3.29 Morphine (Opium Alkaloid) (Phenanthrene group → Alkaloid.)

Introduction. Morphine was the first alkaloid to be isolated from *serturner plant* (1806). In opium, it is present in a quantity of 10-23 per cent along with other substances like fats, resins, proteines, carbohydrates, mineral salts, meconic acid and about 20 or more alkaloids.

Codeine and thebaine are the other closely related alkaloids to morphine. These three are commonly known as *morphine alkaloids* and form a sub-group of the *opium alkaloids.* In all morphine alkaloids, phenanthrene nucleus is present. Due to this, these are also known as *phenanthrene alkaloids.*

The morphine alkaloids have been studied comparatively more due to the following reasons :

(*i*) These are widely used as analgesic agents, and

(*ii*) These undergo a wide variety of molecular rerrangements.

Isolation (*Separation of opium alkaloids*) Morphine is extracted from opium by involving the following steps :

(*i*) First of all, the raw opium is extracted with cold dicholoromethane repeatedly. Papaverine, narcotine and gum go into the dichloromethane layer whereas morphine and other substances remain in the *insoluble residue.* Dichloromethane layer is separated.

(*ii*) The dichloromethane layer obtained from step (*i*) is evaporated to dryness to yield a residue which is extracted with hot dilute HCl, then treated with charcoal and finally filtered. The filtrate is neutralised with ammonia when papaverine and narcotine are precipitated out. When precipitate is shaken with hot alcohol, papaverine goes into alcohol. From this, papaverine is precipitated out as acid oxalate and then purified by recrystallisation. The crude narcotine present in the residue from the alcohol extraction is similarly purified.

(*iii*) The residue obtained from the dichloromethane extraction is agitated with lime water at temperature below 20°C. Morphine, codeine and thebaine are present in lime water which when extracted several times with benzene removes codeine and thebaine in the benezene layer. Then, the pH is raised to 8 when the crude morphine is precipitated out. The filtrate still contains morphine. This filtrate, when evaporated in vacuum and then extracted with amyl alcohol, yields further amount of crude morphine. The two samples of the crude morphine are mixed.

(*iv*) The crude morphine obtained from step (*iii*) is dissolved in dilute hydrochloric acid and filtered through alcohol. Then the filtrate is neutralised with ammonia followed by the addition of alcohol. This results in the precipitation of morphine. The precipitated morphine is dissolved in minimum quantity of dilute HCl and the resulting solution so obtained on concentration and cooling yields crystals of morphine hydrochloride.

(*v*) The benzene extract obtained from step (*iii*) is evaporated to yield a residue. This is then treated with hot alcohol, followed by cooling and filtration. The filtrate when treated with sulphuric acid yields a precipitate of codeine sulphate which is filtered out. To the resultant filtrate, tartaric acid is added to precipitate out thebaine as thebaine acid tartrate.

Properties. Morphine is a colourless prismatic substance which melts at 247°C. It has a bitter taste and is laevorotatory having a specific rotation of —131°. It has little solubility in water, ether, benzol and chloroform but has sufficient solubility in alcohol and alkali solution.

Morphine acts as a monoacid base and forms well defined salts with acids.

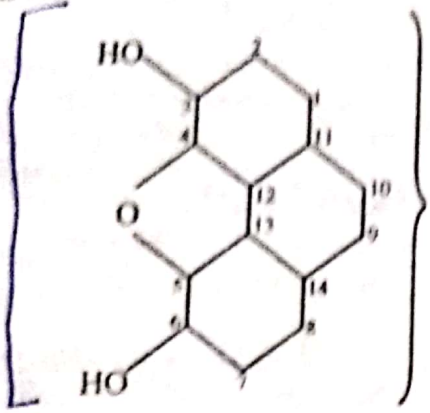
In medicine, morphine is used as its chloride. However, it is also used as the diacetyl derivative under the trade name *heroin* which is more habit forming than the morphine itself.

Codeine sulphate is less effective and is also used as an analgesic and as an antitussive; Codeine also causes addiction.

Thebaine is having little medicinal value and produces convulsion.

Structure of morphine

(i) As pointed out earlier that morphine forms monobromo derivative with bromine and monosodium salt with sodium hydroxide, indicating that morphine contains one benzenoid structure. Further, ethylene is formed as one of the products during the exhaustive methylation of codeimethines (step 8) and dimethylaminoethanol (IV) (step 7). Both these products favour that a $—CH_2—CH_2—CMe$ chain must be present in morphine. Also, a double bond and a tertiary nitrogen atom are present in it. On taking all these facts in view, the partial structure of morphine may be written as follows :



+ $NMe—CH_2—CH_2—$ + one double bond
(Formed as ethylene)

skeletal framework

= morphine

Now the problem arises : What are the positions of double bond and side chain $—CH_2—CH_2—\overset{|}{N}Me$ in morphine so as to explain all the reactions of morphine.

(ii) ***Point of the linkage of the $—CH_2—CH_2—\overset{|}{N}Me$ chain.*** Codeine (methylated morphine) when oxidised gently with chromic acid (CrO_3) yields some hydroxy codeine along with codeinone. The hydroxy codeine when subjected to exhaustive methylation yields ketocodeimethine which on heating with Ac_2O yields methoxydiacetoxyphenanthrene. The latter when oxidised further yields a quinone with loss of acetoxy group. Thus, all these reactions may be summarised as follows :

$$\text{Codeine} \xrightarrow[CrO_3]{\text{Oxidation}} \underset{\text{(Codeinone)}}{\text{Hydroxy Codeine}} \xrightarrow[\text{methylation}]{\text{Exhaustive}} \text{Ketocodeimethine} \xrightarrow[\text{Acetolysis}]{\text{Acetic annydride}}$$

$$\text{Methoxydiacetoxyphenanthrene} \xrightarrow{\text{Oxidation}} \text{Methoxymonoacetoxy phenanthraquinone}$$

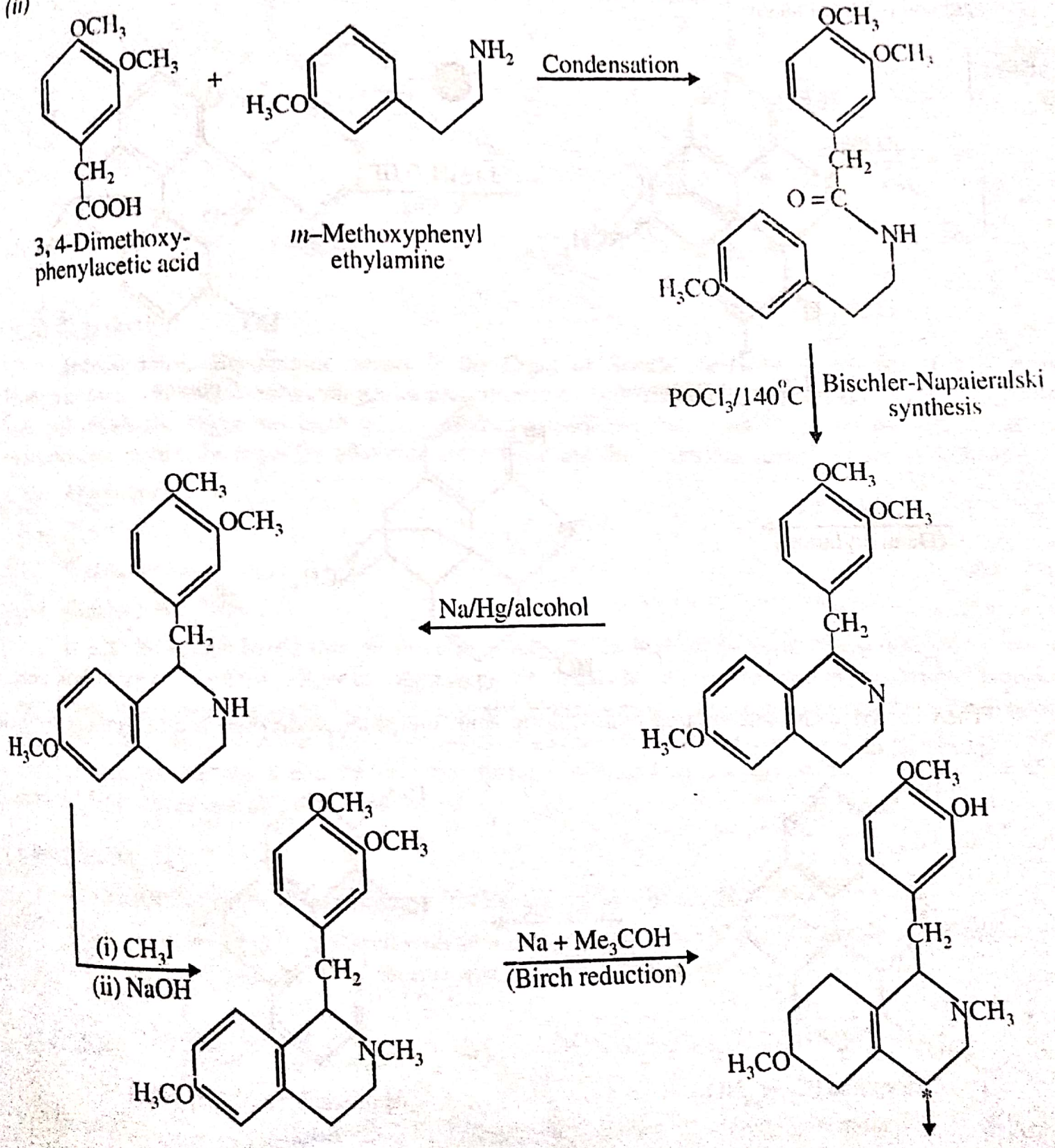
As there occurs the loss of an acetyl group in the oxidation of methoxydiacetoxyphenanthrene to methoxymonoacetoxyphenanthraquinone, this reveals that one of the acetoxy groups in the former compound must be present either C_9 or at C_{10}. Now since the acetoxyl group, which is lost in the oxidation, is inserted in position *via* the ketonic group during the acetolysis, it means that the keto group in keto codemethine and therefore the new hydroxyl group in hydroxycodine should be present either at C_9 or C_{10}. On the basis of steric consideration, the attachment at C_9 is most probable.

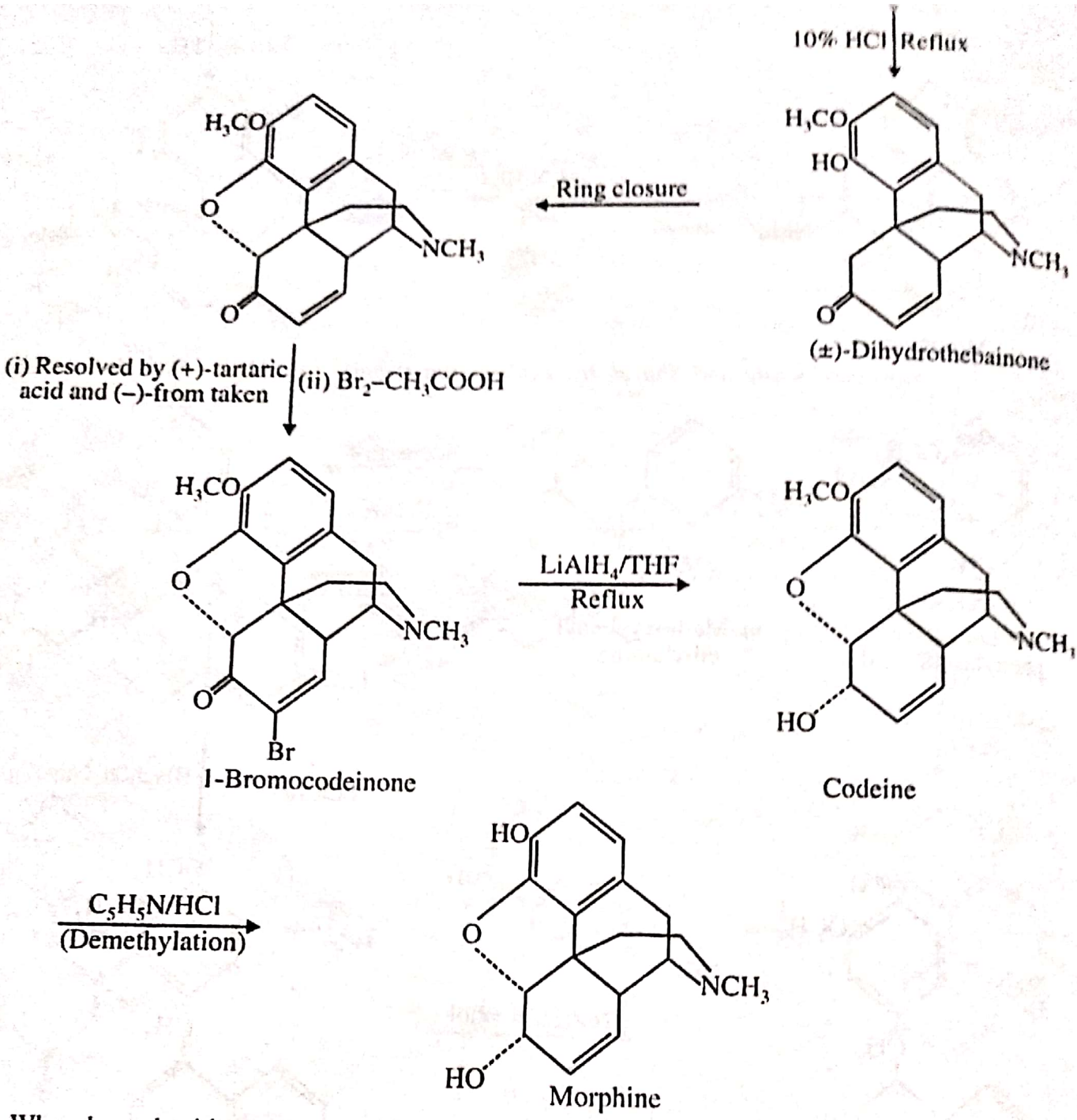
Now since the new hydroxyl group of hydroxycodeine is changed into a keto group during the Hofmann exhaustive methylation, a double bond must be introduced between C_9 and C_{10} during the fission of the nitrogen ring and thus the nirtogen must be linked at C_9 or C_{10}. The exact point of linkage of nitrozen at C_9 has been established after the synthesis of morphine.

Morphine

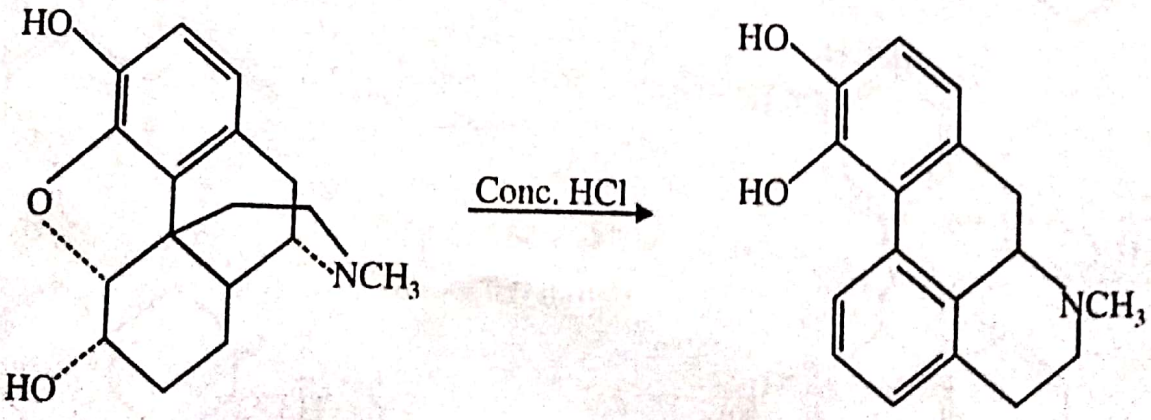
Morrison, Waite and Shavel Jr., Tetrahedron Letters. No. 41, P. 4055, 1967.

(ii)





When heated with concentrated hydrochloric acid, morphine undergoes rearrangement to yield apomorphine.



Morphine ($C_{17}H_{19}NO_3$)

Apomorphine ($C_{17}H_{17}NO_2$)