**3**

**Tautomerism**

**in**

**Heterocyclic Compounds**

**Tautomerism in Heterocyclic Compounds (3 )**

**Tautomerism**.A phenomenon where isomers exist in rapid and easy equilibrium, associated with actual movement of electrons as well as one or more hydrogen atoms. The most common example of tautomerism involves the shift of a proton between carbon and oxygen , nitrogen or sulfur.

In keto-enoltautomerism, the more stable form is the keto form, but if the enol form is aromatic the equilibrium is shifted towards the enol form



Imine - enaminetautomerismand thioketone – thioenoltautomerismis also possible.



In polyhydroxyphenols like phloroglucinol, the keto form contribute to stability more than aromaticity and the equilibrium is shifted towards the triketone



**1. Six membered Heterocycles.**



In 2-hydroxypyridine the keto form is an amide and more stable, and at equilibrium the compound is shifted towards the amide (One of the resonance structures is aromatic), and 4-hydroxypyridine is similar



In 3-hydroxypyridine the keto form is a ketone with no special stability, and the compound in the enol form is important.



In 2,4-dihydroxypyridine, the amide form(1) has been shown to be preferred over the vinylogous amide form(2).



For fused ring heterocycles it seems that benzene does not affect tautomerism. For example the following quinolone exist in the keto form:



In compounds with more than one heteroatom things become complicated and needs careful analysis.

In general keto form predominate if it is α-or γ- to the heteroatom, as in hydroxypyridine.

4-Hydroxypyrimidine, an important naturalsystem, exist in the amide form and not the vinylogousamide(3)



Thymine and cytosine, both are pyrimidine bases in nucleic acids, exist in the amide form and not the vinylogous amide.



Fused ring structures are similar in behavior to monocyclic compounds, for example a nucleic acid base such as purine called guanine. The stable tautomer is the following:



Heterocyclic thiophenolsare similar to the heterocyclic phenols in behavior. They exist in thioamide or thiourea form when possible, analogous to theoxo compounds as in thiophenol, the thioamide is the stable form.



In imine- enaminetautomerism the imine form is much less stable than the keto form and the amino is more favored than in phenols as in 2-aminopyridine and 4,6-diaminopyrimidine.



**2. Five membered heterocycles.**

Five membered heterocyclic compounds can exhibit tautomerism. Aromatic stabilization is in the order of:thiophene>pyrrole> furan, the enol form is more stable for thiophenol. Aminothiophenes are the most likely of all the compounds of this type to exist in the aromatic form.

There are three tautomers in the 2-substiduted compounds, and two in the 3-substituted ones.



The least likely to exist as the aromatic tautomers is 2-hydroxyfuran, there is evidence that 2-hydroxythiophene and 2-hydroxypyrrole exist as ketonic tautomer.

3-Hydroxyfuran and, 3-hydroxythiophene exist as mixture of tautomers. Fusion to benzene makes the keto form more likely as in the following compound.



It is expected that 2-aminopyrrole, thiophenes and furans will existin the aromatic tautomer form, as with other amino-substituted hetero-aromatic compounds.



The 3-substituted series is less understood than the 2-substituted ones. 3-Aminofuran shows both forms.



Thiophene, substituted at position 2- and 3- with a thiol group, favors the aromatic forms.



Fused systems can be predicted based on simple ones as in the following examples.



**In summary**:

-α-or γ- Oxo heterocycles prefers the carbonyl form.

- Amino heterocycles nearly always exist as amino tautomer.

- Sulfur analogues exist asthione in six member compounds,

and as thiols in five member rings.