poured into a separatory funnel containing cold saturated $NaHCO_3$. The aqueous layer was extracted with four 60-mL portions of cold ether, and the combined ether layers were washed 4 times with 60-mL portions of cold water, 1 time with saturated $NaHCO_3$, and 1 time with brine. Drying over magnesium sulfate, filtering, and rotary evaporation yielded 0.659 g of oil which contained a fair amount of MeOTs. The mixture was taken up in ether and washed 2 times with Et_3N. After workup of the ether layer, 0.278 g of a dark yellow oil was isolated, which appeared to be ca. 60% methyl enol ether and 40% cyclododecanone by GC analysis and as evidenced by the methyl singlet at δ 3.41 and a broad triplet at δ 4.27 (vinyl proton).

2-Hydroxy-5,6,9,10,11,12,13,14-octahydro-8(7*H*)-Benzocyclododecenone (12d). A solution of 0.0296 g of **13** in 1 mL of 48% HBr and 1 mL of acetic acid was stirred at reflux for 5 h. The cooled reaction was worked up by neutralizing with saturated $NaHCO_3$, extracting with ether, and washing with ether layer 2 times with saturated $NaHCO_3$ and 1 time with brine. After drying ($MgSO_4$), rotary evaporation gave 0.0199 g (71% yield) of **12d** as light yellow crystals: NMR ($CDCl_3$) δ 7.06 (d, J = 9 Hz, 1 H), 6.72–6.59 (m, 2 H), 5.25 (br s, 1 H), 2.80–2.27 (m, 8 H), 2.04–1.05 (m, 10 H); IR (neat) 3700–3100, 3040, 2950, 2875, 2705, 1705, 1620, 1595, 1510, 1475, 1455, 1375, 1355, 1290, 1250, 1170, 1135, 1115, 1035, 970, 920, 880, 830, 740 cm^{-1}; mass spectrum, m/e (relative %) 246 (100.0), 213 (24.6), 173 (26.4), 159 (51.7).

One-Carbon Expansion of 12b. The Me_3SiCN ring expansion procedure that was used earlier to prepare **7b** was applied to **12b** but only gave a low yield (<15%) of product. Analysis by GLC showed relative amounts of starting material (ca. 9%), an uncharacterized component of longer retention time (ca. 18%), and the major component, which corresponded to product, with the longest retention time (ca. 73%). The NMR spectrum of this mixture looked very similar to that of starting material, except there were two peaks of approximately equal height separated by about 1 Hz, corresponding to the methoxy hydrogens. The IR also was similar (carbonyl at 1710 cm^{-1}). A GC sample of the major component was collected for high-resolution mass spectrum, m/e 274.193 (calcd for $C_{18}H_{26}O_2$, 274.193).

Acknowledgment. This investigation was supported by NIH Research Grant R01 HDO 8550 with some supplemental support from NIH Biomedical Support Grant RRO 7079. We also thank the National Science Foundation for NMR instrument funding and the N. L. Tartar Research Fellowship Fund for a summer fellowship (J. R.P.). We also thank Susan Randall for capable NMR assistance and Richard Weilesek for mass spectra on the CEC 110B instrument at the University of Oregon.

Registry No. 2, 80262-93-7; **3b**, 80262-94-8; **3c**, 80262-95-9; **4a**, 830-77-3; **4b**, 80262-96-0; **4c**, 80262-97-1; **5b**, 80262-98-2; **6b**, 80262-99-3; **7a**, 80263-00-9; **7b**, 80263-01-0; **7c**, 80263-02-1; **8a**, 80263-03-2; **8a**-K, 80263-04-3; **8b**, 80263-05-4; **8c**, 80263-06-5; **9**, 80263-07-6; **10a**, 80263-08-7; **11a**, 80263-09-8; **12a**, 80263-10-1; **12b**, 80263-11-2; **12c**, 80263-12-3; **12d**, 80263-13-4; **13**, 80263-14-5; cycloheptanone, 502-42-1; *p*-bromoanisole, 104-92-7; cyclododecanone, 830-13-7.

New Dimeric Indole Alkaloids from *Stenosolen heterophyllus*: Structure Determinations and Synthetic Approach[1]

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Structures of eight new dimeric indole alkaloids of the ervafoline 1–4 and ervafolidine series 5–8, isolated from *Stenosolen heterophyllus* (Vahl) Mgf (Apocynaceae), were investigated by use of mass spectrometry, ^1H and ^{13}C nuclear magnetic resonance, and X-ray crystallography. A biogenetic pathway was proposed to take into account the formation of these unusual alkaloids, and, finally, a synthetic approach based on this proposal has been developed.

Introduction

Examination of the leaves of *Stenosolen heterophyllus* (Vahl) Mgf (Apocynaceae),[3,4] a shrub from French Guyana, has resulted in the isolation of several monomeric[1c,5] and two classes of four dimeric indole alkaloids.

Preliminary communications from our laboratories described the structural determination of the four dimeric alkaloids 1–4 of the ervafoline family.[1a-1c] In this paper we report the structural investigation of the second ervafolidine family of alkaloids 5–8 as well as X-ray studies concerning both series. Finally, in support of our efforts directed toward the synthesis of the new type of dimer, we present a synthetic approach inspired from our pro-

(1) Part of this work was published as preliminary communications: (a) Henriques, A.; Kan, C.; Ahond A.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1978**, 3707–3710. (b) Henriques, A.; Kan, S.-K.; Lounasmaa, M. *Acta Chem. Scand.*, **1979**, **B 33**, 775-776; (c) Henriques, A.; Kan, C.; Husson, H.-P.; Lounasmaa, M. *Acta Chem. Scand., Ser. B* **1980**, *34*, 509–512. (d) Henriques, A.; Husson, H.-P. *Tetrahedron Lett.* **1981**, *22*, 567–570.

(2) To whom all correspondance should be sent.

(3) (a) Vahl, M. *Ecol. Am.* **1798**, *2*, 22. (b) Vahl, M. *Icones Pl. Am.* **1799**, *2*, Table 14.

(4) Markgraf, F. *Notizbl. Botan. Gart. Berlin 16* **1938**, 122.

(5) Henriques, A.; Kan, C.; Jasor, Y.; Moretti, Y.; Husson, H.-P., unpublished results.

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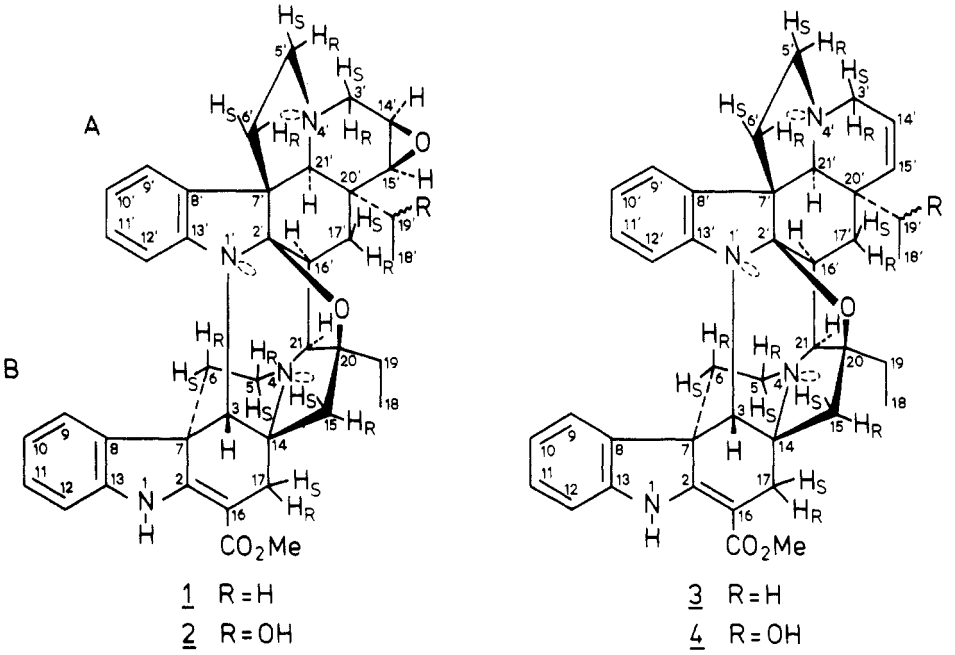


Figure 1.

posed biogenetic hypothesis.

Results and Discussion

A. Structural Determination. Ervafoline Series (1–4;[6] Figure 1). Ervafoline 1: $C_{40}H_{44}N_4O_4$ (high-resolution mass spectrometry, exact mass M^+· 644.3344, calcd 644.3362). Compound 1 gave the following spectral data: IR ($CHCl_3$) 1680, 1610 cm^{-1}; UV (ethanol) λ_{max} 252 (log ϵ 3.86), 306 (3.95), 326 nm (4.03); ^1H NMR ($CDCl_3$, Me_4Si, δ = 0 ppm) δ 3.74 (CO_2CH_3). The existence of a dihydroindolic and of a β-anilinoacrylic ester chromophores was inferred from these results.

When the NMR spectrum of ervafoline 1 was run in $CDCl_3$ containing a small amount of CF_3COOH, the triplet (6 H) located at δ 0.94 split into two three-proton triplets at δ 0.97 and 1.06, demonstrating the presence of two ethyl side chains. Treatment of 1 with acetic anhydride/pyridine did not result in acetylation, indicating that the two remaining oxygen atoms were probably present in the molecule as ether functions. This hypothesis is consistent with the ^{13}C NMR spectrum (supplementary material) which revealed the presence of a N–C–O linkage (s at 103.4) and an epoxide unit between C-14 and C-15 (2 d at δ 51.7 and 57.0) of an aspidosperma skeleton.[7] The observation of only one indolic nitrogen (^1H NMR δ 9.20 (s); mass spectrum, fragment at m/e 333 shifted 1 mass unit higher after deuteration) suggested the possible involvement of the other nitrogen in a bond between the two moieties of the dimer.

Ervafoline 1 was unreactive under the usual acidic conditions used for the cleavage of dimeric indole alkaloids.[8] On the basis of spectral data alone, it was not possible to conclusively assign the structure of ervafoline 1, although it was probable that it was composed of two aspidosperma-type units.

The complete structure and relative stereochemistry of ervafoline 1 were determined by a single-crystal X-ray study (see discussion below). With the knowledge of the structure of 1, it was then possible to make a complete analysis of its ^{13}C NMR spectrum (supplementary material) and of the 400-MHz ^1H NMR spectrum.[1b] Characteristic were the singlet at δ 3.86 for H-3 and the multiplet at δ 5.64 for the aromatic proton at C-12′ (that was identified by ^1H–^{13}C selective decoupling). The unusual shielding of the later proton could be due to an anisotropic effect of the neighboring aromatic ring.

These spectral features and the fragment at m/e 333 in the mass spectrum (part B of the dimer, see above) provided a good diagnostic tool for identification of the other unknown alkaloids 2, 3, and 4 of the ervafoline series.

19′-Hydroxyervafoline 2: $C_{40}H_{44}N_4O_5$ (high-resolution mass spectrometry, exact mass M^+· 660.333, calcd 660.3311). The UV spectrum of 2 was identical with that of 1 and the ^1H NMR[1] and mass spectra exhibited the same characteristic features described above for 1. The observation of the mass spectral fragment at m/e 333 indicated that the additional oxygen atom was located in the A part of the molecule. Formation of the monoacetate of 2 (mass spectrum, M^+· at m/e 702; IR 1750 cm^{-1}; ^1H NMR δ 2.07) demonstrated the presence of a hydroxyl group whose position was finally inferred from the appearance of CH_3-18′ as a doublet in the ^1H NMR spectrum (δ 1.38, J = 7 Hz). Application of consecutive double-resonance experiments and comparison with the ^1H NMR data for ervafoline 1 permitted once again the assignment of all the protons of 2.[1c]

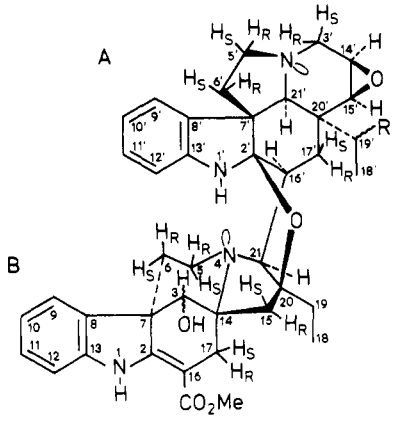
Ervafolene 3: $C_{40}H_{44}N_4O_3$ (microanalysis); mass spectrum, M^+· at m/e 628 with the noteworthy fragment at m/e 333 (vide supra). Peaks at m/e 135, 122, and 121[9] suggested that the epoxy group present in ervafoline 1 has been replaced by a C=C double bond in the piperidine ring of part A. This was confirmed by careful analysis of the 400-MHz NMR spectrum.[1c] By comparison with the

(6) The name ervafoline was previously given by Lathulliere, P.; Oliver, L.; Levy, J.; Le Men, J. *Ann. Pharm. Fr.* **1970**, *28*, 57–62, to an alkaloid of unknown structure isolated from *Ervatamia pandacaqui*, which proved to be identical with alkaloid 1 from *Stenosolen*. The utilized nomenclature follows that proposed by J. Le Men et al., except for isoervafolidine which we prefer to call epiervafolidine. The authors thank Mrs. Le Men for the gift of a sample of ervafoline.

(7) Kunesch, N.; Cave, A.; Hagaman, E. W.; Wenkert, E. *Tetrahedron Lett.* **1980**, *21*, 1727–1730.

(8) Neuss, N.; Gorman, M.; Hargrove, N.; Cone, N. J.; Biemann, K.; Büchi, G.; Manning, R. E. *J. Am. Chem. Soc.* **1964**, *86*, 1440–1442.

(9) Budzikiewicz, H.; Djerassi, C.; Williams, D. H. "Structure Elucidation of Natural Products by Mass Spectrometry"; Holden-Day: San Francisco, 1964; Vol. 1.



5 (3R), R=H
6 (3S), R=H
7 (3R,19'R), R=OH
8 (3S), R=OH

Figure 2.

spectrum of 1 the following changes were observed: disappearance of the two protons at δ 3.25 (H-14') and 3.03 (H-15') and appearance of two olefinic protons at δ 5.92 (H-14') and 5.75 (H-15').

19'-Hydroxyervafolene 4: $C_{40}H_{44}N_4O_4$ (high-resolution mass spectrometry, exact mass $M^{+\cdot}$ 644.3347, calcd 644.3362). It was evident from the mass spectrum that this new alkaloid was isomeric with respect to 1 and bore one more oxygen than 3. It was deduced from the ^1H NMR spectrum that the molecule possessed a double bond between C-14' and C-15' as in 3 (two protons at δ 6.02 and 5.66) and a secondary hydroxyl group at C-19' as in 2 [CH_3-18', δ 1.23 (d, J = 7 Hz)]. Catalytic hydrogenation of 4 gave a dihydro derivative (mass spectrum, $M^{+\cdot}$ at m/e 646) and acetylation afforded a mono-*O*-acetate derivative (mass spectrum $M^{+\cdot}$ at m/e 686), providing chemical proof for the presence of both the double bond and hydroxy group. In conjunction with the ^1H and ^{13}C NMR data (see ref 1c and supplementary material), it was thus concluded that 4 represented the correct structure.

Ervafolidine Series (5–8; Figure 2). Ervafolidine 5: $C_{40}H_{46}N_4O_5$ (high-resolution mass spectrometry, exact mass $M^{+\cdot}$ 662.3495, calcd 662.3468). Compound 5 gave the following spectral features: IR (neat) 3400, 3280 (NH, OH), 1685 (C=O), 1610 (C=C); UV (ethanol) λ_{max} 234 (sh), 248 (log ϵ 4.11), 306 (4.19), 324 nm (4.24) (β-anilinoacrylic and dihydroindolic chromophores).

Ervafolidine 5 was therefore related to ervafoline 1 but contained one additional oxygen and two additional hydrogen atoms which implied the opening of one ring.

The presence of an epoxy-substituted piperidine ring as found in the A part of 1 was inferred from the observation of fragments at m/e 108 and 138 in the mass spectrum.[10] The absence of the fragment at m/e 333 suggested a change in the B moiety of 5.

Comparison of the ^1H NMR spectrum for 5 (supplementary material) with that for 1[1b] showed the presence of two unsubstituted ethyl chains (2 t at δ 0.82 and 1.08, J = 7 Hz) and confirmed the presence of the epoxy group (H-15' d at δ 2.92, J = 4.5 Hz coupled to H-14' br dd at 3.26). A one-proton singlet at δ 3.87 was shifted significantly downfield to δ 5.20 on acetylation of 5 (mono-*O*-acetate derivative, mass spectrum, $M^{+\cdot}$ at m/e 704; IR 1750 cm^{-1}), suggesting the presence of a secondary hydroxyl group surrounded by two quaternary centers.

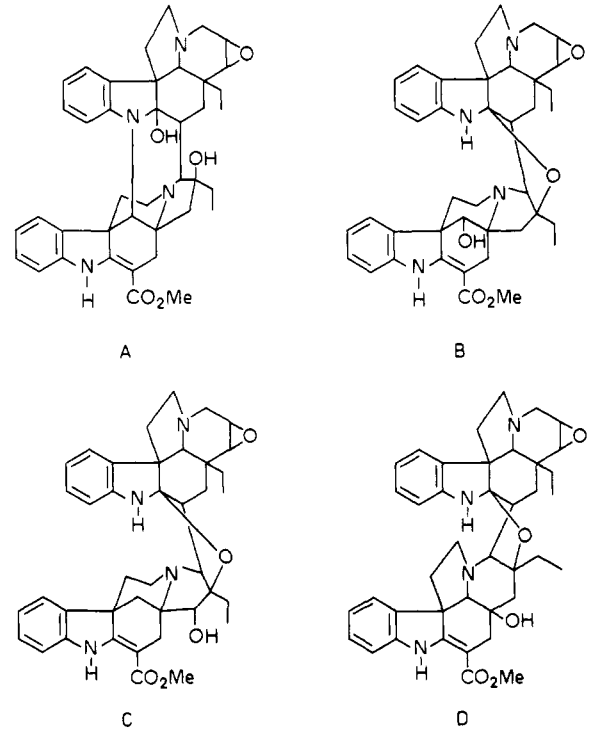


Figure 3.

This result eliminated the structures A and D from the four hypothetic structures A–D (Figure 3) that could be proposed in accordance with a biogenetic hypothesis (vide infra). The structure B for 5 was finally inferred by comparison of the 400-MHz ^1H NMR spectrum (supplementary material) with that obtained for 6, its epimer at C-3, whose structure was determinated by X-ray crystallography (vide infra).

3-*epi*-Ervafolidine 6. The structure of this alkaloid was determined by X-ray crystallography (vide infra and vide supra). A significant difference existed in the ^1H NMR spectra of ervafolidine 5 (3*R*) and its C-3 epimer 6 (3*S*). The H-3 changed from a singlet (δ 3.87) for 5 to a doublet (4.14, J = 5 Hz) for 6 due to coupling with the hydroxyl proton (demonstrated by exchange with deuterium oxide). This characteristic feature allows the attribution of the configuration at C-3 in these series.

19'(*R*)-Hydroxyervafolidine 7: $C_{40}H_{46}N_4O_6$, (high-resolution mass spectrometry, exact mass $M^{+\cdot}$ 678.3357, calcd 678.3417). The UV spectrum for 7 was identical with that for ervafolidines 5 and 6. The ^1H NMR spectrum suggested that 7 has one more OH on an ethyl chain [δ 1.19 (d, J = 7 Hz), 3.74 (q, J = 7 Hz, CH_3CHOH). This was confirmed by acetylation of 7 to its di-*O*-acetate derivative (mass spectrum, $M^{+\cdot}$ at m/e 762; IR 1760; NMR δ 1.74, 1.88 (2 s, CH_3C=O), 4.83 (m, H-19'), 5.51 (s, H-3)]. The supplementary hydroxyl group was proved to be located at C-19' by the observation in the ^{13}C NMR spectrum (supplementary material) that the quaternary C-20' at δ 40.2 was shielded (+4 ppm, β effect).

It is important to note that in the ervafolidine series the dihydroindolic nitrogen is in a sterically crowded environment which prevents its acetylation.

A striking resemblance was noted in the ^1H and ^{13}C NMR spectra of 5 and 7 (supplementary material) for all centers except for those in the region of C-20', indicating that the two molecules were strongly related.

The configuration *R* at C-19' of 7 was finally determined by an X-ray analysis (vide infra) that confirmed the proposed structure for 7.

(10) Moza, B. K.; Trojanek, J.; Bose, A. K.; Das, K. G.; Funke, P. *Lloydia* **1964**, 417.

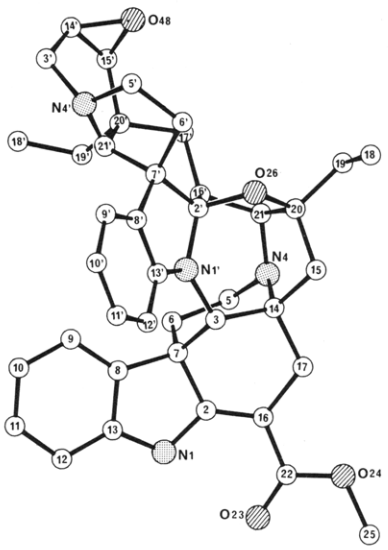


Figure 4. Perspective view of ervafoline **1** with X-ray nomenclature.

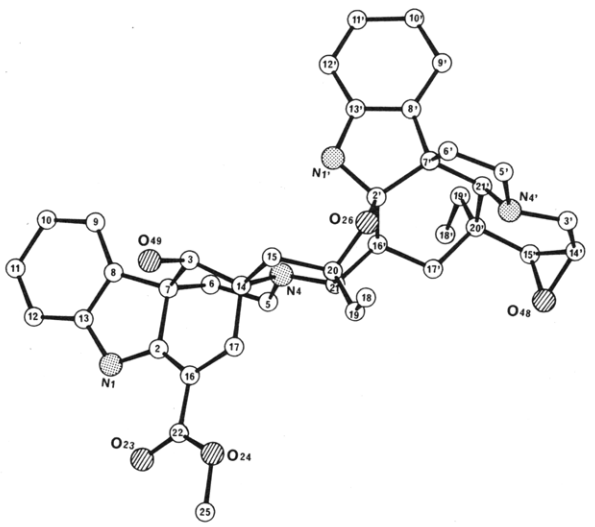


Figure 5. Perspective view of epiervafolidine **6** with X-ray nomenclature.

19′-Hydroxyepiervafolidine 8: $C_{40}H_{46}N_4O_6$ (high-resolution mass spectrometry, exact mass $M^{+\cdot}$ 678.3390, calcd 678.3417). The spectral data (mass, UV, ^1H and ^{13}C NMR) of **7** and **8** showed great similarities. A comparison of the ^1H and ^{13}C NMR spectra (supplementary material) established the identity of the structures. However, a significant shift difference was observed for H-3 (δ 4.16, d), indicating that **8** belonged to the 3-epi series. Similarly the differences found for the chemical shifts for H-16′ and the H-17′s can be interpreted as the result of an epimeric configuration at C-19′ between **7** (*R*) and **8** (*S*).

B. X-ray Diffraction Analysis of Alkaloids 1, 6, and 7. Figures 4, 5 and 6 represent a perspective view of the molecules. The absolute configurations were deduced from the relative configurations, if one admits that the lower moiety B is derived from 20-*epi*-pandoline, whose absolute configuration is known.[11]

Epiervafolidine **6** and 19′(*R*)-hydroxyervafolidine **7** which are in an extended general shape adopt identical conformations. The N(4) lone pair of electrons was found to be trans with respect to the C(14)–C(17) bond in both

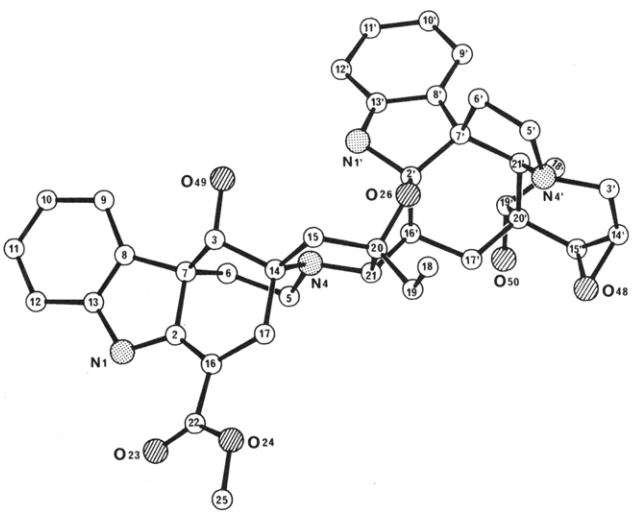


Figure 6. Perspective view of 19′-hydroxyervafolidine **7** with X-ray nomenclature.

molecules. In contrast, a cis conformation was observed in the crystal structure of ervafoline **1**, where C(3) was linked to N(1′). We observed also in these alkaloids an inversion of configuration of the nitrogen atom N(4′) with respect to ervafoline **1**. Comparative lists of bond lengths, bond angles, and torsion angles are given in the supplementary material. A relatively good agreement for equivalent values was noted.

In ervafoline **1** an intramolecular hydrogen bond of 2.703 Å exists between atoms N(1) and O(23) and the crystal cohesion is a result of normal van der Waals contacts only.

Epiervafolidine **6** and 19′(*R*)-hydroxyervafolidine **7** crystallize in the same space group $P2_12_12$ with methanol (in **6**) and acetone (in **7**) as solvents. Intramolecular hydrogen bonds were observed in the crystal structures of **6** and **7**. In **6**, between atoms N(1) and O(23), N(1)–H···O(23) = 2.75 Å and between atoms N(4) and N(1′), N(4)···HN(1′) = 3.21 Å. In **7**, between atoms N(1) and O(23), N(1)–H···O(23) = 2.76 Å and probably between atoms N(4) and O(49), N(4)···H–O(49) = 2.86 Å (hydrogen atom H(49) not located).

In epiervafolidine **6** (predominant isomer)[28] the methanol molecule bridges two neighboring molecules through two hydrogen bonds according to the scheme N(1′)···H–OMe(1)···H–O(49) with the respective distances of 2.98 and 2.84 Å. In the crystal structure of 19′(*R*)-hydroxyervafolidine **7**, an intramolecular hydrogen bond O(49)···H–N(1′) = 3.07 Å links two different molecules.

C. Biogenetic Considerations. The structural originality of the alkaloids in the ervafoline series poses several interesting biogenetic questions.

According to all evidence the A moiety of the dimer comes from a tabersonine-type molecule which, by decarboxylation, can give rise to the enamine **11**.

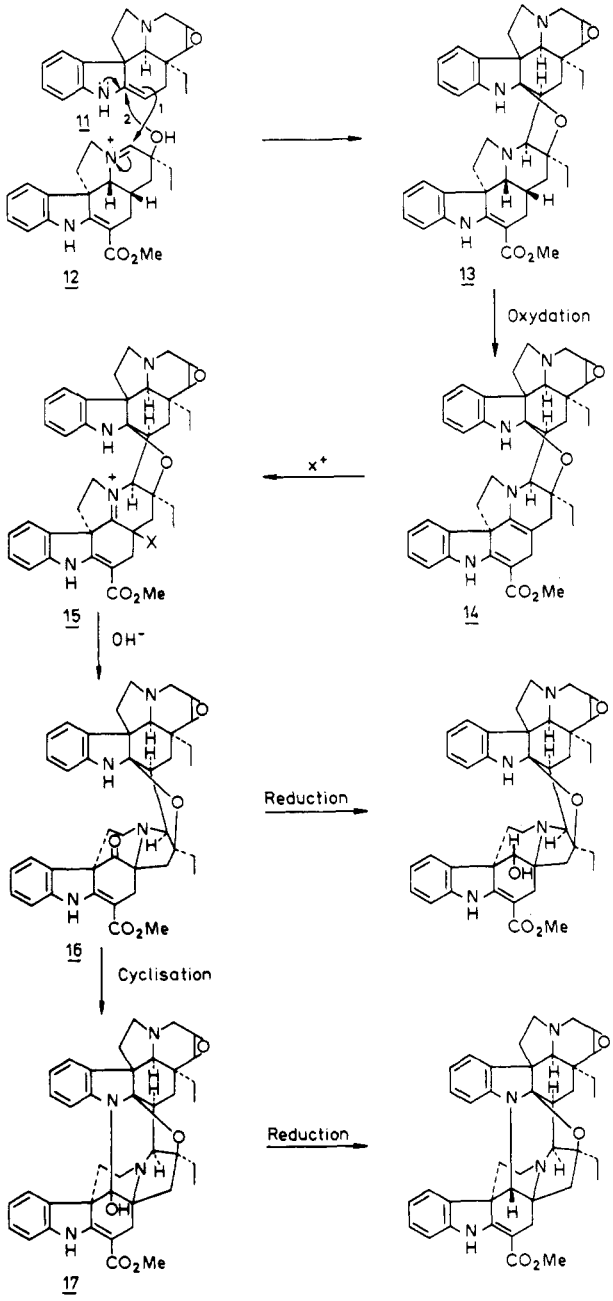
The B moiety is connected to the pandoline-type series[11] found in the same plant.[1c] However, this moiety has to be modified in a manner not yet found.

It can be expected that the coupling of the enamine **11** with the iminium **12** (Scheme I), formed from epipandoline **9** by oxidation, leads to intermediate **13**. After the rearrangement of **13** to the spiroketone **16**,[29] two routes are possible: reduction to ervafolidines **5**–**8** or cyclization to the carbinol amine **17**, followed by reduction to ervafolines **1**–**4**.

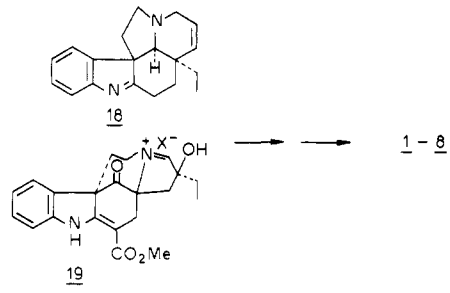
The proposed biogenetic hypothesis has inspired a synthetic scheme for these alkaloids (vide infra). The results obtained demonstrate the possibility of the formation of two of the three bonds between the moieties.

(11) Hoizey, M. J.; Sigaut, C.; Le Men-Olivier, L.; Levy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, 1601–1604.

Scheme I



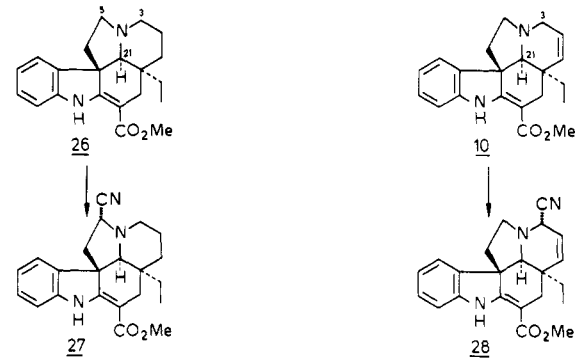
Scheme II



D. Synthetic Approach. Two strategies were considered for synthesizing the ervafoline system on the basis of biogenetic considerations.

The first consisted of the condensation of an enamine **11** derived from tabersonine **10** with an iminium **12** (or its equivalent **29**, Scheme IV), derived from 20-epipandoline **9**, followed by a ring contraction in the epipandoline unit (Scheme I).

Scheme III



The second convergent approach would involve an initial contraction of the ring D of epipandoline (Scheme IV) followed by oxidation to the iminium **19** (Scheme II) and final condensation with the above mentioned enamine **11**. Concerning the second route it must be noted that the monomeric alkaloids derived from **19** are not as yet known, which probably means that the ring contraction occurs after the dimerization step in the biosynthesis (Scheme I).

The first route was finally adopted due to the orientation of the oxidation of epipandoline toward **29** (= **12**) instead of **24** (vide infra).

Epipandoline Moiety. The oxidation of the piperidine ring nitrogen in the alkaloids of the aspidosperma type has been achieved by both chemical[22] or photochemical[23] means. However, neither of these methods produces an iminium system, a possible precursor of **24**. We therefore had to devise another method for effecting this transformation.

The Polonovski–Potier reaction has become an established method for the preparation of iminium ions,[24] which can be readily isolated as the corresponding α-amino nitriles.[25] The regioselectivity of this reaction was examined, using two readily available alkaloids in the aspidosperma series: vincadifformine **26** and tabersonine **10**.

On treatment of the *N*-oxide of vincadifformine **26** with trifluoroacetic anhydride followed by an aqueous solution of KCN buffered to pH 4, the 5α-cyano compound **27** (Scheme III) was obtained. The position of the substitution was determined by ^{1}H and ^{13}C NMR spectra.[23]

In contrast, treatment of the *N*-oxide of tabersonine **10**, under the same conditions, led to the 3α-cyano compound **28** (Scheme III), the reaction having been directed toward the allylic position. The ^{1}H and ^{13}C NMR spectra results were consistent with introduction of cyanide at the 3α-position.[23]

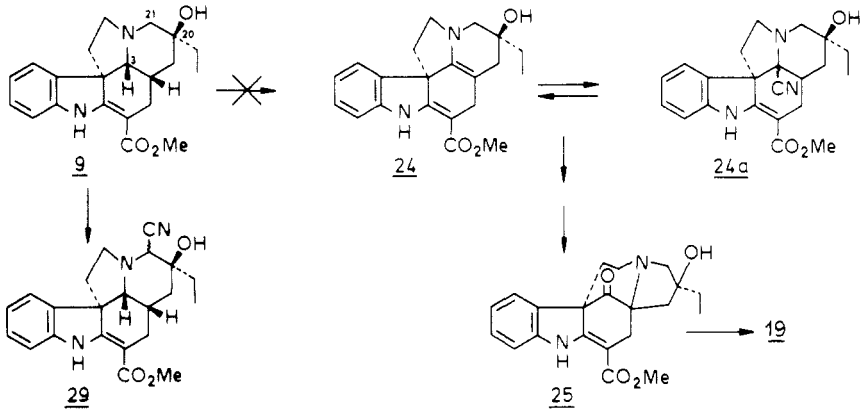
In neither case was it possible to isolate a C-21 oxidation product, although at least in the case of vincadifformine **26**, its formation could be logically expected. On the other hand, the relatively modest yields ($\simeq$50%) of the isolated products do not totally exclude its formation and thus the possible oxidation of epipandoline **9** to **24** (Scheme IV).

Epipandoline **9** possesses the same relative configuration as vincadifformine **26** and tabersonine **10**, but the ethyl side chain is in a different position (pseudoaspidosperma structure), which would permit the formation of the enamine **24** if the oxidation takes place at C-3 (equivalent of C-21 in **26**).[26]

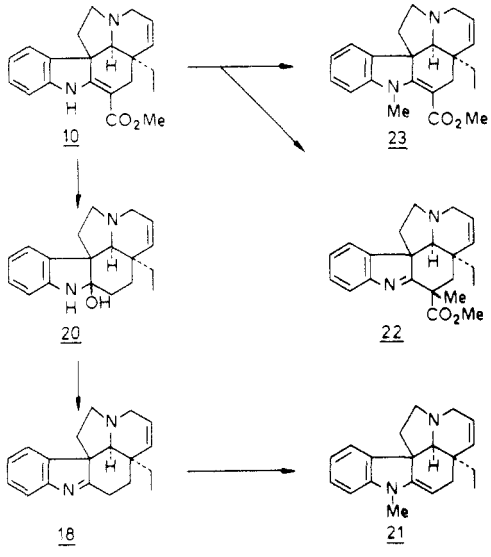
However, the *N*-oxide of epipandoline **9** gave under Polonovski–Potier reaction conditions the oxidation product **29** only, after trapping with cyanide (Scheme IV). The structure of **29** was determined by ^{1}H and ^{13}C NMR spectroscopy.

It appeared that the position of the oxidation is a

Scheme IV



Scheme V



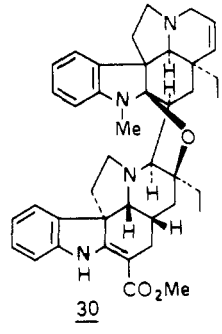


Figure 7.

function of the structure of each alkaloid under examination. Indeed, the presence of an hydroxyl group at C-20 in epipandoline **9** orients the oxidation to take place in a different position than it was found in the case of vincadifformine **26**.

Tabersonine Moiety. According to the adopted synthetic strategy, the imine **18** (Scheme V) or its equivalent represents the precursor of the A moiety of the dimer.

In order to enhance the enamine-type reactivity of **18** and to suppress side reactions (N-alkylation), we transformed **18** to its NCH_3 derivative **21**.

Two routes were considered for the preparation of **21**: (a) initial methylation of tabersonine **10**, followed by decarboxylation, and (b) methylation of the imine **18** obtained after decarboxylation of tabersonine **10**. The decarboxylation reaction, according to a known procedure,[11] was reported to lead to **18** (Scheme III).

However, treatment of **10** in 10 N aqueous HCl, under reflux conditions, yielded mainly the carbinol amine **20** (2/3) together with **18** (1/3). The dehydration of **20** to the desired product **18** was finally achieved by treatment with tosylic acid in benzene. The methylation of **18** to **21** was performed by treatment with methyl iodide in anhydrous THF in the presence of NaH.

Poor yield of the transformation of tabersonine **10** to *N*-methyl derivative **23** under the above conditions led us to abandon the first synthetic route.

Dimerization Reaction. It has been shown previously that α-cyanopiperidines are equivalent and stable forms of iminium salts.[25] As a consequence, α-cyanopiperidine **29** should be able to react electrophilically with the enamine **21**. Indeed, when a mixture of **29** (0.15 mmol) and **21** (0.15 mmol) was allowed to react in a THF solution, in the presence of $AgBF_4$ (0.15 mmol) under nitrogen for 4 at room temperature, the dimer **30** (Figure 7) was obtained (yield, 20 %). Its structure was inferred from its spectral data, particularly from the complete interpretation of its ^{13}C NMR spectrum. Characteristic were the resonances at δ 104.1 (C-2′, which is comparable with that for ervafoline **1**, 103.4) and δ 35.3 (C-6′, 1,3-diaxial interactions; γ effect, 8 ppm). These results, combined with the stereochemistry of the hydroxyl group in epipandoline **9** are consistent with a β-oriented ether bridge. The stereochemistry at C-2′ and C-16′, as depicted in Figure 7, is the same as that in the present natural analogues and appears to be the most likely; it produces the least steric interactions between the two reactive species during its formation.

The achievement of the synthesis of **30** supports the previously proposed mode of biogenetic formation of two of the three bonds in the ervafoline series (Scheme I).

Although the desired rearrangement of **30** to the spiropyrolidine analogue could not be achieved, the presented approach had permitted the preparation of a derivative whose natural occurrence cannot be a priori totally excluded.

Experimental Section

Infrared spectra (IR) were recorded on a Perkin-Elmer 257 spectrophotometer. Ultraviolet spectra (UV) were run in ethanol solution on a Bausch and Lomb Spectronic 505 spectrophotometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (Me_4Si as an internal standard, δ = 0 ppm) on a laboratory-built, 400-MHz, high-resolution spectrometer (IEF 400)[27] and obtained by collecting 8–128 free-induction decay signals for a ~0.005 *M solution of the sample* in 450 μL of $CDCl_3$. ^{13}C NMR spectra were recorded in $CDCl_3$ on either a Bruker HX 90 E (22.63 MHz) or WP 60 (15.08 MHz) instrument and high-resolution mass spectrometry was performed on an AEI MS 50 at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette). The elementary composition of the products was determined either by microanalysis or by high-resolution mass spectrometry.

Table I

	ervafoline 1	epiervafolidine 6	19′(*R*)-hydroxyervafolidine 7
molecular formula	$C_{40}H_{44}N_4O_4$	$C_{40}H_{46}N_4O_5$, CH_3OH	$C_{40}H_{46}N_4O_6$, $1.5CH_3COCH_3$
molecular weight	644	662 + 32	678 + 87
system	monoclinic	orthorhombic	orthorhombic
space group	$P2_1$	$P2_12_12$	$P2_12_12$
Z	2	4	4
a, Å	10.326 (1)	24.469 (4)	26.964 (7)
b, Å	14.738 (2)	18.246 (2)	13.791 (4)
c, Å	11.645 (1)	8.064 (1)	10.706 (4)
β, deg	111.65 (7)	90	90
V, Å^3	1647.17	3600.26	3981.14
D_c, g cm^{-3}	1.30	1.28	1.28
no. of collected reflctn	3109	3701	3915
no. of obsd reflctn	2702	2677	2973
final R value (for the obsd reflctn)	0.047	0.077	0.100
final R_w	0.053	0.089	0.120

Isolation of the Alkaloids. Extraction of the dry leaves of *Stenosolen heterophyllus* (2.5 kg) in the classical manner gave 10 g of crude alkaloids. After dissolution in the mixture $CHCl_3$–CH_3OH (30/70) and filtration through a column of Sephadex LH20, the monomeric and dimeric alkaloids were separated. The dimers were further purified by column chromatography on aluminum oxide followed by preparative TLC on silica gel and crystallization, yielding ervafolidine **1** (305 mg), 19′-hydroxyervafoline **2** (108 mg), ervafolene **3** (7 mg), 19′-hydroxyervafolene **4** (148 mg), ervafolidine **5** (57 mg), 3-*epi*-ervafolidine **6** (50 mg), 19′(*R*)-hydroxyervafolidine **7** (120 mg), and 19′-hydroxy-3-*epi*-ervafolidine **8** (240 mg).

The alkaloids exhibited the following characteristics: ervafoline **1**, mp 258 °C (acetone), $[\alpha]^{20}_D$ +279° (*c* 1, $CHCl_3$); 19′-hydroxyervafoline **2**, mp 258 °C (methanol), $[\alpha]^{20}_D$ +247° (*c* 1, $CHCl_3$); ervafolene **3**, amorphous, $[\alpha]^{20}_D$ +236° (*c* 1, CH_3OH); 19′-hydroxyervafolene **4**, mp 248 °C (acetone–hexane), $[\alpha]^{20}_D$ +284° (*c* 1, $CHCl_3$); ervafolidine **5**, mp 240 °C (ether–hexane), $[\alpha]^{20}_D$ +20° (*c* 0.5, $CHCl_3$); 3-*epi*-ervafolidine **6**, mp >260 °C (methanol), $[\alpha]^{20}_D$ +52° (*c* 0.5, $CHCl_3$); 19′(*R*)-hydroxyervafolidine **7**, mp 260 °C (acetone), $[\alpha]^{20}_D$ +33° (*c* 0.5, pyridine); 19′-hydroxy-3-*epi*-ervafolidine **8**, mp 260 °C (acetone–ether), $[\alpha]^{20}_D$ +74° (*c* 1, pyridine).

X-ray Diffraction Analysis. For the three compounds, intensity data were measured on a Philips PW 1100 diffractometer using graphite monochromated Cu Kα radiation (λ = 1.5418 Å) and the (ω–2θ) scan technique up to θ = 68°. Only intensities with $I > 3\sigma(I)$ were considered as observed, $\sigma(I)$ being derived from counting statistics. Corrections for Lorentz and polarization effects were applied but not for absorption. Cell parameters were refined by least-squares fitting of well-centered axial reflections. X-ray experimental data are given in Table I.

The structures were determined by direct methods. For ervafoline **1**, the MULTAN program was used, the best E map revealing most of the atoms and a Fourier synthesis the remaining ones. For epiervafolidine **6** and 19′(*R*)-hydroxyervafolidine **7**, the DEVIN 80 program was used.[13] Fifteen reflections were automatically chosen, three of them defining the origin of the unit cell. A phase function[14] was calculated in a 12-dimensional space, using selected quartets and quintets and a modified magic integers procedure.[15] The 200 best solutions were selected and subjected to phase extension and refinement by the tangent formula.[16] They were ranked according to the R Karle value and negative quartet criterion.[17] On the first E map, 35 of the 50 atoms expected were identified. The remaining atoms were located on successive Fourier synthesis.

Refinement of the Structures. The structures were refined by standard full-matrix least-squares methods, minimizing the quantity $\sum\omega(|F_o| - |F_c|)^2$, where the weight assigned to each reflection was $\omega = 1/\sigma^2(F_o)$. Atomic scattering factors were taken from the "International Tables for X-ray Crystallography".[18]

Ervafoline 1. Refinement was carried out with anisotropic thermal factors, all the hydrogen atoms being located on successive Fourier difference syntheses. Except those of the methyl groups, they were replaced geometrically (d(C–H) = 1.0 Å) and assigned the equivalent isotropic thermal factor of the attached C or N atom. The final standard residual R ($R = \sum ||F_o| - |F_c||/\sum|F_o|$) was 0.047 for the 2702 observed reflections (R_ω = 0.053).

Epiervafolidine 6. Anisotropic refinement for epiervafolidine **6** converged to an R value of 0.098. A difference Fourier synthesis calculated at this stage clearly revealed the following: (a) disorder of the ethyl chain C(19)–C(18) which occupies two different staggered positions with relative weights of 0.66 and 0.34 (refined values), (b) the presence of a methanol molecule of crystallization, and (c) hydrogen atoms. After two cycles of refinement and difference Fourier maps, it appeared that the methanol molecule was disordered, the molecule occupying two positions of relative weights 0.74 and 0.26 (refined values), the methyl group of which being practically superposed. So, the methanol was treated as two rigid groups with a fixed C–O distance of 1.430 Å. All hydrogen atoms were located except those of the methyl groups at C(18) and C(25). Their positions were idealized (C–H = 1.0 Å), except for the H atoms attached to N atoms. On all previous calculated difference Fourier syntheses, and even on the first E map, a peak linked to C(3) was present with a relative height 3 times that of H atoms. It became clear that epiervafolidine **6** and its C(3)-α epimer ervafolidine **5** (good crystals were obtained by slow evaporation of methanol solution of a mixture of the C(3)-α and C(3)-β epimers,) cocrystallize with relative proportions of 0.80 and 0.20 (refined values). Difference Fourier showed the predominant methanol molecule (experimental occupation factor 0.74) is hydrogen bonded to the C(3)-β predominant epimer. The disorder of the methanol molecule is thus a consequence of the cocrystallization of the two C(3) epimers. In the last cycles of refinement the sum of occupation factors of the disordered atoms was constrained to be equal to 1 and the isotropic temperature factor of the less important atom equal to that of the more important one. In this compound, the final R and R_ω values were respectively 0.077 and 0.089 for 2677 observed reflections.

19′(*R*)-Hydroxyervafolidine 7. Isotropic refinement of 19′(*R*)-hydroxyervafolidine **7** converged with standard residual $R = \sum||F_o| - |F_c||/\sum|F_o|$ of 0.15. At this stage a difference Fourier electron density map showed the presence of an acetone molecule of crystallization. Introduction of anisotropic temperature factors for the alkaloid atoms lowered the R value to 0.13. A new difference synthesis revealed the existence of a second molecule of acetone lying on a binary axis. This molecule, seeming to suffer from excessive thermal motion, was not refined. Anisotropic refinement was carried out, the solvent molecules being kept isotropic. Hydrogen atoms were found on successive difference Fourier maps, except those of the methyl groups C(18) and C(25) and hydroxyl groups O(49) and O(50). Their positions were idealized (C–H = 1.0 Å), except for the H atoms attached to N

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atoms. The final R and R_w values were respectively 0.10 and 0.12 for 2973 observed reflections.

For the three alkaloids **1**, **6**, and **7**, tables of the final atomic coordinates and thermal parameters, with a list of the observed and calculated structure factors are given in the supplementary material.

Modified Polonovski Reaction on Vincadifformine *N*-Oxide 26 → 27. To a solution of 598 mg (1.7 mmol) of vincadifformine **26** in 10 mL of $CHCl_3$ at 0 °C under nitrogen was added 328 mg (1.7 mmol) of *p*-nitroperbenzoic acid in 10 mL of $CHCl_3$. The mixture was stirred for 10 min, washed several times with a saturated $NaHCO_3$ solution and then with water, and dried over Na_2SO_4. Evaporation of the organic phase at room temperature afforded 520 mg (82%) of vincadifformine *N*-oxide. To a stirred solution of 250 mg (0.7 mol) of vincadifformine *N*-oxide in 4 mL of dry CH_2Cl_2 under nitrogen was added 0.2 mL of $(CF_3CO)_2O$. After 1-h reaction time at 0 °C followed by 1 h at room temperature, the mixture was evaporated to dryness. The mixture was dissolved in 4 mL of CH_2Cl_2 and 5 mL of an aqueous solution of KCN was added. The pH of the solution was adjusted to 4 either with CF_3COOH or with CH_3COOK. The mixture was vigorously stirred during 15 min, and reaction mixture was made basic with Na_2CO_3 and extracted with $CHCl_3$. After the normal workup, the crude product was purified by preparative layer chromatography (PLC; $CHCl_3$/MeOH, 95/5, silica gel), yielding 133 mg (50%) of 5α-cyanovincadifformine **27**.

5α-Cyanovincadifformine 27:[23] mp 212 °C (acetone; UV (EtOH) λ_{max} 328, 302, 231 nm; IR ($CHCl_3$) 2225, 1680, 1610 cm^{-1}; mass spectrum (70 eV, 200 °C), *m/e* 363 ($M^{+\cdot}$, 100), 336 (10), 214 (98); ^1H NMR ($CDCl_3$) δ 0.63 (3 H, t, *J* = 7 Hz, CH_3), 3.78 (3 H, s, CO_2CH_3), 3.9 (1 H, m, H-5), 6.7–7.48 (4 H, m, aromatic); ^{13}C NMR ($CDCl_3$) 166.8 (C-2), 48.6 (C-3), 53.4 (C-5), 47.3 (C-6), 54.9 (C-7), 135.5 (C-8), 123.1 (C-9), 121.3 (C-10), 128.2 (C-11), 109.7 (C-12), 143.6 (C-13), 21.8 (C-14), 32.6 (C-15), 93.4 (C-16), 24.8 (C-17), 7.1 (C-18), 29.0 (C-19), 38.7 (C-20), 69.8 (C-21), 169.2 (C=O), 51.2 (OCH_3), 118.0 (C≡N).

Modified Polonovski Reaction on Tabersonine *N*-Oxide 10 → 28. One gram (2.9 mmol) of tabersonine *N*-oxide prepared from tabersonine **10** analogously to vincadifformine *N*-oxide (vide supra) furnished 630 mg (60%) of 3α-cyanotabersonine **28**.

3α-Cyanotabersonine 28:[23] mp 210 °C (acetone); UV (EtOH) λ_{max} 330, 300, 230 nm; IR (neat) 2225, 1680, 1610 cm^{-1}; mass spectrum (70 eV, 180 °C), *m/e* 361 ($M^{+\cdot}$, 100), 334 (12), 214 (55); ^1H NMR ($CDCl_3$) δ 0.70 (3 H, t, *J* = 7 Hz, CH_3), 3.82 (3 H, s, CO_2CH_3), 4.48 (1 H, d, *J* = 4.5 Hz, H-3), 6.0 (3 H, m, H-14, H-15), 6.8-7.5 (4 H, m, aromatic); ^{13}C NMR ($CDCl_3$) 166.0 (C-2), 50.0 (C-3), 48.5 (C-5), 43.7 (C-6), 54.4 (C-7), 136.9 (C-8), 121.1 (C-9), 119.9 (C-10), 128.1 (C-11), 109.5 (C-12), 143.0 (C-13), 121.8 (C-14), 137.8 (C-15), 91.5 (C-16), 26.0 (C-17), 7.3 (C-18), 27.1 (C-19), 41.9 (C-20), 65.3 (C-21), 168.6 (C=O), 51.1 (OCH_3), 115.7 (C≡N).

Modified Polonovski Reaction on Epipandoline *N*-Oxide 9 → 29. A solution of 227 mg (0.64 mmol) of epipandoline **9** in 6 mL of EtOH/CH_2Cl_2 (1/1) was stirred 48 h at 60 °C with 0.2 mL of H_2O_2 (30%). Excess of H_2O_2 was destroyed by Pd/C (5%). Stirring was continued 24 h at room temperature. The mixture was filtered on Celite and evaporated to dryness, yielding 221 mg (96%) of epipandoline *N*-oxide which, treated analogously to the described in conection with vincadifformine *N*-oxide (vide supra), afforded 70 mg (30%) of 21-cyanoepipandoline **29**.

21-Cyanoepipandoline 29: amorphous; UV (EtOH) λ_{max} 330, 304, 234 nm; IR ($CHCl_3$) 2228, 1680, 1610 cm^{-1}; mass spectrum (70 eV, 280 °C), *m/e* 379 ($M^{+\cdot}$, 50), 352 (10), 214 (100); ^1H NMR ($CDCl_3$) δ 1.00 (3 H, t, *J* = 7 Hz, CH_3), 3.51 (1 H, d, *J* = 4 Hz, H-3), 3.74 (3 H, s, CO_2CH_3), 4.05 (1 H, s, H-21), 6.78 (1 H, d, *J* = 8 Hz, H-12), 6.88 (1 H, t, *J* = 8 Hz, H-10), 7.10 (1 H, t, *J* = 8 Hz, H-11), 7.28 (1 H, d, *J* = 8 Hz, H-9); ^{13}C NMR ($CDCl_3$) 165.2 (C-2), 61.7 (C-3), 48.9 (C-5), 43.7 (C-6), 54.6 (C-7), 136.9 (C-8), 122.2 (C-9), 121.2 (C-10), 128.3 (C-11), 109.5 (C-12), 143.7 (C-13), 35.0 (C-14), 36.9 (C-15), 95.8 (C-16), 24.5 (C-17), 7.9 (C-18), 33.7 (C-19), 71.9 (C-20), 61.8 (C-21), 168.4 (C=O), 51.1 (OCH_3), 115.8 (C≡N).

Decarboxylation of Tabersonine 10 → 18 + 20. One gram (3.0 mmol) of tabersonine **10**, dissolved in 10 mL of 10 N HCl, was heated at 105 °C under nitrogen for 10 min. The solution was diluted with 50 mL of ice–water, alkalized with a 50% NaOH solution, and extracted with $CHCl_3$. The organic phase was washed with water, dried over Na_2SO_4 and evaporated to yield 731 mg (93%) of a mixture of two products. The crystallization in ether furnished 524 mg (65%) of carbinol amine **20**. From the mother liquor 207 mg (28%) of pure indolenine **18** was obtained. Alternatively, 500 mg of tabersonine **10** (1.5 mmol) was hydrolyzed as above. After alkalinization with NH_4OH, followed by extraction and purification, 196 mg (49%) of carbinol amine **20** and 152 mg (41%) of indolenine **18** were obtained.

Carbinol Amine 20: mp 124 °C (ether); UV (EtOH) λ_{max} 242, 298 nm; IR (film) 3400, 3350 cm^{-1}; mass spectrum (70 eV, 200 °C), *m/e* 278 ($M^{+\cdot}$, 100), 134 (17), 122 (10), 121 (17); ^1H NMR ($CDCl_3$) δ 0.78 (3 H, t, *J* = 8 Hz, CH_3), 2.75 (1 H, s, H-21), 3.75, 3.88 (1 H each, br s, HO, NH), 5.49 (1 H, dd, *J* = 10 Hz, H-15), 5.64 (1 H, ddd, *J* = 10, 5, 2 Hz, H-14), 6.56 (1 H, d, *J* = 8 Hz, H-12), 6.70 (1 H, t, *J* = 8 Hz, H-10), 6.99 (1 H, t, *J* = 8 Hz, H-11), 7.01 (1 H, d, *J* = 8 Hz, H-9); ^{13}C NMR ($CDCl_3$) 94.0 (C-2), 53.3[a] (C-3), 53.5[a] (C-5), 32.4[b] (C-6), 55.7 (C-7), 135.9 (C-8), 122.7 (C-9), 119.8 (C-10), 127.7 (C-11), 110.5 (C-12), 147.1 (C-13), 122.7 (C-14), 134.5 (C-15), 32.3[b] (C-16), 28.0[c] (C-17), 7.88 (C-18), 28.5[c] (C-19), 39.0 (C-20), 66.1 (C-21) (a, b, c indicates assignments may be interchanged).

Indolenine 18: amorphous; UV (EtOH) λ_{max} 224, 260 nm; mass spectrum (70 eV, 220 °C), *m/e* 278 ($M^{+\cdot}$, 100); ^1H NMR ($CDCl_3$) δ 0.62 (3 H, t, *J* = 8 Hz, CH_3), 2.70 (1 H, s, H-21), 5.51 (1 H, dd, *J* = 10, 2 Hz, H-15), 5.70 (1 H, ddd, *J* = 10, 5, 2 Hz, H-14), 7.15–7.51 (4 H, m, aromatic); ^{13}C NMR ($CDCl_3$) 190.3 (C-2), 51.6 (C-3), 53.6 (C-5), 35.8 (C-6), 61.0 (C-7), 147.2 (C-8), 127.7 (C-9), 125.4 (C-10), 121.3 (C-11), 120.2 (C-12), 154.4 (C-13), 124.6 (C-14), 134.4 (C-15), 24.7 (C-16), 29.1 (C-17), 8.2 (C-18), 30.0 (C-19), 40.4 (C-20), 73.4 (C-21).

Dehydration of Carbinol Amine 20 → 18. To a stirred solution of 180 mg of anhydrous tosylic acid in anhydrous benzene under nitrogen was added 80 mg (0.27 mmol) of carbinol amine **20**. The mixture was refluxed for 1 h, evaporated, treated with Na_2CO_3 solution, and extracted with $CHCl_3$. The organic phase was washed with water, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by PLC ($CHCl_3$/MeOH, 98/2, NH_3 saturated, silica gel), yielding 32 mg (43%) of indolenine **18**, identical with the compound described above.

Methylation of Tabersonine 10 → 22 + 23. A 580-mg (1.7 mmol) sample of tabersonine **10** was methylated analogously to the methylation of indolenine **18** (vide supra). The excess of NaH was decomposed by adding 10 g of alumina. After the normal workup the crude product was purified by PLC ($CHCl_3$, silica gel), yielding 345 mg (60%) of indolenine **22** and 118 mg (20%) of *N*-methyltabersonine **23**.

Indolenine 22: mp 151 °C (MeOH); UV (EtOH) λ_{max} 232, 274 nm; IR ($CHCl_3$) 1735 cm^{-1}; mass spectrum, (70 eV, 200 °C), *m/e*

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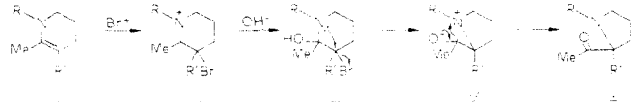
(28) The probable hydrogen bonding scheme for the minor isomer (ervafolidine **5**) is N(4)···H–O(49′) = 2.81 Å and N(1′)···HO–Me(2) = 3.14 Å.
(29) The rearrangement of the piperidine ring into a spiropyrrolidine (**13** → **14** → **15** → **16**; Scheme I) is supported by a similar reaction found earlier.[19-21] When the enamine i is brominated the bromo iminium ii is formed. Its attack by an OH^- ion leads to the carbinol amine iii and then to the aziridinium intermediate iv, which can open to give the ketone v.



350 (M^+·, 100), 135 (82), 122 (28), 107 (36); ^1H NMR ($CDCl_3$) δ 1.83 (3 H, s, 16-CH_3), 3.86 (3 H, s, OCH_3, 5.53 (1 H, dd, J = 10, 2 Hz, H-15), 5.74 (1 H, ddd, J = 10, 5, 2 Hz, H-14), 7.20 (1 H, t, J = 8 Hz, H-11), 7.27 (1 H, t, J = 8 Hz, H-10), 7.30 (1 H, d, J = 8 Hz, H-12), 7.56 (1 H, d, J = 8 Hz, H-9); ^{13}C NMR ($CDCl_3$) 188.2 (C-2), 52.4 (C-3), 54.1 (C-5), 44.5 (C-6), 61.0 (C-7), 147.5 (C-8), 121.1 (C-9), 124.3 (C-10), 127.4 (C-11), 120.4 (C-12), 152.3 (C-13), 125.8 (C-14), 134.4 (C-15), 49.2 (C-16), 27.5(C-17), 8.3 (C-18), 26.5 (C-19), 40.4 (C-20), 72.9 (C-21).

***N*-Methyltabersonine 23**: amorphous; UV (EtOH) λ_{max} 310, 338 nm; IR ($CHCl_3$) 1680, 1630 cm^{-1}; mass spectrum (70 eV, 180 °C), m/e (M^+·, 88), 122 (100); ^1H NMR ($CDCl_3$) δ 0.56 (3 H, t, J = 7 Hz, CH_3), 3.25 (3 H, s, NCH_3), 3.86 (3 H, s, CO_2CH_3), 5.48 (1 H, dd, J = 10, 2 Hz, H-15), 5.63 (1 H, ddd, J = 10, 5, 2 Hz, H-14), 6.9-7.4 (4 H, m, aromatic).

Methylation of Indolenine 18 → 21. To a stirred solution of 200 mg (0.72 mmol) of indolenine **18** in 12 mL of anhydrous THF under nitrogen was added 18 mg (0.75 mmol) of NaH. After 15 min 0.1 mL (1.6 mmol) of CH_3I was added and the mixture was stirred for 17 h at room temperature. The mixture was poured in water and extracted with CH_2Cl_2. After the normal workup the crude product was purified by PLC ($CHCl_3$/MeOH, 95/5, silica gel), yielding 39 mg (19%) of enamine **21**.

Enamine 21: amorphous; UV (EtOH) λ_{max} 225, 258, 279 nm; mass spectrum (70 eV, 200 °C), m/e 292 (M^+·, 48), 135 (100); ^1H NMR ($CDCl_3$) δ 0.55 (3 H, t, J = 8 Hz, CH_3), 2.88 (3 H, s, NCH_3), 5.43 (1 H, m, H-16), 5.60 (1 H, dd, J = 10, 2 Hz, H-15), 5.58 (1 H, m, H-14), 7.0-7.5 (4 H, m, aromatic).

Coupling of Enamine 21 with 21-Cyanoepipandoline 29. To a solution of 60 mg (0.15 mmol) of 21-cyanoepipandoline **29** in anhydrous THF under nitrogen were added 30 mg (0.15 mmol) of $AgBF_4$ in anhydrous THF and then 45 mg (0.15 mmol) of enamine **21** equally in anhydrous THF. The mixture was kept in darkness at room temperature for 3 h. The mixture was filtered on Celite and washed with 10% NH_4OH solution and then with CH_2Cl_2. This was repeated 3 times. The organic phase, after normal workup, afforded the crude product, which was purified on PLC (EtOAc/hexane, 2/35, alumina), yielding 21 mg (20%) of the dimer **30**.

Dimer 30: amorphous; UV (EtOH) λ_{max} 324 (log ϵ 4.18), 298 (4.14), 252 (4.00), 236 nm (sh); IR ($CHCl_3$) 1680, 1610 cm^{-1}; mass spectrum (70 eV, 250 °C), m/e 644 (M^+·, 75), 379 (100), 291 (50), 278 (40), 135 (40), 122 (35), 121 (20), 107 (24); ^1H NMR ($CDCl_3$) 0.57 (3 H, t, J = 7 Hz, CH_3 (C-18')), 1.00 (3 H, t, J = 7 Hz, CH_3 (C-18)), 2.86 (3 H, s, NCH_3), 3.79 (3 H, s, CO_2CH_3), 5.46 (1 H, dd, J = 10, 2 Hz, H-15'), 5.72 (1 H, m, H-14'), 6.30 (1 H, d, J = 8 Hz, H-12), 6.65 (1 H, t, J = 8 Hz, H-10), 6.84 (1 H, d, J = 8 Hz, H-12'), 6.95 (1 H, t, J = 8 Hz, H-10'), 7.05 (1 H, t, J = 8 Hz, H-11), 7.07 (1 H, d, J = 8 Hz, H-9), 7.19 (1 H, t, J = 8 Hz, H-11'), 7.23 (1 H, d, J = 8 Hz, H-9'); ^{13}C NMR ($CDCl_3$) 164.9 (C-2), 72.5 (C-3), 49.0[a] (C-5), 43.1 (C-6), 54.1 (C-7), 136.4 (C-8), 120.2[c] (C-9), 119.3 (C-10), 126.6 (C-11), 108.0 (C-12), 142.4 (C-13), 31.9 (C-14), 35.6[b] (C-15), 95.2 (C-16), 23.0 (C-17), 7.2 (C-18), 32.7 (C-19), 75.6 (C-20), 56.8 (C-21), 167.3 (C=O), 49.5 (OCH_3), 104.1 (C-2'), 50.7[a] (C-3'), 52.7 (C-5'), 35.3[b] (C-6'), 55.0 (C-7'), 136.2 (C-8'), 121.0[c] (C-9'), 116.2 (C-10'), 126.0 (C-11'), 103.5 (C-12'), 150.0 (C-13'), 122.6 (C-14'), 135.0 (C-15'), 33.8 (C-16'), 29.1 (C-17'), 7.2 (C-18'), 32.7 (C-19'), 38.0 (C-20'), 72.5 (C-21'), 26.7 (N'CH_3) (a, b, c indicates assignments may be interchanged.

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Registry No. **1**, 70545-44-7; **2**, 77784-40-8; **3**, 77784-39-5; **4**, 77794-87-7; **5**, 80293-76-1; **6**, 80338-95-0; **7**, 80293-77-2; **8**, 80293-78-3; **9**, 56698-80-7; **9** *N*-oxide, 80263-44-1; **10**, 4429-63-4; **10** *N*-oxide, 67249-34-7; **18**, 32975-46-5; **20**, 78346-69-7; **21**, 78346-70-0; **22**, 80263-45-2; **23**, 80263-46-3; **26**, 3247-10-7; **26** *N*-oxide, 38199-35-8; **27**, 66148-07-0; **28**, 66148-10-5; **29**, 78346-71-1; **30**, 78355-82-5.

Supplementary Material Available: Tables containing ^1H NMR data for **5**-**8**; ^{13}C NMR data for **1**, **2**, **4**, **5**, and **8**; mass spectral data for **1**-**8**; comparative lists of bond lengths, bond angles, and torsion angles and final atomic coordinates and thermal parameters for **1**, **6** and **7** (19 pages). Ordering information is given on any current masthead page.

Tricyclic Diterpenes from the Brown Marine Algae *Dictyota divaricata* and *Dictyota linearis*

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Mixed collections of two toxic brown seaweeds, *Dictyota linearis* and *D. divaricata*, were studied from five collection sites in the Honduras Bay Islands. The two known dolastane diterpenes **3** and **4** were isolated. Five new dolastanes, **5**-**9**, were also characterized. Compounds **5**-**8** were each converted to **4**. A combination of ^{13}C and ^1H NMR experiments or chemical correlations supported structural and stereochemical assignments. Several of these compounds showed interesting pharmacological properties.

Dense mats of two brown seaweeds attracted our attention while we were collecting specimens from the coral reefs of the Honduras Bay Islands in Apr 1978. A chemical study of these intertwined algae, mixture of *Dictyota linearis* (C. Ag.) and *Dictyota divaricata* (lamour), was initiated because their crude extracts showed toxicity to goldfish at 400 μg/mL (death in 90 min).[1] Seaweed extracts of the Dictyotaceae family often contain fascinating diterpeniods.[2] Not surprisingly, one of the simplest components of our toxic crude extracts seemed to be a diterpene because 20 carbons, and five methyl equivalents were evident from its NMR properties. While our work was proceeding we learned that two other laboratories had

(1) Based upon as assay procedure used by: Bakus, G. J. *Science* **1981**, *211*, 498 and references within.

(2) Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233 and references within.

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