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Solution and Crystal Conformations of Myrionine, a New 8β-Alkyl-*cis*-decahydroquinoline of *Myrioneuron nutans*

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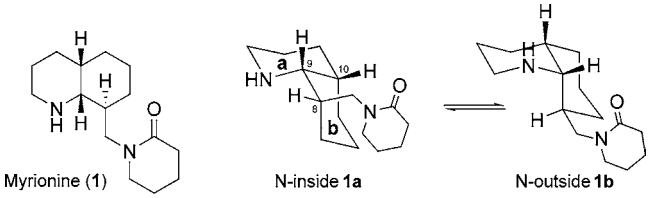
ABSTRACT



Myrionine (1), a new 8β-alkyl-*cis*-decahydroquinoline, was isolated from *Myrioneuron nutans*. Its structure was determined by spectral methods and then confirmed by X-ray analysis and total synthesis. In solution, 1 gives rise to an N-in/N-out equilibrium. The solvent has weak influence on the N-in/N-out ratio for myrionine (1), whereas together with the anions, it plays an important role for myrionine hydrochloride (9) and hydroiodide (10). The two N-in and N-out conformations obtained separately by crystallization of 9 and 10, respectively, were analyzed by X-ray diffraction.

As part of our program on alkaloids from plants of Vietnam, we have selected *Myrioneuron nutans*, a small tree belonging to the Rubiaceae family. Herein, we describe the isolation, structure determination, and asymmetric synthesis of a new alkaloid, myrionine (**1**), a *cis*-decahydroquinoline derivative (*cis*-DHQ). Its conformation in solution was studied by NMR and in the solid state by X-ray crystallography. In fact, due to ring inversion, *cis*-DHQs can occur in two chair−chair forms termed N-inside (N-in) and N-outside (N-out) and are biconformational molecules as *cis*-decalins. Conformational equilibrium of *cis*-DHQs has attracted a great deal of attention[1a−k] as the conformation of flexible biomolecules is important for their biological properties. An understanding of the factors determining the conformer equilibrium is needed in order to control the conformer populations. The preferred conformation depends upon a number of factors such as solvent, pH, or substituents on the ring framework.[2a,b]

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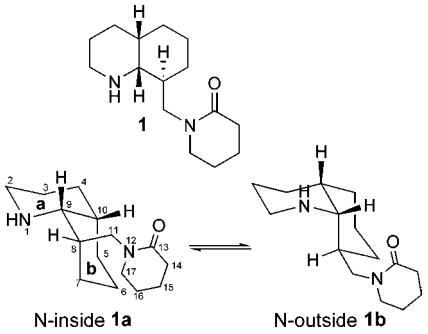
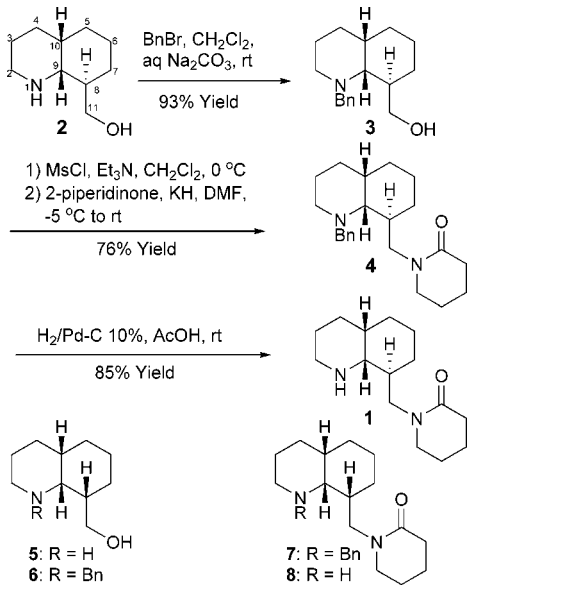
Previous conformational studies on *cis*-DHQs only deal with the solution structures of the N-in and N-out equilibrium analyzed by various methods, especially by NMR. To our knowledge, no study deals with the solid structure of the two conformers obtained and analyzed individually. We report here for the first time the X-ray structure of the two conformers, N-in and N-out of one *cis*-DHQ derivative (myrionine). Generally, natural *cis*-DQHs have been reported from animal sources, such as amphibians or tunicates, but rarely from plants.[3a,b]



Myrionine (**1**) was isolated from the leaves of *M. nutans* as an optically active oil ($[\alpha]^{20}_D$ −16.1 (*c* 1, MeOH)). The ESI-MS showed the protonated molecular $[M + H]^+$ ion at *m*/*z* 251.2129 (calcd 251.2123 for $C_{15}H_{27}N_2O$), indicating the molecular formula $C_{15}H_{26}N_2O$. The IR spectrum depicted an amide bond at 1634 cm^{-1}. The ^1H and ^{13}C NMR spectra of **1** in $CDCl_3$ at 298 K as well as in C_5D_5N showed broad signals, suggesting a conformational equilibrium. The gross structure of **1** in C_5D_5N was elucidated from its NMR spectra at 328 K in which all of the signals were present and sharp. The $^1H-^1H$ COSY data allowed the determination of an 8-substituted DHQ and a 2-piperidinone moiety, which were further connected as indicated in structure **1** from the observed HMBC correlations between the carbonyl at C13 and the protons of both methylenes CH_2-11 and CH_2-17. Proton H9 had two coupling consants with H10 (3.1 Hz) and H8 (6.2 Hz) indicating that H9 and H10 were in a cis-relative disposition. In addition, the NOE interaction between H9 and H10 confirmed the cis-fused junction for the a/b-rings of **1**, and the NOEs between methylene CH_2-11 and H10 indicated the 8-substituent to be in β-disposition on the cyclohexane b-ring. However, at 328 K, as the observed conformation was an average, no definitive stereochemistry for C8 could be deduced. To confirm its structure and establish its absolute configuration, myrionine (**1**) was synthesized (Scheme 1).

Synthon **2** (8*S*,9*R*,10*S*) was prepared in four steps from cyclohexanone according to the previously reported method.[4a,b] The amino group of **2** was protected by benzylation[5] and the resulting **3** coupled with 2-piperidinone after hydroxyl activation with mesyl chloride in the presence of KH to afford synthetic **1** ($[\alpha]^{20}_D$ −16.8 (*c* 1, MeOH)) (Scheme 1). By using the same procedure, 8-*epi*-myrionine (**8**; $[\alpha]^{20}_D$ −21.8 (*c* 2, MeOH)) was synthesized starting from 8*R*,9*R*,-10*S*-8α-methanol-DHQ (**5**)[4a,b] via benzyl-protected compounds **6** and **7**. Comparison of NMR data and optical activities of the synthetic compounds with myrionine (**1**) under the same conditions revealed that they were identical. The absolute configuration of the chiral centers was thus established as 8*S*,9*R*,10*S*, with H9 and H10 in a cis-relationship.

Scheme 1. Synthesis of **1** and Its 8-Epimer (**8**)



The conformational equilibrium of **1** observed by NMR resulted from the ring inversion of the *cis*-DHQ motif to form the two chair−chair conformers **1a** and **1b**. To determine the **1a**/**1b** ratio, **1** was analyzed in $CDCl_3$ at low temperature (233 K) and the ^1H NMR spectrum then displayed two sets of sharp signals. The signal for H9 appeared as a broad singlet in **1a**, whereas it was a doublet of doublet (J = 4.7 and 14.5 Hz) in **1b**. Complete assignment for the two conformers by 2D-NMR indicated that H9 was in a gauche- and anti-relationship with H8 in **1b** and **1a**, respectively. The 70:30 ratio for **1a**/**1b** was determined from the ^1H NMR spectrum. When analyzed either in CD_3COCD_3 or in CD_3OD at 233 K, no significant change in the **1a**/**1b** ratio was observed.

To ascertain if the conformational equilibrium resulted from the ring inversion and not from inversion of the pyramidal nitrogen N1, myrionine hydrochloride (**9**) and myrionine hydroiodide (**10**) were prepared by treatment of **1** with HCl and HI, respectively, and analyzed by NMR. Broad signals were observed in the ^1H NMR spectra of **9** and **10** in CD_3OD at 298 K, confirming that the conformational equilibrium was still observable and not due to pyramidal inversion. To determine the N-in/N-out ratio for each of them, **9** and **10** were analyzed at low temperature in

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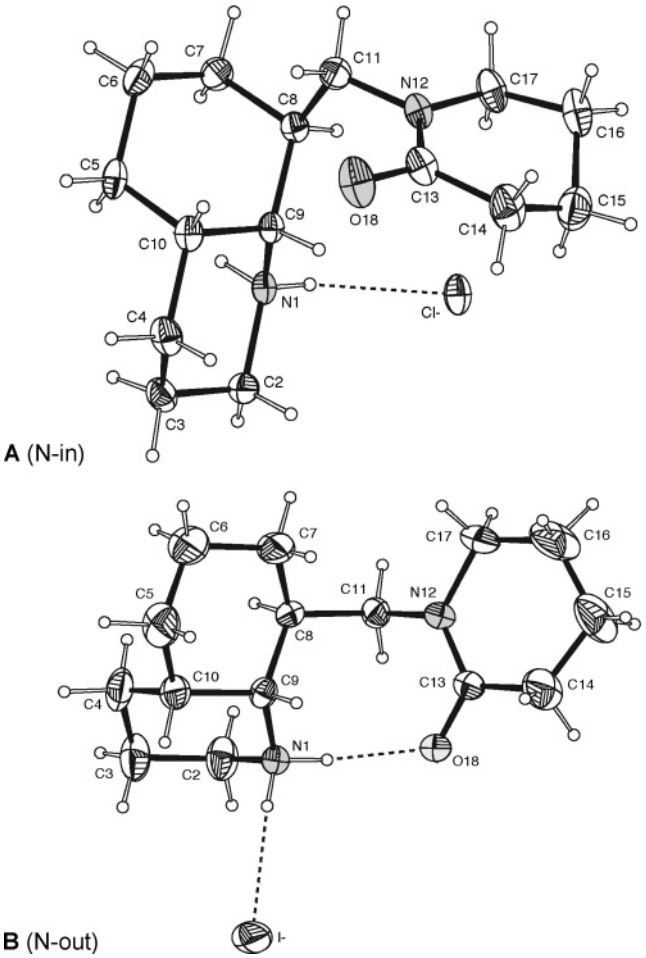

Figure 1. X-ray structures of myrionine salts: **9** (A) and **10** (B) drawn by ORTEP. (Displacement ellipsoids are shown at the 30% probability level.)

CD_3OD and in $CDCl_3$. At 233 K in CD_3OD, two sets of sharp signals were observed for **9** and **10**. Each set of signals was identified from 2D-NMR. Then the N-in/N-out ratios measured from the ^1H NMR spectra were 65:35 for **9** and 55:45 for **10**. Surprisingly, the N-in/N-out ratio for **10** in $CDCl_3$ at 233 K was 20:80, whereas it was 70:30 for **9** under the same conditions. This corroborated that the solvent and the nature of the counterion played an important role in the conformational equilibrium of the two salts, **9** and **10**.

Myrionine hydrochloride (**9**) was crystallized in EtOAc/EtOH (8:2) and myrionine hydroiodide (**10**) in MeOH to give suitable crystals for X-ray diffraction (Figure 1).[6] Attempts to crystallize **9** in MeOH and **10** in EtOAc/EtOH (8:2) were unsuccessful. Analysis confirmed the configuration C8(*S*), C9(*R*), C10(*S*) for both molecules. In each molecule, the two rings of the DHQ moieties were in a chair conformation,

(6) CCDC 619064 and CCDC 619065 contain the supplementary crystallographic data for the respective compounds **9** and **10**. These data can be obtained free of charge at www.ccdc.cam.ac.uk /conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB 1EZ, UK; fax / (internat.) +44-1223/336-033; E-mail : deposit@ccdc.cam.ac.uk].

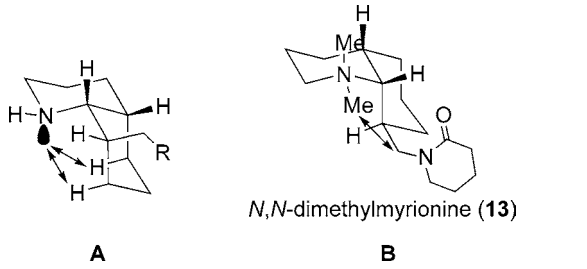

Figure 2. (A) 1,4-Hydrogen−lone pair interactions in the N-in form of β-alkyl-*cis*-DHQs. (B) *syn*-Pentane interaction between equatorial *N*-methyl- and 1-methyl-2-piperidinone groups in the N-out form of *N*,*N*-dimethylmyrionine (**13**).

cis-fused along the C9/C10 bond, with atoms H9 and H10 in the β-position. A slight flattening was noted at C9 in **9**. In this structure, H8 and H9 were in the gauche position, while they were in the trans-diaxial position in **10**, with respective torsion angles H8−C8−C9−H9 = 78.9 (**9**) and 176.7° (**10**). The conformation of the two molecules differed notably, resulting in an inversion of rings, as shown by the full equivalent torsion angle values with opposite signs. In **9**, the 1-methyl-2-piperidinone group fixed at C8 was in an axial position, avoiding interactions with the six-membered rings, while it was equatorial in **10**. Furthermore, in **9**, the piperidinone ring exhibited a perfect half-chair conformation (with atoms C15 and C16, respectively, deviated by −0.402 and 0.379 Å from the mean plane of the four other atoms), while in **10**, this ring with disordered atoms C15 and C16 exhibited a nearly envelope conformation, either in C15 or in C17.

The molecular packing of **9** showed that the two hydrogen atoms of nitrogen N1 were hydrogen bonded to two Cl^- anions. In fact, the chloride ions bridged together the two molecules of the cell, linking in chains the different cells along the *b*-axis. In the molecular packing of **10**, each of the four molecules per cell beared a positive charge on the nitrogen atom N1. Electroneutrality in the unit cell was therefore ensured by the presence of four iodide counterions in special positions with a weight of $^1/_2$, plus four triiodide linear anions, all with an occupancy factor refined to $^1/_2$. The two hydrogen atoms of nitrogen N1 were hydrogen bonded, one with the iodide of the molecule, the other one with O18 realizing an intramolecular hydrogen bond. Surprisingly in the crystals, the pure N-in form was obtained for **9**, whereas in the case of **10**, only the pure N-out conformer was present.

Comparison of various *cis*-DHQs substituted at C8 permitted understanding of the factors which control the distribution of the N-in and N-out isomers in this series. The unsubstituted *cis*-DHQ (**11**) was previously reported to be in the 90:10 ratio, in favor of the N-in conformer.[1g] An explanation referred to the possibility that the NH could be equatorial, leading to two 1,4 hydrogen−lone pair interactions for the N-in conformer (Figure 2A). These interactions are considerably smaller than the corresponding 1,4 hydrogen−hydrogen ones in the N-out conformer.[1g] Another possible explanation

is the stronger stereoelectronic interactions (nitrogen lone pair and σ^* acceptors, C−H and C−C bonds; σ-donor C−H and σ^*-acceptor C−N bonds) in the N-in over the N-out conformers.[1b,d,7]

Vierhapper and Eliel have demonstrated that the N-out conformer slightly predominated (N-out/N-in ratio 59:41) for 8β-methyl-*cis*-DHQ (**12**).[2a] The equilibrium thus shifted to the N-out conformer by introducing a methyl group at the 8β-position. In addition, for the synthetic 8β-hydroxymethyl-*cis*-DHQ (**2**), the sharp signals observed at 298 K in the ^{1}H NMR spectrum ($CDCl_3$) suggested the presence of only one conformer (>95%) according to NMR sensitivity. The coupling constants of H9 (dd, 10.6 and 2.8 Hz) allowed assigning its trans-diaxial relationship with H8. The predominant conformation of **2** was thus N-out. This could be explained by the intermolecular hydrogen bonding between the NH and the oxygen atom that stabilizes the N-out form. This effect was also observed in the 5-hydroxy-*cis*-DHQ derivatives.[2b] The intramolecular hydrogen bonding was also observed in the N-out conformer of myrionine salt **10**. However, the N-in conformer of **1** was preferred. This observation suggested that such an intramolecular hydrogen bond was not a predominant stabilizing factor in the case of myrionine. The preference of **1a** over **1b** could be then explained by the strong gauche interaction between the 1-methyl-2-piperidinone and the nitrogen of the *cis*-DHQ in **1b**. Such an interaction was previously proposed for 8β-*tert*-butyl-*cis*-DHQ in which the ratio of 93:7 in favor of the N-in conformer was observed.[8] To verify the role of these interactions, *N*,*N*-dimethylmyrionine (**13**) was prepared by methylation of **1** with methyl iodide and analyzed by NMR. The sharp signals were observed in the 1D NMR spectra at 298 K, **13** was presumably conformationally homogeneous. As anticipated, **13** adopted the N-in conformation characterized by a broad doublet (J_{H9-H8} = 5.1 Hz, J_{H9-H10} < 1 Hz) for H9, indicating its gauche-couplings with H8 and H10. The shifting (from N-out to N-in), by introducing methyl groups on the DHQ nitrogen atom of myrionine (**1**), could be clearly explained by the strong *syn*-pentane interaction between the equatorial *N*-methyl and the 1-methyl-2-piperidinone group, which destabilizes the N-out conformer (Figure 2B). Thus, for the 8β-alkyl-*cis*-DHQ series, the distribution of the conformers is controlled by competition between two types of 8β-alkyl group interactions with either the DHQ nitrogen or the axial H10 and H-6$_{ax}$ on the cyclohexane b-ring (Figure 3).

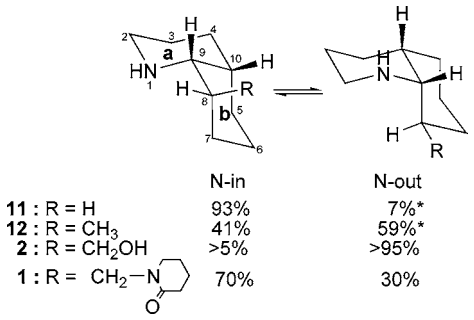

Figure 3. Distribution of the N-in/N-out conformers for various 8β-alkyl-*cis*-DHQ in $CDCl_3$. *Results taken from ref 2a.

It is important to note that myrionine (**1**) is in a conformer equilibrium, whereas the 8-alkyl-*cis*-DHQ derivatives, myrioxazines A and B previously isolated from *M. nutans*, are N-out and N-in conformers, respectively. This is explained by the fact that these two forms are constrained by the O−CH_2−N bridge.[4a]

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Supporting Information Available: Crystallographic data for **9** and **10**, NMR spectra, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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