Medicinal chem (sem II)

Unit - IV

Analgesic & Anti-inflammatory Drugs

1) Analgesics :

Introduction :

Analgesia may be defined as a state of relative insensibility to pain where the capacity to tolerate pain is increased without the loss of Consciousness

→ Analgesics are the agents which reduces the pain without the loss of Consciousness.

→ These drugs decreases the sensation of pain by virtue of their action on the CNS.

→ These are one of the most imp. group of therapeutic agents as the pain killers.

★ Mode of Action :

- The main function of analgesics is to decrease the sensation to pain & also there is no unconsciousness.
- Actually the analgesics act by increasing the threshold of pain which may be defined as 'the lowest perceptible intensity of pain which is induced by stimulus'.
- The stimulus served as the measure of variations of pain threshold
- If greater stimulus is required, the threshold of pain is said to be higher & if a lower or less stimulus is needed the threshold of pain to be low.

When analgesics are used the pain is not decreased but only threshold of pain is increased & therefore patient does not feel the pain.

★ Classification :

Analgesics are classified into two main classes such as :

1) Narcotic analgesics
2) Non-narcotic analgesics.

.....

1) Narcotic analgesics :

- These are Centrally acting drugs produces analgesia having ability to produce drug dependance.
- These are mainly the opium alkaloids & their synthetic or semisynthetic derivatives.

eg.

Morphine, Codeine, petridine etc.

- The chronic use of these drugs leads to addiction
- These are more potent i.e. quick action.

2) Non-narcotic Analgesics

- These are peripherally acting drugs produces analgesia without narcosis i.e. it does not produces drug dependance.
- The use of these drugs does not cause addiction
- Which are less potent than narcotic analgesics

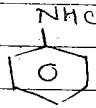
eg.

Aspirin, Analgein etc.

A) Aniline Derivatives :- (1886 - Hepp & Cohn)

1) Synthesis of Antifebrin

i) structure :



Antifebrin

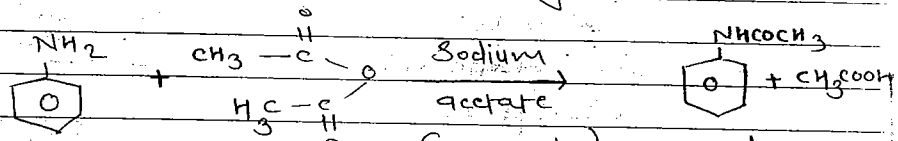
Also called as Acetanilide, N-phenylacetamide

ii) Synthesis :

It may be prepared from aniline in two different ways :-

a) From aniline & acetic anhydride :

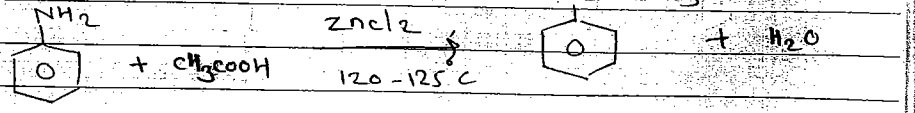
Interaction of aniline & acetic anhydride in the presence of Sodium acetate gives antifebrin.



Aniline Acetic anhydride Antifebrin

b) From Aniline & acetic acid :

Antifebrin may also be prepared by reacting together redistilled aniline & glacial acetic acid in the presence of zinc chloride at an elevated temp. of 120 - 125°C

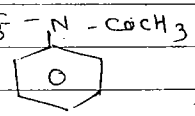


Aniline glacial acetic acid Antifebrin

- It is one of the cheapest antipyretic (Fever reducing agents) analgesics with high toxicity due to liberation of free aniline in vivo.

2) Synthesis of Exalgin :

Structure :

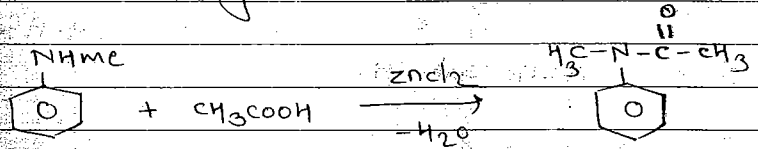


Exalgin

Also called as N-methyl acetanilide or N-methyl-N-phenyl acetamide.

Synthesis :

It is to be prepared from N-methyl aniline & glacial acetic acid in the presence of $ZnCl_2$ on refluxing.

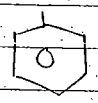


N-methyl aniline + Glacial acetic acid → Exalgin

It is another aniline derivative which is antipyretic analgesic but also have toxicity.

3) Synthesis of Euphorin :

Structure :



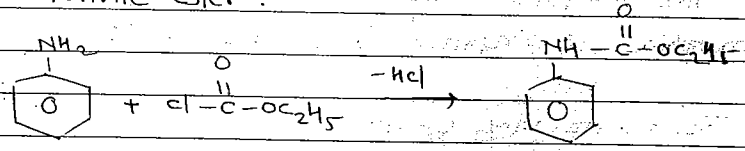
Euphorin

→ Also called as ethyl N-phenyl Carbamate or ethyl carbanilate

→ chemically it is phenyl urethane (i.e. ester of Carbonic acid)

Synthesis :

It can be obtained by the action of aniline with chloroformic ester.

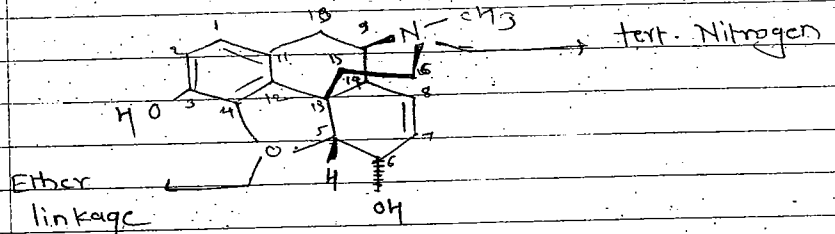


Aniline + chloroformic ester → Euphorin (ethyl chloroformate)

It is less toxic having strong analgesic action without antipyretic action

B) Quinoline Derivatives :

1) Morphine & related Compounds :



Morphine

→ Morphine is a narcotic analgesic drug, Continued use of morphine results in addiction.

→ The features responsible for analgesic activity in morphine & related Compounds are:

1) The quaternary C-atom (C_{13})
2) The direct attachment of quaternary C-atom to aromatic ring.
3) The seperation of tert. Nitrogen from quaternary C-atom by two $-CH_2$ groups
4) The Phenolic $-OH$ group at C_3 & alcoholic $-OH$ group at C_6.

★ Structure activity relationship :

Concerted efforts have been made to prepare morphine substituents that should be free from harmful effects of morphine while maintaining its pharmacological properties.

↓ 1) Any modification on phenyl ring generally diminishes analgesic activity.

2) Alteration of phenolic ($-OH$) group at C_3 in morphine & related Compound by etherification or esterification decreases morphine action i.e. decreases analgesic activity.

eg. Codeine is a methyl ether has 1/1 potency of morphine, whereas diacetyl derivative, heroin has twice potency of morphine.

3) changing the alcoholic $-OH$ group at C_6 by oxidation to keto group or substitution with halogen or hydrogen increases analgesic activity but parallely there is increase in toxicity too.

↓ 4) A shift in position of alc. $-OH$ group from position 6 to 8, results in decrease in pharmacological action

↓ 5) opening of the ether bridge & substitution in aromatic ring decreases its activity

6) The saturation of 7,8 - double bond, the resulting Compound usually exhibit increased pharmacological action.

eg.

Dihydromorphinone obtained by catalytic reduction of morphine & its methyl ether dihydrocodeinone prepared from Codeine have been used as substituents for morphine

- They are 8-5 times as effective as parent Comp. & also possess higher physical dependence liability.

7) Introduction of 14 -OH group in dihydroforms gives still more potent derivatives

8) Bridging of C_6 & C_{14} through ethylene linkage increases potency of drug.

eg.

Etorphine is 200 times more potent than morphine.

g) cleavage of ring between C_9 & nitrogen abolishes activity.

10) Replacement of N-methyl group by phenylethyl group enhances analgesic activity.
N-allyl & N-cycloalkyl methyl functions impart narcotic antagonistic properties to molecule.

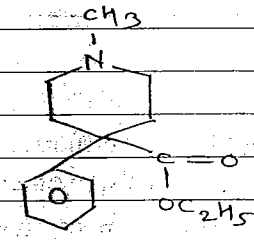
c) Piperidine Derivatives :

A large No. of piperidine derivatives had been Synthesized. several of these Compounds turned out to exhibit marked analgesic activities in addn to atropine like action.

- The most imp. Comp. in this series has been meperidine.

1) Mepridine :

Structure :



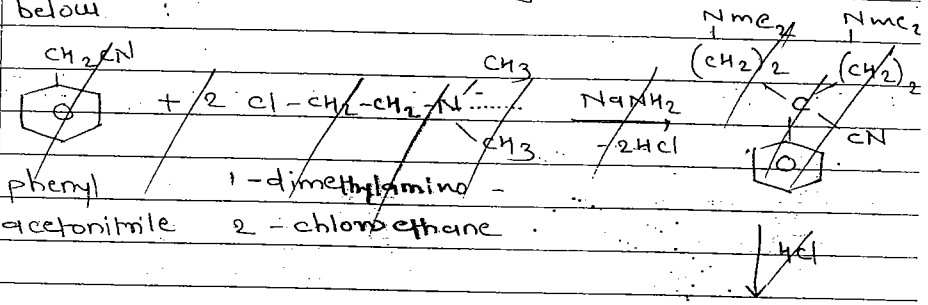
Mepridine (pethidine)

- It is 1-methyl-4-Carbethoxy-4-phenyl piperidine.
- It has become most accepted substitute for morphine for moderate to severe pain.
- It is Synthetic opioids (Narcotic) which is also called as penthidine.

- It is White Crystalline odourless powder.
- It's M.P is 189°C - 186°C

Synthesis :

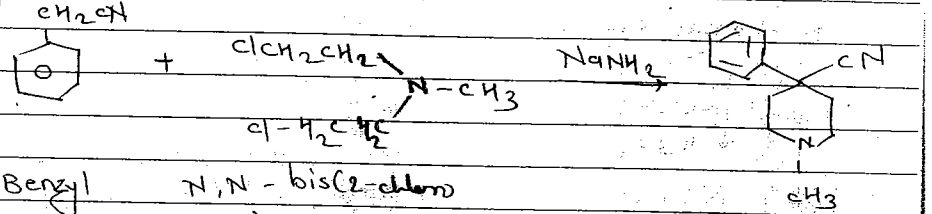
1) A simple Synthetic route for the preparation of meperidine starts with phenyl acetonitrile as shown below :



phenyl acetonitrile — 1-dimethylamino-2-chloroethane

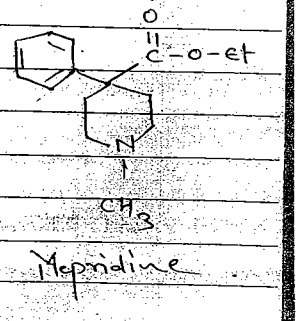
HCl

1)



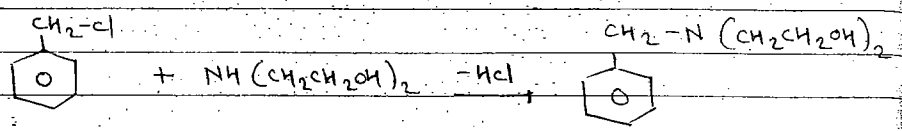
Benzyl cyanide — N,N-bis(2-chloroethyl)-N-methyl amine

$EtOH$
H_2O
$NaOH$



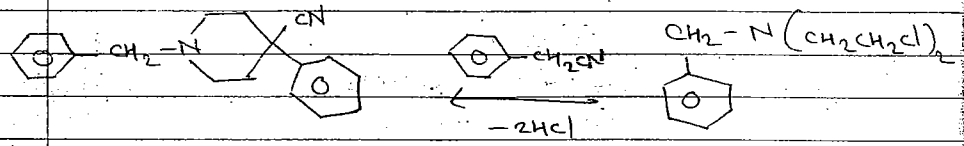
Mepridine

2) This method involves preparation of meperidine using benzyl chloride & diethanolamine.



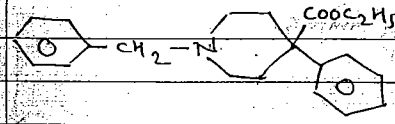
Benzyl chloride Diethanolamine Benzyl diethanol amine

↓ SOCl2



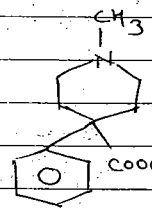
4-cyano-4-phenyl-N-benzyl piperidine

↓ C_2H_5OH, H_2SO_4



Ethyl-4-phenyl

i) H_2/Pd
ii) HCHO
iii) catalytic hydrogenation



Meperidine

Structure Activity Relationship :

A very large no. of piperidine analogs have been prepared & the imp. derivatives are described below in terms of str. activity relationship :

a) Replacement of 4-phenyl group by -R, -Ar, -H, arylalkyl or heterocyclic group reduces activity.

b) Presence of phenyl & ester group at 4-position of 1-methyl piperidine gives optimum activity.

c) A substituent in para position of benzene ring either abolishes activity or does not improve it.

d) Larger ester functions & groups like amide, nitrile, Carbinol in position 4 of piperidine nucleus have decreased analgesic activity.

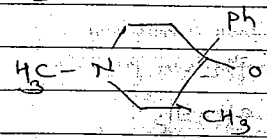
e) Replacement of N-methyl group by various aryl, alkyl group can increase analgesic activity

f) Introduction of meta-hydroxy group in phenyl ring increases activity similar to C_3-OH of morphine
ex: Bemidone

g) Replacement of ester moiety by ketone in bemidone produces ketobemidone which is equivalent to morphine in activity & 20 times more potent than meperidine

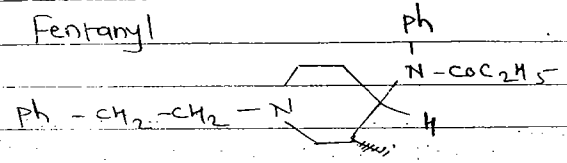
h) Reversed ester of meperidine, propionoxy Comp. Has more active, being 5 times more active than meperidine.

i. Prodine



i) When phenyl & acyl group are seperated from piperidine ring by N-atoms it gives a powerful analgesic.

eg : Fentanyl

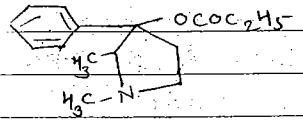


J) Enlarging piperidine ring to 7-membered hexahydroazepine ring, gives more active analgesic agents.

eg : Proteptazine.

K) Contraction of piperidine ring to 5 membered pyrolidine ring was also goal activity.

eg ∝-prodine, prodilidine.

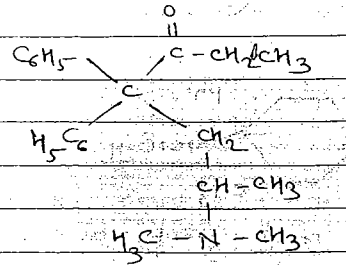


D) Phenylpropylamine Analogs :

1) Methadone :

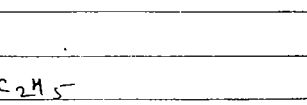
- Methadone is a representative agent of this series.
- It resembles morphine in its pharmacological actions.
- The levo isomer is twice as active as morphine & dextro isomer is 1/10 is effective as morphine.

Structure :

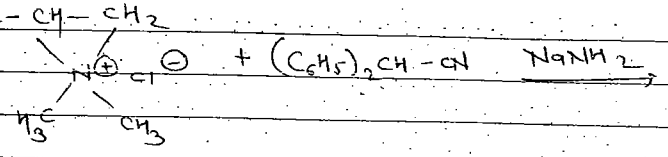


- chemically methadone is 6-dimethylamino-4,4-diphenyl 3-heptanone.

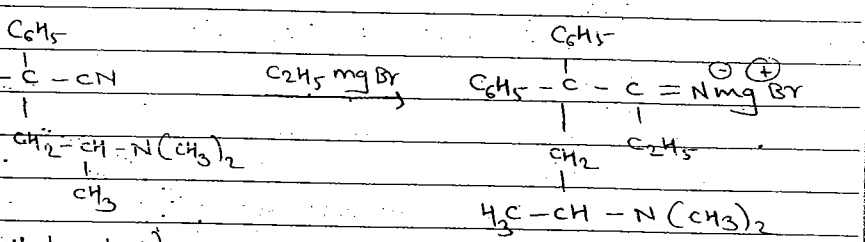
Synthesis :



1)

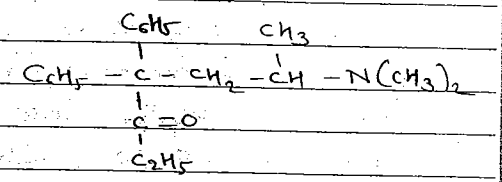


2-chloro-1-dimethylamino Diphenylacetonitrile Propane (Cyclised form)



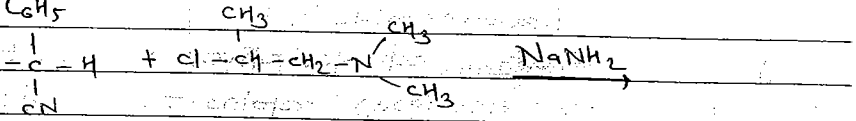
4-(dimethylamino)-2,2-diphenyl Valeronitrile

(H⊕Cl) | Hydrolysis



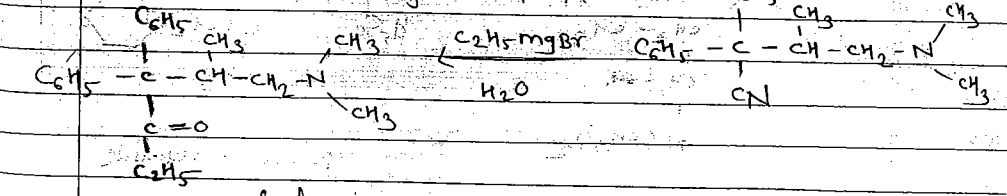
Methadone

2)



Diphenyl aceto nitrile

N,N-dimethyl 2-chloro propane amine / 2-dimethyl aminopropyl chloride



Methadone

SAR of methadone :

A large No of the methadone derivatives are prepared & tested for their analgesic activity as below :

a) The levo isomer of methadone & isomethadone are twice active as its racemates.

b) Removal of any of phenyl ring decreases activity.

c) Introduction of meta hydroxyl group in phenyl ring decreases activity.

d) Methadone derivatives are more potent than iso-methadone series.

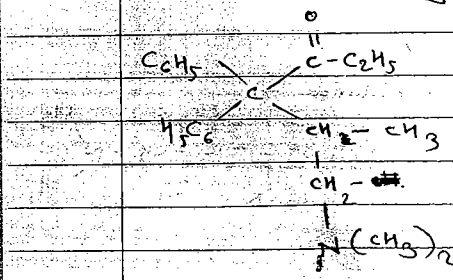
e) Replacement of propionyl group ($-CO-C_2H_5$) by $-H$, $-OH$ or acetyloxy group leads to decrease analgesic activity

f) Replacement of propionyl group by amide group gives the Compound racemoramide is more active than methadone.

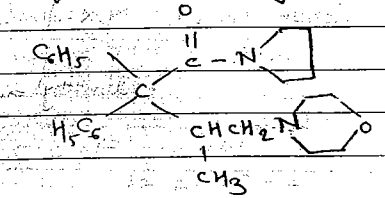
g) The derivatives in which dimethylamino group by heterocyclic ring like morpholine, piperidine etc. are potent as methadone with morphine like activity.

ex : Racemoramide.

h) N-dimethylated derivatives of metabolites of methadone analogous retains the analgesic activity



Isomethadone



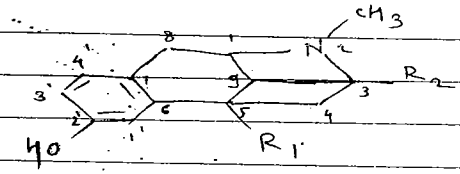
Racemoramide

E) Morphan Analogs :

The fact that the removal of ether bridge & all the peripheral groups in the alicyclic ring of the morphine did not destroy its analgesic activity encouraged may & murphy to synthesize a new series of Compounds known as benzomorphans

i) 6,7 - Benzomorphans :

i) structure :



$R_1 = R_2 = H$

6,7 - benzomorphans

ii) Synthesis :

Synthesis of 6,7 - benzomorphan is given below

The 6,7 - benzomorphan structure Comprises of
a) benzene nucleus b) a quaternary carbon Carbon attached to this nucleus
c) a tertiary nitrogen atom with 2 - methylene groups away from quaternary Carbon possess features similar to morphine.

iii) SAR :

1) Amongst various substitutions at 2' position, following SAR is observed

OH > H > NH_2 , NO_2 , F & Cl.

2) The trimethyl Comp. ($R_1 = R_2 = CH_3$) is about 3 times more potent than the dimethyl analogue ($R_1 = H$, $R_2 = CH_3$)

3) Insertion of methyl group at C_9 increases analgesic activity.

4) Insertion of hydroxyl group at C_9 decreases the activity.

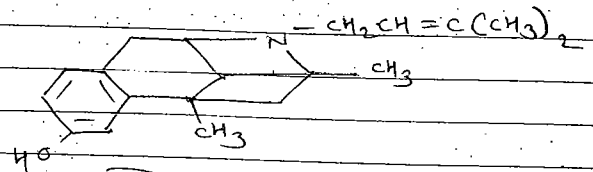
5) The N-phenylethyl analogus always possess greater potency over N-methyl analogues

6) The two isomeric forms of it (cis & trans) shows different activity & addition liability. In between enantiomers of cis isomer (-)isomer is stronger analgesic without addition while (+) isomer is weak analgesic with addition ability.

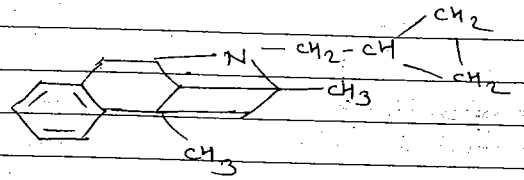
7) The Compound α - 2' hydroxy - 5,9 - dimethyl - 2 - phenylethyl - 6,7 - benzomorphan is clinically useful agent & it is 3-5 times as active as morphine in man & also has lower dependence liability.

8) The another derivative β (±) 5 - ethyl - 2,9 - dimethyl - 2' - hydroxy - 6,7 - benzomorphan is more than 30 times as potent as morphine

9) Pentazocine & Cyclazocine are the classic antagonist from benzomorphan series.



Pentazocine



Cyclazocine

Anti - inflammatory Drugs :

Introduction :

Inflammation may be defined as the series of changes that occur in living tissues following injury. It is recognised by the following symptoms:

1) Calor (heat)
2) Rubor (Redness)
3) Tumour (swelling) &
4) Dolor (Pain)

→ The drugs or agents which are used for the treatment & prevention of inflammation called as anti-inflammatory drugs.

→ The anti-inflammatory analgesics also popularly known as non-narcotic or non-steroidal anti inflammatory analgesics.

→ Almost two decades ago, steroids namely dexamethasone, betamethasone etc. were considered to be the drug of choice as anti-inflammatory agents.

→ But due to several adverse side effects caused by long or short term use, these have been more or less replaced by much safer & better tolerated non-steroidal anti-inflammatory drugs. (NSAID)

→ The prototype of this class is aspirin & hence through this class comprises the chemically unrelated heterogenous group of comp., these are often referred to a 'aspirin-like' drugs. These agents are also associated with analgesic & antipyretic activities.

★ Classification :

Non-steroidal anti-inflammatory drugs may be classified on the basis of their basic chemical structures as follows :

1) Heteroaryl acetic acid analogues :
eg.
Indomethacin, Sulindac, Zomepirac Sodium etc.

2) Arylacetic acid analogues :
eg. Ibuprofen, Ibufenac
~~Flurbiprofen~~, ~~indoprofen~~, ~~ketoprofen~~ etc.

3) Aryl proplonic acid analogues :
eg.
Flurbiprofen, indoprofen, ketoprofen etc.

4) Napthalene acetic acid analogues :
eg.
Naproxen

5) Gold Compounds :
eg.
Auranofin, Aurothioglucose

6) Miscellaneous anti-inflammatory drugs.
eg.
Proxicam, Tenoxicam

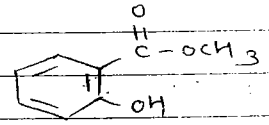
7) Pyrazolones :
eg.
Phenyl butazone.

8) Salicylates :

eg. Salicylic acid, aspirin

★ SAR of Methyl salicylate :

structure :



Methyl salicylate

- It is a salicylic acid derivative which shows analgesic, antipyretic, anti-inflammatory activity but also associated with irritation.

SAR :

1) Various substitutions on the Carbonyl or hydroxyl group result into change in potency & toxicity also
2) The ortho position of -OH group is an imp. feature for the action of Salicylate
3) The other alkyl (other than $-CH_3$) & aryl esters are used externally, mainly as Counterirritants. These Compounds have very little analgesic value.
4) The few inorganic salicylates of methyl salicylate are used internally as analgesics. These Compounds vary in their stomach irritation property eg. Sodium salicylate, Sodium thiosalicylate, magnesium salicylate, ammonium salicylate, lithium salicylate etc.

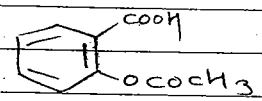
5) Replacement of methyl group by - phenyl group gives phenyl salicylate in which both Componants in it are active but also shows toxicity with low analgesic anti-inflammatory activity.
6) 5 - chloro substitution gives Compound which is active but toxic also
7) 4 - amino salicylic acid is not active Compound as anti-inflammatory drug.

Uses :

1) Used in high Conc^{n} as rubefacient & analgesic in deep heating liniments to treat joint and muscular pain. It's effectiveness is weak, but stronger for acute pain than chronic pain.

★ SAR of Aspirin :

structure :



- It is a salicylate analog which is probably still most extensively employed analgesic, antipyretic and anti-inflammatory agent.
- The name was Coined by adding 'a' for acetyl to spirin for Spiraea, the plant species from which Salicylic acid was once prepared.
- Side effects associated with aspirin are allergic reactions (eg. asthma etc) & gastric irritation.
- In the body, aspirin is rapidly Converted into Salicylic acid which is responsible for most of the action.

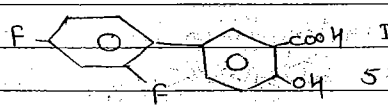
SAR :

1) Aluminium, Calcium aspirin i.e. salts of aspirin appear to have fewer undesirable side effects and induce analgesia faster than aspirin.

2) Introduction of 3-methyl group (i.e. adjacent to acyloxy group) produces 3-methyl aspirin which displays a slower metabolic excretion. The methyl group at C_3 position slows hydrolysis of acetyl group & also slows formation of metabolite i.e. 3-methyl salicylic acid.

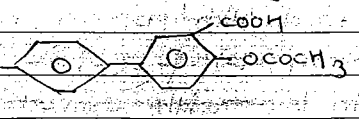
3) ortho position of $-COOH$ & $-OCOCH_3$ group w.r.t each other is an imp. feature for action of aspirin.

4) Synthesis of aspirin derivatives containing a hydrophobic aryl group in position 5 has led to greater anti-inflammatory activity than is found with aspirin eg. Diflunisal, recently introduced.



Diflunisal
5(2,4-difluorophenyl) Salicylic acid

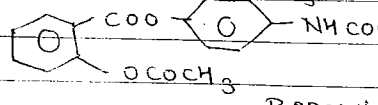
5) Introduction of hydrophobic group at 5 position gives another derivative flufenisal which is more potent, longer acting & with less gastric irritation



2-Acyl-5(4-Fluorophenyl) Salicylic acid
= Flufenisal.

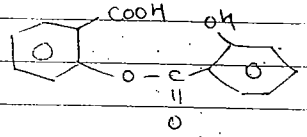
6) Replacement of hydrogen from carboxylic acid group by P-acetamidophenyl group gives Benorilate is again an active comp.

*12) on introducing an aryl group in 5 position of aspirin, great anti-inflammatory activity is found.



Benorylate

8) Salsalate is another derivative of aspirin formed b/t two salicylic acid molecules, has antipyretic, analgesic & anti-inflammatory properties similar to those of aspirin but causes less gastric irritation



Salsalate

9) The acute gastric irritancy of aspirin may be associated with its carboxylic acid group. Therefore modification of acidic charastristic of carboxylic group might be a way to reduce gastric irritancy which retaining anti-inflammatory activity.

10) Various substitutions on the hydroxyl or ~~hydroxyl~~ Carboxyl group results into change in potency as well as toxicity.

11) The ortho position of the OH group is an imp. feature for the action of the salicylates.

12)

Uses :

1) Aspirin & the analgesic salicylates are widely used to relieve headache, backache, muscle & joint pain.

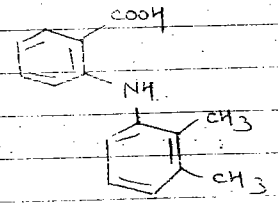
2) Used as an antipyretic agent, effective in fever of any origin.

3) Used to give relief from Rheumatoid Arthritis.

4) Used to delay ~~pre~~ labour pain, but it is risky.

★ SAR of Mefenamic Acid :

Structure :



Mefenamic acid

→ Mefenamic acid belongs to a family of N-aryl anthranilic acids which are nitrogen analogs of salicylic acid.

→ It is also known as Ponstel & N-(2,3-xylyl) anthranilic acid. It is absorbed slowly mainly from the small intestine & reaches maximal blood levels in 2 - 4 hrs.

→ Replacing phenolic -OH group in salicylic acid by an aryl substituted imino group which results in isoesters of aryl ethers of salicylic acid

→ Mefenamic acid has moderate anti-inflammatory activity & mainly used as a short term analgesic

→ side effects associated with it are diarrhoea, drowsiness, headache etc.

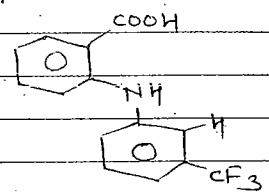
SAR :

1) The substitution at position 2,3 & also at 6 position of ring attached to anthranilic acid nitrogen atom, is an imp. feature for greater anti-inflammatory & analgesic activity.

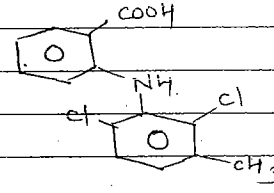
2) The most active disubstituted Compounds are the 2,3 - derivatives. This indicates that most activity resides in Compounds in which the N-aryl moiety is kept out of Coplanarity with the anthranilic acid by ortho substituents such as methyl & chloro function in mefenamic acid.

3) Replacement of nitrogen of mefenamic acid by the isosteric groups O, S & -CH reduces activity.

4) Flufenamic acid & Meclofenamic acid are clinically useful fenamates.



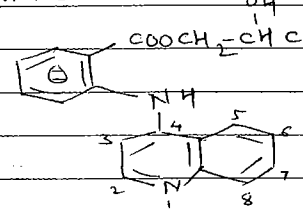
Flufenamic acid



Meclofenamic acid

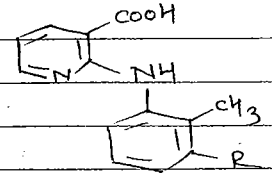
- Flufenamic acid is 1-6 times as potent as phenyl butazone & mefenamic acid.

5) The heterocyclic isosters clonixin, flunixin, glaphenine & floctafenine possessed only weak anti-inflammatory activities.



7-Cl → Glaphenine

8-CF_3 → Floctafenine

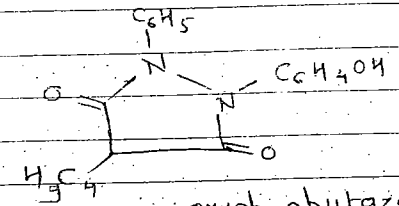


R = Cl → clonixin

R = CF_3 → flunixin

★ SAR of oxyphenbutazone :

Structure :



oxyphenbutazone

It is 1-(P-hydroxyphenyl)-2-phenyl-4-n-butyl-3,5-pyrazolidinedione.

SAR :

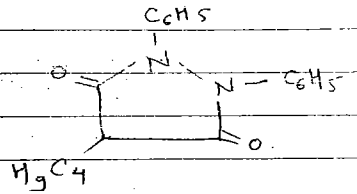
1) Oxyphenbutazone is an analog of phenyl butazone. It is equally potent as phenyl butazone but have less toxic side effects
2) Replacement of one of the nitrogen atom in pyrazolidine nucleus with an oxygen atom yields an isooxazole analog with Comparable anti-inflammatory activity.
3) Comp. in which a Cylopentane or Cyclopentene ring takes the place of the pyrazolidine ring, however, are inactive.

Uses :

1) It is used to treat Fever, Swelling, pain, diff. inflamation.
2) It is acting as antireumatic agent which is used to cure pain.

★ Synthesis of phenyl butazone

Structure :

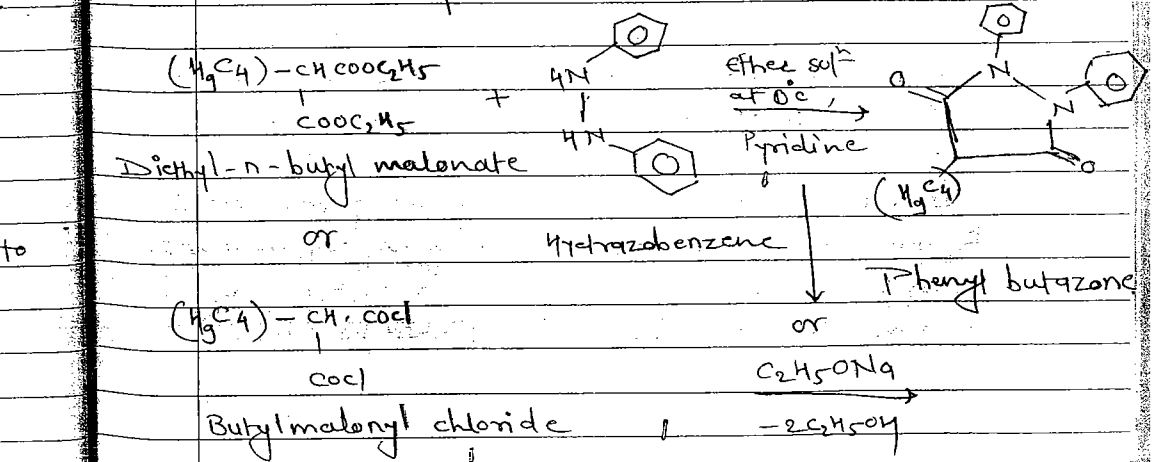


phenyl butazone

- It is 1,2-diphenyl-4-n-butyl-3,5-pyrazolidinedione.
- It is one of the pyrazolidinedione derivative.
- It is the most antiarthritic Compound.
- It also possesses anti-inflammatory & uricosuric actions similar to that of aspirin & therefore it exerts a potent analgesic action in arthritis, gout etc but it is less effective than aspirin in modifying the perception of pain in CNS.

Synthesis :

Phenylbutazone is synthesized by a Condensation reaction of hydrazobenzene & diethyl n-butyl malonate in presence of sod. ethoxide as shown below



SAR :

Many modifications of the phenyl butazone str. have been made in an attempt to increase activity or reduce toxicity.

1) There is a close relationship betn the acidity & biological activity of the phenyl butazone derivatives. Increasing the acidity decreases the anti-inflammatory activity & sodium retaining potency, but greatly increases the uricosuric effect.

2) Replacement of the hydrogen atom at C_4 of phenylbutazone by a methyl group to give a 4-butyl-4-methyl-1,2-diphenyl-3,5-pyrazolidinedione destroys the anti-inflammatory activity.

3) The butyl group at C_4 may be replaced by a propyl or allyl group, in which case the anti-inflammatory activity is retained.

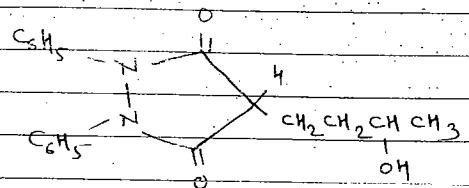
4) The presence of keto group in the γ-position of butyl side chain it produces an active Comp. Called γ-ketophenylbutazone

5) Activity also persists when the para position of one or both benzene rings is substituted by methyl, chloro or nitrogroups.

6) Replacement of n-butyl group by $(CH_2)_2SOC_6H_5$ gives sulfinpyrazone increases analgesic & uricosuric activity.

7) Introduction of hydroxyl group at para position of one of the benzene ring gives oxyphenbutazone which is equally potent anti-inflammatory analgesic as phenylbutazone but it is slightly less toxic.

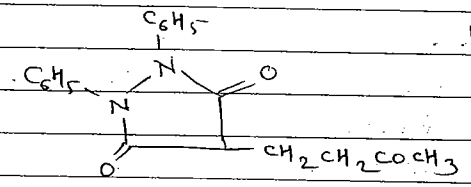
8) Phenylbutazone Completely undergoes metabolism by liver microsomal enzymes to oxyphenbutazone & γ-hydroxy-phenylbutazone.



γ-hydroxyphenylbutazone

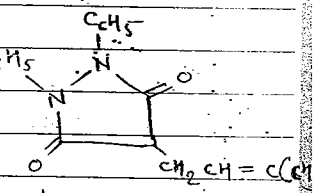
9) There are some derivatives having similar activity as phenylbutazone.

a)



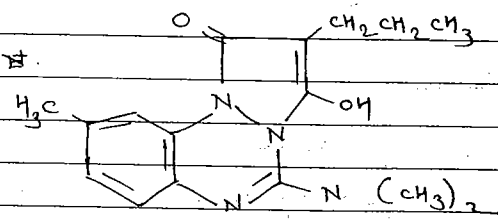
Kebuzone

b)



Phenazone

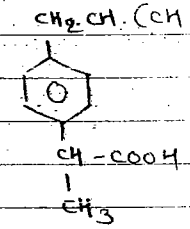
c)



Azapropazone

Synthesis of Ibuprofen :

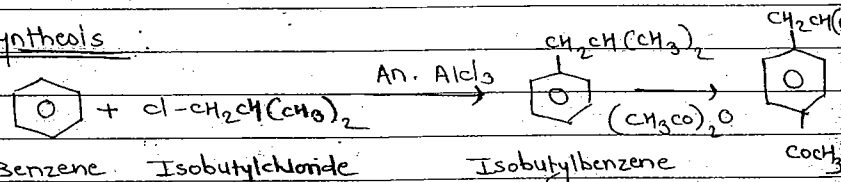
Structure :



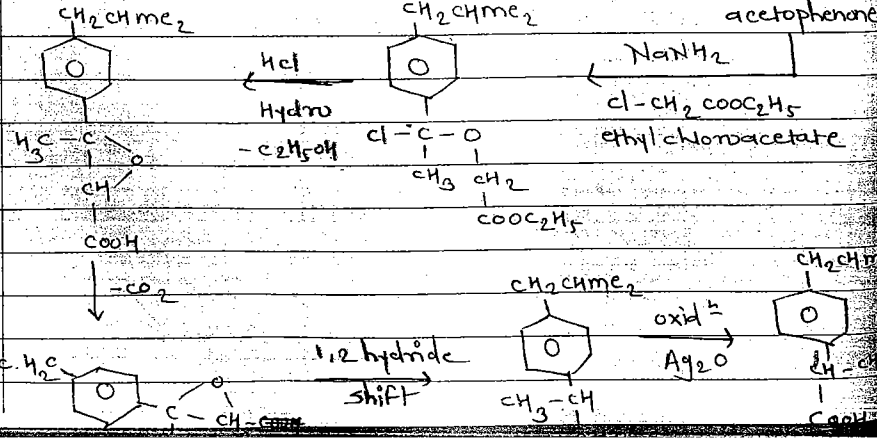
- It is an arylacetic acid derivative
- It is also known as 2-(4-isobutyl phenyl) propionic acid.
- It is an anti-inflammatory drug that possesses anti-pyretic & analgesic actions. Ibuprofen also used to inhibit prostaglandin synthesis.
- It is used in the treatment of mild or moderate pain in rheumatoid arthritis, osteoarthritis and primary dysmenorrhea.

Synthesis :

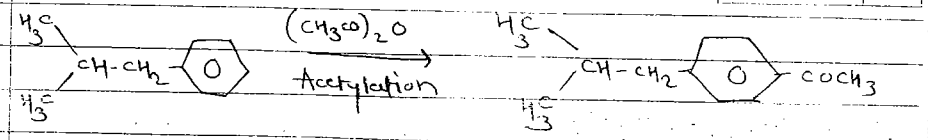
1)



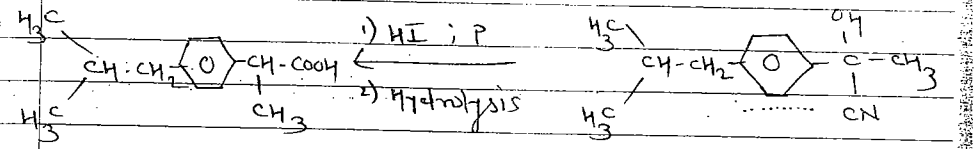
Benzene Isobutylchloride Isobutylbenzene P-isobutyl acetophenone



2)

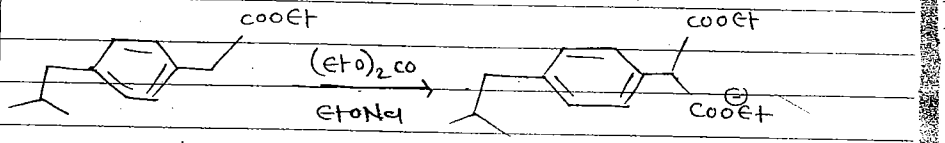


Isobutyl benzene P-isobutyl acetophenone

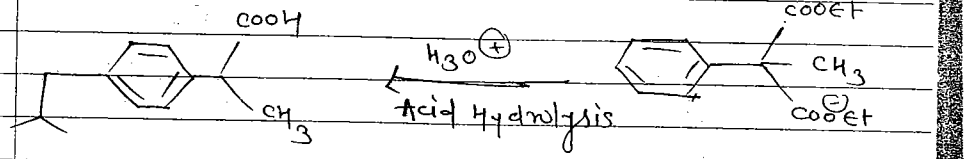


Ibuprofen Cyanohydrin

3)



Diethylester Ibufenac Malonate Carbanion



Ibuprofen

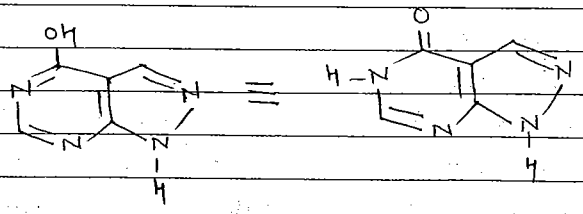
Treatment of Gout :

Introduction :

- Gout is a term represents a heterogenous group of genetic & acquired diseases manifested by hyperuricemia & an acute inflammatory arthritis [Hyperuricemia = increase of uric acid in urine]
- These diseases induced by crystals of monosodium urate monohydrate.
- Some patients develop aggregated deposits of crystals (tophi) in & around joints lead to severe crippling.
- Primarily gout is chiefly a disease of adult man but frequency of gout is increased in patients taking diuretics (increases secretion of urine).
- The end product of the purine biosynthesis is crystals of sod. urate.
- Hence, both increased purine biosynthesis and decreased renal excretion of uric acid play imp. role in pathogenesis of primary hyperuricemia.
- once the uric acid is filtered by renal glomeruli, it is Completely reabsorbed into circulation from proximal tubules (situated at middle).
- In normal circumstances, some of reabsorbed uric acid is again driven back into urine by distal tubules.
- Because low solubility of urate crystals there is deposition of crystals in the joints, cavities & articular cartilages Such deposition of urate results into inflammatory reactions probably release of lactic acid which lowers the pH of medium which leads to further deposition of uric acid.
- The phagocytosis of urate crystals releases glycoprotein which produces acute gout arthritis.
- The treatment of gout involves the uricosuric agents which enhance rate of excretion of uric acid by reducing rate of its tubular reabsorption.
- They thus relieve signs & symptoms of acute attack of gout & offer symptomatic relief in this Condition.
- The drugs used in treatment of gout are colchicine, allopurinol etc.
- ~~Chol~~ colchicine is an alkaloid obtained from colchicum autumnale. It was clinically introduced for the treatment of acute attacks of gout in 1763 by Von Storck.
- It is effective against acute gouty arthritis.
- It probably acts to inhibit the release of lactic acid during phagocytosis of the urate crystals.

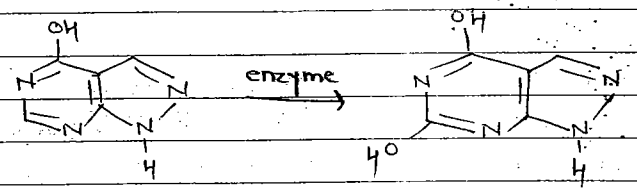
Allopurinol :

structure :



- chemically it is 1H-pyrazolo [3,4-d] pyrimidin-4-ol or 1,5-dihydro-4H-pyrazdo [3,4-d] pyrimidin-4-one
- chemically, allopurinol is a structural analog of hypoxanthine.
- It inhibits the formation of uric acid by antagonising 'xanthine oxidase enzyme'.

- This enzyme catalyses the Conversion of hypoxanthine to xanthine which is a precursor for uric acid synthesis
- Due to structure similarity instead of hypoxanthine allopurinol is attacked by xanthine oxidase and converted to oxypurinol which is also effective enzyme inhibitor.
- Thus by inhibiting the uric acid formation, it lowers down hyperuricemia & prevents formation of uric acid stones.
- Side effects associated with allopurinol are nausea, Vomiting, diarrhoea, gastric irritation, headache, fever, drowsiness etc.

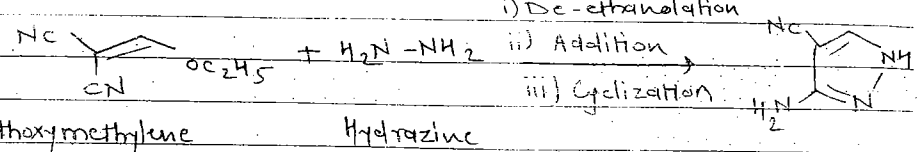


Allopurinol oxypurinol

Uses :

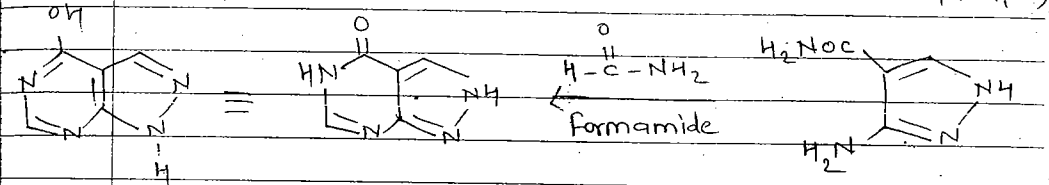
1) Allopurinol is structural analog of hypoxanthine & classified as xanthine oxidase inhibitor.
2) It is administered for an indefinite duration in the treatment of chronic gout.
3) It helps to decrease the Conc^{n} of uric acid in plasma by blocking the Conversion of hypoxanthine & xanthine to uric acid.
4) It reduces purine Synthesis
5) It causes gradual resolution of tophi & minimise the risk of the formation of uric acid calculi.

Synthesis :



ethoxymethylene malonitrile Hydrazine 3-amino-4-Cyano-pyrazde

H_2SO_4 (Hydrolysis)



Allopurinol 3-amino-4-amido Pyrazole

★ Antifungal Agents :

A) Introduction :

- Fungus is a parasite. The human fungi parasitic relationship results in mycotic (related to fungi) illness which involves the superfacial invasion of skin (i.e. attack by fungi on upperside of skin) or mucous membranes of body orifices.
- These are diff. from algae, protozoa, bacteria et
- The diseases which are caused due to infection of fungus called as mycoses.
- These mycotic infections may be catagorised broadly as :

1) Dermatophytoses : (skin infection)

It is of Contagious nature mainly caused by trichophyton, microsporum & epidermophyton. It includes infections of keratinized tissues like hairs, nails etc.

2) Candidiasis :

It involves mainly the skin & mucous membrane infection. It is caused by Candida albicans.

- These infections mainly develop in mouth, bowel etc. Also called as local infections. may be systematic & Contagious.

3) Systematic fungal infections :

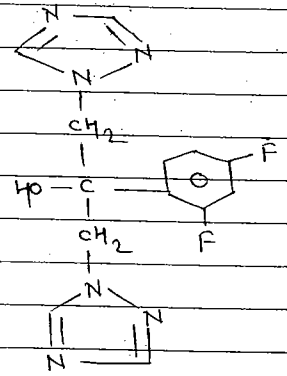
It involves fungal infections of bones, lungs, & meninges. i.e. Osteomyelitis, Aspergillosis & meningitis respectively.

The drugs or agents which are used for the treatment of mycoses i.e. diseases caused due to fungal infections are called as the antifungal agents

ex : Miconazole, Clotrimazole.

B) Synthesis of Fluconazole :

Structure :

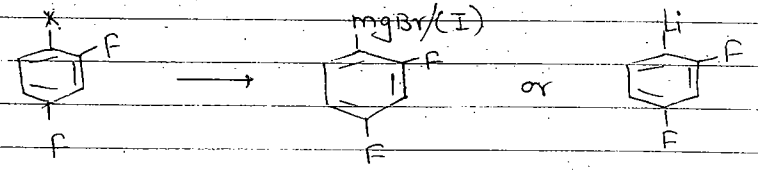


Fluconazole

- It is a triazole derivative. It has relatively low mol. wt. (305), water soluble, weakly protein bound with high bioavailability penetrates well into CSF (cerebro-Spinalfluid)
- It is excreted largly unchanged in urine.
- It can be administered intravenously. It is useful drug in patients with menipgitis caused by susceptible fungal strains.

Synthesis :

Fluconazole is synthesised by using lithiated or Grignard difluorobenzene as follows :

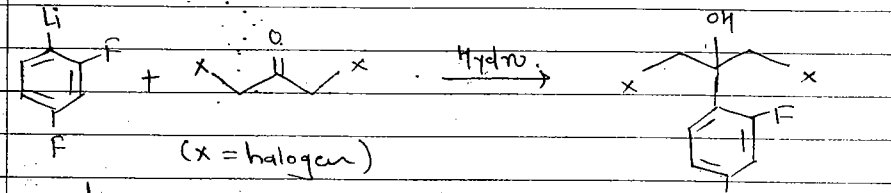


X ⟶ Br, I

1-halo-2,4-difluorobenzene

Grignard difluorobenzene derivative

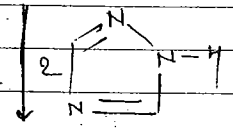
Lithiated difluorobenzene derivative



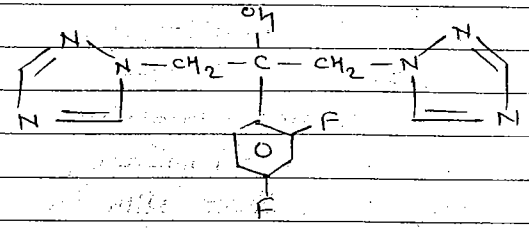
(X = halogen)

Lithiated difluorobenzene derivative

1,3-dihalo acetone



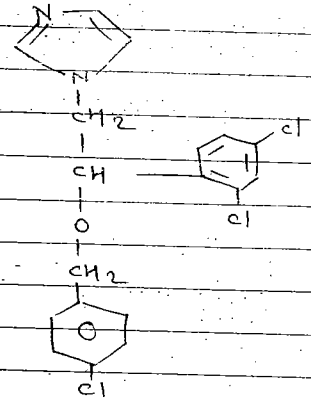
1,2,4-triazole



Fluconazole

c) Econazole

str.



- It is an imidazole derivative. It is used topically for treatment of superficial fungal infections of skin.
- Econazole / triamcinolone is a combination drug, consisting of econazole (an imidazole antifungal) & triamcinolone (a group III topical steroid).
- It is used as a topical cream against fungal skin infections, including trichophyton mentagrophytes, T. rubrum, candida albicans.