

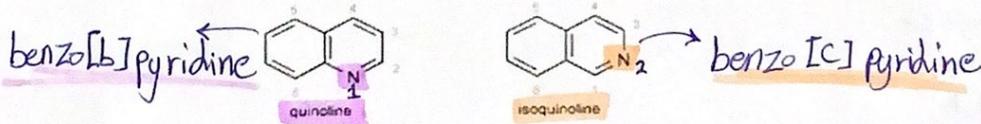
CH₈

benzene + Pyridine

(Quinolines and Isoquinolines: Reactions and Synthesis)

weak Bases

في السابق السابقة غطينا (monocyclic)
 وفي هذا السابق سنتحدث عن (Bi cyclic)



- Quinoline is a high-boiling liquid; isoquinoline is a low-melting solid; each has a sweetish odour.
- Both bases have been known for a long time: quinoline was first isolated from coal tar in 1834, isoquinoline from the same source in 1885. (تم اكتشاف ال quinolin وبعده سنة تقريباً اكتشفوا Iso quinolin من نفس المصدر (البتارين) (زيت))
- Shortly after the isolation of quinoline from coal tar, it was also recognised as a pyrolytic degradation product of cinchonamine, an alkaloid closely related (to quinine) from which the name quinoline is derived; the word quinine, in turn, derives from quina, a Spanish version of a local South American name for the bark of quinine-containing Cinchona species

* قلعة: المركبات النباتية التي فيها النيتروجين (alkaloid compound) بسماها

$(E)^+$ * الشرجين لا يبطى الا $(E)^+$

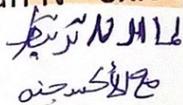
Less basic than Pyridine
tertiary amine
(aliphatic amine)

E^+

• Reactions with **Electrophilic** Reagents

• 9.1.1 Addition to Nitrogen

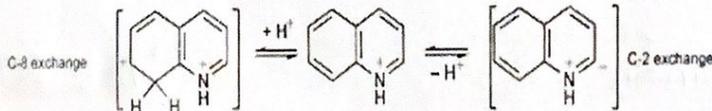
• All the reactions noted in this category for pyridine which involve donation of the nitrogen lone pair to electrophiles, also occur with quinoline and isoquinoline, for example the respective pK_aH values, 4.94 and 5.4, show them to be of similar basicity to pyridine. Each, like pyridine, readily forms an **N-oxide** and quaternary salts.



alkyle مع الكبريت

pK_a
قوة حمضية

electron deficient
قوة E^+ مع الكبريت
N لا يبطى
electron rich
قوة E^+ مع الكبريت



• Substitution at **Carbon**

• **Proton Exchange (Benzene ring) C-protonation**, and thence exchange via N-protonated quinoline, requires strong (sulfuric acid) and occurs fastest at (C-8, then at C-5 and C-6); comparable exchange in

isoquinoline takes place somewhat faster at (C-5 than at C-8)

• 1 At lower acid strengths each system undergoes exchange to nitrogen, at C-2 for quinoline and C-1 for isoquinoline.

• These processes involve a zwitterion produced by deprotonation of the N-protonated heterocycle

8 > 5 > 6 position حسب التفاعل quinoline note

كثير مواقع ممكن
يستقبل (E^+)

5 > 8 Isoquinoline
مواقع بديلة

quinoline

protonation بواسطة (H_2SO_4)
(N) لا يبطى

H_2SO_4 مع الكبريت

other sites

تبادل بروتون

proton exchange

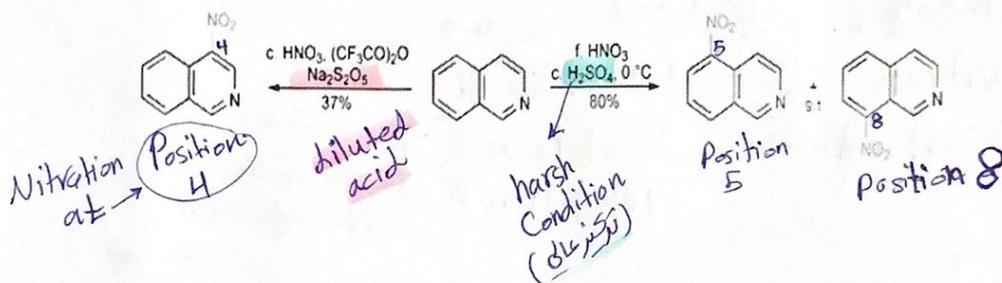
والتفاعل مع

الحمض

(Concentrated or diluted)

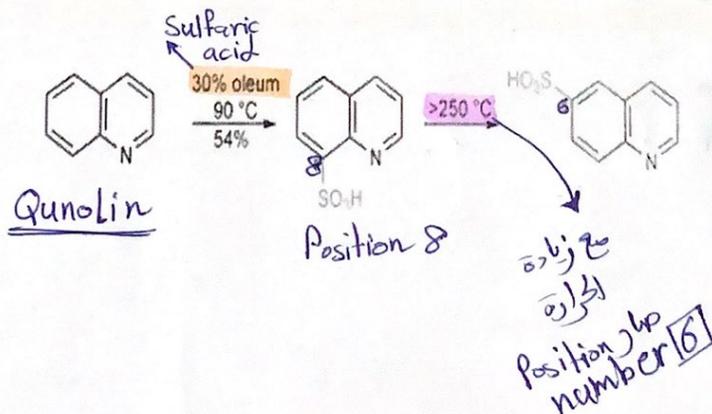
• Nitration

- The positional selectivity for proton exchange is partly mirrored in nitrations, quinoline gives approximately equal amounts of 5 - and 8 - nitro - quinolines, whereas isoquinoline produces almost exclusively the 5 - nitro - isomer



Sulfonation

- Sulfonation of quinoline gives (largely) the 8 - sulfonic acid, whereas isoquinoline affords the 5 - acid.
- Reactions at higher temperatures produce other isomers, under thermodynamic control, for example both quinoline 8 - sulfonic acid and quinoline 5 - sulfonic acid are isomerised to the 6 - acid



acetyl group

alkyl group

مجموعة على الكربون

- Acylation and Alkylation There are no generally useful processes for the introduction of carbon substituents by electrophilic substitution of quinolines or isoquinolines.

* صحتن ياجي سوال شوفه تقلا ال Electrophilic
Substitution? (بشكل عام)

Nitration [E]

halogenation [I]

Sulfonation [E]

Acylation [E]

Alkylation [E]

لا يجرى على
quinolin
& Isoquinolin

Halogenation

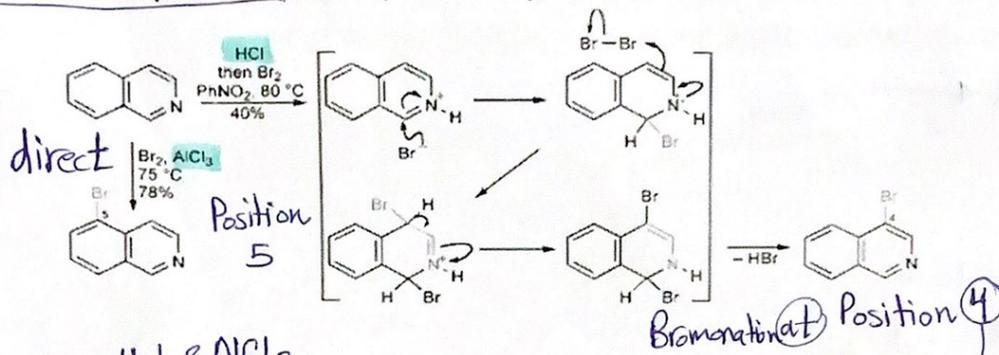
halogen group

highly reactive so reaction is more easy.

- Ring substitution of quinoline and isoquinoline by halogens is rather complex, products depending on the conditions used.
- In concentrated sulfuric acid, quinoline gives a mixture of 5- and 8-bromo derivatives; comparably, isoquinoline is efficiently converted into the 5-bromo-derivative in the presence of aluminium chloride, 8 or with N-bromosuccinimide in concentrated sulfuric acid

nitrogen
itself

- Introduction of halogen to the hetero - rings occurs under remarkably **mild conditions** in which halide addition to a salt initiates the **HCL** sequence. Thus treatment of **quinoline** or **isoquinoline hydrochlorides** with **bromine** produces **3 - bromoquinoline** and **4 - bromoquinoline**, respectively, as illustrated below for the latter



HCl & AlCl₃
(mild condition)
بمركب ضعيف من
acid

وذلك لتعويض نقص

سؤال: هل يمكن إجراء bromination
at position 4?

الجواب: True = Indirect
(in Isoquinoline)

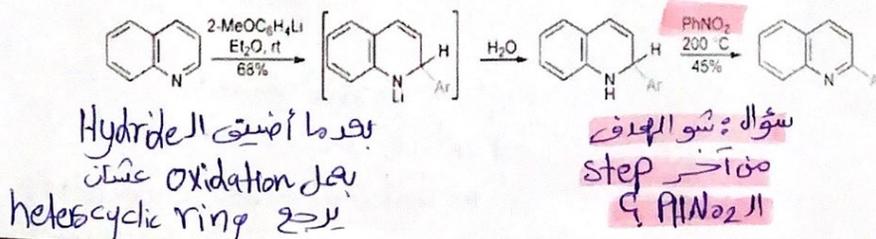
Reactions with Nucleophilic Reagents

Grignard

alkyl (R)

ArYL (aromatic group + Li)

- Nucleophilic Substitution with 'Hydride' Transfer Reactions of this type occur **fastest** at **C - 2** in quinoline and at **C - 1** in isoquinolines.
- Alkylation and Arylation
- The immediate products of addition of alkyl and aryl Grignard reagents and alkyl - and aryl lithiums are dihydro - quinolines and - isoquinolines and can be characterised as such, but can be oxidised to afford the C - substituted, (**re - aromatised heterocycles**;) illustrated below is a 2 - arylation of quinoline



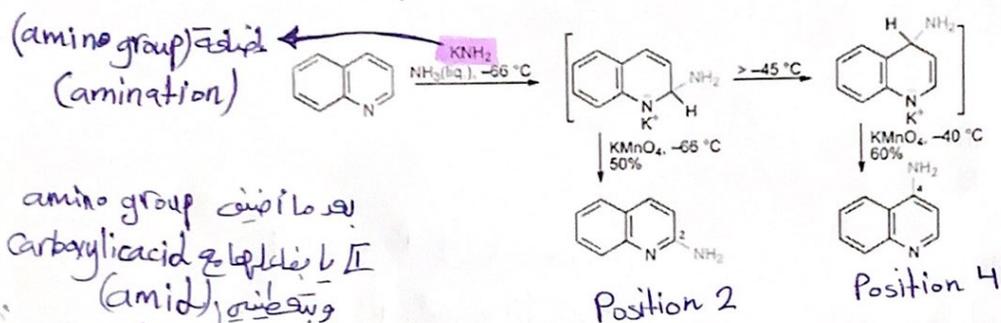
بعدما أضيق الhydride
oxidation على
heterocyclic ring

سؤال: شو الهدف
من آخر step
PhNO₂

يمكن إضافة alkyl group
قبل من خلال Nu
لكن استخدام
alkyl halide لا يجوز
لأنه E⁺ ولا يمكن
إضافة كما ذكرنا سابقاً.

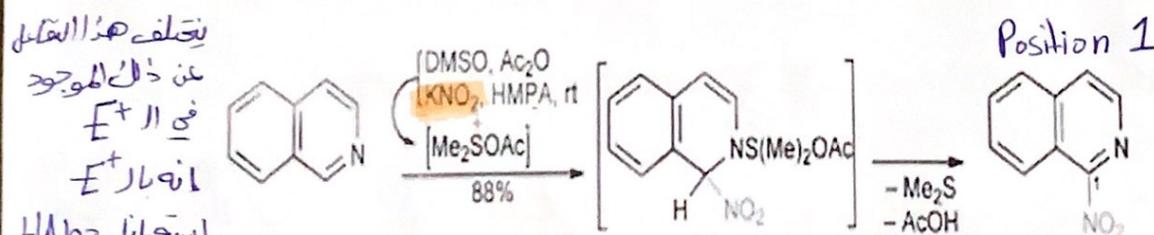
Amination and Nitration

- Sodium amide reacts rapidly and completely with quinoline and isoquinoline, even at -45°C , to give dihydro - adducts with initial amide attack at C - 2 (main) and C - 4 (minor) in quinoline, and C - 1 in isoquinoline.
- The quinoline 2 - adduct rearranges to the more stable 4 - aminated adduct at higher temperatures. 21 Oxidative trapping of the quinoline adducts provides 2 - or 4 - aminoquinoline; isoquinoline reacts with potassium amide in liquid ammonia at room temperature to give 1 - aminoisoquinoline



لظروف (Condition)

- The introduction of a nitro group at C - 1 in isoquinolines can be achieved using a mixture of potassium nitrite, dimethylsulfoxide and acetic anhydride. The key step is the nucleophilic addition of nitrite to the heterocycle previously quaternised by reaction at nitrogen with a complex of dimethylsulfoxide and the anhydride



(aqueous media) وسط
lipophile كوسط
dimethylsulfoxide Condition

على غلظها وحسنها وبارت
 UTI Infection و تنسيف
 + Respiratory tract Infection
 hydroxy group (OH) → Nu

quinolin & Isoquinolin
 anti-malaria يسهل
 وارتبها كقوى للجلد الكوب
 antibiotic

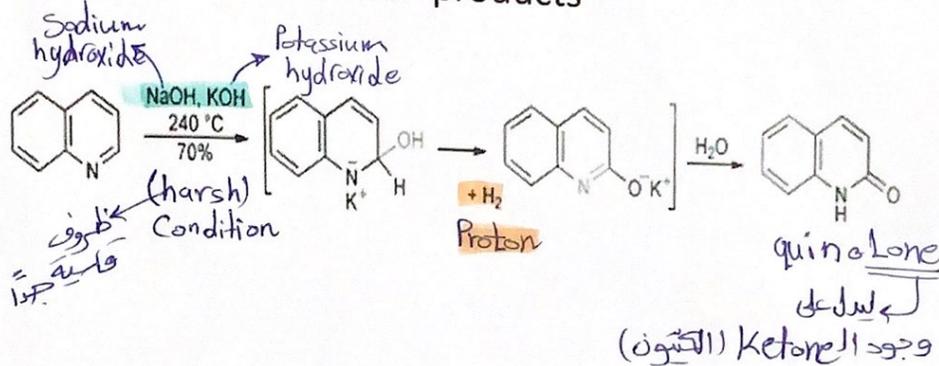
Floroquinolone ← فلاو

anti-bacterial
 Compound

for gram Negative bacteria

Hydroxylation

Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen. **2-Quinolone** ('carbostyryl') and **1-isoquinolone** ('isocarbostyryl') are the isolated products

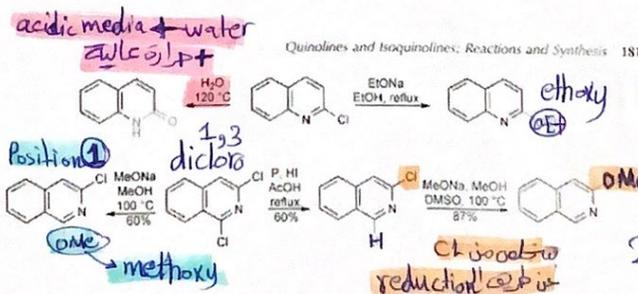


نوع ثالث من التفاعلات

Nucleophilic Substitution with Displacement of Good Leaving Groups

The main principle here is that halogen on the homocyclic rings of quinoline and isoquinoline, and at the quinoline - 3 - and the isoquinoline - 4 positions, behaves as would a halo - benzene. In contrast, 2 - and 4 - halo - quinolines and 1 - halo - isoquinolines have the same susceptibility as α - and γ - halopyridines. 3 - Halo - isoquinolines are intermediate in their reactivity to nucleophiles

إذا سعى halogen على ring يبدل فيسبب الهالوجين و فقط (group R) التي يبدلها

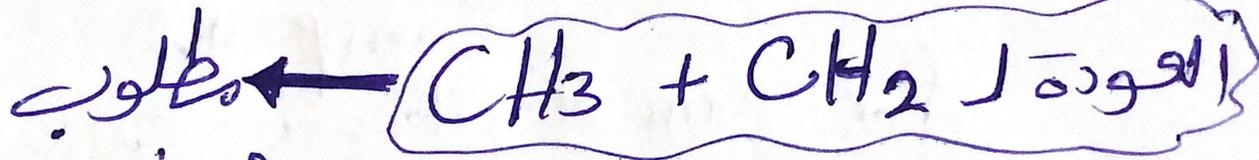


وهذا التفاعل يكون (تفاعل استبدال) في وسط الجاهز الكوب
 2 Steps (تفاعل استبدال) في وسط الجاهز الكوب

note: Cl is the best leaving group

Synthesis : ch. 2 and 3

كيف يتم تصنيع الـ Quinolin ؟



وهو ما نعرفه
كيف بتصنعو