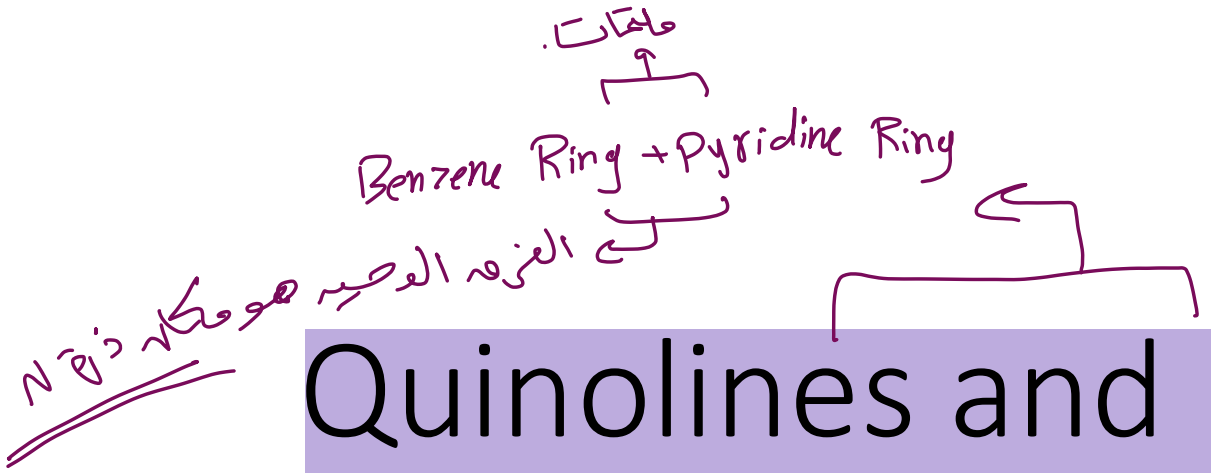
لجان الدفعات

PHARMACEUTICAL ORGANIC CHEMISTRY"2"

MORPHINE ACADEMY



Quinolines and Isoquinolines: Reactions and Synthesis

- 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.
- 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

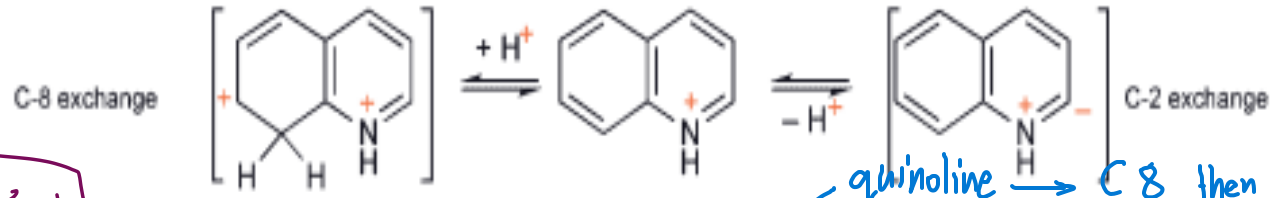
هون ال lone pair تبع ال N. هاجم ال electrophiles

- Reactions with Electrophilic Reagents
- 9.1.1 Addition to Nitrogen

$\ddot{N} + H^+ \rightarrow NH^+$ → protonated quinoline. / protonated isoquinoline.

- 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 p KaH 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.

⟸ الإضافة بتكون على النيتروجين لأن quinoline و isoquinoline سلوكهم نفس سلوك بيريدين اللي على ذرة N
اللي فيه lone pair تتفاعل مع مركبات أخرى.



- **Substitution at Carbon**
  - strong sulfuric acid
    - quinoline → C 8 then C5 and C6
    - isoquinoline → C 5
  - lower acid strength
    - quinoline → C2
    - isoquinoline → C1

- 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 α 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

neutral = ⁺ ⁻ (positive and negative charges)

remove proton (H^+)

isoquinoline
C5 حيلة ك

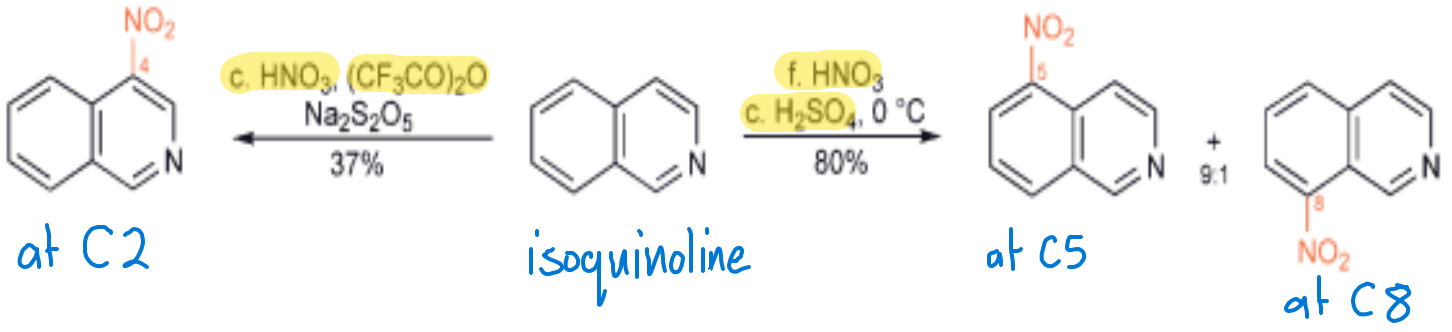
8 → substitution.
8, 5 → nitration.

substitution

nitration

- Nitration → quinoline equal amount at position C5 and C8 when nitration
  → isoquinoline at C5
- 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

المركب	أكثر موقع تفاعل
Quinoline	C8 ثم C5
Isoquinoline	C5
	بالحموضة الأقل
Quinoline → C2	
Isoquinoline → C1	
	النترتة
Quinoline → 5 و 8	
Isoquinoline → 5 فقط	



at C2

isoquinoline

at C5

at C8

substitution تفاعل

Sulfonation

↳ add sulfur group SO_3H (salfonic acid)

quinoline → at C8 → Result: quinoline-8-sulfonic acid.

isoquinoline → at C5 → Result: isoquinoline-5-sulfonic acid.

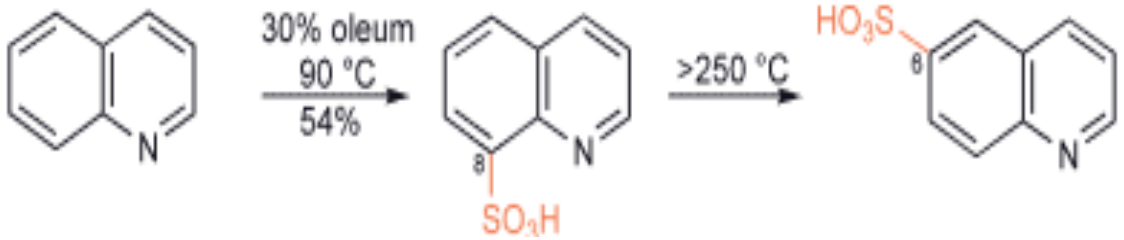
at higher tempreture >250c° → quinoline and isoquinoline → at C6

- 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

يعني لما يزيد درجة الحرارة (>250°C)

الايزومرات بتتحول لبعض

Rearrangement or isomerization تفاعل إعادة الترتيب



C8 > C5 ⇒ C6, because C6 is thermodynamically more stable.

(C5 او C8) .kinetic products ← easiest pathway ← ↓ Ea ← ↓ Temp.

(C6) .Thermodynamic product ← become more stable ← Rearrangment ← ↑ Temp.

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

Friedel-crafts تفاعلات
ما تنفع بشكل مفيد مع isoquinoline, quinoline
لانه ذرة N تسبب الية فيتغير الطاقة:
* فقيرة بالـ e.
* اقل نشاط بـ electrophilic substitution
بتغير الطاقة Deactivated
Friedel-crafts صعوبة مع شروط
اللي تعتمد على حلقة غنية بالـ e.

التفاعل	Quinoline	Isoquinoline
Nitration	C5 + C8	C5
Sulfonation	C8	C5
	حرارة عالية	
	الكل يحب يتحول لـ C6	

Cl Br I

Halogenation

↳ add halogen

- presence concentrated sulfuric acid
  - quinoline → at C5 and C6
  - isoquinoline → at C8 or with N
- presence aluminium chloride → isoquinoline → at C5

- Ring substitution of quinoline and isoquinoline by halogens is rather complex, products depending on the conditions used.

مكان دخول الهالوجين يعتمد على الظروف.

- 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

Quinoline بال sulfuric acid

mix :يعني

5 Bromo + 8 Bromo

C8 و C5 بسبب Br يعني ال

نفس ال Nitration تقريبا.

isoquinoline

يعني :

5-Bromoisoquinoline

صفوفًا مع :

* $AlCl_3$ → Because it's Lewis acid
* NBS

يعني بإمكانه تكوين electrophile قوي مع الهالوجين.

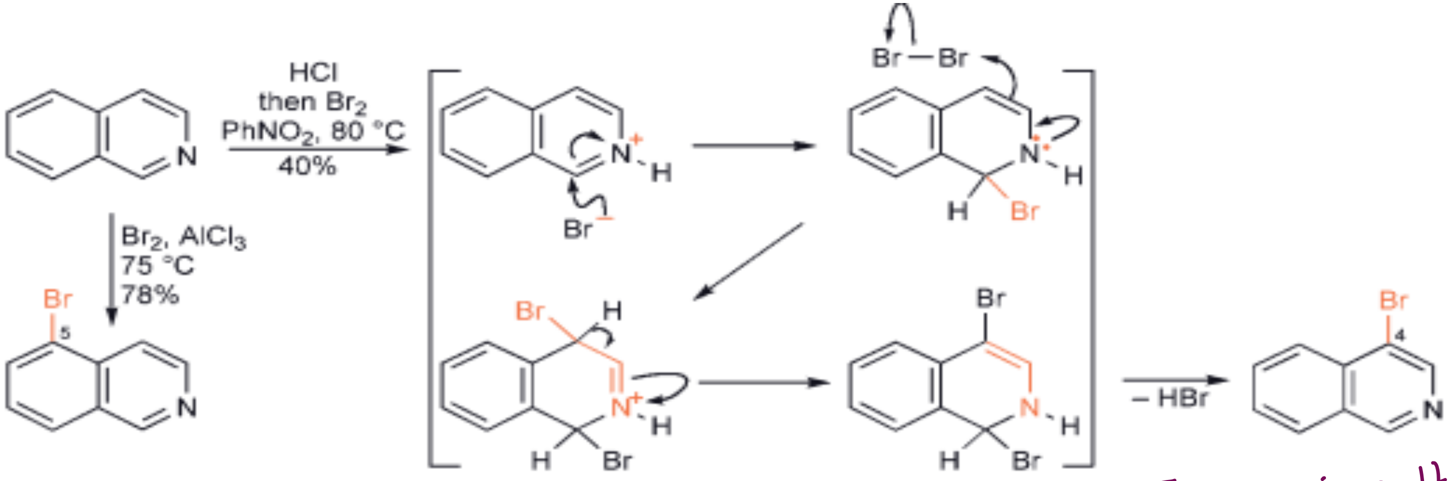
يعني بإمكانه الهالجنة تحت

Halid addition to salt initiate → quinoline at C3 / isoquinoline at C4

هون الهالوجين ما بدخل ع حلقة البنزين ولكنا ع الحلقة الي فيها N
. quinoline بال C3
. isoquinoline بال C4

quinoline + HCl → quinolinium chloride. ثم Br_2 ثم يبدأ التفاعل

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



المركب	الهلجنة على heteroring
Quinoline	C3
Isoquinoline	C4

أما الهلجنة العادية على الحلقة البنزية

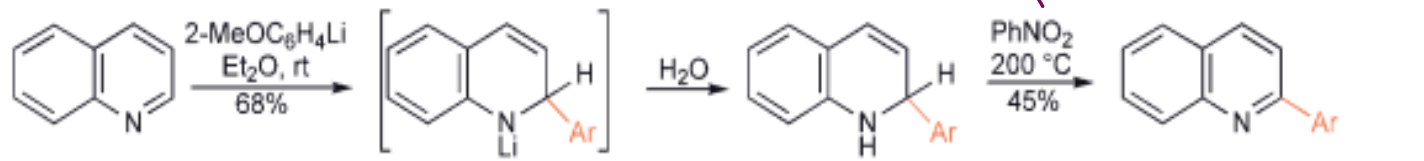
المركب	الموقع المفضل
Quinoline	C5 و C8
Isoquinoline	C5

لسبب اختلاف المكان هون لأنه تكوين ال salt بغير توزيع الشحنة ع الحلقة، فالمواقع الاكثر استقرار بتصير C3 لل Q و C4 لل iso.

التفاعل	Quinoline	Isoquinoline
Nitration	C5 + C8	C5
Sulfonation	C8	C5
Halogenation	C5 + C8	C5
Halogenation after salt formation	C3	C4

Reactions with Nucleophilic Reagents

- 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



Amination and Nitration

NaNH2

quinoline → at C2 (main), C4 (minor)
↳ more stable at high tempreture (from C2 to C4)

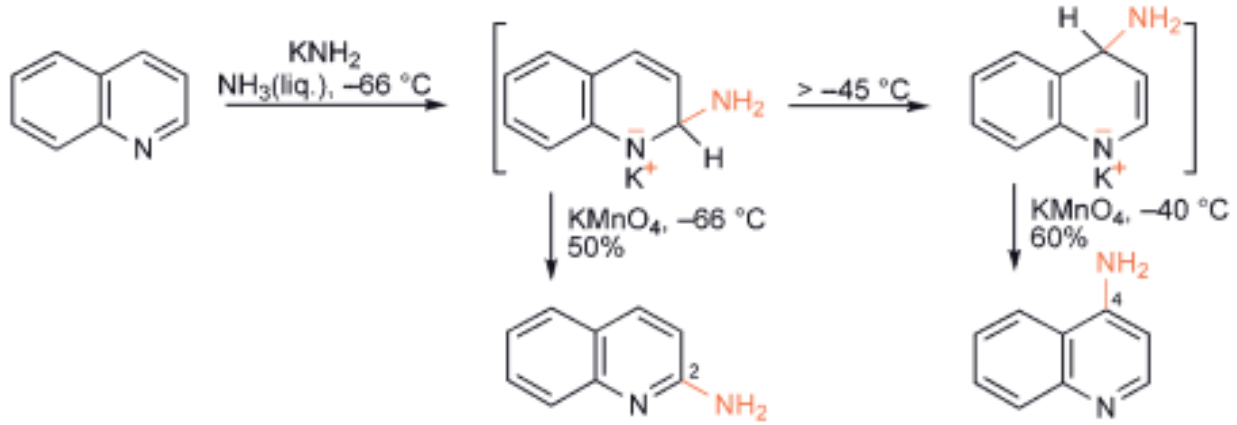
isoquinoline → at C1

very strong nucleophile

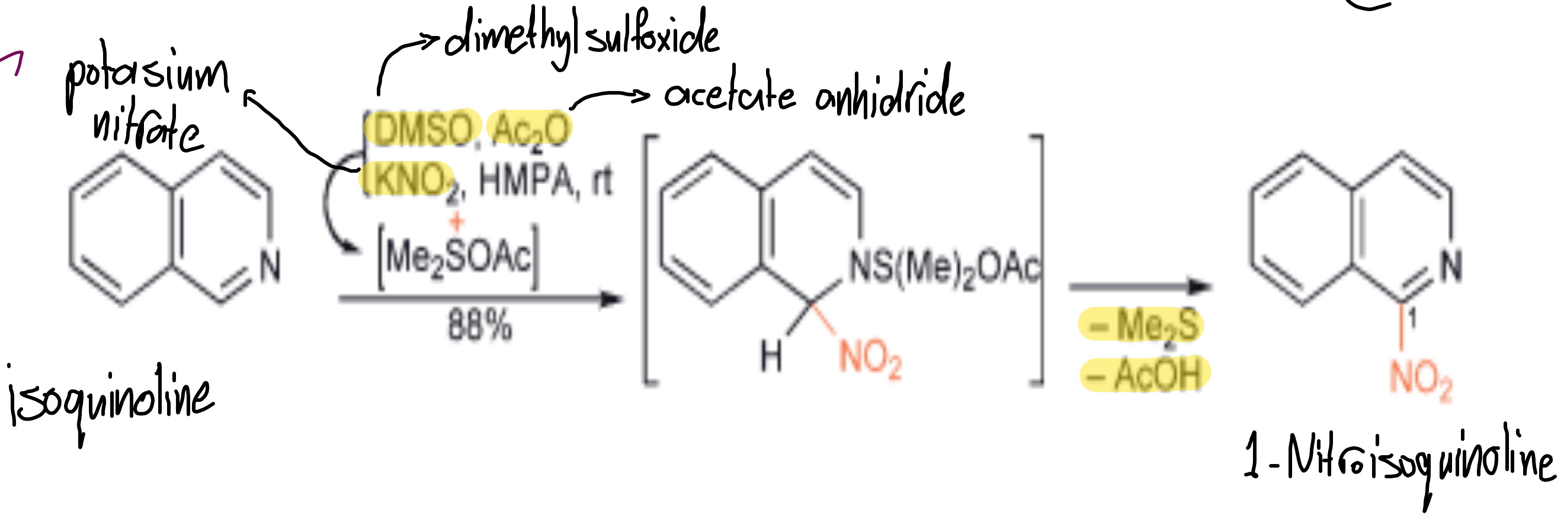
NaNH2

- 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

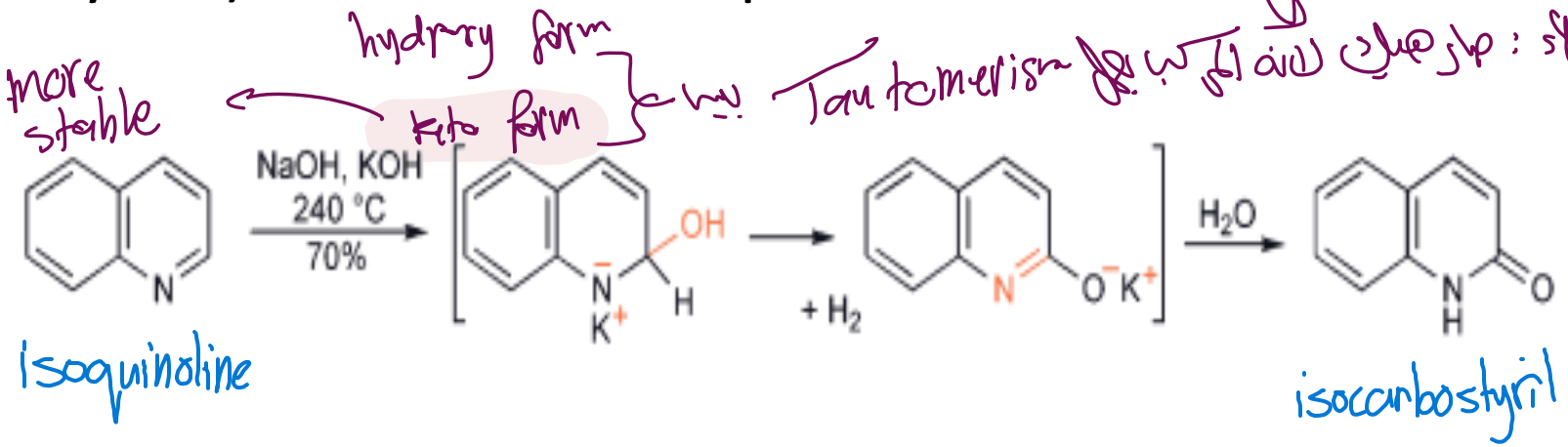


- The introduction of a nitro group at C - 1 in isoquinolines can be achieved using a mixture of potassium nitrite, dimethylsulfoxide and acetic anhydride. The key step is the nucleophilic addition of nitrite to the heterocycle previously quaternised by reaction at nitrogen with a complex of dimethylsulfoxide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



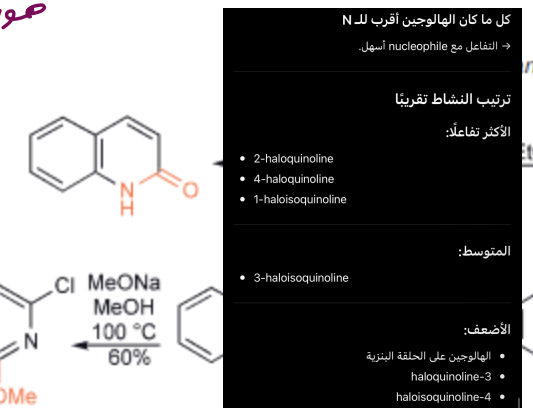
- Hydroxylation

- Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen. 2 - Quinolone (‘ carbostyril ’) and 1 - isoquinolone (‘ isocarbostyril ’) are the isolated products



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



التفاعل	Quinoline	Isoquinoline	ملاحظات
Nucleophilic attack (عام)	C2 (main), C4 (minor)	C1	النيوكليوفيل ينجذب قرب الـ N
Hydride transfer	C2	C1	أسرع موقع للهجوم
Grignard / organolithium alkylation & arylation	C2	C1	ثم oxidation لإرجاع aromaticity
Amination ($NaNH_2$)	C2 بالحرارة ثم يتحول لـ C4	C1	4-aminoquinoline أكثر stability
Nucleophilic nitration	—	C1	يعطي 1-nitroisoquinoline
Hydroxylation (KOH + heat)	C2 → 2-quinolone	C1 → 1-isoquinolone	quinolone forms
Halo derivatives الأكثر نشاطًا	2-halo و4-halo	1-halo	قريب من N leaving group
Halo derivatives الأقل نشاطًا	على الحلقة البنزية + 3 halo-haloquinoline	4-haloisoquinoline	مثل halobenzene
Intermediate reactivity	—	3-haloisoquinoline	نشاط متوسط

التفاعل	Quinoline	Isoquinoline	ملاحظات
Electrophilic substitution (عام)	C8 > C5 > C6	C5	الإلكتروفيل يبتعد عن الـ N
Nitration	C5 + C8	C5	أشهر نواتج النترتة
Sulfonation	C8	C5	الحرارة العالية تعطي C6
Halogenation	C5 + C8	C5	مشابه للنترتة
Halogenation after salt formation	C3	C4	بعد تكوين hydrochloride salt
Less strongly acidic conditions	C2	C1	عند حموضة أقل
Friedel–Crafts alkylation/acylation	لا يحدث عمليًا	لا يحدث عمليًا	الحلقة deactivated بسبب N

المركب	Electrophile	Nucleophile
Quinoline	C8 ثم C5	C2 ثم C4
Isoquinoline	C5	C1