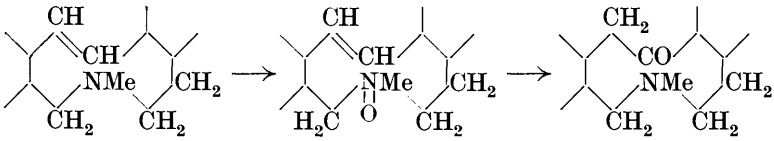
CCXXXV.—*Synthesis of Cryptopine and Protopine.*

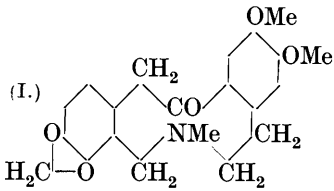
By Robert Downs Haworth and William Henry Perkin, jun.

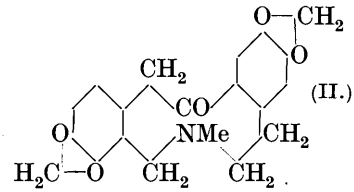
In a recent communication (this vol., p. 446), a synthesis of β-homochelidonine was described which is based on the conversion of anhydrotetrahydromethylberberine by oxidation with perbenzoic acid into the amine oxide and subsequent treatment with acetic and hydrochloric acids, when isomeric change to β-homochelidonine

takes place. This process, conveniently represented by the partial formulæ,

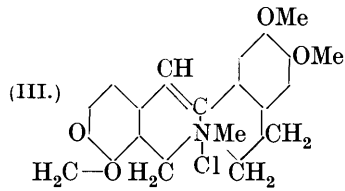


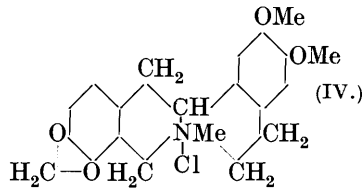
may be capable of development in various directions and the present communication contains an account of its use in the synthesis of cryptopine (I) and protopine (II).





When these alkaloids are digested with phosphorus oxychloride (Perkin, J., 1916, **109**, 883, 1023), they are converted into *iso*cryptopine chloride (III) and *iso*protopine chloride (as III), respectively, which in turn can be reduced to *iso*dihydrocryptopine chloride (IV) and *iso*dihydroprotopine chloride (as IV).





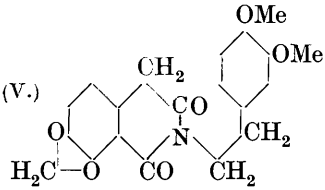
The latter are clearly closely related to tetrahydroberberine methochloride and should therefore be capable of conversion into cryptopine and protopine by a simple extension of the method which was so successful in the conversion of tetrahydroberberine methochloride into β-homochelidonine. A complete synthesis of cryptopine or protopine necessitates, therefore, the following two stages, (1) the synthesis of *iso*dihydrocryptopine chloride or *iso*dihydroprotopine chloride and (2) the conversion of these quaternary salts into cryptopine or protopine.

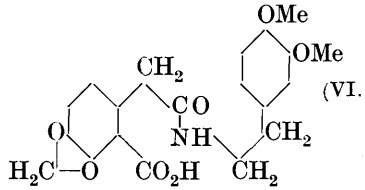
The method which has been adopted for the synthesis of *iso*dihydrocryptopine chloride (IV) and *iso*dihydroprotopine chloride (as IV) is a simple extension of the method devised by Haworth, Perkin, and Pink (J., 1925, **127**, 1709) for the preparation of substances allied to oxyberberine, which depends in the first place on a condensation between the requisite homophthalic acid and β-phenyl-

ethylamine derivatives, and in the present synthetical experiments 3 : 4-methylenedioxyhomophthalic acid (see preceding paper) was employed.

3 : 4-Methylenedioxyhomophthalic acid readily condenses with β-*veratrylethylamine* * to yield N-β-*veratrylethyl*-3 : 4-*methylenedioxyhomophthalimide* (V), which, on careful hydrolysis with sodium hydroxide, is converted into N-β-*veratrylethyl*-3 : 4-*methylenedioxyhomophthalamic acid* (VI), an acid which is also obtained by con-

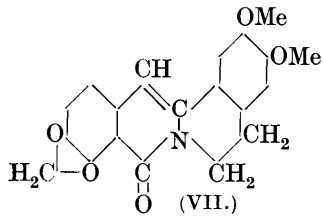
(V.)



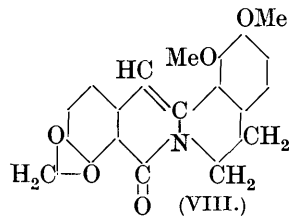


(VI.)

densing 3 : 4-methylenedioxyhomophthalic anhydride with β-veratrylethylamine. The *methyl* ester of the acid (VI), obtained by the action of methyl iodide on an ethereal suspension of the silver salt, on treatment with phosphorus oxychloride gives a 90% yield of a substance $C_{20}H_{17}O_5N$ (m. p. 240°), possessing the properties of a substance of the oxyberberine type. From its method of formation this may be represented by formula (VII) or (VIII), but the latter is very improbable because its formation necessitates a condensation occurring in the ortho-position to a methoxyl group



(VII.)



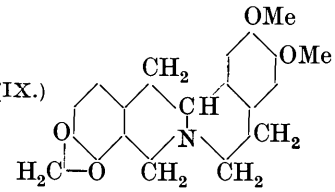
(VIII.)

in preference to condensation in the far more reactive para-position, which has so far always been the experience in *iso*quinoline condensations of this type. That the condensation follows the normal course with the production of (VII) and not (VIII) is shown by the fact that the substance $C_{20}H_{17}O_5N$ (m. p. 240°) is identical with oxy*epi*berberine, obtained from *iso*cryptopine chloride by the method described by Perkin (J., 1918, **113**, 518) and in which the methoxyl groups must be oriented as in formula (VII) in order to account for the production of *m*-hemipinic acid (Rainy Brown and Perkin, P., 1891, **6**, 166) and 4 : 5-dimethoxy-2-β-dimethylaminoethyl-

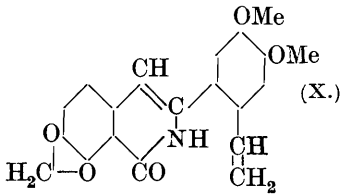
* This nomenclature has been adopted in conformity with the suggestions of Perkin, Ray, and Robinson (this vol., p. 947).

benzaldehyde (Perkin, J., 1916, **109**, 901) from cryptopine. The synthetical oxy*epi*berberine (VII) is reduced electrolytically * in alcoholic sulphuric acid solution to a colourless, crystalline base, $C_{20}H_{21}O_4N$ (m. p. 170°), which yields a sparingly soluble, crystalline hydrochloride and is identical in all respects with tetrahydro*epi*berberine (IX) obtained by Perkin (J., 1918, **113**, 512) from *iso*cryptopine chloride. Since tetrahydro*epi*berberine has been oxidised to *epi*berberinium chloride (Perkin, *loc. cit.*), it follows that this synthesis is a direct synthesis of *epi*berberine and its derivatives.

(IX.)

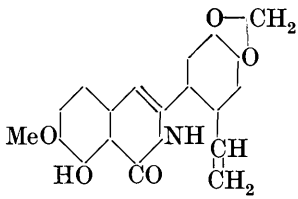


(X.)



When synthetical tetrahydro*epi*berberine (IX) is treated with methyl iodide, it is converted into a sparingly soluble methiodide, which with silver chloride is transformed into a *methochloride*, occurring in two readily separable crystalline modifications which

(XI.)

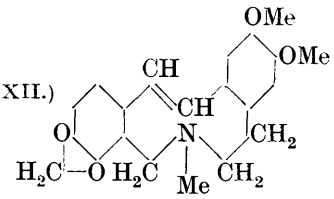


are identical with the α- and β-forms of *iso*dihydrocryptopine chloride (IV) obtained either by reducing *iso*cryptopine chloride

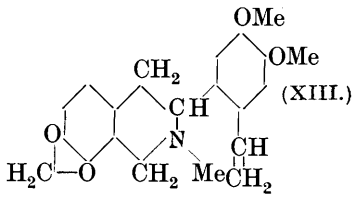
* It is interesting to note that, during an electrolytic reduction of oxy-*epi*berberine in which the temperature rose to 45°, only a small yield of tetrahydro*epi*berberine (IX) was obtained and a comparatively large quantity of a non-basic, sparingly soluble, high-melting substance was produced which proved to be *iso*oxy*epi*berberine (Perkin, *loc. cit.*, p. 519). In view of the alteration which has been made in the suggested structure of *iso*oxyberberine (see Bland, Perkin, and Robinson, J., 1912, **101**, 262; Perkin, Ray, and Robinson, *ibid.*, 1925, **127**, 744; Faltis, *Monatsh.*, 1910, **31**, 557), it is important to note that new analyses show that *iso*oxy*epi*berberine contains two methoxyl groups, and therefore the structure (X) suggested by Perkin for this substance does not appear to require the modification which was necessary in the case of *iso*oxyberberine. It is somewhat remarkable that the vinyl group does not undergo reduction in the cell, but this is not unusual and may be partly due to the insolubility of the *iso*oxy*epi*berberine. Owing to the similarity in properties between *iso*oxyberberine and *iso*oxy*epi*berberine, the structure of the former can still not be regarded as definitely settled, since this substance may have, for example, the constitution represented by (XI).

(III) with sodium amalgam (Perkin, J., 1919, **115**, 748) or better by reducing it electrolytically. Owing to the indefinite m. p.'s of these salts, identity was confirmed by conversion into the anhydro-bases and it was found that both the synthetical *iso*dihydrocryptopine chlorides and the salts obtained directly from cryptopine on digestion with silver hydroxide and evaporation in a vacuum gave the same anhydrodihydrocryptopine A (XII) and B (XIII).

(XII.)



(XIII.)

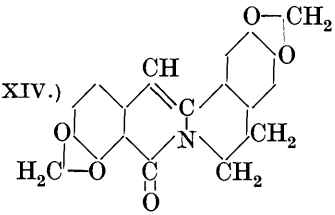


The conversion of anhydrodihydrocryptopine A (XII) into cryptopine was carried out exactly as in the case of the conversion of anhydrotetrahydromethylberberine into β-homochelidonine (Haworth and Perkin, *loc. cit.*). The base (XII) is oxidised by perbenzoic acid in ethereal solution to the *amine oxide*, which separates from water in crystals, m. p. 135° (decomp.), and yields a stable crystalline *hydrochloride*. When this amine oxide is heated with acetic and hydrochloric acids, it is converted into a base, m. p. 220—221°, which careful comparison proved to be cryptopine. In this way, therefore, the complete synthesis of cryptopine has been accomplished.

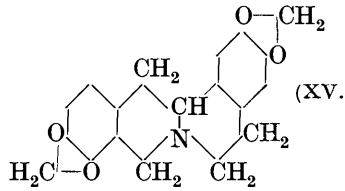
The method employed in the synthesis of protopine was similar to that outlined above in the case of cryptopine. 3 : 4-Methylenedioxyhomophthalic acid condenses with β-piperonylethylamine to yield N-β-*piperonylethyl*-3 : 4-*methylenedioxyhomophthalimide* (as V), which on careful hydrolysis is converted into N-β-*piperonylethyl*-3 : 4-*methylenedioxyhomophthalamic acid* (as VI), and the same acid is obtained by condensing 3 : 4-methylenedioxyhomophthalic anhydride with β-piperonylethylamine. The *methyl* ester of this acid is converted in good yield by the action of phosphorus oxychloride into a substance $C_{19}H_{13}O_5N$ (m. p. 292°) with properties characteristic of a compound of the oxyberberine type and this is reduced electrolytically to a base, $C_{19}H_{17}O_4N$ (m. p. 218°), which gives a very sparingly soluble hydrochloride. By analogy with the synthesis of oxy*epi*berberine it might be assumed that the substance $C_{19}H_{13}O_5N$ (m. p. 292°) is 2 : 3 : 9 : 10-*bismethylenedioxyoxyprotoberberine* (XIV) (for nomenclature see Buck, Perkin, and Stevens, J., 1925, **127**, 1462) and that the reduction product is 2 : 3 : 9 : 10-*bismethylenedioxytetrahydroprotoberberine* (XV), and structures similar to (VIII)

are excluded by the preparation of (XIV) and (XV) from *iso*protopine chloride. It may be pointed out that the methylenedioxy-groups in

(XIV.)

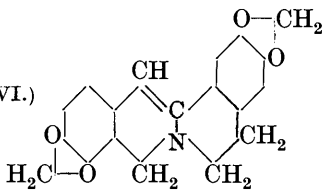


(XV.)

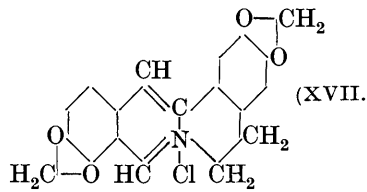


*iso*protopine chloride must be oriented as in (III) (with two methylenedioxy-groups) in order to account for the production of hydrastic acid (Danckwortt, *Arch. Pharm.*, 1912, **250**, 590) and 4 : 5-methylenedioxy-2-β-dimethylaminoethylbenzaldehyde (Gadamer and Bruchhausen, *ibid.*, 1922, **260**, 110, 128) from protopine. When *iso*protopine chloride * is carefully heated under diminished pressure, methyl chloride is lost much more readily than in the case of *iso*cryptopine chloride and a good yield of 2 : 3 : 9 : 10-*bismethylenedioxydihydroprotoberberine* (XVI) can be obtained. This yellow crystalline

(XVI.)



(XVII.)



substance, which has not previously been described, is readily reduced by zinc dust and dilute sulphuric acid to a colourless base which is identical with the base $C_{19}H_{17}O_4N$ (m. p. 218°) (XV) obtained by the reduction of the synthetical derivative of the oxyberberine type (XIV). When the dihydroprotoberberine (XVI) is oxidised with mercuric acetate, it yields 2 : 3 : 9 : 10-*bismethylenedioxyprotoberberinium chloride* (XVII), a bright orange-coloured salt crystallising with one molecule of water of crystallisation which, as in the case of other compounds of this type, is retained at 120°. On heating with sodium hydroxide, the chloride (XVII) undergoes a transformation in the same manner as berberinium chloride, yielding a mixture of dihydro-base identical with (XVI) and an oxyberberine-type derivative identical with the 2 : 3 : 9 : 10-bismethylenedioxyoxyprotoberberine (XIV) obtained by the action of phosphorus oxychloride on the methyl ester of the amic acid (as VI).

* Our thanks are due to Professor Gadamer for a gift of protopine which enabled this work to be carried out.

When synthetical 2 : 3 : 9 : 10-bismethylenedioxytetrahydroprotoberberine (XV) is treated with methyl iodide, a methiodide is obtained which gives rise to a *methochloride*, and this, as in the case of *iso*dihydrocryptopine chloride, exists in α- and β-modifications which are readily separated by crystallisation from water. The more soluble α-chloride, produced in the smaller quantity, is more readily decomposed by silver hydroxide than the β-chloride, but in both cases evaporation of the methohydroxide under reduced pressure leads to the production of an anhydro-base $C_{20}H_{19}O_4N$ (m. p. 120°). In the course of experiments which aimed at the formation of the anhydro-base from protopine it was found that only poor yields of iso*dihydroprotopine chloride* (as IV) are obtained by reducing *iso*protopine chloride (as III) with sodium amalgam, and no improvement is effected in this case by reducing it electrolytically. However, the *iso*dihydroprotopine chloride obtained by either of these methods exists in two forms, identical with the α- and β-modifications of 2 : 3 : 9 : 10-bismethylenedioxytetrahydroprotoberberine methochloride, and on decomposition with silver hydroxide yields *anhydrodihydroprotopine A* (as XII), which is identical with the anhydro-base $C_{20}H_{19}O_4N$ (m. p. 120°) obtained as described above. When this base is digested with hydrochloric acid, it is converted into *iso*dihydroprotopine β-chloride and this fact indicates that it has a structure similar to (XII) and not to (XIII) (compare Pyman, J., 1913, **103**, 825; Perkin, *ibid.*, 1916, **109**, 841). Owing to the small quantities used in these experiments, it has been impossible to isolate anhydrodihydroprotopine B (as XIII) from the product of the reaction.

Anhydrodihydroprotopine A (as XII) yields an *amine oxide* (m. p. 140°, decomp.) which crystallises from water and gives a stable crystalline *hydrochloride*. When the amine oxide is heated with hydrochloric and acetic acids, it is converted into a base (m. p. 207°) which is identical with protopine (II). It is in this way that the complete synthesis of protopine has been accomplished.

EXPERIMENTAL.

β-*Veratrylethylamine*.—β-3 : 4-Dimethoxyphenylpropionic acid was prepared as described by Haworth, Perkin, and Pink (*loc. cit.*, p. 1714) and converted into β-3 : 4-dimethoxyphenylpropionamide as follows :

A solution of dry β-3 : 4-dimethoxyphenylpropionic acid (100 g.) in chloroform (300 c.c.) was treated with thionyl chloride (70 g.), kept for 12 hours at room temperature, and then gradually poured into a solution containing concentrated ammonia (1200 c.c.), sodium hydroxide (10 g.), and water (1200 c.c.). The chloroform was

removed by distillation from the water-bath, the residual liquid treated with charcoal, filtered and cooled; the amide then separated in a state sufficiently pure for conversion into β-veratrylethylamine as described by Buck and Perkin (J., 1924, **125**, 1679).

N-β-*Veratrylethyl*-3 : 4-*methylenedioxyhomophthalimide* (V).—A mixture of 3 : 4-methylenedioxyhomophthalic acid (2·8 g.) and β-veratrylethylamine (2·5 g.) was heated at 165—175° for 3 hours. The gum produced, which rapidly hardened on treatment with methyl alcohol, in which it was sparingly soluble, crystallised from glacial acetic acid in almost colourless prisms, m. p. 181—182° (Found : C, 64·9; H, 5·2. $C_{20}H_{19}O_6N$ requires C, 65·0; H, 5·1%). The imide (V) dissolves in sodium hydroxide to a yellow solution with a green fluorescence, but on boiling for some time the solution becomes colourless owing to hydrolysis taking place.

For comparison purposes, a small quantity of N-β-*veratrylethyl*-4 : 5-*methylenedioxyhomophthalimide* was prepared by condensing β-veratrylethylamine with 4 : 5-methylenedioxyhomophthalic acid under conditions similar to those described above. This imide crystallises from glacial acetic acid in colourless plates, m. p. 162° (Found : C, 64·8; H, 5·1. $C_{20}H_{19}O_6N$ requires C, 65·0; H, 5·1%). It dissolves in sodium hydroxide to a yellow solution with a green fluorescence, but the m. p. of a mixture with an equal amount of imide (V) is 148—155°.

N-β-*Veratrylethyl*-3 : 4-*methylenedioxyhomophthalamic acid* (VI).—(*a*) The imide (V) (2·6 g.) was heated with *N*-sodium hydroxide (20 c.c.) for 12 hours, the solution cooled, saturated with carbon dioxide, filtered from traces of unchanged imide, the filtrate acidified with hydrochloric acid, and the light brown, granular precipitate collected.

(*b*) 3 : 4-Methylenedioxyhomophthalic anhydride (6 g.) and β-veratrylethylamine (5·5 g.) were heated in benzene (50 c.c.) for 2 hours, the semi-solid mass was then dissolved by shaking with 5% sodium hydroxide solution, the benzene separated, the alkaline solution acidified with hydrochloric acid, and the granular precipitate collected. N-β-*Veratrylethyl*-3 : 4-*methylenedioxyhomophthalamic acid* (VI) prepared by either method separates from dilute acetic acid (1 : 1) in colourless prisms, m. p. 185—186° (Found : C, 61·7; H, 5·5. $C_{20}H_{21}O_7N$ requires C, 62·0; H, 5·4%).

The *methyl* ester was prepared as follows : The amic acid (3·8 g.) was dissolved in a boiling solution of sodium bicarbonate (0·84 g.) in water (50 c.c.) and treated with silver nitrate (1·7 g.) dissolved in a little water. The silver salt separated in thin plates, which, after cooling, were collected, washed successively with water, alcohol, and ether, and dried thoroughly in an evacuated desiccator. The

dry silver salt was suspended in dry ether, gently refluxed with an excess of methyl iodide for 12 hours, the ethereal suspension filtered, and the filtrate concentrated; a small quantity of the methyl ester then separated. The main yield of ester, however, was extracted from the silver residue with boiling methyl alcohol, from which it separated in colourless needles, m. p. 131—132° (Found: C, 61·6; H, 6·0. $C_{21}H_{23}O_7N$ requires C, 61·7; H, 5·9%).

Oxyepiberberine (VII).—The methyl ester (2·5 g.) was boiled with phosphorus oxychloride (5 c.c.) for 10 minutes, a bright red solution being obtained. The excess of phosphorus oxychloride was removed by distillation in a vacuum, and the residue dissolved completely in hot water to an orange-red solution, which no doubt contained the hydrochloride of a base similar in structure to that obtained by Haworth, Perkin, and Pink (*loc. cit.*, p. 1714, formula XXIII) by the action of phosphorus oxychloride on oxyberberine. The red solution was made alkaline by the addition of sodium hydroxide, the grey solid collected, washed first with water and then with methyl alcohol, and finally crystallised from boiling glacial acetic acid containing a little water in almost colourless, slender needles (2·0 g.), m. p. 240—241° (Found: C, 68·1; H, 4·9. Calc.: C, 68·3; H, 4·8%). When mixed with a specimen of oxy*epi*berberine obtained by the action of sodium hydroxide on *epi*berberinium chloride (Perkin, J., 1918, **113**, 517), no depression in m. p. was observed on heating. The synthetical compound was dissolved in a little boiling glacial acetic acid; an *acetate* separated, on cooling, in deep yellow needles which were decomposed to oxy*epi*berberine by the action of heat or moisture. Further, the colourless benzene solution of the synthetical compound exhibits a bluish-violet fluorescence, whilst its solution in glacial acetic acid becomes orange on the addition of concentrated sulphuric acid, and thereafter deep purple on the addition of a drop of dilute nitric acid. Oxy*epi*berberine obtained from natural sources exhibits identical reactions.

*Tetrahydro*epi*berberine* (IX).—Synthetical oxy*epi*berberine (1 g.) was dissolved in a mixture of ethyl alcohol (60 c.c.) and concentrated sulphuric acid (30 c.c.) and reduced in an electrolytic cell with a current of 6 amp. for 24 hours, the temperature throughout being below 30°. The colourless solution was diluted with water, filtered, the filtrate made alkaline with ammonia, the solid collected, and a further small crop obtained by extracting the filtrate with chloroform, drying the extract with sodium sulphate and removing the solvent. The crude product so obtained was crystallised first from alcohol and then from acetone, colourless prisms, m. p. 169—170° (Found: C, 70·7; H, 6·3. Calc.: C, 70·8; H, 6·2%) being obtained. No alteration in m. p. was observed on heating a mixture with a speci-

men of tetrahydro*epi*berberine prepared from *iso*dihydrocryptopine chloride. The synthetical base yields a *hydrochloride* which is sparingly soluble in dilute hydrochloric acid, from which it separates in small needles identical in appearance with the hydrochloride of tetrahydro*epi*berberine. Further, the solution of the base in glacial acetic acid gives a colourless solution on the addition of concentrated sulphuric acid which gradually turns blue and later becomes deep violet, whilst tetrahydro*epi*berberine shows the same reaction.

iso*Oxy*epi*berberine* (X).—As mentioned in the introduction (p. 1772, footnote), this substance was obtained during an electrolytic reduction carried out exactly as described above with the exception that the temperature was maintained at 45° for 6 hours; a brown solid had then separated from the colourless solution. This was collected, boiled with glacial acetic acid, in which it was sparingly soluble, and crystallised from pyridine, separating in pale yellow needles which darken at 300° and melt with decomp. at about 370° (Found: C, 68·3; H, 5·0; O·CH_3, 17·0. Calc.: C, 68·3; H, 4·8; O·CH_3, 17·6%). This substance exhibits all the reactions described for *iso*oxy*epi*berberine (Perkin, *loc. cit.*).

iso*Dihydrocryptopine Chloride.*—(*a*) *iso*Dihydrocryptopine chloride was best prepared from *iso*cryptopine chloride as follows: *iso*-Cryptopine chloride (10 g.) dissolved in hot dilute 5% sulphuric acid (250 c.c.) was reduced at 90—95° during 3 hours with a current of 5 amp. The sulphuric acid was removed by the addition of barium chloride, and the hot solution filtered. On cooling, *iso*dihydrocryptopine β-chloride (6 g.) separated, and the addition of mercuric chloride to the mother-liquor produced a copious precipitate of a double salt which after decomposition with hydrogen sulphide yielded *iso*dihydrocryptopine α-chloride (1·5 g.).

(*b*) Synthetical tetrahydro*epi*berberine (0·7 g.) was heated in a sealed tube at 100° with an excess of methyl iodide for 1 hour. The product was suspended in water (200 c.c.), digested with silver chloride for 3 hours, filtered off, and the filtrate concentrated; long, slender needles (0·5 g.) then separated, identical with *iso*dihydrocryptopine β-chloride obtained either by method (*a*) or by the action of sodium amalgam on *iso*cryptopine chloride. When the mother-liquor was treated with mercuric chloride as described in method (*a*), a small quantity of a salt (0·1 g.), identical with *iso*dihydrocryptopine α-chloride, was obtained.

Anhydrodihydrocryptopine A (XII) and *anhydrodihydrocryptopine* B (XIII) were obtained by decomposing an aqueous solution of *iso*dihydrocryptopine α- or β-chloride, obtained by either method (*a*) or (*b*), with silver hydroxide and evaporating the filtered solution in a good vacuum as described by Pyman (*loc. cit.*). The residue

was extracted with hot acetone and the bases A (m. p. 173—175°) and B (m. p. 125°) were separated as described by Perkin (J., 1916, **109**, 937).

Anhydrodihydrocryptopine Oxide.—A solution of anhydrodihydrocryptopine A (3 g.) in cold chloroform (15 c.c.) was slowly added to an ice-cold solution of perbenzoic acid (2·5 g.) in ether (140 c.c.). After 12 hours, the ether–chloroform was decanted from the mass of prisms which had separated, the latter suspended in hot water, made faintly alkaline with potassium hydroxide, and filtered from a trace of impurity. The *amine oxide* (2·2 g.) separated from the filtrate on cooling and a further small crop was obtained by concentrating the ether–chloroform mixture in a vacuum and extracting the residual oil with hot dilute potassium hydroxide. The oxide crystallises from hot water in slender, colourless needles, m. p. 135° (decomp.). After drying over phosphorus pentoxide in an evacuated desiccator or after being heated at 110°, the crystals still retained one molecule of water of crystallisation (Found in material dried at 110°: C, 65·2; H, 6·4. Found in material dried over phosphorus pentoxide: C, 65·3; H, 6·4. $C_{21}H_{23}O_5N,H_2O$ requires C, 65·1; H, 6·4%). The *hydrochloride* crystallises from hot water in small, rectangular prisms, m. p. 215° (decomp.) (Found: C, 62·1; H, 6·2. $C_{21}H_{24}O_5NCl$ requires C, 62·1; H, 5·9%).

Cryptopine (I).—The amine oxide (1 g.), glacial acetic acid (10 c.c.), and concentrated hydrochloric acid (8 c.c.) were heated on a water-bath for 1 hour. The solution was diluted with water, made alkaline with potassium hydroxide, and the brown base was collected and washed with methyl alcohol, which removed the coloured impurity. The almost colourless base was dissolved in boiling pyridine, the solution diluted with double the volume of boiling alcohol and allowed to cool; cryptopine then separated in almost colourless prisms, m. p. 220—221° (corr.), which showed no depression in m. p. when mixed with a specimen of naturally occurring cryptopine. The synthetical base yielded an oxalate with the characteristic properties (compare Perkin, J., 1916, **109**, 879). When the base was dissolved in glacial acetic acid and treated with concentrated sulphuric acid, a pink solution was obtained which rapidly became bluish-violet, the colours being indistinguishable from those observed with naturally occurring cryptopine under the same conditions.

N-β-*Piperonylethyl*-3 : 4-*methylenedioxyhomophthalimide* (as V).—3 : 4-Methylenedioxyhomophthalic acid (4 g.) and β-piperonylethylamine (3·6 g.) were heated at 180° for 3 hours, the solid product triturated with alcohol, collected, and crystallised from glacial acetic acid, separating in slender prisms, m. p. 214—215° (Found: C, 64·3; H, 4·3. $C_{19}H_{15}O_6N$ requires C, 64·6; H, 4·2%). This

imide is sparingly soluble in organic solvents, but dissolves in dilute aqueous sodium hydroxide to a yellow solution with a green fluorescence which disappears when the solution is boiled for a few minutes.

N-β-*Piperonylethyl*-3 : 4-*methylenedioxyhomophthalamic Acid* (as VI).—(*a*) *N*-β-Piperonylethyl-3 : 4-methylenedioxyhomophthalimide (1·4 g.) was heated on the water-bath with *N*-sodium hydroxide (10 c.c.) for 12 hours, the colourless solution cooled, saturated with carbon dioxide, filtered, and the filtrate acidified with dilute hydrochloric acid, and the grey solid collected.

(*b*) 3 : 4-Methylenedioxyhomophthalic anhydride (2 g.) and β-piperonylethylamine (2 g.) were heated in benzene (30 c.c.) for 2 hours; a semi-solid separated, which dissolved on shaking with a solution of sodium hydroxide. The benzene layer was removed, the alkaline solution acidified with dilute hydrochloric acid, and the solid collected. N-β-*Piperonylethyl*-3 : 4-*methylenedioxyhomophthalamic acid* (as VI) prepared by either method dissolves readily in boiling glacial acetic acid and, after the addition of an equal bulk of boiling water, separates in glistening plates, m. p. 194—195° (Found : C, 61·3; H, 4·8. $C_{19}H_{17}O_7N$ requires C, 61·4; H, 4·6%). The *methyl* ester, prepared from the silver salt as described on page 1776, separates from dry methyl alcohol in colourless nodules, m. p. 170—171° (Found : C, 62·1; H, 5·0. $C_{20}H_{19}O_7N$ requires C, 62·3; H, 4·9%).

2 : 3 : 9 : 10-*Bismethylenedioxyoxyprotoberberine* (XIV).—The methyl ester (1·3 g.) was boiled with phosphorus oxychloride (3 c.c.) for 5 minutes, the phosphorus oxychloride removed in a vacuum, the residue dissolved in water, the red solution made alkaline with sodium hydroxide, the grey solid collected, washed successively with water and methyl alcohol, and recrystallised from boiling glacial acetic acid containing a little water, separating in almost colourless, slender prisms (0·8 g.), m. p. 292° (Found : C, 68·1; H, 4·1. $C_{19}H_{13}O_5N$ requires C, 68·0; H, 3·9%). This oxyberberine-type derivative is sparingly soluble in organic solvents with the exception of boiling glacial acetic acid, and its colourless benzene solution exhibits a beautiful violet fluorescence. Its solution in glacial acetic acid becomes orange on the addition of concentrated sulphuric acid and then becomes red on the addition of a drop of dilute nitric acid. It dissolves fairly readily in hot glacial acetic acid and, on cooling, the *acetate* separates in bright yellow needles, which are readily decomposed by heat or moisture to the oxyberberine-type derivative (XIV).

2 : 3 : 9 : 10-*Bismethylenedioxytetrahydroprotoberberine* (XV).—The oxyberberine-type derivative (XIV) (0·5 g.) was dissolved in alcohol

(60 c.c.) and concentrated sulphuric acid (30 c.c.), and the orange-coloured solution reduced electrolytically with a current of 6 amp. for 36 hours at 25—30°. The colourless solution was diluted with water, filtered, the filtrate made alkaline with ammonia, and the solid crystalline base collected, washed with water, dried, and crystallised from benzene, separating in colourless, slender prisms, m. p. 219° (Found: C, 70·7; H, 5·3. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3%). This base (XV) is sparingly soluble in ether and alcohol, moderately soluble in acetone, and readily soluble in chloroform and hot benzene. A solution of the base in glacial acetic acid slowly turns green on the addition of concentrated sulphuric acid, whilst the further addition of a drop of dilute nitric acid produces a red coloration. The *hydrochloride* is very sparingly soluble in dilute hydrochloric acid and crystallises from much boiling water in clusters of small needles, m. p. 275—278° (decomp.).

iso*Dihydroprotopine Chloride* (as IV).—(*a*) When *iso*protopine chloride is reduced electrolytically as described in the case of *iso*-cryptopine chloride (page 1778), a large amount of unchanged *iso*protopine chloride is obtained and increasing the amperage and time of reduction made no appreciable difference in the yield of reduction product. The mixture of *iso*protopine and *iso*dihydroprotopine chloride (10 g.) was recovered from the attempted electrolytic reduction, dissolved in boiling water (200 c.c.), and heated on the water-bath with 4% sodium amalgam (250 g.) for 1 hour. A large quantity of a viscid base * separated and the filtrate after acidification and cooling deposited *iso*dihydroprotopine β-chloride (2·8 g.). The mother-liquor was treated with mercuric chloride, the double compound suspended in boiling water, decomposed with hydrogen sulphide, and the filtrate concentrated to a small bulk; *iso*dihydroprotopine α-chloride (1·2 g.) was thus obtained.

(*b*) 2 : 3 : 9 : 10-Bismethylenedioxytetrahydroprotoberberine (0·7 g). was heated in a sealed tube with methyl iodide for 1 hour at 100°. The sparingly soluble methiodide so obtained was suspended in boiling water (250 c.c.) and digested with a large excess of silver chloride for 4 hours, the solution was filtered and concentrated until *iso*dihydroprotopine β-chloride separated; *iso*dihydroprotopine α-chloride was isolated by the mercuric chloride treatment described above.

iso*Dihydroprotopine β-chloride*, prepared by method (*a*) or (*b*), crystallises from hot water in beautiful, colourless plates which decompose to a red froth at about 270° (Found: C, 63·9; H, 5·5.

* This viscid base, which has not been obtained in the crystalline state, no doubt contains tetrahydroanhydro*iso*protopine (compare Perkin, J., 1919, **115**, 748).

$C_{20}H_{20}O_4NCl$ requires C, 64·2; H, 5·3%). iso*Dihydroprotopine α-chloride*, obtained by either method (*a*) or (*b*), is much more soluble in water than the β-chloride, and crystallises from concentrated solution in small, stout prisms, m. p. about 90°. These crystals contain water of crystallisation which is lost at 100°, the crystals becoming a sandy powder which softens at 155° and melts to a red froth at 175° (Found : C, 64·1; H, 5·4. $C_{20}H_{20}O_4NCl$ requires C, 64·2; H, 5·3%).

Anhydrodihydroprotopine A (as XII).—(*a*) *iso*Dihydroprotopine β-chloride (prepared by either method *a* or *b*) (2 g.) was dissolved in hot water, digested with silver hydroxide, the filtrate evaporated to dryness in a good vacuum, and the residue extracted with hot dry acetone. A large amount of acetone-insoluble material remained which dissolved in hot water, and the solution deposited crystals of *iso*dihydroprotopine β-chloride, after acidification and cooling. The acetone extract was concentrated; anhydroprotopine A then gradually separated.

(*b*) *iso*Dihydroprotopine α-chloride (prepared by either method *a* or *b*) (1 g.) was decomposed by silver hydroxide as described above. In this case very little acetone-insoluble product was obtained and anhydrodihydroprotopine A (0·4 g.) was isolated by concentrating the acetone extract.

Anhydrodihydroprotopine A separates from acetone in colourless needles, m. p. 118—120°. It is readily soluble in hot benzene, hot alcohol and chloroform, rather sparingly soluble in ether, and almost insoluble in petroleum (Found : C, 71·1; H, 5·8. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6%). The base dissolves easily in cold dilute hydrochloric acid and continued evaporation on the water-bath with dilute hydrochloric acid gradually converts it into the characteristic plates of *iso*dihydroprotopine β-chloride, m. p. 270° (decomp.).

Anhydrodihydroprotopine Oxide.—Anhydrodihydroprotopine A (0·4 g.) was oxidised with perbenzoic acid as described in the case of anhydrodihydrocryptopine, and the *amine oxide* (0·3 g.) isolated in a similar manner. The oxide crystallises from much hot water in colourless needles, m. p. 140° (decomp.) (Found : C, 67·8; H, 5·5. $C_{20}H_{19}O_5N$ requires C, 68·0; H, 5·4%). The *hydrochloride* is sparingly soluble in water and separates from much hot water in colourless nodules, m. p. 221° (decomp.).

Protopine (II).—The oxide (0·2 g.), glacial acetic acid (3 c.c.), and concentrated hydrochloric acid (2 c.c.) were heated on the water-bath for 1 hour. The solution was diluted with water, made alkaline with potassium hydroxide, and the base extracted with chloroform. After removing the chloroform, the residual brown base was twice

crystallised from methyl alcohol and was thus obtained in pale brown prisms, m. p. 207 °(corr.). A specimen in the form of colourless prisms, m. p. 207° (corr.), was obtained by dissolving the substance in chloroform, adding ethyl alcohol, and allowing the base to separate slowly during 2 days. No depression in m. p. was observed in a mixture with a specimen of naturally occurring protopine. A trace of the synthetical base, dissolved in glacial acetic acid, gave a deep bluish-violet coloration on the addition of concentrated sulphuric acid, and naturally occurring protopine gave the same reaction under similar conditions.

2 : 3 : 9 : 10-*Bismethylenedioxydihydroprotoberberine* (XVI).—Pure dry *iso*protopine chloride (1 g.) was placed in a small distillation flask, which was exhausted to 1·5 mm. The flask was then gradually warmed with a free flame, when methyl chloride was evolved and the pressure rose to about 10 mm. for about 20 seconds. After being carefully heated for 3 minutes, the flask was allowed to cool, the brown residue powdered, extracted with dilute acetic acid, the solution filtered, the filtrate made alkaline with ammonia, the brown base collected, washed successively with water and methyl alcohol, and crystallised from acetone, separating in large, yellow prisms, m. p. 194—196° (decomp. with previous darkening) (Found : C, 71·0; H, 4·8. $C_{19}H_{15}O_4N$ requires C, 71·0; H, 4·7%). This base is sparingly soluble in hot ether, methyl or ethyl alcohol, and readily soluble in hot acetone or chloroform to a yellow solution with a green fluorescence. It dissolves in dilute mineral acids, and the *hydrochloride* separates from dilute hydrochloric acid in small, bright yellow needles.

When the base was dissolved in dilute sulphuric acid and reduced on the water-bath with a large excess of zinc dust, the solution became colourless after about 3 hours. It was then filtered, the filtrate made alkaline with ammonia, the grey base collected, washed with alcohol, dried, and crystallised from benzene, separating in slender needles, m. p. 218°. This reduced base is identical with 2 : 3 : 9 : 10-bismethylenedioxytetrahydroprotoberberine (XV) obtained by the electrolytic reduction described on page 1780, and no alteration in m. p. was observed on heating a mixture of the two. The hydrochlorides of the bases obtained by the two methods are identical and the colour reactions are indistinguishable.

2 : 3 : 9 : 10-*Bismethylenedioxyprotoberberinium Chloride* (XVII).—2 : 3 : 9 : 10-Bismethylenedioxydihydroprotoberberine (XVI) (3 g.) was dissolved in 20% acetic acid (30 c.c.) and heated on the water-bath for 1 hour with a solution of mercuric acetate (prepared by dissolving 4 g. of mercuric oxide in hot glacial acetic acid). The solution rapidly became bright red, and mercurous acetate was

precipitated. After cooling, the latter was collected, washed well with water, the filtrate and washings were saturated with hydrogen sulphide and filtered, the filtrate was concentrated to about 50 c.c. and treated with concentrated hydrochloric acid. On cooling, the chloride (XVII) separated; it crystallised from much hot water, containing a little hydrochloric acid, in orange, slender prisms which darkened at 280°, but did not melt at 300°. The air-dried salt contains 1 mol. of water which is not removed at 120° (Found: C, 60·9; H, 4·4. $C_{19}H_{14}O_4NCl,H_2O$ requires C, 61·0; H, 4·3%). When the chloride is dissolved in warm aqueous acetone and treated with sodium hydroxide, 2 : 3 : 9 : 10-*bismethylenedioxyanhydroprotoberberine-acetone* separates in pale yellow, hexagonal plates which, after crystallisation from acetone, melt at 195° (decomp.).

Action of Alkalis on the Chloride (XVII).—Although an aqueous solution of the protoberberinium chloride (XVII) is not decomposed by warming with ammonia, decomposition readily occurs with sodium hydroxide. The chloride (XVII) (1 g.) was heated with 20% sodium hydroxide (50 c.c.) for 1 hour in the water-bath, when the orange colour of the solution rapidly vanished and a green solid was precipitated. After dilution with water, the solid was collected, washed with hot water, and then thoroughly extracted with hot dilute hydrochloric acid. The pale yellow, insoluble residue, after being washed with methyl alcohol, crystallised from glacial acetic acid containing a little water in pale yellow prisms, m. p. 292°, which, although more highly coloured, were identical with those of 2 : 3 : 9 : 10-bismethylenedioxyoxyprotoberberine (XIV) described on page 1780. No depression in m. p. was shown by a mixture of the two, and the properties of the acetates and the colour reactions were identical.

The yellow hydrochloric acid extract was rendered alkaline with ammonia, the base collected, washed with methyl alcohol, and crystallised from acetone, separating in large, yellow prisms, m. p. 194—196° (decomp.), which were identical with the dihydroprotoberberine (XVI) obtained by the action of heat on *iso*protopine chloride (page 1783).

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