COMPREHENSIVE HETEROCYCLIC CHEMISTRY

The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds

Volume 5

ALAN R. KATRITZKY, FRS

CHARLES W. REES, FRS

Part 4A

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Volume 5

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Part 4A

Five-membered Rings with Two or More Nitrogen Atoms

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COMPREHENSIVE HETEROCYCLIC CHEMISTRY

IN 8 VOLUMES

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).

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Volume 5 (Part 4A: Five-membered Rings with Two or More Nitrogen Atoms)

Volume 8 (Part 6: Indexes)

JOURNAL CODES FOR REFERENCES

For explanation of the reference system, see p. 905.

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

4.01

Structure of Five-membered Rings with Two or More Heteroatoms

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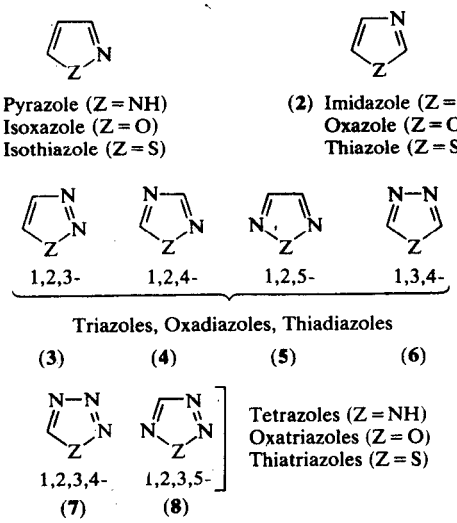
4.01.1 SURVEY OF POSSIBLE STRUCTURES

We classify compounds as aromatic, if there is continuous conjugation around the ring, or non-aromatic. Aromatic compounds are further subdivided into those without exocyclic double bonds and those in which important canonical forms containing exocyclic double bonds contribute.

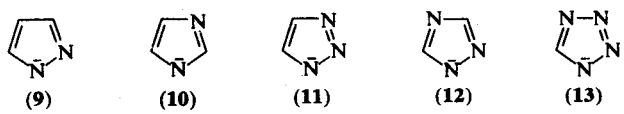
4.01.1.1 Aromatic Systems without Exocyclic Conjugation

The neutral aromatic azole systems (without exocyclic conjugation) are shown in Scheme 1; throughout, Z is O, S or NR. There are, thus, 24 possible systems; however, for NR = NH, tautomerism renders (3) ≡ (5), (4) ≡ (6), and (7) ≡ (8). Ring-fused derivatives without a bridgehead nitrogen atom are possible for systems (1), (2), (3) and (5). Ring-fused derivatives with a bridgehead nitrogen atom can be derived from all except (5) and (8).



Scheme 1 Neutral aromatic azoles (no exocyclic double bonds) (Z = O, S or NR)

The five possible azole monoanions are shown (one canonical form only) in Scheme 2; all heteroatoms are now nitrogens.



Scheme 2 Monoanionic aromatic azoles

The aromatic azole monocations are given in Scheme 3; here Z and Y are both O, S or NR; there are therefore three mixed sets. If Z = Y, then (16) ≡ (18), (20) ≡ (21), (22) ≡ (24), and (25) ≡ (26). Hence there are (3 × 14) + (3 × 10) = 72 possible systems.

4.01.1.2 Aromatic Systems with Exocyclic Conjugation

Each of the aromatic monocationic systems (14)–(27) can be converted into a neutral system by substitution of an anionic O, S or NR group on to a ring carbon atom. However, (14) and (15) each give three such systems, (16)–(21) two each, and (22)–(27) one each. The resulting 24 systems can be divided into two groups: 12 systems for the azolinones and related compounds (Scheme 4) and 12 systems for the mesoionic (betaine) compounds (Scheme 5).

Of the mesoionic systems, (40) and its aza derivatives (43), (44) and (49) have been designated as Class B by Ollis ⟨76AHC(19)1⟩, including compounds with X = CRR′; there