Heterocyclic compounds

(Nomenclature)

M.Sc (SEM IV)
Elective Course 1c
Organic Chemistry Special

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Nomenclature of heterocyclic compounds

- Three systems for naming heterocylic compounds:

1) The common nomenclature: no structural information but it still widely used.

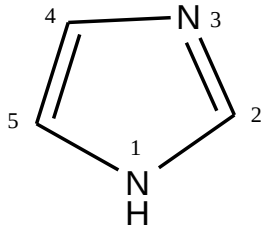
2) The replacement method

3) The Hantzsch-Widman (IUPAC or Systematic) method which is designed so that one may deduce from it the structure of the compound.

I- Common Nomenclature

ϖ Each compound is given the corresponding trivial name. This usually originates from the compounds occurrence, its first preparation or its special properties.

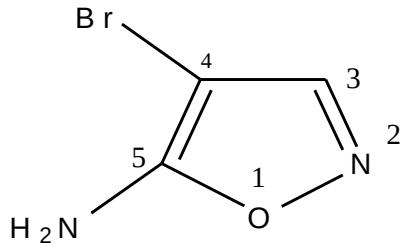
ϖ If there is more than one hetroatom of the same type numbering starts at the saturated one, e.g. imidazole.



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

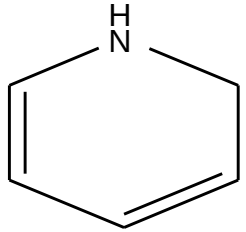
I-Common Nomenclature

- If subsituents 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

ϖ 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.

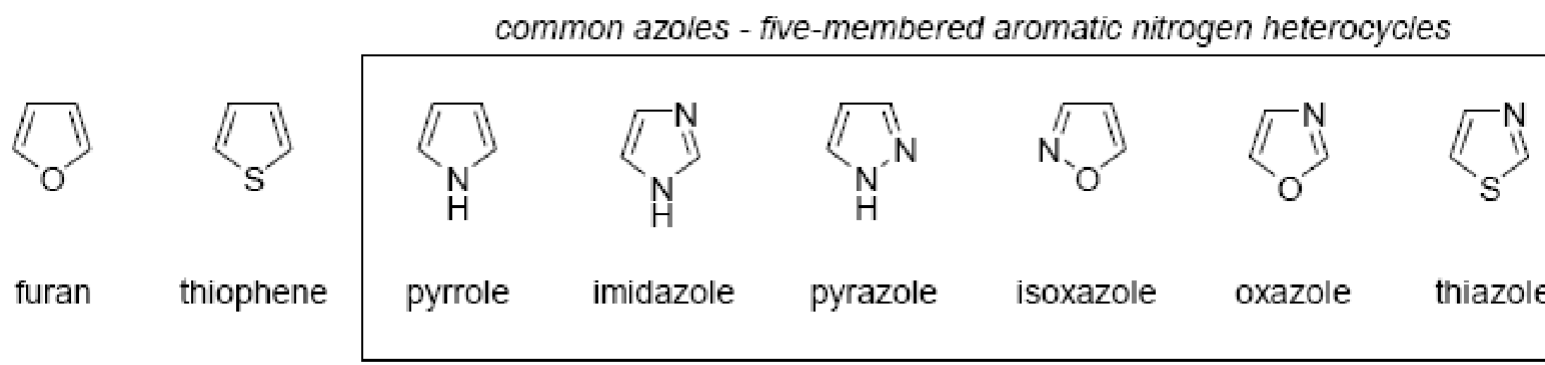


1,2-Dihydro-pyridine

Trivial names

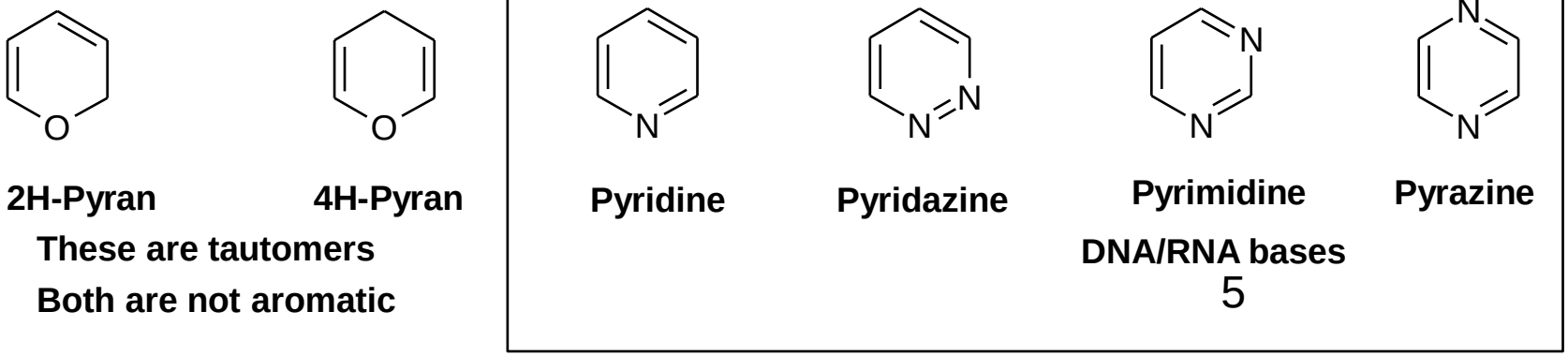
1) 5-membered heterocycles with one or two heteroatoms

common azoles - five-membered aromatic nitrogen heterocycles



2) 6-membered heterocycles with one or two heteroatoms

Common azines-six-membered aromatic nitorgrn heterocycles



These are tautomers

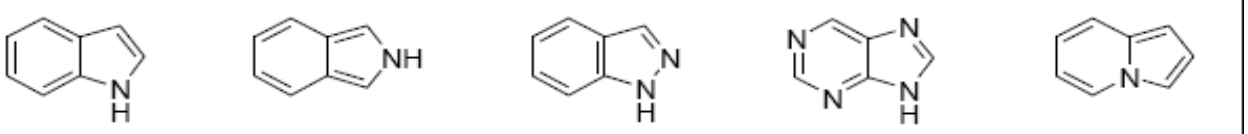
Both are not aromatic

DNA/RNA bases

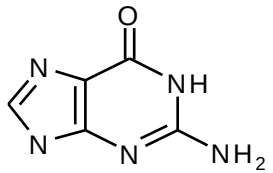
Trivial names

3) Fused heterocycles

common ring-fused azoles

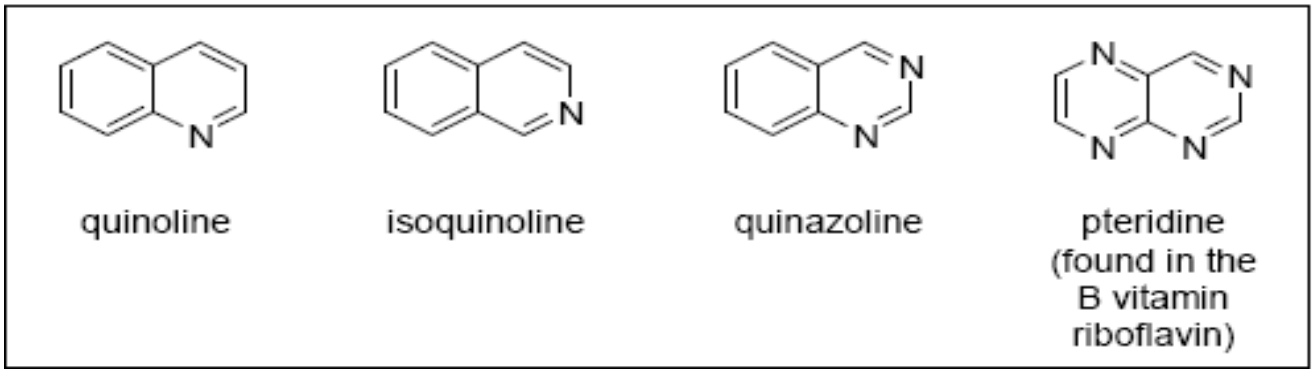


indole (found in the amino acid tryptophan) | isoindole | indazole | purine (DNA/RNA base) | indolizidine

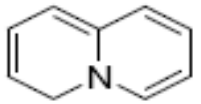


Guanine

common ring-fused azines



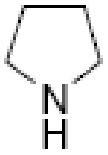
quinoline | isoquinoline | quinazoline | pteridine (found in the B vitamin riboflavin)



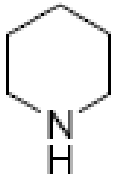
quinolizidine

Trivial names

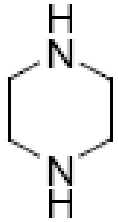
4) Saturated heterocycles



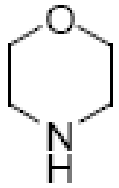
pyrrolidine



piperidine



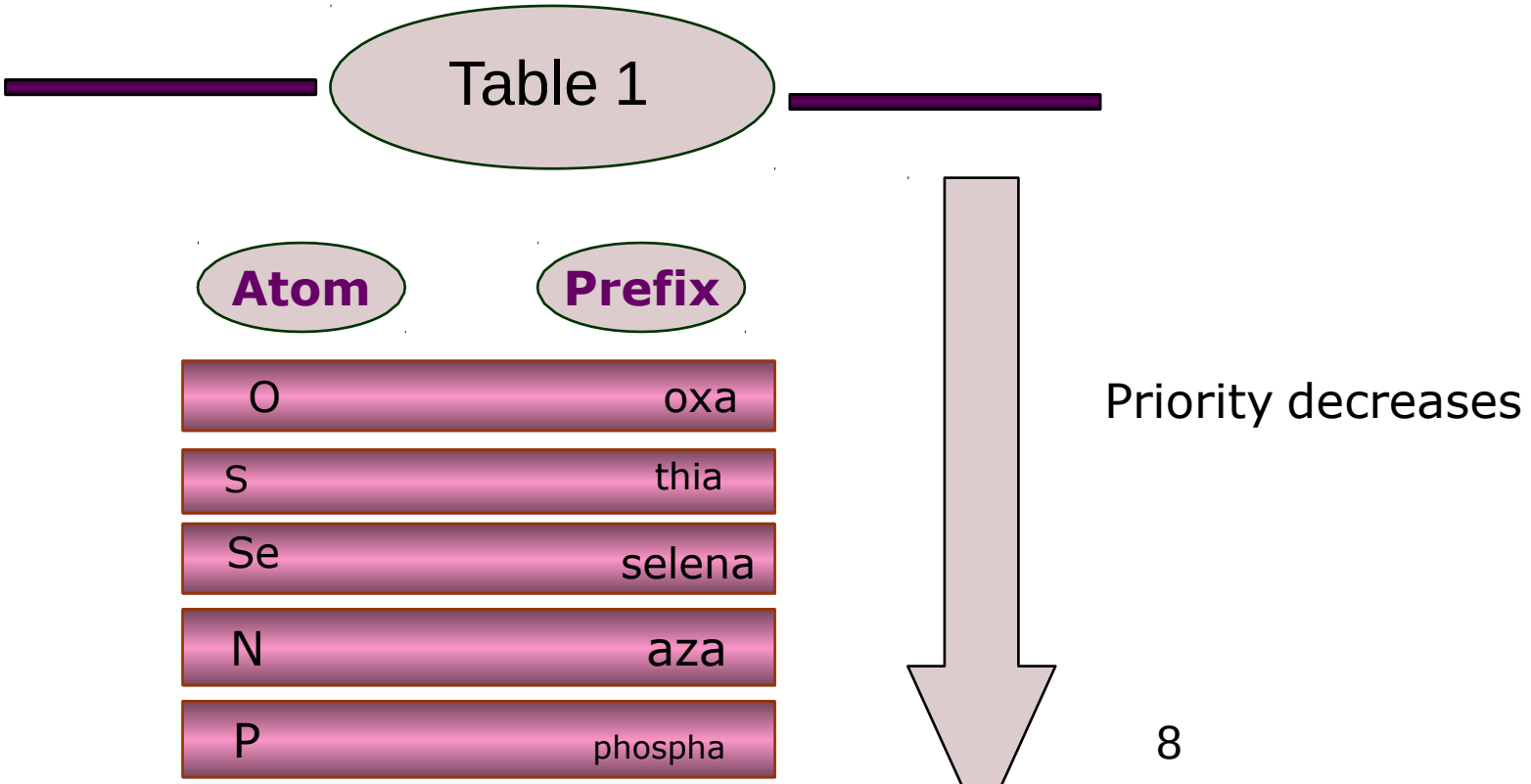
piperazine



morpholine

II- Replacement nomenclature

- 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).



II- Replacement nomenclature

Benzene

Cyclopentadiene

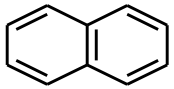
Cyclopentadiene

Cyclopropane

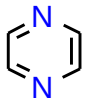
Cyclopropene

Cyclopentadiene

Cyclohexane

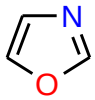


Naphthalene



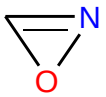
1,4-Diazabenzene

Oxacyclopenta-2,4-diene



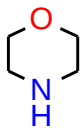
1-Oxa-3-azacyclopenta-2,4-diene

Oxacyclopropane

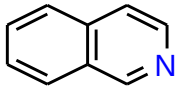


Oxazacyclopropene

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



1-Oxa-4-azacyclohexane



2-Azanaphthalene

III-Hantzsch-Widman nomenclature (IUPAC)

- German chemists Arthur Hantzsch and Oskar Widman, proposed similar systematic naming of heterocyclic compounds in 1887 and 1888 respectively.

- three to ten-membered rings 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 and the degree of unsaturation

- In addition, the suffixes distinguish between nitrogen-containing heterocycles and heterocycles that do not contain nitrogen

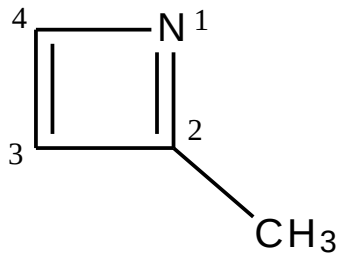
- IUPAC name = locants+ prefix + suffix

Hantzsch-Widman rules for fully saturated and fully unsaturated heterocycles

1) Identify the hetroatom present in the ring and choose from (table 1 on slide 8) the corresponding prefix .

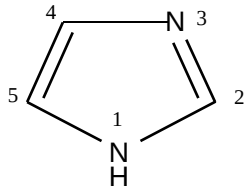
2) The position of a single heteroatom control the numbering in a monocyclic compound. The heteroatom is always assigned position 1 and if substituents present are then counted around the ring in a manner so as to take the lowest possible numbers.

For example:



Hantzsch-Widman rules

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

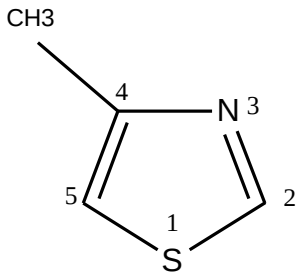


4) If more than one type of hetroatoms present in the ring the name will include more than one prefix with locants to indicate the relative position of the heteroatoms.

- 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).

Hantzsch-Widman rules

- 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 the prefix corresponding to the following compound is 4-Methyl-1,3-Thiaza….



5) Choose the appropriate suffix from (table 2) depending on whether or not nitrogen atom is present in the ring, the size of the ring and presence or absence of any double bonds

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

Hantzsch-Widman rules

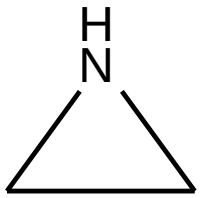
Table 2

Ring size	N-present		N-absent	
	Unsat	sat	Unsat	sat
	irine	iridine	irene	irane
	ete	etidine	ete	etane
	ole	olidine	ole	olane
	ine	a	in	ane
	epine	a	epin	epane
	ocine	a	ocin	ocane
9	onine	a	onin	onane
10	ecine	a	ecin	ecane

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

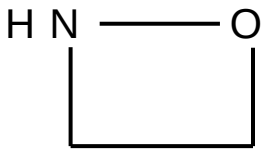
Hantzsch-Widman rules

- Examples



- 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**

Hantzsch-Widman rules



- This ring contains (O ,N) and (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

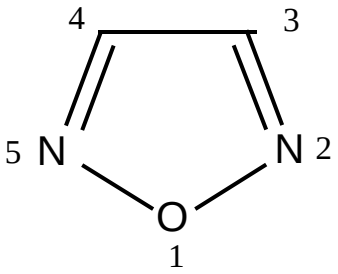
  1,2-Oxaza

- 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

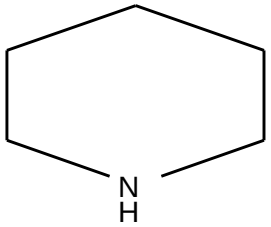
Hantzsch-Widman rules



- This ring contains (O) → prfix1 (oxa), and two (N) → prfix2 diaza
- Locants, since (O) is higher priority than (N) so it is in position 1 by default and the two (N) are therefore at positions 2 and 5, this gives the combined prefixes as 1,2,5-oxadiaza (note that the a in oxa is not dropped)
- It is 5-membered,fully unsaturated ring with (N) → the suffix is ole
- By combining the prefixes and the suffix and dropping the appropriate vowels we get the correct name as

1,2,5-Oxadiazole

Hantzsch-Widman rules



ϖ The ring is 6-memberd, fully saturated with N ⇒

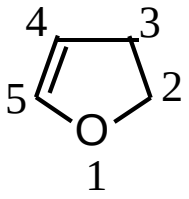
Prefix perhydro followed by the name of fully unsaturated 6-memberd ring with nitrogen ⇒ azine

ϖ Thus the full name is **perhydroazine**

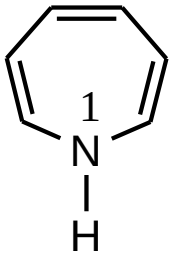
Hantzsch-Widman rules for partially unsaturated heterocycles

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

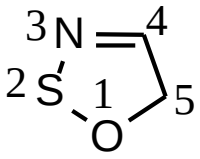
a) The position of nitrogen or carbon atoms which bear extra hydrogen atoms must be indicated by numbers and italic capital H (e.g. 1*H*, 2*H*, etc.) followed by the name of maximally unsaturated ring.



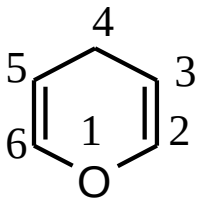
2*H*, 3*H*-Oxole



1*H*-Azepine



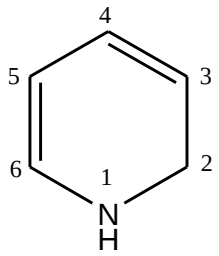
5H-1,2,3-Oxathiazole



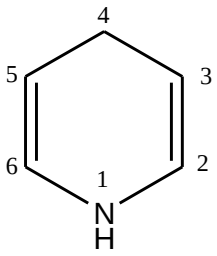
4*H*-Oxin

Hantzsch-Widman rules for partially unsaturated heterocycles

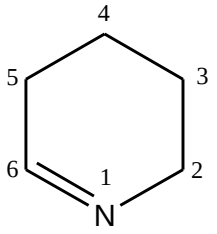
b) The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated Hantzsch-Widman name.



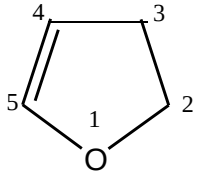
1,2-Dihydroazine



1,4-Dihydroazine



2,3,4,5-Tetrahydroazine



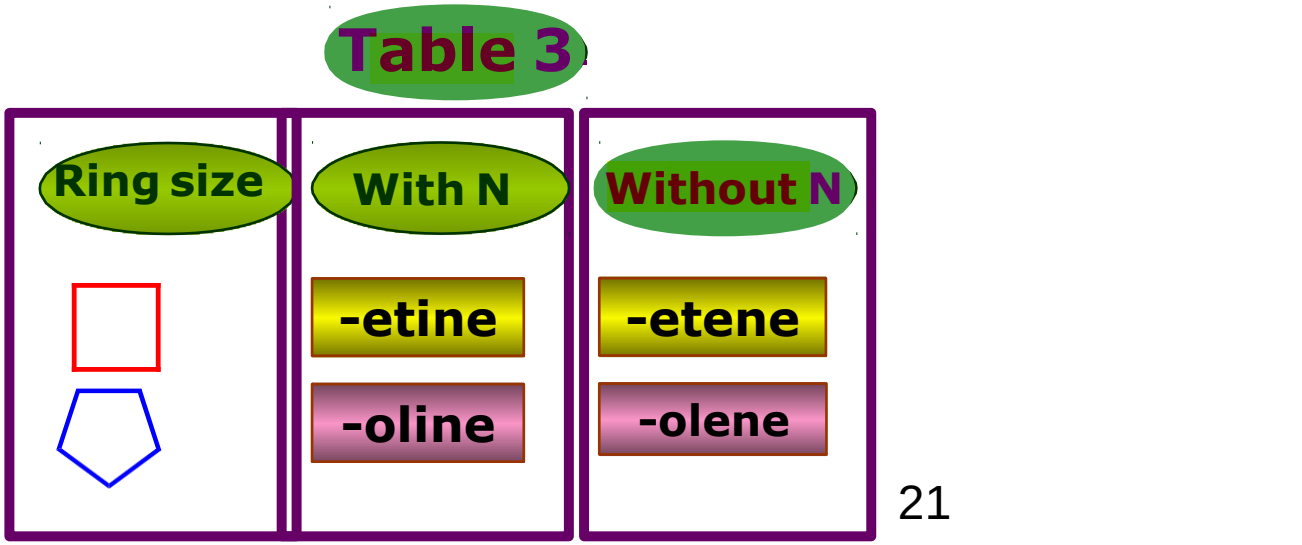
2,3-Dihydrooxole

Hantzsch-Widman rules for partially unsaturated heterocycles

c) Alternatively, the partially unsaturated 4 and 5 rings (i.e. rings contain one double bond) are given special Hantzsch-Widman suffixes as in table 3 and the double bond is specified as Δ^1, Δ^2, Δ^3, etc.. Which indicates 1 and 2; 2 and 3; 3 and 4 atoms respectively have a double bond

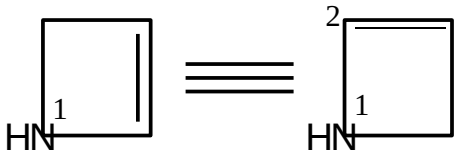
(i.e. Name : Δ + Prefix + special suffix)

(x= locant of the double bond)

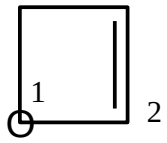


Hantzsch-Widman rules for partially unsaturated heterocycles

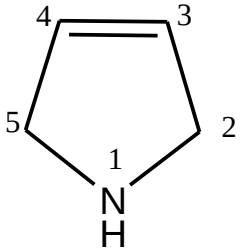
- Examples



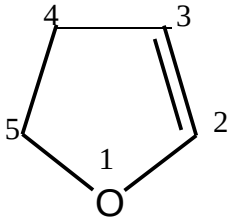
Δ^2 -Azetine



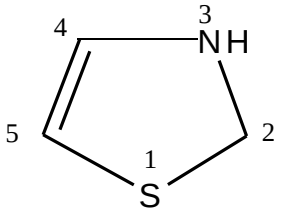
Δ^2 -Oxetene



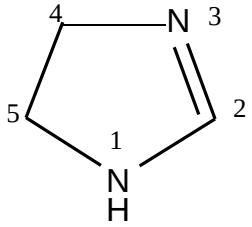
Δ^3 -Azoline



Δ^2 -Oxolene



Δ^4 -1,3-Thiazoline

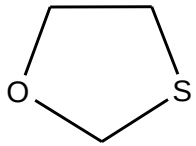


Δ^2 -1,3-Diazoline

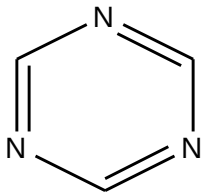
Hantzsch-Widman rules

- Exercise:

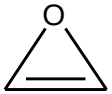
  Explain how can you name the following heterocycles.



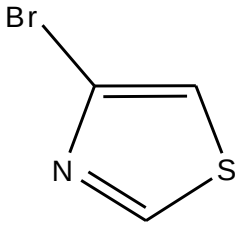
1,3-Oxathiolane



1,3,5 triazine



Oxirene



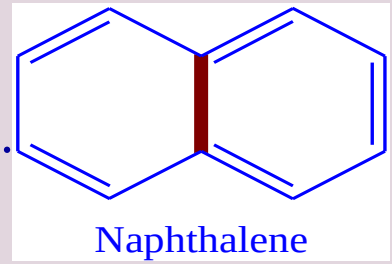
4 bromo 1,3 thiazole

Heterocyclic Nomenclature

Nomenclature of Fused Systems

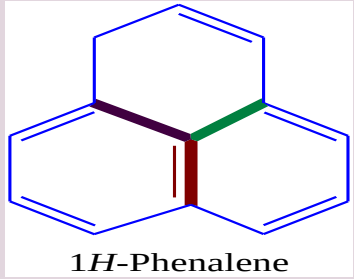
Definitions:

- 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.


Naphthalene

- *Ortho-fused* rings: are those rings that have only two common atoms and one bond, example; 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).


1*H*-Phenalene

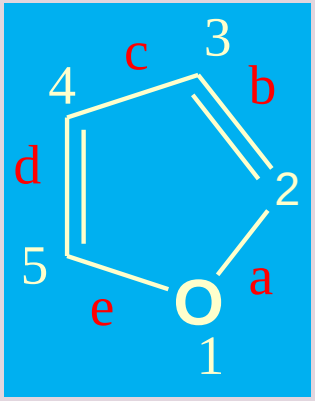
- 1*H*-phenalene is considered as being composed of three benzene rings, each is *ortho-peri*-fused to the other two.

- Polycyclic compounds incorporating one heterocyclic ring or fused heterocylic 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

Heterocyclic Nomenclature

Nomenclature of Fused Systems

A. Nomenclature of benzofused compounds:

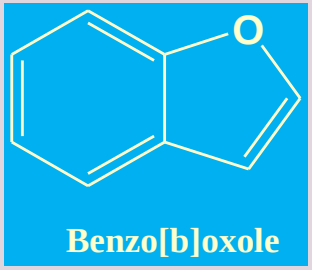


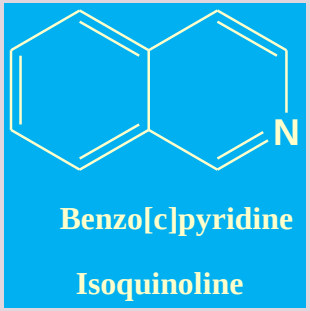
Polycyclic compounds incorporating one heterocyclic ring or fused heterocylic system fused to benzene are known benzoheterocycles and is named by:

1. prefix: the word benzo
2. letter in square brackets: indicating the position of fusion
3. name of heterocyclic ring: (common or IUPAC name).

Name= Benzo[letter]name of heterocyclic ring

(the connected bond take letter (a,b,c …)





Heterocyclic Nomenclature

Nomenclature of Fused Systems

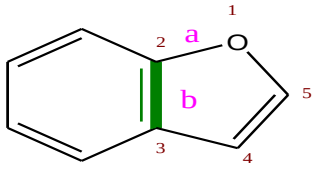
For designating the position of fusion the following rule is followed

1. Numbering the H.C.R

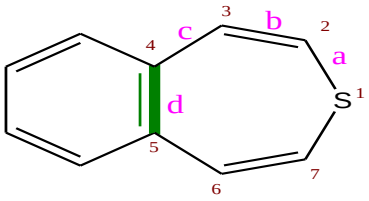
a. When numbering a ring with one heteroatom, the heteroatom is #1 and continues in the direction that is closer to the fused bond.

b. When numbering a ring with more than one heteroatom, the highest priority atom is #1 and continues in the direction that gives the next priority atom the lowest number.

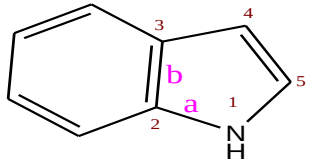
2. The bonds of the heterocyclic ring are assigned by alphabetical letters staring with the 1,2-bond



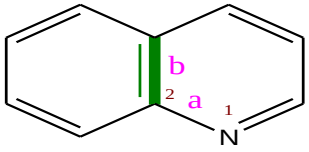
Benzo[b]furan



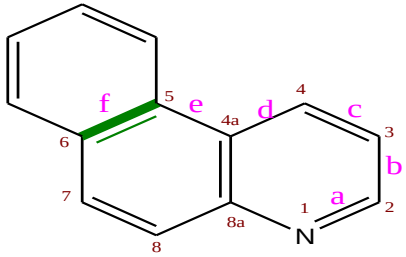
Benzo[d]thiepine



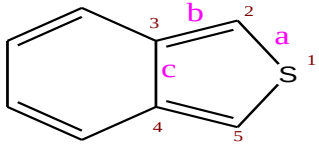
Benzo[b]pyrrole
Indole



Benzo[b]pyidine
Qunioline



Benzo[f]qunioline



Benzo[c]thiophene

B. Nomenclature of fused heterocylic compounds:

Naming a fused heterocyclic systems composed of two monoheterocyclic units or benzoheterocycles (e.g. chromene) fused with anotehr hetrocycle ring is based upon considering one system as the parent (base) and the second is considered as subsitituent

The name is formed of :

name of substituent ring (minor ring)[number, number-letter] name of base ring (major ring

❖The name of the minor ring is derived by writing a contracted prefix for the substituent ring present

Furo	from	Furan
Imidazo	from	Imidazole
pyrido	from	Pyridine
Pyrimido	from	Pyrimidine
Thieno	from	Thiophene
Pyridazino	from	pyridazine
Pyrazino	from	pyrazine
Chromeno	from	chromene

B. Nomenclature of fused heterocylic compounds:

- The numbers indicate which atoms in the minor ring are common to the major ring (fusion sites in minor ring).
- The order of the numbers indicates which atom of the minor ring is encountered closest to atom 1 in the major numbering system (i.e. these numbers may be written in ascending or descending order e.g.2,3 or 3,2)
- The letter defines the position of attachment of the minor ring to the major ring (fusion sites in base component)
- Finally a suffix indicate the name of the base ring is written.
- The numbering system for the whole fused system is not the same as the numbers in the square brackets (i.e. there are three numbering systems; one for minor ring, one for major ring and the third is for the system as a whole)

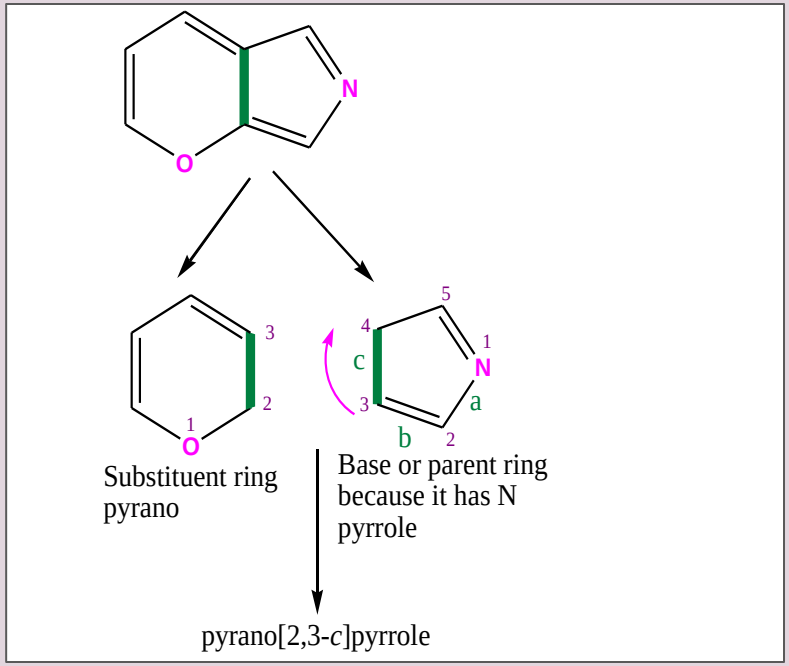
B. Nomenclature of fused heterocylic compounds:

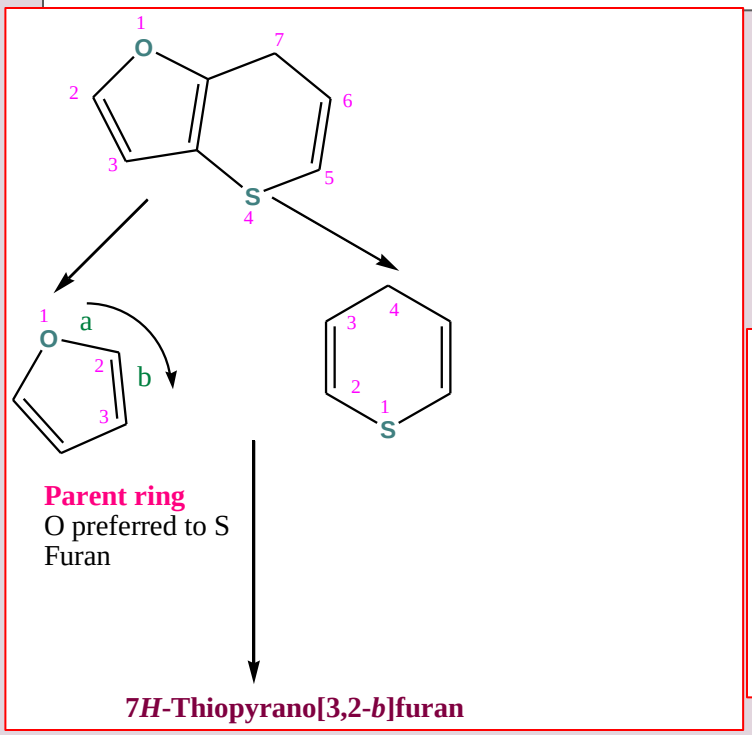
Priority order of component ring systems:

- Selection of a parent or base ring is based on the following rules which are applied in order

Rule 1: A heterocyclic ring containing the heteroatom occurring earliest in the order N, O, S,

(i.e. ring containing N preferred to the rings does not contain N or containing O, or S)



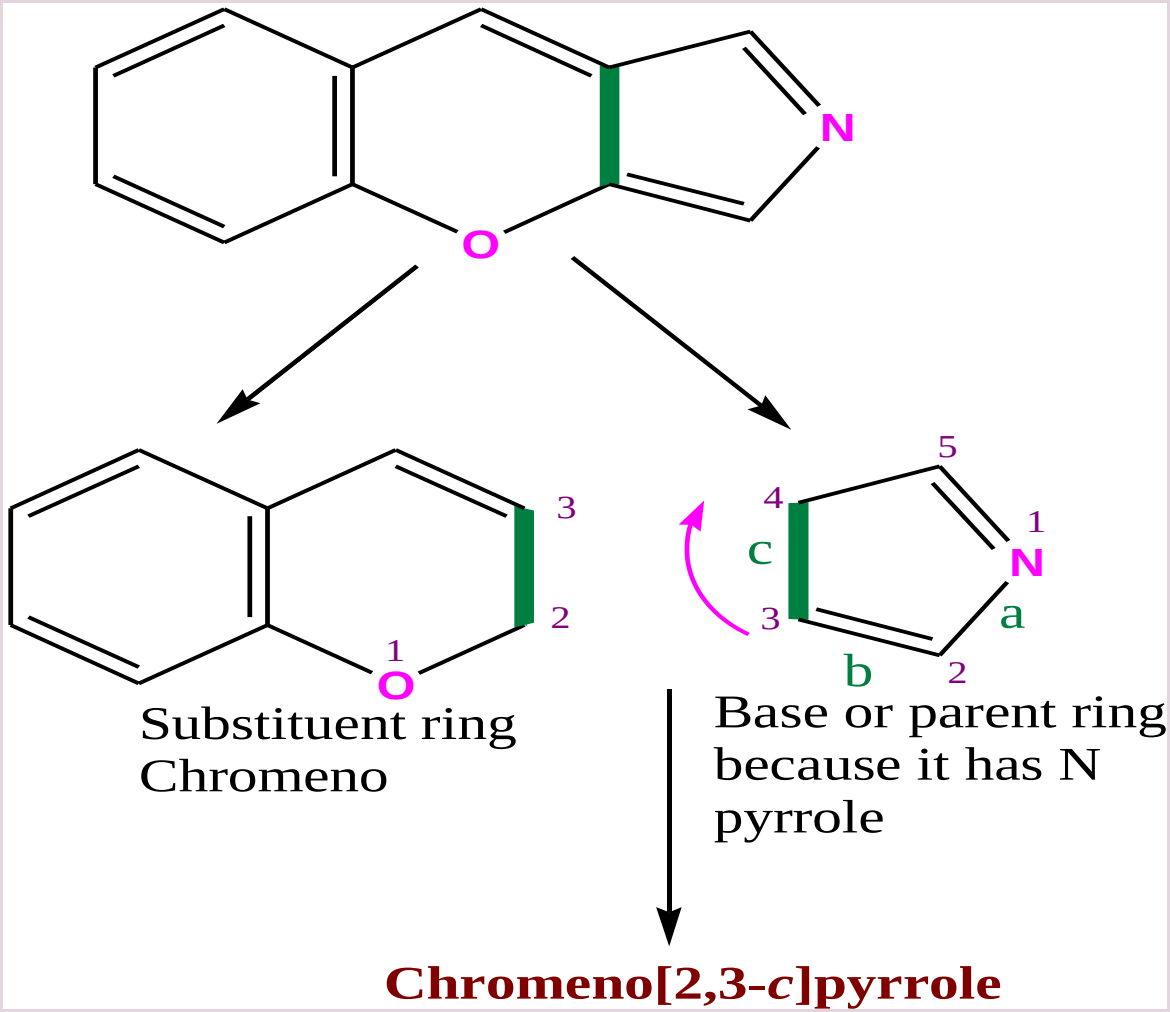


Note: The numbering system for the whole fused system is not the same as the numbers in the square brackets (i.e. there are three numbering systems; one for parent ring, one for substituent ring and the third is for the system as a whole)

B. Nomenclature of fused heterocylic compounds:

Priority order of component ring systems:

Rule 1: more example

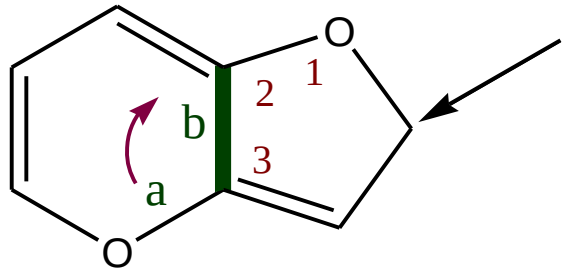


Heterocyclic Nomenclature

Nomenclature of Fused Systems

Priority order of component ring systems:

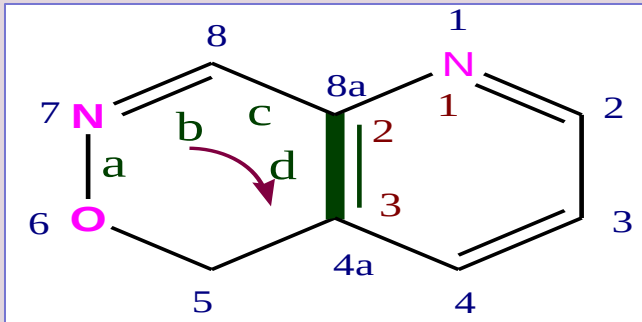
Rule 2: A heterocyclic component containing the largest possible individual ring



2*H*-Furo[3,2-*b*]pyran
(pyran [6] preferred to furan [5])

Numbering the whole system is started from O in furan ring to give the two heteroatoms 1,4 while starting from O in pyran ring gives them 1,5, thus the indicated H takes 2

Rule 3: A heterocyclic component containing the greater number of heteroatom of any kind



5*H*-Pyrido[2,3-*d*][1,2]oxazine
(Oxazine preferred to pyridine)

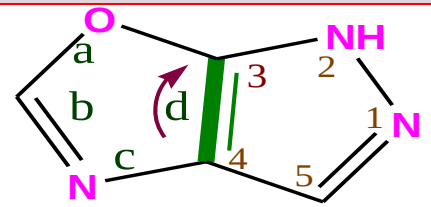
Note: The whole molecule is numbered starting from pyridine ring to give the three heteroatom the lowest possible number (1,6,7), however, stating from oxazine ring will give them (2,3,5) or (2,3,8).

Heterocyclic Nomenclature

Nomenclature of Fused Systems

Priority order of component ring systems:

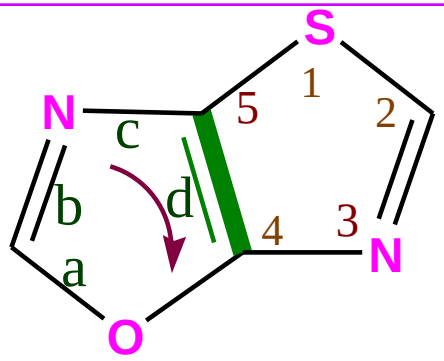
Rule 4: A heterocyclic component containing the greater variety of heteroatom



1*H*-Pyrazolo[4,3-*d*]oxazole
(O & N preferred to N only)

Note: The whole molecule is numbered starting from pyrazole ring to give the four heteroatom the lowest possible number (1,2,4,6). While starting from oxazole ring give them (1,3,4,5) or (1,3,5,6).

Rule 5: A heterocyclic component containing the greater number of heteroatoms most preferred when considered in order O, S,N,



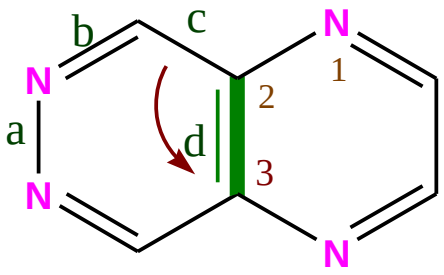
[1,3]Thiazolo[5,4-*d*][1,3]oxazole
(N & O preferred to N & S)

Heterocyclic Nomenclature

Nomenclature of Fused Systems

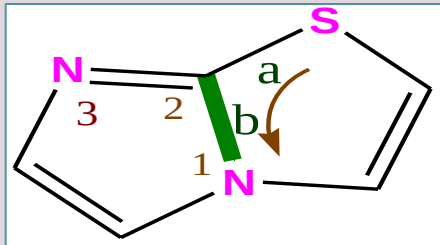
Priority order of component ring systems:

Rule 6: A heterocyclic component with the lower possible number for heteroatoms



Pyrazino[2,3-*d*]pyridazine
(pyridazine [2N-1,2] preferred to pyrazine [2N-1,4]

Rule 7: If a position of fusion is occupied by a heteroatom the name of the component rings to be used are so chosen as both to contain the heteroatom.



Imidazo[2,1-*b*]thiazole

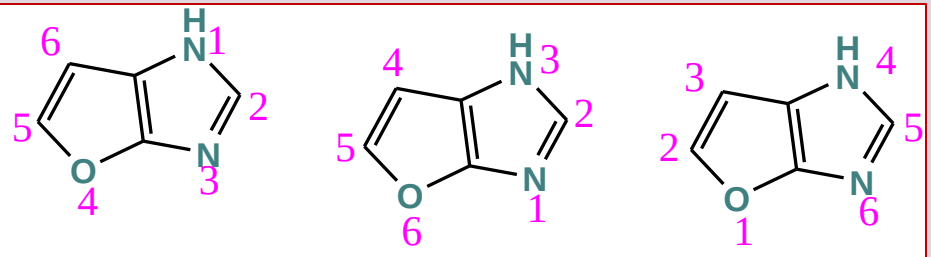
Heterocyclic Nomenclature

Nomenclature of Fused Systems

Order of preference between alternative numbering system of the whole molecule

Numbering the whole fused system should start from the first atom after fusion in any direction to fulfill the following rules in order:

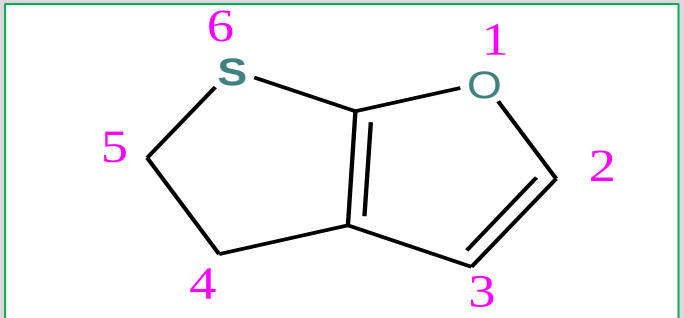
a)Give low numbers for the heteroatoms as a set



1*H*-Furo[2,3-*d*]imidazole

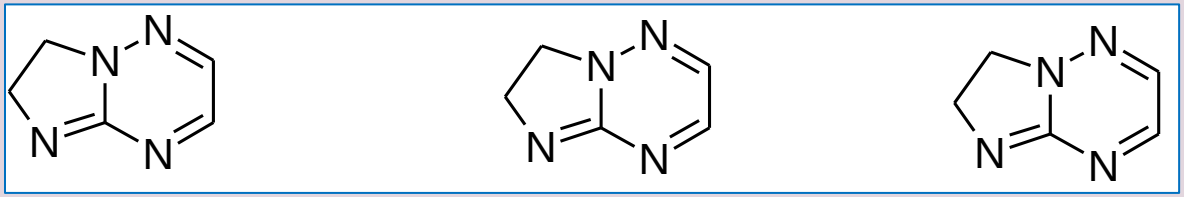
(heteroatoms 1,3,4 is preferred to 1,3,6 or 1,4,6)

b)Give low numbers for heteroatoms of higher priority O,S, N



4,5-Dihydro-thieno[2,3-*b*]furan

c) Give low numbers to fusion carbon atom



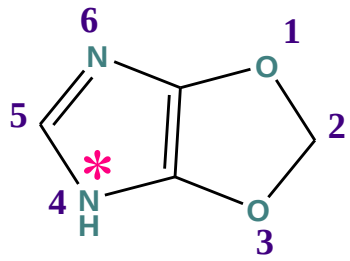
6,7-dihydroimidazo[1,2-*b*][1,2,4]triazine

Fusion carbon 4a is preferred to 7a

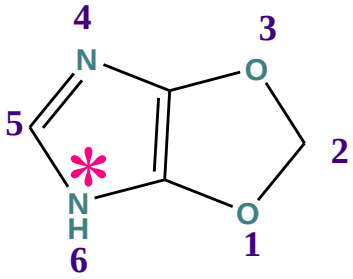
Heterocyclic Nomenclature

Nomenclature of Fused Systems

D) Give low numbers to indicate hydrogen atom



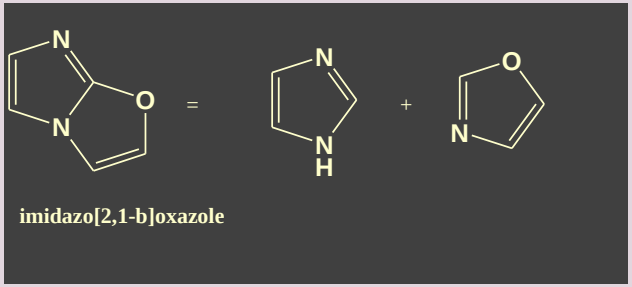
Not



4*H*-[1,3]dioxolo[4,5-d]imidazole

B)- If there is a heteroatom at the position of the fusion …)

divide the components such that the common heteroatom is a member of both component parts



Heterocyclic Nomenclature

Summary of Nomenclatures Rules

Scheme for deriving the base component of' a fused ring system

1. **Is there only one ring which contains nitrogen?**
   (YES:. choose this as base component)
2. **Are the two rings have the same heteroatoms but their size is different ?**
   (Yes: choose the larger one)
3. **Are the two rings of the same size but have different heteroatoms?**
   (YES: choose the ring containing a heteroatom of the highest priority i.e. O >S)
4. **Are the rings of the same size but contain different numbers of heteroatoms?**
   (Yes: choose the ring with the greater number)
5. **Are the two rings of the same size and the same number of different heteroatoms?**
   (Yes: choose the ring with the greatest variety of heteroatoms

7-Are the two rings have the same size and the same number and type of heteroatoms?

(yes: choose the ring with the lower numbers for heteroatoms)