The Structure of Scandomelidine, Bisindole Alkaloid from Melodinus scandens

H. Mehri, and M. Plat

J. Nat. Prod., **1992**, 55 (2), 241-244• DOI:
10.1021/np50080a017 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 55, No. 2, pp. 241-244, February 1992

THE STRUCTURE OF SCANDOMELIDINE, BISINDOLE ALKALOID FROM *MELODINUS SCANDENS*

H. MEHRI and M. PLAT*

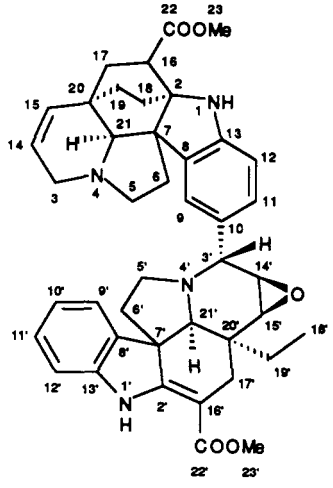
Universite de Paris-Sud, Faculte de Pharmacie, Laboratoire de Chimie therapeutique II (S.D.I. 62330 au C.N.R.S.), rue J.B. Clement, F92296 Chatenay-Malabry Cedex, France

ABSTRACT.—Scandomelidine [**1**] is one of the five quasi-dimeric alkaloids isolated from stems and leaves of *Melodinus scandens*. Its structure was established on the basis of spectroscopic evidence and results from the coupling of venalstonine [**2**] to pachysiphine [**3**] by a 10,3' bond.

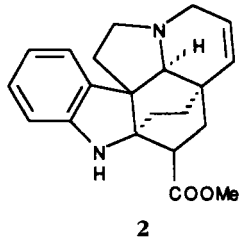
From stems and leaves of *Melodinus scandens* Forst. (Apocynaceae), five dimeric monoterpenoid indole alkaloids have been isolated: scandomelonine, scandomeline, their 19-epimers, and now scandomelidine [**1**]. Compound **1** was obtained in minute amounts from the mother liquors of scandomeline; the yield of **1** from the dried raw material was only 2.5 ppm (1). Structures of the first four alkaloids have been reported in a previous paper (2). The structure of scandomelidine [**1**] is discussed below.

Amorphous **1**, $C_{42}H_{46}N_4O_5$, deduced from elemental analysis, eims *m/z* $[M]^+$ 686, $[\alpha]^{20}D$ −160° ($CHCl_3$, $c = 1$), showed a uv spectrum λ max nm (log ε) 225 (3.85), 297 (3.89), 326 (4.12), shoulder 233 (4.05), which appeared to be the sum of two chromophores: one tabersonine-like (3) and the other aspidofractinine-like (4). This postulation was confirmed by the ir spectrum (1610, 1680, 1740, 3400 cm^{-1}) (5) and ^1H nmr [8.88 (2 × N*H* exchangeable for D), 3.76 (2 × COO*Me*)]. Further evidence regarding the moieties possessing these chromophores, given by the eims ions at $[M-214]^+$ *m/z* 472 and *m/z* 214, showed that the first half of the quasi-dimer is closely related to vincadifformine (6) and, furthermore, that the second half must be linked to the piperidine part of the vincadifformine-like moiety. Ions at *m/z* 143–144 showed that C-5 bears only hydrogens. The ^1H-nmr spectrum revealed also (methyl pattern at 0.80 ppm) that the two-carbon (C-18, -19) side chain borne by C-20 is an ethyl group.

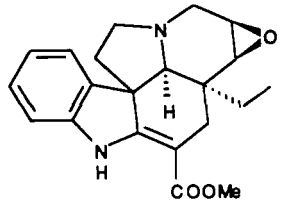
The structure of the second half of this binary alkaloid was determined to be



1



2

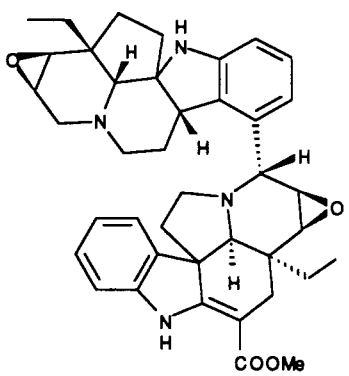


3

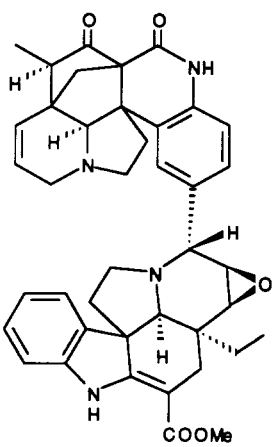
venalstonine on the basis of the spectroscopic data which are nearly identical with those of venalstonine: ir (1740 cm^{-1}); ^1H nmr (s, 3.76 ppm); unconjugated COO*Me*; eims ions $[M-28]^+$ (*m/z* 658), *m/z* 107, and *m/z* 122 (7).

From these results, it became obvious that the fifth oxygen atom of scandomelidine [**1**] must be located on the above-mentioned piperidine part of the vincadifformine portion only. The eims spectrum exhibited an $[M-16]^+$ (*m/z* 670) ion indicating either an *N*-oxide or an epoxide function. The latter hypothesis was supported by unsuccessful treatment of scandomelidine by Fe/HOAc at room temperature and by aqueous $FeSO_4$. The presence of an epoxide function on the D ring of tabersonine-like alkaloids is quite common and was formerly reported for lochnericine by Moza *et al.* (8) who could localize it by ms and added chemical evidence: its opening by HOAc (100°) gave the monoacetate of a diol. Since then, numerous alkaloids possessing this function have been isolated: monomers hörhammericine and hörhammerinine (9), ervincinine (10), hazuntine (11), hazuntinine (12), pachysiphine (13,14), epimisiline (15), and 14,15-epoxy-3-oxovincadifformine (16); and quasi-dimers voafoline, voafolidine, isovoafoline, 14-isovoafolidine, folicangine (14), scandomeline, scandomelonine, and their 19-epimers (2), peyceline, peycelanine, peylankine, (17), ervafoline (18), ervafolidine, its 3-epimer, and their 19-hydroxy derivatives (19), criophylline (20), and pandicine (24). The ms and nmr experience gained during their structure elucidation, sometimes supplemented by single-crystal X-ray analysis (18), gave such security in the location of the epoxide that chemical proofs were no longer involved. Furthermore a ^{13}C-nmr correlation between several alkaloids (12) has shown that upfield shifts of oxymethine carbons 14 and 15 (about 20 ppm) are typical of epoxides (cyclohexene-oxide 51.3 ppm); for a given configuration of C-20 and C-21, the shifts of C-17, C-19, C-20, and C-21 are indicative of the α or β orientation of the epoxide ring (12,17); α-alkylation of C-3 generates downfield shifts of C-14 (ca. 5 ppm) and C-3 (8.9 ppm) and upfield shifts of C-5 (3 ppm), C-15 (2.8 ppm), and C-21 (8.8 ppm) (20). The orientation of epoxide rings for most of these alkaloids was shown to be β, with exceptions for lochnericine and lochnerinine (α) (17,25,26).

Comparison of ^{13}C-nmr spectra (Table 1) of scandomelidine [**1**] and criophylline [**4**] (8) showed that the epoxide carbons C-14′ and C-15′ do appear, respectively, at 56.5 and 54.4 ppm for the former and at 56.8 and 54.2 ppm for the latter, indicating a pachysiphine moiety (14β,15β-oxido).



4



5

TABLE 1. ^{13}C nmr of Scandomelidine [**1**], Venalstonine [**2**], Pachysiphine [**3**], Criophylline [**4**], and Scandomelonine [**5**].

Carbon	Compound		Carbon	Compound			
	1	**2**[a]		**1**	**3**[b]	**4**[c]	**5**[d]
C-2	67.1	66.5	C-2′	165.4	166	165	164.6
C-3	49.3	49.0	C-3′	58.6	49.2	58.1	57.4
C-5	50.3	50.0	C-5′	48.3	51.4	48.4	47.8
C-6	36.8	36.4	C-6′	42.6	43.4	42.4	42.1
C-7	56.5	56.1	C-7′	54.2	54.8	54.2	53.8
C-8	140.1	139.5	C-8′	138.2	138.0	138.0	137.2
C-9	122.0	121.1	C-9′	121.5	121.0	121.5	121.2
C-10	126.0	119.0	C-10′	120.4	120.5	120.2	120.8
C-11	128.2	126.8	C-11′	127.3	127.4	127.6	127.3
C-12	110.9	110.9	C-12′	109.3	109.3	109.1	108.9
C-13	149.1	149.0	C-13′	143.2	143.4	143.1	142.5
C-14	127.7	126.5	C-14′	56.5	51.8	56.8	56.2
C-15	132.8	132.5	C-15′	54.4	57.0	54.2	53.5
C-16	43.8	43.4	C-16′	91.1	90.7	90.8	90.2
C-17	29.8	29.6	C-17′	23.9	23.3	23.9	23.6
C-18	31.9	31.6	C-18′	7.5	7.0	7.3	7.3
C-19	34.4	34.0	C-19′	27.0	26.3	27.0	26.6
C-20	35.5	35.0	C-20′	36.9	36.8	36.6	36.5
C-21	67.16	66.8	C-21′	62.2	70.8	70.2	61.5
C=O	174.1	173.7	C=O′	169.0	168.8	168.8	168.4
OMe	52.0	51.6	OMe	51.0	50.7	50.9	50.8

[a]Values for this compound are from Shamma and Hindenlang (27).
[b]Values for this compound are from Rolland *et al.* (14).
[c]Values for this compound are from Cave *et al.* (20).
[d]Values for this compound are from Daudon *et al.* (2).

The assignment of the carbons involved in the coupling was straightforward according to the nmr data. It could be seen, in the ^{13}C-nmr spectrum of scandomelidine [**1**], that C-3′ has a chemical shift (58.6 ppm) very similar to those of criophylline [**4**] (58.1 ppm) and scandomelonine [**5**] (57.4 ppm) (2). These data were confirmed by the presence, in the ^{13}C-nmr spectrum of **1**, of a signal at 4.60 ppm (1H) assigned to H-3′. The α substitution on C-3′ was also responsible for a downfield shift (4.7 ppm) of C-14′, and an upfield shift of C-15′ (2.6 ppm) and C-5′ (3.1 ppm) in **1** vs. **3**.

In the ^{13}C-nmr spectrum of **1**, C-10 (126 ppm) underwent a 7 ppm downfield shift vs. that in **2** (119 ppm) (21). These shifts were comparable with those observed for C-10 of scandomelonine vs. meloscandonine (5.7 ppm) (2), criophylline vs. andrangine (6.3 ppm) (20), and 5-methylindole vs. indole (6.49) (22). This showed C-10 to be the site of the linkage with the pachysiphine unit. H-12 was observable in the 200 MHz ^1H-nmr spectrum as a doublet (8.4 Hz). Its chemical shift was close to that of a similarly substituted indoline (23), confirming this assignment. The structure **1** was thus assigned to scandomelidine.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations were measured in a 1 dm tube at 528 nm with a Zeiss electronic polarimeter. Uv spectra were recorded in EtOH on a Unicam SP 800 spectrophotometer (1 cm cells). Ir spectra were recorded in KBr pellets using a Perkin-Elmer 841 spectrophotometer. The 220 MHz ^1H-nmr and 25 MHz ^{13}C-nmr spectra were recorded using Varian HR 220 and HA 100 spec-

trometers. The eims were recorded on an AEI MS 9 mass spectrometer. Elemental analysis was performed on a Perkin-Elmer 240 microanalyser.

ISOLATION OF SCANDOMELIDINE [**1**].—Pure scandomelidine [**1**] (32 mg) was isolated after concentration of the mother liquors of scandomeline. Scandomeline was previously separated by cc of crude extracts from dried stems and leaves (13 kg) of *M. scandens* (1). Purification was carried out by preparative tlc on Merck Al_2O_3 and elution with Et_2O-MeOH (20:1). Compound **1**: white amorphous powder; $[\alpha]^{20}D$ −160° ($CHCl_3$, $c=1$). *Anal.* found C 73.20%, H 6.78%, N 8.12%, calcd for $C_{42}H_{46}N_4O_5$ C 73.44%, H 6.75%, N 8.15%. λ max EtOH (log ε) 225 (3.85), 297 (3.89), 326 (4.12), sh 223 (4.05) nm; ir (KBr) 3400, 3340, 2950, 2790, 1740, 1680, 1610, 1470, 1440, 750 cm^{-1}; eims *m/z* (rel. int.) 686 (53), 670 (5.5), 658 (49), 629 (4.5), 599 (14), 590 (29), 472 (61), 376 (100), 363 (20), 349 (59), 337 (24), 335 (24), 266 (20), 214 (47), 168 (58), 154 (37), 149 (34), 144 (20), 138 (23), 135 (69), 122 (40), 121 (30), 107 (88); ^1H nmr ($CDCl_3$) ppm 0.80 (t, 7.0, H-18′), 3.76 (s, H-23, -23′), 4.60 (s, H-3′), 5.60 (m, H-14, -15), 6.25–7.30 (m, H-9, -9′, -10′, -11, -11′, -12′), 7.43 (brd, 8.4, H-12), 8.88 (brs, H-1, -1′); ^{13}C nmr see Table 1.

LITERATURE CITED

1. H. Mehri and M. Plat, *Plant. Med. Phytother.*, **2**, 143 (1974).
2. M. Daudon, H. Mehri, M. Plat, E.W. Hagaman, and E. Wenkert, *J. Org. Chem.*, **41**, 3275 (1976).
3. M.-M. Janot, H. Pourrat, and J.Le Men, *Bull. Soc. Chim. Fr.*, 707 (1954).
4. N. Neuss, in: "Physical Data of Indole and Dihydroindole Alkaloids." Ed. by Eli Lilly Company, Indianapolis, 1960.
5. M.-M. Janot, J. Le Men, and C. Fan, *Compt. Rend.*, **248**, 3005 (1959).
6. M. Plat, J. Le Men, M.-M. Janot, J.M. Wilson, H. Budzikievicz, L.J. Durham, Y. Nakagawa, and C. Djerassi, *Tetrahedron Lett.*, 271 (1962).
7. B.C. Das, K. Biemann, A. Chatterjee, A.B. Ray, and P.L. Majumder, *Tetrahedron Lett.*, 2239 (1965).
8. B.K. Moza, J. Trojanek, A.K. Bose, K.G. Das, and P. Funke, *Tetrahedron Lett.*, **37**, 2561 (1964).
9. D.J. Abraham, N.R. Farnsworth, W.D. Loub, and R.N. Blomster, *J. Org. Chem.*, **34**, 1575 (1969).
10. D.A. Rakhimov, V.M. Malikov, and S.Y. Yunusov, *Khim. Prir. Soedin.*, **4**, 331 (1968).
11. P. Potier, A.-M. Bui, B.C. Das, J. Le Men, and P. Boiteau, *Ann. Pharm. Fr.*, **26**, 621 (1968).
12. E. Wenkert, D.W. Cochran, E.W. Hagaman, F.M. Schell, N. Neuss, A.S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973).
13. M.B. Patel and J. Poisson, *Bull. Soc. Chim. Fr.*, 427 (1966).
14. Y. Rolland, N. Kunesch, J. Poisson, E.W. Hagaman, F.M. Schell, and E. Wenkert, *J. Org. Chem.*, **41**, 3270 (1976).
15. K.A. Alvi and K.T. De Silva, *Phytochemistry*, **26**, 543 (1987).
16. N. Aimi, Y. Asada, S. Sakai, and J. Haginiwa, *Chem. Pharm. Bull.*, **26**, 1182 (1978).
17. N. Kunesch, A. Cave, E.W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, **21**, 1727 (1980).
18. A. Henriques, S.K. Kan, and M. Lounasmaa, *Acta Chem. Scand., Ser. B*, **33**, 775 (1979).
19. A. Henriques, C. Kan, A. Chiaroni, C. Riche, H.P. Husson, S.K. Kan, and M. Lounasmaa, *J. Org. Chem.*, **47**, 803 (1982).
20. A. Cave, J. Bruneton, A. Ahond, A.-M. Bui, H.-P. Husson, C. Kan-Fan, G. Lukacs and P. Potier, *Tetrahedron Lett.*, 5081 (1973).
21. A. Ahond, M.-M. Janot, N. Langlois, G. Lukacs, P. Potier, R. Rasoanaivo, M. Sangare, N. Neuss, M. Plat, J. Le Men, E.W. Hagaman, and E. Wenkert, *J. Am. Chem. Soc.*, **96**, 633 (1974).
22. R.G. Parker and J.D. Roberts, *J. Org. Chem.*, **35**, 996 (1970).
23. T.A. Van Beek, R. Verpoorte, A. Baerheim Svendsen, and R. Fokkens, *J. Nat Prod.*, **48**, 400 (1985).
24. C. Kan-Fan, G. Massiot, B.C. Das, and P. Potier, *J. Org. Chem.*, **46**, 1481 (1981).
25. G.A. Cordell, in: "The Alkaloids." Ed. by R.H.F. Manske, Academic Press, New York, 1979, Vol. 17, p. 215.
26. G. Blasko and G.A. Cordell, in: "The Alkaloids." Ed. by A. Brossi, Academic Press, New York, 1990, Vol. 37, p. 52.
27. M. Shamma and D.M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids," Plenum Press, New York, 1979, p. 228.

Received 1 April 1991