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Pdf for IV semester (Organic special)
Paper – M.Sc. CH Ec Ic
Unit – I (Alkaloids)

ATROPINE

Atropine is very important member of tropane alkaloids. The compound is optically active, $[\alpha]_D = -22^\circ$. It is obtained in its racemic form when l-hyoscyamine is warmed with alcoholic KOH solution.

The compound is crystalline solid (m.p – 118°C) and is a teritary base of pKa ~ 10.0

It is used to dilate pupil of eyes and its single drop containing 1 part of atropine and 40,000 parts of water is sufficient to dilate the pupil of eyes. The compound is used also to relieve the night sweats which are a dressing feature of tuberculosis and to diminish the activity of the salivary and gastric glands.

2-

Constitution of Atropine

Following are the different steps through which we can derive the structure of Atropine —

(1) The elemental analysis and the molecular weight determination indicates that the molecular formula of the compound is $C_{17}H_{23}NO_3$.

(2) The compound is easily converted into a mono-acetyl derivative when allowed to react with acetyl chloride.

$$C_{17}H_{23}NO_3 \xrightarrow[Py]{AcCl} C_{17}H_{22}NO_2\left(O-\overset{\overset{O}{\|}}{C}-CH_3\right)$$

This indicates the presence of a hydroxyl group in the molecule.

The compound is easily oxidised into a monocarboxylic acid, indicating the presence of a primary alcoholic group in the molecule.

$$C_{17}H_{23}NO_3 \equiv C_{16}H_{20}NO_2(-CH_2OH) \xrightarrow{[O]} C_{16}H_{20}NO_2(-COOH)$$

(3) The compound does not indicates the presence of either a carbonyl group or an acid group.

(4) On alkaline hydrolysis [with $Ba(OH)_2$] followed by the acidification, the compound breaks

into two components; (A) having molecular formula $C_9H_{10}O_3$ and (B) with the m.f. $C_8H_{15}NO$.

$$C_{17}H_{23}NO_3 + H_2O \xrightarrow{\Delta} \underset{(A)}{C_9H_{10}O_3} + \underset{(B)}{C_8H_{15}NO}.$$

As (A) is identified as monocarboxylic acid and (B) as a secondary alcohol, indicating the presence of an ester group in the molecule.

Hence, in order to arrive at the structure of the Atropine, we must have to identify the compounds (A) and (B).

(5) Identification of (A) [$C_9H_{10}O_3$ → Tropic acid]

(a) The double bond ring equivalent (DBRE) for the compound is five, which indicates that the compound may be either aromatic or polycyclic.

$$DBRE = \left(a - \frac{1}{2}b + \frac{1}{2}c + 1\right) = \left(9 - \frac{1}{2}\times 10 + \frac{1}{2}\times 0 + 1\right)$$
$$= 5.$$

(b) It can form a monoacetyl derivative and gives positive response to the $NaHCO_3$ test.

(i) $C_9H_{10}O_3 \xrightarrow[Py]{AcCl} C_9H_9O_2(O-\overset{O}{\overset{\|}{C}}-CH_3)$ test of an alcoholic group

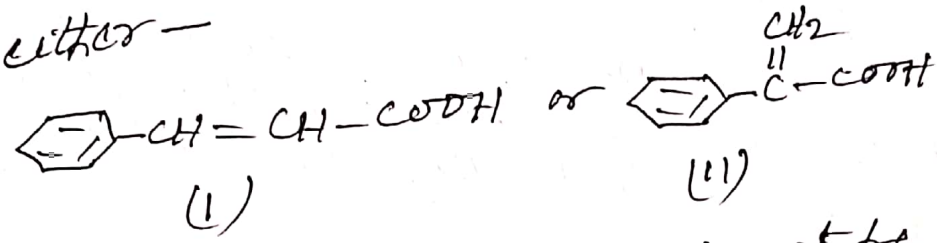
(ii) $C_9H_{10}O_3 \xrightarrow[NaHCO_3]{aq.} CO_2\uparrow$ (test of -COOH group)

4. (c) On strong heating, tropic acid is dehydrated to form α,β-unsaturated mono-carboxylic acid (atropic acid) which on oxidation gives benzoic acid.

$C_9H_{10}O_3 \xrightarrow[-H_2O]{\Delta}$ atropic acid $\xrightarrow{[O]}$ Benzoic acid.

This indicates the presence of a benzene ring in the molecules and the presence of $-COOH$ group in the side chain.

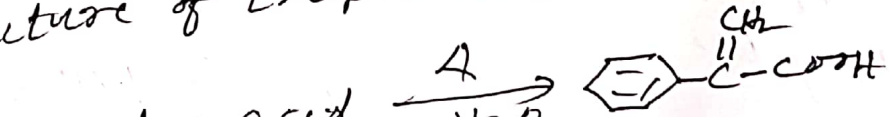
Hence, the atropic acid is either —



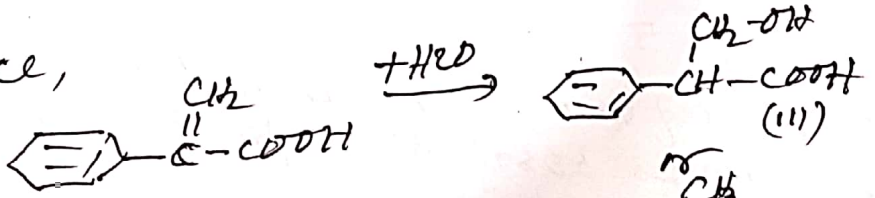
(I) or (II)

As (I) is cinnamic acid, (II) must be our compound Atropic acid.

Using the structure of Atropic acid, we can easily arrive at the structure of tropic acid.

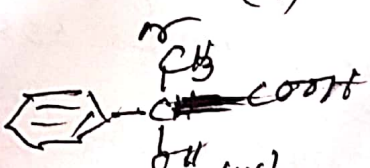


Hence,



(III)

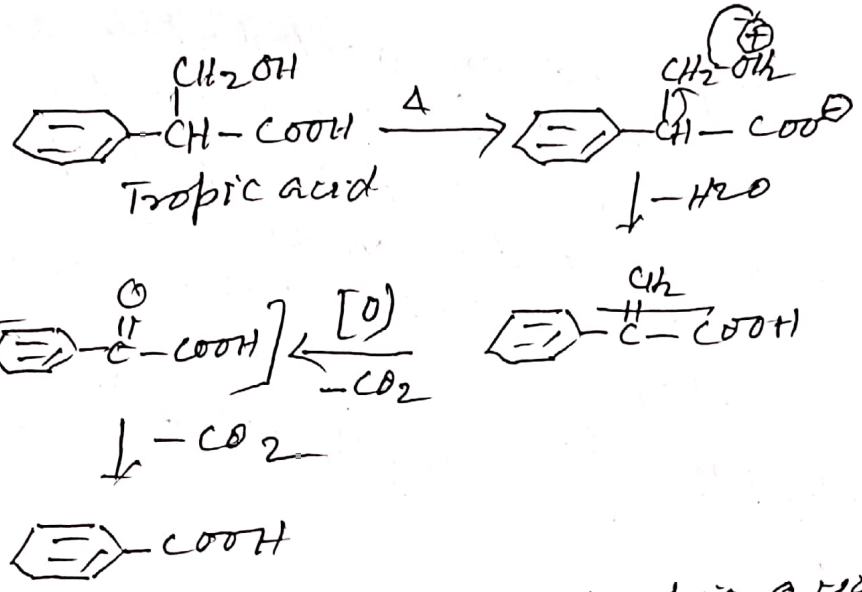
or



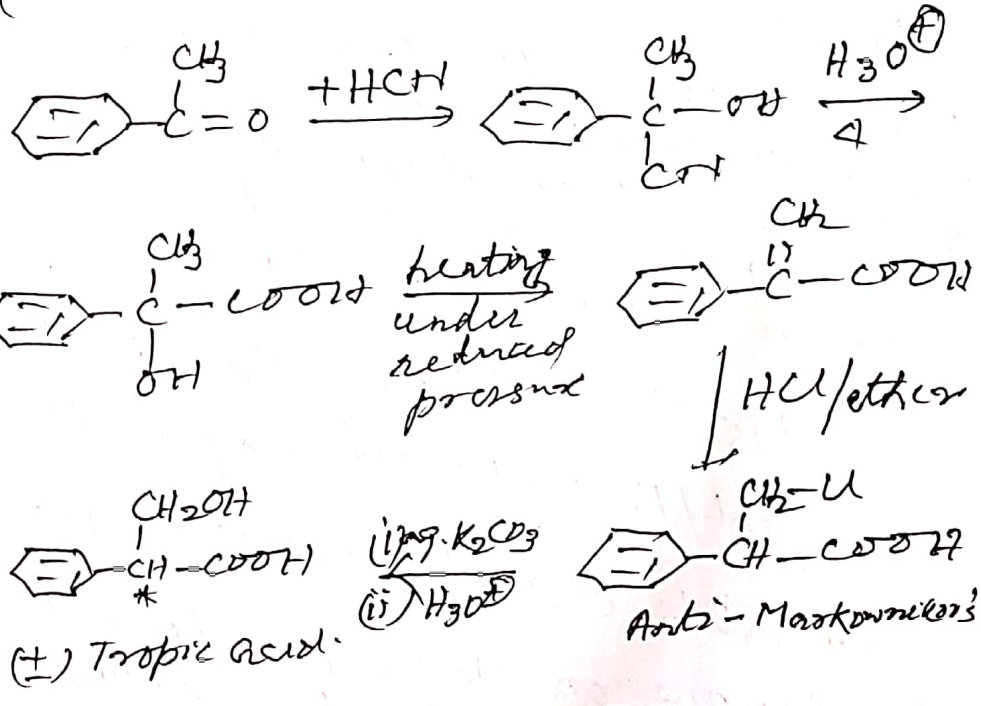
(IV)

The dehydration of (III) is easier than (IV) because in former stable carbo-cation intermediate exists.

Hence, the tropic acid can be represented by (III) which can easily explain the above reactions.



(d) The structure (III) for tropic acid is finally confirmed by its synthesis. (Meckenzie and Wood Synthesis)



(±) Tropic acid.

(6) Identification of (B) [$C_8H_{15}NO$ → Tropine]

(a) The DBRE for the compound is two, which is obtained as —

$$DBRE = \left[a + \frac{1}{2}c + 1 - \frac{1}{2}b\right]$$
$$= \left[8 + \frac{1}{2}\times 1 + 1 - \frac{1}{2}\times 15\right] = 2$$

This indicates that the compound is non-aromatic and it may be either bicyclic or unsaturated.

6.

(b) The compound on acetylation gives a monoacetyl derivative indicating the presence of a hydroxyl group. Tropine on chromic acid oxidation gives a ketone, indicating the presence of a secondary alcoholic group.

$$C_8H_{15}NO \xrightarrow[Py]{AcCl} C_8H_{14}N\left(-O-\overset{O}{\overset{\|}{C}}-CH_3\right)$$

$$\downarrow [O]\ CrO_3$$

$C_8H_{13}NO$
Ketone
(tropinone)

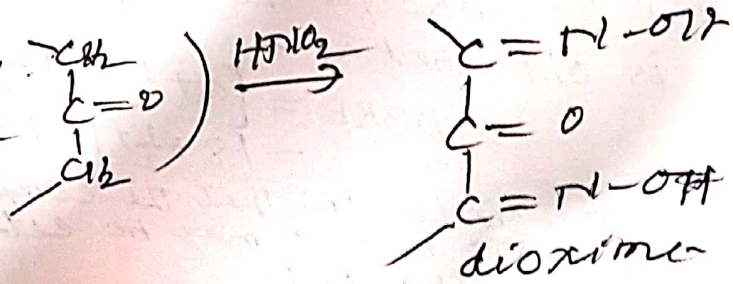
(c) When allowed to react with CH_3I, tropine absorbs one mole of CH_3I giving crystalline addition compound. This shows the presence of a tertiary nitrogen in the molecule.

$$C_8H_{15}NO \xrightarrow{+CH_3I} C_8H_{15}O\left(\overset{+}{N}-CH_3\right)I^{-}$$

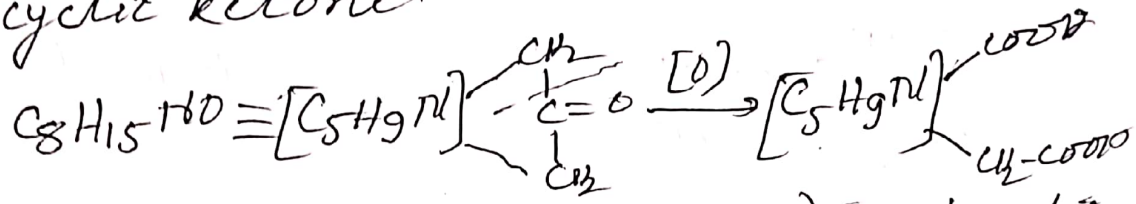
$$\downarrow HI/150^{\circ}C \quad \text{(Herzig-Mayer's test)}$$

$C_7H_{13}OH + CH_3I$ (presence of $>N-CH_3$)

(d) Tropinone on $HONO_2$ treatment, gives a dioxime, which is the characteristic of $-CH_2-\overset{O}{\overset{\|}{C}}-CH_2-$ in the molecule.

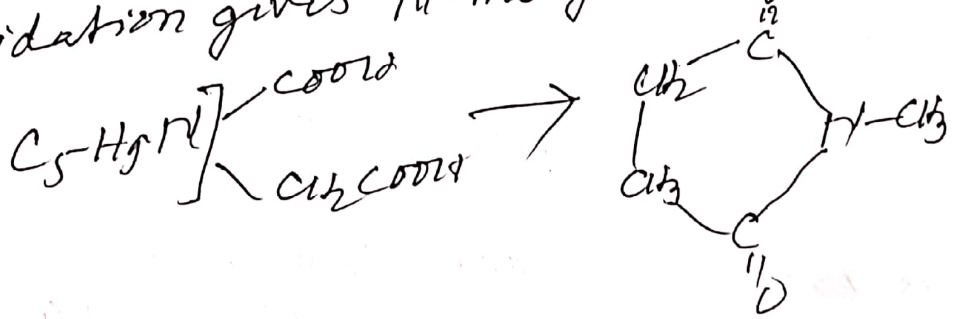


Tropinone on further oxidation with CrO_3, gives a dicarboxylic acid, indicating that the compound is a cyclic ketone.



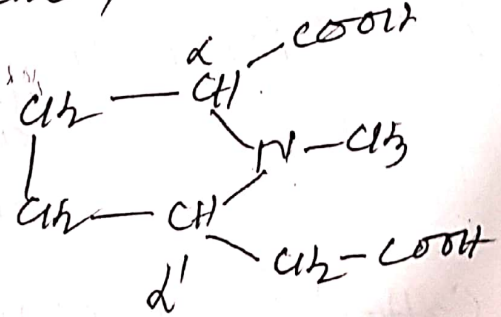
Dicarboxylic acid (Tropinic acid)

This dicarboxylic acid on further oxidation gives N-methylsuccinamide.



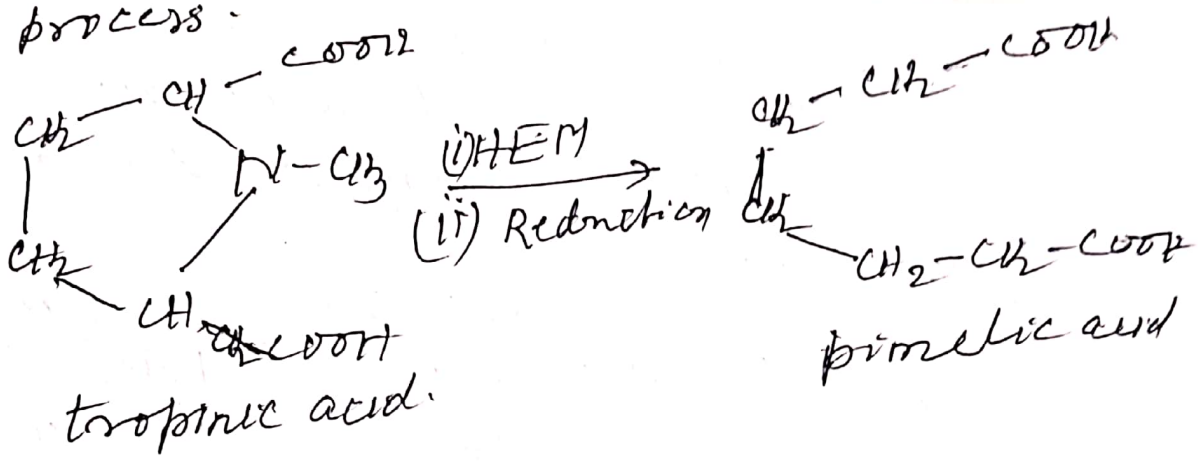
(N-Methylpyrrolidone ring)

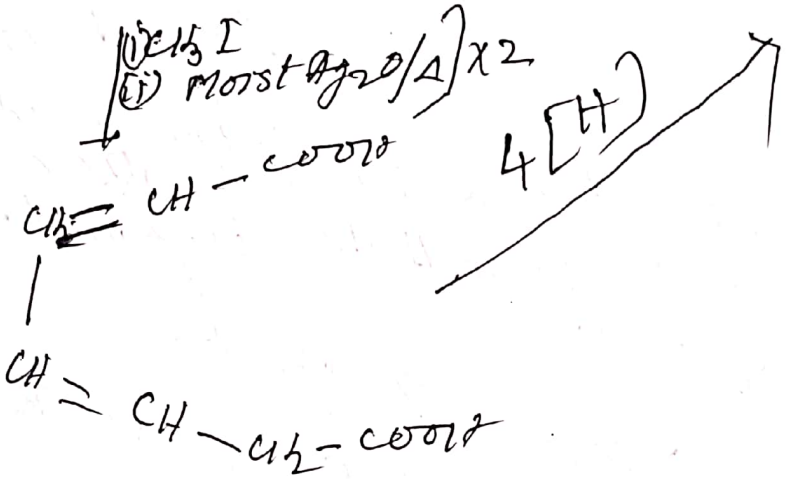
Hence, the tropinic acid may be.



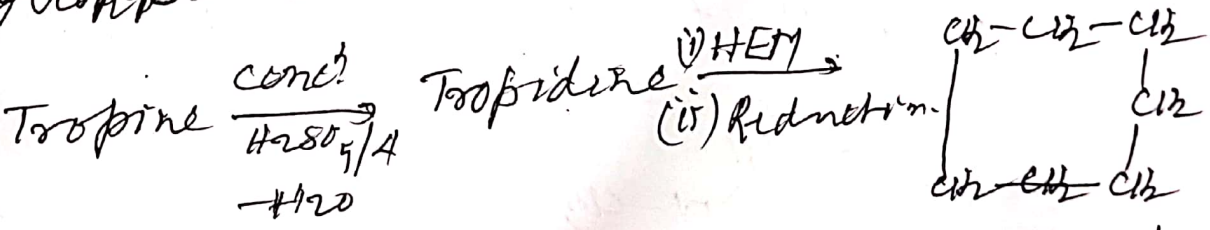
This structure of tropinic acid is conformired by Hofmann's exhaustive methylation followed by the reduction

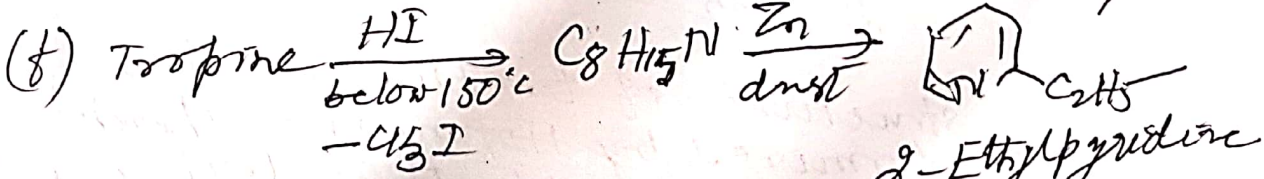
8. process.





(e) As tropine on dehydration gives a compound with one double bond (tropidine) which on Hofmann's exhaustive methylation gives Tropilidene (cyclic triene). This compound on reduction gives cycloheptane



(f) 

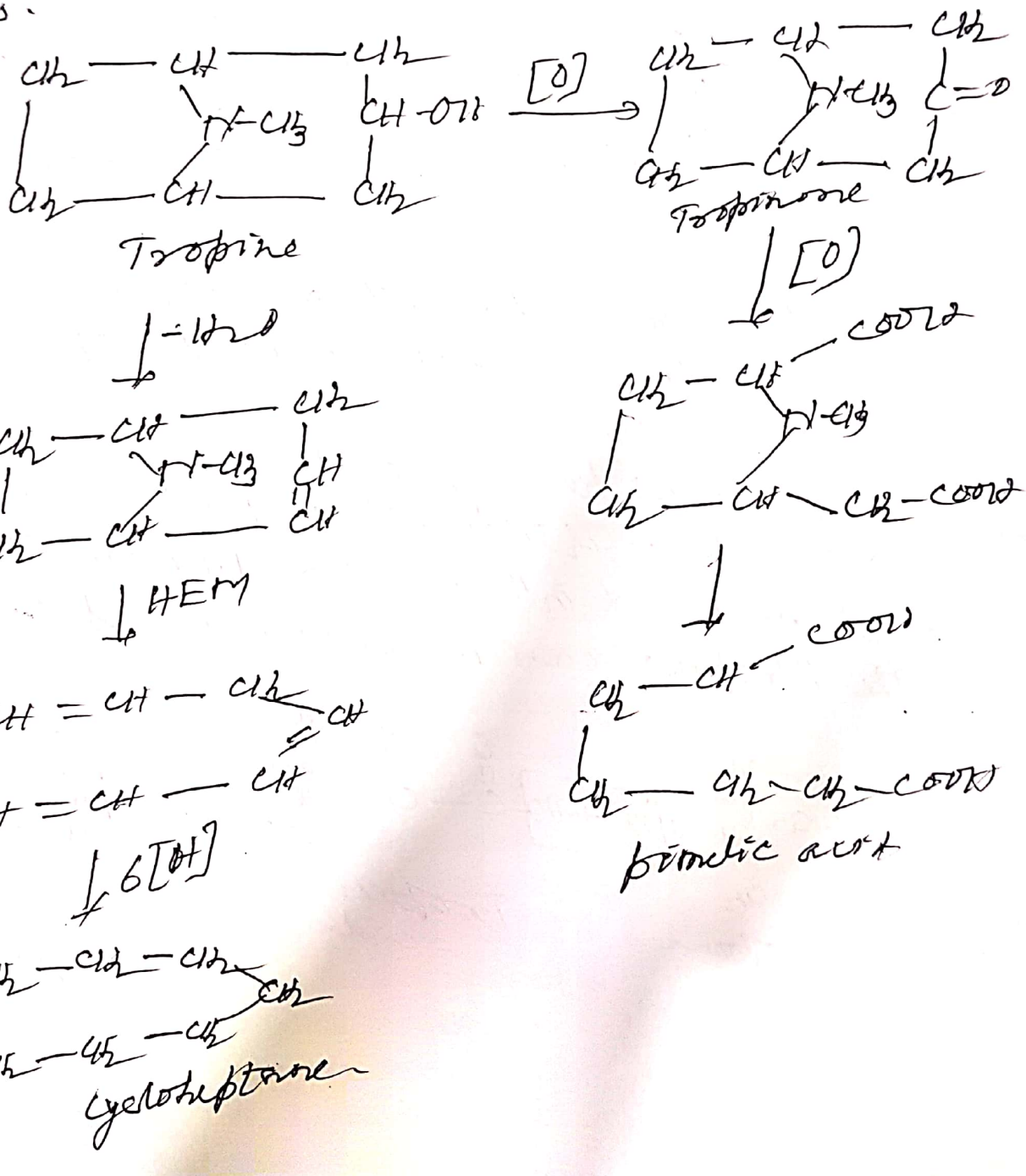
Hence,

(i) tropine has a seven membered ring with secondary alcoholic group.

(ii) It has a five membered N-CH_3 ring.

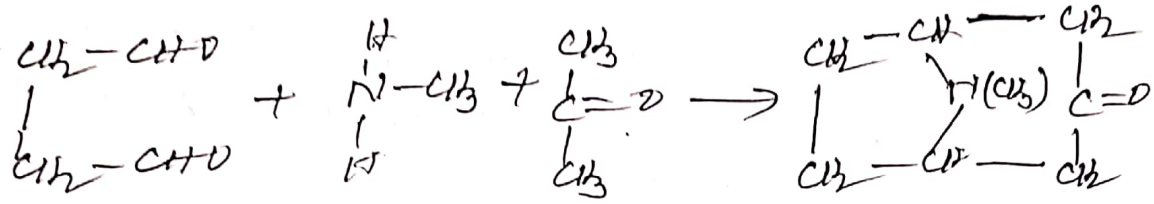
(iii) It has also a seven membered piperidine ring.

As only one nitrogen is present in the compound, it can be represented as.



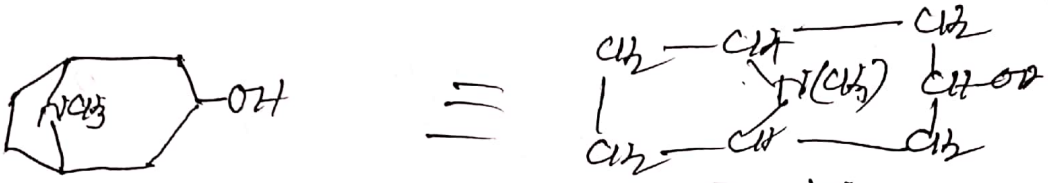
10. (f) Finally the structure of tropine is confirmed by its synthesis —

Mannich Reaction (Robinson synthesis)



Succinaldehyde

Reduction

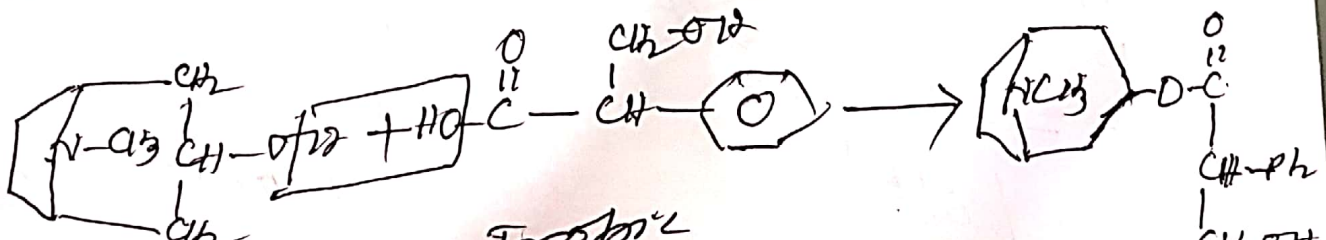


Tropine

Tropine

Point of Attachment of Tropic acid with tropine in Atropine

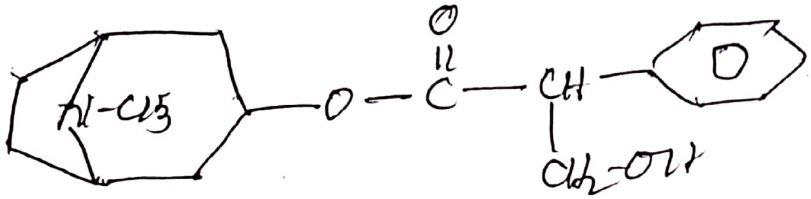
As Atropine having a primary alcoholic group, the $-CH_2OH$ unit of tropic acid is not involved in the ester linkage. Thus the Atropine can be represented as —



Tropine

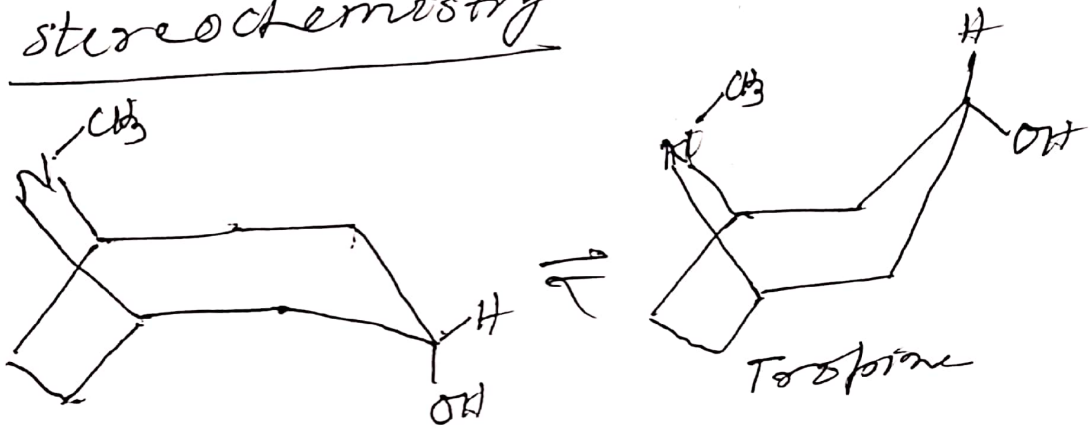
Tropic acid

Atropine

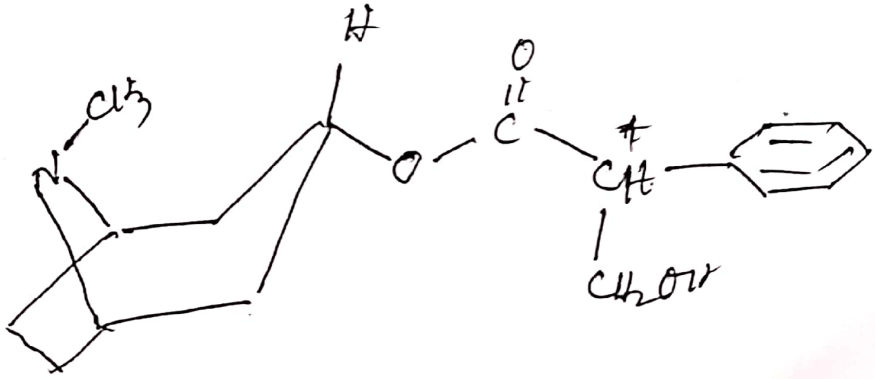


Atropine

stereochemistry



Tropine



Atropine

—x—