

Medicinal Chemistry

Philanthropy → Origin of medicine?

philistine & man (anthropy) ??

↓
person hostile or indifferent
to culture or arts.

alkaloid - A molecule ① isolated from a natural source (Plant or animal)

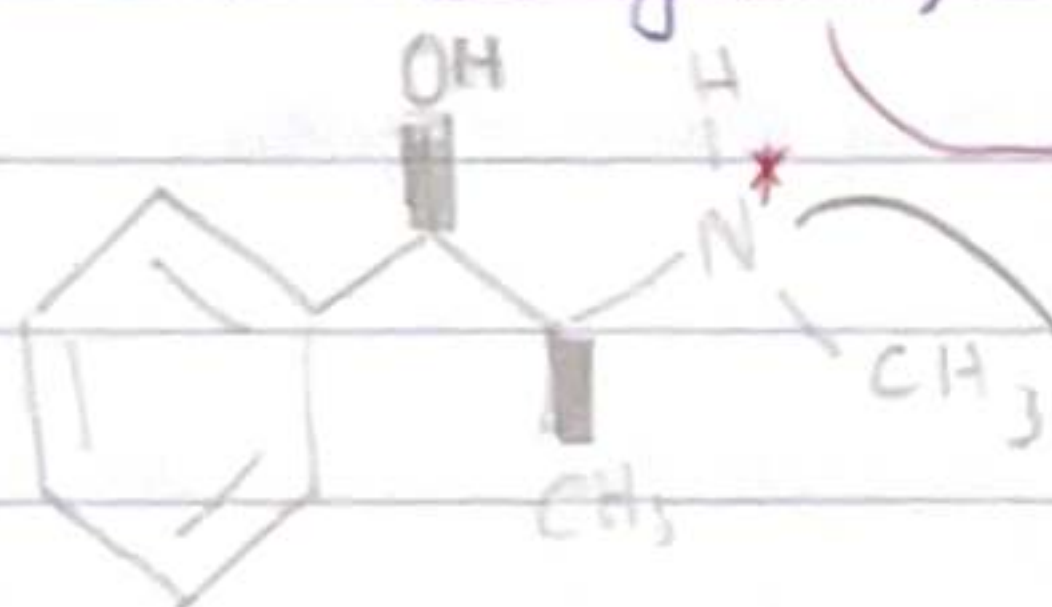
↳ Nicotine ??

② With a basic nitrogen*

③ With a degree of complexity.

eg. Ephedrine from Ma-huang Shrub (Japan)

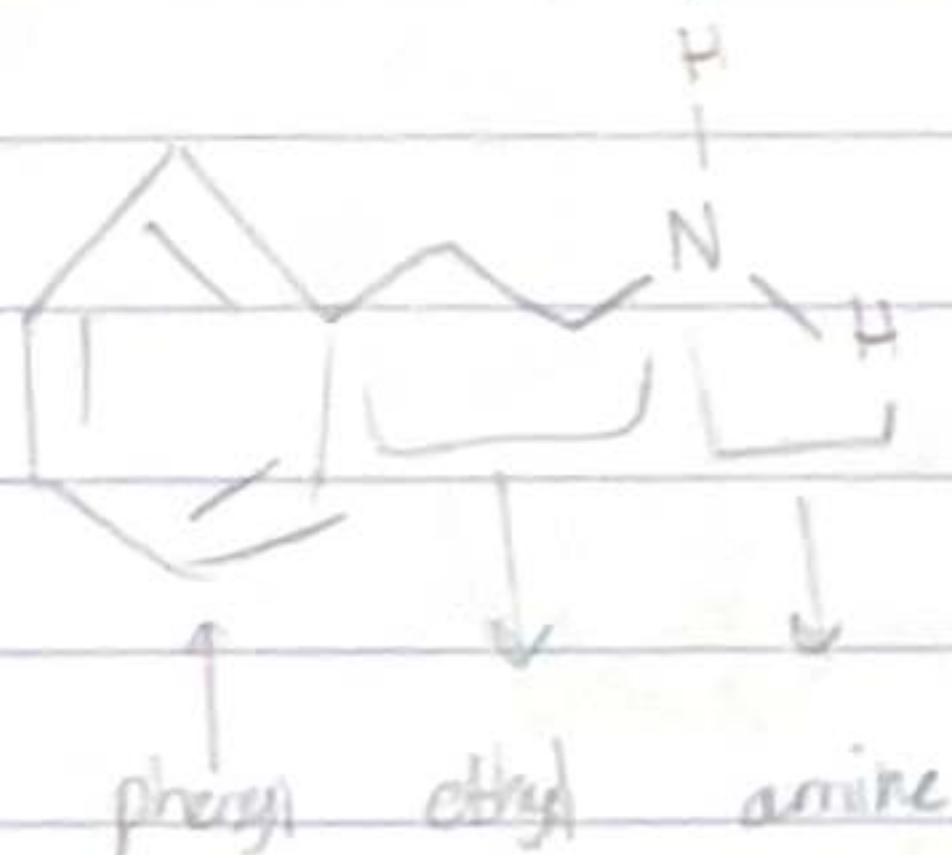
↳ Tea has decongestant, anti-cough & stimulant properties



Vasconstrictor

Nitrogen has a lone pair & readily reacts with acids

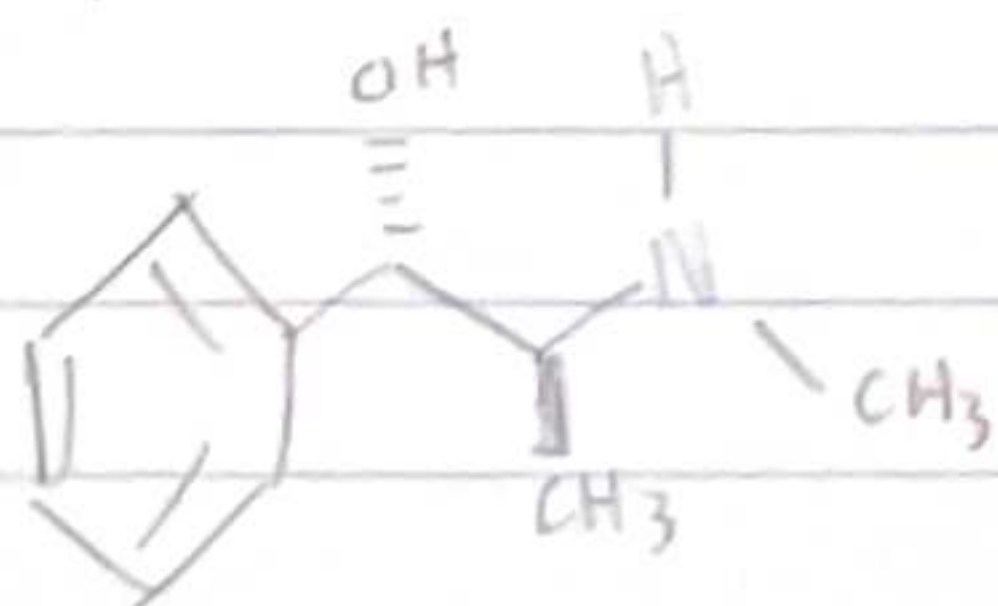
↳ Ephedrine also forms part of a class of compounds called phenethylamine.



• parent Scaffold System

• Neurotransmitter

Pharmacophore - minimal level of a structure that is required to maintain ~~at~~ a level of activity.



pseudoephedrine (Sudafed)

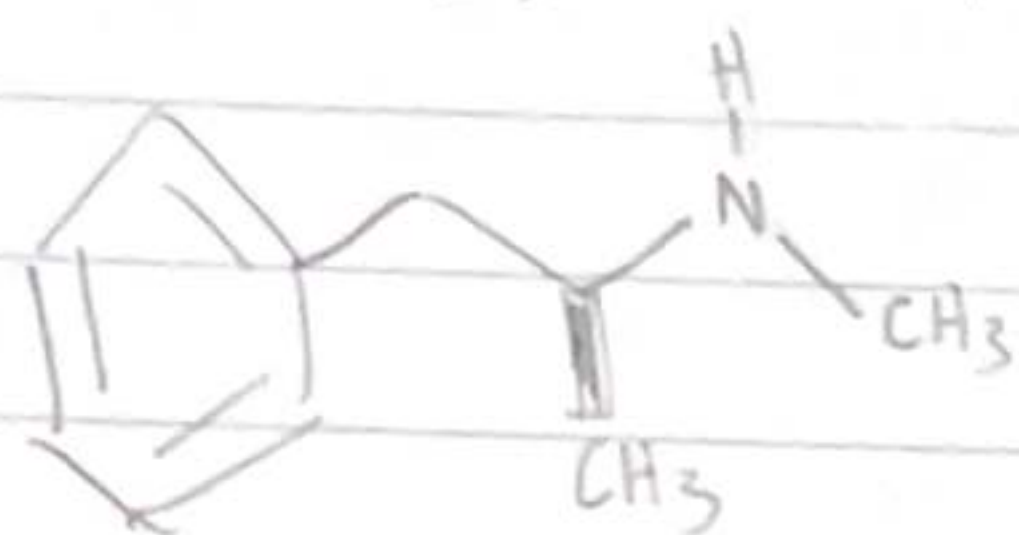
decongestant.

position of (-OH) different

Stereoisomerism of ephedrine

↳ Also has stimulant properties like phenethylamines.

The stimulant property can be explained



Methamphetamine (Meth)
Stimulant

Addictive

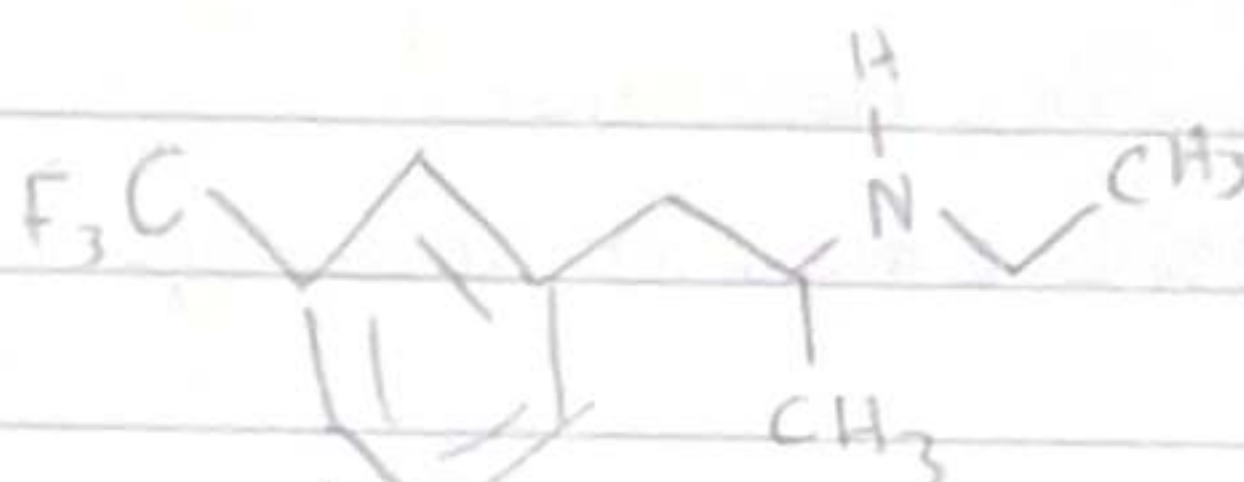
Can be used
as diet pills

Sensation of having energy w/o food

Sudafed can be converted to Methamphetamine by carrying out a reaction to remove (-OH) and obtain a crystal powder compound in crystalline form.

* phentermine (Adipex P) appetite suppressant

fenfluramine (Pondimin)
appetite suppressant



Combination of these 2 yield a drug with high potency.

Cause heart defect (heart valve)

Later found that fenfluramine
caused heart valve defect.

Adverse Effect

A drug reaction that greatly undermines the therapeutic value of the drug. (Very Severe)

Side effect

A drug reaction that is generally minor compared to the condition being treated. (Less Severe)

off-label usage

Use of a medication in a fashion that was not tested or approved.

Opiates, Opoids & their pharmacophores.

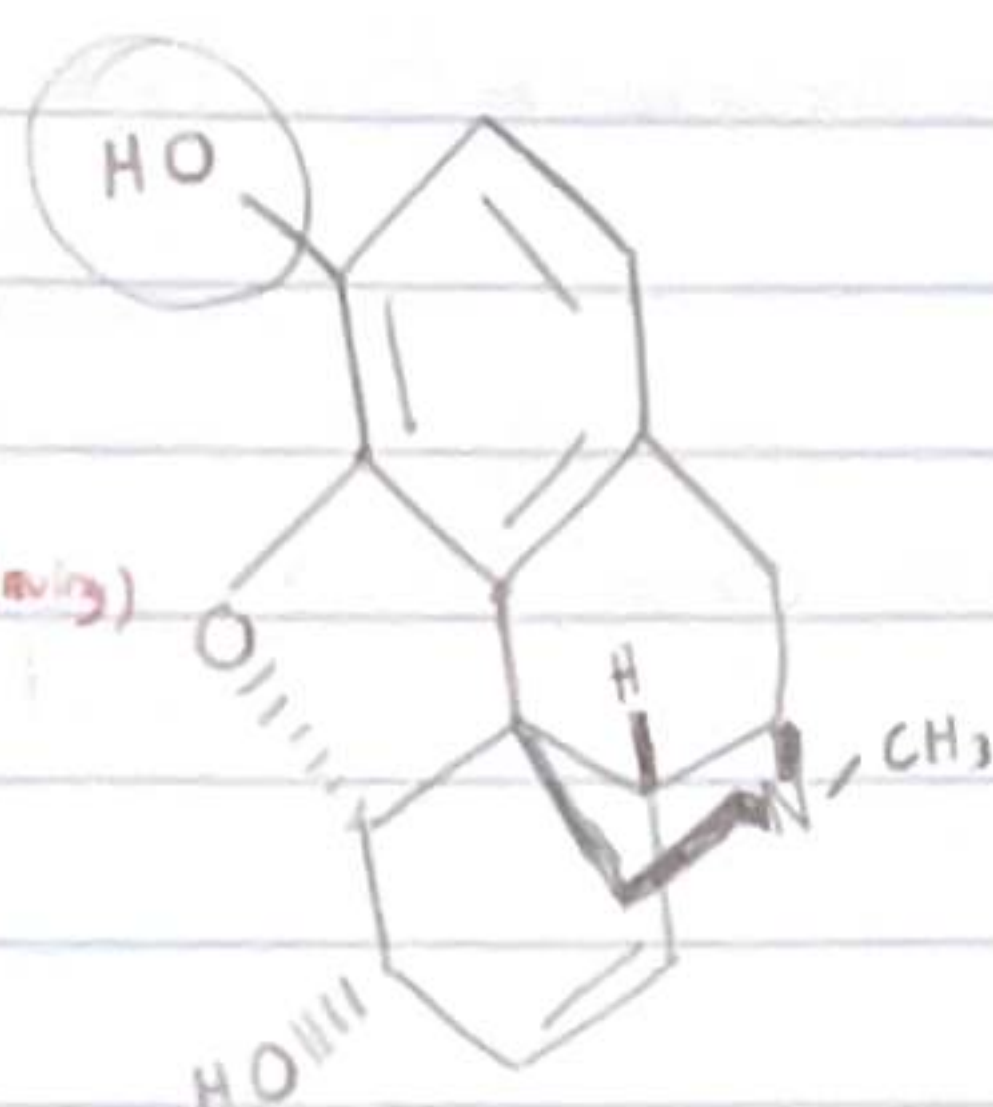
Morphine



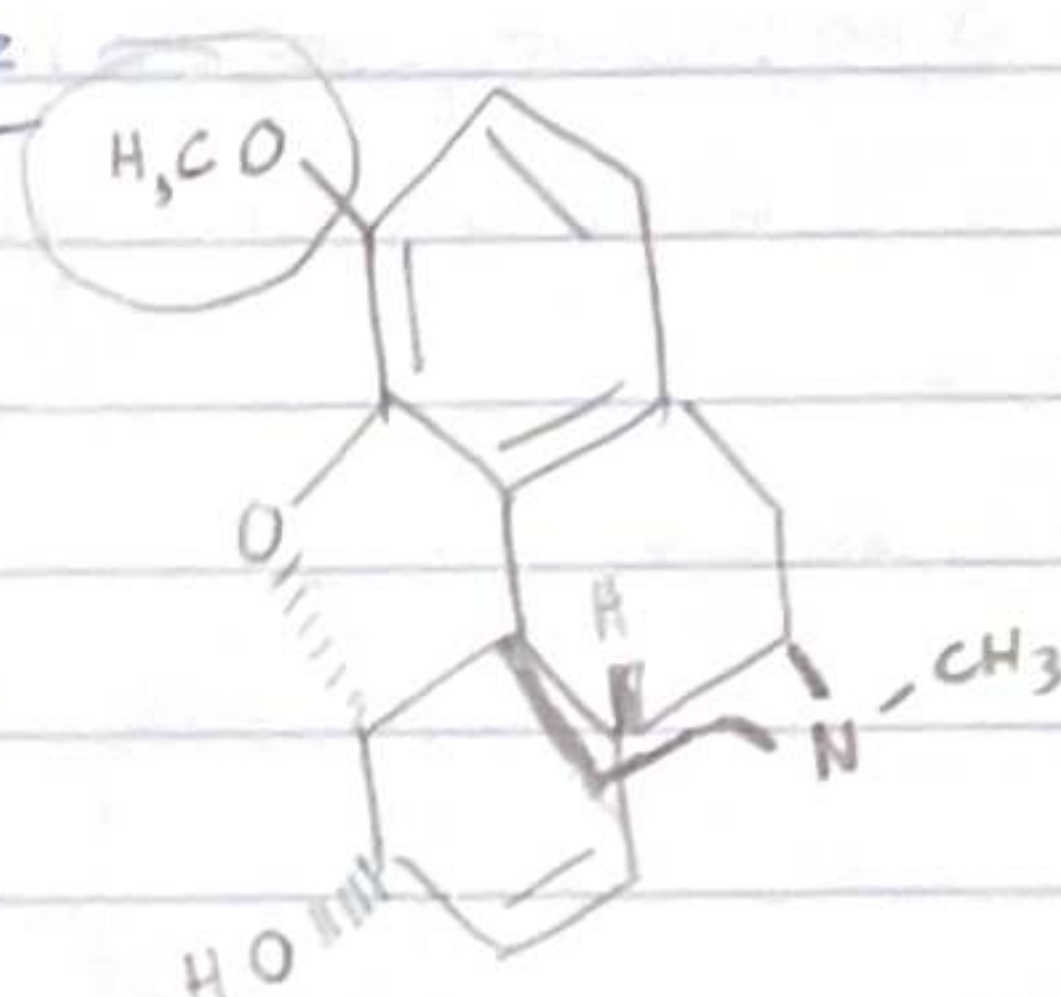
Complex alkaloid

• Very potent analgesic (pain killing)

highly addictive



Codeine

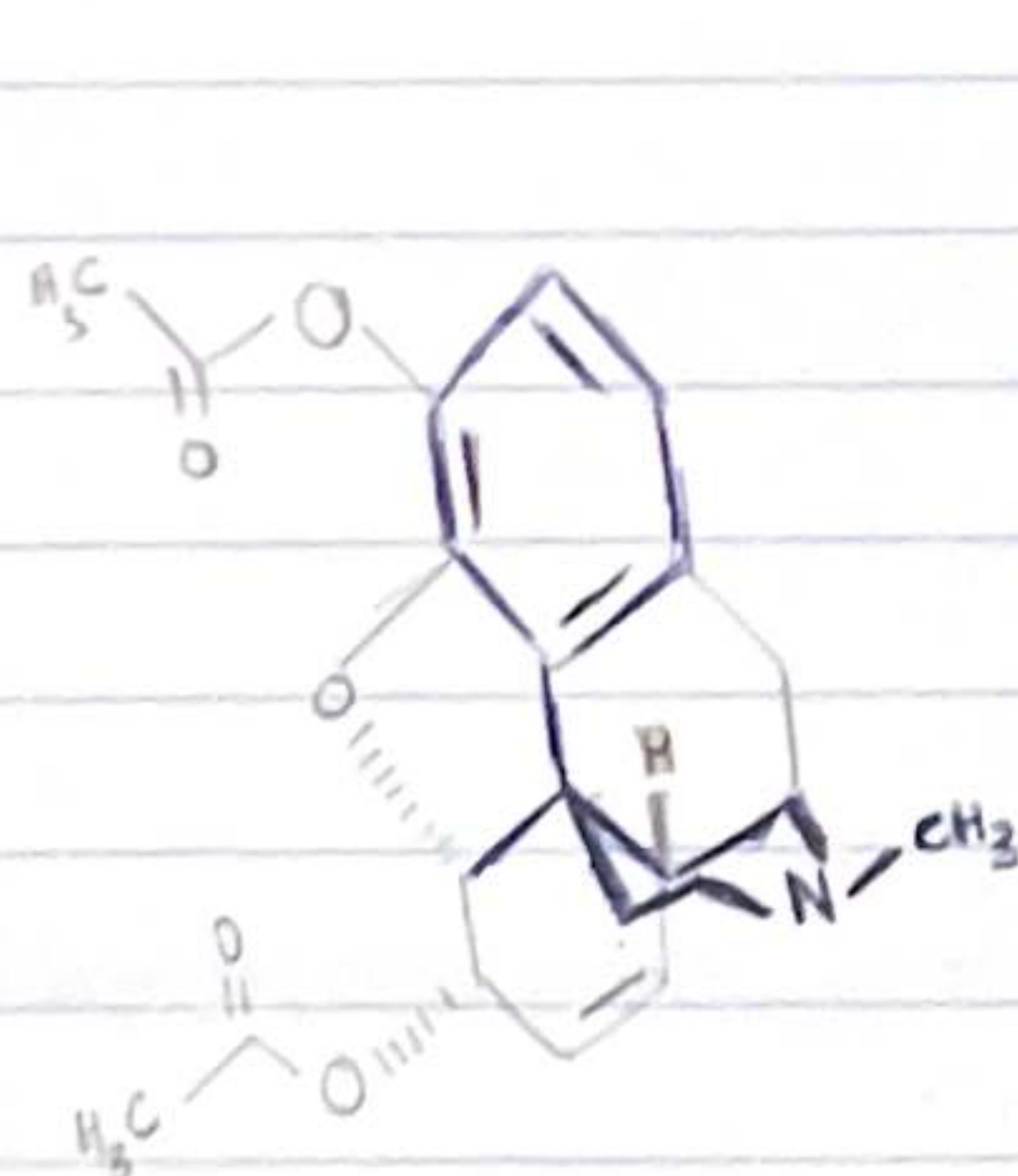


Morphine is not the only compound found in opium. Opium contains approx. two dozen other compounds including Codeine. Morphine & Codeine are both known as opiates.

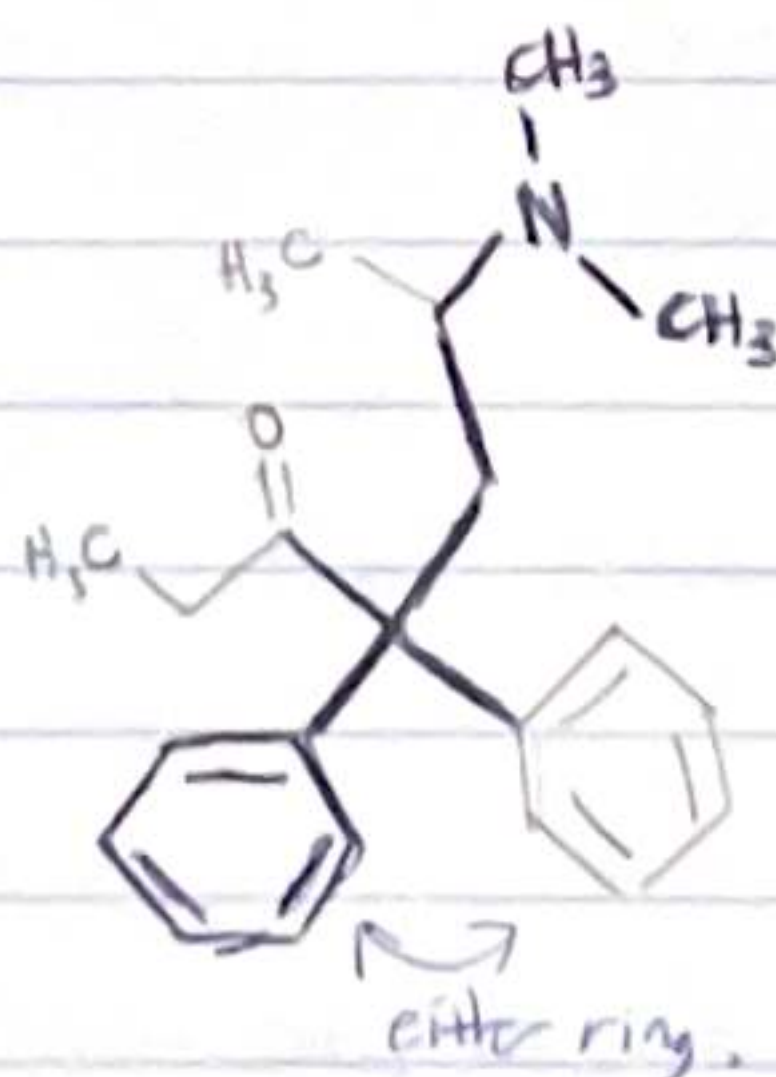
Opiates are naturally occurring compounds that share the same activity as morphine.

Compounds similar to morphine & codeine can be synthesised in labs. Examples of Synthetic & Semi-Synthetic morphine analogues are heroin and methadone.

Unnatural compounds with morphine-like activity are called opoids.



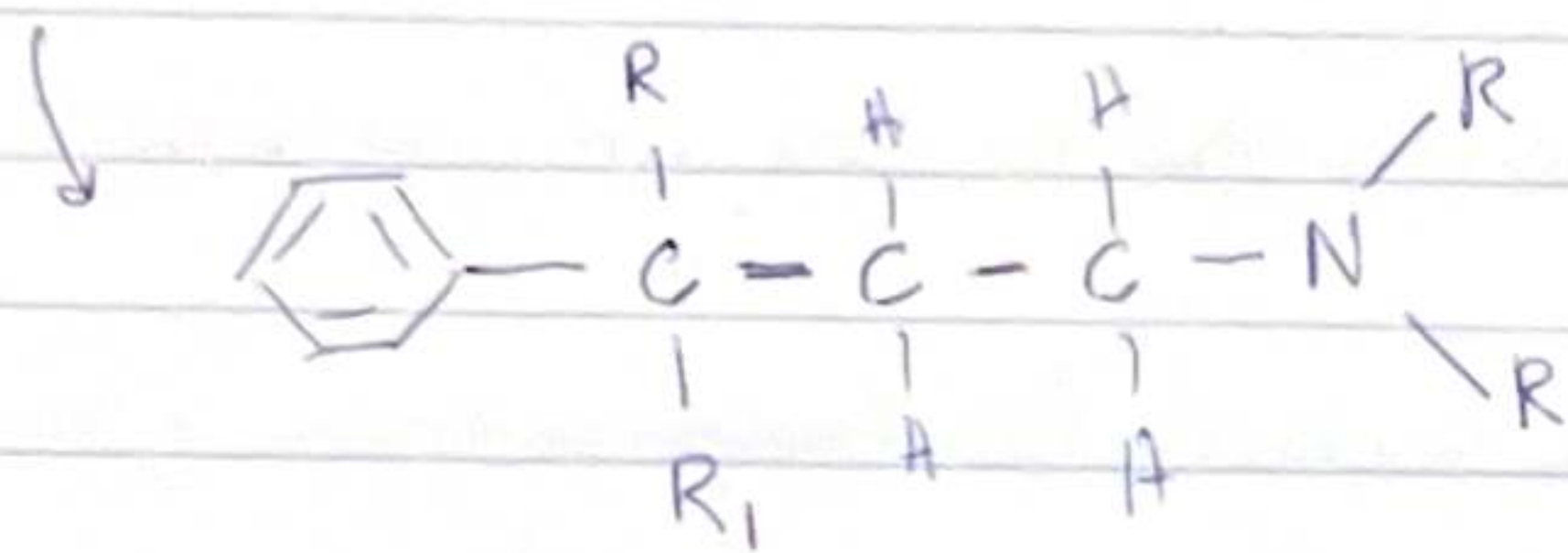
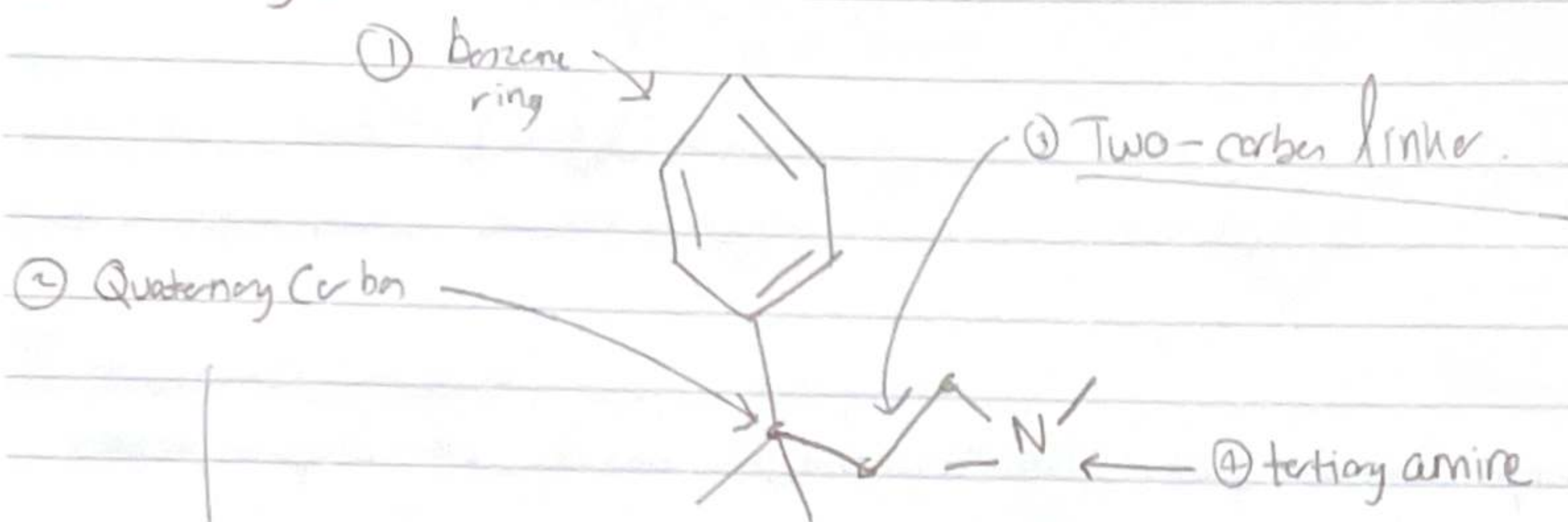
heroin



Methadone

Almost all opioids and opiates share a common structural feature known as the morphine rule. The morphine rule stipulates the structural requirement for a compound to have morphine-like activity. Specifically, the morphine requires to have

- ① A benzene ring
- ② attached to a quaternary carbon connected by
- ③ a two carbon spacer to
- ④ a tertiary amine.



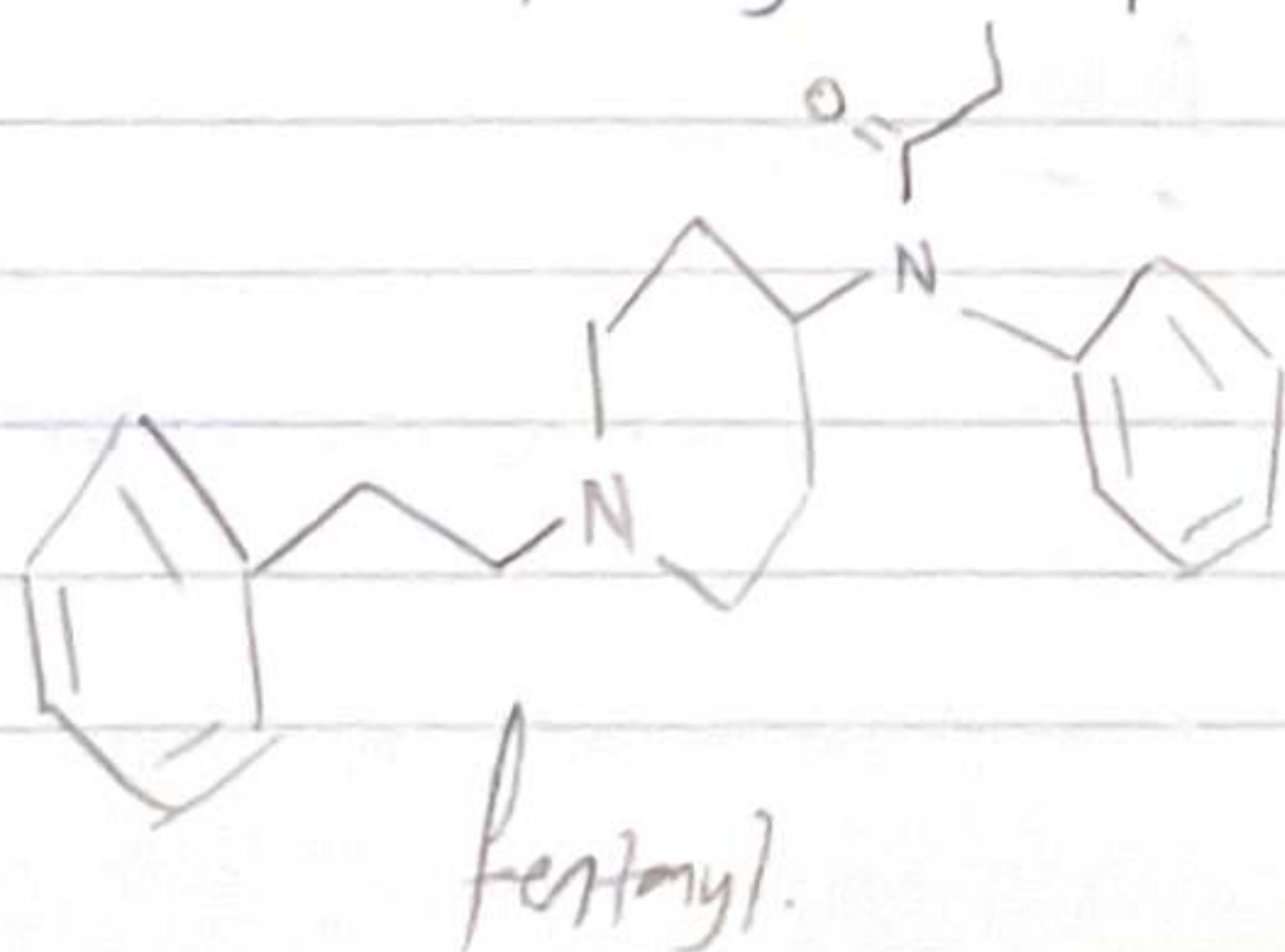
Opioids & opiates play a key-role in pain management but are not suitable for long-term use. (addictive)

For post-operative surgery they are effective & safe.

4° Carbon

Carbon with 4 Carbons bonded to it.

Note: Fentanyl does not obey morphine rule → Carfentanyl shows X100 potency of fentanyl.
 → Shows X100 potency of morphine as analgesic



Alpha drugs (Synthetic Drugs)

In the late 1800s, chemists were able to reliably synthesize organic molecules in laboratory

* Ehrlich's magic bullet

A chemical that can kill an invading microorganism while not affecting the host.

(won nobel prize in 1908) ↓

↑
Paul Ehrlich

Dyes were the interest of biologists based on their ability to stain (or select) a particular type of cell and not the other

* ↓ Dyes could be used as chemical agents to kill one type of cell and not another.

Arsenicals

A very early class of drugs built around an arsenic atom with antimicrobial properties and considerable toxicity.

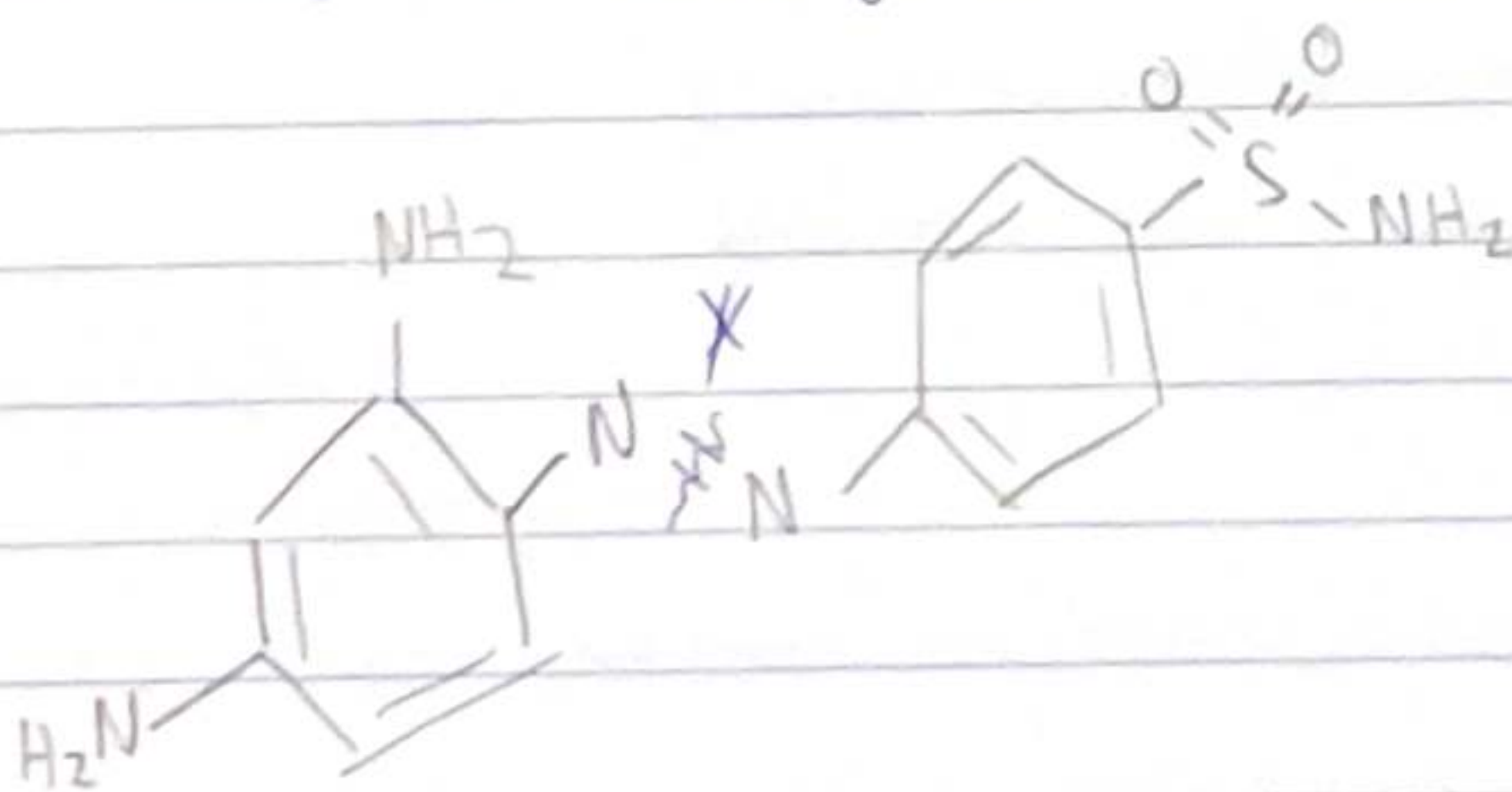
Ehrlich developed a compound for the treatment of Syphilis (bacteria)
(Not so toxic)

~~Despite~~

Domagk also focused on the use of dyes as antibiotics (1920)

Had potent antibiotic activity.

↓
Received
Nobel prize
for
Protonil
Rubrum



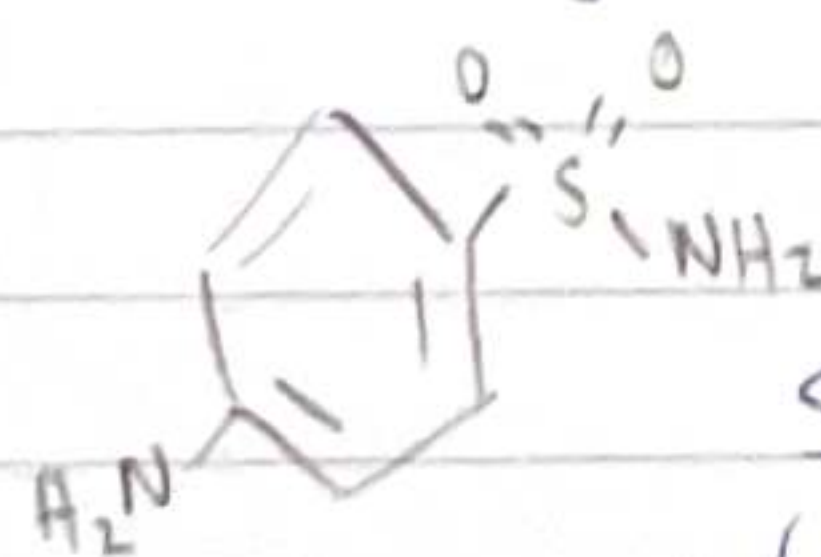
Protonil Rubrum
Red dye and antibiotic

Later French researchers discovered that the dye itself had no antibacterial activity

Prodrug

Drugs that are administered in an inactive form and then converted to a new active form in the body.

For Protonil Rubrum N=N bond is cleaved by metabolic reactions * to obtain



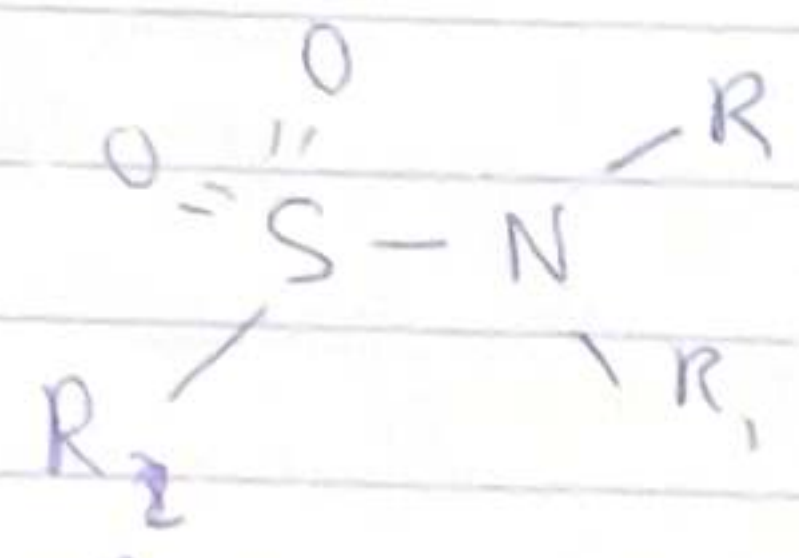
Active → (Antibiotic)

Sulfanilamide → Used as antibiotic by both sides in WWII

Sulfanilamide is the parent molecule in a class of molecule called the Sulfa drugs.

Sulfa drugs → Among first synthetic drugs prepared in a lab (History)

An early class of antibiotics developed from industrial dyes and named after the Sulfonamide group (SO_2N)



↑ Typically describing for sulfa drugs

pharmacophore of Sulfa drugs.



Sulfa drugs were so widely used that bacteria developed resistance.

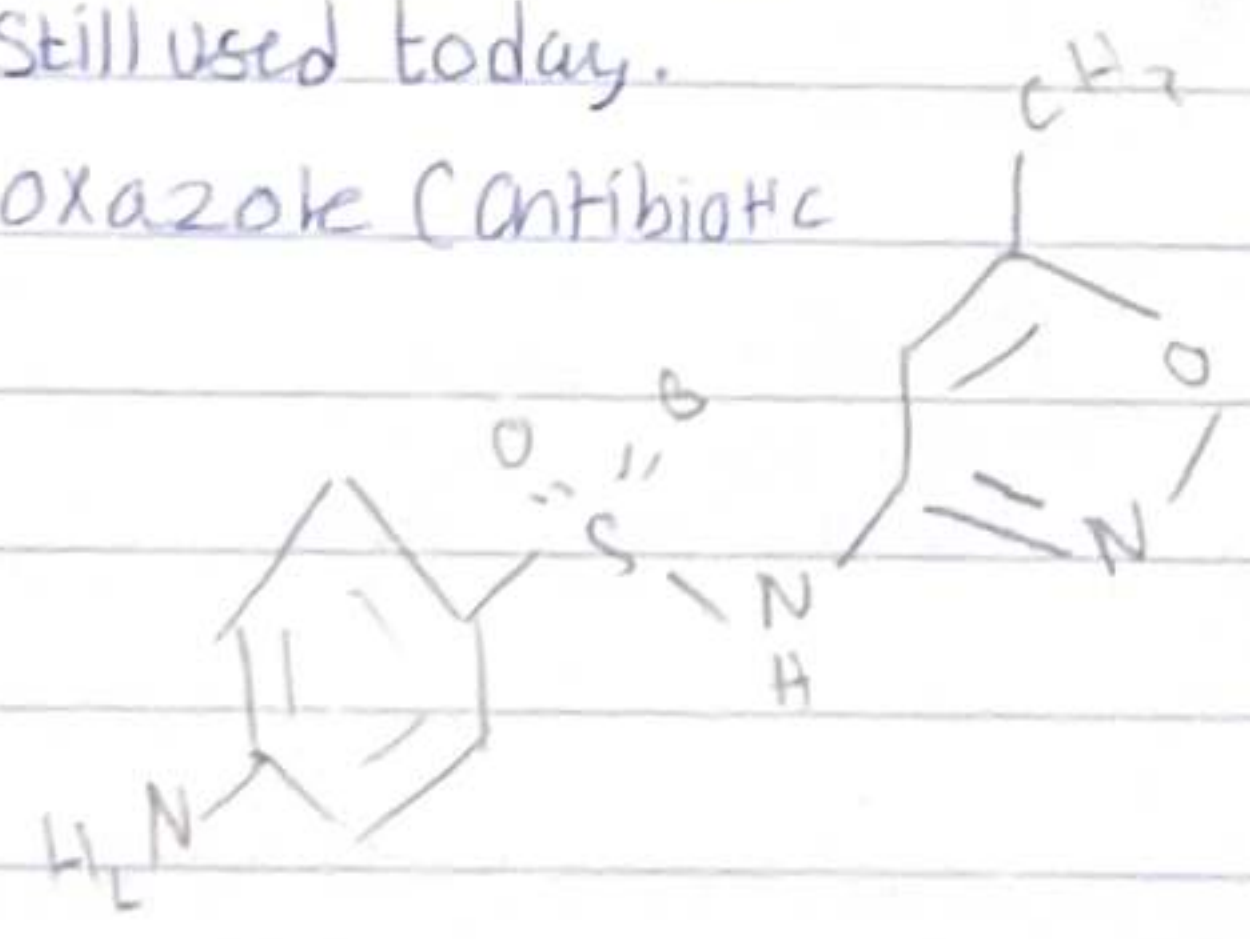
→ Selective pressure applied

Mutational resistance

Increased ability to fight off drug treatments through genetic adaptations by organisms

Sulfa drugs still used today.

Sulfamethoxazole Antibiotic

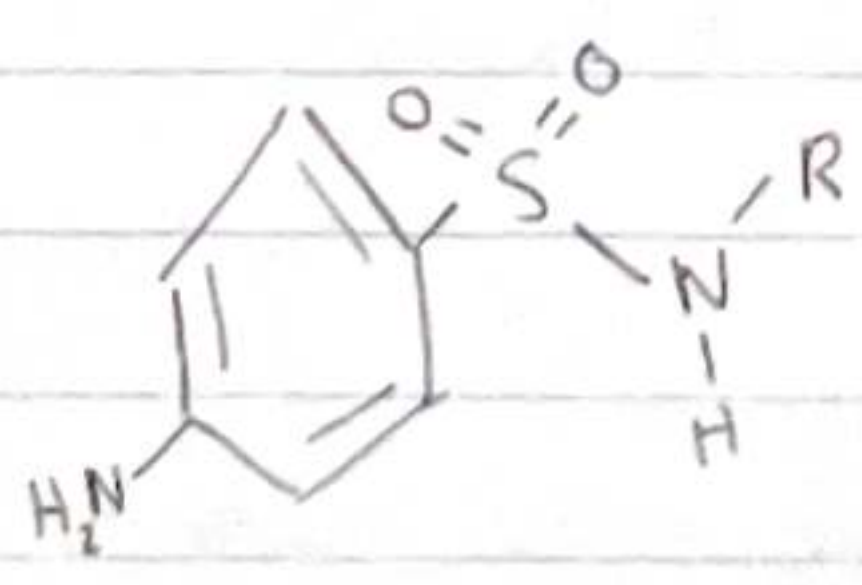


→ middle ear infections in children.

Pharmacophore of Sulfa drugs

Consists of a 4-aminosulfonamide core with tolerance for aryl and acyl groups on the sulfonamide nitrogen

$\text{R} = \text{H}, \text{aryl}, \text{heteroaryl}, \text{acyl}$

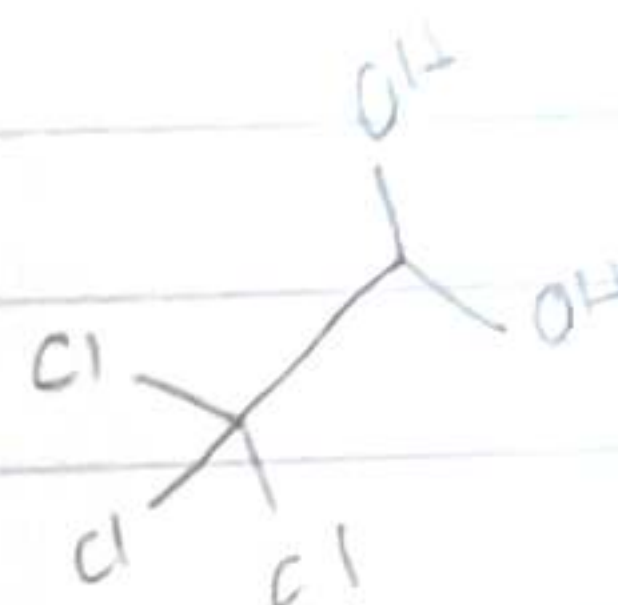


Sulfonamide pharmacophore

Synthetic drugs

• Chloral hydrate

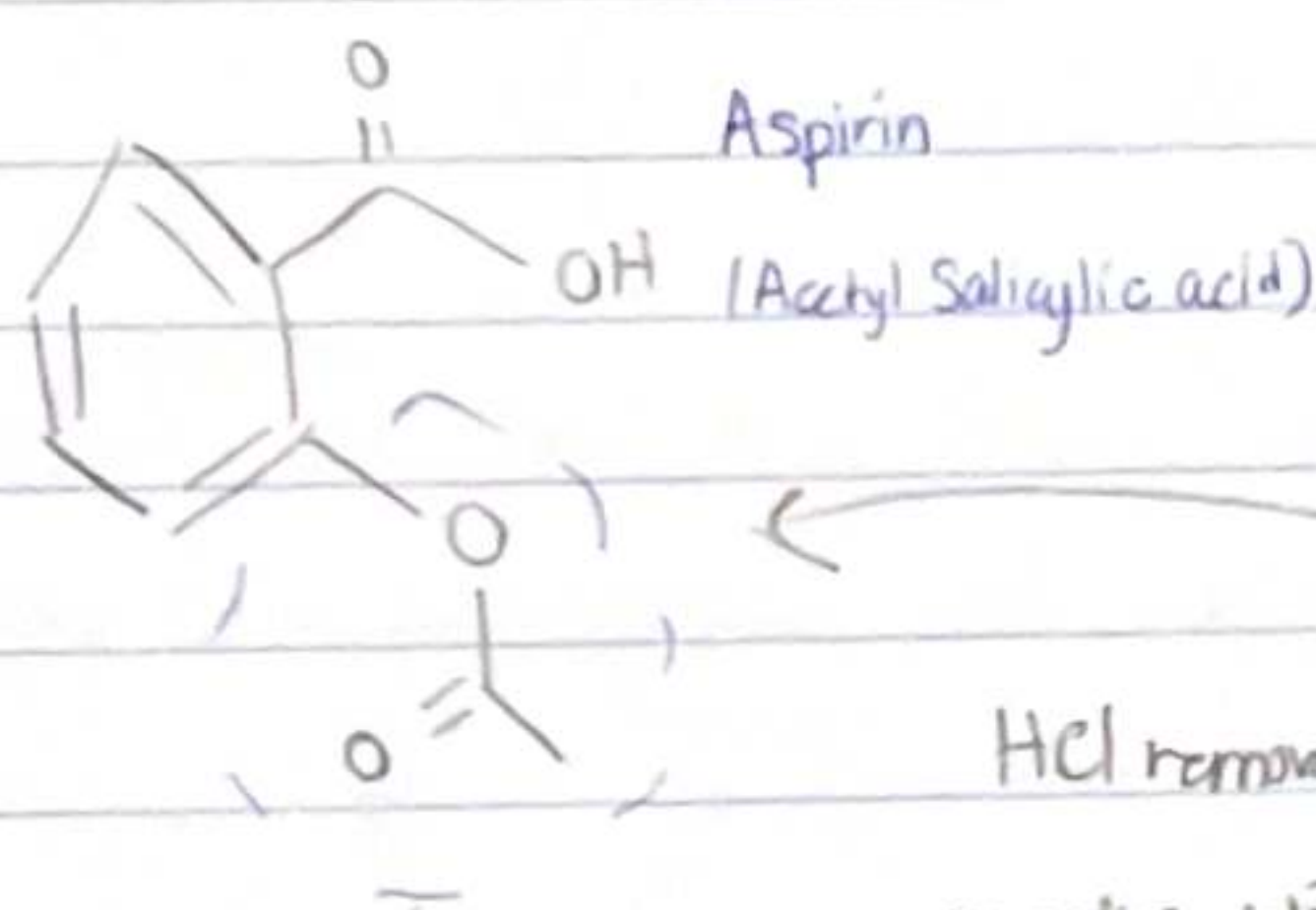
- Formed by reaction of trichloroacetaldehyde with water
- potent sedative (discovered in 1870), used in medicine but also for crime



• Aspirin → prepared around 1900 by a Scientist at Bayer

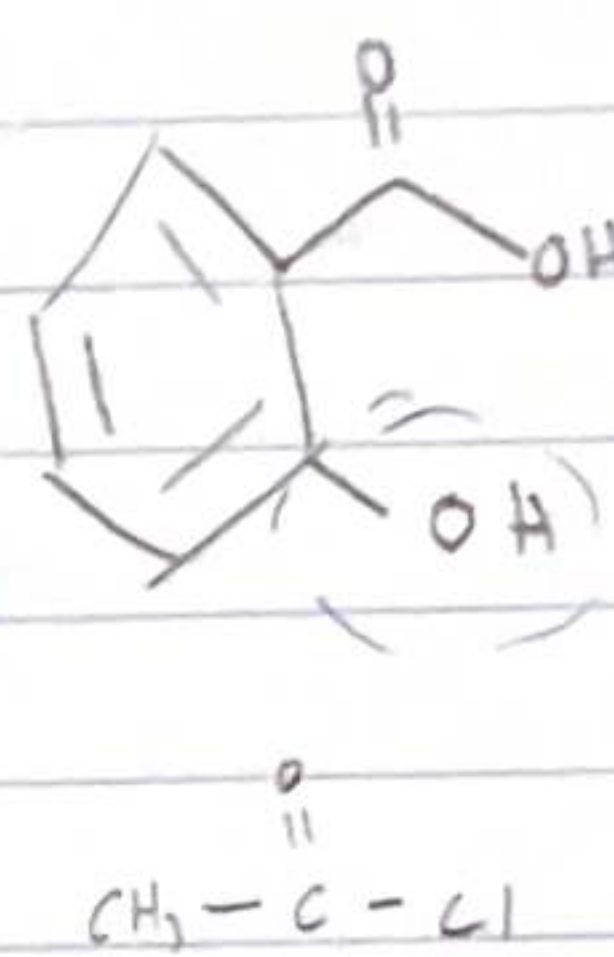
→ Hoffmann (10 Aug 1897)

Derives from natural compound Salicylic Acid, Aspirin (Acetyl salicylic acid) was prepared



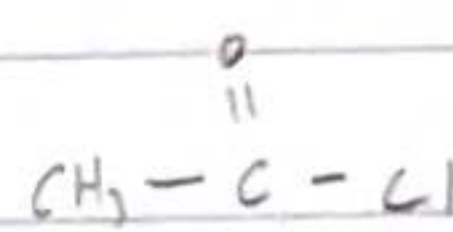
Aspirin

(Acetyl Salicylic acid)



Salicylic Acid

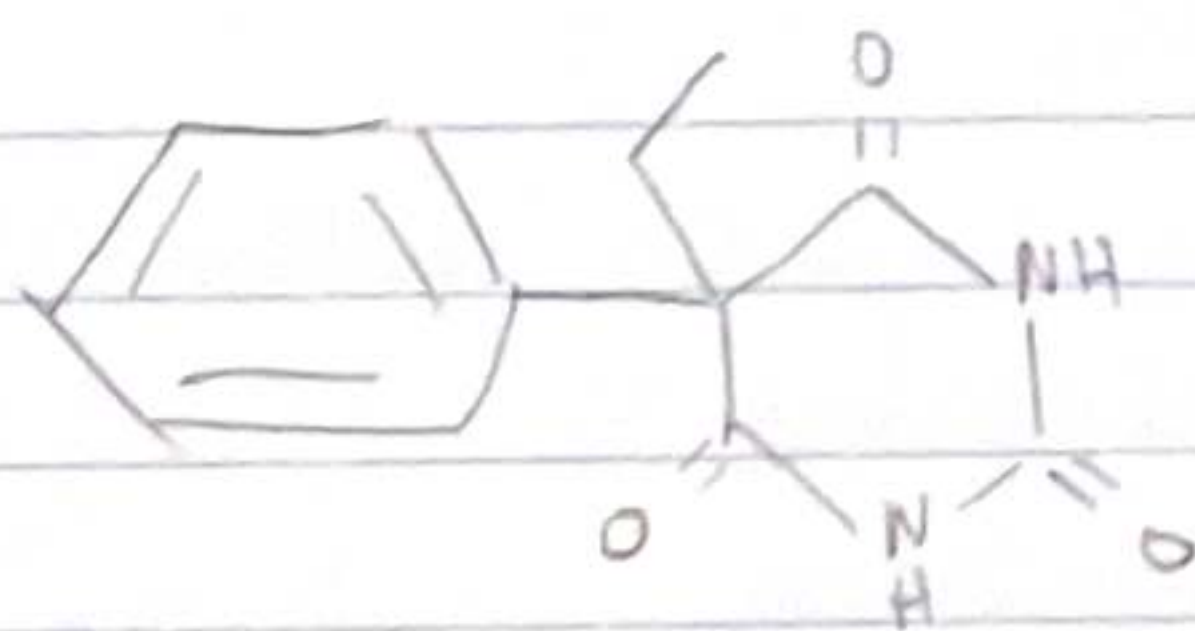
HCl removed from
reaction with Acyl chloride??
(cannot use Acyl Chloride as it
would react with carboxylic group)??



✓ (Still used today)

• Phenobarbital → Anticonvulsant

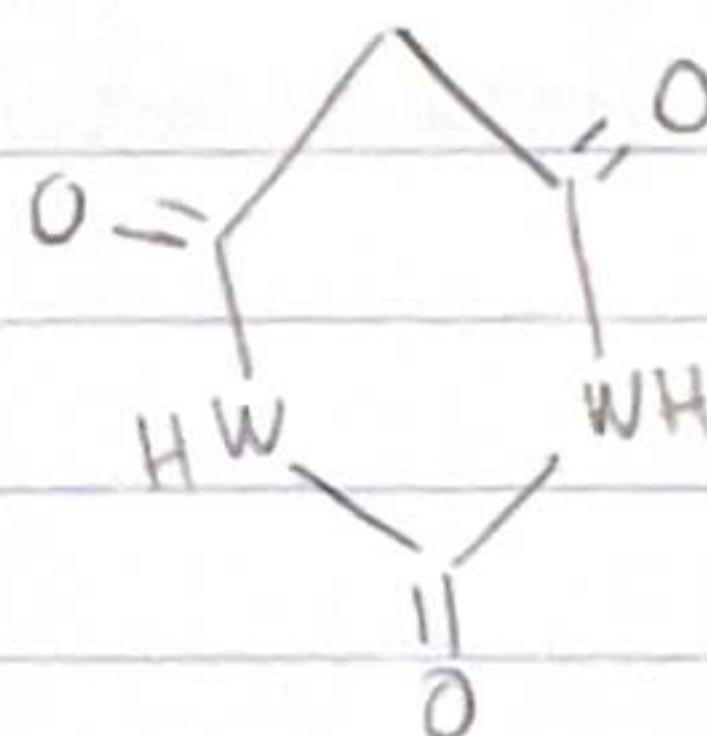
used in 1900 by ~~researchers~~ early research in the
area of barbiturates as anticonvulsants and sedatives. ✓



phenobarbital.

Barbiturate

→ Compound derived from
Barbituric acid



Barbituric acid.