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NEW SEMIDIMERIC ALKALOIDS FROM *STRYCHNOS DALE*

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Summary: Two new alkaloids from the leaves of *Strychnos dale* have been assigned the structures 10,10'-dimethoxy-3S,17S-Z-tetrahydrousambarensine and 10,10'-dimethoxy-N_4,-methyl-3S,-17S-Z-tetrahydrousambarensine.

From the leaves of *Strychnos dale* De Wild (1,2) the two major alkaloids were isolated. Both alkaloids had similar UV-spectra with maxima at 227, 280, 290, 296 and 308 nm which is typical for a 10-methoxy-indole chromophore. The mass spectra showed molecular weights of 496 and 510, a difference of one methyl group. The major fragments at m/z 199, 215, 249, 250, 251 and 252 as well as the molecular weights point to a semidimeric-type alkaloid of the tetrahydrousambarensine-cinchophylline type (3,4).

The ^{1}HNMR spectrum showed the presence of two O-methyl groups (Table 1) in both alkaloids. One of the alkaloids also had a three proton singlet at 2.46 ppm, attributable to a N-methyl group. The aromatic region of the ^{1}HNMR was similar to that of the cinchophylline-type of alkaloids (4), which also have 10-methoxy groups. Both alkaloids had an one-proton quartet at 5.36 ppm which coupled with a three proton doublet at 1.67 ppm, typical for a 19,20 double bond. The alkaloids are thus of the tetrahydrousambarensine type. To determine the stereochemistry at C-3 and C-17 a more detailed study was made of the ^{1}HNMR spectrum. The 10,10'-dimethoxy-tetrahydrousambarensine type of alkaloid (1) did show only one aliphatic signal downfield of 4 ppm, assigned to H-17, as it is a broad doublet at 4.15 ppm (see Table 1) (4,5). The N-methyl derivative (2) did not show any aliphatic proton downfield from 4 ppm. It was thus concluded that H-3 is upfield from 4.00 ppm. This does not comply with the known 3S (H3-α) tetrahydrousambarensine alkaloids which have H-3 at 4.2-4.3 ppm (5,6), due to the deshielding of this proton in the 3α-cis conformation of the C/D quinolizidine ring system (7). It was concluded that either a 3α- or a 3β-trans quinolizidine system is present, which have H-3 upfield from 4.00 ppm (7,8,9). The shifts observed for C-3 and C-6 in the ^{13}CNMR of 1 and 2 (59.5 and 21.6 ppm respectively) are also in accordance with a trans conformation (see Table 2) (10,11,12,13,14). The presence of Bohlman bands in the IR-spectrum (2840, 2800, 2760 cm^{-1}) further support this stereochemistry (7). It thus leaves only to establish the configuration at C-3. From the CD spectrum [(1) (λ,$\Delta\varepsilon$) 308 (-1.6), 303 (0), 280 (+15), 245 (0), 235 (-7.0), 229 (0)] (4,15), which was similar to that of 3S,17S cinchophylline, it was learned that both C-3 and C-17 have the S-configuration. The ^{13}CNMR was indeed similar to that of 3S,17S-cinchophylline (see Table 2) and clearly different from that of 3S,17S-tetrahydrousambarenine (5).

The isolated alkaloids are thus concluded to have a 3S configuration and a 3α-trans conformation of the quinolizidine ring system. This is different from the usual conformation of the usambarensine type of alkaloids, which all have a 3α-cis conformation. The 3α-trans conformation is only found for the alkaloids with a saturated 19,20 double bond (nigritanines, usambarines, ochrolifuanines) (6,16,17,18,19,20) or with a 18,19 double bond (cinchophyllines) (3,4). The difference in the conformation was thus thought to be due to a difference in the stereochemistry of the 19,20 double bond, e.g. instead of the E-configuration a Z-configuration. A different stereochemistry at C-15 is not likely due to biosynthetic reasons. The configuration of the usambarensine-type alkaloids at C-19 is known from X-ray crystallography of usambarensine to be E (21). By chemical conversions the other usambarensine type of alkaloids has been proved to have the same stereochemistry. By using 2D NMR techniques (COSY and NOESY) the spectra of the two alkaloids could be assigned completely (see Table 1) and interactions between the various protons be determined. For alkaloid 2 a NOE could be observed for H-18 and H-21, whereas no clear NOE's were observed for H-19, other than with H-18. For alkaloid 1 clear cross peaks could be observed for H-18 and H-21 and for H-19 with H-16 and H-17. A NOE difference experiment with 1 further proved the interaction of H-19 with H-16 and H-17 (see Fig. 1). A Z-configuration of the alkaloids 1 and 2 is thus firmly established. Similar to the sitsirikine type of alkaloids the tetrahydrousambarensine type of alkaloids also occur with E and Z configuration at C-19 (9). The alkaloids 1 and 2 are thus identified as 10,10'-dimethoxy-3S, 17S-Z-tetrahydrousambarensine and 10,10'-dimethoxy-N_4'-methyl-3S,17S-Z-tetrahydrousambarensine.

In the isositsirikine series a similar change of conformation is observed under the influence of the configuration of the 19,20 double bond (9). The E-configuration leads to a cis conformation, due to an interaction of C-18 with the C-15 side chain, the Z-configuration leads to a trans conformation which allows the C-15 side chain to be in equatorial position. A similar explanation applies also for the usambarensine type of alkaloids. The shift of H-19, 5.35-5.37 ppm, is more upfield in the Z-form of the usambarensines than in the E-form (5.4-5.5 ppm), which also parallels the situation for the isositsirikines (Z: 5.36-5.48 ppm, E: 5.52-5.64 ppm) (9) and deplancheine (Z: 5.4 ppm, E: 5.5 ppm) (22).

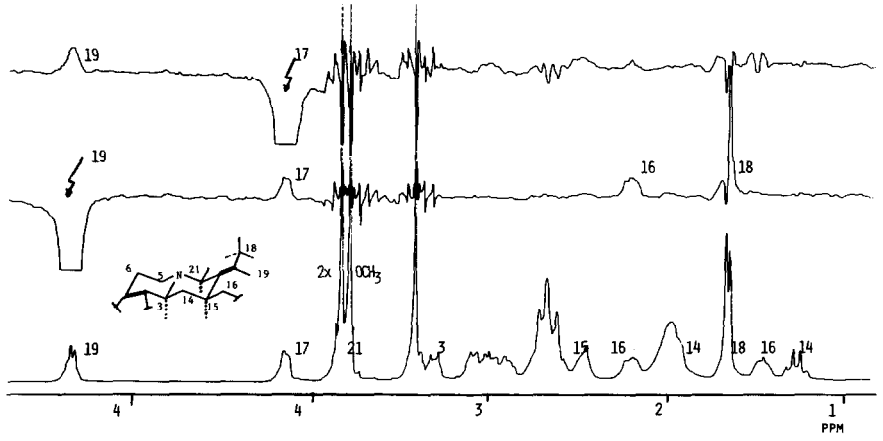


Fig. 1 NOE-difference spectra of 10,10'-dimethoxy-3α,17α-Z-tetrahydrousambarensine (300 MHz, $CDCl_3$)

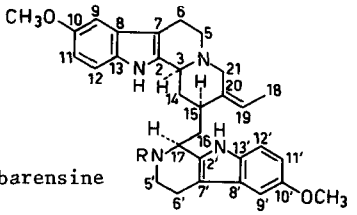
TABLE 1: ^{1}H-NMR data of 10,10'-dimethoxy-Z-tetrahydrousambarensine (1) and 10,10'-dimethoxy-$-N_4$,-methyl-Z-tetrahydrousambarensine (2) ($CDCl_3$, 300 MHz, TMS = 0 ppm).

1			2		
δ in ppm	J (Hz)	H no.	δ in ppm	J (Hz)	H nr.
8.29	brs	NH	7.92	brs	NH
8.17	brs	NH	7.78	brs	NH
7.18	d, 8.7	12'	7.17	d, 8.7	12'
7.03	d, 8.7	12	7.01	d, 2.4	9'
6.95	d, 2.4	9'	6.93	d, 8.6	12
6.86	d, 2.4	9	6.84	dd, 8.6, 2.4	11'
6.81	dd, 8.7, 2.4	11'	6.82	d, 2.5	9
6.71	dd, 8.7, 2.4	11	6.71	dd, 8.7, 2.5	11
5.37	q, 6.2	19	5.35	q, 6.7	19
4.15	bd, 7.8	17	3.91	s	10'-OCH_3
3.86	s	10'-OCH_3	3.82	d	21β
3.88	d	21β	3.81	s	10-OCH_3
3.81	s	10-OCH_3	3.72	m	17
3.45	bd, 12	3	3.28	bd, 12	3
3.35	ddd, 13, 6, 4	5'β	3.20	m	5'β
3.15	m	5β	3.05	m	5β
3.05	ddd, 13, 8, 5	5'α	2.85	m	6β,5'α,6',6'
2.95	m	6β	2.65	brd, 13	21α
2.7	m	5α,6α,6',6',21α	2.60	m	5α,6α
2.50	brm	15	2.55	m	15
2.25	ddd, 14, 7.8, 3	16	2.49	s	N-CH_3
1.95	ddd, 12, 2, 2	14α	2.35	m	16
1.70	d, 6.2	18	1.72	d, 6.7	18
1.48	ddd, 14, 9, 5	16	1.65	ddd, 14, 8.5, 5.5	16
1.30	ddd, 12, 12, 12	14β	1.50	m	14α
			1.00	ddd, 12, 12, 12	14β

TABEL 2: ^{13}C NMR spectral data (δ in ppm, $CDCl_3$) on some 3α-cis, 3α-trans, 3β-cis and 3β-trans indole alkaloids (1 = 10,10'-dimethoxy-3S,17S-Z-tetrahydrousambarensine; 2 = 10,10'-dimethoxy-N_4,-methyl-3S,17S-Z-tetrahydrousambarensine; 3 = 3S,17S-E-tetrahydrousambarensine (5); 4 = 3S,17S-cinchophylline (4); 5 = 3-epi-E-dihydrousambarensine (6); 6 = pseudoyohimbine (10).

Carbon no.	1	2	3	4[x]	5	6	Carbon no.	1	2	3	4	5
2	131.4	131.1	136.0	132.6	135.7	134.0	2'	130.9	130.9	137.5	132.3	125.7
3	59.6	59.5	53.3	60.4	55.2	53.7	5'	42.6	49.9	42.1	42.5	48
5	51.9	52.5	51.3	53.3	52.3	50.7	6'	22.4	19.7	22.4	23.4	19.4
6	21.6	21.6	18.3	22.6	21.9	16.4	7'	106.9	107.1	106.9	107.6	117.8
7	108.2	108.2	108.2	108.3	108.2	105.9	8'	127.3	127.2	127.4	128.6	127.4
8	127.7	127.4	127.4	128.8	129.0	127.2	9'	100.3	100.0	117.8	100.8	118.1
9	100.3	100.3	117.8	100.8	119.1	117.2	10'	153.5	153.6	121.4	154.4	124.9
10	153.8	153.9	121.4	154.4	121.3	118.1	11'	111.5	111.9	119.2	112.1	120.3
11	111.7	111.5	119.2	112.1	120.3	120.1	12'	111.1	111.3	111.3	110.9	112.3
12	110.8	110.6	111.3	110.9	111.1	111.1	13'	135.6	137.7	136.1	139.4	136.5
13	136.9	136.4	136.5	137.4	137.3	135.5						
14	37.9	37.1	33.3	38.3	34.2	32.2	Carbon					
15	36.6	33.8	30.9	38.3	32.6	32.4	no.	1	2	3	4	5 6
16	37.9	35.8	37.8	40.6	38.1	52.4						
17	51.1	58.1	51.3	53.3	160.9	66.6	NMe		42.3			
18	13.0	13.1	13.0	116.3	12.4	30.9	OMe	55.8	55.8		55.8	51.2
19	116.8	115.7	121.4	140.8	121.3	23.0	OMe	55.8	55.8		55.8	
20	136.3	135.6	134.5	49	134.9	39.5	C=0					172.9
21	55.4	55.5	54.0	61.8	60.3	51.5						

[x] in pyridine



1 R=H 10,10'-dimethoxy-3α,17α-Z-tetrahydrousambarensine

2 R=CH_3 10,10'-dimethoxy-N_4,-methyl-3α,17α-Z-tetrahydrousambarensine

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