4.9. MORPHINE

Morphine was isolated in 1806 from opium and it was the first alkaloid isolated from a plant. Opium contains 10-23% morphine alongwith around 20 other alkaloids. Morphine, codeine and thebain are three structurally related opium alkaloids having phenanthrene carbon skeleton and are known as morphine or phenanthrene alkaloids. These morphine alkaloids have analgesic properties and their rearrangements have been studied extensively. Morphine diacetate is famous by its trade name, heroin.

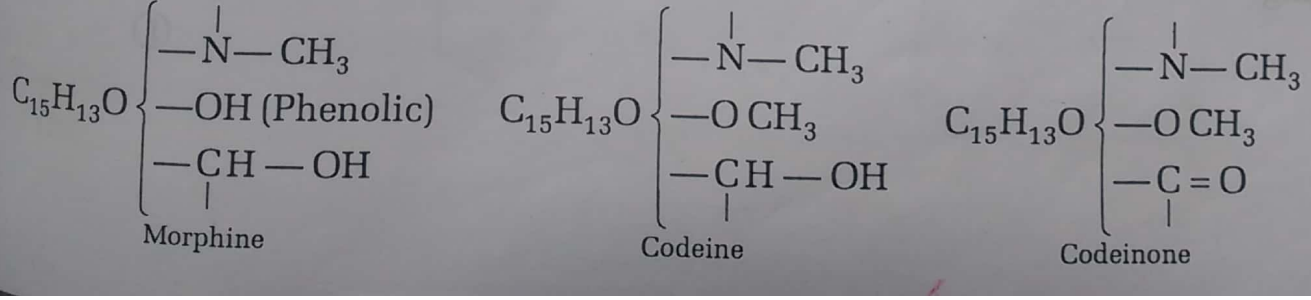
Morphine, having molecular formula $C_{17}H_{19}NO_3$, is a colourless, optically active ($[\alpha]_D = -131°$), bitter prismatic solid (m.p. 247 °C). It is soluble in alcohol and alkaline solution but slightly soluble in water, ether or chloroform.

Morphine forms quaternary salt with one molecule of methyl iodide (tertiary amine), yields methyl iodide when heated with hydroiodic acid at 150°C (presence of $>N–CH_3$) and does not lose nitrogen when subjected to Hofmann degradation (N is part of a ring).

It forms diacetate and dibenzoate (two hydroxyl groups present), forms mono sodium salt when treated with aqueous sodium hydroxide and regenerates morphine when CO_2 is passed through this solution of sodium salt (one hydroxyl group is phenolic). Heating morphine with methyl iodide in aqueous potassium hydroxide gives a methyl ether (phenolic ether), which was found identical with codeine, $C_{18}H_{21}NO_3$. Oxidation of codeine with chromic acid gave a ketone named codeinone ($C_{18}H_{19}NO_3$) confirming the nature of second hydroxyl as secondary. Third oxygen atom in morphine did not respond to any chemical test and was, therefore, inferred to be an ether function.

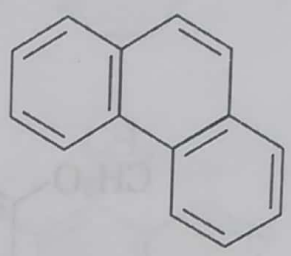
Codeine absorbs one molecule of hydrogen in the presence of palladium catalyst confirming the presence of an olefinic bond.

On the basis of foregoing discussion, the structural features of morphine, codeine and codeinone may be represented as given :



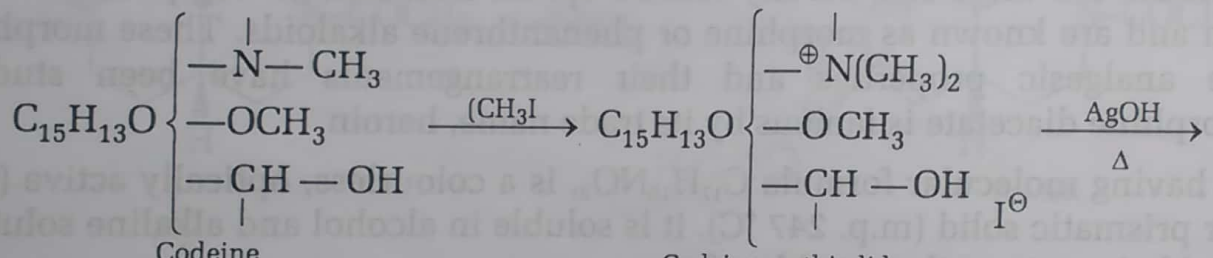
Morphine Codeine Codeinone

The most important structural information about morphine was obtained by distillation with zinc dust which produced phenantherene beside several other products. It indicated that morphine has phenathrene carbon skeleton.

Morphine $\xrightarrow[\text{Distill}]{\text{Zn dust}}$ 

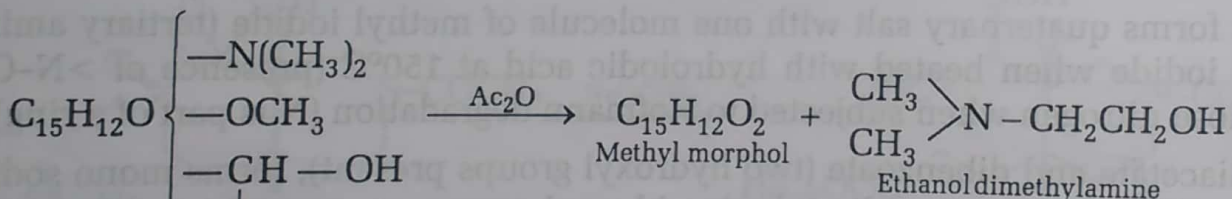
Phenanthrene

When subjected to Hofmann exhaustive methylation, codeine gives α-codeimethine which when treated with acetic anhydride forms methyl morphol and ethanoldimethylamine. Some of the α-codeimethine isomerizes to β-codeimethine. Structure determination of methyl morphol established the position of methoxyl group in codeine and therefore phenolic group in morphine.



Codeine

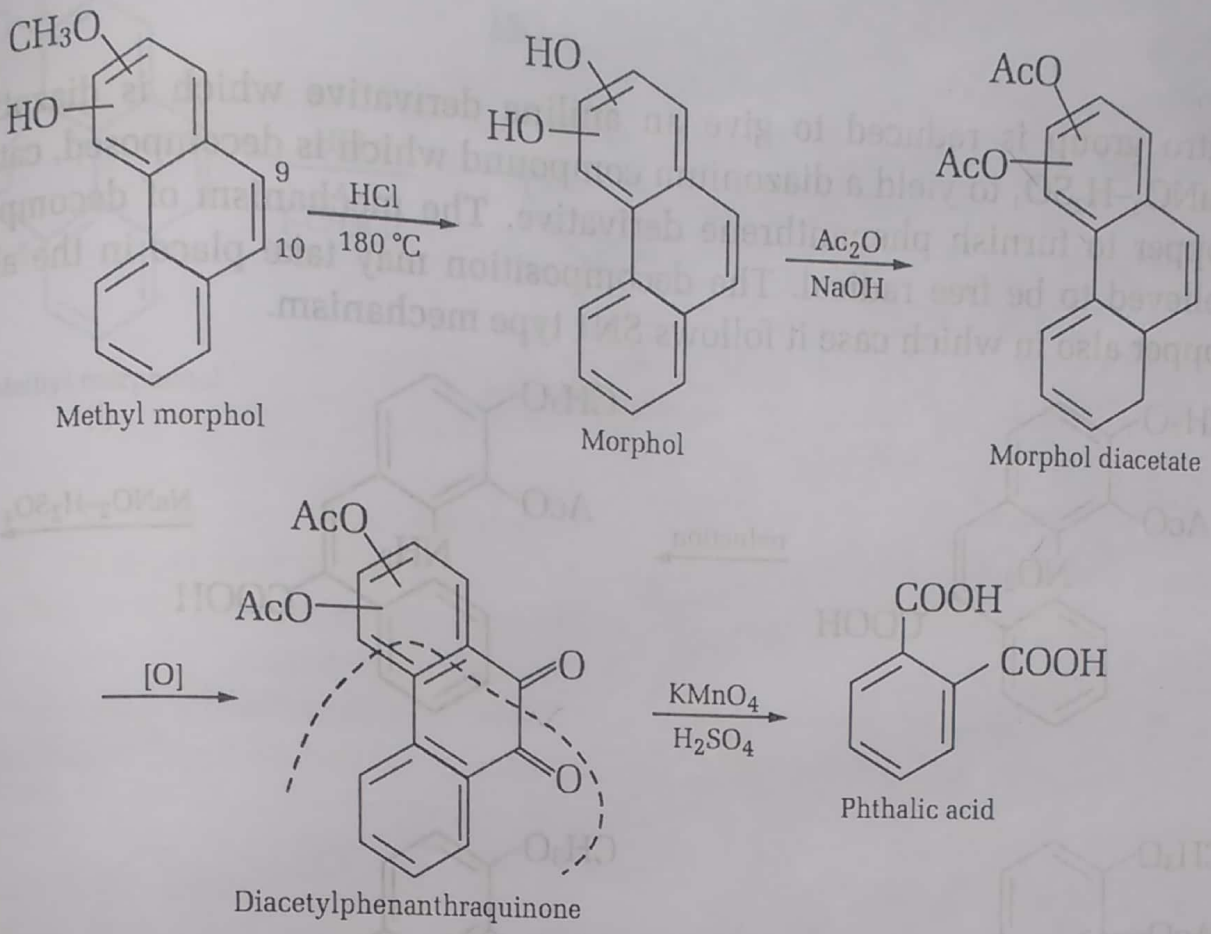
Codeine methiodide



α-Codeimethine

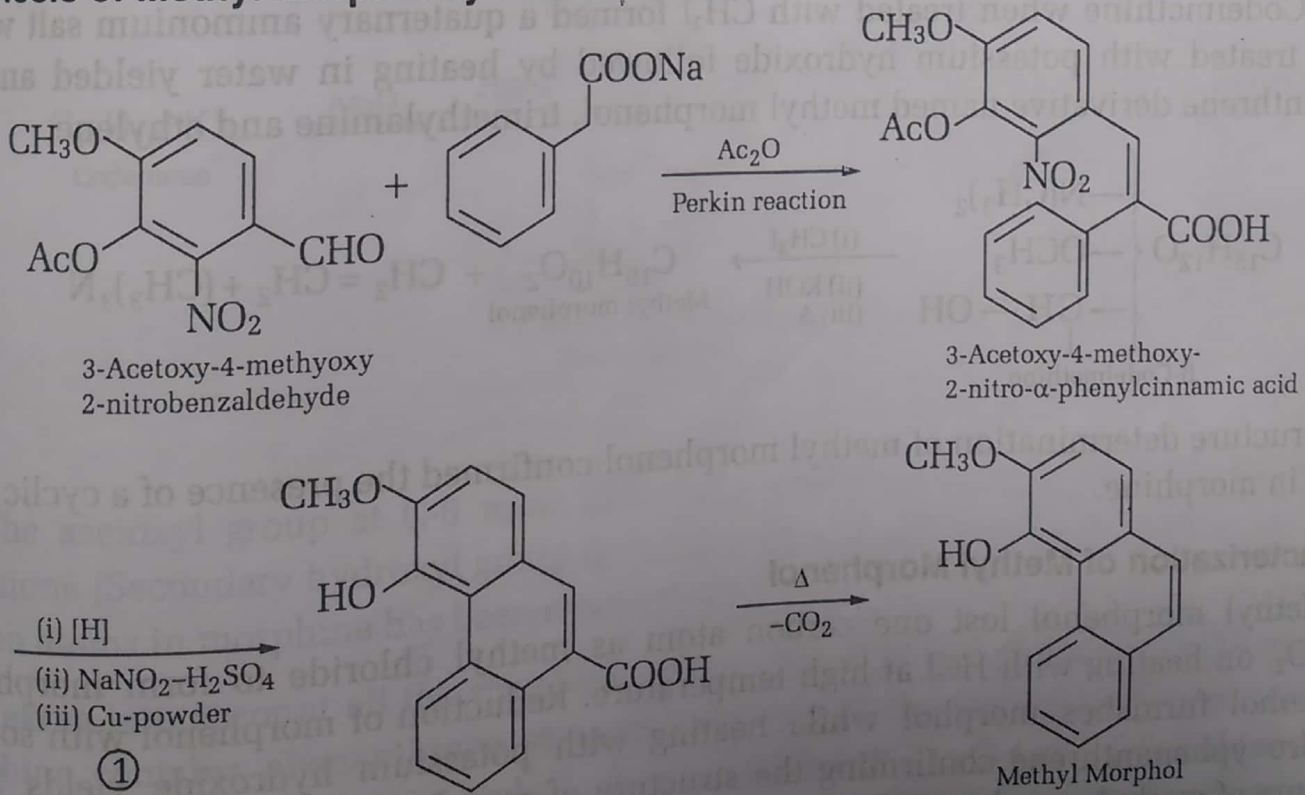
Characterization of Methyl Morphol

Heating methyl morphol with hydrochloric acid at 180 °C formed morphol and methyl chloride. Molecular formula of morphol, $C_{14}H_{10}O_2$ corresponds to 10 DBEs which indicated it to be a phenanthrene derivative. Morphol gave a diacetate on acetylation which confirmed the presence of both the O atoms as hydroxyl (phenolic) groups. Oxidation of diacetylmorphol yielded diacetylphenanthraquinone confirming that 9 and 10 position are not substituted. Further oxidation of quinone derivative with acidic potassium permanganate yielded phthalic acid confirming the presence of both the hydroxyl groups on one ring.



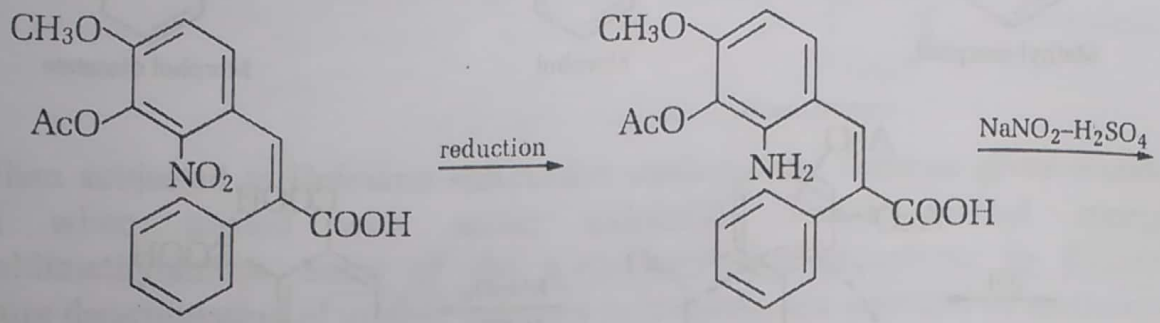
Structure of morphol was confirmed to be 3,4-dihydroxyphenanthrene by synthesis of Pschorr *et. al.* who later synthesized methyl morphol and showed it to be 4-hydroxy-3-methyoxyphenanthrene.

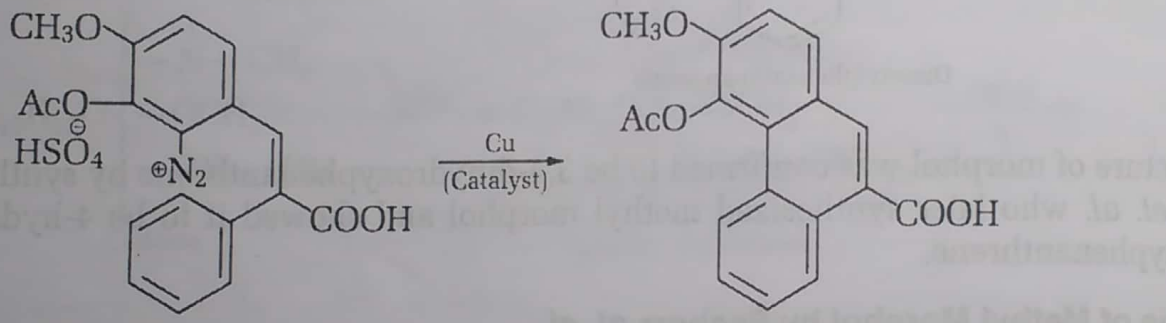
Synthesis of Methyl Morphol by Pschorr *et. al.*



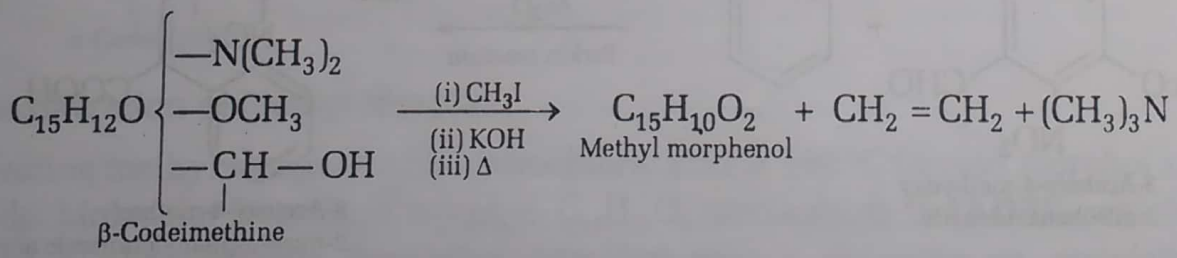
Remark

(1) Nitro group is reduced to give an aniline derivative which is diazotised with $NaNO_2$–H_2SO_4 to yield a diazonium compound which is decomposed, catalysed by copper to furnish phenanthrene derivative. The mechanism of decomposition is believed to be free radical. The decomposition may take place in the absence of copper also in which case it follows SN1 type mechanism.





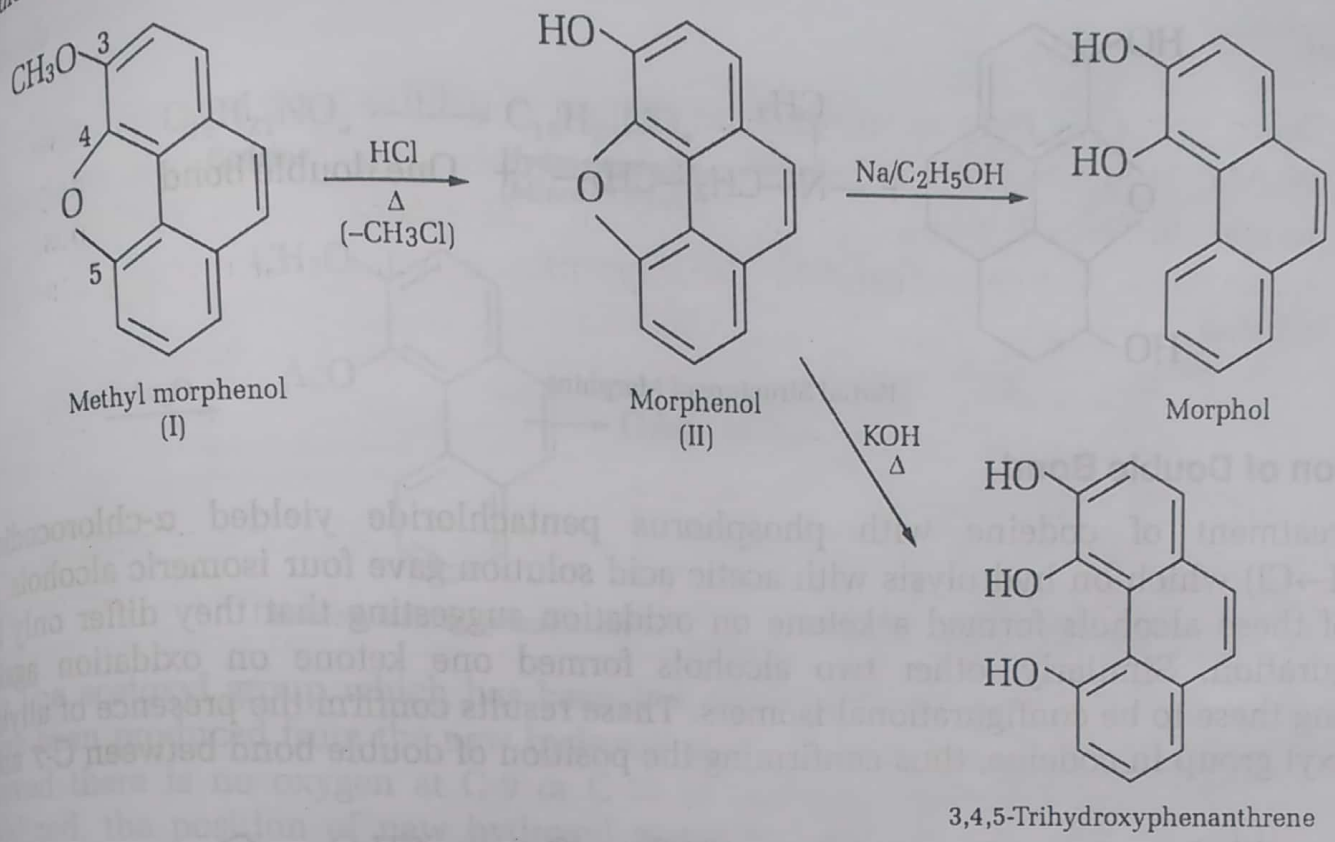
β-Codeimethine when treated with CH_3I formed a quaternary ammonium salt which when treated with potassium hydroxide followed by heating in water yielded another phenanthrene derivative named methyl morphenol, trimethylamine and ethylene.



Structure determination of methyl morphenol confirmed the presence of a cyclic ether group in morphine.

Characterization of Methyl Morphenol

Methyl morphenol lost one carbon atom as methyl chloride to form morphenol, $C_{14}H_8O_2$, on heating with HCl at high temperature. Reduction of morphenol with sodium in alcohol furnishes morphol while heating with potassium hydroxide yields 3,4,5-trihydroxyphenanthrene confirming the structure of morphenol as II and, therefore, the structure of methyl morphenol must be I.



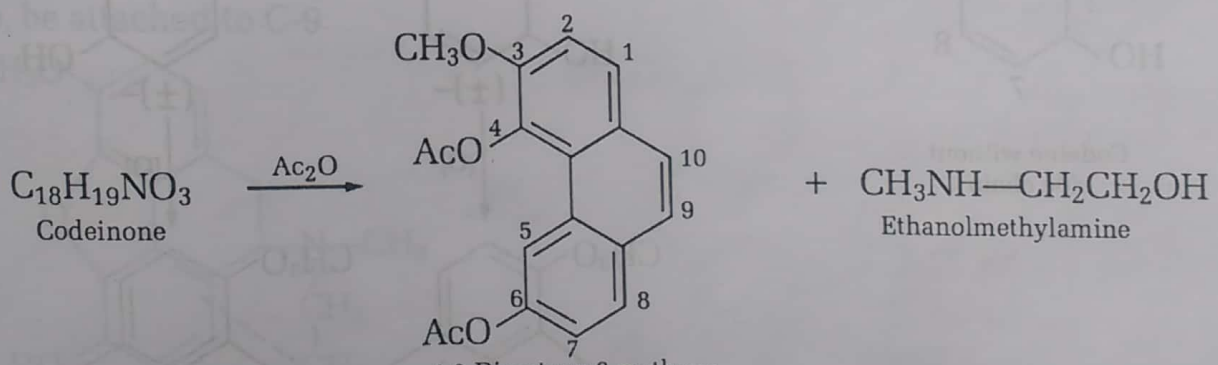
Methyl morphenol (I)

Morphenol (II)

Morphol

3,4,5-Trihydroxyphenanthrene

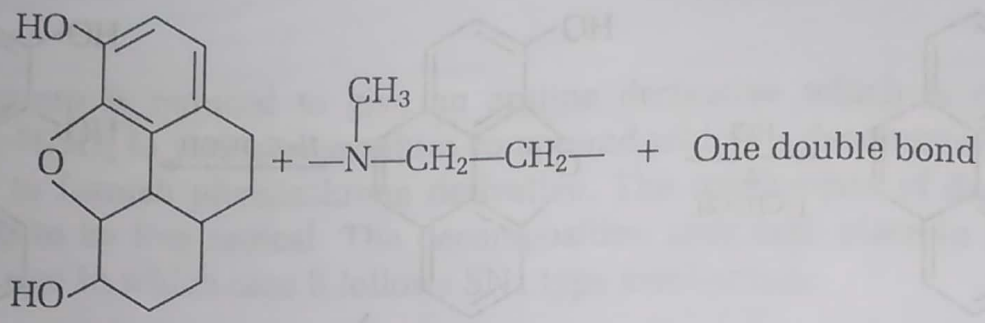
The position of secondary hydroxyl group in morphine was established by heating codeinone with acetic anhydride which formed 4,6-diacetoxy-3-methoxyphenanthrene and ethanol methylamine.



4,6-Diacetoxy-3-methoxy-phenanthrene

The acetoxyl group at C-6 must have been produced from the ketonic oxygen in codeinone (Secondary hydroxyl group in codeine and morphine). Thus, position of all the oxygen atoms in morphine has been established.

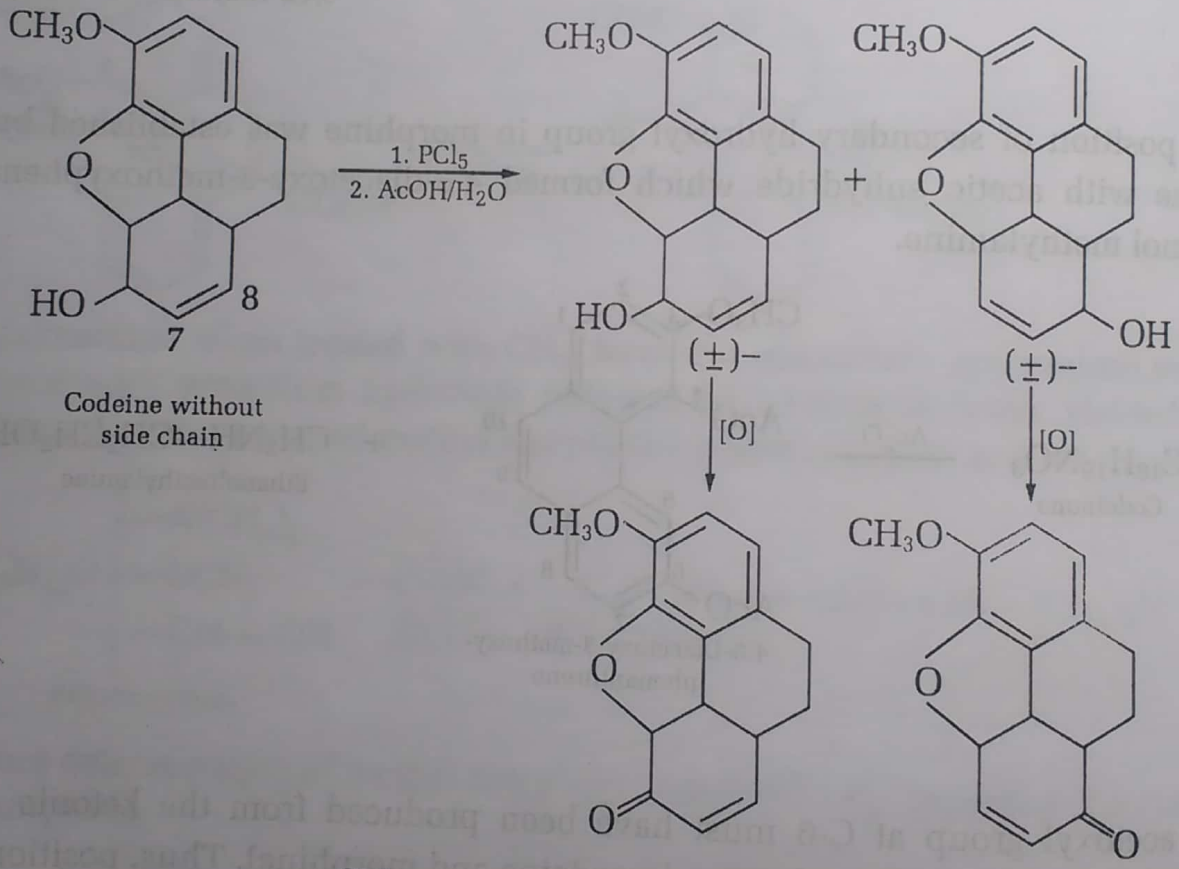
Taking into account all the structural information obtained so far, it can be said that morphine contains phenanthrene skeleton with one of the terminals ring as aromatic, hydroxyl groups at C-3 and C-6 and an ether oxygen bonded to C-4 and C-5. This accounts for 7DBE of 9 for morphine. One double bond and one N-containing ring accounts for 1 DBE each. The partial structure for morphine may be given as :



Partial Structure of Morphine

Position of Double Bond

Treatment of codeine with phosphorus pentachloride yielded α-chlorocodide (—OH→Cl) which on hydrolysis with acetic acid solution gave four isomeric alcohols. A pair of these alcohols formed a ketone on oxidation suggesting that they differ only in configuration. Similarly, other two alcohols formed one ketone on oxidation again showing these to be configurational isomers. These results confirm the presence of allylic hydroxyl group in codeine, thus confirming the position of double bond between C-7 and C-8.

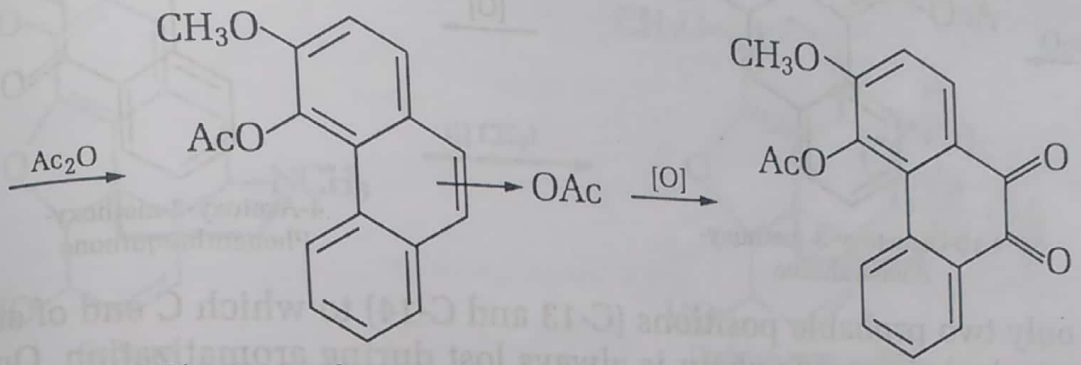


Codeine without side chain

Points of Attachment of $-\overset{\overset{CH_3}{|}}{N}-CH_2-CH_2-$ Unit

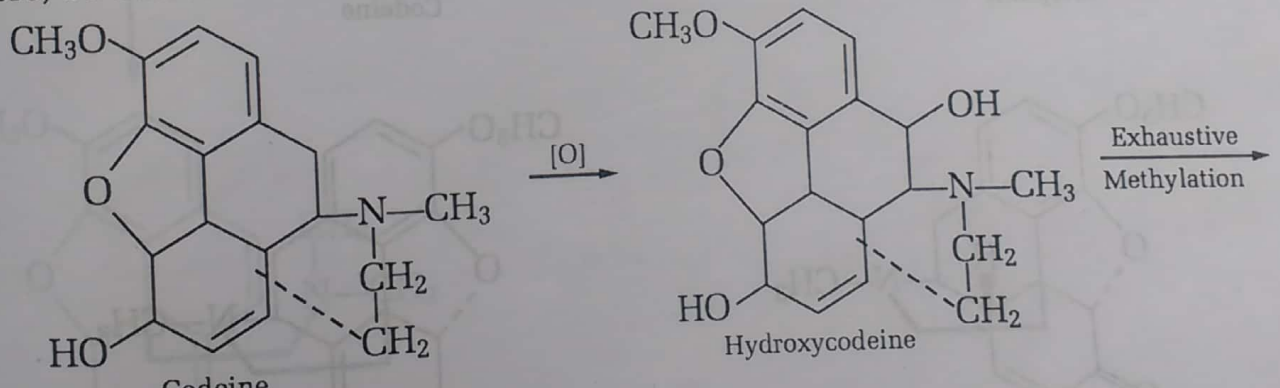
Gentle oxidation of codeine with chromic acid gives codeinone and a minor product, hydroxycodeine. Exhaustive methylation of hydroxycodeine yielded, ketocodeimethine which when heated with acetic anhydride yields a diacetoxymethoxyphenanthrene derivative which on further oxidation formed phenanthraquinone derivative with the loss of one acetoxyl group.

$C_{18}H_{21}NO_3$ (Codeine) $\xrightarrow{[O]}$ $C_{18}H_{21}NO_4$ (Hydroxycodeine (Minor Product)) $\xrightarrow[\text{Methylation}]{\text{Exhaustive}}$ $C_{19}H_{23}NO_4$ (Ketocodeimethine)

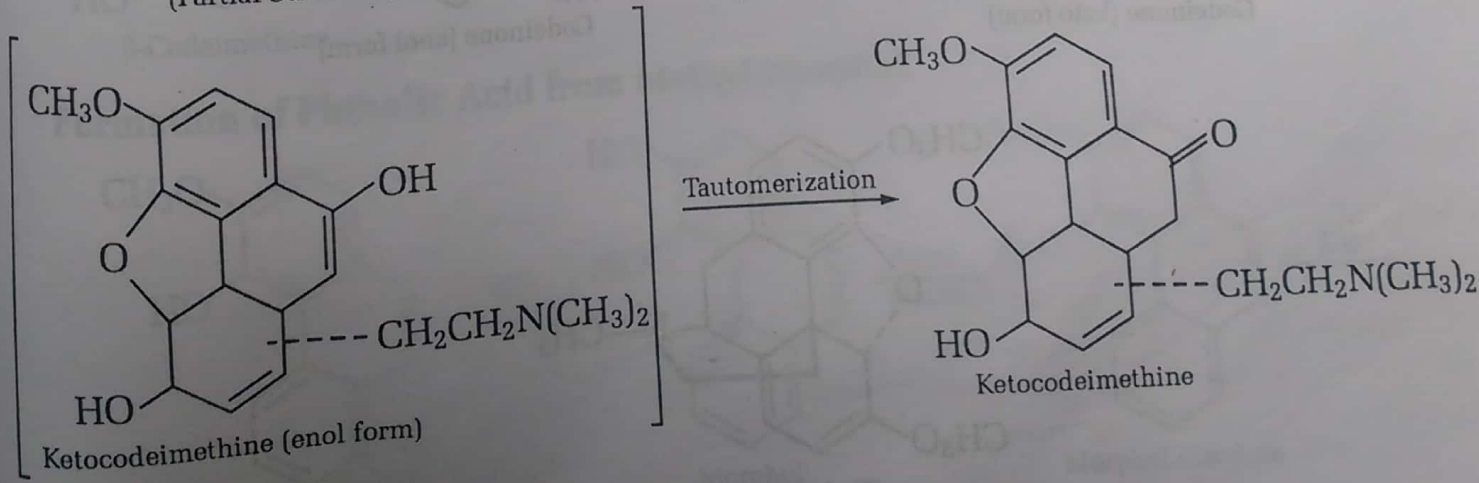


Diacetoxymethoxyphenanthrene — 4-Acetoxy-3-methoxyanthraquinone

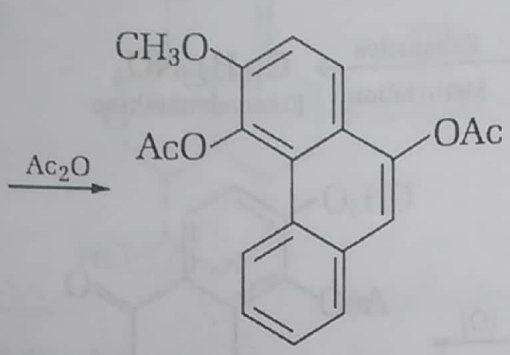
The acetoxyl group which has been lost must be either at C-9 or C-10 which must have been produced from the new hydroxyl group in hydroxycodeine because as already proved there is no oxygen at C-9 or C-10 in codeine. Since benzylic carbon is easily oxidized, the position of new hydroxyl group was assigned at C-10. The formation of ketocodeimethine from hydroxycodeine can be explained by formation of new bond between C-9 and C-10 on exhaustive methylation giving an enol which will yield ketocodeimethine on tautomerization. Nitrogen end of $-N(CH_3)-CH_2-CH_2-$ unit must, therefore, be attached to C-9.



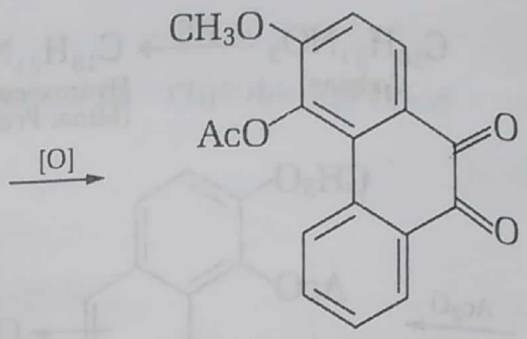
Codeine (Partial Structure) — Hydroxycodeine



Ketocodeimethine (enol form) — Ketocodeimethine

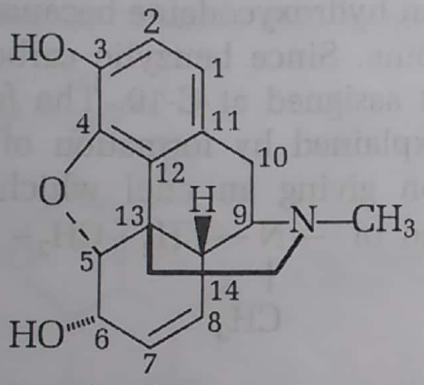


4,10-Diacetoxy-3-methoxy-Phenanthrene

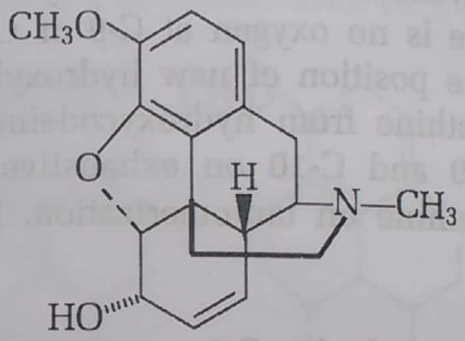


4-Acetoxy-3-methoxy-Phenanthraquinone

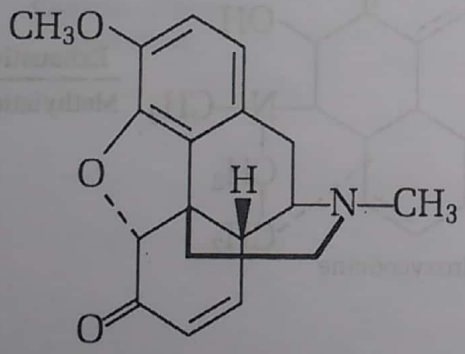
There are only two probable positions (C-13 and C-14) to which C end of ethanamine unit could be attached since side chain is always lost during aromatization. On the basis of extensive experimental work on morphine alkaloids, Gulland and Robinson proposed following structures to morphine and related alkaloids.



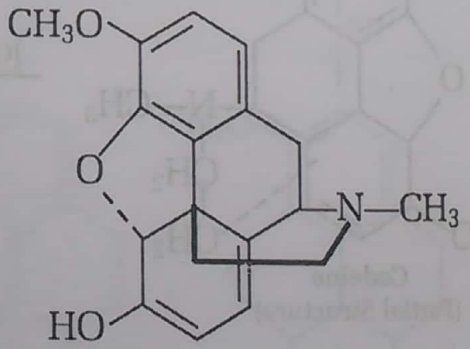
Morphine



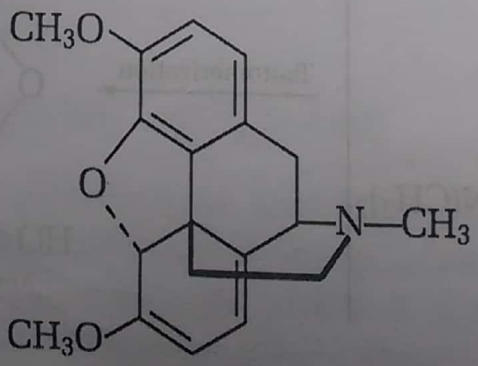
Codeine



Codeinone (keto form)



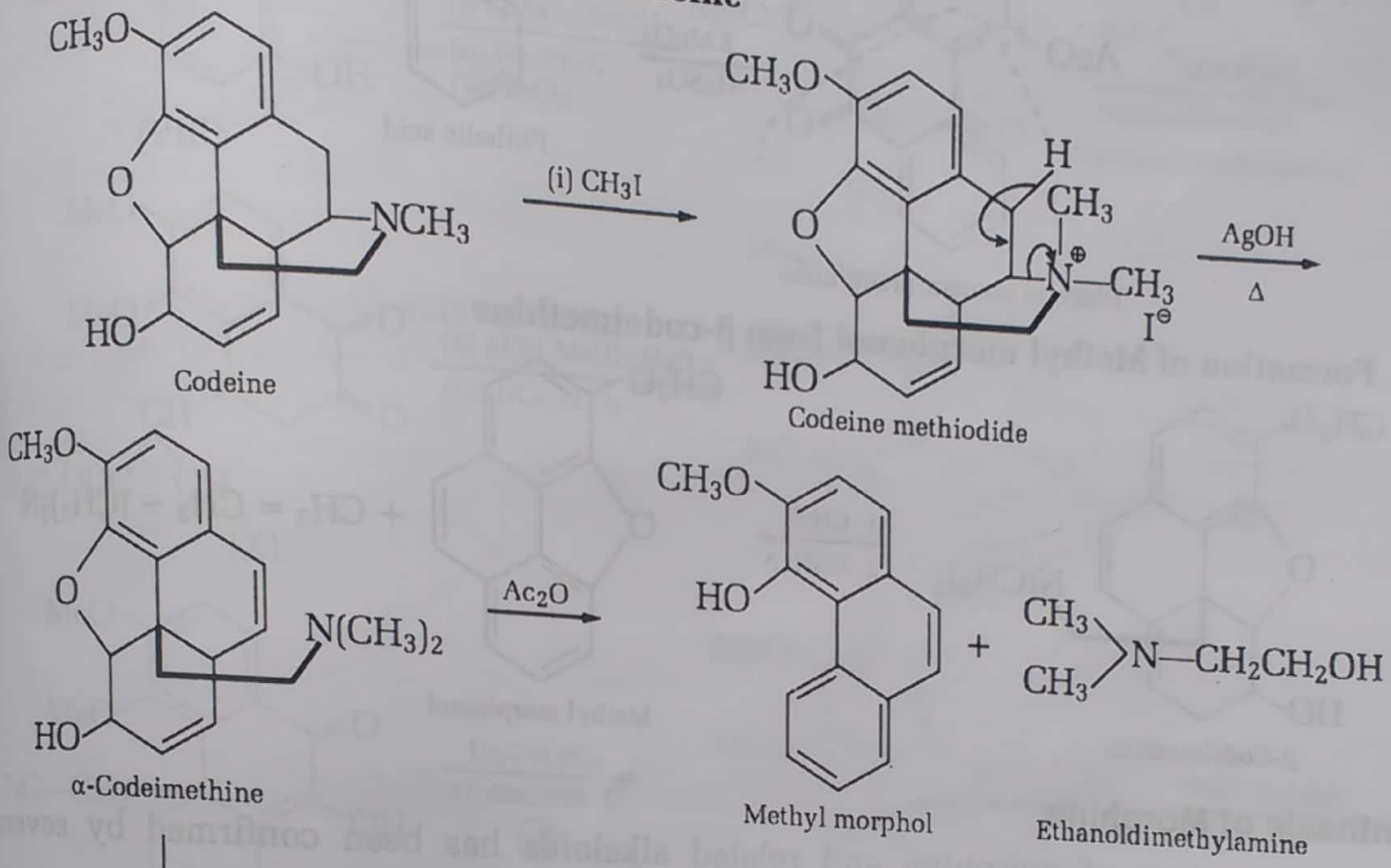
Codeinone (enol form)



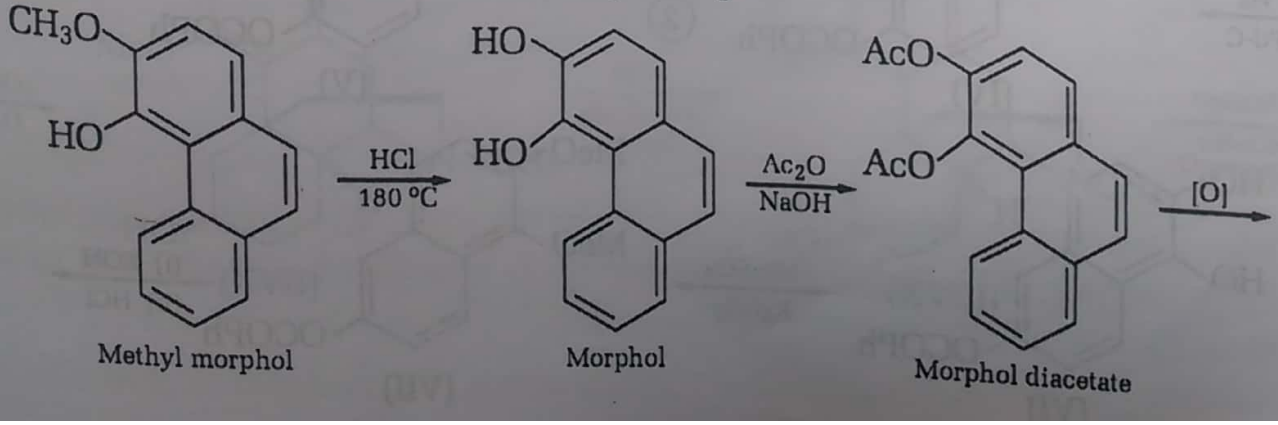
Thebaine

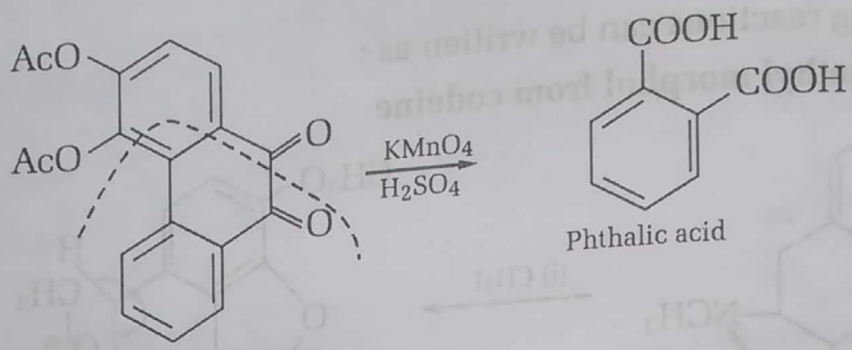
All the foregoing reactions can be written as :

Formation of methyl morphol from codeine



Formation of Phthalic Acid from Methyl Morphol

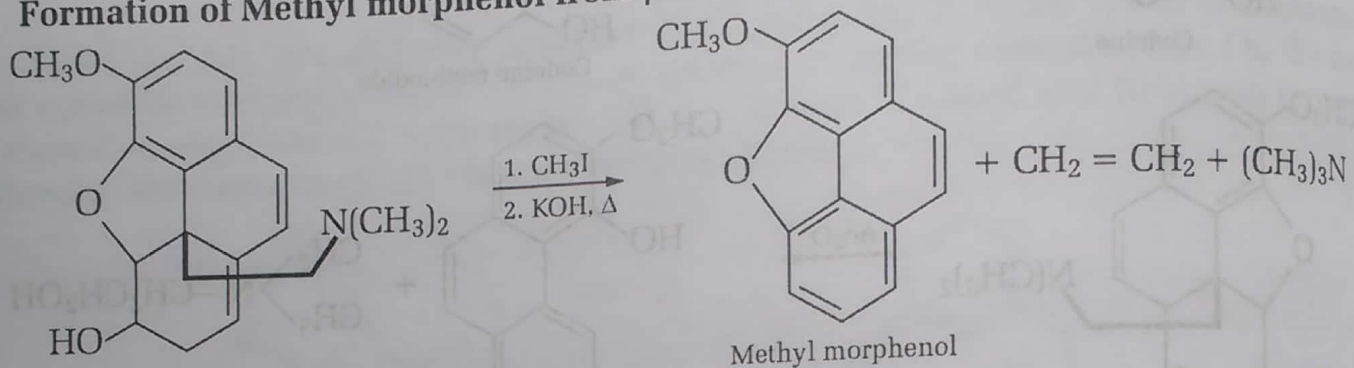




Diacetyl phenanthraquinone

Phthalic acid

Formation of Methyl morphenol from β-codeimethine



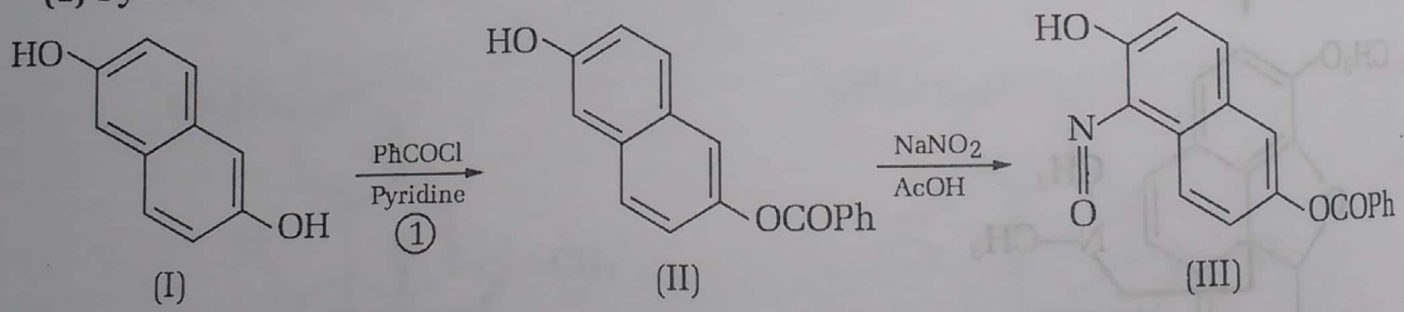
β-Codeimethine

Methyl morphenol

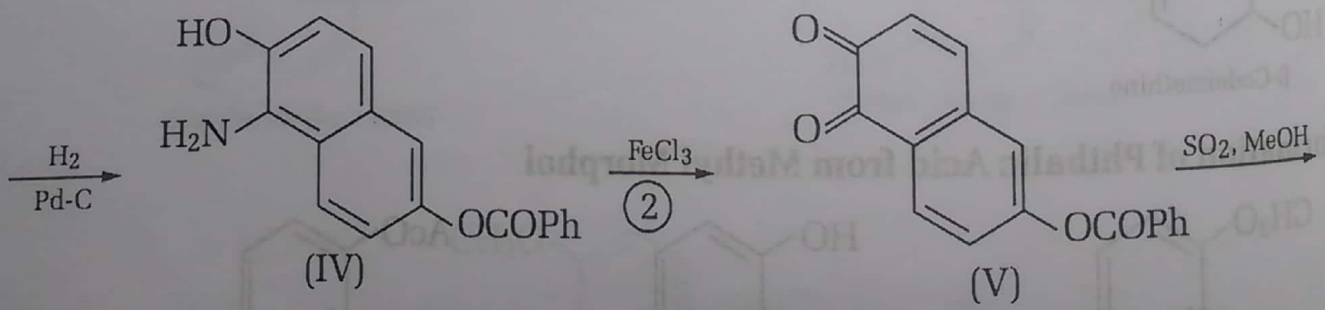
Synthesis of Morphine

The structure of morphine and related alkaloids has been confirmed by several syntheses.

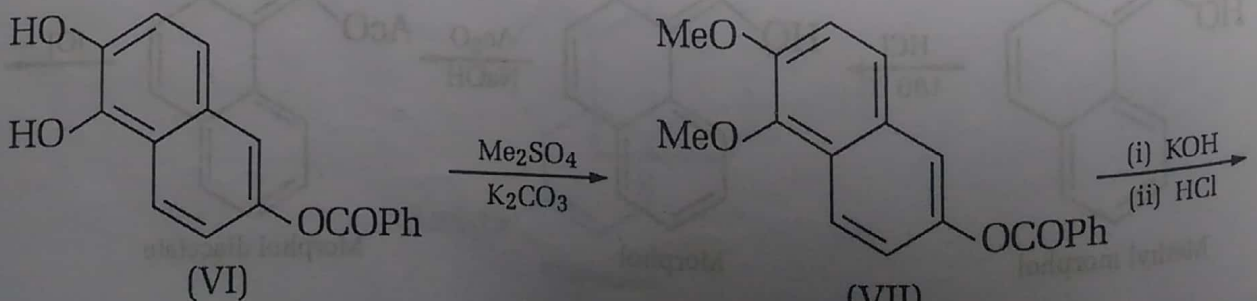
(1) Synthesis of Gates *et.al.* (1956)



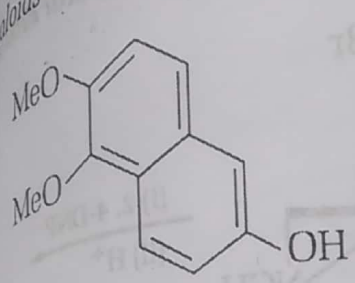
(I) (II) (III)



(IV) (V)

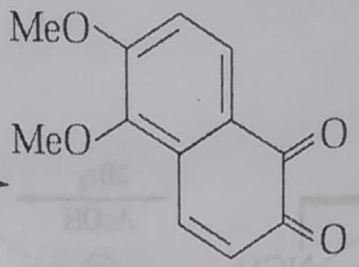


(VI) (VII)

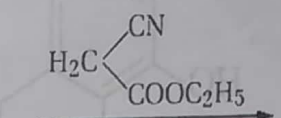


(VIII)

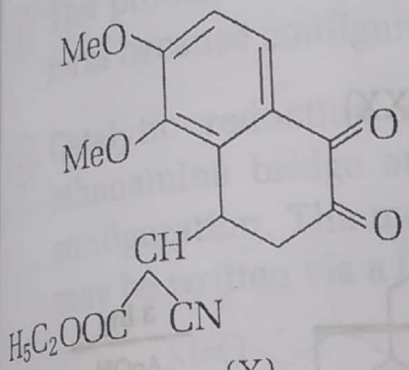
(i) $NaNO_2$-AcOH
(ii) H_2, Pd-C
(iii) $FeCl_3$



(IX)

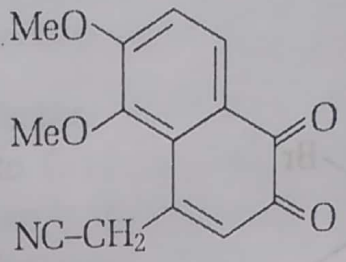


$(C_2H_5)_3N—H_2O$
(Michael condensation)



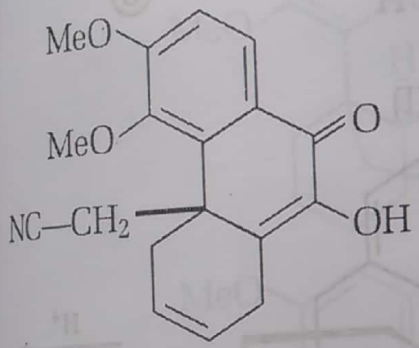
(X)

(i) $K_3[Fe(CN)_6]$
(ii) KOH-MeOH-H_2O
(iii) HCl, $-CO_2$



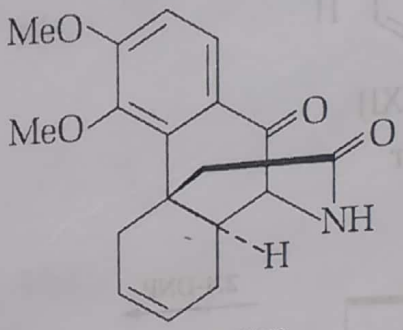
(XI)

1,3-Butadiene
Diels-Alder reaction
③



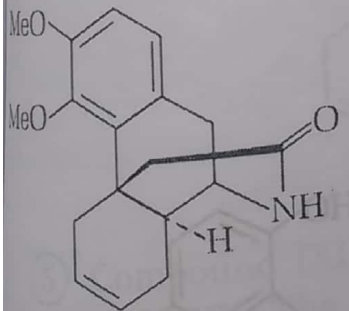
(XII)

$H_2/CuCrO_2$
27 atm, 130 °C
④



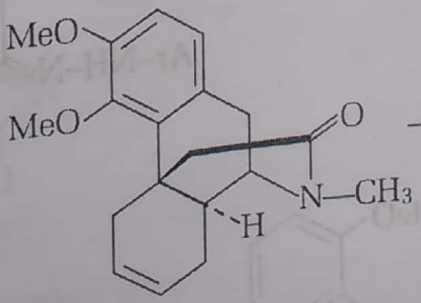
(XIII)

Wolff-Kishner Reduction



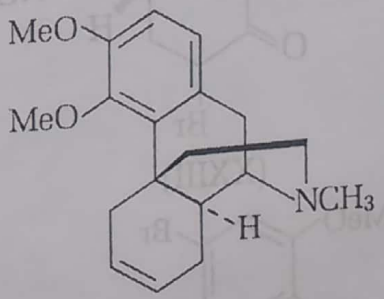
(XIV)

NaH
MeI

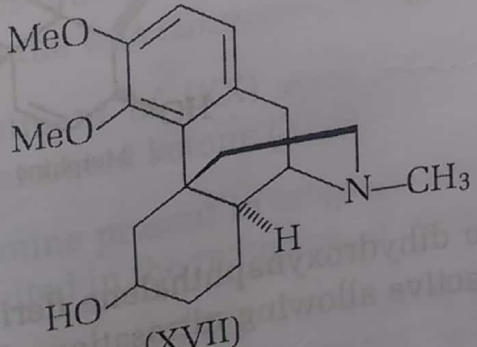


(XV)

$LiAlH_4$



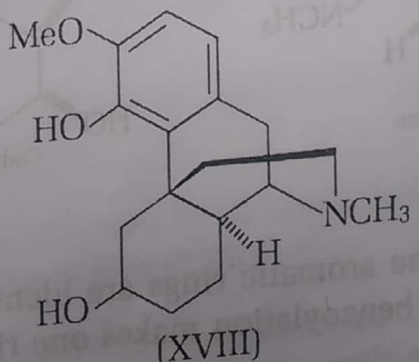
(XVI)



(XVII)

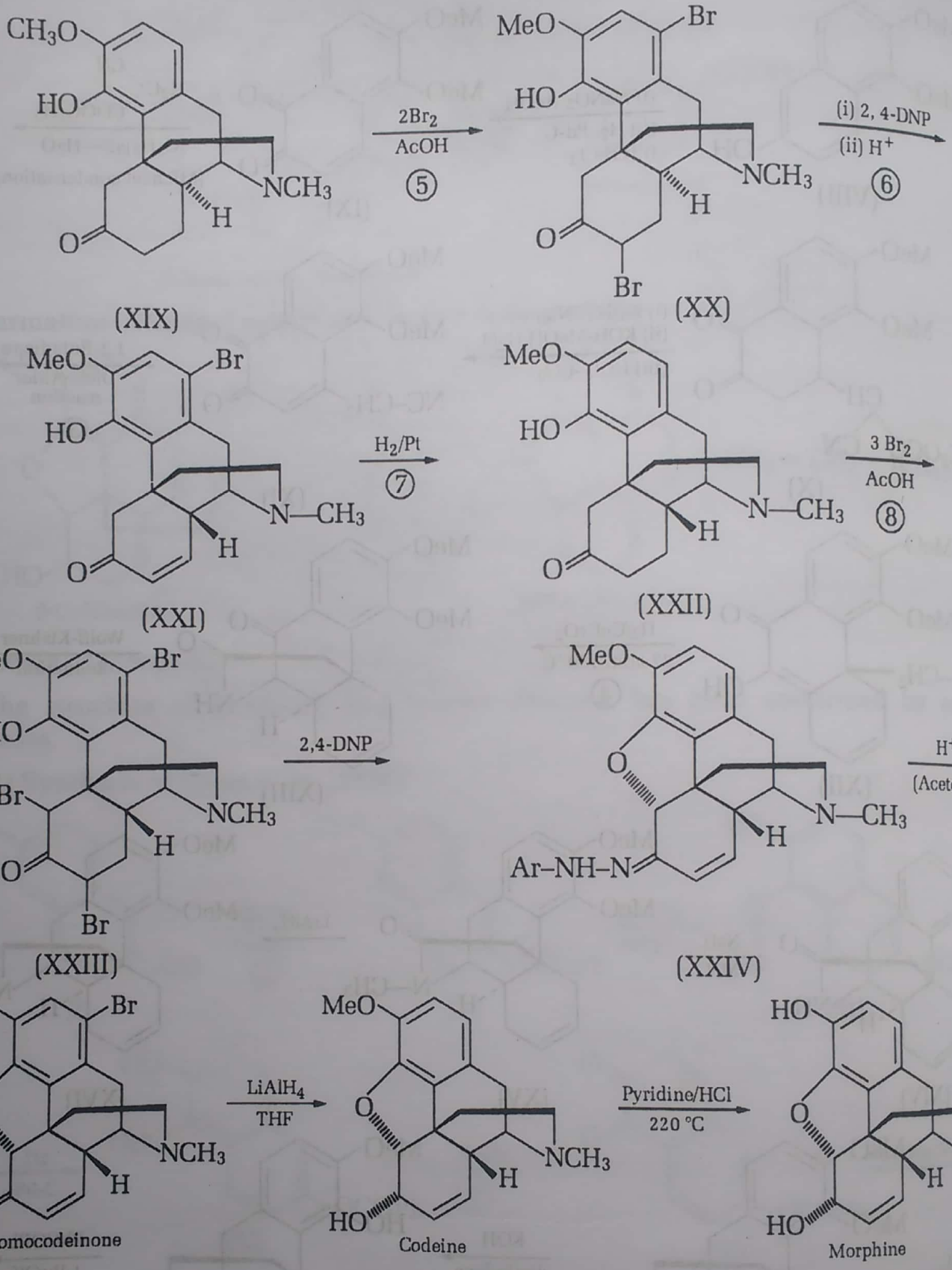
H_2SO_4
H_2O

KOH
diethylene glycol



(XVIII)

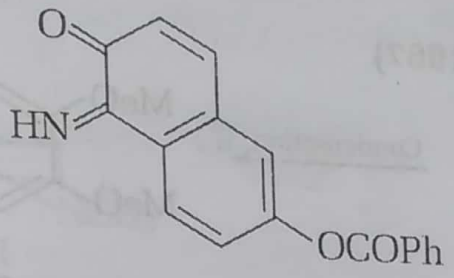
PhCOPh
t-BuOK
(Oppenauer)



Remarks

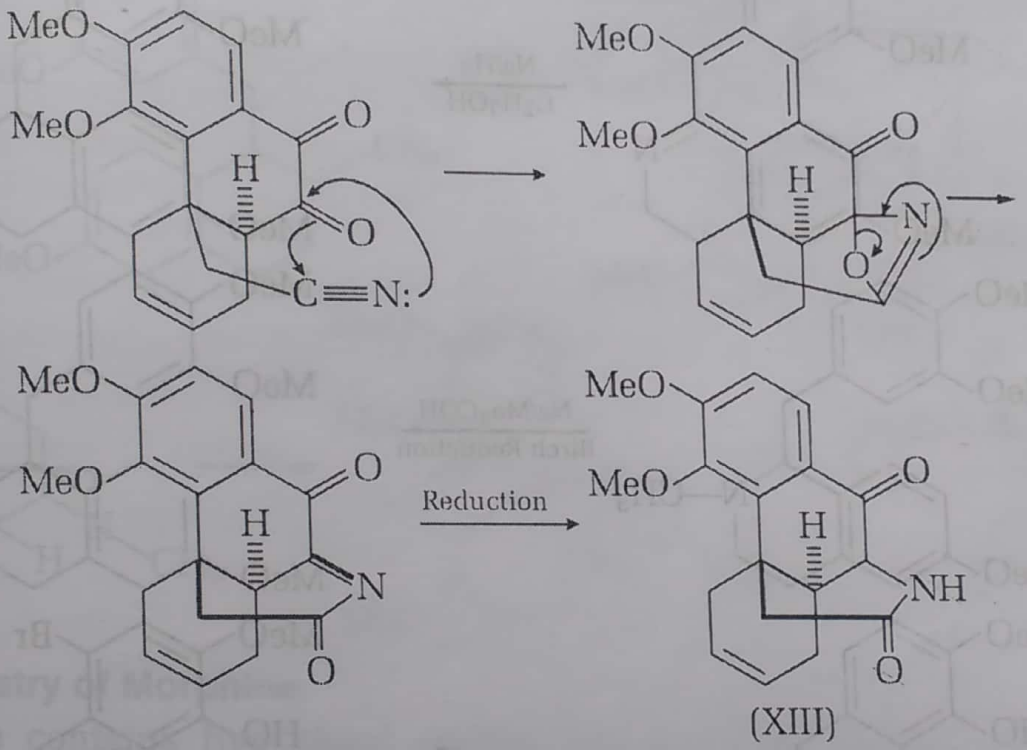
(1) Both the aromatic rings are identical in the dihydroxynaphthalene derivative (I). Partial benzoylation makes one ring less reactive allowing nitrosation of phenolic ring.

(2) Oxidation of (IV) yields following product which is hydrolysed to give o-quinone derivative (V)



③ The product obtained by Diel's-Alder reaction of (XI) was probably in the enolic form because configuration at the ring junction was not *cis*.

④ Catalytic reduction of (XII) yielded lactam derivative (XIII) in which the ethanamine bridge at C-13 was *trans* to C-14 hydrogen which was undersired configuration. The mechanism of this step is uncertain. The probable mechanism may be written via a four membered cyclic intermediate.



(XIII)

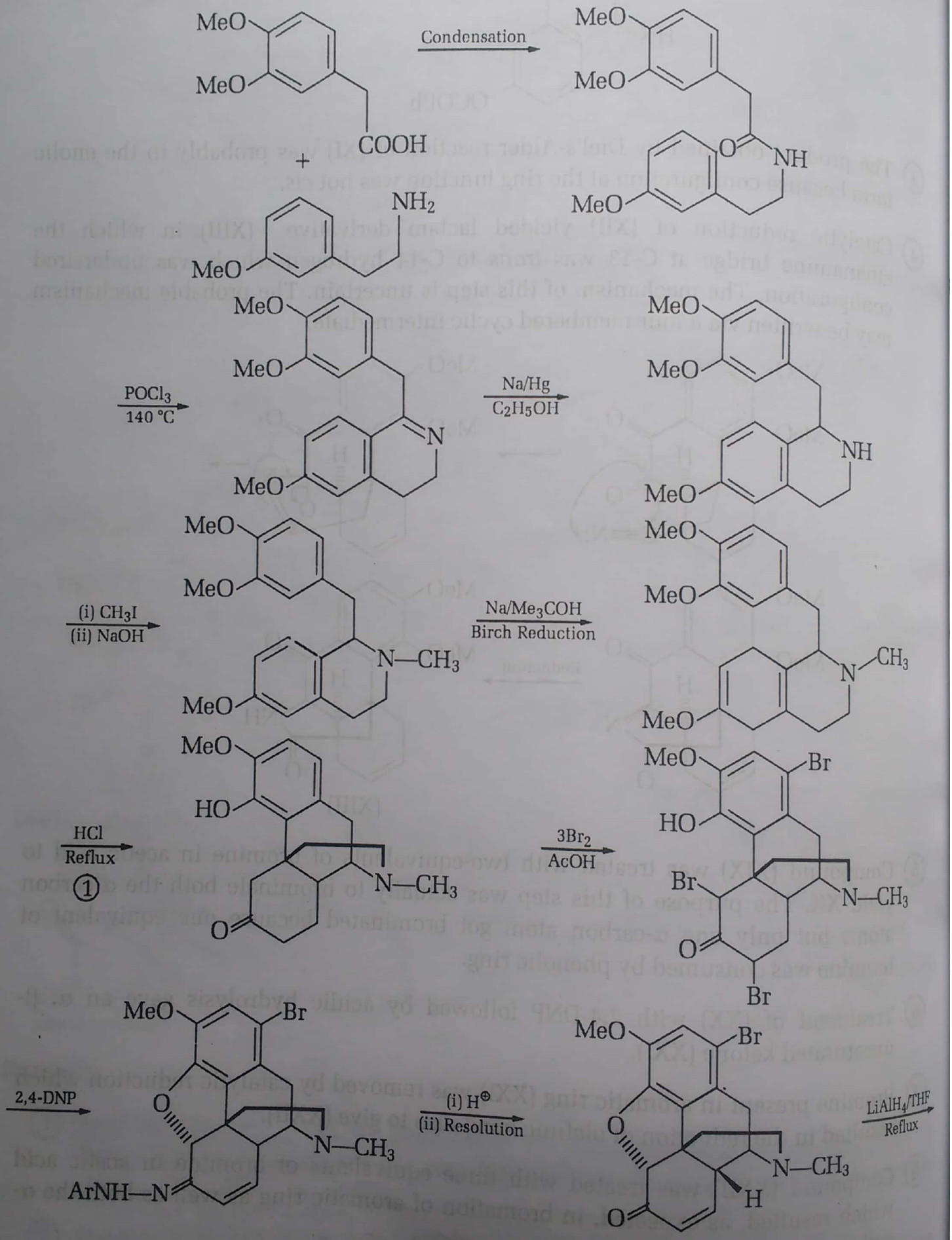
⑤ Compound (XIX) was treated with two-equivalents of bromine in acetic acid to yield XX. The purpose of this step was actually to brominate both the α-carbon atoms but only one α-carbon atom got brominated because one equivalent of bromine was consumed by phenolic ring.

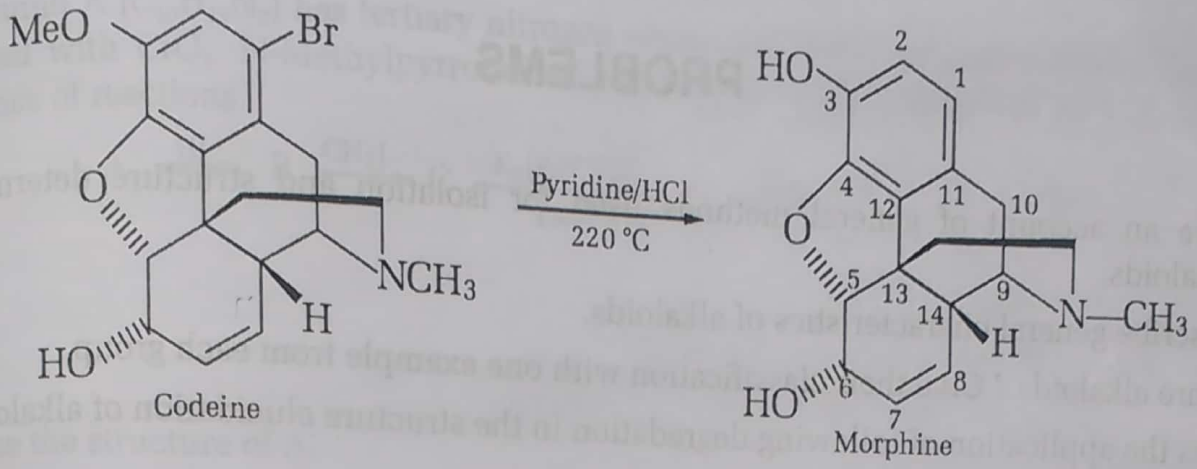
⑥ Treatment of (XX) with 2,4-DNP followed by acidic hydrolysis gave an α, β-unsaturated ketone (XXI).

⑦ Bromine present in aromatic ring (XXI) was removed by catalytic reduction which resulted in the reduction of olefinic bond also to give (XXII).

⑧ Compound (XXII) was treated with three equivalents of bromine in acetic acid which resulted, as expected, in bromation of aromatic ring as well as both the α-carbon atoms.

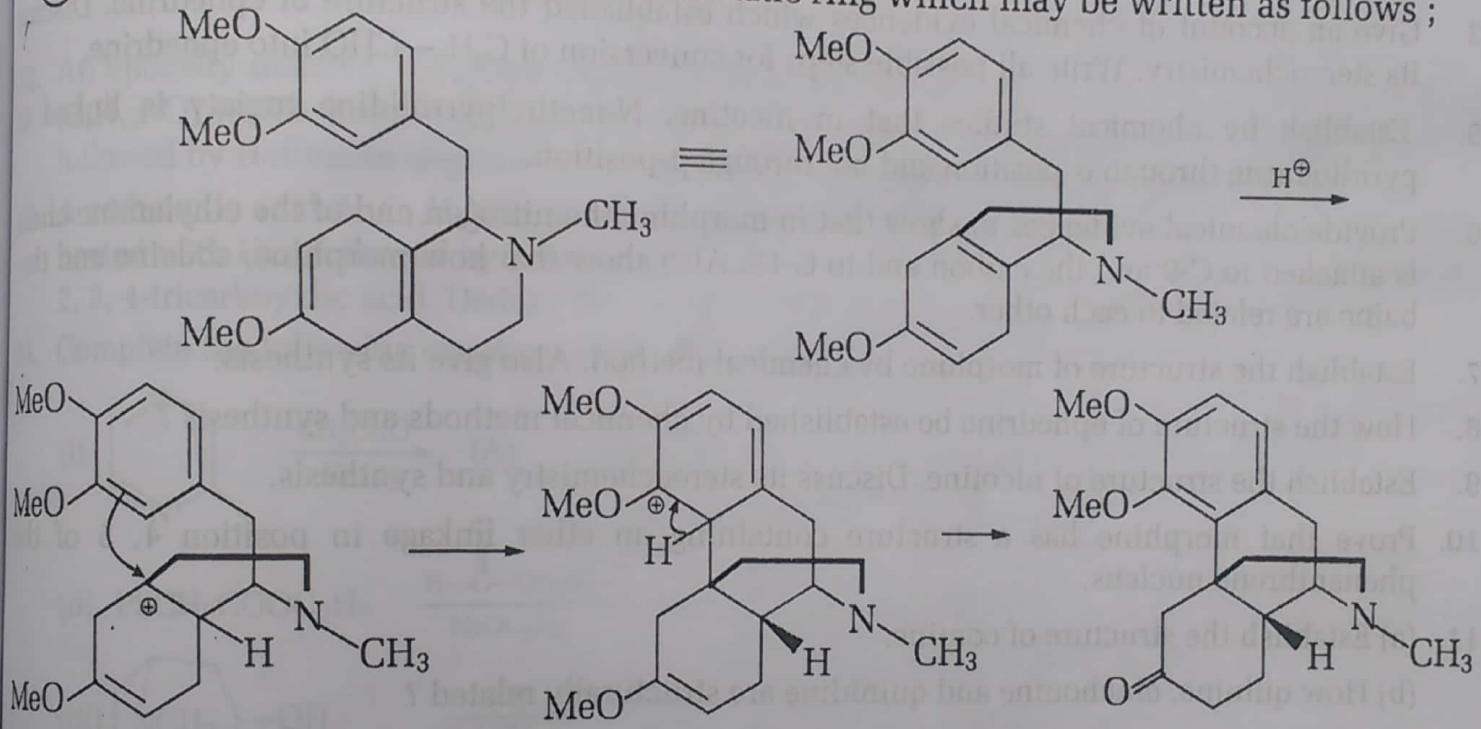
(2) Morrison *et. al.* Synthesis (1967)





Remark

(1) This step is simple alkylation of aromatic ring which may be written as follows ;



Stereochemistry of Morphine

Morphine contains five chiral centers but since the bridged ring system across positions, 9, 13 must be *cis*, eight pairs of enantiomers are possible for morphine. The configuration of morphine was confirmed on the basis of a great deal of work which is given here.