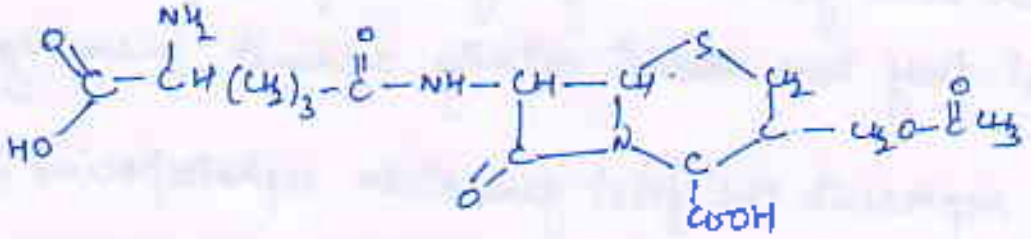
Cephalosporins



Cephalosporins are β-lactam antibiotics containing dihydrothiazine ring with D-α-aminoadipic acid as acyl moiety.

The discovery of cephalosporins started in 1945 when G. Brotzu cultivated "cephalosporium acremonium" from sea water near sewage outlet on the coast of Sardinia. He found that the crude filtrate from this culture possess therapeutic activity against staphylococcal infections and typhoid fever. Further studies with Cephalosporium species produced seven antibiotics which were termed as cephalosporins

Out of the seven antibiotics - five were lipid soluble and one of them was shown to be steroidal (cephalosporin P_1). The other two were hydrophillic and were designated as cephalosporin N and cephalosporin C.

The cephalosporins are bactericidal and like penicillins they act by inhibiting synthesis of the bacterial cell wall. Cephalosporins are generally classified by generations, based on the antibacterial profiles and also the period of their introduction.

First generation

Cephalosporins have good activity against gram positive bacteria and they have modest activity against gram negative bacteria.

Cefalotin represents the first generation cephalosporins and was first to be introduced. other members of this gp are -

- ⇒ Cefapirin
- ⇒ Cephaloridine
- ⇒ Cephalexin
- ⇒ Cefradine
- ⇒ Cefadroxil
- ⇒ Cefatrizine
- ⇒ Cefazolin

Second Generation

Cephalosporins are slightly less active against gram positive bacteria but are more stable to hydrolysis by beta lactamases produced by gram negative bacteria and have enhanced activity against many of the Enterobacteriaceae and Haemophilus influenzae.

The first member of the second generation cephalosporins to become available was cefamandole. The other members are

- ⇒ Cefaclor
- ⇒ Cefoxitin
- ⇒ Cefuroxime
- ⇒ Cefuroxime axetil

Third generation

Cephalosporins are even more resistant to hydrolysis by beta lactamases than the second generation drugs. They have a wider spectrum of activity and are more active against gram negative organisms. The activity against gram positive organism is found to be less than that of first generation agents. The first member of this group to become available was cefotaxime. The other members are-

⇒ Ceftriaxone
⇒ Cefixime
⇒ Ceftazidime
⇒ Cefoperazone

Fourth Generation

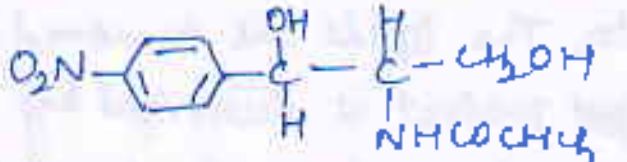
Cephalosporins have broad spectrum of activity as compared to the third generation and have increased stability from hydrolysis by beta lactamases. eg- Cefepime. It is active against a wide range of gram positive and gram negative aerobic organisms.

Synthesis by fermentation

Cephalosporin C is produced by 'Acremonium chrysogenum' on the fermentation medium at 28°C for 144 hr is characterised by rapid consumption of sucrose to form biomass at beginning of the process. The pH of the medium is kept 7.2 and temp is maintained 28°C by passing water through jacket. pH is maintained by using 2M KOH and 2M HCl. Dissolved oxygen is maintained above 30% saturation by agitation & aeration. After the depletion of carbohydrate by the slow consumption of sucrose during which most of the Cephalosporin is produced is called <u>idiophase</u>.

Max Cephalosporin C has been obtained at 120 hr of fermentation while highest cell growth occurs at 42 hr of fermentation. Accumulation of 2° metabolites occur in idiophase after growth phase. Cephalosporin C is separated from the liquid by the use of diff. separation and distillation techniques in a sequential stepwise manner depending on interacting chemical nature of obtained product.

Chloramphenicol



Chloramphenicol was first isolated from cultures of 'Streptomyces venezuelae' an organism from a soil sample collected from venezuela.

Chloramphenicol is an antibiotic with a broad spectrum Profile. It is active against gram-positive and gram -ve micro-organism. It is reserved for use in typhoid and other Salmonellal infections and in the treatment of bacterial meningitis

Chloramphenicol acts by inhibiting protein synthesis in bacteria. It binds reversibly to the 50s subunit of the bacterial ribosome and inhibits bacterial protein synthesis

Chloramphenicol is usually given orally in capsules or as a suspension of chloramphenicol palmitate. Chloramphenicol sodium succinate may be given intravenously. chloramphenicol is applied locally for the treatment of ear, eye and skin infections

Synthesis by fermentation.

The fermentation is carried out in a fermenter containing 1% glycerol, yeast extract, 0.5% NaCl and pH is adjusted to 7.5. The fermentation is carried out at 25°C for 3-4 days.

Chloramphenicol is extracted from the clarified broth. The filtrate is extracted either with ethyl acetate or diluted with

kerosene and then washed with dil acetic acid, sodium carbonate and water. The lipids are removed by petroleum ether. The crude ~~pet~~ product is decolorized by passing the organic solution through a column of charcoal or alumina. The purified product is recrystallised from ethylene or ether and petroleum ether mixture

note: Chemical synthesis of chloramphenicol has already been done in the class.

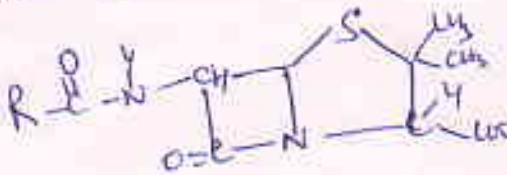
Penicillins

discovered by Alexander Fleming in 1929. In the beginning isolation of the antibiotic was a problem as it was unstable at acidic pH. Fermentation procedures were developed to isolate the ~~the~~ material in pure state. Two types of fermentation methods were developed - (a) Surface culture fermentation (b) Submerged culture fermentation.

Surface culture fermentation the mould was grown on a simple synthetic medium in flat rectangular vessels. The penicillin was extracted from the organic phase into an aqueous solution containing barium hydroxide. It was decolourized with charcoal, acidified ~~to~~ and reextracted ~~to~~ ether. The ether extract was chromatographed on a column of alumina that was eluted with phosphate buffer. The eluate was frozen, lyophilized and brown powder of the antibiotic ~~was~~ obtained.

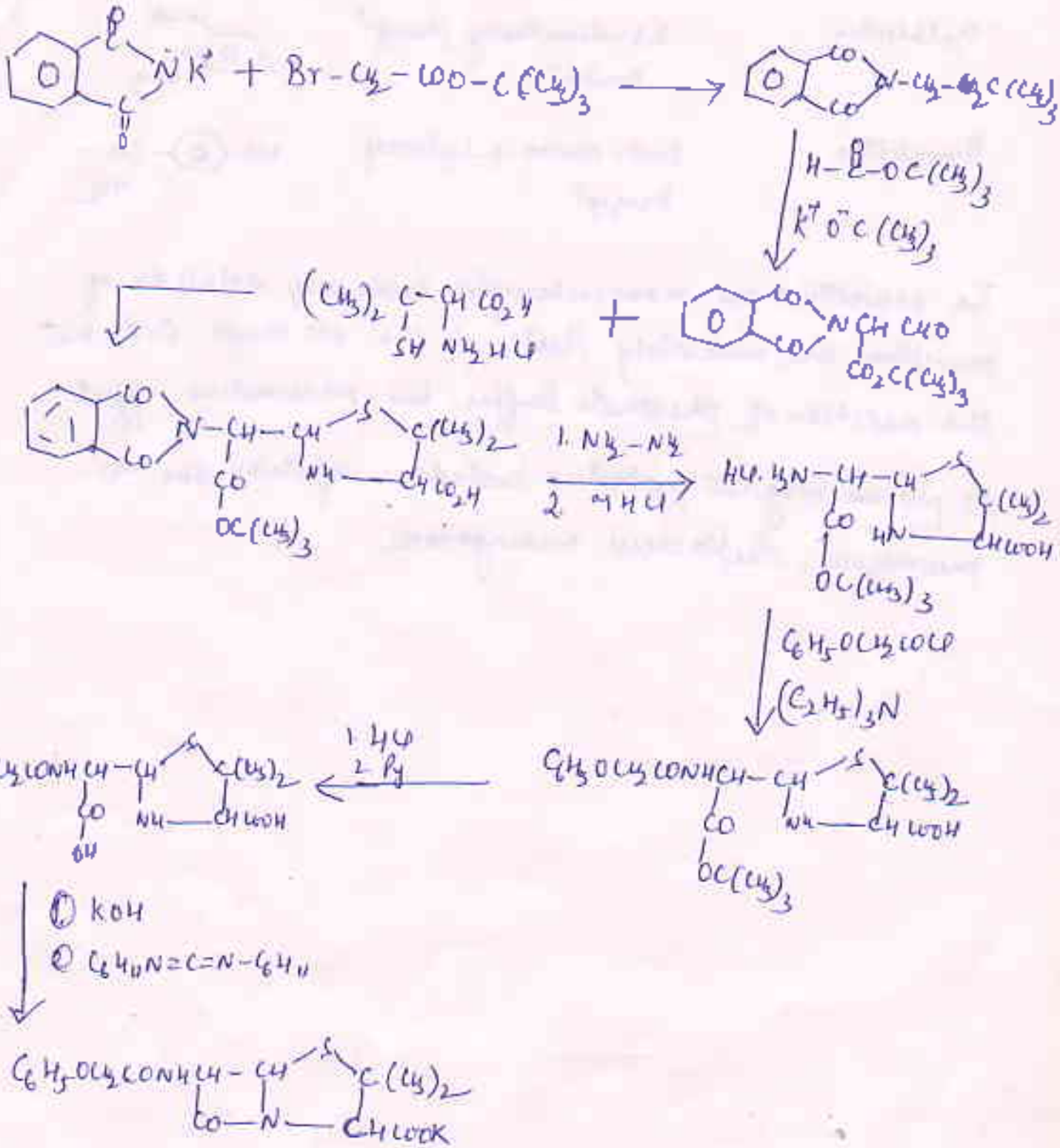
Submerged culture - the mould is grown in upright cylindrical tanks filled with agitators and devices for introducing oxygen during the period of growth. The fermentation is performed under sterile conditions as many bacteria produce ~~many~~ enzyme which destroys penicillin. The yield of penicillin could be increased by the use of corn steep liquor in the fermentation media. eg. phenethylamine, a precursor of benzyl penicillin.

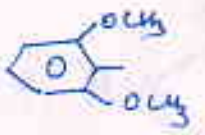
The most imp. development in the penicillin field is the isolation of 6-aminopenicillanic acid from Penicillium chrysogenum carried out in the absence of side chain precursor.



Penicillin

Synthesis of Penicillin G Phenoxymethylpenicillin



Generic name	Chemical name	R
Penicillin G	Benzyl- Penicillin	$C_6H_5CH_2-$
Methicillin	2,6-dimethoxy phenyl penicillin	
Amonicillin	D-α-amino-p-hydroxy benzyl	

The penicillins are monocarboxylic acids, aq. solution of penicillins are moderately stable in the pH range 6-7 but the addition of phosphate buffer has preservative effect.

Its pharmacological properties include - infection due to pneumococci, streptococci, meningococci.