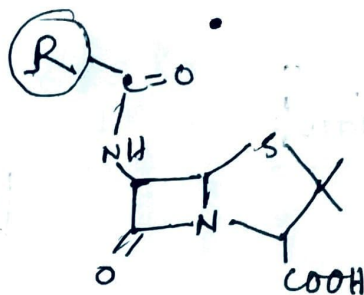
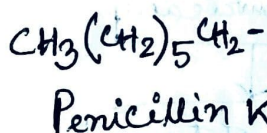
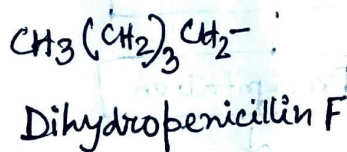
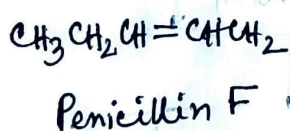
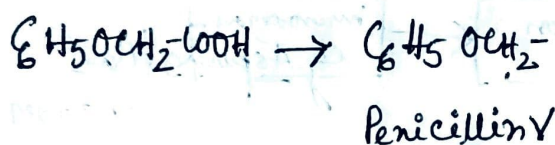
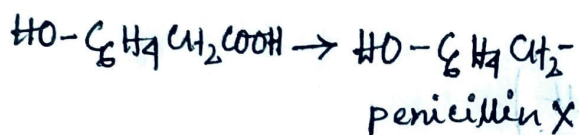


Production to Penicillin :-

Precursor

R Side chain
and penicillin type

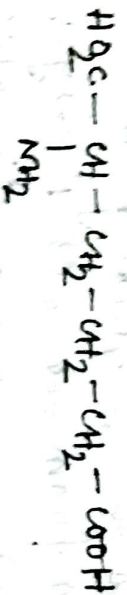


If penicillin fermentation is carried out without the addition of side chain precursor, the natural penicillins are formed - which are only benzylic side chain (R). However - the desired penicillin can be obtained by adding suitable side chain precursor into the medium. Such penicillins are called as semi synthetic penicillins.

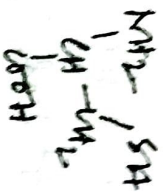
Biosynthesis of Penicillin :-

The β -lactam thiazolidine ring of penicillin is formed by the condensation of L-cystine and L-valine. The biosynthesis occurs in a non-ribosomal process by

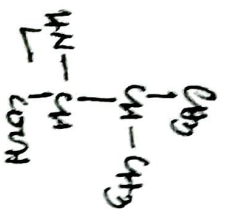
means of dipeptide compound of L- α -amino adipic acid (α -AAA). The first product of cyclization of the tripeptide which can be isolated is isopenicillin N which leads to Benzyl penicillin, intermediate steps are not well understood.



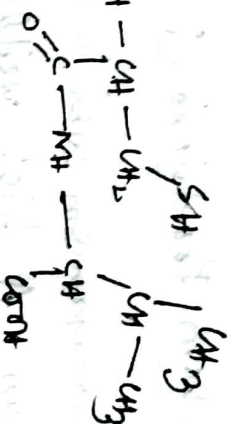
L- α -Aminoadipic acid (α -AAA)



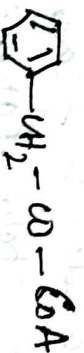
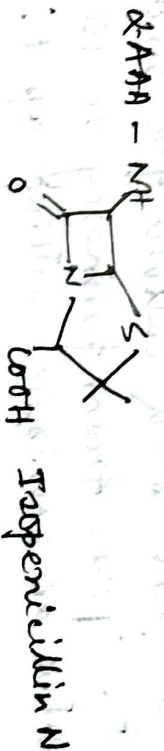
α -AAA-cys



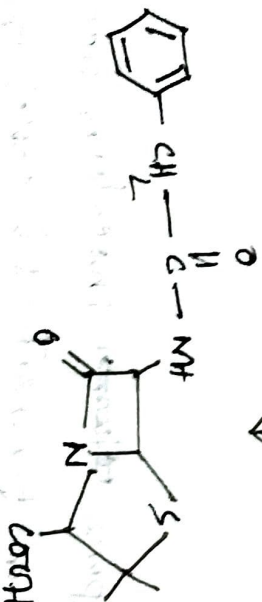
α -AAA-NH-CH-CH-CH₃



↓ cyclization



→ α -AAA-CoASA



Benzyl penicillin

Fermentation process of Penicillin:

This process can be described under following heads -

1. Strain development:

The variety of molds which yield greater amount of penicillin is called as high yielding strain. They are generally developed from the wild P. chrysogenum by a process called sequential genetic selection. For better yield, P. chrysogenum is mutated by a series of mutagenic agent or exposing to ultraviolet radiation or both.

2. Inoculum Production:

The microorganism which is used is called as the inoculum. A high yielding strain of P. chrysogenum is used as inoculum. A strain of the fungus is sub-cultured from stock culture for inoculum development. Spores from primary source are suspended in water or non-toxic wetting agent. Then this spores are added to flask with nutrients at a rate for heavy spore formation. The resulting spores are directly used to inoculate inoculum tanks or stirred fermentors.

3. Inoculation:

Introduction of pure ~~strain~~ inoculum into the production tanks or fermentors is called inoculation. As spores are hydrophobic some wetting agent like sodium lauryl sulphate is used. Suitable medium are generated in the production tanks.

(Glucose, sucrose, glycerol or sorbitol are used as 'C' source and ammonium sulphate or ammonium acetate are used for 'N' source, corn-steep liquid is widely used for this purpose, all the nutrients and - minerals required are supplied by this.

4. Extraction and purification

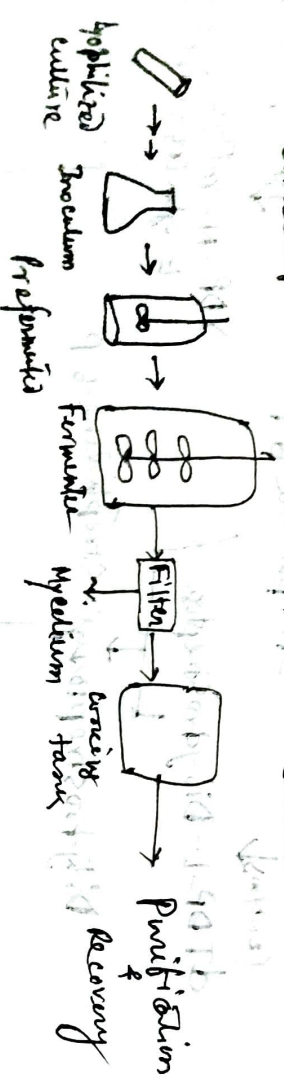
Penicillin-F and Penicillin-K are the naturally produced penicillins synthesis by P. notatum and P. chrysogenum respectively. But, if phenylacetic acid is supplied in the medium, P. chrysogenum produces Penicillin-G instead of Penicillin-K. Similarly, desired synthetic penicillins can be obtained ~~with~~ by adding the medium with suitable - precursors.

4. Extraction and purification:-

(i) Separation of mycelium: is separated by rotary vacuum filter. This process is vital, here, have to avoid contamination of penicillins enzyme produced by micro organism which convert penicillin to penicillic acid.

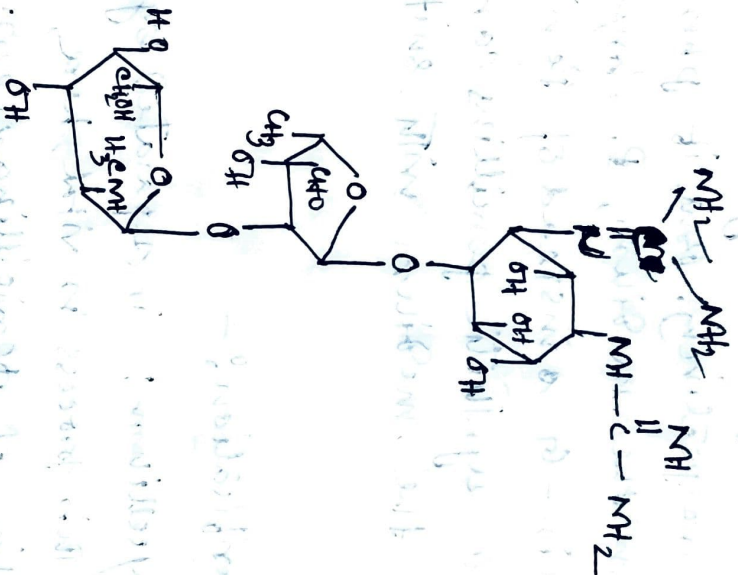
(ii) Extraction:- extracted by organic solvents such as amyl acetate or butyl acetate or methyl isobutyl ketone.

(iii) Treatment of crude:- The resulting soln. is charcoalized, concentrated and crystallized.

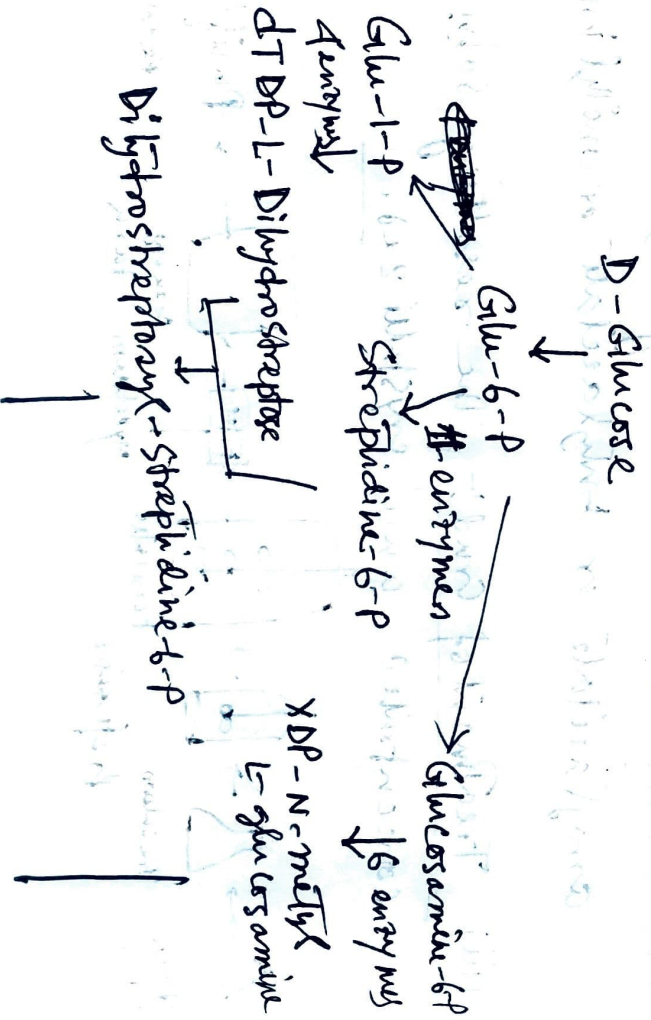


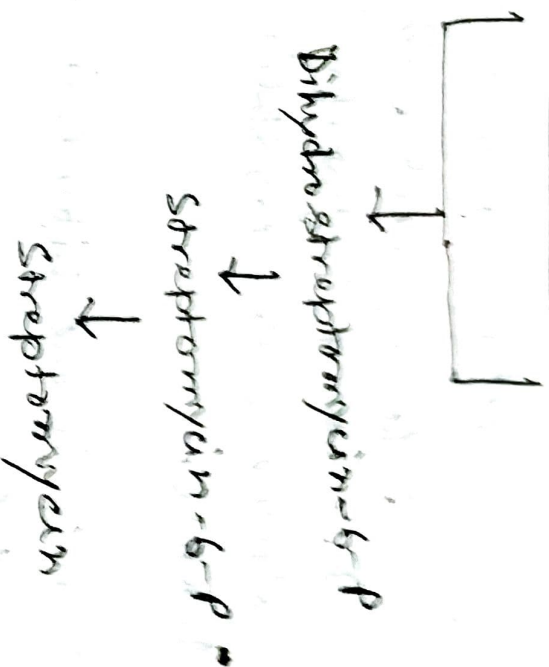
Production of Streptomycin:

Streptomycin, produced by Streptomyces griseus, is active against Gram(-)ve bacteria and against tuberculous bacterium, *Mycobacterium tuberculosis*. It is also useful in treatment of some Gram(+)ve bacteria which are resistant to penicillin.



Biosynthesis - Streptomycin is directly derived from glucose. Though all the steps of enzymes are still unknown.





Fermentation process:-

(i) The Inoculum Production:-

Spores of S. griseus maintaining an oil stock or lyophilized in a carrier such as sterilized skimmed milk, is employed as stock culture. The spores from these stock cultures are then transferred to a sporulation medium to provide enough sporulation growth.

(ii) Preparation of medium: It contains 'C' & 'N' source. Glucose is one of the best 'C' source. Apart from glucose, fructose, maltose, lactose, galactose, mannitol, xylose and starch are also used.

Peptones, soya extracts, meat extracts, amino-acids, vitamins are used as 'N' source. Mg, Ca, K, B, Mo salts are also used for mineral source.

(iii) Fermentation:-

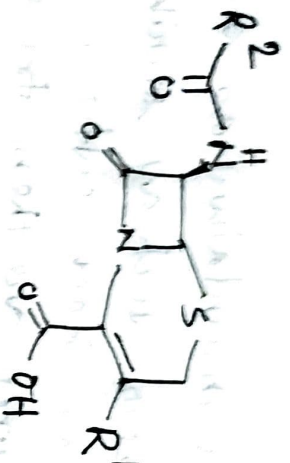
Sterilized liquid medium with all above substances is fed to the production fermenter. The fermentation goes through several stages during two days in presence of ~~the~~ air (O₂).

(iv) Recovery:- After completion of fermentation.

The broth is filtered, acidified, filtered and neutralized. Then it is purified by ion exchange resin column. Then crystallized or precipitated by methanol.

N.B: Vit-B₁₂ is the riboflavin obtained in the fermentation.

Cephalexin:



Name

R¹

R²

Cefadroxil



Cefadine



Cefprozil



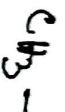
Cefaclor



Cefaclor



Cefalexin



etc.

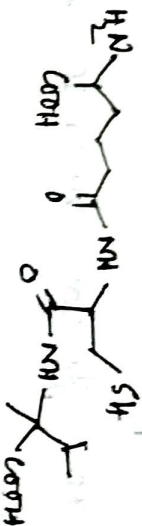
Bio-synthesis of Cephalosporin

Lysine

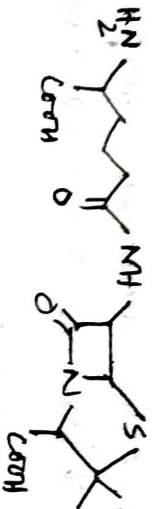
↓ LYS-6-aminotransferase

Piperidine-6-
carboxylic acid → L-α-Aminoadipic
Acid

L-cysteine
↓
L-Valine
↓
ACV Synthetase



↓ ACV Cyclase



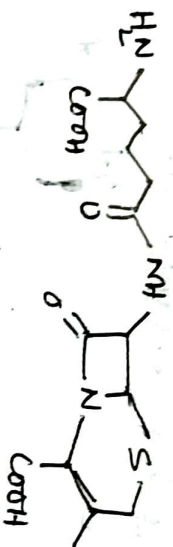
Penicillin G.

IPN Acyltransferase

↓ Isoopenicillin N epimerase
isopenicillin N

Penicillin N

↓ Penicillin N expandase



O-carbonyl-DAC

↓ DAC hydroxylase

7-α-hydroxy
DAC

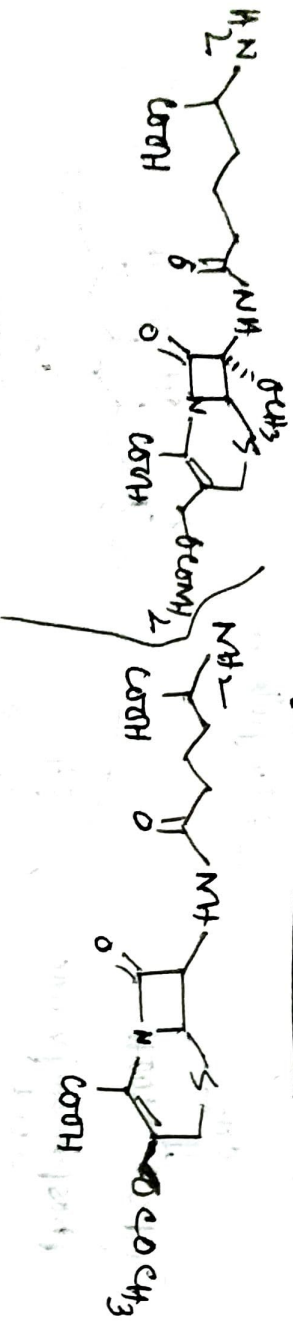


COOH

~~Cephalexin~~
Cepharmycin C

↓ DAC-Acetyl transferase

Cephatoapornin C



"Fermentation of Cephalosporin"

Cephalosporin fermentation is an ~~an~~ aerobic process and fermented by Acremonium chrysogenum.

The industrial process is same like penicillin.

Carbon source: glucose, sucrose, fructose, molasses and lactose.

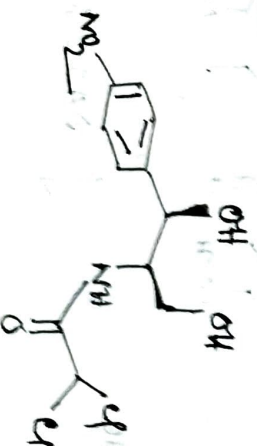
Organic & inorganic nitrogen source: peptone, urea, meat extract, casein, ammonium sulphate, or other amino acids. Methionine are also added as a vit nutrient.

Condition: (i) sufficient oxygen supply (740%)

(ii) Appropriate pH maintain (7-2)

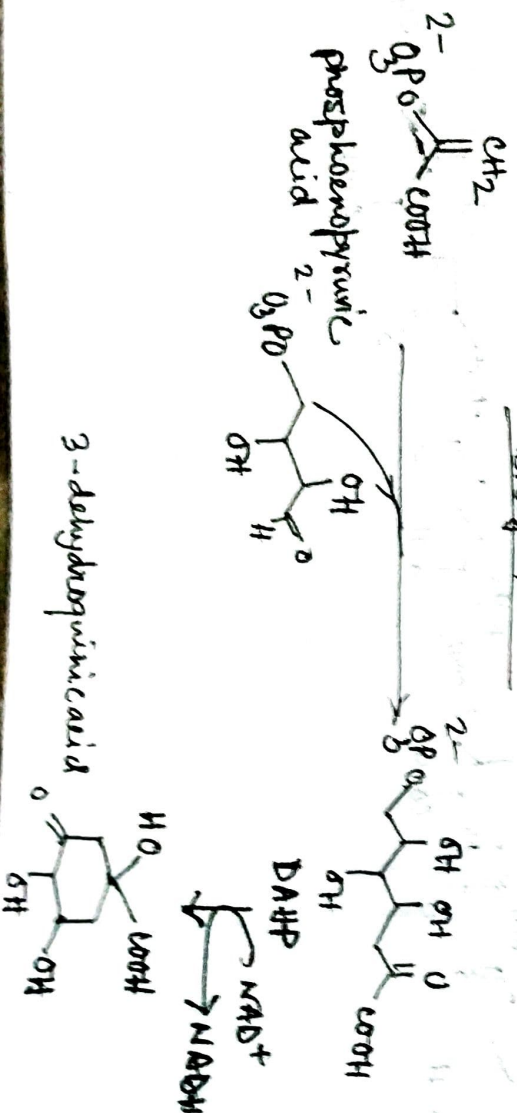
(iii) optimum temper (28°C)

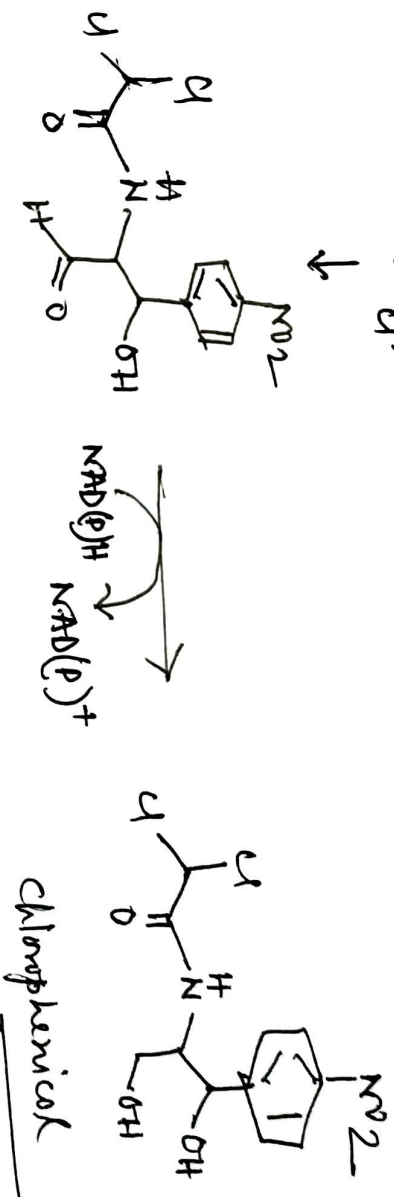
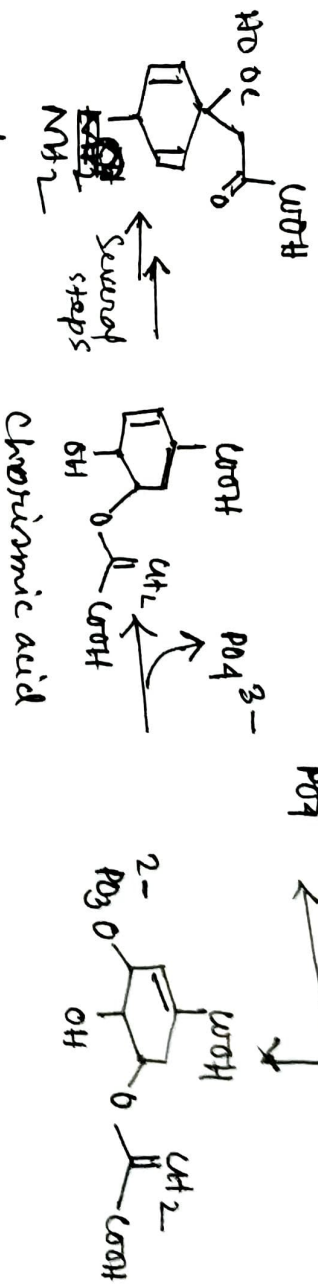
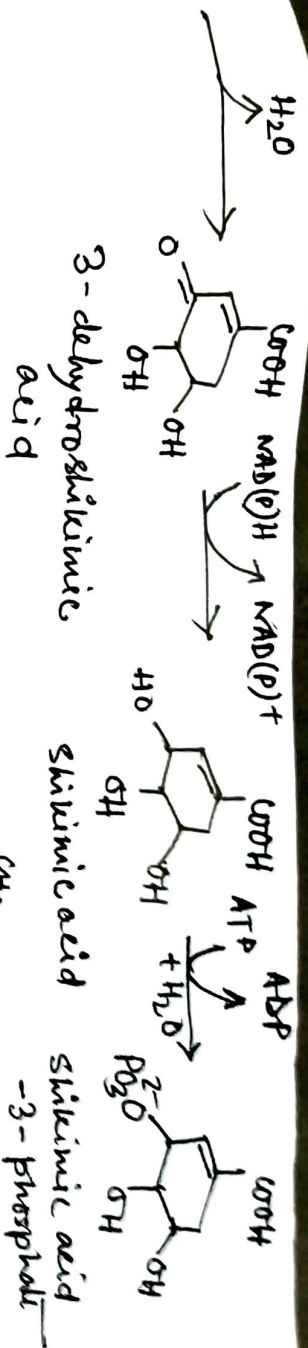
Chloramphenicol Production



chloramphenicol have another name chlorphenicol, is a ~~best~~ bacteriostatic antibiotic that inhibits protein synthesis by binding with bacterial ribosome. ~~As a~~ fermentation used the micro organism streptomyces venezuela.

Biosynthesis





Fermentation of chlorogenic acid:

The fermentation is carried out in 30Lt fermenter containing 18 Lt medium consisting of glycerol (1%), yeast extract or tryptone, NaCl (0.5%) and pH is adjusted to 7.5, temp 25°C for 3-4 days. Chlorogenic acid is extracted from clarified broth, filtrate is extracted and characterized, purified by chromatography and crystallized.