RETROSYNTHESIS

Introduction :

- There are many biological natural substance in nature that have strong medicinal properties and can be used for medical purpose to treat, suppress and even cure diseases

Retrosynthesis helps to understand the complex nature of these natural products and provides several options for synthetic pathways from which the most cost-effective and environmentally friendly pathway can be chosen. This technique is particularly useful for planning the synthesis of organic compounds

Organic Synthesis :

The construction of larger (or) complex organic molecules from small molecules (or) units using several chemical transformations is called organic synthesis

(Or)

The preparation of a desired organic compound (or) Target molecule from a readily available starting material is known as Organic synthesis.

Retrosynthesis :

- Professor Elias. J. Corey of Harvard university won the nobel prize for introducing the concept of retrosynthetic analysis in 1990.
- The process of working backward from the target molecule into sample easily available (or) commerially available starting material from which a chemical synthesis can be developed.

This process is called Retrosynthesis and the art of planning the synthesis of a target molecule is called Retrosynthesis

* This process of simplification should be contributed until you reach molecules which are commerically available
* The retrosynthesis is defined as the strategy used in organic chemistry to design a synthesis pathway for complex molecules by breaking the down into simple, more readily available (commerically available) or easily synthesized precursor molecule".
* Retrosynthetic analysis is based on known reactions (eg: oxidation, reduction, additions, eliminations, substitution and named organic reactions etc)

* An open arrow symbol is used to indicate a transform, and is drawn from the taget to the precursor

Target Molecule (X) $\Longrightarrow$ C $\Longrightarrow$ B $\Longrightarrow$ starting (A)

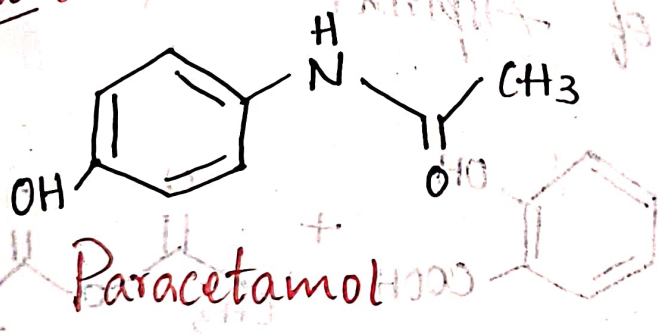
precursor 1 precursor 2

Important terms In Retrosynthesis :

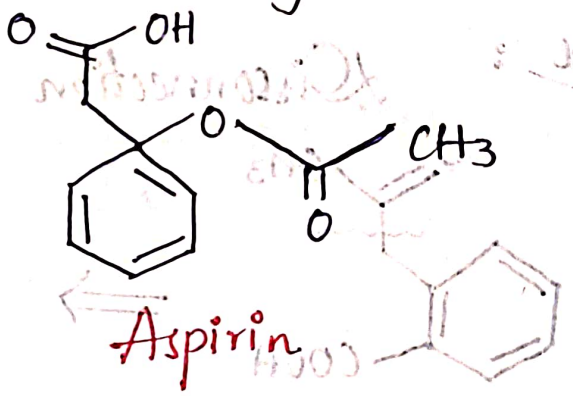
(1) Target molecule (TM)

The complex molecule that needs to be synthesized is called Target molecule.

Ex :



Paracetamol



Aspirin

(2) Dis. connection :

In retrosynthesis, a disconnection refers to the conceptual process of breaking down a target molecule into simpler, smaller fragments

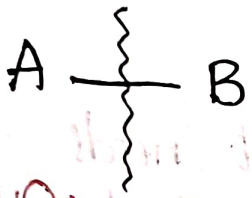
(OR)

The cleavage of a bond to break. The target molecule into immediate precursors (or) possible starting material is known as disconnection.

* This step is crucial for planning the synthesis of complex organic compounds. The

goal of disconnection is to identy the bonds of target molecule that, if broken would lead to simpler molecules (or) synthons that are closer to readily available starting materials

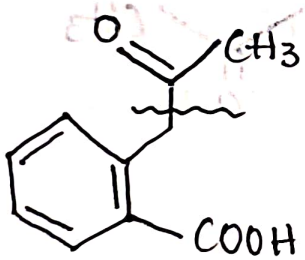
* It can be represented as by a wavy line (or) curved line ~~~~ (or) ~



$\Longrightarrow$ A + B

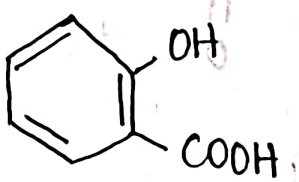
Disconnection

Ex: Disconnection of Aspirin.



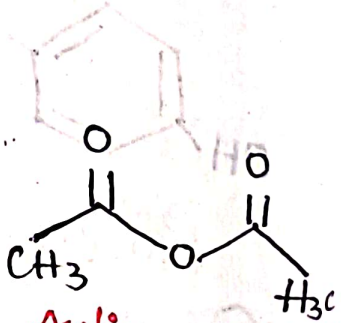
Aspirin

$\Longrightarrow$



Salicyclic acid

+



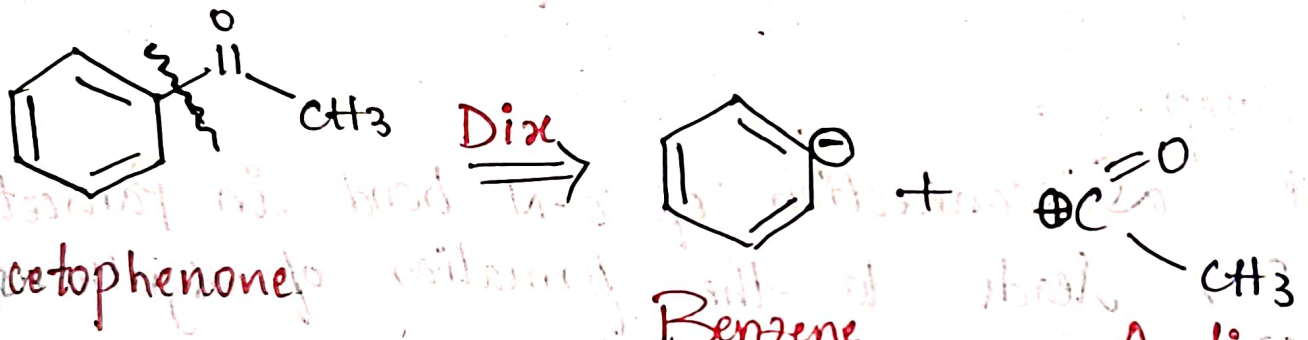
Acetic anhydride

Synthons:

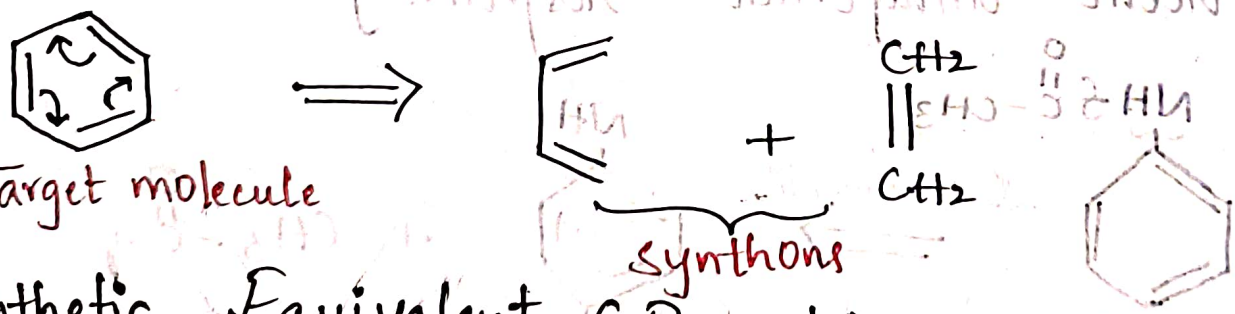
* Synthons are idealized fragments resulting from a disconnection and are not the actual reagents.
* The products of disconnection are synthons which can be anionic (and) (carbanion) (or) cationic (carbocation) (or) neutral atoms (free radicals) are formed
* Positively polarized synthons are called Acceptor synthons and acts as Electrophiles, and they are denoted as 'a',

Negatively polarized synthons are called Donor synthons and act as Nucleophiles, and they are denoted as 'd^n'.

Ex: This disconnection of acetophenone gives phenyl carbanion and acylium ion these two fragments are called Synthons.



Note: The concerted transform leads to the formation of neutral species.

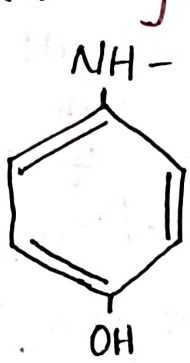


Synthetic Equivalent (Reagents):

* The real chemical compound used as the source of synthons is called

Retrosynthetic Analysis of Paracetmol

Structure :



(Target molecule)

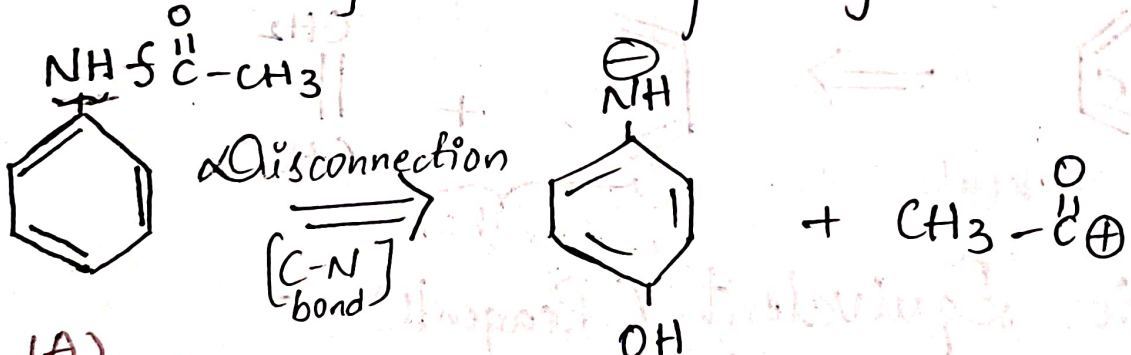
(N- Acyl 4- Amino phenol)

Retrosynthesis :

Step I :

* Disconnection of C-N bond in Paracetmol (A) leads to the formation of synthons (B) and (C).

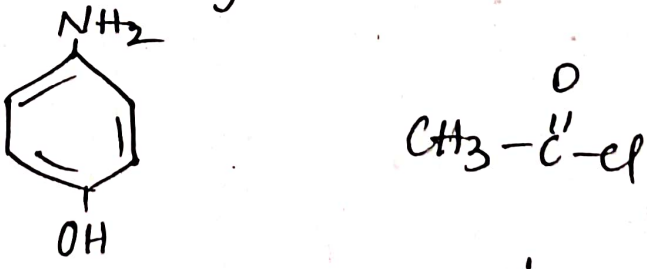
The synthetic equivalence of (B) and (C) are 4- amino phenol and Acetyl chloride or acetic anhydride respectively.



(A)

(B) (C)

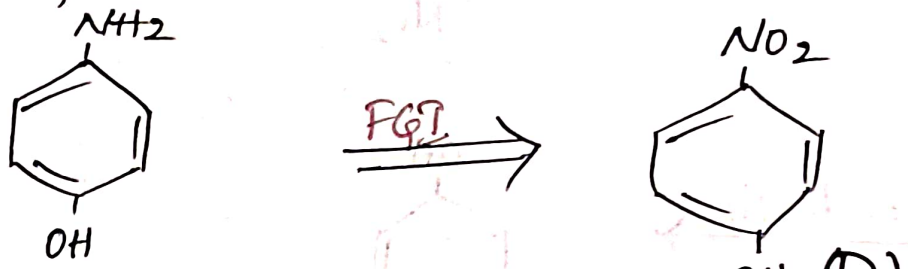
||| Synthons |||



Synthetic equivalent

Step 2:

* The 4-amino phenol can be interconverted into 4-nitro phenol by the functional group interconversion (F.G.I)

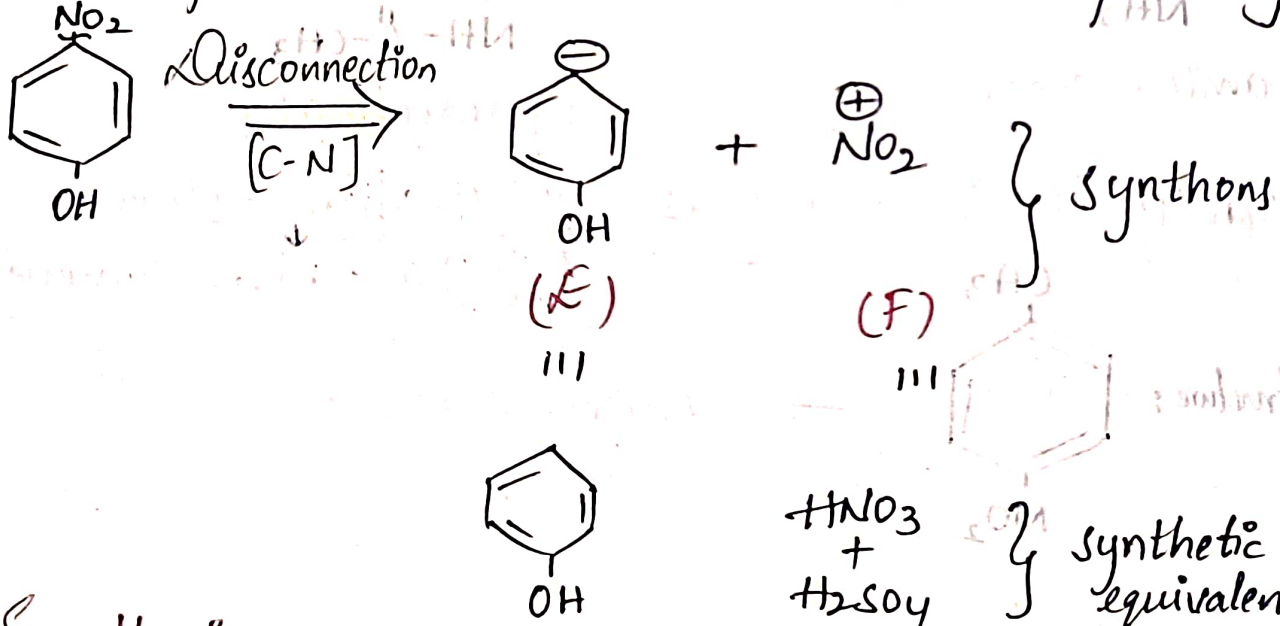


4-amino phenol — 4-nitro phenol

Step 3:

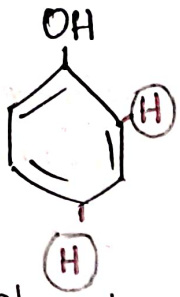
* Disconnection of C-N bond in (D) leads to the formation of synthons (E) & (F)

The synthetic equivalence of (E) and (F) are phenol and Nitric acid respectively.



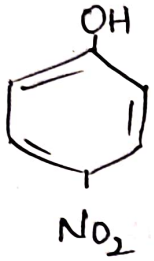
Synthesis:

* phenols undergoes nitration reaction with nitration mixture (or) Sodium nitrate and dil. H_2SO_4 to form 4-nitro phenol
* The 4-nitro phenol is reduced to 4-amino phenol by using reducing agents (Sn + HCl) and finally the 4-amino phenol is on Acetylation gives Paracetmol.

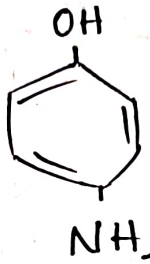
i) 
phenol

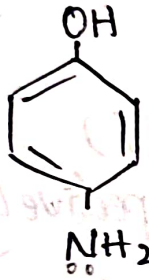
Nitration ($NO_2^{\oplus}$)


p-nitro phenol

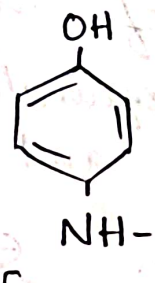
ii) 
p-nitro phenol

Reduction (Sn + HCl)

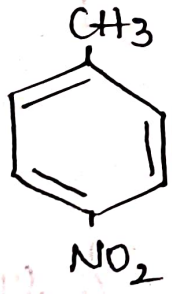

p-amino phenol

iii) 
p-amino phenol

Acetylation ($CH_3-\overset{O}{\overset{\|}{C}}-Cl$)

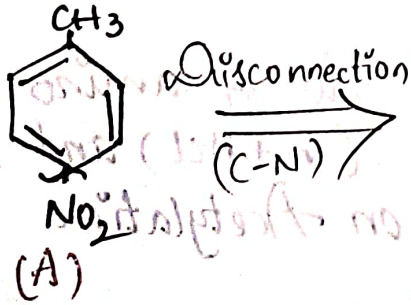

[paracetmol]

Retrosynthetic Analysis of 4-Nitro toluene
[Para-nitro toluene]

Structure:  — Target molecule
(A)

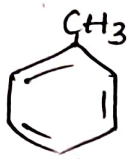
Retrosynthesis:

* Step: Disconnection of C-N bond in 4-nitro toluene leads to the formation of synthons [(B) and (C)]



(A) (B) (C)

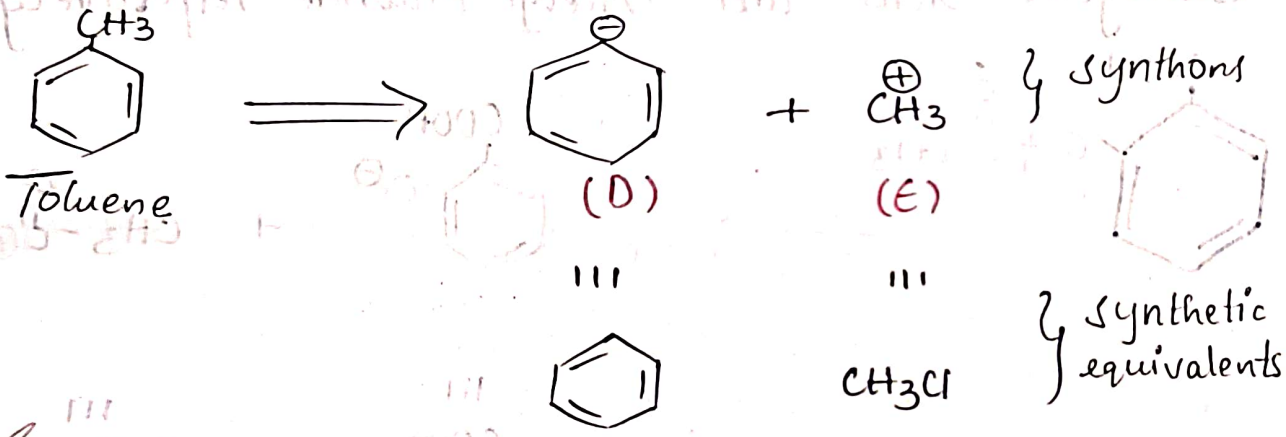
The synthetic equivalents of B and C are toluene and nitric acid respectively.



Toluene + HNO_3 (nitric acid) } synthetic equivalents

Step 2 : Disconnection of C-C bond in toluene leads to the formation of synthons (D) and (E)

The synthetic equivalents of (D and E) are benzene and methyl chloride respectively.

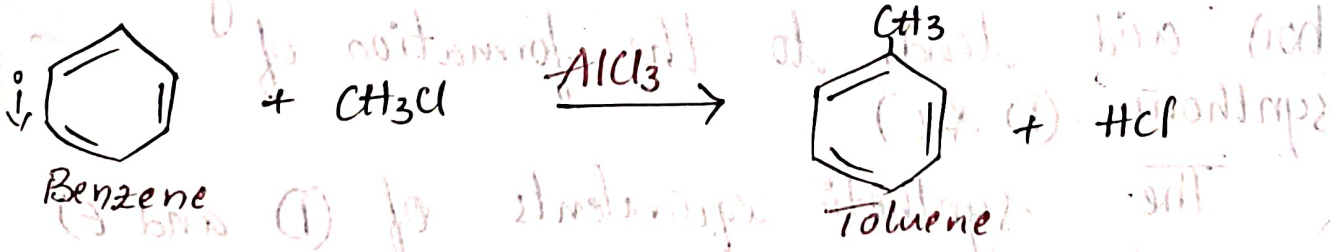


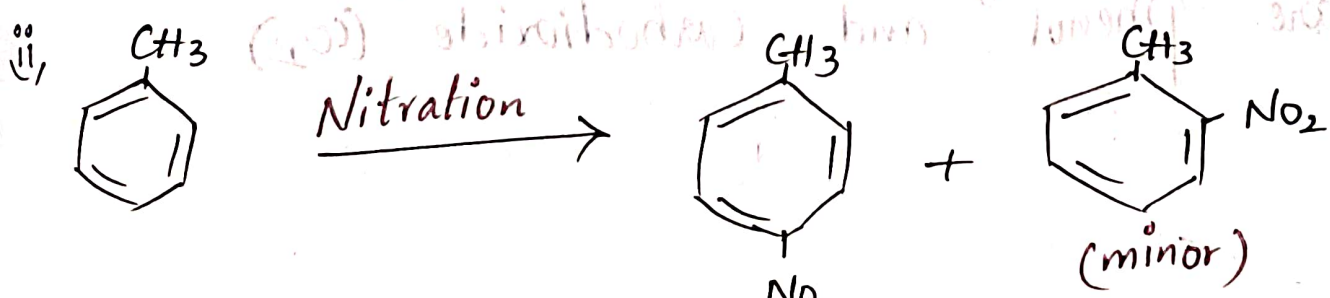
} synthons

} synthetic equivalents

Synthesis :

* Benzene undergo friedal Crafts Alkylation with $AlCl_3$ to form toluene
* Toluene undergo nitration with nitration mixture to form para- nitro toluene

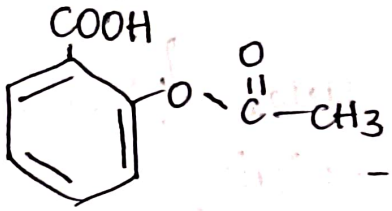




4- nitro- toluene

Retrosynthetic Synthetic Analysis of Aspirin

Structure :

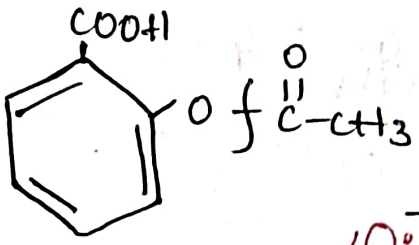


- Target molecule.

Retrosynthesis :

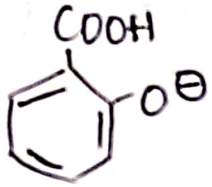
* Step 1: Disconnection of C-O bond in Aspirin leads to the formation of synthons (B and C)

The synthetic equivalents of (B & C) are Salicyclic acid and Acetyl chloride respectively



(A)

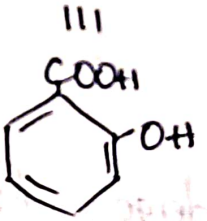
Disconnection ⟹



(B)

+ $CH_3-C^{+}=O$

(C)

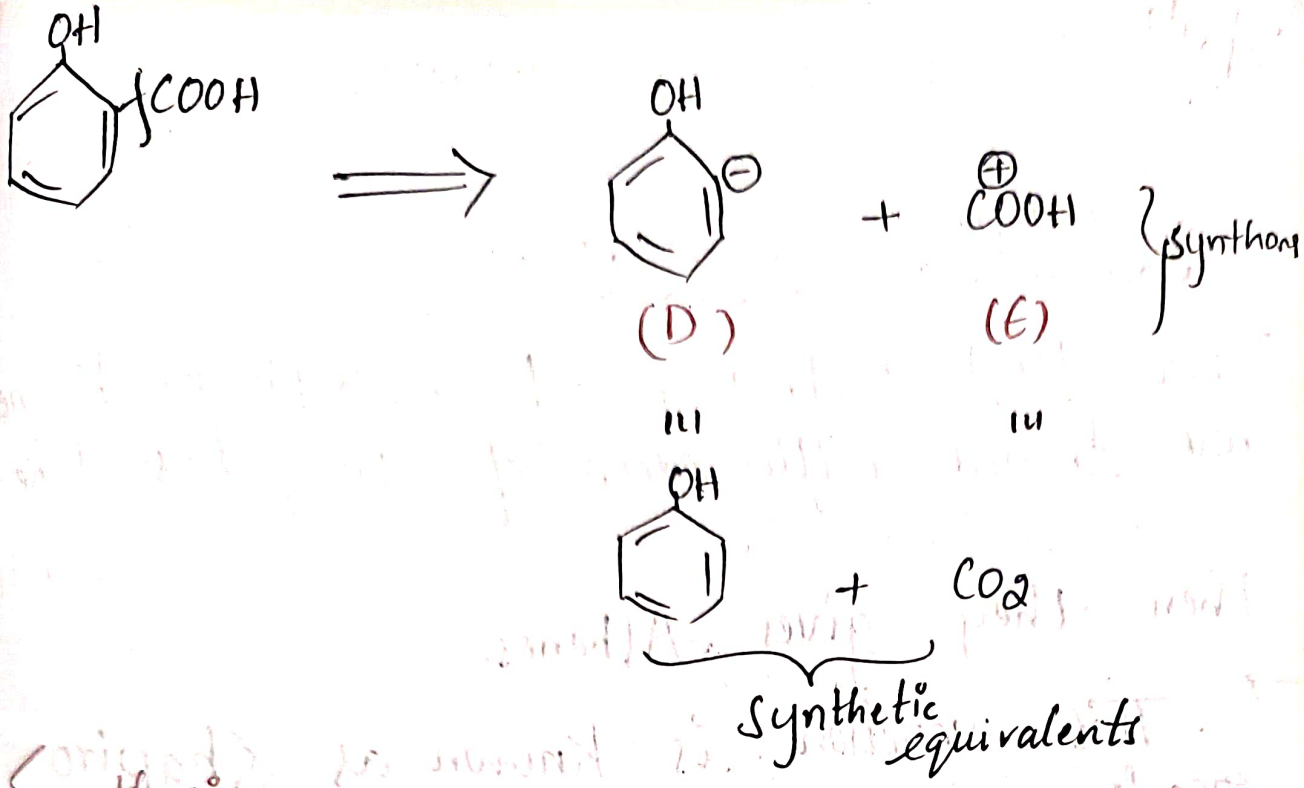


Synthetic equivalents

* Step 2 :

Disconnection of C-C bond in salicyclic acid leads to the formation of synthons (D & E)

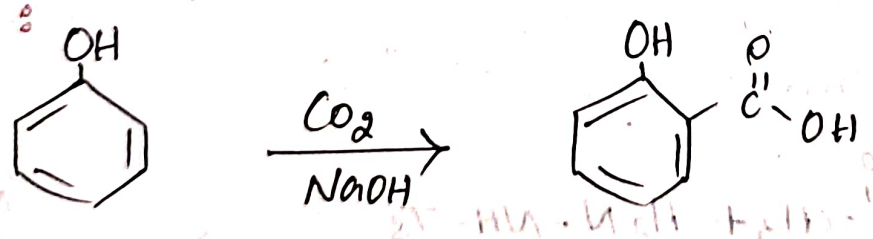
The synthetic equivalents of (D and E) are Phenol and Carbodioxide (CO_2)



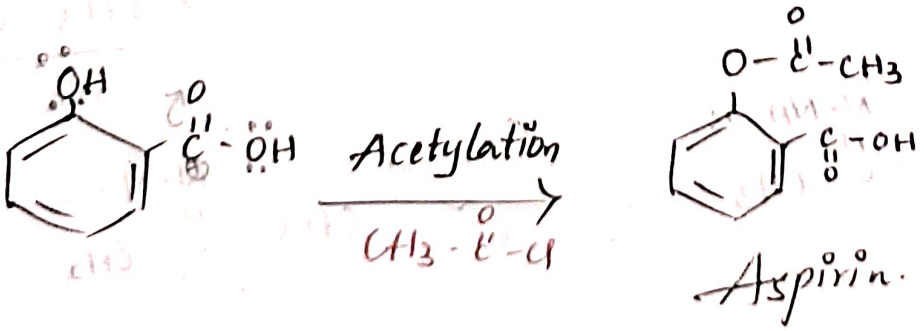
Synthesis :

* phenol undergo Kolb- Schimidt reaction with (CO_2 / NaOH) to form Salicyclic acid
* Salicyclic acid undergo acetylation to give Aspirin.

Step 1 :



Step 2 :



Aspirin.

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