FUNDAMENTALS OF HETEROCYCLIC CHEMISTRY

Importance in Nature and in the Synthesis of Pharmaceuticals

LOUIS D. QUIN
Adjunct Professor, University of North Carolina Wilmington
James B. Duke Professor Emeritus, Duke University
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To our wives, Gyöngyi Szakal Quin and Ann Marie Tyrell,
with deep appreciation for their understanding and support
during the preparation of this book

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PREFACE

FOR WHOM THIS BOOK IS WRITTEN

For some 30 years I taught a graduate-level course in heterocyclic chemistry at Duke University and later at the University of Massachusetts. Then in 1997 I was given the opportunity at the University of North Carolina Wilmington to tailor the level of the course so as to be appropriate for undergraduates who had completed only the basic two-semester course in organic chemistry. This new one-semester course was described as a special topics course and met a curriculum requirement. The course was also open to first-year graduate students working toward the M.S. degree.

This book grew out of the lectures in that course. The subject is of course enormous, and the course had to be designed to introduce an appreciation of the vast number of parent heterocyclic systems and the importance of their derivatives (especially in medicine), both in synthetic and in natural structures, without going into excessive detail. Similarly, fundamental aspects of synthesis of representative ring systems and of their special properties as heterocycles were topics given major attention but again without going into the great detail found in more advanced books on this subject. After the first offering of the course, it was apparent that the students would benefit from a brief review of some of the reactions and properties they had encountered in their basic organic course, before these were applied to heterocyclic systems. Such reviews are included in this book.

The emphasis in this book, then, is to *teach* the elements of heterocyclic chemistry; it is not to serve as a broad reference work, and it is not competitive with the numerous more advanced books in this field. It should be noted, however, that chemists at all levels might find it useful to assist them when first entering the field, as for example those headed to research in medicinal chemistry where heterocycles abound.

A subsequent development was the offering of this course on an online basis for chemists working in pharmaceutical and other chemical industries, using the same material given in the lecture course. This course was designed and executed by my colleague Dr. John A. Tyrell and is available through the University of North Carolina Wilmington.

A solutions manual to the end-of-chapter review exercises is available for academic adopters registering through the book's Wiley website: http://www.wiley.com/WileyCDA/WileyTitle/productCd-0470566698.html.

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Durham, NC

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We are indebted to Dr. Kenneth C. Caster for reviewing the entire manuscript and for making numerous valuable comments.

CHAPTER 1

THE SCOPE OF THE FIELD OF HETEROCYCLIC CHEMISTRY

We must start out by examining what is meant by a heterocyclic ring system. To do this, we must use as examples some structures and their names, but we defer discussion of the naming systems for heterocyclic compounds to Chapter 2.

Heterosubstituted rings are those in which one or more carbon atoms in a purely carbon-containing ring (known as a carbocyclic ring) is replaced by some other atom (referred to as a heteroatom). In practice, the most commonly found heteroatom is nitrogen, followed by oxygen and sulfur. However, many other atoms can form the stable covalent bonds necessary for ring construction and can lead to structures of considerable importance in contemporary heterocyclic chemistry. Of note are phosphorus, arsenic, antimony, silicon, selenium, tellurium, boron, and germanium. In rare cases, even elements generally considered to be metallic, such as tin and lead, can be incorporated in ring systems. In a 1983 report, the International Union of Pure and Applied Chemistry (IUPAC) recognized 15 elements coming from Groups II to IV of the Periodic System capable of forming cyclic structures with carbon atoms.[1]

The compound pyridine is an excellent example of a simple heterocycle. Here, one carbon of benzene is replaced by nitrogen, without

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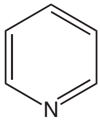
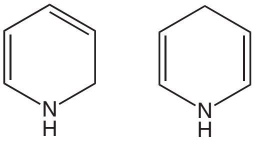
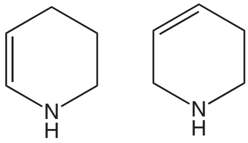
interrupting the classic unsaturation and aromaticity of benzene. Similarly, replacement of a carbon in cyclohexane by nitrogen produces the saturated heterocycle piperidine. Between these extremes of saturation come several structures with one or two double bonds.



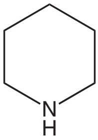
pyridine



dihydro

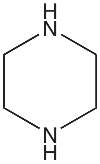


tetrahydro

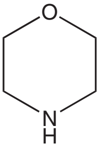


piperidine

Rings may have more than one heteroatom, which may be the same or different, as in the examples that follow.

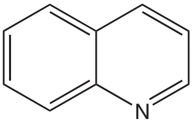


piperazine

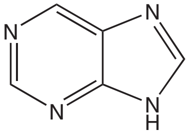


morpholine

To broaden the field, other rings may be fused onto a parent heterocycle. This gives rise to many new ring systems.



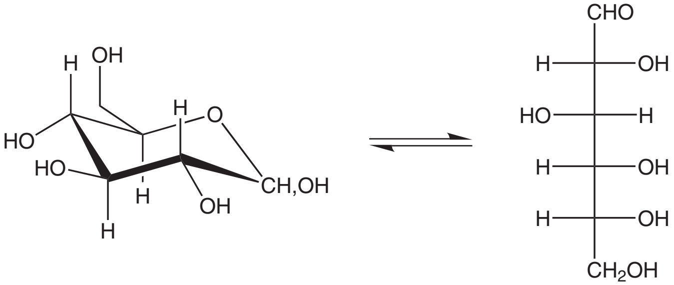
quinoline



purine

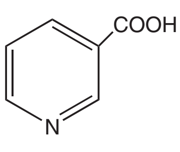
By such bonding arrangements, 133,326 different heterocyclic ring systems had been reported by 1984,[2] and many more have been reported since then. But that is not the whole story; hydrogens on these rings can be replaced by a multitude of substituents, including all the functional groups (and others) common to aliphatic and aromatic compounds. As a result, millions of heterocyclic compounds are known, with more being synthesized every day in search of some with special properties, which we will consider in later chapters. A recent analysis of the organic compounds registered in *Chemical Abstracts* revealed that as of June 2007, there were 24,282,284 compounds containing cyclic structures, with heterocyclic systems making up many of these compounds.[3]

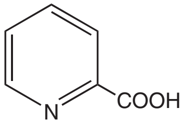
Heterocyclic compounds are far from being just the result of some synthetic research effort. Nature abounds in heterocyclic compounds, many of profound importance in biological processes. We find heterocyclic rings in vitamins, coenzymes, porphyrins (like hemoglobin), DNA, RNA, and so on. The plant kingdom contains thousands of nitrogen heterocyclic compounds, most of which are weakly basic and called alkaloids (alkali like). Complex heterocyclic compounds are elaborated by microorganisms and are useful as antibiotics in medicine. Marine animals and plants are also a source of complex heterocyclic compounds and are receiving much attention in current research efforts. We should even consider that the huge field of carbohydrate chemistry depends on heterocyclic frameworks; all disaccharides and polysaccharides have rings usually of five (called furanose) or six (called pyranose) members that contain an oxygen atom. Similar oxygen-containing ring structures also are important in monosaccharides, where they can be in equilibrium with ring-opened structures, as observed in the case of D-glucose.

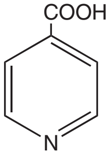


However, in this book we will not give additional attention to carbohydrates, which constitute a field all to themselves.

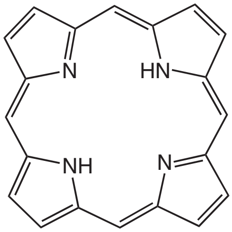
A low concentration of nitrogen and sulfur heterocycles also can be found in various petroleums. Coal was for years the major source of pyridine-based heterocycles, obtained by pyrolysis in the absence of oxygen (destructive distillation). An intriguing new detection of heterocycles in nature has occurred in the field of chemistry of the solar system. Pyridine carboxylic acids have been detected in a meteorite that landed in Canada (near Tagish Lake).[4] Nicotinic acid and its two isomers were isolated along with 12 methylated and other derivatives.







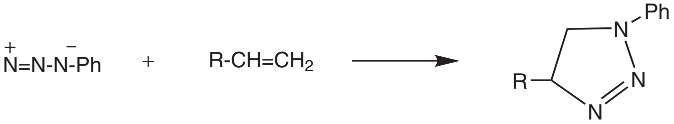
Here, great caution had to be exerted to ensure that contamination by terrestrial compounds had not occurred. One wonders what other heterocycles can be detected (and confirmed) in the current intensive research activity in astrochemistry. In this connection, molecules known as porphyrins that contain the porphin nucleus have been tentatively identified spectroscopically on the moon.



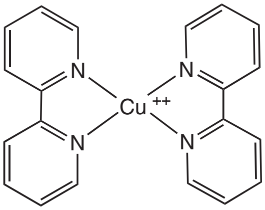
porphin

As we shall find in later chapters, heterocyclic compounds can be synthesized in many ways. Although some of this work is performed to study fundamental properties or establish new synthetic routes, much more is concerned with the practical aspects of heterocyclic chemistry. Thus, many synthetic (as well as natural) compounds are of extreme value as medicinals, agrochemicals, plastics precursors, dyes, photographic chemicals, and so on, and new structures are constantly being sought in research in these areas. These applications are discussed in Chapter 11. Medicinal chemistry especially is associated intimately with heterocyclic compounds, and most of all known chemicals used in medicine are based on heterocyclic frameworks. We shall observe many of the prominent biologically active heterocyclic compounds as this book proceeds to develop the field of heterocyclic chemistry.

Is heterocyclic chemistry somehow different from the much more familiar aliphatic and aromatic chemistry studied in basic organic chemistry courses? Certainly, many reactions used to close rings and to modify ring substituents are common to these fields, and as they are encountered, the reader should review them in a basic organic chemistry textbook. However, some reactions can be found only in heterocyclic chemistry. An excellent example is the cycloaddition of 1,3-dipolar compounds with unsaturated groups, as in the example that follows, which has no counterpart in purely carbon chemistry.



Heterocyclic compounds find use in other synthetic processes. In some cases, heterocyclic ring systems can be opened to give valuable noncyclic compounds useful in synthetic work. Acting through their lone electron pairs or pi-systems, they can be useful ligands in the construction of coordination complexes. An example of a heterocycle frequently used for this purpose is 2,2′-bipyridyl, which is shown here as complexed to cupric ion.



A large amount of literature is available on the subject of heterocyclic chemistry. There are advanced textbooks to help expand the knowledge imparted in this book, and there are expansive collections that cover almost all types of heterocycles and are exhaustive in providing methods of synthesis and treatment of their properties. Information on these books is given in the Appendix of this chapter. Particularly valuable is the series *Comprehensive Heterocyclic Chemistry*,[5] and this is often the first place to go for detailed information on a particular heterocyclic family. The third edition (2008) consists of 15 volumes. Other series cover physical properties or provide detailed reviews of topics or compound families in heterocyclic chemistry. There are also many books on specific topics or types of heterocycles, but these are not listed in the Appendix.

REFERENCES

(1) W. H. Powell, *Pure Appl. Chem*., **55**, 409 (1983).

(2) American Chemical Society, *Ring Systems Handbook*, Chemical Abstracts, Columbus, OH, 1984, p. 2.

(3) A. H. Lipkus, Q. Yuan, K. A. Kucas, S. A. Funk, W. F. Bartelt III, R. J. Schenck, and A. J. Trippe, *J. Org. Chem.*, **73**, 4443 (2008).

(4) S. Pizzarello, Y. Huang, L. Becker, R. J. Poreda, R. A. Nieman, G. Cooper, and M. Williams, *Science*, **293**, 2236 (2001).

(5) A. R. Katritzky, C. A. Ramsden, E. F. V. Screeven, and R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry III*, Elsevier, New York, 2008.

APPENDIX

1. Some textbooks published since 1980 include the following:

   D. I. Davies, *Aromatic Heterocyclic Chemistry*, Oxford University Press, Oxford, UK, 1992.

   T. Eichner and S. Hauptmann, *The Chemistry of Heterocycles*, Second Edition, Wiley-VCH, Weinheim, Germany, 2003.

   T. L. Gilchrist, *Heterocyclic Chemistry*, Third Edition, Prentice Hall, Upper Saddle River, NJ, 1997.

   R. R. Gupta, M. Kumar, and V. Gupta, *Heterocyclic Chemistry*, Vols. 1-2, Springer Verlag, Berlin, Germany, 1998.

   J. A. Joule, *Heterocyclic Chemistry*, Wiley, New York, 2000.

   J. A. Joule and K. Mills, *Heterocyclic Chemistry at a Glance*, Blackwell Publishing, Oxford, UK, 2007.

   A. R. Katritzky, *Handbook of Heterocyclic Chemistry*, Second Edition, Pergamon, Oxford, UK, 2000.

   G. R. Newkome and W.W. Paudler, *Contemporary Heterocyclic Chemistry*, Wiley, New York, 1982.

   A. F. Pozharskii, A. T. Soldatenkov, and A. R. Katritzky, *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine and Agriculture*, Wiley, New York, 1997.

2. Reference works

   A. R. Katritzky, C. A. Ramsden, E. F. V. Screeven, and R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry III*, Elsevier, New York, 2008.

   A. R. Katritzky, *Advances in Heterocyclic Chemistry*, Academic Press, New York, 2009.

   A. R. Katritzky, *Physical Methods in Heterocyclic Chemistry*, Academic Press, New York, 1974.

   R. C. Elderfield, *Heterocyclic Compounds*, Wiley, New York, 1950

   A. Weissberger, *The Chemistry of Heterocyclic Compounds*, Wiley, New York, 2008.

D. H. R. Barton and W. D. Ollis, Editors, *Comprehensive Organic Chemistry*, Vol. 4, Pergamon, Oxford, UK, 1979.

American Chemical Society, *Ring Systems Handbook*, Chemical Abstracts, Columbus, OH, 1984.

G. W. Gribble and J. A. Joule, *Progress in Heterocyclic Chemistry*, Elsevier, Oxford, UK, 2009.

R. R. Gupta, *Topics in Heterocyclic Chemistry*, Springer, Berlin, Germany, 2009.

CHAPTER 2

COMMON RING SYSTEMS AND THE NAMING OF HETEROCYCLIC COMPOUNDS

2.1. GENERAL

Heterocyclic compounds are among the earliest organic compounds to be purified and recognized as discrete substances, although their structures remained unknown for a long time. The science of chemistry was advancing rapidly in the first half of the nineteenth century thanks to the studies of some brilliant chemists. The structure of organic compounds remained a mystery, however, until about 1860 when the work of Archibald Couper of Scotland, Friedrich Kekulé of Germany, and Alexander Butlerow of Russia led to the recognition of the tetrahedral nature of the carbon atom and the devising of the first structural formulas. The structural formulas we use today are most closely associated with the name of Kekulé. These were exciting days in chemistry, as the true nature of organic compounds began to unfold and many new compounds were being made. A brief but informative account of the development of organic chemistry has been given by H. W. Salzberg in a monograph published by the American Chemical Society.[1] There was no systematic naming system in use in these early days, and chemists simply assigned what we now call common names to these compounds.

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By and large, these early heterocyclic compounds were isolated from natural sources; versatile synthetic procedures followed only after many years of research. Some examples of early compounds are as follows:

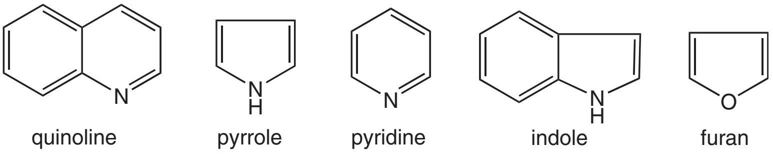
Uric acid (1776, by Scheele from human bladder stones)
Alloxan (1818, by Brugnatelli on oxidation of uric acid)
Quinoline (1834, by Runge from coal distillates, called coal tar)
Melamine (1834, by Liebig by synthesis)
Pyrrole (1834, by Runge in coal tar, but first purified by Anderson in 1858)
Pyridine (1849, by Anderson by pyrolysis of bones)
Indole (1866, by Baeyer from degradation of indigo)
Furan (1870, from wood and cellulose destructive distillation)

Note that not all of the compounds represent the unmodified parent ring; often these were obtained many years later. The structures are given in Table 2.1.

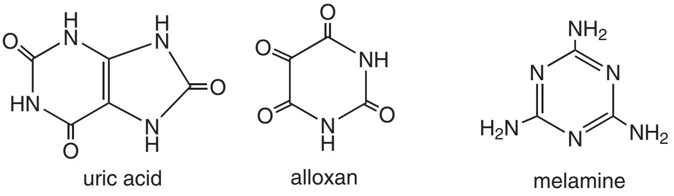
Natural compounds can be complex, beyond the ability of the early chemists to understand them. An excellent example is the first isolation of what proved many years later to be deoxyribonucleic acid (DNA). This was accomplished by Friedrich Miescher in Germany in 1869, who

Table 2.1. Some Early Heterocyclic Compounds of Natural Origins

A. Compounds That Are Parent Rings



B. Compounds With Functional Groups



isolated the substance from cell nuclei. He gave it the name nuclein, which was a precursor of our present name nucleic acid. He recognized that it differed from a protein and contained nitrogen and phosphorus, but it could go no further structurally. Many years later, it was recognized that nuclein was rich in several heterocyclic "bases," and from our present viewpoint, we can claim it as a discovery in heterocyclic chemistry (it also is claimed by phosphorus and carbohydrate chemists), and ultimately, its composition and stereo structure as the famous double helix were established. A fascinating discussion of Miescher's truly pioneering work, which is now generally unrecognized, is given by R. Dahm.[2] We will examine its structure in Chapter 9.

It is no different in heterocyclic chemistry than in other branches of organic chemistry; with millions of compounds to deal with, convenient, generally accepted systems must be available for the naming of the compounds, so that they can be classified and their all-important structures can be deduced universally from their names. Many of the early common names are still in use today (e.g., pyridine, quinoline, and nicotinic acid), but as the great proliferation of heterocyclic compounds commenced in the latter half of the nineteenth century, the need for effective nomenclature systems became clear, and a highly versatile system was created by A. Hantzsch in 1887 and independently by O. Widman in 1888 for the naming of 5- and 6-membered rings containing nitrogen. The system was later applied to different ring sizes and to rings with other heteroatoms. It is now known as the Hantzsch–Widman system and is the basis of the nomenclature used today by the International Union of Pure and Applied (IUPAC) and (with some minor differences) by *Chemical Abstracts*. Cyclic compounds can be considered as derived from a small number of monocyclic, bicyclic, tricyclic, or larger parent rings. The IUPAC rules of nomenclature allow the continued use of well-established common names for some of these fundamental ring systems, but as we will find, there are systematic names also in use for them. Parent rings are known where the number of atoms in the rings can be from 3 to 100, but much of heterocyclic chemistry is centered around rings of 5 or 6 members, just as is true of all-carbon (carbocyclic) systems. The naming of complex heterocycles can be a difficult task and is beyond the purpose of the present discussion. Here, we will concentrate on the simpler cases, but more complete discussions can be found in the published IUPAC rules[3] and also in *Chemical Abstracts*.

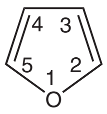
2.2. NAMING SIMPLE MONOCYCLIC COMPOUNDS

The common, accepted names of most of the important monocyclic parents are given in Table 2.2, along with the systematic names from the Hantzsch–Widman naming system. The latter names are derived from the following four rules:

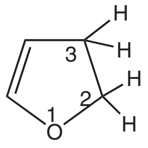
1. The heteroatom is given a name and is used as a prefix: N, aza-; O, oxa-; S, thia-; P, phospha-; As, arsa-; Si, sila-; Se, selena-, B, bora, and so on. The "a" ending is dropped if the next syllable starts with a vowel. Thus "aza-irine" is properly written "azirine."
2. Ring size is designated by stems that follow the prefix: 3-atoms,-ir-; 4-atoms, -et-; 5-atoms, -ol-; 6-atoms, -in-; 7-atoms, -ep-; 8-atoms, -oc-; 9-atoms, -on-; and so on.
3. If fully unsaturated, the name is concluded with a suffix for ring size: 3-atoms, -ene (except -ine- for N); 4-, 5-, and 6-atoms, -e; 7-, 8-, and 9- atoms, -ine.
4. If fully saturated, the suffix is -ane for all ring sizes, except for N, which uses -idine for rings of 3-, 4-, or 5-atoms, and for 6-atoms, a prefix of hexahydro- is used. Also, the name oxane, not oxinane, is used for the 6-membered ring with O present. Other exceptions exist for P, As, and B rings, but they will not be given here.

Table 2.2 shows the application of the above rules to several N, O, and S rings. However, it is preferable and acceptable to use the common names in some cases, and these are included in parentheses.

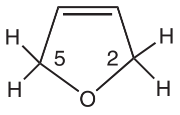
The naming system easily accommodates the case of partial saturation of the double bonds by designating with numbers the positions on the ring where hydrogen has been added. For this purpose, the heteroatom is designated position 1 on the ring, and the numbering proceeds through the site of hydrogenation. If one double bond is removed, the prefix dihydro- is used; with two double bonds removed, it is tetrahydro-. The following examples will make this system clear.



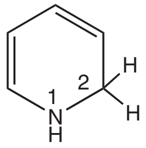
furan



2,3-dihydrofuran



2,5-dihydrofuran



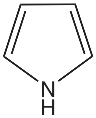
1,2-dihydropyridine

Table 2.2. IUPAC and Common Names for Monocyclic Heterocycles

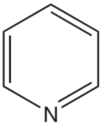
A. Nitrogen Heterocyclic Parents

azirine

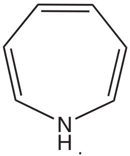
azete



azole
(pyrrole)



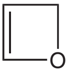
azine
(pyridine)



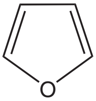
azepine

B. Oxygen Heterocyclic Parents

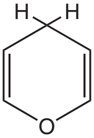
oxirene



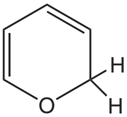
oxete



oxole
(furan)



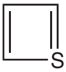
γ-pyran
(1,4-pyran)



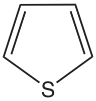
α-pyran
(1,2-pyran)

C. Sulfur Heterocyclic Parents

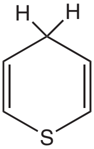
thiirene



thiete



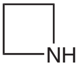
thiole
(thiophene)



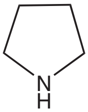
γ-thiopyran

D. Some Saturated Rings

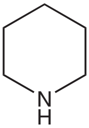
aziridine
(ethyleneimine)



azetidine

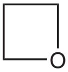


azolidine
(pyrrolidine)

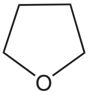


hexahydropyridine
(piperidine)

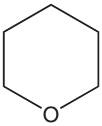
oxirane
(ethylene oxide)



oxetane



oxolane
(tetrahydrofuran)



oxane
(tetrahydropyran)