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DIMERIC INDOLE ALKALOIDS OF A NEW TYPE
A SYNTHETIC APPROACH TO THE ERVAFOLINE SERIES

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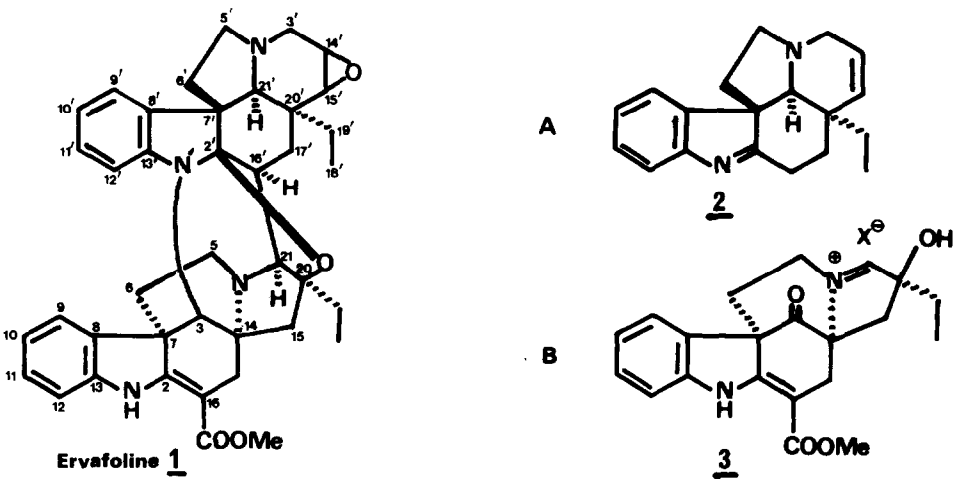
Summary : A synthetic approach towards the dimeric ervafoline indole alkaloids has been achieved via a route inspired from a biogenetic hypothesis.

Isolation of ervafoline 1, a dimeric indole alkaloid of a new type, from Stenosolen heterophyllus (Apocynaceae)[1] raises the problem of its biogenesis and of its synthesis. In order to identify the unknown alkaloids of the same series and to ascertain a biogenetic hypothesis[1] we have undertaken a biomimetic type synthetic approach to the ervafoline series.

Ervafoline 1 possesses the feature of having three bonds between the two constitutive moieties A and B. The C-16', C-21 bond can be formed initially by an enamine-iminium salt condensation between 2 and 3 and the C-20-O, C-2' bond formation follows by addition of the tertiary alcohol onto the resulting N'+=C-2' iminium salt (scheme 1). We can envisage the contraction of the piperidine ring of the B moiety via an aziridinium ion that is opened during the formation of the third bond or by nucleophilic attack of an hydroxyl ion.



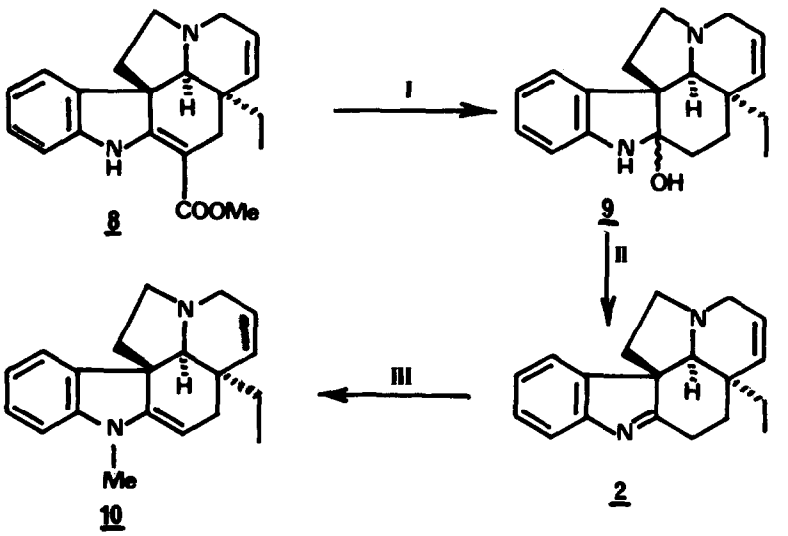
Scheme 1

The upper moiety A of ervafoline 1 can be considered as derived from tabersonine 8[2] and the lower one B from 20-epi-pandoline 4[3], an alkaloid found in the same plant[4].

The required reactive moieties for achieving the coupling reaction, according to the above-mentioned proposal, are the derivatives 2 and 3 (scheme 1) or their equivalents.

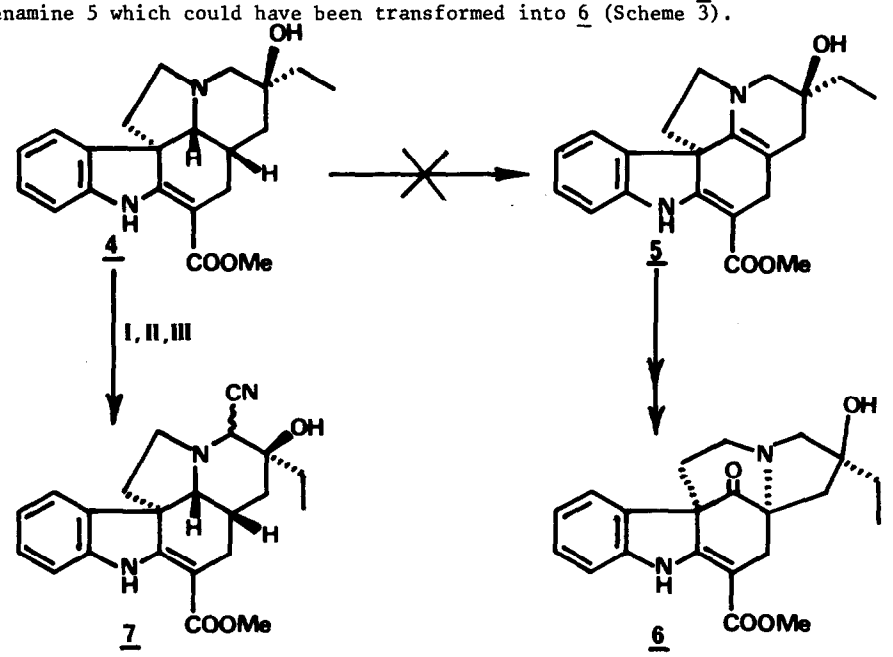
The imine 2 can be prepared by decarboxylation of tabersonine 8[15](scheme 2) according to a known procedure[3a] (HCl 10N, reflux, 10 min., under nitrogen). However, we have

isolated in high yield a mixture of the carbinolamine 9 (2/3)[5] and the expected imine 2 (1/3)[6]. Dehydration of 9 into 2 was achieved in boiling benzene in the presence of TsOH. In order to direct the reactivity of 2 as an enamine and to suppress side reactions, it was treated in THF with CH_3I in the presence of NaH to afford the N-methyl derivative 10[7].



Scheme 2 : Reagents : I, HCl 10 N, Δ, 10 mn, N_2 ; II, C_6H_6, TsOH, Δ, 1h. ; III, NaH, THF, CH_3I, 4h., r.t.

The formation of the spiro derivative 3 could be imagined from the enamine 5 derived from 20-epi-pandoline 4. Ring contraction of 5 by bromination and treatment of the resultant bromo iminium with NaOH[8-10] would give 6 a precursor of 3. Unfortunately, a modified Polonovski reaction[11] performed on the N-oxyde of 20-epi-pandoline 4 did not lead to the required enamine 5 which could have been transformed into 6 (Scheme 3).

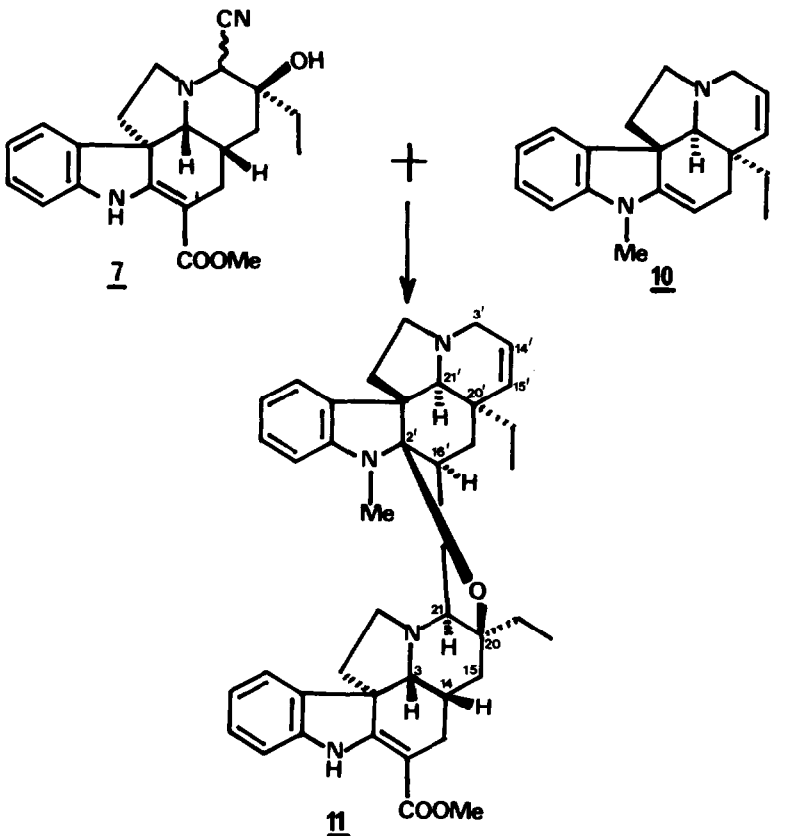


Scheme 3 : Reagents : I, H_2O_2, $CHCl_3$-EtOH (50 : 50), 50°, 24h ; C|Pd 10 % ; II, $(CF_3CO)_2O$, CH_2Cl_2, 0°, 2h ; III, KCN, H_2O, pH4, 15 mn.

Instead, after trapping the resultant sensitive iminium ion with cyanide[12], the α-cyano enamine 7 was obtained in 30 % yield. The structure of 7 was assigned on consideration of its spectral data[13], in particular the presence of the H-21 α to nitrile group as a singlet at δ 4.05 ppm in the ^{1}H NMR spectrum. It has not been possible to isolate any other oxidation products.

The occurrence of dimers of unknown structures, along with ervafoline 1 in the same plant[4], prompted us to use the intermediate 7, in coupling reactions to synthesize natural products or biogenetic intermediates having only two bonds between the two moieties.

We have previously demonstrated that α-cyano piperidines are equivalent and stable forms of iminium salts[12]. Thus, 7 is able to react electrophically with the enamine 10. A mixture of 7 (0.15 mmole) and 10 (0.15 mmole) was allowed to react in a THF solution, in the presence of $AgBF_4$ (0.15 mmole)[12] under a nitrogen atmosphere for 4 hours in the dark at room temperature. From the reaction mixture the dimer 11 (21 mg, Y : 20 %) was isolated on silica gel preparative tlc. Its structure was inferred from its spectral data, in particular from a complete interpretation of ^{13}C NMR spectrum[14].



Scheme 4

The proposed stereochemistry at C-2' and C-16', as depicted on scheme 4, is the same as in the natural product and appears to be the most likely ; it is that which requires the smallest steric interactions between the two reactive species during its formation.

The achievement of the synthesis of 11 demonstrates the probability that the mode of biogenetic formation of two of the three bonds in ervafoline 1 is that which was previously proposed.

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5 - 9 : amorphous ; MS m/e (relative intensity) : 278 (M-18, 100) ; UV λ_{max}^{EtOH} (qualitative) : 242, 298 nm ; ^{13}C NMR ($CDCl_3$, 15.08 MHz, TMS δ = 0) : 32.3, 32.4 (2t C-6, C-16 carbons not attributed) 94 (s C-2).

6 - 6 : amorphous ; MS m/e (relative intensity) : $M^{+\cdot}$ 278 (100 %) ; UV λ_{max}^{EtOH} (qualitative): 224, 260 nm ; ^{13}C NMR ($CDCl_3$, 15.08 MHz, TMS δ = 0) : 154.4 (s C-2)

7 - 10 : unstable product : MS m/e (relative intensity) : $M^{+\cdot}$ 292 (48), 135 (100), 107 (40); UV λ_{max}^{EtOH} (qualitative) : 225, 258, 279 nm ; $NaBH_4$ reduction in methanol gave the dihydroderivative, MS m/e (relative intensity) : $M^{+\cdot}$ 294 (100), 158 (48), 135 (92), 107 (20) ; UV λ_{max}^{EtOH} (qualitative) ; 256, 306 nm ; ^1H NMR ($CDCl_3$, 240 MHz, TMS δ = 0) : 2.65 (NCH_3).

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13 - 7 : amorphous ; MS m/e (relative intensity) : $M^{+\cdot}$ 379 (50), 214 (100) ; UV λ_{max}^{EtOH} (qualitative) ; 226, 298, 327 nm. ^1H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) : 3.51 (d, C-3 H), 3.74 (s, CO_2CH_3), 4.05 (s, C-21 H) ; ^{13}C NMR ($CDCl_3$, 15.08 MHz, TMS δ = 0) : 61.8 (d, C-21), 115.8 (s C≡N).

14 - 11 : amorphous; MS m/e (relative intensity) : $M^{+\cdot}$ 644 (75), 508 (72), 379 (100) ; UV λ_{max}^{EtOH} (quantitative , log ε) : 236 shoulder, 252 (4), 298 (4.14), 324 (4.18) nm ; ^1H NMR ($CDCl_3$, 240 MHz, TMS δ = 0) : 0.57 (t, C-18' H_3), 1 (t, C-18 H_3), 2.86 (s, $N-CH_3$), 3.79 (s, CO_2CH_3) - ^{13}C NMR ($CDCl_3$, 15.08 MHz, TMS δ = 0) : 33.8 (d, C-16'), 35.3 (t, C-6'), 56.8 (d, C-21), 72.5 (2d, C-3, C-21'), 75.6 (s, C-20), 104.1 (s, C-2').

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