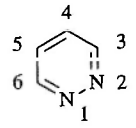
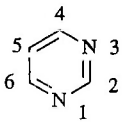
10. Pyrimidines

10.1 Introduction

Formal replacement of a CH unit in pyridine **5.1** by a nitrogen atom leads to the series of three possible diazines, pyridazine **10.1**, pyrimidine **10.2**, and pyrazine **10.3**. Like pyridine they are fully aromatic heterocycles. The effect of an additional nitrogen atom as compared to pyridine accentuates the essential features of pyridine chemistry. Electrophilic substitution is difficult in simple unactivated diazines because of both extensive protonation under strongly acidic conditions and the inherent lack of reactivity of the free base. Nucleophilic displacements are comparatively easier.



10.1



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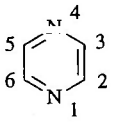

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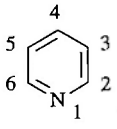
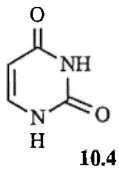


5.1

Interestingly, the second electronegative heteroatom reduces the capacity of the diazines to tolerate the positive charge resulting from protonation. Pyridazine **10.1** (pK_a= 2.24), pyrimidine **10.2** (pK_a = 1.23), and pyrazine **10.3** (pK_a = 0.51) are all far less basic than pyridine (pK_a = 5.23).

The most important of the diazines is pyrimidine **10.2**. Pyrimidine derivatives uracil **10.4**, thymidine **10.5**, and cytosine **10.6** are the monocyclic 'bases' of nucleic acids. The bicyclic bases are the purines adenine **10.7** and guanine **10.8**. The purine ring is essentially a fusion of the pyrimidine and imidazole rings.



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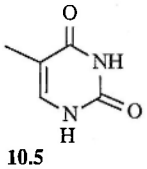

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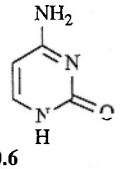

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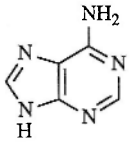

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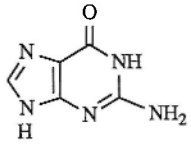
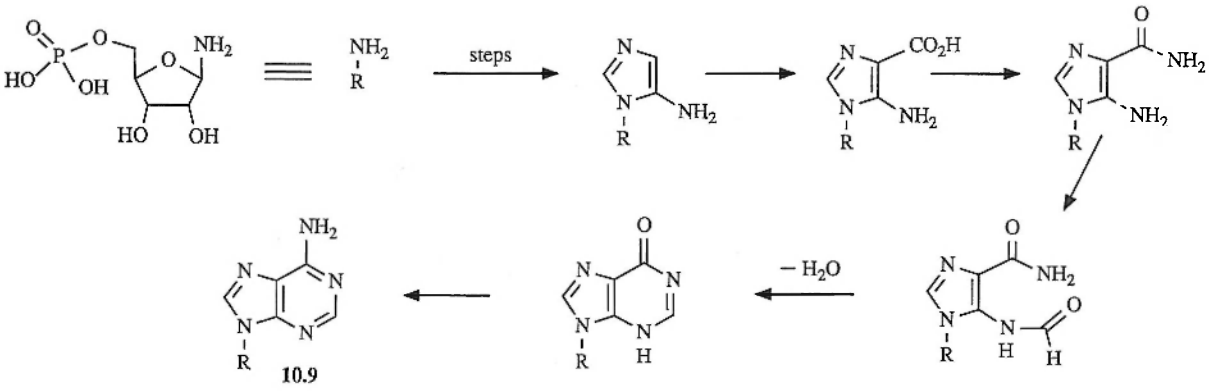


10.8

Nucleotides are the monomeric building blocks of deoxyribonucleic acid (DNA) in which is stored the genetic information of the cell.

The actual biosynthesis of purines (illustrated below in abbreviated form for the nucleotide adenosine monophosphate AMP **10.9**) involves construction of a pyrimidine ring onto a pre-formed imidazole.



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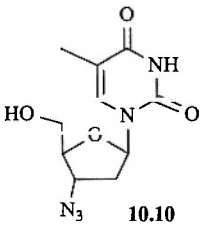


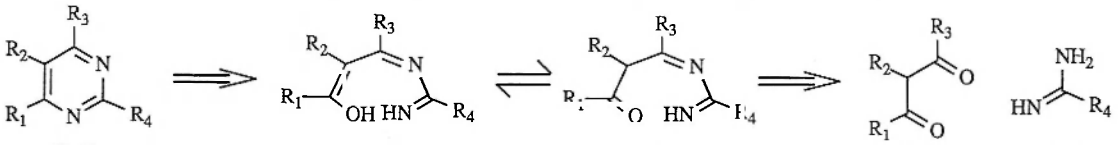
10.10

The enzymes that manipulate nucleotides, nucleic acids, etc. are the points of therapeutic intervention for a number of diseases involving cell replication disorders such as cancers and viral infections. For instance, AZT **10.10**, an inhibitor of the enzyme reverse transcriptase, is an anti-viral drug currently used in the treatment of AIDS.

We shall now go on to consider the synthesis and chemistry of the pyrimidine ring system.

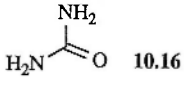
10.2 Synthesis of pyrimidines

Disconnection of the N1–C6 bond in generalised pyrimidine **10.11** in the usual way produces enol **10.12**, which exists as ketone **10.13**. Similarly, disconnection of the carbon–nitrogen double bond in **10.13** yields a dicarbonyl compound **10.14** and an amidine **10.15**. This retrosynthetic analysis, suggesting the combination of bis-electrophilic and bis-nucleophilic components, is the basis of a very general pyrimidine synthesis.



10.11 **10.12** **10.13** **10.14** **10.15**

Where R_4 is a hydrogen or carbon atom, **10.15** is simply an amidine. However, urea **10.16**, thiourea **10.17**, or guanidine **10.18** and their derivatives may be used. These nucleophiles may be condensed with ester and nitrile functionalities as well as with aldehydes and ketones. Such condensations to afford pyridimidine derivatives are usually facilitated by acid or base catalysis, although certain combinations of reactive electrophilic and nucleophilic compounds require no catalyst at all. Some examples are shown below.



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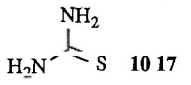

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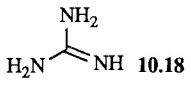
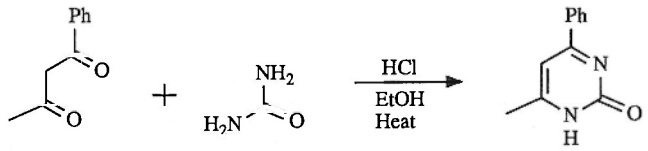
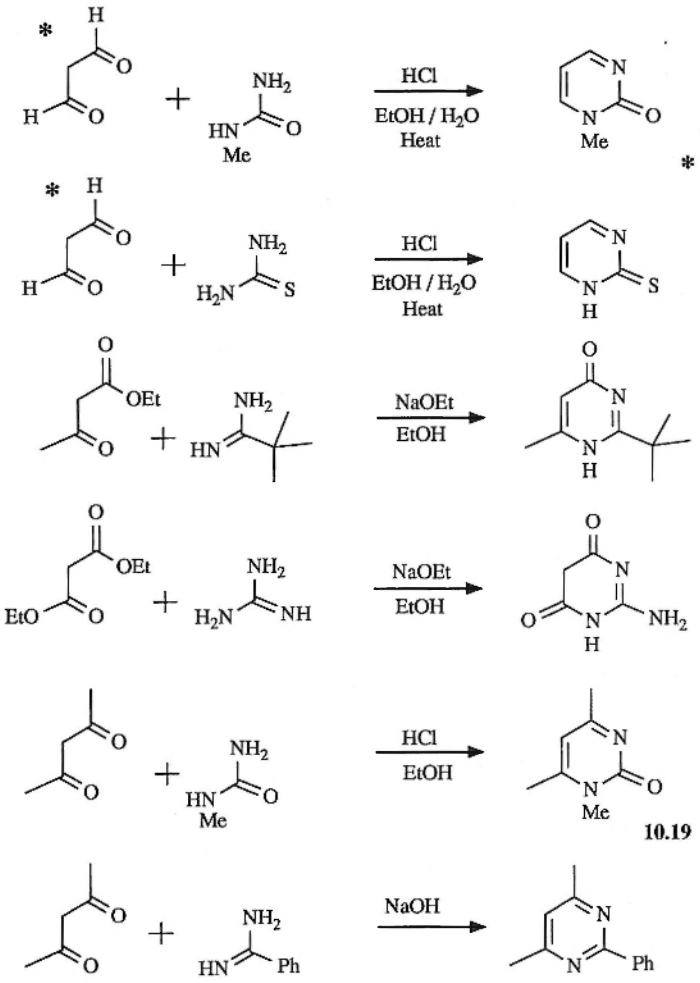
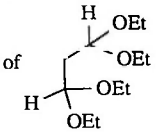


10.18

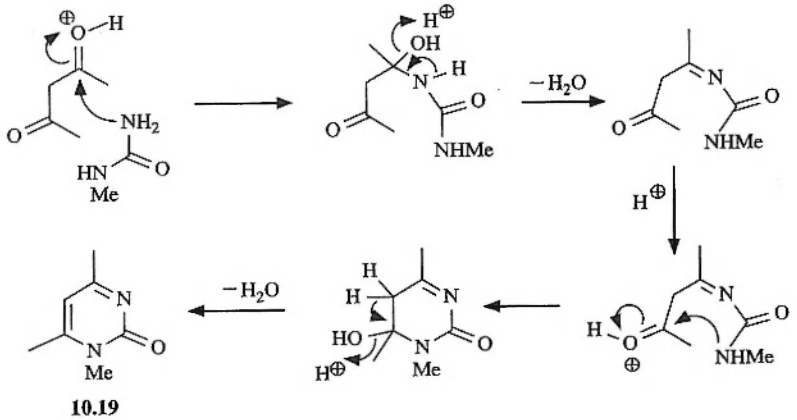




* Prepared by *in situ* hydrolysis of



Note that several of these examples produce pyrimidones, analogous to the pyridones previously encountered in Chapter 5. A representative mechanism is shown for the preparation of 2-pyrimidone **10.19**, and is simply two consecutive condensations.



10.3 Electrophilic substitution of pyrimidones

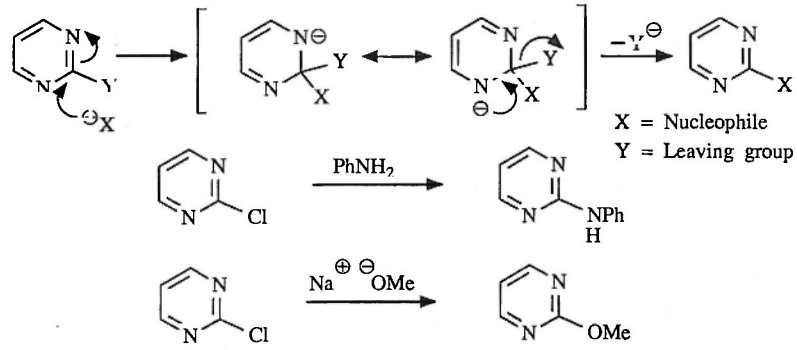
As mentioned earlier, electrophilic substitution on unactivated pyrimidines is of little importance. But, as with pyridine, the pyrimidine nucleus can be activated towards electrophilic attack by employing N-oxides or pyrimidones, for the same reasons as were discussed in Chapter 5.

For instance, nitration of 2-pyrimidone **10.20** affords nitropyrimidone **10.21**. With doubly-activated systems such as **10.22,** nitration to give **10.23** can occur without heating.

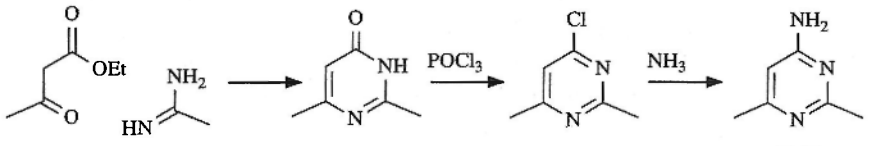
10.20 **10.21** **10.22** **10.23**

10.4 Nucleophilic substitution of pyrimidines

Leaving groups at the C2, C4, and C6 positions of pyrimidines can be displaced by nucleophiles, with the negative charge of the intermediate delocalised over both nitrogen atoms.



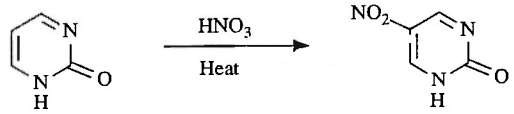
Chlorinated pyrimidines themselves are often accessible from the corresponding pyrimidones by reaction with phosphorus oxychloride. (Again, see Chapter 5 for an explanation of this sort of reaction.) For instance, aminopyrimidine **10.24** can be synthesised by the classical sequence depicted below.



10.24

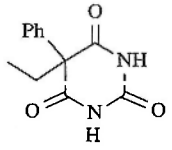
10.5 Problems

1. Write a mechanism for this nitration, but starting from an alternative mesomeric representation of **10.20** that helps to explain the increased susceptibility of such pyrimidones to electrophilic attack.



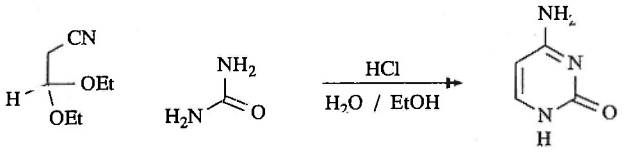
10.20 **10.21**

2. Barbiturates (pyrimidine triones such as **10.25**) used to be widely used as sedatives, but have now largely been superseded by drugs with fewer side-effects. Suggest a synthesis of **10.25**.



10.25

3. There are several preparations of cytosine **10.6** available, one of which is the condensation of nitrile **10.26** with urea **10.16**. Propose a mechanism for this reaction.



10.26 **10.16** **10.6**

10.6 References

Brown, D.J. (1962). In *The pyrimidines (The chemistry of heterocyclic compounds* [ed. A. Weissburger and E.C. Taylor], Vol. 16). Wiley Interscience, New York.

Brown, D.J. (1970). In *The pyrimidines (The chemistry of heterocyclic compounds* (ed. A. Weissburger and E.C. Taylor], Vol. 16, Supplements 1 and 2). Wiley Interscience, New York.

Furniss, B.S., Hannaford, A.J., Smith, P.W.G., and Tatchell, A.R. (1989). *Vogel's textbook of practical organic chemistry* (5th edn), p.1177 (preparation of barbiturate **10.25**). Longman, Harlow.

Hurst, D.T. (1980). *An introduction to the chemistry and biochemistry of pyrimidines, purines, and pteridines.* Wiley, New York.