Tetrahedron Vol 49, No 12, pp 2567-2576, 1993
Printed in Great Britain

0040-4020/93 $6 00+ 00

Predominant Conformations of N_a-Boc-deformyl-Z- and N_a-Boc-deformyl-E-geissoschizine, the Latter a Possible Synthetic Intermediate in the Preparation of Sarpagan and Ajmalan Ring Systems

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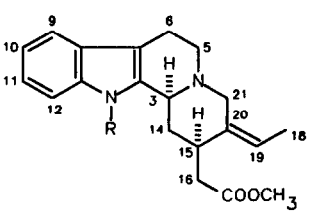
(*Received in UK* 10 *December* 1992)

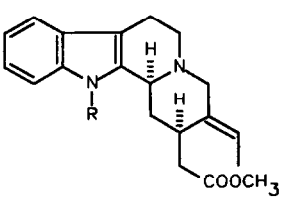
Abstract - Predominant conformations were determined for N_a-Boc-deformyl-Z- and N_a-Boc-deformyl-E-geissoschizines **1** and **2** and for their unprotected counterparts **3** and **4**.

INTRODUCTION

Our aim was to investigate the predominant conformations of N_a-Boc-deformyl-Z- and N_a-Boc-deformyl-E-geissoschizines **1** and **2**, which are indolo[2,3-a]quinolizidine derivatives. Earlier studies[1,2] in our laboratory had indicated, that the predominant conformations of N_a-Boc-protected indolo[2,3-a]quinolizidines tend to differ from those of the corresponding unprotected compounds. In the favorable case, compounds of the present type could be potential synthons in the preparation of sarpagan and ajmalan ring systems (vide infra).[3,4]



1 R=Boc
3 R=H

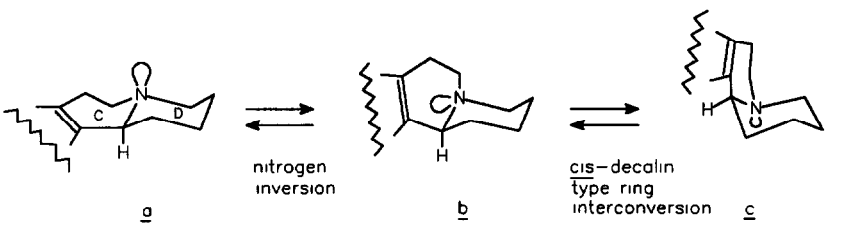


2 R=Boc
4 R=H

RESULTS AND DISCUSSION

Some time ago we developed an easy way to prepare deformyl-Z-geissoschizine **3** and deformyl-E-geissoschizine **4**,[5,6] from which the corresponding N$_a$-Boc-protected counterparts **1**[7] and **2** could easily be obtained

In general, the indolo[2,3-a]quinolizidine skeleton can exist in three conformations, owing to nitrogen inversion and cis-decalin type ring interconversion (Scheme 1) The contribution of the different conformations to the conformational equilibrium is strongly influenced by the substituents present



Scheme 1. Conformational equilibrium of the indolo[2,3-a]quinolizidine skeleton. Ring D is presented in a chair conformation.

Arguments, based mainly on ^{1}H-nmr and ir measurements have been presented for the preponderant existence of the indoloquinolizidine skeleton of the Z-isomer **3** in the trans-quinolizidine conformation (conformation a), with ring D in chair conformation (Figure 1).[8,9] Similarly based arguments have been presented for the preponderant existence of the indoloquinolizidine skeleton of the E-isomer **4** in one of the cis-quinolizidine conformations (conformation c) with ring D in chair conformation (Figure 2).[8,9]

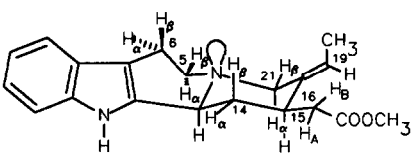


Figure 1 Deformyl-Z-geissoschizine **3** in the indoloquinolizidine skeleton conformation a with ring D in chair conformation (predominant conformation)

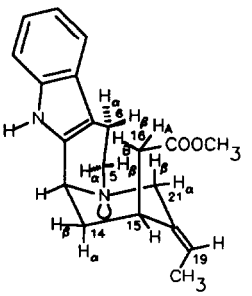


Figure 2 Deformyl-E-geissoschizine **4** in the indoloquinolizidine skeleton conformation c with ring D in chair conformation (predominant conformation).

Geissoschizine **5**, a biogenetically important alkaloid, is structurally related to the E-isomer **4** Different predominant conformations have been proposed for geissoschizine **5**. Winterfeldt et al.[8] supported the preponderance of one of the cis-quinolizidine conformations (conformation b) with ring D in twist-boat conformation (Figure 3), whereas Potier et al.[10] favored the other cis-quinolizidine conformation (conformation c) with ring D in boat (or slightly twisted boat) conformation (Figure 4) Just recently, however, Sakai et al.[11] presented convincing evidence for the preponderant existence of geissoschizine **5** in the trans-quinolizidine conformation (conformation a) with ring D in twist-boat conformation (Figure 5).

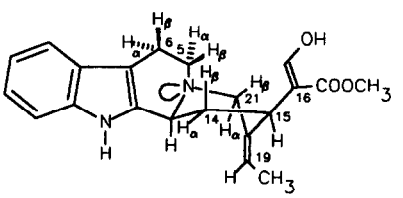


Figure 3 Geissoschizine **5** in the indoloquinolizidine skeleton conformation b with ring D in twist-boat conformation (Winterfeldt et al.[8]).

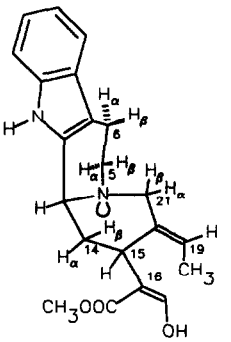


Figure 4 Geissoschizine **5** in the indoloquinolizidine skeleton conformation c with ring D in boat conformation (Potier et al.[10])

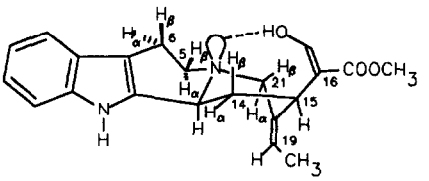


Figure 5. Geissoschizine **5** in the indoloquinolizidine skeleton conformation a with ring D in twist-boat conformation (Sakai et al.[11])

Although the structure of compound **4** (and in lesser amount that of compound **3**), due to the absence of the formyl group, is not quite analogous to that of geissoschizine **5**, we considered it necessary to confirm the correctness of the above presented predominant conformations of compounds **3** and **4**, before going on to determine the predominant conformations of the N_a-Boc-protected deformyl-Z- and deformyl-E-geissoschizines **1** and **2**. This was mainly done using ir, ^{1}H-nmr, and ^{13}C-nmr data (for ^{1}H-nmr, see Table 1; for ir and ^{13}C-nmr, see Refs 5 and 6)

In the case of compound **3**, especially the H-3 signal at δ 3 59 (br d) in the ^{1}H-nmr spectrum, the C-6 signal at δ 21.6 in the ^{13}C-nmr spectrum, and the Bohlmann bands at 2830 and 2780 cm^{-1} in the ir spectrum were characteristic and supported the presented predominant conformation (Figure 1). This was further confirmed by NOE difference measurements. Irradiation at H-21α resulted in an NOE (3.5%) at H-3 (excludes

Table 1. ^{1}H-nmr data of compounds **1** and **2** and their unprotected counterparts, compounds **3** and **4** [12] The coupling constants between the aromatic protons are omitted

	1	2	3	4
H-3	4 63 dd	4 42 dd	3.59 br d	4 29 br s
H-5α	2 7 m	2 8 m	2.7 m	3.2 dd
H-5β	3 06 m	2 95 m	3.18 m	3.28 ddd
H-6α	2 8 m	2.8 m	2.8 m	2.65 ddd
H-6β	2.8 m	2.8 m	3.00 m	3.03 dddd
H-9	7 39 d	7.40 d	7 46 d	7.48 d
H-10	7 20 t	7.21 t	7.07 t	7.10 t
H-11	7 25 t	7.26 t	7 13 t	7 15 t
H-12	8.13 d	8 10 d	7.30 d	7 36 d
H-14α	2 19 ddd	2 24 ddd	2 25 ddd	2.31 ddd
H-14β	1 45 ddd	1.65 m*	1.39 ddd	2 19 ddd*
H-15	2 8 m	3.24 ddd	2.8 m	3 1 m
H-16$_A$	2 24 dd	2.44 dd	2.30 dd	2 15 def d
H-16$_B$	2 66 dd	2.70 dd	2 72 m*	2.19 def d
H-18	1 71 d	1.68 d	1.71 d	1.65 d
H-19	5.29 q	5.48 q	5 24 q	5 49 q
H-21α	3.39 d	3 47 d	2 83 d	2.97 d
H-21β	3.97 d	3.39 d	3.91 d	3.55 d
CO_2Me	3 67 s	3 65 s	3.74 s	3 70 s
$C(CH_3)_3$	1.69 s	1 67 s		
NH			7 99 br s	8.62 br s

* partly masked

Coupling constants.

Compound **1**

$J_{3,14\alpha}$ = 3 5 Hz; $J_{3,14\beta}$ = 12 Hz, $J_{14\alpha,14\beta}$ = 12 Hz, $J_{14\alpha,15}$ = 3 5 Hz; $J_{14\beta,15}$ = 12 Hz; $J_{15,16A}$ = 6 5 Hz; $J_{15,16B}$ = 8 Hz; $J_{16A,16B}$ = 15 Hz, $J_{18,19}$ = 6 5 Hz; $J_{21\alpha,21\beta}$ = 14 Hz

Table 1. contd.

Compound **2**

$J_{3,14\alpha}$ = 3 Hz; $J_{3,14\beta}$ = 10 Hz; $J_{14\alpha,14\beta}$ = 13.5 Hz; $J_{14\alpha,15}$ ~1 Hz; $J_{14\beta,15}$ = 8 Hz, $J_{15,16A}$ = 9 Hz; $J_{15,16B}$ = 6 Hz; $J_{16A,16B}$ = 15 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 12.5 Hz

Compound **3**

$J_{3,14\alpha}$ = 3.5 Hz; $J_{3,14\beta}$ = 12 Hz; $J_{14\alpha,14\beta}$ = 13 Hz, $J_{14\alpha,15}$ = 4 Hz; $J_{14\beta,15}$ = 12 Hz; $J_{15,16A}$ = 10 Hz; $J_{16A,16B}$ = 17 Hz; $J_{18,19}$ = 6.5 Hz; $J_{21\alpha,21\beta}$ = 12 Hz

Compound **4**

$J_{3,14\alpha}$ = 3.5 Hz; $J_{3,14\beta}$ = 5 Hz; $J_{5\alpha,5\beta}$ = 12 Hz; $J_{5\alpha,6\alpha}$ = 4.5 Hz; $J_{5\alpha,6\beta}$ = 12 Hz; $J_{5\beta,6\alpha}$ = 1.5 Hz; $J_{5\beta,6\beta}$ = 6 Hz, $J_{6\alpha,6\beta}$ = 13 Hz; $J_{14\alpha,14\beta}$ = 14 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 12 5 Hz

conformation c), and irradiation at H-21β caused an NOE (1 3%) at H-5β (excludes conformation b). Moreover, irradiation at H-21β showing a strong NOE (11.7%) at C-18 protons indicated that ring D is in chair conformation.

In the case of compound **4**, particularly the H-3 signal at δ 4 29 (br s) in the ^{1}H-nmr spectrum, the C-6 signal at δ 17.8 in the ^{13}C-nmr spectrum, and the absence of Bohlmann bands in the ir spectrum were indicative and supported the suggested predominant conformation (Figure 2) Further confirmation was provided by NOE difference measurements Irradiation at H-3 resulted in an NOE (3.7%) at H-5α (excludes conformation b), and irradiation at H-21β showing an NOE (2.2%) at C-16 protons indicated that ring D is in chair conformation

Once the correctness of the predominant conformations of compounds **3** and **4** (Figures 1 and 2) was confirmed, we proceeded to investigate the N_a-Boc-protected deformyl-Z- and deformyl-E-geissoschizines **1** and **2**

Detailed examination of the Boc-protected Z-isomer (compound **1**) (for ^{1}H-nmr, see Table 1) showed the indoloquinolizidine skeleton to exist mainly in conformation b (Scheme 1) This was confirmed by NOE difference measurements irradiation at H-14β resulted in a 7% NOE at H-5β, which could only be true for conformation b (Scheme 1) The existence of ring D in a chair conformation was demonstrated by the 1.5% and 8% NOEs between C-16 protons (H-16$_A$ and H-16$_B$) and H-19 (Figure 6).

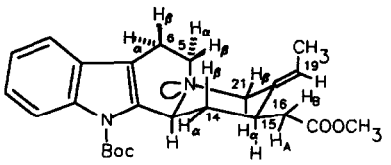


Figure 6 N_a-Boc-deformyl-Z-geissoschizine **1** in the indoloquinolizidine skeleton conformation b with ring D in chair conformation (predominant conformation).

These results led us to think that if the indoloquinolizidine skeleton of the Boc-protected E-isomer (compound **2**) likewise was in conformation b (Scheme 1), then ring D, in order to avoid the interaction between the side-chains in the chair conformation, might adopt a boat conformation In boat conformation, C-16 and C-5 would be in the immediate vicinity of each other (Figure 7) and an elegant route might then be open to the sarpagan and ajmalan ring systems The interaction between the side-chains would also be prevented, however, if the ring D were to adopt a twist-boat conformation (vide supra).

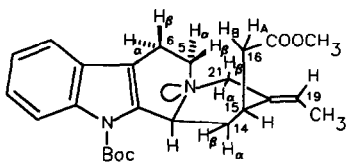


Figure 7 N_a-Boc-deformyl-E-geissoschizine **2** in the indoloquinolizidine skeleton conformation b with ring D in boat conformation.

NOE difference measurements were used to resolve these conformational questions. Irradiation at H-14β resulted in a weak (1%) NOE at H-5β, which confirmed that the indoloquinolizidine skeleton was indeed mainly in conformation b (Scheme 1) If the main conformation of ring D were boat, one would expect an NOE between H-21β and H-19, and a strong NOE between H-5β and at least one of the C-16 protons (H-16_A and H-16_B) (Figure 7) As it turned out, no NOE was observed at H-16_A or H-16_B when H-5β was irradiated, nor at H-5β when H-16_A or H-16_B was irradiated Moreover, no NOE was found to exist between H-21β and H-19.

We went on, therefore, to consider the other possibility: that ring D adopts a twist-boat conformation (Figure 8) In this case one would expect an NOE between H-21α and H-19, and no NOE between H-5β and the C-16 protons (H-16$_A$ and H-16$_B$) In our NOE difference measurements, irradiation at H-21α resulted in a 6% NOE at H-19, while no NOE was observed between H-5β and H-16$_A$ or H-16$_B$ (vide supra). The findings were in good agreement with the twist-boat conformation.

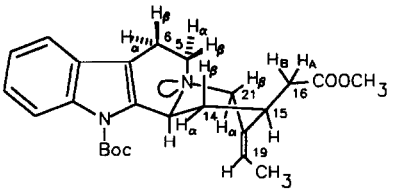


Figure 8. N$_a$-Boc-deformyl-E-geissoschizine 2 in the indoloquinolizidine skeleton conformation b with ring D in twist-boat conformation (predominant conformation).

Although the main conformation of ring D turned out to be a twist-boat, the energy barrier between a twist-boat and a boat is small [13] Thus the twist-boat conformation does not necessarily rule out the possible use of the N$_a$-Boc-protected analogues of compound 2 for the formation of sarpagan and ajmalan ring systems. Further studies are in progress.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using $CHCl_3$ as solvent. Ir absorption bands are expressed in reciprocal centimeters (cm^{-1}). ^{1}H- and ^{13}C-nmr spectra were measured with a Varian Unity-400 NMR spectrometer working at 399 952 MHz (^{1}H-nmr) and 100.577 (^{13}C-nmr) in $CDCl_3$. Chemical shifts are given in ppm by reference to TMS (^{1}H-nmr; δ_H = 0 00 ppm) and $CDCl_3$ (^{13}C-nmr, δ_C = 77.00 ppm). In typical ^{1}H measurements the spectral width was 6000 Hz, acquisition time 3.744 s, and pulse width 7 0 μs. NOE difference spectroscopy was done at 30°C Spectra were obtained by direct subtraction using a 90° composite pulse. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compounds 1, 3, and 4:

For the preparation of compounds **1**, **3**, and **4**, and for their ir, ^{13}C-nmr and ms spectral data, see Refs. 2, 5, and 6 For their ^{1}H-nmr data, see Table 1.

Preparation of compound 2:

A solution of deformyl-E-geissoschizine **4** (34 mg, 0.11 mmol), di-t-butyl dicarbonate [$(Boc)_2O$] (30 mg, 1 3 equiv), and p-dimethylamino pyridine (DMAP) (1.3 mg, 0 1 equiv.) in dry CH_2Cl_2 (6 ml) was stirred at room temperature for 2 h (Ar atm.) Normal work-up and flash chromatographic purification (silica gel, CH_2Cl_2/MeOH, 99/1) led to compound **2**.

Compound **2**. Y 30 mg (64%). Ir· 1730 (br, 2xC=O) ^{1}H-nmr· See Table 1 ^{13}C-nmr: 13.14 (C-18), 21.26 (C-6), 27 82 [C-($\underline{C}H_3)_3$], 33.63 (C-14), 34.13 (C-15), 39 15 (C-16), 46 63 (C-5), 51 34 ($CO_2\underline{Me}$), 54.91 (C-3), 60 52 (C-21), 83 76 [$\underline{C}$-$(CH_3)_3$], 115 59 (C-12), 118.02 (C-9), 121.02 (C-19), 122 55 (C-10), 123 84 (C-11), 129 06 (C-8), 135 22 (C-2), 136.64 (C-13), 150 14 (N-C=O), 172 89 ($\underline{C}O_2Me$). Ms: 424 (M^+), 367 (100%), 323, 309, 295, 249, 170,169, 156 HRms: Found 424.2399. Calcd for $C_{25}H_{32}N_2O_4$: 424.2362

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