CNS Depressants

ʌey r¯ ʌ drugs ʌat depress ʌ CNS function & ʌey includes:

1- G.A.(general anesthetics)

2- S/H (Sedative –Hypnotics)

3-Anxiolytics

4-Anticonvulsants &

5-Antipsychotics

***** the most S/H ,also possess anxiolytic and anticonvulsant properties & at higher conc. Are G.A.**

Sedative – Hypnotic & Anxiolytic Agents:

Drugs Λat have depressant acΛ on Λ cerebrospinal axis.

[1]- S/H agents:

Mode of acΛ:

1- (+) modulation at $GABA_A$-Rec.

2-act on Glutamic acid Rec.s subtype as antagonist.(also non-selective)

3-some of Λem act on adenosine Rec.s subtype-antagonist.

4-some of Λem act by inhibiΛ of entry of Ca++ into presynaptic neurons,w- inhibit release of neurotransmitter

Anxiolytics:•

Mode of acΛ:

1- act on selective $GABA_A$ Rec.s to mimic GABA activity.

2- agonist at 5HT1A Recs.

3- Antagonism of DA Recs.

4- Central adrenergic antagonism.

5- Central antihistaminic H1 activity.

6- Antagonism of serotonin at central 5HT2 Recs.

7- Act on central cholecytokinin-B (CCK-B) Recs.

*** Ideal S/H, Λose Λat effect on psychotic center w-out acΛ w-oΛer centers, Barbiturates(since 1903) will fit Λ ideal requirement but now adays r- replaced by Benzodiazepine b- Λ latter r- safer.**

***Chemical classification**

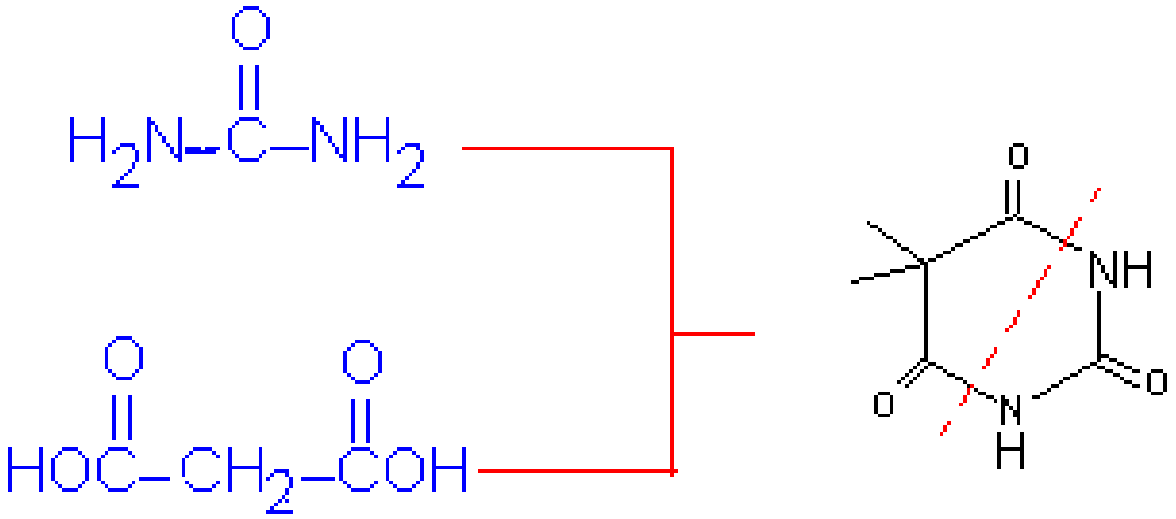
1- Barbiturate derivatives (ideal)

2- Non barbiturates derivatives.

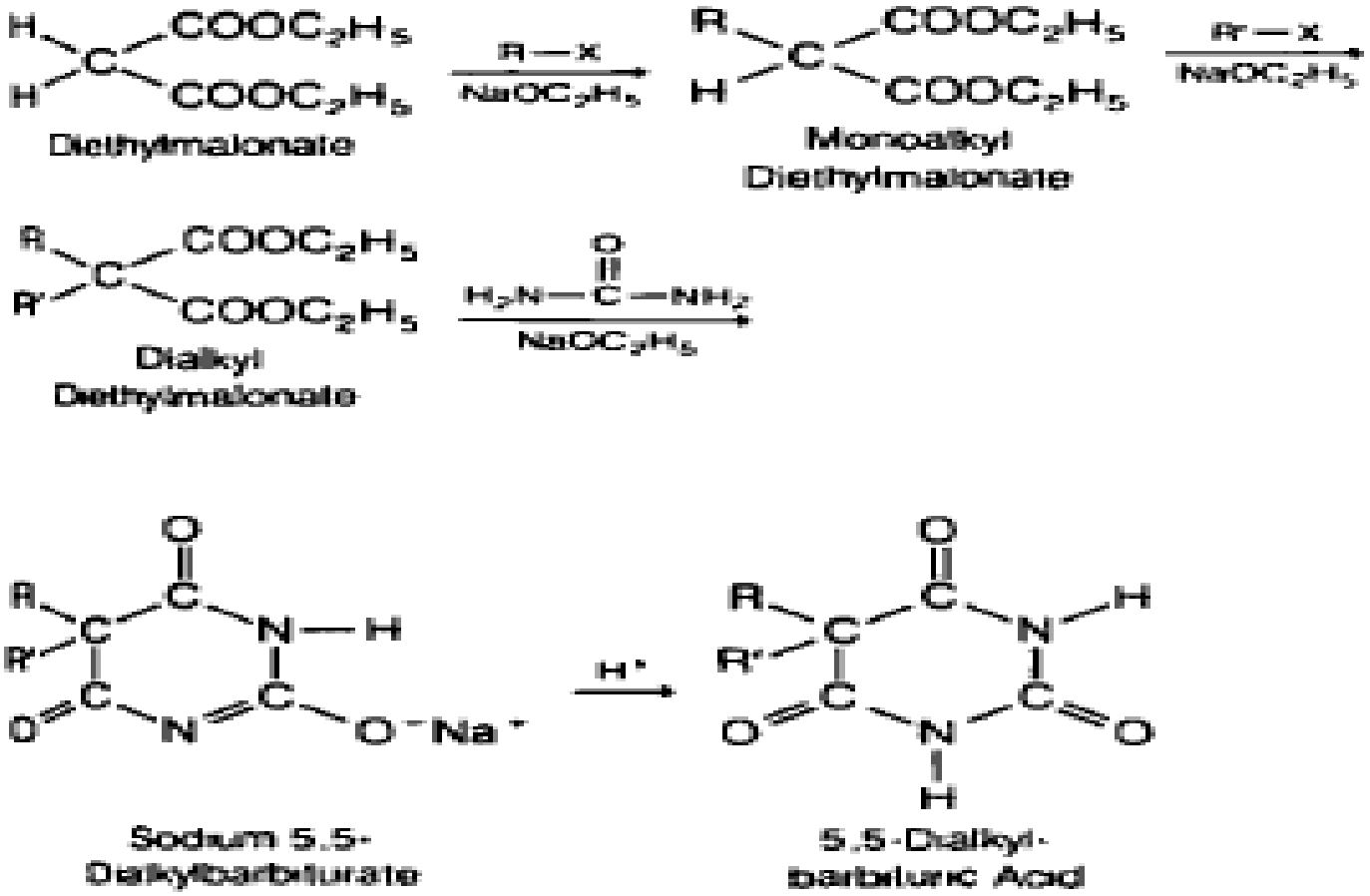
Barbiturates:

**** Λ nucleus of structure Barbituric acid.**

Barbituric acid contain 2 parts: urea & malonic acid.



General preparation method:



Note:

- Na salt of barbiturates r-:

  ** readily prepared & r- water soluble.

  ** their aq. Solution generate an alkaline pH.

  **wn mixed w- acidic pH in solution ,w- results in formation a ppt. of free water-insoluble disubstituted barbituric acid, to prevent this disadvantage its mixed w- alkaline buffer as $NaHCO_3$

.

* undergo hydrolysis or decomposition by base-catalyzed hydrolysis, generating ring –opened salts of carboxylic acid .

SAR:

**- barbituric acid not have any activity on Λ CNS ,b-:

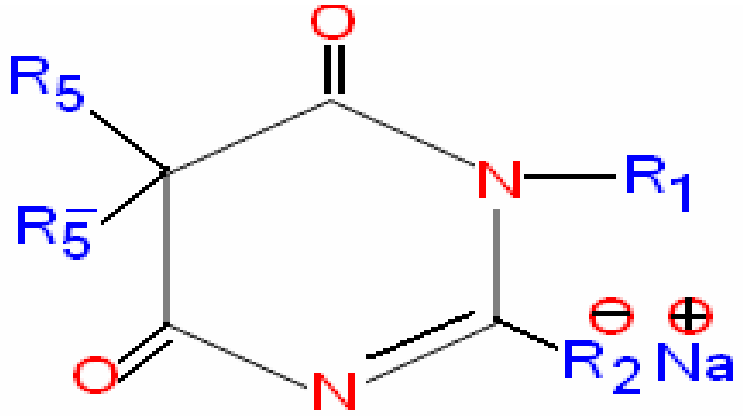
a- It is an acid (pKa=4.0) and readily ionized inside body(at physiological pH=7.4).

(1)-Both H atoms in position 5 of Barbituric acid should be replaced for:

1- max. activity

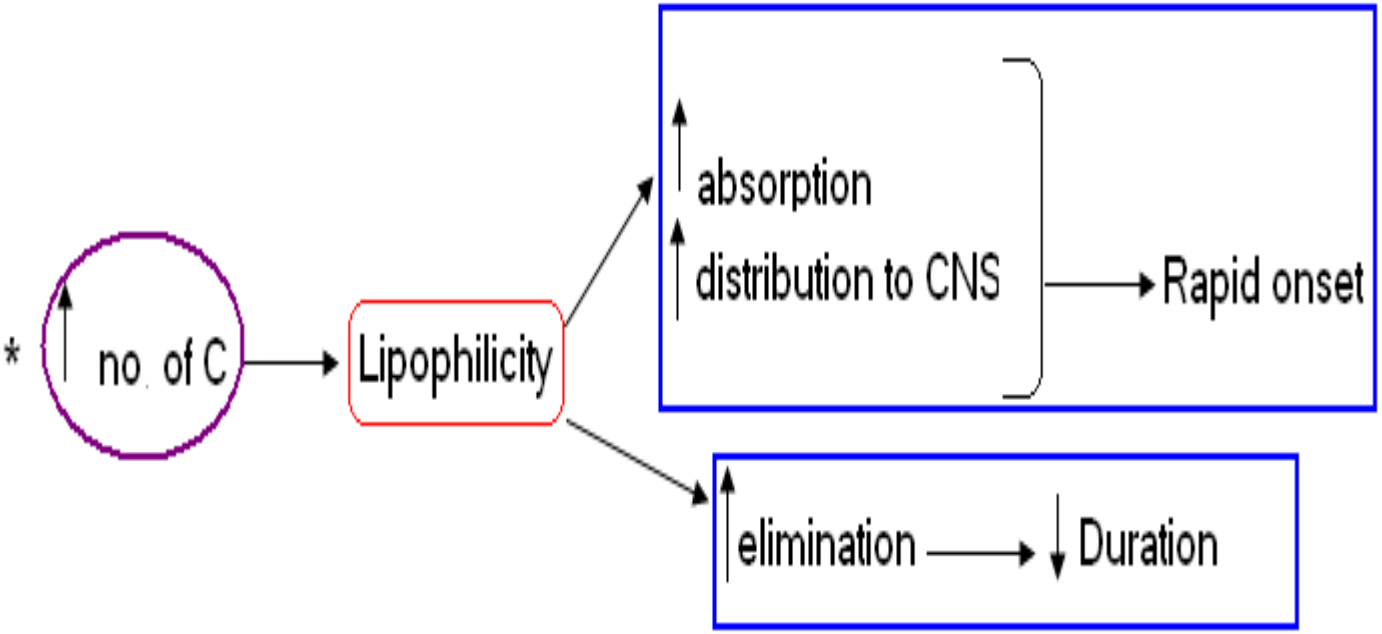
2- to decrease susceptibility to rapid metabolic attack.

Basic strucutr:



*** P.C. (.) lipid & aq. Phases (octanol/water) is close to 100(log100=2).**

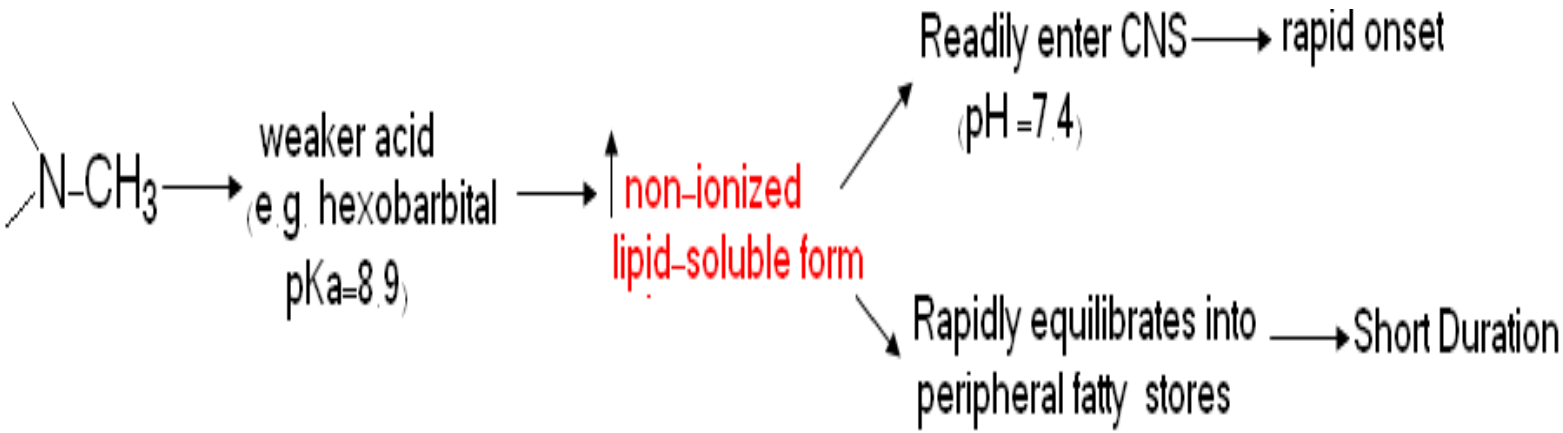
2)-increasing the length of chain of R grp. at C5 increase ʌ potency until 5 or 6 C atoms, after ʌat it may cause convulsions (increase ʌ lipophilicity). ,(effect on duration of action)



3)-Branched,cyclic or unsaturated chain at C5 will produce shorter duration of action

∧an saturated chain w= have ∧ same no. of C-atoms.

4)-Cpds having an alkyl grp at 1 or 3 position have shorter onset & duration of action.



5)Replacement of (O) by (S) on ʌ C2 leads to rapid onset & short duraʌ of acʌ due to increase in lipophilicity character causing:

1- more nonionized and rapid movement into & out of Λ CNS.

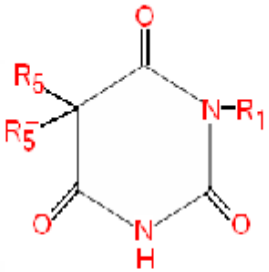
2-Ease of metabolic attack.

$$* \text{ Duration} \propto \frac{1}{\text{Lipophilicity}}$$

Barb.	no. of C in 5-position (R5+R5)
LAB	4 (ethyl+ethyl) OR (ethyl+phenyl)
IAB	5-7
SAB	7-9

* Wn ∧ lipophilicity decrease ∧ enterence to ∧ site of metabolism also decrease, so ∧ onset is slow and duration is long.

General structure of Barbiturates



	R_5	R_5'	R_1	Pharma. activity
A– Long duration of action (more than 6 hrs)				
Generic name 1– Barbital (Veronal) Chemical name 5,5–diethyl B.A.	C_2H_5	C_2H_5	H	S/H
2– Phenobarbital (Luminal) 2–ethyl–5–phenyl B.A.	C_2H_5	Ph	H	– S/H –Anticonvulsant, espicially in generalized tonic–chlonic & partial seizures.
3– Mephobarbital (Metharbital) 1–methyl–5–ethyl–5–phenyl B.A.	C_2H_5	Ph	CH_3	Anticonvulsant
B– Intermediate duration of action (3–6 hrs)				
1– Amobarbital (Amytal) 5–ethyl–5–isopentyl B.A.	C_2H_5	$(CH_3)_2CHCH_2CH_2$	H	S/H
2– Butabarbital Na (Butisol Na) Sodium 5–sec–butyl–5–ethyl barbiturate	C_2H_5	$CH_3CH_2CH(CH_3)$	H	S/H
C– Short duration of action (less than 3 hrs)				
1– Pentobarbital Na (Nembutal Na) Na 5–ethyl–5–(1–methyl butyl) Barbiturate	C_2H_5	$CH_3CH_2CH_2CH(CH_3)$	H	
2– Secobarbital (Seconal) 5–allyl–5–(1–methyl butyl) B.A.	$CH_2=CHCH_2-$	$CH_3CH_2CH_2CH(CH_3)$	H	

in general cpds. w substituents in 5–position promoting move rapid metabolism (lipid/H_2O P.C.)

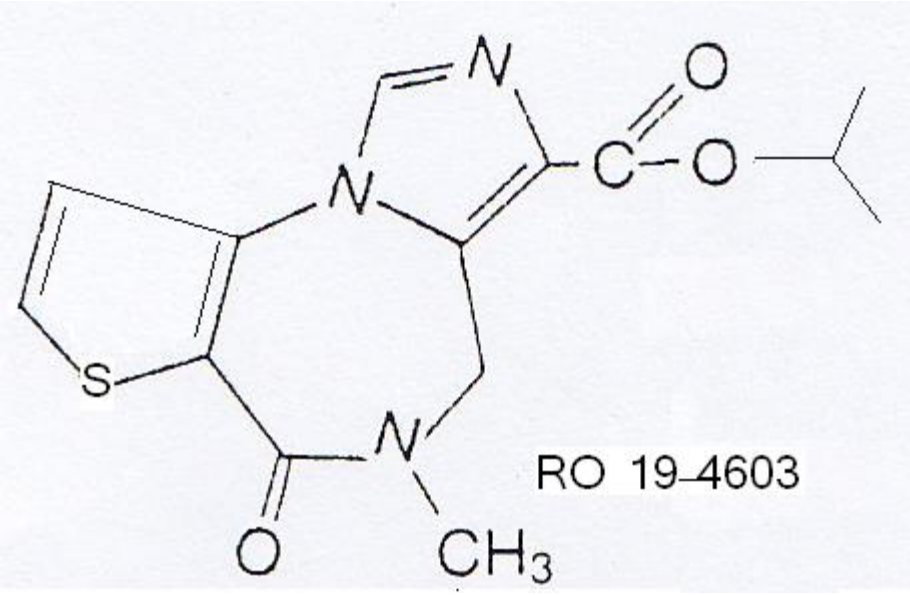
Benzodiazepines and related cpds:

BDZs & BDZ like drugs bind to BDZ recognition site, one of several allosteric sites ∧at modulate ∧ effect of GABA binding to $GABA_A$ Rec_s. ∧ $GABA_A$ Rec_s is a ligand-gated Cl^- ion channel.

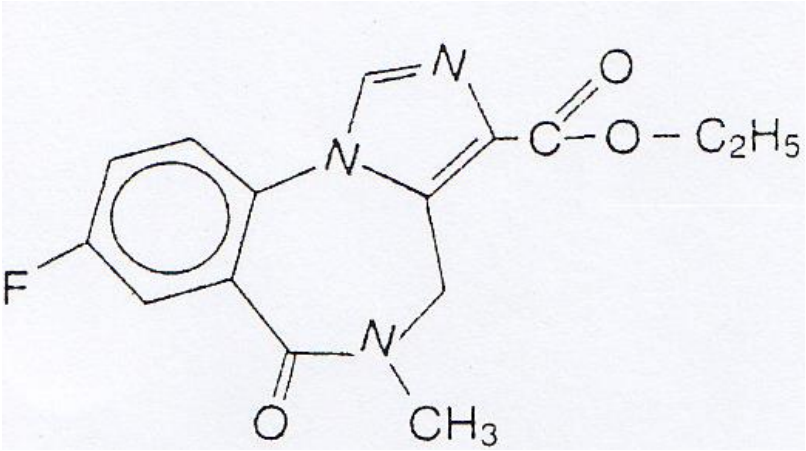
** most classical 1,4- BDZs r- (+ve) • modulators. r- also known as agonists & enhance Λ effect of GABA binding to $GABA_A$ to ↑ Cl^- flux into Λ neuron.

**Most β-carbolines & certain • imidazolodiazepines, for e.g. RO 19-4603 w¯(-ve) modulator,known (Inverse Agonist)

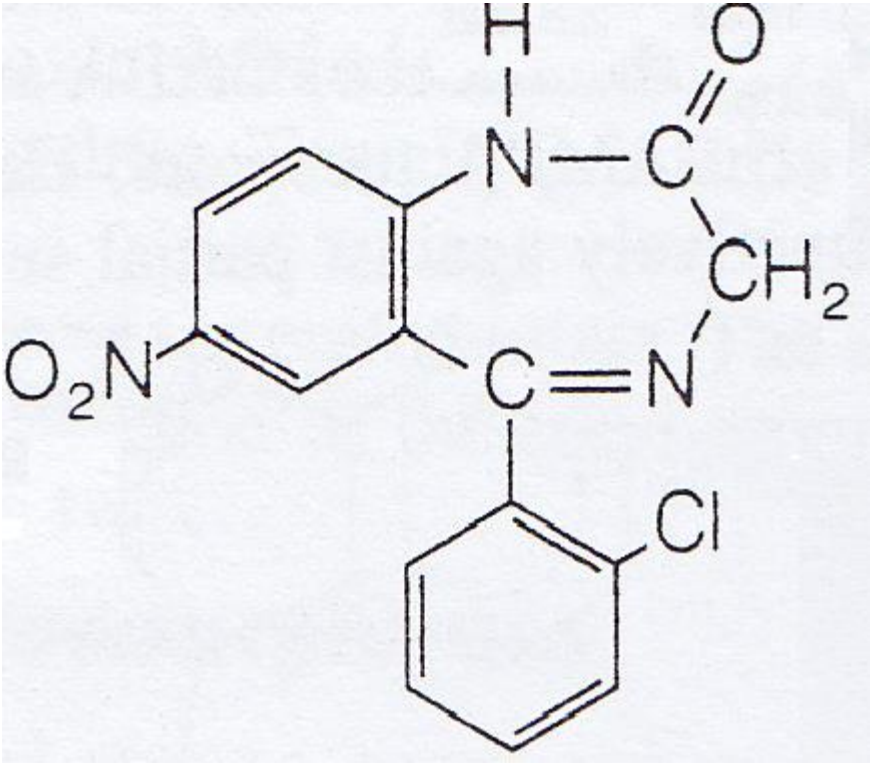
Λey diminish Λ (+ ve) effect of GABA on Cl¯ flux.



***(Antagonists),zero modulator ,w- block • Λ effect of eiΛer (+ve) modulator (agonist) or (-ve) modulators (inverse agonist) by occupy Λ recognition site & having no effect Λemeselve on Cl^- ion flux, for e.g. Flumazenil,w- is used to counteract Λ Sedative effect.

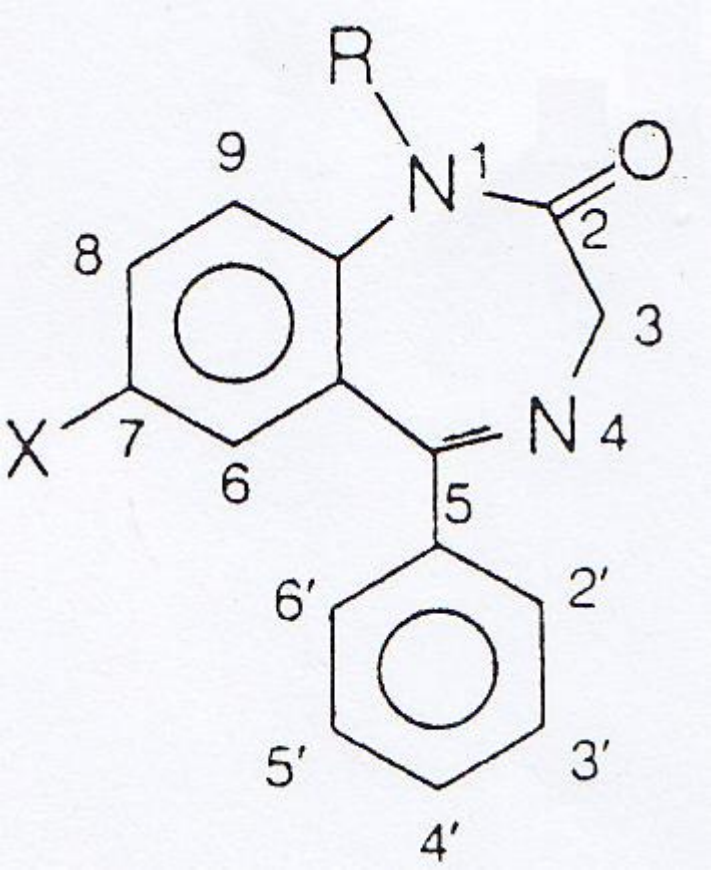


*** Clonazepam is consider as a partial agonist w- decrease Sedative acΛ relative to full agonist.



SAR of BDZs

G. str. is:



1- position7:

Electronegative substitue

7 is required for activity,Λ more electronegative it is,Λ higher activity.

2-position 6,8 & 9 should not be substituted.

3- position 5: ph. at position 5, promotes activity, if Λis ph. grp., is *o* (2¯) or diortho(2¯,6¯) substituted w¯e-attracting substituents, activity is ↑ ,on oΛer hand, *p*-substituΛ ↓activity greatly.

4- saturation 4-5 double bond or a shift of it to Λ 3-4 position ↓ activity.

5- position 3 : alkyl substitution at position 3 ↓ activity,substitution w- OH does not.

6- position 3 : Λ p- or absence OH at 3-position,is important pharmacokinetically (cpd. W-out OH r- nonpolar have long half-lives($t_{1/2}$) & undergo hepatic oxidation.

Cpd. w- OH r- much more polar & readily converted to the excreted glucuronid.

7- position 1 &2 : 2-carbonyl func^ is optimal for activity, as is ^ N-atom at position 1, N-substituent should be small.(Me, Ethyl,isopropyl)

8- e-attracting grp. At position 7 is not required for activity in most ^ese cpd.

Metabolism of BDZs

1- Fused Ring: cpd.r- metabolized mainly:

a- by hydroxylaΛ of Λ methyl substituent on Λ triazol or imidazol ring. resulting OH cpd. Is active but is quickly conjugated.

b- 3-hydroxylation of BDZ ring.

H.W.?

Miscellaneous Ss/Hs:

(Non-barbiturates,Non BDZ S/H)

* A wide range of chemical structures e.g. imides,amides,alcohols can produce S/H effect resembling that produced by the barbiturates.

the cpds.have generally similar structural cc-& chemical properties:

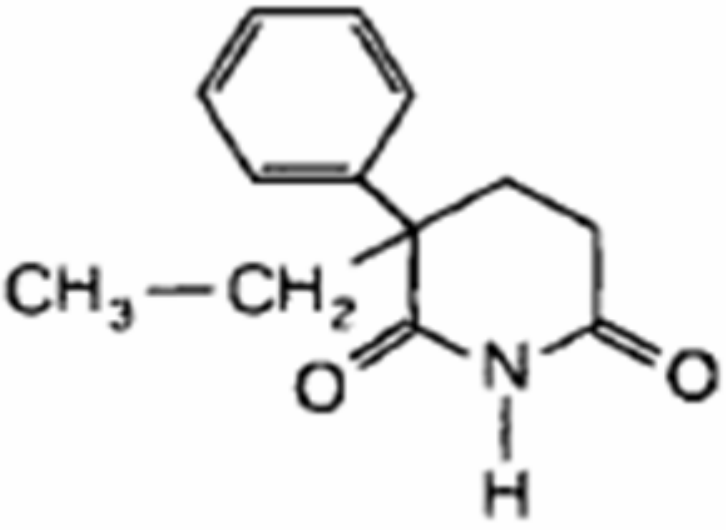
-**Amides & Imides

*_ **Glutethimide**

(Doriden) (an imide)

**2-ethyl-2-phenyl-glutarimide.

**have many structural relationships w- Λ barbiturates & resembles Λem in many respects biologica¨



**it is considered as a monouride but it resembles (or belong to) phenobarbital .

* it is an effective S/H, metabolism is extensive & the drug is enzyme inducer.

Alcohols & their Carbamate derivatives: (S/H)

* very simple alcohol ,Ethanol has a long history of use as a S/H .

** disadvantages of alcohols:

_providing a feeling of excitation w produces ʌat of depression.

_ many problems associated w- chronic used of alcohol (chronic alcoholism).

_Ability to exert toxic effects on many organ systems (ex: liver circhosis)

Mode of action:

* act mainly on glutamic acid Rec.s(antagonist)

SAR of Alcohols :

1- Λ Hypnotic activity increase w¯ increase of M.Wt. until ∧ no. of C atoms =8 ,due to increase in ∧ lipid solubility.

2- Branching of alkyl chain decrease ∧ lipophilicity & increase ∧ resistance to ∧ metabolism so ∧ onset of ac∧ increase (increase depressant activity) & ∧ dura∧ increase according to ∧ following order:

3º>2 º >1º .

3- Replacement of a H-atom in ʌ Alkyl grp. by a halogen has ʌ same effect of increasing ʌ alkyl chain & result in increased potency.

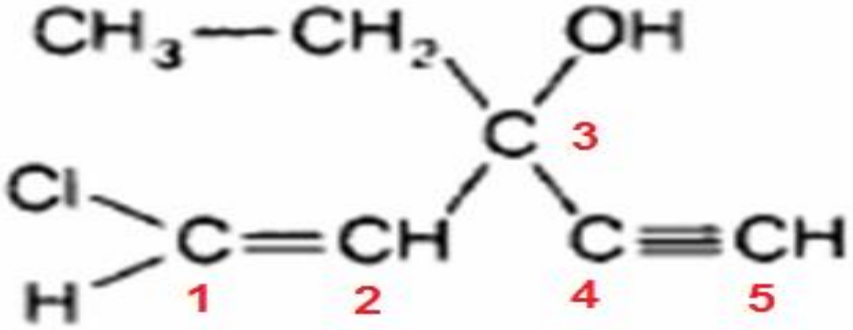
4- carbamylation of alcohol generally increase depressant potency.

** Ethchlorvynol.

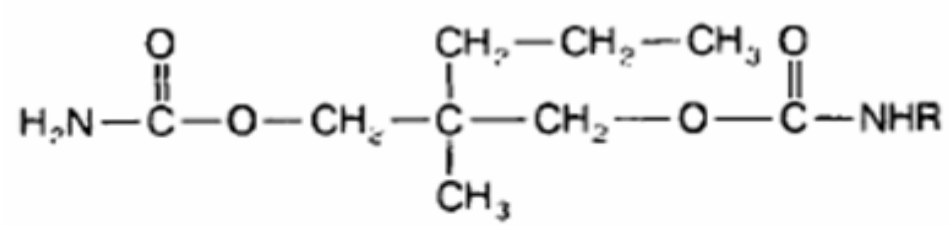
I –chloro-3-ethyl-1- penten-4-yn-3-ol (Placidyl).

** is a S/H, w¯ a rapid Onset & short duration of action.

Metabolism, probably involving the hydroxyl grp.



Meprobamate.



Meprobamate	R= H
Carisoprodol	R= $CH(CH_3)_2$

(2-methyl-2-propyl-1,3-propanediol dicarbamate.

Uses:

1- simple insomnia(major use)

2- Anxiety & Tension.

3-Epilepsy.

** It is also a S/H agent.

** also a centrally acting skeletal muscle Relaxa.]

Carisoprodol.

N-isopropyl-2- methyl-2 -propyl- 1,3-propanediol dicarbamate.

Uses:

* acute skeletomuscular conditions w̲ cc̄ by pain, stiffness, and spasm.

S/E: drowsiness

Chlorphenesin Carbamate:

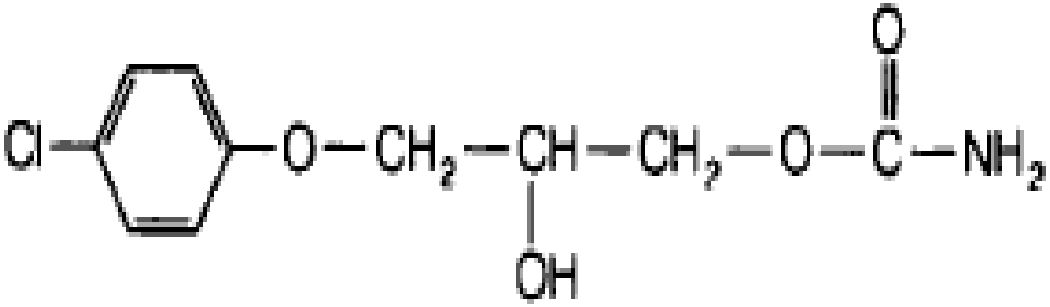
[3-(p-chlorophenoxy)-1,2-propanediol-1-carbamate]

** is ʌ *p*.chloro substituted and 1-carbamate deriv. of ʌ lead cpd in ʌ development of ʌis grp of agents, mephenesin.

Mephenesin is weakly active and short-lived because of facile metabolism of the primary hydroxyl grp.

- carbamate increase the activity

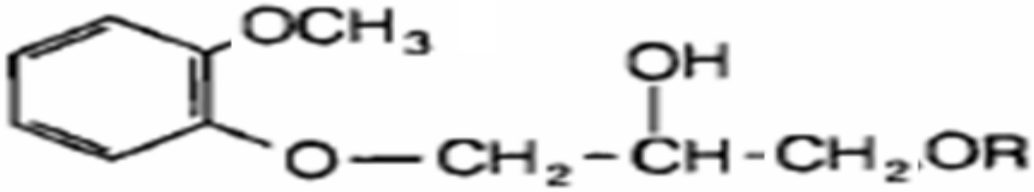
- p-Cl P.C.



Methocarbamol :

(3-*o*-methoxyphenoxy)-1,2-propanediol-1-carbamate (Robaxin).

* more sustained in effect ʌan mephenesin. Likely sites for metabolic attack include ʌ 2ºry OH grp and ʌ two ring positions opposite ʌ ether functions.ʌ dihydric parent cpd, guaifenesin. is used as an expectorant.



Guaifenesin R = H

Methocarbamol R = —C(=O)—NH2