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Studies in Protoberberine Alkaloids: Part IV*†—Synthesis of 13-Methyl-Ψ-coptisine

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Tetrahydro-13-methyl-ψ-coptisines (V) (m.p. 195°) and (VI) (m.p. 131°) have been synthesized from 1-(α-methyl-3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (IV) by treating it with formaldehyde and hydrochloric acid. The products obtained as a mixture have been separated by column chromatography over silica using chloroform for eluting the column. Mercuric acetate oxidation of V afforded 13-methyl-Ψ-coptisine (VII). Comparison of the melting points of the iodides and chlorides of VII and worenine suggests that worenine may be 13-methyl-Ψ-coptisine.

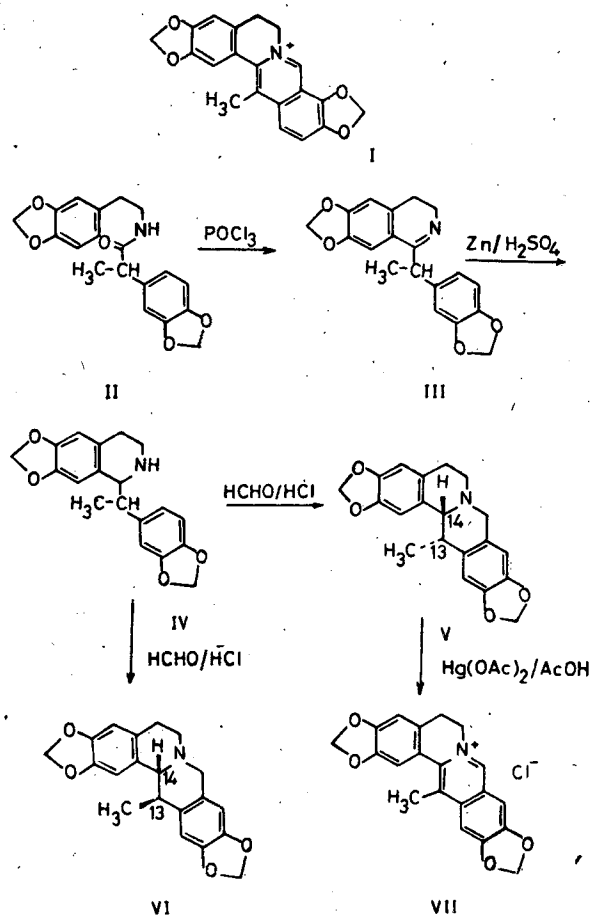
WORENINE is a protoberberine alkaloid, isolated by Kitasato from the plant *Coptis japonica*[1,2] and by Schramm and Tang from *Coptis chinensis*[3]. In *Coptis japonica*, worenine occurs along with berberine and coptisine. Worenine contains one more methyl group than coptisine. Kitasato proposed that worenine was 13-methylcoptisine (I). He also reported the melting points of worenine chloride and iodide as 295° and 300° respectively, and that of tetrahydroworenine as 213-4°. The melting points of the methochloride and methiodide of tetrahydroworenine were also recorded. Apart from these no other details regarding this alkaloid are available.

The structure I of worenine is the same as that deduced years later for another alkaloid corysamine. The non-dentity of these two alkaloids (i.e. worenine and corysamine) was apparent[4] from the considerable discrepancies between the reported melting points of the corresponding salts and of the respective tetrahydro compounds. I was synthesized from coptisine and found to be identical with corysamine, thus establishing the latter's structure unequivocally[4]. Hence, Kitasato's proposal that worenine had structure I became untenable.

Jeffs[5] has recently proposed that worenine may be 13-methyl-Ψ-coptisine (VII). We report in this article the synthesis of VII through its tetrahydro derivative V and the probable identity of VII with worenine.

13-Methyl-Ψ-coptisine was synthesized by the classical protoberberine route, adapted recently by Shamma *et al.*[6] for 13-methylprotoberberines.

Condensation of 2-(3,4-methylenedioxyphenyl)propionic acid with homopiperonylamine yielded the amide II. Cyclization of II with $POCl_3$ afforded the dihydroisoquinoline III which was reduced with zinc and sulphuric acid. The major product of the resultant diastereoisomeric mixture of tetrahydroisoquinoline derivatives IV, was obtained crystalline, m.p. 100°, and characterized. Mixture IV itself was treated with formaldehyde and hydrochloric acid to give 13-methyltetrahydro-Ψ-coptisine



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V and VI, which were separated by chromatography on silica column. The major isomer V, m.p. 195°, exhibited a methyl doublet at δ 0·94 ppm in the NMR spectrum while the minor isomer VI, m.p. 131°, had the doublet at δ 1·44 ppm. These chemical shifts corresponded closely to those of the methyl doublets in *dl*- and *meso*-thalictricavines respectively[7]. It was, therefore, possible to assign relative stereochemistry of C(13)-CH_3 and C(14)-H in V and VI as shown. Formaldehyde cyclization of the pure tetrahydroisoquinoline, m.p. 100°, gave only V*.

The hydrochloride and hydroiodide of V were prepared as well as its methiodide. V was further oxidized by mercuric acetate to give 13-methyl-Ψ-coptisine (VII), characterized as chloride, iodide and picrate. In Table 1 are listed the melting points of these derivatives and those reported for worenine and tetrahydroworenine derivatives. Unfortunately, no sample of the natural alkaloid was available. However, comparison of the melting points of various derivatives suggests that worenine may indeed have structure VII. There is good concurrence, for example, in the case of chloride, iodide and methiodide (Table 1). The discrepancy in the melting points of tetrahydro bases may be due to either in the rate of heating or due to differences in crystal structure.

Table 1 — Comparison of Melting Points of the Salts of the Two Bases

Form	13-Methyl-Ψ-coptisine	Worenine
Chloride	288-9°	295°
Iodide	297-9°	300°
Picrate	233°	—
Tetrahydro base	195°	213-14°
Hydrochloride	252-4°	—
Hydriodide	274°	—
Methiodide	270°	263°
Methochloride	—	281°

Experimental Procedure

N-(3,4-*Methylenedioxyphenylethyl*)-2-(3,4-*methylenedioxyphenyl*)*propionamide* (II)— A mixture of 2-(3,4-methylenedioxyphenyl)propionic acid[6] (9 g), thionyl chloride (7 g), dry ether (40 ml) and one drop of pyridine was kept overnight at room temperature. Ether and excess thionyl chloride were removed and the oily acid chloride dissolved in dry chloroform (50 ml). The chloroform solution was added dropwise to a stirred, ice-cooled mixture of homopiperonylamine (7·7 g) in chloroform (75 ml) and sodium carbonate (10·5 g) in water (50 ml). After stirring for an additional 15 min the chloroform layer was separated, washed with water, HCl (10%) and water again, and dried (Na_2SO_4). Evaporation gave a residue which crystallized on rubbing with pet. ether. The solid was recrystallized from benzene as colourless crystals (15 g), m.p. 127-8° (Found: C, 66·68; H, 5·81; N, 4·25. $C_{19}H_{19}NO_5$ requires C, 66·85; H, 5·57; N, 4·11%); ν_{max}^{Nujol} 1660 cm^{-1} (C=O); NMR ($CDCl_3$): δ 1·45 (3H, *d*, *J*=7 Hz, C—CH_3), 2·62 (2H, *t*, Ar—CH_2), 3·2-3·65 (3H, *m*, —CH_2—NH, —CH), 5·89 (2H, *s*, —O—CH_2—O—), 5·93 (2H, *s*, —O—CH_2—O—), 5·45 (1H, very broad singlet, NH), 6·3-6·7 (6 aromatic H) ppm.

1-(α-*Methyl*-3,4-*methylenedioxybenzyl*)-3,4-*dihydro*-6,7-*methylenedioxyisoquinoline* (III)— A mixture of the above amide II (5 g), freshly distilled $POCl_3$ (10 ml) and dry toluene (75 ml) was refluxed for 1 hr. Excess $POCl_3$ and toluene were removed *in vacuo*, the residue dissolved in cold methanol (5 ml) and poured into water (100 ml). The aqueous solution was washed with ether, basified with ammonia and extracted with chloroform. The chloroform layer was separated, washed with water and dried (Na_2SO_4). Evaporation provided a light yellow oil, which solidified on rubbing with pet. ether. The solid was crystallized from benzene-hexane as colourless crystals (4 g), m.p. 121°, perchlorate, m.p. 190° (from methanol) (Found: C, 53·60; H, 4·25; N, 3·63. $C_{19}H_{18}O_8NCl$ requires C, 53·84; H, 4·25; N, 3·31%); NMR (of the base in $CDCl_3$): δ 1·50 (3H, *d*, *J*=7 Hz, C—CH_3), 2·57 (2H, approx. *t*, Ar—CH_2), 3·72 (2H, approx. *t*, N—CH_2), 4·18 (1H, *q*, *J*=7 Hz, —C—H), 5·83 (4H, *s*, two —O—CH_2—O—) ppm.

1-(α-*Methyl*-3,4-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (IV)— The above base (4 g) was dissolved in sulphuric acid (2*N*; 30 ml). Two drops of 10% aq. copper sulphate and powdered zinc (3·25 g) were added and the mixture heated on a steam-bath for 5 hr. The colourless solution was filtered and cooled. The hydrosulphate salt crystallized out. It was collected and basified with ammonia and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4). Evaporation yielded a white solid, which crystallized from benzene-hexane (3·1 g), m.p. 100° (Found: C, 70·00; H, 6·17; N, 4·70. $C_{19}H_{19}O_4N$ requires C, 70·15; H, 5·85; N, 4·31%); NMR ($CDCl_3$): δ 1·10 (3H, *d*, *J*=7 Hz, —C—CH_3), 2·60-3·70 (6H, Ar—CH_2, Ar—CH, N—CH_2, N—CH), 4·05 (1H, *q* with fine structure, *J*=7 Hz, —CH), 5·87 (2H, *s*, —O—CH_2—O—), 5·92 (2H, *s*, —O—CH_2—O), 6·53-6·83 (5H, *m*, aromatic protons) ppm.

13-*Methyltetrahydro*-Ψ-*coptisine* (V *and* VI)— The above isoquinoline (IV) (1 g) was dissolved in methanol (6 ml) and the solution treated with sodium bicarbonate (0·5 g) and warmed on a steam-bath. Formalin (37%; 10 ml) was gradually added. After a few minutes, water (5 ml) and ice (20 g) were added. The gummy hydroxymethyl adduct was extracted into chloroform, after saturating the mixture with sodium chloride. The chloroform extract was washed with saline water, dried (Na_2SO_4) and solvent removed. The gummy residue was triturated with conc. HCl (5 ml) and allowed to stand at room temperature for 4 hr. Water (20 ml) was then added and basified with ammonia. The solution was extracted with chloroform, and the extract washed with water, and dried (Na_2SO_4). Evaporation yielded an oily product (0·62 g), consisting mainly of the two diastereoisomeric tetrahydroprotoberberines V and VI. This

*The appearance of 4 singlets for the 4 aromatic protons in the NMR spectra of V and VI confirms that HCHO cyclization has occurred on the carbon indicated.

mixture was chromatographed over a column of silica gel and eluted with chloroform. The initial chloroform extracts gave V while the later eluates gave VI. V crystallized from benzene as colourless plates (0·4 g), m.p. 195° (Found: C, 71·00; H, 5·87; N, 4·45. $C_{20}H_{19}O_4N$ requires C, 71·22; H, 5·64; N, 4·16%); λ_{max}^{EtOH} 293, 235 (inflex.) nm (log ε, 4·00, 4·00); NMR ($CDCl_3$): δ 0·94 (3H, *d*, *J*=7 Hz, C—CH_3), 5·88 (2H, *s*, —O—CH_2—O—), 5·90 (2H, *s*, —O—CH_2—O—), 6·50, 6·57, 6·62, 6·67 (4H, all singlets, aromatic H) ppm. V formed a hydrochloride, m.p, 252-4° (from methanol-ether) (Found: C, 63·92; H, 5·74; N, 3·75. $C_{20}H_{20}O_4NCl$ requires C, 64·25; H, 5·36; N, 3·74%), a hydroiodide, m.p. 274° (from methanol) (Found: C, 51·84; H, 4·60; N, 3·07. $C_{20}H_{20}O_4NI$ requires C, 51·60; H, 4·30; N, 3·01%) and a methiodide, m.p. 270° (from methanol) (Found: C, 52·64; H, 4·48; N, 2·99. $C_{21}H_{22}O_4NI$ requires C, 52·61; H, 4·59; N, 2·92%). VI crystallized from benzene-hexane as white crystals (75 mg), m.p. 131° (Found: C, 70·95; H, 5·66; N, 4·51. $C_{20}H_{19}O_4N$ requires C, 71·22; H, 5·64; N, 4·15%); λ_{max}^{EtOH} 293, 235 nm (log ε, 4·03, 3·85); NMR ($CDCl_3$): δ 1·44 (3H, *d*, *J*=7 Hz, C—CH_3), 5·87 (4H, *s*, two —O—CH_2—O), 6·47, 6·55, 6·63, 6·68 (4H, all singlets, aromatic protons) ppm.

13-*Methyl*-Ψ-*coptisine* (VII)—V (1 g) dissolved in glacial acetic acid (2 ml) was added to mercuric acetate (4 g) in glacial acetic acid (10 ml). The solution was heated on a steam-bath for 30 hr. Mercurous acetate was filtered off, the filtrate diluted with water and treated with H_2S and filtered. The yellow filtrate was concentrated *in vacuo*, cooled and treated with hydrochloric acid (5 ml), when a yellow solid separated; it was collected, washed with cold water and crystallized from water as yellow needles (0·6 g), m.p. 288-9° (Found: C, 61·98; H, 4·80; N, 4·27. $C_{20}H_{16}O_4NCl.H_2O$ requires C, 61·93; H, 4·65; N, 3·61%); λ_{max}^{EtOH} 338 (sh), 314, 287, 264, 236 nm (log ε 4·14, 4·38, 4·47, 4·45, 4·14); NMR ($CDCl_3$-DMSO-d_6): δ 2·88 (3H, *s*, C—CH_3), 3·20 (2H, very broad singlet, Ar—CH_2), 4·78 (2H, very broad singlet, N—CH_2), 6·13 (2H, *s*, —O—CH_2—O—), 6·40 (2H, *s*, —O—CH_2—O—), 7·03, 7·32, 7·65, 7·78 (4H, all singlets, aromatic protons), 10·08 (1H, —CH=N, broad singlet) ppm. VII formed an iodide, m.p. 297-9° (from ethanol) (Found: C, 51·80; H, 3·60; N, 3·08. $C_{20}H_{16}O_4NI$ requires C, 52·06; H, 3·47; N, 3·04%), and a picrate, m.p. 233° (from methanol) (Found: C, 55·31; H, 3·31; N, 9·99. $C_{26}H_{18}O_{11}N_4$ requires C, 55·52; H, 3·20; N, 9·97%).

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