HETEROCYCLES, Vol. 24, No. 6, 1986

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

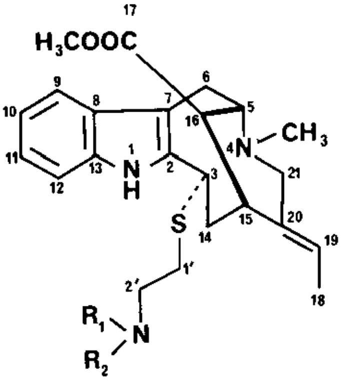
Geneviève Baudouin, François Tillequin, and Michel Koch*
Département de Pharmacognosie de l'Université René Descartes, U.A. au
C.N.R.S. n°484, Faculté des Sciences Pharmaceutiques et Biologiques,
4, avenue de l'Observatoire F. 75006 Paris, France

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 spectroscopic 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-Caledonia[1,2]. The search for the alkaloidal constituents of the stem bark has previously led to the isolation and structure determination of two novel indole alkaloids, pagicerine[3] and ceridimine[4]. 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 species[5] and named pagisulfine[6].

Pagisulfine (1) was obtained as a colourless amorphous solid, $[\alpha]_D^{20} = +42°$ (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 λ^{EtOH} nm (log ε) : 224(4.36), 284(3.89), 291(3.92) and 298(3.86) was consistent with an indole chromophore. The ir spectrum afforded typical bands at ν_{max}^{KBr} cm^{-1} : 3360 (NH), 2950 (CH) and 1730 (C=O ester). The general feature of the ms, m/z (%) : 413(10), 369(3), 338(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 presence[4,7] of a vobasine-derived unit. In good agreement with this statement, the ^1H nmr spectrum[8] exhibited all the characteristic signals of a 3-vobasinyl 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_2O, 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. $HCHO/NaBH_3CN/AcOH$/30°C/2 h/72 % yield) of pagisulfine (1) which led to a dimethyl-derivative (2), $M^+ = 441$ which had a ^1H nmr spectrum very similar to that of 1 except for an additional 6H-singlet at 2.24 ppm (NMe_2). Upon acetylation (Ac_2O/C_5H_5N/20°C/48h) pagisulfine 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 pagisulfine as 1.



1 $R_1=R_2=H$

2 $R_1=R_2=CH_3$

3 $R_1=H$ $R_2=COCH_3$

Finally, pagisulfine was synthetized by condensation of vobasinol[11] with an excess of 2-mercaptoethylamine (MeOH saturated with gaseous HCl/reflux/2h). This reaction gave rise to a single product identical with natural pagisulfine in almost quantitative yield and provided evidence for the absolute stereochemistry at C-3 since 2-mercaptoethylamine is assumed to add to the intermediate vobasinol-derived iminium salt from the less hindered α-side of the molecule[12]. Pagisulfine is to our knowledge the first sulfur containing indole-monoterpene 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[14] clearly emphasizes the high reactivity of vobasinol as an electrophilic reagent.

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. Ethnopharm., 1984, **10**, 1.
3. M. Bert, G. Baudouin, F. Tillequin and M. Koch. Heterocycles, 1985, **23**, 2505.
4. G. Baudouin, F. Tillequin, M. Bert and M. Koch. J. Chem. Soc. Chem. Comm., 1986, 3.
5. The plant material has been collected at the Rivière Bleue (New Caledonia) in September 1983. Herbarium samples (PUCH 642) are held 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. X.Z. Feng, C. Kan, H.P. Husson, P. Potier, S.K. Kan and M. Lounasmaa, J. Nat. Prod., 1981, **44**, 670.
8. Pagisulfine (1) : ^{1}H nmr (270 MHz, $CDCl_3$, TMS) : δ ppm = 8.86 (1H, s, D_2O 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) ; 5.37 (1H, q, J = 7Hz, H-19) ; 4.51 (1H, dd, J = 13Hz, 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 = 16Hz, J' = 8Hz, H-6b) ; 3.05-2.40 (7H, m, CH_2-1', CH_2-2', H-14a, H-21b, H-16) ; 2.55 (3H, s, N-CH_3) ; 2.40 (3H, s, $COOCH_3$) ; 2.30 (2H, m, D_2O exch., NH_2) ; 2.10 (1H, m, H-14b) ; 1.67 (3H, dd, J = 7Hz, J' = 1Hz, CH_3-18).
9. J.P. Kutney, A. Horinaka, R.S. Ward and B.R. Worth, Can. J. Chem., 1980, **58**, 1829.
10. M. Urrea, A. Ahond, A.M. Bui and P. Potier, Bull. Soc. Chim. Fr.II, 1981, 147.
11. U. Renner, D.A. Prins, A.L. Burlingame and K. Biemann, Helv. Chim. Acta, 1963, **46**, 2186.

12. G. Büchi, R.E. Manning and S.A. Monti, J. Am. Chem. Soc., 1964, **86**, 4631.

13. For a recent review on sulfur-containing alkaloids, see J.T. Wróbel, in A. Brossi,"The Alkaloids", Academic Press, New York, 1985, **26**, 53.

14. Atta-ur-Rahman and A. Basha, "Biosynthesis of indole alkaloids", Clarendon Press, Oxford, 1983 and references cited.

Received, 27th February, 1986