KRISHNAVENI DEGREE & PG COLLEGE

Under affiliated by

ACHARYA NAGARJUNA UNIVERSITY (ANU)

2nd YEAR M.Sc

IV Semester

Paper-IV: Chemistry of Antibiotics and Drugs

(R22OC44A)

Department of Chemistry

Krishnaveni Degree & PG College

Narasaraopet – 522601

ACHARYA NAGARJUNA UNIVERSITY
DEPARTMENT OF CHEMISTRY

M.Sc. ORGANIC CHEMISTRY :: SEMESTER–IV

PAPER–IV (Elective–A): CHEMISTRY OF ANTIBIOTICS AND DRUGS (R22OC44A)

(For the students admitted from the A.Y. 2022-2023 onwards)

Max. Marks: 100 (Internal-30M & External-70M)

SYLLABUS

Learning Objectives:

- ✓ To know the basics on antibiotics, their importance and various drugs in medicinal chemistry.
- ✓ To know the chemistry of structures and synthesis of some antimalarials, sulpha drugs, antiseptic and antifungals.
- ✓ To know the classification of herbal drugs and their therapeutic efficacy and isolation.
- ✓ To know the types & classification of Antiseptics.
- ✓ To know the CNS stimulants.

UNIT-I **12H**

Antibiotics:

Synthesis of penicillin-G, ampicillin, amoxicillin, chloramphenicol, cephalosporin. Streptomycin, tetracyclines, Terramycin, aureomycin, gramicidin.

UNIT-II **12H**

Drugs and Medicinal chemistry:

Anticancer Agents: Synthesis & Activity relationship of Taxol, Vinblastine, Vincristine, Camptothecin.

CNS Stimulants: Strychnine (CNS activity only), caffeine, Nicotine; CNS depressants, General anesthetics, mode of action of Sedatives & Hypnotics.

UNIT-III **12H**

Antimalarials: Paludrin – quinacrin – chloroquin – camoquine– pamaquine– sontoquine.

Sulpha Drugs: Sulphanilamide – Dihydrocurprine – Prontosil

UNIT-IV **12H**

Antiseptics and Antifungal agents

Antiseptics: Common types, triclosan, aminacrine hydrochloride. Antiseptics *Vs* Disinfactants-Properties, Mechanism of action, classification

Antifungal Agents: 1,8-dihydroxyanthranol – griseofulvin.

UNIT-V 12H

Herbal Drugs: i) Classification of herbal drugs- Pharmacological and Chemical classification. ii) Adulteration and evaluation of drugs. iii) Different chemical groups of Herbal drugs- Alkaloids, Terpenoids, Glycosides, Volatile oils, Isolation of volatile oils, Tannins, and carbohydrates. iv) Herbal drugs and their therapeutic efficacy. Isolation of- Laxative-Aloe-emodin from Aloes. Anti-diabetics- Neem oil (Neem); Anti-malarial- Quinine (cinchona); Anti-hypertensive- Reserpine (rauwolfia).

Reference Books:

1) Introduction to Medicinal Chemistry – Wiley VCH.
2) Text Book of Organic Medicinal and Pharmaceutical Chemistry, Wilson and Gisvild, (ed Robert F. Dorge)
3) An introduction to drug design by SS Pandeya
4) Buger's Medicinal Chemistry and drug discovery Vol.I by (Ed) ME Wolff – John – Wileyby A. Burger
5) The Organic Chemistry of drug design and drug action by RB Silverman, Academic press
6) Principles of Medicinal Chemistry by William O. Foye, Lea & Febiger, Philadelphia/London, 1989.
7) Natural products. By P.S.Kalsi
8) Medicinal chemistry. By Chatwal.- And By Ashtoshkar.
9) Chemistry of Drugs. By V.N.Ivers.
10) May's chemistry of synthetic drugs. Hand Book of Reagents for organic synthesis. By Reich,Rigby
11) Top Drugs: The synthetic routes. J.Saunders
12) Organic natural products By Barton and Ollis
13) Organic natural products by OP Agarwal
14) Organic natural products By Barton and Ollis.

Learning Outcomes:

- ✓ Students under the basics on antibiotics, their importance and various drugs used in medicinal chemistry.
- ✓ Students are able to understand chemistry and synthesis of antimalarials, sulpha drugs, antiseptic and antifungals used in medicine.
- ✓ Students can identify the classification of herbal drugs in various types and understand their therapeutic afficacy and isolation methods.
- ✓ Students understand the types of Antifungal agents.
- ✓ To understand the mode of action of sediatives.

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Paper-IV: Chemistry of Antibiotics and Drugs

UNIT - I

Antibiotics: Inhibitors of Bacterial protein Synthesis

protein biosynthesis is perhaps one of the important process that provides peptides. These may be assembled as per the needs of the organism, in the proper sequence to biosynthesis various enzymes and or nucleic acids. The important events in the protein synthesis can be outlined as

a. Amino acid activation

b. - Formation of amino acyl t-RNA

c. peptide bond formation

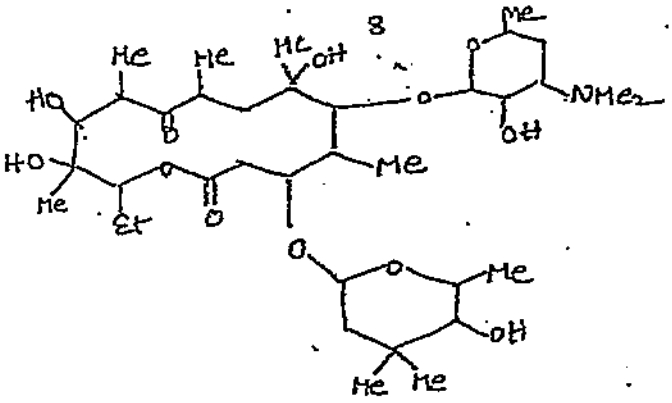
d. translation

The antibacterial activity results due to the attack of the drug on one or more of the above events occuring on the ribosomal (or-RNA) surface.

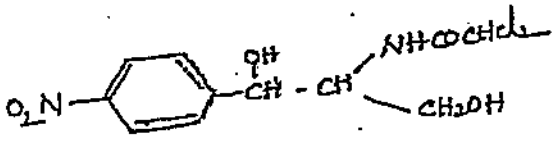
The bacterial ribosomes differ from mammalian ribosomes. The difference has been figured out by their sedimentation coefficients.
Solid material settled at the bottom of the liquid.

Eg: Bacterial ribosomes have the sedimentation coefficient of 70C 70S) with two subunits 30S and 50S. while the mammalian cyto plasmic ribosomes are 80S and give rise to 40S and 60S subunits. Mitochondria Contain similar ribosomes. Hence the degree of selectivity of an antibiotic will define its clinical effectiveness.

Eg: Erythromycin does not bind to the mamianlian ribosomes. Its selectivity inhibits bacterial protein synthesis by binding to the 50S ribosomal subunits of sensitive strains of micro organisms protein Synthesis in microorganisms is affected by many antibicrobial as well as anti Cancer agents.

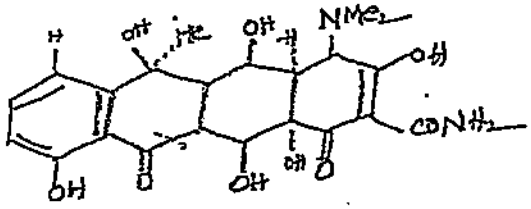


Erythromycin



Chloramphenicol

Chloramphenical, macrolides and lincomycin bind to 50s ribosomes while tetracyclines block the reaction between amino and t-RNA and ribosome on m-RNA. All these antibiotics destabilise ribosomes by inhibiting transpeptidation



Terramycin.

polyribosomes by inducing conformational changes in ribosomes they also interfere with translocation reaction.

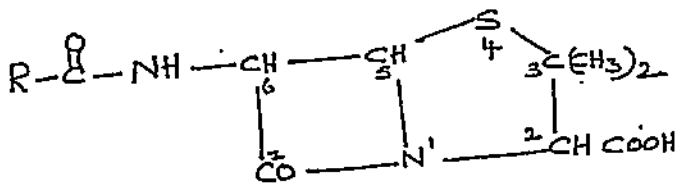
It seems that the antibiotic bound ribosomal subunit still can offer the space and activity sufficient to produce small chain peptides. Thus the ribosome cycle continues but polypeptide elongation is prevented. Similarly tetracyclins and Streptomycin also bind to and inhibit the attachment of the 30s subunits to the m-RNA.

Penicillins.

The antibiotic penicillin is extracted from the penicillium mycelium. penicillium agaricus is the another species of penicillium, which produces penidure antibiotics. The long acting penidure bacteria extracts chemical substances in absence of oxygen. Hence the long acting penicillins are produced from the anaerobic micro organisms. The natural antibiotics containing sulphur is only the penicillin antibiotic.

penicillin is the name given to the mixture of natural compounds having the molecular formula $C_9H_{11}N_2O_4SR$, and differing in the nature of R.

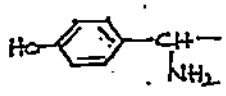
Structure of penicillins.



There are atleast six natural penicillins

Generic Name	Chemical Name	R-Group.
penicillin-G or I	Benzyl penicillin	$C_6H_5CH_2-$
penicillin-V	Phenoxyl methyl penicillin	$C_6H_5OCH_2-$
Penicillin-F or II	pent 2-enyl penicillin	$CH_3CH_2CH=CH-CH_2-$
penicillin-X or III	p-hydroxy benzyl penicillin	$HO\,C_6H_4CH_2-$
penicillin-K or IV	n-Heptyl penicillin	$CH_3(CH_2)_6-$
Dihydro-F. penicillin	n-amyl penicillin	$CH_3(CH_2)_4-$

Ampicillin — D-α- Amino benzyl penicillin — $C_6H_5CH(NH_2)-$

Amoxicillin — D-α- Amino p-hydroxyl benzyl penicillin — 

Constitution :—

1. The General formula for the penicillins is $C_9H_{11}N_2O_4SR$
2. They form mono salt indicating the presence of Carboxyl group.
3. Penicillins are not found to possess a free amino or thiol group.
4. On hydrolysis with hot dilute inorganic acids all the penicillins are degraded to the equimolecular amount of an amine, penicillamine and an aldehyde, penilloaldehyde along with the elimination of one carbon atom as Carbondioxide.

$$C_9H_{11}N_2O_4SR + 2H_2O \xrightarrow{Hcl} \underset{\text{penicillamine}}{C_5H_{11}NO_2S} + \underset{\text{penilloaldehyde}}{C_8H_4NO_2R} + CO_2$$

Since the fragment R comes in the aldehyde portion, all penicillins give the same amines, but different aldehydes.

5. Structure of D- penicillamine (β,β-dimethyl cysteine):—

(i) The molecular formula of penicillamine is $C_5H_{11}NO_2S$.

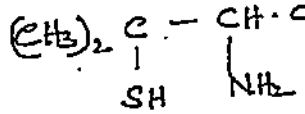
(ii) It gives colour reactions with sodium nitro pruside and ferric chloride indicating the presence of a thiol (SH) group.

(iii) Electrometric titrations of penicillamine shows three pka values. 1.8, 7.9 and 10.5 corresponding to Carboxyl, α-amino and thiol groups, respectively.

(iv) penicillamine when treated with acetone gives an isopropylidene derivative. The later does not contain any free amino or thiol group and is hydrolysed back to penicillamine. This set of reactions indicates that amino and thiol groups are present on the adjacent carbon atoms of penicillamine.

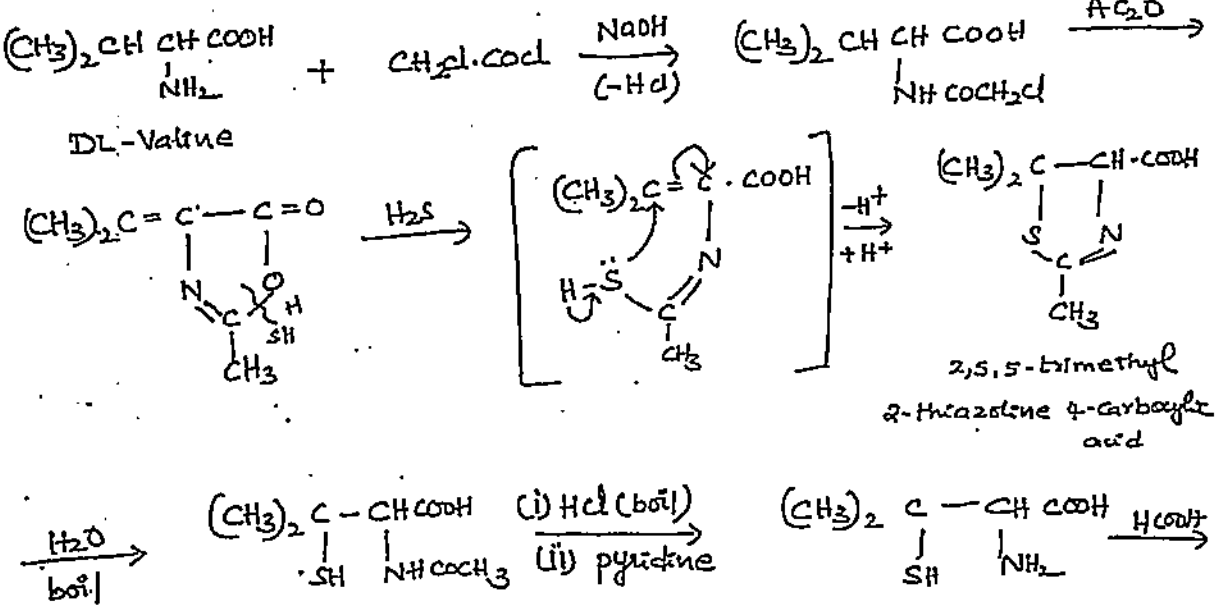
(v) The Kuhn-Roth determination of methyl side chains gave a very low value (~ 0.2 molecules) indicating that the compound contain isopropyl end group and not a methyl end-groups.

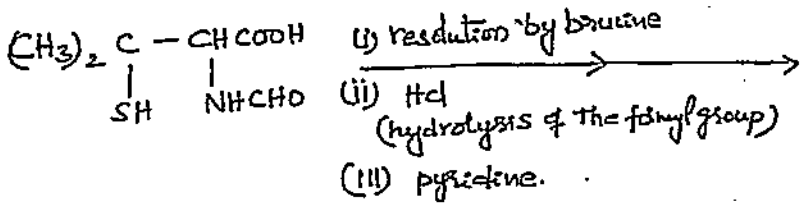
On the basis of above points, penicillamine may be given the following structure.



Penicillamine (β,β-dimethyl cysteine).

(vi) Finally, penicillamine is proved to be D-β,β-dimethyl cysteine by its synthesis.





D-Penicillamine.

6. penicillin on treatment with diazomethane is converted into its methyl ester which on treatment with an aqueous solution of mercury chloride gives the methyl ester of penicillamine. This set of reactions clearly indicates that the carboxyl group of penicillamine is the carboxyl group of penicillin itself.

7. Structure of penilloaldehyde :—

(i) The molecular formula of penilloaldehyde is $C_3H_4NO_2R$

(ii) The structure of penilloaldehyde as acylated derivatives of amino acetaldehyde is proved by their vigorous hydrolysis to aminoacetaldehyde and a substituted acetic acid.

$$R\,CO\,NH\,CH_2\,CHO + H_2O \longrightarrow R\text{-}COOH + H_2N\cdot CH_2CHO$$

penilloaldehyde — aminoacetaldehyde.

(iii) The above structure for penilloaldehyde has been confirmed by synthesis from the corresponding acid chloride and amino acetal.

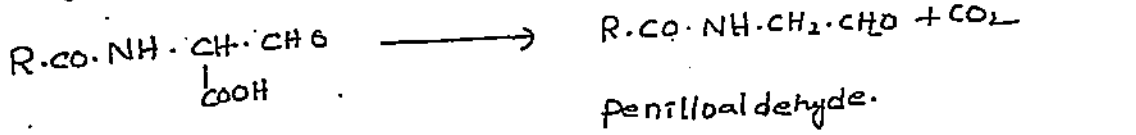
$$R\text{-}COCl + H_2N\,CH_2\cdot CH(OC_2H_5)_2 \xrightarrow{HCl} R\cdot CO\cdot NH\cdot CH_2CH(OC_2H_5)_2$$

$$\xrightarrow{H^+} R\text{-}CO\cdot NH\cdot CH_2\cdot CHO$$

penilloaldehyde.

(iv) From point 4 it is obvious that a molecule of Carbondioxide is obtained during the acidic hydrolysis of penicillin. The formation of CO_2 molecule, suggests that some unstable acid is formed as an intermediate which on decarboxylation gives Carbondioxide. Such an acid is β-keto acid and hence penilloaldehyde - Carboxylic acid

(penaldic acid) must be formed as an intermediate in the hydrolysis of penicillin.

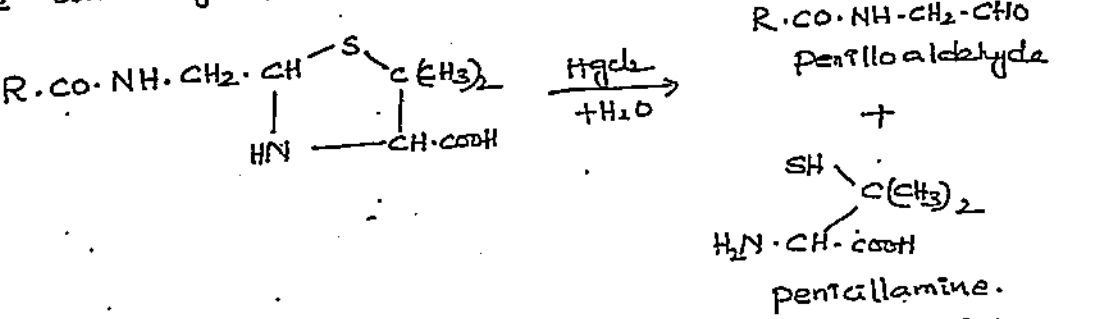


Penaldic acid

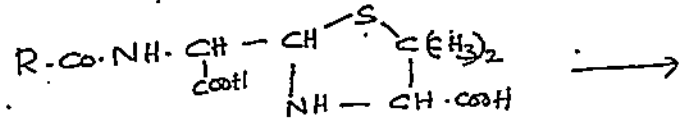
8. Point of linkage between penicillamine and penilloaldehyde :-

penicillins on hydrolysis with dilute alkali gives a dicarboxylic acid, penicilloic acid, which readily eliminates a CO_2 molecule to yield a mono carboxylic acid, penilloic acid. This suggests that in penicilloic acid one of the carboxylic group is the β-position with respective to the negative group.

The structure of penilloic acid is established by its hydrolysis with aqueous mercuric chloride to penicillamine and penilloaldehyde (a characteristic reaction of thiazolidine ring). The thiazolidine type of nucleus in penicillin is proved by the fact that it has neither free amino group nor a free thiol group.



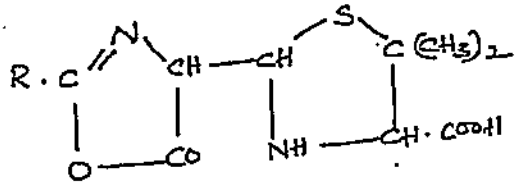
Hence penicilloic acid must have the following structure.



Penicilloic acid.

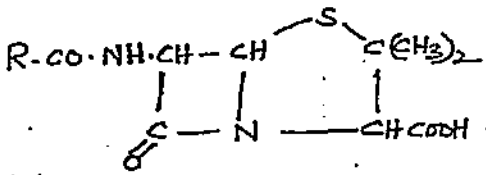
penilloic acid + CO_2

9. But we know that penicillin is a monocarboxylic acid and the carboxyl group is present in the penicillamine molecule which is coming from the thiazolidine nucleus, the second carboxyl group of penicilloic acid may be present either as oxazolone or as β-lactum and thus penicillin might be I or II



I

Oxazolone structure



II

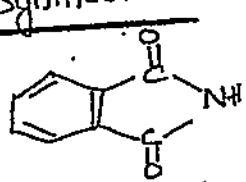
β-lactum structure.

(10) Infra red spectra of the methyl ester and sodium salts of benzyl penicillin correspond to the functional groups of the β-lactum type structure and not to oxazolone type structure. Moreover, the X-ray analysis of the sodium, potassium and rubidium salts of benzyl penicillin showed the presence of a β-lactum ring.

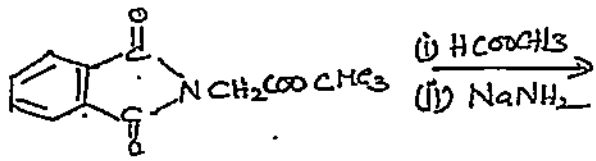
Hence the structure II is correct structure for penicillin.

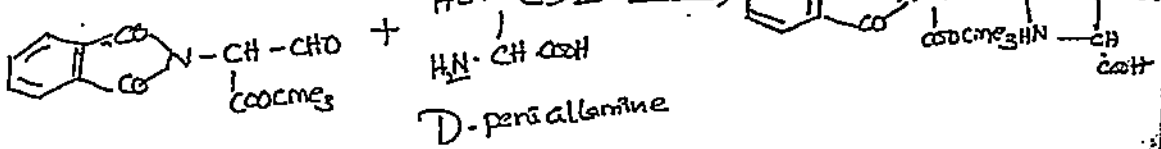
(11) Finally, the structure of penicillin is confirmed by its synthesis.

Synthesis :-

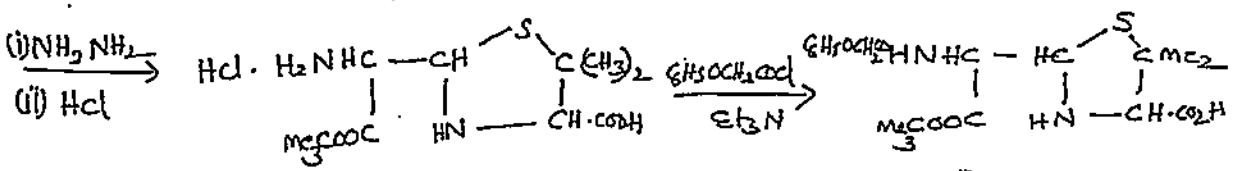


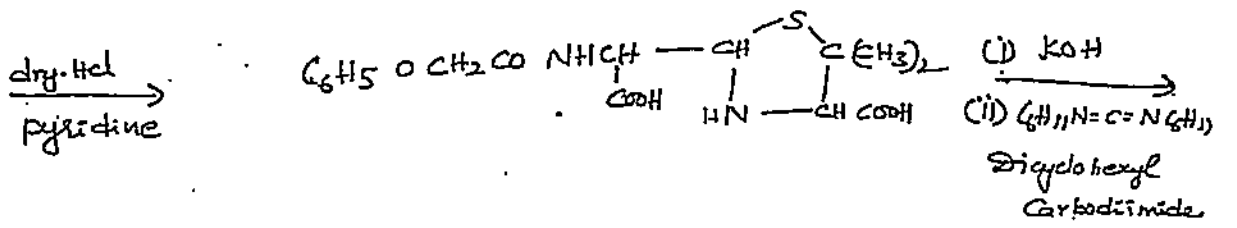
phthalimide

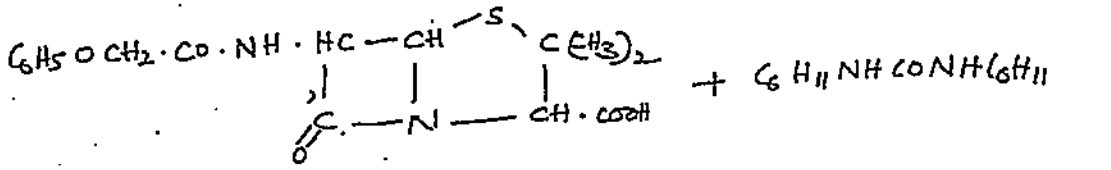




D-penicillamine







Penicillin-V

Therapeutic applications:—

Penicillin is considered as the queen of drugs.

(i) penicillin is active against Gram-positive micro organisms including staphylococci.

(ii) It is in active, with certain exceptions, against Gram-negative forms.

A partial list of diseases that respond to adequate penicillin therapy include anthrax, tetanus, diphtheria, pneumonia, scarlet fever, child birth fever; gonorrhea etc.

(iii) penicillin is the least toxic of all the antibacterial drugs.

*Penicillin-G:—

1. It is a bactericidal drug.
2. It is active Vs Gram positive bacilli (staphylococci, meningitis, gonorrhopa) and many Gram negative cocci
3. It is Non toxic.

4. Non active against a wide range of bacteria.

5. Ineffective when taken orally. penicillin-G can only be administred by injection.

6. Sensitive to all known β-lactamines. These are enzymes produced by penicillin resistant bacteria which Catalyse the degradation of penicillin.

7. Allergic reactions are suffered by some bacteria.

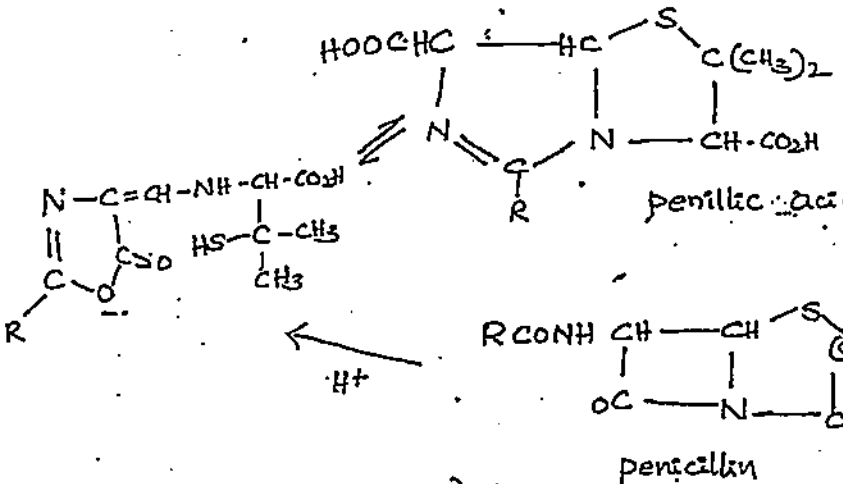
Penicillin-V :-

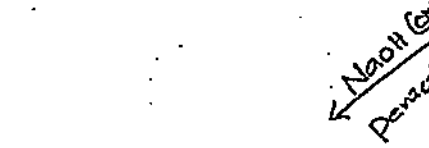
1. It is resistant to hydrolysis by gaustric juices.

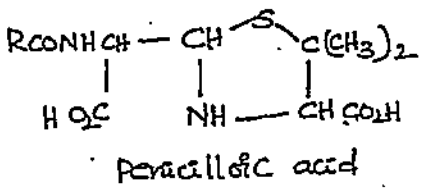
2. It is used in treating mild or moderately serious injections of the respiratory track, produced by Gram positive organasisms such as Streptococci and pneumococci.

3. It is very useful in the prophylaxis or rheumatic fever and acute nephritis in juvenile who have had these disease earlier.

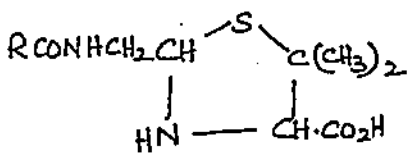
Degradation of penicillin gives the following products







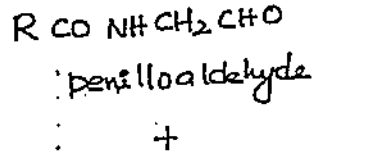
Penicilloic acid



$-CO_2$

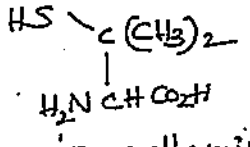
Penilloic acid

$H_2O - HgCl_2$



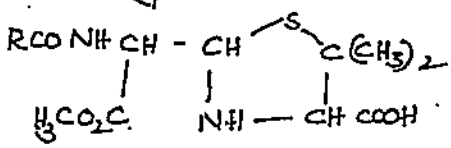
Penilloaldehyde

+



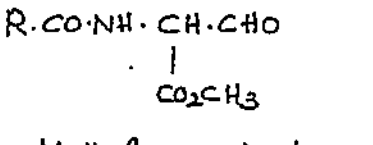
Penicillamine.

CH_3OH



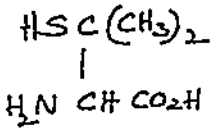
Methyl penicilloate

$H_2O - HgCl_2$



Methyl penaldate

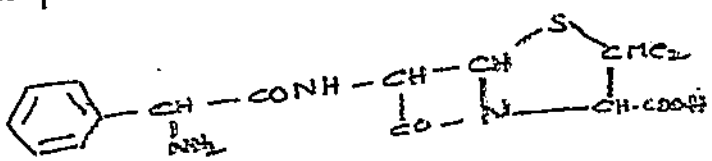
+



Penicillamine.

Ampicillin

Ampicillin is a benzyl penicillin analog in which one of the hydrogen atom of the side chain, phenyl acetic acid has been replaced with a primary amino group to produce D-phenyl glycine moiety.



with ampicillin an antibacterial spectrum broader than that of penicillin-G has been obtained.

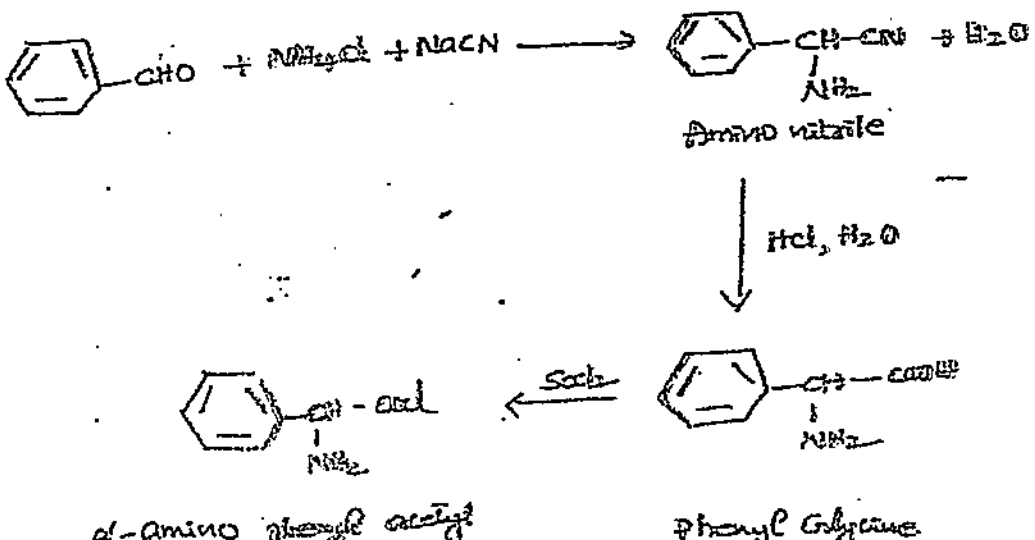
Synthesis:-

Chemically ampicillin is 6R-6(α-phenyl D-alkyl amino)-penicillanic acid.

It is prepared by the acylation of 6-aminopenicillanic acid (6APA) with phenyl glycine

Step 1:-

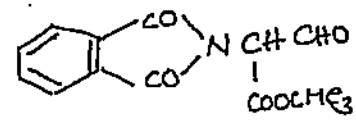
Synthesis of phenyl glycine:-



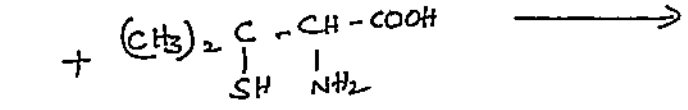
Step II :-

Synthesis of 6-Amino penicillanic Acid (6-APA):-

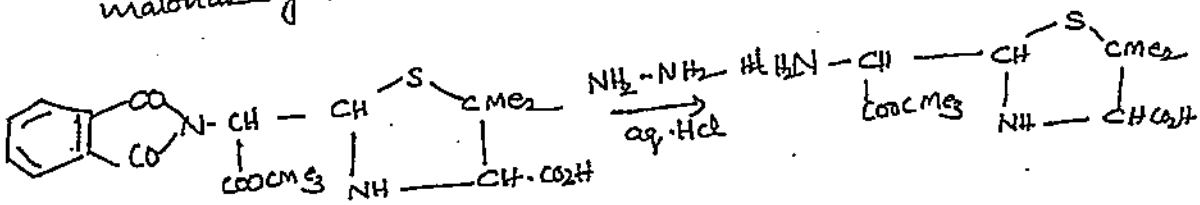
Condensation of D-penicillamine (which is synthesised from D-Valine) and t-butyl α-phthalimide malonaldehyde yields an intermediate embeded with a phthalimido ester and a thiazoridine ring. Treatment of this with hydrazine followed by HCl helps the removal of phthaloyl moiety as phthalyl hydrazide and gives an amine hydrochloride. This product when subjected to stream of HCl at 0°C, in pyridine helps to remove the blocking t-butyl function there by yielding penicilloic acid. The resulting acid undergoes cyclisation is afford 6APA by stirring for 20 min with a solution of N, N¹-dicyclo hexyl Carbodimide in dioxane.

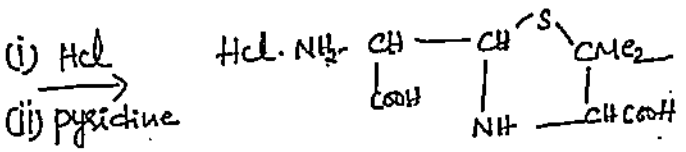


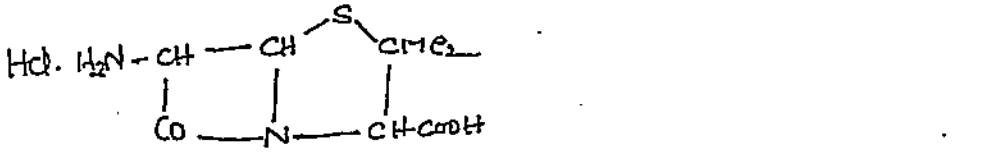
t-butyl α-phthalimido malonaldehyde



D-penicillamine



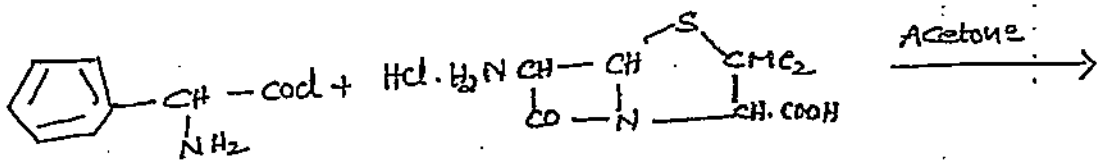


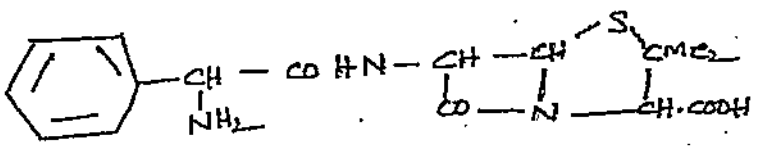


6-Amino penicillinic Acid.

Step III :-

Condensation of I and II





Ampicillin.

Properties and Uses :-

1. Ampicillin is water soluble and stable to acid.
2. It is administrated orally and is absorbed from the intestinal track.
3. D(-) ampicillin prepared from D(-) α-amino phenyl acetic acid is significantly more active than L(+) ampicillin
4. Ampicillin is not resistant to penicillinase, and it produces the allergic reactions and other untoward effects that are found in penicillin sensitive patients.
5. It may be used in some infections caused by gram negative bacilli. However, ampicillin is not so widely active that it should be used as a broad spectrum antibiotic in the same manner as the tetracyclins.
6. It is particularly useful for the treatment of acute urinary track infections caused by E. coli or proteus and is the agent of choice against Haemophilus influenza infections.

Ampicillin together with probenecid to inhibit its acute tubular excretion has also become a treatment of choice for gonorrhea in recent years.

Amoxicillin

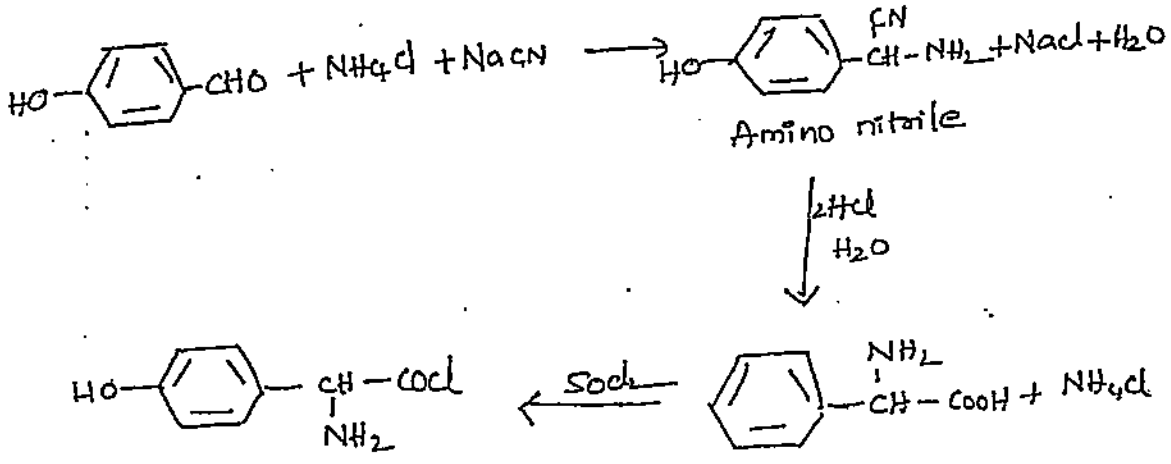
Amoxicillin is a close analogue of ampicillin in which a paraphenolic hydroxyl group has been introduced into ten side chain amide moiety. This adjusts the isoelectric point, of the drug to a more acidic value and perhaps enhances blood levels obtained with amoxicillin compared with ampicillin.

Synthesis :-

Chemically ampicillin is 6-(D(-) α-amino p-hydroxy phenyl acetamido)- penicillanic acid.

Amoxicillin is a semisynthetic penicillin is simply the p-hydroxy analogue of ampicillin prepared by the acylation of 6-amino penicillanic acid (6-APA) with p-hydroxy phenyl glycine

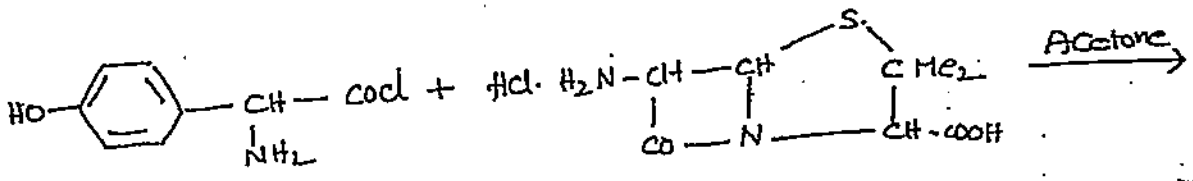
a. Synthesis of p-hydroxy phenyl glycine:—

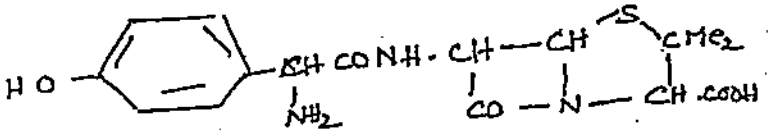


b. Synthesis of 6-amino penicillanic acid (6-APA)

Same as in ampicillin

c. Condensation of a and b :-





Amoxicillin.

Properties and Uses:-

1. Amoxicillin is a fine, white crystalline powder that is sparingly soluble in water.

2. The antimicrobial spectrum and clinical uses of amoxicillin are approximately same as those of ampicillin itself and it is presently one of the most popular drugs in an america.

3. Early clinical preparts indicates that orally administated amoxicillin possesses significant advantage over ampicillin indicating complicated gastro intestinal adsorption to give higher plasma and urine levels, less diarrhea and little or no effect of food on absorption, thus it appears that amoxicillin replace ampicillin for the treatment of certain systamatic and urinary track infections.

4. Amoxicillin is reported to be less effective than ampicillin in the treatment of bacillary dysentry because of its greater gastrointestinal absorption.

Chloramphenicol (or) Chloromycetin.

Chloramphenicol is a broad-spectrum antibiotic that is produced by Streptomyces Venezuelae. It is very effective in the treatment of, typhoid fever. Chloramphenicol was the first antibiotic produced synthetically on a commercial basis.

Constitution :-

(I) The molecular formula of chloramphenicol is $C_{11}H_{12}Cl_2N_2O_5$.

(II) Chloramphenicol on reduction with tin and hydrochloric acid followed by diazotisation and coupling with β-naphthol gives an orange-red precipitate indicating the presence of an aromatic nitro group.

(III) Its ultraviolet spectrum is found to be similar to that of nitrobenzene.

(IV) On catalytic reduction over palladium as a catalyst, Chloramphenicol gives a product which shows an absorption spectrum similar to that of p-toluidine, and the solution contains ionic chlorine.

The observation indicates that chloramphenicol is a p-nitrobenzene substituted compound and its chlorine atom is present in the side chain.

(V) It contains neither free amino group nor carbonyl group.

(VI) On acetylation with acetic anhydride in pyridine, it gives diacetyl derivative indicating the presence of two hydroxyl groups.

(VII) on hydrolysis with acid or base, it gives dichloro acetic acid and an optically active base.

$$C_{11}H_{12}N_2O_5Cl_2 + H_2O \longrightarrow \underset{\text{base}}{C_9H_{12}N_2O_4} + \underset{\text{dichloro acetic acid}}{CHCl_2\text{-}COOH}$$

(VIII) Structure of optically active base :-

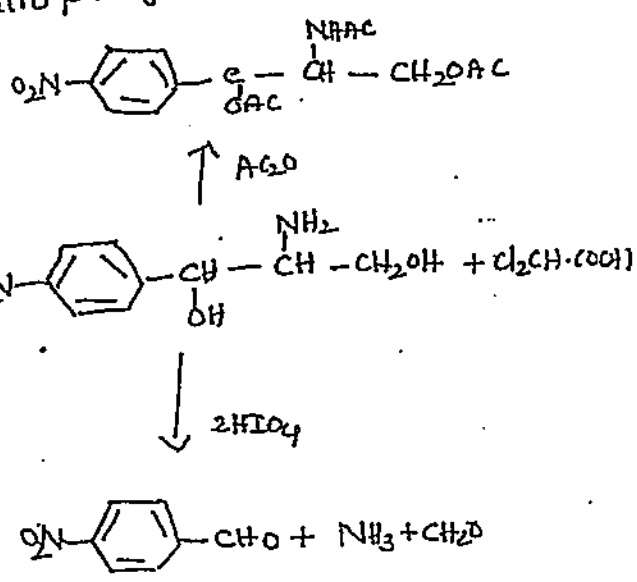
(a) the molecular formula of optically active base is $C_9H_{12}N_2O_4$.

(b) It is found to have one primary amino group.

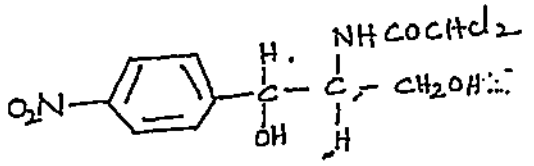
(c) On acetylation with acetic anhydride in pyridine yields triacetyl derivative, confirming the presence of two hydroxyl group. The third acetyl derivative is from amino group.

$$C_9H_8NO_2\begin{cases}-NH_2\\-(OH)_2\end{cases} + 3Ac_2O \longrightarrow C_9H_8NO_2\begin{cases}-NHCOCH_3\\-(OCOCH_3)_2\end{cases}$$

(d) on oxidation with periodic acid, it utilizes two equivalents of periodic acid to form p-nitro benzaldehyde, formaldehyde and ammonia. This suggests that in the base a propyl group is present para to the nitro group with an amino group on the second carbon atom. i.e. the base is 2-amino 1-p.nitro phenyl propane-1,3-diol.

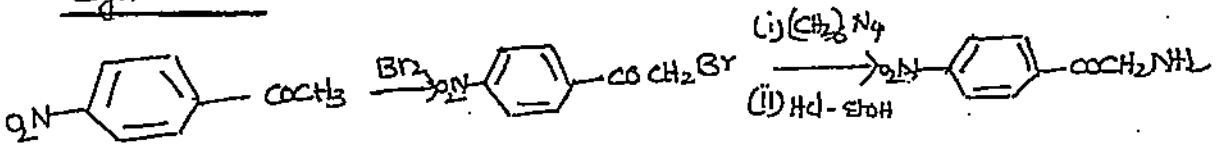


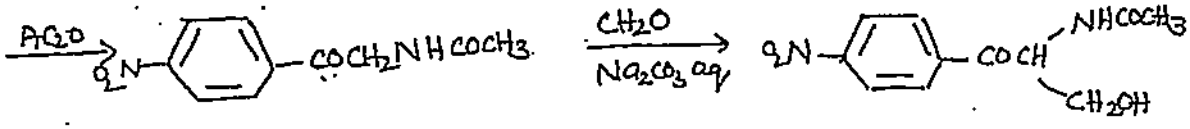
(IX) Chloromycetin does not react with periodic acid which indicates that the amino group is blocked and hence chloromycetin will be D(-) - threo 2- dichloro acetamido 1- p-nitrophenyl propane - 1,3-diol.

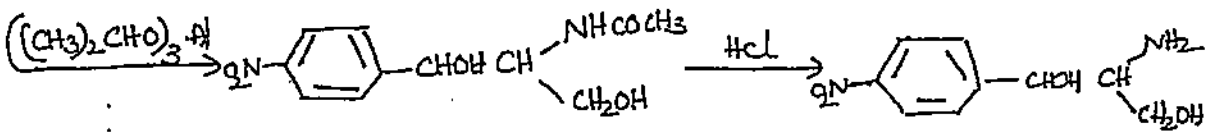


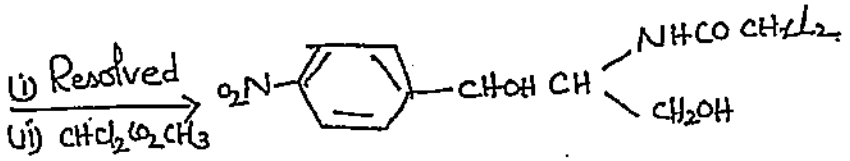
(X) Finally the structure of chloromycetin is confirmed by its synthesis.

Synthesis.









Clinical properties :-

(i) It has the wide range of activity without causing any side effects.

(ii) chloromycetin is a broad-spectrum antibiotic being effective against diseases caused by spirochetes, Gram-negative bacteria, rickettsial and pneumonia virus etc.

(iii) It is generally used for typhoid fever.

Streptomycin.

Streptomycin is the most important antibiotic isolated from streptomyces griseus. It is the drug which has been of the greatest service in the treatment of tuberculosis and remains the only drug in the treatment of this disease. It is effective against Gram -ve bacteria.

Constitution :-

(I) The molecular formula of streptomycin is $C_{21}H_{39}N_7O_{12}$

(II) Since the molecule forms a trihydrochloride, its three nitrogen atoms must be basic.

$$C_{21}H_{39}N_7O_{12} + 3HCl \longrightarrow C_{21}H_{39}N_7O_{12}\cdot 3HCl$$

streptomycin trihydrochloride (crystalline)

(III) In strong acid solutions streptomycin is hydrolysed to two products namely streptidine, and streptobiosamine.

$$C_{21}H_{39}N_7O_{12} + H_2O \longrightarrow C_8H_{18}N_6O_4 + C_{13}H_{23}NO_9$$

streptomycin — streptidine — strepto biosamine

(IV) Structure of streptidine :-

(a) the molecular formula of streptidine is $C_8H_{18}N_6O_4$.

(b) streptidine on oxidation with $KMnO_4$ gives two molecules of guanidine, indicating that two guanido groups are present in streptidine.

$$C_8H_{18}N_6O_4 \xrightarrow[KMnO_4]{(O)} 2\ NH_2-\underset{\underset{NH}{\|}}{C}-NH_2$$

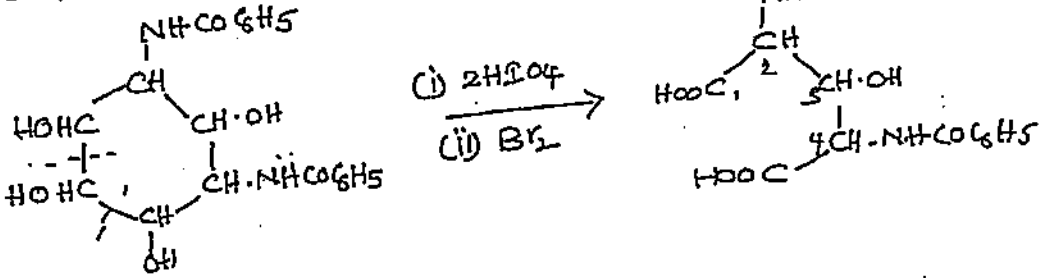
(c) Streptidine on alkaline hydrolysis, further degraded to give streptamine and ammonia.

$$C_8H_{18}N_6O_4 + 4H_2O \longrightarrow C_6H_{14}N_2O_4 + 4NH_3 + 2CO_2$$

Streptidine — Streptamine

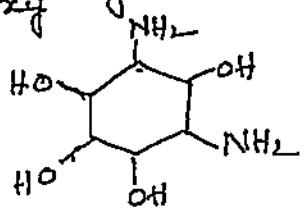
Streptamine is proved to be diamino tetra hydroxy Cyclohexane.

N,N'-Dibenzoyl streptamine on oxidation with periodic acid consumes two moles of the reagent to form dialdehyde which on further oxidation with bromine water gives 2,4-dibenzamido 3-hydroxy glutaric acid.

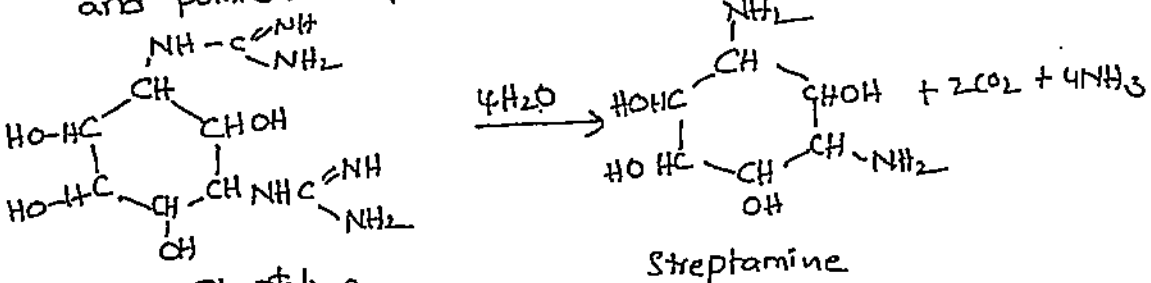


N,N'-dibenzoyl streptamine

Hence in streptamine two amino groups are in alternative positions and thus it must be 1,3-diamino 2,4,5,6-tetrahydroxy cyclohexane.

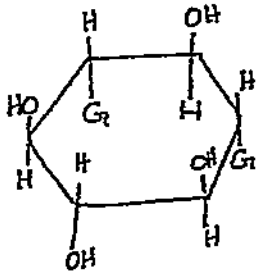


(d) From the knowledge of the structure of Streptamine and point (b) streptidine is given the following structure.



Streptidine — Streptamine

(c) Since streptidine is not optically active, it was assigned meso-configuration with the two guanido groups cis to each other.



where $G = -NH \cdot C(=NH)NH_2$

(V) Structure of Streptobiosamine :—

(a) The molecular formula of streptobiosamine is $C_{13}H_{23}NO_7$

(b) Streptomycin is found to possess only one carbonyl group which takes part in the reaction when streptomycin hydrochloride is treated with methanolic hydrogen chloride to give streptidine dihydro chloride and streptobiosaminide dimethyl acetal.

$$C_{21}H_{39}N_7O_{12}\cdot 3HCl + 3CH_3OH \xrightarrow[-H_2O]{} \underset{\text{Streptidine dihydrochloride}}{C_8H_{18}N_6O_2\cdot 2HCl} + \underset{\text{Methyl streptobiosaminide dimethyl acetal}}{C_{13}H_{22}NO_7(OCH_3)_3\cdot HCl}$$

Streptomycin trihydrochloride

The dimethyl acetal derivative gives methyl acetal on drastic alkaline hydrolysis showing the presence of a methyl amino group.

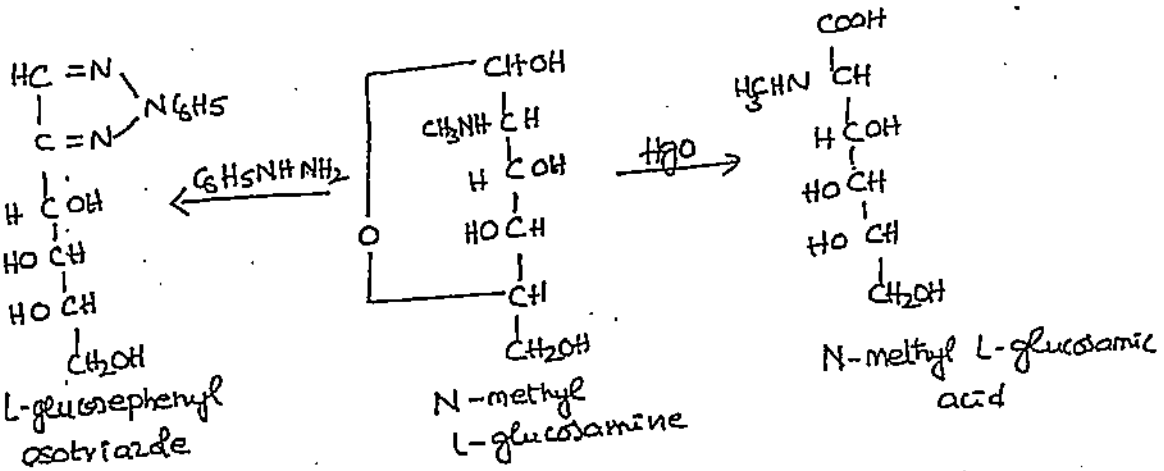
Dimethyl acetal derivative on less drastic degradation with acetic anhydride and hydrochloric acid gives an identifiable sugar derivative (N-methyl glucosamine) and fragment of hexose sugar (streptose). Thus it was decided that streptobiosamine is probably a glycoside of N-methyl L-Glucosamine and Streptose.

Structure of N-methyl L-Glucosamine :-

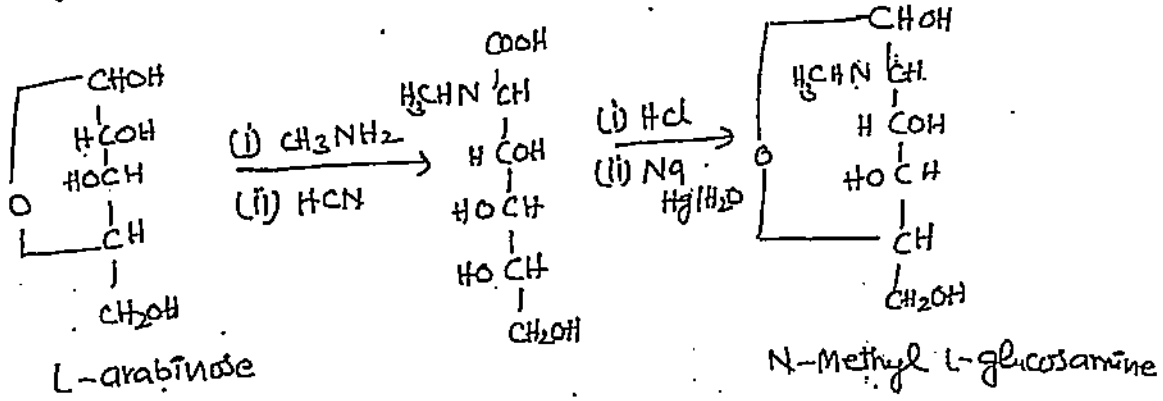
(a) on treatment with phenyl hydrazine it gives phenyl-hydrazone which can be converted to the phenyl triazole having the same M.P but opposite configuration as D-glucosephenyl osotriazde.

(b) on oxidation with HgO it is again converted to an acid identical to N-methyl L-glucosamic acid but again with opposite sign of specific rotation.

Hence the compound obtained from Streptomycin is N-methyl L-glucosamine.



Finally, the structure is confirmed by its synthesis from L-arabinose.

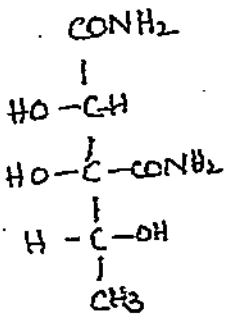


Structure of Streptose:-

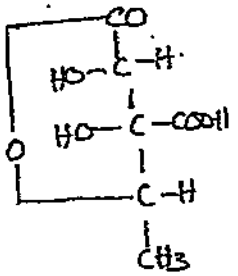
The structure of Streptose has been established by the degradative reaction on streptomycin and Streptobiosamine.

Streptobiosamine on oxidation with bromine followed by hydrolysis gives streptosonic acid monolactone $C_6H_8O_6$. This lactone is converted into amide which consumes two moles of periodic acid indicating the presence of three hydroxyl groups.

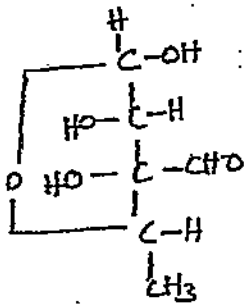
Thus streptosonic acid diamide, streptosonic acid monolactone and streptose are given the following structures which are also confirmed by infrared analysis.



Streptosonic acid diamide

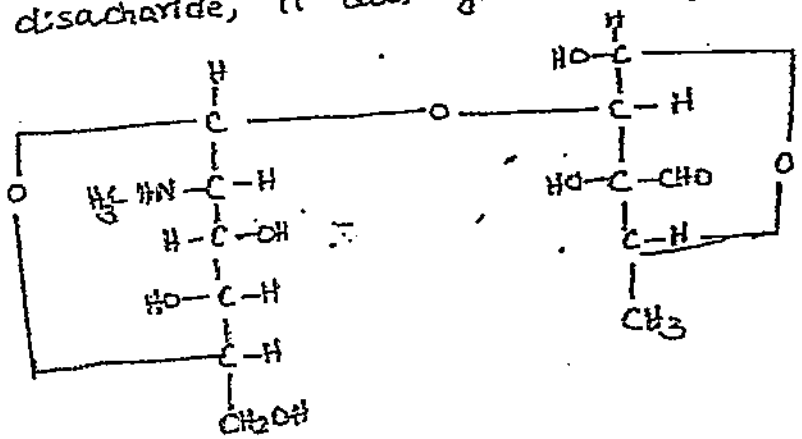


Streptosonic acid monolactone



Streptose

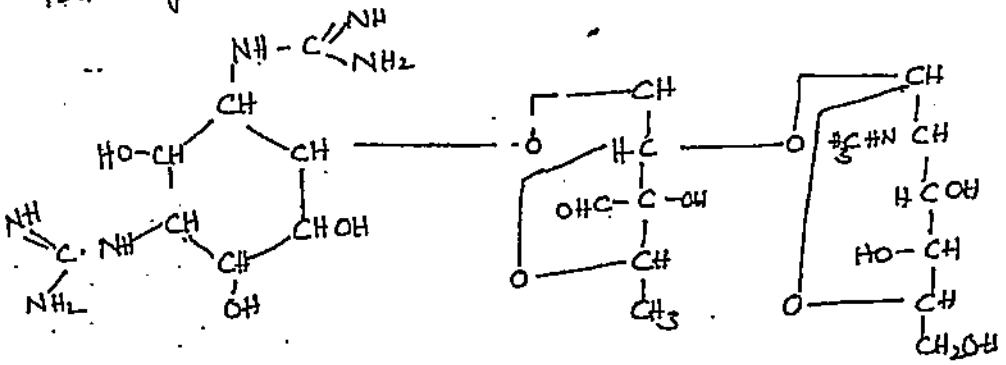
From the structure of N-methyl L-glucosamine and streptose, and from the fact that streptobiosamine is a disaccharide, it was given the following structure.



Streptobiosamine

(VI) Point of linkage between streptidine and streptobiosamines—

Merck suggested that the C_1 of streptose is glycosidically linked to the C_4 of the streptidine fragment i.e. hydroxyl group adjacent to one of the carbon atoms attached to the guanidino groups of streptidine, to give the following final structure of streptomycin.



Streptomycin.

Clinical properties :—

(i) Streptomycin is used in the treatment of tuberculosis

(ii) It is also used in the treatment of plague, pneumonia, influenzal meningitis caused by Haemophilus influenza etc.

(iii) Streptomycin is of low toxicity, but repeated large doses over longer periods of time may damage the auditory nerve and have been known to lead to permenant deafness in humans.

Cephalosporins

The cephalosporins are β-lactum antibiotics isolated from cephalosporium species or prepared semisynthetically.

Cephalosporin N :-

Cephalosporin N is an antibiotic produced by a species of cephalosporium, and was shown to be a penicillin in which the R group is $HO_2C\,CH(NH_2)\,CH_2CH_2CH_2-$

Cephalosporin C

Cephalosporin C was another antibiotic isolated from Cephalosporin N. Unlike penicillins it was resistant to hydrolysis by the enzyme penicillase.

Constitution :-

(i) Molecular formula of Cephalosporin C is $C_{16}H_{21}N_3O_8S$.

(ii) It give a positive ninhydrin reaction indicating the presence of an α-amino acid.

(iii) Cephalosporin C on acid hydrolysis yields one molecule of each one molecule of D-α-amino adipic acid and two molecules of ammonia.

$$C_{16}H_{21}N_3O_8S \xrightarrow[\text{hydrolysis}]{\text{acid}} HO_2C\,CH(NH_2)\,(CH_2)_3\,CO_2H + 2NH_3 + CO_2$$

(iv) on heating with Raney nickel followed by hydrolysis, it yields D-α-amino adipic acid, L-alanine and some DL-Valine.

$$C_{16}H_{21}N_3O_8S \xrightarrow[\text{(ii) hydrolysis}]{\text{(i) heating with Raney Ni}} HO_2C\,CH(NH_2)(CH_2)_3\,CO_2H + CH_3CH(NH_2)CO_2H + (CH_3)_2CH\,CH(NH_2)CO_2H$$

D-α-amino adipic acid — L-alanine — DL-Valine

(V) On heating with Raney nickel followed by controlled hydrolysis, it gives dipeptide together with D-α-amino adipic acid and α,β-diamino propionic acid

$$C_{16}H_{21}N_3O_8S \xrightarrow[\text{Controlled hydrolysis}]{\text{Raney Nickel, heating}} HO_2C\,CH(NH_2)(CH_2)_3\,CONH\,CH(CO_2H)CH_2NH_2$$

dipeptide

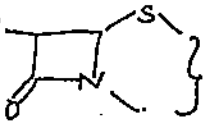
$$+\; HO_2C\,CH(NH_2)(CH_2)_3\,CO_2H + CH_2(NH_2)CH(NH_2)CO_2H$$

(VI) Cephalosporin c, on hydrolysis in neutral aqueous solution at 37°c, yields D-2-(4-amino 4-carboxy butyl) thiazole 4-carboxylic acid.

$$C_{16}H_{21}N_3O_8S \xrightarrow[\text{aq. neutral}]{37^\circ C} HO_2C\,CH(NH_2)(CH_2)_3$$

(VII) Basing on the above facts and consideration of IR data, the partial structure of Cephalosporin c is

$$HO_2C\,CH(NH_2)(CH_2)_3\,CONH$$



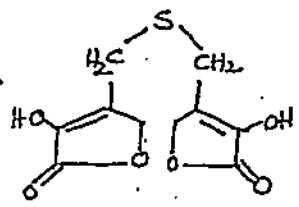
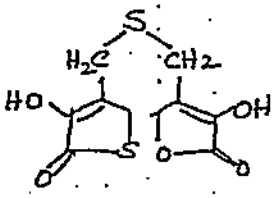
$C_7H_8O_4$

(VIII) Cephalosporin c on hydrolysis with H_2SO_4 yields one molecule of acetic acid

$$C_{16}H_{21}N_3O_8S \xrightarrow[\text{hydrolysis}]{H_2SO_4} CH_3COOH + \text{other products}$$

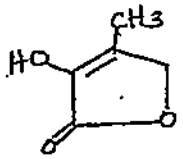
Basing on the formation of acetic acid and IR data it was concluded that acetoxyl group ($CH_3CO-O-C$) was present in the fragment $C_7H_8O_4$.

(IX) Hydrolysis of Cephalosporin c with 1.25N Hcl at 100°c give two lactones contained sulphur given below

$C_{16}H_{21}N_3O_8S$ $\xrightarrow{1.25\ N\ HCl}$  

α-tetronic acid (I) Thio lactone (II)

Both compounds, on treatment with Raney nickel yields β-methyl α-tetronic acid.

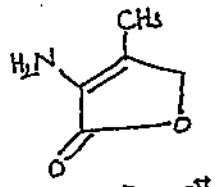
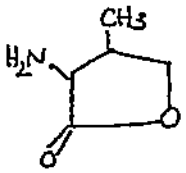


β-methyl α-tetronic acid

The formation of I, and II were attributed to the five-carbon fragments from two molecules of cephalosporin C.

(X) Cephalosporin C, when dissolved in 0.1 N HCl at room temperature, it lost an O-acetyl group and gave a lactone, Cephalosporin C_c. This lactone on treatment with Raney nickel gave a α-amino β-methyl butenolide and this on hydrogenation gave γ-hydroxy valine lactone.

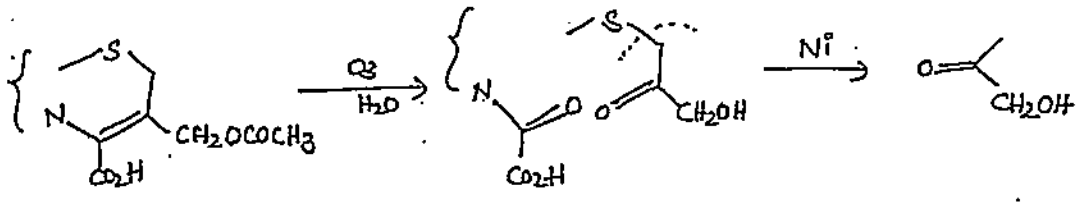
Cephalosporin C $\xrightarrow[\text{room temp}]{HCl}$ Cephalosporine C_c $\xrightarrow{\text{Raney nickel}}$

 $\xrightarrow{\text{hydrogenation}}$ 

α-amino β-methyl butenolide

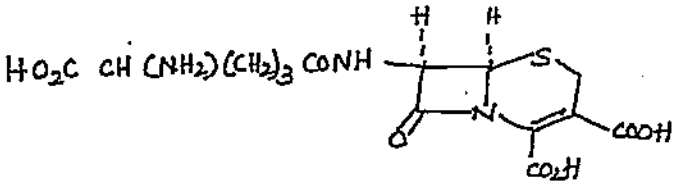
γ-hydroxy valine lactone

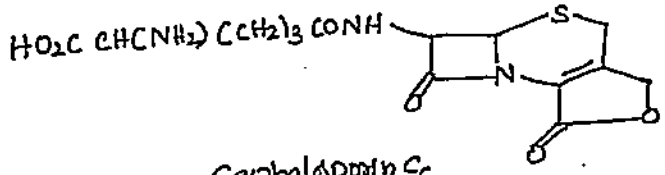
(XI) The position of the double bond was deduced to be that given in III since this was consistent with the isolation of the 2,4-dinitrophenyl hydrazone of hydroxy acetone after cephalosporin C had been subjected to ozonolysis and resulting product treated with Raney nickel.



III

Basing on the above facts, the structure of Cephalosporin c is

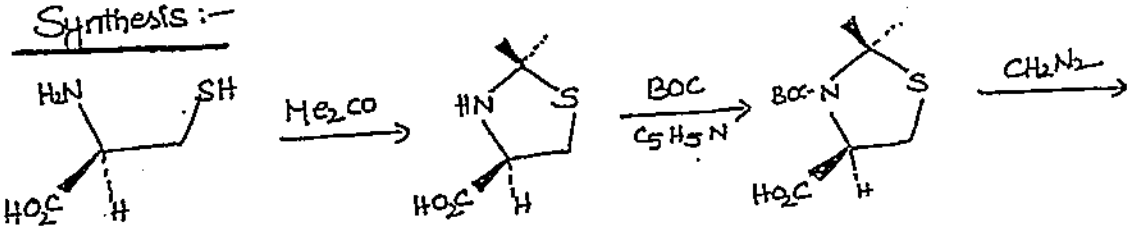


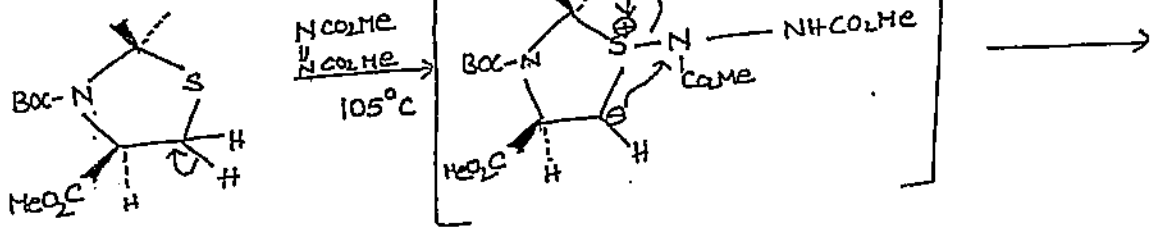


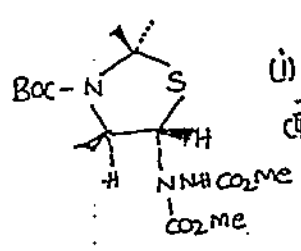
Cephalosporin C_c

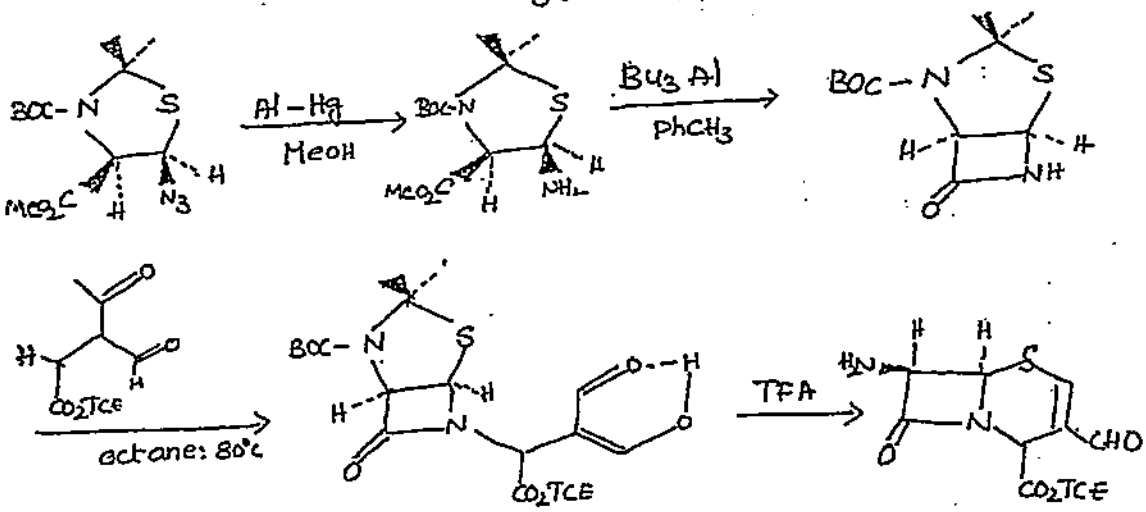
Finally the structure of Cephalosporin C_c is confirmed by its synthesis.

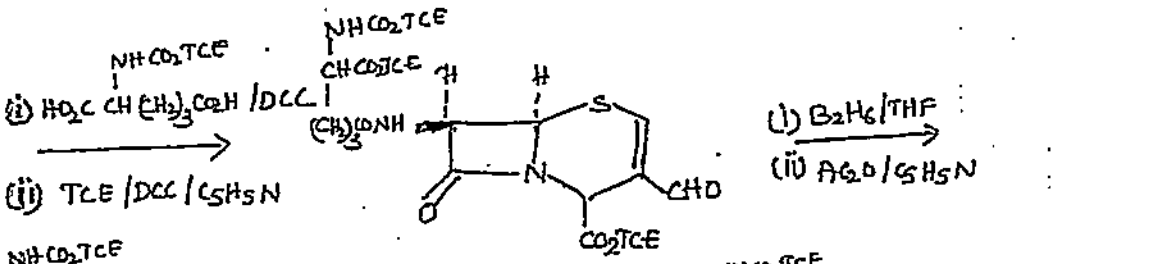
Synthesis :-

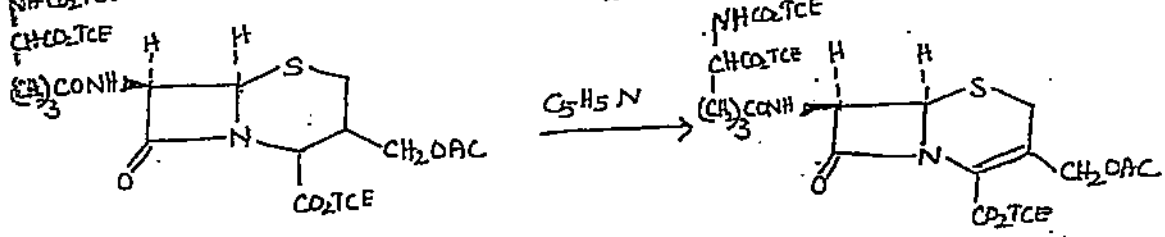


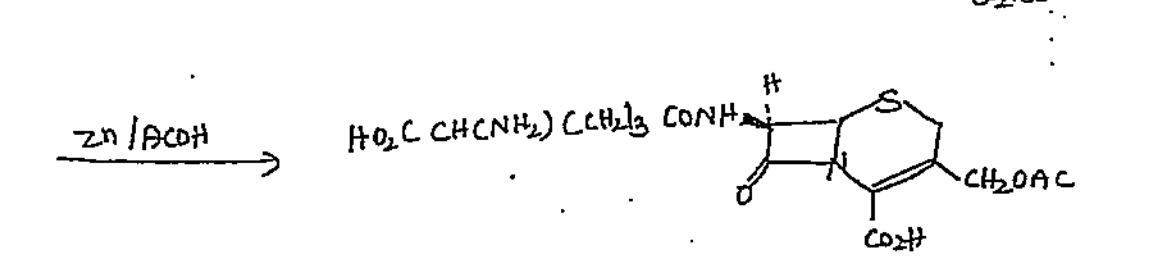


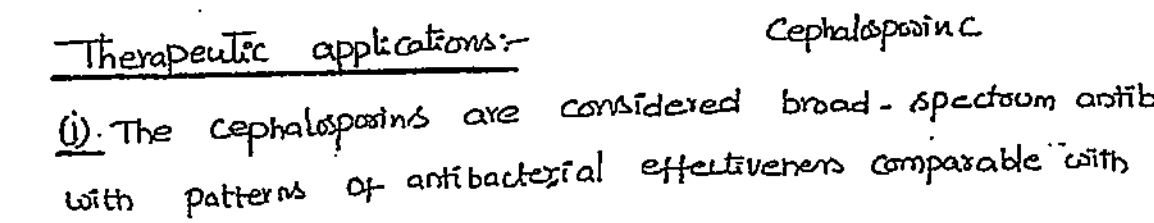












Cephalosporin C

Therapeutic applications:-

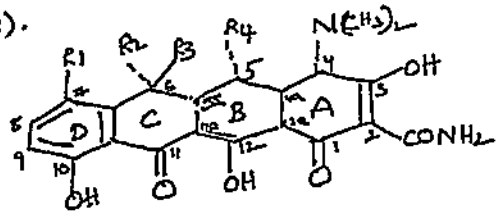
(i). The cephalosporins are considered broad-spectrum antibiotics with patterns of antibacterial effectiveness comparable with ampicillins.

(ii) Cephalosporins are much more resistant to inactivation by β-lactamases particularly those produced by gram-+ve bacteria, than in ampicillin.

Tetracyclines

The tetracycline antibiotics contain the hydronaphthacene skeleton as a characteristic structural unit. These are yellow amphoteric substances, forming salts with acids or bases, or complexes with such metals as aluminium, magnesium Calcium, or iron.

The three most important members of the group are tetracycline, aureomycin (chlorotetracycline) and terramycin (oxy-tetracycline).



R_1	R_2	R_3	R_4	
H	CH_3	OH	H	Tetracycline
Cl	CH_3	OH	H	Aureomycin
H	CH_3	OH	OH	Terramycin.

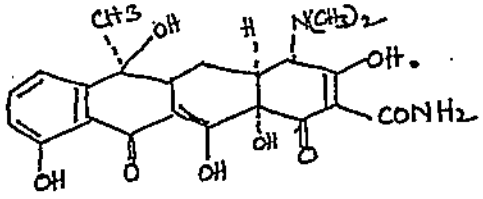
Thus from the above reactions it is obvious that terramycin is a hydroxy tetracycline and Aureomycin is the corresponding chloro tetracycline and the three are mutually interconvertable.

The tetracyclines are truly broad-spectrum antibiotics with the broadest spectrum of any known antibacterial agents.

They are active against a wide range of gram-positive and gram-negative bacteria spirochetes, mycoplasmas, rickettsiae and clamydiae.

Tetracycline

Tetracycline was obtained from Streptomyces aureofaciens as well as the fermentation of other Streptomyces species.



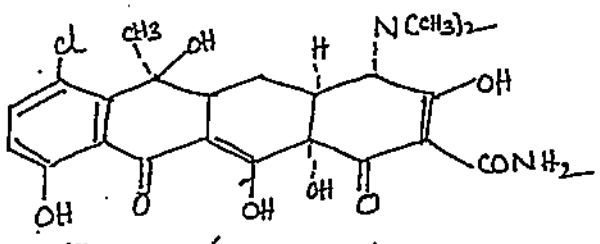
It is a bright yellow crystalline salt that is stable in air, but darkness in colour upon exposure to strong sunlight.

Tetracycline hydrochloride is used for topical and ophthalmic administration.

It was recommended for the treatment of a variety of infections including pneumonia, actinomycosis, brucellosis, urinary infections, Rocky mountain stopped fever and typhus fever.

Aureomycin (chlorotetracycline)

Aureomycin is produced by a strain of streptomyces aureofaciens.



∴ chlorotetracycline

Aureomycin is stable in air, but is slightly photosensitive and should be protected from light.

Aureomycin is effective against many bacteria over much the same range as chloramphenicol.

It is well tolerated by the patient and is really absorbed from the gastro-intestinal tract.

It has been found to be helpful in cases of chicken pox, small pox, measules and hepatitis.

Terramycin
(Oxy-tetracycline)

Terramycin is the most recent of the widely used antibiotics. It is a yellow, crystalline, amphoteric substance, forming well defined salts with acids or bases.

Terramycin is isolated from Streptomyces rimosus.

Constitution :-

(i) The molecular formula of terramycin is found to be $C_{22}H_{24}N_2O_9$

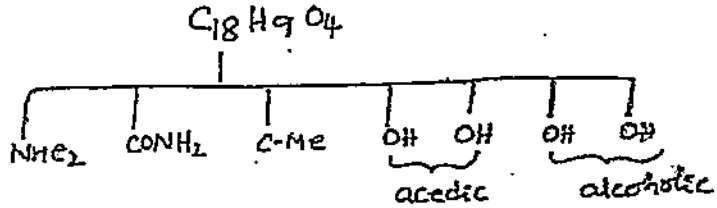
(ii) It forms dimethyl terramycin with diazomethane indicating the presence of two acidic groups. Furthermore, two acidic groups are found to be enolic as the drug gives positive test with $FeCl_3$ and found to possess no Carboxyl group.

(iii) On acetylation with acetic anhydride, terramycin gives diacetyl terramycin which still has two acidic groups, indicating the presence of two alcoholic groups in terramycin.

(IV) Alkaline hydrolysis of teramycin gives one mole each of ammonia and dimethylamine indicating the presence of one amide and one dimethyl amino group.

(V) By the usual analytical tests it is found to have one C-methyl group.

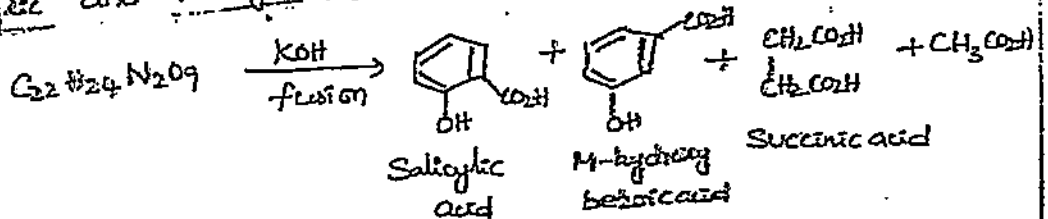
From the knowledge of the above points: terramycin may be represented as below.



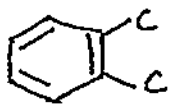
(VI) The complete structure of terramycin was established by its various degradative reactions given below

(A) Alkaline degradation :-

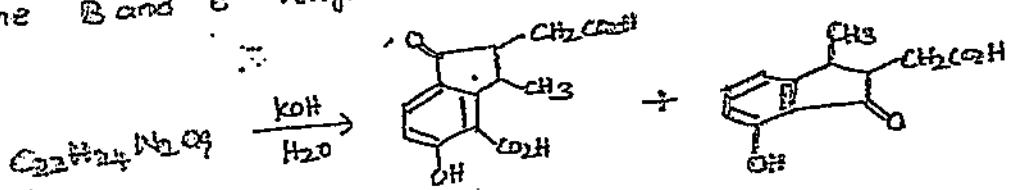
(a) on fusion with alkali, terramycin gives acetic, succinic, Salicylic and m-hydroxy benzoic acids.



The above degradation indicates that terramycin has the following type of structure.



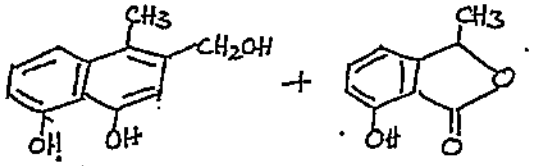
(b) Terramycin on treatment with aqueous alkali gives mainly terracinoic acid and isodecarboxy terracinoic acid which are believed to be formed by the fundamental rearrangement in the molecule following scissions of carbon-carbon bonds in the B and C rings of the antibiotic.



Terracinoic acid

Iso decarboxy terracinoic acid.

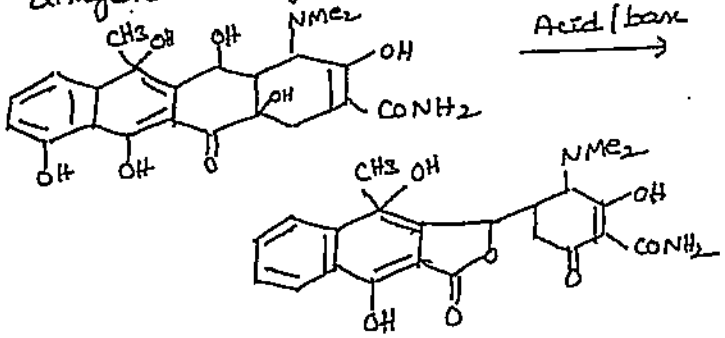
(c) When terramycin is treated with alkali in presence of zinc, terranaphthol, and methyl phthalide are formed.

$C_{22}H_{24}N_2O_9 \xrightarrow[\text{aq. NaOH.}]{Zn}$ 

Terranaphthol. + Methyl phthalide

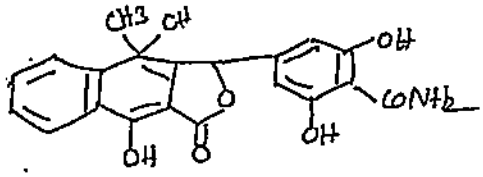
B. Acidic Degradation :-

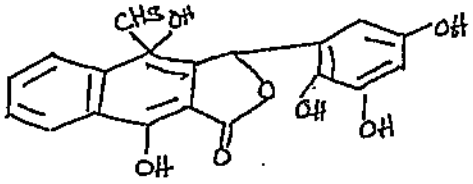
a. when terramycin is treated with dil. acid anhydro terramycin again it is treated with acid / base gives α,β-epoterramycin.

$C_{22}H_{24}N_2O_9 \xrightarrow{\text{dil. acid}}$ anhydro terramycin. $\xrightarrow{\text{Acid / base}}$ 

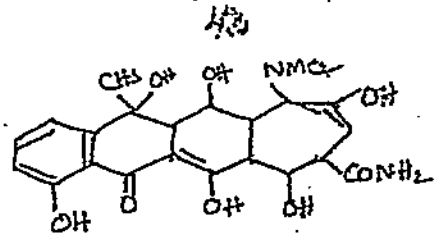
α,β - epoterramycin

b. when terramycin is treated with 0.5 M HCl, 60°C forms terrinolide this on treated with 1.5 N HCl gives Decarboxamide terrinolide.

$C_{22}H_{24}N_2O_9 \xrightarrow[9\text{hrs}]{0.5\text{M HCl}, 60^\circ C}$ 

$\xrightarrow[\text{reflux}]{1.5\text{N HCl/N}_2}$ 

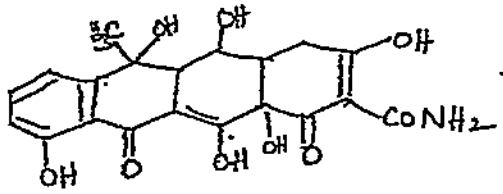
From this acidic degradation the probable structure for terramycin.



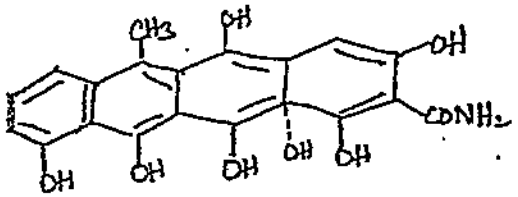
(C) Reductive degradation:-

Oxy tetracycline on reduction with zinc and acetic acid under mild conditions gives des dimethyl amino terramycin (elimination of the dimethyl amino group). The later compound on reduction under more drastic conditions leads to the loss of one oxygen atom to form deoxydes dimethyl amino terramycin which on zinc dust distillation gives naphthacene

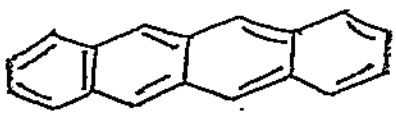
$C_{22}H_{24}N_2O_9$ $\xrightarrow[CH_3COOH]{Zn}$



$\xrightarrow{H^+}$

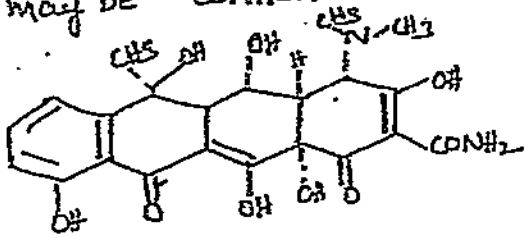


$\xrightarrow{Zn}$



naphthacene

Basing on the above facts the structure of terramycin may be written as below



clinical properties:-

(i) Terramycin is more stable than aureomycin and possess the same wide antibacterial range of activity. It is readily assimilated and well tolerated.

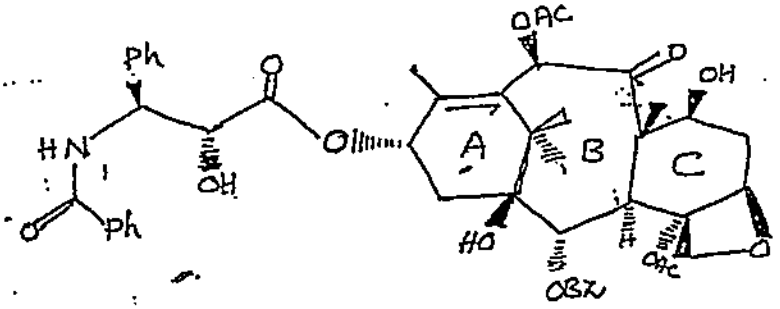
(ii) Terramycin is successfully used against trachoma.

Paper-IV: Chemistry of Antibiotics and Drugs

UNIT - II

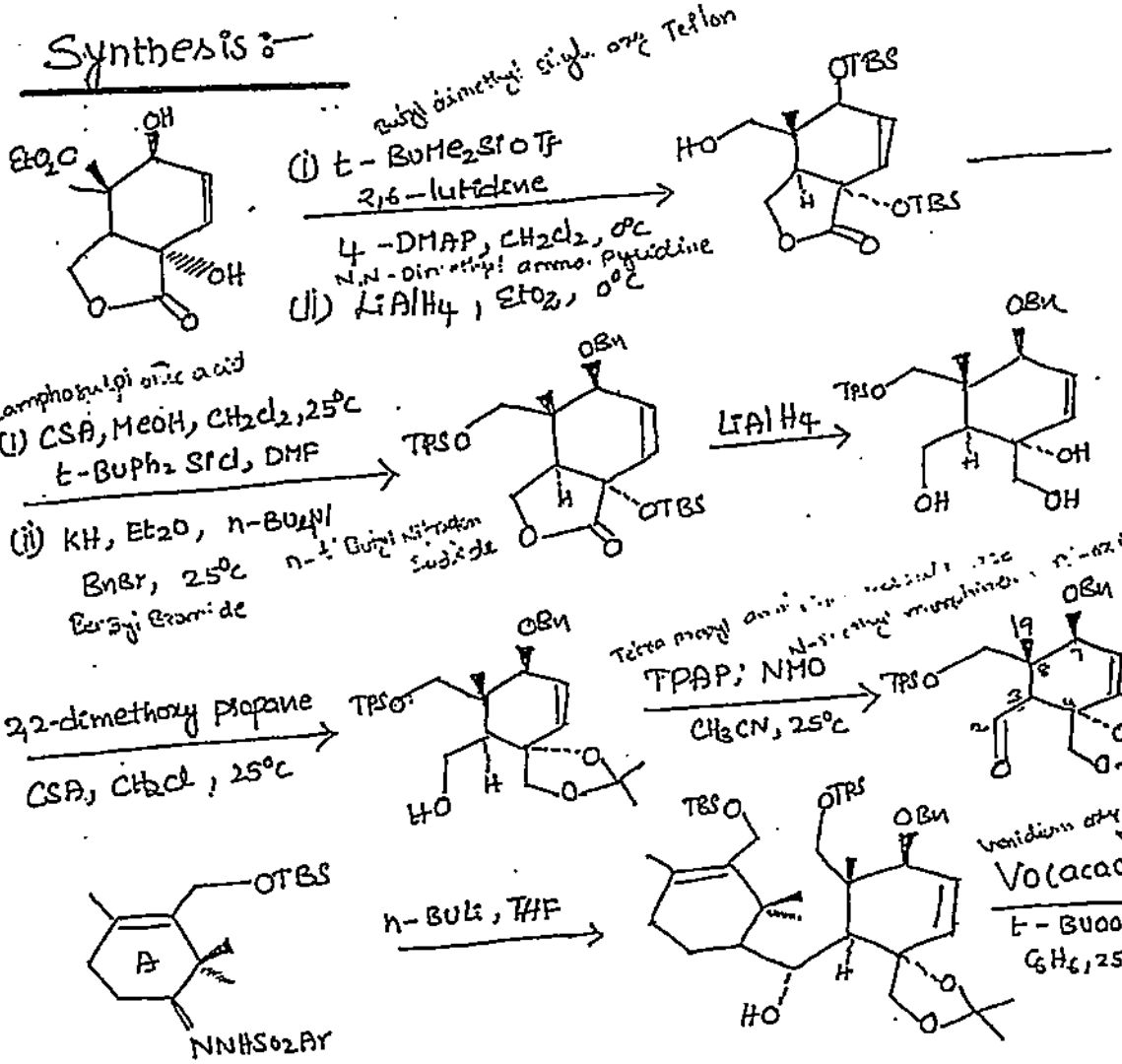
Synthesis of Anticanceragents

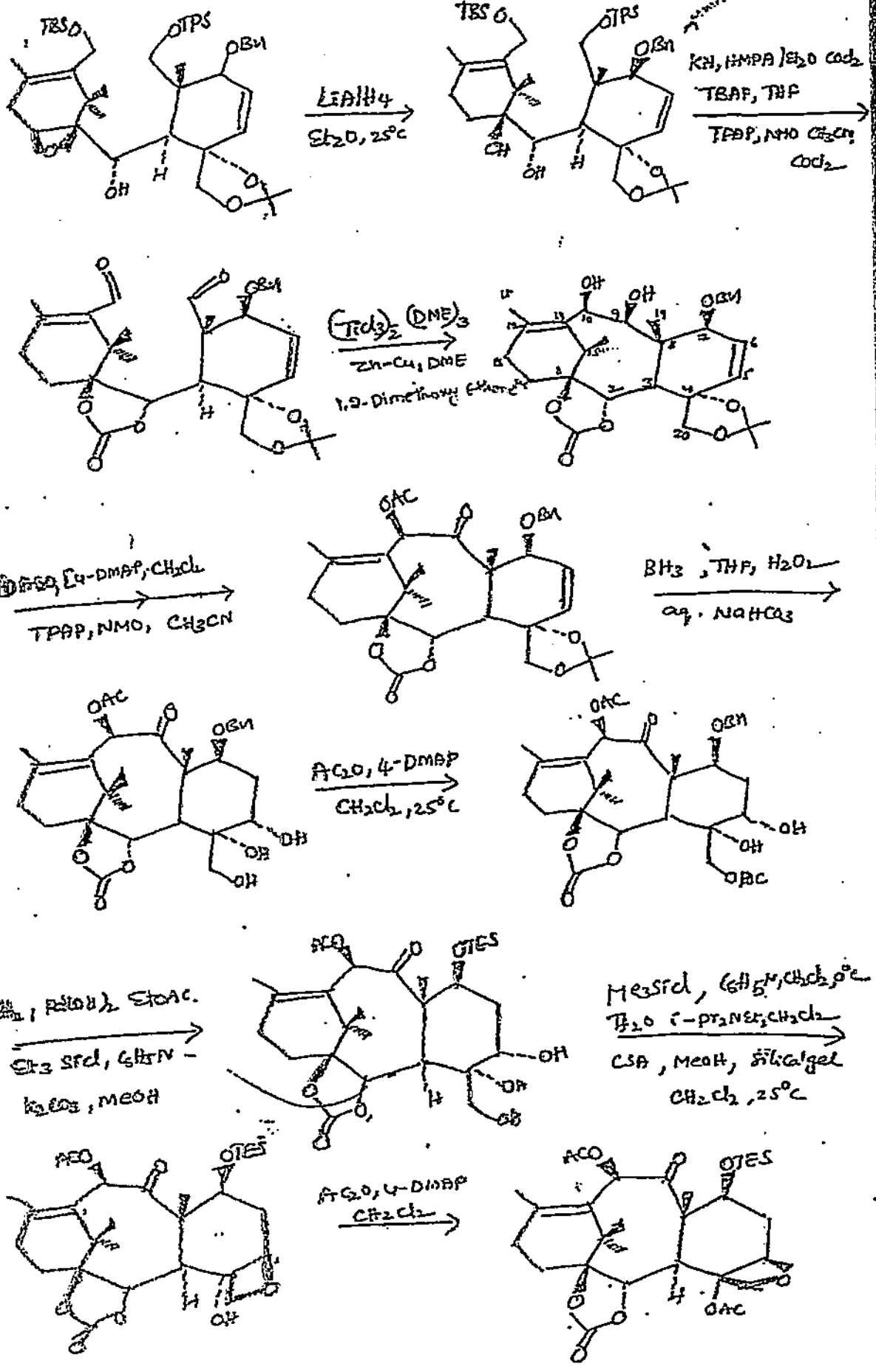
TAXOL



Taxol was isolated from the pacific yew tree in the early 1960's and its structure was determined by wall and wani in the late 1960's.

Synthesis :-




LiAlH4
Et2O, 25°C
KH, HMPA / Et2O cod2
TBAF, THF
TPAP, NMO CH3CN
cod2
(TiCl3)2 (DME)3
Zn-Cu, DME
1,2-Dimethoxy Ethane
TPAP, NMO, CH3CN
BH3, THF, H2O2
aq. NaHCO3
Ac2O, 4-DMAP
CH2Cl2, 25°C
Et3 SiCl, C5H5N
K2CO3, MeOH
Me3SiCl, C5H5N, CH2Cl2, 0°C
Tf2O i-Pr2NEt, CH2Cl2
CSA, MeOH, Silicagel
CH2Cl2, 25°C
Ac2O, 4-DMAP
CH2Cl2

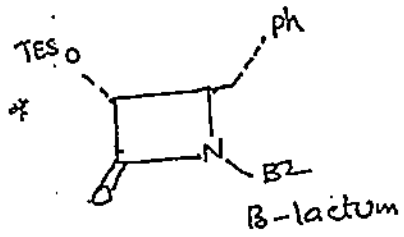
(I) PhLi, THF
(II) PCC, NaOAc, reflux → Taxol
(III) $NaBH_4$, MeOH
(IV) $NaN(SiMe_3)_2$, *β-lactum
(V) HF – pyridine

Activity:

Taxol was proved to be remarkable effective in treating certain type of ovarian and brest cancer, even in cases where other forms of chemotherapy failed.

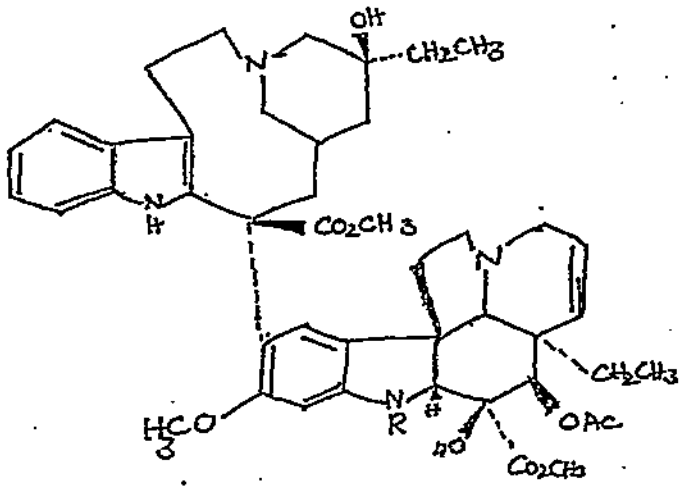
Taxol inhibits cell division by acting on micro tubules. It does this in two ways. It stimulates microtubule polymerisation and stabilizes the resulting structural units. Before cell division can take place, the cell must disassemble these units and taxol prevents this disassembly. Because cancer cells are the fastest dividing cells, taxol effectively controls their spreading.

Some taxol derivatives are also showing promise. Taxol acts in a different fashion from that of the vinca alkaloids. Taxol is an antimitotic agent.



β-lactum

Vinblastine and Vincristine

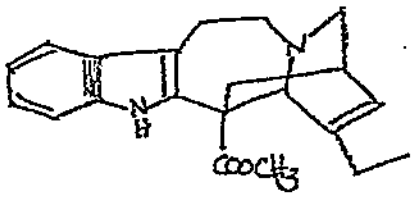


R = CH_3 Vinblastine

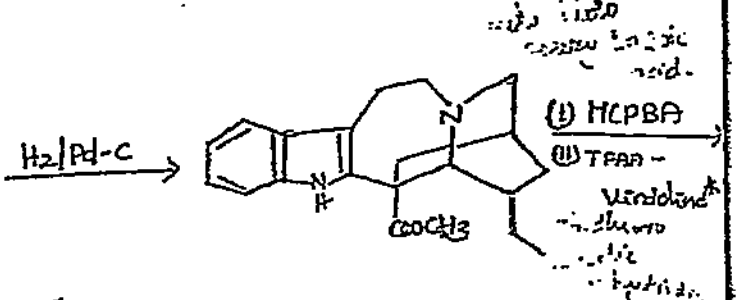
R = CHO Vincristine

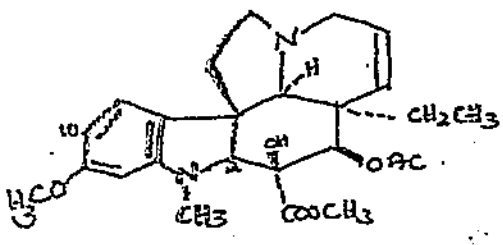
Vinblastine and Vincristine are alkaloids obtained from the periwinkle plant, Vinca roseatum. Vincristine and Vinblastine have well established roles in the contemporary treatment of cancer.

Preparation of these bis indole alkaloids from Catharanthine as starting material:

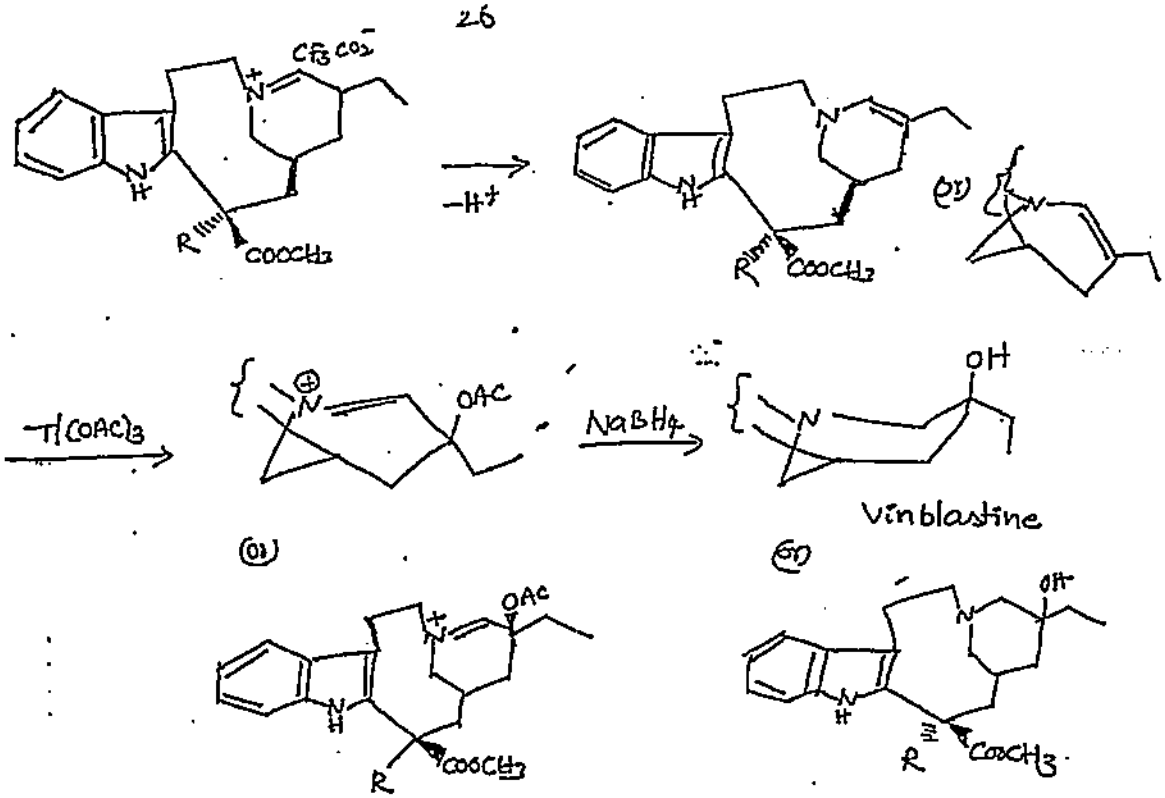


Catharanthine





R = 10-Vindolinyl



The most commonly used plant products in chemical use have been the sulphates of vinblastine (Vincaleukoblastine) and vincristine (Leurocristine).

Activity :-

Vinblastine :

Vinblastine has been used for the palliation (reduces pain without curing the disease) of a variety of Neoplastic diseases. It is one of the most effective single agents against Hodgkin's disease (staging of cancer), and it may be used in combination chemotherapy for patients who have relapses after treatment by the MOPD program (reappearance of disease, treatment).

Advanced testicular germinal cell tumors respond to vinblastine alone or in combination.

Benficial affects are also obtained against lymphocytic lymphoma, histiocytic lymphoma, mycosis fungoides (skin cancer), Kaposi's Sarcomas, Letterer - Siwe disease (year of death), resistant choriocarcinoma

and Carcinoma of the breast.

The limiting toxicity is leukopenia, which reaches its nadir in five to days after the last dose. Gastro intestinal and neurologic symptoms occur and are dose-dependent. Extravasation during injection can lead to Cellulitis and phlebitis.

Vinblastine sulphate is soluble in water and alcohol.

Vincristine

Vincristine is effective against acute leukemia. In combination with prednisone it produces complete remission in 90% of children with acute-lymphoblastic leukemia. It is used in the MOPP programm of Combination Chemotherapy for Hodgkin's disease.

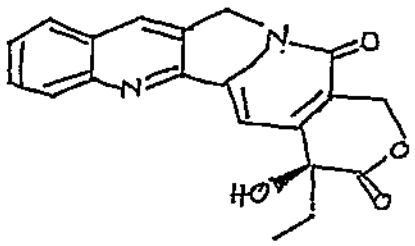
Other tumors that respond to Vincristine in Combination with other antineoplastic agents include lymphosarcoma, reticulum cell Sarcoma, rhabdomyosarcoma, neuroblastoma, and Wilm's tumor. Although the tumor Spectra of Vinblastine Vincristine are similar, there is a lack of cross-resistance between the two.

Because Vincristine is less myelosopressive than Vinblastine, it is preferred in Combination with myelotoxic agents. The most serious clinical toxicity of Vincristine is neurologic, with paresthesias, loss of deep-tendon reflexes, pain and muscle weakness occuring

These symptoms can usually be reversed by lowering the dose or suspending therapy. Constipation and alopecia (loss of hair) also occur. The rapid action of Vincristine in destroying cancer cells may result in hyperuricemia (increase of uric acid in blood). This complication can be prevented by administering alloporinol.

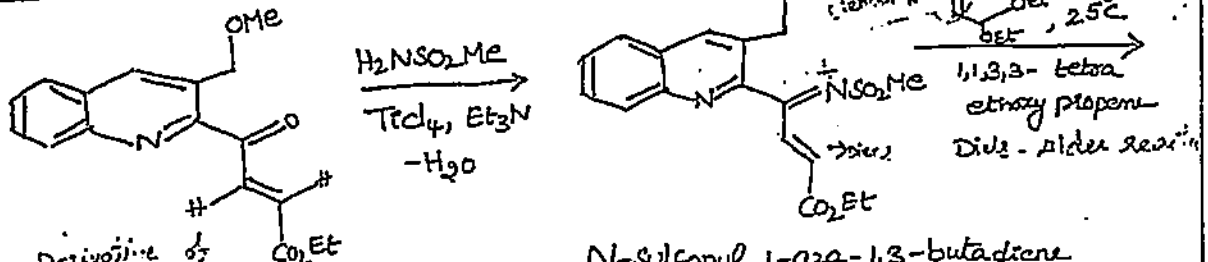
Vincristine sulphate is soluble in water.

Camptothecin



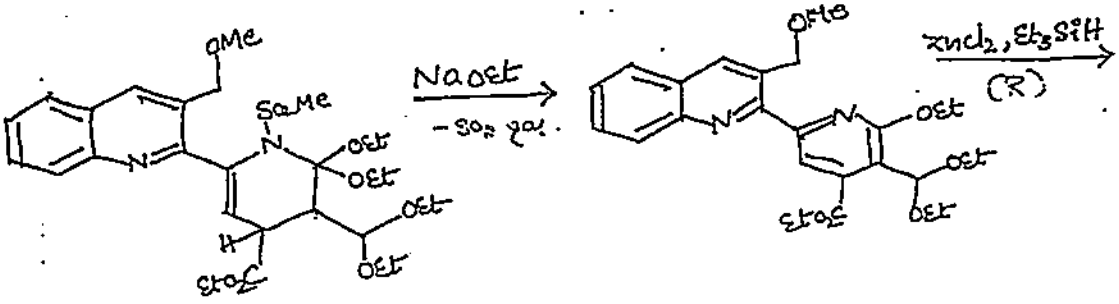
(+) - Camptothecin is a pentacyclic alkaloid isolated and characterized by Wall and Co workers from Camptotheca accuminata.

Synthesis:-

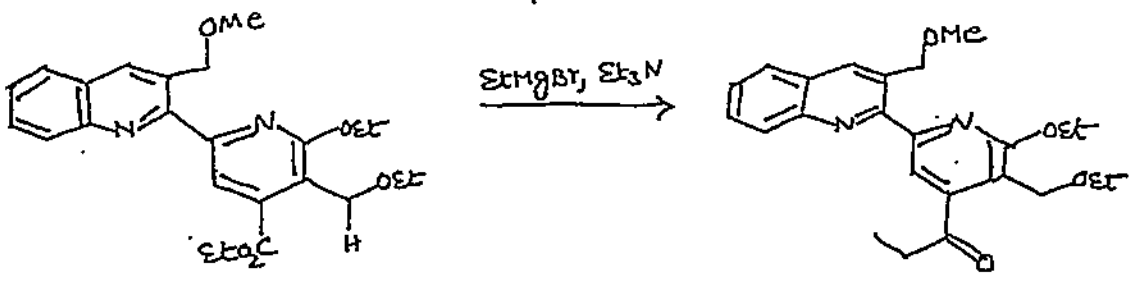


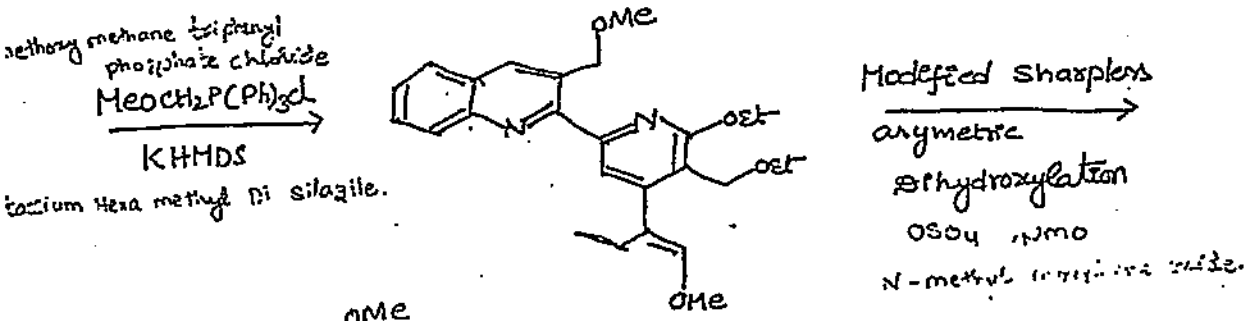
Derivative of trans-ketone

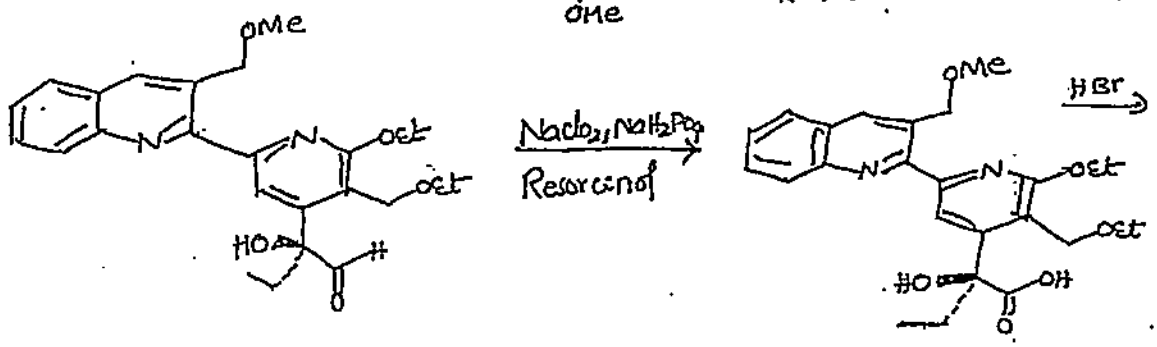
N-Sulfonyl 1-aza-1,3-butadiene

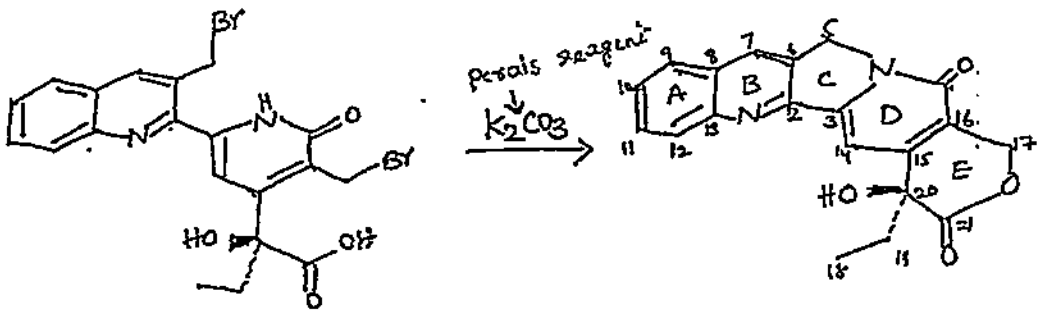


Adduct.









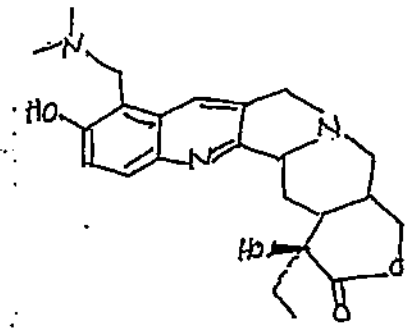
Activity :-

(i) Camptothecin exhibit potent cytotoxic activity against a range of tumor cell lines.

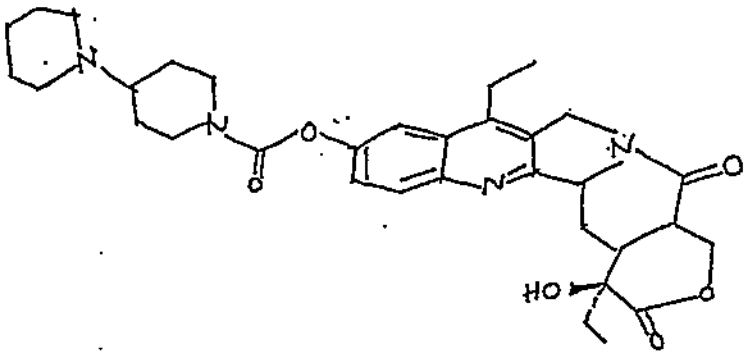
(ii) Camptothecin Stabilize the cleavable Complex of double standed DNA.

(iii) Camptothecin have Strong anti leukemia and tumor inhibiting activity.

Although Camptothecin itself is not used clinically for the treatment of cancer, two closely related analogues Topotecan and Irinotecan have proven effective in the clinic.



Topotecan



Irinotecan

As the dose is increased, side effects indicative of excessive stimulation, such as restlessness, anxiety, nervousness, and tremulousness become more masked. With further increases in dosage, convulsions can occur.

Tranquillizers

(Selective Modifiers of CNS)

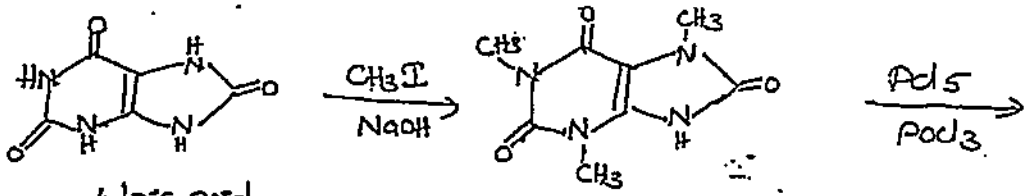
Tranquillizers are drugs which are employed in the treatment of mental disorders. These produce a specific improvement in the mood and behaviour of a patient suffering from mental disorders. Sometimes these are also known as psycholeptic because these decrease psychomotor without causing sedation. These exert a unique type of selective central nervous system depression.

In general, tranquillizers bring about reduced mental tension, relieve anxiety and result in a more calm outlook without producing any masked degree of sedation or hypnosis or without grossly altering the level of consciousness. These are effective in such mental disorders when ordinary hypnotics and sedatives and central nervous system relaxants fail.

Various tranquillizers are grouped in the following classes.

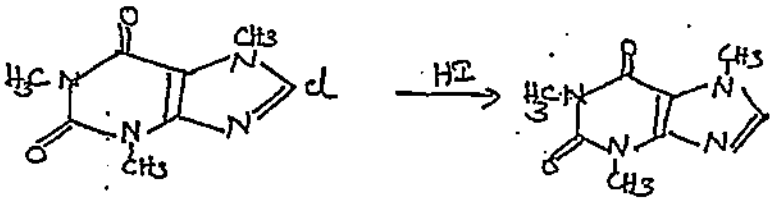
exhausting work.

Synthesis:



Uric acid

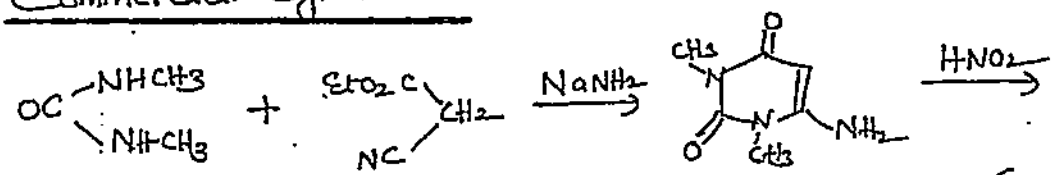
1,3,7 - trimethyl Uric acid

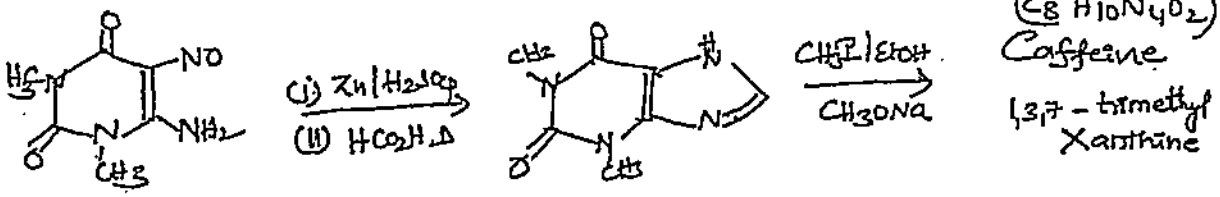


Chloro caffeine

Caffeine

Commercial Synthesis:-





($C_8H_{10}N_4O_2$)

Caffeine

1,3,7 - trimethyl Xanthine

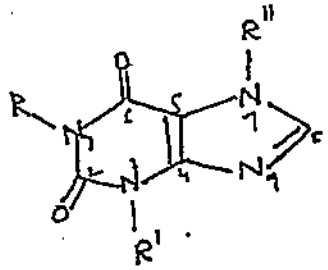
A cup of Brewed Coffee contains about 85mg of caffeine and brewed tea contains about 60mg of caffeine. Caffeine is employed in headaches of certain kinds, such as in neuralgia, rheumatism, migraine and in those due to fatigue, frequently combined with other analgesics such as phenacetin and aspirin.

In most subjects 85 to 250mg of caffeine acts as a cortical stimulant and facilitates clear thinking wakefulness, promotes an ability to concentrate on the task at hand.

Purines or Xanthines

Purines occur widely distributed among natural products eg in uric acid, coffee, tea, cocoa nucleic acid and enzymes. The naturally occuring Xanthine derivatives are Caffeine, theophylline and theobromine.

These have stimulating action on the central nervous system. This stimulating action is almost physiological in nature, and helps to combat fatigue and sleepiness.



Xanthine (R, R^{I}, R^{II} = H)

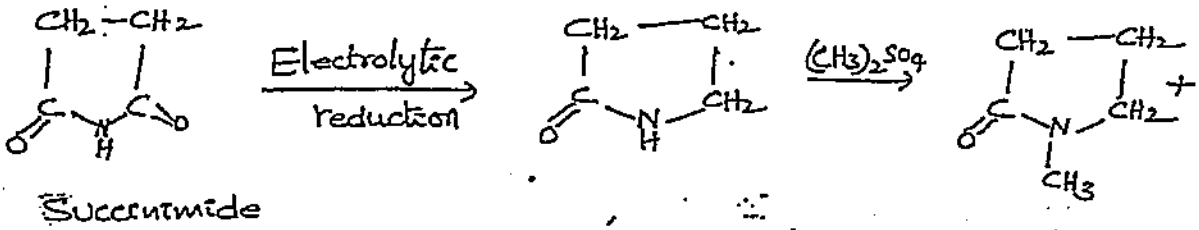
Compound	R	R^{I}	R^{II}	Common source
Caffeine	CH_3	CH_3	CH_3	Coffee, Tea
Theophylline	CH_3	CH_3	H	Tea
Theobromine	H	CH_3	CH_3	cocoa

Caffeine

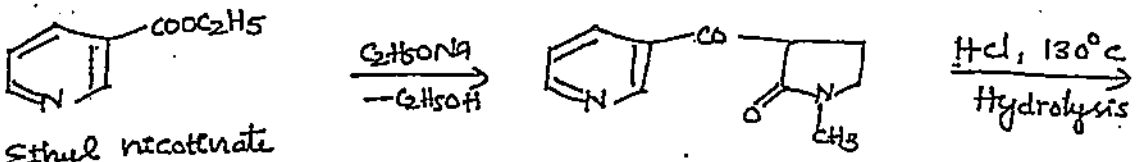
Caffeine enjoys wide use as a CNS stimulant. Caffeine is the most potent Xanthine, producing cortical and medullary stimulation and even spinal stimulation in large doses.

Controversy exists on the extent of cortical stimulation, although caffeine can stimulate mental alertness and overcome fatigue. It also prolongs the length of time an individual is able to do physical

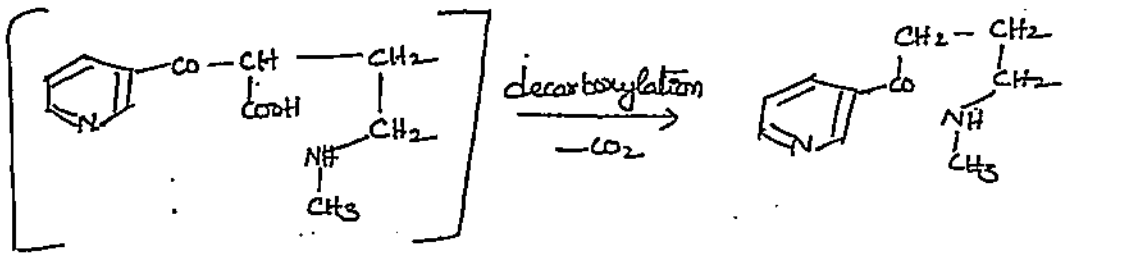
Synthesis :-

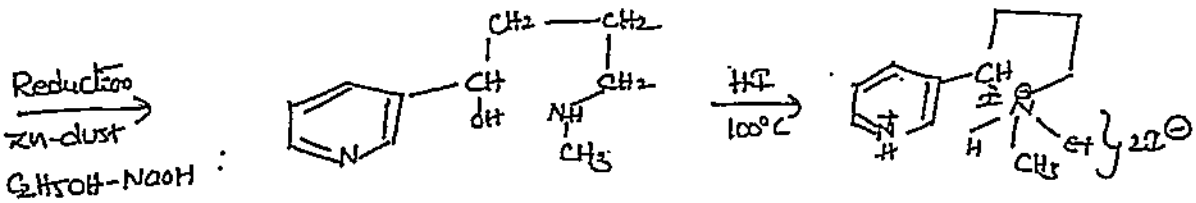


Succinimide



Ethyl nicotinate





Nicotine.

For human consumption tobacco of low alkaloid content is desirable as nicotine is extremely toxic. For instance the fatal dose for man is said to be 40mg approximately.

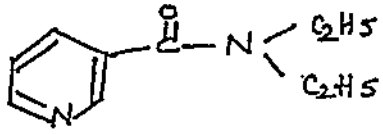
Enough evidence is available which reveals that cigarette smoking increases the heart beat and thus causes constriction of blood vessels, resulting in an increase in B.P. and hence disturbing the blood distribution.

the urine.

Pharmacologically it is used as an aid in determining how certain sedative – hypnotics and anticonvulsants acts at the molecular level.

Nikethamide

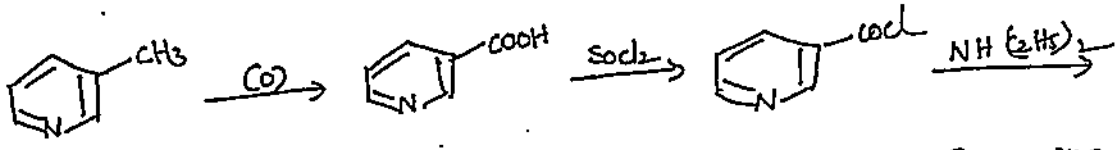
N,N– Diethyl nicotinamide (Coramine) appears to act by facilitating excitatory processes rather than by depressing inhibitory ones.



Nikethamide.

Preparation:–

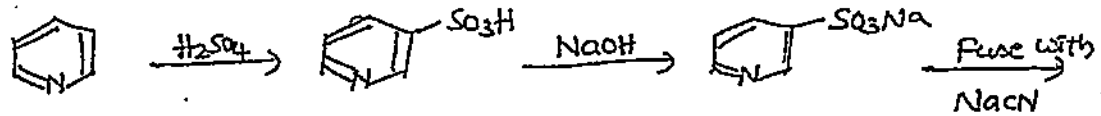
β-picoline is oxidised to nicotinic acid which is converted into corresponding acid Chloride by treating with thionyl chloride. This acid chloride when treated with dimethyl amine yields Caramine.

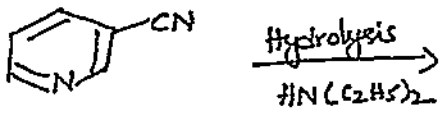


Caramine

(or)

Pyridine on sulphonation gives β-sulphonic acid. It is neutralised with NaOH and the sodium salt when fused with sodium cyanide forms 3-cyanopyridine. This compound on hydrolysis in the presence of diethyl amine forms Nikethamide.





Caramine.

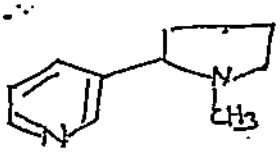
It is a cardiovascular drug having a direct action on heart. It has been used to promote coronary flow in mycocardial infection.

It is possible to stimulate respiration with the drug without inducing generalized CNS stimulation. However, selectivity is very low. The drug is absolete in managing poisoning from sedative-hypnotic drugs.

It may have a very limited place in treating acute respiratory insufficiency in COPD. It may also have value in correcting respiratory depression caused by oxygen therapy in COPD.

Nicotine.

It is the most important tobacco alkaloid occuring in Nicottana tabacum L and other Nicottana species. The molecular formula of Nicotine is $C_{10}H_{14}N_2$



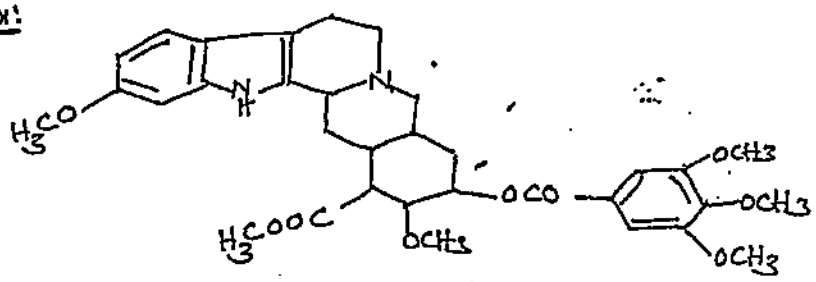
Nicotine

I. Antipsychotics or Neuroleptics (Major tranquillizers)

These are the following types

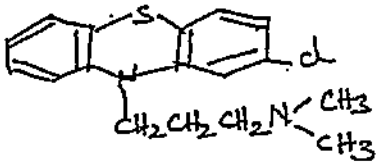
1. Rauwolfia alkaloids

Ex:

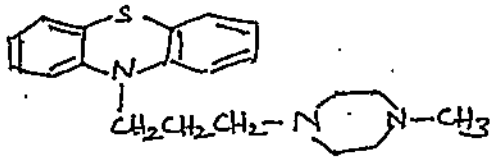


Reserpine

2. Phenothiazine derivatives:

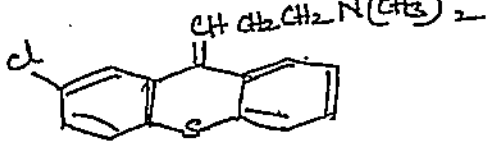


Chloropromazine



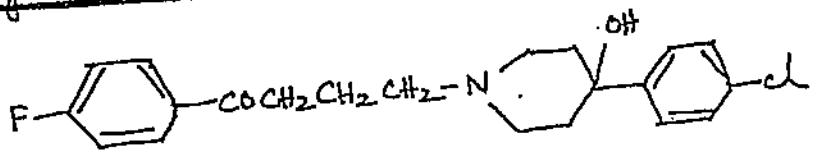
prochloroperazine.

3. Thioxanthene derivatives:



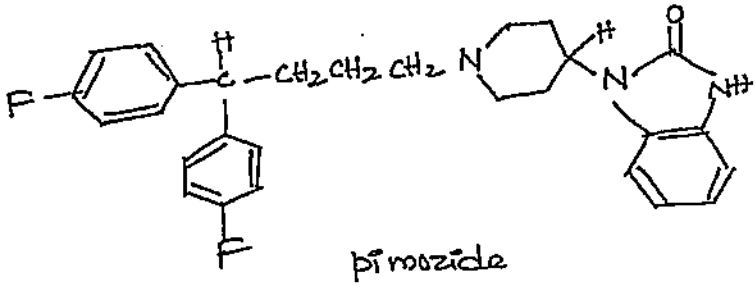
chloroprothixene

4. Butyrophenone derivatives:



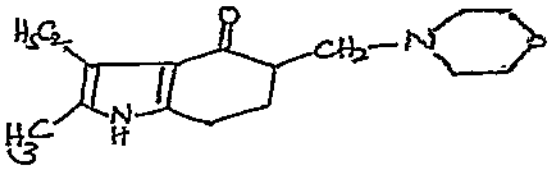
Haldol.

5. Diphenyl butyl piperidines.



pimozide

6. Indole derivatives



Molendone

In general these are able to reduce the agitation and disturbed behaviour which are often associated with delusion and hallucinations in schizophrenic or senile illness.

XII Antianxiety Agents:

(Anxiolytics, Minor transquillizers, relaxants and antineurotic agents)

These possess a calming effect in the anxiety state which are associated with neurotic personality, situation crisis or some physical disease. These are further divided as follows.

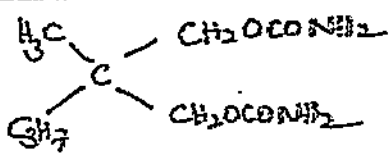
a) Muscle Relaxants

1. Mepa bromate
2. Benzodiazepines.

b) Ataractics

3. Diphenyl methanes. (anti histaminic and anticholinergic)

1. Meprobamate and its analogues:



Meprobamate

Central Nervous System Depressants

The agents included in this chapter can all be characterized as possessing a depressant action the Central Nervous system (CNS). The general anesthetics (inhalation anesthetics) and the intravenous barbiturates produce a rather non selective and general depression of the CNS.

The term anesthetics is derived from Greek word anaesthesia which means insensibility and hence anesthetics may be defined as those drugs which produce insensibility to the vital functions of all types of cells. especially those of the nervous system.

The effect produced by anesthetic is reversible which means that the effected organs return to the normal state as soon as the concentration of the anesthetic is decreased. Thus an anesthetic produces temporary insensibility to pain or feeling in the whole body or a particular organ which has to undergo the surgical operation.

Classification :-

As anesthetics may produce unconsciousness all over the body or in a particular organ, they may be classified into two groups on the basis of their applications.

a. General or Central anesthetics :

These depress the central nervous system to such an extent that all sensitivity to pain or feeling is lost. i.e. they produce unconsciousness all over the body.

b. Local anesthetics:

These do not effect the whole body but make only a part of the body insensitive to pain or feeling.

General Anesthetics:

General Anesthetics are agents that produce insensibility by a successive or progressive depression of CNS function. The successive levels of depression were first observed and described with diethyl ether as the anesthetic agent.

Diethyl ether is highly soluble in blood. The progression of effects on the CNS proceed slowly, which permits anesthesiologists to observe the successive phases of anesthesia.

Stage 1: (Cortical Stage):

This is the stage proceeding upto un-consciousness. The patient is sleepy, analgesia is produced, and some types of surgery that do not require muscle relaxation can be performed.

Stage II: (Delirium):

This is the stage between unconsciousness and surgical anesthesia. Depression of higher centres produces a variety of effects including excitement, involuntary activity, and increased skeletal muscletone.

Stage III:- (surgical anesthesia):

In this stage excitement is lost and skeletal muscle relaxation is produced. Most types of surgery are done in this stage. There are four planes to this

based on eyeball, movements, pupil size, presence of reflexes and nature of the respiration

Stage IV (Medullary depression):

Respiratory and circulatory failure occurs as depression of the vital centers of the medulla and brain stem occur.

It is possible to devide general anesthetics into two categories depending on their mode of administration.

(i) Volatile and gaseous anesthetics which may get administered by inhalation.

(ii) Intravenous anesthetics.

(i) Volatile and gaseous anesthetics:

a. Ether:

It was the first compound to be used as an anesthetic. Anesthetic ether is diethyl ether ($CH_3CH_2OCH_2CH_3$). It finds use as a volatile anesthetic, usually as a mixture with other anesthetics like nitrous oxide. It is having irritant action on the mucous membrane and bring about the secretion of saliva and mucus from bronchial tissues.

Advantages:

Ether is a safe anesthetic. Its principal site action is the central nervous system. It is inexpensive, and when stored properly it is comparitively stable.

Disadvantages:

Ether boils at low temperature and is difficult to administer in tropical temperatures. Its vapours are flammable and some what irritating to mucous membrane. The blood solubility of ether is high and induction period is slow and often stormy.

(b) Chloroform:

It is among the most widely used general anesthetics.

preparation:-

$$CH_3CHO + 3Cl_2 \longrightarrow CCl_3CHO + 3HCl$$

$$2CCl_3CHO + Ca(OH)_2 \longrightarrow CHCl_3 + (HCOO)_2Ca.$$

Chloroform occurs as a colourless, volatile liquid having a characteristic odour and sweet burning taste.

Chloroform for anesthetic purpose must be kept protected from light and air, otherwise decomposition will occur, forming the toxic phosgene. Anesthesia with chloroform may be induced using the open drop method or rebreathing in a closed circuit.

Its various disadvantages are that it is Cardiotoxic, hepatotoxic and its rapid decomposition by air, light or moisture into phosgene ($COCl_2$), a poisonous gas.

(c) Nitrous oxide:-

It was the first anesthetics. It is prepared by heating ammonium nitrite upto 200°c. It is purified and liquified.

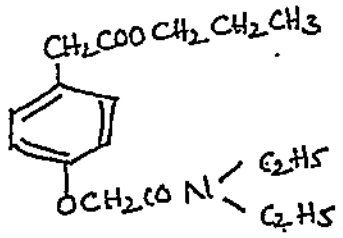
$$NH_4NO_2 \longrightarrow N_2O + H_2O$$

It is a weak anesthetic but is exerting strong analegesic properties. It is non-irritant. For general anesthesia. It is generally used along with other anesthetics

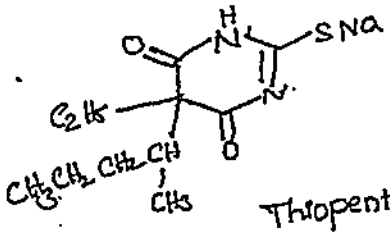
(II) Intravenous Anesthetics:

Intravenous anesthetics are able to produce unconsciousness when they are allowed to administer parenterally. The intravenous drugs offer flexibility and allow the administration of lower doses of inhalation agents. These also find use, to induce anesthetic rapidly.

Ex:



Propanidid.



Thiopentone Sodium.

Sedatives and Hypnotics

Sedatives and Hypnotics are general depressants.

A sedative produces mild depression and calm anxiety and excitation without causing drowsiness or impaired performance (or)

Sedatives are central nervous system depressants that reduce restlessness and emotional tension without producing sleep.

A hypnotic compels the user to sleep, a stronger form of depression (or)

Hypnotics are also central nervous system depressants

that produce sleep to reduce restlessness and emotional tension. The patient cannot be easily awakened until the effect of the hypnotic wears out.

From the above definitions, one cannot draw a definite line among the various groups of hypnotics and sedatives. Usually, their action varies with the dosage. For instance phenobarbital administered on dosage 25-30mg is considered a mild sedative, while in a 100mg dose it is a hypnotic.

Generally hypnotics when used in very large amounts may produce anesthesia poisoning and even death in some cases. The progressive effects may be depicted as follows.

Sedation ⇌ Hypnosis ⇌ Anesthesia ⇌ Coma ⟶ Death.

In pharmacologic terms, sedation represents depression or calmness. It is characterized by consciousness without any loss of the righting reflex.

On the otherhand, hypnosis is characterized by temporary loss of arousability and the righting reflex.

The sedative-hypnotic drugs are not characterized by common structural features. Instead, a wide variety of chemical compounds have been used in clinical therapy. An arbitrary classification is as follows.

(I) Barbiturates
(II) Aldehydes
(III) Acetylene derivatives
(IV) Acyclic hypnotics containing nitrogen
(V) piperidinediones.

(VI) · Benzodiazepines

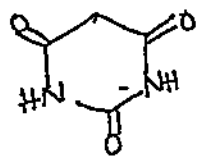
(VII) Imidazo pyridines

(VIII) Cyclo pyrrolones.

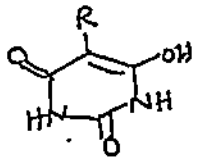
Barbiturates:

This is the general term which is used for the derivatives of barbituric acid.

Barbituric acid is 2,4,6-trioxo-hexa hydro pyramidine which is a cyclic ureide and formed by the condensation of urea with malonic acid ester. Barbituric acid itself has no central nervous system depressants activity. The substitution by alkyl or aryl group at its position 5 confers hypnotic-sedative activity.



Barbituric acid

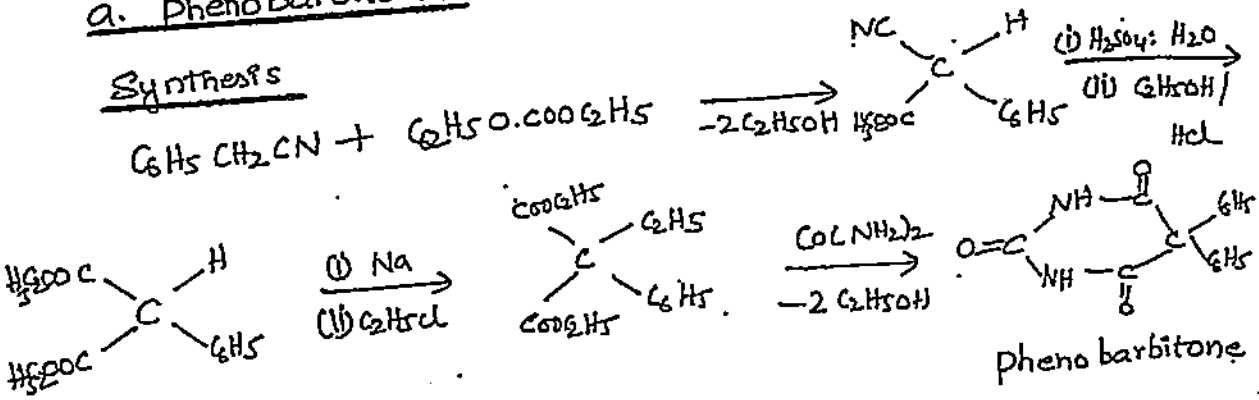


Tautomeric form of barbituric acid

Some official barbiturates are as follows

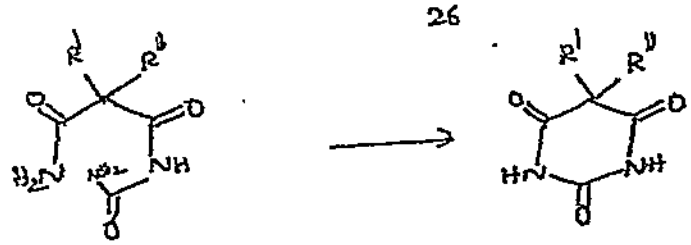
a. Phenobarbitone:

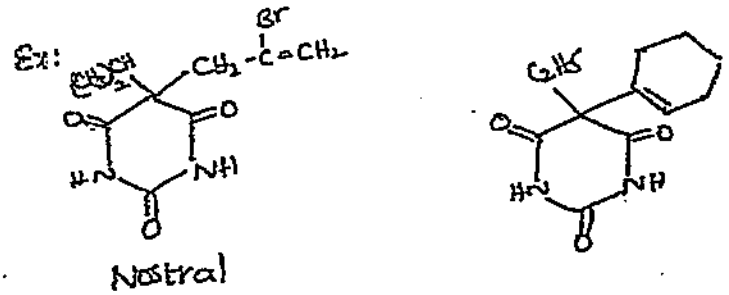
Synthesis



Phenobarbitone

Cyclization of N-substituted urease in an alkaline medium also produces barbiturates.





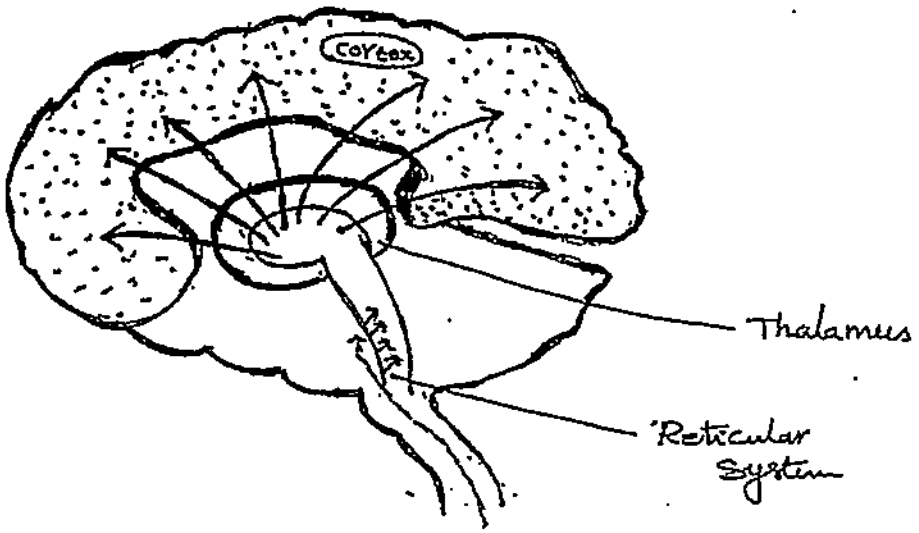
The barbiturates exert a depressants effect on the cerebrospinal axis. These drugs depress neuronal activity as well as skeletal muscle, smooth muscle, and cardiac muscle activity.

Mode of Action:-

Barbiturates modify the mechanism of synaptic transmission, rather than intraneuronal condition. These drugs in sufficient concentrations reduce the excitability of the postsynaptic cell by altering the permeability of the cell membrane. In general, excitatory synaptic transmission is depressed by barbiturates where as inhibitory synaptic transmission is usually unaffected or enhanced.

Barbiturates exert their action on the central synaptic transmission process of the reticular activating system, and the cerebral cortex becomes deactivated. Barbiturates are antidepolarizing non transferable blocking agents because they prevent the generation excitatory postsynaptic potential these drugs raise the threshold and extend the refractory period of the post-synaptic cell.

The depressant activity of barbiturates can be followed very well on the electroencephalogram. The cerebral electrical activity of normal individuals increases with emotional tension, anxiety or consumption of a CNS stimulant. The increased cerebral electrical activity is caused by intensified reticular activation of the cortex. Administration of barbiturates in sufficient doses has a general calming effect, which is observed clearly on the electroencephalogram. Cerebral electrical activity returns to normal as the result of the suppressing influence of barbiturates on reticular activation.

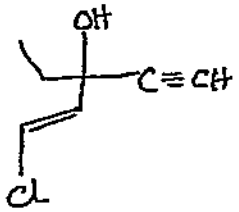


A paradoxic effect of barbiturates also occurs. Small doses bring about hyperexcitation and agitation instead of sedation, because the barbiturate concentration is not great enough to depress the reticular activating system. On the otherhand, the concentration of barbiturate is great enough to impede the inhibitory synapses normally present with in the cortex. Pyrodendrite excitability in the cortex is increased.

In addition to the effect on the reticular activating system, barbiturates act on the limbic, hypothalamic, and thalamic synaptic system.

Acetylene Derivatives:-

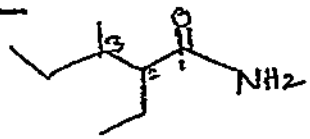
Ethchloruynol (1-chloro, 3-ethyl, 1-penten-4-yn 3-ol):



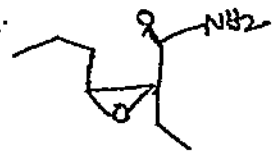
This drug is a mild hypnotic with a quick onset (attack) and short duration of activity. It resembles the short-acting barbiturates because it produces similar changes in the electroencephalogram. It may induce habituation (habit) and tolerance. The sedative dose is 100 to 200mg the hypnotic dose is 500mg.

Acyclic Hypnotics Containing Nitrogen:

Amides:-



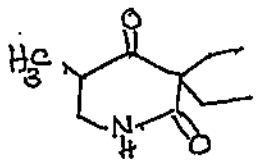
Valnoctamide
(2-ethyl 3-methyl valeramide)



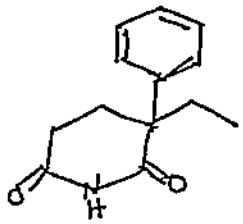
oxanamide
(2,3-epoxy 2-ethyl hexanamide)

Valnoctamide and oxanamide are also potent muscle relaxants. It has been reported that the therapeutic index of simple amides increase rapidly with increasing size in the alkyl substituent.

Piperidinediones



Methyprylon



Glutethimide

Methyprylon:

It supresses REM sleep in a dose of 300mg. It has no adverse respiratory or gastrointestinal effects.

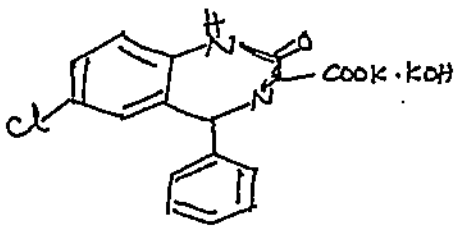
Glutethimide:

Glutethimide significantly suppresses REM sleep at the hypnotic dose of 500mg. withdrawal causes a rebound increase in sleep.

Benzodiazepines:

Benzodiazepines are specifically promoted as sleep inducers.

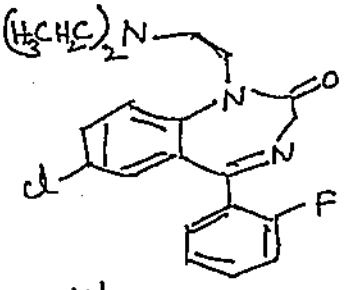
Ex:



Potassium clorazepate

Benzodiazepines are also used for the treatment of insomnia.

Ex:



Flurazepam

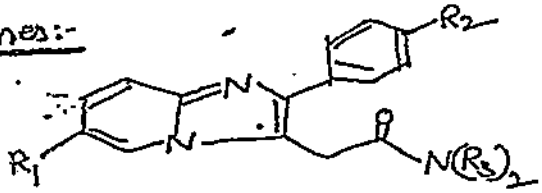
Mode of action:

The identification of specific, high-affinity binding sites for the benzodiazepines in the CNS was achieved by using radiolabeled benzodiazepines. In the CNS, the benzodiazepines interact with a macromolecular membrane complex that also has recognition sites for GABA (γ-amino butyric acid) and a chloride ionophore. Consequently several subtypes of benzodiazepine receptors have been identified.

It is possible, but not proven, that each of these receptors sub classes may mediate independently the anxiolytic, sedative, muscle, relaxants, anticonvulsant and similar properties respectively associated with benzodiazepines.

Benzodiazepines have a potent interaction with the GABA inhibitory neurotransmitter system. It has been shown that benzodiazepines synergistically increase the effects of ionotophoretically applied GABA and similarly elevation of brain GABA levels by GABA transminase inhibitors increases the electrophysiologic effects of benzodiazepine

Imidazopyridines:-

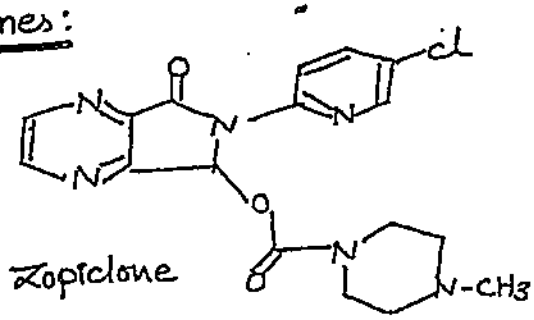


$R_1 = R_2 = R_3 = CH_3$ Zolpidem

$R_1 = R_2 = Cl$ $R_3 = CH_2CH_2CH_3$ Alpidem

Zolpidem acts at the high-affinity benzodiazepine receptors subtype in the brain. Zolpidem reduces the time to onset and increases the duration of sleep in patient with insomnia. On the other hand alpidem displays primarily anxiety and not sedative effects.

Cyclopyrrolones:



Zopiclone

Zopidone, a nonbenzodiazepine hypnotic agent, acts at the high affinity benzodiazepine receptors subtype in the brain. At 7.5mg dose, Zopiclone decreases sleep latency, increases total sleep duration, reduces the number of awakenings and increases the sleep efficiency.

Paper-IV: Chemistry of Antibiotics and Drugs

UNIT - III & IV

M.Sc. (Final) Chemistry, Semester - IV

Paper - IV Paper ⓘ Antibiotics and Drugs

UNIT - III & IV

I. Antimalarials

Antimalarials are chemotherapeutic agents which are used for the prevention and treatment of malaria. The organisms responsible for malaria belong to the genus plasmodium which is of the class of protozoa known as sporazoa.

There are four different species which are responsible for human malaria. They are

1. plasmodium malaria
2. plasmodium vivax
3. plasmodium falciparam
4. plasmodium ovale.

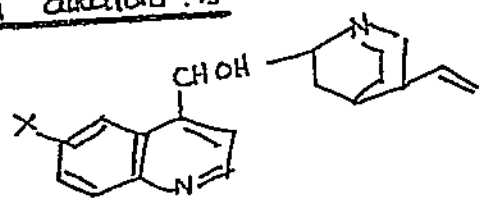
The protozoa have complex life cycles embodying both the female anopheles mosquito and the liver & the erythrocycle of the human host. Thus an ideal antimalarial must be able to exert an effect on two fronts simultaneously. i.e. to eradicate the microzoan from the blood and also from the tissues inorder to produce an effective radical cure.

Classification :-

The antimalarials are classified on the basis of their basic chemical nucleus. They are classified as follows.

1.

1. Cinchona alkaloid :-

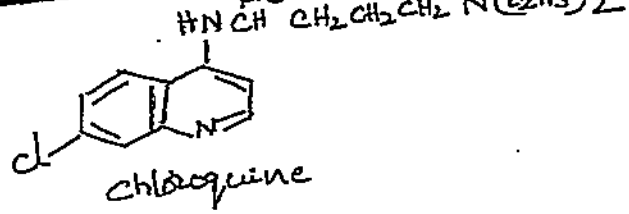


X = $-OCH_3$ Quinine

X = H cinchonine.

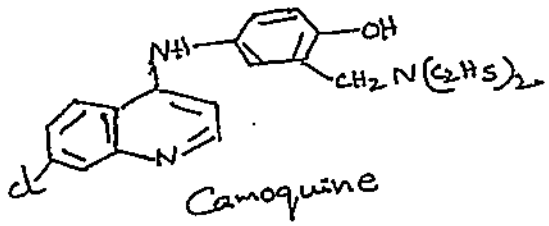
2. 4 - Aminoquinolines :-

(i)



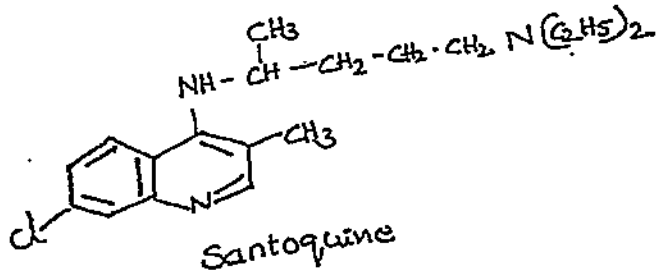
Chloroquine

(ii)



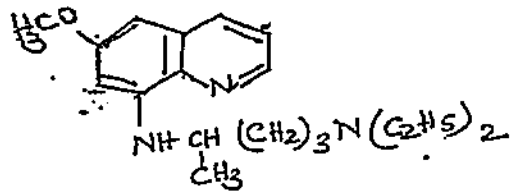
Camoquine

(iii)



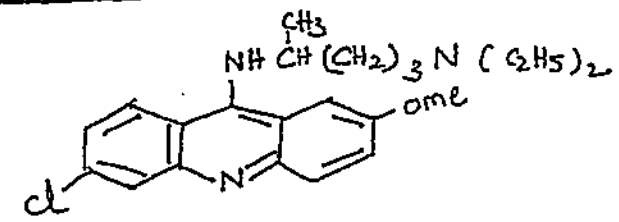
Santoquine

3. 8 - Amino Quinolines :-



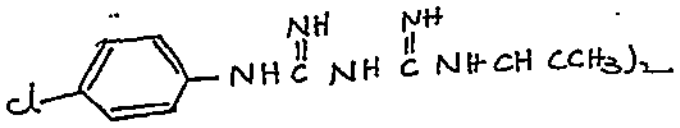
Pamaquine.

4. 9-Amino acridines:-



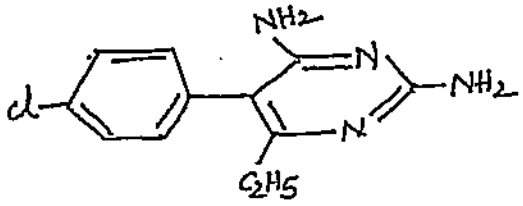
Quinacrine

5. Biguanides:-



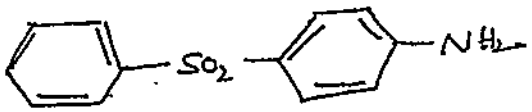
Paludrin.

6. Pyrimidines:-



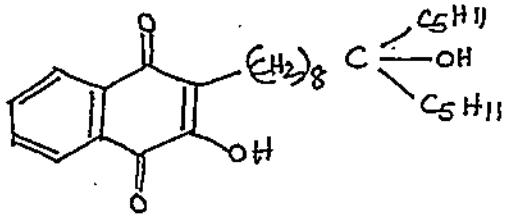
Pyrimethamine

7. Sulphones:-



Dapsone (DDS)

8. Miscellaneous antimalarials:-



Lapinone

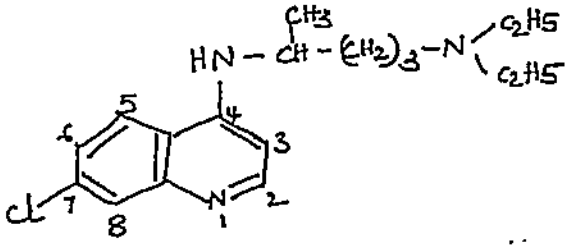
Synthesis of Antimalarials:-

4- amino quinoline analogues:-

When 4-amino quinolines are duly substituted produces antimalarial agents. These drugs are found to be active against the erythrocytic forms of mat malarial parasites ultimately affecting a clinical cures. These drugs do not cause prevention of the disease and these are inactive against the liver infecting forms.

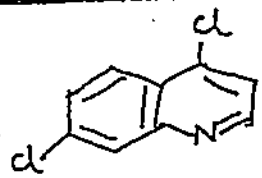
A. Chloroquine :-

(7-chloro-4[4-(diethyl amino)-1-methyl) butyl] quinoline

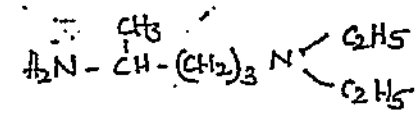


Chloroquine is having two major parts in its structure

1. 4,7-dichloroquinoline



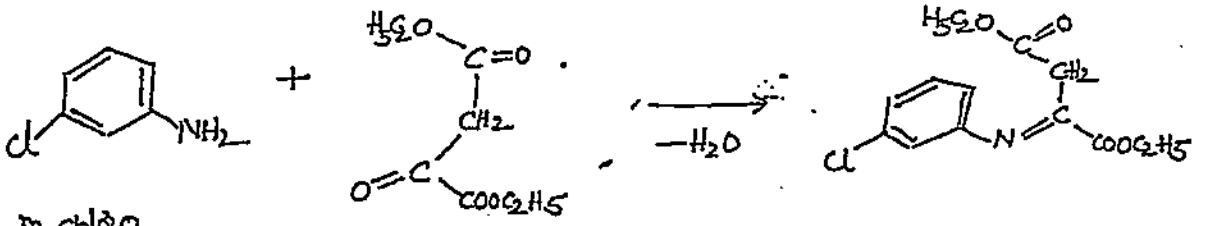
2. 2-amino 5-diethyl amino pentane (or) 4-amino 1-diethyl amino pentane



Synthesis :-

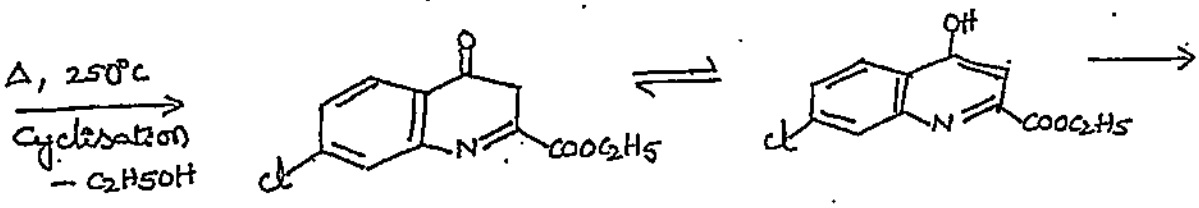
Chloroquine is synthesised in three steps

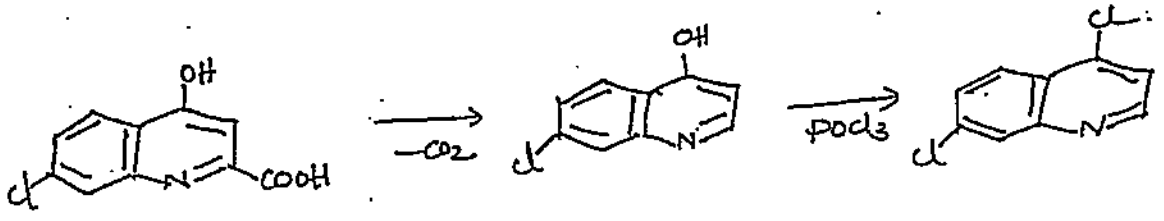
1. Synthesis of 4,7 dichloro quinoline :-



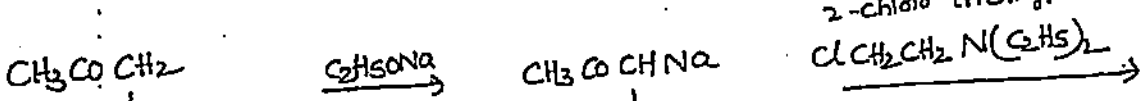
m-chloro aniline

Oxal acetic ester

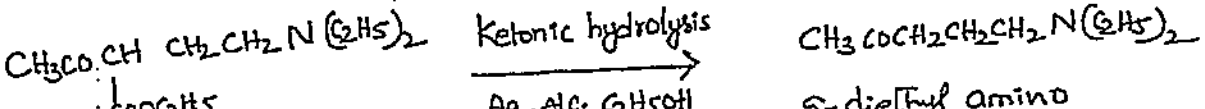




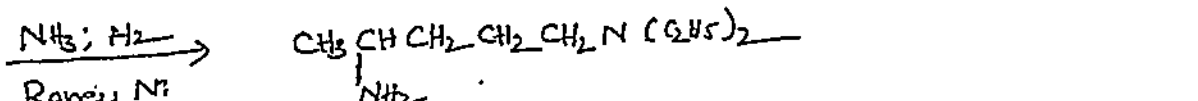
II. Synthesis of 4-amino 1-diethyl amino pentane :-



Aceto acetic Ester

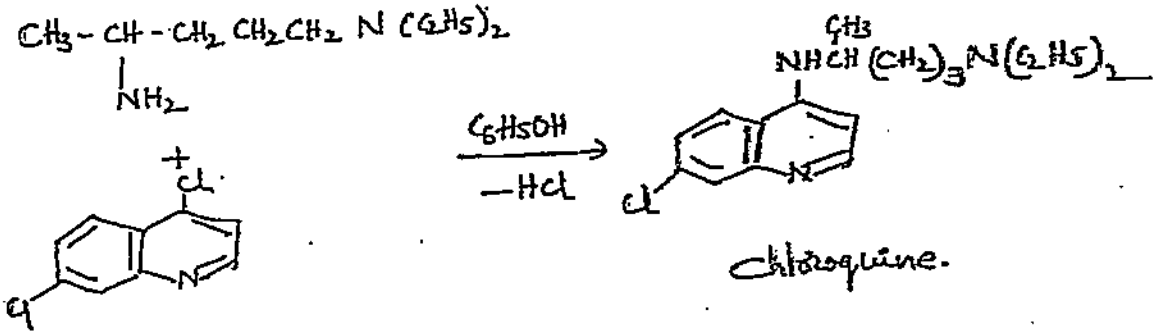


5-diethyl amino 2-pentanone



1-diethyl amino 4-amino pentane.

(III) 4,7- Dichloroquinoline on Condensation with 1-diethyl amino 4-amino pentane in phenol yields Chloroquine.



Chloroquine.

Therapeutic applications:-

1. Chloroquine hydrochloride is used for injections whereas its sulphate and phosphate are used as tablets.

2. It has been found to be very active against vivax and falciparam malaria and its activity is three to four times that of quinine.

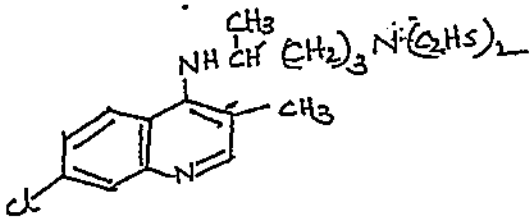
3. It does not show curative or prophylatic activity in case of relapse after one to three months has been reported.

4. It has many side effects such as symptoms of general weakness uneasiness in epigastrium, loss of appetite, vomiting diarrhoea and occasional insomnia have been also observed as side effects.

However these symptoms tend to disappear as soon as the use of the drug is stopped.

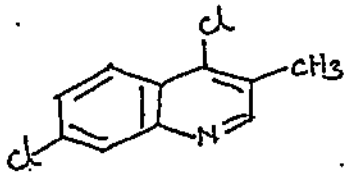
B. Santoquine :-

7-chloro-4[4-(diethyl amino)-1-methyl butyl amino)-3-methyl quinoline

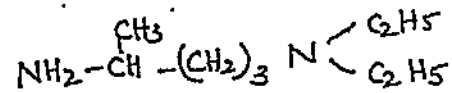


Santoquine is having two major parts in its structure

1. 4,7-dichloro 3-methyl quinoline :-



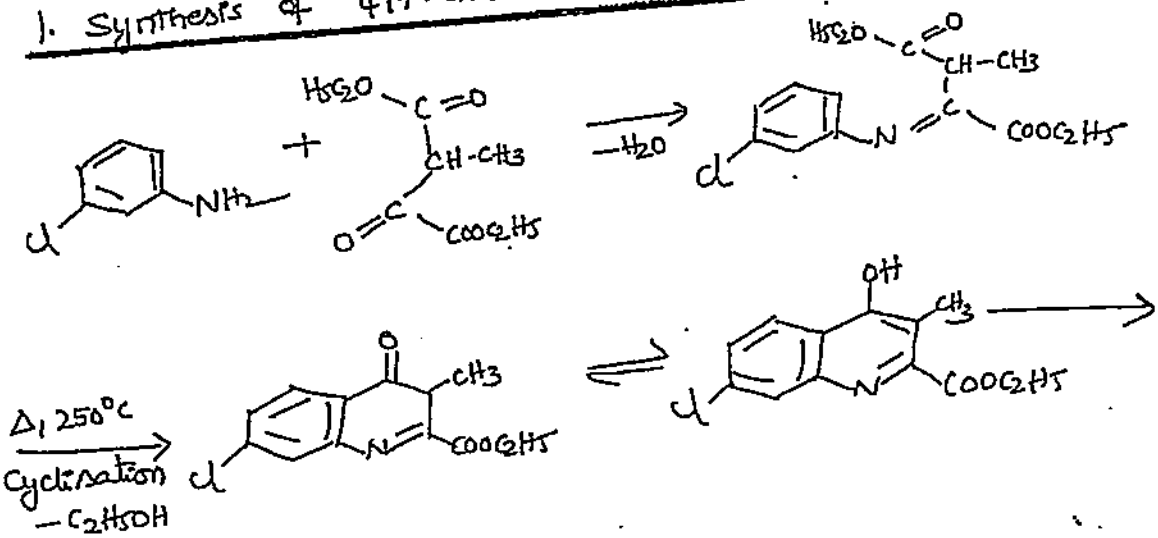
2. 4-amino 1-diethyl amino pentane

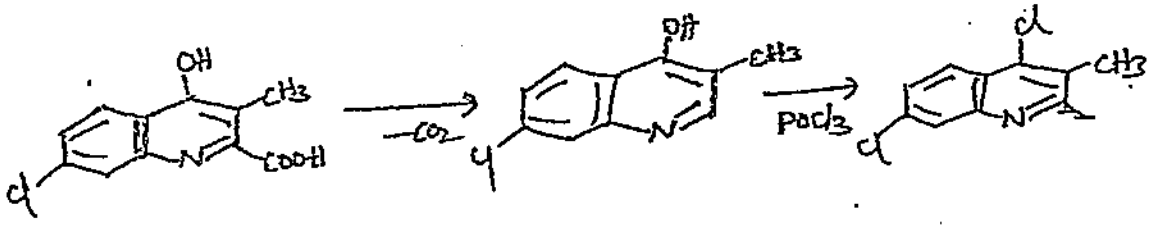


Synthesis :-

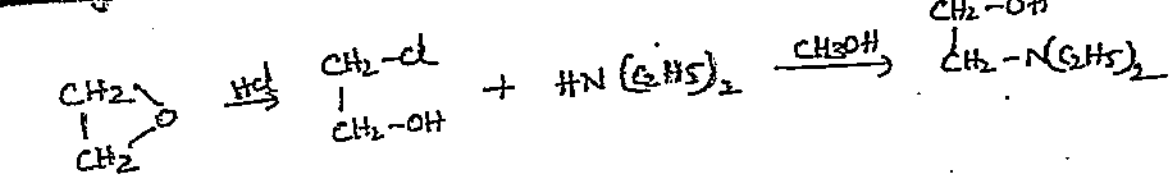
Santoquine is synthesised in three steps.

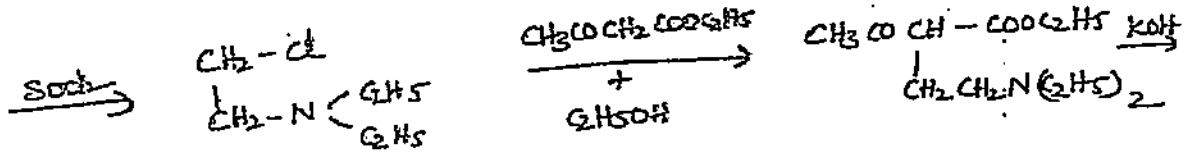
1. Synthesis of 4,7-dichloro 3-methyl quinoline :-

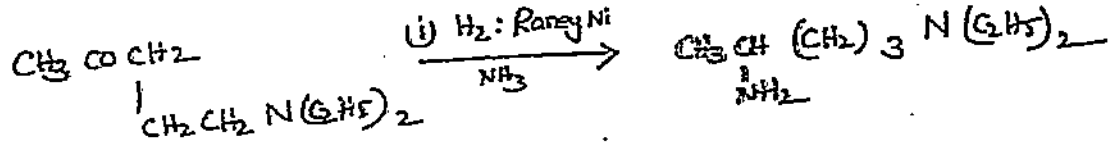




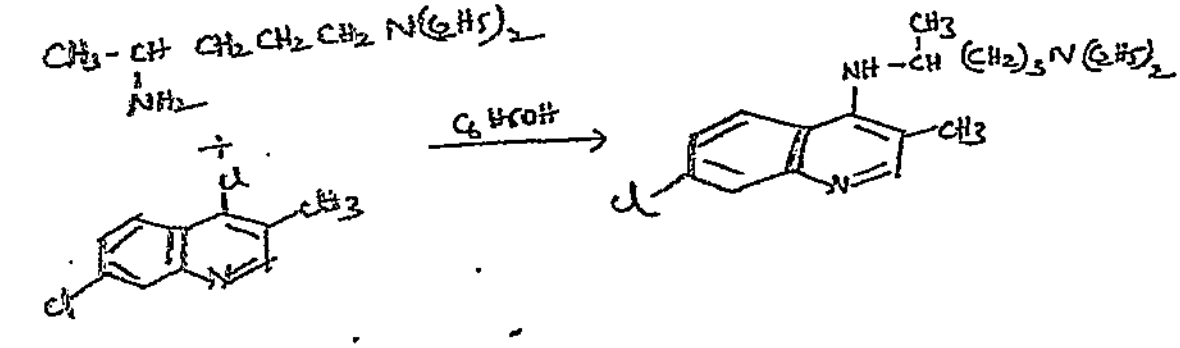
(II) Synthesis of 4- amino 1-diethyl amino pentane:-





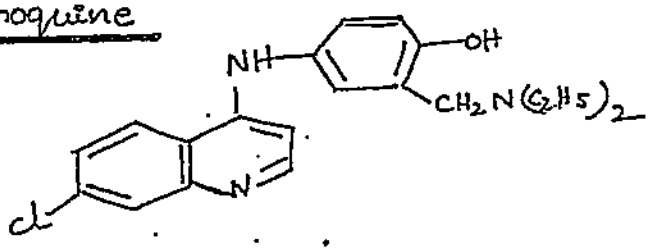


(III) 4,7 - dichloro 3-methyl quinoline on Condensation with 1-diethyl amino 4-amino pentane in phenol yields Sontoquine.



It has one additional methyl group in position 3 in the quinoline ring of chloroquine. It has been found to be less reactive than Chloroquine

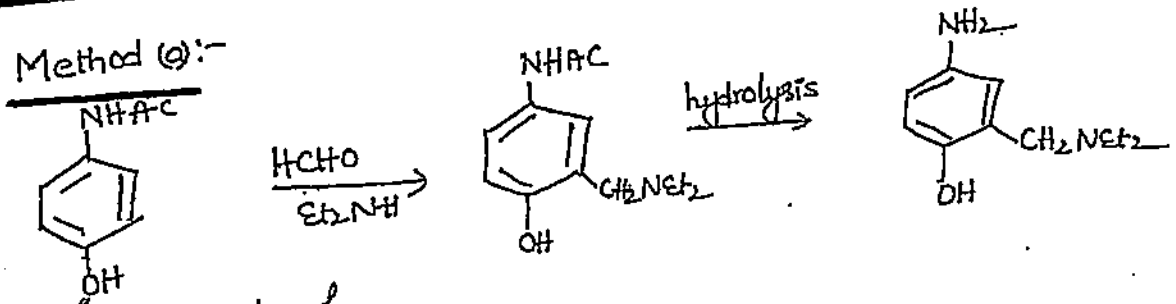
C. Camoquine



It may be obtained by the condensation of 4,7-dichloroquinoline with 4-amino 2-diethyl amino methyl phenol.

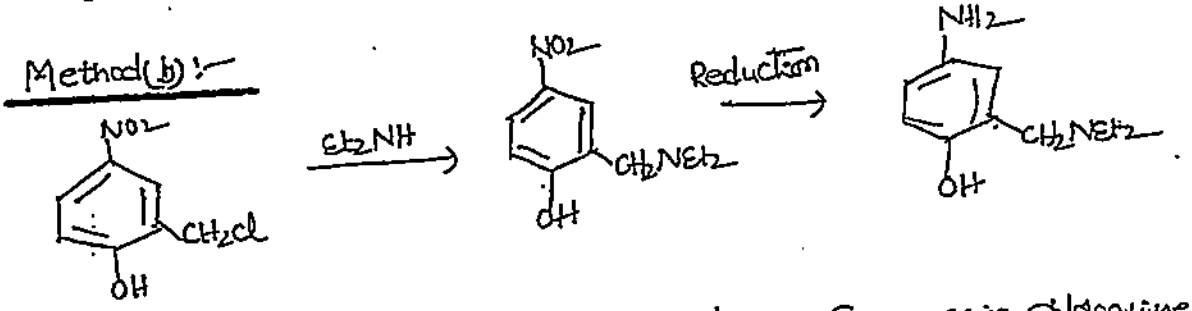
(I) Synthesis of 4-amino 2-diethyl amino methyl Phenol:-

Method (a):-



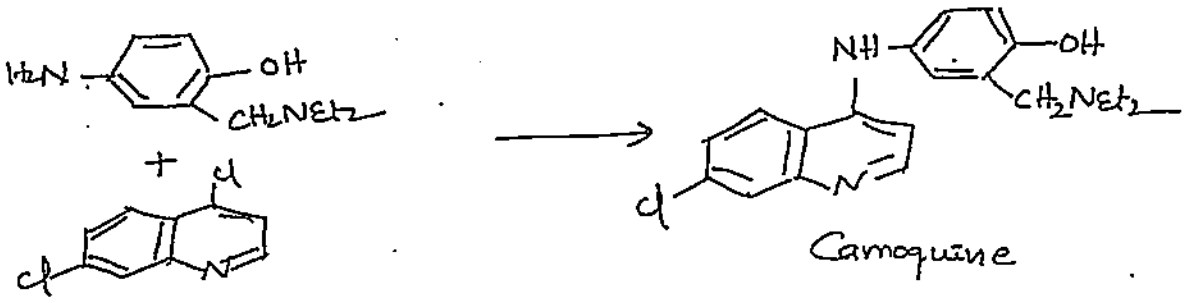
p-acetyl amino phenol

Method (b):-



(II) Synthesis of 4,7-dichloro quinoline:- Same as in chloroquine

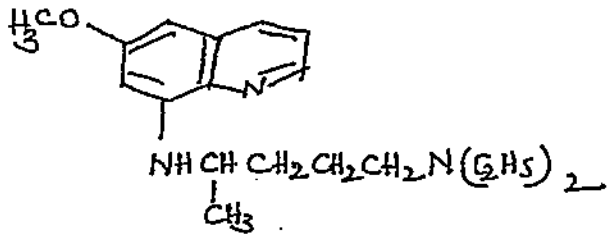
(III) Condensation of 4,7-dichloroquinoline with 4-amino 2-diethyl amino methyl phenol.



Camoquine

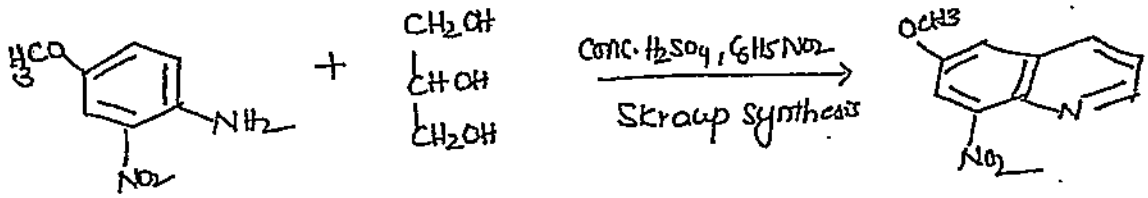
8-amino quinoline analogues:-

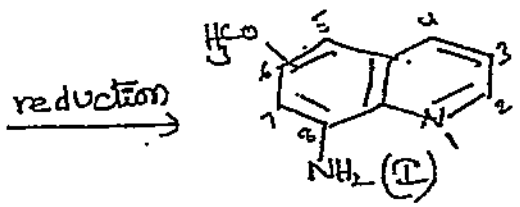
D. Pamaquine or plasmoquine or plasmochin:-



It was the first succesful 8-amino quinoline derivative. It may be synthesised by the condensation of 6-methoxy 8-amino quindine with 1-diethyl amino 4-bromo pentane.

I. Synthesis of 6-methoxy 8-amino quindine:-





II. Synthesis of 1-diethyl amino 4-bromo pentane:-

$CH_3CHO \xrightarrow{CH\equiv CH} CH_3CHOH\,C\equiv CH \xrightarrow{HO\,CH_2N(C_2H_5)_2}$

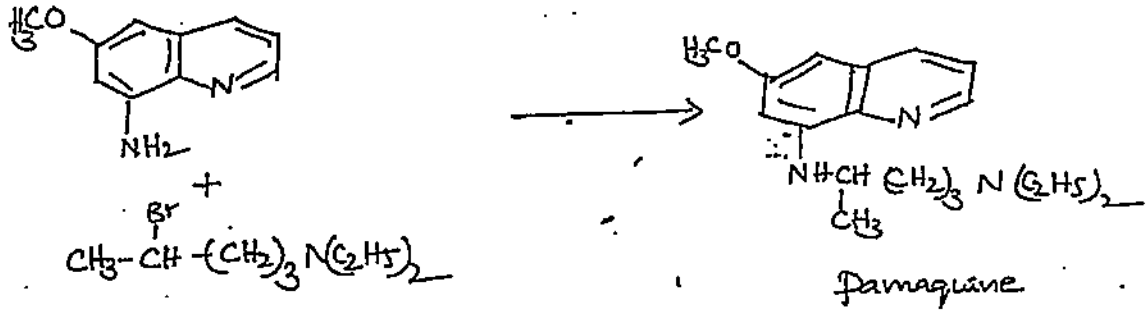
$CH_3\,CHOH\,C\equiv C\,CH_2\,N(C_2H_5)_2 \xrightarrow{\text{reduction}} CH_3\,\underset{\text{OH}}{CH}\,(CH_2)_3\,N(C_2H_5)_2$

amino alcohol

$\xrightarrow{SOBr_2} CH_3\,\underset{Br}{CH}\,(CH_2)_3\,N(C_2H_5)_2$

II

(III) Condensation of (I) and (II) forms pamaquine



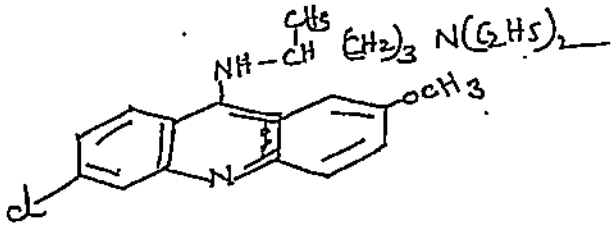
Pamaquine

Therapeutic applications:-

(i) Pamaquine is a gametocidal agent. i.e. lethal to gametocytes but is not safe enough to be used for complete elimination of a sexual forms (schizonts) from blood.

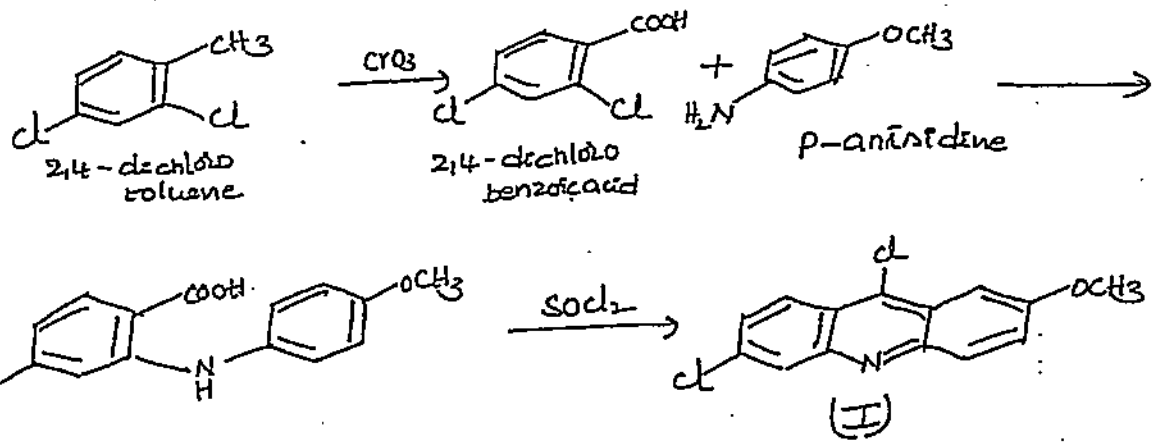
(II) In combination with quinine it has been used to reduce the relapse rate in vivax malaria. However it is fairly toxic.

E. Quinacrine, Mepacrine, atabrin, chinacrine (or) atebrin:

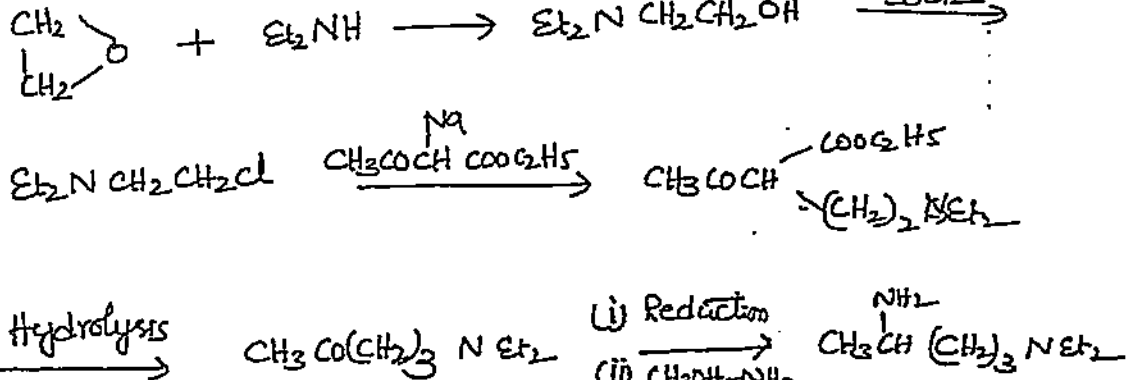


It may be prepared by the condensation of 2-methoxy-6,9-dichloro acridine with 1-diethyl amino-4-amino pentane in the following manner.

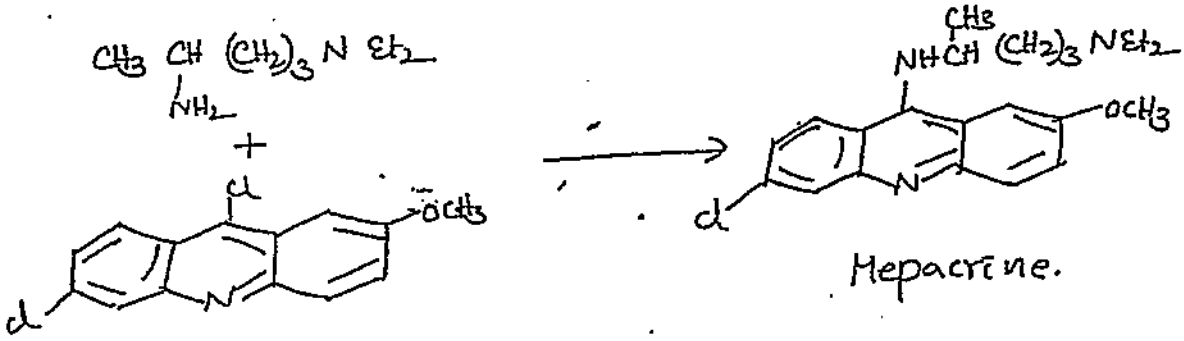
(I) Synthesis of 2-methoxy - 6, 9 dichloro acridine :-



(II) Synthesis of 1-diethyl amino 4-amino pentane :-



(III) Condensation of I and II :-



Hepacrine.

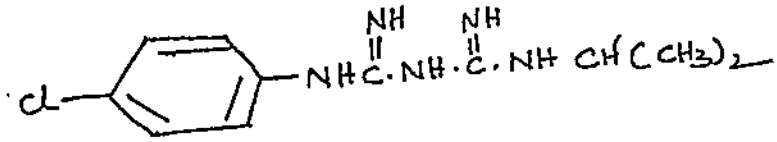
Therapeutic applications :-

(i) Quinacrine acts as an erythrocytic schizontocide in all kinds of human malaria. It has some effectiveness as a gametocytocide in P. vivax and P. malariae infections.

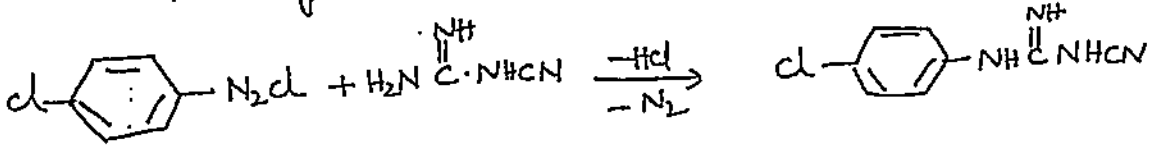
(ii) It may be employed in the treatment of black water fever when the use of quinine is contraindicated.

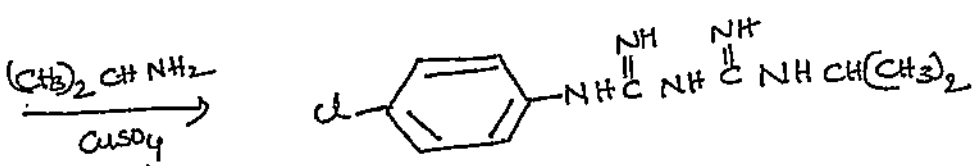
(iii) Its bitter taste and skin coloration (yellow) are quite objectionable properties.

(F) Paludrine (or) proguanil (or) chloroguanide :



It is a biguanide derivative which was synthesised in the following manner.





Therapeutic applications :-

(i) It is a folic acid antagonist and is useful prophylactically against non-resistant strains of plasmodia. It is superior to all the antimalarials known. It is least toxic antimalarial.

Sulpha Drugs antibacterials

Introduction :-

These are synthetic chemotherapeutic agents which contain sulphonamide, SO_2NH_2 group in their structure. These are the first effective chemotherapeutic agents to be widely used for the cure of bacterial infections in human.

They have also been found to be active against certain gram-positive and gram-negative cocci, certain gram-negative bacilli and protozoa.

At present, sulphonamides or sulpha drugs have been largely replaced by antibiotics in the treatment of most bacterial diseases but they are still used either alone or preferably in combination with the one or the other antibiotic.

Classification :-

From a therapeutic point of view the sulphanilamide have been classified as follows.

1. Compounds which are readily absorbed and readily excreted.

   Ex: Sulphamerazine, sulphadiazine etc.

2. Compounds which are readily absorbed but slowly excreated

   Ex: Sulphamethoxy pyridazine.

3. Compounds which are poorly absorbed

Ex: Sulphaguanidine

4. Compounds with special indication

Ex: sulpha pyridine

5. Absolute Compounds

Ex: Sulphanilamide.

Some times they have also been classified according to their therapeutic utility as follows.

A Sulphonamides used for the treatment of systemic infection.

They are usually administered orally. They are further subdivided according to the duration of their action.

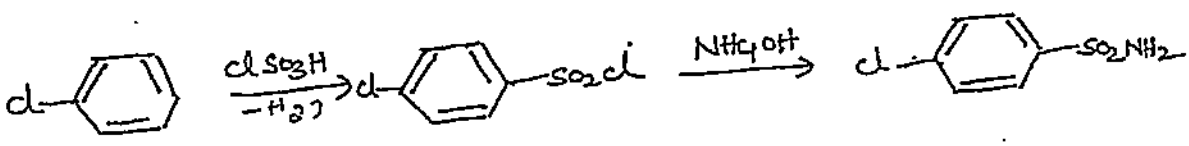
a. Short acting sulphonamides: Eg: Sulphanilamide
b. Intermediate acting Sulphonamide Eg: Sulphaphenazole
c. Long acting sulphonamides Eg: Sulphadimethoxine

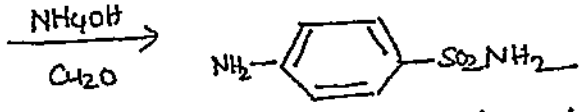
B Sulphonamides used for the treatment of local gastrointestinal infections.

Ex: Sulphaguanidine etc.

1. Sulphanilamide (p-amino benzene sulphonamide)

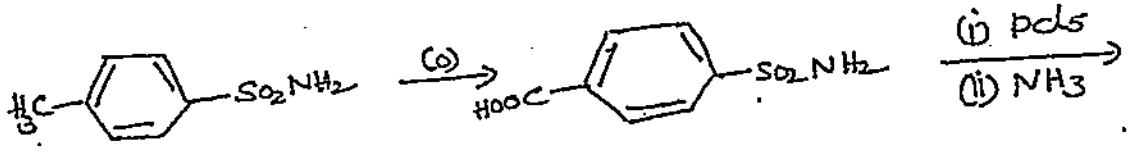
Sulphanilamide may be prepared by the chloro-sulphonation of chlorobenzene to get p-chloro benzene sulphonyl chloride which upon treatment with NH_4OH at 160°C in the presence of Cu_2O as a catalyst yields sulphanilamide.

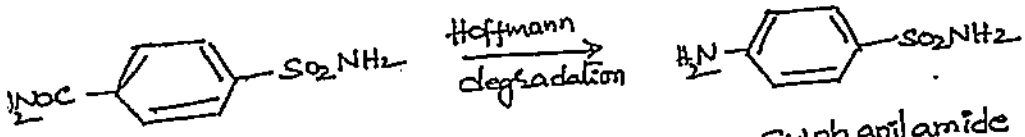




Sulphanilamide

Alternative Method:





Sulphanilamide

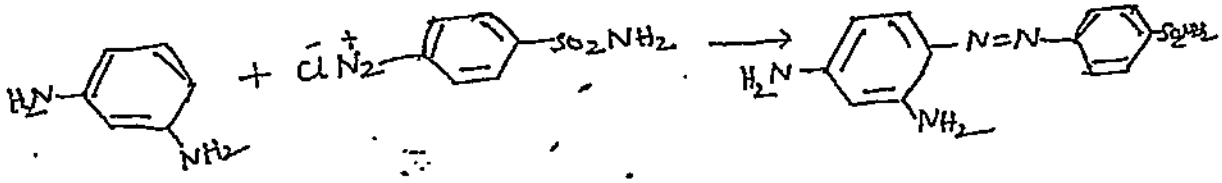
Therapeutic applications:-

(i) Sulphonilamide is important in the control of infections such as pneumococci, streptococci, meningococci and gonocci.

(ii) Sulphanilamide is cheapest of all the sulpha drugs but it is only seldom used now-a-days.

2. Prontosil (4-Sulphonamido-2',4'-diamino azobenzene):-

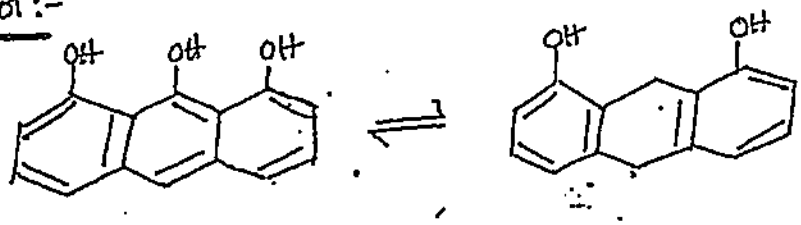
It was the first sulphonamide to be used in medicine. It is prepared by diazotising sulphanilamide and then coupling with m-phenylene diamine.



This drug breaks down in the body to sulphanilamide which acts against bacteria.

1 1,8 - dihydroxy anthranol : (1,8,9 - trihydroxy anthracene)

Dithranol :-

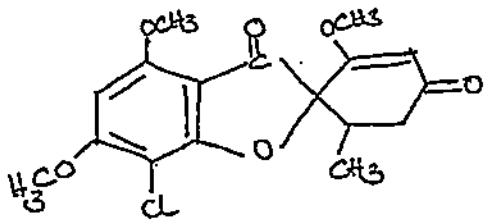


It is a phenolic compound dithranol (deoxyanthrand ; antralin) which finds use in the treatment of psoriasis. It acts as a fungicide and finds us in the treatment of ring worm infections and chronic dermatoses. Dithranol has been a mixture of 1,8,9 - anthracentriol and its tautomers. In the B.P., It is regarded as a mixture of 1,8 - dihydroxy 9-anthrone and its tautomers. It occurs as a yellowish - brown powder. It is practically insoluble in water. It is soluble in solution of alkale hydroxides. It is kept in well closed, light resistant containers.

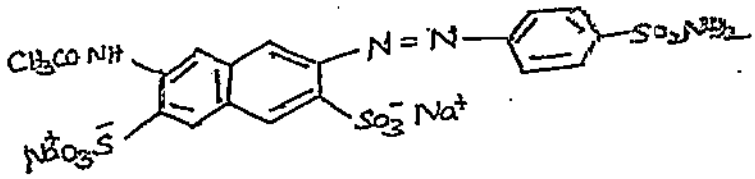
Therapeutic applications :-

(1) this drug is commonly used in the treatment of superficial mycosis. this drug is used for external mycosis infections and mainly fungistatic infections.

2. Griseofulvin :-

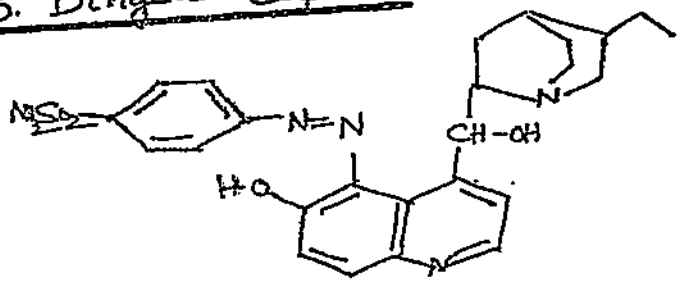


It is the naturally occuring antifungal agent. It is obtained from the cultures of penicillium griesofulvum. It is active against fungi



prontosil S

3. Dihydro Cuprine:



Therapeutic applications

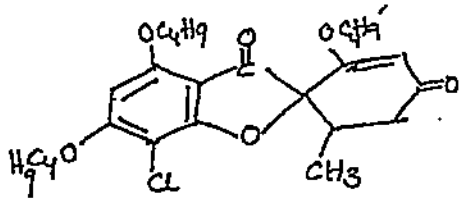
It has antibacterial activity. It has also some side effects and carcinogenic effect.

Antifungal Agents

Antifungal agents are used in the treatment of a variety of fungal infections. Some are active orally while others are mostly applied topically in the form of ointment, creams, lotions, suspensions.

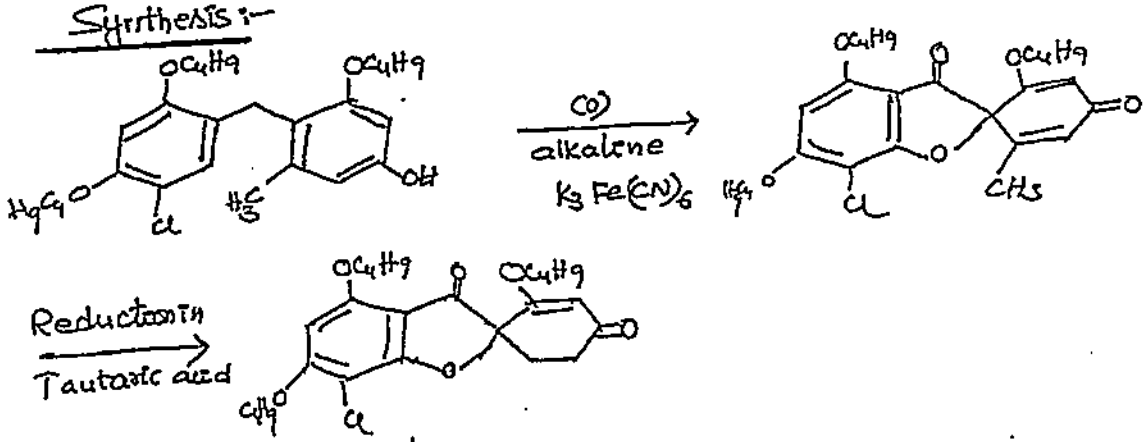
Antifungal agents have been generally used in the treatment of infections of the hair, mucous membranes, nail or skin by the fungi of the genera Candida (candidiasis), Epidermophyton, Microsporum and Trichophyton (tinea, ringworm).

The replacement of methoxy group with ethoxy group in griseofulvin, the activity remains same. But introducing propoxy (or) butoxy groups increases the activity by 20-50 times. The artificial drug which exhibits higher activity is butoxy substituted compound.



Artificial griseofulvin

Synthesis:-



Therapeutic applications:-

(i) It has specific action against ringworm infections of the body, nails and the scalp and athlete's foot. It is used orally.

The treatment has to be carried out for months because this antibiotic prevents the growth of the organism in new tissues, but the old tissue supports the fungi already present.

Therefore the treatment with griseofulvin has to be continued till the old tissues becomes completely exfoliated.

(ii) The side effects of this drug are gastric discomfort, diarrhea and head ache, urticaria and rash.

Antiamoebic Agents

Amoebic dysentry is a condition caused by action of the protozoan organism, Entamoeba histolytica with in the alimentary canal.

These causative organisms are usually acquired by ingesting (taking) food and/or water which are contaminated by faecal matter having amoebic cysts. It is these cysts which are resistant to freezing and partial drying and transmit infection from person to person.

The cyst may remain dormant (inactive) for a prolonged period. when it enters the organism, it hatches and liberates the trophozite. It can enter into the blood stream to affect remote regions like liver, lung, stomach, brain, skin etc.

Any chemotherapeutic (treatment of disease by chemicals) agent put forward for use in amoebic disorder is known as amoebicide.

An amoebicide must have the following characteristics.

(i) It should be able to kill E. histolytica with out leaving any protozoa so that the infection might not takeplace.

(ii) It should be able to kill the amoeba but not the patient.

The presently available amoebicides are divided into two groups.

(i) those effective against intestinal infection

(ii) those effective against extraintestinal infection.

From the chemical point of view the amoebicides may be classified as follows:

I Alkaloids of ipecac Ex:- Emetine.

II Quinoline derivatives

Ex: Chinofon, Resotren, Iodochlorohydroxyquin

III Organic arsenicals.

Ex: Carbarsone.

IV Antibiotics.

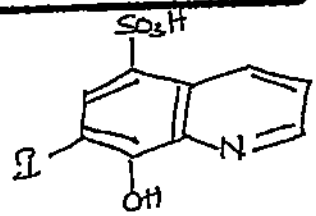
V Miscellaneous antiprotozoals.

Ex: Niradazole.

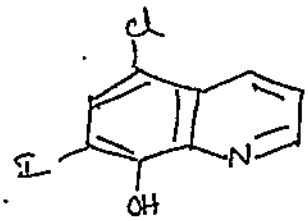
Halogenated Quinolines:-

Many iodinated quinoline derivatives such as Chiniofon, Iodochlorohydroxyquin and di-iodohydroxyquin (Resotren, Diodoquin) are known which are quite safe but effective amoebicidal compounds.

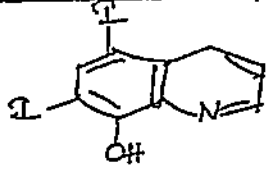
A. Chiniofon (or) Yatren:



B. Iodochlorohydroxyquin (or) Vioform:



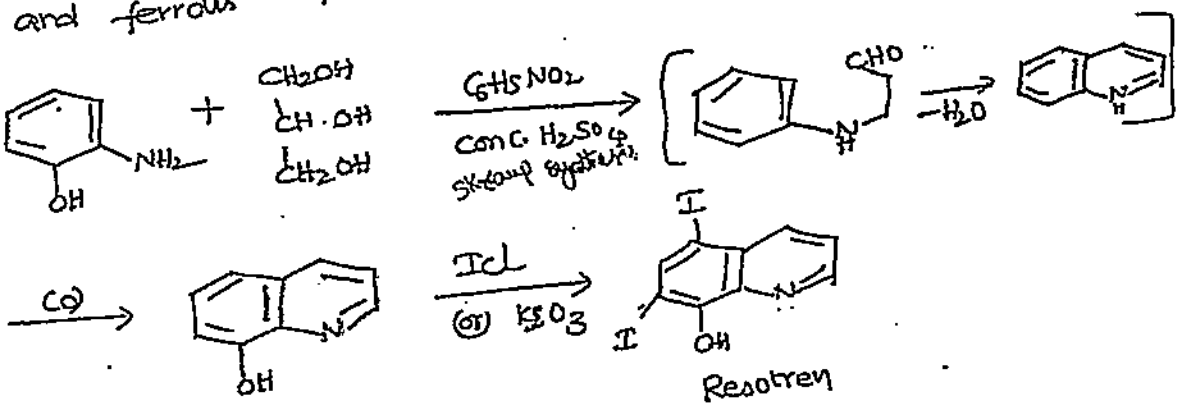
C. Resotren (or) di-iodohydroxyquin (or) Diiodoquin



Synthesis:-

It is prepared by treating potassium iodate (or) preferably iodine monochloride with 8-hydroxy quinoline when iodine enters the activated benzenoid ring in the o-and p- positions to the directing OH groups.

8-hydroxy quinoline is prepared by using Skraup synthesis which invdves heating of o-amino phenol with glycerol in the presence of conc. H_2SO_4, nitro benzene and ferrous sulphate.



Therapeutic applications:-

1. These 3 are useful for intestinal forms of the disease. The amoebicidal properties of these compounds may be probably due to the liberation of iodine because after taking these drugs blood-iodine level is increased.

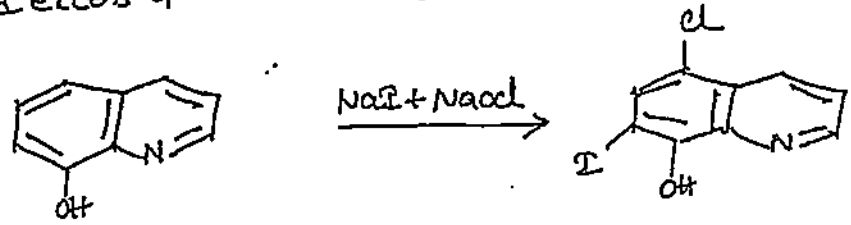
(ii) these drugs have been found to be ineffective in extraintestinal amoebiasis. However, these drugs acts as trichomon acids.

(iii) Among the halogenated quinolines, diodoquin is most widely used because it has less tendency to produce nausea and diarrhoea.

(iv) Diodoquin is used for the treatment of amoebic dysentry and the infeestation by trichomonas vaginitis.

Vioform Synthesis :-

It is an almost non-poisonous odourless substitute for iodoform. It is obtained by the iodination of 8-hydroxy quinoline with one mole of Sodium Iodide and excess of Sodium hypo chlorite.



8-hydroxy quinoline

Vioform.

Antiseptics

The term septic is derived from the Greek word septikos which means putrefyor rot. In medicine it indicates the state of being infected with pus forming microorganisms.

An antiseptic is a substance which prevents the growth of micro organisms as long as it remains in contact with them.

The ideal antiseptic would destroy bacteria, spores, fungi, viruses and other infective agents without harming the tissues of the host. However, most of them have a limited spectrum of activity and many show an adverse effect on tissues. Hence, the value of antiseptics is greately affected by their tissue toxicity

The use of an antiseptic in medicine is always local because of systematic toxicity. (Which these agents may produce. This prevents other routes of administration which depends on absorption by the body.

Types of antiseptics

The commonly used antiseptics may be classified under the following heads.

(i) Alcohols and aldehydes

Eg: Ethyl alcohol, isopropyl alcohol, formaldehyde etc.

(ii) Aromatic acids and ester:

Eg: Salicylic acid, Benzoic acid, Phenyl Salicylate (Salol)

(iii) Oxidising agents:

These act as antiseptics. Their disinfectant action is dependent on evolution of nascent oxygen.

Ex:- Hydrogen peroxide, potassium permanganate, ozone etc.

(iv) Surfactants:-

These poses hydrophobic as well as hydrophilic groups. These get accumulated in the interfaces and act on bacterial cell membrane that contain lipids.

Ex: $C_6H_5 \cdot CH_2 - \overset{CH_3}{\underset{CH_3}{N^{\oplus}}} - (CH_2)_{15} - CH_3 Cl^{\ominus}$

(v) Metal containing antiseptics:

Ex: Mercury

(vi) Halogens and halogenated Compounds

Ex: Vioform.

(VII) Dyes:

Ex: 9-amino acridine hydrochloride

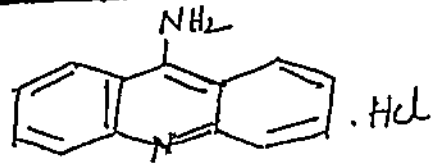
(VIII) phenols and its derivatives:

Ex: Dettol, chlorophene.

Disinfectants:-

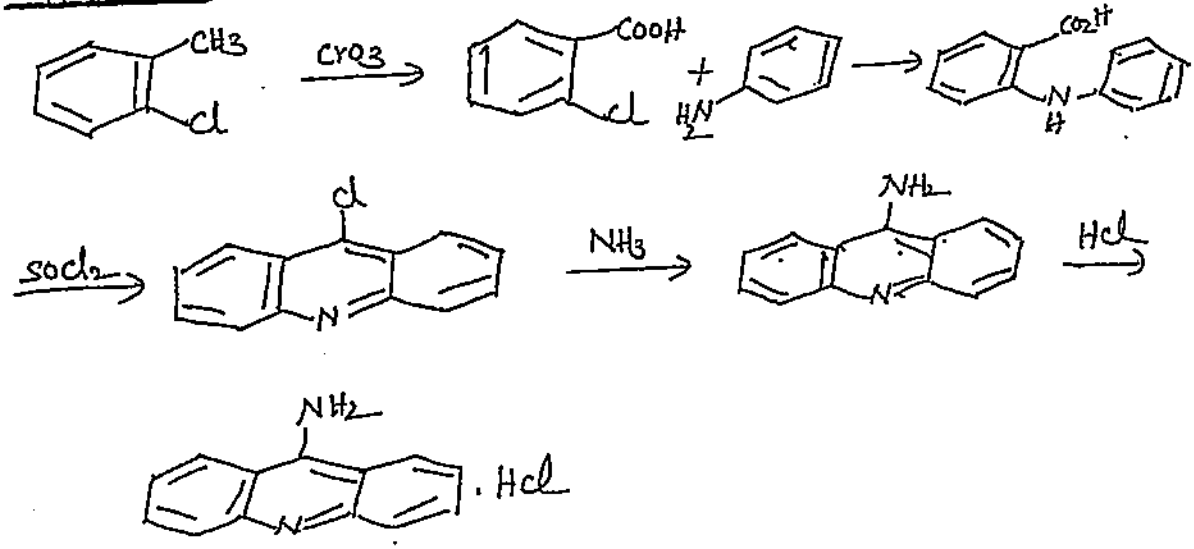
Disinfectant are bactericides which are applied to non living surfaces or inanimate surfaces. They rapidly produce irreversible lethal effects.

(1) Aminacrine hydrochloride:



It is chemically 9-amino acridine hydro chloride. It is a pale yellow crystalline powder, odourless bitter to taste. It is soluble in water, alcohol and glycerine.

Synthesis:-

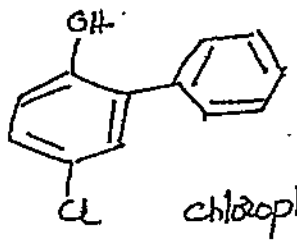


Therapeutic applications:-

(i) It finds use as general purpose antiseptic for topical applications in creams, ointment etc. or for dressing of wounds in 0.1 to 1% concentration.

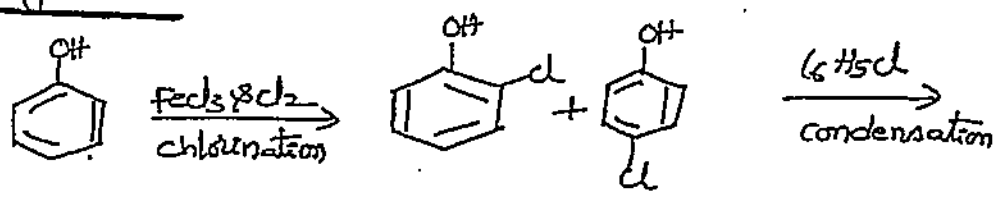
(ii) It finds use against many Gram-positive bacteria. Solutions have been used for the treatment of local infections of the ear, mouth or throat.

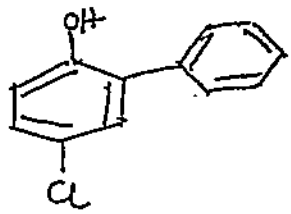
2. Chlorophene



chlorophene

Synthesis



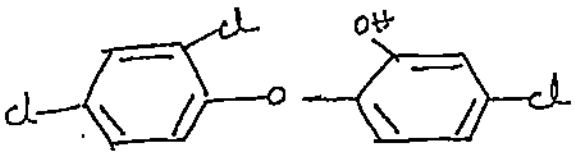


Therapeutic applications:-

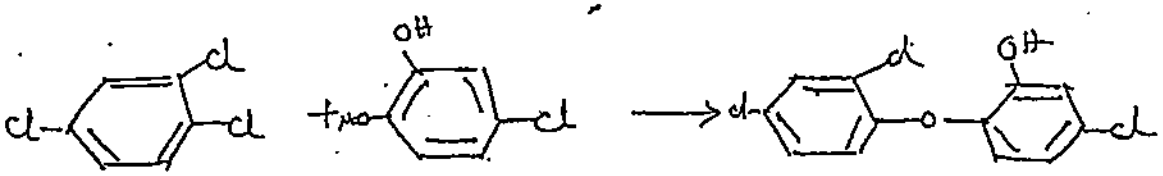
(i) chlorophene is active against viruses, protozoa and fungi.

(ii) chlorophene is used to clean the floor, walls, furniture in hospitals and in surgical rooms.

2,4,4' – trichloro -2'-hydroxy diphenyl ether:



Synthesis:–



1,2,4 - trichloro benzene

2-hydroxy 4-chloro sodium phenoxide

Therapeutic applications:–

(1) :- This compound is used for the control of Trypanosoma infections.