23. New Spermine Alkaloids from *Aphelandra tetragona* (VAHL) NEES

by **Bassem F. Tawil**[1]), **Ji-ping Zhu**, **Umberto Piantini**, and **Manfred Hesse***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH–8057 Zürich

Dedicated to Prof. Dr. *D. Gröger* on the occasion of his 60th birthday

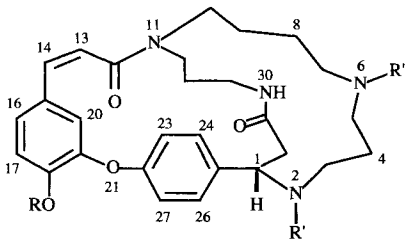
(17.XI.88)

18-*O*-Methylchaenorpine (**1a**) and iso-18-*O*-methylchaenorpine (**1b**) two novel stereoisomeric spermine alkaloids were isolated from the roots of *Aphelandra tetragona* (VAHL) NEES. Their structures were established by chemical and spectroscopic studies.

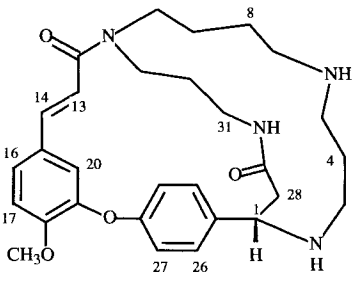
To date, aphelandrine is the sole spermine alkaloid isolated from the roots of *Aphelandra tetragona* (VAHL) NEES [1]. The structure elucidation of aphelandrine was accomplished by chemical and spectroscopic studies [2], and its absolute configuration has been recently confirmed by X-ray analysis [3].

In a further study of *A. tetragona* in our laboratory, it was found that the roots contained besides aphelandrine five new alkaloids. Two of them were identified as 18-*O*-methylchaenorpine (**1a**) and iso-18-*O*-methylchaenorpine (**1b**).

The FAB-MS of 18-*O*-methylchaenorpine showed an $[M + 1]^+$ ion at *m/z* 507, and its EI-MS at *m/z* 506. The ^{1}H-NMR spectrum (*Table 1*) showed an *AB quartet* centered at 6.45 and 5.89 ppm (1 H each, J = 12.8 Hz) attributed to H–C(14) and H–C(13), respectively. The magnitude of the olefinic coupling constant is clearly comparable with those observed for similar compounds and supports the (*Z*)-configuration around the double bond. In fact, in chaenorpine (**2**), the corresponding olefinic protons resonate at 6.33 and 5.93 ppm with J = 12.7 Hz [4], while in chaenorhine [5] J = 12.5 Hz.



1a 18-*O*-Methylchaenorpine R = CH_3, R' = H
1c R = CH_3, R'= $COCH_3$
2 Chaenorpine R = R' = H



1b Iso-18-*O*-methylchaenorpine

[1]) Part of the thesis of *B.F.T.*, University of Zürich, in preparation.

The 2D-COSY experiment facilitated the assignment of the aromatic protons of **1a**. The substitution pattern of the trisubstituted benzene ring is deduced by the *ABX*-spin system corresponding to H–C(17), H–C(16), and H–C(20) (J(H–C(16), H–C(17)) = 8.5 Hz and J(H–C(16), H–C(20)) = 2.1 Hz). The corresponding values in the spectrum of chaenorpine (**2**) are J = 8.3 and 2.0 Hz, respectively. The presence of a second benzene ring, a 1,4-substituted Ph moiety, is established by the resonances of H–C(23) and H–C(27) as well as those of H–C(24) and H–C(26) at 6.85 and 7.18 ppm, respectively, in a characteristic *AA'BB'* pattern with a J_{vic} = 8.8 Hz. The appearance of only two signals for this aromatic ring indicates that this ring is free to rotate, and that the double bond is not conjugated with the benzene ring, while in isochaenorhine [6] the rotation of the benzene ring is hindered. In the case of chaenorpine, these signals were registered at 6.97 and 7.44 ppm (J = 8.6 Hz; *Table 1*).

Table 1. *^{1}H-NMR Chemical Shifts* [ppm] *of 18-O-Methylchaenorpine and Related Compounds* (J in Hz)

	18-*O*-Methylchaenorpine (**1a**) ($CDCl_3$, 400 MHz)	Chaenorpine (**2**) ($CDCl_3$, 400 MHz) [4]	Chaenorhine (1N D_2SO_4/CD_3OD, 100 MHz) [5]
H–C(14)	6.45 (J = 12.8)	6.33 (J = 12.7)	6.87 (J = 12.5)
H–C(13)	5.89	5.93	6.27
H–C(23) and H–C(27)	6.85 (J = 8.8)	6.97 (J = 8.6)	7.6 (J = 8.8)
H–C(24) and H–C(26)	7.18 (J = 8.8)	7.44 (J = 8.6)	

The 3-H *singlet* at 3.89 ppm is assigned to the MeO group and its irradiation gave a NOE of H–C(17), thus, its position in the aromatic moiety is determined. Another important signal is that of H–C(1): in 18-*O*-methylchaenorpine (**1a**) it is found to be a *multiplet* at 4.25 ppm which is comparable with the shieldings of protons surrounded by a similar environment as in other polyamine alkaloids, namely chaenorpine (**2**, 4.05 ppm), *O*-methylorantine [7] (4.10 ppm), verbascenine [8] (3.9–4.15 ppm), and celacinnine [9] (3.97 ppm). From the 2D-COSY experiment, the assignment of 2 H–C(28) has been accomplished (3.05 and 2.55 ppm). These two protons did not show couplings with other protons except with H–C(1) and, thus, supported the structure **1a**. On the other hand, the UV spectrum (*Fig. 1*) of **1a** offered evidence that **1a** is of the same chromophore as **2**; furthermore, the CD spectrum (*Fig. 2*) indicated the same chirality for **1a** and **2**. These data, together with the fact that **2** and **1a** show the same fragmentation pattern under electron impact, led to the assumption that **1a** is an analogue of chaenorpine.

Supporting this assumption, acetylation of the new alkaloid **1a** afforded the *N,N*-diacetate **1c** which is identical with 2,6-diacetyl-18-*O*-methylchaenorpine [4] (TLC; see *Exper. Part*).

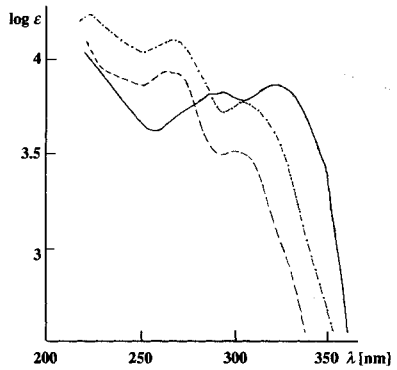


Fig. 1. *UV Spectra of 18-O-methylchaenorpine* (**1a**, ---) *and iso-18-O-methylchaenorpine* (**1b**,—) *in EtOH, and chaenorpine* (**2**,-·-) *in MeOH*

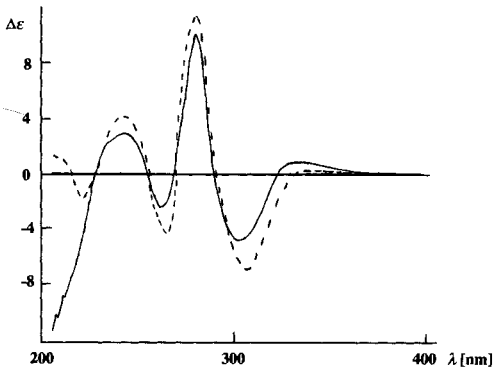


Fig. 2. *CD Spectra of 18-O-methylchaenorpine* (**1a**,—) *and chaenorpine* (**2**,- - -) *in EtOH*

Iso-18-*O*-methylchaenorpine (**1b**), exhibits M^+ peak at *m/z* 506. With respect to the configuration around the double bond, **1b** is a diastereoisomer of **1a**. The UV spectrum (*Fig.1*) of **1b** with maxima at 295 nm (log ε 3.82) and 323 (3.86), supports an (*E*)-cinnamoyl structure (*cf. e.g.* [10]). The signals of the (*E*)-olefinic protons are observed in the ^{1}H-NMR spectrum (*Table 2*) as one *AB quartet* centered at 7.53 and 6.06 ppm with J_{trans} = 15.1 Hz. Likewise, in *Table 2* ^{1}H-NMR chemical shifts of the olefinic protons of some polyamine alkaloids with similar (*E*)-cinnamoyl partial structures are indicated, namely: of maytenine [11][12], verbascenine [8], celacinnine [13], codonocarpine diacetate [14], and lunarine [15]. In the aromatic region of the ^{1}H-NMR spectrum of **1b**, H–C(16), H–C(17), and H–C(20) form an *ABX* spin system at 6.96, 6.91, and 6.25 ppm, respectively (*J*(H–C(16), H–C(17)) = 8.3 Hz and *J*(H–C(16), H–C(20)) = 1.9 Hz). Moreover, by 2D-COSY experiment, it is shown that H–C(16) is also coupled with H–C(14) leading to a very small coupling constant (*J* = 0.5 Hz). Irradiation of the MeO group at 4.02 ppm led to a NOE for H–C(17). From this experiment the position of the MeO group in the cinnamoyl moiety was established. As of **1a** and **2**, H–C(23) and H–C(27) as well as H–C(24) and H–C(26) of **1b** form two apparent *doublets* (2 H each) at 7.20 and 7.49 ppm (*J* = 8.5 Hz), respectively.

Table 2. *^{1}H-NMR Chemical Shifts* [ppm] *of the Olefinic Protons of Iso-18-O-methylchaenorpine* (**1b**) *and of Compounds with Similar Partial Structures*

	H–C(14)	H–C(13)	J_{trans} [Hz]
Iso-18-*O*-methylchaenorpine (**1b**) ($CDCl_3$, 400 MHz)	7.53	6.06	15.1
Verbascenine ($CDCl_3$, 200 MHz) [8]	7.72	6.83	15.5
Codonocarpine diacetate ($CDCl_3/CD_3OD$, 60 MHz) [14]	7.57	7.41	15.5
Lunarine ($CDCl_3$, 60 MHz) [15]	7.52	6.03	15.5
N-Methylmaytenine ($CDCl_3$, 270 MHz) [11][12]	6.62	6.37	15.8

The ^{13}C-NMR spectrum of **1b** showed 15 aliphatic (1 CH_3O, 11 CH_2, 3 CH); 10 aromatic[2]) (5 CH, 2 quaternary C, 3 C–O) and 2 C=O signals. The signal for C(12) was observed at 166.16 ppm; in maytenine [11] the corresponding signal is located at 166.0 ppm and in verbascenine at 169 ppm. The signal corresponding to C(29) at 171.75 ppm is in well agreement with the observations made for the C=O group of verbascenine at 170.1 ppm and *O*-methylorantine at 168.8 ppm. On the other hand, the chemical shifts of C(13) and C(14) at 116.80 and 141.43 ppm, respectively, are close to those values of verbascenine (118.8 and 140.2 ppm, respectively) and of maytenine (121.1 and 140.6 ppm, respectively). Likewise, the signal for C(1) of **1b** appears at 57.14 ppm compared to the corresponding values of 58.0 ppm for chaenorpine (**2**), 58.6 ppm for verbascenine , 59.2 ppm for ephedradine B, and 57.5 ppm for ephedradine C [16].

The new alkaloids **1a** and **1b** have been shown to display an interesting photoisomerization with respect to the double bond [6]. Under ambient light, **1b** was transformed to **1a**, thus, providing the evidence that **1b** has the same chirality (CD, UV, and TLC) as **1a**. The reversibility of this photoisomerization has been also observed. So far, this behaviour has not been well-known for spermine alkaloids, though photoisomerizations have been reported for some simple cinnamic-acid derivatives [17].

This work was supported by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung*.

Experimental Part

1. *General.* All solvents were distilled before use. Column chromatography (CC): *Merck* silica gel *60* (0.04–0.06 mm). $[\alpha]_D^{22}$: *Zeiss LEP A2*. UV spectra: *Perkin-Elmer 555*, in nm (log ε). CD spectra: *JASCO J-500A*, in nm ($\Delta\varepsilon$). IR spectra: *Perkin-Elmer 781*, in KBr, in cm^{-1}. NMR spectra in ppm relative to $CDCl_3$. ^{1}H-NMR (400 MHz): *Bruker AM 400*, in $CDCl_3$, unless otherwise stated. ^{13}C-NMR (50.4 MHz): *Varian XL 200*, in $CDCl_3$. EI-MS (70 eV): *Finnigan-MAT 90*, in *m/z* (rel.%).

2. *Isolation.* Well-grounded roots of *Aphelandra tetragona* (VAHL) NEES (1.8 kg; nearly 10-years old, grown in green houses in the Zürich area) were extracted several times with AcOH/MeOH 19:1 at r.t. The percolate was then concentrated *in vacuo*, and treated with 0.5N HCl. The acidic soln. was extracted with Et_2O to remove non-alkaloidal material, then basified to pH 8 with aq. 20% Na_2CO_3 soln., and extracted with $CHCl_3$. The org. phase was dried *in vacuo* and the residue purified by CC (silica gel; $CHCl_3$/MeOH/25% NH_4OH 78:19:3): 700 mg of aphelandrine [2] and 50 mg of a crude alkaloidal mixture containing *18-O-methylchaenorpine* (**1a**) and *iso-18-O-methylchaenorpine* (**1b**). The separation of **1a** and **1b** was achieved by CC (silica gel 230-400 mesh; $CHCl_3$/MeOH/$(i\text{-}Pr)_2NH$ 90:8:2): 13 mg of **1a** (fast running) and 20 mg of **1b**.

3. *18-O-Methylchaenorpine* (= *(13Z)-β',N-(1,5-Diazanonane-1,9-diyl)-α',β'-dihydro-4-methoxy*-N,N'-*(propane-1,3-diyl)-3,4'-oxydi[benzenepropenamide]; **1a***). Amorphous white solid. $[\alpha]_D^{22} = -74.0°$ (MeOH, c = 0.10). UV: see *Fig. 1*. CD: see *Fig. 2*. IR: 3460, 3380 (NH), 2980, 1610 (C=O), 1510, 1465 (arom. ring, C=C), 1385 (arom.). ^{1}H-NMR: 8.97 (br. NH); 7.43 (*d*, *J* = 8.8, H–C(24), H–C(26)); 7.01 (*d*, *J* = 8.3, H–C(17)); 6.98 (*d*, *J* = 8.8, H–C(23), H–C(27)); 6.45 (*d*, *J* = 12.8, H–C(14)); 5.89 (*d*, *J* = 12.8, H–C(13)); 4.25 (*m*, H–C(1)); 3.89 (*s*, CH_3O); 3.05 (*dd*, H–C(28)); 2.55 (*dd*, H–C(28)). ^{1}H-NMR (C_6D_6/$CDCl_3$): 7.18 (*d*, *J* = 8.8, H–C(24), H–C(26)); 6.85 (*d*, *J* = 8.8, H–C(23), H–C(27)); 6.75 (*dd*, *J* = 8.5, 2.1, H–C(16)); 6.64 (*d*, *J* = 8.5, H–C(17)); 6.60 (*d*, *J* = 2.1, H–C(20)); 6.19 (*d*, *J* = 12.8, H–C(14)); 5.63 (*d*, *J* = 12.8, H–C(13)). EI-MS: 506 (100, $M^{+\cdot}$), 505 (7), 478 (7), 477 (6), 464 (11), 463 (38), 435 (6), 434 (9), 421 (7), 420 (9), 406 (6), 381 (17), 365 (6), 363 (6), 337 (9), 307 (7), 294 (9), 293 (8), 281 (8), 280 (19), 279 (34), 278 (9), 267 (25), 266 (15), 265 (16), 253 (7), 252 (12), 251 (8), 239 (19),

---

[2]) The signals corresponding to C(23) and C(27) are found at 122.73 ppm, and those for C(24) and C(26) at 128.27 ppm. In chaenorhine, the corresponding signals are located at 120 and 128.2 ppm, respectively.

169 (11), 160 (35), 149 (14), 146 (13), 124 (27), 119 (21), 98 (40), 84 (47), 83 (42), 77 (15), 70 (31), 57 (40), 45 (43), 44 (29), 43 (46), 41 (46).

4. *Iso-18-*O*-methylchaenorpine* (= *(13*E*)-***1a**; **1b**). $[\alpha]_D^{22} = +108.9°$ (MeOH, $c = 0.235$). UV: see *Fig. 1*. CD (EtOH): 229 (–1.00), 231 (0), 243 (+4.00), 261 (0), 265 (–0.25), 268 (0), 287 (+8.70), 325 (0). IR: 3460, 3400 (NH), 2950, 1640, 1610, 1510, 1425, 1260 (arom. C–O), 1125. ^{1}H-NMR: 9.17 (br. NH); 7.53 (*d*, $J = 15.1$, H–C(14)); 7.49 (*d*, $J = 8.8$, H–C(24), H–C(26)); 7.20 (*d*, $J = 8.8$, H–C(23), H–C(27)); 6.96 (*dd*, $J = 8.3, 1.9$, H–C(16)); 6.91 (*d*, $J = 8.3$, H–C(17)); 6.25 (*d*, $J = 1.9$, H–C(20)); 6.06 (*d*, $J = 15.1$, H–C(13)); 4.22 (*m*, H–C(1)); 4.02 (*s*, CH_3O); 2.95 (*dd*, H–C(28)); 2.75 (*dd*, H–C(28)). ^{13}C-NMR: 171.57 (*s*, C(29)); 166.16 (*s*, C(12)); 154.45 (*s*, C(18)); 150.19 (*s*); 149.82 (*s*); 141.43 (*d*, C(14)); 137.95 (*s*, C(25)); 128.27 (*d*, 2 C); 127.96 (*s*, C(15)); 124.40 (*d*); 122.73 (*d*, 2 C); 116.80 (*d*, C(13)); 111.80 (*d*); 111.69 (*d*); 57.14 (*d*, C(1)); 48.44 (*t*); 47.20 (*q*, CH_3O); 46.98 (*t*); 45.53 (*t*); 45.05 (*t*); 37.80 (*t*); 35.09 (*t*); 30.45 (*t*); 26.85 (*t*); 24.54 (*t*); 21.45 (*t*). EI-MS: 506 (100, M^+), 505 (9), 478 (13), 477 (12), 464 (14), 463 (45), 435 (6), 434 (8), 421 (6), 420 (9), 406 (6), 381 (13), 365 (6), 363 (5), 337 (8), 307 (6), 294 (9), 293 (7), 281 (6), 280 (18), 279 (33), 278 (9), 267 (15), 266 (13), 265 (13), 253 (9), 251 (7), 239 (17), 238 (6), 169 (8), 160 (29), 146 (10), 119 (19), 98 (33), 84 (42), 77 (7), 70 (21), 56 (18), 44 (92) 41 (15).

5. *2,6-Diacetyl-18-*O*-methylchaenorpine* (**1c**). To 1 ml of Ac_2O, 5 mg of **1a** in dry pyridine (1 ml)were added and the soln. was stirred for 24 h at r.t. The resulting product was identified as **1c** [4] on three different TLC systems: R_f ($CHCl_3$/MeOH/NH_4OH 93:6:1) 0.5 on *Merck* TLC aluminium sheets silica gel *60* F_{254} precoated; R_f($CHCl_3$/MeOH/NH_4OH 90:9:1) 0.147 on *Merck* TLC plastic sheets silica gel *60* F_{254} precoated; R_f($CHCl_3$/MeOH/NH_4OH 95:4.5:0.5) 0.56 on *Merck* HPTLC plates NH_2 $F_{254}S$ precoated.

REFERENCES

[1] H. Bosshardt, A. Guggisberg, S. Johne, M. Hesse, *Pharm. Acta Helv.* **1978**, *53*, 355.
[2] P. Dätwyler, H. Bosshardt, H.O. Bernhard, M. Hesse, S. Johne, *Helv. Chim. Acta* **1978**, *61*, 2646.
[3] A. Guggisberg, R. Prewo, M. Hesse, *Helv. Chim. Acta* **1986**, *69*, 1012.
[4] J.P. Zhu, A. Guggisberg, M. Hesse, *Helv. Chim. Acta* **1988**, *71*, 218.
[5] H.O. Bernhard, I. Kompiš, S. Johne, D. Gröger, M. Hesse, H. Schmid, *Helv. Chim. Acta* **1973**, *56*, 1266.
[6] B.F. Tawil, A. Guggisberg, U. Piantini, M. Hesse, in preparation.
[7] P. Dätwyler, H. Bosshardt, S. Johne, M. Hesse, *Helv. Chim. Acta* **1979**, *62*, 2712.
[8] K. Seifert, S. Johne, M. Hesse, *Helv. Chim. Acta* **1982**, *65*, 2540.
[9] H.H. Wasserman, R.P. Robinson, H. Matsuyama, *Tetrahedron Lett.* **1980**, *21*, 3493.
[10] C. Poupat, H.-P. Husson, B.C. Das, P. Bladon, P. Potier, *Tetrahedron* **1972**, *28*, 3103.
[11] G. Englert, K. Klinga, Raymond-Hamet, E. Schlittler, W. Vetter, *Helv. Chim. Acta* **1973**, *56*, 474.
[12] E. Schlittler, U. Spitaler, N. Weber, *Helv. Chim. Acta* **1973**, *56*, 1097.
[13] S.M. Kupchan, H.P.J. Hintz, R.M. Smith, A. Karim, M.W. Cass, W.A. Court, M. Yatagai, *J. Org. Chem.* **1977**, *42*, 3660; H. Yamamoto, K. Maruoka, *J. Am. Chem. Soc.* **1981**, *103*, 6133.
[14] R.W. Doskotch, A.B. Ray, J.L. Beal, *J. Chem. Soc., Chem. Commun.* **1971**, 300; R.W. Doskotch, A.B. Ray, W. Kubelka, E.H. Fairchild, C.D. Hufford, J.L. Beal, *Tetrahedron* **1974**, *30*, 3229.
[15] C. Poupat, H.-P. Husson, B. Rodriguez, A. Husson, P. Potier, M.-M. Janot, *Tetrahedron* **1972**, *28*, 3087.
[16] M. Tamada, K. Endo, H. Hikino, *Heterocycles* **1979**, *12*, 783; C. Konno, M. Tamada, K. Endo, H. Hikino, *Heterocycles* **1980**, *14*, 295.
[17] C. Sandris, *Tetrahedron* **1968**, *24*, 3569; G. Kahnt, *Phytochemistry* **1967**, *6*, 755.