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Method Developments of Pyridine Pyrimidine and Dioxane Activity of Heterocyclic Compounds

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Abstract: *The heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as part of the ring.[1] They may be either simple aromatic rings or non-aromatic rings. Some examples are pyridine (C_5H_5N), pyrimidine ($C_4H_4N_2$) and dioxin ($C_4H_8O_2$).Heteroatom's as well as heterocyclic scaffolds are frequently present as the common cores in pharmaceutical natural products. Pyridine and pyrimidine derivatives have received in pharmacological research; these are used in the treatment of myeloid leukemia, breast cancer and idiopathic pulmonary fibrosis. Quantitative assessment of any medication is fundamental contraption in industry. Find that unpleasant material, generally engaging things and moreover last things meet its points of interest and are of required quality. Measure of pharmaceuticals and medication definitions brought into business portion has been stretching out at maddening rate. Couples of medications are open as pharmaceutical unobtrusive components to control illnesses. Frameworks for separating and measure for controlling social event of these synthetic compounds in plans and in living body are significant. Pharmaceutical assessment remembers essential part for legal accreditation of medications and their definitions either by business or by administrative powers. Adaptable nature of issues experienced in pharmaceutical assessment got together with centrality of accomplishing selectivity, speed, cost, straightforwardness, affectability, exactness and precision brings about new strategies for assessment being immediately gotten by pharmaceutical business.*

Keywords: Pyridine, Pyrimidine, Dioxin Activity of Heterocyclic Compounds

I. INTRODUCTION

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur the permutations and combinations of such a replacement are numerous.
Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as part of the ring. They may be either simple aromatic rings or non-aromatic rings. Some examples are pyridine (C_5H_5N), pyrimidine ($C_4H_4N_2$) and dioxin ($C_4H_8O_2$).

1.1 Nomenclature

Devising a systematic nomenclature system for heterocyclic compounds presented a formidable challenge, which has not been uniformly concluded. Many heterocyclic, especially amines, were identified early on, and received trivial names which are still preferred. Some monocyclic compounds of this kind are shown in the following chart, with the common name in bold and a systematic name based on the Hantzsch- Widman system given beneath it in blue. The rules for using this system will be given later.
Examples of this nomenclature are: ethylene oxide = oxacy clopropane, furan = oxacyclopenta-2,-4diene, pyridine = azabenzene, and morpholine = 1-oxa-4-azacyclohexane.

Element	oxygen	sulfur	selenium	nitrogen	phosphorous	silicon	boron
Valence	II	II	II	III	III	IV	III
Prefix	Oxa	Thia	Selena	Aza	Phospha	Sila	Bora

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1.2 Classification:

Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.

1. Aliphatic heterocyclic compounds
2. Aromatic heterocyclic compounds

Examples: Aziridine, ethylene oxide, oxetane, azetidine, thietane, 1, 2-dioxane, pyrrolidine, piperidine etc.

However, aromatic heterocyclic compounds are analogous of benzene. The aromatic heterocyclic compounds also follow the Huckel's rule. According to Huckel's rule an aromatic compounds must be cyclic in nature with planar geometry due to conjugate double bonds and must have (4n+2) π electrons.

Examples: Furan, pyrrole, thiophene, indol, benzofuran etc.

Based on the variety of structure, the heterocyclic compounds may also be divided in to three categories.

1. Five membered heterocyclic compounds: These heterocyclic compounds may be considered to be derived from benzene by replacing one C=C bond by a hetero atom with a lone pair of electron. Based on number of hetero atom present in the cyclic ring this class of heterocyclic compounds may be further subdivided in to following categories.

Examples: Furan, theophany and pyrrole.

2. Heterocyclic compounds with more than one hetero atom: These hetero atoms may be same or different. Common examples of this category of heterocyclic compounds are Examples: pyrazole, imidazole, thiazole, oxazole, triazole and tetrazole etc.

1.3 Objectives of the Work

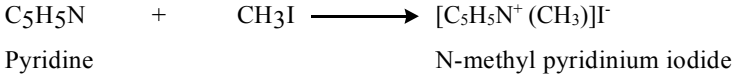
1. To develop method for pyridine, Pyrimidine and dixonae.
2. To validate the developed method of pyridine, Pyrimidine and dixonae.
3. To develop the most important simple heterocyclic ring systems containing heteroatomand their systems of nomenclature and numbering.

II. Research Methodology

2.1 Structure and Aromaticity of Pyridine

Structure and aromaticity of Thiophene can be discussed according to following points.

1. The molecular weight determination method and related analytical studies revealed that the molecular formula of Pyridine as C5H5N.
2. Pyridine does not react with acetyl chloride and nitrous acid it confirms that pyridine does not have primary or secondary amino group. The above fact also confirms that the pyridine is a mono-acidic tertiary base.
3. Pyridine also reacts with equimolar amount of methyl iodide to form a quaternary ammonium salt.



4. The molecular formula also indicates that it is a highly unsaturated compound; however, pyridine does not give the simple addition reactions like alkenes.
5. Pyridine is also found stable towards the oxidizing agents.
6. Pyridine exhibits aromatic character like benzene and give electrophilic substitution reactions such as halogenations, nitration and sulphonation.
7. Last two reactions confirm the aromatic character of pyridine.

Resonance in pyridine molecule is supported by the following points:

1. All the carbon, nitrogen and hydrogen atoms lie in the same plane all the carbon and nitrogen atoms of pyridine are sp2 hybridized.
2. Each sp2- hybridized carbon forms two π -bonds with neighboring atoms and one bond with hydrogen atom.
3. 4. The hybridized p-orbital of each carbon atom is involved to form the -bond with neighboring atoms.
4. The two of three sp2- hybridized orbitals of nitrogen contain one- one electron in each sp2- hybridized orbital; however, the third sp2- hybridized orbital of nitrogen contains lone pair of electron. The hybridized orbitals of nitrogen contain one electron which is involved to form π -bond with any of the neighboring carbon atoms.
5. All the carbon-carbon bonds in pyridine are of equal length (i.e. 1.39 Å).

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a. The carbon-nitrogen bonds are also of equal length (1.37 Å).
b. These properties resists the pyridine from simple addition reaction of C=C double bond. Since in pyridine there is no true C=C double bond.
c. The resonating structures represent that the more electron density at C-3, hence electrophilic substitution in pyridine takes place at C-3.
d. The two of three sp2- hybridized orbital's of nitrogen contain one- one electron in each sp2- hybridized orbital; however, the third sp2- hybridized orbital of nitrogen contains lone pair of electron. The hybridized p orbital of nitrogen contains one electron which is involved to form π -bond with any of the neighboring carbon atoms.
e. All the carbon-carbon bonds in pyridine are of equal length (i.e. 1.39Å).
f. The carbon-nitrogen bonds are also of equal length (1.37Å).
g. These properties resists the pyridine from simple addition reaction of C=C double bond. Since in pyridine there is no true C=C double bond.
h. The resonating structures represent that the more electron density at C-3, hence electrophilic substitution in pyridine takes place atC-3.

6. The delocalized electron cloud in pyridine is shown in figure16.

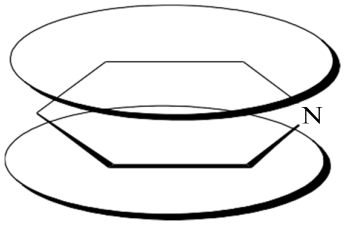

Figure 1.1: Delocalized electron cloud above and below the pyridine ring

2.2 Properties of Pyridine

- **Physical Properties of Pyridine:** Pyridine is a colorless liquid. Its boiling point is 115.5° C. It has a characteristic unpleasant odor. It is soluble in water and most organic solvents.
- **Chemical properties of Pyridine:** Chemical properties of pyridine are discussed as follow:

A. Basic Character of Pyridine

Pyridine is basic in nature. Its pKb is 8.75. It reacts with strong acids to form salts. The basic nature of pyridine is due to the freely available lone pair of electrons in sp^2hybridized orbital pyridine, which does not participate in the formation of delocalized π -molecular orbital. Pyridine is less basic in comparison to aliphatic amines whereas, it is more basic than aniline and pyrrole. This is because the lone pair of electrons in aliphatic amines exists in sp^3hybridized orbital, however, in case of pyridine the lone pairs of electrons exist in sp^2hybridized orbital. Electrons are held more tightly by the nucleus in a sp^2hybridized orbital than ansp^3hybridized orbital. Hence the lone pair of electrons in pyridine is less available for protonation. The less basicity of pyrrole and aniline can be explained in terms of non-availability of these lone pair of electrons on nitrogen atom. These lone pair of electrons is involved in the formation of delocalized π -molecular orbital.

B. Reduction

Under catalytic hydrogenation of pyridine hexahydropyridine is formed. It is also known as Pepperdine.

Electrophilic Substitution Reactions

Pyridine is also an aromatic compound. It is less aromatic than benzene and pyrrole. Pyridine usually considered a highly deactivated aromatic nucleus towards electrophilic substitution reactions. Therefore highly vigorous reaction conditions should be used for these reactions to take place. The low reactivity of pyridine towards the electrophilic substitution reactions is due to the following reasons:

The higher electro negativity of nitrogen atom reduces electron density on the ring, thus deactivate the ring.

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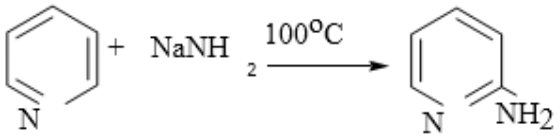
Pyridine is highly sensitive to acidic medium; it readily forms pyridiniumcation with a positive charge on nitrogen atom. Similarly, electrophile itself may also react with pyridine to form corresponding pyridiniumion. This positive charge on nitrogen atom decreases electron density on nitrogen atom, consequently, the electron density on ring alsodecreases.

Nucleophile Substitution Reactions

As we have discussed in previous section that pyridine generally deactivated the aromatic ring towards electrophilic substitution reaction. The deactivation of aromatic ring towards electrophilic substitution resulted due to the electron withdrawing nature of nitrogen atom. Due to such deactivation, pyridine also gives nucleophile substitution reaction. Nucleophile substitution in pyridine rings occurs at position C-2. Approach of the nucleophilic at position C-2 leads the formation of three resonating structures (I, II and III); similarly, approach of nucleophile at position C-3 also leads the formation of three resonating structures (IV, V and VI). The resonating structures for intermediate resulting from the attack of nucleophile at position C-2 are more stable than those of position C-3, since more electronegative nitrogen atom hold – ve charge in one of the resonating structure (III) obtained from the attack of nucleophile at position C-2. Hence, the nucleophile substitution in pyridine at position C-2 is always favored. Following mechanism is suggested for the electrophilic attack at positionC-2.

Reaction with Sodium Amide

Pyridine reacts with sodium amide to give 2- amino pyridine via nucleophile substitution.



Pyridine Pyridin-2-amine

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