BENZOPYRIDINES:
QUINOLINES AND ISOQUINOLINES

1. General

a) Typical representatives
b) Comparative basicity
c) Comparative reactivity between rings

2. Syntheses

2.1. Quinoline

a) *Skraup* methodology
b) *Doebner & Mille*r methodology
c) *Friedlander* methodology
d) Syntheses of 4-quinolones

2.2. Isoquinoline

a) General
b) *Bischler & Napieralsky* methodology
c) *Pictet & Spengler* methodology

3. Reactivity

3.1. Reactions at pyridine nitrogen and synthetic utility

3.1.1. *N*-Alkylation

a) *N*-Alkylation of quinoline
b) *N*-Alkylation of isoquinoline

3.1.2. *N*-Acylation of quinoline

a) *Reissert* compounds
b) Increased reactivity of alkylquinolines against electrophiles: *N*-acylium cations

3.2. Reactions by electrophilic substitution and synthetic utility

3.3. Reactions by nucleophilic substitution and synthetic utility

3.3.1. Nucleophilic substitution of hydrogen

3.3.2. Nucleophilic substitution of leaving groups

3.4. Reactivity of quinoline and isoquinoline carbanions

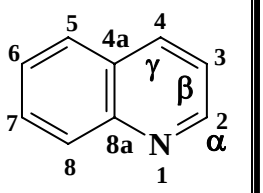
Modifications (improvements, additions, corrections, up to dates *etc.*) are subjected to no notice.

Mircea Darabantu MASTER **VII D-1**

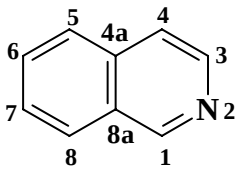
BENZOPIRIDINE: CHINOLINE SI IZOCHINOLINE

1. Generalitati:

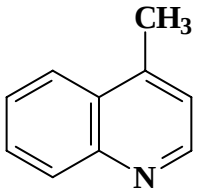
a) reprezentanti tipici:



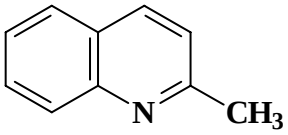
CHINOLINA
QUINOLINE
Quinoléine



IZOCHINOLINA
ISOQUINOLINE
Isoquinoléine



Lepidina



Chinaldina

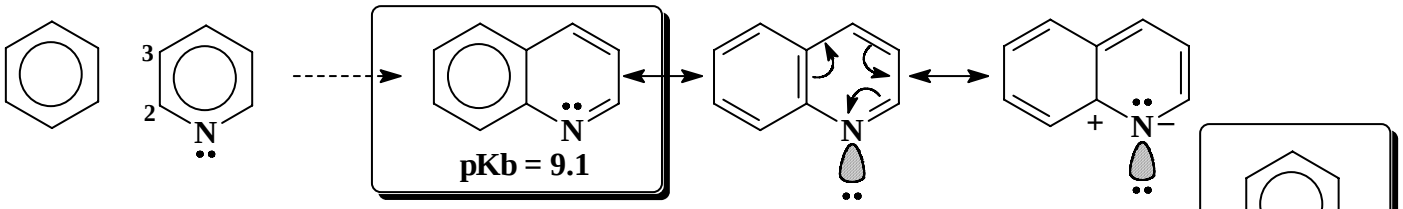
Nota : numerotarea pozitiilor se face dupa **sistemul hidrocarburilor aromatice condensate** (aici **naftalenul**)

b) bazicitatea comparativa:

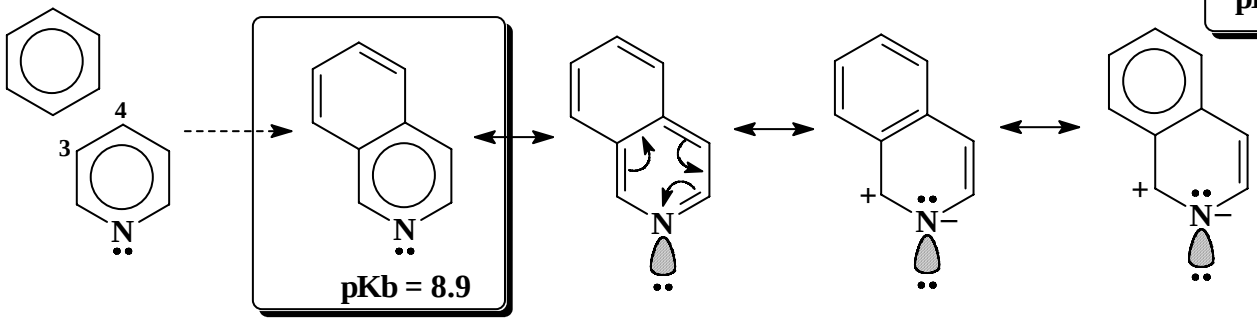
Nota 1: condensarea (**formala si reprezentata echivalent)** cu un ciclu benzenic **scade bazicitatea** ciclului piridinic comparativ cu piridina

Nota 2: condensarea care perturba **cel mai putin** aromaticitatea **ciclului benzenic** furnizeaza structura cu **caracterul bazic cel mai pronuntat**

condensare 2 - 3



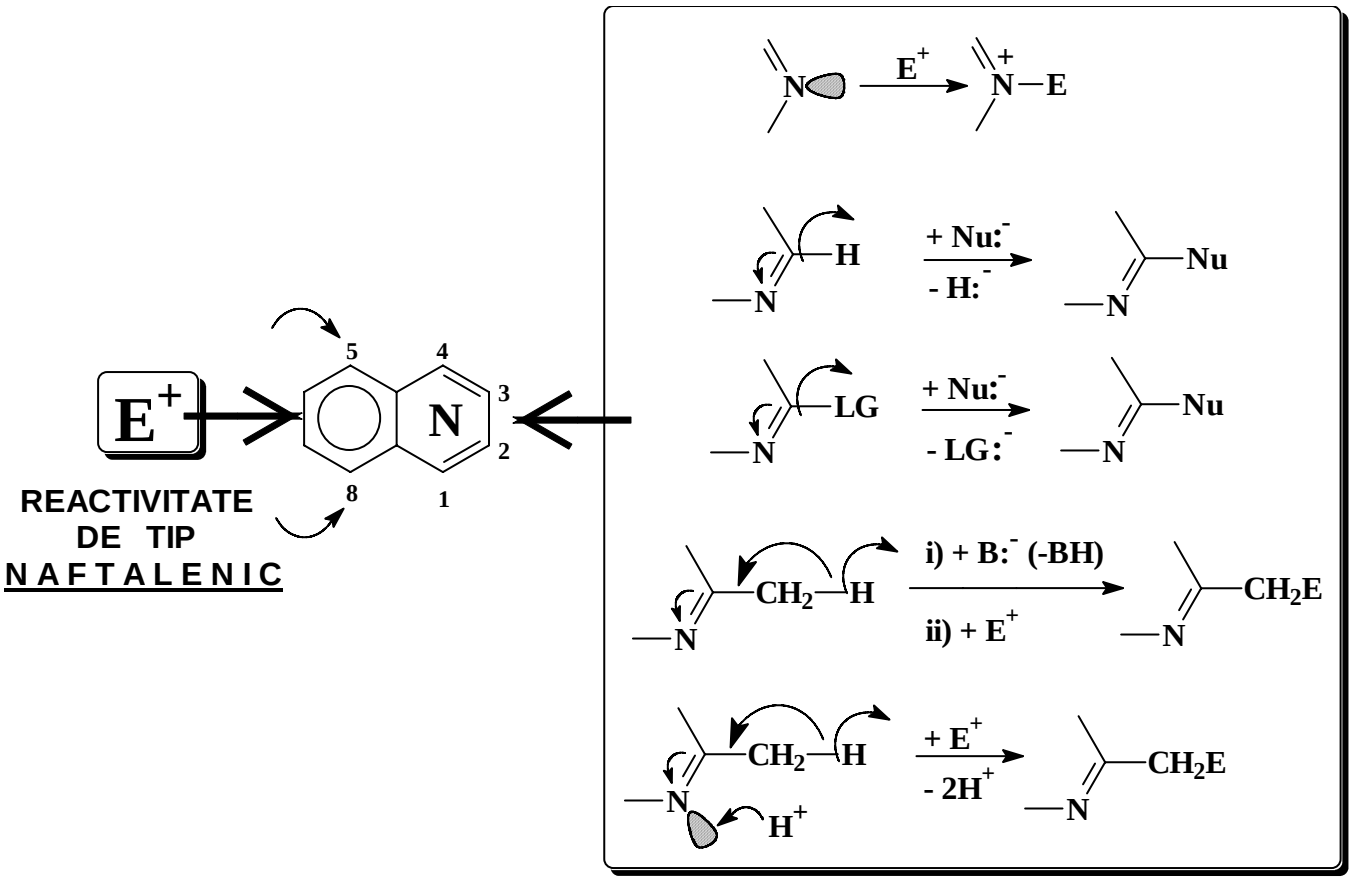
condensare 3 - 4



Consecinta 1: chinolina si **izochinolina** pot fi **usor separate** intre ele, din surse naturale, pe **cale chimica**, exact pe baza **diferentei de bazicitate**

Consecinta 2: starea de agregare: chinolina (p.t. = -22°C, p.f. = +238°C); **izochinolina** (p.t. = + 24°C, p.f. = +240°C).

c) reactivitatea comparativa intre cicluri:



REACTIVITATE DE TIP **PIRIDINIC**

Observatie: se regaseste, **in totalitate**, reactivitatea de **tip piridinic**; cea de **tip naftalenic** se regaseste in reactii **SE in partea benzenica**, **dezactivata** de catre heterociclul cu care este condensata.

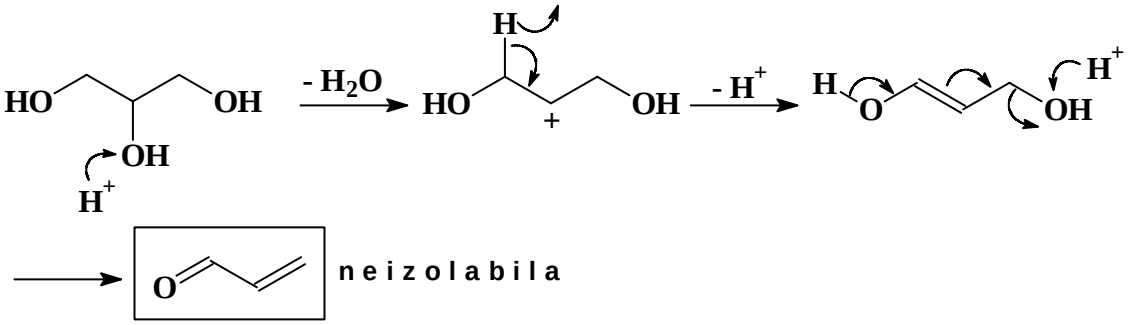
2. Sinteze:

2.1. Chinolina:

a) Metoda Skraup (1880):

- prima metoda de preparare a chinolinei.
- conditii: **anilina + glicerina / H_2SO_4 conc.** la cald, in prezenta unui **oxidant bland (nitrobenzen); acroleina** intermediara este **neizolabila** in **aceste conditii.**
- admite **generalizarea** pentru o larga **varietate de aniline substituite pe ciclu**

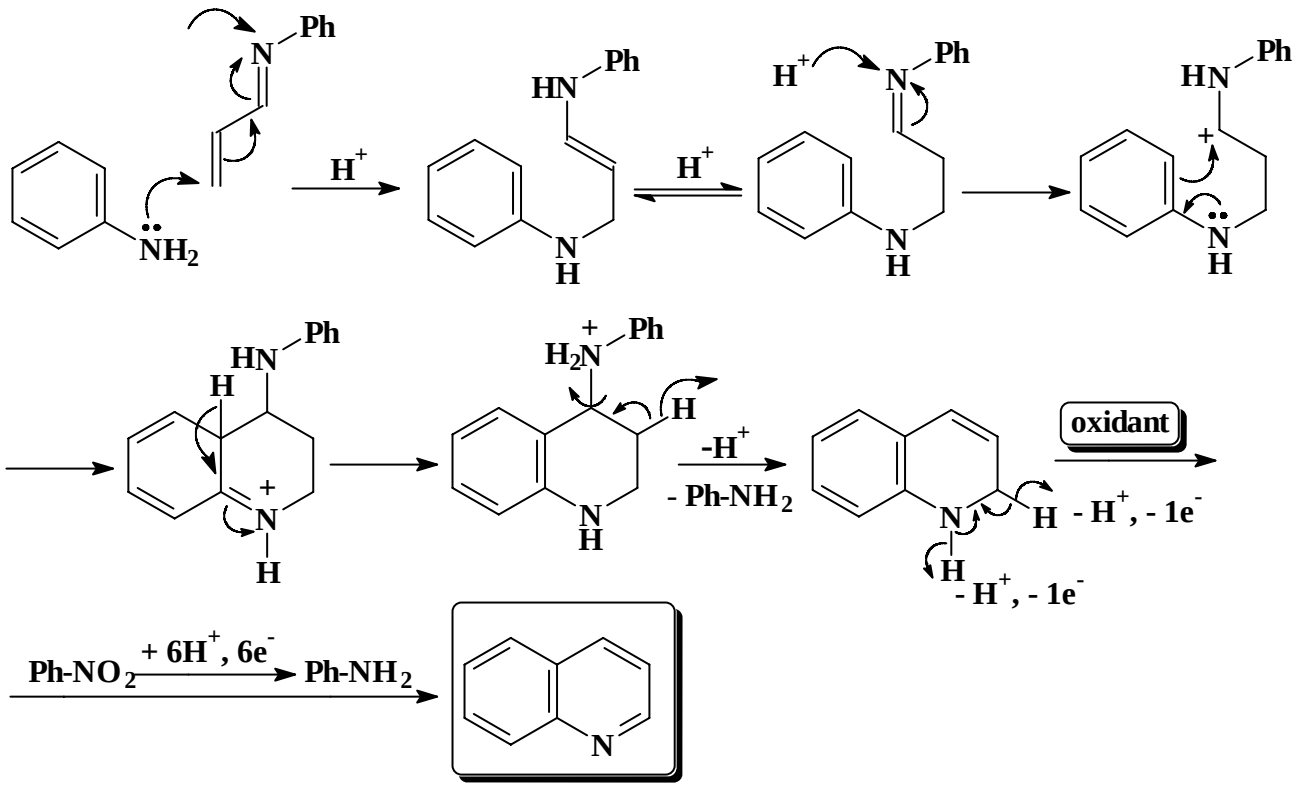
i) generarea *in situ* a acroleinei din glicerina:



ii) generarea ***in situ*** **a *N* - fenilacrolein- iminei** (AN + E la **–CH=O**) (Baza Schiff)

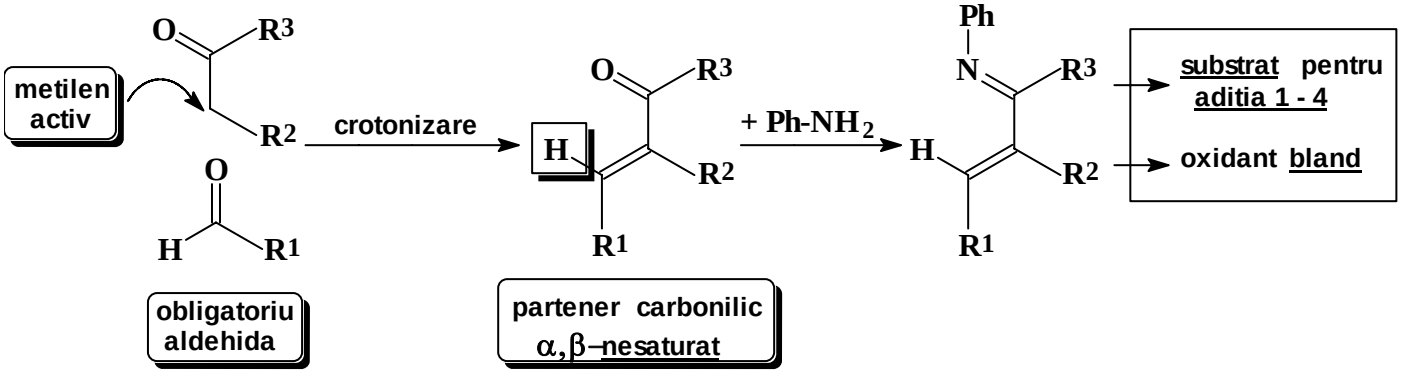
$$CH_2{=}CH{-}CH{=}O + Ph{-}NH_2 \xrightarrow{rapid} CH_2{=}CH{-}CH{=}N{-}Ph + H_2O$$

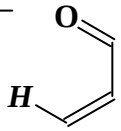
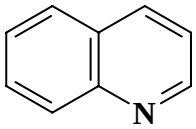
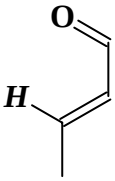
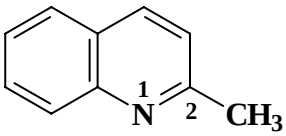
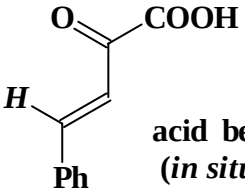
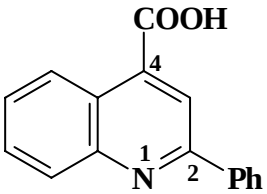
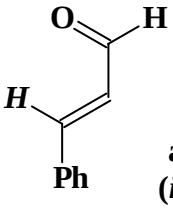
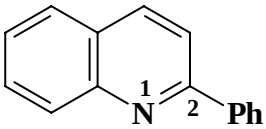
iii) **ciclizarea** cu **anilina** prin **aditie 1 – 4** la Baza Schiff**; aromatizarea prin oxidare blanda** (nitrobenzen)

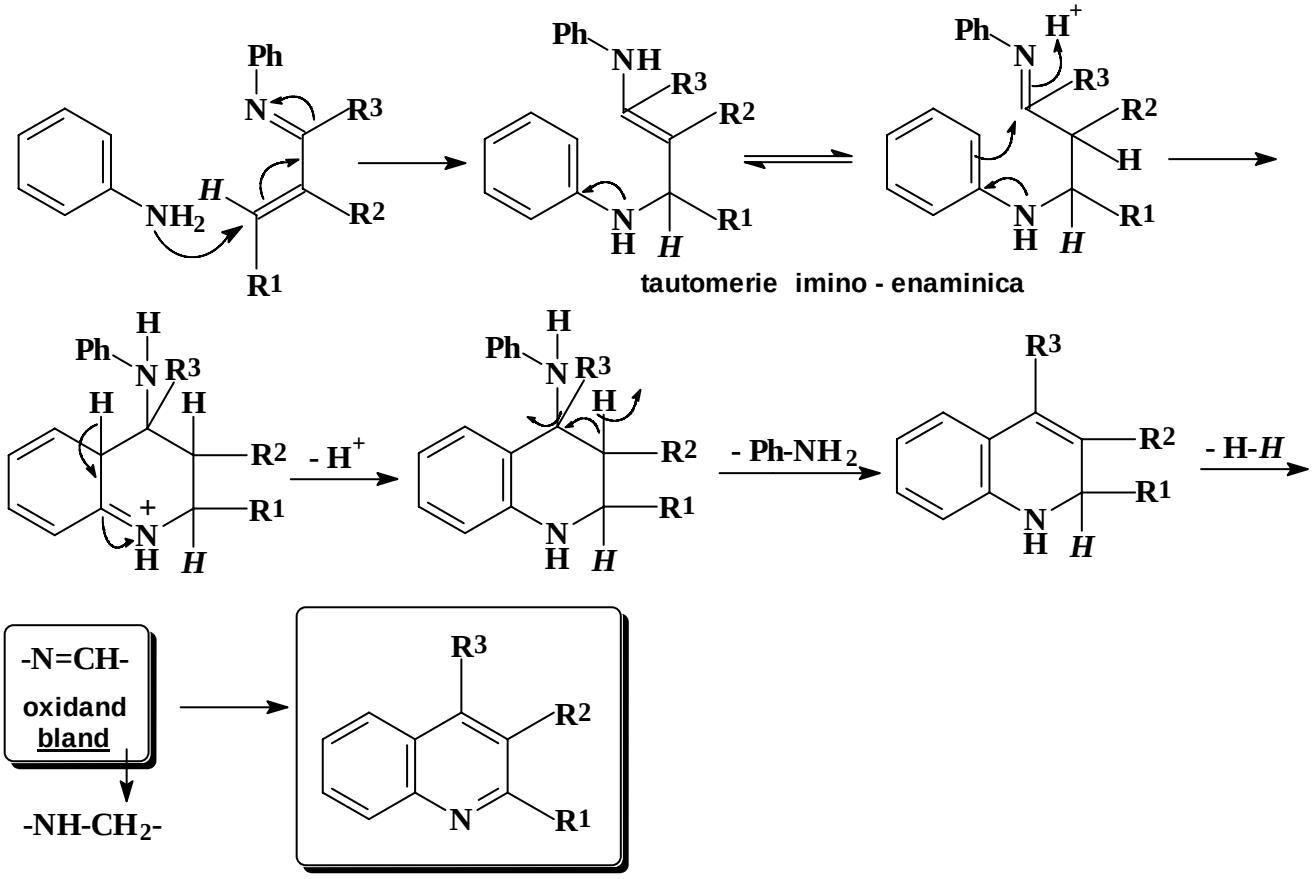


b) Metoda Doebner - Miller (1881):

- **generalizare a metodei Skraup** (daca se considera, **formal:**
  $CH_2O + CH_3CH{=}O \rightarrow CH_2{=}CH{-}CH{=}O + H_2O$)
- **obiectiv**: prepararea de **chinoline substiutuite** in **partea piridinica**
- **nu necesita oxidant**, deoarace acest **rol** este indeplinit de catre **Bazele Schiff intermediare**
- in conditiile sintezei Doebner – Miller, **metoda Skraup** este doar un **caz particular**
- **conditii generale**: la cald, in prezenta de **HCl / $ZnCl_2$**

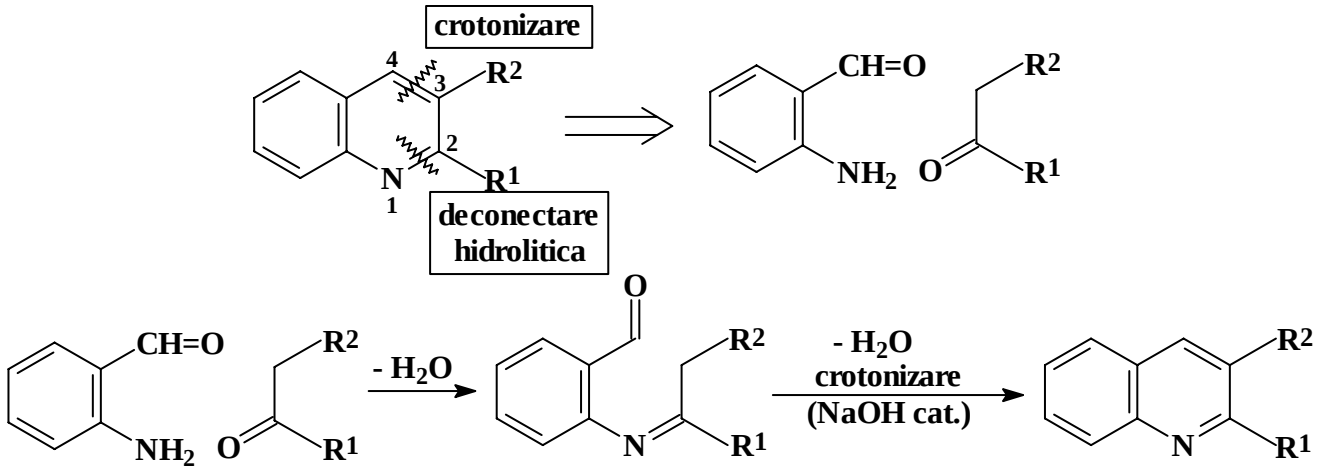


Substituenti agreati			Partener carbonilic α,β–nesaturat	Chinolina
R^1	R^2	R^3		
H	H	H	 acroleina (*in situ*, Skraup)	
Me	H	H	 crotonaldehida (*in situ* sau *a priori*)	 2-Methylquinoline (CHINALDINA)
Ph	H	COOH	 acid benzilidenpiruvic (*in situ* sau *a priori*)	 2-Phenyl-4-quinoline-4-yl carboxylic acid
Ph	H	H	 aldehida cinamica (*in situ* sau *a priori*)	 2-Phenylquinoline

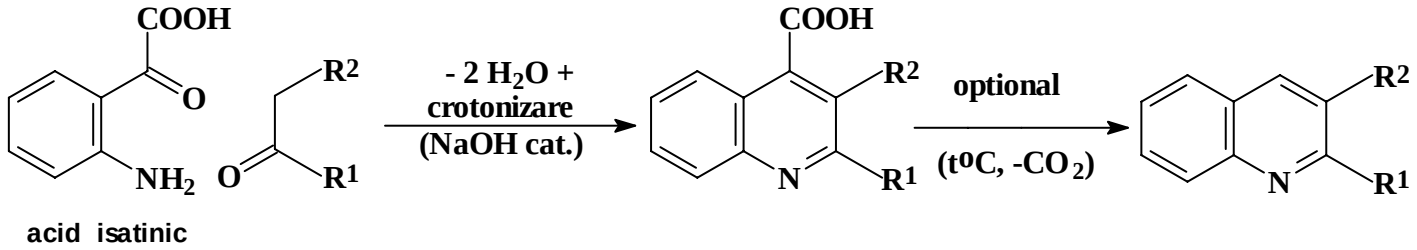


c) Metoda Friedlander (1882):

- **obiectiv:** prepararea de chinoline substituite in partea piridinica **doar** la ***C* - 2, - 3**
- **retrosinteza:** deconectare hidrolitica ***N – C – 2*** si retrocrotonica ***C* - 3, *C* - 4**



Nota 1: partenerul carbonilic poate fi, rezonabil, oricare, daca este de forma **R^2-C*H*$_2$-CO-R^1**
Nota 2: limitele metodei provin din **instabilitatea 2-aminobenzaldehidei** (tendinta de **autocondensare**)
Nota 3: pentru a inlatura neajunsul de mai sus, este recomandata ***modificarea Pfitzinger* (1886):**

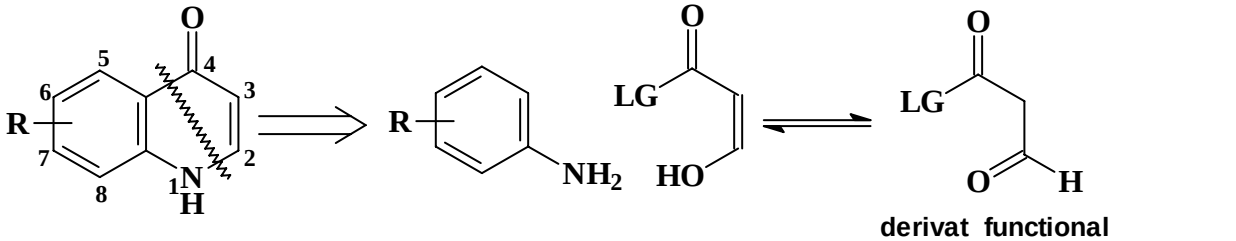


acid isatinic

d) Sinteze de 4 - chinolone:

- sunt **tautomerii lactamici**, **stabili** in acesta forma **4- hidroxichinolinelor**
- sunt **structuri fundamentale** de constructie a **preparatelor farmaceutice** cu **actiune *tipica* farmaceutica (antibiotice si antimalarice)**
- **regioizomerii 2-chinolonici** se obtin, cel mai avantajos, **prin functionalizarea 2-chinolinelor**

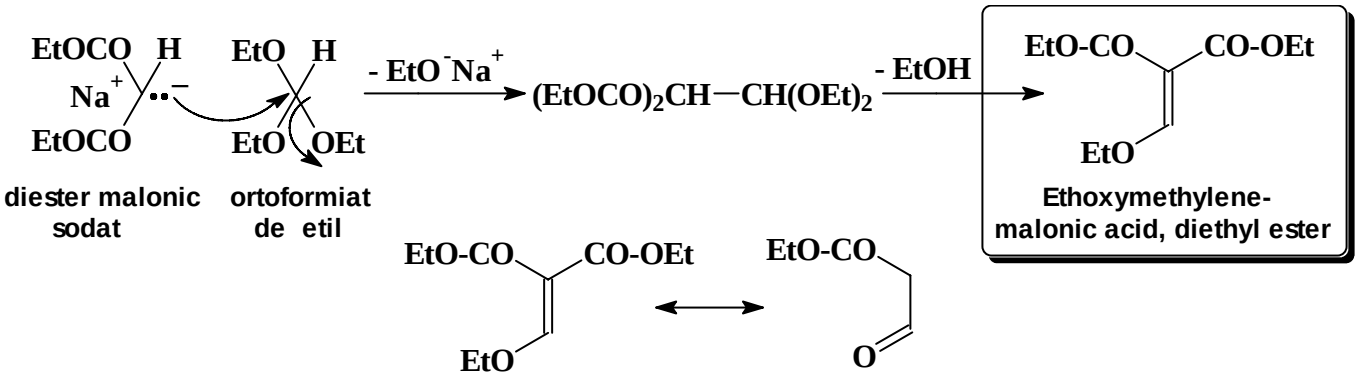
- retrosinteza:



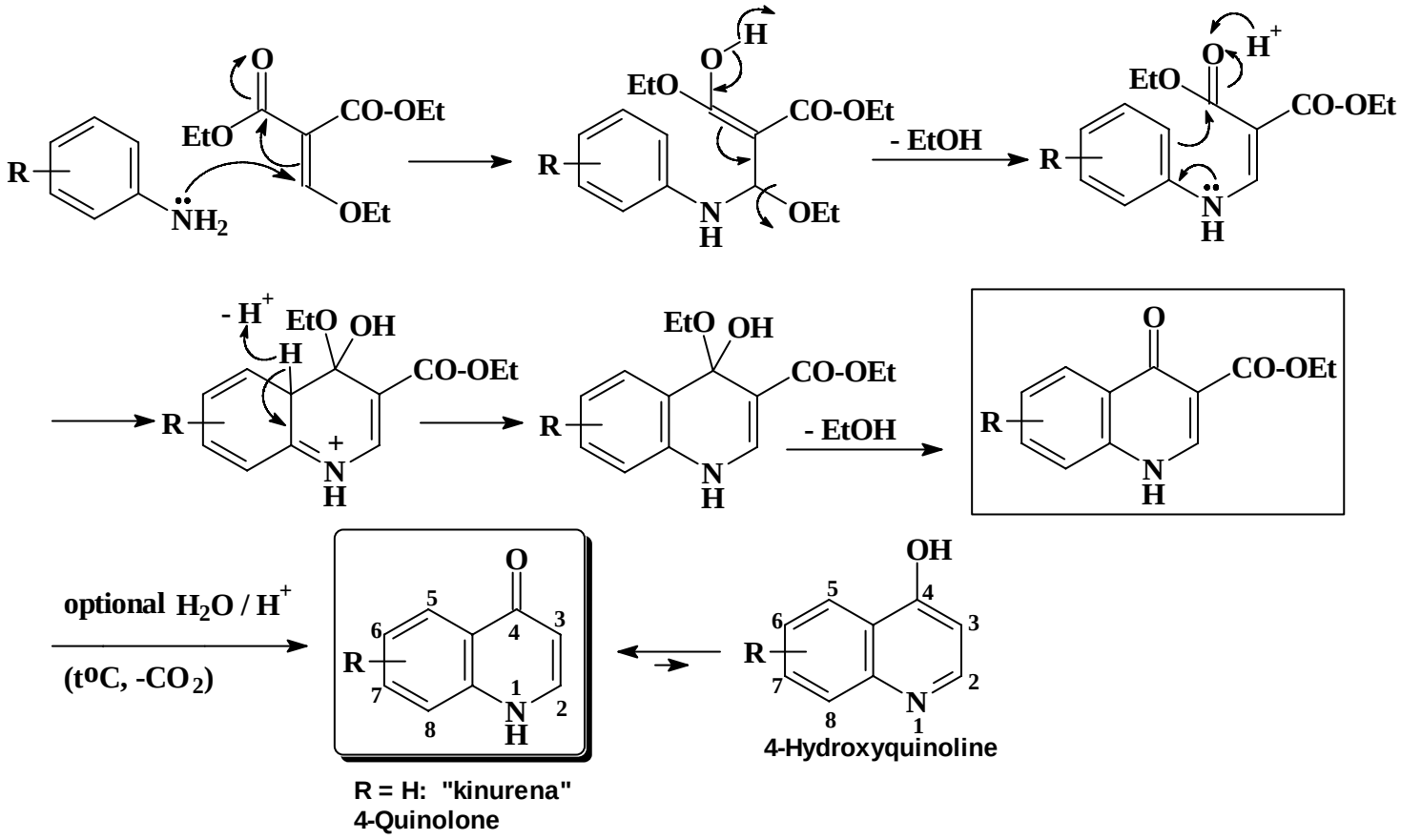
derivat functional al acidului formil acetic (R = OH)

Nota 1: acidul formil acetic (**O=CH-CH$_2$-COOH**) este **instabil ca atare**, sau sub forma **derivatilor sai functionali utilizabili** in sinteza de mai sus.

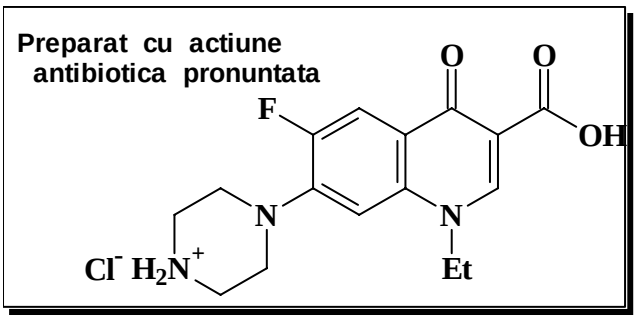
Nota 2: se utilizeaza un **echivalent sintetic** al esterului formil acetic, in varianta **Gould – Jacobson:** ***etoximetilendietilmalonatul*** mai **s t a b i l**



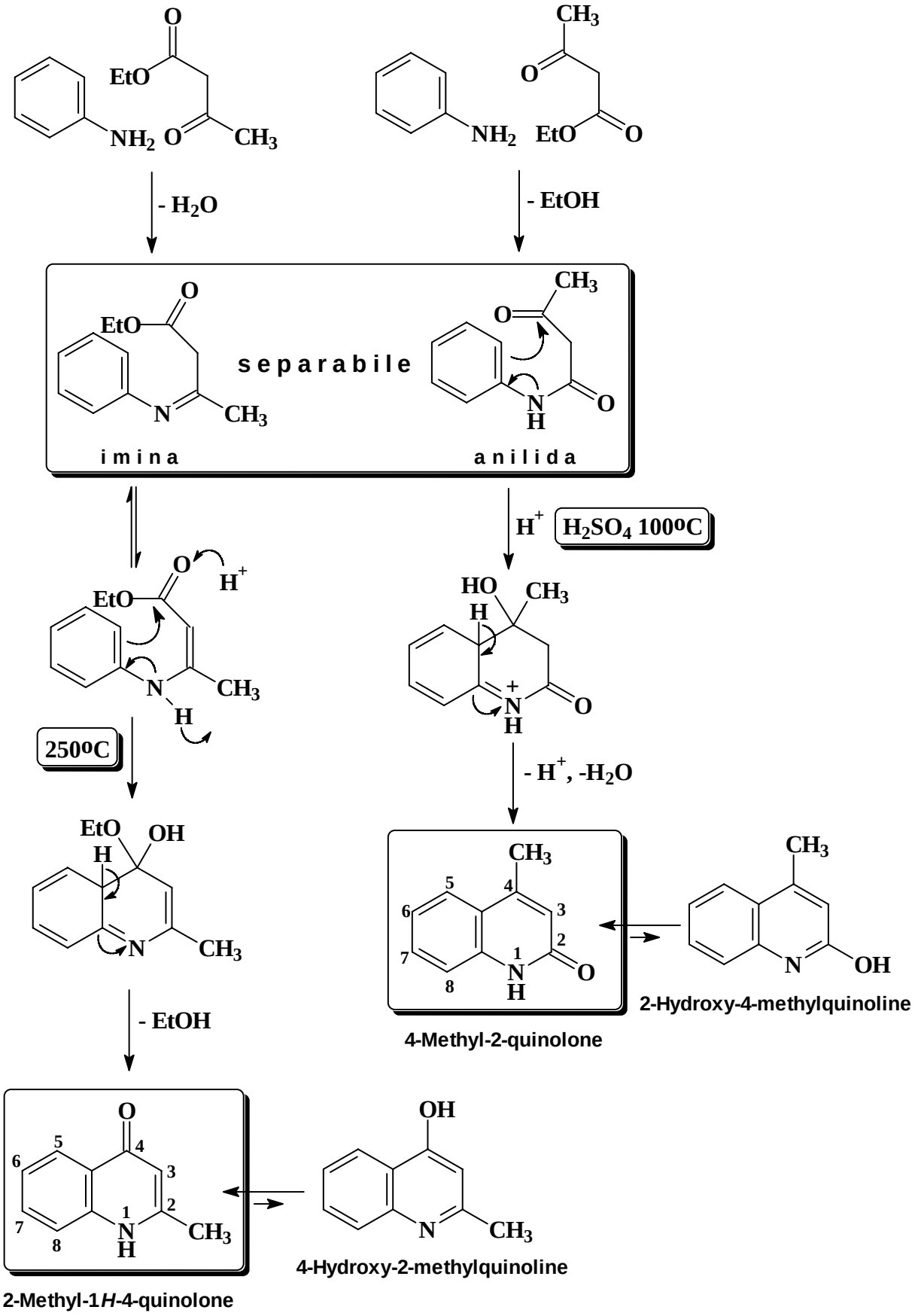
Exemplu de aplicare:



Exemplu de utilizare:



Nota 3: analog, pentru **4-chinolonele 2-substituite** se poate folosi un alt derivat de alt **acid β-carbonilacetic**, **s t a b i l**, de exemplu, **esterul acetilacetic**.

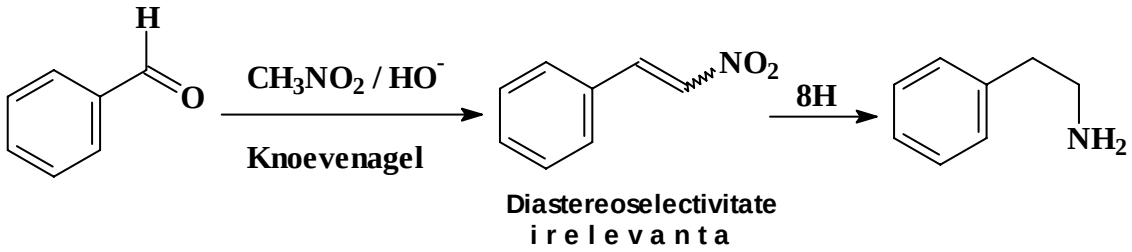


Observatie: fiind forme **deja oxidate** ale chinolinei, **necesitatea oxidarii dupa ciclizare dispare,** indiferent de tautomer sau regioizomer.

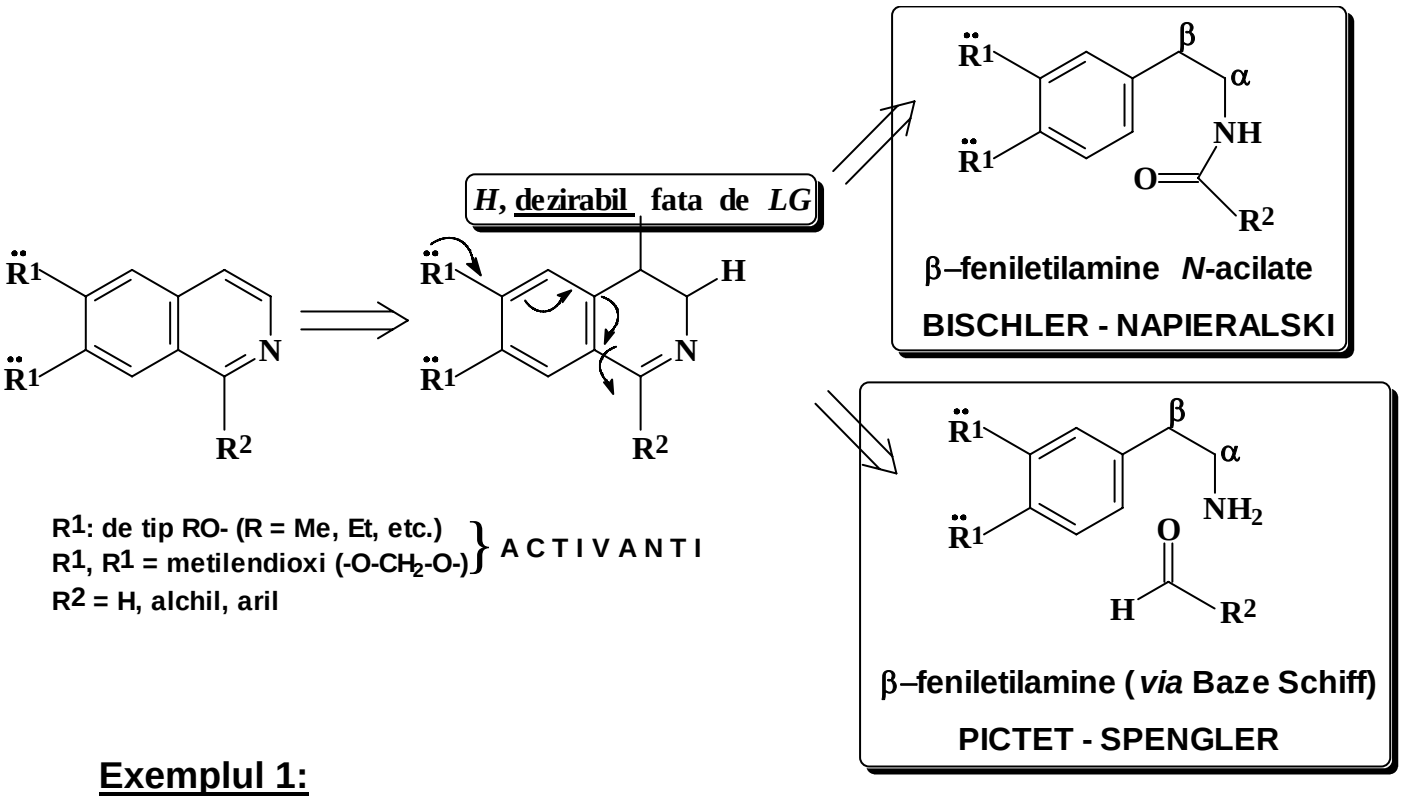
2.2. Izochinolina:

Generalitati:

- **materia prima** cea mai uzuala este o **β-feniletilamina (sinteza foarte convenabila)**

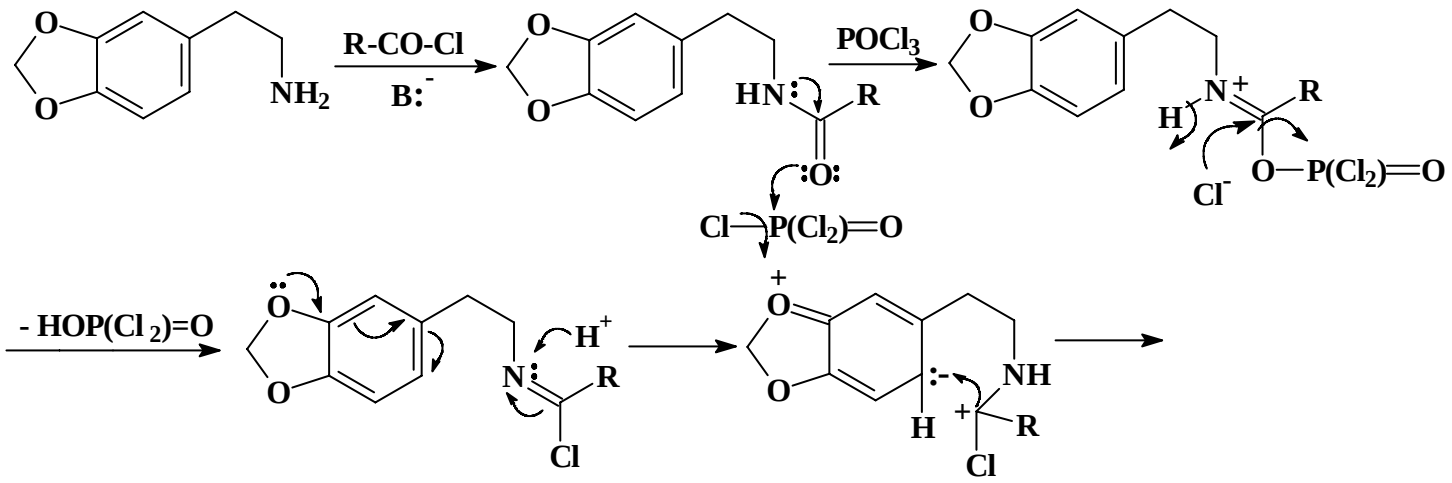


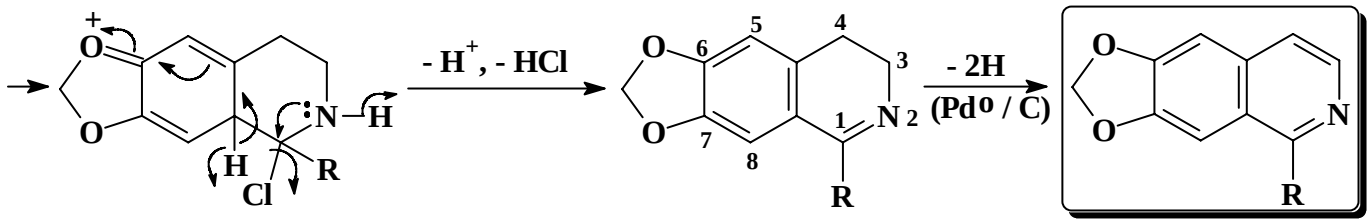
- **metodele se diferentiaza** intre ele prin **modul in care are loc ciclizarea**
- este **foarte necesar** ca **inelul benzenic** sa aiba **substituenti activanti (+E)** in ***para*** fata de pozitia in care are loc ciclizarea.



Exemplul 1:

- **varianta Bischler – Napieralski (1893):**





Nota 1: ciclizarea reclama **temperaturi ridicate** si prezenta:

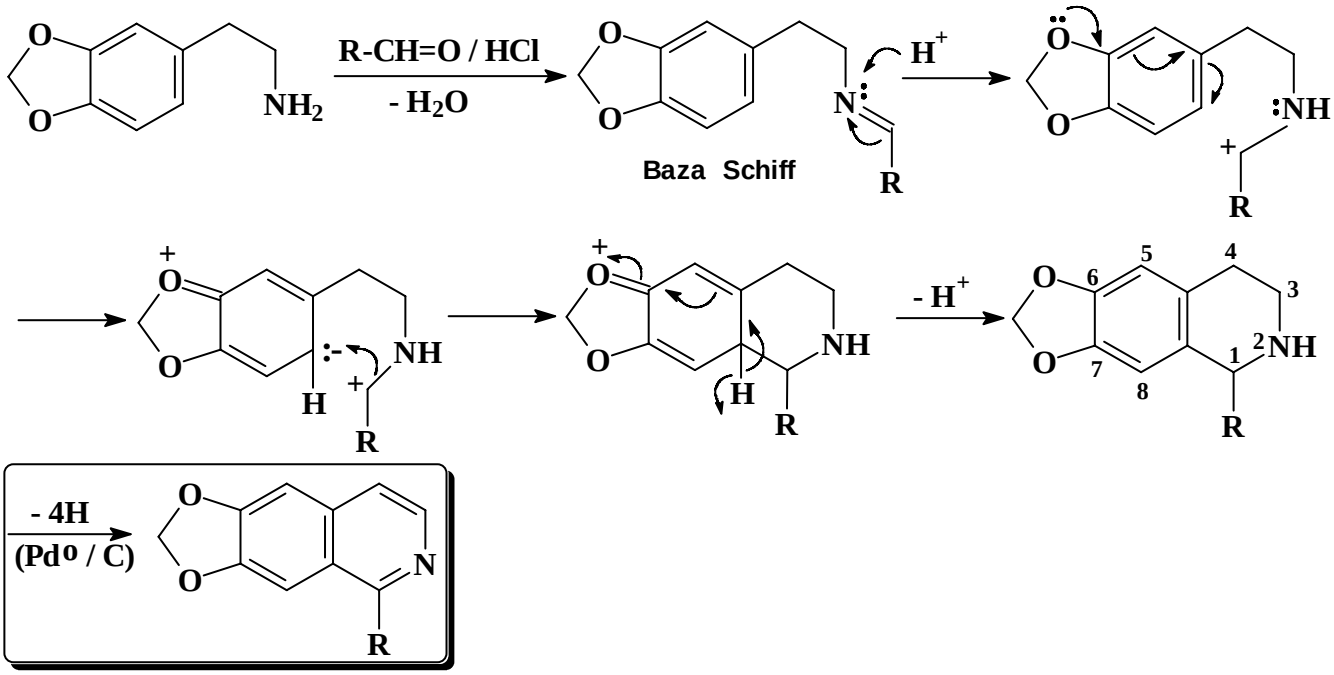
a) deshidratantilor de tip P_2O_5

b) clorurantilor nucleofili (*via* clorura de imidoil: $POCl_3$, PCl_5)

Nota 2: daca **R = H** si **grupele activante lipsesc** (***N*-formil-β-feniletilamina**) **randamentele scad** foarte mult (→ **izochinolina ca atare**)

Exemplul 2:

- varianta Pictet – Spengler (1911):



Nota 1: fata de metoda anterioara , este necesara o **oxidare mai avansata** deoarace **specia electrofila** are un **grad de oxidare inferior** (**+2** fata de **+3**).

Nota 2: **importanta preparativa** consta in aceea ca **pot fi valorificate** si **tetrahidroizochinolinele** intermediare

Nota 3: sunt **valabile aceleasi cerinte electronice** ca si pentru metoda **Bischler – Napieralski**

3. Reactivitatea:

3.1. Reactii la *N* – piridinic si valoarea preparativa

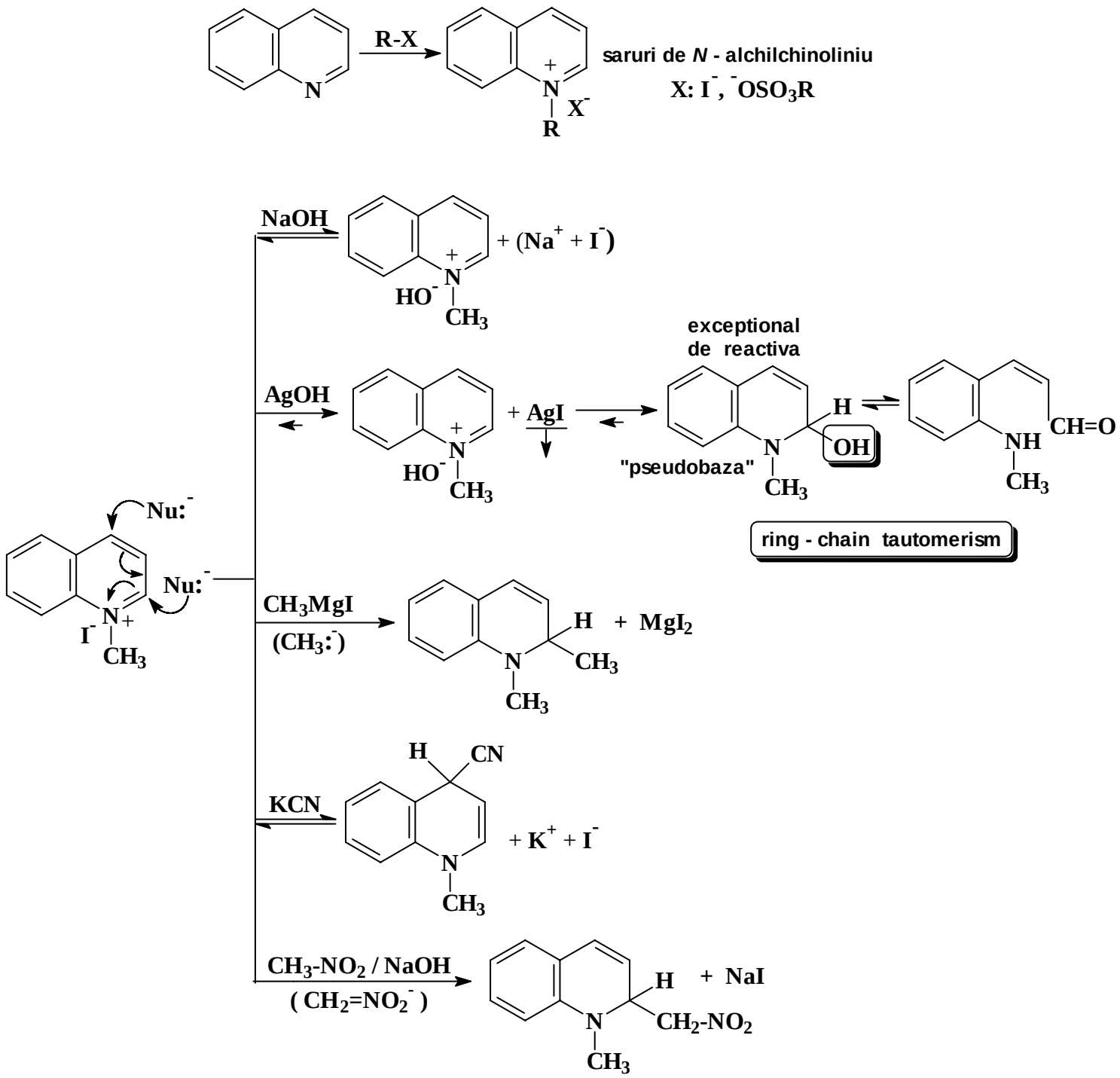
3.1.1. *N* – alchilarea

Generalitati:

- **reactivitate similara** sau **superioara piridinelor**
- **procese**, in general, **reversibile**
- **compusii rezultati** manifesta **afinitate deosebita** pentru **nucleofili**

a) ***N* – alchilarea chinolinei**

- are loc la cald (**P + t^{o}C**)



Nota 1: ionul de iodura **nu se manifesta ca nucleofil** in aceste procese

Nota 2: reversibilitatea depinde de:

a) nucleofilicitatea partenerului, comparativ cu a **ionului de iodura**

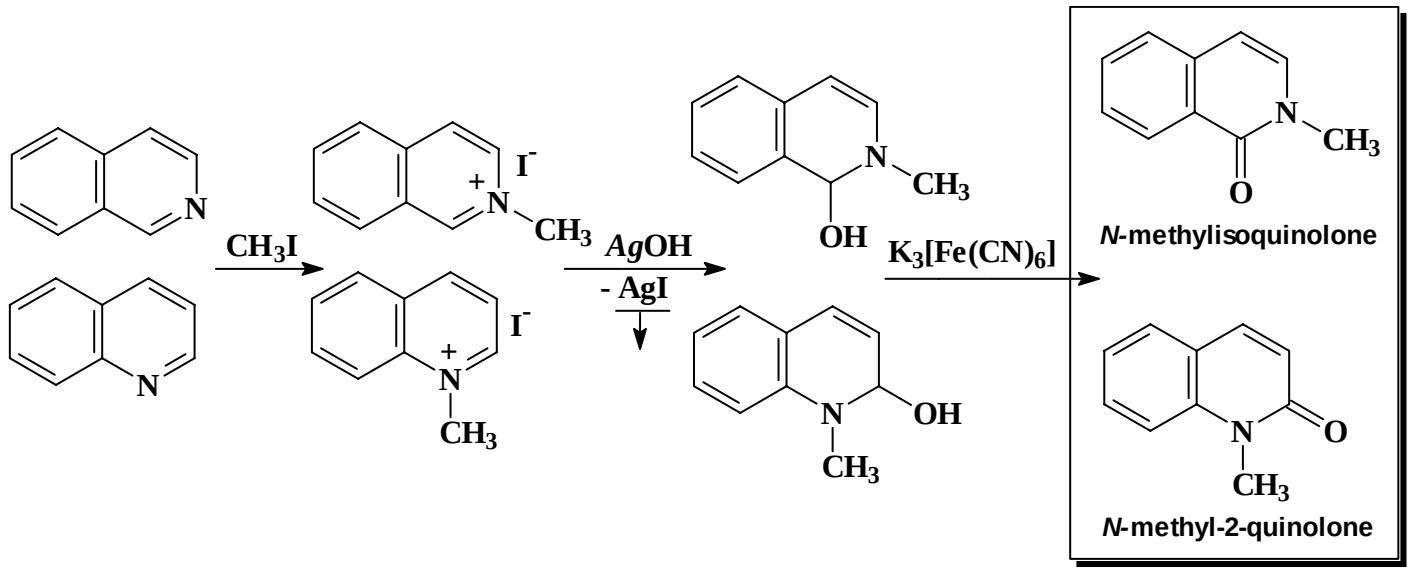
b) tipul de legatura nou formata

Nota 3: de la proprietatea "**pseudobazelor"** de a da genera **tautomeria inel – catena** deriva proprietatea de **functionalizare mai departe a carbonilului aldehidic (structura *Z* !)**.

Nota 4: reactivitatea se limiteaza la **ciclul piridinc, in conditii blande**

b) *N* – alchilarea izochinolinei:

- reactivitate de importanta restransa, in raport cu chinolina, desi **similara:**

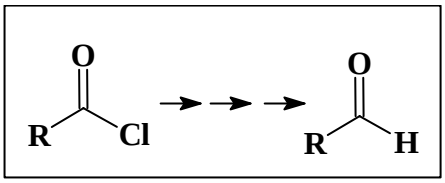


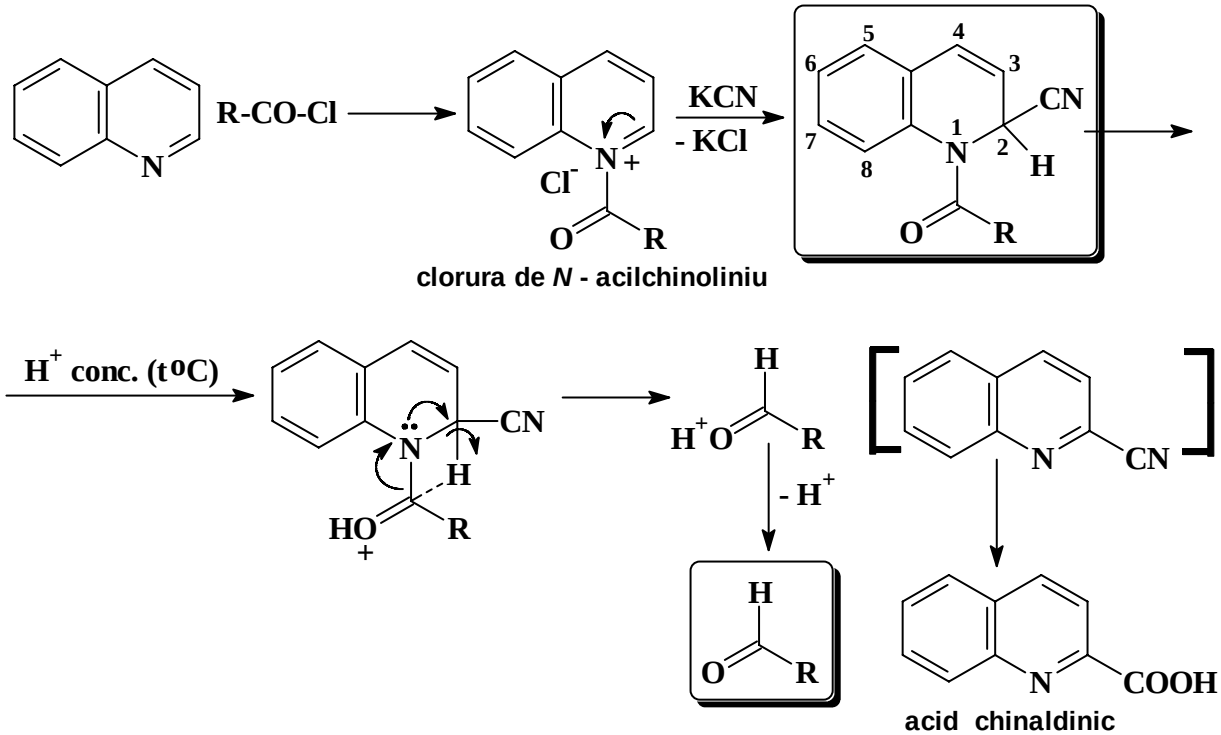
Nota: reactia admite **generalizar**e pentru grupe alchil provenite din **reactivi "traditionali" de *N* - alchilare**: ioduri sau sulfati de alchil

3.1.2. *N* – acilarea chinolinei

a) Compusi Reissert

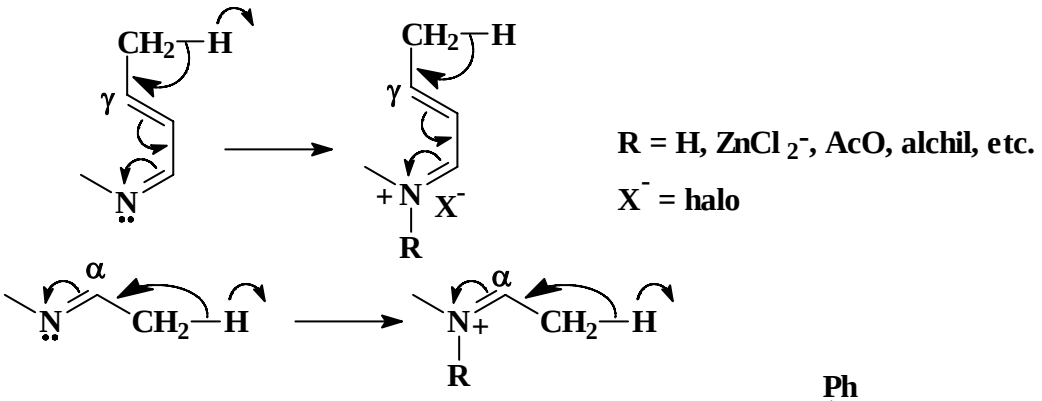
- sunt derivati ***N* - acilati 2-ciano-1-acil-1,2-dihidrochinolinei** utilizati la **prepararea aldehidelor** din cloruri acide; **analogii izochinolinei nu au aceasta proprietate**



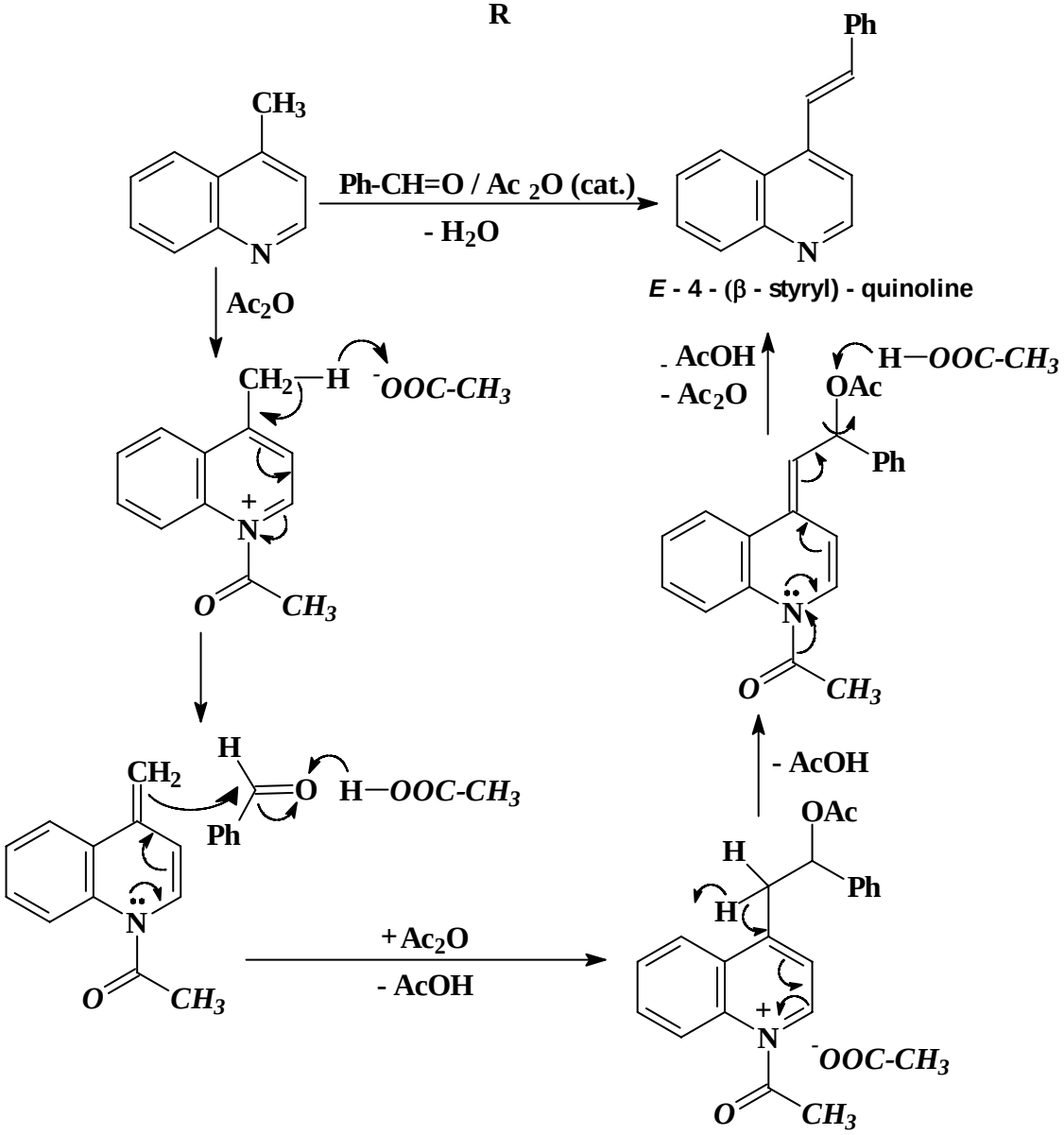


b) accentuarea reactivitatii alchilchinolinelor fata de electrofili: cationi *N* – aciliu

- este **o particularizare** a activarii **efectului –E al azotului piridinic** prin care **grupe metil** legate in **pozitii α sau γ** cu acesta devin **metileni inca mai activi** in reactie cu **electrofili**



Exemplu:



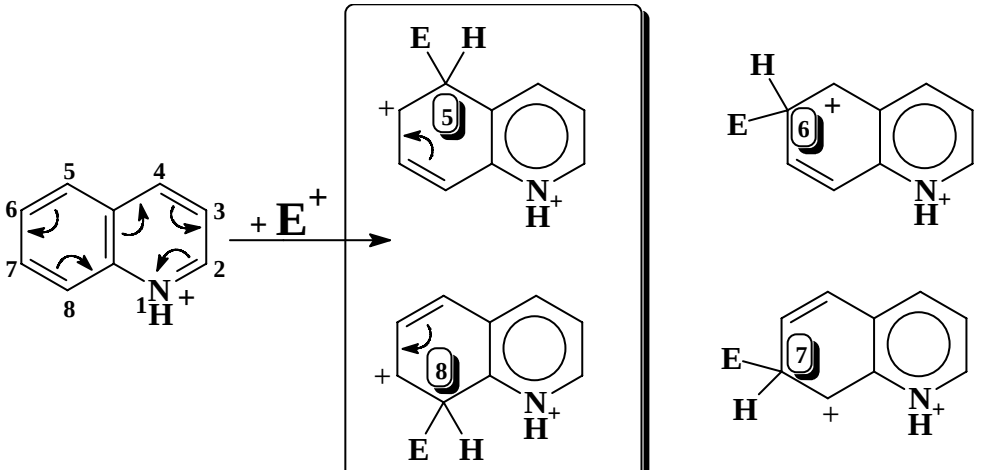
Nota 1: sunt catalizate, pe aceasta cale, **condensari crotonice** cu implicarea **grupelor metil de la *C* - 4** si ***C* - 2**

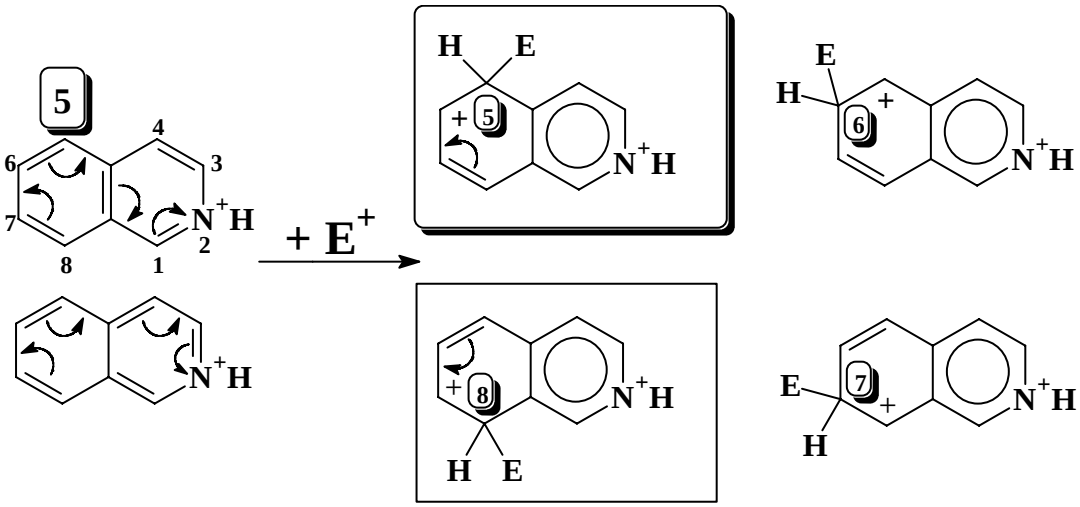
Nota 2: rezultate similare se obtin si in prezenta catalitica a **acizilor Lewis**

3.2. Reactii SE si valoarea preparativa

Generalitati:

- in **reactiile SE** la ciclu, **chinolina** si **izochinolina** se comporta **similar naftalenului** α **-** respectiv β **- substituit** cu o grupa cu un **puternic efect -E** (aici **–N=**)



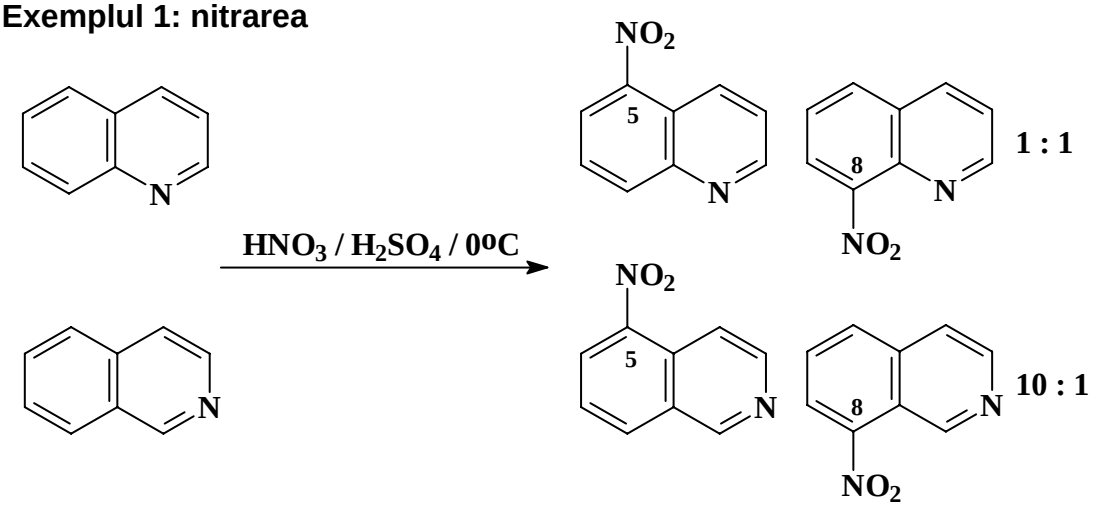


Nota 1: substitutia electrofila este **dirijata totdeauna** in **ciclul benzenic**, mai putin dezactivat, deoarece, pe langa **dezactivarea proprie piridinei**, efectele electronice **nu se transmit integral** de la un ciclu la celalalt (**similar naftalenului**).

Nota 2: pozitiile susceptibile a fi **atacate** de catre electrofili sunt cele care duc la **intermediari carbocationici** a caror **stabilizare nu implica, formal, heterociclul piridinc** ci doar ciclul benzenic: **chinolina: *C* - 5 si *C* - 8**; **izochinolina, preponderent *C* – 5** (influenta minora a ***N* - piridinc**)

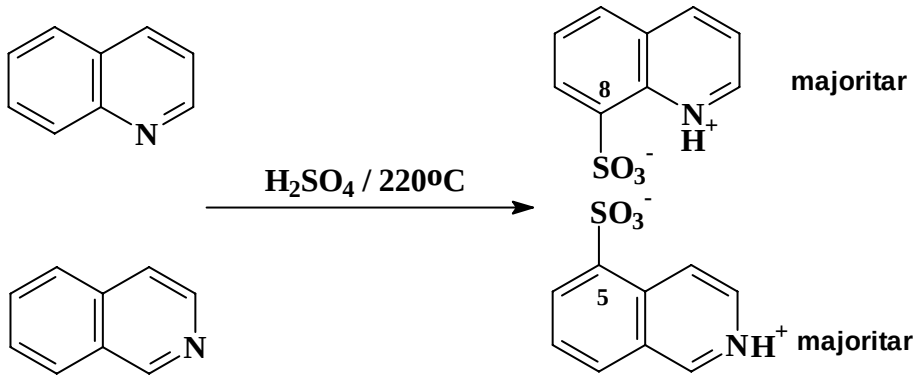
Nota 3: similar piridinei, **speciille reactive** din partea substratului sunt **forme cationice** (protonare la ***N* - piridinic**) ceea ce duce la conditii de **reactie dure.**

Exemplul 1: nitrarea



Observatie: este mult mai regioselectiva in cazul izochinolinei

Exemplul 2: sulfonarea



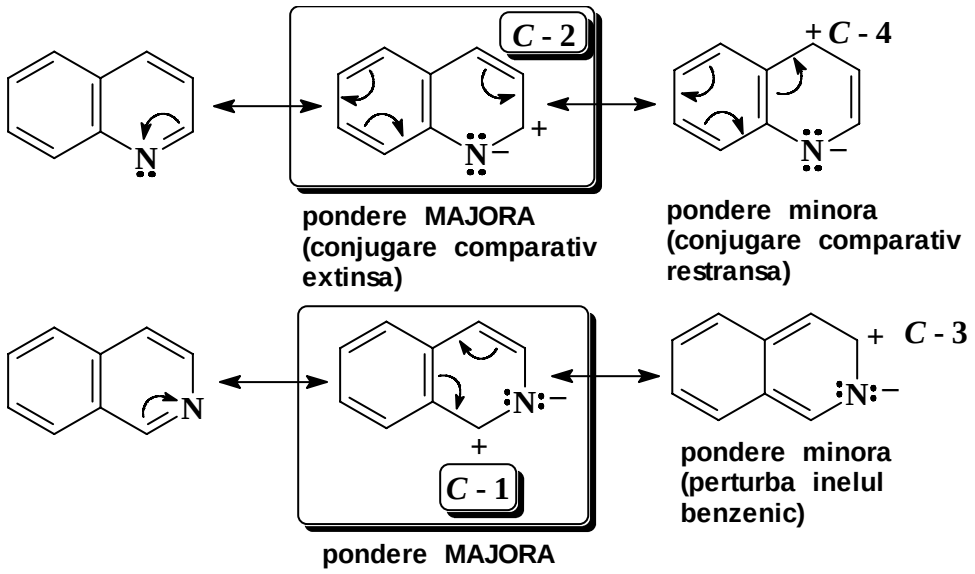
3.3. Reactii SN si valoarea preparativa

Generalitati:

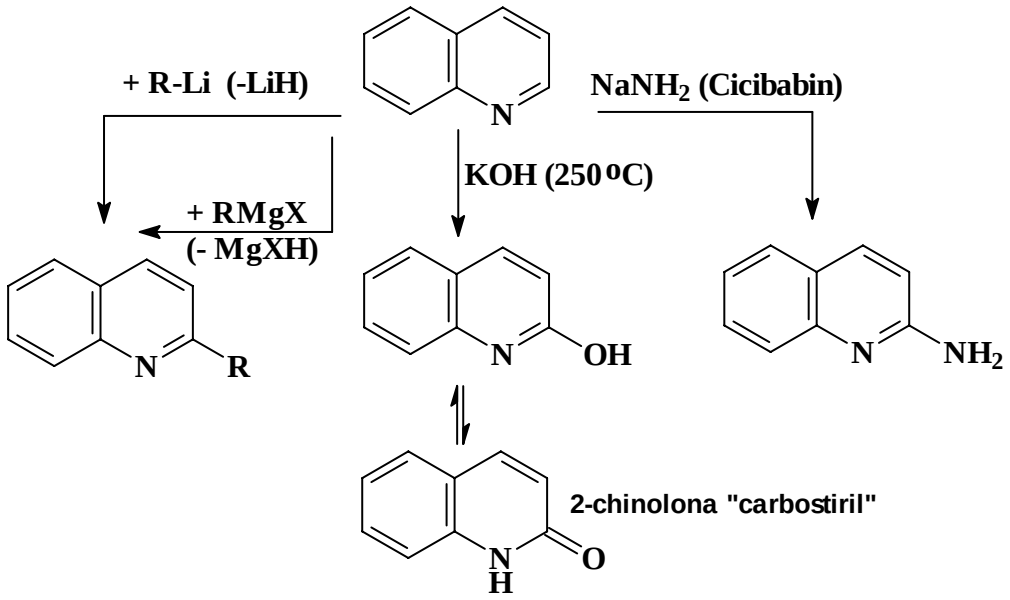
- reactivitatea se manifesta practic exclusiv in **partea piridinica** si **este similara piridinei**
- **sunt grupe fugace:** H, halogenii, grupele diazo, sulfonice (in partea benzenica), etc.

3.3.1. Substitutia nucleofila a hidrogenului

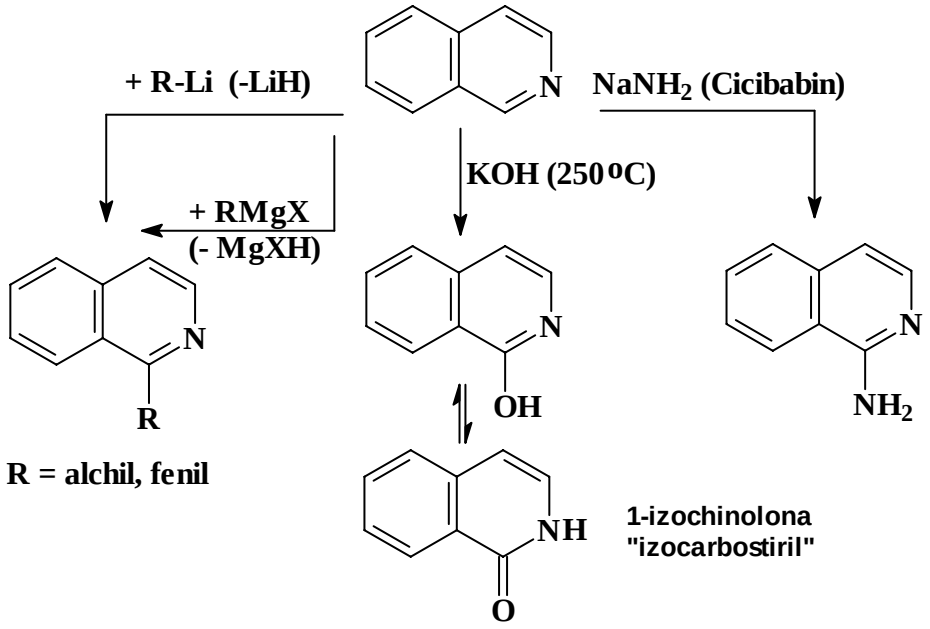
- in cazul **chinolinei** are loc, preponderent la ***C* - 2**
- in cazul **izochinolinei**, are loc, preponderent la ***C* - 1**



Exemplu: cazul chinolinei



Exemplu : cazul izochinolinei



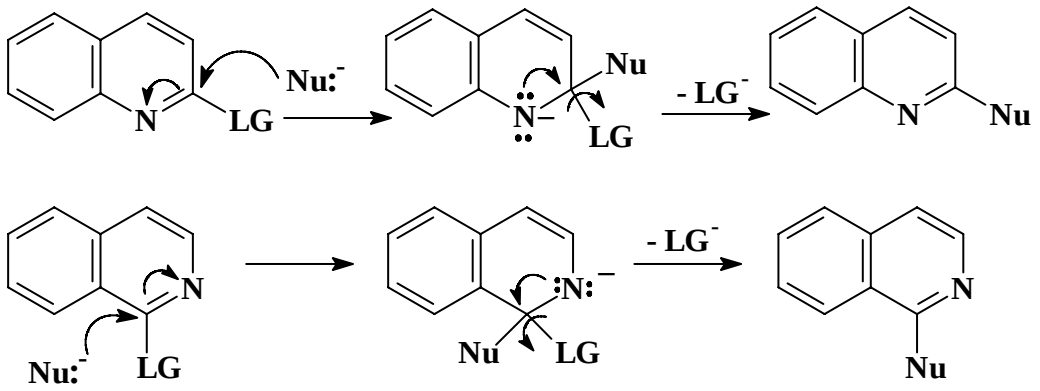
Nota 1: reactivitatea sistemelor ilustrata mai sus reflecta **functionalizarea directa** a acestora **ca atare,** fara a mai fi prezenta vreo **alta grupare fugace** sau **deprotonabila.**

Nota 2: protonii heterociclici sunt insuficient de acizi pentru ca **metalarea sa aiba loc direct la ciclu**, analog piridinelor nesubstituite.

3.3.2. Substitutia nucleofila a grupelor fugace

- urmeaza **mecanismul general al S_N2Ar** in care **rolul labilizant** revine ***N* – piridinic**
- **sunt labilizate**, dupa regula generala:
  a) **in chinolina, grupele de la *C* - 2,** - 4
  b) **in izochinolina, grupele de la *C* - 1 (majoritar)** si *C* - 3 (minoritar)
- conditiile de reactie pot fi atat **bazice cat si acide**.

Schemele generale de mecanism:

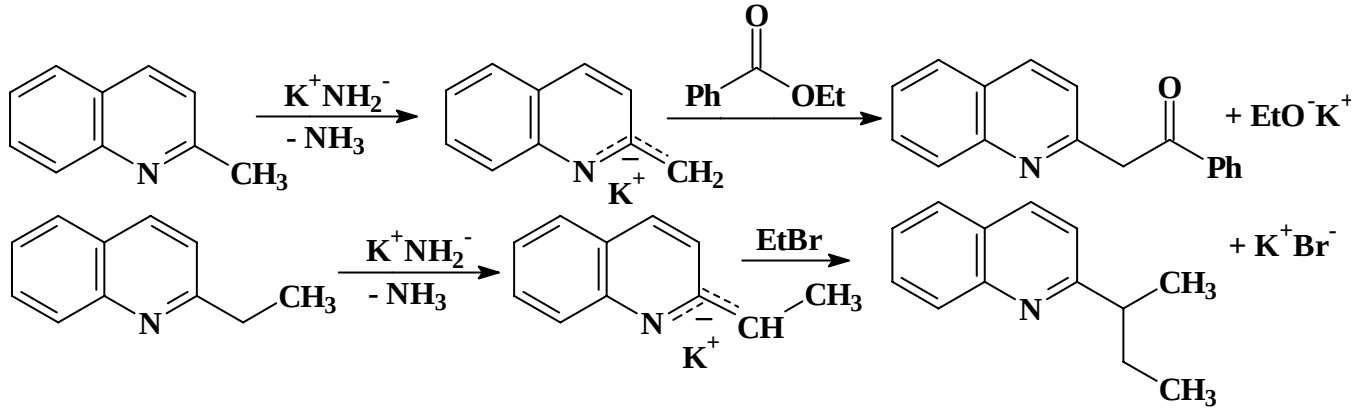


Principalele transformari functionale ale chinolinei *C*- 2 substituite cu grupe fugace

Nucleofil (Nu:$^-$)	Grupa fugace (LG$^-$)	Conditii	Observatii
Cl^-	**HO^-** ca $HOP(Cl_2)=O$	acide, anhidre	$POCl_3$, PCl_5
Br^-	**HO^-** ca $HOP(Br_2)=O$	acide, anhidre	$POBr_3$, PBr_5
Cl^-	**$-N^+\equiv N$**	HCl conc.	Diazoniul neizolabil
Br^-	**$-N^+\equiv N$**	HBr conc.	Diazoniul neizolabil
RO^-	**Cl^-**	RO^-Na^+	Anhidru
HO^- ca H_2O	**Cl^-**	H_2O	-
$R\text{-}NH^-$	**Cl^-**	Reactiv $R\text{-}NH_2$	Anhidru
NH_2^- ca NH_3	**Cl^-**	Reactiv NH_3	Bazic
HO^- ca H_2O	**NH_2^-** ca NH_3	-	Bazic, apos

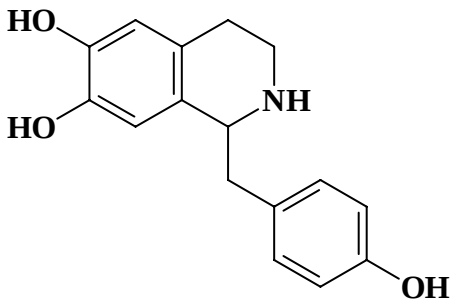
3.4. Reactivitatea unor carbanioni derivati ai chinolinei si izochinolinei

- sunt generati **carbanioni stabilizati prin conjugare in β (sau δ) din chinoline** fata de azotul piridinc (imina mascata) exact ca in piridine
- au **valoare preparativa** deprotonarile sub **actiunea bazelor tari** asupra 2-alchilchinolinelor
- fata de acestea, **bazele tari** se manifesta **prin deprotonare** si **nu ca nucleofili**
- **reactivitatea alchilchilizochinolinelor** se manifesta **similar,** la ***C* – 1** (slab la C-3).



P – 7

P-7.1. Prezentati succesiunea de transformari necesare pentru a obtine alcaloidul natural de mai jos pornind de la materii prime de baza: piperonal si acid 4-metoxifenilacetic (sau *p*-metoxifenilacetaldehida).



P-7.2. Prezentati succesiunea de transformari necesare pentru a obtine preparatul antibiotic de mai jos pornind de la materii prime de baza: 3-cloro-4-fluoroanilina, piperazina, precum si alte componente necesare ciclizarii si funtionalizarii