M.Sc (SY)
- Sem - III
Mundhe Madam
(Medicinal Chem)

Page No.:
Date:
YOUVA

Metabolism may results

1) Inactivation : After metabolism some drugs gives inactive metabolite & can't give proper therapeutic effect. eg. Procaine, Lidocaine → Anaesthetics

2) Active metabolite From active drug :
Codeine → Morphine

3) Activation of inactive drug : (Prodrug)
(Parkinson's disease) Levodopa → Dopamine

Drug Metabolism

Page No.:
Date:
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→ After a pharmacological response, the drugs are required to be excreated from the body.

→ Drugs & other foreign Comp. which enter a living organisms are stored in the body or removed from it after a period of time. While inside the body, they may remain intact or undergo chemical transformation, giving comp. (a) less active or (b) more active or (c) having similar or diff. activity. This process of chemical alteration of drug inside the living organism is called drug metabolism.

→ Drug metabolism usually leads to detoxication, oxidation, reduction & other enzyme-catalyzed reactions, therefore may form a metabolite having toxic or therapeutic effect.

→ Drug metabolism / Biotransformation leads to the conversion of one form of drug into other form of drug.

→ Drug metabolism is very imp. for proper action of drug as well as elimination of drug from body.

→ Although liver is the major site of drug metabolism however, some drug metabolizing enzymes are also found in kidneys, lungs, plasma, nervous tissue & the gastrointestinal tract. etc.

→ By enzymes of liver & various other tissues, the drug may undergo a variety of chemical changes.

→ The ability of the liver to metabolize a sub. in one pass is called 'first-pass effect'.

→ Several orally administered drugs undergo liver first-pass metabolism during their movement to the systemic circulation from the gastro-intestinal tract.

→ Hence, the liver can remove chemicals from the blood after their absorption from the gastrointestinal tract. In this manner, the toxic substances are prevented from distribution to the other parts of the body.

→ Before being excreted, most of the biologically active lipid soluble compounds which are foreign to the body, are changed chemically by the drug metabolizing enzymes which makes them more water soluble readially eliminated from body through kidney. ~~in the form of urine~~.

Drug (lipid soluble) Biotransformation Polar (water soluble)

↓

elimination ← kidney

→ The principal route of drugs & their metabolites excretion occurs in the urine, bile, saliva, Lungs, sweat etc.

→ The bile has been recognized as a major route of excretion for various exogenous & endogenous substances.

→ The detoxication product of cyanide i.e. isocyanate is excreted through saliva.

★ Factors Affecting Drug Metabolism

There are various factors which affect drug metabolism. Such factors may change not only the kinetics of an enzyme reaction, but also the whole pattern of metabolism.

1) Genetic factors : Individual variation may result from genetic differences in metabolizing enzymes.

2) Physiologic factors : Physiologic factors include age, gender, liver disease, nutritional status, pregnancy, change in intestinal microflora & hormones particularly which are induced by stress etc. can influence drug metabolism.

3) Environmetal factors : Poisoning of drug metabolizing enzymes by toxic chemicals such as carbon mono-oxide or pesticide synergists may alter drug metabolism.

4) Pharmacodynamic factors : Dose, frequency, tissue distribution, route of administration & protein binding of the drug can also influence drug metabolism.

5) substances influencing drug metabolism, other than enzyme inducers are lipids, metals, Vitamin & proteins. Dietary lipid & protein deficiency decrease microsomal drug metabolizing activity.

★ Pathways of Drug metabolism :

The pathways of drug metabolism have been divided into two main categories such as :

1) Phase I reaⁿ :

→ This is biotransformation process & and consists of oxidⁿ, redⁿ & hydrolysis enzymatic reactions

→ In phase - I reactions, either a New functional group is introduced into the drug molecule or a pre-existing functional group undergo modification

→ Hence, drug becomes more polar & therefore it can be excreted more readily

2) phase II reaⁿ :

→ The phase II reactions are Conjugation reactions

→ These are enzymatic Synthesis in which a functional group is masked by the addition of a new group which increase the polarity of the drug & cause rapid excretion

★ Microsomal Reactions :

The reactions occured by the enzymes which are found in microsomes of livee.

→ They need co-factor both molecular oxygen and NADPH.

eg. 1) NADPH - Cytochrome P-450 reductase
2) Hemoprotein - Cytochrome P-450

★ Non-microsomal reactions :

The reactions occured by the enzymes which are found in cytoplasm & mitochondria & liver cells.

I) Phase I Reactions :

1) Oxidation :

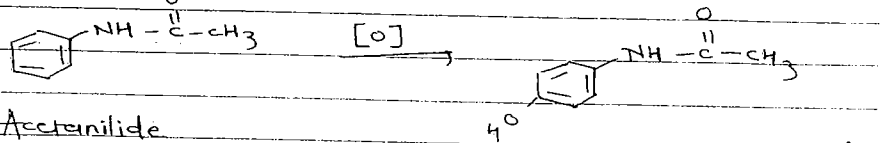
oxidation is the most imp. drug metabolizing reaction. This reaⁿ involves addition of oxygen or removal of hydrogen.

→ The examples are oxygenation at carbon, N or S atoms, hydroxylation, N or O dealkylation, oxidative deamination etc.

→ Generally, oxidative reaⁿ occur by a group of monooxygenases in the livee. These enzymatic processes Posses a Cyt-P-450 haemo protein, NADPH, Cyt P-450 reductase & O_2

a) Hydroxylation :

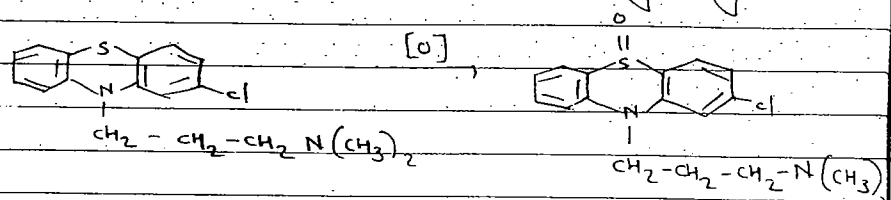
Acetanilide on hydroxylation gives Acetaminophen



Acetanilide (Paracetamol → used to treat Pain & Fever) Acetaminophen

b) S-oxidation :

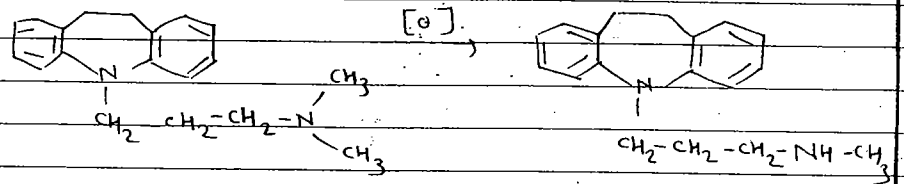
Thioethers i-e. chlorpromazine oxidized to their Sulphoxides in the following way.



Chlorpromazine — chlorpromazine Sulphoxide

(Psychotic disorders, Nausea vomiting & chronic hiccups)

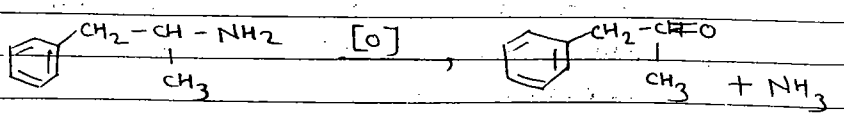
c) N-dealkylation :



Imipramine on dealkylation gives Desimparmine
(Tricyclic antidrepsant → used to treat depression)

d) Deamination :

on deamination of Amphetamine gives phenylacetone



Amphetamine — phenylacetone

(central Nervous System Stimulant used to treat attention deficit hyperactivity disorder, narcolapsy & obesity) disorder that

e) Reduction :

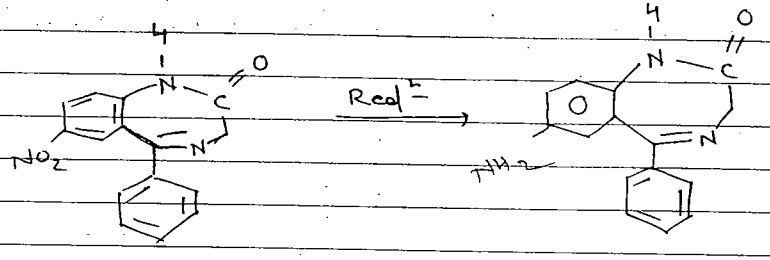
Reduction is the opp. process of oxidation. In this reaction Cyt P-450 enzymes work in the reverse direction.

→ For the metabolism of drugs, some enzymes are capable of reducing azo & Nitro groups of the drugs.

→ These enzymes are found in microsomal systems.

eg. Nitroreductase

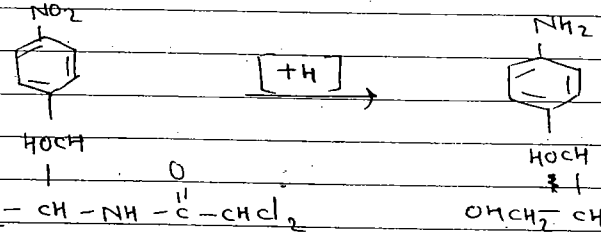
Nitrogroup of Nitrazepam is reduced to 7-Amino derivative.



Nitrazepam — 7-Amino derivative

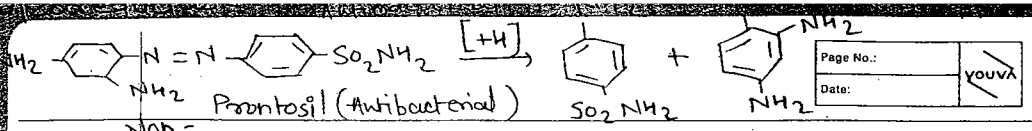
(treatment of sleeping problems)

eg. chloramphenicol is reduced to Arylamine



chloramphenicol — Arylamine

(Antibiotic used for treatment of bacterial infections)



Prontosil (Antibacterial)

→ Non-Microsomal enzymes are oxidates & dehydrogenases

→ They acts as reductase & may be Common for pri. & sec. alcohols.

eg. chloralhydrate get metabolised trichloroethanol

$CCl_3CH(OH)_2 \xrightarrow{(O)} CCl_3CH_2OH$

Chloral hydrate — Trichloroethanol

(Sedative used for short term treatment of Insomnia)

→ chloral hydrate is metabolised by alcohol dehydrogenase in liver to its active metabolite trichloroethanol

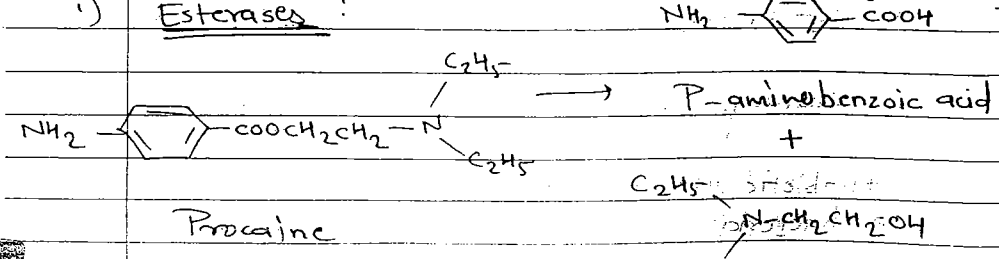
3) Hydrolysis :

Hydrolysis is a cleavage reaⁿ of drug molecule by using a molecule of water in presence of enzyme.

→ Examples are pethidine, oxytocin, procain, Ledocaine etc.

→ Hydrolysis occurs in the liver, intestine, plasma & other tissues by esterases, Amidases, peptidases etc. The bulky esters get slowly hydrolysed & may often get excreted unchanged.

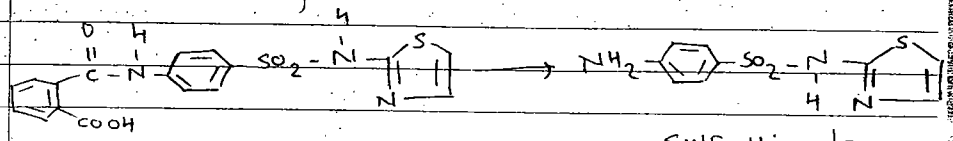
1) Esterases :



Procaine

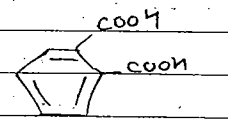
2) Amidases :

When phthalyl sulfathiazole undergoes hydrolysis in the presence of Amidase enzyme gives sulfathiazole & phthalic acid

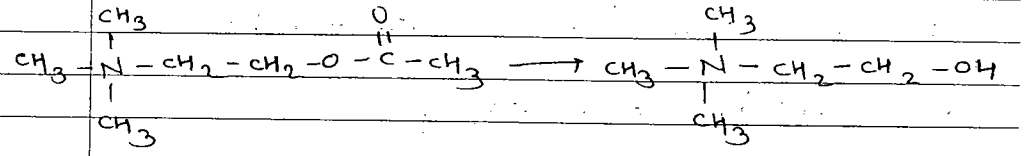


Phthalyl Sulfathiazole → Sulfathiazole + Phthalic acid

(Anti Microbacterial drug)



★ The cleavage of acetylcholine by the enzyme acetylcholinesterase is the most imp. example of this process



Acetylcholine → Choline + Acetic acid

e) Phase II reaction : High energy requirement

→ The metabolites formed by this biotransf^{n} are mostly inactive

→ Phase II reactions are Conjugation reaction

→ These are enzymatic synthesis in which a functional groups is masked by the addition of a new group which increase the polarity of drug & causes rapid elimination.

→ The phase II reactions follow phase I reactions & occur mostly in the products derived from phase - I reactions.

→ In these reactions, a suitable moiety such as glucuronic acid, glutathione, sulphate, glycine etc get conjugated to the metabolites of phase I reaction

→ The metabolites Above mentioned moieties are larger in size & strongly polar in nature.

→ These reactions are catalysed by a variety of transferase enzymes.

→ These reactions are of following types

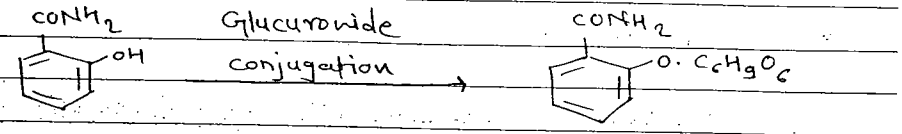
1) Glucuronide Conjugation.

→ This is the reaction where a compound which contains hydroxyl or carboxylic acid group can be easily conjugated with glucuronic acid.

→ Glucuronic acid is derived form glucose.

→ Not only drugs but endogenous substrates such as Steroidal hormones, thyroxine, bilirubin etc. are metabolized by this pathway.

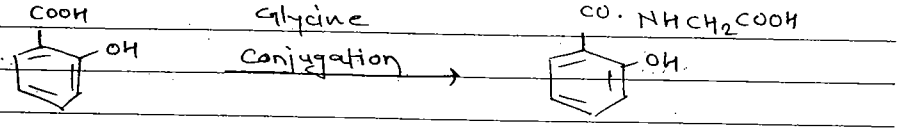
→ Drug conjugated with glucuronide is excreted in bile & can be hydrolysed by bacteria in gut



Salicylamide — Salicylamide glucuronide

2) Glycine Conjugation.

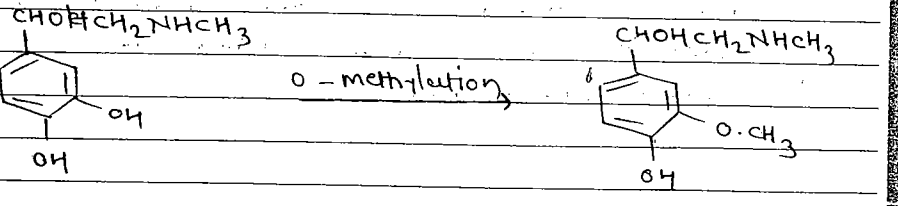
This is a minor pathway of biotransformation. The drugs containing carboxylic acid group, such as Salicylic acid, Conjugate with glycine



Salicylic acid — Salicyluric acid

3) Methylation.

Drugs Containing amines or phenols can be biotransformed by methylation.
eg. Adrenaline, histamine etc.



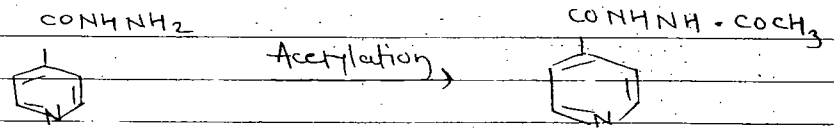
Adrenaline — 3-O-methyladrenaline

4) Acetylation :

Compounds Containing amino or hydrazine residues are conjugated with the help of acetyl coenzyme - A & show acetylation reaction

eg.

Sulfonamide, hydralazine, isoniazid etc.



isoniazid

5) Sulphate Conjugation :

This reaction occurs in the presence of enzyme Sulfokinases, the Compounds of phenols and Steroids can be sulphated easily

6) Glutathione Conjugation :

When Some drugs form highly reactive metabolites such as quinone or epoxide intermediates, glutathione is conjugated with them & makes them inactivated.

Antimycobacterial Agents

Mycobacteria are a genus of acid-fast bacilli belonging to the mycobacteriaceae family which include the organisms responsible for tuberculosis & leprosy, as well as less common other diseases.

→ The agents or drugs used for treatment of mycobacterial diseases called as antimycobacterial agents.

A) Antitubercular Drugs :

Tuberculosis :- (TB)

→ Tuberculosis is a disease caused by mycobacteria species.

→ TB is ~~caused~~ caused by either micobacterium tuberculosis in man or by micobacterium bovis in animals.

→ It is a chronic bacterial infection caused by micobacterium tuberculosis, an acid-fast aerobic bacillus with an unusual cell wall.

→ This cell wall contain high degree of lipid content resulting in high degree of hydrophobicity and resistant to alcohol, acids, alkali & some disinfectants.

→ TB is a disease of respiratory transmission i.e. m. tuberculosis is transmitted via respiratory route.

→ A person gets infected when he comes in Contact with environment Contaminated with tubercle bacilli which are expelled during coughing, Sneezing or talking.

tachychardia : abnormal rapid heart rate

→ It is a disease that mainly affects the lungs.

→ It can spread through the blood stream & lymphatic System to the brain, bones, eyes & skin (extrapulmonary tuberculosis).

→ When such tubercle bacilli are inhaled by a person, it reaches to alveoli (air sack of lungs usually present at the apex of lungs) & are ingested in pulmonary macrophages (is cell) which plays imp. role in organisation & repair of tissues.

→ Tubercles are formed due to accumulation of macrophages at infected site.

→ These macrophages secretes a substance which stimulate surrounding fibroplast to enclose infection site leading to formation of tubercles or granulomas

→ Tubercles are formed in infected organs during course of disease hence called as tuberculosis.

→ The main symptoms of TB are Cough, respiratory failure, tachycardia etc.

→ Depending upon site of infection TB has following types :

1) Pulmonary tuberculosis (respiratory tract)
2) Genitourinary TB (Genitourinary tract)
3) Tuberculosis meningitis (Nervous Sytem)
4) Miliary TB (Wide spread infection)

bacteriostatic → Prevent the growth of bacteria

* characteristics of a antitubercular drug :

→ A drug used for treatment of tuberculosis is known as antitubercular drugs.

→ An ideal antitubercular drug posses following characteristics :

1) It may be effective as bacteriocidal or bacteriostatic in relatively very low conc.
2) It should be highly diffusiable & thus capable of reaching all tissues of body or all infected site.
3) Since tubercle bacillus may multiply & survive within mononuclear cells, it must be able to penetrate a cell membrane.
4) It should be less toxic, highly effective & less expensive.
5) It should be relatively stable for resonable length of time & not excreted rapidly or not altered so rapidly by host.

* classification :

The imp. antitubercular drugs can be divided into two groups

1) first line agents :

→ These are also called as pri. or std. standard chemotherapeutic agents.

→ The first line agents are having high activity & minimum toxicity.

→ It includes Streptomycin, isoniazid, ethambutol & rifampicin etc dihydro Streptomycin, 4-amino salicylic acid etc.

2) Second line agents :

→ These are also called as Secondary antitubercular drugs.

→ These are the drugs having less efficiency & significant toxicity.

→ It includes ethionamide, rifampicin, ethambutol, paraaminoo salicylic acid, Cycloserine, viomycin, thioacetazone etc.

→ These drugs are relatively toxic Hence they should be used only when the organism develops resistances to the first line agents.

→ chemotherapy of tuberculosis faced some special problems because of slow growth rate of micobacteria & their intracellular location.

→ Since the disease is chronic by its nature hence needs about 1-2 year treatment in most cases.

→ In such a chronic treatment, if only single drug is used, the risk of development of drug resistant strain of micobacteria is high, also there a risk of drug toxicity.

→ To overcome this problem Combination therapy is used in which two or more drugs are used together.

★ First line Agents :

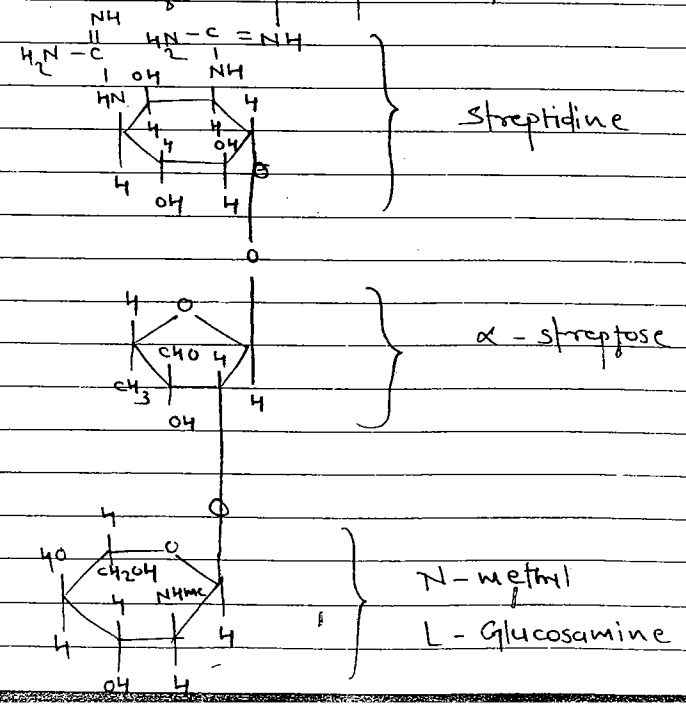
1) Streptomycin : $C_{21}H_{39}N_7O_{12}$ (STM)

→ streptomycin was 1st introduced in 1944 by Waksman as an antitubercular drug isolated from culture of Streptomyces griseous.

→ It is solid, water soluble with basic properties with leavo rotation composed of their main units.

a) α - streptose
b) N - methyl L-glucosamine
c) Streptidine

→ The Str. of Streptomycin is.



→ Streptomycin belongs to the group aminoglycoside antibiotics.

→ It is less or not absorbed in gastrointestinal (GI) tract hence not given orally. It is given by an injection.

Mechanism of action :

→ It is both tuberculostatic & tuberculocidal in vitro depending upon the Conc^n but in vivo it mainly acts as tuberculostatic agent.

→ STM inhibits → protein synthesis.

→ It damages membranes resulting in bactericidal action. STM diffuses across outer membrane of M. tuberculosis and finally penetrates cytoplasmic membrane.

→ Binding of STM to 30S ribosomal subunit appears to be primary site of action. As a result of this binding there is disturbance of normal protein synthesis leading to inhibition of protein synthesis as well as abnormal protein.

Structure activity relationship :

→ Modifications of the streptose portion of STM has been exctu extensively studied such as

1) Reduction of ald. group (-CHO) to alcohols ($-CH_2OH$) results in a Comp. dihydrostreptomycin which has activity similar to STM with greater potential for producing delayed severe deafness.

2) oxidⁿ of ald. (-CHO) to schiff's base derivative (oxime, semicarbazone or hydrazone) results in inactive analogous / loss of activity.

3) oxidⁿ of $-CH_3$ group in streptose moiety to $-CH_2OH$ group gives an active analogous but with no advantage over STM.

4) Modification of aminomethyl (-NHMe) group in glucosamine portion of STM by demethylation or by replacement with larger alkyl groups, reduces activity.

5) Modification of either guanidine ($-NH-\overset{NH_2}{\overset{|}{C}}=NH$) in the streptidine nucleus of STM results in decreased activity.

→ When STM used alone, bacterial resistance develops in 3-5 months but when it is used in combⁿ with other antitubercular drugs, the development of resistance may be delayed for a year or more.

2) Dihydrostreptomycin :

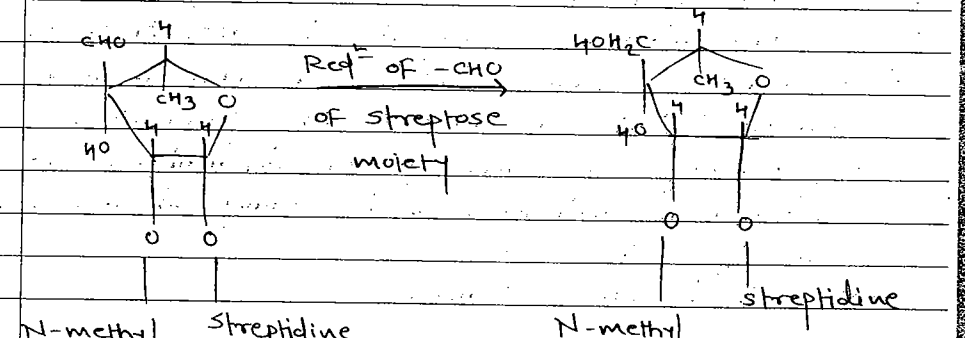
→ Dihydrostreptomycin is a derivative of STM obtained by reducing the aldehyde (-CHO) group of streptose moiety of STM to alcohol ($-CH_2OH$).

→ It shows similar activity as STM.

→ But it is with a greater potential for producing delayed severe deafness.

→ Though it has same activity as STM but it is more stable especially in alkaline medium.

→ It is less disturbing to vestibular function and auditory branch of 8th cranical nerve.



STM Dihydrostreptomycin

$C_6H_7N_3O$

3) Isoniazid (INH) (Isonicotinic acid hydrazide)

→ Introduced in 1952, INH is an extremely effective & safe antimycobacterial agent. chemically it is hydrazide of isonicotinic acid.

→ It is generally considered as primary drug for treatment of TB.

→ It exhibits bacteriostatic action on the intracellular & extracellular bacilli.

→ It is a drug used for treatment of pulmonary & extrapulmonary TB.

→ It interfees with cell wall development of m. tuberculosis.

→ Though INH resistant strains grises rapidly, it is given in Combination of streptomycin, PAS or refampcin.

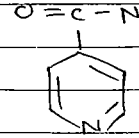
→ The INH - PAS Combination is superior whereas INH - rifampcin Combination is more favoured.

→ However, studies have shown that isoniazide alone is as good as any of the Combination.

→ Because of wide spread distribution in the body (i.e. highly diffusable), it is equally effective against all types of TB.

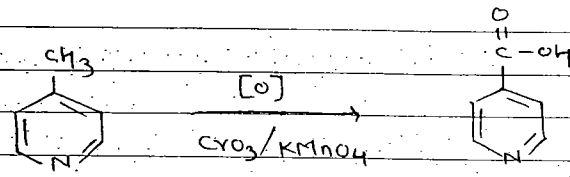
→ It is given orally.

★ Structure :



isoniazide

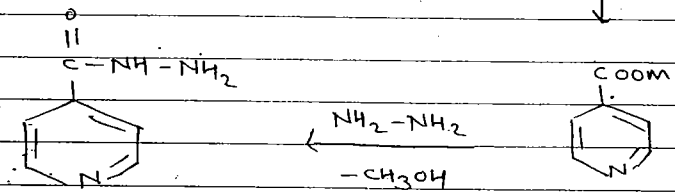
★ Synthesis :



γ - picoline / 4-methyl pyridine

γ - picolinic acid / isonicotinic acid

MeOH / HCl



isoniazid

methyl isonicotinate

→ oxidation of 4 - methyl pyridine in the presence of CrO_3 or $KMnO_4$ gives isonicotinic acid which on esterification gives ester methyl isonicotinate.

→ The ester undergoes condensation with hydrazine yields isoniazid.

★ Mechanism of Action :

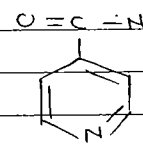
→ INH acts as an inhibitor for conversion of saturated fatty acid to unsaturated fatty acid by blocking formation of desaturase enzyme.

→ These unsaturated acid acts as precuesor for the formation of mycolic acid which is a key component in the development of bacterial cell wall.

★ Structure Activity Relationship :

An extensive series of derivatives of nicotinaldehyde, iso-nicotinaldehyde & substituted nicotinic acid hydrazides have been prepared & investigated for their tuberculostatic activity.

1) Isoniazide hydrazones are prepared found to posses antitubercular activity but these Comp. were shown to be unstable in (GI) gastrointestinal tract releasing active INH.



isoniazid hydrazone

It shows that their activity is due to formation of INH & not due to hydrazone str.

2) Substitution of benzene, piperidine or a thiazole ring for the pyridine nucleus destroys all its activity against strain $H_{37}Rv$ bacilli.

3) The γ - position is the position of choice for the hydrazide group., if changes to α or β activity ↓is

4) Substitution of alkylidene, cycloalkidene & aryl - alkylidine group for H^2 & H^3 (i.e. N_2 hydrogen atoms) has no effect on activity.

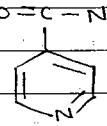
5) Substitution of alkyl group for both H^2 & H^3 gives highly active comp. but the activity diminishes as the size of alkyl group increases.

6) Substitution of alkyl groups for both H^1 & H^2 gives Compounds with reduced activity.

7) Replacement of H^1, H^2 & H^3 with alkyl groups produces total loss of activity.

→ None of the derivatives of INH is more active than itself.

→ However the isopropyl derivative i.e. iproniazide has tuberculostatic activity higher than isoniazid in humans but at the same time possess toxic side reactions.



It has also found to exhibit psychomotor stimulant activity.

4) P-amino Salicylic acid :

→ PAs as an antitubercular drug proposed by Lehmann in 1964.

→ Because of its sour taste & irritant property it is mainly used in its Sodium, potassium & calcium salts.

→ It is orally active & readily administered in gastro-intestinal tract.

→ The main fun of PAs is, it delays the development of resistance of bacteria against antitubercular drug.

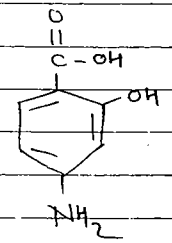
→ It is bacteriostatic in both vivo & vitro.

→ Side effects are milder includes (GI) gastro-intestinal disturbances with occasional skin rashes.

→ PAS when co-administered with INH is found to reduce the acetylation of INH (which diminishes activity of INH).

→ The calcium salt shows less irritation to the GIT than the sodium salts.

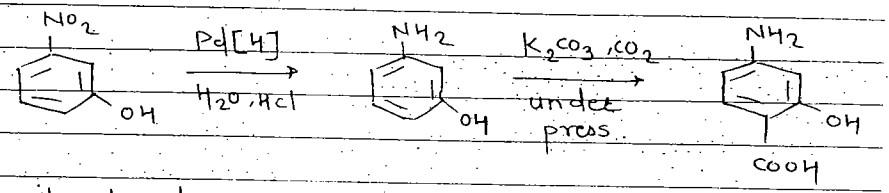
Structure :



P-amino Salicylic acid

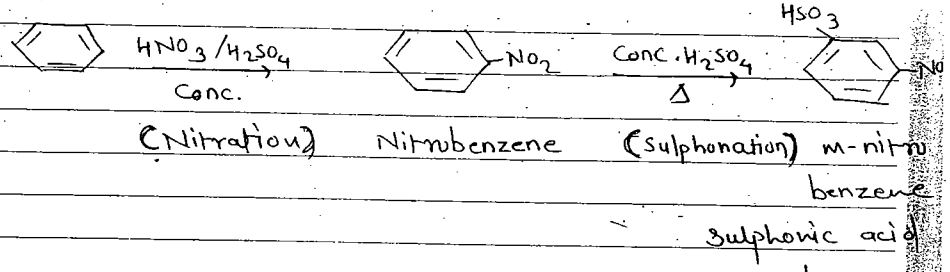
★ Synthesis :

1)

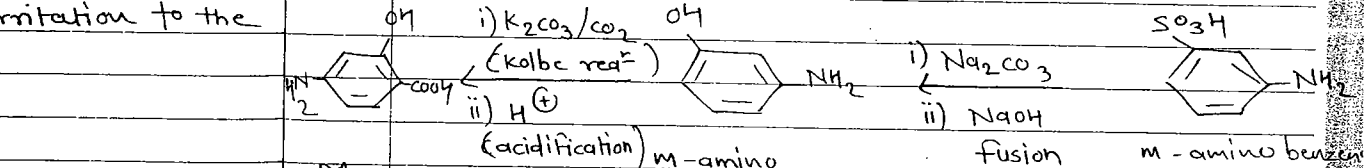


m-nitrophenol → m-aminophenol → PAS

2)

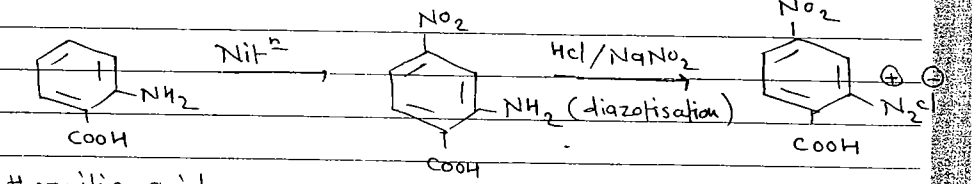


(Nitration) Nitrobenzene (Sulphonation) m-nitro benzene sulphonic acid

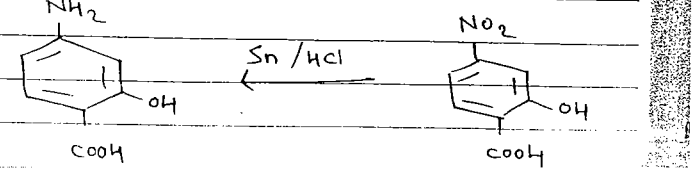


PAS ← m-amino phenol ← fusion ← m-amino benzene sulphonic acid

3)



Anthranilic acid



★ SAR :

Modification in the structures of P-amino Salicylic acid normally results in loss of activity unless the parent molecule is readily regenerated

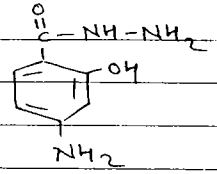
→ Replacement of pri. amino group with hydroxy, alkoxy, ter. amines & amides results in inactive compounds.

→ Masking the hydroxyl group as the ether or ester or replacing it with thiol, halogen, CN, OCH_3, NO_2, H, $-NH_2$ Causes less in biological activity

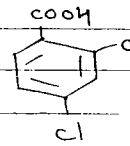
→ Conversion of carboxylic acid group to alkyl esters, amidines, amides or nitrates also results in inactivity.

→ Substitution of PAS by diff. functional groups reduces its activity.

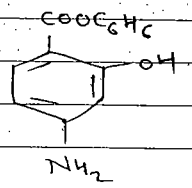
→ The PAS - hydrazide is a active derivative of PAS.



→ The para - chloro PAS have the activity in the bovine strain of tuberculosis bacteria.



→ The phenyl ester of PAS have the similar activity as that of PAS. because they can be slowely hydrolysed to the free acid.



★ Second line Agents :

1) Rifampian :

→ It is firstly discovered in 1957 by a researcher's group while analysing a soil sample from pine forest. They found a new bacterium which produced a new class of molecules with antibiotic activity.

→ After 2 years of attempts to obtain more stable Semisynthetic products, a new molecule with high efficiency & good tolerability was produced & named as Rifampicin. And it was approved by FDA in 1971

→ Rifampicin is an orally active bactericidal semi-Synthetic derivative of rifamycin B, an antibiotic isolated from streptomyces mediterranei.

→ It is most active against gram +ve & many viruses.

→ Rifampicin is used for the treatment of tuberculosis in Combination with other antibiotics, such as pyrazinamide isoniazid & ethambutol.

→ Combination therapy is used to prevent the development of resistance & to shorten the length of treatment.

→ Rifampicin is also used to treat non-tuberculous mycobacterial infections including leprosy (Hansen's disease) & mycobacterium kansasii.

→ It is well distributes throughout the body and also well penetrates into cerebrospinal fluid so also useful for treatment of tuberculous meningitis.

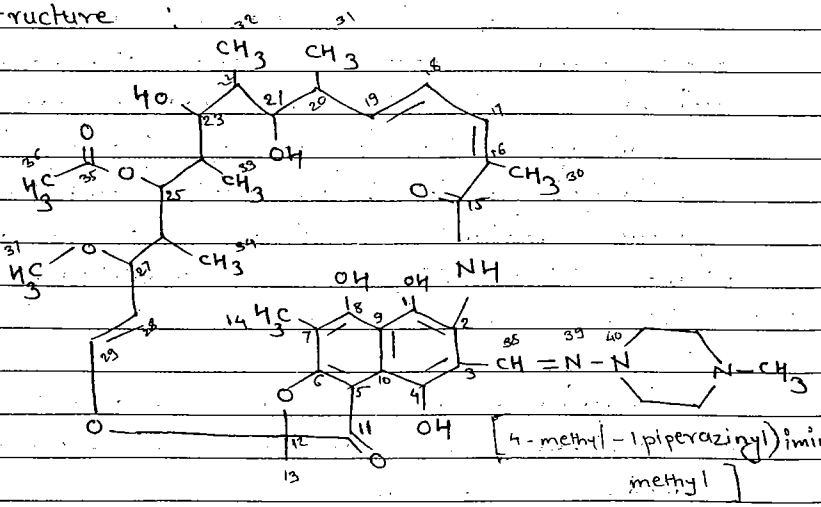
Mechanism of Action :

→ Rifampicin inhibits bacterial DNA-dependent RNA Synthesis by inhibiting bacterial DNA-dependent RNA Polymerase (DDRP)

→ DDRP is an enzyme necessary for RNA Synthesis.

→ This rifampicin is highly active against DDRP Causes inhibition of bacterial RNA synthesis, by binding to DDRP β subunit.

Structure :



SAR :

1) The intact macro cyclic molecule is required for antimycobacterial activity.

2) The opening of macro-cyclic ring results in decreased activity.

3) Reduction of the double bond causes the loss in activity of rifampicin.

4) The free -OH groups should be present at C_1, C_8, C_{21}, C_{23}. These groups appear to lie in a plane & appear to be important binding groups for attachment to DDRP.

5) When the hydroxyl groups at these positions are removed Completely or substituted to give another derivative causes the Complete loss in antitubercular activity.

6) Acetylation of -OH group at C_{21} & C_{23} causes loss in activity.

7) The presence of antibacterial activity is due to presence of aromatic Napthalene ring. If it is replaced causes loss in activity of the drug.

2) Ethambutol : (1961)

→ Available as generic medicines.

→ It is a orally effective bacteriostatic agents.

→ It is a water soluble, chemically ethylenediamine-di-1-butanol.

→ Activity is stereospecific.

→ Dextro isomers are having maximum about 200-500 times more antimycobacterium activity than levo form.

→ The difference in activity between the two isomers suggests a specific receptor for its site of action.

→ It is belived to be effective against rapidly replicating bacteria.

→ It is usually given in Combination with other tuberculosis medications, such as isonazid, rifampicin, & pyrazinamide.

structure :

$C_2H_5-CH(CH_2OH)NH-CH_2-CH_2-NH-CH(CH_2OH)C_2H_5$

Mechanism of Action :

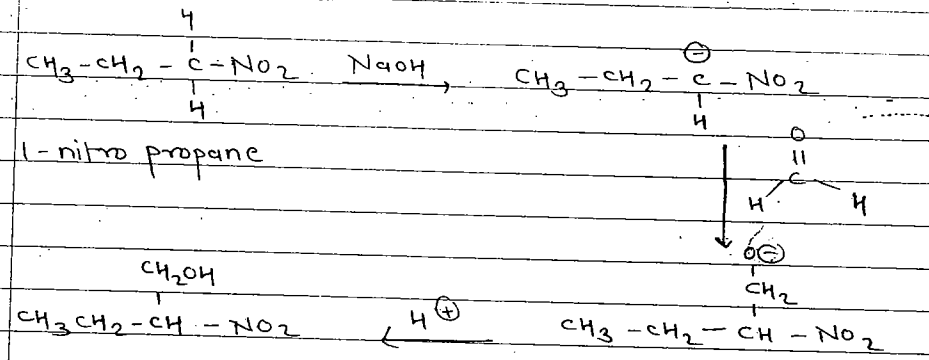
→ It works by disturbing the formation of cell wall. Mycolic acids attach to the 5'-hydroxyl groups of D-arabinose residues of arabinogalactan and form mycolyl-arabinogalactan-peptidoglycan Complex in the cell wall of bacteria.

→ It disrupts arabinogalactan synthesis by inhibiting the enzyme arabinosyl transferase.

→ Disruption of the arabinogalactan Synthesis inhibits the formation of this Complex & leads to increased permeability / thining of cell wall.

→ In this way ethambutol inhibits the cell wall formation.

Synthesis :



2) $2\ CH_3CH_2CH(NO_2)-CH_2OH \xrightarrow[[H]]{\text{Raney Ni}} 2\ CH_3CH_2CH(NH_2)-CH_2OH$

2-Nitro-1-butanol → 2-amino-1-butanol

↓ $Cl-CH_2-CH_2-Cl$

$C_2H_5-CH(CH_2OH)-NH-CH_2-CH_2-NH-CH(CH_2OH)-CH_2CH_3$

SAR :

1) The presence of two basic amino groups are essential for biological activity.

2) The acylation of amino group causes loss in activity.

3) Extension of ethylene diamine chain, replacement of either nitrogen, increasing size of N-substituents & moving the location of hydroxy methyl groups are all changes that drastically reduces or destroys biological activity of ethambutol.

4) SAR studies indicated that the nature of ~~branching~~ branching, distance between two nitrogen & extent of N-alkylation are activity governing factors of ethambutol.

3) Ethionamide : (thioisonicotinamide)

→ It is a secondary drug especially used for treatment of pulmonary tuberculosis.

→ Ethionamide was Synthesized in 1956

→ chemically it is 2-ethyl thio isonicotinamide.

→ It is a thioamide analog of INH

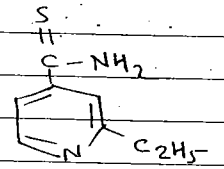
→ It is a analog of nicotinamide.

→ It is orally effective agent.

→ It is poor in vitro action

MOA → Ethionamide inhibits peptide Synthesis in mycobacteria by blocking incorporation of amino acids Containing sulfur (cysteine & methionine)

Structure :



~~SAR~~ MOA :

→ It may inhibit mycobacterial mycolic acid synthesis

→ It may affect dehydrogenase systems in tubercle bacilli.

→ It may form a substituted isonicotinic acid derivative that may interfere with NAD-dependent Systems.

SAR :

→ Conversion of the thioamide into an amide, amidine or thiourea results in inactive Compounds.

2) Moving the thioamide to position 2 or 3 also decreases activity.

3) Replacement of the pyridine ring with pyrazine or benzene causes loss in activity.

→ Thus the testing of various analogs showed that 2-ethyl isothionicotinamide (ethionamide) is most active derivative.

4) Cycloserine :

→ chemically cycloserine is D-4 amino-3-isoxazolidone was isolated in 1955.

→ It is isolated from three different species of Streptomyces ;

1) Streptomyces garyphalus
2) S. Lavendulae
3) S. Orchidaceae (mainly from it)

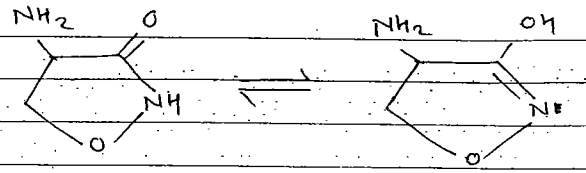
→ It is found in both isomeric form i.e. dextro & leavo form. Both are active but dl mix. is more active than pure enantiomer.

→ It is mainly tuberculostatic.

→ It is effective against tuberde bacilli which develops resistance against INH & STM although its antitubercular activity is less than that of these two drugs.

→ It interfers in cell wall synthesis of m. tuberculosis.

Structures :



keto form. enol form

Mechanism of Action :

→ Cycloserine interferes ~~with~~ Cell wall Synthesis by inhibiting D-alanine incorporation into bacterial cell walls results in its antibiotic activity.

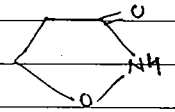
→ During the early stages of cell wall synthesis, L-alanine is converted into D-alanine, and then two D-alanine molecules are coupled.

→ Cycloserine acts as an analog of D-alanine and inhibits both the processes competitively.

SAR :

1) The D-isomer of Cycloserine has only 10% of the activity of the L-isomer.

2) Removal of 4-amino group produces 3-isoxazolidone which is an inactive comp.



3) The replacement of $-NH_2$ group by $-ONH_2$ (aminooxy) group, the obtained derivative is an active tuberculo-static agent.

4) The substitution in the heterocyclic ring decreases the antibacterial activity.

Synthesis :