

Contents

Preface to the Fifth Edition

P.1 Hazards

P.2 How to Use This Textbook

Acknowledgements

References

Web Site

xix

xxi

xxi

xxii

xxii

xxii

Biography

xxiii

Definitions of Abbreviations

xxv

1 Heterocyclic Nomenclature

1

2 Structures and Spectroscopic Properties of Aromatic Heterocycles

5

2.1 Carbocyclic Aromatic Systems

5

2.1.1 Structures of Benzene and Naphthalene

5

2.1.2 Aromatic Resonance Energy

6

2.2 Structure of Six-Membered Heteroaromatic Systems

7

2.2.1 Structure of Pyridine

7

2.2.2 Structure of Diazines

7

2.2.3 Structures of Pyridinium and Related Cations

8

2.2.4 Structures of Pyridones and Pyrones

8

2.3 Structure of Five-Membered Heteroaromatic Systems

9

2.3.1 Structure of Pyrrole

9

2.3.2 Structures of Thiophene and Furan

10

2.3.3 Structures of Azoles

10

2.3.4 Structures of Pyrrol and Related Anions

11

2.4 Structures of Bicyclic Heteroaromatic Compounds

11

2.5 Tautomerism in Heterocyclic Systems

12

2.6 Mesoionic Systems

12

2.7 Some Spectroscopic Properties of Some Heteroaromatic Systems

13

2.7.1 Ultraviolet/Visible (Electronic) Spectroscopy

13

2.7.2 Nuclear Magnetic Resonance (NMR) Spectroscopy

14

References

17

3 Substitutions of Aromatic Heterocycles

19

3.1 Electrophilic Addition at Nitrogen

19

3.2 Electrophilic Substitution at Carbon

20

3.2.1 Aromatic Electrophilic Substitution: Mechanism

20

3.2.2 Six-Membered Heterocycles

21

3.2.3 Five-Membered Heterocycles

22

3.3	Nucleophilic Substitution at Carbon	24
3.3.1	Aromatic Nucleophilic Substitution: Mechanism	24
3.3.2	Six-Membered Heterocycles	24
3.3.3	Vicarious Nucleophilic Substitution (VNS Substitution)	26
3.4	Radical Substitution at Carbon	27
3.4.1	Reactions of Heterocycles with Nucleophilic Radicals	27
3.4.2	Reactions with Electrophilic Radicals	30
3.5	Deprotonation of <i>N</i> -Hydrogen	30
3.6	Oxidation and Reduction of Heterocyclic Rings	31
3.7	<i>ortho</i> -Quinodimethanes in Heterocyclic Compound Synthesis	31
	References	33
4	Organometallic Heterocyclic Chemistry	37
4.1	Preparation and Reactions of Organometallic Compounds	37
4.1.1	Lithium	37
4.1.2	Magnesium	45
4.1.3	Zinc	47
4.1.4	Copper	48
4.1.5	Boron	48
4.1.6	Silicon and Tin	52
4.1.7	Mercury	54
4.1.8	Palladium	54
4.1.9	Side-Chain Metallation ('Lateral Metallation')	54
4.2	Transition Metal-Catalysed Reactions	56
4.2.1	Basic Palladium Processes	56
4.2.2	Catalysts	59
4.2.3	The Electrophilic Partner; The Halides/Leaving Groups	61
4.2.4	Cross-Coupling Reactions	64
4.2.5	The Nucleophilic (Organometallic) Partner	65
4.2.6	Other Nucleophiles	70
4.2.7	The Ring Systems in Cross-Coupling Reactions	71
4.2.8	Organometallic Selectivity	77
4.2.9	Direct C–H Arylation	79
4.2.10	<i>N</i> -Arylation	83
4.2.11	Heck Reactions	87
4.2.12	Carbonylation Reactions	89
	References	90
5	Methods in Heterocyclic Chemistry	97
5.1	Solid-Phase Reactions and Related Methods	97
5.1.1	Solid-Phase Reactions	97
5.1.2	Solid-Supported Reagents and Scavengers	99
5.1.3	Solid-Phase Extraction (SPE)	100
5.1.4	Soluble Polymer-Supported Reactions	100
5.1.5	Phase Tags	101
5.2	Microwave Heating	103
5.3	Flow Reactors	104
5.4	Hazards: Explosions	105
	References	105

6	Ring Synthesis of Aromatic Heterocycles	107
6.1	Reaction Types Most Frequently Used in Heterocyclic Ring Synthesis	107
6.2	Typical Reactant Combinations	108
6.2.1	Typical Ring Synthesis of a Pyrrole Involving Only C–Heteroatom Bond Formation	108
6.2.2	Typical Ring Synthesis of a Pyridine Involving Only C–Heteroatom Bond Formation	109
6.2.3	Typical Ring Syntheses Involving C–Heteroatom C–C Bond Formations	109
6.3	Summary	111
6.4	Electrocyclic Processes in Heterocyclic Ring Synthesis	112
6.5	Nitrenes in Heterocyclic Ring Synthesis	113
6.6	Palladium Catalysis in the Synthesis of Benzo-Fused Heterocycles	113
	References	114
7	Typical Reactivity of Pyridines, Quinolines and Isoquinolines	115
8	Pyridines: Reactions and Synthesis	125
8.1	Reactions with Electrophilic Reagents	125
8.1.1	Addition to Nitrogen	125
8.1.2	Substitution at Carbon	128
8.2	Reactions with Oxidising Agents	130
8.3	Reactions with Nucleophilic Reagents	131
8.3.1	Nucleophilic Substitution with ‘Hydride’ Transfer	131
8.3.2	Nucleophilic Substitution with Displacement of Good Leaving Groups	133
8.4	Metallation and Reactions of C-Metallated-Pyridines	134
8.4.1	Direct Ring C–H Metallation	134
8.4.2	Metal–Halogen Exchange	137
8.5	Reactions with Radicals; Reactions of Pyridyl Radicals	138
8.5.1	Halogenation	138
8.5.2	Carbon Radicals	138
8.5.3	Dimerisation	138
8.5.4	Pyridinyl Radicals	139
8.6	Reactions with Reducing Agents	139
8.7	Electrocyclic Reactions (Ground State)	140
8.8	Photochemical Reactions	140
8.9	Oxy- and Amino-Pyridines	141
8.9.1	Structure	141
8.9.2	Reactions of Pyridones	142
8.9.3	Reactions of Amino-Pyridines	144
8.10	Alkyl-Pyridines	146
8.11	Pyridine Aldehydes, Ketones, Carboxylic Acids and Esters	148
8.12	Quaternary Pyridinium Salts	148
8.12.1	Reduction and Oxidation	148
8.12.2	Organometallic and Other Nucleophilic Additions	150
8.12.3	Nucleophilic Addition Followed by Ring Opening	152
8.12.4	Cyclisations Involving an α -Position or an α -Substituent	153
8.12.5	<i>N</i> -Dealkylation	153
8.13	Pyridine <i>N</i> -oxides	153
8.13.1	Electrophilic Addition and Substitution	154
8.13.2	Nucleophilic Addition and Substitution	155
8.13.3	Addition of Nucleophiles then Loss of Oxide	155

8.14	Synthesis of Pyridines	156
8.14.1	Ring Synthesis	156
8.14.2	Examples of Notable Syntheses of Pyridine Compounds	165
	Exercises	166
	References	168
9	Quinolines and Isoquinolines: Reactions and Synthesis	177
9.1	Reactions with Electrophilic Reagents	177
9.1.1	Addition to Nitrogen	177
9.1.2	Substitution at Carbon	177
9.2	Reactions with Oxidising Agents	179
9.3	Reactions with Nucleophilic Reagents	179
9.3.1	Nucleophilic Substitution with 'Hydride' Transfer	179
9.3.2	Nucleophilic Substitution with Displacement of Good Leaving Groups	180
9.4	Metallation and Reactions of C-Metallated Quinolines and Isoquinolines	181
9.4.1	Direct Ring C-H Metallation	181
9.4.2	Metal-Halogen Exchange	182
9.5	Reactions with Radicals	182
9.6	Reactions with Reducing Agents	183
9.7	Electrocyclic Reactions (Ground State)	183
9.8	Photochemical Reactions	183
9.9	Oxy-Quinolines and Oxy-Isoquinolines	183
9.10	Amino-Quinolines and Amino-Isoquinolines	185
9.11	Alkyl-Quinolines and Alkyl-Isoquinolines	185
9.12	Quinoline and Isoquinoline Carboxylic Acids and Esters	185
9.13	Quaternary Quinolinium and Isoquinolinium Salts	186
9.14	Quinoline and Isoquinoline N-Oxides	188
9.15	Synthesis of Quinolines and Isoquinolines	188
9.15.1	Ring Syntheses	188
9.15.2	Examples of Notable Syntheses of Quinoline and Isoquinoline Compounds	198
	Exercises	199
	References	200
10	Typical Reactivity of Pyrylium and Benzopyrylium Ions, Pyrones and Benzopyrones	205
11	Pyryliums, 2- and 4-Pyrones: Reactions and Synthesis	209
11.1	Reactions of Pyrylium Cations	209
11.1.1	Reactions with Electrophilic Reagents	209
11.1.2	Addition Reactions with Nucleophilic Reagents	210
11.1.3	Substitution Reactions with Nucleophilic Reagents	212
11.1.4	Reactions with Radicals	212
11.1.5	Reactions with Reducing Agents	212
11.1.6	Photochemical Reactions	212
11.1.7	Reactions with Dipolarophiles; Cycloadditions	213
11.1.8	Alkyl-Pyryliums	213
11.2	2-Pyrones and 4-Pyrones (2 <i>H</i> -Pyran-2-ones and 4 <i>H</i> -Pyran-4-ones; α - and γ -Pyrones)	214
11.2.1	Structure of Pyrones	214
11.2.2	Reactions of Pyrones	214

11.3	Synthesis of Pyryliums	218
11.3.1	From 1,5-Dicarbonyl Compounds	218
11.3.2	Alkene Acylation	219
11.3.3	From 1,3-Dicarbonyl Compounds and Ketones	220
11.4	Synthesis of 2-Pyrones	220
11.4.1	From 1,3-Keto(aldehydo)-Acids and Carbonyl Compounds	220
11.4.2	Other Methods	221
11.5	Synthesis of 4-Pyrones	222
	Exercises	224
	References	225
12	Benzopyryliums and Benzopyrones: Reactions and Synthesis	229
12.1	Reactions of Benzopyryliums	229
12.1.1	Reactions with Electrophilic Reagents	229
12.1.2	Reactions with Oxidising Agents	230
12.1.3	Reactions with Nucleophilic Reagents	230
12.1.4	Reactions with Reducing Agents	231
12.1.5	Alkyl-Benzopyryliums	231
12.2	Benzopyrones (Chromones, Coumarins and Isocoumarins)	232
12.2.1	Reactions with Electrophilic Reagents	232
12.2.2	Reactions with Oxidising Agents	232
12.2.3	Reactions with Nucleophilic Reagents	233
12.3	Synthesis of Benzopyryliums, Chromones, Coumarins and Isocoumarins	237
12.3.1	Ring Synthesis of 1-Benzopyryliums	237
12.3.2	Ring Synthesis of Coumarins	238
12.3.3	Ring Synthesis of Chromones	240
12.3.4	Ring Synthesis of 2-Benzopyryliums	242
12.3.5	Ring Synthesis of Isocoumarins	243
12.3.6	Notable Examples of Benzopyrylium and Benzopyrone Syntheses	243
	Exercises	244
	References	245
13	Typical Reactivity of the Diazine: Pyridazine, Pyrimidine and Pyrazine	249
14	The Diazines: Pyridazine, Pyrimidine, and Pyrazine: Reactions and Synthesis	253
14.1	Reactions with Electrophilic Reagents	253
14.1.1	Addition at Nitrogen	253
14.1.2	Substitution at Carbon	255
14.2	Reactions with Oxidising Agents	255
14.3	Reactions with Nucleophilic Reagents	255
14.3.1	Nucleophilic Substitution with 'Hydride' Transfer	256
14.3.2	Nucleophilic Substitution with Displacement of Good Leaving Groups	256
14.4	Metallation and Reactions of C-Metallated Diazines	259
14.4.1	Direct Ring C-H Metallation	259
14.4.2	Metal-Halogen Exchange	260
14.5	Reactions with Reducing Agents	261
14.6	Reactions with Radicals	261
14.7	Electrocyclic Reactions	261
14.8	Diazine N-Oxides	262

14.9	Oxy-Diazines	263
14.9.1	Structure of Oxy-Diazines	263
14.9.2	Reactions of Oxy-Diazines	264
14.10	Amino-Diazines	271
14.11	Alkyl-Diazines	272
14.12	Quaternary Diazinium Salts	273
14.13	Synthesis of Diazines	273
14.13.1	Pyridazines	274
14.13.2	Pyrimidines	275
14.13.3	Pyrazines	279
14.13.4	Notable Syntheses of Diazines	281
14.14	Pteridines	282
	Exercises	283
	References	284
15	Typical Reactivity of Pyrroles, Furans and Thiophenes	289
16	Pyrroles: Reactions and Synthesis	295
16.1	Reactions with Electrophilic Reagents	295
16.1.1	Substitution at Carbon	296
16.2	Reactions with Oxidising Agents	303
16.3	Reactions with Nucleophilic Reagents	303
16.4	Reactions with Bases	304
16.4.1	Deprotonation of <i>N</i> -Hydrogen and Reactions of Pyrrol Anions	304
16.4.2	Lithium, Sodium, Potassium and Magnesium Derivatives	304
16.5	C-Metallation and Reactions of C-Metallated Pyrroles	305
16.5.1	Direct Ring C-H Metallation	305
16.5.2	Metal-Halogen Exchange	305
16.6	Reactions with Radicals	306
16.7	Reactions with Reducing Agents	306
16.8	Electrocyclic Reactions (Ground State)	307
16.9	Reactions with Carbenes and Carbenoids	308
16.10	Photochemical Reactions	308
16.11	Pyrrol-C-X Compounds	309
16.12	Pyrrole Aldehydes and Ketones	309
16.13	Pyrrole Carboxylic Acids	309
16.14	Pyrrole Carboxylic Acid Esters	310
16.15	Oxy- and Amino-Pyrroles	310
16.15.1	2-Oxy-Pyrroles	310
16.15.2	3-Oxy-Pyrroles	311
16.15.3	Amino-Pyrroles	311
16.16	Synthesis of Pyrroles	311
16.16.1	Ring Synthesis	311
16.16.2	Some Notable Syntheses of Pyrroles	317
	Exercises	319
	References	320
17	Thiophenes: Reactions and Synthesis	325
17.1	Reactions with Electrophilic Reagents	325
17.1.1	Substitution at Carbon	325
17.1.2	Addition at Sulfur	329

17.2	Reactions with Oxidising Agents	330
17.3	Reactions with Nucleophilic Reagents	330
17.4	Metallation and Reactions of C-Metallated Thiophenes	331
17.4.1	Direct Ring C-H Metallation	331
17.4.2	Metal-Halogen Exchange	331
17.5	Reactions with Radicals	333
17.6	Reactions with Reducing Agents	333
17.7	Electrocyclic Reactions (Ground State)	333
17.8	Photochemical Reactions	334
17.9	Thiophene-C-X Compounds: Thenyl Derivatives	334
17.10	Thiophene Aldehydes and Ketones, and Carboxylic Acids and Esters	335
17.11	Oxy- and Amino-Thiophenes	335
17.11.1	Oxy-Thiophenes	335
17.11.2	Amino-Thiophenes	336
17.12	Synthesis of Thiophenes	336
17.12.1	Ring Synthesis	336
17.12.2	Examples of Notable Syntheses of Thiophene Compounds	340
	Exercises	342
	References	342
18	Furans: Reactions and Synthesis	347
18.1	Reactions with Electrophilic Reagents	347
18.1.1	Substitution at Carbon	347
18.2	Reactions with Oxidising Agents	351
18.3	Reactions with Nucleophilic Reagents	352
18.4	Metallation and Reactions of C-Metallated Furans	352
18.4.1	Direct Ring C-H Metallation	352
18.4.2	Metal-Halogen Exchange	353
18.5	Reactions with Radicals	353
18.6	Reactions with Reducing Agents	353
18.7	Electrocyclic Reactions (Ground State)	353
18.8	Reactions with Carbenes and Carbenoids	356
18.9	Photochemical Reactions	356
18.10	Furyl-C-X Compounds; Side-Chain Properties	356
18.11	Furan Carboxylic Acids and Esters and Aldehydes	356
18.12	Oxy- and Amino-Furans	357
18.12.1	Oxy-Furans	357
18.12.2	Amino-Furans	358
18.13	Synthesis of Furans	358
18.13.1	Ring Syntheses	359
18.13.2	Examples of Notable Syntheses of Furans	363
	Exercises	364
	References	365
19	Typical Reactivity of Indoles, Benzo[b]thiophenes, Benzo[b]furans, Isoindoles, Benzo[c]thiophenes and Isobenzofurans	369
20	Indoles: Reactions and Synthesis	373
20.1	Reactions with Electrophilic Reagents	373
20.1.1	Substitution at Carbon	373

20.2	Reactions with Oxidising Agents	385
20.3	Reactions with Nucleophilic Reagents	386
20.4	Reactions with Bases	386
20.4.1	Deprotonation of <i>N</i> -Hydrogen and Reactions of Indolyl Anions	386
20.5	C-Metallation and Reactions of C-Metallated Indoles	388
20.5.1	Direct Ring C-H Metallation	388
20.5.2	Metal-Halogen Exchange	390
20.6	Reactions with Radicals	391
20.7	Reactions with Reducing Agents	392
20.8	Reactions with Carbenes	392
20.9	Electrocyclic and Photochemical Reactions	393
20.10	Alkyl-Indoles	394
20.11	Reactions of Indolyl-C-X Compounds	395
20.12	Indole Carboxylic Acids	396
20.13	Oxy-Indoles	397
20.13.1	Oxindole	397
20.13.2	Indoxyl	398
20.13.3	Isatin	399
20.13.4	1-Hydroxyindole	399
20.14	Amino-Indoles	400
20.15	Aza-Indoles	400
20.15.1	Electrophilic Substitution	401
20.15.2	Nucleophilic Substitution	401
20.16	Synthesis of Indoles	402
20.16.1	Ring Synthesis of Indoles	402
20.16.2	Ring Synthesis of Oxindoles	416
20.16.3	Ring Synthesis of Indoxyls	417
20.16.4	Ring Synthesis of Isatins	418
20.16.5	Synthesis of 1-Hydroxy-Indoles	418
20.16.6	Examples of Notable Indole Syntheses	418
20.16.7	Synthesis of Aza-Indoles	421
	Exercises	422
	References	423
21	Benzo[<i>b</i>]thiophenes and Benzo[<i>b</i>]furans: Reactions and Synthesis	433
21.1	Reactions with Electrophilic Reagents	433
21.1.1	Substitution at Carbon	433
21.1.2	Addition to Sulfur in Benzothiophenes	434
21.2	Reactions with Nucleophilic Reagents	435
21.3	Metallation and Reactions of C-Metallated Benzothiophenes and Benzofurans	435
21.4	Reactions with Radicals	436
21.5	Reactions with Oxidising and Reducing Agents	436
21.6	Electrocyclic Reactions	436
21.7	Oxy- and Amino-Benzothiophenes and -Benzofurans	437
21.8	Synthesis of Benzothiophenes and Benzofurans	437
21.8.1	Ring Synthesis	437
	Exercises	443
	References	443

22	Isoindoles, Benzo[<i>c</i>]thiophenes and Isobenzofurans: Reactions and Synthesis	447
22.1	Reactions with Electrophilic Reagents	447
22.2	Electrocyclic Reactions	448
22.3	Phthalocyanines	449
22.4	Synthesis of Isoindoles, Benzo[<i>c</i>]thiophenes and Isobenzofurans	449
22.4.1	Isoindoles	449
22.4.2	Benzo[<i>c</i>]thiophenes	450
22.4.3	Isobenzofurans	451
	Exercises	452
	References	452
23	Typical Reactivity of 1,3- and 1,2-Azoles and Benzo-1,3- and -1,2-Azoles	455
24	1,3-Azoles: Imidazoles, Thiazoles and Oxazoles: Reactions and Synthesis	461
24.1	Reactions with Electrophilic Reagents	461
24.1.1	Addition at Nitrogen	461
24.1.2	Substitution at Carbon	464
24.2	Reactions with Oxidising Agents	466
24.3	Reactions with Nucleophilic Reagents	466
24.3.1	With Replacement of Hydrogen	466
24.3.2	With Replacement of Halogen	466
24.4	Reactions with Bases	467
24.4.1	Deprotonation of Imidazole <i>N</i> -Hydrogen and Reactions of Imidazolyl Anions	467
24.5	C-Metallation and Reactions of C-Metallated 1,3-Azoles	467
24.5.1	Direct Ring C–H Metallation	467
24.5.2	Metal–Halogen Exchange	468
24.6	Reactions with Radicals	468
24.7	Reactions with Reducing Agents	469
24.8	Electrocyclic Reactions	469
24.9	Alkyl-1,3-Azoles	470
24.10	Quaternary 1,3-Azolium Salts	470
24.11	Oxy- and Amino-1,3-Azoles	471
24.12	1,3-Azole <i>N</i> -Oxides	473
24.13	Synthesis of 1,3-Azoles	473
24.13.1	Ring Synthesis	473
24.13.2	Examples of Notable Syntheses Involving 1,3-Azoles	478
	Exercises	479
	References	480
25	1,2-Azoles: Pyrazoles, Isothiazoles, Isoxazoles: Reactions and Synthesis	485
25.1	Reactions with Electrophilic Reagents	486
25.1.1	Addition at Nitrogen	486
25.1.2	Substitution at Carbon	487
25.2	Reactions with Oxidising Agents	488
25.3	Reactions with Nucleophilic Reagents	488
25.4	Reactions with Bases	488
25.4.1	Deprotonation of Pyrazole <i>N</i> -Hydrogen and Reactions of Pyrazolyl Anions	488

25.5	C-Metallation and Reactions of C-Metallated 1,2-Azoles	489
25.5.1	Direct Ring C-H Metallation	489
25.5.2	Metal-Halogen Exchange	490
25.6	Reactions with Radicals	490
25.7	Reactions with Reducing Agents	490
25.8	Electrocyclic and Photochemical Reactions	491
25.9	Alkyl-1,2-Azoles	492
25.10	Quaternary 1,2-Azolium Salts	492
25.11	Oxy- and Amino-1,2-azoles	493
25.12	Synthesis of 1,2-Azoles	494
25.12.1	Ring Synthesis	494
	Exercises	498
	References	498
26	Benzanellated Azoles: Reactions and Synthesis	503
26.1	Reactions with Electrophilic Reagents	503
26.1.1	Addition at Nitrogen	503
26.1.2	Substitution at Carbon	504
26.2	Reactions with Nucleophilic Reagents	505
26.3	Reactions with Bases	505
26.3.1	Deprotonation of <i>N</i> -Hydrogen and Reactions of Benzimidazolyl and Indazolyl Anions	505
26.4	Ring Metallation and Reactions of C-Metallated Derivatives	505
26.5	Reactions with Reducing Agents	506
26.6	Electrocyclic Reactions	506
26.7	Quaternary Salts	506
26.8	Oxy- and Amino-Benzo-1,3-Azoles	507
26.9	Synthesis	507
26.9.1	Ring Synthesis of Benzo-1,3-Azoles	507
26.9.2	Ring Synthesis of Benzo-1,2-Azoles	509
	References	512
27	Purines: Reactions and Synthesis	515
27.1	Reactions with Electrophilic Reagents	516
27.1.1	Addition at Nitrogen	516
27.1.2	Substitution at Carbon	519
27.2	Reactions with Radicals	521
27.3	Reactions with Oxidising Agents	521
27.4	Reactions with Reducing Agents	521
27.5	Reactions with Nucleophilic Reagents	521
27.6	Reactions with Bases	524
27.6.1	Deprotonation of <i>N</i> -Hydrogen and Reactions of Purinyl Anions	524
27.7	C-Metallation and Reactions of C-Metallated Purines	524
27.7.1	Direct Ring C-H Metallation	524
27.7.2	Metal-Halogen Exchange	525
27.8	Oxy- and Amino-Purines	525
27.8.1	Oxy-Purines	526
27.8.2	Amino-Purines	527
27.8.3	Thio-Purines	529

27.9	Alkyl-Purines	530
27.10	Purine Carboxylic Acids	530
27.11	Synthesis of Purines	530
27.11.1	Ring Synthesis	530
27.11.2	Examples of Notable Syntheses Involving Purines	534
	Exercises	535
	References	536
28	Heterocycles Containing a Ring-Junction Nitrogen (Bridgehead Compounds)	539
28.1	Indolizines	539
28.1.1	Reactions of Indolizines	540
28.1.2	Ring Synthesis of Indolizines	541
28.2	Aza-Indolizines	543
28.2.1	Imidazo[1,2- <i>a</i>]pyridines	543
28.2.2	Imidazo[1,5- <i>a</i>]pyridines	545
28.2.3	Pyrazolo[1,5- <i>a</i>]pyridines	546
28.2.4	Triazolo- and Tetrazolo-Pyridines	547
28.2.5	Compounds with an Additional Nitrogen in the Six-Membered Ring	549
28.3	Quinolizinium and Related Systems	551
28.4	Pyrrolizine and Related Systems	551
28.5	Cyclazines	552
	Exercises	553
	References	553
29	Heterocycles Containing More Than Two Heteroatoms	557
29.1	Five-Membered Rings	557
29.1.1	Azoles	557
29.1.2	Oxadiazoles and Thiadiazoles	569
29.1.3	Other Systems	574
29.2	Six-Membered Rings	574
29.2.1	Azines	574
29.3	Benzotriazoles	579
	Exercises	581
	References	581
30	Saturated and Partially Unsaturated Heterocyclic Compounds: Reactions and Synthesis	587
30.1	Five- and Six-Membered Rings	588
30.1.1	Pyrrolidines and Piperidines	588
30.1.2	Piperideines and Pyrrolines	589
30.1.3	Pyrans and Reduced Furans	590
30.2	Three-Membered Rings	592
30.2.1	Three-Membered Rings with One Heteroatom	592
30.2.2	Three-Membered Rings with Two Heteroatoms	596
30.3	Four-Membered Rings	597
30.4	Metallation	598
30.5	Ring synthesis	599
30.5.1	Aziridines and Azirines	600
30.5.2	Azetidines and β -Lactams	602
30.5.3	Pyrrolidines	602

30.5.4	Piperidines	603
30.5.5	Saturated Oxygen Heterocycles	604
30.5.6	Saturated Sulfur Heterocycles	605
References		606
31	Special Topics	609
31.1	Synthesis of Ring-Fluorinated Heterocycles	609
31.1.1	Electrophilic Fluorination	609
31.1.2	The Balz–Schiemann Reaction	611
31.1.3	Halogen Exchange (Halex) Reactions	612
31.1.4	Ring Synthesis Incorporating Fluorinated Starting Materials	612
31.2	Isotopically Labelled Heterocycles	616
31.2.1	Hazards Due to Radionuclides	616
31.2.2	Synthesis	616
31.2.3	PET (Positron Emission Tomography)	617
31.3	Bioprocesses in Heterocyclic Chemistry	619
31.4	Green Chemistry	620
31.5	Ionic Liquids	620
31.6	Applications and Occurrences of Heterocycles	621
31.6.1	Toxicity	622
31.6.2	Plastics and Polymers	622
31.6.3	Fungicides and Herbicides	623
31.6.4	Dyes and Pigments	623
31.6.5	Fluorescence-Based Applications	624
31.6.6	Electronic Applications	625
References		626
32	Heterocycles in Biochemistry; Heterocyclic Natural Products	629
32.1	Heterocyclic Amino Acids and Related Substances	629
32.2	Enzyme Co-Factors; Heterocyclic Vitamins; Co-Enzymes	630
32.2.1	Niacin (Vitamin B ₃) and Nicotinamide Adenine Dinucleotide Phosphate (NADP ⁺)	631
32.2.2	Pyridoxine (Vitamin B ₆) and Pyridoxal Phosphate (PLP)	631
32.2.3	Riboflavin (Vitamin B ₂)	632
32.2.4	Thiamin (Vitamin B ₁) and Thiamine Pyrophosphate	632
32.3	Porphobilinogen and the 'Pigments of Life'	633
32.4	Ribonucleic Acid (RNA) and Deoxyribonucleic Acid (DNA); Genetic Information; Purines and Pyrimidines	635
32.5	Heterocyclic Natural Products	637
32.5.1	Alkaloids	637
32.5.2	Marine Heterocycles	639
32.5.3	Halogenated Heterocycles	639
32.5.4	Macrocycles Containing Oxazoles and Thiazoles	640
32.5.5	Other Nitrogen-Containing Natural Products	640
32.5.6	Anthocyanins and Flavones	641
References		642
33	Heterocycles in Medicine	645
33.1	Mechanisms of Drug Actions	646
33.1.1	Mimicking or Opposing the Effects of Physiological Hormones or Neurotransmitters	646

33.1.2	Interaction with Enzymes	646
33.1.3	Physical Binding with, or Chemically Modifying, Natural Macromolecules	646
33.2	The Neurotransmitters	647
33.3	Drug Discovery and Development	647
33.3.1	Stages in the Life of a Drug	647
33.3.2	Drug Discovery	649
33.3.3	Chemical Development	649
33.3.4	Good Manufacturing Practice (GMP)	650
33.4	Heterocyclic Drugs	650
33.4.1	Histamine	650
33.4.2	Acetylcholine (ACh)	652
33.4.3	5-Hydroxytryptamine (5-HT)	653
33.4.4	Adrenaline and Noradrenaline	654
33.4.5	Other Significant Cardiovascular Drugs	654
33.4.6	Drugs Affecting Blood Clotting	655
33.4.7	Other Enzyme Inhibitors	656
33.4.8	Enzyme Induction	658
33.5	Drugs Acting on the CNS	658
33.6	Anti-Infective Agents	659
33.6.1	Anti-Parasitic Drugs	659
33.6.2	Anti-Bacterial Drugs	660
33.6.3	Anti-Viral Drugs	661
33.7	Anti-Cancer Drugs	661
33.8	Photochemotherapy	663
33.8.1	Psoralen plus UVA (PUVA) Treatment	663
33.8.2	Photodynamic Therapy (PDT)	664
	References	664
	Index	665