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ALKALOIDS OF HERNANDIA OVIGERA: THE CHARACTERIZATION AND STRUCTURES OF FIVE NEW APORPHINE BASES

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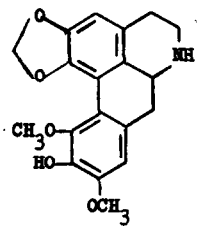
The genus Hernandia (Hernandiaceae) has been little investigated chemically. Thus far, the bisbenzylisoquinoline base chondodendrine has been said to be a constituent of Hernandia ovigera L.,[2] while the otherwise unreported aporphine base hernandine (I) has been found in H. bivalvis Benth.[3] We now wish to report the isolation and characterization of five new aporphines (II, III, VII, VIII and X) from the bark of H. ovigera.[4]

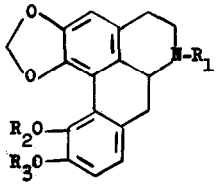
Nandigerine (II), $C_{18}H_{17}O_4N$, crystallized from methanol either as needles of the solvent-free base, m.p. 176-177°, $[\alpha]_D$ + 248° (EtOH), or as plates of the methanol solvate, $C_{18}H_{17}O_4N \cdot CH_3OH$, m.p. 99-100°; it was characterized also as the crystalline hydrochloride, $C_{18}H_{17}O_4N \cdot HCl$, m.p. 245-247° dec.[5] The ultraviolet spectrum of nandigerine [$\lambda_{max.}^{EtOH}$ 225 mμ (log ε4.40), 271 (4.13), 314 (3.74)] is consistent with its formulation as an 11-substituted aporphine[6]; its NMR spectrum revealed the presence

of three aromatic protons (6.84 - 6.61), one methylenedioxy group (close doublets at 6.01 and 5.82), one methoxyl (3.60) and the absence of an N-methyl function.

N-Methylation of nandigerine (catalytic reduction in the presence of formaldehyde) afforded the amorphous N-methylnandigerine (III), characterized as its crystalline hydrobromide, $C_{19}H_{19}O_4N \cdot HBr$, m.p. 243-245°dec., $[\alpha]_D$ +170°(H_2O); the NMR spectrum of III was essentially identical with that of II, except for a new peak at 2.53 attributable to the N-methyl group. N-Methylnandigerine was isolated also as a naturally occurring alkaloid from H. ovigera.



I

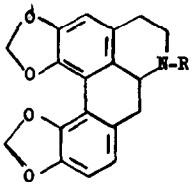


II: R_1=H, R_2=CH_3, R_3=H
III: R_1=CH_3, R_2=CH_3, R_3=H
IV: R_1=H, R_2=R_3=CH_3
V: R_1=CH_3, R_2=R_3=CH_3
VI: R_1=CH_3, R_2=H, R_3=CH_3

Both O-methylation (with CH_2N_2) of N-methylnandigerine and N-methylation (CH_2O-HCO_2H) of the amorphous O-methylnandigerine (IV, prepared from II and CH_2N_2) afforded O,N-dimethylnandigerine, m.p. 129-130°, $C_{20}H_{21}O_4N$, which was identical (mixed m.p., IR) with authentic bulbocapnine methyl ether (V). Since both thin layer chromatography and IR spectroscopy showed N-methylnandigerine to be different from bulbocapnine (VI), nandigerine must be assigned structure II.

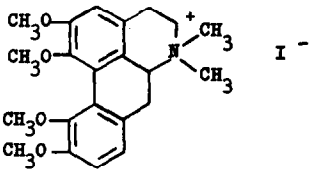
Ovigerine (VII) crystallized only as the hydrochloride, $C_{18}H_{15}O_4N \cdot HCl$, m.p. 300°dec., $[\alpha]_D$ + 177° (H_2O). Its ultraviolet spectrum [$\lambda_{max.}^{EtOH}$ 234 mμ (log ε 4.29), 270 (4.10), 317 (3.77)] was suggestive of a 1, 11-disubstituted aporphine structure. The NMR spectrum of the free base showed no signals characteristic of either N-methyl or methoxy, but complex signals characteristic of two superimposed methylenedioxy groups appeared (4 protons) centered at 5.88 and 6.01.

N-Methylation of ovigerine (CH_2O-HCO_2H) afforded amorphous N-methylovigerine (VIII), characterized both as the hydrobromide, $C_{19}H_{17}O_4N \cdot HBr$, m.p. 243-245°dec. and as the methiodide, $C_{19}H_{17}O_4N \cdot CH_3I$, m.p. 252-253° dec. N-Methylovigerine was isolated also as a naturally occurring alkaloid from H. ovigera.



VII: R=H

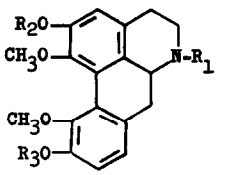
VIII: R=CH_3



IX

The orientation of the methylenedioxy groups in ovigerine was proven in the following manner. N-Methylovigerine was heated for 15 hours with phloroglucinol and aqueous sulfuric acid in order to effect hydrolysis of the methylenedioxy groups. Treatment of the resulting crude phenolic base with excess diazomethane, followed by methyl iodide, afforded crystalline 0,0-dimethylmagnoflorine iodide (IX), identical (mixed m.p., IR) with authentic IX from natural sources. Ovigerine must, therefore, be assigned structure VII.

Hernovine (X), $C_{18}H_{19}O_4N$, crystallized from methanol as very sparingly soluble plates, m.p. 234-236° dec.[7] Like nandigerine and ovigerine, hernovine had ultraviolet absorbtion [$\lambda_{max.}^{EtOH}$ 221 (log4.41), 272 (4.01), 306 (3.64)] characteristic of a 1,11-disubstituted aporphine. N-Methylation of hernovine (CH_2O-$NaBH_4$) gave the amorphous N-methylhernovine (XI), characterized as its crystalline hydrochloride, $C_{19}H_{21}O_4N \cdot HCl$, m.p. 245-247° dec. The NMR of N-methylhernovine revealed, in addition to the N-methyl group (2.55), two methoxyls at 3.43 and 3.50. O-Methylation of hernovine (with CH_2N_2) afforded the crystalline O,O-dimethylhernovine (XII), m.p. 174-175° confirming the presence of two phenolic hydroxyl groups in X. N-Methylation of O,O-dimethylhernovine, followed by treatment of the resulting N,O,O-trimethylhernovine with methyl iodide, gave O,O-dimethylmagnoflorine iodide (IX), identical (mixed m.p., IR) with material from natural sources.



X: R_1=R_2=R_3=H

XI: R_1=CH_3, R_2=R_3=H

XII: R_1=H, R_2=R_3=CH_3

The two methoxyls in hernovine are assumed to be at positions 1 and 11 of the aporphine system, since they appear in the NMR at quite high fileds (3.43 and 3.50 in XI), consistent only with a 1,11-dimethoxy-

aporphine formulation.[8] Hernovine must, therefore, be assigned structure X. A further confirmation of the structure of hernovine by total synthesis is in progress.

In addition to the five new aporphines described above, H. ovigera contains other alkaloids. These include the known compounds isocorydine and thalicarpine, as well as several new bases, the structures of which will be described in due course.

REFERENCES

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2. V. S. Sokolov, "Alkaloid Plants of the USSR," Akademiia Nauk Moscow, USSR (1952).

3. R. Greenhalgh and F. N. Lahey, "Heterocyclic Chemistry," Chemical Society (London), Butterworths, 1958, pp. 100-102.

4. These compounds were isolated via pH partition into fractions followed by chromatographic separations. Detailed procedures will be described in a subsequent publication.

5. All molecular formulae indicated in this paper were supported by acceptable elemental analyses. Melting points are uncorrected. All NMR spectra were run in $CDCl_3$, with $(CH_3)_4$ Si as standard; data are recorded in δ (delta) units.

6. A. W. Sangster and K. L. Stuart, Chem. Rev., 65, 69 (1965).

7. The NMR and $[\alpha]_D$ of this compound were not measured because of its low solubility.

8. W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach and B. Douglas, J. Chem. Soc., 4778 (1964).