An Introduction to Heterocyclic Chemistry

Reference: A Textbook of Organic Chemistry, Tewari and Vishnoi

This is only the introduction part of the unit on heterocyclic chemistry. Please refer textbook for detailed information.

Introduction
Cyclic compound having only carbons as the ring members, such as benzene are called carbocyclic compounds. As only carbon forms the backbone of the ring, it is also a homocyclic compound.

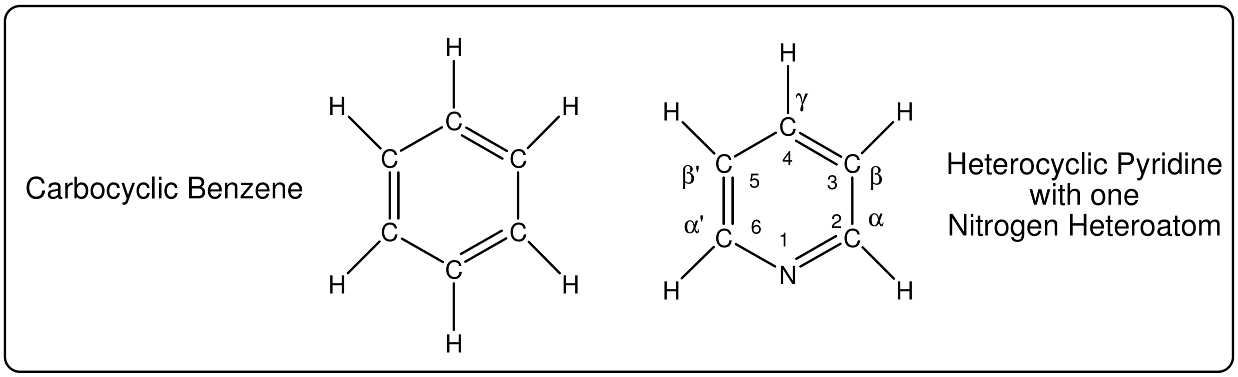


Figure 1: Structure of Homocyclic Benzene and Heterocyclic Pyridine

In contrast, cyclic compounds having at least one atom other than carbon as ring members, (e.g. Pyridine with nitrogen replacing one of the carbon atom) may be termed as **heterocyclic compounds**. These atoms are termed as **heteroatoms**. The structure of benzene and pyridine are provided in figure 1 above.

Nomenclature of Heterocyclic Compounds
Heterocyclic compounds are popularly known by their common names. However, IUPAC has provided a systematic nomenclature with prefix and suffix as discussed below. According to IUPAC, the numbering starts with the heteroatom as shown in figure 1. According to common names, the greek letters, α, β, γ etc are followed as shown in figure 1.

Order of Seniority	Prefix	Suffix
1	Oxa for oxygen	
2	Thia for sulfur	-ole for 5 membered rings
3	Aza for nitrogen	-ine for 6 membered rings
4	Phoshpha for phosphorus	-epine for 7 membered rings
5	Bora for boron	

Table 1: Nomenclature of Heterocyclic compounds

When more than one heteroatom is present in a molecule, an order of seniority exists for the naming and numbering system, with the number preference given for oxygen first followed by other atoms as shown. So when oxygen is present, the prefix is specified is oxa etc. These compounds end with –ole, -ine and –epine for 5, 6 and 7 membered rings as shown. This naming convention has been followed in all the examples provided below.

Heterocyclic Compounds

*By definition (as per textbook), heterocyclic compounds are five and six membered **ringed** compounds, that contain atleast one **hetero-atom**, relatively **stable** and show **aromaticity**.* (However, other sources claim that aromaticity is not a prerequisite for defining heterocyclic compounds. But, we will stick to the textbook definition!)

So, let us check below the significance of the terms defined above: (i) Atleast one heteroatom, (ii) Five and Six Membered Rings, (iii) Relatively Stable and (iv) Show Aromaticity.

(i) Heteroatom

Although any atom (other than carbon) can form the heterocyclic ring, usually N, O, and S are the heteroatoms found in nature, especially in biological macromolecules.

(ii) Five and Six Membered Ringed Structures Containing a Heteroatom

A ring system can be theoretically made up of 3, 4, 5, 6 or more ring members. Examples of such compounds containing one heteroatom is depicted in the figure 2. All compounds in the first 3 columns have saturated carbon atoms and **do not** possess a conjugated bond system are **not aromatic** compounds. The last 3 columns contain compounds that contain unsaturation, however **not all of them are aromatic** (as defined below).

(iii) Stability

The 3 and 4 membered ring compounds however are **not stable** due to the strain in the ring system. Hence, by definition of heterocyclic compounds these compounds are not heterocyclic compounds.

(iv) Aromaticity

Aromatic compounds should satisfy the following 4 conditions:

a) A system of conjugated and delocalized pi bonds
b) A planar molecule
c) A ring system following **Huckle's rule**, which requires 4n+2 pi electrons in the ring system (where n=0,1,2,3…). So, aromaticity normally exists when n=2, 6, 10… pi electrons exist in the ring system. In special cases, a pair of pi electrons may be substituted by non-bonding, "n" electrons. Hence a conjugated bond system with 2, 6, or 10 pi or n electrons is a prerequisite for aromaticity.
d) A relatively stable structure

Benzene is a typical aromatic compound which is planar, having a system of conjugated and delocalized pi bonds. It has a ring structure with 6 pi electrons forming 3 pi bonds and obeying the huckle rule (n=1, so 4n+2 = 6) as shown in the figure 3.

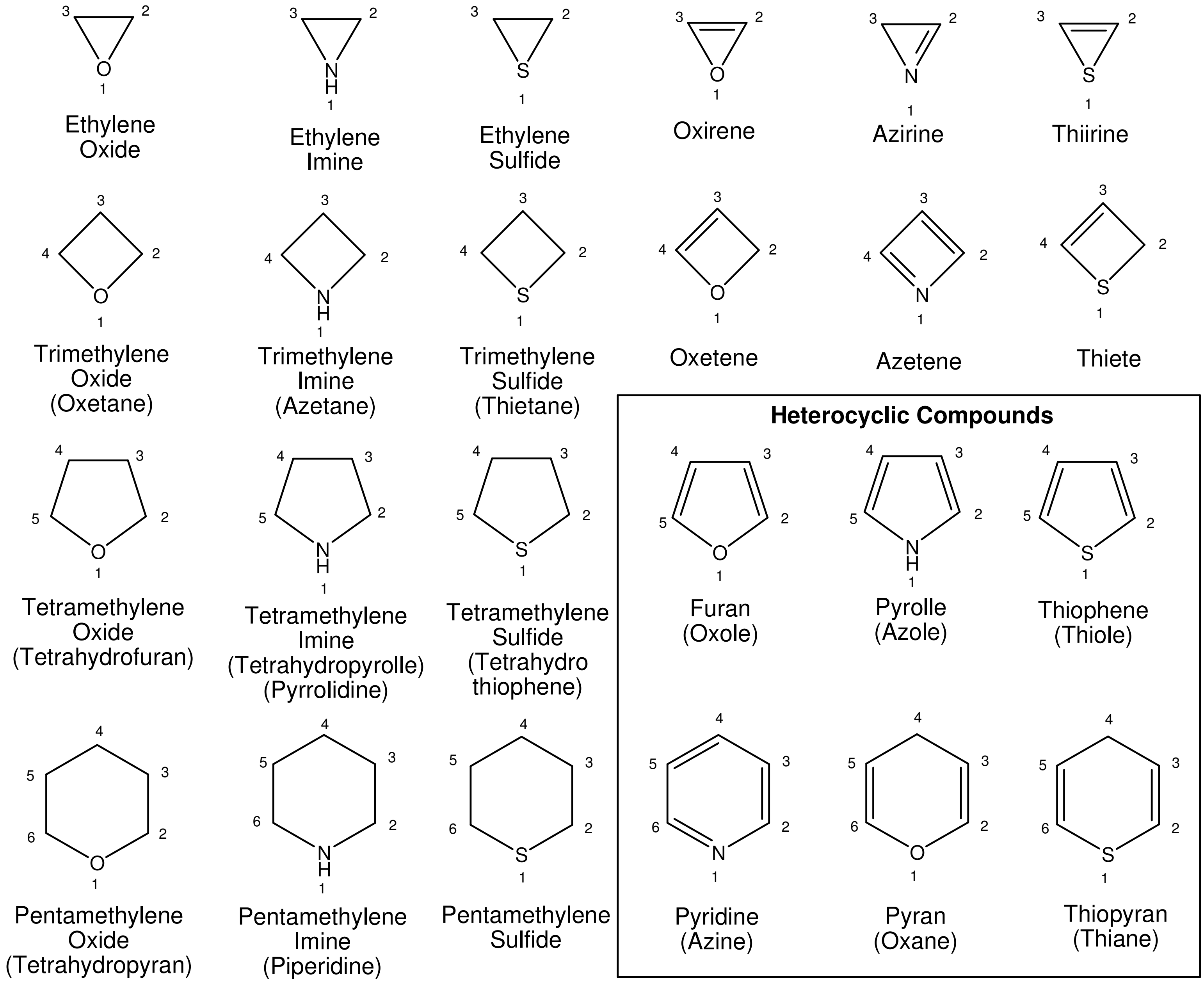


Figure 2: Ringed Compounds with heteroatoms. Heterocyclic Compounds are depicted in the square box

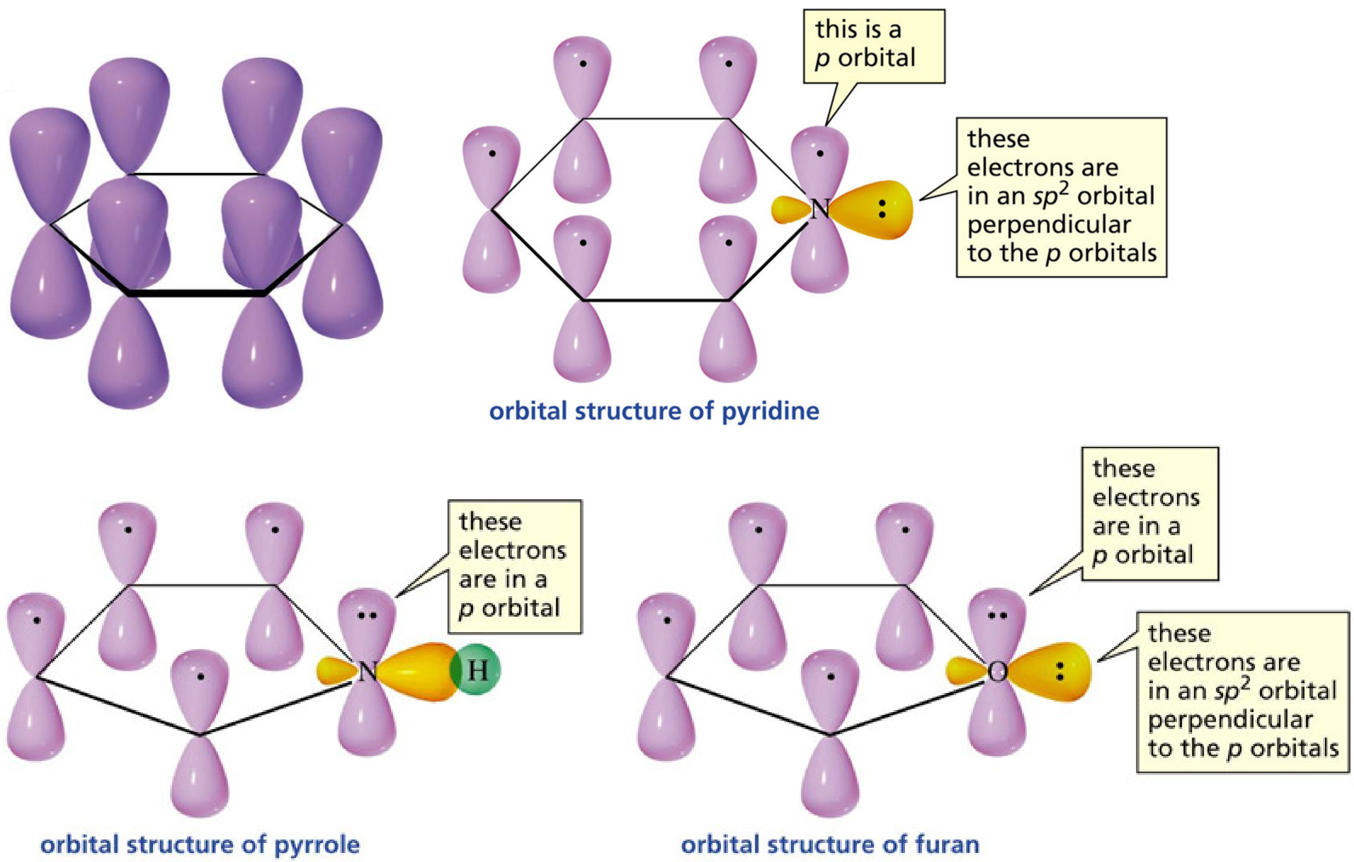


Figure 3: Orbital structure of (a) Benzene (Top left), (b) Pyridine (Top right), (c) Pyrolle (Bottom left) and (d) Furan (Bottom right).

By definition, all heterocyclic compounds have aromaticity. Eg. in Pyridine as shown in figure 3, there are only 5 pi electrons of carbon, but endocyclic nitrogen contributes one electron to have 6 pi electrons needed for aromaticity. The lone-pair electrons in pyridine are held in a sp2 hybrid orbital perpendicular to the orbitals in the pi system, so they are not part of the pi system.

Hence, by definition, only compounds present in the **box** in figure 2, **Furan, Thiophene, Pyrolle, Pyridine, Pyran and Thiopyran** are heterocyclic compounds because they are 5 or 6 membered ring structures with atleast one atom, relatively stable and show aromaticity.

Heterocyclic Compounds with more than one heteroatom
Some 5 and 6 membered ringed structures with one or two heteroatoms, that are relatively stable and possess aromaticity are depicted in the figures 4. By definition, these are **heterocyclic compounds.**

Classification of Heterocyclic Compounds
Heterocyclic compounds may be classified into three types: (i) Five Membered, (ii) Six Membered and (iii) Fused or Condensed Heterocyclic compounds.

Five-membered heterocyclic compounds bearing one more heteroatom
The five membered membered heterocyclic compounds containing one heteroatom is shown in the figure4. In these cases, oxygen, nitrogen and sulfur with non-bonding lone pair of electrons contribute to conjugated pi bond system in 5 membered ring system and are therefore have stable aromatic structures, "**furan, pyrolle** and **thiophene**" respectively.

The nomenclature suggested earlier is followed here, however the "a" in the prefix is dropped while conjugating it with the suffix. So, a 5-membered aromatic ring with oxygen is "oxa + ole = oxole". Similar rule is utilized for naming "azole" and "thiole".

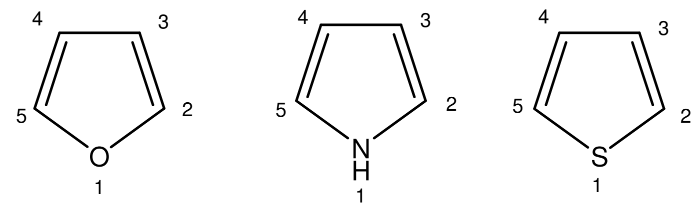
Nitrogen is also found in many 5-membered heterocyclic compounds bearing more than one heteroatom as shown in the figure above. **Pyrazole, imidazole, triazole, tetrazole** are examples of 5-membered heterocyclic compound with multiple nitrogen atoms. Pyrazole and imidazole are isomers bearing two nitrogen atoms. Triazole and tetrazole bear 3 and 4 nitrogen atoms. Again, trivalent nitrogen is able to replace carbon effectively to maintain conjugated bond system, essential for aromaticity. The naming system is followed here also with 1,2-diazole, 1,3-diazole, 1,2,3-triazole, 1,2,3,4-tetrazole respectively.

Examples of 5-membered heterocyclic compounds with 2 heteroatoms are **oxazole** and **thiazole** as shown above. Oxazole and thiazole have oxygen and sulfur apart from nitrogen in their 5-membered ring structures. The nomenclature seniority order is used in the naming these compounds. In oxazole, with oxygen being awarded seniority over nitrogen, the numbering starts with oxygen in the ring system. The naming follows, oxygen (oxa) followed by nitrogen (aza) in a five membered rings system (ole). So "oxa + aza + ole = oxazole". The "a" in the "oxa" and "aza" are removed during the conjugation of the name (similar to oxa + ole = oxole as described earlier).

It is again interesting to note that trivalent nitrogen atoms have replaced tetravalent carbon in these compounds. Inspite of this replacement, the conjugated bond system is maintained and aromaticity is preserved. The conjugated bond system would be lost if the carbon is replaced with divalent oxygen or sulfur!

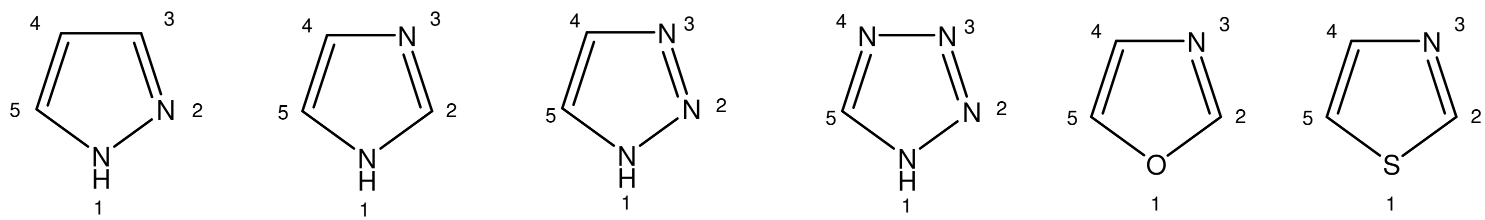
Six-membered heterocyclic compounds bearing one more heteroatom
Amongst the 6-membered heterocyclic compounds, **pyridine, pyran** and **thiopyran** bear nitrogen, oxygen and sulfur in their ringed structures as shown in figure 4.

Again, trivalent nitrogen forms conjugated bond system in pyridine facilitating aromaticity and providing additional stability to the molecule. Divalent sulfur and oxygen do not form conjugated bond systems with 6-membered ringed compounds and therefore are non-aromatic compounds.



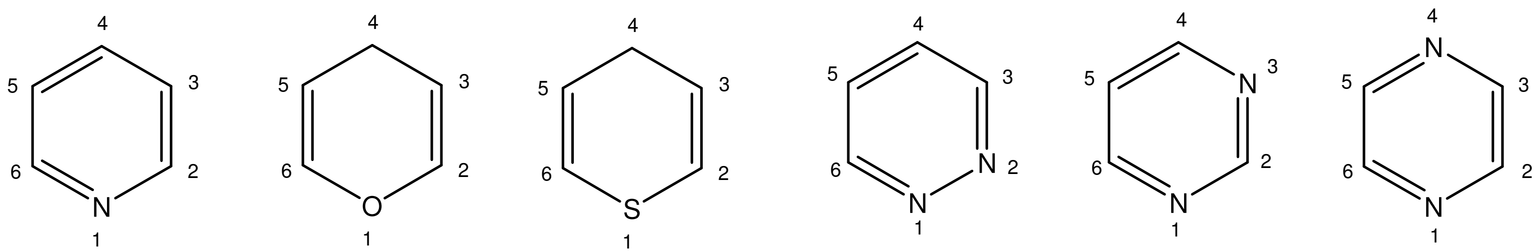
Furan (Oxole) | Pyrolle (Azole) | Thiophene (Thiole)

Five membered heterocyclic compounds bearing one eteroatom



Pyrazole (1,2-Diazole) | Imidazole (1,3-Diazole) | Triazole (1,2,3-Triazole) | Tetrazole (1,2,3,4-Tetrazole) | Oxazole (1,3-Oxazole) | Thiazole (1,3-Thiazole)

Five membered heterocyclic compounds bearing more than one heteroatom



Pyridine (Azine) | Pyran (Oxane) | Thiopyran (Thiane) | Pyridazine (1,2-Diazine) | Pyrimidine (1,3-Diazine) | Pyrazine (1,4-Diazine)

Some six-membered heterocyclic compounds bearing one and two heteroatoms

Figure 4: Some Five and Six membered Heterocycles with one and two heteroatoms

Nitrogen is also found in many 6-membered heterocyclic compounds bearing more than one heteroatom. Isomers, **pyridzine, pyrimidine, pyrazine** are examples which bear two nitrogen atoms as shown and support aromaticity with a conjugated bond system.

Fused Heterocyclics or Condensed Heterocyclics

They are formed due to the condensation of two cyclic compounds, of which atleast one would be heterocyclic compound. Examples are indole, quinoline and isoquinoline as shown below.

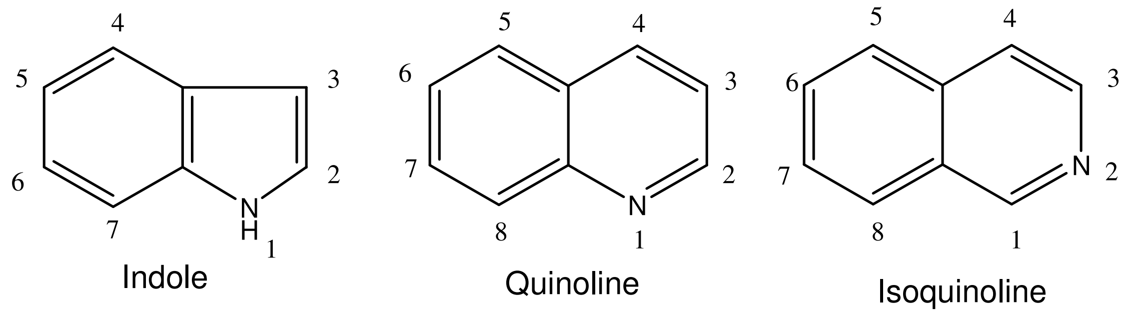


Figure 5: Fused Heterocyclic Compounds

In fused heterocyclics, the number system starts from the heteroatom. However, isoquinoline is an exception as shown in figure 5. The hierarchy for heteroatoms, O followed by S and N for nomenclature is applicable here also.

Five Membered Heterocyclic Compounds

Important members of interest are furan, thiophene and pyroole as listed in first row of figure 4.

Occurrence:

- Thiophene and pyrolle occur in coal tar in very small amounts.
- Thiophene also occurs in shale oil.
- Pyrolle also occurs in bone oil.
- Pyrolle ring is a constituent of in many naturally occurring substances such as chlorophyll, vitamin B12 etc.
- Furan is present in distillate of pine-wood.

Nomenclature and Isomerism

Nomenclature has already been discussed. However, isomerism in five-membered heterocyclic compounds with one-heteroatom depends on the number and type of substitutions present in the molecule. Figure 6 show the isomers possible with mono and di-substituted heterocyclic furan.

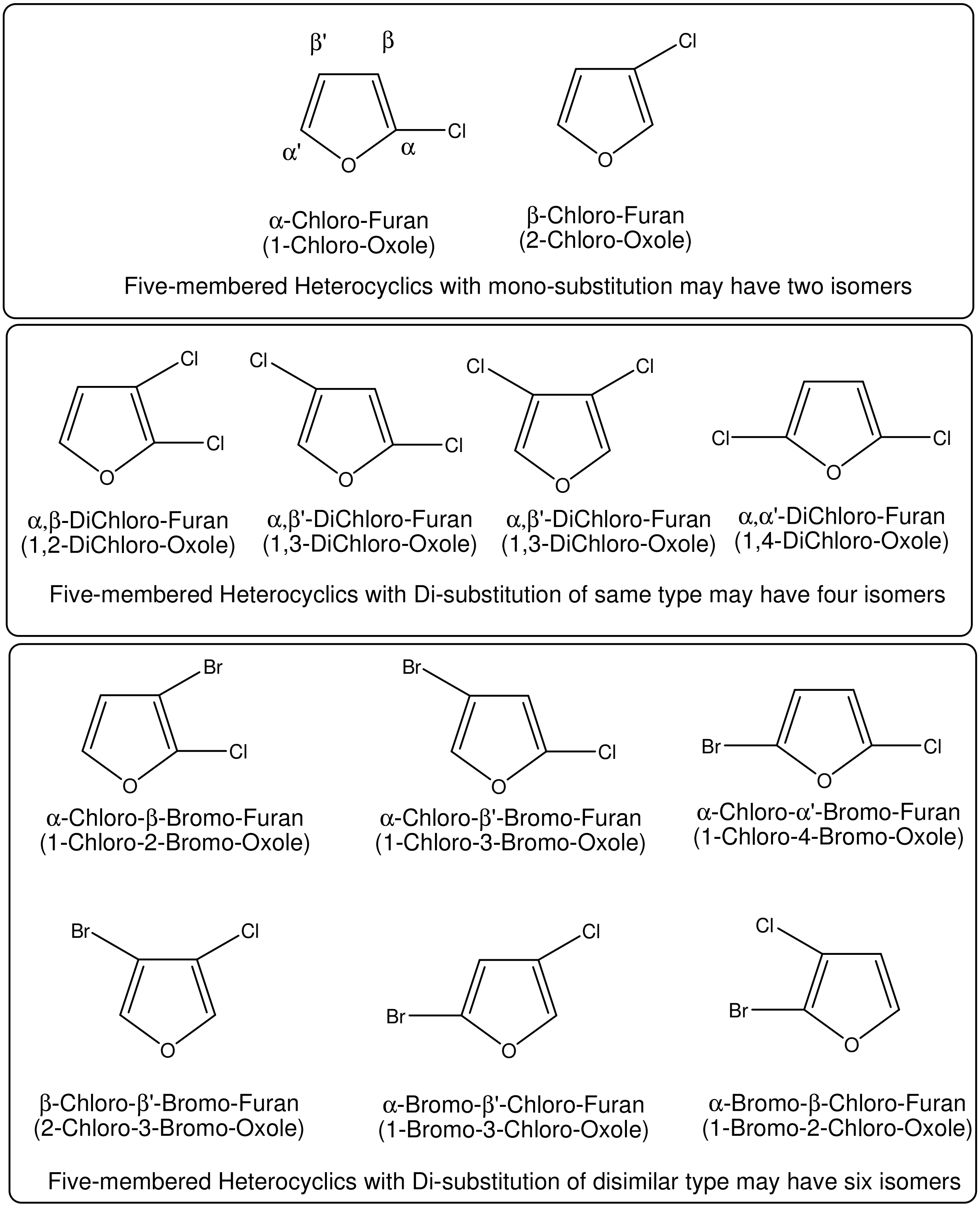


Figure 6: Isomerism in five-membered heterocyclics