University Of Anbar
College Of Pharmacy

Pharmaceutical Organic Chemistry

Fourth grade

Syntheses of Medicinal Compounds

Paracetamol synthesis

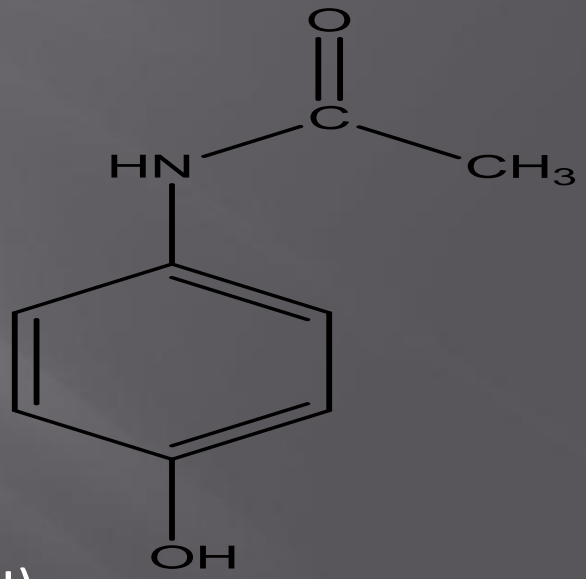
Chapter 5

Prepared by
A.L. Abdulkareem H. Ayfan

PREPARATION OF PARACETAMOL (P-ACETAMIDO PHENOL)

M.wt=151.2(gm/mole)

Acetaminophen is a P- acetamido phenol or it is N-acetyl P-aminophenol or 4-hydroxy acetanilide.



Physical properties:

Odorless , white crystals with bitter taste.

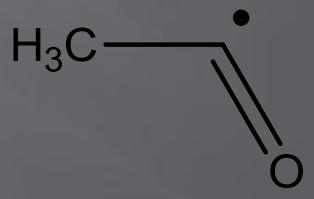
M.pt. = 169-172 C0

Solubility: one part(slightly soluble in water and ether) in 70 parts of water and in 7 parts Of alcohol ,soluble in alkali solution(like NaOH), soluble in boiling water(1:20)

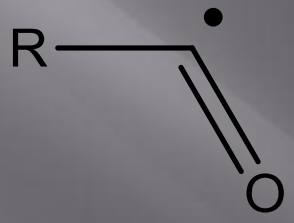
Acetylation methods:

Introduction

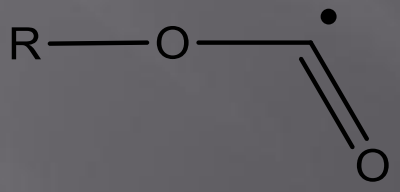
The replacement of '*active hydrogen*' of compounds belonging to the class **ROH** (phenols or alcohols), in addition to compounds of the category **RNH_2** and **R_2NH** (*i.e.*, *primary*- and *secondary*-amines may be acetylated directly, whereby the reactive H-atom is specifically replaced by the **acetyl radical "acetylation"**



And may be it done by acylation



Also by esterification process



Preparation of paracetamol

- ***Action and uses:*** it has analgesic and antipyretic actions but has no anti-inflammatory properties.
- ***Side effects:*** like that of acetanilide, affect heart and may cause skin reaction and a jaundice condition (they occur less frequently and less severity) .in doses used for analgesia ,it is relatively safe drug.
- ***Preparation:***It may prepared by reduction of P-nitrophenol in glacial acetic acid . acetylation of P-nitrophenol by using acetic anhydride.

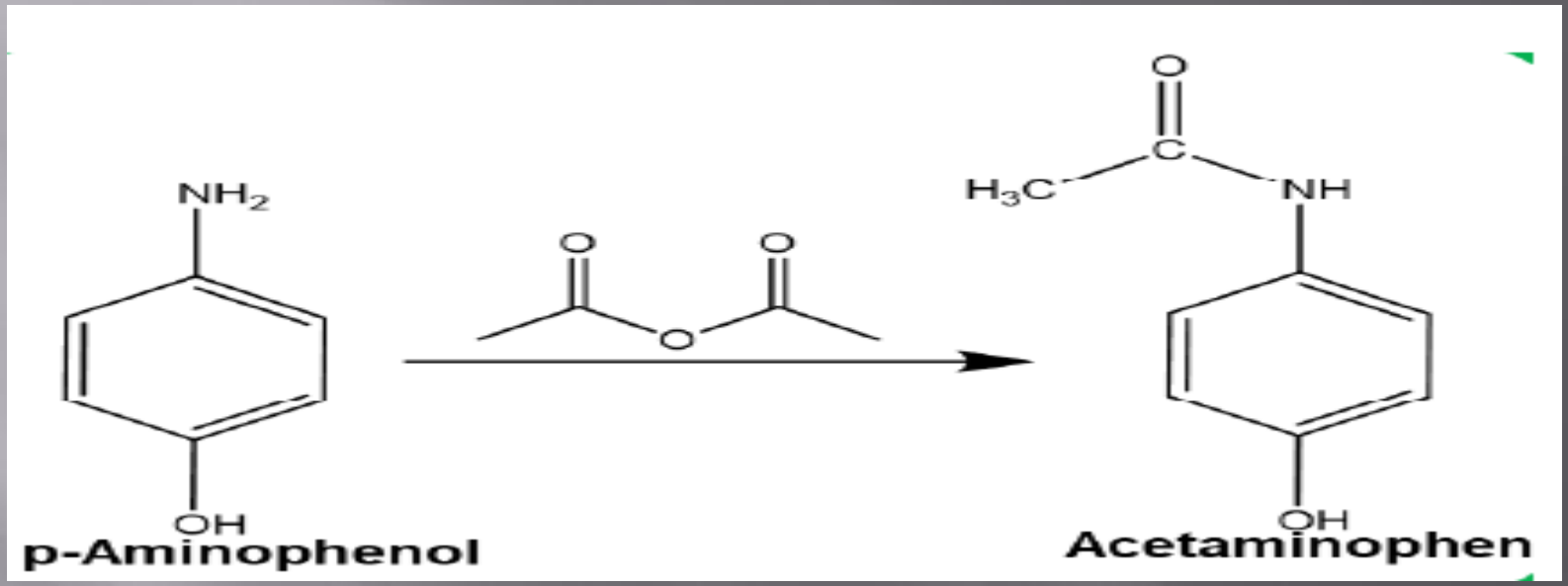
Reactivity towards acetylation:

Acetyl chloride > acetic anhydride > acetic acid

The best one: acetic anhydride.

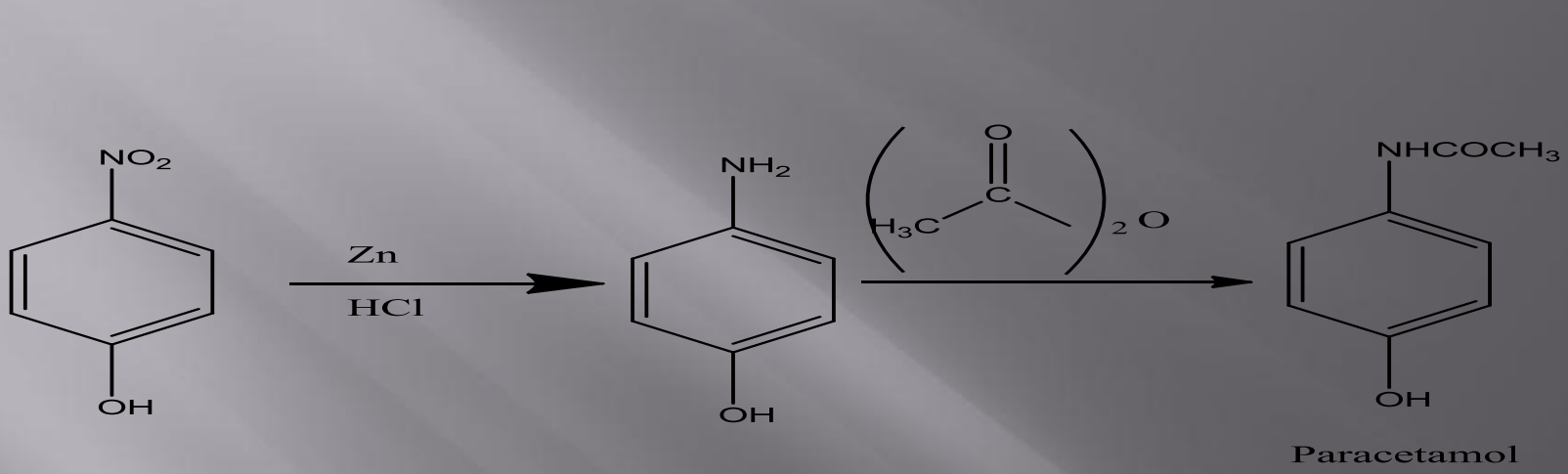
Easily handled, safe and reaction can easily be controlled.

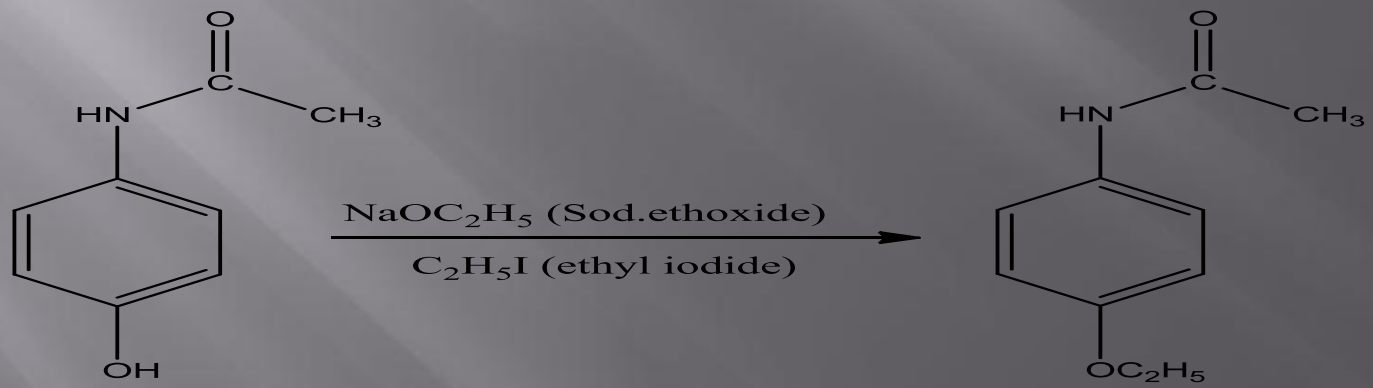
MAIN REACTION OF PARACETAMOL:



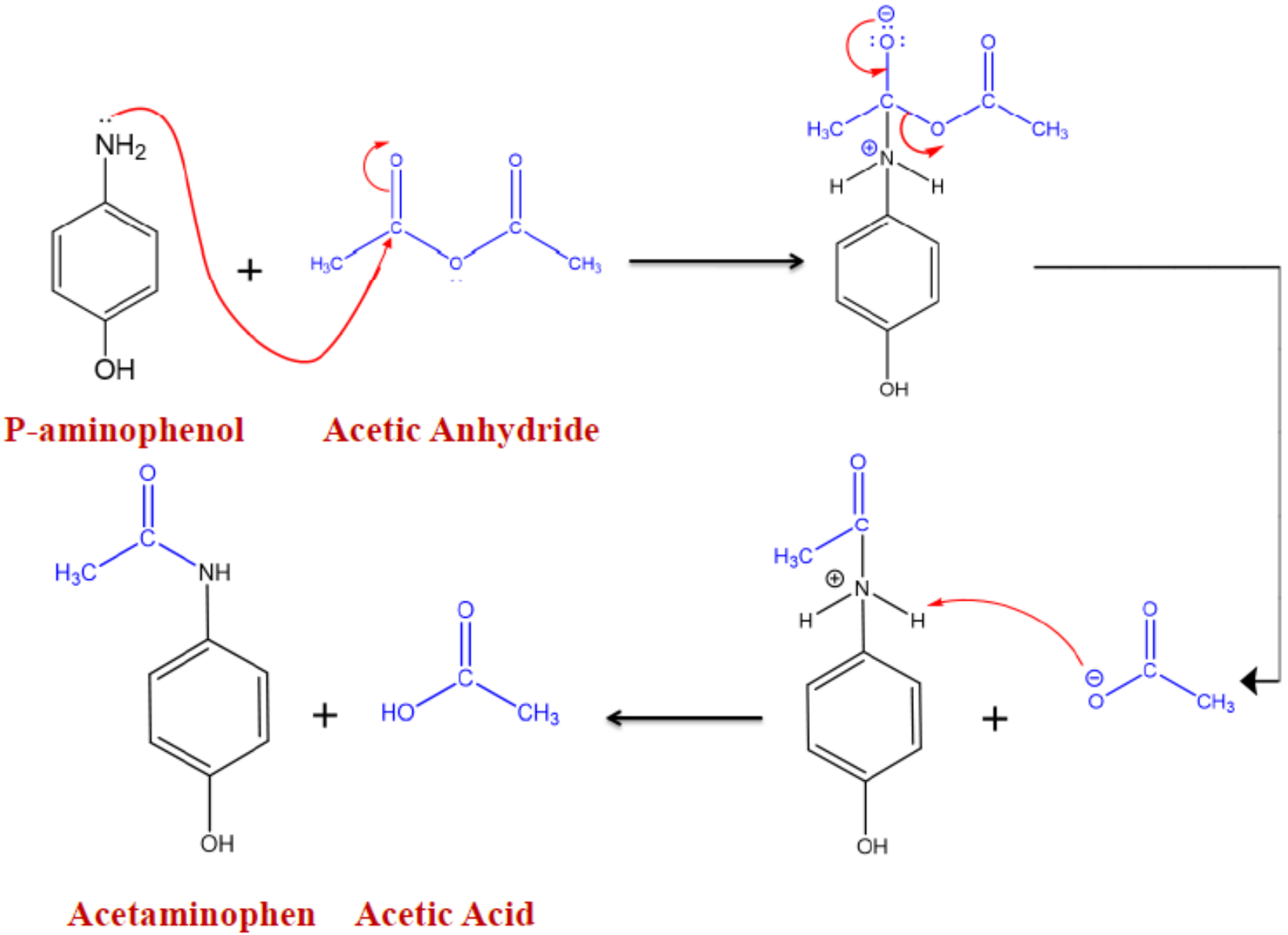
- Their characteristic reactions are with nucleophilic reagents, acetic anhydride reacts with compound containing active hydrogen atom to form derivatives containing acetyl group

Preparation of paracetamol





Main Mechanism of Preparation of paracetamol



Preparation of paracetamol

- ***Physical properties of phenacitin:*** stable ,white ,glistening crystals or powder.it is odorless and has a slightly bitter taste.
- ***Solubility:*** Very slightly soluble in H2O , soluble in alcohol and chloroform but slightly soluble in ether .it is sparingly soluble in boiling H2O it is a neutral compound and will not dissolve in either acids or alkalis.
- ***Action and uses:*** it is used widely as an analgesic and antipyretic. the toxic effects are the same as that of acetaminophen (the active form of phenacetin in that it is converted in the body to paracetamol)
- ***Toxicity:*** phenacetin may damage the kidneys when used in large dose or for long period of time.

PRECAUTIONS:
(1) ALL GLASS APPARATUS WHICH ARE USED IN THE SYNTHESIS MUST BE PERFECTLY DRY.
(2) CONCENTRATED SULPHURIC ACID SHOULD ALWAYS BE ADDED WITH GREAT CAUTION.
(3) TO COMPLETE THE REACTION MIXTURE IT MUST BE WARMED AT 60°C FOR 20–25 MINUTES.

Recrystallization:

Dissolve the crude product in 70% (*v/v*) ethanol and warm it to 60°C ; add 2 g of powdered animal charcoal (decolorizing carbon). Filter and concentrate the filtrate over a water-bath. Allow it to cool and large monoclinic crystals will separate out.

The yield of the pure paracetamol (mp 169–170.5°C) is 6.5 g.

PROCEDURE:

1) IN A ROUND-BOTTOMED FLASK (100 ML) PLACE 1.375 G OF P-AMINOPHENOL, AND THEN ADD 3.75 ML OF DISTILLED WATER.

2) TO THIS MIXTURE, DROP CAREFULLY 1.5 ML OF ACETIC ANHYDRIDE. ADJUST THE LIEBIG CONDENSER AND HEAT UNDER REFLUX FOR 20 MINUTES AT (115-120 C)

3) AFTER THE SUBSTRATE HAS DISSOLVED, COOL DOWN THE SOLUTION BY PLACING THE ROUND-BOTTOMED FLASK IN AN ICE-BATH FOR FEW MINUTES, THEN IN THE FREEZER FOR 10-15 MINUTES, AND THE CRYSTALS OF PRODUCT SHOULD APPEAR IN THE FLASK.

4) FILTER THE PRODUCT ON THE BÜCHNER FUNNEL AND WASH WITH COLD WATER. DRY ON AIR ON PETRI DISH.

Calculations:

Theoretical yield/Practical yield

Wight of *p*-Aminophenol on acetylation with Volume of acetic anhydride yields Paracetamol = Wight g

Hence, Theoretical yield of Paracetamol = **g**
Reported Practical yield = g
Therefore, Percentage Practical yield = Practical yield Theoretical yield 100 =

THANKS:

A.L. Abdulkareem Hamad