Tetrahedron Vol. 27, pp 2639 to 2643. Pergamon Press 1971. Printed in Great Britain

DEHYDROOCOPODINE, DICENTRINONE, AND OTHER ALKALOIDS FROM *OCOTEA MACROPODA* AND *HERNANDIA JAMAICENSIS*

M. P. CAVA* and A. VENKATESWARLU

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

(*Received in USA* 2 *March* 1971; *Received in the UK for publication* 16 *March* 1971)

Abstract—The new aporphines dehydroocopodine (V) and dicentrinone (VI) have been isolated from *Ocotea macropoda*; eleven known alkaloids have been isolated from *Hernandia Jamaicensis*. The structures of the new alkaloids are based upon spectroscopic evidence, as well as on partial synthesis from closely related bases.

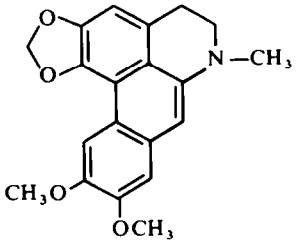
WE PREVIOUSLY reported the isolation of a number of new aporphine alkaloids from *Ocotea macropoda*. These include dehydrodicentrine (I),[1] ocopodine (II),[1] predicentrine (III)[2] and nordicentrine (IV).[2] We now describe the isolation and characterization of two additional new bases from this plant, namely dehydroocopodine (V) and dicentrinone (VI).

Dehydroocopodine (V). $C_{21}H_{21}NO_5$, crystallizes from ethanol as golden yellow plates, m.p. 113°, and is optically inactive. Its UV spectrum [λ_{max}^{EtOH} 220 mμ (log ε 4·37), 262 sh (4·65), 267 (4·66), 340 (4·50)] indicates a highly conjugated system similar to that of dehydrodicentrine (I).[1] Its NMR spectrum reveals an N-Me group (δ 3·07), three OMe's (4·02, 3·97 and 4·00), a methylenedioxy group (singlet at 6·15) and three unsplit aromatic protons (6·83, 6·89 and 8·26); the aromatic proton at low field and the deshielded N-Me group are typical of a C-11 proton and of the N-Me group of a dehydroaporphine.[1] Confirmation of the new base as dehydroocopodine (V) was obtained by preparing it (27% yield) from ocopodine (II) by mild permanganate oxidation.

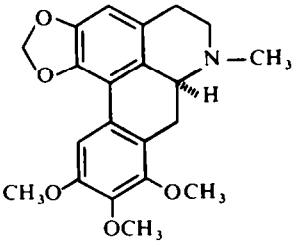
Dicentrinone (VI). $C_{19}H_{13}NO_3$, crystallizes from chloroform–ethanol as small, bright yellow needles, m.p. 300° (dec), and is optically inactive. Its UV spectrum [λ_{max}^{EtOH} 213 mμ (log ε 4·57), 250 (4·54), 272 (4·45), 310 sh (4·05), 352 (4·07), 396 (3·62), 433 (3·60)] and its IR spectrum (KBr, conjugated CO at 1650 cm^{-1}) are typical of those of oxoaporphines.[3] Its NMR spectrum in CF_3COOH reveals all thirteen protons as follows: two OMe's (δ 4·30 and 4·33), a methylenedioxy group (singlet at 6·85), three unsplit aromatic protons (7·75, 8·28 and 8·58, C-3, C-8 and C-9 respectively) and two adjacent aromatic protons (8·67 and 9·00, J = 7 Hz, C-4 and C-5 respectively). This data and the occurrence of dicentrine and related bases as companion alkaloids in the plant suggested that the new alkaloid was dicentrinone (VI). Confirmation of this structure was obtained by direct comparison of VI with the identical material obtained in low yield (2%) by the chromium trioxide oxidation of nordicentrine (VI).[3]

In continuation of the chemotaxonomic survey of the genus *Hernandia*, we have examined the bark of the Jamaican species *H. jamaicensis* and have isolated the

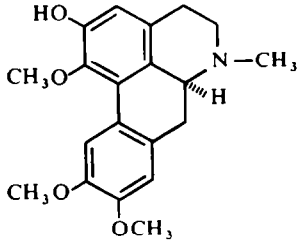
* To whom correspondence should be directed at the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104.



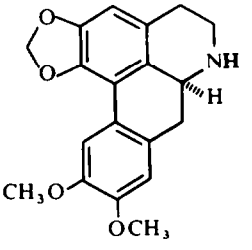
I



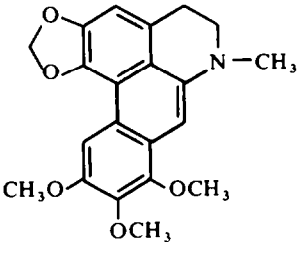
II



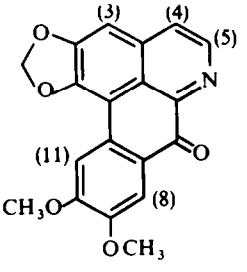
III



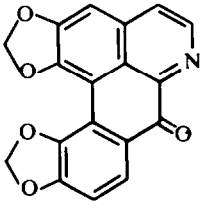
IV



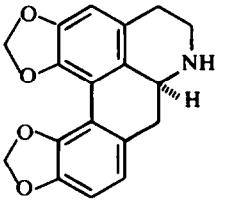
V



VI



VII



VIII

following known alkaloids, most of which were found earlier in the other Jamaican species, *H. catalpifolia*:[4] (+)-isocorydine, (+)-ovigerine, (+)-N-methylovigerine, (+)-O,O-dimethylcorytuberine, (+)-catalpifoline, (+)-reticuline, (+)-nandigerine, (+)-N-methylnandigerine, (+)-hernovine, and (+)-laurotetanine. In addition, *H. jamaicensis* contained an unreported non-phenolic, optically inactive base, $C_{18}H_9NO_5$, which crystallizes from chloroform-methanol as bright yellow needles, m.p. 298–300° (dec). Its UV spectrum [λ_{max}^{EtOH} 226 mμ (log ε 4·65), 255 sh (4·51), 267 (4·52), 300 sh (4·08), 368 (4·16), 433 (4·13)] and its conjugated CO IR band at 1650 cm^{-1} are very similar to those of the oxoaporphine dicentrinone. Its NMR spectrum (CF_3COOH) indicates the absence of any OMe, and the presence of two methylenedioxy groups (singlets at δ 6·58 and 6·36), as well as an unsplit aromatic proton (7·6, C-3) and two pairs of adjacent aromatic protons (8·5 and 8·75, J = 7 Hz, C-4 and C-5 respectively; 7·24 and 8·38, J = 8·5 Hz, C-9 and C-8 respectively). This data suggested that the compound should be assigned structure VII, confirmation of which was obtained by an independent synthesis of VII (24% yield) by light-induced oxidation (O_2 gas) of ovigerine (VIII) in t-butyl alcohol solution.[5] After the completion of our work, a report appeared describing the isolation of VII, named hernandonine, from a different species of *Hernandia* (*H. ovigera*).[6]

EXPERIMENTAL

All m.ps were determined in open tubes using a Thomas–Hoover Uni-melt apparatus and are uncorrected. Specific rotations were measured on a Perkin–Elmer Model 141 Polarimeter. UV and visible spectra were measured in 95% EtOH with a Perkin–Elmer Model 202 spectrophotometer. IR spectra were recorded in KBr with a Perkin–Elmer Model 137 spectrophotometer. The NMR spectra were obtained in $CDCl_3$ (unless otherwise noted), using a Varian A–60A instrument; chemical shifts are reported as ppm (δ) downfield from TMS. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Countercurrent separations were performed with a 200-tube, 10/10 ml, fully automatic Craig apparatus (Model B-3 of H.O. Post and Co., New York). The identity of all known alkaloids isolated was confirmed by direct comparison (IR, TLC, rotation) with authentic samples from our collection.

Isolation of dehydroocopodine (V) *and dicentrinone* (VI). A sample of residual tertiary bases from *Ocotea macropoda*[1,2] was chromatographed on a column of ten times its weight of silica gel; the column was eluted successively with C_6H_6–$CHCl_3$ (1:1), $CHCl_3$, and $CHCl_3$ containing from 2% to 40% of MeOH. The $CHCl_3$ fraction was purified by preparative TLC (2% MeOH in $CHCl_3$) to give, after several crystallizations from EtOH, yellow plates of *dehydroocopodine* (V), m.p. 113°. (Found: C, 68·51; H, 5·90; N, 4·06. Calc. for $C_{21}H_{21}NO_5$: C, 68·65; H, 5·76; N, 3·81).

The 10% MeOH in $CHCl_3$ fraction from the silica column afforded a residue which was purified by repeated $CHCl_3$ crystallization, Norite treatment (hot MeOH), and $CHCl_3$–EtOH crystallization to give yellow needles of *dicentrinone* (VI), m.p. 300° (dec). Dicentrinone formed a red soln in 6 N HCl and exhibited a green fluorescence in $CHCl_3$ soln. (Found: C, 68·23; H, 4·12; N, 3·98. Calc. for $C_{19}H_{13}NO_5$: C, 68·06; H, 3·91; N, 4·18). The alkaloid was identical (IR, TLC) with the ketoaporphine formed in 2% yield by CrO_3 oxidation of nordicentrine (IV).[3]

Permanganate oxidation of ocopodine (II). A soln of $KMnO_4$ (0·2 g) in pure acetone (25 ml) was added dropwise at room temp during 1 hr to a stirred soln of ocopodine (0·202 g) in pure acetone (15 ml). After 6 hr of additional stirring, the soln was filtered and evaporated. Purification of the product by silica chromatography (C_6H_6–$CHCl_3$ 1:2), and subsequent ether crystallization, afforded V (0·054 g, 27%), m.p. 94–97°. The recrystallized material was identical (IR, m.m.p., R_f) with the naturally derived alkaloid.

Oxydation of ovigerine (VIII). A slow stream of O_2 was passed through a soln of ovigerine (0·035 g) and t-BuOK (0·01 g) in t-BuOH (25 ml) at room temp for one day, during which time the mixture was irradiated by a 200-watt sun lamp. The usual work-up, followed by preparative TLC on silica (10% MeOH in $CHCl_3$) and crystallization from $CHCl_3$–MeOH, gave pure VII (0·009 g, 24%), identical (IR, m.m.p.) with the natural alkaloid.

Isolation of the tertiary bases of Hernandia jamaicensis. The bark of the tree *Hernandia jamaicensis* Britton and Harris was collected near Niagara, Jamaica, by one of the authors (M. P. Cava) in 1963 and verified botanically by Dr. C. D. Adams, Botany Department, University of the West Indies. A 2 kg sample of dried bark was extracted with alcohol. The concentrated extract was treated with ammonia and EtOAc, the organic phase was extracted with 5% H_2SO_4, and the tertiary bases (10·3 g) were recovered from the aqueous acid by basification with ammonia followed by $CHCl_3$ extraction. A later collection of bark furnished an additional 62 g of bases. A portion (57 g) of the crude bases was separated by 10% NaOH aq into alkali-insoluble bases (11·49 g, Fraction A) and alkali-soluble bases (32·8 g, Fraction B).

Constituents of fraction A from H. jamaicensis. Fraction A (11·49 g) was triturated with benzene–hexane 2:1 (60 ml) to give insoluble solid A_1 (2 g) and soluble portion A_2 (8·74 g). The $CHCl_3$ soluble portion of A_1 afforded on crystallization from C_6H_6–$CHCl_3$ followed by MeOH–$CHCl_3$, yellow needles of *hernandonine* (VII, 0·275 g), m.p. 298–300° (dec). Hernandonine formed a red soln in 6 N HCl and exhibited a green fluorescence in $CHCl_3$ solution. (Found: C, 67·68; H, 3·01; N, 4·42. Calc. for $C_{18}H_{19}NO_5$: C, 67·71; H, 2·84; N, 4·39).

Treatment of Fraction A_2 with dry HCl in EtOAc–Et_2O solution gave a ppt which, on crystallization from EtOH, afforded *ovigerine hydrochloride* (0·68 g), m.p. 298–300° (dec), $[\alpha]_D^{28}$ + 182° (*c*, 0·4; H_2O). The remaining bases from A_2 were chromatographed on a column of silica (120 g). The bases were eluted by pure $CHCl_3$ and by 5% MeOH in $CHCl_3$, fractions being combined on the bases of TLC behavior. Earlier $CHCl_3$ fractions gave, with HBr in EtOH, N-*methylovigerine hydrobromide* (0·018 g), m.p. 240–244° (dec), $[\alpha]_D^{28}$ + 161° (*c*, 0·4; MeOH). Later $CHCl_3$ fractions crystallized from EtOH to give *isocorydine* (0·73 g), m.p. 182–184° $[\alpha]_D^{26}$ +195·5° ($CHCl_3$). Earlier MeOH–$CHCl_3$ fractions gave, on reaction with (−)-tartaric acid in EtOH, O,O-*dimethylcorytuberine* (−)-*tartrate*, m.p. 226–227° (dec), $[\alpha]_D^{28}$ +147° (*c*, 0·7; H_2O). Later MeOH–$CHCl_3$ fractions contained mixtures of ovigerine and catalpifoline, separable by chromatography on neutral alumina ($CHCl_3$ and 2% MeOH in $CHCl_3$) to give catalpifoline hydrochloride (0·121 g), m.p. 267–268° (dec), further characterized as free catalpifoline, m.p. 173–175° $[\alpha]_D^{28}$ +225° (*c*, 0·8; MeOH).

Constituents of fraction B from H. jamaicensis. Fraction B (30 g) was dissolved in $CHCl_3$ (325 ml) and extracted exhaustively with McIlvain buffers of pH 6·4, 5·0, 4·0 and 2·2; only the bases from the pH 6·4 and 5·0 fractions (B_1 and B_2, respectively) were further investigated.

Fraction B_1 gave, by a combination of direct crystallization from EtOH and silica chromatography (10% MeOH in $CHCl_3$), *nandigerine* (6·2 g), m.p. 174–176°, $[\alpha]_D^{28}$ + 242·8° (*c*, 0·75; EtOH). Trituration of the residual bases with $CHCl_3$ gave (+)-*hernovine* (0·090 g), m.p. 243–245°. The remaining B_1 bases were chromatographed on silica, using $CHCl_3$ containing increasing amounts of MeOH (5% up to 50%) as eluant. The 5% MeOH fraction gave, with HBr in EtOH, N-*methylnandigerine hydrobromide* (0·15 g), m.p. 244–245° (dec), $[\alpha]_D^{28}$ + 165° (*c*, 0·4; H_2O); the free base formed a benzene-cyclohexane solvate (NMR analysis), m.p. 99–100°, which retained solvent even after vacuum drying at 60° for 3 days. The 20% MeOH fraction was rechromatographed to give amorphous (+)-*reticuline* (1·17 g), characterized by conversion to *reticuline perchlorate*, m.p. 204–206°, $[\alpha]_D^{28}$ + 84 (*c*, 0·5, EtOH). The > 20% MeOH fractions (1·33 g) gave, by a combination of crystallization and counter-current distribution (pH 5·8 McIlvain buffer and $CHCl_3$), the following: (a) (+)-*hernovine* (0·370 g); (b) (+)-*reticuline*, as its perchlorate (0·132 g); (c) amorphous (+)-*laurotetanine* (0·115 g). A portion of the latter was treated with CH_2O aq in MeOH, followed by $NaBH_4$ to give the N-Me derivative, isolated as the crystalline N-*methyllaurotetanine hydrobromide*, m.p. 226–227° (dec), $[\alpha]_D^{28}$ + 71·8° (*c*, 0·6, EtOH).

A portion of Fraction B_2 (8·99 g total) was separated chromatographically on silica in the usual manner to give only nandigerine, reticuline, and laurotetanine.

Acknowledgements—We thank the Smith, Kline and French Laboratories, Philadelphia, Pennsylvania, for generous financial support of this investigation. We are also grateful to Dr. K. L. Magnus, Chemistry Department, University of the West Indies, for help in obtaining a portion of the *H. jamaicensis* bark used in this work.

REFERENCES

[1] M. P. Cava, Y. Watanabe, K. Bessho, and M. J. Mitchell, *Tetrahedron Letters* 2437 (1968)

[2] M. P. Cava, Y. Watanabe, J. Kunitomo, K. Bessho, M. J. Mitchell, A. I. daRocha, B. Hwang, J. A. Weisbach, and B. Douglas, *Abstracts of Papers, The Second Natural Products Symposium* p. 3. Mona, Kingston, Jamaica, Jan. 2–5 (1968)

[3] M. P. Cava, K. V. Rao, B. Douglas, and J. A. Weisbach, *J. Org. Chem.* 33, 2443 (1968)

[4] M. P. Cava, K. Bessho, B. Douglas, S. Markey, and J. A. Weisbach, *Tetrahedron Letters* 4279 (1966)
[5] For a previous report of the use of this general oxidation procedure see M. P. Cava and D. R. Dalton, *J. Org. Chem.* **31**, 1281 (1966)
[6] K. Ito and H. Furukawa, *Tetrahedron Letters* 3023 (1970)