NORMAVACURINE AND MINFIENSINE, TWO NEW ALKALOIDS WITH $C_{19}H_{22}N_2O$ FORMULA FROM *STRYCHNOS* SPECIES

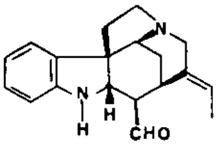
Georges Massiot[a*], Philippe Thépenier[a], Marie-José Jacquier[a], Louisette Le Men-Olivier[a], and Clément Delaude[b]

[a] U.A. n°492 au C.N.R.S., Laboratoire de Pharmacognosie, Faculté de Pharmacie,
51 rue Cognacq-Jay, 51096 Reims Cedex, France

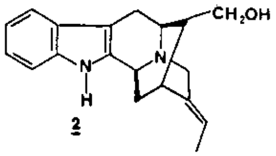
[b] Centre de Recherches Phytochimiques, Université de Liège, Belgique

Abstract - Minfiensine and normavacurine are two novel $C_{19}H_{22}N_2O$ alkaloids from *Strychnos minfiensis, S. potatorum* and *S. longicaudata*. Minfiensine is characterized by a N-1 — C-3 bond instead of the usual N-1 — C-2 bond.

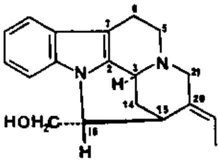
$C_{19}H_{22}N_2O$ formulae belong to secoiridoid deriving indole alkaloids, which have lost the methoxycarbonyl unit without suffering further oxidation or reduction. Typical examples found in African Strychnos are 18-desoxy-Wieland-Gumlich aldehyde 1 from *S. dolichothyrsa* [1], *S. kasengaensis* [2] and *S. matopensis* [3] and normacusine B 2 from *S. dolichothyrsa* [4], *S. malacoclados* [5], *S. madagascariensis* [6], and *S. potatorum* [6]. We wish to report isolation and structural elucidation of two new bases having the same composition and gross carbon skeleton : normavacurine 3 from *S. minfiensis, S. potatorum* and *S. longicaudata* and minfiensine 4 from *S. minfiensis*. Erroneously alkaloid 3 from *S. longicaudata* was first given formula 5 of 1,2-dehydrodeacetylretuline [7].



1

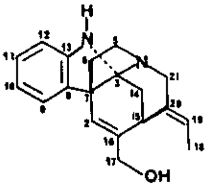


2

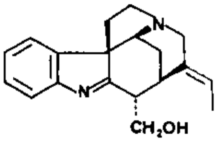


3

6 N_4^+-CH_3



4



5

Formulae 3 and 5 are characterized by the same array of protons and differ in the nature of their chromophores. Alkaloid 3 [8] was first thought to have an indolenine chromophore, owing to the lack of structure of its long wavelenght uv absorption band (λ=287 nm, log ε=3.6) but ^{13}C nmr, now available on the more abundant sample from *S. minfiensis*, unambiguously allows its identification as a N-substituted indole (Table I). In order to respect the proton arrangement (determined by a COSY experiment), the simplest way to obtain an indole is to shift C-3 and C-16 from C-7 and C-2 to C-2 and N-1 respectively, thus leading to structure 3 = normavacurine. The abnormal chemical shift of one of the H-21 (δ=1.03 ppm) is another evidence for its belonging to the pleiocarpamine series [9]. Further proof concerning the flat structure of 3 and the relative configurations of its asymmetric centers is provided by comparison of the ^{13}C nmr spectra of 3 and of mavacurine 6[10] (Table I).

	3	6[10]	4		3	6[10]	4
C-2	138.0	133.7	124.5	C-13	140.6	141.4	147.3
C-3	51.6	63.3	90.1	C-14	24.2	19.7	32
C-5	49.4	64.1	53.3	C-15	30.1	29.1	31.4
C-6	20.5	18.3	38.4	C-16	60.5	61.3	140.8
C-7	109.3	112.7	55.3	C-17	65.1	65.3	65.5
C-8	128.9	127.8	135.5	C-18	12.5	13.1	13.7
C-9	120.2	120.6	122.6	C-19	121.1	131.8	119.5
C-10	121.6	122.2	118.5	C-20	134.9	131.8	133.4
C-11	128.3	124.9	127.7	C-21	55.6	60.5	53.8
C-12	110.1	112.6	109.8				

Table I - ^{13}C nmr data for 3, 4 (75 MHz, $CDCl_3$) and 6[10].
Assignments of ^{13}C nmr spectra of 3 and 4 are based on C-H and H-H COSY experiments.

The mass spectrum of minfiensine 4[11] displays a molecular ion at m/z 294 (hrms : found : 294.1730, calcd for $C_{19}H_{22}N_2O$: 294.1731) and little fragmentation in the high masses range. Its uv spectrum shows three maxima at λ 213 nm (log ε : 3.98), 243 (3.54) and 295 (3.25), shifted at 212, 234 and 288 nm in acidic medium. The 300 MHz ^{1}H nmr spectrum shows signals for four aromatic protons, for a tryptamine unit and for a $N{-}CH_2{-}C{=}CH{-}CH_3$ unit ; it also shows at high field an ABX system with J_{AB}= 12Hz, and a vinylic proton long range coupling to a hydroxymethylene (δ=6.05 ppm, 1H and 4.10 ppm, 2H). The part of the ABX system (δ=3.41 ppm) also long range couples to the CH_2OH and to the vinylic proton of the ethylidene chain ; they can thus be assigned to H-15 and CH_2-17 of the skeleton of compound 1. In order to introduce a supplementary unsaturation, the N-1 to C-2 bond may be cleaved and to comply with ms data, N-1 is linked to C-3 which does not possess any hydrogen. This leads to structure 4 which is further supported by the ^{13}C nmr spectrum which shows ten olefinic or aromatic carbons and a deshielded signal for a C-3 substituted by two heteroatoms (δ=90.1 ppm) ; this situation also accounts for the hypsochromic shift of the uv spectrum recorded under acidic conditions. A NOESY experiment (600 ms mixing time) shows several meaningful correlations : H-2 — H-9, H-2 — H-17, H-17 — H-15 and H-15 — CH_3-18, thus bringing more evidences in favor of structure 4.

Whereas alkaloids 2 and 3 are members of well represented classes of alkaloids, there is no precedent for the isolation of a compound such as minfiensine 4. Its genesis is based upon two chemical events : a) ring cleavage between N-1 and C-2, and b) ring closure with formation of N-1 to C-3 bond. Event a) requires some activation of C-2 or C-16 which exists, for example, in 2,16 dehydroderivatives or in compounds with aldehyde or ester functions at C-17 and event b) demands oxidation of C-3 or of N-4, two related possibilities which are not rare among Strychnos alkaloids.

ACKNOWLEDGEMENTS

Support of this work by "Ministère de la coopération au développement de Belgique" (Etude Phytochimiques de flores africaines research project) is gratefully acknowledged. The authors are indebted to Dr H. BREYNE for identification of vegetable material.

REFERENCES

1. R. Verpoorte and A. Baerheim-Svendsen, J. Nat. Prod., 1976, 39, 357.
2. G. Massiot, B. Massoussa, M.J. Jacquier, P. Thépenier, L. Le Men-Olivier, C. Delaude, and R. Verpoorte, Phytochemistry, 1988, 27, 3293.
3. P. Thépenier, M.J. Jacquier, G. Massiot, L. Le Men-Olivier, and C. Delaude, Phytochemistry, 1984, 23, 2659.
4. R. Verpoorte, M.J. Verzijl, and A. Baerheim-Svendsen, Planta Med., 1982, 44, 21.
5. R. Verpoorte, Pharm. Weekblad, 1978, 113, 1249.
6. Unpublished work from this laboratory. Plant material was collected in Zaire, South Africa, and Cameroon ; full description of the alkaloids and of the extraction procedure will be reported elsewhere.
7. G. Massiot, P. Thépenier, M.J. Jacquier, J. Lounkokobi, C. Mirand, M. Zèches, L. Le Men-Olivier, and C. Delaude, Tetrahedron, 1983, 39, 3645.

8. Normavacurine 3 : amorphous solid, $(\alpha)_D$ =127° (c=0.67, $CHCl_3$) uv and ^{13}C nmr, see text ; ir ($CHCl_3$) : 3380 (br), 1640, 1610, 1450 cm^{-1} ; ms (rel. int.) : 294 (M^+, 80), 279 (5), 277 (2), 264 (35), 263 (100), 234 (30), 230 (15), 180 (50) ; ^1H nmr (300 MHz, $CDCl_3$) : 7.56 (dd, J=1.8, 7.2 Hz) ; 7.50 (dd, J=1.8, 7.0 Hz) ; 7.17 (m, 2H) ; 5.13 (d of quartets, J=2.0, 6.9 Hz, H-19) ; 4.22 (dd, J=5.5, 9.1 Hz, H-17) ; 4.10 (m, 2H, H-17+16) ; 3.78 (dd, J=2.2, 3.6 Hz, H-3) ; 3.28 (ddd, J=2.7, 10.3, 16.0 Hz, H-5) ; 3.24 (bs, H-15) ; 3.15 (ddd, J=2.7, 8.6, 15.0 Hz, H-6) ; 2.63 (ddd, J=6.1, 10.3, 16.0 Hz, H-5) ; 2.56 (ddd, J=2.2, 4.0, 13.5 Hz, H-14), 2.50 (br d, J=13.4 Hz, H-21) ; 2.18 (ddd, J=6.1, 8.6, 15.0 Hz, H-6) ; 1.96 (ddd, J=2.5, 3.6, 13.5 Hz, H-14) ; 1.57 (dd, J=2.3, 6.9 Hz, CH_3-18) ; 1.03 (d of quintets, J=13.4, 2.3 Hz, H-21).

9. M. Hesse, W.v. Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W.I. Taylor, H. Schmid, and P. Karrer, Helv. Chim. Acta, 1964, 47, 878.

10. C.A. Coune, M. Tits, and L. Angenot, J. Pharm. Belg., 1982, 37, 189.

11. Minfiensine 4 : amorphous solid, uv and ^{13}C nmr, see text ; colour red upon Ce IV spraying, $(\alpha)_D$ =134° (c=0.82, $CHCl_3$) ; ms (rel. int.) : 294 (M^+, 100), 263 (15), 234 (15), 197 (20), 180 (25), 168 (25), 167 (20), 130 (15), 97 (20), 82 (55), ir ($CHCl_3$) : cm^{-1} : 3300, 1610, 1485, 1115, 1065, 1020, 750 ; ^1H nmr (300 MHz, $CDCl_3$) : 7.11 (dd, J=7.5, 1.4 Hz, H-9) ; 7.02 (dt, J=1.3, 7.5 Hz, H-11) ; 6.71 (dt, J=1.0, 7.5 Hz, H-10) ; 6.57 (ddd, J=7.5, 1.3, 1.0 Hz, H-12) ; 6.05 (t, J=1.4 Hz, H-2) ; 5.39 (quartet of quartets, J=7.2, 1.3 Hz, H-19) ; 4.10 (d, 2H, J=1.4 Hz, H-17) ; 3.68 (d of quintets, J=15.0, 1.6 Hz, H-21) ; 3.41 (br t, J=3.1 Hz, H-15) ; 3.30 (ddd, J=5.1, 7.2, 10.0 Hz, H- 5) ; 3.17 (d of quintets, J=15.0, 1.4 Hz, H-21) ; 2.63 (dt, J= 10.0, 7.6 Hz, H-5) ; 2.04 (m, 2H-6) ; 1.94 (m, 2H-14) ; 1.71 (dt, 3H, J=7.2, 1.4 Hz, CH_3-18).

Received, 22nd March, 1989