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# Studies in Protoberberine Alkaloids: Part II*—Structure of Isooxyberberine & Isooxyepiberberine

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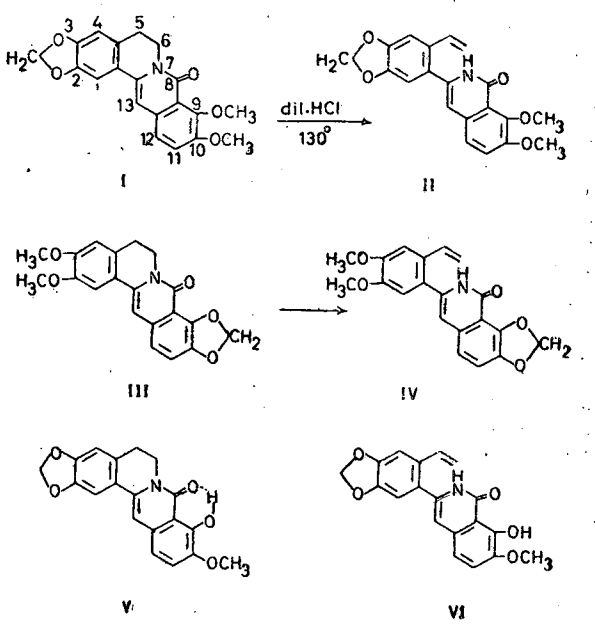
**Isooxyberberine reported to be formed by hot acid treatment of oxyberberine (I) is shown to have structure V arising from I by selective cleavage of one methoxyl group. Structure IV assigned previously to isooxyepiberberine, obtained from oxyepiberberine (III), has been corrected to VII; the conversion of 1,2-dihydro-2-methyl-7,8-methylenedioxy-1-oxo-isoquinoline (VIII), with part structure of III, to the corresponding 7,8-dihydroxy compound (IX) under acid conditions has been used as a model for assignment of structure VII.**

BLAND *et al.*[1] obtained a compound, $C_{20}H_{17}NO_5$, by heating oxyberberine (I) at 130° for 5 hr with dil. hydrochloric acid. They assigned structure II to this compound. Oxyepiberberine (III) upon heating at 150-60° with dil. hydrochloric acid was likewise converted to a high melting product which gave a green ferric reaction. This was assigned structure IV by Perkin[2].

Later Perkin *et al.*[3] revised the structure of isooxyberberine to V when they found that it was identical with methylnoroxyberberine, $C_{19}H_{15}NO_5$, of Faltis[4] and had only one methoxyl group. However, they reported that they could not reconvert V into oxyberberine (I) even by vigorous treatment with dimethyl sulphate and methyl alcoholic potassium hydroxide. Haworth and Perkin[5] in the course of one of their electrolytic reductions of oxyepiberberine to tetrahydroepiberberine, isolated isooxyepiberberine earlier obtained by Perkin[2] and on the basis of methoxyl estimation (2-$OCH_3$ groups) concluded that structure IV earlier suggested by Perkin for their substance "does not appear to require the modification which was necessary in the case of isooxyberberine". The authors suggested that in view of the similarities in properties between isooxyberberine and isooxyepiberberine, the structure of the former could not still be regarded as definitely settled; they were of the opinion that isooxyberberine may also be represented by structure VI.

Structures II and VI suggested for isooxyberberine as also structure IV for isooxyepiberberine seemed unlikely to us and we felt that the application of modern spectroscopic techniques should enable definite assignment of structures to these compounds.

Accordingly, we prepared isooxyberberine following Perkin's procedure from readily available berberine. The compound analysed correctly for




$C_{19}H_{15}NO_5$ and the molecular formula was confirmed by molecular weight determination by mass spectrometry (Found: mol. wt 337. $C_{19}H_{15}NO_5$ requires 337); methoxyl estimation by the Zeisel method confirmed the presence of one methoxyl (Found: $OCH_3$ 10·3. Calc. 9·8%). The UV spectrum was very similar to that of oxyberberine. In alcoholic sodium hydroxide solution there was a very slight shift towards the longer wavelength. A study of the NMR spectrum of isooxyberberine in comparison with oxyberberine was particularly instructive. In $CDCl_3$, the latter spectrum showed the following features: C-1, C-4, C-11, C-12 protons, two singlets at 6·7, 7·28 ppm for 2H each; C-13 proton, singlet at 7·20 ppm for 1H; -O-$CH_2$-O- protons, singlet at 6·0 ppm for 2H; C-6 protons,

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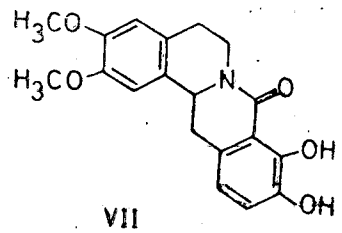
approximate triplet at 4·28 ppm for 2H; C-9-$OCH_3$, singlet at 4·02 ppm for 3H; $C_{10}$-$OCH_3$, singlet at 3·93 ppm for 3 H; and C-5 protons, approximate triplet at 2·85 ppm for 2H.

Isooxyberberine was insoluble in $CDCl_3$ or even in DMSO-$d_6$. However, its NMR spectrum could be run in trifluoracetic acid. Unexpectedly, except for 2 aromatic protons and the reference TMS, all other peaks were considerably broadened, besides exhibiting the usual solvent-caused downfield shifts. Nevertheless, the following assignments could be made with confidence: 3 aromatic protons, broad singlet at 7·8 ppm for 3H; 1 aromatic proton, singlet at 7·37 ppm for 1H; 1 aromatic proton, singlet at 6·88 ppm for 1H; -O-$CH_2$-O- protons, broad singlet at 6·10 ppm for 2H; C-6 protons, broad hump at 4·67 ppm for 2H; -$OCH_3$ protons, broad singlet at 4·17 ppm for 3H; and C-5 protons, broad hump at 3·17 ppm for 2H. These data leave no doubt that isooxyberberine does not have a vinyl group and that it is to be represented by structure V.

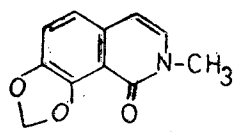
The phenolic hydroxyl in V is strongly chelated to the carbonyl group; accordingly, no hydroxyl peak is seen in the IR spectrum of isooxyberberine; the relatively small alkali-induced UV shift is also thus explained. Acetylation of isooxyberberine, according to the directions of Bland *et al.*[1], yielded an acetate whose IR spectrum showed clearly a band at 1760 $cm^{-1}$ for a phenolic acetate.

As a consequence of the chelation of the hydroxyl group with the C=O in V, V would be expected to be alkylated only under vigorous conditions. On refluxing isooxyberberine with anhydrous potassium carbonate, dry acetone and freshly distilled dimethyl sulphate for over 100 hr, oxyberberine was obtained in 37% yield. A possible reason for the selective ease of cleavage of one methoxyl group in oxyberberine under acid conditions is that the attachment of a proton to the methoxyl function at position 9 is facilitated by strong chelation to the lactam carbonyl group. Similar selective dealkylation of methoxyl group *peri* to a carbonyl function has been reported by Brossi *et al.*[6].

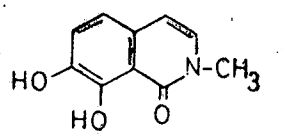
On the basis of analogy, the structure of isooxyepiberberine should be VII which fits in with its reported properties — presence of 2-methoxyls and green ferric colour reaction. Since we could not readily have sufficient quantity of epiberberine to prepare the oxy compound and then study its behaviour towards dil. hydrochloric acid, it was thought worth while to study the reaction on 1-oxo-2-methyl-1,2-dihydro-7,8-methylenedioxyisoquinoline (VIII) which has the part structure of III. VIII was obtained by the alkali-induced disproportionation of 2-methyl-7,8-methylenedioxyisoquinolinium iodide. Treatment of VIII with hydrochloric acid under conditions used for oxyepiberberine gave a crystalline product which analysed for $C_{10}H_9O_3N$ and gave a green ferric colour. Its NMR spectrum in DMSO did not have sharply defined peaks for any proton except those of reference TMS. Nevertheless, the singlet due to a -$OCH_2O$- group was definitely absent. Structure IX was thus established for the acid treatment product of VIII. Structure VII then follows by analogy for isooxyepiberberine.




VII




VIII




IX

It may be pointed out that this facile and selective cleavage of methoxyl and methylenedioxy groups in oxyberberine and oxyepiberberine gives access to phenolic compounds which can be further converted to partially methylated protoberberine alkaloids.

## Experimental Procedure

*Isooxyberberine* (V) — Oxyberberine[3] (I) (2 g) was heated at 150° for 5 hr with water (14 ml) and conc. hydrochloric acid (4 ml), during which the yellow colour changed to grey. The solid that separated was then collected and crystallized from glacial acetic acid (0·85 g), m.p. 245° [Found: C, 67·61; H, 4·85; N, 4·24; (O)$CH_3$, 10·26. $C_{19}H_{15}NO_5$ requires C, 67·66; H, 4·45; N, 4·15; (O)$CH_3$, 9·8%]. $\lambda_{max}^{EtOH}$ 260 (inflex.), 350, 375, 395 mμ (log ε 4·17, 4·27, 4·25, 4·17) [for oxoberberine, $\lambda_{max}^{EtOH}$ 255 (inflex.), 345, 370, 390 mμ (log ε 4·38, 4·65, 4·49, 4·32)].

*Isooxyberberine acetate* — A mixture of isooxyberberine (1 g), anhydrous sodium acetate (1 g) and acetic anhydride (10 ml) was boiled until a clear solution was obtained. After decomposing excess acetic anhydride with water, a bright yellow solid was obtained. This was collected, dried and crystallized from acetic acid containing acetic anhydride to give the acetate (0·35 g), m.p. 260-62° (IR: Ar-O-CO-$CH_3$ peak at 1760 $cm^{-1}$).

*Conversion of isooxyberberine into oxyberberine* — Isooxyberberine (V) (0·2 g) suspended in dry acetone (25 ml) containing dry potassium carbonate (1·8 g) and dimethyl sulphate (freshly washed with ice-cold water) (4 ml) was heated under reflux for 4 days. Acetone was removed *in vacuo*, the residue treated with water and extracted with chloroform. The chloroform extract was washed with water, dried ($Na_2SO_4$) and evaporated to give a residue, which crystallized from methanol to give oxyberberine (I) (75 mg), m.p. 200-202°, identical with an authentic sample (m.m.p. and comparison of IR spectra).

*2-Methyl-7,8-methylenedioxyisoquinolinium iodide* — A solution of 7,8-methylenedioxyisoquinoline[7] (3 g) in dry methanol (15 ml) containing methyl iodide (9 ml) was kept in the ice-chest for a day. Yellow crystals of the methiodide separated out, which were filtered and crystallized from methanol (2·9 g), m.p. 234-6° (Found: C, 41·95; H, 3·45; N, 4·53. $C_{11}H_{12}INO_2$ requires C, 41·65; H, 3·81; N, 4·42%).

*1,2-Dihydro-2-methyl-7,8-methylenedioxy-1-oxo-isoquinoline* (VIII) — The above methiodide (1 g) was dissolved in water (12 ml) and sodium hydroxide solution (40%; 20 ml) added. The resultant mixture was refluxed on a water-bath for 30 min. The oil which separated was extracted with chloroform, the solvent evaporated and the resulting brown gum purified by chromatography over silica using benzene for initial elution and benzene-methanol (100: 2) subsequently. The oxo compound crystallized out from benzene-hexane (200 mg), m.p. 154-7° (Found: C, 65·28; H, 4·56; N, 6·54. $C_{11}H_9NO_3$ requires C, 65·02; H, 4·46; N, 6·89%). NMR (in $CDCl_3$) $\delta$ 3·50 ($N\text{-}CH_3$; *s*), 6·20 ($\text{-}O\text{-}CH_2\text{-}O$; *s*), 6·35 (C-4H; *d*; $J = 7{\cdot}5$ cps), 6·85 (C-3H; $J = 7{\cdot}5$ cps), 6·95 (C-5H; *d*; $J = 8$ cps), 7·15 ppm (C-6H; *d*; $J = 8$ cps).

*1,2-Dihydro-7,8-dihydroxy-2-methyl-1-oxo-isoquinoline* (IX) — The above compound (0·2 g) was heated at 150° for 5 hr with water (14 ml) and conc. hydrochloric acid (5 ml). The brown solid separated was filtered and recrystallized from dil. acetic acid (75 mg); it did not melt up to 300° (Found: C, 62·30; H, 5·41; N, 6·72. $C_{10}H_9O_3N$ requires C, 62·84; H, 4·71; N, 7·25%).

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