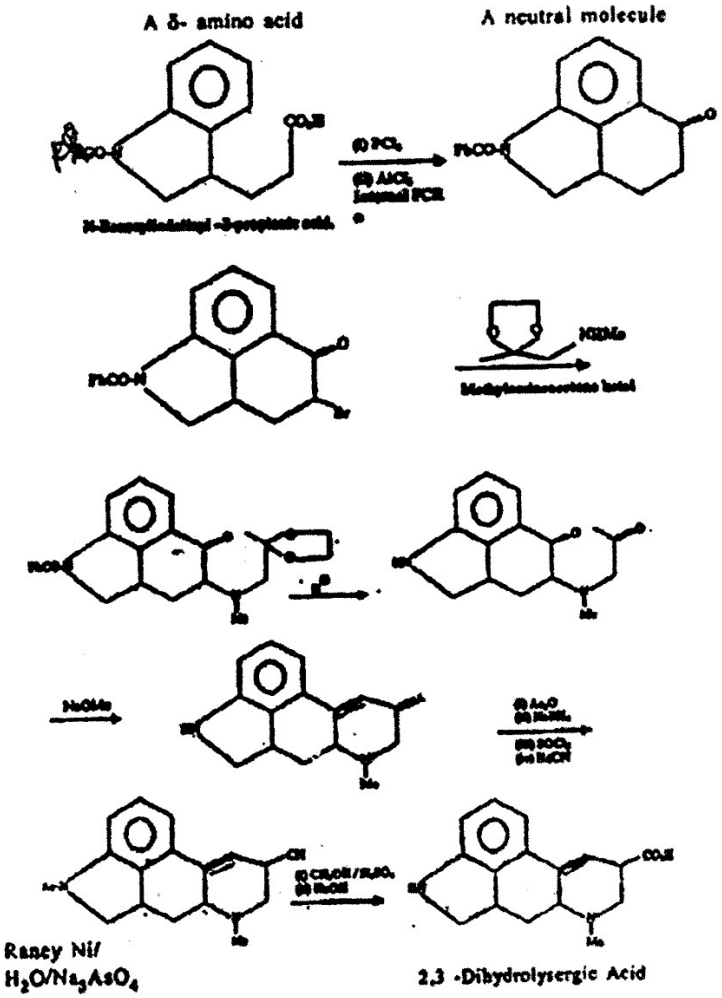
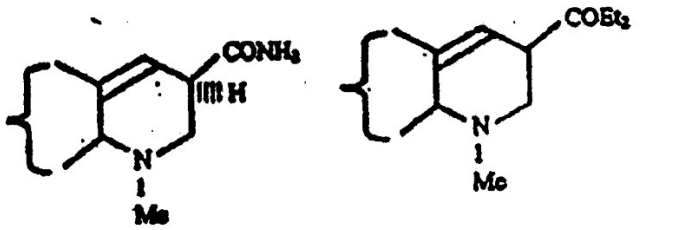


ACID

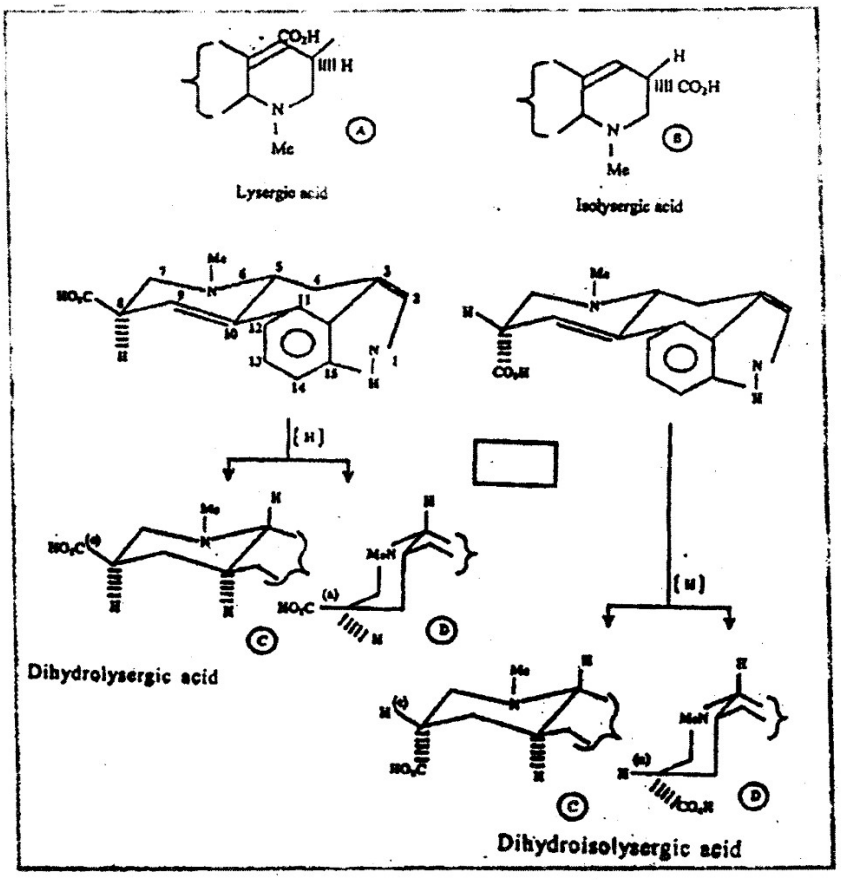
COMPOUNDS OF LYSERGIC ACID



Ergine **Lysergic acid diethylamide (LSD)**

STEREOCHEMISTRY

Catalytic hydrogenation products of Lysergic acid and isolysergic acid are indicated through structures C to F.



Hydrogenation of lysergic acid and it's alkaloids yielded only dihydrolysergic acid., viz. dihydrolsergic acid C. whereas the iso – series gave both dihydrosolysergic acids (E) & (F) with greater proportion of the latter.

The formation of only one stercoisomer from the hydrogenation of lysergic acid may be explained by assuming that the carboxyl group at C_8 and the hydrogen atom at C_5 are on the same side of the molecule in lysergic acid, thereby shielding the double bond from 'top - side' attack'. The addition of hydrogen has to take place, naturally and necessarily from the bottom face, giving the trans – product.

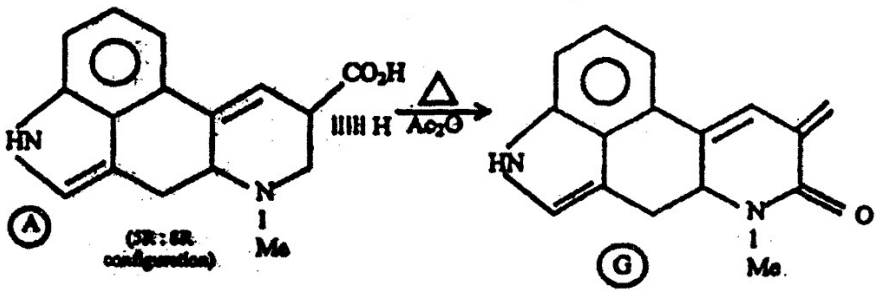
Rapid formation of dihydroisolysergic acid (F) indicates cis-configuration in the iso – series.

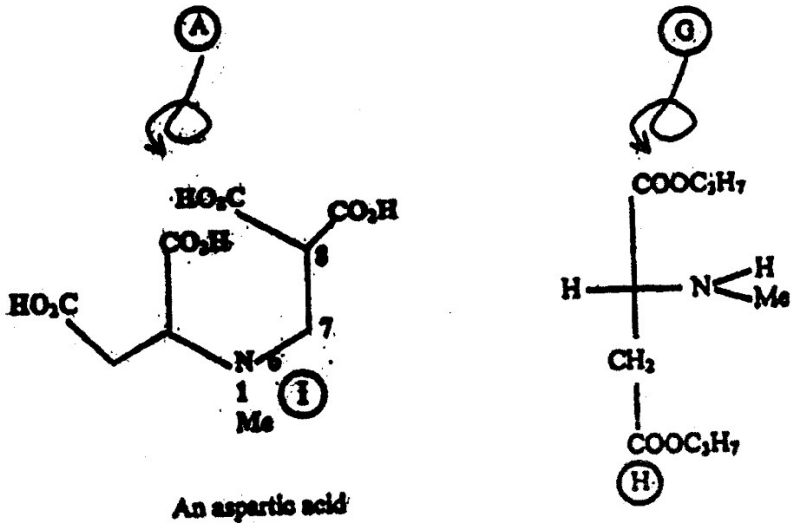
Under alkaline conditions, dihydroisolysergic acid (E) was irreversibly rearranged to from ©. The reverse is not true for the (F) – series. From this, it may be infrerred that © and (F) contain the carboxyl group in equatorial position.

The above discussions point only the relative spatial arrangement at the various asymmetric centers of isomeric lysergic and dihydrolysergic acids. The absolute configuration was deduced from ORD measurements. It was concluded from ORD studies, that the configuration of hydrogen at C_5 is 'beta' in natural lysergic acid.

This was confirmed by oxidative degradation of the d – lysergic acid lactam (G) to a D – aspartic acid derivative (H). Degradatrion with d – lysergic acid afforded an aspartic

acid (I), dialkylated at the nitrogen that was to racemize quickly. (aspartic acid = aminosuccinic acid).





An aspartic acid

The compound (H) obtained from (A) through a series of reactions was found to be identical with an authentic sample of D-(+)-N- methylaspartic acid di-n-propyl ester.

Thus natural lysergic acid has the (5R : 8R) configuration depicted by the formula (A).

* * * *

UNIT – III
CHEMOTHERAPY

Introduction :

Enrich (1909) introduced the term "Chemotherapy". The term chemotherapy is used in the sense of the treatment of diseases due to bacterial invasion by chemical compounds which destroy the micro organism without affecting, the host tissues.

There are many terms associated with chemotherapy (i) disinfectants, (ii) drugs (iii) chemotherapeutic agents (anti – bioties)

Disinfectants:

Compounds like formaldehyde, phenol, iodine etc., are active in destroying bacteria. These compounds are applied externally and are found to destroy tissues. Such compounds are thus not called, therapeutic agents, but disinfectants.

Drugs:

Compounds which exert various physiological effects of therapeutic values are called as drugs.

There methods are adopted in developing a drug towards a particular disease.

(i) Trial and error method. Here all kinds of compounds including natural and synthetic are tried and an effective drug developed towards a particular disease.

(ii) The cell system of the disease causing becateria is studied. Then compounds which could act on them is synthesized.

(iii) Starting from a compound with required activity and by systematically changing the structure of it to improve its quality, is the third method. The last one is the most prevalent one in pharmacology e.g. sulpha durgs.

ANTIBIOTICS

Antibiotics are chemical substances produced by microorganisms, which may inhibit the growth of other microorganisms or even destroy them.

Classification of Antibiotics

Antibiotics are classified in a number of ways. They are,

1. First classification: They are broadly divided into two types

(a) Broad spectrum antibiotics:

This is based on the curative effect of the antibiotics against several ailments. Examples of this category are, penicillin, chloramphenicol, tetracycline etc.,

(b) Narrow spectrum antibiotics:

These are highly specific in their action. Examples are bacitracin, nystatin etc.

2. Second classification:

This classification rests upon the type of bacteria (Gram positive or gram negative) the antibiotic can destroy. This is based on the Chritian Gram's Staining method.

Grams staining method.

In this method the fixed bacterial smear is treated with, first a solution of crystal violet (a dye), then with a solution of iodine. The smear is then washed with alcohol. The becteria which retain the colour of the crystal violet and appear deep violet in colour are known as Gram – Positive bacteria (example, staphylococcus, streptococcus). On the other hand, becteria which lose the violet colour and get counter stained by safranin and appear red in colour are called Gram – nega ve becteria. (example: Coil and typhoid bacillus).

3. Third classification:

This classification of antibiotics is based on their chemical structures. Though they have greatvariations in their chemistries, they have similarities in their structure. It has been suggested that such antibioties are produced through similar mechanisms in different organisms and they also show similar therapeutic actions.

Examples are:

(a) Penicillins: They are derived from amino acids. Examples, penicillins, cephalosporins etc.,

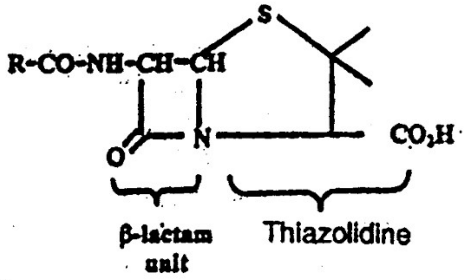
(b) Chloramphenicol and synthetic analogues.

(c) Tetracyclins: These have a four six – membered fused ring system. Examples are tetracycline (achromycin) aureomycin, terramycin etc.,

PENICILLINS

Introduction:

Penicillin is the name given to the mixture of natural compounds which have molecular formula $C_9H_{11}N_2O_4SR$ and differ only in the nature of R. The general structure of penicillin is;



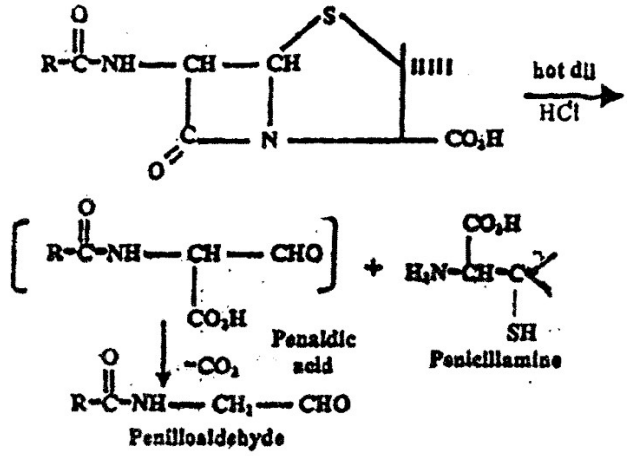
If R = pent - 2 - enyl = penicillin (or) F
Benzyl = penicillin II (or) G
p - Hydroxybenzyl = penicillin III (or) X
n - Heptyl = penicilline IV (or) K
Phenoxymethyl = penicillin V

Structure Elucidation: (For convenience the reactions are formulated with the known structure).

1. From element analysis and molecular weight determination the molecular formula of penicillin has been found to the $C_9H_{11}N_2O_4SR$.

2. Formation of monsodio salts with bicarbonatic indicate the presence of one carboxyl group. It has a pKa value of 3. it is stable at $p^H 6 \geq 7$. penicillins are lable at lower p^H due to the cleavage of the β - lactam ring.
3. From usual tests, it has been shown that penicillin do not possess a free amino (or) thiol group.
4. When penicillins are hydrolysed by hot dil. Inorganic acids, equimolecular amounts of penicilliamine and penilloaldehyde are formed. During the formation of these two products one carbon is lost in the form of carbon – di- dioxde.

Fig II

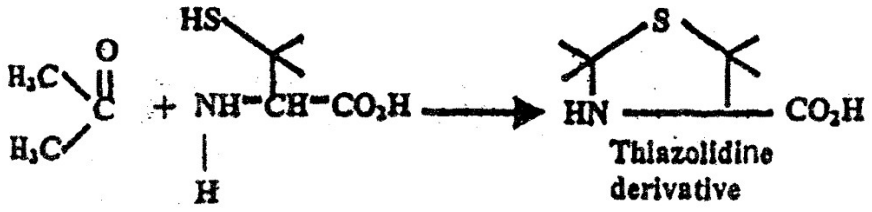


5. So if we know the structure of penicillamine and penilloaldeyde, we can arrive at the structure of pencillin.

Structure of Penicillamine:

1. Indigo colour reaction with ferric chloride suggests that it is a disubstituted cysteine a – amino. (This is a characteristic test for a amino acids (cysteins) containing sulphur). B – mercapto – b, dimethylpropionic acid.
2. Van Slyke determination indicates the presence of one amino group (eudiometric method)
3. From kuh-Roh estimation it is found to have a gen dimethyl group.
4. Penicillamine readily condenses with acetone giving a thiazolidine derivative.

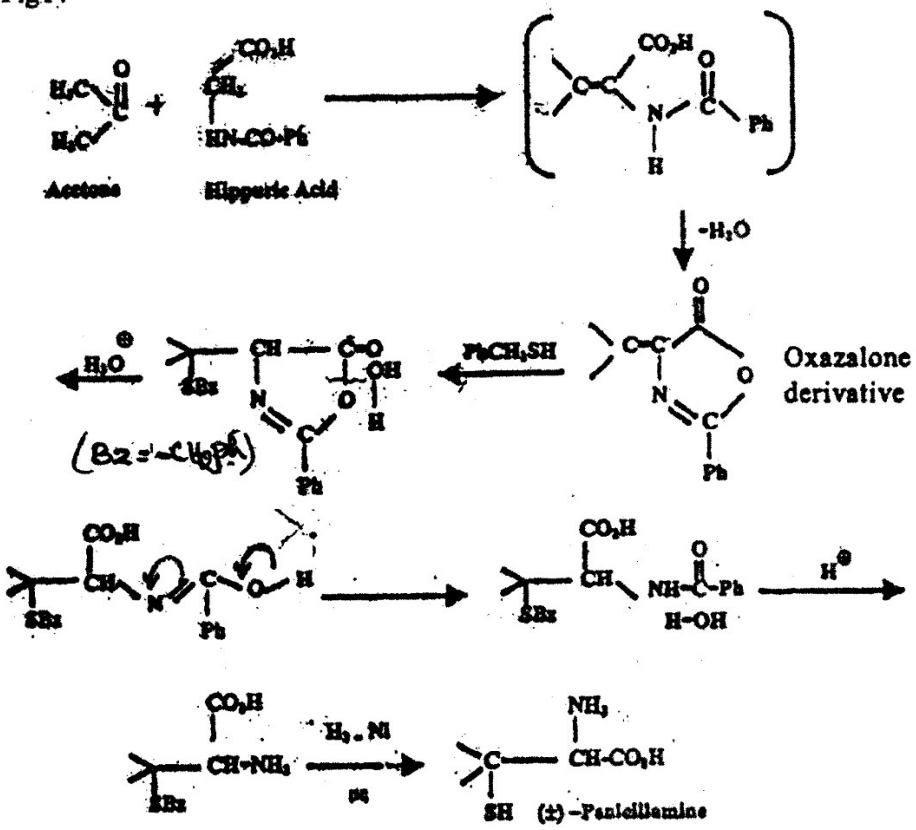
Fi



The formation of this derivation shown that the thiol and amino group are on adjuacent carbon atoms.

Synthesis : Finally it's structure has been confirmed by its synthesis.

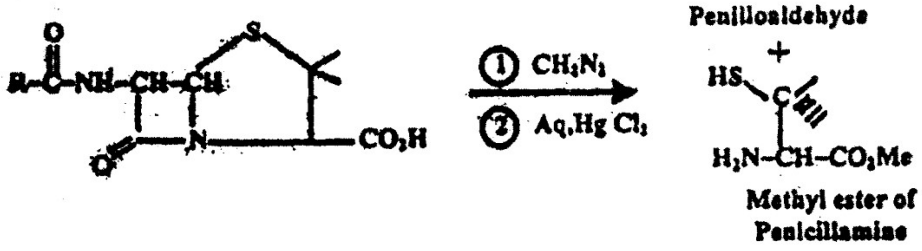
Fig IV



The racemic amine was resolved, as its formyl derivative, using brucine. D – penicillamine is obtained by the hydrolysis of the formyl group. This is found to be identical with the natural penicillamine by mixed m.pt. depression.

When penicillin is treated with diazomethane, it is converted into its methyl ester. The latter on hydrolysis with aqueous metcuric chloride solution gives the methyl ester of penicilamine and penilloaldehyde. Thus the carboxyl group in penicilamine is that in penicillin itself.

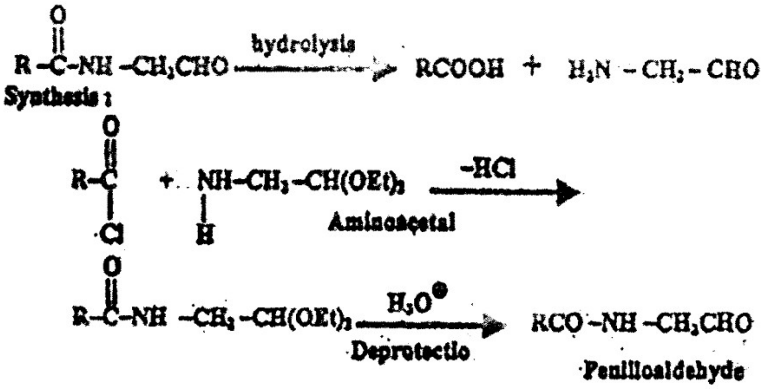
Fig V



Structure of Penilloaldehyde:

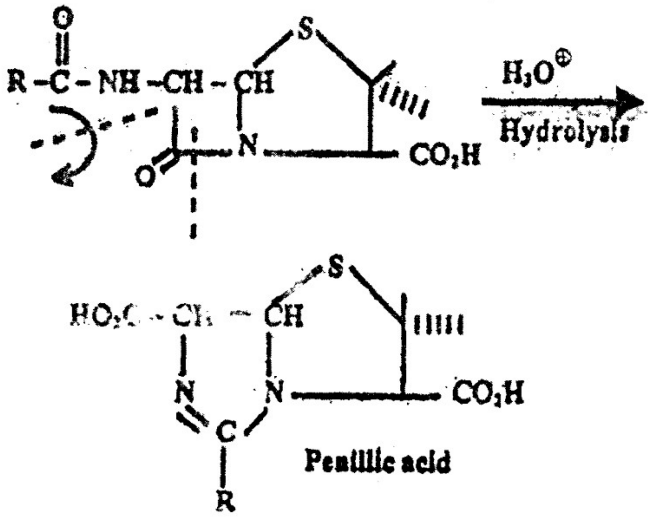
One hydrolysis it gives a substituted monobasic acid and aminoacetaldehyde. So penilloadldehyde is an acyl derivative of aminoacetaldehyde.

Fig : VI



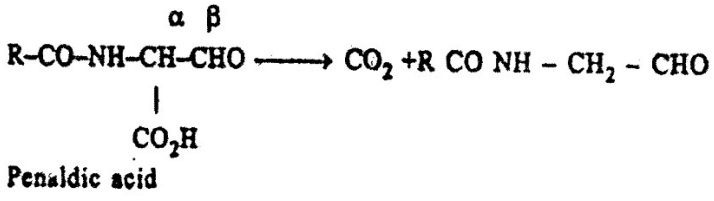
When penicillin is treated with moderately concentreated acid solution, it undergoes a rearrangement to give penillic acid.

Fig : VII



As pointed out earlier, penicillin gives on acid hydrolysis, pencillamine, penilloadldehde and carbon dioxide. The formation of carbon dioxide is believed to take place by the formation of an unstable acid, probably a β - keto acid. So as possible explanation is that penilloaldehyde – acid (penaldic acid) is formed as an intermediate in the hydrolysis of penicllin.

Fig. VIII

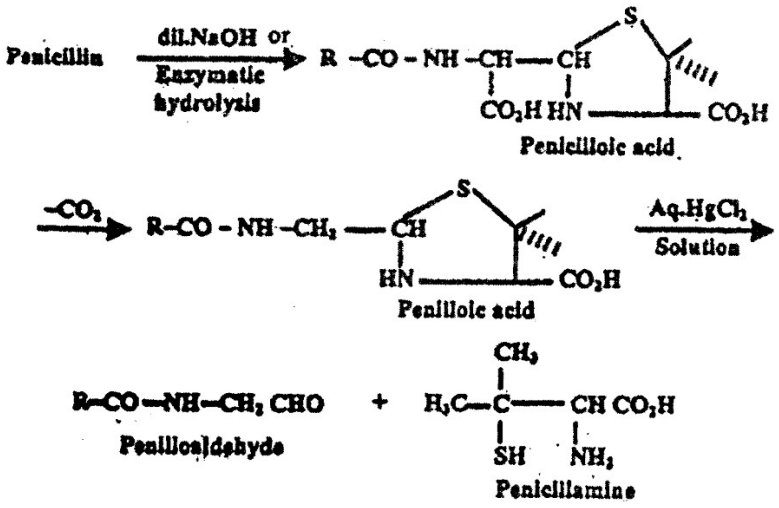


Now the problem is to identify, how these two fragments are joined in penicillin. Let us look at the following two degradations.

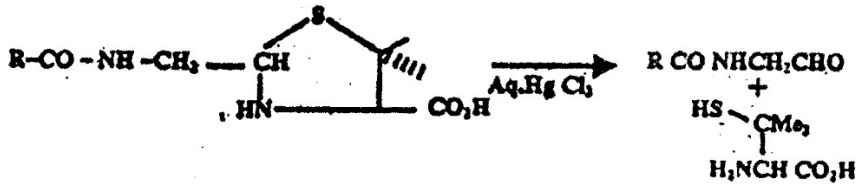
Degradation:

Pencillin on dil. Sodium hydroxide hydrolysis (or) enzymatic (pencilase) hydrolysis gives penicilloic acid, a dicarboxylic acid. Thus readily looses a molecule of carbon dioxide to form penilloic acid. This suggests the presence of a carboxyl group in the β - position with respect to the negative group. Penilloic acid, on hydrolysis with aq./ mercuric chloride, gives penicillamine and penilloaldehyde.

Fig IX.

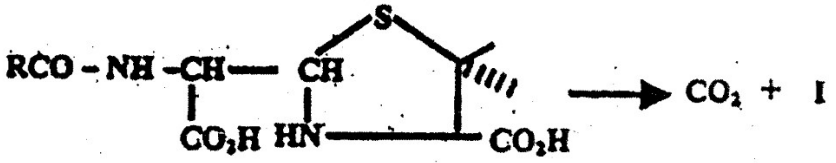


This hydrolysis is characteristic of compounds containing a thiazolidine ring. Thus penilloic acid could be (I), since this structure would give the required products.



(I)

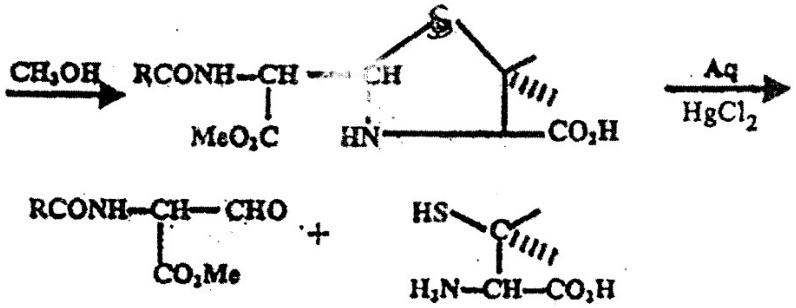
Hence, if structure (I) is penilloic acid, then penicilloic acid would be structure (II).



(II)

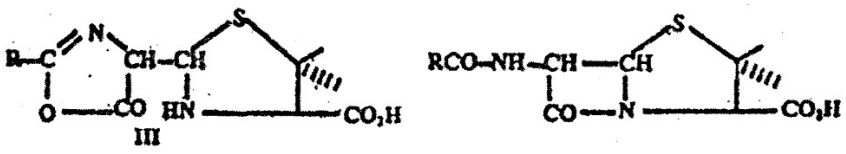
Structure (11) is supported by the fact that the treatment of penicillin with methanol give methyl penicilloate, which on hydrolysis with aq.mercuric chloride, gives methyl penaldate and penicillamine.

Fig : XII



On the basis of the foregoing evidence, two structures are possible for penicillin viz. (III) & (IV)

Fig : XIII



Oxazolone structure **β-Lactam structure**

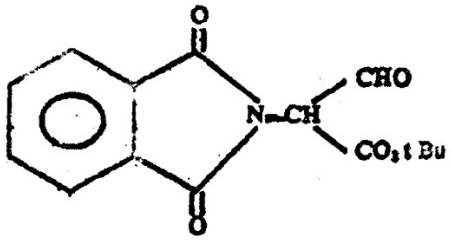
Since penicillin under goes molecular rearrangements when treated with dil. Acids, it is difficult to assign the correct structure for penicillin.

Finally, the blactam structure has been assigned as the correct structure fro penicillin on the basis of IR and X – ray diffiaction studies. This structure for penicillin has been confirmed by Sheedhan's systhesis.

SYNTHESIS:

The starting material for this synthesis is t – butylphthalimido malonaldehydate.

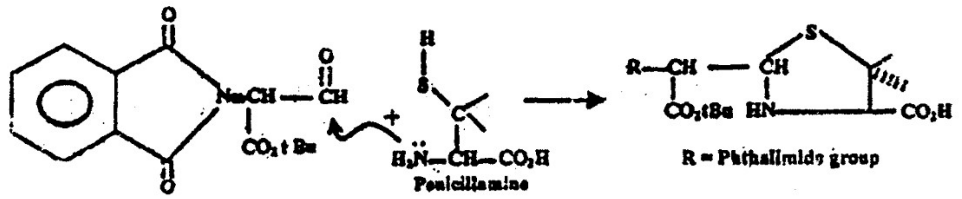
Fig : XIV

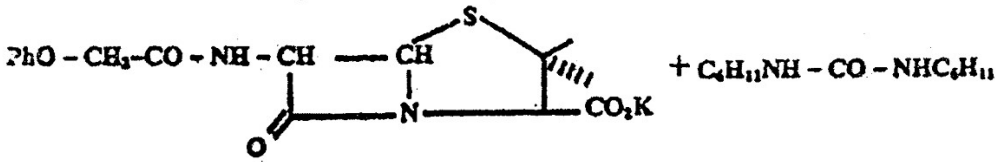


What is special about it? The amino group is protected in the form of phthalimido group to prevent self condensation, with the aldehydic group of a second molecule. The carboxyl group is a β - carbonyl compound, which are unstable. So to withstand the rigorous conditions of the synthesis the carboxyl group is protected as its ester. Why a tertiary butyl group, of all the alkyl groups? T- Butyl group is a labile alkyl group. So can be removed easily at the desired stage.

Note : All the reactions in this synthesis are carried out at room temperature.

Fig : XV.





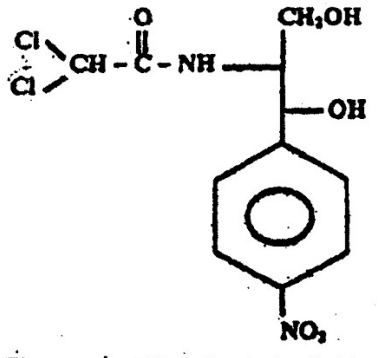
Penicillin – IV (as its potassium salt)

CHLORAMPHENICOL (OR) CHLOROMYCETIN

Introduction:

It is a broad spectrum antibiotic and is the first one to be produced synthetically on a commercial basis. Excessive use of this antibiotic may cause aplastic anaemia.

Fig : XVI

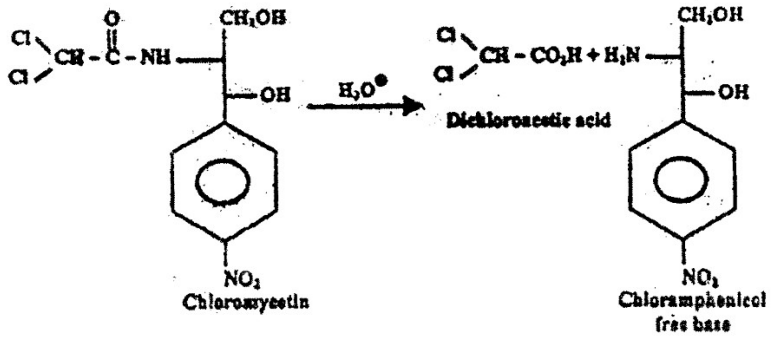


D (–) Threo -1-p-Nitrophenyl -2- dichloroacetamindo - propan – 1,3 - diol

Structure Elucidation:

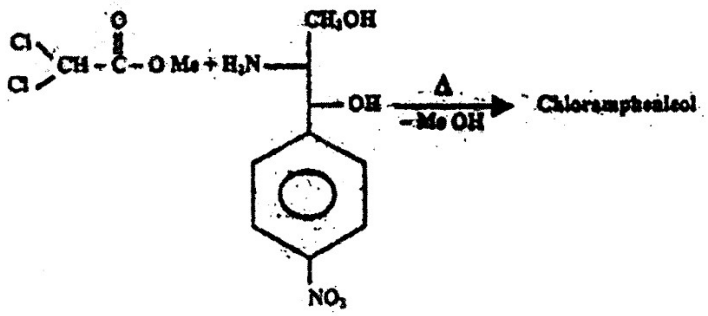
(i) From analytical data the molecular formula of the compound is found to be $C_{11}H_{13}O_5N_2Cl_2$.

(ii) Acid hydrolysis of chloramphenicol gives dichloroaceticacid and an optically active base, $C_9H_{12}O_4N_2$ called "Chloramphenicol free base".



(iii) The antibiotic doesn't answer for van Slyke determination. However the hydrolysed product shows a positive reaction for van Slyke determination. That means the amino group is free and primary in the hydrolytic product and not in the antibiotic. This clearly established that the antibiotic is an amide and not an ester.

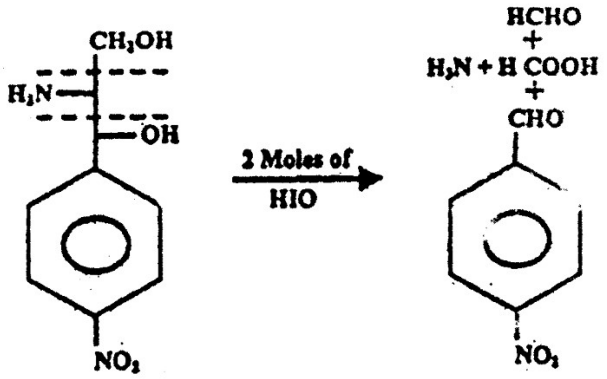
(iv) A partial synthesis of this could be effected by treating the "free base" with the methyl ester of dichloroacetic acid (or) methyldichloroacetate. This means the acid hydrolysis of this antibiotic is very simple and direct without involving any molecular rearrangement (or) side reaction.



(v) Acetylation of the antibiotic shows the presence of two hydroxyl groups. But only one of them could be easily acetylated indicating that one of the hydroxyl is primarly and the other secondary. (The second one requires pyridine as catalyst for acetylation)

(vi) The structure of the "free base" has been clearly revealed by periodicacid oxidation of it. It produces p-nitrobenzaldehyde, formic acid, ammonia and formaldehyde.

Fig : XIX

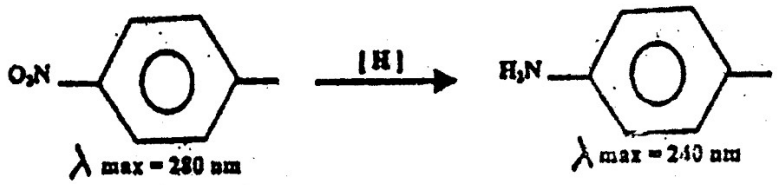


(vii) The antibiotic itself is unreactive towards periodic acid. This combined with the cleavage that can be effected on the product of acid hydrolysis tells us that the hydroxyl groups must be 1,3 – position but not vicinal.

(viii) Knowing that one of the hydroxyl group is primary and the group are at 1,3 – positions, it is clear that the amide substitution should be at C2.

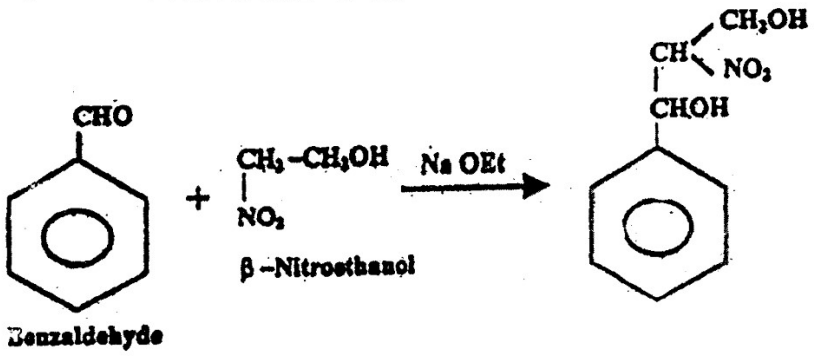
(ix) Hydrogenation of the "alkali degradation product" of the antibiotic gave an aniline derivative identified by diazotisability and λ max at 280 mm indicates the presence of p – nitrophenyl group.

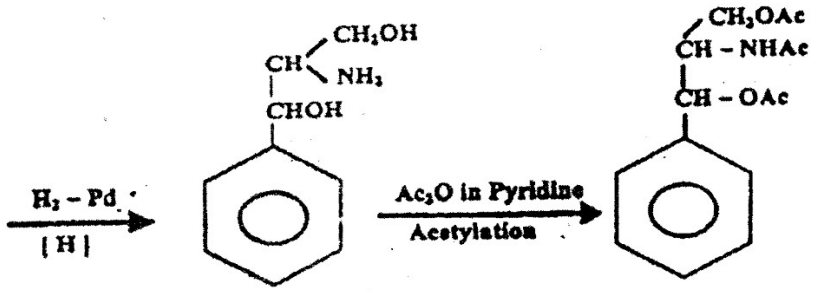
Fig : XX

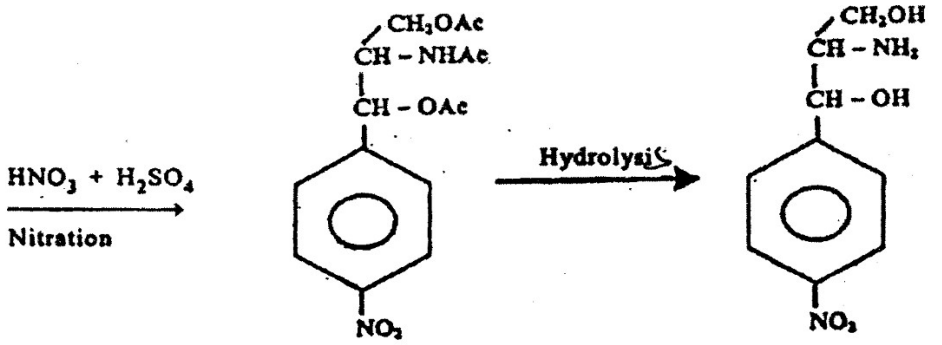


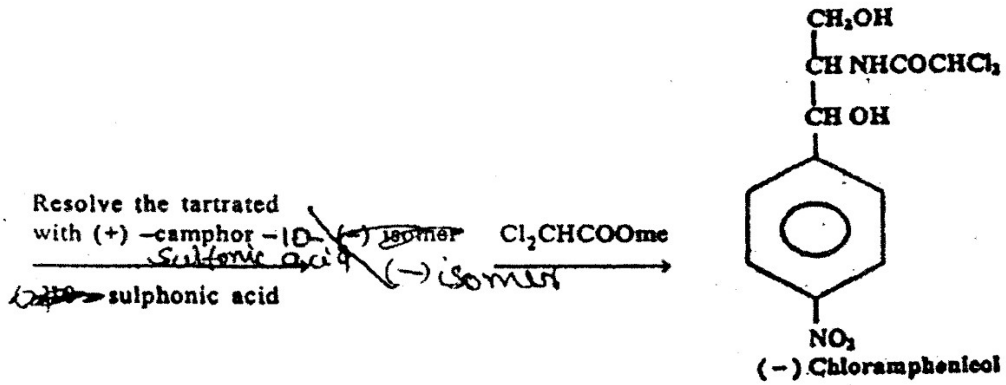
(x) It was further confirmed by the reduction of chloramaphenicol with tin and - hydrochloric acid followed by diazotisation and then coupling with β – naphthol to give an orange red precipitate. Finally its structure has been confirmed by the synthesis of chloramphenicol.

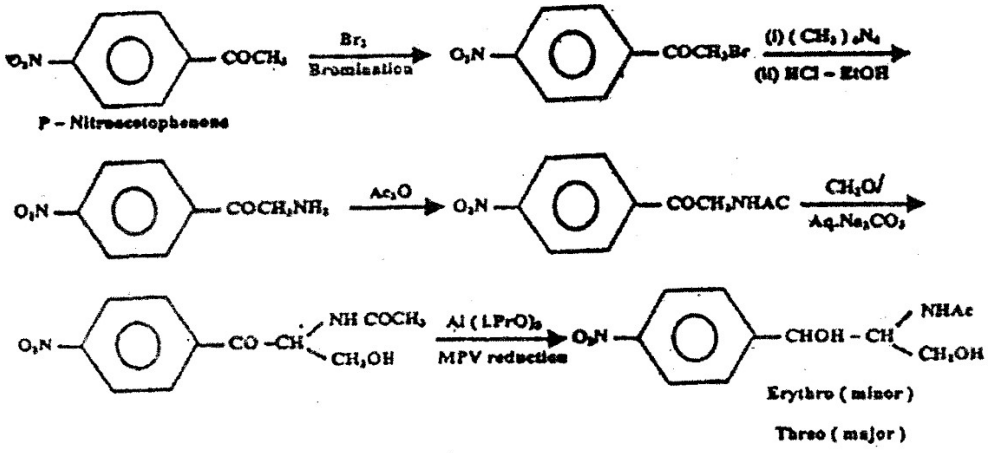
SYNTHESIS: (CONTROULIS ETAL – 1949)

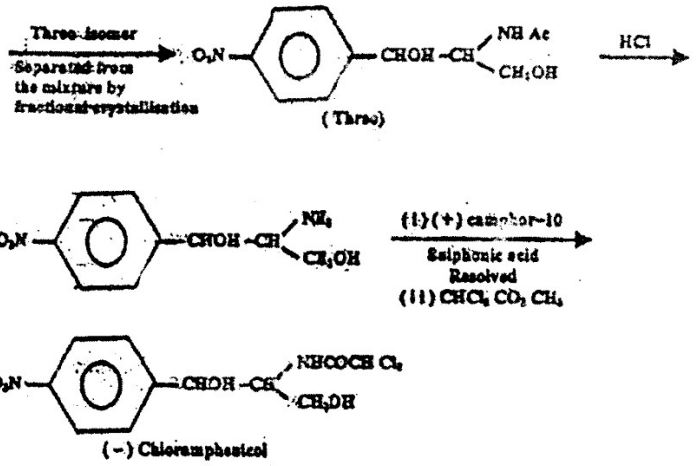



CH₂OH
CH
NH₂
CHOH
H₂ – Pd
[H]
Ac₂O in Pyridine
Acetylation
CH₂OAc
CH – NHAc
CH – OAc


CH₂OAc
CH – NHAc
CH – OAc
HNO₃ + H₂SO₄
Nitration
NO₂
Hydrolysis
CH₂OH
CH – NH₂
CH – OH
NO₂


Resolve the tartrated
with (+) –camphor – 10 – sulphonic acid
(–) isomer
Cl₂CHCOOme
CH₂OH
CH NHCOCHCl₂
CH OH
NO₂
(–) Chloramphenicol


O₂N
COCH₃
P – Nitroacetophenone
Br₂
Bromination
COCH₂Br
(i) (CH₃)₆N₄
(ii) HCl – EtOH
COCH₂NH₂
Ac₂O
COCH₂NHAC
CH₂O/
Aq.Na₂CO₃
CO –CH
NH COCH₃
CH₂OH
Al (iPrO)₃
MPV reduction
CHOH – CH
NHAc
CH₂OH
Erythro (minor)
Threo (major)



CEPHALOSPORIN – C

Introduction:

This antibiotic was isolated by Abraham etal from crude cephalosporin N (an antibiotic produced by a species of cephalosporium). Cephalosporin – C is found to have antibacterial activity and is much more stable to acid, cephalosporin N. this is resistant to hydrolysis by the enzyme penicillase; unlike the simple penicillin.

Structure Elucidation:

Analytical data indicate the formula of cephalosporin – C to be $C_{16}H_{21}N_3O_8S$.

The presence of an α - amino acid is inferred from positive ninhydrin reaction. Further more, cephalosporin-C, behaved like an aminodicarboxylic acid on electromeric titration; there ionisable group were found with pKa values <2.6, 3.1 and 9.8 respectively. The IR band at 1783 Cm^{-1} in IR).

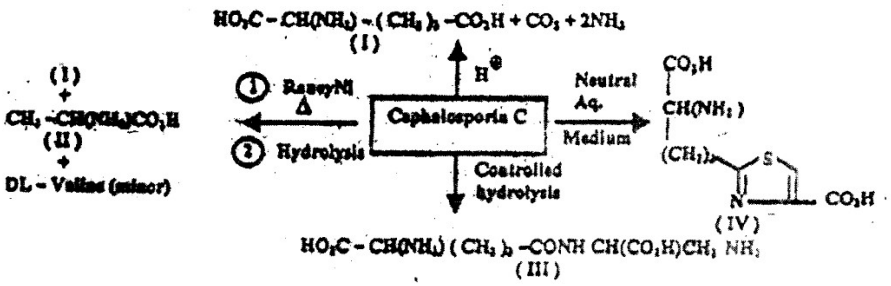
The structure of cephalosporin C is revealed through a number of hydrolytic studies.

a.) Acid hydrolysis of cephalosporin C gives one molecule of carbon dioxide, one molecule of D - α amino – adipic and (1) and two molecules of ammonia.

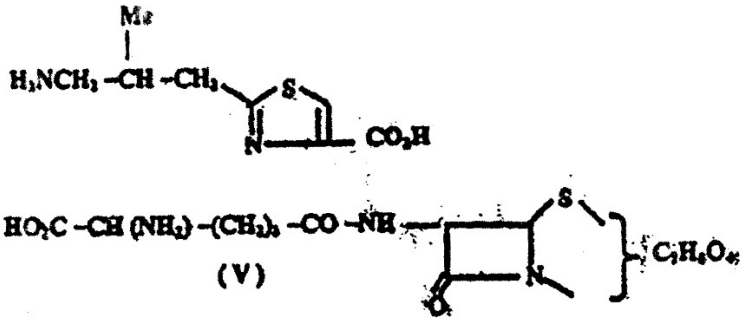
b.) When the antibiotic is heated with Raney nickel (hydrogenolysis) and the product hydrolysed L – alaine (II) and some DL – Valine are obtained along with compound (I).

c.) Controlled hydrolysis of the antibiotic gives a dipeptide (III) together with (I) and α, β - diaminopropionic acid.

d.) Hydrolysis of the antibiotic in neutral aqueous medium at 37°C gives D – 2 (4-amino 4-carboxybut) thiazole – 4 carboxylic acid (IV).



Electrometric titration of (V) indicated the presence of a basic group (pKa 9.9) and two acide groups (pKa – 2.6 and 4.0 respectively). The UV spectrum of (IV) (λ max 237mm (H_2O) and 233 (NHCl) is found to be similar to that of -2 (1 amino -2 methyl-propyl) thiazole-4 carboxylic acid. This along with other evidences led to the suggestion of structure (IV). Based on this and IR data the partial structure for the antibiotic has been given as,



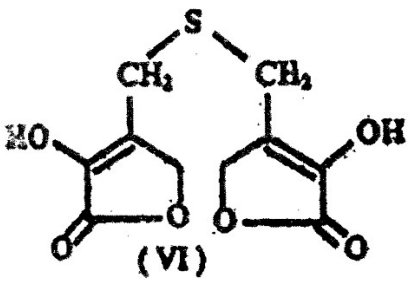
(V)

Cephalosporin C on hydrolysis with sulphuric acid gives one molecule of acetic acid. Bands at 1773 and 1031 cm^{-1} are observed in the IR spectrum of the antibiotic. The former band suggests the presence of an acetoxyl group. Hence the latter may be attributed to O – C (stretch) in the grouping CH3 – CO – O – C; an acetoxyl group is present in the fragment $C_7H_8O_4$, this leave only five carbon atoms in the fragment (structure V).

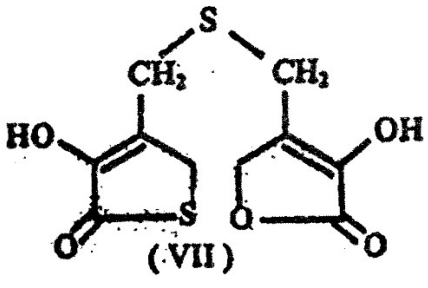
Now the antibiotic on hydrogenolysis with Raney nickel gives among other products, DL – Valine and α-oxo-isovaleric acid. But penicillin under the same conditions gave D – valine (from the penicillamine fragment by removal of the sulphur atom). Furthermore, Cephalosporin C, unlike the penicillins, does not give penicillamine on hydrolysis.

Thus the structures of the fragment attached to the β - lactum ring in cephalosporin C and the penicillins are quite different. This is evident from the absence of a signal at 2.10 δ in the NMR spectrum of cephalosporin C. (This signal correspondsto a gemdimethyl group). A sharp peack observed at 2.6δ is attributed to one methyl group, and may be assigned to the methyl in an acetoxyl group. The signal at 5.7 is assigned to a CH-CH group. (This signal is observed for benzylpenicilline also).

Cephalosporin C on hydrolysis with 1.25 N hydrochloric acid at 100° C gave two lactones which contained sulphur. Analysis of their physical and chemical properties led to the conclusion that these lactones have the following structures.



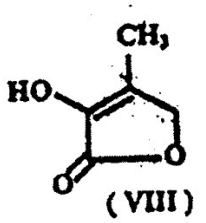
(VI)



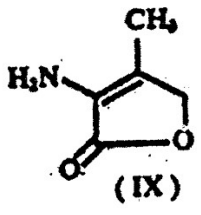
(VII)

Compound (VI) is called α - tetronic acid and the latter is the corresponding thiolactone. Both (VI) & (VII) give - methyl-α-tetronic acid (VIII), on treatment with Raney nickel. The above two lactones may be the product of fivecarbon fragments from two molecules of cephalosporin C.

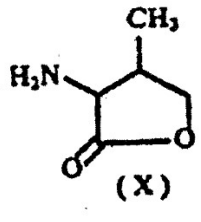
Cephalosporin C give C gives Cephalosporin Cc, (λ max 257 mm) a lactone, when dissolved in 0.1 N HCL at room temperature. In its formation an O- acetyl group is lost. Cephalosporin Cc on treatment with Raney nickel gives α amino - β methyl - butenolide (IX). The latter on hydrogenation (Pt-PtO) give γ - hydroxyvaline lactone. (X).



(VIII)

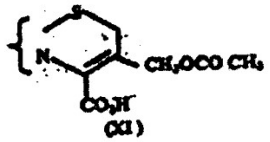


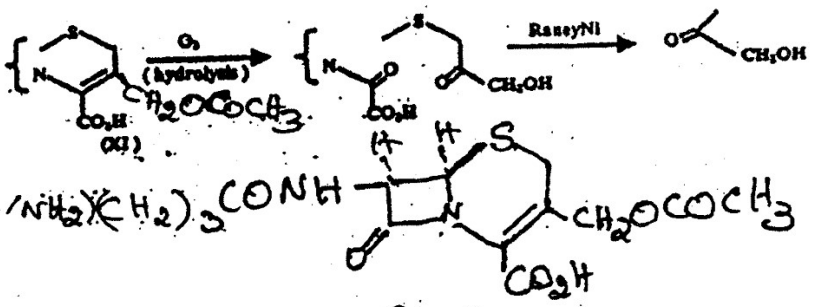
(IX)



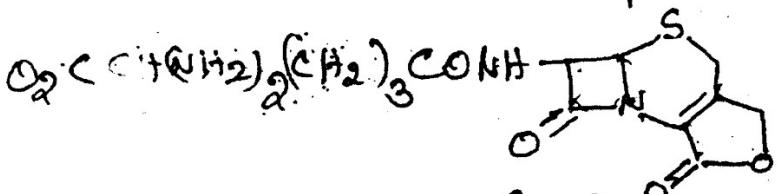
(X)

Based on the formation of (VI), (VIII) and (IX), it concluded that the antibiotic may contain the following grouping. The position of double bond in (IX) is consistant with the isolation of the 2,4 dinitrophenyl – hydrazone of hydroxyacetone. The latter is obtained by the ozonolysis of antibiotic, followed by treatment with Reney nickel.





(XII) Cephalosphorin C



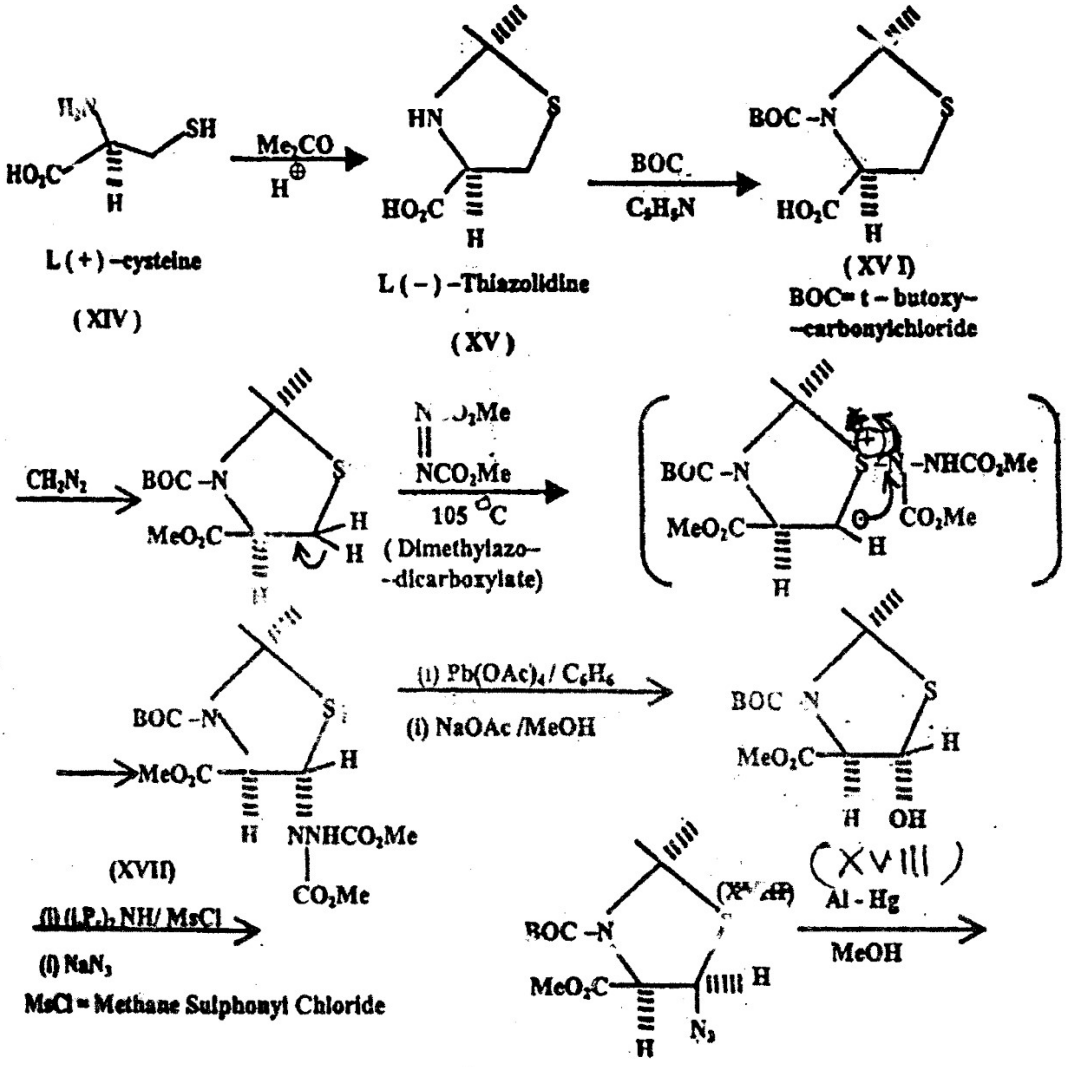
(XIII) Cephalosporin Cc

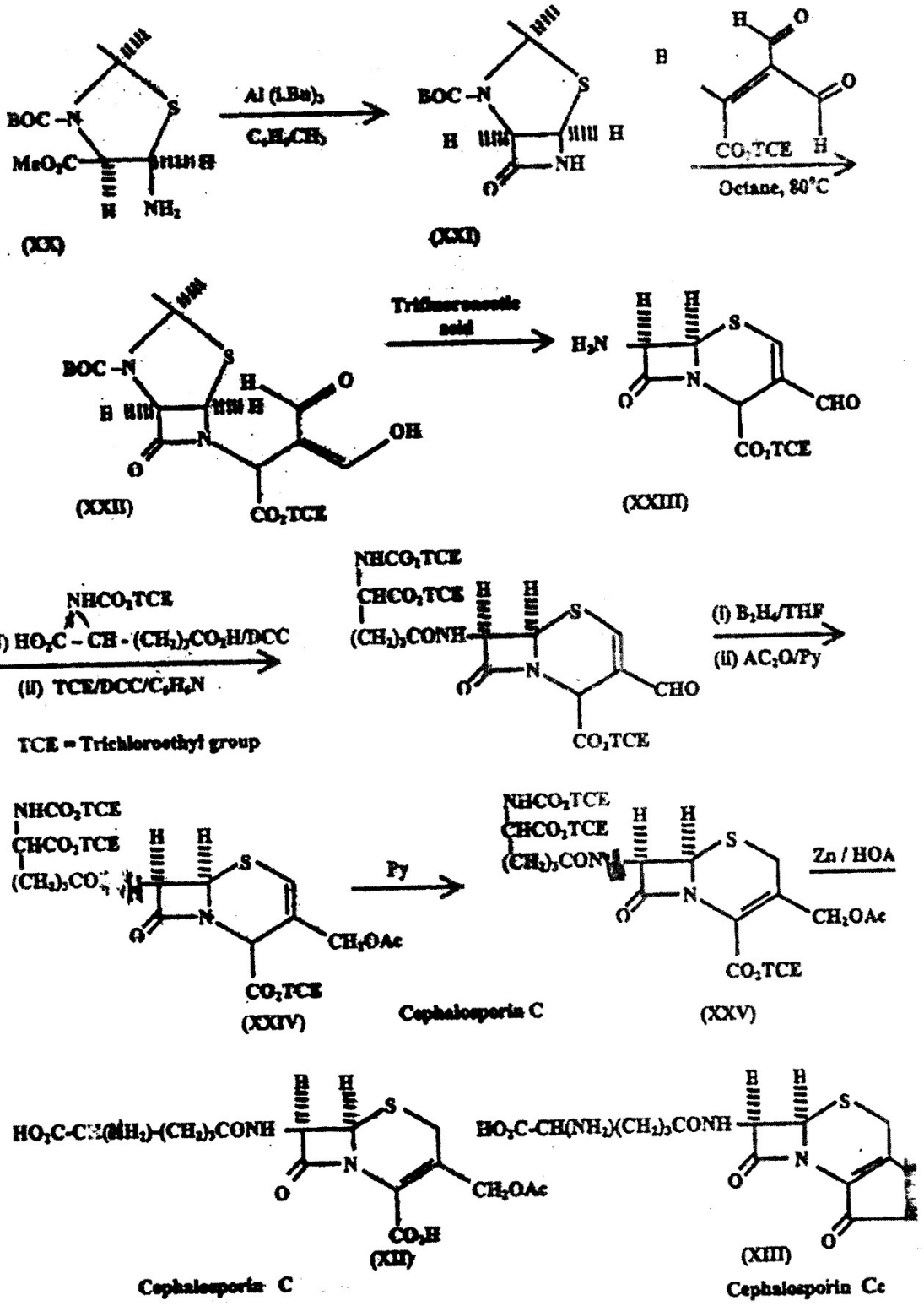
Based on the above chemical works. Abraham et al have proposed structure (XII) for cephalosphorin C and structure (XIII) for cephalosporin Cc.

The structure of the antibiotic has been further confirmed by its synthesis.

TOTAL SYNTHESIS:- WOODWARD ETAL (1966).

First, the β - lactam ring with substituents in the proper sterechemical orientation is prepared. Next, the dihydrothiazing ring is added with retention of configuration of the chiral centers in the β - lactam ring. This eliminated the necessity for resolution in this synthesis. Here the β - lactam ring is somewhat stable compared to that in penicillin.




BOC –N
MeO2C
NH2
(XX)
Al (tBu)3
C6H5CH3
(XXI)
B
CO2TCE
Octane, 80°C
Trifluoroacetic acid
H2N
CHO
CO2TCE
OH
(XXII)
(XXIII)
NHCO2TCE
(i) HO2C – CH - (CH2)2CO2H/DCC
(ii) TCE/DCC/C5H5N
TCE = Trichloroethyl group
(i) B2H6/THF
(ii) AC2O/Py
CHCO2TCE
(CH2)3CONH
Py
Zn / HOA
CH2OAc
(XXIV)
Cephalosporin C
(XXV)
HO2C-CH(NH2)-(CH2)3CONH
CO2H
(XIII)
Cephalosporin C
Cephalosporin Cc

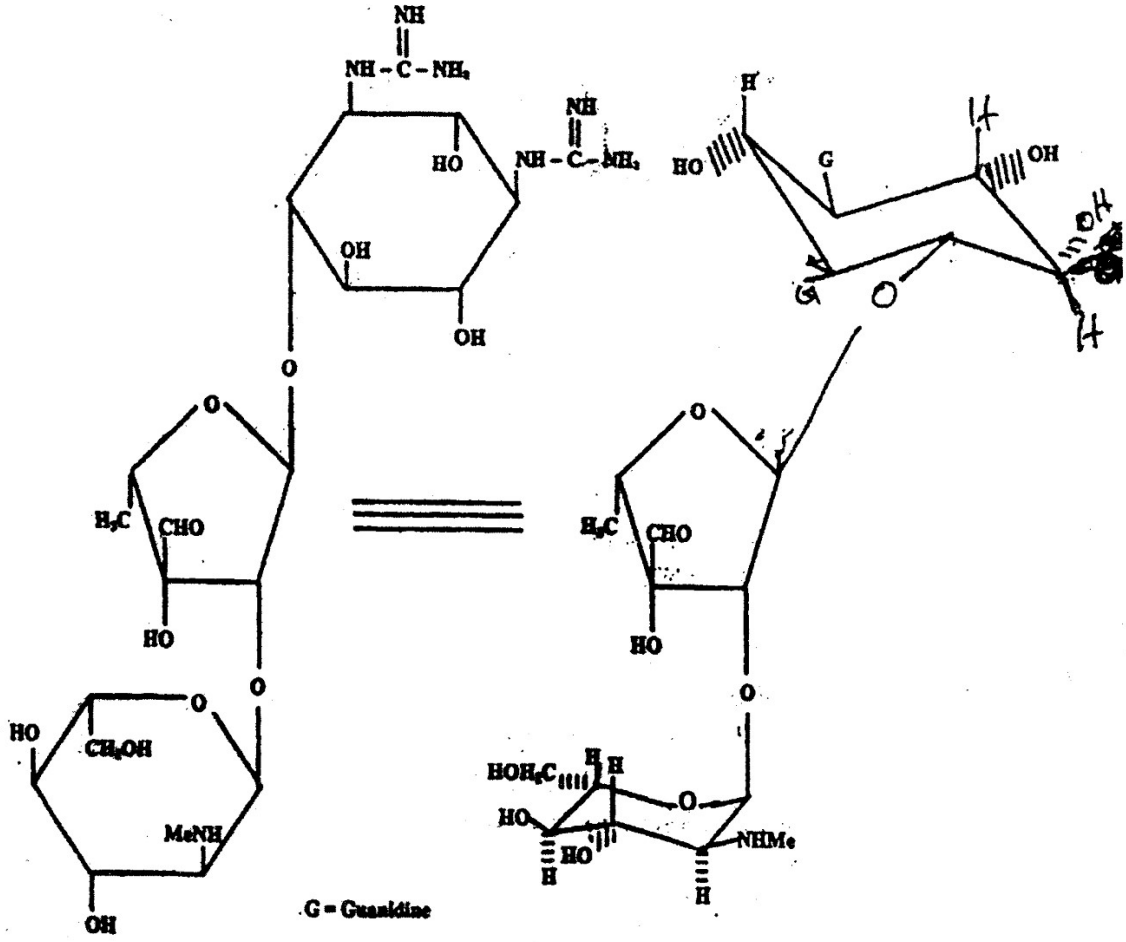
STREPTOMYCIN

Introduction :

This antibiotic is first isolated by Waksman etal (1944) from cultures of *Streptomyces Griseus*

This antibiotic is very effective in the treatment of tuberculosis, meningitis and pneumonia.

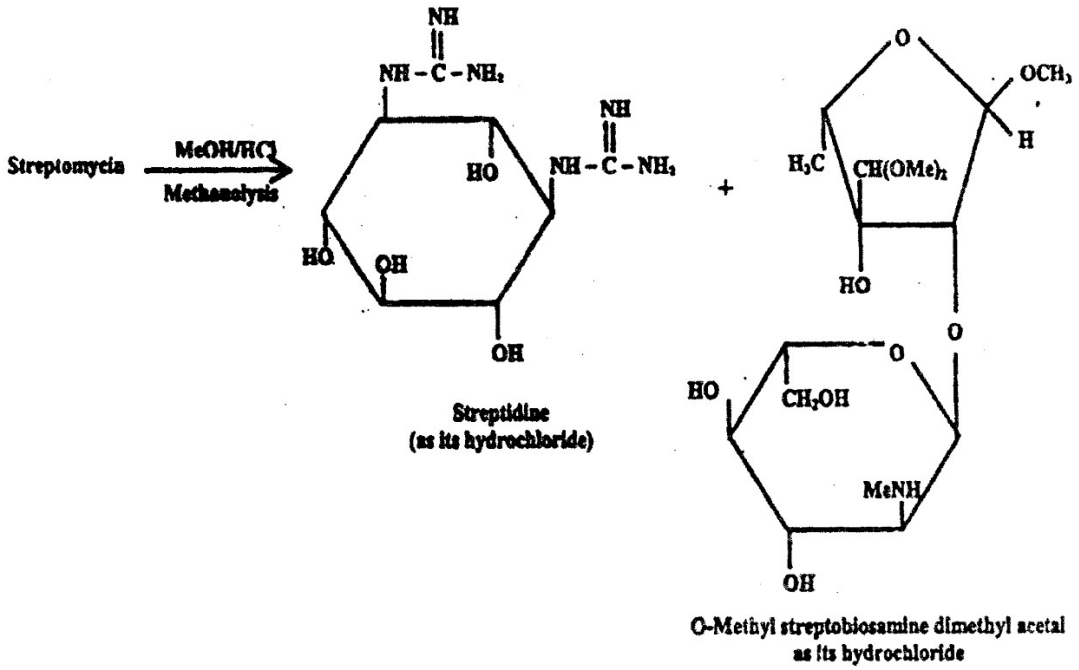
STRUCTURE ELUCIDATION :



Analytical data indicate the molecular formula of streptomycin to be $C_{21} H_{39} O_{12} N_7$.

The antibiotic forms forms a trihydrochloride. This shows that three nitrogen atoms out of seven are strongly basic.

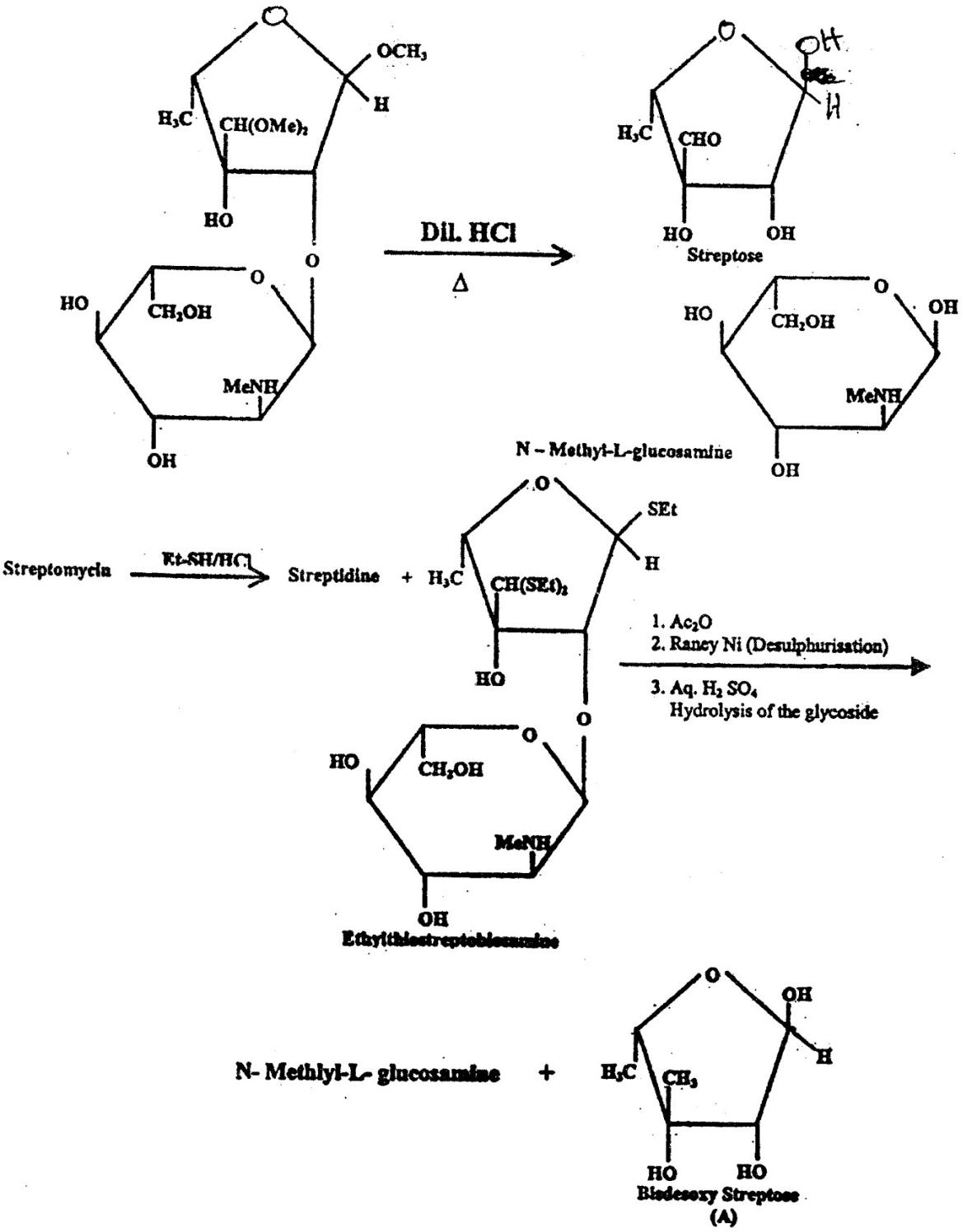
The above hydrochloride on treatment with methanolic hydrochloric acid undergoes, "methanolysis" to give two products.



The antibiotic on treatment with dil. Hydrochloric acid at room temperature is probably cleaved in the same manner as indicated above. But only streptidine alone was isolated.

The above compound is heated with aqueous hydrochloric acid to give streptose and N – methyl – L – glucosamine.

Similar to methanolic acid cleavage, streptomycin is cleaved using ethane thiol and hydrochloric acid.

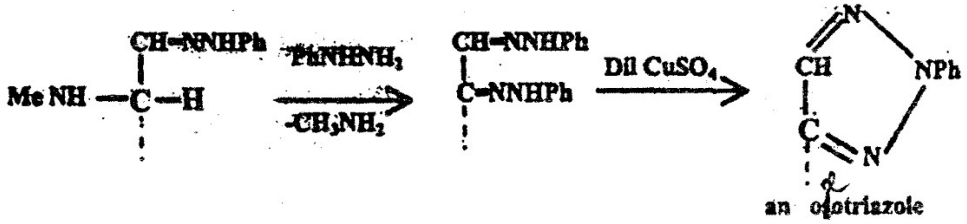

OCH3
H3C
CH(OMe)2
H
HO
O
HO
CH2OH
MeNH
OH
Dil. HCl
Δ
OH
H3C
CHO
HO
OH
Streptose
HO
CH2OH
MeNH
OH
OH
N – Methyl-L-glucosamine
Streptomycin
Et-SH/HCl
Streptidine
+
H3C
CH(SEt)2
SEt
H
HO
1. Ac2O
2. Raney Ni (Desulphurisation)
3. Aq. H2SO4
Hydrolysis of the glycoside
HO
CH2OH
MeNH
OH
Ethylthiostreptobiosamine
N- Methlyl-L- glucosamine
+
H3C
CH3
OH
H
HO
HO
Bisdesoxy Streptose
(A)

Comparison of the molecular formulae of the hydrolytic products and antibiotic showed a difference of 2 eater molecules. This indicated the glycoside formation at two points. Thus the antibiotic streptomycin is built up of the above three units: the 4th hydroxyl of streptidine is glycosidised by streptose, whose 2nd hydroxyl is glycosidised by N – Methyl L – glucosamine.

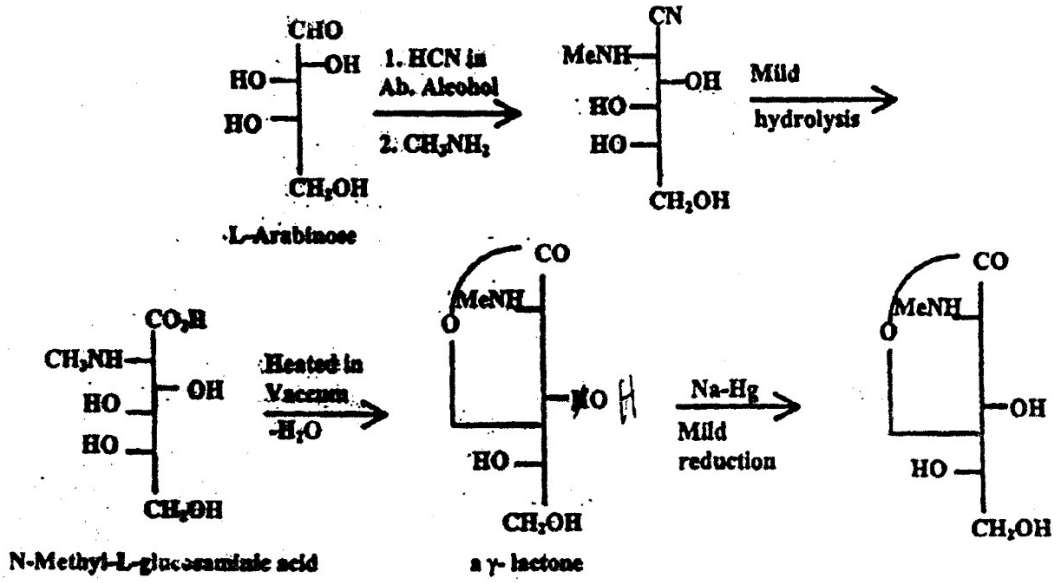
Now we may look at the structures of these three units.

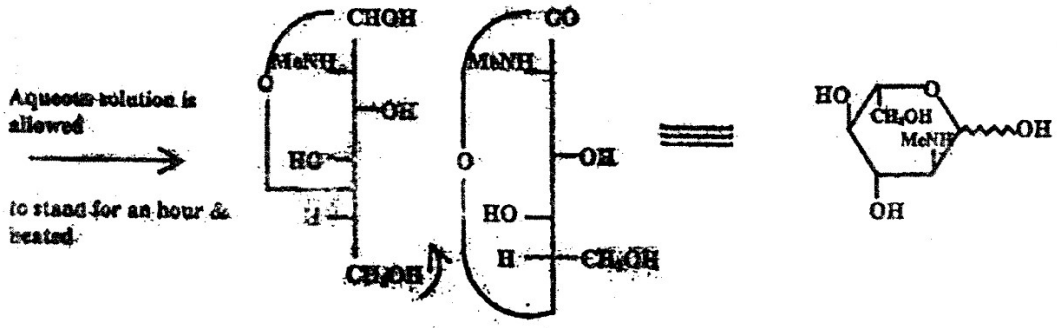
a). Structure of N – Mehyl L – glucosamine

This forms an osazone with phenythydrazine. The former on treatment with dil. Copper sulphate solution forms an osotriazole. This compound showd an optical rotation and m.pt. as an authentic sample of osotriazole of D – glucose. The of rotation, of course is opposite.



The above unit upon oxidation with mercuric oxide gives N-methyl - L - glucosaminic acid. This product has the same m.pt. and rotation as the known acid with opposite sign of rotation. It's structure is confirmed by its synthesis (Folken etal).





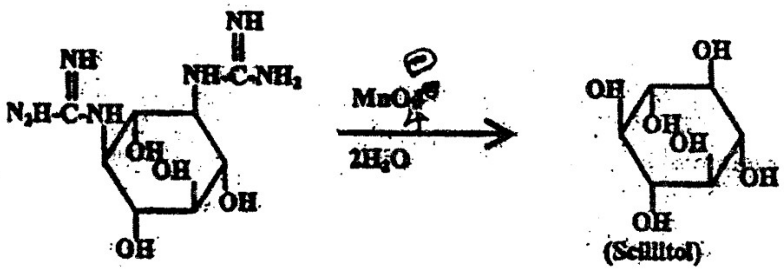
B) Structure of Streptidine :

(i). It forms a dihydrochloride salt with hydrochloric acid. Thus it is dibasic in nature.

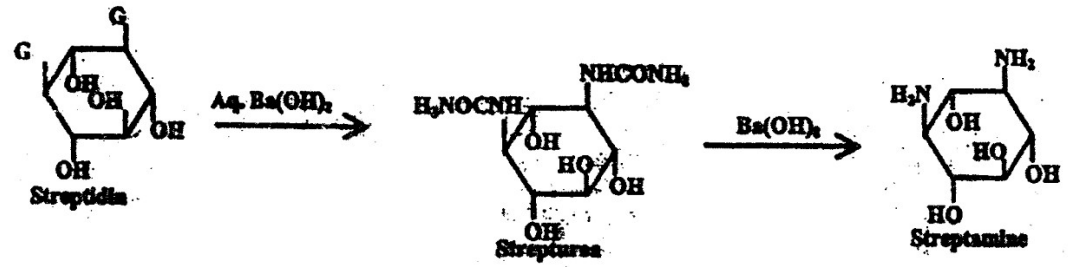
(ii). The presence of guanidino group is inferred by the permanganate oxidation, of streptidine. The guanidine formed in this oxidation is detected by using sagakuchi reaction.

Sagakuchi Reaction :

Guanidine on reaction with - naphthol and sodium hypobromite gives a red colour.

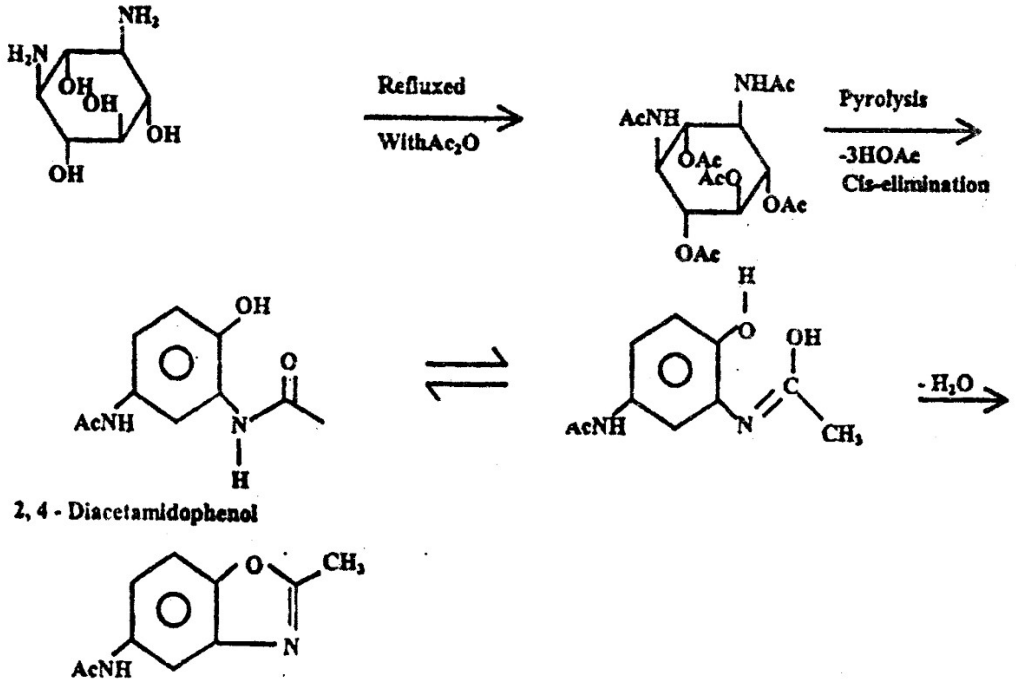


Alkaline hydrolysis with baryta degraded the molecule in 2 stages.



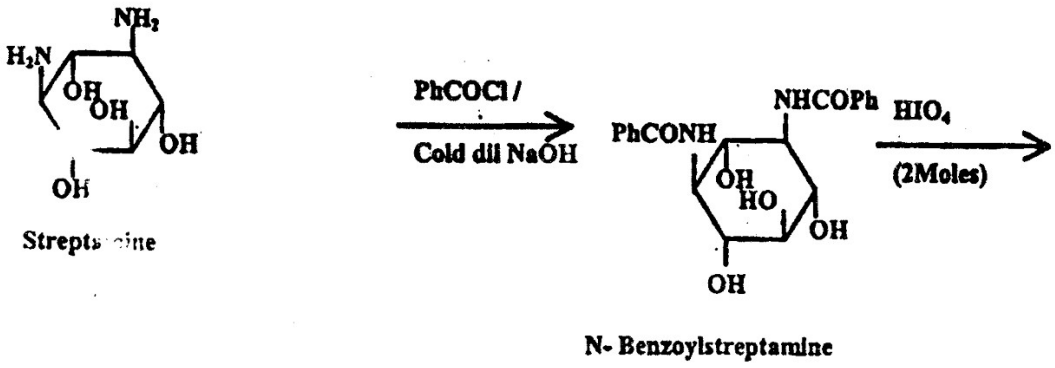
STREPTAMINE :

The presence of guanidino groups at 1,3 position is evidenced from the formation of 2-methyl-5-acetamidobenzoxazole, in the following sequence of reactions.



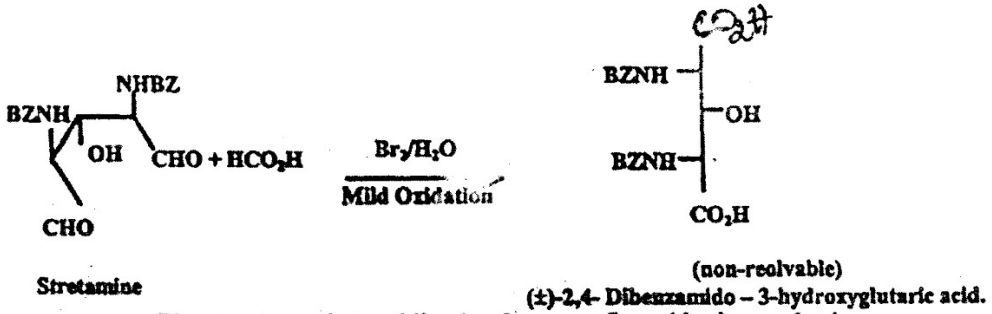
The two guanidino groups at 1 and 3 positions are cis-to each other is indicated as follows.

Benzoylation of streptamine gives Di-N-Obenzoyl derivative. The latter on periodic oxidation followed by treatment with bromine water gives meso - 2, 4 - dibenzamido - 3 - hydroxygluatric acid.



Streptamine

N- Benzoylstreptamine

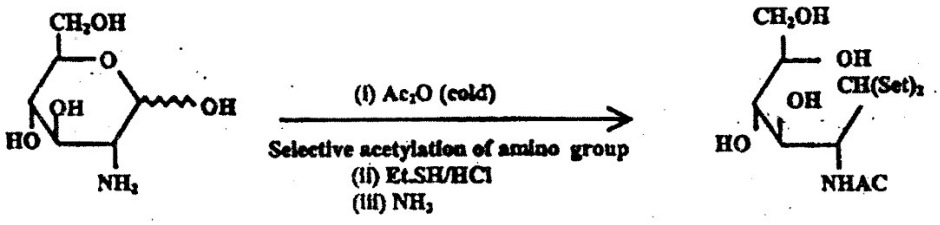


Stretamine

(non-resolvable)
(±)-2,4- Dibenzamido – 3-hydroxyglutaric acid.

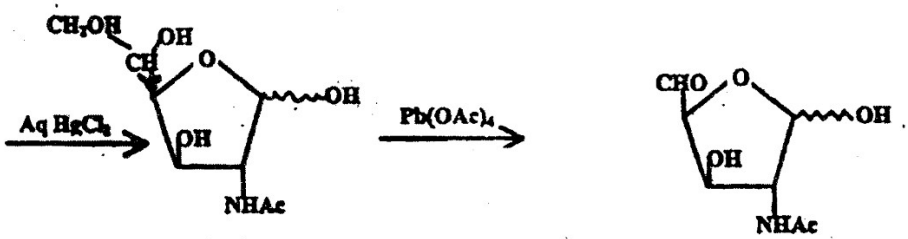
The structure of streptidine has been confirmed by its synthesis.

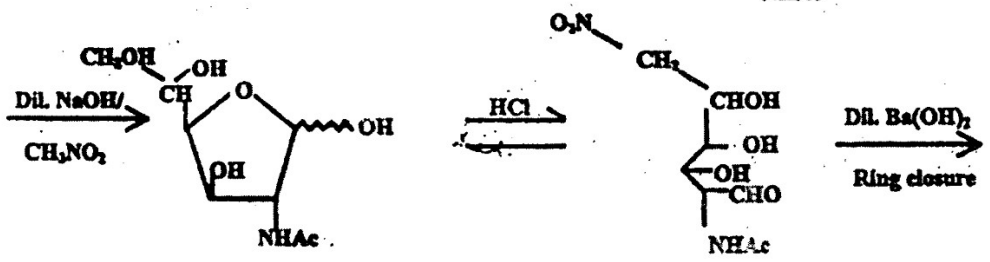
SYNTHESIS (WOLFROM etal)

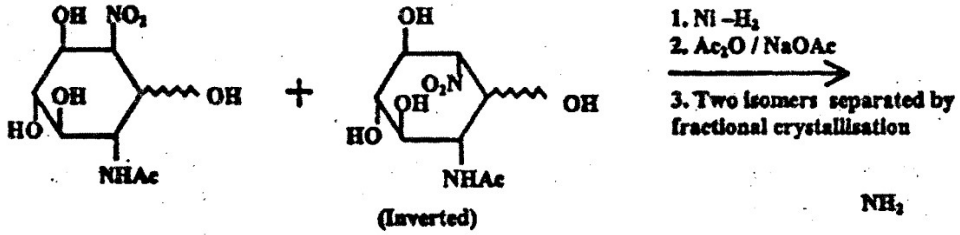


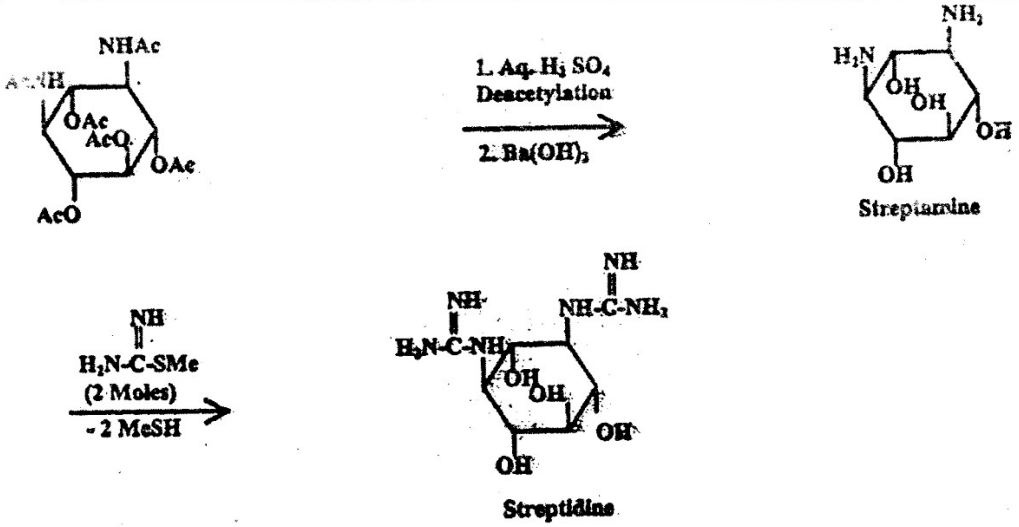
D- Glucosamine

N- Acetyl-D-glucosaminediethylmercaptal

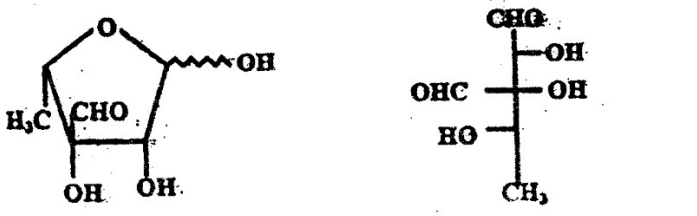








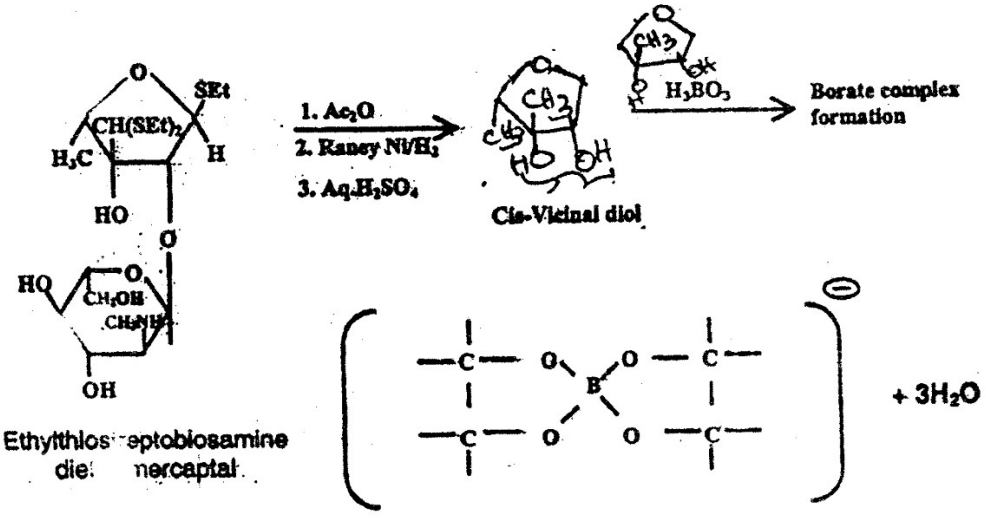
Structure of streptose :



3-Formyl-5-desoxy-L-lyxose

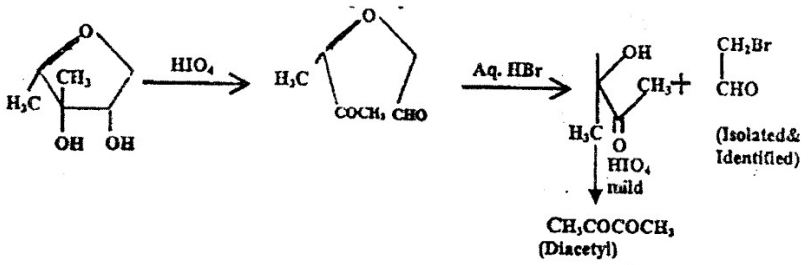
This compound is unique in that it contains two formyl groups a tertiary hydroxyl and a desoxyhyd methyl groups.

Ethylthiostreptobiosaminediethylmercaptal on desulphurisation with Raney nickel gives a product known as bisdesoxy streptose and this product enhanced the strength of boric acid, indicating the presence of two cis-vicinal hydroxyls.

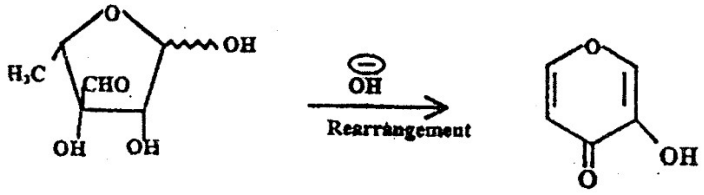


Ethylthiostreptobiosamine diethylmercaptal

The above bisdesoxy compound is subjected to periodic acid oxidation as follows.



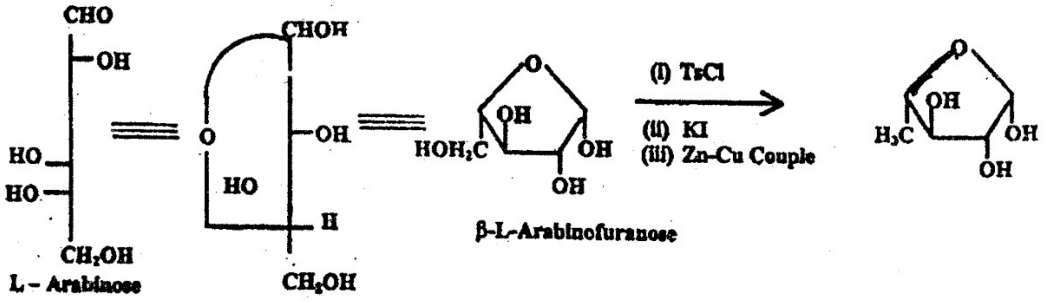
Streptose or even the antibiotic streptomycin undergoes a unique molecular rearrangement when treated with dil.alkali, the product is called "maltol" and the rearrangement is "Maltol rearrangement".

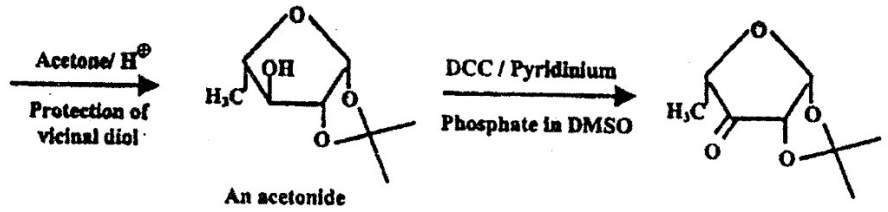


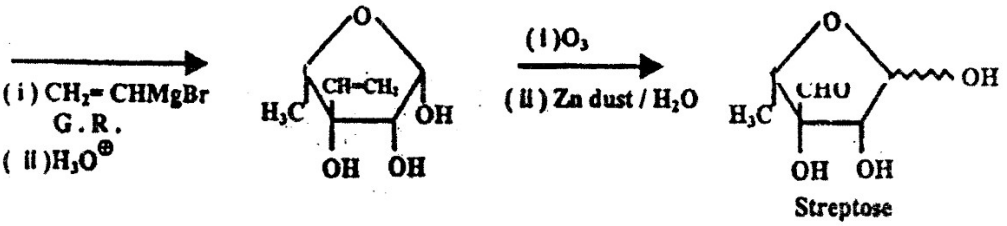
2-Methyl -3-hydroxy-γ-pyrone (or) Maltol

This rearrangement normally occurs in the case of a furanose system, only if the aldehydic group of C_1, is used in a furanose ring with a 3-formyl group, being potentially free. Its structure has been confirmed by its synthesis.

Synthesis :



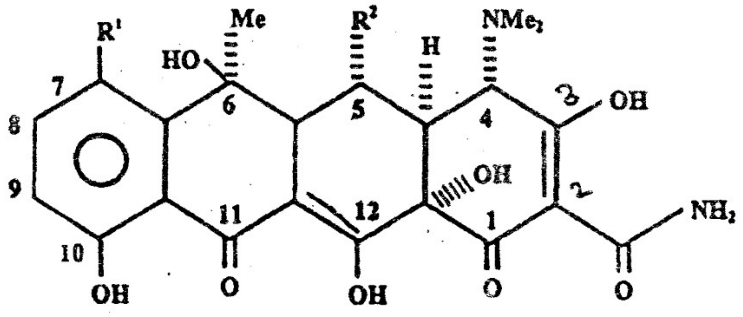




TETRACYCLINES

Introduction:

Tetracyclins are broad spectrum antibioties and are produced by moulds. Aureomycin was isolated from cultures of ***streptomyces aurefaciens***. This is used in the treatment of typhoid fever. Terramycin was isolated from cultures of **streptomyces rimosus**. This is very effective in the treatment of trachoma. Their physical and chemical similarities suggested even at the outset that they have the same skeleton. The structures of these antibiotics are given below.



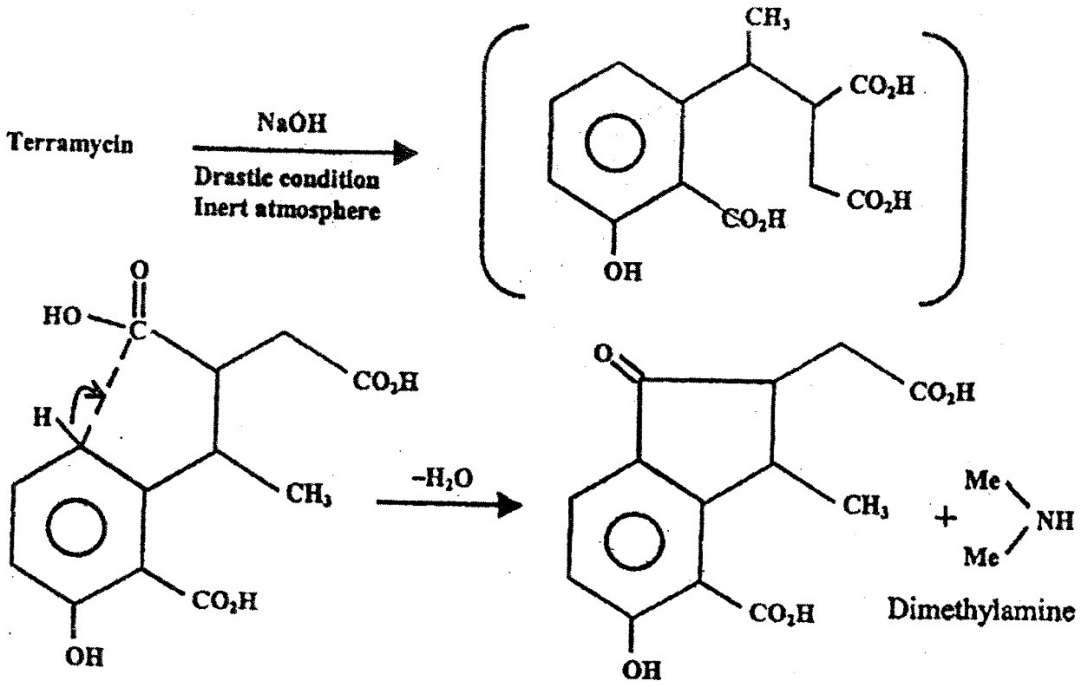
Aureomycin : R^1 = Cl ; R^2 = H
Terramycin : R^1 = H ; R^2 = OH

Structure elucidation of terramycin:

It is an yellow amphoteric substance with a molecular formula, $C_{22}H_{24}O_9N_2$. Zerewittinoff's active hydrogen determination indicated the presence of 6 - active hydrogens (ie. 6-OH groups)

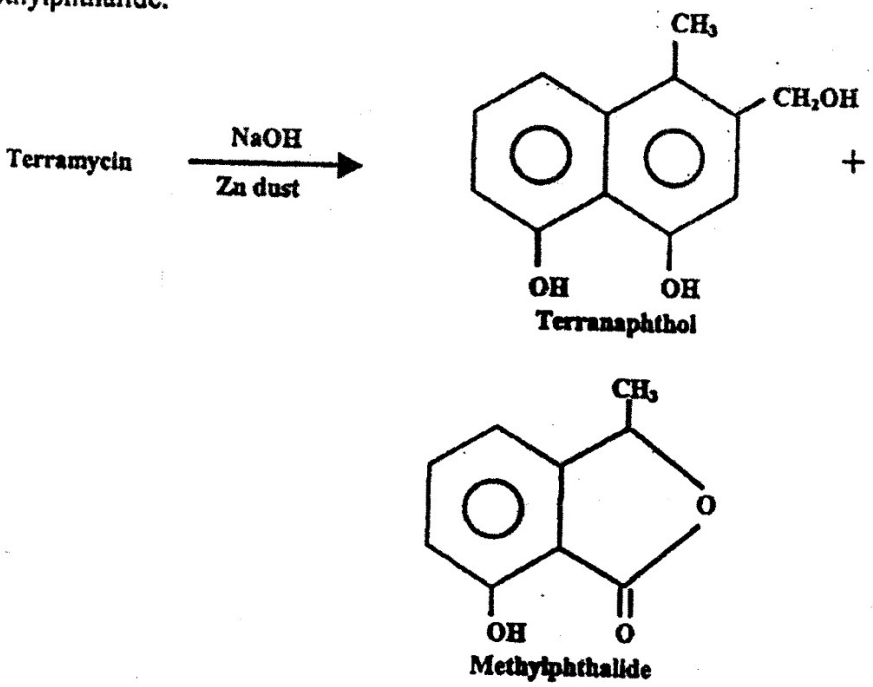
24 hours treatment of terramycin with 20% sodium hydroxide gives dimethylamine, ammonia and acetic acid. So presence of dimethylamino groups and an amide group is inferred.

Drastic alkali degradation of terramycin gives terracinoic acid, terranaphthol and methylphthalide.

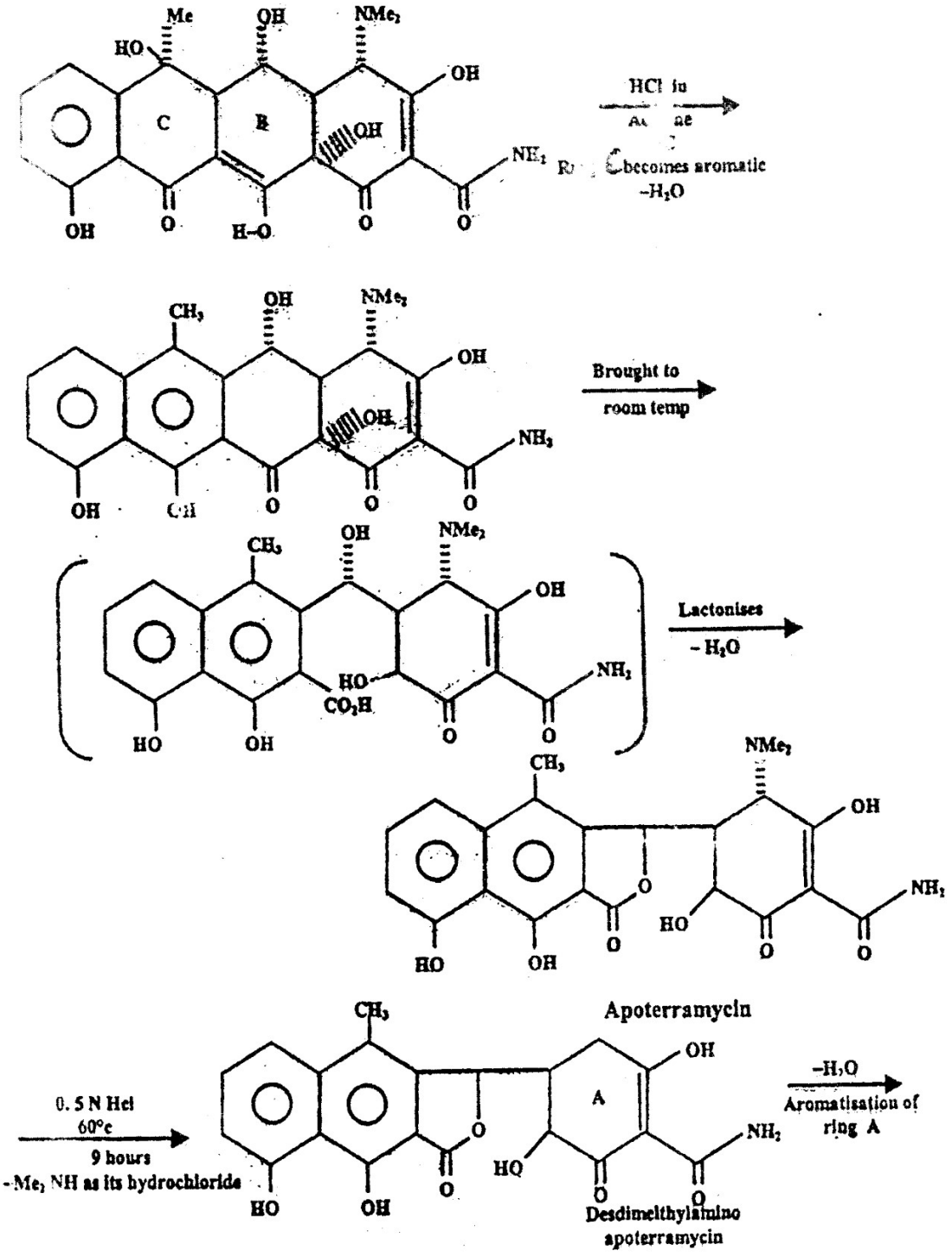


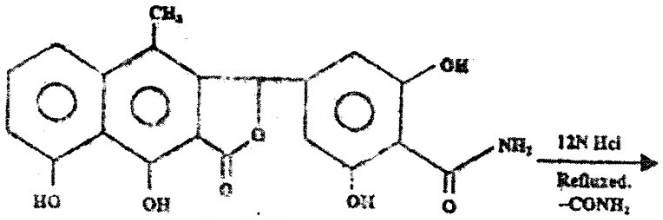
Terracinoic acid + NH_3 + CH_3COOH etc

Alkali degradation in the presence of zinc dust gave terranaphthol and methylphthalide.

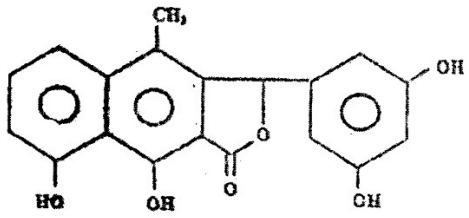


The following acid degradation was carried out under mild conditions.


Me
OH
NMe2
HO
OH
C
B
OH
NH2
OH
O
H-O
O
O
HCl in
Ac ae
C becomes aromatic
-H2O
CH3
OH
NMe2
OH
OH
NH2
OH
OH
O
O
O
Brought to
room temp
CH3
OH
NMe2
OH
HO
CO2H
NH2
HO
OH
O
O
Lactonises
- H2O
CH3
NMe2
OH
O
NH2
HO
HO
OH
O
O
Apoterramycin
CH3
OH
A
O
NH2
HO
HO
OH
O
O
0. 5 N Hcl
60°c
9 hours
-Me2 NH as its hydrochloride
-H2O
Aromatisation of
ring A
Desdimethylamino
apoterramycin



terrinolide

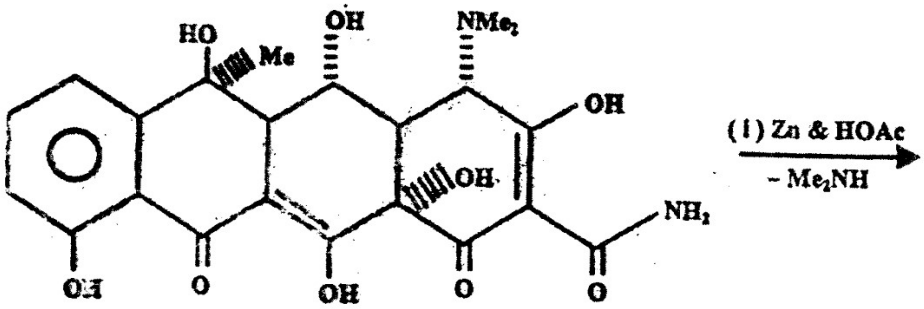


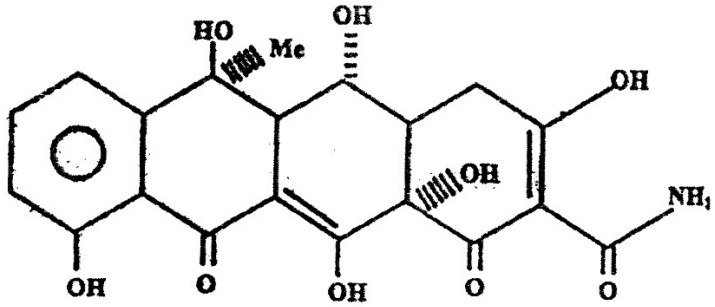
decarboxamidoterrinolide

The presence of 1, 8 - dihydroxynaphthalene skeleton in the above compounds has been proved by UV and NMR and increase in the acidity conferred on boric acid.

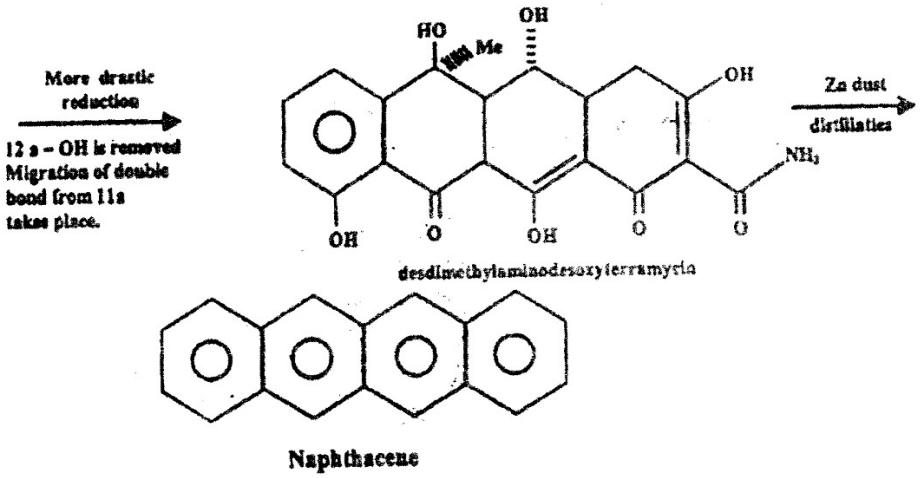
Reductive degradation with zinc and Acetic acid :

The tetracyclic nature of the antibiotic has been proved by the reduction experiments.

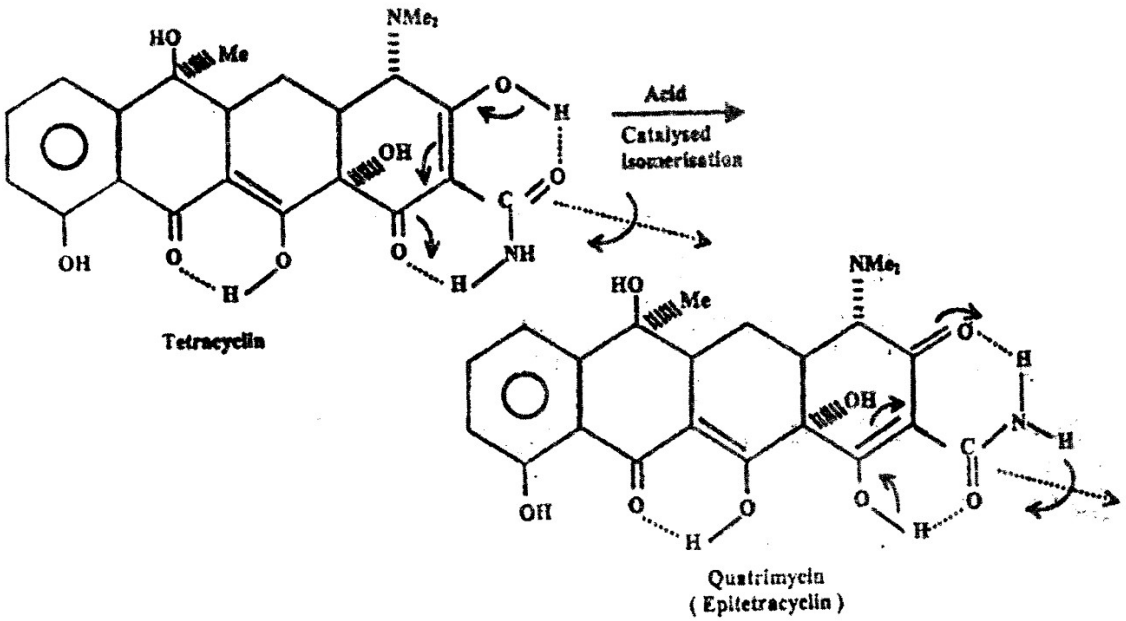




desdimethylaminoterramycin



At about this stage stephens et al isomerised tetracyclin to epitertacyclin which is more often referred to as quatrimycin. This isomerisation is due to the two different modes of chelated structure.

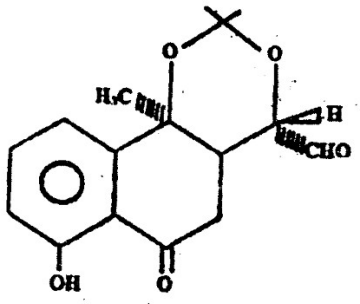


Finally the structure of terramycin has been confirmed by its synthesis.

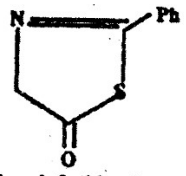
SYNTHESIS : (Muxfoldt, Kardtmann, Kathawala Vedjs and Moobery).

REF : JACS 90, 6534 (1968).

The following three units whose syntheses earlier achieved has been brought together.

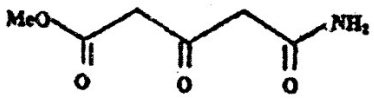


unit–I



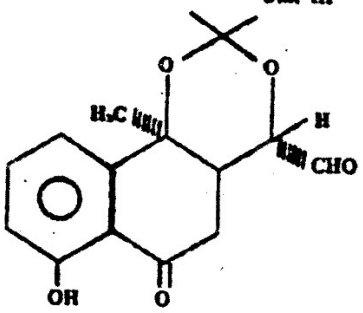
2–Phenyl–5–thiazolone

unit–II

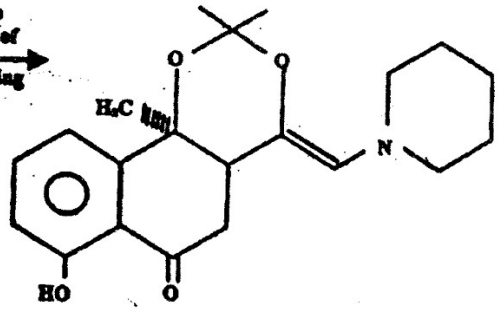


Methyl –3 –Ozoglutaramate

Unit III



Piperidine and a trace of acid in refluxing benzene $-H_2O$

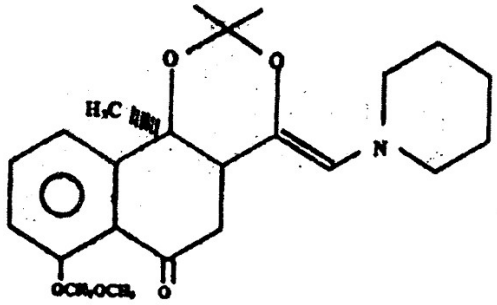


(i) NaOH

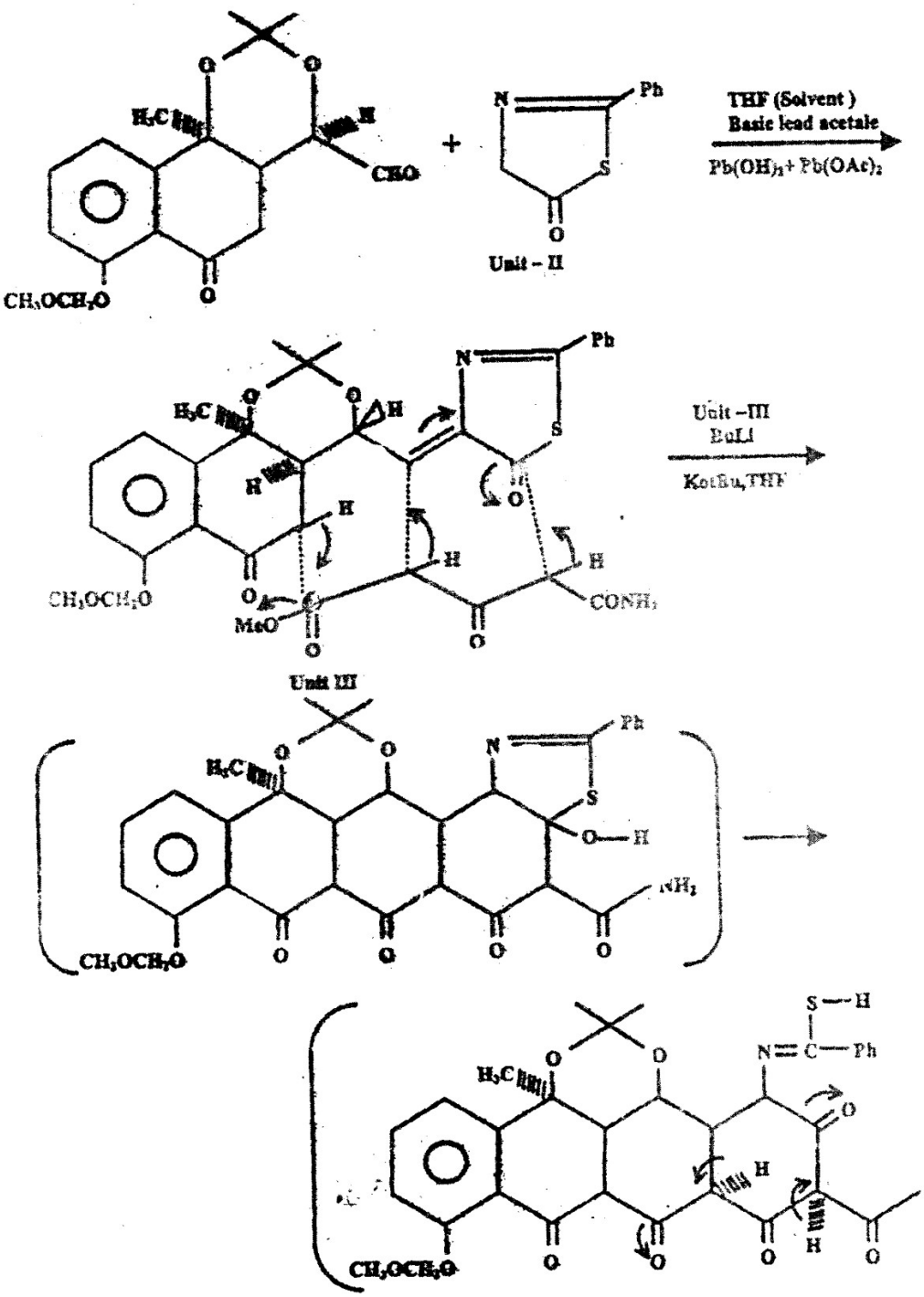
(ii) Cl CH_2OCH_3

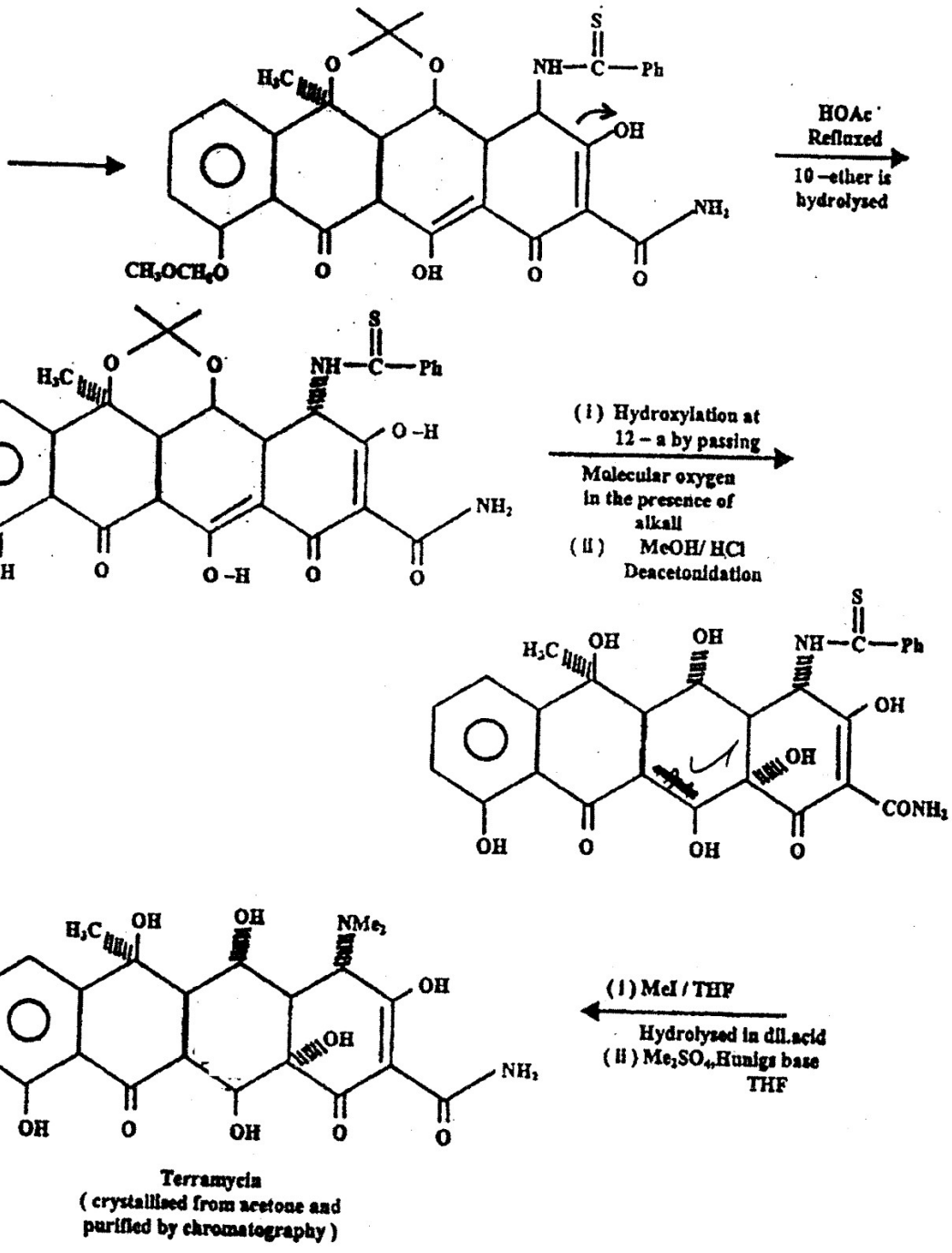
$-NaCl$

Protection of phenolic –OH



Silica gel partially Deactivated by acid. Mild hydrolysis of the enamine

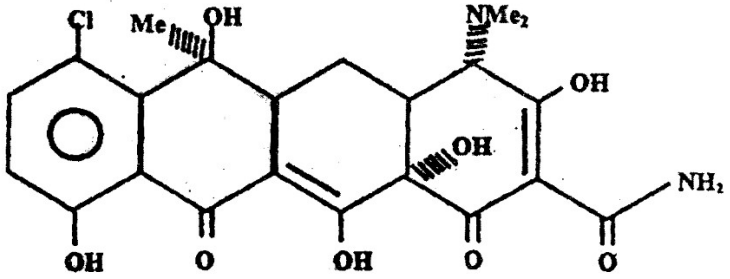

THF (Solvent)
Basic lead acetate
Pb(OH)2+ Pb(OAc)2
Unit - II
Unit –III
EtLi
KotBu,THF
Unit III



Terramycin
(crystallised from acetone and purified by chromatography)

Aureomycin

[(or) 5-desoxy - 7- chloroterramycin (or) 7-chlorotetracyclin]



Introduction :

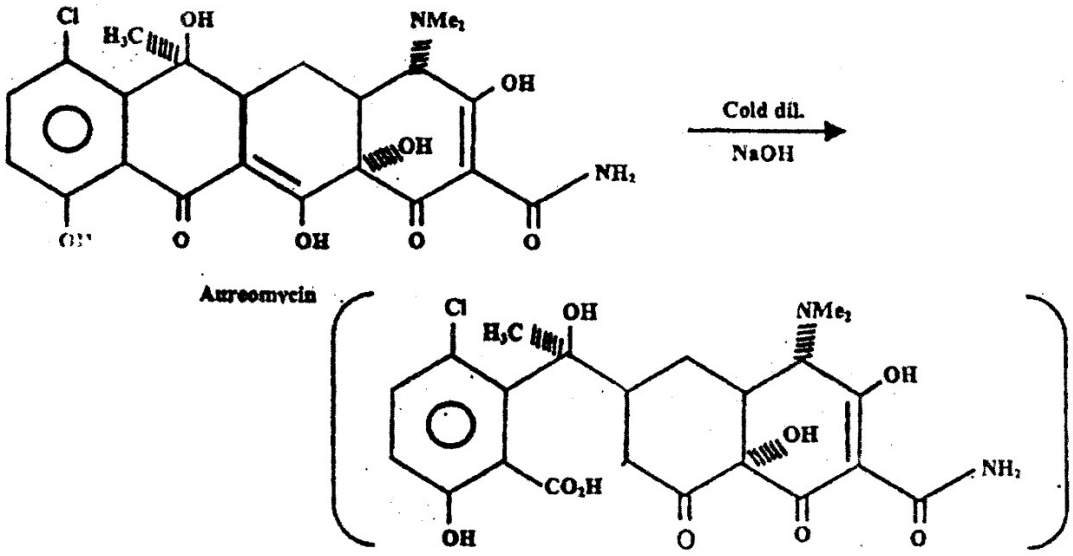
Auremycin and Terramycin display identical UV spectra and have similar physical and chemical properties. They do show the same physiological activities.

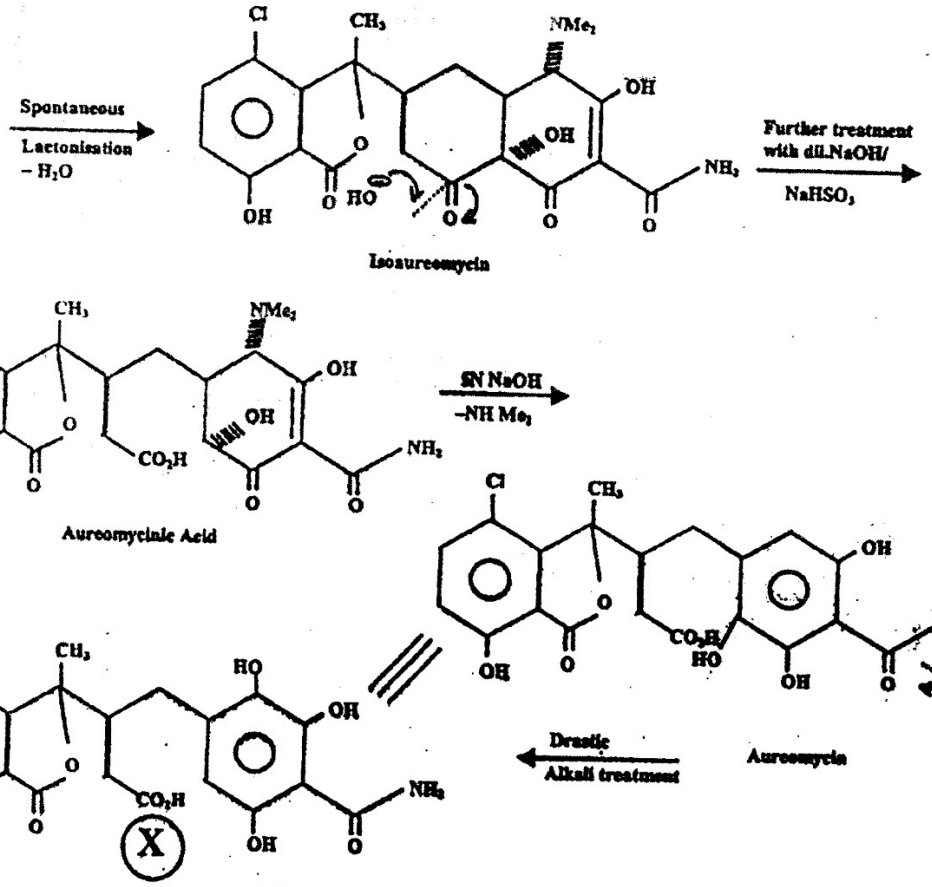
Structure Elucidation :

From analytical data the molecular formula of aureomycin has been deduced as $C_{22}H_{23}O_8N_2Cl$.

Its structure has been revealed through various degradative studies.

Degradation of aureomycin with alkali was done as follows;

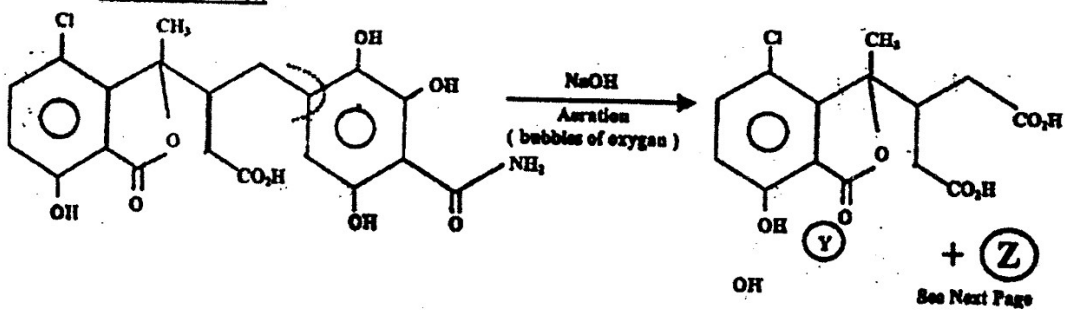




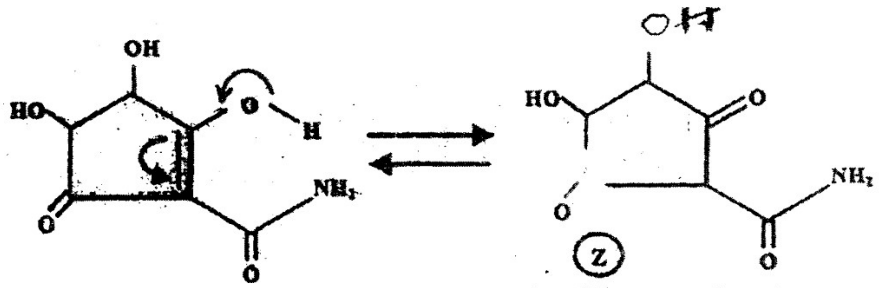
Desdimethylaminoaureomycinic acid

Compound X was subjected to (i)continuous alkali treatment to give compounds Y and Z, (ii) Acid degradation to aureonamide.

Alkali treatment:



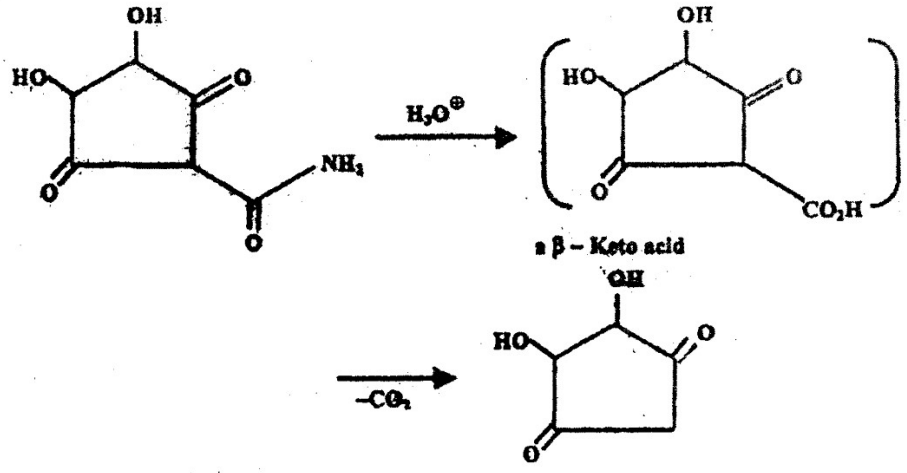
See Next Page



3,4 –Di' oxycyclopentan–
2,5–dione–1–carboxamide

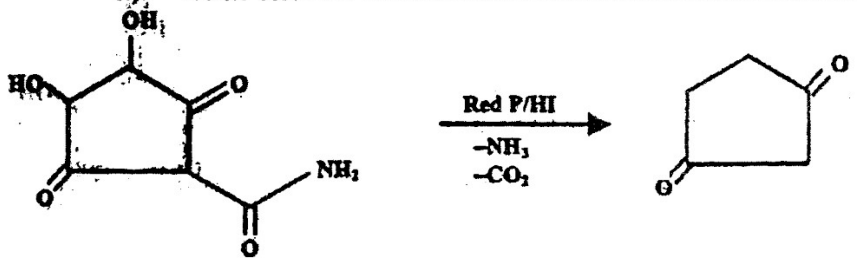
Compound Z has been characterized by the following studies.

i). It is hydrolysed by acid to an unstable monocarboxylic acid, which is spontaneously by decarboxylated (being a - Keto acid).

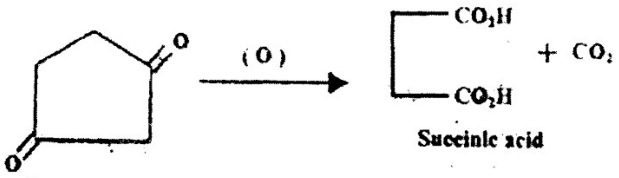


a β – Keto acid

ii). When refluxed with red P/HI it loses ammonia and carbon dioxide.

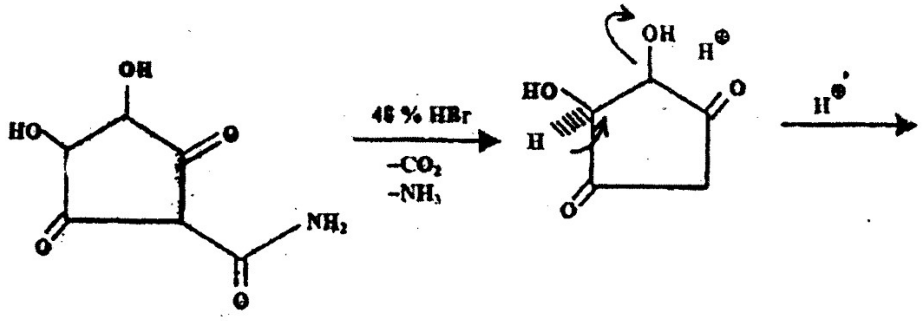


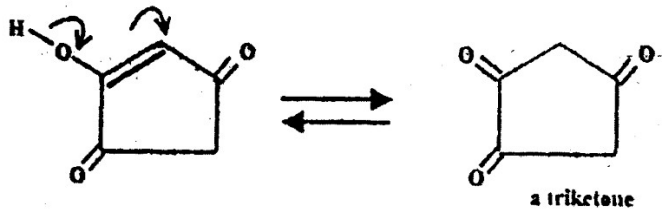
iii). This product has been oxidized to succinic acid confirming the above formulation.



Succinic acid

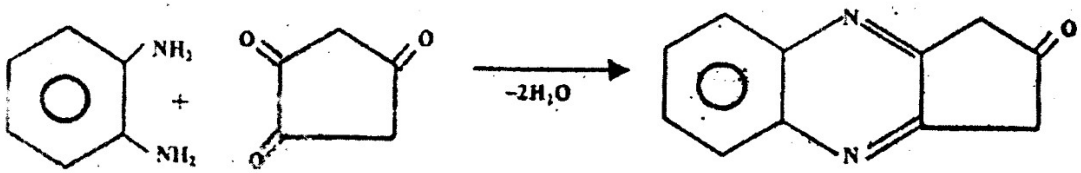
iv) Compound Z reacts with 48% hydrobromic acid losing ammonia and carbon dioxide and giving a triketone.





a triketone

This triketone gives a quinoxaline derivative, indicating it to be an α-diketone.



Quinoxaline derivative

Compound X on degradation with sulphuric acid gives aureonamide.