On the Assignment of Stereochemistry of 1,3-Disubstituted Tetrahydro-β-carbolines using ^{13}C N.M.R. Spectroscopy

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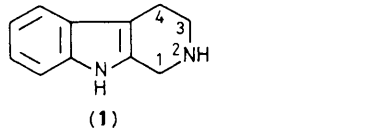
In *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines the chemical shift of C-1 in the ^{13}C n.m.r. spectrum is upfield of that for the corresponding peak of the *cis*-isomer, even for N^b-benzylated analogues; however, the chemical shift of the C-3 carbon is dependent on the N^b-substituent.

There is considerable interest in the synthesis of pharmacologically active alkaloids that contain the tetrahydro-β-carboline moiety (**1**). In particular, there has been much effort towards the synthesis of optically active 1,3-disubstituted tetrahydro-β-carbolines, which can be modified to heteroyohimbine precursors by removal of the C-3 functionality,[1] or are natural precursors to more cage-like alkaloids such as ajmaline.[2] In either case, it is essential to have a rapid and reliable method for determining the relative stereochemistry of C-1 and C-3 in 1,3-disubstituted tetrahydro-β-carbolines.

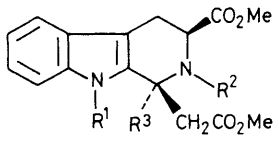
Several years ago, it was noted that *trans*-1,3-disubstituted tetrahydro-β-carbolines give chemical shifts for C-1 and C-3 that are consistently upfield of those for the corresponding *cis*-isomers.[3] This was believed to be due to the compression effect resulting from 1,3-diaxial interactions,[4] and has been used extensively in the assignment of stereochemistry.[5]

During the course of work on a modified Pictet–Spengler reaction,[6] we prepared several new 1,3-disubstituted and 1,1,3-trisubstituted tetrahydro-β-carbolines, (**2**) and (**3**).[7] It rapidly became clear that the ^{13}C n.m.r. spectra would not necessarily give an unambiguous indication of the stereochemistry. For example, one of the reactions yielded a 1:3 mixture of diastereoisomers [(**2b**) + (**3b**); R^1 = H, R^2 = CH_2Ph, R^3 = H], from which the CH carbons could be easily identified using the DEPT technique[8] [Figures 1(a) and 1(b)]; there was an obvious contradiction in the implied stereochemistry, and we therefore sought to determine whether it was the C-1 or the C-3 chemical shift that was proving to be unreliable.

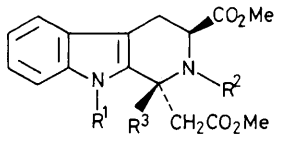
The C-1 carbon was identified for the (1*R*,3*S*)-isomer (**3b**)† as follows: irradiation of the indole N–H in the ^1H n.m.r. spectrum gave nuclear Overhauser enhancement for a single proton multiplet at δ 4.3; irradiation of this proton in the fully coupled ^{13}C spectrum caused the peak at δ 52.42 to collapse to a broad singlet, thereby identifying this as the C-1 carbon. The ^{13}C assignments for all of the other analogues were either straightforward (R^3 = CO_2Me), or could be deduced simply by correlation with related compounds. For example, it was apparent that analogues with R^3 = CO_2Me possessed a C-1 signal that was about 10—13 p.p.m. downfield of that for the



(**1**)

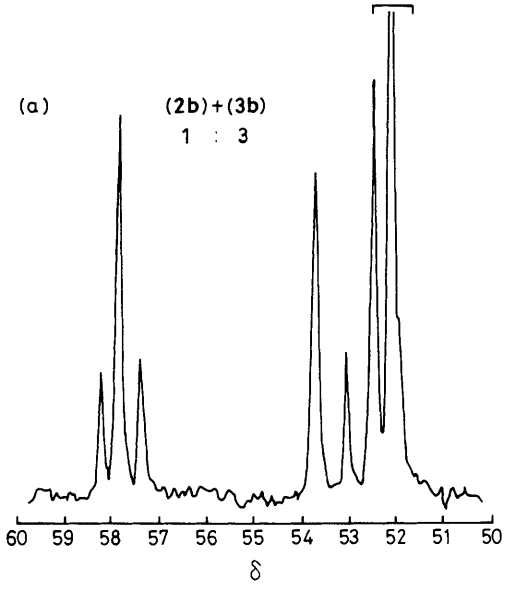


(**2**)



(**3**)

R^1 = H or Me
R^2 = H or CH_2Ph
R^3 = H or CO_2Me



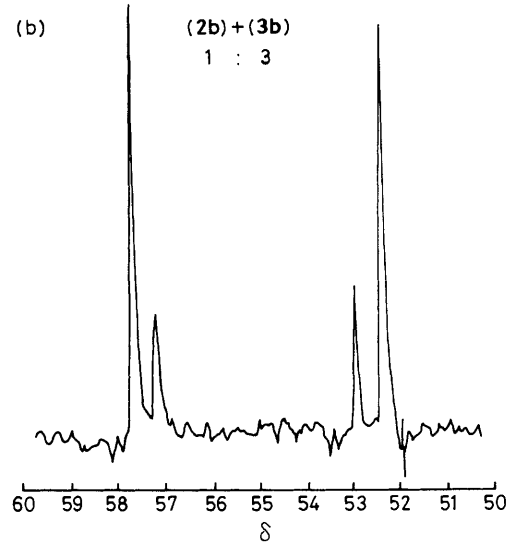


Figure 1. (a) Fully decoupled ^{13}C n.m.r. spectrum, range δ 50—60. (b) ^{13}C N.m.r. spectrum using the 'DEPT' technique (CH carbons only), range δ 50—60. Only C-1 and C-3 should give peaks in this region.

† The absolute stereochemistry of the two chiral centres in (**3b**) and (**2e**) was determined from single crystal *X*-ray structure determination. All other stereochemistries were deduced by stereospecific modification of these analogues (ref. 7).

Table 1.

Compound[a]	R^1	R^2	R^3	δ(C-1)	C-1 Chemical shift of (**3**) relative to (**2**)	δ(C-3)	C-3 Chemical shift of (**3**) relative to (**2**)
(**2a**)	H	H	H	49.46	Upfield	56.34	Upfield
(**3a**)				46.86		52.71	
(**2b**)	H	CH_2Ph	H	52.80	Upfield	57.10	Downfield
(**3b**)				52.42		57.73	
(**2c**)	Me	H	H	48.88	Upfield	55.65	Upfield
(**3c**)				47.30		51.15	
(**2d**)	Me	CH_2Ph	H	53.88	Upfield	55.29	Downfield
(**3d**)				52.99		56.24	
(**2e**)	H	H	CO_2Me	60.08	None	53.74	Upfield
(**3e**)				60.08		52.55	
(**2f**)	H	CH_2Ph	CO_2Me	65.72	Upfield	57.27	Upfield
(**3f**)				62.20		56.39	
(**2g**)	Me	H	CO_2Me	59.59	Downfield	53.48	Upfield
(**3g**)				60.73		51.09	
(**2h**)	Me	CH_2Ph	CO_2Me	66.81	Upfield	59.11	Upfield
(**3h**)				63.55		54.07	

[a] (**2a—h**) have (1*S*,3*S*) configurations; (**3a—h**) have (1*R*,3*S*) configurations.

corresponding analogue with R^3 = H, whereas the C-3 signal was affected by <4 p.p.m.

It was therefore possible not only to relate chemical shifts to the stereochemistry of 1,3-disubstituted tetrahydro-β-carbolines, but also to investigate the applicability of this method to 1,1,3-trisubstituted analogues. From the results summarised in Table 1, we were able to conclude that: (a) *trans*-1,3-disubstituted tetrahydro-β-carbolines have a chemical shift for C-1 that is upfield of that for the *cis*-isomer, even when the N^b-position is benzylated; (b) the C-1 chemical shift is *not* a reliable guide to the stereochemistry of 1,1,3-trisubstituted tetrahydro-β-carbolines.

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