Sedative-Hypnotic Drugs

9. Lecture

Assoc.Prof. Omer Tahir Gunkara

Sedative-Hypnotic Drugs

Sedative-Hypnotic Drugs

- Chemical substances used to reduce tension and anxiety and induce calm (sedative effect) or to induce sleep and drowsiness (hypnotic effect).

- Most such drugs exert a quieting or calming effect at low doses and a sleep-inducing effect in larger doses.

Example of Sedative-Hypnotic Drugs

Barbiturates e.g. Methohexitone, Phenobarbital, Pentabarbital Thiopentone,Thiamylal

Benzodiazepines e.g. Diazepam (Valium), Midazolam (Versed), Clonazepam (Klonopin) Nitrazepam (**Ormodon)** Flunitrazepam (**Rohypnol)**

Glutethimide : Piperidinediones

Meprobamate : Propanediol carbamates

Alcohols : Ethanol, Chloral hydrate, Paraldehyde

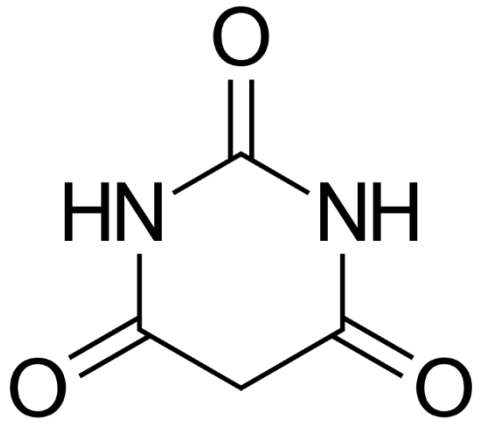
Buspirone : Azaspirodecanedione

Zolpidem : Imidazopyridine

Zaleplon : Pyrazolopyrimidine

Barbiturates

– Derivatives of barbituric acid
– Hypnotic/anxiolytic effect discovered in the early 20th century (Veronal®, 1903)
– Until the 60s the largest group of hypnotics (more hypnotic than anxiolytic)
– Act by both enhancing GABA responses and mimicking GABA (open Cl-channels in the absence of GABA) => increased inhibition of the CNS (also block glutamate receptors)
– High risk of dependence (severe withdrawal symptoms)
– Strong depressant activity on the CNS => anesthesia
– At higher doses respiratory and cardiovascular depression => very little use today as hypnotics (only for epilepsy and anesthesia)



Barbutiric acid

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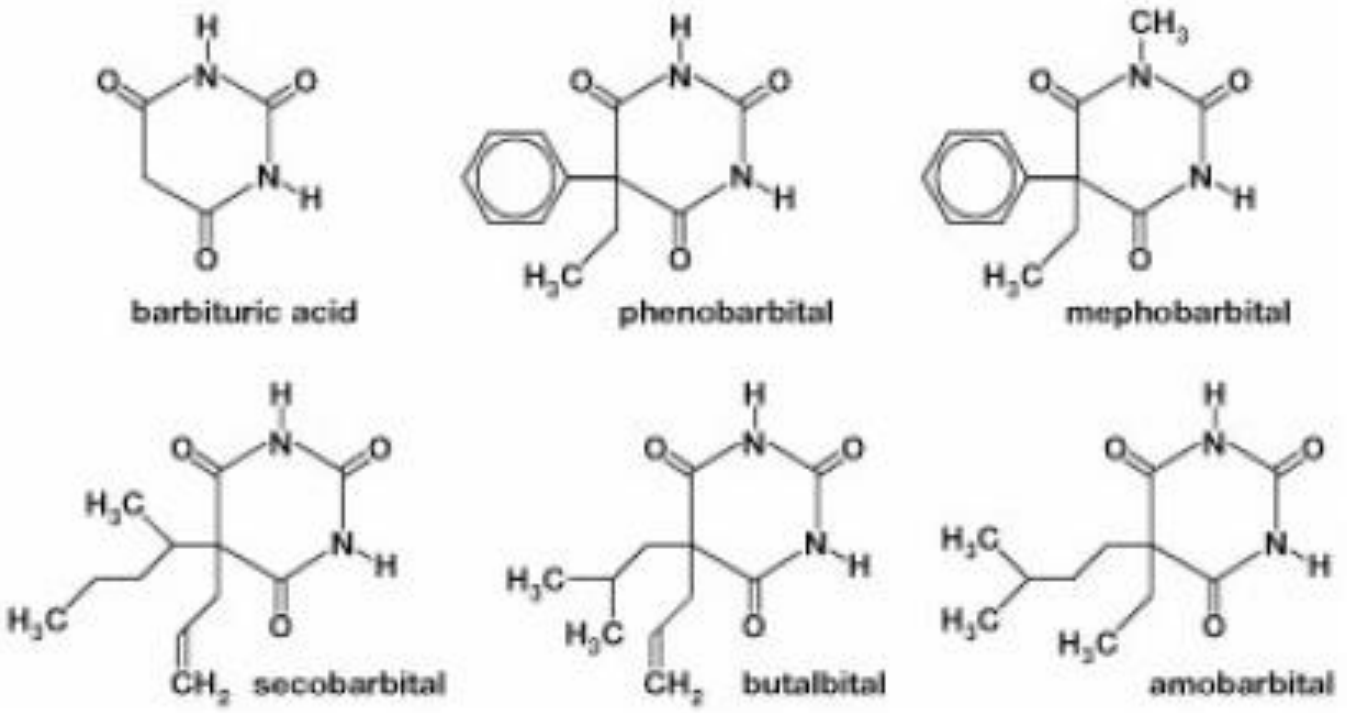
Barbiturates



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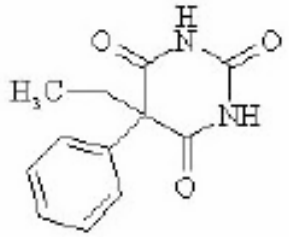
Barbiturates

Different barbiturates vary mostly in their duration of action

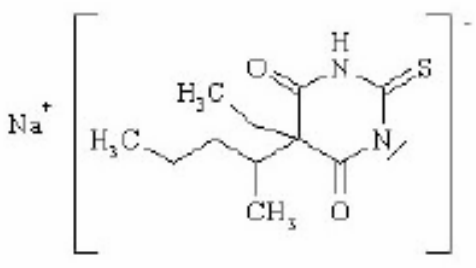
• **Phenobarbital**
– Long-acting: used for anticonvulsive therapy



5-ethyl-5-phenylbarbituric acid

• **Thiopental**
– Very short acting (very lipophilic => redistributed from the brain into the fat tissue)

⇒CNS concentration falls below effective levels: used for i.v. anesthesia



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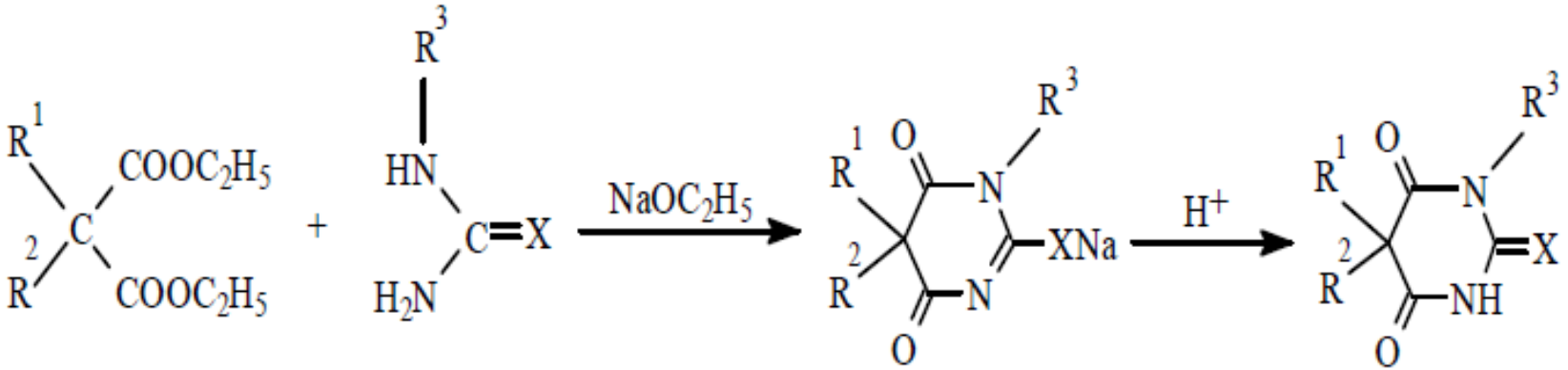
Barbiturates

General Synthesis Method for Barbiturates

✓ Substituted malonic acid esters undergo condensation with urea or thiourea in the presence of a base to give the desired barbiturates

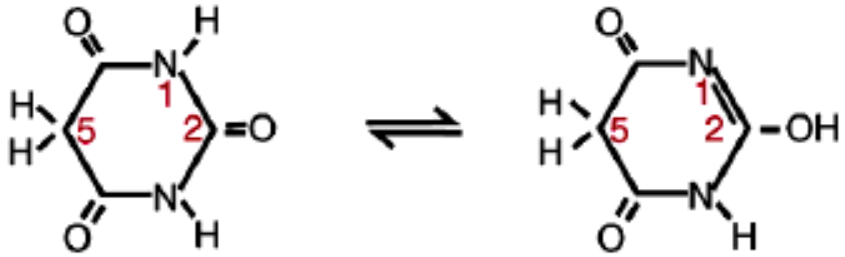


X : O, barbituric acid derivatives
X : S, thiobarbituric acid derivatives

Barbiturates

Structure-Activity Relationship of Barbiturates

The **keto and enol tautomeric** forms of barbituric acid with the sites of substitution in the hypnotically active barbiturates identified as 1, 2, and 5.



Barbiturates

Structure-Activity Relationship of Barbiturates

Substitution at carbon 5

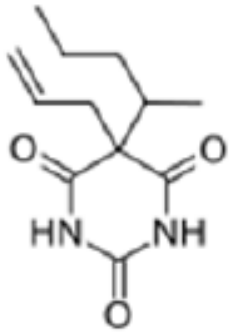
* Hypnotic activity is introduced

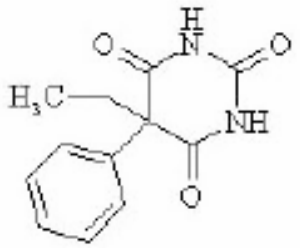
✓ Branched chain --> greater hypnotic activity than straight chain

✓ Phenol group (like phenobarbital) --> Greater anticonvulsant activity

✓ Presence of hydrophilic groups such as –OH, -SH, -NH_2, -COOH, -SO_2 decreases lipophilicity so decreases activity

Secobarbital





phenobarbital

Barbiturates

Structure-Activity Relationship of Barbiturates

Carbon 2

* No substitution (oxygen) - **oxybarbiturates** (ex. pentobarbital and secobarbital)
* Substitution with sulfur - **thiobarbiturates** (ex. thiopental and thiamylal)
* **Sulfuration at carbon 2** increases lipid solubility

✓ Greater hypnotic potency

✓ More rapid onset, but shorter duration of action e.g. thiopental has faster onset and shorter duration than pentobarbital

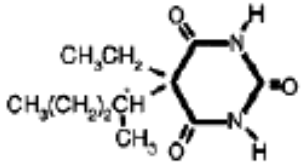
Barbiturates

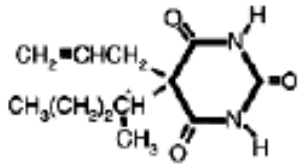
Structure-Activity Relationship of Barbiturates

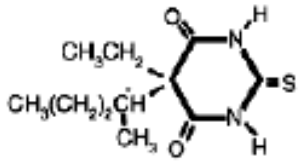
Nitrogen 1

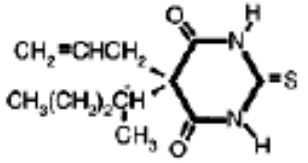
* Addition of a methyl group to nitrogen (e.g. methohexital)

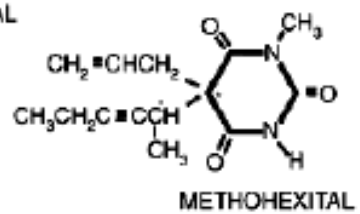
✓ Short duration of action











Hypnotics / Sedatives: Benzodiazepines

- **Benzodiazepines** have sedative, hypnotic, anti-anxiety, anticonvulsant, and muscle relaxant properties.

- They are the most widely used anxiolytic drugs **used to treat anxiety, insomnia** ,and a range of other conditions.

- **Benzodiazepines** have largely replaced barbiturates and meprobamate in the treatment of anxiety, because they are safer (less side effects and dependence) and more effective

- At low doses are useful sedatives and high doses produce a hypnotic effect

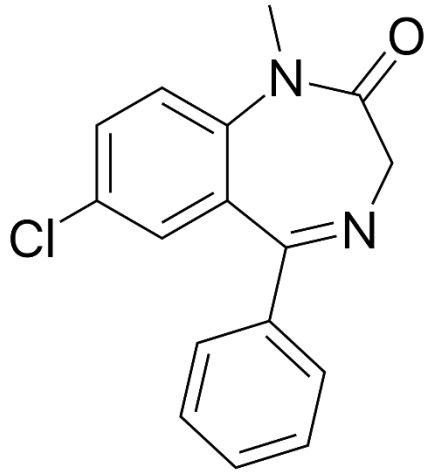
Hypnotics / Sedatives: Benzodiazepines

- **Absorption and distribution**: The benzodiazepines are lipophilic, and they are rapidly and completely absorbed after oral administration and distribute throughout the body.

- The benzodiazepines are excreted in the urine as **glucuronides or oxidized metabolites**.

Hypnotics / Sedatives: Benzodiazepines

- ✓ Derivatives of Benzodiazepine
- ✓ Valium (diazepam) in 1962
- ✓ Characteristic seven-membered ring fused to aromatic ring
- ✓ Used to treat anxieties of all kinds (phobias, preoperative anxiety, myocardial infarction (prevent cardiac stress due to anxiety…)



Valium - Diazepam

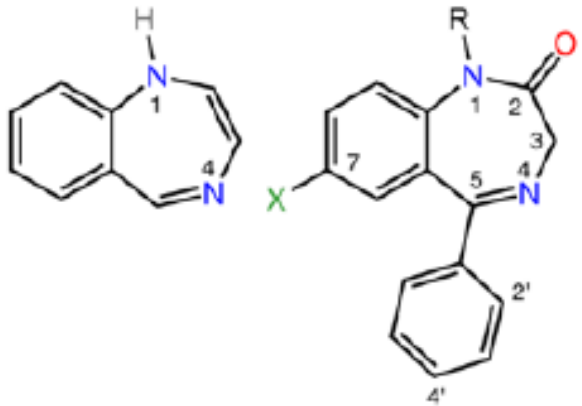
Hypnotics / Sedatives: Benzodiazepines

Mechanism of Action of Benzodiazepines

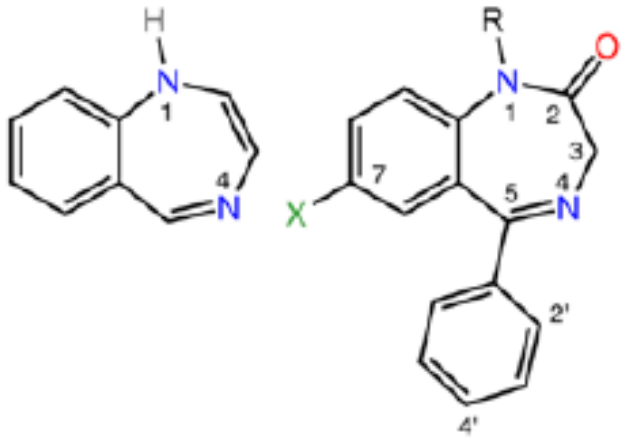
Benzodiazepines work by enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) - which is responsible for reducing the activity of neurons that cause stress and anxiety.

The Core Structure of Benzodiazepines

- Heterocyclic ring system which is a fusion between benzene and diazepine ring system.
- This heterocycle has two nitrogen atoms, five carbon atoms and maximum possible number of cumulative double bonds.
- **"Benzo"** prefix benzene ring fused onto the diazepin ring
- **"R"** labels denote common locations of side chains, which give different benzodiazepines their unique properties.



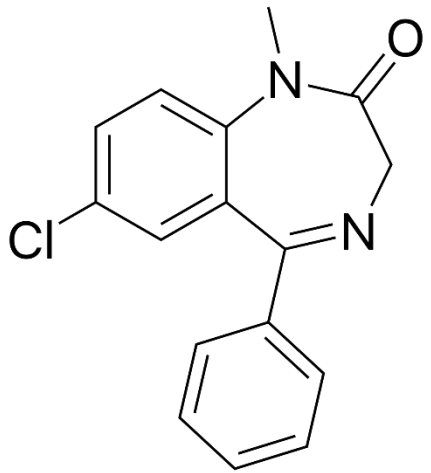
The Core Structure of Benzodiazepines



Left: The 1,4-benzodiazepine ring system.

Right: 5-phenyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one forms the skeleton of many of the most common benzodiazepine pharmaceuticals, such as diazepam (7-chloro-1-methyl substituted).

Diazepam (valium)



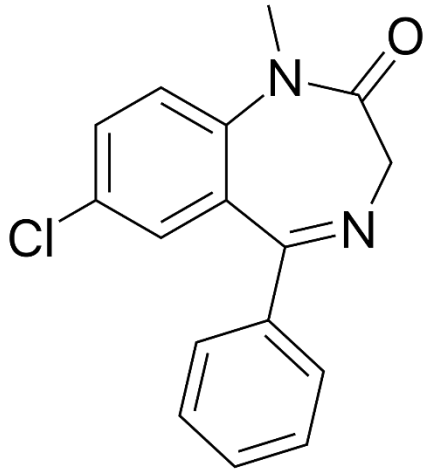
7- Chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one

What are the different types of benzodiazepines?

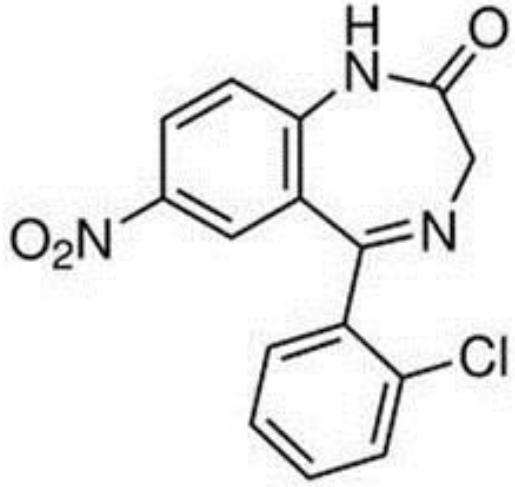
There are many different benzodiazepines and they all have differences in potency, speed at which they are metabolized, and "half-life" (time required for the quantity of the drug in the bloodstream to decrease to half its value), and therapeutic use.

- Different benzodiazepines vary mostly in their duration of action
- A substituent in the 7 position, such as a halogen or a nitro group, is required for sedative-hypnotic activity

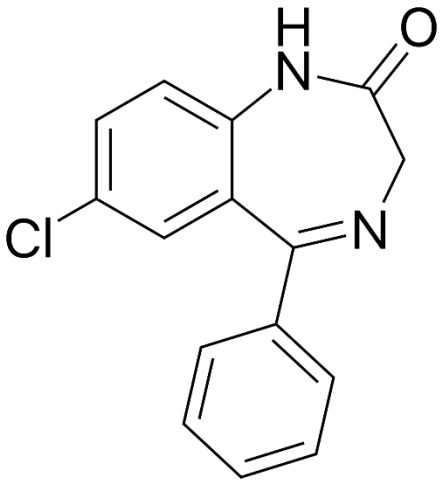
Biologically active compounds – 9. Lecture



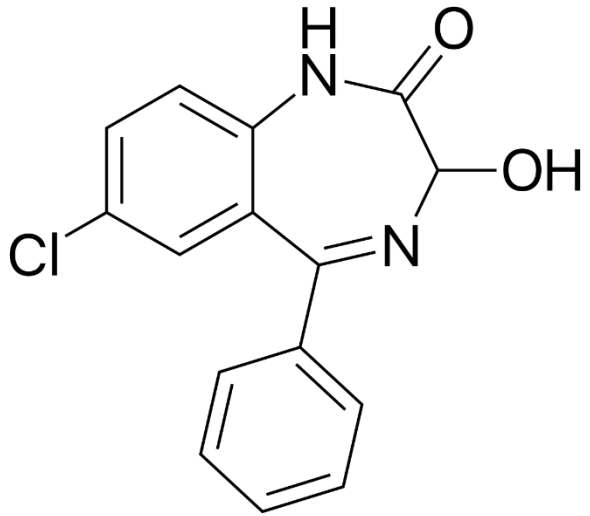
Valium - Diazepam



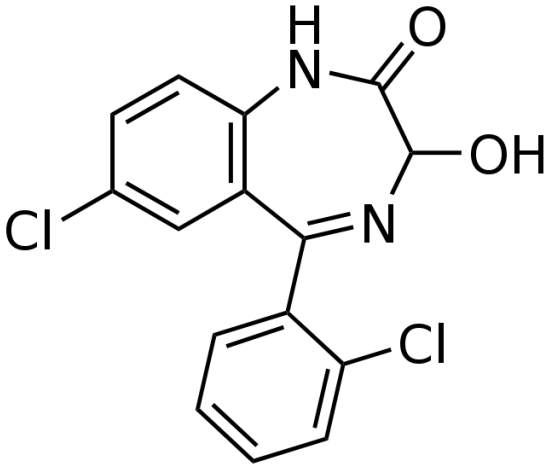
Clonazepam



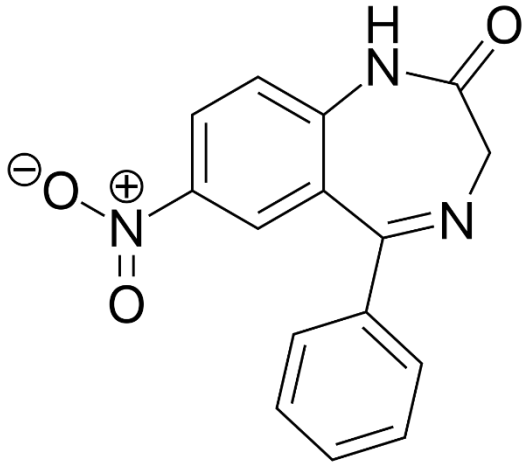
Nordazepam



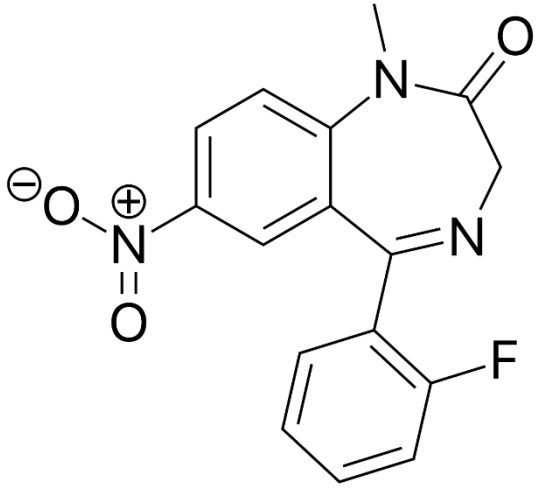
Oxazepam



Lorazepam



Nitrazepam



FuliNitrazepam

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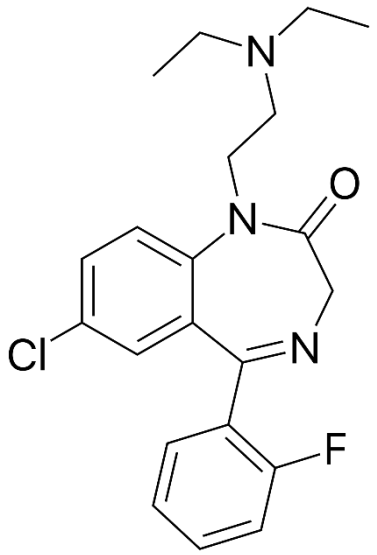
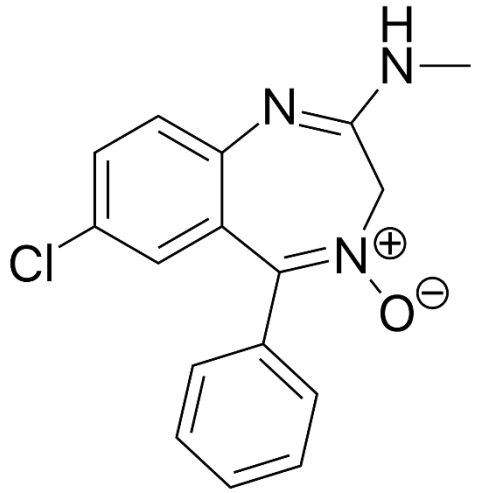
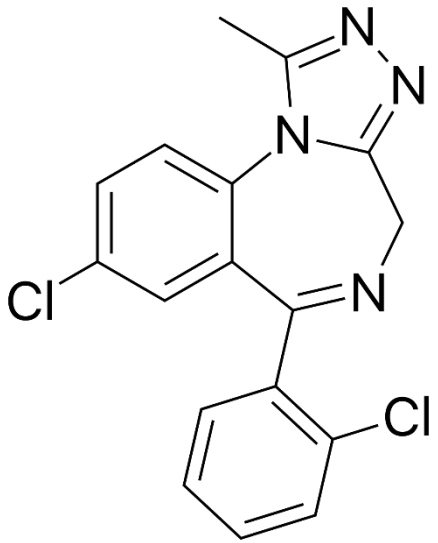
Biologically active compounds – 9. Lecture



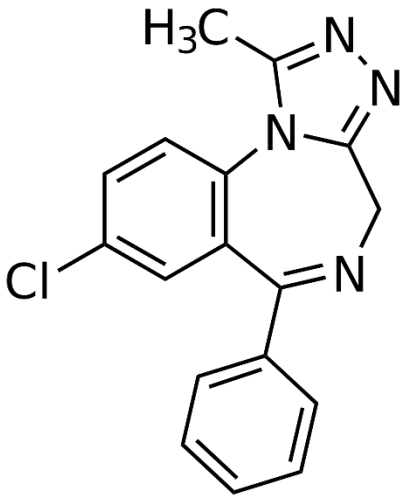
Flurazepam



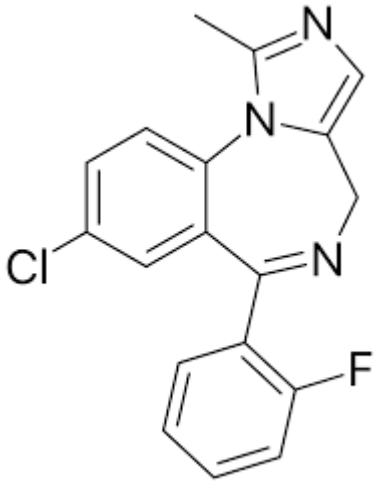
Chlordiazeperoxide



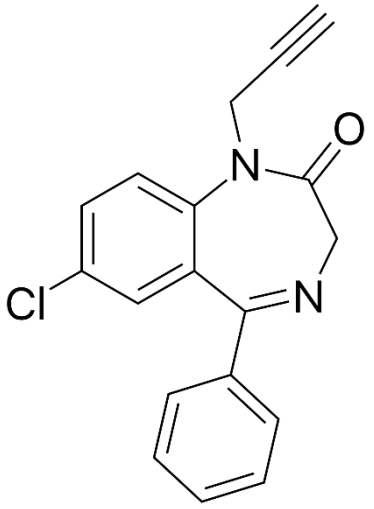
Triazolam



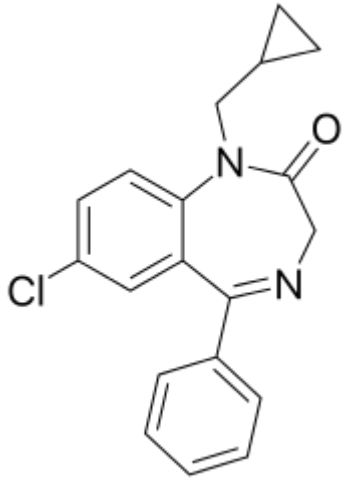
Oxazepam



Midazolam



Pinazepam



Prazepam

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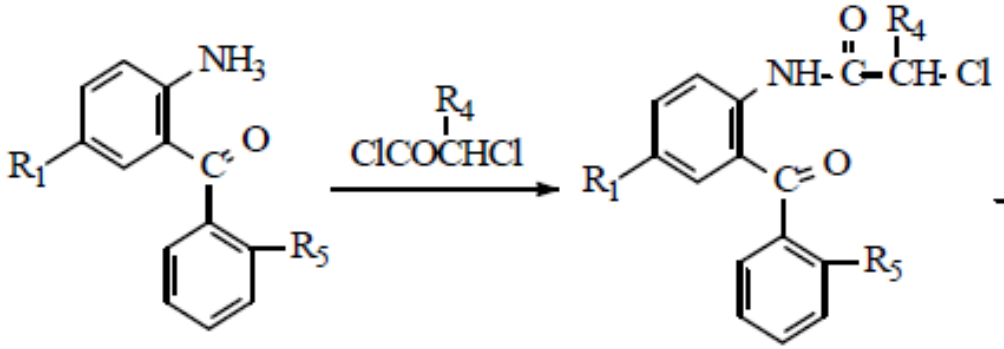
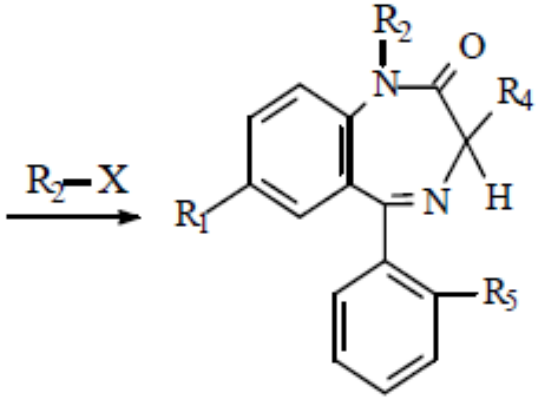
General Synthesis Method for Benzodiazepines

Reaction of 2-aminobenzophenone derivatives and chloroacetyl chloride, followed by reaction with ammonia gives **1,3-dihydro-2H-1,4-benzodiazepin-2-on derivatives.**

Alkylation will then gives **1-substituted-1,3-dihydro-2H-1,4-benzodiazepin-2-on derivatives**

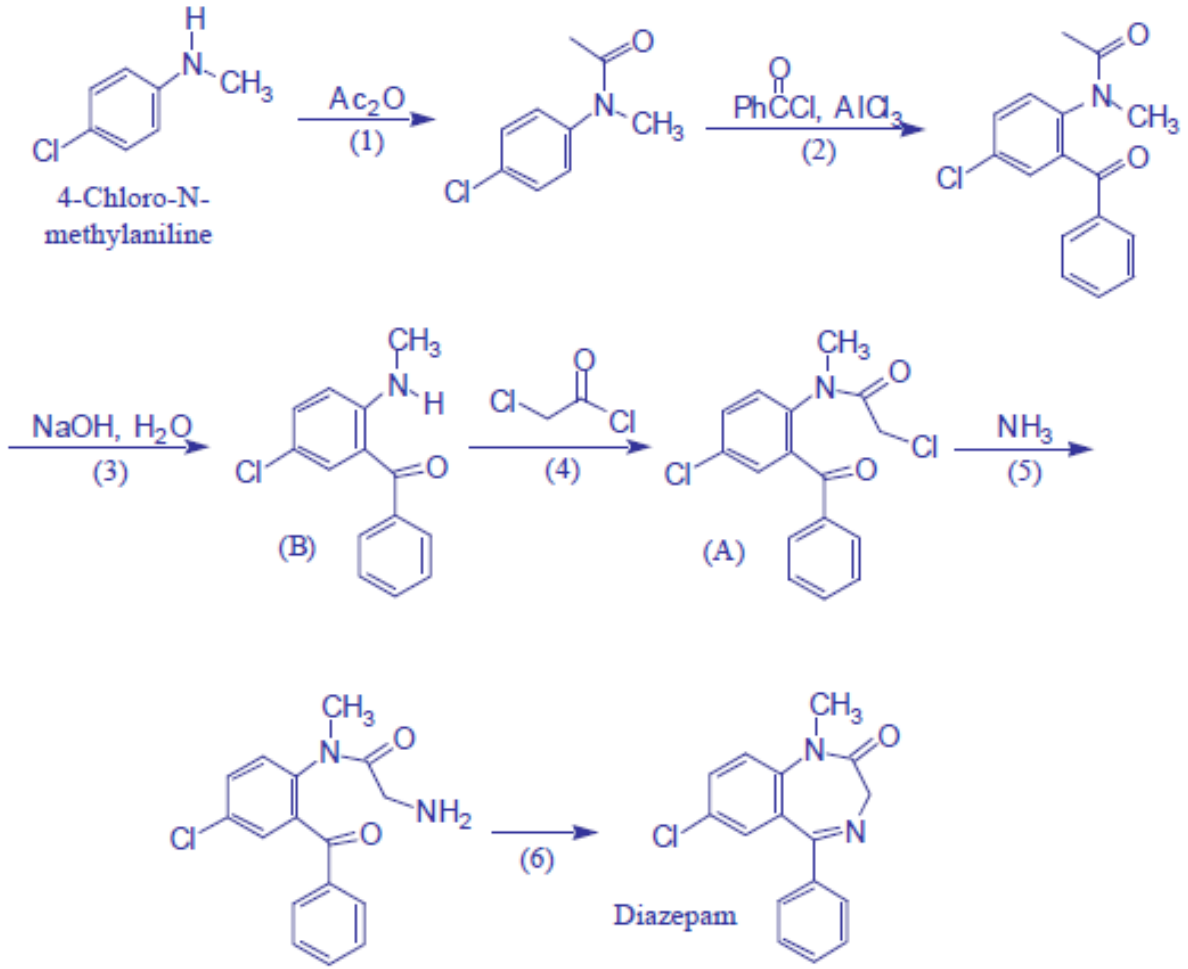


Clonazepam
Nitrazepam
Lorazepam
Nordazepam
Oxazepam

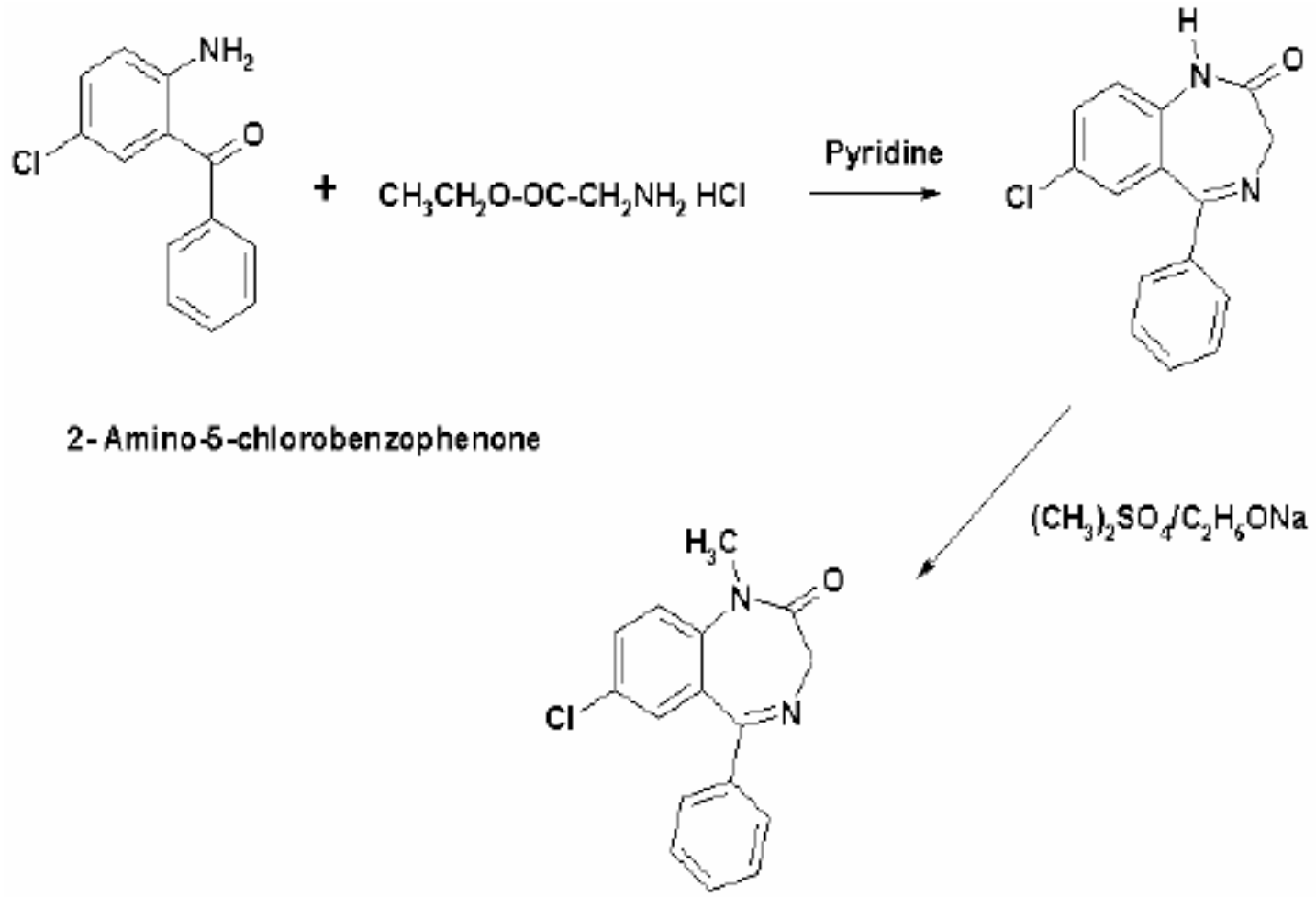


Diazepam
Flunitrazepam
Flurazepam
Pinazepam
Prazepam
Lormetazepam

Diazepam (Valium Synthesis)



Diazepam (Valium Synthesis)



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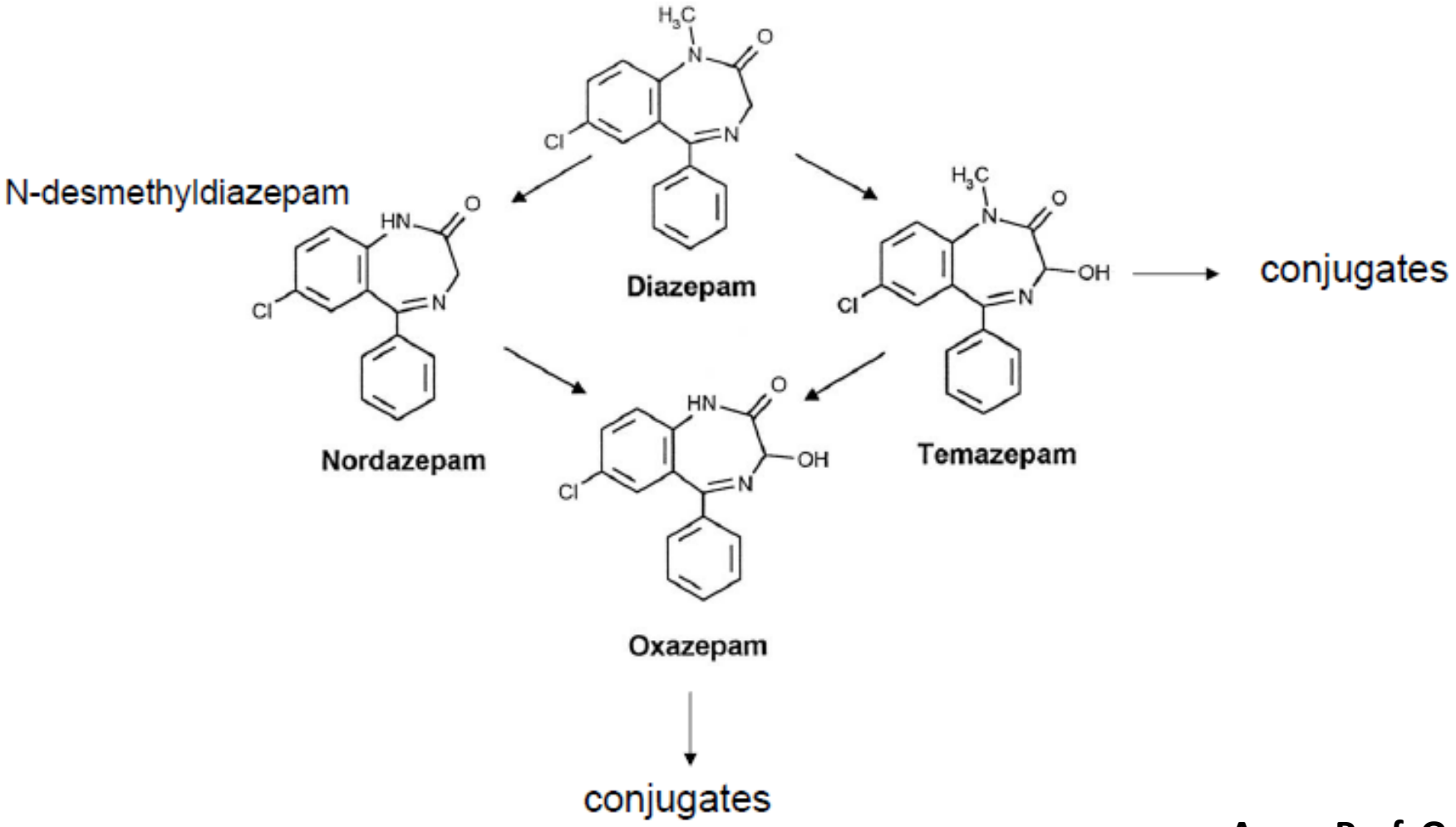
Metabolism of Diazepam



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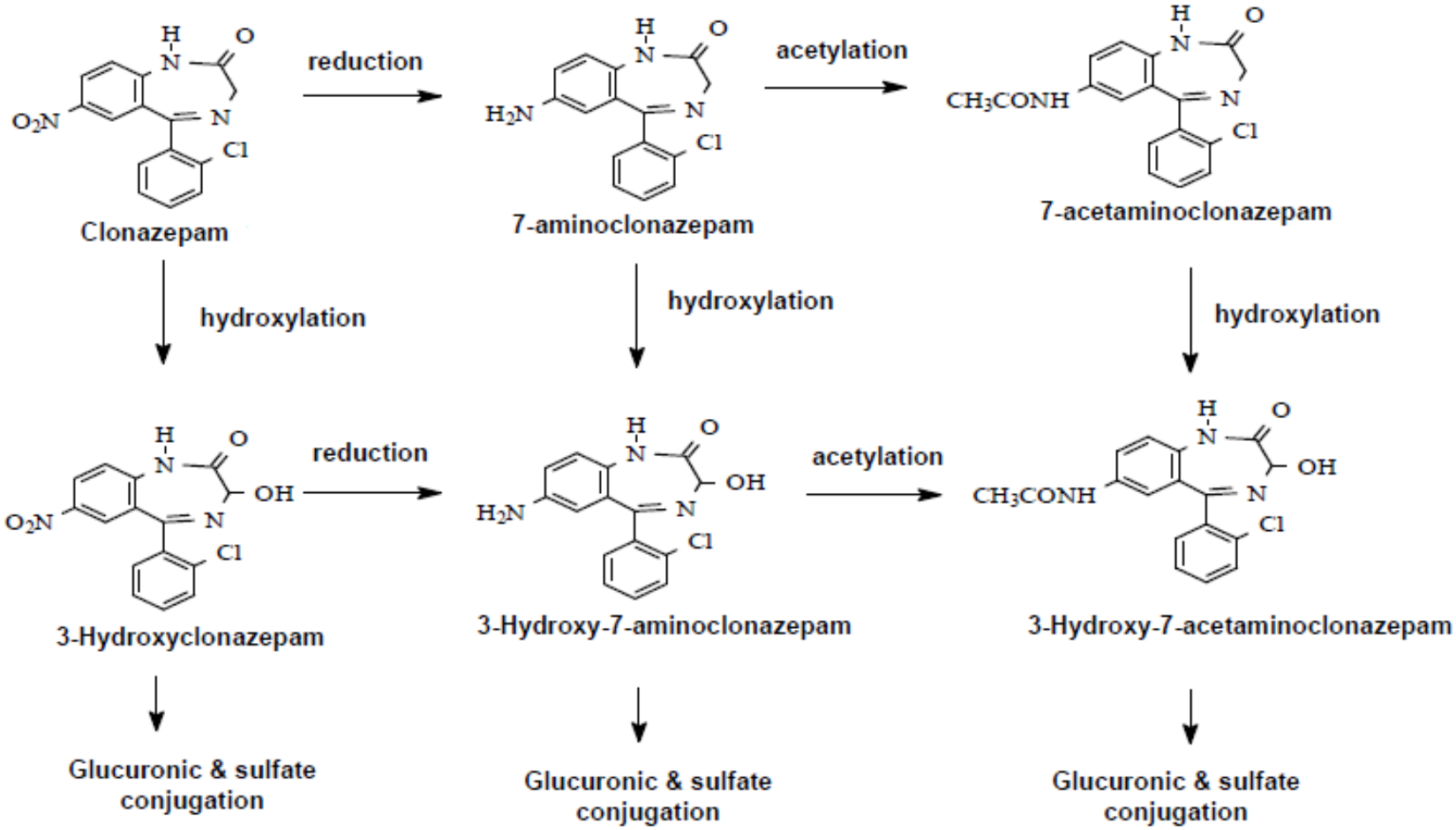
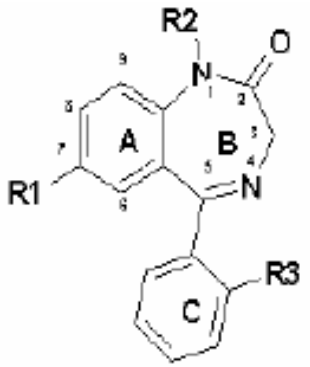
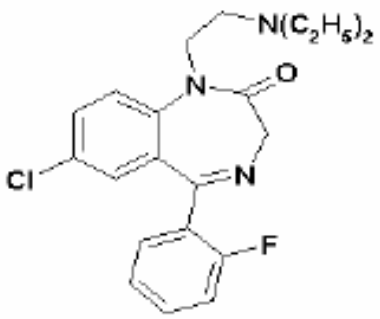
Metabolism of Clonazepam



Structure Activity Relationship of Benzodiazepines



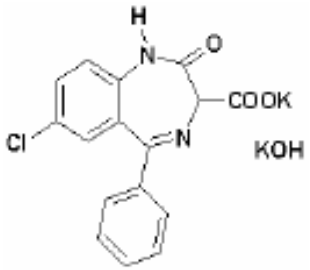


Flurazepam
(Dalmane)

- In ring A an electron withdrawing group such as Cl, Br, NO_2, or CN at position 7 increases activity
- A small group like methyl group attached to the nitrogen atom in position 1 in ring B has optimal activity. However, substituents at position 1 that are metabolically related are still clinically useful e.g. Flurazepam.
- Replacement of the carbonyl function with two hydrogens in position 2 gives medazepam, less effective than diazepam.

Structure Activity Relationship of Benzodiazepines

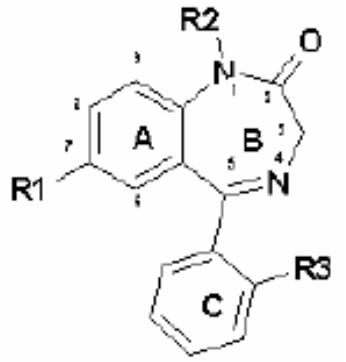
- Introduction of a carbonyl function in the 3 position increases the duration of action and also favours formation of water soluble salts.



Clorazepate
(Tranxene)

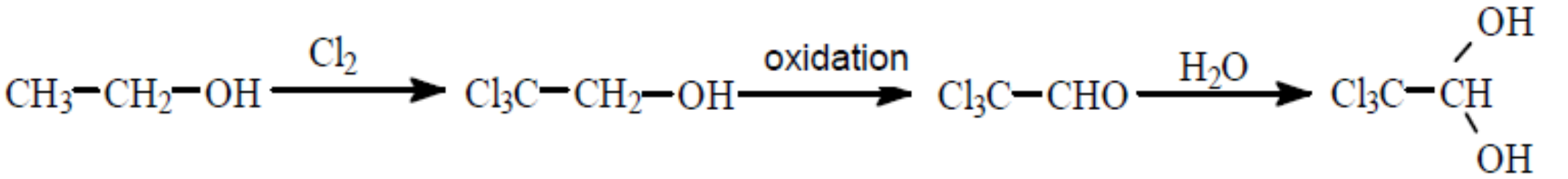
- A phenyl substituent at 5 position increases activity. If this phenyl group has electronegative substituents such as Cl or F at the ortho and di ortho positions activity is improved.

- Saturation of the 4,5- double bond reduces potency, as does a shift of the unsaturation into the 3,4-position.



Chloral Hydrate

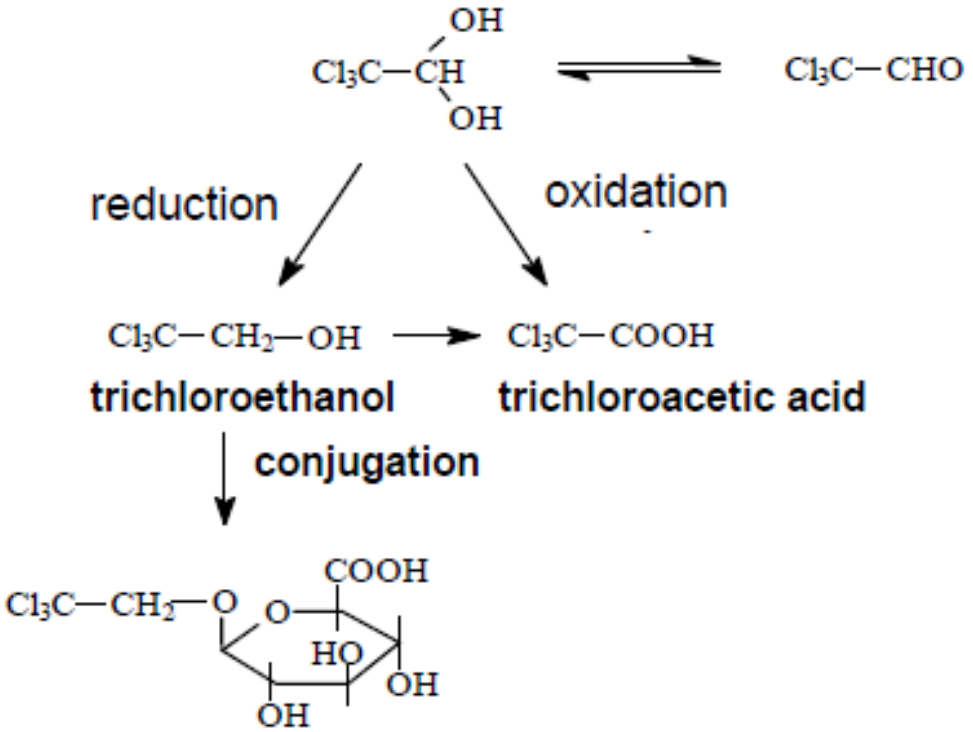
Chloral hydrate, (trichloroacetaldehyde monohydrate) a sedative, is used in the short-term treatment of insomnia and to relieve anxiety and induce sleep before surgery.



2,2,2-trichloroethane-1,1-diol

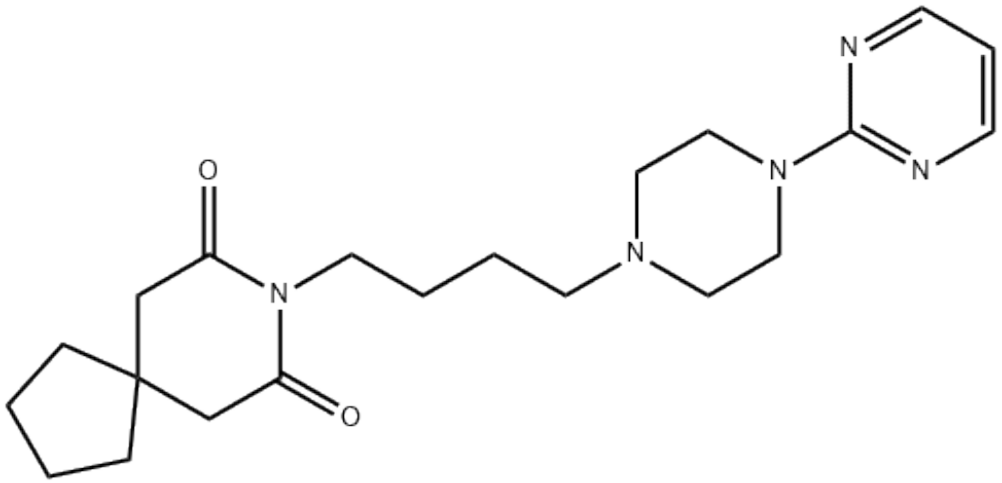
Chloral Hydrate

Metabolism: Chloral hydrate is converted to the active metabolite, trichloroethanol, in the body.



Buspirone

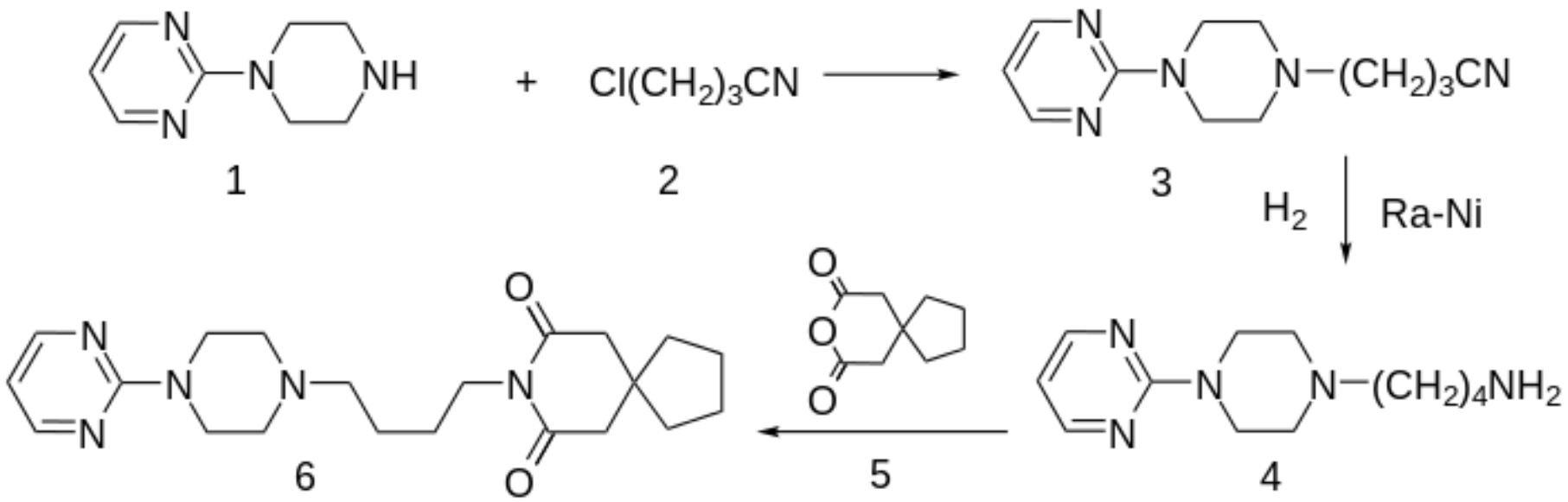
Buspirone is useful in the treatment of generalized anxiety disorder and has an efficacy comparable to that of the benzodiazepines.



8-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4.5]decane-7,9-dione

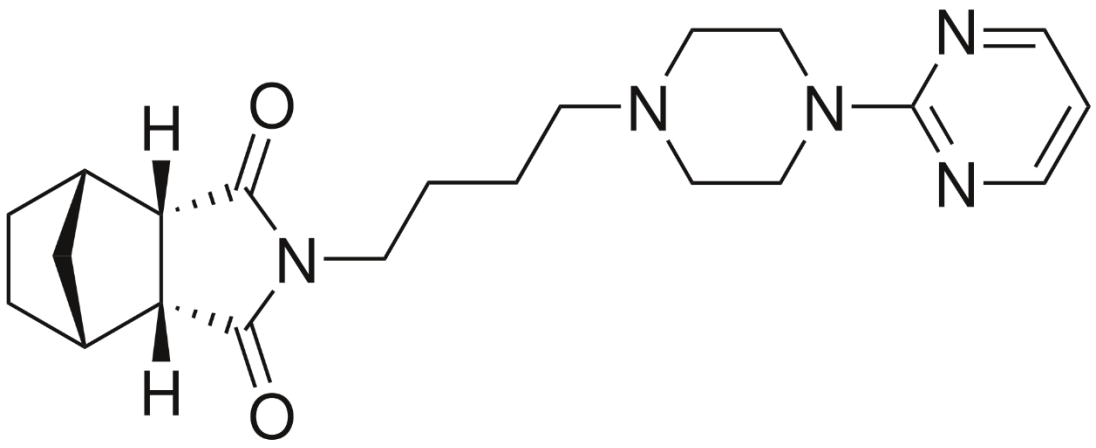
Buspirone - Synthesis

Synthesis: begins with N-alkylation 1-(2-pyrimidyl)piperazine with 4-chlorobutyronitrile followed by hydrogenation nitrile over Raney nickel catalyst. The primary amine product of the previous step is reacted with the spirocyclic acid anhydride in order to yield buspirone.

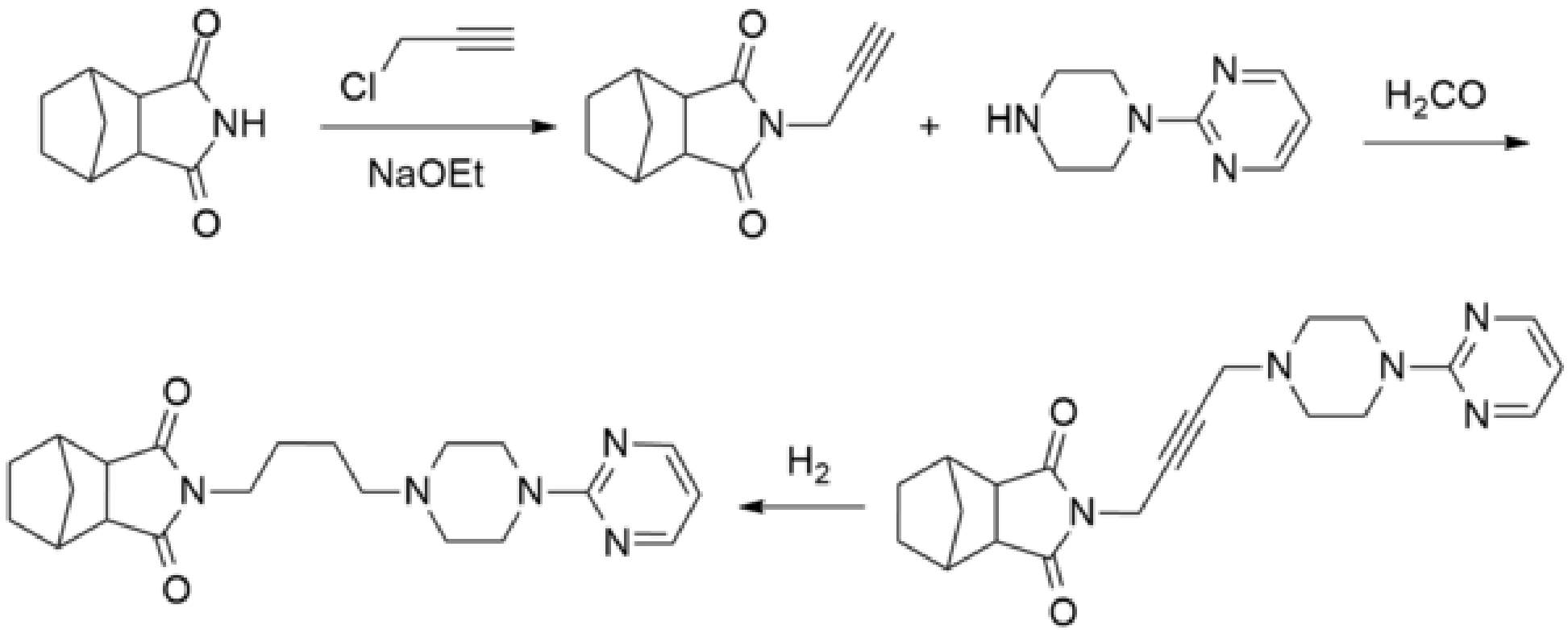


Tandospirone

Tandospirone (brand name Sediel) is an anxiolytic and antidepressant drug used in China and Japan, where it is marketed by Dainippon Sumitomo Pharma. It is a member of the azapirone class of drugs and is closely related to other azapirones like buspirone and gepirone.

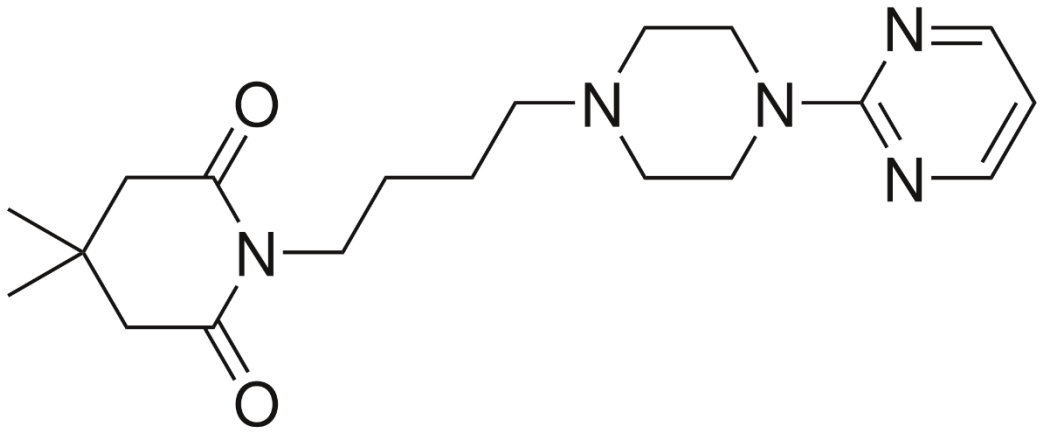


Tandospirone - Synthesis



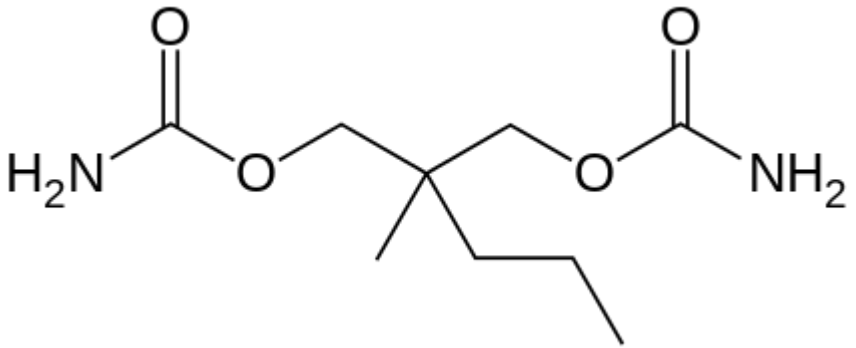
Gepirone

Gepirone is an antidepressant and anxiolytic drug of the azapirone group that was synthesized by Bristol-Myers Squibb in 1986 and has been under development for the treatment of depression but has yet to be marketed.



Meprobamate

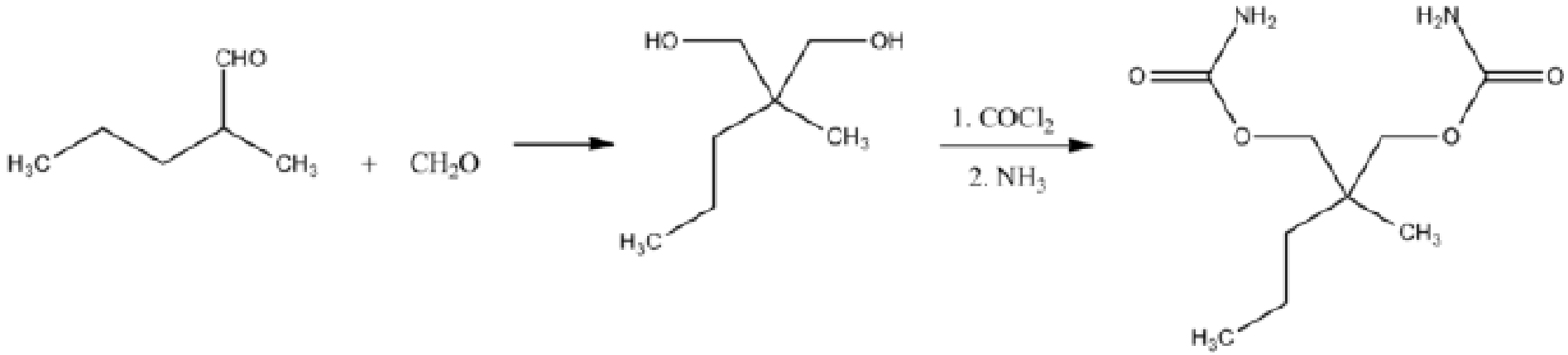
Meprobamate (**Miltown**, **Equanil**, **Meprospan**) is a carbamate derivative which is used as an sedative drug.



2-methyl-2-propyl-1,3-propandiol dicarbamate

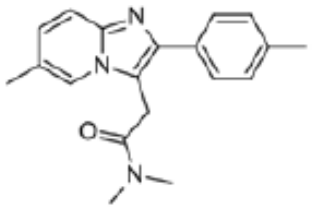
Meprobamate

Synthesis: by the reaction of 2-methylvaleraldehyde with two molecules of formaldehyde and the subsequent transformation of the resulting 2-methyl-2-propylpropan-1,3-diol into the dicarbamate via successive reactions with phosgene and ammonia

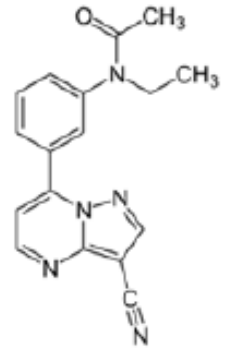


Other Nonbenzodiazepine Sedatives

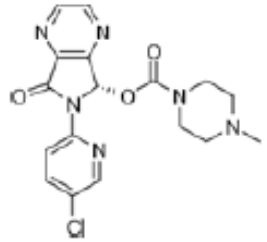
The hypnotic **zolpidem** (Ambien, Stilnox) is not a benzodiazepine in structure, but it acts on a subset of the benzodiazepine receptor family



Zaleplon (Sonata, Starnoc and Andante) is very similar to zolpidem in its hypnotic actions, but it causes fewer residual effects functions compared to zolpidem or the benzodiazepines.



Eszopiclone (Lunesta) is an oral nonbenzodiazepine hypnotic and is also used for treating insomnia.



Ethanol has anxiolytic and sedative effects, but its toxic potential outweighs its benefits.

CH_3CH_2OH