

STEREOCHEMISTRY OF HETEROCYCLIC COMPOUNDS

Part II Oxygen; Sulfur; Mixed N, O, and S;
and Phosphorus Heterocycles

W. L. F. ARMAREGO

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W. L. F. ARMAREGO

*The Australian National University
Canberra, Australia*

With a chapter on phosphorus heterocycles by
M. J. GALLAGHER

*The University of New South Wales
Sydney, Australia*

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STEREOCHEMISTRY OF HETEROCYCLIC COMPOUNDS

GENERAL HETEROCYCLIC CHEMISTRY SERIES

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INTRODUCTION TO THE SERIES

General Heterocyclic Chemistry

The series, "The Chemistry of Heterocyclic Compounds," published since 1950 by Wiley-Interscience, is organized according to classes of compounds. Each volume deals with syntheses, reactions, properties, structure, physical chemistry, etc., of compounds belonging to a specific class, such as pyridines, thiophenes, and pyrimidines, three-membered ring systems. This series has become the basic reference collection for information on heterocyclic compounds.

Many aspects of heterocyclic chemistry have been established as disciplines of *general* significance and application. Furthermore, many reactions, transformations, and uses of heterocyclic compounds have specific significance. We plan, therefore, to publish monographs that will treat such topics as nuclear magnetic resonance of heterocyclic compounds, mass spectra of heterocyclic compounds, photochemistry of heterocyclic compounds, X-Ray structure determination of heterocyclic compounds, UV and IR spectroscopy of heterocyclic compounds, and the utility of heterocyclic compounds in organic synthesis. These treatises should be of interest to *all* organic chemists as well as to those whose particular concern is heterocyclic chemistry. The new series, organized as described above, will survey under each title *the whole field of heterocyclic chemistry* and is entitled "General Heterocyclic Chemistry." The editors express their profound gratitude to Dr. D. J. Brown of Canberra for his invaluable help in establishing the new series.

Department of Chemistry
Princeton University
Princeton, New Jersey

Research Laboratories
Eastman Kodak Company
Rochester, New York

Edward C. Taylor

Arnold Weissberger

PREFACE

In 1974, the periodical *Tetrahedron* commemorated the centenary of van't Hoff and Le Bel's proposal of the tetrahedral carbon atom by devoting 500 pages to articles on stereochemistry. Over the years many aspects of the stereochemistry of organic compounds have been reviewed, but the stereochemistry of heterocyclic compounds has never been considered separately and described in its entirety. It is therefore timely that the stereochemistry of heterocyclic compounds should be collected in a systematic form in two volumes.

The availability of nuclear magnetic resonance spectrometers in the early sixties is mainly responsible for the explosion in the number of publications containing stereochemical data on heterocycles. Not only has nuclear magnetic resonance been useful in deducing relative configurations at chiral centers and conformational preferences with a high degree of certainty, but it has also provided thermodynamic and kinetic data for a variety of equilibria from which stereochemical data have been evaluated. For this reason a large proportion of the literature surveyed in these volumes is post-1960. The literature has been covered until the end of 1974 and incompletely for 1975. More than 4500 references on the stereochemistry of nitrogen, oxygen, sulfur, and phosphorus heterocycles are included in the two volumes, and to keep the books to a reasonable size it was necessary to limit the discussions for many references. Only a few leading references to the stereochemistry of natural products are given to identify them with the ring systems under discussion. These monographs take the form of "guides" into the literature and at the same time give a panoramic view of the stereochemistry of nitrogen heterocycles (in Part I) and oxygen; sulfur; mixed N, O, and S; and phosphorus heterocyclic compounds (in Part II).

No words can express my gratitude to Dr. D. J. Brown for his continued and inspiring guidance, and for his provision of every facility possible during the months of writing. The manuscript would have taken much

longer to produce but for the efficient and accurate work of my research assistant, Mrs. Beverly A. Milloy, B. Sc, who carried out the painstaking job of checking the references and the typescript, and whose artistic talent has turned all the formulas into proper drawings that show the three-dimensional structures. My wife assisted immensely in reading and proofreading the whole manuscript. Finally, I am thankful to Mrs. A. Sirt for carrying out the arduous task of typing the manuscript.

W. I. F. ARMABECCO

Canberra, Australia

The Australian National University, Canberra

June 1976

CONTENTS

Chapter 1 Introduction

I. General Stereochemical Properties of Heterocyclic Compounds	1
II. Organization of Stereochemical Data	4
III. Nomenclature	5
IV. Energy Terms and Optical Activity	6
V. References to Other Works	7
VI. References	8

Chapter 2 Oxygen Heterocycles

I. Introduction	12
II. Oxiranes (Ethylene Oxides)	13
A. Syntheses of Oxiranes	13
1. By Oxidation of Olefins	13
2. By 1,3-Elimination Reactions	17
3. From Carbonyl Compounds	17
B. Configuration and Conformation of Oxiranes	20
C. Reactions of Oxiranes	23
1. C-O Bond Cleavage Reactions	23
2. C-C Bond Cleavage Reactions	29
3. Rearrangements	30
4. Miscellaneous	32
III. Di- and Trioxiranes (Bis- and Trisethylene Oxides)	33
IV. Oxetanes (Trimethylene Oxides)	36
A. Syntheses	37
B. Configuration and Conformation of Oxetanes	40
C. Reactions of Oxetanes	41
V. 1,2-Dioxetanes (Ethylene Peroxides)	42

VI.	Reduced Furans	43
A.	Syntheses of Reduced Furans	44
1.	Reduction of Furans	44
2.	By Addition and Cycloaddition Reactions	45
3.	By Intramolecular Cyclization	49
4.	By rearrangement	51
5.	Miscellaneous	52
B.	Configuration and Conformation of Reduced Furans	53
C.	Reactions of Reduced Furans	56
VII.	Condensed Furans	57
A.	2,3-Dihydrobenzofurans	57
B.	Oxabicyclo[3.3.0]octanes	60
C.	Oxabicyclo[4.3.0]nonanes	62
D.	Miscellaneous	66
VIII.	1,3-Dioxalanes	68
A.	Syntheses of 1,3-Dioxalanes	68
B.	Configuration and Conformation of 1,3-Dioxalanes	71
C.	Reactions of 1,3-Dioxalanes	73
IX.	Trioxalanes	76
X.	Reduced Pyrans	78
A.	Syntheses of Reduced Pyrans	79
B.	Configuration of Reduced Pyrans	83
C.	Conformation of Reduced Pyrans (Including the Anomeric Effect)	84
D.	Reactions of Reduced Pyrans	88
XI.	Condensed Pyrans	90
A.	Benzopyrans and Isobenzopyrans	90
1.	Benzopyrans and Isobenzopyrans Reduced in the Oxygen Ring (Chromans and Isochromans)	90
2.	Benzopyrans and Isobenzopyrans Reduced at the Bridgehead Carbon Atoms (Oxabicyclo[4.4.0]decanes)	94
B.	Miscellaneous Oxabicycloalkanes	95
C.	Reduced Xanthenes	97
D.	Oxatwistanes, Oxaadamantanes, and Related Compounds	98
XII.	Dioxanes	100
A.	1,2-Dioxanes	100
B.	1,3-Dioxanes	100
1.	Syntheses of 1,3-Dioxanes	101
2.	Configuration and Conformation of 1,3-Dioxanes	101

3. Reactions of 1,3-Dioxanes	107
4. Condensed 1,3-Dioxanes	109
C. 1,4-Dioxanes	113
1. Syntheses of 1,4-Dioxanes	114
2. Configuration and Conformation of 1,4-Dioxanes	116
3. Reactions of 1,4-Dioxanes	118
4. Condensed 1,4-Dioxanes	119
XIII. 1,3,5-Trioxanes and 1,2,4,5-Tetraoxanes	122
XIV. Miscellaneous Oxygen Compounds	123
A. Oxepins and Related Compounds	123
B. Transannular Reactions Involving the Ring Oxygen Atom	126
C. Oxygen Containing Ansa Compounds	131
D. Oxygen Heterocycles with Eight-Membered and Larger Rings—Crown Ethers	135
E. Miscellaneous	139
XV. References	141

Chapter 3 Sulfur Heterocycles

I. Introduction	172
II. Thiiranes (Ethylene Sulfides, Episulfides, or Thiacyclopropanes)	172
A. Syntheses of Thiiranes	173
B. Configuration of Thiiranes	176
C. Reactions of Thiiranes	177
III. Thietanes (Propylene Sulfides)	179
A. Syntheses of Thietanes	180
B. Configuration and Conformation of Thietanes	183
C. Reactions of Thietanes	185
IV. Thiolanes and Thiolenes	186
A. Syntheses of Thiolanes and Thiolenes	186
B. Configuration and Conformation of Thiolanes and Thiolenes	190
C. Reactions of Thiolanes and Thiolenes	192
V. Condensed Thiolanes and Thiolenes	194
VI. Dithiolanes	198
A. 1,2-Dithiolanes	198
B. 1,3-Dithiolanes	200
VII. Trithiolanes	201

VIII	Thianes	202
	A. Syntheses of Thianes	203
	B. Configuration and Conformation of Thianes	203
	C. Reactions of Thianes	206
	D. Condensed Thianes	208
IX.	Dithianes	210
	A. 1,2-Dithianes	210
	B. 1,3-Dithianes	214
	C. 1,4-Dithianes	217
X.	Trithianes	219
XI.	1,2,4,5-Tetra- and Pentathianes	221
XII.	Seven- and Larger-Membered Sulfur-Containing Rings	221
	A. Seven-Membered Rings	221
	B. Eight- and Larger-Membered Rings	225
	C. Transannular Interactions Involving the Sulfur Atom	227
	D. Sulfur-Containing Cyclophanes	230
XIII.	Thiabicyclo[x,y,z]alkanes	234
XIV.	Miscellaneous	242
	A. Thioxanthenes and Thianthrenes	242
	B. Chiral Thienyls	244
	C. Chiral Sulfur Compounds Derived from 2,2'-Disubstituted Biphenyls	246
	D. Heterohelicenes Derived from Thiophenes	250
	E. Thiapropellanes	251
XV.	References	251

Chapter 4 Mixed Nitrogen, Oxygen and Sulfur Heterocycles

I.	Introduction	269
II.	Nitrogen and Oxygen Heterocycles	269
	A. Three-Membered Rings	269
	B. Four-Membered Rings	270
	C. Five-Membered Rings	271
	1. Isoxazolines and Isoxazolidines	271
	2. Oxazolines and Oxazolidines	276
	D. Six-Membered Rings	284
	1. Reduced 1,2-Oxazines	284
	2. Reduced 1,3-Oxazines	287
	3. Reduced 1,4-Oxazines (Including Morpholines)	291
	4. Miscellaneous	294
	E. Two or More Rings Containing N and O Heteroatoms in Each Ring	295

F. Seven- and Larger-Membered Rings.	299
III. Nitrogen and Sulfur Heterocycles	301
A. Four-Membered Rings	301
B. Five-Membered Rings	302
1. Isothiazolidines	302
2. Thiazolines and Thiazolidines	302
C. Six-Membered Rings	307
1. Reduced 1,2-Thiazines	307
2. Reduced 1,3-Thiazines	308
3. 1,4-Thiazanes (Including Phenothiazines)	309
D. Miscellaneous	312
IV. Sulfur and Oxygen Heterocycles	314
A. Four-Membered Rings	314
B. Five-Membered Rings	314
1. 1,2-Oxathiolanes	314
2. 1,3-Oxathiolanes	315
3. 1,3,2-Dioxathiolanes	317
C. Six-Membered Rings	319
1. 1,2-Oxathianes	319
2. 1,3-Oxathianes	320
3. 1,4-Oxathianes	321
4. 1,3,2-Dioxathianes	322
D. Miscellaneous	324
V. Nitrogen, Oxygen, and Sulfur Heterocycles	325
VI. References	326

Chapter 5 Phosphorus Heterocycles (Including some Arsenic and Antimony Heterocycles) by M. J. Gallagher

I. Introduction	340
II. Nomenclature	342
III. Spectroscopy	343
A. Introduction	343
B. Chemical Shift Data	344
1. ^{31}P Chemical Shifts	344
2. ^{13}C Chemical Shifts	345
3. Other Nuclei	346
C. Coupling Constant Data	346
1. $^1J_{\text{PX}}$	346
2. Angular Dependence of $^2J_{\text{PX}}$ and $^3J_{\text{PX}}$	347
3. $^2J_{\text{PX}}$	347
4. $^3J_{\text{PXCu}}$	348

	D. Shift Reagents	349
	E. Conclusion	350
IV.	Tables of Spectroscopic and Structural Data	351
	A. Bond Angles (Table I)	351
	B. Bond Lengths (Table II)	351
	C. Five-Membered Rings (Table III)	352
	D. Six-Membered Rings (Table IV)	354
V.	P (II) Compounds	357
VI.	P (III) Compounds	357
	A. Introduction	357
	B. P (III) Three-Membered Ring Compounds (Phosphiranes)	361
	C. P (III) Four-Membered Ring Compounds (Phosphetanes)	362
	D. P (III) Five-Membered Ring Compounds (Phospholanes)	363
	1. Reaction Stereochemistry of P (III) Five-Membered Ring Compounds	367
	E. P (III) Six-Membered Ring Compounds (Phosphorinanes)	369
	1. Reaction Stereochemistry of P (III) Six-Membered Ring Compounds	373
	2. Bicyclic Structures with a Bridgehead Heteroatom	376
	F. P (III) Seven-Membered Ring and Larger Ring Compounds	378
VII.	P (IV) Compounds	380
	A. Introduction	380
	B. P (IV) Four-Membered Ring Compounds (Phosphetanes)	382
	1. Reaction Stereochemistry of P (IV) Four-Membered Ring Compounds	384
	C. P (IV) Five-Membered Ring Compounds (Phospholanes)	386
	1. Reaction Stereochemistry of P (IV) Five-Membered Ring Compounds	391
	D. P (IV) Six-Membered Ring Compounds (Phosphorinanes)	392
	1. Reaction Stereochemistry of P (IV) Six-Membered Ring Compounds	396
	E. P (IV) Seven-Membered Ring and Larger Ring Compounds	397
VIII.	P (V) Compounds	399
	A. Introduction	399
	B. Permutational Isomerization Processes (π -Processes)	399
	1. Nomenclature of Permutational Isomerization Processes	405

2. Factors Influencing Positional Isomerism in Phosphoranes	405
3. Energy Barriers in π -Processes	409
C. Stereoisomerism and Optical Activity	411
1. Absolute Configuration	415
D. Diastereoisomerism	415
E. Reaction Stereochemistry of P (V) Compounds	416
1. P (V) Intermediates and Transition States	418
2. Sterically Controlled Reactions	426
F. As (V) Compounds	428
IX. P (VI) Compounds	429
X. References	431
Index	446

1 INTRODUCTION

I. General Stereochemical Properties of Heterocyclic Compounds	1
II. Organization of Stereochemical Data	4
III. Nomenclature	5
IV. Energy Terms and Optical Activity	6
V. References to Other Works	7
VI. References	8

One generally associates heterocyclic compounds with planar molecules because heterocycles are not usually regarded in three-dimensional terms. A glance at the reviews in the well established series *Advances in Heterocyclic Chemistry*¹ will confirm this statement. There are, however, a large number and variety of heterocyclic compounds that possess stereochemical properties. Many (but not all) of these heterocycles belong to the known classes of heterocyclic compounds, and in a large number of cases are related to or derived from them by reduction. It is the purpose of this monograph to describe systematically the stereochemical aspects of oxygen; sulfur; mixed N, O, and S; and phosphorus heterocycles (the nitrogen heterocycles are in Part I).

I. GENERAL STEREOCHEMICAL PROPERTIES OF HETEROCYCLIC COMPOUNDS

The stereochemical properties of heterocyclic compounds arise in a variety of ways. The first to be considered is the transition state in the electrophilic and nucleophilic substitution reactions of "aromatic" heterocycles. Here the stereochemistry of the approach of the reagent and the departure of the substituent involved, together with the nonplanar structure of the transition state, have to be accounted for in a full understanding of the processes. Cycloaddition reactions must also be considered in the above terms.

Reduced heterocyclic compounds possess many of the stereochemical features of their carbocyclic analogues. The presence of substituents on

2 Introduction

the carbon atoms in the ring can introduce chiral centers and display cis and trans isomerism. In addition to these properties, the heteroatom also alters the geometry of the ring with respect to the carbocyclic analogue by changing the bond distances and bond angles adjacent to the heteroatom. The alterations may be small or large depending on the heteroatom, the number of heteroatoms, and the relative positions of the heteroatoms in the ring. These changes are not relatively large when one heteroatom is involved, and the general structure of the reduced heterocycle can be extrapolated from the known structure of the analogous carbocycle. The differences are, however, subtle and show up in the nonbonded interactions and consequently in the conformational properties of the molecules.

The heteroatom in reduced heterocycles introduces properties which are characteristic of the heteroatom itself. Pyramidal atomic inversion² is a property which distinguishes nitrogen, oxygen, sulfur, and phosphorus atoms from tetravalent carbon. Trivalent nitrogen in a conformationally flexible ring, for example, inserts another conformational property to the ring. The hydrogen atom or substituent on the nitrogen atom in a ring can attain two equilibrating conformations by virtue of the inverting nitrogen atom. This points out the conformational property of the nitrogen lone pair of electrons, and considerable attention has been devoted in several laboratories to the "size" (space demand) of the nitrogen lone pair. The rate of atomic inversion is affected by the size of the ring in which the nitrogen atom is inserted and by the substituents. An oxygen atom directly attached to the ring nitrogen atom can decrease its inversion rate to the extent that the nitrogen atom is almost "locked" in a chiral configuration, and it introduces a source of optical activity. The inversion rate, and the effect of substituents on it, varies from one heteroatom to another. The oxygen heteroatom also undergoes inversion, but it is not as interesting as the nitrogen atom because it is divalent. Inversion of the oxygen atom does not alter the situation because it has two lone pairs of electrons which exchange place during the inversion without effecting a serious alteration. Oxonium ions derived from saturated oxygen heterocycles, on the other hand, will exhibit pyramidal inversion, but these present experimental difficulties because of their chemical reactivity. The properties of some oxonium ions, however, have been reported. The oxygen atom in reduced heterocycles produces strong dipolar effects with respect to polar substituents particularly on the adjacent carbon atoms. It tends to force the substituents into an axial conformation (anomeric effect) which affects the conformational properties of the molecule as a whole. Sulfur heterocycles are similar to oxygen heterocycles, but in addition the sulfur atom can expand its valency shell. Oxidation of the sulfur atom yields sulfoxides