College of Pharmacy - Tikrit University

Organic ChemistryIII
Heterocyclic Lecture(7)
2nd semester 2nd stage

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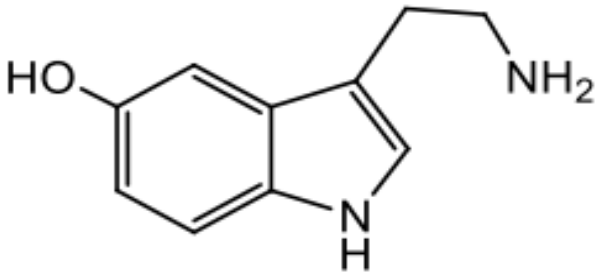
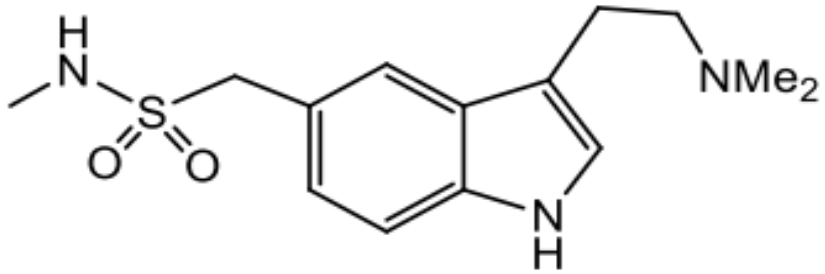
Indole:-

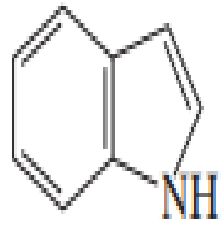
1. Indole is an aromatic heterocyclic organic compound with formula C_8H_7N. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five membered nitrogen-containing pyrrole ring. Indole occurs in coal-tar and in the oils of jasmine and orange blossoms . It is also found as a part of the total structure of a number of alkaloids and amino acids e.g., **serotonin, reserpine, and tryptophan**.



Serotonin: Neurotransmitter



Sumatriptan: Medicine for migraine



Indole in the enamine form

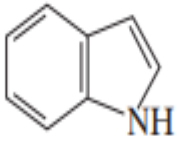
Medicinal Importance of indole

List of drugs containing indole

Drug	*Application*	*Drug*	*Application*	*Drug*	*Application*
Vincristine	Anticancer	**Vincamine**	Vasodilator	**Roxindole**	Schizophrenia
Vinblastine	Anticancer	**Reserpine**	Antihypertensive	**Delavirdine**	Anti-HIV
Vinorelbine	Anticancer	**Peridopril**	Antihypertensive	**Atevirdine**	Anti-HIV
Vindesine	Anticancer	**Pindolol**	Antihypertensive	**Arbidol**	Antiviral
Mitraphylline	Anticancer	**Binedaline**	Antidepressant	**Zafirlukast**	Anti-Asthmatic
Cediranib	Anticancer	**Amedalin**	Antidepressant	**Bucindolol**	β-Blockers
Panobinostat	Anti-leukamic	**Oxypertine**	Antipsychotic	**Pericine**	Opioid agonist

Properties of indole:-

- **Aromatic**: Indole is a planar molecule and follows Huckel's rule [(4n+2) π electrons]. All
- atoms in indole are sp2 hybridized and each of them possesses one un hybridized p-orbital.
- These p-orbitals overlap to generate π-molecular orbital containing 10 electrons (eight
- electrons from eight carbons and two lone pair electrons from N).



Indole in the enamine form

- It is resonance hybrid of several canonical structures. Because of the aromatic stability of the benzene ring, the most important contributing structure of indole to its resonance hybrid is its enamine form.
- Indole is a π-excessive (electron rich) heterocycle, so their chemistry is mostly dominated by electrophilic substitution reactions.
- ➢ Indole is markedly less reactive than corresponding monocyclic heterocycles
- **Basic and Acidic Character:-**
- Like pyrrole, indole is a weak base In presence of a strong acid
- protonation of the nitrogen atom would disrupt the aromaticity of the five-membered ring
- and also a weak acid. It is react with potassium hydroxide and polymerized by strong acids and also react with Grignard reagents.

Resonance structures of indole:-

It appears from these resonance structures that
all C atoms bear –ve charge while the hetero atom bears+ve charge

Synthesis of Indole:-

- **The Fisher-Indole synthesis:** This is the most widely used method for the synthesis of Indole. The synthesis involves cyclization of arylhydrazones under heating conditions in presence of protic acid or lewis acids such as ZnCl2, PCl3, FeCl3, .. etc.
- ➢ The starting material arylhydrazoles can be obtained from aldehydes, ketones, keto acids, keto
- esters and diketones etc.
- ➢ Reaction produces 2,3-disubtituted

The reactivity order in the electrophilic substitution:-

- Generally indole and its analogs are less reactive
- compared to the corresponding single heterocyclic rings therefore the electrophilic aromatic substitution is slower with these compounds
- This can be attributed to the fact that the share
- Of each carbon atom of the –ve charge in these
- compound is lesser due to delocalization of the
- charge on the benzene (as appeared from the resonance structure of indole.
- Reactivity order in electrophilic aromatic substitution:

The regioselectivity in E. substitution reactions:-

The pyrrole ring in indole is very electron rich, in comparison to the benzene ring, therefore, electrophile's attack always takes place in the five-membered ring

The preferred site of electrophilic substitution is C-3, because the cation formed by the C-3 attack of electrophile is more stable than that of the C-2 attack. In case of C-3 attack, transition intermediate formed has positive charge adjacent to N atom that can be stabilized by the delocalization of lone pair of electrons of nitrogen. Whereas, the positive charge of transition intermediate formed by the C-2 attack, cannot be stabilized without disturbing aromaticity of benzene ring. If C-3 position is occupied, then electrophilic substitution takes place at C-2 and if both of them are occupied then electrophile attacks at C-6 position.

Electrophilic substitution reactions:-

- 1-Protonation:-

2-Nitration:-

3-Halogenations

4-Sulphonation:-

5-Alkylation:-Indoles do not react with alkyl halides at room temperature. Indole itself begins to react with methyl iodide in di methyl formamide at about 80°C, to give main product 3-methyl indole(skatole). As the temperature is increased, further methylation takes place resulting in 1,2,3,3-tetramethyl-3*H*-indolium iodide.

Acylation:-

➢ Indoles react with acetic anhydride in acetic acid above 140°C to afford 1,3-diacetylindole predominantly.

- ➢ On the other hand, acetylation in the presence of sodium acetate or 4- di methyl amino pyridine,
- affords exclusively 1–acetyl indole.
- ➢ Acylation occurs at C-3 position before N in 1,3-diacetylindole as, N-acylated product
- showed resistance to conversion to 1,3-diacetylindole but 3-acetylindole showed easy
- conversion to 1,3-diacetylindole.

The Vilsmeier Haack reaction:

The Vilsmeier reaction is a very efficient method for the formylation of electron rich aromatic rings by the use of acid chloride ($POCl_3$) and DMF. Indoles can be readily formylated to 3-formyl-indoles via Vilsmeier reaction. Even indoles carrying an electron-withdrawing group at the 2-position, for example ethyl indole-2-carboxylate, undergo smooth Vilsmeier 3-formylation.

Mannich Reaction:

Indole undergoes Mannich reaction with formaldehyde and dimethylamine to give 3-dimethylaminomethylindole (Gramine).

Oxidation

Indole may be oxidized by ozone in formamide to give 2-formamido-benzaldehyde.

Reduction

Mild reduction of indole with zinc (or tin) and hydrochloric acid yields 2,3-dihydroindole (Indoline). Catalytic reduction hydrogenates both rings and produces ocata-hydroindole