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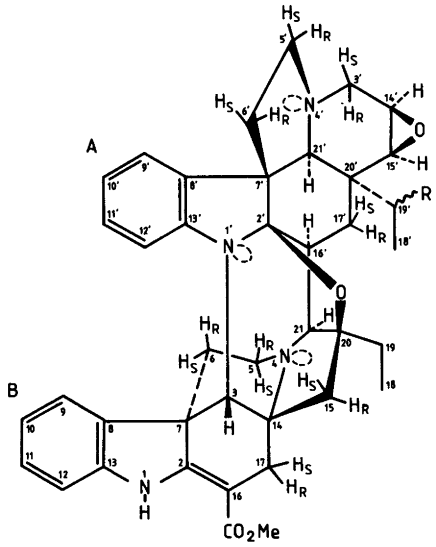
Determination of Structures by ^{1}H NMR at 400 MHz: Alkaloids of *Stenosolen heterophyllus*

AMELIA HENRIQUES,[a] CHRISTIANE KAN,[a] HENRI-PHILIPPE HUSSON,[a] SIEW-KWONG KAN[b] and MAURI LOUNASMAA[a]

[a] Institut de Chimie des Substances Naturelles, F-91190 Gif-sur-Yvette, France and [b] Institut d'Electronique Fondamentale, Université de Paris-Sud, F-91405 Orsay, France

The structures of three new dimeric indole alkaloids of ervafoline type from the leaves of *Stenosolen heterophyllus* (Vahl) Mgf (Apocynaceae) are described.

The leaves of *Stenosolen heterophyllus* (Vahl) Mgf (Apocynaceae),[1–3] a shrub from French Guyana, afforded five monomeric and eight dimeric indole alkaloids. One of the dimeric alkaloids, ervafoline, was shown by X-ray crystallography to possess the structure *1*.[4] To get useful ^{1}H NMR data for the structure determinations of the other dimeric indole alkaloids present, a detailed 400 MHz ^{1}H NMR study of ervafoline *1* was recently undertaken.[5] In the present communication we describe the structures of three of the eight dimeric alkaloids: 19′-hydroxyervafoline *2*, ervafolene *3* and 19′-hydroxyervafolene *4*. The five monomeric alkaloids proved to be identical with the known compounds voacangine hydroxyindolenine *5*,[6] voacangine *6*,[7] conoflorine *7*,[8,9] pandoline *8* [10] and pandine *9*.[11,12]



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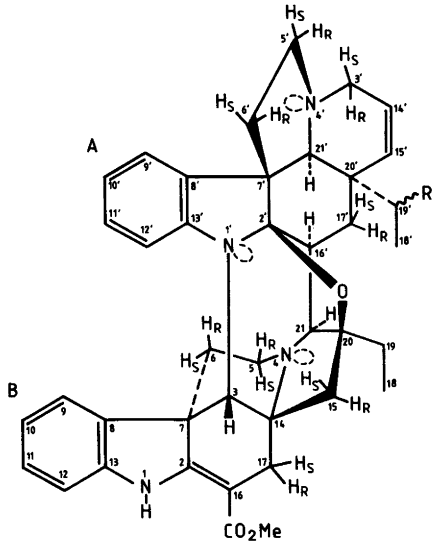

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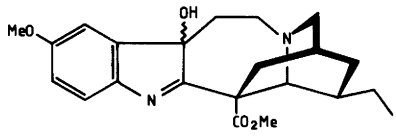

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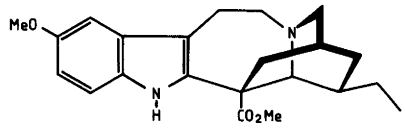

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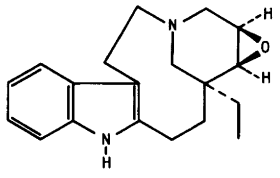

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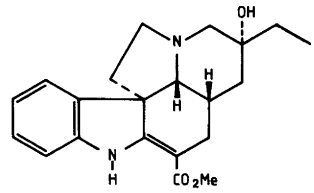

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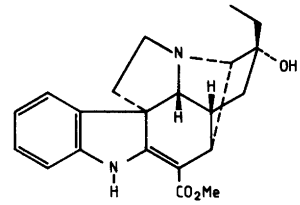

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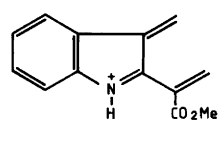
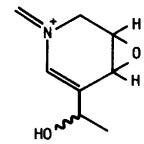
19′-Hydroxyervafoline *2*. M.p. 258 °C (dec.), $[\alpha]_D^{20}$ +247° (*c*, 1, $CHCl_3$), IR ($CHCl_3$) *v* OH 3330, C=O 1690, C=C 1630 cm^{-1}, UV (EtOH) λ_{max} (log ε) 252 (3.85), 306 (4.01), 326 (4.08) nm (β-anilinoacrylic and dihydroindolic chromophores). The mass spectrum showed a molecular ion at *m/e* 660 corresponding to $C_{40}H_{44}N_4O_5$ (high resolution). Other noteworthy peaks were at *m/e* 446 (M−214), 333,[4] 214 and 154 (Fig. 1). Acetylation of compound *2* transforms it to a monoacetate (MS M^+ at *m/e* 702; IR ($CHCl_3$) *v* C=O 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (3H, s, $-OCOCH_3$), 5.07 (1H, q, H−19′)). These first analytical data suggest that compound *2* is a hydroxy derivative of ervafoline *1*, with the hydroxy group situated in the A moiety of the molecule (*cf.* formula *2* and Ref. 4, *m/e* 333).

Ervafolene *3*.[13] Amorphous, $[\alpha]_D^{20}$ +236° (*c*, 0.2, MeOH), IR ($CHCl_3$) *v* C=O 1690, C=C 1620 cm^{-1}, UV (EtOH) λ_{max} (qualitative) 256, 310, 326 nm (β-anilinoacrylic and dihydroindolic chromophores). The mass spectrum showed a molecular ion at *m/e* 628 corresponding to $C_{40}H_{44}N_4O_3$ (centesimal analysis). Other noteworthy peaks were at *m/e* 414 (M−214), 333,[4] 214 and 122 (*vide supra*). On the basis of these first analytical data, compound *3* would appear to be a derivative of ervafoline *1*



$C_{13}H_{12}NO_2$
m/e 214



$C_8H_{12}NO_2$
m/e 154

Fig. 1. The fragments *m/e* 214 and *m/e* 154.

Table 1. ^1H NMR data of 19′-hydroxyervafoline *2*, ervafolene *3* and 19′-hydroxyervafolene *4*. Spectra were run in $CDCl_3$ at 400 MHz. Values are in δ (TMS=0), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad. The coupling constants between the aromatic protons are not included. The Hanson prochirality nomenclature system[14,15] is applied to distinguish between the H-atoms of different $-CH_2-$ groups. The signals due to the OH-groups are omitted.

Chemical shifts	*2*	*3*	*4*
H−3	3.84 s	3.90 s	3.87 s
H_R−5	2.83 br dd	2.9[b] m	2.8[f] m
H_S−5	3.4 m	3.5[b] m	3.4[f] m
H_R−6	1.8 m	1.8 m	1.8 m
H_S−6	1.74 br dd	1.7 m	1.8 m
H−9	6.36	6.42	6.40
H−10	6.35	6.40	6.34

Table 1. Continued.

H−11	6.97	6.98	6.95
H−12	6.72	6.75	6.71
H_R−15	2.10 d	2.15 d	2.12 d
H_S−15	2.00 d	2.01 d	2.00 d
H_R−17	2.94 d	2.95 d	2.94 d
H_S−17	2.49 d	2.50 d	2.49 d
H−18	0.96 t	0.96 t	0.96 t
H_R−19	1.8 br q	1.8 br q	1.76 br q
H_S−19	1.8 br q	1.8 br q	1.76 br q
H−21	3.54 d	3.50 d	3.49 d
CO_2Me	3.76 s	3.78 s	3.75 s
N−H	9.18 br s	9.24 br s	9.22 br s
H_R−3′	3.15 br d	3.18 br d	3.15 br d
H_S−3′	3.46 dd	3.38 dd	3.38 dd
H_R−5′	3.0[a] m	3.0[c] m	3.0[g] m
H_S−5′	3.1[a] m	3.1[c] m	3.1[g] m
H_R−6′	2.17 br dd	2.34 br dd	2.35 br dd
H_S−6′	1.24 br dd	1.2 m	1.15 br dd
H−9′	7.17	7.22	7.22
H−10′	6.50	6.53	6.51
H−11′	6.61	6.60	6.58
H−12′	5.66	5.64	5.64
H−14′	3.25 br dd	5.92 ddd	6.02 ddd
H−15′	3.03 d	5.75 br d	5.66 br d
H−16′	3.28 br dd	3.12 br d	3.58 br dd
H_R−17′	1.82 dd	−[d]	1.82 dd
H_S−17′	1.90 dd	−[d]	1.52 dd
H−18′	1.38 d	0.90 t	1.23 d
H_R−19′	3.9 br q	1.5[e] m	3.9 br q
H_S−19′		1.6[e] m	
H−21′	2.58 s	2.75 s	2.95 s

Coupling constants

2: $J_{15_R,15_S}=12$ Hz; $J_{17_R,17_S}=17$ Hz; $J_{18,19_R}=7.5$ Hz; $J_{18,19_S}=7.5$ Hz; $J_{21,16'}<0.3$ Hz; $J_{3'_R,3'_S}=14$ Hz; $J_{3'_R,14'}<0.3$ Hz; $J_{3'_S,14'}=1.5$ Hz; $J_{5'_R,6'_R}=12$ Hz; $J_{5'_R,6'_S}\approx 0.5$ Hz; $J_{5'_S,6'_R}=6$ Hz; $J_{5'_S,6'_S}=6$ Hz; $J_{6'_R,6'_S}=15$ Hz; $J_{14',15'}=4.5$ Hz; $J_{16',17'_R}\approx 2.5$ Hz; $J_{16',17'_S}=12$ Hz; $J_{17'_R,17'_S}=13$ Hz; $J_{18',19'}=7$ Hz.

3: $J_{15_R,15_S}=12$ Hz; $J_{17_R,17_S}=17.5$ Hz; $J_{18,19_R}=7.5$ Hz; $J_{18,19_S}=7.5$ Hz; $J_{21,16'}<0.3$ Hz; $J_{3'_R,3'_S}=14$ Hz; $J_{3'_R,14'}<0.5$ Hz; $J_{3'_S,14'}=5$ Hz; $J_{3'_R,15}<0.5$ Hz; $J_{3'_S,15'}<0.3$ Hz; $J_{5'_R,6'_R}=12$ Hz; $J_{5'_R,6'_S}\approx 0.5$ Hz; $J_{6'_R,6'_S}=15$ Hz; $J_{14',15'}=9.5$ Hz; $J_{16',17'_S}=12$ Hz; $J_{18',19'_R}=7$ Hz; $J_{18',19'_S}=7$ Hz.

4: $J_{15_R,15_S}=12$ Hz; $J_{17_R,17_S}=17$ Hz; $J_{18,19_R}=7.5$ Hz; $J_{18,19_S}=7.5$ Hz; $J_{21,16'}<0.3$ Hz; $J_{3'_R,3'_S}=14$ Hz; $J_{3'_R,14'}<0.5$ Hz; $J_{3'_S,14'}=5$ Hz; $J_{3'_R,15'}<0.5$ Hz; $J_{3'_S,15'}<0.3$ Hz; $J_{5'_R,6'_R}=12$ Hz; $J_{5'_R,6'_S}\approx 0.5$ Hz; $J_{5'_S,6'_R}=6$ Hz; $J_{5'_S,6'_S}=6$ Hz; $J_{6'_R,6'_S}=15$ Hz; $J_{14',15'}=9.5$ Hz; $J_{16',17'_R}\approx 2.5$ Hz; $J_{16',17'_S}=12$ Hz; $J_{17'_R,17'_S}=13$ Hz; $J_{18',19'}=7$ Hz.

[a,b,c,e,f,g] Assignments may be interchanged. [d] Impurities in the sample made it impossible to determine the H_R-17' and H_S-17' signals with certainty.

where the 14′,15′-epoxy group is replaced by a C=C double bond.

19′-Hydroxyervafolene *4*. M.p. 248 °C, $[\alpha]_D^{20}$ +284° (*c*, 1, $CHCl_3$), IR ($CHCl_3$) *v* OH 3330, C=O 1690, C=C 1610 cm^{-1}, UV (EtOH) λ_{max} (log ε) 254 (4.32), 303 (4.45), 326 (4.56) nm (β-anilinoacrylic and dihydroindolic chromophores). The mass spectrum showed a molecular ion at *m/e*

644 corresponding to $C_{40}H_{44}N_4O_4$ (high resolution). Other noteworthy peaks appeared at *m/e* 430 (M−214), 333,[4] 214 and 138 (*vide supra*). Catalytic hydrogenation of compound *4* gives a dihydro-derivative (MS M^+ at *m/e* 646). Acetylation of compound *4* transforms it to a monoacetate (MS M^+ at *m/e* 686). These first analytical data suggest that compound *4* is a hydroxy derivative of ervafolene *3* where the hydroxy group is situated in the A moiety of the molecule (*cf.* formula *4*).

The structures of the dimeric alkaloids *2*−*4* were verified by a detailed ^1H NMR study at 400 MHz. Application of consecutive double resonance experiments and comparison with the earlier ^1H NMR data of ervafoline *1* [5] permitted all of the protons in all three alkaloids *2*−*4* to be assigned. The chemical shifts and the coupling constants that were assigned are presented in Table 1. The results are in good agreement with the proposed structures *2*−*4*.

EXPERIMENTAL

Extraction of the air-dried leaves of *Stenosolen heterophyllus* (Vahl) Mgf (Apocynaceae) in the classical manner gave the total alkaloids in a 0.4 % yield. The monomeric and dimeric alkaloids were fractionated by filtration on Sephadex LH20. The monomers and dimers so separated were further fractionated by column chromatography on alumina followed by preparative layer chromatography on silica gel.

The plant material used was collected in July 1976 at the Ile de Cayenne in French Guyana. A botanical sample of *Stenosolen heterophyllus* has been deposited at the *Muséum National d'Histoire Naturelle de Paris* under the reference C. Moretti 130.

The NMR spectra were recorded on a laboratory-built 400 MHz ^1H high resolution spectrometer (I.E.F. 400)[16] and obtained by collecting 8 to 64 (32 to 254 for ervafolene *3*) free-induction decay signals for a 0.01 M (0.002 M for ervafolene *3*) solution of the sample in 450 μl of $CDCl_3$.

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