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THE STRUCTURE OF HERNANDINE

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The aporphine **alkaloid, hernandine** was isolated from *Hernandia bivalvis* and given the structure 3-hydroxy-2,4-dimethoxy-5,6-methylenedioxy*nor*aporphine by Greenhalgh and Lahey(1). Later Phillips(2) synthesised 2,3,4-trimethoxy-5,6-methylenedioxyaporphine methiodide and found that it was not identical with O,N-dimethyl hernandine methiodide. This led to the re-examination of the structure of hernandine by the use of N.M.R. spectroscopy and on the basis of this work and further chemical degradation we now propose structure (Ia) for hernandine.

The Table shows the N.M.R. data for hernandine, O,N-dimethyl hernandine methiodide, bulbocapnine, o-methylbulbocapnine methiodide and ocoteine.

These data confirm the chemical evidence that hernandine is an aporphine with two methoxyl groups and one methylenedioxy group but without an N-methyl group. Two one proton doublets at τ3.85 and 4.06 (J 1.5 c/s) in the spectrum of hernandine, are similar to those found in the spectra of other aporphines having a methylenedioxy group in the 5-6 position.

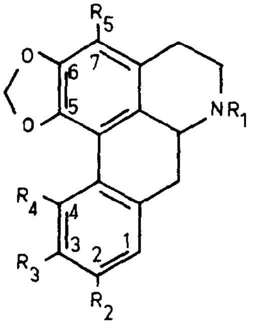
TABLE I

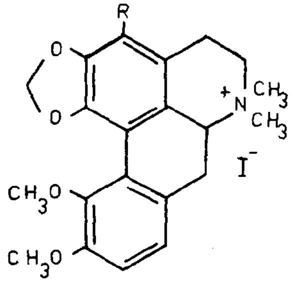
Chemical Shift Data (τ units) For Aporphine Alkaloids

Name	OCH_3				OCH_2O	Aromatic Protons			
	2	3	4	7	doublets	1	2	4	7
Hernandine (Ia)	-	-	6.35	5.90	3.85 4.06	3.03	3.03	-	-
O,N-Dimethyl hernandine methiodide (IIa)	-	6.13	6.21	5.87	3.83 3.97	2.88[a]		-	-
Bulbocapnine (Ib)	-	6.10	-	-	3.88 4.02	3.11	3.11	-	3.31
O-methylbulbocapnine methiodide (IIb)	-	6.10	6.18	-	3.84 3.97	2.86[b]		-	3.22
Ocoteine(5) (Ic)	6.13	6.13	-	6.07		3.27	-	2.43	-

a AB-quartet, $\Delta\nu$=19.6 c/s, J=8.3 c/s

b AB-quartet, $\Delta\nu$=17.7 c/s, J=9.0 c/s





	R_1	R_2	R_3	R_4	R_5
(Ia)	H	H	OH	OCH_3	OCH_3
(Ib)	CH_3	H	OCH_3	OH	H
(Ic)	CH_3	OCH_3	OCH_3	H	OCH_3

(IIa) R = OCH_3

(IIb) R = H

Of the three aromatic protons in the spectrum of bulbocapnine, the assignment of the highest signal at 3.31τ to the aromatic proton at position 7 has been firmly established in a paper by Baarschers, W.H. and co-workers(3). Also the absence of this aromatic proton signal in ocoteine, due to a methoxyl substituent at position 7 is in accordance with the structure of this alkaloid which has been established by synthesis(4).

From the Table it is seen that this aromatic signal at 3.31τ in the spectrum of bulbocapnine is absent in the spectrum of hernandine as well as in the spectrum of O,N-dimethylhernandine methiodide. This would suggest that the position 7 is occupied, in this case, by a methoxyl group. The τ value for this methoxyl group agrees well with the τ value for the methoxyl group at position 7 of the alkaloid ocoteine(5) (see Table I).

Similar τ values for the methoxyl group in position 7 of the aporphine alkaloids, cassythine, cassythidine(6), guatterine and atherospermidine(7) have been recorded in the recent literature.

The assignment of the methoxyl group to position 7 is confirmed by the isolation of isocotarnic acid characterized by the formation of the anhydride from alkaline potassium permanganate oxidation on hernandine. Isocotarnic acid is considered to be derived by the mono-decarboxylation of the intermediate, 4-methoxy-5,6-methylenedioxy hemi-mellitic acid. Tschesche, Welzel, Moll and Legler(8) also reported a similar decarboxylation in the permanganate oxidation of the O-ethyl derivative of N-methyl laurelliptine which yielded 4-ethoxy-3-methoxy-phthalic acid.

In the earlier paper it was suggested that in hernandine, position 3 carried the phenolic hydroxyl group by the observation that hernandine, unlike bulbocapnine which has a free para position to the phenolic group failed to give a colour test with Gibbs' reagent. This is confirmed by a consideration of the N.M.R. data in the Table. Goodwin, Schoolery and Johnson(9) have attributed the higher chemical shifts of methoxyl groups at positions 4 and 5 of the aporphine nucleus compared with those at 2,3,6 and 7 to the hindrance associated with positions 4 and 5 in the non-planar diphenyl system. The signal at 6.35τ in hernandine is therefore assigned to the methoxyl at position 4. This is in line with the observation that when the phenolic group at position 3 in hernandine is methylated, the expected normal τ value of 6.13 for this new methoxyl was obtained. Also the chemical shift difference between the methoxyls at positions 3 and 4 in O-methyl bulbocapnine methiodide is similar to the chemical shift difference between the methoxyls at positions 3 and 4 in O,N-dimethyl hernandine methiodide, each being 0.08τ units. Hernandine is thus 3-hydroxy-4,7-dimethoxy-5,6-methylenedioxy<u>nor</u>-aporphine (Ia).

Baarschers, W.H. and co-workers(3) reported that when the bottom ring of the aporphine alkaloid contains two methoxyl groups in positions 3 and 4, as in corydine and bulbocapnine methyl ether, a normal AB-type quartet was found for the protons in positions 1 and 2 centered at 2.99τ (J = 8.5 c/s for corydine and J = 8.3 c/s for bulbocapnine methyl ether).

A similar situation arises in O,N-dimethyl hernandine methiodide and O-methyl bulbocapnine methiodide, where symmetrical 4 line-AB patterns of the protons in positions 1 and 2 are observed, centered at 2.88τ (J = 8.3 c/s) and 2.86τ (J = 9.0 c/s) respectively, (see Table I). In hernandine, where the methoxyl group at position 3 is replaced by a hydroxyl group, no splitting is observed.

In the present work, we isolated hemipinic acid methylimide from alkaline potassium permanganate oxidation on O,N-dimethyl hernandine methiodide (IIa). Vernengo and co-workers(10) (1957) also reported the isolation of m-hemipinic acid methylimide from similar oxidation on ocoteine. In both cases, the formation of the methyl imide of the corresponding acids is rather difficult to explain.

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