

the Chemistry
of Heterocyclic
Compounds

G. M. Badger

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of
Heterocyclic Compounds

G. M. BADGER

*Department of Organic Chemistry, University of Adelaide
Adelaide, South Australia*

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Preface

In the last twenty-five years the various branches of organic chemistry have made enormous progress. In particular the heterocyclic compounds have been extensively studied not only for their intrinsic interest, but also because many natural products, many drugs and medicinals, and many dyestuffs belong to this group. It seems likely that more than a third of the known organic compounds are heterocyclic. The present book has been designed as an introduction to the chemistry of the heterocyclic compounds and it is primarily directed to senior undergraduate and to graduate students.

In view of the size of the field to be covered, considerable thought has been given to the arrangement and to the selection of the material. As far as possible the most important ring systems have been included. However, no two chemists will agree on the relative importance of all the different topics in heterocyclic chemistry, and no doubt many readers will feel that some interesting ring systems have been unduly neglected, or at least have been treated with less consideration than they deserve.

There is an increasing tendency to divorce the chemistry of natural products from the more fundamental studies; but I believe that this approach should be avoided. In this book, therefore, I have taken the opportunity of discussing the chemistry of selected natural products as an adjunct to the discussions on the electronic structures, the reactions, and the syntheses of the different ring systems. The chapter on pyrrole, for example, includes discussions on the evidence for the aromaticity of this ring system, on its various substitution and other reactions, and on the methods available for the synthesis of pyrroles. Finally attention is directed to the structures of the porphyrins and related compounds and to the problem of the biogenesis of these natural products. Key references have been given throughout the book and, wherever possible, attention has been drawn to review articles and sometimes to general articles on the fringe of the actual subject under consideration. No doubt many important papers have been overlooked, and some errors of fact or of misinterpretation probably remain undetected. I should be grateful if readers could let me know of these.

It is a pleasure to record my thanks to many friends who have given largely of their time, and shown an interest in this work. I am particularly grateful to Dr. H. J. RODDA and to Dr. J. W. CLARK-LEWIS for very helpful criticisms of the manuscript. I am also greatly indebted to Mr. W. A. COWAN and Miss M. MITCHELL for their help with the proofs. Finally, I should like to thank Mrs. M. MORITZ and Mrs. J. NILSSON for skilled secretarial help.

G.M.B.

Adelaide, Australia.
June, 1961.

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CHAPTER 1

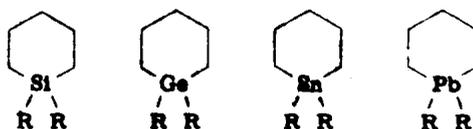
The Nature of Heterocyclic Compounds

Heterocyclic compounds are cyclic organic substances which contain in the ring system at least one atom other than carbon. About a third of the known organic compounds fall in this category, and it would be difficult to exaggerate the importance of this branch of organic chemistry. Many alkaloids, vitamins, antibiotics, and many synthetic medicinals and dyestuffs are heterocyclic, and so also are many substances (such as the nucleic acids) which are most intimately connected with the processes of life.

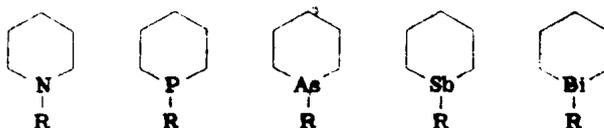
Presumably any atom which can form two covalent bonds is capable of forming a heterocyclic compound. However, with a few exceptions (e.g., mercury, iodine), all the known heterocyclic compounds involve an element from group IVb, group Vb, or group VIb of the periodic table. The most important "heteroatoms" are nitrogen, oxygen, and sulfur.

Carbon is the first member of group IV of the periodic table. Its four valence electrons have the configuration $2s^2, 2p_x, 2p_y$ in the ground state, but in most of its compounds it is tetravalent and uses four equivalent sp^3 hybrid orbitals directed to the corners of a tetrahedron. The higher members of the group, silicon, germanium, tin, and lead, have similar configurations in the ground state (Table 1.1) and are also capable of forming sp^3 hybrid orbitals. It is therefore reasonable to expect that these elements should be capable of replacing carbon in a saturated cyclic system, and this has been found to be the case. All the members of this group are known to form heterocyclic compounds which may be regarded as analogs of cyclohexane (Chart 1.1).

CHART 1.1

Heterocyclic Analogs of Cyclohexane

Group IVb heteroatoms (valence, 4)



Group Vb heteroatoms (valence, 3)



Group VIb heteroatoms (valence, 2)

TABLE 1.1
GROUP IVb ELEMENTS

Element	Symbol	Electro- negativ- ity ^a	Covalent radii ^a		Valence states ^b	Electronic configuration of valence electrons ^a
			Single bond radius	Double bond radius		
Carbon	C	2.5	0.77	0.665	4, 3, 2	2s ² , 2p _x , 2p _y
Silicon	Si	1.8	1.17	1.07	4, 2	3s ² , 3p _x , 3p _y
Germanium	Ge	1.7	1.22	1.12	4, 2	4s ² , 4p _x , 4p _y
Tin	Sn	1.7	1.40	1.30	4, 2	5s ² , 5p _x , 5p _y
Lead	Pb	—	—	—	4, 2	6s ² , 6p _x , 6p _y

^a L. Pauling, "The Nature of the Chemical Bond," 2nd ed. Cornell Univ. Press, Ithaca, New York, 1948.

^b H. Remy, "Treatise on Inorganic Chemistry," (Translated by J. S. Anderson). Elsevier, Amsterdam, 1956.

Unlike the group IVb elements, which have four valence electrons, the group Vb elements have five. The first member of the group is nitrogen, the valence electrons for which have the configuration $2s^2, 2p_x, 2p_y, 2p_z$ in the ground state. The higher members, phosphorus, arsenic, antimony, and bismuth have similar configurations, with higher principal quantum numbers (Table 1.2).

TABLE 1.2
GROUP Vb ELEMENTS

Element	Symbol	Electro- negativ- ity ^a	Covalent radii ^{a, b}		Valence states ^c	Electronic configuration of valence electrons ^a
			Single bond radius	Double bond radius		
Nitrogen	N	3.0	0.74	0.60	1, 2, 3, 4, 5	$2s^2, 2p_x, 2p_y, 2p_z$
Phosphorus	P	2.1	1.10	1.00	1, 3, 4, 5	$3s^2, 3p_x, 3p_y, 3p_z$
Arsenic	As	2.0	1.21	1.11	3, 5	$4s^2, 4p_x, 4p_y, 4p_z$
Antimony	Sb	1.8	1.41	1.31	3, 5	$5s^2, 5p_x, 5p_y, 5p_z$
Bismuth	Bi	—	—	—	3, 5	$6s^2, 6p_x, 6p_y, 6p_z$

^a L. Pauling, "The Nature of the Chemical Bond," 2nd ed. Cornell Univ. Press, Ithaca, New York, 1948.

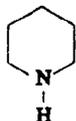
^b V. Schomaker and D. P. Stevenson, *J. Am. Chem. Soc.*, 63, 37 (1941).

^c H. Remy, "Treatise on Inorganic Chemistry," (Translated by J. S. Anderson), Elsevier, Amsterdam, 1956.

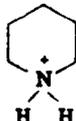
These elements have a usual valence of three, and they form hydrides of the formula XH_3 . Therefore two electrons (the "lone-pair" electrons) are not involved in bond formation. Ammonia is thus saturated with respect to hydrogen, but not to hydrogen ions, and can form an ammonium ion by addition of a proton. However, the basicity of the hydrides of the elements of group Vb, that is, the tendency to form XH_4^+ ions, falls off very rapidly according to the series $NH_3 > PH_3 > AsH_3 > SbH_3 > BiH_3$. Bismuthine is apparently devoid of basic properties.

These elements likewise form heterocyclic compounds analogous to cyclohexane (Chart 1.1). Two valence electrons are involved in the formation of covalent bonds to the adjacent carbon atoms in the ring; one valence electron is involved in the bond to a hydrogen atom or an alkyl or aryl group, and two electrons (the "lone-pair" electrons) are not involved in bond formation. Piperidine, like ammonia, is therefore saturated with respect to hydrogen, but not to hydrogen ions, and can form a piperidinium ion by addition of a proton; in addition, piperidine

derivatives form quaternary salts. Piperidine is, in fact, a very strong base with a pK_a of 11.1.¹



Piperidine



Piperidinium salt



Quaternary salt

The analogous heterocyclic compounds involving the group Vb elements of higher atomic weight have not been extensively investigated, and few examples are known.² These are very much less basic than piperidine derivatives, but it may be noted that several derivatives of this type which involve phosphorus and arsenic are known to form quaternary salts.

The group VIb elements differ from those in group Vb in having one additional valence electron. Oxygen has the electronic configuration $2s^2, 2p_x^2, 2p_y, 2p_z$ in the ground state, and sulfur, selenium, tellurium, and polonium are similar except that their electrons have higher principal quantum numbers (Table 1.3).

TABLE 1.3
GROUP VIb ELEMENTS

Element	Symbol	Electro-negativity ^a	Covalent radii ^{a, b}		Valence states ^c	Electronic configuration of valence electrons ^a
			Single bond radius	Double bond radius		
Oxygen	O	3.5	0.74	0.55	2	$2s^2, 2p_x^2, 2p_y, 2p_z$
Sulfur	S	2.5	1.04	0.94	2, 4, 6	$3s^2, 3p_x^2, 3p_y, 3p_z$
Selenium	Se	2.4	1.17	1.07	2, 4, 6	$4s^2, 4p_x^2, 4p_y, 4p_z$
Tellurium	Te	2.1	1.37	1.27	2, 4, 6	$5s^2, 5p_x^2, 5p_y, 5p_z$
Polonium	Po	—	—	—	2, 4, 6	$6s^2, 6p_x^2, 6p_y, 6p_z$

^a L. Pauling, "The Nature of the Chemical Bond," 2nd ed. Cornell Univ. Press, Ithaca, New York, 1948.

^b V. Schomaker and D. P. Stevenson, *J. Am. Chem. Soc.* **63**, 37 (1941).

^c H. Remy, "Treatise on Inorganic Chemistry" (Translated by J. S. Anderson). Elsevier, Amsterdam, 1956.

¹ A. Albert, *Chem. & Ind.*, p. 51 (1947).

² F. G. Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth and Silicon," Interscience, New York, 1950; F. G. Mann, *Progr. in Organic Chem.* **4**, 217 (1958).

Oxygen has a valence of two and readily forms covalent bonds with carbon. Most of the other elements in this group are known to behave similarly, so that heterocyclic analogs of cyclohexane involving these elements would be expected (Chart 1.1), and some are known.

The above compounds, whether known or unknown, are all saturated, six-membered ring systems containing one heteroatom; but many other arrangements are possible. The ring may contain fewer than or more than six members; the ring may be unsaturated or partly saturated; the ring may contain more than one heteroatom; in the latter case, the heteroatoms may be either alike or different. With all these possibilities, a simple nomenclature is of the greatest importance, and the system recommended by the International Union of Pure and Applied Chemistry has been widely accepted. According to this system, monocyclic compounds containing one or more heteroatoms in a three- to ten-membered ring are named by combining the appropriate prefix or prefixes from Table 1.4 (eliding "a" where necessary) with a stem from Table 1.5. The state of hydrogenation is indicated either in the stem, as shown in Table 1.5, or by the prefixes "dihydro-," "tetrahydro-," etc.¹ Under this system the simple heterocyclic nitrogen compounds are readily named. The three-membered ring system is aziridine;² the four-membered compounds are azete and azetidene³ (the latter ring is present in

TABLE 1.4
HETEROATOMS AND PREFIXES

Element	Group	Valence	Prefix	Element	Group	Valence	Prefix
Oxygen	VIb	2	Oxa	Antimony	Vb	3	Stiba ^a
Sulfur	VIb	2	Thia	Bismuth	Vb	3	Bisma
Selenium	VIb	2	Selena	Silicon	IVb	4	Sila
Tellurium	VIb	2	Tellura	Germanium	IVb	4	Germa
Nitrogen	Vb	3	Aza	Tin	IVb	2	Stanna
Phosphorus	Vb	3	Phospha ^a	Lead	IVb	2	Plumba
Arsenic	Vb	3	Arsa ^a	Mercury	IIB	2	Mercura

^a When immediately followed by "-in" or "-ine," "phospha-" should be replaced by "phosphor-," "arsa-" should be replaced by "arsen-," and "stiba-" should be replaced by "antimon-."

¹ International Union of Pure and Applied Chemistry, "Nomenclature of Organic Chemistry," Butterworths, London, 1958.

² For a review, see J. S. Fruton, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 1, p. 61. Wiley, New York, 1950.

³ For a review, see S. A. Ballard and D. S. Molstrom, in "Heterocyclic Compounds," (R. C. Elderfield, ed.), Vol. 1, p. 78. Wiley, New York, 1950.

penicillin); the five-membered ring systems are azole and azolidine; the six-membered compounds are azine and perhydroazine; and the seven-membered compounds are azepine and perhydroazepine.

TABLE 1.5
STEMS AND RING SIZE

No. of members in the ring	Rings containing nitrogen		Rings containing no nitrogen	
	Unsaturation ^a	Saturation	Unsaturation ^a	Saturation
3	-irine	-iridine	-irene	-irane ^d
4	-ete	-etidine	-ete	-etane
5	-ole	-olidine	-ole	-olane
6	-ine ^b	c	-in ^a	-ane ^d
7	-epine	c	-epin	-epane
8	-ocine	c	-ocin	-ocane
9	-onine	c	-onin	-onane
10	-ecine	c	-ecin	-ecane

^a Corresponding to the maximum number of noncumulative double bonds, the hetero-elements having the normal valences shown in Table 1.4.

^b For phosphorus, arsenic, antimony, see the special provisions of Table 1.4.

^c Expressed by prefixing "perhydro" to the name of the corresponding unsaturated compound.

^d Not applicable to silicon, germanium, tin, and lead. In this case, "perhydro-" is prefixed to the name of the corresponding unsaturated compound.

^e The syllables denoting the size of rings containing 3, 4, or 7-10 members are derived as follows: "ir" from tri, "et" from tetra, "ep" from hepta, "oc" from octa, "on" from nona, and "ec" from deca.

In point of fact, however, many of these compounds have been given trivial names over the years, and many of these will continue to be used. Azole and azolidine, for example, are more commonly known as pyrrole and pyrrolidine, respectively; azine is better known as pyridine, and perhydroazine as piperidine. Many of the benzo derivatives have also been given trivial names. These include indole, carbazole, β -carboline, quinoline, isoquinoline, acridine, and phenanthridine.

Heterocyclic compounds containing oxygen are also easily named according to the International system, but here again many of the most common ring systems are more generally known by trivial names. The three- and four-membered ring systems are oxirane¹ and oxetane,¹

¹ For a review, see S. Winstein and R. B. Henderson, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 1, p. 1. Wiley, New York, 1950.



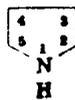
Aziridine



Azete



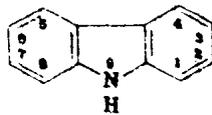
Azetidone

Pyrrole
(Azole)Pyrrolidine
(Azolidine)Pyridine
(Azine)

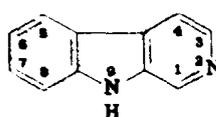
Azepine



Indole



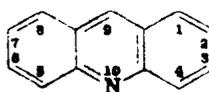
Carbazole

 β -Carboline

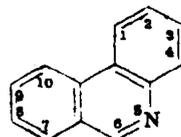
Quinoline



Isoquinoline



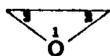
Acridine



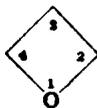
Phenanthridine

respectively. The unsaturated five-membered compound is oxole; but this is generally known as furan, and so on. The situation is similar in the benzo derivatives and also in the heterocyclic derivatives of sulfur. It will be convenient to summarize some of the most commonly known names, and it may be noted that in nearly all these structures the numbering begins with the heteroatom.

When a ring system contains two heteroatoms of the same kind, this is indicated by the prefix "di-," "tri-," etc. placed before the appropriate



Oxirane
(Ethylene oxide)



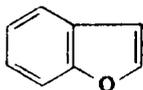
Oxetane
(Trimethylene oxide)



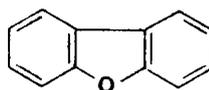
Furan
(Oxole)



Tetrahydrofuran
(Oxolane)



Benzo[b]furan



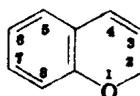
Dibenzo[bd]furan



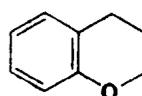
2H-Pyran
(α -Pyran)



4H-Pyran
(γ -Pyran)



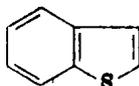
2H-Chromene
(Benzopyran)



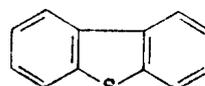
Chroman



Thiophene
(Thiole)



Benzo[h]thiophene



Dibenzo[bd]thiophene

term from Table 1.4. When the heteroatoms are different, two or more prefixes from Table 1.4 must be used, the order of citation being that given in the table (that is, by *descending group number* in the Periodic Table and *increasing atomic number* in the group). The same rule applies



1, 2, 4-Triazine



1, 2-Oxathiolane



1, 3-Thiazole

to numbering: the heteroatom which is highest in Table 1.4 is given the number 1 and the direction of numbering is then chosen to give the lowest numbers to the heteroatoms. These rules are illustrated by 1,2,4-triazine, 1,2-oxathiolane, and 1,3-thiazole.



Pyridazine



Pyrimidine



Pyrazine



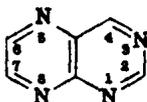
Cinnoline



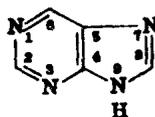
Quinazoline



Quinoxaline



Pteridine



Purine



Imidazole



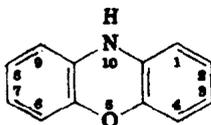
Pyrazole



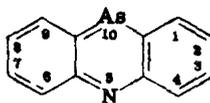
Isoxazole



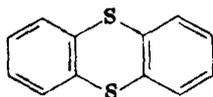
Isothiazole



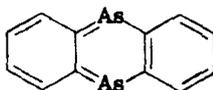
Phenoxazine



Phenarsazine



Thianthrene



Arsanthrene