COMPREHENSIVE HETEROCYCLIC CHEMISTRY

The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds

Volume 7

ALAN R. KATRITZKY, FRS

CHARLES W. REES, FRS

Part 5

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Volume 7

Chairman of the Editorial Board
ALAN R. KATRITZKY, FRS
University of Florida

Co-Chairman of the Editorial Board
CHARLES W. REES, FRS
Imperial College of Science and Technology
University of London

Part 5

Small and Large Rings

EDITOR
WALTER LWOWSKI
New Mexico State University

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Foreword

Scope

Heterocyclic compounds are those which have a cyclic structure with two, or more, different kinds of atom in the ring. This work is devoted to organic heterocyclic compounds in which at least one of the ring atoms is carbon, the others being considered the heteroatoms; carbon is still by far the most common ring atom in heterocyclic compounds. As the number and variety of heteroatoms in the ring increase there is a steady transition to the expanding domain of inorganic heterocyclic systems. Since the ring can be of any size, from three-membered upwards, and since the heteroatoms can be drawn in almost any combination from a large number of the elements (though nitrogen, oxygen and sulfur are the most common), the number of possible heterocyclic systems is almost limitless. An enormous number of heterocyclic compounds is known and this number is increasing very rapidly. The literature of the subject is correspondingly vast and of the three major divisions of organic chemistry, aliphatic, carbocyclic and heterocyclic, the last is much the biggest. Over six million compounds are recorded in *Chemical Abstracts* and approximately half of these are heterocyclic.

Significance

Heterocyclic compounds are very widely distributed in Nature and are essential to life; they play a vital role in the metabolism of all living cells. Thus, for example, the following are heterocyclic compounds: the pyrimidine and purine bases of the genetic material DNA; the essential amino acids proline, histidine and tryptophan; the vitamins and coenzyme precursors thiamine, riboflavine, pyridoxine, folic acid and biotin; the B_{12} and E families of vitamin; the photosynthesizing pigment chlorophyll; the oxygen transporting pigment hemoglobin, and its breakdown products the bile pigments; the hormones kinetin, heteroauxin, serotonin and histamine; together with most of the sugars. There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine and reserpine, and cardiac glycosides such as those of digitalis. However, the large majority are synthetic heterocyclics which have found widespread use, for example as anticancer agents, analeptics, analgesics, hypnotics and vasopressor modifiers, and as pesticides, insecticides, weedkillers and rodenticides.

There is also a large number of synthetic heterocyclic compounds with other important practical applications, as dyestuffs, copolymers, solvents, photographic sensitizers and developers, as antioxidants and vulcanization accelerators in the rubber industry, and many are valuable intermediates in synthesis.

The successful application of heterocyclic compounds in these and many other ways, and their appeal as materials in applied chemistry and in more fundamental and theoretical studies, stems from their very complexity; this ensures a virtually limitless series of structurally novel compounds with a wide range of physical, chemical and biological properties, spanning a broad spectrum of reactivity and stability. Another consequence of their varied chemical reactivity, including the possible destruction of the heterocyclic ring, is their increasing use in the synthesis of specifically functionalized non-heterocyclic structures.

Aims of the Present Work

All of the above aspects of heterocyclic chemistry are mirrored in the contents of the present work. The scale, scope and complexity of the subject, already referred to, with its correspondingly complex system of nomenclature, can make it somewhat daunting initially. One of the main aims of the present work is to minimize this problem by presenting a comprehensive account of fundamental heterocyclic chemistry, with the emphasis on basic principles and, as far as possible, on unifying correlations in the properties, chemistry and synthesis of different heterocyclic systems and the analogous carbocyclic structures. The motivation for this effort was the outstanding biological, practical and theoretical importance of heterocyclic chemistry, and the absence of an appropriate major modern treatise.

At the introductory level there are several good textbooks on heterocyclic chemistry, though the subject is scantily treated in most general textbooks of organic chemistry. At the specialist, research level there are two established ongoing series, 'Advances in Heterocyclic Chemistry' edited by Katritzky and 'The Chemistry of Heterocyclic Compounds' edited by Weissberger and Taylor, devoted to a very detailed consideration of all aspects of heterocyclic compounds, which together comprise some 100 volumes. The present work is designed to fill the gap between these two levels, *i.e.* to give an up-to-date overview of the subject as a whole (particularly in the General Chapters) appropriate to the needs of teachers and students and others with a general interest in the subject and its applications, and to provide enough detailed information (particularly in the Monograph Chapters) to answer specific questions, to demonstrate exactly what is known or not known on a given topic, and to direct attention to more detailed reviews and to the original literature. Mainly because of the extensive practical uses of heterocyclic compounds, a large and valuable review literature on all aspects of the subject has grown up over the last few decades. References to all of these reviews are now immediately available: reviews dealing with a specific ring system are reported in the appropriate monograph chapters; reviews dealing with any aspect of heterocyclic chemistry which spans more than one ring system are collected together in a logical, readily accessible manner in Chapter 1.03.

The approach and treatment throughout this work is as ordered and uniform as possible, based on a carefully prearranged plan. This plan, which contains several novel features, is described in detail in the Introduction (Chapter 1.01).

ALAN R. KATRITZKY
Florida

CHARLES W. REES
London

Contributors to Volume 7

Professor A. G. Anastassiou
Department of Chemistry, University of Petroleum & Minerals, Dhahran, Saudi Arabia

Professor F. A. L. Anet
Department of Chemistry, University of California, Los Angeles, CA 90024, USA

Dr G. R. Baker
Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA

Professor E. Block
Department of Chemistry, State University of New York at Albany, 1400 Washington Avenue, Albany, NY 12222, USA

Dr D. R. Boyd
Department of Chemistry, Queen's University of Belfast, Belfast BT9 5AG, UK

Dr D. E. Davies
Department of Organic Chemistry, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK

Professor D. C. Dittmer
Department of Chemistry, Syracuse University, 108 Bowne Hall, Syracuse, NY 13210, USA

Dr G. L. Dunn
Assistant Director, Research Chemistry, Smith Kline & French Laboratories, 1500 Spring Garden Street, PO Box 7929, Philadelphia, PA 19101, USA

Professor A. D. Hamilton
Department of Chemistry, Princeton University, Princeton, NJ 08544, USA

Professor H. Hart
Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA

Dr K. G. Holden
Deputy Director, Research Chemistry, Smith Kline & French Laboratories, PO Box 7929, Philadelphia, PA 19101, USA

Professor E. G. Lewars
Department of Chemistry, Trent University, Peterborough, Ontario K9J 7B8, Canada

Professor W. Lwowski
Department of Chemistry, New Mexico State University, PO Box 3C, Las Cruces, NM 88003, USA

Dr D. N. McGregor
Bristol Laboratories, PO Box 657, Syracuse, NY 13201, USA

Professor J. A. Moore
Department of Chemistry, University of Delaware, Newark, DE 19711, USA

Professor G. R. Newkome
Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA

Professor A. Padwa
Department of Chemistry, Emory University, Atlanta, GA 30322, USA

Professor Dr E. Schmitz
Zentralinstitut fur Organische Chemie, Akademie der Wissenschaften der DDR, Rudowere Chaussee 5, 1199 Berlin, German Democratic Republic

Professor S. Searles
Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA

Dr J. T. Sharp
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK

Dr R. K. Smalley
Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, UK

Dr R. C. Storr
Department of Organic Chemistry, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK

Professor J. W. Timberlake
Department of Chemistry, University of New Orleans, Lake Front, New Orleans, LA 70122, USA

Dr J. G. Traynham
Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA

Dr A. D. Woolhouse
Chemistry Division, Department of Scientific & Industrial Research, Private Bag, Petone, New Zealand

Contents of All Volumes

Volume 8 (Part 6: Indexes)

JOURNAL CODES FOR REFERENCES

For explanation of the reference system, see p. 781.

ABC	Agric. Biol. Chem.
ACH	Acta Chim. Acad. Sci. Hung.
ACR	Acc. Chem. Res.
AC(R)	Ann. Chim. (Rome)
ACS	Acta Chem. Scand.
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AJC	Aust. J. Chem.
AK	Ark. Kemi
ANY	Ann. N.Y. Acad. Sci.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AX	Acta Crystallogr.
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chem. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochem. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CB	Chem. Ber.
CC	J. Chem. Soc., Chem. Commun.
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CI(L)	Chem. Ind. (London)
CJC	Can. J. Chem.
CL	Chem. Lett.
CPB	Chem. Pharm. Bull.
CR	C.R. Hebd. Seances Acad. Sci.
CR(C)	C.R. Hebd. Seances Acad. Sci., Ser. C
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CZ	Chem.-Ztg.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B
DOK	Dokl. Akad. Nauk SSSR
E	Experientia
EGP	Ger. (East) Pat.
EUP	Eur. Pat.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GEP	Ger. Pat.
H	Heterocycles
HC	Chem. Heterocycl. Compd. [Weissberger–Taylor series]
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
IC	Inorg. Chem.
IJC	Indian J. Chem.
IJC(B)	Indian J. Chem., Sect. B
IJS	Int. J. Sulfur Chem.
IJS(B)	Int. J. Sulfur Chem., Part B
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JCP	J. Chem. Phys.
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JMC	J. Med. Chem.
JMR	J. Magn. Reson.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)

JPC	J. Phys. Chem.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KGS	Khim. Geterotsikl. Soedin.
LA	Liebigs Ann. Chem.
M	Monatsh. Chem.
MI	Miscellaneous [book or journal]
MIP	Miscellaneous Pat.
MS	Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds', Wiley, New York, 1971
N	Naturwissenschaften
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi
NMR	T. J. Batterham, 'NMR Spectra of Simple Heterocycles', Wiley, New York, 1973
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PAC	Pure Appl. Chem.
PC	Personal Communication
PH	'Photochemistry of Heterocyclic Compounds', ed. O. Buchardt, Wiley, New York, 1976
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RRC	Rev. Roum. Chim.
RTC	Recl. Trav. Chim. Pays-Bas
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SH	W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds', Wiley, New York, 1977, parts 1 and 2
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
T	Tetrahedron
TH	Thesis
TL	Tetrahedron Lett.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
USP	U.S. Pat.
YZ	Yakugaku Zasshi
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe-Seyler's Z. Physiol. Chem.

Contents

5.01

Structure of Small and Large Rings

W. LWOWSKI
New Mexico State University

5.01.1 INTRODUCTION

Part 5 of Comprehensive Heterocyclic Chemist. contains two groups of systems, with little of their structural properties in common. This chapter is, therefore, divided into two parts, dealing separately with small and with large heterocyclic rings.

5.01.2 STRUCTURE OF SMALL HETEROCYCLIC RINGS

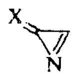
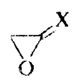
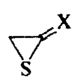
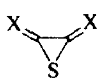
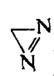
5.01.2.1 Known Small Heterocycles

A very large number of different arrangements of the same heteroatoms are possible in large rings. For three- and four-membered ones, however, it is still possible to write down all combinations of C, N, O and S, from plausible to outrageous ones. With the help of new techniques, the border between the plausible and the outrageous ones is shifting towards more and more strained and unstable systems. It seems that chemists have often underestimated the activation barriers separating thermodynamically unfavorable species from their more stable isomers or fragmentation products. Tables 1 and 2 list the three- and four-membered rings, respectively, which have been made or for which there is strong evidence (such as from isotope or stereochemical studies). A spectacular addition to the list is a triaziridine, a long sought for molecule, which turns out to be relatively stable after all.

5.01.2.2 Bond Lengths and Bond Angles

The geometry of three- and four-membered rings has been determined mainly by X-ray diffraction on crystalline materials ⟨72PMH(5)1, p. 12⟩, and also by electron diffraction,

Table 1 Structures of Known Three-membered Heterocyclic Compounds

Skeleton	*Name*	*Evidence*[a]	*Ref.*	*Chapter or section number*
	Aziridine	IP, XR, MW		5.04
	1-Azirine	IP, XR		5.04
	Aziridinone Alkylideneaziridine Aziridineimine	IP, XR IP	80AG(E)276 80AG(E)276 80AG(E)276	5.04 5.04 5.04
	Aziridinedione	MI	80JA6902	5.04
	Azirinimine	TH	73CC435	5.04
	2-Azirine	CE, TH	80PAC1623	5.04.2.1
	Oxirane	IP, XR, MW		5.05
	Oxiranone Alkylideneoxirane Oxiranimine	MI, GP, IP IP CE	82CC362 80AG(E)276 80AG(E)276	5.05 5.05 5.05
	Oxirene	CE		5.05.6
	Thiirane	IP, XR		5.06
	Thiiranone Thiiranimine Alkylidenethiirane	IP, XR IP, XR IP, XR	80AG(E)276 80AG(E)276 80AG(E)276	5.06 5.06 5.06
	Thiiranediimine	CE	79CC160	5.06
	Thiirene	IP, MI, CE	80PAC1623	5.06
	Diaziridine	IP		5.08
	1-Diazirine	IP, MW, TH		5.08
	Diaziridinone Diaziridinimine	IP, XR IP, XR	80AG(E)276 80AG(E)276	5.08 5.08
	Oxaziridine	IP, XR		5.08