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CLXXXII.—iso*Quinoline Derivatives. Part II. The Constitution of the Reduction Products of Papaverine.*

By Frank Lee Pyman.

In a previous paper (this vol., p. 1266) it was shown that laudanosine can be readily oxidised to 4 : 5-dimethoxy-2-β-methylaminoethylbenzaldehyde by means of sulphuric acid and manganese dioxide, and it consequently became of interest to investigate the action of this reagent on other similarly constituted compounds, amongst others on the hitherto unknown *N*-benzoyltetrahydropapaverine. For this purpose, a quantity of tetrahydropapaverine was required, and the preparation of this compound was accordingly commenced by Goldschmiedt's method. This chemist (*Monatsh.*, 1886, **7**, 485; 1898, **19**, 324) obtained by the reduction of papaverine a crystalline base melting at 200—201° which he termed "tetrahydropapaverine," together with an amorphous base from which no crystalline derivative was obtained. Some years later, Freund and Beck (*Ber.*, 1904, **37**, 3321) obtained by the electrolytic reduction of papaveraldine an amorphous base, from which they prepared, through the nitrosoamine, a crystalline hydriodide; analyses of this salt were in agreement with the formula $C_{20}H_{25}O_4N,HI$, and they named the base provisionally "*iso*tetrahydropapaverine," while pointing out that no such isomeride of Goldschmiedt's tetrahydropapaverine would be expected from consideration of Goldschmiedt's papaverine formula, and suggesting as an alternative that the base might have been formed by reduction and condensation of two molecules of papaveraldine to form a pinacone, and subsequent further reduction to a compound, $(C_{20}H_{24}O_4N)_2$.

It is shown in the present communication that the amorphous base resulting from the reduction of papaverine (I) is *tetrahydropapaverine* (II), and is identical with Freund and Beck's "*iso*tetrahydropapaverine," and that Goldschmiedt's so-called "tetrahydropapaverine" is, in reality, a dihydropapaverine, namely, 6 : 7-dimethoxy-1-veratryl-1 : 2-dihydro*iso*quinoline, which it is proposed to designate 1 : 2-dihydropapaverine (III), in order to differentiate it from the 3 : 4-dihydropapaverine (IV) of Pictet and Finkelstein (*Ber.*, 1909, **42**, 1987).

The amorphous base obtained by the reduction of papaverine, either by Goldschmiedt's method, or more conveniently by the method given later, can be roughly separated from the crystalline base accompanying it by means of its easy solubility in ether, and

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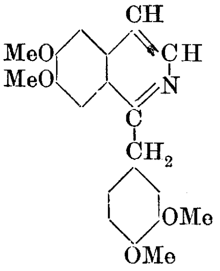
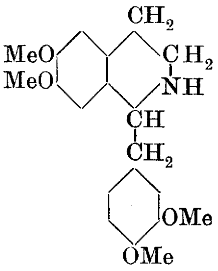
then purified through the hydriodide. It readily yields crystalline salts, of which the *hydrochloride*, hydriodide, *aurichloride*, and


(I.)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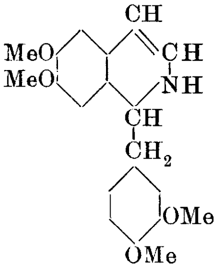
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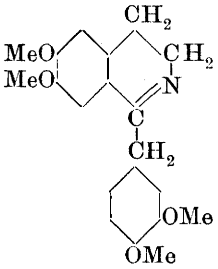
(IV.)

picrate have been prepared, and the analyses of these lead to the empirical formula of tetrahydropapaverine, $C_{20}H_{25}O_4N$, for this base; the amorphous nature of this base, the properties of its hydriodide, m. p. 259—260° (corr.), and those of its nitrosamine, m. p. 135—136° (corr.), show that it is identical with Freund and Beck's "*iso*tetrahydropapaverine," of which the hydriodide is stated to melt at 255° and the nitrosamine at 138°.

The amorphous base readily yields a crystalline N-*benzoyl* derivative, $C_{27}H_{29}O_5N$, of which the molecular weight has been determined, and shown to be that required by the simple formula, and the action of bromine on this benzoyl derivative in chloroform solution results in the formation of a crystalline *bromo*-derivative, $C_{27}H_{28}O_5NBr$.

The oxidation of the *N*-benzoyl derivative (V) leads to an important result, for there are formed benzoic acid, veratraldehyde, and a new base, 6 : 7-*dimethoxy*-3 : 4-*dihydro*iso*quinoline* (VI), the methochloride of which is identical with 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolinium chloride (VII). Since the latter compound has been obtained by the action of hydrochloric acid on 4 : 5-dimethoxy-2-β-methylaminoethylbenzaldehyde (VIII), which has been prepared by the oxidation of laudanosine (IX) (*N*-methyltetrahydropapaverine), it follows that the amorphous base is

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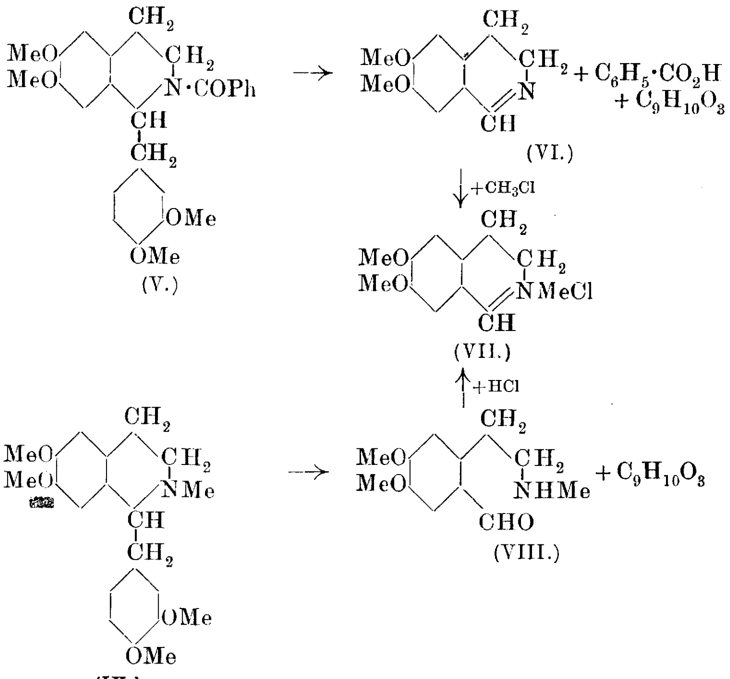
tetrahydropapaverine. This argument is illustrated by the following scheme:



(V.) (VI.) (VII.) (VIII.) (IX.)

The foregoing conclusion is further borne out by the fact that the amorphous base actually yields laudanosine on methylation. Freund and Beck (*loc. cit.*) state that the amorphous base yields, with methyl iodide in ethereal solution, crystals which are probably the hydriodide of the methylated base. The reaction is, however, less simple; on adding methyl iodide to an ethereal solution of tetrahydropapaverine, an amorphous deposit was obtained, which was separated by fractional crystallisation from alcohol into tetrahydropapaverine hydriodide, *laudanosine hydriodide*, and laudanosine methiodide, which appear to be formed in approximately equal parts according to the equation:

$$3R{:}NH + 3MeI = R{:}NH,HI + R{:}NMe,HI + R{:}NMe,MeI \quad (R = C_{20}H_{24}O_4).$$

It is, therefore, proved beyond question that the amorphous base is tetrahydropapaverine.

Since Goldschmiedt's papaverine formula only allows of the formation of one optically inactive tetrahydropapaverine, it is clear that this chemist's so-called "tetrahydropapaverine" must possess another constitution. Now, an examination of Goldschmiedt's

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analytical numbers shows that, whereas some of the results obtained by the analysis of the base and its derivatives are in good agreement with those calculated for the formula $C_{20}H_{25}O_4N$, others approximate more closely to those required by the formula $C_{20}H_{23}O_4N$. For example, the analyses of the hydrochloride and nitrosamine, as well as that of the base given in his second paper, show in round figures 0·3 per cent. of hydrogen less than that calculated for the formula $C_{20}H_{25}O_4N$. On the other hand, the analytical results obtained by Pope and Peachey (Trans., 1898, **73**, 893) for the racemic and optically active forms of this base are in excellent agreement with this formula. It was therefore necessary to reinvestigate this base. The base, its hydrochloride, and N-*benzoyl* derivative were accordingly carefully purified and analysed, when the results obtained decided definitely in favour of the formula $C_{20}H_{23}O_4N$. Further, the corresponding papaveroline derivative was also prepared by the removal of the four methyl groups, and its *hydrochloride* gave, on analysis, figures agreeing with those required by the formula $C_{16}H_{15}O_4N,HCl$, corresponding with the formula of the methylated compound $C_{20}H_{23}O_4N$; *tetrahydropapaveroline hydrochloride*, on the other hand, which was prepared from tetrahydropapaverine for the purpose of comparison, gave, on analysis, figures agreeing with the expected formula $C_{16}H_{17}O_4N,HCl$, corresponding with the formula of the methylated compound $C_{20}H_{25}O_4N$; this result is important, since the difference in hydrogen content between the formulæ of the two hydrochlorides amounts to 0·6 per cent. A determination of the molecular weight of the base proved it to have the simple formula. The only possible conclusion from these facts is that this crystalline base obtained by the reduction of papaverine is a dihydropapaverine, and, since Pope and Peachey (*loc. cit.*) have resolved it into its optically active forms, and thereby shown that it contains a hydrogen atom in the 1-position, and Goldschmiedt has prepared a nitrosoamine from it, thus proving it to contain an imino-group, this base must consequently be 1 : 2-dihydropapaverine.

1 : 2-Dihydropapaverine is a compound of considerable stability, and has thus far resisted attempts to effect its reduction. In this respect it differs from a compound of similar type, 1-benzyl-2-methyl-1 : 2-dihydro*iso*quinoline, recently described by Freund and Bode (*Ber.*, 1909, **42**, 1762), which readily yields 1-benzyl-2-methyltetrahydro*iso*quinoline when reduced with tin and hydrochloric acid, although the reduction is incomplete when sodium and alcohol are employed. This difference in behaviour between 1 : 2-dihydropapaverine and 1-benzyl-2-methyl-1 : 2-dihydro*iso*quinoline must probably be ascribed to the presence of the free

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imino-group in the former, and this view is supported by the fact that the unknown *N*-methyl ether of 1:2-dihydropapaverine has not been obtained in the reduction of papaverine methochloride, in which hitherto only laudanosine has been isolated (Pictet and Athanasescu, *Ber.*, 1900, **33**, 2346).

N-Benzoyl-1:2-dihydropapaverine is also a very stable compound; it is not readily attacked either by bromine or by sulphuric acid and manganese dioxide, thus differing markedly from *N*-benzoyltetrahydropapaverine.

EXPERIMENTAL.

Reduction of Papaverine.

One hundred grams of papaverine were dissolved in a mixture of 400 c.c. of alcohol and 400 c.c. of concentrated hydrochloric acid, and boiled with 200 grams of granulated tin under a reflux condenser for five hours. Further quantities of 50 grams of tin and 200 c.c. of hydrochloric acid were then added, and the mixture boiled for another seven hours. The alcohol was then removed by distillation, and the acid liquor cooled and diluted with water, which caused the precipitation of double salts of tin and the alkaloids in a white, amorphous condition. These were collected, washed with water, dissolved in 3 litres of boiling water, and decomposed with hydrogen sulphide. The resulting solution of the hydrochlorides was filtered from tin sulphide, rendered strongly alkaline with sodium carbonate, and completely extracted, first with ether, and then with chloroform.

The ethereal residue amounted to 65 grams of sticky oil; this dissolved to a clear solution in dilute hydrochloric acid, and the solution gave, on the addition of solid potassium iodide, an amorphous precipitate, which became crystalline after boiling with absolute alcohol, and furnished 55 grams of pure tetrahydropapaverine hydriodide, melting at 259—260° (corr.).

The chloroform residue amounted to about 15 grams of a brown, viscid oil, and gave 14 grams of a crystalline hydrochloride when mixed with dilute hydrochloric acid. On dissolving this in water, adding aqueous sodium carbonate, and recrystallising the separated base from absolute alcohol, more than 8 grams of 1:2-dihydropapaverine, melting at 201—202° (corr.), were obtained.

The mother liquors obtained in the purification of the two bases contained further quantities of these compounds.

Tetrahydropapaverine (II, p. 1611).

This base has only been obtained in an amorphous form; it remains as a colourless, viscid gum on the evaporation of its

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solutions in various solvents. It is moderately readily soluble in water, insoluble in light petroleum, and readily soluble in the other usual organic solvents. On dissolving this base in hydrochloric acid and adding an excess of sodium nitrite solution, tetrahydropapaverinenitrosoamine separates as a sticky oil, which becomes crystalline on stirring with alcohol, and separates from alcohol in short needles which melt at 135—136° (corr.).

Tetrahydropapaverine forms beautifully crystalline salts.

The hydriodide, of which the preparation has already been described, crystallises from water in prisms which melt at 259—260° (corr.) after becoming yellow a few degrees below this point. This salt is anhydrous, and is very sparingly soluble in water or alcohol:

0·1512 gave 0·2832 CO_2 and 0·0748 H_2O. C = 51·1; H = 5·5.
0·1885 ,, 0·0942 AgI. I = 27·0.
$C_{20}H_{25}O_4N,HI$ requires C = 51·0; H = 5·6; I = 27·0 per cent.

The *hydrochloride* was obtained by double decomposition of the hydriodide with silver chloride; it crystallises from water in glistening prisms, which sinter at 81° and melt at 83—85° (corr.) to an opaque liquid, and contains $4\frac{1}{2}$ molecules of water of crystallisation, of which $3\frac{1}{2}$ are lost at 100°. After recrystallisation from absolute alcohol, this salt is obtained as an anhydrous, crystalline powder, which melts at 217—219° (corr.). It is sparingly soluble in water, and very sparingly so in alcohol:

0·6950 hydrated salt, air-dried, lost 0·0967 at 100°. H_2O = 13·9.
0·1610 ,, ,, dried at 100°, gave 0·3590 CO_2 and 0·0977 H_2O. C = 60·8; H = 6·8.
$C_{20}H_{25}O_4N,HCl,4\frac{1}{2}H_2O$, losing $3\frac{1}{2}H_2O$, requires loss = 13·7 per cent.
$C_{20}H_{25}O_4N,HCl,H_2O$ requires C = 60·3; H = 7·1.
0·1527 anhydrous salt gave 0·3540 CO_2 and 0·0953 H_2O. C = 63·2; H = 7·0.
0·1900 anhydrous salt gave 0·0699 AgCl. Cl = 9·1.
$C_{20}H_{25}O_4N,HCl$ requires C = 63·2; H = 6·9; Cl = 9·3 per cent.

The *aurichloride* crystallises from absolute alcohol in radial clusters of deep yellow needles, which blacken and decompose at 176° (corr.). This salt is anhydrous, and is very sparingly soluble in water and sparingly so in alcohol:

0·2546 gave 0·0739 Au. Au = 29·0.
$C_{20}H_{25}O_4N,HAuCl_4$ requires Au = 28·9 per cent.

The *picrate* crystallises from absolute alcohol in clear, yellow, irregular prisms, which begin to sinter at 155° and decompose at 161—162° (corr.). This salt gradually becomes orange superficially; it is anhydrous, and is very sparingly soluble in water or alcohol:

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0·1295 gave 0·2578 CO_2 and 0·0536 H_2O. C = 54·3; H = 4·6.
$C_{20}H_{25}O_4N,C_6H_3O_7N_3$ requires C = 54·5; H = 4·9 per cent.

Methylation of Tetrahydropapaverine.

Seventeen grams of pure tetrahydropapaverine hydriodide were mechanically shaken with 100 c.c. of chloroform and 100 c.c. of 10 per cent. aqueous sodium carbonate for fifteen minutes, and the chloroform solution evaporated to low bulk. The residue was mixed with 50 c.c. of moist ether, and 15 grams of methyl iodide were then added. The solution became turbid almost immediately, and deposited a light brown, amorphous solid. After twelve hours, the supernatant liquor was poured off, and gave, on evaporation, 0·4 gram of light brown oil, which was added to the solid residue. The amorphous deposit was fractionally extracted with boiling absolute alcohol, and the various crops of crystals obtained from the extracts were separated by fractional crystallisation, and gave the following products:

(1) 4·8 Grams of tetrahydropapaverine hydriodide. This salt melted at 259—260° (corr.), and its melting point suffered no depression when the salt was mixed with the pure substance:

0·1520 gave 0·2860 CO_2 and 0·0771 H_2O. C = 51·3; H = 5·7.
0·1978 „ 0·0984 AgI. I = 26·9.
$C_{20}H_{25}O_4N,HI$ requires C = 51·0; H = 5·6; I = 27·0 per cent.

(2) 4·8 Grams of laudanosine methiodide. This salt melted at 213—215° (corr.), and its melting point suffered no depression when the salt was mixed with the pure substance:

0·1519 gave 0·2945 CO_2 and 0·0825 H_2O. C = 52·9; H = 6·1.
0·1519 „ 0·0726 AgI. I = 25·8.
$C_{21}H_{27}O_4N,CH_3I$ requires C = 52·9; H = 6·0; I = 25·5 per cent.

(3) 1·1 Grams of *laudanosine hydriodide*. This salt melted at 201—203° (corr.), and its melting point suffered no depression when the salt was mixed with the pure substance prepared by neutralising laudanosine with hydriodic acid. This salt is anhydrous, and is sparingly soluble in water or cold absolute alcohol:

0·1534 gave 0·2900 CO_2 and 0·0814 H_2O. C = 51·6; H = 5·9.
0·2010 „ 0·0965 AgI. I = 25·9.
$C_{21}H_{27}O_4N,HI$ requires C = 51·9; H = 5·8; I = 26·2 per cent.

Besides the above quantities of pure salts, a number of fractions consisting of mixtures were obtained. These were combined, dissolved in water, and mixed with aqueous sodium carbonate; this caused the precipitation of 2·0 grams of a brown oil, which solidified on cooling, and proved to contain a large proportion of laudanosine.

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N-*Benzoyltetrahydropapaverine* (V, p. 1612).

This compound was prepared by benzoylating tetrahydropapaverine in a manner similar to that applied to 1 : 2-dihydropapaverine.

N-*Benzoyltetrahydropapaverine* crystallises from absolute alcohol in clusters of glistening, prismatic needles, which melt at 159—160° (corr.). It is very sparingly soluble in water or ether, sparingly so in acetone or alcohol, but readily so in chloroform. It is insoluble in dilute acids or alkalis:

0·1527 gave 0·4050 CO_2 and 0·0911 H_2O. C = 72·3; H = 6·7.
0·1538 „ 4·2 c.c. N_2 at 22° and 754 mm. N = 3·1.
$C_{27}H_{29}O_5N$ requires C = 72·4; H = 6·5; N = 3·1 per cent.

Molecular weight determination by the ebullioscopic method:

0·2270 in 12·37 benzene gave Δt 0·110. M.W. = 445.
0·4070 „ 12·37 „ „ Δt 0·195. M.W. = 451.
$C_{27}H_{29}O_5N$ requires M.W. = 447.

Bromo-N-*benzoyltetrahydropapaverine*, $C_{27}H_{28}O_5NBr$.

Two grams of *N*-benzoyltetrahydropapaverine were dissolved in 20 c.c. of chloroform, and a solution of 1 gram of bromine in 30 c.c. of chloroform was added. The mixture was kept for forty hours, and then allowed to evaporate spontaneously; the gummy residue was dissolved in a little alcohol, and mixed with aqueous ammonia, when 2·2 grams of bromo-*N*-benzoyltetrahydropapaverine separated as an oil, which became crystalline on keeping; this yield represents 93 per cent. of the theoretical.

Bromo-N-*benzoyltetrahydropapaverine* crystallises from absolute alcohol in clusters of colourless, square leaflets, which melt at 185—186° (corr.); it is insoluble in water, dilute acids, or alkalis, and sparingly soluble in cold alcohol:

0·1456 gave 0·3303 CO_2 and 0·0721 H_2O. C = 61·9; H = 5·5.
0·1961 „ 0·0706 AgBr. Br = 15·3.
$C_{27}H_{28}O_5NBr$ requires C = 61·6; H = 5·4; Br = 15·2 per cent.

Oxidation of N-*Benzoyltetrahydropapaverine: Formation of* 6 : 7-*Dimethoxy*-3 : 4-*dihydro*iso*quinoline* (VI, p. 1612).

Thirty-five grams of *N*-benzoyltetrahydropapaverine, melting at 159—160° (corr.), were ground to a fine powder with 200 c.c. of water, mixed with a solution of 70 grams of sulphuric acid in 1 litre of water and 17·5 grams of pyrolusite, containing 80 per cent. of manganese dioxide, and well stirred. The temperature

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was gradually raised to the full heat afforded by the steam-bath, and after one hour the suspension had given place to a nearly clear, pale yellow liquor containing a quantity of resinous matter. The latter was removed by filtration; it weighed 18 grams, of which 3 grams consisted of inorganic material, and gave 9 grams of unchanged *N*-benzoyltetrahydropapaverine after crystallisation from alcohol; the sticky mother liquors from this were neglected.

The filtrate from the resinous matter was completely extracted with ether, and this in turn with aqueous sodium carbonate; the ether left on evaporation 5·5 grams of crude veratraldehyde, and the alkaline extract gave on acidification 4·5 grams of benzoic acid.

The aqueous solution of the basic products was then rendered alkaline with sodium carbonate, and completely extracted with chloroform; on then adding sodium hydroxide and again extracting with chloroform, no further quantity of material was obtained.

The chloroform extract from the sodium carbonate solution gave on distillation a quantity of brown oil, which was purified by distillation under 24 mm. pressure, when more than 5 grams of 6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline distilled at 205—208° (corr.), and formed a viscid, yellow oil with a faint blue fluorescence, which did not crystallise on keeping:

0·1948 gave 0·4905 CO_2 and 0·1250 H_2O. C = 68·7; H = 7·2.

$C_{11}H_{13}O_2N$ requires C = 69·1; H = 6·9 per cent.

6 : 7-*Dimethoxy*-3 : 4-*dihydro*iso*quinoline* is readily soluble in water and the usual organic solvents, with the exception of light petroleum. It forms crystalline salts with acids, and combines with methyl halides in ethereal solution, forming methyl salts which are identical with the salts obtained by the action of the corresponding acids on 4 : 5-dimethoxy-2-β-methylaminoethylbenzaldehyde.

The base is precipitated as an oil on the addition of aqueous sodium carbonate to concentrated solutions of its salts. The addition of aqueous potassium cyanide to the hydrochloride in concentrated aqueous solution causes the separation of an oil, which is no doubt 1-cyano-6 : 7-dimethoxytetrahydro*iso*quinoline.

The *hydrochloride* crystallises from aqueous acetone in pale yellow, glistening needles, which melt at 72—75° (corr.), and contain 3 molecules of water of crystallisation. After drying at 100°, this salt melts and decomposes at 208° (corr.). It is very readily soluble in water or alcohol, giving neutral solutions, which, when dilute, show a blue fluorescence, but insoluble in acetone:

0·1548, air-dried salt, gave 0·2685 CO_2 and 0·0983 H_2O. C = 47·3; H = 7·1.

0·2051, air-dried salt, gave 0·1070 AgCl. Cl = 12·9.

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0·2020, air-dried salt, lost 0·0380 at 100°. $H_2O=18·8$.

$C_{11}H_{13}O_2N,HCl,3H_2O$ requires $C=46·9$; $H=7·2$; $Cl=12·6$; $H_2O=19·2$ per cent.

0·1500, dried at 100°, gave 0·3197 CO_2 and 0·0868 H_2O. $C=58·1$; $H=6·5$.

$C_{11}H_{13}O_2N,HCl$ requires $C=58·0$; $H=6·2$ per cent.

The *picrate* crystallises from absolute alcohol in fine, golden, silky needles, which melt at 206—208° (corr.), after sintering several degrees earlier.

The *methochloride* was obtained as follows. An ethereal solution of 6:7-dimethoxy-3:4-dihydro*iso*quinoline was mixed with methyl iodide, when a deep yellow oil, which quickly became crystalline, separated. This was dissolved in water and shaken with silver chloride; the resulting liquor was filtered, evaporated to low bulk, and mixed with acetone, when the methochloride separated as a yellow, crystalline powder, which melted at 61—62° (corr.), and proved to be identical with 6:7-dimethoxy-2-methyl-3:4-dihydro*iso*quinolinium chloride.*

The *methobromide* was prepared directly by the action of methyl bromide on the base in ethereal solution; after recrystallisation from moist acetone it formed primrose needles, which sintered at 87—90° (corr.), both alone and when mixed with 6:7-dimethoxy-2-methyl-3:4-dihydro*iso*quinolinium bromide prepared from 4:5-dimethoxy-2-β-methylaminoethylbenzaldehyde.

Tetrahydropapaveroline, $C_{16}H_{17}O_4N$.

Five grams of tetrahydropapaverine hydrochloride, containing $4\frac{1}{2}H_2O$, were heated with 50 c.c. of concentrated hydrochloric acid for three hours at 170—175°. On opening the tube, methyl chloride escaped, and a clear liquid containing brown, serrated needles remained; the latter were collected and weighed 3·5 grams, that is, 97 per cent. of the theoretical.

Tetrahydropapaveroline hydrochloride crystallises from water in colourless, microscopic, glistening prisms, which melt and decompose at 291—293° (corr.), after gradually sintering and turning yellow from about 280°. It is very sparingly soluble in water or alcohol, and is anhydrous:

0·1509 gave 0·3266 CO_2 and 0·0764 H_2O. $C=59·0$; $H=5·7$.

0·1764 „ 0·0793 AgCl. $Cl=11·1$.

$C_{16}H_{17}O_4N,HCl$ requires $C=59·3$; $H=5·6$; $Cl=11·0$ per cent.

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* The statement (this vol., p. 1271) that this salt crystallises "from aqueous solution in a mass of primrose needles . . . . " should read "from aqueous acetone in a mass of primrose needles . . . ."

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This salt readily reduces cold ammoniacal silver nitrate solution, and liberates cuprous oxide from Fehling's solution on boiling. It gives with ferric chloride, in the first instance, a deep green colour, which quickly passes through a neutral tint to amethyst; on the addition of aqueous sodium carbonate, black flakes are deposited, and the supernatant liquor becomes colourless.

Concentrated solutions of this salt give with alkalis a white turbidity, due to the corresponding base; this is soluble in excess, giving a pale amethyst coloration; alkaline solutions, however, very quickly blacken when left in contact with air.

1 : 2-*Dihydropapaverine* (III, p. 1611).

This base has previously been described by Goldschmiedt under the name tetrahydropapaverine, and is stated to be precipitated from the solution of its hydrochloride on the addition of ammonia in anhydrous needles, and to melt at 200—201°, after sintering at 198°. It has now been found, however, that the colourless needles obtained by the addition of ammonia to an aqueous solution of the hydrochloride, whether this is prepared by the above method or by Goldschmiedt's, represent a hydrated form of the base, containing $3H_2O$, which, after air-drying, sinters at 65°, and finally melts at 201—202° (corr.):

0·2062, air-dried precipitated base, lost 0·0295 at 110°. $H_2O = 14·3$.

$C_{20}H_{23}O_4N,3H_2O$ requires $H_2O = 13·7$ per cent.

0·1673, dried at 110°, gave 0·4305 CO_2 and 0·1038 H_2O. $C = 70·2$; $H = 7·0$.

$C_{20}H_{23}O_4N$ requires $C = 70·3$; $H = 6·8$ per cent.

($C_{20}H_{25}O_4N$ „ $C = 70·0$; $H = 7·3$ „ „)

After crystallising this base from alcohol, it becomes anhydrous, and melts at 201—202° (corr.); this melting point is unchanged by crystallising the base from xylene, from which it separates in large prisms. For analysis, the base was recrystallised, first from alcohol, and then from xylene, and dried at 110°:

0·1549 gave 0·4016 CO_2 and 0·0972 H_2O. $C = 70·7$; $H = 7·0$.

0·1516 „ 0·3918 CO_2 „ 0·0915 H_2O. $C = 70·5$; $H = 6·8$.

Molecular weight determination by the ebullioscopic method:

0·1439 in 12·05 benzene gave Δt 0·090. M.W. = 354.

0·3556 „ 12·05 „ „ Δt 0·230. M.W. = 343.

$C_{20}H_{23}O_4N$ requires M.W. = 341.

The hydrochloride is stated by Goldschmiedt to decompose at 290°, and contain 3 molecules of water of crystallisation, of which 1½ are gradually lost in dry air. After preparing this salt from the carefully purified base, it was found, however, to decompose

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at about 325° (corr.). It forms beautifully crystalline rods from water, which contain 5 molecules of water of crystallisation; this salt has also been obtained with $8H_2O$:

0·4012 air-dried lost 0·0789 at 110°. $H_2O = 19·7$.
$C_{20}H_{23}O_4N,HCl,5H_2O$ requires $H_2O = 19·3$ per cent.
0·2134 air-dried lost 0·0592 at 100°. $H_2O = 27·7$.
$C_{20}H_{23}O_4N,HCl,8H_2O$ requires $H_2O = 27·6$ per cent.
0·1544, dried at 110°, gave 0·3567 CO_2 and 0·0895 H_2O. C = 63·0; H = 6·5.
0·1511, dried at 110°, gave 0·3505 CO_2 and 0·0874 H_2O. C = 63·3; H = 6·5.
0·1527, dried at 110°, gave 0·0562 AgCl. Cl = 9·1.
$C_{20}H_{23}O_4N,HCl$ requires C = 63·5; H = 6·4; Cl = 9·4 per cent.
($C_{20}H_{25}O_4N,HCl$ „ C = 63·2; H = 6·9; Cl = 9·3 per cent.)

The picrate was prepared from the pure hydrochloride in the usual manner, and formed long, yellow needles, which began to darken at 270°, and decomposed at 285° (corr.). Goldschmiedt states that this salt turns black at 245°, and decomposes at 270°.

Attempts to effect the reduction of 1 : 2-dihydropapaverine by means of (1) tin and fuming hydrochloric acid in alcoholic solution, and (2) sodium and alcohol, proved unsuccessful; in each case the base was recovered unchanged.

N-*Benzoyl*-1 : 2-*dihydropapaverine*, $C_{27}H_{27}O_5N$.

Five and a-half grams of 1 : 2-dihydropapaverine were benzoylated in chloroform solution by the Schotten-Baumann method; the resulting chloroform solution of the benzoyl derivative was mechanically shaken with a large excess of 10 per cent. aqueous sodium hydroxide, separated, dried, and evaporated. The brown oil obtained was then moistened with alcohol and again evaporated in an open dish, this process being repeated a second time, and then dissolved in about twice its volume of absolute alcohol. On cooling, 4·9 grams of pure *N*-benzoyl-1 : 2-dihydropapaverine separated as a crystalline powder, the yield amounting to 68 per cent. of the theoretical.

N-*Benzoyl*-1 : 2-*dihydropapaverine* crystallises from absolute alcohol in colourless, transparent, glistening prisms, which melt at 234—235° (corr.). It is very sparingly soluble in water or ether, sparingly so in alcohol or acetone, and readily so in chloroform:

0·1542 gave 0·4101 CO_2 and 0·0856 H_2O. C = 72·5; H = 6·2.
0·1530 „ 4·2 c.c. N_2 at 24° and 774 mm. N = 3·1.
$C_{27}H_{27}O_5N$ requires C = 72·7; H = 6·1; N = 3·1 per cent.

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On leaving this substance in contact with bromine (2 atoms to 1 molecule) in chloroform solution for forty hours, allowing the chloroform to evaporate, dissolving the residue in a little alcohol, precipitating it with dilute aqueous ammonia, and crystallising the precipitate from alcohol, a considerable proportion is recovered unchanged; after the evaporation of the alcohol, the residue forms a yellow gum, which does not contain bromine.

On attempting to oxidise *N*-benzoyl-1 : 2-dihydropapaverine with dilute sulphuric acid and manganese dioxide under the conditions previously described for *N*-benzoyltetrahydropapaverine, more than 70 per cent. was recovered unchanged, and no crystalline degradation products were obtained except a trace of benzoic acid.

1 : 2-*Dihydropapaveroline*, $C_{16}H_{15}O_4N$.

This compound has previously been described by Goldschmiedt under the name "tetrahydropapaveroline." Comparison of the colour reactions given here for 1 : 2-dihydropapaveroline and tetrahydropapaveroline with those given by Goldschmiedt (*loc. cit.*) for his compound indicate that the latter probably contained a certain amount of tetrahydropapaveroline.

Three grams of 1 : 2-dihydropapaverine hydrochloride (containing $8H_2O$) were heated with 30 c.c. of concentrated hydrochloric acid for three hours at 170—175°. On opening the tube, methyl chloride escaped, and a pale yellow liquid containing pale brown crystals remained; the latter were collected, and weighed 1·4 grams, that is, 74 per cent. of the theoretical.

1 : 2-*Dihydropapaveroline hydrochloride* crystallises from water in nearly colourless prisms, which decompose at 296° (corr.). This salt contains half a molecular proportion of water of crystallisation, and is easily soluble in water:

0·2750 air-dried lost 0·0095 at 120°. $H_2O = 3{\cdot}5$.

0·1734, dried at 120°, gave 0·3783 CO_2 and 0·0798 H_2O. $C = 59{\cdot}5$; $H = 5{\cdot}2$.

0·1530, dried at 120°, gave 0·3349 CO_2 and 0·0689 H_2O. $C = 59{\cdot}7$; $H = 5{\cdot}0$.

$C_{16}H_{15}O_4N,HCl,\frac{1}{2}H_2O$ requires $H_2O = 2{\cdot}7$ per cent.

$C_{16}H_{15}O_4N,HCl$ requires $C = 59{\cdot}7$; $H = 5{\cdot}0$ per cent.

This salt readily reduces cold ammoniacal silver nitrate solution, but does not liberate cuprous oxide from Fehling's solution on boiling. It gives with ferric chloride a persistent, deep green colour, and, on the addition of aqueous sodium carbonate, dark flakes are deposited, leaving a violet-coloured supernatant liquor.

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Concentrated solutions of this salt give with alkalis a white precipitate, which is soluble in excess, giving a pale yellowish-green solution; alkaline solutions, however, very quickly blacken on exposure to air.

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