^{13}C-NMR of 1,3-Disubstituted-1,2,3,4-tetrahydro-β-carbolines

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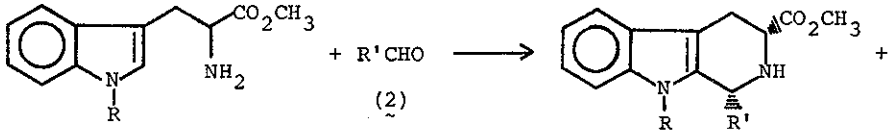
Summary

The stereochemistry of cis and trans-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines has been determined by ^{13}C-NMR for a variety of 1-phenyl- and 1-cyclohexyl-β-carboline derivatives. The signals due to carbon atoms 1 and 3 in the trans isomers appear consistently at higher field in the ^{13}C-NMR spectra than the analogous carbons of the cis isomers. This is presumably due to the 1, 3 interactions present in the trans bases which do not occur in the cis compounds.

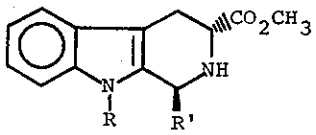
The chemistry of β-carbolines has been of interest for many years because of the occurrence of this ring system in natural products (1,2). Many times the proton NMR of such compounds has been complex and has led to difficulties in assignment of structure. The increased availability of ^{13}C-NMR has enabled application of this technique to a variety of problems. Natural abundance ^{13}C-NMR has been employed either independently or as a complementary method for the assignment of alkaloid structures (3) which has led to the correction of the structures of certain bases such as vindolinine (4).

We have been studying the chemistry of 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines en route to the synthesis of some potential antihypertensive agents (5). During the course of this work it became necessary to differentiate between cis and trans isomers formed in Pictet-Spengler reactions of tryptophan methyl ester (1) with aldehydes (2) (eq 1).



(1), R = H, CH_3

(3)



(4)

Two groups (6,7) had previously reported the stereochemical assignments of the cis and trans isomers of 3-methoxycarbonyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline. However, from similar spectral data, conflicting assignments were made. In order to resolve this problem, and to provide a general method for stereochemical assignments in this series we have resorted to the use of ^{13}C-NMR as an independent means of assigning stereochemistry.

Axial substituents in six-membered rings are known to cause an upfield shift of the signals for carbons 1 and 3 in the ^{13}C-NMR spectrum (8). This shift occurs as a result of the steric interaction of the axial substituent with the C-H bonds at the

C-3 centers. These 1,3 interactions can be shown (Fig. 1) to be present in the trans 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines (4). They do not occur in the cis compounds (3), which exist predominantly in the diequatorial conformation. These

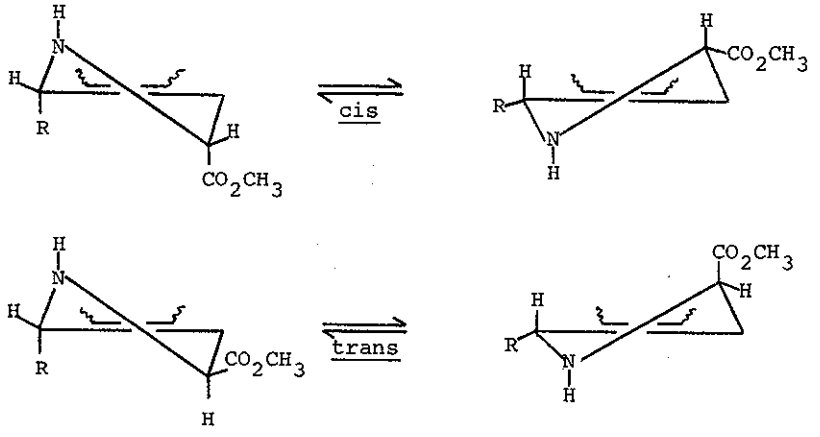


Figure 1

interactions should result in an upfield shift of the signals for centers 1 and 3 in the trans isomer relative to the same centers in the cis isomer.

The data reported in Table 1 clearly demonstrate that the resonances for C-1 and C-3 in compounds (4a) and (4b) are consistently upfield of those for β-carboline derivatives (3a) and (3b). For this reason (4a) and (4b) have been assigned the trans configuration.

Further support for these assignments was obtained by synthesis of the ind-N-methyltryptophan methyl ester derivatives (4c) and (4d). Examination of space-filling molecular models

clearly shows that the steric interaction of the N_a-methyl group with the phenyl or cyclohexyl group forces the latter into the axial position which results in the trans configuration. The reactions with N-methyltryptophan methyl ester produced one stereoisomer (4c or 4d, respectively) in overwhelming excess over the other. This product would have to be the trans isomer on steric grounds.

The spectra of compounds (4c) and (4d) were run and the chemical shifts of carbon centers 1 and 3 were found to be virtually superimposable with those of the corresponding unsubstituted derivatives (4a) and (4b) which had previously been assigned the trans configuration.

The additional data obtained from the N-methyltryptophan derivatives lend considerable support to the utility of ^{13}C-NMR as a method for making stereochemical assignments in tetrahydro-β-carbolines (9). This information provides an independent method for the assignment of stereochemistry in β-carboline alkaloids which should be more useful than IR and ^{1}H-NMR since those often provide complex spectra.

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Table 1. ^{13}C Chemical Shifts of Carbon Atoms 1 and 3.

Compound[a]	R	R'	C-3[b,c,d]	C-1	Melting Point[e] (°C)	R_f[f]
(3a) cis	H	C_6H_5	56.90	58.69	201-3	0.56
(4a) trans	H	C_6H_5	52.29	54.89	175-7	0.43
(3b) cis	H	C_6H_{11}	56.60	57.69	153-5	0.70
(4b) trans	H	C_6H_{11}	53.41	55.35	147-9	0.59
(4c) trans	CH_3	C_6H_5	52.80	54.86	196-8	0.57
(4d) trans	CH_3	C_6H_{11}	52.80	54.56	145-7	0.56

[a]Satisfactory spectral data and microanalyses were obtained for all compounds. [b]All shifts measured in ppm downfield to TMS. [c]All spectra run in $CDCl_3$. [d]^{13}C spectral assignments made by comparison with previously assigned compounds and some work with coupled spectra. [e]All melting points were taken on a Fisher plate apparatus and are uncorrected. [f]TLC on 0.25 mm silica gel plates with CH_2Cl_2:CH_3OH (24:1).

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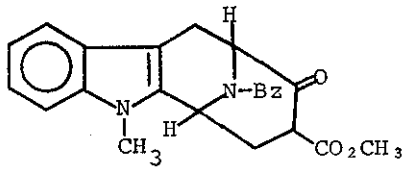
9 Epimerization of the substituents at positions 1 and 3 of these tetrahydro-β-carbolines occurs in alkaline or acidic medium and has precluded chemical verification of the stereochemistry in these systems. For example, both the cis and the trans 1,3-disubstituted precursors to (A) are reported to *isomerize and then to cyclize to the tetracyclic derivative* (A). N. Yoneda, Chem. Pharm. Bull., 1965, 13, 1231.



(A)

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