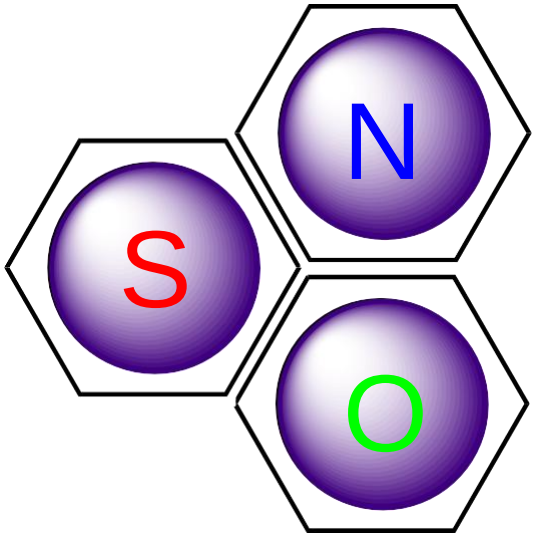
Unit-I
Nomenclature of Heterocyclic compounds



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Subject: Pharmaceutical Organic chemistry-III (B.Pharm II/I sem , 15R00303)

Nomenclature of heterocyclic compounds

- Three systems for naming heterocylic compounds:

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

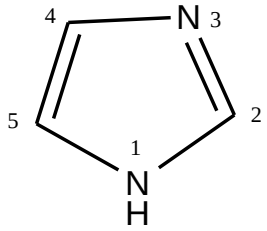
2) The replacement method

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.

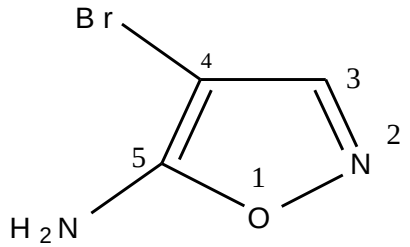
ϖ If there is more than one hetroatom of the same type numbering starts at the saturated one, e.g. imidazole.



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.

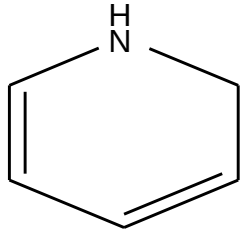
I-Common Nomenclature

- 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.

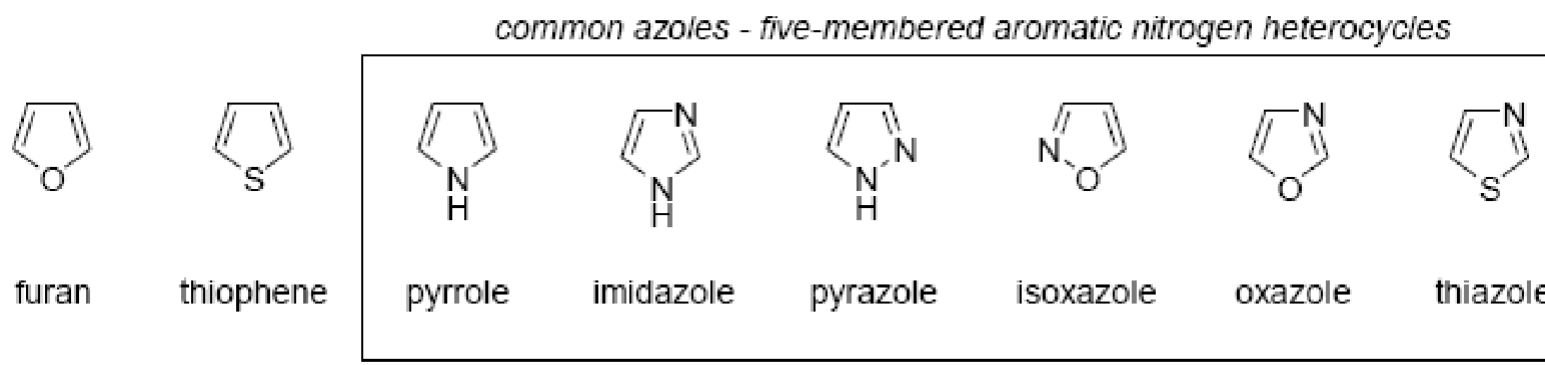


1,2-Dihydro-pyridine

Trivial names

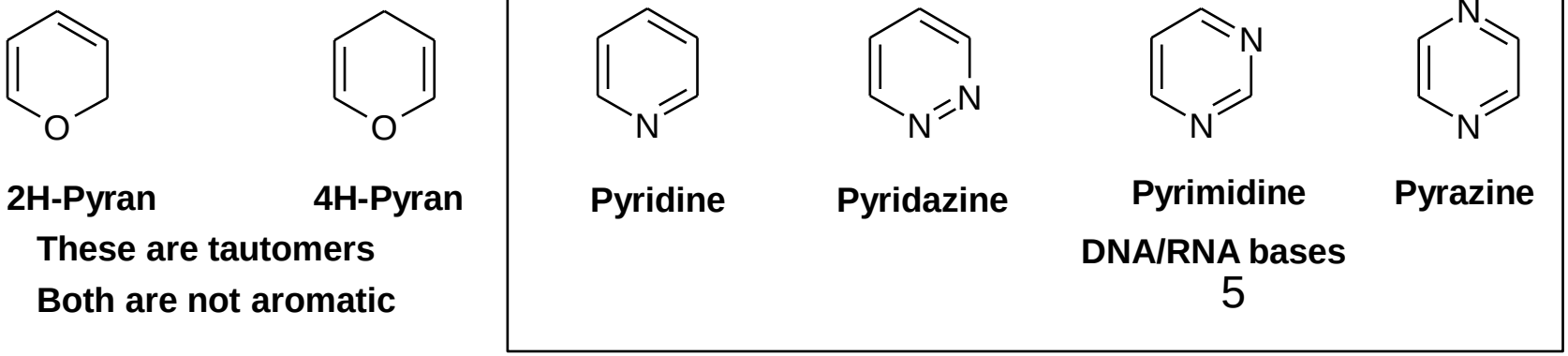
1) 5-membered heterocycles with one or two heteroatoms

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

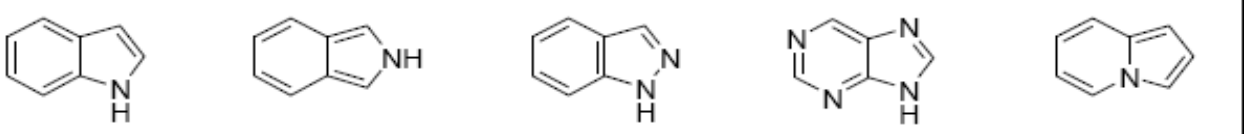
Both are not aromatic

DNA/RNA bases

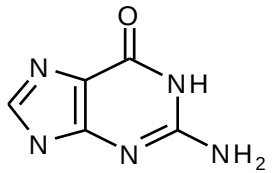
Trivial names

3) Fused heterocycles

common ring-fused azoles

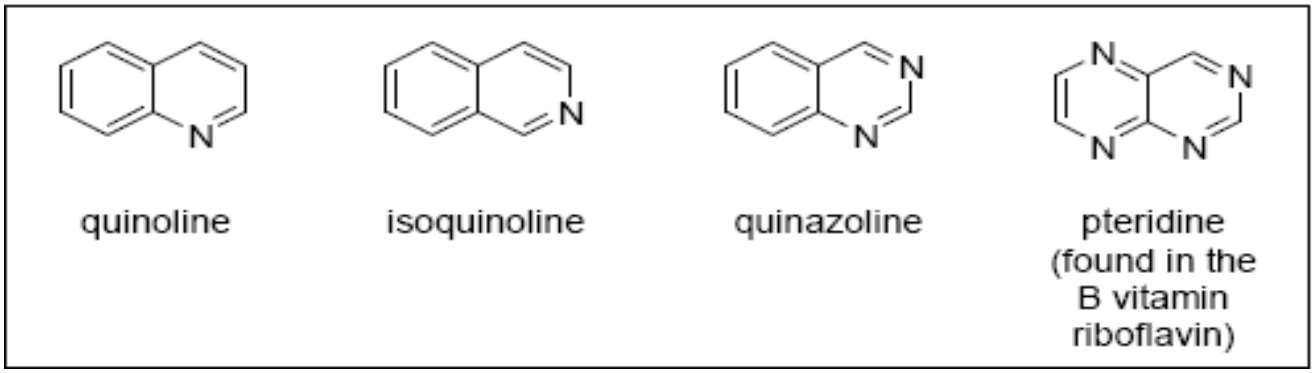


indole (found in the amino acid tryptophan) | isoindole | indazole | purine (DNA/RNA base) | indolizidine

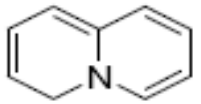


Guanine

common ring-fused azines



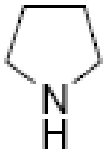
quinoline | isoquinoline | quinazoline | pteridine (found in the B vitamin riboflavin)



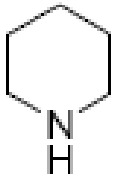
quinolizidine

Trivial names

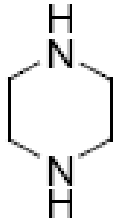
4) Saturated heterocycles



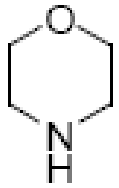
pyrrolidine



piperidine



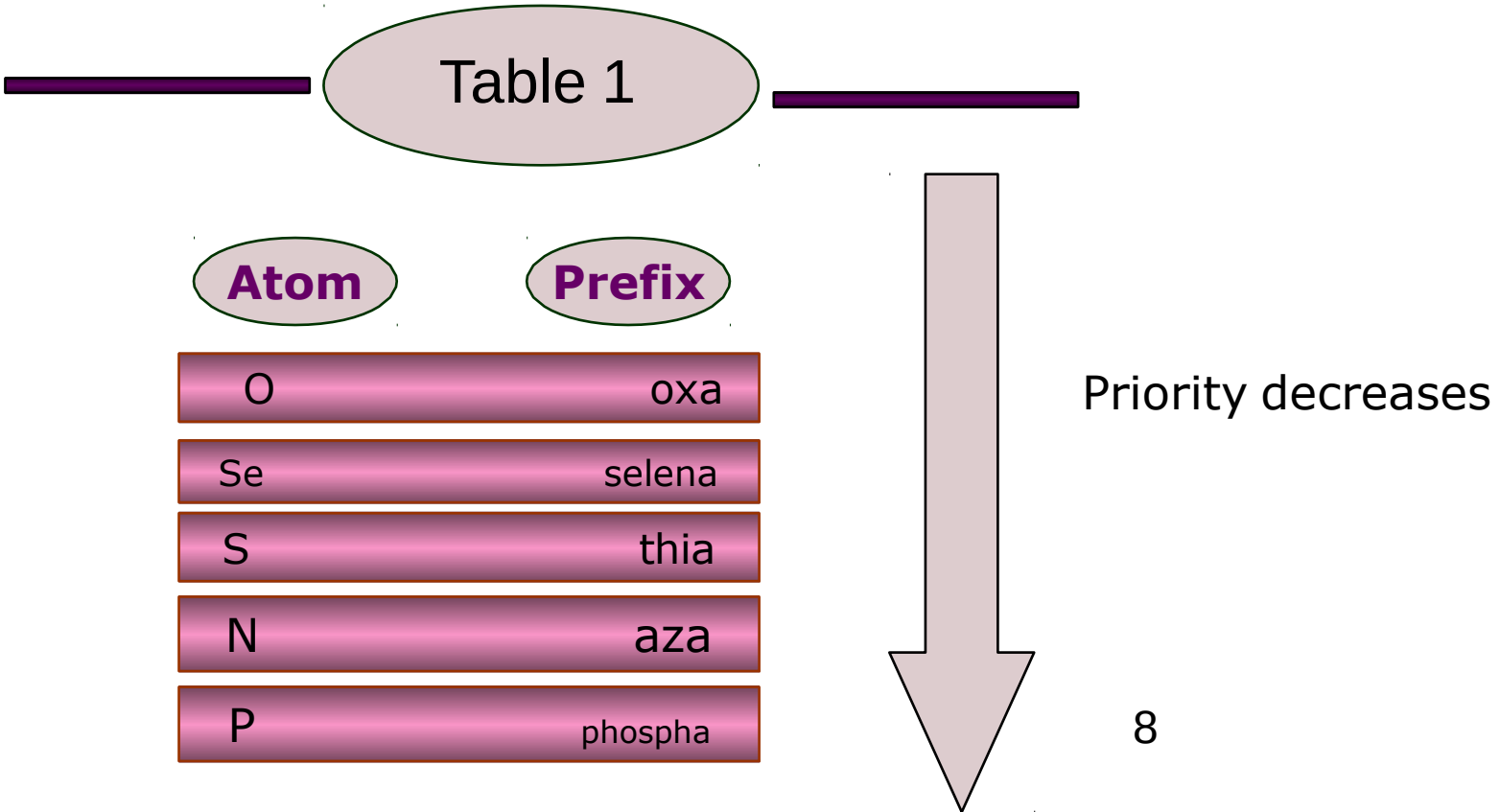
piperazine



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

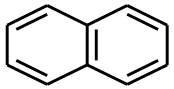
Cyclopentadiene

Cyclopropane

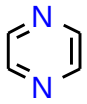
Cyclopropene

Cyclopentadiene

Cyclohexane

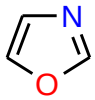


Naphthalene



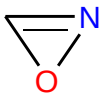
1,4-Diazabenzene

Oxacyclopenta-2,4-diene



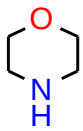
1-Oxa-3-azacyclopenta-2,4-diene

Oxacyclopropane

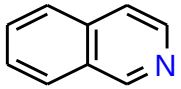


Oxazacyclopropene

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

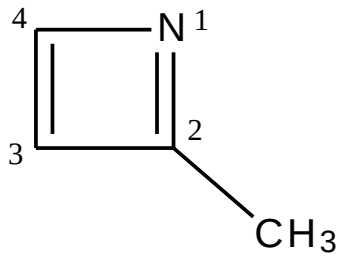
- IUPAC name = locants+ prefix + suffix

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 .

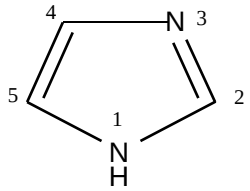
2) The position of a single heteroatom control the numbering in a monocyclic compound. The heteroatom is always assigned position 1 and if substituents present are then counted around the ring in a manner so as to take the lowest possible numbers.

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….

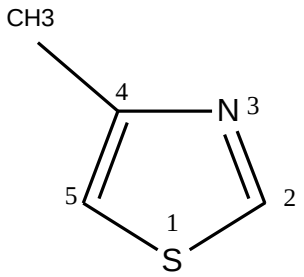


4) If more than one type of hetroatoms present in the ring the name will include more than one prefix with locants to indicate the relative position of the heteroatoms.

- 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

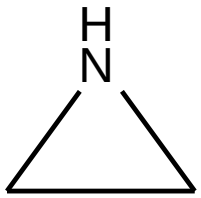
Table 2

Ring size	N-present		N-absent	
	Unsat	sat	Unsat	sat
3	irine	iridine	irene	irane
4	ete	etidine	ete	etane
5	ole	olidine	ole	olane
6	ine	a	in	ane
7	epine	a	epin	epane
8	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

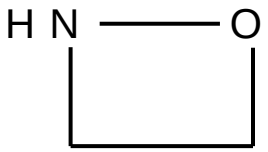
Hantzsch-Widman rules

- 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

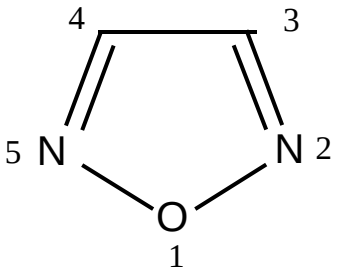
  1,2-Oxaza

- 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

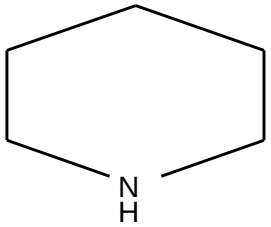
Hantzsch-Widman rules



- 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 ⇒

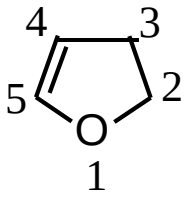
Prefix perhydro followed by the name of fully unsaturated 6-memberd ring with nitrogen ⇒ azine

ϖ Thus the full name is **perhydroazine**

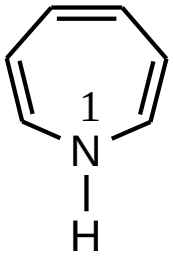
Hantzsch-Widman rules for partially unsaturated heterocycles

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

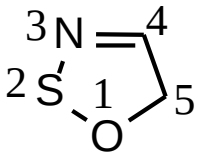
a) The position of nitrogen or carbon atoms which bear extra hydrogen atoms must be indicated by numbers and italic capital H (e.g. 1*H*, 2*H*, etc.) followed by the name of maximally unsaturated ring.



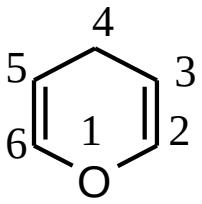
2*H*, 3*H*-Oxole



1*H*-Azepine



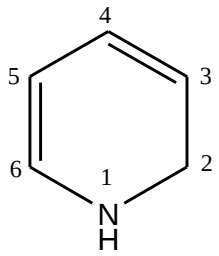
5H-1,2,3-Oxathiazole



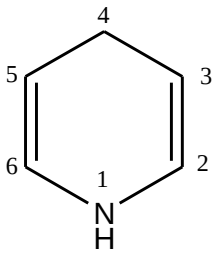
4*H*-Oxin

Hantzsch-Widman rules for partially unsaturated heterocycles

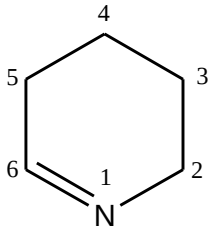
b) The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated Hantzsch-Widman name.



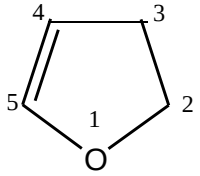
1,2-Dihydroazine



1,4-Dihydroazine



2,3,4,5-Tetrahydroazine

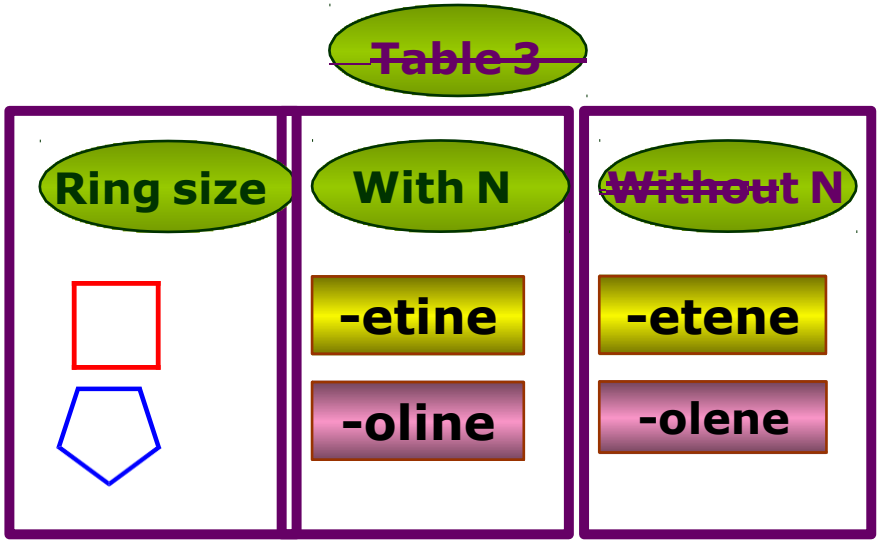


2,3-Dihydrooxole

Hantzsch-Widman rules for partially unsaturated heterocycles

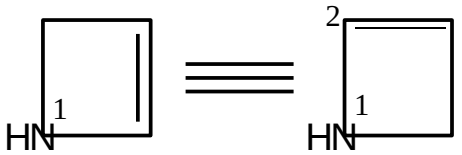
c) Alternatively, the partially unsaturated 4 and 5 rings (i.e. rings contain one double bond) are given special Hantzsch-Widman suffixes as in table 3 and the double bond is specified as Δ^1, Δ^2, Δ^3, etc.. Which indicates 1 and 2; 2 and 3; 3 and 4 atoms respectively have a double bond

(i.e. Name : Δ^x + Prefix + special suffix)
(x= locant of the double bond)

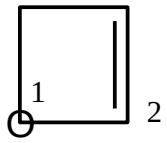


Hantzsch-Widman rules for partially unsaturated heterocycles

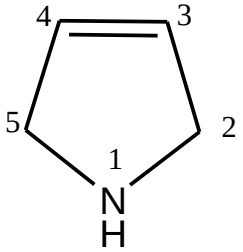
- Examples



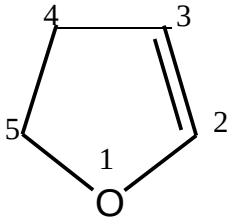
Δ^2 -Azetine



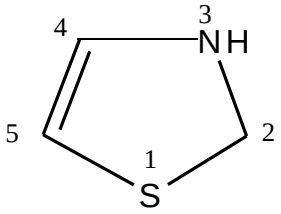
Δ^2 -Oxetene



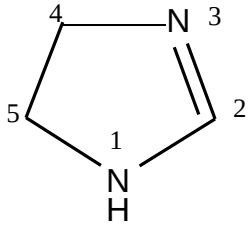
Δ^3 -Azoline



Δ^2 -Oxolene



Δ^4 -1,3-Thiazoline

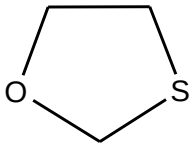


Δ^2 -1,3-Diazoline

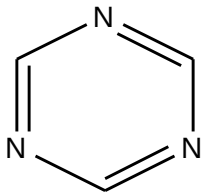
Hantzsch-Widman rules

- Exercise:

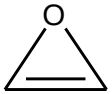
  Explain how can you name the following heterocycles.



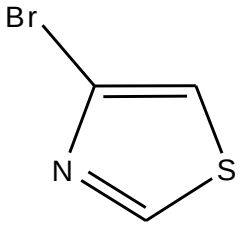
1,3-Oxathiolane



1,3,5 triazine



Oxirene



4 bromo 1,3 thiazole