102. *Preliminary Synthetic Experiments in the Morphine Group. Part III. Some Derivatives of Papaveroline and Laudanosoline.*

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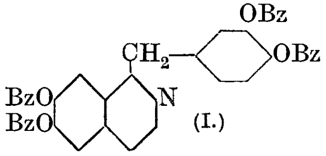
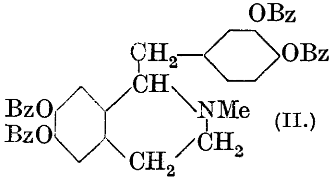
WITH the ultimate object of studying the conditions for the coupling of the aromatic nuclei in phenolic bases of the laudanosine type (compare Part I; J., 1931, 3163) we have examined the fully demethylated substances, papaveroline and laudanosoline, especially with a view to their characterisation. The tetrabenzoyl derivatives (I) and (II) are moderately satisfactory for the purpose, although (II) must be converted into a *picrate* or *hydrochloride*.

N-Methylpapaverolinium chloride is converted by pyridine into a well-defined *phenol-betaine* (III), analogous to the phenol-betaine (IV) prepared from *N*-methylpapaverinium hydroxide by Decker, Durrant, and Eichler (*Annalen*, 1908, **358**, 288; 1913, **395**, 377. Compare Späth and Epstein, *Ber.*, 1926, **59**, 2791). In the latter case the reaction involves demethylation and only one phenolic hydroxyl is present; it has been proved to occupy the position illustrated. In (III), however, the pure phenol-betaine formula does not indicate which of the phenolic hydroxyls is implicated and our choice is therefore based on the theory that the substance is an anhydronium base (compare Armit and Robinson, J., 1925, **127**, 1604) and that its constitution is intermediate between the phenol-betaine (III) and the quinone (V).


(I.)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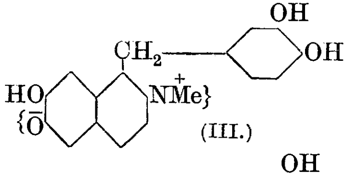
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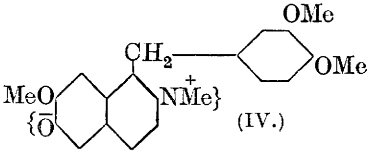
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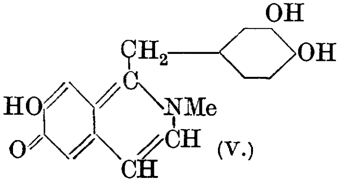
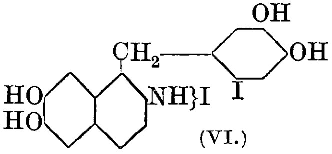

(V.)


(VI.)

The alternative is that the substance is *N*-methyl*iso*papaverinol, but the properties of the base and the formation of a tribenzoyl derivative are in better agreement with the anhydronium-base structure.

The action of iodine on papaveroline hydriodide in alcoholic solution yields an *iodo*-compound of the probable structure (VI).

EXPERIMENTAL.

Papaveroline Salts.—The hydriodide has been prepared by a modification of the method of Goldschmiedt (*Monatsh.*, 1885, **6**, 966). A mixture of papaverine (50 g.), hydriodic acid (300 g.; *d* 1·7), and acetic anhydride (5 c.c.) was heated for 3 hours in a bath at 135—138°. The salt was isolated by the addition of ether and a little water and was sufficiently pure for most purposes. A specimen, crystallised from hot water, was quite colourless, m. p. 230° (decomp.) (Found in anhydrous material: C, 46·8; H, 3·5. Calc. for $C_{16}H_{14}O_4NI$: C, 46·7; H, 3·4%). The action of iodine on an acidic solution of the salt in alcohol gives, even at the ordinary temperature, an *iodo*-derivative, which crystallises from aqueous alcohol in pale reddish-brown prisms, m. p. *ca.* 202° (decomp.) (Found: C, 33·3; H, 2·9. $C_{16}H_{13}O_4NI_2,2H_2O$ requires C, 33·5; H, 3·0%).

The *hydrochloride* separates when hydrogen chloride is led into a concentrated aqueous-alcoholic solution of the hydriodide and the use of silver chloride is thus avoided. It crystallises from dilute aqueous or alcoholic hydrochloric acid in colourless needles, m. p. *ca.* 250° (decomp.) (Found in anhydrous material: C, 60·0; H, 4·6. $C_{16}H_{14}O_4NCl$ requires C, 60·1; H, 4·4%). The salt is moderately readily soluble in alcohol or water, sparingly so in presence of hydrogen chloride. On reduction with tin and hydrochloric acid it affords tetrahydropapaveroline hydrochloride, colourless needles, m. p. *ca.* 295° (decomp.), from hot water (Found: C, 59·3; H, 5·5. Calc. for $C_{16}H_{18}O_4NCl$: C, 59·4; H, 5·6%), having the properties ascribed by Pyman (J., 1909, **95**, 1610) to the salt obtained by the demethylation of tetrahydropapaverine by means of concentrated hydrochloric acid. Ferric chloride added to an aqueous or alcoholic solution of the salt develops a green coloration that becomes deep bluish-green on warming.

O-*Tetrabenzoylpapaveroline* (I).—Benzoyl chloride (3 c.c.) was added to a suspension of papaveroline hydrochloride (1 g.) in pyridine (5 c.c.) and after 5 minutes' shaking the reaction was completed by gentle heating. The product was added to dilute ammonium carbonate solution and ice and after some hours the solid was collected, dissolved in alcohol, and the solution concentrated in an evacuated desiccator. The crystals which separated were recrystallised from benzene–light petroleum, forming colourless rosettes, m. p. 148° (Found: C, 75·4; H, 4·3; N, 2·3. $C_{44}H_{29}O_8N$ requires C, 75·5; H, 4·1; N, 2·0%). This *derivative* is readily soluble in most organic solvents. It is formed by simple *O*-benzoylation, whereas Oberlin (*Arch. Pharm.*, 1927, **265**, 265) has stated that benzoylation of papaveraldoline furnishes an *N*-benzoyl-*O*-tetrabenzoyl derivative free from halogen. The theoretical basis of this observation is obscure.

N-*Methylpapaveroline Derivatives.*—Methylpapaverinium iodide was prepared from the methosulphate and sodium iodide in aqueous solution and demethylated as described above for papaverine. When the reaction mixture was cooled, methylpapaverolinium iodide separated; it was collected (yield, 80%) after the addition of ether. The salt crystallised from water in small colourless prisms, m. p. 208° (decomp.) (Found: C, 47·8; H, 4·0. Calc. for $C_{17}H_{16}O_4NI$: C, 48·0; H, 3·8%).

Claus and Kassner (*J. pr. Chem.*, 1897, **56**, 344) describe this salt as reddish-brown crystals, m. p. 77° (hydrated).

The chloride was obtained from the iodide by means of silver chloride in aqueous solution, and addition of hydrochloric acid to the filtrate from silver iodide. It crystallised from alcohol in colourless prisms, m. p. 264° (decomp.) (Claus and Kassner, *loc. cit.*, give m. p. 235°) (Found: C, 61·1; H, 4·8. Calc. for $C_{17}H_{16}O_4NCl$: C, 61·2; H, 4·8%).

Anhydro-N-*methylpapaverolinium Hydroxide* (III and V).—When a solution of *N*-methylpapaverolinium chloride (2 g.) in dry pyridine (40 c.c.) was boiled, the new substance began to separate after a few minutes: after 1 hour the mixture was cooled and the solid collected. It crystallised from alcohol in colourless prisms, which do not melt at 300° (yield, quantitative) (Found: C, 68·5; H, 5·1. $C_{17}H_{15}O_4N$ requires C, 68·7; H, 5·0%). The hydrochloride of this *phenol-betaine* was found to be identical with *N*-methylpapaverolinium chloride in all respects.

The *picrate* (N-*methylpapaverolinium picrate*) was prepared by mixing an alcoholic solution of the base with ethereal picric acid; it crystallised from alcohol–benzene in yellow rhombohedra, m. p. 210° (decomp.) after softening at 196° (Found: C, 52·3; H, 3·3. $C_{23}H_{18}O_{11}N_4$ requires C, 52·5; H, 3·4%).

When *N*-methylpapaverolinium chloride was gently warmed with benzoyl chloride and anhydrous pyridine under conditions similar to those employed for papaveroline, and the product worked up in a similar manner, and finally crystallised from alcohol, pale yellow prisms, m. p. *ca.* 217° (Found: C, 74·8; H, 4·7; N, 2·7. $C_{38}H_{27}O_7N$ requires C, 74·9; H, 4·4; N, 2·3%), were obtained. This substance is evidently *anhydro*-N-*methyl*-O-*tribenzoylpapaverolinium hydroxide*. It is changed to a chloride by the action of dilute hydrochloric acid and gives a brownish-violet coloration with ferric chloride in aqueous-alcoholic solution.

On the other hand, when *moist* pyridine was used under otherwise similar conditions, the product crystallised from alcohol in small colourless prisms, m. p. 180° (Found : C, 71·6; H, 4·2. $C_{45}H_{32}O_8NCl$ requires C, 72·0; H, 4·3%). This substance is a *chloride*, is much more readily soluble in alcohol than the tribenzoyl-phenol-betaine, gives no ferric reaction, and is evidently N-*methyl*-O-*tetrabenzoylpapaverolinium chloride.*

Laudanosoline Derivatives.—The *hydrochloride* was prepared by reduction of *N*-methylpapaverolinium chloride by means of tin and hydrochloric acid under conditions similar to those used by Pyman (*loc. cit.*) for the reduction of papaverine. After elimination of the tin, the salt was isolated by concentration of the filtrate. The same substance was more conveniently obtained by demethylation of *dl*-laudanosine by means of hydriodic acid and acetic anhydride at 138° as described under papaveroline (above). The iodide crystallised on cooling and addition of ether and was converted into *chloride* by direct treatment with hot, moderately concentrated hydrochloric acid. The salt crystallised from dilute hydrochloric acid in minute colourless prisms, m. p. 244° (Found : C, 60·9; H, 6·0. $C_{17}H_{20}O_4NCl$ requires C, 60·5; H, 5·9%) (yield, 85%), freely soluble in water, less readily soluble in alcohol. In aqueous or alcoholic solution, on addition of ferric chloride, a bluish-green coloration is developed, which becomes more intense on heating.

Free *laudanosoline* was precipitated as a colourless powder when ammonium carbonate was added to a solution of its hydrochloride; the substance was collected, washed, and dried in a desiccator (Found : C, 67·5; H, 6·2. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3%). The dry substance is stable in air, but when moist and especially in the presence of bases it rapidly becomes discoloured.

The sulphate has been previously described by Oberlin (*loc. cit.*), who converted the product of the action of aluminium chloride on laudanosine into this derivative. Obtained from the above-mentioned free laudanosoline it crystallised from dilute sulphuric acid in colourless prisms that soften at 260° and melt at 267° (decomp.) (Oberlin, *loc. cit.*, gives m. p. *ca.* 230°) (Found in anhydrous material: C, 58·2; H, 5·8. Calc. for $C_{34}H_{40}O_{12}N_2S$: C, 58·3; H, 5·7%). The *hydriodide*, from the hydrochloride and sodium iodide, crystallised from water in colourless prisms that have no definite melting point but soften and decompose at about 239° (Found : C, 43·7; H, 5·0. $C_{17}H_{20}O_4NI,2H_2O$ requires C, 43·9;

H, 5·1%). The *hydrobromide*, from the free base and aqueous hydrobromic acid, separated from the latter in spear-head-shaped crystals, m. p. 230° (Found in anhydrous material: C, 53·2; H, 5·1. $C_{17}H_{20}O_4NBr$ requires C, 53·4; H, 5·2%).

O-Tetrabenzoyl-laudanosoline (II) was obtained from laudanosoline hydrochloride by a method like that used for tetrabenzoylpapaveroline. The crude product was converted into a *picrate* in alcoholic solution, and this derivative crystallised from ethyl acetate–alcohol in yellow tablets, m. p. 212° (Found: C, 64·9; H, 4·2; N, 6·1. $C_{51}H_{38}O_{15}N_4$ requires C, 64·7; H, 4·0; N, 5·9%). The same picrate was isolated after benzoylation by the Schotten–Baumann method with sodium carbonate and only a few drops of aqueous sodium hydroxide.

A suspension of the picrate in water was agitated with chloroform, and sodium carbonate added; the chloroform layer was washed with aqueous sodium carbonate, dried, and evaporated. The residue could not be induced to crystallise and was converted into a *hydrochloride*, which crystallised from aqueous-alcoholic hydrochloric acid, by slow evaporation of the alcohol, in colourless prisms, m. p. 190° (anhydrous) (Found in anhydrous material: C, 71·9; H, 5·1. $C_{43}H_{36}O_8NCl$ requires C, 71·7; H, 4·8%).

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