

THOMAS L GILCHRIST

HETEROCYCLIC CHEMISTRY

杂环化学 第3版

世界图书出版公司

THIRD EDITION

Heterocyclic Chemistry

Third Edition

Thomas L. Gilchrist

University of Liverpool

世界图书出版公司

书 名: Heterocyclic Chemistry 3rd ed.
作 者: Thomas L. Gilchrist
中译名: 杂环化学 第3版
出版者: 世界图书出版公司北京公司
印刷者: 北京世图印刷厂
发 行: 世界图书出版公司北京公司 (北京朝内大街 137 号 100010)
联系电话: 010-64015659, 64038347
电子信箱: kjsk@vip.sina.com
开 本: 24 印 张: 18
出版年代: 1997 年 9 月第 1 版 2003 年 11 月第 2 次印刷
书 号: 7-5062-3398-3 / O · 200
版权登记: 图字:01-97-0959
定 价: 60.00 元

世界图书出版公司北京公司已获得 Addison Wesley Longman Limited 授权在中国大陆
独家重印发行。

Addison Wesley Longman

Addison Wesley Longman Limited,

Edinburgh Gate, Harlow,

Essex CM20 2JE, England

and associated companies throughout the world

© T. L. Gilchrist 1985, 1992.

This Edition © Addison Wesley Longman Limited 1997

The right of Thomas L. Gilchrist to be identified as the author of this work has been asserted by him in accordance with the Copyright, Designs and Patents Act 1988

All rights reserved; no part of this publication may be reproduced, stored in any retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without either the prior written permission of the Publishers or a licence permitting restricted copying in the United Kingdom issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE

First published in Great Britain 1985 by Pitman Publishing Ltd

Reprinted by Longman Scientific & Technical 1987

Second Edition 1992

Second Impression 1993

Third Impression 1994

Third Edition 1997

British Library Cataloguing in Publication Data

A catalogue entry for this title is available from the British Library

ISBN 0-582-27843-0

Library of Congress Cataloging-in-Publication Data

A catalog entry for this title is available from the Library of Congress

This edition of **Heterocyclic Chemistry, Third edition** is published by arrangement with Addison Wesley Longman Limited, London

Licensed for sale in the mainland territory of the People's Republic of China only.

Not for sale in Hong Kong

Preface to the third edition

The material of the second edition has been revised with two principal aims in mind. The first is to bring the contents up to date. To this end, Chapter 1 and several parts of other chapters have been rewritten, the references have been updated (with more emphasis given to recent review articles) and several new reaction schemes have been introduced. These new schemes are intended to illustrate aspects of heterocyclic chemistry that are becoming more important. Organopalladium and other organometallic species are increasingly used in ring synthesis and in substitution reactions; some of the new schemes provide examples. New applications of heterocyclic compounds as pharmaceuticals, as intermediates in organic synthesis and as ligands are also illustrated.

The second aim has been to make the text more 'user friendly'. The text and structure drawings have been completely reset and the layout redesigned. I am indebted to Alexandra Seabrook, Shuet-Kei Cheung and their colleagues at Addison Wesley Longman for making this possible. Some of the obscurities in the text have been removed and captions have been added to all the reaction schemes. Worked examples have been introduced into most chapters, both to illustrate mechanistic points and to extend the chemistry. There are also some new problems at the end of several chapters.

I am grateful to Professor Hans Neunhoeffer and Dr Ian O'Neil for very helpful suggestions for improving the text and to Dr Eric Scriven for advice on the manufacture and uses of pyridines. As always I have relied greatly on my wife, Lorraine, who has patiently worked with me to produce and check the manuscript.

Preface to the second edition

I have received several very helpful comments and criticisms of the first edition and I have tried to take these into account in producing a second edition. I have also taken the opportunity to update some of the original material. The most substantial additions have been made to the chapter on the synthesis of heterocycles (Chapter 4). There have been important advances in the use of 1,3-dipolar cycloaddition and Diels–Alder cycloaddition in heterocyclic synthesis; the sections covering these topics have therefore been enlarged and reorganized. Other general methods that have gained increased prominence, such as radical cyclization, are also discussed more fully. The introductory chapter and that on the properties of aromatic heterocycles (Chapter 2) have also been substantially revised. Elsewhere new material has been added to reflect the increasing importance of topics such as the use of organolithium reagents in heterocyclic chemistry and the value of heterocycles as intermediates in synthesis. Several new problems have also been added.

Another major change is a cosmetic one: the order of the later chapters has been altered. This has been done because the simpler six- and five-membered aromatic heterocycles seem to be taught first in most courses on heterocyclic chemistry. The chapters on the various classes of ring system (Chapters 5 to 10) are, however, largely self-contained and the material can be presented in any sequence.

There is rarely time to cover all the material presented here in a course on heterocyclic chemistry. The book is therefore intended also to serve as a reference source and as a guide to the enormous literature of heterocyclic chemistry. The reference list has been updated, mainly to include recent review articles. In doing this I have adopted the policy of making little specific reference to review chapters in *Comprehensive Heterocyclic Chemistry* (ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984). This work is nevertheless the best place to start a search for more detailed information on heterocyclic chemistry and its literature. The periodic guides to the literature provided in *Advances in Heterocyclic Chemistry* (ed. A. R. Katritzky, Academic Press, San Diego) are also invaluable: the latest of these, by L. I. Belen'kii and N. D. Kruchkovskaya, is in Volume 55 (1992).

I am most grateful to those who have made suggestions for changes to the original edition. In particular, I should like to thank Professor Wilhelm Flitsch, Professor Charles Rees, Dr John Boulton, and Dr Derek Hurst, who provided detailed written comments. If their suggestions have not all been incorporated it is because I have had to restrict the length of the book. I am also grateful to Dr Dick Storr, who read part of the new material, to Dr Frank King for his help with Chapter 1, to Dr Michael Rodgers for commissioning a second edition, and to the staff of Longman Higher Education and Reference for their expert guidance.

Preface to the first edition

In this book I have aimed to present a description of the preparation and properties of heterocyclic compounds which can be used by anyone with a good background knowledge of organic chemistry. The number of different heterocyclic systems and their structural diversity make it difficult to gain a good understanding of the subject by studying individual ring systems in isolation. I have therefore tried to identify and emphasize general features of the properties of heterocyclic compounds throughout the book.

The concept of aromaticity has long proved useful in rationalizing the chemistry of many unsaturated heterocycles. The meaning of the term aromaticity, as applied to heterocyclic compounds, is discussed in Chapter 2. This is intended to provide a firm basis for understanding the chemistry of particular ring systems described later in the book. The chemistry of nonaromatic heterocycles is often regarded as a simple extrapolation of aliphatic and alicyclic chemistry. Although this undoubtedly has some justification there are some important special features of the properties of nonaromatic heterocycles which are discussed in Chapter 3. Chapter 4 is intended to provide a framework for rationalizing the vast literature on heterocyclic synthesis. The approach I have taken is to identify the reactions involved in the ring-forming processes and to classify the synthetic methods accordingly. There are many examples in this chapter, presented in tabular form, which are given to emphasize the common features involved in the synthesis of different ring systems. Many of these examples are referred to in later chapters.

Descriptive accounts of the more important ring systems are presented in Chapters 5 to 10. The ring systems are described in order of increasing ring size and complexity, but the material in this part of the book need not be read in the order in which it is presented. For example, the reader may prefer to study the chemistry of pyridines (Chapter 8) before that of pyrroles (Chapter 6). Imidazole and the other azoles have an interesting and diverse chemistry which is sometimes given little attention in textbooks. I have felt justified in describing these ring systems in more detail (Chapter 7) because of their apparently increasing importance as pharmaceuticals. In all of the chapters covering particular ring systems examples of currently important derivatives are given, and the diverse roles of the

heterocycles as synthetic intermediates in organic chemistry are illustrated. A guide to the various nomenclature systems for heterocycles is presented in Chapter 11.

Each chapter is followed by a summary, listing the main points in the text, and by a set of problems. Most of these problems are taken from the literature, and a list of references to the original papers is given at the end of the book. Literature citations are also given throughout the text. These can be ignored by the reader who simply wants an introduction to the topics being discussed, but they are provided to allow access to the original work on much of the factual material. Where this is not possible, for reasons of space, references are given to reviews. Heterocyclic chemistry is well served by specialized reviews, notably those in the series *The Chemistry of Heterocyclic Compounds*, edited by A. Weissberger and E. C. Taylor, and in the *Advances in Heterocyclic Chemistry* series edited by A. R. Katritzky and A. J. Boulton. An important additional source of specialized information, which has become available since this text was written, is *Comprehensive Heterocyclic Chemistry*, edited by A. R. Katritzky and C. W. Rees.

In writing the book I have been fortunate to have the expert guidance of the staff of Pitman Publishing Ltd. I should like to thank them, and particularly Mr Navin Sullivan, for their help. I am also indebted to the referees who read parts of the manuscript and made invaluable suggestions for its improvement, and to my colleagues at Liverpool who have read and commented upon parts of the text. My wife Lorraine typed most of the manuscript and was a constant source of advice, encouragement and practical assistance during its preparation.

T. L. Gilchrist. September 1984
University of Liverpool

Acknowledgements

We are grateful to the following for permission to reproduce copyright material:

Verlag Chemie GmbH and Professor Dr G. Schröder for Fig. 2.19 from a figure, p. 242 (Gilb & Schröder, 1982).

Whilst every effort has been made to trace the owners of copyright material, in a few cases this has proved impossible and we take this opportunity to offer our apologies to any copyright holders whose rights we may have unwittingly infringed.

Contents

<i>Preface to the third edition</i>	xii
<i>Preface to the second edition</i>	xiii
<i>Preface to the first edition</i>	xv
<i>Acknowledgements</i>	xvii

1 Introduction: uses of heterocyclic compounds	1
2 Aromatic heterocycles	8
2.1 The common structural types	8
2.1.1 Six-atom, six- π -electron heterocycles	8
2.1.2 Five-atom, six- π -electron heterocycles	12
2.1.3 Benzo-fused ring systems	14
2.1.4 Other fused heterocycles	15
2.2 Some criteria of aromaticity in heterocycles	16
2.2.1 Bond lengths	16
2.2.2 Ring current effects and chemical shifts in ^1H NMR spectra	18
2.2.3 Molecular orbitals and delocalization energy	19
2.2.4 Resonance energies	22
2.2.5 Dewar resonance energies and other calculated resonance energies	24
2.2.6 General conclusions	25
2.3 Aromatic character and other types of unsaturated heterocycles	26
2.3.1 Monocyclic systems that conform to the Hückel rule	26
2.3.2 Other unsaturated heterocycles	28
2.4 Reactivity of heteroaromatic compounds	29
2.5 Tautomerism of heteroaromatic compounds	32
Summary	35
Problems	35

3	Nonaromatic heterocycles	38
3.1	Introduction	38
3.2	Bond angle strain	39
3.2.1	Angle strain and bonding in small-ring heterocycles	39
3.2.2	Some consequences of bond angle strain in small rings	41
3.2.3	Angle strain in larger rings	44
3.3	Torsional energy barriers	44
3.3.1	Single bonds	44
3.3.2	Double bonds and partial double bonds	46
3.4	Influence of bond lengths and van der Waals radii: conformational preferences of flexible heterocycles	48
3.4.1	Saturated six-membered heterocycles	48
3.4.2	Four- and five-membered heterocycles	50
3.5	Other types of interaction in saturated heterocycles	51
3.5.1	'Through-bond' orbital interactions: the anomeric effect	51
3.5.2	Attractive 'through-space' interactions	56
	Summary	57
	Problems	58
4	Ring synthesis	61
4.1	Introduction	61
4.2	Cyclization reactions	62
4.2.1	Reaction types	62
4.2.2	Displacement at saturated carbon	68
4.2.3	Intramolecular nucleophilic addition to carbonyl groups	70
4.2.4	Intramolecular addition of nucleophiles to other double bonds	73
4.2.5	Cyclization on to triple bonds	76
4.2.6	Radical cyclization	79
4.2.7	Carbene and nitrene cyclization	83
4.2.8	Electrocyclic reactions	84
4.3	Cycloaddition reactions	89
4.3.1	Reaction types	89
4.3.2	1,3-Dipolar cycloaddition	91
4.3.3	Hetero-Diels-Alder reactions	106
4.3.4	[2 + 2] Cycloaddition	115
4.3.5	Cheletropic reactions	118
4.3.6	Ene reactions	120
	Summary	121
	Problems	121

5	Six-membered ring compounds with one heteroatom	125
5.1	Introduction	125
5.2	Pyridines	125
5.2.1	Introduction	125
5.2.2	Ring synthesis	127
5.2.3	General features of the chemistry of pyridines	133
5.2.4	Basicity	136
5.2.5	Alkylation, acylation and complexation on nitrogen	137
5.2.6	Electrophilic substitution at carbon	138
5.2.7	Nucleophilic substitution	142
5.2.8	Didehydropyridines (pyridynes)	147
5.2.9	Radical substitution	149
5.2.10	Palladium-catalysed coupling reactions and Heck reactions	149
5.2.11	Reduction of pyridines and pyridinium salts: dihydropyridines	150
5.2.12	Photochemical isomerization	152
5.2.13	Pyridine <i>N</i> -oxides, <i>N</i> -imides and <i>N</i> -ylides	153
5.2.14	Hydroxy- and aminopyridines	154
5.2.15	Alkyl- and alkenylpyridines	156
5.2.16	Pyridinecarboxylic acids	158
5.3	Quinolines and isoquinolines	158
5.3.1	Introduction	158
5.3.2	Synthesis of quinolines	159
5.3.3	Synthesis of isoquinolines	162
5.3.4	General features of the chemistry of quinolines and isoquinolines	164
5.3.5	Electrophilic substitution	165
5.3.6	Nucleophilic substitution	167
5.3.7	Nucleophilic addition	168
5.3.8	Oxidative cleavage	169
5.3.9	<i>N</i> -Oxides and <i>N</i> -imides	170
5.3.10	Properties of substituents	170
5.3.11	Cyanine dyes	171
5.4	Other fused pyridines	172
5.4.1	Quinolizines	172
5.4.2	Acridines	173
5.4.3	Phenanthridines	175
5.4.4	Indolizines	175
5.5	Ring systems containing oxygen	176
5.5.1	Pyrylium salts	176
5.5.2	2 <i>H</i> -Pyran-2-ones	178
5.5.3	4 <i>H</i> -Pyran-4-ones	181
5.5.4	Benzo-fused systems	183

Summary	186
Problems	187
6 Five-membered ring compounds with one heteroatom	192
6.1 Introduction	192
6.2 Pyrroles	193
6.2.1 Introduction	193
6.2.2 Ring synthesis	194
6.2.3 Acidity and metallation reactions	197
6.2.4 Substitution at nitrogen	197
6.2.5 Substitution at carbon	198
6.2.6 Addition and cycloaddition reactions	204
6.2.7 Properties of substituted pyrroles	205
6.2.8 Porphyrins and related pyrrolic natural products	207
6.3 Furans	208
6.3.1 Introduction	208
6.3.2 Ring synthesis	210
6.3.3 Reactions with electrophiles	212
6.3.4 Radical substitution and nucleophilic substitution	216
6.3.5 Cycloaddition reactions	216
6.3.6 Ring-cleavage reactions	219
6.3.7 Some properties of substituted furans	221
6.4 Thiophenes	221
6.4.1 Introduction	221
6.4.2 Ring synthesis	222
6.4.3 Electrophilic substitution	223
6.4.4 Nucleophilic and radical substitution	226
6.4.5 Addition and cycloaddition reactions	228
6.4.6 Reductive desulfurization	228
6.4.7 Photochemical isomerization	229
6.4.8 Properties of some substituted thiophenes	230
6.5 Indoles and related compounds	231
6.5.1 Introduction	231
6.5.2 Ring synthesis	233
6.5.3 Reaction with electrophiles	237
6.5.4 Radical substitution and coupling reactions	241
6.5.5 Oxidation and reduction	241
6.5.6 Properties of some substituted indoles	243
6.6 Other benzo[<i>b</i>]-fused heterocycles	244
6.6.1 Benzofurans	244
6.6.2 Benzo[<i>b</i>]thiophenes	246
6.6.3 Carbazoles	248
6.7 Benzo[<i>c</i>]-fused heterocycles	249

6.7.1	Introduction	249
6.7.2	Synthesis	249
6.7.3	Chemical properties	250
6.7.4	Phthalocyanines	251
	Summary	252
	Problems	253
7	Six-membered ring compounds with two or more heteroatoms	257
7.1	Introduction	257
7.2	General aspects of the chemistry of diazines, triazines and tetrazines	257
7.3	Pyrimidines and purines	261
7.3.1	Introduction	261
7.3.2	Synthesis of pyrimidines	264
7.3.3	Synthesis of purines	266
7.3.4	Reactions of pyrimidines	268
7.3.5	Reactions of purines	274
7.3.6	Pyrimidines and purines in nucleic acids	275
7.4	Other diazines, triazines and tetrazines	276
7.4.1	Introduction	276
7.4.2	Methods of ring synthesis	278
7.4.3	Chemical properties	280
7.5	Some fused ring systems	284
7.5.1	Introduction	284
7.5.2	Ring synthesis	285
7.5.3	Chemical properties	286
7.6	Oxazines and thiazines	288
7.6.1	Introduction	288
7.6.2	1,3-Oxazines	289
7.6.3	Phenothiazines	291
	Summary	292
	Problems	293
8	Five-membered ring compounds with two or more heteroatoms	295
8.1	Introduction	295
8.2	Imidazoles	298
8.2.1	Introduction	298
8.2.2	Ring synthesis	299
8.2.3	Reactions	301
8.3	Pyrazoles, triazoles and tetrazoles	304
8.3.1	Introduction	304
8.3.2	Ring synthesis	305
8.3.3	Substitution reactions	308

8.3.4	Ring cleavage	311
8.3.5	Azoles as <i>ortho</i> -directing groups for metallation	314
8.4	Benzodiazoles and benzotriazoles	315
8.5	Oxazoles and thiazoles and their benzo derivatives	319
8.5.1	Introduction	319
8.5.2	Ring synthesis	320
8.5.3	Chemical properties	322
8.6	Isoxazoles, isothiazoles and their benzo derivatives	328
8.6.1	Introduction	328
8.6.2	Ring synthesis	329
8.6.3	Chemical properties	332
8.7	Oxadiazoles, thiadiazoles and related systems	335
8.7.1	Introduction	335
8.7.2	Ring synthesis	336
8.7.3	Chemical properties	336
8.8	Betaines and mesoionic compounds	340
8.8.1	<i>N</i> -Oxides and <i>N</i> -imides	341
8.8.2	Mesoionic compounds	341
	Summary	344
	Problems	345
9	Three- and four-membered ring compounds	350
9.1	Introduction	350
9.2	Aziridines	350
9.2.1	Introduction	350
9.2.2	Ring synthesis	351
9.2.3	Functionalization at nitrogen	352
9.2.4	Ring-opening reactions	353
9.2.5	Fragmentation reactions	354
9.3	Oxiranes	354
9.3.1	Introduction	354
9.3.2	Ring synthesis	355
9.3.3	Reactions	357
9.4	Thiiranes	359
9.5	2 <i>H</i> -Azirines	360
9.6	Diaziridines and 3 <i>H</i> -diazirines	363
9.7	Oxaziridines	364
9.8	Azetidines and azetidinones	365
9.9	Other four-membered heterocycles	367
9.9.1	Oxetanes	367
9.9.2	Thietanes	368
9.9.3	Some unsaturated four-membered rings	369
	Summary	370
	Problems	371

10 Seven-membered ring compounds	373
10.1 Introduction	373
10.2 Azepines	374
10.3 Oxepins and thiepins	376
10.4 Diazepines and benzodiazepines	379
Summary	381
Problems	382
11 Nomenclature	384
11.1 Introduction	384
11.2 Trivial names of common ring systems	385
11.3 Systematic (Hantzsch–Widmañ) nomenclature for monocyclic compounds	387
11.4 The naming of fused ring systems	389
11.5 Replacement nomenclature	392
Summary	392
Problems	393
Answers and references to selected problems	394
Index	400