UNIT III

HETEROCYCLIC COMPOUNDS

Nomenclature, classification, Synthesis, Reaction & Medicinal Uses of

- # Pyrrole & basicity
- # furan
- # Thiophene

] Relative Aromaticity & Reactivity

Other than C atm is also present in cyclic ring are known as Heterocyclic compounds. (cyclic compounds with one or more hetero atom.)

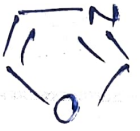
Heterocyclic Compounds

1. 5-Membered

Pyrrole

furan

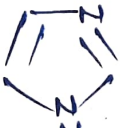
Thiophene



Oxazole

Thiazole

1H-pyrazole



1H-Imidazole

1H-Tetrazole

6. Six-Membered

pyridine

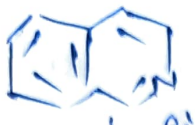
pyridiazine

pyrimidine

pyrazine

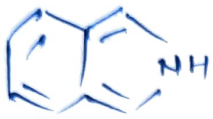
3. Fused Ring System

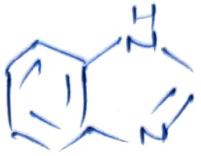

Quinoline


Isoquinoline


Quinazoline


Indole


Isoindole


Benzimidazole

Nomenclature

Commonly known by their Common Name

IUPAC Name - Prefix + Suffix

Order of priority

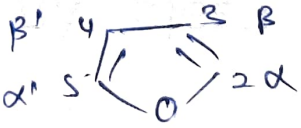
			Prefix	Suffix
1	O_2	-	oxa	Depend on ring
2	S_2	-	thia	
3	N_2	-	aza	
4	P	-	phospha	

Ring main Suffix

5 - ole

6 - ine

7 - epine



anticlock

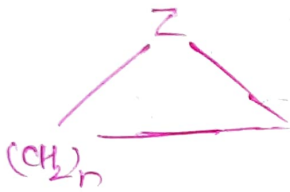
⇒ Size	Prefix	without N	with N Unsat-	Saturate
3	ir	irane	irine	ridine
4	et	-ete	etc	etidine
5	ol	ole	ole	olidine
6	in	ine	ine	~~inane~~
7	ep	epine	epira	~~apane~~
8	oc	ocin	ocine	—
9	on	onin	onine	—
10	ec	ecin	ecine	—

Heteroatom		Prefix
O	N	Oxaza
N	O	Oxaza
S	O	Oxathia
S	N	Thiaza

Prefer : O > S > N

Nomenclature

1. The Hentzsch-Widman Nomenclature
2. Common System ↳ Widly accepted (used in IUPAC)
3. The replacement methode



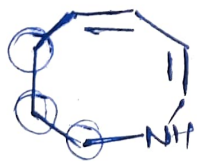
Z : Type of heteroatom

O - Oxa
N - aza
S - Thia
P - phospha
Se - Selena

n : Size of ring n = 1, 2, 3, 4, 5 . . .

Nature of ring - Saturated, Unsaturated, or Saturated with N

ex.



Hydra Trihydra

Iretot in epoe on eclairs

ring	Root	Saturated	unsaturate	Sat. + N
3	tri	ir	irane - ine	irine	iridine
4	tetra	et	etane	ete	etidine
5	penta	ole	olane	ole	olidine
6	~~hepta~~ hexa	ine	inane	~~ine~~ inine	
7	hepta	ep	epane	epine	
8	octo	oc	ocane	ocine	
9	nano	on	onane	onine	
10	deca	ec	ecane	ecine	

(etane, olane, inane : +ene; epane, ocane, onane, ecane : +ine)

Oxa + irane = Oxirane

Thia + irane - Thirane

Aza + iridine → Aziridine

oxa + etane → Oxetane

Thia + etane → Thietane

Aza + etidine - Azetidine

oxa + olane → Oxolane

Thiolane

Azolidine

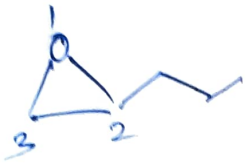
Aza + inane - Azinane

pyridine (Common name)

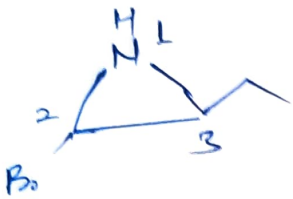
Aza + ine ~~Azirine~~ (Azine)

~~Fu~~ furane

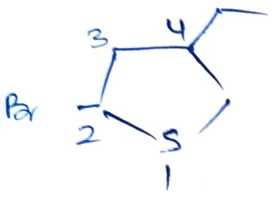
Oxa + ole = Oxole



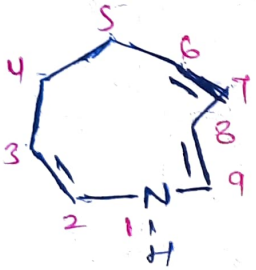
2-propyl oxirane



2-bromo-3-ethyl Aziridine

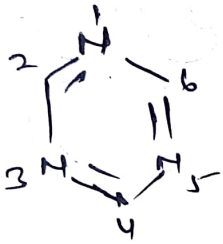


2-bromo 4 ethyl Thiolane



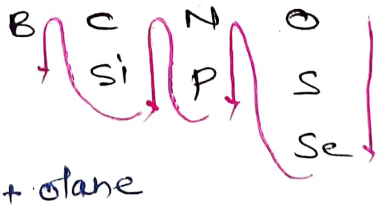
priority to Saturated

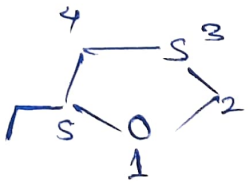
4,5-dihydro (Aza + onine)
Azonine



1,3,5-TriAzine

Different Heteroatom Priority

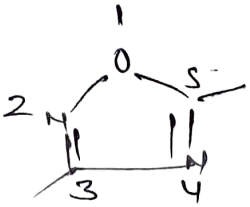




1,3 Oxa + thia + olane

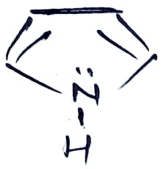
5-ethyl-1,3-Oxathiolane

1,4-Oxa + Aza + inine
1,4-Oxazinine



2-chloro-5-methyl-1,2,4-Oxadiazole

AROMATIC CHARACTER OF PYRROLE, FURAN & THIOPHINE


Pyrrole

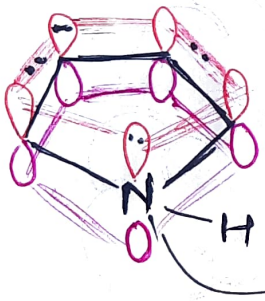

Furan


Thiophene

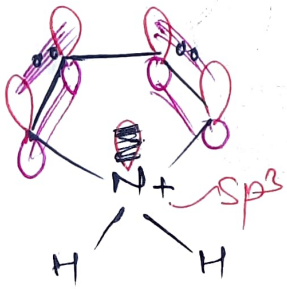
↳ Cyclic
↳ Conjugate π el⁻
↳ sp^2 hybridized
↳ planner
↳ $4n+2$ π el⁻
$n = 0, 1, 2, 3$

Planner Pentagons
sp^2 Hybridized C-atom
$4n+2$ π el⁻ followed $(4n+2) = 6$ π el⁻, $n = 1$

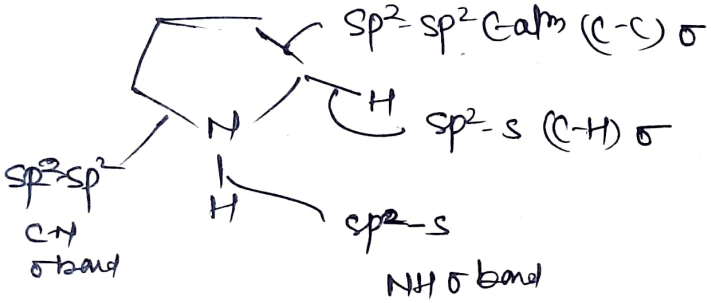
PYRROLE

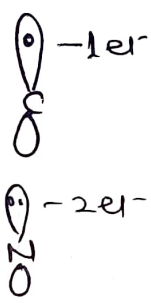


⇒ $pK_b = 13.6$
⇒ weak base
⇒ Aromatic Compound



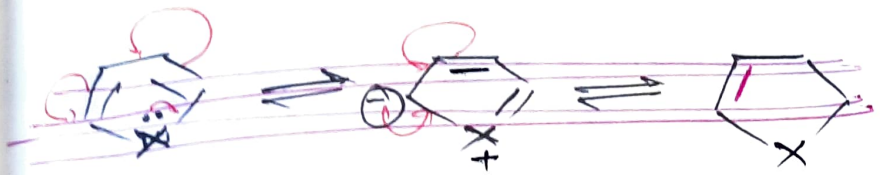
- N-protonated Pyrrole
- Anti aromatic / Non-aromatic
- $pK_a = 0.4$
- Strong Acid

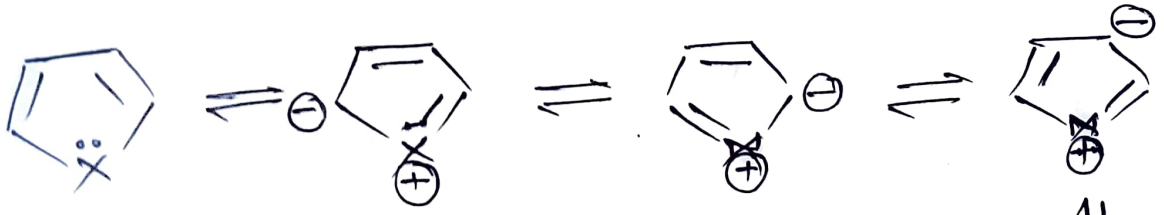


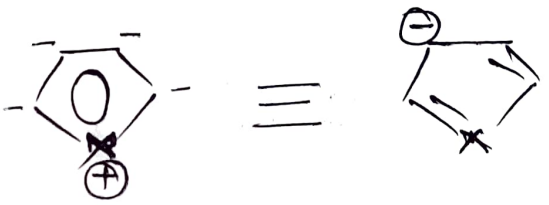


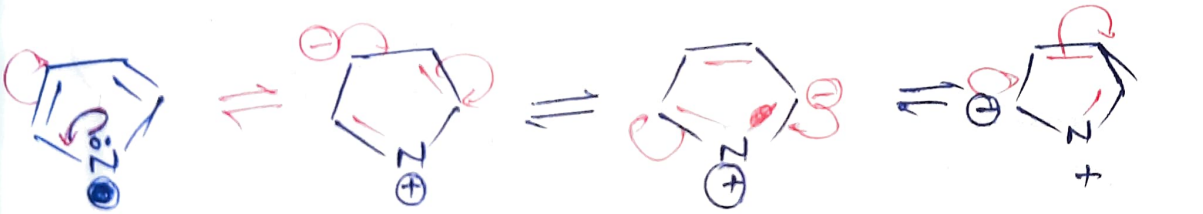
Rasonance Structure for Pyrrole, Furan & Thiophene

X = O, NH, S



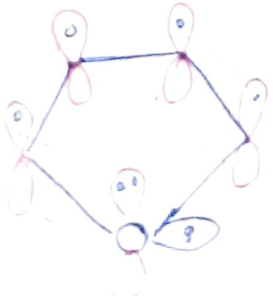




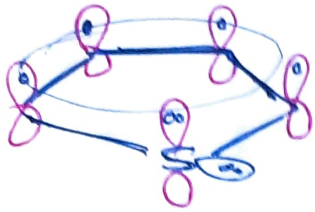


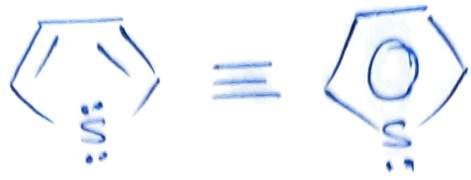
FURANE

→ All sp^2 hybridized



Thiophene





Relative Aromaticity Order

electronegativity Order : O > N > S

O has least tendency to donate the el⁻ pair to aromatic ring

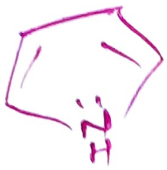
thus Stability Resonance or Aromaticity Order

Furan < Pyrrole < Thiophene < benzene

Aromaticity →

← Reactivity

PYRROLE



"Azole"

Physical Properties -

- # C_4H_5N
- # Colourless liquid
- # B.P = 131°C, it turn brown in exposure to air
- # ~~Sfla~~ Slightly soluble in water
- # Soluble in ether & alcohol

pyrrole occurs in Coal tar & Bone oil
Bone oil is obtained by distillation (dry) or pyrolysis of animal by product such as horns, bones & hooves

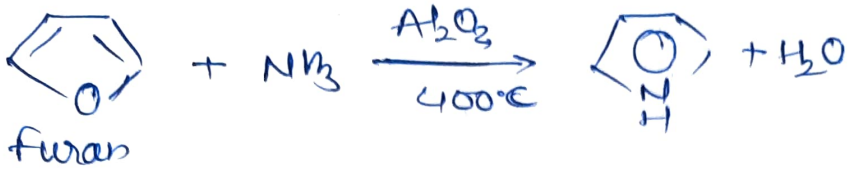
extracted Bone oil
↓
wash with alkali
↓
fractional Distillation
↓
Temp at (100-~~150~~°C)
↓
pyrrole (purified by KOH steam distillation)
↓
pyrrole (131°C)

Occurs also in many natural substances like. alkaloid, chlorophill, haemoglobin

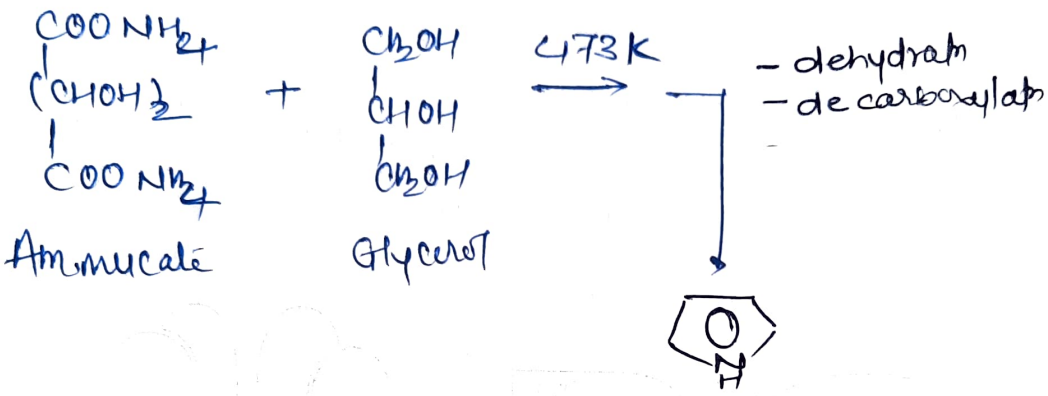
Methods of Preparation

From - ① Furan & Ammonia
② Ammonium Mucate
③ acetylene
④ Succinic acid
⑤ Syn. of 2,5-derivative (Paal-Knorr Synthesis)
⑥ Syn. of 2,3,5-deriv. (Hantzsch Pyrrole Synthesis)

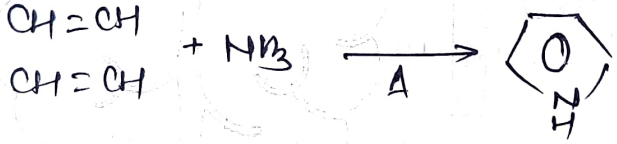
(I) From Furan & Ammonia (Industrial Method)



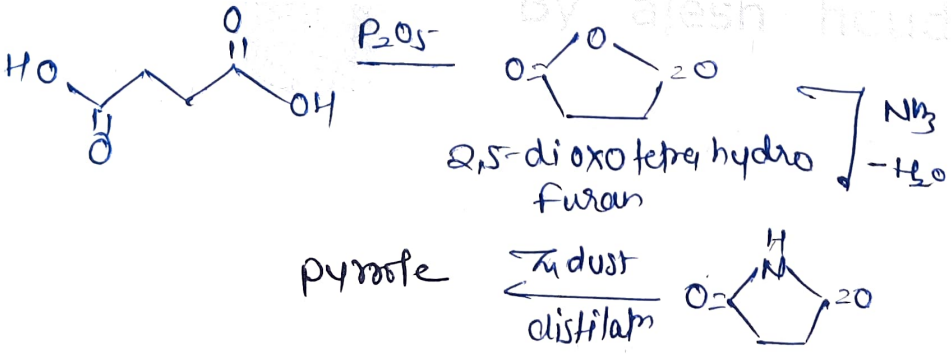
(II) From Ammonium mucate



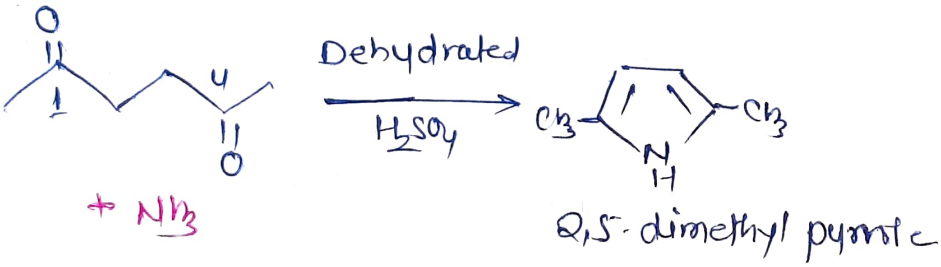
(III) From Acetylene



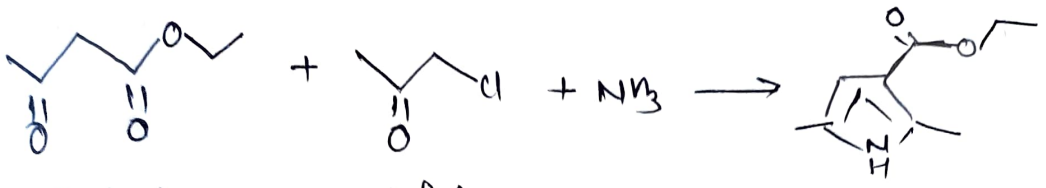
(IV) From Succinic Acid



(V) Paal-Knorr Synthesis (1,4-diketone & heloketone)

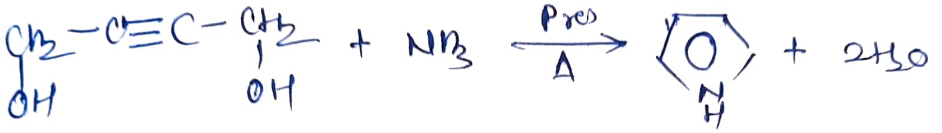


(6) Hantzsch Synthesis (2,3,5-derv.)



Ketoester + Haloketone + NH_3 → ethyl 2,5-dimethyl 1H pyrrole-3-carboxylate

(7)



2-butyen-1,4-diol → Pyrrole + $2H_2O$

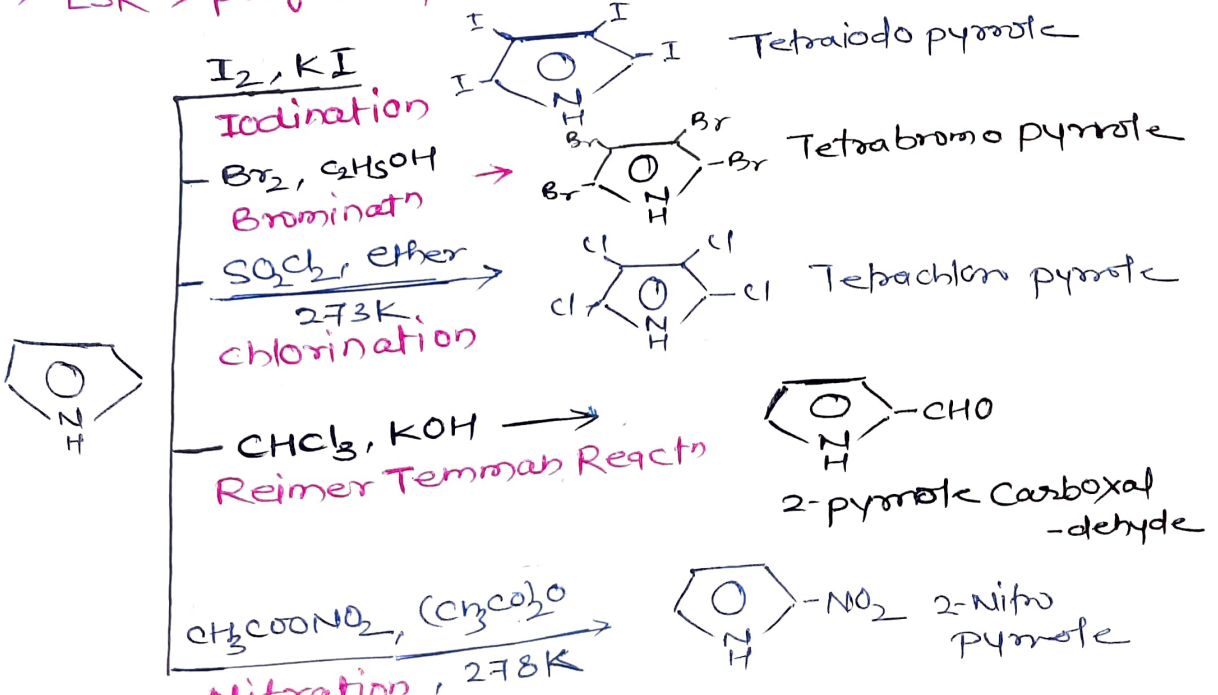
CHEMICAL REACTIONS OF PYRROLE

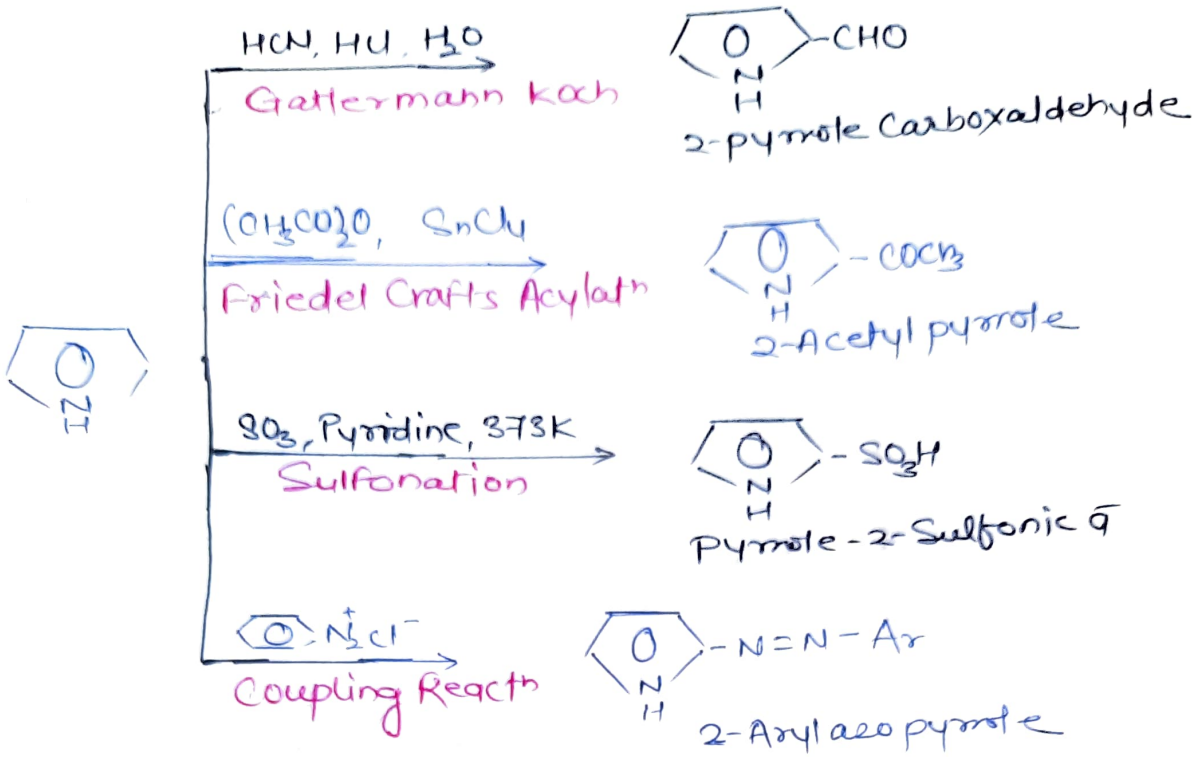
A) Electrophilic Substitution Reactions

↳ electron density at pyrrole ring or C-atoms of pyrrole is much higher as compared to benzene due to the ability of N_2 to donate its lone pair to π el⁻ cloud.

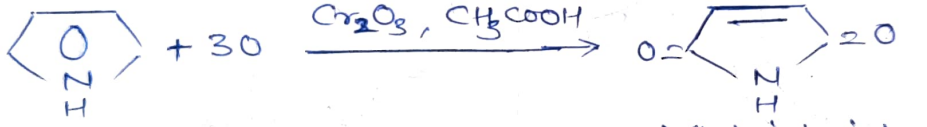
Thus Reactivity → Pyrrole > Benzene

↳ ESR → preferably at α or 2-position, then β or 3-position

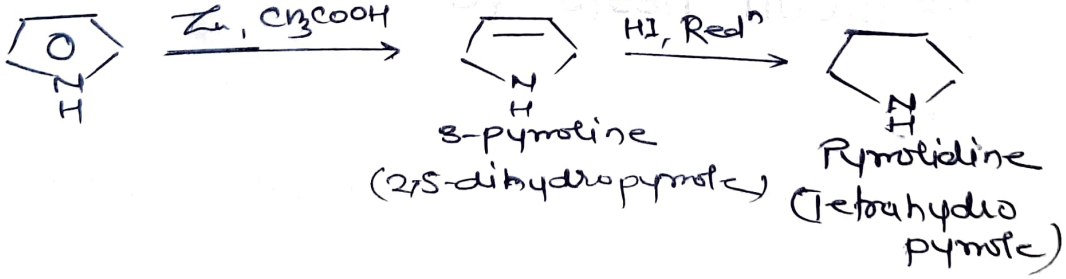




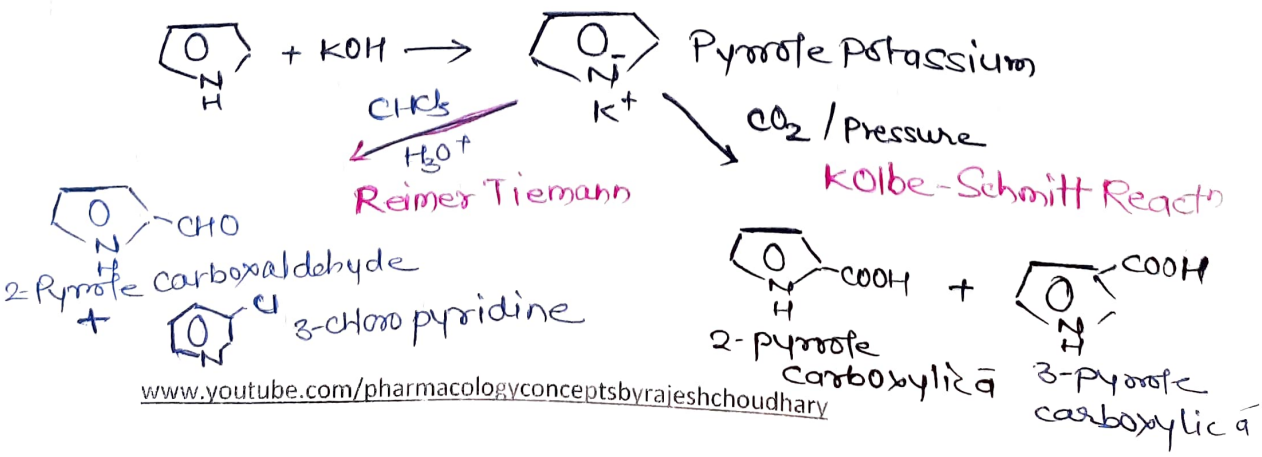
B. Oxidation :-



C. Reduction :- Pyrrole → Pyrroline → Pyrrolidine



D. Others :-



Medicinal Uses of Pyrrole

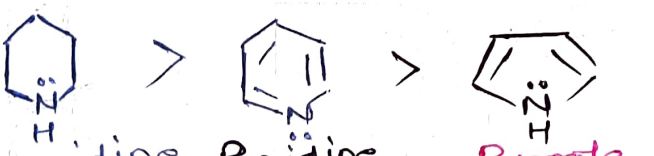
↳ Used in preparation of various medicinal agents like antibiotics, antiinflammatory, antihypertensive agents, ~~etc~~, anticancer, antifungal, antiviral, antioxidants, etc.

examples –

Atorvastatin → antihyperlipidemic
Ondansetron → anti-emetic
Captopril, Enalapril (ACEIs) – Antihypertensive
Lincomycin, clindamycin → Antibiotics
Bepridil → calcium channel blocker
Triprolidine → Antihistaminics

BASICITY OF PYRROLE

Order



Piperidine > Pyridine > Pyrrole

	Piperidine	Pyridine	Pyrrole
pK_b	2.9	8.8	13.6 (approx)

↳ Pyrrole is the weak base because lone pair of e^- of Nitrogen atom contributes to the aromatic π e^- cloud, therefore availability of these e^- is decreased for reaction, resulting in very weak base as compared to pyridine & piperidine

↳

Possibility is much lesser because lone pair e^- is already involved in delocalization & is not available for new N–H bond formation

#

↳ Smaller hybrid orbital (more s-character)
↳ lone pair closer to N_2-atom (less available)
↳ Weak base

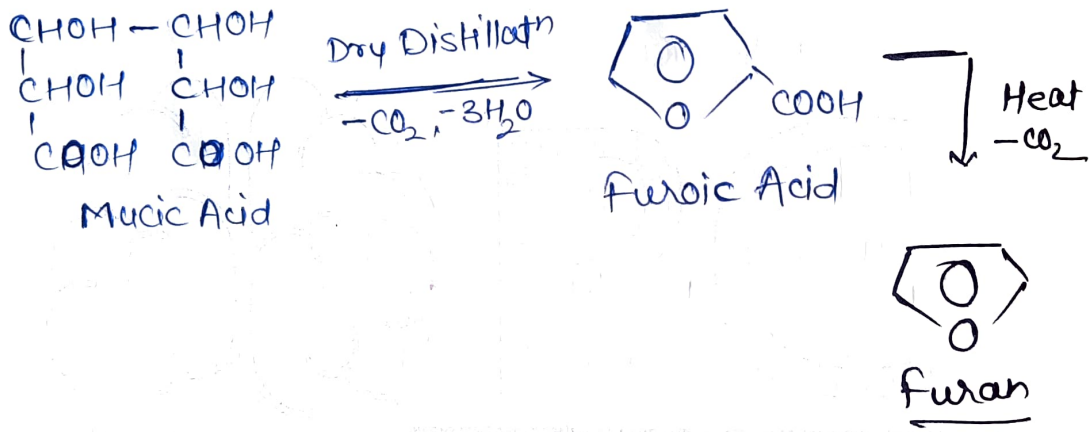
FURAN

(Oxole)

- C_4H_4O
- Five membered heterocyclic aromatic compound
- Mwt = 68 g/mol
- Colourless, volatile liquid
- BP = 31.3 °C

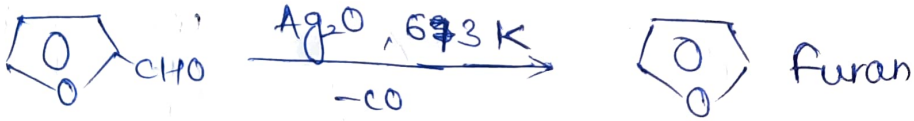
SYNTHESIS :->

1. From Mucic Acid

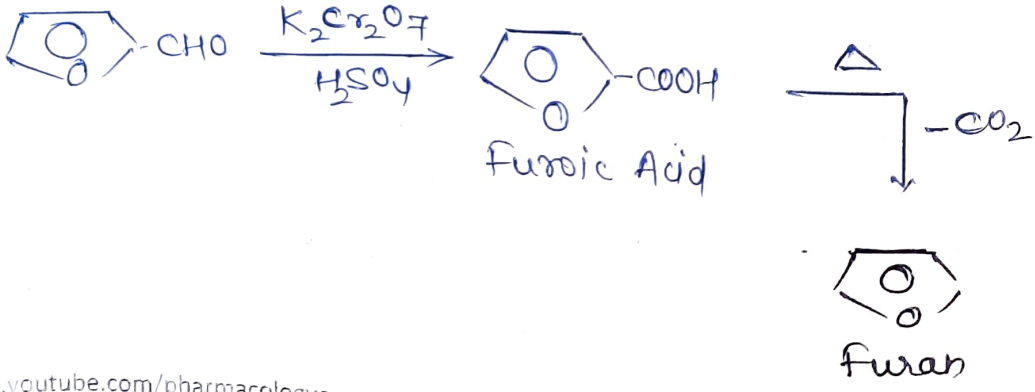


2. From Furfural

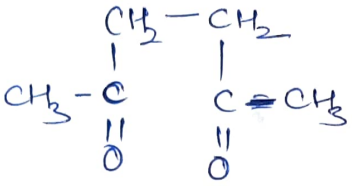
(1) By Decarboxylation



(2) By Oxidation



3. **Paal-Knorr Synthesis** – By dehydration of 1,4-dicarbonyl compound

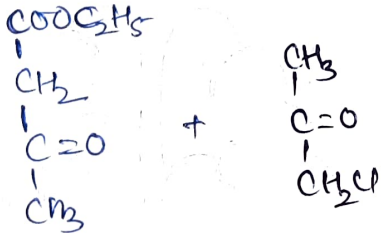


Hexane-2,5-dione

P_2O_5, Heat, $-H_2O$

2,5-dimethyl furan

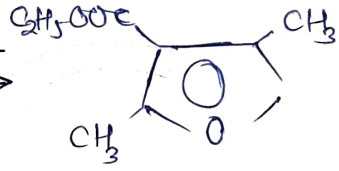
4. **Feist Benary Synthesis** – Involve reaction between β-ketoester and an α-haloketone in presence of pyridine



Ethyl acetoacetate (β-ketoester)

α-Chloro Acetone

Pyridine, $-HCl, -H_2O$



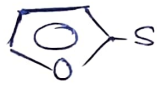
Ethyl 2,5-dimethyl Furan-3-Carboxylate

CHEMICAL REACTION

1 Electrophilic Substitution Reaction → at α or 2-position

Furan

SO_3, Pyridine — Sulphonation

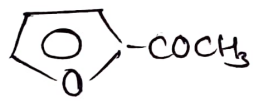


Furan-2-Sulphonic acid

CH_3COONO_2, — Nitration

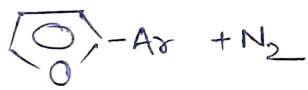
2-Nitro furan

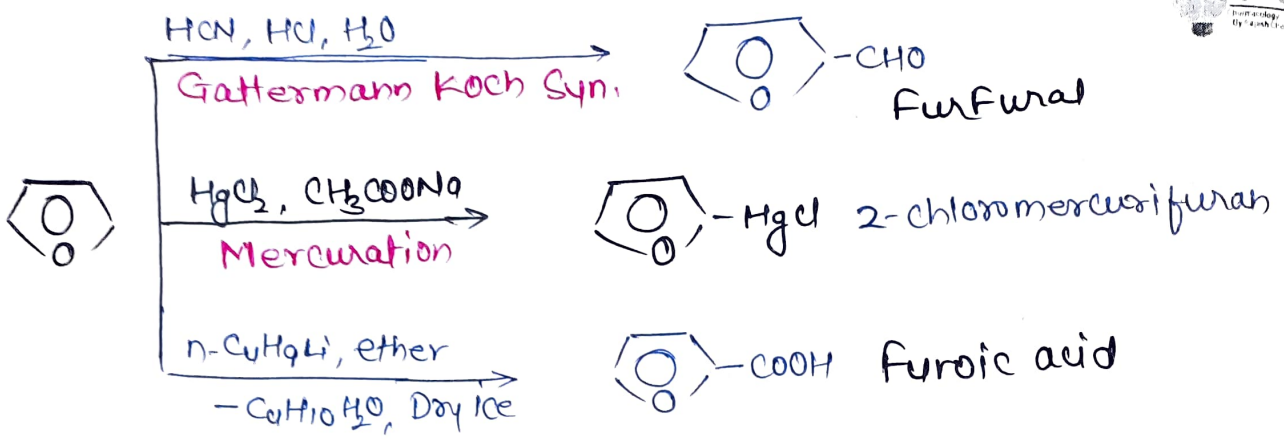
$(CH_3CO)_2O$, $(C_2H_5)_2O$, BF_3 — Friedel Craft Acylation



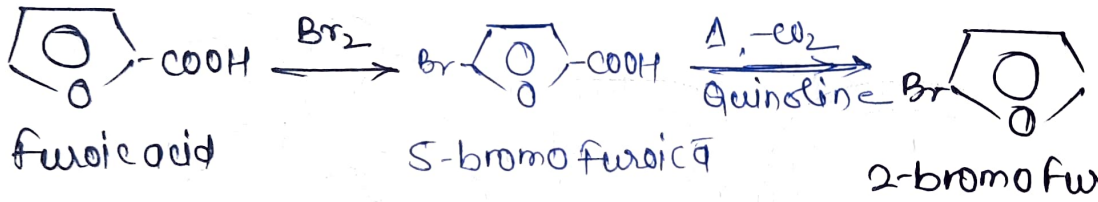
2-Acetyl furan

ArN_2Cl, NaOH — Gomberg Reactn

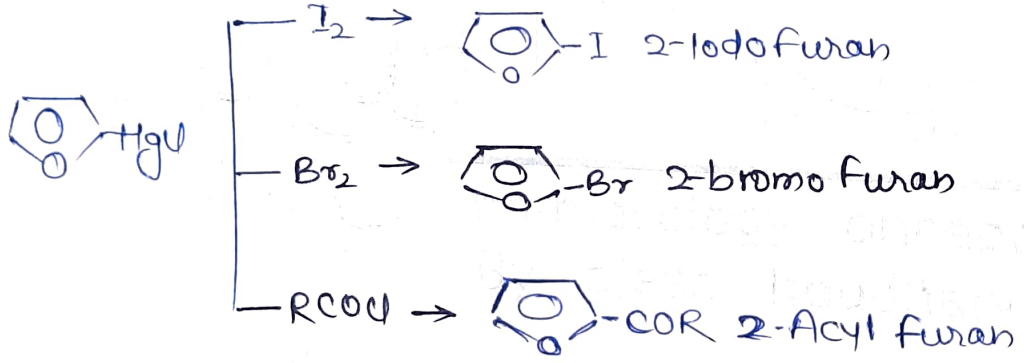




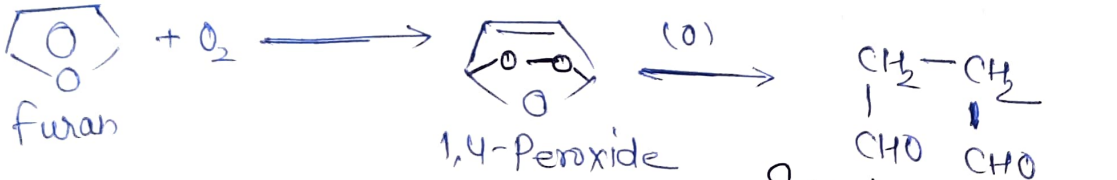
2. **Halogination** :- Due to polymerizatn of liberated acid, direct halogination is not possible, therefore, halogination of furan are obtained indirectly

① 

Furoic acid — 5-bromo furoic acid — 2-bromo furan

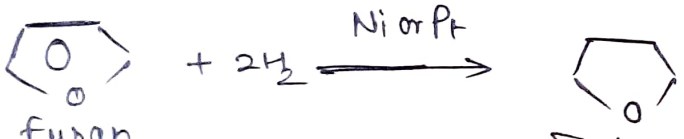
① 

3. **Oxidation**



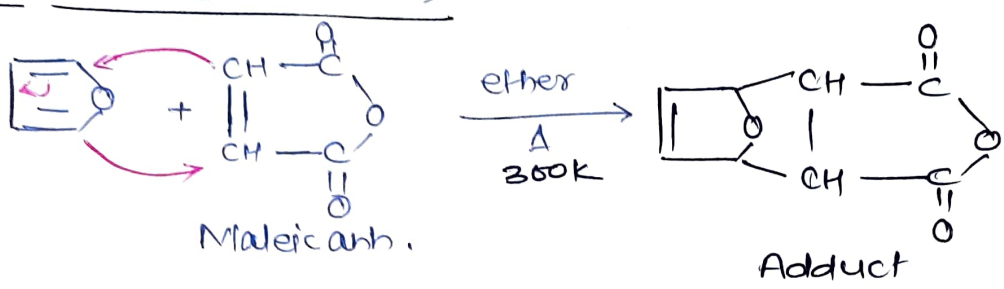
furan — 1,4-Peroxide — Succinaldehyde

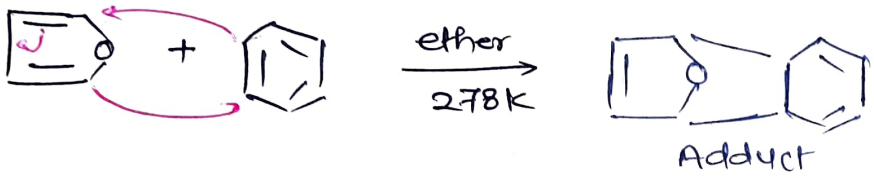
4. **Reduction**



furan — Tetrahydrofuran (THF)

5. Diels-Alder Reaction





MEDICINAL USES

Furan & its derivatives shows various pharmacological activities such as antidepressant, analgesics, antiinflammatory, muscle relaxant, antihypertensive, Antimicrobial, antiulcer, diuretics, antiparkinson etc.

example

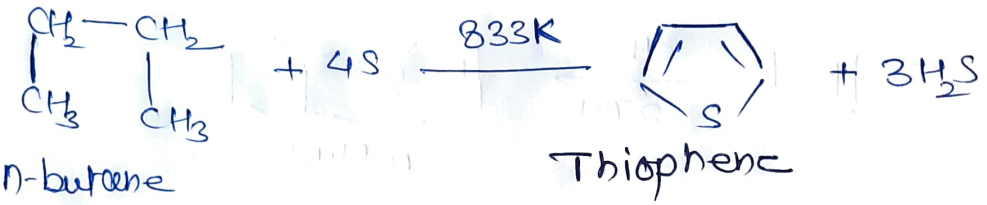
- Vilazodone – Antidepressant
- Firocoxib – NSAIDs
- Prazosin – α_1 blocker antihypertensive
- Amiodarone – antiarrhythmic
- Nitrofurantoin – antimicrobial for UTI
- Ranitidine – H_2 receptor blocker
- Furosemide – loop diuretic
- Fluticasone – Corticosteroid

THIOPHENE

- C_4H_4S, 84.14 g/mol
- BP - 84°C
- Colourless liquid

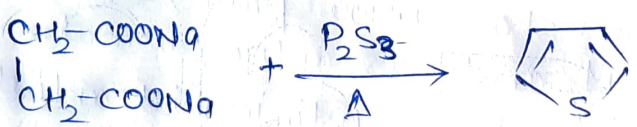
SYNTHESIS

1. From n-butane

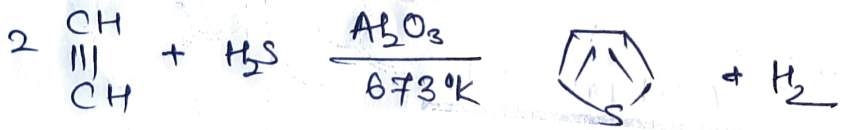


n-butane → Thiophene

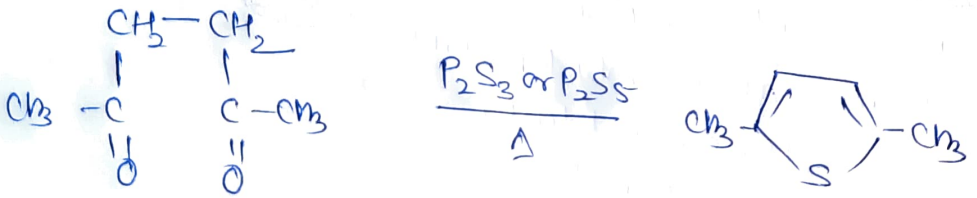
2. From Sod. Succinate



3. From Acetylene



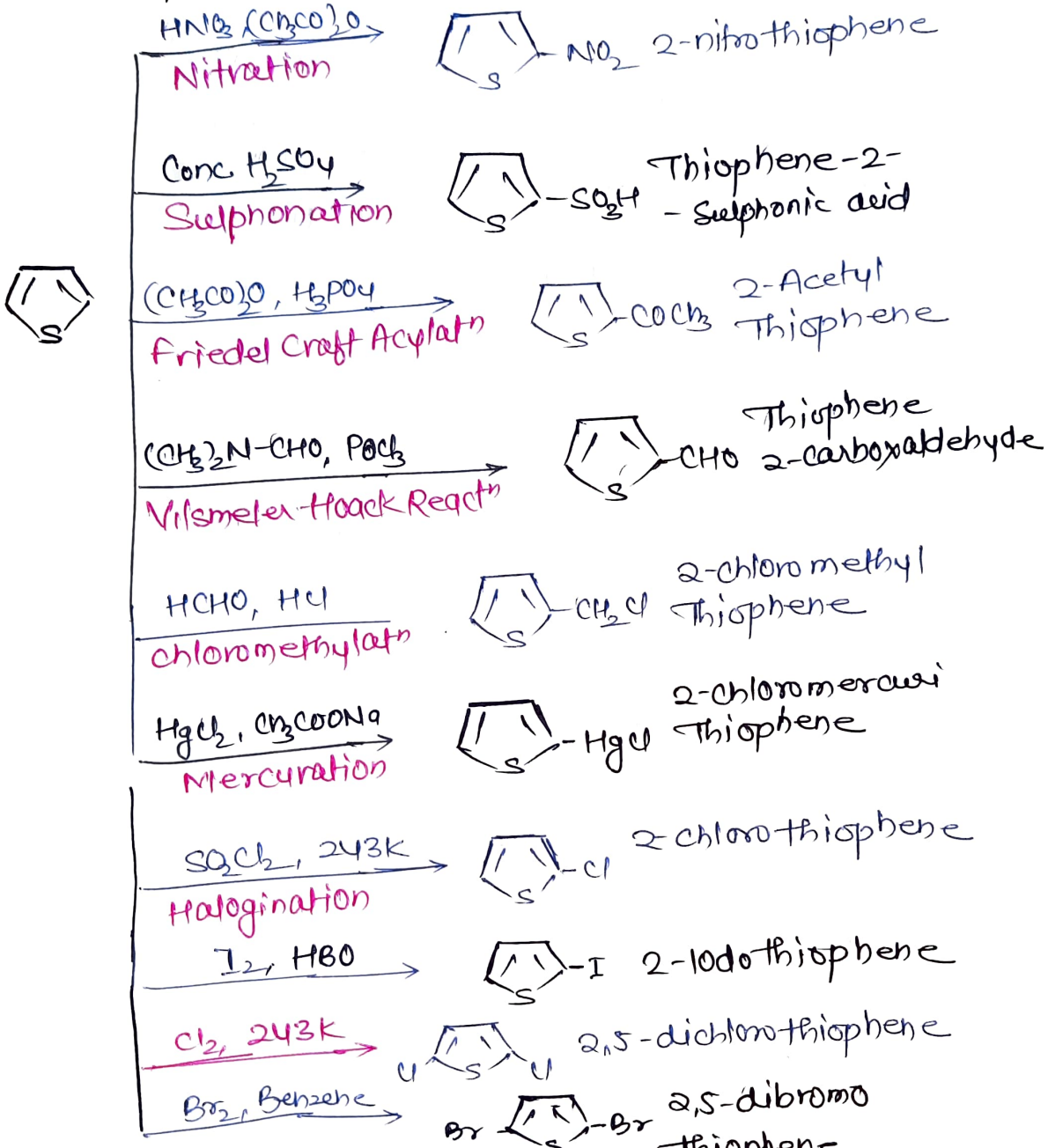
4. Paal knoor Synthesis



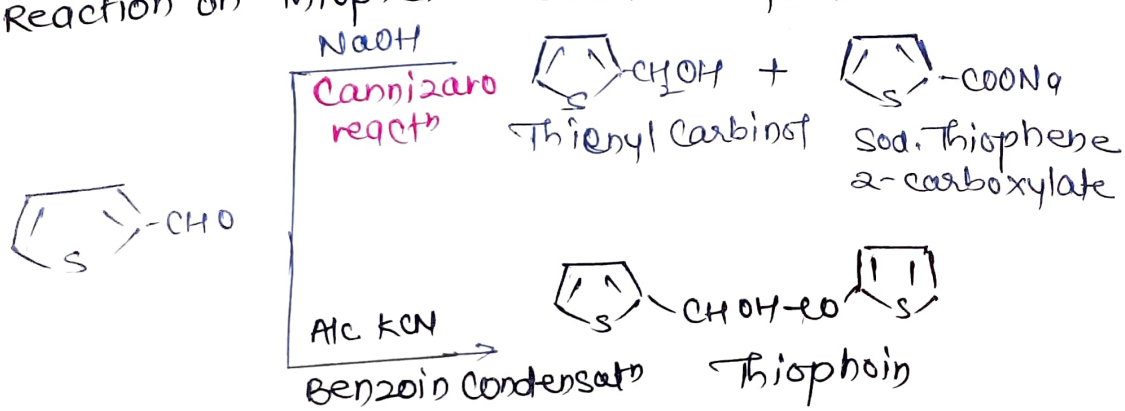
Hexane-2,5-dione → 2,5-dimethyl Thiophene

CHEMICAL REACTION

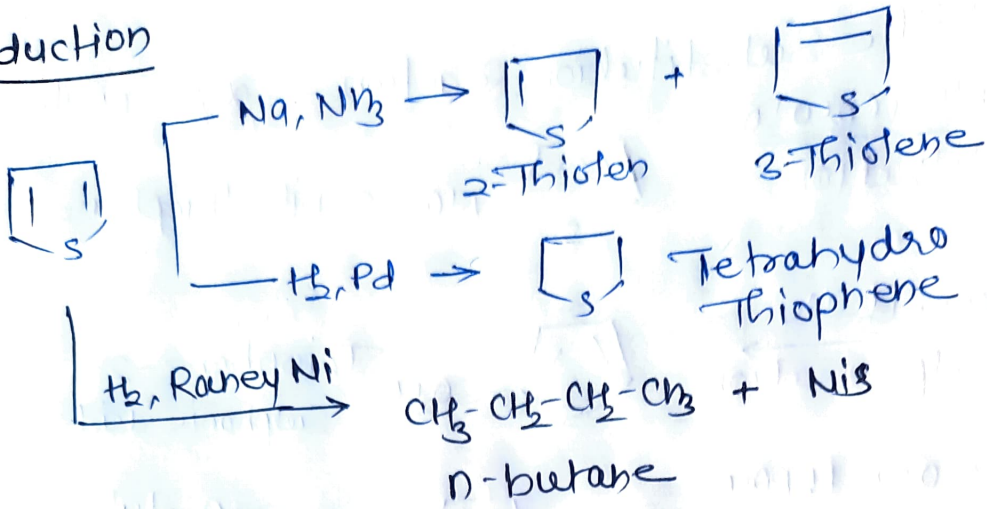
1. Electrophilic Substitution Reaction – α / 2-position



2. Reaction on Thiophene-2-Carboxaldehyde



3. Reduction



MEDICINAL USES

Antimicrobial → Cephelosporins
Anticancer → Raltitrexed
Antiinflammatory → Tinoridine, Tiaprofenic acid
Antihypertensive → Tiamenidine
CNS Activity - Clotiazepam