

## 1

## Heterocyclic Compounds: An Introduction

Julio Álvarez-Builla and José Barluenga

## 1.1

### Heterocyclic Compounds: An Introduction

The *IUPAC Gold Book* describes *heterocyclic compounds* as:

“Cyclic compounds having as ring members atoms of at least two different elements, e.g. quinoline, 1,2-thiazole, bicyclo[3.3.1]tetrasiloxane” [1].

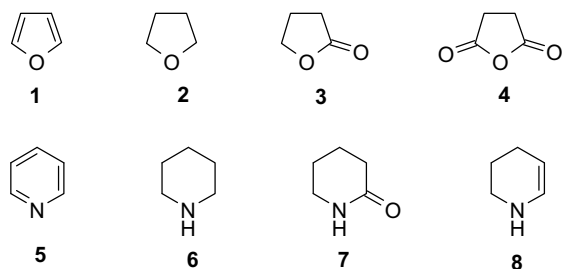
Usually they are indicated as counterparts of *carbocyclic compounds*, which have only ring atoms from the same element. Another classical reference book, the *Encyclopaedia Britannica*, describes a heterocyclic compound, also called a *heterocycle*, as:

“Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulfur” [2].

Although heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen [3]. Since non-carbons are usually considered to have replaced carbon atoms, they are called heteroatoms. The structures may consist of either aromatic or non-aromatic rings.

*Heterocyclic chemistry* is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles.

Heterocyclic derivatives, seen as a group, can be divided into two broad areas: aromatic and non-aromatic. In Figure 1.1, five-membered rings are shown in the first row, and the derivative **1** corresponds to the aromatic derivative, furan, while tetrahydrofuran (**2**), dihydrofuran-2-one (**3**), and dihydrofuran-2,5-dione (**4**) are not aromatic, and their reactivity would be not unlike that expected of an ether, an ester, or



**Figure 1.1** Examples of heterocyclic compounds.

a carboxylic anhydride, respectively. The second row shows six-membered rings, initially in an aromatic form as pyridine (5), while piperidine (6), piperidin-2-one (7), and 1,2,3,4-tetrahydropyridine (8) are not aromatic; their reactivity would not be very different from that expected of an amine, amide, or enamine, respectively. In general, the reactivity of aromatic heterocycles, which is a combination of that expected from an aromatic system combined with the influence of the heteroatoms involved, is usually more complex, while the reactivity of the non-aromatic systems is not too different from the usual non-cyclic derivatives. Thus, most books on heterocyclic chemistry are mainly devoted to the reactivity of aromatic compounds.

Tables 1.1–1.4 indicate models of the heterocyclic derivatives described in these volumes. Table 1.1 shows simple heterocyclic systems of three or four members. In this case, the literature examples are mainly non-aromatic, as indicated in the table, and the expected reactivity is always related to the ring strain present in all of them, which produces a release of energy when they are opened to give aliphatic products.

**Table 1.1** Main three- and four-membered heterocycles.

Ring size	Heteroatom				
	N	O	S	Other	
3	 Aziridine	 Oxirane	 Thiirane		
	 Diaziridine	 Dioxirane		 Oxaziridine	
4	 Azetidine	 Oxetane	 Thietane	 Selenetane	 Phosphetane

Table 1.2 Main five-membered heterocycles.


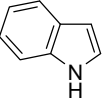

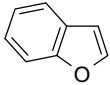







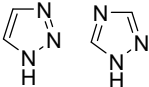
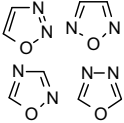
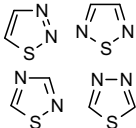

Ring size	Heteroatom				
	N	Benzo	O	Benzo	S
5	 Pyrrole	 Indole	 Furan	 Benzofuran	 Thiophene
5	 Pyrazole		 Isoxazole		 Isothiazole
	 Imidazole		 Oxazole		 Thiazole
	 Triazoles		 Oxadiazoles		 Thiadiazoles
	 Tetrazole				

Table 1.2 indicates five-membered heterocyclic systems, such as pyrrole, furan, their benzo derivatives, and thiophene, and a set of heterocycles with more than one heteroatom, as 1,2-azoles, 1,3-azoles, triazoles, oxa- and thiadiazoles, and tetrazole.

Table 1.3 shows six-membered rings, namely, pyridine, its benzo derivatives quinoline and isoquinoline, the pyrilium cation, and, as in Table 1.2, other common heterocycles with more than one heteroatom, such as diazines, triazines, and tetrazines.

Finally, Table 1.4 shows the simplest seven-membered ring, that is, azepine and its benzo derivative, as well as examples of the nitrogen bridgehead bicyclic systems, pyrrolizine, indolizines, and quinolizinium cation.

Other additional chapters have been included with special systems relevant from different points of view: 2-azetidinones or  $\beta$ -lactams, benzodiazepines, and two general chapters on new materials based on heterocyclic systems and solid phase and combinatorial chemistry related to heterocyclic derivatives.

Table 1.3 Main six-membered heterocycles.


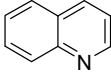

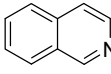










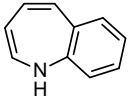
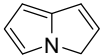
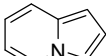
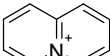
Ring size	Heteroatom		
	N	Benzo	O
6	 Pyridine	 Quinoline	 Pyrilium
	 Isoquinoline		
	   Diazines Pyridazine Pyrimidine Pyrazine		
	   Triazines		
	   Tetrazines		

Table 1.4 Other simple heterocycles.

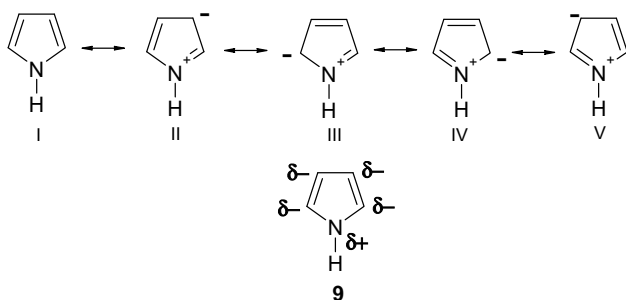
Ring size	Heteroatom		
	N	Benzo	
7	 Azepine	 Benzoazepine	
5-5, 5-6, 6-6	 Pyrroline	 Indolizine	 Quinolizinium

## 1.2

## Structure and Reactivity of Aromatic Five-Membered Systems

As is indicated in most handbooks of heterocyclic chemistry [3, 4], a pictorial valence bond resonance description is used in most chapters, as a simple way to rationalize the reactivity of the most important aromatic heterocycles. Two examples are described in detail as representative of most of the aromatic rings considered: pyrrole as a model of the  $\pi$ -excessive rings, and pyridine as a model of the  $\pi$ -deficient ones.

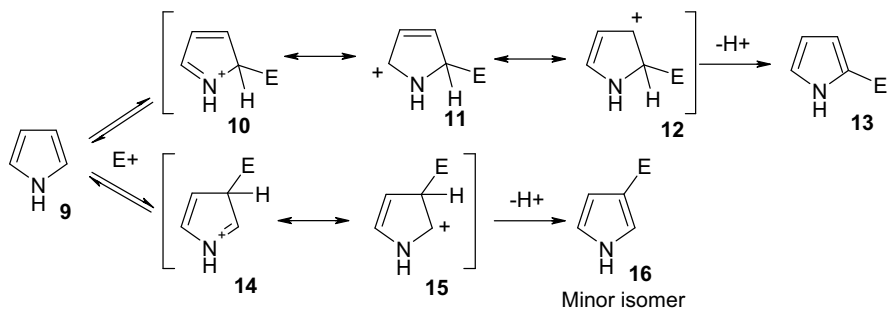
Pyrrole has a structure that is isoelectronic with the cyclopentadienyl anion, but is electrically neutral, having a nitrogen atom with a pair of electrons, which is part of the aromatic sextet, and its resonance hybrid can be represented as a combination of main forms I–V (Scheme 1.1), one without charge, and the others with charge separation. As expected, not all forms contribute equally to the structure of the pyrrole, with the order of importance being  $I > III, IV > II, V$ , that is, the major contribution is produced by the non-charged form, and, of the charged ones, those in which the nitrogen is using its lone pair of electrons. As a combination of all forms, structure **9** indicates how the heteroatom bears a partial positive charge, while the carbon positions show an increase in electronic density, compared with the typical aromatic system, benzene. Thus, a  $\pi$ -excessive system such as pyrrole would be easily attacked by electrophiles and not by nucleophiles.



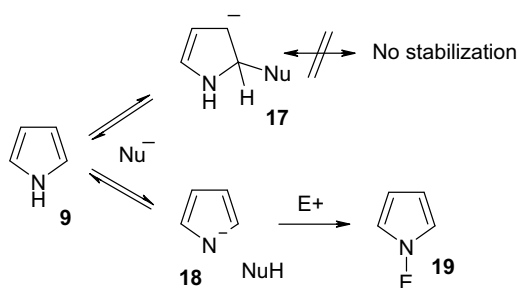
**Scheme 1.1** Resonance hybrids of pyrrole.

Scheme 1.2 indicates how the attack of an electrophile usually proceeds. The major isomer **13** is formed through intermediates **10–11–12**, of which the intermediate **10** contributes most to the stabilization of the intermediate. Alternatively, a minor isomer **16** is produced through the less stable intermediates **14** and **15**.

Alternatively, Scheme 1.3 shows the attack of a nucleophile on pyrrole. Intermediate **17** is not stabilized, and the lone pair of electrons on the heteroatom does not contribute to the progress of the process. The only process that usually can be detected is deprotonation of the N–H bond to generate the pyrrolate (**18**), which can be used to make a bond with a suitable electrophile (i.e., an alkyl halide) to produce the N-substituted pyrrole **19**.



**Scheme 1.2** Electrophilic attack on pyrrole.



**Scheme 1.3** Attack on pyrrole by nucleophiles.

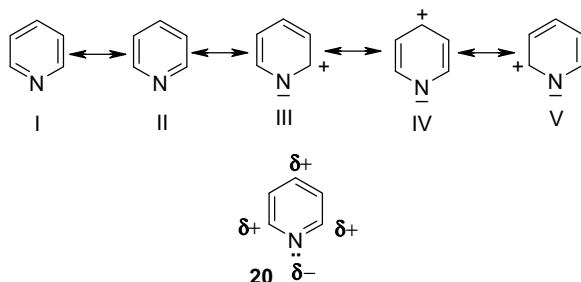
This behavior can be extended with small differences to other  $\pi$ -excessive heterocycles, with the limit due to the existence or not of a N–H bond at position 1. In the case of rings like thiazole or isoxazole, the lack of the acidic bond makes the process 9–18–19 impossible. Attack by radicals or complex organometallic reagents are more complex and are discussed in every chapter.

### 1.3

#### Structure and Reactivity of Aromatic Six-Membered Systems

The structure of pyridine is analogous to that of benzene, with one of the carbons replaced by a nitrogen atom. This produces alterations in the geometry, which is no longer perfectly hexagonal, due to the shorter CN bonds; the existence of an unshared pair of electrons, not related with the aromatic sextet, gives the pyridine basic character, along with a permanent dipole in the ring, due to the electronegative character of the heteroatom compared with carbon.

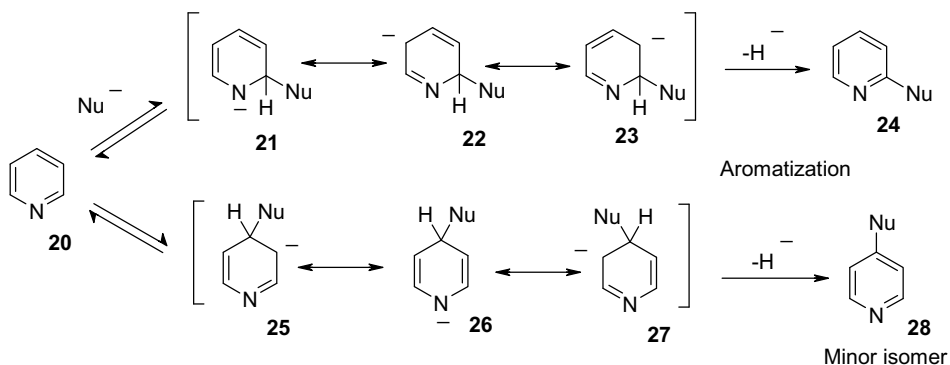
Scheme 1.4 indicates the main canonical forms (I–V) that contribute to the resonance hybrid of the structure of pyridine. Obviously, not all of them contribute equally – the two Kekulé forms I and II, which are not charged, are the more stable



**Scheme 1.4** Resonance hybrids of pyridine.

forms, followed by those in which nitrogen is negatively charged. Other forms can be envisaged, but their contributions can be neglected. Thus, the combination of the main forms can be represented as structure **20**, in which the nitrogen bears a partial negative charge, and positions 2, 4, and 6 are electron deficient; usually, positions 2 and 6 are the most deficient due to the inductive effect produced by the heteroatom. Positions 3 and 5 can be considered neutral, comparable to benzene carbons. Thus, the more characteristic reactivity of the pyridine ring would be against nucleophiles, which would attack the more electron-deficient positions.

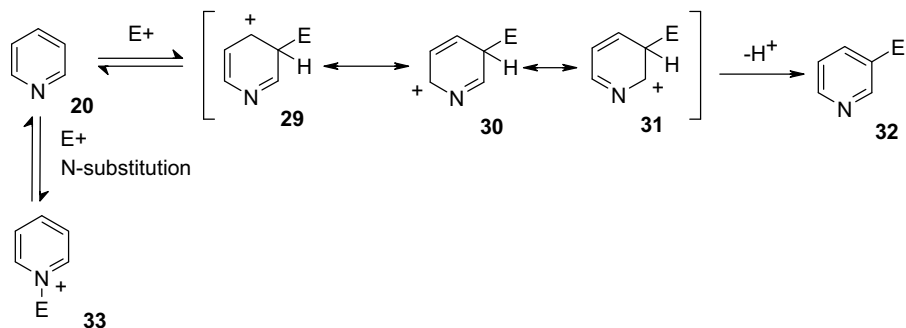
As expected from the structure of pyridine, Scheme 1.5 describes the attack of a nucleophile on the system. The main process goes through intermediates **21–22–23** to produce the major isomer **24**, substituted at position 2. Alternatively, attack can also occur at position 4, through intermediates **25–26–27**, yielding the minor isomer **28**.



**Scheme 1.5** Nucleophilic attack on pyridine.

Scheme 1.6 describes an electrophilic attack on pyridine. The initial attack of the electrophile usually takes place on the pyridine nitrogen. When the attacking species can produce a stable bond, the product should be the pyridinium salt **33**, but when this product is not stable enough the process goes through intermediates **29–30–31**,

that is, by attacking the neutral carbons, to produce the 3-substituted derivative **32**. As a general view, the reactivity of pyridine can be taken as a model for other  $\pi$ -deficient systems, and can be easily extended to diazines, triazines, or pyrilium derivatives. Other processes, like radical attack or reaction with complex organometallic reagents are described in every chapter.



**Scheme 1.6** Electrophilic attack on pyridine.

## 1.4

### Basic Literature on Heterocyclic Compounds

To introduce the recent literature in heterocyclic chemistry, it is necessary to indicate, among the textbooks available [3–6], two of them: one [3] from Eicher and Hauptmann with a highly structured organization, which is simple and efficient and can be used as the basis of a heterocyclic course. The other [4], from Joule and Mills, combines the condensed format with extensive information about the basic heterocycles considered. As reference books, it is necessary to cite the collection *Comprehensive Heterocyclic Chemistry* from Katritzky and colleagues [7–9]; this is associated with the *Handbook of Heterocyclic Chemistry* [10], which is regularly updated with the *Comprehensive* edition. Heterocyclic series are also of great interest, becoming readable collections that allow an update of the literature in the field. *Progress in Heterocyclic Chemistry* [11] describes mostly the advances in every relevant field of heterocyclic chemistry in a yearly volume. The series of monographs *Advances in Heterocyclic Chemistry* [12], which consists of 101 volumes to date, covers in depth very different topics in the field.

Other recent monographs are of interest in various topics on the field, a good guide called *Name Reactions in Heterocyclic Chemistry* has been given by Li [13] and the monograph *Aromaticity in Heterocyclic Compounds* [14] is also a good basic help for heterocyclic chemists, as is the *Synthesis of Heterocycles via Multicomponent Reactions* [15]. Other recent monographs have centered on synthetic techniques such as palladium chemistry [16], chemistry of heterocyclic carbenes [17–19], or synthesis



with microwaves [20]. In addition, a recent monograph on general heterocyclic chemistry emphasizes the importance of heterocyclic compounds in the field of medicinal chemistry and natural products [21].

## References

- IUPAC (2009) IUPAC Compendium of Chemical Terminology - the Gold Book heterocyclic compounds: <http://goldbook.iupac.org/H02798.html> (accessed on).
- Encyclopædia Britannica, Encyclopædia Britannica Online. The official website: heterocyclic compound <http://www.britannica.com> (accessed on).
- Eicher, T. and Hauptmann, S. (2003) *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd edn, Wiley-VCH Verlag GmbH, Weinheim.
- Joule, J.A. and Mills, K. (2000) *Heterocyclic Chemistry*, 4th edn, Blackwell, Oxford.
- Sainsbury, M. (2002) *Heterocyclic Chemistry*, Royal Society of Chemistry, Cambridge.
- Nylund, K., Johansson, P., Puterova, Z., and Krutosikova, A. (2010) *Heterocyclic Compounds: Synthesis, Properties and Applications*, Nova Science Publishers, Hauppauge, New York.
- Katritzky, A.R. and Rees, C.W. (eds) (1984) *Comprehensive Heterocyclic Chemistry I*, Pergamon Press, Oxford.
- Katritzky, A.R., Rees, C.W. and Scriven, F.V. (eds) (1996) *Comprehensive Heterocyclic Chemistry II*, Pergamon Press, Oxford.
- Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., and Taylor, R.J.K. (2008) *Comprehensive Heterocyclic Chemistry III*, Elsevier, Amsterdam.
- Katritzky, A.R., Ramsden, C.A., Joule, J.A., and Zhdankin, V.V. (2010) *Handbook of Heterocyclic Chemistry*, 3rd edn, Elsevier, Amsterdam.
- Gribble, G.W. and Joule, J. (eds) (2009) *Progress in Heterocyclic Chemistry*, Elsevier, Amsterdam.
- Katritzky, A.R. (ed.) (2010) *Advances in Heterocyclic Chemistry*, Elsevier, Amsterdam.
- Li, J.J. (2004) *Name Reactions in Heterocyclic Chemistry*, John Wiley & Sons, Inc., Hoboken, New Jersey.
- Krygowski, T.M. and Cyranski, M.K. (2009) *Aromaticity in Heterocyclic Compounds (Topics in Heterocyclic Chemistry)*, Springer, Heidelberg.
- Orru, R.V.A., Ruijter, E., and Maes, B.U.W. (2010) *Synthesis of Heterocycles via Multicomponent Reactions I (Topics in Heterocyclic Chemistry)*, Springer, Heidelberg.
- Li, J.J. and Gribble, G.W. (2006) *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, 2nd edn, Pergamon, Amsterdam.
- Nolan, S.P. (2006) *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH Verlag GmbH, Weinheim.
- Kühl, O. (2010) *Functionalised N-Heterocyclic Carbene Complexes*, John Wiley & Sons, Ltd., Chichester.
- McGuinness, D. (2009) *Heterocyclic Carbene Complexes: Reaction Chemistry and Catalytic Applications*, Lambert Academic Publishing, Koeln.
- Van der Eycken, E. and Kappe, C.O. (2006) *Microwave-Assisted Synthesis of Heterocycles (Topics in Heterocyclic Chemistry)*, Springer, Heidelberg, [http://www.amazon.com/Comprehensive-Heterocyclic-Chemistry-III-15-/dp/0080449913/ref=sr\\_1\\_26?s=books&ie=UTF8&qid=1280185250&sr=1-26](http://www.amazon.com/Comprehensive-Heterocyclic-Chemistry-III-15-/dp/0080449913/ref=sr_1_26?s=books&ie=UTF8&qid=1280185250&sr=1-26).
- Quin, L.D. and Tyrell, J. (2010) *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*, John Wiley & Sons, Inc., Hoboken, New Jersey.

