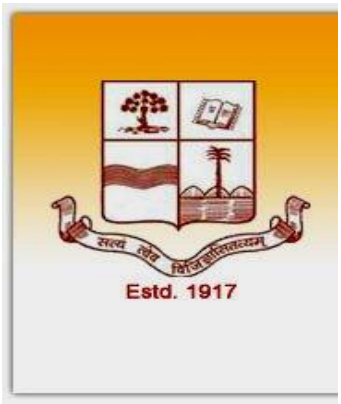
SYNTHESIS OF DRUGS

PART-1



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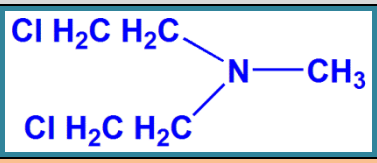
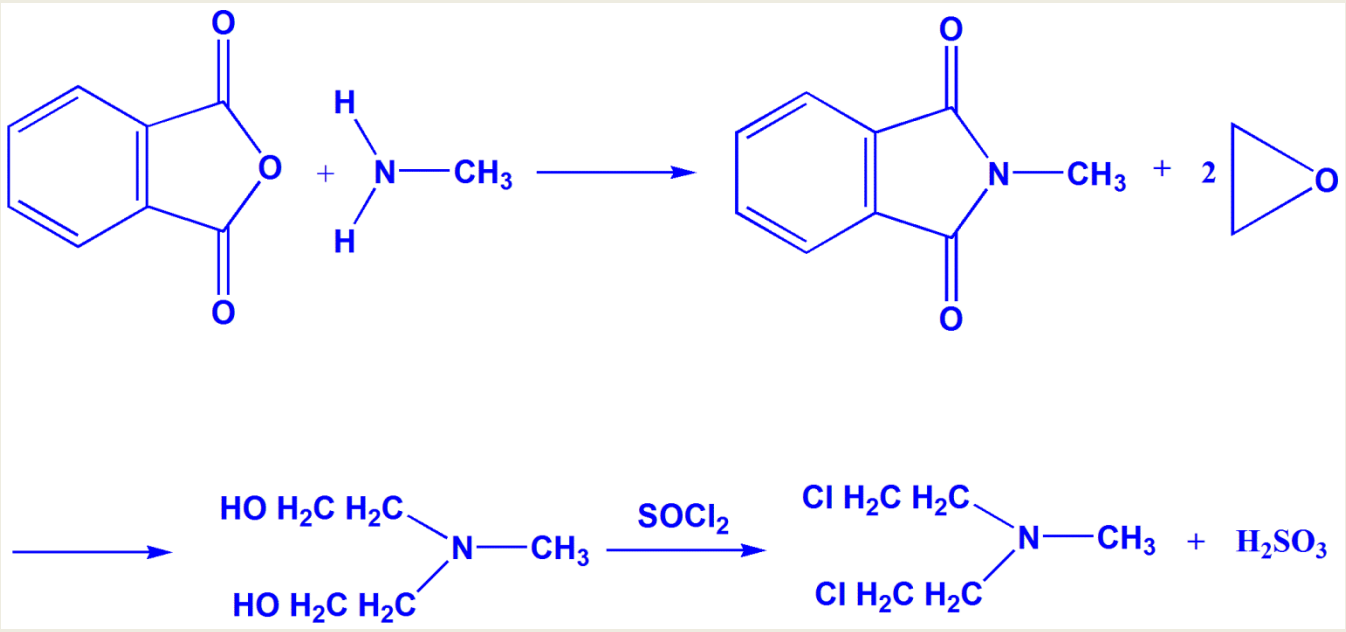
SYNTHESIS OF SOME ANTINEOPLASTIC DRUGS

1. Mechloroethamine : N,N-bis(2-chloroethyl)-N-methylamine

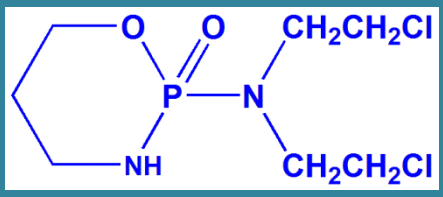


The starting material for the synthesis are phthalic anhydride and N-methylamine. As a result of initial condensation, N-phthalimido-N-methyl amine is formed. This is followed by reacting the phthalimido product with ethylene oxide. Synthesis is completed by reaction with thionyl chloride to afford the desired product and sulphurous acid as side product.

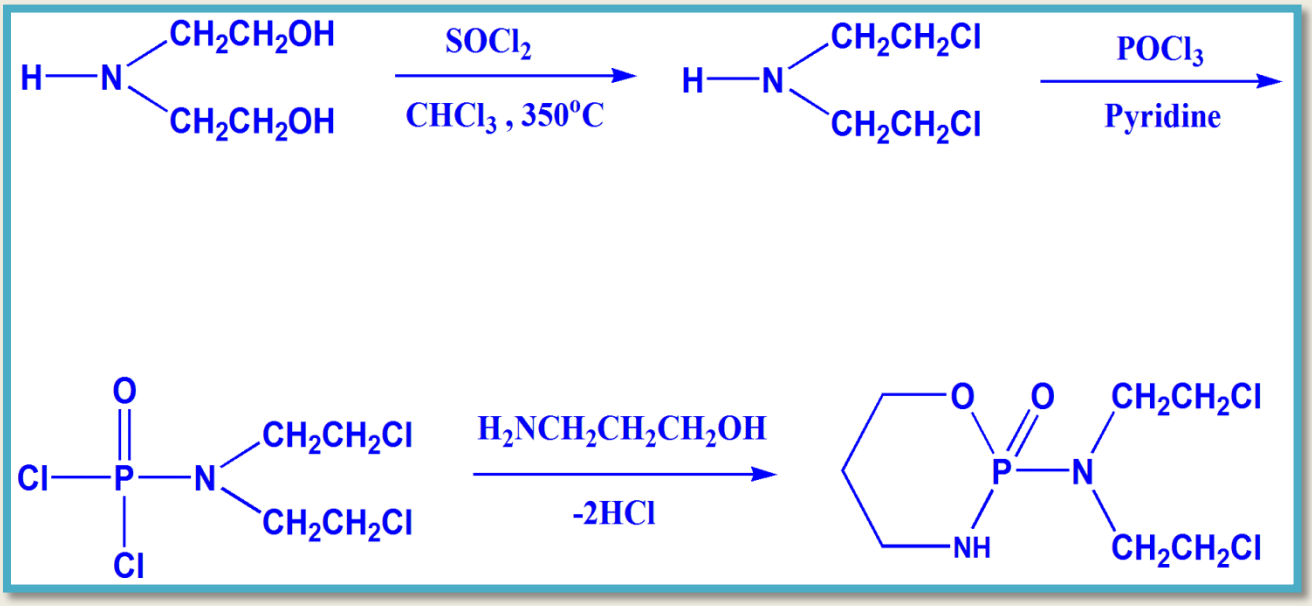


2. Cyclophosphamide

N,N-bis(2-chloroethyl)-1-oxo-6-oxa-2-aza-1λ^5-phosphocyclohexan-1-amine

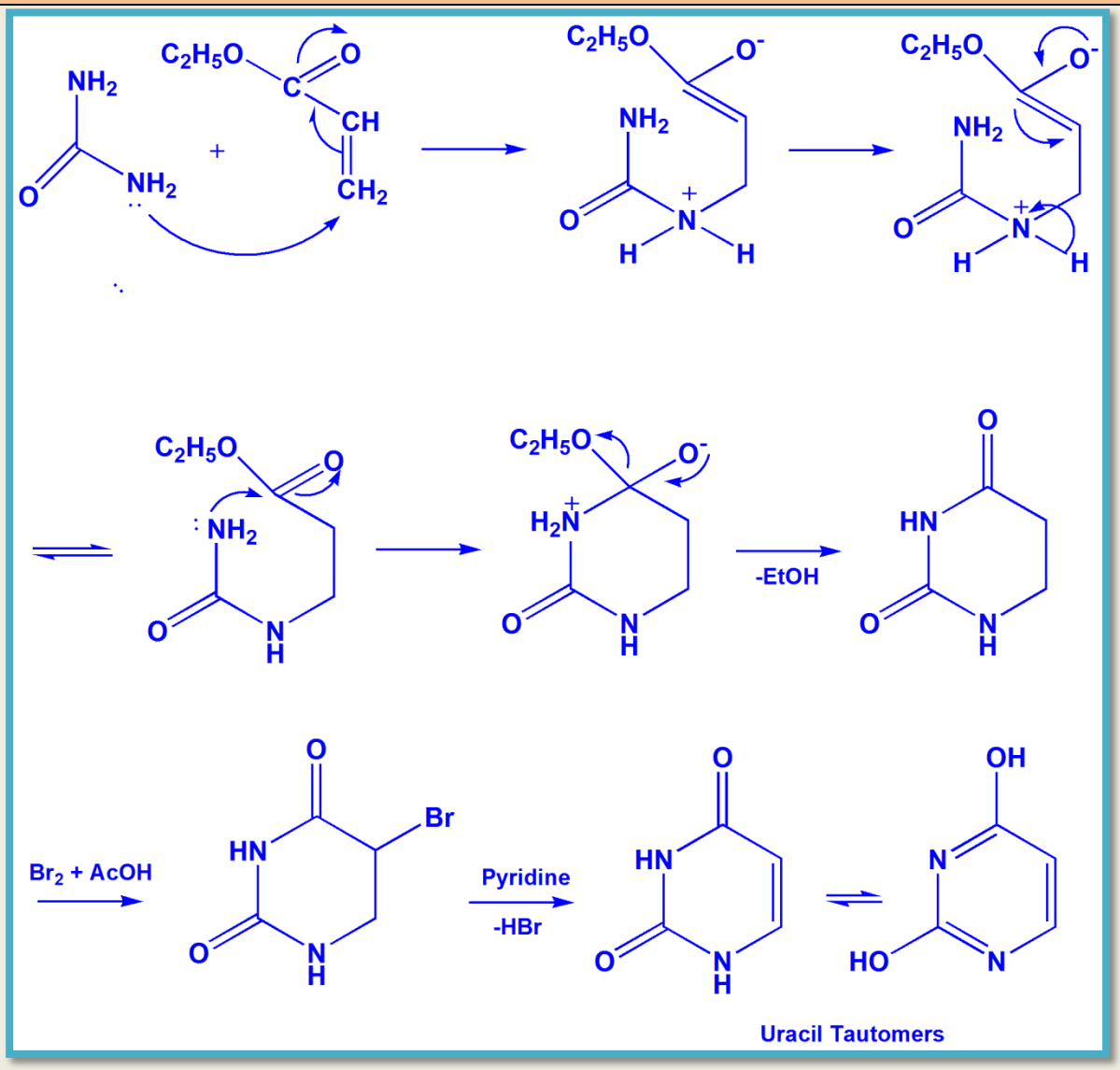


The proposed synthesis begins with chlorination of bis(2-hydroxyethyl)amine using thionyl chloride in chloroform solvent under strong heating conditions. Bis(2-chloroethyl)amine is phosphorylated by means of $POCl_3$ in pyridine. The final step of synthesis involves cyclization with 3-aminopropan-1-ol.

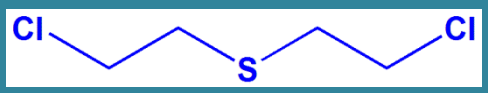


3. Uracil : 2,4-Dihydroxypyrimidine

The synthesis starts with initial interaction between Urea and Ethyl acrylate at an elevated temperature of about 210°C. After initial nucleophilic attack by Urea nitrogen at olefinic carbon, there is internal proton shift. Next, there is second nucleophilic attack by another nitrogen of urea, ethoxide is removed being a good leaving group. Subsequent steps involve selective bromination using Br_2 + AcOH followed by β-elimination of HBr.



4. Mustards : Bis(2-chloroethyl)sulphide



Several methods are available for the synthesis of mustards and a few can be identified as the following:

1. Depretz method : It consists in reacting sulphur dichloride with ethylene.

2. Levinstein method : This method involves reaction between disulphur dichloride and ethane.

3. Meyer method : First thiodiglycol is produced from chloroethanol and potassium sulfide which is finally chlorinated with phosphorustrichloride.

4. Meyer-Clarke method : It utilizes Concentrated HCl in place of PCl_3 of Clarke method.

1. Depretz method : $SCl_2 + 2C_2H_4 \longrightarrow (ClCH_2CH_2)_2S$

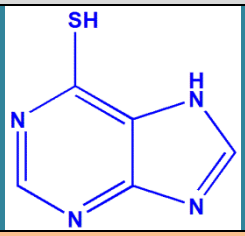
2. Levinstein method : $8\ S_2Cl_2 + 16C_2H_4 \longrightarrow 8\ (ClCH_2CH_2)_2S + S_8$

3. Meyer method : $2CH_3CH_2OH \xrightarrow{K_2S} (HOCH_2CH_2)_2S$

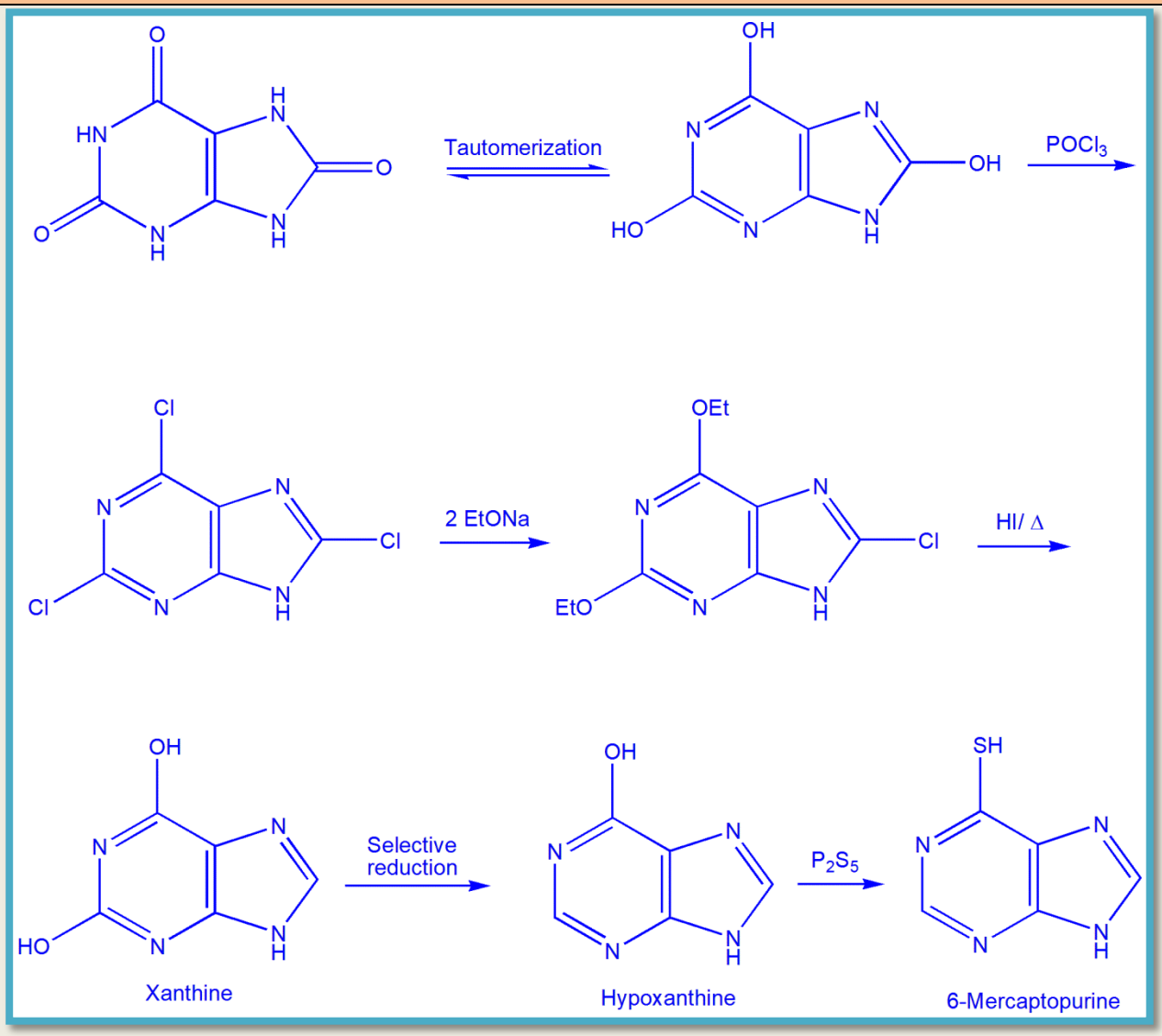
$3\ (HO\ CH_2CH_2)S + 2\ PCl_3 \longrightarrow 3\ (ClCH_2CH_2)_2S + 2\ P(OH)_3$

4. Meyer-Clarke method : $(HO\ CH_2CH_2)S + 2\ HCl \longrightarrow (ClCH_2CH_2)_2S + 2\ H_2O$

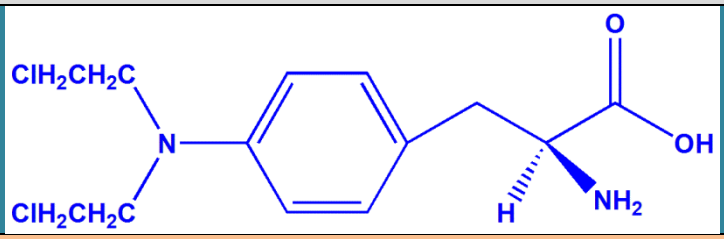
5. 6-Mercaptopurine



6-mercaptopurine can be synthesized from hypoxanthine on treatment with P_2S_5. However, hypoxanthine is synthesized starting with uric acid followed by selective reduction of one of the OH groups on pyrimidine ring.



6. Melphalan
4-[bis(2-chloroethyl)amino]-L-phenylalanine



This synthesis involves initial interaction between L-stereoisomer of N-phthalimido-p-aminophenyl alanine ethyl ester and ethylene oxide (1:2 mole ratio). The steps to be followed involve treatment with $POCl_3$ and finally hydrolysis.