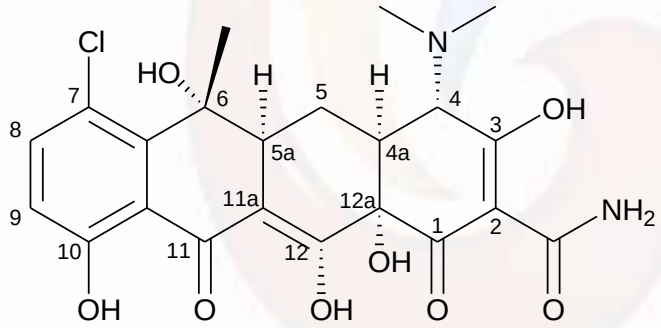
Tetracycline

Disclaimer

All the content material provided here is only for teaching purpose.

Tetracyclines

- Are bacteriostatic antibiotics having broad spectrum of activity.
- Isolated from ***Streptomyces bacteria***.
- First one isolated was chlortetracycline (1948).



Chlortetracycline

- They inhibit protein biosynthesis by binding to 30s ribosomal subunit and prevent aminoacyl tRNA from binding to the A-site.

Mechanism of action

- Tetracyclines could inhibit protein synthesis in human, but they normally can not penetrate the mammalian cell membrane.
- The transport of tetracycline into the cell (especially the gram –ve bacteria) needs:
    1. a passive diffusion through porines, this process is pH dependent and required proton-driven carrier protein. This protein is only present in bacteria not in human cell.
    2. Active transport: requires Mg^{++} and ATP.
- This is why tetracyclines are quite selective on the bacterial cell.

Clinical uses of tetracyclines

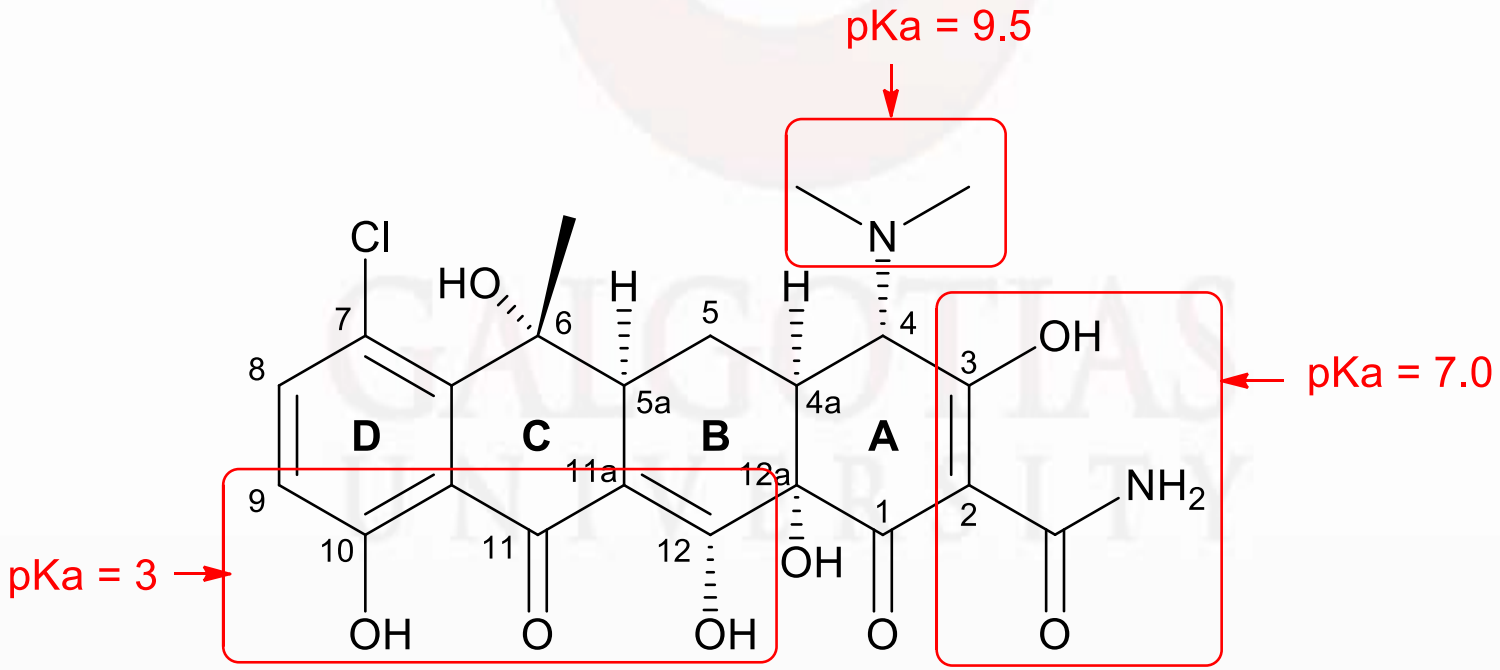
- They have the broadest spectrum of activity, on both gram +ve, gram – ve and atypical bacteria.
- Resistance has been developed rapidly against tetracyclines, as a result of that penicillins have replaced them in many infections, especially the respiratory infections.
- Tetracyclines are still used in rickettsia, Chlamydia, mycoplasma and acne infections.
- Some of them have antiparasitic properties such as the use of Doxycycline in the treatment and prophylaxis of malaria.
- They have bacteriostatic action, not recommended in life threatening infections such as septicemia, endocarditis and meningitis

Clinical uses of tetracyclines

- Tetracyclines should be avoided in children and pregnant women: they bind to the growing teeth and bones…. Lead to tooth discolorations and toxicity in fetus.
- Tetracyclines can be divided according to the duration of action into:
  1. Short acting: chlortetracycline ($t_{1/2}$ = 7hr).
  2. Intermediate acting: tetracycline and demeclocycline ($t_{1/2}$ 10-15hr).
  3. Long acting: Doxycycline and minocycline ($t_{1/2}$ = > 16hrs)

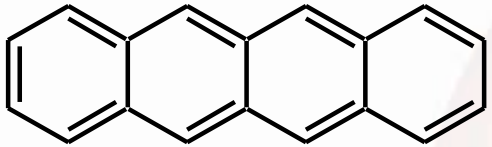
Tetracycline chemical structure

- They are derivatives of octahydronaphthacene which comprise four fused six-membered rings.
- The structure have 5 or 6 chiral centres.
- They have acidic and basic characteristics.

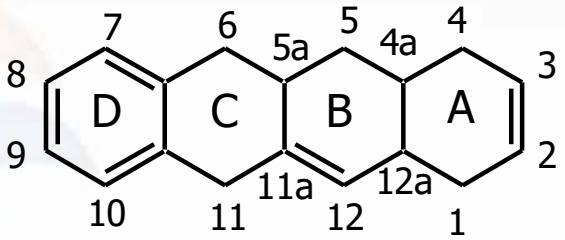


Chemical properties:

- Derived from Octahydro Naphthacene ring system:

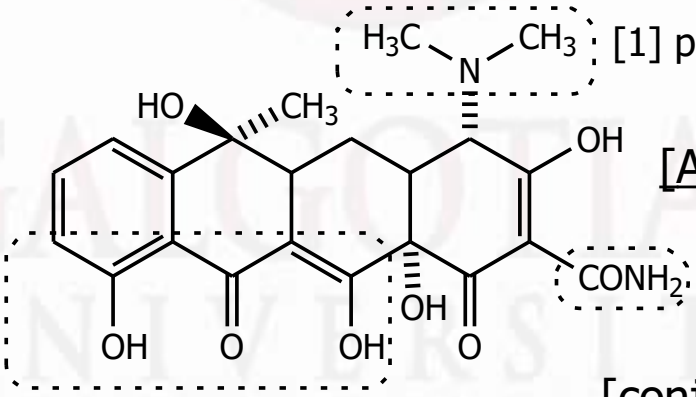


Naphthacene ring
[9 double bonds]



Octahydronaphthacene
[5 double bonds]

They are amphoteric substances: [form salts with acids or bases].
They are with 3 pka values:



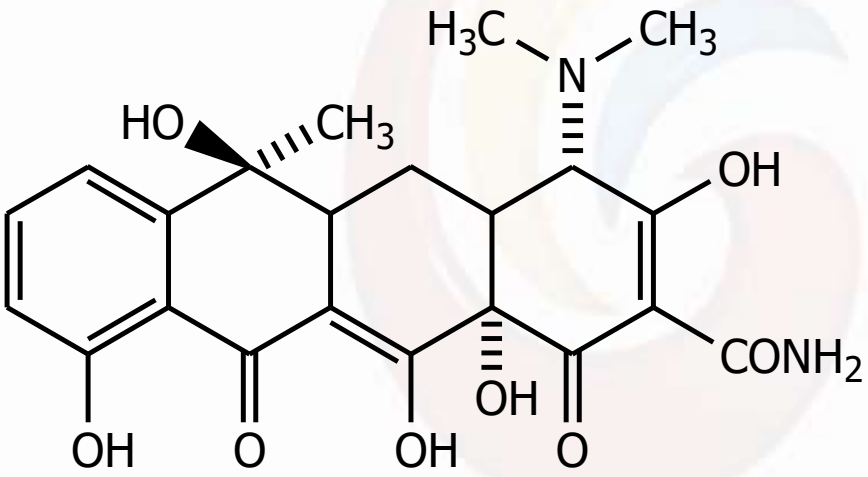
[1] pka_3 = 9.7
[Basic]
[Amonium cation moeity]

[2] pka_1 =3.3
[Acidic]
[conjugated trione system]

[3] pka_2 = 7.5
[Neutral]
[extending enone system : C_{10}-C_{12}]

►Commercially available tetracyclines are relatively **water-soluble HCl salts**.

Tetracycline



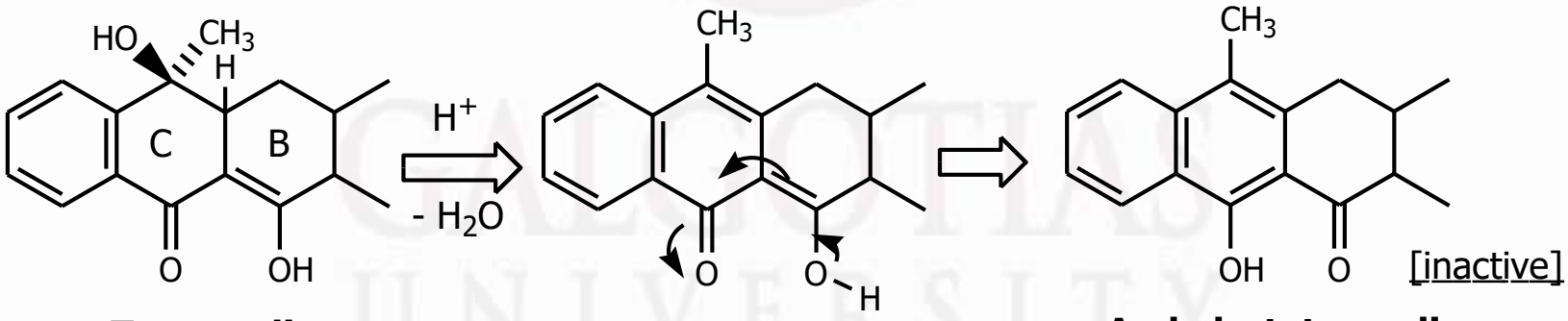
4-α-dimethyl amino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11- dioxo-2-Naphthacene Carboxamide.

Chemical stability of Tetracyclines

[1] Action of acids :

→Dehydration [at C6] followed by Aromatization of ring C

- ► Occur in presence of strong acids pH < 2 [stomach acidity]: [**for tetracyclines with 6-OH in the form of tertiary alcohol**]
- ► Dehydration by removal of 6-OH [if 3ry OH] → double bond formation between C5a & C6 Aromatization of ring C → Naphthalene derivative: Anhydrotetracycline [inactive]
- ► If tetracycline with 2ry 6-OH → more stable ≠ dehydration.

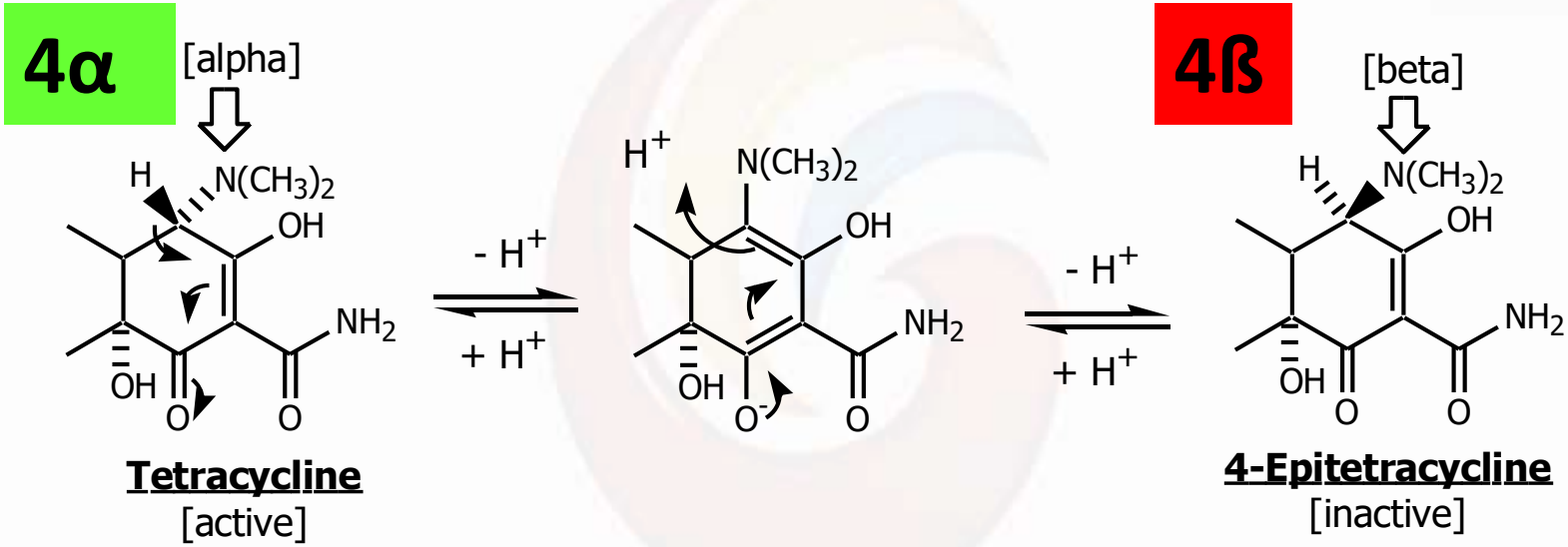


Tetracycline
[active]

Andydrotetracycline
[ring C become aromatic]

[2] Epimerization: [at C4]

Occur at intermediate pH [**pH= 2 – 6** i.e. weak acidity] especially in solutions.
Leads to formation of **4-Epitetracycline** [with ß-configuration] →Inactive.

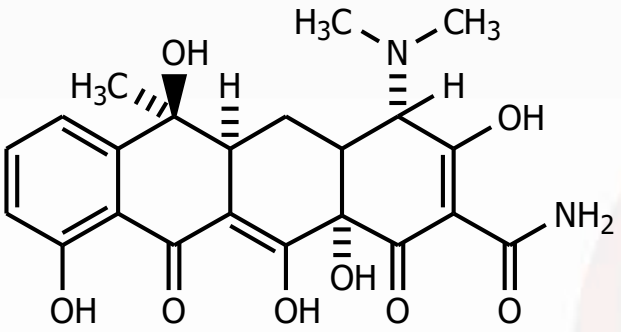


Presence of Epitetracycline is not recommended for two reasons:

1- Epitetracycline is inactive. So, capsules are overfilled by about 15% excess during manufacture to give longer half life.

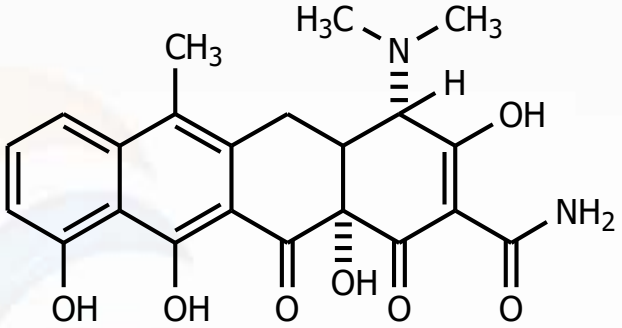
2- Dehydration in acidic medium → 4-Epianhydrotetracyclines [which is **nephrotoxic** degradation product].

So, commercial tetracyclines products must be tested for the presence of 4-Epianhydrotetracycline.

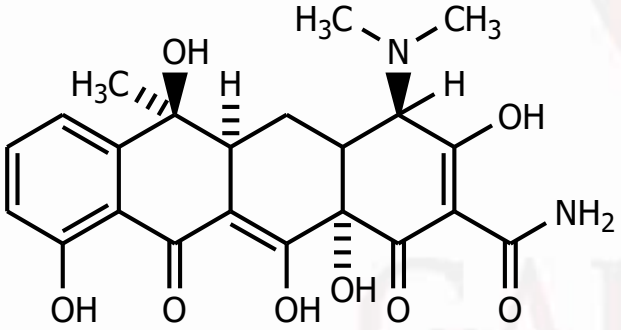


Tetracylcine
[active]

H^+

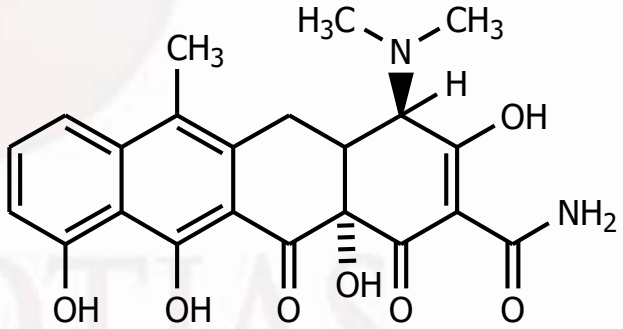


Anhydrotetracycline
[inactive]



4-Epitetracycline
[inactive]

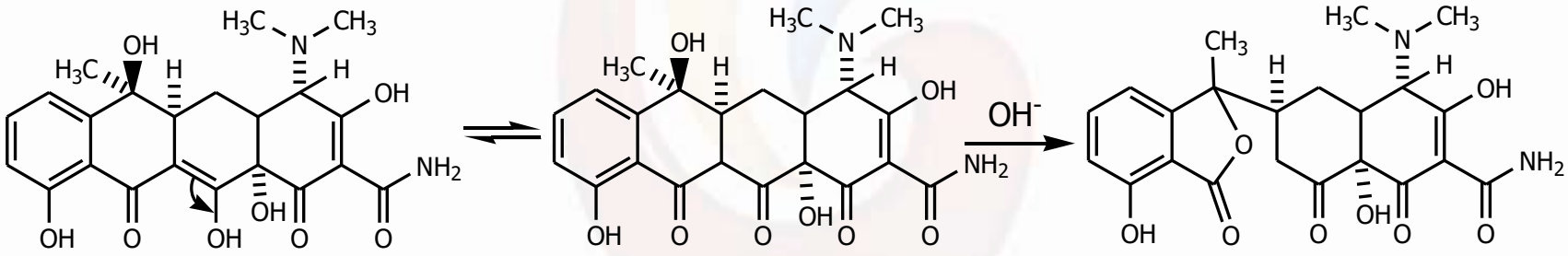
H^+



4-Epianhydrotetracycline
[inactive + renal toxic]

[3] Action of bases :[Base-catalyzed instability] : = Lactonization

➢ Strong bases → cleavage of ring C in tetracyclines having 6-OH → Isotetracycline [lactonic product] which is inactive.



Tetracyclines with no 6-OH :

1- Resist actions of acids & bases.

2- Higher lipid solubility & so, better absorption.

[4] Chelation & Incompatibility

(1)- Tetracyclines form chelation by forming insoluble non-absorbable salts in GIT with poly valent metal ions [as Fe^{+2}, Ca^{+2}, Mg^{+2}, Al^{+3}].

They are incompatible with :

►Milk : by chelation with Ca^{+2} ↓ absorption of tetracyclines & ↓ absorption of Ca^{+2}

►Antacids : as $Mg(OH)_2$ & $Al(OH)_3$.

►Anti-anemics [agents with Fe^{+2}].

So, to avoid that take ion preparation 1 hr before or 2 hrs after taking tetracyclines.

(2)- They are painful upon I.M. injection: due to chelation with Ca^{+2} present in muscles →insoluble complex → precipitation → pain & irritation.

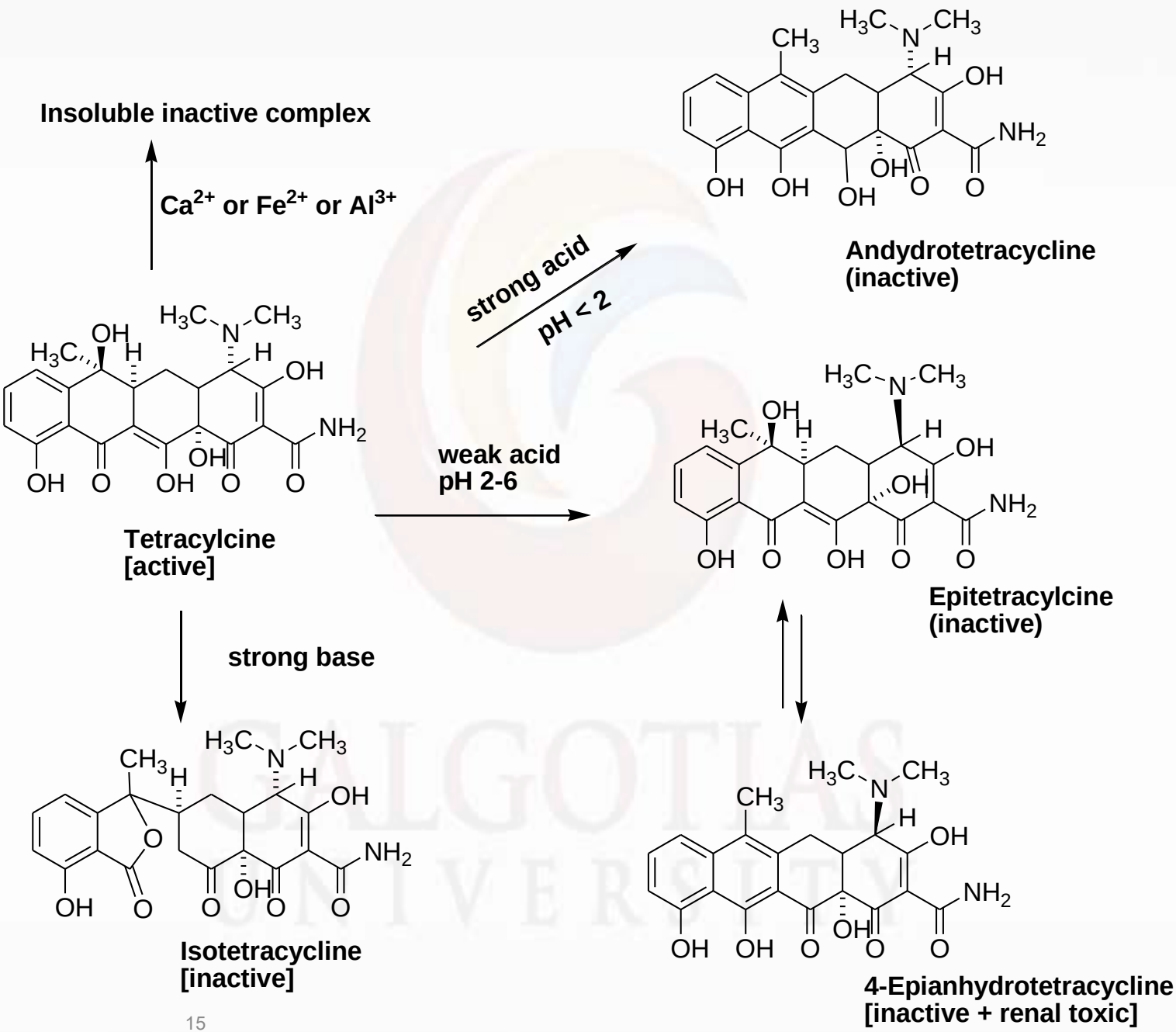
So, to solve this problem.

Add EDTA to injectable product [to form water soluble complex with Ca^{+2} & so, no available Ca^{+2} for chelation].

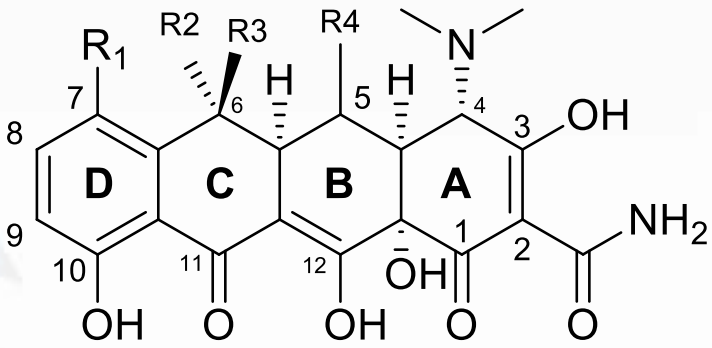
Buffer solution at acidic pH [chelation is less & water solubility of the complex ↑↑]

(3)- They are not recommended for pediatrics or children: this is due to chelation with Ca^{+2} making insoluble complex that precipitate in teeth making dark colored teeth & deprive bones & teeth from Ca^{+2}.

Tetracyclines is not given to children 6-12 years (discoloration for teeth), pregnant or lactating mothers.

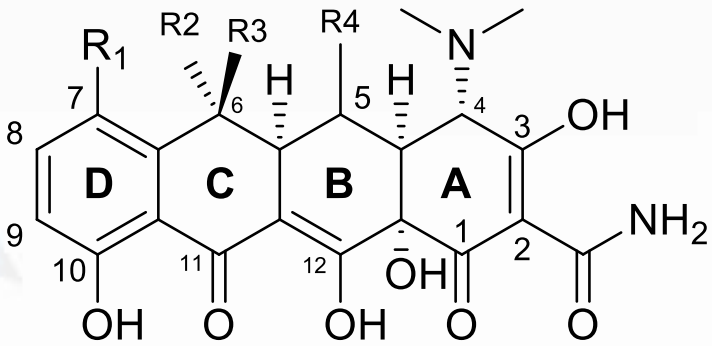

Insoluble inactive complex
Ca2+ or Fe2+ or Al3+
strong acid
pH < 2
Andydrotetracycline
(inactive)
Tetracylcine
[active]
weak acid
pH 2-6
Epitetracylcine
(inactive)
strong base
Isotetracycline
[inactive]
4-Epianhydrotetracycline
[inactive + renal toxic]

SAR in tetracyclines



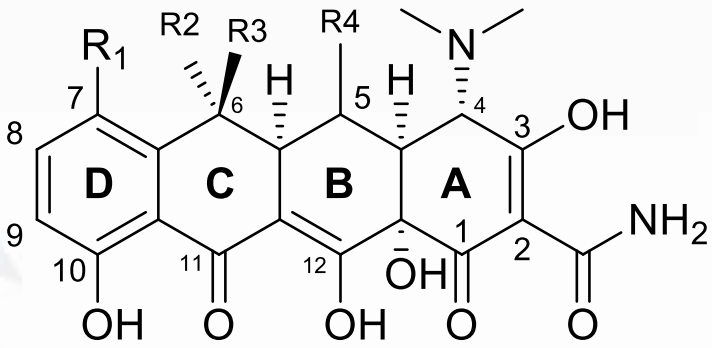
- Derivatives with less than four fused rings were inactive.
- The simplest structure with retained activity was 6-demethyl-6-deoxytetracycline.
- Substituents at C1,2,3,4,10,11,11a,12 can not be modified for better activity.
- Slight modifications on ring A found tolerable without dramatic loss in activity.

SAR in tetracyclines



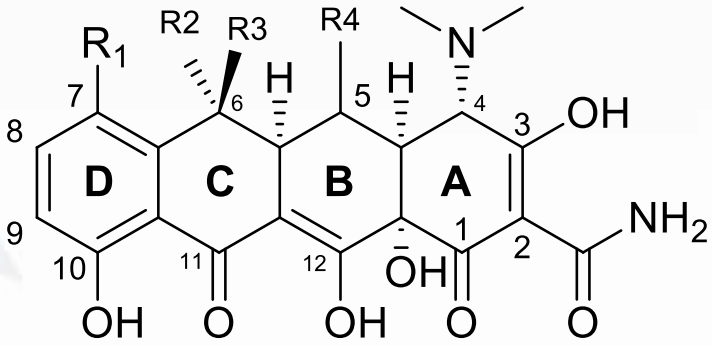
- Regarding Ring A:
  - The enolized carbonyl system between C1 and C3 is essential for activity and can not be modified especially the amide group:
    1. Replacement of the amide with nitro or aldehyde abolished the activity.
    2. Monoalkylation of the amide reduced the activity.
  - Dimethylamino at C4 can be free amine or *N*-methylamino, but can not accept larger alkyl than methyl.
  - Dimethylamino must have an α-orientation, the other isomer is much less active.

SAR in tetracyclines

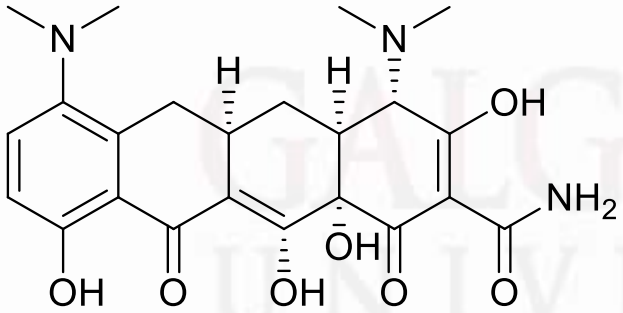


- Ring A and B should have cis-fusion with OH at C12a.
- OH group at C12a must be free, esterification abolished the activity.
- Hydrophobic substitution at C5,5a,6,7,8,9 resulted in retention and sometimes improvement in activity.
- The presence of 5-OH does not have important role in activity (such as in demeclocycline and oxytetratcycline compared to minocycline and doxycycline)

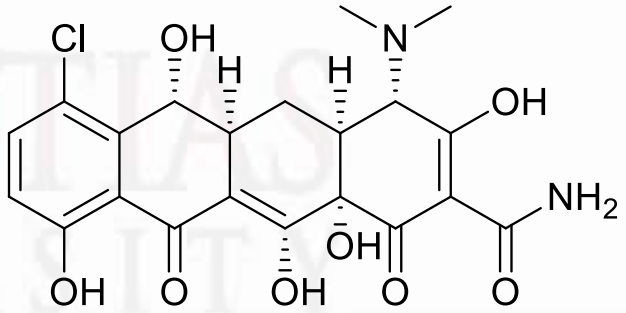
SAR in tetracyclines



- Acid stable scaffold (6-deoxy or 6-demethyl-6-deoxytetracyclines) were used to prepare derivatives with mono and disubstitutions at C7 (mainly) and C9… either EDG or EWD:

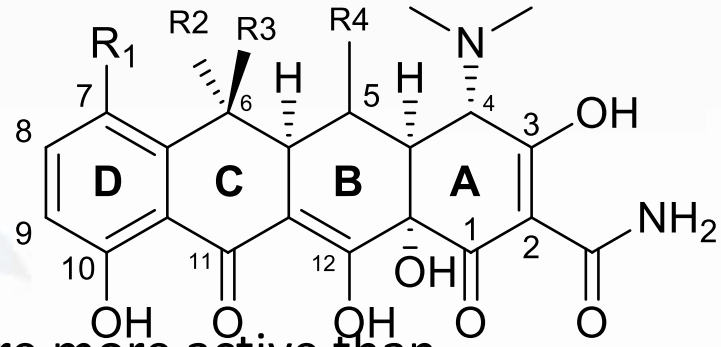


Minocycline



Demeclocycline

SAR in tetracyclines

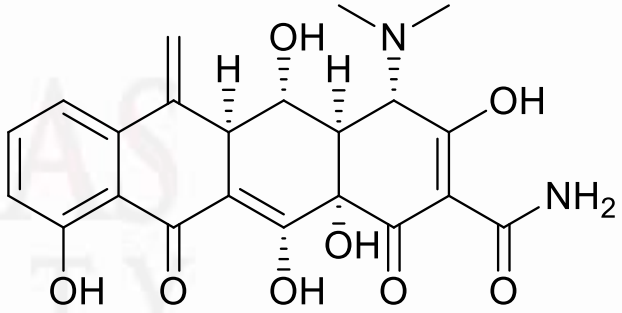


- Neither 6α nor 6β-OH is essential

  for activity (Doxycycline and methacycline are more active than oxytetracycline).
  - These derivatives are also more stable toward acid and base inactivation.
  - More lipid soluble… better absorbed

    orally (>90% orally available).
  - High protein binding… have long

    duration of action.



Methacycline

$t_{1/2}$ = 12 hrs

more potent than 6-oxytetracycline

SAR:

4 linear rings are essential
* Derivatives with < 4 rings are inactive.
* Opening of rings or aromatization of additional rings give inactive compounds.

Hydrophobic region [C_5-C_9]

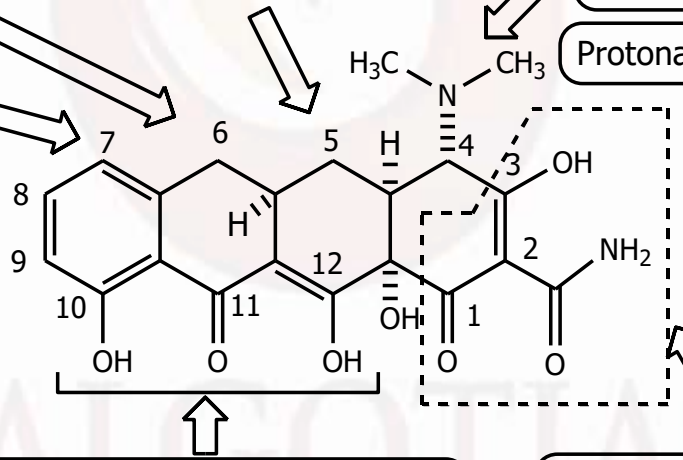
6 alpha-methyl & 6 beta-OH are NOT essential

removal of 5-OH : give 5-deoxy compound [not affect activity]

4-**alpha** dimethyl amino is essential for activity that it forms zwitterion which is for optimum distribution

Protonated dimethyl amino enhance activity

strong e-withdrwaing group at C_7 enhance activity [as Cl , NO_2] OR strong e-donating group [as dimethyl amino] : i**ncrease activity**



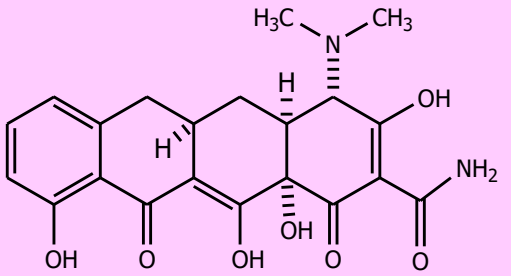
Phenoldiketone moeity is essential

Conjugation between C_{10}-C_{12} is essential

Presence of enolized tricarbonylmethan system at C_1-C_3 is essential for activity

Carbonyl gp of amide at C_2 is essential.

one amide H atom may be replaced , but if both; inactive



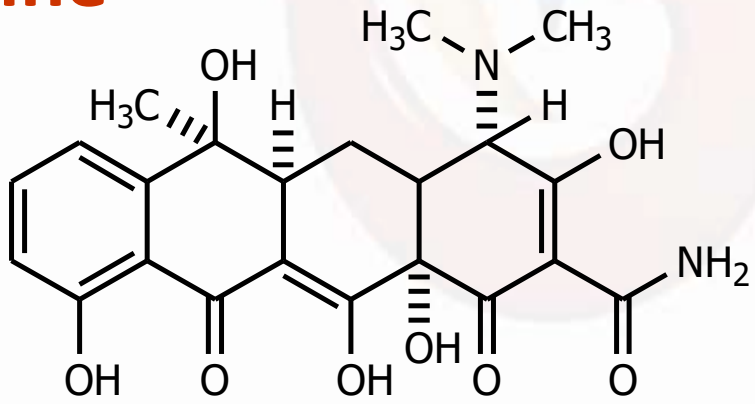
Sancycline

➢ Pharmacophore of this group is Sancycline [it's with full biological activity but clinically Not important antibiotic].

Classes of Tetracyclines

[I] Natural Tetracyclines

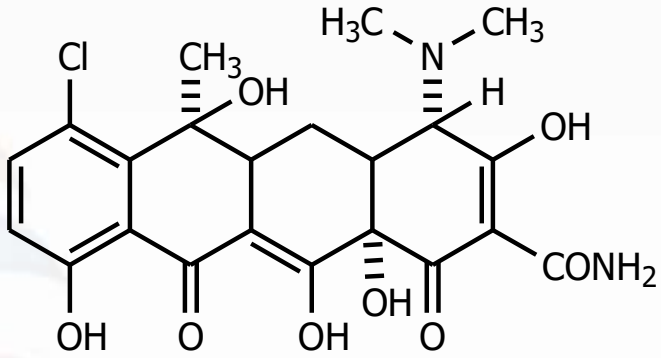
Tetracycline



(1) Produced by fermentation of *Streptomyces aureofaciens* OR by catalytic reduction of chlorotetracycline.
(2) Most widely used in tetracyclines, cheap antibiotic.
(3) Its blood level after oral administration is irregular; due to inactivation by acidic medium in stomach or basic medium in intestine.
(4) The drug of 1st choice in ACNE.

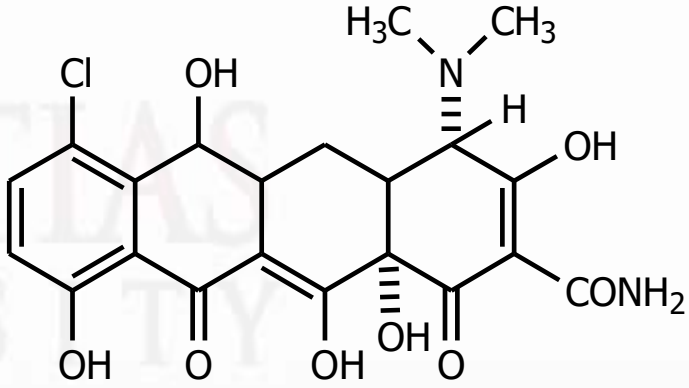
Chlorotetracycline

►Isolated from *Streptomyces aureofaciens*.
7-chloro is e-withdrawing group that ↑ activity.
►It's used as chlorotetracycline HCl orally as CAPSULES to avoid bitter taste. & may be administered parentrally [I.V].

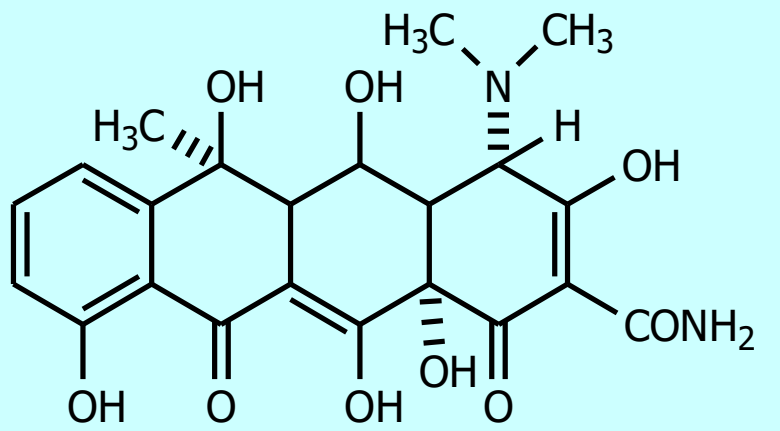


Demeclocycline

►Produced by fermentation of mutant strain of *Streptomyces aureofaciens*.
►It lacks 6-methyl of tetracycline → present as 2ry alcohol → more stable > tetracycline & chlorotetracycline to both acids & bases.



Oxytetracycline[Terramycin®]

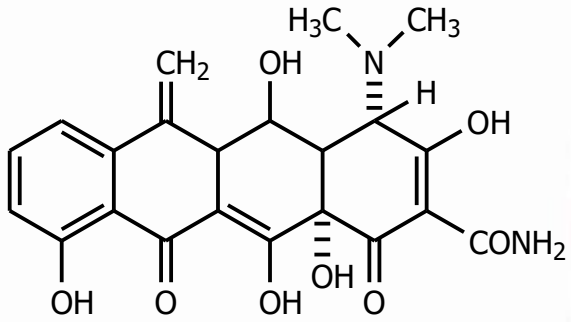


Produced by fermentation of *Streptomyces rimosis* & other soil m.o.
The <u>most hydrophilic tetracycline</u>.

**<u>Note that</u>:
(1) All tetracyclines concentrate in liver → part metabolized & conjugated to form soluble glucuronides.
(2) Most tetracyclines → reabsorption in intestine & enter urine by glumerular filtration.

[II] Semi-synthetic Tetracycline

Methacycline

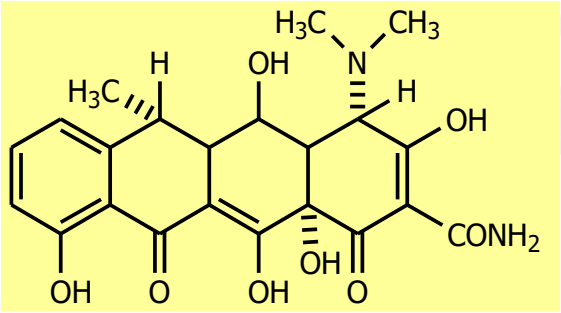


►Produced by chemical modification of Oxytetracycline.

►Removal of 6-OH → ↑ stability ≠ acids & bases → **longer serum $t_{1/2}$**

►The chemical precursor for Doxycycline.

Doxycycline [Vibramycin®]

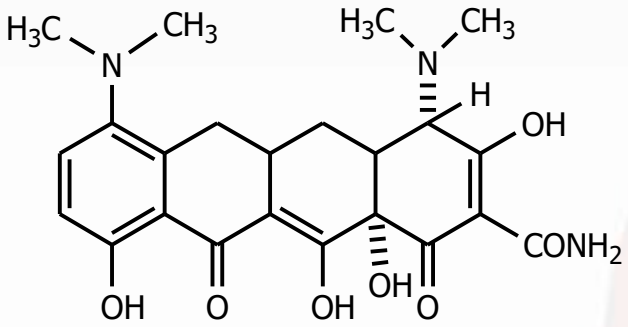


1- One of the most important of current tetracyclines.

2- Its metabolite is preferentially **excreted via bile into faces**

3- Can be given to **uremic patients** with infections outside urinary tract. It causes ↓ GIT disturbance.

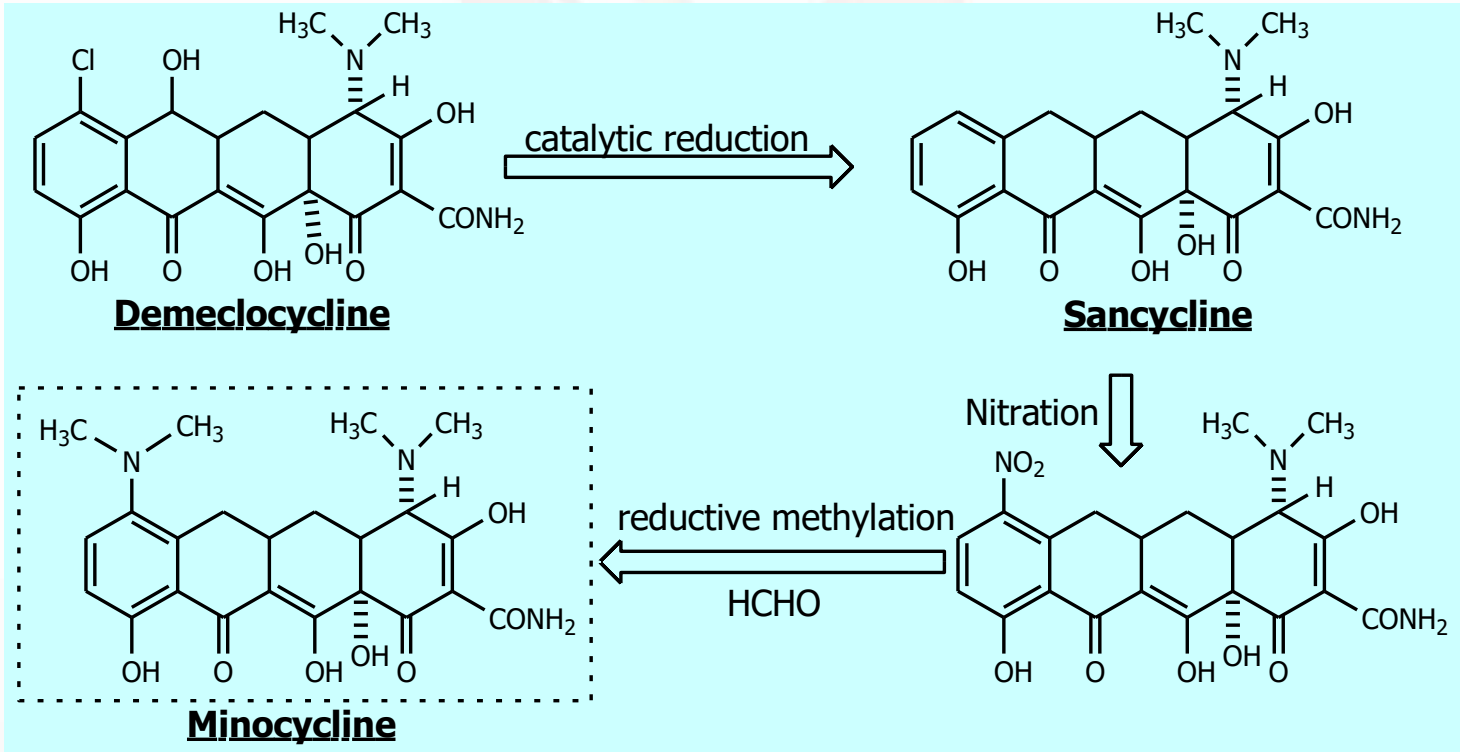
Minocycline



►Minocycline is the **most lipid-soluble** of the tetracycline-class antibiotics, giving it the greatest penetration into the prostate and brain.

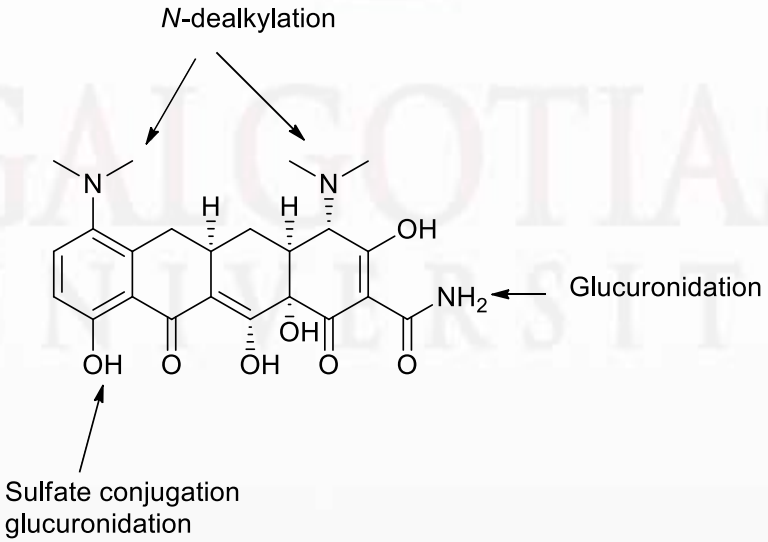
►But also the greatest amount of central nervous system (CNS)-related side effects, such as vertigo .

Semi-synthesis: From Demeclocycline



Metabolic transformations in tetracyclines

- Most of them are excreted unchanged in urine.
- Sulfate and glucuronide conjugates were detected in urine especially for Doxycycline and minocycline.
- The major metabolite found to be the *N*-dealkylated at C4, and to a little extent at C7 (for minocycline).



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