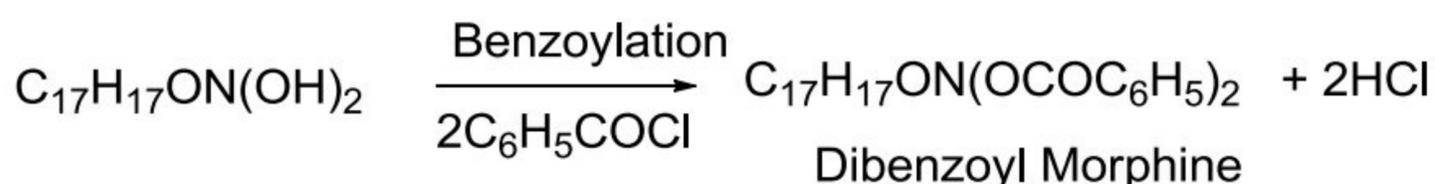
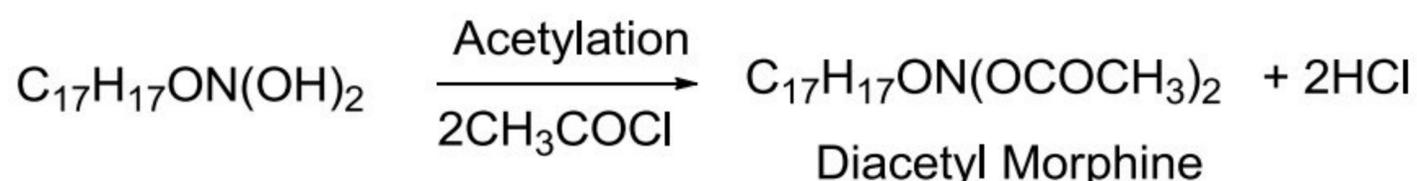


### 1.15.2 Constitution of Morphine:

Molecular formula is  $C_{17}H_{19}O_3N$ .

Nature of nitrogen atom: It adds on one molecule of  $CH_3I$  to form quaternary salt, indicating the presence of tertiary nitrogen atom. By Herzig-Meyer method, reveals the presence of  $N-CH_3$  group in morphine.

Nature of oxygen atoms: Morphine is acetylated or benzoylated forming diacetyl or dibenzoyl derivative indicating that morphine contains two hydroxyl groups.



With Ferric Chloride, Morphine yields a characteristic violet colour which is soluble in  $NaOH$  to form monosodium salt which is reconverted to morphine indicating the hydroxyl group are phenolic in nature.

Morphine is treated with halogen acids, to form monohalogen derivative i.e., one hydroxyl group is replaced by halogen acid. Hence, one of the hydroxyl group is alcoholic in nature.

Morphine is heated with  $CH_3I$  in the presence of aqueous  $KOH$ , it is methylated to yield codeine,  $C_{18}H_{21}O_3N$ . As codeine doesn't give colour with  $FeCl_3$  and it is not soluble in  $NaOH$  it follows that phenolic  $OH$  in morphine is methylated.

Further, codeine on oxidation with chromic acid, it yields codeinone, a ketone indicating that the hydroxyl group in codeine is a secondary alcoholic in nature. Codeine is a monomethyl ether of morphine.

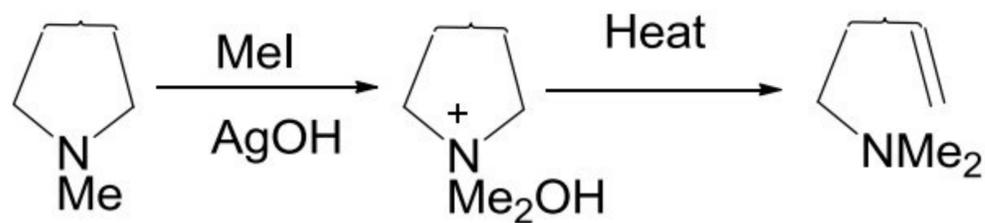
The third oxygen atom is highly unreactive indicating its nature as an ether linkage.

Presence of ethylenic Bond:

Codeine is reduced catalytically in the presence of palladium, suggesting both codeine and morphine contains one ethylenic bond.

Presence of Benzene Nucleus: On bromination, morphine forms monobromo derivative with  $HBr$ , indicating the presence of benzene nucleus.

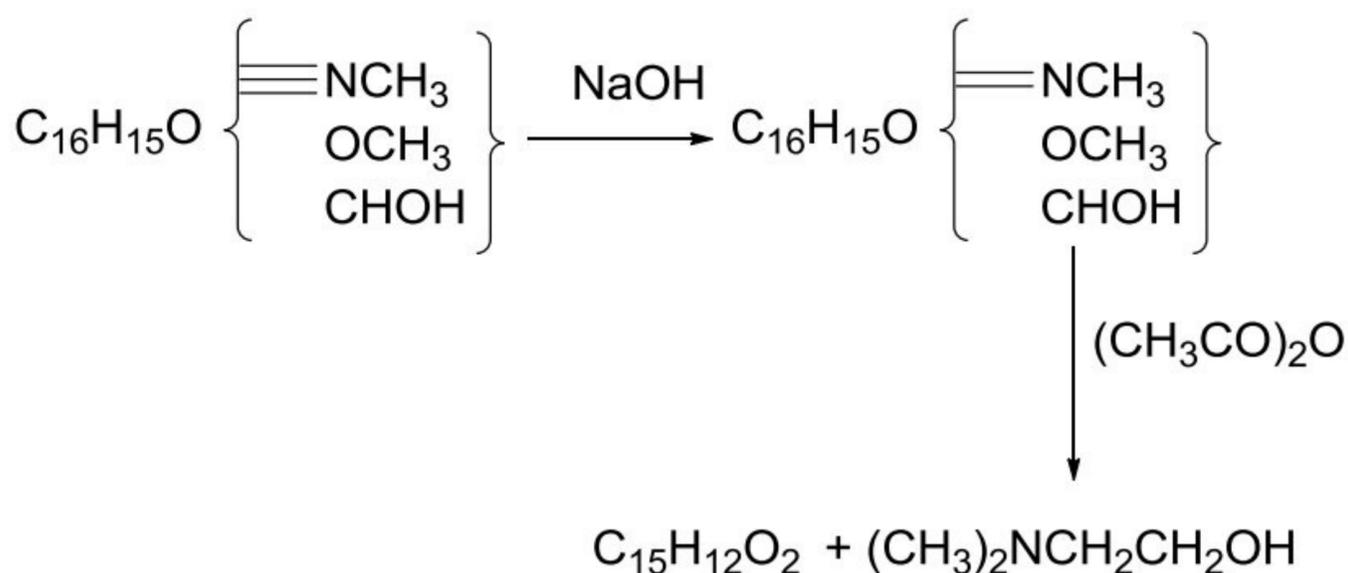
Presence of cyclic tertiary base system: Codeine on exhaustive methylation yields  $\alpha$ -codeimethine, contains one  $-CH_2$  group more than codeine and the nitrogen remains intact indicating the presence of cyclic t-amine.



Presence of Phenathrene: Morphine on distillation with Zn dust it yields a phenathrene and a number of bases.

Codeine on treating with  $\text{CH}_3\text{I}$  it yields codeine methiodide, on boiling with  $\text{NaOH}$  yields methylmorphimethine on further boiling with acetic anhydride yields a mixture of methyl morphol and ethanoldimethyl amine.

Reactions:



**a) Structure of Methyl morphol:**

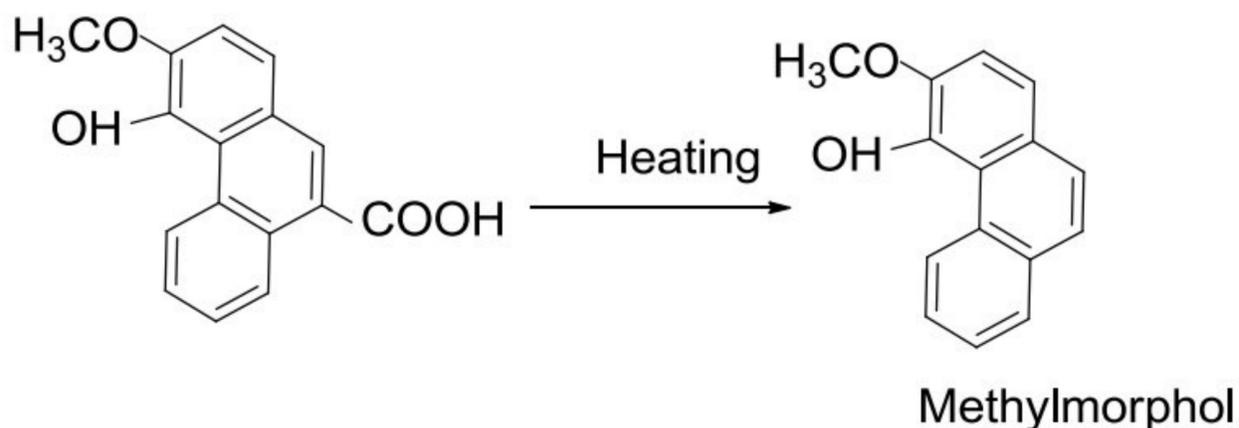
Heating the compound  $\text{C}_{15}\text{H}_{12}\text{O}_2$  with  $\text{HCl}$  at  $180^\circ\text{C}$  yields methyl chloride and dihydroxy phenanthrene ie morphol is obtained.

Diacetylmorphol on oxidation yields diacetyl phenanthraquinone indicating that the positions 9 and 10 are free.

Diacetylphenanthraquinone on oxidation with  $\text{KMnO}_4$  yields phthalic acid indicating that the two hydroxyl groups are in the same ring.

Methylmorphol is 4-hydroxy3-methoxyphenathrene.

Reactions:

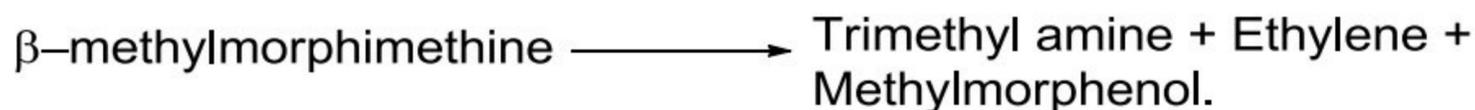


Presence of  $-NCH_3$  group:

The formation of ethanoldimethyl amine from methylmorphimethine reveals that both codeine and morphine contains a  $N-CH_3$  group.

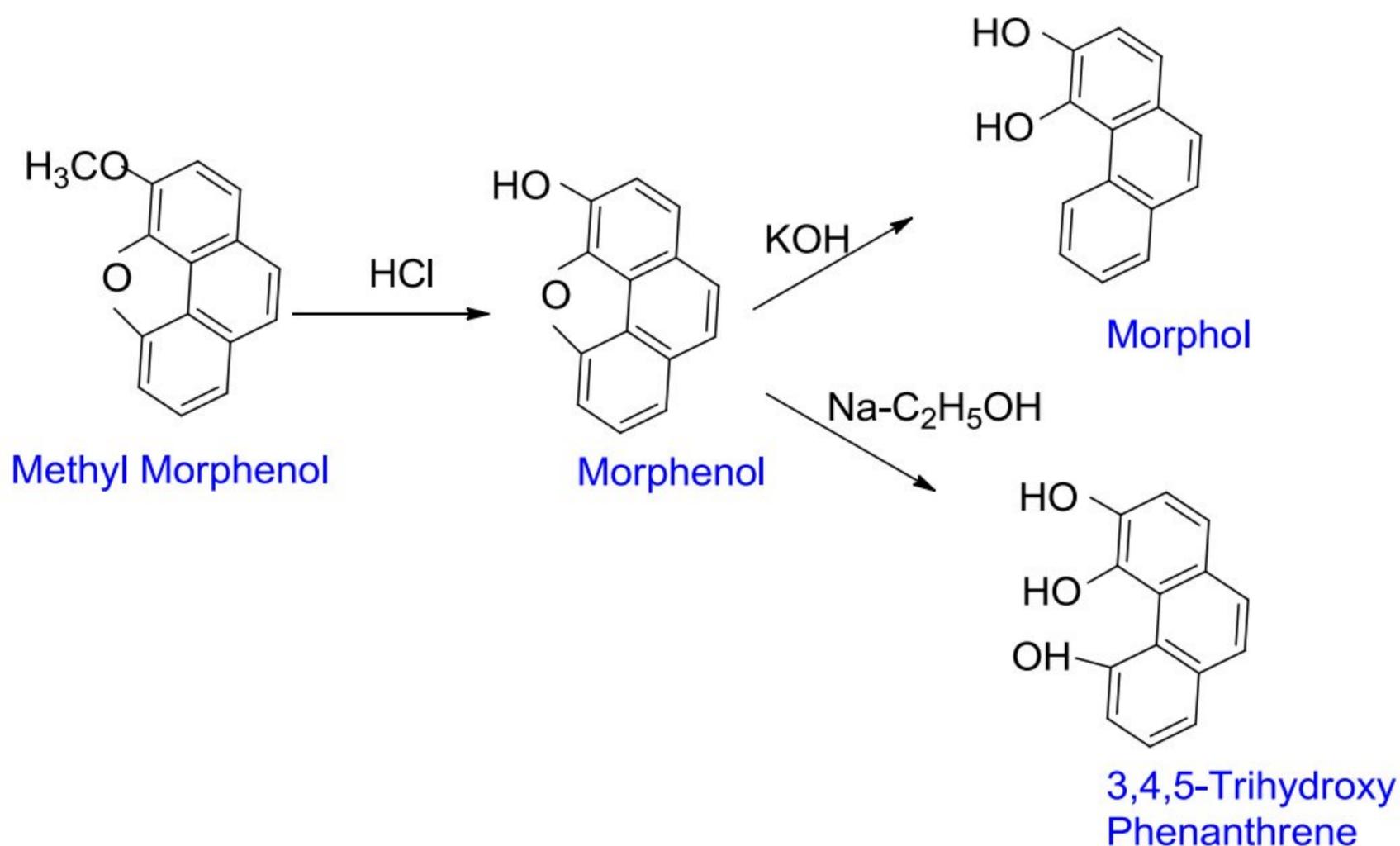
**b) Structure of Morphenol:**

When  $\beta$ -methylmorphimethine is heated with water, it yields a mixture of trimethyl amine, ethylene and methyl morphenol.



Methylmorphenol on demethylated with HCl, it yields morphenol, a compound with one phenolic hydroxyl group and an inert oxygen atom.

When morphenol is fused with KOH, it yields 3,4,5-trihydroxyphenanthrene. Also morphenol on reduction with  $Na-C_2H_5OH$  it yields morphol.



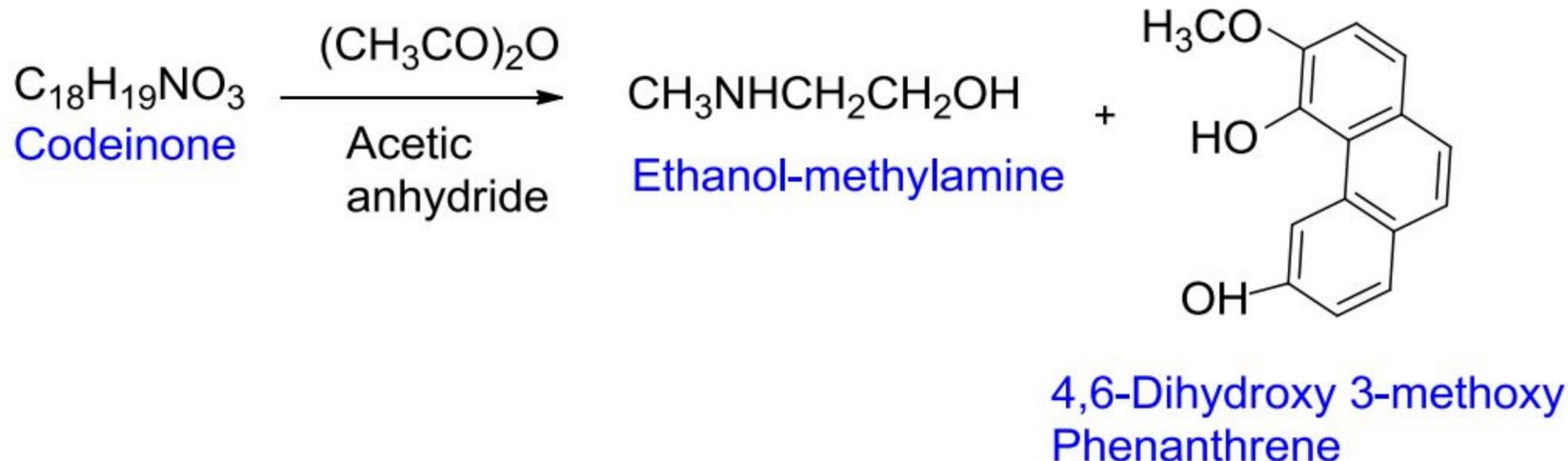
Thus, Morphenol contains an ether linkage at position 4 and 5 of the phenanthrene nucleus.

The structure of morphenol and its production from codeine reveals that the two of the three oxygen atoms (i.e) One at C3, and the other ether linkage at C<sub>4</sub> and C<sub>5</sub> of the phenanthrene nucleus.

Position of third oxygen:

Codeinone on heating with acetic anhydride yields ethanoldimethyl amine and diacetyl derivative of 4,6-dihydroxy 3-methoxy phenanthrene.

Reactions:



The hydroxyl group in the 6 position must be from the oxygen of the keto group in codeinone.

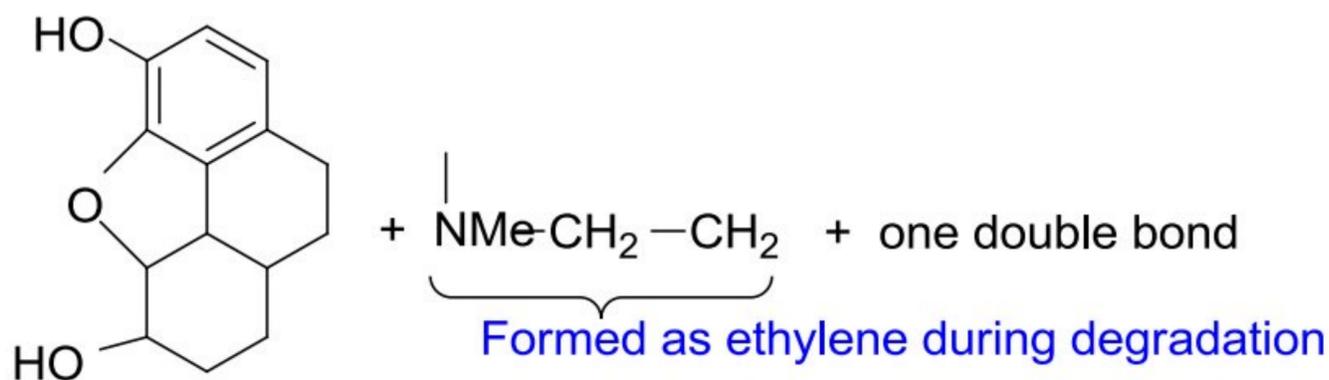
Position of **all three oxygen atoms** in morphine are : One at C<sub>3</sub>- Phenolic; Other at C<sub>4</sub> and C<sub>5</sub> (Ether) and third (secondary alcohol) at C<sub>6</sub> of the phenanthrene nucleus.

**c) Structure of Morphine:**

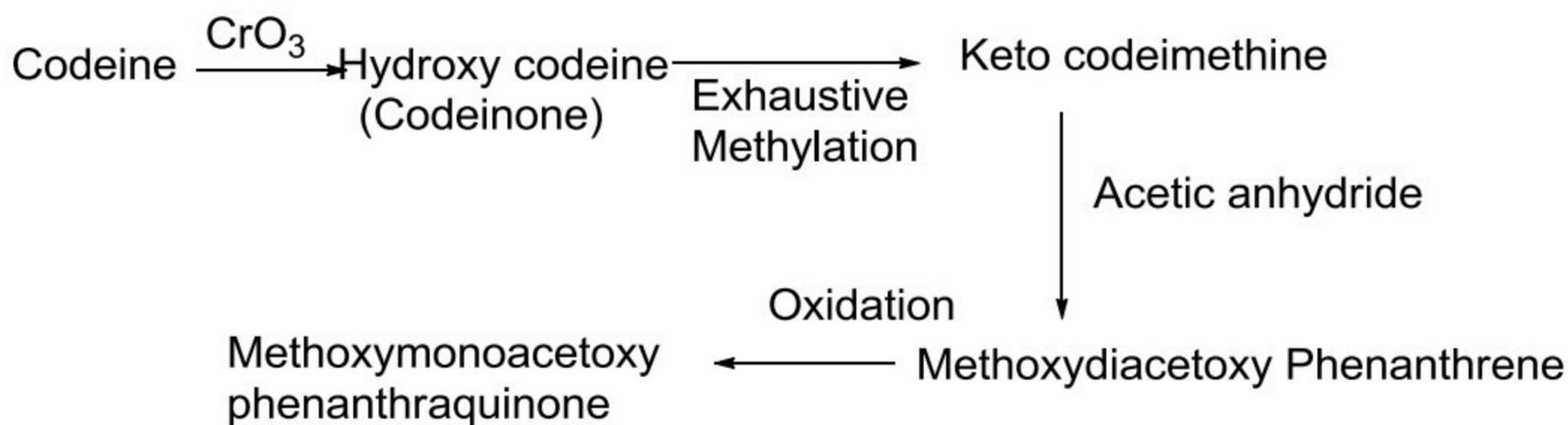
Morphine forms monobromo derivative with bromine and monosodium salt with NaOH, indicating that morphine contains a benzenoid structure.

On exhaustive methylation of codeimethines, ethylene and ethanol dimethyl amine is formed as the products, reveals the presence of N-CH<sub>3</sub> group.

Also a double bond and a tertiary nitrogen has to be present in morphine. Hence, the partial structure of morphine is,



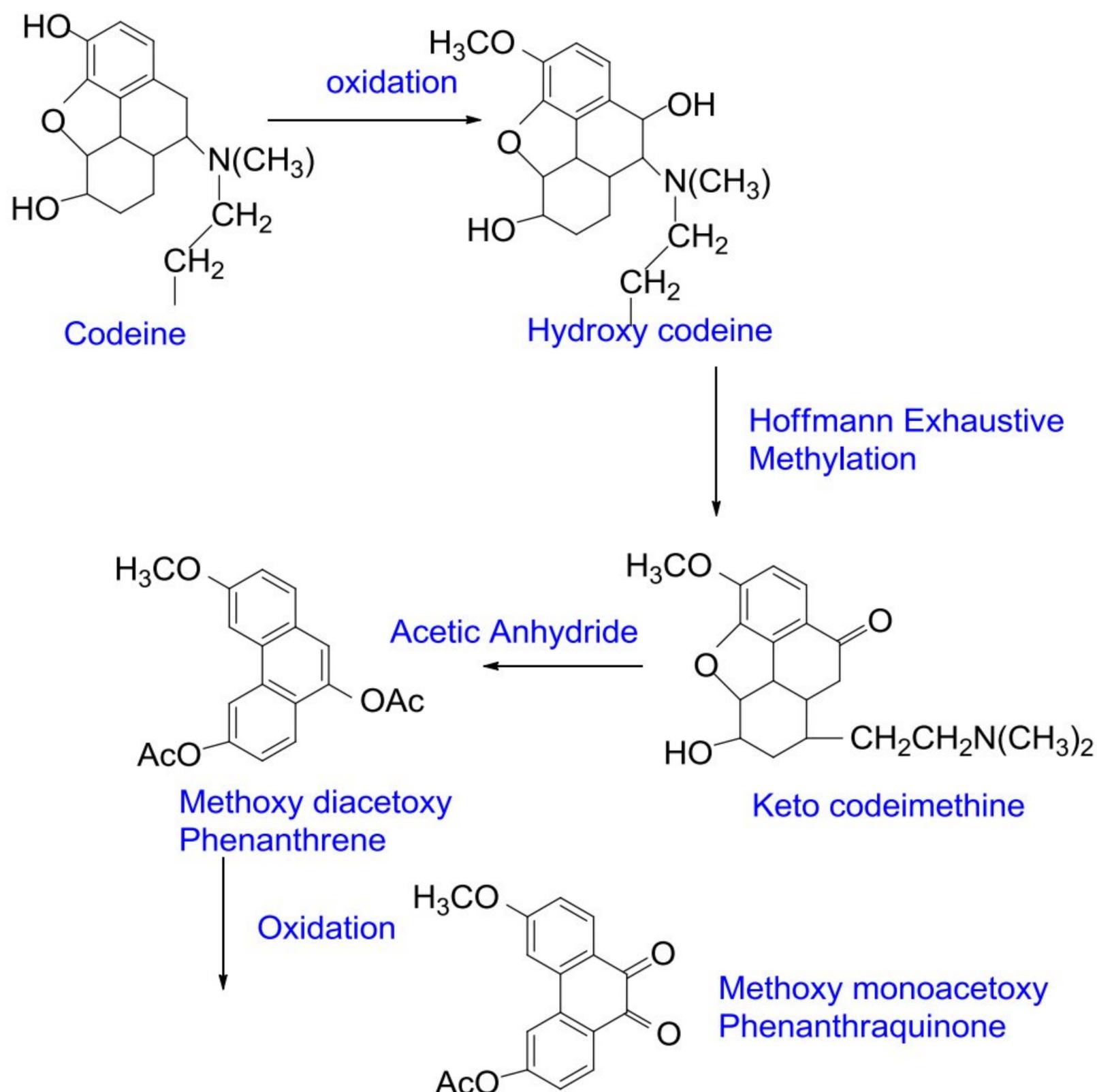
**d) Point of linkage of CH<sub>2</sub>-CH<sub>2</sub>-N Me group:**



Loss of acetyl group reveals that one of the acetoxy groups must be present either at C<sub>9</sub> or C<sub>10</sub>. The acetyl group is inserted via ketonic group which concludes that the new hydroxyl group in hydroxy codeine is present either at C<sub>9</sub> or C<sub>10</sub>. On the basis of steric consideration, the attachment at C<sub>9</sub> is most probable.

Hydroxyl group in hydroxycodeine is changed to keto group and a double bond is introduced between C<sub>9</sub> and C<sub>10</sub> during the fission of the nitrogen ring. Nitrogen must be linked either to C<sub>9</sub> or C<sub>10</sub>. The exact point of linkage of nitrogen is at C<sub>9</sub>, confirmed by its synthesis.

Reactions:



The carbon end of the side chain must be located at the angular position so that its extrusion from that position takes place during aromatisation at position C<sub>13</sub> and C<sub>14</sub>. The former is explained as this structure explains the formation of thebaine to thebenine.