

54.556
C737
:6-4B

COMPREHENSIVE HETEROCYCLIC CHEMISTRY

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

Volume 6

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 4B

Five-membered Rings with Two or More Oxygen, Sulfur or Nitrogen Atoms

EDITOR

KEVIN T. POTTS

Rensselaer Polytechnic Institute, New York

PERGAMON PRESS

OXFORD · NEW YORK · TORONTO · SYDNEY · PARIS · FRANKFURT

U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon Press Canada Ltd., Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, N.S.W. 2011, Australia
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, Hammerweg 6, D-6242 Kronberg-Taunus, Federal Republic of Germany

Copyright © 1984 Pergamon Press Ltd.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means: electronic, electrostatic, magnetic tape, mechanical, photocopying, recording or otherwise, without permission in writing from the publishers

• First edition 1984

Library of Congress Cataloging in Publication Data

Main entry under title:

Comprehensive heterocyclic chemistry.

Includes indexes.

Contents: v. 1. Introduction, nomenclature, literature, biological aspects, industrial uses, less-common heteroatoms -

v. 2. Six-membered rings with one nitrogen atom - [etc.] -

v. 8. Indexes.

1. Heterocyclic compounds. I. Katritzky, Alan R. (Alan Roy)

II. Rees, Charles W. (Charles Wayne)

QD400.C65 1984 547'.59 83-4264

British Library Cataloguing in Publication Data

Comprehensive heterocyclic chemistry

1. Heterocyclic compounds.

I. Katritzky, Alan R. II. Rees, Charles W.

547'.59 QD400

ISBN 0-08-030706-X (vol. 6)

ISBN 0-08-026200-7 (set)

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).

ALAN R. KATRITZKY
Florida

CHARLES W. REES
London

Contributors to Volume 6

Professor G. V. Boyd
Department of Chemistry, Chelsea College, Manresa Road, London SW3 6LZ, UK

Professor L. B. Clapp
Department of Chemistry, Brown University, Providence, RI 02912, USA

Dr M. R. Detty
Research Laboratories, Eastman Kodak Company, Rochester, NY 14650, USA

Dr O. P. Dhingra
Monsanto Agricultural Products Co., 800 N Lindberg Boulevard, St Louis, MO 63167, USA

Dr A. J. Elliott
62 Seven Lakes Drive, Sloatsburg, NY 10974, USA

Professor G. W. Fischer
Forschungsstelle fuer Chemische Toxikologie der AdW der DDR, DDR-7050 Leipzig,
Permoserstrasse 15, German Democratic Republic

Dr J. E. Franz
Monsanto Agricultural Products Co., 800 N Lindberg Boulevard, St Louis, MO 63167, USA

Professor H. Gotthardt
FB-9 Organische Chemie, Universität Gesamthochschule Wuppertal, Wuppertal-Elberfeld,
Gaussstrasse 20, Postfach 100127, 5600 Wuppertal 1, Federal Republic of Germany

Dr J. Hill
Department of Chemistry & Applied Chemistry, University of Salford, Salford M5 4WT, UK

Dr A. Holm
Department of General and Organic Chemistry, University of Copenhagen, The H.C. Orsted
Institute, DK 2100 Copenhagen, Denmark

Dr G. Kornis
Parasitology Research, The Upjohn Company, Kalamazoo, MI 49001, USA

Dr I. Lalezari
240 Garth Road, 4F-2, Scarsdale, NY 10583, USA

Dr S. A. Lang, Jr.
Medical Research Division, American Cyanamid Company, Lederle Laboratories, Pearl
River, NY 10965, USA

Dr Y.-i Lin
Medical Research Division, American Cyanamid Company, Lederle Laboratories, Pearl
River, NY 10965, USA

Professor N. Lozac'h
17 rue du Docteur Georges Maugeais, 14000 Caen, France

Professor D. M. McKinnon
Department of Chemistry, University of Manitoba, Winnipeg, Manitoba, Canada R3T 2N2

Professor J. Metzger
Université de Droit, d'Economie et des Sciences d'Aix-Marseille, Laboratoire de Chimie Organique A, Faculté des Sciences et Techniques de Saint Jerome, rue Henri Poincare, 13397 Marseille Cedex 4, France

Mr D. L. Pain
May & Baker Ltd., Dagenham, Essex RM10 7XS, UK

Dr R. M. Paton
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK

Dr B. J. Peart
May & Baker Ltd., Dagenham, Essex RM10 7XS, UK

Dr K. H. Pilgram
Shell Development Company, Biological Sciences Research Center, PO Box 4248, Modesto, CA 95352, USA

Dr C. A. Ramsden
May & Baker Ltd., Dagenham, Essex RM10 7XS, UK

Dr M. P. Sammes
Department of Chemistry, University of Hong Kong, Pokfulam Road, Hong Kong

Dr I. Shinkai
Process Research, Merck Sharp & Dohme Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

Dr E. W. Thomas
Diabetes and Atherosclerosis Research, The Upjohn Company, Kalamazoo, MI 49001, USA

Dr K. Undheim
Department of Chemistry, University of Oslo, Blindern, Oslo 3, PO Box 1033, Norway

Dr L. M. Weinstock
Director, Process Research, Merck Sharp & Dohme Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

Dr K. R. H. Wooldridge
May & Baker Ltd., Dagenham, Essex RM10 7XS, UK

Dr T. Zimmermann
Forschungsstelle fuer Chemische Toxikologie der AdW der DDR, DDR-7050 Leipzig, Permoserstrasse 15, German Democratic Republic

Contents of All Volumes

Volume 1 (Part 1: Introduction, Nomenclature, Review Literature, Biological Aspects, Industrial Uses, Less-common Heteroatoms)

- 1.01 Introduction
- 1.02 Nomenclature of Heterocyclic Compounds
- 1.03 Review Literature of Heterocycles
- 1.04 Biosynthesis of Some Heterocyclic Natural Products
- 1.05 Toxicity of Heterocycles
- 1.06 Application as Pharmaceuticals
- 1.07 Use as Agrochemicals
- 1.08 Use as Veterinary Products
- 1.09 Metabolism of Heterocycles
- 1.10 Importance of Heterocycles in Biochemical Pathways
- 1.11 Heterocyclic Polymers
- 1.12 Heterocyclic Dyes and Pigments
- 1.13 Organic Conductors
- 1.14 Uses in Photographic and Reprographic Techniques
- 1.15 Heterocyclic Compounds as Additives
- 1.16 Use in the Synthesis of Non-heterocycles
- 1.17 Heterocyclic Rings containing Phosphorus
- 1.18 Heterocyclic Rings containing Arsenic, Antimony or Bismuth
- 1.19 Heterocyclic Rings containing Halogens
- 1.20 Heterocyclic Rings containing Silicon, Germanium, Tin or Lead
- 1.21 Heterocyclic Rings containing Boron
- 1.22 Heterocyclic Rings containing a Transition Metal

Volume 2 (Part 2A: Six-membered Rings with One Nitrogen Atom)

- 2.01 Structure of Six-membered Rings
- 2.02 Reactivity of Six-membered Rings
- 2.03 Synthesis of Six-membered Rings
- 2.04 Pyridines and their Benzo Derivatives: (i) Structure
- 2.05 Pyridines and their Benzo Derivatives: (ii) Reactivity at Ring Atoms
- 2.06 Pyridines and their Benzo Derivatives: (iii) Reactivity of Substituents
- 2.07 Pyridines and their Benzo Derivatives: (iv) Reactivity of Non-aromatics
- 2.08 Pyridines and their Benzo Derivatives: (v) Synthesis
- 2.09 Pyridines and their Benzo Derivatives: (vi) Applications
- 2.10 The Quinolinizinium Ion and Aza Analogs
- 2.11 Naphthyridines, Pyridoquinolines, Anthyridines and Similar Compounds

Volume 3 (Part 2B: Six-membered Rings with Oxygen, Sulfur or Two or More Nitrogen Atoms)

- 2.12 Pyridazines and their Benzo Derivatives
- 2.13 Pyrimidines and their Benzo Derivatives

- 2.14 Pyrazines and their Benzo Derivatives
- 2.15 Pyridodiazines and their Benzo Derivatives
- 2.16 Pteridines
- 2.17 Other Diazinodiazines
- 2.18 1,2,3-Triazines and their Benzo Derivatives
- 2.19 1,2,4-Triazines and their Benzo Derivatives
- 2.20 1,3,5-Triazines
- 2.21 Tetrazines and Pentazines
- 2.22 Pyrans and Fused Pyrans: (i) Structure
- 2.23 Pyrans and Fused Pyrans: (ii) Reactivity
- 2.24 Pyrans and Fused Pyrans: (iii) Synthesis and Applications
- 2.25 Thiopyrans and Fused Thiopyrans
- 2.26 Six-membered Rings with More than One Oxygen or Sulfur Atom
- 2.27 Oxazines, Thiazines and their Benzo Derivatives
- 2.28 Polyoxa, Polythia and Polyaza Six-membered Ring Systems

Volume 4 (Part 3: Five-membered Rings with One Oxygen, Sulfur or Nitrogen Atom)

- 3.01 Structure of Five-membered Rings with One Heteroatom
- 3.02 Reactivity of Five-membered Rings with One Heteroatom
- 3.03 Synthesis of Five-membered Rings with One Heteroatom
- 3.04 Pyrroles and their Benzo Derivatives: (i) Structure
- 3.05 Pyrroles and their Benzo Derivatives: (ii) Reactivity
- 3.06 Pyrroles and their Benzo Derivatives: (iii) Synthesis and Applications
- 3.07 Porphyrins, Corrins and Phthalocyanines
- 3.08 Pyrroles with Fused Six-membered Heterocyclic Rings: (i) *a*-Fused
- 3.09 Pyrroles with Fused Six-membered Heterocyclic Rings: (ii) *b*- and *c*-Fused
- 3.10 Furans and their Benzo Derivatives: (i) Structure
- 3.11 Furans and their Benzo Derivatives: (ii) Reactivity
- 3.12 Furans and their Benzo Derivatives: (iii) Synthesis and Applications
- 3.13 Thiophenes and their Benzo Derivatives: (i) Structure
- 3.14 Thiophenes and their Benzo Derivatives: (ii) Reactivity
- 3.15 Thiophenes and their Benzo Derivatives: (iii) Synthesis and Applications
- 3.16 Selenophenes, Tellurophenes and their Benzo Derivatives
- 3.17 Furans, Thiophenes and Selenophenes with Fused Six-membered Heterocyclic Rings
- 3.18 Two Fused Five-membered Rings each containing One Heteroatom

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

- 4.01 Structure of Five-membered Rings with Two or More Heteroatoms
- 4.02 Reactivity of Five-membered Rings with Two or More Heteroatoms
- 4.03 Synthesis of Five-membered Rings with Two or More Heteroatoms
- 4.04 Pyrazoles and their Benzo Derivatives
- 4.05 Pyrazoles with Fused Six-membered Heterocyclic Rings
- 4.06 Imidazoles and their Benzo Derivatives: (i) Structure
- 4.07 Imidazoles and their Benzo Derivatives: (ii) Reactivity
- 4.08 Imidazoles and their Benzo Derivatives: (iii) Synthesis and Applications
- 4.09 Purines
- 4.10 Other Imidazoles with Fused Six-membered Rings
- 4.11 1,2,3-Triazoles and their Benzo Derivatives
- 4.12 1,2,4-Triazoles
- 4.13 Tetrazoles
- 4.14 Pentazoles
- 4.15 Triazoles and Tetrazoles with Fused Six-membered Rings

Volume 6 (Part 4B: Five-membered Rings with Two or More Oxygen, Sulfur or Nitrogen Atoms)

- 4.16 Isoxazoles and their Benzo Derivatives
- 4.17 Isothiazoles and their Benzo Derivatives
- 4.18 Oxazoles and their Benzo Derivatives
- 4.19 Thiazoles and their Benzo Derivatives
- 4.20 Five-membered Selenium-Nitrogen Heterocycles
- 4.21 1,2,3- and 1,2,4-Oxadiazoles
- 4.22 1,2,5-Oxadiazoles and their Benzo Derivatives
- 4.23 1,3,4-Oxadiazoles
- 4.24 1,2,3-Thiadiazoles and their Benzo Derivatives
- 4.25 1,2,4-Thiadiazoles
- 4.26 1,2,5-Thiadiazoles and their Benzo Derivatives
- 4.27 1,3,4-Thiadiazoles
- 4.28 Oxatriazoles and Thiatriazoles
- 4.29 Five-membered Rings (One Oxygen or Sulfur and at least One Nitrogen Atom)
Fused with Six-membered Rings (at least One Nitrogen Atom)
- 4.30 Dioxoles and Oxathioles
- 4.31 1,2-Dithioles
- 4.32 1,3-Dithioles
- 4.33 Five-membered Rings containing Three Oxygen or Sulfur Atoms
- 4.34 Dioxazoles, Oxathiazoles and Dithiazoles
- 4.35 Five-membered Rings containing One Selenium or Tellurium Atom and One
Other Group VI Atom and their Benzo Derivatives
- 4.36 Two Fused Five-membered Heterocyclic Rings: (i) Classical Systems
- 4.37 Two Fused Five-membered Heterocyclic Rings: (ii) Non-classical Systems
- 4.38 Two Fused Five-membered Heterocyclic Rings: (iii) 1,6,6aλ⁴-Trithiapentalenes
and Related Systems

Volume 7 (Part 5: Small and Large Rings)

- 5.01 Structure of Small and Large Rings
- 5.02 Reactivity of Small and Large Rings
- 5.03 Synthesis of Small and Large Rings
- 5.04 Aziridines, Azirines and Fused-ring Derivatives
- 5.05 Oxiranes and Oxirenes
- 5.06 Thiiranes and Thiirenes
- 5.07 Fused-ring Oxiranes, Oxirenes, Thiiranes and Thiirenes
- 5.08 Three-membered Rings with Two Heteroatoms and Fused-ring Derivatives
- 5.09 Azetidines, Azetines and Azetes
- 5.10 Cephalosporins
- 5.11 Penicillins
- 5.12 Other Fused-ring Azetidines, Azetines and Azetes
- 5.13 Oxetanes and Oxetenes
- 5.14 Thietanes, Thietes and Fused-ring Derivatives
- 5.15 Four-membered Rings with Two or More Heteroatoms and Fused-ring Derivatives
- 5.16 Azepines
- 5.17 Oxepanes, Oxepins, Thiepanes and Thiepins
- 5.18 Seven-membered Rings with Two or More Heteroatoms
- 5.19 Eight-membered Rings
- 5.20 Larger Rings except Crown Ethers and Heterophanes
- 5.21 Crown Ethers and Cryptands
- 5.22 Heterophanes

Volume 8 (Part 6: Indexes)**Subject Index****Author Index****Ring Index****Data Index**

JOURNAL CODES FOR REFERENCES

For explanation of the reference system, see p. 1071.

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	Ann. 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. [Weissberger-Taylor series]
B	Biochemistry	HCA	Helv. Chim. Acta
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.	HOU	Methoden Org. Chem. (Houben-Weyl)
BAU	Bull. Acad. Sci. USSR, Div. Chem. Sci.	IC	Inorg. Chem.
BBA	Biochim. Biophys. Acta	IJC	Indian J. Chem.
BBR	Biochem. Biophys. Res. Commun.	IJC(B)	Indian J. Chem., Sect. B
BCJ	Bull. Chem. Soc. Jpn.	IJS	Int. J. Sulfur Chem.
BEP	Belg. Pat.	IJS(B)	Int. J. Sulfur Chem., Part B
BJ	Biochem. J.	IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
BJP	Br. J. Pharmacol.	JA	J. Am. Chem. Soc.
BRP	Br. Pat.	JAP	Jpn. Pat.
BSB	Bull. Soc. Chim. Belg.	JAP(K)	Jpn. Kokai
BSF	Bull. Soc. Chim. Fr.	JBC	J. Biol. Chem.
BSF(2)	Bull. Soc. Chim. Fr., Part 2	JCP	J. Chem. Phys.
C	Chimia	JCR(S)	J. Chem. Res. (S)
CA	Chem. Abstr.	JCS	J. Chem. Soc.
CB	Chem. Ber.	JCS(C)	J. Chem. Soc. (C)
CC	J. Chem. Soc., Chem. Commun.	JCS(D)	J. Chem. Soc., Dalton Trans.
CCC	Collect. Czech. Chem. Commun.	JCS(F1)	J. Chem. Soc., Faraday Trans. 1
CCR	Coord. Chem. Rev.	JCS(P1)	J. Chem. Soc., Perkin Trans. 1
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)	JGU	J. Gen. Chem. USSR (Engl. Transl.)
CI(L)	Chem. Ind. (London)	JHC	J. Heterocycl. Chem.
CJC	Can. J. Chem.	JIC	J. Indian Chem. Soc.
CL	Chem. Lett.	JMC	J. Med. Chem.
CPB	Chem. Pharm. Bull.	JMR	J. Magn. Reson.
CR	C.R. Hebd. Seances Acad. Sci.	JOC	J. Org. Chem.
CR(C)	C.R. Hebd. Seances Acad. Sci., Ser. C	JOM	J. Organomet. Chem.
CRV	Chem. Rev.	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
		SAP	S. Afr. Pat.
		SC	Synth. Commun.
		SH	W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds', Wiley, New York, 1977, parts 1 and 2
N	Naturwissenschaften	SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
NEP	Neth. Pat.	T	Tetrahedron
NJC	Nouv. J. Chim.	TH	Thesis
NKK	Nippon Kagaku Kaishi	TL	Tetrahedron Lett.
NMR	T. J. Batterham, 'NMR Spectra of Simple Heterocycles', Wiley, New York, 1973	UKZ	Ukr. Khim. Zh. (Russ. Ed.)
OMR	Org. Magn. Reson.	UP	Unpublished Results
OMS	Org. Mass Spectrom.	USP	U.S. Pat.
OPP	Org. Prep. Proced. Int.	YZ	Yakugaku Zasshi
OR	Org. React.	ZC	Z. Chem.
OS	Org. Synth.	ZN	Z. Naturforsch.
OSC	Org. Synth., Coll. Vol.	ZN(B)	Z. Naturforsch., Teil B
P	Phytochemistry	ZOB	Zh. Obshch. Khim.
PAC	Pure Appl. Chem.	ZOR	Zh. Org. Khim.
PC	Personal Communication	ZPC	Hoppe-Seyler's Z. Physiol. Chem.
PH	'Photochemistry of Heterocyclic Compounds', ed. O. Buchardt, Wiley, New York, 1976		

Contents

Foreword	vii
Contributors to Volume 6	ix
Contents of All Volumes	xi
4.16 Isoxazoles and their Benzo Derivatives S. A. LANG, JR. and Y.-i LIN, <i>American Cyanamid Company, Pearl River</i>	1
4.17 Isothiazoles and their Benzo Derivatives D. L. PAIN, B. J. PEART and K. R. H. WOOLDRIDGE, <i>May & Baker Ltd., Dagenham</i>	131
4.18 Oxazoles and their Benzo Derivatives G. V. BOYD, <i>Chelsea College, University of London</i>	177
4.19 Thiazoles and their Benzo Derivatives J. METZGER, <i>Université d'Aix-Marseille</i>	235
4.20 Five-membered Selenium-Nitrogen Heterocycles I. LALEZARI, <i>Montefiore Medical Center and Albert Einstein College of Medicine, New York</i>	333
4.21 1,2,3- and 1,2,4-Oxadiazoles L. B. CLAPP, <i>Brown University, Providence</i>	365
4.22 1,2,5-Oxadiazoles and their Benzo Derivatives R. M. PATON, <i>University of Edinburgh</i>	393
4.23 1,3,4-Oxadiazoles J. HILL, <i>University of Salford</i>	427
4.24 1,2,3-Thiadiazoles and their Benzo Derivatives E. W. THOMAS, <i>The Upjohn Company, Kalamazoo</i>	447
4.25 1,2,4-Thiadiazoles J. E. FRANZ and O. P. DHINGRA, <i>Monsanto Agricultural Products Co., St Louis</i>	463
4.26 1,2,5-Thiadiazoles and their Benzo Derivatives L. M. WEINSTOCK and I. SHINKAI, <i>Merck Sharp & Dohme Research Laboratories, Rahway</i>	513
4.27 1,3,4-Thiadiazoles G. KORNIS, <i>The Upjohn Company, Kalamazoo</i>	545
4.28 Oxatriazoles and Thiatriazoles A. HOLM, <i>University of Copenhagen</i>	579

4.29	Five-membered Rings (One Oxygen or Sulfur and At Least One Nitrogen Atom) Fused with Six-membered Rings (At Least One Nitrogen Atom) K. UNDHEIM, <i>University of Oslo</i>	613
4.30	Dioxoles and Oxathioles A. J. ELLIOTT, <i>Schering-Plough Corporation, Bloomfield</i>	749
4.31	1,2-Dithioles D. M. MCKINNON, <i>University of Manitoba</i>	783
4.32	1,3-Dithioles H. GOTTHARDT, <i>Universität Wuppertal</i>	813
4.33	Five-membered Rings containing Three Oxygen or Sulfur Atoms G. W. FISCHER and T. ZIMMERMANN, <i>Academy of Sciences of the G.D.R., Leipzig</i>	851
4.34	Dioxazoles, Oxathiazoles and Dithiazoles M. P. SAMMES, <i>University of Hong Kong</i>	897
4.35	Five-membered Rings containing One Selenium or Tellurium Atom and One Other Group VI Atom and their Benzo Derivatives M. R. DETTY, <i>Eastman Kodak Company, Rochester</i>	947
4.36	Two Fused Five-membered Heterocyclic Rings: (i) Classical Systems K. H. PILGRAM, <i>Shell Development Co., Modesto</i>	973
4.37	Two Fused Five-membered Heterocyclic Rings: (ii) Non-classical Systems C. A. RAMSDEN, <i>May & Baker Ltd., Dagenham</i>	1027
4.38	Two Fused Five-membered Heterocyclic Rings: (iii) 1,6,6a λ^4 -Trithiapentalenes and Related Systems N. LOZAC'H, <i>Université de Caen</i>	1049
	References	1071

4.16

Isoxazoles and their Benzo Derivatives

S. A. LANG, JR. and Y.-i LIN

American Cyanamid Company, Pearl River

4.16.1 INTRODUCTION	2
4.16.2 STRUCTURE	3
4.16.2.1 Theoretical Methods	3
4.16.2.1.1 Molecular orbital calculations	3
4.16.2.2 Molecular Dimensions	4
4.16.2.2.1 X-ray diffraction	4
4.16.2.3 Molecular Spectra	4
4.16.2.3.1 UV spectroscopy	4
4.16.2.3.2 Photoelectron spectroscopy	5
4.16.2.3.3 IR and Raman spectroscopy	5
4.16.2.3.4 Nuclear magnetic resonance spectroscopy	5
4.16.2.3.5 Mass spectrometry	6
4.16.2.3.6 Electron paramagnetic resonance spectroscopy	7
4.16.2.3.7 Microwave spectroscopy	8
4.16.2.4 Thermodynamic Effects	8
4.16.2.4.1 Intermolecular forces	8
4.16.2.4.2 Stability	10
4.16.2.4.3 Conformation	10
4.16.2.4.4 Potentiometric properties	10
4.16.2.5 Tautomerism	11
4.16.3 REACTIVITY OF ISOXAZOLES	12
4.16.3.1 Reactions at Aromatic Rings	12
4.16.3.1.1 General survey of reactivity	12
4.16.3.1.2 Thermal and photochemical reactions	12
4.16.3.1.3 Electrophilic attack at nitrogen	20
4.16.3.1.4 Electrophilic attack at carbon	21
4.16.3.1.5 Nucleophilic attack at carbon	28
4.16.3.1.6 Nucleophilic attack at hydrogen	29
4.16.3.1.7 Reactions with cyclic transition states	35
4.16.3.2 Reactions of Non-aromatic Compounds	36
4.16.3.2.1 2-Isoxazolines	36
4.16.3.2.2 3-Isoxazolines	44
4.16.3.2.3 4-Isoxazolines	44
4.16.3.2.4 Isoxazolidines	45
4.16.3.3 Reaction of Substituents	48
4.16.3.3.1 Fused benzene rings	48
4.16.3.3.2 Other C-linked substituents	48
4.16.3.3.3 N-Linked substituents	54
4.16.3.3.4 O-Linked substituents	56
4.16.3.3.5 S-Linked substituents	57
4.16.3.3.6 Halogen atoms	58
4.16.3.3.7 Metal- and metalloid-linked substituents	58
4.16.3.3.8 Substituents attached to ring nitrogen atoms	59
4.16.3.3.9 Special reactions of side-chain substituents: rearrangements involving three-atom side chains	60
4.16.4 SYNTHESIS	61
4.16.4.1 Isoxazoles	61
4.16.4.1.1 Introduction	61
4.16.4.1.2 [3+2] Routes	61
4.16.4.1.3 [4+1] Routes	71
4.16.4.1.4 [5+0] Routes	73
4.16.4.1.5 [3+1+1] Routes	76

4.16.4.1.6	Dehydrogenation of isoxazolines to isoxazoles	78
4.16.4.1.7	Ring transformations leading to isoxazoles	78
4.16.4.2	Isoxazole Derivatives	82
4.16.4.2.1	Isoxazole	82
4.16.4.2.2	Alkylisoxazoles	83
4.16.4.2.3	Phenylisoxazoles	83
4.16.4.2.4	Alkylaryl isoxazoles	84
4.16.4.2.5	Isoxazole aldehydes	84
4.16.4.2.6	Isoxazole ketones	84
4.16.4.2.7	Isoxazolecarboxylic acids	85
4.16.4.2.8	Halogen derivatives	86
4.16.4.2.9	N-Linked derivatives	86
4.16.4.2.10	O-Linked derivatives	87
4.16.4.2.11	S-Linked derivatives	88
4.16.4.3	2-Isoxazolines	88
4.16.4.3.1	By cycloaddition of nitrile oxides	89
4.16.4.3.2	From α,β -unsaturated ketones and hydroxylamine	93
4.16.4.3.3	From ylides and nitrile oxides	94
4.16.4.3.4	By the activation of alkyl nitro compounds	95
4.16.4.3.5	From β -halo (tosyl) ketone oximes	96
4.16.4.3.6	From 2-isoxazoline N-oxides	97
4.16.4.3.7	Miscellaneous methods	97
4.16.4.4	3-Isoxazolines	98
4.16.4.5	4-Isoxazolines	99
4.16.4.6	Isoxazolinols	100
4.16.4.7	Isoxazoline N-oxides	102
4.16.4.8	Isoxazolin-5-ones	103
4.16.4.8.1	From hydroxylamine	104
4.16.4.8.2	By the reaction of nitrile oxides	104
4.16.4.8.3	Miscellaneous syntheses	104
4.16.4.9	Isoxazolin-5-imines	105
4.16.4.10	Isoxazoline-5-thiones	105
4.16.4.11	Isoxazolin-3-ones	106
4.16.4.12	Isoxazolin-4-ones	106
4.16.4.13	Bis(isoxazolines)	107
4.16.4.14	Spiro Fused Isoxazolines	107
4.16.4.15	Bis(spiroisoxazolines)	108
4.16.4.16	Other Spiroisoxazolines	108
4.16.4.17	Isoxazolidines	108
4.16.4.17.1	By cycloaddition of nitrones and alkenes	108
4.16.4.17.2	Cycloaddition of nitronic esters	110
4.16.4.17.3	By the reaction of tetranitromethane and halotritnitromethanes with alkenes	111
4.16.4.17.4	Other methods	111
4.16.4.18	Isoxazolidinones	112
4.16.4.18.1	3-Isoxazolidinones	112
4.16.4.18.2	4-Isoxazolidinones	113
4.16.4.18.3	5-Isoxazolidinones	113
4.16.4.18.4	Isoxazolidine-3,5-diones	113
4.16.4.19	Benzisoxazoles	114
4.16.4.19.1	1,2-Benzisoxazoles	114
4.16.4.19.2	2,1-Benzisoxazoles	120
4.16.5	APPLICATIONS	127
4.16.5.1	Pharmaceutical Applications	127
4.16.5.2	Agricultural Applications	129
4.16.5.3	Other Applications	130

4.16.1 INTRODUCTION

Isoxazole (1), 2-isoxazoline (2), isoxazolidine (3), 1,2-benzisoxazole (4) (sometimes termed indoxazene) and 2,1-benzisoxazole (5) (often referred to as anthranil) are numbered as shown. The chemistry of isoxazoles (79AHC(25)147, 63AHC(2)365, 62HC(17)1), isoxazolines (62HC(17)1, p. 95), isoxazolidines (77AHC(21)207, 62HC(17)1, p. 229) and benzisoxazoles

