PHENOL

The phenol parent compound is white crystalline solid (melting point 39–40°C), which becomes pink and finally black on long standing. It is soluble in water 1:13 and is a weak acid, pKa 10. Its biological activity resides in the ***undissociated molecule***.

PHENOL AND ANTIBACTERIAL ACTION

1. *The more acidic phenol have stronger antibacterial action*: the acidity of the hydroxyl group results from the electron withdrawing effect of the aromatic ring which weakens the O-H bond. ***The acidic strength of the phenol increases with the strength of electron withdrawal***. Thus electron withdrawing substituents such as nitro or chloro groups increase the acidity of the phenol. The effects of such substituents are greatest in the ***ortho*** and ***para*** positions. ***Nitration*** confers specific biological properties on the molecule increasing both *the toxicity of phenol towards bacteria and the systemic toxicity* by enabling it to interfere with oxidative phosphorylation by acting as ***uncoupler***, example; 2,4-nitrophenol.
2. *The amphiphilic nature of phenol means that it is surface active and can absorb on membrane surfaces such as bacterial membranes.* ***How can this property be modified??***

ROLE OF PHENOL IN DRUG DESIGN

1. **Binding with the receptors**

a. ***Hydrogen bonding***: the *oxygen can act as hydrogen bond acceptor*, and the *hydrogen can act as hydrogen bond donor*. One or all of these interactions may be important in binding the drug to the binding site.

b. ***Aromatic ring*** *is commonly involved in van der Waals interactions with flat hydrophobic regions of the binding site*.

2. **Amoxicillin:** *Phenolic group adjust isoelectric point to more acidic value* which is believed to be ***partially*** responsible, along intestinal peptide transporter, for *enhanced blood levels obtained with amoxicillin*. [***comparison of ampicillin against amoxicillin***]

Synthesis of Ether from Phenolic Compounds

O-Alkylation in Drug Design [Williamson Ether Synthesis]

1st Objectives

- ***To make Students Familiar with O-Alkylation Procedure in Drug Design***
- ***SAR study to evaluate the effect of (R) group on activity of the new derivative***

(1) **(2)**

a. ***If compound (2) is more active than compound (1) this means that***

1. ***R group is responsible for enhance activity by forming hydrogen bonds with the receptor by***

- Carbonyl group of amide group (acts as hydrogen bond acceptor)
- Hydrogens of NH_2 (act as hydrogen bond donors)

2. OH group in compound (1) is not essential for activity.

b. ***If compound (1) is more active than compound (2) this means that***

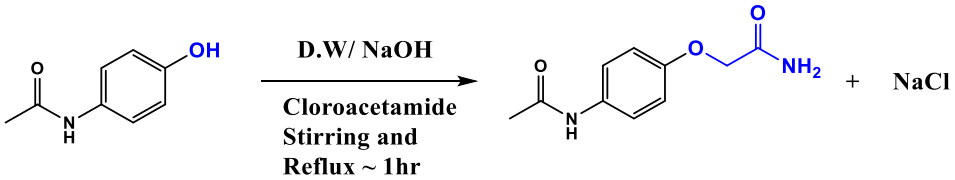
1. R group is bad for activity.

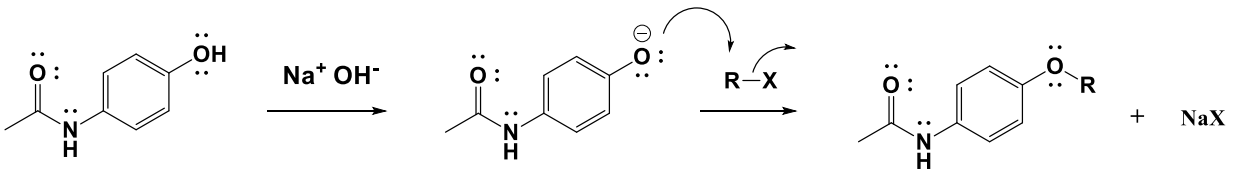
2. OH group in compound (1) is essential for activity.

c. If there is no difference in activity, there is no need for this modification.

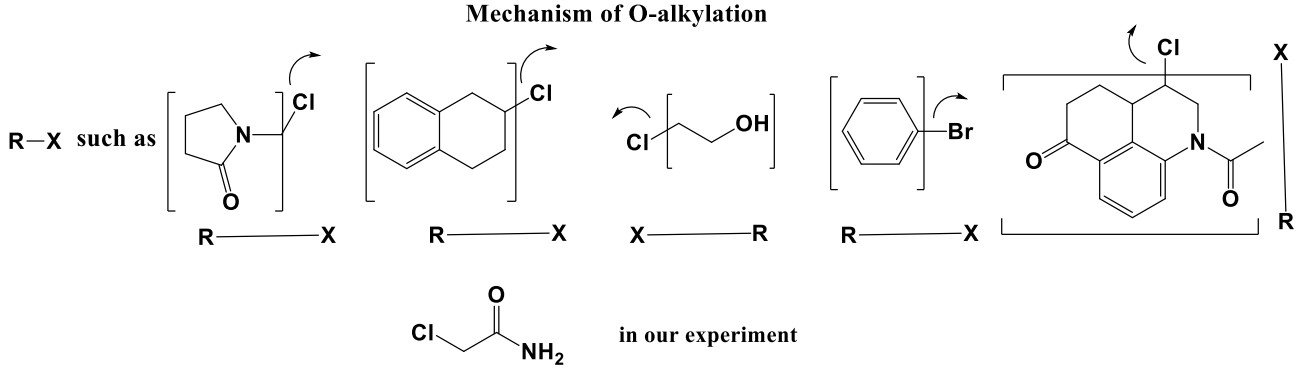
2nd PROCEDURE

1. Suspend **0.5g** of Paracetamol in round-bottomed flask containing **5ml** of D.W.
2. While gentle stirring add **0.124g** of **NaOH**; observe the formation of clear solution.
3. To that clear solution add **0.29g** of chloroacetamide.
4. Reflux for **1h**; observe the changes……. Turn off the heat and put the flask aside for cooling.
5. Filter the formed precipitate, dry, and weigh.





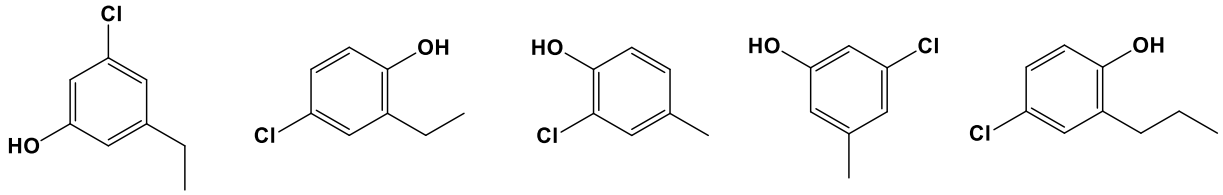
Mechanism of O-alkylation



QUESTIONS

a. *Name the reaction?*

b. *Arrange the following according to antibacterial activity (from low to high)*



a **b** **c** **d** **e**