# A 400 MHz ¹H NMR Study of the Dimeric Indole Alkaloid Ervafoline

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From the leaves of *Stenosolen heterophyllus* (Vahl.) Mgf (Apocynaceae) several dimeric indole alkaloids have recently been isolated.[1] One of these, ervafoline, was shown by X-ray crystallography to possess the structure *1*. In order to get useful ¹H NMR data for the structure determinations of the other dimeric indole alkaloids present,[2] we undertook a 400 MHz ¹H NMR study of ervafoline *1*. The results of this NMR study are presented in the present communication.
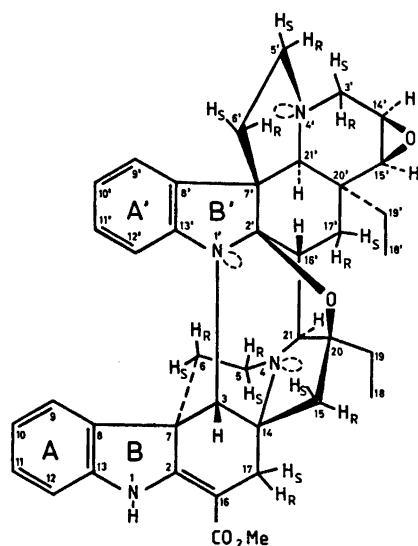


*1*

The application of consecutive double resonance experiments permitted all of the 44 protons in ervafoline *1* to be discovered. The chemical shifts and the coupling constants that were assigned are presented in Table 1.

The three-proton singlet resonance at $\delta$ 3.75 was assigned to the $-CO_2Me$ group. The other singlet signals (one proton each) at $\delta$ 9.20, 3.86 and 2.58 were assigned to protons H-1 (NH), H-3 and H-21', respectively.

The doublet signal at $\delta$ 3.54 ($J_{21,16'} < 0.3$ Hz) (*vide infra*) was assigned to the proton H-21,

*Table 1.* ¹H NMR data of ervafoline *1*. Spectra were run in $CDCl_3$ at 400 MHz. Values are in $\delta$ (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[3] is applied to distinguish between the H-atoms of different $-CH_2-$ groups.

Chemical shifts

| | | | |
|---|---|---|---|
| H-3 | 3.86 s | $H_R$-3' | 3.10 br d |
| $H_R$-5 | 2.8ᵃ m | $H_S$-3' | 3.47 dd |
| $H_S$-5 | 3.5ᵃ m | $H_R$-5' | 3.10ᶜ m |
| $H_R$-6 | 1.8 m | $H_S$-5' | 3.15ᶜ m |
| $H_S$-6 | 1.68 br dd | $H_R$-6' | 2.15 br dd |
| H-9 | 6.36 | $H_S$-6' | 1.24 br dd |
| H-10 | 6.35 | H-9' | 7.17 |
| H-11 | 6.97 | H-10' | 6.50 |
| H-12 | 6.72 | H-11' | 6.59 |
| $H_R$-15 | 2.11 d | H-12' | 5.64 |
| $H_S$-15 | 2.00 d | H-14' | 3.25 br dd |
| $H_R$-17 | 2.94 d | H-15' | 3.03 d |
| $H_S$-17 | 2.49 d | H-16' | 3.10 br d |
| H-18 | 0.96 t | $H_R$-17' | 1.92 dd |
| $H_R$-19 | 1.78ᵇ br q | $H_S$-17' | 1.35 dd |
| $H_S$-19 | 1.80ᵇ br q | H-18' | 0.97 t |
| H-21 | 3.54 d | $H_R$-19' | 1.51ᵈ dq |
| $CO_2Me$ | 3.75 s | $H_S$-19' | 1.63ᵈ dq |
| N−H | 9.20 s | H-21' | 2.58 s |

Coupling constants

$J_{5_R,5_S} \sim 1$ Hz; $J_{5_S,6_S} = 6.5$ Hz; $J_{5_R,6_S} = 13.5$ Hz; $J_{15_R,15_S} = 12$ 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; $J_{3'_R,14'} < 0.3$ Hz; $J_{3'_S,14'} = 1.5$ Hz; $J_{5'_R,6'_R} = 12$ Hz; $J_{5'_R,6'_S} \sim 0.5$ 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; $J_{14',17'_R} = 12$ Hz; $J_{14',17'_S} \sim 2.5$ Hz; $J_{17'_R,17'_S} = 13$ Hz; $J_{18',19'_R} = 7$ Hz; $J_{18',19'_S} = 7$ Hz; $J_{19'_R,19'_S} = 14$ Hz.

ᵃ,ᵇ,ᶜ,ᵈ Assignments can be interchanged.

and the doublet signal at $\delta$ 3.03 ($J_{15',14'} = 4.5$ Hz) to H-15'. The irradiation of the latter signal permitted the identification of H-14' which appeared as a multiple resonance at $\delta$ 3.25. Subsequent irradiation at $\delta$ 3.25 allowed the identification of both H-3' signals ($\delta$ 3.47 and 3.10).

The doublet absorption signals at $\delta$ 2.94 and 2.49, and $\delta$ 2.11 and 2.00 represent two AX systems (geminal couplings) which were assigned to $H_R$-17 and $H_S$-17 (allylic positions) and to $H_R$-15 and $H_S$-15, respectively.

The doublet-of-doublet signal at $\delta$ 1.35, the triplet-like signal at $\delta$ 1.92 and the broad doublet signal at $\delta$ 3.10 were found to form a system which could be assigned to $H_S$-17', $H_R$-17' and H-16', respectively. The chemical shift of

$H_R$-17' was assigned on the basis of its proximity to the lone-pair of electrons on N-1'. The absorption due to H-16' was assigned on its proximity to the oxygen atom between C-20 and C-2', as well as on the basis of a weak coupling with the proton H-21. The latter observation confirms the correctness of the assignment of the δ 3.54 signal to H-21 (*vide supra*).

The protons of the two ethylene bridges (C(5) − C(6) and C(5') − C(6')) form two separate systems which were easily resolved. The distinction between these systems (Table 1) is based on the assumption that the highest field signal (δ 1.24) belongs to $H_S$-6' as it appears to be the most shielded by the π-system of ring A'.

The triplet signal at δ 0.96 and the quartet signals centered at δ 1.78 and 1.80 were found to form a system which could be distinguished from a similar system comprising a triplet signal at δ 0.97 and two multiple signals centered at δ 1.51 and 1.63. These systems were assigned to the two ethyl side-chains (Table 1). The distinction between these systems was based on the inspection of a molecular model that revealed that, due to steric hindrance to the rotation of the C(18') − C(19') side-chain, the chemical shifts of $H_R$-19' and $H_S$-19' can be expected to be clearly different.

The assignment of the aromatic proton signals of ervafoline *1* has been discussed earlier.[1]

As far as we know, the present case is the first one in which it has been possible to assign all the protons in the ^{1}H NMR spectrum of a dimeric indole alkaloid.

*Experimental.* The NMR spectra were recorded on a laboratory-built 400 MHz ^{1}H high resolution spectrometer (I.E.F. 400)[4−6] and obtained by collecting 8 to 64 free-induction decay signals for a 0.01 M solution of the sample in 450 μl of CDCl₃.

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# Deuteride Reduction of Ethyl (S)-2-Tosyloxypropionate

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In connection with stereochemical studies of reactions mediated by citrate synthase, we undertook reductions of ethyl (*S*)-2-tosyloxypropionate (*1*) with sodium borodeuteride (SBD) and lithium aluminium deuteride (LAD). Since both reactions constituted simple syntheses of versatile, stereospecifically deuterated compounds (*2* and *4* respectively) a detailed account is presented.
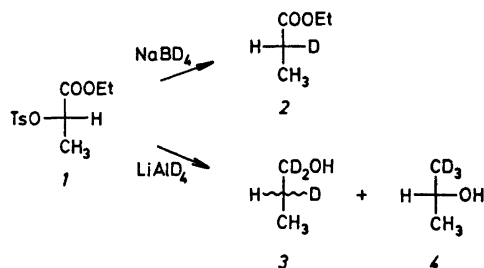


Reduction of *1* with SBD was carried out at 100 °C without the use of solvent. Ethyl (*R*)-(2-[2]H₁)propionate (*2*) and triethyl borate were the principal products. Hydrolysis of *2* gave sodium (*R*)-(2-[2]H₁)propionate with a slightly weaker specific rotation than that of a sample in which the chirality had been introduced microbially.[1] The specific rotation of the corresponding acid was, however, distinctly stronger than the rotations previously reported for this acid[2,3] or its enantiomer.[2−4] Sodium cyanoborodeuteride in HMPA (110 °C) has been used in the case of (+)-methyl O-mesylmandelate to obtain an analogous substitution.[5]

Reduction of *1* with LAD in refluxing tetrahydrofuran gave a product mixture which contained ethanol, optically active (1,1,2-[2]H₃)-1-propanol (*3*) and (*R*)-(1,1,1-[2]H₃)-2-propanol (*4*) ni the molar ratios 1.00:0.47:0.52 (GLC). The components were separated by spinning band column distillation and *3* was oxidised to sodium (2-[2]H₁)propionate which showed [α]₃₆₅²³ − 1.13°. For the optically pure *R* isomer a value of − 3.61° has been estimated.[1] The enantiomeric composition of *3* should thus be 66 % *R*, 34 % *S*. This low optical purity as well as the formation of *4* can be accounted for by a reduction along the paths in Fig. 1. Support for the view that *5* is formed initially was obtained from a reaction carried out at 23 °C which yielded ethanol but practically no