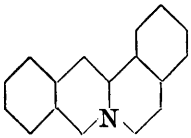
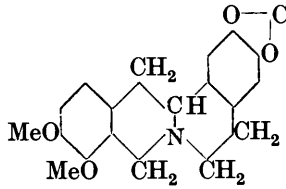
CCCIII.—*Synthetical Experiments in the* iso*Quinoline Group. Part VII. A Synthesis of* 3 : 11-*Dimethoxyprotoberberinium Salts.*

By SATYENDRA NATH CHAKRAVARTI, ROBERT DOWNS HAWORTH, and WILLIAM HENRY PERKIN, jun.

A COMPARISON of the constitutional formulæ of groups of alkaloids brings to light many curious generalities. It is difficult to understand why so many of these substances are built up on a common skeleton and why certain groups, and more particularly methoxy- and methylenedioxy-groups, should play so prominent a part in their structure. Attention has already been directed to the fact (J., 1926, 33) that the alkaloids palmatine, berberine, corydaline, and many others are all derived from the same angular structure (I),

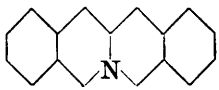
a point clearly illustrated by the formula of tetrahydroberberine (II). It was also pointed out that β-homochelidonine, cryptopine,

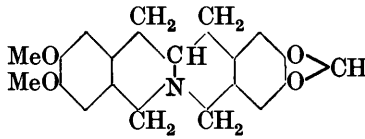
(I.) 



(II.)

and protopine, although not actually derivatives of (I), readily yield quaternary salts which are built up on this skeleton. In order to obtain some light on the reason why the skeleton (I) is so commonly selected by nature, the alkaloid 2 : 3-methylenedioxy-11 : 12-dimethoxy-6 : 15 : 16 : 17-tetrahydroparaberine (IV),* isomeric with tetrahydroberberine, but differing from it in containing the linear structure (III), was synthesised (*loc. cit.*, p. 42).

(III.) 



(IV.)

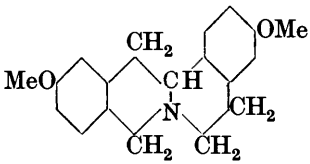
During the course of those experiments, it soon became evident that the various stages in the synthesis did not proceed so smoothly as in the case of the corresponding stages in the synthesis of tetrahydro-ψ-berberine, and furthermore, the properties of the substance (IV) were not nearly so definite and characteristic as those of tetrahydroberberine. In particular, the property of yielding highly coloured quaternary salts on treatment with iodine or other oxidising agents, so strikingly shown by tetrahydroberberine, fails entirely in the case of the paraberine analogue (*loc. cit.*, p. 37). These observations led to the suggestion that the greater ease of formation and more characteristic properties of alkaloids built up on the angular type may have some bearing on the occurrence and preferential selection of this type in nature.

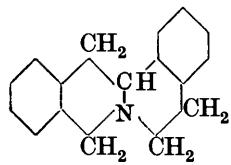
Another remarkable feature, not only of the alkaloids of the berberine group, but also of many others of widely different origin, *e.g.*, narcotine, cryptopine, corycavidine, and glaucine, is the occurrence in the molecule of two catechol nuclei, usually modified by methoxy- or methylenedioxy-groups, although in some cases, *e.g.*, corydine and corytuberine, a hydroxy-group remains free. There can be no doubt that the presence of these methoxy- and methylenedioxy-groups has a profound bearing on the ease of synthesis and

* This alkaloid is actually more directly related to tetrahydro-ψ-*epi*berberine (J., 1924, **125**, 1677).

characteristic properties of these alkaloids, and there are also indications, to which reference has been made (this vol., p. 2262), that these groups also greatly influence the possibility of converting the alkaloids into derivatives of the ten-membered ring type (compare J., 1926, 446), and consequently into alkaloids of the β-homochelidonine group. In view of these considerations it seemed to be of interest to attempt to prepare alkaloids which, although built up on the angular skeleton (I), do not contain a catechol nucleus, and to compare the ease of synthesis and characteristic properties of such substances with these features in the case of the alkaloids of the palmatine–berberine type.

The present communication deals with the synthesis of 3 : 11-*dimethoxytetrahydroprotoberberine* (V) * containing two methoxy-groups, and in the succeeding investigation we describe the synthesis of tetrahydroprotoberberine itself (VI), which contains no methoxy-groups and to which special interest attaches because it is the parent of the whole palmatine–berberine group of alkaloids.

(V.) 

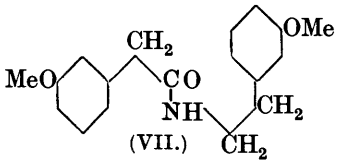
 (VI.)

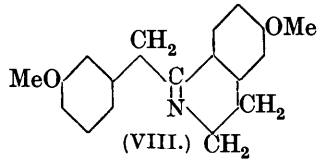
The synthesis of 3 : 11-dimethoxyprotoberberine and its derivatives was conducted in the following manner. β-*m*-Methoxyphenylethylamine, prepared by a slight modification of the method of Helfer (*Helv. Chim. Acta*, 1924, **7**, 945), was condensed with *m*-methoxyphenylacetic acid, prepared by a method similar to that employed by Pschorr (*Annalen*, 1912, **391**, 41), and the m-*methoxyphenylaceto*-β-m-*methoxyphenylethylamide* (VII) so obtained was converted, in a yield of 80%, into a syrupy base of which the *picrate* is crystalline. This base, which is probably 6-*methoxy*-1-(3′-*methoxybenzyl*)-3 : 4-*dihydro*isoquinoline (VIII), oxidises rapidly on exposure to air and is readily reduced by zinc and sulphuric acid to 6-*methoxy*-1-(3′-*methoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (IX), an oily base yielding a crystalline *sulphate* and *picrate*. Ring-closure of the *formyl* derivative was effected in the usual manner with phosphorus oxychloride, giving a 66% yield of a yellow crystalline base, m. p. 130°, which is doubtless 3 : 11-*dimethoxydihydroprotoberberine* (X).

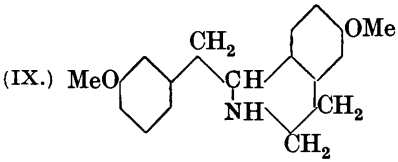
Although we have no direct evidence that the two ring-closures, *i.e.*, the conversion of (VII) into (VIII) and (IX) into (X), have taken place in the para-positions to the methoxy-groups, there can be little doubt that this is the case, since, judging from analogy,

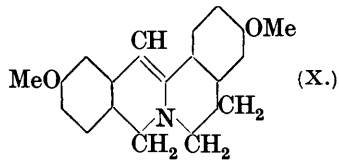
* The nomenclature is discussed in J., 1925, **127**, 1462.

ring-closure in the ortho-positions is most unlikely. Synthetical experiments which are in progress will, we hope, decide this point.

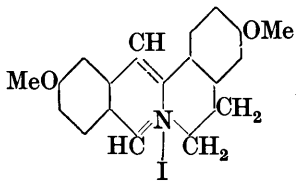




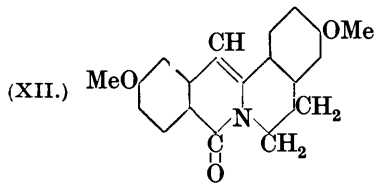


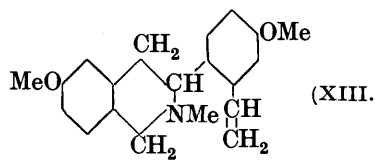


Dimethoxydihydroprotoberberine (X) gives well-characterised, pale yellow salts of which the *hydrochloride*, the *hydriodide*, and the *picrate* are described. It is reduced by zinc dust and sulphuric acid to 3 : 11-dimethoxytetrahydroprotoberberine (V), a colourless crystalline base, m. p. 111°, which may also be obtained, although in smaller yield, from (IX) by condensation with formaldehyde. Of the colourless crystalline salts, the *hydrochloride*, *hydriodide*, and *picrate* are described.



When 3 : 11-dimethoxytetrahydroprotoberberine (V) is oxidised with iodine in alcoholic solution, it yields 3 : 11-*dimethoxyprotoberberinium iodide* (XI), a yellow quaternary salt from which the corresponding yellow *chloride* was prepared. The iodide (XI) is decomposed in the usual manner by potassium hydroxide giving 3 : 11-*dimethoxyoxyprotoberberine* (XII) and dimethoxydihydroprotoberberine (X), which are readily separated, in that the former is insoluble and the latter soluble in dilute mineral acids.





3 : 11-*Dimethoxytetrahydroprotoberberine methiodide*, obtained by heating the base (V) with methyl iodide, was readily separated into

α- and β-forms by crystallisation from water (compare Pyman, J., 1913, **103**, 825; Haworth and Perkin, J., 1926, 1772), and these were converted into the corresponding *methochlorides*, of which the β-form is crystalline, whereas the α-modification is a syrup. The methiodide was next converted into *anhydromethyl*-3 : 11-*dimethoxytetrahydroprotoberberine B* (XIII) by the action of alcoholic potassium hydroxide, and the interesting observation was made that this is the only base which is obtained when the methiodide is converted by silver hydroxide into the corresponding methohydroxide and the aqueous solution is evaporated in a good vacuum. The structure assigned to this base is confirmed by its stability towards aqueous methyl alcohol and chloroform, and by its yielding a stable and sparingly soluble *hydrochloride*. It is clear from these experiments that the presence of two methoxy-groups attached to the annular skeleton of tetrahydroberberine as in (V) does not allow the formation of the ten-membered ring, at all events under the usual conditions.

The other points of general interest which emerge from this investigation are (i) that the synthetical experiments described proceed almost as readily, if perhaps not quite so smoothly, when only two methoxy-groups are present as they do in the case of the corresponding syntheses in the berberine series, and (ii) that the deep yellow colour of the salts of berberine and allied alkaloids becomes much less intense when only two methoxy-groups are present in the molecule.

EXPERIMENTAL.

m-Methoxybenzaldehyde is obtained in a yield of 80% by the following method : *m*-Hydroxybenzaldehyde (250 g.), methyl alcohol (750 c.c.), and sodium hydroxide (85 g.), dissolved in the minimum of water, are heated on the steam-bath, and freshly distilled methyl sulphate (290 g.) is added sufficiently rapidly to maintain brisk ebullition; a further quantity of methyl sulphate (200 g.) is then added, the mixture being kept alkaline by the addition of 50% sodium hydroxide. The product is kept for ½ hour, the methyl alcohol removed by distillation, and the residue diluted with water and extracted with ether. The extract is dried with sodium sulphate, the ether removed, and the *m*-methoxybenzaldehyde distilled under reduced pressure. *m*-Methoxycinnamic acid was prepared by heating *m*-methoxybenzaldehyde (100 g.), malonic acid (160 g.), and piperidine (5 c.c.) in pyridine (250 c.c.) solution for 1½ hours on the steam-bath, and then boiling for 15 minutes on the sand-bath. The product, on being poured into excess of dilute hydrochloric acid, gave an almost quantitative yield of *m*-methoxycinnamic acid, m. p. 117°. This acid was reduced with sodium amalgam to β-*m*-methoxyphenylpropionic acid in the manner described by Helfer (*loc. cit.*).

m-Methoxyphenylacetic acid was prepared by the method of Pschorr (*loc. cit.*), but a different procedure was adopted in the separation of the products of the hydrolysis of the az-lactone. After hydrolysing the latter with sodium hydroxide, the solution was saturated with sulphur dioxide, the benzoic acid collected, the filtrate acidified and boiled, and the m-*methoxyphenylpyruvic acid* collected and recrystallised from glacial acetic acid, separating in small crystals, m. p. 150° (Found : C, 61·6; H, 5·1. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·1%). This acid is readily soluble in hot alcohol but rather sparingly soluble in cold acetic acid or toluene. It was oxidised in cold alkaline solution with hydrogen peroxide, and *m*-methoxyphenylacetic acid, m. p. 68°, was obtained in good yield on acidifying the alkaline solution.

m-*Methoxyphenylacet*-β-m-*methoxyphenylethylamide* (VII).—(i) Equivalent quantities of β-*m*-methoxyphenylethylamine (Helfer, *loc. cit.*) and *m*-methoxyphenylacetic acid were heated at 180° for 3 hours. Alternatively, (ii) *m*-methoxyphenylacetic acid (6 g.), dissolved in a little chloroform, was gently boiled for ½ hour with thionyl chloride (3·5 g.); the chloroform was removed and the residual yellow oil added to an emulsion of β-*m*-methoxyphenylethylamine (5 g.) in potassium hydroxide (40 c.c. of 10%), the mixture being well shaken during the addition. By either method, the *amide* was obtained as an oil which did not crystallise in contact with the usual solvents.

6-*Methoxy*-1-(3′-*methoxybenzyl*)-3 : 4-*dihydro*isoquinoline (VIII). —The amide just described (20 g.) was heated with phosphorus oxychloride (50 c.c.) for 2 hours on the steam-bath and then kept over-night. The mixture was decomposed and extracted with hot water (charcoal), filtered from tar, the filtrate made alkaline with sodium hydroxide, and extracted several times with benzene (A). Some of the benzene extract was dried over potassium carbonate, the solvent removed, and the oily base dissolved in alcohol and mixed with an alcoholic solution of picric acid. The yellow *picrate* of (VIII) which separated is sparingly soluble in alcohol and readily soluble in hot glacial acetic acid, from which it separates in small needles, m. p. 155° (Found : C, 56·3; H, 4·6. $C_{24}H_{22}O_9N_4$ requires C, 56·5; H, 4·3%).

6-*Methoxy*-1-(3′-*methoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (IX).—This was obtained by extracting the benzene extract (A) with dilute sulphuric acid, and reducing the acid solution with zinc dust. The solution was made alkaline with ammonia, the tetrahydro-base extracted with chloroform, dried over potassium carbonate, and the solvent removed, leaving the base as an oil. The *hydrochloride*, obtained by dissolving the oil in hot dilute hydro-

chloric acid, and cooling, separated in needles, m. p. 192° (decomp.) (Found : C, 67·9; H, 6·9. $C_{18}H_{22}O_2NCl$ requires C, 67·6; H, 6·9%). The *sulphate* is readily soluble in hot water and crystallises in rhombs. The *picrate*, prepared in alcoholic solution, is sparingly soluble in hot alcohol, and separates from glacial acetic acid as a crystalline powder, m. p. 148° (Found : C, 56·6; H, 4·6. $C_{24}H_{24}O_9N_4$ requires C, 56·3; H, 4·8%).

3 : 11-*Dimethoxydihydroprotoberberine* (X).—The N-*formyl* derivative of (IX) was prepared by adding a slight excess of formic acid to a dry benzene solution of the base; the benzene was removed, and the residue heated in an oil-bath at 200° for 2 hours. The whole (13 g.) was dissolved in dry toluene (50 c.c.), phosphorus oxychloride (30 c.c.) added, and the mixture boiled for 1½ hours. The product was diluted with petroleum ether, the dark brown oil which separated was dissolved in alcohol, made alkaline with sodium hydroxide, and diluted with water; when the sides of the vessel were scratched vigorously, the *base* (X) separated as a yellow powder (8 g.), which crystallised from alcohol or benzene in shining, yellow, rhombic prisms, m. p. 130° (Found : C, 78·0; H, 6·6. $C_{19}H_{19}O_2N$ requires C, 77·8; H, 6·5%). This base is sparingly soluble in alcohol, more soluble in benzene, and readily soluble in chloroform. It is a strong base yielding pale yellow, crystalline salts with mineral acids. The solution in concentrated sulphuric acid is yellowish-brown and becomes deep red on the addition of a crystal of potassium nitrate. The *hydrochloride* is rather sparingly soluble in water or dilute hydrochloric acid, and crystallises from the former in silky needles containing $4H_2O$ which is lost at 105° (Found : loss at 105°, 17·0. Calc. for $4H_2O$: 17·9. Found in material dried at 105° : C, 68·7; H, 6·1. $C_{19}H_{20}O_2NCl$ requires C, 69·2; H, 6·1%). The *hydriodide*, obtained by adding sodium iodide to the aqueous solution of the hydrochloride, is a yellow, crystalline powder, very sparingly soluble in boiling water (Found : C, 54·6; H, 4·8. $C_{19}H_{20}O_2NI$ requires C, 54·2; H, 4·8%). The *picrate*, prepared in alcoholic solution, is very sparingly soluble in alcohol, and separates from glacial acetic acid as a bright yellow, crystalline powder, m. p. 232° (Found : C, 57·4; H, 4·1. $C_{25}H_{22}O_9N_4$ requires C, 57·5; H, 4·2%).

3 : 11-*Dimethoxytetrahydroprotoberberine* (V).—This substance was obtained in two ways. (i) Dimethoxydihydroprotoberberine (X) was reduced by zinc dust and dilute sulphuric acid until the solution became colourless; the product was filtered, the filtrate made alkaline with ammonia, the base extracted with chloroform, dried over potassium carbonate, the solvent removed, and the residue dissolved in dilute hydrochloric acid, from which the *hydrochloride* of the base separated on cooling. This was collected, dissolved in

water, decomposed with concentrated ammonia, and the almost colourless 3 : 11-*dimethoxytetrahydroprotoberberine* crystallised from alcohol or dry benzene. (ii) The tetrahydro-base (IX; p. 2270) was dissolved in methyl alcohol, mixed with sodium bicarbonate and a slight excess of 40% formaldehyde, and the mixture warmed for a few minutes on the steam-bath; on the addition of water and some salt, a gum separated, which was thoroughly washed with cold water and heated with concentrated hydrochloric acid on the steam-bath for a few minutes; the gummy hydrochloride was redissolved in water, decomposed with ammonia, the base extracted with chloroform, and the solvent removed. The residual syrup was rubbed with ether, which removed unchanged tetrahydro-base, and the sparingly soluble residue of dimethoxytetrahydroprotoberberine was crystallised from alcohol or benzene. The yield was small, however, and various modifications of this method failed to effect much improvement.

3 : 11-Dimethoxytetrahydroprotoberberine separates from alcohol or dry benzene in jagged prisms, m. p. 111° (Found: C, 77·6; H, 7·1. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·1%), readily soluble in chloroform, or in methyl or ethyl alcohol; the base and its salts are rather more soluble than dimethoxydihydroprotoberberine and its salts. The hydrochloride is readily soluble in hot water, from which it separates in characteristic, colourless rosettes, m. p. 199° (Found: C, 68·8; H, 6·7. $C_{19}H_{22}O_2NCl$ requires C, 68·8; H, 6·6%). The *hydriodide*, obtained by adding sodium iodide to the aqueous solution of the hydrochloride, is moderately soluble in boiling water and separates as a crystalline powder with a very slight yellow tinge, m. p. 205° (Found: C, 54·4; H, 5·2. $C_{19}H_{22}O_2NI$ requires C, 53·9; H, 5·2%). The *picrate*, prepared in alcoholic solution, separates from glacial acetic acid or alcohol in bright yellow needles, m. p. 139—140° (decomp.) (Found: C, 57·5; H, 4·9. $C_{25}H_{24}O_9N_4$ requires C, 57·3; H, 4·6%).

The 3 : 11-*Dimethoxyprotoberberinium Salts*.—Dimethoxytetrahydroprotoberberine (V), dissolved in the minimum of boiling alcohol, was mixed with anhydrous sodium acetate, and an alcoholic solution of iodine slowly added until a permanent coloration remained. The dark brown granular *periodide* was collected, washed with water, suspended in hot water, and decomposed by adding aqueous sulphurous acid. The pale yellow *iodide* (XI) separated from water, in which it is very sparingly soluble, in pale yellow needles, m. p. 242° (Found: C, 54·2; H, 4·4. $C_{19}H_{18}O_2NI$ requires C, 54·4; H, 4·3%). The *chloride* is readily obtained by digesting an aqueous suspension of the iodide with excess of silver chloride for 2 hours on the steam-bath; after filtering, concentrating, and adding hydrochloric acid,

the mass of pale yellow needles of the chloride is recrystallised from dilute hydrochloric acid and left on porous porcelain exposed to air for 2 days, m. p. 200° (decomp.). The salt contains $3H_2O$ which is lost at 105° (Found: loss at 105°, 13·5. Calc. for $3H_2O$: 14·1. Found in material dried at 105°: C, 69·3; H, 5·8. $C_{19}H_{18}O_2NCl$ requires C, 69·6; H, 5·5%). The *picrate* was obtained, by adding aqueous picric acid to the hot aqueous solution of the chloride, as yellow flocks almost insoluble in alcohol and sparingly soluble in glacial acetic acid, from which it separates as a feathery mass of long, yellow needles, m. p. 238° (Found: C, 55·5; H, 3·9. $C_{25}H_{22}O_{10}N_4$ requires C, 55·8; H, 4·1%).

3 : 11-*Dimethoxyoxyprotoberberine* (XII).—A boiling aqueous solution of 3 : 11-dimethoxyprotoberberinium chloride (2 g.) was added to a hot solution of potassium hydroxide (8 g.) in water (32 c.c.), and the whole heated on the steam-bath for 2 hours. The yellow mass which separated was collected and thoroughly extracted with dilute hydrochloric acid (A); the residue was dissolved in hot glacial acetic acid, mixed with an equal volume of boiling water, and allowed to stand, the oxy-derivative (XII) then separating as a mass of colourless needles, m. p. 143° (Found: C, 74·1; H, 5·7. $C_{19}H_{17}O_3N$ requires C, 74·3; H, 5·5%). 3 : 11-*Dimethoxyoxyprotoberberine* is sparingly soluble in the usual solvents, except glacial acetic acid, and insoluble in dilute mineral acids. It dissolves in concentrated sulphuric acid to a yellow solution which changes to brown on the addition of a crystal of potassium nitrate.

The hydrochloric acid extracts (A) gradually deposited a mass of pale yellow needles, which were collected, dissolved in water, and precipitated with ammonia. The precipitate was washed and recrystallised from alcohol; the resulting yellow rhombic prisms, m. p. 130°, proved to be identical with the 3 : 11-dimethoxydihydroprotoberberine (X) described on p. 2271.

3 : 11-*Dimethoxytetrahydroprotoberberine Methiodide*.—The base (V; 10 g.) and methyl iodide (15 c.c.) were boiled for 15 minutes, the excess of methyl iodide was removed, and the residue dissolved in boiling water (300 c.c.) and cooled; the β-*methiodide* separated and was crystallised from water as colourless prisms, m. p. 245° (decomp.) (Found: C, 54·9; H, 5·7. $C_{20}H_{24}O_2NI$ requires C, 54·9; H, 5·5%). The α-*methiodide*, obtained by concentrating the mother-liquors, separated from water in colourless nodules, m. p. 224° (Found: C, 55·2; H, 5·6). The methochlorides were obtained by digesting an aqueous suspension of the mixed methiodides with silver chloride. The filtered solution was evaporated to dryness, the pale yellow syrup dissolved in alcohol, and ether slowly added; the β-*methochloride* then separated in colourless needles, m. p. 245° (decomp.)

(Found: C, 69·2; H, 7·1. $C_{20}H_{24}O_2NCl$ requires C, 69·4; H, 6·9%). The *α-methochloride* was precipitated as a syrup by the addition of more ether to the alcohol–ether mother-liquor of the β-methochloride. It was not obtained in a crystalline state, but the addition of sodium iodide to its aqueous solution precipitated the α-methiodide, m. p. 224°.

Anhydromethyl-3 : 11-*dimethoxytetrahydroprotoberberine* (XIII).—(i) The mixed methochlorides (1 g.) were boiled with 25% methyl-alcoholic potassium hydroxide (6 c.c.) for 2 hours, the mixture was diluted with water, the oily base extracted with ether, and the solvent removed, leaving the crude base as a colourless oil which did not solidify; it was soluble in the usual organic solvents and yielded the sparingly soluble *hydrochloride* (see below) when it was stirred with dilute hydrochloric acid. (ii) An aqueous solution of the mixed methiodides or methochlorides was decomposed with silver hydroxide, filtered, the filtrate concentrated in a good vacuum, and the residue extracted with benzene. This left a small amount of material which was dissolved in water and concentrated, giving crystals of 3 : 11-*dimethoxytetrahydroprotoberberine methocarbonate*, m. p. 216°, which dissolved with effervescence in dilute hydrochloric acid (Found: C, 67·9; H, 6·9. $C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·7%). The benzene extract, on concentration, yielded an oil which gave a sparingly soluble hydrochloride and was identical with the oil obtained by method (i); all its properties showed that it was an anhydro-base of the "B" type. *Anhydro*-3 : 11-*dimethoxytetrahydroprotoberberine B* is an oil which decolorises a solution of bromine in chloroform and also an acid solution of permanganate. It is recovered after boiling for several hours with aqueous alcohol or chloroform. The sparingly soluble hydrochloride crystallises from water in small needles, m. p. 236° (decomp.), and is recovered unchanged after boiling with dilute hydrochloric acid for 6 hours (Found: C, 69·2; H, 6·9. $C_{20}H_{24}O_2NCl$ requires C, 69·4; H, 6·9%). When the base (XIII) was mixed with perbenzoic acid, no crystalline material separated. The mixture was extracted with dilute hydrochloric acid, the acid extract evaporated in a vacuum, and the resulting gum warmed with glacial acetic acid and concentrated hydrochloric acid. The reddish solution obtained yielded an amorphous, dark slime on the addition of ammonia, but no crystalline substance could be isolated from it.

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