Piperine

8. **Nicotine, $C_{10}H_{14}N_2$.**—It is the chief alkaloid of the tobacco plant (*Nicotiana tobacum*) wherein it is present as a salt of malic or citric acid. In leaves of tobacco its concentration is the highest. It varies from 0·6 to 8% depending upon the kind of tobacco.

The alkaloid is conveniently prepared from tobacco leaves. Raw tobacco of high nicotine content is crushed and its soluble constituent extracted with cold water. The hydrocarbons present in the extract are removed by acidifying the solution and extracting with ether. The residual solution is made alkaline and nicotine set free is extracted with ether.

Properties. Freshly prepared nicotine is a colourless oily liquid (b.p. 519·2K under 730 mm pressure) readily soluble in water. Pure nicotine has an unpleasant smell unlike that of tobacco. It has a burning taste and is very poisonous (lethal dose being 30 to 50 mg). In air it rapidly turns brown and resinifies and can be distilled without decomposition only in vacuum or in a current of hydrogen. The natural alkaloid is laevo-rotatory $[\alpha]_D = -169°$.

In admixture with soap solution it is one of the most effective exterminating agents for green fly and other insect pests.

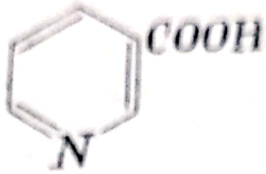
Constitution. (1) Molecular formula of nicotine as deduced from its analytical data and molecular mass determination is $C_{10}H_{14}N_2$.

(2) Nicotine reacts with methyl iodide to form dimethiodide and two monomethiodides but it does not form an acetyl or benzoyl derivative. This shows that the two nitrogen atoms in nicotine are tertiary.

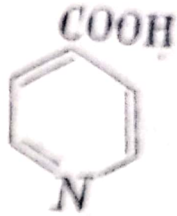
(3) Nicotine on oxidation with chromic acid or permanganate gives nicotinic acid ($C_5H_4N.COOH$). Three pyridinecarboxylic acids

By elimination, ...

Picolinic acid



Nicotinic acid

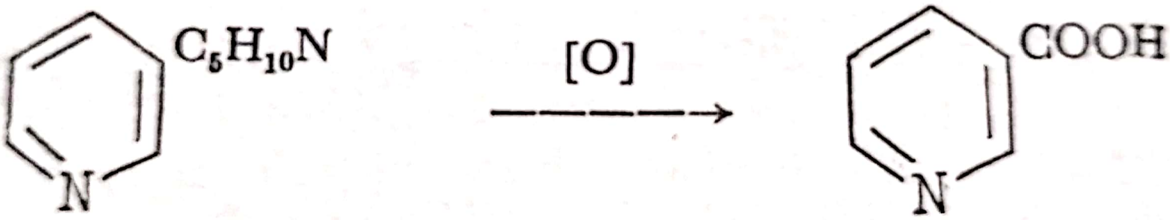


Isonicotinic acid

Now since nicotine on oxidation followed by heating at 460K yields nicotinic acid (3-pyridinecarboxylic acid), it suggests that nicotine contains a pyridine ring with some sort of group attached to it at the β-position. This group attached to pyridine ring is

$$C_{10}H_{14}N_2 - C_5H_4N = C_5H_{10}N$$

and the oxidation can be formulated as follows :



Nicotine Nicotinic acid

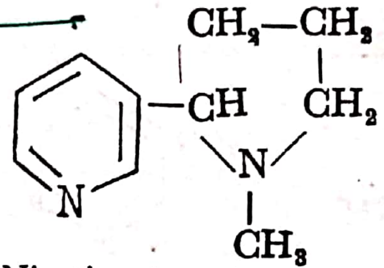
(4) Nicotine hydriodide on treatment with methyl iodide gives a methiodide. This on oxidation yields hygrinic acid (*N*-methylpyrrolidine-α-carboxylic acid). This indicates the presence of pyrrolidine ring with a methyl group attached to N-atom and carrying some other group in 2-position. The transformation can be indicated as follows :

Nicotine

(Mol. formula C_5H_{10}.N.COOH)
Hygrinic acid

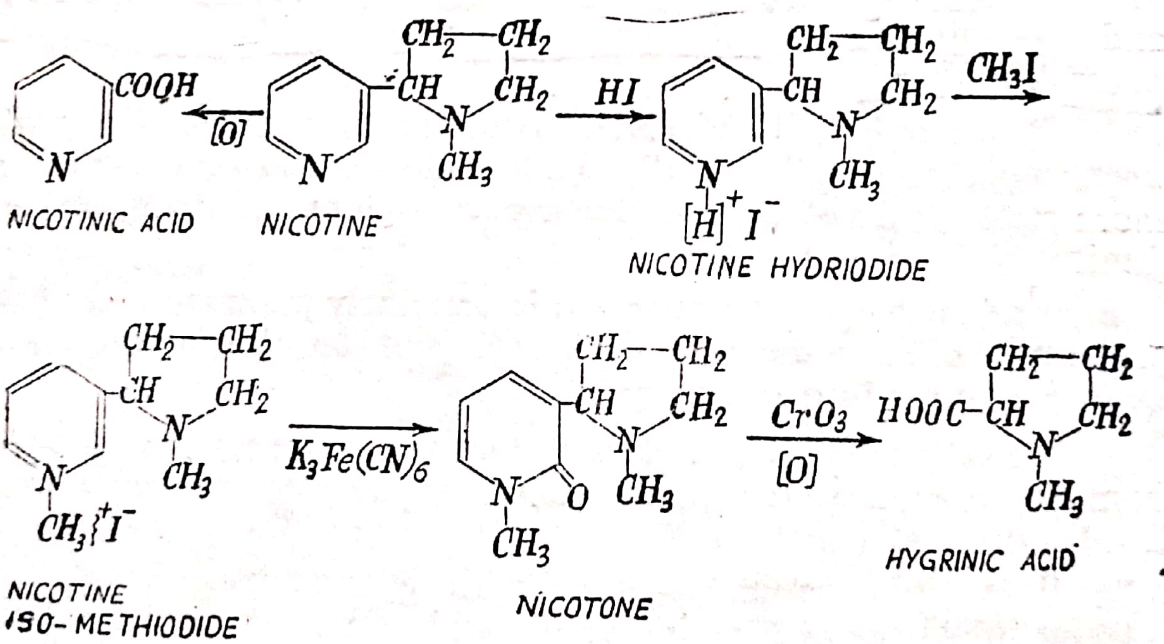
This indicates that pyridine ring has been destroyed during the transformation and the group $-C_5H_{10}N$ attached to the pyridine ring in β-position is *N*-methylpyrrolidine.

(5) Pyridine and pyrrolidine nuclei are joined through carbon atoms at β-position in pyridine and 2-position in pyrrolidine. This gives the structure of nicotine as

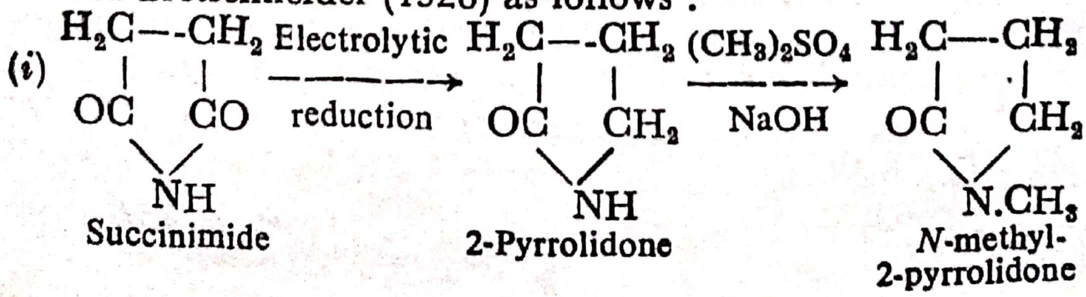


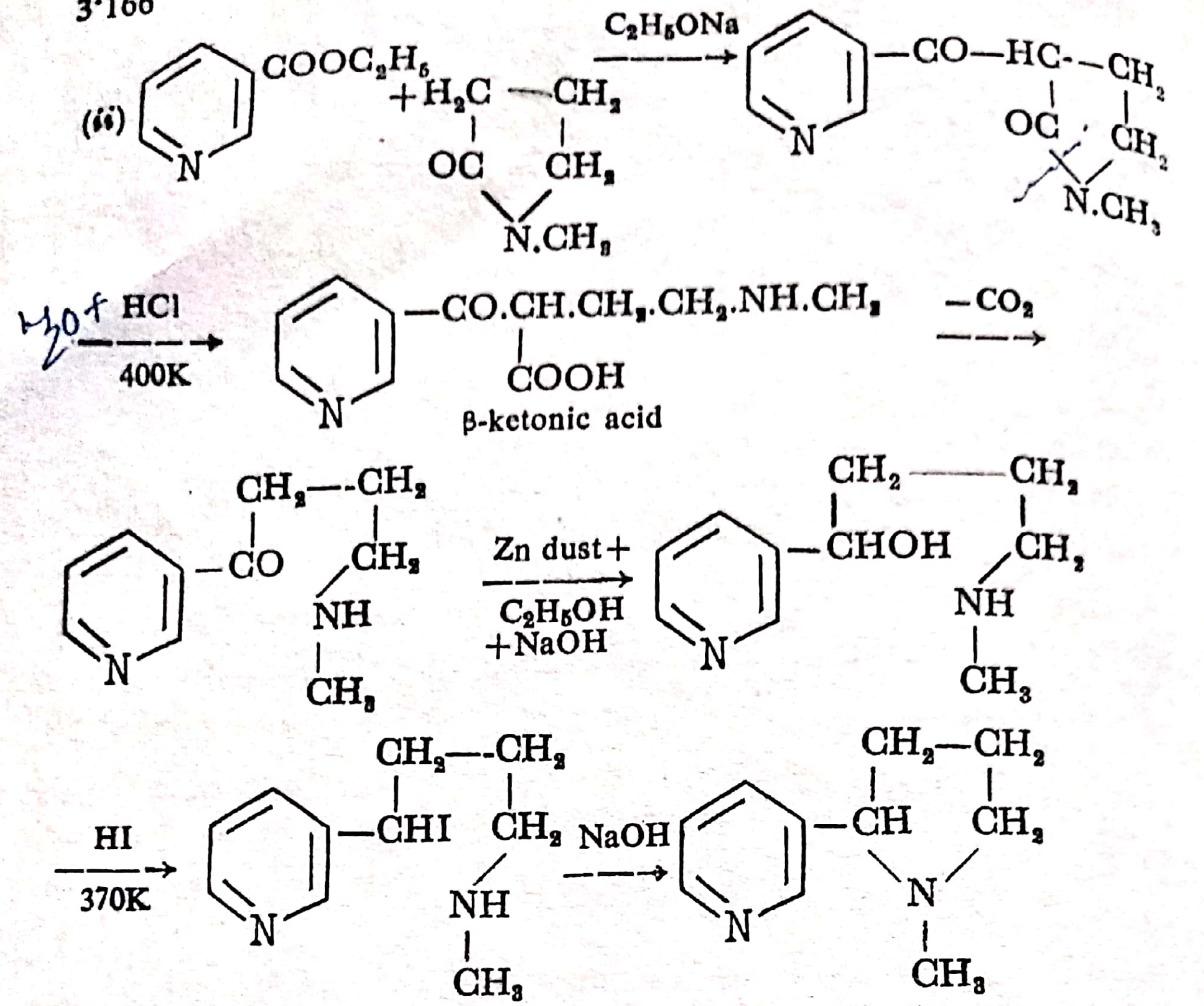
Nicotine (1-methyl-2-β-pyridylpyrrolidine)

(6) The conversion of nicotine into nicotinic acid and hygrinic acid has been formulated as under :



(7) This formula has been further confirmed by its synthesis by Spath and Bretschneider (1928) as follows :





dl-Nicotine

The (±)-mixture was resolved by means of (∓)-tartaric acid and (−)-nicotine thus obtained was found to be identical with the natural product.

9. Atropine, $C_{17}H_{23}O_3N$.—Atropine (m.p. 391K) along with *hyosyamine* occurs in deadly nightshade (*Atropa belladonna*) and thorn-apple (fruits of *dhatura stramonium*)—plants of the Solanaceae family.

It has a sharp bitter taste and is extremely poisonous. It has a property of dilating the pupil of the eye and on this account finds an extensive use in eye-surgery.

Constitution. (*i*) Molecular formula of atropine as deduced from its analytical data and molecular weight determination is $C_{17}H_{23}O_3N$.

(2) Atropine occurs together with hyosyamine. Hyosyamine is optically active and on warming with ethanolic alkali solution racemises to atropine. Thus atropine is (±) hyosyamine.

(3) Atropine undergoes hydrolysis, when warmed with barium hydroxide solution, to give (±) tropic acid and tropine (an alcohol). This suggests that atropine is the tropine ester of tropic acid.

$$\underset{\text{Atropine}}{C_{17}H_{23}O_3N} + H_2O \xrightarrow{Ba(OH)_2} \underset{\text{Tropic acid}}{C_9H_{10}O_3} + \underset{\text{Tropine}}{C_8H_{15}ON}$$

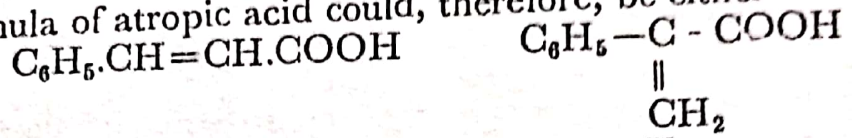
(4) Constitution of Tropic acid.

(*i*) Its molecular formula as deduced from its analytical data and molecular weight determination is $C_9H_{10}O_3$.

(*ii*) It does not decolorise bromine water, showing it to be a saturated compound.

(*iii*) It shows the presence of one carboxyl group and one alcoholic group from usual tests.

(*iv*) Tropic acid loses a molecule of water, when heated strongly, and gives atropic acid with molecular formula, $C_9H_8O_2$. This on oxidation gives benzoic acid. This suggests that tropic and atropic acids both contain a benzene ring with a side chain. Possible structural formula of atropic acid could, therefore, be either I or II.



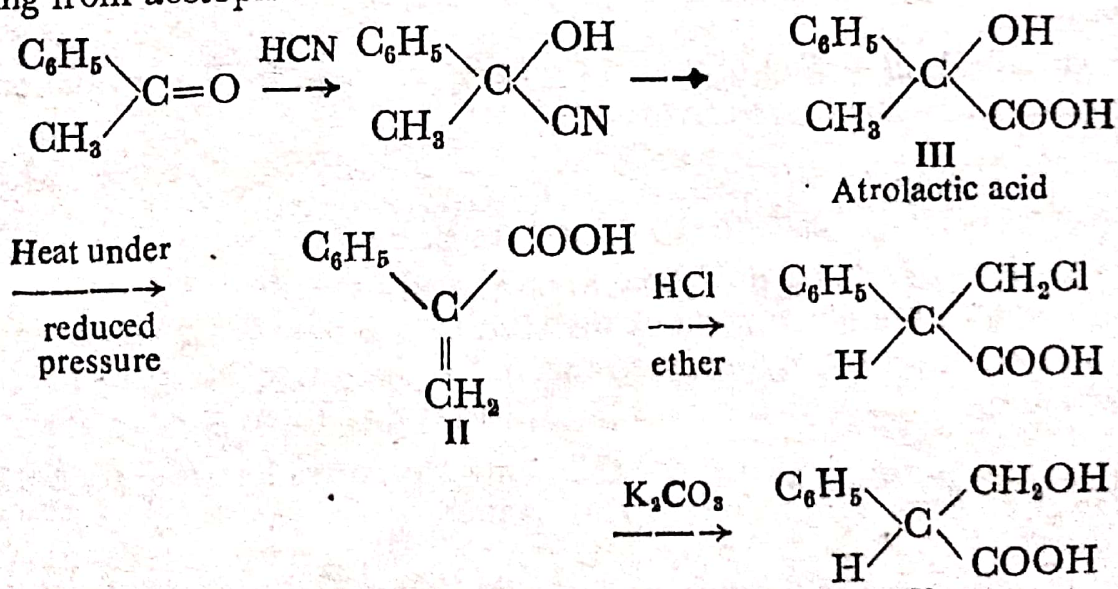
I, II

But **I** is known to be structural formula of cinnamic acid. Hence **II** is the structural formula of atropic acid.

(*v*) Atropic acid is the dehydration product of tropic acid. Hence structural formula of tropic acid can be written by adding a molecule of water to atropic acid. It can be either **III or IV**.

III, IV

(*vi*) Mackenzie and Wood (1919) synthesised tropic acid starting from acetophenone and showed that its structure was **IV**.



III Atrolactic acid; II; IV Tropic acid

III is the structural formula of atrolactic acid. Its dehydration to **II** confirms the structural formula of atropic acid. Addition of HCl to **II** takes place contrary to Markownikoff's rule due to the inductive effect of COOH group. Tropic acid is optically active and racemic variety is obtained in the above synthesis.

(*vii*) Willstatter (1895—1901) studied the products obtained on oxidation of tropine with chromic anhydride.

$$\underset{\text{Tropine}}{C_8H_{15}ON} \xrightarrow{CrO_3} \underset{\text{Tropinone}}{C_8H_{13}ON} \xrightarrow{CrO_3} \underset{(\pm)\text{-Tropinic acid}}{C_8H_{13}O_4N}$$

Since tropinone behaved as a ketone, tropine must be a secondary alcohol which gives the ketone on oxidation.

He also showed that tropinone forms a dibenzylidene derivative with benzaldehyde and a di-oximino derivative when treated with amyl nitrite and hydrochloric acid. This suggests the presence of $-CH_2.CO.CH_2-$ grouping in tropinone. No such group is possible in the oxidation product obtained on the basis of Merling formula which is, therefore, untenable.

Willstatter, therefore, proposed three structures for tropine but eliminated two on the consideration of its reactions. He was thus left with only the following formula which contains a pyridine nucleus as well as a pyrrole nucleus with the nitrogen atom common to both.