MEDICINAL CHEMISTRY-I

B. Pharm IV th Semester

UNIT-IV

(A)

Shailesh Pathak

* Drug Acting on CNS ⇒

A) SEDATIVE AND HYPNOTICS :-

⇒ Sedative are central Nervous System (CNS) depressant that reduce excitement, tension and produce relaxation

⇒ Both sedative and hypnotic action may reside in the same drug.

⇒ At lower dose ⇒ Sedative

⇒ At higher dose ⇒ Hypnotic

Uses ⇒
- Antianxiety agents
- Anticonvulsant
- Muscle relaxant
- General anaesthetic
- Preanaesthetic medication
- Antipsychotic
- To potentiate analgesic
- Co-drug in the treatment of Hypertension

Classification of Sedative and Hypnotic drug

(1) Benzodiazepines.
- Chlordiazepoxide.
- * Diazepam
- Oxazepam
- Lorazepam
- Clorazepate
- Zolpidem

(2) Barbiturates
- * Barbital
- Phenobarbital.
- Mephobarbital
- Amobarbital
- Butabarbital
- Pentobarbital
- Secobarbital

(3) Miscellaneous
a) Amide & imides-
- Glutethimide

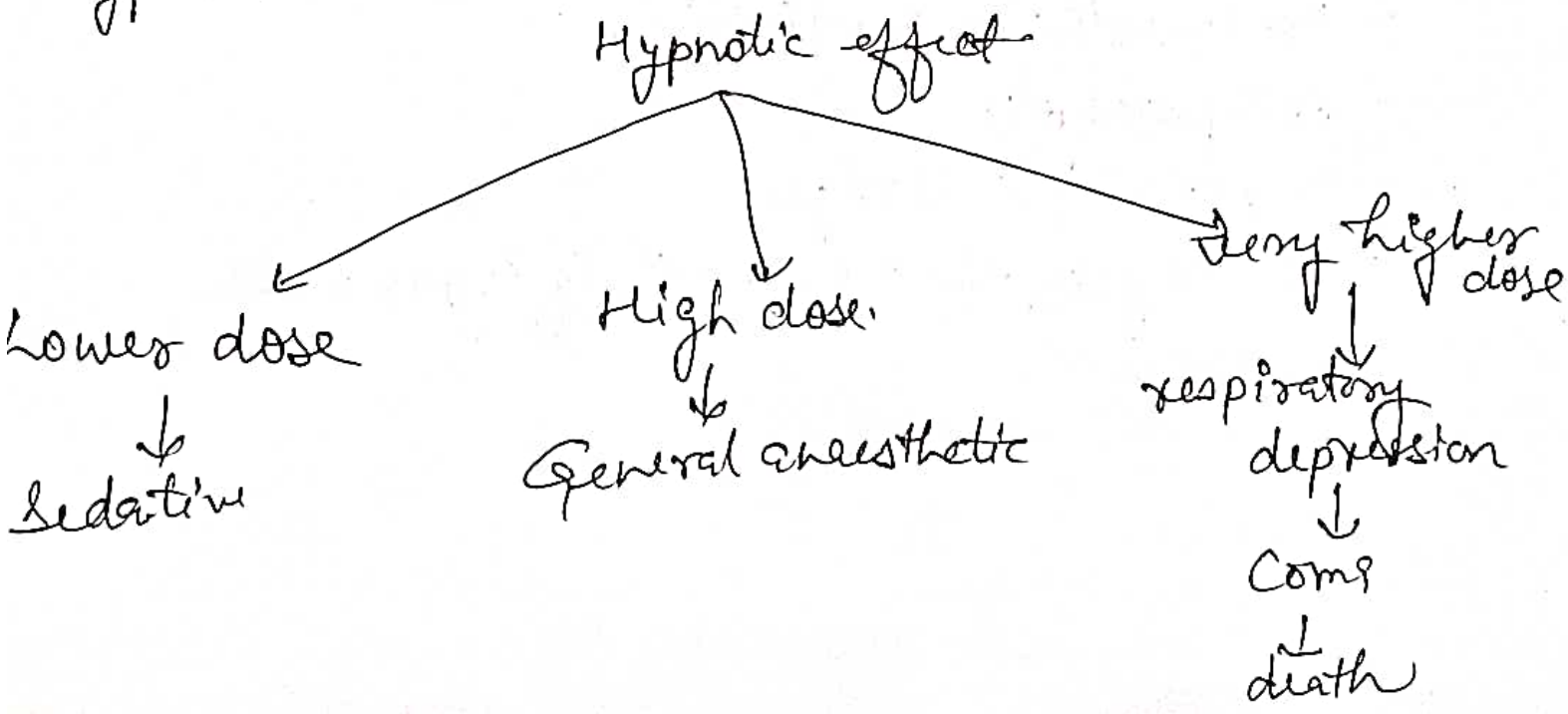
b) Alcohol & their Carbamate derivatives-
- Meprobamate
- Ethchlorvynol

c) Aldehyde and their derivative
- Triclofos sodium
- Paraldehyde.

*Difference b/n Sedative and Hypnotic drug :-

⇒ Sedatives are drugs that decreases activity and have a calming, relaxing effect. Peoples use these drugs mainly to reduce anxiety. At higher dose, Hypnotic usually cause sleep.

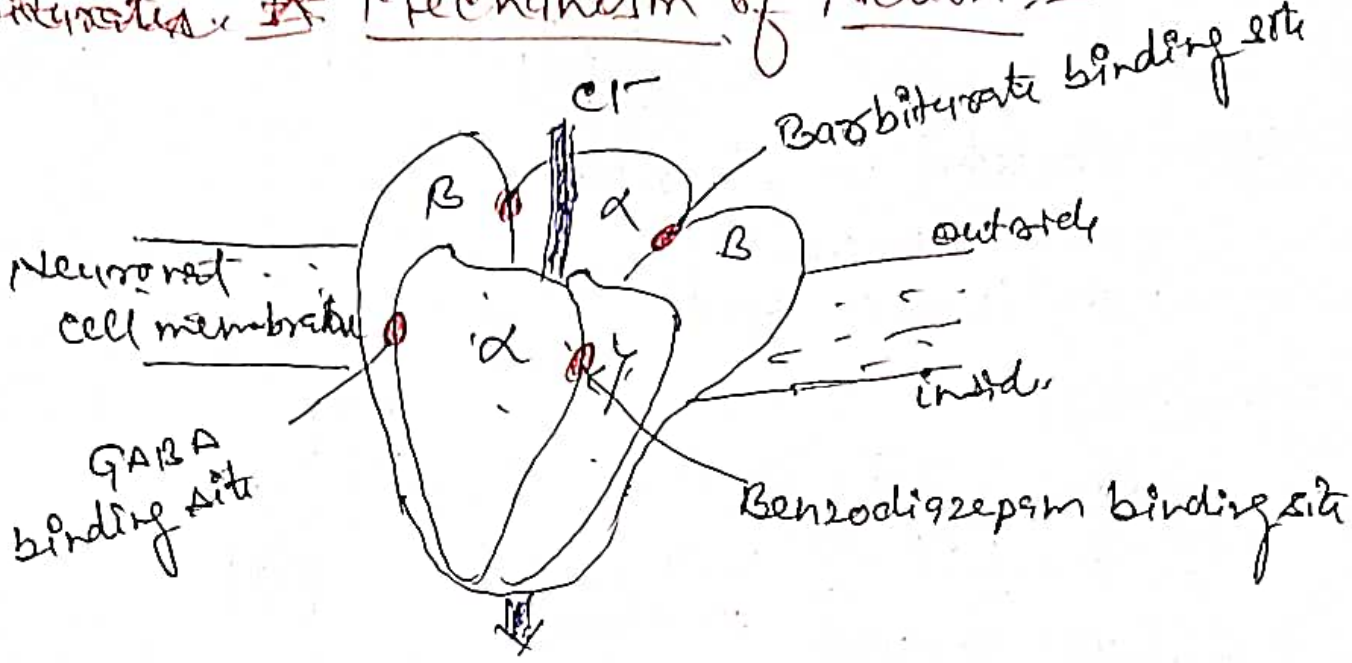
⇒ Lower dose cause sedative & higher dose cause hypnotics



Classification of Sedative & Hypnotic

↓

① Barbiturates ⁂ Mechanism of Action:-



Benzodiazepam (BZD)

↓

Bind to modulatory site on $GABA_A$ receptor

↓

Potentiate the inhibitory effect of GABA

↓

↑ the frequency of Cl^- channel opening

↓

↑ in Cl^- conductance

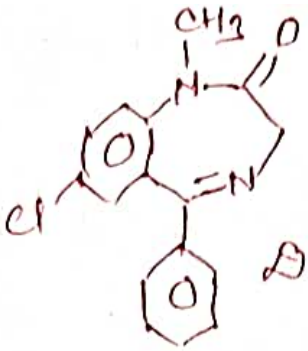
↓

Membrane hyperpolarization

↓

CNS depression

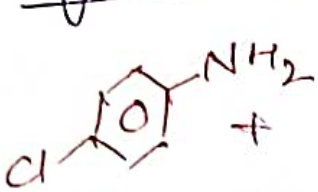
① Diazepam :-



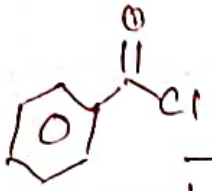
Diazepam

Uses :- Skeletal muscle relaxant
- Anticonvulsant
- Antianxiety agent

Synthesis :-

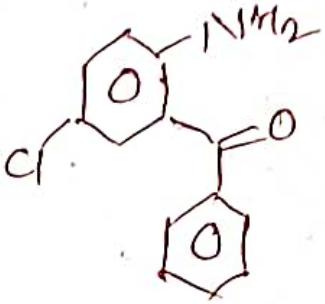


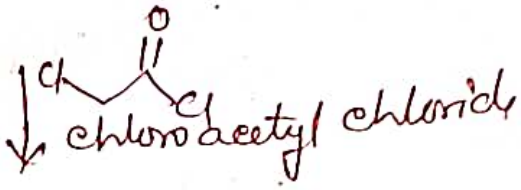
4-chloroaniline



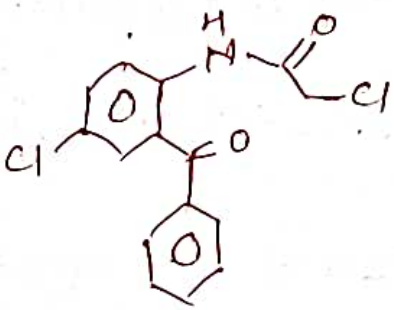
Benzoyl chloride

$ZnCl_2$, Fe acylation

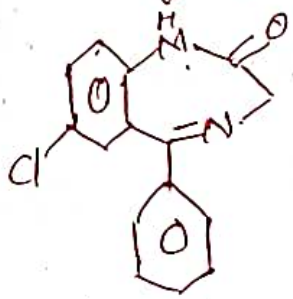




chloroacetyl chloride

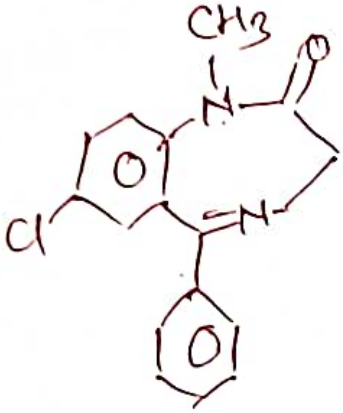


$-HCl$, $-H_2O$ | NH_3 cyclization

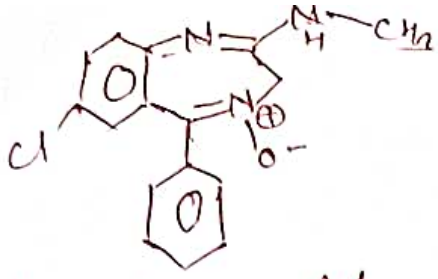


Nordiazepam

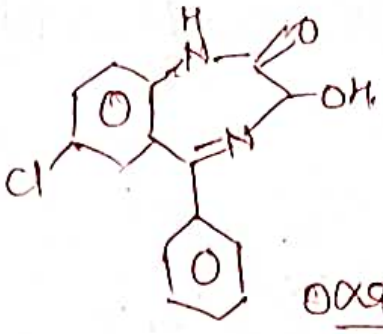
CH_3I



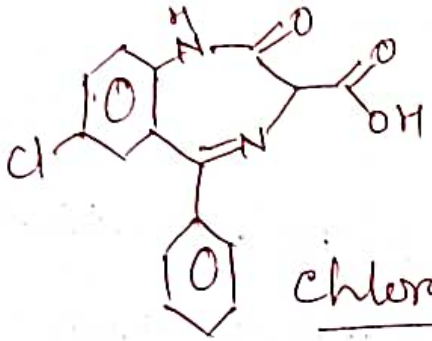
Diazepam



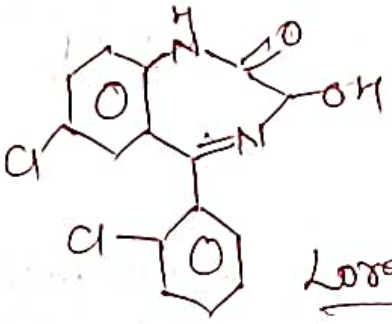
Chlordiazepoxide.



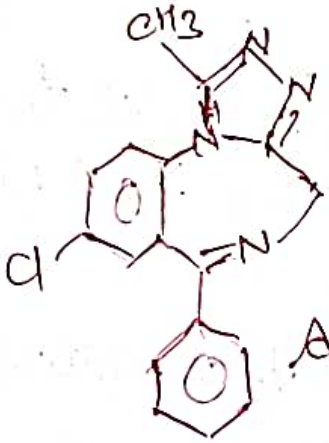
Oxazepam



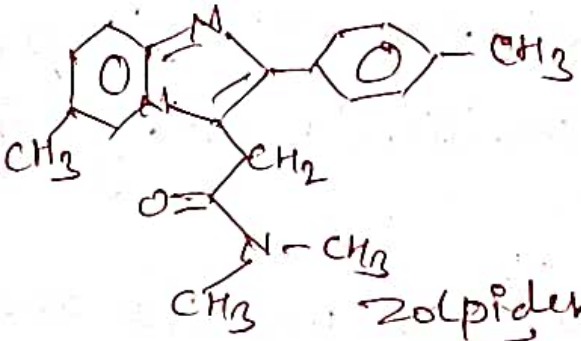
Chlorazepate



Lorazepam



Alprazolam



Zolpidem

MOA of Zolpidem :-

Bind to selectively to BZD receptor

↓

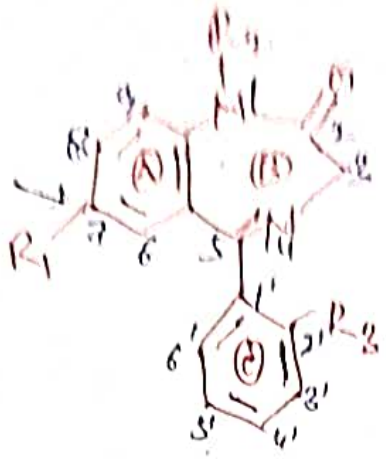
GABA mediated neuronal Inhibition

↓

CNS depression

SAR of Benzodiazepine :-

(NO2, CN, CO
EWG
↓
↑ electronegativity
↓
↑ activity



① Ring A →

a) The minimum requirement for 5-phenyl-1,4-benzo diazepin-2-one derivative to BZD include an aromatic or heteroaromatic ring

b) An electronegative group (halo or Nitro) substituted at R1 position markedly increase activity and binding affinity

c) Substitution on 6, 8 and 9 position ↓ the activity

d) Replacement of ring A with heterocyclic ring have weak activity and affinity as compared to phenyl derivatives

② Ring B -

a) Alkyl substitution at R-2 position will increase the activity

b) A- proton accepting group e=o (carbonyl oxygen) at 2nd position of ring B is necessary to interact with receptor binding site

c) Substitution at 3rd position methylene or imine nitrogen is sterically unstable

d) Substitution at 3rd position with hydroxy moiety have comparable potency to CH analogue but are excreted faster.

e) phenyl substitution at 5th position increase the activity

Ring C:

a) Replacement of Ring C with aromatic heterocyclic ring increases the anxiolytic activity.

b) Substitution at R3 position with halogen increases th activity

c) Substitution at 4th position is unfavourable activity

Barbiturates :-

Barbiturates are derivatives of barbituric acid.

All derivatives of Barbituric acid are CNS depressant. They are effective as anxiolytics, hypnotics, anticonvulsants and analgesics.

They have addiction potential both physical and psychological.

Thus benzodiazepines have largely replaced them in term of sedative-hypnotic

Mode of Action of barbiturates :-

Barbiturates

↓

Bind to other modulatory site on GABA$_A$ receptor.

↓

Potentiate the inhibitory effect of GABA receptor

↓

↑se the frequency of Cl^- channel opening

↓

↑ses in Cl^- ion conductance

↓

Membrane hyperpolarization

↓

CNS depressant

SAR of Barbiturates

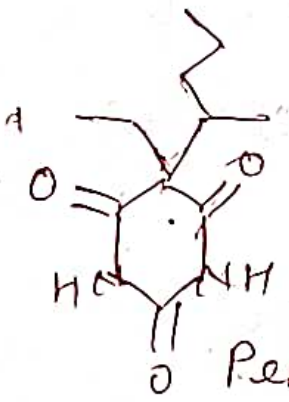
R_1 = alkyl → ↑ lipophilicity → rapid onset
→ Quicker onset & shorter duration of action

5,5-disubstitutents are important for activity and duration of action

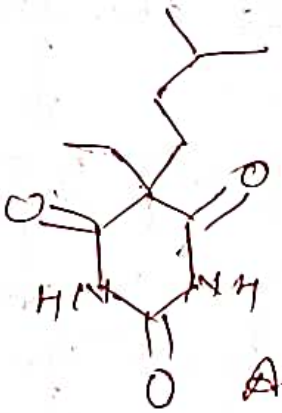
⇒ Barbituric acid itself does not possess any hypnotic properties.

⇒ Activity requires a balance of acidic and lipophilic properties.

⇒ The branched chain isomer exhibits greater activity but shorter duration. The greater the branching the more potent is the drug (eg- pentobarbital > amobarbital)

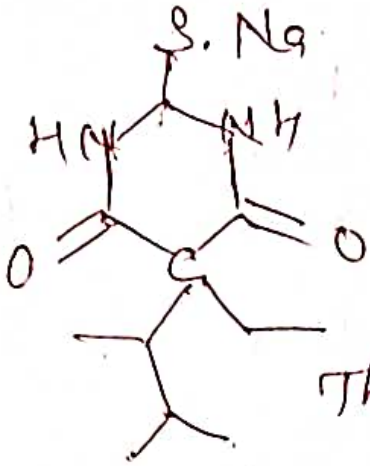


Pentobarbital



Amobarbital.

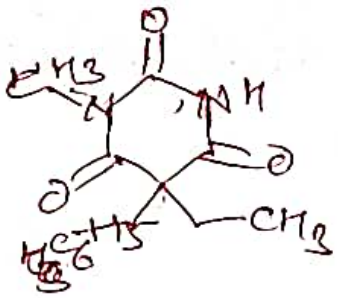
⇒ The replacement of O-atom with an S-atom, at C-2 position of the barbiturates significantly enhances the lipid solubility resulting modification exert a rapid onset of activity Eg- Thiopental sodium



Thiopental Sodium

Both hydrogen atoms in position 5- of barbituric acid must be replaced for maximal activity

Compounds with alkyl groups in the 1 or 3 position may have a shorter onset & duration of action. Eg Mephobarbital.

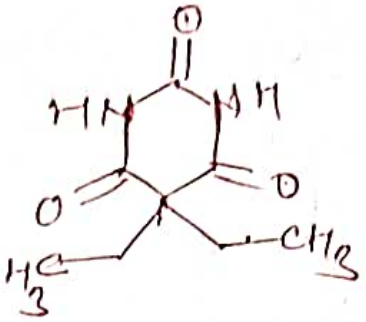


Methyl phenobarbitone (Mephobarbital.

- Replacement of oxygen by sulphur atoms at C-4 & C-6 position reduce the hypnotic activity

- Inclusion of polar groups (eg. OH, CO, COOH, NH_2, RNH and SO_3H) in the 5-alkyl moiety reduce potency

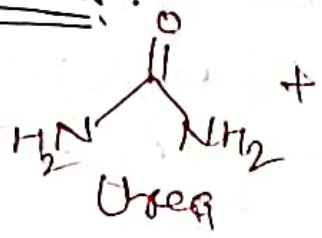
① Barbital :



Barbital.

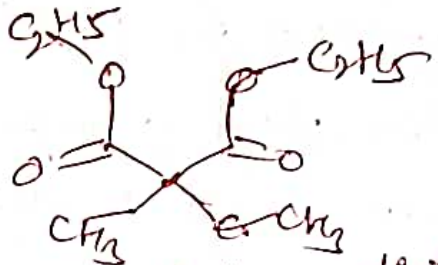
Uses :- Sedative & hypnotics.
- Treatment of seizure
- Anticonvulsants.
- Preoperative sedation

Synthesis :-



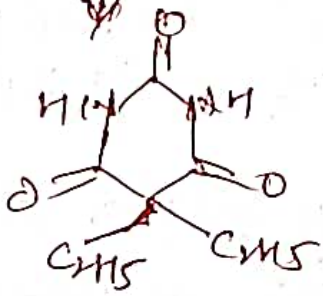
Urea

+



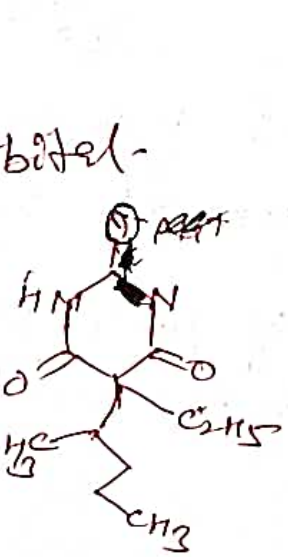
diethyl, 2,2-diethyl malonate

C_2H_5ONa



Barbital.

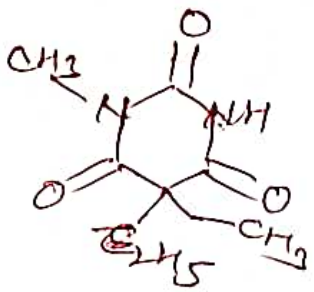
② Pentobarbital ⇒



Pentobarbital

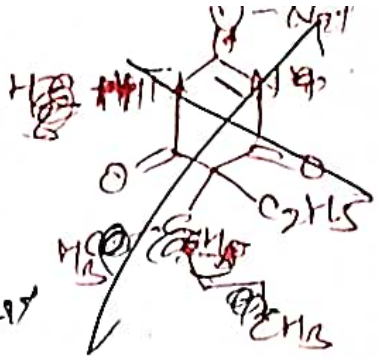
Uses ⇒ Sedative Hypnotics.
- Preanaesthetic medication
- Antiepileptic

③ Mephobarbital ⇒

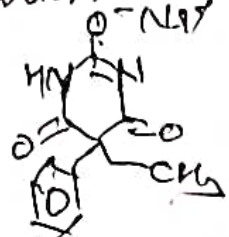


Uses. Strong sedative
- mild hypnotics.
- Anticonvulsant
- Anxiety, epileptics

(4) Phenobarbitel ⇒

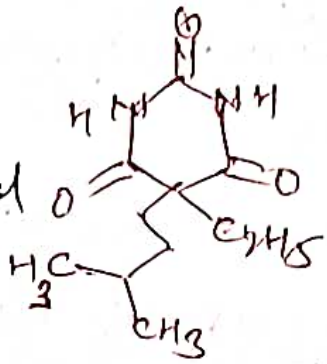


Uses ⇒ Sedative hypnotics.
- Preanesthetic medication



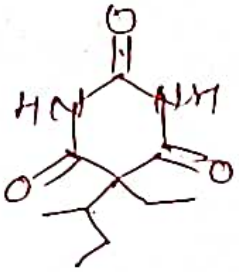
Phenobarbitel

(5) Amobarbitel ⇒



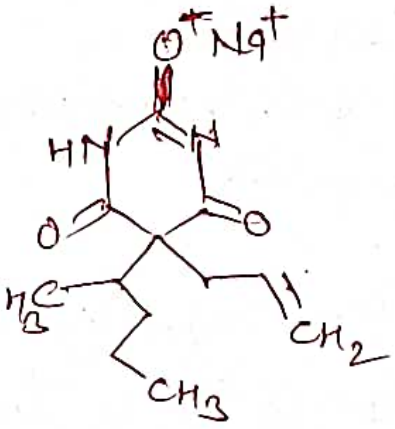
Uses ⇒ Hypnotics & Sedative

(6) Butabarbitel ⇒



Uses ⇒ Severe Insomnia
- Preoperative anxiety.

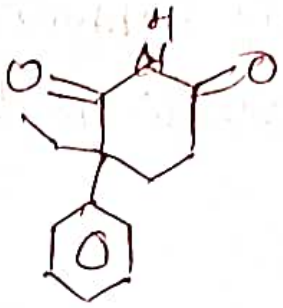
(7) Secobarbitel ⇒



Uses ⇒ Epileptic
- Local anesthetics

(3) Miscellaneous ⇒ (a) Amides & Imides

(1) Glutethimide :-

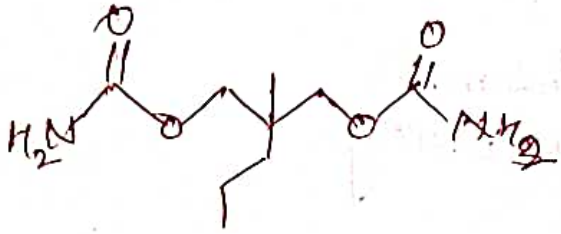


Uses :- Hypnotic to induce sleep without depressing respiration

MOA ⇒ It binds at the GABA receptor which increase the effects of GABA which is a inhibitory neuro-transmitter that depress CNS

(5) Alcohol and their carbamate derivatives :-

(2) Meprobamate :-



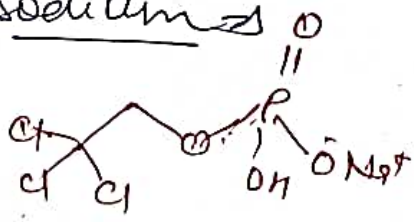
Uses ⇒

- anxiety disorder
- Skeletal muscles relexant

(3) Ethchlorvynol ⇒

Uses ⇒ Short term hypnotic therapy in mangement of insomnia,

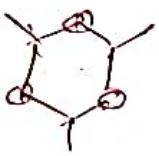
(4) Triclofos sodium ⇒



Uses ⇒

=Hypnotics

(5) Paraldehyde ⇒



Uses ⇒

- Hypotic & sedative
- Antiepileptic
- Anticonvulsant

MEDICINAL CHEMISTRY-I

B.PHARM. IV^TH SEM.

UNIT-IV

(B)

Shailesh Pathak

ANTIPSYCHOTICS:-

⇒ Psychosis ⇒ They are psychogenic mental disorders involving a loss of contact with reality.

⇒ The psychoses (eg- schizophrenia) are among the most severe mental illness.

⇒ The most common schizophrenia, in which perception, thinking, communication, social functioning and attention are altered.

⇒ The symptoms of schizophrenia can be divided into two types, positive and negative.

⇒ Positive symptoms are those that are not normally found in healthy individuals, including hallucinations * (sensory perceptions that feel real but are not, occuring in the absence of an external stimulus), delusions (what is real from what is imaginary) and though disorder (due to excessive dopamine)

⇒ Negative symptoms represent the loss of qualities normally present in healthy individual including impoverishment of thought, blunted emotion, attention (due to shortage of dopamine)

⇒ Tranquillizers are used primarily for the treatment of symptoms of mental disease

⇒ Many of these drugs also act as skeletal muscle relaxants, antihypertensive, antiemetics and antiepileptics. (2)

* Antipsychotics are the drugs that have specific sedative effect and which improves the attitudes and calm behavior of psychotic patient
* Antipsychotic drug have a significantly stronger effect on the CNS, but they are not CNS depressant

Classification of ① Antipsychotic drug (Neuroleptics)
② Typical Antipsychotic agent

① Phenothiazine
⇒ Promazine HCl
⇒ Chlorpromazine HCl
⇒ Trifluopromazine.
⇒ Thioridazine HCl
⇒ Piperacetazine HCl
⇒ Prochlorperazine maleate
⇒ Trifluoperazine. HCl.
⇒ Fluphenazine.
* clozapine
* dozapine.
* Mesoridazine

② Butyrophenone
* Haloperidol
* Droperidol
* Respiridone.

③ Benzamide derivatives.
* Sulpiride.
* Metoclopramide

④ β-amino ketone.
- Molindone HCl

⑤ Atypical Antipsychotics
⇒ Respiridone.
⇒ Sulpride.
⇒ Olanzapine
⇒ Quetiapine.
⇒ Lurasidone

Mode of Action :-

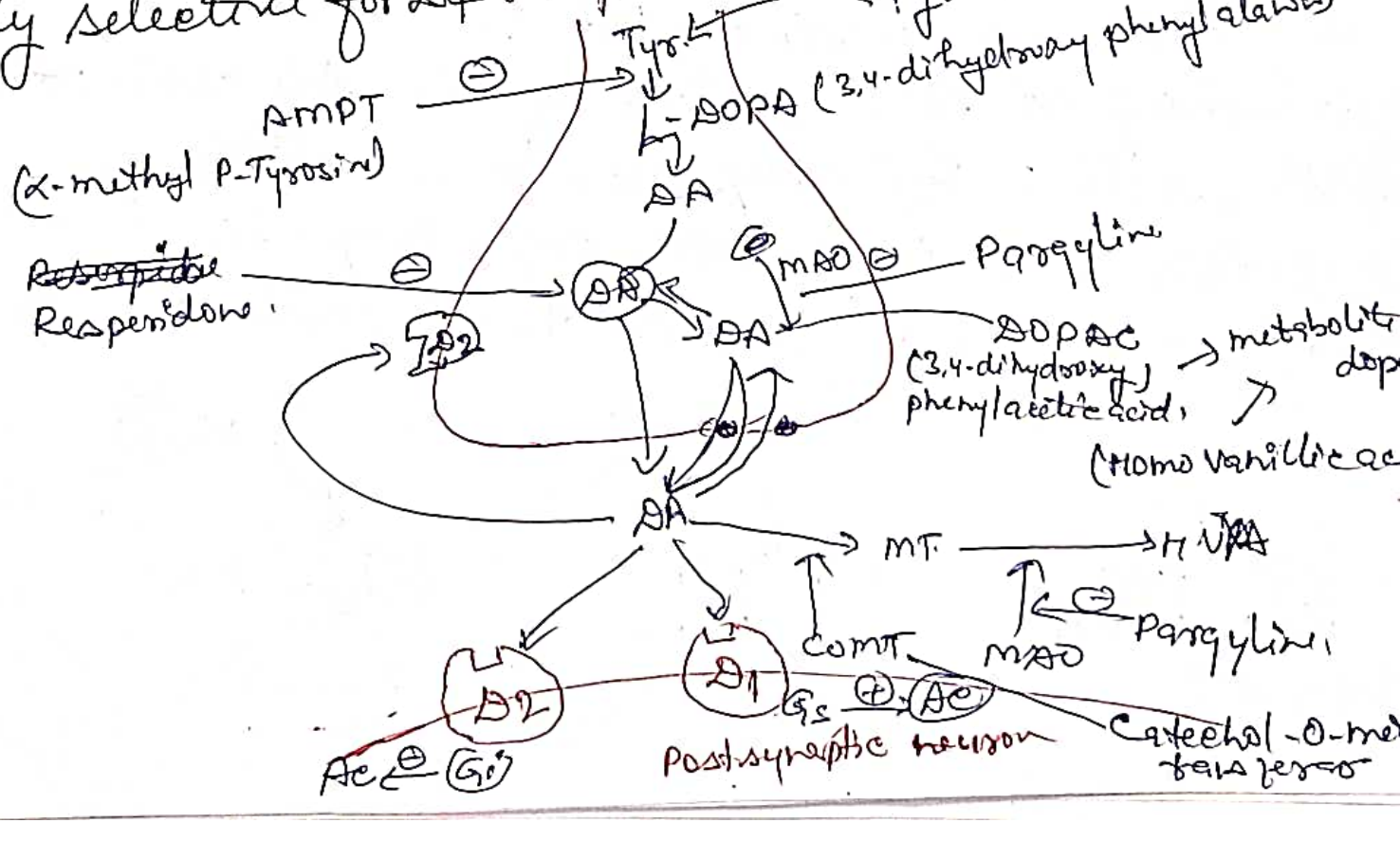
⇒ All typical abatipsychotic agents currently employed clinically block post synaptic dopaminergic D_2 receptors in the mesolimbic and prefrontal cortex regions of the brain and act as a competitive antagonist of dopamine.

⇒ The blockade of D_2 receptors is responsible for decreasing the positive symptoms of schizophrenia.

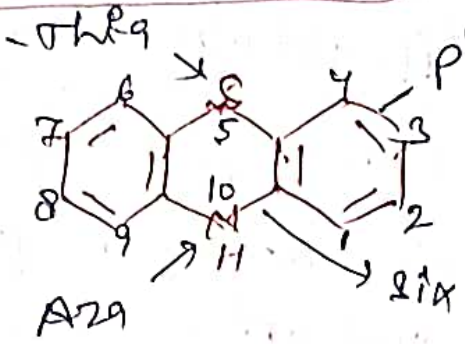
⇒ For example, the drug of the phenothiazine series are non selective, competitive D_1 and D_2 antagonists.

⇒ Unlike phenothiazines, antipsychotic of the butyrophenone series such as haloperidol display selective action only on D_2 receptors.

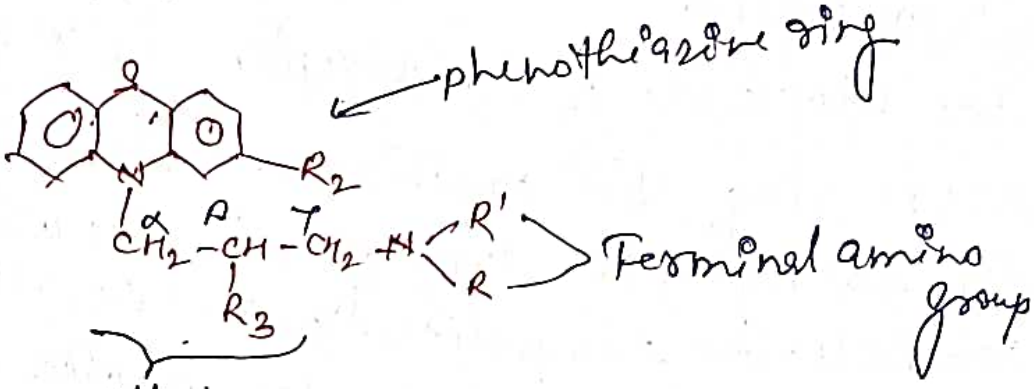
⇒ clozapine, Resperidone, Sulpiride and Fluorobutyro-phenones and other atypical antipsychotic have significant 5-HT2 and α_1 blocking action and are relatively selective for D_4 receptor



SAR of Phenothiazines ⇒



pheno + thia + A2a + ine = phenothiazine



⇒ Unsubstituted phenothiazines has no activity but has enough lipophilicity for good brain penetration

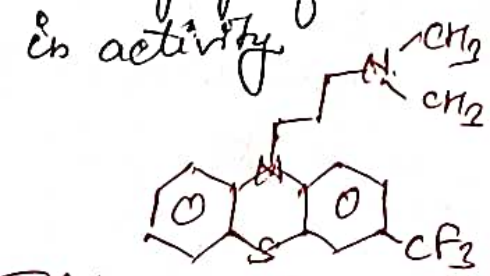
A) Alkyl side chain :-

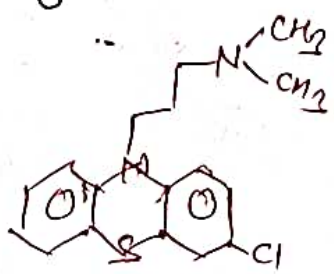
⇒ Nitrogen of phenothiazine ring and the more basic side chain nitrogen is connected with three carbon side chain show maximum potency

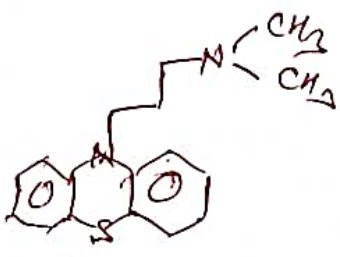
⇒ Branching at the β-position of the side chain with small methyl group decrease in activity

⇒ β-position substitution with larger group - Loss in activity

⇒ Bridging of position 3 of the side chain to position 1 - Loss in activity


Trifluopromazine


Chlorpromazine


Promazine

(B) Basic amino group :-

⇒ Amino alkylated phenothiazine having tertiary amino group show maximum potency.

⇒ Alkylation of basic amino group with groups larger than methyl group decreases activity

⇒ Piperidinyl derivatives are less potent than dimethyl amine derivatives

⇒ Substitution at 4th position of the piperazinyl or piperidinyl propyl substituted phenothiazine has been varied

⇒ Hydroxy ethyl - enhance the activity

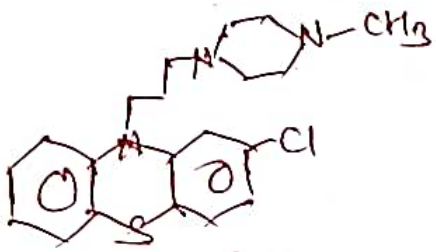
⇒ Acetoxy group - even more potent

⇒ n-methyl and n-propyl derivatives - ↓ activity

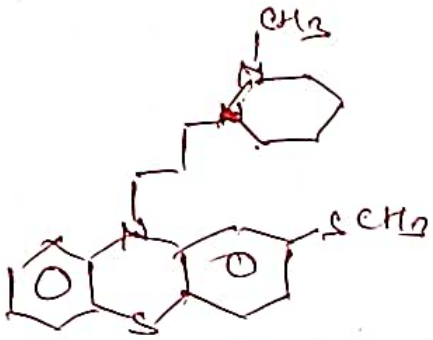
⇒ At terminal amino substituent must present at N-10

⇒ At terminal amino substituent must present at N-10

Piperazine ethanol > piperazine group > piperidine group > aliphatic side cha



Prochlorperazine



Thioridazine

© Phenothiazine ring substitution (Position-2).

⇒ Potency decreases in the following order of position of ring substitution. 1 < 4 < 3 < 2

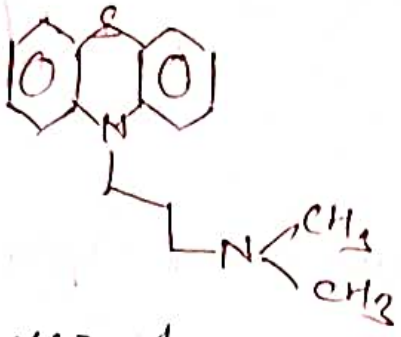
⇒ C2 must have an electron withdrawing group show activity $-SO_2NR_2 > CF_3 > -COCH_3 > Cl$

⇒ Oxidation of S-sulphur → decrease in activity

⇒ 1,2,3,4-azo-phenothiazine - more potent

⇒ 1-aza analogue of promazine - more potent than parent compounds

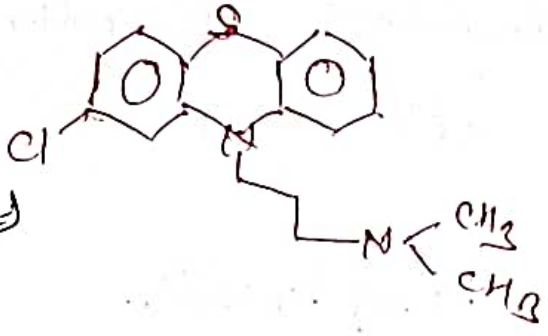
① Promazine HCl ⇒



MOA ⇒ High sedative effect
- High hypotensive action

Uses ⇒ Dopamine antagonist receptor.

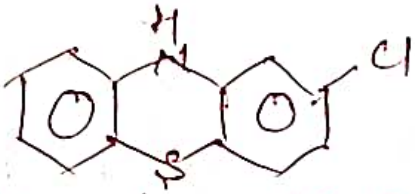
② Chlorpromazine HCl ⇒



MOA ⇒ Dopamine antagonist (D_2)

Uses ⇒ Sedative & hypnotic

Synthesis ⇒

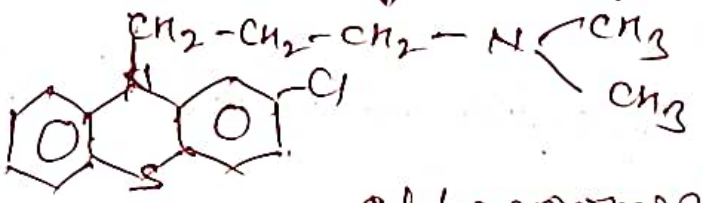


2-chlorophenothiazine

+ $Cl-CH_2-CH_2-CH_2-N(CH_3)_2$

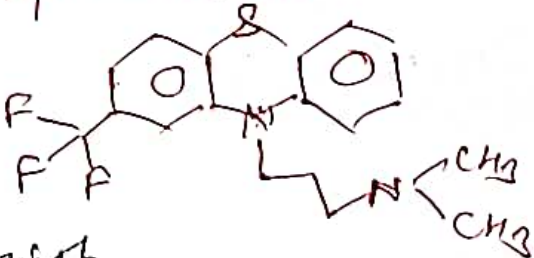
3-chloropropyl-dimethylamine

↓ Reflux in the presence of toluene and sodamide



chlorpromazine

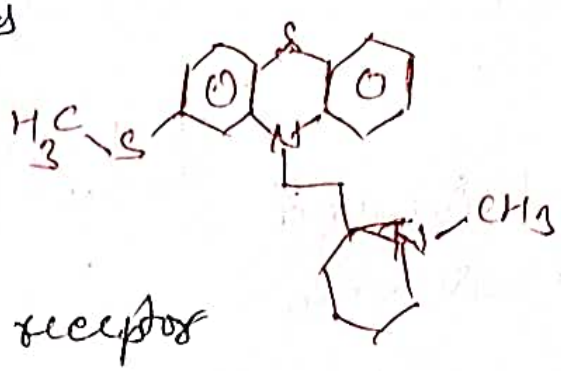
③ Trifluopromazine ⇒



MOA ⇒ Dopamine receptor antagonist

Uses ⇒ - Lower sedative and hypotensive effect than Chlorpromazine
- Greater potency as an antipsychotic

(4) Thioridazine HCl ⇒

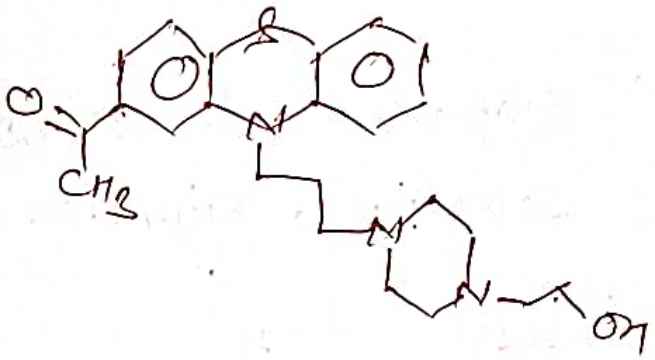


MoA ⇒

Dopamine antagonistic receptor

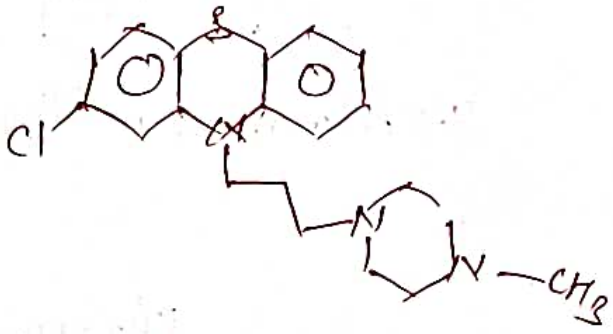
Uses ⇒ - Sedative - Hypnotic
- Psychotic disorder

(5) Piperacetazine HCl ⇒



Uses ⇒ Schizophrenia.

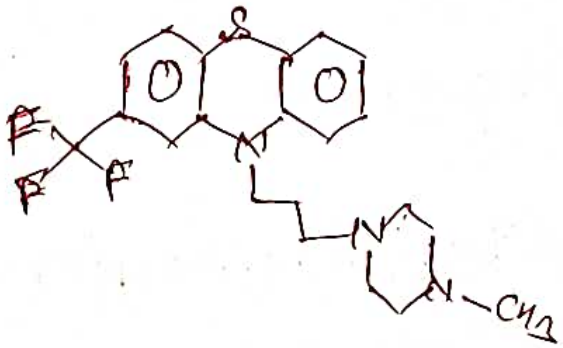
(5) Prochlorperazine Maleate ⇒



Uses ⇒ Mainly used for antiemetic

MoA ⇒ Dopamine receptor antagonist

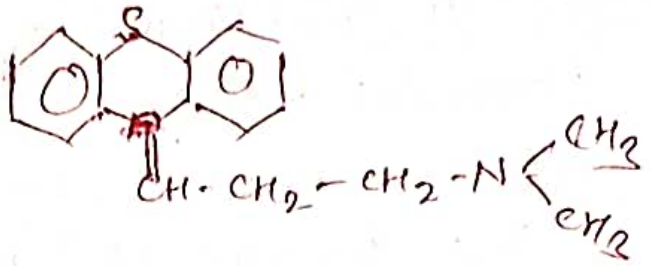
(7) Trifluoperazine ⇒



Uses ⇒ - Antipsychotic
- Antiemetic

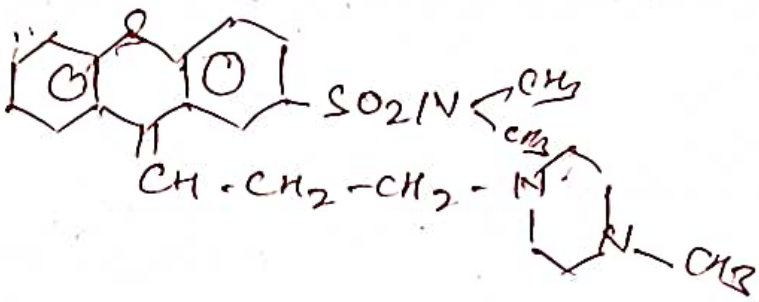
* Ring Analogus of phenothiazine ⇒

1) Chlorprothixene :-



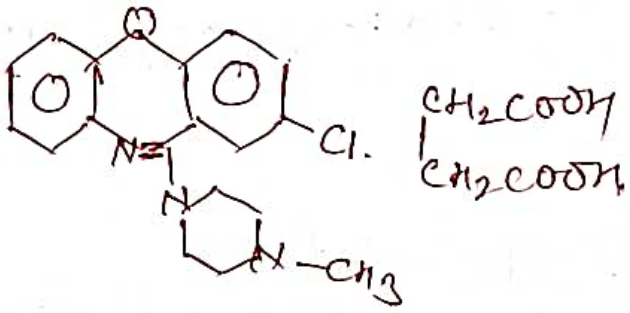
Uses ⇒ - Acute & chronic schizophrenia
- Anxiety
- agitation

2) Thiothixene ⇒



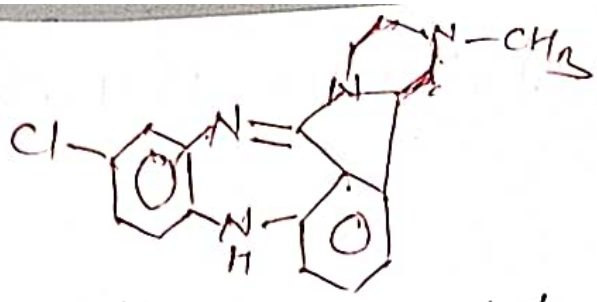
Uses ⇒ Antipsychotic agent
- Schizophrenia
- hallucinations, tension and suspiciousness
- Slow antidepressant

3) Loxapine succinate ⇒



Uses ⇒ Schizophrenia

(4) Clozapine ⇒



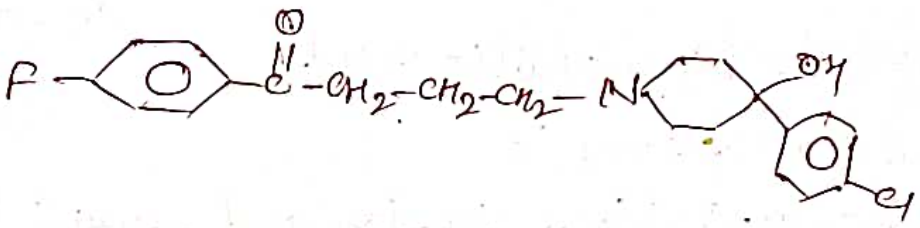
MOA ⇒ It has more affinity for D_1 and less for D_2 dopamine receptor selectivity to D_4.

Uses ⇒ It may have its unique profile due to the blocked of D_1 receptor and M_1 muscarinic activity

↳ Antipsychotic (Schizophrenia.

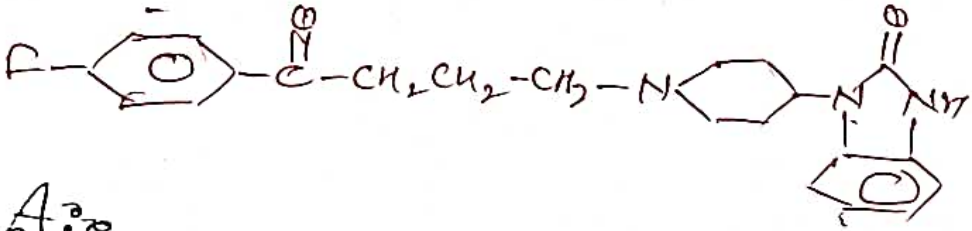
(5) Fluoro butorophenones ⇒

(1) Haloperidol ⇒



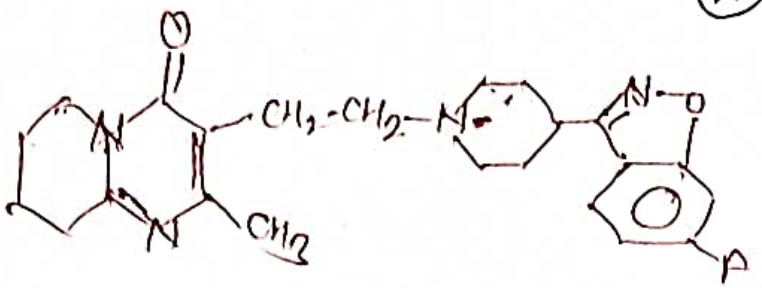
Uses ⇒ Antiemetic
- Neuroleptic (Schizophrenia)
- Choice for Tourette's syndrome (neurological disorder that cause tics)

(2) Droperidol ⇒



Uses ⇒ Neuroleptic
- produce sedation and reduce incidence of nausea and vomiting

③ Risperidone ⇒

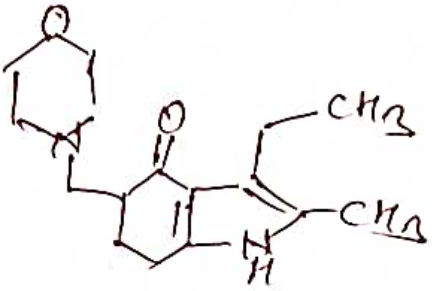


Uses ⇒ Schizophrenia

MOA ⇒ Serotonin / dopamine antagonist (SDA)

* β-Amino Ketone ⇒

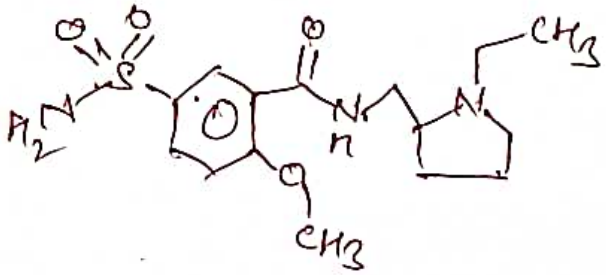
Ⓐ Molindone HCl ⇒



Uses ⇒ Schizophrenia.

Benzamide ⇒

* Sulpiride ⇒



Uses ⇒ - Antidepressant
- Antiemetic
- Antipsycholic agent.

MEDICINAL CHEMISTRY-I

B.PHARM IV^th SEM.

UNIT-IV ©

Shailesh Pathak

* **ANTICONVULSANTS** ⇒ Anticonvulsants are drugs that are used to arrest convulsion or seizures caused in epilepsy.

* **Seizures**:- It is associated with abnormal episodic high frequency discharge of impulses by a group of neurons in brain which starts local abnormal discharge & then spray to the other area of brain

* **Convulsion**:- body muscles are contract and release rapidly & repeatedly, resulting in uncontrol shaking of body

* **Epilepsy** ⇒ These are a group of disorder of the CNS characterized by paroxysmal cerebral dysrhythmia, brief episodes (seizure) or disturbance of consciousness with or without characteristic body movement (Convulsion.

Types of seizure/Epilepsy.

1. Focal (Partial seizure)
   - ⇒ Simple partial seizure
   - ⇒ Complex partial seizure

② Generalized seizure.
- Tonic clonic
- Absence
- clonic
- Tonic
- Atonic.

(1) Focal (Partial seizure) - These abnormal electric surge happens within a limited area of the brain. Also called as focal seizures.

a) Simple partial seizure - Depending on the affected brain area, patient may have unusual feelings or uncontrollable jerking movements.
- In simple partial seizure patient remains conscious and aware of the surrounding.

b) Complex partial seizure - Involve a loss or change in consciousness.

2) Generalized seizure - Entire brain is involved.

a) Absence seizures - most often in children. characterized by brief loss of awareness (blank staring)

b) Tonic seizures - Associated with stiffening of muscles or increase muscle tone.

c) Myoclonic seizure - They are sudden brief jerks of muscles.

d) Atonic seizure - Also known as drop attacks, characterized by a sudden loss of muscles tone. Person may collapse or drop down

e) clonic seizures - Associated with rhythmic jerking muscles movements. Most common affected areas are neck, face, arms and legs.

f) Tonic-clonic seizures - Also known as convulsive seizure. These are combination of muscles. stiffening and jerking. Also involve loss of consciousness and sometimes. loss of bladder control.

* Classification of Anticonvulsant drugs. (2)

1) Barbiturates :- phenobarbidone, Methabarbital.
2) Hydantoins :- phenytoin*, Mephenytoin, Ethotoin.
3) Oxazolidine diones :- Trimethadione, Paramethadione.
4) Succinimide :- Phensuximide, Methsuximide, ethosuximide.
5) Urea and monoacyl urea :- Phenacemide, Carbamazepine**
6) Benzodiazepines :- clonazepam, Diazepam
7) Miscelleneous :- Primidone, Valproic acid, Gabapentin, Felbamate.

* Mechanism of Anticonvulsant action :-

* The anticonvulsant mediated by these drugs through neurotransmission inhibition in the brain

⇒ By inhibition of sodium channels. (phenytoin).
⇒ By inhibiting GABA transaminase enzyme. (Vigabatrin).
⇒ By inhibition of T-type calcium currents. (ethosuximide valproate)
⇒ By GABA agonistic activity (benzodiazepine).

① Barbiturates :- →

Bind to other modulatory site (barbiturate side) the GABA. receptor

↓

Potentiate the inhibitory effect of GABA

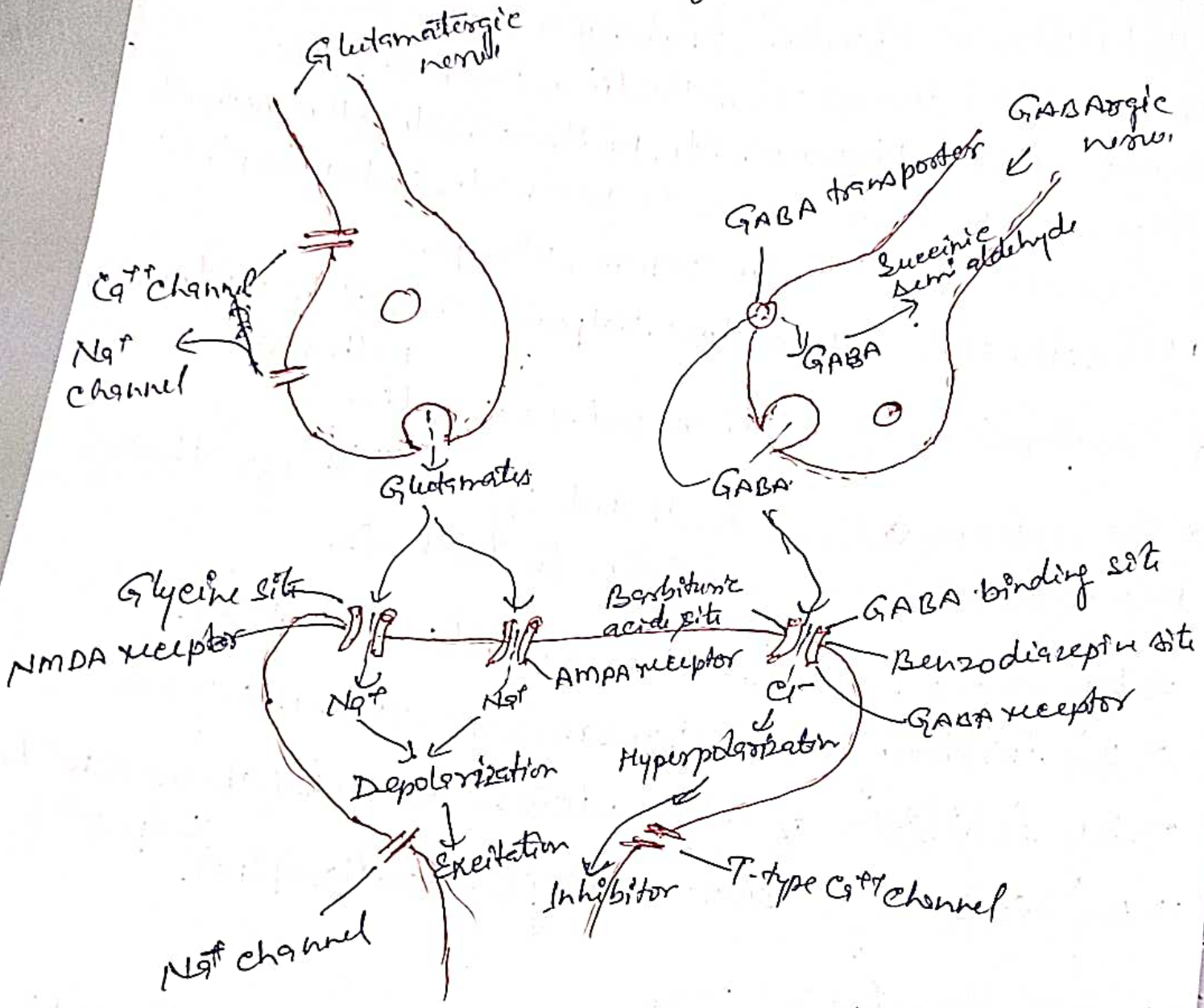
↓

↑ses the frequency of Cl^- channel opening

↓

↑se in Cl^- conductance.

↓
Membrane hyperpolarization
↓
Antiepileptic effect.



GABA = Gamma amino butyric acid.

NDA - N. methy D - Aspartate

MPA - Alpha amino-3-hydroxy-5-methyl-4-Isoxazolepropionic acid Receptor

(2) Hydantoins ⇒ & Ureas and monocarbamates –
phenytoin bind to neuronal membrane receptor.
↓
Voltage dependent Na^+ channel (inactivated state)
↓
Prevent further entry of Na^+ ions into the neuron
↓
Results in reduces the intraneuronal Na^+ ion conch
↓
Inhibition the generation of action potential,
↓
Reduces the spreading of seizure discharge.

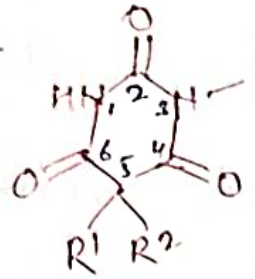
(3) Oxazolidinediones and Succinimides :

Blocks T-type Ca^{++} channels in thalamic neurons to contract the slow, spike and wave, firing pattern thought to be important in absence epilepsy

(4) Benzodiazepines - same as BZD.

* SAR of Anticonvulsant drug :-

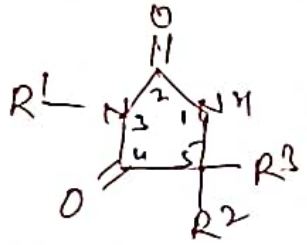
① Barbiturates-



Name.	R_1	R_2	R_3
Phenobarbitone.	C_2H_5	C_6H_5	H
Mephobarbitone.	C_2H_5	C_6H_5	CH_3
Metharbital	CH_3	CH_3	CH_3

⇒ Most of the barbiturates are sedative and hypnotics.
⇒ Only few drugs show anticonvulsant activity they are — phenobarbitone, mephobarbitone, Metharbital
SAR
⇒ Optimal activity is obtained when one of the substituent at C_5 is phenyl.
⇒ The 5,5-diphenyl derivatives have less activity than phenobarbitone.
⇒ Substituent at N_3 some case cause increased activity
⇒ 5,5-dibenzyl barbituric acid cause convulsion

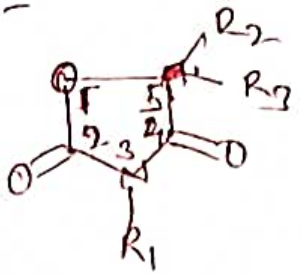
② Hydantoin



Name-	R_1	R_2	R_3
Phenytoin	C_6H_5	C_6H_5	H
Mephenytoin	C_6H_5	C_2H_5	CH_3
Ethotoin	C_6H_5	H	C_2H_5

⇒ A phenyl or other aromatic substituents at C5 is essential for the activity
⇒ Alkyl substitution at position 5 may contribute to sedation a property absent in phenytoin.
1,3-disubstituted hydantoin which exhibit activity against chemically induced convulsion

(3) Oxazolidinediones :-

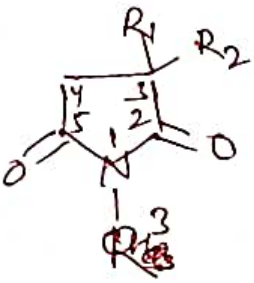


⇒ Replacement of the -NH group at position 1 of the hydantoin system with an oxygen atom yields the oxazolidinedione system.

⇒ Alkyl substitution (lower alkyl substituent) at R_2 or R_3 position leads toward absence seizure drugs.

⇒ N-alkyl substitution does not alter the activity since all the clinically used agents from this class undergo N-dealkylation in metabolism.

4. Succinimide -



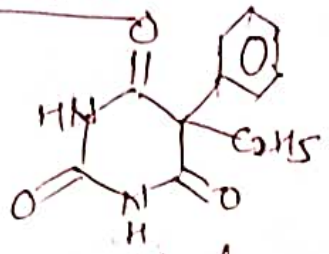
Name	R_1	R_2	R_3
Phensuximide	C_6H_5	H	CH_3
Methsuximide	C_6H_5	CH_3	CH_3
Ethosuximide	C_2H_5	CH_3	H

⇒ Replacement of the O atom at position 1 of the oxazolidinedione system with CH_2 yields the succinimide system.

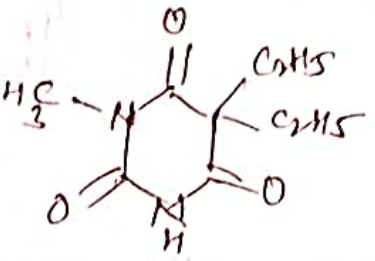
⇒ N-Methylation (R_1 position) decreases activity against electric shock seizures and impart more activity against chemically induced convulsion.

⇒ Alkyl and phenyl substitution at R2 and R3 leads to potent activity.

① Barbiturates ⇒

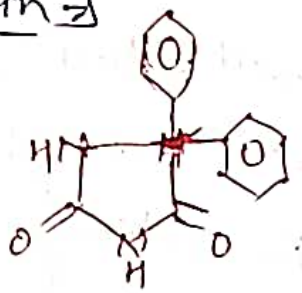


phenobarbidel

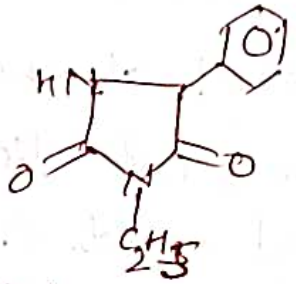


Methobarbidel

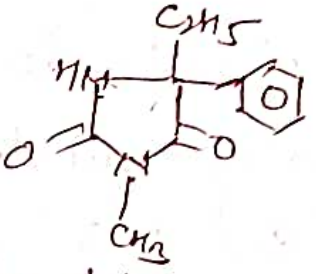
② Hydantoin ⇒



phenytoin

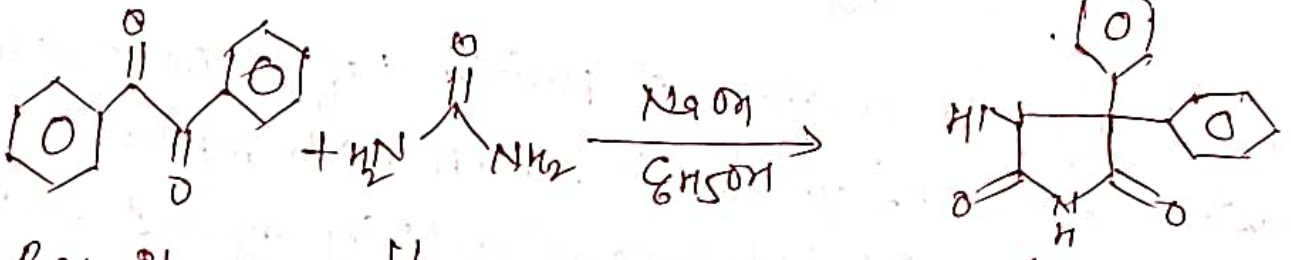


Ethotoin



Mephenytoin

Synthesis of phenytoin ⇒

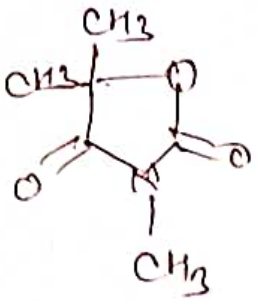


Benzil

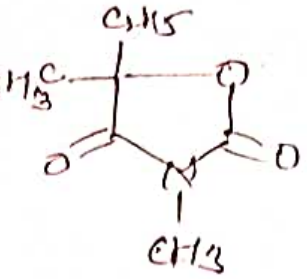
Urea

phenytoin

(3) Oxazolidine dione :-

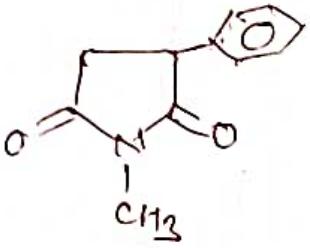


Trimethadione

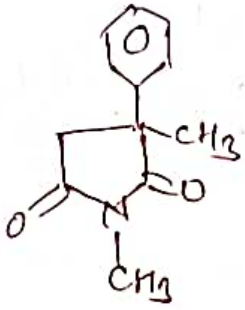


Paramethadione

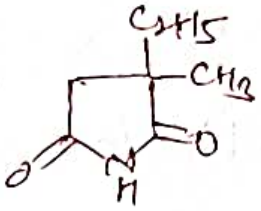
(4) Succinamides :-



phensuximide.

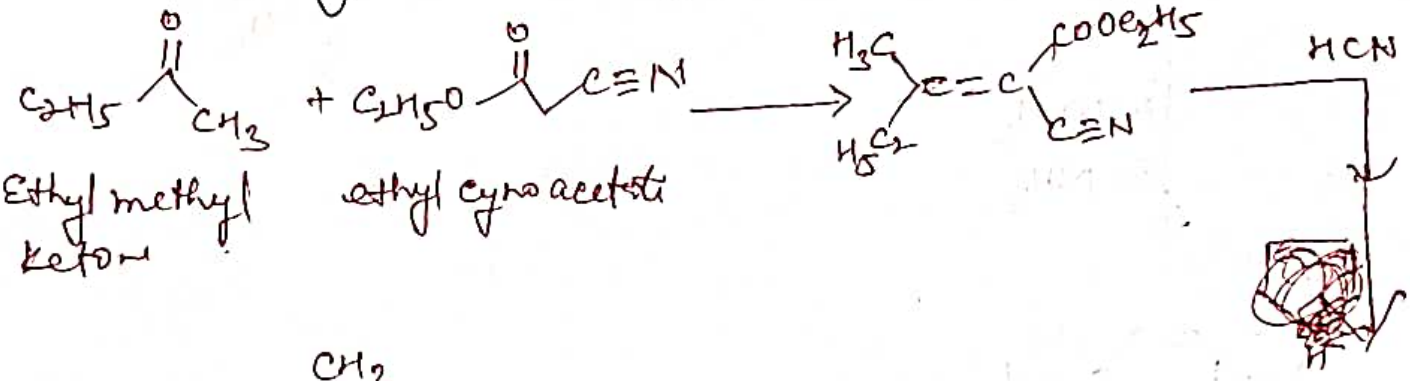


Methsuximide



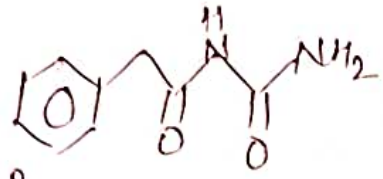
Ethosuximide.

Synthesis of Ethosuximide :-

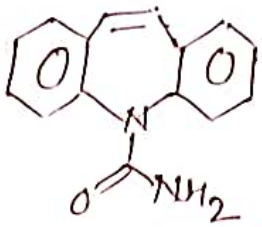


Ethosuximide

(5) Urea and monoacylureas ⇒

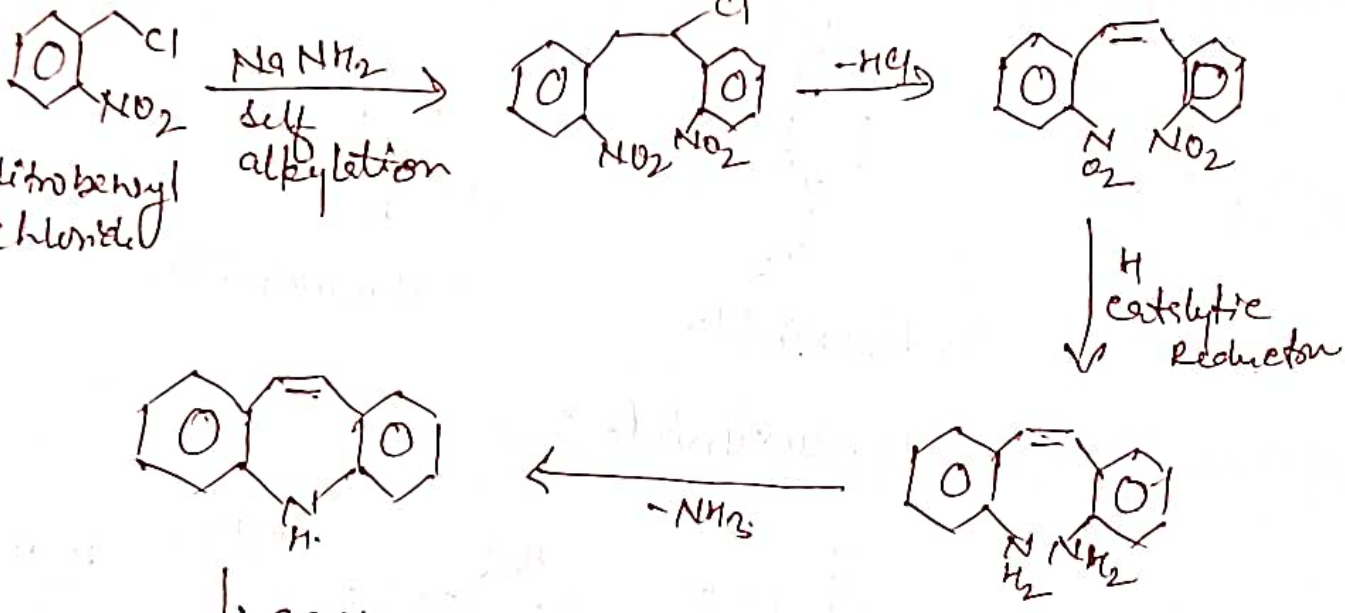


phenacimide



Carbamazepine

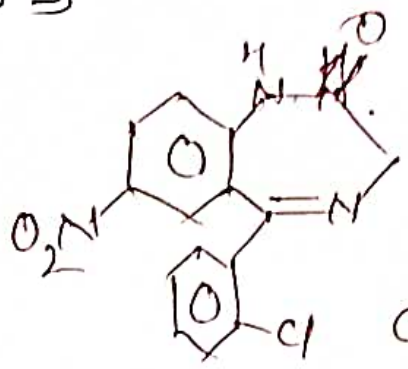
Synthesis of Carbamazepine ⇒



2-Nitrobenzyl Chloride

Carbamazepine

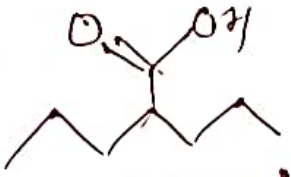
* Benzodiazepines ⇒



Clonazepam

* Miscellaneous :-

① Valproic acid :-

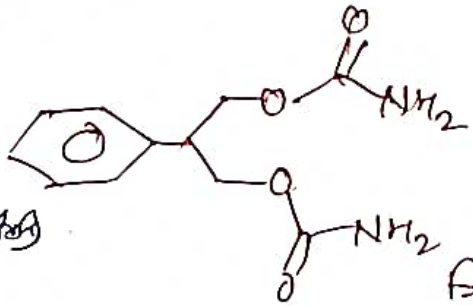


valproic acid.

MOA ⇒ phenytoin like.
prolongation of Na^+ channel inactivation

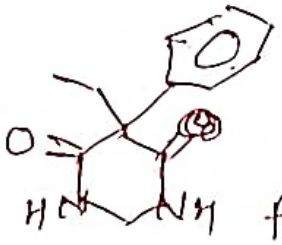
② Gabapentin :- Action on voltage ~~gated~~ activated Ca^{++} channels to block Ca^{++} entry

③ Felbamate -
(GABA receptor)



Felbamate

④ Primidone - (barbiturate)



Primidone