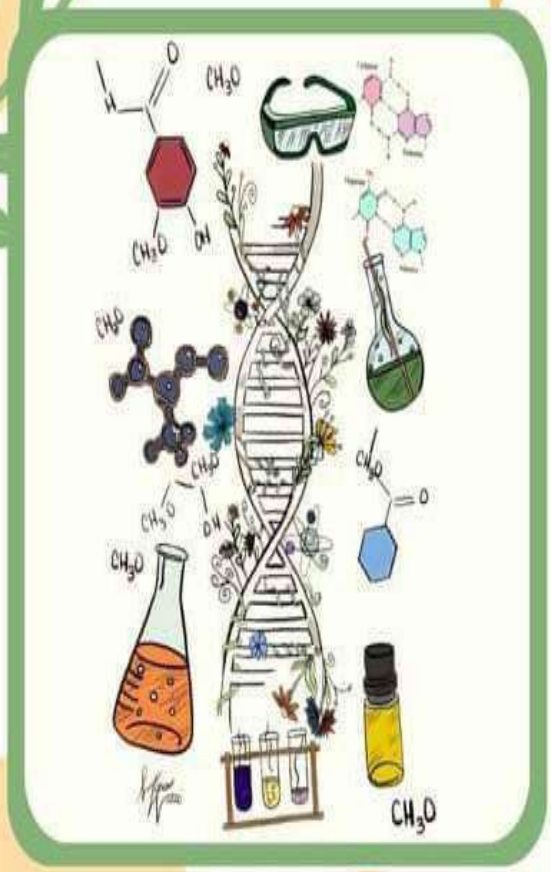
تفريغ عقاقير



اسم الموضوع: تفريغ CH_{12}

Part 1

إعداد الصيدلاني/ـة: شـــــماء المسلـــمي

Soul Academy

لجان الدفعات

Final

[بتسمي ال Alkaloid بناء على جاي منين A.A]

جاي من A.A

Isoquinoline Alkaloids and Benzylisoquinoline

Dr. Rand Shahin

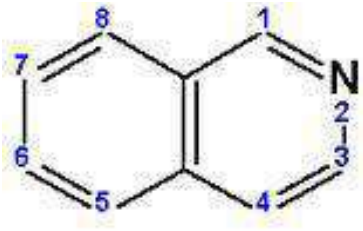
- Alkaloids :

Nitrogenous substances comes from A.A

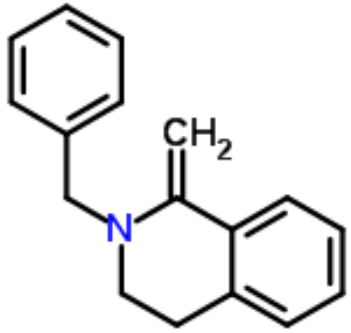
- Aliphatic إذا ← Aliphatic Alkaloids
- Aromatic إذا ← Aromatic Alkaloids

الأربعة كلهم Alkaloids جاي من Isoquinoline

- In this chapter we will disscuss very important compounds (① Opium (morphine), ② Morphinan) alkaloids as well as alkaloids of ③ curare and the alkaloids of ④ ipecac.
- This is the basic structure of Isoquinoline and Tetrahydroisoquinoline.

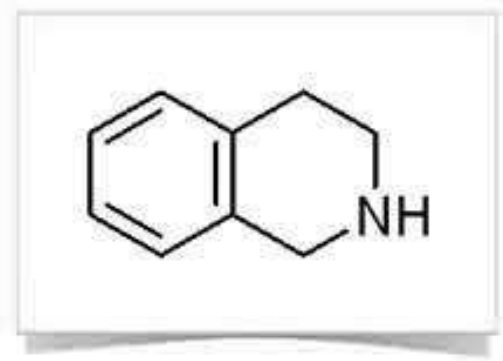


Isoquinoline

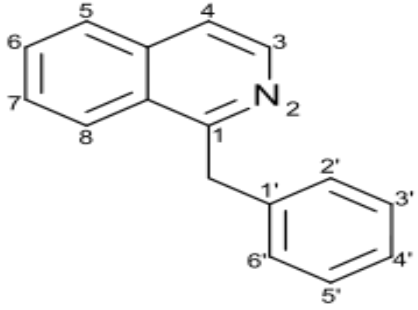


Benzyltetrahydroisoquinoline

حيار مشبع +4H ←



Tetrahydroisoquinoline

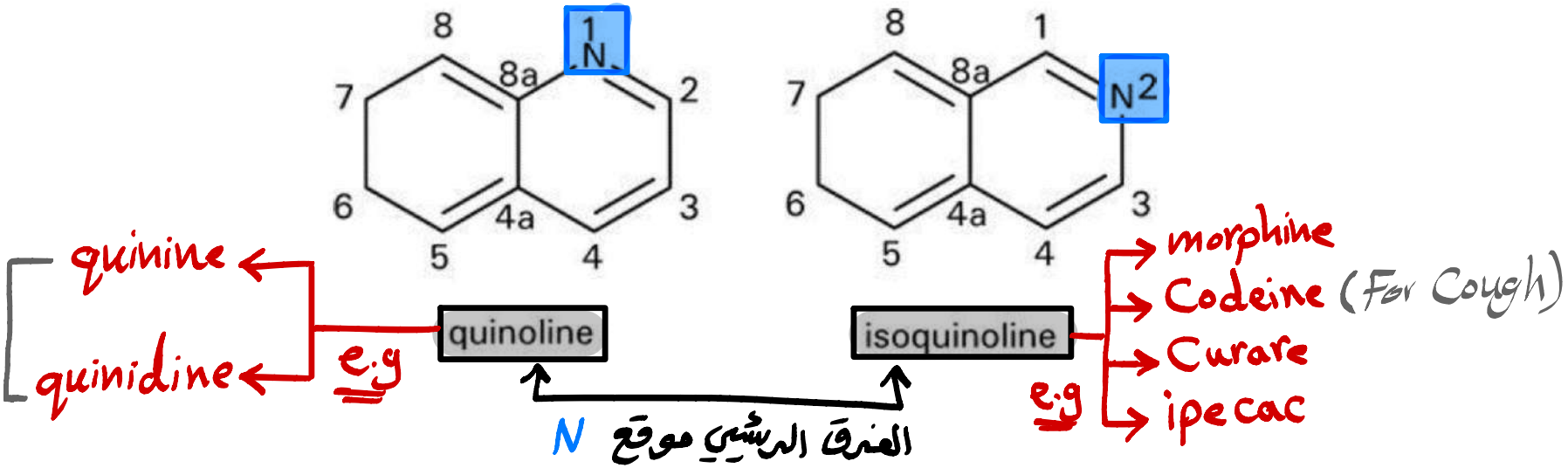


Benzylisoquinoline (Isoquinoline + Benzyl group)

↳ CH_2 – Aromatic ring

Quinoline alkaloids:

- **Isoquinoline** alkaloids come form **tyrosine** while **quinolines** come from **tryptophan**, the **difference** between quinoline and isoquinoline is the place of the **nitrogen atom**.
- In **isoquinoline**: nitrogen atom has a number of **2**.
- In **quinoline**: nitrogen atom has the number **1**.



موجودين بنبات Cinchona ويستخدموا العلاج لـ Malaria

Morphine + Codeine + ...

Opium Alkaloids

الأفيون

- Now we'll talk about the opium alkaloids that are until the moment being manufactured from the opium powder. And there is no way that it can be prepared in the lab to give the exact effect.

- The understanding of these compounds and how they work led to alternatives that would give the analgesic effect but without the addiction which is one of the drawbacks of opium alkaloids that are used as analgesics and known as **narcotic analgesic** compounds. مرضى في المراحل الأخيرة

  مسكّن الألم اللي بسبب إدمان → [used For patients in their end - stage disease]

- Of course narcotic effect is different from one compound to another and the most narcotic effect is found in morphine

Opium Alkaloids

- Opium is considered among the first compounds that were used and studied by human, it was used to treat diarrhea since it has constipating effect. Also it was used to treat pain and to do surgeries, and its use goes back to 4000 years B.C and many ancient cultures have used it in many countries except for Africa.
- Morphine was the first product to be isolated from the opium powder, and its structure was identified by the chemists according to the old techniques like the hydrolytic method which means that we extensively study the hydrolytic products to be able to know the original compound, and this method Is before NMR or mass spectroscopy were invented.
- Today India is the country licensed to grow the opium puppy for the extraction of active products for industrial purposes

New drugs from old poisons

داخل الزهرة يكون في عِلَف مواد زي Morphine Morphinan + codeine

The reductionist approach to medicine began with the isolation of opium alkaloids

Opium

المادة اللي بتنزل من الوردة لما بجرحها
ومن هاي المادة بجيب Morphine .

- Origin: is the **air-dried latex or milky exudate** obtained by incision from the **unripe capsules** of *Papaver somniferum*: Papaveraceae.
- It is worked into irregularly shaped masses and is known in commerce as *Indian opium*
- *somniferum*: produces sleep

Opium Alkaloids

- Opium powder is obtained from the puppy capsule the scientific name is Papaver somniferum from the family of Papaveraceae. And this milky material (latex) is obtained by making cuts in the outer layer of the capsule which is immature and has different colors, and when the capsule color turns from purple to green then it is the perfect time to collect it.
- It was called opium from the Greek word (opion) which means pain; it was then called opium because it is easier.
- Now this material that comes out of the capsule's cuts is colored white (like milk) and once it is in contact with air it will be oxidized and turns brown.
- after making the cuts in the capsule the latex will start to come out, we call it . (oozing of the latex)
- The latex will solidify and accumulate and the collected by special knives in a stainless-steel or aluminum container, and its texture is elastic and sticky with a uniform brown color.

Opium alkaloids

- By exposure to air, the opium acquires a suitable consistency for packing. *Fresh opium is pale to dark brown and plastic.*
- It contains **9-12 % morphine**.
- Note that the opium powder is colored brown not white like the cocaine!
- We have this thing that is called the poppy seeds that are used sometimes at the bakery stores and on certain types of bread
- these seeds have nothing to do with morphine! They are seeds collected after the full maturation of the opium capsule and does not contain any addictive material.
- There are people who take opium as injection others smoke it and some even eat it and all of that leads to addiction.
- The capsule is v. small, if we didn't cut it to get the latex out then the capsule will turn into a beautiful flower that is similar to النعمان شقائقbut the later flower has no opium alkaloids at all!

بذور الخشخاش (آمنة).

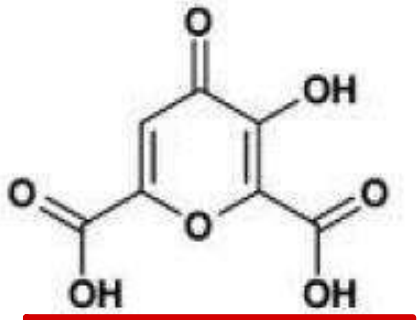
الـ Capsule بعد ما تتفتح زهورها تشبه زهور شقائق النعمان.

Opium Alkaloids

- Opiates are anything prepared from the natural opium powder, and the percentage of morphine in it is 10% and called standardized opium powder and we use* lactose as diluent and some poor countries may* use coconut hair.
- To make sure that my opium powder sample has the needed amount of opium alkaloids we do an analysis to inspect the presence of meconic acid.

كيف يغشوا الـ Opium؟

الطريقة اللي بنفحصها فيها opium powder للتأكد من إنه يحتوي الكمية المناسبة من opium Alkaloid الحقيقي.



Meconic Acid

إذا لقيناه بالعينة معناها فيها الكمية الصحيحة ومش مغشوشة.

History of use

- Crude opium has been used as **analgesic** and **sleep-inducer** (narcotic) and for the **treatment of coughs**
- Powdered opium was *combined* with powdered Ipecacuanha to give a **sedative and diaphoretic** effect to take at the onsets of colds and influenza
- It has traditionally been smoked for pleasure

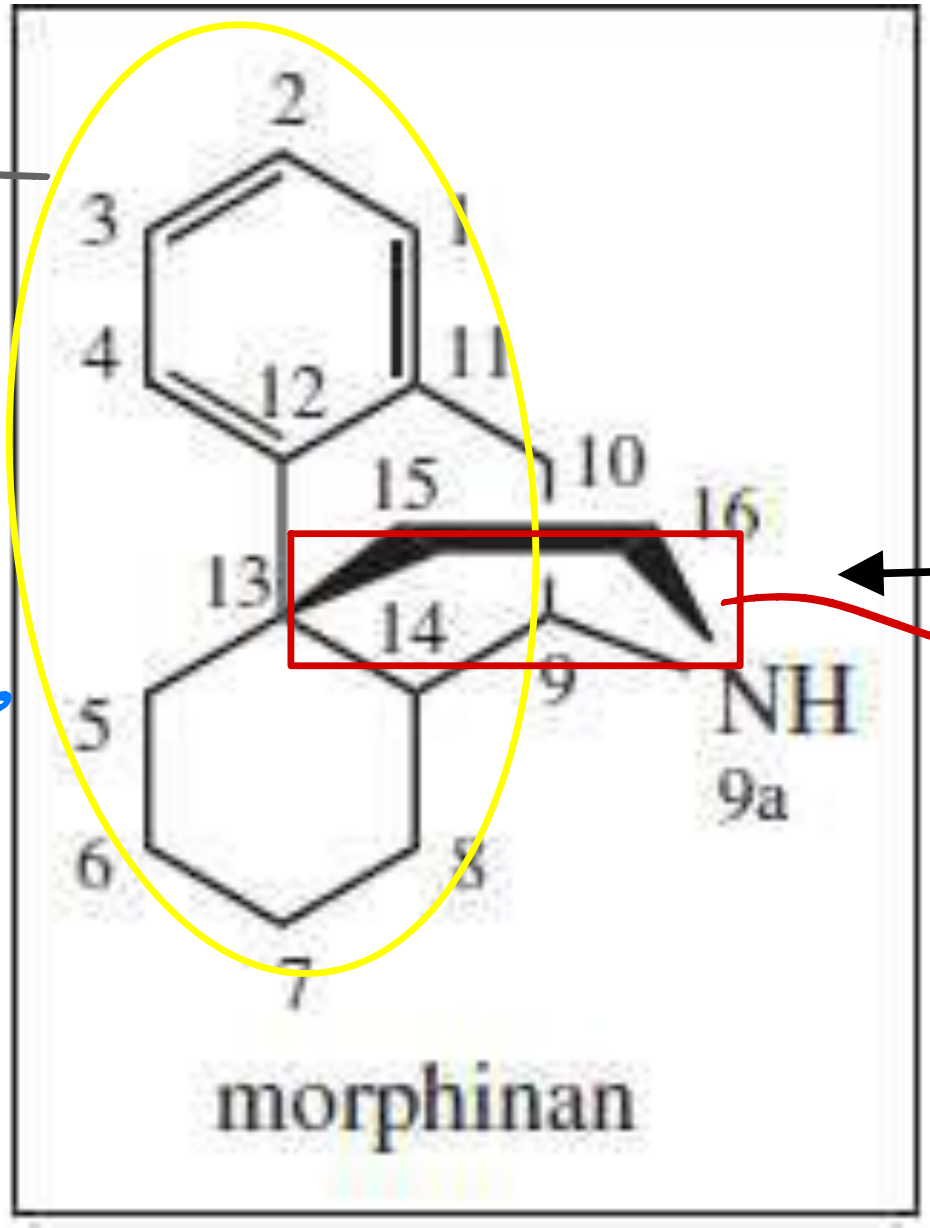
Principal compounds found in the opium powder:

- Morphine (the most used compound in the world from the opium alkaloids)
- Codeine, Thebaine, Papaverine, Noscapine and Narcotine.
- To classify them according to basicity:
- 1-strong basic compounds (because of the presence of tertiary or secondary N and usually around it are a group of electron donating functional group that increases basicity) Morphine, Codeine and Thebaine.
- 2- Weak basic compounds (because they are close to electron withdrawing groups and so
- their basicity is less): Papverine, Noscapine and Narcotine.

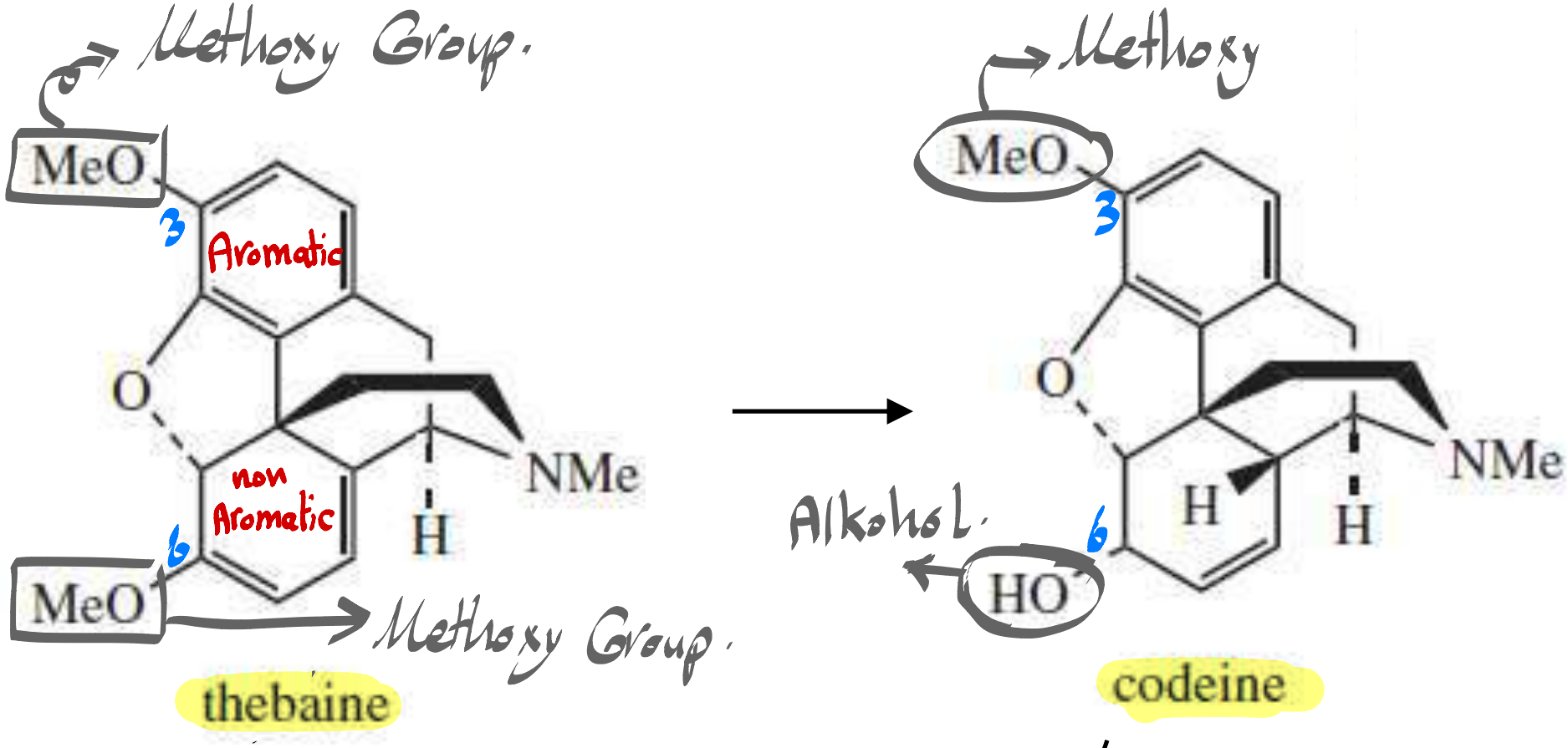
٣ حلقات هم phenanthrene ...

1) morphine
2) Codeine
3) Thebaine

بصنفهم كـ Morphinans والسبب ؟ وجود phenanthrene backbone



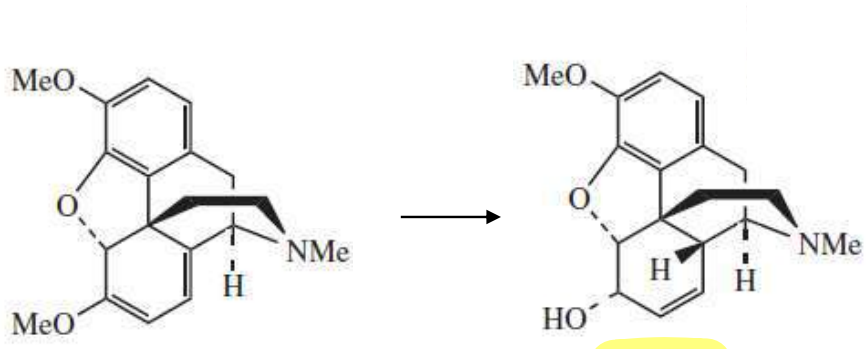
الحلقة ٤ من فوق Piperidine حلقة



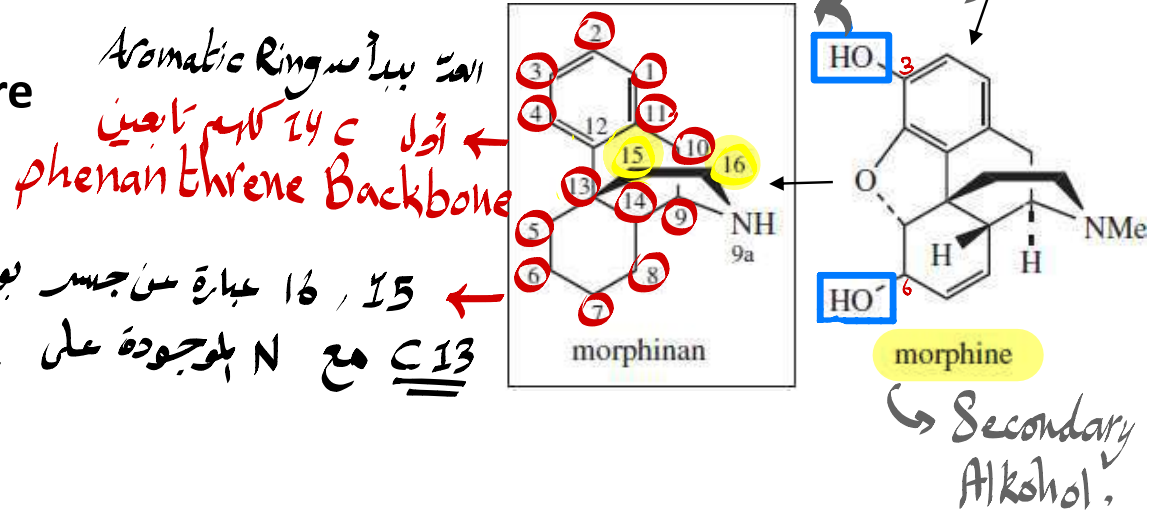
The difference between Thebaine, Codeine, Morphine is the Substituents on Carbon 3, 6

The biosynthesis of Morphine is strange in that we started with methylated compound which is Thebaine and by demethylation we obtain morphine.

Crude opium contains 10% morphine in best cases 20% and this is considered a huge amount.



Morphinan alkaloids are Thebaine, Codeine and Morphine only.



Cough Drug

ولكن يحول بسبب قليلة لـ Morphine لذلك سيتاء استخدامه أحياناً

وما سبب إدمان

Codeine

- In fact, it is the most widely therapeutically used opium alkaloids (main representative).
- Antitussive and mild analgesic agent.
- it is 3-O methyl morphine.
- it can be metabolized partially by liver enzymes (de-methylated) to produce **morphine** →so it produces morphine-like analgesic effects but little euphoria. شعور السعادة
- it's about one –tenth (1/10) the potency of morphine.
- →So, relatively it is a safe non-addictive medium analgesic –for sure- when used within the therapeutic doses, if exceeded or used for a **prolong period of time** there will be -definitely- dependence, addiction and also **constipation**.

إذا استخدم لفترات طويلة سبب إدمان + أبرزها الإمساك.

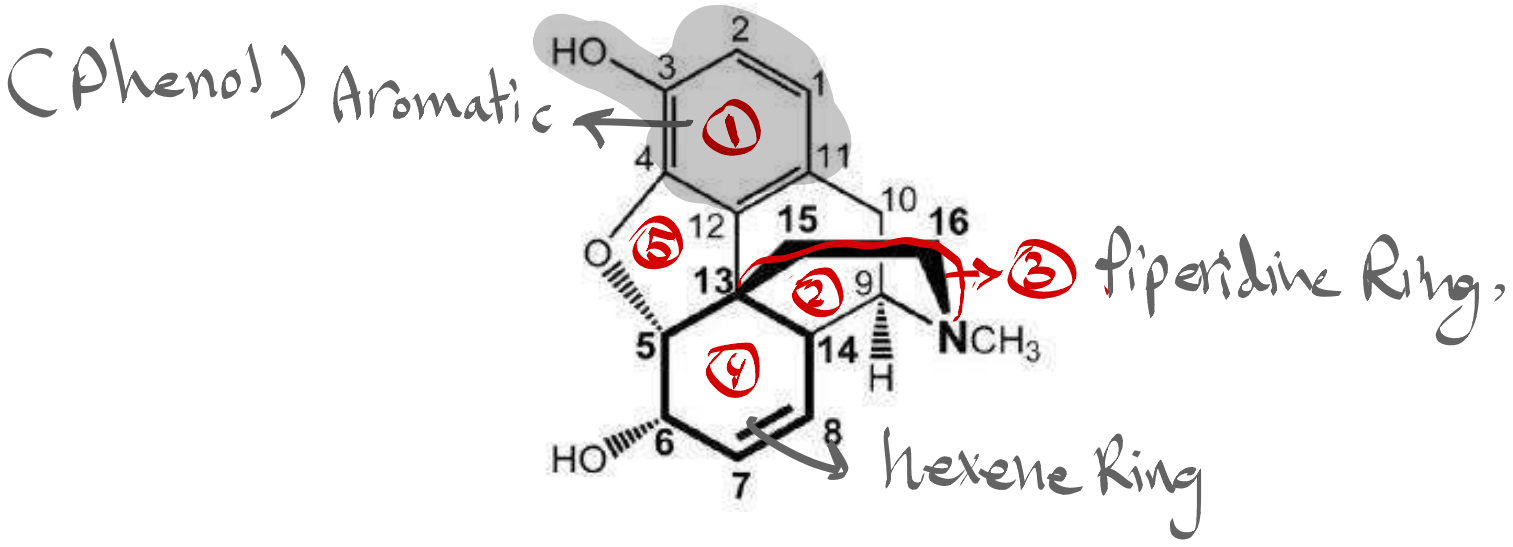
Thebaine

ما إله أي استخدام علاجي .

- In fact, Thebaine **hasn't** been introduced to the therapeutic utilization,- instead- it has been considered as a one of the most important raw materials used in the production of other morphinan drugs such as morphine, codeine and semi-synthetic opiates.
- Nowadays, some countries cultivate a **genetically** modified papaver somniferum which produce thebaine as a major constituent rather than morphine and codeine. جينيًا طوروا نبتة لانتج الا Thebaine والهدف ضمان عدم ايساءة استخدام هاي النبتة كمخدّر
- Why??
- To overcome obtaining direct morphine which can be easily converted to heroine
- →It is a way to restrict the misusing of opium alkaloids.
- *One of the countries which -restrictly- cultivates this modified papaver somniferum is Australia, it doesn't produce morphine or codeine as major constituents anymore instead all morphinan alkaloids are based on Thebaine production which is **semi-synthetically** demethylated to any of them, only according to the demands .

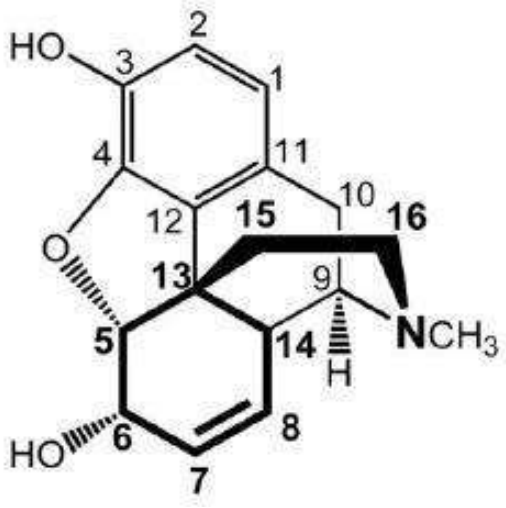
Morphine

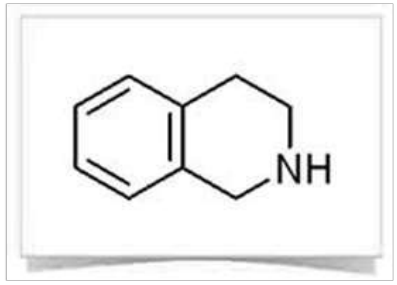
- Morphine: which is the major component of the opium powder and belongs to the group of morphinans (which are a phenanthrene structures and at the second ring of this structure we have a carbon-nitrogen ring (2 carbon bridge-N bridge) (carbon
- no.13 is attached to the nitrogen via 2 carbons (15 and 16) that gives another ring that is found on another plane.



Phenol الوحيد المحتوي على ← **Morphine**

- So the morphine structure is a 5 ring structure containing one aromatic ring, piperidine ring and 1 benzene and 1 hexene ring which is partially saturated because we have a double bond between carbon no.7 and 8).
- Morphine is a phenolic compound (because the benzene ring has a hydroxyl grpon carbon no.3) and also carbon no.6 (which carries a hydroxyl grp and makes an alcoholic functional grp).
-





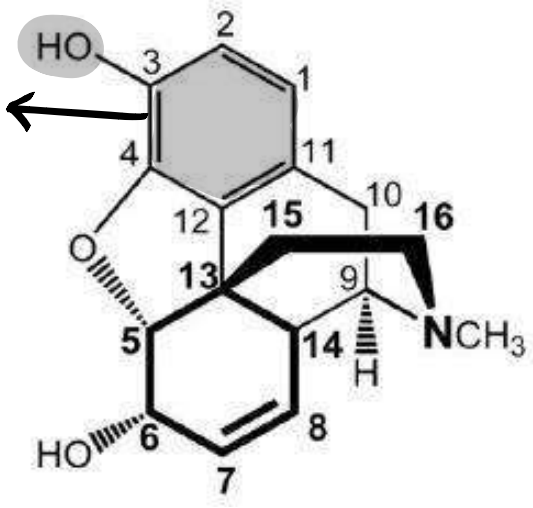
Tetrahydroisoquinoline

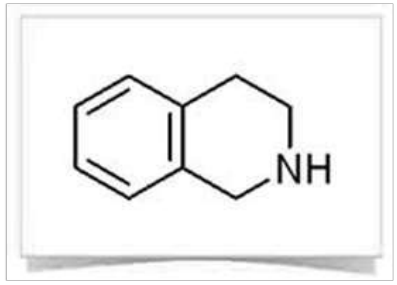
Morphine

- In another way we have a phenolic and alcoholic function. Grps in the morphine and it's the basic difference between the morphine and codeine. And it is used to make sure that we have a morphine and codeine structures in the opium powder.
- For example: If we want to distinguish morphine as a powder from codeine (both have a white powder) then we can use the phenolic grp of the morphine which can easily react with strong basic compounds like NaOH or KOH

* Acid-Base Titrations

Phenol لإنه الوحيد اللي عنده
بقدر أعمل عليه خواص
NaOH و KOH





Tetrahydroisoquinoline

Morphine

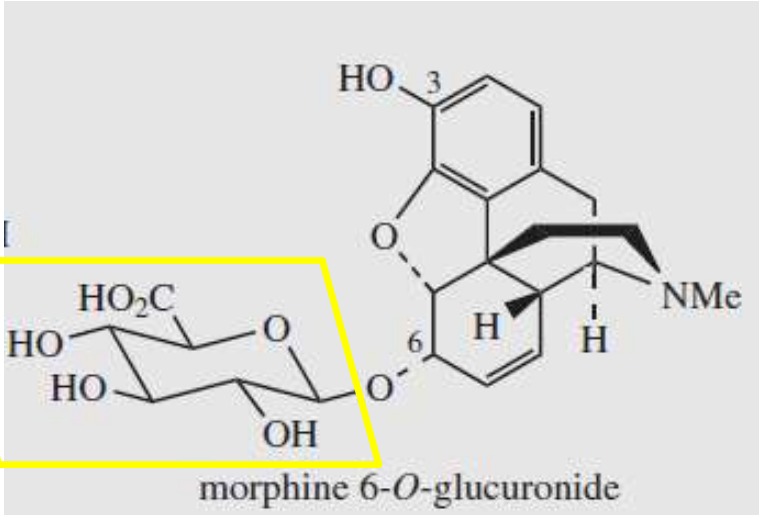
- Morphine is a narcotic compound (easily separated) that causes euphoria and addiction.
- And one of its adverse effects is the **constipating effect** (that's why they use it as a treatment for diarrhea).
- Withdrawal symptoms need a long time for the person to get rid of it (takes from 2-3 weeks
- Another problem about morphine is the nausea and vomiting associated with its use and so we usually give the patient an anti-nauseating agent along with the drug.
- Morphine has both injectable and oral form (tablet form and is under strict observation from the government and only by a prescription), while the injectable form is a salt form.

Morphine

إضافة مجموعة إنزيمات الكبد ⊕

- **M**orphine is metabolized in our body form to **glucoronides** which are readily excreted.
- →In fact, **theoretically** we have 2 –OHs in the structure of morphine at positions (3 and 6) so we can form: morphine-3-glucoronide, morphine-6-glucoronide or morphine-3,6- diglucoronides. مش مستقر
- * But what has been found in our bodies that morphine-3-glucoronide metabolite is **not** very stable as morphine-6-glucoronide, the bond between the aglycon and the sugar part (glucoronic acid) can be easily broken down during metabolism. ← This form is more stable.
- →So, morphine is **eliminated** from our bodies in form of **morphine-6-glucoronide**.

glucoronide ←



morphine 6-*O*-glucuronide

اكتشفوا إنه مادة الجاي بعد
morphine-6-glucoronide أيض المورفين اللي هي
إلها تأثير مسكن أقوى من المورفين
نفسه فصنعوه وصاروا يعطوه بدلاً
من المورفين

Morphine

- *Scientists isolate this metabolite (morphine-6-glucoronide) and by analysis it has been found that it possesses a very potent **analgestic** activity even **more potent** than morphine itself.
- →Accordingly, morphine-6-glucoronide (هي الـ metabolite) has been prepared semi-synthetically to be used with terminal cancer patients (مرضى السرطان في آخر المراحل) since it is significantly hydrolyzed in the gut; it is much less effective taken orally than when administered by injection.

- Injection بال منه أقل orally هو وهي أكثر

لا Thebaine, Codeine بالمقابل
يعتبروا أحماض ة الوحيد
بيعتبر حمضي لانه عنده phenol

- 2-**morphine** which is considering as an acidic compound although it has a N. →this acidity is related to the presence of a phenolic –OH in its structure.
- Why this is important?- أهمية عمليته ؛
- →This acidity will facilitate the isolation of morphine from crude opium alkaloids extract.

Inhalation Anesthetics

- Ibn al- Quff was an Arab physician and surgeon and author , he was used anesthesia by inhalation , by using anesthetic spong.
- The sponge was soaked in a boiled solution made of water with cannabis (from Arabic hasheesh حشيش), opium(from Arabic afiun افيون) and belladonna (from Arabic cit alhuscin ست الحسن).
- The anesthetic sponge was placed it over the patient face, the liquid which is absorbed by the mucous membrane of nose and mouth .

Opium مواد اخرى في morphinane لكن ليست

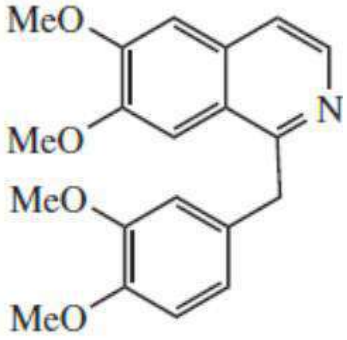
Alkaloid

Papaverine

- Papaverine itself is an ingredient of crude opium (opium alkaloids) but it is **not** a morphinan alkaloid.
- Structurally, it is **not** a benzyltetrahydroisoquinoline but it is a benzyl-isoquinoline since it possess a double bond in the heterocycle.
- →**Morphinan alkaloids are Thebaine, Codeine and Morphine only.**
- *It has **no** analgesic or hypnotic properties, but it relaxes smooth muscle in
- blood vessel and as a spasmolytic agent.
- Until the discovery of the **oral** sildenafil (Viagra®), it has been used as an effective treatment for male impotence, being administered by direct **injection.**
- →Nowadays, this use is neglected.

يرخي العضلات

إذا تم حقنه يشبه تأثير دواء



papaverine

② Noscapine (narcotine in the past)

اسمه القديم

- very potent antitussive agent compared to codeine.
- Despite many years of use as an antitussive, the finding that Noscapine may have teratogenic properties (i.e. may deform a fetus) has resulted in noscapine preparations being **withdrawn from the market**.
- * It has **no** analgesic or narcotic action so its original name 'narcotine' was changed to reflect this **lack** of narcotic action.
- *based on the fact that all toxic substances are investigated for their antitumor activity, it has been found that noscapine is possessing this activity in a similar mechanism to that of colchicine →antimitosis.

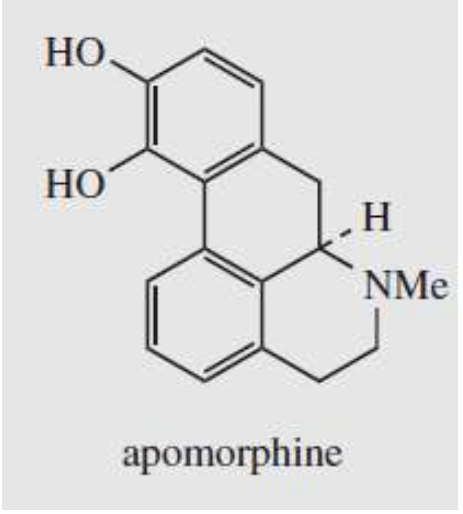
بتشوه الأجنة

- But because of the teratogenicity, it is still unsafe for this purpose.
- → Recent studies are held in order to decrease this teratogenicity and increase the antimitotic activity by the production of possible semi-synthetic derivatives of noscapine.

③ Apomorphine

- Obtained by heating morphine in the presence of acid which lead to a completely changed structure (ex; the ether linkage is eliminated)
- has **no** analgesic properties, but morphine's side-effects of **nausea** and **vomiting** are **highly** emphasized.
- is a powerful emetic and can be injected for emergency treatment of poisoning (differs from other emetics in being parentally rather than orally).

بسبب قيء شديد لهيك تستخدم لحالات التسمم.



apomorphine

مشتقات صناعية (٤)

Synthetic derivatives:

① Dextromethorphan:

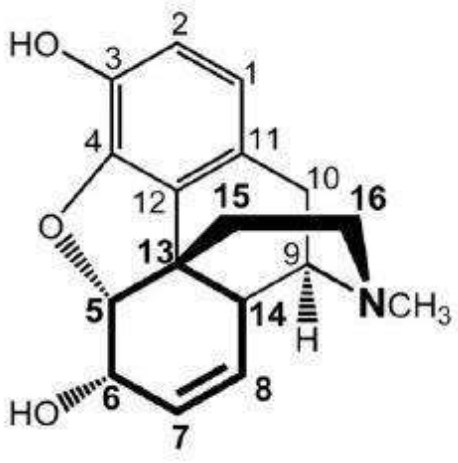
- One of the most widely used morphine analogues in the therapeutic purposes.
- potent antitussive agent.
- in lab preparations we obtain both isomers: **dextromethorphan** and **levomethorphan** but it has been found that **dextromethorphan** is **lacking** the analgestic activity with **potentiated antitussive activity**. While levomethorphan is possessing analgetic and antitussive activities.
- →In fact, since this combination is not requested, dextromethorphan alone is the preferred drug material, being completely non-addictive.
- **Now**, the other synthetic derivatives of morphine which we will discuss now, all are possessing analgetic activity differing in their duration of action …etc

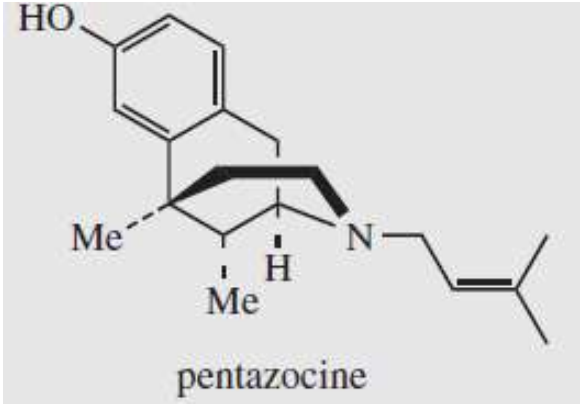
المشكل الفعّال

Synthetic derivatives:

② Pentazocine

- * Structurally, a morphine-like structure where the ether bridge has been omitted and the cyclohexene ring has been replaced by simple methyl group and the N-methyl is replaced by aliphatic chain.
- * Pentazocine has both competitive agonist properties, and although it is a good analgesic, it can induce withdrawal symptoms.
- **Note**: all synthetic cpds do possess CNS euphoria addiction and tolerance.

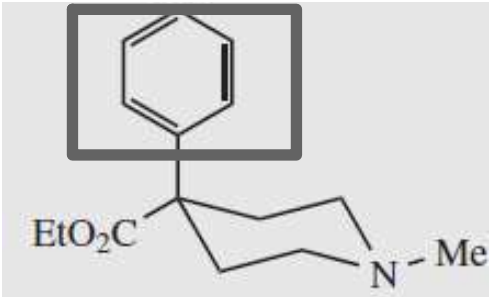




3

Pethidine (meperidine):

- *very simple in structure (because it has been found in order to produce a morphine-like-activity in the human brain the requirements are aromatic ring and piperidine system possessing a chiral center).
- * Short-acting, quick and short-duration analgesia, used nowadays as a pain killer parentally in surgery.



pethidine
(meperidine)

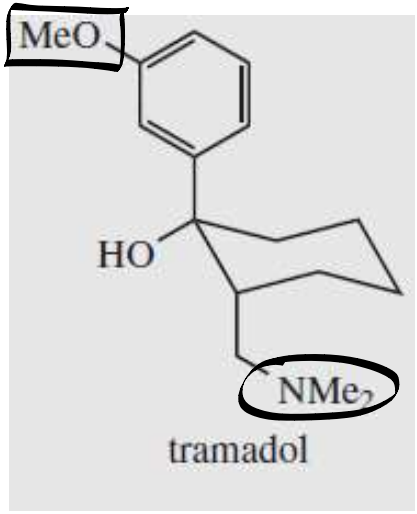
4

Tramadol:

أحد المشتقات الصناعية للـ Morphine

قد يسبب الإدمان

- * is a recent drug firstly synthesized in 1980 as an analgesic, it wasn't causing addiction but recent studies show that tolerance can be developed.

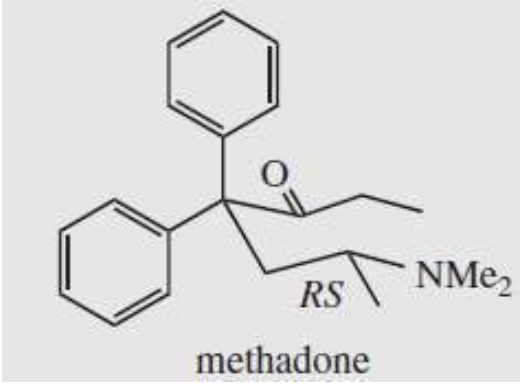


tramadol

دواء يعطى للمدمنين يشبه تأثير المورفين
لكن euphorigenic أقل

Methadone:

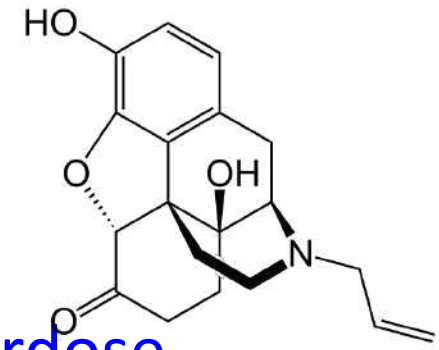
- *Methadone is orally active, has similar activity to morphine, but is less euphorigenic and has a longer duration of action. Although it is as potentially addictive as morphine, **the withdrawal symptoms are different and much less severe** than with other drugs such as heroin**, so** that methadone and **Buprenorphine** (a semi-synthetic derivative of thebaine) are widely used for the **treatment and rehabilitation of heroin addicts**.
- Ex: withdrawal symptoms with methadone don't appear before 48 hours but in morphine or heroine a second urgent dose needed within the next 24 hours.



methadone

أحد الأدوية التي تعطى في حالات الجرعة الزائدة من Heroin

Naloxone



- **Naloxone is** pure antagonists especially in overdose.
- **Naloxone**, sold under the brand name **Narcan**
- Administration to opioid-dependent individuals may cause symptoms of opioid withdrawal, including restlessness, agitation, nausea, vomiting, a fast heart rate and sweating. To prevent this, small doses every few minutes can be given until the desired effect is reached.
- Naloxone is a pure opioid antagonist. It works by reversing the depression of the central nervous system and respiratory system caused by opioids.[
- The drug was approved for opioid overdose by the Food and Drug Administration in 1971.

الآثار الجانبية لهذا الدواء

هذا الدواء عكس أنواع الهيروين

هبوط الجهاز العصبي

ضعف عضلات التنفس