PI-EXCESSIVE RING SYSTEMS

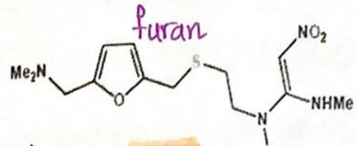
بكون مُشبع بالإلكترونات

ring is rich in electron (Partially Negative)

تركيزنا على الحلقات الخماسية "5" → تحمل Loan Pairs of e⁻

مثال عليه: 5-membered ring with one hetero atom.

furan



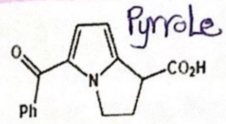
anti-histamine ← ranitidine

→ (مش حفظ)

• Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H_2-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers

بشتغل عليهم — قرحة المعدة

Pyrrole

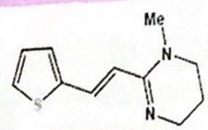


ketorolac

• Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug

من عائلة الأنسولين

Thieophene



banminth

• Pyrantel (Banminth®, Phibro) is an anthelminthic agent and is used to treat worms in livestock

لعلاج الديدان في GI tract

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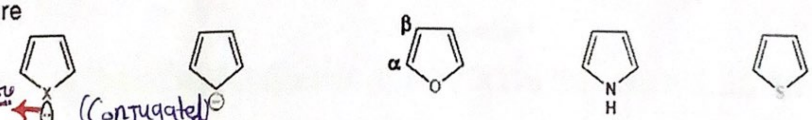
توضيح 6π electron → S و O و N كلهم فيهم Loan pair وهي تعادل دبل بوند وتعطي إلكتروناتها للحلقة

أشهر الحلقات الخماسية

(Furans ① , Pyrroles ② and Thiophenes ③) – Structure

Structure

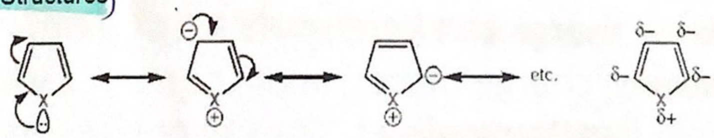


بحسبهم مع الدبل بوند (Conjugated)

• 6 π electrons, planar, aromatic, (isoelectronic with cyclopentadienyl anion) → لأنه ضفناله إلكترونات الهيترو الأتية

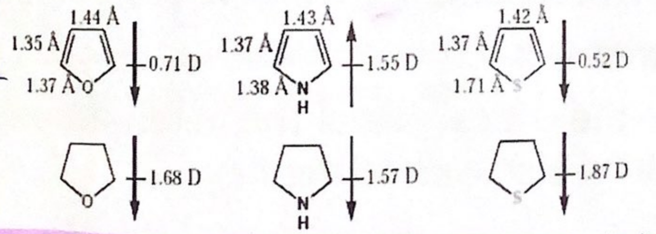
→ does'nt undergo addition reactions

(Resonance Structures) → to make it Fully aromatic



S, N, O ← aromatic ring بشاركو e مع ال

• Electron donation into the ring by resonance but inductive electron withdrawal



N, O, S بعتبرهم electron withdrawal (تسحب ال e⁻) وعندي قوة معاكسة إلها ناتجة عن ال resonance وهي e donating

Justify: why? * Pyrrole is Pi-excessive system? لأنه عندي e متوزعة على ال ring عن طريق ال (resonance).

• O and S are more electronegative than N and so inductive effects dominate

لكن الي بتفوز هي (resonance)

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Chemical Properties of Pyrroles

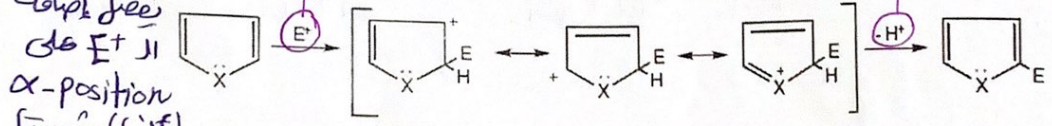
Electrophilic Substitution.

A significant feature of the pi excessive (Pi – excessive) ring systems is that they are highly reactive to electrophilic species, totally unlike the pi-deficient rings.

The reactivity is greater than that of benzene and is in roughly the same range as found for benzenes bearing electron releasing groups as in aniline.

As a result, many useful substitution reactions are known for these heterocycles.

- The greater electron density in these rings accounts for this higher reactivity. The order of reactivity in aromatic substitutions is generally (pyrrole > *furan* > *thiophene*.)



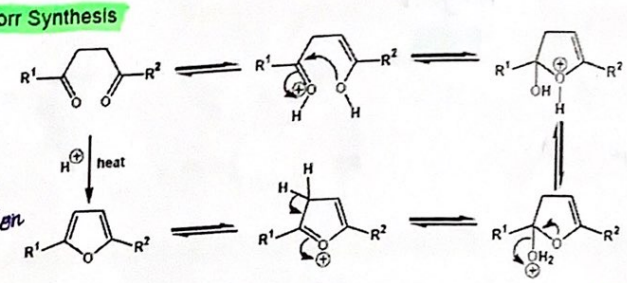
Scheme 7.2

- For all three heterocycles, electrophilic attack is favored at the alpha carbon of the ring. An attack at this position leads to an intermediate whose positive charge can be dispersed to all other ring positions; charge dispersal of course is a well-known stabilizing effect. The charge dispersal is shown in Scheme 7.2 with the use of resonance structures.
- Note the critical role of the heteroatom in donating electrons to the ring.

1,4-dicarbony compound
furan& pyrrole ,thiophene
& Thiophene

Furans – Synthesis

① Paal Knorr Synthesis

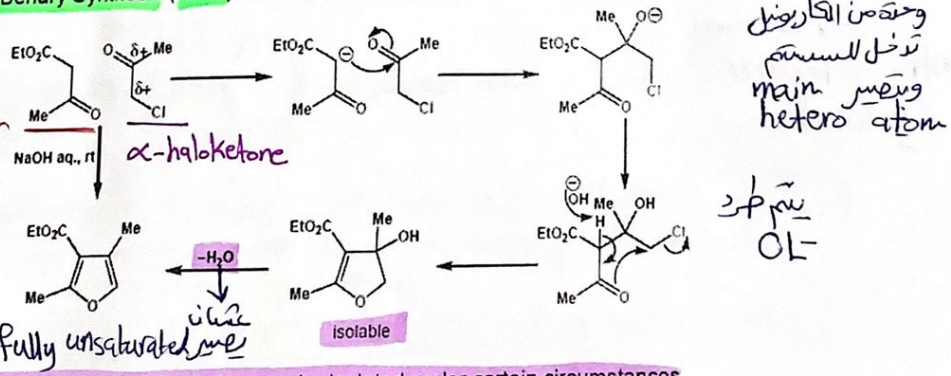


1,4-dicarbonyl
water
in acidic condition
(2 intramolecular Cyclization)

- The reaction is usually reversible and can be used to convert furans into 1,4-diketones
- A trace of acid is required – usually TsOH (p-$MeC_6H_4SO_3H$)

(Cyclo-addition reaction)
to get Cyclized compound
and end up with Subsituted furan.

② Feist-Benary Synthesis ("3+2")



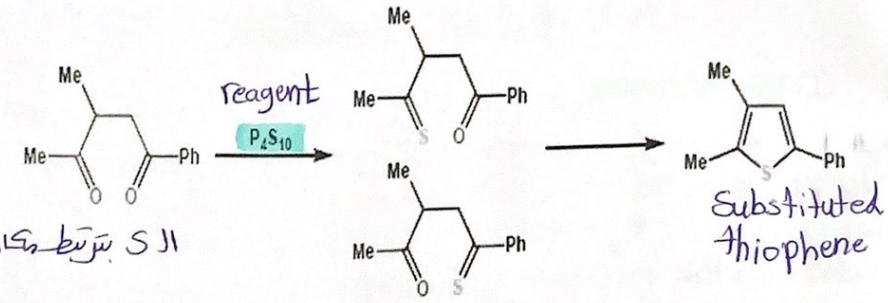
β-ketoester
α-haloketone
NaOH aq., rt
isolable
Fully unsaturated

- The product prior to dehydration can be isolated under certain circumstances
- Reaction can be tuned by changing the reaction conditions

(S) Sulfer ← main hetero

Thiophenes – Synthesis

Synthesis of Thiophenes by Paal Knorr type reaction ("4+1")



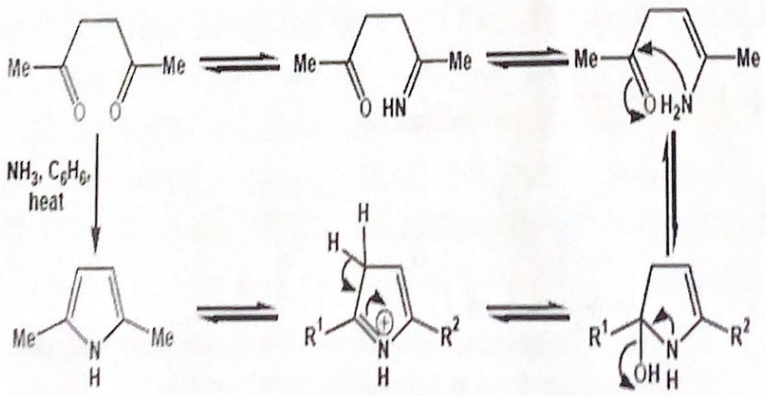
بترتبط بالكاون وحدة من الـ O الـ S

- Reaction might occur *via* the 1,4-*bis*-thioketone

N لهم ← # Pyrroles – Synthesis

Paal Knorr Synthesis ("4+1")

بيتفاعل عن طريق intramolecular Cyclization.



- Ammonia or a primary amine can be used to give the pyrrole or *N*-alkyl pyrrole

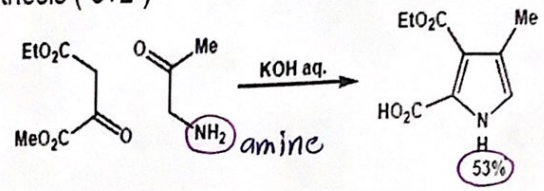
N اذا بيي ← unsubstituted

N اذا بيي ← Substituted

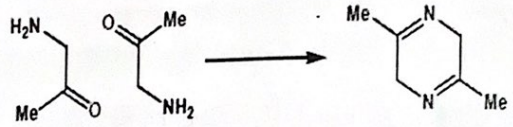
Pyrroles – Synthesis

Knorr Pyrrole Synthesis ("3+2")

(Cyclo addition)



ممكن يحدث تفاعل جانبي يتفاعل الـ 2N ويدخلو التنين على بعض



فينتج dihydropyrazine

- Use of a free amino ketone is problematic – dimerisation gives a (dihydropyrazine)

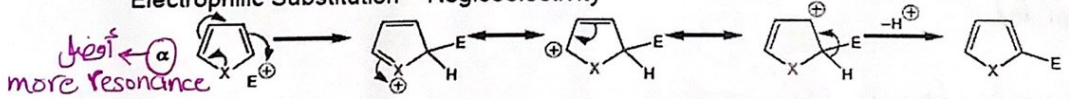
* ما هو المركب الذي ينتج عند تكوين الـ pyrrole والغير مرغوب فيه Undesired

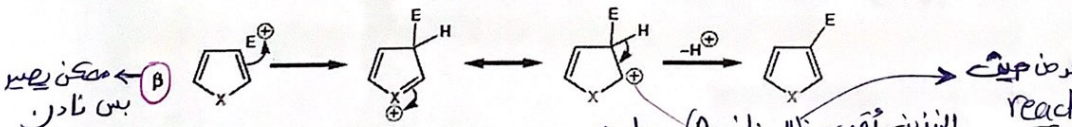
الجواب

Furans, Pyrroles Thiophenes – Electrophilic Substitution

ما يحتاج ظروف تفاعل صعبة (room tempreture) فيصير على الـ thiophene الرغم من أنه aromatic أكثر حلقة Less reactive than furan & pyrrole لأنه نواته كبيرة فيصير حامل

Electrophilic Substitution – Regioselectivity



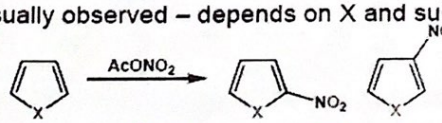


note: البنزين أقوى من الـ Pyridine

آخر واحد من اليمين reactively الـ لأنه مستقر

- Pyrrole > furan > thiophene > benzene
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions
- α-Substitution favoured over β-substitution more resonance forms for intermediate and so the charge is less localised (also applies to the transition state)
- Some β-substitution usually observed – depends on X and substituents

nitration لو بدي أعمل (hetero cycle) الـ



Pyrrole ← X = NH 4:1
furan ← X = O 6:1

نسبة (α:β)

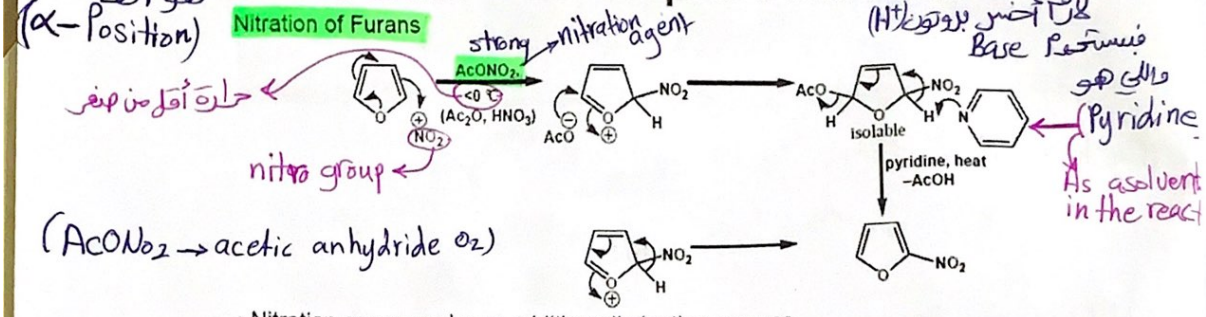
ونسبة حدوث α أكبر

بحذروا بـ mild Condition (ظروف خفيفة)

أفضل موقع لـ E^+ Substitution هو ألفا (α-Position)

Furans – Electrophilic Substitution

Nitration of Furans

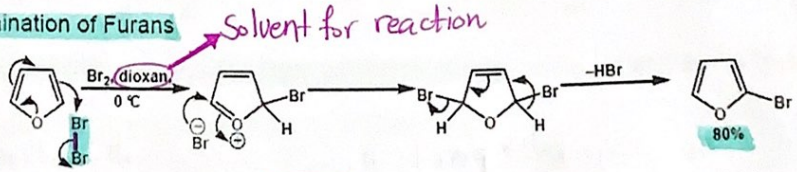


($AcONO_2$ → acetic anhydride O_2)

- Nitration can occur by an addition-elimination process
- When NO_2BF_4 is used as a nitrating agent, the reaction follows usual mechanism

weak يستخدم أيضاً بنفس الظروف السابقة (nitrating agent)

Bromination of Furans



- Furan reacts vigorously with Br_2 or Cl_2 at room temp. to give polyhalogenated products
- It is possible to obtain 2-bromofuran by careful control of temperature

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* كون الحرارة "0" لو كانت أعلى من "0" ما رح يتكون (2-Bromo Furan) ⟹ رح يصير عليه كلهم (2,3,4) Br

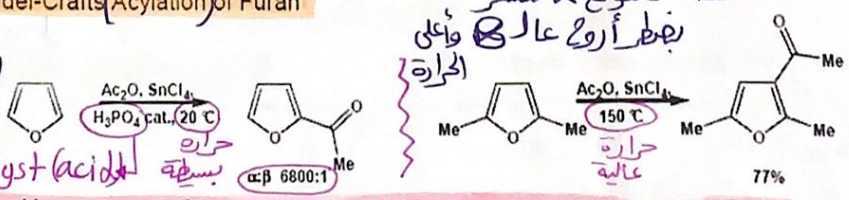
يعني لو بدي أتحكم يصير عندي mono or poly substitution بتحكم بالحرارة.

فوشان أتجنب عملية الـ (Poly halogenated product) ⟵ temprature around zero.

Furans – Electrophilic Substitution

Friedel-Crafts (Acylation) of Furan

لذا كان موقع X مسكر بضطر أروح عالـ β وأعلى الحرارة

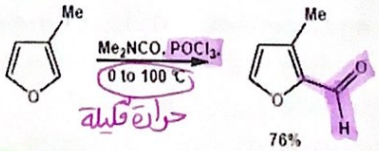


acetyl group يضيف (acetyl anhydride)

Block لو عملت Position الألفا بضيف الـ Beta Position (الحالة الوحيدة)

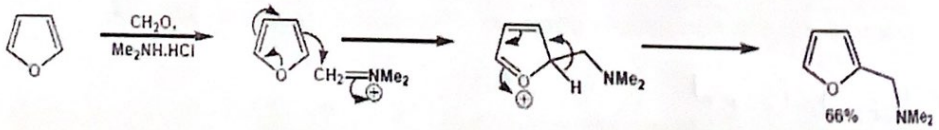
Blocking groups at the α positions and high temperatures required to give β acylation

Vilsmeier Formylation of Furan



formyle group يضيف furan لـ (aldehyde group)

Mannich Reaction of Furans



إضافة Secondary amine لـ furan

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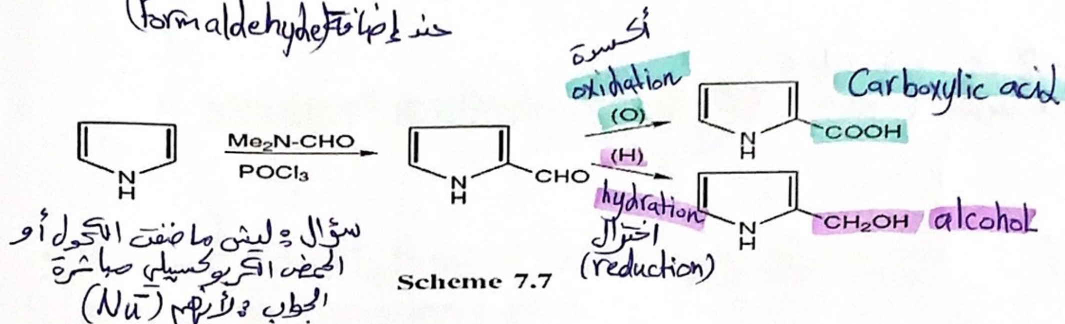
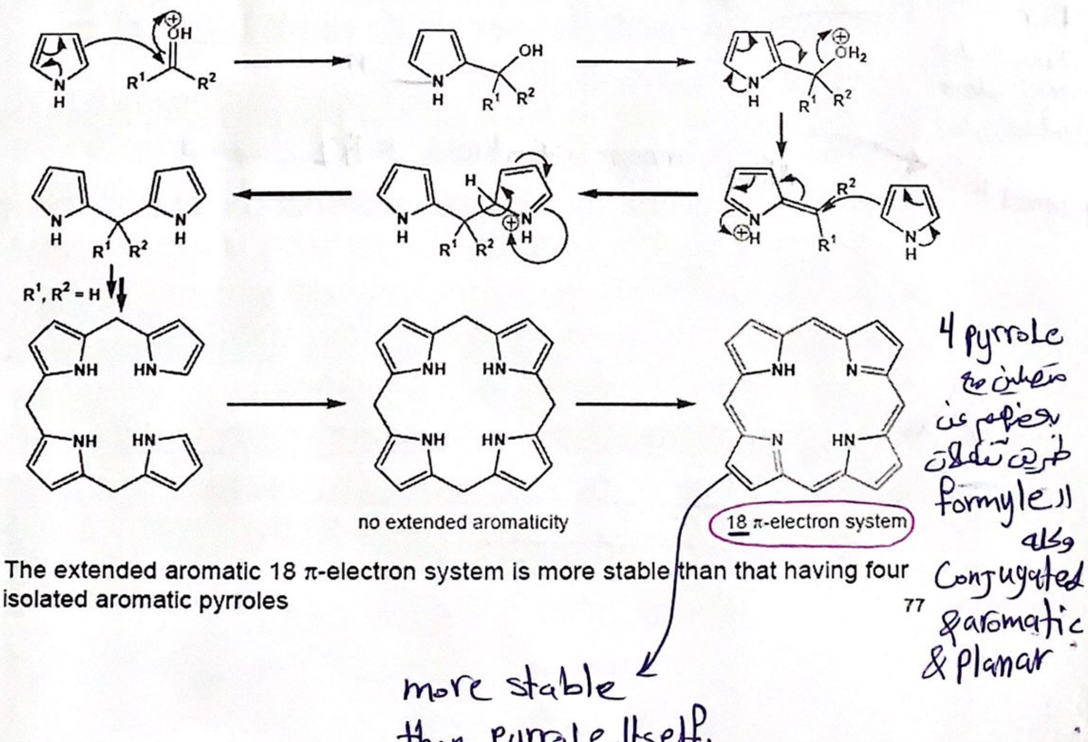


Scheme 7.7

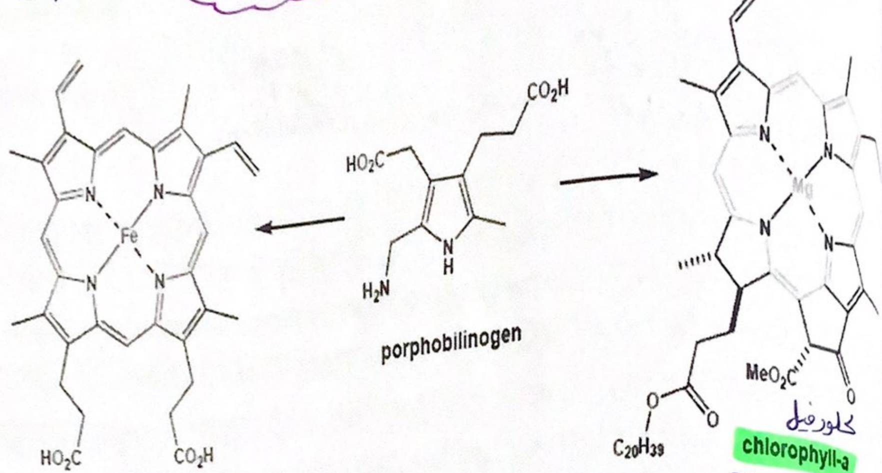
Vilsmeier–Haack Formylation with N,N-Dimethylformamide. *In*the presence of phosphorus oxychloride *(POCl3), the—CHO group* of N,N-dimethylformamide can be attached to the pyrrole ring (Scheme 7.7). This is a highly useful process for the synthesis of pyrrole aldehydes, which are precursors of pyrrole acids by oxidation, of pyrryl carbinols by reductions with LiAlH4, and of other products(Scheme 7.7).

Pyrroles – Porphyrin Formation



- The extended aromatic 18 π-electron system is more stable than that having four isolated aromatic pyrroles

Porphyrin Natural Products

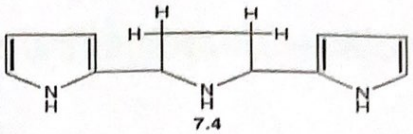


haem — porphobilinogen — chlorophyll-a

- The pigment haem is found in the oxygen carrier haemoglobin
- Chlorophyll-a is responsible for photosynthesis in plants
- Both haem and chlorophyll-*a* are synthesised in cells from porphobilinogen

Basic and Acidic Properties of Pyrroles.

- ***The low electron***density at nitrogen in pyrroles make them weak bases (for pyrrole,Kb about 10−17; cf. to noncyclic amines at about 10−5)
- *it is not* possible to make salts of pyrroles with aqueous acids
- In fact, as willbe shown next, protonation takes place on carbon, not on nitrogen.
- pyrroles do not form quaternary salts with alkylating agents, or amine oxides with peroxy compounds.
- This is in stark contrast with pyridines.
- Another explanation for the unavailability of the electron pair on nitrogen in pyrroles is that the aromatic sextet (and its energy of stabilization) would be destroyed if it were used in forming a bond.



7.4

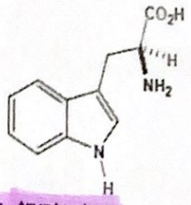
- When pyrrole is heated with strong acids, a crystalline compound is
- formed that contains three pyrrole units. Its structure has been established as **7.4. Strong acids can also cause the undesirable formation** of polymeric products from pyrrole.

These processes depend on the protonation of carbon of the ring, not of nitrogen.

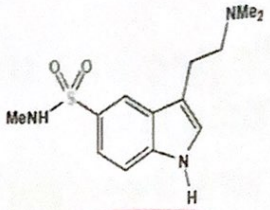
Benzo Derivatives of Pyrroles (Indoles)

- The indole family is one of the most important of all heterocyclic families, and the chemistry of this system is vast.
- Many natural products and synthetic medicinals contain this nucleus.
- Electrophilic substitutions occur readily with an attack on the electron-rich pyrrole moiety rather than the benzene ring. The 3-position is entered in preference to the 2-position, but if the 3-position is blocked, substitution occurs at the 2-position,

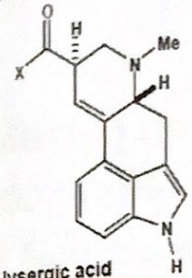
Indoles – Bioactive Indoles



tryptophan

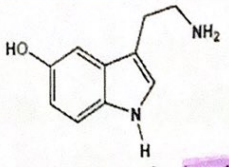


sumatriptan



X = OH lysergic acid
X = NEt_2 lysergic acid diethyamide (LSD)

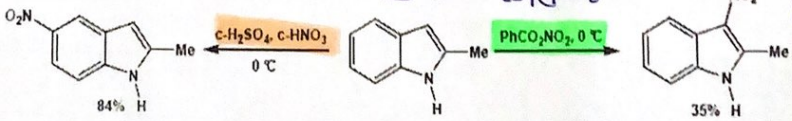
- Tryptophan is one of the essential amino acids and a constituent of most proteins
- Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS
- LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural product of the ergot fungus



5-hydroxytryptamine (serotonin)

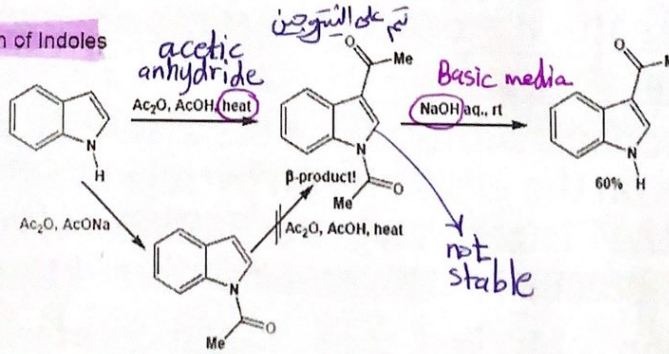
Indoles – Electrophilic Substitution

Nitration of Indoles



- Polymerisation occurs when there is no substituent at the 2-position
- Halogenation is possible, but the products tend to be unstable

Acylation of Indoles



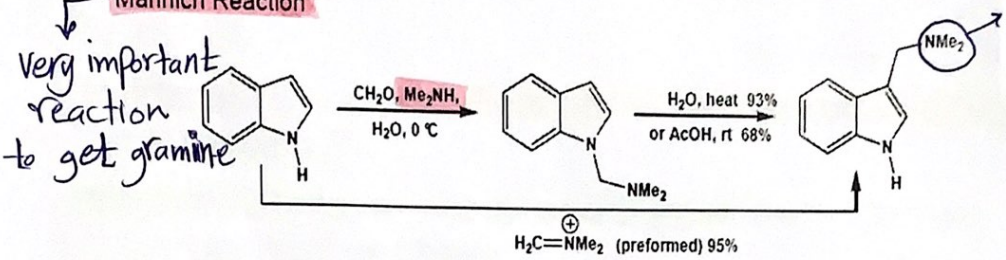
- Acylation occurs at *C* before *N* because the *N*-acylated product does not react

Indoles – Electrophilic Substitution

Mannich Reaction

very important reaction to get gramine

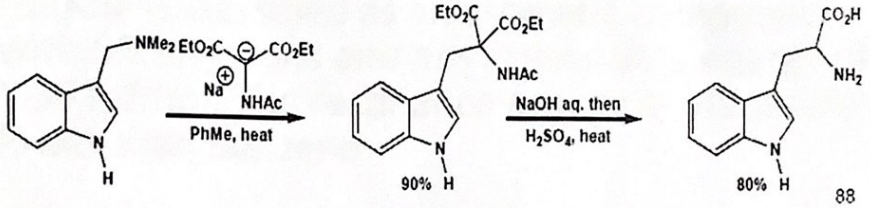
dimethyle amino



- A very useful reaction for the synthesis of 3-substituted indoles
- The product (gramine) can be used to access a variety of other 3-substituted indoles

المركب الناتج ← → Starting material of many reaction

Synthesis of Tryptophan from Gramine



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(Carboxylic acid) بعدما أضيع الـ gramine بضيفله

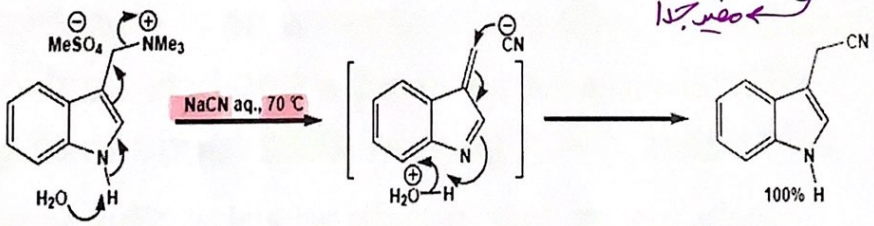
(dimethyleamino) ← وبعدها بتخلص من

(Tryptophan) عشان أحصل على

Indoles – Electrophilic Substitution

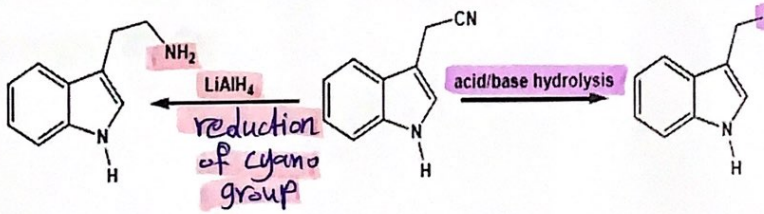
Synthesis of Other 3-Substituted Indoles from Gramine

ممكن أستغل الـ gramine وأضيع مركبات الـ Cyano (CN) ← سامة جداً



- The nitrile group can be modified to give other useful functionality

بستفيد شغلتين من الـ Cyano



فبحصل على Primary amine

أو بأكسد الكربون وبحصل على Carboxylic derivative