

An Introduction
to the
**CHEMISTRY OF
HETEROCYCLIC
COMPOUNDS**

R. M. ACHESON

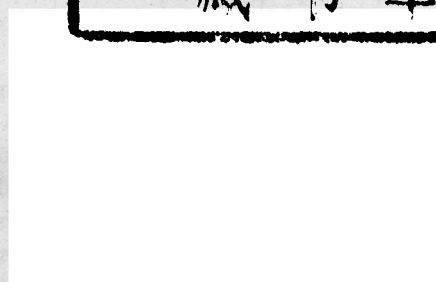
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An Introduction to the Chemistry of Heterocyclic Compounds

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PREFACE

IN recent years many specialised works on specific topics in heterocyclic chemistry have appeared, while at the same time the more general text-books on organic chemistry have not given this important part of the subject the attention it deserves. The specialised works, while valuable to research workers and occasionally to advanced students, contain so much detail that it is virtually impossible for the average undergraduate to separate the wheat from the chaff and to recognise even the major features of heterocyclic chemistry in the time available to him. This time is proportionately too little in most teaching schools when it is considered that heterocyclic chemistry at the moment accounts for about 26% of the organic chemistry papers published. An attempt has been made, in this work, to present to the student a concise account of the more important properties, and chemical reactions, of the basic heterocyclic systems with which he should have some acquaintance. This account, if it is to serve its purpose, cannot be complete. It is more difficult to decide on what to leave out than what to put in, and every writer has his own ideas on this matter. The present author is no exception, in consequence a great deal has been left out, including the sugars and alkaloids, which have been described at the appropriate level elsewhere. However, attempts have been made to include recent pertinent physical data, to use modern electronic and mechanistic concepts where possible, and to deal briefly with biochemical discoveries concerning the metabolism and biosynthesis of some important compounds. A general bibliography has been placed at the end of each chapter, references have been kept to a minimum, and review articles are quoted whenever possible.

I should be most grateful to know of errors, for which I accept sole responsibility and which have inevitably crept into this book in spite of the vigilance of many of my friends and pupils. I thank Professor R. L. Huang, of the University of Malaya, for reading most of the manuscript, and Dr. M. J. T. Robinson and Dr. R. Brettle for reading the complete manuscript and offering most constructive criticism. I am also indebted to Dr. E. Schlittler and Dr. N. F. Taylor for reading the

proofs and for making valuable suggestions. I thank Professor W. C. Gibson, of the University of British Columbia, for encouragement which was much appreciated during the early stages of writing, the staff of the Radcliffe Science Library for their help and co-operation, Mrs. M. Little for the typing, and the officers of Interscience Inc., who have made my task as easy as possible. I also thank my wife for her help at all stages of the book.

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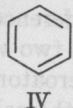
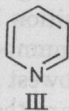
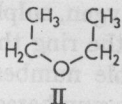
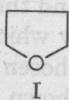
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INTRODUCTION AND NOMENCLATURE

A HETEROCYCLIC compound is one which possesses a cyclic structure with at least two different kinds of atoms in the ring. The most common types, discussed here, contain largely carbon atoms. Nitrogen, oxygen, and sulphur are the most common heteroatoms, but many other elements, including even bromine, can also serve. The heterocyclics containing the less common atoms have been subject to much investigation in recent years, but will not be considered here.

Heterocyclic compounds are very widely distributed in nature, and are essential to life in various ways. Most of the sugars, and their derivatives, including vitamin C, for instance, exist largely in the form of five-membered (furan) or six-membered (pyran) rings containing one oxygen atom. Most members of the vitamin B group possess heterocyclic rings containing nitrogen. One example is vitamin B₆ (pyridoxine), which is a derivative of pyridine essential in amino-acid metabolism. Many other examples of the importance of heterocyclic compounds in biological systems can be given. Most of the alkaloids, which are nitrogenous bases occurring in plants, and many antibiotics, including penicillin, also contain heterocyclic ring systems. A large number of heterocyclic compounds, obtainable only by laboratory syntheses, have valuable properties as chemotherapeutic agents, drugs, dyestuffs, copolymers, etc.

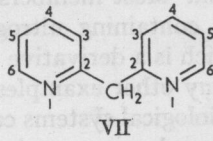
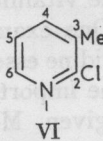
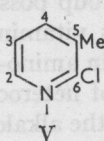
Heterocyclic compounds can be aliphatic or aromatic in character, depending upon their electronic constitution. In general, the aliphatic heterocyclics, where specific effects due to the constitution of the compound are excluded, are very similar chemically to their open-chain aliphatic analogues. For instance, tetrahydrofuran (I) has many properties characteristic of diethyl ether (II). In a similar way the



aromatic heterocyclic compounds have many properties resembling their aromatic carbocyclic analogues, a specific example being a comparison of pyridine (III) and benzene (IV). In general, many well-developed syntheses of aromatic heterocyclic rings are available in

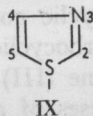
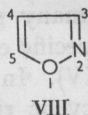
contrast to the benzene series, where very few practical syntheses of the aromatic ring itself are known. This is because while the parent compound, benzene, is readily available and easy to substitute, and in consequence direct syntheses of the ring have attracted little attention, most unsubstituted heterocyclic systems are either difficult to obtain or are not susceptible to substitution.

There are a number of conventions, concerning the numbering of the atoms and substituents in simple heterocyclic rings, which are generally accepted and are used by *Chemical Abstracts*, the world's most important and useful chemical abstract journal and index. The atoms of a simple heterocyclic ring are numbered from the heteroatom, which is counted as one. Substituents are given the lowest possible numbers and then are arranged in alphabetical order. For example, the chloromethylpyridine shown could be numbered and described as 5-methyl-6-chloro-pyridine (V), but it is better numbered the other way round and called 2-chloro-3-methyl-pyridine (VI). It should be found under the last name in most chemical indexes. In *Chemical Abstracts* it would be



found under "pyridine, 2-chloro-3-methyl-", as derivatives are indexed under what is arbitrarily considered the "parent" part of the molecule. Compound VI is therefore not usually known as a derivative of methane; it could be called 3-(2-chloropyridyl)methane. However, in the case of VII, when the pyridine ring might be considered as "parent" and the compound named 2-(2-pyridylmethyl)pyridine, it is customary to treat the compound as a derivative of methane and to name it bis-2-pyridylmethane. Because of difficulties of this sort it is always advisable to look up the several alternative names, when ambiguity exists in the first instance, when conducting a literature search.

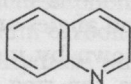
Where the heterocyclic ring contains more than one heteroatom the order of preference for position 1 is oxygen, sulphur, and then nitrogen. If there are two ways of numbering the ring the way which gives the second heteroatom the lowest possible number is chosen. Isoxazole (VIII) and thiazole (IX) are therefore numbered as shown below.



Nomenclature and numbering become more complicated for condensed or fused-ring systems, where a part of one ring is also a part of another. Generic terminology showing the genesis of the structures may be used. On this basis, the structure XI, usually known by the trivial name of quinoline, may be called 2,3-benzopyridine, showing that a benzene ring has been fused on to the 2,3 side of the pyridine ring (X). Another system which is commonly used is to label the side of the heterocyclic system—a, b, c, . . . as shown for pyridine (XII), starting from the atom number one. Structure XI can then be called benzo-



X



XI



XII

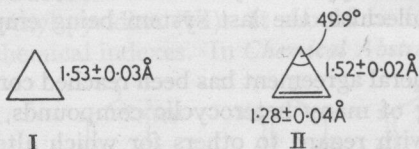
[b]pyridine. These types of systematic nomenclatures are often used for complex molecules, the last system being employed by *Chemical Abstracts*.

Although general agreement has been reached concerning the naming and numbering of many heterocyclic compounds, agreement has not been reached with regard to others for which alternative names and numberings are used. This can lead to much difficulty in the use of original literature. It is therefore advisable to ascertain at an early stage which name is in vogue for the compound in the particular journal, when making a search, for the name can change from journal to journal, and occasionally different names are used for the same compound in the same journal. The *Ring Index* (Patterson and Capell, A.C.S. Monograph No. 84, Reinhold, New York, 1940) is a most useful compilation of mainly heterocyclic ring systems with their alternative names and numbers. It is often very useful to consult this reference work before making a search for less common heterocyclic compounds in the literature.

CHAPTER I

HETEROCYCLIC ANALOGUES OF CYCLOPROPANE

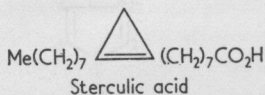
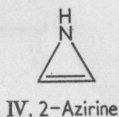
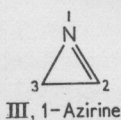
ALL THREE-MEMBERED rings have one major property in common—a strained ring which confers great reactivity on the compounds in comparison with their open-chain analogues. This strain is reflected in the compression of the normal bond angles and by a shortening of the bond lengths from normal, as is shown by modern physical methods. The presence of a double bond in the ring increases the strain, and the molecular dimensions of cyclopropane (I) and cyclopropene (II) are now given for comparison with those of the heterocyclic compounds



described in this chapter. The bonds between the atoms are drawn straight, although it is suspected that a bent line in the form of an arc would better represent the electronic distribution in these molecules¹. Three-membered rings involving nitrogen, oxygen, or sulphur as heteroatoms are much more easily opened than cyclopropane, as the heteroatoms facilitate the attack of both anionic and cationic reagents. The synthesis of three-membered heterocyclic rings from appropriate three-atom intermediates is on the whole quite easy, for although the “strain energy” of the molecule must be provided, the atoms which must combine are largely oriented so that cyclisation is preferred to intermolecular reaction and polymerisation.

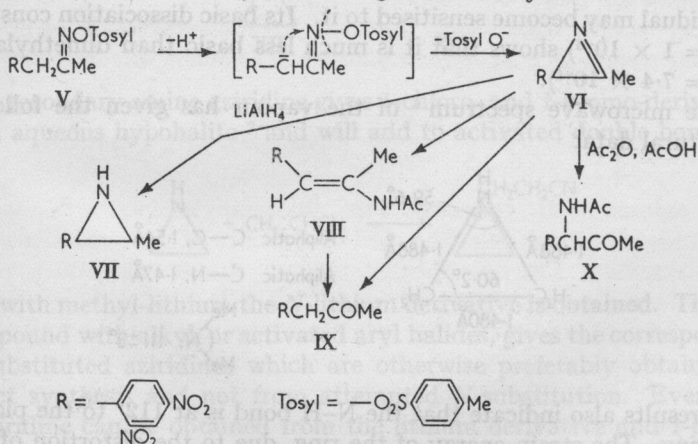
1. AZIRINE

One of the simplest heterocyclic compounds is the hypothetical azirine, or azacyclopentene. It could have structures III or IV, and is yet unknown, although some complex derivatives of 1-azirine have been described and their structures adequately confirmed.



Azirine is a nitrogen analogue of cyclopropene, one derivative of which, sterculic acid, has been found in nature. No physical measurements have yet been reported on the azirine ring, which from classical considerations must be even more strained than that of the saturated aziridine (ethylenimine, p. 6).

Neber in 1932 isolated an unstable intermediate in one of his syntheses of α -aminoketones from oxime 4-toluenesulphonyl derivatives. He gave an azirine structure (VI) to the intermediate. Cram and Hatch² recently confirmed this structure and extended the work. Treatment of the oxime 4-toluenesulphonate [V, $R = C_6H_3(NO_2)_2$] with cold pyridine followed by sodium carbonate gave the azirine (VI). This with acetic acid and acetic anhydride was converted to the acylamino-ketone (X) of Neber, which can also be obtained from the oxime derivative (V) by successive treatment with pyridine and acetic acid-acetic anhydride. Hydrogenation of the azirine over Raney nickel, followed by purification, gave 2,4-dinitrophenylacetone (IX) presumably via the imine. With palladium on charcoal as catalyst in acetic anhydride both *cis* and *trans* isomers of VIII were obtained, and both isomers on hydrolysis again gave 2,4-dinitrophenylacetone. Reduction of the azirine with lithium aluminium hydride also gave a small yield of the aziridine

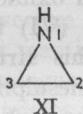


(VII) which was characterised. It is of interest that the nitro groups were not affected by the reagents which reduced the three-membered ring. These reactions, coupled with the confirmatory infrared and ultra-violet absorption spectra of the compounds, leave no doubt as to the correctness of the azirine structure. Some attempts to prepare azirines lacking the nitro groups from oxime 4-toluenesulphonates and potassium ethoxide gave other products (p. 11).

2. AZIRIDINE

A. Introduction

Dihydroazirine (XI), better known as aziridine or ethylenimine and occasionally as azacyclopropane, was first obtained by Gabriel in 1888, although its structure as a cyclic compound was first recognised by

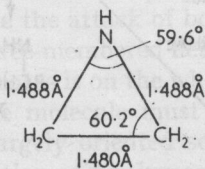


Markwald in 1900. Interest in ethylenimine and its derivatives has increased greatly in recent years, and these compounds have much academic and industrial importance today.

B. Physical Properties and Structure

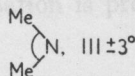
Aziridine is a colourless liquid with a strong ammoniacal smell. It is miscible with water and boils at 56° . It is strongly caustic to the skin, and it should always be used under a hood (*cf.* p. 14). Inhalation of the vapour causes acute inflammation of the eyes, nose, and throat, and an individual may become sensitised to it. Its basic dissociation constant³ ($K_b = 1 \times 10^{-6}$) shows that it is much less basic than dimethylamine ($K_b = 7.4 \times 10^{-4}$).

The microwave spectrum⁴ of the vapour has given the following structural data:



Aliphatic C—C, 1.54 Å

Aliphatic C—N, 1.47 Å



The results also indicate that the N—H bond is at 112° to the plane of the ring. The strain energy of the ring, due to the distortion of most of the bond angles and distances from normal, has been estimated⁵ approximately as 14 kcal./mole from combustion data. The strain in the ring is also reflected in the change of the C—H bending frequency in the infrared⁶ from normal (1465 cm^{-1}) to 1475 cm^{-1} , and the N—H vibration frequency (1441 cm^{-1}) is lower than normally encountered in secondary amines (1460 cm^{-1}). These physical data completely confirm the much earlier deduction, made from the many facile ring-opening