* المادة بس (تدخل) الجسم بتكون في عندها (balance hydrophilic-hydrophobic Properties)

لكن بس (تخرج) عبر الكلى لازم تكون (Water soluble) وتكون الـ molecular weight قليل

* كيف بدنا نخول هاد الدواء اللي فيه hydrophobic Properties إلى دواء يكون Water soluble ؟ عن طريق الـ metabolism

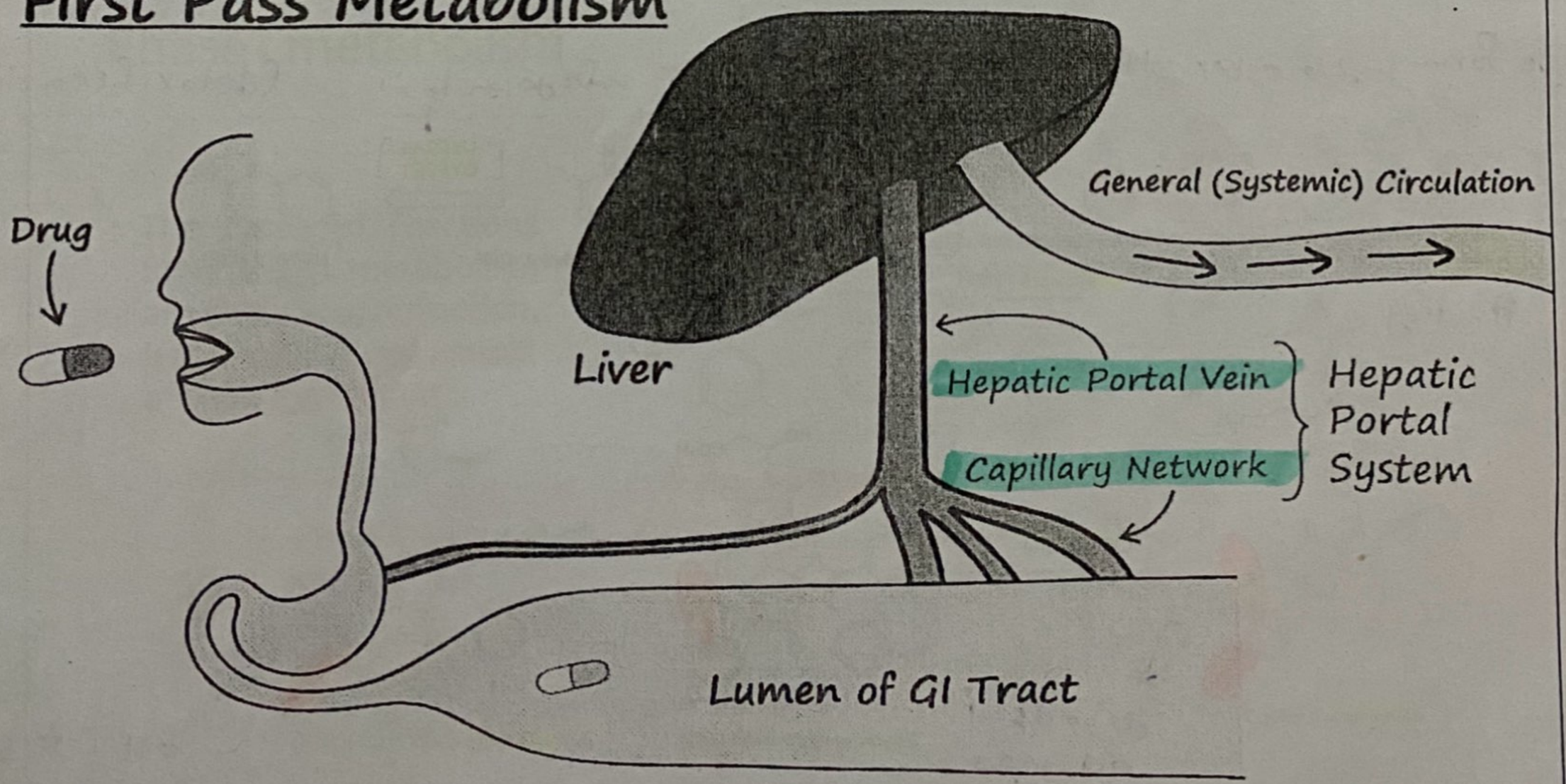
ADME
Drug Metabolism

رميلتكم ريماس الشوابكه

- رح افرغلكم كل مادة السكند إن شاء الله بكون لتعريف واضح ومفهوم.
- وحتى لوفي سلايدات معجوقة شوي بعضي، بكون فعلياً كتبت كل اشي اللي فالكتاب.

* عندما تنتقل بعض الأدوية عن طريق (hepatic portal vain) أو ابتدا بعين تدخل للكبد قبل ما تروح لـ (General Circulation) وبصير metabolism (First Pass effect) وهو الجزء للدوائية تنقل لهاد الدواء الي صار له metabolism عن طريق

First Pass Metabolism



* ماهو العضو الي بخلي المركبات (more water soluble) ؟ (liver)

ROLE OF METABOLISM

- The role of metabolism step is to degrade or modify the foreign structure, such that it can be more easily excreted. As a result, most drugs undergo some form of metabolic reaction, resulting in structures known as **metabolites**.

Metabolites may:

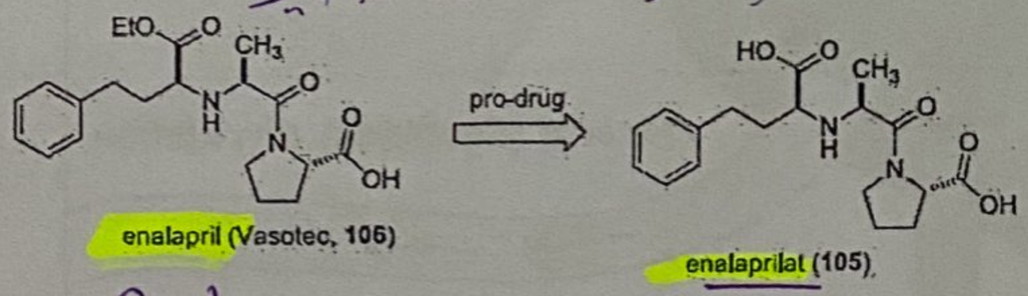
1- Lose the activity of the original drug (**DETOXIFICATION**).

2- Retain a certain level of activity.

3- Be more active than the parent drug (**BIOACTIVATION: PRODRUGS**)

- Aside from water and most hydrophilic dugs, all other molecules/drugs are metabolized. This is actually essential because lipophilic drugs would circulate in the body for a long time, causing untoward side effects if not eliminated in due course. In most cases, metabolism converts lipophilic compounds to hydrophilic metabolites, which are then eliminated/excreted from the body.
- Metabolism is chemical alteration of the drugs in the body. The primary site for drug metabolism is the liver, which is of the uttermost importance with regard to a drug's biotransformations. Other sites of metabolism are the kidney, intestine, lungs, and plasma.

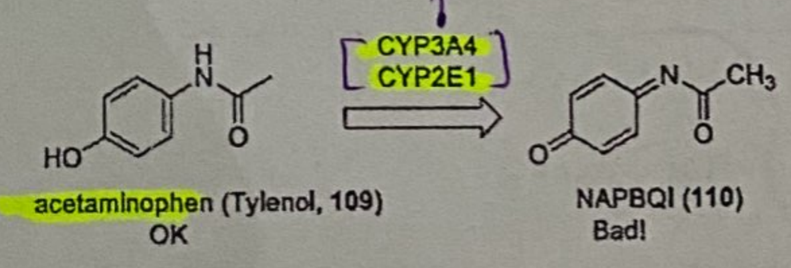
Examples



enalapril (Vasotec, 106)

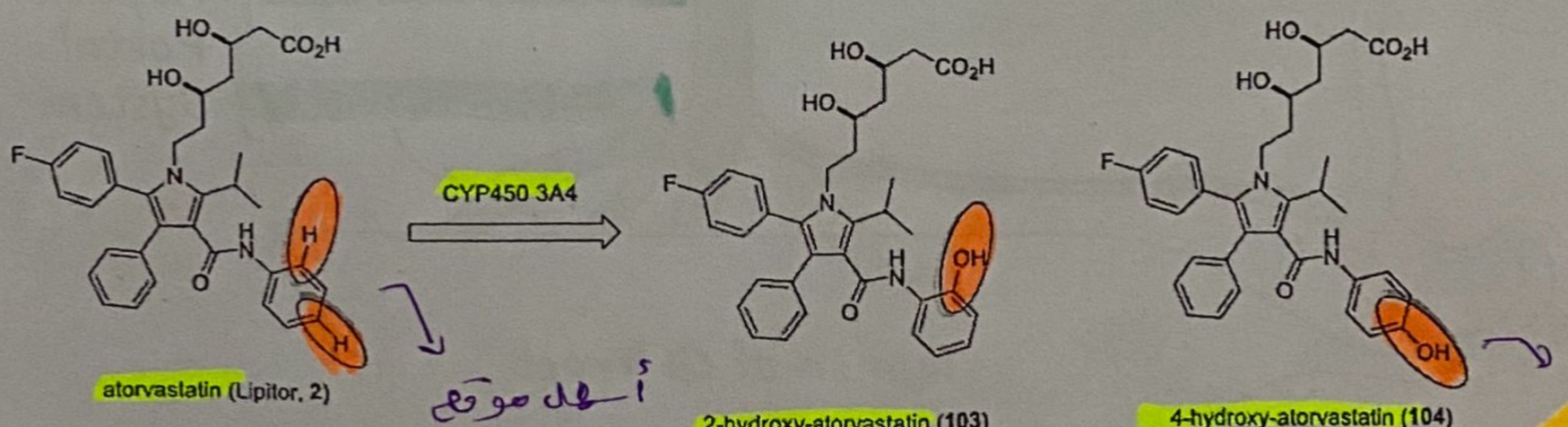
enalaprilat (105)

Pro drug



acetaminophen (Tylenol, 109)
OK

NAPBQI (110)
Bad!



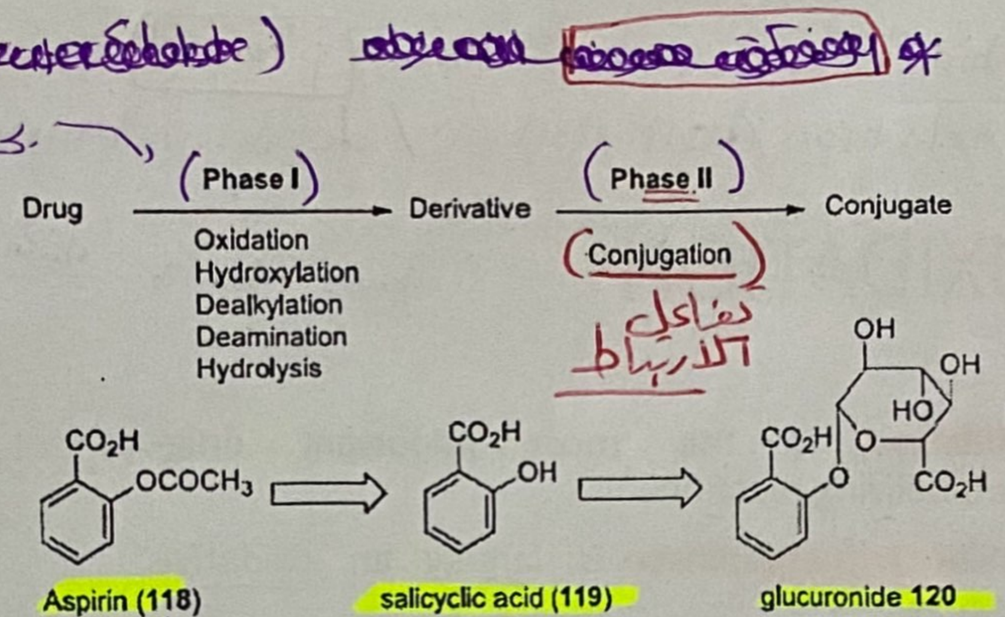
atorvastatin (Lipitor, 2)

2-hydroxy-atorvastatin (103)

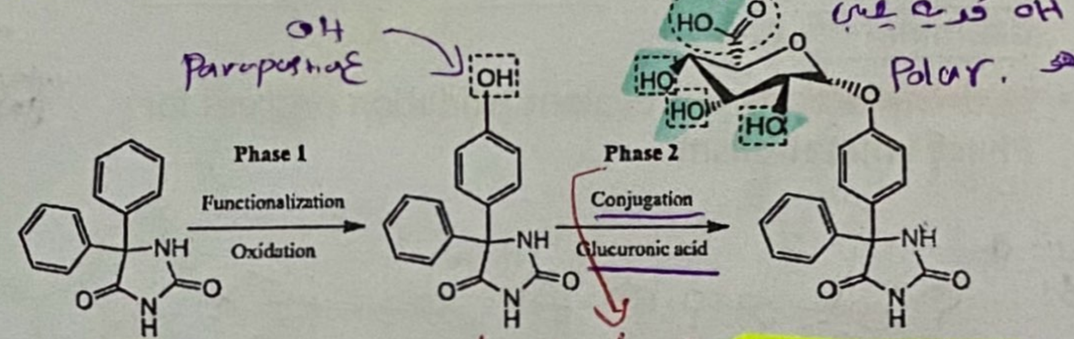
4-hydroxy-atorvastatin (104)

Scanned with CamScanner

Phases of Metabolism



- Drug metabolism may be divided to two phases: Phase I metabolism and Phase II metabolism. *Phase I metabolism* refers to functional group transformations of the original drug, converting it to a more polar molecule(s).
- *Phase II metabolism*, also known as conjugation, is the process of appending a very polar and highly hydrophilic molecule (glucose or sulfate, for example) to appropriately functionalized (parent compound or Phase I metabolite.



ارسطوزي لسب بدنم لفتحوا الباب (:) — بال Phase II بلنيجي نفتح هاد الباب

بال Phase I لسا لتدخلوا ايديكم ع الباب → زي لسا نخط glucoronidation

حبني Phase I لسا نخط OH — لنفهموا هاد الاشيا لقدام حاليا لسا فكرة.

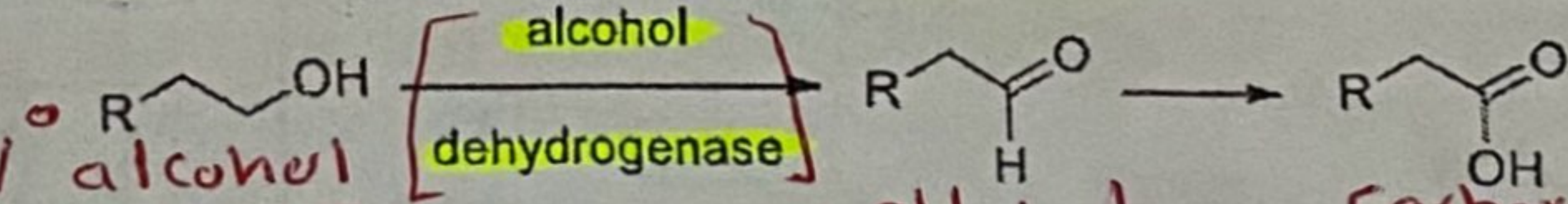
Phase I metabolism

[Major]

- The types of reactions for Phase I metabolism are oxidation, reduction, hydrolysis, cyclization, and de- cyclization.

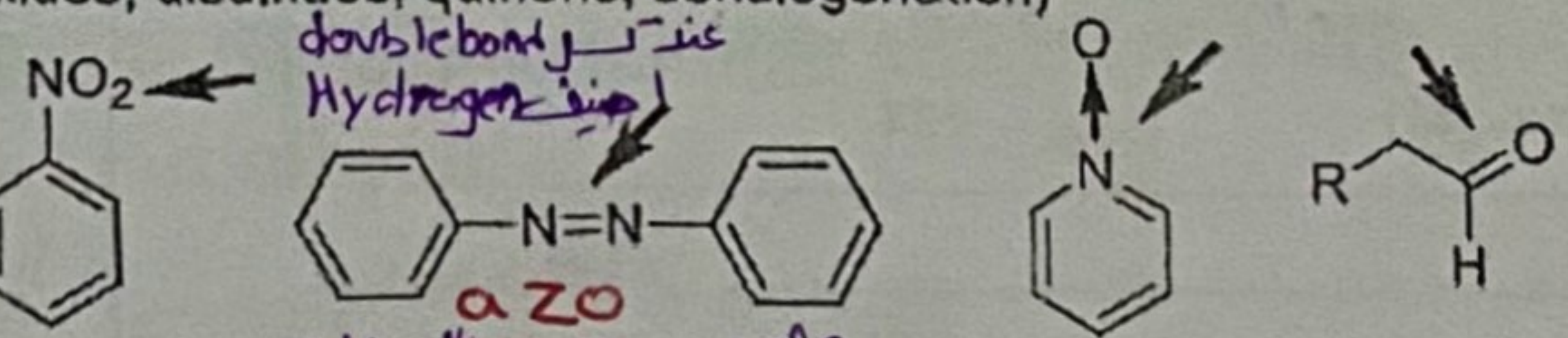
(hydrolysis ← كسر ال ester.)

Oxidation (alcohols and aldehydes) — أهم واحد — هاد الانزيم — اللي نحول



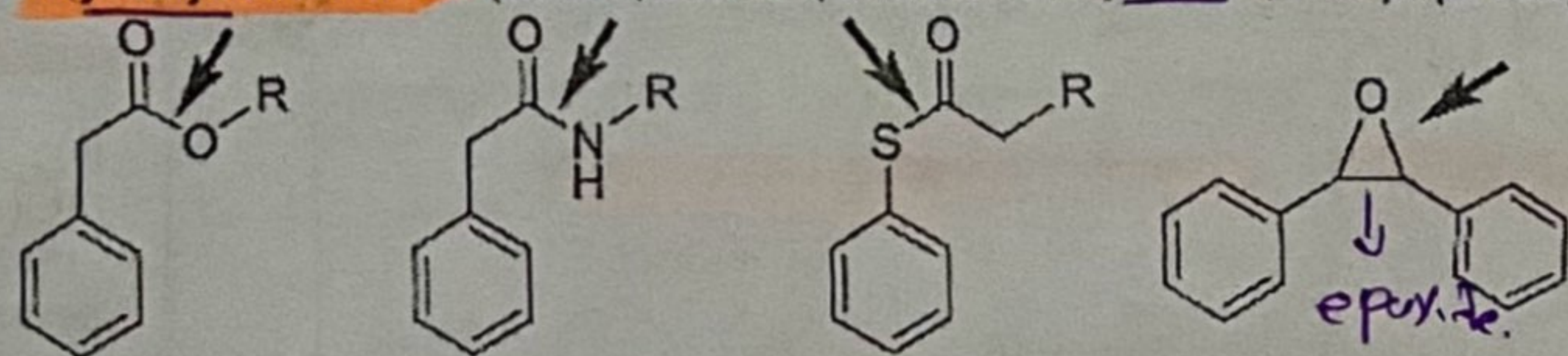
1° alcohol → aldehyde → carboxylic acid.

Reductions: (ketones, double bonds, nitro and azo compounds, sulfoxides and N-oxides, disulfides, quinone, dehalogenation)



(عند ال double bond نضيف Hydrogen — azo — غير موجود بجسم الانسان)

Hydrolytic reactions (esters, amides, thioesters, epoxides, and peptides) — كسر ال ester



كسر ال ester او حول من amide.

* مراجعة of oxidation: اضافة اوكسجين او ازالة هيدروجين

1° alcohol → aldehyde → carboxylic acid
2° → Keton.
3° → مابصير oxidation.

* oxidation :- you add oxygen or remove hydrogen (ازالة dehydrogenas enzyme)
* reduction :- you remove oxygen or you add hydrogen → (azo reductase) اسم الانزيم

* طلعوا هاي للفهم بس :- بيكون واحد مع inflamtory بال GIT وبدي هاد الدواء يوصل intestine فبعطي دواء antiinflammatory / anti bacterial بدي هدول الدوائين مابصيرلهم اشي بالمعدة بدي يوصل للintestine فبربط هدول الدوائين برابط azo compound.

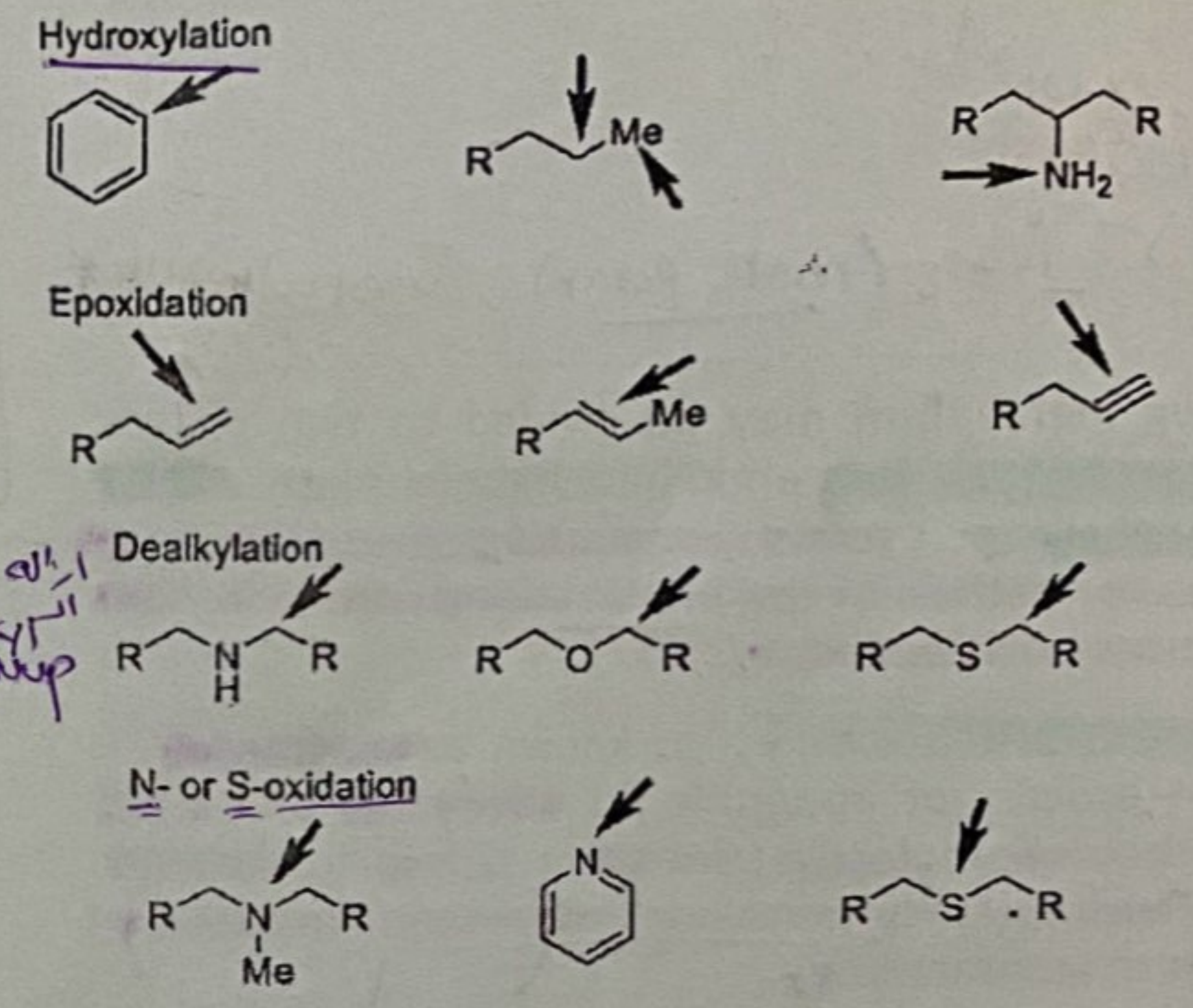
← فبوصل هاد الدواء للامعاء بتكسر الانزيم الرابطة هاي عن طريق اضافة الهيدروجين وبصير عندي دوائين

* ال phase 1 كيميائياً تتكون من (oxidation)
hydroxylation / dealkylation / deamination

OXIDATION

double bond تتحول epoxide

- Oxidation is the most important drug-metabolizing reaction.
- Phase I metabolism is largely an oxidative process.
- Various oxidative metabolisms are hydroxylation; oxygenation at carbon, nitrogen, or sulfur atoms; N-dealkylation or O-dealkylation, oxidative deamination, etc.
- Hydroxylation is a prevalent oxidation process for Phase I metabolism.



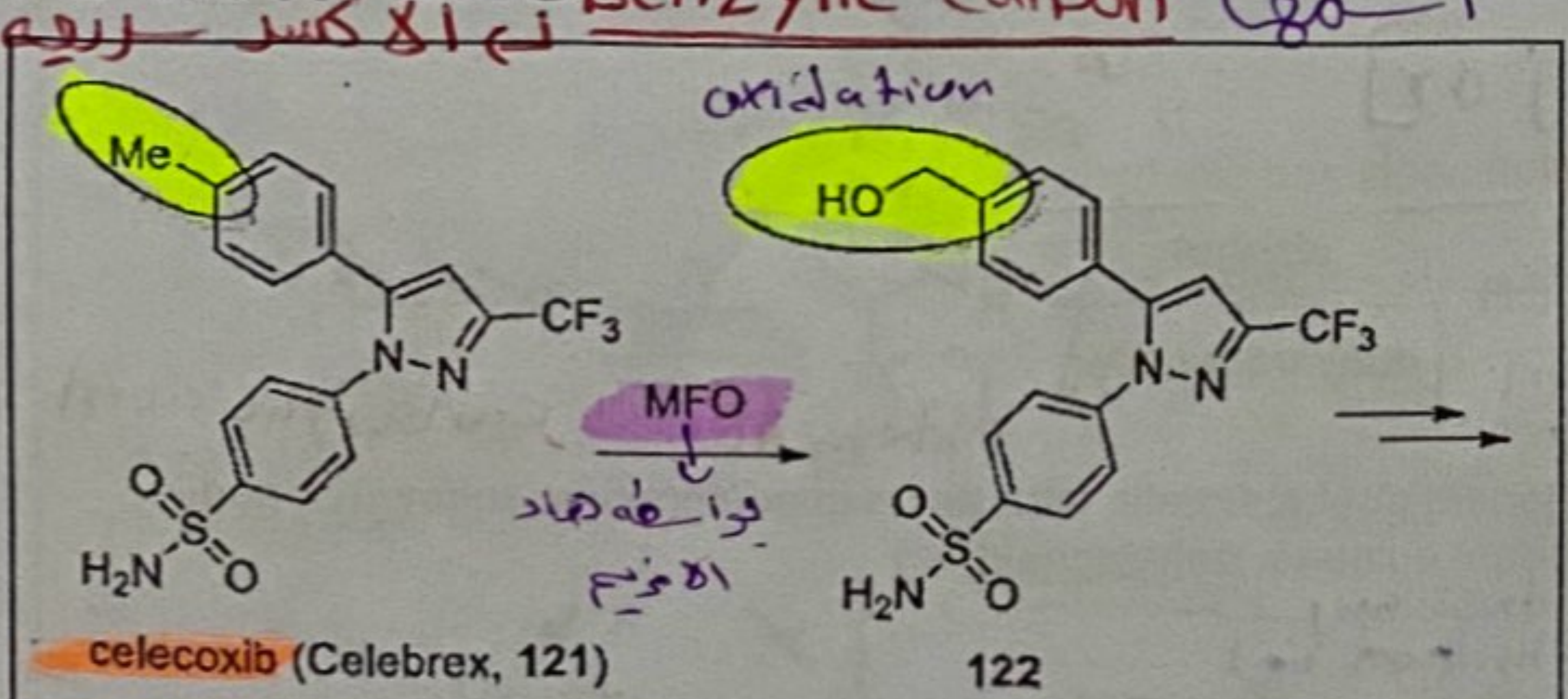
شرح السلايد اللي قبل

* كيف يظهر ال aspirin بالبول؟
- إذا فحصنا بول المريض رح يطلع عندي (glucuronidation derivative)

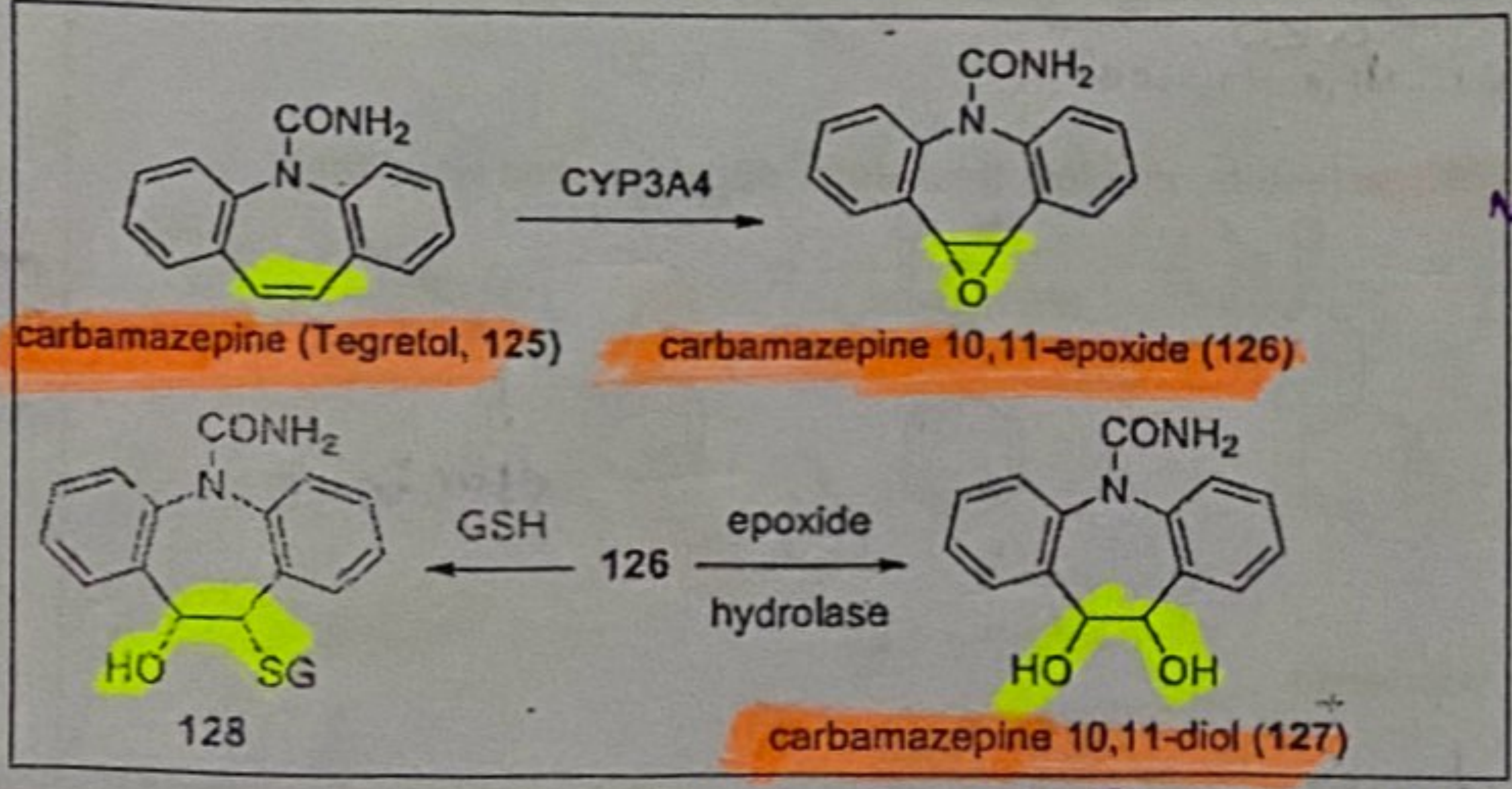
* المستقلبات بتطلع معنا بالبول ويتم فحصها عن طريق جهاز / Gas Chromatography

EXAMPLES

* الكربون الي ع aromatic ring اسمها benzylic carbon



celecoxib (Celebrex, 121) 122

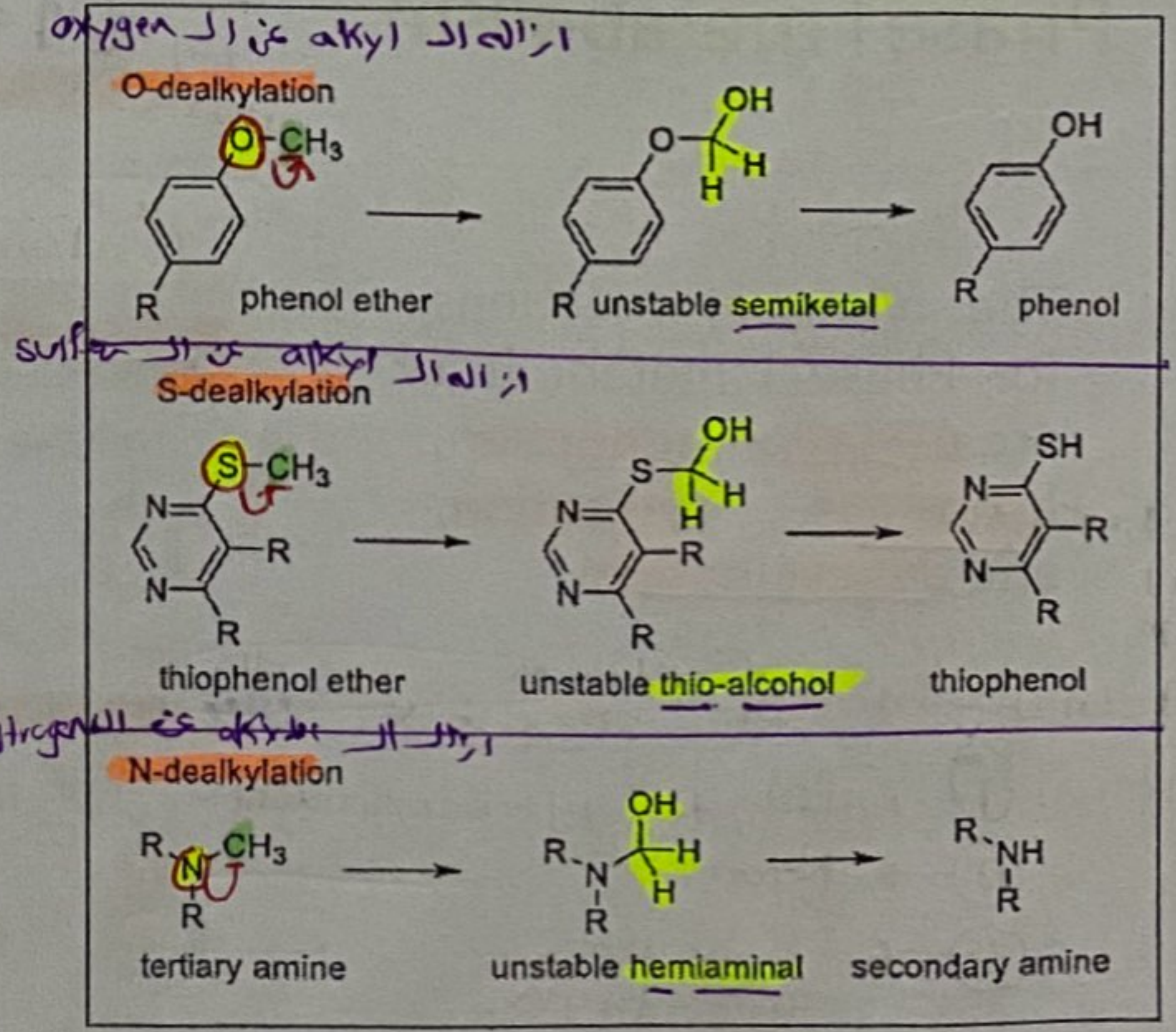


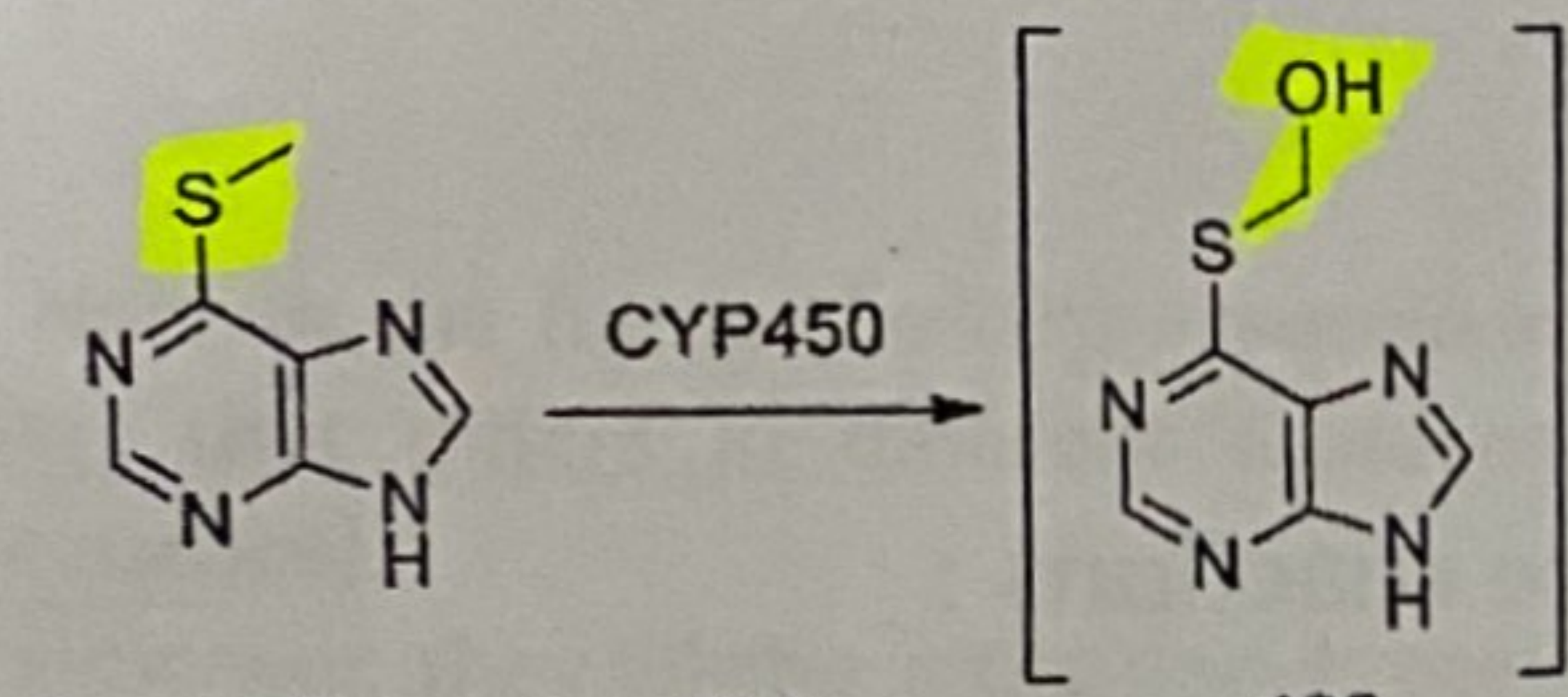
carbamazepine (Tegretol, 125) carbamazepine 10,11-epoxide (126)

128 carbamazepine 10,11-diol (127)

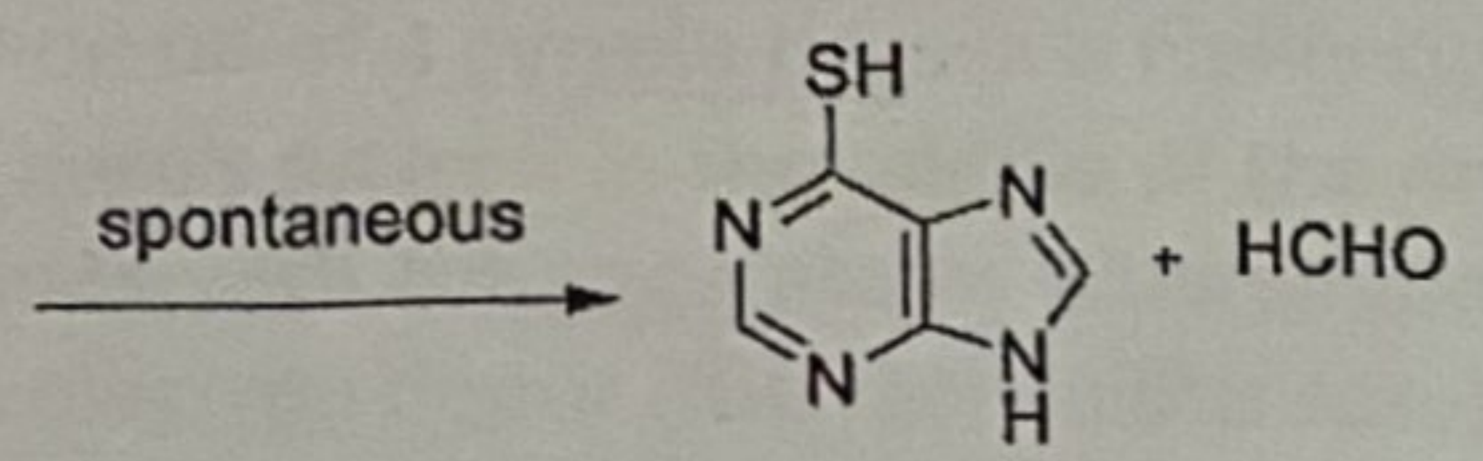
*Note → double bond تتحول epoxide (مش stable)

Dealkylation (إزالة) أحد أنواع الأكسدة

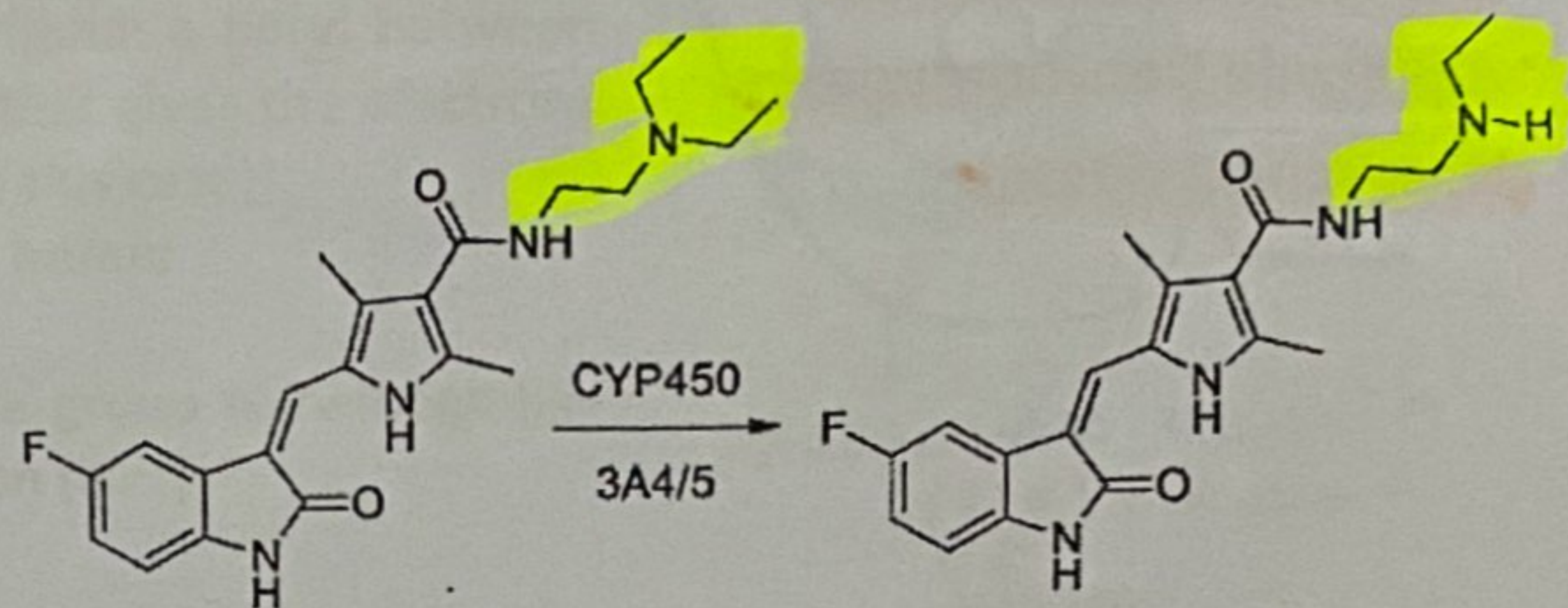




6-methylthiopurine (**134**) **135**



6-mercaptoopurine (**136**)



sunitinib (Sutent, **132**) SU-12662 (**133**)

aromatic ring / alcohol لـ oxidation بالعادة بتعمل mixed / benzilic carbon مش functional group معينة.

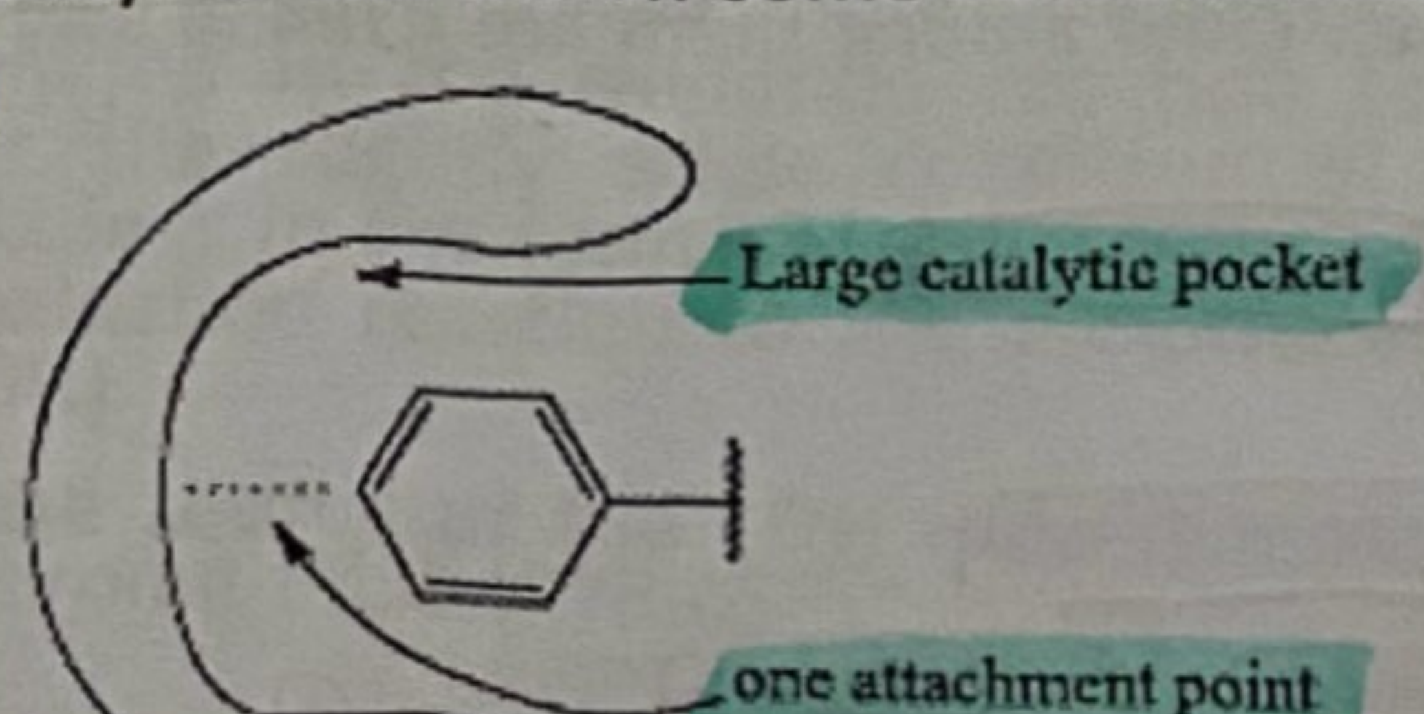
* تحفيض الـ drug والـ toxic

- Oxidation probably is the most common reaction in xenobiotic metabolism.
- Hydroxylation is performed mainly by group of metabolic enzymes that are found in the liver mainly.
- These hepatic enzymes are called **Mixed-function oxidases** (MFO) (1) / **Microsomal oxidases** or (2) **Cytochrome P450 (CYP450) Enzymes.**

غنية بالـ oxidases enzyme → microsomal هاد الـ شي مش موجود بجسم الإنسان * باختبرها بأخذو الكبد ويعملوا عليه homogenize بطلع Microsomal

- They can oxidize various substrates in the same way; they're not 'substrate-specific'. This property is due to having large catalytic pockets (no hindrance) and they can attach or handle their substrate in a single attachment (having multiple attachment sites means the enzyme can act on some substrates but not others).

لانه هو بقدر يعمل oxidation لـ functional group كثير.



يكفي بس one attachment حتى يصير له oxidation داخل هاد الانزيم.

يدخل بسهولة لأنه (large)

This low number of attractive interactions leads to low affinity, (low specificity,) no selectivity, and slow turnover. Therefore, they're slow rate enzymes

* المشكلة انه هاي الانزيمات بتاخذ وقت بعملية الـ (oxidation) فرح يكون عندك slow rate of metabolism

- Other metabolic enzymes involved in Oxidative reactions :
- **flavin-containing Monooxygenases**
- **Monoamine Oxidases**
- Alcohol Dehydrogenases
- Aldehyde Dehydrogenases
- Xanthine Oxidase

Cytochrome P450 (CYP450) Enzymes

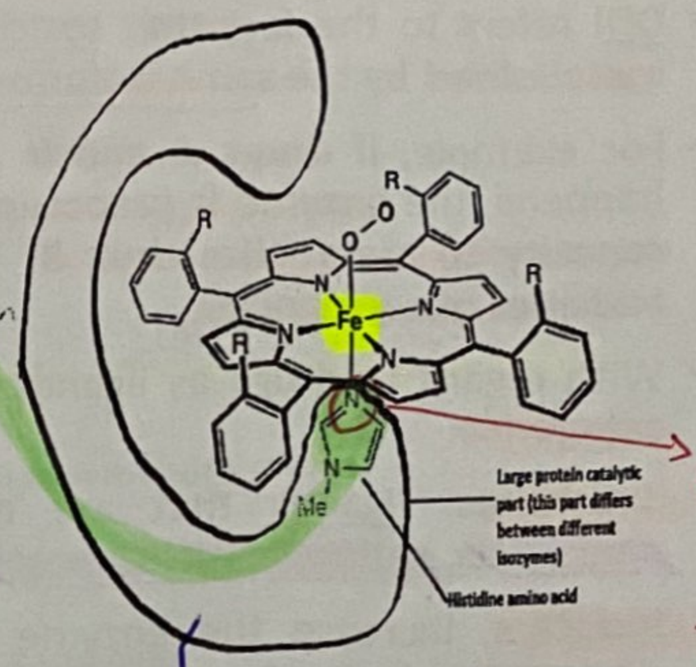
يتم استقلاب الادوية عن طريق :-

- Drugs are metabolized mostly by a class of enzymes called cytochrome P450 (CYP450) enzymes. they belong to a general class of enzymes called the **monooxygenases.**
- They are so named because they are bound to membranes within a cell (cyto) and contain a heme pigment (chrome and P) that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide.
- CYP450 enzymes are a superfamily of 18 heme-containing enzyme families, which may be further divided into 43 subfamilies and more than 200 CYP450 isoforms. Chief among them are **CYP450 3A4** and **2D6.** اهم شي
- CYP 3A4 carries out biotransformations of the largest number (~50%) of drugs.
- Other important CYPs are 1A2, 2C9, 2C19, and 3A5. تحفظ الجدول معنى
- In all, these six CYP enzymes are responsible for metabolizing 90% of drugs.
- In addition to the liver these isoforms are expressed in the intestine and the kidney too.
- Inhibitors of CYP450 3A4: erythromycin (1), clarithromycin (2), verapamil (3), ketoconazole (4), itraconazole (5), diltiazem (6), and a constituent of grapefruit juice (7): responsible for unwanted interactions with many drugs.

مسؤولين عن كثير تفاعلات غير مرغوب بها.

- Note in the figure the large protein catalytic part; this is the part that differs in different oxidases (different amino acid sequence).
- However, they **all share the non-protein part (heme cofactor)**
- As you can also see the **porphyrin ring** in the catalytic ring; made up of 4 pyrrole rings in a highly conjugated system.
- There's an Iron in the middle of the ring that forms coordinate bonds with Nitrogen atoms [Coordinate bond: a bond between an electron donor (Nitrogen in this case) that gives the electrons to the empty d-orbitals of a metal (Iron in this case)].
- The Iron in the porphyrin ring forms the **heme;**
- **The Iron is in the ferric state** (Fe^{+3}).

A similar molecule that contains a heme group is hemoglobin but the Iron in hemoglobin is a ferrous iron (Fe^{2+}).



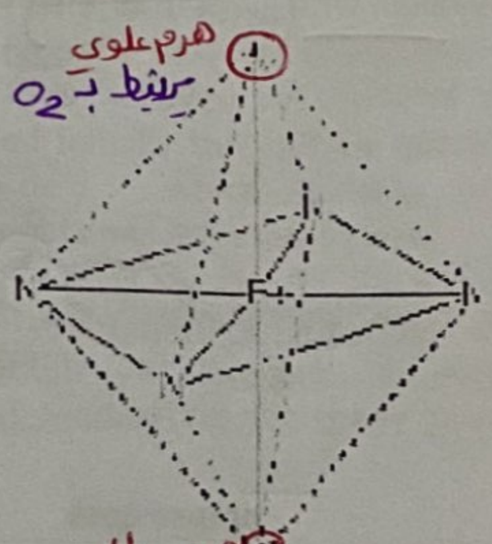
ال imidazole ring مربوط بـ Fe

*Catalytic domain
(a.a) تتكون من
هو Histidine
لأنه يتميز بوجود (imidazol ring) في تركيبه.

(Coordinate) روابط 6 بشكل ← Fe^{2+} / Fe^{3} *سواء كان
⇒ bipyramidal system

- The Iron (whether a ferrous or a ferric ion) can form up to **6 coordinate bonds** in a bipyramidal system as you can see in the figure.
- In the porphyrin ring the Iron forms 4 bonds with the Nitrogen atoms in the pyrrole ring so that means there are two bonds left for the Iron to form:
- - One of the two bonds (**the 5th bond**) is formed with a Nitrogen atom in the imidazole group found in the amino acid histidine; this bond is responsible for holding this porphyrin ring structure in the catalytic pocket of the oxidase enzyme.
- The **6th bond** is formed between the Iron and **Oxygen molecule (O_2)**. This oxygen is very important since it's the oxygen atom that is donated in the oxidation reaction (act as oxidizing agent). Under the slightly acidic condition of the liver, the oxygen molecule is in the form of (—O—OH) and this –OH is donated in the oxidation reaction to the metabolized compounds to form (R—OH).
- **So, the source of the –OH** is the oxygen bound to the Iron in cytochrome P450 (CYP-450).

Bipyramidal System.



$$\text{Drug—H} + \text{O}_2 + \text{NADPH} + \text{H}^+ \xrightarrow[\text{enzymes}]{\text{Cytochrome P450}} \text{Drug—OH} + \text{NADP} + \text{H}_2\text{O}$$

تحول الـ hydrogen الى ع إلدواء الى Hydroxyl وهذه تابعة لـ Cytochrome P450

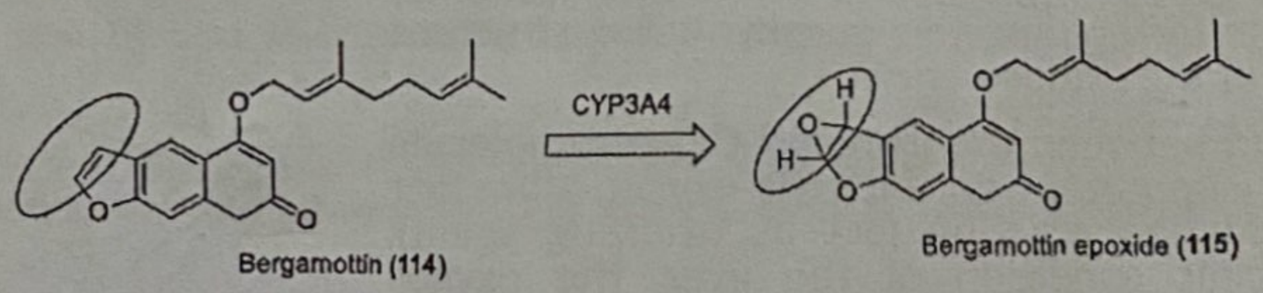
(H) يضيف الـ O_2 باستبدال

Drug–Drug Interactions

- DDI refers to the fact that toxicity often ensues when two co-administered drugs are metabolized by the same isoform of CYP450 enzymes.
- For example, if drugs A and B are both metabolized by CYP450 3A4, as it so often happens, the enzyme is preoccupied by metabolizing drug A, it no longer possesses the capacity to metabolize drug B. Without the benefit being biotransformed, untoward toxicities often manifest
- With regard to drugs as ligands for CYP450 enzymes, they may be divided into three categories:

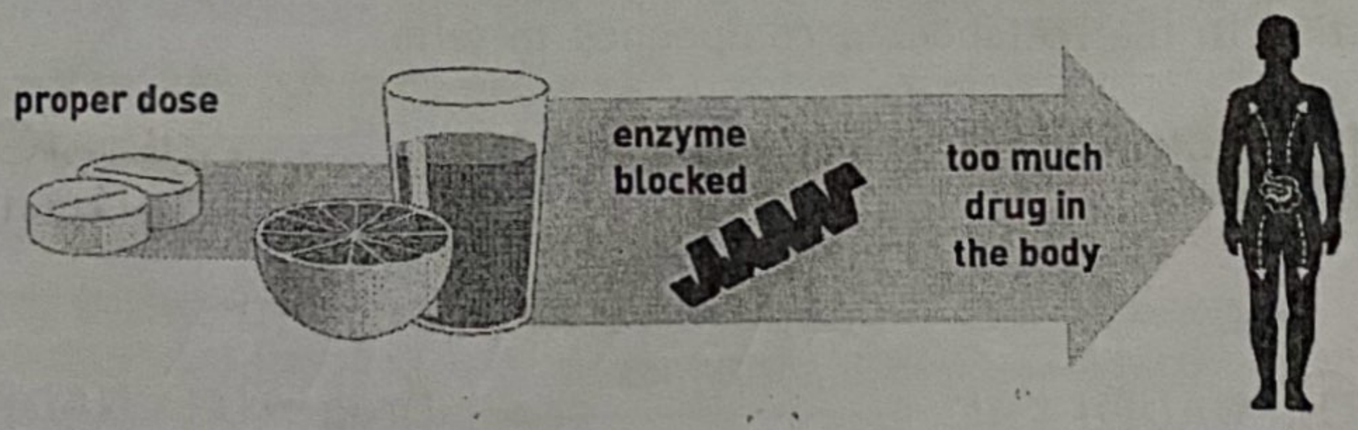
- Substrates: ligands that are metabolized by the enzymes. Examples: macrolide antibiotics, antifungal ketoconazole and grapefruit juice.
- inducers, increase the enzyme activity by increasing enzyme synthesis. Examples: rifampicin, phenytoin, carbamazepine and phenobarbital
- inhibitors: slow down the metabolism of substrates leading to an increased drug effect (reversible inhibitors and irreversible inhibitors). Examples: fluoxetine, ketoconazole, grapefruit

- Drinking a glass of juice in the morning is good for you. But if you take your medicine with it, you should be aware of *the grapefruit juice effect*.
- Grapefruits contain furanocoumarin derivatives that are rapid, potent, mechanism-based inhibitors (MBIs) of intestinal CYP3A4. Its major ingredient bergamottin is oxidized by CYP3A4 to bergamottin epoxide. Bergamottin inhibits CYP3A4 via protein modification. It also inhibits CYP1A2, 2A6, 2C9, 2C19, 2D6, and 2E1. Therefore, when a drug is taken with grapefruit juice, its bioavailability is frequently boosted.



Bergamottin (114)

Bergamottin epoxide (115)



Oxidative Reactions

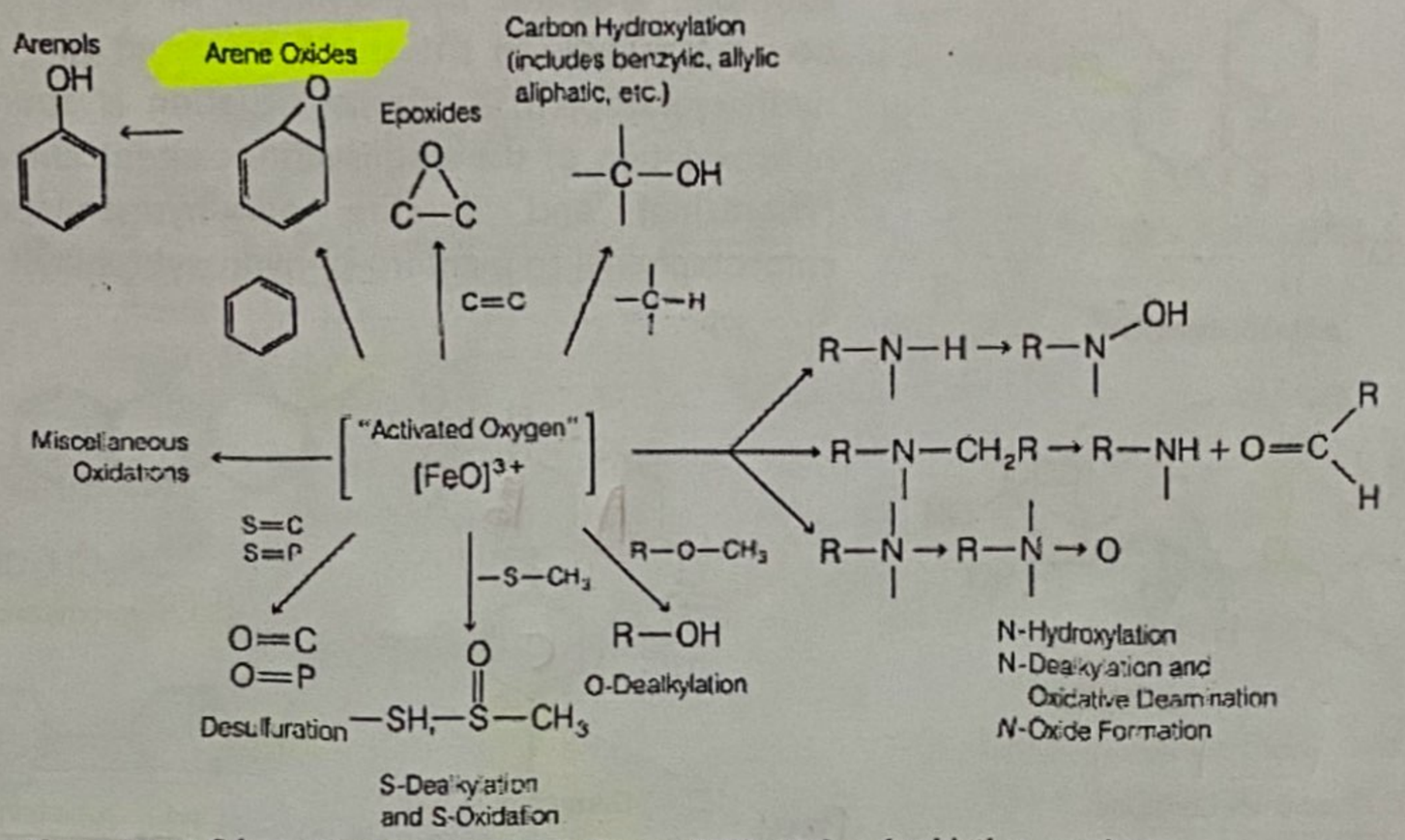


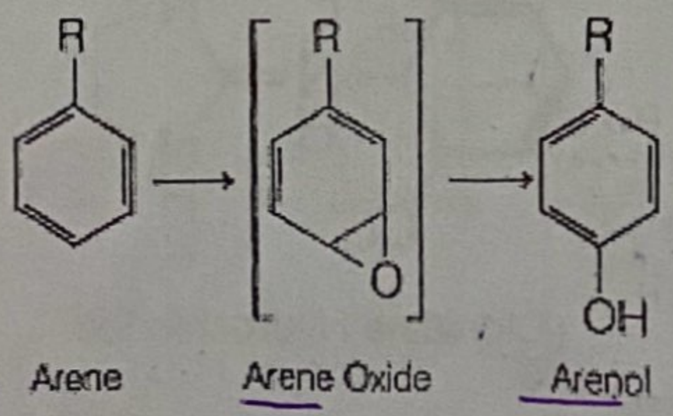
Figure 3.3 • Schematic summary of cytochrome P450-catalyzed oxidation reactions. (Adapted from Ullrich, V.: Top. Curr. Chem. 83:68, 1979.)

Aromatic ← OH ← oxidation بصير فيه عندي استبدال H → OH

CH3 methyl ← الكربون ع

benzilic carbon ← oxidation ← الكربون ع

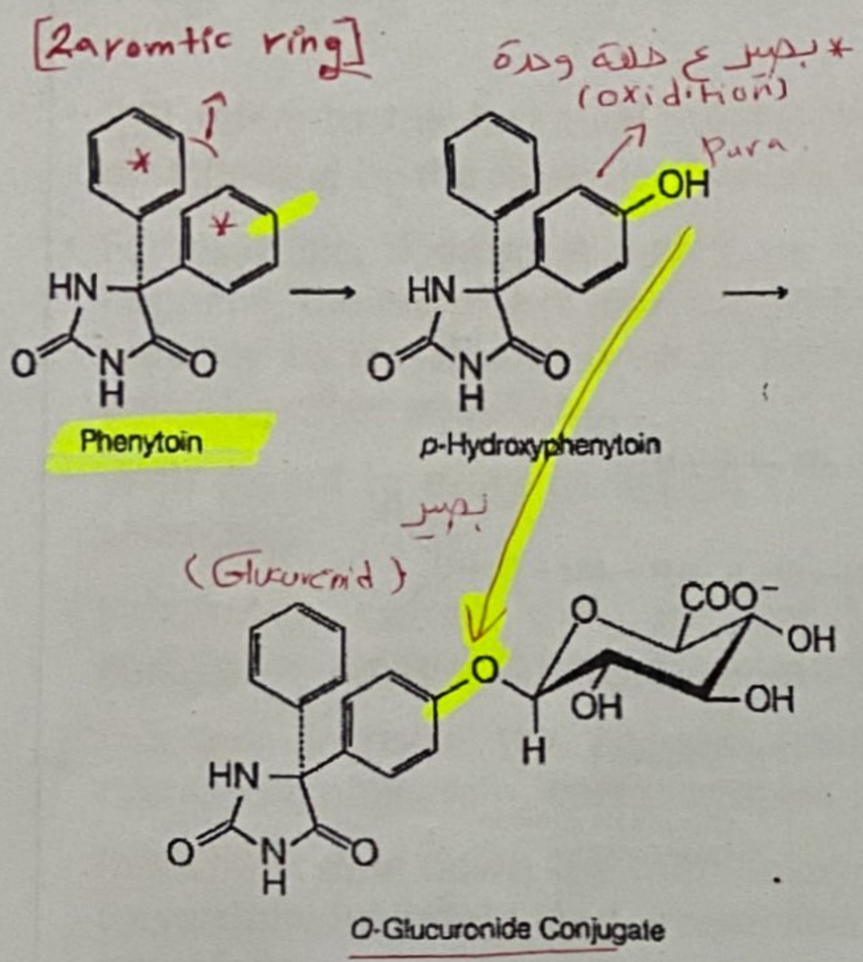
Aromatic oxidation



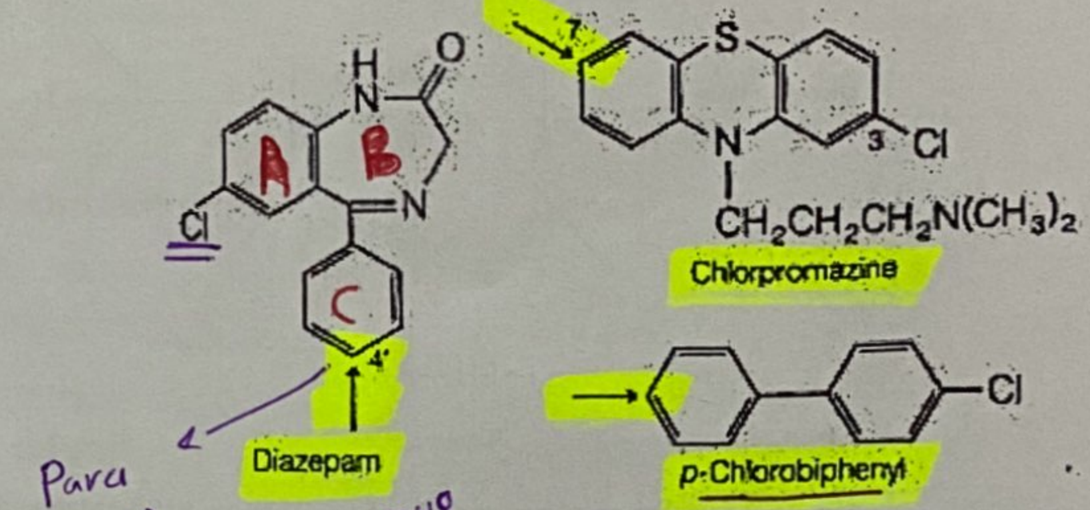
The term **aromatic hydroxylation** refers to the mixed functional oxidation of aromatic compounds (arenes) to their corresponding phenolic metabolites (arenols). It is believed that almost all aromatic hydroxyl reactions proceed initially through an epoxide intermediate called "arene oxide" which quickly and spontaneously rearranges to the arenol product in most cases.

Most foreign compounds containing aromatic moieties are susceptible to aromatic oxidation. In humans, aromatic hydroxylation is a major route of metabolism for many drugs containing phenyl groups.

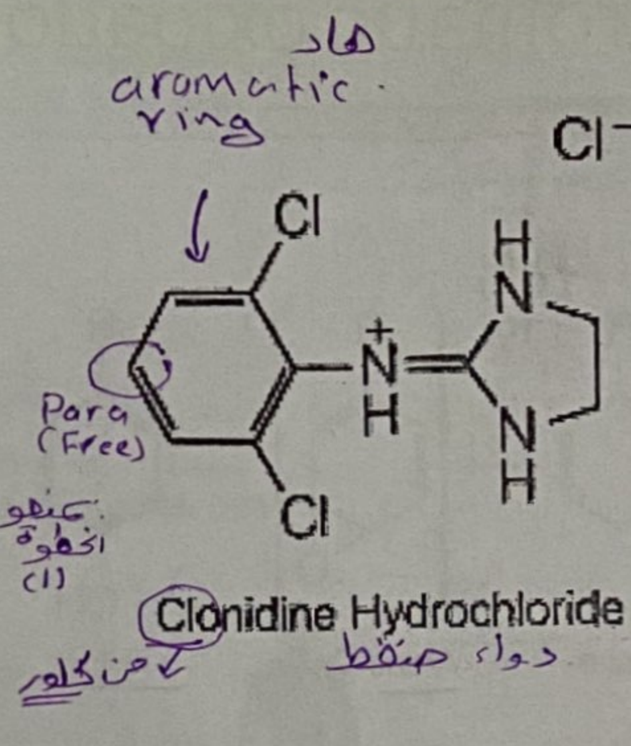
Important therapeutic agents such as propranolol, phenobarbital, phenytoin- , atorvastatin, 17α- ethinylestradiol and S- warfarin undergo extensive aromatic oxidation. In most of the drugs just mentioned, hydroxylation occurs at the para position.



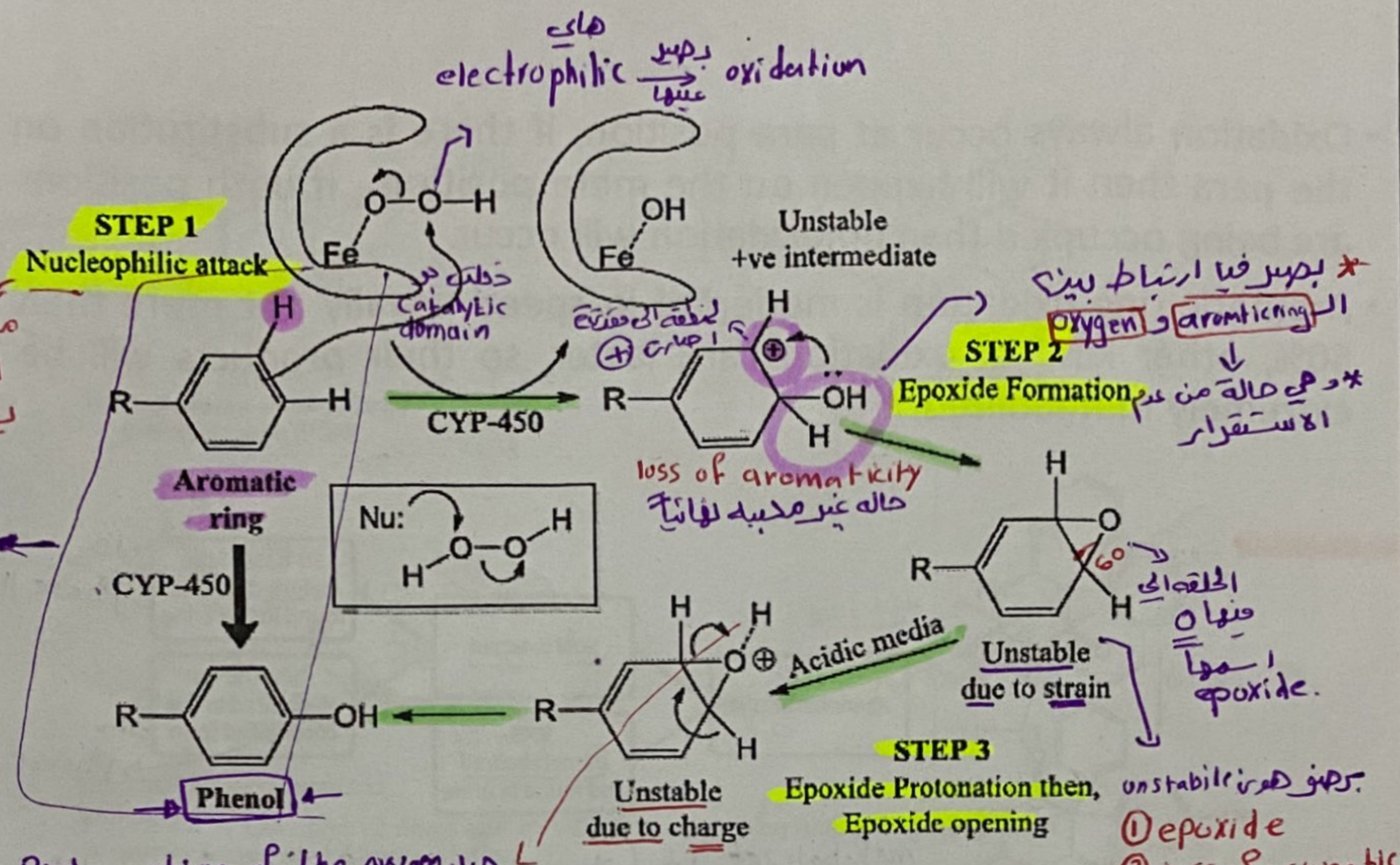
In compounds with **two aromatic rings,** hydroxylation occurs preferentially in the **more electron-rich ring**. For example, aromatic hydroxylation of diazepam (Valium) occurs primarily in the more activated ring to yield 4'-hydroxydiazepam. A similar situation is seen in the 7-hydroxylation of the antipsychotic agent chlorpromazine (Thorazine) and in the para-hydroxylation of p-chlorobiphenyl to p-chloro-p'-hydroxybiphenyl.



Often, the substituents attached to the aromatic ring may influence the ease of hydroxylation. As a general rule, microsomal aromatic hydroxylation reactions appear to proceed most readily in **activated (electron-rich) rings,** whereas deactivated aromatic rings (e.g., those containing electron-withdrawing groups Cl, -N+R3, COOH, SO2NHR) are generally slow or resistant to hydroxylation. The deactivating groups present in the antihypertensive clonidine may explain why this drug undergoes little aromatic hydroxylation in humans.



*ح-تجي سؤال عليها بالامتحان.



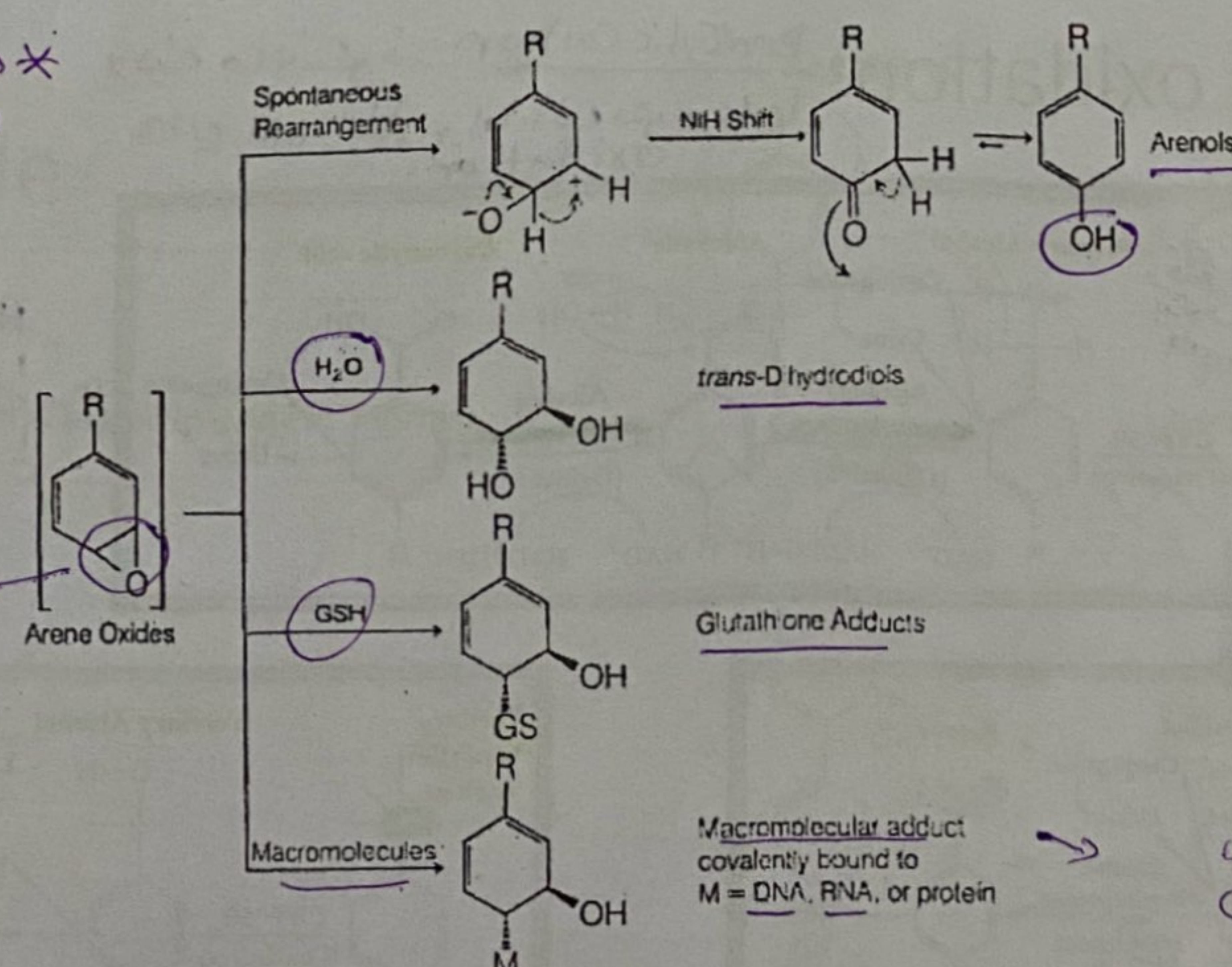
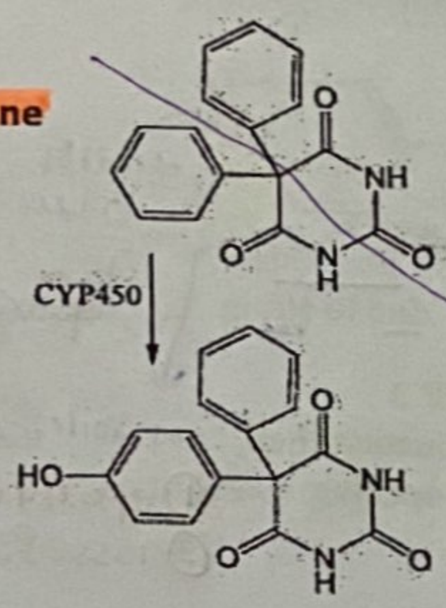
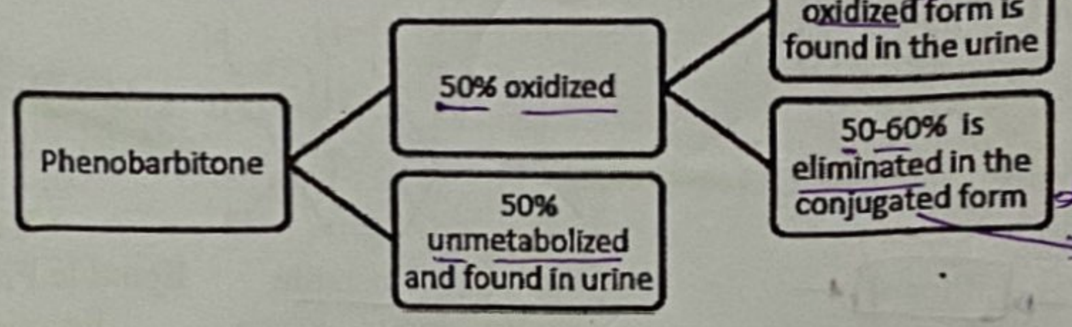


Figure 3.5 • Possible reaction pathways for arene oxides. (Data are from Daly, J. W., et al.: Experientia 28:1129, 1972; Jerina, D. M., and Daly, J. W.: Science 185:573, 1974; and Kaminsky, L. S.: In Anders, M. W. [ed.]. Bioactivation of Foreign Compounds. New York, Academic Press, 1985, p. 157.)

- Oxidation always occur at para position, if there is a substitution on the para then it will happen on the meta position , if both positions are being occupied then no oxidation will occur.
- Aromatic ring oxidation is moderate in speed usually not more than 50%, other kind of oxidations are faster, so their products will be extremely metabolized.

Phenobarbitone





metabolized وضل (phenobarbitone) هيك مريض أخذ
واخذنا عينة البول من بكريفة ← وطلعت
50% ← unmetabolized
50% ← oxidized.

aromatic ring ← aromaticity ← كربونة

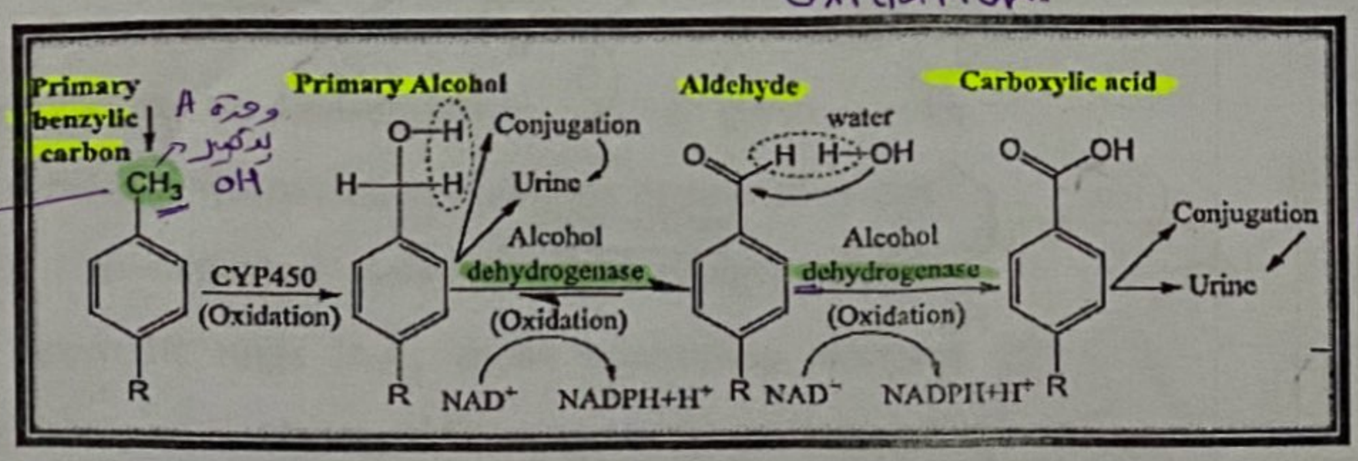
oxidation تصير

2. Benzylic oxidation

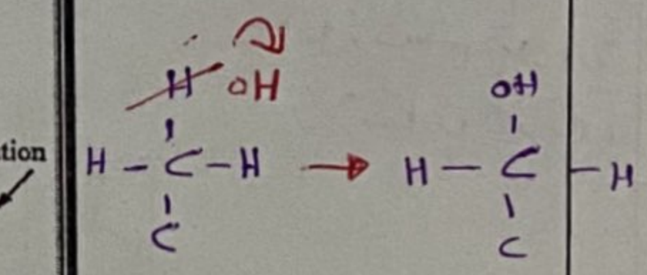
Benzylic Carbon ← وهيك ما بتشوف هاي هي الكربونة اللي بتصير عليها oxidation.

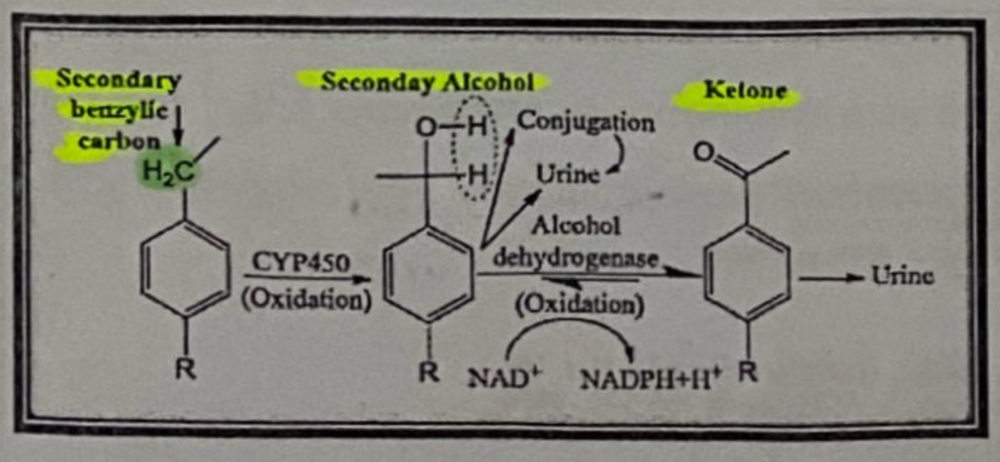
عملية الأكسدة هي إما اضافة O او ازالة H

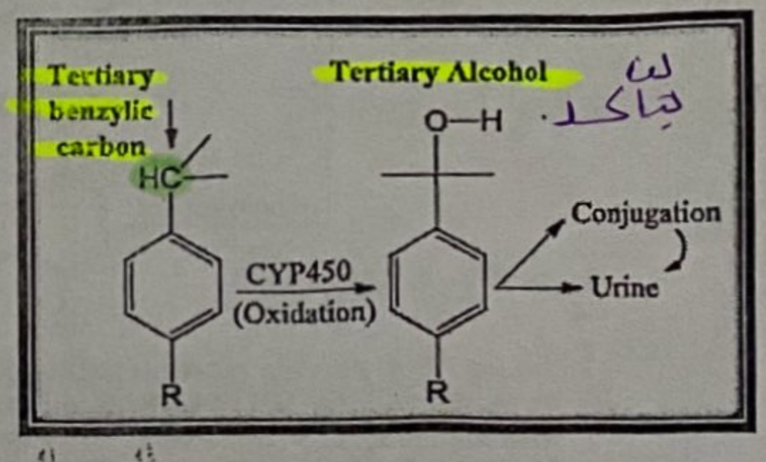
(Benzylic Carbon) ← ال ← aromatic ring بتكون



وحدة A بدكون OH

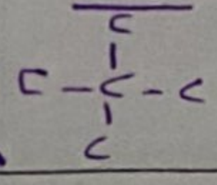


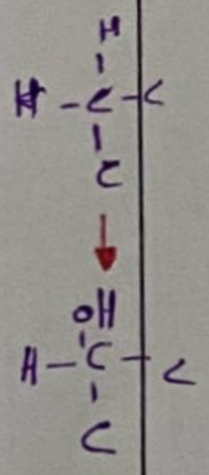


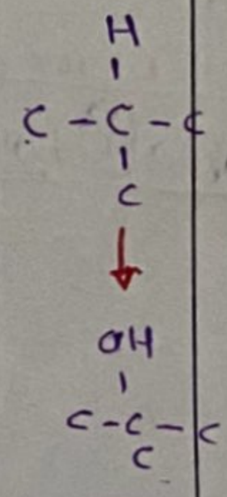


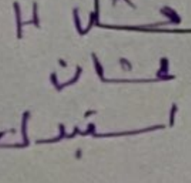
بتاكد.

4° carbon, no oxidation because there is no H to replace (remember that H must exist to replace it with –OH).

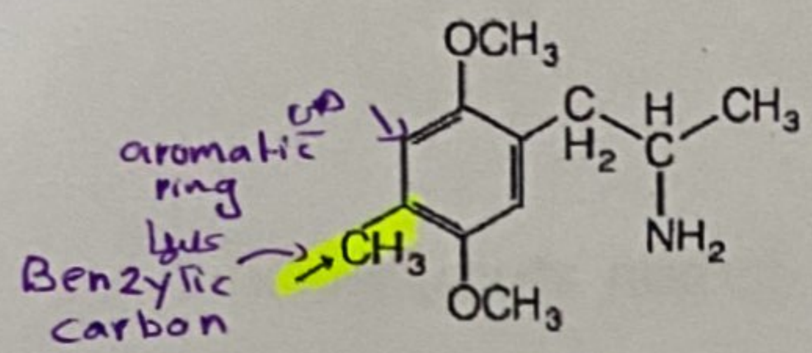




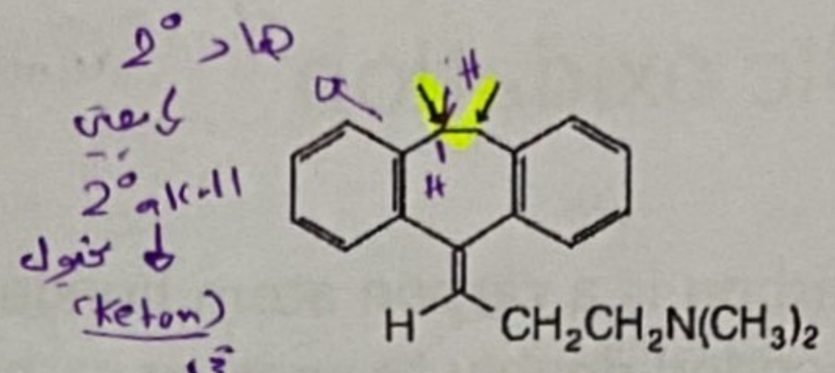




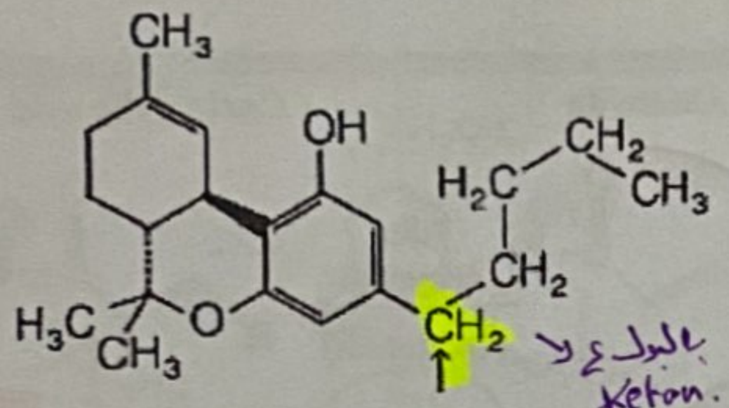
لحتى استبدك



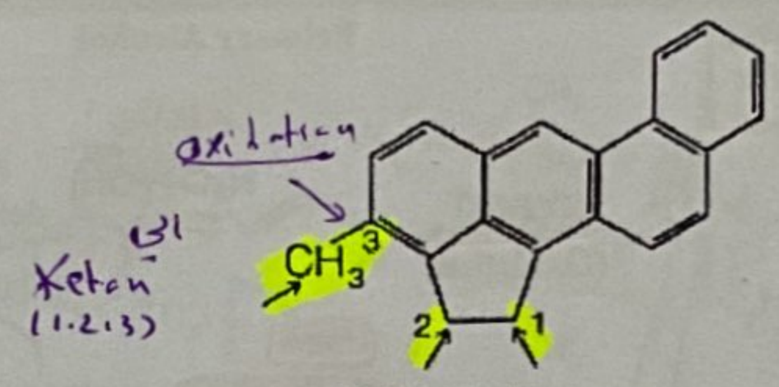
"STP"
1-(2,5-Dimethoxy-4-methylphenyl)
-2-aminopropane (DOM)



Amitriptyline



·Δ^1-Tetrahydrocannabinol



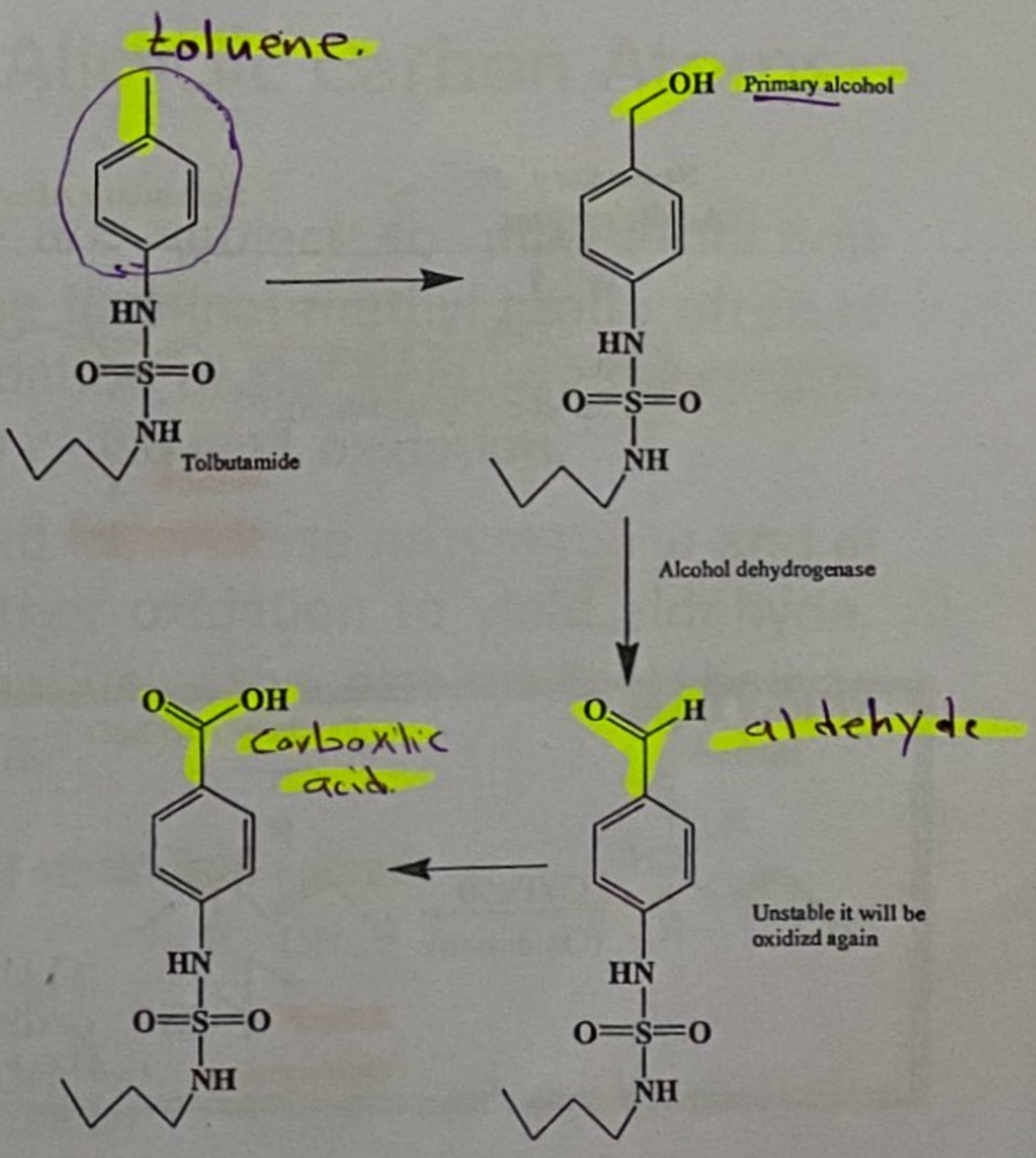
3-Methylcholanthrene

Figure 3.8 • Examples of drugs and xenobiotics undergoing benzylic hydroxylation. *Arrow* indicates site of hydroxylation.

Example

Tolbutamide will be eliminated in urine in 3 forms:

1. Alcohol
2. Carboxylic acid
3. Conjugated

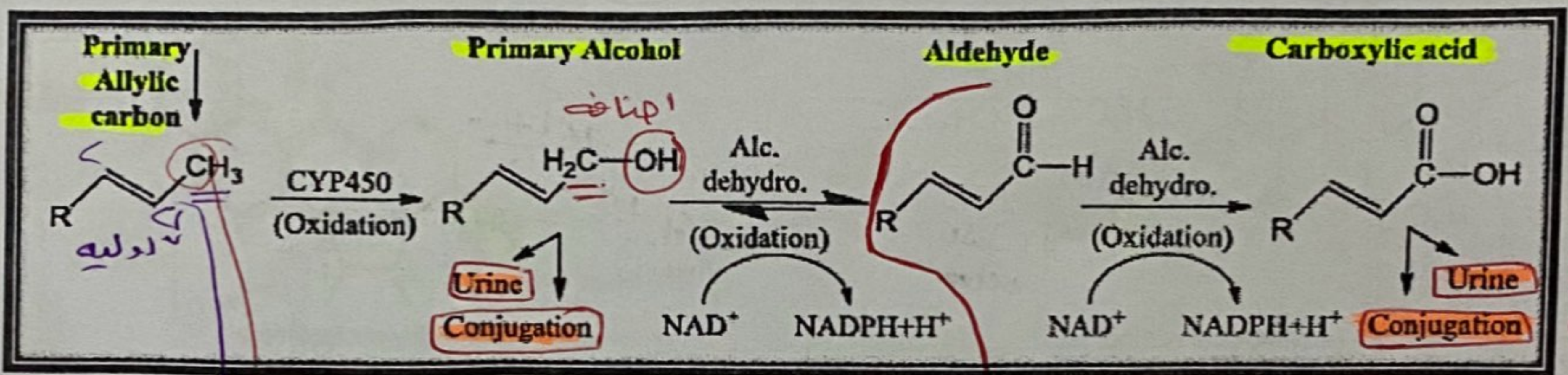


* أسرع كربونة يصير لها oxidation:
*(1) Benzylic carbon *(2) aromatic ring *(3) Allylic oxidation
* كل ما زاد غنى الكربونة بال electrons زاد (oxidation) عليها. (أسرع اشي)

اضافة OH — الكربونة الي ع aromatic ring

3. Allylic oxidation

Allylic carbon is a carbon atom bonded to another carbon atom, which in turn is bonded doubly to another carbon atom
Considered as fast oxidation reaction.

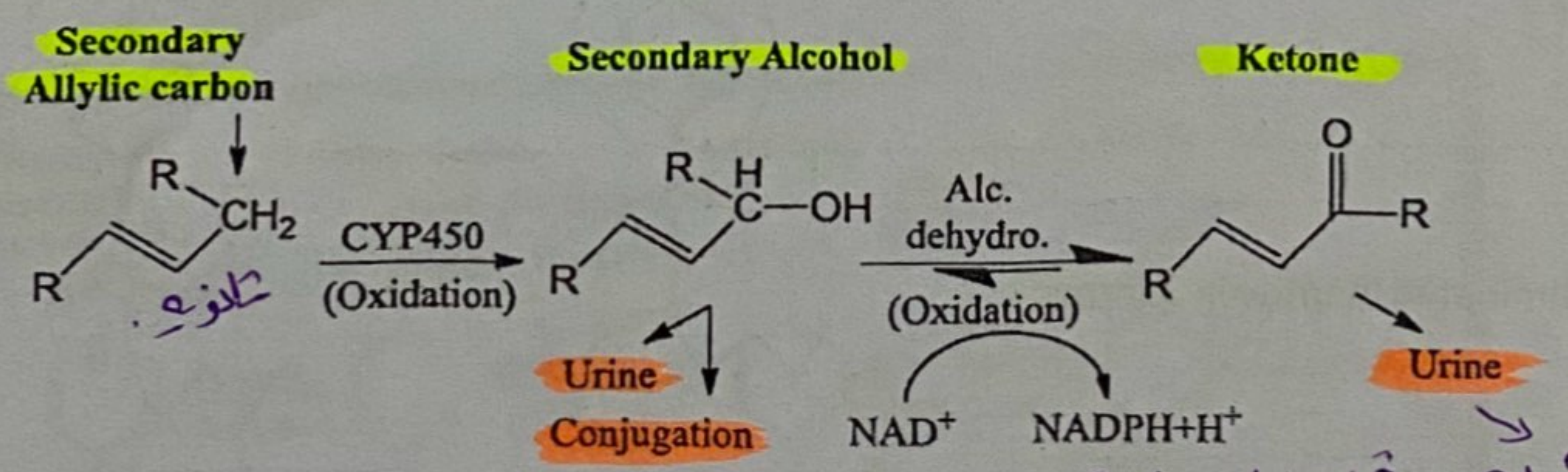


في اي مرحلة بتكون فيها الكحول بيصير في عندي (Conjugation) قوي جدا.

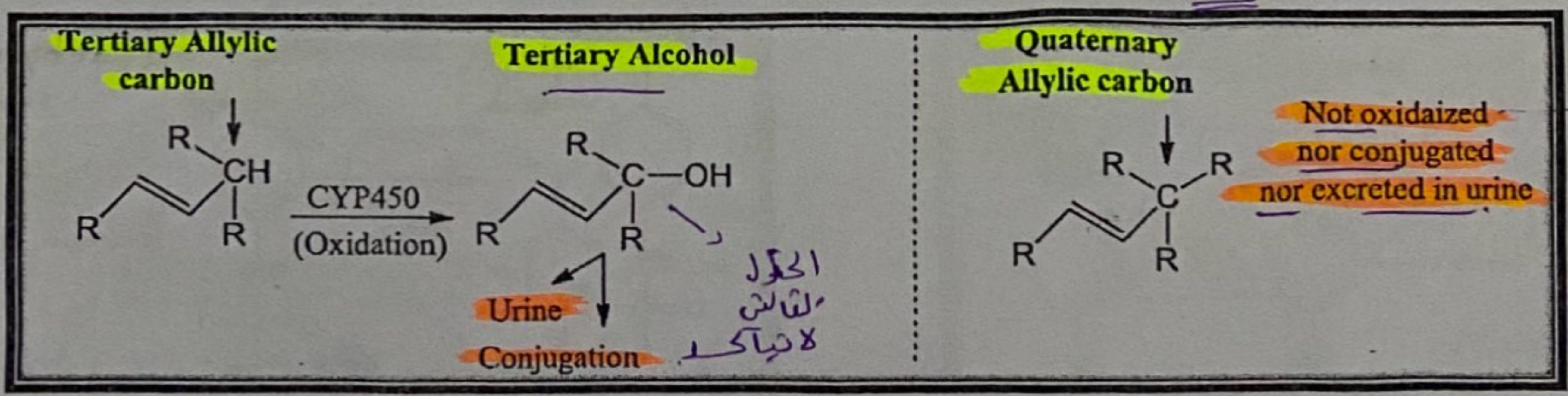
كربونة وكربونة وبينهم double bond. هاي الي عندهم نتحكى عنها Allylic carbon.

* هاد بشكل ما بطلع بال urine لانه مباشرة بصيرلو (oxidation)

هاد ال (carboxylic acid). يا اما بروح بطلع بال urin او بصيرلو (Conjugated)



مش رح يصير في Conjugation لانه فش OH

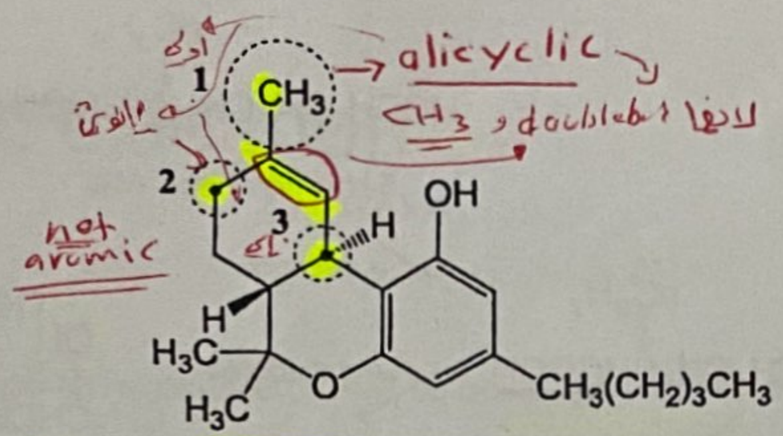


الكحول الثالث لا يتأكسد.

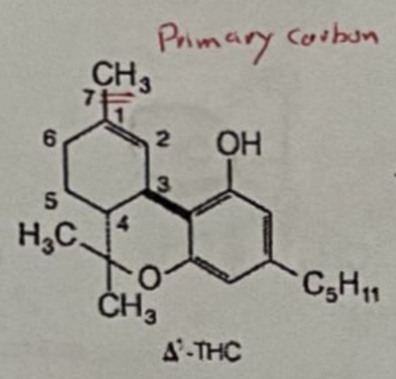
لانه ما في H ع ال C

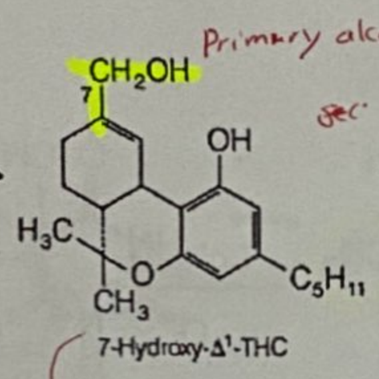
المركب لفعال
* أهم جدًا (الموجود بالكثرة)

attack الـ
major بصير ع
1
بعدها
2
3
(very very minor).

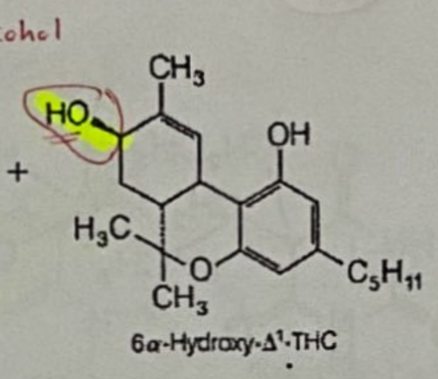


Tetrahydrocannabinol

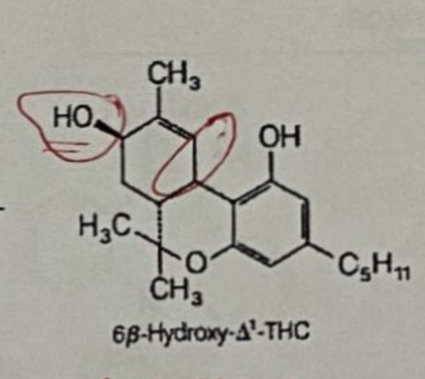




احتمال (1)
(Major)
(بشوفهم بالـ Urin)



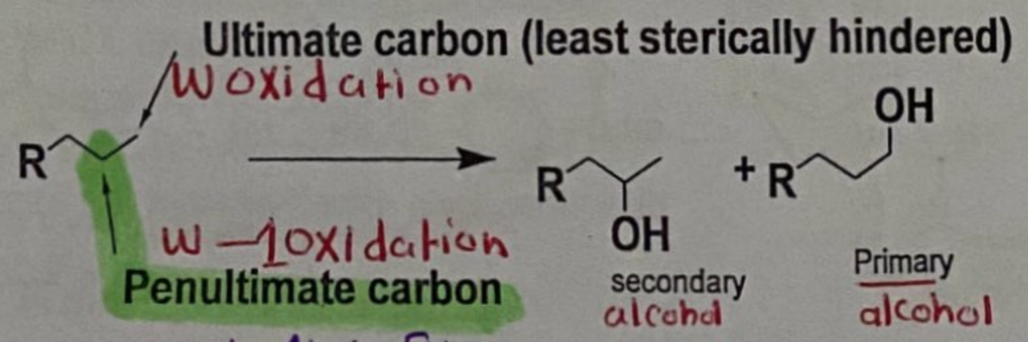
احتمال (2)
بتلاقيهم بشكل هيلف بالـ urine



احتمال (3).
very very minor
(ما بتنحسب)

Oxidation at Aliphatic and Alicyclic Carbon Atoms

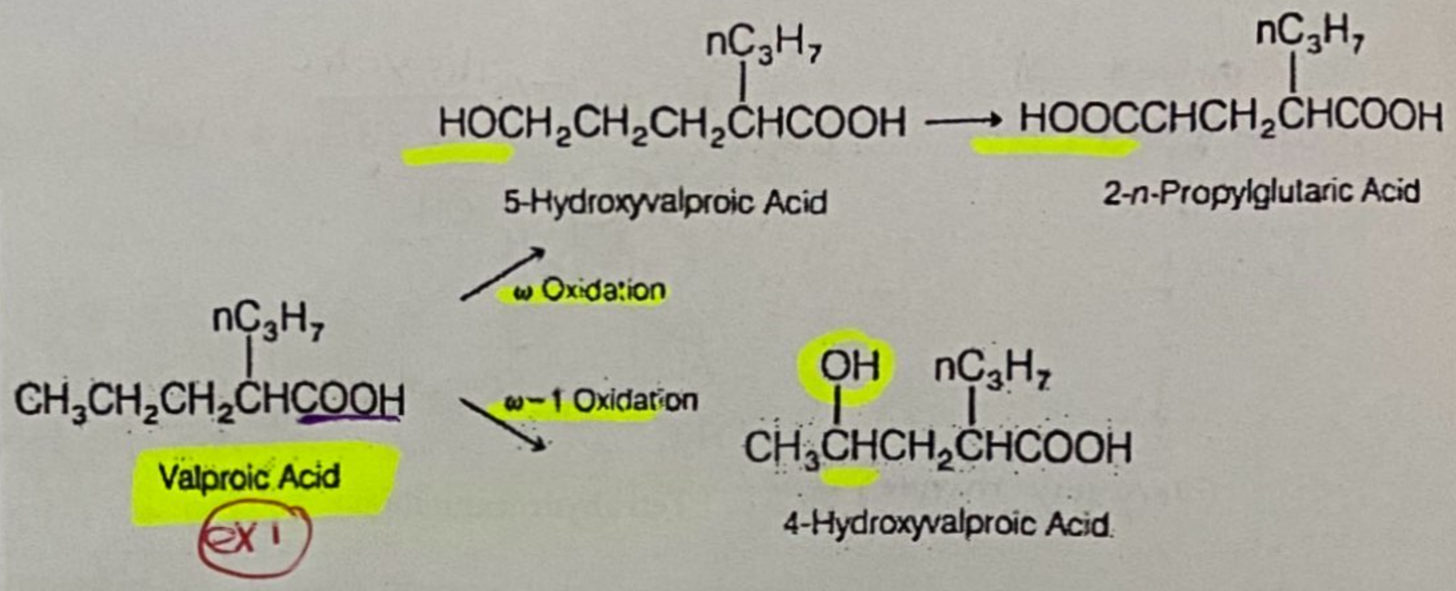
- Alkyl or aliphatic carbon centres are subject to mixed-function oxidation. Metabolic oxidation at the terminal methyl group often is referred to as ω -oxidation, and oxidation of the penultimate carbon atom (i.e., next-to-the-last carbon) is called ω -1 oxidation.
- The initial alcohol metabolites formed from these enzymatic ω and ω -1 oxidations are susceptible to further oxidation to yield aldehyde, ketones, or carboxylic acids. Alternatively, the alcohol metabolites may undergo glucuronide conjugation.



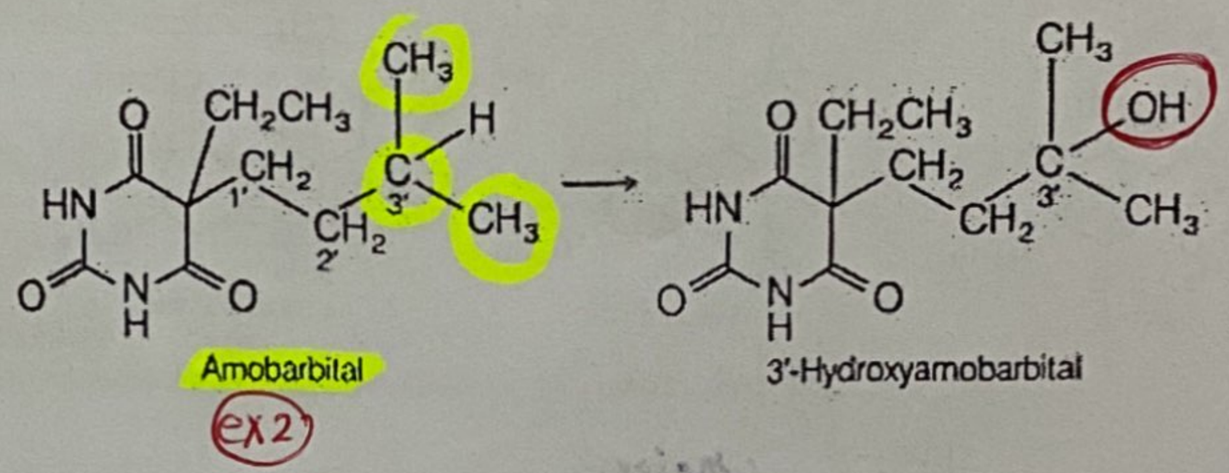
* الكربونة اللي جنب الكربونة الطرفية.

* الـ secondary, primary ممكن يتحولوا زي ما حكينا قبل (conjugation) أو يعملوا

Valproic acid (Anti-seizure; Depakin®)
This drug has a carboxylic acid group so it's readily filtered and actively secreted to be eliminated in the urine unchanged.
It also gets oxidized, around 5%, in a ω and ω-1 oxidation. But mostly is eliminated unchanged.



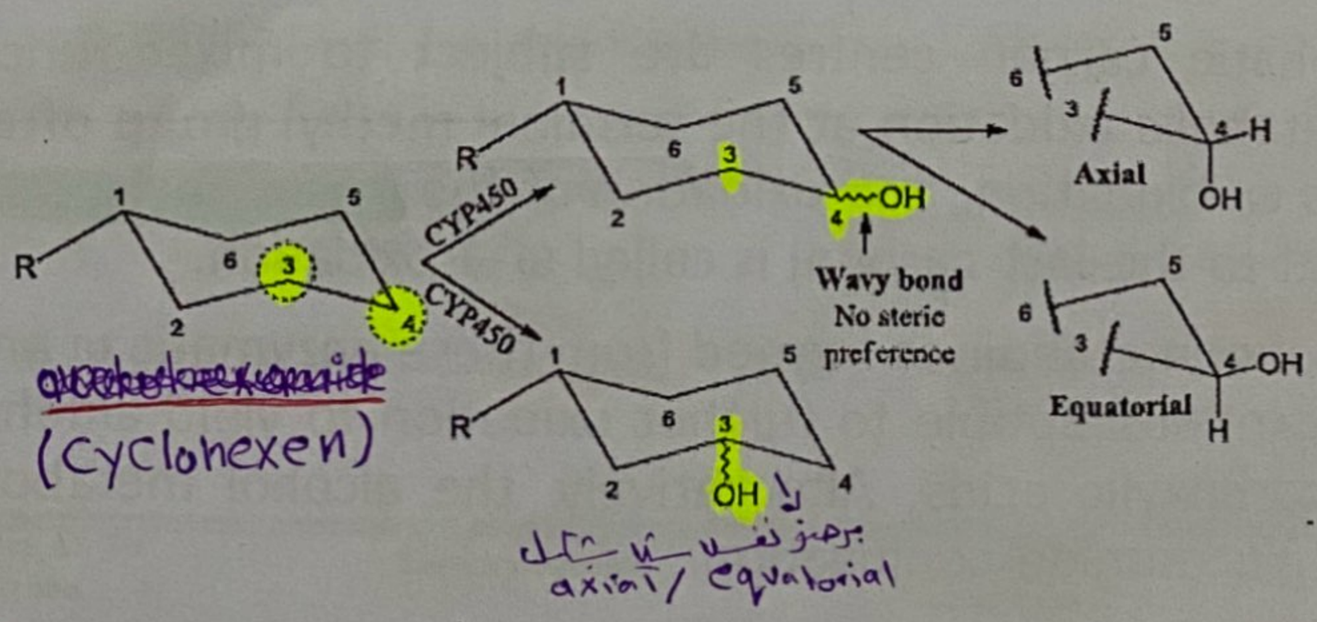
ex1



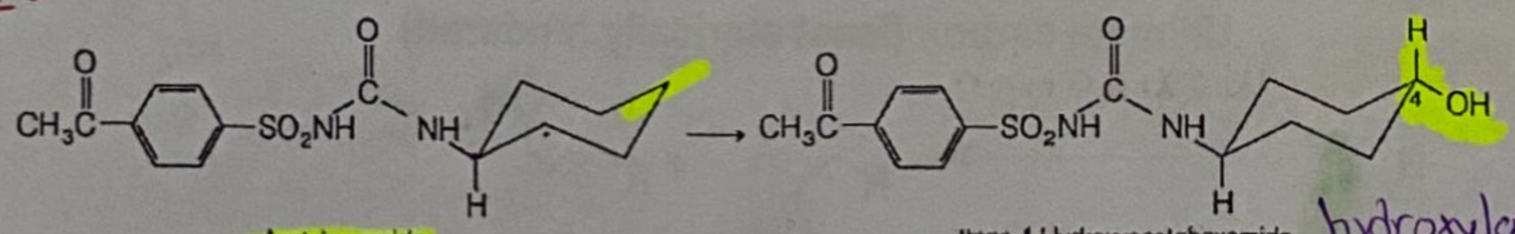
ex2

طلعت مشارع تدخل دهب هيك كيما 3°

سس ← هاي عين مش معدد يا axial أو Equatorial



example :-



ex1

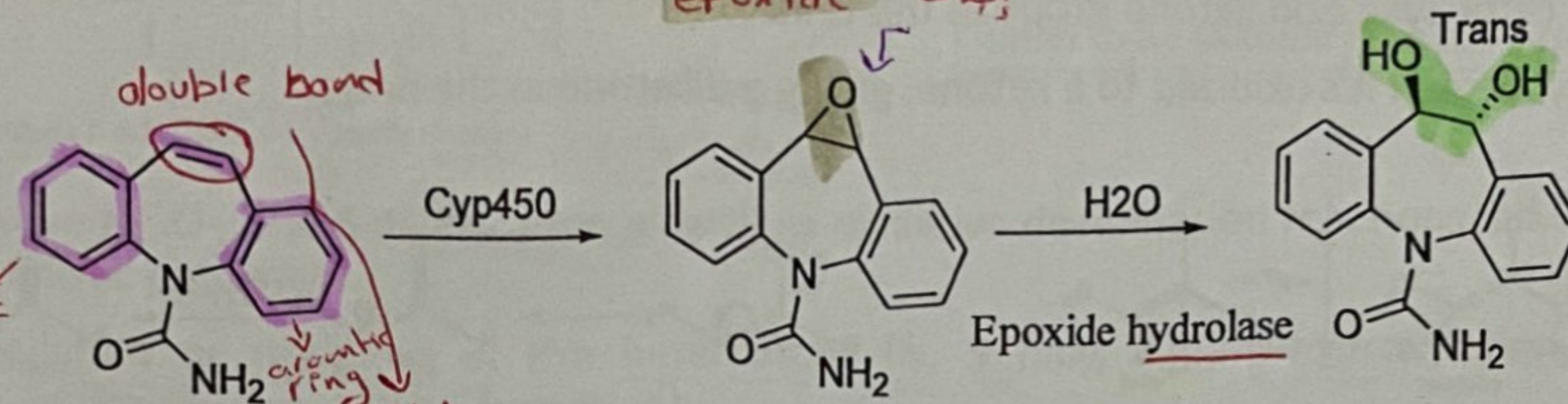
hydroxylation بتكون ع اجو كربونة عشان أفكك

وهاد كيما بكون اسهل كل ما قلت

① Allilic
② Aliphatic
③ Alicyclic
④ double bond oxidation
⑤ aromatic
⑥ benzylic

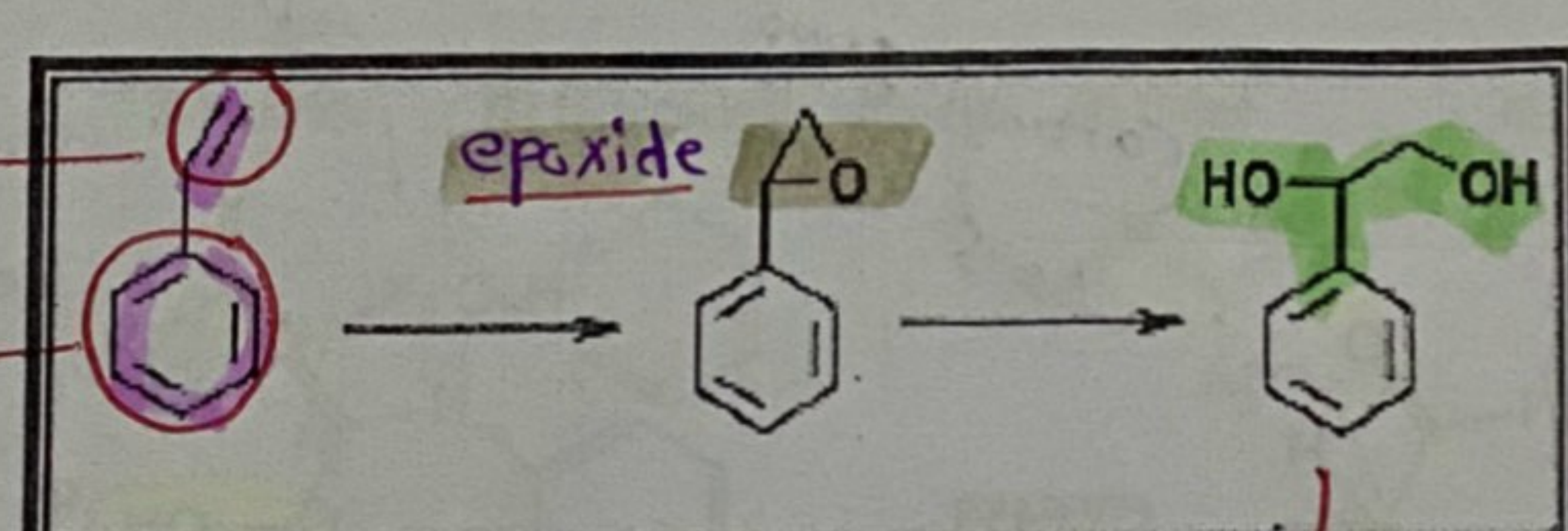
Double bond oxidation

- Alkene epoxidation:
- In order for a double bond to be oxidized it has to be conjugated to at least one aromatic ring
- - Rate is similar to aromatic ring oxidation but slightly higher; still moderate rate
- - Yield 50-60%.



Carbamazipine

Styrene (polystyrene monomer)



What is the fate of this styrene glycol?

(1) Further oxidation by alcohol dehydrogenase on one of the OH or both. It could give:

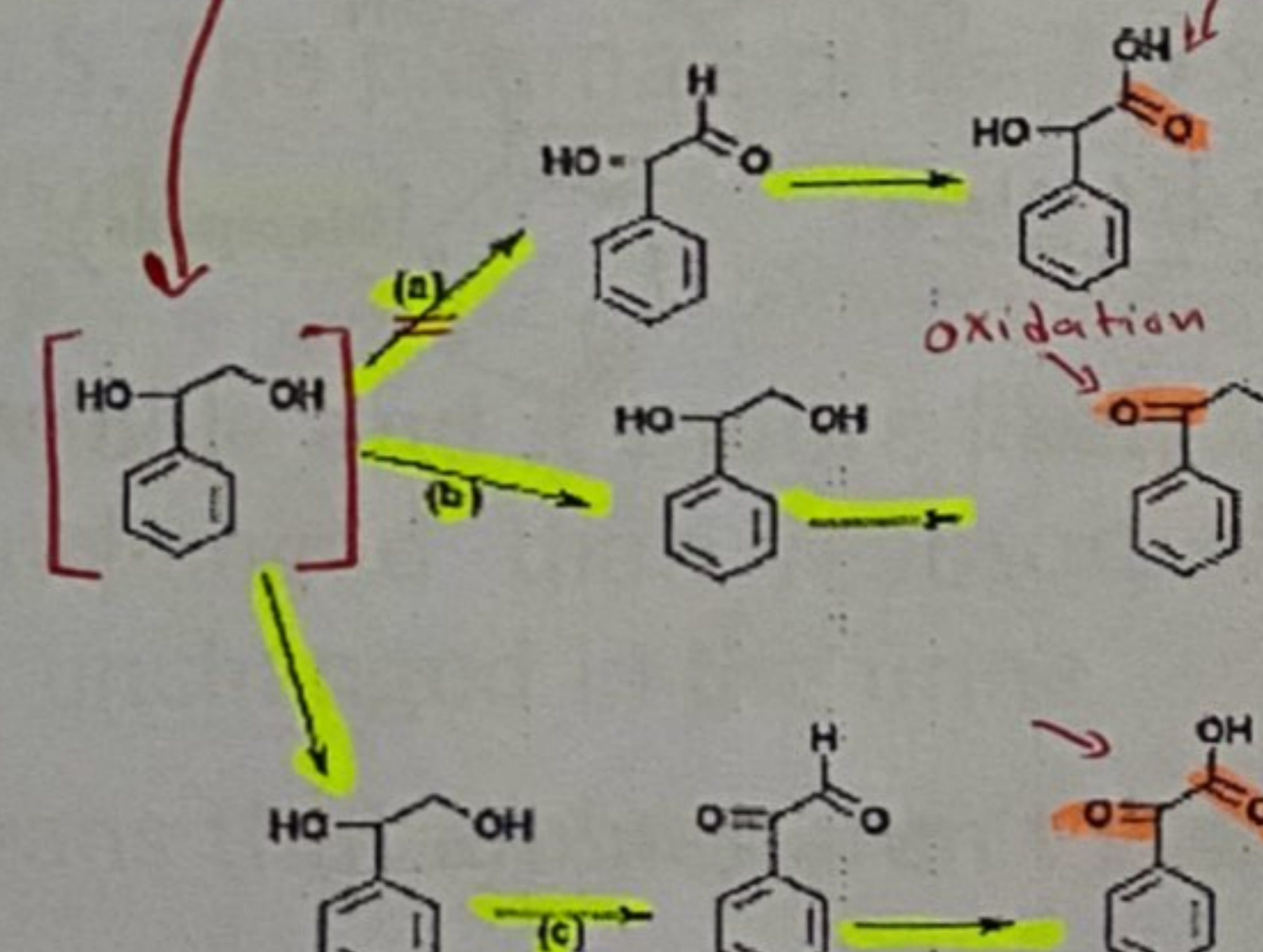
(a) An aldehyde which gets further oxidized into a carboxylic acid. An alcohol carboxylic acid is found in the urine.

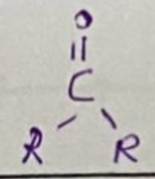
(b) A ketone. An alcohol ketone is eliminated in the urine.

(c) A ketone and a carboxylic acid. (eliminated in the urine).

(2) Gets conjugated on one of the hydroxyls with glucuronic acid and eliminated.

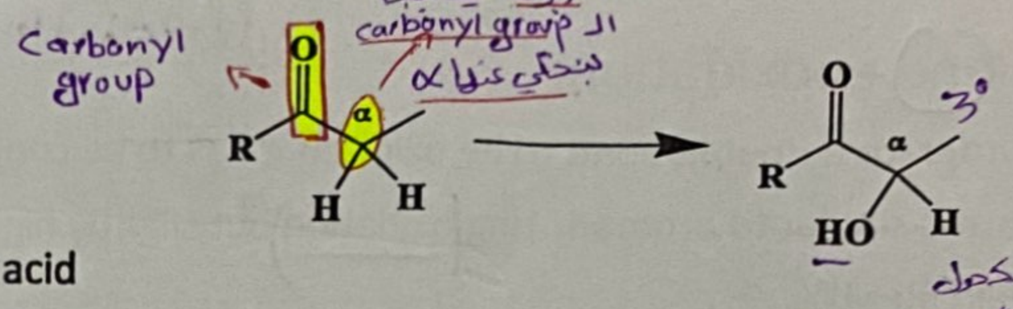
(3) Eliminated in the urine as the oxidized form (glycol).

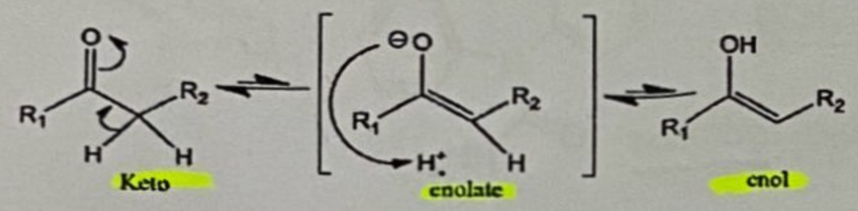


Carbonyl group = 

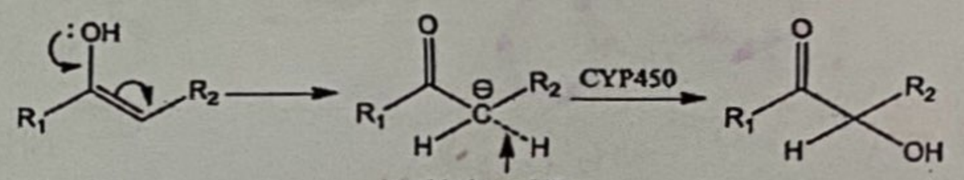
Oxidation to α carbon to carbonyl

- Aldehyde, Ketone, Ester, Enole, Carboxylic acid, Thioester
- Carbonyl is electron withdrawing group→ α carbon is electron rich
- Very fast reaction: 90-100% yield
- Fate of the oxidized drug:
- Eliminated in its oxidized form in the urine
- Good candidate for conjugation to glucuronic acid
- Further oxidation by alcohol dehydrogenase: If a primary alcohol it's oxygenated to a carboxylic acid and gives a carboxylic acid ketone group in the urine.
- If it's a secondary alcohol it's oxidized to a ketone, giving a diketone in the urine.

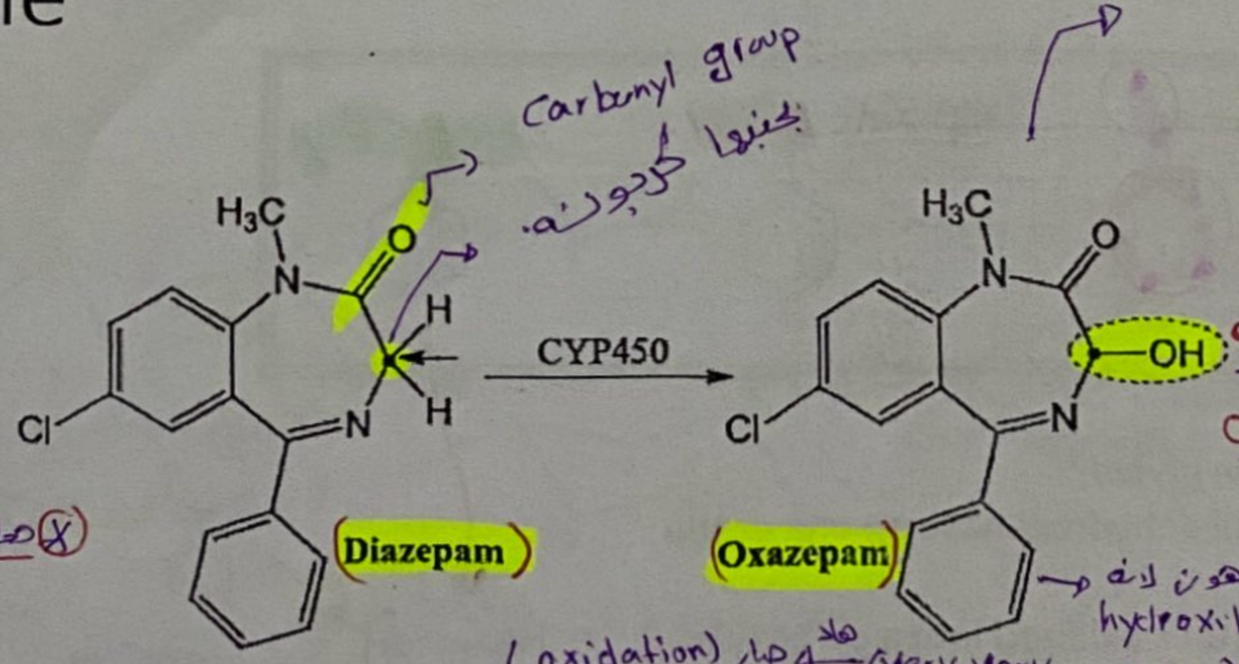




keto-enol tautomerism



Example

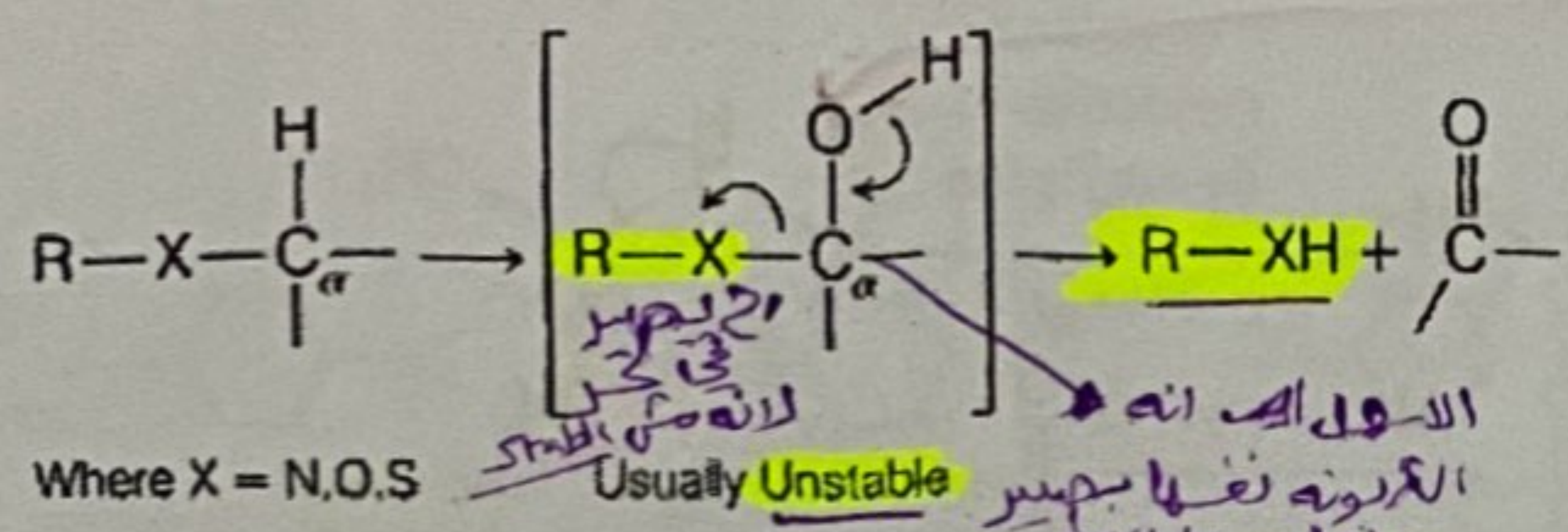


Aromatic ring oxidation is very minor because it's slower. The oxidation of the alpha carbon is much faster and more likely to happen.

Oxidation Involving Carbon-Heteroatom Systems

- Nitrogen and oxygen functionalities are commonly found in most drugs and foreign compounds; sulfur functionalities occur only occasionally.
- Metabolic oxidation of carbon-nitrogen, carbon-oxygen, and carbon-sulfur systems involve two basic types of biotransformation processes:

1. Hydroxylation of the carbon atom directly attached to the heteroatom (N, O, S). The resulting intermediate is often unstable and decomposes with the cleavage of the heteroatom-carbon bond:



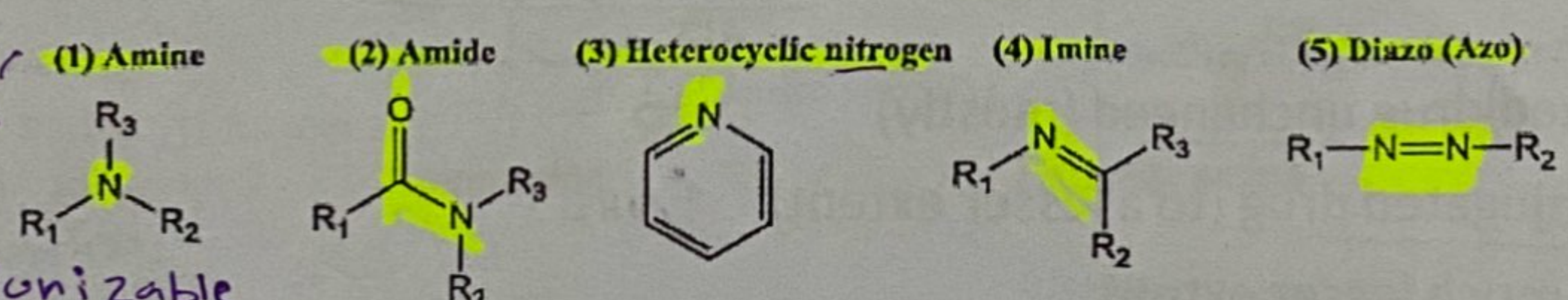
nitrogen is more electrophilic than carbon, the α-carbon is likely to get oxidized and is easier to be oxidized than the nitrogen

Oxidative N-, O-, and S-dealkylation as well as oxidative deamination reactions fall under this mechanistic pathway.

2. Hydroxylation or oxidation of the heteroatom (N, S only, e.g., N-hydroxylation, N-oxide formation, sulfoxide, and sulfone formation).

S=O O=S=O

N- systems



ionizable
PKa = 9.5
PHa = 7.5

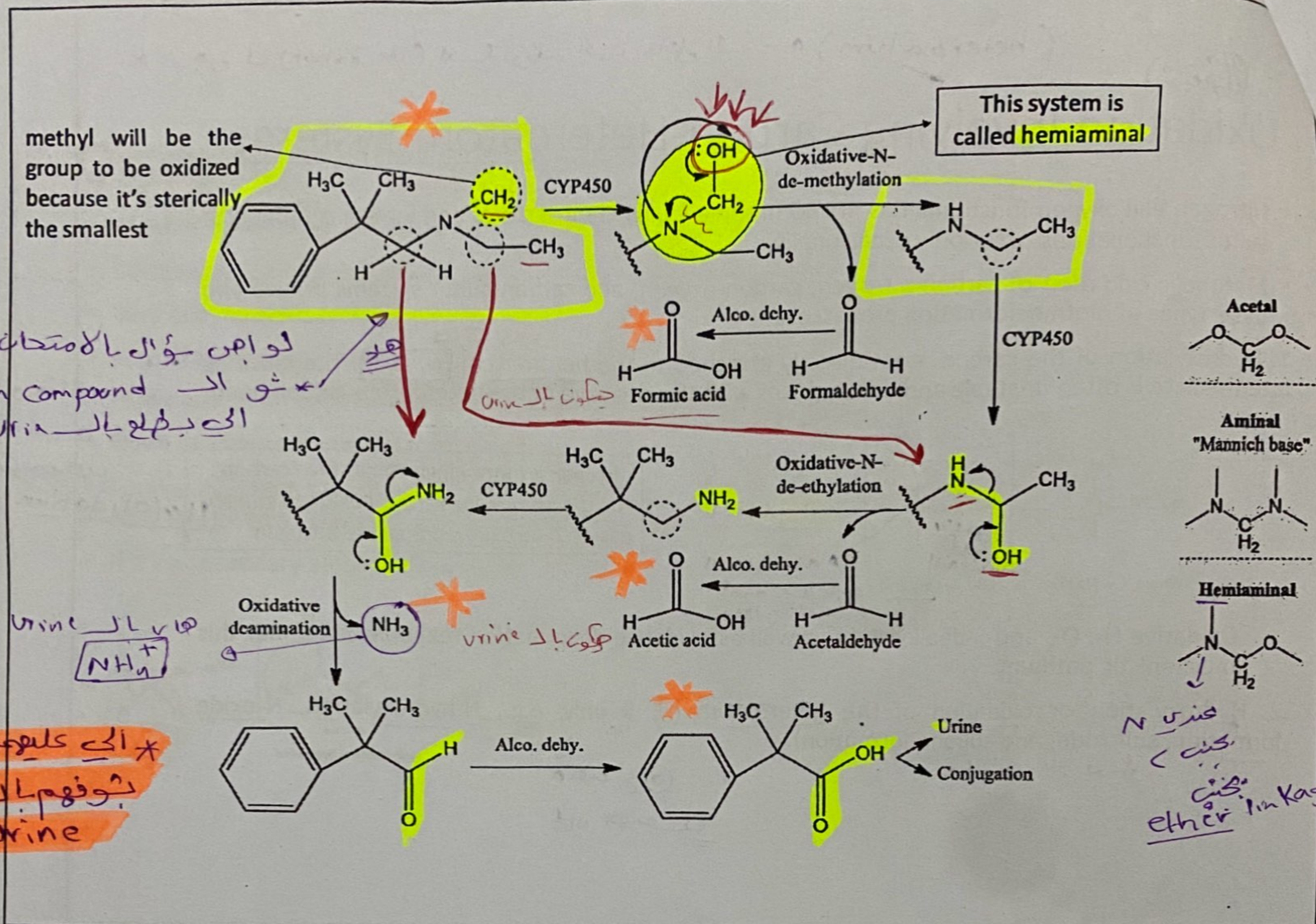
Amines are ***ionizable*** groups with a pKa= 9.5. The plasma's pHa= 7.5 so amines are ionized in physiological conditions.

How does that affect its renal elimination?

Since it's ionizable that means it's water soluble and it's more likely to get eliminated in the urine **mainly** unchanged than reabsorbed. around **80%** of the amines get eliminated unchanged in the urine

- and around **10%** get conjugated. This means that amines aren't good candidates for metabolism by **CYP450**.

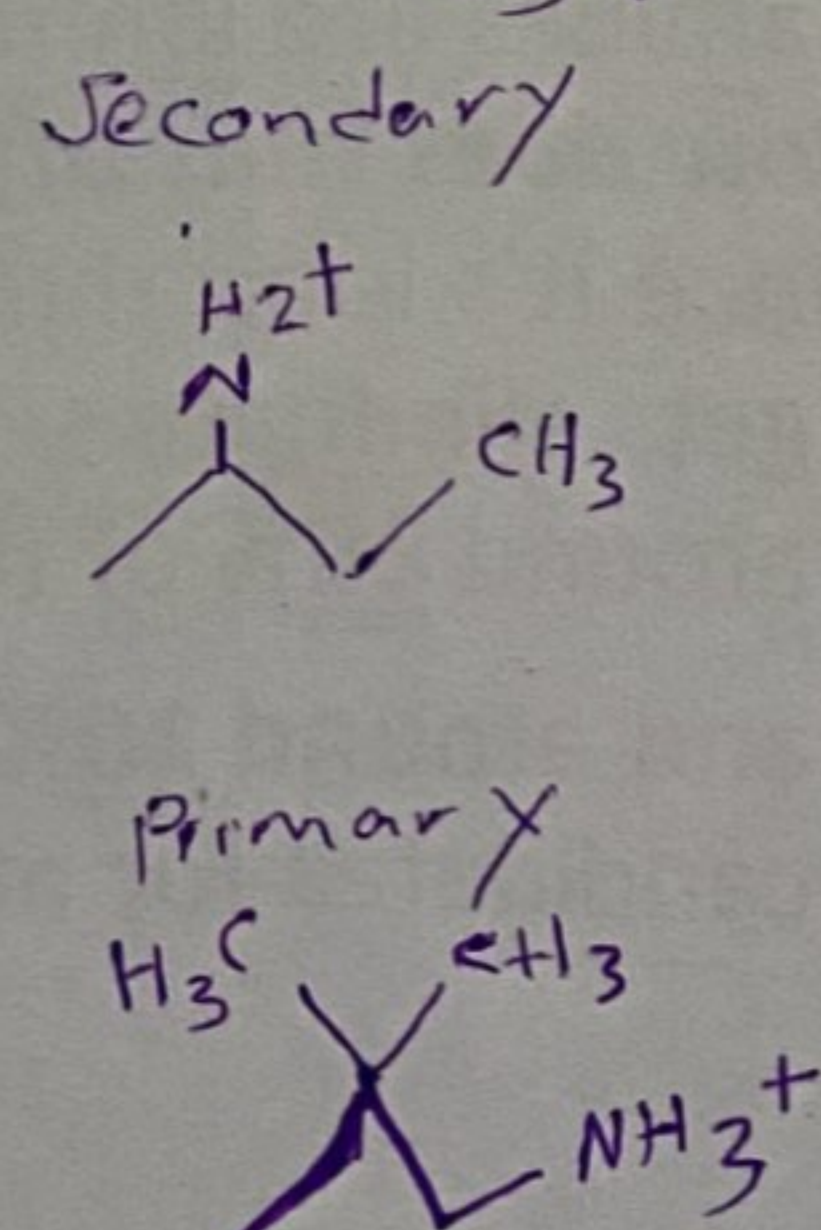
* شو ممكن يجيبوا بال 10% ؟؟



N-systems: What do we find in the urine?

مش معمول عليه metabolism

- 90% ① (Ionized) drug unchanged (mostly)
- ② - Conjugated drug (to a lesser extent) ε_{NH_2}
- ③ 10% To a much lesser extent:
  - ④ Ionized secondary and primary amines and their conjugates
  - ⑤ Ammonia
  - ⑥ Carboxylic acids (formic acid, acetic acid and the final carboxylic acid product of the last reaction)
  - ⑦ **NO** aldehyde (unstable)
  - ⑧ **NO** hemi-aminal (unstable)



*هلّق هون اذا سألكم بالامتحان. ← جيبب تطلع جالك NH_3 وتكون (Very very minor).

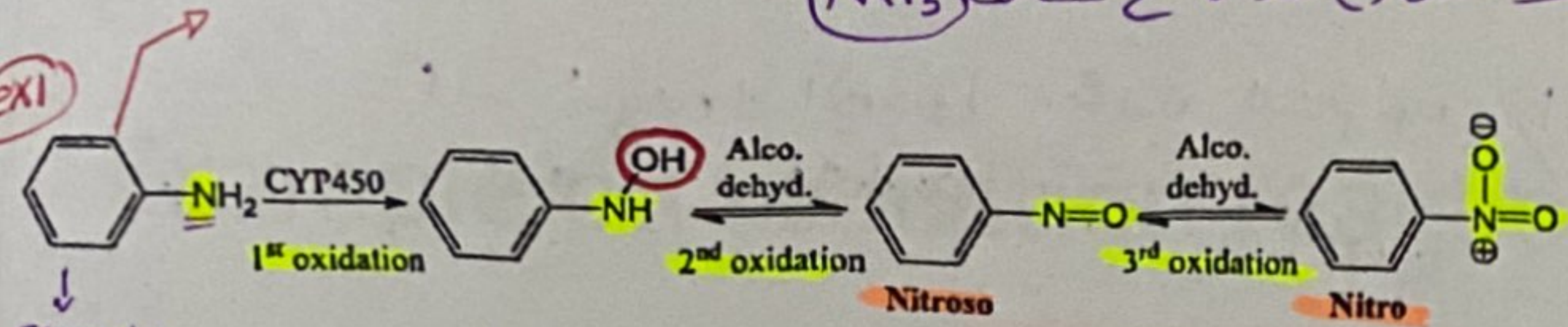
الـ alanin بهاد الشكل مش رح تكون protonated

جزء قليل حيكون protonated لانه pKa=5-7.

فـ مش رح تكون ع شكل (NH_3)

N-oxidation

ex1

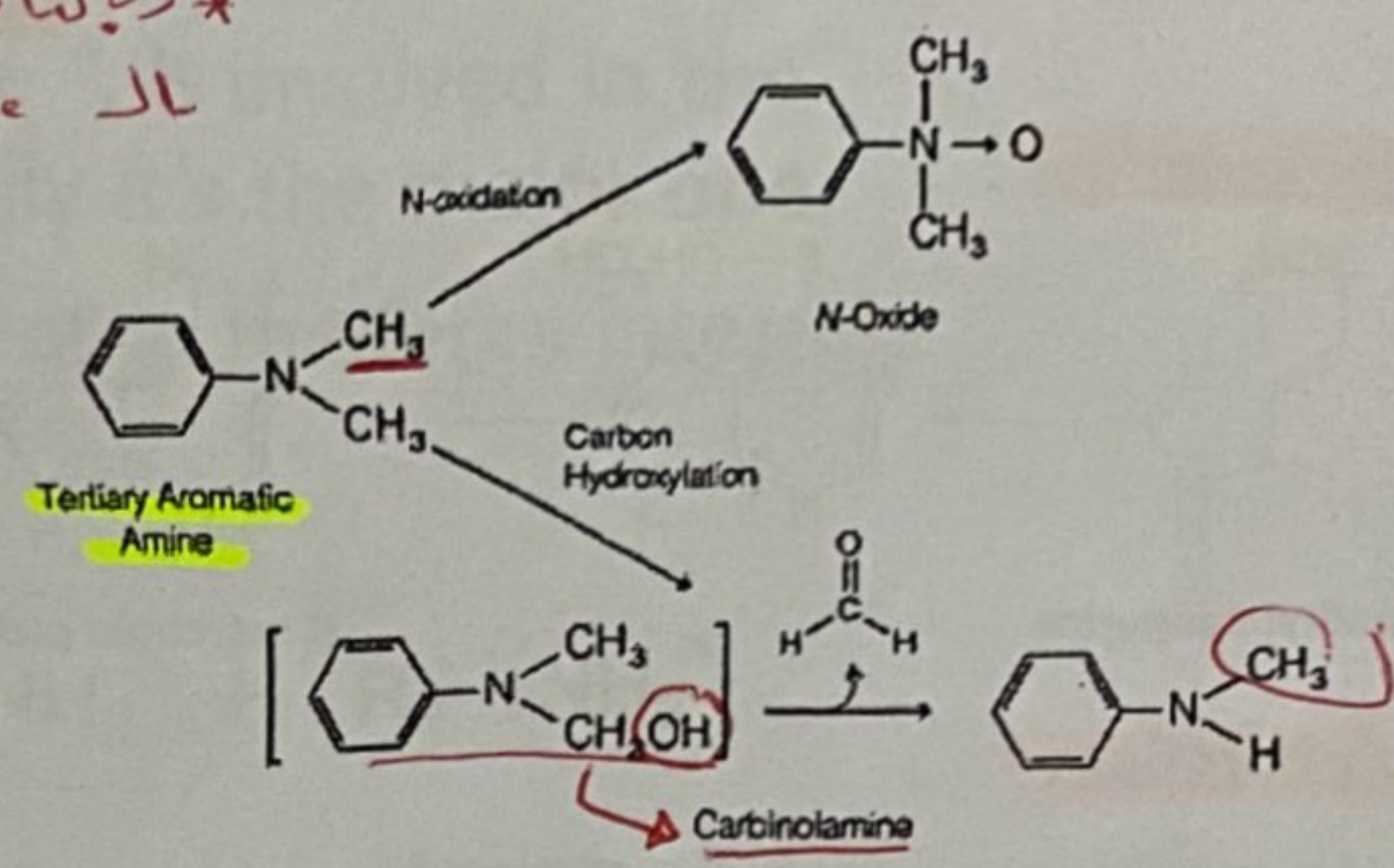


aromatic ring

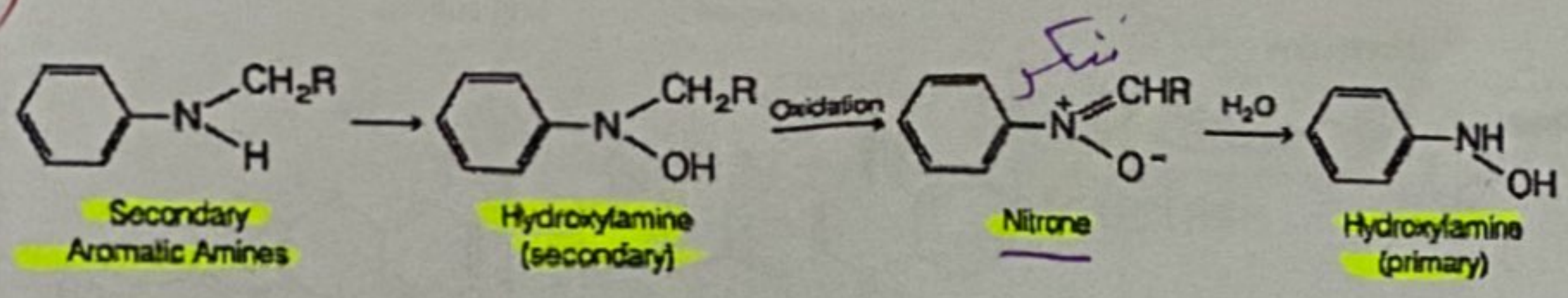
*جميعهم بصير oxidation الإ ي (N)

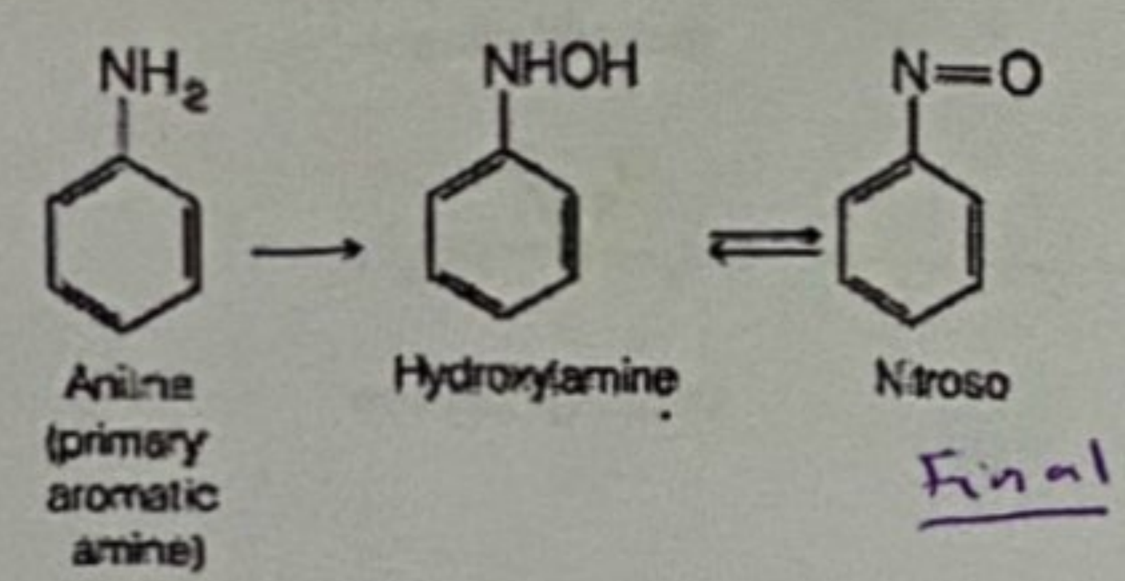
*رح الكل الي هلّق يطلع الـ urine بجهولة

ex2

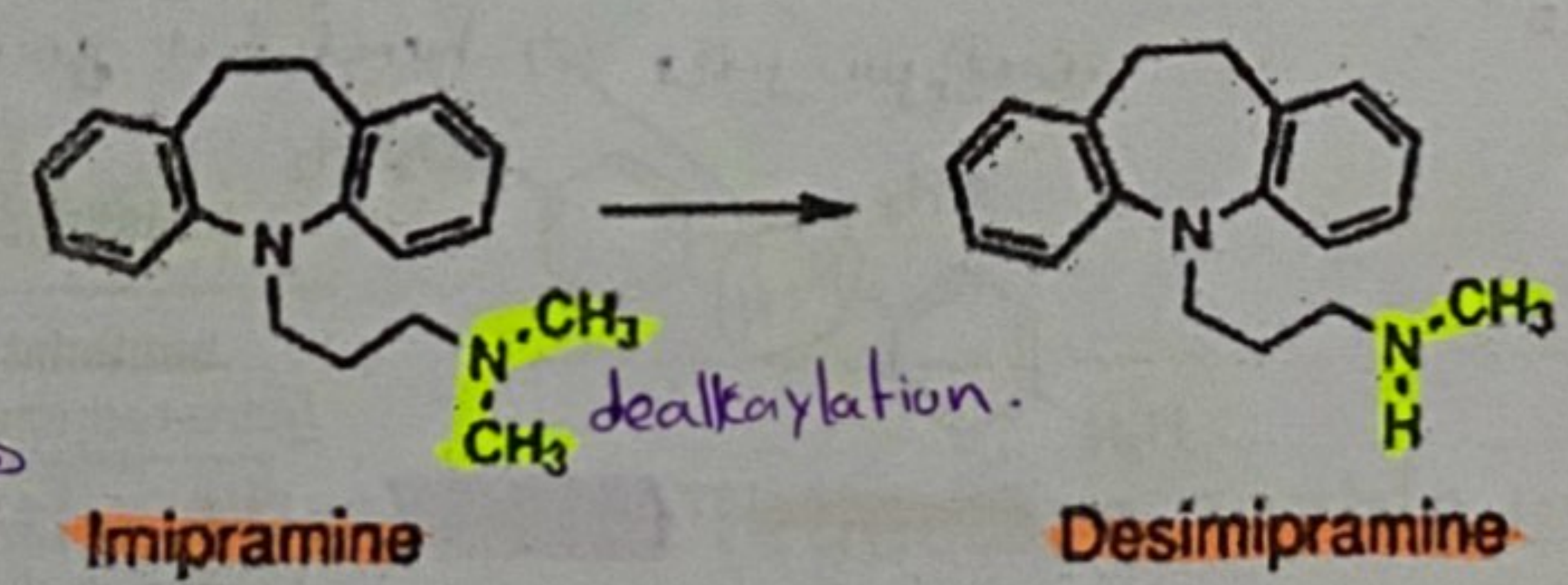


ex3

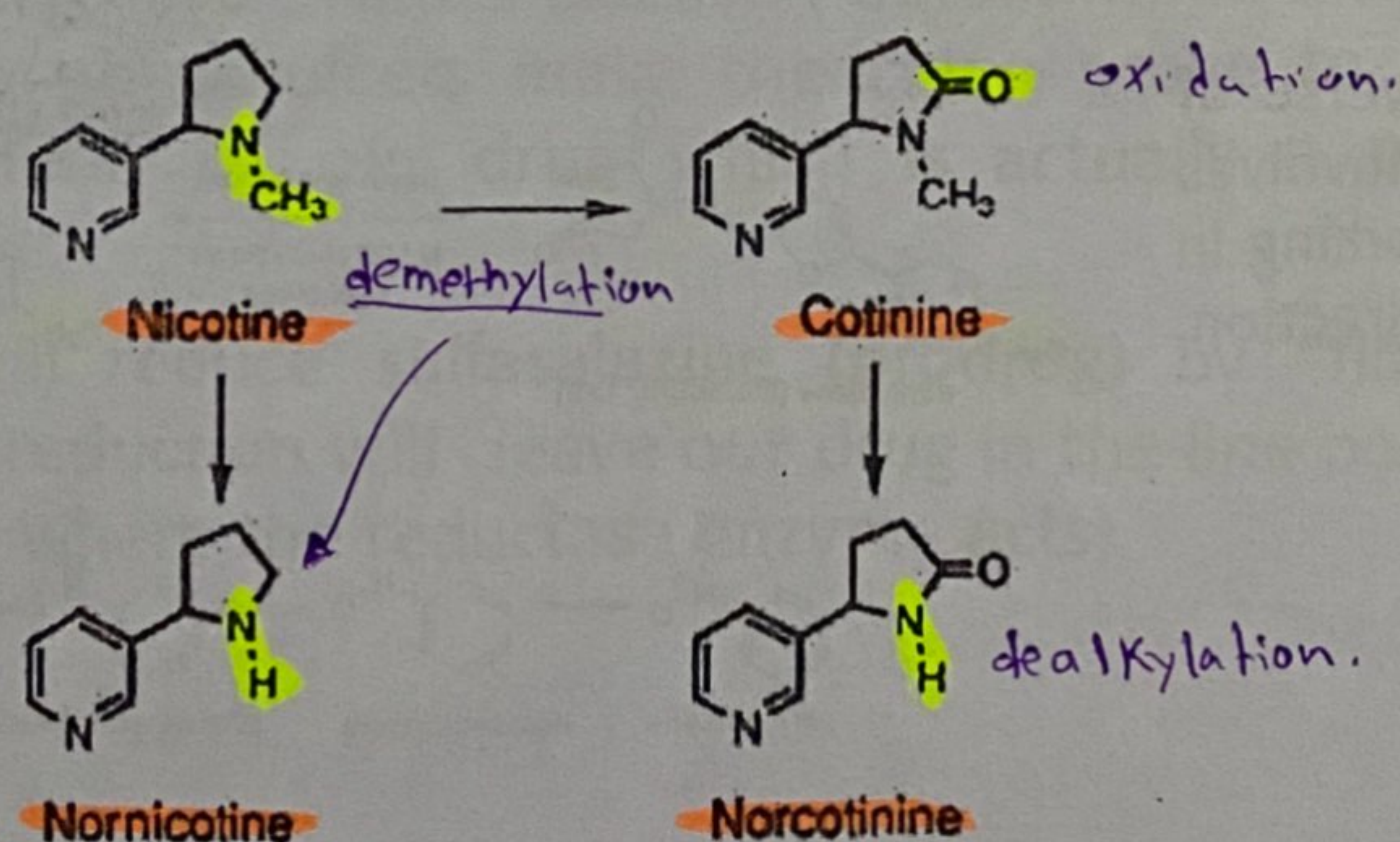




Example

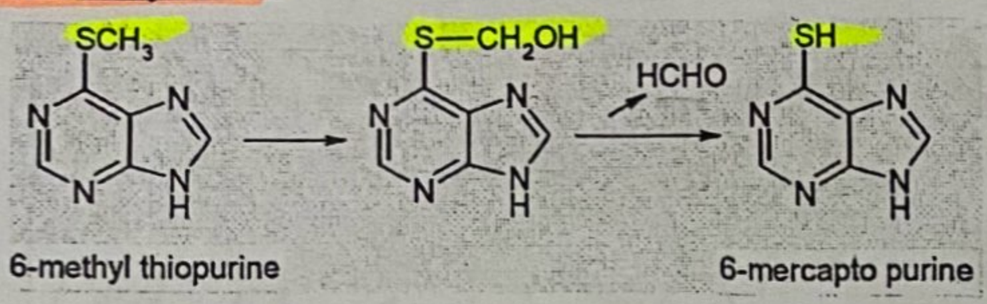


هاد بشكل يطلع بالـ urine عادي. زي ما هو لانه Protonated.



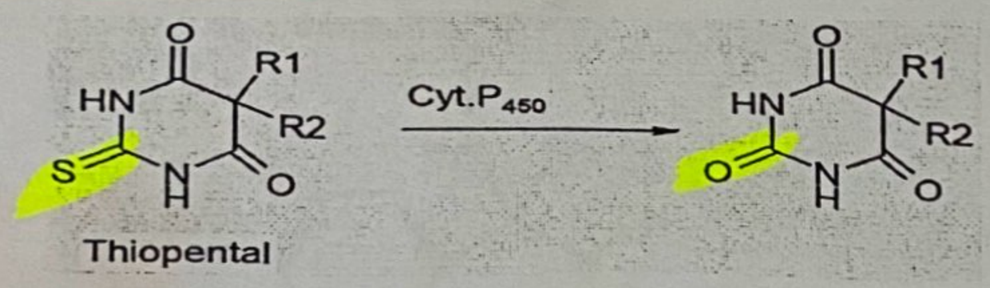
S-Oxidation

1) S-dealkylation:



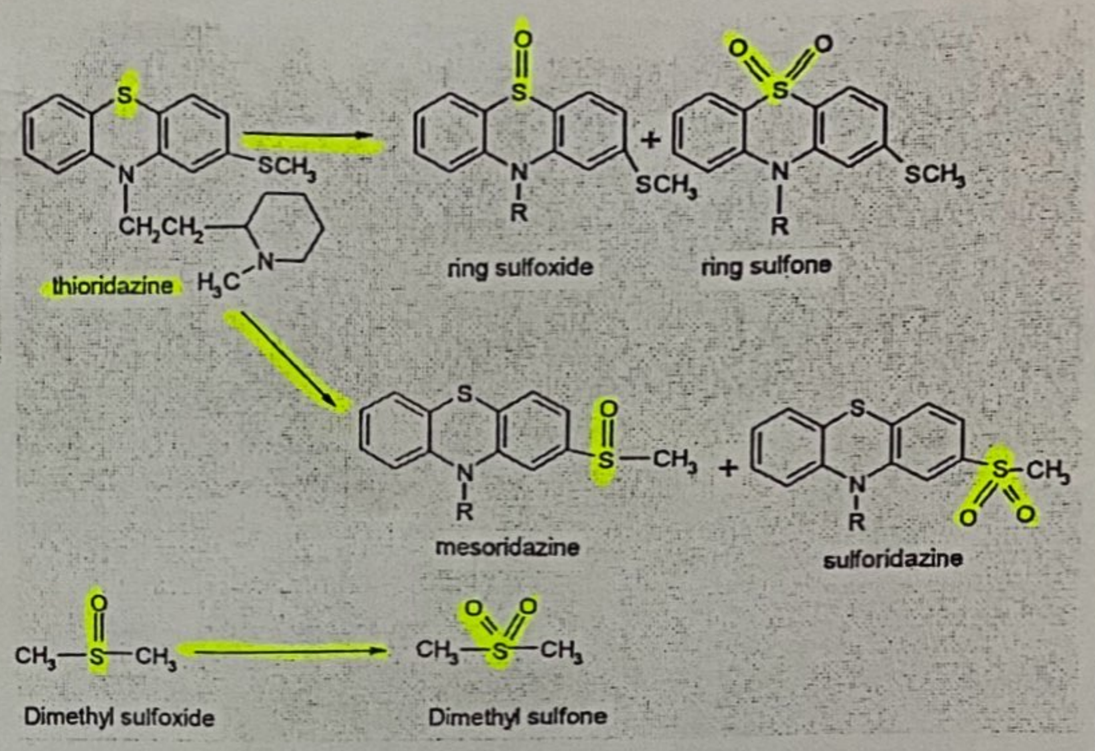
6-methyl thiopurine — 6-mercapto purine

2) Desulphuration:



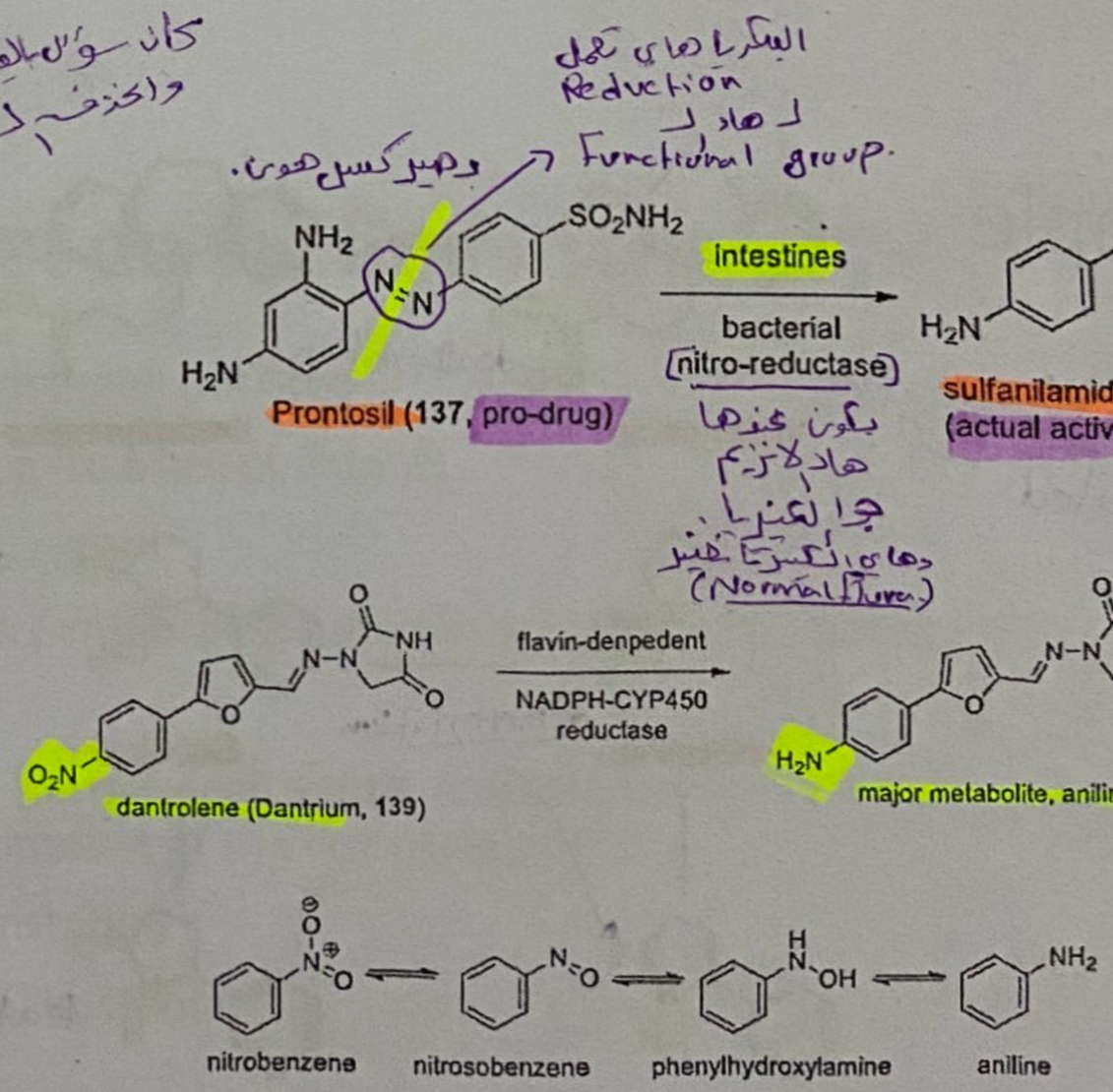
Thiopental

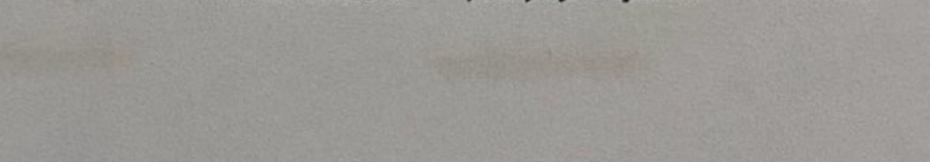
3) S-oxidation:



REDUCTION

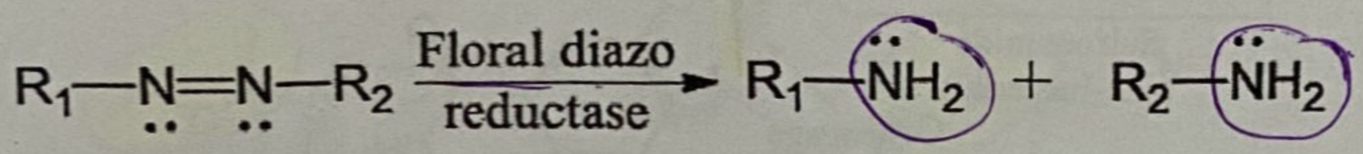
- Reduction is the reverse of oxidation and involves CYP450 enzymes working in the (opposite) direction.





Example on reduction reactions

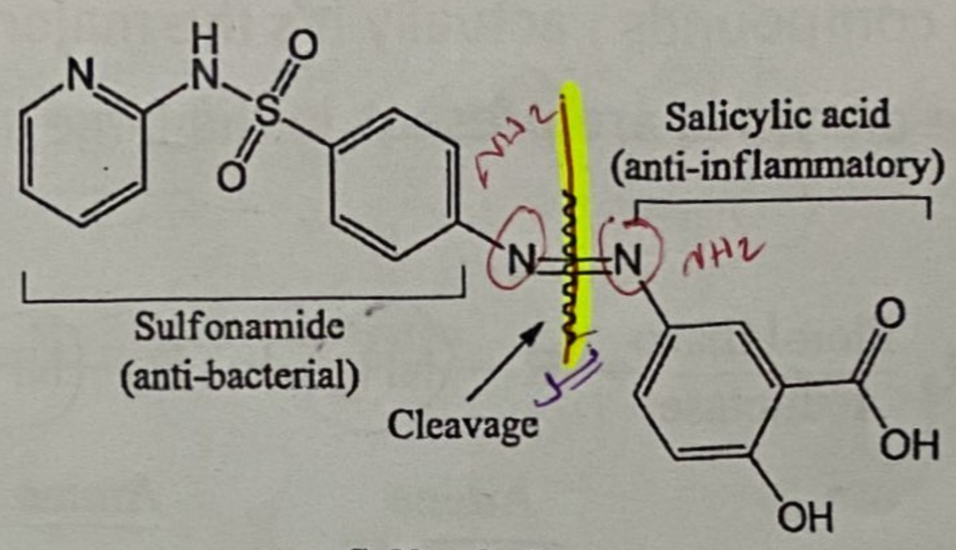
- An enzyme called " floral diazo reductase ", is involved in the metabolism of Diazo compounds , actually it's the major one.
- floral diazo reductase enzymes are present in the large intestine



Sulfasalazine

- The presence of the floral Diazo reductase enable us to build prodrug to treat a disease called Crohn's disease (autoimmune disease leads to colon ulcers , these ulcers make the colon prone to infectious agents like bacteria) , our drug which is actually a prodrug is **Sulfasalazine**
- Normal flora will reduce sulfasalazine (prodrug) by "floral Diazo reductase ", the reduction will cleave our drug in the line position. (At the Diazo group, where the reductase enzyme acts)

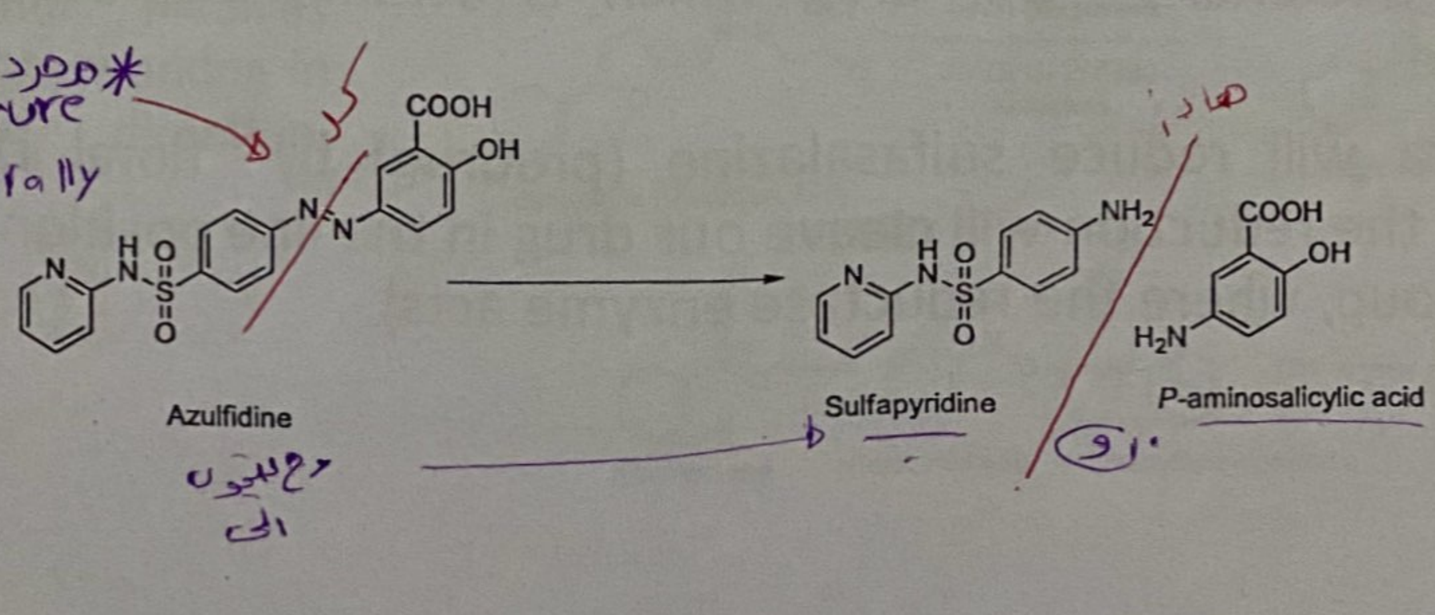
Sulfasalazine is not absorbable, so it acts locally
at the large intestine .and it is a prodrug that has to be activated in vivo,



Sulfasalazine

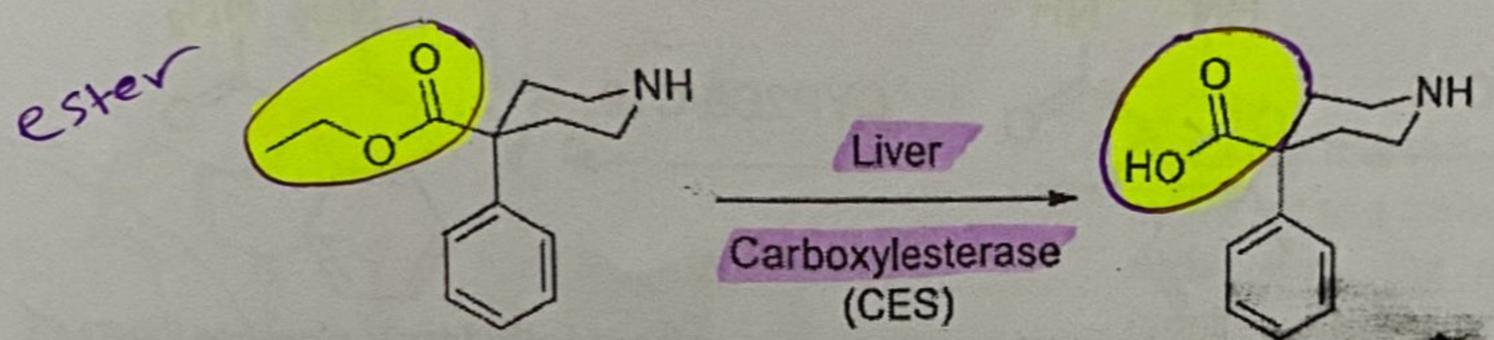
Azo and Nitro Reduction

- A number of azo compounds, such as Prontosil and sulfasalazine, are converted to aromatic primary amines by azoreductase



HYDROLYSIS → Water يعني بدخل

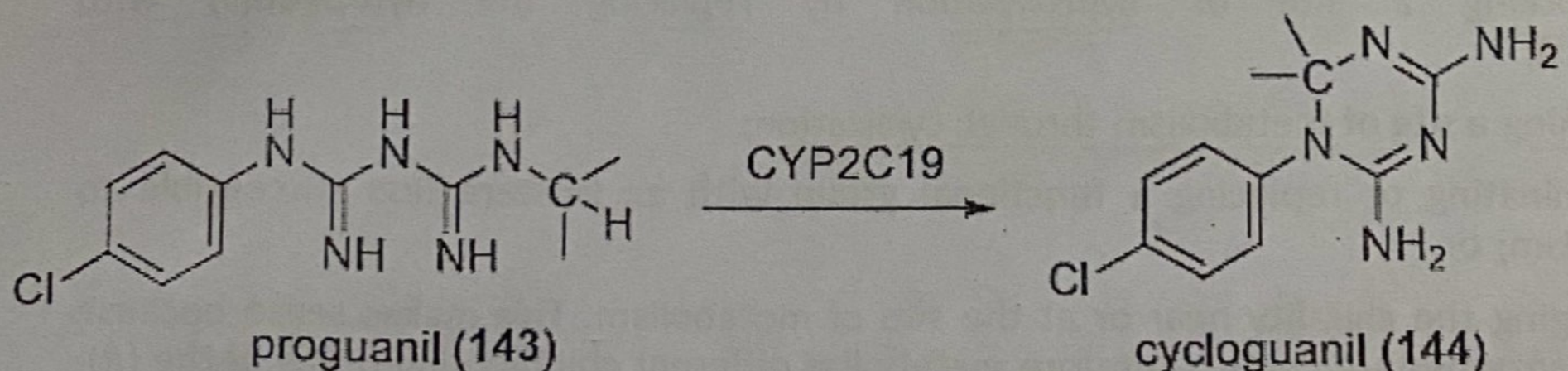
- Hydrolysis means adding water. For an ester-containing drug, hydrolysis is cleavage of the ester by taking up a molecule of water employing esterase. Similarly, amides and polypeptides are hydrolyzed by amidases and peptidases, respectively. Hydrolysis occurs in the liver, intestines, plasma, and other tissues.



pethidine (Demerol, 141) pethidinic acid (142)

CYCLIZATION Very minor

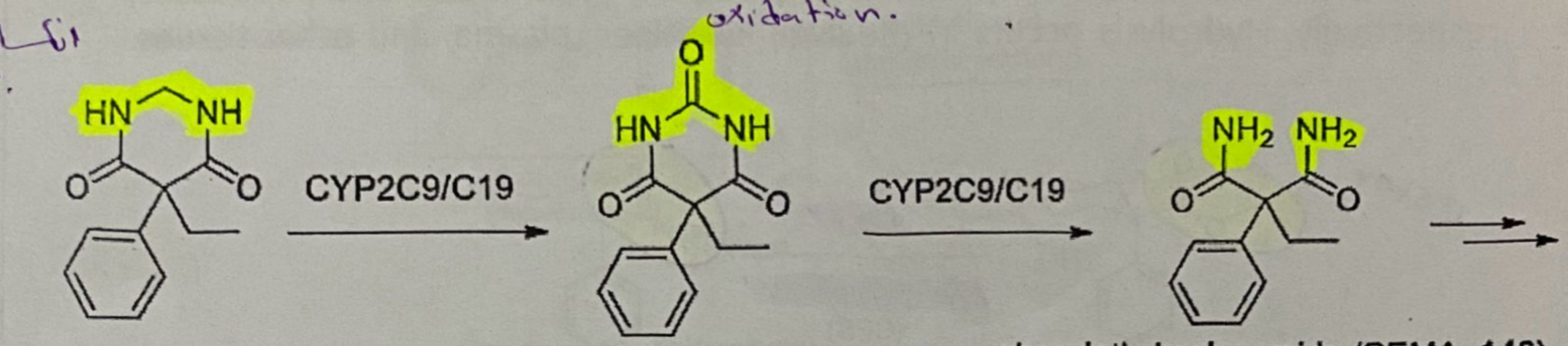
- Metabolic cyclization is formation of a ring structure from a straight-chain compound



proguanil (143) cycloguanil (144)

DECYCLIZATION

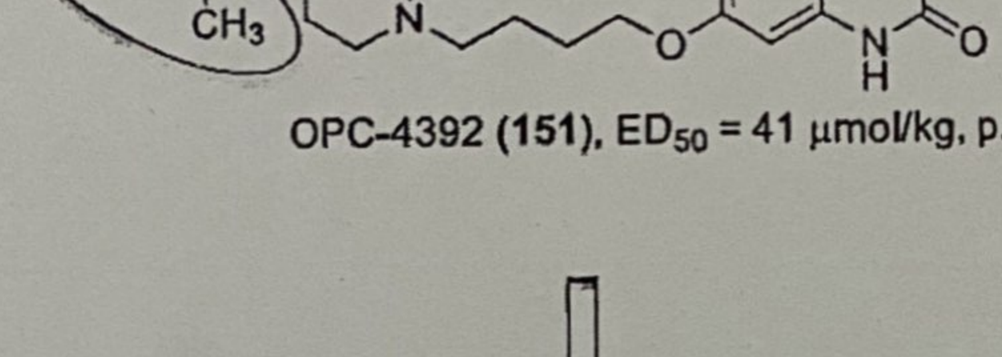
- Metabolic decyclization is ring-opening of a cyclic molecule such as phenytoin and barbiturates.



primidone (**145**) phenobarbital (Luminal, **100**) phenylethylmalonamide (PEMA, **146**)

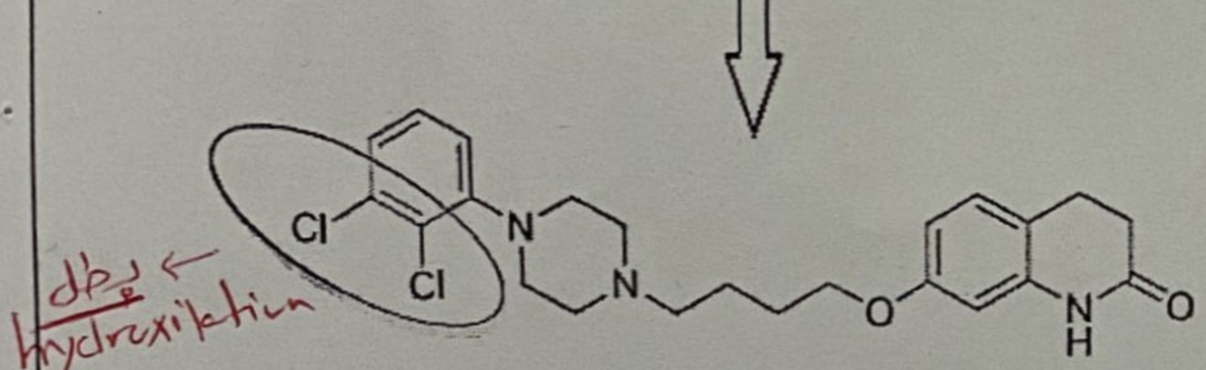
- Phase I metabolism is often problematic if the compound undergoes extensive metabolism to afford inactive metabolites, or worth still, reactive metabolites. There are many approaches to address Phase I metabolism issues:

- (i) Reducing the lipophilicity of the drug;
- (ii) Blocking a site of hydroxylation by replacing the hydrogen(s) with fluorine(s);
- (iii) Blocking a site of metabolism through cyclization;
- (iv) Eliminating or replacing a functional group with an isostere less susceptible to metabolism; or
- (v) Changing the chirality near or at the site of metabolism. This makes sense because the CYP enzymes are chiral, therefore metabolize different chirality differently. If the (*R*)-stereochemical center is metabolized, chances are the corresponding (*S*)-stereochemical center may be resistant to the metabolism.



OPC-4392 (**151**), ED_{50} = 41 μmol/kg, p.o.

The two methyl groups readily underwent hydroxylation and the diols were further oxidized to the corresponding inactive carboxylic acids.



aripiprazole (Abilify, **152**), ED_{50} = 0.6 μmol/kg, p.o.
Otsuka/BMS, 2002

Switching the two methyl groups to two chlorine atoms led to a molecule that is more resistant to the metabolism. The resulting compound OPC-14597 (aripiprazole, Abilify, **152**) is more efficacious with an ED_{50} of 0.6 mmol/kg, p.o.
It was approved by the FDA in 2002 as an effective and unique antipsychotic.