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HANDBOOK OF HETEROCYCLIC CHEMISTRY- 3RD EDITION

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Part 1

Preliminaries

1.1

Foreword

The text *Heterocyclic Chemistry* by A. R. Katritzky and J. M. Lagowski was the subject's first modern treatment; it appeared 50 years ago, treating structure, reactivity, and synthesis systematically in terms of molecular structure. This text and its sequels, which were translated into Chinese, French, German, Greek, Italian, Japanese, Polish, Russian, and Spanish, revolutionized the practice and teaching of the subject worldwide. The 1st Edition of *Handbook of Heterocyclic Chemistry* (Handbook-I) followed in 1985 as part of *Comprehensive Heterocyclic Chemistry* 1st Edition (CHEC-I). Handbook-II appeared in 2000 alongside CHEC-II. We now present Handbook-III following the publication of CHEC-III in 2008.

The importance and extent of the subject matter of heterocyclic chemistry continues to grow such that it is now clearly the largest subdivision of organic chemistry. It plays a crucial role in biochemistry – increasingly so in medicine – and manifest other areas of chemistry as applied to subjects as diverse as construction and agriculture. Such is the rate of growth that this update is clearly needed.

Handbook-III retains the essentials of the treatments of Handbooks-I and -II in dividing the subject into the three main areas of structure, reactivity, and synthesis. We have striven both to be reasonably comprehensive and to keep the physical size of Handbook-III to a minimum, so it can be conveniently handled and consulted.

Handbook-III has four authors; three have prime responsibility for one section each: C. A. R. for Structure, J. A. J. for Reactivity, and V. V. Z. for Synthesis. Although much of the original content has been retained, each author has brought his own major experience throughout the revision, rewriting, and insertion of new material into the old.

Alan R. Katritzky, Christopher A. Ramsden, John A. Joule, and Viktor V. Zhdankin

1.2

Detailed Contents

1 Preliminaries	1
2 Structure of Heterocycles	29
2.1 Overview	30
2.1.1 Relationship of Heterocyclic and Carbocyclic Aromatic Compounds	30
2.1.2 Arrangement of Structure Chapters	30
2.1.3 Nomenclature	31
2.1.4 Computer-Aided Studies of Heterocycles	32
2.1.4.1 Hückel Calculations and Related π -Electron Methods	33
2.1.4.2 Semiempirical Methods	33
2.1.4.3 <i>Ab Initio</i> and DFT Calculations	34
2.1.4.4 Molecular Mechanics	35
2.1.5 Glossary of General Terms Used in Chapters 2.2–2.5	35
2.2 Structure of Six-membered Rings	37
2.2.1 Survey of Possible Structures and Nomenclature	38
2.2.1.1 Nitrogen Rings Without Exocyclic Conjugation	38
2.2.1.1.1 <i>Fully-conjugated aromatic rings</i>	38
2.2.1.1.2 <i>Fully-conjugated nonaromatic rings</i>	40
2.2.1.1.3 <i>Rings without cyclic conjugation</i>	40
2.2.1.2 Nitrogen Rings with Exocyclic Conjugation	41
2.2.1.2.1 <i>Pyridones and related systems</i>	41
2.2.1.2.2 <i>Mesomeric betaines (1,3-dipoles and 1,4-dipoles)</i>	42
2.2.1.2.3 <i>N-Oxides and related systems</i>	42
2.2.1.3 Oxygen and Sulfur Rings Without Exocyclic Conjugation	43
2.2.1.3.1 <i>Fully-conjugated aromatic rings</i>	43
2.2.1.3.2 <i>Fully-conjugated nonaromatic rings</i>	43
2.2.1.3.3 <i>Rings without cyclic conjugation</i>	43
2.2.1.4 Oxygen and Sulfur Rings with Exocyclic Conjugation	44
2.2.1.5 Rings Containing Nitrogen with Oxygen and/or Sulfur	44
2.2.2 Theoretical Methods	45
2.2.2.1 General Trends	45
2.2.2.2 Calculation of Molecular Properties	48
2.2.2.2.1 <i>Geometries</i>	48
2.2.2.2.2 <i>Magnetic properties</i>	49
2.2.2.2.3 <i>Tautomerism</i>	50
2.2.3 Structural Methods	51
2.2.3.1 X-Ray Diffraction	51
2.2.3.2 Microwave Spectroscopy	54
2.2.3.3 ^1H NMR Spectra	54
2.2.3.3.1 <i>Chemical shifts</i>	54
2.2.3.3.2 <i>Coupling constants</i>	59

2.2.3.4	^{13}C NMR Spectra	59
2.2.3.4.1	<i>Aromatic systems: Chemical shifts</i>	59
2.2.3.4.2	<i>Aromatic systems: Coupling constants</i>	62
2.2.3.4.3	<i>Saturated systems</i>	62
2.2.3.5	Nitrogen and Oxygen NMR Spectra	64
2.2.3.6	Ultraviolet and Related Spectra	66
2.2.3.7	IR and Raman Spectra	68
2.2.3.8	Mass Spectrometry	70
2.2.3.9	Photoelectron Spectroscopy	73
2.2.4	Thermodynamic Aspects	73
2.2.4.1	Intermolecular Forces	73
2.2.4.1.1	<i>Melting and boiling points</i>	73
2.2.4.1.2	<i>Solubility</i>	73
2.2.4.1.3	<i>Gas-liquid chromatography</i>	73
2.2.4.2	Aromaticity of Fully-Conjugated Rings	74
2.2.4.2.1	<i>Background</i>	74
2.2.4.2.2	<i>Energetic criteria</i>	75
2.2.4.2.3	<i>Structural criteria</i>	76
2.2.4.2.4	<i>Magnetic criteria</i>	77
2.2.4.3	Conformations of Partially- and Fully-Reduced Rings	78
2.2.5	Tautomerism	79
2.2.5.1	Prototropic Tautomerism	79
2.2.5.1.1	<i>Prototropic tautomerism of fully-conjugated rings</i>	79
2.2.5.1.2	<i>Prototropic tautomerism of rings without cyclic conjugation</i>	82
2.2.5.2	Ring-Chain Tautomerism	83
2.2.5.3	Valence Tautomerism	83
2.2.6	Supramolecular Structures	84
2.3	Structure of Five-Membered Rings with One Heteroatom	87
2.3.1	Survey of Possible Structures and Nomenclature	88
2.3.1.1	Rings Without Exocyclic Conjugation	88
2.3.1.1.1	<i>Fully-conjugated rings</i>	88
2.3.1.1.2	<i>Rings without cyclic conjugation</i>	90
2.3.1.2	Rings with Exocyclic Conjugation	91
2.3.1.2.1	<i>Fully-conjugated rings</i>	91
2.3.1.2.2	<i>Rings without cyclic conjugation</i>	92
2.3.2	Theoretical Methods	93
2.3.2.1	General Trends	93
2.3.2.2	Calculation of Molecular Properties	96
2.3.2.2.1	<i>Structure and energy</i>	96
2.3.2.2.2	<i>Reactions and equilibria</i>	98
2.3.3	Structural Methods	99
2.3.3.1	X-Ray Diffraction	99
2.3.3.2	Microwave Spectroscopy	103
2.3.3.3	^1H NMR Spectroscopy	104
2.3.3.3.1	<i>Parent aromatic compounds</i>	104
2.3.3.3.2	<i>Substituted aromatic compounds</i>	105
2.3.3.3.3	<i>Saturated and partially-saturated compounds</i>	108

2.3.3.4	¹³ C NMR Spectroscopy	108
2.3.3.5	Heteroatom NMR Spectroscopy	111
2.3.3.6	UV Spectroscopy	113
2.3.3.7	IR Spectroscopy	116
2.3.3.7.1	<i>Ring vibrations</i>	116
2.3.3.7.2	<i>Substituent vibrations</i>	119
2.3.3.8	Mass Spectrometry	119
2.3.3.8.1	<i>Parent monocycles</i>	120
2.3.3.8.2	<i>Substituted monocycles</i>	120
2.3.3.8.3	<i>Benzo derivatives</i>	121
2.3.3.8.4	<i>Saturated compounds</i>	122
2.3.3.9	Photoelectron Spectroscopy	123
2.3.3.9.1	<i>Parent monocycles</i>	123
2.3.3.9.2	<i>Substituted monocycles</i>	123
2.3.3.9.3	<i>Benzo derivatives</i>	124
2.3.3.9.4	<i>Reduced compounds</i>	125
2.3.3.9.5	<i>Core-ionization energies</i>	125
2.3.4	Thermodynamic Aspects	126
2.3.4.1	Intermolecular Forces	126
2.3.4.1.1	<i>Melting and boiling points</i>	126
2.3.4.1.2	<i>Solubility</i>	126
2.3.4.1.3	<i>Gas chromatography</i>	126
2.3.4.2	Aromaticity of Fully-Conjugated Rings	126
2.3.4.2.1	<i>Background</i>	126
2.3.4.2.2	<i>Energetic criteria</i>	126
2.3.4.2.3	<i>Structural criteria</i>	127
2.3.4.2.4	<i>Magnetic criteria</i>	128
2.3.4.3	Conformations of Heteroaryl Derivatives: Rotamers and Atropisomers	128
2.3.4.3.1	<i>Rotamers</i>	128
2.3.4.3.2	<i>Atropisomers</i>	131
2.3.4.4	Conformations of Partially- and Fully-Reduced Rings	132
2.3.5	Tautomerism	133
2.3.5.1	Prototropic Tautomerism of Fully-Conjugated Rings	133
2.3.5.1.1	<i>Annular tautomerism</i>	133
2.3.5.1.2	<i>Oxo-hydroxy tautomerism</i>	134
2.3.5.1.3	<i>Thiono-mercapto and amino-imino tautomerism</i>	137
2.4	Structure of Five-membered Rings with Two or More Heteroatoms	139
2.4.1	Survey of Possible Structures and Nomenclature	140
2.4.1.1	Nitrogen Rings without Exocyclic Conjugation	140
2.4.1.1.1	<i>Fully-conjugated aromatic rings</i>	140
2.4.1.1.2	<i>Rings without cyclic conjugation</i>	142
2.4.1.2	Nitrogen Rings with Exocyclic Conjugation	143
2.4.1.3	Oxygen and Sulfur Rings without Exocyclic Conjugation	143
2.4.1.3.1	<i>Fully-conjugated aromatic rings</i>	143
2.4.1.3.2	<i>Rings without cyclic conjugation</i>	144

2.4.1.4	Oxygen and Sulfur Rings with Exocyclic Conjugation	144
2.4.1.5	Rings Containing Nitrogen with Oxygen and/or Sulfur	145
2.4.2	Theoretical Methods	145
2.4.2.1	General Trends	145
2.4.2.2	Calculation of Molecular Properties	149
2.4.2.2.1	<i>Structure and energy</i>	149
2.4.2.2.2	<i>Magnetic properties</i>	151
2.4.2.2.3	<i>Reactions and equilibria</i>	151
2.4.3	Structural Methods	153
2.4.3.1	X-Ray Diffraction	153
2.4.3.2	Microwave Spectroscopy	157
2.4.3.2.1	<i>Aromatic rings</i>	157
2.4.3.2.2	<i>Partially- and fully-saturated ring systems</i>	160
2.4.3.3	¹ H NMR Spectroscopy	160
2.4.3.3.1	<i>Fully-conjugated aromatic rings</i>	160
2.4.3.3.2	<i>Other ring systems</i>	166
2.4.3.4	¹³ C NMR Spectroscopy	167
2.4.3.5	Nitrogen and Oxygen NMR Spectroscopy	173
2.4.3.6	UV Spectroscopy	177
2.4.3.6.1	<i>Parent compounds</i>	177
2.4.3.6.2	<i>Benzo derivatives</i>	177
2.4.3.6.3	<i>Effect of substituents</i>	178
2.4.3.7	IR Spectroscopy	179
2.4.3.7.1	<i>Aromatic rings without carbonyl groups</i>	179
2.4.3.7.2	<i>Azole rings containing carbonyl groups</i>	179
2.4.3.7.3	<i>Substituent vibrations</i>	183
2.4.3.8	Mass Spectrometry	184
2.4.3.9	Photoelectron Spectroscopy	186
2.4.4	Thermodynamic Aspects	187
2.4.4.1	Intermolecular Forces	187
2.4.4.1.1	<i>Melting and boiling points</i>	187
2.4.4.1.2	<i>Solubility of heterocyclic compounds</i>	187
2.4.4.1.3	<i>Gas-liquid chromatography</i>	187
2.4.4.2	Aromaticity of Fully-Conjugated Rings	187
2.4.4.2.1	<i>Background</i>	187
2.4.4.2.2	<i>Energetic criteria</i>	191
2.4.4.2.3	<i>Structural criteria</i>	192
2.4.4.2.4	<i>Magnetic criteria</i>	193
2.4.4.2.5	<i>N-Heterocyclic carbenes (NHCs)</i>	194
2.4.4.3	Conformations of Heteroaryl Derivatives	195
2.4.4.4	Conformations of Partially- and Fully-Reduced Rings	196
2.4.5	Tautomerism	199
2.4.5.1	Prototropic Tautomerism of Rings	199
2.4.5.1.1	<i>Annular tautomerism</i>	199
2.4.5.1.2	<i>Annular elementotropy</i>	202

2.4.5.2	Prototropic Tautomerism of OH, NH ₂ , and SH Substituents	203
2.4.5.2.1	<i>Pyrazoles, isoxazoles, and isothiazoles</i>	203
2.4.5.2.2	<i>Imidazoles, oxazoles, and thiazoles</i>	204
2.4.5.3	Ring-Chain Tautomerism	206
2.4.5.4	Valence Tautomerism	207
2.5	Structure of Small and Large Rings	210
2.5.1	Survey of Possible Structures and Nomenclature	211
2.5.1.1	Three- and Four-Membered Rings	211
2.5.1.1.1	<i>Without exocyclic conjugation</i>	211
2.5.1.1.2	<i>With exocyclic conjugation</i>	211
2.5.1.2	Seven-Membered Rings	213
2.5.1.3	Larger Rings	213
2.5.2	Theoretical Methods	214
2.5.2.1	Three- and Four-Membered Rings	214
2.5.2.2	Seven- and Eight-Membered Rings	216
2.5.2.3	Larger Rings	217
2.5.3	Structural Methods	218
2.5.3.1	X-Ray Diffraction	218
2.5.3.2	Microwave Spectroscopy	222
2.5.3.3	¹ H NMR Spectroscopy	223
2.5.3.3.1	<i>Three- and four-membered rings</i>	223
2.5.3.3.2	<i>Seven or more ring atoms</i>	224
2.5.3.4	¹³ C and Heteronuclear NMR Spectroscopy	225
2.5.3.5	UV Spectroscopy	225
2.5.3.5.1	<i>Electronic spectra of small-ring heterocyclic compounds</i>	225
2.5.3.5.2	<i>Electronic spectra of large-ring heterocyclic compounds</i>	226
2.5.3.6	IR Spectroscopy	227
2.5.3.7	Mass Spectrometry	227
2.5.3.8	Photoelectron spectroscopy (PES)	230
2.5.4	Thermodynamic Aspects	230
2.5.4.1	Stability and Stabilization	230
2.5.4.1.1	<i>Ring strain</i>	230
2.5.4.1.2	<i>Aromaticity and antiaromaticity</i>	231
2.5.4.2	Conformation	233
2.5.4.2.1	<i>Small rings</i>	233
2.5.4.2.2	<i>Large rings</i>	234
2.5.5	Tautomerism	235
2.5.5.1	Annular Tautomerism	235
2.5.5.2	Valence Tautomerism	236
3	Reactivity of Heterocycles	239
3.1	Overview	240
3.1.1	Reaction Types	240
3.1.2	Heteroaromatic Reactivity	240
3.1.3	Arrangement of the Reactivity Sections	241

3.2 Reactivity of Six-membered Rings	242
3.2.1 Reactivity of Aromatic Rings	245
3.2.1.1 General Survey of Reactivity	245
3.2.1.1.1 <i>Pyridines</i>	245
3.2.1.1.2 <i>Azines</i>	246
3.2.1.1.3 <i>Cationic rings</i>	246
3.2.1.1.4 <i>Pyridones, N-oxides, and mesomeric betaines</i>	247
3.2.1.1.5 <i>Anionic rings</i>	248
3.2.1.1.6 <i>Aromaticity and reversion to type</i>	248
3.2.1.2 Intramolecular Thermal and Photochemical Reactions	248
3.2.1.2.1 <i>Fragmentation</i>	248
3.2.1.2.2 <i>Rearrangement to or elimination via Dewar heterobenzenes</i>	249
3.2.1.2.3 <i>Rearrangement to or via heteroprismanes and heterobenzvalenes</i>	251
3.2.1.2.4 <i>Rearrangement to or via 1,3-bridged heterocycles</i>	252
3.2.1.2.5 <i>Ring opening</i>	253
3.2.1.3 Electrophilic Attack at Nitrogen	253
3.2.1.3.1 <i>Introduction</i>	253
3.2.1.3.2 <i>Effect of substituents</i>	254
3.2.1.3.3 <i>Orientation of reaction of azines</i>	254
3.2.1.3.4 <i>Proton acids</i>	254
3.2.1.3.5 <i>Metal ions</i>	256
3.2.1.3.6 <i>Alkyl and aryl halides and related compounds</i>	257
3.2.1.3.7 <i>Acyl halides and related compounds and Michael-type reactions</i>	258
3.2.1.3.8 <i>Halogens</i>	259
3.2.1.3.9 <i>Peracids</i>	260
3.2.1.3.10 <i>Aminating agents</i>	261
3.2.1.3.11 <i>Other Lewis acids</i>	261
3.2.1.4 Electrophilic Attack at Carbon	261
3.2.1.4.1 <i>Species undergoing reaction and the reaction mechanism</i>	261
3.2.1.4.2 <i>Reactivity and effect of substituents</i>	262
3.2.1.4.3 <i>Orientation</i>	263
3.2.1.4.4 <i>Nitration</i>	263
3.2.1.4.5 <i>Sulfonation</i>	265
3.2.1.4.6 <i>Acid-catalyzed hydrogen exchange</i>	265
3.2.1.4.7 <i>Halogenation</i>	266
3.2.1.4.8 <i>Acylation and alkylation</i>	269
3.2.1.4.9 <i>Mercuration</i>	270
3.2.1.4.10 <i>Nitrosation, diazo coupling, Mannich reaction, Kolbe reaction, and reaction with aldehydes</i>	270
3.2.1.4.11 <i>Oxidation</i>	271
3.2.1.5 Attack at Ring Sulfur Atoms	272
3.2.1.5.1 <i>Reactions with electrophiles</i>	272
3.2.1.5.2 <i>Reactions with nucleophiles</i>	272
3.2.1.6 Nucleophilic Attack at Carbon	272
3.2.1.6.1 <i>Ease of reaction</i>	272
3.2.1.6.2 <i>Effect of substituents</i>	274
3.2.1.6.3 <i>Hydroxide ion</i>	274

3.2.1.6.4	<i>Amines and amide ions</i>	280
3.2.1.6.5	<i>Sulfur nucleophiles</i>	284
3.2.1.6.6	<i>Phosphorus nucleophiles</i>	284
3.2.1.6.7	<i>Halide ions</i>	285
3.2.1.6.8	<i>Carbon nucleophiles</i>	285
3.2.1.6.9	<i>Chemical reduction</i>	294
3.2.1.7	<i>Nucleophilic Attack at Ring Nitrogen</i>	297
3.2.1.8	<i>Attack by Bases at Hydrogen Attached to Ring Carbon or Ring Nitrogen</i>	297
3.2.1.8.1	<i>Metallation at a ring carbon atom</i>	298
3.2.1.8.2	<i>Hydrogen exchange at ring carbon in neutral azines, N-oxides, and azinones</i>	300
3.2.1.8.3	<i>Hydrogen exchange at ring carbon in azinium cations</i>	300
3.2.1.8.4	<i>Proton loss from a ring nitrogen atom</i>	301
3.2.1.9	<i>Reactions with Radicals and Electron-Deficient Species; Reactions at Surfaces</i>	302
3.2.1.9.1	<i>Carbenes and nitrenes</i>	302
3.2.1.9.2	<i>Radical attack at ring carbon atoms</i>	302
3.2.1.9.3	<i>Electrochemical reactions and reactions with free electrons</i>	304
3.2.1.9.4	<i>Other reactions at surfaces</i>	305
3.2.1.10	<i>Reactions with Cyclic Transition States</i>	306
3.2.1.10.1	<i>Introduction</i>	306
3.2.1.10.2	<i>Heterocycles as inner dienes in [2 + 4] cycloadditions</i>	306
3.2.1.10.3	<i>Heterocycles as inner dienes in [1 + 4] cycloadditions</i>	309
3.2.1.10.4	<i>Heterocycles as 1,3-dipoles</i>	311
3.2.1.10.5	<i>Heterocycles as dienophiles</i>	312
3.2.1.10.6	<i>[2 + 2] Cycloadditions</i>	313
3.2.1.10.7	<i>Heterocycles as 4π-components in [4 + 4] cycloaddition</i>	313
3.2.2	<i>Reactions of Nonaromatic Compounds</i>	314
3.2.2.1	<i>8π-Electron Systems: 1,2- and 1,4-Dioxins, -Oxathiins, and -Dithiins</i>	314
3.2.2.1.1	<i>Intramolecular thermolysis and photolysis reactions</i>	314
3.2.2.1.2	<i>Reactions with electrophiles</i>	314
3.2.2.1.3	<i>Reactions with nucleophiles</i>	315
3.2.2.2	<i>Thiabenzenes and Related Compounds</i>	316
3.2.2.3	<i>Dihydro Compounds</i>	317
3.2.2.3.1	<i>Introduction</i>	317
3.2.2.3.2	<i>Annular tautomerism</i>	317
3.2.2.3.3	<i>Aromatization</i>	318
3.2.2.3.4	<i>Electron loss to form radicals</i>	321
3.2.2.3.5	<i>Electrocyclic ring opening (valence tautomerism)</i>	321
3.2.2.3.6	<i>Proton loss to an 8π-electron-conjugated system</i>	322
3.2.2.3.7	<i>Electrophilic substitution</i>	322
3.2.2.3.8	<i>Cycloaddition reactions</i>	323
3.2.2.3.9	<i>Other reactions</i>	325
3.2.2.4	<i>Tetra- and Hexahydro Compounds</i>	326
3.2.2.4.1	<i>Tautomeric equilibria</i>	326
3.2.2.4.2	<i>Aromatization</i>	327
3.2.2.4.3	<i>Ring fission</i>	327
3.2.2.4.4	<i>Other reactions</i>	328
3.2.2.4.5	<i>Stereochemistry</i>	328

3.2.3	Reactions of Substituents	329
3.2.3.1	General Survey of Reactivity of Substituents on Ring Carbon Atoms	329
3.2.3.1.1	<i>The carbonyl analogy</i>	329
3.2.3.1.2	<i>Effect of number, type, and orientation of heteroatoms</i>	329
3.2.3.1.3	<i>The effect of one substituent on the reactivity of another</i>	331
3.2.3.1.4	<i>Reactions of substituents not directly attached to the heterocyclic ring</i>	331
3.2.3.2	Benzenoid Rings	332
3.2.3.2.1	<i>Fused benzene rings: Unsubstituted</i>	332
3.2.3.2.2	<i>Fused benzene rings: Substituted</i>	334
3.2.3.3	Alkyl Groups	336
3.2.3.3.1	<i>Reactions similar to those of toluene</i>	336
3.2.3.3.2	<i>Alkyl groups: Reactions via proton loss</i>	336
3.2.3.3.3	<i>Alkylazines: Reactions involving essentially complete anion formation</i>	337
3.2.3.3.4	<i>Alkylazines: Reactions involving traces of reactive anions or traces of methylene enamines</i>	337
3.2.3.3.5	<i>Alkyl-azonium and -pyrylium compounds</i>	339
3.2.3.3.6	<i>Tautomerism of alkyl derivatives</i>	341
3.2.3.4	Further Carbon Functional Groups	341
3.2.3.4.1	<i>Aryl groups</i>	341
3.2.3.4.2	<i>Carboxylic acids and derivatives</i>	342
3.2.3.4.3	<i>Aldehydes and ketones</i>	344
3.2.3.4.4	<i>Other substituted alkyl groups</i>	344
3.2.3.4.5	<i>Vinyl groups</i>	345
3.2.3.5	Amino and Imino Groups	345
3.2.3.5.1	<i>Orientation of reactions of aminopyridines and -azines with electrophiles</i>	345
3.2.3.5.2	<i>Reaction of aminoazines with electrophiles at the amino group</i>	346
3.2.3.5.3	<i>Diazotization of amino compounds</i>	347
3.2.3.5.4	<i>Reactions of amino compounds with nucleophiles and bases</i>	347
3.2.3.5.5	<i>Intramolecular reactions of amino group producing rings</i>	348
3.2.3.5.6	<i>Amino-imino tautomerism</i>	349
3.2.3.6	Other N-Linked Substituents	349
3.2.3.6.1	<i>Nitro groups</i>	349
3.2.3.6.2	<i>Nitramino compounds</i>	350
3.2.3.6.3	<i>Hydrazino groups</i>	350
3.2.3.6.4	<i>Azides</i>	350
3.2.3.6.5	<i>Nitroso groups</i>	351
3.2.3.7	Hydroxy and Oxo Groups	351
3.2.3.7.1	<i>Hydroxy groups and hydroxy-oxo tautomeric equilibria</i>	351
3.2.3.7.2	<i>Pyridones, pyrones, thiinones, azinones, etc.: General pattern of reactivity</i>	352
3.2.3.7.3	<i>Pyridones, pyrones, and azinones: Electrophilic attack at carbonyl oxygen</i>	353
3.2.3.7.4	<i>Pyridones, pyrones, and azinones: Nucleophilic displacement of carbonyl oxygen</i>	354
3.2.3.7.5	<i>Heterocyclic quinones</i>	356
3.2.3.8	Other O-Linked Substituents	356
3.2.3.8.1	<i>Alkoxy and aryloxy groups</i>	356
3.2.3.8.2	<i>Acyloxy groups</i>	358
3.2.3.9	S-Linked Substituents	359
3.2.3.9.1	<i>Mercapto-thione tautomerism</i>	359

3.2.3.9.2	<i>Thiones</i>	359
3.2.3.9.3	<i>Alkylthio, alkylsulfinyl, and alkylsulfonyl groups</i>	360
3.2.3.9.4	<i>Sulfonic acid groups</i>	360
3.2.3.10	<i>Halogen Atoms</i>	360
3.2.3.10.1	<i>Pattern of reactivity</i>	360
3.2.3.10.2	<i>Replacement of halogen by hydrogen or a metal (including transmetallation) or by coupling</i>	360
3.2.3.10.3	<i>Reactions via hetarynes</i>	362
3.2.3.10.4	<i>The S_{RN} mechanistic pathway</i>	362
3.2.3.10.5	<i>ANRORC reactions</i>	363
3.2.3.10.6	<i>Nucleophilic displacement by classical S_{AE} mechanism</i>	363
3.2.3.11	<i>Metals and Metalloids</i>	367
3.2.3.11.1	<i>Organometallic nucleophiles</i>	367
3.2.3.11.2	<i>Transition metal-catalyzed processes</i>	368
3.2.3.12	<i>Substituents Attached to Ring Nitrogen Atoms</i>	375
3.2.3.12.1	<i>Introduction</i>	375
3.2.3.12.2	<i>Alkyl groups</i>	376
3.2.3.12.3	<i>Other C-linked substituents</i>	377
3.2.3.12.4	<i>N-Linked substituents</i>	378
3.2.3.12.5	<i>O-Linked substituents</i>	380
3.2.3.12.6	<i>Other substituents attached to nitrogen</i>	382
3.2.3.13	<i>Substituents Attached to Ring Sulfur Atoms</i>	382
3.3	Reactivity of Five-Membered Rings with One Heteroatom	383
3.3.1	<i>Reactions at Heteroaromatic Rings</i>	385
3.3.1.1	<i>General Survey of Reactivity</i>	385
3.3.1.1.1	<i>Comparison with aliphatic series</i>	386
3.3.1.1.2	<i>Effect of aromaticity</i>	386
3.3.1.2	<i>Thermal and Photochemical Reactions Involving No Other Species</i>	386
3.3.1.3	<i>Electrophilic Attack on Ring Heteroatoms</i>	388
3.3.1.3.1	<i>Pyrrole anions</i>	388
3.3.1.3.2	<i>Thiophenes, selenophenes, and tellurophenes</i>	393
3.3.1.4	<i>Electrophilic Attack on Carbon: General Considerations</i>	394
3.3.1.4.1	<i>Relative reactivities of heterocycles</i>	394
3.3.1.4.2	<i>Directing effects of the ring heteroatom</i>	395
3.3.1.4.3	<i>Directing effects of substituents in monocyclic compounds</i>	396
3.3.1.4.4	<i>Directing effects of fused benzene rings</i>	397
3.3.1.4.5	<i>Range of substitution reactions</i>	397
3.3.1.5	<i>Electrophilic Attack on Carbon: Specific Reactions</i>	398
3.3.1.5.1	<i>Proton acids</i>	398
3.3.1.5.2	<i>Nitration</i>	399
3.3.1.5.3	<i>Sulfonation</i>	400
3.3.1.5.4	<i>Halogenation</i>	401
3.3.1.5.5	<i>Acylation</i>	403
3.3.1.5.6	<i>Alkylation</i>	408
3.3.1.5.7	<i>Reactions with aldehydes and ketones</i>	412
3.3.1.5.8	<i>Mercuration</i>	416
3.3.1.5.9	<i>Diazo coupling</i>	416

3.3.1.5.10	<i>Nitrosation</i>	417
3.3.1.5.11	<i>Electrophilic oxidation</i>	417
3.3.1.6	Reactions with Nucleophiles and Bases	420
3.3.1.6.1	<i>Deprotonation at nitrogen</i>	420
3.3.1.6.2	<i>Deprotonation at carbon</i>	420
3.3.1.6.3	<i>Reactions of cationic species with nucleophiles</i>	421
3.3.1.6.4	<i>Vicarious nucleophilic substitution and related reactions</i>	422
3.3.1.6.5	<i>Nucleophilic attack on sulfur</i>	424
3.3.1.7	Reactions with Radicals and Electron-Deficient Species; Reactions at Surfaces	424
3.3.1.7.1	<i>Carbenes and nitrenes</i>	424
3.3.1.7.2	<i>Radical attack</i>	426
3.3.1.7.3	<i>Electrochemical reactions</i>	429
3.3.1.7.4	<i>Reactions with free electrons</i>	429
3.3.1.7.5	<i>Catalytic hydrogenation</i>	430
3.3.1.7.6	<i>Reduction by dissolving metals</i>	430
3.3.1.7.7	<i>Desulfurization</i>	430
3.3.1.8	Reactions with Cyclic Transition States	430
3.3.1.8.1	<i>Heterocycles as inner ring dienes</i>	430
3.3.1.8.2	<i>Five-membered heterocycles as dienophiles</i>	434
3.3.1.8.3	<i>[2 + 2] Cycloaddition reactions</i>	435
3.3.1.8.4	<i>Other cycloaddition reactions</i>	436
3.3.2	Reactivity of Nonaromatic Compounds	437
3.3.2.1	<i>2H</i> -Pyrroles (Pyrrolenines) and <i>3H</i> -Indoles (Indolenines)	437
3.3.2.2	Thiophene Sulfones and Sulfoxides	437
3.3.2.3	Dihydro Derivatives	439
3.3.2.3.1	<i>Aromatization of dihydro compounds</i>	439
3.3.2.3.2	<i>Behavior analogous to aliphatic analogues</i>	440
3.3.2.3.3	<i>Other reactions</i>	440
3.3.2.4	Tetrahydro Derivatives	441
3.3.2.5	Ring Carbonyl Compounds and their Hydroxy Tautomers	442
3.3.2.5.1	<i>Survey of structures</i>	442
3.3.2.5.2	<i>Interconversion and reactivity of tautomeric forms</i>	443
3.3.2.5.3	<i>Reactions of hydroxy compounds with electrophiles</i>	443
3.3.2.5.4	<i>Reactions of anions with electrophiles</i>	444
3.3.2.5.5	<i>Reactions of carbonyl compounds with nucleophiles</i>	445
3.3.2.5.6	<i>Reductions of carbonyl and hydroxy compounds</i>	446
3.3.3	Reactivity of Substituents	446
3.3.3.1	General Survey of Reactivity	446
3.3.3.1.1	<i>Reaction types</i>	446
3.3.3.1.2	<i>Nucleophilic substitution of substituents</i>	446
3.3.3.2	Fused Benzene Rings	447
3.3.3.2.1	<i>Electrophilic attack</i>	447
3.3.3.2.2	<i>Nucleophilic attack</i>	448
3.3.3.2.3	<i>Reactions with electrons – reduction reactions</i>	448
3.3.3.2.4	<i>Reactions of substituents on benzene rings</i>	449

3.3.3.3	Other C-Linked Substituents	449
3.3.3.3.1	<i>Alkyl groups</i>	449
3.3.3.3.2	<i>Vinyl groups</i>	449
3.3.3.3.3	<i>Substituted alkyl groups: General</i>	451
3.3.3.3.4	<i>Halomethyl</i>	453
3.3.3.3.5	<i>Hydroxymethyl</i>	453
3.3.3.3.6	<i>Aminomethyl</i>	454
3.3.3.3.7	<i>Carboxylic acids, esters, and anhydrides</i>	455
3.3.3.3.8	<i>Acyl groups</i>	456
3.3.3.4	N-Linked Substituents	457
3.3.3.4.1	<i>Nitro</i>	457
3.3.3.4.2	<i>Amino</i>	458
3.3.3.4.3	<i>Azides</i>	459
3.3.3.5	O-Linked Substituents	459
3.3.3.6	S-Linked Substituents	459
3.3.3.7	Halo Groups	460
3.3.3.7.1	<i>Nucleophilic displacement</i>	460
3.3.3.7.2	<i>Reductive dehalogenation</i>	460
3.3.3.7.3	<i>Rearrangement</i>	461
3.3.3.7.4	<i>Formation of Grignard reagents</i>	461
3.3.3.8	Metals and Metalloids	461
3.3.3.8.1	<i>General</i>	461
3.3.3.8.2	<i>Formation of C–C bonds</i>	462
3.3.3.8.3	<i>Formation of C–O bonds</i>	464
3.3.3.8.4	<i>Formation of C–S bonds</i>	464
3.3.3.8.5	<i>Formation of C–N bonds</i>	465
3.3.3.8.6	<i>Formation of C–halogen bonds</i>	465
3.3.3.8.7	<i>Ring-opening reactions</i>	465
3.3.3.8.8	<i>Transition metal-catalyzed cross-coupling reactions</i>	466
3.3.3.8.9	<i>Mercury derivatives</i>	470
3.3.3.9	Substituents Attached to the Pyrrole Nitrogen Atom	471
3.3.3.10	Substituents Attached to the Thiophene Sulfur Atom	472
3.4	Reactivity of Five-membered Rings with Two or More Heteroatoms	473
3.4.1	Reactions at Heteroaromatic Rings	476
3.4.1.1	General Survey of Reactivity	476
3.4.1.1.1	<i>Reactivity of neutral azoles</i>	476
3.4.1.1.2	<i>Azolium salts</i>	477
3.4.1.1.3	<i>Azole anions</i>	477
3.4.1.1.4	<i>Azolinones, azolinethiones, azolinimines</i>	478
3.4.1.1.5	<i>N-Oxides, N-imides, N-ylides of azoles</i>	478
3.4.1.2	Thermal and Photochemical Reactions Formally Involving No Other Species	479
3.4.1.2.1	<i>Thermal fragmentation</i>	479
3.4.1.2.2	<i>Photochemical fragmentation</i>	482
3.4.1.2.3	<i>Equilibria with open-chain compounds</i>	483
3.4.1.2.4	<i>Rearrangement to other heterocyclic species</i>	484
3.4.1.2.5	<i>Polymerization</i>	486

3.4.1.3	Electrophilic Attack at Nitrogen	486
3.4.1.3.1	<i>Introduction</i>	486
3.4.1.3.2	<i>Reaction sequence</i>	486
3.4.1.3.3	<i>Orientation in azole rings containing three or four heteroatoms</i>	487
3.4.1.3.4	<i>Effect of azole ring structure and of substituents</i>	487
3.4.1.3.5	<i>Proton acids on neutral azoles: Basicity of azoles</i>	488
3.4.1.3.6	<i>N-Hydrogen acidity of azoles</i>	489
3.4.1.3.7	<i>Basicity and acidity in gas phase</i>	490
3.4.1.3.8	<i>Metal ions</i>	491
3.4.1.3.9	<i>Alkyl halides and related compounds: Azoles without a free NH group</i>	492
3.4.1.3.10	<i>Alkyl halides and related compounds: Compounds with a free NH group</i>	494
3.4.1.3.11	<i>Acyl halides and related compounds</i>	498
3.4.1.3.12	<i>Halogens</i>	499
3.4.1.3.13	<i>Peracids</i>	499
3.4.1.3.14	<i>Aminating agents</i>	500
3.4.1.3.15	<i>Other electrophiles</i>	501
3.4.1.4	Electrophilic Attack at Carbon	501
3.4.1.4.1	<i>Reactivity and orientation</i>	501
3.4.1.4.2	<i>Nitration</i>	503
3.4.1.4.3	<i>Sulfonation</i>	504
3.4.1.4.4	<i>Acid-catalyzed hydrogen exchange</i>	504
3.4.1.4.5	<i>Halogenation</i>	504
3.4.1.4.6	<i>Acylation, formylation, and alkylation</i>	506
3.4.1.4.7	<i>Mercuration</i>	507
3.4.1.4.8	<i>Diazo coupling</i>	507
3.4.1.4.9	<i>Nitrosation</i>	508
3.4.1.4.10	<i>Reactions with aldehydes and ketones</i>	508
3.4.1.4.11	<i>Oxidation</i>	509
3.4.1.4.12	<i>Other electrophiles</i>	510
3.4.1.5	Attack at Sulfur	510
3.4.1.5.1	<i>Electrophilic attack</i>	510
3.4.1.5.2	<i>Nucleophilic attack</i>	511
3.4.1.6	Nucleophilic Attack at Carbon	512
3.4.1.6.1	<i>Hydroxide ion and other O-nucleophiles</i>	513
3.4.1.6.2	<i>Amines and amide ions</i>	516
3.4.1.6.3	<i>S-Nucleophiles</i>	519
3.4.1.6.4	<i>Halide ions</i>	519
3.4.1.6.5	<i>Carbanions</i>	520
3.4.1.6.6	<i>Reduction by complex hydrides</i>	522
3.4.1.6.7	<i>Phosphorus nucleophiles</i>	524
3.4.1.7	Nucleophilic Attack at Nitrogen Heteroatom	524
3.4.1.8	Base Attack at Hydrogen Attached to Ring Carbon or Ring Nitrogen	524
3.4.1.8.1	<i>Metallation at a ring carbon atom</i>	525
3.4.1.8.2	<i>Hydrogen exchange at ring carbon in neutral azoles</i>	527
3.4.1.8.3	<i>Hydrogen exchange at ring carbon in azolium ions and dimerization</i>	528
3.4.1.8.4	<i>C-Substitution via electrophilic attack at N, deprotonation, and rearrangement</i>	529

3.4.1.8.5	<i>Formation and reactions of stable carbenes</i>	530
3.4.1.8.6	<i>Ring cleavage via C-deprotonation</i>	530
3.4.1.8.7	<i>Proton loss from a ring nitrogen atom</i>	532
3.4.1.9	Reactions with Radicals and Electron-Deficient Species; Reactions at Surfaces	532
3.4.1.9.1	<i>Carbenes and nitrenes</i>	532
3.4.1.9.2	<i>Radical attack at the ring carbon atoms</i>	533
3.4.1.9.3	<i>Thiation</i>	533
3.4.1.9.4	<i>Electrochemical reactions and reactions with free electrons</i>	534
3.4.1.9.5	<i>Other reactions at surfaces (catalytic hydrogenation and reduction by dissolving metals)</i>	535
3.4.1.10	Reactions with Cyclic Transition States	537
3.4.1.10.1	<i>Heterocycles as inner ring dienes</i>	537
3.4.1.10.2	<i>Heterocyclic derivatives as inner-outer ring dienes</i>	541
3.4.1.10.3	<i>Heterocyclic derivatives as outer ring dienes</i>	541
3.4.1.10.4	<i>Heterocycles as dienophiles</i>	542
3.4.1.10.5	<i>[2+2] Cycloaddition reactions</i>	543
3.4.1.10.6	<i>Other cycloaddition reactions</i>	544
3.4.2	Reactions of Nonaromatic Compounds	544
3.4.2.1	Isomers of Aromatic Derivatives	544
3.4.2.1.1	<i>Compounds not in tautomeric equilibrium with aromatic derivatives</i>	544
3.4.2.1.2	<i>Compounds in tautomeric equilibria with aromatic derivatives</i>	546
3.4.2.2	Dihydro Compounds	546
3.4.2.2.1	<i>Tautomerism</i>	546
3.4.2.2.2	<i>Aromatization</i>	546
3.4.2.2.3	<i>Ring contraction</i>	548
3.4.2.2.4	<i>Other reactions</i>	549
3.4.2.3	Tetrahydro Compounds	553
3.4.2.3.1	<i>Aromatization</i>	553
3.4.2.3.2	<i>Ring fission</i>	553
3.4.2.3.3	<i>Other reactions</i>	554
3.4.3	Reactions of Substituents	555
3.4.3.1	General Survey of Substituents on Carbon	555
3.4.3.1.1	<i>Substituent environment</i>	555
3.4.3.1.2	<i>The carbonyl analogy</i>	556
3.4.3.1.3	<i>Two heteroatoms in the 1,3-positions</i>	556
3.4.3.1.4	<i>Two heteroatoms in the 1,2-positions</i>	556
3.4.3.1.5	<i>Three heteroatoms</i>	556
3.4.3.1.6	<i>Four heteroatoms</i>	556
3.4.3.1.7	<i>The effect of one substituent on the reactivity of another</i>	556
3.4.3.1.8	<i>Reactions of substituents not directly attached to the heterocyclic ring</i>	557
3.4.3.1.9	<i>Reactions of substituents involving ring transformations</i>	557
3.4.3.2	Fused Benzene Rings	559
3.4.3.2.1	<i>Electrophilic substitution</i>	559
3.4.3.2.2	<i>Oxidative degradation</i>	559
3.4.3.2.3	<i>Nucleophilic attack</i>	560
3.4.3.2.4	<i>Rearrangements</i>	561

3.4.3.3	Alkyl Groups	562
3.4.3.3.1	<i>Reactions similar to those of toluene</i>	562
3.4.3.3.2	<i>Alkylazoles: Reactions involving essentially complete anion formation</i>	563
3.4.3.3.3	<i>Reactions of alkylazoles involving traces of reactive anions</i>	564
3.4.3.3.4	<i>C-Alkyl-azoliums, -dithiolyliums, etc.</i>	565
3.4.3.4	Other C-Linked Substituents	567
3.4.3.4.1	<i>Aryl groups: Electrophilic substitution</i>	567
3.4.3.4.2	<i>Aryl groups: Other reactions</i>	567
3.4.3.4.3	<i>Carboxylic acids</i>	568
3.4.3.4.4	<i>Aldehydes and ketones</i>	569
3.4.3.4.5	<i>Vinyl and ethynyl groups</i>	570
3.4.3.4.6	<i>Ring fission</i>	570
3.4.3.5	Aminoazoles	571
3.4.3.5.1	<i>Dimroth rearrangements</i>	571
3.4.3.5.2	<i>Reactions with electrophiles (except nitrous acid)</i>	572
3.4.3.5.3	<i>Reaction with nitrous acid; diazotization</i>	573
3.4.3.5.4	<i>Deprotonation of aminoazoles</i>	575
3.4.3.5.5	<i>Aminoazolium ions/neutral imines</i>	575
3.4.3.5.6	<i>Oxidation of aminoazoles</i>	575
3.4.3.6	Other N-Linked Substituents	576
3.4.3.6.1	<i>Nitro groups</i>	576
3.4.3.6.2	<i>Azidoazoles</i>	576
3.4.3.6.3	<i>Benzotriazole</i>	577
3.4.3.7	O-Linked Substituents	577
3.4.3.7.1	<i>Tautomeric forms: Interconversion and modes of reaction</i>	577
3.4.3.7.3	<i>3-Hydroxyazoles, heteroatoms-1,2</i>	579
3.4.3.7.4	<i>5-Hydroxyazoles with heteroatoms-1,2</i>	579
3.4.3.7.5	<i>4- and 5-Hydroxyazoles with heteroatoms-1,3 and 4-hydroxyazoles with heteroatoms-1,2</i>	579
3.4.3.7.6	<i>Hydroxy derivatives with three heteroatoms</i>	580
3.4.3.7.7	<i>Alkoxy and aryloxy groups</i>	580
3.4.3.8	S-Linked Substituents	581
3.4.3.8.1	<i>Mercapto compounds: Tautomerism</i>	581
3.4.3.8.2	<i>Thiones</i>	581
3.4.3.8.3	<i>Alkylthio groups</i>	582
3.4.3.8.4	<i>Sulfonic acid and sulfonyl groups</i>	583
3.4.3.9	Halogen Atoms	583
3.4.3.9.1	<i>Nucleophilic displacements: Neutral azoles</i>	583
3.4.3.9.2	<i>Nucleophilic displacements: Haloazoliums</i>	586
3.4.3.9.3	<i>Other reactions</i>	587
3.4.3.10	Metals and Metalloids	588
3.4.3.10.1	<i>Reactions of organometallic nucleophiles</i>	588
3.4.3.10.2	<i>Transition metal-catalyzed cross-coupling reactions</i>	589
3.4.3.11	Fused Heterocyclic Rings	592
3.4.3.12	Substituents Attached to Ring Nitrogen Atoms	592
3.4.3.12.1	<i>N-Linked azole as a substituent</i>	592
3.4.3.12.2	<i>Aryl groups</i>	592

3.4.3.12.3	Alkyl and alkenyl groups	594
3.4.3.12.4	Acyl and carboxy groups	598
3.4.3.12.5	N-Amino groups	600
3.4.3.12.6	N-Nitro groups	601
3.4.3.12.7	N-Hydroxy groups and N-oxides	602
3.4.3.12.8	N-Halo groups	603
3.4.3.12.9	N-Silicon, phosphorus, sulfur, and related groups	603
3.5	Reactivity of Small and Large Rings	605
3.5.1	General Survey	605
3.5.1.1	Neutral Molecules	606
3.5.1.2	Cations	606
3.5.1.3	Anions	606
3.5.1.4	Radicals	606
3.5.2	Thermal and Photochemical Reactions, Not Formally Involving Other Species	607
3.5.2.1	Fragmentation Reactions	607
3.5.2.2	Rearrangements	609
3.5.3	Electrophilic Attack on Ring Heteroatoms	612
3.5.3.1	Protonation	612
3.5.3.2	Complex Formation	614
3.5.3.3	Alkylation, Arylation, and Acylation	614
3.5.4	Nucleophilic Attack on Ring Heteroatoms	616
3.5.5	Nucleophilic Attack on Ring Carbon Atoms	618
3.5.5.1	Reactions of Three-Membered Rings	618
3.5.5.2	Reactions of Four-Membered Rings	623
3.5.5.3	Reactions of Carbonyl Derivatives of Four-Membered Rings	624
3.5.5.4	Large Rings	625
3.5.6	Base Attack on Protons Attached to Ring Atoms	626
3.5.7	Attack by Radicals or Electron-Deficient Species. Oxidation and Reduction	628
3.5.7.1	Reactions with Radicals and Carbenes	628
3.5.7.2	Oxidation	630
3.5.7.3	Reduction	631
3.5.8	Reactions with Cyclic Transition States	632
3.5.8.1	[2 + 4] Cycloadditions	632
3.5.8.1.1	Heterocycles as dienophiles	632
3.5.8.1.2	Heterocycles as dienes	632
3.5.8.2	1,3-Dipolar Cycloadditions	634
3.5.9	Reactivity of Transition Metal Complexes	636
3.5.10	Reactivity of Substituents Attached to Heteroatom or Ring Carbon Atoms	637
3.5.10.1	C-Linked Substituents	637
3.5.10.2	N- and S-Linked Substituents	639
4	Synthesis of Heterocycles	641
4.1	Overview	642
4.1.1	Aims and Organization	642
4.1.2	Ring Formation from Two Components	643
4.1.2.1	By Reaction between Electrophilic and Nucleophilic Centers	643

4.1.2.2	Ring Formation via Cycloaddition	643
4.1.2.2.1	[2 + 2] Cycloadditions	644
4.1.2.2.2	1,3-Dipolar cycloadditions	644
4.1.2.2.3	Diels–Alder reactions	646
4.1.3	Ring Closure of a Single Component	646
4.1.3.1	By Reaction between Electrophilic and Nucleophilic Centers	648
4.1.3.2	Electrocyclic Reactions	648
4.1.3.3	By Radical, Carbene, or Nitrene Intermediates	649
4.1.3.4	By Intramolecular Cycloadditions	649
4.1.4	Modification of an Existing Ring	649
4.1.4.1	Ring Atom Interchange	649
4.1.4.2	Incorporation of New Ring Atoms: No Change in Ring Size	650
4.1.4.3	Ring Expansions	650
4.1.4.4	Ring Contractions	651
4.1.4.5	Ring Closure with Simultaneous Ring Opening	651
4.2	Synthesis of Monocyclic Rings with One Heteroatom	652
4.2.1	Rings Containing No Endocyclic Double Bonds	653
4.2.1.1	From Acyclic Compounds by Concerted Formation of Two Bonds	653
4.2.1.1.1	Three-membered rings	653
4.2.1.1.2	Four-membered rings	657
4.2.1.1.3	Five-membered rings	658
4.2.1.2	From Acyclic Compounds by Formation of One or Two C–Z Bonds	659
4.2.1.2.1	Three-membered rings	659
4.2.1.2.2	Four-membered rings	661
4.2.1.2.3	Five-membered rings	663
4.2.1.2.4	Six-membered rings	664
4.2.1.2.5	Larger rings	665
4.2.1.3	From Acyclic Compounds by Formation of One C–C Bond	666
4.2.1.4	From Carbocyclic Compounds	667
4.2.1.5	From Other Heterocyclic Compounds	668
4.2.1.5.1	Reactions involving ring expansion	668
4.2.1.5.2	Reactions without change in ring size	669
4.2.1.5.3	Ring contraction	670
4.2.2	Rings Containing One Endocyclic Double Bond	671
4.2.2.1	From Acyclic Compounds by Concerted Formation of Two Bonds	671
4.2.2.2	From Acyclic Compounds by Formation of One or Consecutive Formation of Two C–Z Bond (s)	673
4.2.2.2.1	Z Atom component acting as nucleophile	673
4.2.2.2.2	Z Atom component acting as electrophile	674
4.2.2.3	From Acyclic Compounds by Ring-Closing Metathesis	674
4.2.2.4	From Carbocycles	675
4.2.2.5	From Heterocycles	675
4.2.3	Rings Containing Two Endocyclic Double Bonds	676
4.2.3.1	Overview	676
4.2.3.2	Synthesis of Pyrroles, Furans, and Thiophenes by Substituent Introduction or Modification	677
4.2.3.3	Synthesis of Pyrroles, Furans, and Thiophenes from Acyclic Precursors	677
4.2.3.3.1	From C ₄ Z or C ₄ units	677

4.2.3.3.2	From C_3ZC or C_3 and CZ units	682
4.2.3.3.3	From C_2 and ZCC units	683
4.2.3.3.4	From C_2 and CZC units	686
4.2.3.3.5	From two C_2 and Z units	688
4.2.3.4	Synthesis of Pyrans, Dihydropyridines, and their Thio and Oxo Derivatives from Acyclic Precursors	688
4.2.3.4.1	From C_5 units	688
4.2.3.4.2	With C–C bond formation	689
4.2.3.5	Synthesis of Four-, Five-, and Six-Membered Rings from Carbocyclic or Heterocyclic Precursors	691
4.2.3.5.1	With ring expansion	691
4.2.3.5.2	No change in ring size	693
4.2.3.5.3	With ring contraction	694
4.2.3.6	Synthesis of Seven- and Eight-Membered Rings	696
4.2.4	Rings Containing Three Endocyclic Double Bonds	698
4.2.4.1	Synthetic Methods for Substituted Pyridines	698
4.2.4.2	Synthesis of Six-Membered Rings from Acyclic Compounds	698
4.2.4.2.1	From or via pentane-1,5-diones	698
4.2.4.2.2	From pent-2-ene-1,5-diones	698
4.2.4.2.3	Other methods	698
4.2.4.3	Synthesis of Six-Membered Rings from Other Heterocycles	701
4.2.4.3.1	From five-membered rings	701
4.2.4.3.2	From other six-membered rings	701
4.2.4.4	Synthesis of Seven-Membered and Larger Rings	702
4.3	Synthesis of Monocyclic Rings with Two or More Heteroatoms	704
4.3.1	Substituent Introduction and Modification	706
4.3.1.1	Overview	706
4.3.1.2	Substituent Introduction and Modification in Azoles	706
4.3.1.3	Substituent Introduction and Modification in Azines	706
4.3.2	Two Heteroatoms in the 1,2-Positions	707
4.3.2.1	Three-membered Rings	707
4.3.2.2	Four-membered Rings	708
4.3.2.2.1	1,2-Diazetidines	708
4.3.2.2.2	1,2-Oxazetidines	710
4.3.2.2.3	1,2-Thiazetidines	711
4.3.2.2.4	1,2-Dioxetanes	712
4.3.2.2.5	1,2-Oxathietanes	713
4.3.2.2.6	1,2-Dithietanes	713
4.3.2.3	Five-membered Rings: Pyrazoles, Isoxazoles, Isothiazoles, etc.	714
4.3.2.3.1	Synthesis from hydrazine, hydroxylamine, and hydrogen disulfide derivatives	714
4.3.2.3.2	Synthesis by Z–Z bond formation	716
4.3.2.3.3	Other methods from acyclic precursors	718
4.3.2.3.4	From other heterocycles	720
4.3.2.4	Six-membered Rings: Pyridazines, 1,2-Oxazines, etc.	722
4.3.2.4.1	Synthesis from hydrazine or hydroxylamine derivatives	722
4.3.2.4.2	By cycloaddition reactions	724

4.3.2.4.3	<i>Other methods from acyclic precursors</i>	726
4.3.2.4.4	<i>From other heterocycles</i>	727
4.3.2.5	Seven-membered Rings	728
4.3.2.5.1	<i>1,2-Diazepines</i>	728
4.3.2.5.2	<i>1,2-Oxazepines and 1,2-thiazepines</i>	731
4.3.2.5.3	<i>1,2-Dioxepans and 1,2-dithiepanes</i>	731
4.3.3	Two Heteroatoms in the 1,3-Positions	732
4.3.3.1	Four-membered Rings	732
4.3.3.1.1	<i>1,3-Diazetidines</i>	732
4.3.3.1.2	<i>1,3-Oxazetidines</i>	733
4.3.3.1.3	<i>1,3-Thiazetidines</i>	733
4.3.3.1.4	<i>1,3-Dithietanes</i>	734
4.3.3.2	Five-membered Rings: Imidazoles, Oxazoles, Thiazoles, Dithiolium Salts, and Derivatives	735
4.3.3.2.1	<i>Overview</i>	735
4.3.3.2.2	<i>Synthesis from $C_2 + ZCZ'$ components</i>	735
4.3.3.2.3	<i>Synthesis of imidazoles, oxazoles, and thiazoles from acylamino ketones</i>	737
4.3.3.2.4	<i>Other syntheses of imidazoles, oxazoles, thiazoles, dithiolyliums, and oxathiolyliums by cyclization of C_2ZCZ' components</i>	738
4.3.3.2.5	<i>Synthesis of imidazoles, oxazoles, and thiazoles by C–C bond formation or 1,3-dipolar addition</i>	741
4.3.3.2.6	<i>Synthesis of azolinones and reduced rings from acyclic precursors</i>	741
4.3.3.2.7	<i>Synthesis from other heterocycles</i>	745
4.3.3.3	Six-membered Rings	747
4.3.3.3.1	<i>$C_3 + ZCZ'$-type cyclizations</i>	747
4.3.3.3.2	<i>$ZC_3Z + C (5 + 1)$ and $(6 + 0)$ cyclizations</i>	749
4.3.3.3.3	<i>[4 + 2] Cyclizations</i>	750
4.3.3.3.4	<i>Syntheses from other heterocycles</i>	752
4.3.3.4	Seven-membered Rings	754
4.3.3.4.1	<i>1,3-Diazepines</i>	754
4.3.3.4.2	<i>1,3-Oxazepines and 1,3-thiazepines</i>	755
4.3.3.4.3	<i>1,3-Dioxepins and 1,3-dithiepins</i>	757
4.3.4	Two Heteroatoms in the 1,4-Positions	758
4.3.4.1	Six-membered Rings	758
4.3.4.1.1	<i>Pyrazines from acyclic compounds</i>	758
4.3.4.1.2	<i>1,4-Dioxins, 1,4-dithiins, 1,4-oxazines, and 1,4-thiazines</i>	760
4.3.4.1.3	<i>Nonaromatic rings from acyclic compounds</i>	762
4.3.4.1.4	<i>From heterocyclic precursors</i>	762
4.3.4.2	Seven-membered Rings	765
4.3.4.2.1	<i>1,4-Diazepines</i>	765
4.3.4.2.2	<i>1,4-Oxazepines and 1,4-thiazepines</i>	766
4.3.4.2.3	<i>1,4-Dioxepins and 1,4-dithiepins</i>	768
4.3.5	Three Heteroatoms in the 1,2,3-Positions	769
4.3.5.1	Three- and Four-membered Rings	769
4.3.5.2	Five-membered Rings	770
4.3.5.2.1	<i>Formation of a bond between two of the heteroatoms</i>	770

4.3.5.2.2	<i>Other methods</i>	773
4.3.5.3	Six-membered Rings	774
4.3.6	Three Heteroatoms in the 1,2,4-Positions	775
4.3.6.1	Five-membered Rings	775
4.3.6.1.1	<i>From acyclic intermediates containing the preformed Z–Z' bond</i>	775
4.3.6.1.2	<i>From acyclic intermediates by formation of the Z–Z' bond</i>	778
4.3.6.1.3	<i>From heterocyclic precursors</i>	779
4.3.6.1.4	<i>By the 'monocyclic rearrangement'</i>	781
4.3.6.2	Six-membered Rings	782
4.3.6.2.1	<i>1,2,4-Triazines</i>	782
4.3.6.2.2	<i>Rings containing O or S atoms</i>	783
4.3.6.3	Seven-membered Rings	785
4.3.6.3.1	<i>Heteroatoms in the 1,2,4-positions</i>	785
4.3.6.3.2	<i>Seven-membered rings with heteroatoms in the 1,2,5-positions</i>	787
4.3.7	Three Heteroatoms in the 1,3,5-Positions	788
4.3.7.1	<i>s-Triazines</i>	788
4.3.7.2	Compounds Containing O or S Atoms	789
4.3.7.3	Synthesis from Heterocyclic Precursors	791
4.3.7.4	Seven-membered Rings	791
4.3.8	Four or More Heteroatoms	792
4.3.8.1	Five-membered Rings	792
4.3.8.2	Six-membered Rings	795
4.4	Synthesis of Bicyclic Ring Systems Without Ring Junction Heteroatoms	797
4.4.1	Synthesis by Substituent Introduction and Modification	798
4.4.1.1	In the Heterocyclic Ring	799
4.4.1.2	In the Benzene Ring	799
4.4.2	One Heteroatom Adjacent to a Ring Junction	799
4.4.2.1	Three- and Four-Membered Rings	799
4.4.2.1.1	<i>Three-membered rings</i>	799
4.4.2.1.2	<i>Four-membered rings</i>	799
4.4.2.2	Five-Membered Rings	801
4.4.2.2.1	<i>Survey of syntheses for indoles, benzofurans, and benzothiophenes</i>	801
4.4.2.2.2	<i>Ring closure by formation of Z–C(2) bond</i>	801
4.4.2.2.3	<i>Ring closure by formation of ring–C bond</i>	806
4.4.2.2.4	<i>Ring closure by formation of C(2)–C(3) bond</i>	812
4.4.2.2.5	<i>Ring closure by formation of ring–Z bond</i>	814
4.4.2.2.6	<i>From other heterocycles</i>	814
4.4.2.3	Six-Membered Rings	815
4.4.2.3.1	<i>Survey of synthetic methods for quinolines, benzo[b]pyrans, and their derivatives</i>	815
4.4.2.3.2	<i>Ring closure of o-substituted anilines or phenols</i>	815
4.4.2.3.3	<i>Formation of a C–C bond by reaction of a multiple bond with a benzene ring</i>	816
4.4.2.3.4	<i>Synthesis via cycloaddition reactions</i>	820
4.4.2.3.5	<i>Synthesis from other heterocycles</i>	821
4.4.2.4	Seven-Membered and Larger Rings	822

4.4.3	One Heteroatom Not Adjacent to a Ring Junction	823
4.4.3.1	Five-Membered Rings: Isoindoles and Related Compounds	823
4.4.3.2	Six-Membered Rings	825
4.4.3.2.1	<i>Overview of ring syntheses of isoquinolines, benzo[c]pyrans, and their derivatives</i>	825
4.4.3.2.2	<i>Ring closure of an o-disubstituted benzene</i>	826
4.4.3.2.3	<i>From a β-phenethylamine</i>	827
4.4.3.2.4	<i>From a benzylimine</i>	828
4.4.3.3	Seven-Membered and Larger Rings	829
4.4.4	Two Heteroatoms 1,2 to a Ring Junction	829
4.4.4.1	Four-Membered Rings	829
4.4.4.2	Five-Membered Rings	830
4.4.4.2.1	<i>Indazoles</i>	830
4.4.4.2.2	<i>Anthranils, benzisothiazoles, and saccharins</i>	831
4.4.4.3	Six-Membered Rings	832
4.4.4.3.1	<i>Cinnolines</i>	832
4.4.4.3.2	<i>Rings containing O or S atoms</i>	834
4.4.4.4	Seven-Membered Rings	835
4.4.5	Two Heteroatoms 1,3 to a Ring Junction	836
4.4.5.1	Five-Membered Rings	836
4.4.5.1.1	<i>Ring closure of an o-disubstituted benzene or hetarene</i>	836
4.4.5.1.2	<i>Other methods</i>	838
4.4.5.2	Six-Membered Rings	838
4.4.5.2.1	<i>Quinazolines and azinopyrimidines by cyclization procedures</i>	838
4.4.5.2.2	<i>Rings containing O or S atoms</i>	840
4.4.5.2.3	<i>From other heterocycles</i>	841
4.4.5.3	Seven-Membered Rings	842
4.4.5.3.1	<i>Seven-membered rings with heteroatoms 1,3 to a ring junction</i>	842
4.4.5.3.2	<i>Seven-membered rings with heteroatoms 2,4 to a ring junction</i>	844
4.4.6	Two Heteroatoms 1,4 to a Ring Junction	845
4.4.6.1	Quinoxalines and Azinopyrazines	845
4.4.6.2	1,4-Benzoxazines and 1,4-Benzothiazines	846
4.4.6.3	Rings Containing Oxygen and/or Sulfur Atoms	848
4.4.6.4	Synthesis from Heterocyclic Precursors	849
4.4.6.5	Seven-Membered Rings with Two Heteroatoms 1,4 to a Ring Junction	849
4.4.6.5.1	<i>1,4-Benzodiazepines</i>	849
4.4.6.5.2	<i>1,4- and 4,1-Benzoxazepines, 1,4- and 1,5-benzothiazepines, and 1,4-benzodioxepins</i>	850
4.4.6.6	Seven-Membered Rings with Two Heteroatoms 1,5 to a Ring Junction	853
4.4.7	Two Heteroatoms 2,3 to a Ring Junction	854
4.4.7.1	Six-Membered Rings	854
4.4.7.2	Seven-Membered Rings	856
4.4.8	Three or More Heteroatoms	858
4.4.8.1	Five-Membered Heterocyclic Rings	858
4.4.8.2	Six-Membered Heterocyclic Rings	859
4.4.8.2.1	<i>Three heteroatoms in the 1,2,3-positions</i>	859
4.4.8.2.2	<i>Three heteroatoms in the 1,2,4- or 1,3,4-positions</i>	861
4.4.8.2.3	<i>Four heteroatoms</i>	864

4.4.8.3	Seven-Membered and Larger Rings	865
4.4.8.3.1	<i>Heteroatoms 1,2,4 to a ring junction</i>	865
4.4.8.3.2	<i>Heteroatoms 1,2,5 to a ring junction</i>	866
4.4.8.3.3	<i>Heteroatoms 1,3,4 to a ring junction</i>	867
4.4.8.3.4	<i>Heteroatoms 1,3,5 to a ring junction</i>	869
4.4.8.3.5	<i>Four or more heteroatoms</i>	870
4.5	Synthesis of Tri- and Polycyclic Ring Systems Without Ring Junction Heteroatoms	872
4.5.1	Two Adjacent Fused Rings, One Heteroatom	872
4.5.1.1	Five-membered Heterocyclic Ring	872
4.5.1.1.1	<i>Overview of synthetic methods for carbazoles, dibenzofurans, and dibenzothiophenes</i>	872
4.5.1.1.2	<i>Formation of C–C bond</i>	873
4.5.1.1.3	<i>Formation of C–Z bond</i>	875
4.5.1.1.4	<i>Miscellaneous methods</i>	876
4.5.1.2	Six-membered Rings	877
4.5.2	Two Adjacent Fused Rings, Two Heteroatoms	878
4.5.3	Two Nonadjacent Fused Rings, One Heteroatom	880
4.5.4	Two Nonadjacent Fused Rings, Two Heteroatoms	882
4.5.4.1	Phenazines	882
4.5.4.2	Phenoxazines and Phenothiazines	882
4.5.4.3	Dibenzo[1,4]dioxin, Phenoxathiin, and Thianthrene	884
4.5.4.4	Dibenzodiazepins, Dibenzoxepins, and Dibenzothiepins	884
4.5.5	<i>peri</i> -Annulated Heterocyclic Systems	886
4.5.6	Three Fused Rings	887
4.6	Synthesis of Fused Ring Systems with Ring Junction Heteroatoms	889
4.6.1	Formation of Three- or Four-Membered Rings with One N Atom at a Ring Junction	890
4.6.2	Formation of a Five-Membered Ring with One N Atom at a Ring Junction	891
4.6.2.1	No Other Heteroatoms	891
4.6.2.1.1	<i>[5-5] Systems</i>	891
4.6.2.1.2	<i>[5-6] Systems</i>	892
4.6.2.2	One Additional Heteroatom	894
4.6.2.2.1	<i>Pyrazolo-fused systems</i>	894
4.6.2.2.2	<i>Imidazo-fused systems</i>	895
4.6.2.2.3	<i>Thiazolo-fused systems</i>	897
4.6.2.2.4	<i>Oxazolo- and isoxazolo-fused systems</i>	899
4.6.2.3	Two Other Heteroatoms	900
4.6.2.3.1	<i>1,2,4-Triazolo[b]-, 1,2,4-thiadiazolo[b]-, and 1,3,4-thiadiazolo[b]-fused systems</i>	900
4.6.2.3.2	<i>1,2,4-Triazolo[c]- and 1,2,4-thiadiazolo[c]-fused systems</i>	903
4.6.2.3.3	<i>1,2,3-Triazolo[c]-fused systems</i>	904
4.6.2.4	Three Other Heteroatoms: Fused Tetrazoles	904
4.6.3	Formation of a Six-Membered Ring with One N Atom at a Ring Junction	905
4.6.3.1	Ring Formation Using a Three-Atom Fragment	905
4.6.3.2	Ring Formation Using a Two-Atom Fragment	907
4.6.3.3	Ring Formation Using a One-Atom Fragment	908
4.6.3.4	Cycloaddition and Ring Transformation Reactions	909
4.6.3.5	Other Methods	911

4.6.4	Formation of a Seven-Membered Ring with One N Atom at a Ring Junction	911
4.6.5	Two Nitrogen Atoms at a Ring Junction	912
4.6.5.1	Five-Membered Rings	912
4.6.5.2	Six-Membered Rings	914
4.6.6	Sulfur at a Ring Junction	915

1.3

Notes on the Arrangement of the Material in the Handbook

Arrangement of Material in the Structure Chapters

The Structure chapters in Handbook-III follow the same general format as those in the Handbook-II with a few relatively minor variations. Within this format, some sections have been largely rewritten whereas others have new material added with mostly minimum changes. New material has been selected to illustrate principles and trends, or to introduce new developments in the subject. Some material from Handbook-II has been deleted and replaced by examples of more recent work. CHEC-III has been the major source of new material and, in addition to references to the primary literature, relevant sections of CHEC-III are widely cited throughout the chapters.

In Chapter 2.1 a new section on computer-aided techniques has been introduced. This gives an overview of the hierarchy of computational methods available to heterocyclic chemists and a guide to some of the terminology used. This is followed by a glossary of general terms used throughout the structure chapters and an indication of sections where examples can be found.

Chapters 2.2–2.5 cover the structures and related properties of heterocycles according to ring size. Each chapter follows the same general format beginning with a survey of possible structures, their nomenclature, including common names, and an emphasis on rings of special importance. Next, sections on theoretical methods are subdivided into coverage of general trends, illustrated using the results of Hückel and AM1 calculations, followed by descriptions of the results of more sophisticated calculations of molecular properties. Sections on experimentally determined structures (X-ray diffraction and microwave spectroscopy) are then followed by sections on spectroscopic methods (including ^1H , ^{13}C , ^{15}N NMR, IR, and UV) and mass spectrometry. Sections on thermodynamic aspects include discussions of aromaticity and antiaromaticity, and conformations of nonconjugated rings. Each chapter concludes with a discussion of tautomerism, which is subdivided into prototropic and valence tautomerism. As appropriate for each ring category, prototropic tautomerism is further subdivided into annular tautomerism, substituent tautomerism, and ring-chain tautomerism.

Chapter 2.2 covers six-membered heterocycles. Chapters 2.3 and 2.4 cover five-membered rings and their benzo derivatives. In this edition the coverage of the structures and spectroscopic properties of bicyclic 5-5 heterocycles has been increased. Recent developments in the measurement of aromaticity using energetic, structural, and magnetic indices are discussed in Chapter 2.2–2.4 and indices tabulated and compared. Chapter 2.5 covers small and large rings and includes heterocycles that are formally antiaromatic if planar. Throughout the structure chapters, numerical data useful to practicing heterocyclic chemists (e.g., bond lengths, chemical shifts, UV spectra) have been presented in Tables for easy reference.

Arrangement of Material in the Reactivity Chapters

The Reactivity chapters in Handbook-III follow the same general format as in the previous edition with only a few relatively minor variations. The philosophy and principles of the categorization and subdivisions of the Reactivity sections have been retained. These include, where relevant, comparisons of heterocyclic reactivity with the chemistry of benzenoid aromatic compounds and with carbonyl/enol/enamine chemistry. The use of ‘nucleophilic attack on ring- or side-chain hydrogen,’ has been changed to ‘base attack on ring- or side-chain hydrogen,’ the term ‘nucleophile’ being reserved for reactions at carbon (or nitrogen or sulfur).

Reactions of organometallic nucleophiles are reviewed mainly under ‘Reactivity of Substituents: Metals and Metalloids’ – this is a change from the Handbook-II policy of considering these under the reactions of ‘Reactivity of Substituents: Halides.’ Transition metal-catalyzed reactions of halides are considered partly under ‘Reactivity of Substituents: Halides’ and partly in the metalloids sections. Transition metal-catalyzed reactions of stannanes, boronic acids, etc., are considered under ‘Reactivity of Substituents: Metals and Metalloids.’ These areas represent the largest proportion of the additional new material since Handbook-II and are certainly the most important.

Much of the material from Handbook II has been retained, but it was necessary to remove and/or replace substantial portions to accommodate new chemistry and results. The new material is taken from CHEC-III and each item is given its original reference. Most of the older references in Handbook-II, and references to early reviews and to CHEC-II have been removed. Clearly, it was possible to include only a very small fraction of new work from CHEC-III, but it was the aim to summarize representative and important results.

Section 3.1 is a brief overview; Section 3.2 deals with six-membered heterocycles, including those with more than one heteroatom in the ring; Section 3.3 deals with five-membered heterocycles with one heteroatom; Section 3.4 deals with five-membered heterocycles with more than one heteroatom in the ring; Section 3.5 covers small (three- and four-membered) and large (>six) ring heterocycles.

In each of the five sections of Chapter 3, the chemistry is reviewed in the following order: (1) Reactivity of aromatic rings (thermal reactions not involving reagents, substitutions at carbon, additions to nitrogen, metallations); (2) Reactions of nonaromatic compounds (this enormous area, which overlaps extensively with nonheterocyclic chemistry, is reviewed with emphasis on the heterocyclic aspects); (3) Reactions of substituents (with emphasis on situations in which substituents behave somewhat differently when attached to a heterocycle; note that for benzene-fused heterocycles, the benzene ring is treated as a substituent).

Arrangement of Material in the Synthesis Chapters

The Synthesis section (Chapters 4.1–4.6) retains the same general concepts and organization of material as in Handbook-II. Within this format, numerous new synthetic methods have been systematically presented along with the most important previous material from Handbook-II. Preference has been given to the procedures most synthetically useful, essential experimental details, reaction conditions, and original references are provided in our schemes. The relevant sections of CHEC-III, which have been used as the major source of new material, are cited in each subsection of the Synthesis part of Handbook-III.

The main aim of this part of the book is to provide an introduction to the most efficient ways of making a heterocyclic compound, either by using a known method or by analogy with existing methods for related compounds. The organization is in accordance with this aim. The synthesis of a heterocyclic compound can frequently be divided into two parts: ring synthesis, and substituent introduction and modification. The basic principles and experimental methodology for substituent introduction and modification are discussed in the Reactivity sections (Chapters 3.1–3.5); however, brief summaries of these methods with reference to the related sections of the reactivity chapters are also provided in the Synthesis chapters. The major part of the Synthesis section deals with ring synthesis.

The introductory Chapter 4.1 provides an overview of the main types of reactions used in the preparation of heterocyclic rings based upon mechanistic considerations. The material in the following Chapters 4.2–4.6 is organized by types of heterocycle according to increasing number of heteroatoms, size of monocyclic ring, number of fused rings, and type of fused rings. Ring-fused systems with ring junction N- or S-atoms are considered separately from their more numerous analogues with only C-atoms at the ring junctions. Mono-, bi-, and tricyclic systems are classified firstly according to the number and orientation of their heteroatoms and secondly by the degree of unsaturation in the system. Within this main classification, syntheses are further combined in groups as follows: (1) those of related classes of compounds, (2) those from similar precursors, and (3) methods related mechanistically.

1.4

Explanation of the Reference System

As in CHEC-I and CHEC-II references are designated by a number-letter coding of which the first numbers record the year of publication, the next one to three letters denote the journal, and the final numbers give the page. The system is based on that previously used in the following two monographs: (1) A. R. Katritzky and J. M. Lagowski, '*Chemistry of the Heterocyclic N-Oxides*', Academic Press, New York, 1971; (2) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, '*The Tautomerism of Heterocycles*', in '*Advances in Heterocyclic Chemistry*', Supplement 1, Academic Press, New York, 1976, and from Volume 40, 1986 generally in *Advances in Heterocyclic Chemistry*.

A list of journal codes is given in alphabetical order together with the journals to which they refer at the end of this Handbook. In addition a full list of references is provided at the end of the volume. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters. Journal volume numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters. Patents are assigned appropriate three-letter codes.

