PREPARATION OF 17-DEOXY-*E*-ISOSITSIRIKINE *cis*-N_b-OXIDES AND THEIR USE AS MODEL COMPOUNDS

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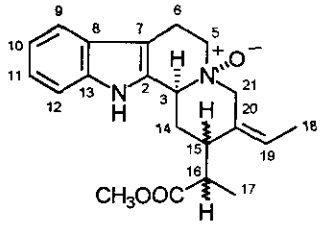
Abstract - Preparation of (16*S**)- and (16*R**)-17-deoxy-*E*-isositsirikine *cis*-N_b-oxides (**5**) and (**6**) is described. Comparison of their ^{1}H-nmr data with those given for *E*-isositsirikine *cis*-N_b-oxides (**7**) and (**8**) from the South American tree *Aspidosperma marcgravianum* suggested that the C-16 configurations presented for the naturally occurring compounds have to be interchanged. ^{13}C-Nmr data of compounds (**5**) and (**6**) are furnished.

We recently used nmr spectroscopy in conformational study and determination of C-16 configurations of *Z*- and *E*-isositsirikine epimers and model compounds.[1-4] In that connection four 17-deoxy-*Z*-isositsirikine *cis*-N_b-oxides (**1**), (**2**), (**3**), and (**4**) were prepared and their nmr data measured.

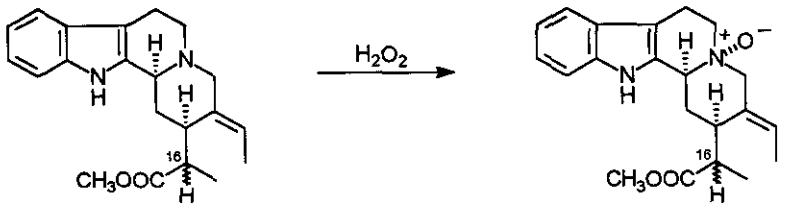


1 H-15 α ; H-16 α
2 H-15 α ; H-16 β
3 H-15 β ; H-16 α
4 H-15 β ; H-16 β

We have now extended our syntheses to 17-deoxy-*E*-isositsirikine *cis*-N_b-oxides (**5**) and (**6**), which seemed to be good "model compounds" for the naturally occurring *E*-isositsirikine *cis*-N_b-oxides (**7**) and (**8**).

RESULTS AND DISCUSSION

The "*model compounds*" (16*S**)-17-deoxy-*E*-isositsirikine *cis*-N_b-oxide (**5**) and (16*R**)-17-deoxy-*E*-isositsirikine *cis*-N_b-oxide (**6**) were prepared by H_2O_2 oxidation from the recently described[2] compounds (16*S**)-17-deoxy-*E*-isositsirikine (**9**) and (16*R**)-*E*-isositsirikine (**10**), respectively (Scheme 1).



9 H-16 β (16*S**)
10 H-16 α (16*R**)

5 H-16 β (16*S**)
6 H-16 α (16*R**)

Scheme 1.

The predominant existence of compounds (**9**) and (**10**) in conformation c[2] (Figure 1) led to the exclusive formation of *cis*-N_b-oxides. No *trans*-N_b-oxides were detected.

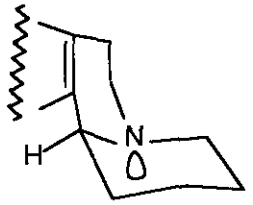
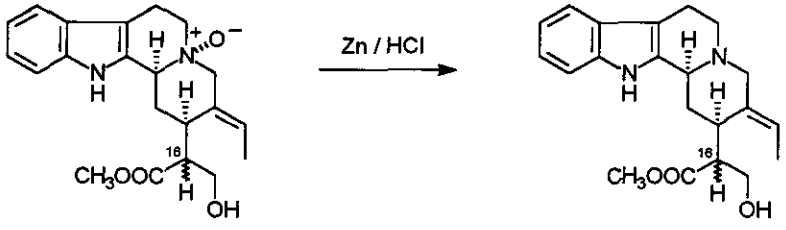


Figure 1. Conformation c.

About ten years ago Robert *et al.*[5] isolated two isositsirikine N_b-oxides from the South American tree *Aspidosperma marcgravianum* Woodson. Their structures were determined as (-)-(16*R*)-*E*-isositsirikine *cis*-N_b-oxide (**7**) [*cf.* ref. 5; 16-epi-isositsirikine 3*S*,4*S*-*N*-oxide, compound (**36**)] and (-)-(16*S*)-*E*-isositsirikine *cis*-N_b-oxide (**8**) [*cf.* ref. 5; isositsirikine 3*S*,4*S*-*N*-oxide, compound (**40**)]. The determination of the structures, especially the C-16

configurations, required the prior reduction (Zn/HCl) of the oxides to compounds which were identified as (16*R*)-*E*-isositsirikine (**11**) [*cf.* ref. 5; 16-epi-isositsirikine, compound (**9**)] and (16*S*)-*E*-isositsirikine (**12**) [*cf.* ref. 5; isositsirikine, compound (**8**)], respectively (Scheme 2).



7 H - 16 β (16*R*)
8 H - 16 α (16*S*)

11 H - 16 β (16*R*)
12 H - 16 α (16*S*)

Scheme 2.

Owing to different priorities for the C-16 ligands, the (16*S**)-17-deoxy-*E*-isositsirikine *cis*-N_b-oxide (**5**) should be the "model compound" for (16*R*)-*E*-isositsirikine *cis*-N_b-oxide (**7**) and the (16*R**)-17-deoxy-*E*-isositsirikine *cis*-N_b-oxide (**6**) that for (16*S*)-*E*-isositsirikine *cis*-N_b-oxide (**8**).

However, comparison of the "characteristic" ^{1}H-nmr data (Table 1) shows similar C-16 configurations for compounds (**5**) and (**8**) and for compounds (**6**) and (**7**). Considering the different priorities for the C-16 ligands (*vide supra*), this means that the C-16 configuration in compound (**7**) is *S* and that in compound (**8**) *R*. Thus the original C-16 configurational assignments H-16*β* (16*R*) and H-16*α* (16*S*) (*vide supra*), given for compounds (**7**) and (**8**), respectively [and corresponding to those given for compounds (**36**) and (**40**) in ref. 5] have to be interchanged.

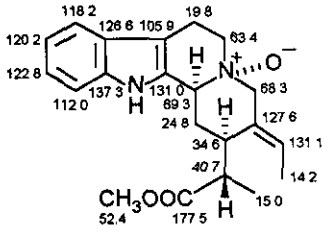
The ^{13}C-nmr values for compounds (**5**) and (**6**) are in full agreement with their structures (Figure 2). This is the first time that ^{13}C-nmr data have been furnished for *E*-isositsirikine *cis*-N_b-oxide derivatives, and it is hoped that

the data will prove useful in future structural determinations of *E*-isositsirikine *cis*-N_b-oxides, so that antecedent reductions to the corresponding parent compounds can be avoided.

Table 1. "Characteristic" ^{1}H-nmr data of compounds (**5**), (**6**), (**7**), and (**8**).

	5	**6**	**7**[a]	**8**[a]
H-18	1.75	1.57	1.60	1.78
H-19	5.85	5.72	5.51	5.95
$COOCH_3$	3.80	3.45	3.60	3.82

[a]Values taken from ref. 5.



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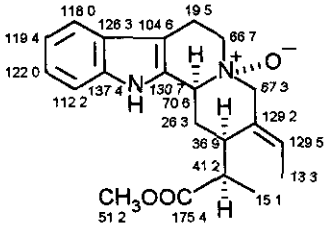

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Figure 2. ^{13}C-Nmr data of compounds (**5**) and (**6**).

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using $CHCl_3$ as solvent. ^{1}H-Nmr spectra were measured with a Varian Unity-400 NMR spectrometer working at 399.952 MHz and ^{13}C-nmr spectra with a Varian Gemini-200 spectrometer working at 50.289 MHz using $CDCl_3$ as solvent. 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). Signal assignments were confirmed by APT and DEPT experiments. Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectrometry (EIms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of (16S)-17-Deoxy-E-isositsirikine cis-N_b-oxide (5).*

A solution of (16*S**)-17-deoxy-*E*-isositsirikine (**9**)[2] (12.4 mg, 0.037 mmol) and H_2O_2 (30%, 11.6 μl) in $CHCl_3$/MeOH (1/1, 5.0 ml) was stirred for 20 h at 60°C (Ar atm). H_2O_2 (30%, 3 μl) was added and the mixture stirred for 1.5 h. Pd/C (10%, 0.8 mg) was added and the mixture stirred for 1 h at 60°C to destroy the excess of H_2O_2. Pd/C was filtered off and washed with MeOH. The filtrate was evaporated and the residue purified by column chromatography (alumina, CH_2Cl_2/MeOH:97/3) to give compound (**5**).

Compound (**5**). Yield 8.6 mg (66%). Amorphous material. Ir: 1720 (s, C=O). ^{1}H-Nmr: 0.85 (3H, d, J=7 Hz, H-17), 1.75 (3H, d, J=7 Hz, H-18), 1.97 (1H, m, H-16), 2.24 (1H, br d, J=15.5 Hz, H-14β), 2.99 (1H, m, H-15), ~3.1 (3H, m, H-6α, H-6β, H-14α), 3.35 (1H, d, J=12 Hz, H-21α), ~3.8 (2H, m, H-5α, H-5β), 3.80 (3H, s, -$COOCH_3$), 4.15 (1H, d, J=12 Hz, H-21β), 4.64 (1H, br s, H-3), 5.85 (1H, q, J=7 Hz, H-19), 7.15 (1H, t, J=7 Hz, H-10), 7.23 (1H, t, J=7 Hz, H-11), 7.43 (1H, d, J=7 Hz, H-12), 7.48 (1H, d, J=7 Hz, H-9), 9.68 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 338, 337, 251, 249 (100%), 170, 169, 156. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found C, 71.02; H, 7.26; N, 7.72.

Preparation of (16R)-17-Deoxy-E-isositsirikine cis-N_b-oxide (6).*

A solution of (16*R**)-17-deoxy-*E*-isositsirikine (**10**)[2] (5.9 mg, 0.017 mmol) and H_2O_2 (30%, 5.6 μl) in $CHCl_3$/MeOH (1/1, 2.0 ml) was stirred for 20 h at 60°C (Ar atm). H_2O_2 (30%, 2 μl) was added and the reaction mixture stirred for 1.5 h. Pd/C (10%, 0.8 mg) was added and the mixture stirred for 1 h at 60°C to

destroy the excess of H_2O_2. Pd/C was filtered off and washed with MeOH. The filtrate was evaporated and the residue purified by column chromatography (alumina, CH_2Cl_2/MeOH: 97/3) to give compound (**6**).

Compound (**6**). Yield 5.1 mg (83%). Amorphous material. Ir: 1720 (s, C=O). ^{1}H-Nmr: 1.23 (3H, d, J=7 Hz, H-17), 1.57 (3H, d, J=7 Hz, H-18), ~2.1 (2H, m, H-14β, H-16), 2.76 (1H, m, H-14α), ~2.9 (1H, m, H-15), ~3.1 (2H, m, H-6α, H-6β), 3.45 (3H, s, -$COOCH_3$), 3.48 (1H, d, J=12 Hz, H-21α), 3.7-3.8 (2H, m, H-5α, H-5β), 4.40 (1H, d, J=12 Hz, H-21β), 4.49 (1H, br s, H-3), 5.72 (1H, q, J=7 Hz, H-19), 7.06 (1H, t, J=7 Hz, H-10), 7.12 (1H, t, J=7 Hz, H-11), 7.38 (1H, d, J=7 Hz, H-12), 7.40 (1H, d, J=7 Hz, H-9) 11.72 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 338, 337, 251, 249 (100%), 170, 169, 156. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found C, 71.08; H, 7.24; N, 7.82.

REFERENCES

1. P. Hanhinen, T. Nurminen, R. Jokela, and M. Lounasmaa, *Heterocycles*,1994, **38**, 2027.
2. M. Lounasmaa, R. Jokela, P. Hanhinen, J. Miettinen, and J. Salo, *Tetrahedron*, 1994, **50**, 9207.
3. M. Lounasmaa, R. Jokela, P. Hanhinen, J. Miettinen, and J. Salo, *J. Nat. Prod.*, 1994 (in press).
4. Biogenetic numbering. J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.
5. G. M. T. Robert, A. Ahond, C. Poupat, P. Potier, and H. Jacquemin, *J. Nat. Prod.*, 1983, **46**, 694. See also, M. Lounasmaa and A. Tolvanen, *"Monoterpenoid Indole Alkaloids"*, ed. J. E. Saxton, Wiley, New York, 1994, pp. 57-159.

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