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An Introduction to Medicinal Chemistry 3/e

*Cholinergic systems - احد مكونات الجهاز العصبي في جميع الاوتان
Cholinergic drugs - هي الادوية التي تثيرها acetylcholine*

Chapter 19

CHOLINERGICS, ANTICHOLINERGICS & ANTICHOLINESTERASES

Part 3: Cholinergics & anticholinesterases

*هاد الشاير وهاهي
اوله ريكورد شرحه الشاير لصفحه 170
ثاني ريكورد عملت مراجعه لبيانه الشاير وعلقت الشاير
الطبيب من دقيقه 28*

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[30 slides]

* ال atropin antagonist ←

ليس يهسر معي لسمم بال atropin

بدي ارفع Ach حتى اعاكس عمله

كيف برفع Ach؟؟

يعطى 1 antiacetylcholinesterase inhibitor.

→ acetylcholinagonist

→ acetylcholinatagonist.

→ acetylcholinestrace inhibitor

↓ يهسر زي
acetylcholinagonist.

(Alzheimer) ينعطبهم ادوية بترفع Ach في دماغهم

* ال

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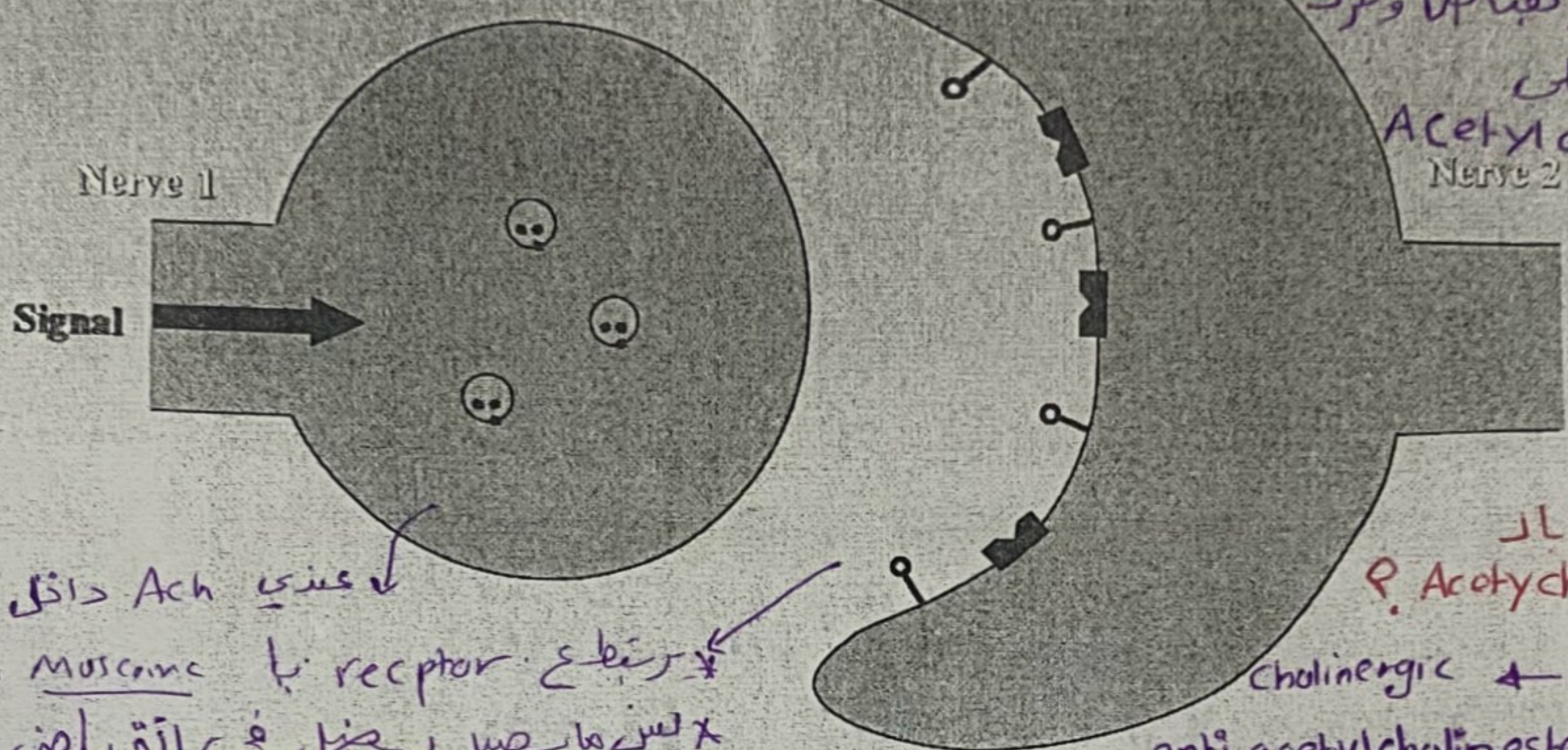
Ach ester في Ach ، يفتت هو بواكس عمل Ach
 * لنفتت انه خلال عملة التنفس عضلات

14. Acetylcholinesterase

14.1 Role

- Hydrolysis and deactivation of acetylcholine
- Prevents acetylcholine reactivating receptor

الفحص الجسمي كلها عضلات
 يجب ان تنقبض ، بس تنقبض (انقباض)
 وارتخا (عابض يصل انقباض موت الانسان)
 كيف يصير انقباض وارتخا ؟
 ال Ach منطلق بتعلق
 مع muscarinic receptor
 ويصير انقباض وترك
 ويروح على
 Acetylcholinesterase
 ويرتكب

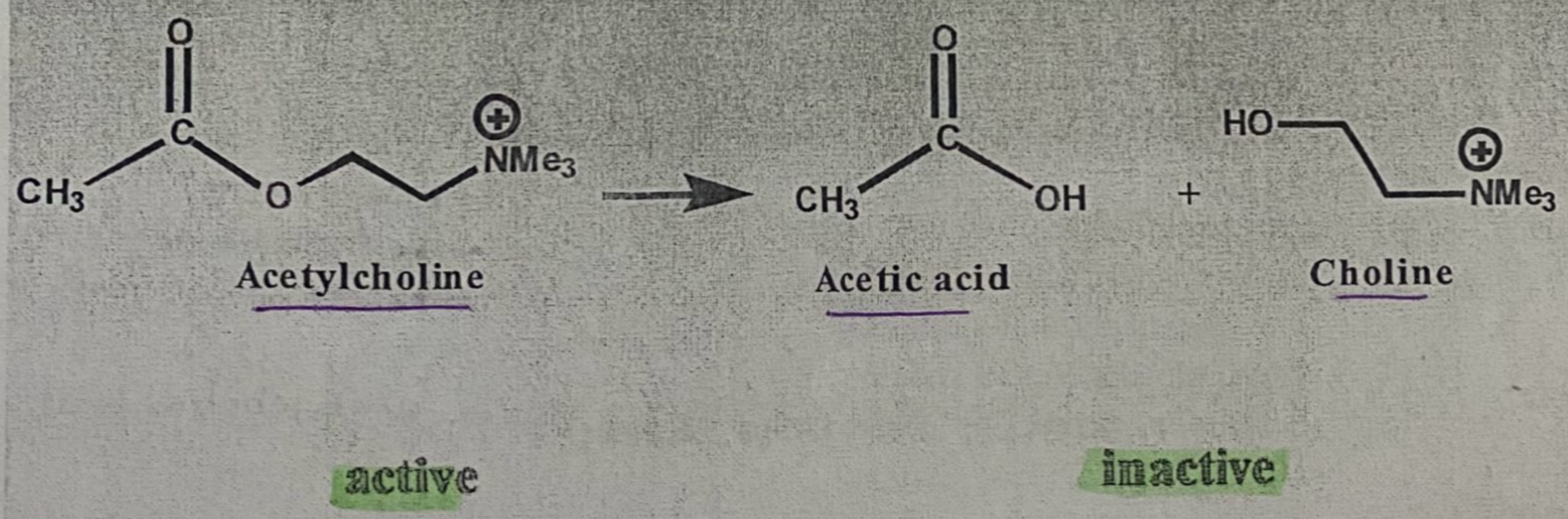


عيني Ach داخل الوصلات
 يرتبط مع receptor يا muscarinic او nicotinic
 * بس ما يصير يضل في انقباض مستمر
 تسفل Ach ← acetylcholinesterase
 هتت يتا ريو الة acetylcholinesterase
 تفتت ال (ester bond) acid alcohol

* مليت اذا ف نقص ال
 Acetylcholinesterase
 1) بويون cholinergic agonist
 2) اوبويون anti acetylcholinesterase enzyme
 لانح يرفع ال (Ach) 1

14. Acetylcholinesterase

14.2 Hydrolysis reaction catalysed



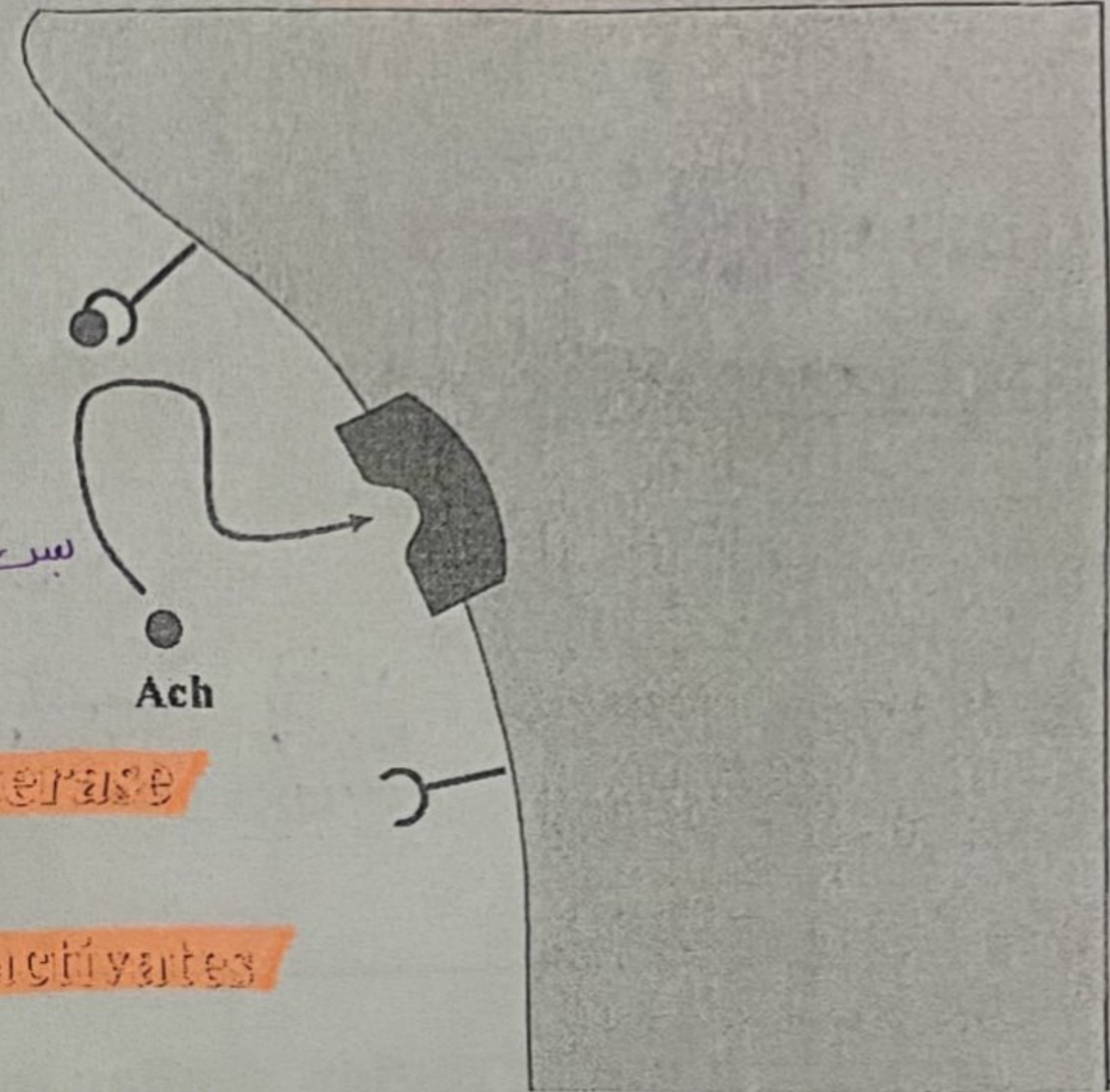
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14. Acetylcholinesterase

14.3 Effect of inhibition

● Enzyme inhibitor (Anticholinesterase)

سواء الـ Ach يدخل إلى receptor



- (1) Inhibitor blocks acetylcholinesterase
- (2) Ach is unable to bind
- (3) Ach returns to receptor and reactivates it
- (4) Enzyme inhibitor has the (same) effect as a cholinergic agonist

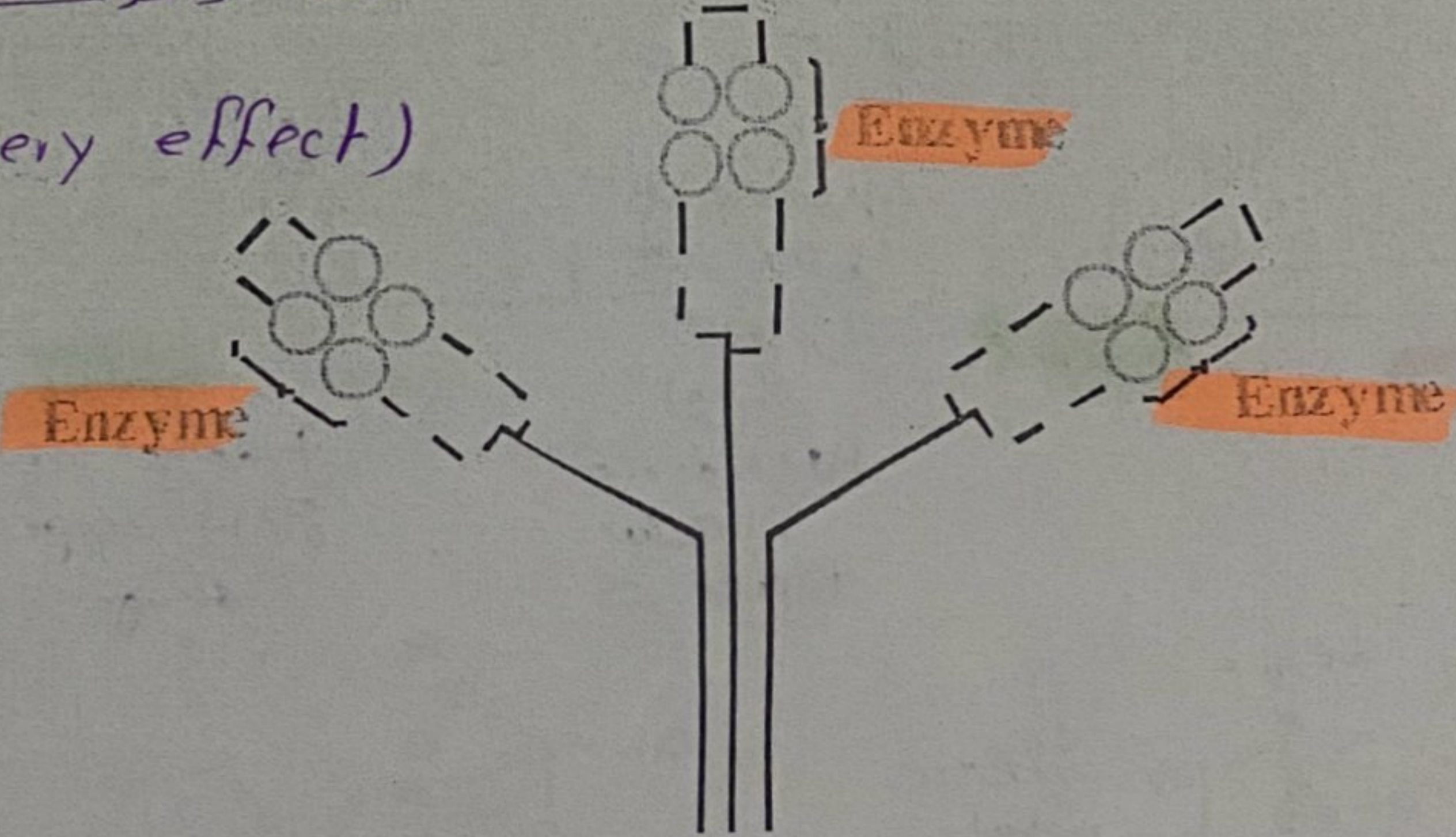
Nerve 2
©1

14. Acetylcholinesterase

14.4 Structure of enzyme complex

لأنه الواحد له ثلاثة
لأنه عبارة عن مركب شديد الفعالية

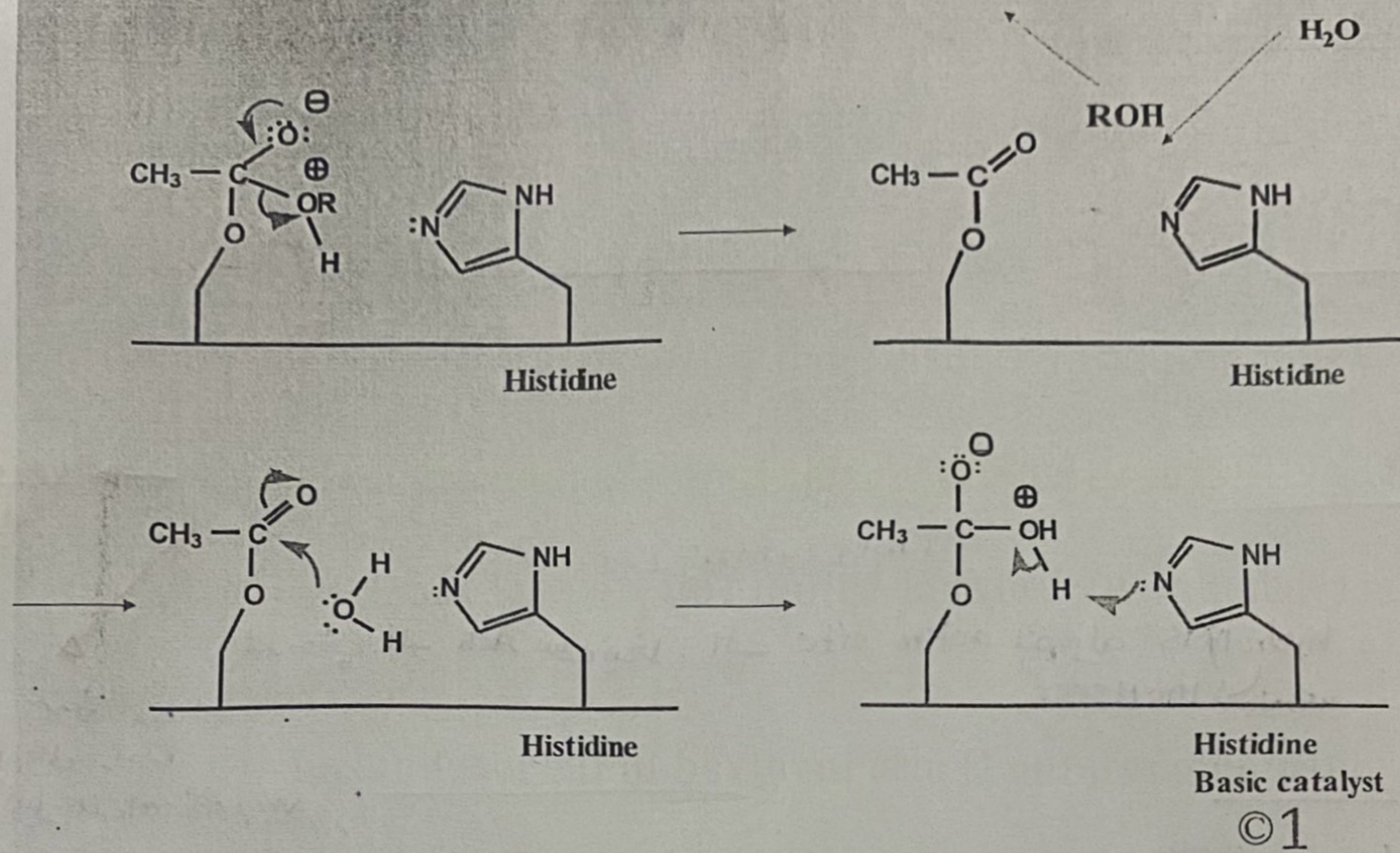
(its very effect)



©1

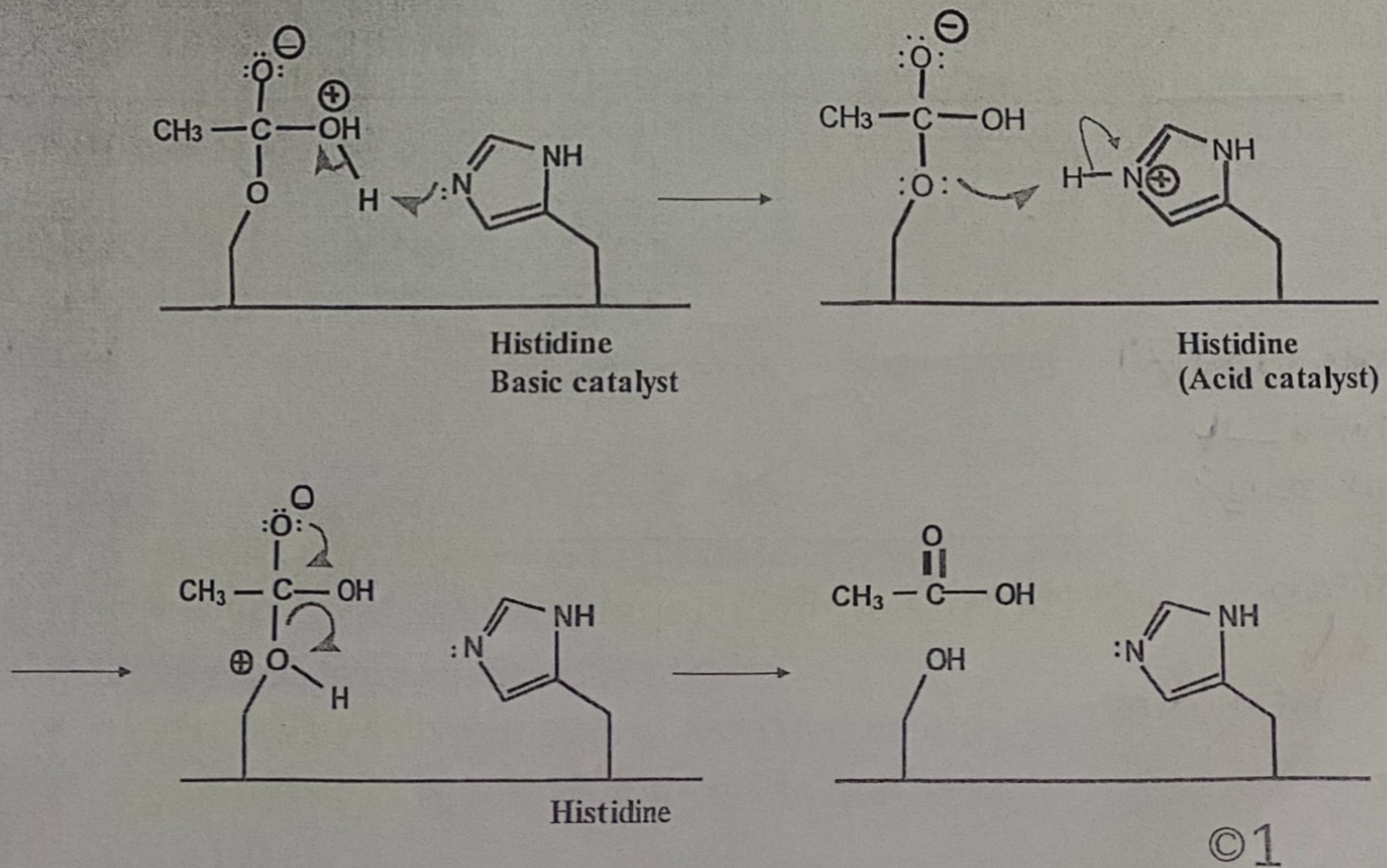
14. Acetylcholinesterase

14.6 Active site - Mechanism of catalysis



14. Acetylcholinesterase

14.6 Active site - Mechanism of catalysis



14. Acetylcholinesterase

- Serine and water are poor nucleophiles
- Mechanism is aided by histidine acting as a basic catalyst
- alcohol part
Choline and serine are poor leaving groups

الكاساس
alcohol
بكره يطلع
hydrolysis
والتي تيسر
انه ال
Serine
بفك
عن
ال
Carbonyl
هو ال
acid catalyst hisidine.

Leaving groups are aided by histidine acting as an acid catalyst

Very efficient - 100×10^6 faster than uncatalysed hydrolysis

Acetylcholine hydrolysed within 100 μ secs of reaching active site
 hydrolysis active site ال
 within \rightarrow 100 Msecs.

A glutamate residue is also involved in the mechanism

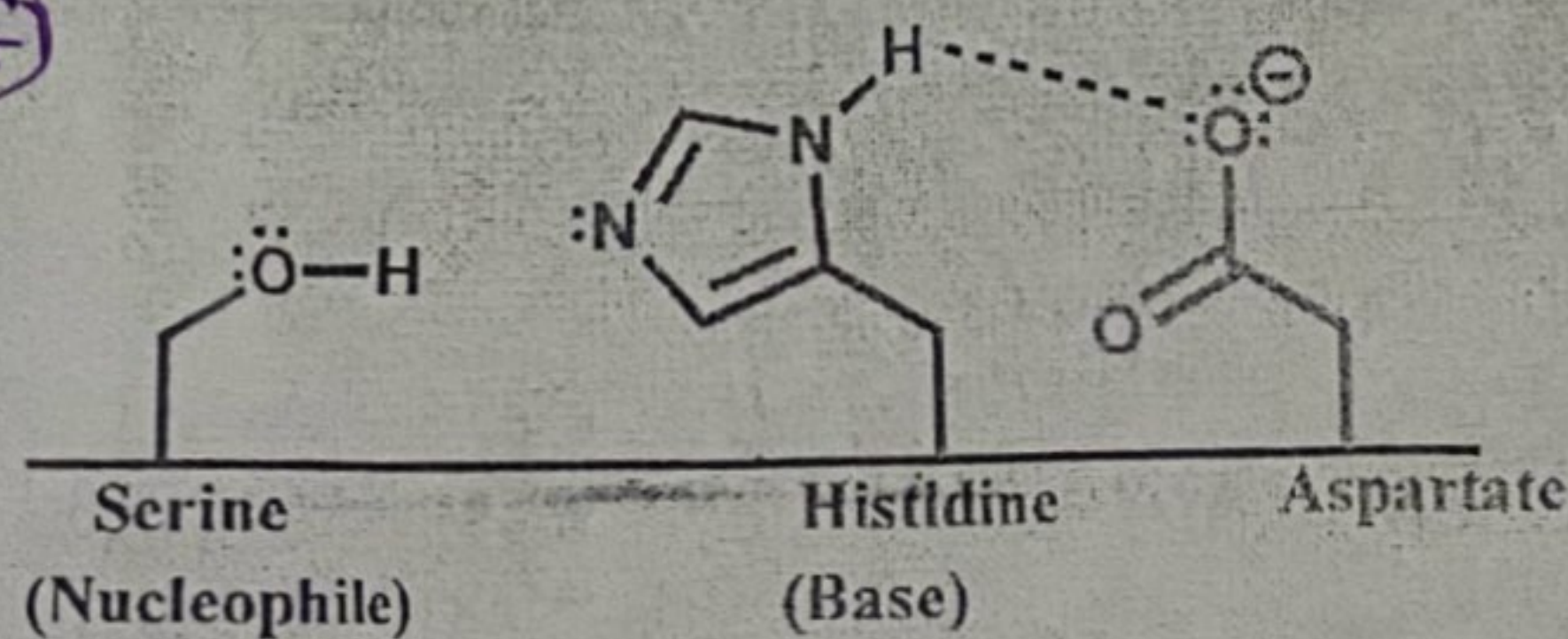
هنا معلومة
مهمة
درت
لصحت بسبب
وجود ال histidine
سرعة التفاعل زادت
بشكل كبير وكانت
very efficient
©1
* احنا بنعرف انه

14. Acetylcholinesterase

The catalytic triad Extra Information

- An aspartate residue interacts with the imidazole ring of histidine to orientate and activate it

* يوجد molecule
بال aspartic acid
زيادة يساهم
position
بال
histidine.



ال catalyst مادة
تدخل للتفاعل وتخرج كما هي
لكنها تزيد سرعة التفاعل
ف بسبب ال histidine
وال acid/base catalyst histidine
سرعة التفاعل زادت حوالي
100 مليون مرة
نت بسبب تفاعل
ما لتجسد تفاعل
وهو روح ويسبب
وهنا بسبب
التفاعل ال
histidine

©1

* بعد ما فهمنا الـ acetylcholinesterase وطريقه عمله سيجي لها
 * خط فيبالنا انه acetylcholinesterase لازم يتكسر عند انهاء عمله
 ولا يوصل الفصلات المتساوية رودة واحكاما جدا طار لا شيا

15. Anticholinesterases

خلايا الدم / خلايا ليف / خلايا GIT

عند العصبية بعد عصبية الفصوات العصبية
 من غيري لمصنعات عصبية الفصوات العصبية
 anticholinergic

- Inhibitors of acetylcholinesterase enzyme
- Block hydrolysis of acetylcholine
- Acetylcholine is able to reactivate cholinergic receptor
- Same effect as a (cholinergic agonist)

تسمية
 وطلبنا
 من ايداع
 المعاصرين
 في كل احوال

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لونه inhibits cholinesterase

15. Anticholinesterases

antidote → atropine.

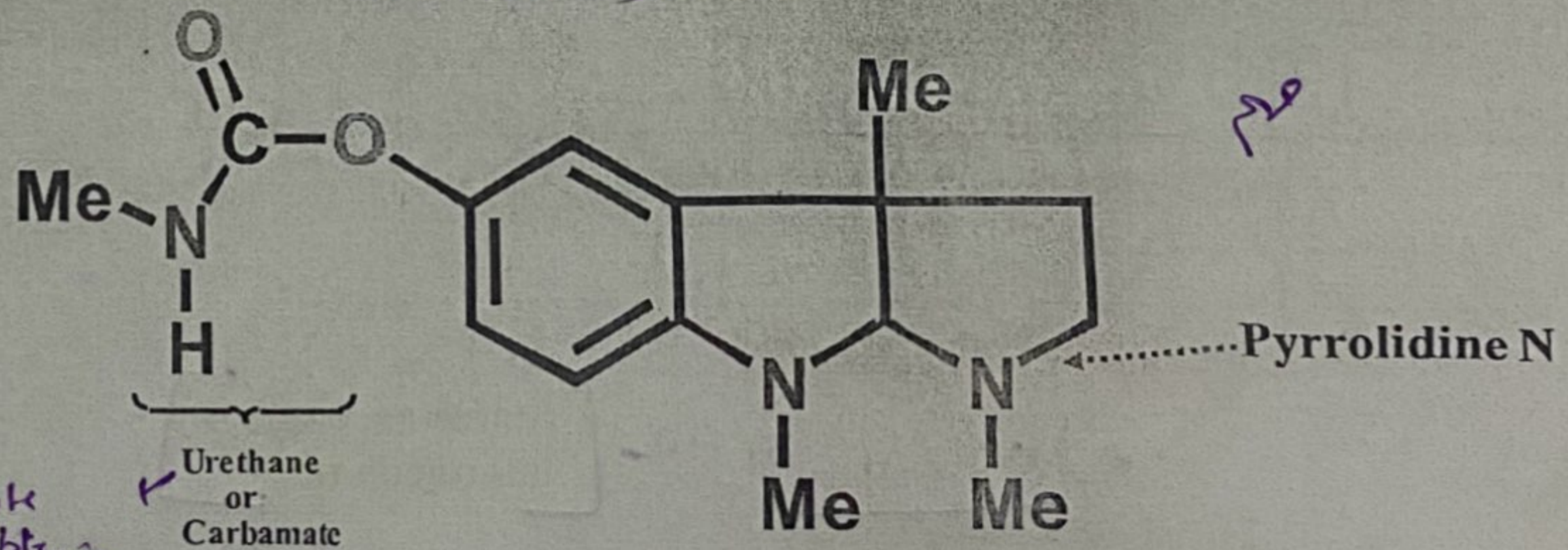
15.1 Physostigmine

حينها هاد اح يدخل على acetylcholinesterase binding bucket
 بالـ binding bucket وتقف هناك
 لانه عنده VdW اكثر

كالمادة طبيعية

* سببه يتربص الـ Ach
 ليس عنده aromatic ring

دائما الـ inhibitor
 عنده VdW اكثر



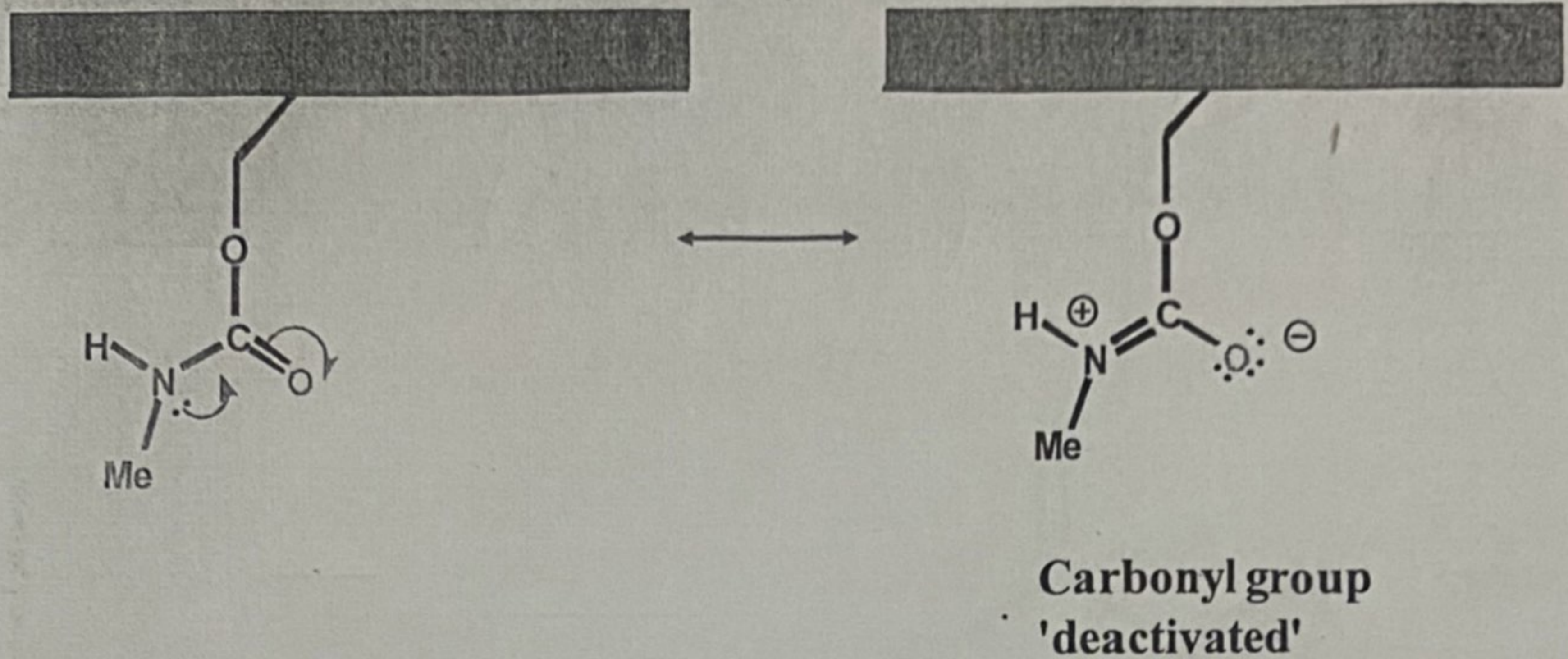
مستقرة
 فوادة مستقرة

Stable carbamate intermediate. (تعتبر مستقرة)
 * Hydrolysis → very slow

- Natural product from the African calabar bean
- Carbamate is essential (equivalent to ester of Ach)
- Aromatic ring is important
- Pyrrolidine N is important (ionised at blood pH)
- Pyrrolidine N is equivalent to the quaternary nitrogen of Ach

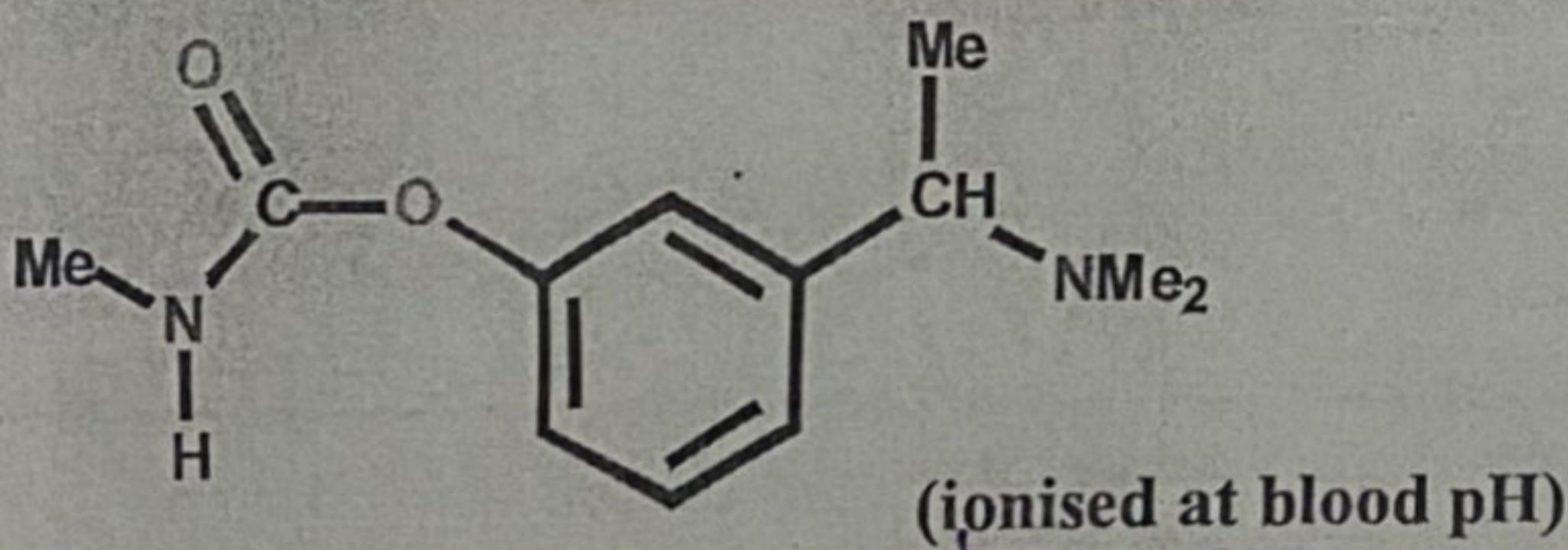
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15.2 Mechanism of action



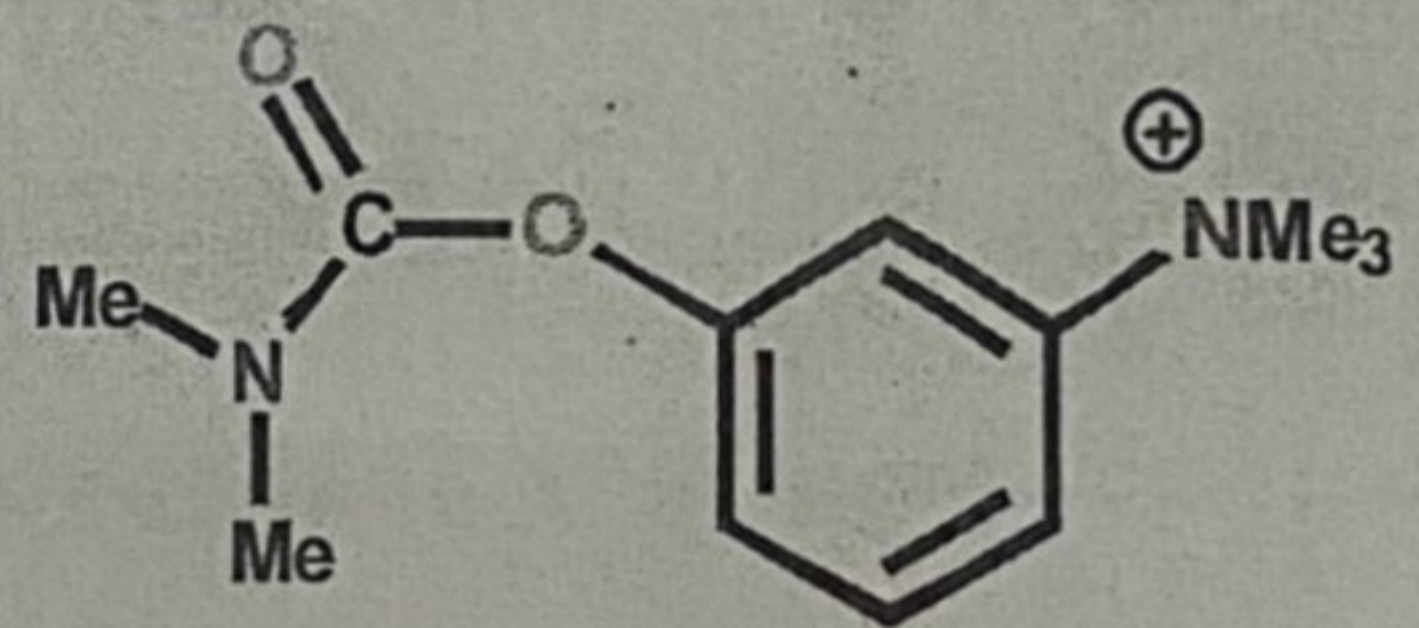
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15.3 Physostigmine analogues



Miotine

- (1) • **Simplified analogue**
- (2) • **Susceptible to hydrolysis**
- (3) • **Crosses BBB as free base**
- (4) • **CNS side effects**



Neostigmine

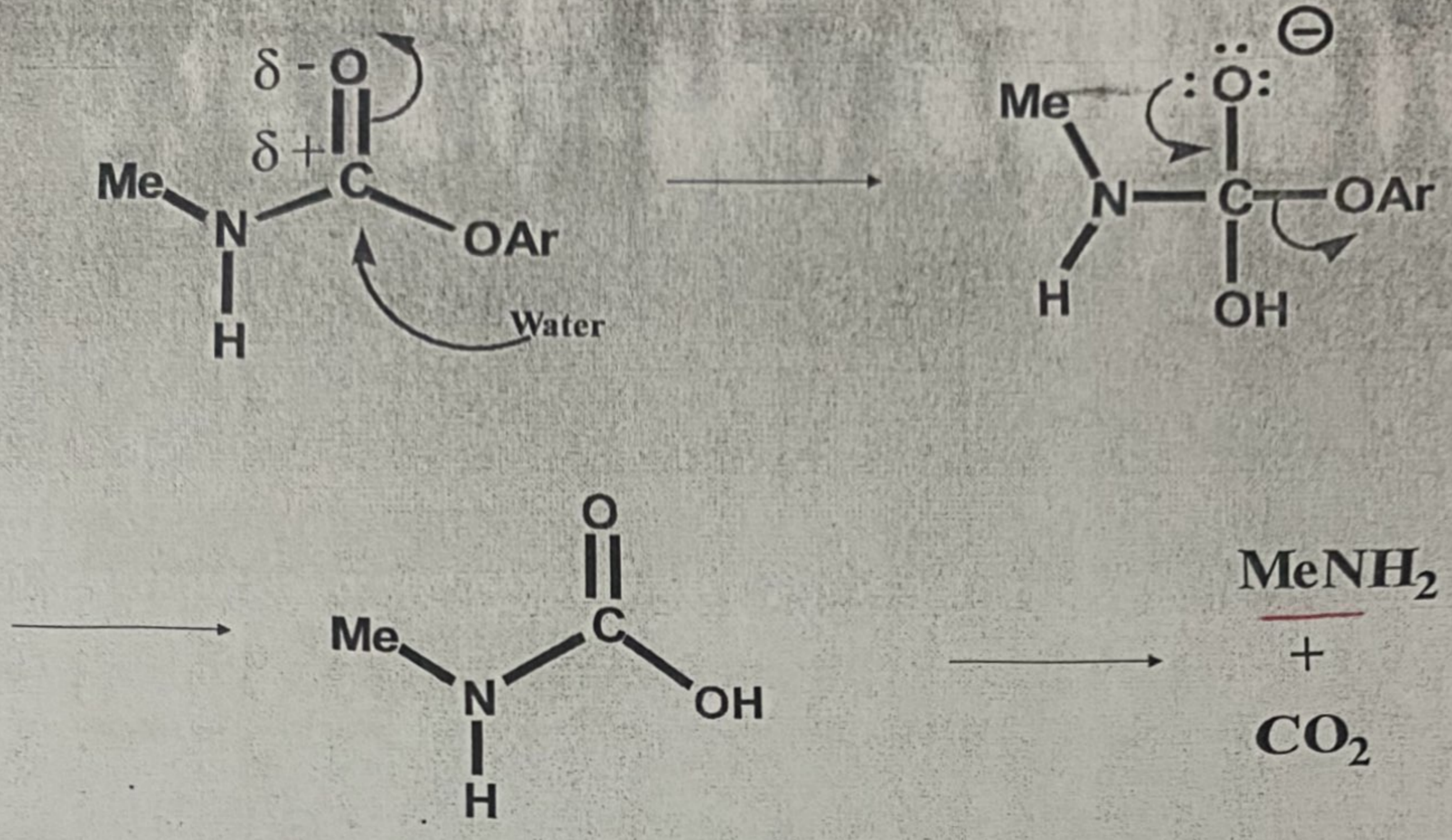
- (1) • **Fully ionised**
- (2) • **Cannot cross BBB**
- (3) • **No CNS side effects**
- (4) • **More stable to hydrolysis**
- (5) • **Extra N-methyl group increases stability**

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① → water nucleophilic attack
 hydrolysis للمحلول
 methylamine + CO₂ وبتفصيل

Hydrolysis mechanisms

Possible mechanism 1

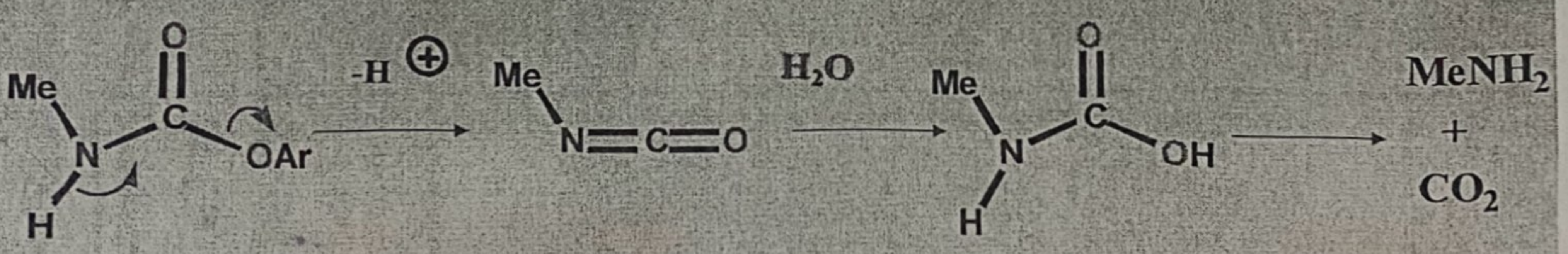


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انفاسه
 انقار
 كقار
 كقار
 كقار

Hydrolysis mechanisms

Possible mechanism 2

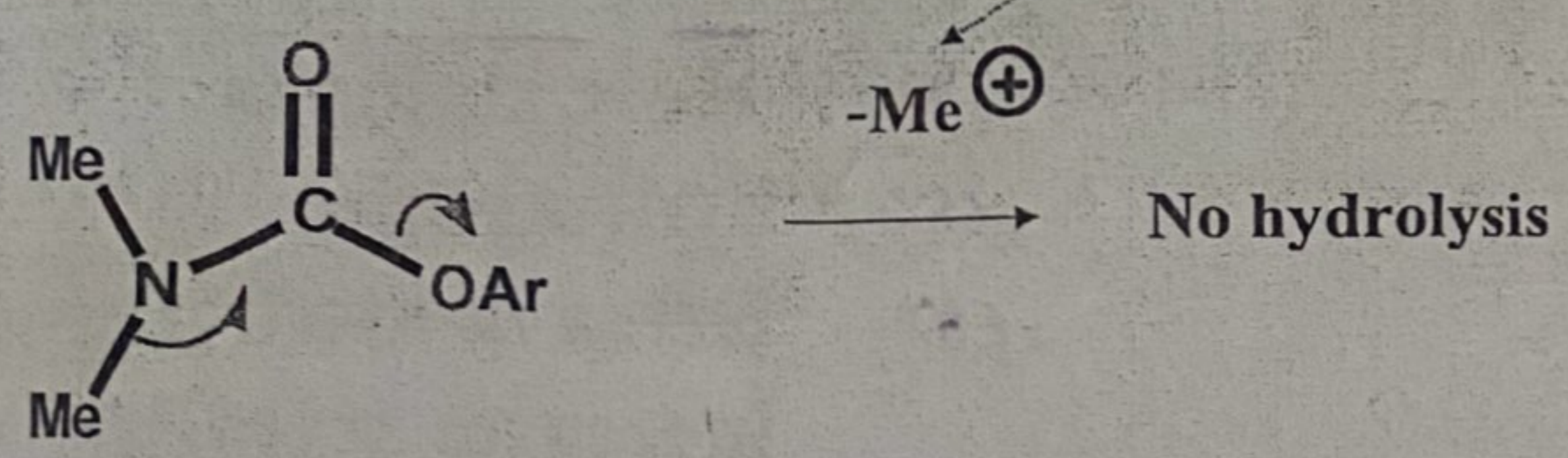


المركب يتفكك → hydrolysis

Too reactive

* يكون عن طريق
 catalyst hydrolysis.

Compare:

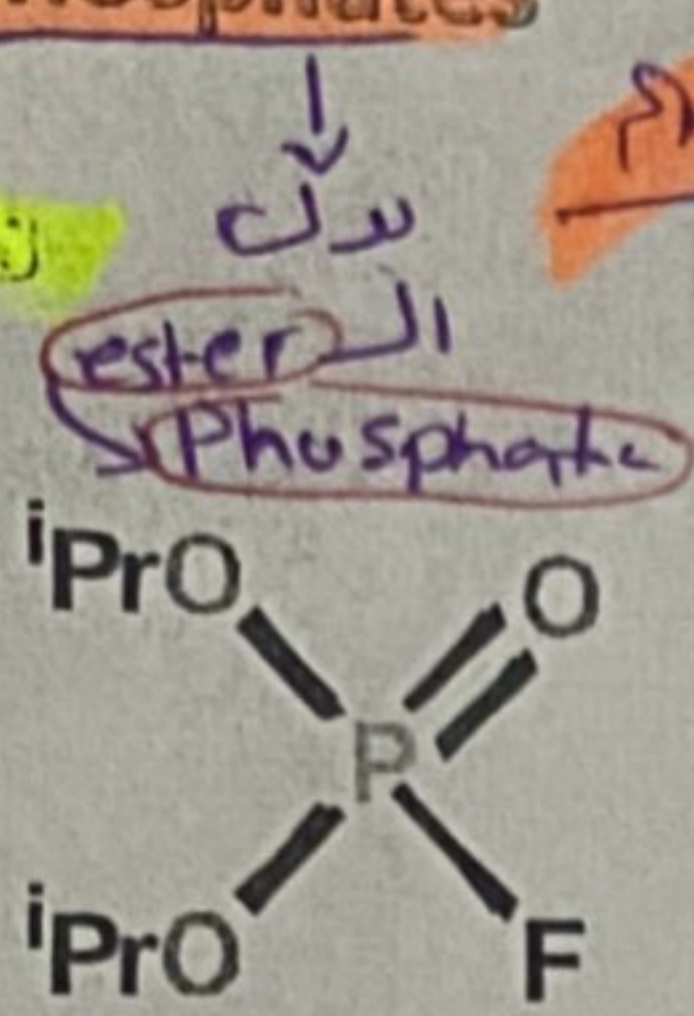


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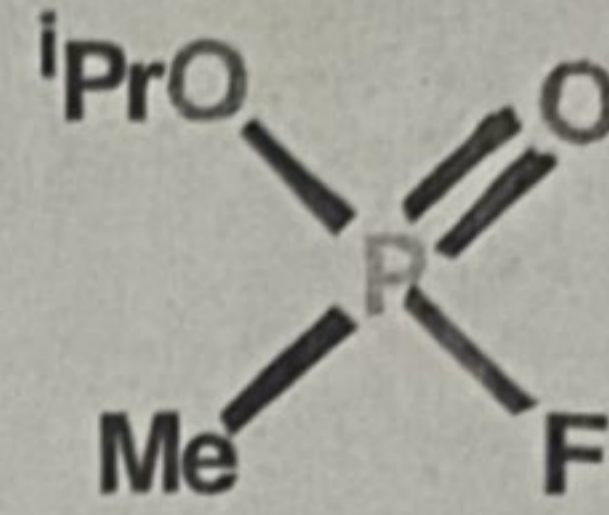
* كل كى دستاهم reversible
 وصاح ولسنخدم ك اذويه

15.4 Organophosphates

a) Nerve gases



(irreversible acetylcholinesterase inhibitors)
 هاد (دهاي عبارة من موم)



* كرتب ال phosphate group
 بيلد ال acetylcholinesterase

Dyflos

(Diisopropyl fluorophosphonate)

تم تطويرها بالحرب العالمية الثانية
 Agents developed in World War 2

Agents irreversibly inhibit acetylcholinesterase

Permanent activation of cholinergic receptors by Ach

Results in death

اذا ما اخذ
 antidote
 مباشره يودي
 للوفات

احنا ما بنتكاه
 عن دواء
 احنا بنتكاه
 عن تركيبه

بفضل ال Ach
 بفضل ال
 عصبتي مستقر

Sarin

هو غاز لسام اذويه

القوات الوريه
 في الحرب عن ريف دمشق
 ولعجوم على خان شيخون
 هو كان هجوم جوي بالسلاح
 الكيميائي

الخطام هاد لغاز

ير الفصلات بالمساء ايه ال هاد بل بالمفسر

ال irreversibly

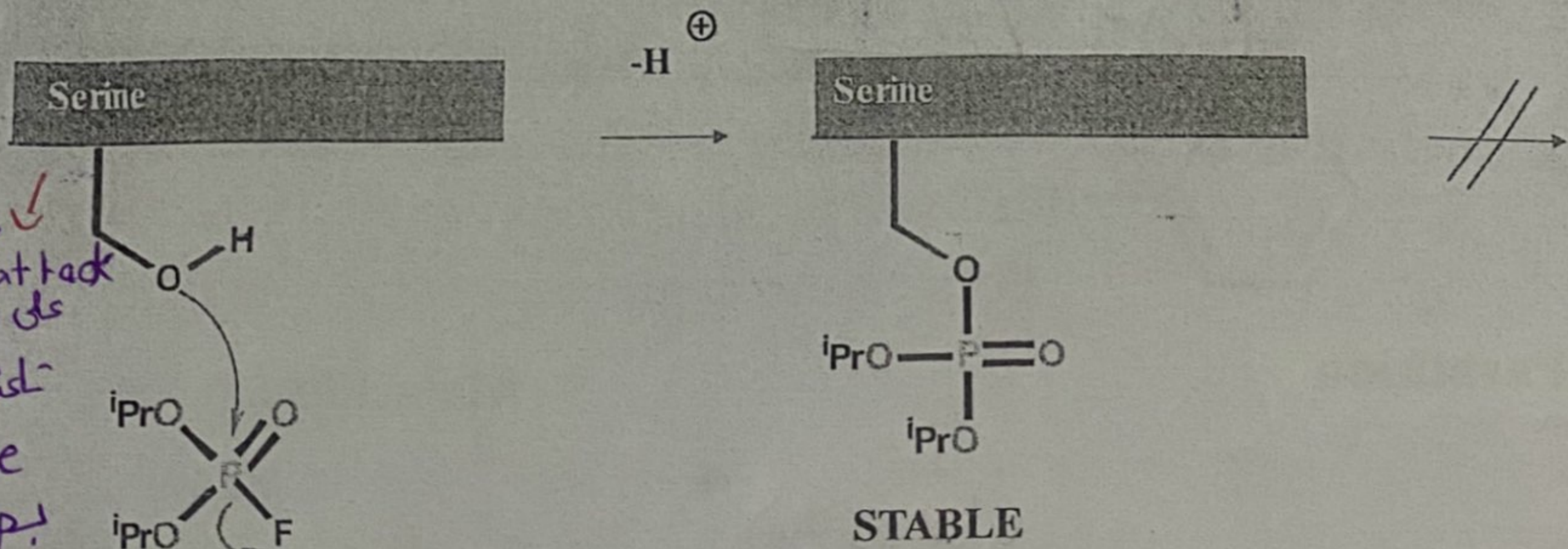
ال acetylcholine بفضل

اثره ففاه خنجر من الفصلات

بكون ارتقاء فبنالي يتوقف تنفس المرين
 الى استنشاق غاز Sarin

15.4 Organophosphates

b) Mechanism of action



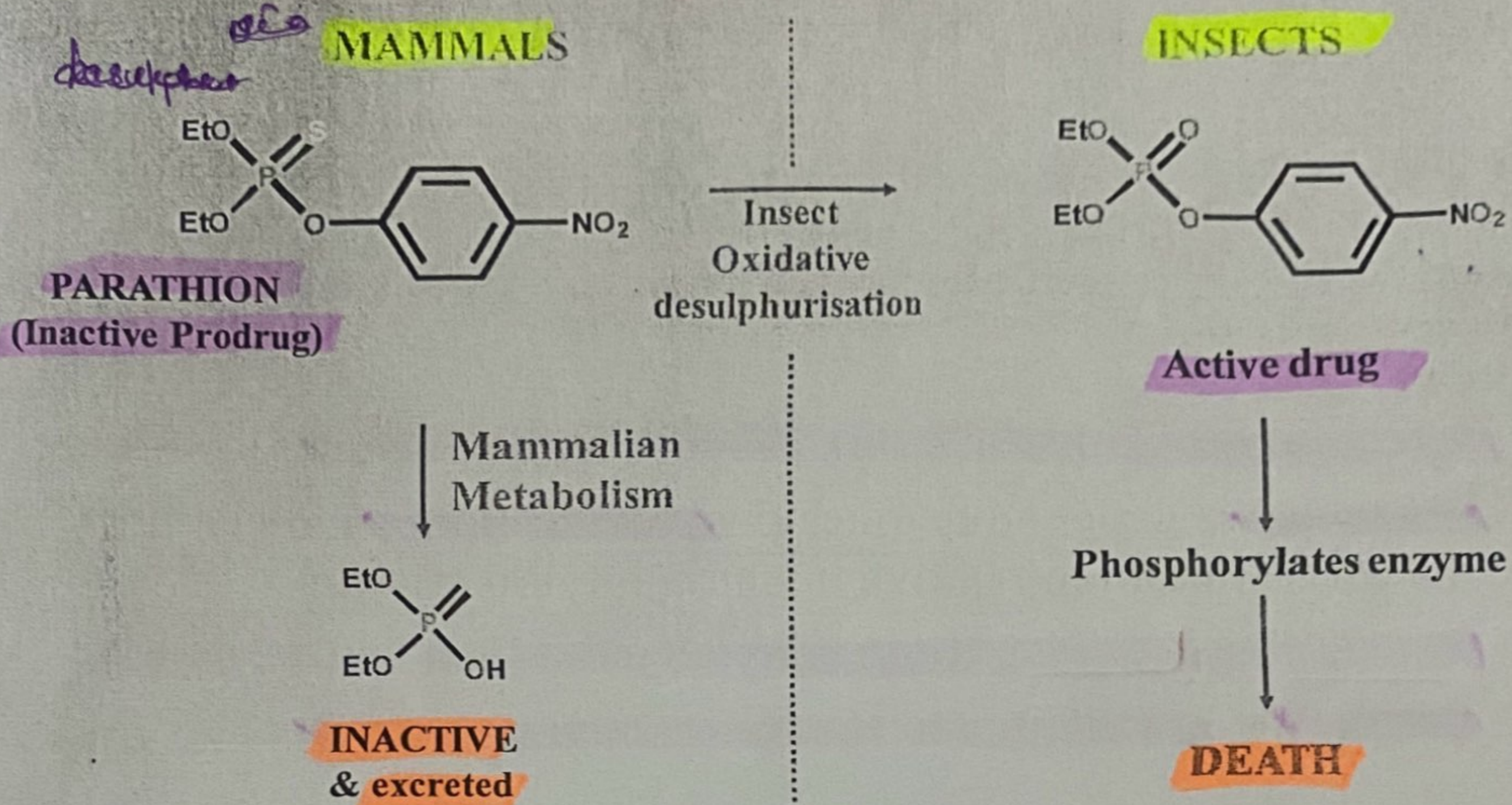
نوك
 nucleophilic attack
 على ال phosphate
 كرتب ال
 phosphonate
 بغير (stable interaction)
 بين Serine
 وال phosphate

Irreversible phosphorylation
 P-O bond very stable

©1

15.4 Organophosphates

d) Organophosphates as insecticides



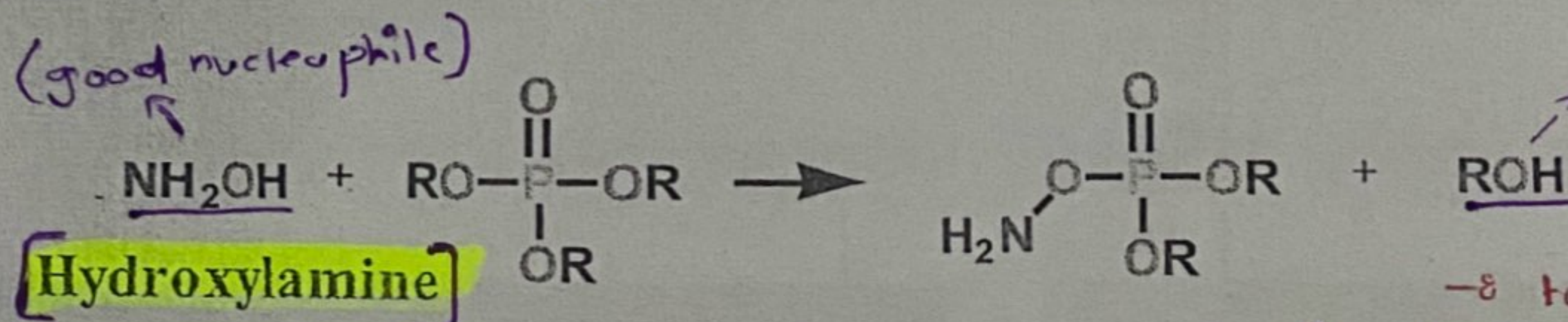
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15.4 Organophosphates

e) Design of Organophosphate Antidotes

Strategy

- Strong nucleophile required to cleave strong P-O bond
- Find suitable nucleophile capable of cleaving phosphate esters
- Water is too weak as a nucleophile
- Hydroxylamine is a (stronger nucleophile)



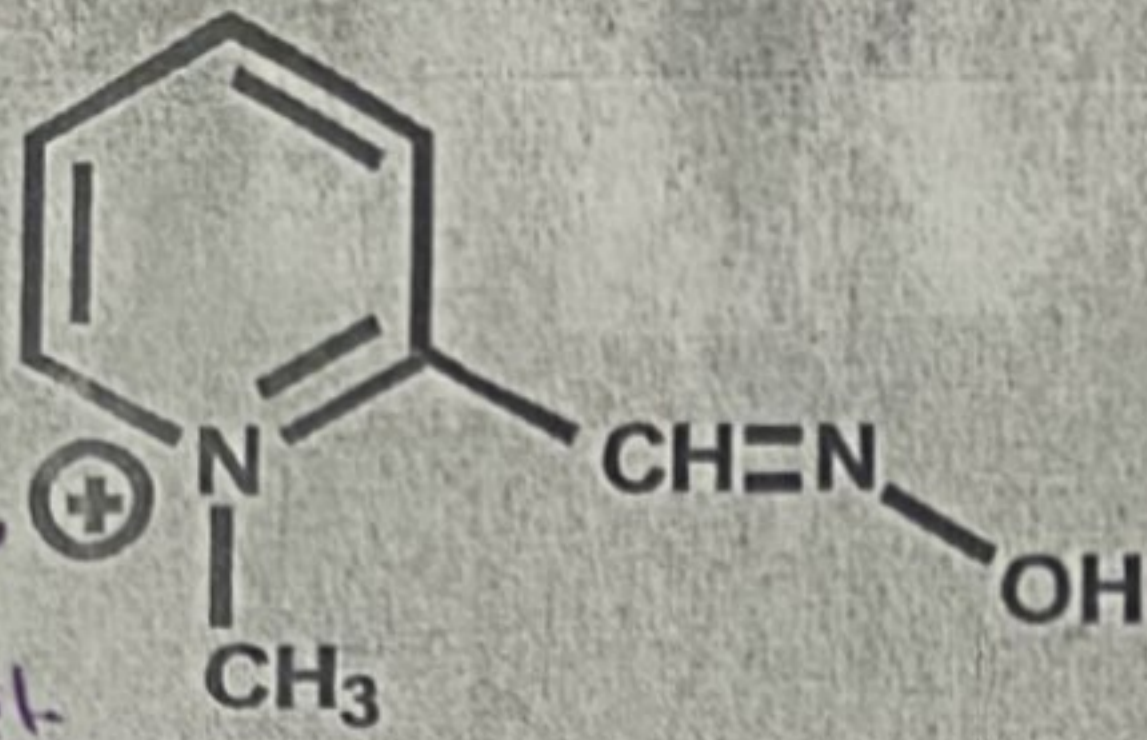
الـ فوسفات الـ (antidote) الـ
 سبب الـ toxicity الـ
 برقبـ يـ كـ (binding bucket)

- Hydroxylamine is (too) toxic for (clinical use)
- Increase selectivity (by) increasing binding interactions with active site

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15.4 Organophosphates

e) Design of Organophosphate Antidotes



Pralidoxime

binding bucket
aspartate. ال

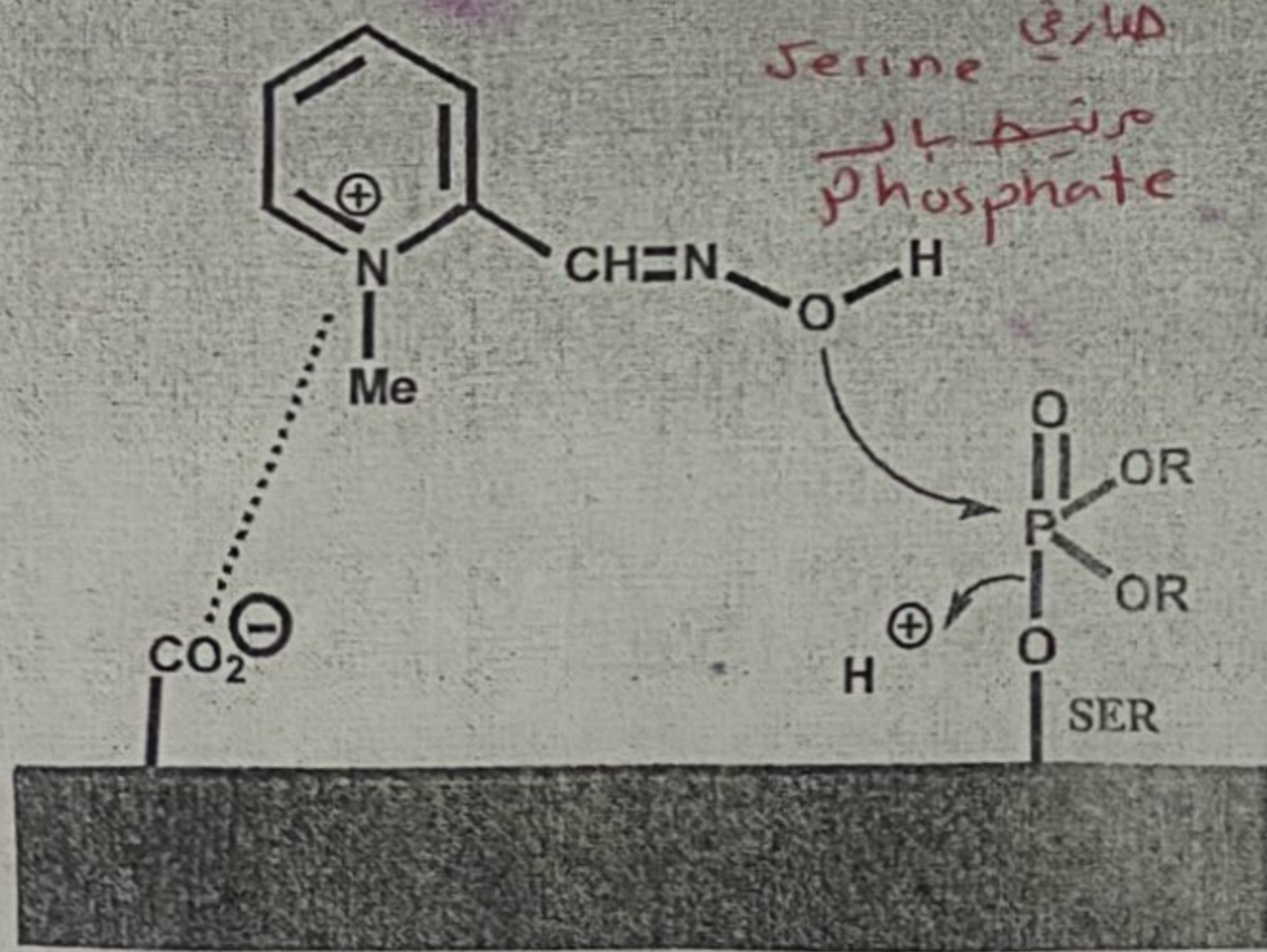
Very good
nucleophile.

- Quaternary N is added to bind to the anionic region
- Side chain is designed to place the hydroxylamine moiety in the correct position relative to phosphorylated serine
- Pralidoxime 1 million times more effective than hydroxylamine
- Cannot act in CNS due to charge - cannot cross blood

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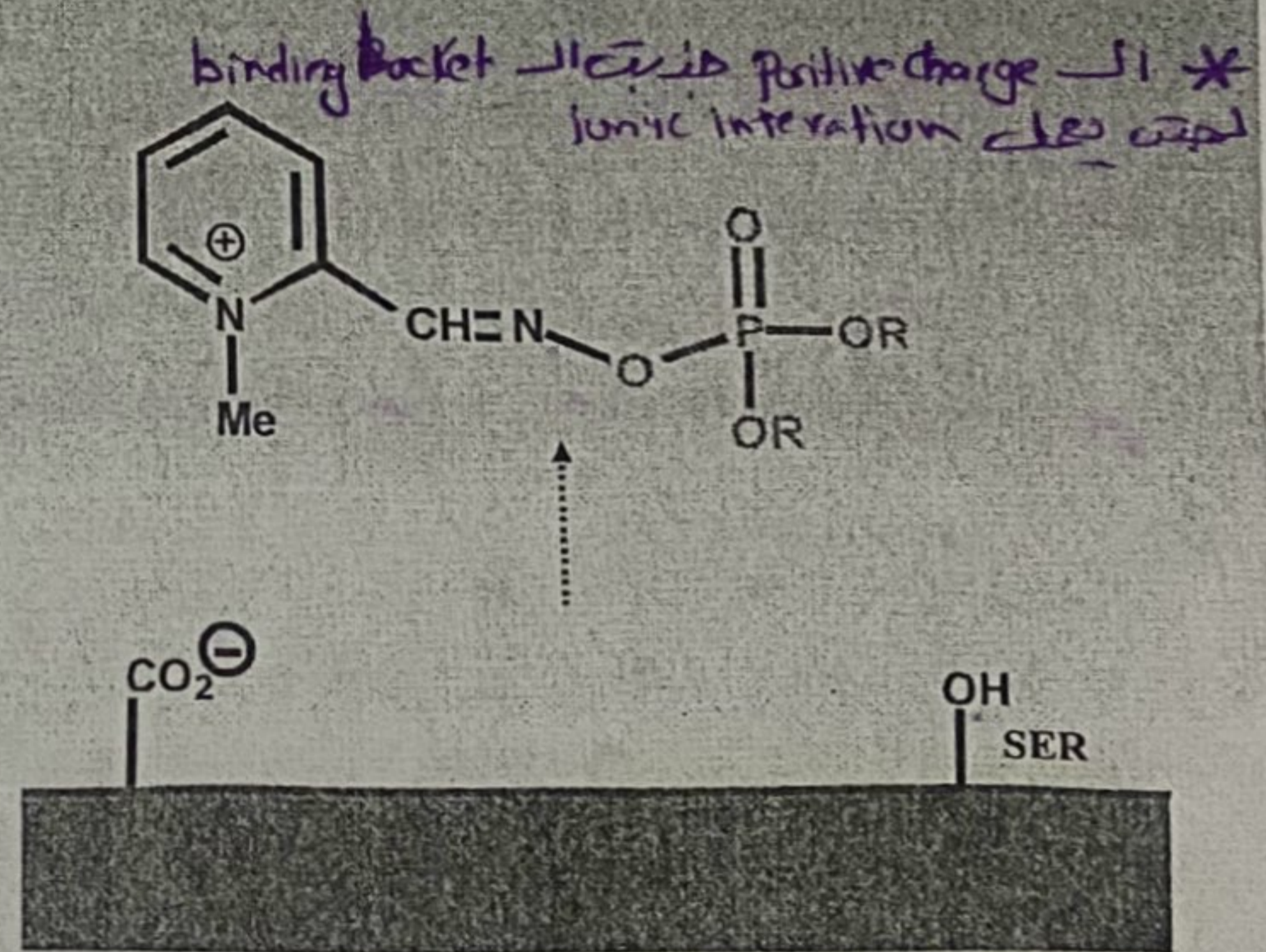
15.4 Organophosphates

e) Design of Organophosphate Antidotes



Active Site (Blocked)

Organophosphate
(Blocked)



Active Site (Free)

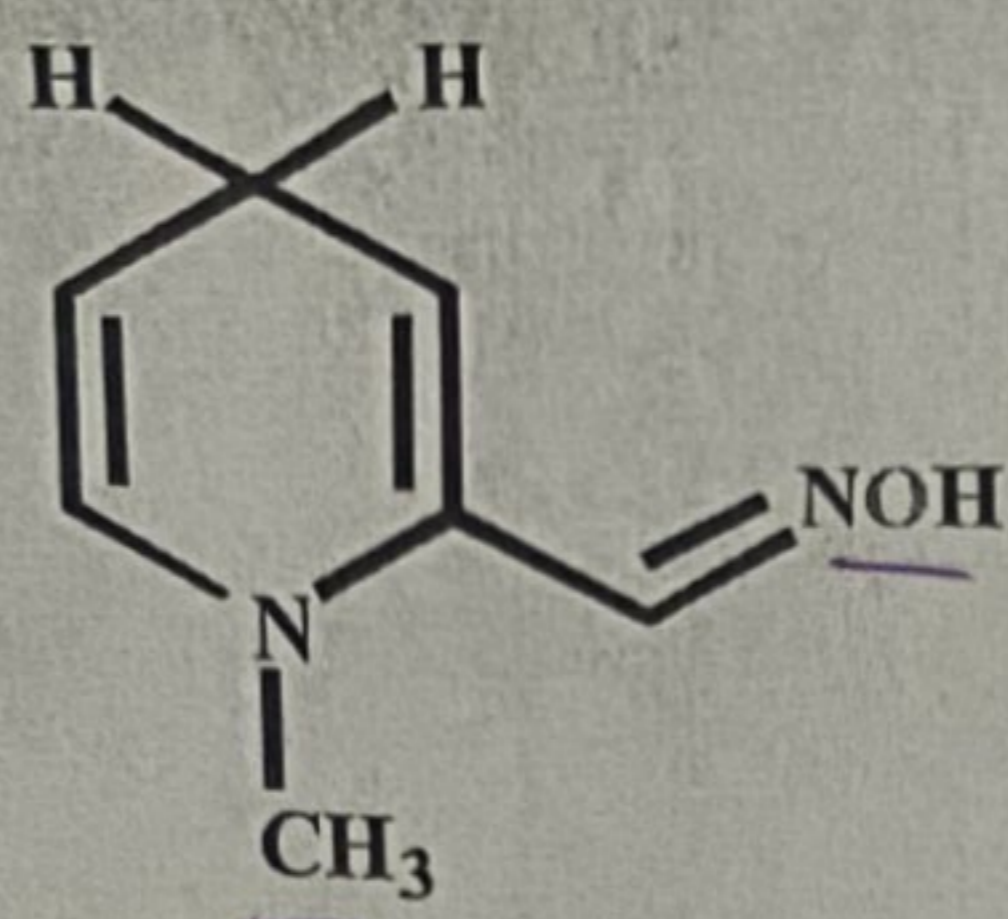
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negostigmine
not leaving group
leaving group. ← Ach

toxic.
organophosphate (Blocked)

15.4 Organophosphates

e) Design of Organophosphate Antidotes



ProPAM

- Prodrug for pralidoxime
- Passes through BBB as free base
- Oxidised in CNS to pralidoxime

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15.5 Anticholinesterases as 'Smart Drugs'

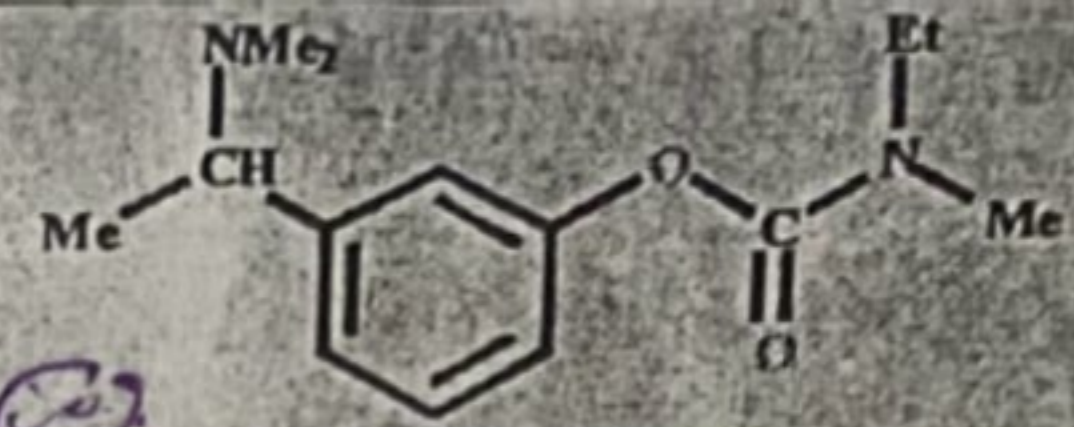
- Act in CNS

للنفاذ يستخدم
لعلاج
Alzheimer

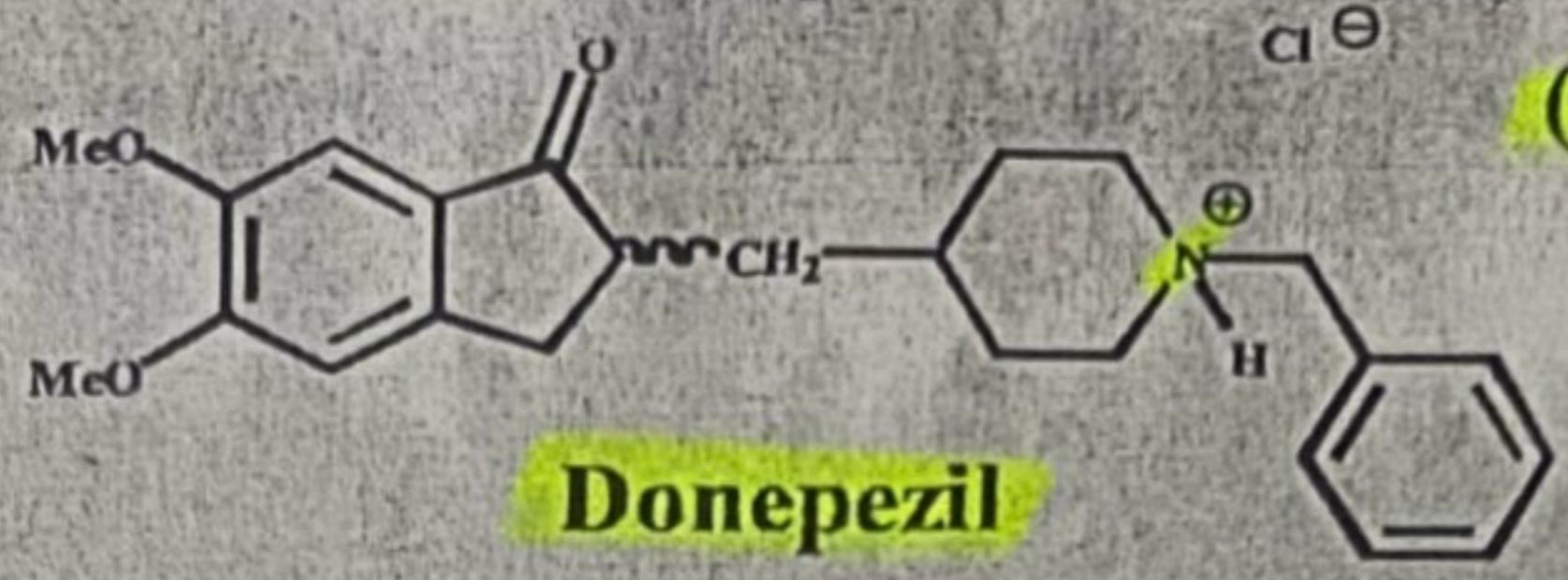
- Must cross blood brain barrier
- Used to treat memory loss in Alzheimers disease
- Alzheimers (causes) deterioration of cholinergic receptors in brain
- Smart drugs inhibit Ach hydrolysis to increase activity at remaining receptors

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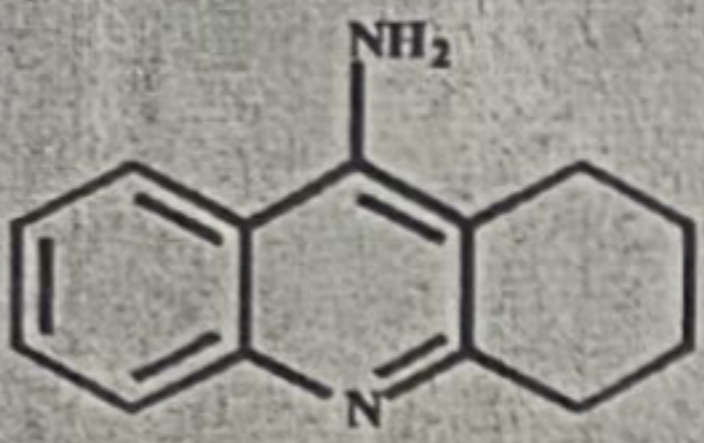
15.5 Anticholinesterases as 'Smart Drugs'



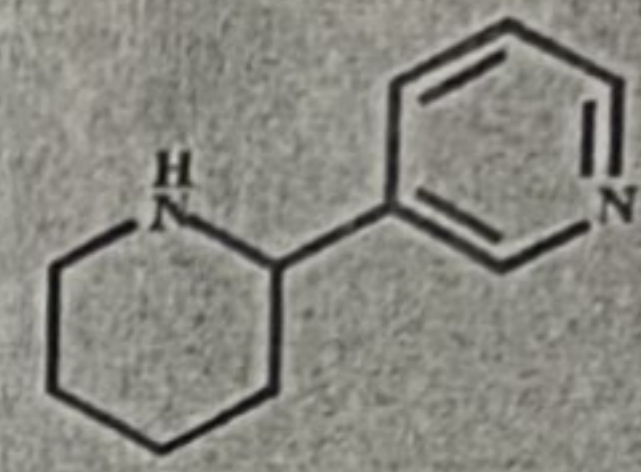
Rivastigmine (Exelon)
(analogue of physostigmine)



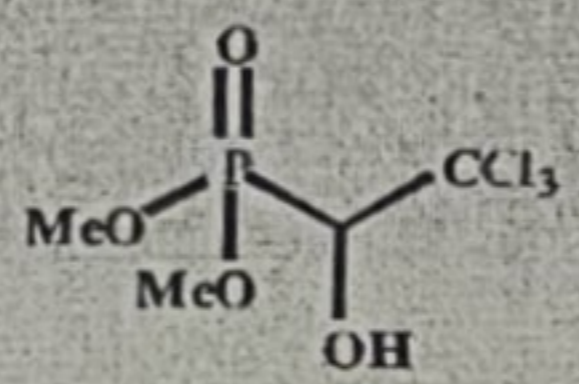
Donepezil



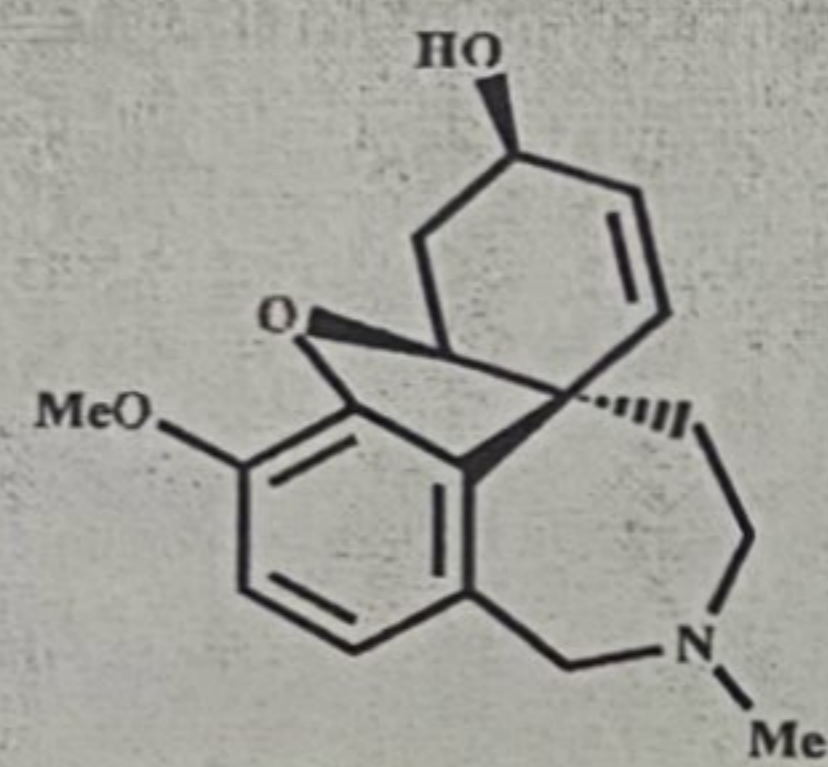
Tacrine (Cognex)
Toxic side effects



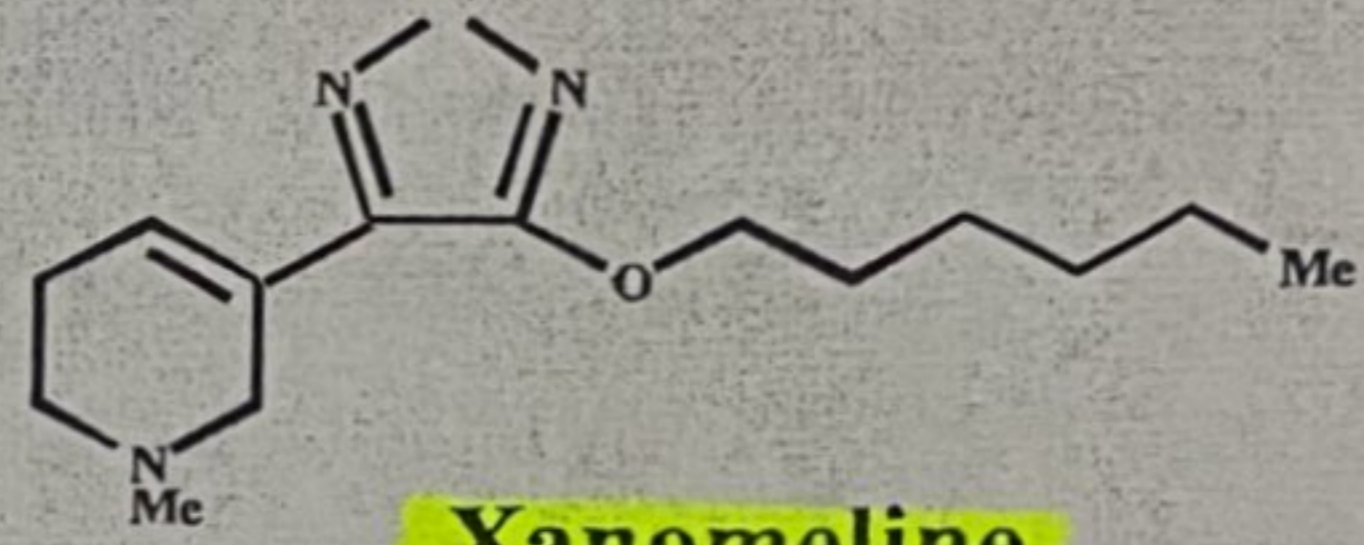
Anabaseine
(ants and marine worms)



Metrifonate
(organophosphate)



Galanthamine
(daffodil and snowdrop bulbs)



Xanomeline