COMPLETE ^{1}H-NMR SPECTRAL ASSIGNMENTS OF SIX 3-ETHYL INDOLO[2,3-*a*]QUINOLIZIDINE *N*-OXIDES. NOE DIFFERENCE SPECTROSCOPY APPLIED TO CONFORMATIONAL ANALYSIS

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Abstract - Complete ^{1}H-nmr spectral assignments of six 3-ethyl-indolo[2,3-*a*]quinolizidine *N*-oxides are reported. The predominant conformations of the compounds were determined by NOE difference spectroscopy.

INTRODUCTION

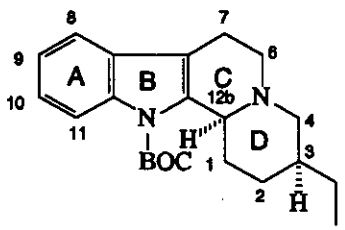
As precursors for iminium ions, amine *N*-oxides, especially indoloquinolizidine *N*-oxides, are important intermediates in indole alkaloid syntheses. Knowing the exact conformation of the indoloquinolizidine *N*-oxides, as well as their preference for *trans*-diaxial elimination, can help in predicting their behaviour in iminium ion formation.[1-13]

Recently we described the stereoselective preparation of several indoloquinolizidine N-oxides.[9] Structures and predominant conformations were determined by ^{13}C-nmr measurements[14] mainly taking advantage of the N→O γ-effects on C-1, C-3 and C-7.

In conformational analysis perhaps the most reliable approach, however, is to take advantage of nuclear Overhauser effects,[15] by means of which the predominant conformation of the indoloquinolizidine molecule (conformations **a**, **b** and **c**) (*vide infra*) and the conformation of ring D can be specified.

RESULTS AND DISCUSSION

The complete ^{1}H-nmr spectra of six 3-ethylindolo[2,3-*a*]quinolizidine *N*-oxides [compounds (**1**), (**2**), (**4**), (**5**), (**6**), and (**8**)] and of the two non-oxidized Boc-protected indoloquinolizidines [compounds (**3**) and (**7**)] used as reference compounds, are interpreted in Table 1. The chemical shifts were confirmed by H,H-COSY and H,C-COSY measurements. Predominant conformations were confirmed with the help of NOE difference measurements (Table 2). Minor differences were found with earlier conformational analyses (*vide infra*).[9]



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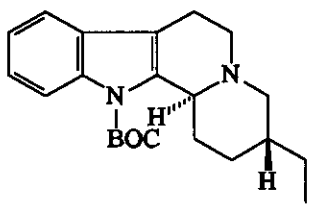

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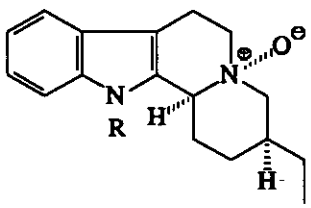

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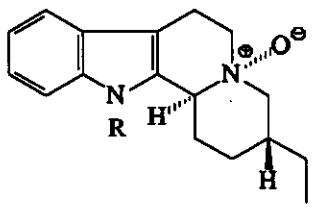
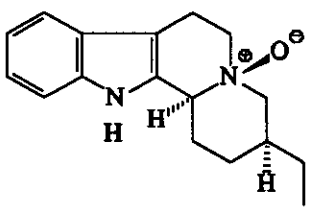
4 R = Boc



5 R = H

8 R = Boc



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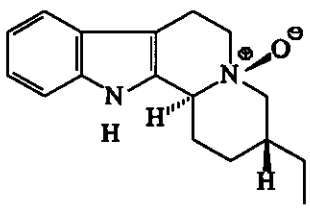

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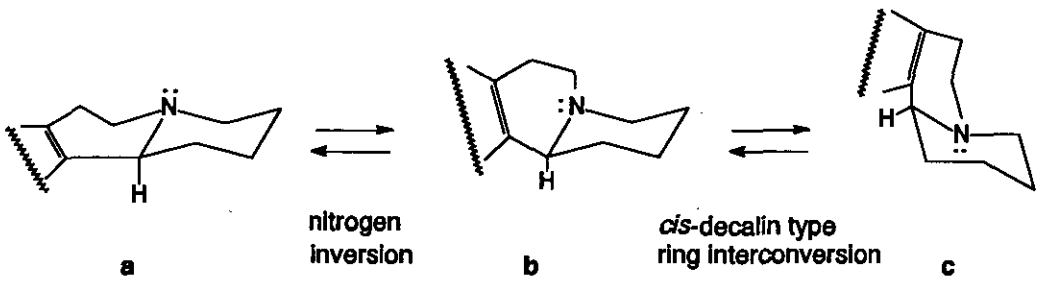
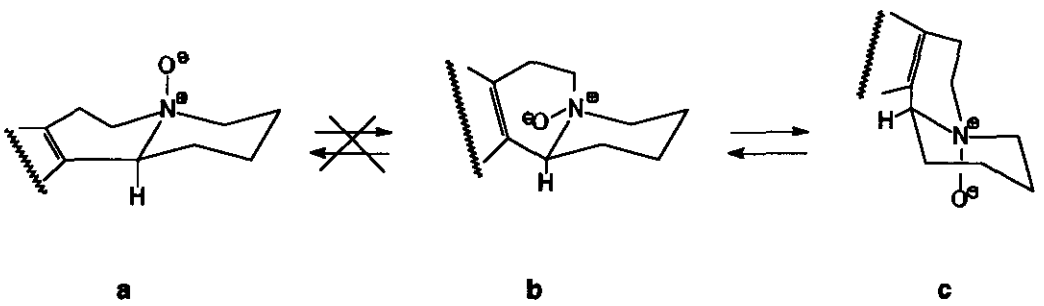
In general, the indolo[2,3-*a*]quinolizidine skeleton can exist in three main conformations, owing to nitrogen inversion and *cis*-decalin type ring interconversion (Scheme 1).



Scheme 1

In the corresponding *N*-oxides the C/D ring juncture (*trans* or *cis*) is fixed, which means that there is no equilibrium between conformations **a** and **b**/**c**. Transition between **b** and **c** is possible, however (Scheme 2).[2,11]



Scheme 2

According to our earlier results[8,9] the contribution of different conformations to the conformational equilibrium is strongly influenced by the substituents present. For example, when the N_a-tert-butyloxycarbonyl group (N_a-Boc) is present, as in the Boc-protected compounds (**3**), (**4**), (**7**), and (**8**) (Table 2), conformation **b** tends to be favoured in the conformational equilibrium.

Table 1. ^{1}H-Nmr data of compounds (**1**) - (**8**). The coupling constants between the aromatic protons are omitted.

	1	2	3	4
	$CDCl_3$	MeOH-d_4	$CDCl_3$	$CDCl_3$
H-1α	2.9 m	2.15 ddd	2.03 ddd	2.71 ddd
H-1β	2.8 m	2.37 ddd	1.5 m	1.99 m
H-2α	1.74 dd	1.9 m	1.7 m	1.2 m
H-2β	0.8 m	1.9 m	1.6 m	1.88 m
H-3	2.41 m	1.84 m	1.5 m	2.26 m
H-4α	3.0 m	3.57 dd	2.8 m	3.57 dd
H-4β	3.1 m	3.40 br d	2.8 m	3.34 dd
H-6α	3.68 ddd	3.64 ddd	2.8 m	3.67 ddd
H-6β	3.79 ddd	3.53 dd	2.96 ddd	3.80 ddd
H-7α	2.9 m	2.83 dd	2.88 ddd	3.0 m
H-7β	3.0 m	3.4 m	2.57 ddd	3.3 m
H-8	7.41 d	7.44 d	7.39 d	7.44 d
H-9	7.09 t	7.01 t	7.20 t	7.27 t
H-10	7.18 t	7.08 t	7.25 t	7.33 t
H-11	7.49 d	7.32 d	8.05 d	8.04 d
H-12b	4.58 br s	4.59 d	3.77 br d	4.90 br s
$CH_{2(A)}$	1.05 m	1.95 m	1.46 m	1.26 m
$CH_{2(B)}$	1.11 m	2.03 m	1.60 m	1.37 m
CH_3	0.85 dd	0.98 dd	0.90 dd	0.94 dd
NH	11.52 br s	- •		
$C(CH_3)_3$			1.65 s	1.65 s

• Due to deuterium exchange the signal is not observed

Table 1 contd.

	5	6	7	8
	MeOH-d_4	MeOH-d_4	$CDCl_3$	$CDCl_3$
H-1α	2.32 ddd	2.3 m	2.14 ddd	2.63 ddd
H-1β	1.63 ddd	2.3 m	1.52 ddd	1.53 ddd
H-2α	1.28 ddd	1.32 ddd	1.2 m	1.4 m
H-2β	1.88 br d	2.06 m	1.95 m	1.95 ddd
H-3	1.74 m	2.45 m	1.6 m	1.79 m
H-4α	3.17 dd	3.14 dd	2.48 dd	3.38 dd
H-4β	3.59 dd	3.36 dd	3.10 dd	3.74 dd
H-6α	3.16 ddd	3.72 ddd	2.70 ddd	3.31 ddd
H-6β	3.87 ddd	3.56 ddd	3.14 ddd	3.88 ddd
H-7α	3.34 ddd	2.89 ddd	2.82 ddd	3.53 m
H-7β	2.88 ddd	3.4 m	2.8 m	2.86 ddd
H-8	7.46 d	7.46 d	7.39 d	7.44 d
H-9	7.02 t	7.02 t	7.21 t	7.24 t
H-10	7.09 t	7.09 t	7.25 t	7.29 t
H-11	7.30 d	7.32 d	8.09 d	8.07 d
H-12b	4.25 dd	4.59 br d	3.96 br d	4.88 dd
CH_2	1.35 m	1.37 m	1.22 m	1.35 m
CH_3	0.99 t	1.00 t	0.92 t	0.97 t
NH	- •	8.51 s		
$C(CH_3)_3$			1.66 s	1.67 s

• Due to deuterium exchange the signal is not observed

Table 1 contd.

Coupling constants:

Compound (1)

$J_{1\alpha,1\beta}$ = 14.5 Hz; $J_{1\alpha,2\alpha}$ ~ 4 Hz; $J_{1\alpha,2\beta}$ ~12.5 Hz; $J_{1\alpha,12b}$ = 5 Hz; $J_{1\beta,2\alpha}$ = 3 Hz; $J_{1\beta,2\beta}$ = 3 Hz; $J_{1\beta,12b}$ = 3 Hz; $J_{2\alpha,2\beta}$ = 13.5 Hz; $J_{2\alpha,3}$ = 2.5 Hz; $J_{2\beta,3}$ = 12 Hz; $J_{6\alpha,6\beta}$ = 13 Hz; $J_{6\alpha,7\alpha}$ = 5.5 Hz; $J_{6\alpha,7\beta}$ ~12 Hz; $J_{6\beta,7\alpha}$ ~1 Hz; $J_{6\beta,7\beta}$ = 5.5 Hz; $J_{CH2(A),CH3}$ = 7 Hz; $J_{CH2(B),CH3}$ = 7 Hz

Compound (2)

$J_{1\alpha,1\beta}$ = 14 Hz; $J_{1\alpha,2\alpha}$ ~ 4 Hz; $J_{1\alpha,2\beta}$ ~4 Hz; $J_{1\alpha,12b}$ = 3 Hz; $J_{1\beta,2\alpha}$ ~12 Hz; $J_{1\beta,2\beta}$ = 4 Hz; $J_{1\beta,12b}$ ~12 Hz; $J_{3,4\alpha}$ = 5 Hz; $J_{4\alpha,4\beta}$ = 12 Hz; $J_{6\alpha,6\beta}$ = 12 Hz; $J_{6\alpha,7\alpha}$ = 5 Hz; $J_{6\alpha,7\beta}$ ~12 Hz; $J_{6\beta,7\alpha}$ ~1 Hz; $J_{6\beta,7\beta}$ = 5.5 Hz; $J_{7\alpha,7\beta}$ = 15.5 Hz; $J_{CH2(A),CH3}$ = 7 Hz; $J_{CH2(B),CH3}$ = 7 Hz

Compound (5)

$J_{1\alpha,1\beta}$ = 15 Hz; $J_{1\alpha,2\alpha}$ = 4 Hz; $J_{1\alpha,2\beta}$ = 3 Hz; $J_{1\alpha,12b}$ = 4 Hz; $J_{1\beta,2\alpha}$ = 12 Hz; $J_{1\beta,2\beta}$ = 4 Hz; $J_{1\beta,12b}$ = 12 Hz; $J_{3,4\alpha}$ = 12 Hz; $J_{3,4\beta}$ ~3 Hz; $J_{4\alpha,4\beta}$ = 12 Hz; $J_{6\alpha,6\beta}$ = 12 Hz; $J_{6\alpha,7\alpha}$ = 6 Hz; $J_{6\alpha,7\beta}$ ~1 Hz; $J_{6\beta,7\alpha}$ ~11 Hz; $J_{6\beta,7\beta}$ = 5 Hz; $J_{7\alpha,7\beta}$ = 15.5 Hz; $J_{CH2,CH3}$ = 7 Hz

Compound (6)

$J_{1\alpha,2\alpha}$ ~ 5 Hz; $J_{1\beta,2\alpha}$ = 12 Hz; $J_{2\alpha,2\beta}$ = 12.5 Hz; $J_{3,4\alpha}$ = 12 Hz; $J_{3,4\beta}$ ~3 Hz; $J_{4\alpha,4\beta}$ = 12 Hz; $J_{6\alpha,6\beta}$ = 12 Hz; $J_{6\alpha,7\alpha}$ = 5 Hz; $J_{6\alpha,7\beta}$ ~12 Hz; $J_{6\beta,7\alpha}$ ~1 Hz; $J_{6\beta,7\beta}$ = 6 Hz; $J_{7\alpha,7\beta}$ = 15.5 Hz; $J_{CH2,CH3}$ = 7 Hz

Compound (7)

$J_{1\alpha,1\beta}$ = 14.5 Hz; $J_{1\alpha,2\alpha}$ = 3.5 Hz; $J_{1\alpha,2\beta}$ = 3 Hz; $J_{1\alpha,12b}$ = 3 Hz; $J_{1\beta,2\alpha}$ ~12 Hz; $J_{1\beta,2\beta}$ = 3.5 Hz; $J_{1\beta,12b}$ = 11 Hz; $J_{2\alpha,2\beta}$ = 12.5 Hz; $J_{3,4\alpha}$ = 12 Hz; $J_{3,4\beta}$ = 3 Hz; $J_{4\alpha,4\beta}$ = 12 Hz; $J_{6\alpha,6\beta}$ ~12 Hz; $J_{6\beta,7\alpha}$ ~11 Hz; $J_{6\beta,7\beta}$ = 5 Hz; $J_{CH2,CH3}$ = 7 Hz

Compound (8)

$J_{1\alpha,1\beta}$ = 15 Hz; $J_{1\alpha,2\alpha}$ = 4 Hz; $J_{1\alpha,2\beta}$ = 3 Hz; $J_{1\alpha,12b}$ = 3 Hz; $J_{1\beta,2\alpha}$ ~12 Hz; $J_{1\beta,2\beta}$ = 3.5 Hz; $J_{1\beta,12b}$ = 11.5 Hz; ; $J_{2\alpha,2\beta}$ = 12 Hz; $J_{2\beta,3}$ ~1 Hz; $J_{3,4\alpha}$ = 12 Hz; $J_{3,4\beta}$ = 3 Hz; $J_{4\alpha,4\beta}$ = 12 Hz; $J_{6\alpha,6\beta}$ = 11.5 Hz; $J_{6\alpha,7\alpha}$ = 6.5 Hz; $J_{6\alpha,7\beta}$ ~1 Hz; $J_{6\beta,7\alpha}$ ~11 Hz; $J_{6\beta,7\beta}$ = 5 Hz; $J_{7\alpha,7\beta}$ = 16 Hz; $J_{CH2,CH3}$ = 7 Hz

The interpretation of the predominant conformations of compounds (1) - (8) from ^{1}H-nmr spectra was unambiguous except for compounds (3) and (4). In particular, the coupling constants of these two compounds (measured at room temperature), indicated that there was no clear preference for a single conformation but rather conformations **b** and **c** both contributed strongly to the conformational equilibrium. The measured values of the coupling constants are thus less informative and are not included in Table 1. The ^{13}C-nmr measurements gave corresponding results for compounds (3) and (4). The peak sharpness declined drastically, especially in compound (4) at C-4 and C-6, which are sites strongly affected by conformational changes.

Table 2. Predominant conformations of compounds (1) - (8)

Compound	Predominant conformation	Observed NOEs (H-12b irradiated) at		Other NOEs observed
		H-4α	H-6α	
1	c, chair*		3.9%	H-2β → H-4β (2.6%); H-1α → H-2α (2.7%), H-1α → H-3 (~2%)
2	a, chair*	2.5%	1.2%	H-3 → H-4α (3.2%), H-3 → H-4β (3.1%)
3	b and c ; b dominating			
4	b and c			
5	b, chair*	3.4%		H-12b → H-2α (1.7%); H-6β → H-3 (6.6%), H-6β → H-1β (4.5%)
6	a, chair*	4.2%	2.1%	H-4α → H-2α (3.9%), H-4α → H-6α (3.5%)
7	b, chair*	5.1%		H-12b → H-2α (2.4%)
8	b, chair*	2.9%		H-12b → H-2α (1.4%); H-6β → H-3 (5.0%), H-6β → H-1β (4.3%)

* conformation of ring D

The nuclear Overhauser effects[15] give valuable information on the three possible conformations of the indoloquinolizidine molecule (*vide supra*). Assuming as a first approximation that ring D is in chair conformation (*vide infra*) the different conformations (**a**, **b** and **c**) can be identified by

irradiation of H-12b. When H-12b is irradiated and if the predominant conformation of the indoloquinolizidine molecule is **a**, there should be a clear NOE at H-4α and H-6α. If the predominant conformation is **b**, an NOE should be observed only at H-4α and not at H-6α. If the predominant conformation is **c**, an NOE should be seen only at H-6α and not at H-4α. The experimental results are presented in Table 2. The approach could not be applied to the conformations of compounds (**3**) and (**4**), where there are two strongly contributing conformations (**b** and **c**).

Other NOEs that were measured not only confirmed the predominant conformation of the indoloquinolizidine ring but indicated the chair conformation for ring D (Table 2). In compound (**2**), with conformation **a** and H-3 equatorially oriented, irradiation of H-3 produced NOEs at both H-4α and H-4β. Contrary to earlier results[9] this indicated the chair conformation for ring D. As shown by the NOEs at H-2α and H-6α when H-4α was irradiated, the conformation of ring D in compound (**6**) with conformation **a** was also chair. Likewise, the NOE at H-2α upon irradiation of H-12b confirmed the chair conformation of ring D for compounds (**5**), (**7**), and (**8**) (all in conformation **b**). When H-1α in compound (**1**) (conformation **c**) was irradiated an NOE was observed at H-3, which again indicated the chair conformation.

EXPERIMENTAL

^{1}H- and ^{13}C-nmr spectra were measured with a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^{1}H-nmr; δ_H = 0.00 ppm) and 100.577 MHz (^{13}C-nmr; δ_C = 77.00 ppm). NOE difference spectra were obtained by direct subtraction using a 90° composite pulse. ^{1}H- and ^{13}C measurements were done at room temperature and NOE difference measurements at 30° C.

Compounds (**1**), (**2**), (**4**), (**5**), (**6**), and (**8**)

For the preparation of compounds (**1**), (**2**), (**4**), (**5**), (**6**), and (**8**) and their ir, ^{13}C-nmr and ms spectral data, see Refs. 9 and 14. For the ^{1}H-nmr data, see Table 1.

Compounds (**3**) and (**7**)

For the preparation of compounds (**3**) and (**7**) and their ir, ^{13}C-nmr and ms spectral data, see Refs. 14 and 16. For the ^{1}H-nmr data, see Table 1.

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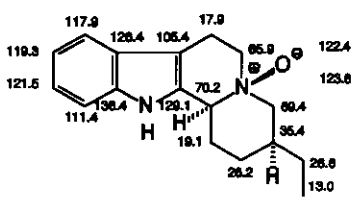
14. Reassignments have been made for some ^{13}C chemical shift values given for compounds (**2**), (**4**) and (**3**) in Refs. 9 and 16 [compounds (**6a**) and (**7b**) in Ref. 9 and compound (**11**) in Ref. 16, respectively).



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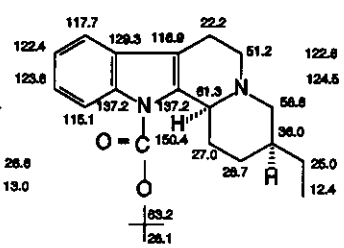

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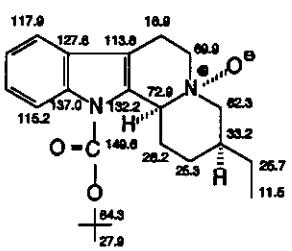

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