PAGISULFINE - THE FIRST SULFUR-CONTAINING INDOLE-MONOTERPENE ALKALOID

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 - The first sulfur-containing indole-monoterpene alkaloid,
pagisulfine (1) has been isolated from the stem bark of Pagiantha cerifera
(Pancher et Sébert) Markgraf. Its structure has been determined by spectro-
scopic studies. Its absolute stereochemistry has been established by its
synthesis, using vobasine as starting material.

Pagiantha cerifera (Pancher et Sébert) Markgraf (= Tabernaemontana cerifera
Pancher et Sébert) is a small tree growing throughout New-Caledonia1,2. The search for the
alkaloidal constituents of the stem bark has previously led to the isolation and
structure determination of two novel indole alkaloids, pagicerine3 and ceridimine4.
In a continuation of our studies, we wish to report here the structural elucidation
and synthesis of a third novel compound isolated from the stem bark of this species5
and named pagisulfine6.

Pagisulfine (1) was obtained as a colourless amorphous solid, \([\alpha]_D^{20} = +42^\circ\) (EtOH,
c = 1) (contents : 0.002 % from the dried plant material). The empirical formula was
established by high resolution mass spectrometry as \(C_{23}H_{31}N_3O_2S\) (Found : 413.2144 ;
Calcd. : 413.2134). The uv spectrum showing absorption maxima at \(\lambda_{\text{EtOH}}\) nm (log c) : 224(4.36), 284(3.89), 291(3.92) and 298(3.86) was consistent with an indole chro-
mophore. The ir spectrum afforded typical bands at \(v_{\text{KBr max}}\) cm\(^{-1}\) : 3360 (NH), 2950
(CH) and 1730 (C=O ester). The general feature of the ms, m/z (%) : 413(10), 369(5),
358(23), 337(100), 336(17), 305(4), 277(8), 233(5), 222(10), 206(6), 194(7), 193(6),
181(10), 180(47), 156(13), 122(35) suggested the presence4,7 of a vobasine-derived
unit. In good agreement with this statement, the $^1$H nmr spectrum$^8$ exhibited all the characteristic signals of a 3-vobasinylin unit$^4,7,9,10$ particularly two 3H-singlets at 2.55 and 2.40 ppm typical for N-Me and COOMe groups in this series. Additional signals accounting for six protons, two of which were exchangeable by D$_2$O, appeared in the aliphatic region and could be assigned to a -S-CH$_2$-CH$_2$-NH$_2$ chain.

Chemical evidence for this free side chain was given by methylation (30 % aq. HCHO/NaBH$_3$CN/AcOH/30°C/2 h/72 % yield) of papisulfine (1) which led to a dimethyl-derivative (2), $M^+ = 441$ which had a $^1$H nmr spectrum very similar to that of 1 except for an additional 6H-singlet at 2.24 ppm (NMe$_2$). Upon acetylation (Ac$_2$O/ C$_5$H$_5$N/20°C/48h) papisulfine led in almost quantitative yield to a monoacetyl-derivative (3), $M^+ = 455$ characterized by a typical ir acetamide absorption at 1655 cm$^{-1}$ and a 3H-nmr singlet at 1.89 ppm. These elements permitted depicting the structure of papisulfine as 1.

Finally, papisulfine was synthetized by condensation of vobasino$^1$ with an excess of 2-mercaptoethylamine (MeOH saturated with gaseous HCl/reflux/2h). This reaction gave rise to a single product identical with natural papisulfine in almost quantitative yield and provided evidence for the absolute stereochemistry at C-5 since 2-mercaptoethylamine is assumed to add to the intermediate vobasino-derived iminium salt from the less hindered α-side of the molecule$^{12}$. Papisulfine is to our knowledge the first sulfur containing indole-monoterpenic alkaloid$^{13}$. It
probably arises from vobasine and cysteine by a biogenetic path very close to
the scheme used for its synthesis. The similarity of its origin with that
described for the vobasine-derived bisindole alkaloids\textsuperscript{14} clearly emphasizes the
high reactivity of vobasinol as an electrophilic reagent.

REFERENCES AND NOTES
1. A. Boiteau and L. Allorge, in A. Aubróville and J.F. Leroy, "Flore de la Nou-
velle-Calédonie et Dépendances", Muséum National d'Histoire Naturelle, Paris,
2. T.A. Van Beek, R. Verpoorte, A. Baerheim-Svendsen, A.J.M. Leeuwenberg and
N.G. Bisset, \emph{J. Ethnopharmac.}, 1984, \textit{\textcircled{10}}, \textit{7}.
1986, \textit{3}.
5. The plant material has been collected at the Rivière Bleue (New Caledonia) in
September 1983. Herbarium samples (PUCII 642) are held in the herbaria of the
Centre ORSTOM de Nouméa.
6. A biogenetic alkaloid numbering is used in this paper according to K.I. Taylor
and J. Le Men, \emph{Experientia}, 1965, \textit{\textcircled{21}}, 508.
Prod.}, 1981, \textit{\textcircled{44}}, 670.
8. Pagiisulfine (1) : \textit{\textcircled{1H} nmr (270 MHz, CDCl\textsubscript{3}, TMS) : 6 ppm = 8.86 (1H, s, D\textsubscript{2}O
exch., NH-1) ; 7.45 (1H, dd, J = 8Hz, J' = 1Hz, H-9) ; 7.22 (1H, dd, J = 8Hz,
J' = 1Hz, H-12) ; 7.08 (1H, td, J = 8Hz, J' = 1Hz, H-11) ; 7.02 (1H, td,
J = 8Hz, J' = 1Hz, H-10) ; 5.67 (1H, q, J = 7Hz, H-19) ; 4.51 (1H, dd,
J = 15Hz, J' = 3Hz, H-3) ; 3.84 (1H, ddd, J = 11Hz, J' = 8Hz, J'' = 2Hz, H-5) ;
3.70 (1H, dq, J = 14Hz, J' = 1Hz, H-21a) ; 3.64 (1H, m, H-15) ; 3.28 (1H, dd,
J = 16Hz, J' = 11Hz, H-6a) ; 3.15 (1H, dd, J = 10Hz, J' = 8Hz, H-6b) ; 3.05-
2.40 (7H, m, CH\textsubscript{2}-1', CH\textsubscript{2}-2', H-14a, H-21b, H-16) ; 2.55 (3H, s, N-CH\textsubscript{3}) ; 2.40
(3H, s, COOCH\textsubscript{3}) ; 2.30 (2H, m, D\textsubscript{2}O exch., NH\textsubscript{2}) ; 2.10 (1H, m, H-14b) ; 1.67
(3H, dd, J = 7Hz, J' = 1Hz, CH\textsubscript{3}-18).
1829.
1963, \textit{\textcircled{46}}, 2186.

\textit{-1569-}

Received, 27th February, 1986