Strellidimine: the First Natural Bis-ellipticine Alkaloid

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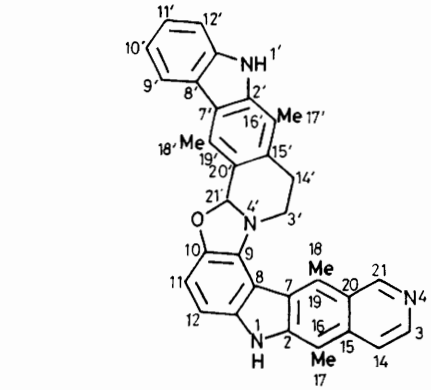
The structure determination and synthesis of strellidimine (**1**), the first ellipticine-derived bisindole alkaloid isolated from *Strychnos dinklagei* (Loganiaceae), are reported.

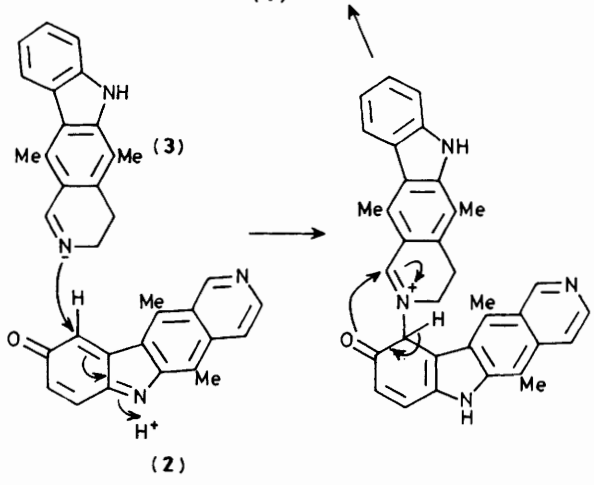
The occurrence of the antitumour alkaloid ellipticine and of some of its derivatives in various plants belonging to the family Apocynaceae is well documented.[1] Our recent work with the stem bark of *Strychnos dinklagei* Gilg (Loganiaceae)[2] has revealed surprisingly that it too contains ellipticine as well as several new naturally occurring derivatives at a higher oxidation level, such as 17-oxoellipticine, 18-hydroxyellipticine, and 10-hydroxyellipticine. We report here the structure elucidation and synthesis of strellidimine (**1**), the first example of a natural dimeric ellipticine-derived alkaloid.

Strellidimine (**1**) was isolated in small amounts from the bark of *Strychnos dinklagei* Gilg† (0.005% of the dried plant material) as a yellow amorphous solid, $C_{34}H_{28}N_4O$, $[\alpha]_D^{20}$ 0° (MeOH, *c* 0.1).‡ The u.v. spectrum displayed characteristic absorptions associated with a highly conjugated polyaromatic system involving at least one pyridine ring, and, in agreement, the i.r. spectrum exhibited a characteristic band at 810 cm^{-1}. No molecular ion of significant intensity could be detected by electron impact mass spectrometry, but a substantial fragment ion at *m/z* 195 suggested the presence of a dimethylcarbazole-derived unit.[3] In contrast, the chemical ionisation mass spectrum (NH_3) showed a prominent molecular ion $(M + H)^+$ at *m/z* 509, together with two fragment ions at *m/z* 263 and 247, typical for hydroxyellipticine and dihydroellipticine units, respectively.[2,4] The ^1H n.m.r. spectrum exhibited most of the characteristic signals of these two units, although there were differences in the aromatic region in comparison with the spectra of 10-hydroxyellipticine[5,6] and 3,14-dihydroellipticine.[4] The two signals typical for H-9 of 10-hydroxyellipticine and H-21 of 3,14-dihydroellipticine were absent from the spectrum of the dimeric compound whereas the two signals of H-11 and H-12 of the hydroxyellipticine moiety appeared as a simple AB system at δ 7.29 and 7.34. In addition, a supplementary singlet typical for an isolated proton at the 2-position of a 2,3-dihydro-oxazole ring appeared at δ 6.55. These elements permitted us to depict the structure of strellidimine as (**1**).

From a biogenetic point of view, strellidimine may be considered as arising from a condensation of the two monomeric units which co-occur in *S. dinklagei* bark.[2] The mechanism shown in Scheme 1 can be envisaged for the dimerisation: oxidation of 10-hydroxyellipticine leads to the electrophilic quinone–imine (**2**) which undergoes addition of dihydroellipticine (**3**) through its nucleophilic dihydropyridine nitrogen, and the quaternary adduct obtained rearranges, leading to the fused oxazole[7] system of (**1**).



(**1**)



(**3**)

(**2**)

Scheme 1

In order to verify the above mechanism, a suspension of 10-hydroxyellipticine and 3,14-dihydroellipticine in phosphate buffer (pH 7.4) was submitted to horseradish peroxidase–H_2O_2 oxidation[7] for 30 min. This reaction led in almost quantitative yield to strellidimine (**1**) identical with the natural product. The lack of optical activity in both natural and synthetic dimers suggests that the formation of the quaternary adduct and its subsequent cyclisation proceed by a non-enzymatic reaction.

The isolation of strellidimine is interesting from both biological and chemical points of view since the reaction

† Vouchers LAA 14790; held at the herbarium of the Centre National de Floristique de la République de Côte d'Ivoire (Abidjan).

‡ Satisfactory elemental and spectroscopic data were obtained for strellidimine (**1**): $C_{34}H_{28}N_4O$; $\lambda_{max.}$ (EtOH) (log ε) 244(4.39), 253(4.42), 265(4.33), 279(4.28), 298(4.38), 327(sh 3.67), 340(3.63), and 410(3.56) nm; $\nu_{max.}$ (KBr) 2910, 2840, 1590, 1445, 1225, and 810 cm^{-1}; *m/z* (desorption chemical ionisation, NH_3) 509 $(M + H)^+$ (100%), 493(10), 263(8), and 247(12); ^1H n.m.r. (CD_3SOCD_3, 270 MHz) δ (Me_4Si) 2.54, 2.82, 3.04, and 3.74 (4 × 3H, 4s, Me-17, -18, -17′, -18′), 3.14 (2H, m, CH_2-14′), 3.43 (2H, m, CH_2-3′), 6.55 (1H, s, H-21′), 7.25 (1H, td, *J* 8 and 1 Hz, H-10′), 7.29 (1H, d, *J* 8 Hz, H-11), 7.34 (1H, d, *J* 8 Hz, H-12), 7.46 (1H, td, *J* 8 and 1 Hz, H-11′), 7.60 (1H, dd, *J* 8 and 1 Hz, H-12′), 7.94 (1H, d, *J* 6 Hz, H-14), 8.28 (1H, dd, *J* 8 and 1 Hz, H-9′), 8.47 (1H, d, *J* 6 Hz, H-3), 9.69 (1H, s, H-21), and 11.30 (2H, br. s D_2O exch., NH-1 and NH-1′).

sequence involved in its formation seems similar to that implied in the alkylation of nucleosides by ellipticine derivatives currently used in anticancer chemotherapy.[7,8]

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