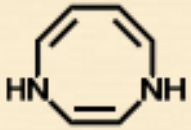
OTHER AROMATIC HETEROCYCLES

➔ Monocyclic heterocycles:

- Can be pyridine-like (C=heteroatom double bond) or pyrrol-like (heteroatom participates with two electrons in the π system.
- Most frequently found: *N*-heterocycles

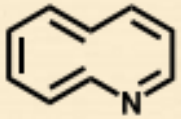
Pyrrol-like



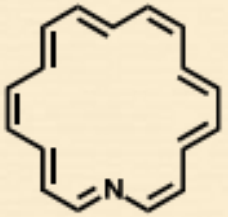
1,4-dihydro-1,4-diazocine
(Hückel: 4x2 + 2 = 10 π e⁻)

1H-azonine
(Hückel: 4x2 + 2 = 10 π e⁻)

Pyridine-like



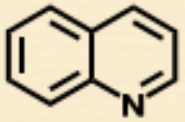
azecine
(Hückel: 4x2 + 2 = 10 π e⁻)



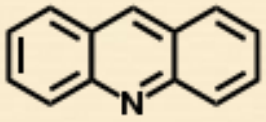
Aza-[18]-annulene
(Hückel: 4x4 + 2 = 18 π e⁻)

➔ Fused policyclic heterocycles:

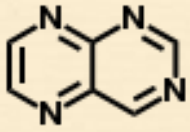
- Incorporate both pyridine-like or pyrrol-like heterocyclic moieties sharing one or more bonds.



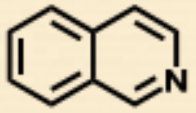
Quinoline
(Hückel: 4x2 + 2 = 10 π e⁻)



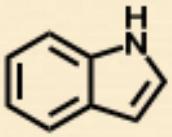
Acridine
(Hückel: 4x3 + 2 = 14 π e⁻)



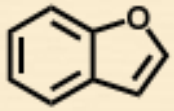
Pteridine
(Hückel: 4x2 + 2 = 10 π e⁻)



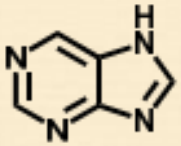
Isoquinoline
(Hückel: 4x2 + 2 = 10 π e⁻)



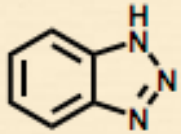
Indole
(Hückel: 4x2 + 2 = 10 π e⁻)



Benzofurane
(Hückel: 4x2 + 2 = 10 π e⁻)



Purine
(Hückel: 4x2 + 2 = 10 π e⁻)



Benzotriazole
(Hückel: 4x2 + 2 = 10 π e⁻)

NON-AROMATIC HETEROCYCLES

- Heterocycles in which the p-ring system is partially or completely saturated.
- Behave chemically like the corresponding acyclic analogues but taking into account the STRAIN (angle strain, steric strain and torsional strain)
- Because of Angle strain, small-size rings tend to react by ring-opening processes, releasing strain and reaching to a more stable situation.

ANGLE STRAIN

Baeyer Strain Theory:

- Explains specific behavior of chemical compounds in terms of bond angle strain.
- It was proposed by Adolf von Baeyer in 1885 to account for the unusual chemical reactivity in ring-opening reactions of cyclopropanes and cyclobutanes where this angle strain is relieved.

Adolf von Baeyer (1835-1917)
Nobel Prize for Chemistry (1905)

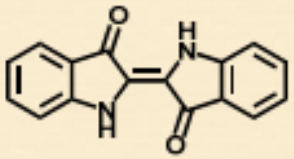
On ring strain he noted in 1885:

"The four valences of the carbon atom act in the directions that connect the center of a sphere with the corners of a tetrahedron and that form an angle of 109.28' with each other. The direction of the attraction can experience a deviation that will, however, cause an increase in strain correlating with the degree of this deviation"

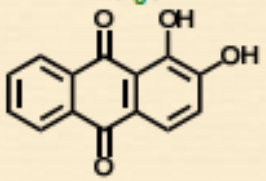
ADOLF VON BAEYER

Johann Friedrich Wilhelm Adolf von Baeyer was born on October 31, 1835, in Berlin, as the son of Johann Jakob Baeyer and Eugenie née Hitzig. He came from a family distinguished both in literature and the natural sciences. His father, a lieutenant-general, was the originator of the European system of geodetic measurement. Even as a child Baeyer was interested in chemical experiments and at the age of twelve found a new double salt of copper. Baeyer devoted his first two years as a student at the University of Berlin (1853-1855) chiefly to physics and mathematics. By 1856, however, his old love for chemistry re-awakened and drew him to Bunsen's laboratory in Heidelberg. His studies here on methyl chloride resulted in his first published work which came out in 1857. During the next year he worked in Kekulé's private laboratory in Heidelberg and was associated with his ingenious structure theory. Baeyer's life work was soon to bring this indeed most brilliant of chemical theories much resounding success. In 1858, in Berlin, he received his doctorate for his work on cacodyl compounds which had been done in Kekulé's laboratory.

For the next year or two Baeyer was again working with Kekulé who had meanwhile become Professor at Ghent. A study of uric acid, which also led him to the discovery of barbituric acid, provided the thesis by which he qualified as a university teacher in 1860. In the same year he became a lecturer in organic chemistry at the "Gewerbe-Akademie" (Trade Academy) in Berlin. He received little money but was given a spacious laboratory. In 1866 the University of Berlin, at the suggestion of A.W. Hofmann, conferred on him a senior lectureship, which, however, was unpaid.



Indigo



Alizarin

It was during the Berlin period that Baeyer began most of the work that was to bring him fame later. In 1865 he started his work on indigo - the blue dye had fascinated him since his youth-and this soon led to the discovery of indole and to the partial synthesis of indigotin. His pupils Graebe and Liebermann, with the help of the zinc-dust distillation developed by Baeyer, clarified the structure of alizarin and worked out the synthesis used industrially. Studies were initiated on condensation reactions which, after Baeyer had gone to Strassburg as Professor in the newly established University (1871) brought to light that important category of dyestuffs - the phthaleins. Baeyer's theory of carbon-dioxide assimilation in formaldehyde also belongs to this period.

Cacodyl: poisonous oily liquid with a garlicky odor. Undergoes spontaneous combustion in dry air. FIRST ORGANOMETALLIC COMPOUND ISOLATED.

In Bunsen's words "*the smell of this body produces instantaneous tingling of the hands and feet, and even giddiness and insensibility...It is remarkable that when one is exposed to the smell of these compounds the tongue becomes covered with a black coating, even when no further evil effects are noticeable*".

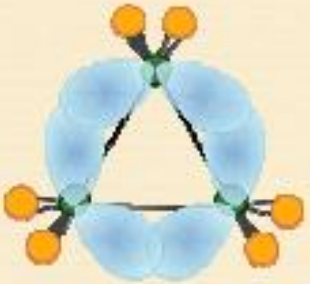
On the death of Justus von Liebig in 1873, Baeyer was called to his Chair in the University of Munich and there, over many years, built up an excellent new chemical laboratory. With his tenure at Munich came elegant total syntheses of indigo, as well as work on acetylene and polyacetylene, and from this derived the famous Baeyer strain theory of the carbon rings; there were studies of the constitution of benzene as well as comprehensive investigations into cyclic terpene. In this connexion the Baeyer-Villiger oxidation of ketones by means of per-acids was discovered. Especial interest was aroused theoretically by his work on organic peroxides and oxonium compounds and on the connexion between constitution and colour.

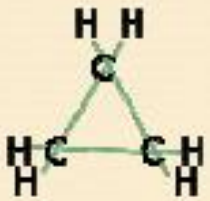
ANGLE STRAIN

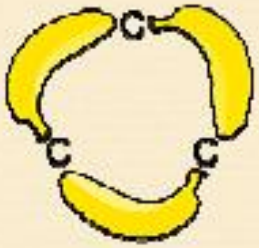
Coulson and Moffit Model

"The maximum overlap between molecular orbitals is not an absolute requisite for bond formation if this leads to significant deviation from the natural angles associated to hybridization"

- Ring strain is reduced if internal sp^2 orbitals acquire higher p character.
- sp^2 Orbitals with a higher p character implies that bond lengths are shorter, with a bond angle closer to 90° and with a curvy geometry (also known as banana bonds)
- The external sp2 orbitals (those linked to H in cyclopropane) acquire less p character (more spherical) and this leads to distorted bond angles ($\phi = 116°$ and not 109°)





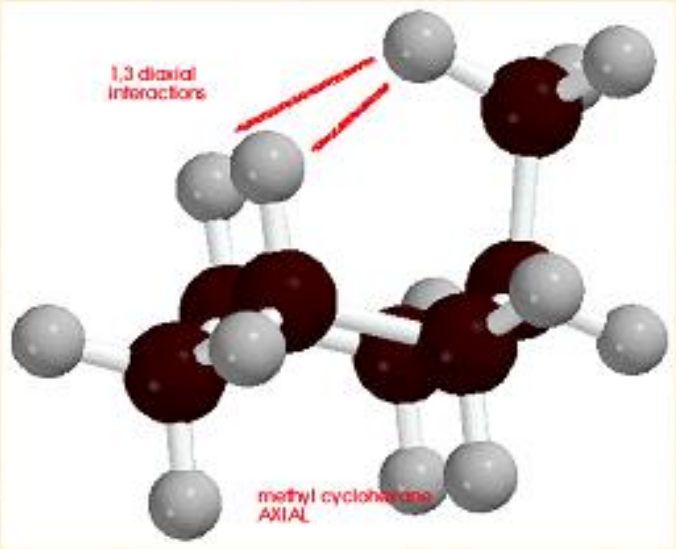


Consequences of Angle Strain: The angle strain of cyclopropane renders the molecule unstable and highly reactive due to the large amount of potential energy stored in the molecule. Cyclopropane, when burned, releases substantially more energy than when propane is burned. This difference cannot be explained solely by the fact that there are two additional hydrogens in propane. The higher heat of combustion of cyclopropane is due to the angle strain. It is known that cyclohexane does not undergo hydrogenation reactions. However, cyclopropane does readily undergo hydrogenation reactions.2 This difference in reactivity is due to the high potential energy stored in cyclopropane, whereas there is little potential energy in cyclohexane.

STERIC STRAIN

- Steric strain results from the electron-electron repulsion of atoms (or groups of atoms) that are too close together.
- Steric strain stores potential energy in a molecule by forcing repelling groups together.

E.g.: 1,3-diaxial interactions in cyclohexanes



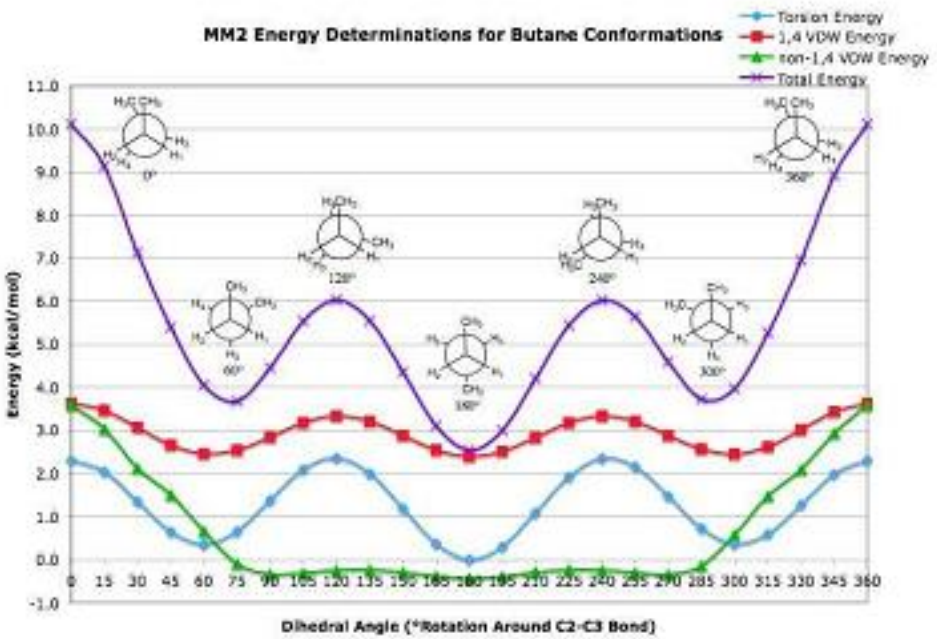
E.g.: s-cis conformation in butadiene

NON-AROMATIC HETEROCYCLES

TORSIONAL STRAIN

➢Steric strain that occurs when there are eclipsed interactions.

E.g.: conformations of n-butane.



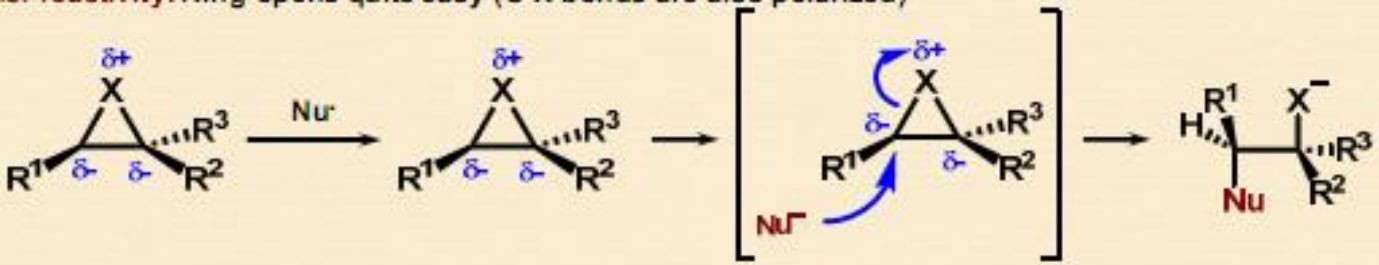
movie

NON-AROMATIC HETEROCYCLES

THREE-MEMBERED HETEROCYCLES

➔Consequences of angle strain and torsional strain.

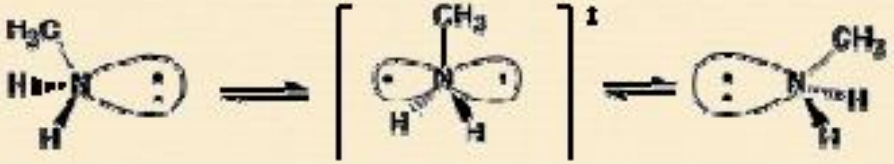
➢Higher reactivity: Ring opens quite easy (C-X bonds are also polarized)

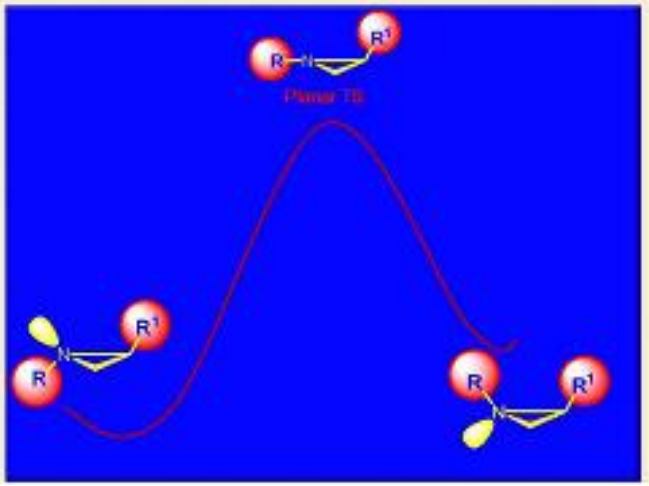


✓Attack on less-hindedred carbon atom (steric control)
✓Inversion of configuration at the attacked carbon atom
✓Retention of configuration at the other carbon atom.

➢Less basicity of the heteroatom lone pair: Aziridines are less basic than other secondary amines because the curved bonds make the sp^2 orbital which contains the lone pair to have more s-character (more spherical) and therefore electrons remain closer to nucleus and more tightly bonded.

➢Increased energy barrier for nitrogen inversion in aziridines: Nitrogen atom in aziridines is highly pyramidal and the required energy to undergo pyramidal inversion is relatively high because the molecule has to go through a highly strained planar intermediate. As a consequence, rotamers can be in some cases isolated.



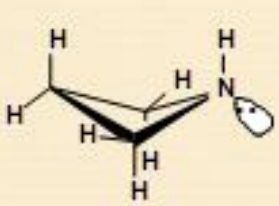


NON-AROMATIC HETEROCYCLES

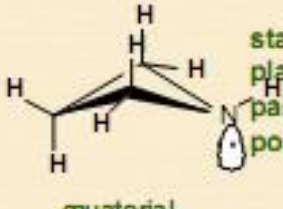
FOUR- AND FIVE-MEMBERED HETEROCYCLES

Azetidine:

- Non-planar molecule: Twisted conformation in order to minimize strain.



axial

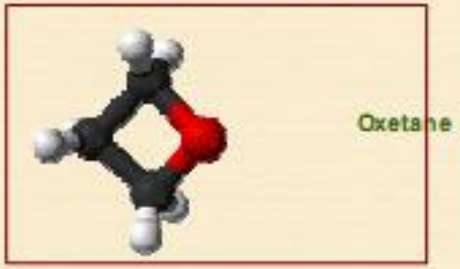


equatorial

The most stable conformation places the nitrogen lone pair in a pseudoaxial position

Oxetane:

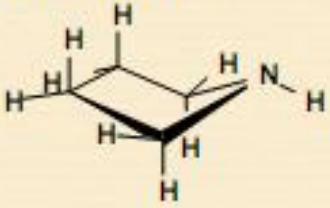
- Planar structure: The lack of substituents at oxygen atom makes torsional strain to be minimal and the energies between twisted and planar structures are very close to each other

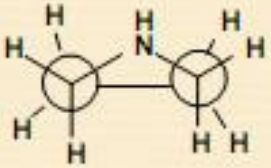


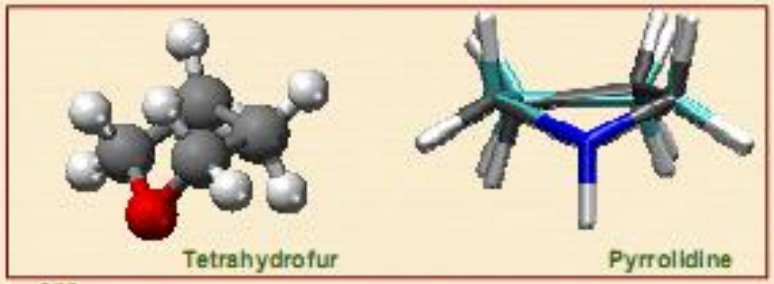
Oxetane

Pyrrolidine and tetrahydrofurane:

- Non-planar molecules: Envelope-like conformations to avoid torsional strain (*no angle strain in five-membered cycles*).
- Heteroatom goes to the out-of-plane position to avoid gauche interactions







Tetrahydrofur ane

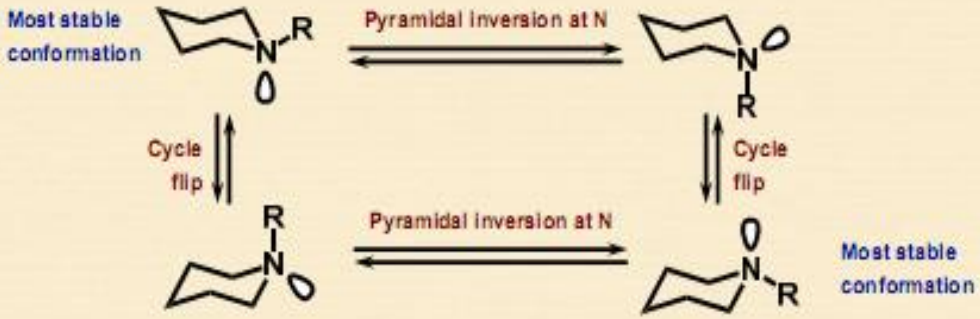
Pyrrolidine

- Pyrrolidine is more basic than acyclic secondary amines (lone pair more exposed on a molecular orbital with full sp^3 character (*no angle strain*)

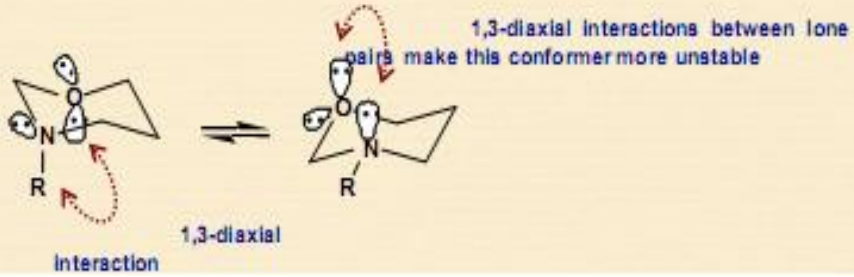
NON-AROMATIC HETEROCYCLES

SIX-MEMBERED HETEROCYCLES

- Non-planar molecules: Chair conformation is the most stable one
- Heteroatom lone pair preferably on axial position (minimizing 1,3-diaxial strain)
- Other issues to take care of when carrying out conformational analysis:
  - Pyramidal inversion of nitrogen atom.
  - The two interchanging chair conformations



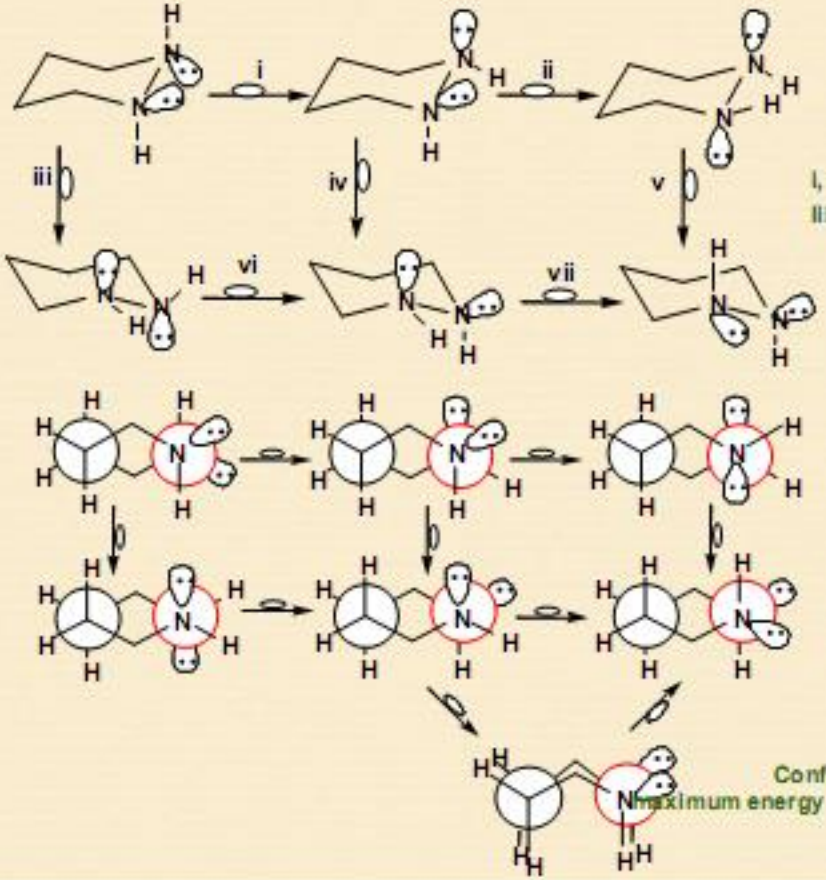
- The Van der Waals interactions between substituents and the lone pairs of the heteroatoms. These are very important on highly electronegative atoms such as oxygen (electrons are closer to the nuclei and electrostatic repulsions become more important)



NON-AROMATIC HETEROCYCLES

SIX-MEMBERED HETEROCYCLES

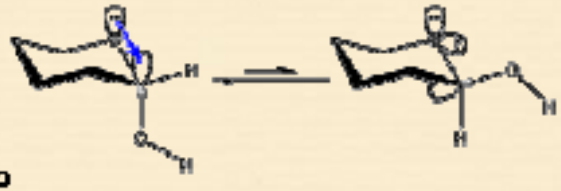
Interactions between contiguous lone pairs: Preference for *gauche* conformation (lone-pair containing orbitals almost perpendicular) because of the possibility for existing overlaps between σ* molecular orbitals which contribute to the stabilization of electron density by delocalization. Maximum energy on eclipsed conformation in which both lone pairs are eclipsed to each other because of electrostatic repulsion.



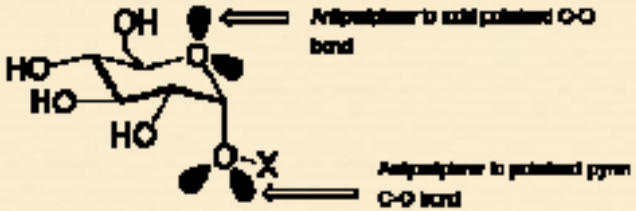
SIX-MEMBERED HETEROCYCLES

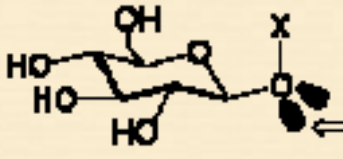
- **Anomeric effect:** Orbital interactions through σ-bonds.
  - The anomeric effect, also known as Edward-Lemieux effect is a stereoelectronic effect that describes the tendency of heteroatomic substituents adjacent to a heteroatom within a cyclohexane ring to prefer the *axial* orientation instead of the less hindered *equatorial* orientation that would be expected from steric considerations.

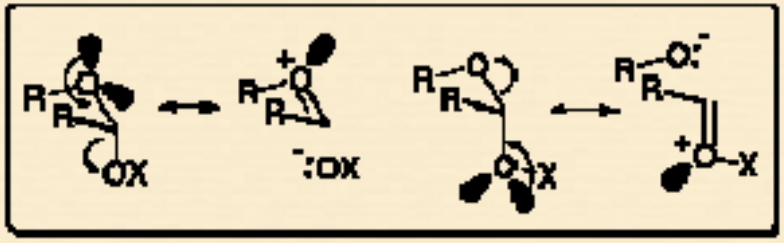
  - The most widely accepted explanation is that there is a stabilizing interaction (hyperconjugation) between the unshared electron pair on the one heteroatom (the endocyclic one in a sugar ring) and the σ* orbital for the axial (exocyclic) C–X bond.

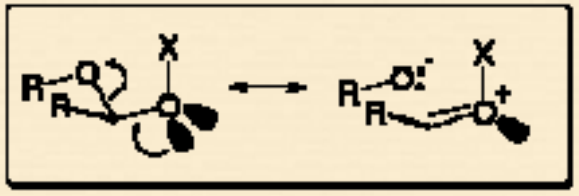


In terms of resonance sructures





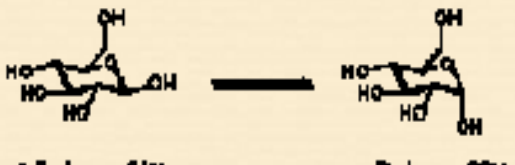




NON-AROMATIC HETEROCYCLES

SIX-MEMBERED HETEROCYCLES

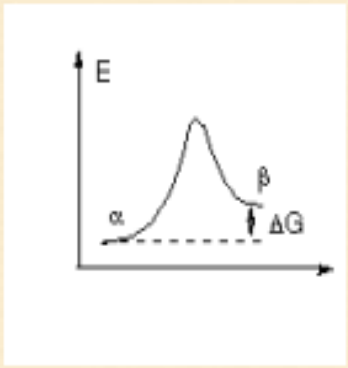
- Anomeric effect:



β-D-glucose 64% α-D-glucose 36%

K = 36 / 64 = 0.56

ΔG = -RTlnK = 1.43 kJmol^{-1}



In cyclohexanes			In tetrahydropyrans		
94.5%	ΔG = 7 kJmol^{-1}	5.5%	99.3%	ΔG = 12 kJmol^{-1}	0.7%
84%	ΔG = 4.1 kJmol^{-1}	16%	46%	ΔG = 0.4 kJmol^{-1}	54%
77%	ΔG = 3.8 kJmol^{-1}	23%	30%	ΔG = 2.1 kJmol^{-1}	70%
72.5%	ΔG = 2.4 kJmol^{-1}	27.5%	5%	ΔG = 7.3 kJmol^{-1}	95%

K roughly constant

K increases with electronegativity

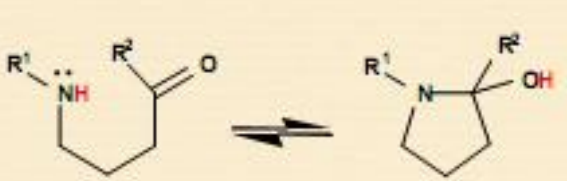
OTHER FACTORS INFLUENCING CONFORMATION

Other different types of interactions can also influence the preferred conformation for non-aromatic heterocycles

- **Intramolecular H-bonding interactions:** Can fix a hypothetically strained conformation because of the stabilizing effect of the intramolecular bond.

More stable

- **Ring-chain tautomerism:**
  - Tautomers are isomers of organic compounds that readily interconvert by a chemical reaction. Because of the rapid interconversion, tautomers are generally considered to be the same chemical compound.
  - Ring-chain tautomerism occurs when the movement of the atoms (generally a proton) is accompanied by a change from an open structure to a ring



γ-aminoketone Pyrrolidin-2-ol

δ-aminoketone Piperidin-2-ol

NOMENCLATURE :-

The name of heterocyclic compound consists of two components

prefix +suffix.

Prefix --------->> Tells about the nature of the hetero atom.
Suffix ------- >> gives information about (i) Ring size.

(ii)Presence/Absence of unsaturation.

Note :-Prefix gives information about the position of the hetero atom.

NOMENCÑLATURE OF HETEROCYCLIC COMPOUNDS

GENERAL RULES (adopted by IUPAC)

- Hetero-atom is to be counted as 1 or as low as possible
- When there is more than one hetero-atom, preference is given to O, then S, then N, then C. Also N-H presides over –N=.
- When there is more than one hetero-atom, numbering should be as direct as possible from one to the other
- Substituents are numbered as low as possible
- Acceptable prefixes include O=Oxa; S=Thia; N=Aza
- Common suffixes for N- and non-N-heterocycles: For partially unsaturated systems, H is(are) are used to indicate the location of saturation
- Hantzsch-Widman System of systematic name of heterocyclic compounds

Ring Size	*Saturated*	*Partly Saturated*	*Unsaturated*
3	-irane	-	-irene
4	-etane	(dihydro)	-ete
5	-olane	(dihydro)	-ole
6	-inane	(di or tetrahydro)	-ine
7	-epane	(di or tetrahydro)	-epine
8	-ocane	(di, tetra, or hexahydro)	-ocine

NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

Hantzsch – Widman Nomenclature (adopted by IUPAC)

Ring Size	*Saturated*	*Partly Saturated*	*Unsaturated*
3	-irane	-	-irene
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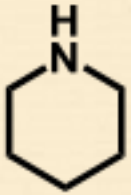
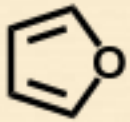
6	-inane	(di or tetrahydro)	-ine
7	-epane	(di or tetrahydro)	-epine
8	-ocane	(di, tetra, or hexahydro)	-ocine

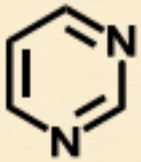
Common name : ethylene oxide
Systematic name : Oxa + irane .... Oxirane



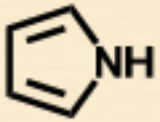
Common name : piperidine
Systematic name : Aza + inane 1H-Azinane



Common name : furan
Systematic name : Oxa + ole .... Oxole



Common name : pyrimidine
Systematic name : two aza at 1, 3 positions + ine .... [1,3]-diazine

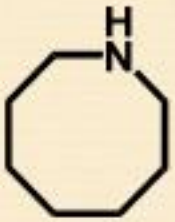


Common name : pyrrole
Systematic name : H at 1 position + Aza + ole 1H-Azole

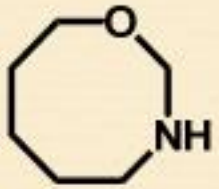
NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

Hantzsch – Widman Nomenclature (adopted by IUPAC)

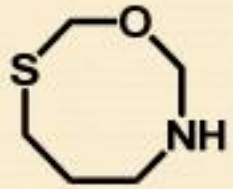
Ring Size	Saturated	Partly Saturated	Unsaturated
3	-irane	-	-irene
4	-etane	(dihydro)	-ete
5	-olane	(dihydro)	-ole
6	-inane	(di or tetrahydro)	-ine
7	-epane	(di or tetrahydro)	-epine
8	-ocane	(di, tetra, or hexahydro)	-ocine



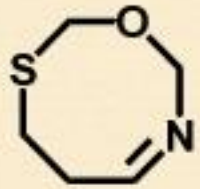
Azocane



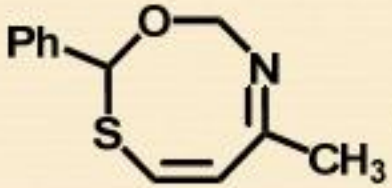
[1,3]-Oxazocane



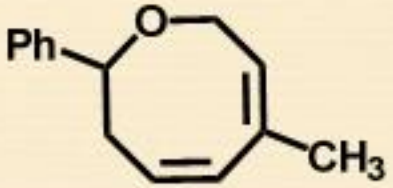
[1,3,7]-Oxathiazocane



4,5-dihydro-2H,8H-
[1,3,7]-oxathiazocine



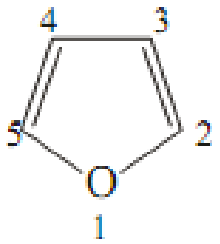
6-Methyl-2-phenyl-
2H,8H-[1,3,7]-oxathiazocine



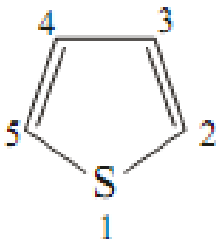
6-Methyl-2-phenyl-
2H,3H,8H-oxocine

Nomenclature of Heterocyclic Compounds

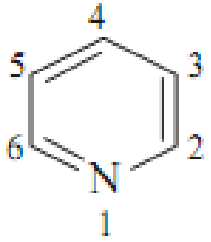
There are a large number of important ring systems which do not possess any systematic names rather non-systematic or common names are used for them. Some of such examples include the following:



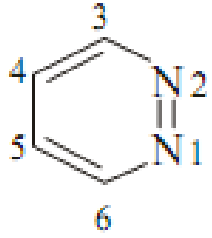
Furan



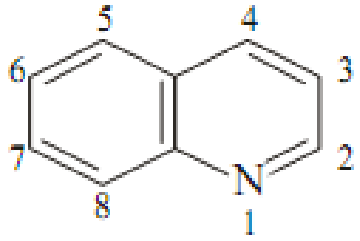
Thiophene



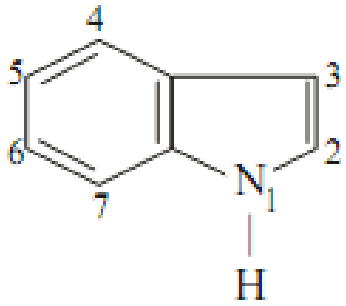
Pyridine



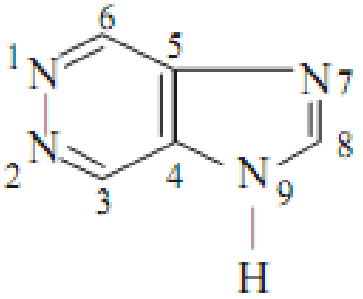
Pyridazine



Quinoline

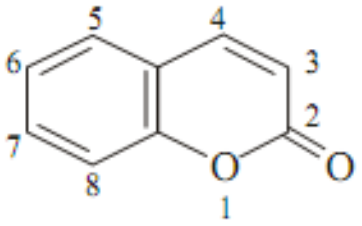


Indole

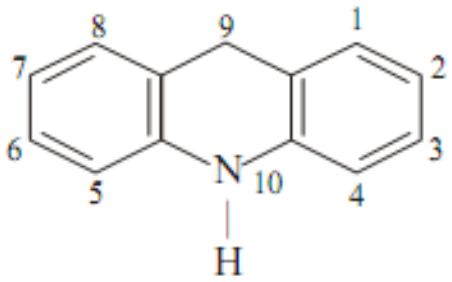


Purine

Nomenclature of Heterocyclic Compounds



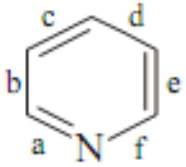
Coumarin



Acridine

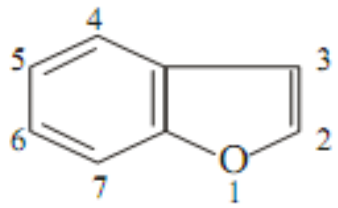
The numbering and nomenclature of heterocyclic rings become more complicated for condensed or fused ring systems, i.e., when a part of one ring is also a part of another ring. Such ring systems, however, are known by non-systematic or common names, such as indole, isatin, isoquinoline, etc., as indicated in the preceeding paragraph.

There is yet another system of nomenclature for fused rings that is commonly employed. According to this system, the side of the heterocyclic ring is labelled by the letters a, b, c, etc., starting from the atom numbered 1. Therefore side '*a*' being between atoms 1 and 2, side '*b*' between atoms 2 and 3, and so on as shown below for pyridine.

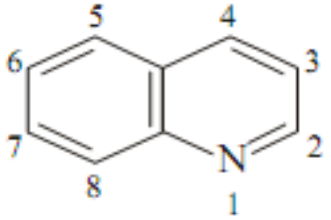


Pyridine

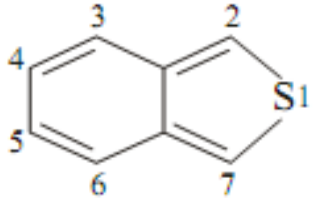
The name of the heterocyclic ring is chosen as the parent compound and the name of the fused ring is attached as a prefix. The prefix in such names has



Benzo [b] furan

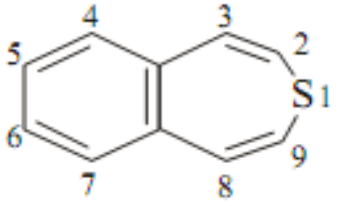


Benzo [b] pyridine

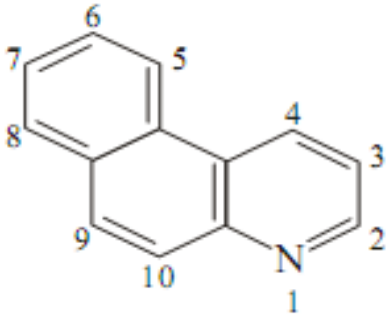


Benzo [c] thiophene

the ending '*o*', i.e., benzo, naphtho and so on. The following examples explain this rule.



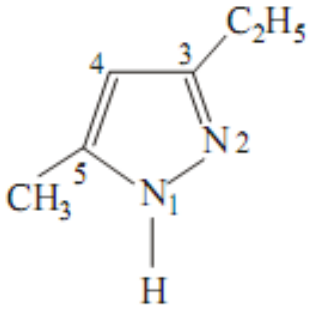
Benzo [d] thiepin



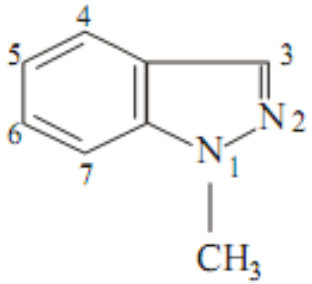
Benzo [f] quinoline

In a heterocyclic ring, other things being equal, numbering preferably commences at a saturated rather than at an unsaturated hetero atom, as depicted in the following examples:

Nomenclature of Heterocyclic Compounds

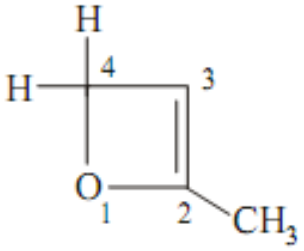


3-Ethyl-5-methylpyrazole

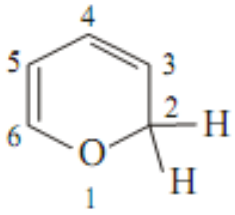


1-Methylindazole

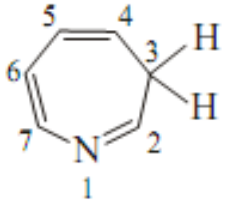
In a heterocyclic ring with maximum unsaturation, if the double bonds can be arranged in more than one way, then their positions are specified by numbering those nitrogen or carbon atoms which are not multiply-bonded, i.e. bear an '*extra*' hydrogen atom, by italic capital '1*H*' '2*H*' '3*H*', etc. The numerals indicate the position of these atoms having the extra hydrogen atom. The following examples illustrate this rule:



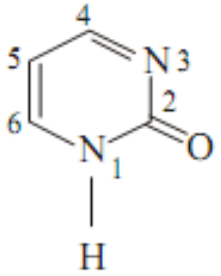
2-Methyl-4*H*-Oxete



2*H*-Pyran

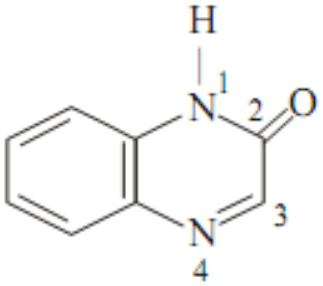


3*H*-Azepine

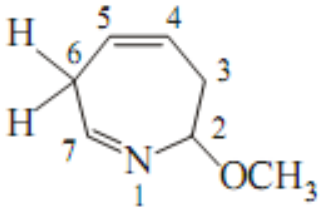


2(1*H*)-Pyrimidinone

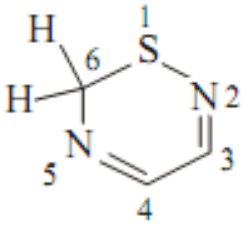
Nomenclature of Heterocyclic Compounds



Quinoxaline-2(1*H*)-one

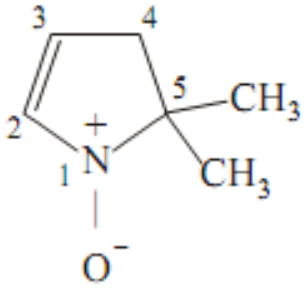


2-Methoxy-6*H*-azepine

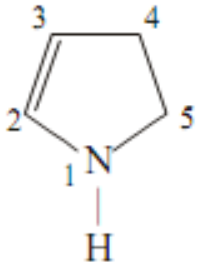


6*H*-1,2,5-Thiadiazine

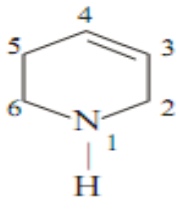
The position of the hydrogen atom in a partially saturated heterocyclic ring can be indicated by writing 1, 2-dihydro, etc. with the name of the compound. Alternatively, the position of the double bond can also be specified as Δ^1, Δ^2, Δ^3.,. etc., which indicates that 1 and 2; 2 and 3; 3 and 4 atoms respectively have a double bond.

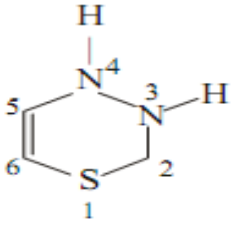


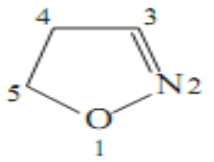
5,5-Dimethyl-Δ^2-pyrroline N-oxide



Δ^2-Pyrroline





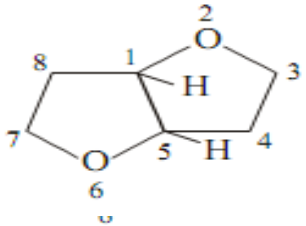


Δ^3-Tetrahydropyridine **Δ^5-Dihydro-1,3,4-thiadiazine** **Δ^2-Oxazoline**

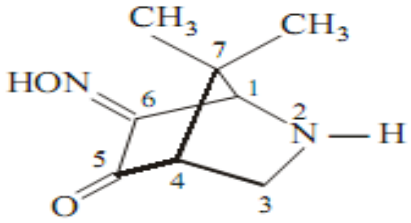
A positively charged ring is denoted by the suffix "-ium".

Groups such as C = S and C = NH present in the ring are denoted by the suffixes "-thione" and "-imine".

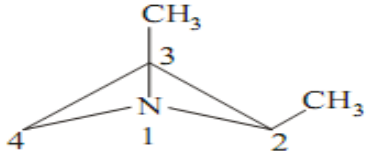
Bicyclic bridged structures are quite common in heterocyclic chemistry. The nomenclature of such a structure consists of the prefix bicyclo, followed in square brackets the number of carbon atoms separating the bridge heads by the three possible routes in descending numerical order. This is followed by the alkane containing the same number of carbon as the whole bicyclic heterocyclic skeleton. The following examples illustrate the use of this rule.



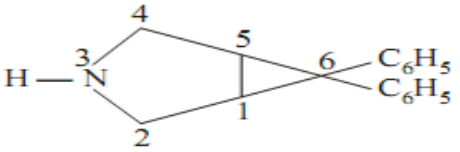
3,6-Dioxabicyclo [3.1.0] octane



6-Hydroxyimino-7, 7-dimethyl-2-azabicyclo [2.2.1] heptan-5-one



2,3-Dimethyl-1-azabicyclo [1.1.0] butane



6,6-Diphenyl-3-azabicyclo [3.1.0] hexane.

Table 1.1 Main three- and four-membered heterocycles.

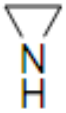
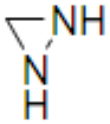
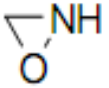
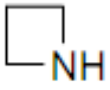
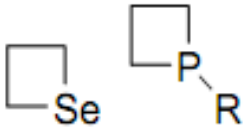
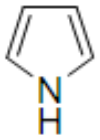
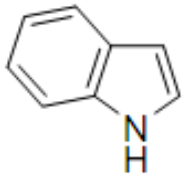
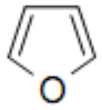
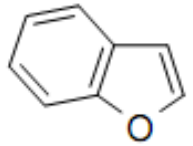
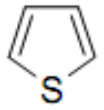
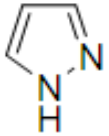
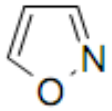
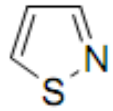
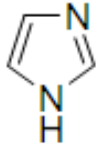
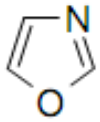
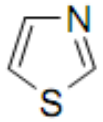
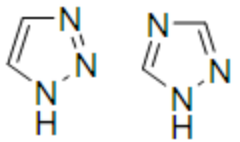
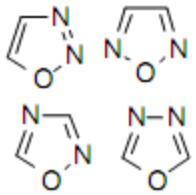
Ring size	Heteroatom			
	N	**O**	**S**	**Other**
3	 Aziridine	 Oxirane	 Thiirane	
	 Diaziridine	 Dioxirane		 Oxaziridine
4	 Azetidine	 Oxetane	 Thietane	 Seletane Phosphetane

Table 1.2 Main five-membered heterocycles.

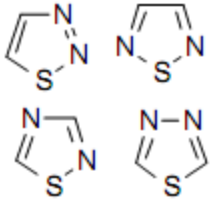
Ring size	Heteroatom				
	N	Benzo	O	Benzo	S
5	 Pyrrole	 Indole	 Furan	 Benzofuran	 Thiophene
5	 Pyrazole		 Isoxazole		 Isothiazole
	 Imidazole		 Oxazole		 Thiazole



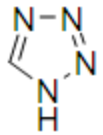
Triazoles



Oxadiazoles

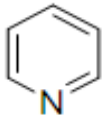
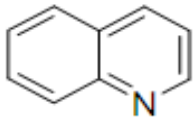
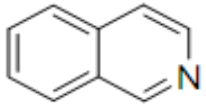
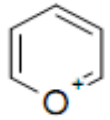
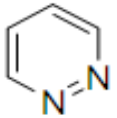
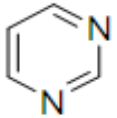
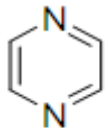


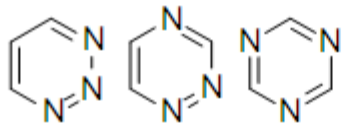
Thiadazoles



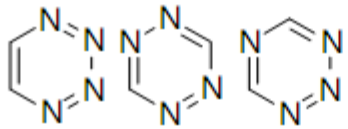
Tetrazole

Table 1.3 Main six-membered heterocycles.

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

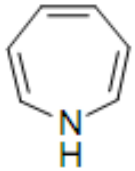
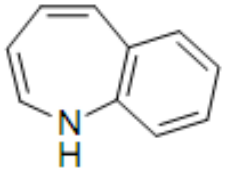
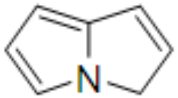
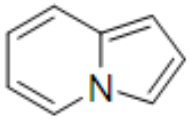
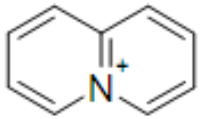


Triazines



Tetrazines

Table 1.4 Other simple heterocycles.

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