UNIT - IV

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Drug Acting on CNS

Sedatives "CNS Depressant Drugs"

that reduce Excitement, tension and produc relaxation.

Hypnotic "CNS Depressant Drugs"

Induces drowsiness and produce sleep similar to natural sleep

Small dose Cause **Sedation**
Medium dose Cause **Hypnosis**
Large dose Cause **Surgical Anesthesia**

Classification

Benzodiazepines, e.g Oxazepam, Diazepam, Alprazolam

Barbiturates e.g Amobarbital, phenobarbital, pentobarbit

Miscellaneous e.g Meprobomate, paraldehyde

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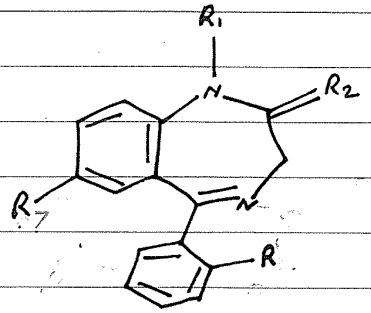
1. Benzodiazepines



Chemically they are a fusion of Benzene ring and a Diazepine ring

Benzodiazepines enhance the effect of the GABA at the GABAA receptor, resulting in sedative, hypnotic anxiolytic, anticonvulsant and muscle Relaxant properties.

Types of Benzodiazepines.

Based on Drug Elimination, there are 3. types.

Long Acting	>24 H	Diazepam, Nitrazepam
Intermidiate Acting	12-24 H	Alprazolam, lorazepam
Short Acting	1-12 H	Midazolam, triazolam.

Mode of Action. (MoA)

They are positive allosteric Effect at GABA receptor and stimulate the pharmacologic Action of GABA which is the principal inhibitory neurotransmitter in the CNS.

Attach to and directly block the Acetylcholine (Ach) receptors in the hippocampus thus causing amnesia

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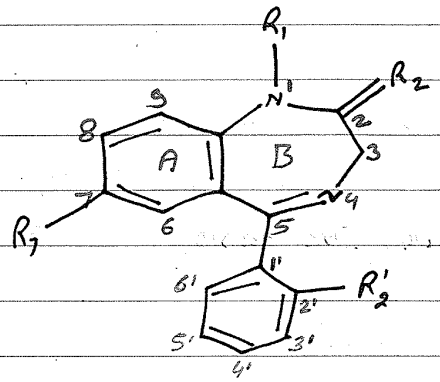
SAR of Benzodiazepines



1. At Electronegative substituent at position 7 is required for Activity. More the Electronegativity, higher will be the Activity.
2. A phenyl at position 5 promotes Activity. If this phenyl gp is 2' or 6' substituted, Activity increases.

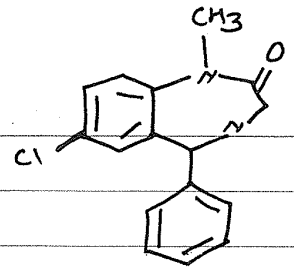
3. Alkyl substitution at pogetion 3 decreases Activity Except -OH group.

≠ Compounds without 3- hydroxyl gp are nonpolar and usually have long half-life.

≠ Compounds with 3- hydroxyl gp have short half-life because of rapid conjugation with glucuronic Acid.

Other compounds

Name	R_1	R_2	R_3	R_7	R'_2
Diazepam	$-CH_3$	=O	-H	-Cl	-H
Oxazepam	-H	=O	-OH	-Cl	-H
Lorazepam	-H	=O	-OH	-Cl	-Cl
Chlorazepate	-H	=O	-COOH	-Cl	-H



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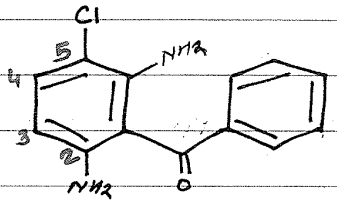
Diazepam

It is a sedative and Hypnotic drug under the benzodiazepin.

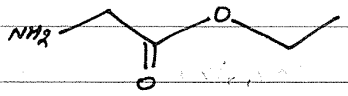
It Acts by Increasing the Effect of the Neurotransmitter GABA. It enhances $GABA_A$ Receptor Activity leading to CNS Depression.

It Used to Managment of Epilepsy, anxiety, trouble sleeping.

Synthesis



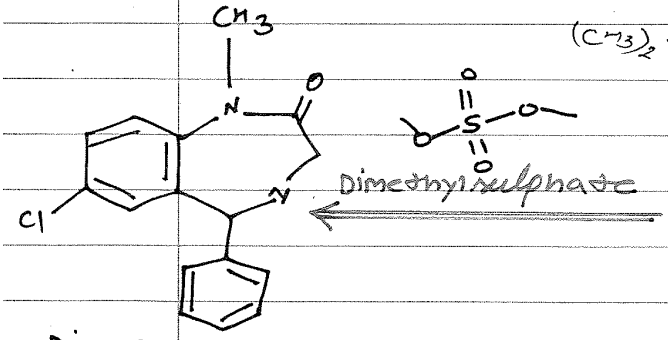
2-amino-5-Chlorobenzophenone



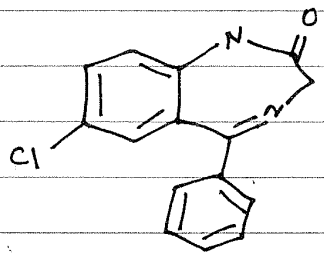
Ethyl-2-aminoacetate

pyridine

$(-CH_3CH_2OH, -H_2O)$



Diazepam



7-Chloro, 1,3-dihydro-5-phenyl 2-H 1,4-benzodiazepin-2-one

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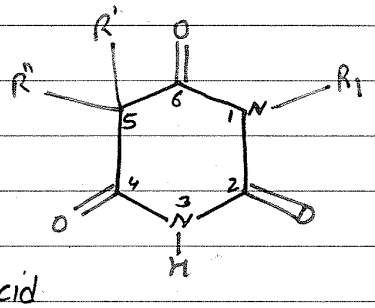
2. Barbiturates



All derivatives of Barbituric Acid

They are CNS depressants. They are Effective as anxiolytics, hypnotics, anticonvulsants and Analgesics.

They have addiction potential, both physical and psychological

Benzodiazepines have largely replaced them in form of Sedative - Hypnotic.

Types of Barbiturates

Name	R_1	R_5	$R_{5'}$
Barbital	$-H$	$-C_2H_5$	$-C_2H_5$
Phenobarbital	$-H$	$-C_2H_5$	$-C_6H_5$
Mephobarbital	$-CH_3$	$-C_2H_5$	$-C_6H_5$
Amobarbital	$-H$	$-C_2H_5$	$-CH_2-CH_2-CH$
Butabarbital	$-H$	$-C_2H_5$	$-CH_2-CH_2-CH_3$
Pentobarbital	$-H$	$-C_2H_5$	$-CH(CH_3)-CH_2-CH_2-CH$
Secobarbital	$-H$	$-CH_2-CH=CH_2$	$-CH(CH_3)-CH_2-CH_2-CH$

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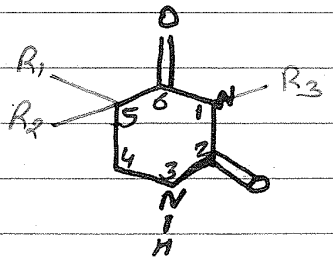
MOA of Barbiturates

These drugs increased the lifetime of Cl- channel opening induced by GABA.

At very high conc.. barbiturates depress voltage sensitive sodium & potassium channel.

They also block excitatory glutamate receptors.

SAR



1. Substituents at position -5 is increased by 5-6 carbon atoms.
2. If length of an alkyl chain at position-5 is increased by 5-6 carbon atoms, potency is enhanced. but Depressant Action Decreases.
3. If one hydrogen atom at position 5 is replaced with phenyl group, the drug attains anticonvulsant properties
4. If one imide hydrogen atom at position 1 or 3 is replaced with alkyl groups, compound give quick Action and ↓ve Duration of Action.
5. If oxygen at pogetion 2 is replaced with a sulphur atom ↓ve Duration of Action, but increased lipid solubility. that rapid Action on CNS.

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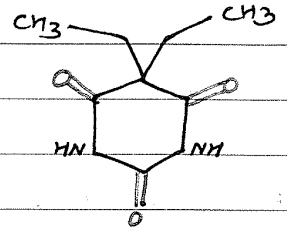
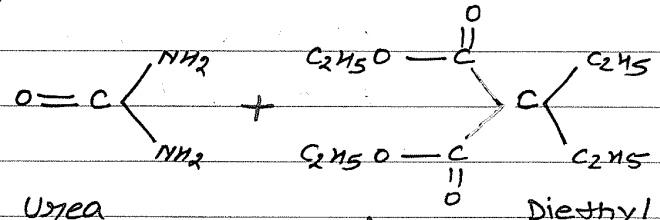
1. Barital



Barbital is a long-Acting Drug

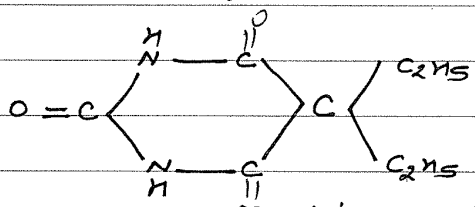
It used as a sedative and hypnotic
Also used as Veterinary Medicin.

Synthesis



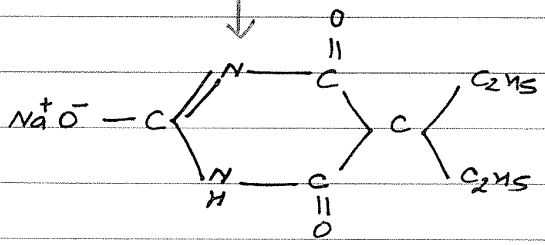
Urea + Diethyl Malonic Ester

C_2H_5ONa / $-CH_3CH_2OH$



Barbitone

NaOH



Barbitone sodium

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5. Miscellaneous

1. Imides & imides : Glutethimide

2. Alcohol & their Carbamate derivatives Ethchlorvynol, Meprobamate

3. Aldehyde & their Derivatives Triclofos sodium, Paraldehyde

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Part - B

Antipsychotics

Antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat Schizophrenia and Effective in other psychotic states, including mania, grandiosity, paranoia, hallucinations and delusions.

Schizophrenia is for life

These drugs Decrease the intensity of Hallucinations and Delusions and permit the person with Schizophrenia to function in a supportive environment.

MOA of Antipsychotic Agents

Dopamine antagonism; All antipsychotic Agents (Except clozapine) possess dopamine (D2) receptor blocking Action in the brain and the periphery.

Antipsychotic Drug

↓

Dopamine receptor blocking

↓

Decreased Intracellular Responce

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Classification

Phenothiazines Promazine, chlorpromazine, Clozapine

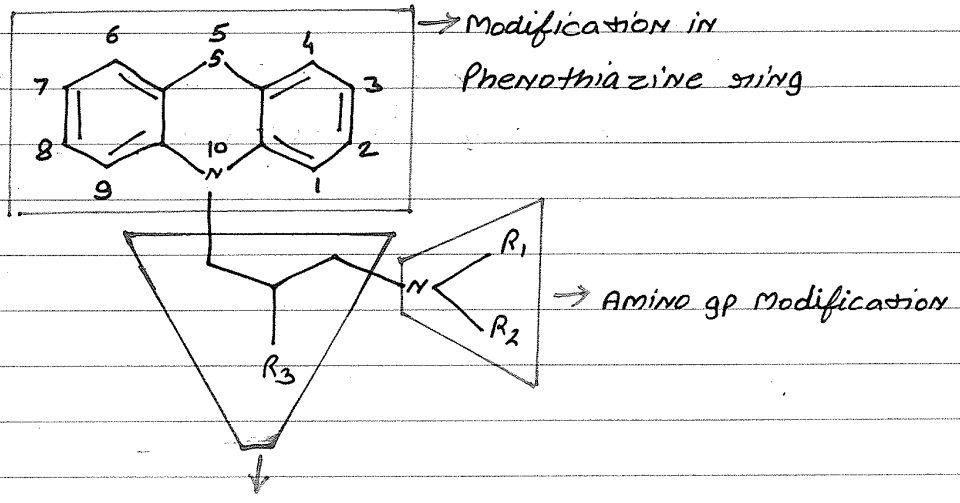
Flurobutyrophenones Haloperidol, Droperidol.

Beta-amino ketones Molindone, Hydrochloride

Benzamide Sulpiride

Miscellaneous Olanzapine, Oxypertine

SAR of Phenothiazine



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Nature of Alkyl Side Chain

Potency is maximum, when there is three carbon b/w two N atom

Introduction of methyl group on cyclopropyl ring at C-1 Decreases antipsychotic Activity and produces imipramine -like Activity.

When oxygen is introduced into C-1 results in potent antidepressent Effect.

Addition of $-CH_2$ at C-2 or C-3 has very little Effect on Activity.

Amino group of Side chain.

3° Nitrogen shows maximum potency and 2° or 1° Nitrogen shows reduced or abolished Activity.

Activity Decreased when Dimethylamino group is replaced by pyrolidinyl, morpholinyl or thiomorpholinyl groups.

Substituents on Aromatic ring

Substitution at C-2 position is optimal for neuroleptic Activity In general, potency at different positions increases in the following order $1 < 4 < 3 < 2$.

Potency of the various groups increase in the following order on $H < CN < CH_3 < Cl < CF_3$

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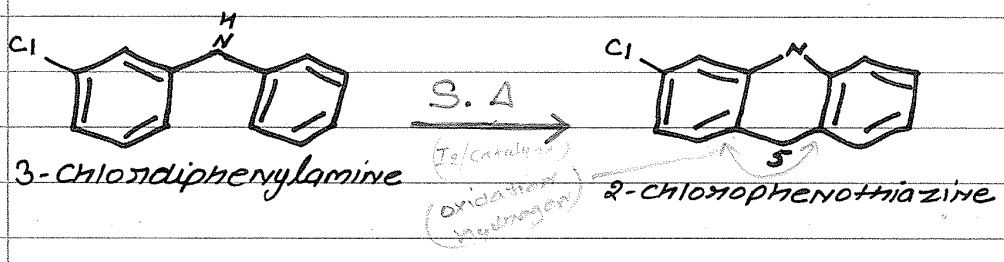
1 Chlorpromazine Hydrochloride

It show antipsychotic Effect, by Blocking postsynaptic dopamine receptor in Brain.
Thus preventing Excess dopamine in Brain.

Used to treat hallucination and delusions.
It also has significant sedative and hypotensive properties.

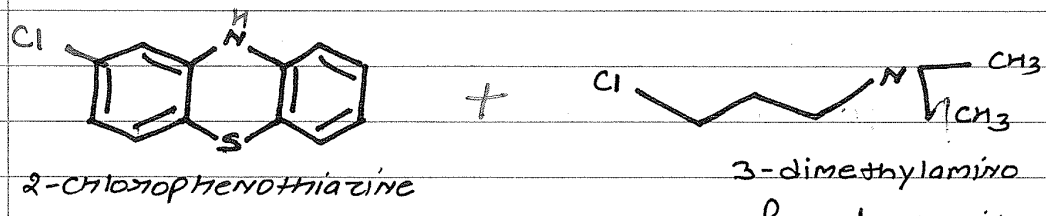
Synthesis

Step - I

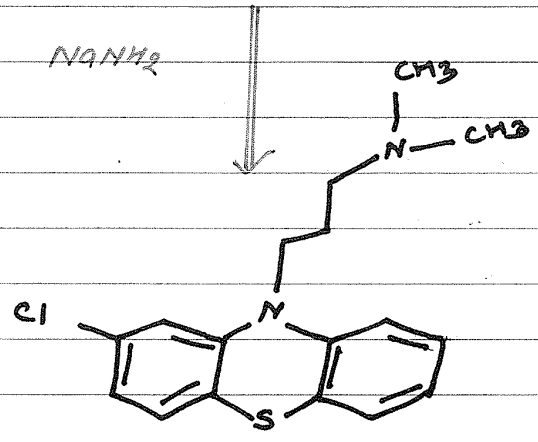


3-Chlorodiphenylamine → 2-Chlorophenothiazine

Step - II



2-Chlorophenothiazine + 3-dimethylamino Propylchloride



Chlorpromazine