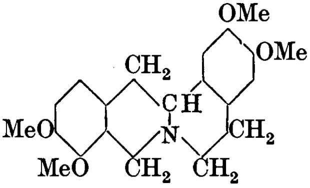
CCCII.—*The Conversion of Palmatine into its Cryptopine Analogue (Cryptopalmatine).*

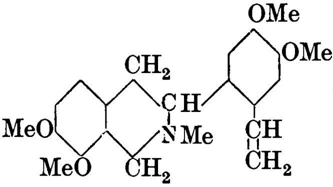
By ROBERT DOWNS HAWORTH, JOSEPH BLAKE KOEPFLI, and WILLIAM HENRY PERKIN, jun.

AN examination of the structural formulæ of the naturally occurring alkaloids of the ten-membered ring type, such as cryptopine and protopine, reveals the relationship between these alkaloids and those of the protoberberine series. Thus the protoberberine alkaloids berberine and coptisine (Kitasato, *Proc. Imp. Acad. Tokyo*, 1926, **2**, 124) are related to the ten-membered ring alkaloids β-homochelidonine and protopine, respectively. These relationships, together with the interconvertibility of the two types, leave little doubt that the further examination of natural products will result in the discovery of new affinities of the same kind. *epi*-Berberine, the protoberberine derivative corresponding to cryptopine, has so far not been isolated from natural sources, whilst the ten-membered ring analogue of palmatine has not been described either as a natural or as a synthetical product. This analogue of palmatine, for which we suggest the name "*cryptopalmatine*" (V), has now been obtained from palmatine by a process similar to that employed in the synthesis of β-homochelidonine, cryptopine, and protopine (Haworth and Perkin, J., 1926, **129**, 445, 1769).

Tetrahydropalmatine (I) * was treated with methyl iodide and thus converted into the *methiodide* which exists in the usual α- and β-modifications, readily separable by crystallisation from methyl alcohol and then from water. The β-*methochloride*, obtained from the methiodide by the action of silver chloride, is a well-defined, crystalline substance, whereas the corresponding α-*methochloride* has only been isolated as a hygroscopic syrup. When the methiodides or methochlorides are heated with methyl-alcoholic potassium hydroxide, *anhydromethyltetrahydropalmatine B* (II) is obtained as a crystalline substance, m. p. 115—116°, the constitution of which is proved by the facts (i) that it is a stable substance remaining unchanged after digestion with methyl alcohol or chloroform, and (ii) that its sparingly soluble, crystalline *hydrochloride* is not converted into tetrahydropalmatine methochloride by prolonged boiling with dilute hydrochloric acid.

(I.)





(II.)

Tetrahydropalmatine methiodide was next converted into the corresponding methohydroxide, by treatment with silver hydroxide in aqueous suspension, and the methohydroxide decomposed by evaporating the solution in a good vacuum, whereby a mixture of *anhydromethyltetrahydropalmatine A* (III) and B (II) was obtained, in which unfortunately the latter modification largely predominated. The former base possesses the properties characteristic of the "A" type, since it is unstable and is converted into tetrahydropalmatine methochloride by warming with dilute hydrochloric acid. Owing to the poor yield of this base, further experiments could only be carried out on a very small scale, and no attempt was made to isolate in a pure condition the amine oxide (IV), which results from the action of perbenzoic acid on the anhydro-base A (III). It was, however, observed that the amine oxide is soluble in water and yields a colourless, sparingly soluble *hydrochloride*. On warming with glacial acetic acid and hydrochloric acid, this amine oxide is readily converted into *cryptopalmatine* (V), a well-defined base which

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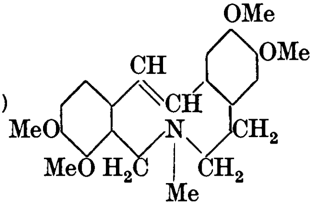
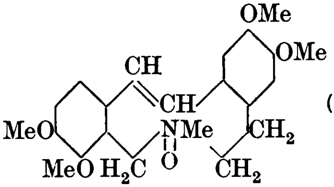
* We are indebted to Professor Späth for some of the palmatine iodide used in this investigation, but most of the material was prepared by us from berberine by the method of Späth and Quietensky (*Ber.*, 1925, **58**, 2267).

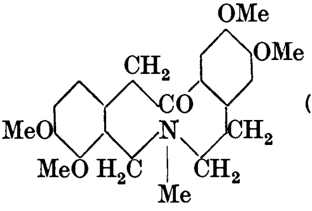
separates from ether in prisms, m. p. 148—150°, and, like cryptopine, gives a characteristic red-violet coloration with sulphuric acid.

(III.)





(IV.)



(V.)

We hope, at a later date, to be able to obtain further quantities of cryptopalmatine, so that it may be possible to make a more complete examination of this interesting base.

EXPERIMENTAL.

Tetrahydropalmatine α- and β-Methiodides.—Tetrahydropalmatine (4 g.), methyl iodide (5 c.c.), and benzene (40 c.c.) were heated on the steam-bath for 4 hours, and the pale yellow methiodide (4·6 g.) was collected, dried, and fractionally crystallised from methyl alcohol (200 c.c.). The first fractions, recrystallised from water, yielded the β-*methiodide* as stout prisms, m. p. 266° (decomp.) * (Found: C, 53·0; H, 5·8. $C_{22}H_{28}O_4NI$ requires C, 53·1; H, 5·6%). This substance is very sparingly soluble in methyl alcohol or water. The last fractions from the crystallisation from methyl alcohol were recrystallised from water, and the α-*methiodide* separated in colourless prisms, m. p. 230°. The crystals contain water of crystallisation, but they lose it at 110° and fall to a powder (Found, in material dried at 110°: C, 53·2; H, 5·9).

Tetrahydropalmatine α- and β-Methochlorides.—The methiodide (*i.e.*, the mixture of the α- and β-forms), suspended in water, was heated with excess of silver chloride on the steam-bath for 3 hours. The filtered solution was concentrated to a small bulk, whereupon the β-*methochloride* separated and was collected. The mother-liquor, on further concentration, yielded the α-*methochloride* as a

* The melting points of the salts given in this and the following papers vary very much with the rate of heating, and must be considered as only approximate.

hygroscopic syrup. The β-methochloride crystallises from water in colourless prisms, m. p. 250° (decomp.) (Found : C, 64·8; H, 7·2. $C_{22}H_{28}O_4NCl$ requires C, 65·1; H, 6·9%). The α-methochloride separates from water as a syrup, which is readily soluble in alcohol and is precipitated as an oil on the addition of ether. It is converted into the α-methiodide, m. p. 230°, by the addition of potassium iodide to the aqueous solution.

Anhydromethyltetrahydropalmatine B (II).—Tetrahydropalmatine methochloride was heated on the steam-bath for 2 hours with excess of 10% methyl-alcoholic potassium hydroxide. The solution was diluted with water, the oily base extracted with ether, and the extract dried, filtered, and concentrated; *anhydromethyltetrahydropalmatine B* then separated in stout, colourless prisms, m. p. 115—116° (Found : C, 71·3; H, 7·5. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·3%). This base is very soluble in the usual organic solvents with the exception of petroleum. It is stable towards hot aqueous methyl alcohol or chloroform and yields a sparingly soluble *hydrochloride* which crystallises from water in nodular clusters of needles, m. p. 210° (decomp.); these contain water of crystallisation some of which is lost at 100°, the crystals falling to a powder, but 1 mol. of water is retained after drying at 110° (Found, in material dried at 110° : C, 63·0; H, 7·1. $C_{22}H_{28}O_4NCl,H_2O$ requires C, 62·4; H, 7·1%).

Anhydromethyltetrahydropalmatine A (III).—Tetrahydropalmatine methiodide (3 g.) was digested with a suspension of silver hydroxide until conversion into the methohydroxide was complete. The filtered solution was evaporated and the residue heated for an hour at 100°, both processes being conducted in a vacuum. The syrup which remained was extracted several times with ether, in order to separate the anhydro-bases from any undecomposed methohydroxide, and the ether allowed to evaporate slowly; *anhydromethyltetrahydropalmatine A* gradually separated in needles (0·1 g.), m. p. 131—132° (Found : C, 71·5; H, 7·1. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·3%), whilst the modification B (1·5 g.) slowly crystallised from the mother-liquors. Anhydromethyltetrahydropalmatine A is an unstable base which dissolves in cold dilute hydrochloric acid and may be liberated from the solution by sodium hydroxide. After boiling in dilute acid for some time, the base does not separate on the addition of sodium hydroxide, conversion into tetrahydropalmatine methochloride evidently having taken place.

Cryptopalmatine (V).—Anhydromethyltetrahydropalmatine A (0·2 g.) in chloroform (5 c.c.) was gradually added to an ice-cold ethereal solution of perbenzoic acid (0·25 g. in 25 c.c.). The mixture was kept over-night during which it acquired a greenish-yellow tint, but no crystalline material separated as in the cases previously examined (Haworth and Perkin, *loc. cit.*). When the mixture was shaken with very dilute hydrochloric acid and the extract concentrated in a vacuum, the *hydrochloride* of the amine oxide (IV) separated in colourless prisms, m. p. 198—200° (decomp.) with previous darkening. Owing to scarcity of material the amine oxide was not isolated, but it was observed to be soluble in water because an aqueous solution of the hydrochloride remained clear on the addition of sodium hydroxide.

The hydrochloride (0·1 g.) was dissolved in glacial acetic acid (2 c.c.) and concentrated hydrochloric acid (2 c.c.), boiled for 2 minutes, the brown solution diluted with water, made alkaline with sodium hydroxide, and the amorphous base extracted with chloroform; when the extract was dried and the solvent removed, a brown semi-solid mass remained. This was dissolved in a little alcohol, mixed with a large volume of ether, filtered from amorphous material, the ethereal solution well washed with water, dried over potassium carbonate, filtered, and the solvent allowed to evaporate slowly, whereupon *cryptopalmatine* separated in small, colourless prisms, m. p. 148—150° (Found: C, 68·6; H, 6·8. $C_{22}H_{27}O_5N$ requires C, 68·8; H, 7·0%). A solution of the base in glacial acetic acid developed a reddish-violet coloration on the addition of concentrated sulphuric acid.

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[*Received, August 5th*, 1927.]
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