

Detailed Table of Contents

Chapter 1	Introduction	1
1.1	Nomenclature of Heterocycles	1
1.2	Aromaticity of Heterocycles	4
1.3	Importance of Heterocycles in Life	5
1.4	Importance of Heterocycles in Drug Discovery	8
1.4.1	Five-Membered Heterocycles with One Heteroatom	9
1.4.2	Five-Membered Heterocycles with Two Heteroatoms	12
1.4.3	Six-Membered Heterocycles with One Heteroatom	13
1.4.4	Six-Membered Heterocycles with Two Heteroatoms	15
PART I FIVE-MEMBERED HETEROCYCLES WITH ONE HETEROATOM		17
Chapter 2	Pyrroles	18
2.1	Introduction	18
2.2	Reactivity of the Pyrrole Ring	22
2.2.1	Protonation	22
2.2.2	C ₂ Electrophilic Substitution	22
2.2.3	C ₃ Electrophilic Substitution	31
2.2.4	Metalation	34
2.3	Construction of the Pyrrole Rings	34
2.3.1	Knorr Pyrrole Synthesis	34
2.3.2	Paal–Knorr Pyrrole Synthesis	37
2.3.3	Hantsch Pyrrole Synthesis	40
2.3.4	Barton–Zard Reaction	43
2.4	Palladium Chemistry of Pyrroles	44
2.5	Possible Liabilities of Pyrrole-Containing Drugs	46
2.6	Problems	49
2.7	References	51
Chapter 3	Indoles	54
3.1	Introduction	54
3.2	Reactivity of the Indole Ring	58
3.2.1	Protonation	58
3.2.2	C ₃ Electrophilic Substitution	58
3.2.3	C ₂ Electrophilic Substitution	62
3.2.4	Metalation	63
3.3	Construction of the Indole Rings	64
3.3.1	Fischer Indole Synthesis	64
3.3.2	Mori–Ban Indole Synthesis	67

Contents

3.3.3	Larock Indole Synthesis	70
3.3.4	Bischler–Möhlau Indole Synthesis	72
3.3.5	Nenitzescu Indole Synthesis	75
3.3.6	Bartoli Indole Synthesis	77
3.3.7	Batcho–Leimgruber Indole Synthesis	80
3.3.8	Gassman Indole Synthesis	83
3.3.9	Cadogan–Sundberg Indole Synthesis	86
3.4	Oxindole-containing Drug Synthesis	88
3.5	Cross-coupling Reactions for Indoles	91
3.5.1	Palladium-Catalyzed Oxidative Coupling	91
3.5.2	Negishi Coupling	92
3.5.3	Suzuki Coupling	95
3.5.4	Sonogashira Coupling	99
3.5.5	Heck Reaction	100
3.6	Azaindoles	104
3.6.1	Larock Reaction	105
3.6.2	Bartoli Reaction	105
3.6.3	Batcho–Leimgruber Reaction	107
3.6.4	Cadogan–Sundberg Indole Synthesis	108
3.7	Possible Liabilities of Drugs Containing 3-Methylindole	109
3.8	Problems	111
3.9	References	113
 Chapter 4 Furans, Benzofurans, Thiophenes, and Benzothiophenes		
4.1	Introduction	119
4.2	Furans and Benzofurans	126
4.2.1	Reactions of Furans and Benzofurans	126
4.2.2	Furan and Benzofuran Synthesis	137
4.2.3	Synthesis of Furan- and Benzofuran-Containing Drugs	153
4.3	Thiophenes and Benzothiophenes	158
4.3.1	Reactions of Thiophene and Benzothiophene	158
4.3.2	Synthesis of Thiophene and Benzothiophene	171
4.3.3	Synthesis of Thiophene- and Benzothiophene-Containing Drugs	182
4.4	Possible Liabilities of Furan- and Thiophene-Containing Drugs	185
4.5	Problems	187
4.6	References	191

PART II FIVE-MEMBERED HETEROCYCLES WITH TWO OR MORE HETEROATOMS	197
Chapter 5 Pyrazoles, Pyrazolones, and Indazoles	198
5.1 Introduction	198
5.1.1 Basicity and Acidity	201
5.1.2 Tautomerization	201
5.2 Reactivities of the Pyrazole Ring	202
5.2.1 Alkylation of the Pyrazole Ring	202
5.2.2 C4 Electrophilic Substitution	203
5.2.3 C5-Metallation	205
5.3 Construction of the Pyrazole and Indazole Rings	206
5.3.1 Knorr Pyrazole Synthesis	206
5.3.2 Variations of the Knorr Pyrazole Synthesis	210
5.3.3 Pechmann Pyrazole Synthesis	214
5.4 Pyrazolone-containing Drugs	217
5.5 Indazole-containing Drugs	220
5.6 Problems	223
5.7 References	226
Chapter 6 Oxazoles, Benzoxazoles, and Isoxazoles	231
6.1 Introduction	231
6.2 Construction of the Heterocyclic Ring	235
6.2.1 Construction of the Oxazole Ring	235
6.2.2 Construction of the Benzoxazole Ring	241
6.2.3 Construction of the Isoxazole Ring	243
6.3 Reactivity	244
6.3.1 Acid/Base Reactivity	244
6.3.2 Electrophilic Substitution	245
6.3.3 Metalation and Nucleophilic Substitution	245
6.3.4 Pericyclic Reactions	249
6.4 Cross-Coupling Reactions	250
6.4.1 Preparation of Halo- and Trifloyl Oxazoles	250
6.4.2 Stille Coupling	253
6.4.3 Suzuki Coupling	257
6.4.4 Negishi Coupling	261
6.4.5 Sonogashira Coupling	264
6.4.6 Heck Coupling	267
6.5 Selected Reactions of Isoxazoles	269
6.6 Possible Liabilities of Oxazole-Containing Drugs	270
6.7 Problems	271
6.8 References	278

Chapter 7 Thiazoles and Benzothiazoles	283
7.1 Introduction	283
7.1.1 Basicity of Thiazoles	290
7.2 Reactions of the Thiazole Ring	290
7.2.1 Electrophilic Attack at Carbon	290
7.2.2 C-Metalation	292
7.2.3 Alkylation	296
7.2.4 N-Oxidation	298
7.2.5 Cycloaddition	299
7.3 Palladium Chemistry Undergone by Thiazoles and Benzothiazoles	300
7.3.1 Suzuki–Miyaura Reaction	300
7.3.2 Negishi Coupling	302
7.3.3 Heck Reaction	304
7.3.4 Sonogashira Coupling	304
7.3.5 Stille Coupling	306
7.4 Construction of the Thiazole Ring	307
7.4.1 Hantzsch Method	307
7.4.2 Cook–Heilbron Synthesis of Thiazoles	312
7.4.3 Gabriel Synthesis of Thiazoles	314
7.5 Construction of the Benzothiazole Ring	315
7.5.1 From 2-Aminobenzenethiols	315
7.5.2 Hugerschoff Synthesis	316
7.5.3 Jacobson Cyclization	318
7.5.4 Miscellaneous Methods to Form Thiazole and Benzothiazole	320
7.6 Possible Liabilities of Drugs Containing Thiazoles and Benzothiazoles	321
7.7 Thiazoles and Benzothiazoles as Bioisosteres	323
7.8 Problems	325
7.9 References	328
Chapter 8 Imidazoles and Benzimidazoles	333
8.1 Introduction to Imidazole	333
8.2 Reactivity of the Imidazole Ring	335
8.2.1 Nitrogen Alkylation	335
8.2.2 Electrophilic C-Substitution	337
8.2.3 Metallation and Direct Pd-Activation	341
8.3 Construction of the Imidazole Ring	341
8.3.1 Debus	342
8.3.2 Weidenhagen	343
8.3.3 Bredereck	344
8.3.4 Radiszewski	344

8.3.5	van Leusen	344
8.3.6	Use of α -Amido-Ketones	345
8.3.7	Use of DAMN Reagent	346
8.3.8	Fused-Imidazole Rings	347
8.3.9	Miscellaneous Imidazole Ring Construction	349
8.4	Conversion of Imidazolines to Imidazoles	353
8.5	Possible Liabilities of Imidazole-Containing Drugs	353
8.6	Introduction to Benzimidazole	354
8.7	Synthesis of Benzimidazoles: Classical Approaches	357
8.8	Construction of the Benzimidazole Core Using Transition Metal-Mediated Approaches	361
8.8.1	C–N Bond Formation from Aryl Halide	361
8.8.2	C–H Functionalization	366
8.9	Alternative Cyclization Approach Toward Benzimidazoles: Process Route Toward BYK405879	367
8.10	Problems	368
8.11	References	370

Chapter 9 Triazoles and Tetrazoles 373

9.1	Introduction	373
9.2	Reactivity of the Triazole and Tetrazole Ring	375
9.2.1	Substitution of the 1,2,3-Triazole	375
9.2.2	Substitution of the 1,2,4-Triazole	377
9.2.3	Alkylation of Triazole	377
9.2.4	Substitution of the Tetrazole	382
9.2.5	Reactions of 1,2,3-Triazoles and Tetrazoles	382
9.3	Construction of the Triazole Ring	384
9.3.1	Construction of the 1,2,3-Triazole Ring	384
9.3.2	Construction of the 1,2,4-Triazole Ring	387
9.3.3	Construction of the Tetrazole Ring	391
9.4	Possible Liabilities of Triazole-Containing Drugs	392
9.5	Problems	393
9.6	References	394

PART III SIX-MEMBERED HETEROCYCLES WITH ONE HETEROATOM 397

Chapter 10	Pyridines	398
10.1	Introduction	398
10.1.1	Pyridine-Containing Drugs	400
10.1.2	Potential Liabilities for Pyridine-Containing Drugs	401
10.2	Reactivity of the Pyridine Ring	404

	10.2.1 Electrophilic Attack at Nitrogen of the Pyridine Ring	404
	10.2.2 C–C/C–N Cross-Coupling Reactions with Organometallic Reagents	409
10.3	Construction of the Pyridine Ring	425
	10.3.1 Synthesis via Condensation Reactions	425
	10.3.2 Synthesis via Cycloaddition Reactions	437
	10.3.3 Synthesis via Rearrangement Reactions	450
	10.3.4 Synthesis via Transformation of Another Heterocycle	455
10.4.	Problems	457
10.5	References	459
Chapter 11 Quinolines and Isoquinolines		471
11.1	Introduction	471
11.2	Reactivity of the Quinoline and Isoquinoline Ring	474
	11.2.1 Protonation	477
	11.2.2 Electrophilic Addition to the Nitrogen Atom	478
	11.2.3 Electrophilic Substitution at Carbon Atom	480
	11.2.4 Nucleophilic Substitution	483
	11.2.5 Amphiphilic Character of Quinoline- <i>N</i> -Oxides	486
	11.2.6 Metallation of Quinolines and Isoquinolines	487
	11.2.7 Palladium-Catalyzed Oxidative Coupling	488
	11.2.8 Cross-Coupling Reactions	488
11.3	Construction of Quinoline Core	492
	11.3.1 Camps Quinoline Synthesis	493
	11.3.2 Combes Quinoline Synthesis	494
	11.3.3 Conrad–Limpach and Knorr Reactions	496
	11.3.4 Friedlander and Pfitzinger Syntheses	499
	11.3.5 Gould–Jacobs Reaction	503
	11.3.5 Meth–Cohn Quinoline Synthesis	506
	11.3.6 Skraup/Doebner–von Miller Reaction	507
	11.3.7 Modern Methods	510
11.4	Construction of Isoquinoline Core	513
	11.4.1 Bischler–Napieralski Reaction	513
	11.4.2 Pictet–Spengler Reaction	516
	11.4.3 Pictet–Gams Isoquinoline Synthesis	519
	11.4.4 Pomeranz–Fritsch Reaction	521
	11.4.5 Gabriel–Colman Rearrangement	522
	11.4.6 Modern Methods	523
11.5	Possible Liabilities of Drugs Containing Quinoline and Isoquinoline Rings	526
11.6	Problems	527
11.7	References	528

PART IV	SIX-MEMBERED HETEROCYCLES WITH TWO HETEROATOMS	535
Chapter 12 Pyrazines and Quinoxalines 536		
12.1	Introduction	536
12.2	Formation of Diazines	539
12.3	Reactivity of the Molecules	545
12.3.1	Reactivity of the Nitrogen	545
12.3.2	Reactivity of the Diazine Ring	548
12.3.3	Metallation of the Diazine Ring	551
12.4	Coupling Reactions	553
12.4.1	Transition-metal Coupling Reactions	553
12.4.2	Palladium-catalyzed Reactions	556
12.5	Problems	562
12.6	References	565
Chapter 13 Pyrimidines 569		
13.1	Introduction	569
13.2	Construction of the Pyrimidine Ring	573
13.2.1	Synthesis Involving Formation of Two Bonds	573
13.2.2	Synthesis Involving Formation of Three or More Bonds	578
13.2.3	Synthesis of Pyrimidine-Fused Systems	581
13.3	Synthesis of Pyrimidine-Containing Drugs	590
13.3.1	Allopurinol	590
13.3.2	Trimethoprim	591
13.3.3	Imatinib	592
13.3.4	Bosentan	595
13.3.5	Erlotinib	598
13.3.6	Rosuvastatin	600
13.3.7	Sildenafil	603
13.4	Problems	608
13.5	References	611
Chapter 14 Quinazolines and Quinazolones 615		
14.1	Introduction	615
14.2	Reactions of Quinazolines and Quinazolinones	618
14.2.1	Reactions at C4	618
14.2.2	Reactions at C2	622
14.2.3	Metal-Mediated Substitution Reactions	623
14.3	Quinazoline and Quinazolinone Synthesis	625
14.3.1	Bischler Reaction	625
14.3.2	Niementowski Reaction	626

