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COMPREHENSIVE HETEROCYCLIC CHEMISTRY

*The Structure, Reactions, Synthesis
and Uses of
Heterocyclic Compounds*

Volume 4

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Part 3

Five-membered Rings with One Oxygen, Sulfur or Nitrogen Atom

EDITORS

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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 B₁₂ 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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JOURNAL CODES FOR REFERENCES

For explanation of the reference system, see p. 1085

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

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

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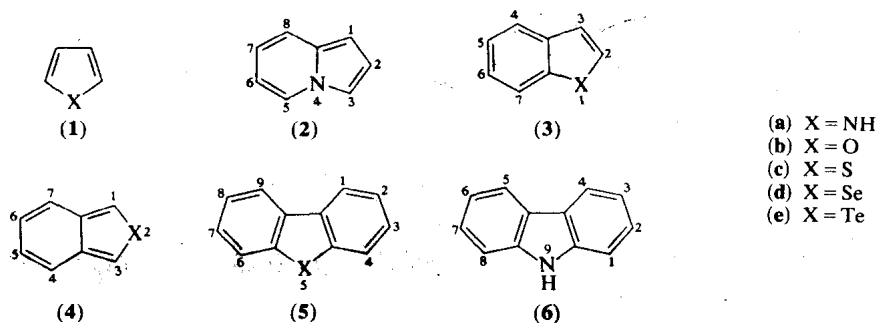
Structure of Five-membered Rings with One Heteroatom

C. W. BIRD and G. W. H. CHEESEMAM
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3.01.1 INTRODUCTION

The parent heterocycles pyrrole (**1a**), furan (**1b**) and thiophene (**1c**) made their respective debuts in the chemical literature in 1857, 1870 and 1882, although odd derivatives had been encountered earlier. Authenticated preparations of selenophene (**1d**) and tellurophene (**1e**) were reported much later in 1927 and 1966 respectively. Despite the highly unsaturated nature indicated by the molecular formulae, the behavior of these heterocycles in undergoing substitution rather than addition reactions inevitably led to comparison with benzene. Thus most of the early structural formulations merely mirrored those attributed to benzene. The most perceptive of these was proposed by Bamberger in 1891 (1891CB1758), and reformulated in electronic terms as the concept of 'The Aromatic Sextet' by Armit and Robinson in 1925 (25JCS1604). Basically the aromatic properties of benzene were perceived as deriving from the possession of six electrons associated with the three formal double bonds. The aromatic properties of the present heterocycles were rationalized by assuming that a pair of electrons associated with the heteroatom could fulfill the same role as those derived from a carbon-carbon double bond so that the requisite Aromatic Sextet was attained. The justification for this concept was provided subsequently by molecular orbital theory in the form of Hückel's Rule.



The involvement of the nitrogen lone pair of electrons in the π -bonding of pyrrole is immediately testified to by its negligible basicity in contrast to what would have been expected for a secondary amine. A broader view of this feature is provided by the comparison of the dipole moments of these heterocycles with those of their fully saturated counterparts in Table 1. The dipoles are directed from the ring towards the heteroatom in all instances except for the pyrroles where the nitrogen has become the positive end of the dipole (72JA8854). In each case there is a marked diminution in the dipole moment on proceeding from the fully reduced heterocycle to its fully aromatic counterpart, consonant with redistribution of the lone pair electrons of the heteroatom into the ring.

Table 1 Dipole Moments of Heterocycles (in Benzene)

X	$\mu(C_4H_8X)(D)$	$\mu(C_4H_4X)(D)$	$\Delta\mu$	Ref.
NH	1.58	-1.80	3.38	72JA8854
NMe	1.10	-1.92	3.02	72JA8854
O	1.75	0.71	1.04	72JA8854
S	1.90	0.52	1.38	72JA8854
Se	1.81	0.52	1.29	73CR(C)(277)203
Te	1.63	0.46	1.17	73CR(C)(277)203

Similarly, the benzo[a] (2), benzo[b] (3) and benzo[c] (4) fused heterocycles can be regarded as heterocyclic analogues of naphthalene, with the dibenzo heterocycles (5) bearing a similar electronic relationship to phenanthrene. As befits their relative antiquity, some of these compounds are still generally known by their trivial names indole (3a), isoindole (4a), carbazole (6) and indolizine (2). The names thianaphthene and pyrrocoline for (3c) and (2) respectively are now little used. Particular confusion can arise in consulting the literature on indolizine (2), where differing numbering systems have been used. It is also important to note that carbazole (6) is an exception to the IUPAC rules for numbering the other dibenzo heterocycles.

3.01.2 THEORETICAL METHODS

The major object of the plethora of semi-empirical molecular orbital calculations on furan, thiophene and pyrrole has been to establish the suitability of various modes of parameterization for reproducing experimentally derivable parameters such as geometry, dipole moments and ionization potentials. It is only relatively recently that it has become practical to apply *ab initio* MO methods to these molecules, which, even so, still require huge amounts of expensive computer time. An apparent early success of such calculations has been to resolve the controversy as to the rôle, if any, of sulfur *d*-orbitals in determining the structural properties and reactivity of thiophene. Inclusion of sulfur 3*d*-orbitals in *ab initio* calculations on thiophene has been found to make little difference to the total energy (70CC319, 72MI0101). Their principal rôle is to act as polarization functions rather than as an extra valence orbital. Thus the population of the 3*d*-orbital is very small but its introduction into the basis set causes considerable changes in the population of 3*s*- and 3*p*-orbitals so that electron density on sulfur is increased at the principal expense of the flanking carbon atoms. This conclusion has received experimental support (76JCP(64)3021)