

STEREOCHEMISTRY OF HETEROCYCLIC COMPOUNDS

Part I Nitrogen Heterocycles
W. L. I. ARMAREGO

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W. L. F. ARMAREGO

*The Australian National University
Canberra, Australia*

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HETEROCYCLIC
COMPOUNDS

Part I: Nitrogen Heterocycles

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Edward C. Taylor and Arnold Weissberger, Editors

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heterocycles

GENERAL HETEROCYCLIC CHEMISTRY SERIES

Edward C. Taylor and Arnold Weissberger, Editors

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by W. L. F. Armarego

Part I, Nitrogen Heterocycles

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

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.

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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 proof-reading the whole manuscript. Finally, I am thankful to Mrs. A. Sirt for carrying out the arduous task of typing the manuscript.

W. L. F. ARMAREGO

Canberra, Australia
June 1976

In 1974, the International Union of Pure and Applied Chemistry (IUPAC) published a report on the nomenclature of stereochemistry. This report was the result of a long and arduous task carried out by a committee of experts in the field of stereochemistry. The report was published in the *Journal of Chemical Education* and is available to all chemists. The report is a valuable contribution to the field of stereochemistry and is a must for all chemists who are interested in the subject. The report is a long and detailed document, but it is well worth the effort to read it. It contains a wealth of information on the nomenclature of stereochemistry, including the rules for the assignment of R and S configurations, the rules for the assignment of E and Z configurations, and the rules for the assignment of M and P configurations. The report also contains a wealth of information on the nomenclature of chiral centers, including the rules for the assignment of R and S configurations, the rules for the assignment of E and Z configurations, and the rules for the assignment of M and P configurations. The report is a valuable contribution to the field of stereochemistry and is a must for all chemists who are interested in the subject.

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. Nitrogen Heterocycles: Three-, Four-, and Five-Membered Rings

I. Three-Membered Rings	12
A. Aziridines	12
1. Synthesis of Aziridines	13
a. Wenker and Related Syntheses	13
b. By Intermolecular Addition of a Nitrogen or Carbon unit	16
c. Hoch-Campbell and Related Syntheses	18
d. From Δ^2 -1,2,3-Triazolines	20
e. By Intramolecular Rearrangement	21
f. From Azirines	23
2. Configuration of Aziridines	23
3. Conformation of Aziridines	27
4. Reactions of Aziridines	31
a. Nitrogen Extrusion Reactions	31
b. C-N Bond Cleavage Reactions	33
c. C-C Bond Cleavage Reactions	35
d. Substitution and Solvolytic Reactions	38
e. Reactions with Asymmetric Induction at 2- α -Carbonyl Groups	40

f.	<i>N</i> -Alkylation Reactions	41
g.	Intramolecular Condensations Involving a 2- α -Carbonyl Group and the Ring <i>N</i> -Atom	42
h.	Ring Expansion Reactions	43
B.	Diaziridines	45
II.	Four-Membered Rings	46
A.	Azetidines and Azetidin-2-ones	46
1.	Syntheses of Azetidines and Azetidin-2-ones	47
2.	Configuration and Conformation of Azetidines and Azetidin-2-ones	54
3.	Reactions of Azetidines and Azetidin-2-ones	56
B.	Diazetidines	61
III.	Five-Membered Rings	62
A.	Introduction	62
B.	Pyrrolidines	62
1.	Synthesis of Pyrrolidines	63
a.	By Intramolecular Cyclization	63
b.	By Cycloaddition	66
c.	By Reduction	67
d.	By Skeletal Rearrangement	68
e.	From Aldimines and Succinic Anhydrides	69
f.	Miscellaneous	69
2.	Configuration of Pyrrolidines	70
3.	Conformation of Pyrrolidines	73
4.	Reactions of Pyrrolidines	74
a.	Interconversion of Substituents	74
b.	Intramolecular Cyclization	74
c.	Alkylation	75
d.	Miscellaneous	75
C.	Spiropyrrolidines	76
D.	Chiral Pyrroles	78
E.	Fused Pyrrolidines	80
1.	2- and 3-Azabicyclo[3.1.0]hexanes	80
2.	2- and 3-Azabicyclo[3.2.0]heptanes	82
3.	2- and 3-Azabicyclo[3.3.0]octanes	83
4.	7-Azabicyclo[4.3.0]nonanes (Perhydroindoles)	85
5.	8-Azabicyclo[4.3.0]nonanes (Perhydroisoindoles)	89
F.	Indoles, Indolines, and Isoindolines	93
G.	Carbazoles and Reduced Carbazoles	100
H.	Diazolines	103
1.	Pyrazolines and Pyrazolidines	103
a.	1-Pyrazolines	104

b. 2-Pyrazolines	109
c. Pyrazolidines	112
2. Imidazolines and Imidazolidines	113
I. Triazolines	117
IV. References	119
Chapter 3. Nitrogen Heterocycles: Six-Membered Rings	141
I. Introduction	143
II. Piperidines	143
A. Syntheses of Piperidines	143
1. Catalytic and Chemical Reduction of Pyridines	144
2. From Dehydropiperidines	145
3. From Piperidones	147
4. By Ring Closure	149
5. Miscellaneous	151
B. Configurations of Piperidines	153
C. Conformation of Piperidines	157
D. Reactions of Piperidines	163
1. Nitrogen Extrusion Reactions	163
2. Reduction and Addition Reactions of 4-Piperidones	164
3. Epimerization of Piperidines and 4-Piperidones	164
4. Rearrangements of Piperidines	165
5. Quaternization of Piperidines	166
6. Fragmentation of 4-Chloropiperidines	168
7. Miscellaneous	169
III. Reduced Pyridazines	170
A. Syntheses of Reduced Pyridazines	170
B. Configuration and Conformation of Reduced Pyridazines	172
C. Reactions of Reduced Pyridazines	175
IV. Reduced Pyrimidines	177
A. Syntheses of Reduced Pyrimidines	178
B. Configuration of Reduced Pyrimidines	180
C. Conformation of 1,3-Diazines (Hexahydropyrimidines)	180
D. Reactions of Reduced Pyrimidines	183
V. Reduced Pyrazines	184
A. Syntheses of Reduced Pyrazines	184
B. Configuration of Reduced Pyrazines	187
C. Conformation of Piperazines	189
D. Reactions of Reduced Pyrazines	191
VI. 1,3,5-Triazanes	193

VII.	1,2,4,5-Tetraazanes	196
VIII.	Reduced Fused Five:Six-Membered Rings	198
	A. Perhydro-1-pyridines	198
	B. Perhydro-2-pyridines	199
	C. Reduced Purines	201
IX.	Reduced Quinolines	203
	A. 1,2,3,4-Tetrahydroquinolines (Including a Few Dihydroquinolines)	203
	1. Syntheses of 1,2,3,4-Tetrahydroquinolines	203
	2. Configuration and Conformation of 1,2,3,4-Tetrahydroquinolines	205
	3. Reactions of Di- and Tetrahydroquinolines	208
	B. Decahydroquinolines	209
	1. Syntheses of Decahydroquinolines	209
	a. By Catalytic Reduction of Quinolines or Partially Reduced Quinolines	209
	b. By Cyclization Reactions	211
	c. By Beckmann and Schmidt Rearrangements and Annulations	212
	2. Configuration of Decahydroquinolines	213
	3. Conformation of Decahydroquinolines	214
	4. Reactions of Decahydroquinolines	217
	a. Dehydrogenation and Quaternization	217
	b. Reactions of 4-Oxodecahydroquinolines	217
	c. Fragmentation of Decahydroquinolines	219
X.	Reduced Isoquinolines	220
	A. 1,2,3,4-Tetrahydroisoquinolines (Including a Few Dihydroisoquinolines)	221
	1. Syntheses of 1,2,3,4-Tetrahydroisoquinolines	221
	2. Configuration and Conformation of 1,2,3,4-Tetrahydroisoquinolines	224
	3. Reactions of 1,2,3,4-Tetrahydroisoquinolines	225
	B. Decahydroisoquinolines	227
	1. Syntheses of Decahydroisoquinolines	227
	a. By Catalytic Reduction of Isoquinolines and Partially Reduced Isoquinolines	227
	b. By Cyclization of 1,2-Disubstituted Cyclohexanes	228
	c. By Cyclization of 1-Aminoethylcyclohex-1-enes	229
	d. Miscellaneous	230
	2. Configuration and Conformation of Decahydroisoquinolines	232

3. Reactions of Decahydroisoquinolines	233
C. Azatwistanes	235
XI. Reduced Fused Six:Six-Membered Rings with More Than One Nitrogen Atom	238
A. Reduced Naphthyridines	238
B. Reduced Cinnolines	239
C. Reduced Phthalazines	241
D. Reduced Quinazolines	242
E. Reduced Quinoxalines	246
F. Reduced Tetraazanaphthalenes	250
1. Reduced Pteridines	250
2. Reduced 1,4,5,8-Tetraazanaphthalenes	252
XII. Reduced Six-Membered Rings Containing Nitrogen Atoms and Two Other Fused Rings	252
A. Reduced Acridines	252
B. Reduced Phenanthridines	255
C. Reduced Benzoquinolines and Benzoisoquinolines	256
D. Reduced Phenazines	257
E. Miscellaneous	258
XIII. Photochemical Reactions	260
A. Pyridines	260
B. Pyridazines	262
C. Pyrimidines	263
D. Quinolines	266
E. Isoquinolines	267
XIV. Aromatic Compounds	268
A. Pyridines	268
B. Quinazolines	270
C. Diheterocycles with Restricted Rotation and Molecular Overcrowding	271
D. Miscellaneous	275
XV. References	276

Chapter 4. Nitrogen Heterocycles: Seven- and Larger-Membered Rings, 1-Azabicyclo[*x.y.0*]alkanes, *n*-Azabicyclo[*x.y.z.*]alkanes and Miscellaneous Cyclic Aza Compounds 303

I. Introduction	304
II. Seven-Membered Rings	305
A. Azepines	305
B. Diazepines	309
III. Eight-Membered Rings	311

A. Azocines	311
B. 1,2-Diazocines	312
C. 1,4- and 1,5-Diazocines and 1,3,5,7-Tetraazocines	313
IV. Nine-Membered Rings: Azonines	315
V. Miscellaneous Medium- and Large-Sized Rings	316
A. Medium-Sized Rings	316
1. Transannular N,C _{co} Interaction	316
2. Azacyclophanes	319
B. Large Rings	323
VI. 1-Azabicyclo[x.y.0]alkanes	327
A. 1-Azabicyclo[3.3.0]octanes: Pyrrolizidines	327
B. 1-Azabicyclo[4.3.0]nonanes: Indolizidines	331
C. 1-Azabicyclo[4.4.0]decanes: Quinolizidines	334
D. Miscellaneous 1-Azabicyclo[x.y.0]alkanes	341
VII. n-Azabicyclo[x.y.z]alkanes	344
A. Azabicyclo[2.2.1]heptanes	344
B. Azabicyclo[2.2.2]octanes	347
1. 1-Azabicyclo[2.2.2]octanes: Quinuclidines	347
2. 2-Azabicyclo[2.2.2]octanes: Isoquinuclidines	349
C. Azabicyclo[3.2.1]octanes	351
1. 1-Azabicyclo[3.2.1]octanes	351
2. 2-, 3-, and 6-Azabicyclo[3.2.1]octanes	352
3. 8-Azabicyclo[3.2.1]octanes: Tropenes	353
D. Azabicyclo[3.3.1]nonanes	357
1. 3-Azabicyclo[3.3.1]nonanes	357
2. 9-Azabicyclo[3.3.1]nonanes	360
3. Miscellaneous Diazabicyclo[3.3.1]nonanes	362
4. Azaadamantanes	362
E. Miscellaneous Azabicyclononanes, -decanes, and -undecanes	364
VIII. Tröger Base and Related Compounds	366
IX. Propellanes	367
X. Azabullvalenes and Related Compounds	368
XI. References	369
Index	387

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 nitrogen heterocycles (the oxygen; sulfur; mixed N, O, and S; and phosphorus heterocycles are in Part II).

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

which have very high barriers to atomic inversion and are therefore possible centers of asymmetry in the molecule. Sulfur forms stable S-S bonds, and these adjacent sulfur atoms in a heterocyclic ring are a source of chirality in their own right by virtue of the helical nature of the C-S-S-C bonding arrangement. The energies involved in altering the torsion angles in this bonding arrangement are greater than in the corresponding carbocyclic systems and therefore have a large effect on the conformational properties of these sulfur containing molecules. Unlike the above heterocycles, many phosphorus heterocycles are known in which the valency state of the phosphorus atom is II, III, IV, V or VI. The phosphorus atom has a particular stereochemistry in each valency state. The heteroatom in phosphorus(III) heterocycles is similar to a nitrogen atom in its pyramidal atomic inversion but is generally much slower. The most interesting examples are found among the P(V) compounds. The trigonal bipyramidal P(V) compounds undergo permutational isomerism (not observed in the other heteroatoms) in which the energy required for substituents to exchange places, for example, in inversion of configuration, without breaking and making bonds may be quite low, and the process may occur very readily. Not only have many of these P(V) structures been postulated as intermediates or transition states in reactions, but a host of them have been isolated and characterized.

Several dissymmetric heterocyclic molecules are known which exhibit optical activity. Biheteroaromatic compounds which owe their dissymmetry to restricted rotation about the bond which joins the two heteroaromatic rings have been resolved into their optical antipodes. Their optical stabilities, when compared with their carbocyclic counterparts, demonstrate the steric and other effects attributed to the heteroatoms. Rigid dissymmetric molecules such as heterotwistanes, heterohelicenes, and heteroadamantanes can also exhibit optical activity if the heteroatoms are placed in appropriate positions. A number of examples are known in which the heteroaromatic ring has a serious effect on the chiroptical properties of a chiral center in a side chain when there is enough interaction between the heteroaromatic ring and the asymmetric center.

The three-dimensional properties of many bi- and polycyclic reduced heterocycles, for example, heterobicyclo[x.y.z]alkanes, may not have special stereochemical features but are discussed in this monograph because a knowledge of the relative arrangement of all the atoms in space is necessary for a complete understanding of the properties and reactions of the systems. Transannular interactions due to the spatial proximity of a heteroatom and another distant atom in the same ring have been observed and have led to interesting polycyclic systems.