NOE DIFFERENCE SPECTROSCOPY APPLIED IN STEREOCHEMICAL INVESTIGATIONS OF TWO DIASTEREOMERIC INDOLOQUINOLIZIDINE ALCOHOLS, SIGNIFICANT IN THE PREPARATION OF GEISSOSCHIZINE-TYPE COMPOUNDS

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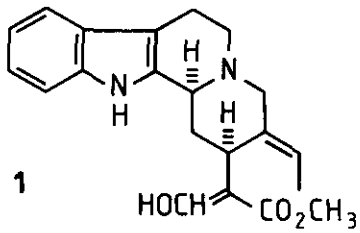
Abstract- Complete ^{1}H-nmr data were recorded for indoloquinolizidine alcohols (**2a**) and (**2b**), significant intermediates in the preparation of geissoschizine-type compounds, and for their benzoyl derivatives (**3a**) and (**3b**). The stereochemistry was deduced from NOE measurements.

INTRODUCTION

Deformylgeissoschizines (*E* and *Z*) are important intermediates in the synthesis of many indole alkaloids, especially in the synthesis of geissoschizine itself (**1**)[1-5] and isositsirikine isomers.



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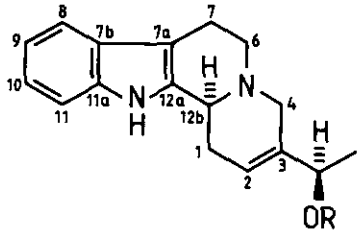
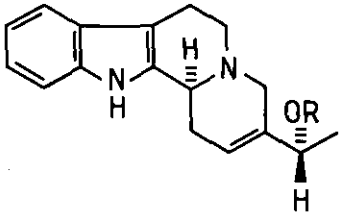
In a series of investigations aiming at the stereoselective preparation of deformylgeissoschizines and other geissoschizine-type compounds,[5-7] we synthesized and isolated two diastereomeric alcohols (**2a**) and (**2b**). Some years earlier their stereochemistry had been indirectly determined through comparision with the stereochemistry of the corresponding Claisen-rearrangement products.[8-9] No effort was ever made, however, to confirm the stereochemistry through direct nmr measurements.



2a R = H



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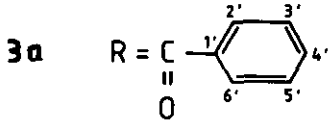
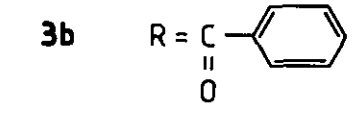


3a R = C(=O)–



3b R = C(=O)–

RESULTS AND DISCUSSION

Because complete ^{1}H-nmr measurements of these two important alcohol intermediates (**2a**) and (**2b**) were not available, and comparison of their ^{1}H-nmr data seemed to be a good method for elucidation of their stereochemistry, we undertook to record their full ^{1}H-nmr spectra. The chemical shifts and coupling constants of the compounds are presented in Table 1. The correct assignment of the chemical shifts was confirmed by H,H-COSY and H,C-COSY measurements (cf. Figure 1). However, as can be seen in Table 1, the chemical shifts of the two compounds are very similar. In all but three cases the differences were 0.01 ppm or less. The only notable difference (0.08 ppm) was found for H-4ß. This indicated that the H-4ß proton was less

shielded in alcohol (**2a**) (δ 3.41) than in alcohol (**2b**) (σ 3.33). Thus the influence of the hydroxyethyl side chain on H-4ß was more pronounced in compound (**2b**) than in compound (**2a**).

Table 1. ^{1}H-nmr data of alcohols (**2a**) and (**2b**) and their corresponding benzoyl derivatives (**3a**) and (**3b**). The coupling constants between the aromatic protons are omitted.

	2a (DMSO-d_6)	**2b** (DMSO-d_6)	**3a** ($CDCl_3$)	**3b** ($CDCl_3$)
H-1α	2.68 br d	2.69 br d	2.54 br d	2.55 br d
H-1β	2.04 dd	2.02 dd	2.33 dd	2.32 dd
H-2	5.68 *d*	5.69 *d*	5.95 d	5.91 d
H-4α	2.95 br d	2.92 br d	3.23 br d	3.10 br d
H-4β	3.41 d	3.33 d	3.55 d	3.63 d
H-6α	2.50 ddd	2.49 ddd	2.68 ddd	2.67 ddd
H-6β	3.10 dd	3.10 dd	3.24 dd	3.25 dd
H-7α	2.64 br d	2.64 br d	2.77 br d	2.77 br d
H-7β	2.80 dddd	2.79 dddd	3.03 dddd	3.04 dddd
H-8	7.37	7.37	7.49	7.49
H-9	6.95	6.95	7.10	7.09
H-10	7.01	7.02	7.15	7.14
H-11	7.29	7.29	7.31	7.29
H-12b	3.36 br d*	3.37 br d*	3.52 br d	3.53 br d
CH-OR	4.10 dq	4.09 dq	5.60 q	5.65 q
CH-OH	4.76 *d*	4.76 *d*		
CH_3	1.18 d	1.17 d	1.51 d	1.51 d
NH	10.76 br s	10.77 br s	7.78 br s	7.90 br s
H-2'			8.07	8.06
H-3'			7.45	7.45
H-4'			7.56	7.56

* Partly masked.

Table 1. contd.

Coupling constants

2a:	$J_{1\alpha,1\beta}$ = 14 Hz;	$J_{1\alpha,2}$ ~ 4 Hz;	$J_{1\alpha,12b}$ ~ 4 Hz;
	$J_{1\beta,2}$ < 1 Hz;	$J_{1\beta,12b}$ ~ 10 Hz;	$J_{4\alpha,4\beta}$ = 16 Hz;
	$J_{6\alpha,6\beta}$ = 11.5 Hz;	$J_{6\alpha,7\alpha}$ = 4 Hz;	$J_{6\alpha,7\beta}$ = 11.5 Hz;
	$J_{6\beta,7\alpha}$ ~ 1 Hz;	$J_{6\beta,7\beta}$ = 4 Hz;	$J_{7\alpha,7\beta}$ = 13 Hz;
	$J_{7\beta,12b}$ ~ 1 Hz;	$J_{CH,OH}$= 4 Hz;	$J_{CH,Me}$ = 6.5 Hz;
2b:	$J_{1\alpha,1\beta}$ = 14 Hz;	$J_{1\alpha,2}$ ~ 4 Hz;	$J_{1\alpha,12b}$ ~ 4 Hz;
	$J_{1\beta,2}$ < 1 Hz;	$J_{1\beta,12b}$ ~ 10 Hz;	$J_{4\alpha,4\beta}$ = 16 Hz;
	$J_{6\alpha,6\beta}$ = 11.5 Hz;	$J_{6\alpha,7\alpha}$ = 4 Hz;	$J_{6\alpha,7\beta}$ = 11.5 Hz;
	$J_{6\beta,7\alpha}$ ~ 1 Hz;	$J_{6\beta,7\beta}$ = 4 Hz;	$J_{7\alpha,7\beta}$ = 13 Hz;
	$J_{7\beta,12b}$ ~ 1 Hz;	$J_{CH,OH}$ = 4 Hz;	$J_{CH,Me}$ = 6.5 Hz;
3a:	$J_{1\alpha,1\beta}$ = 16 Hz;	$J_{1\alpha,2}$ ~ 4 Hz;	$J_{1\alpha,12b}$ ~ 4 Hz;
	$J_{1\beta,2}$ < 1 Hz;	$J_{1\beta,12b}$ = 10 Hz;	$J_{4\alpha,4\beta}$ = 16 Hz;
	$J_{6\alpha,6\beta}$ = 11.5 Hz;	$J_{6\alpha,7\alpha}$ = 4 Hz;	$J_{6\alpha,7\beta}$ = 11.5 Hz;
	$J_{6\beta,7\alpha}$ ~ 1 Hz;	$J_{6\beta,7\beta}$ = 4 Hz;	$J_{7\alpha,7\beta}$ = 13 Hz;
	$J_{7\beta,12b}$ ~ 1 Hz;	$J_{CH,Me}$ = 6.5 Hz;	
3b:	$J_{1\alpha,1\beta}$ = 16 Hz;	$J_{1\alpha,2}$ ~ 4 Hz;	$J_{1\alpha,12b}$ ~ 4 Hz;
	$J_{1\beta,2}$ < 1 Hz;	$J_{1\beta,12b}$ = 10 Hz;	$J_{4\alpha,4\beta}$ = 16 Hz;
	$J_{6\alpha,6\beta}$ = 11.5 Hz;	$J_{6\alpha,7\alpha}$ = 4 Hz;	$J_{6\alpha,7\beta}$ = 11.5 Hz;
	$J_{6\beta,7\alpha}$ ~ 1 Hz;	$J_{6\beta,7\beta}$ = 4 Hz;	$J_{7\alpha,7\beta}$ = 13 Hz;
	$J_{7\beta,12b}$ ~ 1 Hz;	$J_{CH,Me}$ = 6.5 Hz;	

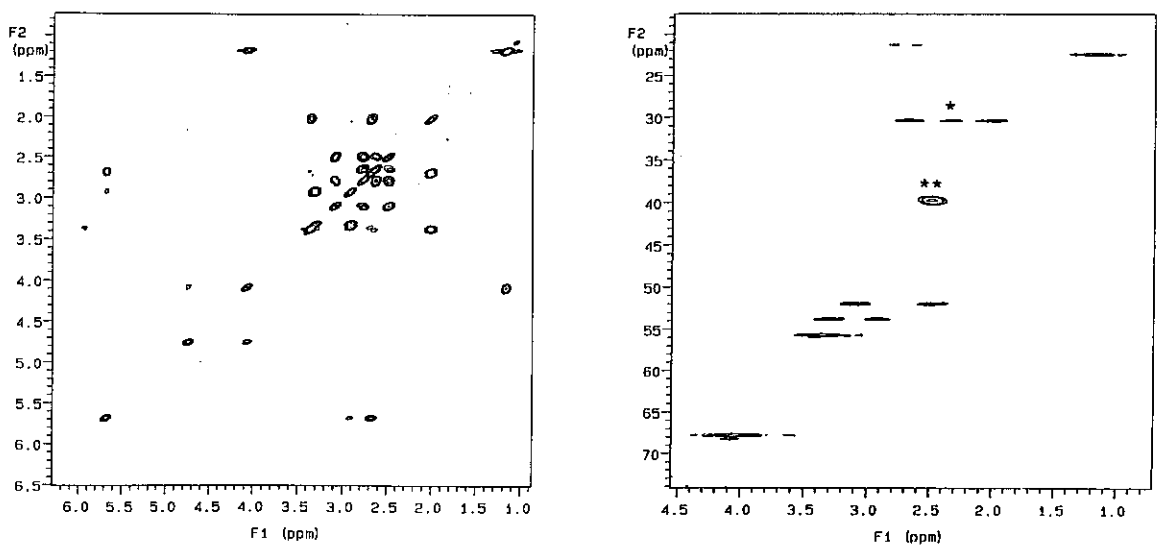


Figure 1. H,H-COSY and H,C-COSY spectra of compound (**2b**) (* artefact, ** DMSO).

Nuclear Overhauser difference spectroscopy[10] suggested itself as an ideal method to confirm the presumed spatial vicinity of H-4ß and the methyl protons in the predominant conformation of compound (**2b**). NOE difference measurements were undertaken for both diastereomers (**2a**) and (**2b**) but still no real difference was apparent in the NOEs at the methyl protons when the 4ß protons were irradiated, and vice versa. It was assumed that this was due to the low energy barrier for the rotation of the side chain. We then attempted to slow down the rotation by introducing a larger functional group to the side chain. The alcohols were esterified with benzoyl chloride, and compounds (**3a**) and (**3b**) were obtained (cf. Experimental). NOE difference measurements of compounds (**3a**) and (**3b**) were carried out and now a difference in the NOEs of H-4ß was seen. When CH_3 of compound (**3b**) was irradiated, there was a clear NOE (10%) at H-4ß but practically no NOE (~ 1%) at H-4α, whereas when CH_3 of compound (**3a**) was irradiated, there were weak NOEs at both H-4α (2%) and H-4ß (2.5%). Irradiation at H-2 resulted in strong NOEs at C<u>H</u>-CH_3 [22% for (**3a**) and 27% for (**3b**)]. Thus in compound (**3b**) the methyl protons and H-4ß had to be spatially closer than in compound (**3a**). In both compounds H-2 and C<u>H</u>-CH_3 had to be spatially close.

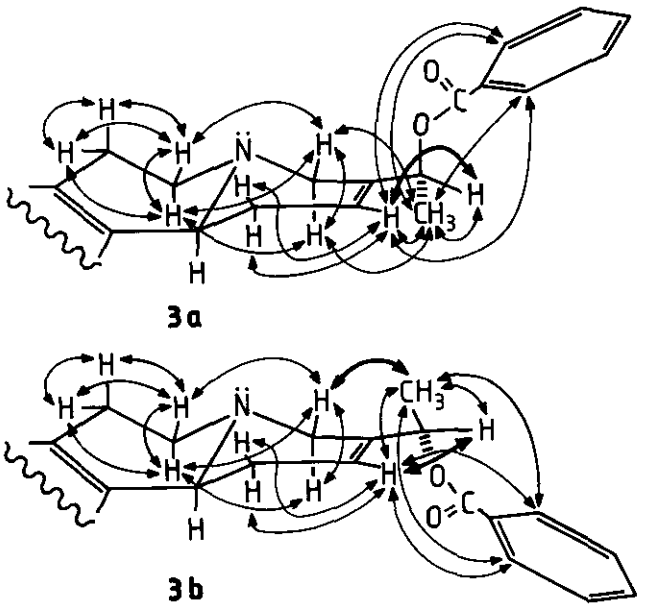


Figure 2. The predominant conformations of compounds (**3a**) and (**3b**) and the results of NOE experiments executed.

Consequently, the configuration of the chiral carbon of the side chain for compounds (**3a**) and (**3b**) could be confirmed as shown in Figure 2, where the compounds are presented in their assumed predominant conformations (excluding the predominant conformation of the benzoyl group).

Other NOEs for compounds (**3a**) and (**3b**), which confirm the proton chemical shifts, were the following (cf. Figure 2). Irradiation at the methyl doublet of the side chain resulted in NOEs at H-2, C<u>H</u>-Me, H-2' and H-6'. Irradiation at the H-2 doublet resulted in NOEs at CH-<u>Me</u>, C<u>H</u>-Me, H-1α, H-1ß, H-2' and H-6'. Irradiation at H-4α resulted in NOEs at H-4ß and H-6α (weak, ~1.5%), and irradiation at H-4ß resulted, in addition to the NOEs at the methyl protons and H-4α, in NOE at H-6ß, which confirmed the chemical shifts of H-6α and H-6ß. A strong NOE (~25%) was to be seen between the geminal protons of H-6α and H-6ß, and H-7α and H-7ß. Moreover, irradiation at H-6α resulted in NOEs at H-4α (weak, ~1%), H-4ß and H-7α (weak, ~1.5%), and irradiation at H-6ß in NOEs at H-4ß, H-7α (weak, ~1%) and H-7ß. All these results confirm our ^{1}H-nmr data for compounds (**3a**) and (**3b**), and, by extension, support our ^{1}H-nmr data for compounds (**2a**) and (**2b**) and the indirect conclusions of Winterfeldt <u>et al.</u>[8] on their stereochemistry.

In summary, also in compound (**2b**), in its predominant conformation, the H-4ß and the methyl protons are spatially closer than in compound (**2a**). The structures of alcohols (**2a**) and (**2b**), which are significant intermediates in the stereoselective preparation of geissoschizine-type indole alkaloids,[5-7] is thus put on a solid foundation.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer in $CDCl_3$. Ir absorption bands are expressed in reciprocal centimetres (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 MHz (^{13}C-nmr). Chemical shift data are given in ppm by reference to TMS (^{1}H-nmr; δ_H = 0.0 ppm) and $CDCl_3$ (^{13}C-nmr; δ_C = 77.0 ppm) or DMSO-

d_6 (^{13}C-nmr; δ_C = 39.5 ppm). In a typical ^{1}H measurement the spectral width was 6000 Hz, acquisition time 3.744 s and pulse width 7.0 μs. 2D-Spectra (H,H-COSY and H,C-COSY) of compounds (**2a**) and (**2b**) were recorded using standard pulse sequences. NOE difference spectroscopy was done at 30°C with sample concentrations of 0.12 mol/l. Spectra were obtained by direct subtraction using a composite 90° pulse. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compounds (2a) and (2b):

For the preparation of compounds (**2a**) and (**2b**) and for their ir, ^{13}C-nmr and ms spectral data, see refs. 11-12. For ^{1}H-nmr data, see Table 1.

Preparation of compounds (3a) and (3b):

Compound (**2a**) or (**2b**) (80 mg, 0.30 mmol), benzoyl chloride (90 mg, 0.64 mmol, added in small portions), pyridine (1 drop) and ethanol (0.5 ml) were stirred at room temperature for 3.5 h. After neutralization with NH_4OH and extraction with CH_2Cl_2 the corresponding ester (**3a**) or (**3b**) was obtained. The esters were purified by column chromatography (silica gel, CH_2Cl_2).

Ester (**3a**): Yield: 85 mg, 76% . Amorphous material. Ir: 3300 (NH), 1720 (C=O). ^{13}C-Nmr: 19.08 (CH_3), 21.44 (C-7), 30.95 (C-1), 52.38 (C-6), 54.18 (C-4), 55.38 (C-12b), 72.46 (CH-CH_3), 108.53 (C-7a), 110.76 (C-11), 118.21 (C-8), 119.46 (C-9), 121.01 (C-2), 121.53 (C-10), 127.14 (C-7b), 128.33 (C-3' and C-5'), 129.62 (C-2' and C-6'), 130.50 (C-1'), 132.92 (C-4'), 134.35 (C-3), 136.25 (C-12a), 136.91 (C-11a). Ms: 372 (M^+), 251 (100%), 250, 170, 169. HRms found: 372.1866. Calcd for $C_{24}H_{24}N_2O_2$: 372.1838.

Ester (**3b**): Yield: 87 mg, 78% . Amorphous material. Ir: 3300 (NH), 1720 (C=O). ^{13}C-Nmr: 19.14 (CH_3), 21.34 (C-7), 30.73 (C-1), 52.30 (C-6), 53.26 (C-4), 55.36 (C-12b), 72.75 (CH-CH_3), 108.41 (C-7a), 110.77 (C-11), 118.17 (C-8), 119.41 (C-9), 121.07 (C-2), 121.50 (C-10), 127.07 (C-7b), 128.36 (C-3' and C-5'), 129.60 (C-2' and C-6'), 130.37 (C-1'), 132.96 (C-4'), 134.21 (C-3), 136.25 (C-12a), 136.32 (C-11a). Ms: 372 (M^+), 251 (100%), 250, 170, 169. HRms found: 372.1854. Calcd for $C_{24}H_{24}N_2O_2$: 372.1838.

REFERENCES

1. C. Szantay, C. Blasko, K. Honty, and G. Dörnyei, "The Alkaloids", ed. A. Brossi, Vol. 27, Academic Press, Orlando, 1986, pp. 131-268 and 407-410 and references therein.
2. S. F. Martin, B. Benage, and J. E. Hunter, J. Am. Chem. Soc., 1988, **110**, 5925.
3. L. E. Overman and A. J. Robichaud, J. Am. Chem. Soc., 1989, **111**, 300.
4. E. Wenkert, M. Guo, M. J. Pestchanker, Y.-J. Shi, and Y. D. Vankar, J. Org. Chem., 1989, **54**, 1166.
5. M. Lounasmaa, R. Jokela, J. Miettinen, and M. Halonen, Heterocycles, in press.
6. M. Lounasmaa, R. Jokela, B. Tirkkonen, J. Miettinen, and M. Halonen, Heterocycles, 1992, **34**, 321.
7. M. Lounasmaa and R. Jokela, Heterocycles, 1990, **31**, 1351.
8. G. Rackur, M. Stahl, M. Walkowiak, and E. Winterfeldt, Chem. Ber., 1976, **109**, 3817.
9. F. E. Ziegler and J. G. Sweeny, Tetrahedron Lett., 1969, 1097. See also F. E. Ziegler, Acc. Chem. Res., 1977, **10**, 227.
10. A. J. Shaka, C. Bauer, and R. Freeman, J. Magn. Reson., 1984, **60**, 479.
11. M. Lounasmaa and M. Puhakka, Acta Chem. Scand. B, 1978, **32**, 77.
12. R. Jokela, A. Juntunen, and M. Lounasmaa, Planta Med., 1987, **53**, 386.

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