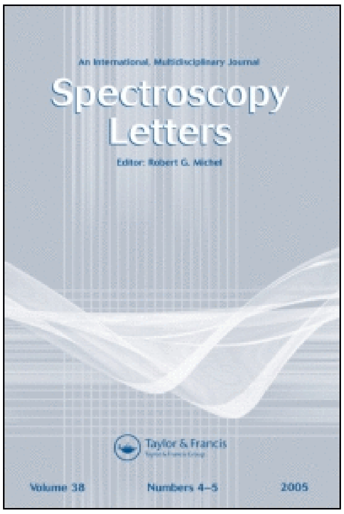

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2D NMR Studies of Octahydroindole Svstems

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2D NMR STUDIES OF OCTAHYDROINDOLE SYSTEMS

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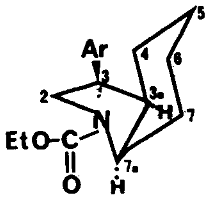
ABSTRACT

The ^{1}H and ^{13}C NMR resonances of title compounds were assigned by using 2D and decoupling techniques. The stereochemistry of ring fusion was identified by using, in particular, NOE and COSY $^{1}H^{1}H$ experiments. The low temperature COSY enables the evaluation of the relative populations (2:1) of N-acyl forms of isomeric octahydroindoles resolvable at -60°C.

As part of our synthetic program dealing with the total synthesis of the montanine-like Amaryllidaceae alkaloids,^{1,2} we have prepared a series of 3-aryl-*cis* or -*trans*-fused octahydroindoles. Although the chemical aspects of the synthesis were readily solved,^{3} two major obstacles still remained, namely, the assignment of the type of ring fusion obtained in the synthetic process and the unequivocal identification of the ring protons.

We now report a thorough high field ^{1}H- and ^{13}C-NMR analysis of two isomeric compounds, (+)-N-ethoxycarbonyl-3-(3,4-methylenedioxyphenyl)-3aα, 7aα-*cis*- (1) and -3aβ, 7aα-*trans*-octahydroindole (2), obtained during the course of our work.*



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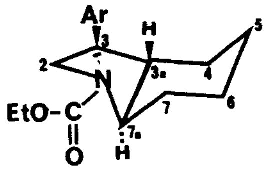

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Ar=3,4(OCH$_2$O)C$_6$H$_3$

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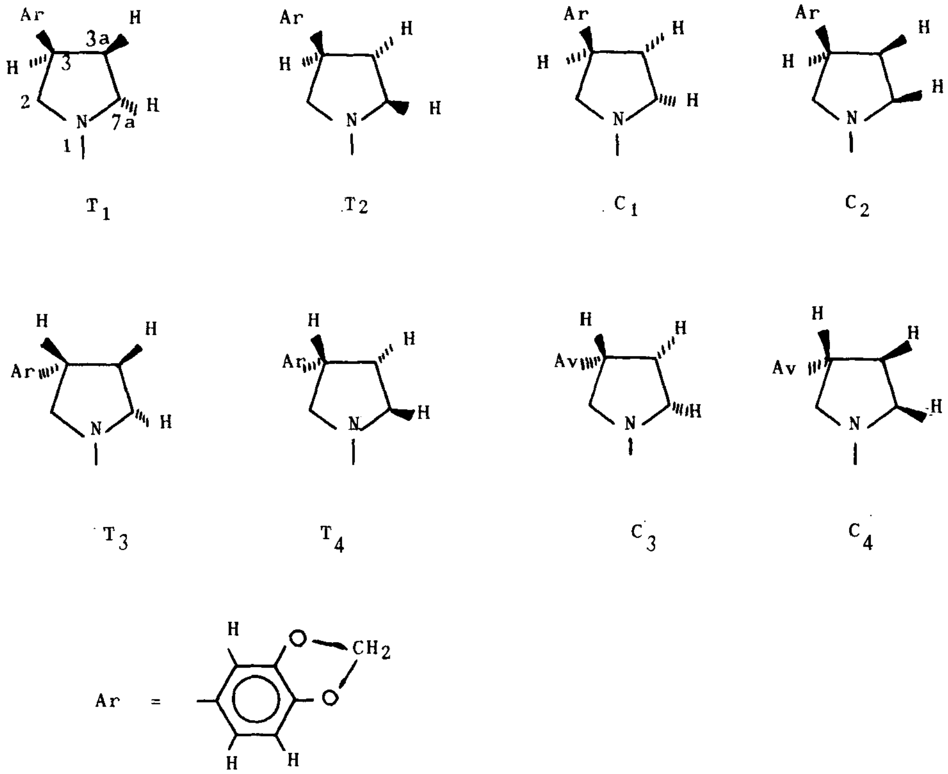
*Note: We are using α and β notations as indicated in the Scheme 1.

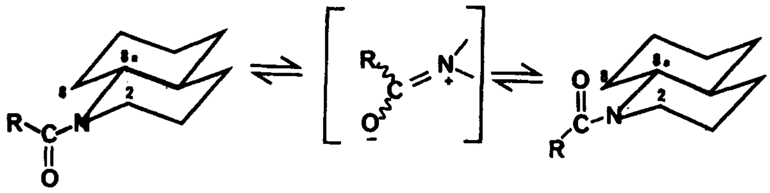


SCHEME I

INTRODUCTION

It has already been reported[5,8] that N-acyl derivatives of <u>cis</u>- and <u>trans</u>-decahydroquinolines show ^1H chemical shifts corresponding to the average of those for the rotational isomers due to the rotation around the N-C=O single bond.

In most amide (i.e., N-acylamino) derivatives, the partial double bond character of the N-C=0 linkage should induce a certain degree of planarity in the vicinity of the nitrogen atom. The ^{1}H-NMR spectra of such compounds are therefore influenced by the rate of interconversion of rotamers such as A$\rightleftharpoons$B and this is a temperature dependent phenomenon. Furthermore, the observed chemical shifts for rotamer A, particularly for protons at positions 2,8 and 8a, are expected to be considerably different from those in B^5.



A B

A similar behavior should be expected for N-acyl derivatives of the cis- or trans-octahydroindole systems and their high frequency (360-500 MHz)^{1}H-NMR spectra should, in this respect, provide useful information.

The octahydroindole system represents four isomers T_1-T_4 for trans and four isomers C_1-C_4 for the cis function of both cycles. In both cases two possibilities of junction cis or trans exist - hydrogen α or β accordingly, structures T_1 and T_4, C_2 and C_3, etc. being enanthiomeric. From this analysis it seems clear that any NOE experiment should be designed in order to indicate the molecular configuration. In the trans series, the presence of NOE between H_3 and H_{7a} allows to eliminate T_2 and T_3 forms where these two protons are on the opposite side of the ring. The NOE observed between H_{3a} and H_{7a} explains the cis junction. According to model studies the NOE could also be observed with one (or both) of ortho protons of the aromatic moiety as well as with one of the H_2 protons. The irradiation of H_3 should then easily identify one of the two H_2 protons which is oriented cis toward it. The proton pairs H_3 , H_{3a}; H_2, H_3 and H_{3a}, H_{7a} are vicinal. The similar magnitude of the NOE on H_3,H_{7a} pair to one of the cis oriented vicinal protons (e.g. H_3 , H_{3a}) could enable to describe the geometry of the heterocyclic moiety. It is possible to associate it with similar interproton distances H_3, H_{3a} and H_3, H_{7a} (Scheme I).

DISCUSSION

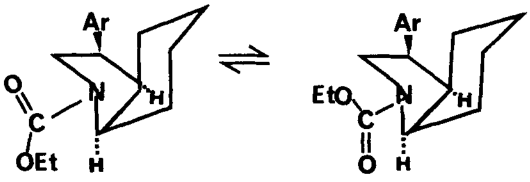
We have performed a series of NMR experiments on octahydroindoles 1 and 2 as follows:

- High resolution 360 MHz ^{1}H-NMR
- ^{1}H-NMR at variable (low) temperatures
- Double resonance NMR; NOE experiments
- ^{1}H, ^{1}H Homonuclear Correlation (HOMO-COSY)
- HOMO-COSY at low temperature
- ^{13}C-NMR (Off Resonance and Noise Decoupling)
- ^{1}H, ^{13}C Heteronuclear Correlation (HET-COSY)

CIS ISOMER 1

The room temperature PMR of compound 1 presents only the average signals due to interconversion of rotamers 1a $\rightleftarrows$ 1b and does not show unambiguous evidence for the existence of such equilibrium.

However, the low temperature proton magnetic resonance of compound 1 presents a set of signals that suggest an equilibrium between 1a and 1b. This behaviour is generally accepted[5a] for several types of amido compounds[5b] (Scheme II) (Figure 1).



1a **1b**

SCHEME II

The proton chemical shifts for this compound were obtained by using temperatures in the range of -60° to +40°C. There are groups of signals such as H_{2a} and H_2 , H_3 and $-OCH_2-CH_3$ that collapse into sharp multiplets when the temperature is increased (Figure 2).

The unambiguous assignment for each proton was performed by using homonuclear correlation[6] HOMO-COSY and also by double resonance experiments (See Table 1).

Figure 3 shows the HOMO-COSY at +40°C which allows the assignment of the proper sequence for various protons: The broad signal at 3.90 assigned to H_{7a} correlates strongly with the signals at 2.28(H_{3a}) and 1.46($H_{7\beta}$). The multiplet at 3.85(H_{2a}) correlates both with the triplet in 3.72($H_{2\beta}$) and the multiplet at 3.30(H_3). The latter signal correlates as well with those at 3.72 and 3.85 and also with the multiplet in 2.28(H_3). Similarly, H_{3a} correlates with H_3,H_{7a} and the two protons $H_{4\alpha}$ and $H_{4\beta}$ (3.30, 3.90, 1.20 and 1.10 ppm, respectively).

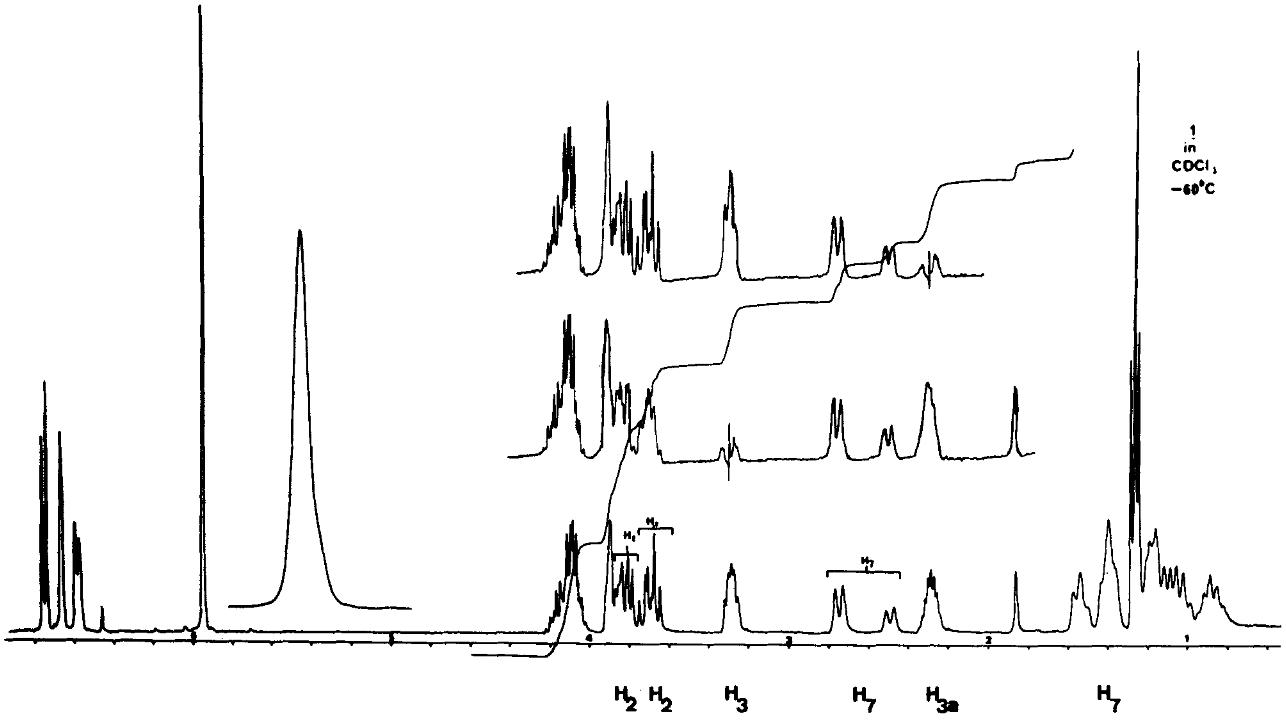


Figure 1 Compound 1: ^{1}H NMR 360 MHz, −60°C (CD Cl$_3$). Inserts shows some decoupling experiments.

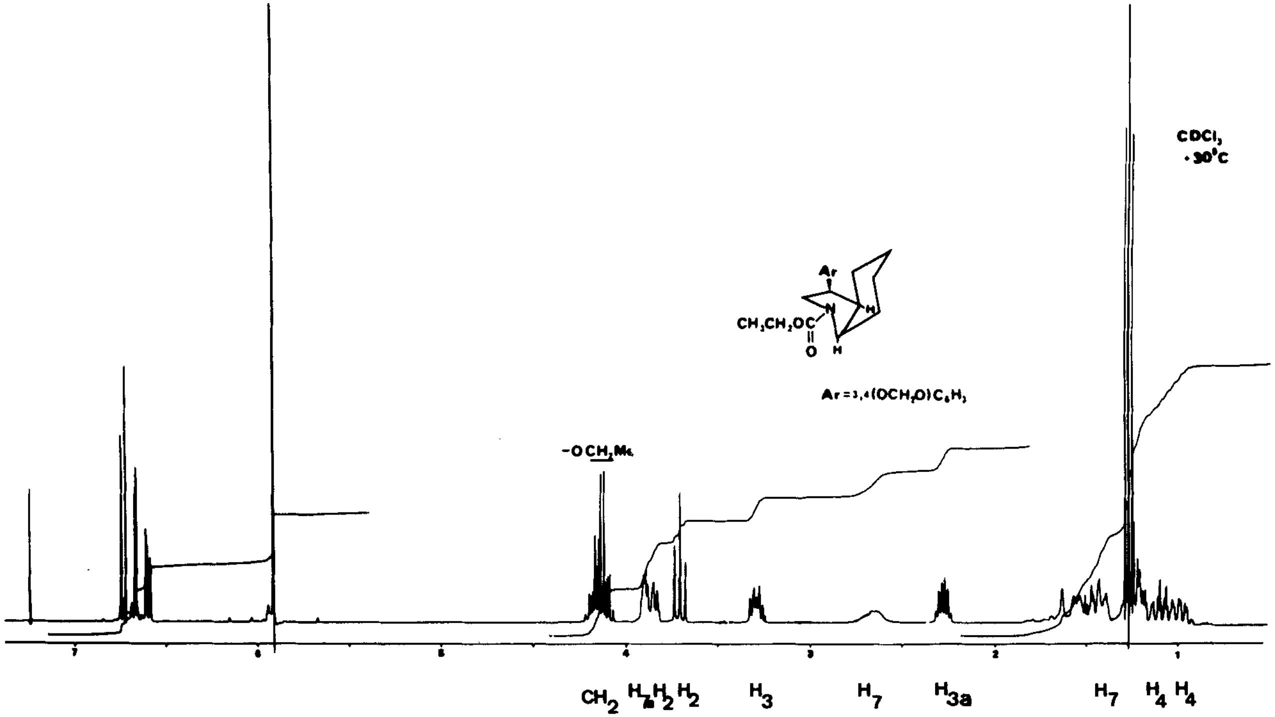


Figure 2 Compound 1: ^{1}H NMR 360 MHz, +30°C (CD Cl$_3$).

TABLE I. 500 MHz ^{1}H-NMR Spectrum of (1) at +40° C

Assignment	Chemical Shift[a] δ,ppm	Multiplicity[b]	Coupling Constants (J), Hz
H-2β	3.72	t	$J_{2-3} = 10.9$, $J_{2-3} = 6.0$
H-2α	3.85	m	$J_{2-2} = -10.9$
H-3	3.30	m	$J_{3-3a} = 6$
H-3a	2.28	m	$J_{3a-7a} = 6$
H-4α	1.20	m	$J_{3a-4\beta} = 12.4$, $J_{4\alpha-4\beta} = -12.4$
H-4β	1.10	m	$J_{4\beta-5\alpha} = 12.4$, $J_{4\alpha-5\alpha} = 3.7$
H-5α	1.54	m	$J_{5\alpha-5\beta} = -12$, $J_{5\alpha-6\beta} = 12$
H-5β	1.06	m	$J_{5\alpha-6\alpha} = 3$
H-7α	2.65	bd	$J_{7\alpha-7\beta} = -12.4$, $J_{7\alpha-6\beta} = 12.4$
H-7β	1.46	m	$J_{7\alpha-7a} = 4$, $J_{7\beta-6\alpha} = 4$
H-7a	3.90	b	
3', 4' OCH_2-O	5.91	s	
-O-CH_2	4.13	m	
CH_3	1.23	t	
H-2'	6.65		
H-5'	6.58	dd	$J_{2'-6'} = 2.5$
H-6'	6.73	d	$J_{5'-6'} = 8.5$

[a] All values refer to internal tetramethylsilane (TMS). Bruker WM-500 Spectrometer.

[b] s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, b = broad.

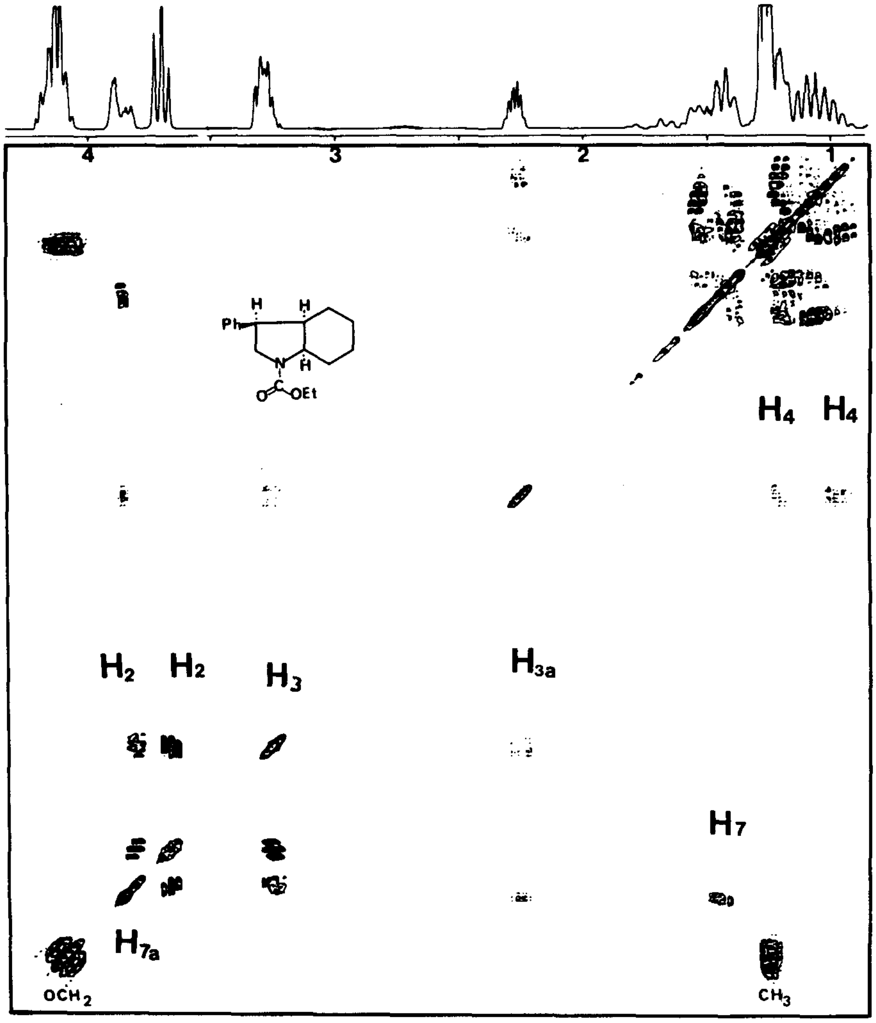
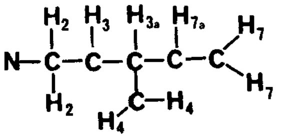


Figure 3 Compound 1: proton two dimensional homonuclear chemical shift correlated spectrum (COSY); off diagonal contours of intensity indicated spin coupling between protons at chemical shifts given by two coordinates. The one dimensional spectrum is represented by contours along the diagonal ($CD\ Cl_3$).

This experiment suggests the following proton sequence:



The NOE experiment has been performed in order to ascertain the geometrical relationship between the various protons. The strong NOE observed among H_{3a} and protons H_3 and H_{7a} shows that H_{3a} and H_3 are <u>cis</u> since H_{7a} and H_3 present a considerable NOE effect. Consequently, the ring fusion is also <u>cis</u>. Furthermore, there is a strong NOE among the aromatic protons with one of the C_2 protons (<u>cis</u> to Ar group) and with H_3, showing some but smaller NOE with H_4 (Figure 6).

The broad signal observed at 2.65 ppm (30°C) gives, between -13 and -60°C, two doublets at 2.5 (J=13Hz) and 2.75 ppm (J=13Hz) of which integration is equivalent to one proton. We have verified that these two doublets collapse when the temperature rises to 30°C to be sure that this phenomenon is temperature dependent.

Supported by HOMO-COSY low temperature (-13°C) assignments of protons from isomers <u>1</u> were performed (Figure 4). The most important features are observed for the two doublets described above. They do not correlate with each other. However, it is very clear that both signals correlate with a proton localized in the overlapped multiplets in 1.46 ppm. This is also supported by double resonance experiments. These considerations allowed us to unambiguously assign these doublets as H_7 from both conformers in equilibrium as described above $1a \rightleftharpoons 1b$. The remaining protons of the systems do not display the important changes.

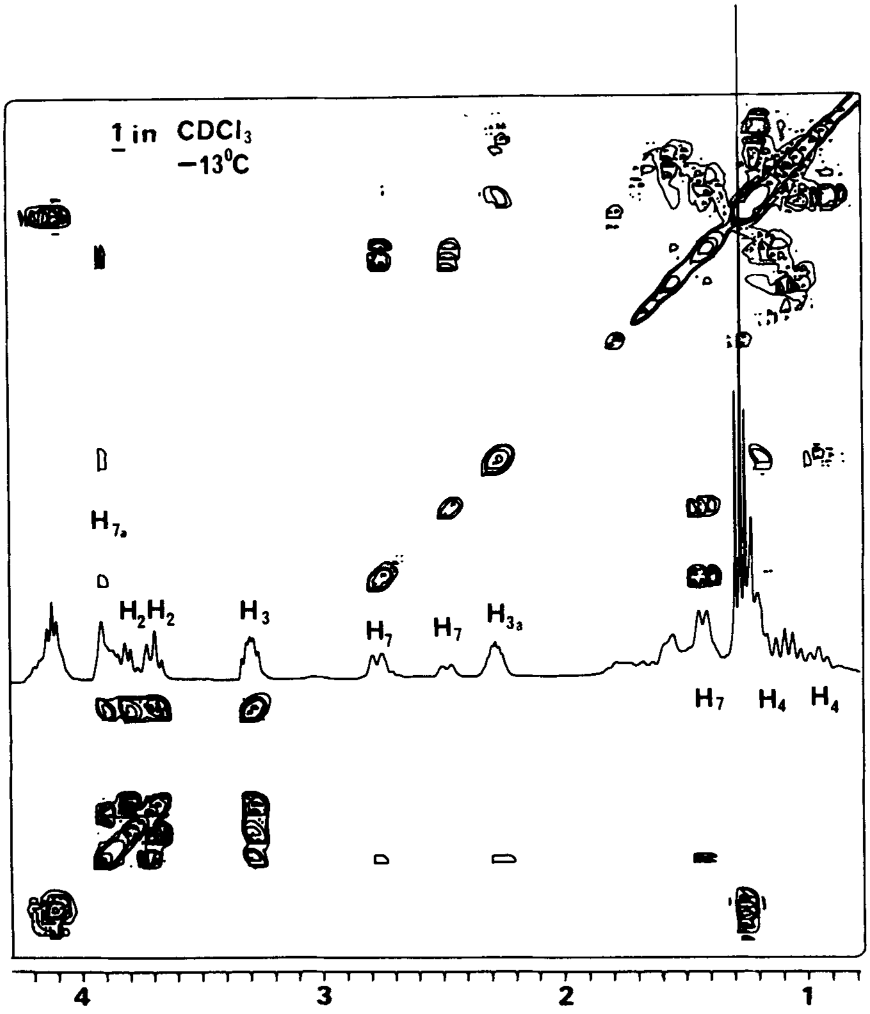


Figure 4 Compound 1: proton two dimensional homonuclear chemical shift correlated spectrum (COSY) -13°C (CD Cl_3).

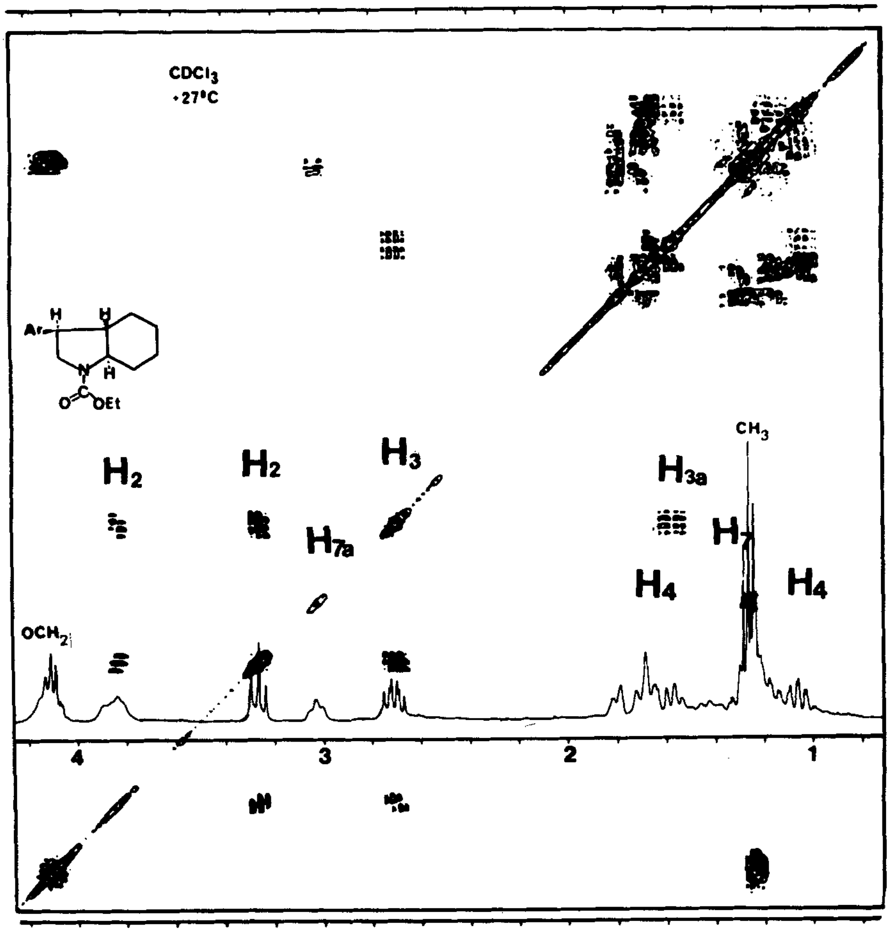


Figure 5 Compound 2: ^{1}H- ^{1}H Homonuclear chemical shift correlation (COSY), +27°C (CD Cl$_3$).

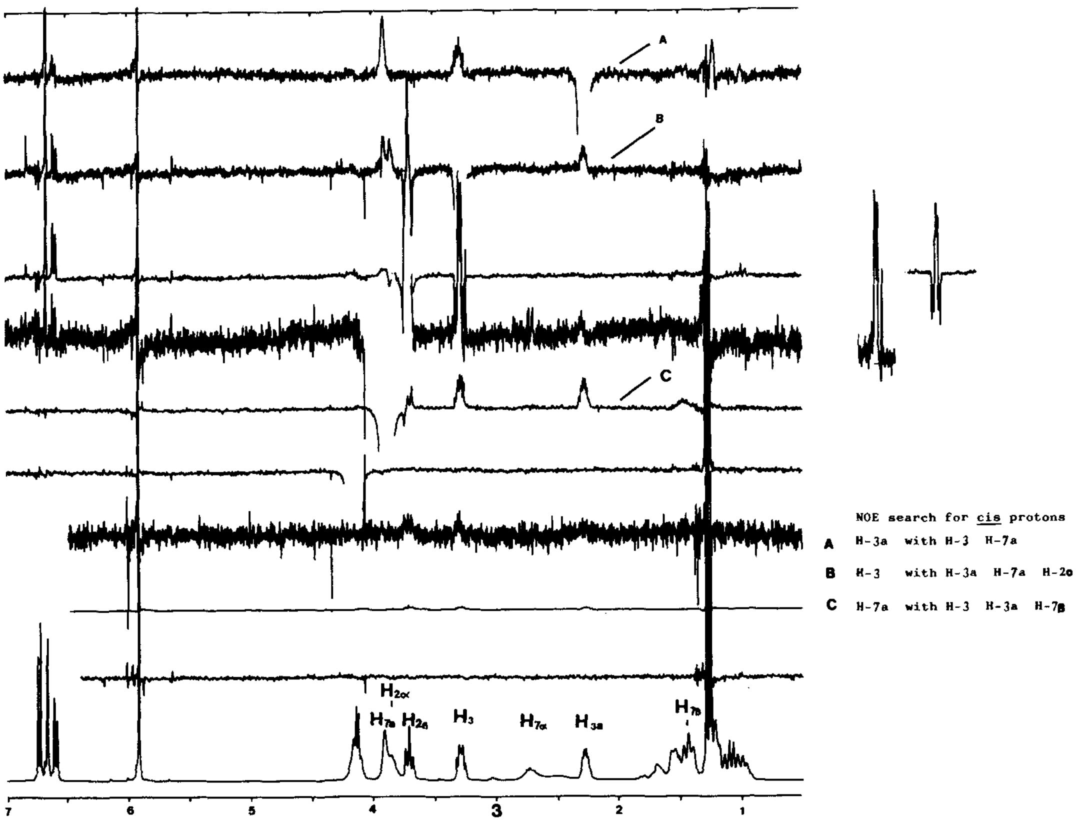


Figure 6 Compound 1: NOE experiment - search for cis protons (three aromatic proton NOE spectra available on request).

In conclusion, the P.M.R. spectrum of the *cis* isomer 1 shows two sets of signals for each H_{2a}, H_{2b} and H_{7b} corresponding to the different unequally populated conformations 1b and 1a. Their relative ratios, with respect to rotation around the N-C=O bond, have been evaluated at 2:1. This provided evidence supporting the slow equilibrium proposed in Scheme 2 on the ^{1}H-NMR time scale.

Figure 1 shows the low temperature PMR (-60°C). The observed signals provide evidence for the equilibrium proposed in Scheme 1. The assignment of each proton was performed using COSY[6] techniques as pointed out before: e.g. the proton H_{7a} is correlated to H_2 and H_3 long distance, to $H_{7\beta}$ (at 2.75 ppm), H_{3a} and to H_{7a} (at 1.46 ppm). The doublets at 2.5 and 2.75 ppm were assigned to $H_{7\beta}$ and the multiplet in 1.46 ppm to $H_{7\alpha}$. There was no correlation between these two doublets. This consideration is supported by double resonance experiments. Therefore, the doublets at 2.5 and 2.75 collapsed into a broad signal at 2.65 ppm (see Figure 2, +30°C). The doublet at 2.5 (J=13Hz) and 2.75 (J=13Hz) was assigned to $H_{7\beta}$, with each component signal being broadened by further couplings. In conclusion, the P.M.R. spectrum of the *cis* isomer 1 shows two sets of signals for each $H_{2\alpha}$, $H_{2\beta}$ and $H_{7\beta}$ corresponding to the different unequally populated conformations 1b and 1a. Their relative ratios with respect to rotation around the N-C=O bond have been evaluated at 2:1.

^{13}C-NMR

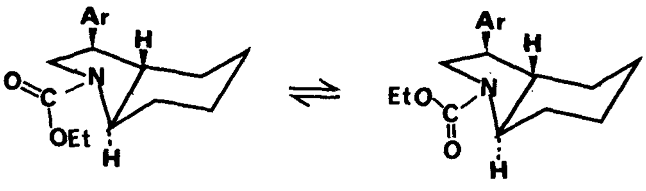
The noise decoupling ^{13}C-NMR from isomer 1 shows eighteen signals for all non equivalent carbons from the molecule. The off resonance experiments allowed us to identify all the carbons present based on their chemical shifts and multiplicity.

The assignment for the carbon atoms in compound 1 is presented in Table II. Each signal was unambiguously assigned using heteronuclear correlation[7] techniques.

The singlet at 60.8 correlates with the protons of the methylene from the O-Et group at 4.14 ppm. The carbon in 58.5 correlates with the proton signal at 3.90 ppm (H_{7a}) and therefore this singlet belongs to C_{7a}. The signal at 49 ppm (C_2) correlates with both the $H_{2\alpha}$ and $H_{2\beta}$ protons. The signal at 45.2 (C_3) correlates with the proton signal at 3.30. The carbon assigned to C_{3a} (42.7) correlates with the proton at 2.28 and of course C_7 (27 ppm) correlates with protons $H_{7\alpha}$ and $H_{7\beta}$.

TRANS ISOMER 2

As expected, the PMR of compound 2 shows additional multiplicity since the equilibrium 2a ⇌ 2b is also present in this case (Scheme III).



2a 2b

SCHEME III

This behaviour is supported by the changes observed in the spectra by using different temperatures (-60° to +40°C). The spectrum recorded at +40°C enables us to assign different signals whose chemical shifts are as

TABLE II. ^{13}C-NMR Spectra of (1)[a]

14.80 (q)	CH_3
20.65 (t)	C-4
23.0 (t)	C-5
24.0 (t)	C-6
27.1 (t)	C-7
42.7 (d)	C-3a
45.2 (d)	C-3
49.1 (t)	C-2
58.5 (d)	C-7a
60.8 (t)	$O-CH_2$
101.0 (t)	$O-CH_2-O$
108.3 (d)	C-5'
108.5 (d)	C-2'
120.6 (d)	C-6'
132.1 (s)	C-1'
146.0 (s)	C-4'
147.7 (s)	C-3'
158.5 (s)	C=O

[a] s = singlet; d = doublet; t = triplet; q = quartet.

shown in Table III. The unambiguous assignment of chemical shifts was performed by using Homonuclear Correlation (Figure 5) experiments as before.

The methylene protons of the urethane moiety at 4.1 correlate strongly with the triplet signal (1.25). One proton ($H_{2\alpha}$) at 3.84 ppm correlates with the triplet at 3.27 ($H_{2\beta}$) and the multiplet at 2.71. The triplet at 3.27 ($H_{2\beta}$) correlates with both signals at 3.84 and 2.71. And of course, the multiplet at 2.71 correlates not only with $H_{2\alpha}$ and $H_{2\beta}$, but also with the signal of H_{3a} at 1.58. Moreover, H_{3a} correlates also with H_3 (2.71) and both protons $H_{4\alpha}$ and $H_{4\beta}$ (1.68 and 1.04). The proton H_{7a} (3.03) correlates weakly with H_{3a} and with H_7 at 1.25 ppm.

Thus, the HOMO-COSY experiment suggests the sequence of protons shown below.

In order to know the geometrical relationship between each pair of protons, high Frequency (360 MHz) Nuclear Overhauser Effect (NOE) experiments have been carried out on isomer 2. NOE between H_{7a} and H_3 is observed since both atoms are close together. Thus the NOE effect is strong when H_{7a} is irradiated. Supported by the experiments pointed out before and the model structures, we concluded that protons H_{7a} and H_3 are cis. The absence of NOE between H_{3a} and H_{7a} should indicate, as opposed to the previously studied isomer, the presence of a trans ring junction.

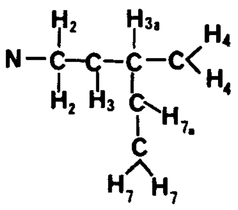
Apart the couplings of protons observed in the previous case, the aromatic protons also display small NOE with H_{3a}. The magnitude of NOE vicinal protons is, however, more variable and therefore indicates that the heterocyclic part of compound 2 is more folded.

TABLE III. 500 MHz ^{1}H-NMR Spectrum of (2) at + 40° C

Assignment	Chemical Shift [a] δ,ppm	Multiplicity[b]	Coupling Constants (J), Hz
$H_{2\beta}$	3.27	t	$J_{2\alpha-3} = 8$, $J_{2\alpha-2\beta} = -10.8$
$H_{2\alpha}$	3.84	m	$J_{2\beta-3} = 10.8$
H_3	2.71	ddd	$J_{3-3a} = 11$
H_{3a}	1.58	bq	$J_{3a-7a} = 10.8$, $J_{3a-4\alpha} = 10.8$ $J_{3a-4\beta} = 2.4$
$H_{4\alpha}$	1.20	m	$J_{4\alpha-4\beta} = -11$, $J_{4\beta-5\alpha} = 3$, $J_{4\alpha-5\beta} = 10.8$
$H_{4\beta}$	1.04	m	
H_7	1.68		$J_{7\alpha\ 7a} = 2.10$, $J_{7\beta-7a} = 9.4$
H_{7a}	3.03	dt	
3',4' OCH_2	5.91	s	
$H_{2'}$	6.68	d	$J_{2'-6'} = 2.5$
$H_{5'}$	6.63	dd	$J_{5'-6'} = 8.5$
$H_{6'}$	6.74	d	
O-CH_2	4.1	m	
CH_3	1.25	t	J = 7

[a] All values refer to internal tetramethylsilane (TMS). Bruker WM-500 Spectrometer.

[b] s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; b = broad.



CONCLUSIONS

The proton and carbon NMR spectra assigned with the help of decoupling, 2D HOMO-COSY and NOE experiments enable us to reach the following conclusions. For the cis derivative 1 the ^{1}H-NMR experiments help to establish the relative conformer (rotamer) population of 1a: 1b as 2:1. It was however, more difficult to establish ratio for the trans isomer 2 since the signals for the relevant protons lied too close to each other. The exact evaluation of the population of the conformers is in this case impossible, but it is close to 1:1.

The stereochemistry on the junction of octahydroindole ring was deduced from these experiments, particularly from NOE and COSY experiments. The trans compound 2 has a pyrolidine part more folded than the cis one. The N-acyl form populations have become resolvable at low temperature and was calculated at -60°C. The low temperature COSY experiments clearly support both the assignment and the interpretation of conformational phenomenon.

In general, the wide implementation of 2D NMR should reduce misassignments in both ^{1}H and ^{13}C spectra, which are due to congestion of the signals, their overlapping or some other peculiarity of the spectrum of the compound.

EXPERIMENTAL

NMR Measurements

The one-dimensional NMR spectra for protons were obtained on Bruker 360. High Frequency Nuclear Overhauser Effect (NOE) were run on Bruker 360 and WM 500 Spectrometer at the Centre d'Etudes Nucléaires de Saclay, France.

Two dimensional experiments were run on Bruker 360 or Nicolet 360 at 90.5 MHz for ^{13}C and 360 MHz for ^{1}H.

The spectrometers were locked on the deuterium signal of the solvents. All experiments were performed on samples of the octahydroindoles of variable weight as c.a. 10% $CDCl_3$ solutions in 10 mm sample tubes for ^{13}C and 5 mm tubes for ^{1}H (0,5 ml of solution used). All chemical shifts are expressed in δ (ppm) using TMS as internal standard. Coupling constants are expressed in Hz.

All spectra were recorded with a Bruker WM 360 WB Spectrometer, equipped with an Aspect 2000 computer, operating in the Fourier Transform mode with quadrature detection at 360 MHz. Without other specification, typical one dimensional spectral acquisition parameters were: spectral width 4000 Hz, pulse width 4 μs ($90^{\circ} = 7.5\ \mu$s) and 16384 time domain addresses. Acquisition time was 2.048s. No relaxation delay was used. Processing was also made with 16384 addresses (accuracy 0.488 Hz).

NOE difference was obtained by substracting two types of spectra, one in which the desired signal was saturated at low power during 5 seconds and the other in which the irradiation was on the left corner of the spectrum.

Saturation power was turned off during acquisition. The resultant spectrum was compared with a standard one for localizing the NOE. The steady state is obtained with two dummy scans.

Two dimensional homonuclear correlated (COSY) spectra were recorded using the pulse sequence (D_1 -90° - D_2 -45° -D_3)n where D_2 and D_3 are the evolution and observation periods respectively. Spectra were recorded with 256 increments of D_2 from 0.003 ms to 128 ms. Acquisition time D_3 was 0.512 s for 2000 Hz of spectral width. Data were acquired in 2048 addresses at each D_2 value with the carrier in the center of the spectra. For 64 scans at each D_2 all data acquisitions time is 7.45 hours with D_1 = 1 s. Processing was performed with 2048 addresses in F_2 and 1024 addresses in F_1 domains. Prior to Fourier transform Free induction decay were multiplied by a non shifted sine bell window function in both domains. The same parameters were used for the COSY acquired at low temperature (-13°C) but with only 16 scans in the aim to reduce the time of acquisition data.

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