HANDBOOK OF HETEROCYCLIC CHEMISTRY

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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

1.3
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 ^{1}H, ^{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.