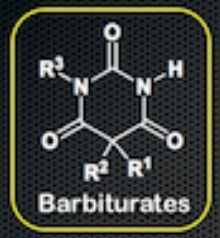
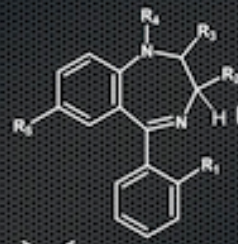
Anxiolytics, Hypnotics & Sedative Part I

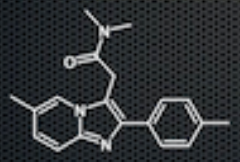
FAR 344/4
Dr. Aisyah Saad
Abdul Rahim

Classes of drugs for anxiolytics & sedative hypnotics

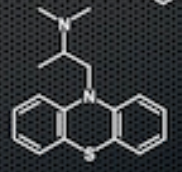




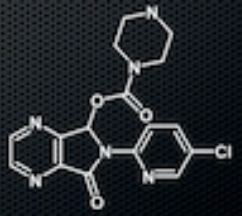
Benzodiazepines (BZDs)



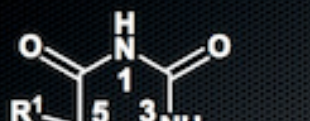
Zolpidem

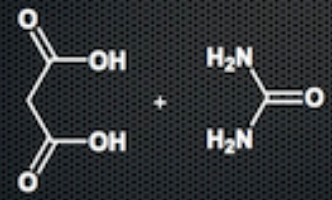


Promethazine



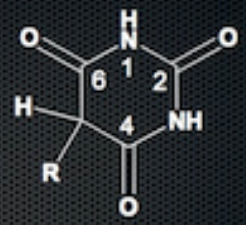
Zopiclone





Barbiturates

Stability of Barbiturates



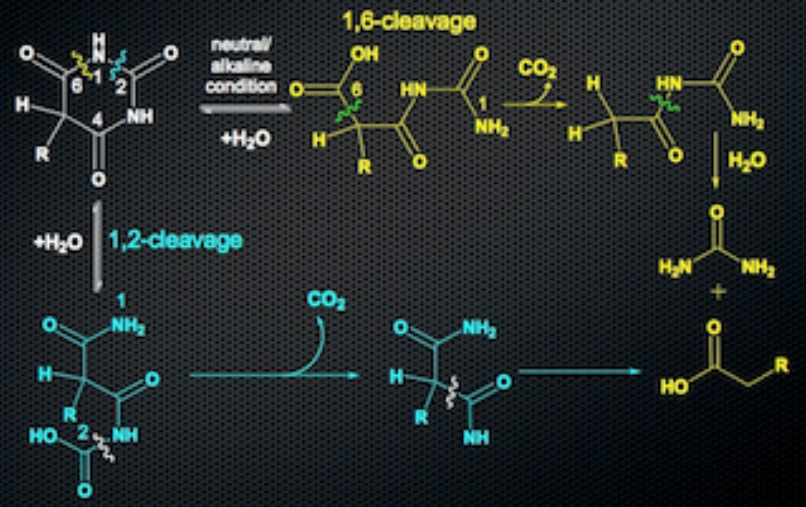
Characteristically prone to hydrolysis esp. in aq. alkaline medium

Pyrimidine ring splits off either at 1,6 or 1,2; though 1,6-cleavage is preferred

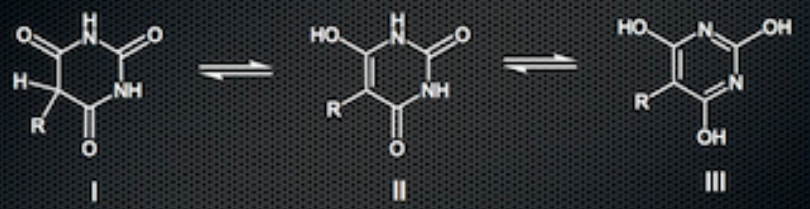
1,2-cleavage is favoured if:
the N at position 1 is methylated, or
C-5 substituents are bulky or unsaturated e.g. a phenyl ring

N-methylated and thiobarbituric acid cleave off easily than non-methylated/sulfur-free substituents

Ring opening of Barbiturates in Neutral/Alkaline conditions



ACIDITY
Tautomeric forms of Barbiturates



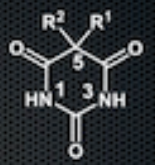
I II III

pKa ~ 4.0

(Acetic acid pKa ~ 4.75)

SAR of Barbiturates

1) Hypnotic activity



If $R^1 + R^2$ =

C11, C12 …

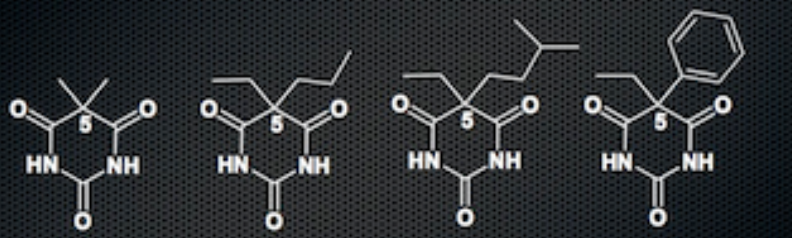
C6 to C10

C1 to C5

Lipophilicity

Hypnotic

2) Hypnotic activity
Branched substituents at C5



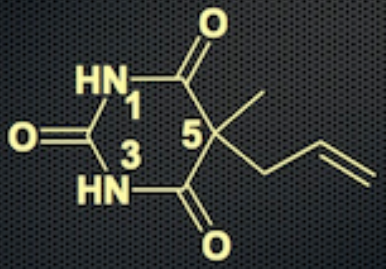
Hypnotic activity and Lipophilicity

Duration of Action

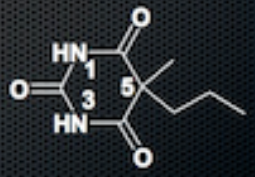
3) Hypnotic activity
Substituents at C5

Unsaturated > Saturated, aliphatic *

a. Allyl



c.f.

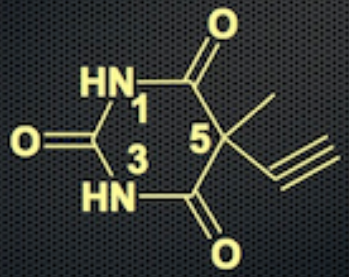


* for derivatives with the same number of carbon atoms

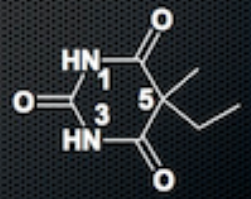
3) Hypnotic activity
Substituents at C5

Unsaturated > Saturated, aliphatic *

b. Alkenyl



c.f.

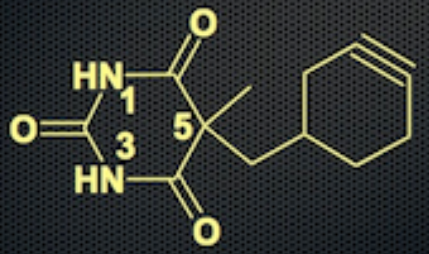


* for derivatives with the same number of carbon atoms

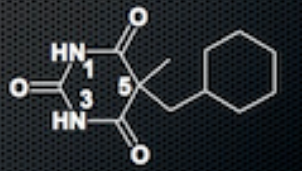
3) Hypnotic activity
Substituents at C5

Unsaturated > Saturated, aliphatic *

c. Cyclic alkenyl

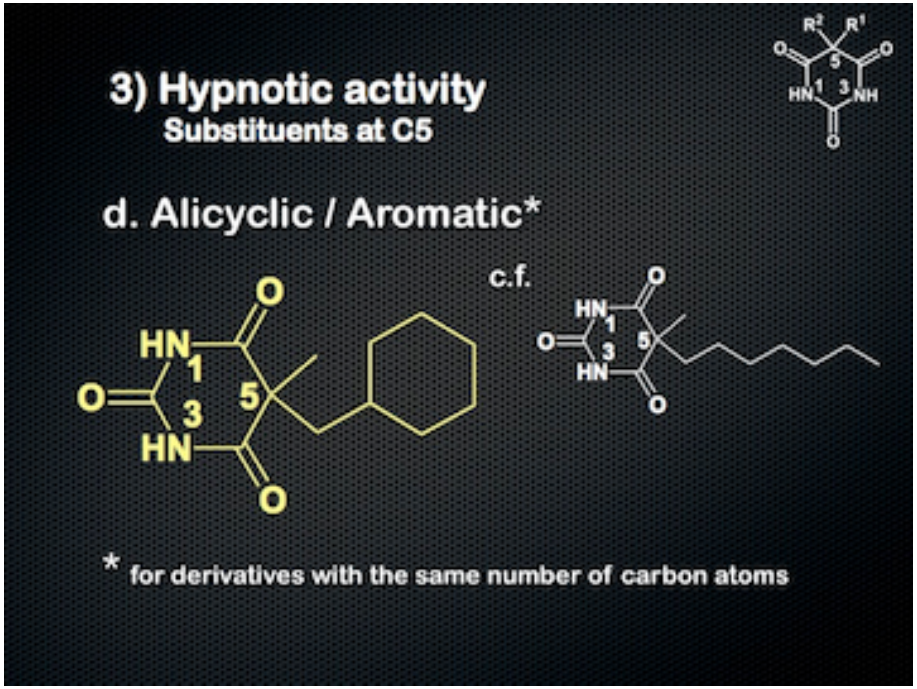


c.f.

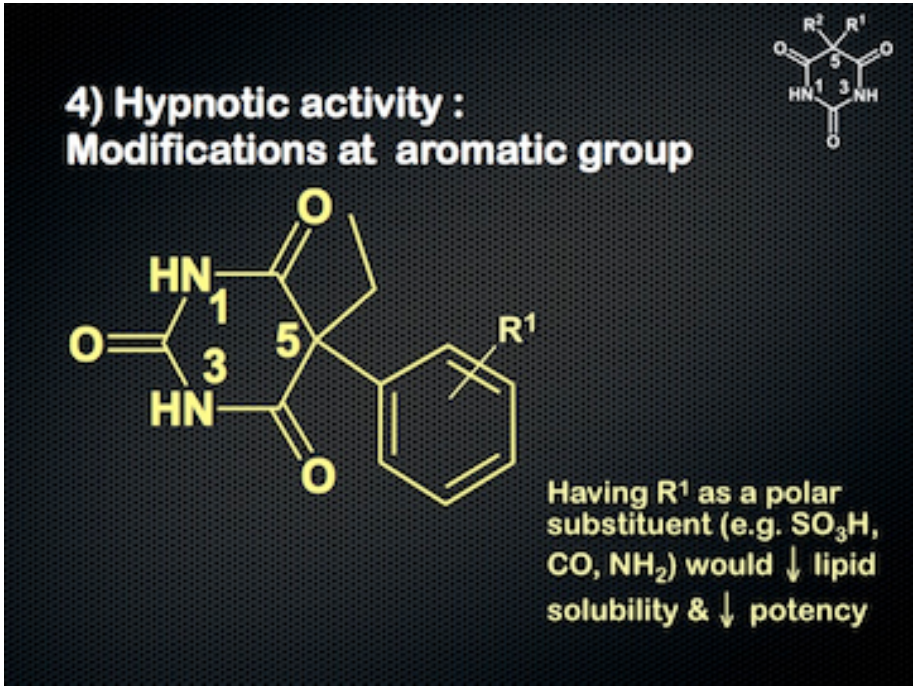


* for derivatives with the same number of carbon atoms

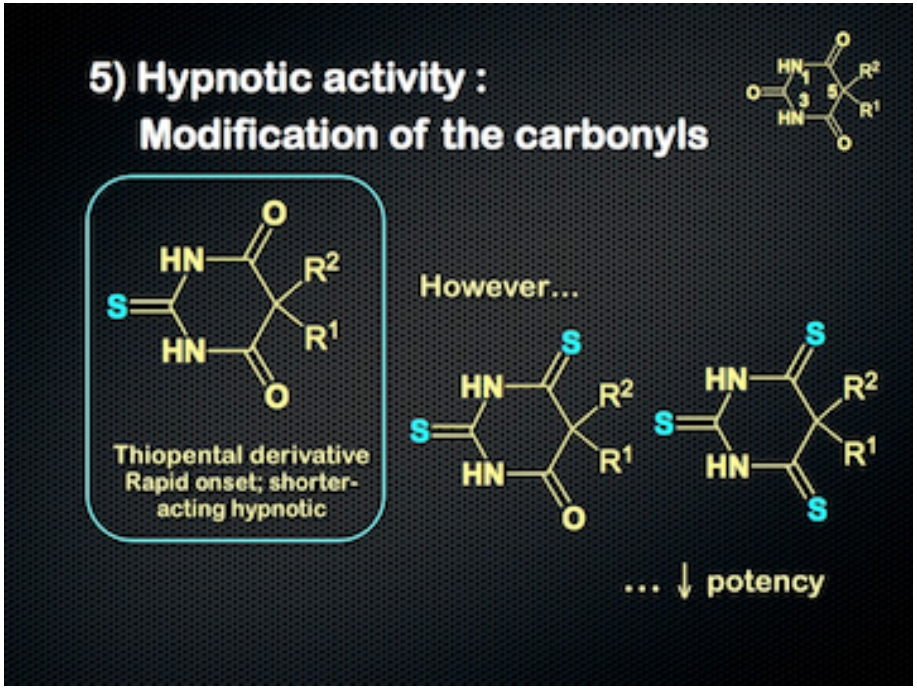
3) Hypnotic activity
Substituents at C5



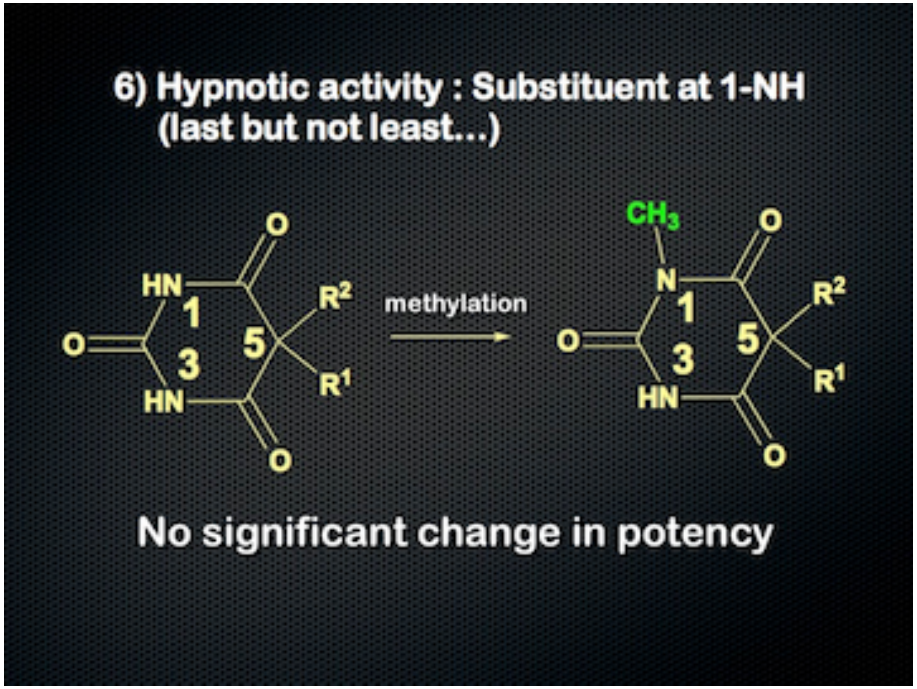
4) Hypnotic activity :
Modifications at aromatic group



5) Hypnotic activity :
Modification of the carbonyls



6) Hypnotic activity : Substituent at 1-NH
(last but not least…)

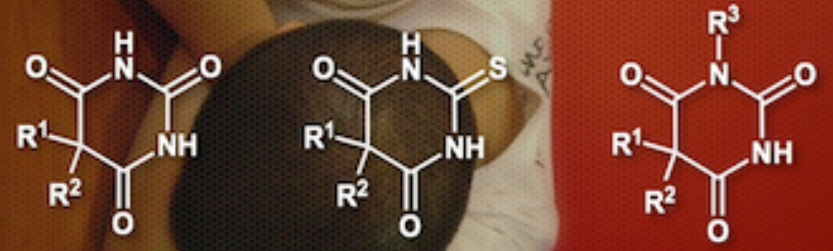


Barbiturate SAR : Conclusions

- Substantial structural modifications appear to be tolerated by the receptors for effecting hypnotic activity
- Thus, the barbiturates (hypnotically) act in a non-specific and non-stereospecific nature

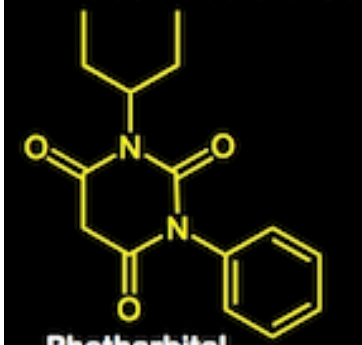
ACIDITY : Classes of barbiturates

Hypnotics



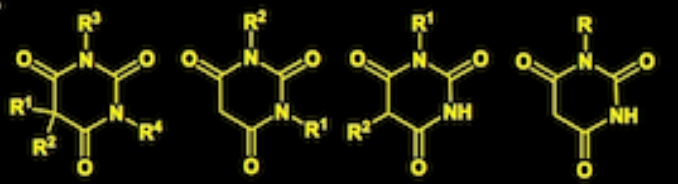
ACIDITY : Classes of barbiturates

Non-Hypnotics



Phetharbital

weakly sedative, anticonvulsant



There's always an exception to the rules…

BUT,

INACTIVE

ACTIVE

Metabolism of Barbiturates

Barbiturates are metabolised in the LIVER

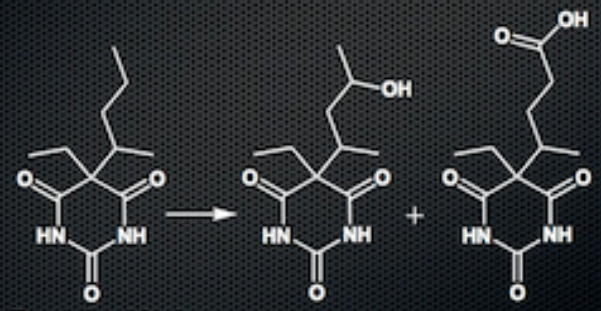
Barbiturates' metabolites are of reduced lipophilic character ∴ ↓ CNS penetration

Barbiturates may undergo FOUR primary metabolic pathways

Metabolism of Barbiturates
1) Oxidation of C5 substituents

The most important metabolic pathway

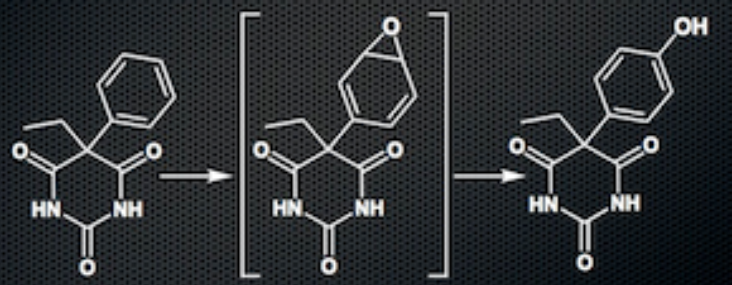
May give alcohols, ketones & carboxylic acids



Pentobarbital

Metabolism of Barbiturates
1) Oxidation of C5 substituents

The oxygenated metabolites may be excreted in the free form or glycosylated or sulphated



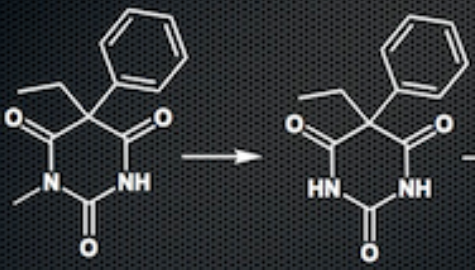
Phenobarbital

Epoxide intermediate

p-hydroxyphenylbarbital

Metabolism of Barbiturates
2) Demethylation

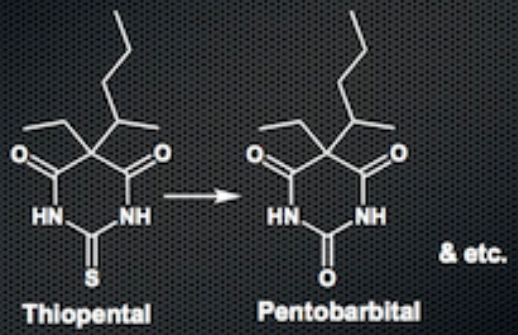
For N-substituted barbiturates



Phenobarbital

Further metabolism

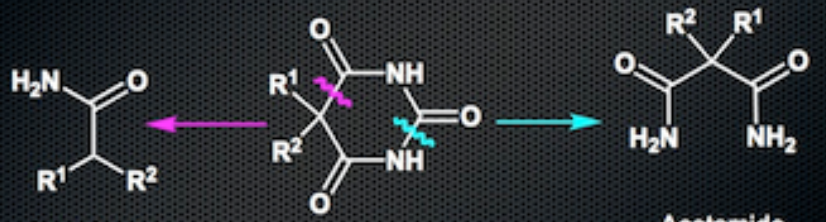
Metabolism of Barbiturates
3) Desulfurisation



Thiopental Pentobarbital

A common metabolic process involving thiopental

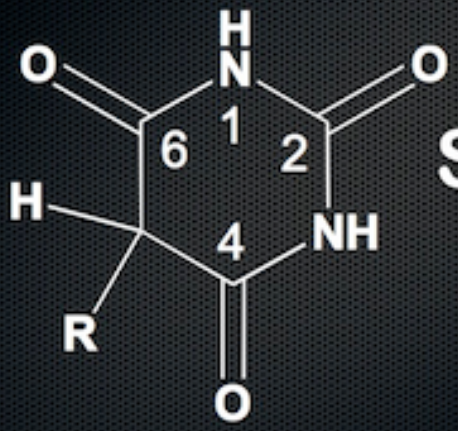
Metabolism of Barbiturates
4) Ring opening



Acetylurea derivative

Acetamide derivative

Barbiturates



Summary

Four metabolic pathways

Oxidation, C5

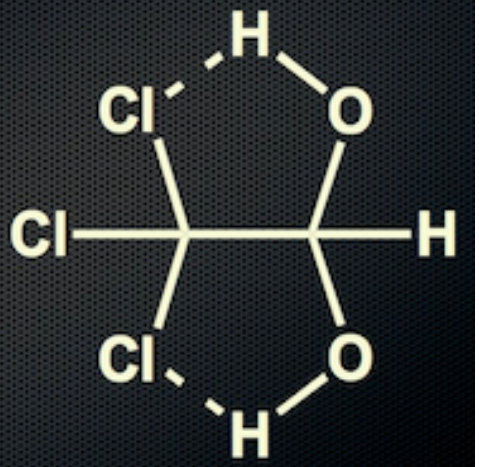
De-sulfurisation

Ring-opening

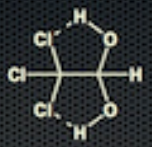
Demethylation

Chloral Hydrate

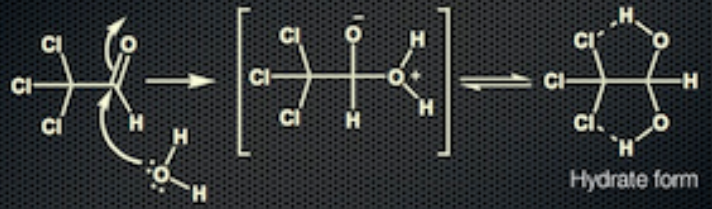
2,2,2-trichloroethane-1,1-diol



Chloral hydrate



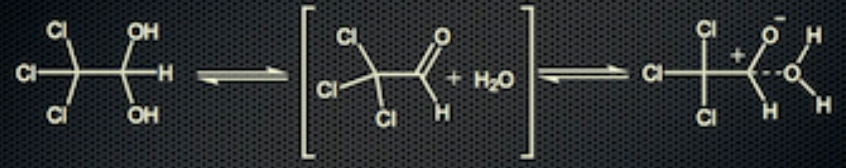
Stability in aqueous solution



Pronounced – I effect exerted by 3 Cl's
This allows a weak nucleophile to attack the C=O
Thus, equilibrium shifts to the right favouring the formation of the hydrate

Chloral hydrate

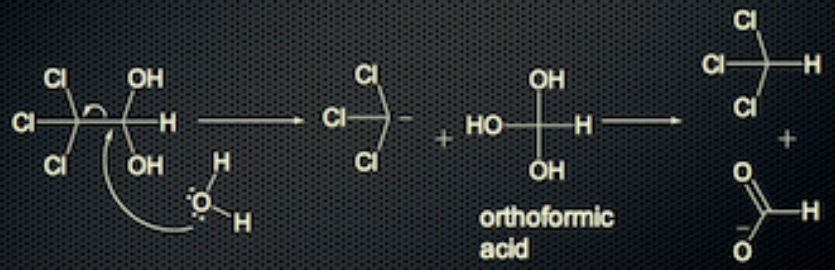
in aq. acid/ neutral/ alkaline solution



Exists in equilibrium in the forms above

Chloral hydrate
Aqueous storage stability

storage : in neutral solution, over a long period of time + under light / in aq. alkali



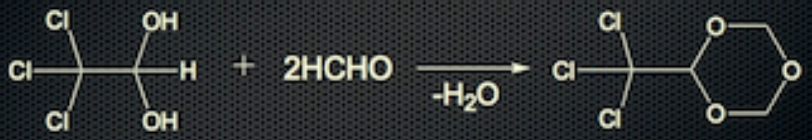
observation : an increase in pH

Chloral hydrate :
Non-aqueous storage stability

in water-free environment + exposure to light & air, chloral hydrate also can be oxidised either way

Chloral hydrate
Tendency to self-polymerise

with a catalytic amount of acid + HCHO
they tend to self-condense → polymers



to inhibit this self-polymerisation rxn,
$HCONH_2$ & DMF are used as stabilisers

Conclusions

Chloral hydrate
it's got 3Cl and 2OH : -I effect
tends to form hydrogen bridges →CRYSTALS

in solution, it's in equilibrium
its best enemies are light & air & a tiny amount of acid → decomposition