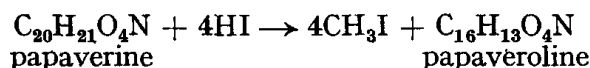


## ISOQUINOLINE GROUP

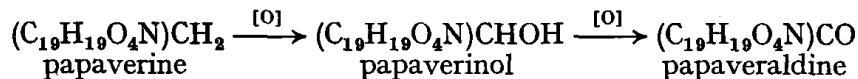
**Opium alkaloids.** Many alkaloids have been isolated from opium, and they are divided into two groups according to the nature of their structure:

- (i) *isoquinoline group*, e.g., papaverine, laudanoline, etc.
- (ii) *Phenanthrene group*, e.g., morphine (see §27).

§26. **Papaverine**,  $C_{20}H_{21}O_4N$ , m.p.  $147^\circ$ , is one of the optically inactive alkaloids; it does not contain any asymmetric carbon atom. The structure of papaverine was established by Goldschmiedt and his co-workers (1883–1888). Since papaverine adds on one molecule of methyl iodide to form a quaternary iodide, the nitrogen atom in the molecule is in the tertiary state. The application of the Zeisel method shows the presence of four methoxyl groups; the demethylated product is known as papaveroline.

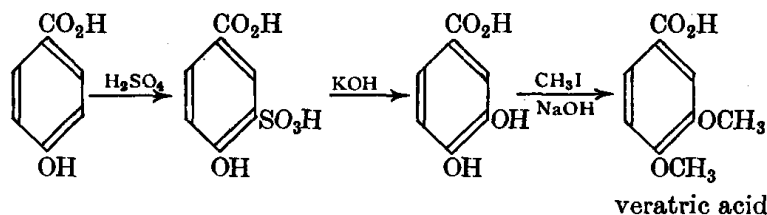


When oxidised with cold dilute permanganate, papaverine is converted into the secondary alcohol papaverinol,  $C_{20}H_{21}O_5N$ . This, on more vigorous oxidation with hot dilute permanganate, is oxidised to the ketone papaveraldine,  $C_{20}H_{19}O_5N$  (it is the formation of this *ketone* that shows that papaverinol is a *secondary* alcohol). Finally, the prolonged action of hot permanganate oxidises papaveraldine to papaverinic acid,  $C_{16}H_{13}O_7N$ . This acid is a dibasic acid and still contains the keto group present in its precursor—it forms an oxime, etc.; papaverinic acid also contains two methoxyl groups. The foregoing reactions lead to the conclusion that papaverine contains a methylene group.



When oxidised with hot concentrated permanganate, papaverine (or the oxidised products mentioned above) is broken down into smaller fragments, *viz.*, veratric acid, metahemipinic acid, pyridine-2 : 3 : 4-tricarboxylic acid and 6 : 7-dimethoxyisoquinoline-1-carboxylic acid. Let us now consider the evidence for the structures of these compounds.

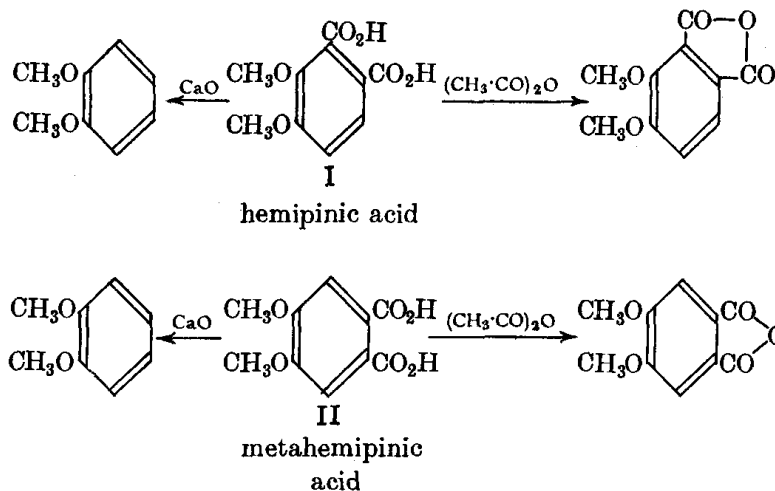
**Veratric acid.** When decarboxylated, veratric acid forms veratrole. Since this is *o*-dimethoxybenzene, veratric acid is therefore a dimethoxybenzoic acid. The position of the carboxyl group with respect to the two methoxyl groups (in the *ortho*-position) is established by the following synthesis.



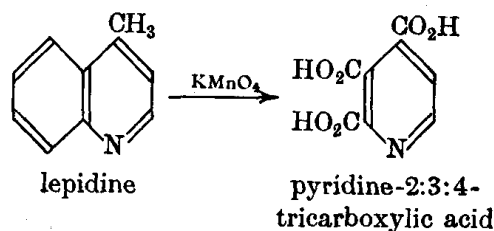
Thus veratric acid is 3 : 4-dimethoxybenzoic acid.

**Metahemipinic acid.** This is a dicarboxylic acid, and when decarboxylated by heating with calcium oxide, veratrole is formed; thus metahemipinic acid contains two methoxyl groups in the *ortho*-position. Furthermore, since the acid forms an anhydride when heated with acetic anhydride, the two carboxyl groups must be in the *ortho*-position. Thus metahemipinic acid is either I or II. Now metahemipinic acid forms only *one* monoester; II permits the formation of only one monoester, but I can give rise to two

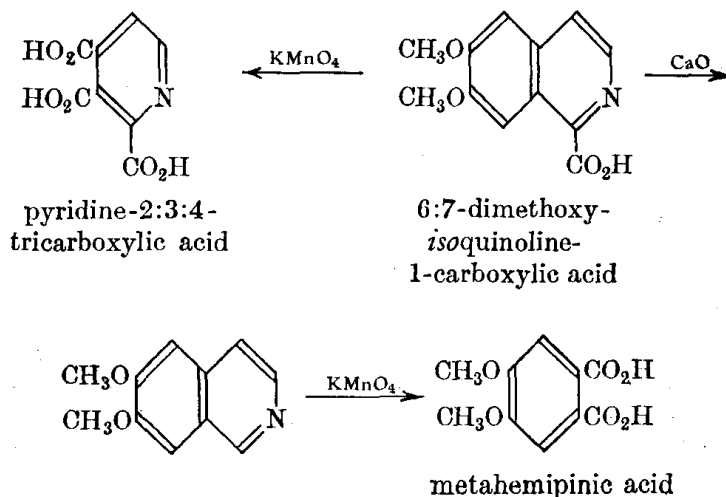
different monoesters. Thus II is metahemipinic acid; I is actually hemipinic acid (this isomer was known before metahemipinic acid).



**Pyridine-2:3:4-tricarboxylic acid.** The routine tests showed that this contains three carboxyl groups, and since decarboxylation gives pyridine, the acid must be a pyridinetricarboxylic acid. The positions of the three carboxyl groups are established by the fact that this pyridinetricarboxylic acid is produced when lepidine (4-methylquinoline) is oxidised.



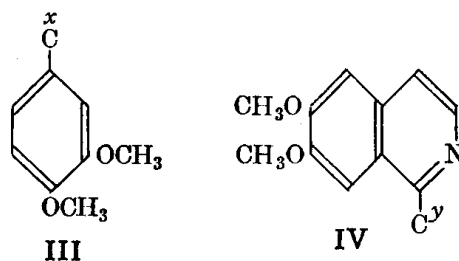
**6:7-Dimethoxyisoquinoline-1-carboxylic acid.** The usual tests showed that this compound contains one carboxyl group and two methoxyl groups. On oxidation, this acid forms pyridine-2:3:4-tricarboxylic acid; when decarboxylated, the acid forms a dimethoxyisoquinoline which, on oxidation, gives metahemipinic acid; thus the structure is established.



We may now deduce the structure of papaverine as follows:

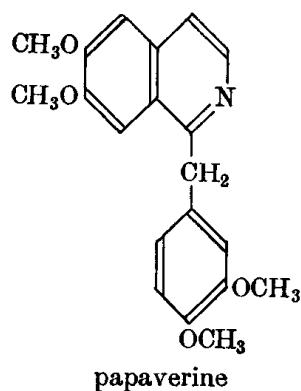
(i) The isolation of veratric acid indicates the presence of group III in papaverine.

(ii) The isolation of 6:7-dimethoxyisoquinoline-1-carboxylic acid indicates the presence of group IV in the molecule.

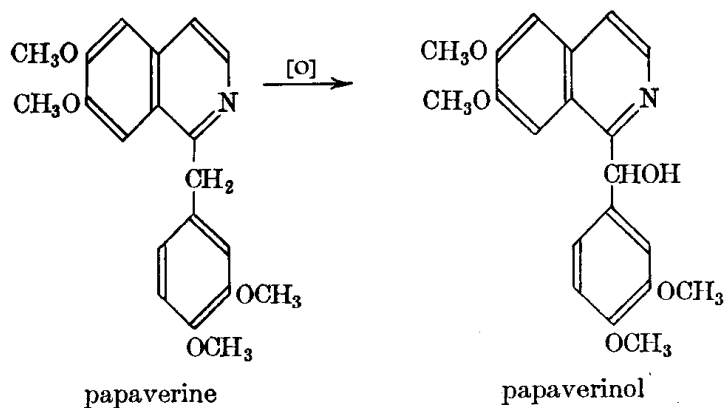


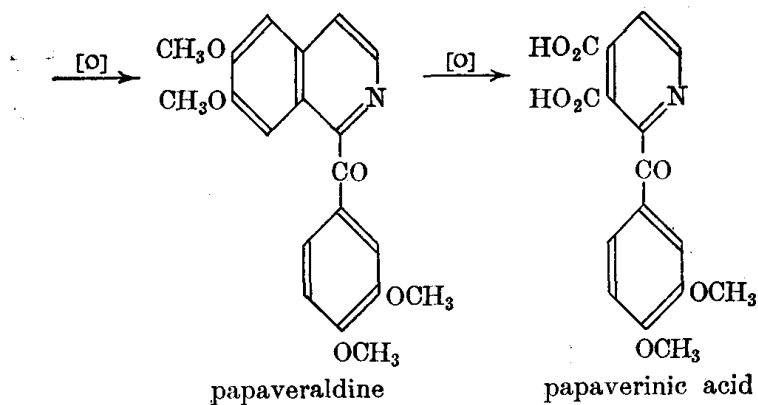
The presence of these two groups also accounts for the isolation of the other two fragments.

(iii) The total carbon content of III (9 carbon atoms) and IV (12 carbon atoms) is 21 carbon atoms. But papaverine contains only 20. There is, however, a  $-\text{CH}_2-$  group present, and if we assume that  $\text{C}^x$  and  $\text{C}^y$  are one and the same carbon atom, *viz.*, the carbon atom of the  $\text{CH}_2$  group, then the following structure of papaverine accounts for all the facts:

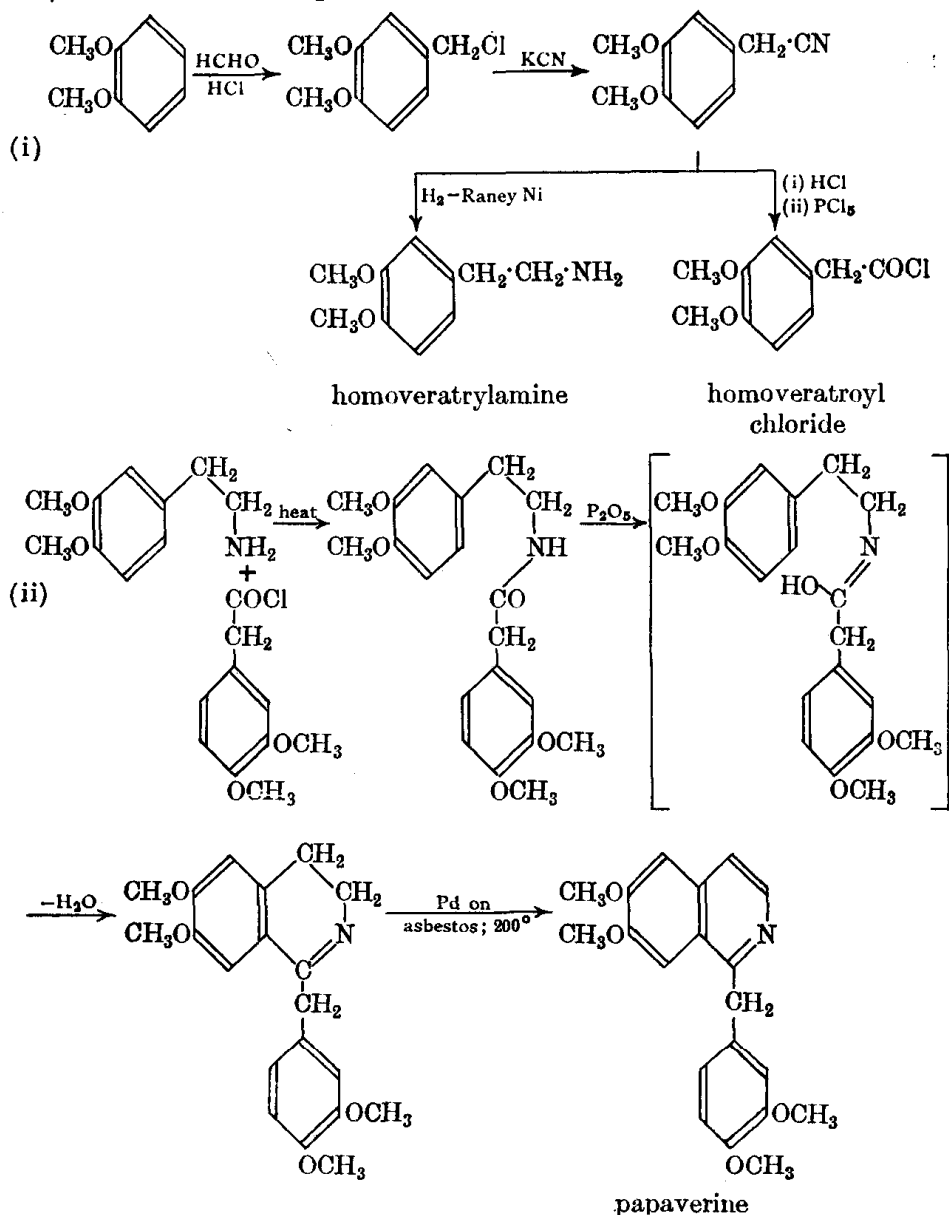


Thus, with this formula, we can formulate the oxidation of papaverine as follows:

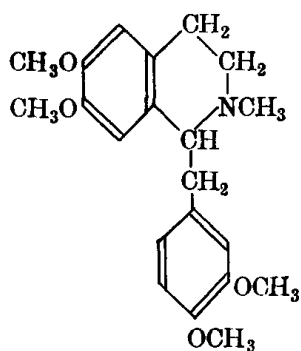




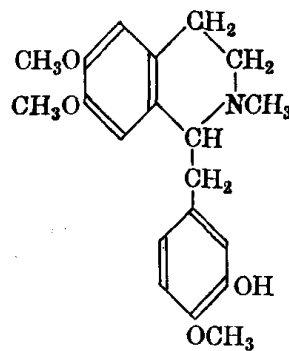
This structure for papaverine has been confirmed by synthesis. The first synthesis was by Pictet and Gams (1909), but Bide and Wilkinson (1945) carried out a simpler one, and it is this that is described here.



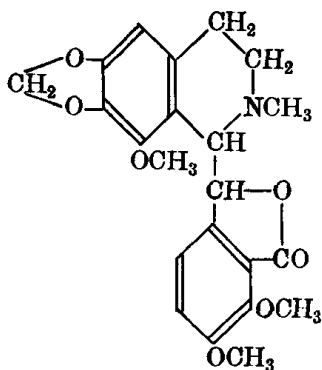
§26a. Some other alkaloids of the *isoquinoline* group are:



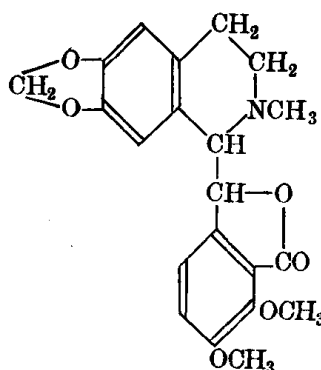
laudanose



laudanine



narcotine



hydrastine

### PHENANTHRENE GROUP

§27. **Morphine, codeine and thebaine.** These are three important opium alkaloids which contain the phenanthrene nucleus.

(-)-*Morphine*, C<sub>17</sub>H<sub>19</sub>O<sub>3</sub>N, m.p. 254°, is the chief alkaloid in opium, and was the first alkaloid to be isolated (Sertürner, 1806). The usual tests show that the nitrogen atom is in the tertiary state, and since morphine forms a diacetate and a dibenzoate, two hydroxyl groups are therefore present in the molecule. Morphine gives the ferric chloride test for phenols, and dissolves in aqueous sodium hydroxide to form a *monosodium* salt, and this is reconverted into morphine by the action of carbon dioxide; thus *one* of the hydroxyl groups is phenolic (Matthiessen *et al.*, 1869). The second hydroxyl group is secondary alcoholic, as is shown by the following reactions. Halogen acids convert morphine into a monohalogeno derivative, one hydroxyl group being replaced by a halogen atom. When heated with methyl iodide in the presence of aqueous potassium hydroxide, morphine is methylated to give (-)-*codeine*, C<sub>18</sub>H<sub>21</sub>O<sub>3</sub>N, m.p. 155° (Grimaux, 1881). Since codeine is no longer soluble in alkalis, it therefore follows that it is only the *phenolic* hydroxyl group in morphine that has been methylated. Furthermore, codeine can be oxidised by chromic acid to *codeinone*, a ketone (Hesse, 1884). Thus the hydroxyl group in codeine (and this one in morphine) is secondary alcoholic, and so codeine is the monomethyl (phenolic) ether of morphine.

(-)-*Thebaine*, C<sub>19</sub>H<sub>21</sub>O<sub>3</sub>N, m.p. 193°, produces two molecules of methyl iodide when heated with hydriodic acid (Zeisel method); hence thebaine is a dimethoxy derivative. When heated with sulphuric acid, thebaine