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Determination of the Stereochemistry of Rotenoids by ^{1}H-NMR Spectroscopy in C_6D_6

Ivanka Kostova*, and **Iliya Ognyanov**

Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria

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The application of ^{1}H-NMR spectroscopy in C_6D_6 for the determination of configurations at C_{12a} and C_{6a} in rotenoids is discussed.

(Keywords: Rotenone; Rotenoids; Stereochemistry; ^{1}H-*NMR)*

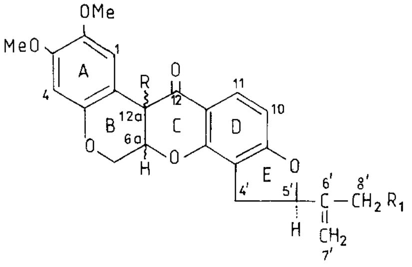
Bestimmung der Stereochemie von Rotenoiden mittels ^{1}H-*NMR-Spektroskopie in* C_6D_6

Es wird die Anwendung der ^{1}H-NMR-Spektroskopie in C_6D_6 zur Bestimmung der Konfigurationen an C_{12a} und C_{6a} in Rotenoiden diskutiert.

Introduction

The *cis*-B/C fused rotenoids differ from the *trans* isomers in their ^{1}H NMR spectra by the chemical shift of 1-H and the splitting pattern of the protons at 6a, 12a, and 6 positions. It is known, however, that there is no way to distinguish the two *cis* $6a\beta, 12a\beta, 5'\beta$ and $6a\alpha, 12a\alpha, 5'\beta$ diastereomers by their ^{1}H NMR spectra in $CDCl_3$; thus CD and ORD data had to be used[1].

Recently, we have reported[2] the correlation between the ^{1}H NMR spectra in C_6D_6 and the stereochemistry of four diastereomeric pairs $(6a\beta, 12a\beta, 5'\beta$ and $6a\alpha, 12a\alpha, 5'\beta)$ of 12a-CH_2OH derivatives of rotenone (*Rt*) **1 a** and amorphigenin (*Amg*) **2 a** and their acetates, whose absolute configurations had been determined by CD. In this communication we report further investigation on ^{1}H spectra of *cis*-B/C rotenoids **1**–**8** with different substituents at C_{12a} and $C_{8'}$, and propose the application of ^{1}H NMR spectra in C_6D_6 for the determination of the stereochemistry of B/C-ring juncture.



1a,b: $R=R^1=H$
2a: $R=H$, $R^1=OH$
3a,b,c,d: $R=OH$, $R^1=OH$
4a,b: $R=OH$, $R^1=H$
5a,b: $R=CH_2OCHO$, $R^1=H$
6a,b: $R=CH_2Cl$, $R^1=H$
7a,b: $R=CH_2OCHO$, $R^1=Cl$
8a,b: $R=CH_2Cl$, $R^1=Cl$

9a,b: $R=CH_2OH$, $R^1=H$
10a,b: $R=CH_2OAc$, $R^1=H$

a 6aβ, 12aβ, 5'β (6a*S*, 12a*S*, 5'*R*)
b 6aα, 12aα, 5'β (6a*R*, 12a*R*, 5'*R*)
c 6aβ, 12aα, 5'β (6a*S*, 12a*R*, 5'*R*)
d 6aα, 12aβ, 5'β (6a*R*, 12a*S*, 5'*R*)

Results and Discussion

The pertinent NMR data of all compounds studied are presented in Table 1. The spectra of the four possible isomers of 12a-OH *Amg*[1], i.e. 6aβ, 12a-βOH *Amg* **3a**, 6aα, 12a-αOH *Amg* **3b**, 6aβ, 12a-αOH *Amg* **3c**, and 6aα, 12a-βOH *Amg* **3d** illustrate the type of B/C-ring juncture: 1-H appears at ~ δ 7.00 for the *cis*-fused rotenoids, and ~ δ 8.00 for the *trans* fused isomers (Table 1). The spectra of natural *Rt* (**1a**, 6aβ, 12aβ, 5'β) and mutarotenone (**1a,b**, 6aβ, 12aβ, 5'β and 6aα, 12aα, 5'β), prepared by a known procedure[3], were also recorded (Fig. 1). In all other cases the NMR spectra of diastereomeric mixtures (6aβ, 12aβ, 5'β and 6aα, 12aα, 5'β) were recorded and the assignments were performed by comparison of the spectra of **1a**, **1a,b**, **3a**, **3b**, **3c**, **3d**, and of the spectra reported[2] for the four diastereomeric pairs of 12a-CH_2OH derivatives of **1a** and **2a**. The data of all compounds are in excellent agreement with our previous observations. For all diastereomeric mixtures the resonances of 5'-H, 4'-H_2 and 8'-CH_3 protons were those most appropriate for solving stereochemical problems. It should be pointed out that, despite of the partial overlapping of signals, the signals of 4'-H_2 and 8'-CH_3 were well-resolved and characteristic patterns could be used to identify each diastereomer (Fig. 1). The ratio of the diastereomers (~ 1 : 1) was determined by integrating the 5'-H, 4'-H_2 or 8'-CH_3 signals.

As discussed[4] previously, the assignment of the two fourline signals (doublets of doublet) to a specific 4' proton is ambiguous, because of the small difference between the vicinal coupling constants (8.5 Hz and

Table 1. ^{1}H *chemical shifts in* C_6D_6 *of selected protons in rotenoids* **1**–**8**[a]

Comp.[b]	6a	12a	5′-αH	4′-αH	4′-βH	8′-CH_3 or —CH_2	1-H
1a	β	β	4.71 t[c]	2.69 d	2.69 d	1.46 s	7.19 s
1a, b	β	β	4.71 t	2.69 d	2.69 d	1.46 s	7.19 s
	α	α	4.86 t	2.86 dd	2.58 dd	1.29 s	7.19 s
3a	β	β	4.75 t	2.67 dd	2.72 dd	3.60 d, 3.49 d	6.92 s
3b	α	α	4.91 t	2.75 dd	2.51 dd	3.79 bs	6.79 s
3c	β	α	4.95 t	2.90 dd	2.86 dd	3.79 bs	8.11 s
3d	α	β	5.08 t	2.96 dd	2.83 dd	3.79 d, 3.71 d	8.14 s
4a, b	β	β	4.58 t	2.57 d	2.57 d	1.42 s	6.84 s
	α	α	4.76 t	2.74 dd	2.50 dd	1.22 s	6.84 s
5a, b	β	β	4.69 t	2.68 d	2.68 d	1.47 s	7.03 s
6a, b	α	α	4.92 t	2.87 dd	2.58 dd	1.28 s	7.03 s
7a, b	β	β	4.82 t	2.70 dd	2.75 dd	overlapped with	7.01 s
8a, b	α	α	5.09 t	2.85 dd	2.48 dd	other protons	7.02 s

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[a] The protons whose chemical shifts are closely depending on the stereochemistry are presented; estimated accuracy 0.01 ppm for the chemical shifts and 0.3 Hz for the coupling constants; J in Hz: 5′-αH, 4′-αH ~ 10.0 Hz, 5′-αH, 4′-βH ~ 8.5 Hz, 4′-αH, 4′-βH ~ 16.0 Hz.

[b] The letters **a** and **b** (or **c** and **d**) denote that NMR spectra of pure diastereomers were studied, while the letters **a**, **b** denote diastereomeric mixtures.

[c] The expected dd ($J = 10.0$ Hz and 8.5 Hz) for 5′-H appears as a triplet.

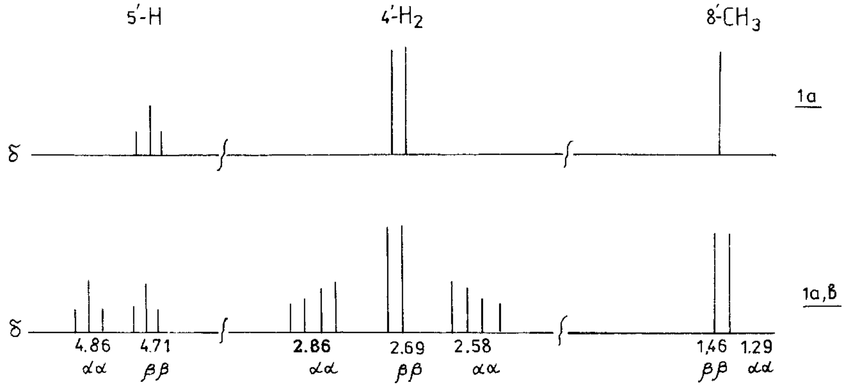

Fig. 1. ^{1}H NMR pattern of 5′-H, 4′-H_2 and 8′-CH_3 protons of natural rotenone **1a** (6aβ, 12aβ, 5′β) and mutarotenone **1a, b** (a mixture of 6aβ, 12aβ, 5′β and 6aα, 12aα, 5′β)

10.0 Hz). This assignment was however possible by the use of the solvent shifts $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$ of 4′, 5′ and 8′ protons of the compounds studied (Table 2). In this table 4′-Ha designates the proton with the larger $J (= 10.0\,\mathrm{Hz})$ and 4′-Hb the proton with the smaller $J (= 8.5\,\mathrm{Hz})$. In C_6D_6 the 5′-H and 4′-Ha of all 6aβ, 12aβ-compounds are shifted upfield, whereas 8′-CH_3 and 4′-Hb of all 6aα, 12aα-compounds show greater upfield shifts. This indicates that 8′-CH_3 and 4′-Hb are on the same β-face of the molecule, whereas 5′-H and 4′-Ha are on the α-face, i.e. 4′-Ha is 4′-αH, and 4′-Hb is 4′-βH. Therefore, $J_{5',4'\text{-}\alpha H}$ is 10.0 Hz (J_{cis}) and $J_{5',4'\text{-}\beta H}$ is 8.5 Hz (J_{trans}). This confirms previous studies[5] that the *Karplus* equation holds for 2,3-dihydrobenzofurans and $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$.

Table 2. *Solvent shifts* ($\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$) *of* 4′-$H_2$, 5′-H *and* 8′-$CH_3$ *protons*

Comp.	5′-αH		4′-Ha≡4′-αH $J = 10.0$ Hz		4′-Hb≡4′-βH $J = 8.5$ Hz		8′-CH_3	
	Stereochemistry at 6a and 12a positions							
	β,β	α,α	β,β	α,α	β,β	α,α	β,β	α,α
1 a, b	0.53	0.40	0.62	0.43	0.28	0.42	0.30	0.43
5 a, b	0.57	0.39	0.60	0.40	0.26	0.39	0.29	0.44
6 a, b	0.59	0.39	0.60	0.42	0.29	0.39	0.32	0.46
9 a, b	0.60	0.47	0.66	0.47	0.30	0.43	0.29	0.44
10 a, b	0.56	0.43	0.58	0.39	0.30	0.39	0.26	0.42
Mean values $\bar{\Delta}$	0.57	0.41	0.61	0.42	0.29	0.40	0.29	0.44
$\bar{\Delta}_{\beta,\beta} - \bar{\Delta}_{\alpha,\alpha}$	+0.16		+0.19		−0.11		−0.15	

A comparison of the average values (Table 2) of the solvent-induced shifts of 5′, 4′ and 8′ protons for the 6aβ, 12aβ ($\bar{\Delta}\beta,\beta$) and 6aα, 12aα ($\bar{\Delta}\alpha,\alpha$) compounds revealed that β,β-compounds showed larger $\bar{\Delta}\beta,\beta - \bar{\Delta}\alpha,\alpha$ for 5′-H and 4′-αH (0.16 and 0.19 ppm, respectively), while those for 4′-βH and 8′-CH_3 were found larger in the α,α-compounds (0.11 and 0.15 ppm, respectively). The remaining protons (1-H, 2,3-O*Me*, 10-H, 11-H, 6 eq, 6 ax, 12a-CH_2) showed no significant difference in $\bar{\Delta}\beta,\beta - \bar{\Delta}\alpha,\alpha$ (less than 0.05 ppm) except 4-H (~0.07 ppm); integration of the latter proton signal allows a quantitative analysis of diastereomeric mixtures.

These results demonstrate a specific correlation between the solvent-induced shifts of 5′-H, 4′-H_2 and 8′-CH_3 and the configurations of 6a and 12a chiral centres—probably caused by formation of different solvent-solute complexes.

It is concluded that the ^{1}H NMR spectra in C_6D_6 of rotenoids possessing an *E*-dihydrofuran ring could be used for stereochemical assignments: a) the chemical shift of 1-H for determination of the type of B/C-ring fusion; b) the pattern of 4′-H_2, 5′-H and 8′-CH_3 for configurational determination at 6a and 12a positions of the *cis*-B/C fused rotenoids with a known configuration at $C_{5'}$.

Experimental

^{1}H NMR spectra were measured (*TMS* as internal standard, chemical shifts in ppm, *J* in Hz) on a Brucker WM 250 spectrometer. The chemical shifts and the coupling constants of 4′-H_2 and 5′-H were estimated by first-order analysis of the ABX system. Compounds **4**–**8** (diastereomeric mixtures—6a β, 12a β, 5′ β and 6a α, 12a α, 5′ β) were prepared from diastereomeric mixtures (6a β, 12a β, 5′ β and 6a α, 12a α, 5′ β) of the 12a-CH_2OH derivatives of **1 a** and **2 a**, and will be reported elsewhere[6].

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