CCCIV.—*Synthetical Experiments in the* iso*Quinoline Group. Part VIII. A Synthesis of Protoberberinium Salts.*

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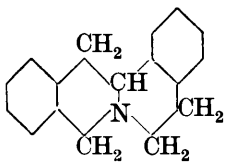
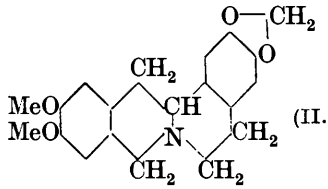
IT is pointed out (preceding paper) that the parent substance of the alkaloids of the palmatine–berberine series is protoberberine, the synthesis of which is now described. It was thought probable that the methods which had proved so successful in the syntheses of ψ-berberine and other similar cases might fail in the present case because the absence of the methylenedioxy- or methoxy-groups might inhibit one or other of the necessary ring-closures. These anticipations were, in fact, largely realised, for although the synthesis was ultimately successful, the yields obtained, especially in the case of the second ring-closure, were so poor that the accumulation of sufficient material for the study of protoberberine was a very tedious process. Clearly, then, the presence of the catechol nuclei is an important factor in facilitating the building up of these alkaloids, and this fact is in harmony with the presence of these nuclei in so many of the naturally occurring alkaloids of this and similar groups.

As in previous cases, the first object was the synthesis of *tetrahydroprotoberberine* (I), and the methods employed were similar to those which had been successful in the synthesis of tetrahydro-ψ-berberine (II) and allied substances. Phenylacet-β-phenylethylamide, prepared from phenylacetic acid and β-phenylethylamine,

(I.)

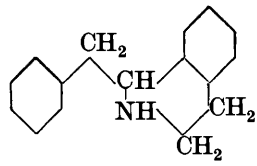


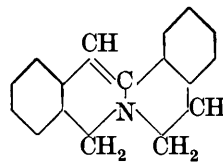


(II.)

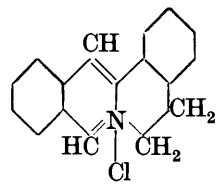
was converted into 1-benzyl-3 : 4-dihydro*iso*quinoline by the action of phosphorus pentoxide (compare Decker and Kropp, *Ber.*, 1909, **42**, 2075; Pictet and Kay, *ibid.*, p. 1976; Forsyth, Kelly, and Pyman, J., 1925, **127**, 1663). On reduction with dilute sulphuric acid and zinc, the dihydro-base yielded 1-benzyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III; compare Forsyth, Kelly, and Pyman, *loc. cit.*, p. 1664), an oily base which gives a crystalline hydriodide and *sulphate*. The conversion of this substance into tetrahydroprotoberberine (I) presented considerable difficulty. The usual con-

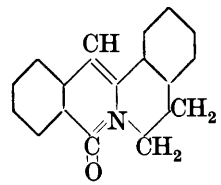
densation with formaldehyde was unsuccessful, but it was ultimately found that treatment of the N-*formyl* derivative with phosphorus

(III.) 

 (IV.)

oxychloride under strictly defined conditions (see p. 2278) yielded small quantities of *dihydroprotoberberine* (IV), the yield under the most favourable conditions not exceeding 10%. (The substitution of phosphorus pentoxide for the oxychloride did not effect any improvement.) The base (IV) was not isolated as such, but was immediately reduced by zinc dust and hydrochloric acid to tetrahydroprotoberberine (I), m. p. 85°, which crystallises well and yields a crystalline *hydrochloride* and *picrate*. When the tetrahydro-base is oxidised in alcoholic solution by iodine, it is converted into *protoberberinium iodide*, which is much less highly coloured than berberinium iodide, crystallises in yellow needles, and is converted by silver chloride into the *chloride* (V). It is interesting

(V.) 

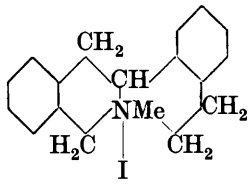
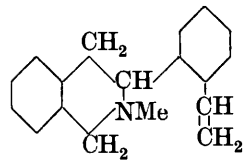
 (VI.)

that this salt crystallises from water with $4H_2O$, thus resembling berberinium chloride and the other analogously constituted chlorides of this series, all of which contain water of crystallisation. In this case, again, the loss of colour is very striking, since the intense yellow so characteristic of berberinium chloride has almost disappeared in the case of protoberberinium chloride, the crystals of which have only a pale yellow tinge.

Protoberberinium chloride is decomposed by potassium hydroxide in the usual manner and yields *oxyprotoberberine* (VI), m. p. 102°, but the dihydroprotoberberine which is evidently produced at the same time could not be isolated in a pure state owing to the small amount of material at our disposal. Attention may be directed to the unexpectedly large effect which the elimination of methoxy- and methylenedioxy-groups has in producing low melting points in the derivatives of protoberberine : thus tetrahydroprotoberberine has m. p. 85°, whereas tetrahydroberberine melts at 170° and

tetrahydropalmatine at 147°; oxyprotoberberine has m. p. 102°, whereas oxyberberine melts at 200° and oxypalmatine at 183°.

Tetrahydroprotoberberine methiodide (VII), prepared by heating the base with excess of methyl iodide, was readily separable into α- and β-forms. When treated with alcoholic potassium hydroxide, the methiodide was converted into *anhydromethyltetrahydroprotoberberine* (VIII), a syrupy base which yields a sparingly soluble *hydrochloride*. The same anhydro-base was obtained when the

(VII.)   (VIII.)

methiodide was digested with silver hydroxide and the solution evaporated in a good vacuum. No trace of the isomeric base containing a ten-membered ring could be isolated, and the constitution (VIII) is assigned to anhydromethyltetrahydroprotoberberine because the base is stable towards methyl alcohol and chloroform, and the sparingly soluble hydrochloride is also stable towards boiling dilute hydrochloric acid—conditions under which the ten-membered isomeride would be converted into a quaternary chloride. It would appear, therefore, that, in the absence of methoxy- or methylenedioxy-groups, there is no tendency towards the formation of the ten-membered anhydro-base.

EXPERIMENTAL.

1-*Benzyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (III).—To a boiling solution in xylene (100 c.c.) of phenylacet-β-phenylethylamide (20 g.), obtained by heating molecular proportions of phenylacetic acid and β-phenylethylamine at 180° (Decker and Kropp, *loc. cit.*), phosphorus pentoxide (40 g.) was added, and the boiling continued for ¼ hour; the mixture was poured into water, the toluene layer removed, and the aqueous layer made strongly alkaline with sodium hydroxide. The 1-benzyl-3 : 4-dihydro*iso*quinoline which separated as an oil (Pictet and Kay, *loc. cit.*) was rapidly extracted with benzene and thence with dilute sulphuric acid; the acid extract gradually deposited the *sulphate* in regular cubes, m. p. 216° (Found : C, 60·4; H, 5·4. $C_{16}H_{15}N,H_2SO_4$ requires C, 60·2; H, 5·3%). The sulphuric acid solution of the sulphate was heated with excess of zinc dust for 1½ hours, reduction then being complete. The hot solution was filtered, decomposed with ammonia, the oily base

extracted with chloroform, the extract dried over potassium carbonate, the solvent removed, and the residual oil dissolved in hot dilute sulphuric acid. The *1-benzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline sulphate*, which gradually formed, crystallised from water with $5H_2O$, of which $4H_2O$ were lost at 100°, m. p. 191° (decomp.) [Found: loss at 100°, 11·2. $(C_{16}H_{17}N)_2,H_2SO_4,5H_2O$ requires $4H_2O$, 11·2. Found in material dried at 100°: C, 67·8; H, 6·7. $(C_{16}H_{17}N)_2,H_2SO_4,H_2O$ requires C, 68·3; H, 6·8%]. This sulphate is less soluble in dilute sulphuric acid than in water.

Tetrahydroprotoberberine (I).—This base could not be obtained by treating the foregoing base with formaldehyde in the usual manner. A variety of conditions were examined and, although small quantities of crystalline hydrochlorides were sometimes formed, they always gave rise to gummy bases on decomposition with alkali. Ultimately the following method was found to give the desired result although the yield was not more than 10%. 1-Benzyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (24 g.) and anhydrous formic acid (5 g.) were heated in an oil bath at 200—205° until effervescence had ceased (3 hours). The product was dissolved in toluene and boiled with phosphorus oxychloride (48 c.c.) for 1½ hours; light petroleum was then added, the clear liquid decanted from the dark-coloured gum, the latter extracted with dilute hydrochloric acid (charcoal), and the solution of dihydroprotoberberine hydrochloride reduced by heating with excess of zinc dust for 2 hours, during which the yellow solution became colourless. The hot liquid was filtered, the filtrate decomposed with ammonia, the base extracted with chloroform, dried over potassium carbonate, the chloroform removed, and the residue dissolved in hot dilute hydrochloric acid, from which *tetrahydroprotoberberine hydrochloride* gradually separated. This was collected, recrystallised from water (charcoal), the purified salt dissolved in water, decomposed with ammonia, the base extracted with ether, dried over potassium carbonate, filtered, and the ether allowed to evaporate slowly, whereupon *tetrahydroprotoberberine* crystallised in clusters of colourless needles, m. p. 85° (Found: C, 87·2; H, 7·3. $C_{17}H_{17}N$ requires C, 86·8; H, 7·2%); it dissolves readily in the usual organic solvents, with the exception of petroleum, and crystallises well from either ether or methyl alcohol. It is a strong base dissolving in dilute acids and giving well-characterised salts. Its solution in concentrated sulphuric acid is colourless even after the addition of a crystal of potassium nitrate. This reaction distinguishes tetrahydroprotoberberine from other alkaloids of this series, for the sulphuric acid solutions of all those containing methoxy- or methylenedioxy-groups develop coloration under these conditions. The colours are probably

due to nitration occurring in the nuclei activated by these substituent groups.

Tetrahydroprotoberberine hydrochloride is readily soluble in water, from which it separates in slender needles, m. p. 232° (Found: C, 75·4; H, 6·8. $C_{17}H_{18}NCl$ requires C, 75·1; H, 6·6%), and very sparingly soluble in dilute hydrochloric acid. The still more sparingly soluble, crystalline *hydriodide* separates when a solution of sodium iodide is added to the aqueous solution of the hydrochloride. The *picrate* crystallises in small yellow needles, m. p. 151°, when an alcoholic solution of the base is mixed with picric acid; it is soluble in glacial acetic acid or hot alcohol, sparingly soluble in cold alcohol, and almost insoluble in water (Found: C, 59·0; H, 4·6. $C_{23}H_{20}O_7N_4$ requires C, 59·5; H, 4·3%).

The Protoberberinium Salts (as V).—Tetrahydroprotoberberine, dissolved in the minimum of boiling alcohol, was mixed with anhydrous sodium acetate, and an alcoholic solution of iodine added until a permanent colour remained. The dark brown, granular precipitate of the *periodide* was collected, washed well with water, suspended in water, decomposed with sulphur dioxide, and the resulting yellow *iodide* recrystallised from boiling water; fine yellow needles, m. p. 232° (decomp.) (Found: C, 56·2; H, 4·1. $C_{17}H_{14}NI$ requires C, 56·2; H, 3·9%). The *chloride* was readily obtained when an aqueous suspension of the iodide was digested with excess of silver chloride for 2 hours on the steam-bath. After filtering, concentrating, and adding hydrochloric acid, the chloride separated as a mass of needles having only a slight yellow tinge; it was recrystallised from water and left on porous porcelain exposed to the air for 2 days. It then had the composition $C_{17}H_{14}NCl,4H_2O$, and after heating at 100° it still retained $\frac{1}{2}H_2O$ (Found: loss at 100°, 18·3. $C_{17}H_{14}NCl,4H_2O$ requires $3\frac{1}{2}H_2O$, 18·5. Found in material dried at 100°: C, 74·2; H, 5·5. $C_{17}H_{14}NCl,\frac{1}{2}H_2O$ requires C, 73·8; H, 5·4%). *Protoberberinium picrate* was obtained as yellow flocks on adding aqueous picric acid to a hot aqueous solution of the chloride; it crystallised from glacial acetic acid, in which it is sparingly soluble, in fine, yellow needles, m. p. 192—193°.

Oxyprotoberberine (VI).—A boiling solution of protoberberinium chloride (0·5 g.) in water (5 c.c.) was added to a hot solution of potassium hydroxide (2·5 g.) in a little water, and the mixture heated on the steam-bath for 3 hours; the oil which separated solidified on long standing. It was usually extracted with ether, the ether removed, and the residual gum extracted several times with very dilute hydrochloric acid. By this treatment the dihydropfotoberberine present was removed, but we were not successful

in isolating the small quantities of this substance in a pure state. The residue, insoluble in dilute hydrochloric acid, was dissolved in hot glacial acetic acid and mixed with a few drops of boiling water; *oxyprotoberberine* then gradually separated and, after a second treatment with acetic acid, it was obtained pure in slender, satiny, colourless needles, m. p. 102° (Found: C, 82·6; H, 5·5. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3%). It is rather sparingly soluble in the usual organic solvents, with the exception of glacial acetic acid, and does not dissolve in dilute mineral acids. The pale yellow solution in concentrated sulphuric acid becomes pale brown on the addition of a crystal of potassium nitrate.

Tetrahydroprotoberberine Methiodides (VII).—Tetrahydroprotoberberine (5 g.) and methyl iodide (10 c.c.) were heated under reflux for ½ hour, the excess of methyl iodide was evaporated, and the solid dissolved in boiling water (250 c.c.); the *β-methiodide*, which separated on cooling, recrystallised from water in colourless prisms, m. p. 230—232° (decomp.) (Found: C, 57·2; H, 5·4. $C_{18}H_{20}NI$ requires C, 57·3; H, 5·3%). The *α-methiodide* gradually separated from the aqueous mother-liquor in colourless nodules, and crystallised from alcohol in small needles, m. p. 212° (Found: C, 57·1; H, 5·2). The *methochloride* was obtained by heating an aqueous suspension of the mixed methiodides with silver chloride. It is very soluble in water and separates as a syrup on concentration.

Anhydromethyltetrahydroprotoberberine (VIII).—Tetrahydroprotoberberine methiodide (or methochloride) was heated with excess of 10% methyl-alcoholic potassium hydroxide for 3 hours. The mixture was diluted with water, the oily base extracted with ether, dried over potassium carbonate, filtered, and the ether removed, leaving the base as an oil which did not crystallise. When triturated with dilute hydrochloric acid, it was converted into the sparingly soluble hydrochloride, and this crystallised from water in small prisms, m. p. 234—235° (decomp.), containing water of crystallisation, which is lost at 100°, the substance falling to a fine powder (Found: C, 75·0; H, 7·0. $C_{18}H_{20}NCl$ requires C, 75·6; H, 7·0%). The same base is the only ether-soluble product obtained when tetrahydroprotoberberine methiodide is treated with silver hydroxide, and the solution evaporated in a good vacuum. The ether-insoluble residue was completely soluble in water and appeared to be undecomposed *methohydroxide*. After being boiled with aqueous methyl alcohol for 4 hours, the base (VIII) was recovered unchanged and identified by conversion into the sparingly soluble hydrochloride. It was also unchanged by boiling with chloroform for 3 hours, whilst the hydrochloride was recovered after being heated with dilute hydrochloric acid on the steam-bath for 6 hours.

We wish to thank Mr. Fred Hall for carrying out the analyses required during this and the two preceding investigations. One of us (S. N. C.) desires to thank the United Provinces Government for a Scholarship which has enabled him to take part in these researches.

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