PAGICERINE - A NEW INDOLE ALKALOID FROM PAGIANTHA CERIFERA (PANCHER ET SÉBERT) MARKGRAF (APOCYNACEAE)

Maryse Bert
Laboratoire de Pharmacognosie, U.E.R. des Sciences Pharmaceutiques,
1, rue Vaubénard F. 14000 Caen, France.

Geneviève Baudouin, François Tillequin, and Michel Koch*
Département de Pharmacognosie de l'Université René Descartes, U.A. au C.N.R.S., n°484, Faculté des Sciences Pharmaceutiques et Biologiques,
4, avenue de l'Observatoire F. 75006 Paris, France.

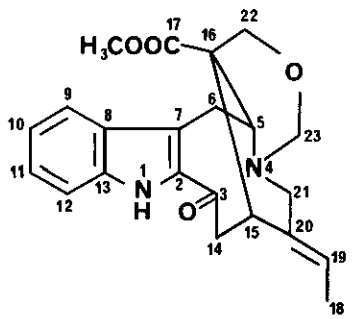
Abstract - A new 2-acylindole alkaloid, pagicerine (1) has been isolated from the stem bark of Pagiantha cerifera (Pancher et Sébert) Markgraf. Its structure has been elucidated on the basis of spectroscopic analyses. It is the first indole alkaloid to present an additional tetrahydro-1,3-oxazine ring.

Pagiantha cerifera (Pancher et Sébert) Markgraf is a small, variable tree growing throughout New-Caledonia[1]. It is sometimes included in the genus Tabernaemontana L. as Tabernaemontana cerifera Pancher et Sébert[2]. Various indole alkaloids had been previously isolated from the leaves of this species[3,4] but the bark had not been so far investigated from a chemical point of view.

A thorough search for the alkaloidal constituents of the bark[5] has now led to the isolation of a new alkaloid which is named pagicerine. The present paper describes the structure determination of pagicerine[6].

Pagicerine (1) has been obtained as a colourless amorphous solid, $[\alpha]_D^{20} = -130°$ ($CHCl_3$, c = 0.7) (contents : 0.002 % from the dried plant material). The empirical formula has been established by high resolution mass spectrometry as $C_{22}H_{24}N_2O_4$ (Found : 380.1735 ; Calcd. : 380.1736). The uv spectrum displayed characteristic absorptions at λ_{max}^{EtOH} nm (log ε) : 219(3.97), 241(4.03) and 316(4.06) associated with a 2-acylindole[7]. In good agreement with this statement, the ir spectrum showed typical bands at ν_{max}^{KBr} cm^{-1} : 3320(NH) and 1730(C=O). The ^1H nmr

spectrum[8] exhibits the characteristic signals of a 2,3-disubstituted indole, of an ethylidene group and of a carbomethoxy. This latter appears as a 3H-singlet at 2.49 ppm strongly shielded by the indole ring, as usual in the vobasine-vincadiffine series[7,9]. Moreover, an AB system representing two protons at 4.63 and 4.79 ppm (J = 9.5 Hz) suggests the presence of a tetrahydro-1,3-oxazine ring[10,11]. The small gem-coupling constant between these two protons is typical to this ring where the bond angle of the CH_2 in position 2 is modified by interaction with the adjacent electron lone-pairs of the α-O and α-N atoms[10]. In good agreement with these elements, the ^{13}C nmr spectrum exhibits signals at 88.3 and 76.5 ppm typical to C-2 and C-6 in a tetrahydro-1,3-oxazine substituted at C-4 and C-5[11,12]. The other signals of this spectrum are quite similar to those previously described in the vincadiffine series[13,14]. Compared to the ^{13}C nmr spectra of vincadiffine itself[14], only slight but significant increases in the chemical shifts of C-5, C-6 and C-15 signals could be noted. The above elements permitted depicting the structure of pagicerine as 1.



1

From a biogenetic point of view, pagicerine may be considered as arising from voacarpine[15,16] through N_b-condensation with formaldehyde. It is, to our knowledge, the first indole alkaloid to present an additional tetrahydro-1,3-oxazine ring. This type of ring is uncommonly encountered in the structures of natural products[12,17].

AKNOWLEDGEMENTS

We wish to thank Dr Nicole Kunesch (Centre d'Etudes Pharmaceutiques, Université de

Paris XI, Châtenay-Malabry, France) for helpful discussions and Pr H. Achenbach (Institut für Pharmazie und Lebensmittelchemie der Universität Erlangen-Nürnberg, F.R.G.) for the communication of unpublished results.

REFERENCES AND NOTES

1. A. Boiteau and L. Allorge, in A. Aubréville and J.F. Leroy "Flore de la Nouvelle-Calédonie et Dépendances". Muséum National d'Histoire Naturelle, Paris, 1981, 10, pp.232-238.
2. T.A. Van Beek, R. Verpoorte, A. Baerheim-Svendsen, A.J.M. Leeuwenberg and N.G. Bisset, J. Ethopharm., 1984, 10, 1.
3. A. Harmouche, H. Mehri, M. Koch, A. Rabaron, M. Plat and T. Sévenet, Ann. Pharm. Franç., 1976, 34, 31.
4. H.P. Ros, E. Schöpp and M. Hesse, Z. Naturforsch., 1978, 33C, 290.
5. The plant material has been collected at the Rivière Bleue (New Caledonia) in september 1983. Herbarium Samples (PUCH 642) are kept in the herbaria of the Centre ORSTOM de Nouméa.
6. A biogenetic alkaloid numbering is used in this paper, according to W.I. Taylor and J. Le Men, Experientia, 1965, 21, 508.
7. D.G.I. Kingston and O. Ekundayo, J. Nat. Prod., 1981, 44, 509 and references cited therein.
8. Pagicerine (1) : ^{1}H nmr (270 MHz, $CDCl_3$, TMS) : δ ppm = 9.17 (1H, s, D_2O exch., NH-1) ; 7.77 (1H, dd, J_{9-10} = 8 Hz, J_{9-11} = 1 Hz, H-9) ; 7.37 (2H, m, H-11, H-12) ; 7.20 (1H, m, H-10) ; 5.37 (1H, q, J_{18-19}= 7 Hz, H-19) ; 4.79 (1H, d, $J_{23a-23b}$= 9.5 Hz, H-23a) ; 4.63 (1H, d, $J_{23a-23b}$= 9.5 Hz, H-23b) ; 4.40 (1H, dq, $J_{21a-21b}$= 16 Hz, J_{18-21a}= 1 Hz, H-21a) ; 4.12 (1H, t, J_{14-15}= 8 Hz, H-15) ; 3.90-3.60 (5H, m, H-5, H-14a, H-14b, H-22a, H-22b) ; 3.37 (1H, d, $J_{21a-21b}$= 16 Hz, H-21b) ; 3.15 (1H, dd, J_{6a-6b}= 14 Hz, J_{5-6a}= 10 Hz ; H-6a) ; 2.80 (1H, dd, J_{6a-6b}= 14 Hz, J_{5-6b}= 7 Hz, H-6b) ; 2.49 (3H, s, $COOCH_3$) ; 1.75 (3H, dd, J_{18-19}= 7 Hz, J_{18-21a} = 1 Hz, CH_3-18) - ^{13}C nmr (50 MHz, $CDCl_3$, TMS, spin echo): δ ppm = 189.6 (C-3) ; 173.0 (C-17) ; 138.6 (C-13) ; 136.9 (C-20) ; 134.5 (C-2) ; 128.3 (C-8) ; 127.1 (C-11) ; 121.1* (C-19) ; 120.8* (C-9) ; 119.0 (C-7) ; 116.7* (C-10) ; 112.0 (C-12) ; 88.3 (C-23) ; 76.5 (C-22) ; 58.8 (C-5) ; 50.9 ($COO\underline{C}H_3$) ; 49.7 (C-21) ; 46.9 (C-16) ; 44.5 (C-14) ; 36.7 (C-15) ; 26.4 (C-6) ; 11.8 (C-18).
9. J. Garnier and J. Mahuteau, Tetrahedron Letters, 1985, 26, 1513.

10. P.J. Halls, R.A.Y. Jones, A.R. Katritzky, M. Sarney and D.L. Trepanier, J. Chem. Soc. (B), 1971, 1320.

11. H. Linde, H. Oelschläger and C. Czirwitzky, Arneimittelforschung, 1978, 28, 937.

12. M. Sangare, F. Khuong-Huu, D. Herlem, A. Millet, B. Spete, G. Berenger and G. Lukacs, Tetrahedron Letters, 1975, 1791.

13. A. Ahond, A.M. Bui and P. Potier, J. Org. Chem., 1976, 41, 1878.

14. Vincadiffine : ^{13}C nmr : δ ppm : 189.7 (C-3) ; 174.1 (C-17) ; 136.7 (C-13) ; 134.8. (C-2) ; 134.7 (C-20) ; 128.6 (C-8) ; 126.8 (C-11) ; 120.9 (C-19) ; 120.3 (C-9) ; 119.7 (C-7) ; 119.7 (C-10) ; 111.9 (C-12) ; 57.9 (C-5) ; 52.2 (C-16) ; 51.5 (C-21) ; 50.7 ($COO\underline{C}H_3$) ; 43.1 (C-14) ; 42.2 (C-23) ; 42.0 (C-22) ; 32.9 (C-15) ; 18.3 (C-6) ; 12.2 (C-18) ; quoted from : B. Raffelsberger, "Alkaloidanalysen von vier Tabernaemontana Arten", Dissertation, Freiburg in Brigau, 1978, pp. 1-242.

15. M. Denayer-Tournay, J. Pecher, R.H. Martin, M. Friedmann-Spiteller and G. Spiteller, Bull. Soc. Chim. Belges, 1965, 74, 170.

16. D.J. Abraham, N.R. Farnsworth, R.N. Blomster and A.G. Sharkley Jr., Tetrahedron Letters, 1965, 317.

17. D. Debourges, R. Hocquemiller, A. Cavé and J. Lévy, J. Nat. Prod., 1985, 48, 310.

Received, 1st July, 1985