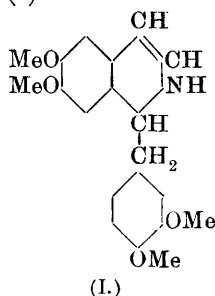


CXX.—*isoQuinoline Derivatives. Part V. The Constitution of the Reduction Products of Papaverine* (continued).

By FRANK LEE PYMAN and WILLIAM COLEBROOK REYNOLDS.

IN Part II of this series (Trans., 1909, **95**, 1610) it was shown by one of us that the amorphous base resulting from the reduction of papaverine is in reality tetrahydropapaverine, and it was further stated that Goldschmiedt's so-called "tetrahydropapaverine" is 1:2-dihydropapaverine (I):



The reasons which led to this conclusion were as follows.

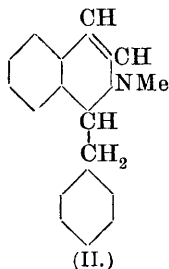
(1) Analyses and molecular weight determinations of the base and its derivatives prove that it has the formula $C_{20}H_{23}O_4N$, and its preparation by the reduction of papaverine, $C_{20}H_{21}O_4N$, therefore shows it to be a dihydropapaverine, unless it is obtained from an impurity in the papaverine, a possibility—at no time likely—which is definitely disproved in the present paper.

(2) The reactions of the base, for instance, the formation of a nitroso-derivative and benzoyl derivative, show that it contains an imino-group, therefore one of the additional hydrogen atoms occupies the 2-position of the *isoquinoline* ring.

(3) The resolution of the base by Pope and Peachey (Trans., 1898, **73**, 893) proves it to contain an asymmetric carbon atom, and on the assumption that this occupied the 1-position, as in alkaloids of the 1-benzyltetrahydro*isoquinoline* type (laudanosine, narcotine, etc.), the position of the remaining hydrogen atom was fixed, and the base designated 1:2-dihydropapaverine.

This base, however, was a compound of considerable stability, its reduction could not be effected, and its *N*-benzoyl derivative was not readily attacked either by bromine or by sulphuric acid and manganese dioxide; its behaviour therefore differed from that of

1-benzyl-2-methyl-1: 2-dihydroisoquinoline (II) (Freund and Beck, *Ber.*, 1909, **42**, 1762), a compound which may readily be reduced



to the corresponding tetrahydroisoquinoline, and which is easily attacked by oxidising agents.

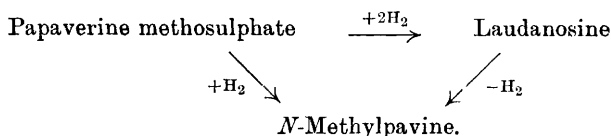
This difference in behaviour was ascribed to the presence of a free imino-group in the former, and some corroboration of this view was adduced from the fact that Pictet and Athanasescu (*Ber.*, 1900, **33**, 2346), in preparing laudanosine by the reduction of papaverine methochloride, did not discover the *N*-methyl derivative of 1: 2-dihydropapaverine. The present authors, however, now find that the reduction of papaverine methyl salts leads to the production not only of laudanosine, but also of a new base, $C_{21}H_{25}O_4N$, which is shown to be the *N*-methyl derivative of 1: 2-dihydropapaverine. Further, the new base is as stable as the parent compound; its reduction cannot be effected either by tin and hydrochloric acid or by sodium and amyl alcohol. It is therefore clear that the difference in behaviour between 1-benzyl-2-methyl-1: 2-dihydroisoquinoline and 1: 2-dihydropapaverine is not merely due to the influence of the imino-group in the latter, and the assumption that this base has the constitution represented by the term 1: 2-dihydropapaverine does not appear to be justified without further experimental evidence.

The further investigation of the constitution of this compound, however, more particularly with regard to the products obtained by its oxidation and degradation by complete methylation, is now in progress, and in order to avoid the use of a designation which may prove to be incorrect, it is proposed to adopt the name *pavine* for this base, $C_{20}H_{23}O_4N$, melting at 201—202°, which has been termed "tetrahydropapaverine" by Goldschmiedt (*Monatsh.*, 1886, **7**, 485; 1898, **19**, 324) and "1: 2-dihydropapaverine" by Pyman (*loc. cit.*); the new base, $C_{21}H_{25}O_4N$, will therefore be *N-methyl-pavine*.

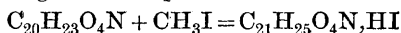
Pavine is always formed together with tetrahydropapaverine in the reduction of papaverine with tin and hydrochloric acid, and has been so obtained by different workers using papaverine having

the correct melting point (Goldschmiedt, Pope and Peachey, Pyman), but the yield is only small, and varies from about 8 to 12 per cent. of the theoretical; it appeared therefore to be possible, although unlikely, that pavine was derived from some impurity in the papaverine. In order to settle this point, the commercial papaverine used in these experiments was on one occasion very carefully purified; on methylation and subsequent reduction, a quantity of *N*-methylpavine was obtained together with laudanosiine, and it therefore follows that *N*-methylpavine is actually derived from *N*-methylpapaverine salts, and consequently that pavine is derived from papaverine.

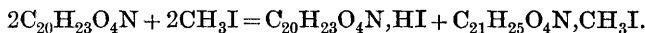
N-Methylpavine is obtained by the reduction of papaverine methyl salts with tin and hydrochloric acid, together with laudanosiine, from which it can be readily separated by either of two methods given in the experimental part of this paper; it is also formed to some extent in the oxidation of laudanosiine with sulphuric acid and manganese dioxide. The relation between these alkaloids is therefore as follows:



N-Methylpavine hydriodide and methiodide are also formed, together with pavine hydriodide, by the action of methyl iodide on pavine according to the equations:



and



As in the case of pavine, so also in that of *N*-methylpavine, base and salts readily crystallise with a considerable amount of water of crystallisation.

EXPERIMENTAL.

Purification of Papaverine.

After a preliminary experiment, in which besides laudanosiine a quantity of *N*-methylpavine was obtained by the reduction of papaverine methosulphate, the papaverine required for the next experiment was very carefully examined.

The base melted at 146—147°; it was converted into the hydrochloride, and this salt crystallised twice from water, being obtained in monoclinic plates, which decomposed at 231° (corr.); after regeneration, the base was converted into the hydrogen oxalate and the salt crystallised twice from alcohol, when it separated in

fine rods, which decomposed at 199° (corr.); the base was then regenerated, but still melted at $146\text{--}147^{\circ}$, or $147\text{--}148^{\circ}$ (corr.), and this melting point remained the same after recrystallisation of a specimen of the base from benzene.*

Reduction of Papaverine Methosulphate.

One hundred and eight-four grams of papaverine, which had been treated as above, were converted into the methosulphate (compare Decker and Pschorr, *Ber.*, 1904, **37**, 3401), and this was reduced with tin and hydrochloric acid in alcoholic solution, the conditions being similar to those previously adopted for the reduction of papaverine (Pyman, *Trans.*, 1909, **95**, 1614). After decomposition of the tin salts with hydrogen sulphide, and removal of the tin sulphide, the liquor was precipitated with sodium carbonate, filtered from the crude laudanosine, and extracted with chloroform; the latter left on distillation a brown gum, which was dissolved in warm dilute hydrochloric acid; this solution, on cooling, deposited *N*-methylpavine hydrochloride in beautiful prisms. The crude laudanosine was purified by crystallisation as hydrogen oxalate, the mother liquors yielding, on regeneration of the base and crystallisation of this as hydrochloride, a further quantity of *N*-methylpavine. Altogether 152 grams of laudanosine and 9 grams of *N*-methylpavine hydrochloride were obtained.

The laudanosine obtained in this manner melts at $115\text{--}116^{\circ}$ (corr.), and the melting point is unchanged after recrystallisation of the base from alcohol. The yield of pure laudanosine is therefore 78 per cent. of the theoretical; Pictet and Athanasescu (*loc. cit.*) obtained 50 to 60 per cent.

Laudanosine hydrogen oxalate crystallises from alcohol in microscopic needles, which contain $1\frac{1}{2}\text{H}_2\text{O}$, and, after drying at 100° , melts and decomposes at $163\text{--}165^{\circ}$ (corr.), after sintering a few degrees earlier. After crystallisation from water, this salt contains $2\frac{1}{2}\text{H}_2\text{O}$, and melts to a turbid, viscous liquid at $80\text{--}82^{\circ}$ (corr.). It is sparingly soluble in cold water or alcohol:

0.1532 † gave 0.3265 CO_2 and 0.0906 H_2O . $\text{C}=58.1$; $\text{H}=6.6$.

0.2009 † lost 0.0110 in a vacuum over H_2SO_4 . $\text{H}_2\text{O}=5.5$.

$\text{C}_{21}\text{H}_{27}\text{O}_4\text{N}, \text{C}_2\text{H}_2\text{O}_4, 1\frac{1}{2}\text{H}_2\text{O}$ requires $\text{C}=58.2$; $\text{H}=6.8$;

$\text{H}_2\text{O}=5.7$ per cent.

0.1855 † lost 0.0155 at 100° . $\text{H}_2\text{O}=8.4$.

$\text{C}_{21}\text{H}_{27}\text{O}_4\text{N}, \text{C}_2\text{H}_2\text{O}_4, 2\frac{1}{2}\text{H}_2\text{O}$ requires $\text{H}_2\text{O}=9.1$ per cent.

* In view of a recent publication by Pictet and Kramers (*Ber.*, 1910, **43**, 1329), it may be of interest to note that, on treatment of the purified papaverine with concentrated sulphuric acid, the crystals were, at first, superficially coloured violet, and then dissolved in the acid, giving a colourless solution.

† Air-dried salt (from alcohol).

‡ Air-dried salt (from water).

Separation of Laudanosine and N-Methylpavine.

That the above method for the separation of laudanosine and *N*-methylpavine is fairly complete is shown by the following experiment.

A mixture of 10 grams of laudanosine and 1 gram of *N*-methylpavine, when converted into acid oxalate and recrystallised from water, gave 12.2 grams of laudanosine hydrogen oxalate; the base regenerated from the mother liquors then crystallised as hydrochloride gave 1.2 grams of *N*-methylpavine hydrochloride; on again regenerating the base from the mother liquors and crystallising as acid oxalate, another 0.9 gram of laudanosine hydrogen oxalate was obtained, and the last mother liquors gave a base yielding a small quantity of hydrochloride, which was not further worked up; the quantities recovered were equivalent to 9.5 grams of laudanosine and 0.8 gram of *N*-methylpavine.

Another method for the separation of the two bases depends on the different solubilities of the bases in alcohol.

A mixture of 10 grams of laudanosine and 1 gram of methylpavine crystallised from a minimum of hot alcohol gave 8.9 grams of laudanosine; the remainder converted into hydrochloride and crystallised from water gave 1.5 grams of *N*-methylpavine hydrochloride, and after regenerating the bases from the final mother liquor and crystallising from alcohol, a further 0.3 gram of laudanosine was obtained; the quantities recovered were thus equivalent to 9.2 grams of laudanosine and 1.0 gram of *N*-methylpavine.

N-Methylpavine, $C_{21}H_{25}O_4N$.

This base is liberated in an amorphous condition when alkalis are added to aqueous solutions of its salts, but the precipitate becomes crystalline on keeping, and then forms colourless prisms, which, after thorough drying in the air, contain $1\frac{1}{2}$ to $2\frac{1}{2}$ H_2O . The hydrated base has no sharp melting point, but begins to soften at about 80° , gradually melts, and then effervesces at 100° ; it loses nearly all its water of crystallisation when kept in a vacuum over sulphuric acid, and remains as a white, amorphous powder, which melts at about 90° :

0.4313 (air dried) lost 0.0380 in a vacuum over H_2SO_4 . $H_2O = 8.8$.

$C_{21}H_{25}O_4N \cdot 2H_2O$ requires $H_2O = 9.2$ per cent.

0.1985 (dried in a vacuum) gave 0.5099 CO_2 and 0.1257 H_2O .

$C = 70.1$; $H_2O = 7.1$.

After dehydration by boiling with benzene and anhydrous sodium sulphate, the base crystallises from benzene in hard prisms, which

are anhydrous, and melt at 140—141° (corr.), after sintering a degree earlier; it crystallises from anhydrous ether in small, glistening prisms having the same melting point. It is sparingly soluble in water, ether, or light petroleum, but readily so in the other usual organic solvents. It dissolves in concentrated sulphuric acid, giving a pale yellowish-green solution:

0.1555 gave 0.4038 CO₂ and 0.0995 H₂O. C=70.8; H=7.2.

0.1514 „ 0.3922 CO₂ „ 0.0971 H₂O. C=70.6; H=7.2.

0.1865 „ 6.2 c.c. N₂ at 22° and 758 mm. N=3.8.

0.2090 „ by Zeisel's method, 0.5360 AgI. OMe=33.9.

0.1529 „ „ „ 0.3915 AgI. OMe=33.8.

C₂₁H₂₅O₄N requires C=70.9; H=7.1; 4OMe=34.9;

N=3.9 per cent.

The *hydrochloride* crystallises from water in large, colourless, well-formed prisms, which melt at 65—81° (corr.), and contain 8 molecules of water of crystallisation, of which 7½ are lost on drying first in a vacuum, and then at 100°. This salt is soluble in about 50 parts of cold water, but easily soluble in hot water or alcohol:

0.5121 (air dried) lost 0.1293 at 100°. H₂O=25.2.

C₂₁H₂₅O₄N.HCl.8H₂O, losing 7½H₂O, requires H₂O=25.2 per cent.

0.1616 * gave 0.3707 CO₂ and 0.0972 H₂O. C=62.6; H=6.7.

0.1598 * „ 0.3664 CO₂ „ 0.0962 H₂O. C=62.5; H=6.7.

0.2124 * „ 0.0733 AgCl. Cl=8.5.

C₂₁H₂₅O₄N.HCl.½H₂O requires C=62.9; H=6.8; Cl=8.8 per cent.

The *hydriodide* crystallises from water in large, nearly colourless prisms, which melt at 70—87° (corr.), and contain 6H₂O. It is easily soluble in hot water or alcohol. After drying, it has no sharp melting point, but gradually softens from about 185° onwards:

0.2194 (air dried) lost 0.0412 at 100°. H₂O=18.8.

C₂₁H₂₅O₄N.HI.6H₂O requires H₂O=18.3 per cent.

0.1704 * gave 0.3242 CO₂ and 0.0845 H₂O. C=51.9; H=5.6.

0.1892 * „ 0.0911 AgI. I=26.0.

C₂₁H₂₅O₄N.HI requires C=52.2; H=5.4; I=26.3 per cent.

The *aurichloride* crystallises from a mixture of acetone and absolute alcohol in terra-cotta coloured needles, which contain a molecule of alcohol of crystallisation and decompose at 198° (corr.). It is almost insoluble in water or alcohol, but readily soluble in acetone:

0.2058 † gave 0.2824 CO₂ and 0.0764 H₂O. C=37.4; H=4.2.

0.1522 † „ 0.2086 CO₂ „ 0.0605 H₂O. C=37.4; H=4.5.

* Dried at 100°.

† Air-dried salt.

0.2287 * gave 0.0607 Au. Au = 26.5.

0.6416 * lost 0.0365 at 100°. $C_2H_6O = 5.7$.

$C_{21}H_{25}O_4N, HAuCl_4, C_2H_6O$ requires C = 37.2; H = 4.4; Au = 26.6;
 $C_2H_6O = 6.2$ per cent.

The *picrate* crystallises from water in small, glistening, yellow needles, which melt at 219° (corr.), after sintering slightly from 200°. It is very sparingly soluble in cold water or alcohol:

0.1576 * lost 0.0014 at 100°. $H_2O = 0.9$.

0.1735 † gave 0.3532 CO_2 and 0.0754 H_2O . C = 55.5; H = 4.9.

$C_{21}H_{25}O_4N, C_6H_3O_7, N_3$ requires C = 55.5; H = 4.8 per cent.

The *methiodide* separates in colourless, glistening rods, which contain $2H_2O$, and decompose at about 280° (corr.) on warming a methyl-alcoholic solution of the base with methyl iodide. It is sparingly soluble in cold water or hot alcohol:

0.5200 * lost 0.0353 at 100°. $H_2O = 6.8$.

$C_{21}H_{25}O_4N, CH_3I, 2H_2O$ requires $H_2O = 6.8$ per cent.

0.1565 † gave 0.3036 CO_2 and 0.0792 H_2O . C = 52.9; H = 5.7.

0.2318 † „ 0.1097 AgI. I = 25.6.

$C_{21}H_{25}O_4N, CH_3I$ requires C = 53.1; H = 5.7; I = 25.5 per cent.

After crystallisation from water, the methiodide forms beautiful, large, clear prisms, which contain $4H_2O$, and, after sintering from 114° and gradually becoming viscous, effervesce at 118—119° (corr.); after drying the fully hydrated salt at 100°, it has no sharp melting point, but begins to sinter at about 165° (corr.), and gradually becomes viscous and effervesces on raising the temperature:

0.1529 * gave 0.2607 CO_2 and 0.0884 H_2O . C = 46.5; H = 6.5.

0.2030 * „ 0.0830 AgI. I = 22.1.

0.2716 * lost 0.0326 at 110°. $H_2O = 12.0$.

$C_{21}H_{25}O_4N, CH_3I, 4H_2O$ requires C = 46.4; H = 6.4; I = 22.3;

$H_2O = 12.7$ per cent.

The *methochloride* was prepared from the methiodide by double decomposition with silver chloride. It crystallises from water in beautiful, colourless prisms, which are sparingly soluble in water, and melt at 75—99° (corr.). The air-dried salt contains $7H_2O$, of which $6\frac{1}{2}$ are lost at 100°; the dried salt sinters at 150—170°, and then effervesces:

0.5173 * lost 0.1161 at 100°. $H_2O = 22.4$.

$C_{21}H_{25}O_4N, CH_3Cl, 7H_2O$, losing $6\frac{1}{2}H_2O$, requires loss = 22.0 per cent.

0.1528 † gave 0.3599 CO_2 and 0.0987 H_2O . C = 64.3; H = 7.2.

$C_{21}H_{25}O_4N, CH_3Cl, \frac{1}{2}H_2O$ requires C = 63.7; H = 7.1 per cent.

The *methohydroxide* was prepared by digesting a hot aqueous

* Air-dried salt.

† Dried at 100°.

solution of the methiodide with silver oxide, filtering from silver iodide, and evaporating the liquor until crystals formed on the surface. On cooling, the base separated in large, transparent prisms, which melted and effervesced at about 100° . It contains a large and variable amount of water of crystallisation. It is very easily soluble in water, giving a strongly alkaline solution, which yields with aqueous potassium iodide a precipitate of the methiodide.

Methylation of Pavine.

Ten grams of pavine were dissolved in about 50 c.c. of chloroform, and gently warmed with 10 grams of methyl iodide, until a reaction set in. A dark oil was deposited, and on keeping overnight, this became a mass of crystals, which were collected, washed with alcohol, and fractionally crystallised, first from absolute alcohol and then from water. The following products were obtained.

(1) 3.5 Grams of *N*-methylpavine methiodide. This salt effervesced at $118-119^{\circ}$ (corr.), and its melting point suffered no depression when the salt was mixed with the pure substance:

0.1636 * gave 0.2819 CO_2 and 0.0931 H_2O . $\text{C}=47.0$; $\text{H}=6.4$.

0.2063 * lost 0.0252 at 100° . $\text{H}_2\text{O}=12.2$.

$\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}, \text{CH}_3\text{I}, 4\text{H}_2\text{O}$ requires $\text{C}=46.4$; $\text{H}=6.4$;
 $\text{H}_2\text{O}=12.7$ per cent.

(2) 7.0 Grams of *N*-methylpavine hydriodide. This salt melted at $70-87^{\circ}$ (corr.), and its melting point suffered no depression when the salt was mixed with the pure substance:

0.1535 * gave 0.2374 CO_2 and 0.0892 H_2O . $\text{C}=42.2$; $\text{H}=6.5$.

0.2045 * lost 0.0374 at 100° . $\text{H}_2\text{O}=18.3$.

$\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}, \text{HI}, 6\text{H}_2\text{O}$ requires $\text{C}=42.6$; $\text{H}=6.5$; $\text{H}_2\text{O}=18.3$ per cent.

(3) 0.8 Gram of *pavine hydriodide*. This salt softened about 75° , but did not melt until about 265° . After drying at 100° , it softens together at 195° (corr.) without really melting, and its melting point suffered no depression when the salt was mixed with the pure substance prepared by neutralising pavine with hydriodic acid. This salt contains about $4\text{H}_2\text{O}$, and is sparingly soluble in cold water.

(a) Salt obtained in the methylation:

0.1967 * lost 0.0276 first in a vacuum, then at 100° . $\text{H}_2\text{O}=14.0$.

0.1578 † gave 0.2950 CO_2 and 0.0740 H_2O . $\text{C}=51.0$; $\text{H}=5.3$.

(b) Salt obtained by neutralising pavine with hydriodic acid:

0.2013 * lost 0.0228 first in a vacuum, then at 100° . $\text{H}_2\text{O}=11.3$.

* Air-dried salt.

† Dried at 100° .

0.1546 * gave 0.2901 CO_2 and 0.0735 H_2O . $\text{C}=51.2$; $\text{H}=5.3$.

$\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}, \text{HI}, 3\text{H}_2\text{O}$ requires $\text{H}_2\text{O}=10.3$ per cent.

$\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}, \text{HI}, 4\text{H}_2\text{O}$ „ $\text{H}_2\text{O}=13.3$ „

$\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}, \text{HI}$ requires $\text{C}=51.2$; $\text{H}=5.2$ per cent.

A number of small fractions consisting of mixtures of the above were also obtained.

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