B. Pharm IV Semesater
MEDICINAL CHEMISTRY 1
UNIT 4

Drugs acting on Central Nervous System

A. SEDATIVES AND HYPNOTICS:

Syllabus

Benzodiazepines: SAR of Benzodiazepines, Chlordiazepoxide, Diazepam*,Oxazepam, Chlorazepate, Lorazepam, Alprazolam, Zolpidem

Barbiturtes: SAR of barbiturates, Barbital*, Phenobarbital, Mephobarbital,Amobarbital, Butabarbital, Pentobarbital, Secobarbital

Miscelleneous: Amides & imides: Glutethmide.

Alcohol & their carbamate derivatives: Meprobomate, Ethchlorvynol.

Aldehyde & their derivatives: Triclofos sodium, Paraldehyde.

4.1. Sedative and Hypnotics Pharmacology

1. **Introduction: https://youtu.be/NAPO7XGiDKI**
2. **Barbiturates Pharmacology: https://youtu.be/geuQ3yzOdb4**
3. **BZDs Pharmacology: https://youtu.be/lHkPoqmOq7o**
4. **Non-Benzodiazepines: https://youtu.be/xOhmrb4k-ME**
5. **Alcohols: https://youtu.be/Va7KbegdeHQ**

Sedatives:

- Drugs which reduce the excitement, anxiety and calm the patient without inducing the sleep and it may produce drowsiness. (Reduce the CNS activity)
- At large dose it may produce hypnotics
- Mainly act on limbic system which regulate the thought and mental functions

Hypnotics:

- Drugs which induce and maintain the normal sleep
- At high dose it may induce General Anesthesia
- Mainly act on Mid brain and Reticular Activating System which maintain the wakefulness.

Classification

1. Barbiturates

- **Long Acting**: Phenobarbitone
- **Short Acting**: Butobarbitone, Pentobarbitone
- **Ultra Short Acting**: Thiopentone, Methohexitone

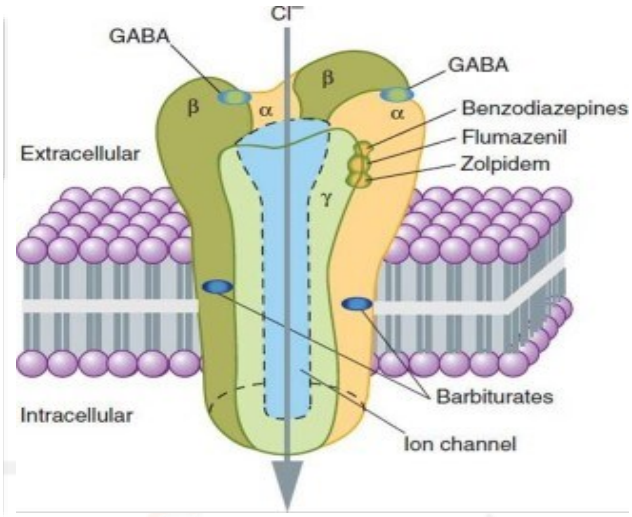
2. Benzodiazepines:

- **Hypnotics**: Diazepam, Flurazepam, Nitrazepam, Alprazolam, Temazepam, Triazolam
- **Antianxiety**: Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Alprazolam
- **Anti-convulsion**: Diazepam, Lorazepam, Clonazepam, Clobazam

3. Newer nonbenzodiazepine hypnotics:

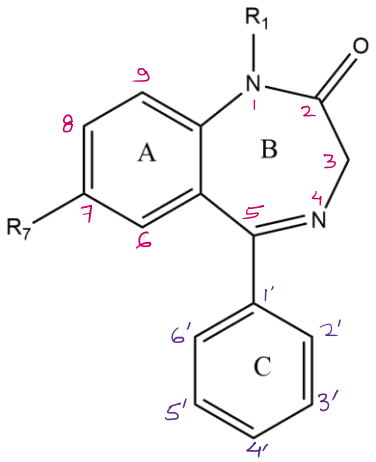
- Zopiclone, Zolpidem, Zaleplon

Mechanism of Action: GABA-A Receptor Mediated Inhibitory Action



Barbiturates	BDZs
• Gaba Mimetic action • More neurological depression • Low margin of safety • respiratory and cardiovascular depression • Suppression of REM sleep	• Gaba Facilitatory action • Less neurological depression • High Margin of safety • No respiratory and cardiovascular effects on hypnotic dose • No effect on REM Sleep

Benzodiazepines



Basic Ring of Benzodiazepines

SAR :

A. Ring 'A':

1.) Activity is increased if electron withdrawing group is substituted at position 7 (halogen, F_3, NO_2, CN etc),

2.) Activity is decreased with substitution at position 8 & 9 and with electron donating group at position 7.

3.) Position 6, 8, and 9 should be unsubstituted for the activity.

B. Ring 'B':

4.) A phenyl substitutent at the 5-position is most satisfactory. Heteroaromatic or cycloalkyl substituents generally reduce the activiuty

5.) Activity is increased if a methyl group is introduced at position 1, activity is decreased when larger substituents than methyl is introduced at position 1.

6.) Potency is decreased by replacements of carbonyl group with two hydrogens.

7.) Introduction of –OH group at position 3, lowers the activity.

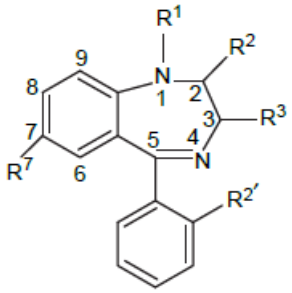
8.) Introduction of a carbonyl function in the 3 position increases the duration of action.

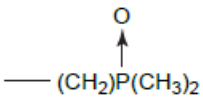
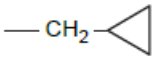
9.) Alkyl substitution at position 3 decreases the activity,

10.) Saturation of 4, 5 double bond or shift of it to the 3, 4 position decreases the activity

C. Ring 'C':

11.) Fluorine or chlorine at the ortho position or disubstitution on both ortho position increases activity. Any substitution at meta position decreases activity.



Name	R^1	R^2	R^3	R^7	$R^{2'}$
Diazepam	$-CH_3$	= O	–H	–Cl	–H
Oxazepam	–H	= O	–OH	–Cl	–H
Chlordesmethyl diazepam	–H	= O	–H	–Cl	–Cl
Fosazepam		= O	–H	–Cl	–H
Prazepam		= O	–H	–Cl	–H
Nitrazepam	–H	= O	–H	$-NO_2$	–H
Nordiazepam	–H	= O	–H	–Cl	–H
Nimetazepam	$-CH_3$	= O	–H	$-NO_2$	–H
Flunitrazepam	$-CH_3$	= O	–H	$-NO_2$	–F
Flurazepam	$-(CH_2)_2N(C_2H_5)_2$	= O	–H	–Cl	–F
Quazepam	$-CH_2CF_3$	= S	–H	–Cl	–F
Halozepam	$-CH_2CF_3$	= O	–H	–Cl	–H
Temazepam	$-CH_3$	= O	–OH	–Cl	–H
Lorazepam	–H	= O	–OH	–Cl	–Cl
Clonazepam	–H	= O	–H	$-NO_2$	–Cl
Doxefazepam	$-CH_2OH$	= O	–OH	–Cl	–F

Uses of Benzodiazepines :

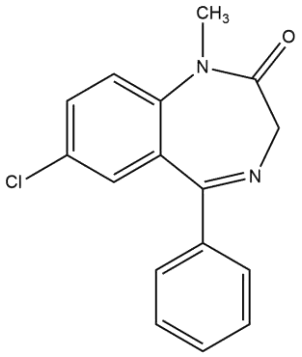
1. Used in the treatment of anxiety and insomnia.
2. Diazepam is used as an adjunct in the management of *Status epilepticus.*
3. Used as preanaesthetic medication.

4. Used as a muscle relaxant.

5. Used in the treatment of alcohol withdrawal.

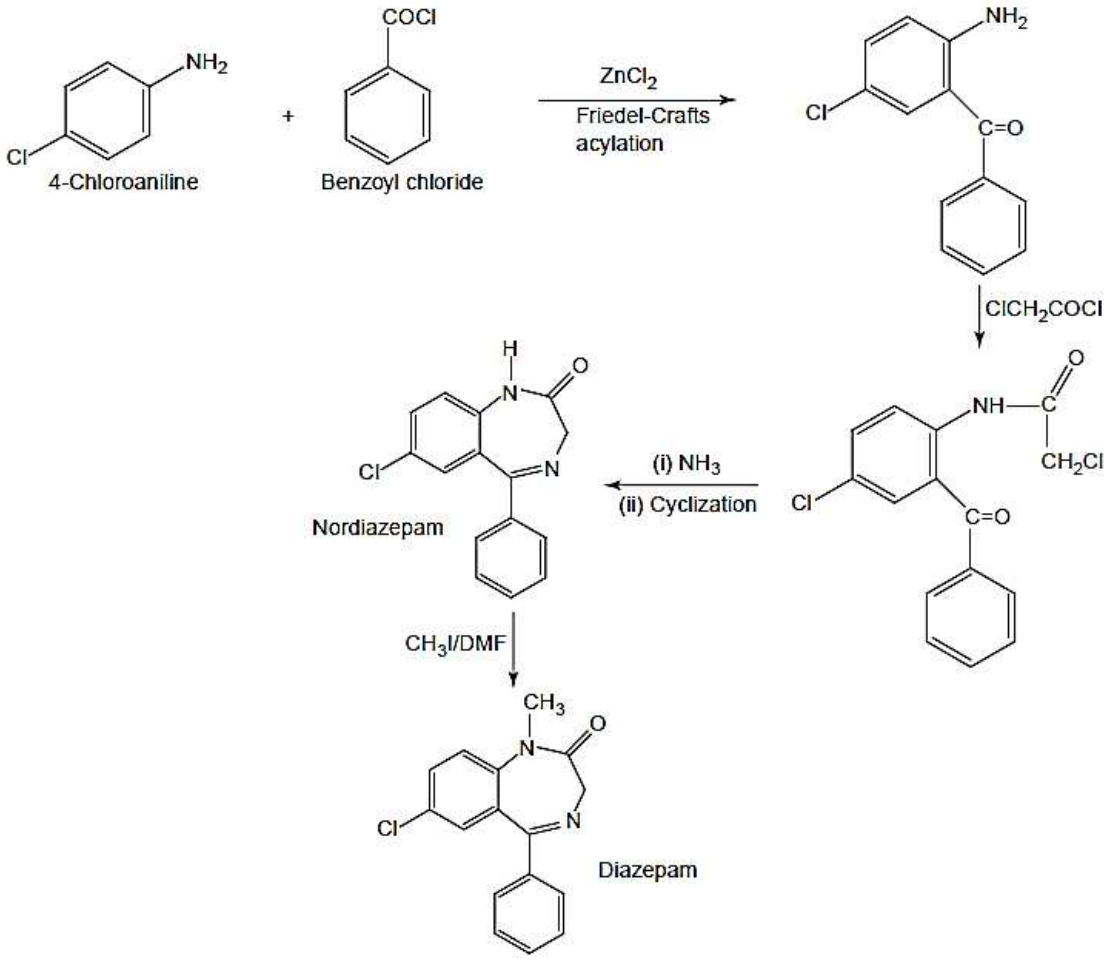
6. Used along with analgesics, NSAID'S, spasmolytics and antiulcer agents.

1) Diazepam*

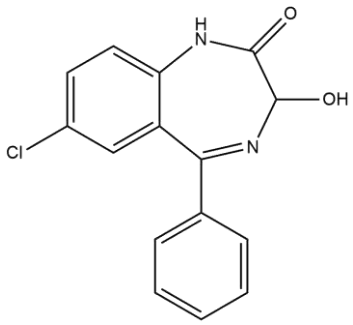


7-chloro-1, 3-dihydro-1-methyl- 5-phenyl-2H-1, 4, benzodiazepin-2-one.

Synthesis

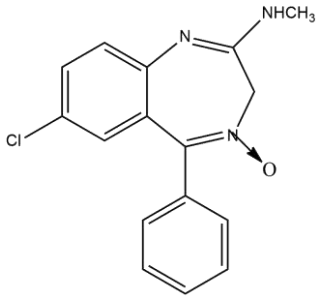


2) Oxazepam



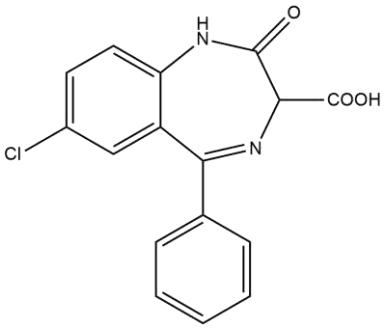
7–chloro –1, 3-dihydro-3-hydroxy-5-phenyl-2H-1,4 – benzodiazepin-2-one

3) Chlordiazepoxide



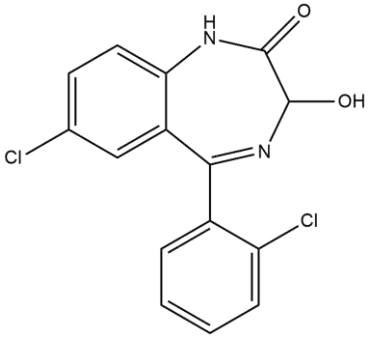
7 – chloro – 2(methyl amino)–5–phenyl–3H–1, 4, –benzodiazepin –4–oxide.

4) Chlorazepate



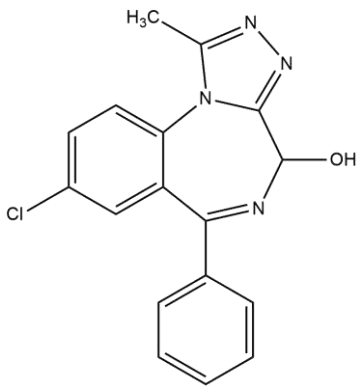
7–chloro–2,3-dihydro–2-oxo–5–phenyl-1H–1, 4– benzodiazepine–3–carboxylic acid

5) Lorazepam



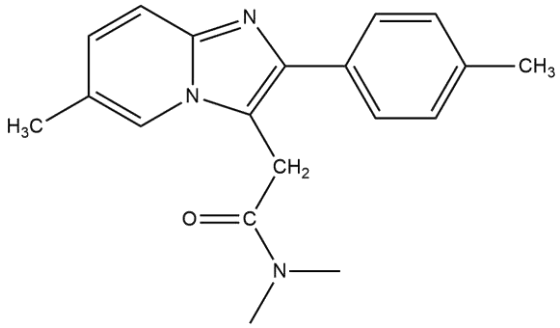
7–chloro–5–(2 chlorophenyl) –1, 3–dihydro–3–hydroxy–2H-1, 4– benzodiazepin–2–one.

6) Alprazolam



8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

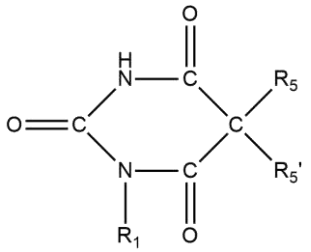
7) Zolpidem



***N*,*N*-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide**

Barbiturates

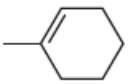
Barbiturtes: SAR of barbiturates, Barbital*, Phenobarbital, Mephobarbital,Amobarbital, Butabarbital, Pentobarbital, Secobarbital



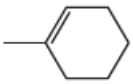
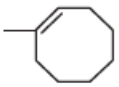
A) Long Acting (>6h)

Name	R^1	R^5	$R^{5'}$
Barbital	–H	$-C_2H_5$	$-C_2H_5$
Phenobarbital	–H	$-C_2H_5$	$-C_6H_5$
Mephobarbital	$-CH_3$	$-C_2H_5$	$-C_6H_5$
Metharbital	$-CH_3$	$-C_2H_5$	$-C_2H_5$

B) Intermediate Acting (3-6 h)

Name	R^1	R^5	$R^{5'}$
Amobarbital	–H	$-C_2H_5$	$-CH_2CH_2CH(CH_3)(CH_3)$
Butabarbital	–H	$-C_2H_5$	$-CH(CH_3)-CH_2-CH_3$
Aprobarbital	–H	$CH_2=CH-CH_2-$	$(CH_3)_2CH-$
Talbutal	–H	$CH_2=CH-CH_2-$	$CH_3CH_2CH(CH_3)-$
Butalbital	–H	$CH_2=CH-CH_2-$	$(CH_3)_2CHCH_2-$
Hexobarbital	$-CH_3$	$-CH_3$	

C) Short Acting (<3h)

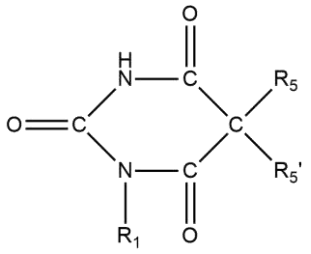
Name	R^1	R^5	$R^{5'}$
Pentobarbital	–H	$-C_2H_5$	$CH_3CH_2CH_2CH(CH_3)-$
Secobarbital	–H	$CH_2=CH-CH_2-$	$CH_3(CH_2)_2CH(CH_3)-$
Cyclobarbital	–H	$-C_2H_5$	
Heptabarbital	–H	$-C_2H_5$	

D) Ultrashort Acting (15 min)

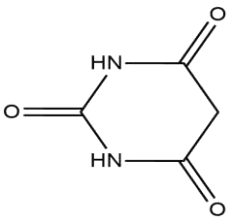
Name	R^1	R^5	$R^{5'}$
Thiopentone	–H	$-C_2H_5$	$CH(CH_2)_2CH_3$ CH_3

(At C – 2 = S instead of = O)

Structural Activity Relationship of Barbiturates



1. Barbiturates are the derivatives of barbituric acid, but barbituric acid itself has not any hypnotic activity.



C-5 Substitutions:

2. dialkyl/aryl substitution at 5 position (R5 & R5') is responsible for hypnotic activity.

3. alkyl/aryl group enhance the lipid solubility.

4. Both H-atom replace for the maximum activity.

5. Alkyl substitutions: Barbital -C_2H_5, Pentobarbitone -$CH(CH_3)$-CH_2-CH_2-CH_3, Amobarbitone -CH_2-CH_2-$CH(CH_3)_2$

- Increase the length of alkyl chain- increases the potency up to 5 to 6 Carbon atom
- Beyond 6 carbon atom- convulsant action produces due to increased lipophilicity

6. Cyclic substitutions: Phenobarbitone (phenyl), Hexobarbital (cyclohexene)

- Branched, cyclic, unsaturated chain-
    - Decreases the duration of action, due to high metabolism
    - Cyclobarbital < Allobarbital < Phenobarbital
    - Increases the activity, due to high lipophilicity

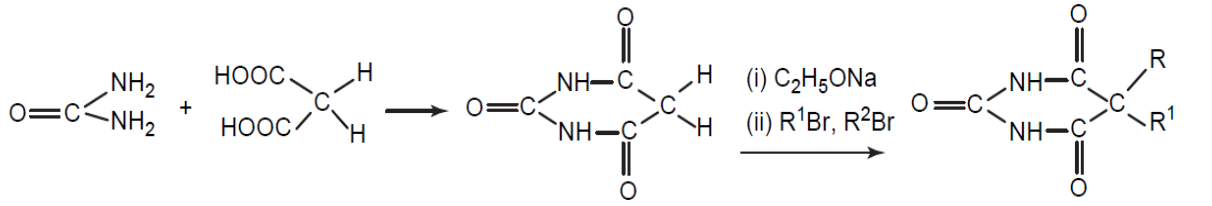
N-1 Substitution

7. N-Methyl substitution (Hexobarbital)-shorten the duration of action and rapid onset of action

C-2 Position

8. Replace O-atom with S-atom (Thiopental)- fast onset of action, and shorter duration pf action, due to increase the lipid solubility

General Synthetic Procedure

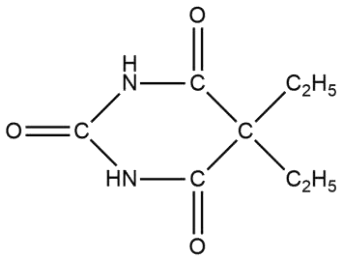


Urea Malonic acid Barbituric acid 5,5[1]-Substituted barbiturate

Mechanism of Action: GABA mimetic action

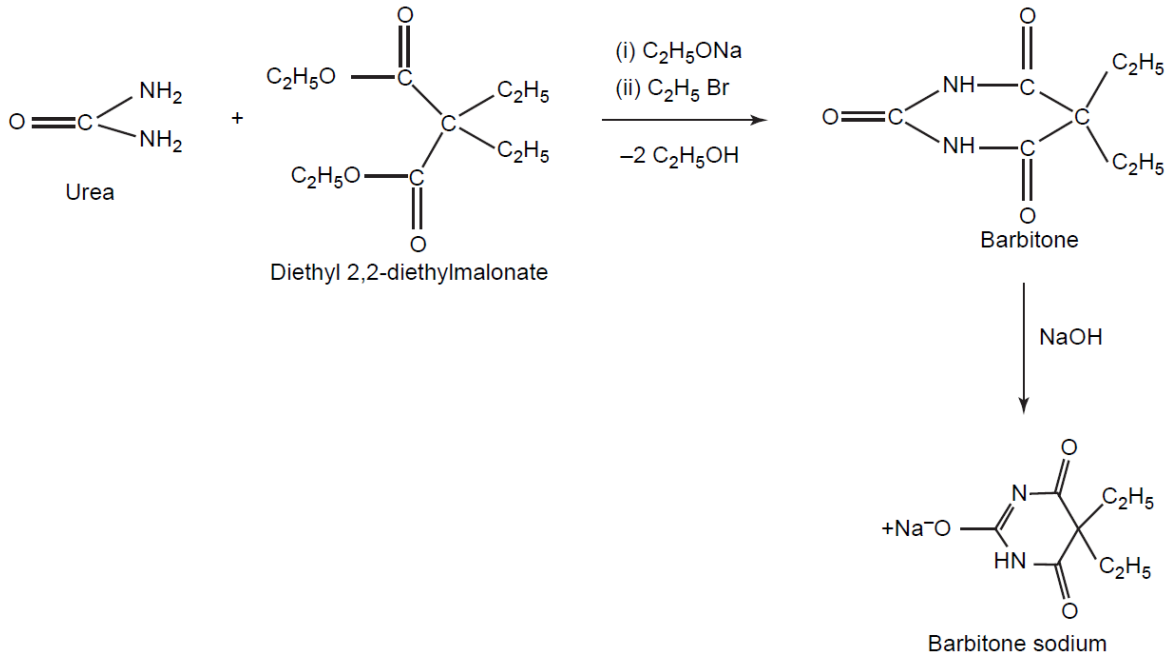
Uses: Hypnotics, Anticonvulsant, General Anaesthetics, Insomnia

1) Barbital*



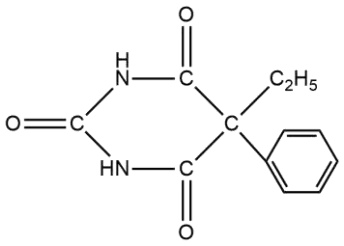
5,5-diethyl barbituric acid

Synthesis



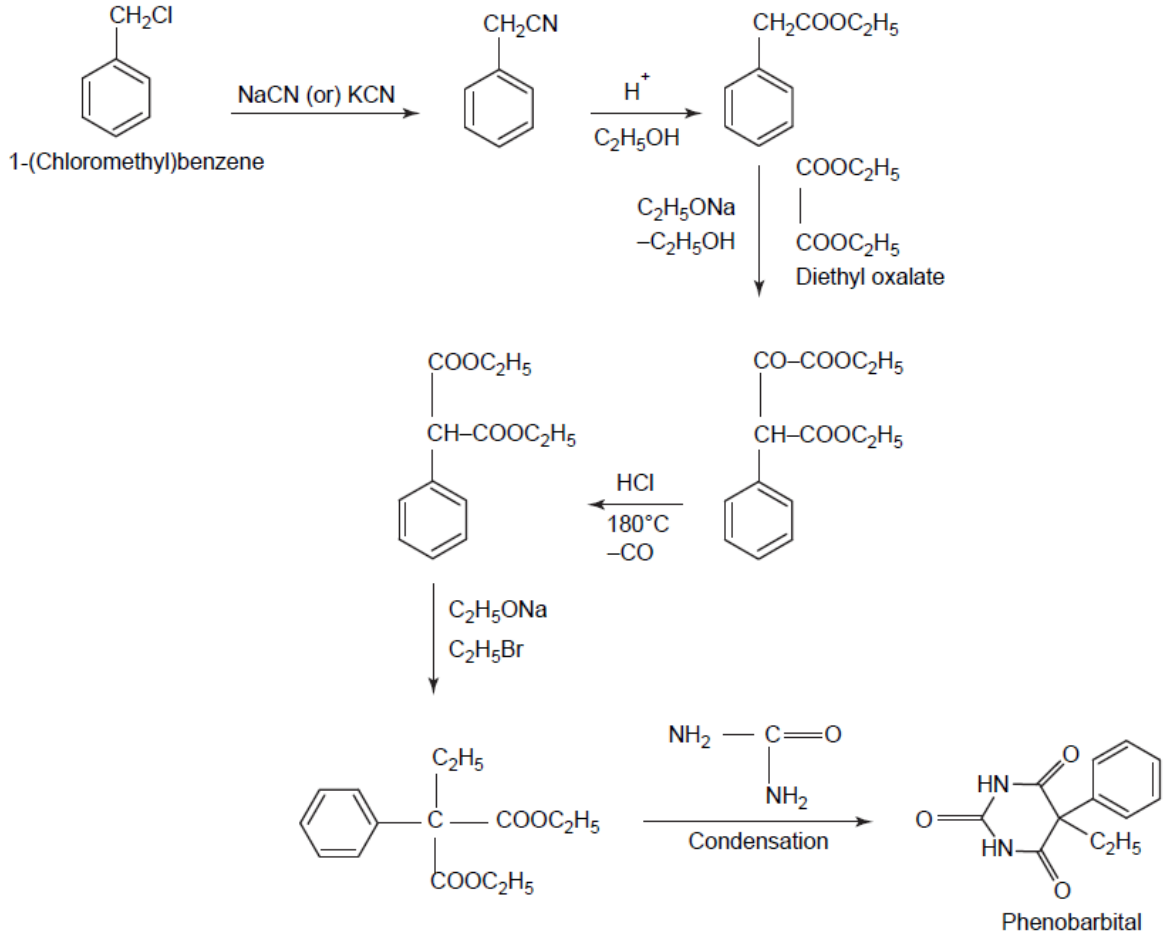
Urea Diethyl 2,2-diethylmalonate Barbitone Barbitone sodium

2) Phenobarbital

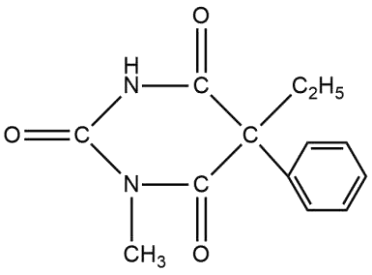


5-ethyl-5-phenyl barbituric acid

Synthesis

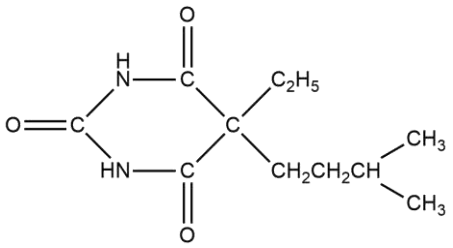


3) Mephobarbital



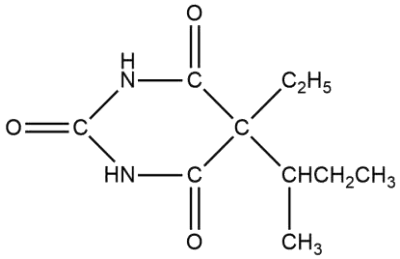
1-methyl-5-ethyl-5-phenyl barbituric acid

4) Amobarbital



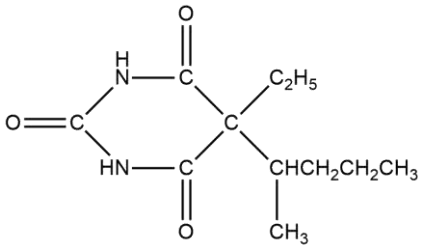
5-ethyl-5-(3-methyl-butyl) barbituric acid

5) Butabarbital



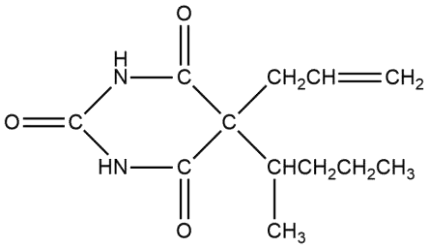
5-ethyl-5-(1-methyl-propyl) barbituric acid

6) Pentobarbital



5-ethyl-5-(1-methyl-propyl) barbituric acid

7) Secobarbital



5-(1-methyl-propyl)-5-prop-2-enyl-barbituric acid

B. Antipsychotics

Phenothiazeines: SAR of Phenothiazeines - Promazine hydrochloride, Chlorpromazine hydrochloride*, Triflupromazine, Thioridazine hydrochloride, Piperacetazine hydrochloride, Prochlorperazine maleate, Trifluoperazine hydrochloride.

Ring Analogues of Phenothiazeines: Chlorprothixene, Thiothixene,Loxapine succinate, Clozapine.

Fluro buterophenones: Haloperidol, Droperidol, Risperidone.

Beta amino ketones: Molindone hydrochloride.

Benzamides: Sulpieride.

C. Anticonvulsants: SAR of Anticonvulsants**,** mechanism of anticonvulsantaction

Barbiturates: Phenobarbitone, Methabarbital.

Hydantoins: Phenytoin*, Mephenytoin, Ethotoin

Oxazolidine diones: Trimethadione, Paramethadione

Succinimides: Phensuximide, Methsuximide, Ethosuximide*

Urea and monoacylureas: Phenacemide, Carbamazepine*

Benzodiazepines: Clonazepam

Miscellaneous: Primidone, Valproic acid , Gabapentin, Felbamate