IVth semester (Organic Special)

PAPAVERINE

Papaverine alongwith twenty four alkaloids occurs in opium poppy to the extent of 0.5 to 8 percent and hence all of them are usually known as opium alkaloids.

The compound is colourless solid (m.p. = 147°C) and is an optically inactive tertiary base.

Constitution :-

The structure of the compound is established as;

1. From the elemental analysis and the molecular weight determination, the established molecular formula for the compound is $C_{20}H_{21}NO_4$.

2. The compound adds one mole of CH_3I to form quaternary methiodide salt indicating the presence of tertiary nitrogen in the compound.

$$C_{20}H_{21}O_4\}N + CH_3I \longrightarrow C_{20}H_{21}O_4\{\rightarrow \overset{+}{N}-CH_3\ I^{-1}$$

3. The DBRE for the compound $\left(=20-\frac{21}{2}+\frac{1}{2}+1\right)$ is equal to eleven, indicating that the compound is polycyclic.

4. The compound fails to form acetyl or benzoyl derivative, indicating the absence of the hydroxyl group in the molecule.

5. Papaverine is unable to respond phenyl hydrazine test and hence the carbonyl group is absent in the molecule.

6. When the compound is boiled with hydroiodic acid (Zeisel's method) and the vapours of CH_3I is passed in the alcoholic $AgNO_3$ solution, the gravimetric estimation through the AgI obtained gives the information of four methoxy group in the molecule.

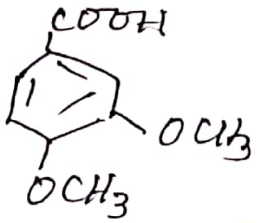
$$C_{20}H_{21}NO_4 \xrightarrow[\Delta]{HI} CH_3I(v) \xrightarrow[C_2H_5OH]{AgNO_3} AgI\downarrow$$

7. Papaverine when treated with cold dilute $KMnO_4$ produces a secondary alcohol because on boiling with this oxidising agent, a ketone is formed. The reaction indicates the presence of a $-CH_2-$ unit in the compound.

$$-CH_2- \xrightarrow[KMnO_4]{aq.} -\underset{OH}{CH}- \xrightarrow[KMnO_4]{aq/\Delta} -\overset{O}{\overset{\|}{C}}-$$

8. On the KOH fusion, the compound is degraded into two new products viz A ($C_{11}H_{11}NO_2$) and B ($C_9H_{12}O_2$) along with a known compound veratric acid.

$$C_{20}H_{21}NO_4 \xrightarrow[\Delta]{KOH} \underset{(A)}{C_{11}H_{11}NO_2} + \underset{(B)}{C_9H_{12}O_2} +$$



Veratric acid.

In order to establish the structure of Papaverine, it is essential to establish the structure of (A) and (B)

9. Identification of the compound (A) with the molecular formula $C_{11}H_{11}NO_2$.

(i) The compound indicates the presence of two methoxy group (Zeisel's Method)

$$C_{11}H_{11}NO_2 \xrightarrow[\Delta]{HI} CH_3I \xrightarrow[C_2H_5OH]{AgNO_3} AgI\downarrow$$

(ii) The DBRE for the compound is seven, (DBRE = $11 - 0.5 \times 11 + 0.5 + 1 = 7$) indicating the presence of polycyclic or aromatic rings in the compound.

(iii) The compound also indicates the presence of a tertiary base.

$$C_{11}H_{11}NO_2 + \underset{1\,mole}{CH_3I} \longrightarrow C_{11}H_{11}O_2\left(\overset{\oplus}{N}-CH_3\right)I^{-1}$$

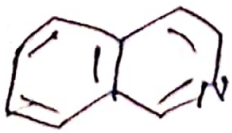
or

$$C_{11}H_{11}O_2\left(\overset{+}{N}-CH_3\right)I^{-1}$$

(iv) The compound on demethylation followed by the Zn-dust distillation gives isoquinoline.

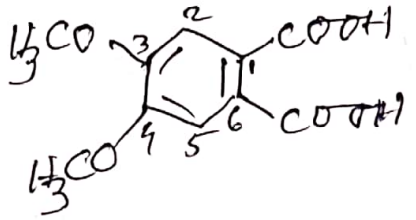
$$C_{11}H_5N(-OCH_3)_2 \xrightarrow[\Delta]{HI} C_{11}H_5N(-OH)_2 \xrightarrow[\Delta]{Zn\text{-}dust}$$

$$\cdot 2CH_3I$$



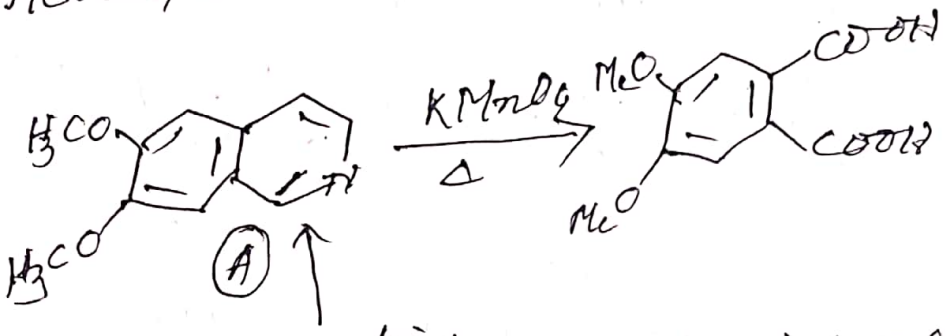
Isoquinoline

(V) The compound on oxidation with aqueous $KMnO_4$ gives m-Hemipinic acid i.e 3,4-dimethoxyphthalic acid.



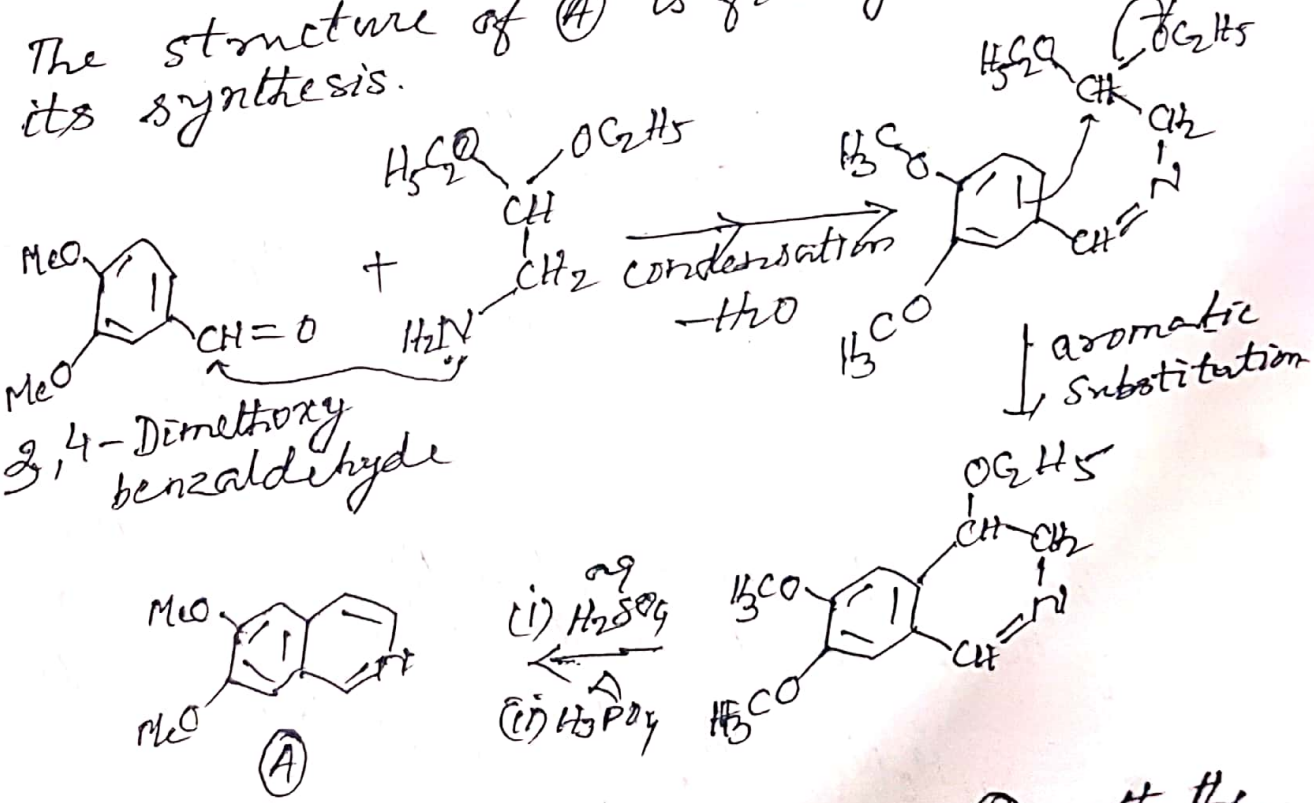
Hemipinic acid

Hence, the compound (A) is —



active towards oxidising agents.

(vi) The structure of (A) is finally confirmed by its synthesis.

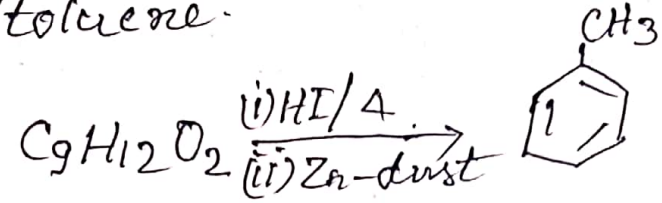


10. Identification of the compound (B) with the molecular formula $C_9H_{12}O_2$.

(i) The compound is tested for two methoxy group (Zeisel's Method)

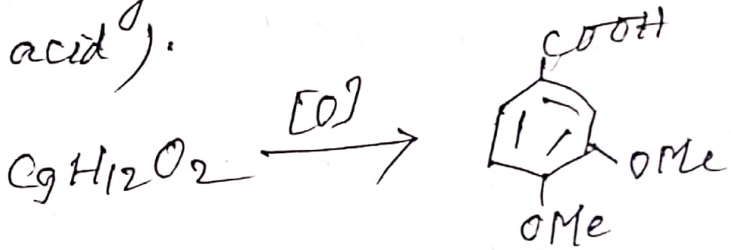
$$C_9H_{12}O_2 \xrightarrow[\Delta]{HI} CH_3I \xrightarrow[C_2H_5OH]{AgNO_3} AgI\downarrow$$

(ii) The compound (B) is benzenoid because on demethylation followed by Zn dust distillation, it gives toluene.

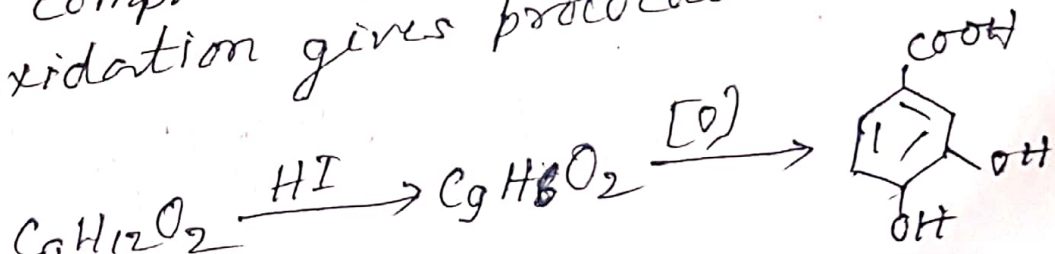


The DBRE for the compound is four.

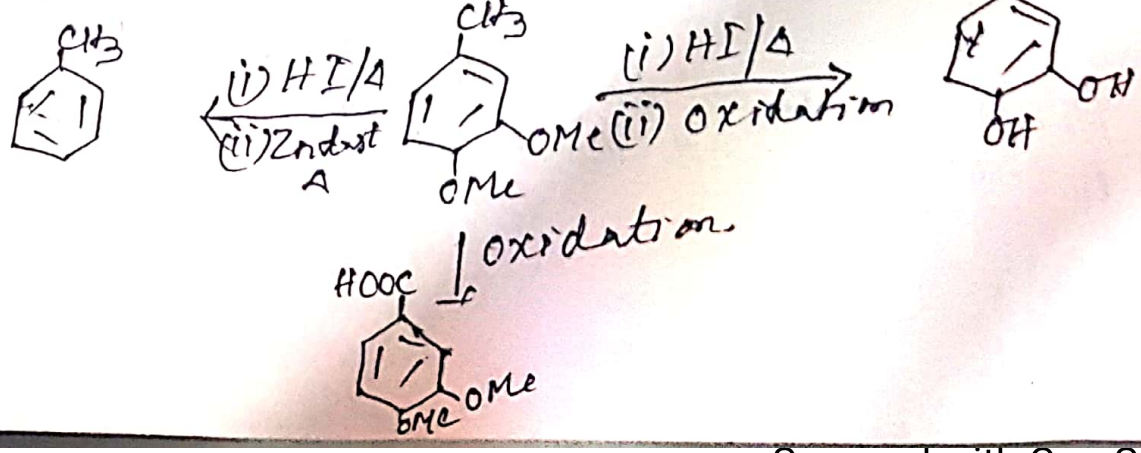
(iii) The compound (B) on [illegible] oxidation gives veratric acid (3,4-dimethoxy benzoic acid).



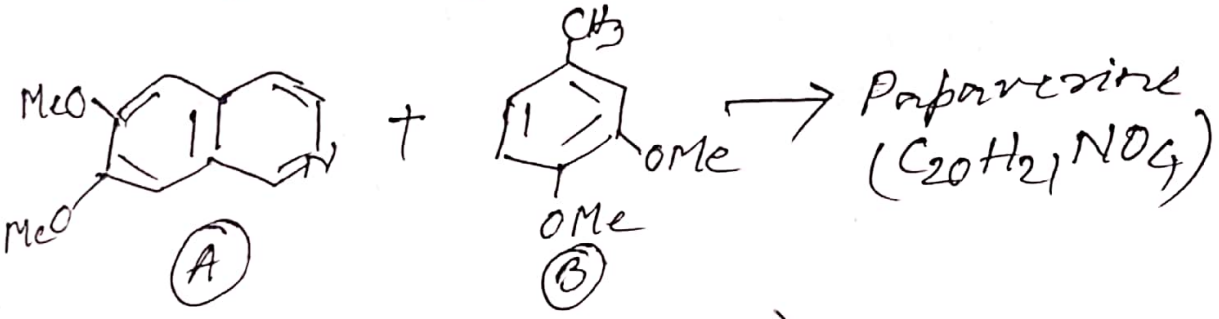
(iv) The compound (B) on demethylation followed by oxidation gives protocatechuic acid.



(v) Hence the compound "B" is 3,4-Dimethoxytoluene, which can explain the above reactions



11. Point of Linkage between (A) and (B)

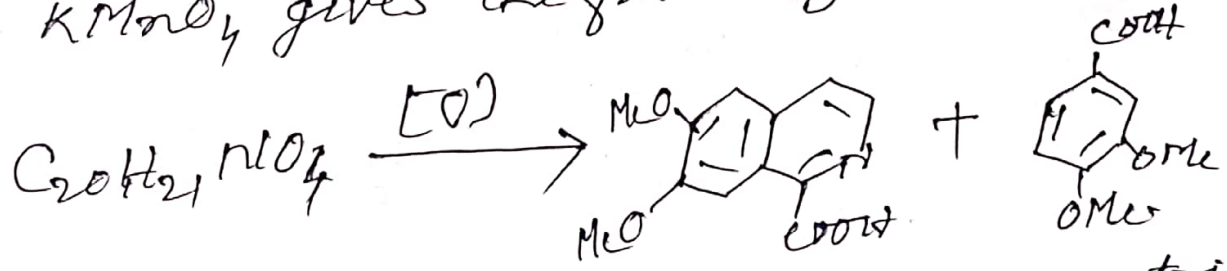


(A) $(C_{11}H_{11}NO_2)$ (B) $(C_9H_{12}O_2)$

The formation of veratric acid during KOH fusion is indication of the linkage of unit (B) through its methyl substituent with the unit (A).

This is also confirmed by the presence of $-CH_2-$ unit in paparverine.

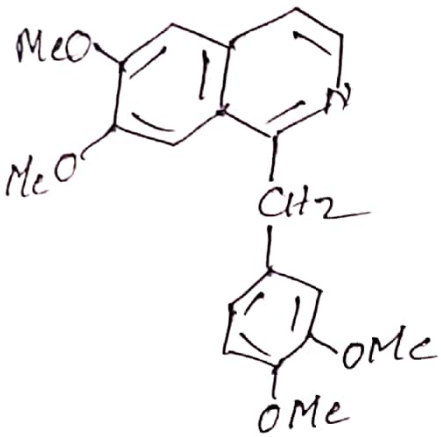
As Paparverine on prolonged oxidation with $KMnO_4$ gives the following two acids -



6,7-Dimethoxy isoquinoline-1-carboxylic acid

Veratric acid.

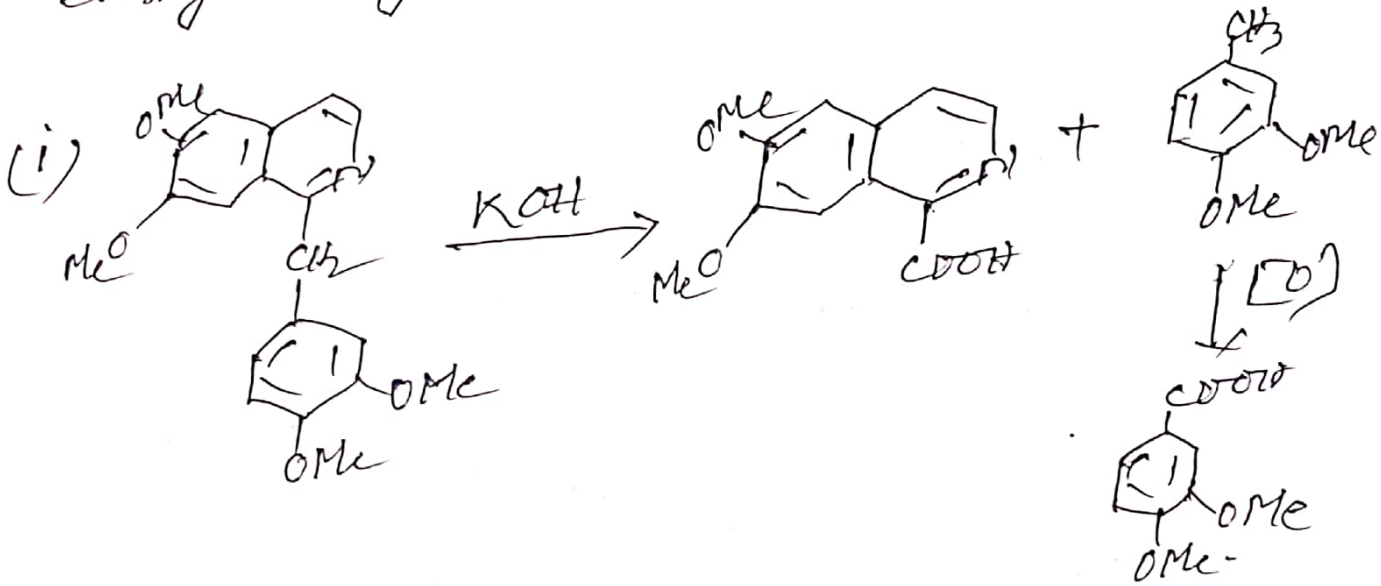
Hence, on this basis the possible linkage between (A) and (B) is expressed as —



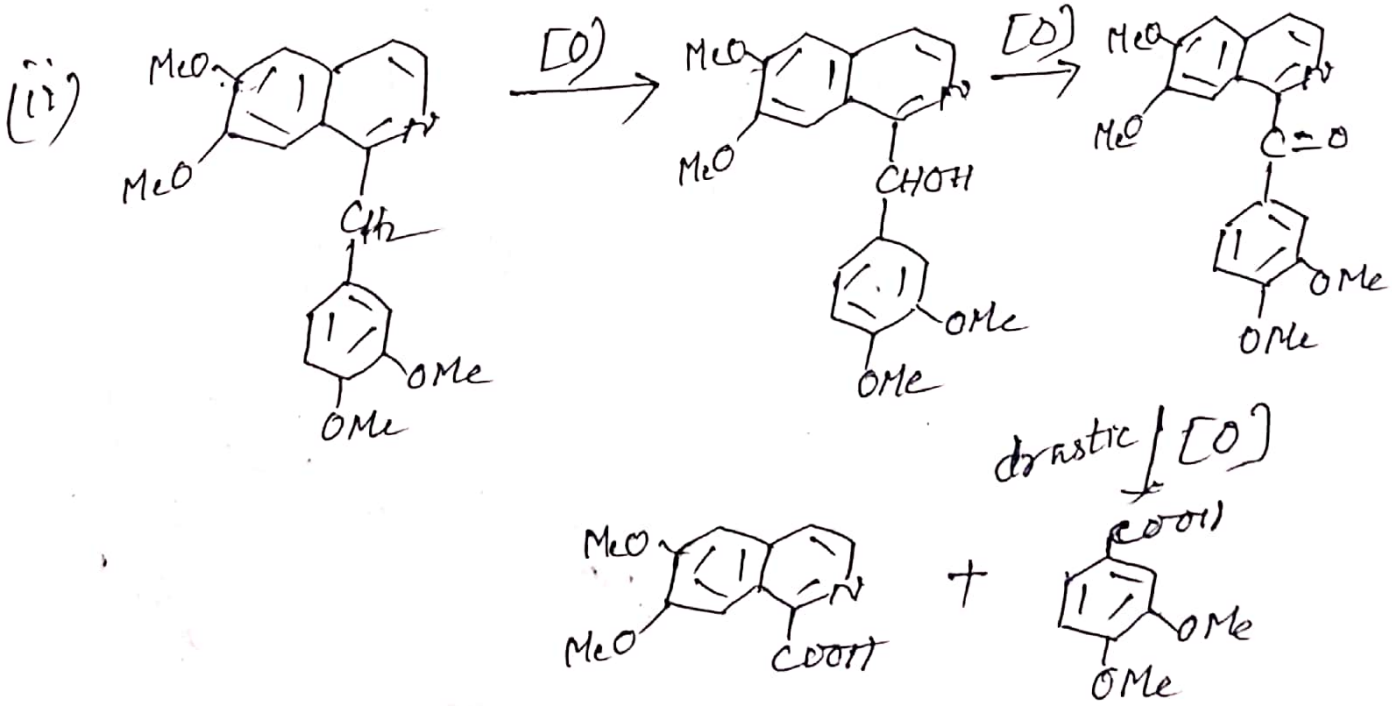
Probable structure of Papaverine (X)

This structure of Papaverine explains easily every reaction mentioned above.

(i)

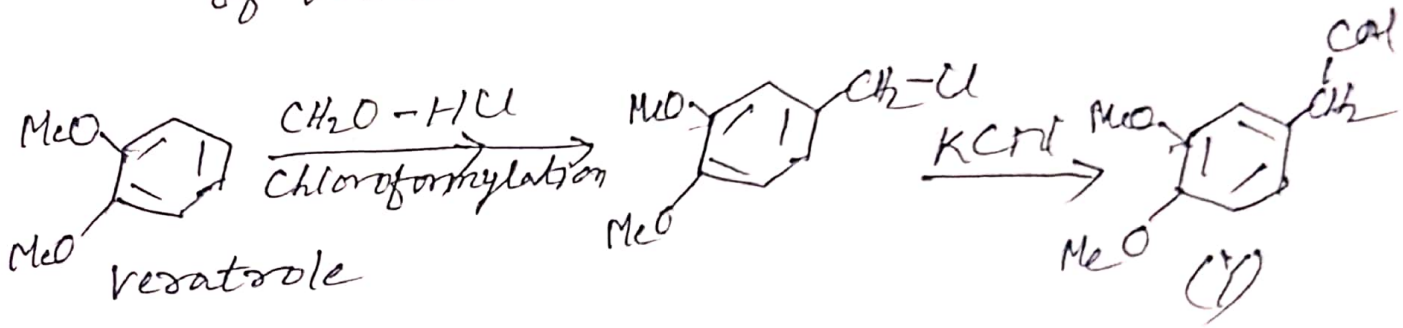


(ii)

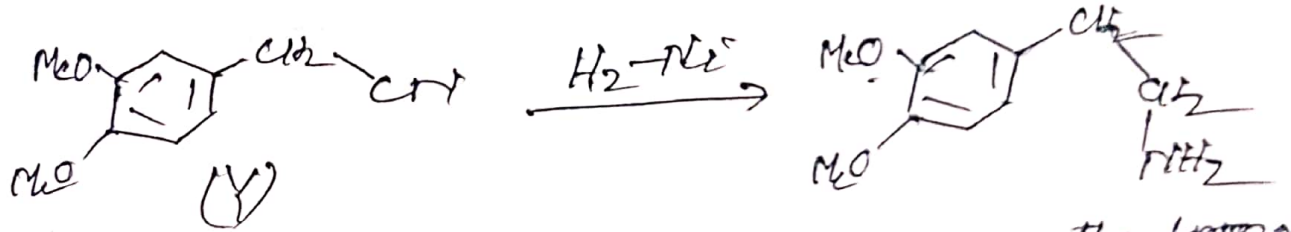


12. Finally the proposed structure (X) of the Papaverine is confirmed by its synthesis.

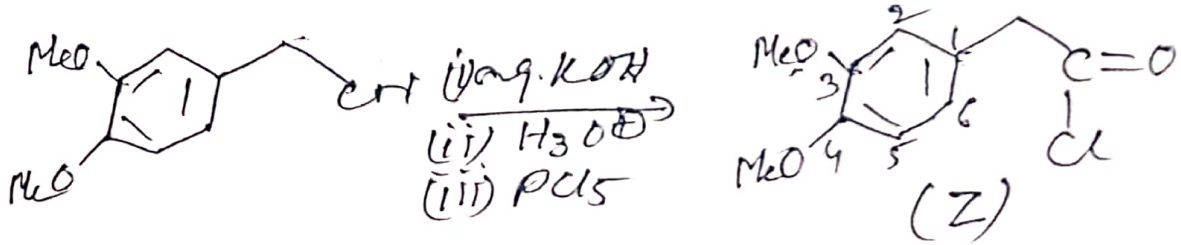
<u>Step I</u> : Synthesis of the starting material of the condensation reaction. The process starts with the formylation of veratrole



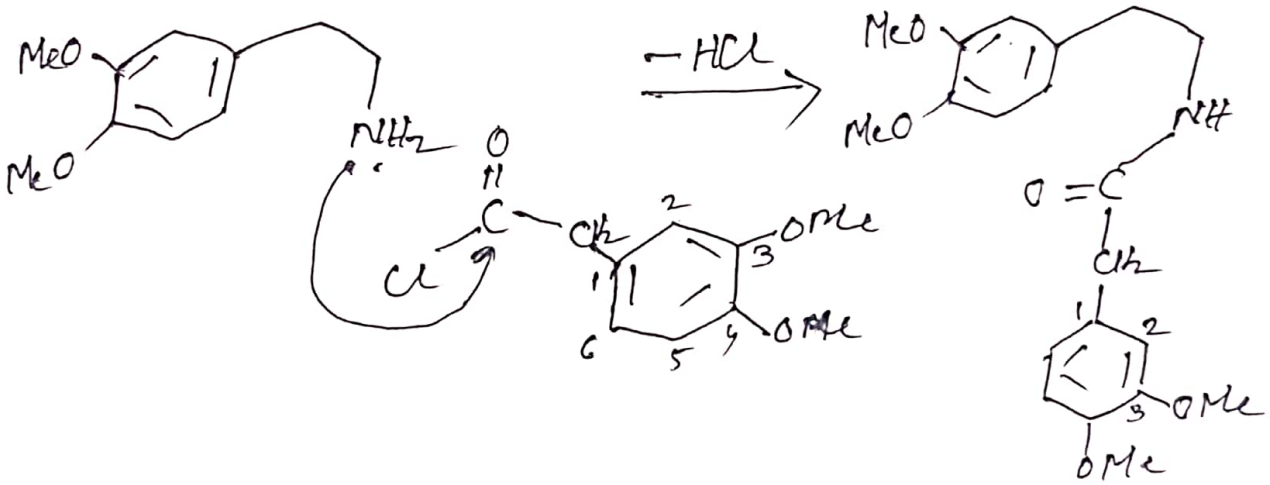
<u>Step II</u> : <u>Reduction of Y</u>



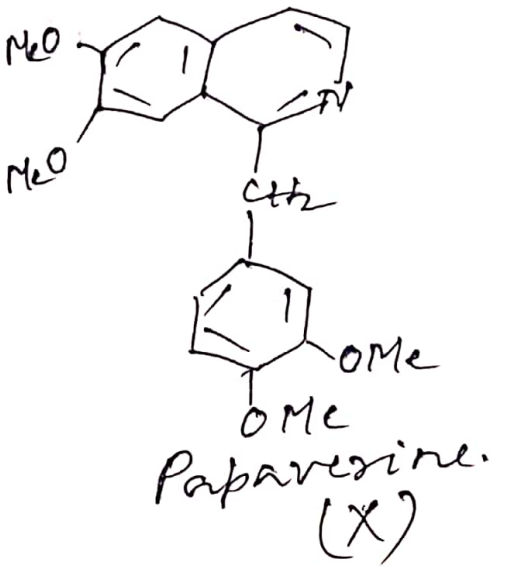
<u>Step III</u> : Alkaline hydrolysis, following for the formation of acid chloride group.



Step IV : Condensation between (Y) and (Z)



(i) tautomerisation



Papaverine. (X)

(i) P_2O_5/Δ

(ii) Pd-C, 200°C (aromatisation)