

CIMICIPHYTINE AND NORCIMICIPHYTINE -- NEW BISINDOLE ALKALOIDS
 FROM HAPLOPHYTON CIMICIDUM (APOCYANACEAE)

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Cimiciphytine and norcimiciphytine, two new lactonic indole alkaloids isolated from Haplophyton cimidum, have been assigned the aspidosperma-canthinone bisindole structures 3 and 4, respectively.

Haplophytine, the major alkaloid of Haplophyton cimidum, has been shown to have structure 1 in the form of its dihydrobromide,¹ whereas in the form of the free base it exists in the skeletally rearranged form 2.² We have subjected the alkali-soluble base residues from the isolation of haplophytine to pH-gradient countercurrent distribution, which has now enabled us to isolate the two new bisindole alkaloids cimiciphytine (3) and norcimiciphytine (4).

Cimiciphytine (3) crystallized from ethanol as small needles, mp 210-212°, $[\alpha]_D = -146^\circ$ (c = 0.1, CHCl₃). The mass spectrum of 3 indicated the composition C₃₇H₄₂N₄O₇, showing a weak molecular ion at m/e 654 (5%) and significant fragment ions at 636(100), 622(45), 595(25), 383(22), 367(25), 336(10), 324(12), 255(39), 172, 170(22) and 158, 159(10). The nmr spectrum of 3 (CDCl₃) revealed two N-methyl functions at δ 2.4 and 3.16 (s, 3 H each), two methoxyls at 3.18 and 3.57 (s, 3 H each), 2 vinyl protons at 5.54 (dd, J = 10,

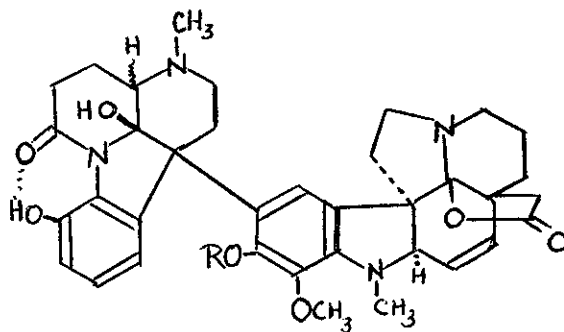
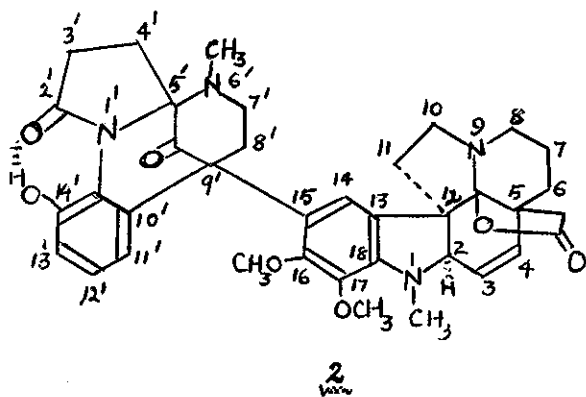
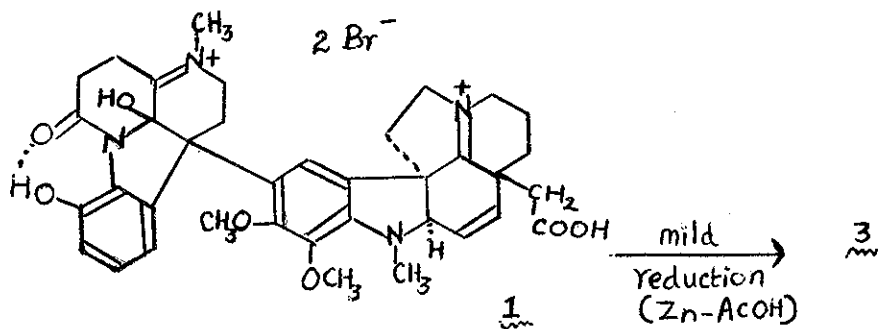
2 Hz, 1 H), 5.86 (dd, $J = 10, 2$ Hz) and four aromatic protons at 6.24 (dd, $J = 6, 2$ Hz, 1 H), 6.78--6.96 (m, 2 H) and 7.21 (s, 1 H). In addition two D_2O exchangeable protons were observed at δ 11.41 and 7.02. The infrared spectrum of cimiciphytine showed carbonyl absorptions at 5.70 (lactone $C=O$) and 6.14 μ (amide $C=O$). Its ultraviolet spectrum (ethanol) had maxima at 222 (ϵ 44,000) 270 (17,400) and 315 nm (2300). Controlled reduction of haplophytine with Zn-AcOH furnished cimiciphytine in 5% yield.

Norcimiciphytine (4) crystallized from ethanol as white needles, mp 240° (decomp.), $[\alpha]_D = -115^\circ$ ($c = 0.086$, $CHCl_3$). The mass spectrum of 4 indicated the composition $C_{36}H_{40}N_4O_7$, showing a weak molecular ion at m/e 640 (4%) and significant fragment ions at 622(100), 607(7), 581(8), 563(26), 507(8), 370(22), 354(10), 324(7), 255(36), 172(17), 170(28), 160(20), 159(15) and 158(10). The nmr spectrum of 4 ($CDCl_3$) showed 2 N-methyl functions at δ 2.42 and 3.13 (s, 3 H each), one methoxyl at 3.67 (s, 3 H), 2 vinyl protons at 5.50 (dd, $J = 10, 2$ Hz, 1 H) 5.90 (dd, $J = 10, 2$ Hz, 1 H) and four aromatic protons at 6.26 (dd, $J = 6, 2$ Hz, 1 H), 6.70--6.90 (m, 2 H) and 7.30 (s, 1 H). In addition a D_2O -exchangeable proton was observed at δ 11.40. The infrared spectrum of norcimiciphytine showed carbonyl absorptions at 5.72 (lactone $C=O$) and 6.15 μ (amide $C=O$). Its ultraviolet spectrum (ethanol) had maxima at 222 (ϵ 26,750) and 265 nm (ϵ 9604) exhibiting a bathochromic shift to 300 nm (ϵ 7721) upon addition of alkali. O-methylation of norcimiciphytine with diazomethane yielded cimiciphytine, indicating that the latter is a monomethyl ether of norcimiciphytine.

The assignment of structures 3 and 4 to cimiciphytine and norcimiciphytine, respectively is justified on the basis of their spectral and chemical properties. The ir band at 5.70μ in 3 and 4 is similar to that exhibited by their companion γ -lactonic alkaloids haplophytine, cimicine and cimicidine.^{2,3} The nmr spectrum of 3 is even more revealing and shows a remarkable similarity to that of haplophytine except for the presence of one extra exchangeable proton and the very low position of the downfield hydrogen-bonded phenolic proton. The formation of 3 (M^+ 654) from haplophytine (M^+ 652) in a mild reductive process in acid medium establishes 3 as a dihydro derivative of haplophytine arising from the reduction of the immonium system of the canthiphytine moiety of acid-salt form (1) of haplophytine. In accord with this interpretation, the downfield phenolic proton of 3 appears at δ 11.40, as expected for a phenol which is hydrogen-bonded to a δ -lactam carbonyl, in contrast to the value of δ 9.05 for the corresponding proton of haplophytine, in which hydrogen bonding to a γ -lactam carbonyl is involved.²

The non-hydrogen bonded phenolic hydroxyl of norcimiciphytine (4) must be placed at C_{16} rather than at C_{17} , since the nmr of 4 reveals the absence of a highly shielded C_{16} methoxyl analogous to those seen in the spectra of both cimiciphytine (3) and haplophytine (2).²

Cimiciphytine (3) and norcimiciphytine (4) thus represent a new type of bisindole system, which is closely related to the structurally unique haplophytine (2), but which contains an unrearranged canthiphytine unit.



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REFERENCES AND NOTES

1. I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, P. Yates, D. E. Zacharias, G. A. Jeffrey, B. Douglas, J. L. Kirkpatrick and J. A. Weisbach, J. Am. Chem. Soc., 1967, 89, 3061.
2. P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham and W. Zeiger, J. Am. Chem. Soc., 1973, 95, 7842.
3. M. P. Cava, M. V. Lakshmikantham, S. K. Talapatra, P. Yates, I. D. Rae, M. Rosenberger, A. G. Szabo, B. Douglas and J. A. Weisbach, Can. J. Chem., 1973, 51, 3102.

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