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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 cimicidum, have been assigned the aspidosperma-canthinone bisindole structures **3** and **4**, respectively.

Haplophytine, the major alkaloid of Haplophyton cimicidum, 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**).

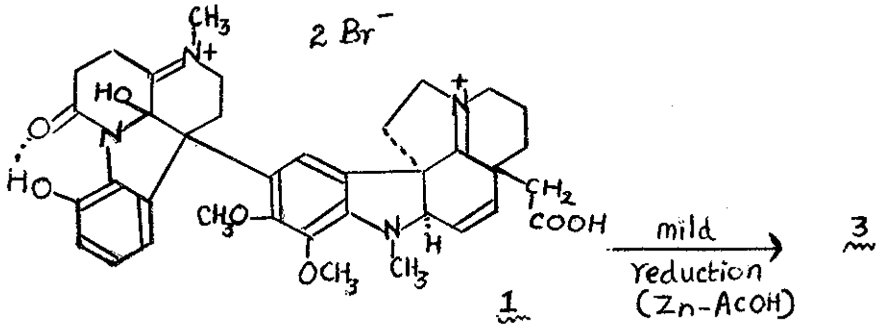
Cimiciphytine (**3**) crystallized from ethanol as small needles, mp 210-212°, $[\alpha]_D = -146^\circ$ (c = 0.1, $CHCl_3$). The mass spectrum of **3** indicated the composition $C_{37}H_{42}N_4O_7$, showing a weak molecular ion at m/e 654 (5%) and significant fragment ions at 636(100), 622(45), 595(25), 383(22), 367(25), 336(10), 324(12), 255(39), 172, 170(22) and 158, 159(10). The nmr spectrum of **3** ($CDCl_3$) 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 5.70 μ 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.


CH3
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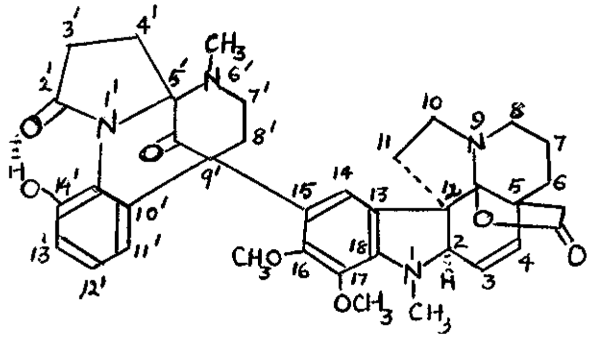
HO
O
N
HO
CH3O
OCH3
CH3
H
+
CH2
COOH
1
mild
reduction
(Zn-AcOH)
3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N
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14'
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10
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18
2
CH3O
16
17
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N
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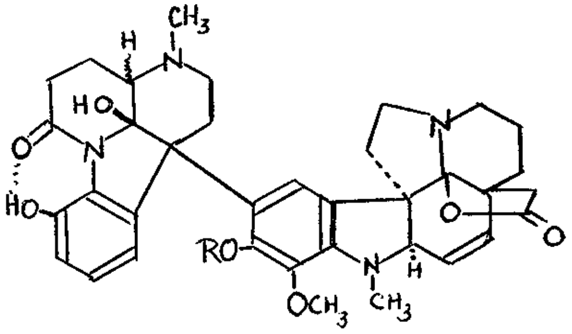
4
3
OCH3
CH3

2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H
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HO
O
N
HO
N
O
O
RO
N
H
OCH3
CH3

3 R= CH_3

4 R=H

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