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ISOPHELLIBILIDINE, A NEW ALKALOID OF PHELLINE BILLIARDIERI : STRUCTURE AND HEMISYNTHESIS

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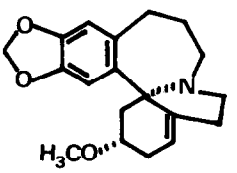
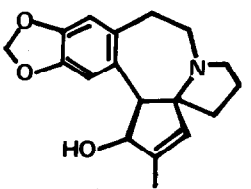
SUMMARY : Structure 3 proposed for isophellibilidine is confirmed by partial synthesis from the major alkaloid of Phelline billiardieri.

The inspection of the structures of the alkaloids present in several species of Cephalotaxus[1,5] and biosynthetic studies[6] show that homoerythrina alkaloids as 1 and esters of cephalotaxine 2 which possess significant antitumour activity[7] are probably derived from a common biogenetic precursor.



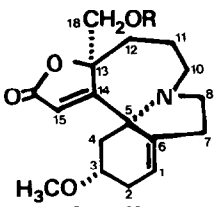
1



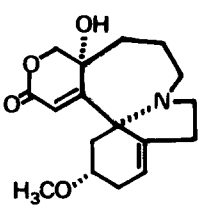
2

Several homoerythrina alkaloids isolated from Cephalotaxus were previously found in Phelline comosa, the first species of Phelline collected in New Caledonia[8]. The biogenetic relationship between 1 and 2 prompted us to investigate new species as Phelline billiardieri[9,10].

During this study, a new alkaloid 3[11] was isolated from the chloroform extract. High resolution mass spectroscopy of 3 shows it to be isomeric with phellibilidine 4[9b] (MW 305, $C_{17}H_{23}NO_4$). Moreover several peaks are common to the spectra of 3 and 4 (m/z : 178, 247, 274) indicating the same partial structure A[9b] :



3 R=H
5 R=Ac



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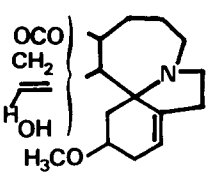


A

The i.r. absorption at 3380 cm^{-1} agrees with the presence of a hydroxyl group ; absorption at 1745 cm^{-1} can be attributed not to an unconjugated ester or δ-lactone but rather to an α,β-unsaturated γ-lactone also compatible with the UV and NMR data : PMR spectrum discloses the presence of two trisubstituted double bonds in addition to a methoxyl group and two

protons of an AB system (3.82 and 3.96 ppm, attributed to $-CH_2-O$) ; the ^{13}C NMR spectrum is very characteristic : comparison between the spectra of 3 and phellibilidine 4 (table 1) shows that the signal of C_{13} is strongly shifted downfield in 3. This high chemical shift (94.8 ppm) is in good agreement with a substitution by an oxygen atom of a γ-lactonic ring as, for example, in loliolide[13,14]. It is also noteworthy that the chemical shift of the methylen CH_2-O- (C_{18}) is smaller in 3 than in 4 and this point can be explained by the presence of a primary alcohol in the alkaloid 3 [the latter is confirmed by the downfield shift of the AB system (4.10 and 4.60 ppm) in PMR of the corresponding acetate 5] .

	C_3	C_5	C_6	C_8 C_{10}	C_{13}	C_{14}	C_1 C_{15}	C_{16}	C_{18}	OCH_3
3	72.9	65.1	140.8	49.2 46.7	94.8	166.1	120.2 118.7	172.5	67.1	56.2
4	73.6	68.2	140.5	49.8 48.0	70.3	159.9	120.0 119.3	164.1	76.9	56.2

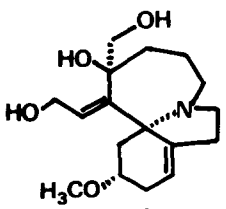
Table 1 (Brucker HX90E ; $CDCl_3$, δ/TMS)

The spectral data of isophellibilidine led to propose the plane structure 3 and allow to assign the pseudo-equatorial position of the methoxyl group at C_3[15].

The interconversion of the alkaloids 4 and 3 was attempted to verify their common configuration at spiro carbon C_5 but trans lactonization experiments[16,17] were unsuccessful.

On the other hand, LAH reductions of 3 and 4 did not lead to the same compound : the alkaloid 3 gave rise to the corresponding triol 6 while 4 afforded the diol 7.

Partial synthesis of isophellibilidine 3 was finally achieved starting from 8, the major alkaloidal constituent of Phelline billiardieri[9a].



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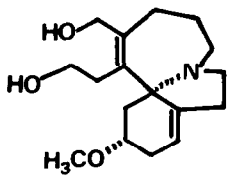

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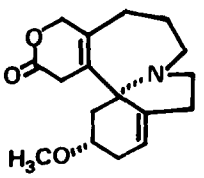
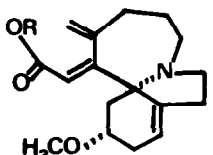
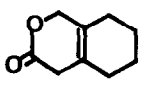


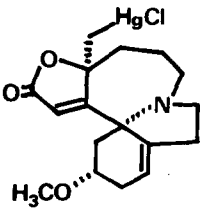
8



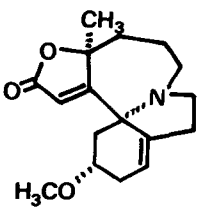
9 R = K
10 R = H



11



12



13

Compound 8 treated with KOH/MeOH 1M at room temperature led to the dienic salt 9 and then to the acid 10 (85%)[18]. This fragmentation reaction is therefore much easier than with the bicyclic lactone 11 in which the abstraction of a proton α to the carbonyl was promoted by a strong base like LDA[17].

Treatment of acid 10 with mercuric acetate (THF) afforded the mercuric derivative 12 , after brine addition. The stereospecificity of this step agrees with the configuration indicated at C_{13}[21].Mercuric derivative 12 in DMF solution was treated by $NaBH_4/O_2$ as described[22] to give a product of reduction 13 (18%)[23] in addition to isophellibilidine 3 itself (53%, comparison of mp , $(\alpha)_D$ and IR, UV, DC, PMR and mass spectra). This result confirms the structure of this new alkaloid and the configuration at C_3 and C_5.

ACKNOWLEDGEMENTS: The author wishes to thank Dr. T. Sévenet for the collection of plant material and Drs. S.K. Kan and R.Z. Andriamialisoa for PMR measurements at 400 MHz[24].

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11. 3 : mp 132° ; $[\alpha]_D$ 204° ($CHCl_3$ C=1.2); UV(EtOH, λ_{max} nm(ε): 213(9500), 280(2200); CD(EtOH), λ_{max}($\Delta\varepsilon$): 210(+28), 243(-7.8), 275(+ 4.2)[12]; MS(m/z): 305($M^{+\cdot}$), 274, 247(100%), 230, 216, 188, 178, 170, 148, 132, 120, 118. PMR(400 MHz, $CDCl_3$ δ/TMS): 5.60 (1H, s, C_{15}-H); 5.54 (1H, m, C_1-H); 3.96 (1H, d, $J_{18a,18b}$ = 12 Hz, C_{18}-H_a) ; 3.82 (1H, d, J=12 Hz, C_{18}-H_b); 3.58 (1H, m, C_3-H_{ax}); 3.41 (3H, s, OCH_3); 2.66 (1H, br d $J_{2a,2b}$=16 Hz, C_2-H_a); 2.56 (1H, dd, $J_{4eq,4ax}$=12 and $J_{3,4eq}$=3.5, C_4-H_{eq}); 1.97 (1H,m, C_2-H_b); 1.50 (1H, dd, $J_{4eq,4ax} \sim J_{3,4ax} \sim$ 12 Hz, C_4-H_{ax}).

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15. The coupling constant $J_{3,4ax}$=12 Hz agrees only with the presence of a pseudo-axial hydrogen at C_3.

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18. 10 :mp 215° ; IR : 1690 cm^{-1}; MS(m/z): 289($M^{+\cdot}$), 274, 258, 244, 186, 178, 170, 146(100%), 132, 120 ; PMR(60 MHz): 9.27(CO_2H); 5.50 (2H, s+m, C_{15}-H + C_1-H); 4.99 and 4.90 (2H, C_{18}-H_a and C_{18}-H_b); 3.30 (3H, s, OCH_3); 1.24 (1H, dd, $J_{4ax,4eq}$=12 Hz, C_4-H_{ax}).

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21. 12 (single TLC spot) was isolated in 93% yield : IR : 1745 cm^{-1} ; MS (m/z) : 525, 523 ($M^{+\cdot}$). The examination of molecular models, with the azepino ring in pseudo-chair conformation, shows that one side of the double bond is less hindered and indicates the stereochemistry of the oxymercuration reaction.

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23. 13 : mp 80° ; $[\alpha]_D$ 181° ($CHCl_3$ C=0.3); IR : 1750 cm^{-1}; UV(EtOH): 216, 280 nm ; CD(EtOH) : 210(+), 245(-), 284(+); MS(m/z): 289 ($M^{+\cdot}$), 274, 258, 231 (100%), 216, 214, 188, 170, 160, 148, 132 ; PMR (400 MHz): 5.54 (1H, m, C_1-H) ; 5.48 (1H, s, C_{15}-H) ; 3.52 (1H, m, C_3-H_{ax}) ; 3.39 (3H, s, OCH_3) ; 1.69 (3H, s, C_{13}-CH_2) ; 1.51 (1H, dd, J $\sim$ 12 Hz, C_4-H_{ax})

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