NORISOHAPLOPHYTINE AND HAPLOCIDIPHYTINE - NEW BISINDOLE ALKALOIDS FROM HAPLOPHYTON CIMICIDUM (APOCYNACEAE)

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Abstract - Norisohaplophytine and haplocidiphytine, two new bisindole alkaloids from Haplophyton cimicidum (Apocynaceae) have been assigned the aspidosperma-canthinone structures 1 and 2 respectively.

In continuation of our study[1-5] of alkaloids from Haplophyton cimicidum (Apocynaceae), we have isolated and determined the structures of two new bisindole alkaloids norisohaplophytine (1) and haplocidiphytine (2). These compounds were obtained by subjecting the alkali-soluble base residue from isolation of haplophytine (3) to repeated pH-gradient countercurrent distruibution[4,5]. Norisohaplophytine (1) crystallized from ethanol as small needles m.p. 291° (decomp.), $[\alpha]_D^{20} = +111.8°$ (C = 0.543 in $CHCl_3$). Its high resolution mass spectrum indicated the molecular composition $C_{36}H_{38}N_4O_7$ as shown by the presence of a weak (2%) molecular ion at m/z 638. The mass spectrum also showed significant ions at m/e 610 ($C_{35}H_{38}N_4O_6$, M^+-CO, 21%), 579 (21), 566 ($C_{34}H_{38}N_4O_4$, M^+ -CO, CO_2, 9), 554 (100), 551 (75), 494 (29), 367 (10), 305 (7), 172 ($C_{12}H_{14}N$, 13), 170 ($C_{12}H_{12}N$, 16) and 158 (4). The nmr spectrum of 1 revealed one aliphatic N-methyl at δ 2.43 (s, 3H), two methoxyls at 3.03 and 3.69 (s, 3H each), two vinyl protons at 5.51 (s, 2H) and four aromatic protons at 6.26 (dd, J = 8, 1Hz, 1H), 6.92 (dd, J = 8, 1Hz, 1H), 7.04 (s, 1H) and 7.06 (t, J = 8Hz, 1H). A singlet (1H) which disappeared upon addition of D_2O was observed at δ 8.95. The KBr infrared spectrum of norisohaplophytine exhibited a sharp absorption at 3344 cm^{-1} as well as carbonyl absorptions at 1742 and 1658 cm^{-1}. Its ultraviolet spectrum (ethanol) exhibited maxima at 230 (ε 15,100), 255 (ε 11,000) and 290 nm (ε 5,900). The band at 260 nm underwent a bathochromic shift to 305 (ε 7,500) upon addition of NaOH, indicating the presence of phenolic function in 1.

The spectral properties of norisohaplophytine are reminiscent of those of haplophytine[1] (3). The mass spectrum of 1 is very similar to that of haplophytine, but displaced downward by 14 mass units in the upper regions thus indicating that 1 has one methyl group less than haplophytine. The ^1H-nmr of 1 is very similar to the nmr of haplophytine except for the absence of an aromatic N-methyl and the occurrence of the two vinyl protons as a singlet at δ 5.51. The nature of the vinyl protons' signal indicated that 1 has a 6,7-douple bond[5] and not a 3,4-double bond as in haplophytine.

The mass and ^{1}H-nmr spectra of 1 thus strongly indicated that 1 is norisohaplophytine. The ^{13}C nmr of 1 (Table 1) supports the assigned structure. The two aromatic methoxyls are observed at δ 58.4 and 59.4 while the aliphatic N-methyl is observed at δ 36.4. The remaining signals are assigned as shown in Table 1.

Reaction of 1 (3 mg) in methanol with excess ethereal diazomethane gave the 14'-methyl ether (3 mg) as a gum which exhibited the following ^{1}H-nmr spectra data in $CDCl_3$ δ 2.45 (s, 3H, N(6') - CH_3), 3.14 (s, 3H, 16 -OCH_3), 3.66 (s, 3H, 17 - OCH_3), 3.94 (s, 3H, 14' - OCH_3), 5.49 (s, 2H), 6.24 (d, J = 8Hz, 1H), 6.85 (d, J = 8Hz, 1H), 7.04 (s, 1H) and 7.07 (t, J = 8Hz, 1H). Catalytic hydrogenation of norisohaplophytine (7 mg) gave the tetrahydro derivative formed by hydrogenolysis of the carbinolamine lactone and the saturation of the double bond. When the tetrahydro derivative was reacted in methanol with excess ethereal diazomethane it gave the expected 14'-methyl ether of tetrahydronorisohaplophytine methyl ester (4 mg, m.p. 277-279°), which after purification on tlc showed the following spectral data: ^{1}H-nmr ($CDCl_3$) δ 2.48 (s, 3H, N (6') - CH_3), 3.10 (s, 3H, 16-OCH_3), 3.56 (s, 3H, - CO-OCH_3), 3.69 (s, 3H, 17 - OCH_3), 3.95 (s, 3H, 14' - OCH_3), 6.25 (d, J = 8Hz, 1H), 6.86 (s, 1H), 6.87 (d, J = 8Hz, 1H), 7.08 (t, J = 8Hz, 1H); mass spectrum (rel. intensity) 670 (M^+, 6%), 642 (M^+-28, 89), 639 (M^+-31, 5), 627 (14), 611 (5), 569 (45), 321 (25), 168 (82) and 149 (100).

Haplocidiphytine (2), $C_{37}H_{38}N_4O_8$ (by high-resolution mass spectrometry) crystallized from ethanol as small needles, m.p. 334° (decomp.), $[\alpha]_D^{20}$ = 91.5° (C = 0.55 in $CHCl_3$). Haplocidiphytine exhibited the following spectral data λ_{max}^{EtOH} 235 (ε 32,900), 265 (ε 20,900) and 290 (infl. ε 7,000), γ_{max}^{KBr} 3344, 1742 (lactone C = O) and 1639 cm^{-1} (lactam C = O); δ $CDCl_3$) 1.30 (t, J = 7Hz, 3H), 3.00 (s, 3H), 5.64 (s, 2H), 6.18 (dd, J = 8, 1Hz, 1H), 6.94 (dd, J = 8, 1Hz, 1H), 6.94 (dd, J = 8, 1Hz, 1H), 6.99 (S, 1H), 7.04 (t, J = 8Hz, 1H) and two D_2O exchangeable signals at 8.97 (s, 1H) and 10.25 (s, 1H); m.s. (relative intensity) 666 ($C_{37}H_{38}N_4O_8$, M^+, 6%), 638 ($C_{36}H_{38}N_4O_7$, M^+ - CO, 100), 622 ($C_{36}H_{38}N_4O_6$, M^+ - CO_2, 7), 607 ($C_{35}H_{35}N_4O_6$, M^+ - CO_2 - CH_3, 44), 594 ($C_{35}H_{38}N_4O_5$, M^+ - CO - CO_2, 19), 579 (19), 551 (24), 172 ($C_{12}H_{14}N$, 17), 170 ($C_{12}H_{12}N$, 12) and 134.

The spectral data of haplocidiphytine were indicative of the assigned structure (2). The ^{1}H nmr of haplocidiphytine clearly defined the aromatic portions of the molecule showing signals for the single aromatic proton on the aspidosperma portion, the three adjacent aromatic protons on the rearranged canthinone portion and a shielded aromatic methoxyl (16 - OMe). The presence of the signal at δ 1.30 (t, 3H) and the D_2O exchangeable signal at 10.25 (s, 1H) indicated the presence of a 17-hydroxyl group that is hydrogen-bonded to the carbonyl function of a N(1)-propionyl group as in cimilophytine[5] and cimicine[3]. The signal at 5.64 (s, 2H) showed that the aspidosperma portion of

haplocidiphytine has a 6,7-double bond as in cimilophytine[5]. The aspidosperma portion of haplocidiphytine is thus similar to the aspidosperma portion of cimilophytine[5]. The occurrence of the second downfield phenolic proton of haplocidiphytine at δ 8.97 instead of at about δ 11.40 indicated[4] that the compound had a rearranged canthiphytine unit as in haplophytine[1] and not an unrearranged canthiphytine unit as in cimiciphytine[4] or cimilophytine[5].

The ^{1}H nmr of 2 had no signal attributable to an aliphatic N-methyl thus indicating that haplocidiphytine lacked an N(6') - methyl group.

The ^{13}C nmr spectrum of haplocidiphytine with 37 distinct signals (Table 1) is in agreement with the assigned structure (2) and confirmed that haplocidiphytine has a rearranged canthiphytine unit as in haplophytine (3). The 16'-carbonyl carbon was observed at δ 197.0 (s) analogous to that (197.2) shown[1] by haplophytine. The remaining three carbonyl groups in 2 were observed at δ 175.5, 174.9 and 172.9. The CH_3 of the N-propionyl function was easily recognisable at δ 9.5. The other signals can be assigned as shown in Table 1.

Catalytic hydrogenation of haplocidiphytine (5 mg) gave the tetrahydro derivative which on methylation in methanol with excess ethereal diazomethane followed by purification on tlc gave the 14'-methyl ether of tetrahydrohaplocidiphytine methyl ester (5, 3 mg, m.p. 259-60°). 5 exhibited the following spectral data: δ ($CDCl_3$) 1.27 (t, J = 7Hz, 3H), 3.07 (s, 3H, 16 - OCH_3), 3.57 (s, 3H, -CO-OCH_3), 3.96 (s, 3H, 14' - OCH_3), 6.18 (d, J = 8Hz, 1H), 6.79 (s, 1H), 6.88 (d, J = 8Hz, 1H), 7.07 (t, J = 8Hz, 1H) and a D_2O exchangeable signal at 10.56 (s, 1H, 17 - OH); m/z (relative intensity), 698 (M^+, 19), 684 (71), 670 (M^+-28, 90), 656 (31), 639 (17), 625 (17), 597 (46), 307 22), 168 (100) and 149 (56). The stereochemistry of 1 and 2 has been put forward as shown by analogy with all other related indole alkaloids having the canthinone-aspidosperma units that have been isolated from Haplophyton cimicidum[1-5].

Norisohaplophytine and haplocidiphytine thus represent new types of bisindole alkaloids. Norisohaplophytine is derived by coupling of a rearranged canthiphytine unit with a norisoaspidophytine unit and haplocidiphytine is derived by the coupling of a rearranged norcanthiphytine unit with a dehydrocimicidine unit.

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Table 1. The ^{13}C nmr chemical shifts of norisohaplophytine (1) and haplocidiphytine (2)[a].

Carbon[b]	1	2	Carbon[b]	1	2
2	64.9(d)	67.6(d)	2'	175.0(s)	174.9(s)
3,4	21.4(t), 34.6(t)	27.3(t), 34.0(t)	3'	38.4(t)	39.2(t)
5	41.3(s)	41.3(s)	4'	22.3(t)	21.4(t)
6,7	129.1(d), 130.0(d)	\25.2(d), 133.0(d)	5'	87.4(s)	83.7(s)
8, 10, 20	43.2(t), 47.4(t), 48.7(t)	40.4(t), 43.3(t), 46.5(t)	7'	47.8(t)	47.5(t)
11	34.6	46.5(t), 34.5(t)	8'	29.7(t)	29.4(t)
12	58.2(s)	56.6(s)	9'	55.0(s)	56.4(s)
13	125.3(s)	130.5(s)	10'	124.6(s)	125.6(s)
14	118.6(d)[d]	112.4(d)	11'	127.9(d)	127.9(d)
15	124.0(s)	128.3(s)	12', 13'	117.9(d), 118.6(d)[d]	118.6(d), 118.7(d)
16	150.4(s)	149.4(s)	14', 15'	138.3[e](s)	138.0(s), 141.1(s)
17	144.2(s)	133.4(s)	16'	197.3(s)	197.0(s)
18	149.0(s)	147.6(s)	N(6')CH_3	36.4(q)	
19	106.3(s)	104.7(s)			
21	175.5(s)	175.5(s)			
22		172.9(s)			
23		28.6(t)			
24		9.5(q)			
OCH_3	58.4(q), 59.4(q)	58.3(q)			

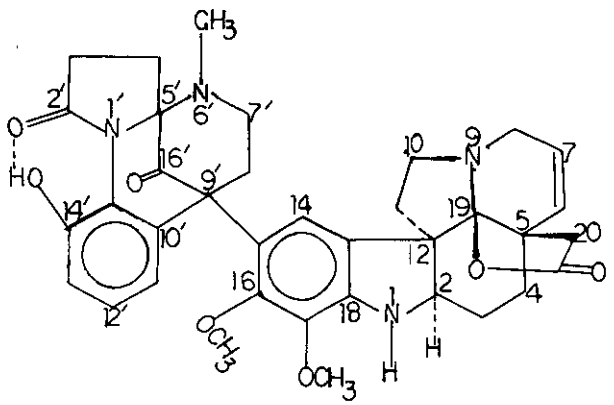
a. The ^{13}C nmr spectra were recorded in $CDCl_3$ solution on a Bruker W. M. 250 fourier transform spectrometer.

b. See structures 1 and 2 for the numbering system.

c. Chemical shifts in Table 1 were measured with respect to [^2H] $CDCl_3$ (77.00 ppm) and are given with respect to $(CH_3)^4Si$ (0 ppm).

d, e. Superimposed signals.

1



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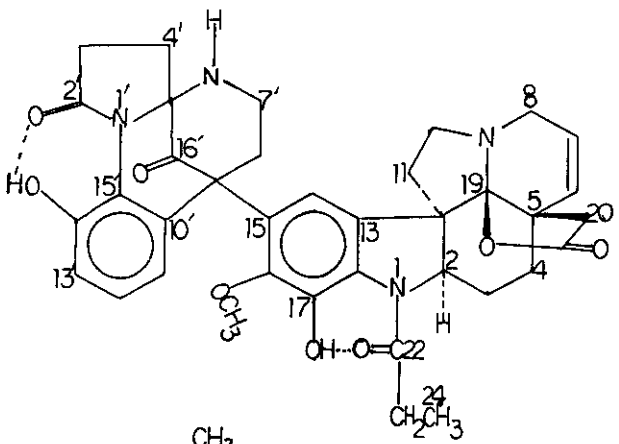

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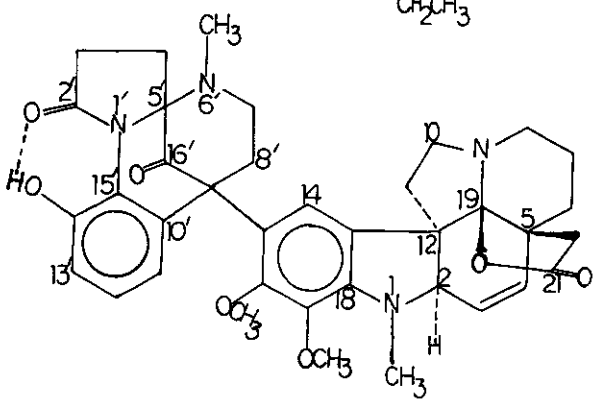

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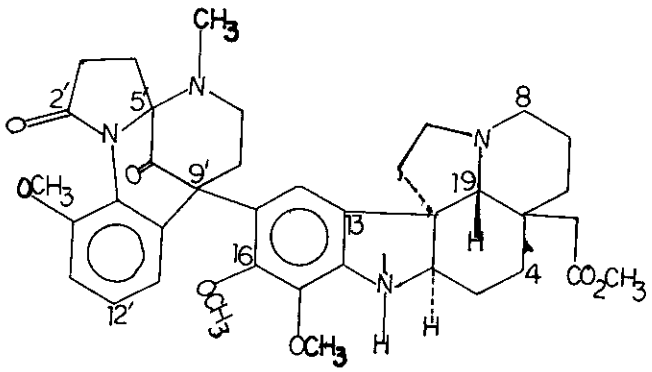

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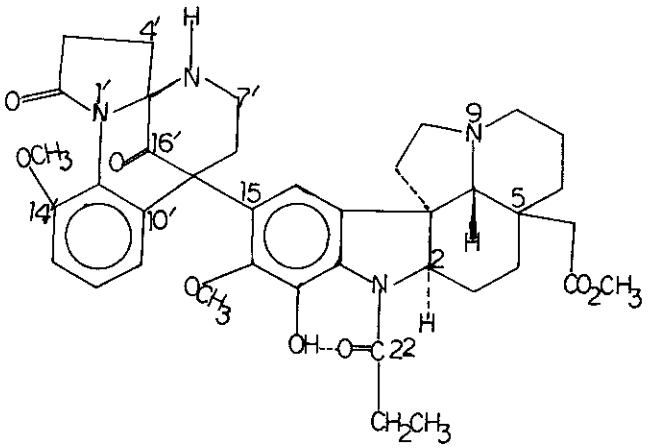

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