

(Table continued)

TABLE LIII *(continued)*

Pyrimidine	M.p.	Reference
1-benzyl-1,2-dihydro-4-methylthio-2-oxo-	148–149°	835
1-benzyl-5-ethoxy-2-ethylthio-1,4-dihydro-4-oxo-	85–86°	588
1-benzyl-5-ethoxy-2-ethylthio-1,6-dihydro-6-oxo-	140–141°	588
1-benzyl-2-ethylthio-1,4-dihydro-5-methyl-4-oxo-	121–122°	1348
1-benzyl-2-ethylthio-1,6-dihydro-5-methyl-6-oxo-	70°	1348
1-benzyl-2-ethylthio-1,4-dihydro-4-oxo-	139°	1348
1-benzyl-2-ethylthio-1,6-dihydro-6-oxo-	77°	1348
4-benzyl-2-ethylthio-6-hydroxy-	131°	1757, 657
5-benzyl-2-ethylthio-4-hydroxy-6-methyl-	166°	86
4-benzyl-6-hydroxy-2-mercapto-	222–223° *or* 216–219°	657, 103, 1157, 2082
5-benzyl-4-hydroxy-2-mercapto-	210–211°	657, 735, 1328
5-benzyl-4-hydroxy-2-mercapto-6-methyl-	256–257°	1761, 86
4-benzyl-6-hydroxy-2-methylthio-	180°	1157
5-benzyl-4-hydroxy-2-methylthio-	178°	735
4-benzyl-2-mercapto-6-methoxy-	65–66°	1757
2-benzylthio-1,4-dihydro-1-methyl-4-oxo-	—	1767
2-benzylthio-1,6-dihydro-1-methyl-6-oxo-	—	1767
5-benzylthio-2,4-dihydroxy-	290°	797
2-benzylthio-1-ethyl-1,4-dihydro-4-oxo-	—	1767
2-benzylthio-5-ethyl-4,6-dihydroxy-	258–260°	2081
2-benzylthio-5-ethyl-4-hydroxy-6-methyl-	160°	107
5-benzylthio-2-ethylthio-4-hydroxy-	155–156°	797
2-benzylthio-4-hydroxy-	191–192°	48, 2083
5-benzylthio-4-hydroxy-2-mercapto-	195–196°	797
2-benzylthio-4-hydroxy-5-methyl-	204–205°	88
2-benzylthio-4-hydroxy-6-methyl-	183–184° *or* 176–178°	1794, 2083
2-benzylthio-4-hydroxy-6-propyl-	131–132°	2083
2-(2-butenylthio)-5-butyl-4,6-dihydroxy-	238–239°	2084

(Table continued)

TABLE LIII *(continued)*

Pyrimidine	M.p.	Reference
5-butyl-4,6-dihydroxy-2-isopropylthio-	257–258°	2081
5-butyl-2-ethylthio-4-hydroxy-6-methyl-	92–93°	1115
4-butyl-6-hydroxy-2-mercapto-	207–209°	103, 1157
4-s.-butyl-6-hydroxy-2-mercapto-	222–224°	103
4-t.-butyl-6-hydroxy-2-mercapto-	178–180°	103
5-butyl-4-hydroxy-2-mercapto-	151–153°	103, 1328
5-butyl-4-hydroxy-2-mercapto-6-methyl-	195° *to* 201°	1115, 2080, 2085
5-butyl-4-hydroxy-6-methyl-2-methylthio-	158°	1115
4-butyl-6-hydroxy-2-methylthio-	127°	1157
2-butylthio-4-hydroxy-5-methyl-	105–106°	631
4-cyclobutyl-6-hydroxy-2-mercapto-	211–212°	109
4-cyclohexyl-6-hydroxy-2-mercapto-	282–285°	103
4-cyclopentyl-6-hydroxy-2-mercapto-	220–222°	109
4-cyclopropyl-6-hydroxy-2-mercapto-	236–239°	109, 2086
4,5-diethoxy-2-ethylthio-	*HCl* 129–130°	625
4,5-diethyl-6-hydroxy-2-mercapto-	214–215°	103
1,3-diethyl-1,2,3,4-tetrahydro-6-methyl-4-oxo-2-thio-	97–98°	1315
1,3-diethyl-1,2,3,4-tetrahydro-4-oxo-2-thio-	—	2087
1,2-dihydro-1,5-dimethyl-4-methylthio-2-oxo-	83°	88
1,2-dihydro-1,6-dimethyl-4-methylthio-2-oxo-	170–171°	1347
1,6-dihydro-1,4-dimethyl-2-methylthio-6-oxo-	94°	86, 1315, 1316 2087, 653 (?)
1,2-dihydro-1-methyl-4-methylthio-2-oxo-	124°	835
1,4-dihydro-1-methyl-2-methylthio-4-oxo-	168–169°	273
1,6-dihydro-1-methyl-2-methylthio-6-oxo-	122–123°	273
1,6-dihydro-4-methyl-2-methylthio-6-oxo-1-phenyl-	147°	1315, 1316
4,6-dihydroxy-5-hydroxyethyl-2-mercapto-	181°	2088

(Table continued)

TABLE LIII *(continued)*

Pyrimidine	M.p.	Reference
4,6-dihydroxy-5-isopropyl-2-methylthio-	247–248°	164
2,4-dihydroxy-5-mercapto-	—	1103, 1104
4,6-dihydroxy-2-mercapto-	*ca.* 235°	161, 148, 160, 207
4,6-dihydroxy-2-mercapto-5-methyl-	244°	65
2,4-dihydroxy-6-mercaptomethyl-5-phenoxy-	182°	872
4,6-dihydroxy-5-methyl-2-methylthio-	303°	65
4,6-dihydroxy-2-methylthio-	—	*crude;* 583
2,4-dihydroxy-6-methylthiomethyl-	221–222°	1794
4,6-dihydroxy-2-selenyl-	193–210°	2131
2,4-dimercapto-5-phenoxy-	287°	1123
2,4-dimethoxy-6-methylthio-	45–46°	637
5-ethoxy-2,4-dimercapto-	255–268°	797
5-ethoxy-4-ethoxymethyl-2-ethylthio-	167°	918
5-ethoxy-4-ethoxymethyl-2-ethylthio-6-hydroxy-	123°	918
5-ethoxy-4-ethoxymethyl-6-hydroxy-2-mercapto-	178°	918
4-α-ethoxyethyl-6-hydroxy-2-mercapto-	206–208°	2063
4-α-ethoxyethyl-6-hydroxy-2-mercapto-5-methyl-	222°	1768
5-β-ethoxyethyl-4-hydroxy-2-mercapto-6-methyl-	202–203°	690
4-ethoxy-2-ethylthio-	138°/18 mm.	654, 804
5-ethoxy-2-ethylthio-	31–32°; *HCl* 120–121°	721
5-ethoxy-2-ethylthio-1,4-dihydro-1-methyl-4-oxo-	149–151°	934
5-ethoxy-2-ethylthio-1,6-dihydro-1-methyl-6-oxo-	50°	934
5-ethoxy-2-ethylthio-4-mercapto-	144–145°	845
4-ethoxy-2-ethylthio-5-methyl-	135–136°/12 mm.	635
4-ethoxy-2-ethylthio-6-methyl-	154°/20 mm.	800
4-ethoxy-2-ethylthio-6-methyl-5-propyl-	—	929
5-ethoxy-4-hydroxy-2-ethylthio-	169°	907
5-ethoxy-4-hydroxy-2-methylthio-	190°	907
5-ethoxy-2-mercapto-	192–193°	721
5-ethoxy-4-mercapto-2-methylthio-	190°	797

(Table continued)

TABLE LIII *(continued)*

Pyrimidine	M.p.	Reference
4-ethoxymethyl-6-hydroxy-2-mercapto-	180–181°	868
4-ethoxymethyl-6-hydroxy-2-mercapto-5-methyl-	190–192°	990, 989
4-ethoxy-6-methyl-2-methylthio-	219°	1985
5-ethyl-4,6-dihydroxy-2-mercapto-	190–192°	65, 165
5-ethyl-4,6-dihydroxy-2-methylthio-	257°	65
1-ethyl-2-ethylthio-1,6-dihydro-6-oxo-	—	1767
4-ethyl-2-ethylthio-6-hydroxoy-	89°	720
5-ethyl-2-ethylthio-4-hydroxy-	119–120°	634
5-ethyl-2-ethylthio-4-hydroxy-6-methyl-	138°	107, 1451
5-ethyl-4-hydroxy-2-mercapto-	190–192°	103, 1328
4-ethyl-6-hydroxy-2-mercapto-5-methyl-	223–224° (*or* 218–219°)	103, 2089
5-ethyl-4-hydroxy-2-mercapto-6-methyl-	216–218° (*or* 212°)	103, 107
5-ethyl-4-hydroxy-2-mercapto-6-phenyl-	233–235°	1540
5-ethyl-4-hydroxy-6-methyl-2-methylthio-	203°	66
4-ethyl-6-hydroxy-2-methylthio-	153°	1157, 1849
5-ethyl-4-hydroxy-2-methylthio-	—	1767
4-α-ethylpropyl-6-hydroxy-2-mercapto-	224–225°	444
2-ethylthio-1,4-dihydro-1,5-dimethyl-4-oxo-	156°	669
2-ethylthio-1,6-dihydro-1,4-dimethyl-6-oxo-	63–64°	1326, 1318
2-ethylthio-1,6-dihydro-1,5-dimethyl-6-oxo-	65°	669
2-ethylthio-1,4-dihydro-1-methyl-4-oxo-	—	835, 2087, 1318
2-ethylthio-1,6-dihydro-1-methyl-6-oxo-	79–80°	835, 2087, 1318
2-ethylthio-4-hydroxy-	152°	66, 48
2-ethylthio-4-hydroxy-5,6-dimethyl-	155–156°	66, 96
2-ethylthio-4-hydroxy-5-methyl-	159°	654, 88, 1129
2-ethylthio-4-hydroxy-6-methyl-	144–145°	1017, 85, 1153
4-ethyl-6-hydroxy-2-mercapto-	228–230°	103, 1157, 104
2-ethylthio-4-hydroxy-5-methyl-6-phenyl-	192–193°	1208

(Table continued)

TABLE LIII *(continued)*

Pyrimidine	M.p.	Reference
2-ethylthio-4-hydroxy-6-methyl-5-propyl	92–93°	1118
2-ethylthio-4-hydroxy-5-phenyl-	158°	841, 1829, 840
2-ethylthio-4-hydroxy-6-phenyl-	226°	799
2-ethylthio-4-methoxy-	—	804
2-ethylthio-4-methoxy-6-methyl- (?)	—	1944
2-ethylthio-4-methoxy-6-methyl-5-propyl-	—	929
hexahydro-1,3,5,5-tetramethyl-4,6-dioxo-2-thio-	80°	2091
4-hexyl-6-hydroxy-2-mercapto-	144–145°	103, 106
5-hexyl-4-hydroxy-2-mercapto-	168–169°	1328
4-hydroxy-5,6-dimethyl-2-mercapto-	283–285°	103
4-hydroxy-5,6-dimethyl-2-methylthio-	225–227°	96
4-hydroxy-2-ethylthio-5-phenoxy-	159°	1318
4-hydroxy-5-β-hydroxyethyl-2-mercapto-6-methyl-	265–267°	103
4-hydroxy-6-hydroxymethyl-2-mercapto-	259°	958
4-hydroxy-5-hydroxymethyl-2-mercapto-6-methyl-	280–290°	1765
4-hydroxy-5-hydroxymethyl-6-methyl-2-methylthio-	220–221°	1765
4-hydroxy-5-isoamyl-2-mercapto-6-methyl-	216°	2080 *cf.* 2079
4-hydroxy-2-isoamylthio-	115°	522
4-hydroxy-6-isobutyl-2-mercapto-	220–221°	103
4-hydroxy-5-isobutyl-2-mercapto-6-methyl-	227°	2080
4-hydroxy-2-isobutylthio-	107°	522
4-hydroxy-5-isopropyl-2-mercapto-	242–244°	103
4-hydroxy-6-isopropyl-2-mercapto-	179–180°	103
4-hydroxy-5-isopropyl-2-mercapto-6-methyl-	257°	2080
2-hydroxy-4-mercapto-	289–290° (*or* 328°)	1108, 48, 835, 578
4-hydroxy-2-mercapto-	*ca.* 340°	48, 1792, 981
4-hydroxy-6-mercapto-	240–242°	1379
4-hydroxy-2-mercapto-5,6-dimethyl-	278–280° (*or* 283–285°)	103, 141, 1113, 96, 1765
4-hydroxy-2-mercapto-5-methoxy-	280°	245, 913

(Table continued)

TABLE LIII *(continued)*

Pyrimidine	M.p.	Reference
4-hydroxy-2-mercapto-6-α-methoxyethyl-5-methyl-	207°	1768
4-hydroxy-2-mercapto-6-methoxymethyl-	221–222°	444
2-hydroxy-4-mercapto-5-methyl-	330°	88
2-hydroxy-4-mercapto-6-methyl-	>250°	1347
4-hydroxy-6-mercapto-2-methyl-	—	*crude;* 786
4-hydroxy-2-mercapto-5-methyl-	—	88, 74
4-hydroxy-2-mercapto-6-methyl-	290° *to* 324°	87, 103, 1157, 1315, 1772, 86, 85, 1017, 2093
4-hydroxy-2-mercapto-5-methyl-6-phenyl-	236–237°	1208
4-hydroxy-2-mercapto-6-methyl-5-phenyl-	—	193
4-hydroxy-2-mercapto-5-methyl-6-propyl-	204–205°	2089
4-hydroxy-2-mercapto-6-methyl-5-propyl-	209–210°	1761, 1118, 2080
4-hydroxy-2-mercapto-6-methylthiomethyl-	284–286°	109
4-hydroxy-2-mercapto-5-phenoxy-	253–254°	797
4-hydroxy-2-mercapto-5-phenyl-	313–315°	1328
4-hydroxy-2-mercapto-6-phenyl-	263–264 *or* 259°	103, 1157, 1328, 799, 829
4-hydroxy-2-mercapto-5-propyl-	218–219°	103
4-hydroxy-2-mercapto-6-propyl-	218–219°	1157, 1156, 103
2-hydroxy-4-methyl-6-methylthio-	174–175°	1347
2-hydroxy-5-methyl-4-methylthio-	205–211°	88
4-hydroxy-2-methyl-6-methylthio-	222–224°	786
4-hydroxy-5-methyl-2-methylthio-	233°	388, 66
4-hydroxy-6-methyl-2-methylthio-	219° *to* 225°	193, 1157, 1985, 1315, 86, 85
4-hydroxy-6-methyl-2-methylthio-5-propyl-	180–181°	1118
4-hydroxy-6-methyl-5-propyl-2-propylthio-	89–90°	1118
4-hydroxy-5-methyl-2-selenyl-	228–229°	75
2-hydroxy-4-methylthio-	205°	835
4-hydroxy-2-methylthio-	199°	611, 66
4-hydroxy-2-methylthio-6-methylthiomethyl-	149–150°	1794
4-hydroxy-2-methylthio-6-phenyl-	240°	1157, 66
4-hydroxy-2-methylthio-6-propyl-	154–155°	1157
4-hydroxy-2-propylthio-	117°	522
4-hydroxy-2-selenyl-	235–236°	75

(Table continued)

TABLE LIII *(continued)*

Pyrimidine	M.p.	Reference
4-mercapto-2,6-dimethoxy-	282–285°	822, 637
4-mercapto-5-methoxy-	209–211°	245
4-methoxy-6-methyl-2-methylthio-	126–130°/12 *or* 18 mm.; 137–139°	925, 1471, 813
1,2,3,4-tetrahydro-1,6-dimethyl-4-oxo-3-phenyl-2-thio-	197–199°	1315
1,2,3,4-tetrahydro-1,3-dimethyl-2-oxo-4-thio-	132–133°	974, 827
2-thiobarbituric acid/5,5-dimethyl-	216° *or* 240°	165, 2042
2-thiobarbituric acid/5,5-dimethylene-	—	1754
2-thiobarbituric acid/1-methyl-	197°	411
2-thiouracil/3-allyl-6-methyl-	189°	1752
2-thiouracil/1-benzyl-	231°	628
2-thiouracil/6-benzyl-3-methyl-	221–222°	2094
2-thiouracil/1,6-dimethyl	235–245°	1315
2-thiouracil/1,5-dimethyl-	229–230°	669
2-thiouracil/3,6-dimethyl-	271–273°	285
2-thiouracil/5,6-dimethyl-3-phenyl-	254–255°	2095
2-thiouracil/5-ethoxy-1-methyl-	210–211°	934
2-thiouracil/1-ethyl-	—	2087
2-thiouracil/3-ethyl-	—	2087
2-thiouracil/5-hydroxy-3-methyl-	—	934
2-thiouracil/6-methyl-1-phenyl-(?)	—	2096
2-thiouracil/6-methyl-3-phenyl-	266° (*or* 256°)	2096, 1315, 285, 2095
2-thiouracil/3,5,6-trimethyl-	255–256°	1825, 2095
2,4,6-trihydroxy-5-mercapto-	—	515, 1155
4,5,6-trihydroxy-2-mercapto-	>200°	83

TABLE LIV. Oxy-Thiopyrimidines with Other Functional Groups

Pyrimidine	M.p.	Reference
5-acetyl-1,6-dihydro-1-isopropyl-2-methylthio-6-oxo-	—	274
5-acetyl-1,6-dihydro-1-methoxyethyl-2-methylthio-6-oxo-	94°	274
2-allylthio-4-hydroxy-5-iodo-6-methyl-	159°	653
1-benzyl-5-bromo-2-ethylthio-1,4-dihydro-4-oxo-	129°	1348

(Table continued)

TABLE LIV *(continued)*

Pyrimidine	M.p.	Reference
2-benzylthio-5-bromo-4-hydroxy-	184°	651
2-benzylthio-4-carboxy-6-hydroxy-	—	958
1-benzyl-4-ethoxycarbonyl-2-ethylthio-1,6-dihydro-5-methyl-6-oxo-	69–71°	1823
2-benzylthio-5-ethoxycarbonyl-4-hydroxy-	174–179°	89, 1698
2-benzylthio-4-formyl-6-hydroxy-	156°	958
2-benzylthio-4-hydroxy-5-iodo-	178–180°	651
2-benzylthio-4-hydroxy-5-iodo-6-methyl-	180–181°	651
1-(2-bromoallyl)-1,6-dihydro-4-methyl-2-methylthio-6-oxo-	89°	696
5-bromo-4-ethoxy-2-ethylthio-	140°/6 mm.	635
5-bromo-4-ethyl-2-ethylthio-6-hydroxy-	172–173°	522
5-bromo-2-ethylthio-4-hydroxy-	189°	654
5-bromo-4-hydroxy-2-mercapto-	270°	651, 652
5-bromo-4-hydroxy-2-mercapto-6-methyl-	268–272°	651, 652
5-bromo-4-hydroxy-6-methyl-2-methylthio-	255–260°	651, 192, 614
5-bromo-4-hydroxy-2-methylthio-	255°, 239°, *or* 219°	651, 629
5-carbamoyl-4-ethoxy 2-ethylthio-	134°	1395
5-carbamoylmethyl-4,6-dihydroxy-2-mercapto-	272°	1377
5-carbamoylmethyl-2-ethylthio-4-hydroxy-	214°	1997
5-carboxy-1,6-dihydro-1-methyl-2-methylthio-6-oxo-	153°	274
5-carboxyethyl-4,6-dihydroxy-2-mercapto-	235–236°	1191
4-carboxy-2-ethylthio-6-hydroxy-	248°	958
5-carboxy-2-ethylthio-4-hydroxy-	167°	90
4-carboxy-2-ethylthio-6-hydroxy-5-methyl-	220°	1129
4-carboxy-6-hydroxy-5-methyl-2-methylthio-	243–244°	388
4-carboxy-6-hydroxy-2-mercapto-	319–321°	1382, 97, 958, 2097
5-carboxy-4-hydroxy-2-mercapto-	288–290°	921, 194
4-carboxy-6-hydroxy-2-methylthio-	250–252°	1382, 958
5-carboxy-4-hydroxy-2-methylthio	234–235°	921, 90

(Table continued)

TABLE LIV *(continued)*

Pyrimidine	M.p.	Reference
5-carboxymethyl-4,6-dihydroxy-2-mercapto-	>230°	1377
1-carboxymethyl-2-ethylthio-1,4-dihydro-4-oxo-	208–209°	1017
5-carboxymethyl-2-ethylthio-4-hydroxy-	184°	1997
4-carboxymethyl-2-ethylthio-6-hydroxy-	155°	1017
5-carboxymethyl-2-ethylthio-4-hydroxy-6-methyl-	255°	809
5-carboxymethyl-4-hydroxy-6-methyl-2-methylthio-	270–272°	809
5-carboxymethyl-4-hydroxy-2-mercapto-	*ca.* 260°	2002
5-carboxymethyl-4-hydroxy-2-mercapto-6-methyl-	295°	601
4-chloro-5-ethoxy-6-ethoxymethyl-2-ethylthio-	165–166°/10 mm.	918
4-chloro-5-ethoxy-2-ethylthio-	46°; 185°/25 mm.	907
4-chloro-6-ethoxy-5-methyl-2-methylthio-	85°	65
4-chloro-5-ethoxy-2-methylthio-	75°	797
5-chloro-2-ethylthio-4-hydroxy-	196–199°	2064
5-chloro-2-ethylthio-4-hydroxy-6-methyl-	188–190°	651, 652
5-chloro-4-hydroxy-2-isopropylthio-6-methyl-	162–163°	651
5-chloro-4-hydroxy-2-mercapto-	264–270°	651, 2098
5-chloro-4-hydroxy-2-mercapto-6-methyl-	265–270°	651
5-chloro-4-hydroxy-6-methyl-2-methylthio-	270°	76
5-chloro-4-hydroxy-2-methylthio-	259–260°	651, 76
4-chloromethyl-6-hydroxy-2-methylthio-	230–235°	76
5-β-chloropropyl-4-hydroxy-2-mercapto-6-methyl-	218–220°	701
5-cyano-2-ethylthio-4-hydroxy-	220–222°	187, 186
5-cyano-2-ethylthio-4-hydroxy-6-methyl-	112–113°	2024
5-cyano-2-ethylthio-4-hydroxy-6-phenyl-	242–243°	2024
5-cyano-4-hydroxy-2-mercapto-	282–283°	103, 368, 1608 (?)
4-diethoxylmethyl-2-ethylthio-6-hydroxy-	128°	473, 488

(Table continued)

TABLE LIV *(continued)*

Pyrimidine	M.p.	Reference
4-diethoxymethyl-2-ethylthio-6-hydroxy-5-methyl-	—	1397
4-diethoxymethyl-6-hydroxy-2-methylthio-	133°	473
4-diethoxymethyl-6-hydroxy-2-mercapto-	160°	473, 488
4-diethoxymethyl-6-hydroxy-2-mercapto-5-methyl-	107–110° *or* 119–120°	2099, 1397
4,6-dihydroxy-2-mercapto-5-nitroso-	300°	162, 255, 548
5-ethoxycarbonyl-1,6-dihydro-2-methylthio-6-oxo-1-phenyl-	128°	274
5-ethoxycarbonyl-2-ethylthio-4-hydroxy-	131°	2102
4-ethoxycarbonyl-2-ethylthio-6-hydroxy-5-methyl-	172–173°	1129
4-ethoxycarbonyl-6-hydroxy-2-mercapto-	196–198°	1382
5-ethoxycarbonyl-4-hydroxy-2-mercapto-	245°	89, 2097
4-ethoxycarbonyl-6-hydroxy-5-methyl-2-methylthio-	201–202°	388
5-ethoxycarbonyl-4-hydroxy-2-methylthio-	134–136°	2100, 921, 90
1-ethoxycarbonylmethyl-2-ethylthio-1,4-dihydro-4-oxo-	129°	1017
4-ethoxycarbonylmethyl-2-ethylthio-6-hydroxy-	131°	119
5-ethoxycarbonylmethyl-2-ethylthio-4-hydroxy-	146–147°	2002, 1997
5-ethoxycarbonylmethyl-2-ethylthio-4-hydroxy-6-methyl-	163–165°	809, 134
5-ethoxycarbonylmethyl-4-hydroxy-2-mercapto-	178–180°	2002
5-ethoxycarbonylmethyl-4-hydroxy-2-mercapto-6-methyl-	218°	601
5-ethoxycarbonylvinyl-4,6-dihydroxy-2-mercapto-	268–269°	2052
4-ethoxy-5-ethoxycarbonyl-2-ethylthio-	175°/8 mm.	635
5-ethoxy-4-ethoxycarbonyl-2-ethylthio-6-hydroxy-	82–83°	918
5-ethoxy-2-ethylthio-4-isothiocyanato-	45–50°; 228–235°/23 mm.	845

(Table continued)

TABLE LIV *(continued)*

Pyrimidine	M.p.	Reference
5-ethoxy-2-ethylthio-4-thiocyanato-	66–67°	845
4-ethyl-5-iodo-6-hydroxy-2-mercapto-	*Na* 234–235°	1102
2-ethylthio-4-formyl-6-hydroxy-	145° *to* 168°	1396, 958, 473, 488, 2101
2-ethylthio-4-formyl-6-hydroxy-5-methyl-	186°	1397
2-ethylthio-5-hydrazinocarbonylmethyl-4-hydroxy-	207–208°	1192
2-ethylthio-4-hydroxy-6-hydroxyiminomethyl-5-methyl-	235°	1397
2-ethylthio-4-hydroxy-5-iodo-	196°	649
2-ethylthio-4-hydroxy-5-isocyanatomethyl-	189–191°	1192
5-formyl-4,6-dihydroxy-2-mercapto-	*deriv.*	1401
4-formyl-6-hydroxy-2-mercapto-	—	473, 2101, 488
4-formyl-6-hydroxy-2-mercapto-5-methyl-	232–233°	1397
4-hydroxy-6-hydroxyiminomethyl-2-mercapto-5-methyl-	233°	1397
4-hydroxy-5-iodo-2-mercapto-	220°	1102, 2098, 651
4-hydroxy-5-iodo-2-mercapto-6-methyl-	270° *or* 285–290°	1102, 651, 652
4-hydroxy-5-iodo-2-mercapto-6-propyl-	*Na* 215–216°	1102
4-hydroxy-2-mercapto-6-trifluoromethyl-	247–249°	444
2-thiouracil/5-acetyl-3-cyclohexyl-	198°	274
2-thiouracil/5-acetyl-3-isopropyl-	144°	274
2-thiouracil/5-acetyl-3-β-methoxyethyl-	137°	274
2-thiouracil/5-acetyl-3-phenyl-	232°	274
2-thiouracil/3-allyl-6-carboxy-	151–152°	2105
2-thiouracil/3-allyl-5-ethoxycarbonyl-	221°	274
2-thiouracil/3-amyl-5-ethoxycarbonyl-	196°	274
2-thiouracil/5-benzoyl-3-butyl-	183°	274
2-thiouracil/5-benzoyl-3-ethyl-	253°	274
2-thiouracil/3-benzyl-5-ethoxycarbonyl-	228°	274

(Table continued)

TABLE LIV *(continued)*

Pyrimidine	M.p.	Reference
2-thiouracil/3-butyl-5-cyano-6-methyl-	234°	274
2-thiouracil/3-butyl-5-ethoxycarbonyl-	192°	274
2-thiouracil/5-carboxy-3-hexyl-	154°	274
2-thiouracil/5-carboxy-3-phenyl-	248°	274
2-thiouracil/5-cyano-3,6-dimethyl-	280°	274
2-thiouracil/5-cyano-3-ethyl-6-methyl-	268°	274
2-thiouracil/5-cyano-6-ethyl-3-phenyl-	263°	274
2-thiouracil/5-cyano-3-isopropyl-	84–85°	274
2-thiouracil/5-cyano-3-methoxyethyl-6-methyl-	207°	274
2-thiouracil/5-cyano-1-methyl-	295°	368
2-thiouracil/5-cyano-1-phenyl-	267°	368
2-thiouracil/3-cyclohexyl-5-ethoxycarbonyl-	194°	274
2-thiouracil/5-ethoxycarbonyl-3-ethyl-	257°	274
2-thiouracil/5-ethoxycarbonyl-3-hexyl-	196°	274
2-thiouracil/5-ethoxycarbonyl-3-isoamyl-	184°	274
2-thiouracil/5-ethoxycarbonyl-3-isobutyl-	189°	274
2-thiouracil/5-ethoxycarbonyl-3-methoxyethyl-	202°	274
2-thiouracil/5-ethoxycarbonyl-3-methyl-	205°	274
2-thiouracil/5-ethoxycarbonyl-3-phenyl-	276°	274
2-thiouracil/5-ethoxycarbonyl-3-propyl-	212°	274

TABLE LV. Oxypyrimidines with Two Minor Functional Groups

Pyrimidine	M.p.	Reference
barbituric acid/5-bromo-1-ethyl-5-nitro-	138–139°	516
barbituric acid/5-bromo-1-methyl-5-nitro-	137–139°	2076, 516
barbituric acid/5-bromo-5-nitro-	108°	516

(Table continued)

TABLE LV *(continued)*

Pyrimidine	M.p.	Reference
barbituric acid/5-chloro-1-methyl-5-nitro-	121°	516, 2076
barbituric acid/5-chloro-5-nitro-	86–87°	516
5-bromo-4-carboxy-2,6-dihydroxy-	288°	1463, 520 (?)
5-bromo-4-carboxy-6-hydroxy-2-methyl-	209–210°	447
5-bromo-4-carboxy-6-hydroxy-2-phenyl-	252°	447
5-bromo-1,3-diethylhexahydro-5-nitro-2,4,6-trioxo-	63–64°	516
5-bromo-4-ethoxy-2-ethylsulphonyl-	90–91°	635
5-bromohexahydro-1,3-dimethyl-5-nitro-2,4,6-trioxo-	*ca.* 152°	516, 2106
4-carboxy-5-chloro-2,6-dihydroxy-	294–296°	699, 658
4-carboxy-2,6-dihydroxy-5-nitro-	>230°	87, 115, 114, 521, 697
4-carboxymethyl-2,6-dihydroxy-5-nitro-	153°	119
4-carboxymethyl-2-hydroxy-6-methyl-5-nitro-	—	536
4-carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitro-2,6-dioxo-	139–140°	1821, 2003
4-chloro-5-cyano-6-ethoxy-2-methyl-	63–64°	627
4-chloro-5-cyano-6-methoxy-2-methyl-	87°	627
4-chloro-6-ethoxy-2-methyl-5-nitro-	81°	780
4-chloro-6-ethoxy-5-nitro-	42°; 143–146°/16 mm.	780
5-chlorohexahydro-1,3-dimethyl-5-nitro-2,4,6-trioxo-	>150°	516, 2106
4,6-dihydroxy-2-hydroxyiminomethyl-5-nitroso-	>310°	584
4-ethoxycarbonyl-2,6-dihydroxy-5-nitro-	250°	521
uracil/1-acetyl-5-bromo-	175–177°	2060
uracil/5-bromo-1-carboxymethyl-	244°	1017
uracil/6-carboxy-3-ethyl-5-nitro-	*hy.* 189°	1811
uracil/1-carboxymethyl-5-nitro-	264–265°	1017
uracil/6-carboxy-1-methyl-5-nitro-	—	1320
uracil/6-carboxy-3-methyl-5-nitro-	—	1321

TABLE LVI. Thiopyrimidines with Two Minor Functional Groups

Pyrimidine	M.p.	Reference
2-benzylthio-4-chloro-5-ethoxycarbonyl-	248°/11 mm.	89
5-bromo-4-carboxy-2-methylthio-	176–177°	462
5-bromo-2-ethylthio-4-isothiocyanato-	78–80°	837, 847
5-bromo-2-ethylthio-4-thiocyanato-	81–82°	837
5-carbamoyl-4-chloro-2-ethylthio-	134°	1395
4-carboxy-5-chloro-2-methylthio-	169–170°	2023
5-carboxymethyl-4-chloro-2-ethylthio-	132°	1997
5-carboxymethyl-4-chloro-2-ethylthio-6-methyl-	118–119°	625
4-chloro-5-chlorocarbonyl-2-ethylthio-	38–40°	1395
4-chloro-5-cyano-2-ethylthio-	35–36°; 163°/13 mm.	187
4-chloro-5-ethoxycarbonyl-2-ethylthio-	203°/20 mm.	806, 89
4-chloro-5-ethoxycarbonylmethyl-2-ethylthio-	174°/4 mm.	843, 2002
4-chloro-5-ethoxycarbonyl-2-methylthio-	58–59°	2100
4-chloro-2-ethylthio-6-formyl-	138–139°/10 mm.	808
2-chloro-4-methyl-6-methylthio-5-nitro-	—	536

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INDEX

The Index covers the text and interspersed Tables of Chapters I–XII in detail. Chapter XIII (Ionization and Spectra) and its Tables are indexed but broadly as befits their content, and the Appendix Tables are entirely excluded. Only the names of authors actually mentioned in the text are included in the Index.

The page numbers immediately following primary entries refer to syntheses or general information. Any number in parentheses indicates that, although the subject is treated on that page, the actual name will not be found in full (or perhaps even at all) in the relevant text. For example, on p. 169 appears: "2-Aminopyrimidine has been iodinated in the presence of mercuric acetate..." The product (2-amino-5-iodopyrimidine) is not mentioned but only implied by the context, so its entry in the index is shown as: (169). The letter *f* occurs after a number when the subject is treated on that and the following page or pages.

A

Acetamidine
  use in syntheses, 31–74, 102
2-Acetamido-5-acetoxy-4-hydroxy-6-methylpyrimidine, 253
4-Acetamido-5-acetylthiomethyl-2-methylpyrimidine, 286
5-Acetamido-4-amino-2,6-dihydroxypyrimidine, 106
5-Acetamido-2-amino-4,6-dimethylpyrimidine, 324
2-Acetamido-5-amino-4-hydroxy-6-methylpyrimidine
  formation of an anil, (322)
5-Acetamido-4-amino-6-hydroxypyrimidine, 324
4-Acetamido-6-amino-2-methylthiopyrimidine, 324
2-Acetamido-5-aminopyrimidine
  deacetylation, 329
2-Acetamido-5-benzamidopyrimidine, 327
2-*p*-Acetamidobenzenesulphonamido-4,6-dimethylpyrimidine, 330
  deacetylation, 330
2-*p*-Acetamidobenzenesulphonamido-4-hydroxy-6-methylpyrimidine, 329
2-*p*-Acetamidobenzenesulphonamidopyrimidine, 331
  deacetylation, 331
p-Acetamidobenzenesulphonyl chloride
  use as acylating agent, 331
p-Acetamidobenzenesulphonylguanidine
  use, 329, 331
2-Acetamido-5-benzylideneamino-4-hydroxy-6-methylpyrimidine, (322)
2-Acetamido-1-carbamoyloctane, 440
  cyclization, 440
5-Acetamido-2,4-diacetylthiopyrimidine, 286
5-Acetamido-2,4-diamino-6-hydroxypyrimidine, 71, 324, 328
4-Acetamido-1,6-dihydro-1,5-dimethyl-6-oxopyrimidine, 325
4-Acetamido-1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine
  desulphurization, 279
4-Acetamido-1,2-dihydro-1-methyl-2-oxopyrimidine, (346)
4-Acetamido-1,6-dihydro-1-methyl-6-oxopyrimidine, 279
4-Acetamido-6-dimethylamino-2-methylthiopyrimidine, 313, 324
  reduction, 313
2-Acetamido-4-*p*-dimethylaminostyryl-6-methylpyrimidine, 126
2-Acetamido-4,6-dimethylpyrimidine, 324
4-Acetamido-2,6-dimethylpyrimidine, 102
5-Acetamido-2,4-dimethylpyrimidine, 324
5-Acetamido-4-hydroxy-2-methylthiopyrimidine, 329
2-Acetamido-4-hydroxypyrimidine, 324
4-Acetamido-2-hydroxypyrimidine, 324, 346
4-Acetamido-6-hydroxypyrimidine, 324
2-Acetamido-4-mercapto-5-methyl-6-phenylpyrimidine, 324
4-Acetamido-6-methoxy-2-methylthiopyrimidine
  desulphurization, 279
4-Acetamido-6-methoxypyrimidine, 279
5-Acetamidomethyl-4-amino-2-methylpyrimidine, 319, 328
5-Acetamidomethyl-2-methyl-4-methylaminopyrimidine, 325

2-Acetamido-5-nitropyrimidine, 324
β-Acetamidononanoic acid, 440
  to amide, 440
5-Acetamido-3-phenylisoxazole, 87
5-Acetamido-2-phenylpyrimidine, 324
2-Acetamido-5-piperidinopyrimidine, 324
4-*p*-Acetamidophenylsulphonyl-2-amino-6-methylpyrimidine (?), 298
3-Acetamidopropylamine, 445
  cyclization, 445
2-Acetamidopyrimidine, 324
  deacetylation, 329
4-Acetamidopyrimidine, 255, 324
5-Acetamidopyrimidine, 324
4-Acetamido-1,2,3,6-tetrahydro-1,3,5,-trimethyl-2,6-dioxopyrimidine,325
5-Acetamido-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine, 325
Acetic anhydride
  reaction with alkylamidines, 102
Acetic formic anhydride
  use in difficult formylations, 326
Acetonin, 6
  constitution, 448
  reduction, 453, 454
Acetonitrile
  reaction with acetylene, 96
  trimerisation, 93
4-Acetonylamino-2-chloro-5-nitropyrimidine, 194
4-Acetonylamino-6-chloro-5-nitropyrimidine, 196
  amination, 196
4-Acetonylamino-6-morpholino-5-nitropyrimidine, 196
4-Acetonyl-2,6-dimethylpyrimidine, 132
  formation of oxime, 319
Acetophenone
  reaction with formamide, 91
  reactions with urea and thiourea, 442
4-Acetoxyamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 344
4-Acetoxy-2,6-dibenzyl-5-phenylpyrimidine
  a doubtful structure, 253
5-Acetoxy-2,4-dihydroxy-6-methylpyrimidine, 253
5-Acetoxy-2,4-dihydroxypyrimidine, 253
5-Acetoxy-2-hydroxy-4,6-dimethylpyrimidine, 253
5-Acetoxymethyl-4-chloro-6-hydroxy-2-methylpyrimidine, 215
5-Acetoxymethyl-4,6-dichloro-2-methylpyrimidine, 215, 253
4-Acetoxymethyl-2,6-dihydroxy-5-methylpyrimidine, 215, 253
  hydrolysis, 215
5-Acetoxymethyl-2,4-dihydroxy-6-methylpyrimidine, 253
5-Acetoxymethyl-2,4-dihydroxypyrimidine, 253
α-Acetoxymethylene-β-ethoxypropionitrile
  use, 61
4-Acetoxymethyl-6-methylpyrimidine, 384
4-Acetoxy-6-methyl-2-phenylpyrimidine
  a doubtful structure, 253
Acetoxypentane-2,4-dione
  use in syntheses, 241
4-Acetoxypyrimidine, 253, 384
Acetoxypyrimidines, 253
5-Acetoxy-2,4,6-trihydroxypyrimidine, 253
Acetylacetone
  use in synthesis, 36*f*, 94, 119
α-Acetyl aminomethylenephenylacetonitrile
  reaction with formamide, 92
5-Acetyl-2-amino-4-methylpyrimidine, 415
5-Acetyl-4-amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 416
  removal of acetyl group, 416
5-Acetyl-4-bromomethyl-2-phenylpyrimidine, 130, 177
  amination, 319
α-Acetyl-γ-butyrolactone, 46
  use in syntheses, 242
2-Acetylcyclohexanone
  use in synthesis, 36, 95
4-Acetyl-2,6-diethoxypyrimidine, 395, (416), 417
  hydrolysis, 395
  to phenylhydrazone, 418
5-Acetyl-4-diethylaminomethyl-2-phenylpyrimidine, 319
2-α-Acetyl-γ-diethylamino-α-phenylethyl-4,6-dimethylpyrimidine, 320
5-Acetyl-4,5-dihydro-2,6-dihydroxypyrimidine, 444

5-Acetyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine, 441
N-Acetyldihydro-4-oxopyrimidine, 253, 357
4-Acetyl-2,6-dihydroxypyrimidine, 395
5-Acetyl-2,4-dihydroxypyrimidine, 43, 415
  reduction, 444
  to a hydrazone, (418)
  to an oxime, (418)
5-Acetyl-4-dimethylaminomethyl-2-phenylpyrimidine, 319
5-Acetyl-2-dimethylamino-4-methylpyrimidine, 415
5-Acetyl-4-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 416
5-Acetyl-2,4-dimethylpyrimidine, 415
5-Acetyl-4-ethoxycarbonyl-2-hydroxypyrimidine, 36, 415
5-Acetyl-1-ethylbarbituric acid, 416
  to a semicarbazone, (418)
5-Acetyl-3-ethyl-2-thiouracil, 48, (415)
2-Acetylhydrazino-4,6-dimethylpyrimidine, 325
2-Acetylhydrazino-4-hydroxy-6-methylpyrimidine, 325
2-Acetylhydrazinopyrimidine, 325
2-Acetylimino-1-benzoylpropane
  use, 94
4-Acetylimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxopyrimidine, 378
  deacetylation, 329
α-Acetyl-α-methylacetone
  use in syntheses, 36
5-Acetyl-1-methylbarbituric acid
  to its hydrazone, (418)
5-Acetyl-4-methyl-2-phenylpyrimidine, 86, 415
  action of phosphorus pentachloride, 124, 181
  bromination, 130, 177
  oxidation, 392, 417
1-Acetyl-5-methyluracil, 253
  instability, 253
5-Acetyl-3-methyluracil, 48, (415)
  action of nitric acid, 417
5-Acetyl-4-morpholinomethyl-2-phenylpyrimidine, 319
5-Acetyl-3-phenyluracil, 83, 358
2-Acetylsulphanilylamino-4,6-dihydroxypyrimidine, 58
2-Acetylsulphanilylamino-4-hydroxypyrimidine, 41
Acetylsulphanilylguanidine
  use in Principal Syntheses, 41, 50, 58
5-Acetyl-1,2,3,4-tetrahydro-1,3-dimethyl-6-*N*-methylacetamido-2,4-dioxopyrimidine, 416
5-Acetyl-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine, 416
4-*N*-Acetylthiocarbamoylthio-2-chloropyrimidine, 420
4-*N*-Acetylthiocarbamoylthio-5-ethyl-2-ethylthiopyrimidine, 420
5-Acetyl-2,4,6-trihydroxypyrimidine, 416
  action of bromine, 172
  to its hydrazone, (418)
  to its oxime, (418)
1-Acetyluracil, 25, 252, 257, 357
  instability, 253
Acetylurea
  use for urea in Principal Synthesis, 68
Acid hydrazides
  reaction with halogenopyrimidines, 200
Acrolein
  failure to condense with urea, 432
Acrolein polymer
  formation from pyrimidine in alkali, 118
Acrylic acid
  use in synthesis of hydropyrimidines, 431
Acryloyl chloride
  condensation with *N*-phenylurea, 432
N-Acryloyl-*N'*-phenylurea, 436
  cyclization, 437
Acylaminopyrimidines
  by acylation, 324f
  by other means, 328f
  deacylation, 329
  interconversion of, 329
Acylated aminomethylene derivatives
  use in syntheses, 85
C-Acylpyrimidines, 415f
  preparation, 415f
  reactions, 417f
  to usual ketone derivatives, 418
Addition reactions, 18
Adenosine triphosphate
  in pyrimidine biosynthesis, 424
Albert, A., 2, 182, 485
β-Aldehydo esters
  use in Principal Synthesis, 38

β-Aldehydo ketones
  use in Principal Synthesis, 34f
β-Aldehydo nitriles
  reaction with amidines, 61f
  reaction with guanidines, 64f
  reaction with thioureas, 60f
  reaction with ureas, 59f
  use in Principal Synthesis, 59f
Alkoxyalkylpyrimidines
  cleavage, 179
Alkoxycarbonylaminopyrimidines, 336f
Alkoxycarbonylpyrimidines
  see: "Pyrimidine esters"
Alkoxy groups
  effect on acidic pK_a, 467
  effect on basic pK_a, 469
Alkoxypyrimidines, 13
  amination, 255, 309
  from halogenopyrimidines, 201f, 246
  from primary syntheses, 245f
  from various reactions, 247f, 420
  hydrolysis, 232, 237, 254, 359
  interconversion of alkoxy groups, 248
  properties, 249f
  rearrangement, 371f
Alkyl-lithium
  addition to pyrimidines, 20
  reaction with halogenopyrimidines, 213
2-Alkylpyridines
  formation, 96
Alkylpyrimidines, 119f
  by introduction of alkyl groups, 123
  direct synthesis, 119
  from alkyl chloropyrimidines, 120
  from carboxy, mercapto, and others, 120f
  halogenation, 130f
  interconversion of alkyl groups, 122
  ionization, 465
  oxidation, 126f
  N-oxide formation, 128
  properties, 124
  reactions, 124f
  removal of alkyl group, 126f, 393
N-Alkylpyrimidines, 356f
  nomenclature, 356
Alkylsulphonylpyrimidines
  formation, 21, 298f
  hydrolysis, 236f
  reactions, 300f
  replacement by alkoxy group, 247
  replacement of alkylsulphonyl group, 15, 247
Alkylthiopyrimidines, 14, 205, 282f, 286f
  action of alcoholic peroxide, 236
  amination, 289f, 309
  desulphurization, 23, 278f, 288
  halogenation, 170f
  hydrolysis, 233f, 289
  replacement of alkylthio group, 15
  to alkoxypyrimidines, 247
  to mercaptopyrimidines, 252, 274f
Alloxan, 6, 21, 106, 260f
  diabetogenesis by, 262
  early preparation, 1, 260
  explosive decomposition, 261
  hydrolysis, 261
  oxidation, 261
  reaction with ammonium sulphide, 343
  reaction with benzene in sulphuric acid, 261
  reaction with *o*-diaminobenzene, 262
  reaction with hydroxylamine, 147, 261
  reaction with phenylhydrazine, 155, 261
  reaction with semicarbazide, 261
  reduction, 238, 260f, 443
Alloxan-4,5-dioxime, 152
  reduction, 152
Alloxan family
  interconversion and relationship, 260
Alloxanic acid, 261
Alloxan-5-phenylhydrazone
  as tautomer of 2,4,6-trihydroxy-5-phenylazopyrimidine, 155
Alloxantin, 21
  action of methylamine, 262
  alkylation and acylation, 262
  dissociation of, 262
  general, 260, 262
  oxidation and reduction, 260
Alloxazine, 262
1-Allyl-4-amino-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxopyrimidine, 84
1-Allyl-6-amino-3-ethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidine, 367
1-Allyl-4-amino-3-ethyl-1,2,3,6-tetrahydro-6-oxo-2-thiopyrimidine, 84
1-Allyl-6-amino-1,2,3,4-tetrahydro-3-methyl-2,4-dioxopyrimidine, 367
Allylation of barbiturates, 53
5-Allyl-5-benzylbarbituric acid, 54
N-Allylcyanoacetamide
  reaction with ethyl isocyanate, 84

N-Allyl-*N*-cyanoacetyl-*N'*-ethylurea
  as intermediate in synthesis, 84
5-Allyl-5-cyclohex-2'-enyl-2-thiobarbituric acid, 54
5-Allyl-2,4-dihydroxy-6-methylpyrimidine
  addition of hydrogen chloride, 181
3-Allyl-5,6-dimethyluracil
  addition of bromine, (181)
Allylguanidine
  use in Principal Synthesis, 50
5-Allyl-5-1'-methylbutylbarbituric acid, 53
3-Allyl-6-methyluracil
  addition of bromine, 181
2-Allyloxy-4,6-dihydroxypyrimidine, 53, 245
2-Allyloxy-4-hydroxy-6-methylpyrimidine, 46, 245
2-Allylthio-1,6-dihydro-1,4-dimethyl-6-oxopyrimidine
  iodination, (171)
2-Allylthio-1,6-dihydro-5-iodo-1,4-dimethyl-6-oxopyrimidine, 171
2-Allylthio-4-hydroxy-5-iodo-6-methylpyrimidine, 171
2-Allylthio-4-hydroxy-6-methylpyrimidine, 283
  iodination, (171)
N-Allylthiourea
  use in Principal Synthesis, 70
5-Allyl-2,4,6-trihydroxypyrimidine, 124
O-Allylurea
  use in Principal Syntheses, 46, 53, 245
5-Allylureido-2,4,6-trihydroxypyrimidine, 339
Amicitin, 6
Amidines
  use in syntheses, 82–111
  use in Principal Synthesis, 31–74
2-Amidinopyrimidine, 406
Amidinopyrimidines
  from cyanopyrimidines, 405*f*
5-Amidinothio-2-(5-carboxyamylamino)-pyrimidine, 212, 293
  reaction with nitromalondialdehyde, 293
5-Amidinothio-2,4,6-trihydroxypyrimidine, 212, 292
  hydrolysis, 212, 292
Aminoalkylpyrimidines
  from halogenoalkylpyrimidines, 215
  usual preparation, 215
4-Amino-5-aminoethyl-2-methylpyrimidine
  formation of anil(?), 322
4-Amino-5-aminoethyl-6-methylpyrimidine
  formation of an anil (?), 322
4-Amino-5-aminomethyl-2-benzylpyrimidine, 316, 317
  acylation, (327)
4-Amino-5-aminomethyl-2-butylpyrimidine, 316
5-Amino-2-aminomethyl-4,6-dihydroxypyrimidine, 148, 319, 413, 414
4-Amino-5-aminomethyl-2,6-dimethylpyrimidine, 316
  action of nitrous acid, (242)
4-Amino-5-aminomethyl-2-ethylpyrimidine, 316, 317
  acylation, (327)
4-Amino-5-aminomethyl-2-ethylthiopyrimidine, 317
2-Amino-4-aminomethyl-6-methylpyrimidine, 319
  acylation, (327)
4-Amino-5-aminomethyl-2-methylpyrimidine, 62, 316, 317, 318, 411
  action of nitrous acid, (242), (333)
4-Amino-5-aminomethyl-6-methylpyrimidine, 317
4-Amino-5-aminomethyl-2-phenylpyrimidine, 316
4-Amino-5-aminomethylpyrimidine, 316
  acylation, (327)
4-Amino-6-(2-amino-4-methylpyrimidin-6-ylamino)-2-methylquinoline, 308
  as bismethochloride, 308
4-Amino-5-(4-amino-2-methylpyrimidin-5-ylmethyliminomethyl)-2-methyl pyrimidine, (410)
  hydrolysis, (410)
  reduction, (410)
2-Amino-5-amyl-4-methylpyrimidine, 35
2-Amino-4-anilino-5-bromo-6-methylpyrimidine, 178
5-Amino-4-anilino-6-chloropyrimidine, 197
4-Amino-2-anilino-5-ethoxypyrimidine, 197
4-Amino-2-anilino-6-hydroxypyrimidine, 72
2-Amino-4-anilino-6-methylpyrimidine

  bromination, 178
  methylation, (379)
4-Amino-2-anilino-6-methylpyrimidine
  methylation, (378)
4-Amino-6-anilino-2-methylthiopyrimidine, 290
  methylation, (378)
4-Amino-6-anilino-5-nitropyrimidine, 196
2-Amino-4-anilinopyrimidine, 189, 289
4-Amino-5-azidocarbonyl-2-hydroxypyrimidine, 401
  to a purine, (401)
4-Amino-5-azidocarbonyl-2-methylpyrimidine, 401
  to a purine *via* isocyanate, 401
2-Aminobarbituric acid, 6
2-Amino-5-benzamido-4-hydroxy-6-methylpyrimidine, 327
4-Amino-5-benzamidopyrimidine, 327
2-*o*-Aminobenzenesulphonamido-5-chloropyrimidine, 330
4-*p*-Aminobenzenesulphonamido-2,6-dimethoxypyrimidine, 331
2-*p*-Aminobenzenesulphonamido-4,6-dimethylpyrimidine, 18, 37, 330, 331
4-*p*-Aminobenzenesulphonamido-2,6-dimethylpyrimidine, 331
2-*p*-Aminobenzenesulphonamido-4-methyl-6-octylpyrimidine, 330
2-*p*-Aminobenzenesulphonamido-4-methylpyrimidine, 331
2-*p*-Aminobenzenesulphonamidopyrimidine, 331
p-Aminobenzenesulphonylguanidine
  use in syntheses, 330
4-Amino-5-benzenesulphonylhydrazinocarbonyl-2-methylpyrimidine, 401, 412
  to 5-aldehyde, 412
2-(*N*-*m*-Aminobenzenesulphonyl-*N*-methylamino)-5-chloropyrimidine
  dechlorination, 211
2-(*N*-*m*-Aminobenzenesulphonyl-*N*-methylamino)pyrimidine, 211
2-Amino-5-benzoyloxy-4-hydroxy-6-methylpyrimidine, 253
2-Amino-4-benzoylthio-6-methylpyrimidine, 286
  rearrangement, 329
5-Amino-4-benzylaminomethyl-6-methyl-2-methylthiopyrimidine, 143
4-Amino-2-benzyl-5-carbamoylmethylpyrimidine, 396
  Hofmann reaction, (317)
2-Amino-5-benzyl-4-chloro-6-methoxypyrimidine, 197
4-Amino-3-benzyl-5-cyano-2,3-dihydro-2-oxopyrimidine, 64
4-Amino-2-benzyl-5-cynaopyrimidine, 86
  reduction, 316
4-Amino-3-benzyl-5-ethoxycarbonyl-2,3-dihydro-2-oxopyrimidine, 64
4-Amino-2-benzyl-5-formamidomethylpyrimidine, 327
2-Amino-5-benzyl-4-hydroxy-6-methylpyrimidine, 44
2-Amino-5-benzyl-4-hydroxypyrimidine, 41
2-Amino-5-benzylideneamino-4-hydroxy-6-methylpyrimidine, 322
4-Amino-5-benzylideneamino-1-methyl uracil, (322)
4-Amino-5-benzylideneamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 322
2-Amino-4-benzyloxyamino-6-methyl-5-nitropyrimidine
  reduction, 311
2-Amino-5-benzyloxy-4,6-dihydroxypyrimidine, 58, (240)
  hydrogenation, (240)
2-Amino-5-benzyloxy-4-hydroxypyrimidine, 40, 239, 246, 259
  hydrogenation, 239
4-Amino-5-benzyloxypyrimidine
  hydrogenation or hydrolysis, 240
4-Amino-6-benzylthio-5-formamidopyrimidine
  debenzylation, 275
4-Amino-2-benzylthio-6-hydroxypyrimidine, 283
5-Amino-4-benzylthio-6-mercaptopyrimidine, 283
2-Amino-4-benzyl-1,3,5-triazine
  anomalous formation, 64
5-Amino-4,6-bismethylaminopyrimidine, 335
2-Amino-5-bromo-4,6-bisbromomethylpyrimidine, 130, 177
2-Amino-5-bromo-4-bromoanilino-6-methylpyrimidine, 178
2-Amino-5-bromo-4-bromomethyl-6-methylpyrimidine, 130, 177

4-Amino-5-bromo-2,6-dihydroxypyrimidine
  action of thiourea *etc.*, (212), 292
  reaction with 6-mercaptopurine, 288
2-Amino-5-bromo-4,6-dimethylpyrimidine, 130, 169, 177
  debromination in ammonia, 211
  hydrolysis of 5-bromo group, 212, 238
4-Amino-5-bromo-2,6-dimethylpyrimidine
  action of thiourea, 340
  hydrolyses, 231
2-Amino-5-bromoethyl-4-methylpyrimidine, 179
  hydrolysis, 215
4-Amino-6-bromo-2-ethylpyrimidine, 190
  amination, 190
4-Amino-5-bromo-2-ethylthiopyrimidine, 199
4-Amino-5-bromo-6-hydroxy-2-mercaptopyrimidine, 170
2-Amino-5-bromo-4-hydroxypyrimidine, (170)
  amination, 211, 314
4-Amino-5-bromo-2-hydroxypyrimidine, 170, 346
4-Amino-5-bromo-6-hydroxypyrimidine
  failure to aminate, 211
2-Amino-5-bromo-4-methoxypyrimidine, 171
4-Amino-5-bromomethyl-2-butylpyrimidine, 179
4-Amino-5-bromomethyl-2-chloropyrimidine, 178
4-Amino-5-bromomethyl-2,6-diethylpyrimidine
  hydrolysis, 232
4-Amino-5-bromomethyl-2-ethylpyrimidine, 179
4-Amino-5-bromomethyl-2-ethylthiopyrimidine, 178
4-Amino-5-bromomethyl-2-methylpyrimidine, 178, 179
  amination, 319
  in syntheses of vitamin B_1, 176
  reaction with sodium bisulphite, (216), 295
  to mercapto and alkylthio analogues, 215
4-Amino-5-bromomethyl-2-methylthiopyrimidine
  reactions with thiourea *etc.*, 215
2-Amino-4-bromo-6-methylpyrimidine, 167
2-Amino-5-bromo-4-methylpyrimidine
  to 5-cyano analogue, 212
4-Amino-5-bromo-2-methylpyrimidine, 310
4-Amino-5-bromo-6-methylpyrimidine
  failure to aminate, 210
6-Amino-5-bromo-1-methyluracil
  action of sodium disulphide, (292)
"2-Amino-4-bromopyrimidine", 167
2-Amino-5-bromopyrimidine, 167
  to 5-cyano analogue, 212, 404
4-Amino-5-bromopyrimidine
  to 5-cyano analogue, (404)
4-Amino-3-butyl-5-carbamoyl-2,3-dihydro-2-oxopyrimidine, 398
4-Amino-3-butyl-5-carboxy-2,3-dihydro-2-oxopyrimidine, 64
4-Amino-2-butyl-6-chloro-5-nitropyrimidine, 195
  reaction with sodium bisulphide, 187
4-Amino-3-butyl-5-cyano-2,3-dihydro-6-methyl-2-thiopyrimidine, 66
4-Amino-2-butyl-5-cyanopyrimidine
  reduction, (316)
4-Amino-1-butyl-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxopyrimidine, 84
4-Amino-2-butyl-5-formamidopyrimidine, 326
  cyclization, 326
5-Amino-1-butyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxopyrimidine
  alkylation, 315
β-Aminobutyric acid
  use in dihydropyrimidine synthesis, 434
2-Amino-1-carbamoyl-1-*p*-chlorophenyl-1-butene
  formation and use, 87
  reaction with dichloroacetyl chloride, 407
4-Amino-5-carbamoyl-2,3-dihydro-2-oxo-3-propylpyrimidine, 64
2-Amino-3-carbamoyl-5,6-diphenylpyrazine
  in pteridine synthesis, 109
4-Amino-5-carbamoyl-2-ethylthiopyrimidine, 399
4-Amino-5-carbamoyl-2-hydroxypyrimidine, 396, 399

- 4-Amino-5-carbamoyl-2-mercaptopyrimidine, 399
- 4-Amino-5-carbamoylmethyl-2-ethylpyrimidine
  - Hofmann reaction, 317
- 4-Amino-5-carbamoylmethyl-2-methylpyrimidine, 396
  - Hofmann reaction, 317
- 4-Amino-5-carbamoylmethyl-6-methylpyrimidine
  - Hofmann reaction, (317)
- 5-Amino-4-carbamoyl-3-methylpyrazole
  - reaction with formamide, 111
- 4-Amino-5-carbamoyl-2-methylpyrimidine, 396, (399)
- 2-Amino-3-carbamoylpyrazine
  - cyclization, 108
- 3-Amino-2-carbamoylpyridine
  - reaction with formamide, 109
- 4-Amino-5-carbamoylpyrimidine, (391), 399
  - hydrolyses, 391
- 4-Amino-6-carbamoylpyrimidine
  - hydrolyses, 391
- 5-Amino-2-carboxyamylaminopyrimidine
  - to 5-hydroxy analogue, 238, 333
- 2-Amino-4-carboxy-5-chloropyrimidine (?), 175
- 4-Amino-5-carboxy-2,3-dihydro-3-methyl-2-oxopyrimidine, 63, 64, 390
  - decarboxylation, 63, 380
  - hydrolysis, 231
- 5-Amino-4-carboxy-2,6-dihydroxypyrimidine, 145, 146
  - diazotization *etc.*, 332
- 4-Amino-5-carboxy-3-ethyl-2,3-dihydro-2-oxopyrimidine, 391
- 2-Amino-4-carboxy-6-hydroxy-5-methylpyrimidine
  - formation *via* a hydantoin, 104
- 2-Amino-5-carboxy-4-hydroxy-6-methylpyrimidine, 391
- 4-Amino-5-carboxymethylaminopyrimidine, 107, 314, 390
- 5-Amino-4-carboxymethylaminopyrimidine, 107, 314
- 4-Amino-5-carboxymethyl-2-ethylthio-6-methylpyrimidine, 199
- 4-Amino-5-carboxy-2-methylpyrimidine, 391, (412)
  - esterification, (394), (412)
- 5-Amino-4-carboxy-2-methylpyrimidine, 211
- 4-Amino-2-carboxymethylthio-5-methylpyrimidine, 283
- 4-Amino-2-carboxymethylthio-6-methylpyrimidine, 283, 286
  - hydrolysis, 286
- 4-Amino-2-carboxymethylthiopyrimidine, 283
- 5-Amino-4-carboxy-2-phenylpyrimidine, 211
- 4-Amino-5-β-carboxypropionamido-6-hydroxypyrimidine, 328
- 3-Amino-2-carboxypyridine
  - to a pyridopyrimidine, 110
- 3-Amino-4-carboxypyridine
  - reaction with urea, 109
- 4-Amino-5-carboxypyrimidine, 279, 391
  - decarboxylation, 393
- 4-Amino-2-chloro-5-chloromethylpyrimidine, 178
- 4-Amino-6-chloro-5-cyano-2-methylpyrimidine, 199
  - reduction, 316
- 2-Amino-4-chloro-6-diethoxymethylpyrimidine, 407
  - dechlorination, 407
- 4-Amino-6-chloro-2-dimethylaminopyrimidine, 193
- 2-Amino-4-chloro-5,6-dimethylpyrimidine, 189
  - amination, 189
- 4-Amino-2-chloro-5,6-dimethylpyrimidine, 189
  - amination, 189
- 4-Amino-2-chloro-5-ethoxycarbonylpyrimidine
  - amination, 396
- 2-Amino-4-chloro-6-ethoxypyrimidine
  - to 4,6-dimethoxy analogue, 248
- 5-Amino-4-chloro-6-ethylaminopyrimidine
  - dechlorination, 186
- 4-Amino-2-chloro-6-ethyl-5-nitropyrimidine, 194
- 2-Amino-4-chloro-6-ethylpyrimidine
  - amination, 189
  - dechlorination, 184
- 5-Amino-2-chloro-4-ethylthiopyrimidine, 205, 283
- 5-Amino-4-chloro-6-furfurylaminopyrimidine, 144

2-Amino-4-chloro-6-α-furylpyrimidine, 189
5-Amino-4-chloro-6-hydroxy-2-methylpyrimidine, 204, 209
  action of phosphoryl chloride, 164
4-Amino-2-chloro-5-hydroxymethylpyrimidine, 243
  to 5-halogenomethyl analogues, 178
2-Amino-4-chloro-6-hydroxy-5-phenylazopyrimidine
  amination, 199
5-Amino-2-chloro-4-mercaptopyrimidine
  S-alkylation, (283)
5-Amino-4-chloro-6-mercaptopyrimidine, 207
  desulphurization, 279
5-Amino-4-chloro-6-methoxy-2-methylpyrimidine
  dechlorination, 187
2-Amino-4-chloro-6-methoxypyrimidine, 186, 197, 203
  dechlorination, 187
  to 4,6-diethoxy analogue, 248
2-Amino-4-chloro-6-methylaminopyrimidine
  dechlorination, 186
5-Amino-4-chloro-6-methylaminopyrimidine, 196
  dechlorination, 186
4-Amino-5-chloromethyl-2,6-diethylpyrimidine
  hydrolysis, 232
4-Amino-5-chloromethyl-2,6-dihydroxypyrimidine, 179
4-Amino-5-chloromethyl-2,6-dimethylpyrimidine
  action of sodium bisulphite, 216, 295
  action of thiourea *etc.*, 216
4-Amino-5-chloromethyl-2-ethylthiopyrimidine, 178
4-Amino-5-chloromethyl-2-methylpyrimidine, 179
  action of *N*-alkylthioureas, 293
  action of sodium bisulphite, 216, 295
  action of thiourea, 215, 277
5-Amino-2-chloro-4-methyl-6-methylthiopyrimidine, 143
2-Amino-4-chloro-6-methyl-5-nitropyrimidine
  amination, 195
  condensation with sodio diethyl malonate, 208
  reaction with benzyloxyamine, 311
  reaction with chloral, 409
4-Anilino-2-chloro-6-methyl-5-nitropyrimidine, 142, 194
  amination, (195)
  dechlorination and reduction, 186
  reaction of diethyl malonate *etc.*, 208
  to 2-mercapto analogue, 207
4-Amino-6-chloro-2-methyl-5-nitropyrimidine, 195
2-Amino-4-chloro-6-methylpyrimidine, 189
  action of alkoxide, 203
  amination, 190, 200
  dechlorination, 184, 186
  failure to react with thiocyanate, 208, 419
  methylation, (379)
  reaction with a quinoline, 308
  reaction with chloral, 409
  reaction with potassium bisulphide, (207)
  reaction with *p*-sulphinoacetanilide, 298
  reaction with *p*-sulphinoaniline, 298
4-Amino-2-chloro-6-methylpyrimidine, 189
  dechlorination, 186
  methylation, 378
  nitration, 141, (342)
  reaction with potassium bisulphide, (207)
4-Amino-5-chloro-2-methylpyrimidine, 310
  dechlorination, 186, 211
4-Amino-6-chloro-2-methylpyrimidine, 164, 190
  amination, 190
  dechlorination, 186, 452
  methylation, (378)
5-Amino-2-chloro-4-methylpyrimidine
  amination, 197
  dechlorination, 186
4-Amino-6-chloro-2-methylthiopyrimidine, 164, 198
  amination, 290
4-Amino-2-chloro-5-nitropyrimidine, 194
  action of alkoxide, (203)
  action of sodium bisulphide, 145, 187, 206
  action of sodium methyl mercaptide, 205, 287
  amination, 195

- 4-Amino-6-chloro-5-nitropyrimidine, 13, 183, 195
  - action of alkoxide, (203)
  - action of sodium bisulphide, 145, 206
  - amination, 13, 195*f*
- 2-Amino-5-*o*-chlorophenoxy-4-hydroxypyrimidine, 40
- 4-Amino-3-*p*-chlorophenyl-5-cyano-2,3-dihydro-2-oxopyrimidine, 64
- 2-Amino-5-*p*-chlorophenyl-4-ethyl-4,5-dihydro-6-hydroxypyrimidine
  - action of phosphorus pentasulphide, 275
- 2-Amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine, 230
- 2-Amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine, 285
- 4-Amino-5-*p*-chlorophenyl-6-ethyl-2-mercaptopyrimidine, 285
- 2-Amino-5-*p*-chlorophenyl-4-ethyl-6-methylthiopyrimidine
  - desulphurization, 279
- 4-Amino-5-*p*-chlorophenyl-6-ethyl-2-methylthiopyrimidine
  - desulphurization, 279
- 2-Amino-5-*p*-chlorophenyl-4-ethylpyrimidine, 279
- 4-Amino-5-*p*-chlorophenyl-6-ethylpyrimidine, 279
- 4-Amino-5-*p*-chlorophenylpyrimidine, 92
- 2-Amino-4-chloropyrimidine, 164, 188, 194
  - amination, 189
  - dehalogenation, 23, 184, 185, 186, 311
  - hydrolysis, 189, 204
  - improvement in dehalogenation by metal salts, 184
  - reaction with alkoxide, 203
- 2-Amino-5-chloropyrimidine, 174, 175
  - action of nitrous acid, (333)
  - hydrolysis, (229)
  - to 2,5-dichloropyrimidine, (167)
- 4-Amino-2-chloropyrimidine, 188, 194
  - amination, 189
  - dechlorination with hydrogen iodide, 184
  - failure to dechlorinate, 184
  - hydrolysis, 189, 204
  - methylation, 378
- 4-Amino-6-chloropyrimidine, 164, 190
  - amination, 190, 191
- 5-Amino-2-chloropyrimidine, 146
- 5-Amino-4-chloropyrimidine, 279
  - action of potassium bisulphide, (207)
- Amino chloropyrimidines
  - catalytic reductive dehalogenation, 186
- 4-Amino-5-chlorosulphonyl-2,6-dihydroxypyrimidine
  - reduction, 276, 292
- 5-Amino-2-chloro-4-thiocyanatopyrimidine, 146
- Aminocinnamamide, 85
- 4-Amino-5-cyanoacetamido-6-hydroxypyrimidine, 328
  - deacylation, 329
- 4-Amino-2-cyanoamino-6-hydroxypyrimidine, 72
- 4-Amino-5-cyano-3-cyclohexyl-2,3-dihydro-2-oxopyrimidine
  - hydrolysis, 231
- 1-Amino-2-cyanocyclopentene
  - reaction with formamide, 92
- 4-Amino-5-cyano-2,6-di-α-furylpyrimidine, 90
- 4-Amino-5-cyano-2,3-dihydro-3-β-methoxyethyl-2-oxopyrimidine, 64
- 4-Amino-5-cyano-2,3-dihydro-3-methyl-2-oxopyrimidine, 64
- 4-Amino-5-cyano-2,3-dihydro-3-methyl-2-thiopyrimidine, 61, 381, 403
- 4-Amino-5-cyano-2,3-dihydro-2-oxo-3-phenylpyrimidine, 64
- 4-Amino-5-cyano-2,6 dimethylpyrimidine, 72
  - reduction, (316)
- 4-Amino-5-cyano-2,6-diphenylpyrimidine
  - anomalous preparation, 72
- 4-Amino-5-cyano-6-ethoxy-2-methylpyrimidine, 66
- 4-Amino-5-cyano-3-ethyl-2,3-dihydro-2-oxopyrimidine, 64
- 4-Amino-5-cyano-2-ethylpyrimidine
  - reduction, (316)
- 4-Amino-5-cyano-2-ethylthiopyrimidine, 61, 287, 403
  - reduction, 317
  - to amide, 399
- 4-Amino-5-cyano-2-hydroxypyrimidine, (403)
  - to amide, (399)
- 4-Amino-5-cyano-2-mercaptopyrimidine, 61, 403
  - to amide, (399)

4-Amino-5-cyanomethylaminopyrimidine, 405
4-Amino-5-cyanomethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 405
  cyclization and oxidation, 405
4-Amino-3-cyanomethyl-1-methylpyrazolo[3,4-d]pyrimidine, 110
2-Amino-5-cyano-4-methyl-6-methylthiopyrimidine, 333, 404
4-Amino-5-cyano-2-methyl-6-methylthiopyrimidine, 66
2-Amino-5-cyano-4-methylpyrimidine, 212
4-Amino-5-cyano-2-methylpyrimidine, 61, 85, 86
  hydrolysis, (391), 412
  reduction, (316), (326), 410*f*
  to 5-aldehyde, 410*f*, 412
  to amide, 399
4-Amino-5-cyano-2-phenylpyrimidine, 61
  reduction, 316
2-Amino-1-cyanopropene
  as cyanoacetone in syntheses, 65
2-Amino-5-cyanopyrimidine, 212, 404
4-Amino-5-cyanopyrimidine, 61, 72, 403, 404
  hydrolysis, (391)
  mechanism of formation, 90
  reduction, (316)
  to amide, (399)
4-Amino-5-cyano-2-trifluromethylpyrimidine, 179
4-Amino-6-cyclohexylamino-5-nitropyrimidine, 196
5-Amino-1-cyclohexyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxopyrimidine
  alkylation, (315)
5-Aminocytidine, 211
5-Aminocytosine, 6
6-Aminocytosine, 6
4-Amino-2,6-dianilinopyrimidine, 290
5-Amino-1,3-dibenzylhexahydro-5-methylpyrimidine, 454
4-Amino-2,6-dibenzyl-5-phenylpyrimidine
  hydrolysis, (229)
4-Amino-5,5-dibromo-5,6-dihydro-2,6-dihydroxypyrimidine, 174, 346
2-Amino-5-(2,4-dibromophenoxy)-4-hydroxypyrimidine, 180
2-Amino-4,6-dibromopyrimidine, 167
5-Amino-4,6-dichloro-2-αα-diacetylmethylpyrimidine, (209)
5-Amino-4,6-dichloro-2-diethoxycarbonylmethylpyrimidine, 209
  hydrolysis *etc.*, 209
2-Amino-5,5-dichloro-4,5-dihydro-4,6-dihydroxypyrimidine, 174
5-Amino-4,6-dichloro-2-α-ethoxycarbonylacetonylpyrimidine, (209)
4-Amino-2,6-dichloro-5-ethylpyrimidine
  reaction with hydriodic acid, 168
5-Amino-4,6-dichloro-2-methylpyrimidine, 164
  dechlorination, 186
  hydrolysis, 204
4-Amino-2,6-dichloro-5-nitropyrimidine, 196
  action of alkoxide, 203
  amination, 196
  hydrogenation, 143
4-Amino-5-αα-dichloropropionamidopyrimidine, 328
2-Amino-4,6-dichloropyrimidine, 164, 191
  action of alkoxide, 203
  amination, 191
  nuclear reduction, 451, 454
  reductive dehalogenation, 22, 184, 186, 311
  reactions with hydriodic acid, 168
4-Amino-2,6-dichloropyrimidine, 191
  action of hydrogen iodide, 184
  amination, 191
  dechlorination, 186
  failure of direct dechlorination, 184
  nuclear reduction, 451
5-Amino-2,4-dichloropyrimidine, 144, 146
  action of alkoxide, 203
  action of sodium ethyl mercaptide, 205
  dechlorination, 186
  diazotization, 332
5-Amino-4,6-dichloropyrimidine, 143, 144 146
  action of potassium bisulphide, 207
  difficult amination, 196, 197
  nuclear reduction, 451
2-Amino-4-diethoxycarbonylmethyl-6-methyl-5-nitropyrimidine, 208
  hydrolysis *etc.*, 208
4-Amino-2-diethoxycarbonylmethylthio-6-hydroxypyrimidine, 283

2-Amino-4,5-diethoxycarbonylpyrimidine, 36, 395
4-Amino-5-ββ-diethoxyethyl-2,6-dihydroxypyrimidine, 68
4-Amino-5-ββ-diethoxyethyl-6-hydroxy-2-mercaptopyrimidine
  desulphurization, 279
4-Amino-5-ββ-diethoxyethyl-6-hydroxypyrimidine, 279
2-Amino-4-diethoxymethyl-6-hydroxypyrimidine, 407
  action of phosphoryl chloride, 407
2-Amino-4-diethoxymethyl-6-methoxymethylpyrimidine, 407
2-Amino-4-diethoxymethyl-6-methylpyrimidine, 407
2-Amino-4-diethoxymethylpyrimidine, 407
2-Amino-4,6-diethoxypyrimidine, 248
5-Amino-2,4-diethoxypyrimidine, 144, 146
4-Amino-2-β-diethylaminoethylamino-5,6-dimethylpyrimidine, 290
4-Amino-6-diethylamino-5-formamido-2-methylthiopyrimidine
  desulphurization, 279
4-Amino-2-diethylamino-5-formamidopyrimidine, 326
4-Amino-6-diethylamino-5-formamidopyrimidine, 279
4-Amino-5-diethylaminomethyl-2-methylpyrimidine, 319
4-Amino-2-diethylamino-6-methyl-5-nitropyrimidine, 195
4-Amino-6-diethylamino-2-methylthio-5-nitrosopyrimidine
  reduction, (150)
4-Amino-2-diethylamino-5-nitropyrimidine, 195
4-Amino-6-diethylamino-5-nitropyrimidine, 196
2-Amino-5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine, 55
  hydrolysis, 230
6-Amino-5,5-diethyl-2,4-dithiouracil, 284
4-Amino-2,6-diethyl-5-methylpyrimidine, 93, 96, 338
  early preparation, 1
  reaction with ethyl chloroformate, (336)
4-Amino-1,3-diethyl-1,2,3,6-tetrahydro-2,6-dioxopyrimidine, 68
5-Amino-1,3-diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxopyrimidine, (150)
4-Amino-5,5-diethyl-1,2,5,6-tetrahydro-6-imino-1-methyl-2-oxopyrimidine, 73
  hydrolysis, 73
4-Amino-1,3-diethyl-1,2,3,6-tetrahydro-6-oxo-2-thiopyrimidine, 70
6-Amino-5,5-diethyl-2-thiouracil, 284
  hydrolysis, 232, 284
6-Amino-5,5-diethyluracil, 68
  action of hydrogen sulphide, 276
4-Amino-1,6-dihydro-1,5-dimethyl-2-methylthio-6-oxopyrimidine
  desulphurization, 279
4-Amino-1,2-dihydro-1,6-dimethyl-5-nitro-2-oxopyrimidine, 367
  hydrolysis, 231, 367
2-Amino-1,4-dihydro-1,6-dimethyl-4-oxopyrimidine, 50, 307, 365, 374
  hydrolysis, 374
2-Amino-1,6-dihydro-1,4-dimethyl-6-oxopyrimidine, 365
  hydrolysis, 365
4-Amino-1,2-dihydro-1,5-dimethyl-2-oxopyrimidine, 365
4-Amino-1,2-dihydro-1,6-dimethyl-2-oxopyrimidine, (365)
  hydrolysis, (229)
4-Amino-1,6-dihydro-1,2-dimethyl-6-oxopyrimidine, 366
4-Amino-1,6-dihydro-1,5-dimethyl-6-oxopyrimidine, 279
  acylation, 325
4-Amino-3,6-dihydro-3,5-dimethyl-6-oxopyrimidine, 279
2-Amino-1,4-dihydro-1,6-dimethyl-4-phenyliminopyrimidine
  see: "4-Anilino-1,2-dihydro-2-imino-1,6-dimethylpyrimidine."
4-Amino-1,2-dihydro-1,6-dimethyl-2-thiopyrimidine, 275
  desulphurization, (280), 378
2-Amino-4,5-dihydro-6-hydroxy-4,5-diphenylpyrimidine, 433
  dehydrogenation by sulphur, 455
2-Amino-4,5-dihydro-6-hydroxy-4-methylpyrimidine, (438)
2-Amino-4,5-dihydro-6-hydroxy-4-oxo-5,5-trimethylenepyrimidine, 57
2-Amino-4,5-dihydro-6-hydroxy-4-phenylpyrimidine, 438

2(4)-Amino-1,4(1,2)-dihydro-4(2)-imino-1-methylpyrimidine, 379
4-Amino-1,6(3,6)-dihydro-6-imino-1(3)-methylpyrimidine, 378
  nitration 380
  rearrangement, 380
4-Amino-3,6-dihydro-2-mercapto-3,5-dimethyl-6-oxopyrimidine
  desulphurization, 279
4-Amino-3,6-dihydro-2-mercapto-3-methyl-6-oxopyrimidine
  desulphurization, 279
1-Amino-1,4-dihydro-2-mercapto-4,4,6-trimethylpyrimidine, (437)
4-Amino-1,6-dihydro-2-methoxy-1-methyl-6-oxopyrimidine
  hydrolysis, 232
4-Amino-1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine, 366
  desulphurization, 279, 366
4-Amino-2,3-dihydro-3-methyl-5-morpholinoformyl-2-oxopyrimidine, 64
4-Amino-1,2-dihydro-1-methyl-5-nitro-2-oxopyrimidine, 367
  acidic pK_a, 476
  hydrolysis, 231, 367
4-Amino-1,6-dihydro-1-methyl-5-nitro-6-oxopyrimidine, (365), 368
  reduction, (365)
4-Amino-2,3-dihydro-3-methyl-5-nitro-2-oxopyrimidine, 63, 64, 139, 367
  hydrolysis, 231
  rearrangement of homologues, 63, 380
2-Amino-1,4-dihydro-1-methyl-4-oxopyrimidine, (365)
2-Amino-1,6-dihydro-1-methyl-6-oxopyrimidine, (365)
4-Amino-1,2-dihydro-1-methyl-2-oxopyrimidine, 198, 255, 346, 364, 373
  acylation, (327), 328, (346)
  methylation, 378
4-Amino-1,6-dihydro-1-methyl-6-oxopyrimidine, 279, 365, 369
  nitration, (368)
4-Amino-2,3-dihydro-3-methyl-2-oxopyrimidine, 364
  attempted preparations, 63, 364
4-Amino-3,6-dihydro-3-methyl-6-oxopyrimidine
  attempted preparation, 279, 366
  rearrangement, 280, 366
3-Amino-3,4-dihydro-4-oxopteridine, 108
4-Amino-2,5-dihydro-2-oxopyrimidine (?), 347
2-Aminodihydropyrimidine, 451
  benzoylation, 456
4-Aminodihydropyrimidine, 451
  benzoylation, 451
5-Aminodihydropyrimidine, 451
  benzoylation, 456
2-Amino-4,5-dihydro-4,4,6-trimethylpyrimidine, 432
2-Amino-4,5-dihydroxy-6-hydroxymethylpyrimidine, 240
4-Amino-2,6-dihydroxy-5-hydroxymethylpyrimidine
  to 5-chloromethyl analogue, (179)
4-Amino-2,6-dihydroxy-5-mercaptopyrimidine, 277
5-Amino-2,4-dihydroxy-6-mercaptopyrimidine, 106, 273, 314
5-Amino-2,4-dihydroxy-6-methylaminopyrimidine, 150
  formation of a urethane, (336)
2-Amino-4,5-dihydroxy-6-methylpyrimidine, 241
  acylation, 253
5-Amino-2,4-dihydroxy-6-methylpyrimidine, 146
  action of nitrous acid, 332
  acylation, 324
  to 5-thioureido analogue, 340
  to 5-ureido analogue, (339)
2-Amino-4,5-dihydroxy-6-nitrosopyrimidine, 152, (259)
  hydrogenation, 152, 259, (310)
2-Amino-4,6-dihydroxy-5-nitrosopyrimidine, 58, 149, 230
  colour of salts, 147
  reduction, (150)
4-Amino-2,6-dihydroxy-5-nitrosopyrimidine, 68, 149
  colour of salts, 147
  reduction, 150, 151
5-Amino-2,4-dihydroxy-6-nitrosopyrimidine
  reduction, (310)
4-Amino-2,6-dihydroxy-5-phenylazopyrimidine, 153
  hydrogenation, 156
  reduction, 157, 329
4-Amino-2,6-dihydroxy-5-phenylureido pyrimidine, 339

cyclization, 339
4-Amino-2,6-dihydroxy-5-purin-6′-ylthiopyrimidine, 288
2-Amino-4,5-dihydroxypyrimidine, 238, 240, 241, 259
  coupling, 154
  nitrosation, 152, 259
2-Amino-4,6-dihydroxypyrimidine, 55
  action of phosphoryl chloride *etc.*, 164
  action of phosphoryl bromide, 167
  chlorination by phosphorus pentachloride, 165
4-Amino-2,5-dihydroxypyrimidine, 232, 239
4-Amino-2,6-dihydroxypyrimidine, 68
  acylation, 326
  alkylation, 366
  chlorosulphonation, 146
  coupling, (153)
4-Amino-5,6-dihydroxypyrimidine, 154, 241, 310
5-Amino-2,4-dihydroxypyrimidine, 144, 146
  diazotization, coupling, *etc.*, 155, 332
  diazotization and action of thiourea, *etc.*, 276, 292
  hydrolysis, 321
  oxidations, 335
  reaction with cyanic acid, 339
5-Amino-4,6-dihydroxypyrimidine, 279
2-Amino-4,5-dihydroxy-6-*p*-sulphophenylazopyrimidine, 154
  reduction, 154, 311
5-Amino-2,4-dihydroxy-6-sulphopyrimidine, 23, 146, 296, 343
  to uric acid and to xanthine, 146
2-Amino-4,6-dihydroxy-5-tetrahydropyran-2′-yloxypyrimidine, 58, (240)
  hydrolysis, (240)
4-Amino-2,6-dihydroxy-5-tetrahydropyran-2′-yloxypyrimidine, 68, (240)
  hydrolysis, (240)
4-Amino-2,6-dihydroxy-5-ureidopyrimidine, 339
  cyclization, 339
2-Amino-4,6-di-iodopyrimidine, 168
5-Amino-2,4-dimercapto-6-methylaminopyrimidine, 12, 276
5-Amino-2,4-dimercapto-6-methylpyrimidine, 145
5-Amino-2,4-dimercaptopyrimidine, 15, 145, 206
  acylation, 286
  failure to aminate, 285
5-Amino-4,6-dimercaptopyrimidine
  S-alkylation, 283
2-Amino-4-dimethoxymethyl-6-methoxymethylpyrimidine, 407
2-Amino-4-dimethoxymethyl-6-methylpyrimidine, 407
4-Amino-2,6-dimethoxy-5-nitropyrimidine, 203
2-Amino-4,6-dimethoxypyrimidine, 203, 248
5-Amino-2,4-dimethoxypyrimidine, 146, 203
4-Amino-6-dimethylamino-5-formamido-2-methylthiopyrimidine, (315)
  reduction, 315
4-Amino-2-dimethylamino-5-formamidopyrimidine, 326
  cyclization, 326
4-Amino-2-dimethylamino-6-hydroxypyrimidine, 72
4-Amino-6-dimethylamino-5-methylamino-2-methylthiopyrimidine, 315
4-Amino-5-dimethylaminomethyl-2-methylpyrimidine 318, 319
  to 5-aminomethyl analogue, 318
2-Amino-4-dimethylamino-6-methyl-5-nitropyrimidine, 195
2-Amino-4-dimethylamino-6-methylpyrimidine, 190
4-Amino-6-dimethylamino-2-methylthio-5-nitrosopyrimidine
  reduction, (150)
4-Amino-6-dimethylamino-2-methylthiopyrimidine
  acetylation, 313, (324)
  indirect alkylation, 313
4-Amino-2-dimethylamino-5-nitropyrimidine, 195
  reduction, (335)
4-Amino-6-dimethylamino-5-nitropyrimidine, 183, 196
2-Amino-5-*p*-dimethylaminophenylazo-4,6-dimethylpyrimidine, 333
5-Amino-2-dimethylaminopyrimidine, 186
4-Amino-5,6-dimethyl-2-methylthiopyrimidine
  amination, 290
2-Amino-4,6-dimethyl-5-nitropyrimidine, 208
4-Amino-2,6-dimethyl-5-nitro-

pyrimidine, 208
2-Amino-4,6-dimethyl-5-phenylazopyrimidine, 152
2-Amino-4,5-dimethylpyrimidine, 35
2-Amino-4,6-dimethylpyrimidine, 37 188, 211, 306
  acylation, 324, 327, 329, 330
  bromination, 130, 169, 177
  failure to react with thiocyanate, 419
  hydrolysis, (229)
  reaction with urethane, 340
  styrylation, 126
4-Amino-2,5-dimethylpyrimidine, 62
4-Amino-2,6-dimethylpyrimidine, 188, 307
  action of nitrous acid, (333)
  direct synthesis from acetonitrile, 93
  hydrolysis, (229)
4-Amino-5,6-dimethylpyrimidine, 188
5-Amino-2,4-dimethylpyrimidine, 314, 338
  acylation, (324)
4-Amino-2,6-dimethyl-5-sulphomethylpyrimidine, 216, 294, 295
5-Amino-1,3-dimethyl-6-thiobarbituric acid, 106
6-Amino-5,5-dimethyl-2-thiouracil
  hydrolysis, 232
4-Amino-2,6-diphenylpyrimidine
  hydrolysis, (229)
4-Amino-5-ethoxycarbonylamino-2,6-dihydroxypyrimidine, 336
  cyclization with ammonia, 339
6-Amino-5-ethoxycarbonylamino-1-ethyluracil, 336
1-Amino-2-ethoxycarbonylcyclohexene
  reaction with cyanic acid, 83
4-Amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-oxopyrimidine, 64
2-Amino-5-ethoxycarbonyl-1,6-dihydro-4-methyl-6-phenylpyrimidine, (458)
  hydrolysis, (458)
4-Amino-5-ethoxycarbonyl-2,3-dihydro-3-methyl-2-thiopyrimidine, 61, 381
4-Amino-5-ethoxycarbonyl-2,6-dimethylpyrimidine, 199
4-Amino-5-ethoxycarbonyl-3-ethyl-2,3-dihydro-2-oxopyrimidine, 64
4-Amino-5-ethoxycarbonyl-2-ethylsulphonylpyrimidine
  action of alkoxide, (247)
  amination, 300
4-Amino-5-ethoxycarbonyl-2-ethylthiopyrimidine, 60, 199, 310, 347
  action of lithium aluminium hydride, 348
4-Amino-5-ethoxycarbonyl-3-hexyl-2,3-dihydro-2-oxopyrimidine, 64
4-Amino-5-ethoxycarbonyl-2-hydroxypyrimidine, 64, 234
  lithium aluminium hydride reduction, 348
  to amide, (396)
  to hydrazide, (397)
4-Amino-5-ethoxycarbonyl-2-mercaptopyrimidine, 61, 403
  desulphurization, (279)
  to 2-hydroxy analogue, (234)
4-Amino-5-ethoxycarbonylmethyl-6-hydroxy-2-methylpyrimidine, 67
4-Amino-5-ethoxycarbonylmethyl-6-hydroxy-2-phenylpyrimidine, 67
2-Amino-5-ethoxycarbonyl-4-methylpyrimidine, 290, 397
4-Amino-5-ethoxycarbonyl-2-methylpyrimidine, 61, 85, 86, 396, 403, (412)
  to amide, (396)
  to hydrazide, (397), (412)
4-Amino-5-ethoxycarbonyl-2-trifluoromethylpyrimidine, (397)
2-Amino-5-ethoxy-4,6-dihydroxypyrimidine, 57
4-Amino-2-ethoxy-5-ethoxycarbonylpyrimidine, 247
2-Amino-5-ethoxyethyl-4-ethyl-6-hydroxypyrimidine, 246
2-Amino-5-ethoxyethyl-4-hydroxy-6-methylpyrimidine, 45
2-Amino-5-ethoxyethyl-4-methylpyrimidine
  splitting by acid, 179
4-Amino-5-ethoxy-2-ethylthiopyrimidine
  complicated hydrolysis, 232, 239
4-Amino-2-ethoxy-6-hydroxypyrimidine, 70
4-Amino-5-ethoxy-2-hydroxypyrimidine, 232
2-Amino-4-ethoxy-6-methoxypyrimidine, 248
4-Amino-5-ethoxymethyleneaminopyrimidine, 327
  cyclization, 327
4-Amino-5-ethoxymethyl-2-methyl-

pyrimidine, 61, 62
  splitting by acid, 179
2-Amino-4-ethoxy-5-nitropyrimidine, 275, 421
  reduction, 146
2-Amino-4-ethoxypyrimidine, 203
2-Amino-4-ethylamino-6-hydroxy-5-phenylazopyrimidine, 199
5-Amino-4-ethylaminopyrimidine, 186
2-Amino-5-ethyl-4,5-dihydro-6-hydroxy-5-hydroxyethyl-4-oxopyrimidine, 242
4-Amino-3-ethyl-2,3-dihydro-5-nitro-2-oxopyrimidine
  attempted preparation, 380
4-Amino-3-ethyl-2,3-dihydro-2-oxo-5-phenylcarbamoylpyrimidine, 64
2-Amino-5-ethyl-4,6-dihydroxypyrimidine, 55
5-Amino-4-ethyl-2,6-dihydroxypyrimidine, 146
4-Amino-2-ethyl-5-formamidomethylpyrimidine, 327
2-Amino-4-ethyl-6-hydroxypyrimidine, 45
4-Amino-2-ethyl-6-hydroxypyrimidine, 197
4-Amino-5-ethyl-6-iodopyrimidine, 168
5-Amino-2-ethyl-4-methylpyrimidine, 314
β-Amino-β-ethylpentanoic acid
  use in dihydropyrimidine synthesis, 434
2-Amino-4-ethylpyrimidine, 184, 188
4-Amino-6-ethylpyrimidine, 188
2-β-Aminoethylpyrimidine, 317
4-β-Aminoethylpyrimidine, 317
4-Amino-2-ethylsulphonyl-5-methylpyrimidine, 199, 300, 343
  hydrolysis of 2-group, 236
4-Amino-1-ethyl-1,2,3,6-tetrahydro-2,6-dioxo-3-propylpyrimidine, 69
4-Amino-3-ethyl-1,2,3,6-tetrahydro-2,6-dioxo-1-propylpyrimidine, 69
4-Amino-1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxopyrimidine, 367
4-Amino-1(or 3)ethyl-1,2,3,6-tetrahydro-6-oxo-3(or 1)propyl-2-thiopyrimidine, 70
4-Amino-6-ethyl-5-thioformamidopyrimidine, 326
4-Amino-2-ethylthio-5-hydroxymethylpyrimidine, 243, 348
  hydrolysis, 243, 348
  to 5-halogenomethyl analogues, (178)
5-Amino-2-ethylthio-4-hydroxypyrimidine, 338
  desulphurization, 279
  reaction with amyl formate, 336
  reaction with ethyl chloroformate, 336
4-Amino-2-ethylthio-6-iminomethylpyrimidine, 199, 407
4-Amino-2-ethylthio-5-iodopyrimidine, (199)
4-Amino-2-ethylthio-5-methylpyrimidine
  action of chlorine, 343
  oxidation, (236)
4-Amino-2-ethylthio-6-methylpyrimidine
  failure to react with thiocyanate, 419
4-Amino-2-ethylthiopyrimidine, 198, 282, 290
  amination, 309
  hydrolysis, 233
  to cytosine, (236)
2-Amino-5-ethylthiothiazolo[5,4-d]pyrimidine, 420
2-Amino-5-ethynyl-4-methylpyrimidine, 124
4-Amino-5-formamido-2,6-dihydroxypyrimidine, 157, 329
4-Amino-5-formamido-6-mercaptopyrimidine, (275), 326
4-Amino-5-formamidomethyl-2-methylpyrimidine, 326
4-Amino-5-formamido-2-methylthiopyrimidine, 315
  cyclization, 326
  reduction, 23, 315
6-Amino-5-formamido-1-methyluracil, 150
6-Amino-5-formamido-3-methyluracil
  deformylation, 329
4-Amino-5-formamidopyrimidine, 326
  cyclization to purine, 326, 333
  failure to reduce, 315
4-Amino-6-formamidopyrimidine, 100
4-Amino-5-formamido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 150
2-Amino-5-formyl-4-hydroxy-6-methylpyrimidine, 409
  oxidation, (391)
  to semicarbazone *etc.*, (414)
2-Amino-5-formyl-4-methyl-6-methylthiopyrimidine, 333, 412

4-Amino-5-formyl-2-methylpyrimidine, 410, 411, 412
  hydrogenation, 244, 411
  to Schiff's base, (414)
4-Amino-5-formyl-2-methylthiopyrimidine, 412
  as oxime, 412
4-Amino-5-formyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, (408)
  to phenylhydrazone, (408)
Amino groups
  effect on acidic pK_a, 471
5-Amino-2-guanidino-4,6-dimethylpyrimidine, 156
2-Aminohexahydropyrimidine, 22, 186, 454
5-Aminohexahydro-1,3,5-trimethylpyrimidine, (454)
2-Amino-4-hexylpyrimidine, 35
4-Amino-5-hydrazinocarbonyl-2-hydroxypyrimidine, 397
  to azide, 401
4-Amino-5-hydrazinocarbonyl-2-methylpyrimidine, (397), 412
  acylation, 401, 412
  to azide, 401
2-Amino-3-hydrazinocarbonylpyrazine
  use in pteridine synthesis, 108
2-Amino-4-hydrazino-6-methylpyrimidine, 200
4-Amino-5-*o*-hydroxybenzylideneamino-1-methyluracil, (322)
4-Amino-5-hydroxy-2,6-bishydroxymethylpyrimidine, 95
  instability, 95
2-Amino-3-hydroxycarbamoylpyrazine
  in pteridine synthesis, 108
2-Amino-5-hydroxy-4,6-dimethylpyrimidine, 212, 238
5-Amino-2-hydroxy-4,6-dimethylpyrimidine, (157)
4-Amino-2-hydroxy-6,7-diphenylpteridine, 109
2-Amino-4-hydroxy-5,6-diphenylpyrimidine, 455
2-Amino-4-hydroxy-5-ethoxypyrimidine, 41
2-Amino-4-β-hydroxyethylamino-5-nitropyrimidine, 195
2-Amino-5-β-hydroxyethyl-4-methylpyrimidine, 215
2-Amino-4-hydroxy-5-hydroxyethyl-6-methylpyrimidine, 242
4-Amino-2-hydroxy-5-hydroxymethylpyrimidine, 243, 347*f*
2-Amino-4-hydroxy-6-hydroxymethyl-5-tetrahydropyran-2′-yloxypyrimidine, (240)
  hydrolysis, (240)
4-Amino-5-hydroxyiminomethyl-2-methylthiopyrimidine, (412)
2-Amino-3-hydroxyimino-2-methylpentan-4-one, 455
4-Amino-2-hydroxy-5-iodopyrimidine, 170
4-Amino-6-hydroxy-2-mercapto-5-nitrosopyrimidine, 70, 148, 149
  action of Raney nickel, 150
  reduction, 150
2-Amino-4-hydroxy-6-mercaptopyrimidine, 59
  desulphurization, 279
4-Amino-6-hydroxy-2-mercaptopyrimidine, 70, 306
  S-alkylation, 283
  alkylation, 366
  bromination, (170)
  desulphurization, 279
  nitrosation, 148
4-Amino-6-hydroxy-2-methoxy-5-methylpyrimidine, 70
2-Amino-4-hydroxy-5-*p*-methoxyphenoxy-6-methylpyrimidine, 44
2-Amino-4-hydroxy-5-methoxypyrimidine, 41
4-Amino-6-hydroxy-2-methoxypyrimidine, 70
5-Amino-2-hydroxy-4-methylaminopyrimidine, 143, 144
4-Amino-5-hydroxymethyl-2,6-dimethylpyrimidine, 242
2-Amino-4-hydroxy-6-methyl-5-*m*-methylbenzylpyrimidine, 45
4-Amino-5-hydroxymethyl-2-methylpyrimidine, 242, 244, 333, 411
  to 5-halogenomethyl analogues, (178), (179)
4-Amino-5-hydroxymethyl-2-methylthiopyrimidine, 243
  oxidation, 412
2-Amino-4-hydroxy-6-methyl-5-nitropyrimidine, 142, 342
4-Amino-2-hydroxy-6-methyl-5-nitropyrimidine

alkylation, 367
4-Amino-6-hydroxy-2-methyl-5-nitrosopyrimidine, 67, 149
  reduction with Raney nickel, 150
4-Amino-6-hydroxy-2-methyl-5-phenylazopyrimidine
  reduction, 157
4-Amino-6-hydroxy-2-methyl-5-piperidinomethylpyrimidine, 133
2-Amino-4-hydroxy-5-methylpyrimidine, 39
  hydrolysis, (229)
2-Amino-4-hydroxy-6-methylpyrimidine, 49
  action of phosphoryl bromide, (167)
  alkylation, 365
  nitration, 142, 342
  persulphate oxidation, (241)
  reaction with chloral, (409)
  reaction with thiocyanate, 419
  reduction, 142
  Reimer-Tiemann reaction, 409
4-Amino-2-hydroxy-5-methylpyrimidine, 234, 236, 347
  alkylation, 365
  colour test, 259
  history, 347
4-Amino-2-hydroxy-6-methylpyrimidine
  formation of 1-methylated derivative, 365
  sulphonation, 296
4-Amino-6-hydroxy-2-methylpyrimidine, 67, 197
  action of phosphoryl chloride, 164
  alkylation, 366
  Mannich reaction, 133
2-Amino-4-hydroxy-6-methyl-5-semicarbazonomethylpyrimidine, 414
4-Amino-2-hydroxy-6-methyl-5-sulphopyrimidine, 296
2-Amino-4-hydroxy-6-methyl-5-thiocyanatopyrimidine, (419)
  to disulphide, (419)
4-Amino-6-hydroxy-2-methylthiopyrimidine, 70
  action of phosphoryl chloride, 164
  nitration, 141
2-Amino-4-hydroxy-6-methyl-5-thiosemicarbazonomethylpyrimidine, 414
2-Amino-4-hydroxy-6-methyl-5-(2,2,2-trichloro-1-hydroxyethyl) pyrimidine, (409)
4-Amino-5-hydroxymethyl-2-trifluoromethylpyrimidine, 243
2-Amino-4-hydroxy-5-morpholinopyrimidine, 211
2-Amino-4-hydroxy-5-nitropyrimidine, 139, 256
4-Amino-2-hydroxy-5-nitropyrimidine, 139, 256, 346
  alkylation, 367
  hydrogenation, 143
  reduction, 144
4-Amino-6-hydroxy-5-nitropyrimidine, 101
  attempted alkylation, 368
4-Amino-6-hydroxy-5-phenylazopyrimidine, 101, 153
2-Amino-4-hydroxy-5-phenylazo-6-trifluoromethylpyrimidine, 45, 179
2-Amino-4-hydroxy-6-phenylpyrimidine
  hydrolysis, (229)
  to 5-thiocyanato derivative, 419
4-Amino-6-hydroxy-2-phenylpyrimidine, 67
2-Amino-4-hydroxy-6-phenyl-5-thiocyanatopyrimidine, (419)
  to disulphide, 292
2-Amino-4-hydroxy-5-piperidinopyrimidine, 211
2-Amino-8-hydroxypurine, 401
2-Amino-4-hydroxypyrido[3,2-d]-pyrimidine, 110
2-Amino-4-hydroxypyrimidine, 39, 189, 204, 255, 279, 309
  action of phosphoryl chloride, 164
  action of phosphoryl bromide, 167
  acylation, 324
  bromination, (170)
  chlorination, 174
  nitration, 139
  reaction with benzaldehyde, 322
4-Amino-2-hydroxypyrimidine, 59, 189, 204, 233, 234, (236), 251, 255, 286, 300, 309
  acylation, 324, 327, 346
  detection, 257
  halogenation, (170), 174, 346
  hydrolysis, (229)
  irradiation of, 346

- methylation, 346, 364
- nitration, 139, 346
- oxidation, 346
- persulphate oxidation (241)
- reaction with benzylamine, 313
- reaction with nitrous acid, 333, 346
- reduction, 443
- review, 346*f*
- sulphonation, 296

4-Amino-5-hydroxypyrimidine, 240

4-Amino-6-hydroxypyrimidine, 101, 279, 308
- action of phosphoryl chloride, 164
- acylation, 324
- alkylation, 365
- 5-hydroxylation, (241)

5-Amino-4-hydroxypyrimidine, 279
- hydrolysis, 238
- thiation, 251

Amino hydroxypyrimidines
- ionization, 470*f*
- lack of zwitterionic structure, 470

4-Amino-2-hydroxy-5-sulphopyrimidine, 296

2-Amino-4-hydroxy-5-tetrahydropyran-2′-yloxypyrimidine, 240
- hydrolysis, 240

2-Amino-4-hydroxy-5,6-tetramethylenepyrimidine, 45

2-Amino-5-iodo-4,6-dimethylpyrimidine, 176, 321, 333

2-Amino-5-iodopyrimidine, (169)

4-Amino-5-iodopyrimidine, 169

4-Amino-6-iodopyrimidine, 184
- amination, 190
- deiodination, 184

2(or 4)-Amino-4(or 2)isopropylamino-2-methylpentane, 454

4-Amino-2-mercapto-6,7-diphenylpteridine, 109

5-Amino-2-mercapto-4-methylaminopyrimidine, 206, 276

5-Amino-4-mercapto-6-methylaminopyrimidine, 145
- *S*-alkylation, (282)

4-Amino-5-mercaptomethyl-2-methylpyrimidine, 215, 277
- acetylation, 286

4-Amino-2-mercapto-6-methyl-5-nitropyrimidine, 207

2-Amino-4-mercapto-5-methyl-6-phenylpyrimidine
- acylation, 324

2-Amino-4-mercapto-6-methylpyrimidine, 207
- *S*-acylation, 286

4-Amino-2-mercapto-5-methylpyrimidine, 285
- *S*-alkylation, (283)
- to 2-hydroxy analogue, 234, 347

4-Amino-2-mercapto-6-methylpyrimidine, 65, 207, 285
- *S*-alkylation, (283)

2-Amino-4-mercapto-5-nitropyrimidine, 275, 421

4-Amino-2-mercapto-5-nitropyrimidine
- reduction, 288

4-Amino-2-mercaptopyrimidine, 285, 286, 346
- *S*-alkylation, (282), (283)
- desulphurization, 279, 311
- to cytosine, 234, 286, 346

5-Amino-4-mercaptopyrimidine, 207, 252
- action of formic acid, 334

Amino mercaptopyrimidines
- ionization, 471

2-Amino-4-mercapto-5,6-trimethylenepyrimidine
- desulphurization, 279

4-Amino-5-methoxycarbonyl-2-methylpyrimidine, 394

4-Amino-5-*o*(and *p*)-methoxyphenylpyrimidine, 92

5-Amino-4-methoxy-2,6-dimethylpyrimidine, 144

2-Amino-4-methoxymethyl-6-methylpyrimidine, 246

4-Amino-5-methoxymethyl-2-methylpyrimidine, 246

2-Amino-4-methoxy-6-methylpyrimidine, 203
- to 2-chloro analogue, (167)

5-Amino-4-methoxy-2-methylpyrimidine, 187

4-Amino-6-methoxy-2-methylthiopyrimidine
- as a wrongly assigned structure, 247
- desulphurization, 279

4-Amino-2-methoxy-5-nitropyrimidine, 203

4-Amino-6-methoxy-5-nitropyrimidine, 203

β-Amino-*β*-*p*-methoxyphenylpropionic acid

use in hydropyrimidine synthesis, 435
2-Amino-4-methoxypyrimidine, 186, 187
  alkylation, 312
  amination, 255
  bromination, (171)
  to 2-chloro analogue, (167)
4-Amino-2-methoxypyrimidine
  hydrolysis, 204
  isomerization, 373
4-Amino-5-methoxypyrimidine
  to 4,5-dihydroxypyrimidine, 239
4-Amino-6-methoxypyrimidine, 279
5-Amino-2-methoxypyrimidine
  5-arylation, 315
4-Amino-2-methylamino-6-hydroxypyrimidine, 71*f*
4-Amino-5-methylamino-2-methylthiopyrimidine, 23, 315
  desulphurization, 279
5-Amino-4-methylamino-6-methylthiopyrimidine, 279, 282
  acylation, (326)
4-Amino-2-methylamino-5-nitropyrimidine, 195
4-Amino-6-methylamino-5-nitropyrimidine, 196, 380
2-Amino-4-methylaminopyrimidine, 186
4-Amino-5-methylaminopyrimidine, 279
4-Amino-6-methylaminopyrimidine, 380
5-Amino-4-methylaminopyrimidine, 106, 186, 279, 313
  acylation, 326
2-Amino-3-methylcarbamoylpyrazine
  cyclization with formic acid, 108
5-Aminomethyl-4-chloro-2-ethylthiopyrimidine, 316
5-Aminomethyl-2,4-dihydroxypyrimidine, 318, 319, 419
  action of nitrous acid, (242), 243
2-Aminomethyl-4,6-dimethylpyrimidine, 319, 329
4-Amino-5-methyl-2,6-diphenylpyrimidine
  hydrolysis, (229)
4-Amino-6-methyl-2,5-diphenylpyrimidine, 65
Aminomethyleneacetylacetone
  use, 86
Aminomethyleneacylurethanes
  use in Shaw Synthesis, 87*f*
1-Amino-3-methyleneaminopropane
  possible equilibrium with hexahydropyrimidine, 453
Aminomethylene derivatives
  primary syntheses involving, 82*f*
  reaction with imidoyl chlorides, 84*f*
  reaction with imino ethers, 84*f*
  reaction with isocyanates, 82*f*
  reaction with thioamides, 85
Aminomethylenemalononitrile
  formation, 72
  reaction with ethyl acetimidate *etc.*, 84, 86
  reaction with thioacetamide, 85
  use as an aldehydo nitrile, 61
Aminomethylenephenylacetonitrile
  cyclization with formamide, 91*f*
  formation, 91
5-Aminomethyl-2-ethylthio-4-hydroxypyrimidine, 419
5-Aminomethyl-4-hydroxy-2-methylpyrimidine, 317
  action of nitrous acid, (242), (321)
4-Aminomethyl-6-hydroxy-2-phenylpyrimidine, 414
4-Amino-2-methyl-5-methylamidinothiomethylpyrimidine, 293
  to disulphide, 294
  to sulphide, 293
2-Amino-4-methyl-4-methylaminopentane
  condensation with diethyl carbonate, 446
4-Amino-2-methyl-6-methylamino-5-thioformamidopyrimidine, 326
5-Aminomethyl-2-methyl-4-methylaminopyrimidine, 325
  acylation, (327)
4-Amino-2-methyl-5-methylthiomethylpyrimidine, 215
2-Amino-4-methyl-6-methylthiopyrimidine
  action of chloral, 409
4-Amino-6-methyl-2-methylthiopyrimidine
  amination, (290)
  methylation, (378)
4-Amino-6-methyl-5-nitropyrimidine, 141
6-Amino-1-methyl-5-nitrosouracil, (366)
  reduction, (366)
  reduction with formic acid and zinc, (150)

4-Amino-5-methyl-2-octylthiopyrimidine, 198
2-Amino-4-methyl-6-oxo-1,3-thiazine, 48
2-Amino-4-methyl-6-phenyl-5-phenylazopyrimidine, 37, 153
6-Amino-1-methyl-5-phenylthioureidouracil, 340
2-Amino-4-methyl-6-phthalimidomethyl pyrimidine, 319
  action of hydrazine, 319
4-Amino-2-methyl-5-piperidinomethylpyrimidine, 319
4-Amino-6-methyl-2-piperidinopyrimidine, 190
  reaction with chloral, 409
2-Amino-4-methylpyrimidine, 34, 35, 134, 184, 186, 308
  acylation, (330), 331
  reaction with benzaldehyde, 332
  reduction, 444, 451
  reductive benzylation, 313
  sulphonation, 296
  to 2-chloro analogue, 167
2-Amino-5-methylpyrimidine, 188
4-Amino-2-methylpyrimidine, 186, 188, (211), 452
4-Amino-6-methylpyrimidine, 186, 188, 342
  methylation, 378
  nitration, 141, (342)
5-Amino-2-methylpyrimidine, 186
5-Amino-4-methylpyrimidine, 186
  reductive alkylation, 315
2-Amino-4-methyl-6-sulphanilylpyrimidine(?), 298
2-Amino-4-methyl-5-sulphopyrimidine, 296
4-Amino-2-methyl-5-sulphomethylpyrimidine, 216, 295
  hydrolysis, 295
2-Amino-4-methyl-6-2′-thienylpyrimidine, 38
5-Amino-1-methyl-6-thiobarbituric acid, 106
4-Amino-2-methyl-5-thiocyanatomethylpyrimidine, 215
2-Amino-4-methyl-5-thioformamidomethylpyrimidine, 327
4-Amino-2-methyl-5-thioformamidopyrimidine
  to 5-formamido analogue, 327
4-Amino-6-methyl-5-thioformamidopyrimidine, 326
4-Amino-2-methyl-5-thioformamido-6-α-xylosidoaminopyrimidine, 326
4-Amino-2-methylthio-5-nitropyrimidine, 205, 287
6-Amino-1-methyl-2-thiouracil, 70
  desulphurization, 366
4-Amino-2-methyl-5-*p*-tolyliminomethylpyrimidine, 414
6-Amino-1-methyluracil, 69, 70, 366
  methylation, (366)
  nitrosation, 366
6-Amino-3-methyluracil, 232
β-Amino-γ-methylvaleric acid, 459
"Aminometradine", 367
5-(2-Aminonaphth-1-ylazo)-2,4-dihydroxypyrimidine, 332
4-Amino-5-α-naphthylpyrimidine
  description as a triazine, 92
4-Amino-5-*p*-nitrophenylpyrimidine, 92
2-Amino-5-nitropyrimidine, 32*f*, 139
  acylation, 324
  facile hydrolysis, 231
2-Amino-5-nitro-4-thiocyanatopyrimidine, 310
  actions of alkoxide, 275, 421
β-Aminonanoic acid
  acetylation, 440
2-Amino-6-oxo-1,3-thiazine, 39
2-Amino-5-phenylazopyrimidine, 33
5-*m*-Aminophenyl-5-ethyl-4,5-dihydro-2,6-dihydroxypyrimidine, 454
  corresponding azoxy compound, (454)
4-β-Amino-β-phenylethyl-2,6-dimethylpyrimidine, 320
5-Amino-3-phenyloxazole
  hydrogenation of, 85
β-Amino-β-phenylpropionic acid
  use in dihydropyrimidine synthesis, 434, 435, 438
2-Amino-4-phenylpyrimidine, 35, 123
  to 2-chloro analogue, (167)
4-Amino-2-phenylpyrimidine, 188
4-Amino-5-phenylpyrimidine, 61, 91, 92
  called a triazine, 92
  methylation, 378
4-Amino-6-phenylpyrimidine, 95
5-Amino-2-phenylpyrimidine, 144
  acylation, (324)
2-*m*-Aminophenylpyrimidine
  to nitro analogue, 143
2-*p*-Aminophenylpyrimidine
  to nitro analogue, 143

6-Amino-1-phenyl-5-ureidouracil, 340
2-Amino-4-piperidinopyrimidine, 289
  acylation, 324
β-Aminopropionic acid
  use in dihydropyrimidine synthesis, 434, 435
4-β-Aminopropyl-2,6-dimethylpyrimidine, 320
2-Amino-4-propylpyrimidine, 35
2-Aminopyrimidine, 12, 23, 34, 167, 184, 185, 186, 188, 311, 329
  acylation, 324, 327, 330, 331
  alkylation, 24, 311, 377, 379
  halogenation, 169
  hydrolysis, 229, (231)
  reaction with phenyl-lithium, 123
  reduction, 444, 451
  reductive alkylation, 312
  sodium salt, 311
  sulphonation, 296
  to 2-chloropyrimidine, 167, 321, 333
  U.V. spectra (Fig.6), 481
4-Aminopyrimidine, 184, 186, 255, 279, 309, 311, (393)
  acylation, 324
  alkylation, 312, 377
  iodination, 169
  reduction, 444, 451
5-Aminopyrimidine, 144, 186, 279
  acylation, 324, 327
  reaction with *p*-nitrobenzaldehyde, 322
  reaction with nitrosobenzene, 156, 335
  reaction with nitrous acid, 238, 331
  reduction, 444, 451
  to 5-iodopyrimidine, 18
Aminopyrimidines, 13, 306*f*
  acylation, 24, 324*f*
  alkylation, 24, 377*f*
  bicyclic compounds from, 333*f*
  diazotization, *etc.*, 24, 331*f*
  from alkoxypyrimidines, 255*f*, 300
  from alkylsulphonylpyrimidines, 300
  from alkylthiopyrimidines, 289*f*, 308
  from mercaptopyrimidines, 17, 284*f*, 308
  from urethanes, 338
  halogenation, 169*f*
  ionization, 468*f*
  properties, 320*f*
  structure, 321
  sundry reactions, 25, 335
  tautomeric form, 484*f*, 494*f*
  to anils, 25, 321*f*
  to chloropyrimidines, 18, 167, 321
  to hydroxypyrimidines, 17, 229*f*, 321, 331*f*
  to mercaptopyrimidines, 275*f*
2-,4-, and 6-Aminopyrimidines, 306*f*
  by direct amination, 308
  by primary syntheses, 307
  by Principal Syntheses, 306
  by various syntheses, 310*f*
  from halogenopyrimidines, 188*f*, 308
  from nitroaminopyrimidines, 342
  from thiocyanatopyrimidines, 309, 420
  see also "Aminopyrimidines"
5-Aminopyrimidines
  acylation, 324*f*
  alkylation, 315
  by primary syntheses, 313
  diazotization, 331*f*
  from acylaminopyrimidines, 329
  from arylazopyrimidines, 156*f*
  from carbamoylpyrimidines, 314
  from halogeno derivatives, 210*f*, 314
  from nitropyrimidines, 143*f*
  from nitrosopyrimidines, 149*f*
  from urethanes, 338
  reactions, 321*f*
  reaction with cyanic acid, 339
  see also "Aminopyrimidines"
  strength as bases, 468
Aminopyrimidines (extranuclear), 316*f*
  action of nitrous acid, 333
  acylation, 324*f*
  by Hofmann of Curtius reactions, 317*f*
  by Mannich reaction, 318
  by primary syntheses, 318*f*
  by reduction of a nitrile, 316*f*
  by various means, 319
  see also: "Aminopyrimidines"
6-Amino-8-selenapurine, 334
β-Amino-β-styrylpropionic acid
  use in dihydropyrimidine synthesis, 434
2-Amino-4-styrylpyrimidine, 313, 322
Aminosuccinic acid
  use in dihydropyrimidine synthesis, 434
4-Amino-2-sulphanilylaminopyrimidine, 255
2-Amino-5-sulphopyrimidine
  failure to prepare by sulphonation, 296
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-

2,6-dioxo-5-phenylhydrazonomethylpyrimidine, (408)
7-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopteridine, 405
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 68, 344, 366
  C-acetylation, 416
  C-formylation, 408
  hydrolysis, 230
5-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine
  action of ethyl chloroformate, (336)
4-Amino-1,2,3,6-tetrahydro-1,3-dimethyl-5-nitroso-2,6-dioxopyrimidine, 149
  reduction, 150, 151
4-Amino-1,2,3,6-tetrahydro-5-*o*-hydroxybenzylideneamino-1,3-dimethyl-2,6-dioxopyrimidine, (322)
5-Amino-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine
  action of ethyl chloroformate, (336)
2-Amino-1,4,5,6-tetrahydro-5-hydroxypyrimidine, 447
4-Amino-2,3,5,6-tetrahydro-3-methyl-2-thiopyrimidine
  failure to make, 84
2-Amino-1,4,5,6-tetrahydropyrimidine, 447,451
  benzoylation, (456)
4-Amino-1,4,5,6(?)-tetrahydropyrimidine, 451
  dibenzoylation, (456)
5-Amino-1,4,5,6-tetrahydropyrimidine, 451
  dibenzoylation, (456)
4-Amino-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxopyrimidine
  acylation, 325
5-Amino-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine
  acylation, 325
2-Amino-4,5-tetramethylenepyrimidine, 34
2-Amino-3-thiocarbamoylpyrazine
  cyclization, 108
4-Aminothio-2,6-dimethoxypyrimidine, 298
  oxidation, 298
4-Amino-5-thioformamidomethylpyrimidine, 327
4-Amino-2,5,6-trialkylpyrimidines
  by Frankland and Kolbe synthesis, 93
2-Amino-4,5,6-trichloropyrimidine, 165
5-Amino-2,4,6-trichloropyrimidine, 143
2-Amino-4,5,6-trihydroxypyrimidine, 240
4-Amino-2,5,6-trihydroxypyrimidine, 152, 154, 240, 260, 263, 310
  hydrolysis, 229
5-Amino-2,4,6-trihydroxypyrimidine, 145, 150, 263
  action of urea or cyanic acid, 339
  nuclear reduction, 443
2-Amino-4,5-trimethylenepyrimidine, 279
4-Amino-5,6-trimethylenepyrimidine, 92
5-Amino-2,4,6-trimethylpyrimidine, 315, 338
4-Amino-2,5,6-triphenylpyrimidine, 105
5-Aminouracil, 6
6-Aminouracil, 6
5-Aminouridine, 211
"Amisometradine", 2, 367
Amobarbital, 53
4-Amylamino-2-mercaptopyrimidine
  desulphurization, 279
4-Amylaminopyrimidine, 279
4-Amyl-2,6-dichloropyrimidine, 163
  dechlorination, 121
4-Amyl-2,6-dihydroxypyrimidine, 281
  action of phosphoryl chloride, 163
5-Amyl-5-ethylbarbituric acid, 56
4-Amyl-6-hydroxy-2-mercaptopyrimidine, 45
  action of hydrogen peroxide, 281
Amylobarbitone, 53
4-Amylpyrimidine, 121
  spurious preparation, 123
"Amytal", 53
Aneurin, 6, 176
4-Anilino-2-benzylaminopyrimidine, 289
2-Anilino-5-bromo-4,6-dimethylpyrimidine, 178
4-Anilino-5-bromo-2,6-dimethylpyrimidine, (178)
2-Anilino-5-bromo-4-hydroxypyrimidine, 290
5-Anilino-4-carboxy-2-methylpyrimidine, 211
4-Anilino-2-carboxymethylthiopyrimidine, 283, 289
  amination, 289
2-Anilino-4-chloro-5-ethoxypyrimidine,
  amination, 197
4-Anilino-6-chloro-2-methylpyrimidine

  methylation, (379)
4-Anilino-6-chloropyrimidine
  alkylation, 312, (379)
2-Anilino-1-cyanopropene
  equivalence to cyanoacetone in syntheses, 65
2-Anilino-4-chloropyrimidine, 164
4-Anilino-6-chloropyrimidine, 191
  amination, 191
4-Anilino-2,6-dichloropyrimidine, 191
2-Anilino-5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine, 58
  hydrolysis, 230
5-Anilino-4,5-dihydro-2,6-dihydroxypyrimidine, 457
  hydrolytic cleavage, 457
4-Anilino-1,6-dihydro-1,2-dimethyl-6-methyliminopyrimidine, 379
  failure to rearrange, 379, 381
4-Anilino-1,2-dihydro-1,6-dimethyl-2-oxopyrimidine, 374
2-Anilino-4,5-dihydro-6-hydroxy-5,5-dimethyl-4-oxopyrimidine, 58
2-Anilino-1,4-dihydro-4-imino-1,6-dimethylpyrimidine, 378
4-Anilino-1,2-dihydro-2-imino-1,6-dimethylpyrimidine, 379
  hydrolysis, 374
4-Anilino-1,6-dihydro-6-imino-1,2-dimethylpyrimidine, 378
  rearrangement, 379
4-Anilino-3,6-dihydro-6-imino-2,3-dimethylpyrimidine, 378
2-Anilino-1,6-dihydro-1-methyl-6-oxo-oxopyrimidine, 365
3-Anilino-5,6-dihydro-6-phenyluracil,(437)
5-Anilino-2,4-dihydroxypyrimidine, 210
2-Anilino-4,6-dimethylpyrimidine, 188, 290
  bromination, 178
4-Anilino-2,6-dimethylpyrimidine
  bromination, 178
2-Anilino-4-ethoxy-5-methylpyrimidine, 300
β-Anilinoethylamine, 457
2-Anilino-4-hydroxy-6-methylpyrimidine, 290, 342
2-Anilino-4-hydroxypyrimidine
  action of phosphoryl chloride, 164
  alkylation, 365
2-Anilino-4-mercapto-5-methylpyrimidine, 285
4-Anilino-2-mercapto-6-methylpyrimidine, 285
2-Anilino-4-mercapto-5-nitropyrimidine, 275
4-Anilino-2-mercaptopyrimidine, 285, 289
  S-alkylation, (283), 289
2-Anilino-4-methoxypyrimidine, 365
4-Anilino-6-methylamino-2-phenylpyrimidine, 312
4-Anilino-2-methylaminopyrimidine, 289
4-Anilino-6-methylaminopyrimidine, 191, 312
4-Anilino-2-methyl-6-methylaminopyrimidine, 312, 379
4-Anilino-6-methyl-2-methylthiopyrimidine
  methylation, (379)
2-Anilino-4-methylpyrimidine, 35
4-Anilino-6-methylpyrimidine, 188
2-Anilino-5-nitro-4-thiocyanatopyrimidine, 310
  actions of alkoxide, 275
3-Anilinopropylamine
  to corresponding urea, 446
N-(3-Anilinopropyl)urea, 447
  cyclization, 447
2-Anilinopyrimidine, 188
Anilinopyrimidines
  bromination, 178
4-Anilino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 198
Anils
  see "Schiff's bases"
Anisamidine
  use in synthesis, 246
4-*p*-Anisidino-2-carboxymethylthiopyrimidine
  desulphurization, 279
4-*p*-Anisidinopyrimidine, 279
4-*p*-Anisylpyrimidine, 118
"Antrycide", 308
Arylazopyrimidines, 152*f*
  by coupling, 153*f*
  direct synthesis, 152*f*
  other syntheses, 155*f*
  reduction, 23, 156*f*
Arylpyrimidines, 119*f*
Arylsulphonamidopyrimidines, 329*f*
Aspartic acid
  in pyrimidine biosynthesis, 424
  use in orotic acid synthesis, 423

Aspinall, 445
Astwood, 301
8-Azaguanine, 334
8-Azapurine, 334
5-Azidocarbonylmethyl-2,4-dihydroxy-6-methylpyrimidine, (337), (401)
  action of acetic acid, 318
  action of alcohol, 337
  to isocyanate, (419)
5-Azidocarbonylmethyl-2,4-dihydroxypyrimidine, 400
  to isocyanate, (419)
5-Azidocarbonylmethyl-2-ethylthio-4-hydroxypyrimidine, (337), 400
  action of alcohols, 337, 401
  to corresponding isocyanate, 401, 419
Azidocarbonylpyrimidines, 400*f*
Azidopyrimidines, 200*f*
4-Azido-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 201
"5-Azinomethyl-4-methyl-6-methylthio-2-piperidinopyrimidine", 414
2,2′-Azobisisobutyronitrile
  as a polymerisation catalyst, 134
Azo coupling
  general conditions, 153

B

Bachstez, 283, 423, 432
Baddiley, 424
Barbital, 53
Barbitone, 53
Barbiturates, 53, 99*f*
  allylation, 53
  reduction, 22
  route *via* amino analogues, 53*f*
  thiation, 251
Barbituric acid, 6, 52*f*, 99
  dihalogenation of derivatives, 172
  early preparation, 1, 52
Barlin, G., 485
Bass
  see: "Levene"
Bayer, 96
Behrend, 2, 400
Belloni, 422
Bendich, 2, 259
5-Benzalbarbituric acid, 123
  reduction, 124
Benzaldehyde
  reaction with barbituric acid, 123
  reaction with urea, 441
  use in making styrylpyrimidines, 125
Benzamidine
  reaction with β-benzoylstyrene, 103
  use in Principal Syntheses, 31–74
α-Benzamidoacetamidine
  use in synthesis, 319
4-Benzamido-1-benzoyl-1,4,5,6-tetrahydropyrimidine, 456
5-Benzamido-1-benzoyl-1,4,5,6-tetrahydropyrimidine, 456
β-Benzamido-1-carbamoyloctane, (440)
  cyclization with acetic anhydride, (440)
  cyclization with benzoyl chloride, (440)
1-Benzamido-3-dibenzoylaminopropane, (456)
4-Benzamido-1,2-dihydro-1-methyl-2-oxopyrimidine, 327, (328)
2-Benzamidodihydropyrimidine, (456)
4-Benzamidodihydropyrimidine, (456)
5-Benzamidodihydropyrimidine, (456)
2-Benzamido-4,6-dimethylpyrimidine, 327
β-Benzamido-β-ethoxycarbonylpropionamide
  cyclization, 439
β-Benzamido-*N*-ethylpropionamide
  cyclization, 439
5-Benzamido-4-hydroxy-2-methylthiopyrimidine, 40, 328
  desulphurization, 279
  to 5-acetamido analogue, 329
4-Benzamido-2-hydroxypyrimidine, 328
5-Benzamido-4-hydroxypyrimidine, 279
  hydrolysis to 4,5-dihydroxypyrimidine, 238
2-Benzamido-4-mercapto-6-methylpyrimidine, 329
2-Benzamidomethyl-4,6-dimethylpyrimidine, 319, 328
  hydrolysis, 319, 329
3-Benzamidopropylamine, 445
  cyclization, 445
2-Benzamidopyrimidine, 327
5-Benzamidopyrimidine, 327
2-Benzamido-1,4,5,6-tetrahydropyrimidine, (456)
2-Benzenesulphonamido-5-bromopyrimidine, (171)
Benzene
  U.V. spectrum (Fig.1), 479
2-Benzenesulphonamido-5-cyanopyrimidine, 212, 404

2-Benzenesulphonamido-4,6-dimethylpyrimidine, 330
2-Benzenesulphonamido-5-iodopyrimidine
  to 5-cyano analogue, 212, 404
2-Benzenesulphonamido-4-methylpyrimidine, 330
2-Benzenesulphonamidopyrimidine, 330
  halogenation, 171
Benzenesulphonhydrazide
  reaction with a chloropyrimidine, 187, 200
2-Benzenesulphonylaminopyrimidine
  see: "2-benzenesulphonamidopyrimidine"
2-Benzenesulphonylhydrazino-5-ethoxycarbonyl-4-methylpyrimidine, 330
Benzonitrile
  trimerization, 95
Benzoylacetaldehyde
  use in syntheses, 35, 94
Benzoylacetone
  use in syntheses, 37, 93, 94
Benzoylacetylene
  use in synthesis, 35
1-Benzoyl-2-butanone
  use, 95
1-Benzoyl-2-chloroethylene
  use, 94
4-Benzoyl-2,6-diethoxypyrimidine, 416
1-Benzoyl-2-diethylaminoethylene
  use, 94
4-Benzoyl-2,6-dihydroxypyrimidine, 417
  reduction, 417
1-Benzoyl-2-dimethylaminoethylene
  use, 94
2-Benzoyl-4,6-dimethylpyrimidine, 417
  oxidation, 417
1-Benzoyl-2-ethoxy-1-propene
  use, 94
N-*β*-Benzoylethyl-*N*-methylurea, (436)
  cyclization, (436)
2-Benzoylhydrazino-4-methylpyrimidine, 200
2-Benzoylhydrazinopyrimidine, 200
1-Benzoyl-2-iminopropane
  as intermediate in Bredereck's synthesis, 93, 94
4-Benzoylimino-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxopyrimidine, 378
1-Benzoyl-2-methoxy-2-phenylethylene
  use, 95
4-Benzoylmethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 416
2-Benzoylmethylthio-4-ethoxy-6-methylpyrimidine (?), 247
2-Benzoylmethylthio-4-hydroxy-6-methylpyrimidine
  supposed *O*-alkylation, (247)
2-Benzoylmethylthio-4-methoxy-6-methylpyrimidine (?), 247
Benzoyl-*p*-nitrobenzoylmethane
  use, 95
1-Benzoyl-2-phenylacetylene
  use, 95
β-Benzoylstyrene
  use in forming hydropyrimidines, 433
1-Benzoyl-1,4,5,6-tetrahydropyrimidine, 451
2-Benzoylthio-1,6-dihydro-6-methyl-4,6-di-*p*-tolylpyrimidine, 458
Benzoylvinylacetate
  use, 49
5-Benzoylvinyl-4-hydroxy-6-methyl-2-piperidinopyrimidine, 415
4-Benzylamino-5-bromo-1,2,3,6-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine
  amination, 210
4-Benzylamino-2-carboxymethylthiopyrimidine, 283
4-Benzylamino-5-dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 210
2-Benzylamino-5-ethoxycarbonyl-4-methylpyrimidine, 290
4-Benzylamino-2-hydroxypyrimidine, 313
4-Benzylamino-2-mercapto-6-methyl-5-nitropyrimidine, 145
4-Benzylamino-2-mercaptopyrimidine, 285
  S-alkylation, (283)
4-Benzylaminomethyl-6-methyl-2-methylthio-5-nitropyrimidine
  hydrogenation, 143
2-Benzylamino-4-methylpyrimidine
  reported formation, 313
2-Benzylaminopyrimidine, 291, 312
  mechanism of formation, 312
2-Benzylamino-4-styrylpyrimidine, 313
5-Benzyl-2,4-bisdimethylaminopyrimidine, 190

5-Benzyl-2,4-bismethylaminopyrimidine, 190
4-Benzyl-5-bromo-2,6-dihydroxypyrimidine, (170)
1-Benzyl-5-bromo-2-ethylthio-1,4-dihydro-4-oxopyrimidine, 370
  hydrolysis, 370
1-Benzyl-5-bromouracil, 370
5-Benzyl-2-chloro-4-dimethylaminopyrimidine, 190
  amination, 190
5-Benzyl-2-chloro-4-methylaminopyrimidine, 190
  amination, 190
2-Benzyl-4-chloro-6-methylpyrimidine
  dechlorination, 121
  reaction with hydriodic acid, (168)
4-Benzyl-2-chloro-6-methylpyrimidine
  dechlorination, 121
4-Benzyl-5,5-dichloro-4,5-dihydro-2,4,6-trihydroxy-4-methoxypyrimidine, 173
5-Benzyl-2,4-dichloro-6-methoxypyrimidine
  amination, 197
5-Benzyl-2,4-dichloropyrimidine
  amination, 190
4-Benzyl-3,4-dihydro-2-hydroxy-5-phenylpyrimidine, 442
1-Benzyl-1,2-dihydro-4-methylthio-2-oxopyrimidine, (362), 369
  hydrolysis, (362), 369
5-Benzyl-5,6-dihydro-1-methyluracil, 435
3-Benzyl-5,6-dihydro-6-phenyluracil, 437
1-Benzyl-5,6-dihydrouracil, (435)
5-Benzyl-4,6-dihydroxy-2-mercaptopyrimidine
  desulphurization, 279
5-Benzyl-4,6-dihydroxy-2-phenylpyrimidine, 56
4-Benzyl-2,6-dihydroxypyrimidine
  bromination, 170
5-Benzyl-2,4-dihydroxypyrimidine
  thiation, 251
5-Benzyl-4,6-dihydroxypyrimidine, 279
5-Benzyl-2,4-dimercaptopyrimidine, 251
4-Benzyl-5-ethoxycarbonyl-3,4-dihydro-2-hydroxy-6-methylpyrimidine, 442
5-Benzylethylamino-2,4-dihydroxypyrimidine, 210
1-Benzyl-2-ethylthio-1,4-dihydro-4-oxopyrimidine, (362), (369)
  hydrolysis, (362), (369)
1-Benzyl-2-ethylthio-1,6-dihydro-6-oxopyrimidine, (362), (369)
  hydrolysis, (362)
Benzyl formylbenzyloxyacetate
  use in synthesis, 239
5-Benzyl-4-hydroxy-6-methyl-2-phenylpyrimidine, 44
2-Benzyl-4-hydroxy-6-methylpyrimidine, 44
1-Benzyl-5-hydroxyuracil, 239
3-Benzyl-5-hydroxyracil, 239
Benzylideneacetophenone
  see: "β-benzoylstyrene"
Benzylideneaminoguanidine
  use, 323
2-Benzylideneamino-4-hydroxypyrimidine, 322
Benzylideneaniline
  stability, 322
5-Benzylidenebarbituric acid
  oxidation, 261
2-Benzylidenehydrazino-4-hydroxy-6-methylpyrimidine, 323
  hydrolysis, 230
Benzylidene-*p*-nitroaniline
  stability, 322
5-Benzylidene-2,4,6-trihydroxypyrimidine, 12
  action of bromine, 172
2-Benzyl-4-iodo-6-methylpyrimidine, 168
4-Benzylmethylamino-2-chloro-6-methyl-5-nitropyrimidine
  action of sodium bisulphide, 145, (206)
4-Benzylmethylamino-2-chloro-5-nitropyrimidine, 194
4-Benzylmethylamino-2-mercapto-6-methyl-5-nitropyrimidine, 206
2-Benzyl-4-methylpyrimidine, 121
4-Benzyl-6-methylpyrimidine, 121
1-Benzyl-6-methyluracil, (361)
  methylation, (361)
Benzyloxyamine
  condensation with a chloropyrimidine, 311
Benzyloxyamino derivatives
  hydrogenation, 311
4-Benzyloxy-2-carbamoyl-6-methylpyrimidine

  hydrogenation, 237
5-Benzyloxycarbonylaminomethyl-2-ethylthio-4-hydroxypyrimidine, 337
4-Benzyloxy-2-cyano-6-methylpyrimidine, 383
5-Benzyloxy-4,6-dihydroxy-2-mercaptopyrimidine, (240)
  desulphurization, (240)
5-Benzyloxy-4,6-dihydroxy-2-methylpyrimidine, 56, (240)
  hydrogenation, (240)
5-Benzyloxy-2,4-dihydroxypyrimidine, 40, 240
  hydrogenation, (240)
5-Benzyloxy-4,6-dihydroxypyrimidine, (240)
  hydrogenation, (240)
2-Benzyloxy-4,6-dimethylpyrimidine, 201
  hydrolysis, 232
4-Benzyloxy-2,6-dimethylpyrimidine, 201
  formation of *N*-oxide, 382
4-Benzyloxy-2,6-dimethylpyrimidine-*N*-oxide, 382
  reduction, 383
5-Benzyloxy-2-ethylthio-4,6-dihydroxypyrimidine, 55, 287
5-Benzyloxy-4-hydroxy-2-mercaptopyrimidine, 40, (239), 240
  desulphurization, (239), 240, 279
5-Benzyloxy-4-hydroxy-2-methylpyrimidine, 40, 240
  hydrogenation, 240
5-Benzyloxy-4-hydroxypyrimidine, (239), 240, 279
  hydrogenation and hydrolysis, 240
  thiation, (239), (252)
5-Benzyloxy-4-mercaptopyrimidine, (239), 252
  desulphurization, (239), 279
4-Benzyloxy-6-methylpyrimidine, 383
  formation of *N*-oxide, 382
4-Benzyloxy-6-methylpyrimidine-*N*-oxide, 382
  reductive cleavage, 237
  Reissert reaction, (383)
  removal of *N*-oxide, 383
5-Benzyloxypyrimidine, 239, 279
  failure to yield 5-hydroxypyrimidine, 239
Benzyloxypyrimidines
  reductive cleavage, 237
5-Benzyloxy-2,4,6-trihydroxypyrimidine, (240)
  hydrogenation, (240)
2-*N*-Benzylsulphamoyl-4,6-dimethylpyrimidine, 298
2-Benzylsulphonyl-4,6-diphenylpyrimidine, 299
1-Benzyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxopyrimidine, 361
1-Benzyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxopyrimidine, 368
2-Benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine
  desulphurization, (280)
2-Benzylthio-4-carboxy-6-hydroxypyrimidine, 283
2-Benzylthio-4-chloropyrimidine, 165
2-Benzylthio-4,6-diphenylpyrimidine, 103, 433
  oxidation, (299)
2-Benzylthio-5-ethoxycarbonyl-4-hydroxypyrimidine, 287
2-Benzylthio-4-formyl-6-hydroxypyrimidine, 283
2-Benzylthio-4-hydroxy-5-iodo-6-methylpyrimidine
  to 2-mercapto analogue, (274)
2-Benzylthio-4-hydroxy-5-iodopyrimidine, 171
  to 2-mercapto analogue, (274)
2-Benzylthio-4-hydroxypyrimidine, 283
  action of phosphoryl chloride, (165)
  hydrolysis, 233
  iodination, (171)
S-Benzylthiourea
  use in synthesis, 103
2-Benzyl-1,3,5-triazine
  description of a pyrimidine as, 92
5-Benzyl-2,4,6-tribromopyrimidine, 167
5-Benzyl-2,4,6-trichloropyrimidine
  amination, 193
5-Benzyl-2,4,6-trihydroxypyrimidine, 124
  action of phosphoryl bromide, 167
Benzyltrimethylammonium hydroxide
  use as condensation catalyst, 33
1-Benzyluracil, 362, 369
  halogenation, 370
  methylation, 369
  structure, (369)

- 3-Benzyluracil, 362
  - structure, (369)
- Bergel, F., 326
- Bicyclouracil, 181
- Biginelli reaction, 440*f*
  - mechanism, 441
- 2,4-Bisacetamido-6-hydroxy-pyrimidine, 324
- 4,6-Bisacetamido-2-methylpyrimidine, 324
- 4,6-Bisacetamidopyrimidine, 324
- Bis-(4-amino-2-methylpyrimidin-5-ylmethyl)amine, (410)
- 4,5-Bisbenzamidopyrimidine, 327
- 2,4-Bisbenzenesulphonylhydrazino-pyrimidine, 187, 200
  - pyrimidine from, 117, 187
- 1,3-Bisbenzylaminopropane
  - condensation with aldehydes, 453
- 1,3-Bisbutylaminopropane
  - use in hydropyrimidine synthesis, 447
- 4,6-Bisbutylaminopyrimidine
  - methylation, (379)
- 2,4-Biscarboxymethylthiopyrimidine, 284
- Biscaro, 422
- 5-Bis(β-chloroethyl)amino-2,4-dihydroxypyrimidine, 178
- 4,6-Biscyclohexylamino-5-nitro-pyrimidine, 196
- 4,5-Bis-αα-dichloropropionamido-pyrimidine, 328
- Bis-2,4-dihydroxypyrimidin-5-yl disulphide, 276, 277
  - reduction, 276
- 2,4-Bisdimethylamino-6-methyl-5-nitropyrimidine, 194, 195
- 2,4-Bisdimethylamino-6-methyl-pyrimidine, 190
- 4,6-Bisdimethylamino-2-methyl-pyrimidine, 191
- 4-Bis(*p*-dimethylaminophenyl)methyl-2,6-dihydroxy-5-methylpyrimidine, 415
- 4,6-Bisdimethylaminopyrimidine, 191
- 4,6-Bis-*p*-dimethylaminostyryl-2-hydroxypyrimidine, 126
- 2,4-Bisethoxycarbonylmethylamino-5-nitropyrimidine, 195
- 4,6-Bisethoxycarbonylmethylamino-5-nitropyrimidine, 196
- 2,4-Bisethylamino-5-nitropyrimidine, 310, 420
- 2,4-Bisethylsulphonylpyrimidine, 299
  - hydrolysis to uracil, 236
- 2,4-Bisethylthio-5-methylpyrimidine, 205
- 2,4-Bisethylthiopyrimidine, 205
- 4,5-Bisformamido-2-methoxy-pyrimidine, 326
- 4,6-Bisfurfurylamino-5-nitro-pyrimidine, 196
- 5-Bis(β-hydroxyethyl)amino-2,4-dihydroxypyrimidine
  - to 5-bischloroethyl analogue, 178
- 1,2-Bis(4-hydroxy-6-methyl-pyrimidin-2-ylthio)ethane, 46
- 1,3-Bisisopropylamino-2-methyl-2-nitropropane
  - condensation with aldehydes, 453
- 2,4-Bismethylamino-5-nitro-pyrimidine, 194, 195, 255, 285, 309
- 4,6-Bismethylamino-5-nitropyrimidine, 196, 255
- 2,4-Bismethylaminopyrimidine, 198, 290
- 4,5-Bismethylaminopyrimidine, 107, 308, 314
- 4,6-Bismethylaminopyrimidine, 191
- *NN'*-Bisphenylcarbamoylformamidine
  - in the Whitehead synthesis, 64
- 2-Bis(piperidinomethyl)methyl-4-hydroxy-6-methylpyrimidine, 132
- 2-Bis(piperidinomethyl)methyl-4-hydroxy-6-piperidinomethyl-pyrimidine, 132
- 4,6-Bistribromomethylpyrimidine, 130, 177
  - to dicarboxy analogue, 216, 393
- Bistrimethylsilylamine
  - effect on cyclizations, 334
- αα-Bisureidotoluene, 441
  - reaction with ethyl acetoacetate, 441
- Blicke, 366
- Bowman, 259
- Bradbury, 448
- Bredereck, H., 92, 116, 119, 210
- Bromination
  - of uracil, barbituric acid, *etc.*, 19
  - see also: "Halogenation"
  - with dibromobarbituric acid, 213
- *p*-Bromoaniline, 213

2-*p*-Bromoanilino-4,6-dimethylpyrimidine, 178
5-Bromo-2-*p*-bromoanilino-4,6-dimethylpyrimidine, 178
5-Bromo-4-*p*-bromoanilino-2,6-dimethylpyrimidine, (178)
4-Bromo-5-bromomethyl-6-chloro-2-methylpyrimidine, 131, 167, 177
  action of alkoxide, 202, 214
5-Bromo-4-carbamoyl-2-methylpyrimidine, (394)
  dehydration, 400
  Hofmann reaction on, 310
5-Bromo-4-carbamoyl-2-methylthiopyrimidine, (394)
5-Bromo-2-carbamoylpyrimidine, 396
  debromination, 211
5-Bromo-2-α-(carboxyamyl) hydrazinopyrimidine, 333
5-Bromo-2-(5-carboxyamylamino)pyrimidine
  action of thiourea, 212, 293
5-Bromo-4-carboxy-2,6-dihydroxypyrimidine, 424
5-Bromo-4-carboxy-6-hydroxypyrimidine, 171
5-Bromo-4-carboxy-2-methylpyrimidine
  amination, 211
  resistance to oxidation, 127
  to acid chloride, (394)
5-Bromo-4-carboxy-2-methylthiopyrimidine, 35, 175
  dehalogenation and desulphurization, 212, 279
5-Bromo-4-carboxy-2-methylpyrimidine, 35, 175, 390
  esterification, (394)
5-Bromo-4-carboxy-2-methylthiopyrimidine, (390)
  to amide *via* acid chloride, (394)
5-Bromo-4-carboxy-2-phenylpyrimidine, 35, 175, 390
  amination, 211
5-Bromo-2-carboxypyrimidine, 128, 130, 216, 393
  debromination, 130
  decarboxylation, 130, 393
  esterification, (394)
5-Bromo-4-chlorocarbonyl-2-methylpyrimidine
  amination to amide, (394)
5-Bromo-5-chloro-4,5-dihydro-2,4,6-trihydroxypyrimidine, 173
5-Bromo-4-chloro-2,6-dimethoxypyrimidine, (171)
5-Bromo-4-chloro-2-ethylsulphonylpyrimidine, 299
5-Bromo-4-chloro-2-ethylthiopyrimidine
  action of thiocyanate, (208)
  amination, 199
  oxidation, 299
5-Bromo-4-chloro-2-methylthiopyrimidine, 165
5-Bromo-4-chloro-2-phenylpyrimidine
  attempted dehalogenation, 121
5-Bromo-4-cyano-2-methylpyrimidine, 400
5-Bromocytidine
  amination, 211
5-Bromodeoxyuridine
  to 5-hydroxy analogue, 238
5-Bromo-2,4-dichloro-6-methylpyrimidine, 164
  dehalogenation, 121, 183, 211
1-Bromo-1,3-dichloro-2-propene
  use in syntheses, 34, 167
5-Bromo-2,4-dichloropyrimidine, 164, 165
  pyrimidine from, 116, 211
5-Bromo-4,6-dichloropyrimidine, 164
4-Bromo-2,6-diethoxypyrimidine, 202
5-Bromo-2,4-diethoxypyrimidine, 247
  formation of a Grignard, 393
  formation of a lithium derivative, 393
5-Bromo-1,3-diethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidine, (170)
5-Bromo-4,5-dihydro-2,6-dihydroxypyrimidine, 457
  dehydrobromination, (457)
  reaction with aniline, 457
  reaction with thiocyanate, 457
5-Bromo-4,5-dihydro-2,4,6-trihydroxy-5-methylpyrimidine, 173, 259, 442
  action of silver carbonate, 442
5-Bromo-5,6-dihydrouracils
  dehydrobromination conditions, 455
5-Bromo-2,4-dihydroxy-6-methylpyrimidine
  action of phosphoryl chloride, (164)
  amination, 210
5-Bromo-2,4-dihydroxypyrimidine, (170), 173

action of phosphoryl chloride *etc.*, (164), (165)
amination, 210, 314
chlorination, 173
hydrolysis, 14, 212, (238)
5-Bromo-4,6-dihydroxypyrimidine, 169
action of phosphoryl chloride, (164)
ring opening by piperidine *etc.*, (211)
5-Bromo-2,4-dimethoxy-6-methylaminopyrimidine, (171)
5-Bromo-2,4-dimethoxypyrimidine
action of butyl-lithium, 213, 393
2-Bromo-4-dimethylamino-6-methylpyrimidine, 190
p-Bromo-*NN*-dimethylaniline, 213
5-Bromo-2,6-dimethyl-4-thioureidopyrimidine, 340
5-Bromo-3,6-dimethyluracil, 171
5-Bromo-4-ethoxycarbonyl-2-methylpyrimidine, 394
5-Bromo-2-ethoxy-4,6-dimethylpyrimidine, 171
5-Bromo-4-ethoxy-2-ethylsulphonylpyrimidine, 299
action of alkoxide, (247)
alkaline hydrolysis of 2-group, 236
5-Bromo-4-ethoxy-2-ethylthiopyrimidine
oxidation, (299)
5-Bromo-4-ethoxy-2-hydroxypyrimidine, 236
5-Bromo-1-ethylbarbituric acid
to chloro analogue, 176
4-Bromo-2-ethyl-6-hydroxypyrimidine, 167, 204
amination, 197
5-Bromo-2-ethylthio-4-hydroxypyrimidine, 171
alkylation, 370
amination, 290
amination failure, 210
5-Bromo-2-ethylthio-4-isothiocyanatopyrimidine, 208
5-Bromo-2-ethylthio-4-mercaptopyrimidine, 275
5-Bromo-2-ethylthiopyrimidine, 170
5-Bromo-2-ethylthio-4-thiocyanatopyrimidine, 208
action of thioacids, (275)
5-Bromo-4-hydrazinopyrimidine, 200
5-Bromo-2-hydroxy-4,6-dimethylpyrimidine, 169
5-Bromo-4-hydroxy-2,6-dimethylpyrimidine, 169, 232
5-Bromo-4-hydroxy-2-mercapto-6-methylpyrimidine, 274
5-Bromo-4-hydroxy-2-mercaptopyrimidine, 274
5-Bromo-4-hydroxy-2-methylthiopyrimidine, 171
action of phosphoryl chloride, (165)
5-Bromo-4-hydroxypyrimidine, 169
debromination, 212
5-(2-Bromoisobutyl)-4-chloro-2-methylpyrimidine, 178
5-Bromo-2-methoxycarbonylpyrimidine, 394
to amide, (396)
5-Bromo-5-methylbarbituric acid
amination, 213
formation of a hydantoin, 213
ready removal of bromine, 213
5-Bromomethyl-4,6-dichloro-2-methylpyrimidine, 131, 177
action of alkoxide, 202, 214
action of silver acetate, 215, 253
5-Bromomethyl-2,4-diethyl-6-hydroxypyrimidine, (232)
5-Bromomethyl-2,4-dihydroxypyrimidine, (178)
5-Bromo-2-methylpyrimidine
styrylation, 125
5-Bromo-2-methylthiopyrimidine, 170
pyrimidine from 117, 212, 279
5-Bromomethyl-2,4,6-trichloropyrimidine, 131, 177
5-Bromo-1-methyluracil
amination, 210
5-Bromo-3-methyluracil
amination, 210
Bromomucic acid
use in syntheses, 35, 390
5-Bromo-5-nitrobarbituric acid
action of pyridine, 214
β-Bromopropionyl isocyanate
reaction with amines, 436
N-*β*-Bromopropionyl-*N*′-phenylurea, 436
cyclization, 436
dehydrobromination, 436
3-Bromopyridine, 118
5-Bromopyrimidine, 130, 168, (393)
amination, 13
reaction with sodium ethyl mercaptide, 210, 288

  reaction with sodium methoxide, 14, 210, 247
5-Bromopyrimidines, 168*f*
  reactions, 210*f*
2-, 4-, and 6-Bromopyrimidines, 167*f*
5-Bromo-2-styrylpyrimidine, 125
  oxidation, 128
N-Bromosuccinimide
  use of, 131, 171, 177
5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine
  debromination, 211
  hydrolysis, 212, 238
5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine
  amination, 210
  dehalogenation, 212
  to 5-chloro analogue, 176
5-Bromo-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine
  from chloro analogue, 171
5-Bromo-2-tribromomethylpyrimidine, 130, 177
  reaction with silver nitrate, 130, 216, 392
5-Bromo-2,4,6-trihydroxypyrimidine, 19, 169, 213
  action of bromine, 172
  action of thiourea, 212, 292
  conversion into chloro analogue, 172
  supposed formation of thiazolo[4,5-d]-pyrimidines, 213
5-Bromouracil, 6
5-Bromouridine
  amination, 211
  to 5-hydroxyuridine, 212, 238
Brown, 2
Brugnatelli, 1, 260
Buchanan, 424
Bunsen, 96
4-Butoxy-2-cyano-6-methylpyrimidine, 383
5-Butoxymethyl-2,4-dihydroxypyrimidine, 248
4-Butoxy-6-methylpyrimidine
  formation of *N*-oxide, 382
4-Butoxy-6-methylpyrimidine-*N*-oxide, 382
  Reissert reaction, (383)
2-Butoxy-5-nitropyrimidine, 202
1-Butylamino-3-(*N*-butylformamido)-propane
  fusion with sulphur, 447
4-Butylamino-6-butylimino-1,6(3,6)-dihydro-1(3)-methylpyrimidine, 379
4-Butylamino-2-hydroxy-5-nitropyrimidine, 139
4-Butylamino-2-hydroxypyrimidine
  nitration, 139
2-Butylamino-4-methylpyrimidine, 35
4-Butylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 198
4-Butylamino-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxopyrimidine, 198
2-Butyl-4-chloro-6-methylpyrimidine
  dechlorination, 121
1-Butyl-5-cyano-1,2-dihydro-6-hydroxy-4-methyl-2-thiopyrimidine, 45
3-Butyl-5-cyano-2,3-dihydro-4-hydroxy-6-methyl-2-thiopyrimidine, 66
2-Butyl-4,6-dichloro-5-nitropyrimidine
  amination, 195
5-Butyl-2,4-dihydroxy-6-methylpyrimidine
  alkylation, (362)
5-Butyl-4,6-dihydroxy-2-methylpyrimidine, 56
2-Butyl-4,6-dihydroxy-5-nitropyrimidine, 140
2-Butyl-4,6-dihydroxypyrimidine, 98
  nitration, 140
Butyl *αγ*-dimethoxyacetoacetate, 46
  use, 246
5-Butyl-2,4-dimethoxy-6-methylpyrimidine
  isomerization, 372
4-Butyl-2-dimethylaminopyrimidine, 123
1-Butyl-5-dimethylamino-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxopyrimidine, 315
5-s-Butyl-5-ethyl-1-methyl-2-thiobarbituric acid, 54
4-Butyl-6-hydroxy-2-mercaptopyrimidine
  antithyrotoxicotic activity, 301
4-t-Butyl-6-hydroxy-2-mercaptopyrimidine

  desulphurization, 279
4-t-Butyl-6-hydroxypyrimidine, 279
2-Butyl-4-methylpyrimidine, 121, 123
4-Butyl-6-methylpyrimidine, 94
1-Butyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxopyrimidine, 361
5-Butyl-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine, 362
2-Butylthio-4-chloro-5-methylpyrimidine, 165
2-Butylthio-4-hydroxy-5-methylpyrimidine
  action of phosphorus pentachloride, (165)
N-Butylthiourea
  use in Principal Syntheses, 45, 66
5-s-Butyl-2,4,6-trichloropyrimidine
  action of alkoxide, 202
5-s-Butyl-2,4,6-triethoxypyrimidine, 202
5-Butyl-2,4,6-trihydroxypyrimidine, 56
5-s-Butyl-2,4,6-trimethoxypyrimidine, 202
5-s-Butyl-2,4,6-tripropoxypyrimidine, 202
3-Butyluracil, 39
Butyramide
  as degradation product, 132
Butyramidine
  use in syntheses, 52, 56

C

Caldwell, 331, 423
Calvin, 2
Cannizzaro reaction, 244, 392
Carbamoylacetamidine
  use in syntheses, 52, 101, 307, 398
4-Carbamoyl-5-chloro-2-methylpyrimidine, (394)
  dehydration, 400
  Hofmann reaction, (310)
4-Carbamoyl-3-cyano-6-methylpyridine
  anomalous reaction with hypochlorite, 109
Carbamoyl dihydrogen phosphate
  in pyrimidine biosynthesis, 424
5-Carbamoyl-4,6-dihydroxy-2-methylpyrimidine, 12, 399
  action of phosphoryl chloride, 165, 400
4-Carbamoyl-2,6-dihydroxypyrimidine, 130, 398, 400
  hydrolysis, (391)
4-Carbamoyl-2,6-dimethoxypyrimidine, 398
2-Carbamoyl-4,6-dimethylpyrimidine, 398
4-Carbamoyl-2,6-dimethylpyrimidine, 399
  to hydrazide directly, (397)
5-Carbamoyl-2,4-dimethylpyrimidine, 396
  Hofmann reaction, 314, 336
2-Carbamoyl-4-ethoxy-6-methylpyrimidine, 399
5-Carbamoyl-2-ethyl-4-methylpyrimidine
  Hofmann reaction, 314, (336)
2-β-Carbamoylethylpyrimidine, 396
  Hofmann reaction, 317
4-β-Carbamoylethylpyrimidine, 396
  Hofmann reaction, 317
5-Carbamoyl-4-hydroxy-6-methyl-2-piperidinopyrimidine, 399
2-Carbamoyl-4-hydroxy-6-methylpyrimidine, 237
  dehydration, 400
2-Carbamoyl-4-methoxy-6-methylpyrimidine, 399
2-Carbamoylmethyl-4,6-diethoxypyrimidine, 396
2-Carbamoylmethyl-4,6-dihydroxypyrimidine, 52, 98, 398
  action of phosphoryl chloride, 400
5-Carbamoylmethyl-2,4-dihydroxypyrimidine, 396
5-Carbamoylmethyl-2,4,6-trihydroxypyrimidine
  hydrolysis, (391)
6-Carbamoyl-1-methyluracil, 130, (370), 400
  hydrolysis, (370)
α-Carbamoyl-α-phenylazoacetamidine
  use in synthesis, 153
2-Carbamoylpyrimidine, (211)
  dehydration, 400
4-Carbamoylpyrimidine, 396
5-Carbamoylpyrimidine, (394), 396, 397
Carbamoylpyrimidines
  degradation to aminopyrimidines, 314*f*, 317*f*
  dehydration, 400
  direct formation from alkylpyrimidines, 130, 399*f*
  from esters, 396*f*
  from nitriles, 398*f*
  from primary syntheses, 398

from unusual routes, 399
hydrolysis, 391
4-Carbamoyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 130, 398, 400
5-Carbamoyl-2,4,6-trihydroxypyrimidine
nitration to 5-nitrobarbituric acid, 140
Carbon
unique preparation, (210)
Carbon bisulphide
use in syntheses, 99
Carbon oxysulphide
use in syntheses, 99
N-*β*-Carboxyacryloylurea, 432
2-*α*-(Carboxyamyl)hydrazino-5-chloropyrimidine, 333
2-Carboxyamylamino-5-hydroxypyrimidine, 238, 333
2-Carboxyamylamino-5-(5-nitropyrimidin-2-yl)sulphonylpyrimidine, 294
2-Carboxyamylamino-5-(5-nitropyrimidin-2-yl)thiopyrimidine, 293
oxidation, 294
5-(2-Carboxy-5-chloroanilino)-2-methoxypyrimidine, 316
4-Carboxy-5-chloro-2,6-dihydroxypyrimidine, (171)
4-Carboxy-5-chloro-2-methylpyrimidine, 175
esterification, (394)
to acid chloride, (394)
4-Carboxy-5-chloro-2-phenylpyrimidine, 175
amination, 211
4-Carboxy-2,6-dichloropyrimidine, 424
5-Carboxy-2,4-dichloropyrimidine, 165
4-Carboxy-2,6-diethoxypyrimidine, 393
action of methyl-lithium, 395, 417
4-Carboxy-4,5-dihydro-2,6-dihydroxypyrimidine, 424, 444
failure to prepare directly, 432
in pyrimidine biosynthesis, 424
5-Carboxy-1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine, 391
4-Carboxy-2,6-dihydroxy-5-hydroxymethylpyrimidine, (as lactone), 244
4-Carboxy-2,6-dihydroxy-5-methylpyrimidine
formation *via* an hydantion, 104
4-Carboxy-2,6-dihydroxy-5-nitropyrimidine, 129, 141, 424
esterification, (394)
4-Carboxy-2,5-dihydroxypyrimidine
claim to be orotic acid, 423
4-Carboxy-2,6-dihydroxypyrimidine, 51, 89, 390, 391, 392, 406, 422*f*
alkylation, 370*f*
bromination, 424
chlorination, 171
esterification, (393)
history, 422
in biosynthesis of pyrimidines, 424
mechanism of synthesis, 104, 423
nitration, 424
oxidation, 422
reaction with formaldehyde, 244
reaction with phosphorus pentachloride, 424
reduction, 444
5-Carboxy-2,4-dihydroxypyrimidine, 235, 392, 411, 422
action of phosphoryl chloride *etc.* (165)
halogenation, 173
4-Carboxy-2,6-dimethoxypyrimidine, 391
5-Carboxy-2,4-dimethoxypyrimidine, 213, 393
2-Carboxy-4,6-dimethylpyrimidine, 127, 391
decarboxylation, 120, 127
4-Carboxy-2,6-dimethylpyrimidine, 391
6-Carboxy-3-ethyl-5-nitrouracil, 129
2-*β*-Carboxyethylpyrimidine, 126
esterification, 394
4-Carboxy-2-ethylthio-6-hydroxy-5-methylpyrimidine
amination, 291
5-Carboxy-2-ethylthio-4-hydroxypyrimidine
to acid chloride, (394)
5-Carboxy-2-ethylthiopyrimidine, 391
4-Carboxy-5-fluoro-2,6-dihydroxypyrimidine, 175
4-Carboxy-6-hydroxy-2-mercaptopyrimidine, 392
alkylations, 283
esterification, (393)
5-Carboxy-4-hydroxy-2-mercaptopyrimidine, 391
S-alkylation, (282)

4-Carboxy-6-hydroxy-5-methyl-2-methylaminopyrimidine, 291
4-Carboxy-6-hydroxy-5-methyl-2-phenylpyrimidine
  to acid chloride, 394
4-Carboxy-6-hydroxy-2-methylthiopyrimidine, 283, (392)
5-Carboxy-4-hydroxy-2-methylthiopyrimidine, 282
2-Carboxy-4-hydroxypyrimidine, 129
4-Carboxy-6-hydroxypyrimidine, 244, 391, 392
  bromination, (171)
5-Carboxy-4-hydroxypyrimidine, 187, 279
5-Carboxymethyl-4-chloro-2-ethylthio-6-methylpyrimidine,
  amination, 199
5-Carboxymethyl-4-chloro-2-ethylthiopyrimidine
  action of thiocyanate, (208)
1-Carboxymethyl-1,4-dihydro-2-mercapto-4,4,6-trimethylpyrimidine, 437
3-Carboxymethyl-5,6-dihydro-6-phenyluracil, (458)
4-Carboxymethyl-2,6-dihydroxypyrimidine, 51, 390
  oxidation to orotic acid, 423
5-Carboxy-4-methyl-2,6-diphenylpyrimidine
  decarboxylation, 120
5-Carboxymethylenehydantoin, 104, 423
  ring expansion, 104, 423
4-Carboxymethyl-2-ethoxy-6-hydroxypyrimidine, 391
2-α-Carboxy-α-methylethylthio-4-hydroxy-6-methylpyrimidine
  hydrolysis to 2,4-dihydroxy analogue, 234
5-Carboxymethyl-2-ethylthio-4-thiocyanatopyrimidine, 208
5-Carboxymethylhydantion, 423, 435
  dehydrogenation, 423
  in pyrimidine biosynthesis, 424
4-Carboxymethyl-2-hydroxy-6-methyl-5-nitropyrimidine, 209
4-Carboxy-6-methyl-2-phenylpyrimidine, 127
5-Carboxy-4-methyl-2-phenylpyrimidine, 392, 417
2-Carboxy-5-methylpyrimidine, 128
  esterification, (394)
4-Carboxy-5-methylpyrimidine, 127
  decarboxylation, 127
4-Carboxy-6-methylpyrimidine, 127
2-Carboxymethylthio-4,6-dihydroxypyrimidine, 283
2-Carboxymethylthio-4,6-dimethylpyrimidine, 283
2-Carboxymethylthio-5-ethoxypyrimidine, 284
2-Carboxymethylthio-4-hydroxy-6-propylpyrimidine, 283
2-Carboxymethylthio-4-methylpyrimidine, 283
2-Carboxymethylthio-4-piperidinopyrimidine
  amination, (289)
4-Carboxy-2-methylthiopyrimidine, 212
2-Carboxymethylthiopyrimidine, 283
  pyrimidine from, 117, 279
Carboxymethylthiopyrimidines
  formation and isolation, 283
  use in converting mercapto- into hydroxy-pyrimidines, 16, 233
S-Carboxymethylthiourea
  use in synthesis, 283
5-Carboxymethyl-2,4,6-trihydroxypyrimidine, 391
5-Carboxy-3-methyluracil, 231
  decarboxylation, (357), 393
6-Carboxy-1-methyluracil, 370
  methylation, 371
6-Carboxy-3-methyluracil, 47, 370
  decarboxylation, 370, 393
  methylation, 370
1-Carboxymethyluracil, 257
6-Carboxy-3-phenyl-2-thiouracil, 90, (273)
5-Carboxy-3-phenyluracil, 83, 235
6-Carboxy-3-phenyluracil
  decarboxylation, 393
2-Carboxypyrimidine, 128, 130
  U.V. spectrum (Fig.3), 480
4-Carboxypyrimidine, 126, 212, 279
  acid chloride formation, (394)
  decarboxylation, 116, 127
  esterification, (393)
  U.V. spectrum (Fig. 3), 480
5-Carboxypyrimidine, 105, 187
  esterification, (393)
  to acid chloride, 394
  U.V. spectrum (Fig.3), 480

Carboxypyrimidines, 389*f*
  acid chlorides from, 394*f*
  decarboxylation, 116, 393
  esterification, 393*f*
  formation by hydrolysis of derivatives, 390*f*
  formation by oxidation, 21, 391*f*
  formation by primary syntheses, 389*f*
  formation from trihalogeno-methyl derivatives, 216
  formation in other ways, 292*f*
  ionization, 466, 467
4-Carboxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 370*f*
5-Carboxy-2,4,6-triphenylpyrimidine, 391
  decarboxylation, 120
5-β-Carboxyvinyl-4-hydroxy-6-methyl-2-piperidinopyrimidine, 415
2-β-Carboxyvinylpyrimidine, 126
  reduction, 126
Carrington, 251, 284, 379
Cavallini, 432
Chargaff and Davidson, (book), 256
Chesney, 301
Chesterfield, 259
Chi, Yuoh-fong, 236
Chloral
  attack at 5-position, 409
  attack at primary amino group, 409
  reaction with methylpyrimidines, 126, 409
Chlorination
  by phosphorus pentachloride, 16, 165*f*
Chloroacetic acid
  use in converting mercapto- into hydroxy-pyrimidines, 233*f*
  use as *S*-alkylating agent, 283
4-Chloroamino-2-ethylsulphonyl-5-methylpyrimidine(?), 299, 343
Chloroaminopyrimidines, 343
4-*p*-Chloroanilino-5-ethyl-6-hydroxy-2-methylpyrimidine, 197
4-Chloro-2,6-bisdimethylaminopyrimidine, 193
4-Chloro-2,6-bismethylaminopyrimidine, (191)
1-Chloro-1-buten-3-one
  use, 94
4-Chlorocarbonylpyrimidine, (394)
  to the ester, (394)
5-Chlorocarbonylpyrimidine, (394)
  to amide, (394), 397
4-Chloro-5-chlorocarbonyl-2-ethylthiopyrimidine, 394
4-Chloro-6-chlorocarbonyl-5-methyl-2-phenylpyrimidine, 394
5-Chloro-4-chlorocarbonyl-2-methylpyrimidine, (394)
  to amide, (394)
2-Chloro-4-β-chloroethylamino-6-methoxycarbonyl-5-nitropyrimidine, 181, 194
5-Chloro-4-chloromethyl-2,6-dihydroxypyrimidine, 173, 181
4-Chloro-5-chloromethyl-2-methylpyrimidine, 178
2-Chloro-5-chlorosulphonylpyrimidine, 296
5-Chloro-2-chlorosulphonylpyrimidine 295
  amination, 297
N-β-Chlorocrotonoyl-*N*′-phenylurea
  use, 89
4-Chloro-5-cyano-2-dimethylaminopyrimidine, 164
2-Chloro-3-cyano-5,6-diphenylpyrazine
  use to make a pteridine, 109
4-Chloro-5-cyano-6-ethoxy-2-methylpyrimidine, 203
4-Chloro-5-cyano-2-ethylthiopyrimidine
  reduction, (316)
4-Chloro-5-cyano-6-methoxy-2-methylpyrimidine, 203
4-Chloro-5-cyano-6-methyl-2-piperidinopyrimidine, 404
4-Chloro-2-cyano-6-methylpyrimidine, 400
5-Chloro-4-cyano-2-methylpyrimidine, 400
2-Chloro-4-diethoxycarbonylmethyl-6-methyl-5-nitropyrimidine, 209
4-Chloro-6-diethoxycarbonylmethyl-2-methyl-5-nitropyrimidine, 209
  hydrolysis *etc.*, 209
4-Chloro-2,6-diethoxypyrimidine, 202
  amination, 197
  dechlorination, 185
2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine

  action of thiophenols, 205
4-Chloro-3,6-dihydro-2,3-dimethyl-6-phenyliminopyrimidine, (379)
  amination and rearrangement, 379
2-Chloro-1,4-dihydro-4-imino-1,6-dimethylpyrimidine, 378
  dechlorination, 184, (378)
4-Chloro-1,2-dihydro-2-imino-1,6-dimethylpyrimidine, 379
  hydrolysis, 374
4-Chloro-1,6-dihydro-6-imino-1,2-dimethylpyrimidine, 378
  dechlorination, 184
4-Chloro-3,6-dihydro-6-imino-2,3-dimethylpyrimidine, 378
  action of sodium methyl mercaptide, 205
  dechlorination, (378)
2-Chloro-1,4-dihydro-4-imino-1-methylpyrimidine, 378
  dechlorination, 378
4-Chloro-1,2-dihydro-1-methyl-2-oxopyrimidine, 370, 376
  amination, (198), 370
4-Chloro-1,6-dihydro-1-methyl-6-oxopyrimidine, 247, 369
  amination, 369
4-Chloro-3,6-dihydro-3-methyl-6-phenyliminopyrimidine, 312, 379
  amination, 312
5-Chloro-4,5-dihydro-2,4,6-trihydroxy-5-methylpyrimidine, 173
5-Chloro-4,5-dihydro-2,4,6-trihydroxy-5-nitropyrimidine, 173
4-Chloro-2,6-dihydroxypyrimidine
  amination, 197
5-Chloro-2,4-dihydroxypyrimidine, 170
  action of phosphoryl chloride, 164
  bromination, 173
5-Chloro-4,6-dihydroxypyrimidine, 169
  action of phosphoryl chloride, 164
4-Chloro-2,6-dimethoxy-5-methylpyrimidine, 202
4-Chloro-2,6-dimethoxypyrimidine, 202, 297
  bromination, 171
  chlorination by phosphorus pentachloride, 166
  dechlorination, 185
  isomerization, 373
  reaction with sodium bisulphide, (207)
5-Chloro-2,4-dimethoxypyrimidine, 203
β-Chloro-αβ-dimethylacrolein
  reaction with formamide, 93
4-Chloro-2-dimethylamino-6-methylaminopyrimidine, 193
2-Chloro-4-dimethylamino-6-methyl-5-nitropyrimidine, 194
4-Chloro-2-dimethylamino-6-methylpyrimidine
  dechlorination, 186
2-Chloro-4-dimethylamino-5-nitropyrimidine, 194
4-Chloro-2-dimethylamino-5-nitropyrimidine, 164
  action of alkoxide, (203)
  dechlorination and reduction, 186
4-Chloro-6-dimethylamino-5-nitropyrimidine, 195
2-Chloro-4-dimethylaminopyrimidine, 190
4-Chloro-2-dimethylaminopyrimidine
  dechlorination, 186
4-Chloro-6-dimethylaminopyrimidine 191
  action of alkoxide, (232)
  amination, 191
4-Chloro-6-*p*-dimethylaminostyrylpyrimidine, 164
4-Chloro-1,2-dimethyl-6-methylthiopyrimidinium iodide
  amination, 198
2-Chloro-4,6-dimethylpyrimidine, 163
  action of alkoxides, 201
  amination, 182, 188, (200)
  reaction with sodio benzyl methyl ketone, *etc.*, 209
  reaction with sodium cyanamide, 340
  reaction with trimethylamine, 345
  to mercapto analogue, 206
4-Chloro-2,6-dimethylpyrimidine
  amination, 188
  dechlorination, 121
  reaction with alkoxides, 201
  reaction with sodium bisulphite, 207, (295)
  to mercapto analogue, (206)
4-Chloro-5,6-dimethylpyrimidine
  amination, (188)
4-Chloro-2,6-diphenyl-5-propylpyrimidine

  reaction with phenyl-lithium, 120
2-Chloro-5-ethoxycarbonyl-1,6-dihydro-4-methyl-6-phenylpyrimidine, (458)
  action of sodium methoxide, (458)
  amination, (458)
4-Chloro-5-ethoxycarbonyl-2,6-dimethylpyrimidine
  amination, 199
4-Chloro-5-ethoxycarbonyl-2-ethylsulphinylpyrimidine, 166
4-Chloro-5-ethoxycarbonyl-2-ethylsulphonylpyrimidine, 166, 299
4-Chloro-5-ethoxycarbonyl-2-ethylthiopyrimidine
  amination, 199, 291
  dechlorination, 185
  oxidation by chlorine, 166, (299)
  reaction with cyanate and thiocyanate, 208, 418
2-Chloro-4-ethoxycarbonylmethylamino-5-nitropyrimidine, 194
4-Chloro-5-ethoxycarbonylmethyl-2-methylpyrimidine
  amination and amide formation, 396
4-Chloro-5-ethoxycarbonyl-2-methylpyrimidine
  hydrogenation, 451
5-Chloro-4-ethoxycarbonyl-2-methylpyrimidine, 394
2-Chloro-5-ethoxycarbonylpyrimidine, 166
4-Chloro-5-ethoxycarbonyl-2-trifluoromethylpyrimidine
  amination, 397
5-Chloro-4-ethoxy-4,5-dihydro-2,6-dihydroxy-5-methylpyrimidine, 177
4-Chloro-6-ethoxy-5-ethoxymethyl-2-methylpyrimidine, (214)
4-Chloro-5-ethoxy-2-ethylthiopyrimidine
  action of thiocyanate, (208), 338
  dechlorination, 185
4-Chloro-6-ethoxy-2-methylaminopyrimidine, 197
4-Chloro-6-ethoxy-2-methyl-5-nitropyrimidine, 202
2-Chloro-4-ethoxy-6-methylpyrimidine
  amination, (200)
4-Chloro-5-ethoxy-2-methylthiopyrimidine
  reaction with potassium bisulphide, 207
4-Chloro-6-ethoxy-5-nitropyrimidine, 202
2-Chloro-5-ethoxypyrimidine, 185
5-Chloro-1-ethylbarbituric acid, 176
4-Chloro-3-ethyl-3,6-dihydro-2-phenylpyrimidine, 439
4-Chloro-5-ethyl-2,6-dimethoxypyrimidine, 202
4-Chloro-5-ethyl-2,6-diphenylpyrimidine
  reaction with Grignard, 120
4-Chloro-5-ethyl-2-ethylsulphonyl-6-methylpyrimidine, 299
4-Chloro-5-ethyl-2-ethylthio-6-methylpyrimidine
  oxidation, (299)
4-Chloro-5-ethyl-2-ethylthiopyrimidine
  action of thiocyanate, (208)
4-Chloro-6-ethyl-2-ethylthiopyrimidine
  dechlorination, 185
4-Chloro-5-ethyl-6-hydroxy-2-methylpyrimidine, 204
  amination, 197
5-Chloroethyl-4-hydroxy-6-methylpyrimidine, 179
  hydrolysis, 215
2-Chloro-4-ethylpyrimidine
  amination, (188)
4-Chloro-6-ethylpyrimidine
  amination, (188)
4-Chloro-2-ethylsulphonyl-5,6-dimethylpyrimidine, 299
4-Chloro-2-ethylsulphonyl-5-methylpyrimidine, (236), 299
  amination, 199, 300
  hydrolysis, (236)
4-Chloro-2-ethylsulphonylpyrimidine, 299
  hydrolysis, 236
  oxidation, 236
4-Chloro-2-ethylthio-5,6-dimethylpyrimidine
  action of thiocyanate, (208)
  oxidation, (299)
4-Chloro-2-ethylthio-6-formylpyrimidine, 407
  amination, 199, 407
  to a hydrazone, (414)
5-Chloro-2-ethylthio-4-hydroxy-6-methylpyrimidine, 170
  to 2-mercapto analogue, 274
5-Chloro-2-ethylthio-4-hydroxypyrimidine

to 2-mercapto analogue, (274)
4-Chloro-2-ethylthio-5-iodopyrimidine
  amination, (199)
4-Chloro-2-ethylthio-5-methylpyrimidine
  action of sodium ethyl mercaptide, 205
  action of thiocyanate, (208)
  oxidation, (236), 299
4-Chloro-2-ethylthio-6-methylpyrimidine
  dechlorination, 185
  reaction with thiocyanate, (208)
  reaction with thiourea, (207)
4-Chloro-2-ethylthio-6-phenylhydrazonomethylpyrimidine, 414
4-Chloro-2-ethylthio-5-phenylpyrimidine
  action of thiocyanate, (208)
4-Chloro-2-ethylthio-6-phenylpyrimidine
  action of thiocyanate, (208)
  hydrolysis, 204
4-Chloro-2-ethylthiopyrimidine, (346)
  amination, 198, 290
  dechlorination, 185
  "nitration" to nitrouracil, 141
  oxidation to a sulphone, 236, 299
  reaction with bisulphite, (207)
  reaction with thiocyanate, 208, 338, 421
  to 2-hydroxy analogue, (236)
1-Chloro-2-formylcyclopentene
  use, 93, 95
4-Chloro-6-furfurylamino-5-nitropyrimidine
  reduction, 144
1-Chloro-1-hexen-3-one
  use, 94
2-Chloro-4-hydrazino-5-methoxypyrimidine, 200
4-Chloro-6-hydrazinopyrimidine, 200
5-Chloro-4-hydrazinopyrimidine, 200
4-Chloro-6-hydroxy-2,5-dimethylpyrimidine, (204)
2-Chloro-4-β-hydroxyethylamino-6-methyl-5-nitropyrimidine, 245
2-Chloro-4-β-hydroxyethylamino-5-nitropyrimidine
  amination, (195)
4-Chloro-5-(2-hydroxyisobutyl)-2-methylpyrimidine
  to 5-bromoisobutyl analogue, (178)
5-Chloro-4-hydroxy-2-isopropylthio-6-methylpyrimidine, 170
5-Chloro-4-hydroxy-2-mercapto-6-methylpyrimidine, 274
5-Chloro-4-hydroxy-2-mercaptopyrimidine, 274
5-Chloro-4-hydroxy-6-methyl-2-methylthiopyrimidine, 44, 177
  to 2-mercapto analogue, (274)
2-Chloro-4-hydroxy-6-methylpyrimidine, 204
4-Chloro-2-hydroxy-5-methylpyrimidine, (236)
4-Chloro-6-hydroxy-2-methylpyrimidine, 204, 228
  action of sodium bisulphide, (207)
  amination, 197
5-Chloro-4-hydroxy-2-methylthiopyrimidine, 40, 170
  to 2-mercapto analogue, 274
4-Chloro-6-hydroxy-2-phenylpyrimidine, (204)
4-Chloro-2-hydroxypyrimidine, (236)
  dechlorination, 185
4-Chloro-6-hydroxypyrimidine, 204
  action of sodium bisulphide, (207)
  methylation, 247, 369
5-Chloro-2-hydroxypyrimidine, 229, 333
  action of phosphoryl chloride, 164
5-Chloro-4-hydroxypyrimidine, 169
2(4)-Chloro-4(2)-iodo-6-methylpyrimidine, 168
2-Chloro-4-isothiocyanatopyrimidine, 341, 421
  action of amines, 341
Chloromalondialdehyde
  use in syntheses, 33, 139, 174
2-Chloro-4-mercapto-6-methyl-5-nitropyrimidine, 206
5-Chloro-2-mercaptopyrimidine, 207
5-Chloro-4-mercaptopyrimidine, 207
2-Chloro-3-methoxycarbonyl-5,6-diphenylpyrazine, 109
2-Chloro-3-methoxycarbonylpyrazine
  use in making pteridines, 109
4-Chloro-6-methoxy-5-methoxymethyl-2-methylpyrimidine, 202, 214
2-Chloro-4-methoxy-6-methylpyrimidine, 164, 167, (384)
  action of sodium methoxide, (384)
  amination, (200)
4-Chloro-5-methoxy-2-methylthiopyrimidine, 200
2-Chloro-4-methoxypyrimidine, 167, 201

  amination, 200
  dechlorination, 248
2-Chloro-5-methoxypyrimidine
  amination, 200
4-Chloro-5-methoxypyrimidine
  amination, (200)
4-Chloro-6-methoxypyrimidine, 201, 247, 369
2-Chloro-4-methylamino-5-nitropyrimidine, 194
  action of alkoxide, 203
  reaction with sodium bisulphide, 12, 206, 276
4-Chloro-6-methylamino-5-nitropyrimidine, 145, 195
4-Chloro-6-methylaminopyrimidine, 191
  to 4-methoxy analogue, 229, 232
3-Chloro-2-methyl-2-butenal
  use, 94
5-Chloromethyl-2,4-diethyl-6-hydroxypyrimidine, 232
4-Chloromethyl-2,6-dihydroxy-5-methylpyrimidine
  action of silver acetate, 253
5-Chloromethyl-2,4-dihydroxy-6-methylpyrimidine, 180
  action of silver acetate, 253
4-Chloromethyl-2,6-dihydroxy-5-phenoxypyrimidine, 179
  to mercaptomethyl analogue, 215
4-Chloromethyl-2,6-dihydroxypyrimidine
  hydrolysis, 214
5-Chloromethyl-2,4-dihydroxypyrimidine, 178, 214
  amination, 194
  reported direct preparation, 131, 177
  dehalogenation, 216
5-Chloromethyl-3,6-dimethyluracil
  displacement of 5-group by bromine, 171
1-Chloro-5-methyl-1-hexen-3-one
  use, 94
4-Chloromethyl-6-hydroxy-2-methylthiopyrimidine
  doubtful preparation, 177
5-Chloromethyl-4-hydroxy-2-methylthiopyrimidine
  hydrolysis, 214
Chloromethyl methyl ether
  reaction with 6-methyluracil, 180
4-Chloromethyl-6-methylpyrimidine, 384
2-Chloro-4-methyl-6-methylthio-5-nitropyrimidine, (206)
  hydrogenation, 143
4-Chloro-6-methyl-2-methylthiopyrimidine
  action of alkoxide, (203)
  amination, (200), 291
2-Chloro-4-methyl-6-nitroaminopyrimidine, 141, 341
4-Chloro-6-methyl-5-nitro-2-(2,2,2-trichloro-1-hydroxyethylamino)pyrimidine, (409)
4-Chloro-5-methyl-2-octylthiopyrimidine
  amination, 198
3-Chloro-2-methyl-3-phenylpropenal
  use, 95
2-Chloro-4-methyl-6-phenylpyrimidine
  dechlorination, 121
4-Chloro-6-methyl-2-phenylpyrimidine
  action of alkoxide, 248
  dechlorination, 121
4-Chloro-6-methyl-2-piperidinopyrimidine
  amination, 190
2-Chloro-4-methylpyrimidine, 163, 167, 183
  amination, 182, 200
  reaction with sodium alkoxide, 201
  reaction with sodium bisulphite, (207), (295)
  reaction with thiosemicarbazide, 341
  unsatisfactory dechlorination, 122
2-Chloro-5-methylpyrimidine
  amination, 188
4-Chloro-2-methylpyrimidine, 163
  amination, 182, 188
  dechlorination, 121
4-Chloro-5-methylpyrimidine, 121, 163, 237
4-Chloro-6-methylpyrimidine, 163
  action of hydriodic acid, 122
  amination, 182, 188, 200
  dechlorination, 121
  reaction with sodium alkoxides, 201
  reaction with sodium methyl mercaptide, 205
  to mercapto analogue, 206
4-Chloro-2-methylthiopyrimidine, 165
  dechlorination, 185
4-Chloro-6-methyl-2-(2,2,2-trichloro-1-hydroxyethylamino)pyrimidine, (409)

4-Chloro-6-morpholino-5-nitropyrimidine, 195
Chloromucic acid
  use in synthesis, 35
5-Chloro-2-*m*-nitrophenylpyrimidine, 139, 175
5-Chloro-2-*p*-nitrophenylpyrimidine, 33, 175
2-Chloro-5-nitropyrimidine, 163
  action of alkoxides, 202
  amination, 193
  reduction, 146
2-Chloro-5-nitro-4-thiocyanatopyrimidine, 208
  amination, 309, 420
  reaction with sodium alkoxide, 420
  reaction with thiourea, 275, 420
  reduction, 146
4-Chloro-3-octen-2-one
  use, 94
1-Chloro-1-penten-3-one
  use, 94
4-*p*-Chlorophenylazo-5,6-dihydroxypyrimidine, 154
  reduction, 154
p-Chlorophenylazomalononitrile
  use in syntheses, 72, 153
1-Chloro-1-phenyl-1-buten-3-one
  use, 94
5-*p*-Chlorophenyl-2-dichloromethyl-4-ethyl-6-hydroxypyrimidine, 46, 87, 407
  action of sodium ethoxide, 408
5-*p*-Chlorophenyl-2-diethoxymethyl-4-ethyl-6-hydroxypyrimidine, 408
2-*p*-Chlorophenyl-4-diethylaminoethylamino-6-methylpyrimidine, 255
5-*m*-Chlorophenyl-5-ethylbarbituric acid, 99
5-*p*-Chlorophenyl-4-ethyl-2,6-dimercaptopyrimidine, 275
  amination, 285
1-Chloro-1-phenyl-1-hexen-3-one
  use, 95
p-Chlorophenylhydrazones
  formation, 181
2-*p*-Chlorophenyl-4-methyl-6-phenoxypyrimidine
  amination, 255
1-Chloro-1-phenyl-1-penten-3-one
  use, 95
2-(*p*-Chlorophenyl)propionylacetonitrile,
  use of enol ether in synthesis, 180
2-Chloro-4-phenylpyrimidine, 167, 183
  amination, (200)
  dechlorination, 121
2-Chloro-5-phenylpyrimidine
  amination, (200)
4-Chloro-2-phenylpyrimidine, 165
  amination, (188)
  dechlorination, 121
4-Chloro-5-phenylpyrimidine
  dechlorination, 121
  nuclear reduction, 450, 451
4-Chloro-6-phenylpyrimidine, 163
  dechlorination, 121
5-Chloro-2-phenylpyrimidine, 33, 175
  dechlorination, 121, 211
2-*p*-Chlorophenylthio-4-β-diethylaminoethylamino-6-methylpyrimidine, 205
2-*p*-Chlorophenylthio-4-hydroxypyrimidine
  abnormal formation, 154
2-Chloro-4-phenylthioureidopyrimidine, 341
4-Chloro-6-piperidinopyrimidine, 191
4-β-Chloropropyl-2,6-diethoxypyrimidine, 178
5-β-Chloropropyl-2,4-dihydroxy-6-methylpyrimidine, 181
2-Chloro-4-2′-pyridylamino-5-nitropyrimidine, 194
2-Chloropyrimidine, 162, 165, 167, 183, 199*f*, 321, 333
  amination, 182, 188, 193
  dechlorination, 116, 451
  nuclear reduction, 451
  pyrimidine from, 116
  reaction with alkoxides, 201*f*
  reaction with sodium bisulphite, (207), 274, 295
  to mercapto analogue, 205, 206
4-Chloropyrimidine, 162
  instability, 188
  reaction of alkoxides, 201*f*
  to mercapto analogue, 206
5-Chloropyrimidine, 184
  lack of known reactions, 210
Chloropyrimidines
  action of hydrogen iodide, 122, 168, 204
  dechlorination, 116*f*
  from amino pyrimidines, 18, 167

  from hydroxypyrimidines, 16, 162*f*
  from mercaptopyrimidines, 166
  kinetics of amination, 182
  melting points, 182
  reaction with trialkylamines, 345
Chloro substituents
  effect on basic pK_a, 469
N-Chlorosuccinimide
  use in 5-chlorination, 170, 177
5-Chloro-2-sulphamoylpyrimidine, (295), 297
5-Chlorosulphonyl-2,4-dihydroxypyrimidine, 296
  amination, 297
  formation of corresponding ester, 297
  reduction, 277, 292
  removal of 5-group, 297
  to sulpho analogue, 296
2-Chlorosulphonyl-4,6-dimethylpyrimidine, 167, 295
  amination, (298)
  loss of sulphur dioxide, 167
2-Chlorosulphonylpyrimidine, 295
  amination, (297)
4-Chloro-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 165, 373
  action of alkoxide, (203)
  amination, (198), 200, 344
5-Chloro-1,2,3,4-tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine, 176
5-Chloro-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine, 171
4-Chloro-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxopyrimidine, 165
  action of alkoxide, (203)
  amination, (198), (200)
2-Chloro-4-thiocyanatopyrimidine, 208
  action of chlorine, 421
  action of thioacetic acid, (420)
  to 4-isothiocyanato isomer, 341, 421
2-Chloro-4-thioureidopyrimidine, 341
5-Chloro-2,4,6-trihydroxypyrimidine, 172
  chlorination, 172
5-α-Chlorovinyl-4-methyl-2-phenylpyrimidine, 124, 181
  dehydrochlorination, 124
Christensen, 451
Cinnamic acid
  use in synthesis of hydropyrimidines, 431
Claisen reaction, 26, 129, 131*f*
Clawson, 301
Clements, 259
Cline, 243
Coghill, 347
Cohen, 347
Colman, 1, 116, 210
Common Synthesis
  see: "Principal Synthesis"
Conrad and Guthzeit, 52
Convicine, 6, 260
Copper
  catalytic effect in aminations, 211
Crotonic acid
  use in synthesis of hydropyrimidines, 431
Curd, 379
Curtius reaction, 317, 336, 401
Cyanmethine, 6
Cyanacetal, 59
Cyanatopyrimidines
  as unknown, 418
Cyanoacetaldehyde acetal
  use in synthesis, 59
Cyanoacetamide
  in Whitehead Syntheses, 64
Cyanoacetic acid
  use in Principal Syntheses, 68*f*
  use in Shaw Syntheses, 88
  use in Whitehead Syntheses, 390
Cyanoacetone
  equivalent for use in synthesis, 65
Cyanoacetyldithiourethane
  intermediate in Shaw Syntheses, 88
Cyanoacetylguanidine
  formation and cyclization, 71
N-Cyanoacetyl-*N*-methylurethane
  intermediate in Shaw Syntheses, 88
Cyanoacetylurea
  intermediate formation in synthesis, 68
2-Cyanoamino-5,5-diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine, 59
2-Cyanoamino-4,6-dihydroxypyrimidine, 55
2-Cyanoamino-4,6-dimethylpyrimidine, 37, 340, 343, 377
  hydrolysis, 340
2-Cyanoamino-4-hydroxy-5-methylpyrimidine, 41, 343
  hydrolysis, (340)
2-Cyanoamino-4-hydroxy-6-methylpyrimidine, 45, 343

2-Cyanoamino-4-hydroxy-6-phenylpyrimidine, 343
2-Cyanoamino-4-methylpyrimidine, 34
Cyanoaminopyrimidines, 343
  hydrolysis to ureidopyrimidines, 340
2-α-Cyanobenzyl-4,6-dimethylpyrimidine, 209
5-Cyano-3-cyclohexyluracil, 231
4-Cyano-3-cyanomethyl-5-ethoxymethyl eneamino-1-methylpyrazole
  reaction with ammonia, 110
5-Cyano-4,6-diethoxy-2-methylpyrimidine, 203
1-Cyano-1,2-dihydro-2-imino-4,6-dimethylpyrimidine, 37, 340, 343, 377
4-Cyano-2,6-dimethoxypyrimidine
  hydrolysis, (391)
  isomerization, 372
  to amide, (398)
  to thioamide, (399)
5-Cyano-2-dimethylamino-4-hydroxypyrimidine
  action of phosphoryl chloride, 164
2-Cyano-4,6-dimethylpyrimidine, 18, 404
  hydrolysis, 391
  to amide, 398
  to ketone, 417
  to thioamide, 399
4-Cyano-2,6-dimethylpyrimidine, 297, 384
  action of alkoxide, 248
  alcoholysis, 396
  hydrolysis, (391)
  to amide, (398), (399)
  to thioamide, (399)
2-Cyano-4-ethoxy-6-methylpyrimidine, 383
  to amide, (399)
α-Cyano-β-ethoxypropionaldehyde
  use in synthesis, 440
N-β-Cyanoethyl-*N*′-ethylurea, 436
  attempted cyclization, 84, 436
N-β-Cyanoethyl-*N*′-methylthiourea
  attempted cyclization, 84
5-Cyano-2-ethylthio-4-hydroxypyrimidine, 61
5-Cyano-2-ethylthio-4-oxo-1,3-thiazine
  as intermediate in Shaw Syntheses, 88
  reaction with amines, 89
Cyanoguanidine
  see: "Dicyandiamide"
5-Cyano-1-β-hydroxyethyluracil, 88
5-Cyano-4-hydroxy-2-mercaptopyrimidine, 61, 403
5-Cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine, 404, 413
  action of phosphoryl chloride, 404
  to amide, (399)
5-Cyano-4-hydroxy-2-methylpyrimidine, 61, 403
5-Cyano-4-hydroxy-2-phenylpyrimidine, 86
Cyanomethanol
  trimerisation, 95
2-Cyano-4-methoxy-6-methylpyrimidine, 19, 384
  action of alkoxide, 248
  to amide, (399)
α-Cyano-β-methoxy-β-methylstyrene
  use in synthesis, 65
2-Cyano-4-methoxypyrimidine, 384
  action of alkoxide, 248
5-Cyanomethyl-4-hydroxy-2-methylpyrimidine, 41, 403
5-Cyano-2-methyl-4-methylaminopyrimidine
  reduction in presence acetic anydride, 325
2-Cyano-4-methyl-6-phenoxypyrimidine, 383
2-Cyano-4-methylpyrimidine, 297, 384
5-Cyano-1-methyl-2-thiouracil, 89, 273
1-Cyano-1-nitro-2-(3-ethylureido)-ethylene
  cyclization, 380
5-Cyano-1-phenyl-3-methyluracil, 87, 88
2-Cyanopyrimidine, 297, 400, 404
  to amidine *via* imino ether, 406
  to phenylamidine, 406
Cyanopyrimidines, 15, 401*f*
  by direct introduction, 405
  by primary syntheses, 401*f*
  from aldoximes, 404
  from an aminopyrimidine, 404
  from carbamoylpyrimidines, 400
  from 5-halogenopyrimidines, 212, 404
  from quaternary aminopyrimidines, 404
  from reduction, 316
  from sulphopyrimidines, 207, 404

  to alkoxypyrimidines, 248
  to amidines, 405f
  to carbamoyl- and carboxy-pyrimidines, 391, 398f
  to formylpyrimidines, 410f
  to ketones (by Grignard), 417
  to thiocarbamoylpyrimidines, 399
4-Cyano-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 372
  to amide, (398)
5-Cyano-2,4,6-trihydroxypyrimidine, (405)
Cyclobarbitone, 53
5-Cyclohex-1′-enyl-1,5-dimethylbarbituric acid, 53
5-Cyclohex-1′-enyl-5-ethylbarbituric acid, 53
5-Cyclohexylamino-2,4-dihydroxypyrimidine, 210
4-Cyclohexyl-5-ethoxycarbonyl-1,4,5,6-tetrahydro-2-hydroxy-6-methylpyrimidine, 450
1-Cyclohexyl-5-ethylamino-1,2,3,6-tetrapydro-3,4-dimethyl-2,6-dioxopyrimidine, 315
  alkylation, 315
1-Cyclohexyl-5-ethylmethylamino-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxopyrimidine, 315
1-Cyclohexyl-3-ethyl-1,2,3,6-tetrahydro-4-methyl-2,6-dioxopyrimidine, (361)
3-Cyclohexyl-6-methyluracil
  alkylation, 361
5-Cyclohexyloxy-4,6-dihydroxypyrimidine, 56
1-Cyclohexyl-1,2,3,6-tetrahydro-3,4-dimethyl-2,6-dioxopyrimidine, (361)
N-Cyclohexylurea
  failure to condense with ethyl cyanoacetate, 69
  use in synthesis, 51
O-Cyclohexylurea
  use in synthesis, 56
Cyclopropyl ethoxycarbonylmethyl ketone, 46
4-Cyclopropyl-6-hydroxy-2-mercaptopyrimidine, 46
Cytidine, 6
  halogenation, 170
  phosphates, 346, 425
Cytidylic acids a and b, 346
  hydrolysis, 346
Cytosine, 6, 346f
  halogenation of derivatives, 172
  see also: "4-Amino-2-hydroxypyrimidine"
  syntheses of derivatives, 62f
Cytosine deoxyriboside, 346
Cytosine deoxyriboside-5′-phosphate, 346
  hydrolysis, 346

D

"Daraprim", 2, 180
Davidson
  see: "Chargaff"
Davidson-Baudisch Synthesis, 38f
Davoll, 259
Dehalogenation, 23, 183f
  by hydrazine and palladium, 185, 212
  via mercapto derivatives, 187
  via other indirect routes, 187
Dehydroxylation
  example, 122
Delépine, 410
"Delvinal", 54
Deoxycytidine, 6
  halogenation, 170
Deoxy-5-methylcytidylic acid, 347
Deoxynucleotides, 346
Deoxyribonucleic acids, 346
  hydrolysis, 258, 346
Deoxyuridine, 6
  action of formaldehyde, 244
Desulphurization
  formation of dihydropyrimidines during, 443
  of mercapto- and methylthio-pyrimidines, 23, 120, 277f
  oxidative, 281
Diabetogenesis
  by alloxan, 262
2,4-Diacetamido-2-methylpentane, 457
4,6-Diacetamido-2-methylpyrimidine, 100
1,3-Diacetamidopropane
  cyclization, 445
Diacetonamine, 448
  reaction with aldehydes or ketones, 448
  reaction with ammonia and acetone, 448

  use in hydropyrimidine syntheses, 436
4-Diacetylamino-1,6-dihydro-1,5-dimethyl-2-methylthio-6-oxopyrimidine
  desulphurization, 279
4-Diacetylamino-1,6-dihydro-1,5-dimethyl-6-oxopyrimidine, 279, 325
4-Diacetylamino-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxopyrimidine, 325
  partial hydrolysis, 325
5-Diacetylamino-1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine, 325
β-Dialdehydes
  use in Principal Synthesis, 32*f*
5,5-Dialkyl-2-thiobarbituric acids
  desulphurization, 23
NN'-Dialkylthioureas
  use in syntheses, 70
1,3-Diallyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine, 51
5,5-Diallylbarbituric acid, 54, 124
NN'-Diallylmalondiamidine
  syntheses from, 100
Dialuric acid, 6, 260
  oxidation, 21
2,4-Diamino-5-aminomethylpyrimidine, 316
  acylation, (327)
2,4-Diamino-5-azidocarbonylpyrimidine, 401
  to a purine, (401)
2,4-Diamino-5-benzamido-6-hydroxypyrimidine, 327
2,4-Diamino-5-benzyl-6-chloropyrimidine
  reaction with hydriodic acid, (168)
2,4-Diamino-5-benzyl-6-iodopyrimidine, 168
4,6-Diamino-2-benzyl-5-nitrosopyrimidine, 73
2,4-Diamino-5-bromo-6-hydroxypyrimidine, 71, 175
  amination, 211
  reaction with thiosalicylic acid, 213
  to iodo analogue, 176
2,4-Diamino-5-bromopyrimidine, (169)
4,6-Diamino-5-bromopyrimidine, (169)
4,5-Diamino-2-butyl-6-mercaptopyrimidine, 187
  desulphurization, 187, 279
4,5-Diamino-2-butylpyrimidine, 187, 279
  acylation, (326)
2,4-Diamino-5-carbamoylpyrimidine, 399
4,6-Diamino-2-carboxymethylthiopyrimidine, (234), 283
  hydrolysis, (234)
2,4-Diamino-5-*o*-carboxyphenylthio-6-hydroxypyrimidine, 213
4,6-Diamino-2-carboxypyrimidine, 100, 390
2,4-Diamino-6-chloro-5-*p*-chlorophenylazopyrimidine
  amination, 199
4,5-Diamino-2-chloro-6-ethylpyrimidine
  dechlorination, 185
4,6-Diamino-2-chloro-5-nitropyrimidine, 196
  reduction, 144
2,4-Diamino-5-*p*-chlorophenylazo-6-dimethylaminopyrimidine, 199
2,4-Diamino-5-*p*-chlorophenylazo-6-methylaminopyrimidine
  reduction, 156
4,6-Diamino-5-*p*-chlorophenylazo-2-methylpyrimidine, 153
2,4-Diamino-5-*p*-chlorophenylazo-6-morpholinopyrimidine, (199)
2,4-Diamino-5-*p*-chlorophenylazopyrimidine, 153, 181
2,4-Diamino-5-*p*-chlorophenyl-6-ethylpyrimidine ("Daraprim"), 180
  action of phosphorus pentasulphide, 276
  hydrolysis, 230
2,4-Diamino-6-chloropyrimidine, 164, 191
  amination, 191
  reaction with hydriodic acid, (168), 184
4,5-Diamino-2-chloropyrimidine, 186
2,4-Diamino-5-chlorosulphonyl-6-methylpyrimidine, 296
4,6-Diamino-5-cyanoacetamido-2-mercaptopyrimidine, 328
2,4-Diamino-5-cyanopyrimidine
  reduction, (316)
  to amide, (399)

Diaminocytosine, 6
4,5-Diamino-2,6-dichloropyrimidine, 143
4,6-Diamino-2,5-dichloropyrimidine, 165
4,6-Diamino-5-$\beta\beta$-diethoxyethyl-2-mercaptopyrimidine, 279
4,6-Diamino-5-$\beta\beta$-diethoxyethylpyrimidine, 279
4,5-Diamino-6-diethylamino-2-methylthiopyrimidine, 150
4,5-Diamino-2-diethylaminopyrimidine
  acylation, 326
2,4(4,6)-Diamino-5,5-diethyl-5,6(2,5)-dihydro-6(2)iminopyrimidine, 377
2,4-Diamino-5,5-diethyl-5,6-dihydro-6-oxopyrimidine, 71
  hydrolysis, 230
4,6-Diamino-5,5-diethyl-2,5-dihydro-2-oxopyrimidine, 73
  hydrolysis, 73
4,6-Diamino-5,5-diethyl-2,5-dihydro-2-thiopyrimidine, 73
2,4-Diamino-5,6-dihydro-5,6-diphenylpyrimidine
  failure to make, 433
4,5-Diamino-1,6-dihydro-1-methyl-2-methylthio-6-oxopyrimidine
  desulphurization, 280
2,4-Diamino-3,6-dihydro-3-methyl-6-oxopyrimidine, 71, 72
4,5-Diamino-1,2-dihydro-1-methyl-2-oxopyrimidine, 143
4,5-Diamino-1,6-dihydro-1-methyl-6-oxopyrimidine, 280, (365)
  reaction with glyoxal, 365
2,4-Diamino-5-(2,3-dihydroxypropyl)-6-hydroxypyrimidine, 242
2,4-Diamino-5,6-dihydroxypyrimidine (divicine), 152, 154, 240, 310
  history, 259
  monograph, 259/
  synthesis, 259
2,5-Diamino-4,6-dihydroxypyrimidine, 150
  as erroneous structure for divicine, 259
4,5-Diamino-2,6-dihydroxypyrimidine, 150, 152, 156, 157, 228, 308, 310, 313
  action of nitrous acid, 235
  as an erroneous structure of divicine, 259
  formation from uric acid, 106, 228
  reaction with ethyl chloroformate, (336)
  reaction with isocyanates, 339
Di(4-amino-2,6-dihydroxypyrimidin-5-yl) disulphide, 212, 292
Di(4-amino-2,6-dihydroxypyrimidin-5-yl) sulphide, 212, 293
4,5-Diamino-6-dimethylamino-2-methylthiopyrimidine, 150
4,5-Diamino-2-dimethylaminopyrimidine, 335
  acylation, (326)
4,6-Diamino-2-dimethylaminopyrimidine, 74
2,4-Diamino-5,6-dimethylpyrimidine, 189
2,5-Diamino-4,6-dimethylpyrimidine
  acylation, 324
  diazotization *etc.*, 175, 321, 333
Di(4-amino-2,6-dimethylpyrimidin-5-ylmethyl) disulphide, 294
  oxidation, 294
Di(4-amino-2,6-dimethylpyrimidin-5-ylmethyl) sulphide, 294
2,4-Diamino-6,7-diphenylpteridine, 109
  formation by Timmis' synthesis, 151
2,4-Diamino-5,6-diphenylpyrimidine
  spurious preparation, 65
1,2-Diamino-1,2-dipyrimidin-4-ylethane, 129
2,4-Diamino-5-ethoxycarbonylpyrimidine, 291, 300, 396
  to hydrazide, (397)
2,4-Diamino-5-ethoxy-6-hydroxypyrimidine, 246
2,5-Diamino-4-ethoxypyrimidine, 146
4,6-Diamino-5-ethyl-2-mercaptopyrimidine, 73
4,6-Diamino-2-ethyl-5-nitrosopyrimidine, 73
2,4-Diamino-6-ethylpyrimidine, 189
4,5-Diamino-6-ethylpyrimidine, (185)
  acylation, (326)
4,6-Diamino-2-ethylpyrimidine, 190
5,6-Diamino-1-ethyluracil
  action of ethyl chloroformate, (336)
2,4-Diamino-5-hydrazinocarbonylpyrimidine, 397
  to azide, (401)
2,4-Diamino-6-hydroxy-5-iodopyrimidine, 170, 176
4,5-Diamino-6-hydroxy-2-mercaptopyrimidine, 150

desulphurization, 278, 280
to 2,6-dihydroxy analogue, 235
2,4-Diamino-5-hydroxy-6-methylpyrimidine, 241
2,5-Diamino-4-hydroxy-6-methylpyrimidine, 142, 342
acylation, (327)
formation of an anil, 322
4,5-Diamino-6-hydroxy-2-methylpyrimidine, (150), (157)
2,4-Diamino-6-hydroxy-5-morpholinopyrimidine, (211)
2,4-Diamino-6-hydroxy-5-nitrosopyrimidine, 71, 149
electrolytic reduction, 150
hydrogenation, 150
hydrolysis, 230
2,4-Diamino-6-hydroxy-5-phenylazopyrimidine
reduction, 157
Di(2-amino-4-hydroxy-6-phenylpyrimidin-5-yl) disulphide, 292
2,4-Diamino-5-α-hydroxypropionamido-6-hydroxypyrimidine, 328
2,4-Diamino-5-hydroxypyrimidine, 241
2,4-Diamino-6-hydroxypyrimidine, 71
action of phosphoryl chloride, 164
acylation, (324)
iodination, (170)
2,5-Diamino-4-hydroxypyrimidine
hydrolysis of 5-amino group, 238
4,5-Diamino-2-hydroxypyrimidine, 105, 143, 144, 313
hydrolysis, 229
4,5-Diamino-6-hydroxypyrimidine, 150, 278, 280, 329
acylation, (324), (328)
4,6-Diamino-2-hydroxypyrimidine, 233, 234, (273), 297
chlorination by phosphorus pentachloride, 165
failure of Principal Synthesis, 73, 233
formation from malondiamidine, 100
2,4-Diamino-6-hydroxy-5-tetrahydropyran-2′-yloxypyrimidine, 71, (240), 259
hydrolysis, (240), 259
2,4-Diamino-6-iodopyrimidine, 168
deiodination, 184
4,5-Diamino-2-mercapto-6-methylpyrimidine
desulphurization, 280
4,5-Diamino-6-mercapto-2-methylpyrimidine, 280
4,6-Diamino-2-mercapto-5-nitrosopyrimidine
reduction, 149
4,5-Diamino-2-mercaptopyrimidine, 105, 145, 187, 206, 288, 313
S-alkylation, 282
desulphurization, 187, 279
4,5-Diamino-6-mercaptopyrimidine, 145, 206
acylation, (326)
S-alkylation, 282
4,6-Diamino-2-mercaptopyrimidine, 73, 234, 273
S-alkylation, (283)
coupling and abnormal product, 154
desulphurization, 279
indirect hydrolysis, 234, 273
to sulphino analogue, (296)
4,6-Diamino-2-*p*-methoxyphenyl-5-nitrosopyrimidine, 73
4,5-Diamino-2-methyl-6-methylaminopyrimidine
acylation, (326)
2,5-Diamino-4-methyl-6-methylthiopyrimidine
diazotization *etc.*, 333, 404, 412
4,6-Diamino-2-methyl-5-*p*-nitrophenylazopyrimidine, 153
2,4-Diamino-6-methyl-5-nitropyrimidine, 140, 311
4,6-Diamino-2-methyl-5-nitropyrimidine, 195
4,6-Diamino-2-methyl-5-nitrosopyrimidine, 73, 148
reduction, 150
2,4-Diamino-2-methylpentane
use in hydropyrimidine synthesis, 446, 453
4,6-Diamino-2-methyl-5-phenylazopyrimidine, 72, 153
failure to prepare by coupling, 153
2,4-Diamino-6-methyl-5-phenylpyrimidine, 65
2,4-Diamino-6-methylpyrimidine, 134, 189, 285, 308
coupling of, 296
5-hydroxylation, 241
nitration, 140
reaction with thiocyanogen, 420
sulphonation, 296

- 2,5-Diamino-4-methylpyrimidine, 197
- 4,5-Diamino-2-methylpyrimidine, 280
- 4,5-Diamino-6-methylpyrimidine, 141, 186, 280
  - acylation, 326
  - condensation with benzil, 334
- 4,6-Diamino-2-methylpyrimidine, 100, 190, 307
  - acylation, (324)
  - coupling, 153
  - nitrosation, 148
- Di(4-amino-2-methylpyrimidin-5-ylmethyl) disulphide, 215, 293, 294
  - oxidation, 216
- Di(4-amino-2-methylpyrimidin-5-ylmethyl) sulphide, 215, (277), 293
- Di(2-amino-4-methylpyrimidin-6-yl) sulphide, 293
  - oxidation, 294, 299
- Di(2-amino-4-methylpyrimidin-6-yl) sulphone, 295, 299
- 4,5-Diamino-2-methylquinoline
  - condensation with a pyrimidine, 308
- 4,6-Diamino-2-methylsulphonylpyrimidine, 299
- 2,4-Diamino-6-methyl-5-*p*-sulphophenylazopyrimidine, 296
- 2,4-Diamino-6-methyl-5-sulphopyrimidine, 296
- 2,5-Diamino-7-methylthiazolo[4,5-d]pyrimidine, 420
- 2,4-Diamino-6-methyl-5-thioformamidopyrimidine, 326
- 4,6-Diamino-2-methyl-5-thioformamidopyrimidine, 326
- 4,6-Diamino-2-methylthio-5-nitrosopyrimidine, 73, 148
  - reduction, 150
- 4,5-Diamino-2-methylthiopyrimidine, 105, 282, 314
  - formylation, 315, (326)
- 4,5-Diamino-6-methylthiopyrimidine, 282
- 4,6-Diamino-2-methylthiopyrimidine, 198
  - acylation, (324)
  - hydrolysis, 233
  - nitrosation, 148
  - oxidation, (299)
- Di(4-amino-2-methylthiopyrimidin-5-ylmethyl) disulphide, 294
- 4,6-Diamino-2-methylthio-5-thioformamidopyrimidine, 326
- 5,6-Diamino-1-methyluracil, (366)
  - formation of a 5-anil, 322
  - reaction with phenyl isothiocyanate, 340
  - to a purine, (366)
- 5,6-Diamino-3-methyluracil, 329
- Di(6-amino-1-methyluracil-5-yl) disulphide, 292
- 4,5-Diamino-2-methyl-6-d-xylosidoaminopyrimidine
  - acylation, (326)
- 4,6-Diamino-5-*p*-nitrophenylazopyrimidine, 142
- 2,4-Diamino-5-nitropyrimidine, 195, 310, 420
  - hydrogenation, 144
  - reduction, 145, 335
- 4,6-Diamino-5-nitropyrimidine, 10, 140
  - hydrogenation, 144
- 4,6-Diamino-5-nitrosopyrimidine, 10, 148, 195
  - hydrogenation, 150
- 2,4-Diaminopentane
  - use in hydropyrimidine synthesis, 445
- 4,6-Diamino-5-phenylazopyrimidine, 72, 100, 153
  - reduction, 156
- 2,4-Diamino-5-phenylpyrimidine, 65
- 4,6-Diamino-2-phenylpyrimidine, 100
- 1,3-Diaminopropane
  - monoacylation, 445
  - reaction with aldehydes, 453
  - use in hydropyrimidine syntheses, 445, 446, 435
- 1,3-Diaminopropan-2-ol
  - condensation with *S*-methylthiourea, 447
- 2,4-Diaminopyrimidine, 12, 184, 189, 198, 255, 290, 309
  - bromination, 169
  - coupling, 153
  - failure to nitrate, 140
  - failure to nitrosate, 148
  - 5-hydroxylation, (241)
  - methylation, 379
- 2,5-Diaminopyrimidine, 329
- 4,5-Diaminopyrimidine, 186, 187, 279, 300
  - acylation, 326, (327), (328)

  cyanomethylation, 405
  hydrolysis to dihydroxypyrimidine, 238
  pteridines from, 107, 323, 334
  reaction with ethyl orthoformate, 327
  reaction with nitrous acid, 334
4,6-Diaminopyrimidine, 100, 190, 279, 297, 307
  acylation, 324
  bromination, 169
  failure of Principal Synthesis of, 72
  methylation, (378)
  nitration, 10, 140
  nitrosation, 10, 148
4,5-Diaminopyrimidines
  bicyclic heterocycles from, 333*f*
  darkening of free bases, 335
4,6-Diamino-2-sulphinopyrimidine, 296
  action of acid, 297
4,5-Diamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 150
  cyanomethylation, 405
  formation of 5-anil, 322
2,6-Diamino-8-thiapurine, 334
2,4-Diamino-5-thioformamidomethylpyrimidine, 327
4,6-Diamino-5-thioformamidopyrimidine, 326
Diaminouracil, 6
2,4-Dianilino-5,6-dimethylpyrimidine, 190
1,3-Dianilino-2-methylpropane
  use, 453
2,4-Dianilino-5-nitropyrimidine, 195
1,3-Dianilinopropane
  condensation with formaldehyde, *etc.*, 453
  condensation with phosgene, 446
2,4-Diazido-6-α-furylpyrimidine, 201
2,4-Diazido-6-methylpyrimidine, 201
2,4-Diazido-6-phenylpyrimidine, 201
2,4-Diazidopyrimidine, 201
"Diazinon", 254
4,6-Diaziridino-2-dimethylamino-5-nitropyrimidine, 196
2,4-Diaziridino-5-nitropyrimidine, 195
4,6-Diaziridino-5-nitropyrimidine, 196
Diazo coupling, 11
Diazoethane
  use of, 363
Diazotization of aminoyprimidines, 331*f*
Diazouracil, 332
  coupling, 332
1,3-Dibenzamidopropane
  reported cyclization, 445
1,3-Dibenzoyl-4-benzoylimino-1,2,3,4-tetrahydro-2-oxopyrimidine, 328
  hydrolysis, 328
1,3-Dibenzoylhexahydro-4,4,6-trimethylpyrimidine, (453), (456)
  cleavage (?), (453), (456)
Dibenzoylmethane
  use in syntheses, 36, 95
1,3-Dibenzylhexahydro-5-methyl-5-nitropyrimidine
  reduction, 454
1,3-Dibenzylhexahydro-2-phenylpyrimidine, 453
2,4-Dibenzyl-6-hydroxy-5-phenylpyrimidine, 229
5,5-Dibromobarbituric acid, 19, 172, 424
  action of pyridine, 214
  conversion into 5-bromobarbituric acid, 172, 213
  formation of a 2-naphthylhydrazone, 156
  reaction with thiourea, 292
  use to brominate aniline, *etc.*, 213
5,5-Dibromo-4,5-dihydro-2,4,6-trihydroxy-4-methylpyrimidine
  oxidation to dibromobarbituric acid, 172
5,5-Dibromo-4,5-dihydro-2,4,6-trihydroxypyrimidine, 19, 172, 174, 346, 442
  to bromouracil, 173
4,5-Dibromo-5-ethoxycarbonyl-1,4,5,6-tetrahydro-2-hydroxy-4-methyl-6-phenylpyrimidine (?), (457)
4,6-Dibromo-2-ethylpyrimidine, 167
  amination, 190
  hydrolysis, 204
5,5-Dibromohexahydro-1,3-dimethyl-2,4,6-trioxopyrimidine
  action of pyridine, 214
1,3-Dibromohexahydro-2,4-dioxopyrimidine, 457
5,5-Dibromohexahydro-4-hydroxy-1,3-dimethyl-2,6-dioxopyrimidine, 174
5,5-Dibromohexahydro-2,4,6-trioxo-1,3-diphenylpyrimidine

  formation of 5-phenylhydrazone, 156
2,4-Dibromo-6-methylpyrimidine
  amination, 190
4-Dibromomethylpyrimidine, 130
1,3-Dibromopropane
  action of benzamidine *etc.*, 449
3-(2,3-Dibromopropyl)-5,6-dimethyluracil, 181
3-(2,3-Dibromopropyl)-6-methyluracil, 181
4,5-Dibromo-2,3,4,5-tetrahydro-3-methyl-2-oxo-6-phenylpyrimidine (?), (457)
4,6-Dibutyl-2-dimethylaminopyrimidine, 20, 123
1,3-Dibutylhexahydro-2-thiopyrimidine, 447
2,3-Dicarbamoylpyrazine
  Hofmann reaction of, 108
2,3-Dicarbamoylpyridine
  use, 109
3,4-Dicarbamoylpyridine
  Hofmann Reaction with, 109
β-Dicarbonyl derivatives
  reaction with formamide, 92/
Dicarboxyacetone
  formation and use, 51, 390
3,5-Dicarboxydihydro-4-phenylpyridine, 441
4,6-Dicarboxy-2-phenylpyrimidine, 127
4,5-Dicarboxypyrimidine, 105, 127, 390
4,6-Dicarboxypyrimidine, 127, 216, 393
  decarboxylation, 116
Dichloroacetamidine
  use in Principal Syntheses, 46, 407
1,3-Dichloroacetone
  condensation with thiourea, 449
Dichloroacetyl chloride
  use, 87
Dichloroacetylurea, 172
5,5-Dichlorobarbituric acid, 151, 172
  action of pyridine, 214
  conversion into barbituric acid, 172
  conversion into 5-chlorobarbituric acid, 172
  formation of a naphthylhydrazone from, 156
2,4-Dichloro-5-chloromethyl-6-methylpyrimidine, 179
  to 5-iodomethyl analogue, 180
4,6-Dichloro-2-cyanomethylpyrimidine, 400
4,6-Dichloro-5-cyano-2-methylpyrimidine, 400
  amination, 199
  to 4-alkoxy analogue, 203
  to 4,6-dialkoxy analogue, 203
4,6-Dichloro-2-diethoxycarbonylmethyl-5-nitropyrimidine, 12
αα-Dichloro-γγ-diethoxypropane
  use in synthesis, 331
5,5-Dichloro-4,5-dihydro-2,4,6-trihydroxy-4-methylpyrimidine, 173
  action of hydrochloric acid, 173, 181
  oxidation, 172
5,5-Dichloro-4,5-dihydro-2,4,6-trihydroxypyrimidine, 172, 173, 174, (346)
1,1-Dichloro-3,3-dimethoxypropane
  use in synthesis, 33
4,5-Dichloro-2,6-dimethoxypyrimidine, 166, 297
4,6-Dichloro-2-dimethylamino-5-nitropyrimidine
  amination, 196
2,4-Dichloro-6-dimethylaminopyrimidine, 193
4,6-Dichloro-2-dimethylaminopyrimidine, 193
  amination, 193
2,4-Dichloro-5,6-dimethylpyrimidine
  action of hydriodic acid, 122
  amination, 189
4,6-Dichloro-2,5-dimethylpyrimidine
  bromination, 131, 167, 177,
  dechlorination, 121
  hydrolysis, (204)
αα-Dichlorodiphenylmethane
  reaction with barbituric acid, 123
2,4-Dichloro-5-ethoxycarbonylpyrimidine, 165, 166
  dechlorination, 187
2,4-Dichloro-5-ethoxypyrimidine
  dechlorination, 185
2,4-Dichloro-6-ethoxypyrimidine, 197, 202
2,4-Dichloro-5-ethyl-6-methoxypyrimidine, 202
4,6-Dichloro-5-ethyl-2-methylpyrimidine
  hydrolysis, 204
2,4-Dichloro-6-ethyl-5-nitropyrimidine

  amination, 194
2,4-Dichloro-6-ethylpyrimidine
  action of hydriodic acid, 122
2,4-Dichloro-6-α-furylpyrimidine
  amination, 189, (200)
2,4-Dichloro-6-guanidinopyrimidine, 344
1,3-Dichlorohexahydro-2,4-dioxopyrimidine, (457)
2,5-Dichloro-4-hydrazinopyrimidine, 200
1,3-Dichloro-2-hydroxypropane
  action of urea, 449
2,4-Dichloro-5-iodomethyl-6-methylpyrimidine, 180
2,4-Dichloro-6-methoxycarbonyl-5-nitropyrimidine
  amination, 181, 194
2,4-Dichloro-5-methoxypyrimidine, 200
  amination, (200)
2,4-Dichloro-6-methoxypyrimidine, 202
  amination, 197
  dechlorination, 185
2,4-Dichloro-6-methylaminopyrimidine, (191)
4,6-Dichloro-2-methylaminopyrimidine, (191)
2,4-Dichloro-6-methyl-5-nitropyrimidine, 163
  amination, 194, 244
  reaction with diethyl malonate, 209
  reaction with sodium bisulphide, 145, 206*f*
4,6-Dichloro-2-methyl-5-nitropyrimidine, 163
  action of alkoxides, 202
  amination, 195
  reaction with diethyl malonate, 209
2,4-Dichloro-6-methyl-5-propylpyrimidine, 202
2,4-Dichloro-5-methylpyrimidine, 259
  dechlorination, 121
2,4-Dichloro-6-methylpyrimidine, 163, 183
  action of alkoxides, (200)
  action of hydriodic acid, 122, 168
  amination, 189, (200)
  chlorination, 130
  dechlorination, 121, 183
  hydrolysis, 204
  to dimercapto analogue, 206
4,6-Dichloro-2-methylpyrimidine, 163
  amination, 190
  dechlorination, 120, 121
  hydrolysis, 204, 228
  reaction with Grignard, 120
4-Dichloromethylpyrimidine, 130
4,6-Dichloro-2-methylthiopyrimidine, 165
  amination, 198
4,6-Dichloro-5-nitro-2-phenylpyrimidine, 163
2,4-Dichloro-5-nitropyrimidine, 163
  amination, 8*f*, 138, 193*f*, 255
  reaction with alkoxides, 202, 232
  reaction with sodium bisulphide, 15, 145, 206
  reaction with thiocyanate, 208
  reaction with thiourea, 15, 206
  reduction, 144, 146
4,6-Dichloro-5-nitropyrimidine, 163
  action of alkoxides, 202*f*
  amination, 13, 183, 195, 255
  hydrogenation, 143
  reduction, 144, 146
  ususual reaction with diethyl malonate, *etc.*, 12, 209
2,4-Dichloro-5-phenylpyrimidine
  nuclear reduction, 450
2,4-Dichloro-6-phenylpyrimidine, 163
  dechlorination, 121, 183
  hydrolysis, 204
4,6-Dichloro-2-phenylpyrimidine
  hydrolysis, 204
4,6-Dichloro-2-propylpyrimidine
  nuclear reduction, 451
2,4-Dichloropyrimidine, 162, 166, 257, 284, 376
  action of alkoxides, 201
  action of hydriodic acid, 122, 205
  amination, 138, 188, 189, 200
  dechlorination, 183, 451
  nuclear reduction, 451
  pyrimidine from, 116
  reaction with benzenesulphonhydrazide, 187
  reaction with sodium methyl mercaptide, 205
  reaction with sodium hydrogen selenide, 207
  reaction with thiocyanate, 208
  to dimercapto analogue, 206
2,5-Dichloropyrimidine, 164, 167
  dechlorination, 184
  pyrimidine from, 116, 211
  reaction with orthanilamide, 330

reaction with thiourea, (207)
4,5-Dichloropyrimidine
  reaction with thiourea, (207)
4,6-Dichloropyrimidine, 163
  action of alkoxides, 201
  amination, 190*f*, 200
  dechlorination, 116, 451
  hydrolysis, 204
  nuclear reduction, 451
  to dimercapto analogue, 206
Di(4-chloropyrimidin-2-yl) disulphide, 164, 284, 292
2,4-Dichloro-6-trichloromethylpyrimidine, 131
Dicyandiamide
  use in Principal Synthesis 34-74, 340, 343
Dicyanoketene diethylacetal
  see: "Diethoxymethylenemalononitrile"
Di(2,4-dihydroxypyrimidin-5-yl) disulphide, 292, 332
  reduction, 295
Di(2,4-dimethoxypyrimidin-6-yl) disulphide, 292
  oxidation, 294
  reduction, 294
β-Diesters
  reaction with amidines, 52
  reaction with guanidines, 55*f*
  reaction with thioureas, 54*f*
  reaction with ureas, 52*f*
  use in Principal Syntheses, 51*f*
Diethoxycarbonylacetone
  use, 44, 395
NN'-Diethoxycarbonyldiethylmalondiamide
  as intermediate in barbiturate synthesis, 100
4,5-Diethoxycarbonyl-2-hydroxypyrimidine, 36
2,4-Diethoxy-6-α-(2,4-dinitrophenylhydrazono)ethylpyrimidine, 417
4,6-Diethoxy-5-ethoxymethyl-2-methylpyrimidine, (214)
2,4-Diethoxy-5-ethyl-6-methylpyrimidine, 247
2,4-Diethoxy-6-α-hydroxybenzylpyrimidine
  oxidation to ketone, 416
2,4-Diethoxy-6-α-hydroxyethylpyrimidine
  oxidation, 416
2,4-Diethoxy-6-β-hydroxypropylpyrimidine
  to 6-chloropropyl analogue, (178)
2,4-Diethoxy-6-methylaminopyrimidine, 197
4-Diethoxymethyl-2,6-dihydroxypyrimidine, 281
  methylation, 129
Diethoxymethylenemalononitrile
  use in Principal Synthesis, 66
4-Diethoxymethyl-2-ethylthio-6-hydroxypyrimidine, 282, (406)
  action of phosphoryl chloride, (406)
  to free aldehyde, (406)
4-Diethoxymethyl-6-hydroxy-2-mercapto-5-methylpyrimidine, (406)
4-Diethoxymethyl-6-hydroxy-2-mercaptopyrimidine, 406, 423
  S-alkylation, 282, (406)
  desulphurization, 280, (406)
  oxidation, (392), (406), 423
  to 2,6-dihydroxy analogue, 281
4-Diethoxymethyl-6-hydroxy-2-methylpyrimidine, 46
4-Diethoxymethyl-6-hydroxy-2-phenylpyrimidine, 407
  to free aldehyde, 407
4-Diethoxymethyl-6-hydroxypyrimidine, 280, 406
  to 4-formyl analogue, 406
2,4-Diethoxy-6-methyl-5-nitropyrimidine, 141
4,6-Diethoxy-2-methyl-5-nitropyrimidine, 202
2,4-Diethoxy-6-methyl-5-propylpyrimidine, 202
2,4-Diethoxy-5-methylpyrimidine, 247
  isomerization, 371
2,4-Diethoxy-6-methylpyrimidine
  nitration, 141
4-Diethoxymethyl-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 129
  oxime formation, 129
2,4-Diethoxy-5-nitropyrimidine, 14, 141, 202
  hydrogenation, 144
  partial hydrolysis, 203
  reduction, 146
2,4-Diethoxy-6-α-phenyhydrazonoethylpyrimidine, 418

3,3-Diethoxy-1-propyne
  use, 94
2,4-Diethoxypyrimidine, 185
  isomerization, 371
  nitration, 141
  partial hydrolyses, (203)
  reaction with bromotetra-acetylglucose, 372
  use in nucleoside syntheses, 372
2,4-Diethoxypyrimidin-6-yl-lithium, 393
  action of carbon dioxide, 393
2,4-Diethoxypyrimidin-6-yl magnesium bromide, (393)
  action of carbon dioxide, (393)
Diethyl α-allyl-α-1-ethylpropylmalonate, 53
2-β-Diethylaminoethylamino-4-hydroxy-5,6-dimethylpyrimidine, 290
2-β-Diethylaminoethylamino-4-methoxypyrimidine, 312
5-β-Diethylaminoethyl-4,6-dihydroxy-2-mercaptopyrimidine, 319
4-Diethylamino-2-ethylsulphonyl-5-methylpyrimidine, (236)
  hydrolysis, (236)
4-Diethylamino-2-ethylthio-5-methylpyrimidine
  oxidation, (236)
4-Diethylamino-2-ethylthiopyrimidine
  to 2-hydroxy analogue, (236)
4-Diethylamino-2-hydroxypyrimidine, 236
4-Diethylamino-2-mercaptopyrimidine
  failure to prepare, 285
5-Diethylamino-5-methylbarbituric acid, 213
Diethyl aminomethylenemalonate
  in primary syntheses, 83
5-Diethylaminomethyl-4-hydroxy-2-mercapto-6-methylpyrimidine
  structure doubt, 134
4-Diethylamino-2-hydroxy-5-methylpyrimidine, (236)
3-Diethylamino-2-methylpropenal
  use, 94
4-γ-Diethylaminopropylamino-2-sulphanilylaminopyrimidine, 255
N-γ-Diethylaminopropylthiourea
  use, 70
Diethyl amylethylmalonate
  use, 56
Diethylaniline
  use with phosphoryl chloride, 163*f*
5,5-Diethylbarbituric acid, 53, 56, 73, 99, 100, 230, 232, 363
  alkylation, 363
  reduction, 443
  thiation, 251
Diethyl benzylmalonate
  use, 56
Diethyl benzyloxymalonate
  use, 55, 56, 58, 240
Diethyl butylmalonate
  use, 56
Diethyl carbonate
  use in syntheses, 99, 446
OO-Diethyl chlorothiophosphate
  use, 254
Diethyl β-diethylaminoethylmalonate
  use in Principal Synthesis, 319
Diethyl diethylmalonate
  use, 55*f*, 59
5,5-Diethyl-2,5-dihydro-4,6-dihydroxy-2-phenylpyrimidine, 439
4,4-Diethyl-4,5-dihydro-2,6-dihydroxypyrimidine, 434
5,5-Diethyl-2,5-dihydro-4,6-dihydroxypyrimidine, 439, 443
  mechanism of formation, 439
5,5-Diethyl-4,5-dihydro-6-hydroxy-4-oxo-2-phenylpyrimidine, 52
5,5-Diethyl-4,5-dihydro-6-hydroxy-4-oxopyrimidine
  attempted formation, 439
Diethyl dimethylmalonate
  use, 57
Diethyl diphenylmalonate
  lability in use, 262
5,5-Diethyl-2,4-dithiobarbituric acid, 282
  amination, 284
Diethyl ethoxycarbonylacetylphosphonate, 46
Diethyl ethoxymalonate
  use, 57
Diethyl ethoxymethylenemalonate
  as equivalent of diethyl formylmalonate, 39
  use in syntheses, 39, 42, 179, 357, 395
Diethyl ethoxymethyleneoxalacetate
  use in synthesis, 395
Diethyl ethylidenemalonate
  use, 49, 52, 432
Diethyl ethylmalonate

  use, 55
Diethyl ethyl(1-methylbutyl)malonate
  use, 57
Diethyl ethylpropylmalonate
  use, 57
Diethyl fluoro-oxalacetate
  use, 44, 175
Diethyl formylmalonate
  in Principal Synthesis, 357
Diethyl isopropylmalonate
  use, 57
OO-Diethyl *O*-(2-isopropyl-4-methyl-6-pyrimidinyl)phosphorothioate, 254
Diethyl malonate
  condensation with chloro-pyrimidines, 208*f*
  use in Principal Syntheses, 51*f*
  use in Remfry-Hull Synthesis, 97*f*
Diethylmalondiamide
  failure to condense with formaldehyde, 439
  use in syntheses, 99, 273
  condensation with benzaldehyde, 439
  condensation with formic acid, 439
Diethylmalononitrile
  use in synthesis, 73, 377
Diethylmalonyl chloride
  use, 55, 58, 99
5,5-Diethyl-1-methylbarbituric acid, 57, 73, 363
Diethyl methylmalonate
  use, 57
2,4-Diethyl-5-methyl-6-phenylureidopyrimidine, (339)
5,5-Diethyl-6-methylthio-2,4-dithiouracil, 282
  hydrolysis, 282
2,4-Diethyl-5-methyl-6-ureidopyrimidine, 338
Diethyl nitrosomalonate
  use, 57, 58, 149
Diethyl oxalacetate
  use, 44, 47
Diethyl propylmalonate
  use, 56
1,3-Diethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidine, 361, 371
  bromination, 170
1,3-Diethyl-1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxopyrimidine
  nitration and nitrosation, 364
1,3-Diethyl-1,2,3,4-tetrahydro-6-hydroxy-5-nitro-2,4-dioxopyrimidine, 364
1,3-Diethyl-1,2,3,4-tetrahydro-6-hydroxy-5-nitroso-2,4-dioxopyrimidine, 364
  reduction, 150
1,3-Diethyl-1,2,3,4-tetrahydro-5-methyl-2,4-dioxopyrimidine, (361)
1,5-Diethyltetrahydro-2-methyl-4,6-dioxo-5-phenylpyrimidine, 98
2,2-Diethyl-1,2,5,6-tetrahydro-4,6,6-trimethylpyrimidine, 448
5,5-Diethyl-2-thiobarbituric acid, 57, 99, 273, 284
  action of sodium amalgam, 443
5,5-Diethyl-4-thiobarbituric acid, 276
NN'-Di(2-ethylthio-4-hydroxypyrimidin-5-ylmethyl)urea, 419
2,4-Diethylthiopyrimidine
  oxidation, (299)
5,5-Diethyl-"triaminobarbituric acid"
  hydrolysis, 230
Diethyl trimethylenemalonate
  use, 57
5,5-Diethyltrithiobarbituric acid, 251
  S-alkylation, 282
  amination, 284
NN'-Diethylurea
  use, 56
Diethyl ureidomethylenemalonate
  formation and use, 42
2,4-Diformyl-6-methylpyrimidine (as *p*-nitrophenylhydrazone), 411
Diguanide
  use in synthesis, 55, 344
5,5-Dihalogenopyrimidines
  formation: see individual compounds
  reactions, 213*f*
2,4-Dihydrazino-6-methylpyrimidine, 200, 291
2,4-Dihydrazinopyrimidine, 200
  action of nitrous acid, 201
4,5-Dihydro-2,6-dihydroxy-4,4-dimethylpyrimidine, 432
4,5-Dihydro-2,6-dihydroxy-4-isobutylpyrimidine
  ring cleavage, 459
4,5-Dihydro-2,6-dihydroxy-4-isopropylpyrimidine
  ring cleavage, 459
4,5-Dihydro-2,6-dihydroxy-5-methyl-4-phenylpyrimidine, 102

4,5-Dihydro-2,6-dihydroxy-4-methylpyrimidine, 431, 434, 438
4,5-Dihydro-2,6-dihydroxy-5-methylpyrimidine, 431
4,5-Dihydro-2,6-dihydroxy-4-phenylpyrimidine, 102, 431, 434
  alkylation, 458
4,5-Dihydro-2,6-dihydroxypyrimidine, 22, 102, 257, 431, 434, 438, 443, 444, 452,
  dehydrogenation, 455
  halogenation, 457
Dihydro-4,6-dihydroxypyrimidine, 278, 443
4,5-Dihydro-2,6-dihydroxy-4-styrylpyrimidine, 434
4,5-Dihydro-2,6-dihydroxy-5-thiocyanatopyrimidine (?), 457
1,2-Dihydro-4,6-dimethoxy-1-methyl-2-oxopyrimidine (?), 373
  hydrolysis, 373
1,2-Dihydro-1,5-dimethyl-4-methylthio-2-oxopyrimidine, 369
  hydrolysis, 369
1,2-Dihydro-1,6-dimethyl-4-methylthio-2-oxopyrimidine, 369
  hydrolysis, 369
1,4-Dihydro-1,6-dimethyl-2-methylthio-4-oxopyrimidine, 361
  hydrolysis, 361
1,6-Dihydro-1,4-dimethyl-2-methylthio-6-oxopyrimidine, 361, 368
  hydrolysis, 361, 368
1,4-Dihydro-1,2-dimethyl-6-methylthio-4-phenyliminopyrimidine, 199
1,4-Dihydro-1,6-dimethyl-2-methylthio-4-phenyliminopyrimidine, 379
1,4-Dihydro-1,2-dimethyl-4-oxopyrimidine, 360, 373
1,4-(3,4)-Dihydro-1,3-dimethyl-4-oxopyrimidine, 360
1,4-Dihydro-1,6-dimethyl-4-oxopyrimidine, (360), 373
1,6-Dihydro-1,2-dimethyl-6-oxopyrimidine, 360
  styrylation of 2-methyl group, 360
1,6-Dihydro-1,4-dimethyl-6-oxopyrimidine, 360
5,6-Dihydro-1,5-dimethyluracil, 435
  bromination and dehydrobromination, 455
1,6-Dihydro-2-hydrazino-1,4-dimethyl-6-oxopyrimidine, 291
4,5-Dihydro-6-hydroxy-2-mercapto-4-*p*-methoxyphenylpyrimidine, 434
4,5-Dihydro-6-hydroxy-2-mercapto-4-phenylpyrimidine, 434
1,6-Dihydro-2-hydroxy-6-methyl-4,6-diphenylpyrimidine, 442, (457)
4,5-Dihydro-6-hydroxy-4-oxo-2-phenyl-5,5-trimethylenepyrimidine, 52
3,4-Dihydro-3-hydroxy-4-oxopteridine, 108
5,6-Dihydro-7-hydroxypteridine, (390)
  ring cleavage, (390)
7,8-Dihydro-6-hydroxypteridine
  a pyrimidine from, 107
4,5-Dihydro-2-hydroxypyrimidine, 432
4,5-Dihydro-2-hydroxy-4,4,6-trimethylpyrimidine, 436
1,4-Dihydro-4-imino-1,2-dimethyl-6-methylthiopyrimidine, 198, 205
1,4-Dihydro-4-imino-1,6-dimethyl-2-methylthiopyrimidine, 378
  action of sodium bisulphide, 275
1,4-Dihydro-4-imino-1,2-dimethylpyrimidine, 378
  hydrolysis, (360), (373)
1,4-Dihydro-4-imino-1,6-dimethylpyrimidine, 185, 280, 378
  hydrolysis, (360), (373)
1,6-Dihydro-6-imino-1,2-dimethylpyrimidine hydriodide, 184
1,6-Dihydro-6-imino-1,4-dimethylpyrimidine
  hydrolysis, (360)
1,4-Dihydro-4-imino-2-methoxy-1-methylpyrimidine (?), 373
  thermal isomerization, 373
1,4-Dihydro-4-imino-1-methyl-5-phenylpyrimidine, 378
  hydrolysis, (374)
1,2-Dihydro-2-imino-1-methylpyrimidine, 24, 311, 377, 379
  rearrangement, 24, 311, 373, 377, 379
  rearrangement mechanism, (381)
  U.V. spectra (Fig.6), 481
1,4-Dihydro-4-imino-1-methylpyrimidine, 185, 312, 377
  hydrolysis, 24, 312, 373, 377
1,2-Dihydro-2-imino-1,4,6-trimethylpyrimidine
  failure to make directly, 377
5,6-Dihydro-1-isopropyluracil, 435

4,5-Dihydro-2-mercapto-4,6-diphenylpyrimidine, 433
1,6-Dihydro-2-mercapto-6-methyl-4,6-di-*p*-tolylpyrimidine
  S-acylation, 458
1,4-Dihydro-2-mercapto-4,4,6-trimethyl-1-phenylpyrimidine, 436, (437)
4,5-Dihydro-2-mercapto-4,4,6-trimethylpyrimidine, 432, 436, 437
1,4-Dihydro-2-mercapto-4,4,6-trimethyl-1-*p*-tolylpyrimidine, (436)
1,2-Dihydro-4-methoxy-1,6-dimethyl-2-oxopyrimidine, 372
  hydrolysis, 232, 372
1,2-Dihydro-4-methoxy-1-methyl-2-oxopyrimidine, 371
  aminations, 255
  hydrolysis, 371
  isomerization by heat, 371
5,6-Dihydro-6-*p*-methoxyphenyl-3-phenyl-2-thiouracil, 435
1,6-Dihydro-4-methyl-2,6-diphenylpyrimidine, 123
1,2-Dihydro-1-methyl-4-methylamino-5-nitro-2-oxopyrimidine, 368
  hydrolysis, 231, 368
1,2-Dihydro-1-methyl-4-methylamino-2-oxopyrimidine, 255
1,6-Dihydro-6-methyl-2-methylthio-4,6-diphenylpyrimidine, 457
  to 2-hydroxy analogue, 457
1,6-Dihydro-2-mercapto-6-methyl-4,6-diphenylpyrimidine, (442)
  S-methylation, 457
1,2-Dihydro-1-methyl-4-methylthio-2-oxopyrimidine, 369
  hydrolysis, 369
1,4-Dihydro-1-methyl-2-methylthio-4-oxopyrimidine, (368)
  desulphurization, 280, 288, 360, 368
  hydrolysis, 233, 360, (368)
1,6-Dihydro-1-methyl-2-methylthio-6-oxopyrimidine, 233, (368)
  desulphurization, 280, 359, 368
  hydrolysis, 359, (368)
  thiation, 252, 274
1,2-Dihydro-1-methyl-2-oxo-4-phenylpyrimidine, 84, 436
  reduction, 444
1,2-Dihydro-1-methyl-2-oxo-5-phenylpyrimidine, 360
  hydrogenation, 450
1,4-Dihydro-1-methyl-4-oxo-5-phenylpyrimidine, (360), 374
1,6-Dihydro-1-methyl-6-oxo-5-phenylpyrimidine, (360)
3,4-Dihydro-3-methyl-4-oxopteridine, 365
  preparation from a pyrazine, 108
1,2-Dihydro-1-methyl-2-oxopyrimidine, 19, 25, 32, 247, 357, 359, 371
  reduction, 278, 452
  resistance to thiation, 376
1,4-Dihydro-1-methyl-4-oxopyrimidine, 280, 288, 312, 356, 360, 368, 373, 377
  action of methyl iodide, 360
  thiation, 252, 376
  U.V. spectra (Figs. 4 and 5), 480
1,6-Dihydro-1-methyl-6-oxopyrimidine, 247, 280, 256, 359, 360, 368, 371
  action of methyl iodide, 360
  thiation, 252, 376
  U.V. spectra (Figs, 4 and 5), 480
1,6-Dihydro-1-methyl-6-oxo-2-styrylpyrimidine
  oxidation *etc.*, 359, 360
5,6-Dihydro-1-methyl-3-phenyluracil, 436
5,6-Dihydro-1-methyl-6-phenyluracil, 435
  alkylation, 458
5,6-Dihydro-3-methyl-6-phenyluracil, 458
  ring cleavage, 458
5,6-Dihydro-6-methyl-3-phenyluracil, 435
1,2-Dihydro-1-methyl-2-thiopyrimidine, 32, 381
  failure to make by thiation, 376
1,4-Dihydro-1-methyl-4-thiopyrimidine, 252, (376)
1,6-Dihydro-1-methyl-6-thiopyrimidine, 252, (376)
5,6-Dihydro-1-methyluracil, 83, 435, 444, 452
  bromination, 83
  oxidation to 1-methyluracil, 83, 361
5,6-Dihydro-3-methyluracil, 435
5,6-Dihydro-3-*β*-naphthyl-6-phenyluracil, 435
Dihydro-orotate dehydrogenase, 424
Dihydro-orotic acid
  in pyrimidine biosynthesis, 424

1,6-Dihydro-4-phenylpyrimidine, 445
5,6-Dihydro-1-phenyluracil, 432, 436f
5,6-Dihydro-3-phenyluracil, 434, 435
2,3-Dihydropyran
  action of ethyl glycollate, 240
Dihydropyrimidines, 431f
  by a modified Principal synthesis, 431f
  by Biginelli reaction, 440f
  by isocyanate and aminopropane derivative, 434f
  by isocyanatopropane derivative and amine, 436f
  by *O*-methylurea and aminopropane derivative, 438
  by reduction of pyrimidine, 442f
  by various syntheses, 442
  dehydrogenation by bromination/dehydrobromination, 455
  from amide intermediates, 438f
  reduction, 450f
4,5-Dihydro-2,4,5,6-tetrahydroxy-5-methylpyrimidine, 442
4,5-Dihydro-2,5,6-trihydroxy-4,4-dimethylpyrimidine, 432
4,5-Dihydro-2,4,6-trihydroxy-5-methyl-5-nitropyrimidine, 258
4,5-Dihydro-2,4,6-trihydroxypyrimidine, 257
  action of acid, 257
1,2-Dihydro-1,4,6-trimethyl-2-oxopyrimidine, 37, 357, (382)
4,5-Dihydro-4,4,6-trimethyl-2-phenylpyrimidine, 433
1,2-Dihydro-1,4,6-trimethyl-2-thiopyrimidine, 37, 381
  hydrolysis to oxo analogue, 382
4,5-Dihydro-2,4,6-triphenylpyrimidine
  formation and oxidation, 103, 433
Dihydrouridine, 443
3,4-Dihydroxybenzaldehyde
  use in making styryl compounds, 126
4,6-Dihydroxy-2-dimethylaminopyrimidine, 55
2,4-Dihydroxy-5,6-dimethylpyrimidine, 253, 254
2,5-Dihydroxy-4,6-dimethylpyrimidine, 21, 241
  acylation, 253
4,6-Dihydroxy-2,5-dipropylpyrimidine, 56
2,4-Dihydroxy-6-α-hydroxybenzylpyrimidine, 417
  oxidation, 417
2,4-Dihydroxy-5-β-hydroxyethyl-6-methylpyrimidine, 235
4,6-Dihydroxy-5-β-hydroxyethyl-2-methylpyrimidine, (242)
4,6-Dihydroxy-5-β-hydroxyethyl-2-phenylpyrimidine, (242)
4,6-Dihydroxy-5-β-hydroxyethylpyrimidine, 242
2,4-Dihydroxy-5-α-hydroxyiminoethylpyrimidine, 418
2,4-Dihydroxy-6-hydroxyiminomethyl-5-methylpyrimidine, 413
4,6-Dihydroxy-2-hydroxyiminomethyl-5-nitrosopyrimidine, 412
  as tautomer of a dinitroso derivative, 412
2,4-Dihydroxy-5-hydroxymethyl-6-methylpyrimidine, 46, 243
  reaction with phosphorus pentachloride, 179
  removal of extra-nuclear hydroxy group, 253
2,4-Dihydroxy-6-hydroxymethyl-5-methylpyrimidine, 215
  removal of extranuclear hydroxy group, 253
2,4-Dihydroxy-5-hydroxymethylpyrimidine, 12, 214, 242, 243
  action of hydrogen chloride, 248
  acylation, 253
  natural occurrence, 243
  oxidation, 392, 411
  removal of extranuclear hydroxy group, 254
  stability, 243
  to halogenomethyl analogues, (178)
2,4-Dihydroxy-6-hydroxymethylpyrimidine, 215, 244
  removal of extranuclear hydroxy group, 253
2,4-Dihydroxy-5-(2′-hydroxy-1′-naphthylazo)pyrimidine, 155
2,4-Dihydroxy-5-iodopyrimidine, (170), 257
  chlorination, 173
4,6-Dihydroxy-5-isoamyl-2-mercaptopyrimidine
  desulphurization, 280
4,6-Dihydroxy-5-isoamylpyrimidine, 280
2,4-Dihydroxy-5-isobutoxy-6-isobutoxymethylpyrimidine

hydrolysis, 239
2,4-Dihydroxy-5-isocyanatomethyl-6-methylpyrimidine, (419)
2,4-Dihydroxy-5-isocyanatomethylpyrimidine, 419
reactions, (419)
4,6-Dihydroxy-5-isopropyl-2-mercaptopyrimidine, 57
S-alkylation, (282)
4,6-Dihydroxy-5-isopropyl-2-methylthiopyrimidine, 282
2,4-Dihydroxy-6-mercaptomethyl-5-phenoxypyrimidine, 215
4,5-Dihydroxy-2-mercapto-6-methylpyrimidine, 239
4,6-Dihydroxy-2-mercapto-5-methylpyrimidine, 57
4,6-Dihydroxy-2-mercapto-5-nitrosopyrimidine, 57, 149
action of Raneynickel, 279
colour of salts, 147
4,6-Dihydroxy-2-mercapto-5-phenylpyrimidine
desulphurization, 278, 443
2,4-Dihydroxy-5-mercaptopyrimidine, 276, 277, 295, 332
anti-tumour activity, 277
oxidation, 292
4,6-Dihydroxy-2-mercaptopyrimidine, 54
S-alkylation, (283)
desulphurization, 278, 443
4,6-Dihydroxy-2-mercapto-5-tetrahydropyran-2′-yloxypyrimidine, (240)
hydrolysis, (240)
2,4-Dihydroxy-6-methoxycarbonyl-5-nitropyrimidine, 394
2,4-Dihydroxy-6-methoxycarbonylpyrimidine, 370, 393
2,4-Dihydroxy-5-methoxy-6-methoxymethylpyrimidine, 234
2,4-Dihydroxy-5-methoxymethylpyrimidine, 248
2,4-Dihydroxy-6-methylamino-5-nitrosopyrimidine
reduction, (150)
2,4-Dihydroxy-5-methylaminopyrimidine, 210, 314
2,4-Dihydroxy-6-methylaminopyrimidine, 197
4,6-Dihydroxy-2-methylaminopyrimidine, 55
4,6-Dihydroxy-5-methylaminopyrimidine, 98, 313
2,4-Dihydroxy-6-methyl-5-methylaminopyrimidine, 210
2,4-Dihydroxy-6-methyl-5-nitropyrimidine, 140
action of phosphoryl chloride *etc.*, 163
alkylation, 364
oxidation, 129
styrylation, 125
4,6-Dihydroxy-2-methyl-5-nitropyrimidine, 140
action of chloral, 409
action of phosphoryl chloride, 163
4,6-Dihydroxy-2-methyl-5-phenylazopyrimidine, 153
2,4-Dihydroxy-6-methyl-5-phenylhydrazonomethylpyrimidine, 414
2,4-Dihydroxy-5-methyl-6-phenyliminomethylpyrimidine, 414
4,6-Dihydroxy-2-methyl-5-piperidinomethylpyrimidine, 12, 133
4,5-Dihydroxy-6-methyl-2-piperidinopyrimidine, 241
2,4-Dihydroxy-6-methyl-5-propylpyrimidine
alkylation, 362
2,4-Dihydroxy-5-methylpyrimidine, 39, 216, 229, 234, 237, 254, 455
N-acylation, 252
alkylation, (361), 362
colour test, 257
coupling, 154
detection, 257
good synthesis, 258
halogenation, 173, 177, 258, 442
Mannich reaction, 134
monograph, 258*f*
oxidation, 259
preparation from natural sources, 258
reaction with nitric acid, 258
reaction with phosphoryl chloride, 258
2,4-Dihydroxy-6-methylpyrimidine, 50, 51, 229, 230, 233, 234, 253, 372, 455
action of formaldehyde, 243
action of phosphoryl chloride, 163
alkylation, 361
chlorination, 173
failure to styrylate, 125
ferricyanide oxidation, 400

  nitration, 140, 141
  nitration and oxidation, 141
  nuclear reduction, 450
  oxidation to orotic acid, 423
  reaction with chloromethyl ether, 180
  reaction with persulphate, 241
  reaction with thiocyanate, 419
  Reimer-Tiemann reaction, (410)
4,5-Dihydroxy-2-methylpyrimidine, 238, 240
4,6-Dihydroxy-2-methylpyrimidine
  action of phosphoryl chloride, *etc.*, 163
  coupling, 153
  dinitrosation, 148, 412
  Mannich reaction, 133
  nitration, 140
  reaction with persulphate, 241
  reaction with urea, 12, 399
4,6-Dihydroxy-2-methyl-5-tetrahydropyran-2′-yloxypyrimidine, (240)
  hydrolysis, (240)
2,4-Dihydroxy-6-methyl-5-thioacetamidopyrimidine, 324
2,4-Dihydroxy-6-methyl-5-thiocyanatopyrimidine, (419)
  to disulphide, (419)
4,6-Dihydroxy-2-methylthiopyrimidine
  action of phosphorus pentachloride, (165)
2,4-Dihydroxy-6-methyl-5-thioureidopyrimidine, 340
2,4-Dihydroxy-6-methyl-5-ureidopyrimidine, (339)
2,4-Dihydroxy-5-morpholinomethylpyrimidine, 134
4,6-Dihydroxy-5-nitro-2-phenylpyrimidine
  action of phosphoryl chloride, 163
2,4-Dihydroxy-5-nitropyrimidine, 139, 141, 257
  action of phosphoryl chloride *etc.*, 163
  alkylation, 363*f*
  attempted thiation, 251
  difficulty in hydrogenation, 144
  halogenation, 173
  isobarbituric acid from, 144, 238
  reduction, 144
  reduction with dithionite, 145*f*, 296, 343
4,6-Dihydroxy-5-nitropyrimidine, 10, 140
  action of phosphoryl chloride, 163
4,6-Dihydroxy-5-nitroso-2-nitrosomethylpyrimidine, 148, 412
  as tautomer of an oxime, 412
  reduction, 319, 413
4,6-Dihydroxy-5-nitrosopyrimidine, 10, 148
2,4-Dihydroxy-5-nitro-6-styrylpyrimidine, 125
4,6-Dihydroxy-5-nitro-2-(3,3,3-trichloro-2-hydroxypropyl)pyrimidine, 409
2,4-Dihydroxy-5-nitro-6-trifluoromethylpyrimidine, 141
2,4-Dihydroxy-5-phenoxy-6-phenoxymethylpyrimidine
  splitting 6-group, 179
2,4-Dihydroxy-5-phenoxysulphonylpyrimidine, 297
2,4-Dihydroxy-6-phenylpyrimidine, 204, 229, 455
  action of phosphoryl chloride, 163
  alkylation, 362
4,6-Dihydroxy-2-phenylpyrimidine
  Reimer-Tiemann reaction, (410)
4,6-Dihydroxy-5-phenylpyrimidine, 98, 278, 443
2,4-Dihydroxy-5-(*N*-phenylsulphamoyl)pyrimidine, 297
4,6-Dihydroxy-2-phenyl-5-tetrahydropyran-2′-yloxypyrimidine, (240)
  hydrolysis, (240)
2,4-Dihydroxy-5-piperidinomethylpyrimidine, 134
2,4-Dihydroxy-5-piperidinopyrimidine, 210
4,6-Dihydroxy-2-piperidinopyrimidine
  Reimer-Tiemann reaction, (410)
2,4-Dihydroxy-5-propionyloxymethylpyrimidine, 253
2,4-Dihydroxy-6-propylpyrimidine
  alkylation, 362
2,4-Dihydroxypteridine
  from a pyrazine, 108
6,7-Dihydroxypteridine
  methylation, 107, 308
2,8-Dihydroxypurine, 401
2,4-Dihydroxypyrido[2,3-d]pyrimidine, 109
2,4-Dihydroxypyrido[3,2-d]pyrimidine, 110
2,4-Dihydroxypyrido[3,4-d]pyrimidine, 109

2,4-Dihydroxypyrimidine, 39, 227, 229, 233, 234, 236, 257, 281, 297, 300, 333, 346, 431, 455
  action of phosphoryl chloride, 162, 163, 257, 284
  N-acylation, 252, 257, 357
  alkylation, 257, 360, 361, 368
  chlorosulphonation, 295
  detection, 257
  failure to nitrosate, 148
  halogenation, 19, 170, 172*f*, 257
  hydrogenation, 257
  isolation from nature, 257
  monograph, 256*f*
  nitration, 10, 139, 257
  oxidation, 257
  photohydration, 20, 257, 442
  reaction with formaldehyde, 11, 178
  reduction, 443, 444, 452
  thiation, 251, 274, 369
4,5-Dihydroxypyrimidine, 238, 239, 240
  coupling, 154
4,6-Dihydroxypyrimidine, 52, 97, 98, 227, 228
  abnormal acidic strength, 466
  action of phosphoryl chloride *etc.*, 163
  amination, 169
  chlorination with iodine monochloride, 167
  nitration, 10, 140
  nitrosation, 10, 148
  ring opening of, 211
  syntheses of derivatives, 97*f*
  unsatisfactory thiation, 252
2,4-Dihydroxypyrimidine-6-phosphonic acid, 46
Di(2-hydroxypyrimidin-4-yl) disulphide, 292
Di(4-hydroxypyrimidin-2-yl) disulphide, 292
  reduction, 294
2,4-Dihydroxyquinazoline, 102
2,4-Dihydroxy-6-ribitylaminopyrimidine, 197
2,4-Dihydroxy-5-sulphoamino-pyrimidine, 296
  a doubtful structure, 145, 343
2,4-Dihydroxy-5-sulphamoyl-pyrimidine, 297, 298
2,4-Dihydroxy-5-sulphopyrimidine, 296
4,6-Dihydroxy-5-tetrahydropyran-2′-yloxypyrimidine, 98, (240)
  hydrolysis, (240)
2,4-Dihydroxy-6-trifluoromethyl-pyrimidine, 46, 179
  nitration, 141
2,4-Dihydroxy-5,6-trimethylene-pyrimidine, 47, 83
2,4-Dihydroxy-5-ureidopyrimidine, 339
2,4-Di-iodo-6-methylpyrimidine, 168
NN′-Di-isopropylurea
  failure to condense with ethyl cyanoacetate, 69
Diketene
  use in Principal Syntheses, 51
  use in primary syntheses, 104
β-Diketones
  use in Principal Syntheses, 36*f*
Dilituric acid, 6
Dilthey, 53
2,4-Dimercapto-6-methyl-5-nitro-pyrimidine, 207
2,4-Dimercapto-5-methylpyrimidine, 251, 252, 274
  amination, 285
2,4-Dimercapto-6-methylpyrimidine, 46, 206, 251
  amination, 285
2,4-Dimercapto-5-nitropyrimidine, 15, 145, 206, 275, 420
  amination, 285, 309
  reduction, 145
2,4-Dimercapto-6-phenylpyrimidine, 251
2,4-Dimercaptopyrimidine, 206, 251, 274 346
  S-alkylation, (284)
  amination, 285, 289, 309, 346
  pyrimidine from, 117, 279
4,6-Dimercaptopyrimidine, 206, 273
1,1-Dimethoxy-3-butanone
  use, 94
2,4-Dimethoxy-6-mercaptopyrimidine, 207
4,6-Dimethoxy-5-methoxymethyl-2-methylpyrimidine, 202, 214
2,4-Dimethoxy-6-methylamino-pyrimidine
  bromination, 171
2,4-Dimethoxy-6-methyl-5-propylpyrimidine, 202
  isomerization, 372
2,4-Dimethoxy-5-methylpyrimidine, 247
  isomerization, 371
2,4-Dimethoxy-6-methylpyrimidine, 202, 248, 384

formation of *N*-oxide, 382
isomerization, 372
2,4-Dimethoxy-6-methylpyrimidine-*N*-oxide, 382
2,4-Dimethoxy-6-methylsulphonylpyrimidine, 299
2,4-Dimethoxy-6-methylthiopyrimidine
oxidation, (299)
2,4-Dimethoxy-5-nitropyrimidine, 202
reduction, 146
4,6-Dimethoxy-5-nitropyrimidine, 202
2,4-Dimethoxypyrimidine, 185, 248
isomerization, 371
2,4-Dimethoxypyrimidin-5-yl-lithium, (393)
action of carbon dioxide, (393)
2,4-Dimethoxypyrimidin-6-yltrimethylammonium chloride
reaction with sulphanilamide, 331
2,4-Dimethoxy-6-sulphamoylpyrimidine, 298
hydrolysis, 298
2,4-Dimethoxy-6-sulphopyrimidine, 294
action of phosphorus pentachloride, 166, 297
hydrolysis, 297
2,4-Dimethoxy-6-thiocarbamoylpyrimidine, 399
Dimethylamine acetate (salt)
use in gentle amination, 194, 195
p-Dimethylaminobenzaldehyde
use in making styrylpyrimidines, 125
1-Dimethylamino-1-buten-3-one
use, 94
4-Dimethylamino-1,2-dihydro-1-methyl-2-oxopyrimidine, 255
2-Dimethylamino-4,5-dihydroxypyrimidine
probable formation, (241)
5-Dimethylamino-2,4-dihydroxypyrimidine, 210
4-Dimethylamino-6-ethylamino-2-methylthiopyrimidine, 313
2-*β*-Dimethylaminoethylaminopyrimidine, 312
3-Dimethylamino-2-ethylpropenal
use, 94
4-*β*-Dimethylaminoethylpyrimidine, 26, 132, 318
2-Dimethylamino-5-formyl-4-hydroxy-6-methylpyrimidine, (409), (410)
4-Dimethylamino-6-furfurylamino-5-nitropyrimidine, 196
3-Dimethylamino-2-heptylpropenal
use, 94
2-Dimethylamino-4-*β*-hydroxyethylpyrimidine, 244
dehydration, 244
2-Dimethylamino-4-hydroxy-6-methylpyrimidine, 49, 307
reaction with chloral, (409)
Reimer-Tiemann reaction, (410)
2-Dimethylamino-4-hydroxy-6-methyl-5-(2,2,2-trichloro-1-hydroxyethyl)-pyrimidine, (409)
hydrolysis, (409)
2-Dimethylamino-4-hydroxy-5-nitropyrimidine
action of phosphoryl chloride, 164
2-Dimethylamino-4-hydroxypyrimidine, 39
action of persulphate, 241
4-Dimethylamino-6-hydroxypyrimidine, 232
3-Dimethylamino-2-isopropylpropenal
use, 94
4-Dimethylamino-2-mercapto-5-methylpyrimidine
failure to prepare, (285)
4-Dimethylamino-2-mercaptopyrimidine, 285
desulphurization, 280
2-Dimethylamino-4-methoxy-5-nitropyrimidine, 203
4-Dimethylamino-6-methoxypyrimidine, 232
4-Dimethylamino-6-methylaminopyrimidine, 191
2-Dimethylamino-4-methylpyrimidine, 186
action of formaldehyde, 244
4-Dimethylamino-6-methylpyrimidine, 188
2-Dimethylamino-5-nitropyrimidine, 193
4-Dimethylaminopteridine, 183
2-Dimethylaminopyrimidine, 186, 188, 193, 312
reaction with butyl-lithium, 123
4-Dimethylaminopyrimidine, 280
4-*p*-Dimethylaminostyryl-2,6-dihydroxypyrimidine, 126
4-*p*-Dimethylaminostyryl-6-hydroxy-2-mercaptopyrimidine, 126

4-*p*-Dimethylaminostyryl-2-hydroxy-6-methylpyrimidine, 126
4-Dimethylaminostyryl-6-hydroxypyrimidine
  action of phosphoryl chloride, (164)
4-*p*-Dimethylaminostyrylpyrimidine, 126
4-Dimethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 198
  C-acylation, (416)
2-Dimethylamino-4-vinylpyrimidine, 244
Dimethylaniline
  use with phosphoryl chloride, 163*f*
5,5-Dimethylbarbituric acid 56, 232, 362
Dimethyl dimethylmalonate
  use, 58
NN-Dimethylguanidine
  use in Principal Syntheses, 39, 49, 55, 72
Dimethyl malonate
  use, 56
Dimethylmalonic acid
  use, 56
NN'-Dimethylmalonic diamide, 258
4,6-Dimethyl-2-methylaminopyrimidine, 37, 377
  hydrolysis, 229
4,6-Dimethyl-2-methylthiopyrimidine, 37, 282, 287
  amination, 290
  desulphurization, 280
4,6-Dimethyl-2-nitroaminopyrimidine
  to 2-hydroxyamino analogue, 344
4,6-Dimethyl-2-*p*-nitrobenzenesulphonamidopyrimidine, 330
  reduction, 330
4,6-Dimethyl-2-*m*-nitrophenylpyrimidine, 134, 139
1,6-Dimethyl-5-nitrouracil, 231, 367
  oxidation *etc.*, 367
2,4-Dimethyl-6-phenacylpyrimidine, 132
  formation of oxime, 320
4,6-Dimethyl-2-*p*-phenoxyanilinopyrimidine, 37
4,6-Dimethyl-2-*α*-phenylacetonylpyrimidine, 209
4,6-Dimethyl-2-phenylpyrimidine, 31, 36, 125
  nitration, 134
  oxidation, 127
2,4-Dimethyl-6-piperidinopyrimidine, 188
2,4-Dimethyl-6-piperonylidenehydrazinocarbonylpyrimidine, 401
3,6-Dimethyl-5-propyluracil, 362
2,4-Dimethylpyrimidine, 96, 121
  attempted nitration, 128*f*
  N-oxide formation, 128
  styrylation, 125
2,5-Dimethylpyrimidine, 121
  styrylation, 26, 125
4,5-Dimethylpyrimidine, 93, 94
  oxidation, 127
4,6-Dimethylpyrimidine, 94, 120, 122, 280, 396
  bromination, 130, 177
  oxidation, 127
  N-oxide formation, 128
2,4-Dimethylpyrimidine-*N*-oxide, 128
  Reissert reaction, 384
4,6-Dimethylpyrimidine-1-oxide, 128
  action of acetic anhydride, 384
  action of toluene-*p*-sulphonyl chloride, 384
Di(4-methylpyrimidin-6-yl) disulphide, 292
2,4-Dimethylpyrimidin-6-yltrimethylammonium chloride
  reaction with sulphanilamide, 331
4,6-Dimethylpyrimidin-2-yltrimethylammonium chloride, 18, 345
  reactions of, 18, 345
  to 2-cyano analogue, 404
2,4-Dimethyl-6-styrylpyrimidine, 125
4,6-Dimethyl-2-styrylpyrimidine, 125, 411
  ozonization *etc.* to aldehyde, 411
5-(*NN*-Dimethylsulphamoyl)-2,4-dihydroxypyrimidine, 297
4,6-Dimethyl-2-sulphamoylpyrimidine, (295), 298
4,6-Dimethyl-2-sulphanilylaminopyrimidine
  see: "2-*p*-Aminobenzenesulphonamido-4,6-dimethylpyrimidine"
2,4-Dimethyl-6-sulphopyrimidine, 15, 207, 295
  action of cyanide, 207, 297
Dimethyl tetrahydropyran-2-yloxymalonate
  use, 58, 263
2,4-Dimethyl-6-thiocarbamoylpyrimidine, 399

4,6-Dimethyl-2-thiocarbamoylpyrimidine, 399
4,6-Dimethyl-2-*p*-toluenesulphonamidopyrimidine, 330
5,5-Dimethyl-2-thiobarbituric acid, 57
Dimethylthiomethylenemalononitrile
  use in synthesis, 66
1,5-Dimethyl-2-thiouracil, 101
3,6-Dimethyl-2-thiouracil, 83, 273
2,4-Dimethyl-6-tridecylpyrimidine, 122
1,5-Dimethyluracil, 101, 358, 361, 369, 455
1,6-Dimethyluracil, 229, 232, 361, 369, 372, 374
  alkylation, 361
  ferricyanide oxidation, 371, (400)
3,5-Dimethyluracil, 361
3,6-Dimethyluracil, 83, 358, 361, 365, 368, 372
  alkylation, 361
NN'-Dimethylurea
  use in Principal Syntheses, 42, 53, 68*f*
4,6-Dimethyl-2-ureidopyrimidine, 340
1,3-Dimethylxanthine, 150
β-Dinitriles
  use in Principal Syntheses, 72*f*
  use in syntheses, 90
5-α(2,4-Dinitrophenylhydrazono)ethyl-2,4-dihydroxypyrimidine, 418
5-(2,4-Dinitrophenylhydrazono)methyl-4,6-dihydroxy-2-piperidinopyrimidine, 414
4-(2,4-Dinitrophenylthio)-2,6-dimethoxypyrimidine, 283
NN'-Dioctylmalondiamidine
  syntheses from, 100
Dioxane dibromide
  as a brominating agent, 170
α,β-Diphenylacrylonitrile
  anomalous reaction with guanidine, 433
1,3-Diphenylalloxan-5-methylphenylhydrazone, 156
4-Diphenylamino-2-mercaptopyrimidine
  failure to prepare, 285
5,5-Diphenylbarbituric acid, 99, 261
Diphenyl carbonate
  use in syntheses, 99, 446
NN'-Diphenylformamidine
  use, 410
NN'-Diphenylguanidine
  use in synthesis, 55
5-Diphenylmethylenebarbituric acid, 123
  reduction, 124
2-Diphenymethylthio-4-hydroxy-6-methylpyrimidine, 283
5-Diphenylmethyl-2,4,6-trihydroxypyrimidine, 124
4,6-Diphenylpyrimidine, 95
1,3-Diphenyl-2-thiobarbituric acid
  desulphurization, 278, 443
NN'-Diphenylthiourea
  use, 54, 381
NN'-Diphenylurea
  use, 56
Di(2-pyrimidin-2-ylamino)methylbenzene, 312
  reduction by formic acid, 312
2,4-Diselenylpyrimidine, 207
2,4-Distyrylpyrimidine, 125
2,4-Dithiobarbiturates
  formation, 251
Dithiouracil, 6
Dithiourethanes
  use in Shaw Synthesis, 88
1,3-Di-*o*-toluidinopropane
  failure to condense with aldehydes, 453
Di-(2,4,6-trihydroxypyrimidin-5-yl) disulphide, 212, 292
Diuretic pyrimidines, 367
Divicine, 6
  monograph, 259
Donnell, 331
Dornow, 85

E

Elbs persulphate reaction, 20*f*, 241
Electrophilic substitution, 10
Elion, 251, 285
English, 331
β-Ester nitriles
  reaction with amidines, 67
  reaction with guanidines, 71*f*
  reaction with thioureas, 70
  reaction with ureas, 68*f*
  use in primary syntheses, 90*f*
  use in Principal Syntheses, 67*f*
β-Ethoxyacrylonitrile
  in cytosine synthesis, 60, 346
1-Ethoxy-1-buten-3-one
  use, 94

5-Ethoxycarbonylacetyl-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine, 53
5-Ethoxycarbonylacetyl-2,4,6-trihydroxypyrimidine, 416
4-Ethoxycarbonylamino-2,6-diethyl-5-methylpyrimidine, 336
  hydrolysis to 4-amino analogue, 338
  reaction with amines, 338
5-Ethoxycarbonylamino-2,4-dimethylpyrimidine
  hydrolysis, 338
5-Ethoxycarbonylamino-2-ethylthio-4-hydroxypyrimidine, 336
  hydrolysis, 338
5-Ethoxycarbonylamino-4-hydroxy-2-methylpyrimidine, 336
  to 4,5-dihydroxy analogue, 238
Ethoxycarbonylaminomaleic anhydride, 423
  intermediate in Shaw Synthesis, 89, 423
Ethoxycarbonylaminomaleimide, (424)
  intermediate in orotic acid synthesis, (424)
5-Ethoxycarbonylaminomethyl-2,4-dihydroxy-6-methylpyrimidine, 337
5-Ethoxycarbonylaminomethyl-2,4-dihydroxypyrimidine, 337
5-Ethoxycarbonylaminomethyl-2-ethylthio-4-hydroxypyrimidine, 337, 401, 419
5-Ethoxycarbonylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine, (336)
5-Ethoxycarbonylamino-1,2,3,4-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine, 336
5-Ethoxycarbonylamino-2,4,6-trimethylpyrimidine, 337
  hydrolysis, (338)
2-α-Ethoxycarbonylbenzyl-4,6-dimethylpyrimidine, 209
α-Ethoxycarbonyl-α-butyrolactone
  use in synthesis, 242
2-Ethoxycarbonylcyclohexanone
  use, 44/
2-Ethoxycarbonylcyclopentanone, 47
5-Ethoxycarbonyl-4,5-dihydro-6-hydroxy-2,4-dimethylpyrimidine, 49, 52, 432
5-Ethoxycarbonyl-1,6-dihydro-2-hydroxy-4-methyl-6-phenylpyrimidine, 440, (441), 458
  acetylation, 456
  bromination, 457
  mechanism of formation, 441
  reaction with phosphoryl chloride, 458
5-Ethoxycarbonyl-1,6-dihydro-2-hydroxy-4-methylpyrimidine, 44
4-Ethoxycarbonyl-4,5-dihydro-6-hydroxy-2-phenylpyrimidine, 439
5-Ethoxycarbonyl-1,6-dihydro-2-hydroxy-6-phenyl-4-trifluoromethylpyrimidine, 441
5-Ethoxycarbonyl-1,6-dihydro-2-mercapto-4-methyl-6-phenylpyrimidine, (441)
  to 2-hydroxy analogue, 441, (458)
5-Ethoxycarbonyl-1,6-dihydro-2-mercapto-6-phenyl-4-trifluoromethylpyrimidine, 441
5-Ethoxycarbonyl-3,4-dihydro-3-methyl-2-methylthio-4-oxopyrimidine, 43
5-Ethoxycarbonyl-1,6-dihydro-2-methylpyrimidine, 440
  nuclear reduction, 451
5-Ethoxycarbonyl-4,5-dihydro-2,4,5,6-tetrahydroxypyrimidine, 442
4-Ethoxycarbonyl-2,6-dihydroxypyrimidine, (370), (393)
  failure of Principal Synthesis, 103
5-Ethoxycarbonyl-2,4-dihydroxypyrimidine, 42, 395
  action of phosphoryl chloride, (165)
5-Ethoxycarbonyl-4-ethoxythiocarbonylamino-2-ethylthiopyrimidine, 338
5-Ethoxycarbonyl-2-ethylamino-4-methylpyrimidine, 290
α-Ethoxycarbonyl-α-ethyl-γ-butyrolactone
  use in synthesis, 242
5-Ethoxycarbonyl-2-ethylsulphonylpyrimidine, 299
4-Ethoxycarbonyl-2-ethylthio-5-fluoro-6-hydroxypyrimidine, 44, 175
5-Ethoxycarbonyl-2-ethylthio-4-isocyanatopyrimidine, 208, 418
  amination, 419
5-Ethoxycarbonyl-2-ethylthio-4-isothiocyanatopyrimidine, (338), 421

action of alcohol, (338)
to thioureide, 422
5-Ethoxycarbonyl-2-ethylthio-4-phenylureidopyrimidine, 419
5-Ethoxycarbonyl-2-ethylthiopyrimidine, 185
action of chlorine, 166, (299)
5-Ethoxycarbonyl-2-ethylthio-4-thiocyanatopyrimidine, 208, 310
isomerization, (421)
5-Ethoxycarbonyl-2-ethylthio-4-thioureidopyrimidine, 422
cyclization, 422
5-Ethoxycarbonyl-2-ethylthio-4-ureidopyrimidine, 208, 419
2-Ethoxycarbonylformylmethylthio-4-hydroxypyrimidine, 408
use as an aldehydo ester (!), 408
5-Ethoxycarbonyl-2-hydrazino-4-methylpyrimidine, 291
acylation, (330)
5-Ethoxycarbonyl-4-hydroxy-2-mercaptopyrimidine, (395)
desulphurization, 235, 279
to 5-carboxyuracil, 235
5-Ethoxycarbonyl-2-hydroxy-4-methylpyrimidine, 43
reduction, 444
5-Ethoxycarbonyl-4-hydroxy-2-methylpyrimidine, 41, 395
5-Ethoxycarbonyl-4-hydroxypyrimidine, 235
5-Ethoxycarbonyl-4-hydroxy-2-trifluoromethylpyrimidine, 179
4-Ethoxycarbonyl-2-mercapto-6-hydroxypyrimidine, 44
5-(*N*-Ethoxycarbonyl-*N*-methylamino)-2,4-dihydroxy-6-methylamino pyrimidine, 336
4-Ethoxycarbonylmethyl-4,5-dihydro-2,6-dihydroxypyrimidine, 444
3-Ethoxycarbonylmethyl-5,6-dihydro-6-phenyluracil, 458
saponification, 458
4-Ethoxycarbonylmethyl-2,6-dihydroxypyrimidine
reduction, 444
5-Ethoxycarbonyl-4-methyl-2,6-diphenylpyrimidine, 455
5-Ethoxycarbonylmethylenehydantoin
conversion into a pyrimidine, 103*f*
1-Ethoxycarbonylmethyl-2-ethylthio-1,4-dihydro-4-oxopyrimidine, 369
4-Ethoxycarbonylmethyl-2-ethylthio-6-hydroxypyrimidine, 44, 396
5-Ethoxycarbonylmethyl-2-ethylthio-4-isothiocyanatopyrimidine, 421
5-Ethoxycarbonylmethyl-2-ethylthio-4-thiocyanatopyrimidine
isomerization, (421)
1-Ethoxycarbonylmethylhexahydro-3-methyl-2,6-dioxo-4-phenylpyrimidine, 458
5-Ethoxycarbonyl-4-methyl-2-methylthiopyrimidine
amination, 290, 291, 396
failure to aminate with hindered amines, 290, 291
1-Ethoxycarbonylmethyl-6-phenyluracil, 362
alkylation, 362
3-Ethoxycarbonyl-1-methyl-4-piperidone
use, 45
1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydro-3-methyl-2,4-dioxo-6-phenylpyrimidine, 362
1-Ethoxycarbonylmethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-4-phenylpyrimidine, 362
2-Ethoxycarbonylmethylthio-4-hydroxy-6-methyl-5-propylpyrimidine, 283
2-Ethoxycarbonylmethylthio-4-hydroxypyrimidine, 283
side-chain formylation, 408
5-Ethoxycarbonyl-3-methyl-2-thiouracil, 43
5-Ethoxycarbonyl-3-methyluracil, 42, 357
hydrolysis, 357, 361
5-Ethoxycarbonyl-3-octyl-2-thiouracil
to corresponding uracil, 235
5-Ethoxycarbonyl-3-octyluracil, 235
5-Ethoxycarbonyl-3-phenyl-2-thiouracil
to corresponding carboxyuracil, 235
6-Ethoxycarbonyl-3-phenyluracil
doubts on structure, 51
4-Ethoxycarbonylpyrimidine, 393
from the acid chloride, 394
to amide, 396
to hydrazide, 397
5-Ethoxycarbonyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidine, 42, 358, 395

5-Ethoxycarbonyl-1,4,5,6-tetrahydro-6-methyl-2,4-diphenylpyrimidine
  oxidation, 455
5-Ethoxycarbonyl-1,4,5,6-tetrahydro-2-methylpyrimidine, 451
5-Ethoxycarbonyl-1,2,3,4-tetrahydro-6-methyl-1,2,3,4-tetraphenylpyrimidine, 449
5-Ethoxycarbonyl-1,4,5,6-tetrahydro-2,4,6-triphenylpyrimidine
  oxidation, 455
5-Ethoxycarbonyl-2,4,6-triphenylpyrimidine, 455
4-Ethoxy-1,2-dihydro-1-methyl-2-oxopyrimidine, 371
  thermal rearrangement, 371
4-Ethoxy-1,2-dihydro-2-oxo-1-tetra-acetyl-β-D-glucosidopyrimidine, 372
5-Ethoxy-2,4-dihydroxypyrimidine, 232
2-Ethoxy-4,6-dimethylpyrimidine, 201
  bromination, (171)
β-Ethoxy-α-ethoxymethoxymethylpropionitrile
  use, 61
5-Ethoxy-4-ethoxythiocarbonylamino-2-ethylthiopyrimidine, (338)
4-Ethoxy-1-ethyl-1,2-dihydro-2-oxopyrimidine, 371
5-β-Ethoxyethyl-4-ethyl-6-hydroxy-2 mercaptopyrimidine
  desulphurization, 281
5-β-Ethoxyethyl-4-ethyl-6-hydroxypyrimidine, 281
4-Ethoxy-5-ethyl-2-ethylsulphonyl-6-methylpyrimidine, 299
  action of alkoxide, (247)
  hydrolysis of 2-group, (236)
4-Ethoxy-5-ethyl-2-ethylthio-6-methylpyrimidine
  oxidation, (299)
4-Ethoxy-5-ethyl-2-hydroxy-6-methylpyrimidine, (236)
α-Ethoxyethylidenemalononitrile
  use as a keto nitrile, 66
4-Ethoxy-2-ethylsulphonyl-6-methyl-5-propylpyrimidine
  hydrolysis of 2-group, 236
4-Ethoxy-2-ethylsulphonyl-5-methylpyrimidine, (236), 299
  alkaline hydrolysis of 2-group, 236
  amination, 300
  to 2-ethoxy analogue, 247
4-Ethoxy-2-ethylsulphonylpyrimidine, 299
  hydrolysis, 236
4-Ethoxy-1-ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-5-ureidopyrimidine, 363
5-Ethoxy-2-ethylthio-1,4-dihydro-1-methyl-4-oxopyrimidine, (369)
5-Ethoxy-2-ethylthio-1,6-dihydro-1-methyl-6-oxopyrimidine, (369)
5-Ethoxy-2-ethylthio-4-hydroxypyrimidine
  alkylation, 368
4-Ethoxy-2-ethylthio-5-methylpyrimidine
  oxidation, 236, (299)
4-Ethoxy-2-ethylthiopyrimidine
  hydrolysis, 233
  oxidation, 299
  to 2-hydroxy analogue, (236)
5-Ethoxy-2-ethylthiopyrimidine, 185, 282
5-Ethoxy-2-ethylthio-4-thiocyanatopyrimidine, 208
4-Ethoxy-2-hydrazino-6-methylpyrimidine, 200
4-Ethoxy-2-hydroxy-6-methyl-5-propylpyrimidine, 236
2-Ethoxy-4-hydroxy-6-methylpyrimidine, 51, 245
4-Ethoxy-2-hydroxy-5-methylpyrimidine, 236
2-Ethoxy-4-hydroxy-5-nitropyrimidine, 14, 203
  amination, 256
4-Ethoxy-2-hydroxy-5-nitropyrimidine, 203
  amination, 256
2-Ethoxy-4-hydroxypyrimidine
  amination, 255, 309
  thiation in damp pyrimidine, 252
4-Ethoxy-2-hydroxypyrimidine, (236)
  amination, 255, 309
5-Ethoxy-4-mercapto-2-methylthiopyrimidine, 207
5-Ethoxy-2-mercaptopyrimidine
  S-alkylation, (282), (284)
β-Ethoxy-α-methoxymethylenepropionitrile use, 61
α-Ethoxymethoxymethylpropionitrile
  use, 62
5-Ethoxymethyl-2,4-dihydroxypyrim-

idine, 248
Ethoxymethyleneacetic acid
  conversion into acid chloride, 101
Ethoxymethyleneacetonitrile
  see: "β-Ethoxyacrylonitrile"
Ethoxymethyleneacetylacetone
  use in synthesis, 415
Ethoxymethyleneacetyl isothiocyanate
  as intermediate in synthesis, 101
N-Ethoxymethyleneacetyl-*N*′-methylthiourea
  cyclization, 101
Ethoxymethyleneacetylurethane
  intermediate in synthesis, 89
Ethoxymethylenemalononitrile
  use as aldehydo nitrile, 61, 86, 179, 403
  in Whitehead Syntheses, 64, 381
α-Ethoxymethylene-α-methylacetyl isocyanate
  amination of, 358
N-(α-Ethoxymethylene-α-methylacetyl)-*N*′-methylurea, (358)
  cyclization, (358)
5-Ethoxymethyl-2-ethyl-4-hydroxypyrimidine, 246
4-Ethoxymethyl-6-hydroxy-2-hydroxymethyl-5-methylpyrimidine, 242
  hydrolysis, 242
4-Ethoxymethyl-6-hydroxy-2-mercapto-5-methylpyrimidine
  desulphurization, 248, 281
4-Ethoxymethyl-6-hydroxy-5-methylpyrimidine, 248, 281
5-Ethoxymethyl-4-hydroxy-2-methylpyrimidine, 86
  action of sodium sulphite, 295
4-Ethoxy-6-methyl-2-phenylpyrimidine, 247 (?)
4-Ethoxy-6-methylpyrimidine, 383
  formation of *N*-oxide, 382
4-Ethoxy-6-methylpyrimidine-*N*-oxide, 382
  reduction, 383
  Reissert reaction, 383
6-Ethoxy-1-methyl-5-ureidouracil, 363
  ethylation, 363
4-Ethoxyoxalylmethylpyrimidine, 26, 132
4-Ethoxy-2-phenylpyrimidine (?), 247
4-Ethoxy-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 203
4-Ethoxythiocarbonylamino-2-ethylthio-5-phenylpyrimidine, 337
4-Ethoxythiocarbonylamino-2-ethylthio-6-phenylpyrimidine, (338)
4-Ethoxythiocarbonylamino-2-ethylthiopyrimidine, 338
Ethoxythiocarbonylpropan-2-thione, 46
Ethyl acetamidocyanoacetate
  use in syntheses, 71, 328
Ethyl acetimidate
  use in syntheses, 86
Ethyl acetoacetate
  reaction with urea, 441
  use, 44*f*
Ethyl amidinomethylenecyanoacetate
  alternative cyclizations, 61
Ethyl β-aminobutyrate
  use in hydropyrimidine synthesis, 435
Ethyl β-aminocrotonate
  reaction with isocyanates, 82*f*, 228, 358
5-Ethylamino-2,4-dihydroxypyrimidine, 210
4-Ethylamino-2-ethylthiopyrimidine, 198
4-Ethylamino-2-hydroxy-5-nitropyrimidine, 380
Ethyl aminomethyleneacetoacetate
  in primary synthesis, 83, 358
Ethyl aminomethylenecyanoacetate
  formation from ethyl cyanoacetate, 67
  reaction with imino ethers, 86
  reaction with thiocetamide, 85, 396
Ethyl α-aminomethylene-β-ethoxypropionate
  use in synthesis, 86
Ethyl aminomethylmethylenecyanoacetate
  formation, 67
5-Ethylamino-4-methylpyrimidine, 315
Ethyl β-amino-α-methylthiocarbamoylcrotonate
  as a by-product, 83
Ethyl β-amino-α-phenylcarbamoylcrotonate
  formation as by-product, 83
Ethyl aminophenylmethylenecyanoacetate
  formation, 67
Ethyl β-amino-β-phenylpropionate
  action of phosgene, 437

- 4-Ethylamino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 198
- 1-Ethylbarbituric acid
  - *C*-acetylation, (416)
- Ethyl benzamidoformylacetate
  - use, 40, 328
- Ethyl benzoimidate
  - use in synthesis, 86
- Ethyl benzoylacetate
  - use, 44, 95
- Ethyl benzylacetoacetate
  - use, 44
- Ethyl benzyloxyformylacetate
  - use, 40, 239, 246
- Ethyl *β*-benzylureido-*β*-phenylpropionate, 437
  - cyclization, 437
- Ethyl bromocyanoacetate
  - use in Principal Syntheses, 71, 175
- Ethyl butyrylacetate
  - use, 45, 283
- Ethyl chloroacetoacetate
  - use, 44
- Ethyl chloroformate
  - use in making urethanes, 336
- Ethyl *o*-chlorophenoxyformylacetate, 40
- Ethyl *α*-*p*-chlorophenyl-*α*-propionylacetate, 46
  - use, 407
- Ethyl cyanoacetate
  - use in Principal Syntheses, 67*f*
- Ethyl *α*-cyano-*γγ*-diethoxybutyrate
  - use, 68
- Ethyl *β*-cyanoformylpropionate
  - use, 41, 403
- Ethyl cyanosuccinate
  - use, 67
- Ethyl *α*-cyclohex-1-enyl-*α*-cyanopropionate
  - use in barbiturate synthesis, 53
- Ethyl (2,4-dibromophenoxy)formylacetate
  - use in synthesis, 180
- Ethyl *γγ*-diethoxyacetoacetate, 46, 423
  - use, 406, 407
- Ethyl *ββ*-diethoxy-*α*-methylpropionate
  - use in synthesis, 38
- Ethyl diethylcyanoacetate
  - use in syntheses, 68, 71
- 5-Ethyl-2,5-dihydro-4,6-dihydroxy-2,5-diphenylpyrimidine, 439
- 5-Ethyl-2,5-dihydro-4,6-dihydroxy-2-methoxy-5-phenylpyrimidine
  - alkylation, 459
- 5-Ethyl-4,5-dihydro-2,6-dihydroxy-5-*m*-nitrophenylpyrimidine, 455
  - reduction, 454
- 5-Ethyl-2,5-dihydro-4,6-dihydroxy-5-phenylpyrimidine, 278, 443
- 5-Ethyl-4,5-dihydro-2,6-dihydroxy-5-phenylpyrimidine
  - nitration, (456)
- 5-Ethyl-4,5-dihydro-2,6-dihydroxypyrimidine, (443)
- 1-Ethyl-1,4-dihydro-6-hydroxy-2-phenylpyrimidine, 440
- 1-Ethyl-1,4-dihydro-2-mercapto-4,4,6-trimethylpyrimidine, 437
- 5-Ethyl-4,6-dihydroxy-2-mercaptopyrimidine
  - desulphurization, 280
- 2-Ethyl-4,6-dihydroxy-5-methylpyrimidine, 97
- 2-Ethyl-4,6-dihydroxypyrimidine, 98
  - action of phosphoryl bromide, (167)
- 4-Ethyl-2,6-dihydroxypyrimidine, 235, 281
- 5-Ethyl-4,6-dihydroxypyrimidine, 97, 280
- 5-Ethyl-2,4-dimethoxy-6-methylpyrimidine, 247
- 4-Ethyl-2,6-dimethylpyrimidine, 122
- 1,2-Ethylene-*bis*-*S*-thiourea
  - use, 46
- Ethyl *α*-ethoxycarbonylamino-*α*-formylacetate
  - use in syntheses, 336
- Ethyl ethoxycyanoacetate
  - use, 246
- Ethyl ethoxyethylacetoacetate
  - use, 45, 246
- Ethyl *α*-ethoxyethylidenecyanoacetate, 45
  - reaction as a keto ester, 66
- Ethyl ethoxyformyacetate
  - use, 41
- Ethyl *β*-ethoxyformylpropionate
  - use, 246
- Ethyl *β*-ethoxymethoxymethylpropionate
  - use, 41
- Ethyl *α*-ethoxy-*α*-methylacetoacetate
  - use in synthesis, 242
- Ethyl ethoxymethyleneacetoacetate

use, 48, 290, 415
Ethyl ethoxymethyleneacetylpyruvate
  use in synthesis, 36
Ethyl ethoxymethylenecyanoacetate
  in syntheses, 60*f*, 62*f*, 347, 403
  in Whitehead Syntheses, 64, 381
Ethyl ethoxymethyleneoxalacetate
  use in synthesis, 36
Ethyl ethylacetoacetate
  failure to undergo Biginelli reaction, 441
  use, 44, 51
Ethyl α-ethyl-α-1-methylbut-1-enylcyanoacetate
  use in making barbiturate, 54
5-Ethyl-2-ethylsulphonyl-4-methoxy-6-methylpyrimidine, 299
  action of alkoxide, (247)
  hydrolysis of 2-group, (236)
5-Ethyl-2-ethylthio-4-isothiocyanatopyrimidine, (341), 421
  amination, (341)
5-Ethyl-2-ethylthio-4-methoxy-6-methylpyrimidine
  oxidation, (299)
5-Ethyl-2-ethylthio-4-phenylthioureidopyrimidine, (341)
4-Ethyl-2-ethylthiopyrimidine, 185
5-Ethyl-2-ethylthio-4-thiocyanatopyrimidine, 208
  isomerization, (421)
  reaction with thioacetic acid, 420
5-Ethyl-2-ethylthio-4-thioureidopyrimidine, 341
Ethyl formylacetate
  use in syntheses, 38*f*, 227
Ethyl formylacetoacetate
  use, 41
Ethyl formylchloroacetate
  use, 40
Ethyl formylfluoroacetate
  use, 40, 175, 245
Ethyl α-formylpropionate
  use in syntheses, 38, 41, 287
Ethyl heptanoylacetate
  use, 44
5-Ethylhexahydro-1,3-bishydroxymethyl-2-methoxy-4,6-dioxo-5-phenylpyrimidine, 244, 459
5-Ethylhexahydro-2-methoxy-4,6-dioxo-5-phenylpyrimidine
  action of formaldehyde, 244
Ethyl hexanoylacetate
  use, 45
2-Ethyl-4-hydroxy-5,6-dimethylpyrimidine, 44
5-Ethyl-4-hydroxy-2-mercapto-6-phenylpyrimidine
  nuclear reduction, (443)
4-Ethyl-6-hydroxy-2-mercaptopyrimidine, 45
  to 6-ethyluracil with nitric acid, 235, 281
5-Ethyl-2-hydroxy-4-methoxy-6-methylpyrimidine, (236)
5-Ethyl-4-hydroxy-2-methoxy-6-methylpyrimidine, 51, 245
5-Ethyl-4-hydroxy-6-methyl-2-methylthiopyrimidine, 44
2-Ethyl-4-hydroxy-6-methylpyrimidine
  direct removal of hydroxy group, 122, 253
4-Ethyl-6-hydroxypyrimidine, 122
Ethyl β-iminobutyrate
  use, 48
5-Ethyl-5-isoamylbarbituric acid, 53
Ethyl β-isocyanato-β-phenylpropionate, 437
  action of benzylamine, 437
Ethylmalononitrile
  use in synthesis, 73
5-(*N*-Ethyl-*N*-methoxycarbonylamino)-2,4-dihydroxy-6-methylaminopyrimidine, 336
Ethyl methoxyformylacetate
  use, 40, 41
Ethyl β-methoxymethylenepropionate
  use, 41
Ethyl *p*-methoxyphenoxyacetoacetate
  use, 44
Ethyl methylacetoacetate
  use, 44, 46, 49
Ethyl β-methylaminopropionate
  use in synthesis, 83
Ethyl *m*-methylbenzylacetoacetate
  use, 45
5-Ethyl-5-1′-methylbut-1′-enylbarbituric acid, 54
5-Ethyl-5-1′-methylbutylbarbituric acid, 53
  thiation, 54

5-Ethyl-5-1′-methylbutyl-2-thiobarbituric acid, 54, 57
Ethyl β-methylcrotonate
  use in synthesis of hydropyrimidines, 431
2-Ethyl-4-methylpyrimidine, 122, 253
3-Ethyl-6-methyluracil
  nitration and oxidation, 129
Ethyl nitrosocyanoacetate
  use in Principal Syntheses, 67, 68, 69, 70, 71, 149
1-Ethyl-5-nitrouracil, 364
  alkylation, 364
Ethyl oxalacetate
  use in syntheses, 51, 370
Ethyl phenylacetimidate
  use in synthesis, 86
Ethyl α-phenylazotrifluoroacetoacetate
  use, 44, 179
5-Ethyl-5-phenylbarbituric acid, 53
  reduction, 450
  thiation, 251
Ethyl β-phenylformylpropionate
  use, 41
C-Ethyl-*C*-phenylmalondiamide
  condensation with aldehydes, 439
4-Ethyl-6-phenylpyrimidine, 95
5-Ethyl-5-phenyl-2-thiobarbituric acid
  abnormal desulphurization, 278, 443
  lithium aluminium hydride reduction, 450
5-Ethyl-5-phenyltrithiobarbituric acid, 251
N-Ethylpiperidine
  use as condensation catalyst, 33
Ethyl propiolate
  reaction with urethane, 89
Ethyl propionylacetate
  use, 45
5-Ethyl-5-propyl-2-thiobarbituric acid, 57
1(or 3)-Ethyl-6-propyluracil, 362
N-Ethyl-*N*′-propylurea
  in Principal Synthesis, 69
4-Ethylpyrimidine, 94, 122
5-Ethylpyrimidine, 94
1-Ethyl-5-α-semicarbazonoethylbarbituric acid, 418
2-Ethylsulphonyl-4-methoxy-5,6-dimethylpyrimidine, 299
2-Ethylsulphonyl-4-methoxy-6-methyl-5-propylpyrimidine
  hydrolysis of 2-group, 236
2-Ethylsulphonyl-4-methoxy-5-methylpyrimidine, (236)
  action of alkoxide, (247)
  hydrolysis, (236)
2-Ethylsulphonyl-5-methyl-4-methylaminopyrimidine, (236)
  hydrolysis, (236)
1-Ethyl-1,2,3,4-tetrahydro-3,6-dimethyl-2,4-dioxopyrimidine, 361
5-Ethyl-1,4,5,6-tetrahydro-2-hydroxy-5-phenylpyrimidine, 450
5-Ethyl-1,4,5,6-tetrahydro-2-hydroxypyrimidine, (443)
5-Ethyl-1,4,5,6-tetrahydro-2-mercapto-5-phenylpyrimidine, 450
1-Ethyl-1,2,3,6-tetrahydro-3-methyl-2,6-dioxopyrimidine, 371
1-Ethyl-1,2,3,4-tetrahydro-3-methyl-5-nitro-2,4-dioxopyrimidine, 364
1-Ethyl-1,2,3,6-tetrahydro-3-methyl-5-nitro-2,6-dioxopyrimidine, 364
Ethyl tetrahydropyran-2-yloxyacetate, 240
  formylation, 240
Ethyl tetrahydropyran-2-yloxycyanoacetate
  use, 68, 71, 259, 263
Ethyl tetrahydropyran-2-yloxyformylacetate
  preparation, 240
  use, 41, 240
2-Ethyl-1,2,5,6-tetrahydro-4,6,6-trimethylpyrimidine, 448
2-Ethylthio-1,4-dihydro-1,5-dimethyl-4-oxopyrimidine, (369)
2-Ethylthio-1,6-dihydro-1,4-dimethyl-6-oxopyrimidine, (361)
  hydrolysis, (361)
2-Ethylthio-1,6-dihydro-1,5-dimethyl-6-oxopyrimidine, (369)
2-Ethylthio-1,4-dihydro-1-methyl-4-oxopyrimidine, 361, (368)
  hydrolysis, 361, (368)
2-Ethylthio-1,6-dihydro-1-methyl-6-oxopyrimidine, 361, (368)
  hydrolysis, 361, (368)
2-Ethylthio-4,5-dimethyl-6-phenylthioureidopyrimidine, (341)
2-Ethylthio-4,5-dimethyl-6-thiocyanatopyrimidine, 208
  action of thioacids, (275), 420

isomerization, (421)
2-Ethylthio-4,5-dimethyl-6-thioureidopyrimidine, 341
2-Ethylthio-5-fluoro-4-hydroxypyrimidine, 175
hydrolysis, 175
2-Ethylthio-5-formamido-4-hydroxypyrimidine, 336
2-Ethylthio-4-formyl-6-hydroxypyrimidine, 406
oxidation to orotic acid, (392)
2-Ethylthio-5-hydrazinocarbonylmethyl-4-hydroxypyrimidine
Curtius reaction on, 318, (337)
to azidocarbonyl analogue, 400
2-Ethylthio-4-hydroxy-5,6-dimethylpyrimidine, 44, 287
2-Ethylthio-4-hydroxy-5-β-hydroxyethyl-6-methylpyrimidine, 282
desulphurization, 280
2-Ethylthio-4-hydroxy-5-iodopyrimidine, 171
2-Ethylthio-4-hydroxy-5-isocyanatomethylpyrimidine, (337), 401, 419
action of alcohol, (337)
action of hot acid, 419
action of water, 419
amination, 419
2-Ethylthio-5-hydroxy-7-mercaptopyrimido[4,5-d]pyrimidine, 422
2-Ethylthio-4-hydroxy-5-methylpyrimidine, 38
alkylation, 368
to 2,4-dimercapto analogue, 252, 274
2-Ethylthio-4-hydroxy-6-methylpyrimidine, 282
alkylation, 361
chlorination, (170)
2-Ethylthio-4-hydroxy-5-phenylureidomethylpyrimidine, 419
2-Ethylthio-4-hydroxypyrimidine, 282
alkylation, 361, 362, 368, 369
amination, 290
bromination, (171)
chlorination, 174, (346)
iodination, (171)
nitrationandoxidationtonitrouracil, 141
to 2-mercapto analogue, 274
2-Ethylthio-4-hydroxy-5-ureidomethylpyrimidine, 419
2-Ethylthio-4-isothiocyanato-5,6-dimethylpyrimidine, (341), 421
amination, (341)
2-Ethylthio-4-isothiocyanato-5-methylpyrimidine, (341)
amination, (341)
2-Ethylthio-4-isothiocyanato-6-methylpyrimidine, (341)
amination, (341)
2-Ethylthio-4-isothiocyanato-5-phenylpyrimidine, (338)
action of alcohol, (338)
2-Ethylthio-4-isothiocyanato-6-phenylpyrimidine, (338)
action of alcohol, (338)
2-Ethylthio-4-isothiocyanatopyrimidine, 208, (341), 422
amination, (341)
2-Ethylthio-4-mercapto-5,6-dimethylpyrimidine, 275, 420
2-Ethylthio-4-mercapto-5-methylpyrimidine, 275
2-Ethylthio-4-mercapto-6-methylpyrimidine, 207
2-Ethylthio-4-mercapto-5-phenylpyrimidine, 275
2-Ethylthio-4-mercapto-6-phenylpyrimidine, 275
2-Ethylthio-4-mercaptopyrimidine, 207
hydrolysis, 233
to 2,4-dimercapto analogue, 274
2-Ethylthio-4-methoxy-5,6-dimethylpyrimidine
oxidation, (299)
2-Ethylthio-4-methoxy-5-methylpyrimidine
oxidation, 236
2-Ethylthio-4-methoxypyrimidine
to 2-hydroxy analogue, (236)
2-Ethylthio-4-methylaminopyrimidine, 198, (290)
to 2-hydroxy analogue, (236)
2-Ethylthio-5-methyl-4-methylaminopyrimidine, (236)
2-Ethylthio-4-methyl-6-phenylthioureidopyrimidine, (341)
2-Ethylthio-5-methyl-4-phenylthioureidopyrimidine, (341)
2-Ethylthio-4-methylpyrimidine, 185
2-Ethylthio-4-methyl-6-thiocyanatopyrimidine, 208
2-Ethylthio-5-methyl-4-thiocyanatopyrimidine, 208
action of thioacids, 275

2-Ethylthio-4-methyl-6-thioureidopyrimidine, 341
2-Ethylthio-5-methyl-4-thioureidopyrimidine, 341
2-Ethylthio-5-nitro-4-thiocyanatopyrimidine
  cyclization on reduction, 420
2-Ethylthio-4-phenyl-6-thiocyanatopyrimidine, 208
  action of thioacids, (275)
2-Ethylthio-5-phenyl-4-thiocyanatopyrimidine, 208
  action of thioacids, (275)
2-Ethylthio-4-phenylthioureidopyrimidine, (341)
2-Ethylthiopyrimidine, 185
  bromination, (170)
  hydrolysis, 233
5-Ethylthiopyrimidine, 210, 288
2-Ethylthio-4-thiocyanatopyrimidine, 208
  rearrangement to isothiocyanate, 208
2-Ethylthio-4-thioureidopyrimidine, 341
S-Ethylthiourea
  use in Principal Syntheses, 40, 44*f*, 55, 60
Ethyl trifluoroacetoacetate, 46
  use in synthesis, 179
5-Ethyl-2,4,6-trihydroxypyrimidine, 53, 230
  nuclear reduction, 443
5-Ethyl-2,4,6-trimethoxypyrimidine, 202
Ethyl trimethylenemalonate
  use, 52
5-Ethyl-2,4,6-triphenylpyrimidine, 95, 120
1-Ethyluracil, 361
3-Ethyluracil, 361
O-Ethylurea
  use in Principal Syntheses, 51, 70, 245
Ethyl β-ureidocrotonate, 50, 441
  action of benzaldehyde, 441
  action of phenylacetaldehyde, 442
  in making methyluracil, 50
5-Ethynyl-4-methyl-2-phenylpyrimidine, 124
"Evipal", 53
"Evipan", 53

F

Fabbrini, 37, 340
Falco, 285
Fink and Fink, 243
Fischer, Emil, 2, 455
Fischer and Dilthey
  synthesis of barbiturates, 53
5-Fluoro-2,4-dihydroxypyrimidine, 175
5-Fluoro-4-hydroxy-2-ethylthiopyrimidine, 40
5-Fluoro-4-hydroxy-2-methoxypyrimidine, 40, 245
5-Fluoro-4-hydroxy-2-methylthiopyrimidine, 40
2-Fluromethyl-4,6-dihydroxypyrimidine, 180
Fluoropyrimidines
  2-, 4-, and 6-, from chloro derivatives, 162
Folkers, 441
Formamide
  syntheses using, 91
Formamidine
  use in Principal Synthesis, 31-74

4-Formamido-2,6-dihydroxypyrimidine, (326)
5-Formamido-4-methylamino-6-methylthiopyrimidine, 326
  cyclization, 326
5-Formamido-4-methylaminopyrimidine, 326
  cyclization, 326
5-Formamidomethyl-2-methyl-4-methylaminopyrimidine, 327
Formylacetic acid
  formation, 38
  use in syntheses, 38, 257, 431
Formylacetone
  use of acetals in synthesis, 34
  use in synthesis, 34
Formylacetylacetone
  see: "Ethoxymethyleneacetylacetone"
α-Formylcyclohexanone
  use in synthesis, 34, 95
4-Formyl-2,6-dihydroxy-5-methylpyrimidine
  to oxime, (413)
  to Schiff's base, (414)
  to triphenylmethane dye analogue, 415
5-Formyl-2,4-dihydroxy-6-methylpyrimidine, 410
  to a hydrazone, (414)
5-Formyl-4,6-dihydroxy-2-phenylpyrimidine, 410

5-Formyl-4,6-dihydroxy-2-piperidinopyrimidine, 410
  to a hydrazone, (414)
4-Formyl-2,6-dihydroxypyrimidine
  Cannizzaro reaction, (244)
  oxidation, 392
5-Formyl-2,4-dihydroxypyrimidine, 411
2-Formyl-4,6-dimethylpyrimidine (as *p*-nitrophenylhydrazone), 411
2-Formylhydrazino-4,6-dimethylpyrimidine, 325
2-Formylhydrazinopyrimidine, 325
4-Formyl-6-hydroxy-2-mercapto-5-methylpyrimidine, (406)
  to oxime, (413)
4-Formyl-6-hydroxy-2-mercaptopyrimidine, 47, 406
  S-alkylation, (283)
  Cannizzaro reaction, (244)
  from acetal, 406
  oxidation, 392
5-Formyl-4-hydroxy-6-methyl-2-methylaminopyrimidine, 409
5-Formyl-4-hydroxy-6-methyl-2-piperidinopyrimidine, 216, 409, (410)
  condensation with nitromethane, 142, 414
  condensation with nitrophenylacetic acid *etc.*, 414
  to oxime, (413)
  to semicarbazone *etc.*, (414)
4-Formyl-6-hydroxy-2-methylthiopyrimidine
  Cannizzaro reaction, (244), (392)
  reduction, (244)
4-Formyl-6-hydroxy-2-phenylpyrimidine, (407)
  to oxime, (413)
4-Formyl-6-hydroxypyrimidine, 406
  Cannizzaro reaction on its acetal, 244, 392
  oxidation, 391
  reduction, (244)
  to a hydrazone, (414)
N-Formylmalondiamide, 439
5-Formylmethyl-4-hydroxy-2-methylpyrimidine
  failure to make by McFadyen and Steven's reaction, 412
5-Formyl-4-methyl-6-methylthio-2-piperidinopyrimidine
  to an aldazine, (414)
Formylpyrimidines (*and* acetals), 11, 21, 128
  by *C*-formylation, 408*f*
  by oxidation processes, 411*f*
  by Principal Syntheses, 406*f*
  by various means, 412*f*
  Cannizzaro reaction, 392
  from cyanopyrimidines, 410*f*
  oxidation, 391*f*
  reaction with active methylene, 414*f*
  reduction, 244
  to hydrazones, 414
  to other heterocycles, 415
  to oximes, 412, 413
  to Schiff's bases, 414
  to semicarbazones, 414
5-Formyl-2,4,6-trihydroxypyrimidine, 410
  action of aniline, 410
Fox, J., 370, 452
Frankland, 1
Frankland and Kolbe Synthesis, 93*f*, 307
  history, 96
  von Meyer's contribution, 96
Friedel-Crafts reaction
  example in pyrimidines, 120
4-Furfurylamino-6-morpholino-5-nitropyrimidine, 196
α-Furoamidine, 90
  use in Principal Synthesis, 56
β-(α-Furyl)-β-aminomethylenemalononitrile
  intermediate, 90
4-α-Furyl-2,6-dihydrazinopyrimidine, 200
2-α-Furyl-4,6-dihydroxypyrimidine, 56
4-α-Furylpyrimidine, 118
Fused pyrimidines
  completion of pyrimidine ring of, 107*f*

G

Gabriel, 1, 2, 116, 210
Godt, 366
Gomberg reaction, 26, 118
Gompper, 116, 119
Grignard reagents
  addition to pyrimidines, 20
  reaction with halogenopyrimidines, 120
Grimaux, 1
Guanidine
  use in primary syntheses, 82–111
  use in Principal Synthesis, 31–74
2-Guanidino-4,6-dihydroxypyrimidine, 55, 344

2-Guanidino-4,6-dimethyl-5-phenylazopyrimidine, 344
  hydrogenation, 156
β-Guanidino-β-phenylpropionic acid, 438
  cyclization, 438
β-Guanidinopropionic acid
  failure to cyclize, 438
Guanidinopyrimidines, 344
Guanine
  inhibition by 8-azaguanine, 334

H

Hale, 340
Halogenation, 11
  of alkylpyrimidines, 130f, 169
  of various classes of pyrimidine, 169f
Halogenonitropyrimidines
  amination, 193f
2-, 4-, and 6-Halogenopyrimidines, 162f, 284
  dehalogenation, 23, 183f
  kinetics of nucleophilic displacement, 181f
  properties of simple members, 181f
  to alkoxypyrimidines, 13, 201f
  to alkylpyrimidines, 120
  to alkylthiopyrimidines, 14, 205, 287
  to aminopyrimidines, 13f, 187f
  to carboxypyrimidines, 209
  to hydroxypyrimidines, 14, 203f, 228
  to mercaptopyrimidines, 14f, 205f, 273f
  to methylpyrimidines, 208f
  to sulphopyrimidines, 15, 207
  to thiocyanatopyrimidines, 15, 208, 337
5-Halogenopyrimidines, 168f
  amination, 210f, 314
  dehalogenation, 211f
  reactivity of halogen, 210f
  replacement by alkyl, 213
  replacement by carboxy (*via* Li derivative), 213
  replacement by cyano, 212, 404
  replacement by hydroxy, 212
  replacement by mercapto(?), 212f
Halogenopyrimidines (extranuclear), 176f
  from ethers, 254
  reactions, 214f
  removal, 216
  to acetoxy derivatives, 253
Hancox, 448
Hantzsch Synthesis
  comparison with Biginelli reaction, 441
Harper, J., 70, 73
Hatt, 448
Heilner, 450
Henze, 251
2-Heptadecyl-1,4,5,6-tetrahydropyrimidine, 445
5-Heptylpyrimidine, 94
2-Heptyl-1,4,5,6-tetrahydro-,4,4,6(or 4,6,6)-trimethylpyrimidine, 445
Hexahydro-1,3-di-isopropyl-5-methyl-5-nitropyrimidine, 453
Hexahydro-4,6-dioxo-1,3-diphenylpyrimidine, 278, 443
Hexahydro-1,3-diphenylpyrimidine, 453
Hexahydro-4-hydroxy-1,3-dimethyl-2,6-dioxopyrimidine, 258
  action of light, 258
Hexahydro-2-methyl-1,3-diphenylpyrimidine, 453
1,2,3,4,5,6-Hexahydro-1-methyl-2-oxo-4-phenylpyrimidine, 84, 436
Hexahydro-1-methyl-3-phenyl-2,4-dioxopyrimidine, 436
Hexahydro-2-oxo-1,3-diphenylpyrimidine, 446
Hexahydro-2,2,4,4,6-pentamethylpyrimidine, 453, 454
  reductive cleavage, 454
  ring-cleavage on acetylation, 457
Hexahydropyrimidine, 453
  possible equilibrium with chain isomer, 453
Hexahydropyrimidines, 452f
Hexahydro-1,3,5-trimethyl-5-nitropyrimidine
  reduction, 454
Hexahydro-4,4,6-trimethylpyrimidine, 453
  dibenzoylation, 453, 456
Hexahydro-1,2,3-triphenylpyrimidine, 453
2,4,6:2′,4′,6′-Hexahydroxy-5,5′-dipyrimidinyl
  nitration to nitrobarbituric acid, 140
Hexobarbital, 53
Hexobarbitone, 53
4-Hexyl-4,5-dihydro-6-hydroxy-2-methylpyrimidine, 440
4-Hexyl-4,5-dihydro-6-hydroxy-2-phenylpyrimidine, (440)
4-Hexyl-6-hydroxy-2-mercaptopyrimidine, 45

Heyl, 361
Hilbert, 362, 371, 378
Hill, 54
Hitchings, 251, 285
Hofmann, 445
Hofmann reaction, 102, 108, 310, 317, 336, 400, 438
Hoogewerf, 434
Hull, R., 97, 241, 414
Hydantoins
  failure of some to yield pyrimidines, 104
  intermediates in pyrimidine synthesis, 89, 103
  mistaken for pyrimidines, 51
Hydrazine
  reaction with chloropyrimidines, 199*f*
  reaction with esters, 397
4-Hydrazinocarbonyl-2,6-dimethylpyrimidine, 397
  Schiff's bases from, 401
5-Hydrazinocarbonylmethyl-2,4-dihydroxy-6-methylpyrimidine, 318, (397)
  action of nitrous acid, 336, (401)
5-Hydrazinocarbonylmethyl-2,4-dihydroxypyrimidine, 397
  Curtius reaction on, 318, (337)
  to azide, (400)
5-Hydrazinocarbonylmethyl-4-hydroxy-2-methylpyrimidine
  Curtius reaction, 317
5-Hydrazinocarbonyl-4-methyl-2-phenylpyrimidine, 397
4-Hydrazinocarbonylpyrimidine, 397
5-Hydrazinocarbonylpyrimidine, 397
Hydrazinocarbonylpyrimidines, 400*f*
  from esters, 397
5-Hydrazinocarbonyl-2,4,6-trimethylpyrimidine, (397)
  action of nitrous acid, 315, 337
5-Hydrazino-2,4-dihydroxy-6-methylpyrimidine, 210
2-Hydrazino-4,6-dimethylpyrimidine, 200
  acylation, 325
  removal of hydrazino group, 122
2-Hydrazino-4-hydroxy-6-hydroxymethylpyrimidine
  reaction with aldehydes, 323
2-Hydrazino-4-hydroxy-5-methylpyrimidine
  reaction with aldehydes, 323
2-Hydrazino-4-hydroxy-6-methylpyrimidine, 142, 145, 291, 342
  acylation, 325
  condensation with aldehydes, 323
  reaction with cyanic acid, (341)
  removal of hydrazino group, 342
  spurious preparation (342)
2-Hydrazino-4-hydroxypyrimidine, 291
4-Hydrazino-2-hydroxypyrimidine, 255
2-Hydrazino-4-methoxy-6-methylpyrimidine, 200
4-Hydrazino-5-methoxy-2-methylthiopyrimidine, 200
2-Hydrazino-4-methoxypyrimidine, 200
  reaction with aldehydes, 323
2-Hydrazino-5-methoxypyrimidine, 200
4-Hydrazino-5-methoxypyrimidine, 200
4-Hydrazino-6-methyl-2-methylthiopyrimidine, 200, 291
2-Hydrazino-4-methylpyrimidine, 200, 255, 291
  acylation, 200
  reaction with thiocyanic acid, 341
  removal of hydrazino group, 122
4-Hydrazino-6-methylpyrimidine, 141, 200, 342
  reaction with cyanic acid, 341
  reaction with thiocyanic acid, (341)
2-Hydrazino-5-phenylazopyrimidine, 289
2-Hydrazino-4-phenylpyrimidine, 200
2-Hydrazino-5-phenylpyrimidine, 200
2-Hydrazinopyrimidine, 199, 255
  acylation, (325)
4-Hydrazinopyrimidine, 255
Hydrazinopyrimidines, 199*f*
  oxidative removal of hydrazino group, 21, 122
  reaction with aldehydes, 323
4-Hydrazino-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, 200
4-Hydrazino-1,2,3,6-tetrahydro-1,3,5-trimethyl-2,6-dioxopyrimidine, 200
5-α-Hydrazonoethyl-1-methylbarbituric acid, 418
Hydriodic acid
  reactions with chloropyrimidines, 122
Hydropyrimidines, 21, 430*f*
  N-acylation, 456*f*
  N-alkylation, 458*f*
  dehydrogenation, 455
  halogenation, 457

- metatheses of mercapto and hydroxy derivatives, 457*f*
- nitration and nitrosation, 455*f*
- oxidations, 455
- reductions, 454
- various reactions, 459

Hydrothymine, 431

Hydrouracil, 6, 431

Hydroxyacetamidine
- use in synthesis, 242

Hydroxyalkylpyrimidines
- to halogenoalkylpyrimidines, 178*f*
- preparation, 242*f*

2-Hydroxyamino-4,6-dimethylpyrimidine, 344

Hydroxyaminopyrimidines, 344

4-Hydroxy-2,6-bishydroxymethyl-5-methylpyrimidine, 242

5-Hydroxydeoxyuridine, 238

4-Hydroxy-5,6-dimethyl-2-methylthiopyrimidine
- amination, 290

4-Hydroxy-2,6-dimethyl-5-nitropyrimidine, 209

2-Hydroxy-4,6-dimethyl-5-nitrosopyrimidine
- a doubtful compound, 148

2-Hydroxy-4,6-dimethyl-5-phenylazopyrimidine, 153
- reduction, 157

2-Hydroxy-4,5-dimethylpyrimidine, 34

2-Hydroxy-4,6-dimethylpyrimidine, 18, 36, 37, 229, 232
- action of nitrous acid, 148
- action of phosphoryl chloride, 163
- bromination, 169
- coupling, 153
- crystallography, 37
- 5-hydroxylation, 20*f*, 241
- styrylation, 126

4-Hydroxy-2,5-dimethylpyrimidine, 41

4-Hydroxy-2,6-dimethylpyrimidine, 49, 229, 333, 383
- bromination, (169)
- Mannich reaction, 132
- reaction with chloral, 409

4-Hydroxy-5,6-dimethylpyrimidine, 49, 122, 281

5-Hydroxy-4,6-dimethylpyrimidine, 241, 280

4-Hydroxy-2,6-dimethylpyrimidine-*N*-oxide, (383)
- reduction, (383)

2-Hydroxy-4,6-dimethylpyrimidin-5-yl hydrogen sulphate, 21, 241
- hydrolysis, 241

4-Hydroxy-2,6-diphenylpyrimidine, 87, 229

5-β-Hydroxyethylamino-5-methylbarbituric acid, 213

5-β-Hydroxyethyl-4-methylthiazole
- use in making vitamin B_1, 176

4-Hydroxyethylpyrimidine, 122, 244

4-Hydroxy-2-ethylthiopyrimidine, 38

Hydroxy groups
- effect on basic pK_a, 470

4-Hydroxy-2-hydroxyamino-6-methylpyrimidine, 342
- hydrolysis (or reduction?), 229

4-Hydroxy-5-β-hydroxyethyl-2-mercapto-6-methylpyrimidine, 280
- *S*-alkylation, (282)
- oxidative hydrolysis of mercapto group, 235

4-Hydroxy-5-β-hydroxyethyl-6-methyl-2-methylthiopyrimidine
- desulphurization, 280

4-Hydroxy-5-β-hydroxyethyl-6-methylpyrimidine, 215, 280

4-Hydroxy-6-hydroxyiminomethyl-2-mercapto-5-methylpyrimidine, 413

4-Hydroxy-5-hydroxyiminomethyl-6-methyl-2-piperidinopyrimidine, 413
- dehydration to nitrile, 404, 413

4-Hydroxy-6-hydroxyiminomethyl-2-phenylpyrimidine, 413
- reduction, (414)

4-Hydroxy-5-hydroxymethyl-2-mercapto-6-methylpyrimidine, 242

4-Hydroxy-6-hydroxymethyl-2-mercaptopyrimidine, 244

4-Hydroxy-2-hydroxymethyl-6-methylpyrimidine, 242

4-Hydroxy-5-hydroxymethyl-2-methylpyrimidine, 242, 321
- to 4-chloro-5-chloromethyl analogue, 178

4-Hydroxy-6-hydroxymethyl-2-methylthiopyrimidine, 244, (392)

4-Hydroxy-6-hydroxymethylpyrimidine, 244, 392

4-Hydroxy-5-(4-hydroxypyrimidin-2-yl)-thio-2-mercaptopyrimidine, 408

4-β-Hydroxyimino-β-phenylethyl-2,6-dimethylpyrimidine, 320

reduction, 320
4-β-(Hydroxyimino)propyl-2,6-dimethylpyrimidine, 320
  reduction, 320
4-Hydroxyimino-2,3,5-triphenylpyrrole
  conversion into pyrimidines, 105
4-Hydroxy-5-iodo-2-mercapto-6-methylpyrimidine, 274
4-Hydroxy-5-iodo-2-mercaptopyrimidine, 274, 275
  antithyrotoxicotic action, 301
4-Hydroxy-5-isobutoxy-6-isobutoxymethyl-2-mercaptopyrimidine
  two-stage hydrolysis, 239
4-Hydroxy-5-isobutoxy-2-mercapto-6-methylpyrimidine, 239
  hydrolysis by hydriodic acid, 239
4-Hydroxy-5-isopropoxy-6-isopropoxymethyl-2-mercaptopyrimidine
  hydrolysis, (239)
4-Hydroxy-2-isopropyl-6-methylpyrimidine, 49, 132, 254
  as intermediate for "Diazinon", 254
4-Hydroxy-2-mercapto-5,6-dimethylpyrimidine, 46
  desulphurization, 281
5-Hydroxy-2-mercapto-4,6-dimethylpyrimidine, 241
  desulphurization, 241, 280
4-Hydroxy-2-mercapto-6-methoxycarbonylpyrimidine, 393
4-Hydroxy-2-mercapto-5-methoxy-6-methoxymethylpyrimidine, 46, 246
  to 2-hydroxy analogue, (234)
4-Hydroxy-2-mercapto-5-methoxypyrimidine, 40, 238
  desulphurization, 238, 280
4-Hydroxy-2-mercapto-6-methyl-5-piperidinomethylpyrimidine, 133
  degradation, 133
  desulphurization, 280
4-Hydroxy-2-mercapto-6-methyl-5-propylpyrimidine
  S-alkylation, (283)
4-Hydroxy-2-mercapto-5-methylpyrimidine, 38
  S-alkylation, (282)
  desulphurization, 280, 281
  isotopic, 38
  thiation, 251
  to thymine, (234)
4-Hydroxy-2-mercapto-5-methylpyrimidine, 48, 300
  alkylation, 361
  S-alkylation, 282, 283, 361
  antithyrotoxicotic activity, 301
  chlorination, 173
  desulphurization, 280 ,281, (288)
  doubtful coupling, 154
  hydrolysis, 233, 234
  Mannich reaction, 133
  "nitration" 141
  thiation, 251
4-Hydroxy-6-mercapto-2-methylpyrimidine, 207
  S-alkylation (282)
4-Hydroxy-2-mercapto-5-phenylazo-6-trifluoromethylpyrimidine, 179
4-Hydroxy-2-mercapto-6-phenylpyrimidine
  desulphurization, 280
  nuclear reduction, 443
  thiation, 251
4-Hydroxy-2-mercapto-6-propylpyrimidine, 45, 300
  S-alkylation, (283)
  antithyrotoxicotic activity, 301
4-Hydroxy-2-mercaptopyrido[3,2-d]pyrimidine
  from a pyridine, 110
2-Hydroxy-4-mercaptopyrimidine, 251, 252, 369
  amination, 251
  desulphurization and reduction, 278, 452
  dipole moment, 28
  oxidation, 292
  to uracil, 234
4-Hydroxy-2-mercaptopyrimidine, 38, 39, 274, 295, 300*f*
  abnormal reaction with diazo compounds, 154
  abnormal reaction with phosphoryl chloride, 164
  action of phosphorus pentachloride, 166, 284
  S-alkylation, 282, 283
  desulphurization, 280
  dipole, 28
  isotopic, 38
  nitration and oxidation, 141, 292
  reaction with hydrogen peroxide, 281
  thiation, 251, 274, 346

to uracil, 234, 257
4-Hydroxy-6-mercaptopyrimidine, 207
4-Hydroxy-2-mercapto-5,6-tetramethylenepyrimidine, 44
4-Hydroxy-2-mercapto-6-trifluoromethylpyrimidine, 179
4-Hydroxy-3-methoxybenzaldehyde
  use in making styryl-type derivatives, 126
4-Hydroxy-5-β-methoxycarbonylethyl-2-methylpyrimidine, 39
2-Hydroxy-4-methoxymethyl-6-methylpyrimidine, 246
2-Hydroxy-4-methoxy-6-methyl-5-propylpyrimidine, 236
2-Hydroxy-4-methoxy-5-methylpyrimidine, (236)
2-Hydroxy-4-methoxy-6-methylpyrimidine, 236, 384
  action of phosphoryl chloride, 164, 384
  isomerization, 372
4-Hydroxy-2-methoxy-6-methylpyrimidine, 51, 245
  isomerization, 372
4-Hydroxy-2-*p*-methoxyphenyl-6-methylpyrimidine, 246
4-Hydroxy-5-methoxy-2-phenylpyrimidine, (239)
  thiation, (239), (252)
2-Hydroxy-4-methoxypyrimidine, (236)
4-Hydroxy-5-methoxypyrimidine, 238, 280
  hydrolysis, 239
  thiation, 238, (252)
2-Hydroxy-4-methylamino-5-nitropyrimidine, 232
  alkylation, 367
  reduction, 144
4-Hydroxy-6-methylamino-5-nitropyrimidine, 139
2-Hydroxy-4-methylaminopyrimidine, 63, 234, 236, 364, 380
4-Hydroxy-6-methylaminopyrimidine, 229, 232, 280
  nitration, 139
4-Hydroxy-2-*N*-methylanilinopyrimidine, 290
2-(2-Hydroxy-α-methylbenzylidene)-hydrazino-4-hydroxy-6-methylpyrimidine, 323
α-Hydroxy-β-methylcrotonamide, 432
  use in synthesis of hydropyrimidines, 432
Hydroxymethylcytosine
  see: "4-Amino-2-hydroxy-5-hydroxymethylpyrimidine"
5-Hydroxymethyldeoxyuridine, 244
4-Hydroxy-5-methyl-2,6-diphenylpyrimidine, 229
Hydroxymethyleneacetophenone
  see: "Benzoylacetaldehyde"
Hydroxymethylenephenylacetaldehyde
  use in syntheses, 33
4-Hydroxy-2-methyl-6-methylamino-5-piperidinomethylpyrimidine, 133
2-Hydroxy-5-methyl-4-methylaminiopyrimidine, (236)
4-Hydroxy-2-methyl-6-methylaminopyrimidine
  Mannich reaction, 133
4-Hydroxy-6-methyl-2-methylaminopyrimidine, 49, 307
  reaction with choral, (409)
4-Hydroxy-6-methyl-2-methylamino-5-(2,2,2-trichloro-1-hydroxyethyl) pyrimidine, (409)
  hydrolysis, (409)
Hydroxymethylmethyleneacetylurethane
  intermediate in synthesis, 89
4-Hydroxy-6-methyl-2-α-methylhydrazinopyrimidine, 291
  reaction with aldehydes, 323
4-Hydroxy-6-methyl-2-methylthio-5-piperidinomethylpyrimidine, 318
  desulphurization, 280
2-Hydroxy-4-methyl-6-methylthiopyrimidine
  amination, 290
4-Hydroxy-2-methyl-6-methylthiopyrimidine, 282
4-Hydroxy-5-methyl-2-methylthiopyrimidine, 38, 282, 287
4-Hydroxy-6-methyl-2-methylthiopyrimidine, 48, 282
  alkylation, 368
  amination, 290
  chlorination, 177
  desulphurization, 280, 288
  Mannich reaction, 133, 318
4-Hydroxy-6-methyl-2-nitroaminopyrimidine, 46, 139, 342
  reaction with amines, 342
  rearrangement, 142, 342
  reduction, 142, 145, 342
  spurious preparation, 142, (342)

4-Hydroxy-6-methyl-5-*p*-nitrostyryl-2-piperidinopyrimidine, 122, 415
4-Hydroxy-6-methyl-5-β-nitrovinyl-2-piperidinopyrimidine, 142, 415
2-Hydroxy-4-methyl-5-phenylazopyrimidine, 153
4-Hydroxy-6-methyl-2-phenylguanidinopyrimidine, 50
4-Hydroxy-6-methyl-2-phenylhydrazinopyrimidine, 291
  hydrolysis, 230
4-Hydroxy-6-methyl-5-phenyliminomethyl-2-piperidinopyrimidine
  action of nitromethane, 142
4-Hydroxy-2-methyl-6-phenylpyrimidine, 44, 87
4-Hydroxy-6-methyl-2-phenylpyrimidine
  supposed *O*-methylation *etc.*, (247)
4-Hydroxy-2-methyl-5-piperidinomethyl-6-piperidinomethylaminopyrimidine, 134
4-Hydroxy-6-methyl-5-piperidinomethylpyrimidine, 280
4-Hydroxy-6-methyl-2-piperidinopyrimidine
  condensation with chloral, 216, 409
  persulphate oxidation, (241)
  Reimer-Tiemann reaction, (410)
4-Hydroxy-6-methyl-2-piperidino-5-thiosemicarbazonomethylpyrimidine, 414
4-Hydroxy-6-methyl-2-piperidino-5-(2,2,2-trichloro-1-hydroxyethyl)pyrimidine, 216, 409
  hydrolysis to aldehyde, 216, 409
8-Hydroxy-2-methylpurine, 401
4-Hydroxy-3-methylpyrazolo[3,4-d]-pyrimidine, 111
4-Hydroxy-6-methyl-2-γ-pyridylmethylenehydrazinopyrimidine, 323
2-Hydroxy-4-methylpyrimidine, 34
  action of phosphoryl chloride, 163
  coupling, 153
4-Hydroxy-2-methylpyrimidine, 39, 227
  action of phosphoryl chloride, 163
  alkylation, 360
  possible oxidation by nitrous acid, 129
4-Hydroxy-5-methylpyrimidine, 280, 281
  action of phosphoryl chloride, 163
4-Hydroxy-6-methylpyrimidine, 122, 237, 280, 281, (288), 342, 383
  action of phosphoryl chloride, 163
  alkylation, 360
Hydroxymethylpyrimidines
  formation, 242f
  oxidation, 21, 416
  reduction, 253, 254
  stability to hydrolysis, 254
4-Hydroxy-6-methylpyrimidine-*N*-oxide, 383
  reduction, 383
4-Hydroxy-5-methyl-2-selenylpyrimidine, 38
4-Hydroxy-6-methyl-2-semicarbazidopyrimidine, 341
4-Hydroxy-2-methyl-5-sulphomethylpyrimidine, 295
4-Hydroxy-2-methyl-5-tetrahydropyran-2′-yloxypyrimidine, 41, (240)
  hydrolysis, (240)
4-Hydroxy-2-methylthio-6-phenylpyrimidine, 44
2-Hydroxy-4-methylthiopyrimidine
  alkylation, 362, 369
4-Hydroxy-2-methylthiopyrimidine, 38, 282
  action of phosphoryl chloride, (165)
  alkylation, (368)
  bromination, (171)
  chlorination, (170)
  hydrolysis, 233
4-Hydroxy-2-methylthio-5,6-tetramethylenepyrimidine, 44
5-Hydroxy-1-methyl-2-thiouracil, 239
5-Hydroxy-3-methyl-2-thiouracil, 239
4-Hydroxy-6-methyl-5-(2,2,2-trichloro-1-hydroxyethyl)-2-(3,3,3-trichloro-2-hydroxypropyl)pyrimidine, 409
5-Hydroxy-1-methyluracil, 239, (363)
5-Hydroxy-3-methyluracil, (363)
Hydroxymethyluracil
  see: "2,4-Dihydroxy-5-hydroxymethylpyrimidine"
4-Hydroxy-5-methyl-2-ureidopyrimidine, 340
6-Hydroxy-1-methyl-5-ureidouracil
  ethylation, 363
5-Hydroxymethyluridine, 244
4-Hydroxy-6-*p*-nitrophenylhydrazonomethylpyrimidine, 414
2-Hydroxy-5-nitropyrimidine, 32, 139, 231
  action of phosphoryl chloride, 163
  alkylation, 363

2-*p*-Hydroxyphenyl-4,6-dimethylpyrimidine
  oxidation, 127
2-Hydroxy-5-phenylpyrimidine, 33
  alkylation, 360
4-Hydroxy-2-phenylpyrimidine
  action of phosphorus pentachloride, (165)
  supposed *O*-methylation, (247)
4-Hydroxy-5-phenylpyrimidine
  methylation, 360
4-Hydroxy-6-phenylpyrimidine, 95, 280
  action of phosphoryl chloride, 163
5-Hydroxy-2-phenylpyrimidine, 239
4-Hydroxy-2-phenyl-5,6-(1,2,3,6-tetrahydro-1-methyl-5,4-pyrido) pyrimidine, 45
4-Hydroxypteridine
  preparation from a pyrazine, 108
6-Hydroxypteridine
  reduction and ring fission, 314
7-Hydroxypteridine
  formation and hydrolysis, 107
  reductive ring fission, 314, 390
2-Hydroxypurine
  degradation to a pyrimidine, 105, 314
4-Hydroxypyrido[3,2-d]pyrimidine, 109
2-Hydroxypyrimidine, 32, 185, 227, 229, (231), 233
  action of phosphoryl chloride *etc.*, 162, 165
  alkylation, 25, 247, 359
  halogenation, 169
  reduction, 22, 278, 452
2-Hydroxypyrimidine methiodide, 357
  see: "1,2-Dihydro-1-methyl-2-oxopyrimidine"
4-Hydroxypyrimidine, 122, 205, (212), 228, 280, 281, 300
  action of phosphoryl chloride, 162
  N-acylation, 357
  alkylation, 247, 357, 359
  halogenation, 169
  U.V. spectra (Figs. 4 and 5), 480
5-Hydroxypyrimidine, 238, 239
  attempt to make, 238
  unsatisfactory methylation, 248
Hydroxypyrimidines, 14, 227*f*
  acylation, 25, 252*f*
  alkylation, 25, 247*f*
  effect of tautomeric form on p*K*a, 465
  halogenation, 169*f*
  ionization as acids, 466
  ionization as bases, 465
  naturally occurring, 256*f*
  preparation (2-, 4-, 6-)
    from alkoxypyrimidines, 232, 237
    from alkylthiopyrimidines, 289
    from aminopyrimidines, 17, 229, 321
    from halogenopyrimidines, 203*f*, 228*f*
    from mercaptopyrimidines, 16*f*, 233*f*
    from primary syntheses, 227*f*
  preparation (5-)
    by minor ways, 237
    by indirect primary syntheses, 238
    by persulphate oxidation, 241
  removal of hydroxy group, 253
  tautomerism, 482*f*, 494
  thiation, 251*f*, 274
  to chloropyrimidines, 16, 162*f*, 250
Hydroxypyrimidines (extranuclear)
  acylation, 253
  amination, 255
  by direct synthesis, 242
  from aldehydes or ketones, 244, 417
  from amino derivatives, 242
  from halogeno derivatives, 214*f*, 243
  from esters, 243
  from formaldehyde, 243*f*
  oxidation, 416
  rearrangement of, 256
  reductive removal of hydroxy group, 253*f*
  to halogeno pyrimidines, 254
4-Hydroxy-2-selenylpyrimidine, 38
2-Hydroxy-5-sulphopyrimidine, 296
  action of phosphorus pentachloride, 296
4-Hydroxy-2,6,7-triphenylpteridine, 109
4-Hydroxy-2,5,6-triphenylpyrimidine, 105
5-Hydroxyuridine, 212, 238
Hydurilic acid
  see: "2,4,6:2′,4′,6′-Hexahydroxy-5,5′ dipyrimidinyl"
Hypobromous acid
  addition to pyrimidines, 19

I

Imidoyl chlorides
  preparation, 85

  use in primary syntheses, 85
2-Imino-5-nitro-1,3-thiazine, 33
2-Imino-4-pentanone
  use, 94
β-Imino-β-phenylpropionitrile
  use, 95
β-Iminopropionitrile
  see: "2-Amino-1-cyanopropene"
Iminopyrimidines, 377*f*
  hydrolysis, 373
  identification by pK_a, 464
  rearrangements of, 373, 379*f*
  strength as bases, 377, 464, 470
Infrared spectra, 494*f*
  assignments of vibrations of pyrimidine, 495*f*
  in tautomerism studies, 494*f*
  of pyrimidine (Fig.7), 481
  utility of, 494
Iodine monochloride
  iodination *or* chlorination with, 169
4-Iodo-6-methylpyrimidine, 122, 168
  amination, 188
5-Iodo-2-*p*-nitrobenzenesulphonamidopyrimidine
  formation of a thioether, 213
5-Iodopyrimidine, 18
Iodopyrimidines, 168
5-Iodo-2-sulphanilylaminopyrimidine, 171
Ionization constants
  alphabetical table of, 472*f*
  utility of, 464
"Iothiouracil"
  see: "4-Hydroxy-5-iodo-2-mercaptopyrimidine"
Isobarbituric acid, 6
4-Isobutylpyrimidine, 94
β-Isocyanatobutyramide
  as intermediate, 438
β-Isocyanatopropionamide
  as an intermediate, 438
Isocyanatopyrimidines, 418*f*
Isocytosine, 6
Isodialuric acid, 6, 263, 335
  alleged structure, 263
5-Isopropylpyrimidine, 94
2-Isothiocyanato-2-methylpentan-4-one, 437
  action of alkylamine, 437
Isothiocyanatopyrimidines, 421*f*
  by isomerization, 15, 208, 421*f*
  to thioureides, 341, 422
  to thiourethanes, 337*f*
Isouracil, 6
Isouramil, 6
Isovioluric acid, 6
Isoxazoles
  pyrimidines from, 104*f*

J

Johnson, T. B., 2, 54, 210, 259, 346, 347, 361, 362, 371, 423, 431, 441, 450
Johnson and Hahn, review, 2

K

"Kemithal", 54
Kenner, 2
Kenner and Todd, review, 2
5-Ketobarbituric acid, 6
β-Keto esters
  use in Principal Syntheses, 48*f*
  reaction with amidines, 49
  reaction with guanidines, 49*f*
  reaction with thioureas, 48*f*
  reaction with ureas, 50*f*
β-Keto nitriles
  use in Principal Syntheses, 65
Klötzer, 398
Kolbe, 1
Kornfeld, 331
Kossel, 258
Kyanäthin, 96
Kyanalkine, 7, 93*f*
Kyanisobutin, 7
Kyanmethin, 6, 96

L

La Forge, 443
Laney, 259
Lengfeld, 434
Levene, 259, 443
Levene and Bass (book), 256
Liddle, 300
Liebig, 1, 260
Light
  catalytic action in a Principal Synthesis, 37
  catalytic action in water addition, 442
Lithium aluminium hydride

  use in nuclear reduction of pyrimidines, 443, 450
  use in reducing acylated aminopyrimidines, 23
  use in reducing ester, 243
Lumazine
  see:"2,4-Dihydroxypteridine"
"Luminal", 53
Lythgoe, 2

M

"Madribon", 331
Maleic acid
  failure to give a dihydropyrimidine with urea, 432
Maleic diamide
  semi-Hofmann-reaction, 101
  use in uracil synthesis, 101
Malic acid
  reaction with sulphuric acid, 38, 257
Malondialdehyde
  availability as acetal, 32
  use in cytosine synthesis, 59
  use of equivalents in syntheses, 33*f*
  use in syntheses, 32, 227, 272, 381
Malondiamide
  self condensation, 98, 398
Malondiamides
  condensation with acid chloride, 98
  condensation with amides, 98
  condensation with carbonic acid derivatives, 99
  condensation with esters, 97*f*, 228
  condensation with oxalyl chloride, 99
  self condensation, 98
Malondiamidine, 100
  condensation with esters, 100
  use in syntheses, 97*f*, 390
Malondithioamide
  attempted use in synthesis, 273
Malonic acid
  use in Principal Syntheses, 51*f*
Malonic esters
  use in Principal Syntheses, 51*f*
Malononitrile
  anomalous reaction with formamidine, 72
  in Principal Syntheses, 72*f*, 273
Malonyl chloride
  use in Principal Syntheses, 53, 55*f*
Mannich, 450
Mannich reaction, 12, 26, 132, 318
Marshall, 477
Mason, S. F., 477
Matter, 448
McFadyen and Stevens reaction, 412
McOmie, J.F.W., 259
"Meralluride", 367
4-Mercapto-2,6-dimethoxypyrimidine, 294
  action of chloramine, 298
  S-arylation, (283)
  oxidation, (292)
2-Mercapto-4,6-dimethylpyrimidine, 37, 206
  S-alkylation, (282), (283)
  desulphurization, 122, 280
  oxidation by chlorine, 167
4-Mercapto-2,6-dimethylpyrimidine, 206
4-Mercapto-5-methoxy-2-phenylpyrimidine, (239), 252
  desulphurization, (239), 280
4-Mercapto-5-methoxypyrimidine, 239, 252
  desulphurization, 239, 248, 280
2-Mercapto-4-methylaminopyrimidine, 285, 309
  desulphurization, 280
  indirect hydrolysis of mercapto group, 234
2-Mercapto-4-*N*-methylanilinopyrimidine, 285
2-Mercapto-1-methylglyoxaline
  as a drug, 301
2-Mercapto-4-methyl-6-phenylpyrimidine
  desulphurization, 122, 280
2-Mercapto-4-methyl-6-piperidinopyrimidine, 280, 285
2-Mercapto-5-methyl-4-piperidinopyrimidine
  failure to prepare, (285)
2-Mercapto-4-methylpyrimidine, 34, 35
  S-alkylation, (283)
  desulphurization, 122, 280
4-Mercapto-6-methylpyrimidine, 206
  oxidation, 292
2-Mercapto-5-phenylazopyrimidine
  S-alkylation, (283)
2-Mercapto-5-phenylpyrimidine
  desulphurization, 122, 280
2-Mercapto-4-piperidinopyrimidine, 285
4-Mercaptopteridine

  preparation from a pyrazine, 108
2-Mercaptopurine
  degradation to a pyrimidine, 105, 313
6-Mercaptopurine
  reaction with a bromopyrimidine, 288
2-Mercaptopyrimidine, 32, 205*f*, 273, 274
  S-alkylation, (282), (283)
  pyrimidine from, 117, 279, 281
4-Mercaptopyrimidine, 206
2-, 4-, and 6-Mercaptopyrimidines, 14*f*, 272*f*
  acylation, 25*f*, 286
  alkylation, 25*f*, 282*f*
  by direct introduction, 276
  desulphurization, 23, 277*f*
  from alkylthiopyrimidines, 252, 274*f*
  from aminopyrimidines, 275
  from halogenopyrimidines, 205*f*, 273*f*
  from hydroxypyrimidines, 16*f*, 251*f*, 274
  from primary syntheses, 272*f*
  from thiocyanatopyrimidines, 275, 420
  halogenation, 170*f*
  ionization as acids, 467
  ionization as bases, 465*f*
  oxidation, 21
  stability in air, 286, 291
  tautomerism, 485
  to alkoxypyrimidines, 247
  to aminopyrimidines, 17, 284*f*
  to halogenopyrimidines, 284
  to hydroxypyrimidines, 17, 233*f*
5-Mercaptopyrimidines
  instability in air, 286
  preparation, 276
Mercaptopyrimidines (extranuclear)
  acylation, 286
  preparation, 277
4-Mercapto-5,6-trimethylenepyrimidine
  desulphurization, 280
Mercury fulminate
  use to introduce cyano group, 405
Mesityl oxide, 448
  addition of ammonia, 448
  use in making hydropyrimidines, 432, 433, 437
Mesoxalylurea
  see: "Alloxan"
"Methiminazole", 301
p-Methoxybenzoylacetaldehyde
  use in synthesis, 35
4-Methoxybutenyne
  as equivalent of formylacetone in synthesis, 35
5-Methoxycarbonylamino-2,4-dimethylpyrimidine, 314, 336
  hydrolysis, 314
2-Methoxycarbonyl-4,6-dimethylpyrimidine, 396
2-β-Methoxycarbonylethylpyrimidine, 394
  to amide, (396)
4-β-Methoxycarbonylethylpyrimidine, 394
  to amide, (396)
2-Methoxycarbonyl-5-methylpyrimidine, 394
2-Methoxycarbonylmethylthio-5-phenylazopyrimidine, 283
  amination, 289
5-Methoxycarbonylpyrimidine, 393
  to amide, 396
  to hydrazide, (397)
4-Methoxy-2,6-dimethyl-5-nitropyrimidine
  hydrogenation, 144
2-Methoxy-4,6-dimethylpyrimidine, 18, 201
4-Methoxy-2,6-dimethylpyrimidine, 248
5-Methoxyiminobarbituric acid
  by methylation of violuric acid, 147
  from alloxan, 147
β-Methoxy-α-methoxymethyleneproprionitrile
  use, 246
β-Methoxy-α-methylacryloyl isothiocyanate
  use, 89
2-Methoxy-4-methylamino-5-nitropyrimidine, 194, 203, 232, 255
  attempted amination, 255
  hydrolysis, 232
4-Methoxy-6-methylamino-5-nitropyrimidine
  attempted amination, 255
4-Methoxy-6-methylaminopyrimidine, 229, 232
  hydrolysis, 229, 232
4-Methoxy-6-methyl-2-methylsulphonylpyrimidine, 236, 299
  alkaline hydrolysis of 2-group, 236
4-Methoxy-6-methyl-2-methylthiopyrimidine, 203

  amination, 291
  oxidation, (299)
2-Methoxy-4-methylpyrimidine, 201
  formation of *N*-oxide, 382
4-Methoxy-6-methylpyrimidine, 201, 360, 383
  formation of *N*-oxide, 382
2-Methoxy-4-methylpyrimidine-*N*-oxide, 382
  Reissert reactions, (384)
4-Methoxy-6-methylpyrimidine-*N*-oxide, 19, 382
  reduction, 383
5-Methoxy-4-methylthiopyrimidine
  to 4,5-dihydroxypyrimidine, 239
2-Methoxy-5-nitropyrimidine, 363
1-Methoxy-1-phenyl-1-buten-3-one
  use, 94
2-Methoxy-5-phenylpyrimidine, 360
4-Methoxy-5-phenylpyrimidine, (360)
5-Methoxy-2-phenylpyrimidine, 280
8-Methoxypurine, 247
2-Methoxypyrimidine, 25, 201, 247, 359
  amination, 200, 255
  isomerization, 25, 371
  U.V. spectrum (Fig. 2), 479
4-Methoxypyrimidine, 185, 201, 247, 248, 359
  amination, 15, 255, 309
  formation of *N*-oxide, 382
  rearrangement, 256, 371
  U.V. spectrum (Fig. 2), 479
  U.V.spectra (Figs. 4 and 5), 480
5-Methoxypyrimidine, 14, 210, 239, 247, 248, 280
  hydrolysis, 239
Methoxypyrimidines, 13
  replacement of methoxy group, 15
  see also: "Alkoxypyrimidines"
4-Methoxypyrimidine-*N*-oxide, 382
  Reissert reaction, (384)
4-Methoxy-2-sulphanilylaminopyrimidine
  amination, 255
Methyl acetimidate
  use in synthesis, 86
Methylacetylacetone
  use in synthesis, 119
α-Methylacrylic acid
  use in synthesis of hydropyrimidines, 431
Methylamine acetate (salt)
  use in amination, 195
β-Methylaminoethyl phenyl ketone
  reaction with cyanic acid, 84
Methylaminomalondiamide
  use in Remfry-Hull Synthesis, 98, 313
2-Methylamino-5-nitropyrimidine, 193
Methyl β-aminopropionate
  use in dihydropyrimidine synthesis, 434
β-Methylaminopropiophenone
  use in hydropyrimidine synthesis, 436
2-Methylaminopyrimidine, 188, 311, 373, 377, 379
  alkylation, 312
  hydrolysis, 229
4-Methylaminopyrimidine, 184, 280
N-Methylated thiopyrimidines
  see: "Thiopyrimidines"
1-Methylbarbituric acid, 56, 273
  alkylation, 362
p-Methylbenzoylacetaldehyde
  use in synthesis, 35
Methyl benzyloxyformylacetate
  use, 40
4-Methyl-2,6-bis-*o*-hydroxybenzylidenehydrazinopyrimidine, 323
2-Methylbutyramide
  as degradation product, 133
Methylcytosine, 6, 347
α-Methyl-β-diethylaminoacrolein
  cyclization with formamide, 93
5-Methyldeoxycytidine, 6
4-Methyl-6,7-diphenylpteridine, 334
4-Methyl-2,6-diphenylpyrimidine, 120, 123
4-Methyl-2,6-distyrylpyrimidine, 411
  ozonization *etc.*, to aldehyde, 411
1-Methyldithiouracil, 252, 376
3-Methyldithiouracil, 252, 274, 376, 382
5-Methylenebarbituric acid, 124
Methyl ethoxycarbonyldithioacetate
  use in Principal Synthesis, 59
Methyl α-formyl-α-methoxyacetate
  use in synthesis, 238
Methyl groups
  effect on acidic pK_a, 466
  effect on basic pK_a, 465
Methylguanidine
  use in Principal Syntheses, 49*f*, 55
2-Methylimino-4-pentanone
  use, 94
Methyl iodide

  catalytic effect on rearrangement of alkoxypyrimidines, 256
β-Methylmalic acid
  use, 39, 258
Methylmalondiamide
  reaction with diethyl methylmalonate, 97
2-Methyl-2-methylaminopentan-4-one, 448
  action of benzaldehyde and ammonia, 448
Methyl β-methylaminopropionate
  use in hydropyrimidine syntheses, 435
2-Methyl-4-methylamino-5-thioformamidomethylpyrimidine, 327
1-Methyl-5-methylaminouracil, 210
3-Methyl-5-methylaminouracil, 210
Methyl α-methyl-β-methylaminopropionate
  use in hydropyrimidine syntheses, 435
9-Methyl-6-methylthiopurine, (326)
4-Methyl-6-methylthiopyrimidine, 205
4-Methyl-2-methylthiopyrimidine
  amination, 291
4-Methyl-6-methylthio-2-(2,2,2-trichloro-1-hydroxyethylamino) pyrimidine, (409)
4-Methyl-6-nitroaminopyrimidine, 141, 341
  acidity of, 342
  reduction, 141, 341
4-Methyl-2-*p*-nitrobenzenesulphonamidopyrimidine, (331)
  reduction, (331)
2-Methyl-5-nitropyrimidine, 32, 139
S-Methyl-*N*-nitrothiourea
  use, 447
1-Methyl-5-nitrouracil, 140, 231, 364, 367*f*
  alkylation, 364
  reduction, 363
3-Methyl-5-nitrouracil, 48, 140, 364, 417
  alkylation, 364
  reduction, 363
"1-Methyl-4-oxopyrimidine"
  as a name for 1,4-dihydro-1-methyl-4-oxopyrimidine, 356
4-Methyl-2-phenoxypyrimidine
  amination, 255
4-Methyl-6-phenoxypyrimidine
  formation of *N*-oxide, 382
4-Methyl-6-phenoxypyrimidine-*N*-oxide, 382
  amination, 383
  Reissert reaction, (383)
4-Methyl-2-phenylpyrimidine, 34, 121
  reaction with phenyl-lithium, 123
4-Methyl-2(+6)-phenylpyrimidine, 123
4-Methyl-6-phenylpyrimidine, 93, 94, 121, 122, 280
  N-oxide formation, 128
5-Methyl-4-phenylpyrimidine, 95, 123
4-Methyl-6-phenylpyrimidine-N-oxide, 128
α-Methyl-β-phenylsuccindiamide
  use in synthesis, 102
6-Methyl-3-phenyl-2-thiouracil, 83, 273
1-Methyl-6-phenyluracil, (362)
  alkylation, (362)
6-Methyl-1-phenyluracil, 89
6-Methyl-3-phenyluracil, 83, 228
4-Methyl-6-piperidinopyrimidine, 280, 383
4-Methyl-6-piperidinopyrimidine-*N*-oxide, 383
  reduction, 383
4-Methyl-2-piperidino-6-(2,2,2-trichloro-1-hydroxyethylamino) pyrimidine, 409
  hydrolysis, 409
5-Methyl-1-propyl-2-thiouracil, 89, 273
9-Methylpurine, 326
  degradation to a pyrimidine, 106, 313
2-Methylpyrimidine, 32, 120, 121
  bromination, 130, 177, 392
  N-oxide formation, 128
  reaction with chloral, 126
  reduction, (451)
  styrylation, 122
4-Methylpyrimidine, 91, 94, 121, 122, (211), 216, 280, 383
  amination, 12, 134, 308
  attempted nitration, 128
  Claisen reaction, 26, 132
  Mannich reaction, 26, 132, 318
  N-oxide formation, 126, 128
  oxidation, 126, 128
  reaction with chloral, 126
  reaction with formaldehyde, 122, 244
  reaction with phenyl-lithium, 123
  reaction with sodamide, 12, 134, 308
  reduction, (451)
  styrylation, 122, 126
5-Methylpyrimidine, 93, 94, 121, 127
  reaction with phenyl-lithium, 123
  N-oxide formation, 128

reduction, (451)
2-Methylpyrimidine-1-oxide, 128
4-Methylpyrimidine-*N*-oxide, 128
  reduction, 383
  Reissert reaction, (384)
5-Methylpyrimidine-1-oxide, 128
Methlpyrimidines
  Claisen reactions, 131*f*
  conversion into styrylpyrimidines, 125
  Mannich reactions, 132*f*
  oxidation, 21, 130, 399*f*
6-Methylselenylpurine, 284
4-Methyl-6-semicarbazidopyrimidine, 341
5-Methyl-2-styrylpyrimidine, 26, 125
  oxidation, 128
α-Methylsuccindiamide
  use, 438
Methylsulphonylpyrimidines, 15
4-Methyl-2-sulphopyrimidine, 207, 295
  action of cyanide, 207, 297
4-Methyl-5,6-tetramethylene-2-phenylpyrimidine, 36
4-Methyl-5,6-tetramethylenepyrimidine, 95
2-Methylthio-5-nitropyrimidine, 33, 139, 287
  action of Raney nickel, 144, 279
2-Methylthio-5-phenylazopyrimidine, 33
2-Methylthiopurine, (326)
  degradation to a pyrimidine, 105, 314
2-Methylthiopyrimidine, 185, 282
  bromination, (170)
4-Methyl-2-thiosemicarbazidopyrimidine, 341
4-Methyl-6-thiosemicarbazidopyrimidine, 341
1-Methyl-2-thiouracil, 101, 273
1-Methyl-4-thiouracil, 252, 376
  amination, 285
  desulphurization and reduction, 278, 452
N-Methylthiourea
  use in Principal Synthesis, 31–74, 381
S-Methylthiourea
  use in Principal Syntheses, 31–74
1-Methyl-5,5-trimethylenebarbituric acid, 57
3-Methyl-5,6-trimethylene-2-thiouracil, 83
5-Methyl-2,4,6-triphenylpyrimidine, 95, 119
1-Methyluracil, 101, 233, 360*f*, 368, 369, 371, 455
  action of phosphoryl chloride, 370, 376
  nitration, 140, 364
  reduction, 444, 452
  structure, 361
  thiations, 252, 376
3-Methyluracil, 42, 233, 358, 359, 361, 368, 370, (393)
  alkylation, 369
  nitration, 140, 364
  structure, 361
  thiation, 252, 376, 382
N-Methylurea
  use in Principal Syntheses, 42*f*, 56
O-Methylurea, 245
  use in Principal Syntheses, 40, 51, 70, 245
δ-Methyl-β-ureidohexanoic acid, 459
  cyclization, 459
β-Methylureido-β-phenylpropionic acid, 458
Methyl β-ureidopropionate, 434
  cyclization, 434
Methylurethane
  use in Shaw Synthesis, 88
3-Methylxanthine, 150, 366
  formation as structural proof, 69
  methylation, 366
Meyer and Jacobson, text book, 2
Miazine, 1, 6
Morlock, 116, 119
Moubasher, 262
Mucobromic acid
  use in synthesis, 175
Mucochloric acid, 175
  use in syntheses, 175
Muller, 423
Murexide, 263
  test, 263

N

2-α-Naphthylmethyl-1,3,5-triazine
  description of a pyrimidine as, 92
"Nembutal", 53
Neumann, 258
Nitration, 10, 139*f*
Nitroaminopyrimidines, 341*f*
p-Nitrobenzaldehyde
  use in making styryl derivatives, 126
m-Nitrobenzamidine
  use in synthesis, 139
2-*p*-Nitrobenzenesulphonamido-5-phenylthiopyrimidine, 213

2-*p*-Nitrobenzenesulphonamidopyrimimidine, 331
  reduction, 331
p-Nitrobenzenesulphonyl chloride
  use as acylating agent, 331
Nitrobenzenesulphonylguanidine
  use in synthesis, 50, 330
5-*p*-Nitrobenzylideneaminopyrimidine, 143, 322
5-Nitro-2,4-bispropylaminopyrimidine, 195
5-Nitro-2,4-diphenoxypyrimidine, 203, 420
Nitro group
  effect on acidic pK_a, 467, 471
  effect on basic pK_a, 469, 471
  effect on other substituents, 138
Nitroguanidine
  use in hydropyrimidine syntheses, 447*f*
  use in Principal Synthesis, 46, 342
Nitromalondialdehyde
  use in syntheses, 32, 139, 287
p-Nitrophenylazomalononitrile
  use in syntheses, 72, 153
4-*p*-Nitrophenyl-6-phenylpyrimidine, 95
5-Nitro-2-phenylpyrimidine
  hydrogenation, 144
2-*m*-Nitrophenylpyrimidine, 134
2-*p*-Nitrophenylpyrimidine, 26, 118
4-*m*-Nitrophenylpyrimidine, 134
4-*p*-Nitrophenylpyrimidine, 26, 118
5-Nitro-2-piperidinopyrimidine, 33
β-Nitropyridine
  analogy to pyrimidine, 465
Nitropyrimidines, 138*f*
  preparation by direct syntheses, 138*f*
  preparation by indirect syntheses, 142*f*
  preparation by nitration, 139*f*
  reduction, 23, 143*f*
Nitrosation, 10, 148
Nitrosobenzene
  reaction with 5-aminopyrimidine, 156, 335
2-(*N*-Nitrosocarboxyamylamino)-pyrimidin-5-yldiazonium chloride, 333
  Sandemeyer reaction, 333
5-Nitroso-1,3-diphenylbarbituric acid
  colour of salts, 147
5-Nitroso-1,3-diphenyl-2-thiobarbituric acid
  colour of salts, 147
Nitrosomalononitrile
  use in Principal Synthesis, 72
6-Nitrosomethyldiazouracil(?), 332
Nitrosopyrimidines, 146*f*
  by direct syntheses, 149
  by nitrosation, 148
  colour, 147
  condensation with methylene groups, 151
  containing 4-nitroso groups, 151*f*
  hydrolysis of amino groups in, 146
  reaction with chlorine, 151
  reduction, 23, 149
  tautomeric with hydroxyiminopyrimidines, 10, 146
Nitrouracil, 6
Nitrous acid
  use in converting amino- to hydroxypyrimidines, 18
Nucleic acids
  photochemistry of, 258
Nucleophilic metatheses, 12*f*
Nucleophilic substitution, direct, 12
  unusual example, 209
Nucleosides
  by Shaw Synthesis, 90
  reduction of, 443
  syntheses, 101
  sugar removal, 443
Nucleotides, 257, 346
  hydrolysis, 257, 346

O

Ochiai, E., 207, 382
Orotic acid, 6, 422*f*
  see also: "4 Carboxy-2,6-dihydroxypyrimidine"
Orotidine, 6
Orotidylic acid
  in pyrimidine biosynthesis, 425
Orotidylic decarboxylase, 425
Orotidylic pyrophosphorylase, 425
Othman, 262
Oxaloacetic acid, 89
Oxalyl chloride
  reaction with malondiamides, 99
1,3-Oxazines
  as pyrimidine intermediates, 104
Oxidation of pyrimidines, 20
5-Oxobarbituric acid
  see: "Alloxan"

Oxopyrimidines, 357*f*
  by alkylation of hydroxypyrimidines, 359*f*
  by hydrolysis of imino derivatives, 373*f*
  by Principal Syntheses, 357
  by rearrangement of alkoxy derivatives, 371*f*
  by sundry syntheses, 358
  melting points, 375
  properties and reactions, 375*f*
  thiation, 252, 376

P

Parbanic acid, 261
Pentobarbital, 53
Pentobarbitone, 53
"Pentothal", 54
Pfleiderer, W., 325
"Phanodorn", 53
Phenobarbital, 53
Phenobarbitone, 53
Phenol,
  use as amination solvent, 195
3-Phenoxyacrolein
  use in synthesis 34
p-Phenoxyphenylguanidine
  use in synthesis, 37
2-Phenoxypyrimidine, 201
Phenylacetaldehyde
  reaction with ethyl ureidocrotonate, 442
  to a dihydropyrimidine with urea, 442
Phenylacetamidine
  use in Principal Syntheses, 44, 49
Phenylacetonitrile
  use in syntheses, 91
2-Phenylamidinopyrimidine, 406
α-Phenyl-aminomethylenephenylacetonitrile
  cyclization with formamide, 92
Phenylazoacetylacetone
  use in Common Syntheses, 152, 344
Phenylazobenzoylacetone
  use in syntheses, 37, 152
Phenylazomalondialdehyde
  use in syntheses, 33
Phenylazomalononitrile
  use in Principal Synthesis, 72, 153
5-Phenylazopyrimidine, 156, 335
1-Phenylbarbituric acid, 56
Phenyl benzoate
  use as acylating agent, 327
Phenyldiguanide
  use in synthesis, 50
2-Phenyl-4,6-distyrylpyrimidine, 125
4-Phenylethylpyrimidine, 122
Phenylformylacetonitrile
  conversion into enol ether, 65
  possible existence as enol, 65
  use, 64
Phenylguanidine
  use in syntheses, 58, 72
Phenyl-lithium
  reaction with alkylpyrimidines, 122, 123
  reaction with halogenopyrimidines, 120
Phenylmalondialdehyde
  use of equivalent in synthesis, 33
5-Phenylmethylenebarbituric acid, 123
  reduction, 124
1-Phenyl-2-propionylacetylene
  use, 95
β-Phenylpropiophenone, 433
4-Phenyl-6-propylpyrimidine, 95
2-Phenylpyridine
  nitration, 134
4-Phenylpyridine
  nitration, 134
2-Phenylpyrimidine, 121, (211), 455
  failure to form an *N*-oxide, 128
  nitration, 134
4-Phenylpyrimidine, 20, 91, 94, 118, 121
  nitration, 134
5-Phenylpyrimidine, 121, 122, 280
3-Phenyl-5,6-trimethyleneuracil, 83
1-Phenyluracil, 89, 455
3-Phenyluracil, (393)
N-Phenylurea
  use, 56
β-Phenylureidopropionic acid, (434)
  cyclization, (434)
9-Phenyluric acid, 339
Phosgene
  use to supply $C_{(2)}$ in pyrimidines, 99
Phosphorus pentabromide
  reaction with hydroxypyrimidines, 167
Phosphorus pentachloride
  C-chlorination with, 165*f*
  for converting hydroxy- into chloropyrimidines, 16, 165*f*
Phosphorus pentasulphide
  use in thiation, 251*f*
Phosphorus trichloride

  use in removing N-oxide, 383
Phosphoryl bromide
  for changing hydroxy to bromo groups, 16, 167
Phosphoryl chloride
  use in replacing hydroxy by chloro groups, 16, 162f
  use with dialkylaniline, 163f
Phthalic diamide
  use to make 2,4-dihydroxyquinazoline, 102
1-Phthalimidopentan-2,4-dione
  use in synthesis, 319
Pinner, 1, 406, 449
α-Piperidinomalondiamide, 211
Piperimidine, 6, 453
pK_a values
  see: "Ionization constants"
Polarography of pyrimidines, 28f
Potassium ferricyanide
  oxidation of methyl to carbamoyl groups, 130
Primary syntheses
  classification of, 82
  by Common Synthesis, 31f
  by other methods, 82f
Principal Synthesis, 31f
  examples, 31f
  modification for dihydropyrimidines, 431f
  scope, 31
  use to make hydroxypyrimidines, 227
  use to make urethanes, 336
Propioloylurethane
  formation, 89
  reaction with aniline, 89
Propionamidine
  reaction with acetic anhydride, 102
  use in Principal Synthesis, 44, 52, 246
Propionitrile
  trimerization to a triazine, 93
Propionylacetone
  use in synthesis, 36
4-Propylpyrimidine, 94
Propynal
  use in synthesis, 34
Pseudouric acid, 6, 339
Pteridine, 300, 334
  acid hydrolysis, 324
Pteridines
  formation from pyrazines, 108f
  pyrimidines from, 106f
Purine, 300, 326, 327, 333
Purines
  formation from glyoxalines, 108
  pyrimidines from, 105f
Purpuric acid, 263
Pyrazine
  dipole moment, 28
  electron density, 27
Pyrazolopyrimidines
  from pyrazoles, 110f
Pyridazine
  dipole moment, 28
  electron density, 27
Pyridine
  bromination, 118
  dipole moment, 28
  electron density, 27
  use as solvent in thiation, 252
Pyridines
  pyridopyrimidines from, 109f
Pyridopyrimidines
  from pyridines, 109f
Pyrimidine
  active 2-, 4- and 6-positions, 7
  analogy to β-nitropyridine, 465
  "aromatic" 5-position, 8
  assignment of vibrations (I.R. and Raman), 495f
  bromination, 11, 118
  by decarboxylation, 116
  by dehalogenation, 116f, 187, (211), 212, 451
  by desulphurization, 279, 281
  by primary syntheses, 94, 116
  decomposition in alkali, 118
  effect of substitution, 8
  π-electron deficiency, 8, 10
  electron-density diagrams, 27
  ionization, 465
  oxidation, 228
  properties, 117
  reaction with alkyl-lithium, 118f
  reaction with Grignards, 118, 444
  reactions, 118
  recovery from mercuric chloride complex, 117f
  reduction, 22, 118, 451
  salts and complexes, 117
  spectra (I.R.; Fig. 7), 481
  spectra (U.V.; Fig. 1), 479
  spectra (U.V.; Fig. 3), 480
  vibration modes (Fig. 8), 497, 498

Pyrimidine acid chlorides, 394
  to esters, 394
  to amides, 394
Pyrimidine aldehydes
  see: "Formylpyrimidines"
Pyrimidine amides
  see: "Carbamoylpyrimidines"
Pyrimidine azides
  see: "Azidocarbonylpyrimidines"
Pyrimidine carboxylic acids
  see: "Carboxypyrimidines"
Pyrimidine disulphides, 21, 212, 291*f*
  reactions, 294*f*
Pyrimidine esters, 393*f*, 395*f*
  capacity to resist ammonia, 396
  hydrolysis, 391
  reactions, 396*f*
  reduction, 243
Pyrimidine hydrazides
  see: "Hydrazinocarbonylpyrimidines"
Pyrimidine ketones
  see: "*C*-Acylpyrimidines"
Pyrimidine methiodide, 18*f*, 117
Pyrimidine nitriles
  see: "Cyanopyrimidines"
Pyrimidine-*N*-oxide, 356
  action of acetic anhydride, 384
Pyrimidine-*N*-oxides, 19, 118, 128, 356, 382*f*
  formation, 382
  reactions, 383*f*
  reduction of, 19, 383
  removal of *N*-oxide, 383
Pyrimidines
  aqueous solubility, 29
  biosynthesis, 424*f*
  dipole moments, 28
  from hydantoins, 102
  from isoxazoles, 104
  from pteridines, 106*f*
  from purines, 105*f*
  from pyrroles, 105
  from quinazolines, 105
  from thiazines, 104*f*
  history, 1
  introduction, 1
  ionization, 27*f*, 464*f*
  meteorites containing, 2
  nomenclature, 1, 3*f*, 430*f*
  nuclear reduction, 442*f*, 450*f*
  numbering, 3*f*
  polarography, 28*f*
  properties (general), 26
  principles of chemistry, 5*f*
  reaction with chloral, 11
  reaction with chloroform, 11
  summary of chemistry, 9*f*
  trivial names, 3, 6*f*
  various colour reactions, 260
Pyrimidine sulphides, 212, 291*f*
  reactions, 294
Pyrimidine sulphinic acids
  see: "Sulphinopyrimidines"
Pyrimidine sulphones
  see: "Alkylsulphonylpyrimidines"
Pyrimidine sulphonic acids
  see: "Sulphopyrimidines"
Pyrimidine thiocyanates
  see: "Thiocyanatopyrimidines"
Pyrimidine thiourethanes, 337*f*
Pyrimidine urethanes, 336*f*
Pyrimido-*m*-thiazine
  degradation of a derivative, 277
Pyrroles
  pyrimidines from, 105

Q

Quaternary amino groups, 18
  replacement of, 18, 345
Quaternization of pyrimidines, 18*f*
Quinalbarbitone, 53
Quinazoline
  oxidation of, 105, 127, 390
Quinazolines
  from benzene derivatives, 107*f*
  pyrimidines from, 105

R

Radziszewski reaction, 399
Ramage and Landquist, review, 2
Raman spectra
  assignment of vibrations in pyrimidine, 495*f*
Raneynickel
  use in desulphurization, 277*f*
Reduced pyrimidines
  definition, 430
  number of possible series, 431
  paucity of data, 431
  see: "Dihydro-, Tetrahydro-, Hexahydro-pyrimidines"
Reduction of pyrimidines, 21*f*, 430*f*

Reimer-Tiemann reaction, 11, 409
Reissert reaction, 19, 383
Remfry, 97
Remfry-Hull Synthesis, 97*f*, 228
Resins
  formation from aminopyrimidines and aldehydes, 323
Ribonucleic acid
  hydrolysis, 257, 346
Ribose-5-phosphate-1-pyrophosphate
  combination with orotic acid, 425
Richardson, Miss D.N., 379
Ritthausen, 259
Roblin, 331
Roeder, 455
Roithner, 438
Rose, F.L., 194, 330
Russell, 285

S

Sandmeyer reaction, 18, 333
Schiff's bases
  from aminopyrimidines, 321*f*
  from formylpyrimidines, 414
  from hydrazides, 401
  stability to acid, 322, 414
Schlieper, 260
Schotten-Baumann reaction, 327, 456
Secobarbital, 53
"Seconal", 53
8-Selenapurines, 334
6-Selenylpurine
  Se-alkylation, 284
Semicarbazidopyrimidines, 341
Shaw synthesis, 87*f*, 228, 273, 358, 403
Shugar, 258
Smith, P. E., 251
Smith, V.E., 451
Sodio sulphanilamide
  use in synthesis, 331
Sodio-urea
  use in synthesis, 53, 56
Sodium dithionite
  in reducing nitrouracil, 145*f*
Spongothymidine, 6
Spongouridine, 6
Stadeler, 448
Stieglitz, 434
Struve, 400
2-Styrylpyrimidine, 122, 125
  hydrogenation, 122
  oxidation, 128
4-Styrylpyrimidine, 122, 125
  hydrogenation, 122
Styrylpyrimidines, 26
  catalysts in formation, 26, 125*f*
  oxidation, 21
  preparation from methylpyrimidines, 125*f*
Succindiamide
  use to make hydrouracil, 102, 438
Sulphadimidine, 331
Sulphadiazine, 331
Sulphamerazine, 331
Sulphamethazine, 331
"Sulphamezathine", 331
2-Sulphamoylpyrimidine, (295), 297
Sulphanilamido derivatives
  see: *corresponding sulphanilylamino derivative*
Sulphanilylguanidine
  use in syntheses, 37, 50
Sulphapyridine, 331
Sulphasomidine, 331
Sulphathiazole, 331
Sulphinopyrimidines, 296
  hydrolysis, 297
Sulphoaminopyrimidines, 343
Sulphonamide drugs, 330*f*
  and kidney blockage, 331
Sulphonation, 11, 295*f*
2-Sulphopyrimidine, 207, 295
  action of cyanide, 207, 297, 404
Sulphopyrimidines, 15
  action of cyanide, 207
  esterification, 297
  formation by oxidation, 21
  preparation, 295*f*
  reactions, 297*f*
Swain, 330

T

Takamizawa, 62
Tartronyl urea, 6
Tautomeric groups, general, 9
  utility of pK_a in studying, 464
  utility of U.V. spectra in studying, 482*f*
Tetra-aminopyrimidine
  action of sulphuryl chloride, 296, 343
  action of sulphamide, 296
  action of thionyl chloride, 334

1,2,4,6-Tetra-azaindenes
  formation, 334
2,4,5,6-Tetrabromopyrimidine, 167, 250
2,4,5,6-Tetrachloropyrimidine, 166, 250
  nuclear reduction, 451
  pyrimidine from, 116
1,2,3,4-Tetrahydro-1,3-diethyl-6-hydroxy-2,4-dioxopyrimidine
  nitrosation, 148
1,2,3,4-Tetrahydro-1,3-diethyl-6-hydroxy-5-nitroso-2,4-dioxopyrimidine, 148
1,4,5,6-Tetrahydro-2,5-dihydroxypyrimidine, 449
1,2,3,4-Tetrahydro-1,3-dimethyl-5,6-bismethylamino-2,4-dioxopyrimidine, (210)
5,6,7,8-Tetrahydro-5,8-dimethyl-6,7-dioxopteridine
  formation and degradation, 107, 308, 314
1,2,3,4-Tetrahydro-1,3-dimethyl-2,6-dioxopyrimidine, (211), 257, 360, 371, 373
  bromination, 174
  hydration in U.V. light, 20, 258
  nitration, 140, 364
  thiation, 252, 376
Tetrahydro-2,5-dimethyl-1,3-diphenylpyrimidine, 453
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dithiopyrimidine, 252, (376)
1,2,3,4-Tetrahydro-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine, 198, (212)
  action of acetic anhydride, 416
1,2,3,4-Tetrahydro-1,3-dimethyl-4-methylimino-2-oxopyrimidine, 378
1,2,3,4-Tetrahydro-1,3-dimethyl-5-nitro-2,4-dioxopyrimidine, 140, 364
1,2,3,4-Tetrahydro-1,3-dimethyl-2-oxo-4-thiopyrimidine, 252, (376)
  thiation, 252, (376)
1,4,5,6-Tetrahydro-5,5-dimethyl-2-phenylpyrimidine, 445
1,2,5,6-Tetrahydro-2,6-dipentamethylene-4,5-tetramethylenepyrimidine, 448
1,2,3,4-Tetrahydro-6-hydroxyamino-1,3-dimethyl-2,4-dioxopyrimidine, 200, 344
  acetylation, 344
  action of diazomethane, 344
  reduction, 344
1,2,3,4-Tetrahydro-5-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine, 144, (212), 238
1,2,3,4-Tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidine, 53, 56, 230, 362
  action of phosphoryl chloride, 165
  C-acylation, (416)
  alkylation, 362
1,2,3,4-Tetrahydro-6-hydroxy-1,3-dimethyl-5-nitroso-2,4-dioxopyrimidine
  chelating properties, 147
1,2,3,4-Tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenyl-5-phenylazopyrimidine, 156
  as tautomer of 1,3-diphenylalloxan-5-phenylhydrazone, 156
1,2,3,4-Tetrahydro-6-hydroxy-2,4-dioxo-1,3-diphenylpyrimidine, 56
  coupling, 156
1,2,3,4-Tetrahydro-6-β-hydroxyethylamino-1,3-dimethyl-2,4-dioxopyrimidine, 198
1,2,3,4-Tetrahydro-5-β-hydroxyethylamino-1,3-dimethyl-6-methylamino-2,4-dioxopyrimidine, (210)
1,2,3,4-Tetrahydro-6-hydroxyiminomethyl-1,3-dimethyl-2,4-dioxopyrimidine, 129, 413
1,2,3,4-Tetrahydro-6-hydroxy-2-imino-4-oxo-1,3-diphenylpyrimidine
  doubtful preparation, 55
1,4,5,6-Tetrahydro-6-hydroxy-2-mercapto-4,4,6-trimethylpyrimidine, 449
1,4,5,6-Tetrahydro-2-hydroxy-1-methyl-4-phenylpyrimidine, 450
1,4,5,6-Tetrahydro-2-hydroxy-1-methylpyrimidine, 278, 452
1,4,5,6-Tetrahydro-2-hydroxy-4-methylpyrimidine, 450
1,4,5,6-Tetrahydro-5-hydroxy-2-nitroaminopyrimidine, 447
1,2,3,4-Tetrahydro-6-hydroxy-5-nitroso-2,4-dioxo-1,3-diphenylpyrimidine
  colour of salts, 147
1,2,3,4-Tetrahydro-6-hydroxy-5-nitroso-4-oxo-1,3-diphenyl-2-thiopyrimidine
  colour of salts, 147

1,2,3,4-Tetrahydro-6-hydroxy-4-oxo-1,3-diphenyl-2-thiopyrimidine, 55, 381
1,4,5,6-Tetrahydro-2-hydroxy-1-phenylpyrimidine, 447
1,4,5,6-Tetrahydro-2-hydroxypyrimidine, 22, 278, 443, 446, 450, 452
1,4,5,6-Tetrahydro-2-hydroxy-1,4,6,6-tetramethylpyrimidine, 446
1,4,5,6-Tetrahydro-2-hydroxy-1-*p*-tolylpyrimidine, 447
1,4,5,6-Tetrahydro-2-hydroxy-4,6,6-trimethylpyrimidine, 446
1,2,3,4-Tetrahydro-4-imino-1,3-dimethyl-2-oxopyrimidine, (329), 373, 378
  hydrolysis, 373
1,4,5,6-Tetrahydro-2-mercapto-1-phenylpyrimidine, (447)
1,4,5,6-Tetrahydro-2-mercaptopyrimidine, 447
1,4,5,6-Tetrahydro-2-mercapto-1-*p*-tolylpyrimidine, 447
1,4,5,6-Tetrahydro-2-mercapto-4,4,6-trimethylpyrimidine, 447
1,2,3,4-Tetrahydro-6-methoxyamino-1,3-dimethyl-2,4-dioxopyrimidine, (344)
1,2,3,4-Tetrahydro-5-methoxy-1,3-dimethyl-2,4-dioxopyrimidine, 248, 363
1,2,3,4-Tetrahydro-6-methoxy-1,3-dimethyl-2,4-dioxopyrimidine, 362
1,2,3,4-Tetrahydro-6-methoxy-1,3,5-trimethyl-2,4-dioxopyrimidine, 203
1,4,5,6-Tetrahydro-4(or 6)-methyl-2-nitroaminopyrimidine, 447*f*
1,2,5,6-Tetrahydro-1-methyl-2-oxo-4-phenylpyrimidine, 84, 444
  disproportionation, 84
  halogenation, 457
1,2,5,6-Tetrahydro-1-methyl-4-phenyl-2-oxopyrimidine, 436
  disproportionation, 436
1,4,5,6-Tetrahydro-2-methylpyrimidine, 445, 451
1,4,5,6-Tetrahydro-4-methylpyrimidine, 451
1,4,5,6-Tetrahydro-5-methylpyrimidine, 451
1,4,5,6-Tetrahydro-2-nitroaminopyrimidine, 447
1,4,5,6-Tetrahydro-2-nonylpyrimidine, 446
1,2,5,6-Tetrahydro-2,2,4,6,6-pentamethyl-5-nitrosopyrimidine, 455
  formation of a benzoyl derivative, 455
  ring cleavage, 455
1,2,5,6-Tetrahydro-2,2,4,6,6-pentamethylpyrimidine, 448
  nitrosation, 455
  reductive cleavage, 454
1,4,5,6-Tetrahydro-2-phenylpyrimidine, 445, 449, 451
  attempted benzoylation, 456
  dehydrogenation, 455
1,4,5,6-Tetrahydro-5-phenylpyrimidine, 451
1,4,5,6-Tetrahydro-2-propylpyrimidine, 451
Tetrahydropyran-2-yloxy group
  as a "protection" for hydroxy group 240
1,4,5,6-Tetrahydropyrimidine, 22, 118, 446
  benzoyl derivative, 118, 451
  oxalate, 118
  preparations, 446, 451
Tetrahydropyrimidines, 445*f*
  by reduction, 450*f*
  from carbonyl compounds and amines, 448
  from 1,3-diaminopropane, 445
  from 1,3-dihalogenopropane derivatives, 449
1,2,5,6-Tetrahydro-1,4,6,6-tetramethyl-2-phenylpyrimidine, 448
1,2,3,4-Tetrahydro-1,3,5-trimethyl-2,4-dioxopyrimidine, 362
1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine, 259, 361
  Claisen reaction at *C*-methyl group, (416)
  nitrosation to an oxime, 413
  oxidation, 371, 400
  oxidation to aldehyde, 129
1,2,3,4-Tetrahydro-1,3,5-trimethyl-6-methylamino-2,4-dioxopyrimidine, 198
1,2,3,4-Tetrahydro-1,3,6-trimethyl-5-nitro-2,4-dioxopyrimidine, 364
1,2,5,6-Tetrahydro-4,6,6-trimethyl-2-pentamethylenepyrimidine, 448
1,4,5,6-Tetrahydro-2,4,6-trimethylpyrimidine, 445

1,2,5,6-Tetrahydro-4,6,6-trimethylpyrimidine, 448
1,4,5,6-Tetrahydro-4,4,6(or 4,6,6)-trimethyl-2-*p*-tolylpyrimidine, 446
1,3,6,8-Tetrahydroxy-2,4,5,7,9,10-hexaazaphenanthrene, 335
2,4,5,6-Tetrahydroxypyrimidine, 229, 238, 240, 260, 263
  action of phosphorus pentabromide, 167, 250
  action of phosphorus pentachloride, 250
  acylation, 253
  general, 262*f*
  nuclear reduction, 443
  oxidation, 260
  reaction with alloxan, 262
Tetramethylenediamine
  see: "1,3-Diaminopropane"
4,5-Tetramethylenepyrimidine, 95
2,4,5,6-Tetramethylpyrimidine, 119
Theobromine, 366
Thialbarbitone, 54
Thiamine, 6
8-Thiapurines, 334
Thiation
  of hydroxypyrimidines, 16
Thiazines
  pyrimidines from, 104*f*
Thiazolo[5,4-d]pyrimidine, 334
Thiazolo[4,5-d]pyrimidines
  formation, 334, 420
Thiazolo[5,4-d]pyrimidines
  formation from pyrimidines, 420
  formation from thiazoles, 108
4-2′-Thiazolylpyrimidine, 118
4-2′-Thienylpyrimidine, 119
2-Thiobarbiturates
  formation, 251
2-Thiobarbituric acid, 6
Thiocarbamoylpyrimidines, 399
Thiocyanatopyrimidines, 15, 419*f*
  amination, 309
  formation, 207*f*, 419*f*, 421*f*
  isomerization, 15, 208
  to alkoxypyrimidines, 420*f*
  to aminopyrimidines, 420
  to mercaptopyrimidines, 275, 420*f*
  to thiazolopyrimidines, 420
"2-Thio-5-keto-4-carbethoxy-1,3-dihydropyrimidine"
  really a thiazole, 449
Thionyl chloride
  use in making extranuclear halogeno derivatives, 178*f*
Thiopentone, 54
2-Thiophen-lithium
  reaction with pyrimidine, 118
Thiopyrimidines, 381*f*
Thiosalicylic acid
  reaction with a 5-bromopyrimidine, 212
Thiosemicarbazidopyrimidines, 341
"4-Thiothymidine disulphide", 292
2-Thiothymine
  see: "4-Hydroxy-2-mercapto-5-methylpyrimidine"
2-Thiouracil, 6
  and homologues as drugs, 300*f*
  estimation of, (and homologues), 300
4-Thiouracil, 6
2-Thiouracil
  use as trivial name, 5
Thiouracils
  numbering of, 4
Thiouramil, 6
Thiourea
  use in primary syntheses, 82–111
  use in Principal Synthesis, 31–74
Thioureidopyrimidines, 340*f*
Thiourethanes, 337*f*
2-Thiouridine, 90, 273
"4-Thiouridine disulphide", 292
Thiouronium salts
  formation, 205*f*
  hydrolysis, 205*f*
Thorpe, 262
Thymidine, 6, 258
Thymine, 7
  monograph, 258*f*
Thyminyl alcohol, 5, 7
Thyrotoxicosis
  treatment by thiouracils, 300*f*
Timmis
  pteridine synthesis, 151
Todd, A.R., 2, 256, 326
2-*p*-Toluenesulphonamidopyrimidine, 330
Toluenesulphonic acid
  as catalyst in syntheses, 91
3-*p*-Toluidinopropylamine
  to corresponding thiourea, 447
N-(3-*p*-Toluidinopropyl)thiourea, 447
  facile cyclization, 447
4-*p*-Tolylpyrimidine, 118, 119
Traube, 2, 68, 99, 149

2,4,6-Triamino-5-benzylpyrimidine, 74
4,5,6-Triamino-2-chloropyrimidine, 144
2,4,6-Triamino-5-ethylpyrimidine, 74
  hydrolysis, 230
2,4,5-Triamino-6-hydroxypyrimidine, (150), 157
  acylation, 324, (327), (328)
2,4,6-Triamino-5-isopropylpyrimidine, 74
4,5,6-Triamino-2-mercaptopyrimidine, (149), 280
  acylation, 328
  to 2-sulphino analogue, 296
2,4,5-Triamino-6-methylaminopyrimidine, 156
2,4,5-Triamino-6-methylpyrimidine, 311
  acylation, (326)
4,5,6-Triamino-2-methylpyrimidine, (150)
  acylation, (326)
4,5,6-Triamino-2-methylthiopyrimidine, (150)
  acylation, (326)
2,4,6-Triamino-5-nitropyrimidine
  reduction by sodium bisulphite, 296
2,4,6-Triamino-5-nitrosopyrimidine, 73
  hydrolysis, 230
  reaction with thiourea, 334
  reduction with bisulphite, 343
2,4,5-Triaminopyrimidine, 144, 145
  darkening in air, 335
2,4,6-Triaminopyrimidine, 74, 191, 198, 290, 306
  acylation, 324
4,5,6-Triaminopyrimidine, 144, (150), 156, 280, 297
  action of selenous acid, 334
  acylation, (326)
4,5,6-Triamino-2-sulphinopyrimidine, 296
  acid hydrolysis to triaminopyrimidine, 297
2,4,6-Triamino-5-sulphoaminopyrimidine, 296, 343
2,4,6-Trianilinopyrimidine, 191
sym.Triazine
  use in hydropyrimidine synthesis, 446
Triazines
  formation instead of pyrimidines, 65
  intermediates for pyrimidines, 93, 95
4-Tribromomethylpyrimidine, 130
2,4,6-Tribromopyrimidine, 167
  action of alkoxide, 202
2,4,6-Tributoxy-5-s-butylpyrimidine, 202
2,4,6-Tricarboxypyrimidine, 391
2,4,5-Trichloro-6-dichloromethylpyrimidine, 131
2,4,6-Trichloro-5-ethylpyrimidine
  action of alkoxides, 202
  amination, 193
5-$\beta\beta\beta$-Trichloro-α-hydroxyethylpyrimidines, 11, 126
  action of alkali, 126
2,4,6-Trichloro-5-methylpyrimidine
  action of alkoxide, (202)
  bromination, 131, 177
  dechlorination, 121
4-Trichloromethylpyrimidine, 130
  dehalogenation, 216
2,4,6-Trichloro-5-nitropyrimidine, 163
  amination, 196
  hydrogenation, 143
2,4,5-Trichloropyrimidine, 164
  action of alkoxide, (203)
  amination, 200
2,4,6-Trichloropyrimidine, 163, 166
  action of alkoxides, 202
  amination, 191*f*, 344
  nuclear reduction, 451
  pyrimidine from, 116
  reaction with tertiary amines, 193
  to trimercaptopyrimidine, 206
4,5,6-Trichloropyrimidine, 164
1,3,3-Triethoxy-1-methoxypropane
  use, 94, 116
  see also: "Malondialdehyde"
1,3,3-Triethoxypropene
  use in syntheses, 33, 94
2,4,6-Triethoxypyrimidine, 202
Triethylamine
  use with phosphoryl chloride, 164
2,4,6-Triethyl-1,3,5-triazine
  formation and isomerisation, 93
Trifluoroacetamidine
  use in synthesis, 179
Trifluoromethyl group
  effect on acidic pK_a, 467
2,4,6-Triformylpyrimidine, 128
  as *p*-nitrophenylhydrazone, 411
  oxidation, (391)
Trihalogenomethylpyrimidines
  action of silver nitrate giving carboxy derivative, 216
2,4,6-Trihydroxy-5-(2′,4′-dihydroxy-5′-pyrimidinylazo)pyrimidine, 155
2,4,6-Trihydroxy-5-α-hydroxyiminoethylpyrimidine, 418

2,4,6-Trihydroxy-5-iminomethylpyrimidine
  to 5-formyl analogue, 410
2,4,6-Trihydroxy-5-isothioureidopyrimidine
  nitration to 5-nitrobarbituric acid, 140
2,4,6-Trihydroxy-5-mercaptopyrimidine, 421
  doubtful preparation, 212
4,5,6-Trihydroxy-2-mercaptopyrimidine, 240
2,4,6-Trihydroxy-5-methylaminopyrimidine, 262
2,4,5-Trihydroxy-6-methylpyrimidine, 239
  acylation, 253
  probable formation, (241)
2,4,6-Trihydroxy-5-methylpyrimidine, 57
4,5,6-Trihydroxy-2-methylpyrimidine, 240
  probable formation, (241)
2,4,6-Trihydroxy-5-2′-naphthylazopyrimidine, 156
2,4,6-Trihydroxy-5-nitropyrimidine, 140, 151
  reaction with bromine, 172
  reaction with phosphoryl chloride *etc.*, 163
  reduction, 145, 263
2,4,5-Trihydroxy-6-nitrosopyrimidine, 10, 151
  oxime formation, 152
  reduction, 152, 310
2,4,6-Trihydroxy-5-nitrosopyrimidine
  colour of salts, 147
  condensation with benzyl phenyl ketone, 151
  formation from alloxan, 147, 261
  formation from barbituric acid, 146, 148, 151
  metal chelate complexes, 147
  methylation, 147
  "nitration" to 5-nitrobarbituric acid, 140, 142
  reaction with bromine, 172
  reaction with chlorine, 151
  reduction, (150), 343
2,4,5-Trihydroxy-6-phenylazopyrimidine, 154
2,4,6-Trihydroxy-5-phenylazopyrimidine, 155
  tautomerism, 155
2,4,6-Trihydroxy-5-α-phenylhydrazonoethylpyrimidine, 418
2,4,6-Trihydroxy-5-phenyliminomethylpyrimidine, 410
  alkaline hydrolysis, 410
2,4,6-Trihydroxy-5-phenylpyrimidine, 99
4,5,6-Trihydroxy-2-phenylpyrimidine, 240
2,6,8-Trihydroxypurine
  see: "Uric acid"
2,4,5-Trihydroxypyrimidine, 14, 212, 229, 232, 238, 239, 240, 321
  acylation, 253
  alkylation, 248, 363
  bromination, 19
  coupling, 154, 332
  formation from nitrouracil, 144
  nitrosation, 10, 151
  reaction with benzaldehyde, 12
  reaction with phosphoryl chloride, 163
2,4,6-Trihydroxypyrimidine, 227, 233, 297
  action of acetic anhydride, 416
  action of diphenylformamidine, 410
  action of phosphorus pentachloride, 165
  alkylation, 124, 362
  coupling, 155, 332
  halogenation, 172
  nitration, 140, 147
  nitrosation, 148
  nuclear reduction, 443, 450
  oxidation, 261
  reaction with benzaldehyde, 123
  reaction with phosphoryl bromide, 167
  reaction with phosphoryl chloride, 163
  thiation, 251
  to 5-cyano derivative, 405
  see also: "Barbituric acid"
4,5,6-Trihydroxypyrimidine, 240
2,4,6-Trihydroxy-5-sulphoaminopyrimidine, 343
2,4,5-Trihydroxy-6-*p*-sulphophenylazopyrimidine, 154
  rearrangement, 154
  reduction, 154
2,4,6-Trihydroxy-5-*p*-sulphophenylazopyrimidine, 154
2,4,6-Trihydroxy-5-tetrahydropyran-2′-yloxypyrimidine, (240)

  - hydrolysis, (240)
- 2,4,6-Trihydroxy-5-thiocyanatopyrimidine
  - action of aqueous alkali, 421
- 2,4,6-Trihydroxy-5-ureidopyrimidine, 339
- 2,4,6-Trimercaptopyrimidine, 206
- 2,4,6-Trimethoxypyrimidine, 202
  - isomerization, 372*f*
- 5,5-Trimethylenebarbituric acid, 57
- 4,5-Trimethylenepyrimidine, 93, 95, 280
- Trimethyleneurea
  - see: "1,4,5,6-Tetrahydro-2-hydroxypyrimidine"
- 2,4,6-Trimethylpyrimidine, 36, 119
  - action of phenyl-lithium, 122
  - Claisen reaction of, 132
  - *N*-oxide formation, 128
  - styrylation, 26, 125, 411
- 2,4,6-Trimethylpyrimidine-1-oxide, 128
- Trimethylpyrimidinylammonium chlorides, 345
- "1-[5-(2,4,6-Trioxohexahydropyrimidyl)] pyridinium betaine", 214
- 3,6,7-Triphenyl-lumazine, 109
- 2,4,6-Triphenylpyrimidine, 36, 95, 103, 120, 433
- 2,4,6-Trisacetamidopyrimidine, 324
- Trisformamidomethane
  - use in syntheses, 91
- 2,4,6-Trismethylaminopyrimidine, (191)
- 2,4,6-Trismethylanilinopyrimidine, 193
- 2,4,6-Tris(trimethylammonium)pyrimidine trichloride, 193
- 2,4,6-Tristyrylpyrimidine, 26, 125, 411
  - ozonization, 128, 411
- Trithiobarbiturates
  - formation, 251
- Trivial names, 4f
  - table, 6*f*
- Tuberculostatic properties of pyrimidine hydrazones, 323

U

- Ultraviolet light
  - action on aqueous uracil, 20
- Ultraviolet spectra, 477*f*
  - changes in intensity with substitution, 488*f*
  - effect of substituents, 478*f*, 486*f*
  - energy considerations, 490*f*
  - need to know pK_a, 464, 477
  - need to record pure species, 477*f*
  - table of simple tautomeric pyrimidines, 492*f*
  - table of simple non-tautomeric pyrimidines, 491
  - theoretical studies, 485*f*
  - the $n \rightarrow \pi$ and $\pi \rightarrow \pi$ bands, 478, 486
  - uses of, 478
- αβ-Unsaturated ketones
  - reaction with amidines, 102
- Uracil, 7
  - halogenation of derivatives, 172*f*
  - monograph, 256*f*
  - numbering, 4
  - see also: "2,4-Dihydroxypyrimidine"
- "Uracilazobarbituric acid", 155
- Uramil, 7
- Urea
  - use in primary syntheses, 82–111
  - use in Principal Synthesis, 31–74
- Ureidopyrimidines, 339*f*, 419
- Ureidosuccinic acid, (423), 435
  - cyclization, (423), 435
  - in pyrimidine biosynthesis, 424
- Urethanes, 336*f*
  - from azides, 401
- Uric acid, 339
  - action of hot ammonium sulphide, 273, 314
  - degradation to pyrimidines, 106, 308
  - oxidation to alloxan, 106, 260
- Uridine, 7, 90, 257
  - action of formaldehyde, 244
  - hydrolysis, 257
  - reduction, 443
- Uridine-5′-monophosphate, 257, 425
- Uridylic acids, 257

V

- Valerylacetone
  - failure in synthesis, 37
- van Dam, 438
- van Dorp, 434
- Van Praag, 452
- "Veronal", 53
- Vicine, 7, 259
- Vilbrans, 340
- Vinbarbital, 54
- Vinbarbitone, 54
- 4-Vinylpyrimidine, 122
  - hydrogenation of, 122

polymerization, 134
Violuric acid, 7, 10
Vitamin B_1, 176, 326
  action of sodium bisulphite, 216, 295
  analogue intermediates, 242
von Meyer, 1, 2, 96
von Pechmann, 38

W

Walker, J., 477
Wang, 174
Water
  addition to uracil, 20
Webster, 301
Weidel, 438
Wempen, 370
Wheeler, 2, 210, 261, 300, 346, 347, 422, 423
Wheeler-Johnson colour test, 257, 263
Whitehead, 42
  Synthesis, 62*f*, 398
Whiteley, 156, 262
Widmann, 1
Wierzchowski, 258
Wiley, 2
Williams, 331
Winnik, 331
Wöhler, 1, 260
Wyatt, 347

Y

Yamanaka, H., 207, 382
Yung, 370

Z

Zinc chloride
  use in synthesis, 91
Zwitterion
  minor contribution to carboxypyrimidines, 466