

Heterocyclic Chemistry

Introduction and Nomenclature of Heterocyclic compounds

Course Name: Heterocyclic Chemistry

Course Code: MDSE(C)-405C

**By: Dr. Ajay Kumar
Assistant Professor
Department of Chemistry,
SBAS, MAU**

Heterocyclic Compounds

- **Heterocycles** form the largest class of organic compounds. In fact, many natural products and most drugs contain heterocyclic rings. The colors of flowers and plants, antibiotics known to all as penicillins, compounds that transport the oxygen we breathe to our vital organs, and the components of DNA responsible for the genetic code are all heterocyclic compounds. From an organic chemist's viewpoint, heteroatoms are atoms other than carbon or hydrogen that may be present in organic compounds.
- The most common heteroatoms are **oxygen, nitrogen, and sulfur**. In heterocyclic compounds, one or more of these heteroatoms replaces carbon in a ring.

The Criteria for Aromaticity and Hückel's Rule

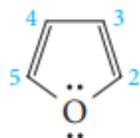
- Aromatic heterocyclic compounds are those have a **heteroatom in a ring** and behave in **a manner similar to benzene** in some of their properties (i.e. react by electrophilic aromatic substitution). Further more, these compounds comply the criteria for Aromaticity and with the general rule proposed by Hückel.

The Criteria for Aromaticity and Hückel's Rule:

1. The compound must be cyclic (a ring of atoms).
2. The molecule is **planar** (all atoms in the molecule lie in the same plane) so that there is continuous or nearly continuous overlap of all p orbitals.
3. The molecule is **fully conjugated** (p orbital at every atom in the ring)
(for C atoms to have p orbitals they must have double bonds, or bear a positive or negative charge i.e. ions)
4. The molecule has a closed loop of **$(4n+2)$ π electrons** in the cyclic arrangement of p orbitals, where **$n = 0, 1, 2, 3, \dots$ integral number**

1- Five-Membered Heterocycles

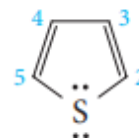
Furan, Pyrrole, and Thiophene



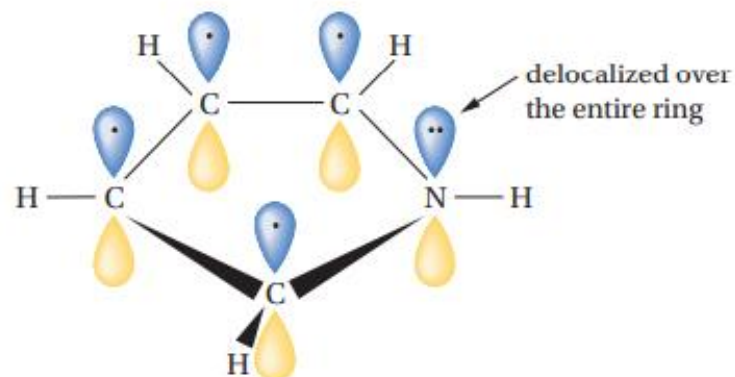
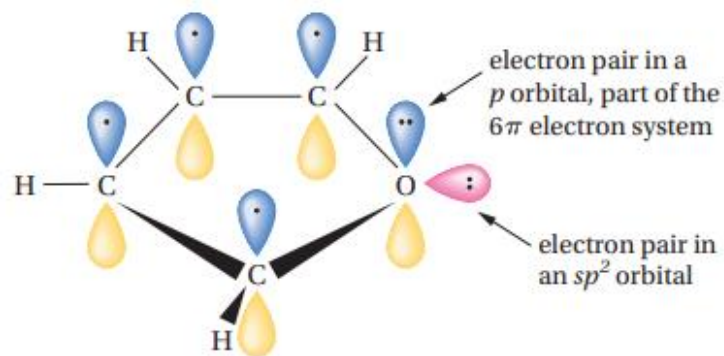
furan
(bp 32°C)



pyrrole
(bp 131°C)

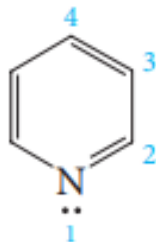


thiophene
(bp 84°C)

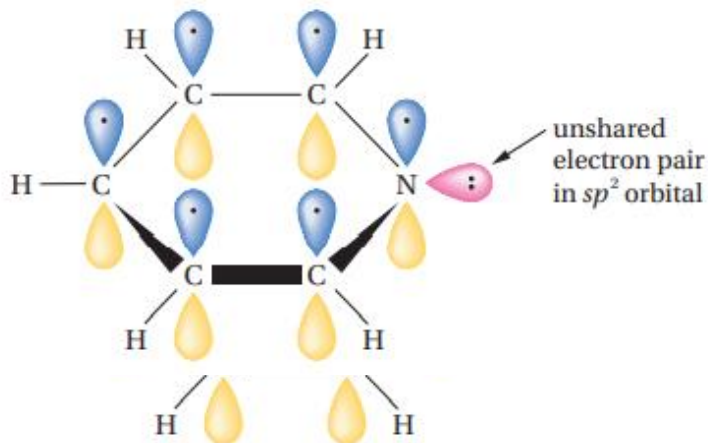


2- Six-Membered Heterocycles

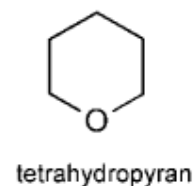
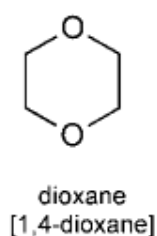
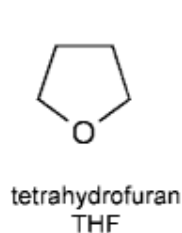
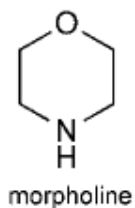
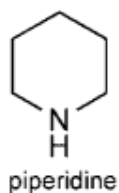
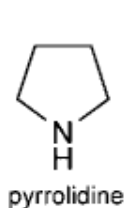
Pyridine



The lone pair of electrons on N occupies an sp^2 orbital in the plane of the ring but is not involved in aromaticity.



3- Saturated heterocycles



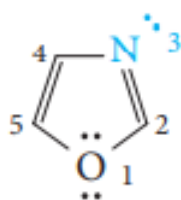
Nomenclature of Heterocyclic Compounds

There are three systems for naming heterocyclic compounds:

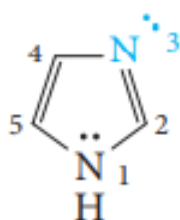
1. The common nomenclature: which convey little or no structural information but it still widely used.
2. The replacement method.
3. The Hantzsch-Widman (IUPAC or Systematic) method.

1-Common Nomenclature

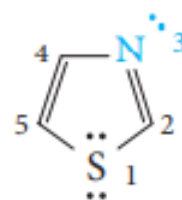
- Each compound is given the corresponding trivial name (which should be memorized, see the following slides). This usually originates from the compounds occurrence, its first preparation or its special properties.
- If there is more than one heteroatom of the same type numbering starts at the saturated one.



oxazole



imidazole

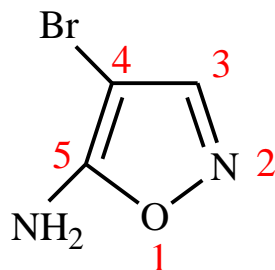


thiazole

- If there is more than one type of the heteroatoms, the ring is numbered starting at the heteroatom of the higher priority ($O > S > N$) and it continues in the direction to give the other heteroatoms the lower numbers as possible.

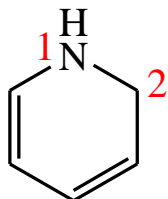
1- Common Nomenclature

- If substituents present, their position should be identified by the number of the atoms bearing them and then they should be listed in alphabetical order.



5-Amino-4-bromoisoxazole

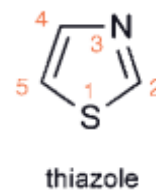
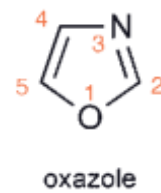
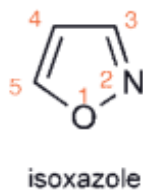
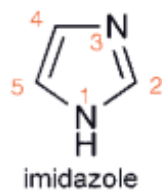
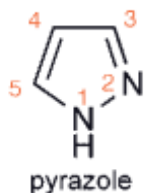
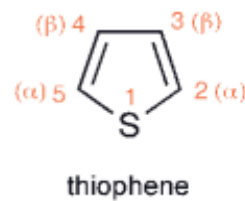
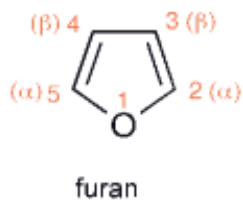
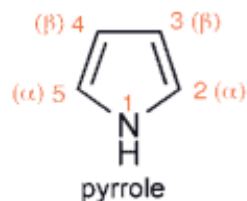
- The words **dihydro** or **trihydro** or **tetrahydro** are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated trivial name.



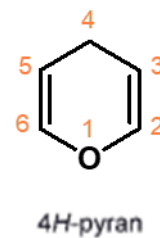
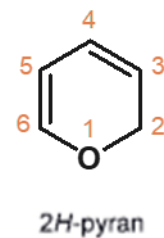
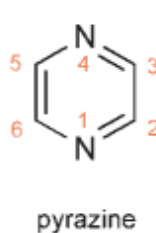
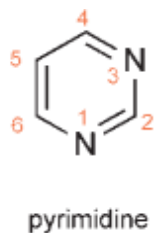
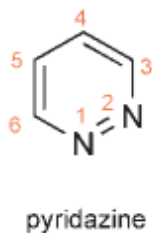
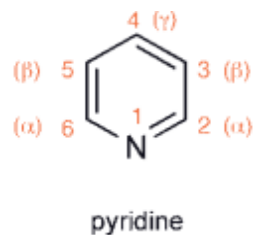
1,2-Dihydro-pyridine

Trivial names

5-membered heterocycles with one or two heteroatoms



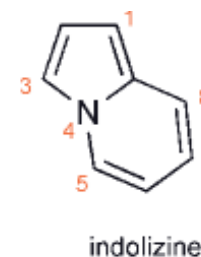
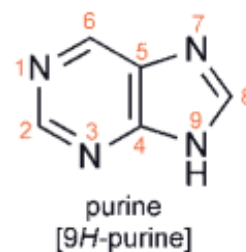
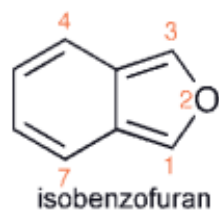
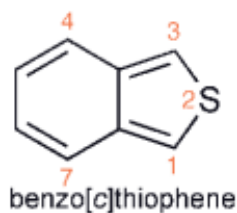
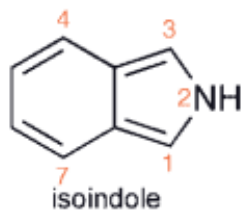
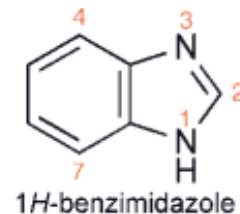
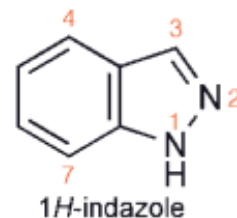
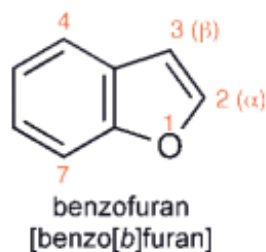
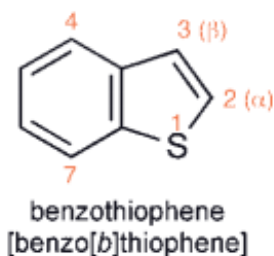
6-membered heterocycles with one or two heteroatoms



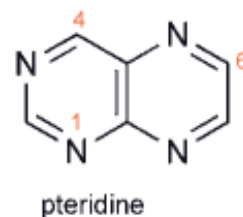
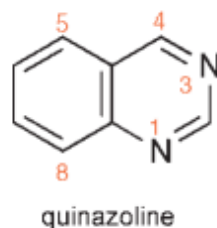
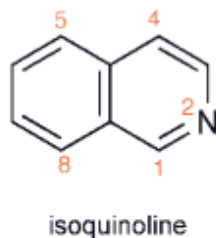
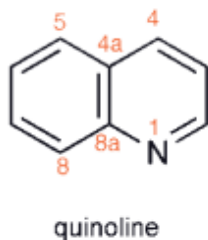
Trivial names

Fused heterocyclic

Common ring-fused azoles

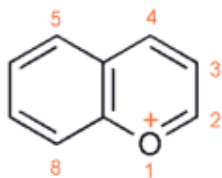


Common ring-fused azines

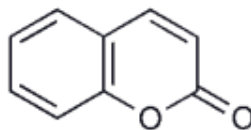


Trivial Names

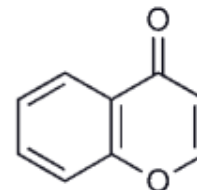
chromylium
(benzo[*b*]pyrylium)
[1-benzopyrylium]



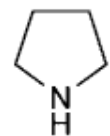
coumarin
[2*H*-1-benzopyran-2-one]



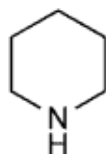
chromone
[4*H*-1-benzopyran-4-one]



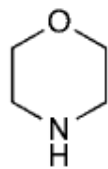
Saturated heterocycles



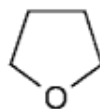
pyrrolidine



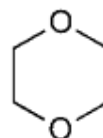
piperidine



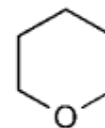
morpholine



tetrahydrofuran
THF



dioxane
[1,4-dioxane]



tetrahydropyran

2-Replacement nomenclature

- In replacement nomenclature, the heterocycle's name is composed of the corresponding carbocycle's name and an elemental prefix for the heteroatom introduced (if more than one heteroatom is present they should be listed according to the priority order shown in table (1). According to this nomenclature, tetrahydrofuran, for instance, is called oxacyclopentane.

Table-1

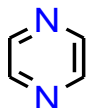
Priority decreases
↓

Atom	Prefix
O	oxa
Se	selena
S	thia
N	aza
P	phospha

2- Replacement nomenclature



Benzene



1,4-Diazabenzene



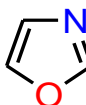
1,3-Cyclopentadiene



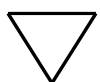
Oxacyclopenta-2,4-diene



1,3-Cyclopentadiene



1-Oxa-3-azacyclopenta-2,4-diene



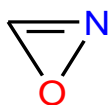
Cyclopropane



Oxacyclopropane



Cyclopropene



Oxazacyclopropene



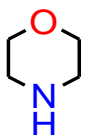
1,3-Cyclopentadiene



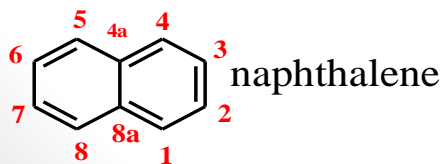
1-Thia-2-azacyclopenta-2,4-diene



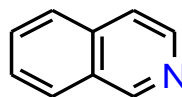
Cyclohexane



1-Oxa-4-azacyclohexane



naphthalene

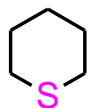


2-Azanaphthalene

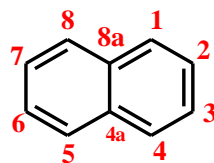
2- Replacement nomenclature



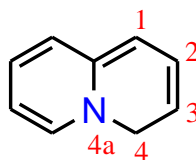
cyclohexane



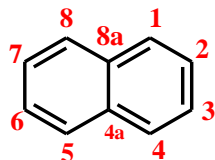
Thiacyclohexane



naphthalene



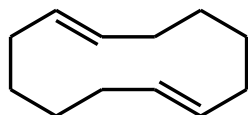
4*H*-4a-azanaphthalene



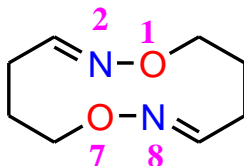
naphthalene



1,4-dithianaphthalene



cyclododecadiene



1,7-Dioxa-2,8-diazacyclododeca-2,8-diene

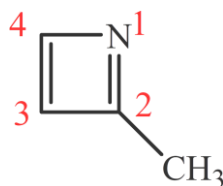
3- Hantzsch-Widman nomenclature (IUPAC)

- Hantzsch-Widman nomenclature is named after the German chemists Arthur Hantzsch and Oskar Widman, who proposed similar methods for the systematic naming of heterocyclic compounds in 1887 and 1888 respectively.
- According to this system three to ten-membered rings are named by combining the appropriate prefix (or prefixes) that denotes the type and position of the heteroatom present in the ring with suffix that determines both the ring size (depending on the total number of atoms in the ring) and the degree of unsaturation (note that fully saturated and fully unsaturated have certain rules for nomenclature while partially unsaturation will be indicated in certain ways). In addition, the suffixes distinguish between nitrogen-containing heterocycles and heterocycles that do not contain nitrogen.

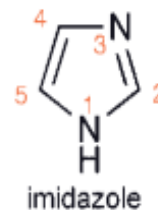
IUPAC name = locants +Prefix + suffix

Hantzsch-Widman rules for fully saturated and fully unsaturated heterocycles

- 1) Identify the heteroatom present in the ring and choose from (table 1 on slide 12) the corresponding **prefix** (e.g. **thia** for sulfur, **aza** for nitrogen and **oxa** for oxygen).
- 2) The position of a single heteroatom controls the numbering in a monocyclic compound. The heteroatom is always assigned position 1 and if substituents are present are then counted around the ring in a manner so as to take the lowest possible numbers.



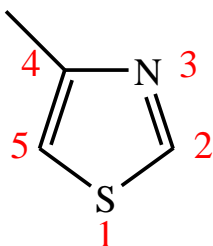
- 3) A **multiplicative prefix** (di, tri, etc.) and locants are used when two or more similar heteroatoms are contained in the ring (two nitrogens indicated by diaza) and the numbering preferably commenced at a saturated rather than an unsaturated atom, as depicted in the following example: **1,3-diazole**



Hantzsch-Widman rules

- 4) If more than one type of heteroatoms present in the ring the name will include more than one prefix with locants to indicate the relative position of the heteroatoms.
- Atom prefixes have a strict order of priority (preference) in which they are to be listed. For example, “**Oxa**” (for oxygen) always comes before “**aza**” (for nitrogen) in a name (see table 1).
 - When combining the prefixes (e.g. oxa and aza) two vowels may end up together, therefore the vowel on the end of the first part should be omitted (**oxaza**).
 - The numbering is started from the heteroatom of the highest priority in such a way so as to give the smallest possible numbers to the other heteroatoms in the ring (the substituents are irrelevant).

For example :



4-Methyl-**1,3-Thiaza**ole

Hantzsch-Widman rules

5) Choose the appropriate **suffix** from (table 2) depending on the ring size.

Table-2

Ring size	Suffix
3	ir
4	et
5	ol
6	in
7	ep
8	oc
9	on
10	ec

Hantzsch-Widman rules

6) The endings indicate the size and degree of unsaturation of the ring.

Tabel-3

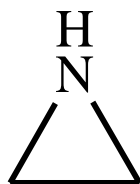
Ring size	With N		Without N	
	Unsat.	Sat.	Unsat.	Sat.
3	irine	iridine	irene	irane
4	ete	etidine	ete	etane
5	ole	olidine	ole	olane
6	ine	a	in	inane
7	epine	a	epin	epane
8	ocine	a	ocin	ocane
9	online	a	onin	onane
10	ecine	a	ecin	ecane

a : means use the prefix **perhydro** followed by **the fully unsaturated name**

7) Combine the prefix (s) and suffix together and drop the first vowel if two vowels came together.

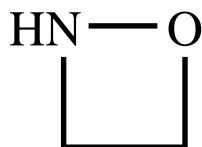
Hantzsch-Widman rules

Examples:



Aziridine

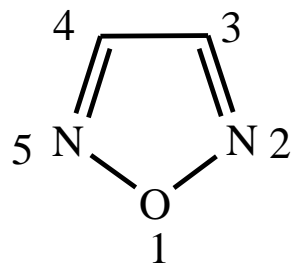
- This ring contains (N): Prefix is **aza**
- The ring is 3-membered and fully saturated: suffix is **iridine**
- By combining the prefix and suffix, two vowels ended up together (**azairidine**), therefore the vowel on the end of the first part should be dropped. This gives the correct name: **Aziridine**



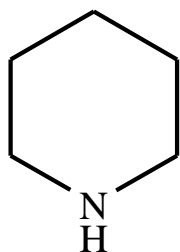
1,2-oxazetidine

- This ring contains (O and N) (O has higher priority than (N) and by starting numbering the ring at (O): Prefix is **1,2-Oxaaza**, but the first vowel must be omitted to give: **1,2-Oxaza**
- The ring is 4-membered and fully saturated: suffix is **etidine**
- By combining the prefix and suffix, two vowels ended up together (**1,2-oaxazaetidine**), therefore the vowel on the end of the first part should be dropped. This gives the correct name: **1,2-oxazetidine**

Hantzsch-Widman rules



Oxa + diaza + ole = 1,2,5-Oxadiazole

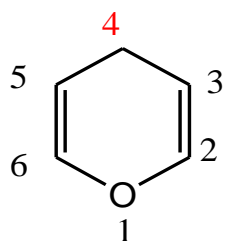


Perhydro + aza + ine = perhydroazine

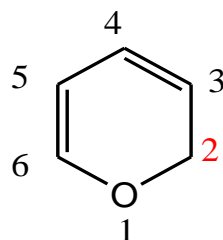
Hantzsch-Widman rules for partially unsaturated heterocycles

- Partial unsaturation in heterocyclic compounds can be indicated by one of the following methods:

a) The position of nitrogen or carbon atoms which bear extra hydrogen atoms must be indicated by numbers and italic capital H (e.g. *1H*, *2H*, etc.) followed by the name of maximally unsaturated ring.

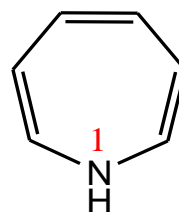


4*H*-Oxin

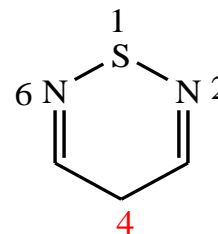


2*H*-Oxin

Not 6*H*-Oxin

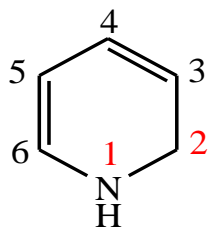


1*H*-Azepine

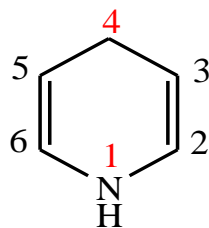


4*H*-1,2,6-Thiadiazine

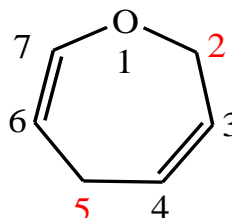
- b) The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated Hantzsch-Widman name.



1,2-Dihydroazine

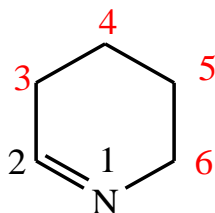


1,4-Dihydroazine



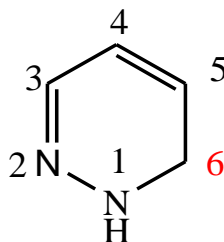
2,5-Dihydrooxepin

Not 1,6-Dihydroazine



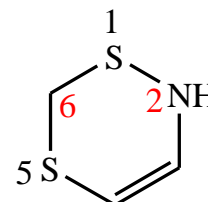
3,4,5,6-Tetrahydroazine

Not 2,3,4,5-Tetrahydroazine



1,6-Dihydro-1,2-diazine

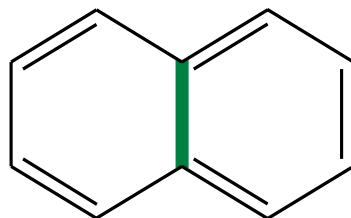
Hint:



2H,6H-1,5,2-Dithiazine

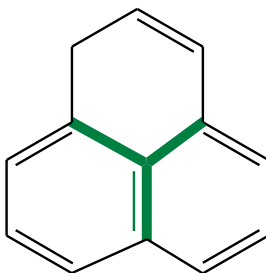
Definitions:

- **Fusion:** This term is used to describe the process of joining two separate rings with the maximum number of non-cumulative double bonds *via* two atoms and one common bond.
- **Ortho-fused rings:** are those rings that have only two common atoms and one bond, example; **Naphthalene**



Naphthalene

- *Ortho-and peri-fused rings:* are those found in a polycyclic compound with a ring that is *ortho*- fused to different sides of two other rings that are themselves *ortho*-fused together (i.e. there are three common atoms between the first ring and the other two), example; *1H-phenalene* is considered as being composed of three benzene rings, each is *ortho-peri*-fused to the other two.



1H-Phenalene

- **Polycyclic compounds** incorporating one heterocyclic ring or fused heterocyclic system fused to benzene are known **benzoheterocycles**.
- Also bicyclic compounds with two fused heterocyclic rings are well known.
- Both types can be named according to certain rules.

Nomenclature of Fused Heterocycles

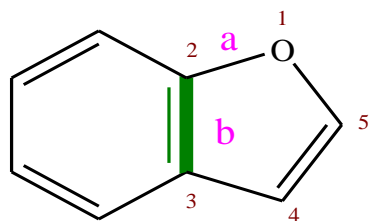
Nomenclature of benzofused compounds:

- Unless listed as a trivially named heterobicycle (see slide 9), a benzene ring fused to a heteromonocycle of five or more members or a heterobicyclic is named by prefixing the word **benzo** to a letter indicating the position of fusion in square brackets by the name of heterocyclic ring (common or IUPAC or modified replacement name).

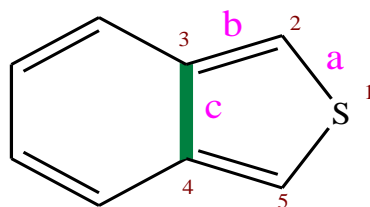
Name = Benzo [letter] name of heterocyclic ring

- For designating the position of fusion, the peripheral bonds of the heterocyclic ring are consecutively assigned alphabetical letters starting with the 1,2-bond as a side and the labeling is continued around the ring to give the common bond the lowest order.

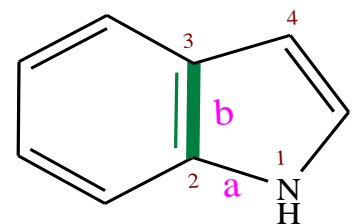
Examples:



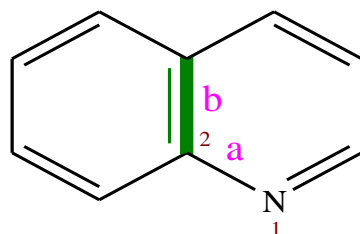
Benzo[*b*]furan



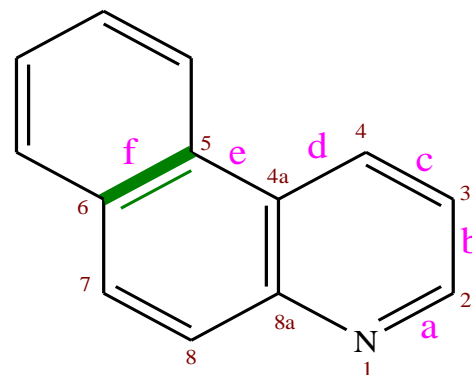
Benzo[*c*]thiophene



Benzo[*b*]pyrrole
Indole



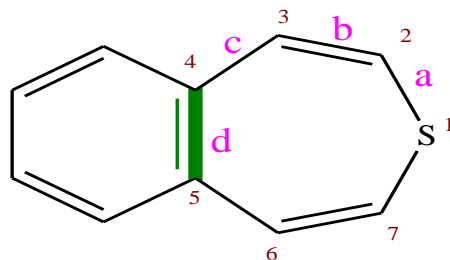
Benzo[*b*]pyridine
Quinoline



Benzo[*f*]quinoline

Nomenclature of Fused Heterocycles

- There is An exception to the two ring systems in which a benzene ring is fused to a hetero ring (which doesn't have a known common name) may be named by prefixing numbers indicating the positions of the hetero atoms to benzo followed by the name of the heterocyclic component.
- Numbering is assigned according to priority order of the hetero atoms i.e.
 $O > S > N$



Benzo[*d*]thiepine