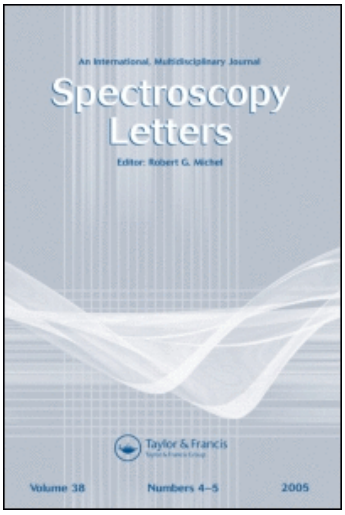

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Identification of Dihydrocarveol Stereoisomers and Their Acetates Using Carbon-13 NMR Spectroscopy

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IDENTIFICATION OF DIHYDROCARVEOL STEREOISOMERS AND THEIR ACETATES USING CARBON-13 NMR SPECTROSCOPY

Keywords : Dihydrocarveol stereoisomers, Dihydrocarvyl acetate, Carbon-13 NMR, Lanthanide induced shift.

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ABSTRACT : The Carbon-13 NMR spectra of dihydrocarveol and dihydrocarvyl acetate stereoisomers are characterized. The chemical shifts are assigned taking account the steric and electronic substituent effects, the lanthanide induced shifts and the proton-carbon correlation.

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INTRODUCTION

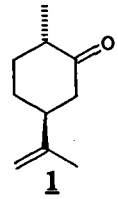
Dihydrocarveol (DHC, 2-methyl-5-isopropenylcyclohexanol) and its stereoisomers are minor constituents of several essential oils[1], and their structure has been known for a long time[2]. However, the unambiguous assignment of substituent stereochemistry was unclear until recently with the availability of spectroscopic properties (^{1}H-NMR, FT-MS, NICI-CID, IR-FT)[3].

In the course of our studies on the analysis of complex natural mixtures using carbon-13 NMR spectroscopy[4], we investigated some essential oils which usually contain dihydrocarveol and/or its stereoisomers. In order to identify these compounds in essential oils, we describe here their carbon-13 NMR spectra and we assign the chemical shift for all the carbons. This work is extended to dihydrocarvyl acetates (DHCA).

EXPERIMENTAL

Mixtures of DHC and DHCA as well as dihydrocarvone stereoisomers (FIG.1, compounds 1-10 are represented with relative stereochemistry) were purchased from Aldrich (mixtures M1 and M5), Extrasynthese (mixture M2) and Janssen (mixture M3). The mixture M4 was obtained from *Thymus herba-barona* Lois. essential oil[5]. Shift reagents Eu(dpm)$_3$ and Yb(fod)$_3$ were procured from SST.

NMR Spectra : All NMR spectra were recorded on a Bruker AC 200 Fourier Transform spectrometer operating at 200.132 MHz for ^{1}H and 50.323 MHz for ^{13}C, in deuteriated chloroform, with all shifts referred to



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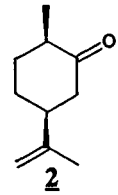
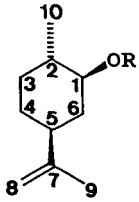
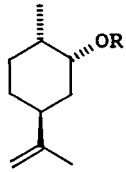


2

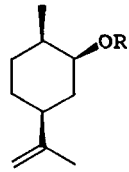
	%	%
M3	79.2	20.8
M4	10.0	90.0



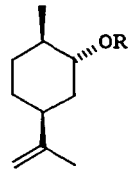
DHC



NEO



NEOISO



ISO

R = H	**3**	**4**	**5**	**6**
	%	%	%	%
R3	63.4	14.7	18.4	2.5
R4	7.8	2.2	80.1	9.9
M1	65.6	13.3	10.2	10.9
M2	45.8	35.2	8.9	10.1
R = Ac	**7**	**8**	**9**	**10**
	%	%	%	%
M5	46.5	35.8	8.6	9.1
A3	62.0	17.5	18.3	2.2
A4	7.1	2.0	80.6	10.3

Figure 1 : dihydrocarvones 1,2, dihydrocarveols 3–6 and dihydrocarvyl acetates 7–10

internal tetramethylsilane (TMS). Carbon-13 and proton NMR spectra were recorded respectively with the following parameters : pulse width (PW) : 3.2 μs (flip angle 45°) and 2 μs (flip angle 25°) ; acquisition time : 1.3 s and 2.3 s for 32K and 16K data table with a spectral width (SW) of 250 ppm and 15 ppm. Carbon-13 spectra were recorded with broad-band decoupling and a digital resolution of 0.763 Hz/pt. The following parameters were used for spin-echo experiments (JMODXH) : PW (90°) : 6.5 μs ; relaxation delay (RD) : 4 s ; 1/J(CH) delay = 7.0 ms ; SW : 12500 Hz.

The number of accumulated scans was 2 000 for each mixture of stereoisomers (0.5 $mol.l^{-1}$ in $CDCl_3$) as well as for each addition of shift reagent. Lanthanide induced shifts (LIS) for all the carbons were obtained by plotting six different values corresponding to the addition of the shift reagent (approximatively 6x3mg) for a 0.5 $mol.l^{-1}$ solution of DHC or DHCA in $CDCl_3$.

The proton-carbon chemical shift correlation utilized the XHCORR sequence with delays optimized for J(C,H) values of 140 Hz. The spectra were acquired with 2K x 256 data points and a data acquisition of 64 x 256 increments in t_1 and a zero filling in the F_1 dimension. The spectral widths were 1400 Hz in the F_2 domain and 600 Hz in the proton F_1 domain. The fixed delays were a 5.0 s relaxation delay, 4.0 ms polarization transfer delay and 2.0 ms refocusing delay. For each value of t_1, 256 transients were accumulated. The data were processed with a sine bell squared window function in each dimension.

Reduction of dihydrocarvones 1 and 2 : A solution of dihydrocarvone stereoisomers M3 (1.090 g, 7.2 mmol) or M4 (0.506 g, 3.3 mmol) in anhydrous ether (5 mL) was added dropwise to a stirred

suspension of lithium aluminium hydride (LAH, 0.320 or 0.150 g, 8.6 or 4.0 mmol) in anhydrous ether (20 mL). The reaction mixture was refluxed 2 hours and worked up by addition of NaOH (15%, 2 mL) and water (2 mL) and then filtered. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure (Yields : 68% and 90%). R3 and R4 are the mixtures of DHC stereoisomers obtained from reduction of mixtures M3 and M4, respectively.

Acetylation of DHC stereoisomers 3–6 : A solution of dihydrocarveol stereoisomers R3, (0.450 mg, 2.9 mmol) or R4 (0.254 g, 1.6 mmol) in pyridine (10 mL) and acetic anhydrid (10 mL) was stirred overnight at room temperature to allow complete elimination of the alcohols. The reaction mixture was extracted by ether (3x20mL). The combined organic layer was washed with saturated $CuSO_4$ solution (3x20mL), saturated Na_2CO_3 solution and water, and dried over $MgSO_4$. The solvent was removed under reduced pressure (Yields : 65% and 34%). A3 and A4 are the mixtures of DHCA stereoisomers obtained from acetylation of mixtures M3 and M4, respectively.

RESULTS AND DISCUSSION

1 – Carbon–13 NMR Spectroscopy of DHC stereoisomers.

The separation of DHC stereoisomers is quite difficult to realize either by chromatography or by other techniques[3]. Therefore, we wanted to check off the carbon–13 resonance values of each stereoisomer from the spectra of several mixtures (M1, M2, R3, R4, FIG.1) in which their ratio is

sufficiently different to allow an unambiguous identification, based on the comparison of relative intensities.

DHC 3 and neoisoDHC 5 are the major components, respectively in samples R3 and R4 resulting from LAH reduction of two different mixtures M3 and M4 of trans and cis dihydrocarvones 1 and 2[6] (FIG.1). The ^{1}H-NMR spectrum of each mixture is complex. Nevertheless, in both cases, it was possible to observe between 3 and 4 ppm the signal of the geminal proton to the OH group of the major stereoisomer. This signal is respectively a triplet of doublets (J=10.0 and 4.0 Hz) for DHC 3 and a doublet of triplets (J=11.5 and 4.5 Hz) for neoisoDHC 5, in full agreement with proton NMR studies on these alcohols[3]. In the following step, the ten ^{13}C resonances of neoDHC 4 are available from mixture M2 and those of isoDHC 6 are obtained by comparison of spectra of mixtures M1, M2, R3 and R4.

The chemical shift assignment of all the carbons (table 1) has been accomplished by taking into account :

i) the number of bonded hydrogens resulting from spin-echo spectra;

ii) the classical electronic and steric effects associated with the presence, as well as the axial or equatorial stereochemistry, of each substituent ;

iii) the shielding effect induced by the disappearance of trans antiperiplanar disposition of vicinal hydrogens[7] ;

iv) the relative values of the Lanthanide Induced Shift (table1, LIS of carbon 1 of each stereoisomer being chosen as reference) ;

v) the heteronuclear proton-carbon correlation which allows the differentiation of carbons bonded to allylic or aliphatic hydrogens.

TABLE 1 : ^{13}C chemicals shifts (δ, ppm) of dihydrocarveol stereoisomers **3–6** and relative LIS

	3		**4**		**5**		**6**	
	δ	LIS	δ	LIS	δ	LIS	δ	LIS
C–1	76.43	1	70.98	1	72.75	1	72.15	1
C–2	40.06	0.28	36.13	0.25	33.72	0.27	36.50	0.31
C–3	33.33	0.14	28.18	0.30	30.64	0.14	27.22	0.25
C–4	31.15	0.14	31.46	0.19	24.64	0.14	26.18	0.18
C–5	44.23	0.16	37.86	0.28	44.08	0.14	38.97	0.25
C–6	40.66	0.44	38.75	0.38	34.11	0.33	34.52	0.29
C–7	149.42	0.06	150.27	0.08	149.52	0.05	149.09	0.12
C–8	108.61	0.04	108.40	0.07	108.61	0.05	109.16	0.08
C–9	20.85	0.04	20.97	0.05	20.94	0.04	21.53	0.06
C–10	18.35	0.29	18.34	0.30	10.74	0.29	17.31	0.16

In every stereoisomer, olefinic carbons C7 and C8, as well as carbon C1 bonded to the hydroxyl group, are identified on the basis of their chemical shifts. Methyls C9 and C10 are differentiated easily because carbon C9 has a chemical shift nearly constant ($20.85 \leqslant \delta \leqslant 21.53$ ppm). Furthermore, these carbons exhibit different relative values of LIS very low for the former (0.04–0.06) much higher for the latter (0.16 – 0.30).

The difficulties lie with the differentiation of methynes C2, C5 in one hand and methylenes C3, C4 in the other, the methylene C6 having a higher chemical shift than the two others (β–effect of hydroxyl and isopropylidene groups) and a higher value of LIS.

Dihydrocarveol 3 bearing all substituents with an equatorial stereochemistry is used as model. Carbon C2 exhibits an higher LIS than C5. Moreover, these two carbons are discriminated using heteronuclear proton–carbon correlation (XHCORR), the latter being bonded to an allylic hydrogen whereas the former is bonded to an aliphatic one. Methylenes C3 and C4 are distinguished taking into account the γ–effect of methyl C9 and methylene C8, in agreement with previous results in these series, relative to trans menthane and trans dihydrocarvone[8] for instance.

Moving from DHC 3 to neoisoDHC 5 (methyl group with an axial stereochemistry) induce a shielding of the chemical shifts of all the carbons, except C5. This shielding is created either by the steric γ–effect of methyl C10 on C4 and C6 ($\Delta\delta \simeq -6.5$ppm) or by the disappearance of the trans antiperiplanar disposition of vicinal hydrogens[7] on C1, C2 and C3 (respectively $\Delta\delta = -3.68$, -6.34 and -2.69 ppm). The LIS values are in perfect agreement with those of DHC 3, the values for C2 and C6 being nearly twice as important as they are for C5, C4, C3.

For the same reasons, a shielding of the chemical shifts of all the carbons (except C4) is observed on neoDHC 4 compared with DHC 3. On this stereoisomer, LIS values differ from those of DHC 3 and neoisoDHC 5. The introduction of an axial hydroxyl function causes comparable values of LIS on carbons C2, C6 and C3, C5. These values confirm the assignment of carbons C3 made on the basis of the γ–effect of the hydroxyl group. Once again methynes C2 and C5, which display very close chemical shifts, are differentiated using proton–carbon correlation.

Relative LIS values for cyclic carbons of isoDHC 6 range between 0.25 and 0.31 except those of C1 (1.00) and C4 (0.18) and allow the chemical shift assignment of C3 and C4. This is not the case for methynes C2 and C5 which display close chemical shifts and relative LIS values. The differentiation of these two carbons is available by comparison of their chemical shifts with those of the corresponding acetate (see below). We observe a shielding of –3.2 ppm on carbon C2 of the acetate 10 compared with the alcohol 6. Conversely, the inversion of the chemical shifts of C2 and C5 would lead to inconsistent values of acetylation induced shifts on carbon C2 (β position relative to the hydroxyl or acetoxyl function).

The carbon chemical shifts assignment of DHC 3 and its stereoisomers 4–6 fits very well with those of Dauzonne, relative to carvomenthols[9].

2 – Carbon–13 NMR Spectroscopy of DHCA stereoisomers.

The same procedure was applied to DHCA 7–10 (FIG.1). Acetylation (Ac_2O/Py) of R3 and R4 gave rise respectively to mixtures A3 and A4 which allowed the identification of the twelve resonances of 7 and

9. Those of 8 and 10 were pointed up as before by comparison of spectra of mixtures A3, A4 and M5.

The assignment of carbon chemical shifts was made by following the same scheme as described for alcohols (table 2). Furthermore, carbon C2 is more easily differentiated from C5 taking into account the shielding effect of acetylation on β carbons. Methylene C6 has always a LIS higher than the two other methylenes while C4 has the lowest LIS. The relative values of LIS for C3 varie from 0.19–0.22 to 0.28–0.29 following the equatorial or axial sterochemistry of the acetoxyl function.

CONCLUSION

In this study, we assigned the carbon chemical shifts of dihydrocarveol, dihydrocarvyl acetate and their stereoisomers, taking into account several NMR parameters : electronic and steric effects of substituents, trans antiperiplanar disposition of vicinal hydrogens, lanthanide induced shifts, acetylation induced shifts, heteronuclear proton–carbon correlation.

By comparison with DHC 3 itself (or its acetate), the introduction of one or two of the three substituents (methyl or hydroxyl or acetoxyl) with an axial stereochemistry lead to steric effects on γ carbons which range from 4.02 to 6.55 ppm. It is likely that isomers 3–5 and 7–9 which possess at least two substituents with an equatorial stereochemistry adopt a chair conformation.

In contrast, the conformation of compounds 6 and 10 should be a twist form which reduces steric interactions between methyl C10 and

TABLE 2 : ^{13}C chemicals shifts (δ, ppm) of dihydrocarvylacetate stereoisomers **7–10** and relative LIS

	7		**8**		**9**		**10**	
	δ	LIS	δ	LIS	δ	LIS	δ	LIS
C–1	78.32	1	73.55	1	75.22	1	74.86	1
C–2	37.21	0.45	35.07	0.43	30.91	0.51	33.31	0.45
C–3	33.22	0.22	29.20	0.29	30.54	0.19	27.56	0.28
C–4	30.96	0.17	31.28	0.23	24.58	0.15	25.91	0.21
C–5	43.77	0.21	38.65	0.30	43.94	0.20	39.42	0.29
C–6	36.97	0.53	35.69	0.50	30.65	0.46	31.28	0.51
C–7	148.90	0.08	149.68	0.13	149.05	0.09	148.51	0.18
C–8	108.88	0.05	108.66	0.09	108.84	0.05	109.49	0.10
C–9	20.83	0.03	20.89	0.09	20.87	0.04	21.37	0.08
C–10	18.22	0.38	18.04	0.36	11.57	0.32	16.95	0.20
C–11	170.78	2.90	170.78	2.82	170.47	2.96	170.53	2.88
C–12	21.22	1.56	21.16	1.02	21.32	1.43	21.37	1.05

carbons C4 and C6. This fact is observed by comparison of the chemical shifts of these carbons in isomers 6 and 10 in one hand, 5 and 9 in the other, and could explain the lack of the drastic shielding of methyl C10 in the two formers.

These results allowed us to identify unambiguously some of these compounds in samples of *Mentha spicata* essential oil, using a computer-aided analysis of ^{13}C spectrum of the mixture[4].

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