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Trapping of Intermediates in the Interconversion of Heteroyohimbine Alkaloids

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The isolation of (*Z*)-isositsirikines *8* and *9* in the course of $NaBH_4$ reduction of 19-epicathenamine *2* demonstrates the intermediacy of the (*Z*)-conjugated iminium salt *5* in the interconversion of the heteroyohimbine alkaloids. A 400 MHz ^1H NMR study carried out on compounds *1*, *2*, and *6*–*9* permitted the determination of all the chemical shifts and most of the coupling constants.

The mechanism of the biosynthetic formation of heteroyohimbine alkaloids is well documented.[1] The intermediacy of the epimeric conjugated iminium salts (*E*)–*3* and (*Z*)–*5* (Scheme 1) has been postulated to explain the formation of cathenamine (19*S*) *1* and epicathenamine (19*R*) *2* heteroyohimbines, respectively.[2,3]

However, only the *E* alkene intermediate (4,21-dehydrogeissoschizine) *3* has been isolated from *Guettarda eximia* (Rubiaceae).[4] Moreover, geissoschizine (the 4,21-dihydro derivative of *3*) and the related alkaloids *6* and *7* all have the *E* configuration.

It has been proposed that the less abundant (19*R*)-heteroyohimbine alkaloids are formed by a 1,4-addition of the enol function onto the *Z* alkene derived from the more stable *E* alkene.[3] Moreover, the facile formation of epicathenamine *2* from cathenamine *1* in chloroform solution in the presence of alumina * implies the intermediacy of a *Z* alkene during the epimerization at C–19.[4]

The $NaBH_4$ reduction of 4,21-dehydrogeissoschizine hydrochloride *3* in methanol has been shown to lead *via* geissoschizine to isositsirikines *6* and *7* (in addition to tetrahydroalstonine), and thus can serve as an indirect method to show the presence of an *E* configurational ethylidene side chain in the initial iminium salt.[4] It has also been found that the $NaBH_4$ reductions of cathenamine *1* and epicathenamine *2* yield mainly tetrahydroalstonine and epiajmalicine, respectively.[3,4]

The $NaBH_4$ reduction in methanol of the equilibrated mixture obtained from the 4,21-dehydrogeissoschizine hydrochloride *3* (*vide infra*) afforded after purification, besides the expected major products tetrahydroalstonine and 19-epiajmalicine, the known *E* isositsirikines *6* and *7* and more interestingly the *Z* isositsirikines *8* and *9* (Scheme 1).

In these conditions the *E* isositsirikines *6* and *7* cannot be expected to form directly from cathenamine *1*.[4] Their formation, along with that of the *Z* isositsirikines *8* and *9*, a consequence of trapping the *E* and *Z* iminium salts *3* and *5*, can be interpreted as the results of an equilibrium (Scheme 1).

Although the presence of dienamine *4*, the necessary intermediate between *3* and *5*, could not be experimentally shown (no 18,19-vinyl derivative was isolated after $NaBH_4$ reduction), its intermediacy has been indirectly shown in a similar epimerization process leading to the yohimbine alkaloids.[5]

To obtain useful ^1H NMR data for the further identification and structure determination of indole alkaloids of similar type we undertook a 400 MHz

* Cathenamine *1* is stable in chloroform solution (in the absence of alumina), whereas epicathenamine *2* slowly epimerises in the same conditions, indicating a lower stability.

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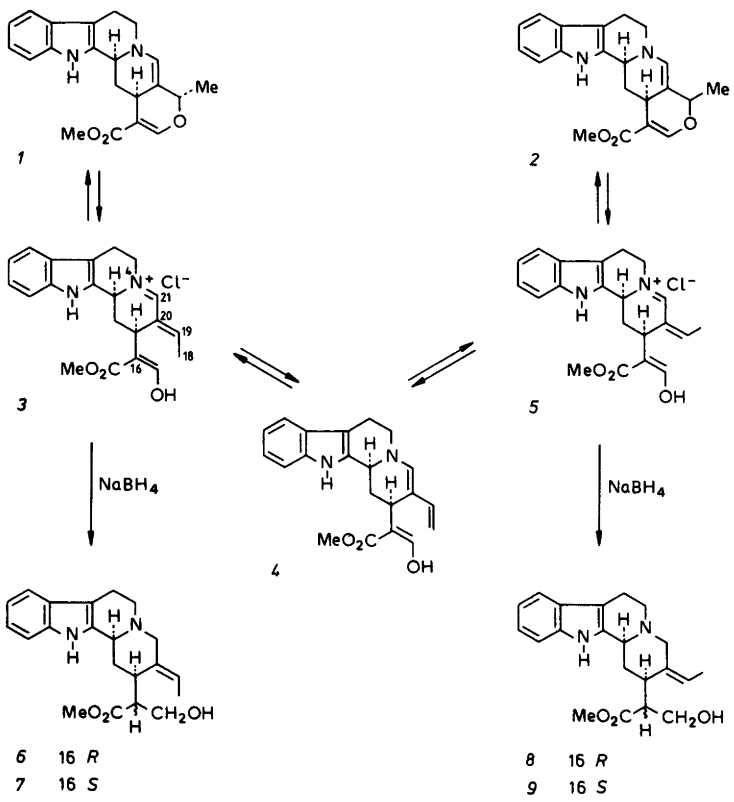

Scheme 1.

Table 1. ^{1}H NMR data of cathenamine *1* and epicathenamine *2*. Spectra were run in $CDCl_3$ at 400 MHz. Values are in δ (TMS=0), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad. The coupling constants between the aromatic protons are not included.

	1	*2*
Chemical shifts		
H−3	4.30 dd	4.34 dd
H−5α	3.33 ddd	3.41 ddd
H−5β	3.28 dd	3.30 dd
H−6α	2.73 br d	2.73 br d
H−6β	2.88 ddd	2.88 ddd
H−9	7.46	7.46
H−10	7.08	7.08
H−11	7.16	7.16
H−12	7.32	7.32
H−14α	3.18 ddd	3.20 ddd
H−14β	1.46 ddd	1.48 ddd
H−15	3.54 br dd	3.54 br dd
H−17	7.54 d	7.64 d
H−18	1.42 d	1.48 d
H−19	4.64 br q	4.46 br q
H−21	6.18 dd	6.21 dd
CO_2Me	3.72 s	3.70 s
NH	7.98 br s	7.98 br s

Coupling constants, compound *1*

$J_{3,14\alpha}=3$ Hz; $J_{3,14\beta}=12$ Hz; $J_{5\alpha,5\beta}=12$ Hz; $J_{5\alpha,6\alpha}\approx 2$ Hz; $J_{5\alpha,6\beta}=6$ Hz; $J_{5\beta,6\alpha}<1$ Hz; $J_{5\beta,6\beta}\approx 5$ Hz; $J_{6\alpha,6\beta}=15$ Hz; $J_{14\alpha,14\beta}=12$ Hz; $J_{14\alpha,15}=5$ Hz; $J_{14\beta,15}=12$ Hz; $J_{15,17}<0.5$ Hz; $J_{15,21}<0.5$ Hz; $J_{18,19}=6.5$ Hz; $J_{19,21}<0.3$ Hz.

Coupling constants, compound *2*

$J_{3,14\alpha}\approx 3$ Hz; $J_{3,14\beta}=12$ Hz; $J_{5\alpha,5\beta}=12$ Hz; $J_{5\alpha,6\alpha}\approx 2$ Hz; $J_{5\alpha,6\beta}\approx 6$ Hz; $J_{5\beta,6\alpha}<1$ Hz; $J_{5\beta,6\beta}\approx 5$ Hz; $J_{6\alpha,6\beta}=15$ Hz; $J_{14\alpha,14\beta}=12$ Hz; $J_{14\alpha,15}=5$ Hz; $J_{14\beta,15}=12$ Hz; $J_{15,17}<0.5$ Hz; $J_{15,21}<0.5$ Hz; $J_{18,19}=6.5$ Hz; $J_{19,21}<0.5$ Hz.

Table 2. ^{1}H NMR data of isositsirikines *6*–*9*. Spectra were run in $CDCl_3$ at 400 MHz. Values are in δ (TMS=0), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad. The signals due to the OH-groups and the coupling constants between the aromatic protons are omitted.

	6	*7*	*8*	*9*
Chemical shifts				
H–3	4.31 br s	3.9 br s	3.64 br d	3.44 br d
H–5α	3.15 ddd	2.84 ddd	2.74 m	2.63 ddd
H–5β	3.27 dd	3.17 dd	3.19 dd	3.11 dd
H–6α	2.65 br d	2.68 br d	2.76 br d	2.73 br d
H–6β	3.0 m	3.0 m	3.0 m	3.0 m
H–9	7.48	7.48	7.48	7.45
H–10	7.10	7.09	7.10	7.06
H–11	7.17	7.14	7.16	7.11
H–12	7.38	7.31	7.33	7.28
H–14α	2.26[a] m	2.27[b] m	2.17 ddd	2.26 ddd
H–14β	2.22[a] m	2.25[b] m	1.72 ddd	1.42 ddd
H–15	3.10 m	3.38 m	2.66 m	2.82 m
H–16	2.52 m	2.66 m	3.01 m	2.94 m
H–17	3.55 br dd	3.92 br dd	3.94 br dd	3.95 br dd
H–17′	3.50 br dd	3.87 br dd	3.85 br dd	3.88 br dd
H–18	1.67 d	1.63 d	1.74 d	1.67 d
H–19	5.64 br q	5.52 br q	5.48 br q	5.36 br q
H–21α	3.54 br d	3.08 br d	2.91 br d	2.76 br d
H–21β	2.93 br d	3.80 br d	3.82 br d	3.85 br d
CO_2Me	3.67 s	3.57 s	3.76 s	3.72 s
NH	8.67 br s	8.23 br s	7.91 br s	8.21 br s

Coupling constants, compound *6*

$J_{5\alpha,5\beta}=12$ Hz; $J_{5\alpha,6\alpha}=4$ Hz; $J_{5\alpha,6\beta}=12$ Hz; $J_{5\beta,6\alpha}\approx1$ Hz; $J_{5\beta,6\beta}=5.5$ Hz; $J_{6\alpha,6\beta}=15$ Hz; $J_{16,17}=7$ Hz; $J_{16,17'}=5$ Hz; $J_{17,17'}=12$ Hz; $J_{18,19}=6.5$ Hz; $J_{19,21\alpha}<0.5$ Hz; $J_{19,21\beta}<0.5$ Hz; $J_{21\alpha,21\beta}=12$ Hz.

Coupling constants, compound *7*

$J_{5\alpha,5\beta}=12$ Hz; $J_{5\alpha,6\alpha}=4$ Hz; $J_{5\alpha,6\beta}=12$ Hz; $J_{5\beta,6\alpha}\approx1$ Hz; $J_{5\beta,6\beta}=5.5$ Hz; $J_{6\alpha,6\beta}=15$ Hz; $J_{16,17}=5$ Hz; $J_{16,17'}=5$ Hz; $J_{17,17'}=12$ Hz; $J_{18,19}=6.5$ Hz; $J_{19,21\alpha}<0.5$ Hz; $J_{19,21\beta}<0.5$ Hz; $J_{21\alpha,21\beta}=12$ Hz.

Coupling constants, compound *8*

$J_{3,14\alpha}=4$ Hz; $J_{3,14\beta}=12$ Hz; $J_{5\alpha,5\beta}=12$ Hz; $J_{5\alpha,6\beta}=12$ Hz; $J_{5\beta,6\alpha}\approx1$ Hz; $J_{5\beta,6\beta}=5.5$ Hz; $J_{6\alpha,6\beta}=15$ Hz; $J_{14\alpha,14\beta}=12$ Hz; $J_{14\alpha,15}=4$ Hz; $J_{14\beta,15}=12$ Hz; $J_{16,17}=7$ Hz; $J_{16,17'}=5$ Hz; $J_{17,17'}=12$ Hz; $J_{18,19}=6.5$ Hz; $J_{19,21\alpha}<0.5$ Hz; $J_{19,21\beta}<0.5$ Hz; $J_{21\alpha,21\beta}=12$ Hz.

Coupling constants, compound *9*

$J_{3,14\alpha}=4$ Hz; $J_{3,14\beta}=12$ Hz; $J_{5\alpha,5\beta}=12$ Hz; $J_{5\alpha,6\beta}=12$ Hz; $J_{5\beta,6\alpha}\approx1$ Hz; $J_{5\beta,6\beta}=5.5$ Hz; $J_{6\alpha,6\beta}=15$ Hz; $J_{14\alpha,14\beta}=12$ Hz; $J_{14\alpha,15}=4$ Hz; $J_{14\beta,15}=12$ Hz; $J_{16,17}=7$ Hz; $J_{16,17'}=5$ Hz; $J_{17,17'}=12$ Hz; $J_{18,19}=6.5$ Hz; $J_{19,21\alpha}<0.5$ Hz; $J_{19,21\beta}<0.5$ Hz; $J_{21\alpha,21\beta}=12$ Hz.

[a,b] Assignments may be interchanged.

^{1}H NMR study of the cathenamines *1* and *2*, and of the four isositsirikines *6*–*9*.

The application of consecutive double resonance operations permitted all the protons in compounds *1*, *2* and *6*–*9* to be discovered and the coupling constants presented in Tables 1 and 2 to be determined.

The H–3 signal of *E* isositsirikine *6* is a broad

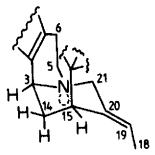

Fig. 1. The predominant conformation of the *E* isositsirikine *6*.

singlet (in reality a badly resolved triplet) at δ 4.31 (*cis*-quinolizidine). This seems to indicate that, owing to a strong interaction in the "normal" conformation (*trans*-quinolizidine) between the methyl group of the *E* ethylidene chain and the side chain at C−15, the predominant conformation is the following (Fig. 1):

The 1,3-interaction between the indole nucleus and the C−15 side-chain seems to be less hampering than in geissoschizine.[6]

The same phenomenon, although less pronounced, is present in the 16-epi *E* isositsirikine *7*. As would be expected this phenomenon is absent from the *Z* isositsirikines *8* and *9*.

The distinction between the *E* isositsirikine *6* and the 16-epi *E* isositsirikine *7* has been made earlier by chemical correlation [7] and recently by a ^{1}H NMR study,[8] in which clearly different chemical shifts were observed for the respective $-CH_2-$ and CH_3COO- groups attached to C−16 (Table 2).

The differences in the corresponding chemical shifts of the isomeric *Z* isositsirikines *8* and *9* (Table 2) are much smaller and do not permit an *a priori* distinction between the two epimers.*

EXPERIMENTAL

The NMR spectra were recorded on a laboratory-constructed 400 MHz ^{1}H high resolution spectrometer (I.E.F. 400)[9] and obtained by collecting 8 to 64 free-induction decay signals for a $\approx$0.01 M solution of the sample in 450 μl of $CDCl_3$. In the case of epicathenamine *2* a 1:1 mixture of cathenamine *1* and epicathenamine *2* was used (*vide infra*).**

One gram of 4,21-dehydrogeissoschizine hydrochloride *3* was equilibrated in 300 ml of chloroform in the presence of 100 g of alkaline alumina [Merck, aluminium oxide 90 active basic (act.1)] during 24 h. The equilibration leads to a 1:1 mixture of cathenamine *1* and epicathenamine *2* (^{1}H NMR). The mixture was filtered, the organic solvent evaporated and the obtained residue immediately reduced with $NaBH_4$ in MeOH containing a trace of acetic acid. After the normal work-up the products (360 mg) were separated by successive TLC (silica gel) treatments yielding besides tetrahydroalstonine and 19-epiajmalicine, *E* isositsirikine *6* and 16-epi *E* isositsirikine *7*, which were identified by direct comparison (TLC, IR, ^{1}H NMR, MS) with authentic samples, as well as *Z* isositsirikine *8* and 16-epi *Z* isositsirikine *9* (^{1}H NMR, MS).

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* The presentation of *Z* isositsirikines in formulas *8* and *9* is arbitrary and could be reversed.

** As we did not succeed in isolating pure epicathenamine *2* we decided to use a 1:1 mixture of cathenamine *1* and epicathenamine *2*.