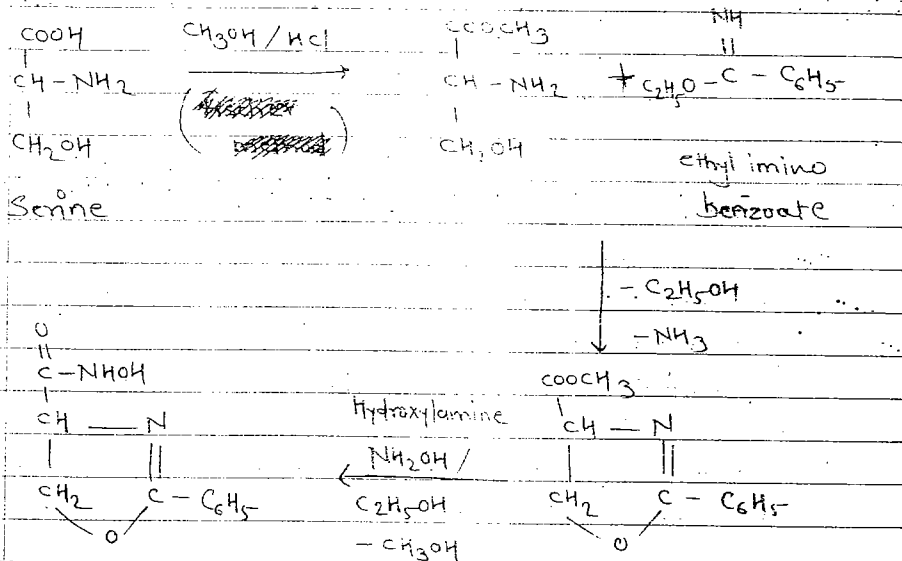
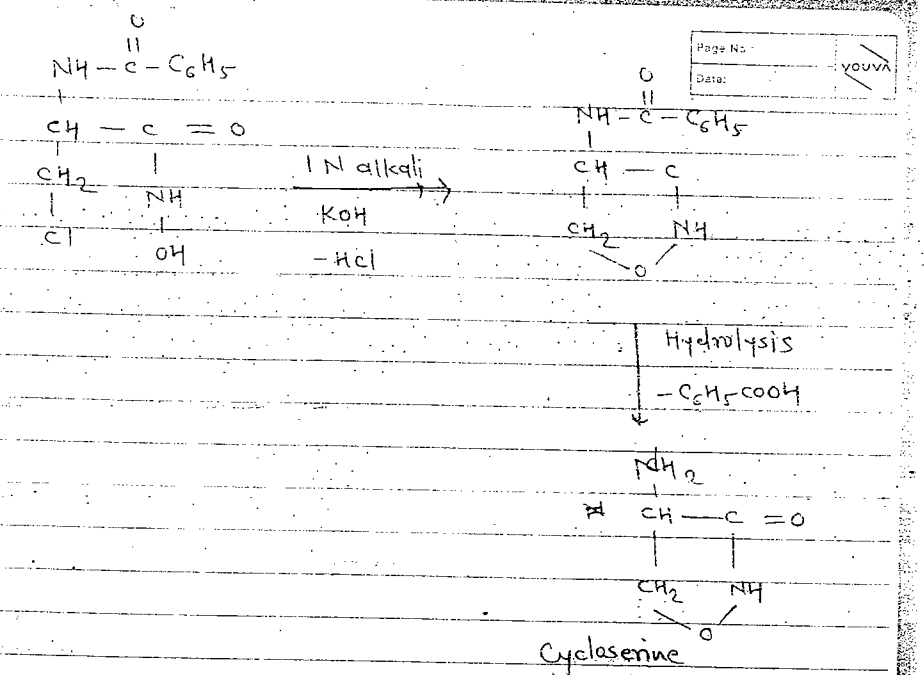
4) The substitution in the heterocyclic ring decreases the antibacterial activity.

Synthesis





4) Thioacetazone :

→ It is chemically thiosemicarbazone.

→ This drug was designed in 1948 by Domagk & Coworkers

→ Because of its toxicity, it is used rarely in very low dosages to treat pulmonary TB & tuberculoid leprosy.

→ It is orally effective & satisfactorily absorbed from GIT.

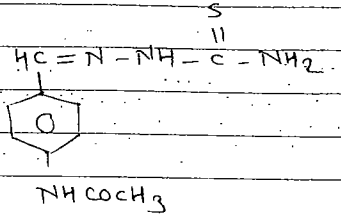
→ It is used along with other antitubercular drug like INH.

→ It's also called as Amithiozone

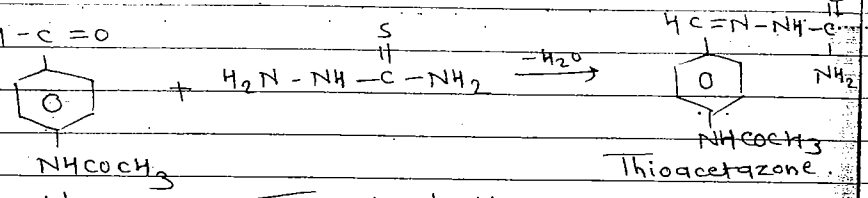
→ The activity of these Comp. is tuberculostatic, not tuberculocidal.

→ They are well absorbed when administered orally.

Structure



Synthesis



P-acetamido benzaldehyde — Thiosemicarbazide — Thioacetazone (A)

SAR :

→ Replacement of thiosemicarbazone group by semicarbazone, hydrazone or oxime yields inactive compound.

→ Substitution on the pri. amine of thiosemicarbazone group with one or two alkyl groups results in loss of activity.

→ Replacement of $-NHCOCH_3$ group by $-NMe_2$ & $-NH_2$ group give Comp. with equal activity.

→ Replacement of $-NHCOCH_3$ group by $-NHCHMe_2$ (isopropyl amine) give Compounds with greater activity.

→ Replacement of $-NHCOCH_3$ group with NO_2 leads to loss of activity.

5) Viomycin

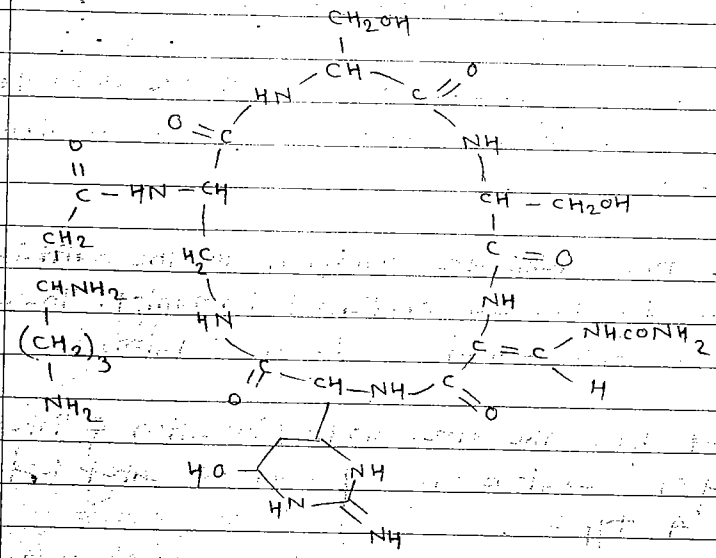
→ Viomycin is produced by Streptomyces pumicens

→ It is also called as Tuberactinomycin B.

→ The imp. side effect of viomycin involve renal damage.

→ viomycin has about 25% of the activity of streptomycin in vitro & vivo.

Structure of Viomycin :



Antileprotic Drugs :

Leprosy :

→ Leprosy is also called as Hansen's disease is a chronic human disease caused due to an acid fast bacillus which produces nodules in the skin & loss of sensation in affected region.

→ It is a dermatological infection caused by mycobacterium leprae & the disease develops very slowly over a period of years.

→ The leprosy bacteria was 1st discovered by Hansen in 1873 hence the name of disease is Hansen's disease.

→ Once the bacilli are multiplied to the sufficient extent by the cell mediated immunity. These reactions are called as lepra reactions.

→ Based upon the area under infection & intensity of lepra reactions leprosy can be categorised into 4 types

1) Tuberculoid leprosy :

It is characterised by presence of infection in restricted area & less pronounced lepra reactions. (Few no. of micro-organisms are present in infected area & of skin. Hence dapsone alone may be effective)

2) Lepromatous Leprosy :

It is characterised by widely spread disease with high no. of infecting micro-organisms. Hence this form needs more drastic (i.e. multidrug) & prolonged treatment.

3) Indeterminate leprosy :

In very early stages of the disease, micro-organisms are not multiplied to the extent to induce lepra reactions. This early form of the disease is known as indeterminate leprosy.

4) Borderline leprosy :

Tuberculoid leprosy & lepromatous leprosy are two extremities of active form of disease. All other forms that lie in between these two extremities are known as borderline leprosy.

★ Antileprotic drugs :

→ The drugs which are used for the treatment of leprosy are called as antileprotic drugs or agents.

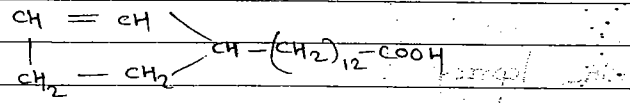
→ Relatively few drugs are available to treat this chronic dermatological disease includes dapsone, Acedapsone, Solapsone, rifampicin, Diaminodiphenyl thiourea etc.

→ An ideal antileprotic agent should be able to control lepra reactions & it should eliminate viable bacilli from the blood & nasal secretions by stopping their multiplication.

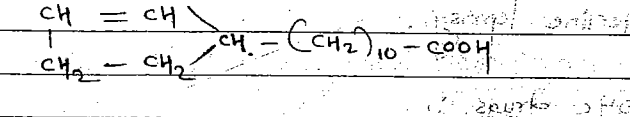
1) Chaulmoogra & Hydnocarpus oil :

→ The oil of chaulmoogra & hydnocarpus are used since from ancient time in the treatment of leprosy.
→ These oils are extracted from the ripped seeds of Hydnocarpus anthelmintica, H. heterophylla & other species of Hydnocarpous :
→ It is also obtained from Taraktogenus species.
→ It Contains glycerides of chaulmoogric acid & hydnocarpic acid.

Structure of chaulmoogric acid :



Structure of Hydnocarpic acid :



Various derivatives were prepared & used for treatment of leprosy. The ethyl esters of these acids were used for a long time in treatment of leprosy.

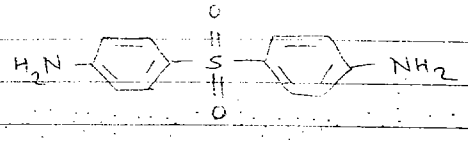
2) Sulfones :

- Because of chemical similarities of Sulfones with Sulfonamides, these were tested for antibacterial activity.
- The diaryl sulfones represent major class of agents to treat leprosy.
- These are orally active & well distributes in diff. body tissues.
- Sulfones such as dapsone, acedapsone, solapson are used as antileprotic drugs.

a) Dapsone : (4,4' - diamino diphenyl Sulfone) (DDS)

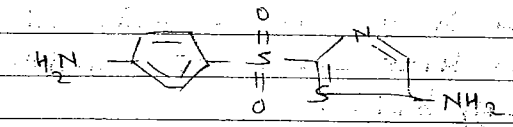
- The Comp. was reported to be very effective but extremely toxic.
- Dapsone & its analogs did not prove as antituberculer drug in humans but they are active against leprosy.
- It is synthesized in 1908 but antibacterial activity was discovered in 1941 acts as antileprotic agent.
- Insoluble in water causes GI irritation.
- It is weakly basic.
- It is bacteriostatic. Activity similar to that of Sulfonamides.

Str.



SAR of Dapsone / Sulfone

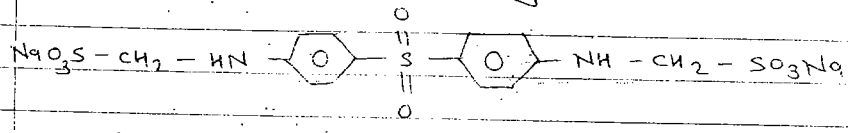
- Analogs of dapsone have substituents on the ring such as hydroxyl, amino, chloro, methyl groups have to be shown to be inactive.
- Replacement of one amino group with hydroxyl, nitro or hydroxylamino or acetyl amino leads to derivatives does not posses significant biological activity.
- When both amino groups are replaced with hydroxyl groups, an inactive Comp. obtains.
- Reduction of sulfone group to sulfoxide reduces its activity.
- Replacement of one of benzene ring by thiazole ring results in formation of thiazole sulfone which is still active but less effective than DDS.



Thiazole Sulfone.

- further reduction of sulfoxide to thioether eliminates activity.

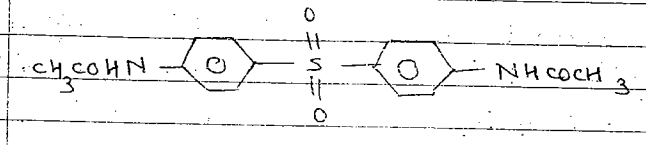
- Aldehyde - bisulfite Complexes of amino functions of sulfones produce active Compounds such as sulfone sulfoxone Sodium which is used in individuals who are unable to tolerate DDS because of GI irritations. It is break down in vivo to regenerate DDS.



Sulfoxone Sodium

b) Acedapsone / DADDS

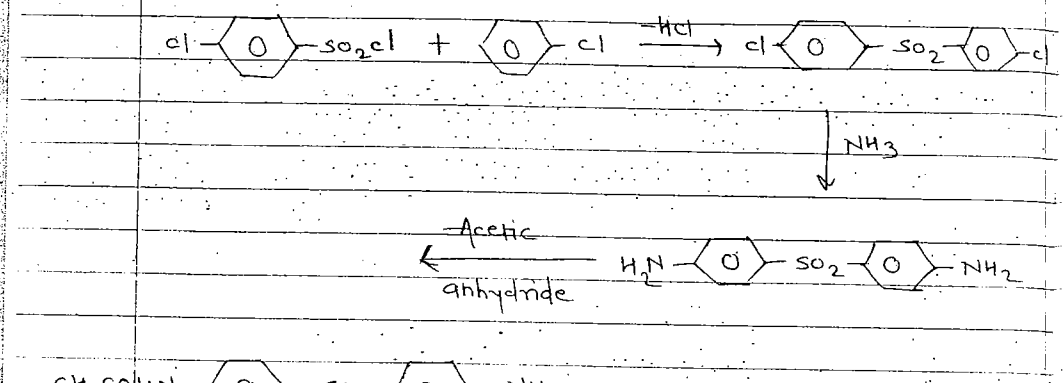
- It is N,N' - diacetylaminodiphenyl sulfone having structure



- Acetylation of DDS form DADDS which is more soluble in water than DDS & easily get absorbed in GIT.
- It is less active than DDS but found to decrease GI irritation.
- It has low toxicity than DDS, used for treatment of tuberculoid leprosy.

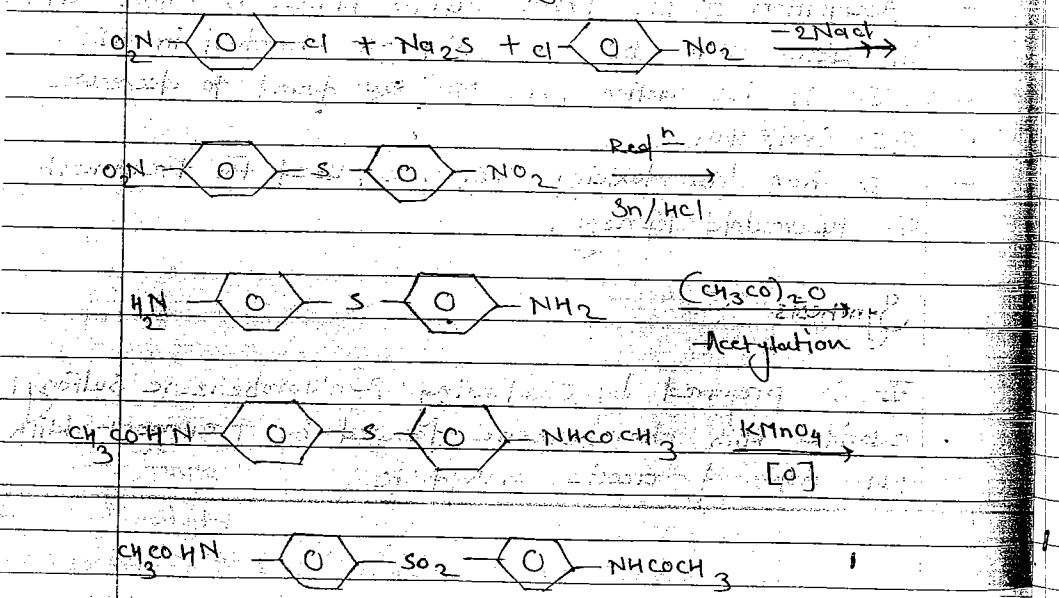
Synthesis

It is prepared by Condensing P-chlorobenzene sulfonyl chloride with chlorobenzene followed by treatment with NH_3 Soln & acetic anhydride



DADDS

- In another Synthesis, two molecules of P-chloronitro-benzene Condensed with excess of Sodium Sulphide form a nitrosulphide. This Comp. is reduced to diamine & then acetylated to yield product which on oxidation with $KMnO_4$ yields acedapsone.



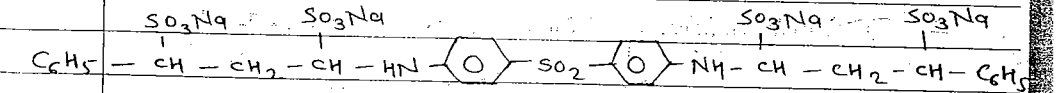
SAR of Acedapsone :

- Reduction of sulfone group to a sulfoxide reduces activity of DADDS
- Further reduction to thioether eliminates activity of DADDS.
- When both acylamino groups are replaced by hydroxyl groups, resulted Comp. with low activity or it is inactive
- Substituents like $-OH$, $-NH_2$, $-Cl$, $-OCH_3$ & $-CH_3$ groups on ring gives Inactive Compound.

c) Solapsone :

- It is a salt of Sodium salt of tetrasulphonic acid.
- It is almost white powder. unlike dapsone it is Very Soluble in water.
- It is more slowly absorbed than DDS
- Solapsone is largely inactive.

Str. :



SAR of Solapsone :

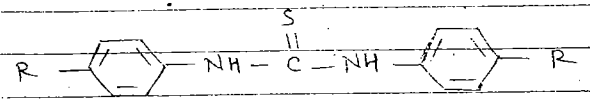
- Replacement of $-CH_2-CH(SO_3Na)C_6H_5$ from both side by $-(CHOH)_4-CH_2OH$ gives glucosulfone Sodium which is active antileprotic agent.
- Replacement of $-CH_2-CH(SO_3Na)C_6H_5$ From both side with hydrogen gives sulfoxone Sodium which is also active form / Comp.

3) Rifampicin:

Same as explained in Antitubercular drugs.

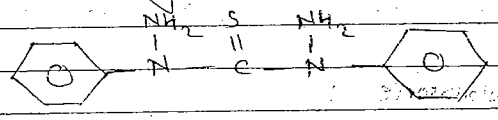
4) Diaminodiphenyl thiourea:

- Some diaminodiphenyl thioureas demonstrated in vitro tuberculostatic activity and some as antileprotic activity.
- The good activity was shown for 4,4'-disubstituted diphenyl thiourea.



4,4'-dialkyl diphenyl thiourea

- They show their mechanism of action by decreasing protein synthesis.
- Diaminodiphenyl thiourea has structure:



- It is a second line antileprotic drug.

SAR:

1) The substitution of $e^{\ominus}$ donating groups on both rings of diphenylthiourea is required for activity. The substituents may be halogen, dialkylamino, alkyl or alkoxy functions.
2) Increased substitutions on phenyl rings results in loss of activity.
3) Movement of substituted groups to meta or ortho positions results in loss of activity.
4) Replacement of phenyl ring with cyclohexyl results in loss of activity.
5) Replacement of thiourea with urea, guanidine etc. also abolishes activity.
6) 4-butoxy-4'-dimethylamino diphenyl thiourea has shown good results in treatment of leprosy.