DRUG SYNTHESIS PART II

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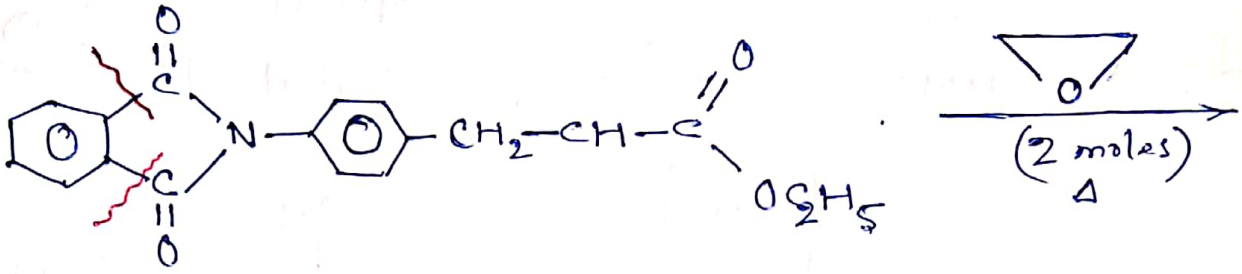
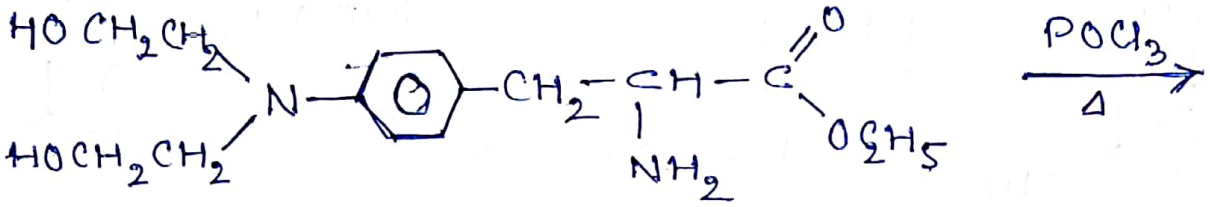
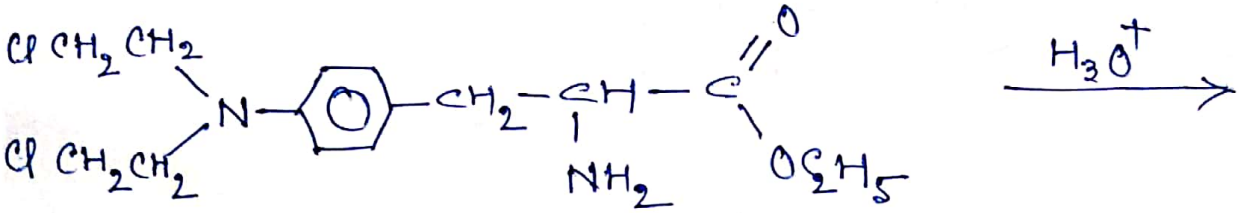
Melphalan: Proposed synthesis involves initial interaction between N-phthalimido-p-aminophenylalanine ethyl ester and oxirane (2 moles). Intermediate formed by hydroxy ethylation of the N-atom when acted upon by $POCl_3$ affords 4-[Bis-(2-chloroethyl)amino]-phenyl alanine ethyl ester. Finally the ester upon acid catalyzed hydrolysis gives the desired product.



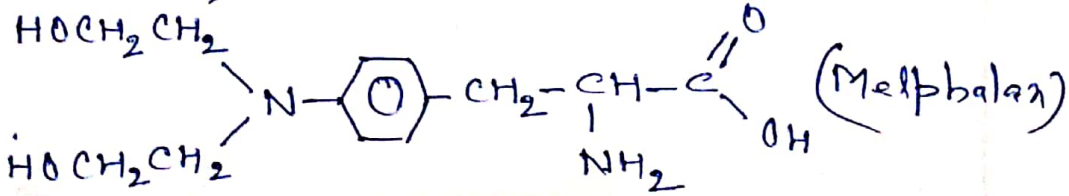
N-phthalimido-p-amino phenyl alanine ethyl ester.



Intermediate Product (L-isomer)

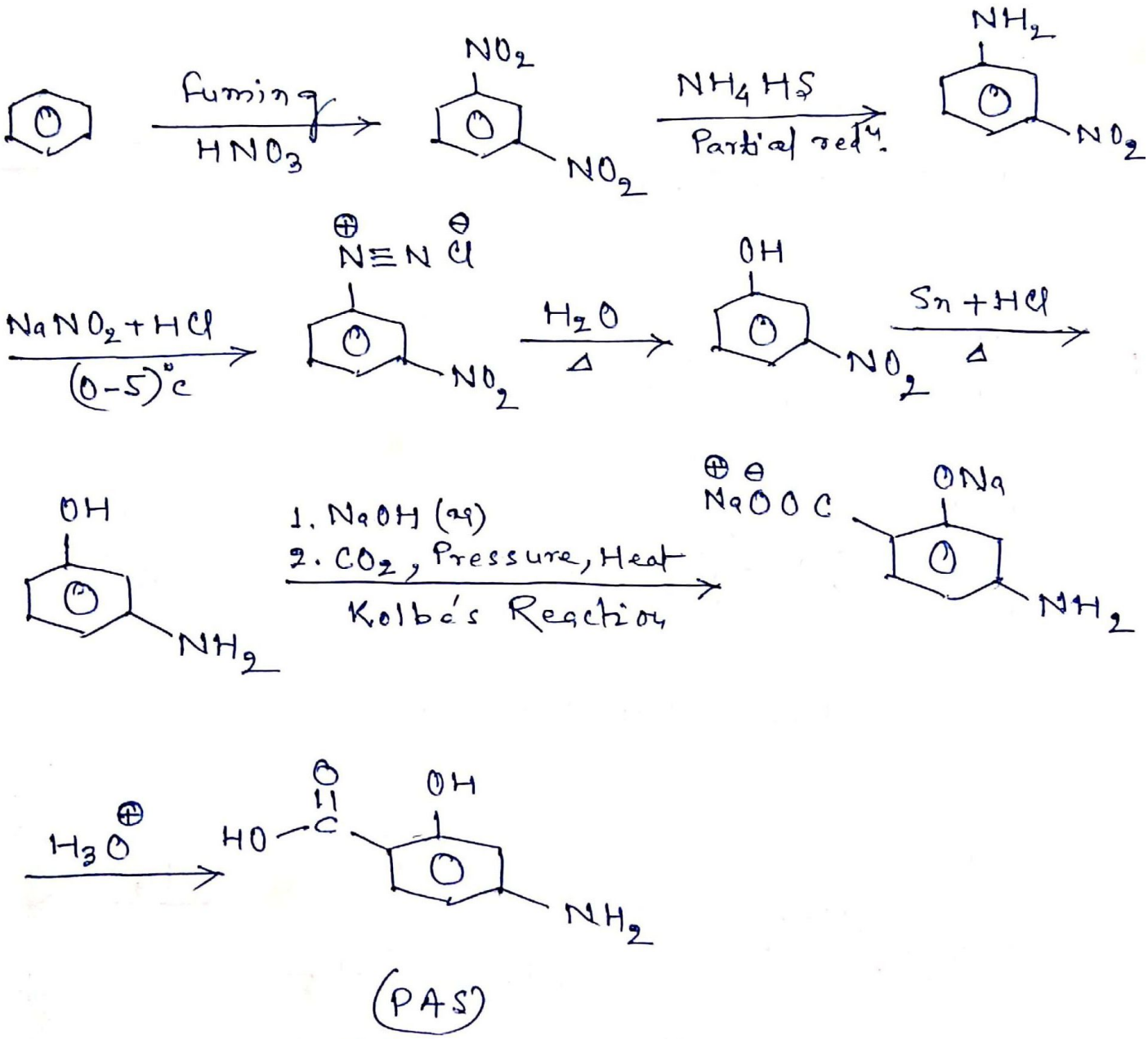


4-[Bis-(2-chloroethyl)amino]-phenyl alanine ethyl ester (L-isomer)



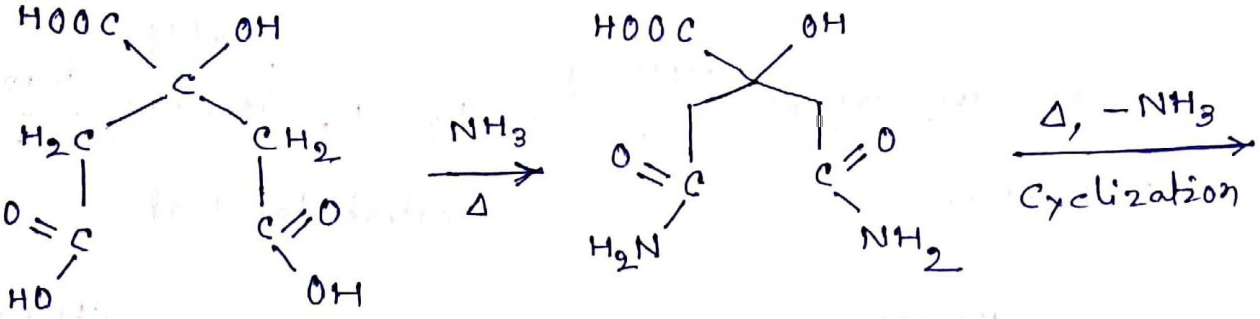
PAS : p-Amino salicylic acid :

Most widely used synthesis involves diazotization of m-nitroaniline followed by hydrolysis and reduction to produce m-aminophenol. Latter is subjected to carboxylation using Kolbe's reaction. final product is obtained by acid catalyzed hydrolysis.



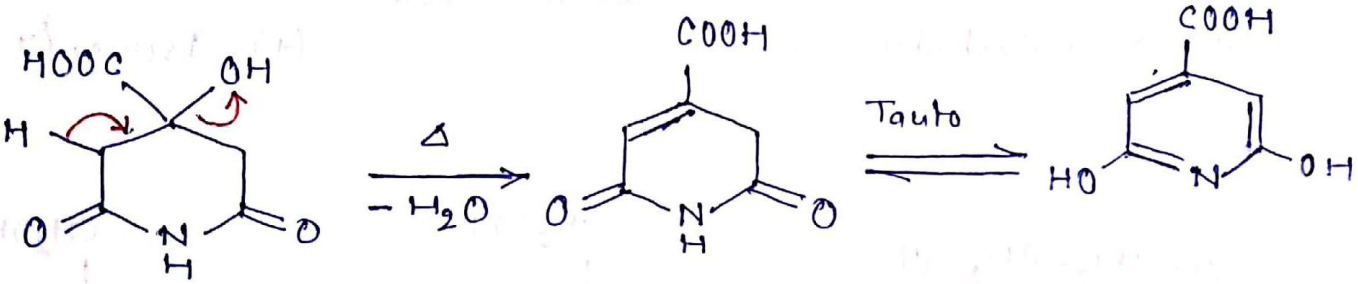
(PAS)

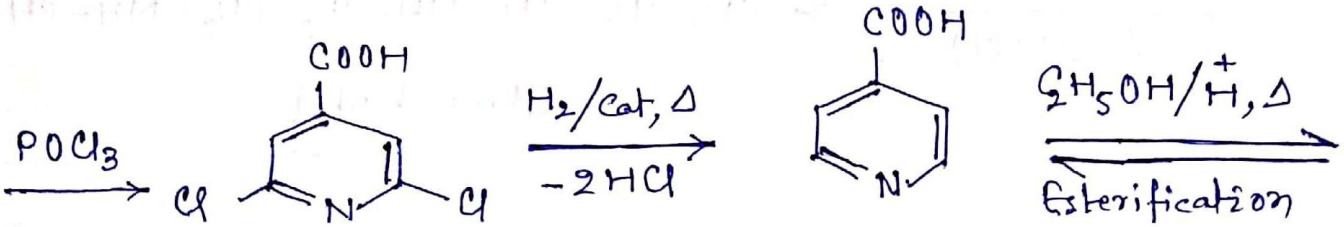
Isoniazid: In the starting step of the synthesis citric acid is selectively subjected to amination of terminal carboxylic groups followed by ring closure to afford 2,6-dihydroxy isonicotinic acid. The latter, on chlorination and catalytic reduction gives isonicotinic acid which on subsequent esterification and hydrazination finally gives isoniazid.



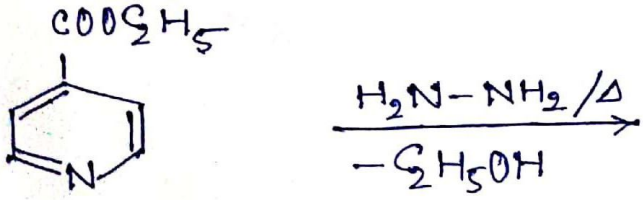
Citric acid

Diamide

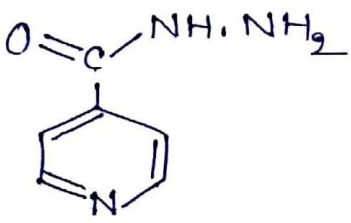




Isonicotinic acid



Ethyl isonicotinate



Isoniazid.

Ethambutol : Proposed synthesis involves vapour-phase nitration of butanol-1 to afford 2-nitrobutan-1-ol. The nitro compound on reduction with Raney-nickel/H_2 gives racemic amino derivative, the racemate on resolution with (+)-glutamic acid affords the desired (+)-enantiomer. Finally 2 moles of (+)-2-aminobutan-1-ol upon condensation with ethylene dichloride gives ethambutol.

$CH_3-CH_2-CH_2-CH_2OH \xrightarrow[\Delta]{HNO_3\,(g)} CH_3-CH_2-\underset{\displaystyle CH_2OH}{\underset{|}{CH}}-NO_2 \xrightarrow[H_2/\Delta]{\text{Raney-Ni}}$

Butan-1-ol

2-nitrobutan-1-ol

$\underset{\displaystyle CH_2OH}{\underset{|}{CH_3-CH_2-CH}}-NH_2$

(±)-2-aminobutan-1-ol

$\xrightarrow[\text{(+)-Glutamic acid}]{\text{Resolve with}}$

$\underset{\displaystyle CH_2OH}{\underset{|}{CH_3-CH_2-CH}}-NH_2$

(+)-Isomer (2 mol)

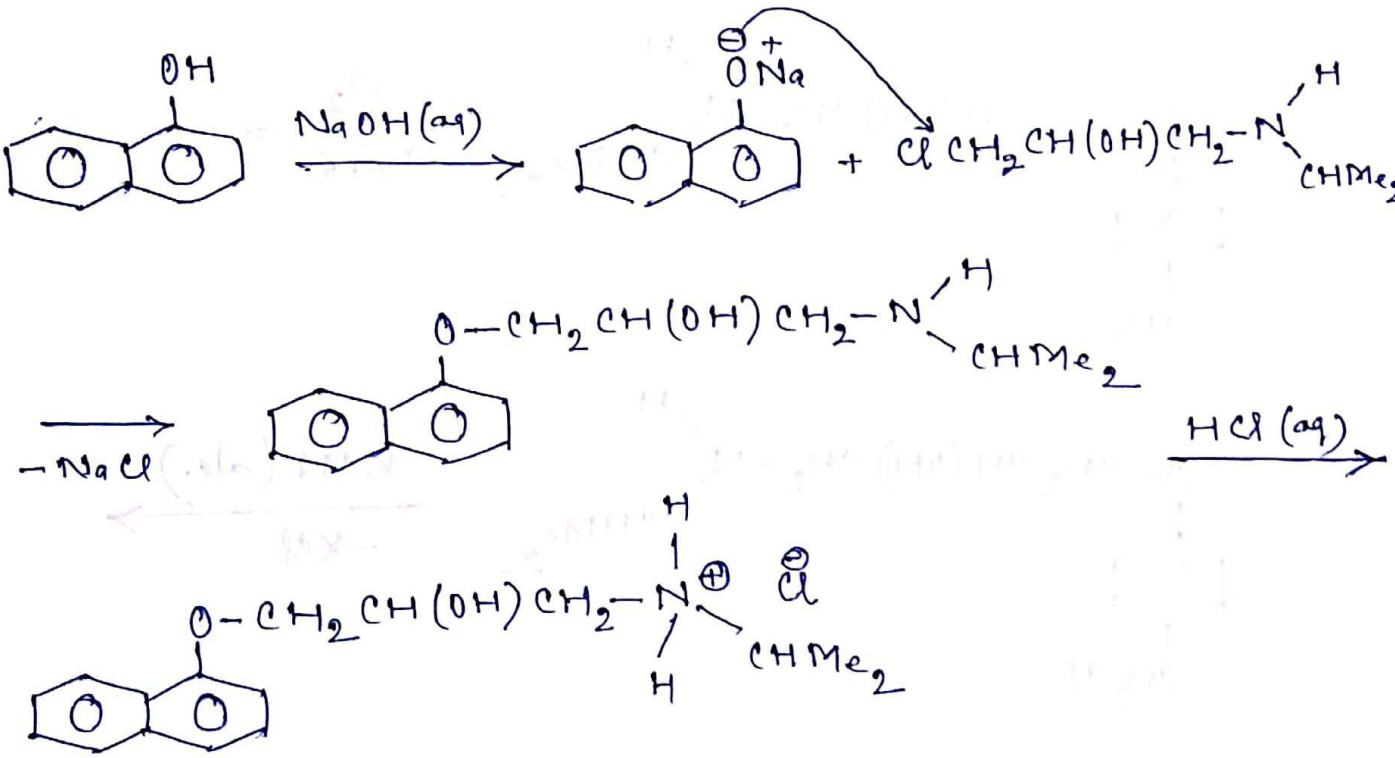
$\xrightarrow[(-2HCl)]{Cl-CH_2-CH_2-Cl}$

$CH_3-CH_2-\underset{\displaystyle CH_2OH}{\underset{|}{CH}}-NH-CH_2-CH_2-NH-\underset{\displaystyle CH_2OH}{\underset{|}{CH}}-CH_2-CH_3$

Ethambutol.

Propranolol hydrochloride :

The drug molecule is synthesized by direct interaction between α-naphthol (dissolved in alkali) and N-4-chloro-3-hydroxypropyl-N-isopropylamine. It is finally obtained as hydrochloride salt to render water-soluble.



Propranolol hydrochloride.

Atenolol : p-cresol dissolved in alkali is first reacted with N-4-chloro-3-hydroxypropyl-N-isopropylamine to give the intermediate product. The latter, on side chain chlorination followed by treatment with alcoholic KCN produces the corresponding nitrile. Finally the nitrile is subjected to partial hydrolysis to give atenolol.

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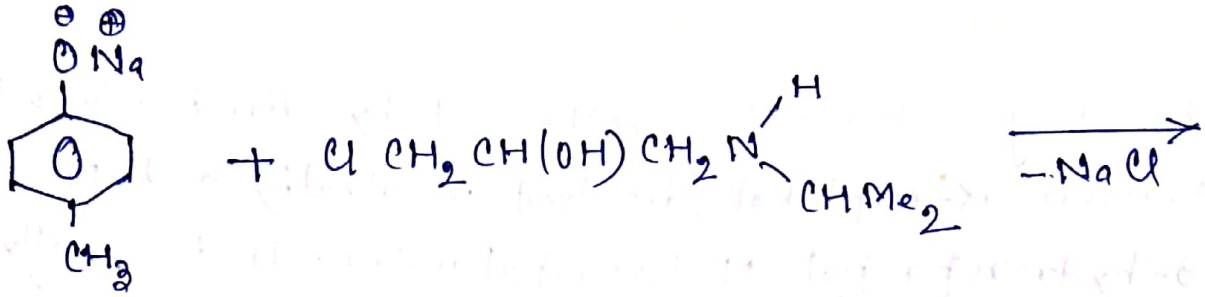
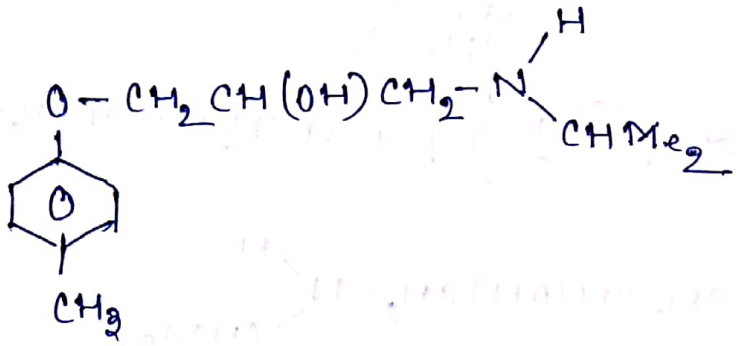
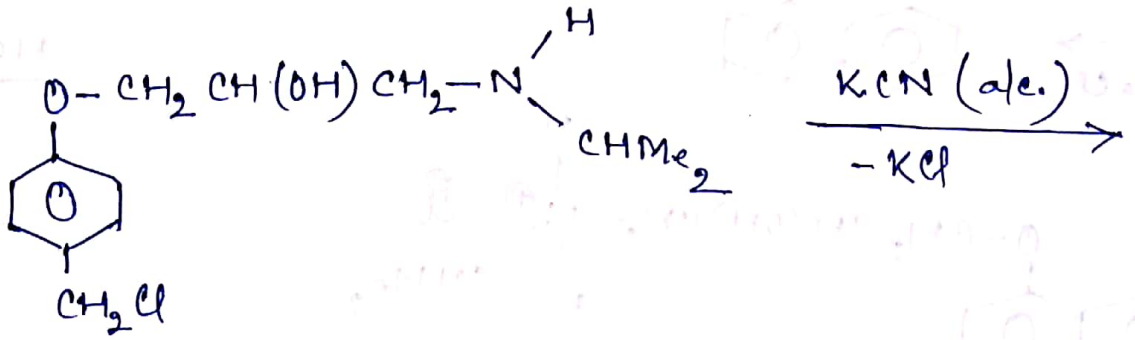
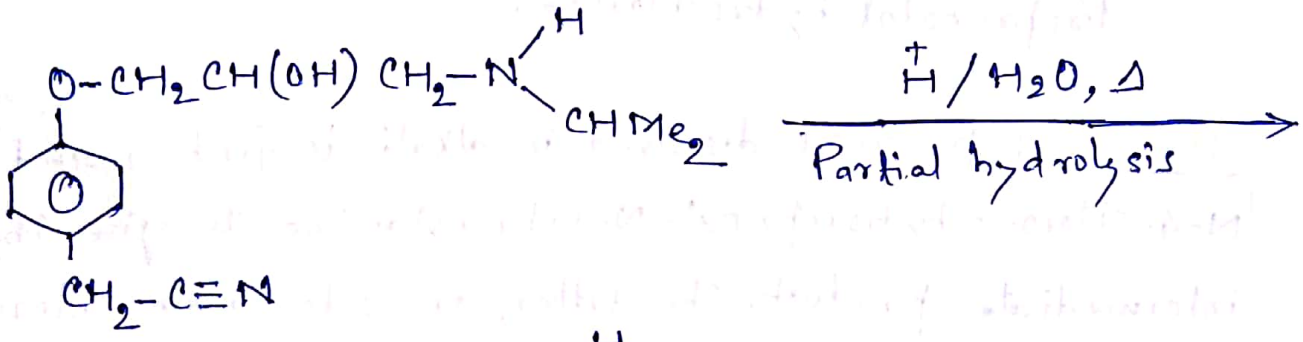
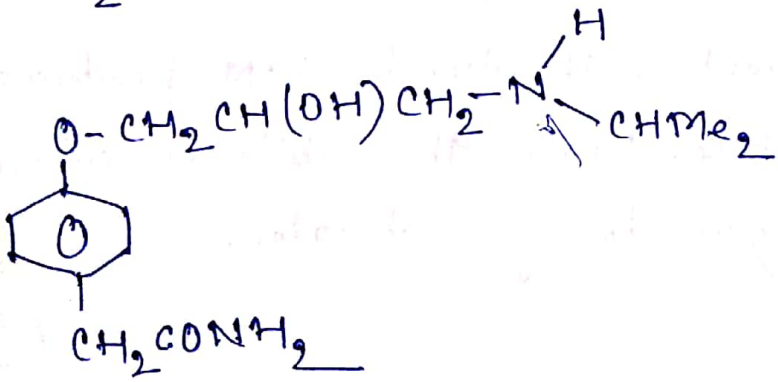


p-Cresol (in alkali)









Atenolol

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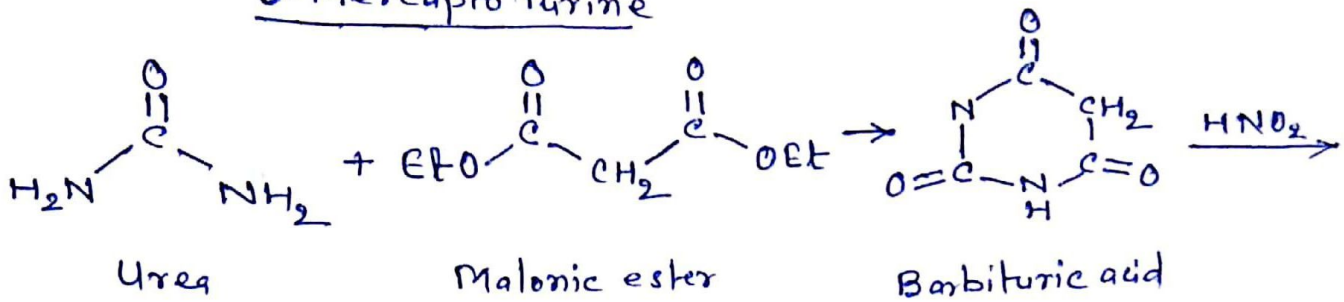
6-Mercapto Purine



Urea Malonic ester Barbituric acid