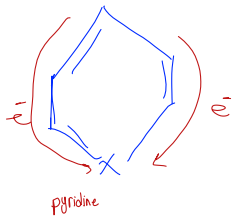
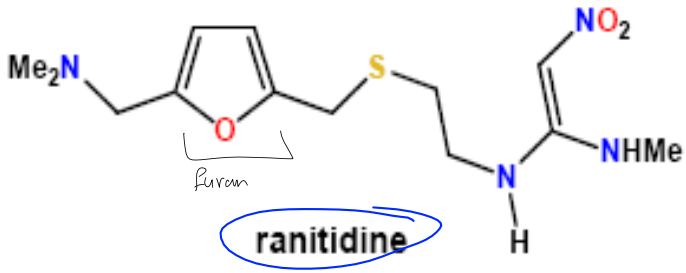
PI-EXCESSIVE RING SYSTEMS

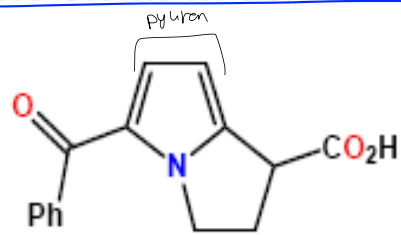


حطيت كل سؤال سنوات بالسلايد اللي أجا منه
عشان تعرفوا كيف بيجي السؤال



ranitidine

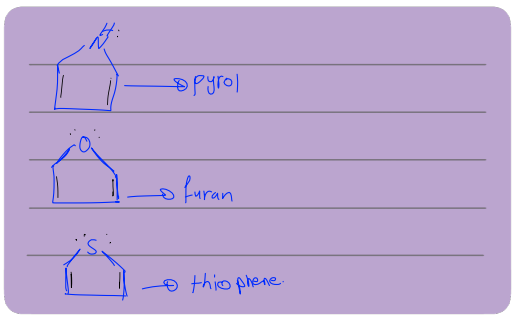
- Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H_2-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers

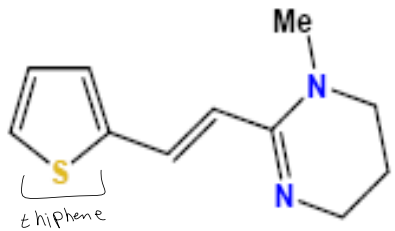


ketorolac

N ← one lone pair of e⁻
O ← 2 lone pair of e⁻

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





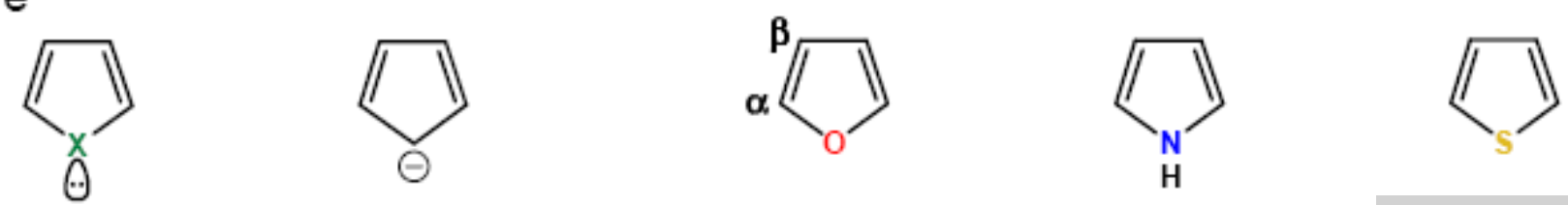
banminth

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

← للقضاء على الديدان بال GI .

Furans, Pyrroles and Thiophenes – Structure

Structure



- 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

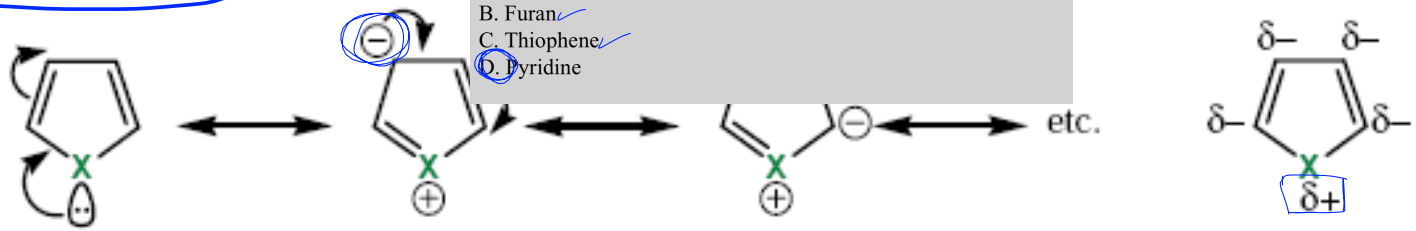
Q6. Which of the following statements about π-excessive heterocycles is correct?

A. All are non-planar
B. All are planar
C. All are anti-aromatic
D. All contain 4π electrons

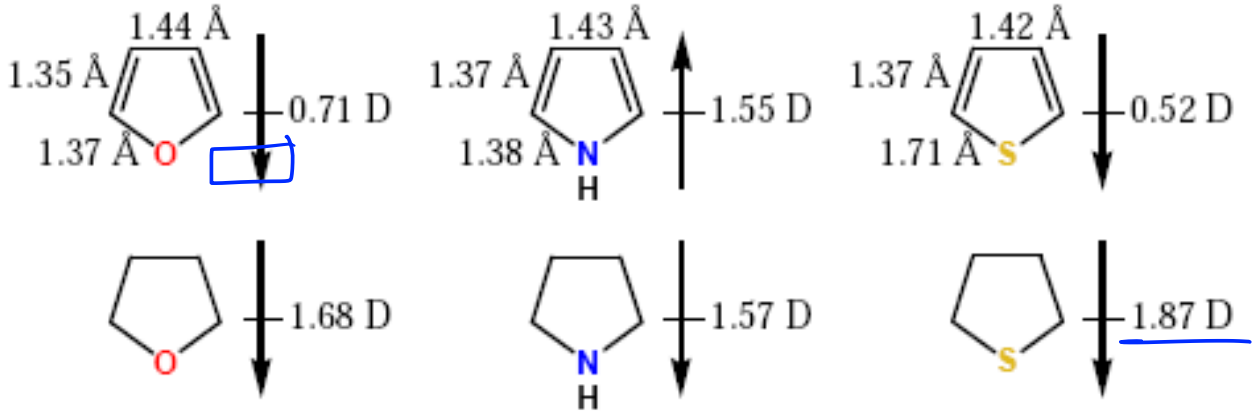
Resonance Structures

Q29. Which of the following is NOT a π-excessive heterocycle?

A. Pyrrole
B. Furan
C. Thiophene
D. Pyridine



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

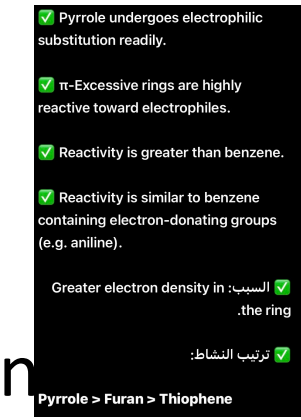


- O and S are more electronegative than N and so inductive effects dominate

Chemical Properties of Pyrroles

Electrophilic Substitution.

A significant feature of the pi excessive



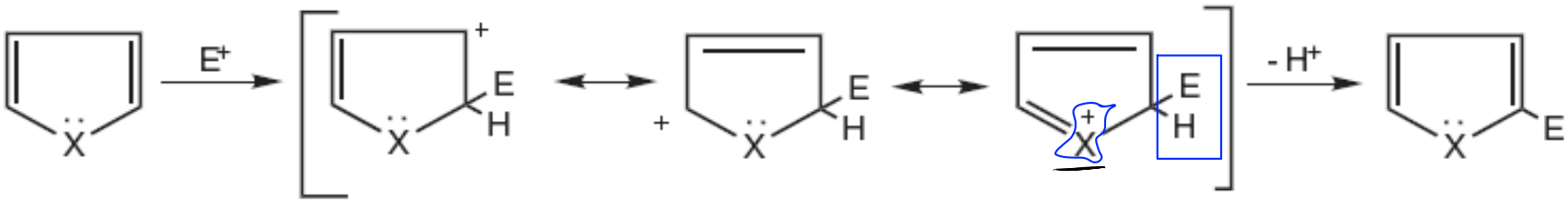
- ring systems is that they are highly reactive to electrophilic

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.*

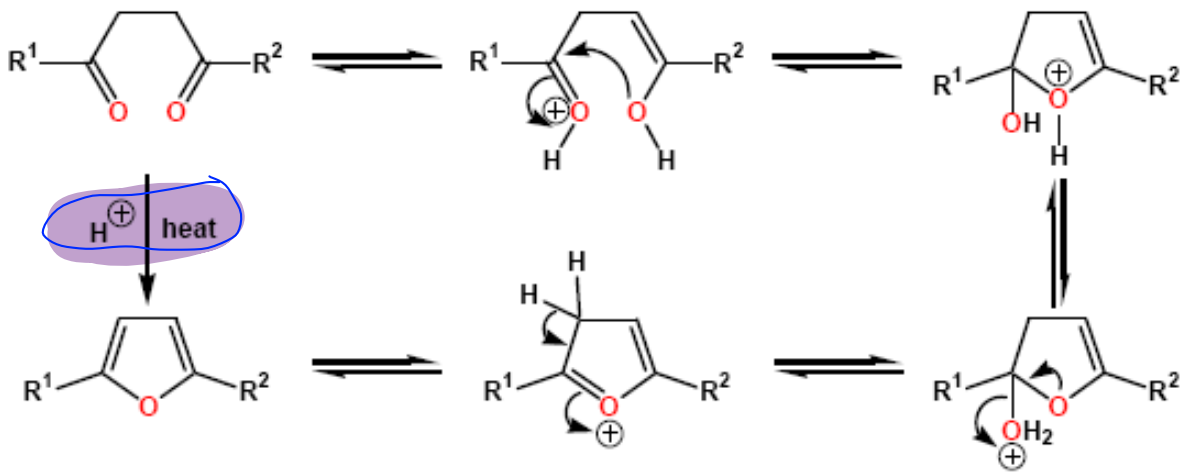


Scheme 7.2

- 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.

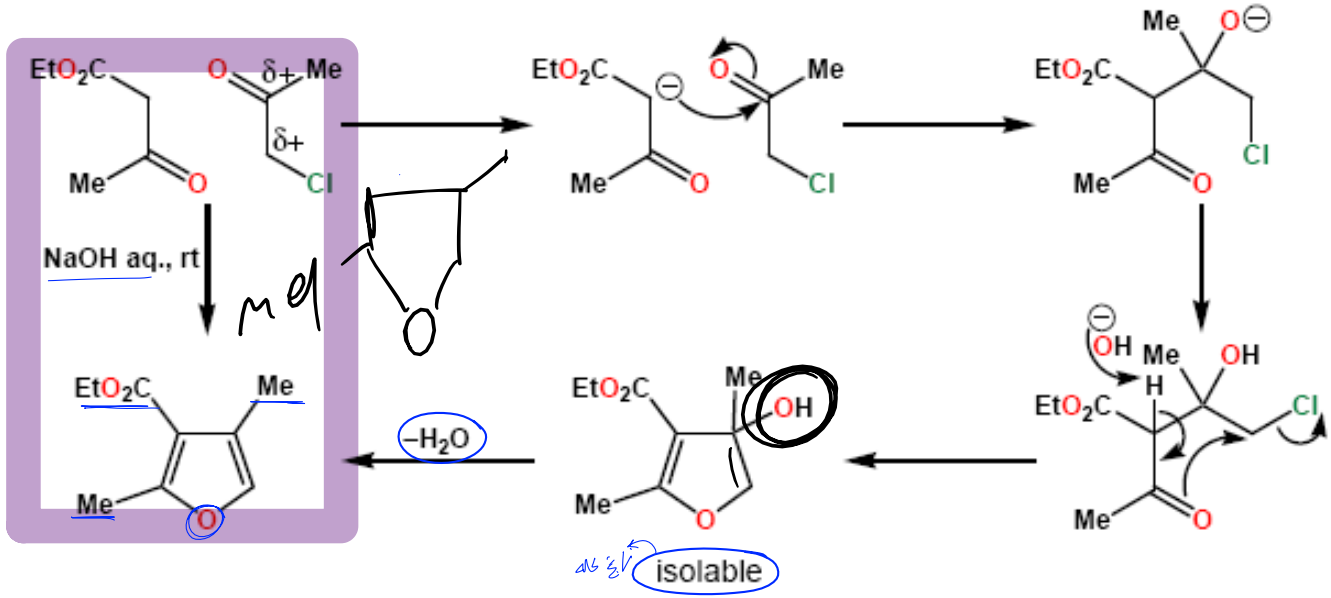
Furans – Synthesis

1. Paal Knorr Synthesis



- 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*-$MeC_6H_4SO_3H$)

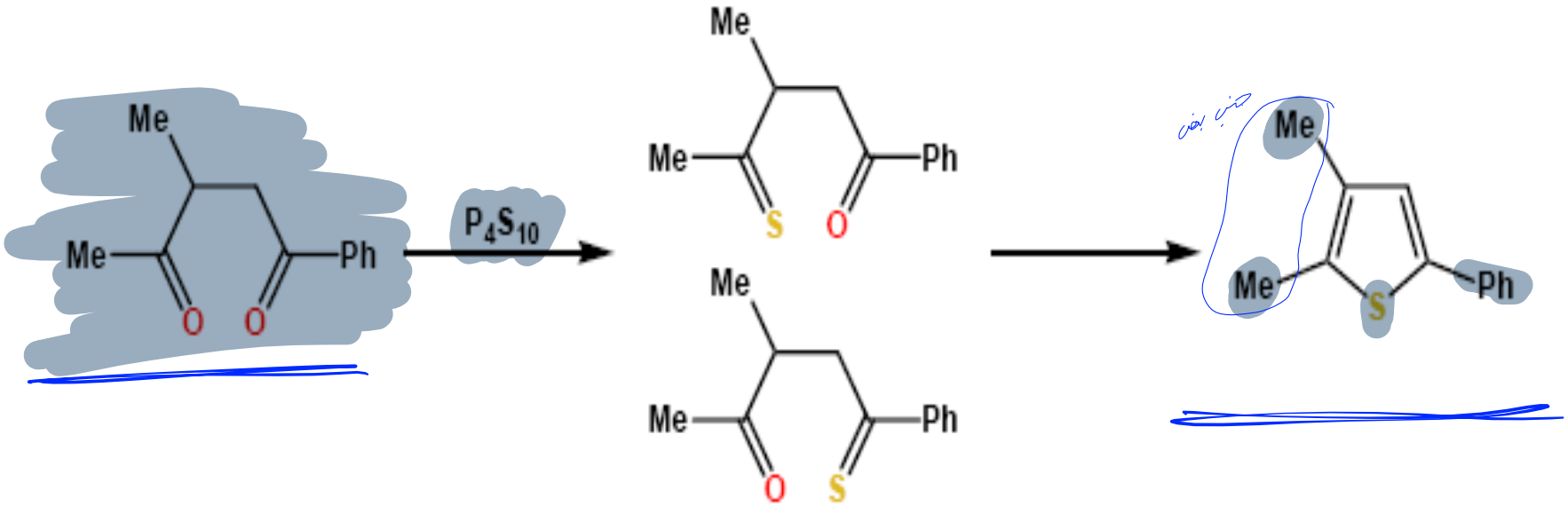
② Feist-Benary Synthesis ("3+2")



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

Thiophenes – Synthesis

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



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

Q38. Paal–Knorr synthesis of thiophenes is an example of:

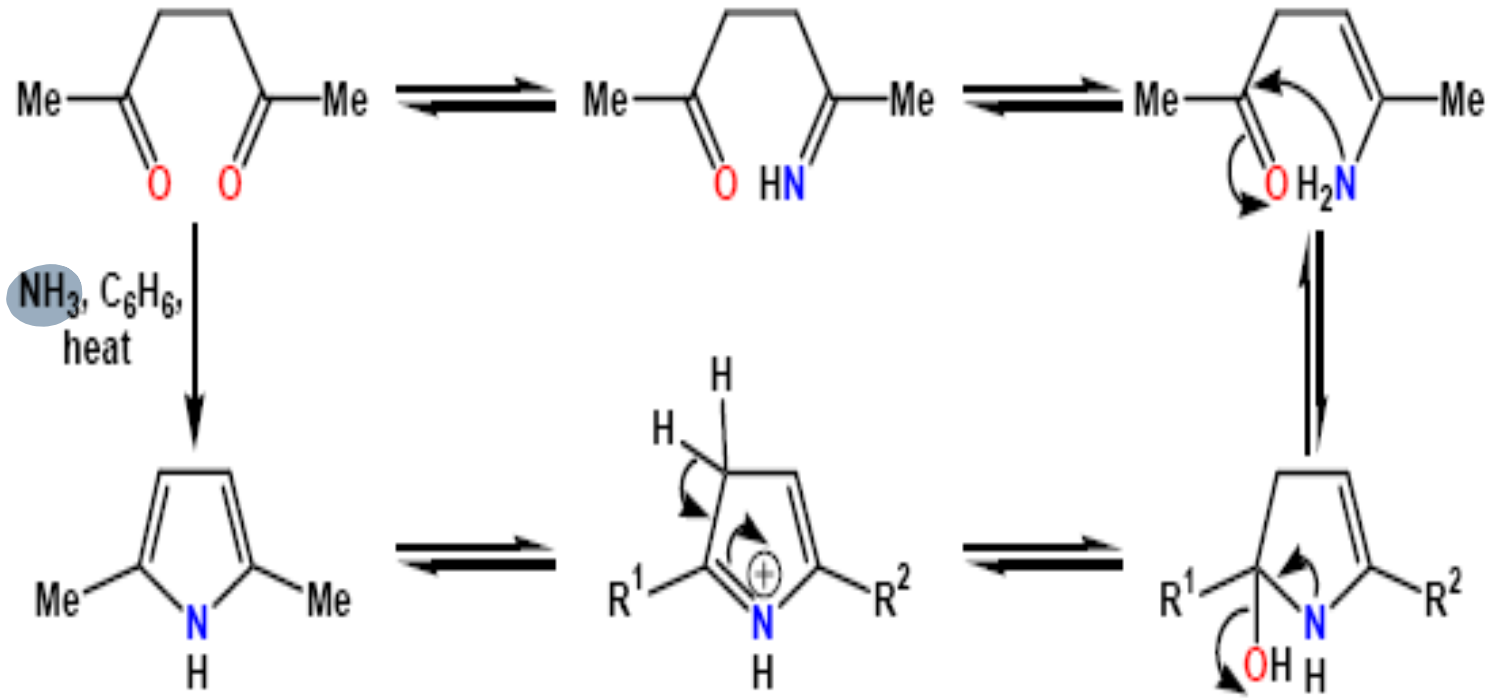
A. 2 + 2 cyclization
B. 3 + 2 cyclization
C. 4 + 1 cyclization
D. 5 + 0 cyclization

* Pyrroles – Synthesis

Q16. The Paal–Knorr synthesis is commonly used to prepare:

A. Pyrroles
B. Diazines
C. Quinolines
D. Tetrazoles

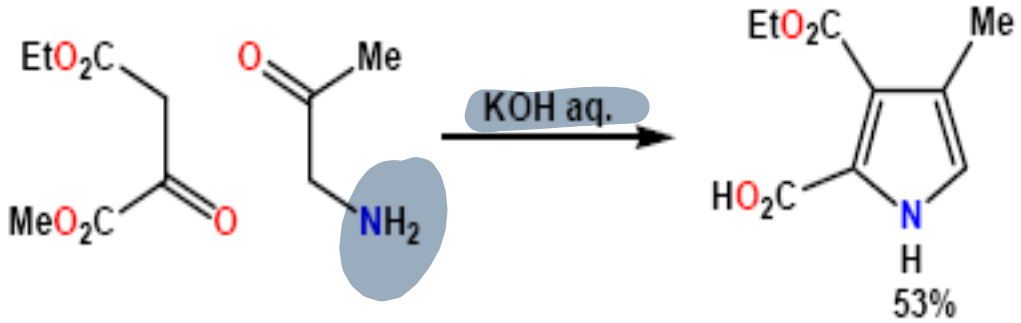
Paal Knorr Synthesis ("4+1")

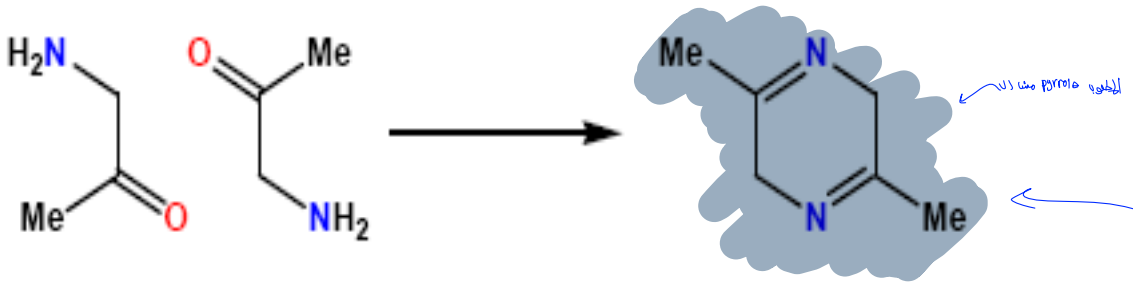


- Ammonia or a primary amine can be used to give the pyrrole or *N*-alkyl pyrrole

Pyrroles – Synthesis

Knorr Pyrrole Synthesis ("3+2")

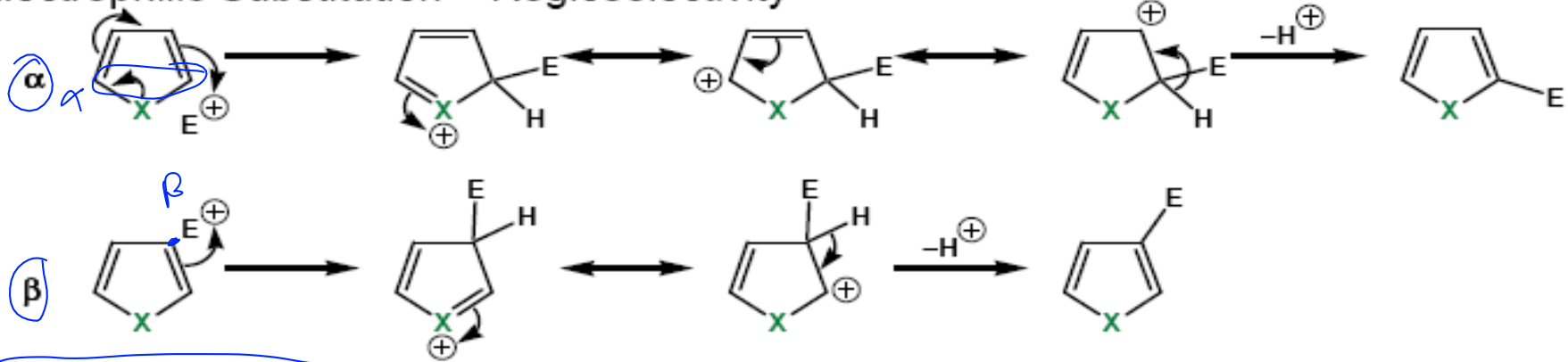




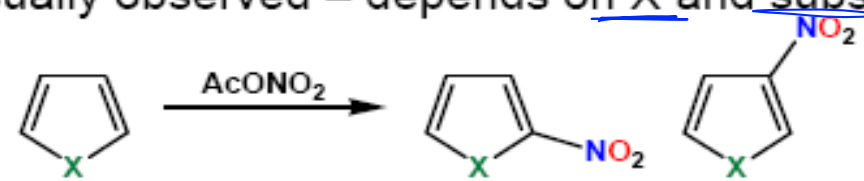
- Use of a free amino ketone is problematic – dimerisation gives a dihydropyrazine

Furans, Pyrroles Thiophenes – Electrophilic Substitution

Electrophilic Substitution – Regioselectivity



- 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

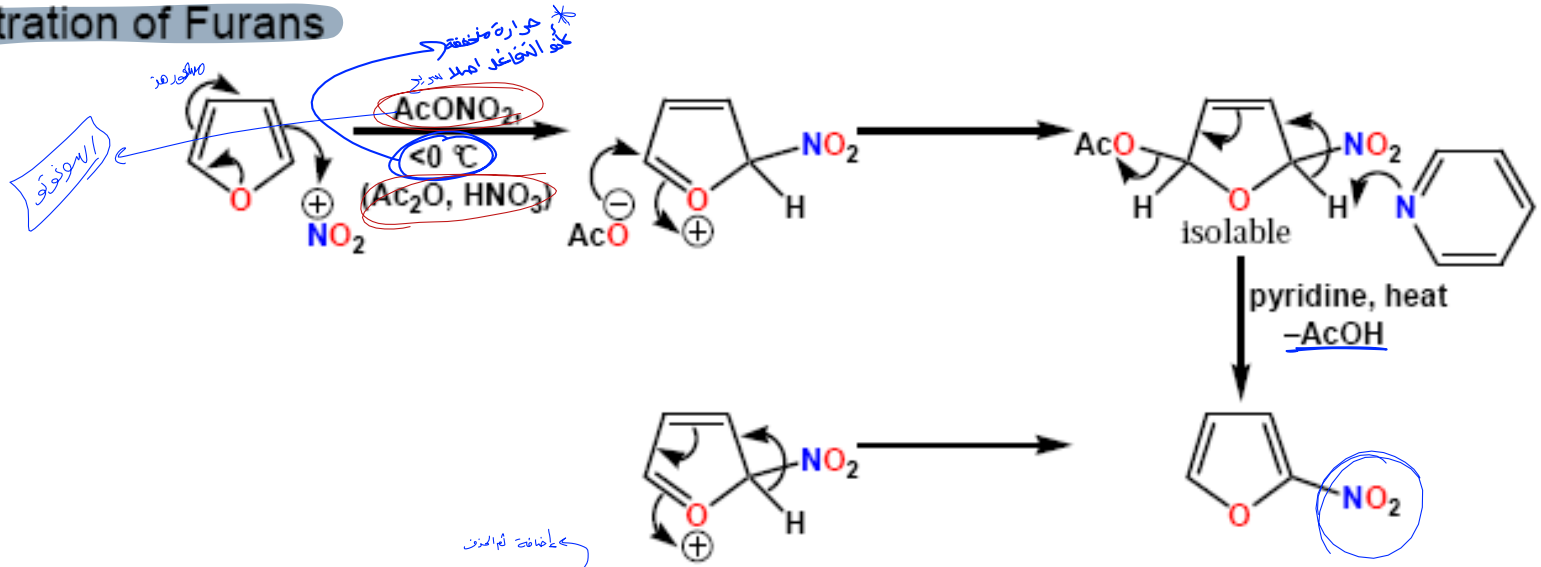


Q17. Electrophilic substitution in furan occurs predominantly at:

A. β-position
B. α-position
C. Oxygen atom
D. Random position

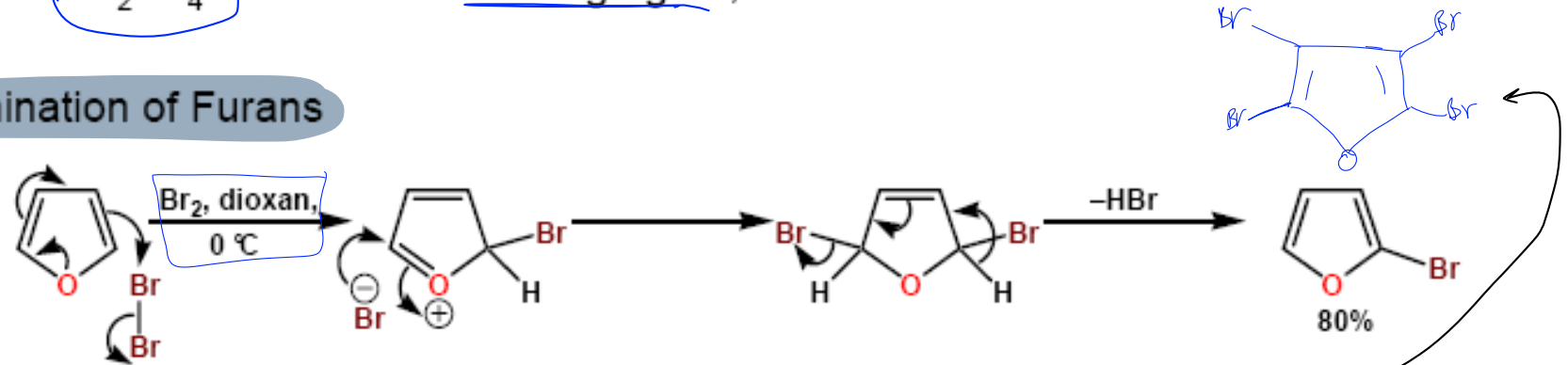
Furans – Electrophilic Substitution

Nitration of Furans



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

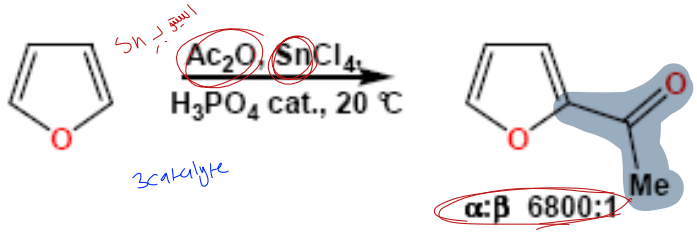
Bromination of Furans

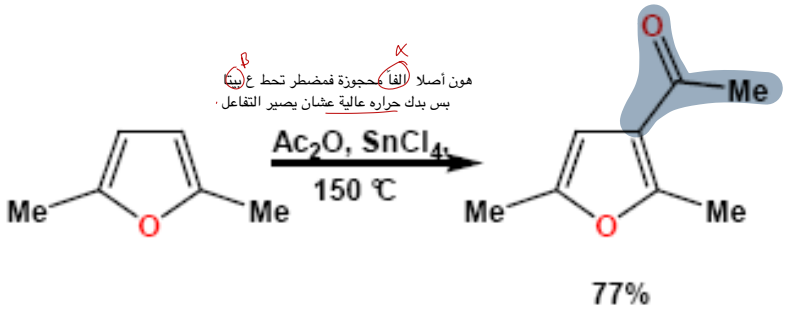


- Furan reacts vigorously with Br_2 or Cl_2 at room temp. to give polyhalogenated products
- It is possible to obtain 2-bromofuran by careful control of temperature

Furans – Electrophilic Substitution

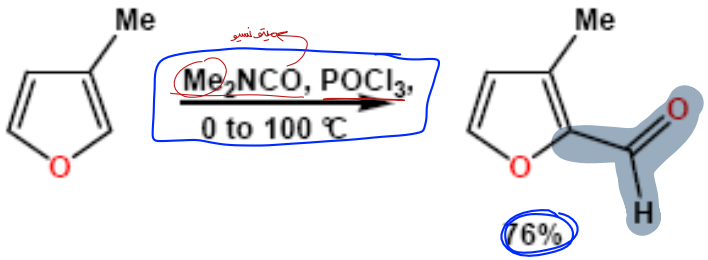
Friedel-Crafts Acylation of Furan



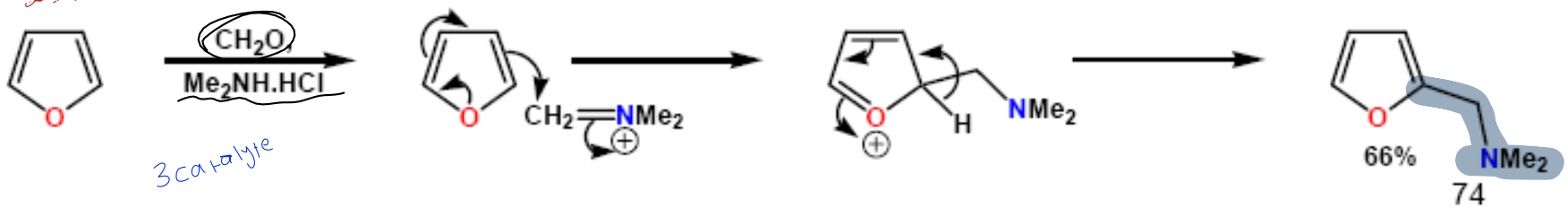


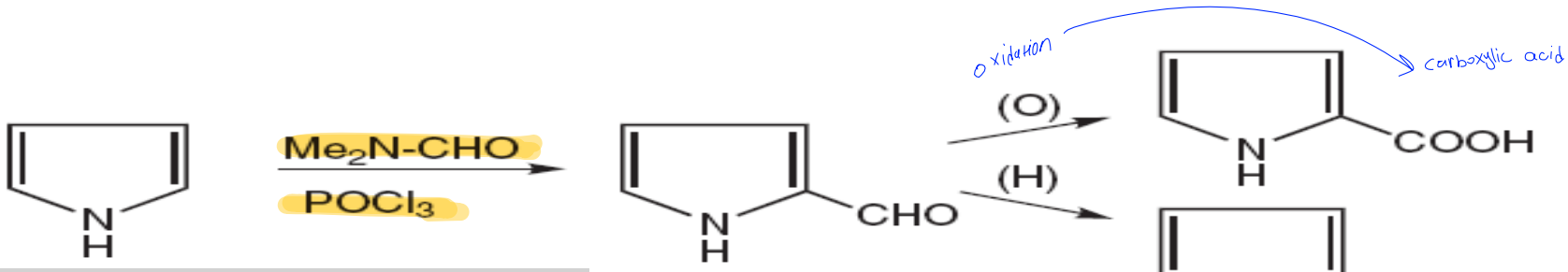
- Blocking groups at the α positions and high temperatures required to give β acylation

Vilsmeier Formylation of Furan



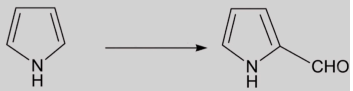
Mannich Reaction of Furans





Q37. What reagent/condition is required for the following reaction?

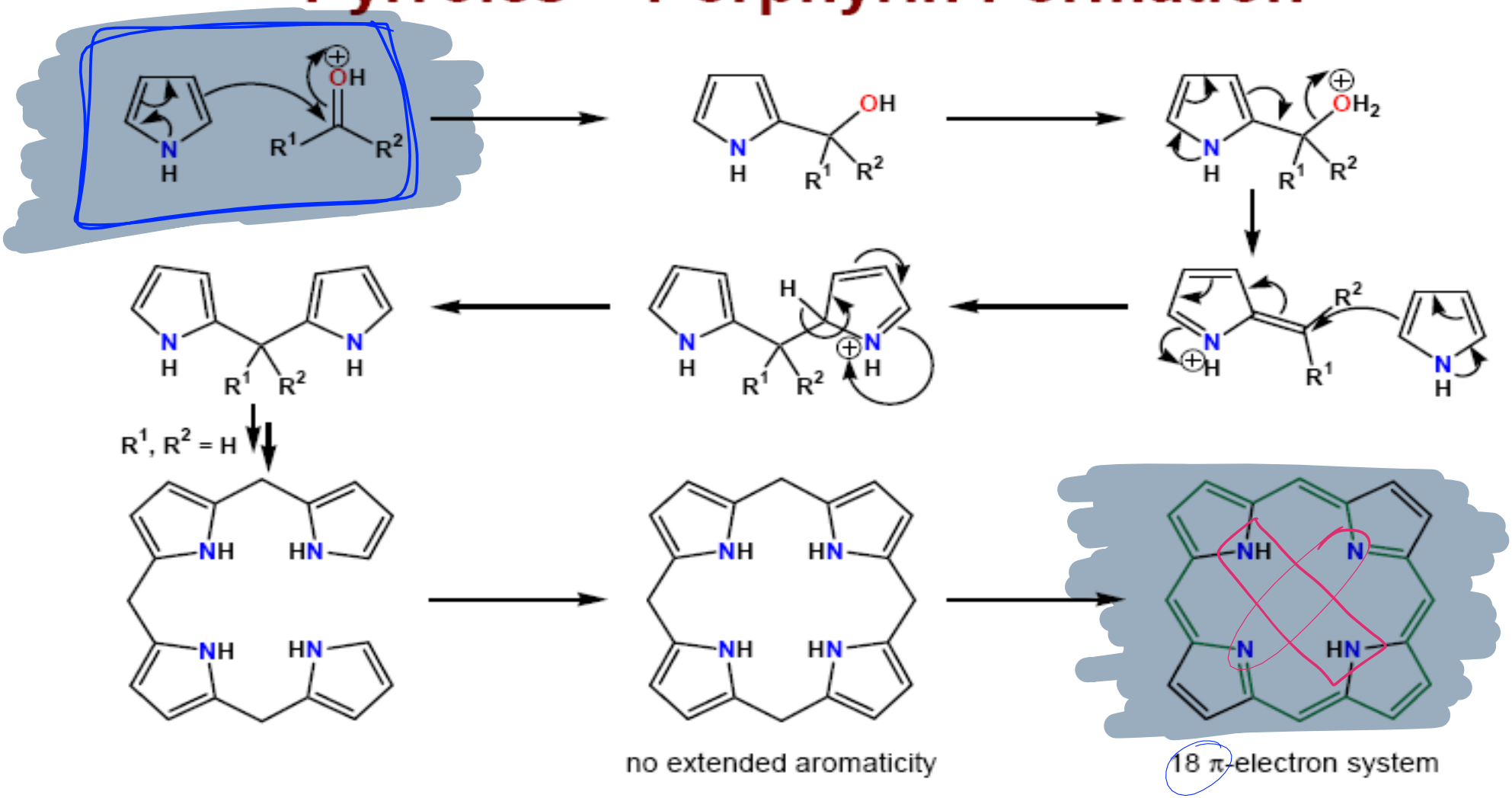
A. $CHCl_3$ / KOH
B. Me_2N-CHO / $POCl_3$
C. HCHO / HCl
D. CO / H_2SO_4



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

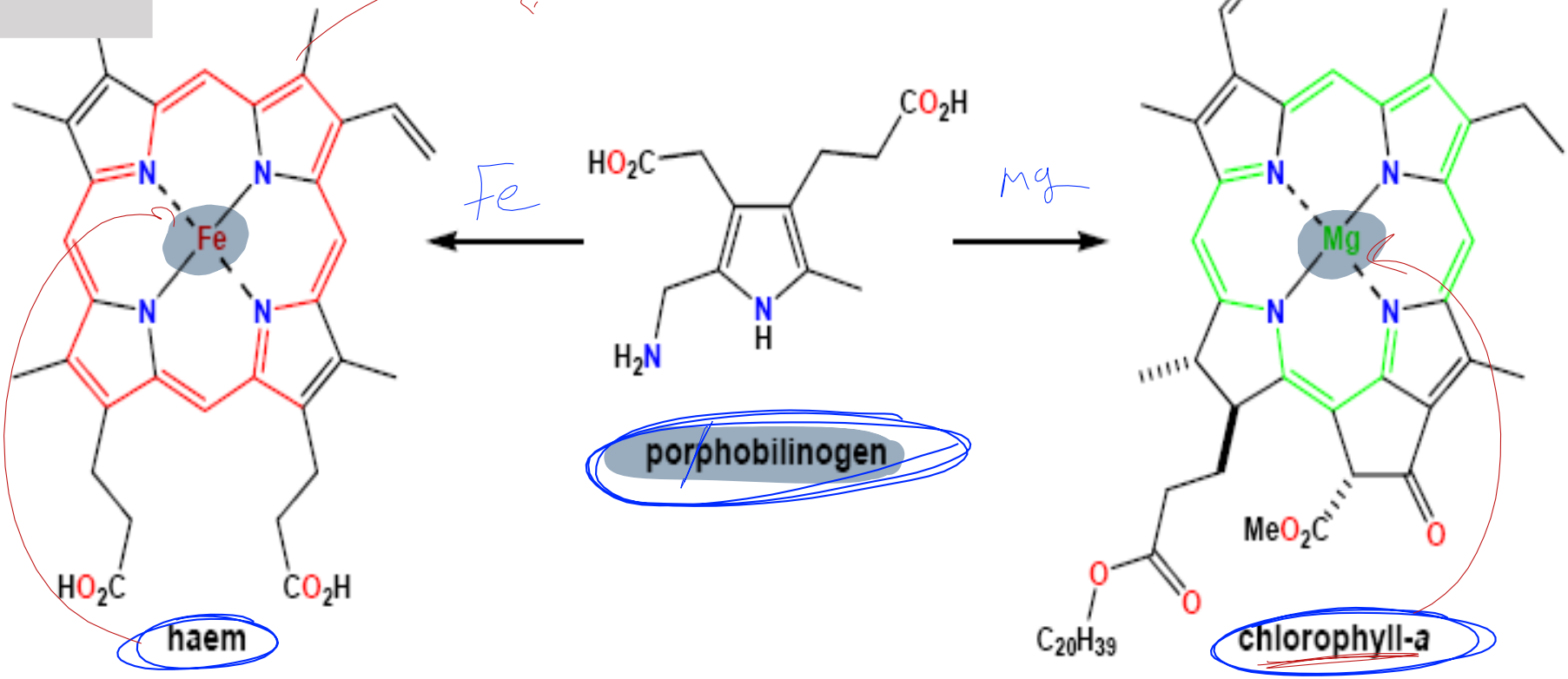


- The extended aromatic 18 π-electron system is more stable than that having four isolated aromatic pyrroles

Q8. Heme consists of:

A. Oxazole with Fe
B. Pyridine with Fe
C. Pyrrole with Fe
D. Imidazole with Fe

Porphyrin Natural Products



- 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

pyrrole → weak bases.

Basic and Acidic Properties of Pyrroles.

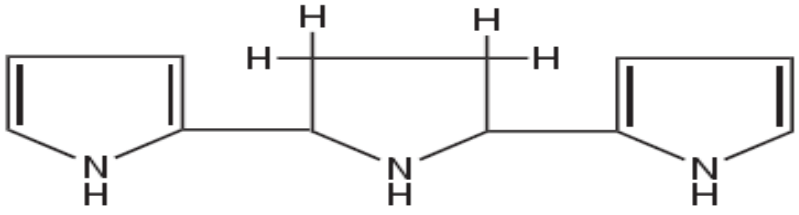
- ***The low electron***density at nitrogen in pyrroles make them weak bases (for pyrrole,Kb about 10−17; cf. to noncyclic amines at about 10−5*)*,
- *it is not* possible to make salts of pyrroles with aqueous acids.
- In fact, as willbe shown next, protonation takes place on carbon, not on nitrogen.
- 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.

Q12. Pyrroles do not form quaternary salts with alkylating agents because:

A. Pyrrole nitrogen is pyridine-like
B. Pyrrole nitrogen lone pair is part of the aromatic sextet
C. Pyrrole is strongly basic
D. Pyrrole is π-deficient

Q40. Pyrroles do not form quaternary salts with alkylating agents or amine oxides with peroxy compounds.

A. True
B. False



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**

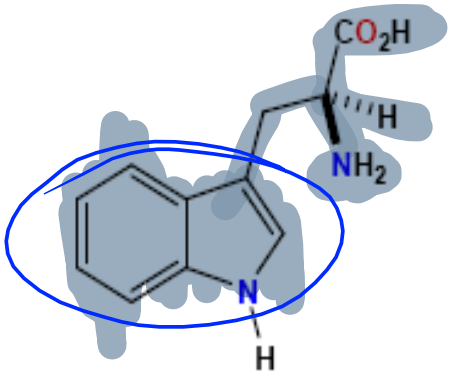
of polymeric products from pyrrole.

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

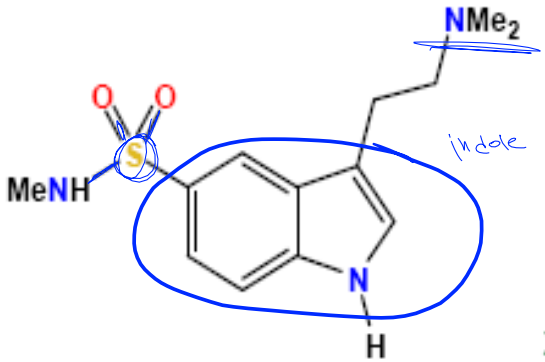
Benzo Derivatives of Pyrroles (Indoles)

- 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,

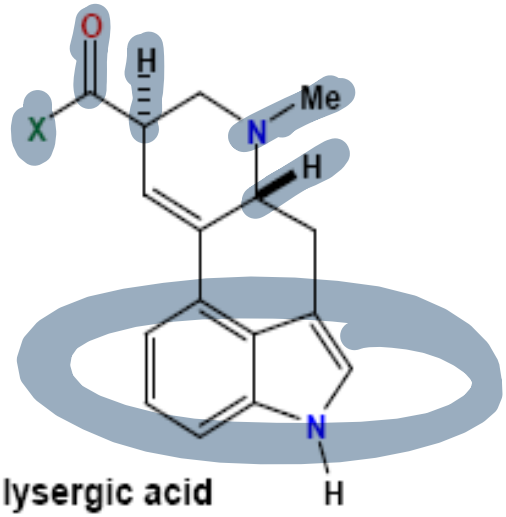
Indoles – Bioactive Indoles



tryptophan



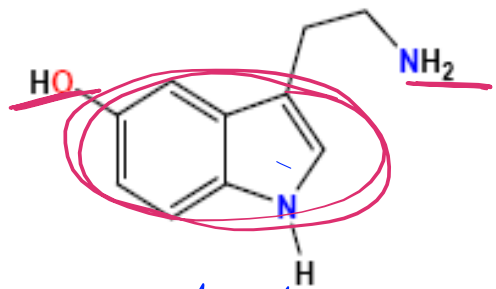
sumatriptan



X = OH lysergic acid

X = NEt_2 *l*ysergic acid *d*iethyamide (LSD)

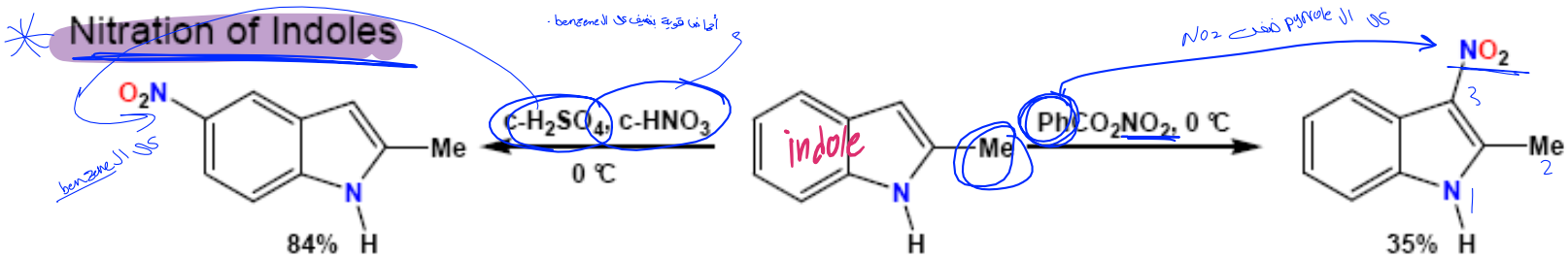
- Tryptophan is one of the essential amino acids and a constituent of most proteins
- Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS
- LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural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



5-hydroxytryptamine (serotonin)

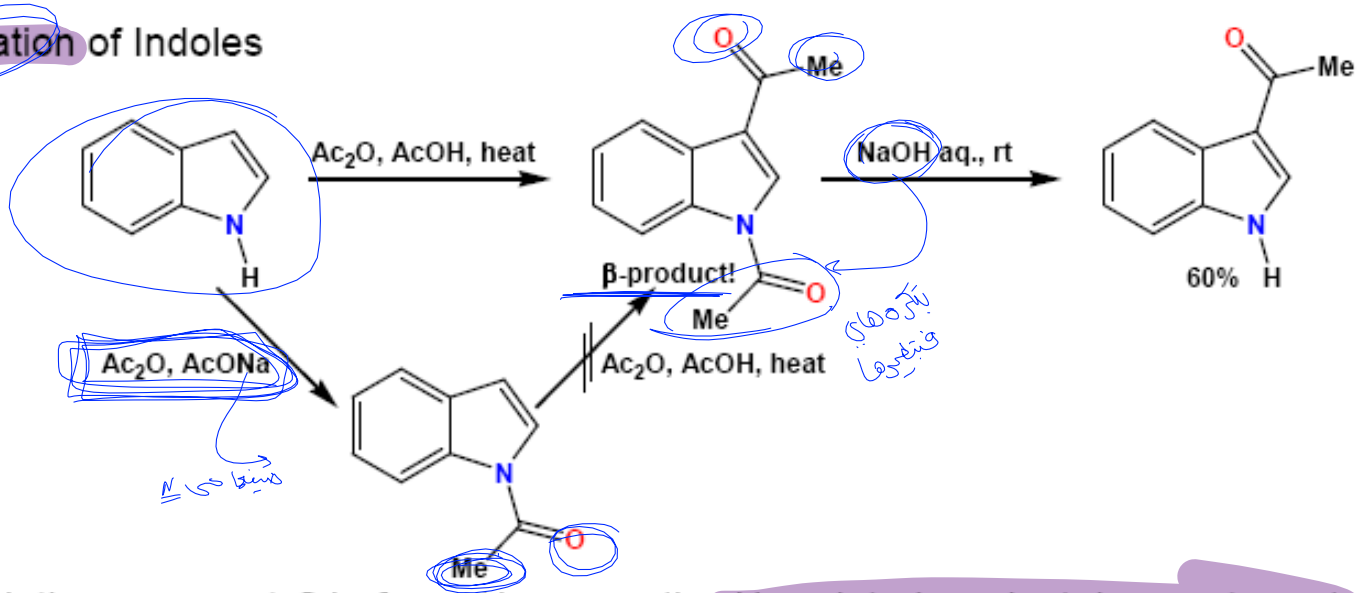
Indoles – Electrophilic Substitution

Nitration of Indoles



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

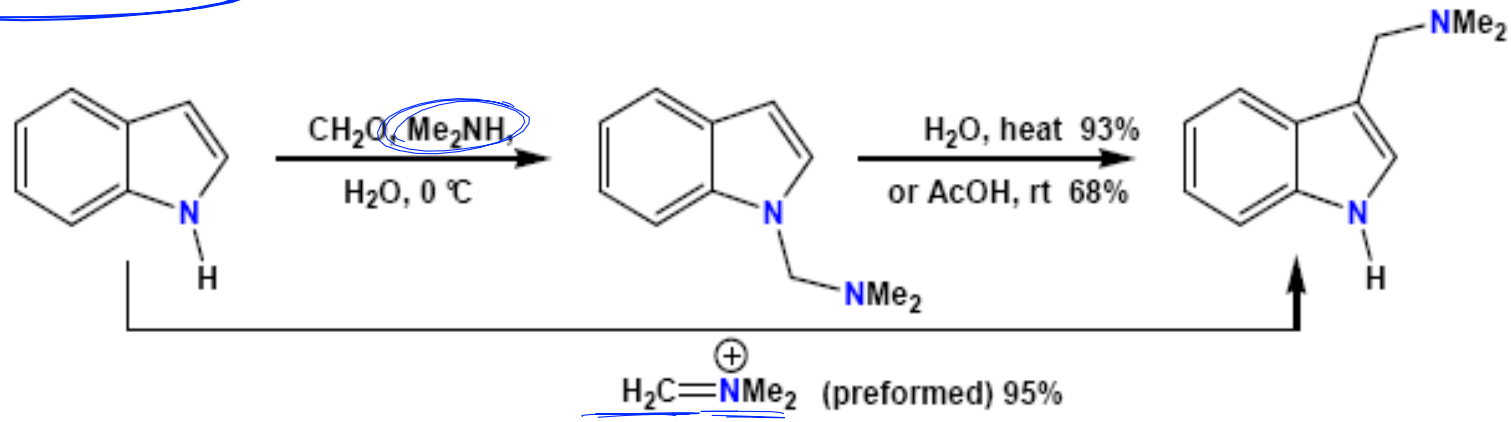
Acylation of Indoles



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

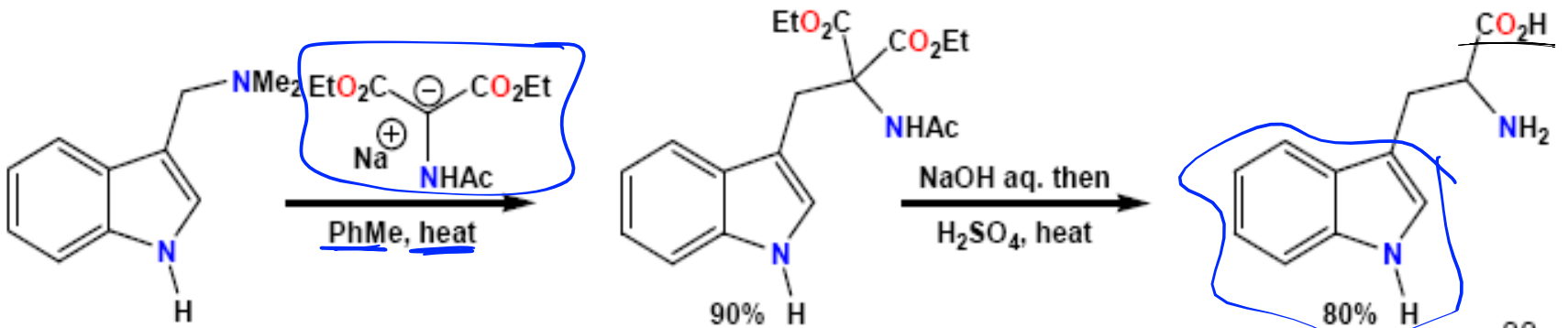
Indoles – Electrophilic Substitution

Mannich Reaction



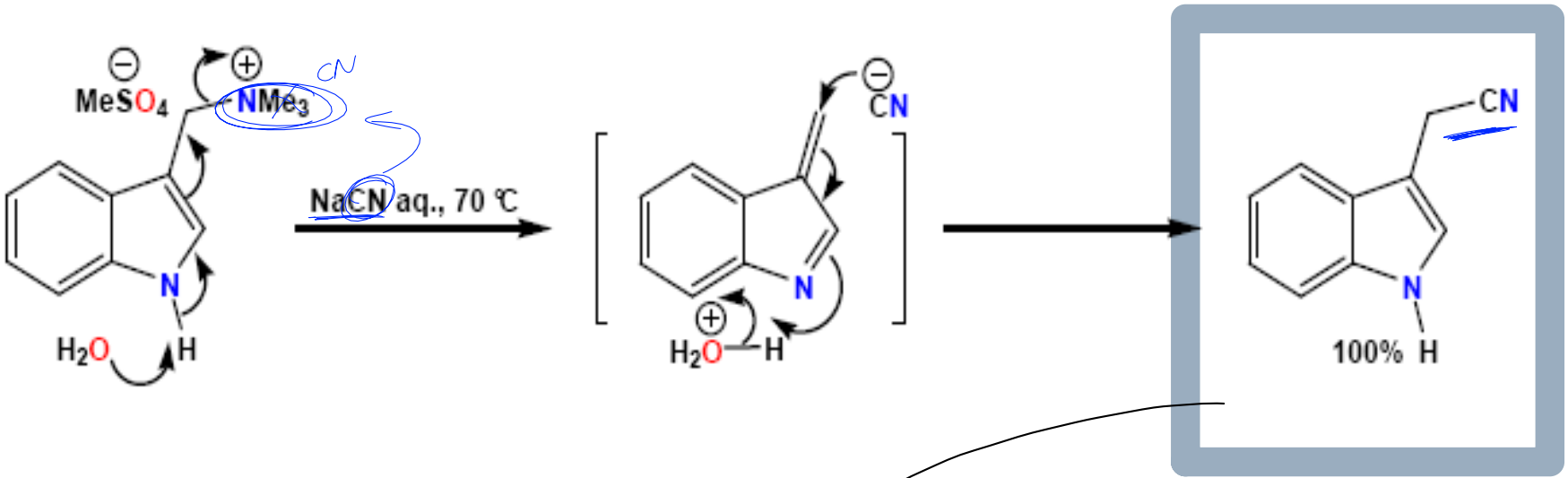
- A very useful reaction for the synthesis of 3-substituted indoles
- The product (gramine) can be used to access a variety of other 3-substituted indoles

Synthesis of Tryptophan from Gramine



Indoles – Electrophilic Substitution

Synthesis of Other 3-Substituted Indoles from Gramine



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