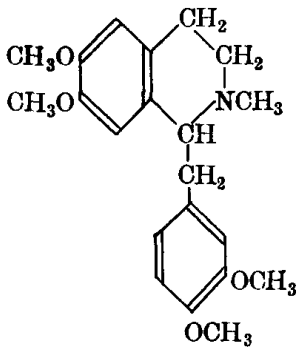
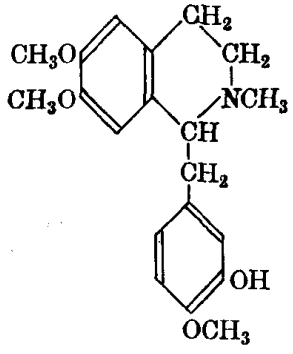
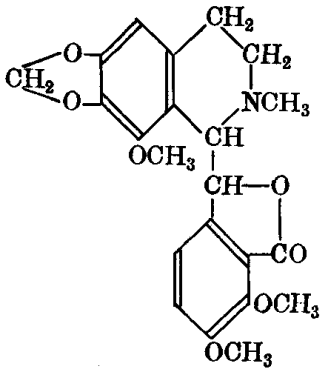
§26a. Some other alkaloids of the *iso*quinoline group are:



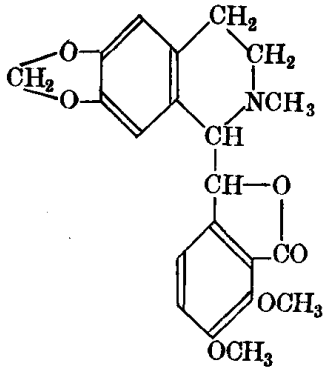
laudanosine



laudanine



narcotine



hydrastine

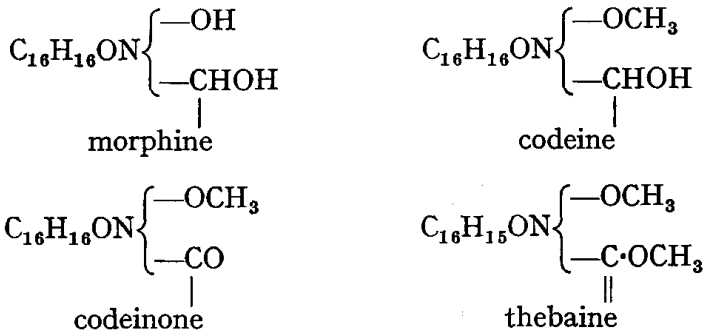
PHENANTHRENE GROUP

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

(−)-*Morphine*, $C_{17}H_{19}O_3N$, 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*, $C_{18}H_{21}O_3N$, 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*, $C_{19}H_{21}O_3N$, 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

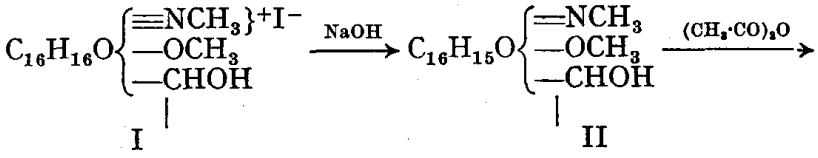
eliminates one methyl group as methyl hydrogen sulphate, and forms codeinone (Knorr, 1906). The formation of a *ketone* led Knorr to suggest that thebaine is the methyl ether of the *enolic* form of codeinone. The foregoing work can thus be summarised by assigning the following formulæ to the compounds described:



So far, we have accounted for the functional nature of two of the oxygen atoms; the unreactivity of the third oxygen atom suggests that it is probably of the ether type (Vongerichten, 1881).

All three alkaloids are tertiary bases (each combines with one molecule of methyl iodide to form a methiodide). When heated with hydrochloric acid at 140° under pressure morphine loses one molecule of water to form *apomorphine*, $C_{17}H_{17}O_2N$. Codeine, under the same conditions, also gives apomorphine (and some other products). Thebaine, however, when heated with dilute hydrochloric acid, forms *thebenine*, $C_{18}H_{19}O_3N$ (a secondary base), and with concentrated hydrochloric acid, morphothebaine, $C_{18}H_{19}O_3N$ (a tertiary base). Thus in the formation of thebenine from thebaine, a tertiary nitrogen atom is converted into a secondary one. For this change to occur, the tertiary nitrogen must be of the type $>N\cdot R$, where the nitrogen is in a ring system; had the nitrogen been in the group $—NR_2$, then the formation of a *primary* base could be expected.

When morphine is distilled with zinc dust, phenanthrene and a number of bases are produced (Vongerichten *et al.*, 1869). This suggests that a phenanthrene nucleus is probably present, and this has been confirmed as follows. When codeine methiodide, I, is boiled with sodium hydroxide solution, α-methylmorphimethine, II, is obtained and this, on heating with acetic anhydride, forms methylmorphol, III, and ethanoldimethylamine, IV (some of II isomerises to β-methylmorphimethine).



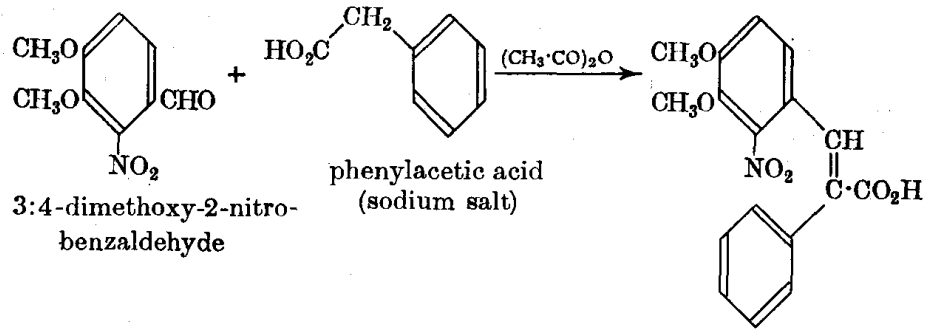
I II

$$C_{15}H_{12}O_2 + (CH_3)_2N\cdot CH_2\cdot CH_2OH$$

III IV

The structure of methylmorphol (III) was ascertained by heating it with hydrochloric acid at 180° under pressure; methyl chloride and a dihydroxyphenanthrene, *morphol*, were obtained. Oxidation of diacetylmorphol gives a diacetylphenanthraquinone; thus positions 9 and 10 are free. On further oxidation (permanganate), the quinone is converted into phthalic acid; therefore the two hydroxyl groups are in the same ring. Since the fusion of morphine with alkali gives protocatechuic acid, this shows that both

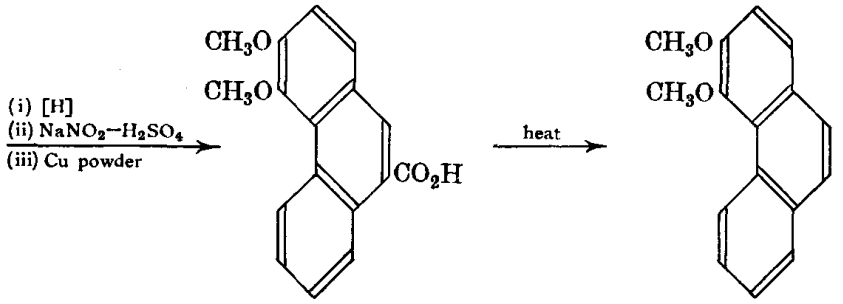
hydroxyl groups in morphol are in the *ortho*-position. Finally, Pschorr *et al.* (1900) showed by synthesis that dimethylmorphol is 3 : 4-dimethoxyphenanthrene (*cf.* Pschorr synthesis, §2 vi*a*. X).



3:4-dimethoxy-2-nitrobenzaldehyde

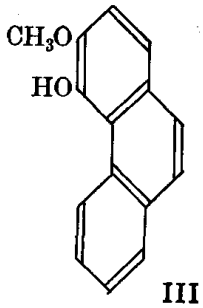
phenylacetic acid (sodium salt)

3:4-dimethoxy-2-nitro-α-phenylcinnamic acid



dimethylmorphol

Then Pschorr *et al.* (1902) synthesised methylmorphol (III), and showed it to be 4-hydroxy-3-methoxyphenanthrene (in this synthesis Pschorr used 3-acetoxy-4-methoxy-2-nitrobenzaldehyde).



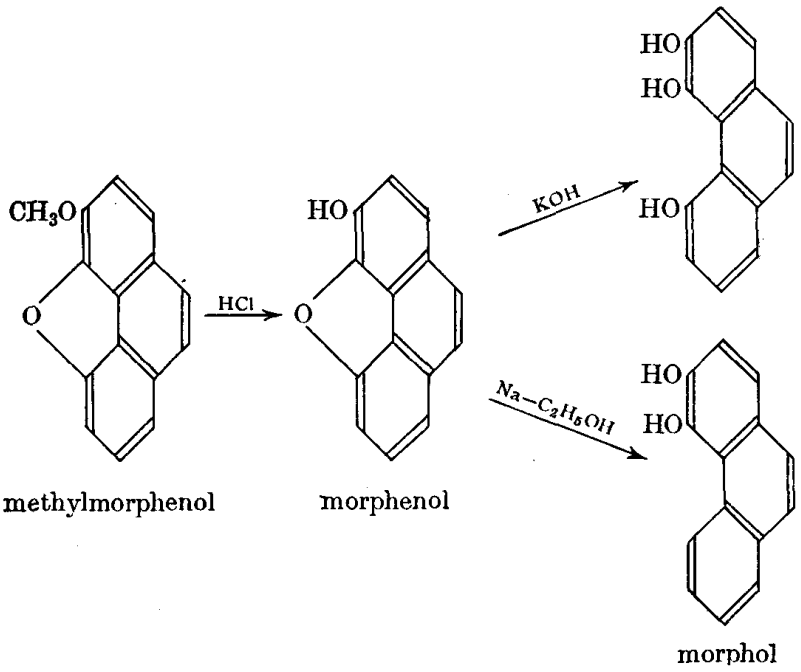
III

methylmorphol

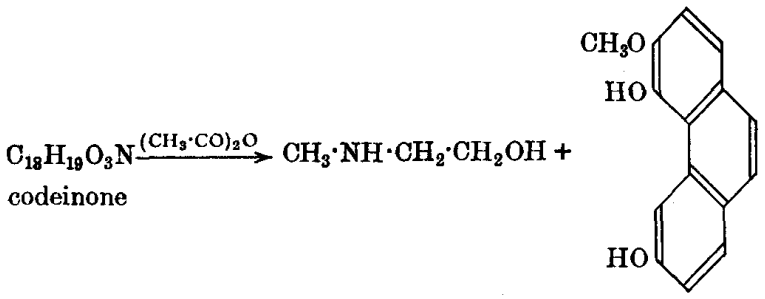
The formation of ethanoldimethylamine (IV) from α-methylmorphimethine indicates that there is a $>NCH_3$ group in codeine (only *one* methyl iodide molecule adds to codeine to form codeine methiodide; it has also been shown above that this nitrogen is in a heterocyclic ring).

When β-methylmorphimethine is heated with water, the products obtained are trimethylamine, ethylene and *methylmorphenol* (Vongerichten, 1896). Demethylation of this compound with hydrochloric acid produces *morphenol*, a compound which contains one phenolic hydroxyl group and an inert

oxygen atom. On fusion with potassium hydroxide, morphenol gives 3 : 4 : 5-trihydroxyphenanthrene (Vongerichten *et al.*, 1906). The structure of this compound was shown by the synthesis of 3 : 4 : 5-trimethoxyphenanthrene, which was found to be identical with the product obtained by methylating the trihydroxyphenanthrene obtained from morphenol (Pschorr *et al.*, 1912). Furthermore, the reduction of morphenol with sodium and ethanol gives morphol (Vongerichten, 1898). These results can be explained by assuming that morphenol has a structure containing an ether linkage in positions 4 : 5 (of the phenanthrene nucleus).

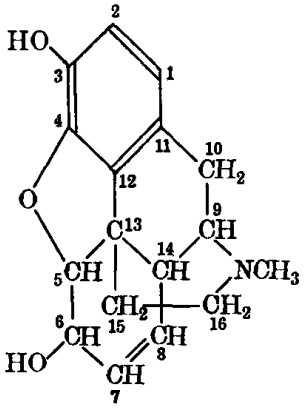


Codeinone, on heating with acetic anhydride, gives ethanolmethylamine and the diacetyl derivative of 4 : 6-dihydroxy-3-methoxyphenanthrene.

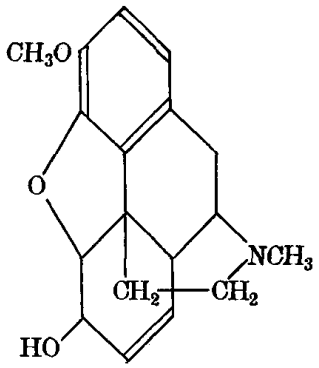


The position 3 of the methoxyl group and the position 4 of the hydroxy group have already been accounted for; the hydroxyl group in the 6-position must therefore be produced from the oxygen of the keto group in codeinone.

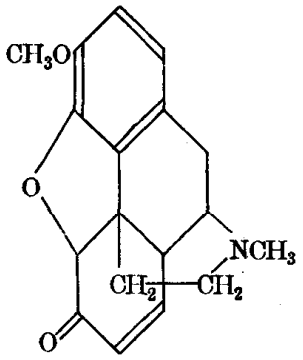
Based on the foregoing evidence, and a large amount of other experimental work, Gulland and Robinson (1923, 1925) have proposed the following structures.



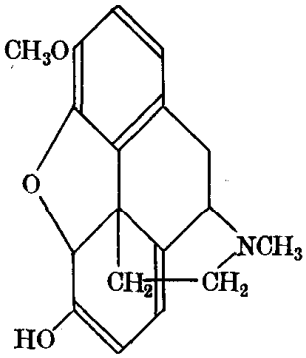
morphine



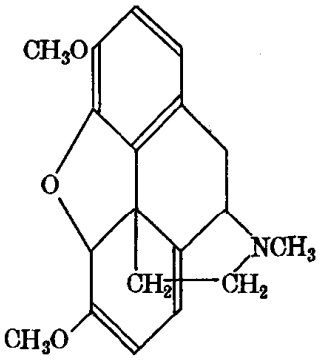
codeine



codeinone
(*keto form*)



codeinone
(*enol form*)



thebaine

Gates *et al.* (1956) have now synthesised morphine.

§28. Biosynthesis of alkaloids. As more and more structures of alkaloids were elucidated, it became increasingly probable that the precursors in the biosynthesis of alkaloids were amino-acids and amino-aldehydes and amines derived from them. A particularly interesting point is that the consideration of biosynthesis has led to deductions in structure, *e.g.*, Woodward (1948) proposed a biosynthesis of strychnine, and from this Robinson (1948) deduced the structure of emetine which was later confirmed by the synthetic work of Battersby *et al.* (1950).

We have already seen (§18. XIII) how keto-acids may be converted into amino-acids, and *vice versa*. There are also enzymes which bring about the decarboxylation of amino-acids to amines and the decarboxylation of α-keto-acids to aldehydes. Thus amino-acids, amines and amino-aldehydes, together with formaldehyde (or its equivalent) are believed to be the units involved in the biosynthesis of alkaloids. The general technique has been to administer labelled precursors to plants and to isolate the alkaloid after some time has elapsed for the growth of the plant.

The following examples of biosynthesis illustrate the principles outlined above. Alkaloids containing a benzene ring are believed to be products of the shikimic acid route (§18. XIII); the amino-acids phenylalanine and tyrosine are the starting points for the biosynthesis of, *e.g.*, ephedrine, hordenine, mezcaline, etc. As an example, we may describe the biosynthesis of adrenaline (§12) from tyrosine; the route is possibly: