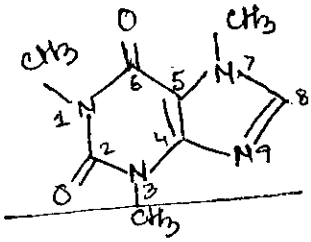
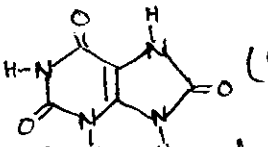
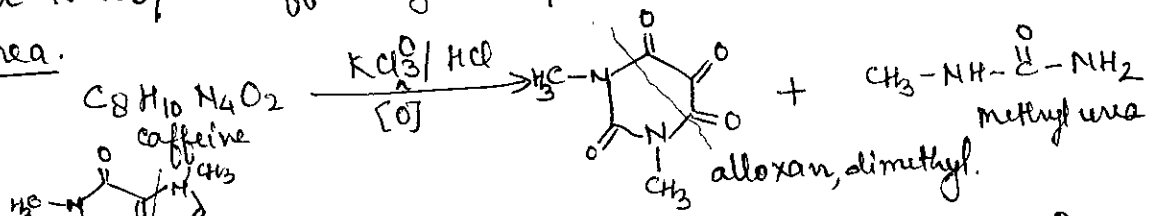


Structure of Caffeine: ($C_8H_{10}N_4O_2$)

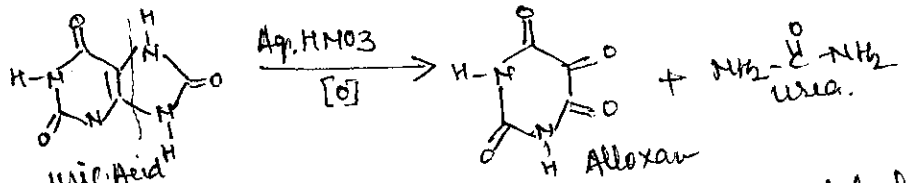
⇒ It is molecular formula is: $C_8H_{10}N_4O_2$, and it is found basically in tea and coffee etc.

⇒ Caffeine is methylated xanthines. It is 1,3,7 trimethyl xanthine.

⇒ It is related with uric acid  ($C_5H_4N_4O_3$); as an oxidation with $KClO_3$/HCl caffeine gives equimolar amount of dimethyl alloxan and methyl urea.

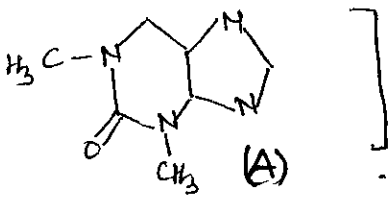


⇒ While uric acid on oxidation with aq. HNO_3 gives alloxan and urea.



These results indicate that caffeine and uric acid have same skeleton structure.

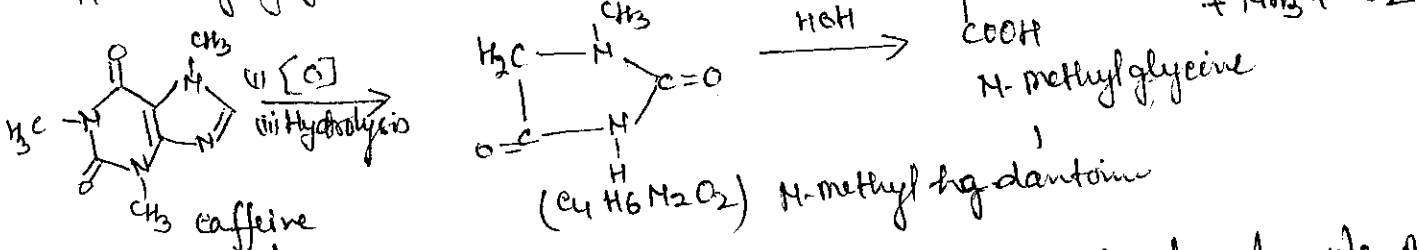
⇒ Thus partial structure of caffeine may have the following one.



(A) → 1- CH_3 group
→ 1- Oxygen atom
] does not accounted for.

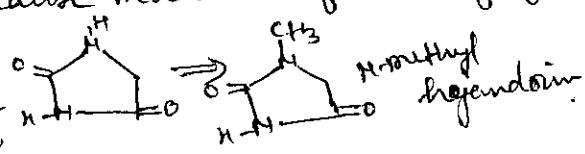
Position of Methyl Groups:

⇒ Fisher on oxidation found the following products which on hydrolysis gave N-methyl glycine, CO_2 and NH_3.

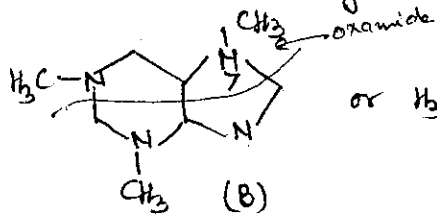


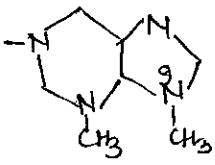
Thus the oxidation product is N-methyl hydantoin because molecular formula of hydantoin is $C_3H_4N_2O_2$.

$C_4H_6N_2O_2 \xrightarrow{-CH_2} C_3H_4N_2O_2$ Hydantoin



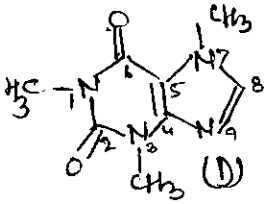
⇒ Fischer also isolated N,N' dimethyl oxamide ($CH_3-NH-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-NH-CH_3$), which can only be obtained if the caffeine has following structure.

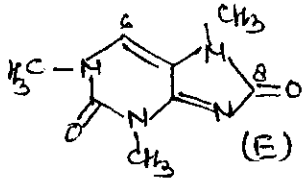


or  (C) This structure is ruled out because it does not give oxamide.

⇒ Thus the 3rd methyl group is present at position 7 not at position 9

Position of oxygen: On the basis of above reaction and conclusion, now caffeine may have following two structures and the position of oxygen may be either at the position 6 or at 8.

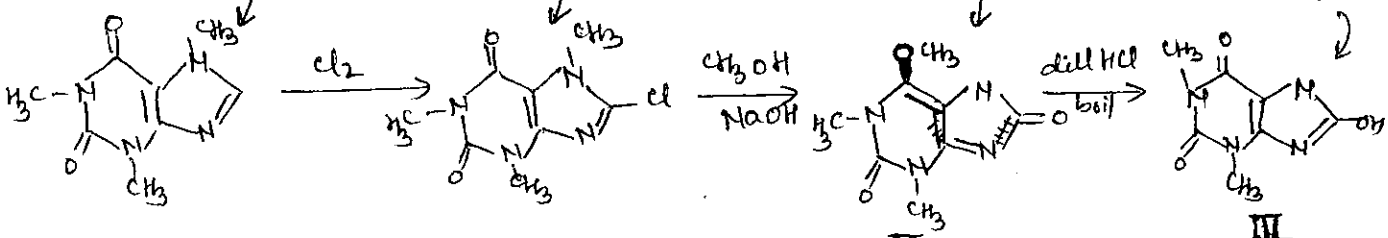

(D)

or 
(E)

⇒ Structure D was accepted by analogy with uric acid. By a series of reaction Fischer showed that structure D is the structure of caffeine as follows:

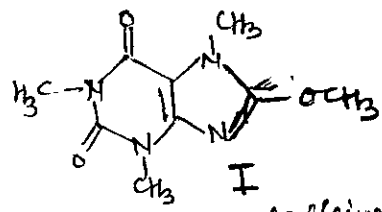
caffeine $\xrightarrow{Cl_2}$ chlorocaffeine $\xrightarrow[NaOH]{CH_3OH}$ Methoxy caffeine $\xrightarrow[boil]{dilHCl}$ oxy caffeine

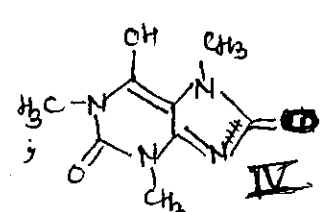
$C_8H_{10}N_4O_2$ $C_8H_9ClN_4O_2$ $C_8H_9N_4O_2-OCH_3$ $C_8H_{10}N_4O_3 + CH_3Cl$



→ oxycaffeine on further methylation in presence of MeI / Ag, NaOH gives tetramethyl uric acid ← methylation MeI / Ag, NaOH oxycaffeine

Therefore oxycaffeine was identical with trimethyluric acid. Thus the structure of methoxy caffeine is either I or II and of oxycaffeine may be either III or IV


I
Methoxy caffeine

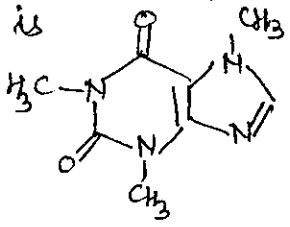

IV
oxycaffeine

⇒ When oxycaffeine or its silver salt, treated with MeI, it gave the mixture of tetramethyl uric acid (having 4 N-methyl groups) & methoxy

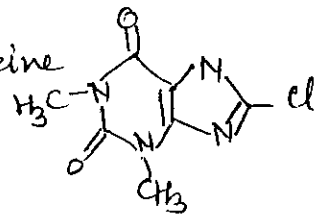
caffeine (having three -N-methyl group & one methoxy group). This means that oxycaffeine is a tautomeric, amido-imidol triad system.

$$-NH-\overset{1}{C}=O \rightleftharpoons -N=\overset{1}{C}-OH$$

This triad system can only exist in imidazole nucleus of oxycaffei because neither nitrogen atom in the pyrimidine ring is attached to a h -gen atom. It means structure IV can give rise this tautomeric systen while V is not. Thus methoxy group in methoxy caffeine is in imidazole nu and consequently chlorine in chloro caffeine. Thus the structure of caf is

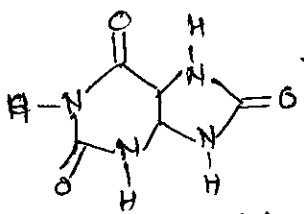


& of chloro caffeine



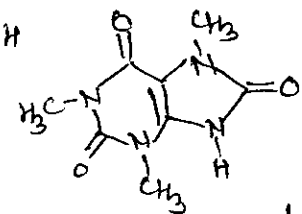
⇒ Finally, the structure of caffeine is confirmed by its synthesis:

(1) Fischer (1899)



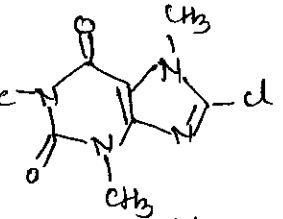
Uric Acid

$CH_3I/NaOH$ 1:3 →



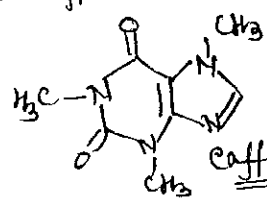
1,3,7 trimethyl uric Acid

PCl_5 or $POCl_3$ →



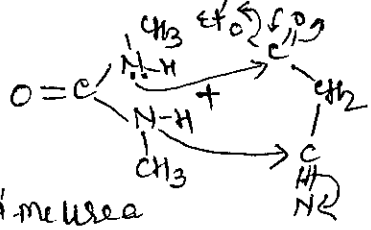
chloro caffeine

HI →



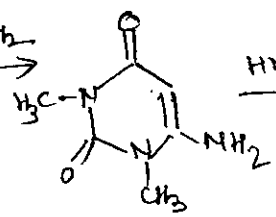
caffeine

Commercially it has been synthesized by Traube's method:

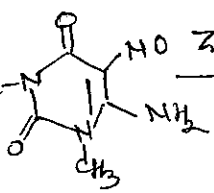


N,N' methyl urea

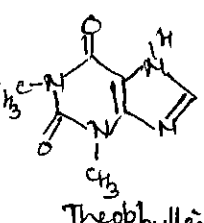
$NaNH_2$ →



HNO_2 →

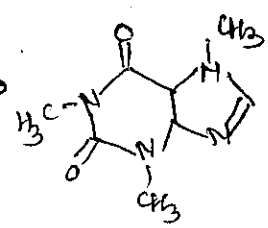


Zn/H_2SO_4, $H-\overset{O}{\overset{\|}{C}}-OH$, △



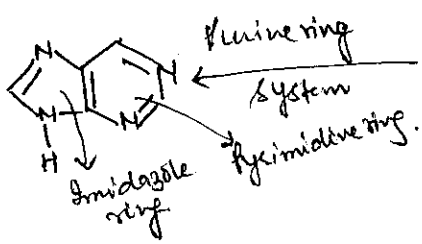
Theophylline

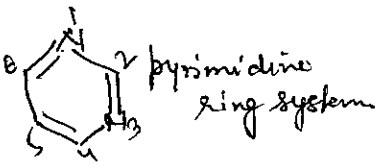
CH_3I / EtOH, $EtONa$ →



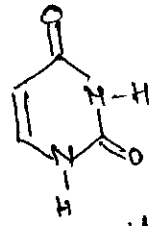
caffeine

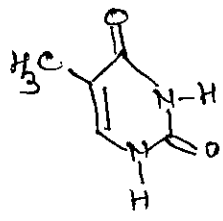
Purines and Pyrimidines

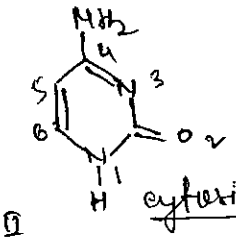




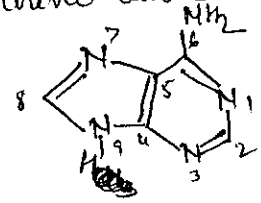
⇒ Pyrimidine bases are uracil I, thymine II and cytosine III

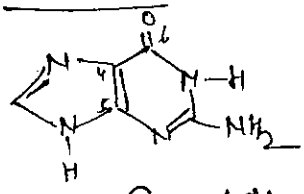

Uracil I

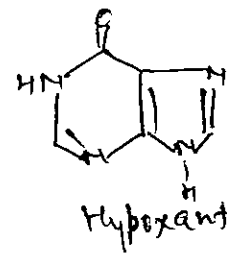

Thymine II


cytosine III

⇒ Purine bases are: Adenine IV and guanidine V.


Adenine IV

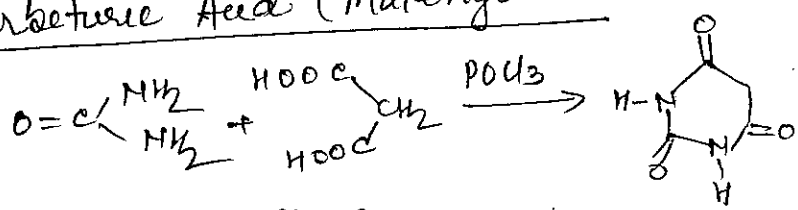

Guanine V

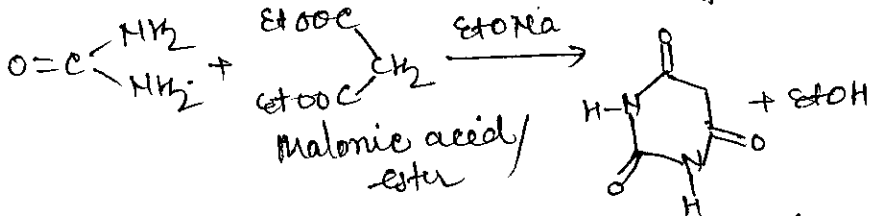

Hypoxanthine.

Pyrimidines:

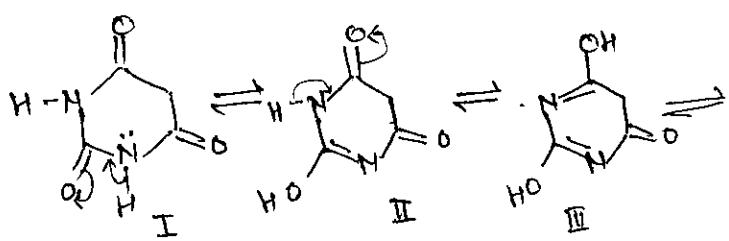
⇒ cyclic ureides containing a six membered ring (i.e. component of urea and acid or anhydride or active methylene compound)

Barbeturic Acid (Malonylurea).





Barbeturic acid is a solid, sparingly soluble in water, mp. 253°C. It can exist in the following tautomeric form:



Imido - enol type tautomerism
2,4,6 trihydroxy pyrimidine,
It explains the acidic nature of barbeturic Acid.

⇒ It can form Oximino derivative with HNO_2 acid. i.e it has active methylene group, hence structure I, II & III are main contributing

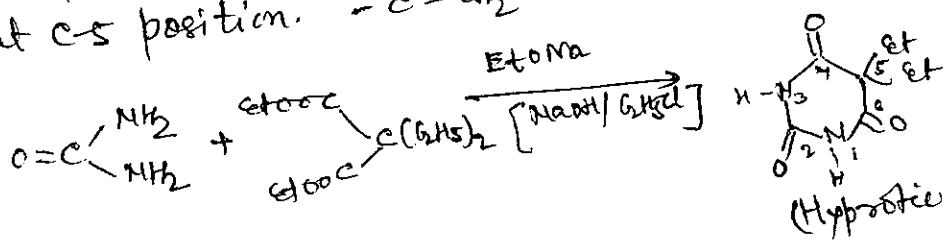
structures. Furthermore, it is very difficult to acylate hydroxyl present at 2,4,6 position. ie structure I is the main contributing structure than II and III.

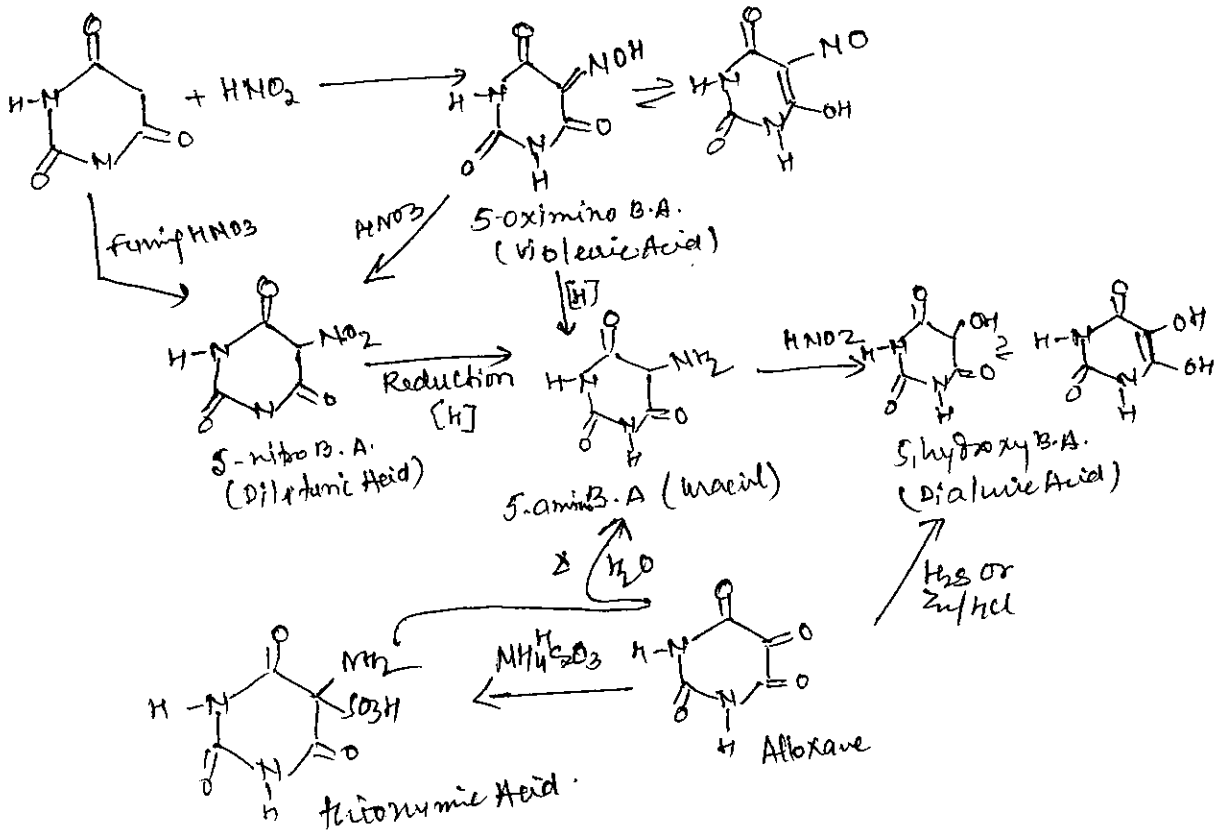
⇒ Methylation (MeI / NaOH) results the formation of N-methyl derivative, which also supports the structure I

⇒ However, it is also possible that all the hydroxyl group get replaced by chlorine atom with $POCl_3$, thus structure IV is main.

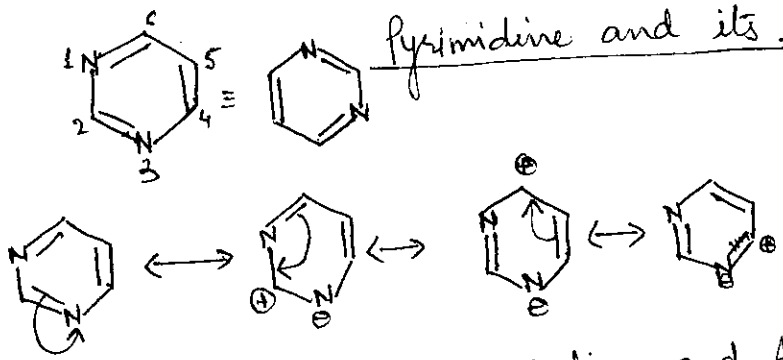
⇒ X-ray analysis has shown that structure I is the major form in the solid state and molecule is also planar.

⇒ Bromination and nitration takes place at C_5 position. It can react with alkali metal to form alkali derivative (like sodium derivative) at C-5 position, so one or two alkyl groups can be introduced at 5 position i.e. Barbeturic Acid behaves as active methylene group at C-5 position. $-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-$





Pyrimidine and its Derivatives



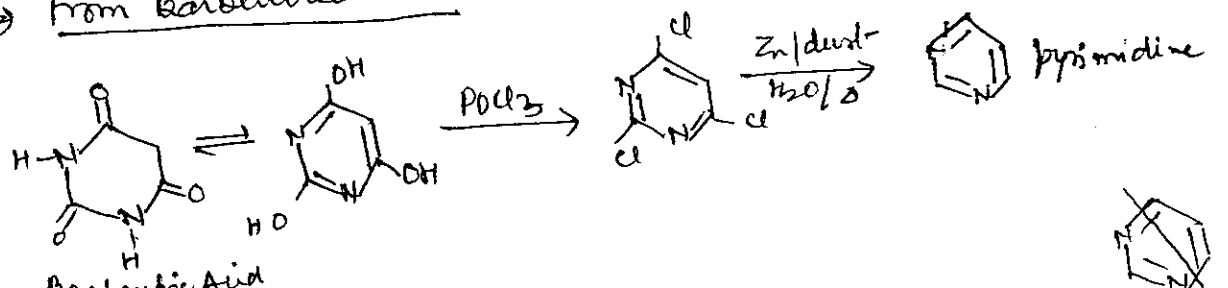
⇒ Pyrimidine is neutral in solution and forms salt with acids i.e. have some basic character. Due to presence of two nitrogen atom as N-C-N unit ring is deactivated and relatively the electron density at C-5 position is more but not much enough to facilitate the easy attack of electrophile.

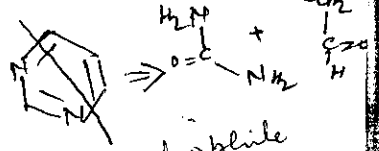
⇒ Nucleophilic reagents attack easily at position ~~two~~, C_2, C_4 & C_6 for e.g. chlorine atom at C_4, C_2, & C_6 can be readily replaced by -OH or $-NH_2$ groups and $-NH_2$ group at C_2 or C_4 is replaced by -OH group by simple boiling with water.

⇒ Pyrimidine ring is aromatic but by the introduction of -OH & $-NH_2$ group at C_2/C_4 or C_6 aromaticity decreases and diminishes.

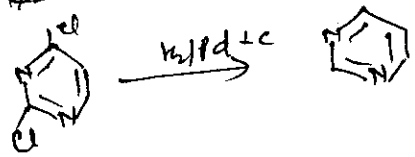
Synthesis of Pyrimidine and its derivative:

⇒ From Barbeuric Acid: (Gabriel 1900)

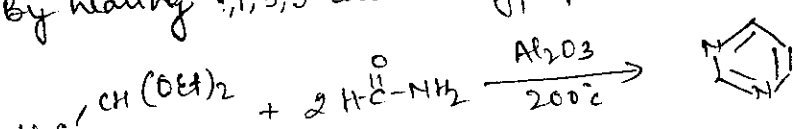




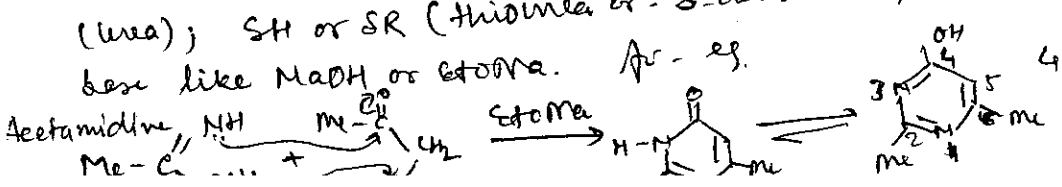
⇒ Reduction of ~~XOR~~ dichloropyrimidine.

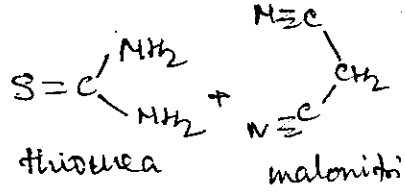


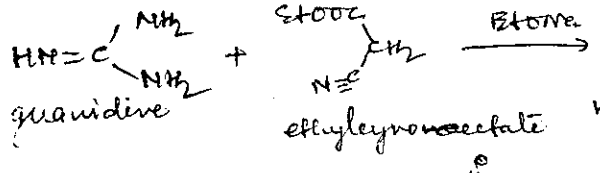
⇒ By heating 1,1,3,3-tetraethoxypropane & formamide

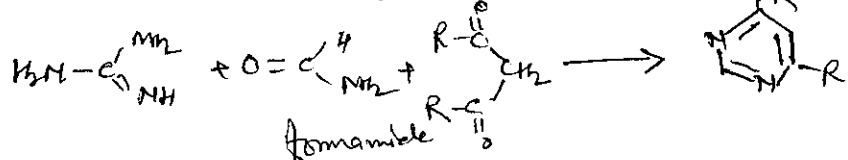


⇒ By the condensation reaction between compound like Y CH_2 Z (where Y & Z = -COR, -COOR, etc) with compound having amidine structure. $R-C(=NH)-NH_2$ (where R = R(amidine), -OR (urea); SH or SR (thiourea or -S-derivative), NH_2 (Guanidine)) in the presence of base like NaOH or ~~KOH~~ KOtBu. Ex - eg.

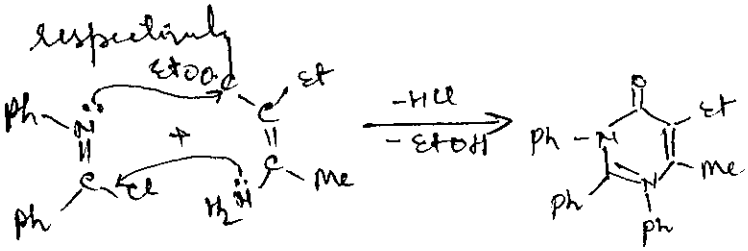


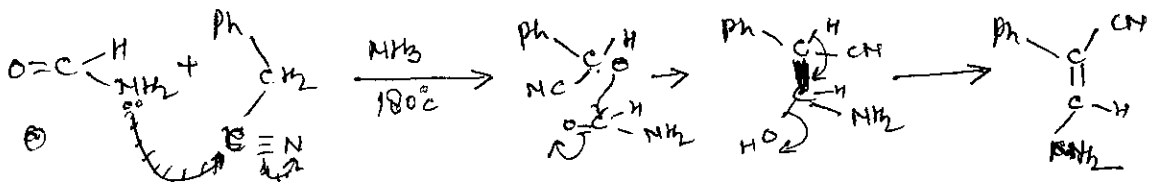
(ii) 
thiourea + malonitrile → 4,6 diamino 2-mercaptopyrimidine.

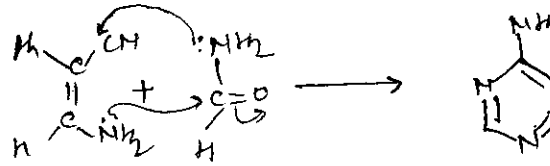
(iii) 
guanidine + ethylcyanoacetate → 2,6 diamino 4, hydroxy pyrimidine

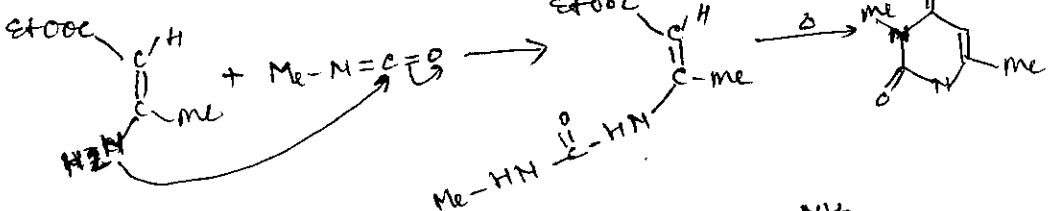
(iv) 
formamide → 4,6-di substituted pyrimidine.

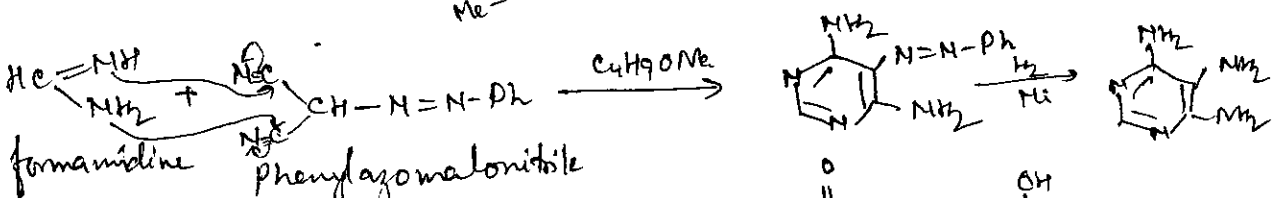
condensation Reaction between molecules containing C-C-C-N & C-N units respectively

(i) 

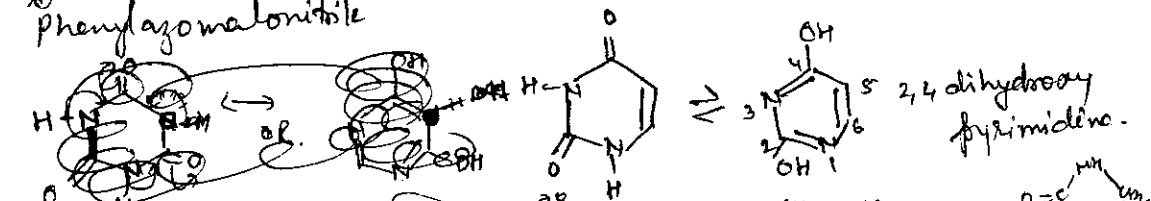
(ii) 

(b) 
4, Phenyl pyrimidine

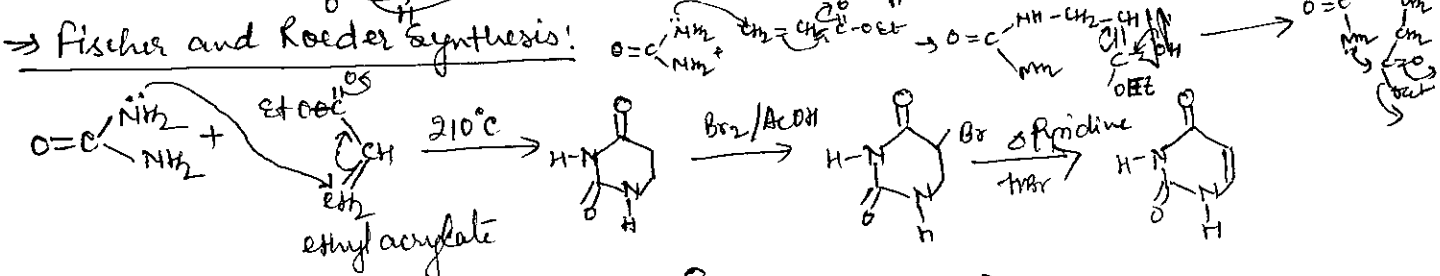
(iii) 

(iv) 
formamidine + Phenylazomalonitrile

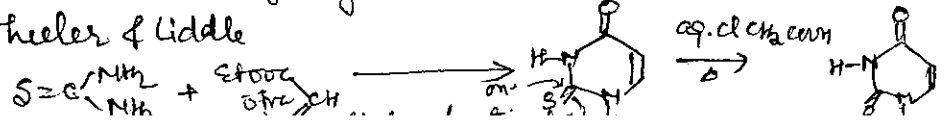
Uracil:


2,4 dihydroxy pyrimidine.

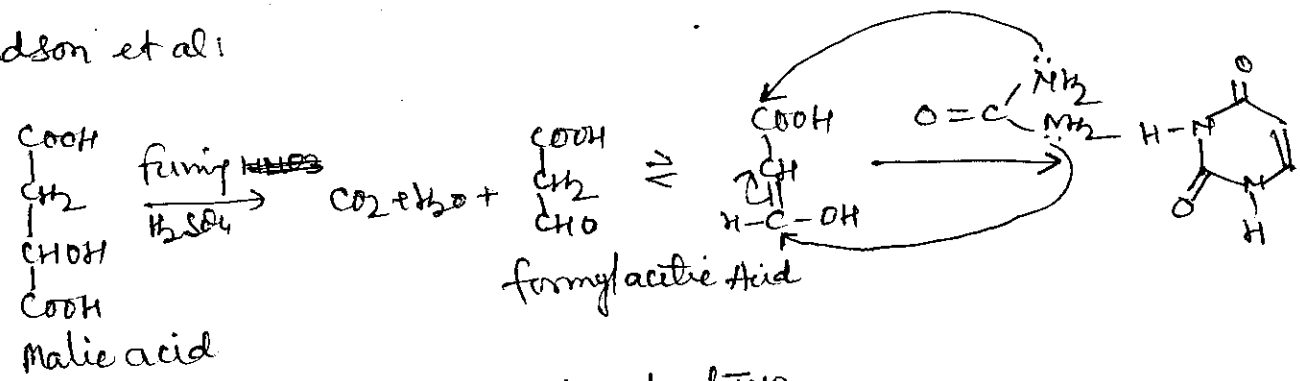
(i) ⇒ Fischer and Roeder Synthesis:


ethyl acrylate

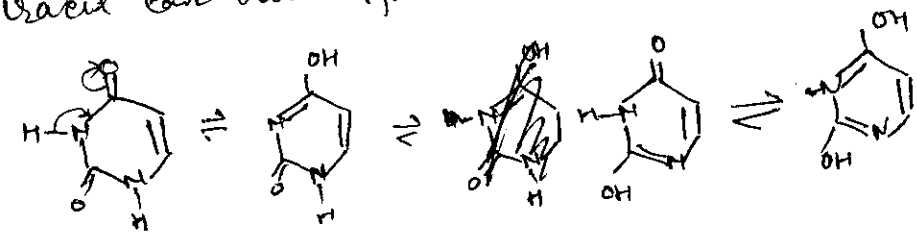
(ii) ⇒ Wheeler & Liddle



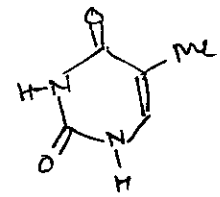
⇒ Davidson et al:



⇒ Uracil can have four tautomeric structures

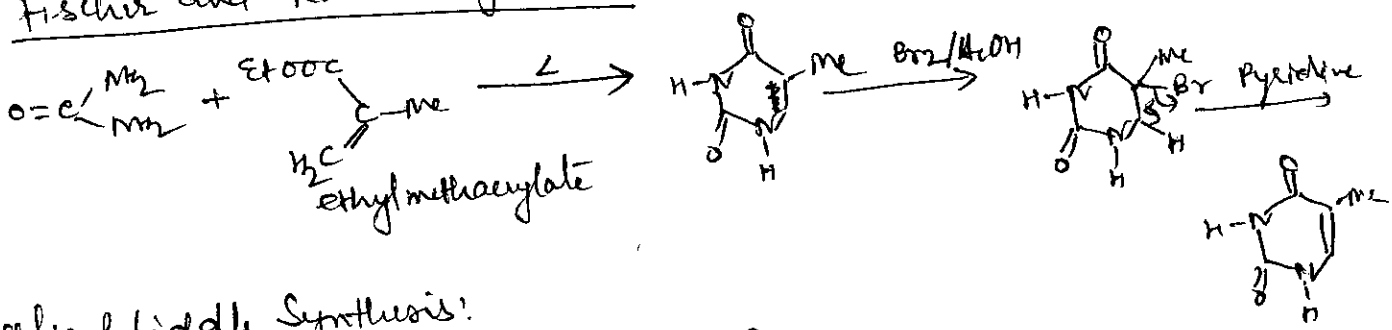


THYMINE (5- Methyl uracil, 2,4 dihydroxy 5-methyl pyrimidine)

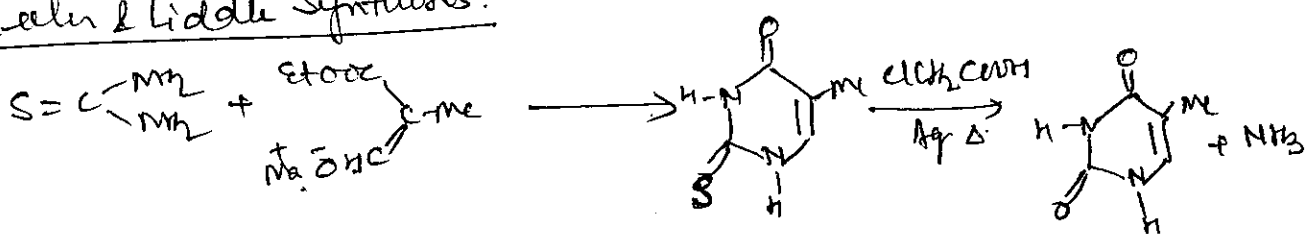


Synthesis:

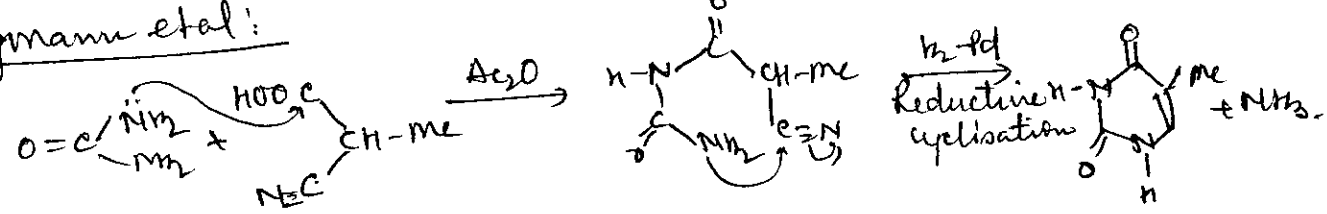
Fischer and Roeder Synthesis:



Wheeler & Liddle Synthesis:

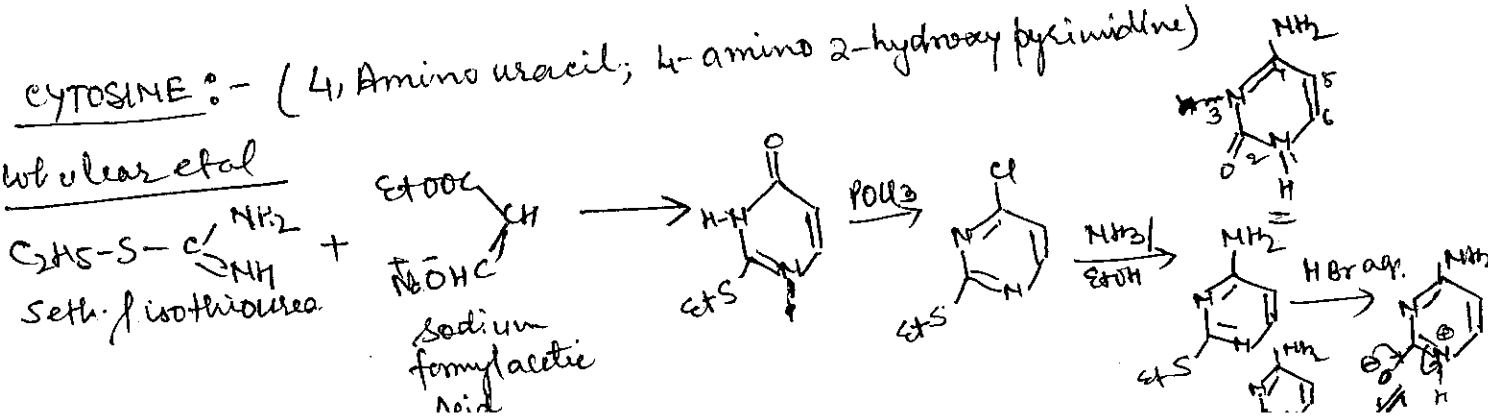


Brugnami et al:

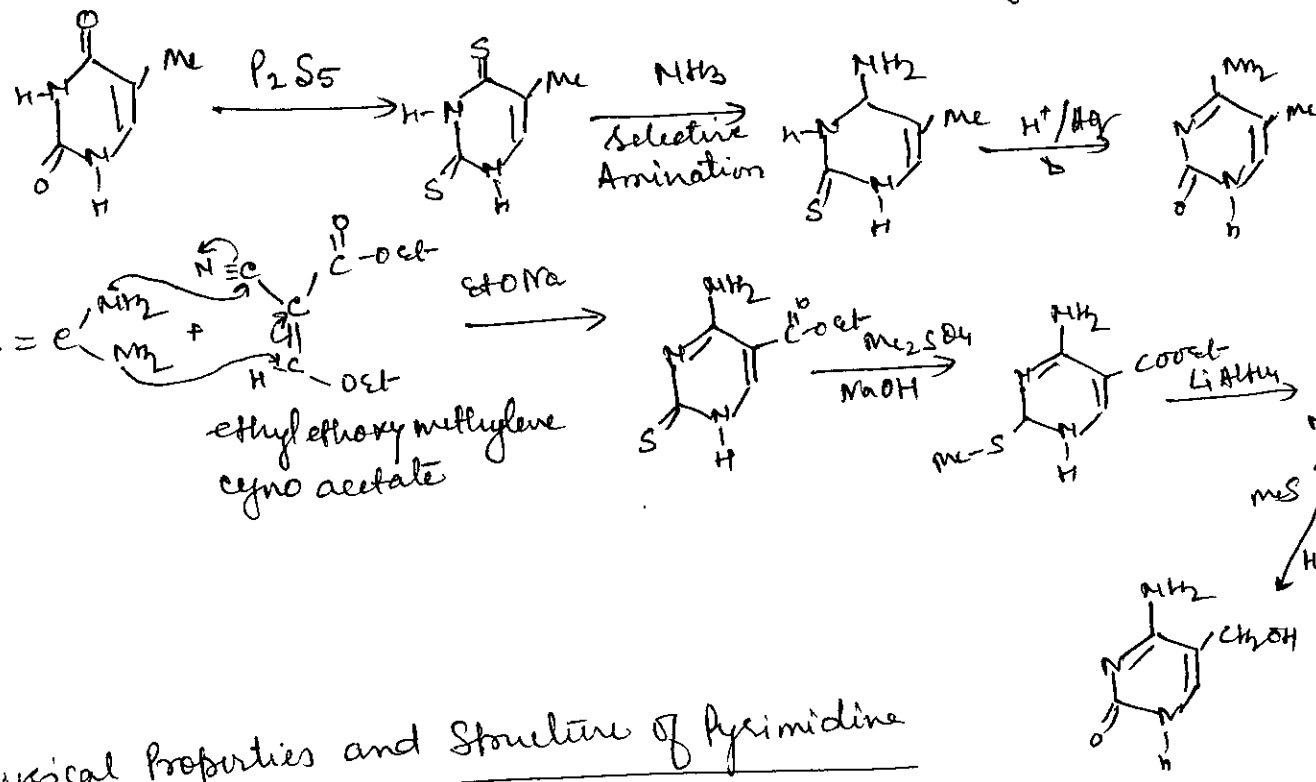


CYTOSINE :- (4, Amino uracil; 4-amino 2-hydroxy pyrimidine)

Wheeler et al

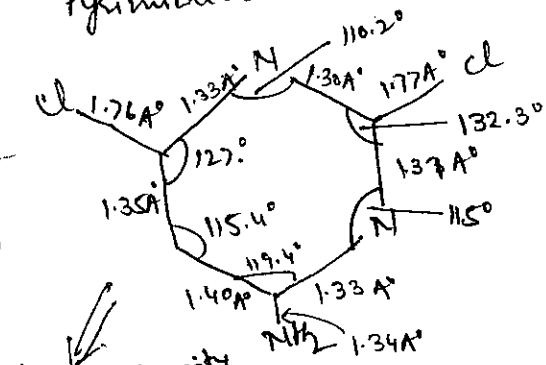


Methylated cytosine has been synthesized by Hitchings et-al. from thymine



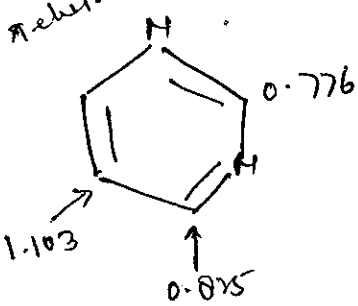
Physical Properties and Structure of Pyrimidine

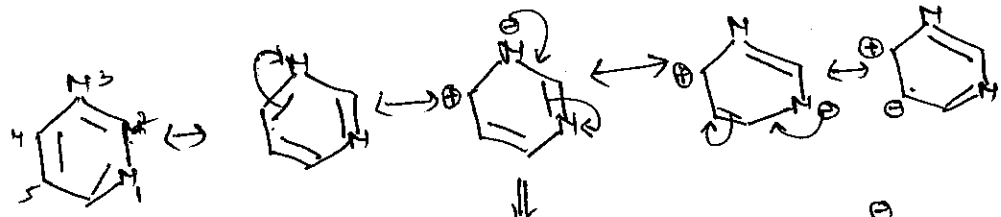
Pyrimidine is colourless compound, m.p = 22.5°C ; BP = 124°C.



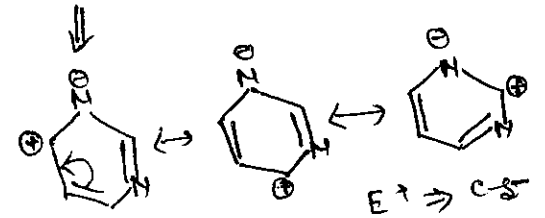
Ring is not symmetrical and difference between the bond length and angles of these ring systems suggests that pyrimidine is the least aromatic R.E calculated by m.o method → Benzene = 36 Kcal/mole ; Pyridine = 31 Kcal/mol, Pyrimidine = 26 Kcal/mol from heat of combustion pyrimidine = 80 Kcal/mol.

π-electron density

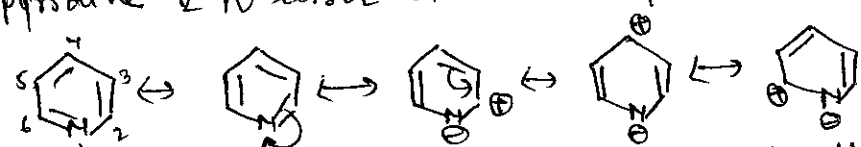




Resonance structure



⇒ Pyrimidine (pKa = 1.3) is much weaker base than pyridine (pKa = 5.23) or imidazole (pKa = 7.2) or Amidine. Pyrimidine can be considered best as a derivative of pyridine & to lesser extent as cyclic amidine.

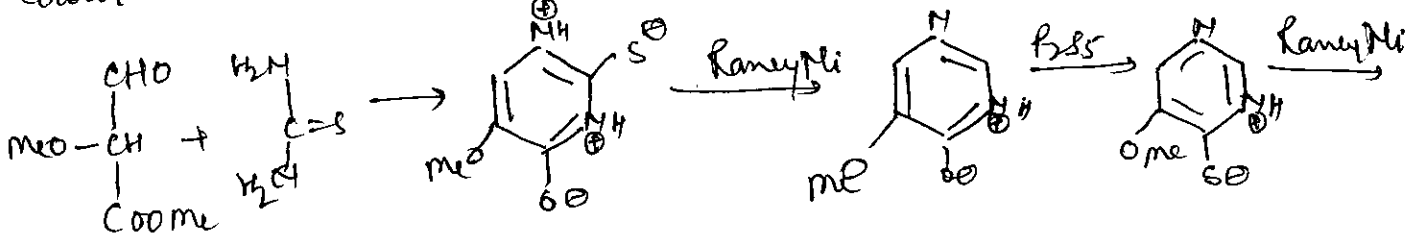
⇒  Pyridine C-3 E+.

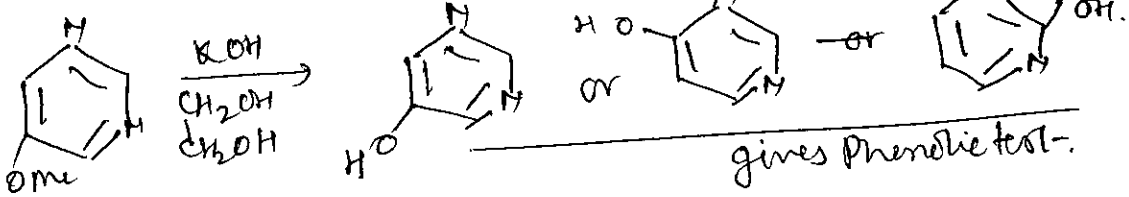
on the basis of charged structure and π e density at respective position of pyridine and pyrimidine; C-5 position of pyrimidine corresponds to C-3 position of pyridine and pyrimidine; C-5 position of pyrimidine corresponds to C-3 position of pyridine and is the most suitable site for electrophilic attack. Pyrimidine hydrochloride

can be brominated at C-5 position like pyridine but no other electrophilic substitution are known.

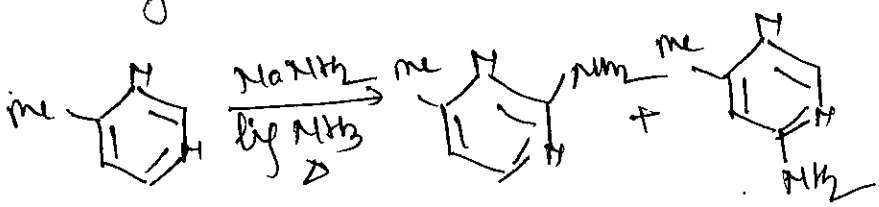
⇒ If activating group like -OH, -NH₂, etc are present then other ES reaction like Nitration, diazo coupling etc can take place but only at C5 position.

⇒ Groups present at C-5 position have similar properties to those exhibited by the same substituents at position C-3 of pyridine or present at benzene ring. e.g. 5-hydroxy pyrimidine. It has phenolic properties and gives red Fecl₃ colour.

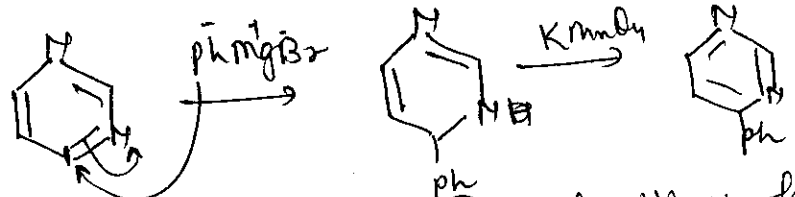




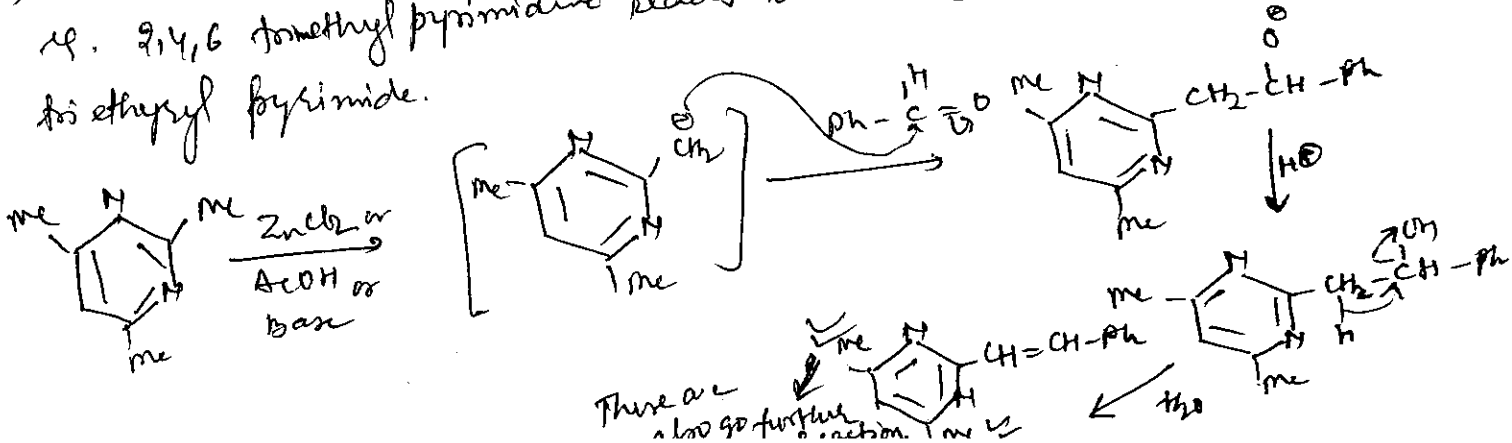
⇒ Similarly C₂, C₄, C₆ positions of pyrimidine corresponds to C₂/C₄ position of pyridine & thus can be attacked by nucleophilic reagents. like NaNH₂ or PhMgBr.



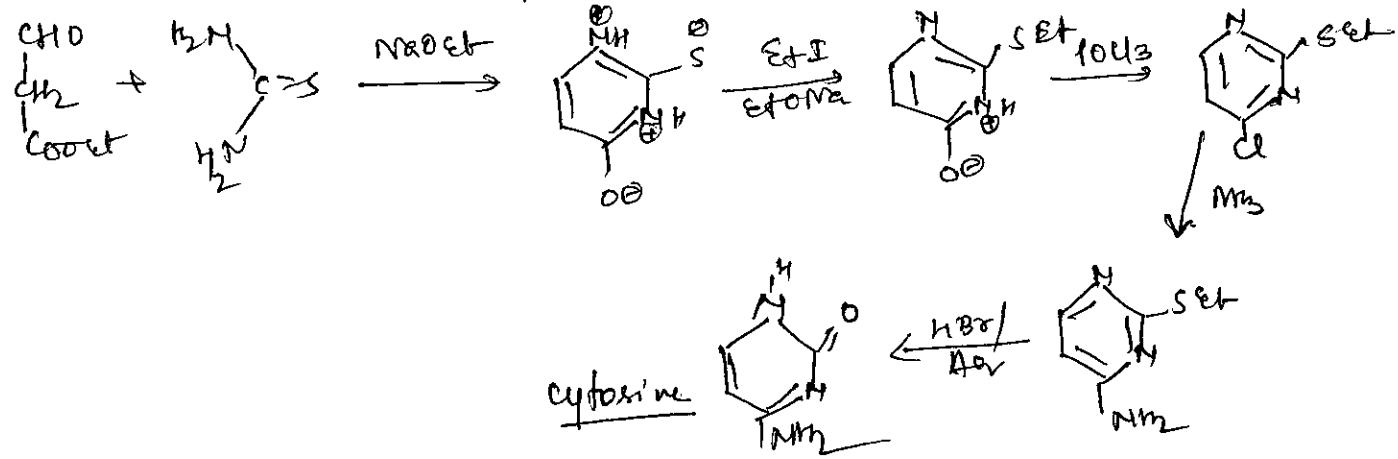
Chichibabin reaction.



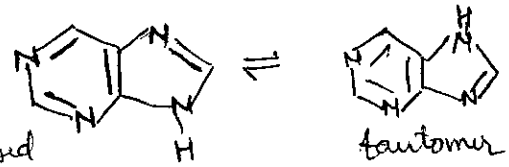
⇒ Substituents at C-2, C4 and C6 positions have comparative reactivities e.g. 2,4,6 trimethyl pyrimidine reacts with benzaldehyde to form 2,4,6 tri ethenyl pyrimidine.



⇒ Halogen atoms & methoxy and methyl mercapto groups at position 2, 4, or 6 in pyrimidine can be replaced by amino group on treatment with NH_3 or by hydroxyl group on hydrolysis with dil HCl.



PURINES



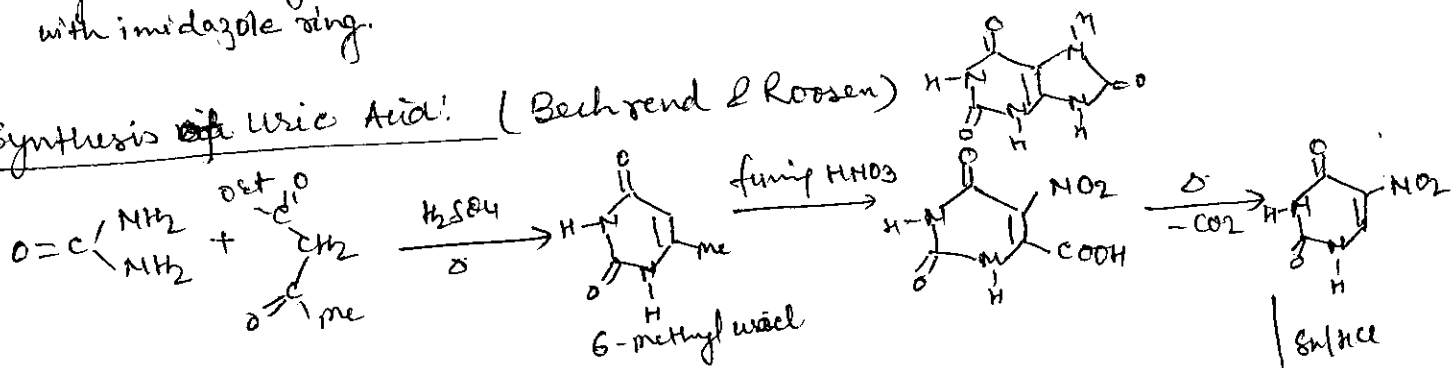
⇌ (Cyclic diureides)

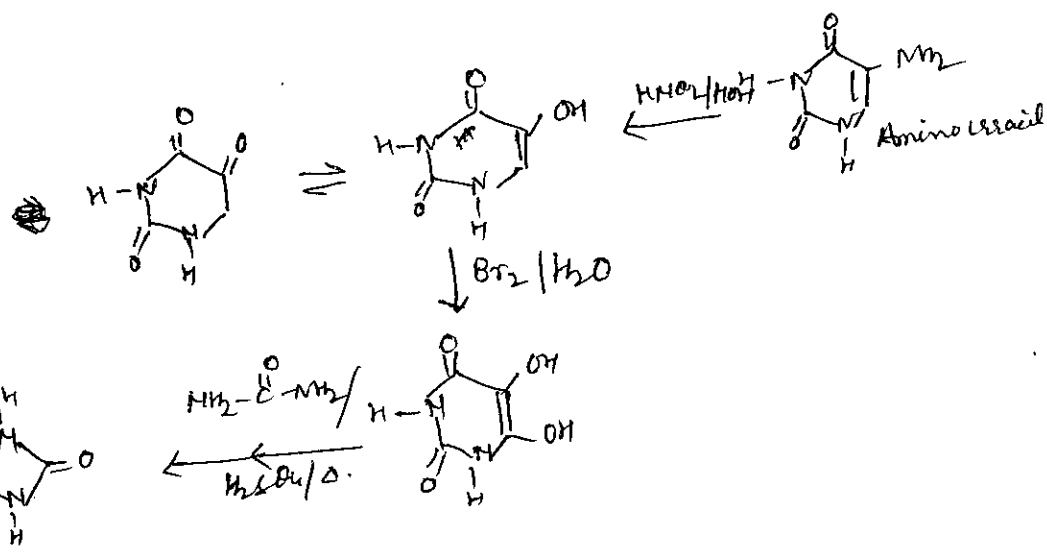
tautomer

⇒ Pyrimidine ring is fused with imidazole ring.

↓ Fischer gives the name

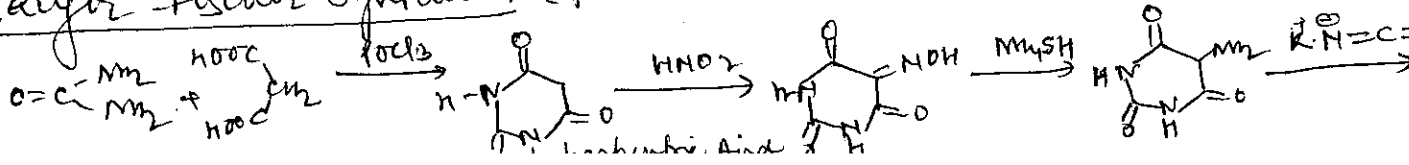
Synthesis of Uric Acid: (Bechrend & Roosen)

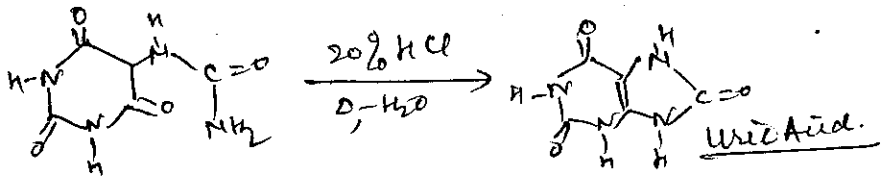




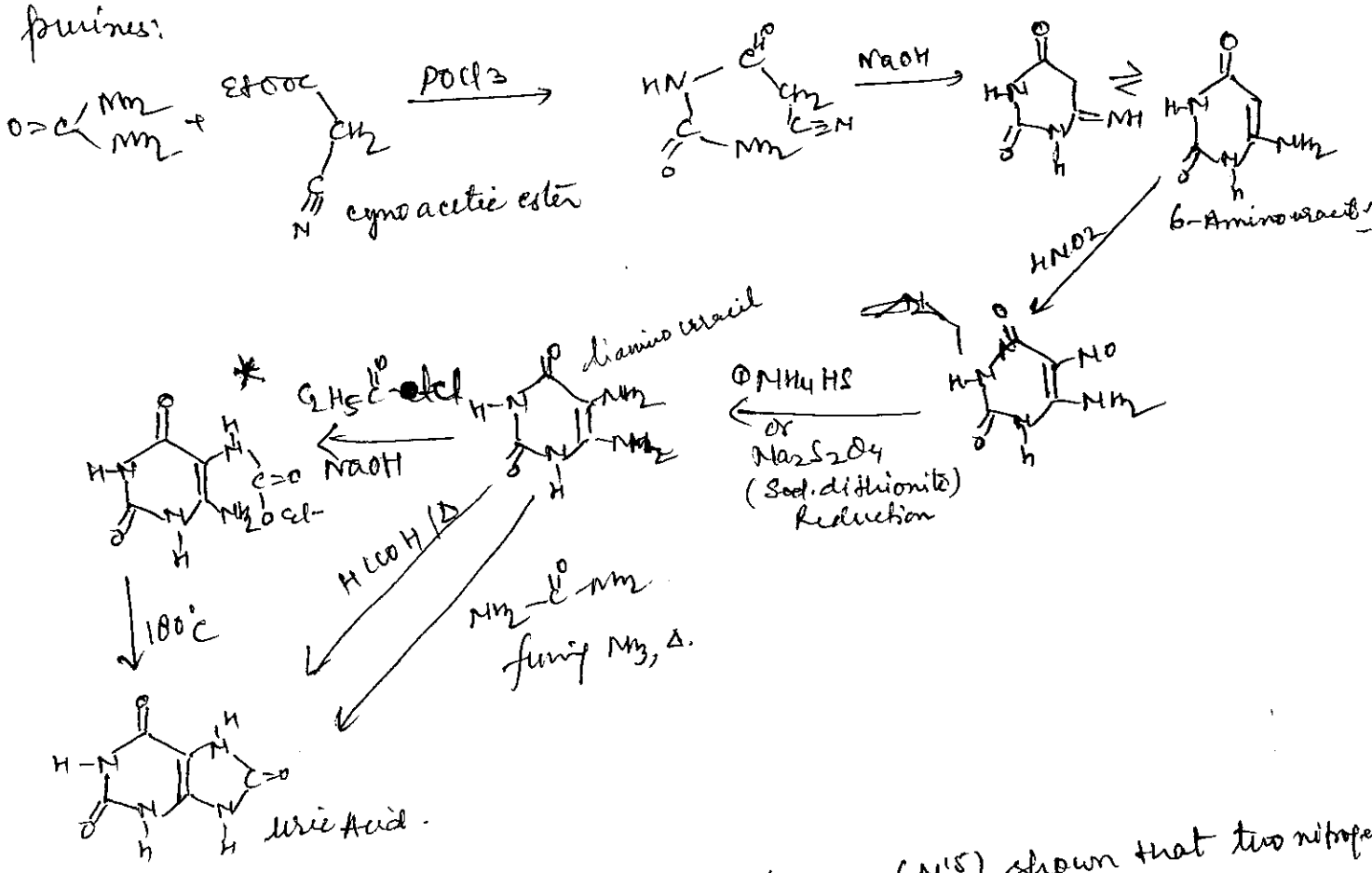
Uric Acid

Bayer-Fischer Synthesis: (from barbituric acid)

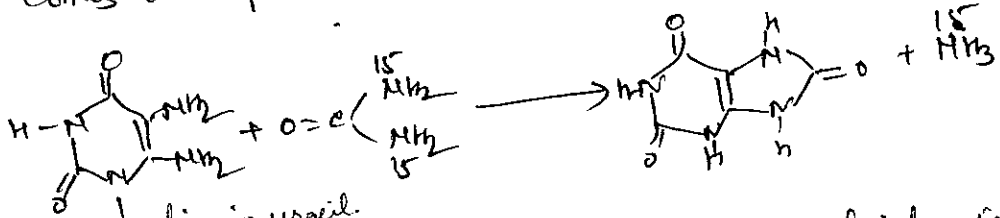




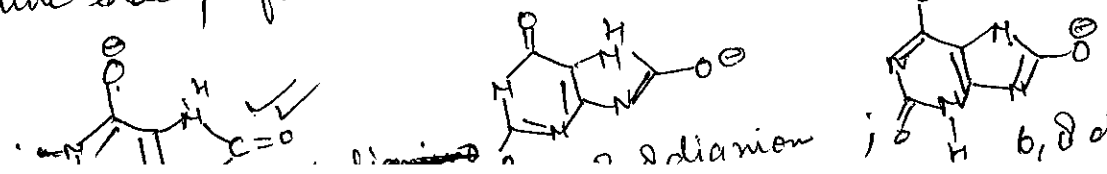
⇒ Traubes Synthesis: This method can be used for commercial preparation of purines:



⇒ Clauis etal: By using the labelled urea (N^{15}) shown that two nitrog atoms in the diamino uracil are retained on fusion with urea & NH_3 is comes out from urea molecule.

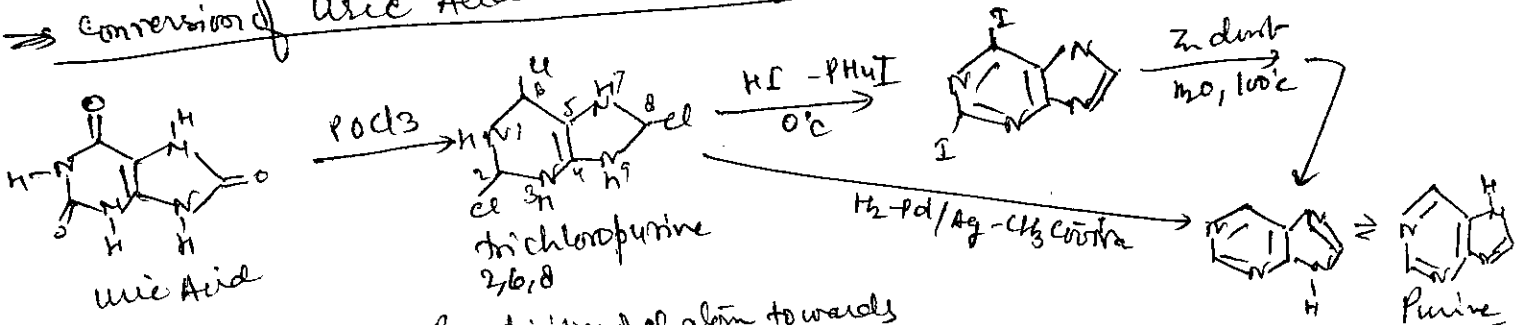


⇒ Uric Acid is a white, crystalline powder which is insoluble in the organic solvents but water soluble. It behaves as a weak dibasic Acid. It can form mono and as well as disodium salt. Thus it can have following forms in which it can form salt but it is still not clear which structure exactly form the salt.



out of above structure the possible structure may be of 2,6 dianion because in this structure pyrimidine ring of purine becomes aromatic and will be stabilized by resonance. This is further supported by the fact that in the 2,6 form the spectra of purine and pyrimidine has some similarity.

⇒ Conversion of Uric Acid to nucleus of purine:



Uric Acid

trichloropurine 2,6,8

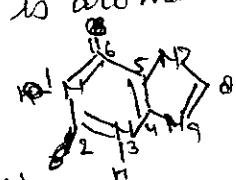
Reactivities of Cl atom towards Nucleophilic reagent 6>2>8

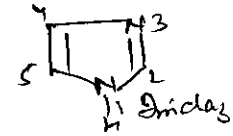
Purine

⇒ Purine also behaves as a weak monoacid base (pKa = 8.96) & can be methylated at C-9 position by diazomethane or dimethylsulphate & alkali

Convert :- Barbeuric Acid to Uric Acid
Purine
"
Uric Acid to purine
Synthesis of Barbeuric Acid
BA to Pyrimidine to phenyl pyrimidine

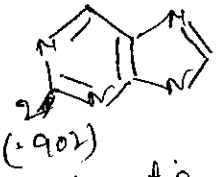
⇒ Purine itself is a colourless compound, mp = 212°C, soluble in water. The inter atomic distances shows that purine ring is aromatic.





Imidazole

⇒ Position 2,6 (and substituents present at these positions) of purine should be similar chemically to position 2 & 4 of pyrimidine & position 8 to the position of 2° imidazole. Purine (pKa 2.4) is a stronger base than pyrimidine (pKa = 1.3) i.e. is a weaker base but much stronger acid (acidic pKa = 8.9) than imidazole.



According to mol. orbital method π electron density.

* position 8 has lowest electron density that is why C-8 position is most susceptible to electrophilic attack.

* π electron density and localisation energy for 8 is in the order of 6>2>8 is only true for purine ring not for substituted ring. ES is dependent upon polarizability of the molecule being attached and on the properties of the molecule as in transition state. * Eg. 2,6,8 trichloropurine is replaced successively in the order 6, 2, 8 by nucleophilic reagent.

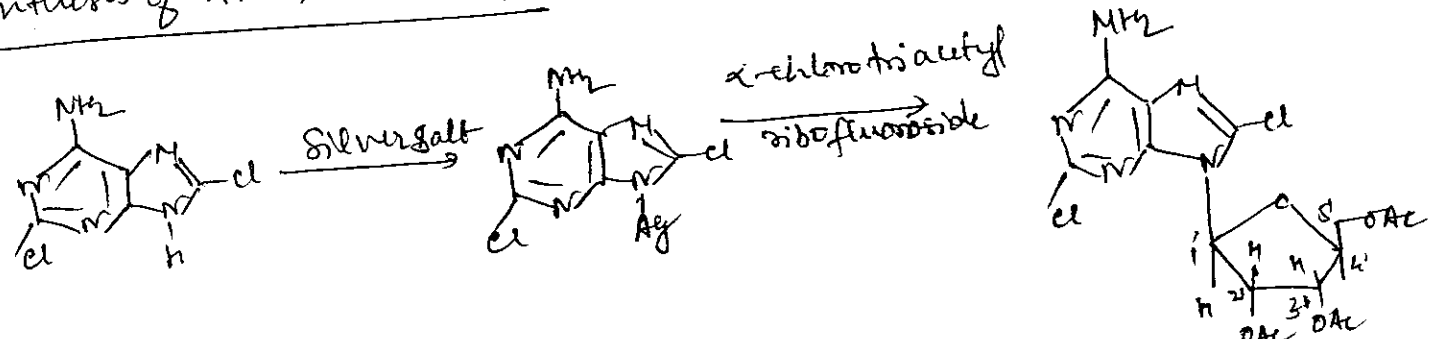
AMP

→ All the pyrimidine and purine nucleosides are hydrolytic product of RNA and DNA

RNA / DNA $\xrightarrow{\text{Hydrolysis}}$ Pyrimidine Purine Nucleosides $\xrightarrow{\text{Hydrolysis}}$ Purine + Pyrimidine bases + D ribose sugar → the spectra confirmed that sugar is attached with purine base at N9 position rather than N7 while pyrimidine at N1.

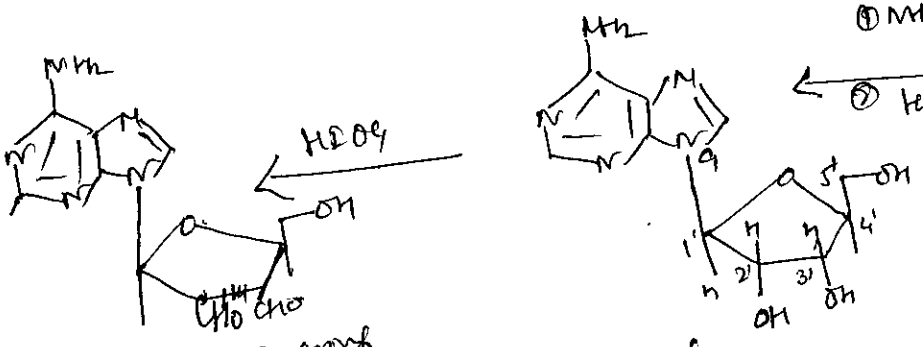
* Periodate oxidation of adenosine gives the dialdehyde & nicotinic Acid, showing that the sugar ring is furanose & linkage is β. X-ray crystallography has also confirmed that linkage b/w ribose sugar & base is through β linkage.

Synthesis of AMP, ADP & ATP:



① NH_3 / MeOH → Hydrolysis of Acetyl group

② H_2-Pd / $BaSO_4$ - Dehalogenation



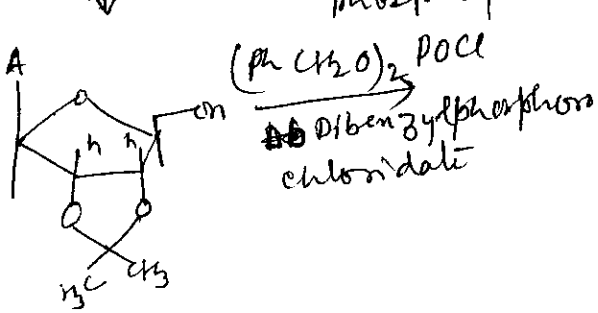
confirming the OH group is cis

$(CH_3)_2CO$ / H+

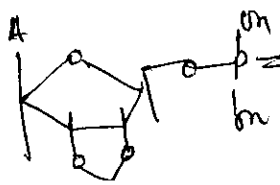
Phosphorylation

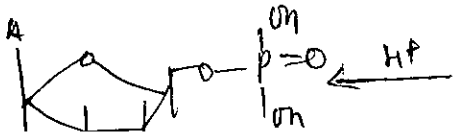
$(PhCH_2O)_2POCl$

Dibenzylphosphorochloridate



H_2 Pd



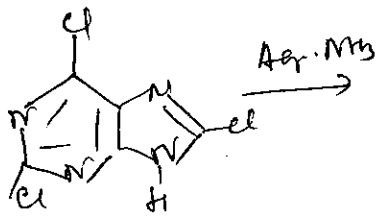


H+

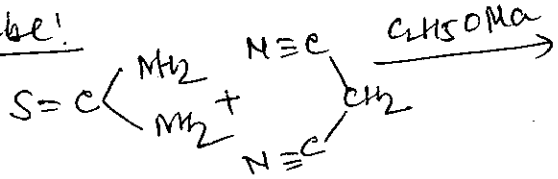
ADP ← ATP

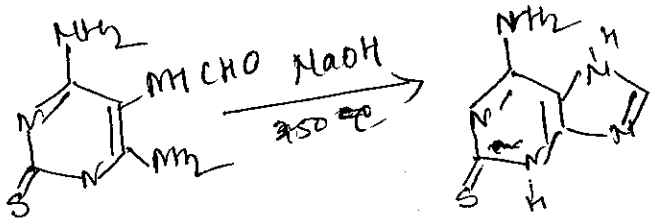
Adenine: (6-Aminopurine) found pancreas of cattle and in tea extra

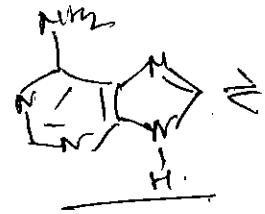
⇒ Fischer 2,6,8 trichloropurine



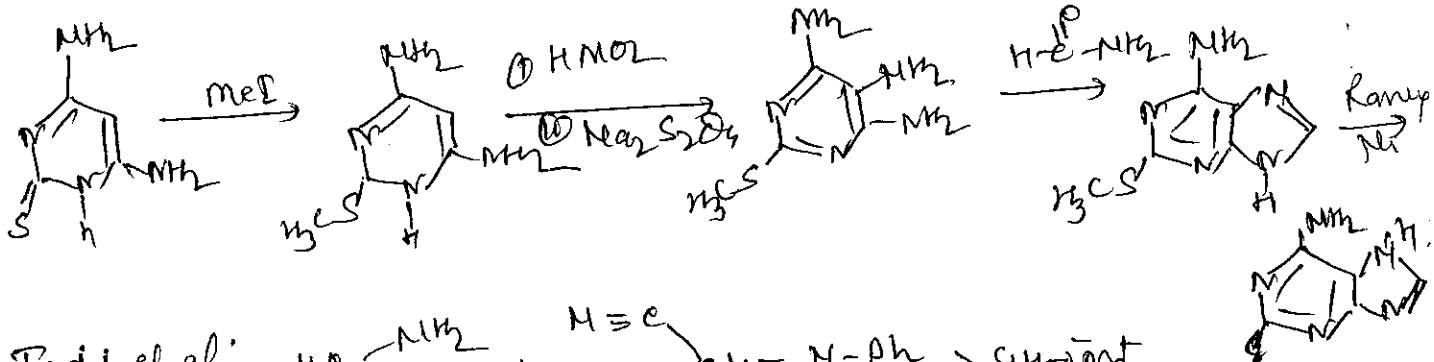
Traube:



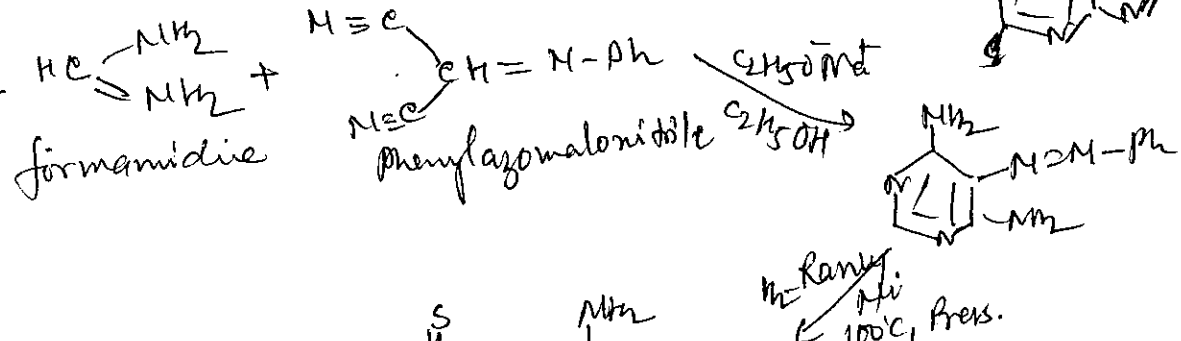


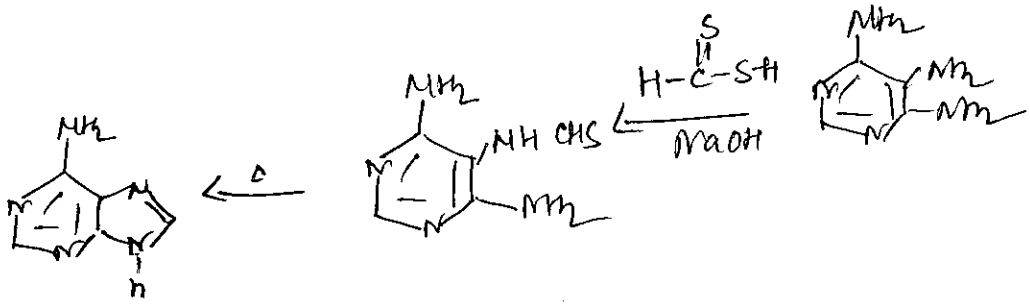


Modified Traube Synthesis:

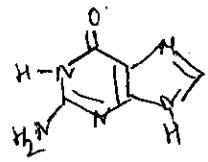


Todd et al:

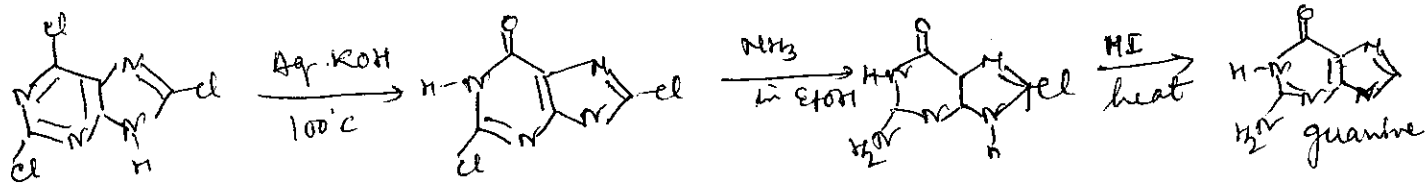




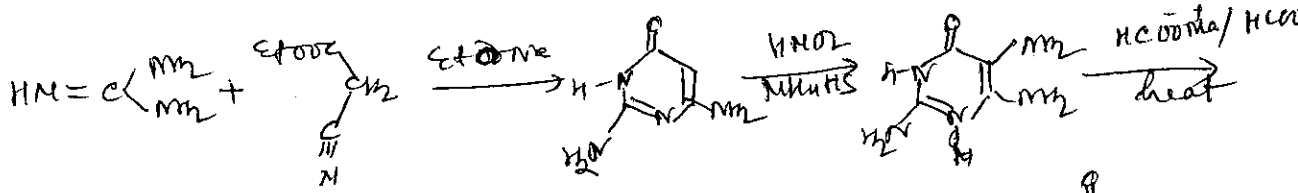
Guanine:

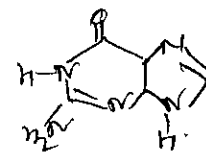


2- Amino 6-hydroxy purine



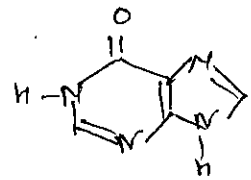
Traube

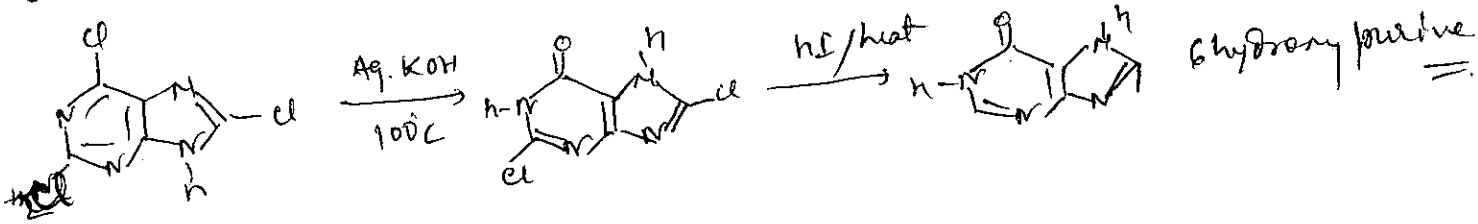




guanine

Hypoxanthein: 6-hydroxyl ~~purine~~ ~~uracil~~





6-hydroxy purine

Other Synthesis of Purines: